Development of a Hetero-Diels-Alder reaction to synthesize 3-hydroxypyridines and its application toward the total synthesis of nosiheptide

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DISSERTATION

von

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Erklärung/Declaration

Hiermit versichere ich an Eides statt, dass ich die vorliegende Arbeit selbständig und nur mit den angegebenen Hilfsmitteln angefertigt habe.

I hereby declare that I performed the work presented independently and did not use any other but the indicated aids.

Dortmund, June 2009

Jin-Yong Lu

Die vorliegende Arbeit wurde unter Anleitung von Dr. Hans-Dieter Arndt am Fachbereich Chemie der Technischen Universität Dortmund und am Max-Planck-Institut für molekulare Physiologie, Dortmund in der Zeit von Mai 2004 bis Mai 2009 angefertigt.

Dedicated to my family

Where there is a will, there is a way.

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Last but not the least I would take the chance to acknowledge my parents for their unconditional love and moral support. The God gifts, my wife and my son, I thank for always supporting and encouraging me.

Content

1. Introduction

Natural products and its analogs play an important role in the continuing effort to find new drug candidates,[1-4] and advance chemical synthesis. We will present our effort toward the total synthesis of nosiheptide and its relied methodology development in this thesis.

1.1 Thiopeptides

The thiopeptide antibiotics are produced by *Actinomyces* bacteria and comprise more than 80 members.[5,6] The first isolated thiopeptide was micrococcin (**1**) in 1948,[7] and the prototypical and easily produced thiostrepton (**2**), in 1954 from *Streptomyces azureus* ATCC 14921,[8] has become the flagship of this family. All thiopeptides are highly modified, sulfur rich, macrocycle containing peptides. They share a number of common features: A highly substituted central pyridine derived six member ring, which acts as the central core of a macrocyclic array consisting of thiazol(in)e, oxazol(in)e, indole and dehydroamino acids such as dehydroalanines and dehydrobutyrines.

The thiopeptide family can be subdivided into three major classes according to the oxidation state of the central pyridine derived heterocycle.[5] One representative of each class is shown in figure 1-1 to illustrate the structural differences.

1) Thiopeptides with a trisubstituted pyridine core (compare to micrococcin P1 (**1**)). Most of the thiopeptides in this class contain one macrocyle and it is the dominant structural motif in this family.

2) Thiopeptides with a trisubstituted piperidine or dehydropiperidine core (such as thiostrepton (**2**)). This series of thiopeptides displays a bis-macrocyclic backbone and contains a quinaldic acid. The structural variations with this class are only minor.

3) 3-Hydroxypyridine containing thiopeptides (e.g. nosiheptide (**3**)). This thiopeptide class possesses closely related structures, is characterized by at least two macrocycles and contains an indole or 1-hydroxyindole connected by an ester or thioester linkage.

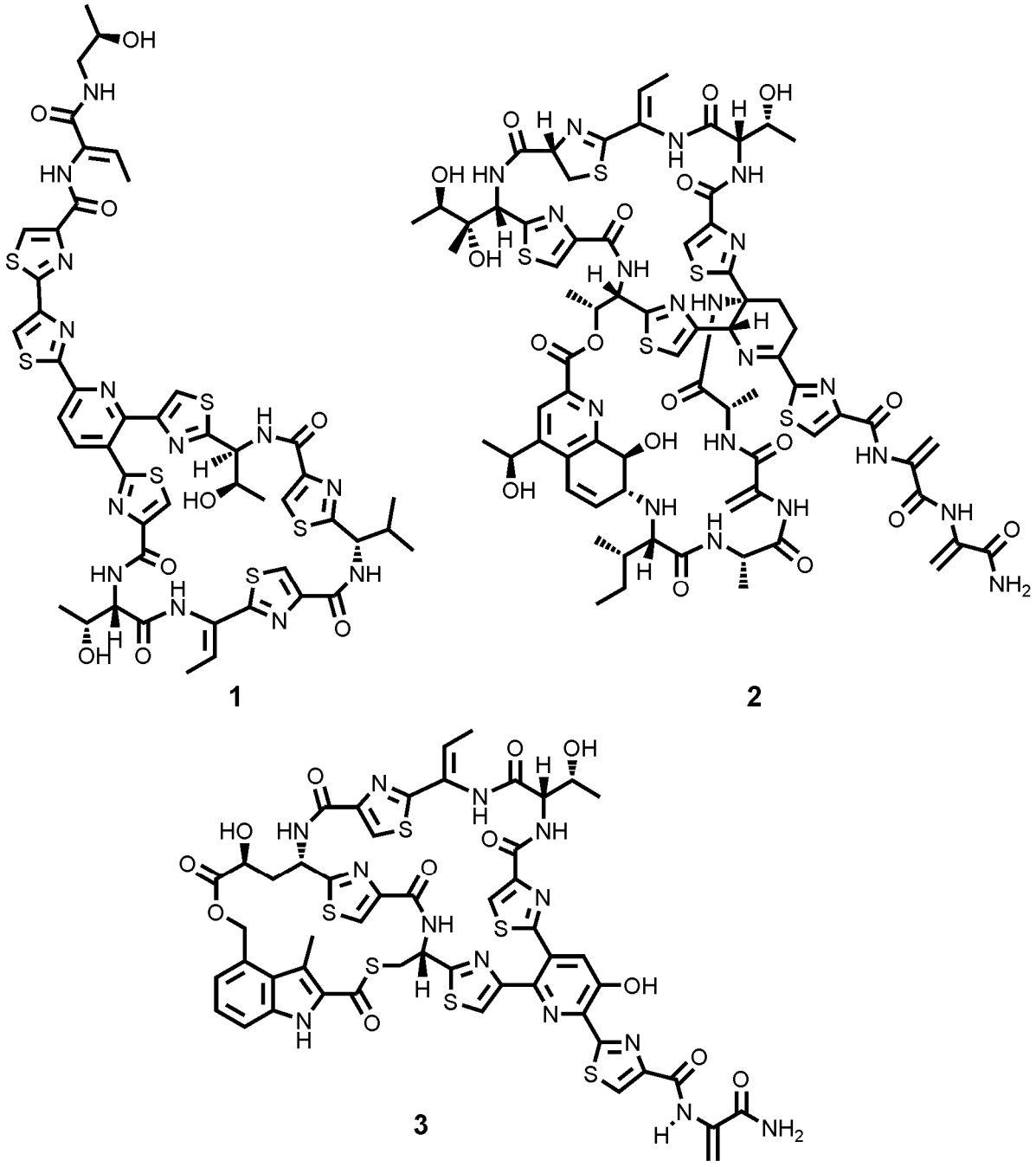


Figure 1-1. Chemical structure of micrococcin P1, thiostrepton and nosiheptide.

All thiopeptides share a common biological profile. They show high activity in inhibiting protein synthesis in Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* strains (MRSA), but much weaker activity against Gram-negative bacteria. They bind within the cleft located between the ribosomal protein L11 and helices 43 and 44 of the 23S rRNA (figure 1-2), which are the components of the ribosomal stalk base, one of the key elements of the GTPase-associated center.[9-11] Some of the thiopeptides like GE2270A interact with EF-Tu, a translation factor involved in peptide elongation.[12,13] Despite of this high in

vitro potency, thiopeptide antibiotics have not been in use for human therapy, mainly due to their poor solubility. However, thiostrepton is routinely used to treat topical infections in livestock and pets, and nosiheptide has been used as growth promotant for hog and poultry farming.

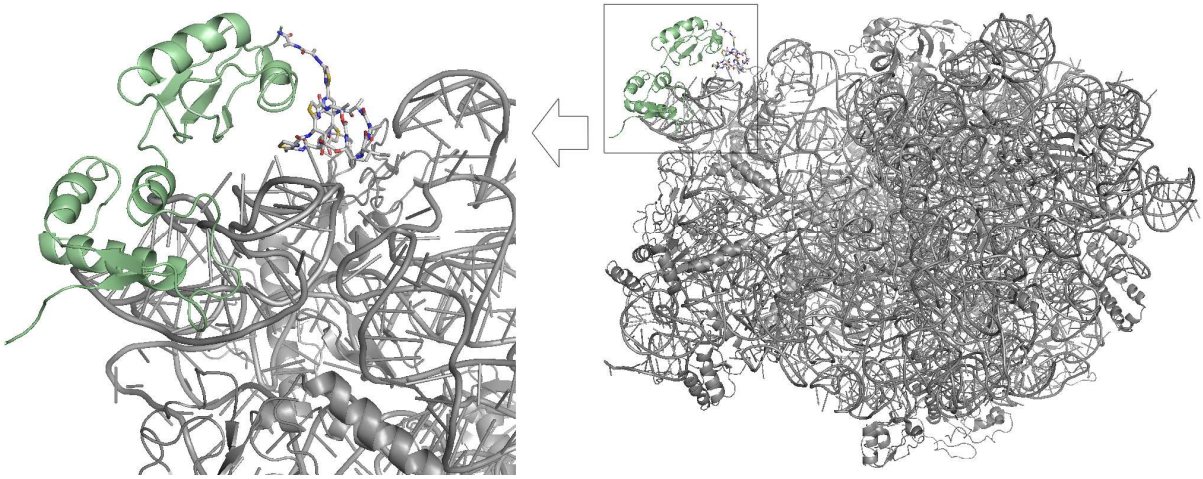


Figure 1-2. Binding position of the thiopeptides on the 50S subunit of ribosome.

1.2 Thiopeptide Biosynthesis

The biosynthesis of nosiheptide and thiostrepton has been elucidated by the incorporation of isotopically labeled amino acid (for example: ^{13}C, ^{14}C, deuterium or tritium), which showed that both thiopeptides are constructed from standard amino acid of the primary metabolism.[14-18] However, the biosynthesis mechanism of the multistep process remained unclear until recently. In principle, peptide natural products can be formed from a precursor peptide that may be synthesized by translation of a genetically encoded mRNA (ribosomal peptide synthesis), followed by posttranslational modifications of the linear chain.[19] Alternatively, multienzyme complexes known as nonribosomal peptide synthetases (NRPS) can assemble peptides from non-proteinogenic amino acids, which often leads to a remarkable structure modifications and high content of uncommon amino acids in the structure.[20]

For a long time it was assumed that thiopeptides have to be assembled by NRPSs, but this hypothesis could never be proven. Surprisingly, four independent studies from different research groups[21-25] now substantiated the unique rationale that thiopeptides are genetically encoded, ribosomally synthesized peptides and require a post-translational machinery for their maturation. These investigations revised the opinion that ribosomally synthesized peptides featured a much lower degree of modification compared to NRPS products. Thiostrepton is

selected as a representative to illustrate the key biosynthetic steps (figure 1-3).[21,23] The architecture of the thiostrepton biosynthesis gene cluster (figure 1-3A) is very similar to the gene cluster of siomycin A[23], thiocillin[24] and the newly identified thiomuracins.[22]

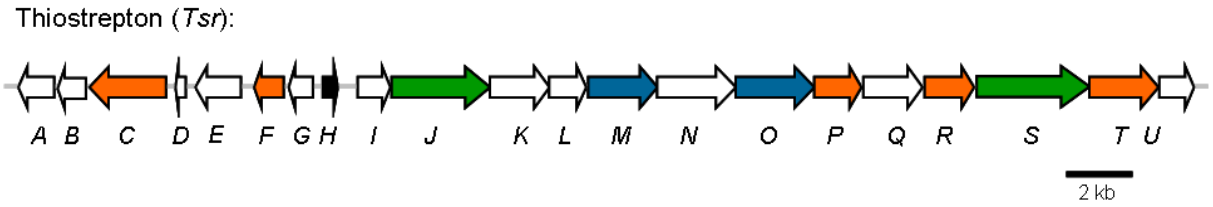


Figure 1-3A. Architecture of the thiostrepton biosynthesis gene cluster, black: structural gene; green: dehydratase; blue: cyclodehydratase or dehydrogenase; orange: tailoring enzymes (monoxygenase, methyl transferase, protease, deaminase, amidotransferase); colorless: Other/unknown open reading frame; *tsr* = thiostrepton, bar: 2 kb.

In all cases, the structural genes encoding the peptide sequence are surrounded by modifying genes. Following the N-terminal 41 amino acid leader peptide (LP), which most likely directs the ensuing modification before the final product or an advanced intermediate is liberated, the 17 amino acid sequence at the C-terminal end is in perfect agreement with the thiostrepton peptide backbone amino acids (figure 1-3B and figure 1-3C). This observation revealed the ribosomal origin of thiostrepton. All Ser/Thr residues of peptide **4** apparently become dehydrated and all cysteine residues become cyclodehydrated to thiazoles or thiazolines. The D-Cys-derived-thiazoline at C-9 must be formed by epimerization during the TsrA maturation.[17] The remarkable central dehydropiperidine core is apparently formed from two dehydroalanines and a neighbouring carboxy group via an intramolecular hetero-Diels-Alder-type cycloaddition likely promoted by specific enzymes. Further enzymatic modifications of the putative intermediate **5** then leads to thiostrepton.

TsrA:

MSNAALEIGVEGLTGLDVDTLEISDYMDETLLDGEDLTVTMIASASCTTCICTCSCSS

Figure 1-3B. Sequence of the thiostrepton structural peptide (one letter code). Leader peptides are highlighted in grey, structural peptides are colour coded (see below).

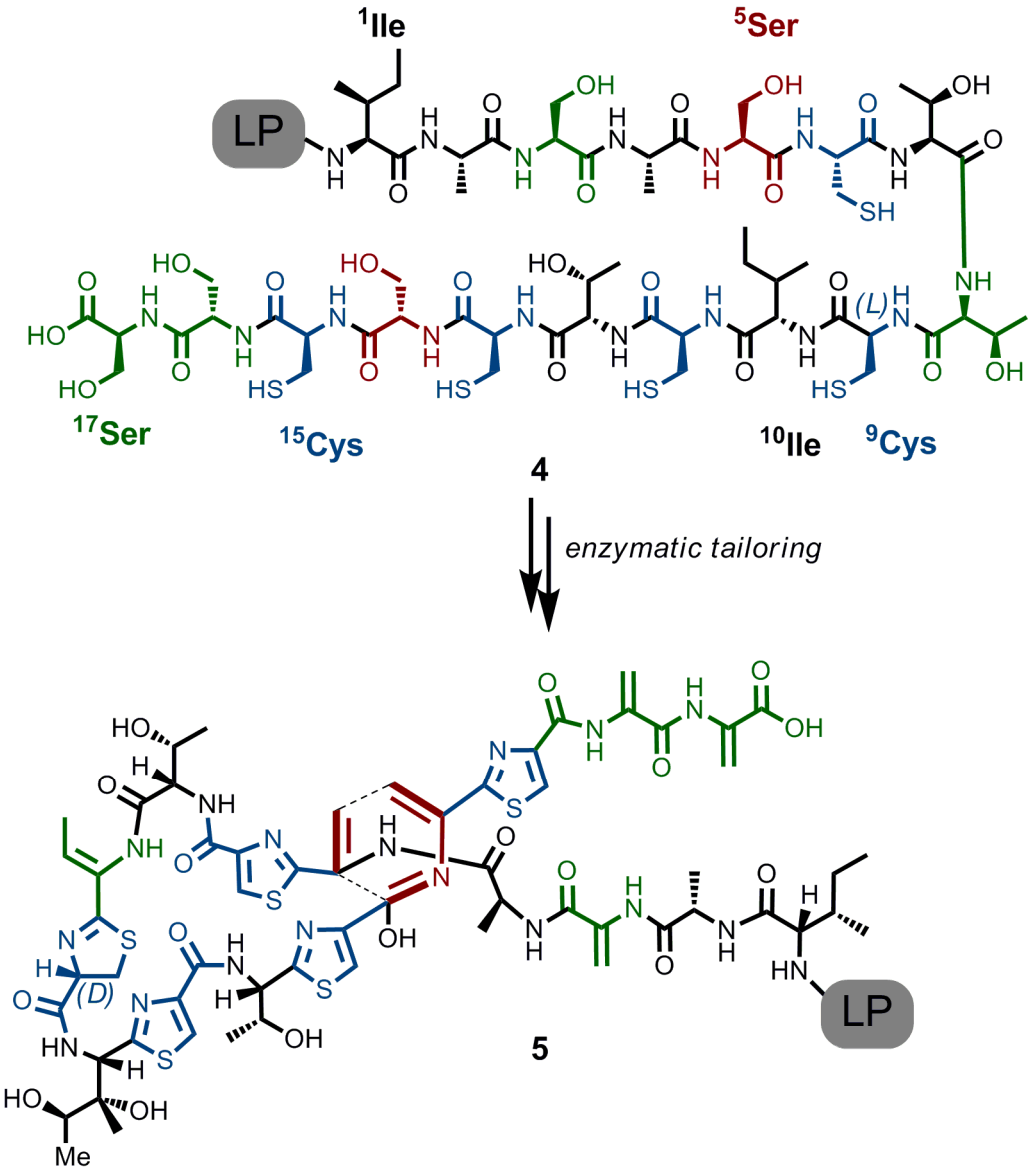


Figure 1-3C. Emerging picture of thiostrepton structural peptide maturation (simplified). green: dehydratase-mediated dehydroalanine/-butyrine formation; blue: cyclodehydratase-initiated heterocycle formation; black: structurally unmodified/peripherally decorated residues; red: dehydroamino acids involved in the formation of the *aza*-heterocyclic nucleus.

1.3 Selected synthetic work on thiopeptide natural products

1.3.1 Total synthesis of thiostrepton by Nicolaou

The intricate molecule architectures have challenged organic synthesis since the principle structure elucidation of thiostrepton by Crowfoot-Hodgkin and colleagues in 1970.[26] Since

then, the structural motifs identified have led to important development in chemical synthesis, and several successful total syntheses demonstrated the progress in the field. This subject has been covered in major recent reviews.[2,5,6] Therefore only selected examples shall be discussed here. The only total synthesis of thiostrepton was realized by the Nicolaou group.[27-30] A brief retrosynthetic analysis of thiostrepton according to their rationale is shown in figure 1-4. Thiostrepton was simplified to the key building blocks dehydropiperidine **6** and the quinaldic epoxide **7**, after disconnection of amide bonds (a), ester formation (b) and nucleophilic epoxide opening (c).

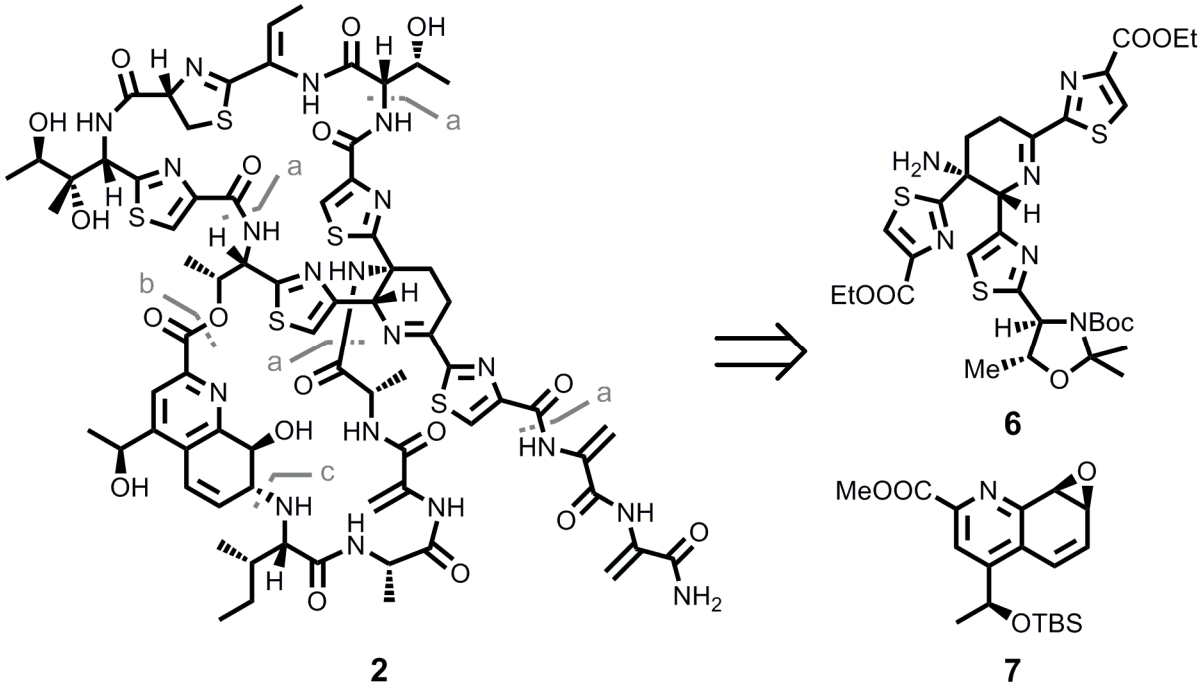


Figure 1-4. Thiostrepton retrosynthetic analysis and key building blocks.

The synthesis of the dehydropiperidine **6** relied on a "biomimetic" Hetero-Diesl-Alder (HAD) reaction[31] and is shown in figure 1-5. The 2-azadiene **9** was generated *in situ* by treatment of thiazolidine **8** with Ag_2CO_3, which was converted to dehydropiperidine **11** by a hetero-Diels-Alder type dimerization via an *endo* transition state **10**. Benzyl amine was applied to induce mild transimination of the imine at 5-amino substituent, which led to the inseparable free amine **6** and its diastereomer **6'**. Unfortunately, this powerful transformation could not be rendered diastereoselective with respect to the pendant threonine side chain (d.r. = 1:1), but the diastereomers could be separated after installing an alanine.

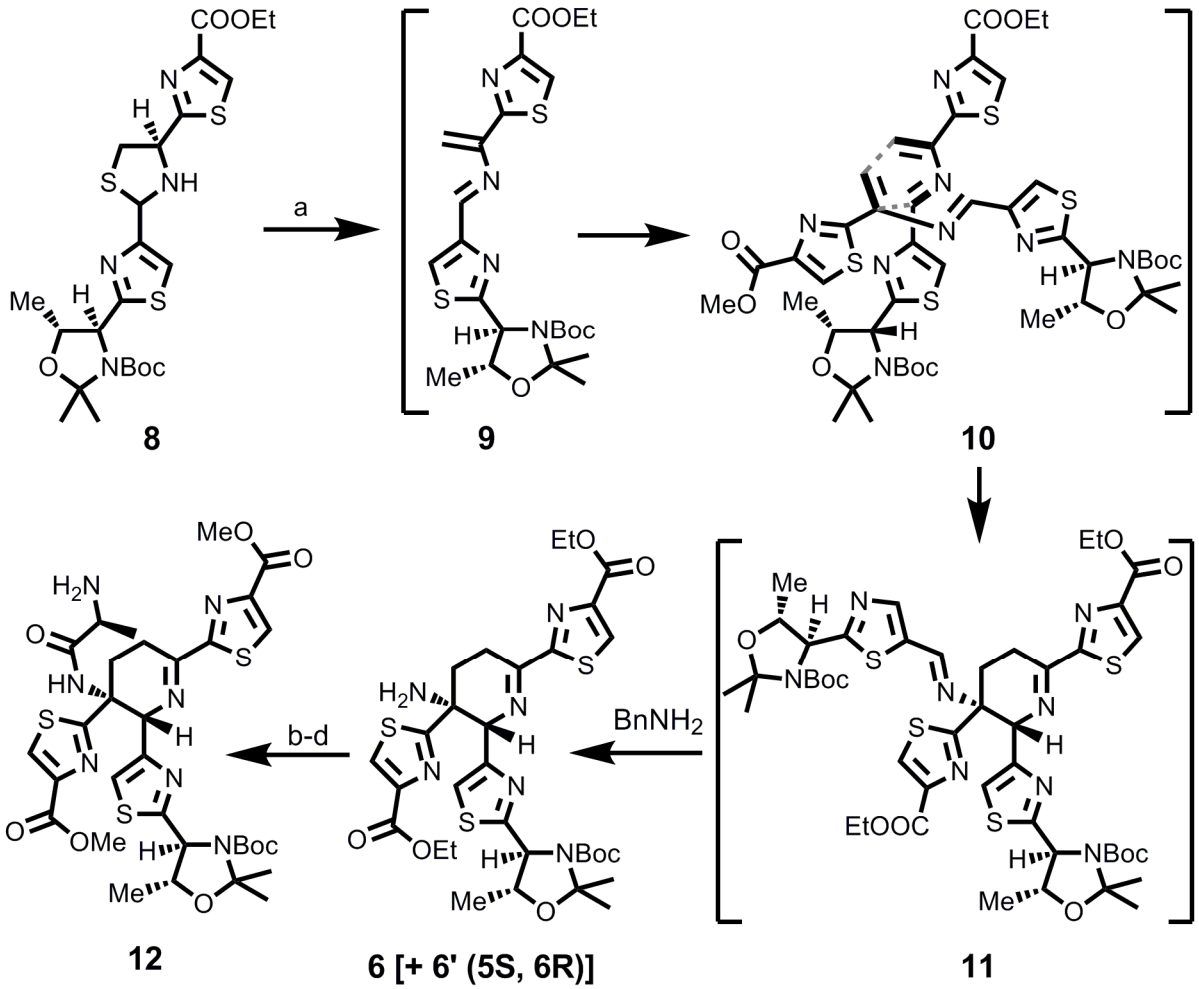


Figure 1-5. Biomimetic synthesis of dehydropiperidine. a) Ag_2CO_3, DBU, pyridine, $BnNH_2$, -12°C ~ 25°C, 60%; b) 2-azido-propanoyl chloride, Et_3N, THF, 70%; c) Bu_2SnO, MeOH, 56%; d) $SnCl_2$, 44%.

The quinaldic epoxide **7** was traced back to 2-quinoline carboxylic acid **13** (figure 1-6).[32] The olefin **14** was generated in 9 steps from **13**. (*R*, *R*)-Katsuki manganese salen catalyst **15**[33] provided the desired epoxide **16**. Radical bromination and subsequent elimination delivered the allylic epoxide **7**, which was opened by L-Ile-OAllyl **17** in a regio- and stereoselective fashion to afford the quinaldic fragment **18** ready for further esterification.

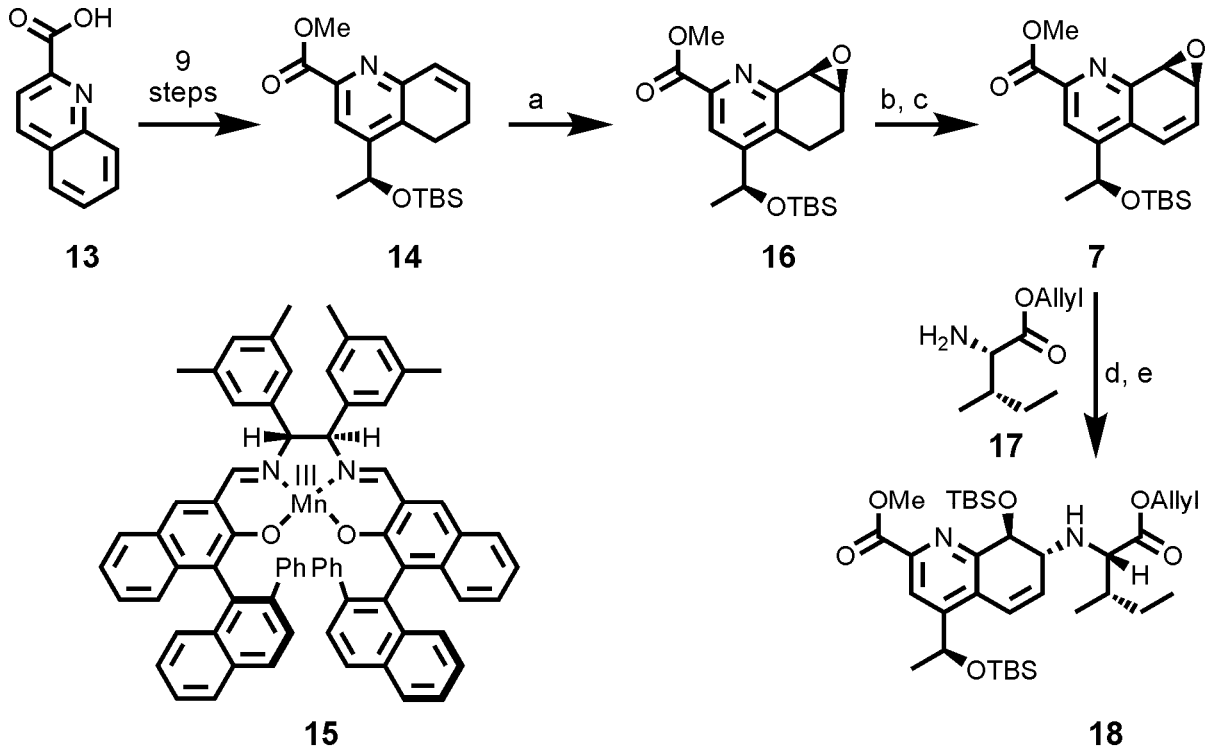


Figure 1-6. Preparation of quinaldic acid derivative. a) **15**, NaOCl, 4-Ph-py-N-oxide, pH 11.5, 82%, d.r. = 87:13; b) NBS, AIBN, CCl_4, 40%; c) DBU, THF, 96%; d) **17**, $LiClO_4$, CH_3CN, 69%; e) TBSOTf, DIPEA, THF, 94%.

With the two key building blocks secured, Nicolaou *et al*. were able to complete a total synthesis of thiostrepton (figure 1-7). The free amine **19** was obtained after protecting **12** with an Alloc group and liberating the threonine. Thiazolyl peptide **20** was assembled using classical Hantzsch thiazole and DAST mediated thiazoline synthesis.[30] HATU mediated amide bond formation led to **21**, which was transformed to the first macrocycle **22** after Me_3SnOH mediated hydrolysis[34] and azide reduction in moderate efficiency (32% yield for the ring closure). The second macrocycle was appended after the installation of the quinaldic building block **18** by esterification and insertion of seleno-alanines as precursors for the dehydro-amino-acids. Oxidative cleavage of the selenium generating the desired alkenes and silyl group deprotection successfully finished thiostrepton **2**. This remarkable synthesis-albeit featuring some peculiar transformations – a generally stands out as the most efficient assembly of bicyclic thiopeptide to date featuring novel methods and chemistry as well as strategies suitable to prepare molecules of this whole class.

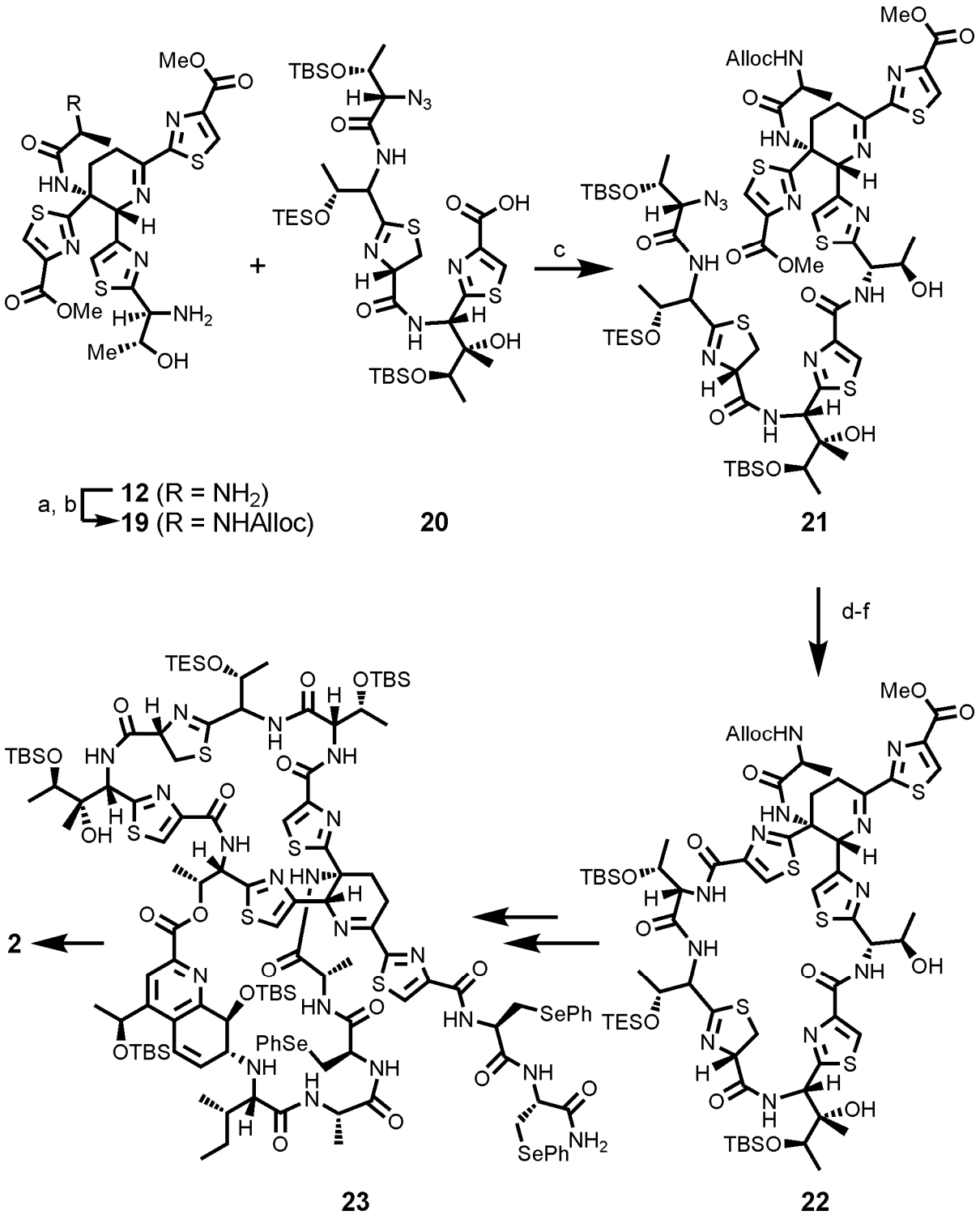


Figure 1-7. Thiostrepton fragment union and macrocycle formation. a) AllocCl, DIPEA, DMAP, THF, 92%; b) 50% TFA in CH_2Cl_2; c) HATU, HOAt, DIPEA, DMF, 73%; d) Me_3SnOH, DCE, 52%; e) PMe_3, THF/H_2O; f) HATU, HOAt, DIPEA, 32%.

1.3.2 Total synthesis of Siomycin A by Nakata

Siomycin A (**24**) was isolated from *Streptomyces sioyaensis* in 1961.[35] With dehydroalanine-valine attached to the quinaldic acid in siomycin A instead of alanine-isoleucine like in thiostrepton, siomycin A is structurally and biologically almost identical to thiostrepton. The total synthesis of siomycin A was completed by a large group around Nakata in 2008.[36-38] Although the generation of the Z configured enamine, the late stage thiazoline formation and the order of macrocycle formation are different from Nicolaou's construction of thiostrepton, the major difference is the chemistry for the synthesis of the dehydropiperidine core **25**. Therefore, only this access to the dehydropiperidine **25** will be discussed here (figure 1-8).

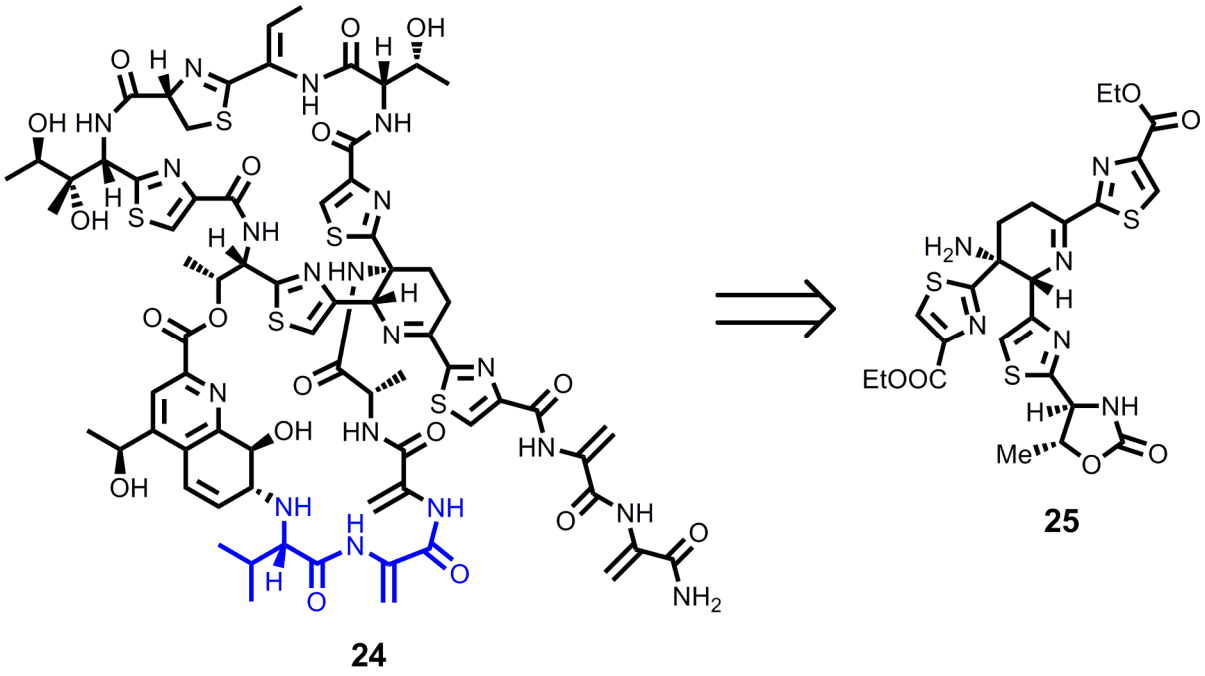


Figure 1-8. Siomycin A and its key dehydropiperidine core.

The synthesis of dehydropiperidine **25** by Nakata features an auxiliary-controlled addition of an aza-enolate to an imine and a ring-enlarging transimination (figure 1-9). The dehydropyrrolidine **26** and sulfimine **27** were prepared from commercially available starting materials.[39] The combination of **26** and **27** in the presence of $LiClO_4$ and Et_3N as base furnished the addition product **29** via the anticipated transition state **28**, which was found more favorable compared to the others (d.r. = 4:1). The dehydropiperidine **25** and **30** were in equilibrium after desulfinylation, which could be derivn to **31** by imine reduction. The imine bond in the six member ring was later regenerated by *t*BuOCl[40] after protecting group exchange and the installation of L-alanine on the 5-amino group.

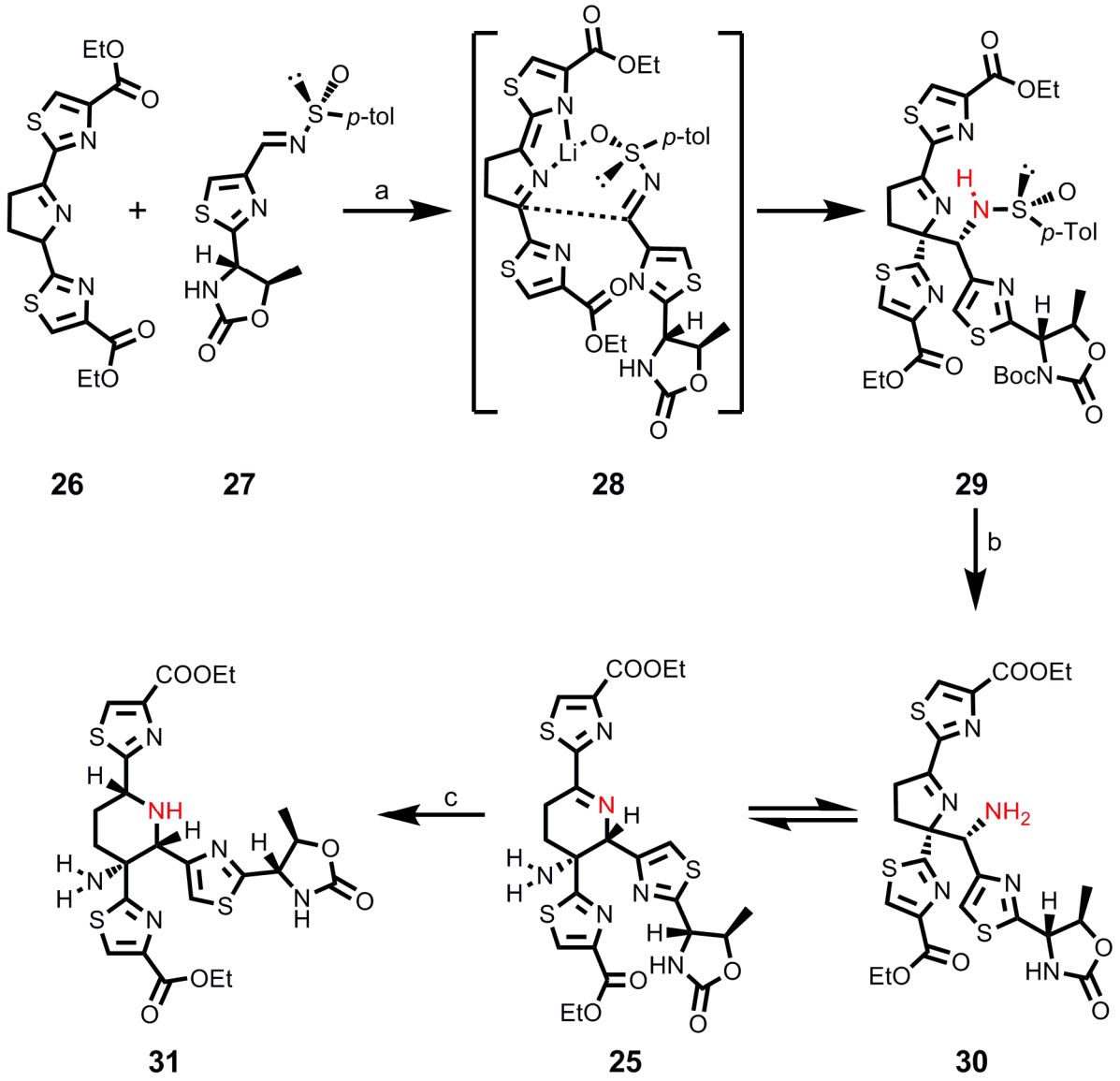


Figure 1-9. Dehydropiperidine synthesis. a) $LiClO_4$, Et_3N, THF, 71%, d.r = 71:17; b) TFA, EtOH; c) $NaBH_3CN$, AcOH, EtOH, 52%.

1.3.3 Nosiheptide.

Nosiheptide (**3**) (figure 1-10), isolated from *Streptomyces actuosus* 40037 in 1977,[41,42] is a thiazole rich polypeptidic antibiotic belonging to the thiopeptide class. The exact structure of nosiheptide has been elucidated by chemical degradation,[43,44] NMR[16,45,46] and X-ray crystallography.[41] Nosiheptide shows strong activity in vitro against gram-positive bacteria, combatting *S. aureus* (resistant to streptomycin, tetracyclin and penicillin) in the nanomolar range (MIC 2.5 nM). However, it shows no activity in experimentally infected mice, which may be tentatively explained by the lability of its prominent thioester bond in the blood

stream. Nosiheptide is not toxic, even at high dose (2.5 g/kg). It is used as a feed additive in chicken and pigs, because it showed a favorable effects on the growth and conversion index.[47] Nonetheless, the thiopeptide antibiotic class is still not used for therapeutic intervention in humans.[5,6]

Nosiheptide contains five thiazoles and two dehydroamino acids. It is structurally distinguished from most other thiopeptide natural products by an indolic macrothiolactone (**B** ring, also called "southern hemisphere")[48] and 3-hydroxypyridine in the center forming the larger macrolactame (**A** ring, also called "northern hemisphere").[48]

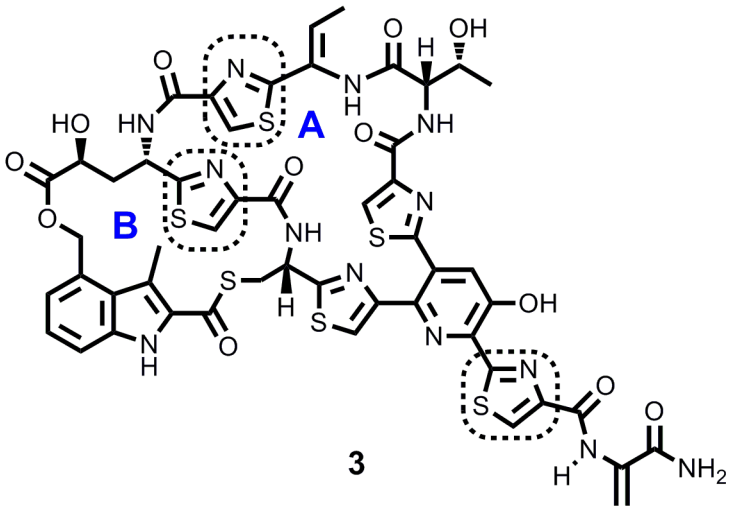


Figure 1-10. Nosiheptide structure.

In the past, several attempts toward the total synthesis of nosiheptide have been reported. Most of them concentrate on building blocks, however, and the most advanced study found this molecule will be presented in the following chapters.

1.3.3.1 Hydroxypyridine synthesis.

The Umemura group[49,50] described the synthesis of the hydroxypyridine fragment **38** from 5-bromo-3-hydroxypyridine **32** (figure 1-11). The first thiazole ring in **33** was installed by a Hantzsch reaction. The second thiazole was attached by the Reissert method; **33** was converted to N-oxide **34** and subsequently treated with TMSCN to give 2-cyanopyridine **35**. The Reissert method was also applied to furnish the pyridone **36**, which led to fully protected pyridine **38** via an enol ether **37**, which was obtained by a Stille type cross coupling reaction. The total yield to pyridine **38** was 7.6% over 14 steps.

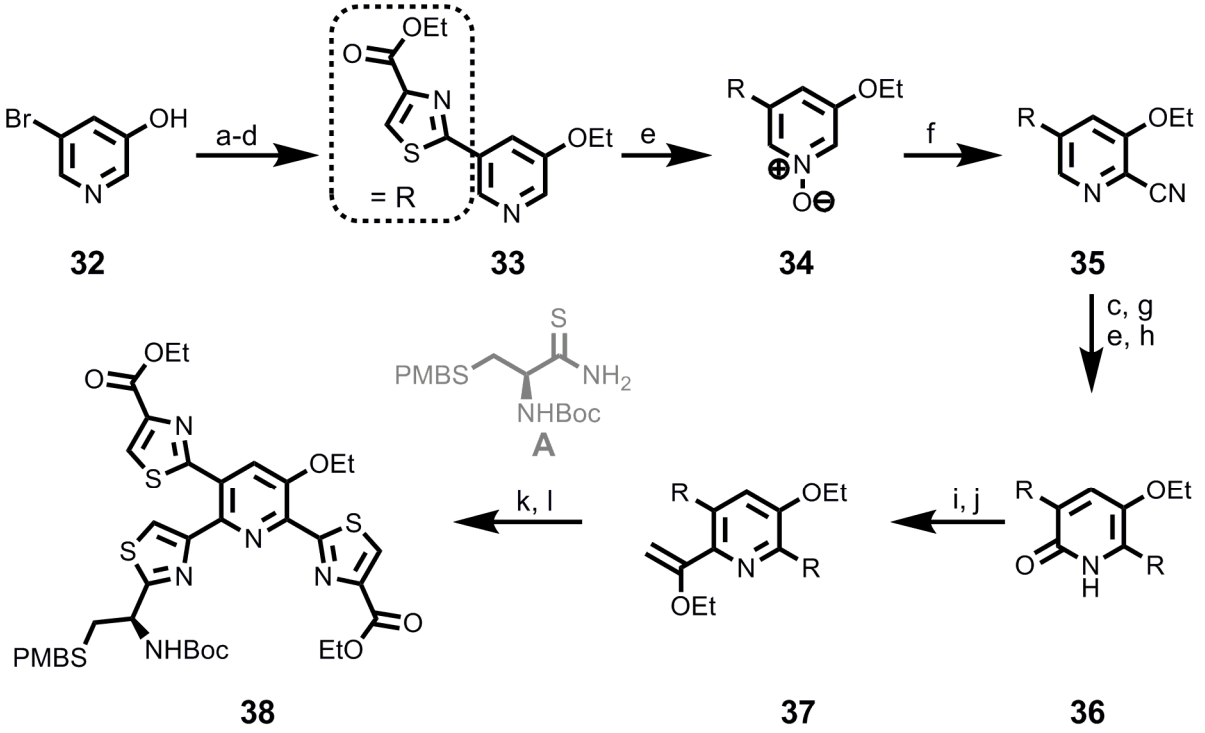


Figure 1-11. Hydroxypyridine fragment synthesis by Umemura. a) CuCN, DMF, 85%; b) Et_2SO_4 K_2CO_3, DMF; c) H_2S, pyridine, Et_3N, 80%; d) $BrCH_2COCOOEt$, EtOH, 81%; e) m-CPBA, CH_2Cl_2, f) TMSCN, Et_3N, CH_3CN, 83%; g) 1. $BrCH_2COCOOEt$, K_2CO_3, THF; 2. TFAA, pyridine, THF, 81%; h) Ac_2O, 97%; i) Tf_2O, DIPEA, DMAP, CH_2Cl_2, 75%; j) CH_2=C(OEt)$SnBu_3$, $Pd(OAc)_2$, dppp, Et_3N, DMF, 85%; k) NBS, H_2O/THF, 85%; l) **A**, EtOH, 39%.

1.3.3.2 Indolic acid synthesis.

Three independent studies were reported for the preparation of the indole building block in nosiheptide. Koerber-Plé *et al.* conducted the synthesis of indole **42** by an intramolecular Heck reaction of **41**.[51] The cross coupling precursor **40** was obtained from methyl anthranilate **39** via a 10 step sequence (figure 1-12).

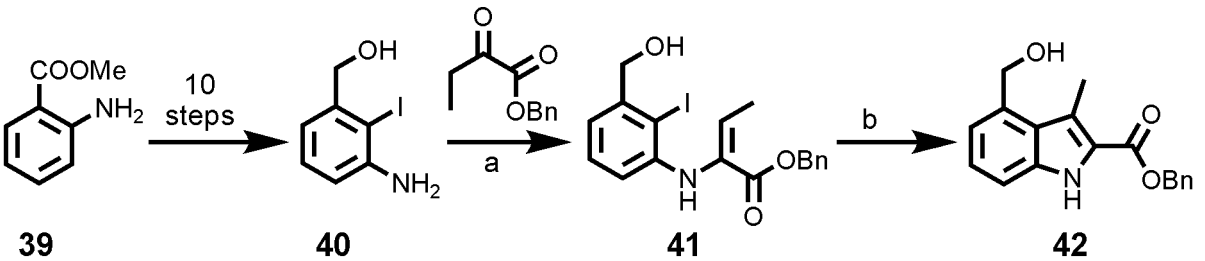


Figure 1-12. Indolic fragment synthesis according to Koerber-Plé. a) *Cat.* glacial CH_3COOH, 75%; b) $Pd(OAC)_2$, $NaHCO_3$, Bu_4NCl, DMF, 46%.

Moody *et al*. synthesized indole **46** by a Fisher indole synthesis from **43** as well as decomposition of α–azido-cinnamate **47**.[52] The chloride substituent in **44** was essential for the regioselectivity, and indole **46** was obtained by removal of the chloride **45**, reduction of the acid and TBS protection of the free alcohol. Thermal decomposition of **47** to the nitrene led to indole **48**, which was converted to indole **46** after several transformations via **49** (figure 1-13).

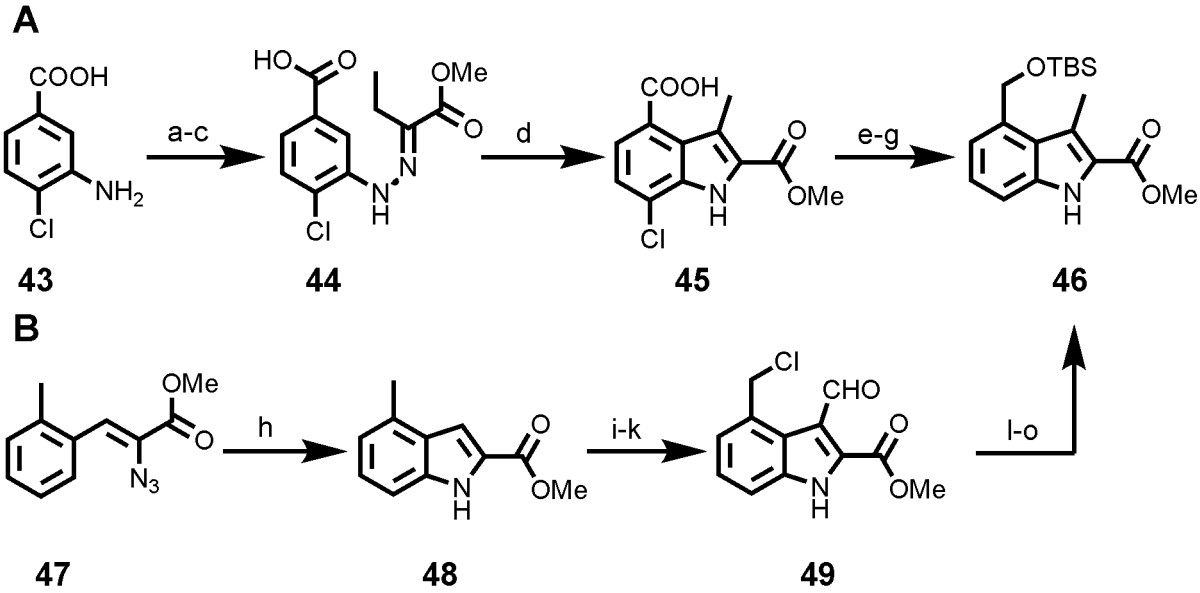


Figure 1-13. Indolic fragment synthesis. a) $NaNO_2$, aq. HCl; b) $SnCl_2$, NaH, HCl; c) EtCOCOOMe, 100%; d) PPA, AcOH, 87%; e) H_2, Pd/C, MeOH, 85%; f) BH_3 x Me_2S, THF, 78%; g) TBSCl, imidazole, DMF, 41%; h) xylene, heat, 100%; i) Boc_2O, DMAP, CH_3CN, 85%; j) NBS, AIBN, CCl_4, 91%; k) $POCl_3$, NMF, DCE, 78%; l) NaI, acetone; m) K_2CO_3, H_2O; n) TBSOTf, pyridine, 54%; o) $NaBH_3CN$, ZnI_2, DCE, 63%.

The Shin group reported a Reissert indole synthesis starting from 2-methyl-3-nitrobenzylalcohol **50**.[53] The indole precursor **51** was transformed by catalytic hydrogenation to furnish the indole **52** in one operation, which was converted to indolic acid **53** via saponification, an indole Grignard reaction and THP deprotection (figure 1-14).

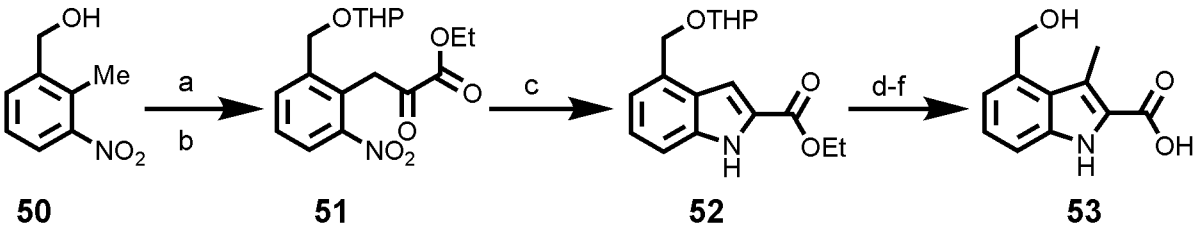


Figure 1-14. Indolic acid synthesis. a) DHP, CH_2Cl_2, 95%; b) $(COOEt)_2$, NaH, DMF, 85%; c) 5% Pd/C, EtOH, 82%; d) LiOH, 94%; e) MeMgI, MeI, Et_2O, THF, 52%; f) 70% CH_3COOH, quantitative.

In our group, it was found that the indole Grignard reaction was difficult to reproduce. The synthesis has therefore been modified and optimized to furnish **55** using a Negishi coupling via an iodoindole **54** (figure 1-15).[54] Orthogonal protecting group exchange leads to indolic alcohol **56** ready for indolic ester formation.[55]

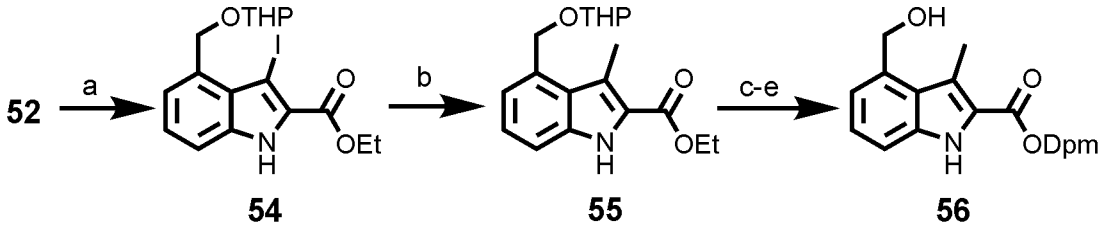


Figure 1-15. Indolic alcohol synthesis. a) K_2CO_3, I_2, DMF, 89%; b) Me_2Zn, $Pd(dppf)Cl_2$, 1,4-dioxane, 96%; c) 10% NaOH, H_2O/EtOH = 1:1; d) 70% CH_3COOH, 73% (2 steps); e) Ph_2CN_2, *cat.* TFA, 68%.

1.3.3.3 Hydroxy glutamate syntheses.

The first reported glutamate derivative **59** of nosiheptide was synthesized from azide **57** by thiazolidine **58** formation and subsequent oxidation after secondary alcohol protection (figure 1-16).[56]

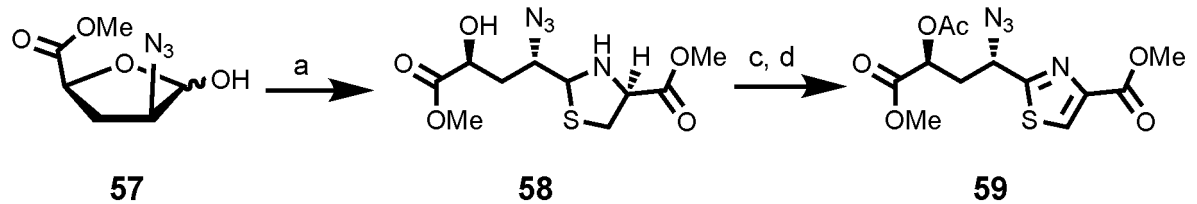


Figure 1-16. Glutamate derivative **59** synthesis. a) L-cysteine methyl ester, 47%; b) Ac_2O, AcOH, $HClO_4$, 40%; c) MnO_2, benzene, 88%.

Umemura *et al.* performed the synthesis of **63** from aminonitrile **60** in 10.6% total yield with 10 linear steps. The lactam **62** was obtained unexpectedly after the oxidation of the free alcohol **61**, but treatment **62** with strong base successfully led to **63** (figure 1-17).[57]

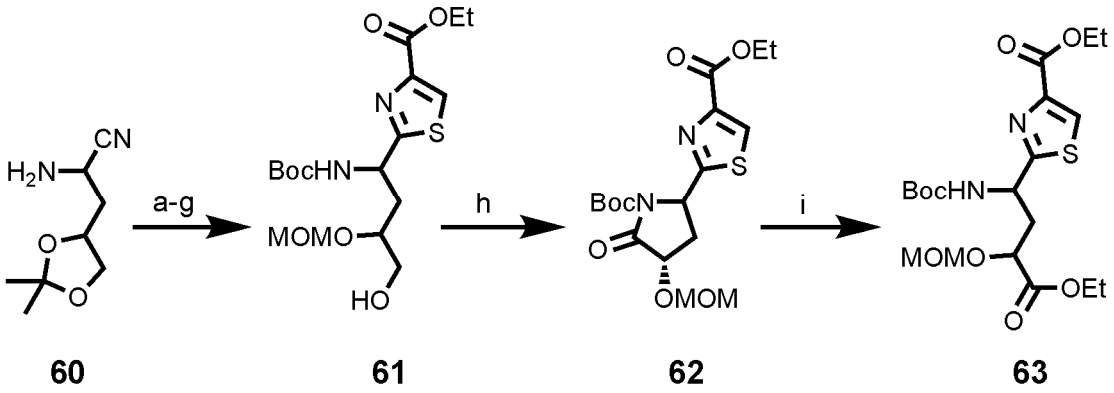


Figure 1-17. Glutamate derivative fragment synthesis. a) Boc_2O, dioxane, 78%; b) H_2S, py, Et_3N, 93%; c) $BrCH_2COCOOEt$, benzene, 61%; d) 30% AcOH, 85%; e) TBDMSCl, DMAP, CH_2Cl_2, 92%; f) MOMCl, DIPEA, CH_2Cl_2, 74%; g) TBAF, THF, 98%; h) PCC, CH_2Cl_2, 81%; i) NaOEt, EtOH, 89%.

1.3.3.4 Bis-azole fragments.

Koerber-Plé *et al.* prepared the thiazole building blocks **64** and **65** in nosiheptide using Hantzsch reactions (figure 1-18).[58]

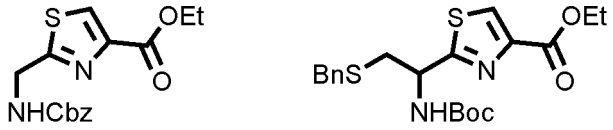


Figure 1-18. Thiazole building blocks by Koerber-Plé.

The Shin group synthesized peptidic thiazole **72** by unifying the fragments **69** and **71** (figure 1-19).[59] The thiazolyl peptide **69** was obtained from building blocks **66** and **67** by condensation to acid **68** and a Hantzsch thiazole synthesis. The thiazole **71** was prepared from 5-oxo-L-proline **70** via a 13 step sequence.

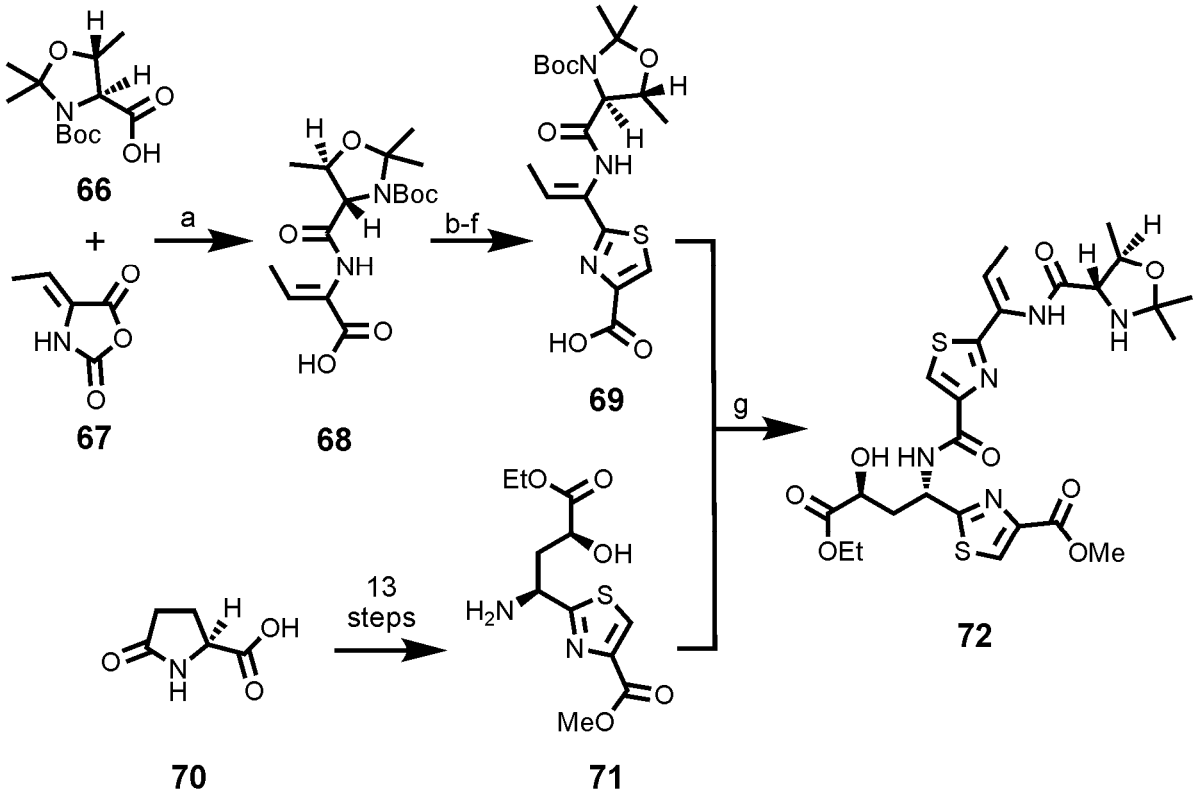


Figure 1-19. Bis-thiazolyl peptide. a) DCC, DMAP; b) 28% NH_3, 82%; c) Lawesson's reagent, 49%; d) $BrCH_2COCOOEt$; e) TFAA, py, 82%; f) 1M LiOH, 85%; g) BOP, DIPEA, 77%.

Thiazolyl peptide **75** was synthesized by Moody *et al.*[60] The alcohol **74** was obtained from Boc protected L-threonine **73** by a 7 step sequence again featuring a Hantzsch reaction. Mesyl chloride and DBU mediated dehydration led to (*Z*) enamine **75** in good yield (figure 1-20).

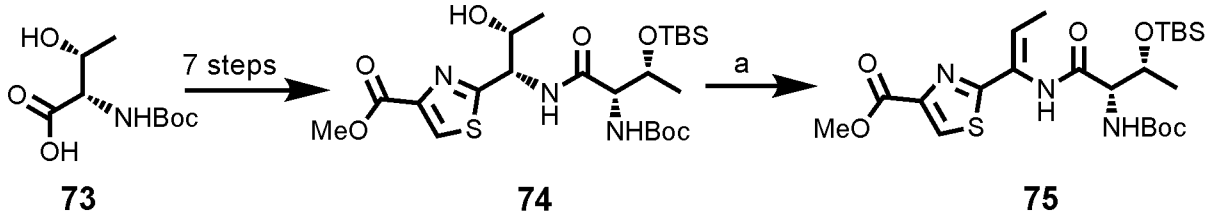


Figure 1-20. Enamine **75**. a) MsCl, Et_3N, DBU, CH_2Cl_2, 81%.

The most advanced study toward nosiheptide was reported from the Moody group[48] concurrent to our studies (figure 1-21). The alcohol **77** was obtained by treatment of **76** with LiHMDS and Davis oxaziridine, which was converted to thiazole **78** in 7 steps.[60] Amide bond formation of **78** led to **80**, which was converted to indolic ester **82** mediated by DCC with

HOAt as the additive. Allyl and trityl deprotection followed by macrothiolactam formation delivered the macrocycle **83** as a model system of the southern hemisphere of nosiheptide.

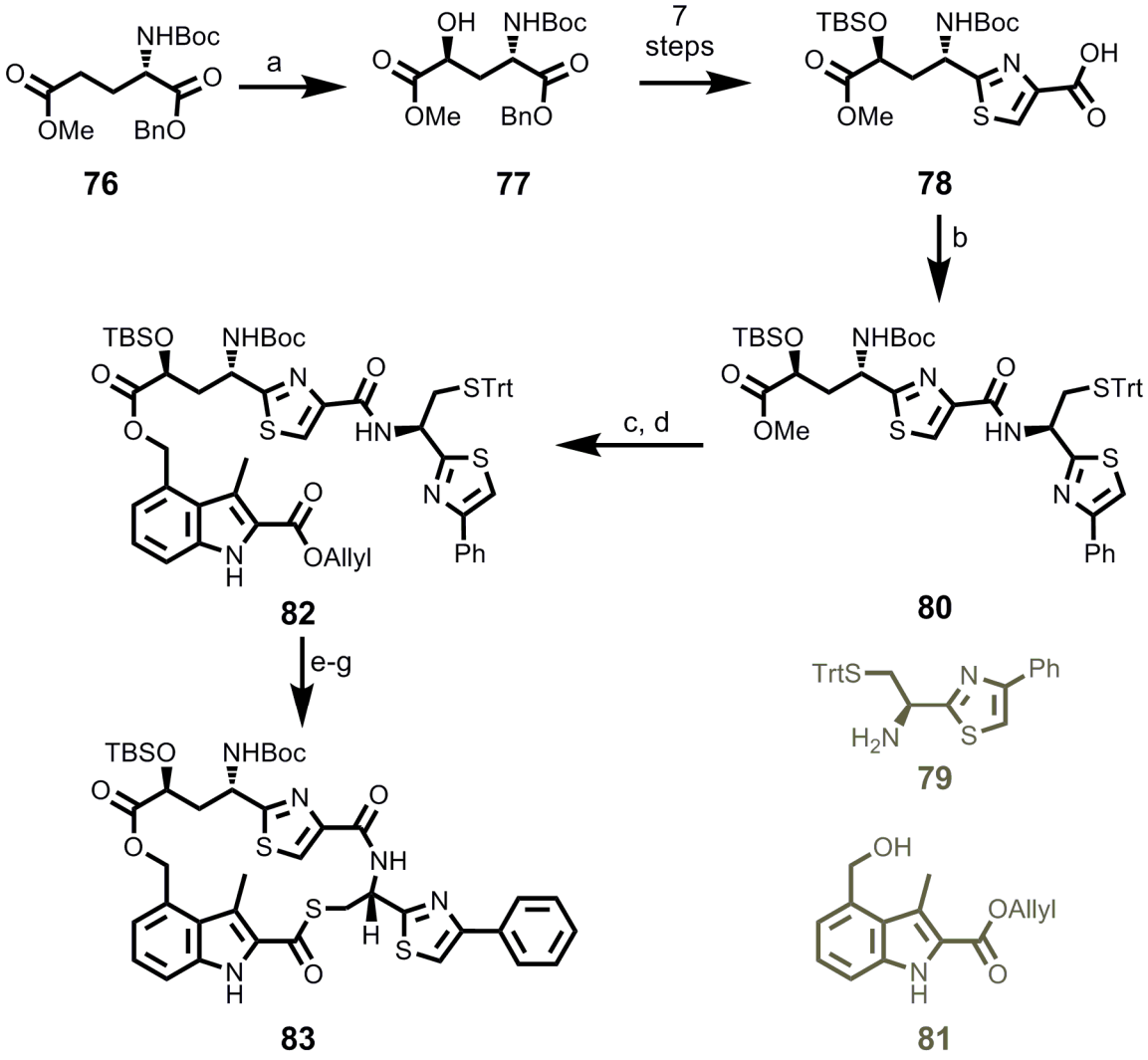


Figure 1-21. Macrocycle synthesis by Moody. a) LiHMDS, THF, Davis oxaziridine; b) **79**, PyBOP, DIPEA, CH_2Cl_2, 81%; c) LiOH, THF, MeOH, H_2O; d) **81**, DCC, DMAP, HOAt, CH_2Cl_2, 69%; e) $Pd(OAc)_2$, PPh_3, morpholine, THF, 93%; f) $AgNO_3$, Py, MeOH, $HSCH_2CH_2OH$, 75%; g) DCC, DMAP, THF, 52%.

1.4 Aims of the thesis

To the best of our knowledge, only very preliminary studies were reported for this natural product at the onset of this thesis. Therefore, we aimed at developing suitable methodologies to synthesize the thiazole rings and 3-hydroxypyridines, to enable a total synthesis of

nosiheptide and –by inference- synthesis of other thiopeptides and thiopeptide-like compounds.

In the previous studies by other groups, only one reported access to the hydroxypyridine from 5-bromo-3-hydroxypyridine, which itself is not readily available. Therefore, it was planned to develop a hetero-Diels-Alder (HDA) reaction with easily accessible alkyne or alkene substrates, which should open up new ways for *de novo* generating highly substituted pyridines and pyridine libraries for organic synthesis, material or pharmaceutical applications.

It was envisioned that an alkyne **84** and an 1-azadiene **85** may undergo a Diels-Alder type reaction to form dihydropyridine **86**. Aromatization should lead to protected pyridine **87** when a suitable leaving group X present at the N1 position. Further manipulations should furnish the pyridine **88** (figure 1-22). Of course, formation of regioisomers had to be anticipated (**89**), therefore, suitable substrates and reaction conditions had to be found to efficiently conduct this transformation (chapter 2).

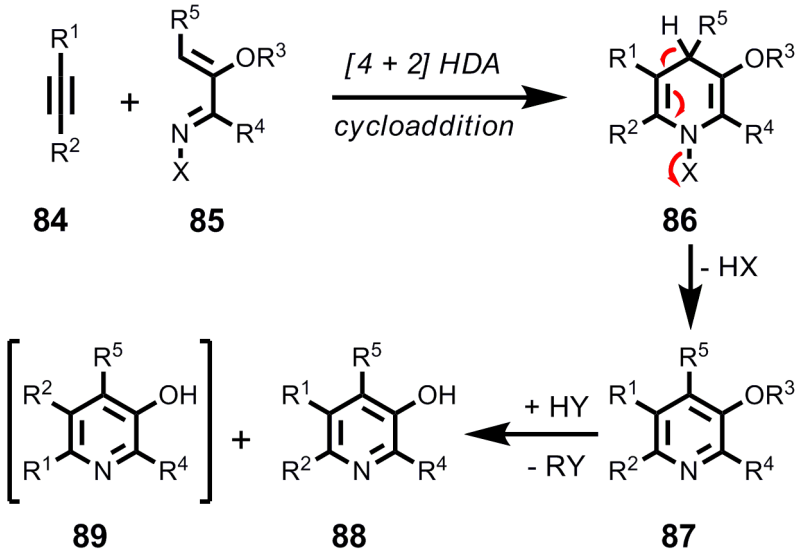


Figure 1-22. Proposed hydroxypyridine formation by hetero-Diels-Alder reaction.

With an efficient HDA reaction developed, an attempt to directly furnish 2,5-bisthiazolyl-3-hydroxypyridine **91** from alkyne **90** was planned. Further manipulation should allow to synthesis hydroxypyridine **93** (figure 1-23), which would be a key building block for nosiheptide synthesis (chaper 3).

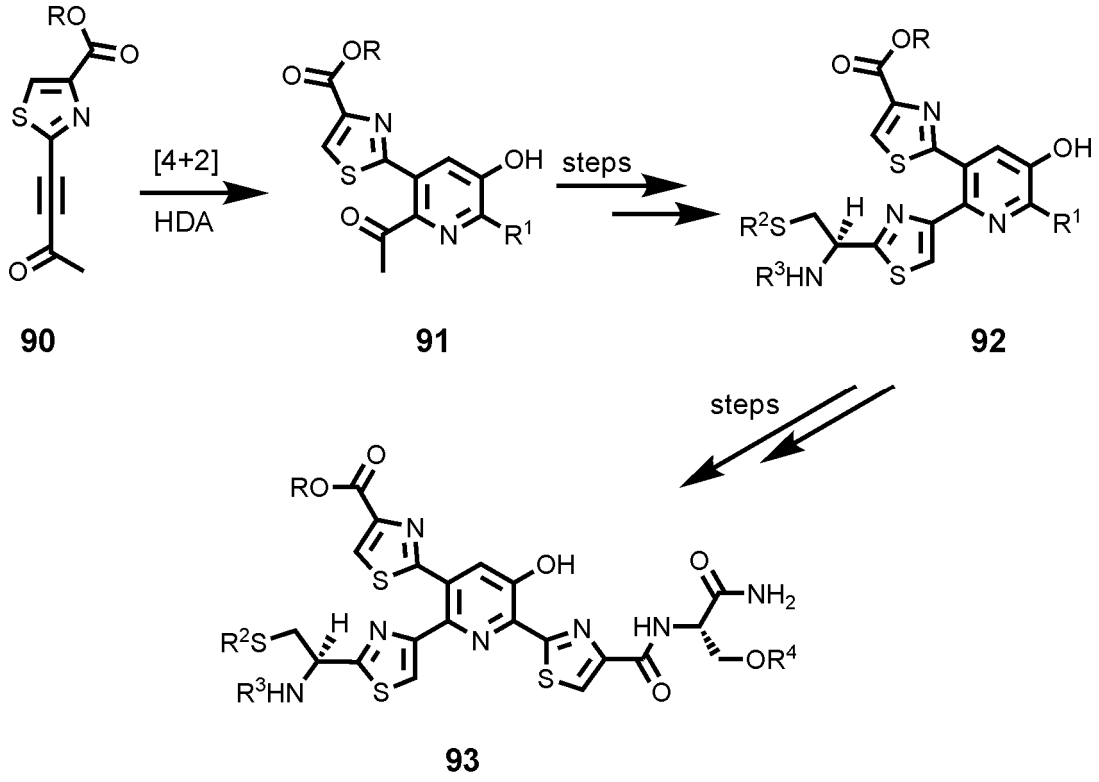


Figure 1-23. Proposed nosiheptide 3-hydroxypyridine formation.

Further work was planned in collaboration with Matthias Riedrich in the group,[55] who developed chemistry toward building block **279** (chapter 3) in parallel. Amide bond and macrolactam formation should lead to macrocycle **94** (A ring). Suitable protecting group patterns and methods have to be found to realize this goal. Finally, it was intended to explore suitable ways of attaching the indole to **94**, and chemistry to close the B ring of nosiheptide.

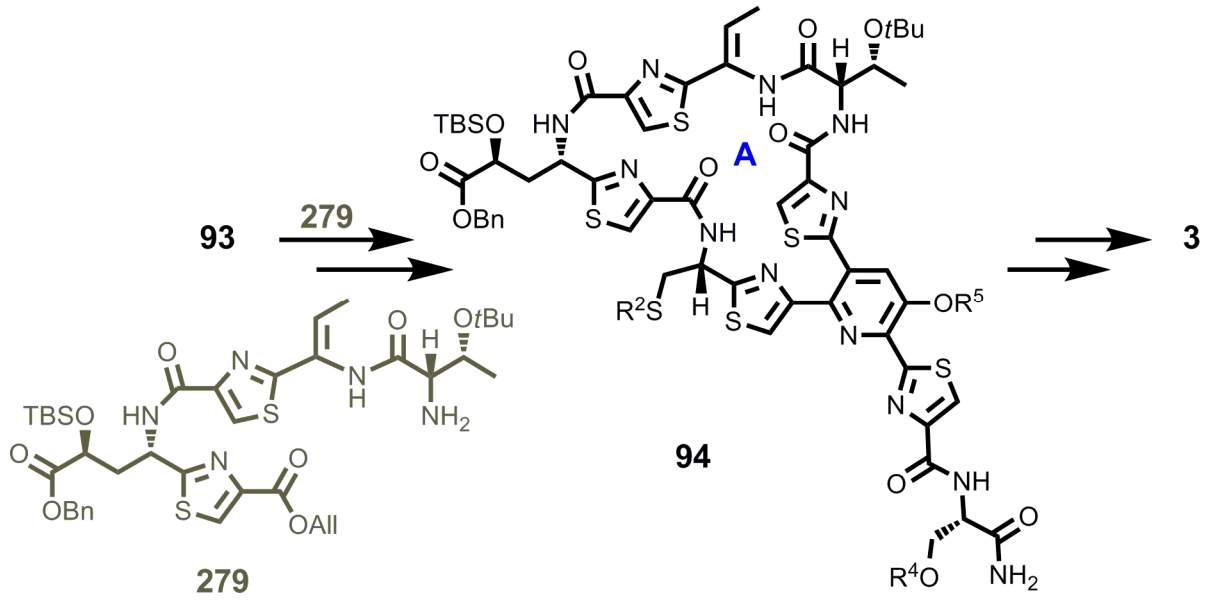


Figure 1-24. Nosiheptide A-ring formation.

2. Hetero-Diels-Alder (HAD) reactions for 3-hydroxypyridine formation

2.1 Introduction

3-Hydroxypyridines[61] are important scaffolds in various molecules endowed with biological activity (figure 2-1). For example, nosiheptide, the arguably most potent antibiotics within the thiopeptide family, was discussed in the former chapter. Pyridoxin **95** (vitamin B6) is a cofactor vital for the enzymes of amino acid metabolism,[62] and both natural 3-hydroxypyridines like caerulomycin B[63] (**96**) as well as non-natural congeners like persynthamide[64] (**97**) are endowed with distinctive modes of action. In terms of their molecular properties, 3-hydroxypyridines cannot form an energetically favoured *keto* tautomer like the closely related 2- and 4-hydroxypyridines, leading to a phenolic character of the parent heterocycle. On the other hand, 3-hydroxypyridines easily adopt a zwitterionic ("betainic") state by O → N proton transfer from the phenolic hydroxyl function (**98**), which confers a considerably polar character.

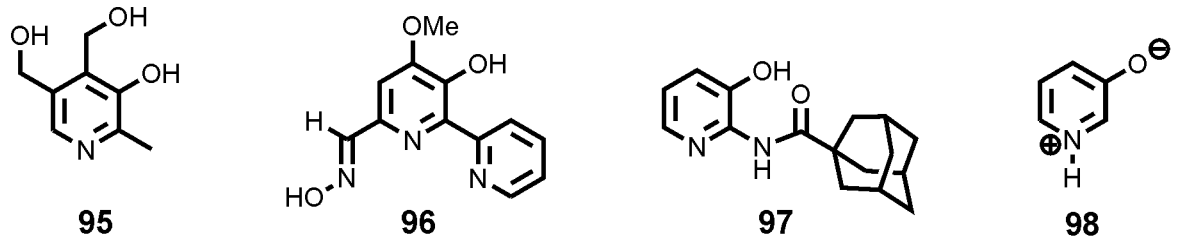


Figure 2-1. 3-hydroxypyridines.

A deeper exploration and utilization of this interesting heteroaromatic scaffold has been hampered by lack of flexible synthetic access. Early approaches often necessitated harsh aromatic (re)functionalization reactions of simpler pyridines, or a step-by-step elaboration from 3-hydroxypyridine(s) itself. Recent advance in this field was reported by Yanagisawa *et al.*[65] A 3-hydroxypyridine **101** could be constructed by Ring-Closing Olefin Methathesis (RCM) of **99** and removal of N1 protecting group in **100** (figure 2-2). However, several steps are needed, and the applicability is limited because of the difficulty in preparing starting materials as well as limitations of the RCM[66] method with respect to functional group tolerance.

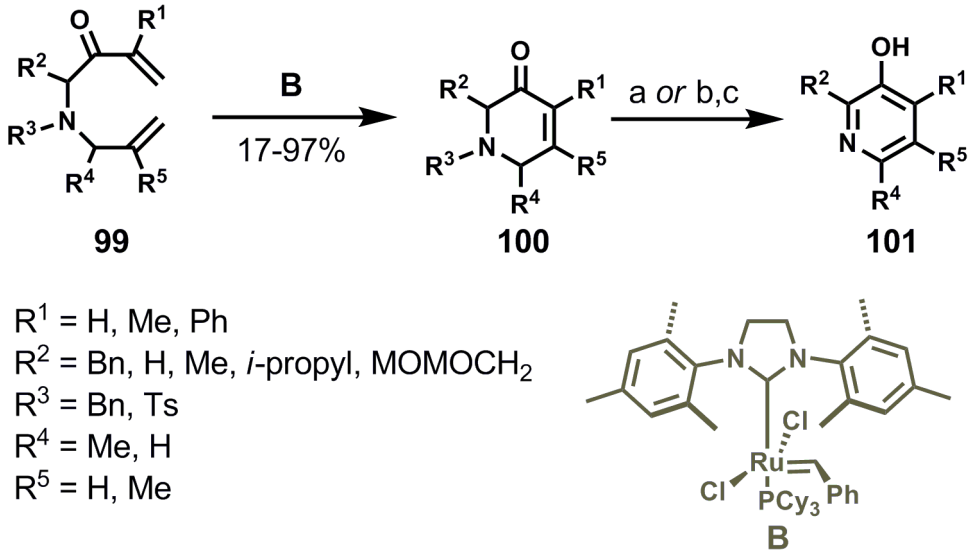


Figure 2-2. 3-hydroxypyridine by RCM. a) DBU, DMF, 71-76%; b) DDQ, 1,4-dioxane; c) Pd/C, H_2, 68-75%.

Within a program toward the total synthesis of nosiheptide we intended to develop a general and flexible methodology to access the 3-hydroxypyridines with diverse substitution patterns based on Diels-Alder reaction.

Since its landmark discovery by Diels and Alder,[67] the Diels-Alder (DA) reaction has been one of the most powerful and elegant methods to construct a six-membered ring with excellent control over chemo-, regio-, diastereo- and enantioselectivity. This [4+2] pericyclic reaction of a diene and a π-bond produces a six-membered ring with up to four new stereo centers in a single step, and has been widely used in the synthesis of a numerous of small and complex molecules which presented both in natural and unnatural products.[68,69]

The Diels-Alder reaction engages two components, a diene and dienophile, and it can be classified as Carbon-Diels-Alder reaction furnishing cyclohexenes, and as Hetero-Diels-Alder (HDA) reactions delivering 6-membered ring heterocycles. The HDA reaction can be subdivided to mainly two classes, oxa-DA reaction (HDA reactions with carbony compounds) and aza-DA reactions (HDA reaction with azadienes or imines[70]). Thiocarbonyl[71] and other hetero atom containing diene derivatives[69] will not be discussed here (figure 2-3).

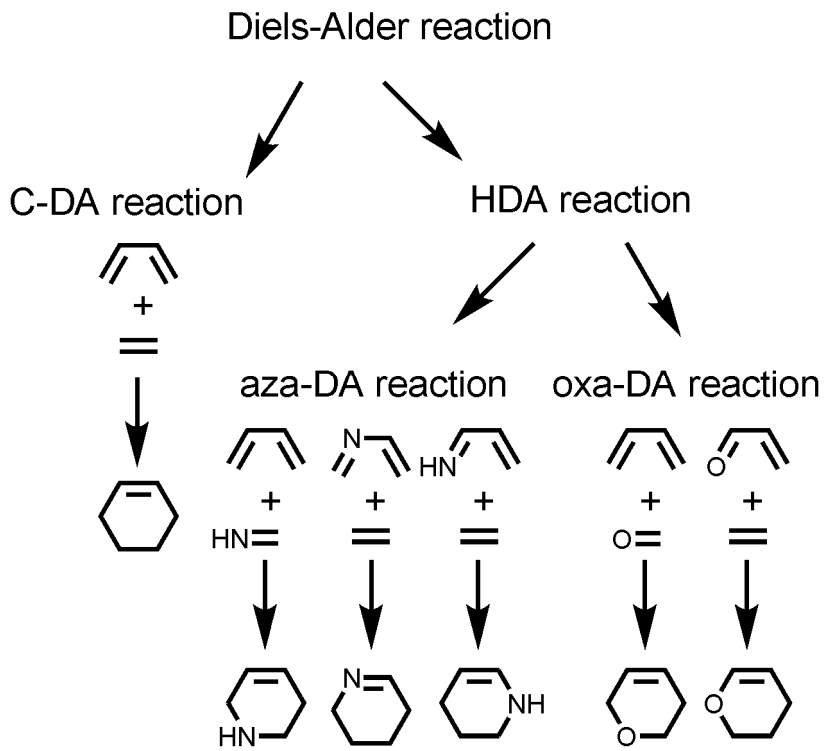


Figure 2-3. DA reaction classification.

The conversion of a given (H)DA reaction depends on the nature of the both reaction partners and the reaction conditions (pressure, heating, catalyst, solvent, etc). In general, matching electron density and overlap of the frontier orbitals, which are Highest Occupied Molecular Orbital (HOMO) and the Lowest Unoccupied Molecular Orbital (LUMO), in the transition state (TS) (figure 2-5, **A**) are the key factors. Therefore, according to the reactivity of the (aza)diene and the descriptions of both pairs of frontier orbitals in the Hückel molecular orbital (HMO) model,[72] the (H)DA reaction can be classified into three categories:[69,73] 1) Normal, $HOMO_{diene}$-controlled; 2) Neutral (H)DA reactions; 3) Inverse, $LUMO_{diene}$-controlled (H)DA reactions. As shown in figure 2-4, the (H)DA reaction efficiency depends on the energy difference between two molecular orbitals (MOs) of the (aza)diene and dienophile. The lower the energy difference the higher the transformation efficiency may become due to matching overlap in the TS. The energy difference depends on the electronic characters of the substituents. In normal (H)DA reactions, electron-donating groups (EDG) on the (aza)diene and electron-withdrawing groups (EWG) on the dienophile decrease the energy gap between the HOMO of the diene and the LUMO of the dienophile. Reversed substitution patterns lead to $LUMO_{diene}$-controlled (H)DA reactions.

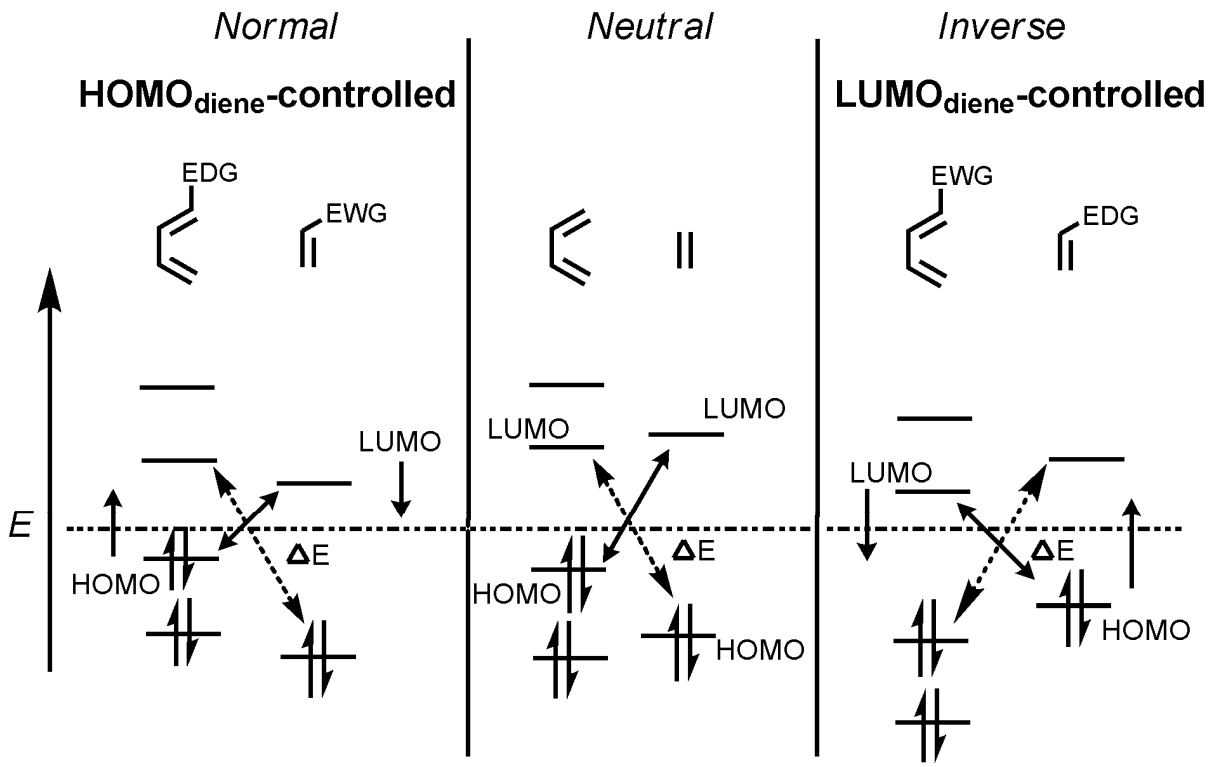


Figure 2-4. HOMO and LUMO of DA reactions.

Mainly two mechanisms have been proposed for the DA reaction, a concerted and a stepwise mechanism, and both have been studied by *ab initio* or quantum mechanical calculations.[73,74] The majority of the experimental observations are in agreement with a concerted mechanism via a transition state (figure 2-5, **A**), which predicts a stereospicific reaction. Few reported results support a stepwise mechanism (**B**),[75] which leads to a non-stereospecific reaction if the rotation of the single bond in **B** is faster than ring closure. It has mainly been reported for polyhalogenated dienes and very electron poor dienophiles, for example: tricyanoalkenes or tetracyanoalkenes.[74]

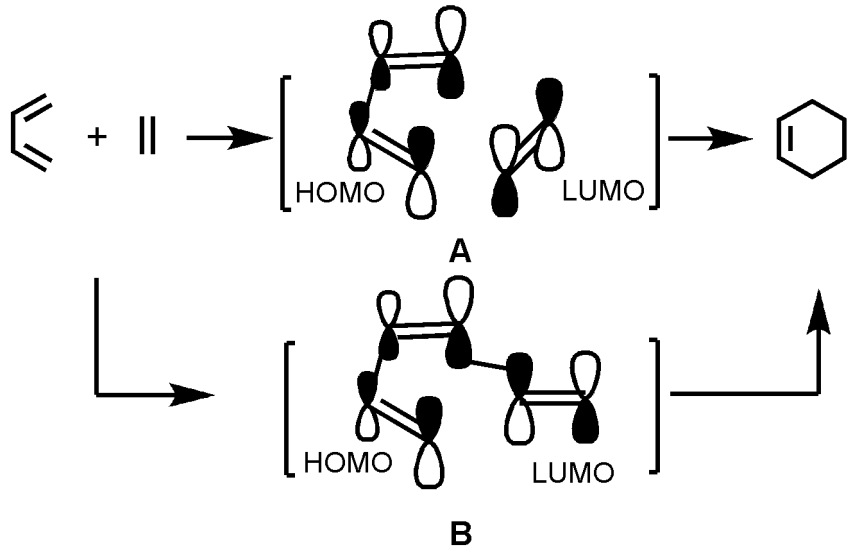


Figure 2-5. Transition state of DA reaction.

In the past decades, the CDA reaction was very well studied, but significant developments till occur in the HDA field. HDA reactions in general provide direct access to oxa- and aza-heterocycles.[73,76]

2.2 Azadiene synthesis

Nitrogen heterocycles are the most extensively used building blocks in pharmaceutical research,[77] and they are present in natural products (all the thiopeptide members contain nitrogen heterocycles) and non-natural bioactive molecules like persynthamide.[64] In the past decades, much effort has been devoted to pyridine synthesis.[73] Cycloaddition reactions provide rapid access to pyridine with different substituted patterns. Importantly, azadienes are extremely versatile scaffolds for *de novo* synthesis of pyridine derivatives. Therefore, a representative collection of 1-azadiene and 2-azadiene based syntheses will be discussed.

2.2.1 2-Azadiene synthesis

In 1975, Aue[78] and Ghosez[79] separately reported the synthesis of 2-azadienes (**104** and **106**). The azadiene **104** was obtained by thermal ring opening of **102** and the [1,5]-H shift of azadiene **103**; the azadiene **106** was furnished by thermal ring opening of azirine **105** (figure 2-6).

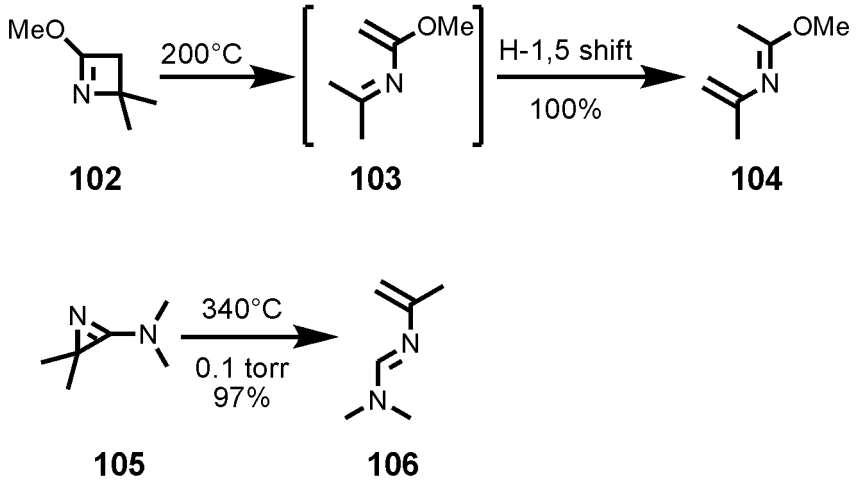


Figure 2-6. 2-Azadiene syntheses by ring opening reaction.

Schmidt group [80] synthesized the 2-azadiene **108** from thiazolidine **107** mediated by Ag_2CO_3 and DBU in aprotic solvents (1,4-dioxane, CH_3CN) (figure 2-7). This reaction was further explored by other groups for transformations with both electron rich and deficient dienophiles.[81]

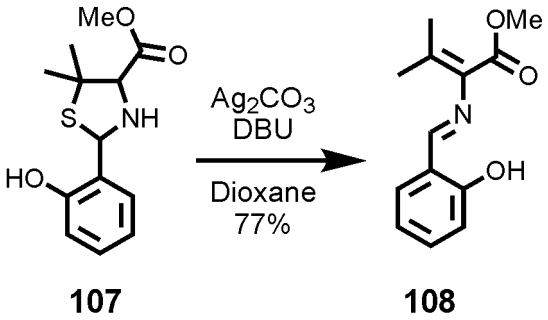


Figure 2-7. 2-Azadiene from thiazolidine.

A storable 2-azadiene **111** was prepared by Ghosez *et al*[82] from aldehyde **109** via Schiff base **110**, which could be kept for several months at -78°C. This broadened the synthetic utility of 2-azadienes. 2-Azadiene **113** could be obtained by heating imine **112** with $HC(OEt)_2CHNMe_2$,[83] 2-azadiene **115** was produced by heating triazoline **114**,[84] which opens an alternative route to 2-azadiene preparation (figure 2-8).

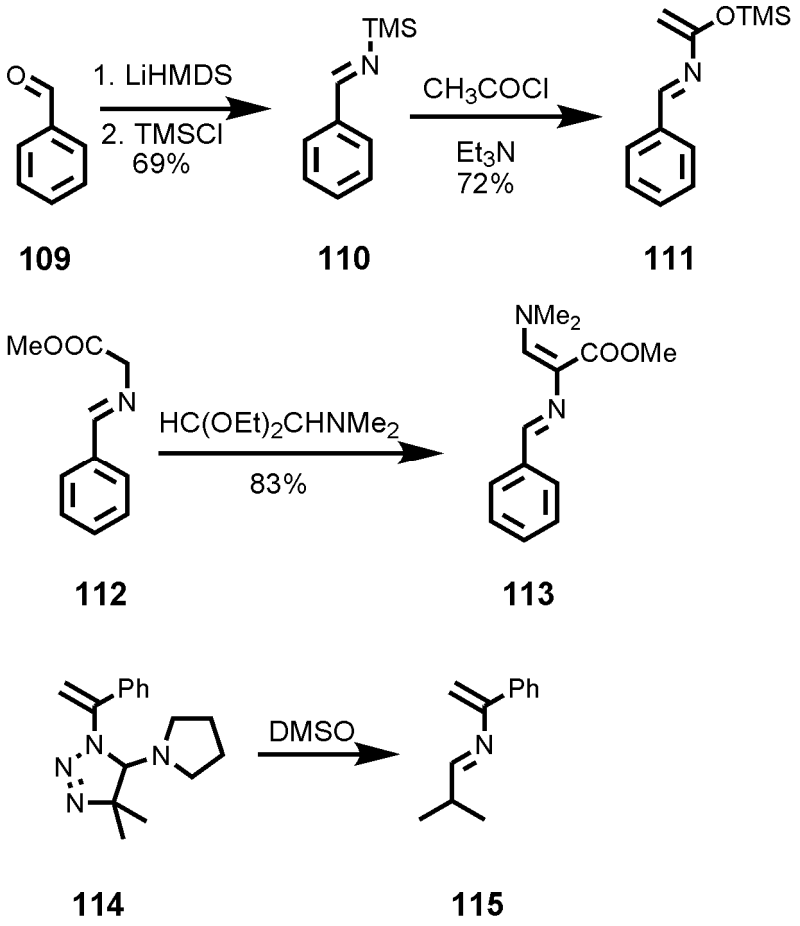


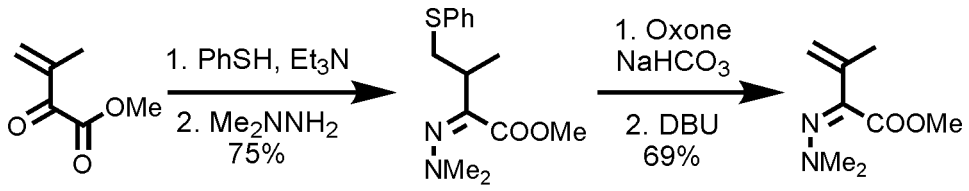
Figure 2-8. Storable 2-azadiene syntheses.

2.2.2 1-Azadiene synthesis

2-Azadienes are often not stable upon storage due to their high reactivity. Compared to 2-azadiene, the reactivity of 1-azadiene is much lower (thermodynamic driving force, $\Delta H \approx 20$ Kcal/mol)[85] (*vide infra*). For a long time, the successful application of 1-azadienes in HDA reactions was limited to intramolecular transformations or to quinone methide imines, due to the low inherent reactivity, the instability of the enamine product, competitive [2+2] imine cycloaddtions and tautomerization of the 1-azadiene itself.[73] In recent years, improvements of this potentially powerful 1-azadiene has been achieved by changing its electronic characters with appropriate substituents. Here, the representative electron rich 1-azadienes, which can undergo the $HOMO_{diene}$-controlled HDA reactions, and electron deficient 1-azadienes which react via $LUMO_{diene}$-controlled HDA reaction will be discussed.

2.2.2.1 Electron rich 1-azadiene synthesis

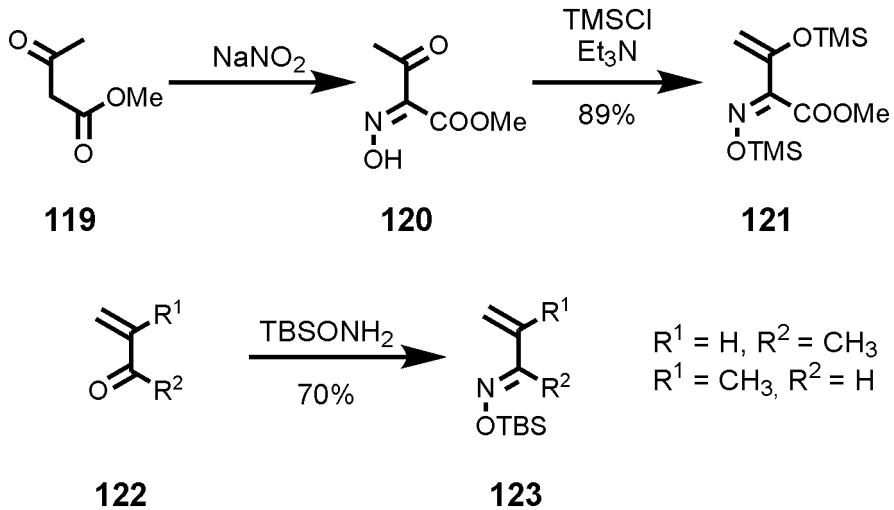
Ghosez *et al*[86,87] found that unsatured hydrazones simply obtained by condensing dimethyl hydrazine and methacrolin could be used as 1-azadienes to react with electron deficient dienophiles under mild conditions. As shown in figure 2-9, when a methyl carboxylate was present in the 2-position of 1-azadiene **118**,[88] direct condensation was ineffective. In order to depress the competitive Michael addition, it was necessary to prepare **118** via a three step procedure by thioether protection of **116**. Hydrazone formation and elimination led to **117**.



116 **117** **118**

Figure 2-9. Unsatured hydrazone preparation.

The doubly silylated 1-azadiene **121** was reported by Furukawa *et al.*[89] Commercially available acetoacetate **119** was oxidized to oxime **120**, which was converted in the protected silyl enol ether in a single step. Another electron rich 1-azadiene **123** was prepared as an E/Z mixture by Behforouz *et al*[90] via the condensation of the vinyl ketone **122** and silyloxyhydroxylamine (figure 2-10).



119 **120** **121**

122 **123**

Figure 2-10. Oxime derivatized 1-azadiene.

Behforouz *et al*[91] reported a concise synthesis of lavendamycin methyl ester **126** by a key intermediate dione **125**, which was synthesized by a HDA reaction from bromodione **124** and silylated 1-azadiene **123** (figure 2-11).

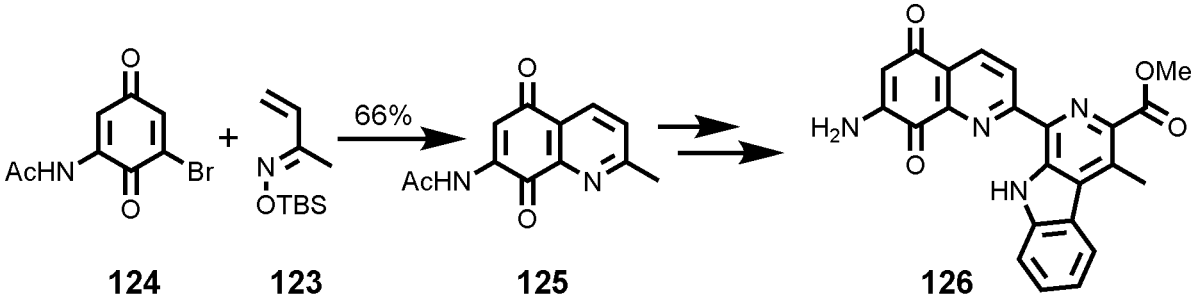


Figure 2-11. Synthesis of lavendamycin methyl ester by a HDA reaction.

2.2.2.2 Electron deficient 1-azadiene synthesis

Boger *et al*[76] have demonstrated that 1-azadiene **129** is a robust synthetic intermediates for the synthesis of variety of pyridines and some natural products. The 1-azadiene **129** could be prepared from oxime **127** by rearrangement of *in situ* generated sulfinyl oxime **128**. Another approach to **129** was a direct condensation of sulfonamides with enone **130** promoted by dehydrating agents ($TiCl_4$, $MgSO_4$, molecular sieves) (figure 2-12).

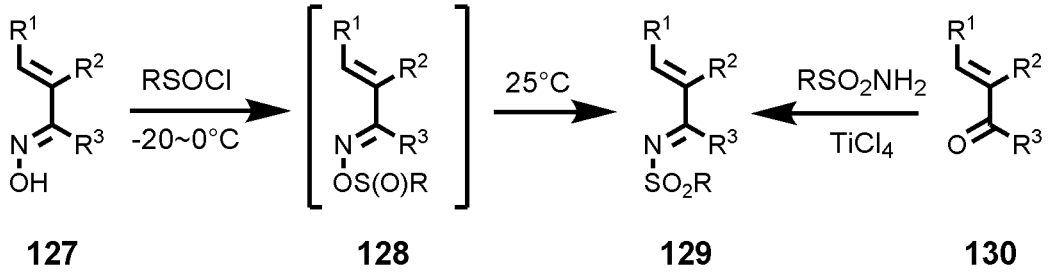
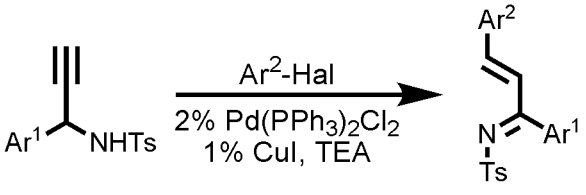


Figure 2-12. Boger's 1-azadiene syntheses.

Müller *et al*[92] found that the 1-azadiene **132** could be generated *in situ* from Sonogashira-cross-coupling-isomerization sequence from propargyl sulfonamides **131**. However, Ar^2 had to be electron deficient in this case (figure 2-13).



Ar^1 = p-MeOPh, p-C_6H_4OPh
Ar^2 = p-CNPh, 2-pyridyl, pyrimidyl

Figure 2-13. Electron-deficient 1-azadiene generation *in situ*.

Boger *et al*[93] reported the synthesis of pyridine **136**, which could be obtained by oxidative elimination of tetrahydropyridine **135**. This was formed by a HDA reaction with an electron deficient 1-azadiene **134** and electron rich dienophile **133** in excellent yield. The pyridine **136** was used as key building block for the total synthesis of Fredericamycin A (figure 2-14).

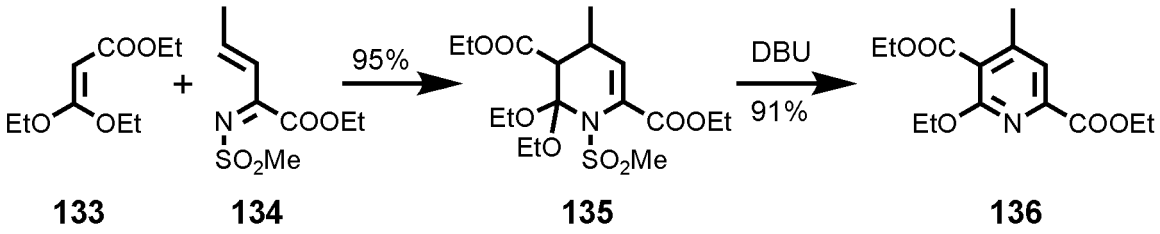


Figure 2-14. Pyridine **136** synthesis by HDA reaction.

2.3 HDA reaction with alkynes

2-Azadienes are much more reactive than the 1-azadienes. However, the lack of diversity and instability (they are normally generated *in situ*) are significant drawbacks. On the other hand, 1-azadienes are known to be intrinsically rather unreactive due to inherent low reactivity and are prone to tautomerization. The cycloaddtion product **139** was the only isolatable product when an equilibrating mixture of 1-azadiene **137** and 2-azadiene **138**,was captured with ethyl vinyl ether (figure 2-15). The HDA product **140** was not detected.[94] 1-Azadienes can be activated and/or stabilized either with electron donating groups[87] or electron withdrawing substituents on the N1-atom.[95] The latter lead into the inverse-electron demand regime so that they react preferentially with electron-rich alkenes, whereas the former have been applied frequently with electron-poor dienophiles - mostly in the form of *N*,*N*-dimethyldrazones which were introduced by Ghosez.[87] With both azadienes, access to 3-hydroxypyridines was not well studied. The only reported 3-hydroxypyridine formation with diene and dienophile was by Furukawa *et al*[89] as part of a mechanistic study. To address a general *de-novo* generation of 3-hydroxypyridine scaffolds, a hetero-Diels-Alder (HDA) type reaction with 1-azadienes was envisioned.

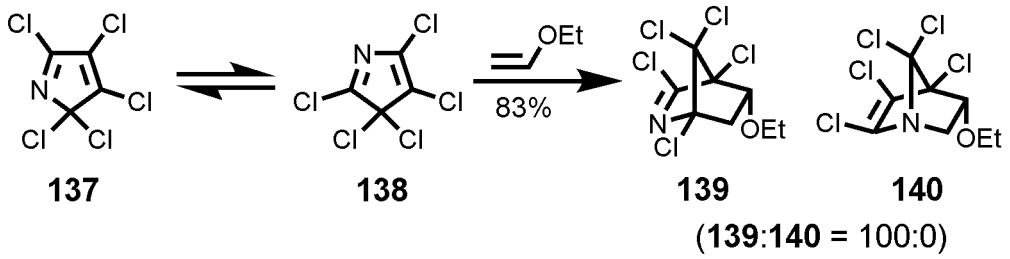


Figure 2-15. The reactivity of 1- and 2-azadiene.

Conceptually, a 3-hydroxypyridine **88** and its isomer **89** could arise from an alkyne **84** and a (Z)-1-azadiene **85** via a [4+2] Hetero-Diels-Alder (HDA) cycloaddition in one operation (figure 2-16) as discussed in the introduction.

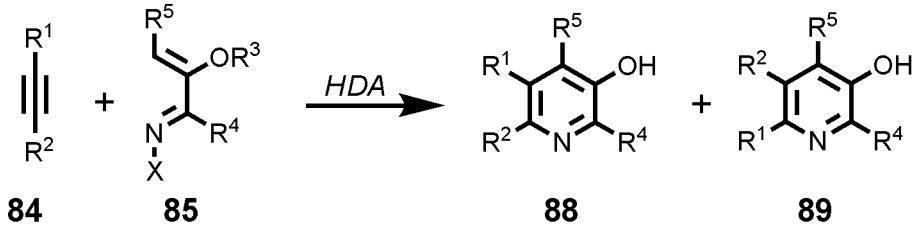


Figure 2-16. 3-Hydroxypyridines formation by HDA reaction.

2.3.1 Result and discussion

In order to realize the proposed concept, a *Z*-configured 1-azadiene would be desirable. An *E*-configured 1-azadiene would depress the reactivity by sterically blocking the approach of the dienophile. As shown in figure 2-17, the oxime **120**[96] was synthesized by nitrosation of the commercially available methyl acetoacetate **119**. An X-ray structure could be obtained by derivatising the oxime **120** to methoxyimino oxobutanoate**141**.[97] The imino group in the crystal was shown to be *Z* configured which verified former studies by NMR and IR techniques.[98-102] Interestingly, the methoxycarbonyl group adopts a dihedral angle of 93° with respect to the coplanar N=C-C=O π–system, which indicates the complete absence of electronic conjugation. From these data we can assume that an *cis* 1-azadiene **121** would be formed when protecting the oxime and simultaneously forming the enol ether.

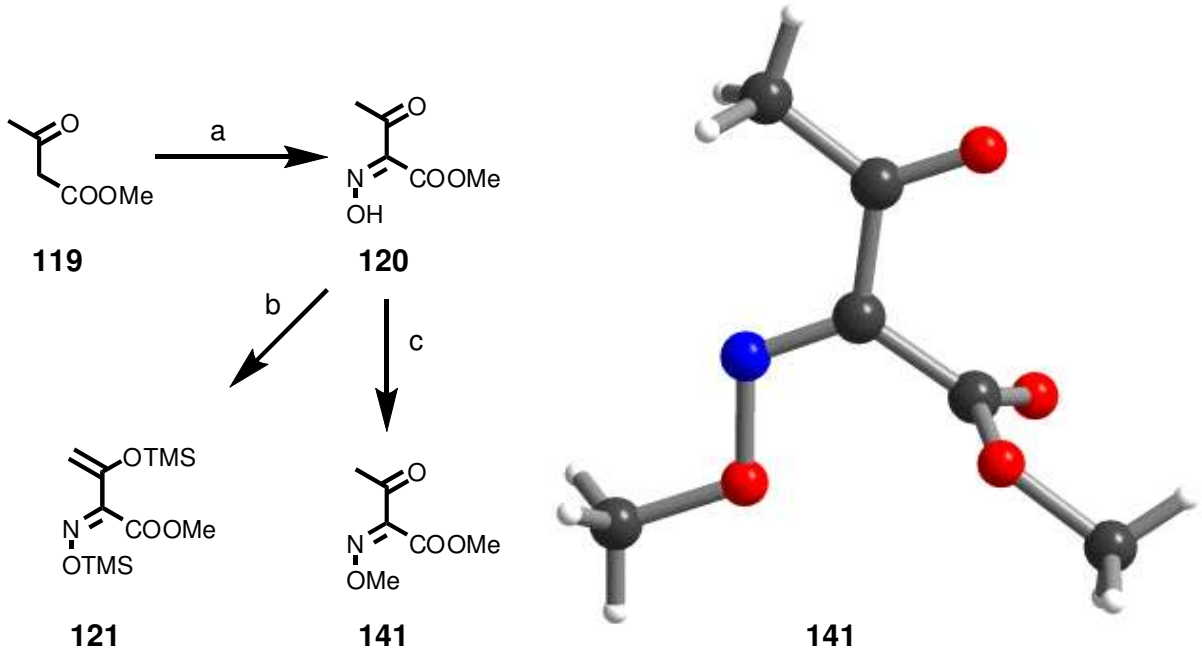
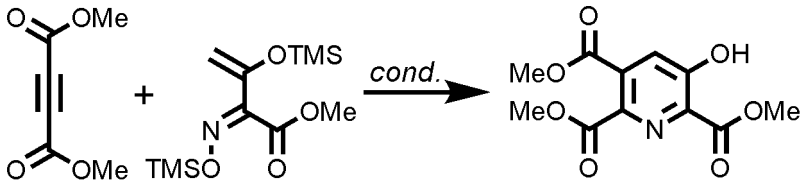


Figure 2-17. 1-Azadiene preparation. a) $NaNO_2$, 84%; b) TMSCl, Et_3N, NaI, 89%; c) Me_2SO_4, K_2CO_3, 96%.

Initially, dimethyl acetylenedicarboxylate (DMAD) **142** was employed to screen for reaction conditions suitable for transforming **121** into 3-hydroxypyridine **143**. It was found that **142** reacted smoothly with the double-silylated oxime enol ether **121** under neutral conditions without any additives. The HDA cycloaddition was only moderately solvent dependend (table 2-1, entries 1-5). The reaction in THF and acetonitrile gave better conversion when compare to toluene, but it was not efficient enough for further optimization. Remarkably, high temperatures increased the cycloaddition efficiency dramatically (entry 6-9). Further screening revealed that neat conditions (high temperature and high concentration) proved to be optimal and gave excellent results in a very short time (entry 10). To reach full conversion of the alkyne, an excess of 1-azadiene **121** had to be applied due to its thermal instability (decomposition to oxime **120** and dimer formation (*vide infra*)). A brief screening of Lewis acids as potential promoters ($LiNTf_2$, LiCl, LiOTf)[88] was not met with success at ambient temperature.



142 **121** **143**

entry	diene (eq)	conditions	yield
1	1.2	toluene (0.3 M), 80°C, 12h	33%
2	1.2	THF (0.6 M), rfx., 20h	48%
3	1.2	CH_3CN (0.6 M), 80°C, 20h	48%
4	1.2	DCE (0.6 M), 80°C, 20h	<25%
5	1.2	MEK, (0.6 M), 80°C, 20h	30%
6	1.2	xylene (0.4 M), 50°C, 24h	<25%
7	1.2	xylene (0.4 M), 80°C, 24h	40%
8	1.2	xylene (0.4 M), 110°C, 9h	42%
9	1.2	xylene (0.4 M), 140°C, 3h	85%
10	**3.0**	**neat (1.5 M), 150°C, 1h**	**99%**

Table 2-1. Condition screening for HDA reaction.

To explore the scope of this HDA cycloaddition further, different 1-azadienes were synthesized. Oxime **146** was obtained from commercial available 3-amino-2-butenethioamide **144** by a Hantzsch reaction to thiazole **145**, and nitrosation in good yield. Importantly, reaction time had to be strictly controlled to achieve high yields. Subsequently, double triethylsilyl protection with TESOTf/lutidine gave 1-azadiene **147** in excellent yield. The unsatured hydrazone **152** was prepared from aniline **148**, which was first oxidized to its diazonium salt, and then captured by methyl acetoacetate to yield the hydrazone **149**. After screening different conditions, it was found that NaH and MeI in THF/DMF mixture were suited well to selectively methylate the secondary amine in the presence of the enolizable ketone to give **151** in excellent yield. Similar condition as for the preparation of **147** was employed to furnish the unsatured hydrazone **152**. The proposed 1-azadiene **150** was used in situ in the HDA reaction after crude work up. The 1-azadienes **154** and **155** were prepared from the respective oximes **153** and **120** as described above (figure 2-18).

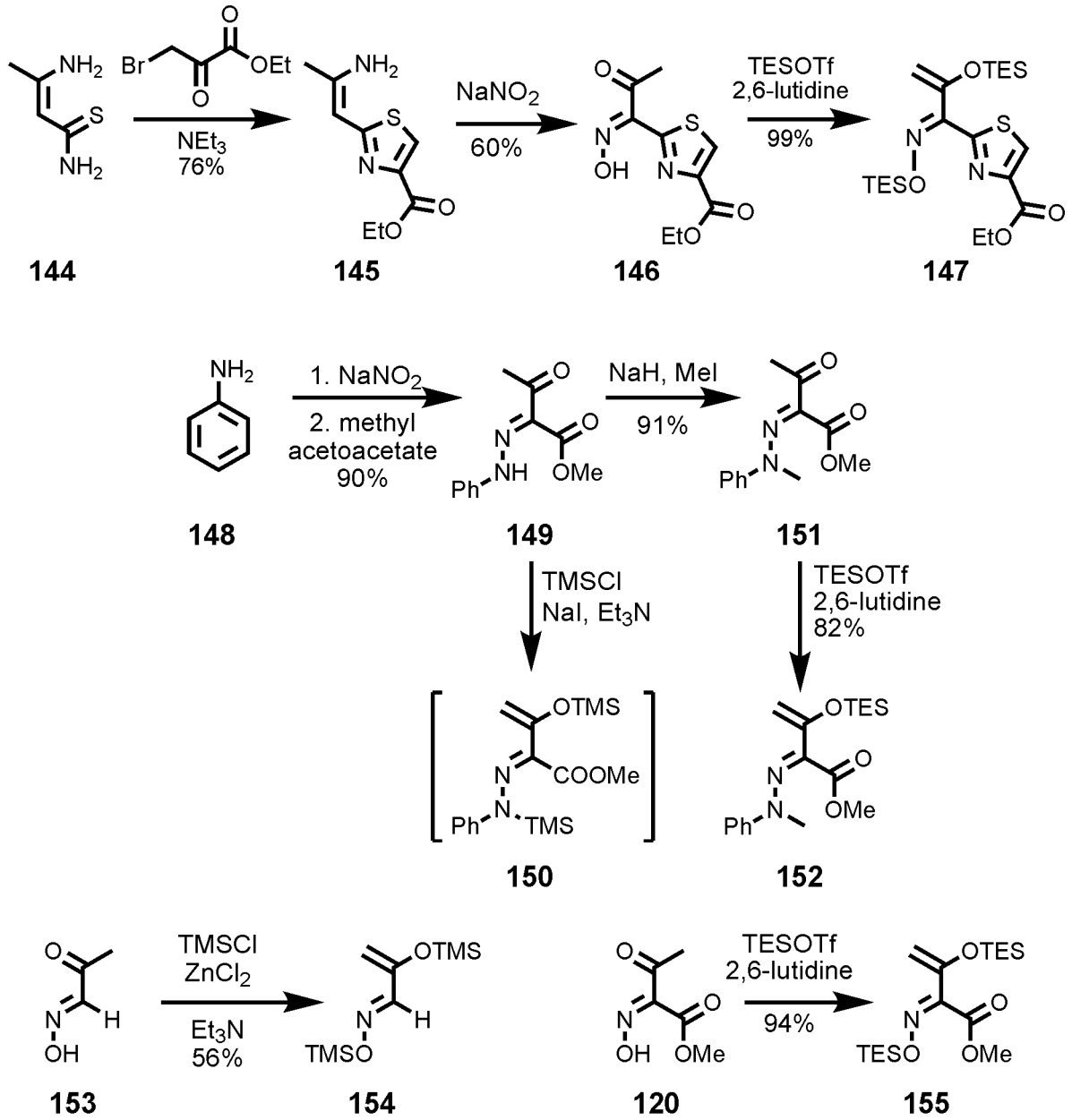
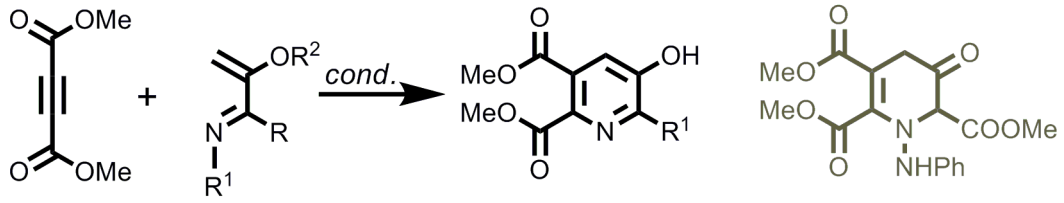


Figure 2-18. 1-Azadiene variations.

Both the unsubstituted 1-azadiene **154** as well as the more complex thiazole-bearing diene **147** transformed well under neat conditions (table 2-2, entry 3, entry 5). Increasing the size of the silyl group (TMS → TES) was found to lead to lower reaction rates, but the 1-azadiene precursors were more stable and could be purified by column chromatography on silica gel, were easier to handle and could be stored for more than 1 year at -20°C. The unsaturated hydrazone **152** was as efficient as the 1-azadiene **121** in acetonitrile, but the long synthetic route limited its further application. Under forcing conditions, a different reaction mode was observed (*vide infra*). The hydrazone derivative **150** (entry 7) led to incomplete elimination of

aniline from the putative dihydropyridine intermediate. Different attempts (DBU, Et_3N, TFA, HCl, PPh_3, reflux in xylene, etc) were applied to cleave the N-N bond, but it was found that pyridone **158** was chemically very stable and could not easily be converted to the corresponding pyridine. Further attempts to conduct the transformations with *in situ* formation of **150** either led to worse ratio of the desired pyridine (entry 8) or gave pure pyridone **158** (entry 9).



142 **143-157** **158**

entry	diene	R^1	R^2	diene (eq)	conditions	pyridine	yield
1	**154**	OTMS	TMS	1.2	toluene, rfx, 12h	**156**[a]	14%
2	**154**	OTMS	TMS	1.2	xylene, 150°C, 7h	**156**	49%
3	**154**	OTMS	TMS	3.0	neat, 150°C, 3h	**156**	58%
4	**155**	OTES	TES	3.0	neat, 150°C, 4h	**143**	64%
5	**147**	OTES	TES	1.0	xylene, 150°C, 5h	**157**[b]	57%
6	**152**	PhNMe	TES	1.3	CH_3CN, rfx, 12h	**143**	42%
7	**150**[a]	PhNH	TMS	3.0	CH_3CN, rfx, 6h	**143/158**	55%/26%
8	**150**	PhNH	TMS	1.0	*in situ*[c]	**143/158**	10%/26%
9	**150**	PhNH	TMS	1.0	*in situ*[d]	**143/158**	0%/16%

Table 2-2. Variation of the 1-azadiene in HDA reactions. [a] R = H; [b] R = thiazol; [c] 2.0 eq TMSOTf, 2.0 eq DIPEA, 1 eq **142**, THF, R, T., 14h; [d] 2.0 eq TMSCl, 2.0 eq DMAP, 0.5 eq NaI, 1.0 eq **142**, toluene/acetonitrile, 60°C, 36h.

Interestingly, when applying TMS- or TES-derivatized 1-azadienes to the cycloaddition reaction, neither 3-*O*-silyl groups nor incomplete elimination product of the dihydropyridine intermediate were observed in the product mixture. This illustrates the pronounced leaving group properties of the betainic 3-hydroxypyridine heterocycle and the high lability of the N-O bond.[61] A close inspection of crude reaction mixtures by NMR and GC-MS revealed that a considerable portion of the presumed initial product **87** suffered loss of the SiR_3-group already under the conditions of the cycloaddition, likely by attack of nucleophilic components of the reaction mixture (eliminated silanol HX, decomposed 1-azadiene) or by attack of adventitious water. Rest of the TMS/TES groups was cleaved during workup (aqueous work

up or column chromatography on silica gel), which saved a deprotection step. The intermediate **87** could be isolated when further increasing the silyl group on the 1-azadiene **159** (R^3 = TBS), but poor conversion was found (microwave, 180°C, 6 h, 31%) (figure 2-19).[103]

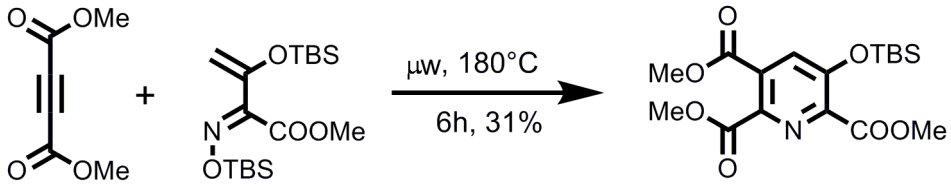
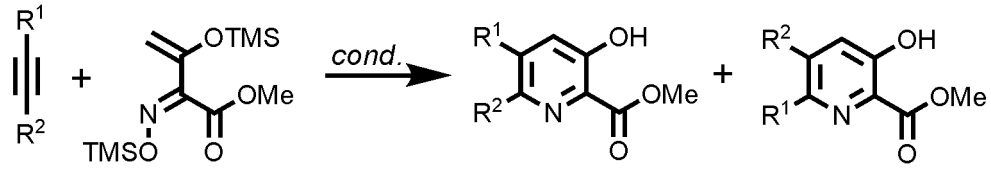


Figure 2-19. HDA reaction with bulky 1-azadiene **159**.

This successful HDA reaction with 1-azadiene and **142** drove us to diversify the alkynes dienophiles (table 2-3). It was pleasing to find out that any alkyne bearing an electron-withdrawing group would participate in good to excellent yields (entry a-h), only limited by volatility (entries f and g). Higher temperatures and elevated pressure slightly enhanced the regioselectivity. Monosubstituted aromatic alkynes were also found to react smoothly (entry e), and electron-withdrawing group containing terminal alkynes led to complete regioselectivity (entry f-h). Electron-rich alkynes were inert under these conditions (entries i-l). All the pyridine isomer **160** and **161** were characterized by 2D-NMR (HSQC, HMBC, COSY), which corroborated the regiochemistry.

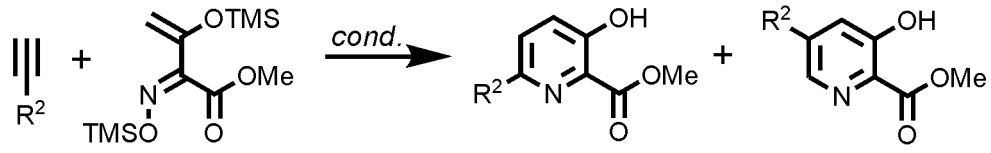


entry	R^1, R^2	time[a]	total yield	ratio **160/161**
a	Ph, COOMe	12h	93%	70:23
b	Ph, C(O)Me	12h	42%	1:1
c	Br, Ph	4h	48%	2:1
d	Ph, Cl	2h	49%	2:1
e	H, Ph	12h	90%	66:24
f	H, C(O)Me	18h[b]	38%	>95:5[c]
g	H, C(O)Me	12h	54%	>95:5[c]
h	H, C(O)Ph	12h	75%	98:2

i	H, C(OH)Me	18h[d]	0%	-
j	Ph, Ph	12h	0%	-
k	TMS, H	12h	0%	-
l	C_9H_{19}, H	12h	0%	-

Table 2-3. 3-Hydroxypyridines from unsymmetrical alkynes. [a] at 150°C neat, with 3 eq. of **121**. [b] at 100°C, neat. [c] minor isomer not isolated. [d] 140°C, neat.

Inspired by these results, further investigation with the terminal alkynes followed and are shown in table 2-4. All terminal alkynes gave moderate to good regioselectivity (entry m-v). Strong electron-withdrawing groups like methoxycarbonyl and pyridinyl gave excellent regioselectivity. Surprisingly, the reactivity of the terminal alkynes was retarded when a para-substituent was present (entry t). For the tosyl acetylene (entry v) only a product with completely reversed selectivity could be isolated in low yield. Other terminal alkynes didn't convert to the corresponding pyridine as a result of the instability of the alkyne upon heating (entry w). Propargyl esters were found unreactive (entry w and x).



84 **121** **160** **161**

entry	R^2	total yield	ratio **160/161**
m	COOMe	56%	>95:5
n	2-pyridinyl	50%	>95:5
o	Ph-(4-OMe)	67%[a]	4:1
p	Ph-(4-CF_3)	63%[a]	4:1
q	Ph-(4-CN)	71%[a]	2:1
r	Ph-(4-NO_2)	61%	2:1
s	Ph-(4-Br)	39%[a]	2:1
t	Ph-(4-Me)	37%[a]	3:1
u	3-thiophenyl	19%	2:1
v	Me-Ph-SO_2-	12%	<5:95[b]
w	COOBn	0%	-
x	CH_2OBz	0%	-

Table 2-4. HDA reaction with termianl alkynes. [a] based on recovered starting material; [a] 8h.

The alkynes **84a** and **84e** were selected to search for suitable Lewis acid promoters. Various Lewis acid were screened, including AgOTf, PPh_3, CuI, CuCl, $Zn(OTf)_2$, $AuPEt_3Cl$, $LiNTf_2$, Et_2AlCl, $Pd(OAc)_2$, $Pd(PPh_3)_4$,[104] $Rh(PPh_3)Cl$ and $AgSbF_6$ in different solvents (CH_3CN, THF, CH_2Cl_2, toluene, etc). For all the Lewis acid tested, none of them delivered the desired pyridine at ambient temperature, some of them only decomposed the 1-azadiene. When $Co(dppe)Br^+$ was used,[105] trimerisation products **162** and **163** of the alkyne **84a** were observed and isolated (figure 2-20, ratio was determined by ^1H NMR). A similar result was reported by Hilt *et al*[106] in the absence of azadiene, which shows that this catalyst chemoselectively promotes alkyne trimerization.

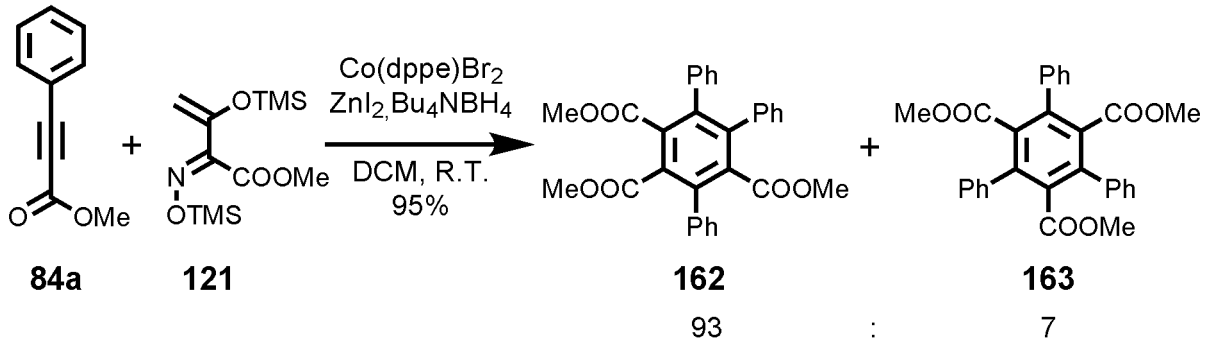


Figure 2-20. Alkyne **84a** trimerisation.

In the attempt to explore convergent synthetic strategies, 1-azadiene **147** was also combined with alkyne **164** (for the preparation see chapter 3), furnishing the functionalized bis-thiazolyl-hydroxypyridine **165** (figure 2-21). However, under a variety of conditions only minor amounts of the sought cycloaddition product could be isolated, along with a larger number of intractable side products which where extremely difficult to separate. Therefore, further application of this HDA reaction with 1-azadiene to more complex system was not investigated.

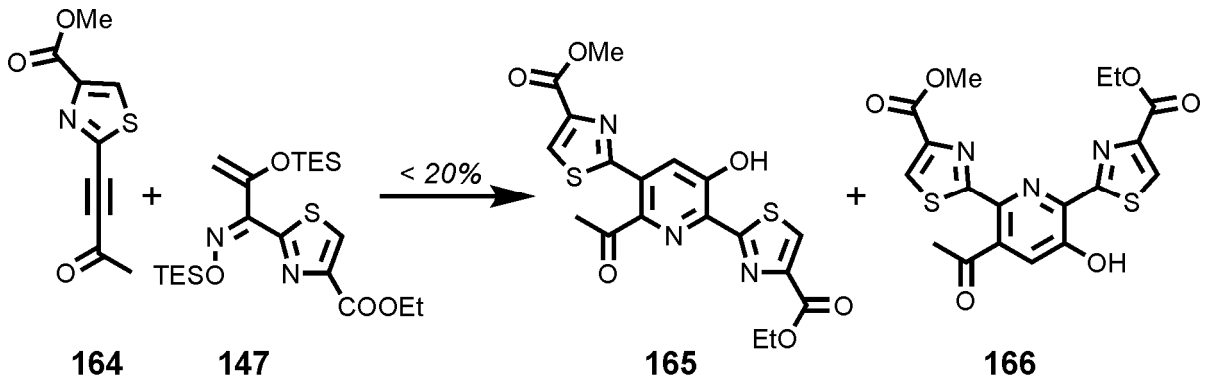


Figure 2-21. Attempted convergent synthesis of a bis-thiazolyl pyridine. *condition*: trichlorobenzene, 200°C, microwave irradiation, <20%.

2.3.2. Pyrrole formation.

The new synthetic strategies for the generation of oligofunctionalized pyrroles are of continuous interest due to its ubiquity of this five-membered heterocycle in natural product and pharmaceutics.[107,108] Recent advances in pyrrole derivative synthesis typically employ isocyanides[109,110] and imines.[111-113] In our 1-azadiene screening for hetero-Diels-Alder reaction to build up nosiheptide pyridine core, the pyrrole derivative **168** (figure 2-22) was isolated as the major product of alkyne **167** and diene **152** and fully characterized (^{1}H NMR, ^{13}C NMR, HSQC, HMBC and HR-MS). The mechanism of the pyrrole **168** formation is not clear till present. Future efforts could concentrate on optimizing this transformation for accessing highly functionalized pyrroles.

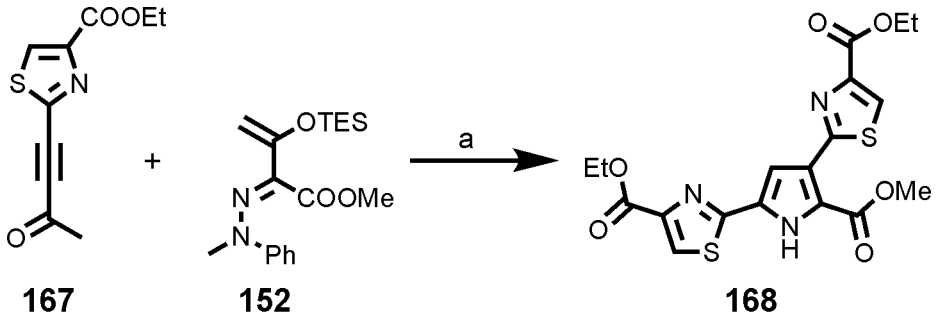


Figure 2-22. Pyrrole formation. a) xylene, 150°C, 11h, 39%.

2.3.3 A plausible mechanism of the side product formation

All the hydroxypyridines were characterized with 2D-NMR (COSY, HSQC, HMBC). In all cases examined, the 3-hydroxypyridine isomer **160** with the more electronegative substituent in the 6-position was favoured (table 2-3 and table 2-4). The 5-isomers **161** were formed in minor amounts for the disubstituted unsymmetrical alkynes, but were easily separable by column chromatography in all the cases. No intermediates or side products were identified apart from the apparent decomposition of diene **121** by two consecutive desilylations (GC-MS) and small amounts (generally <5%) of the homodimer **169** of the diene **121** (figure 2-23).

Under forcing conditions, the homodimer **169** was reproducibly formed (figure 2-23) always as a single 6-substituted regioisomer, as confirmed by extensive 2D-NMR analysis (COSY,

HSQC, HMBC). The regiochemistry and high selectivity was surprising, as presumably the 5-substituted isomer **173** could be formed likewise via a typical Diels-Alder reaction (figure 2-23, bottom). With 2-azadiene homodimers, similar end-to-end fusion Diels-Alder products have been reported.[31,114,115] Interestingly, the TES-activated 1-azadiene **155** was found to be completely stable and unreactive to itself under prolonged heat treatment up to 270°C, which indicated that the *bis*-silylated 1-azadienes **121** themself are unlikely to homodimerize under thermal conditions. Given the fact that the TMS-activated 1-azadiene **121** is slowly loosing TMS groups upon thermal stress (as monitored by TLC and GC-MS), the clean formation of dimer **169** likely involves a desilylated oxime **170** or **171**, which could directly react further with **121**. Another possibility would be an intramolecular *β*-elimination of the enol ether **171** to a terminal alkyne **172**,[116] which might occur under these forcing conditions. Alkyne **172** would quickly be captured by the excess of 1-azadiene **121** present in the mixture to form the apparent homodimer **169** with the same high regioselectivity as observed for the alkynyl ketones.

However, if the enol ether TMS group was first cleaved under the thermal condition, a free ketone would present. This ketone would be chemically very stable and be unreactive.

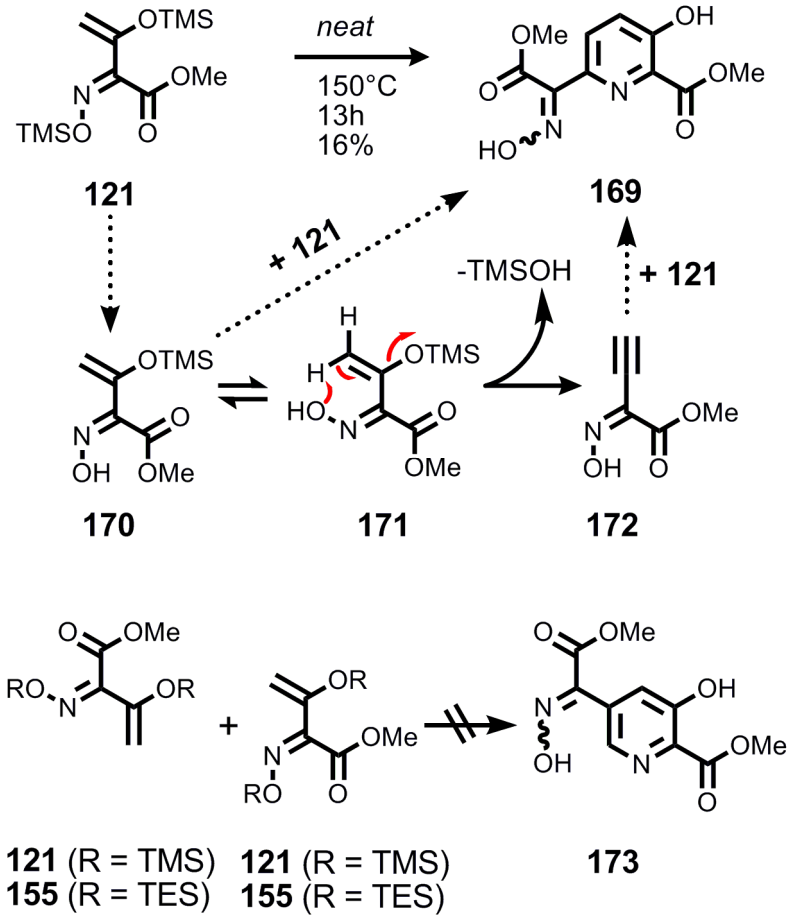


Figure 2-23. Plausible mechanistic pathways for homodimer formation.

Ketone **174** was selected to clarify this hypothesis by monitoring for cross-reactivity (figure 2-24). Interestingly, only the 1-azadiene dimer **169** was identified (both in the reaction mixture and after work up), and the ketone **174** was recovered. This observation supports the notion that the intermediate **170** might be indeed formed first. Further experiments were conducted with dienophiles **174-177** under standard conditions (neat, 150°C), but no cycloaddition product was detected in all the cases. This indicated that the elimination product **172** might be indeed involved, because it shows that the reactivity of the azadiene **121** is not sufficient to transform typical Diel-Alder dienophile dienes.

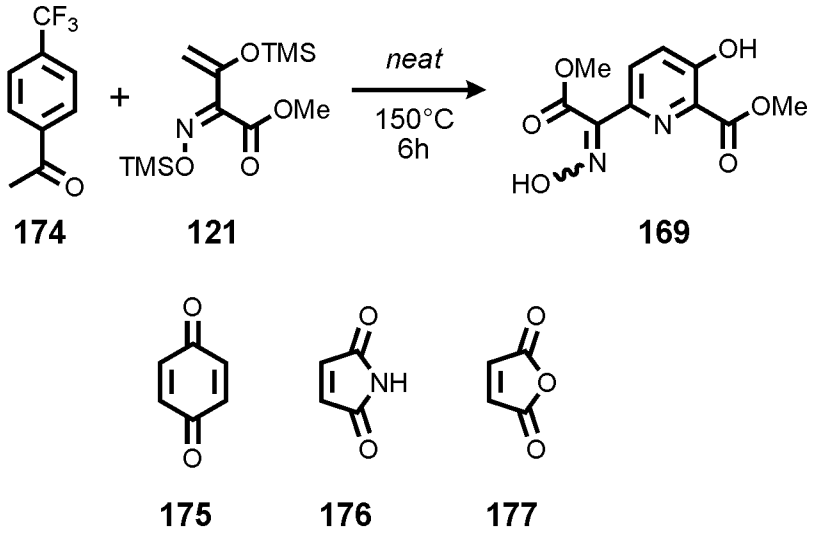


Figure 2-24. HDA reaction with ketone and active alkene.

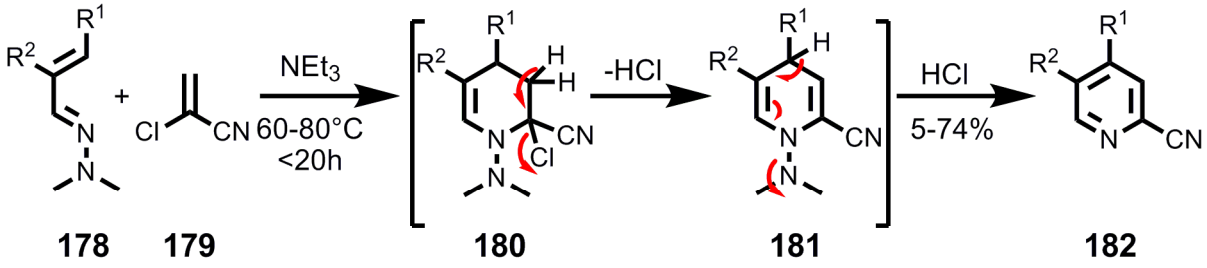
All the data for the alkyne dienophiles above are in line with the notion that a normal-electron demand hetero-Diels-Alder reaction pathway is operative for these azadiene-alkyne HDA reactions. The regioselectivity would result in each case from a matching HOMO/LUMO pairing of the polarized dienes and dienophiles,[117] with the diene being a 1-aza analog of Danishefsky's diene.[117] However, other mechanistic pathways like a stepwise-polar transformation could be unequivocally ruled out at this stage,[118] especially not in case of the side product **169**.

2.4 HDA reaction with dicyano alkenes.

2.4.1 Introduction.

In order to expand the scope of 1-azadiene cycloadditions, we explored alkenes that may regenerate double-bonds by 1,2-elimination as alkyne surrogates.[119] For azadienes, some precedence can be found.

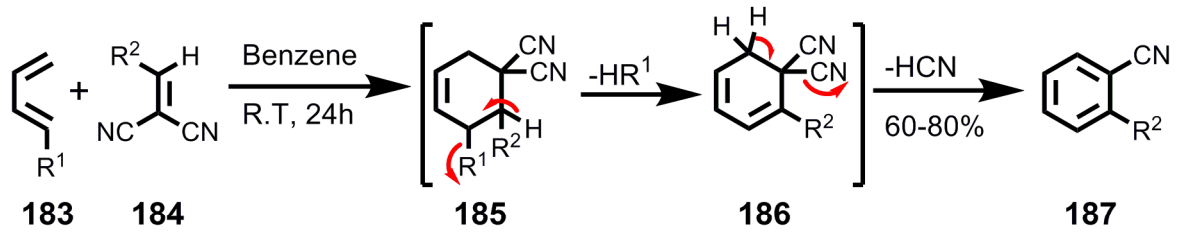
In 1989, Waldner[120] reported that pyridine **182** could be synthesized regiospecifically in two steps from alkene **179** (figure 2-25), An apparent [4+2] cycloaddition occurred to form tetrahydropyridine **180**, followed by elimination of HCl to form the dihydropyridine **181**, which was converted to pyridine **182** upon treatment with anhydrous HCl in 1,4-dioxane. The rather active 1-aza-diene **178** had to be used to achieve good yield and the alkene **179** was the only reported dienophile.

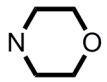


R^1 = CH_3, H
R^2 = CH_3, C_2H_5, *n*-C_4H_9, *i*-C_3H_7
R^1 = R_2 = $CH_2CH_2CH_2CH_2$

Figure 2-25. Pyridine formation with chlorocyanonitrile.

In 1990, Sandhu *et al*[121] reported the biaryls formation from diene **183** and alkene **184** (figure 2-26), a typical Diels-Alder cycloaddition. The concomitant amine elimination gave diene **186**, which aromatized by releasing HCN. The dienamine **183** was essential in this sequence, other dienes led to stable cycloadducts **185**.[122]



R^1 = NEt_2, 

R^2 = Ph, *p*-$MeOC_6H_4$, *p*-$MeOC_6H_4$, *p*-MeC_6H_4,
p-$O_2NC_6H_4$, *p*-ClC_6H_4, *p*-FC_6H_4, 2-thiophenyl

Figure 2-26. Biaryl formation with dicyanoalkene.

2.4.2 Result and discussion.

Suitable alkyne surrogates would be alkenes bearing an additional leaving group. Initially the easily available azadiene **121** was investigated in thermal cycloadditions with alkenes **188a-d** and **184a** (figure 2-27).[123-126] Interestingly, the alkenes **188a-d** remained unproductive, but a clean transformation to the pyridine **191** (Z = CN) occurred for *bis*-cyano alkene **184a** without apparent formation of the intermediary *bis*-nitrile **189**[121,122] or dihydropyridines (e.g. **190**)[120]. This suggested rapid elimination of HCN and TMSOH by putative 1,2- and 1,4-elimination processes followed by loss of the phenolic TMS during workup. The initial analysis indicated the presence of a single regioisomer only.

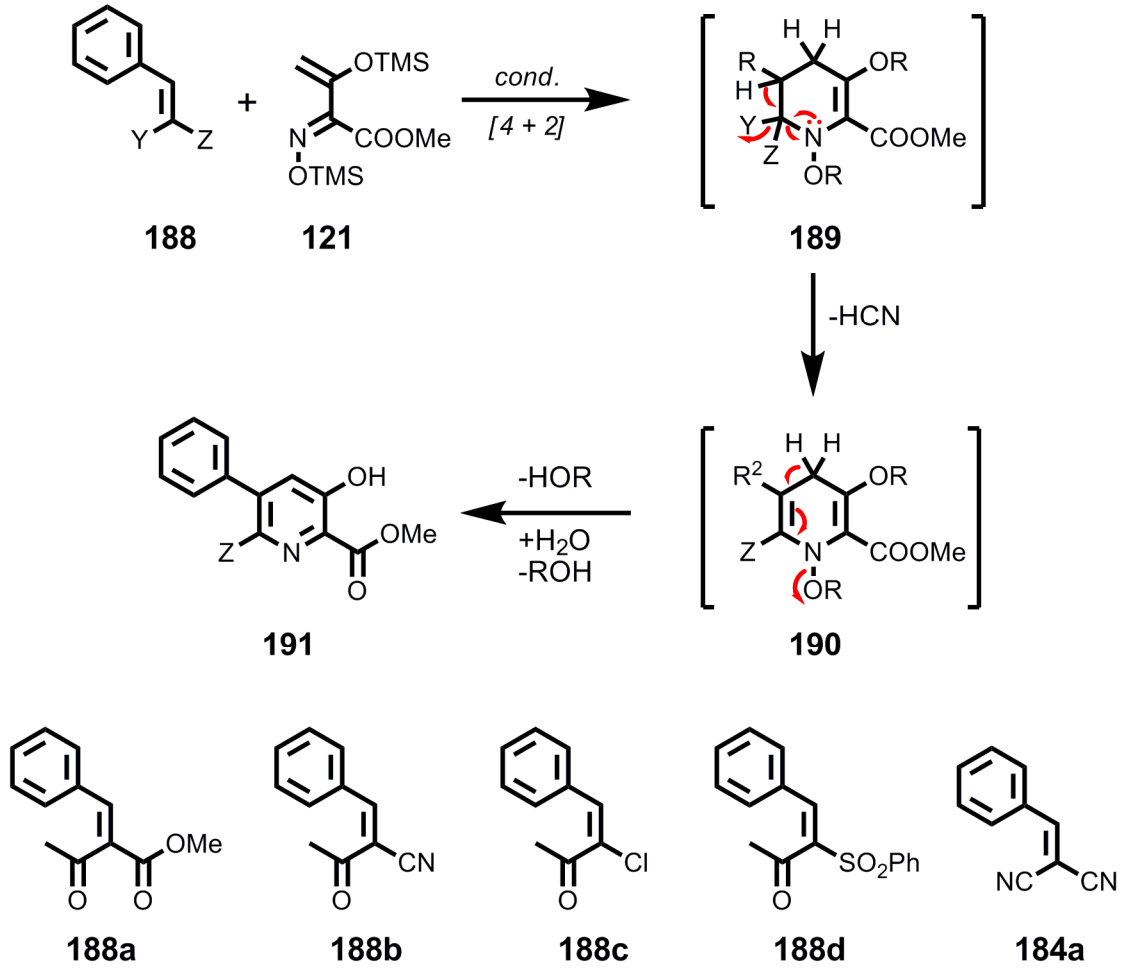
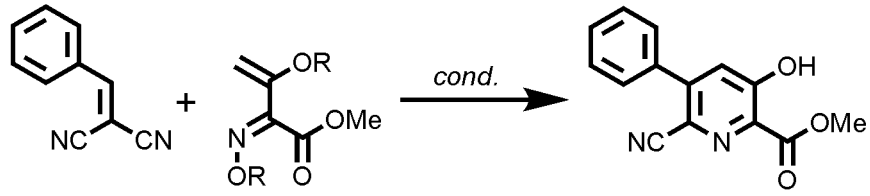


Figure 2-27. Alkene screening for hetero-Diels-Alder reaction.

This transformation delivered the 6-cyanohydroxypyridine in a complete regioselective pattern, but with rather low yield (40%, table 2-5, entry 5-6). Increasing the size of silyl group (TMS → TES) led to lower reactivity (20%, table 2-5, entry 1). The cycloaddtion was moderately solvent dependent (table 3-1, entry 2-6), but neat conditions gave the best result.

Various Lewis acid (LiOTf, $Cu(OTf)_2$, $Zn(OTf)_2$, $Pd(OAc)_2$, $Ni(PPh_3)_2Cl_2$, $Sc(OTf)_3$, $BF_3 \times Et_2O$, $(NH_3)PtCl_6$,) and solvents were screened, but only either recovered starting material or decomposed diene could be identified.

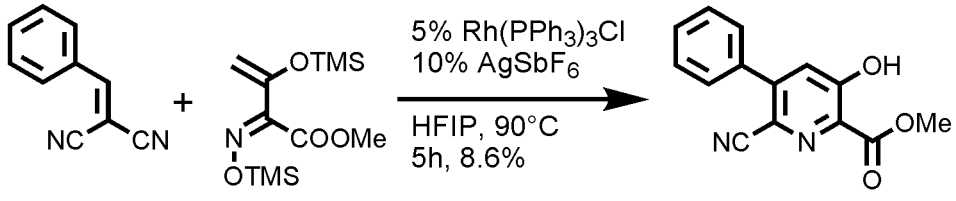


184a **121** (R = TMS) **155** (R = TES) **191a**

entry	diene	*Cond.*	Yield
1	**155**	Tol, 120°C, 60h	20%
2	**121**	HFIP, 100°C, 7h	7%
3	**121**	CH_3CN, 150°C, 12h	19%
4	**121**	DCE, 150°C, 13h	25%
5	**121**	CH_3COOEt, 150°C, 12h	21%
6	**121**	Tol, 150°C, 17h	40%
7	**121**	**neat, 150°C, 12h**	**40%**

Table 2-5. Solvent screening for 6-cyanohydroxypyridine formation.

Only one catalyst system (5% $Rh(PPh_3)_3Cl$, 10% $AgSbF_6$, HFIP, 90°C, 5h)[127] gave the 6-cyanohydroxypyridine **191a** under milder conditions (figure 2-28), however, because of low yield (8.6%) and minor efficiency (table 2-5, entry 2) this hit was not pursued further.

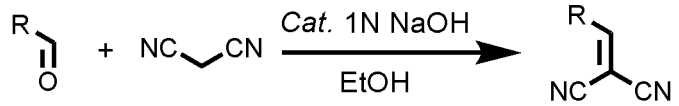


184a **121** **191a**

Figure 2-28. $Rh(PPh_3)_3Cl$ mediated HDA reaction.

In the case of 1-aza-diene hetero-Diels-Alder reaction with alkynes, it has been found that electron-withdrawing groups would enhance the reactivity, but electron-rich alkynes were inert.[128] In order to examine the effect of substituents on the dicyano alkene on this transformation, a small collection of α,α-dicyano alkene (table 2-6) with various substitutent properties was obtained from aldehyde **192** and malonodinitrile **193** by Knoevenagel

condensation.[126] All the dicyanoalkenes could be conveniently purified by recrystallization from ethanol and water.



192 **193** **184**

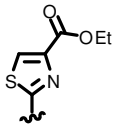
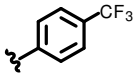
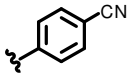
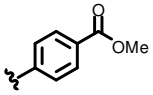
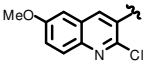
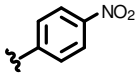
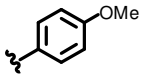
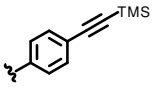
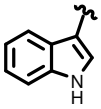
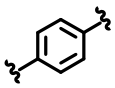
alkene	**R**	yield	alkene	**R**	yield
184a		97%	**184j**		66%
184b		92%	**184k**		88%
184c		75%	**184l**		71%
184d		94%	**184m**		66%
184e		82%	**184n**		40%
184f		84%	**184q**		80%
184g		93%	**184o**		72%
184h		53%	**184p**		72%
184i		92%	**184s**		94%

Table 2-6. Dicyano alkene formation by Knoevenagel condensation.

A small library of 6-cyanohydroxypyridines with different substituents was synthesized from alkene **184** in moderate to good yield by thermal cycloaddition. Most types of substituents were tolerated, including electron poor aromatics, heteroaromatics, and alkyl substituents (figure 2-29). Electron-withdrawing groups on the phenyl ring (**191e**) and the electron deficient heteroaromatic (**191j**) slightly increased the reactivity, electron-rich groups (**184f**)

on the phenyl ring gave rather poor conversion (<5%). Importantly, only one regioisomer was observed in all cases, and proven to be the 6-isomer by 2D-NMR and X-ray crystallography.

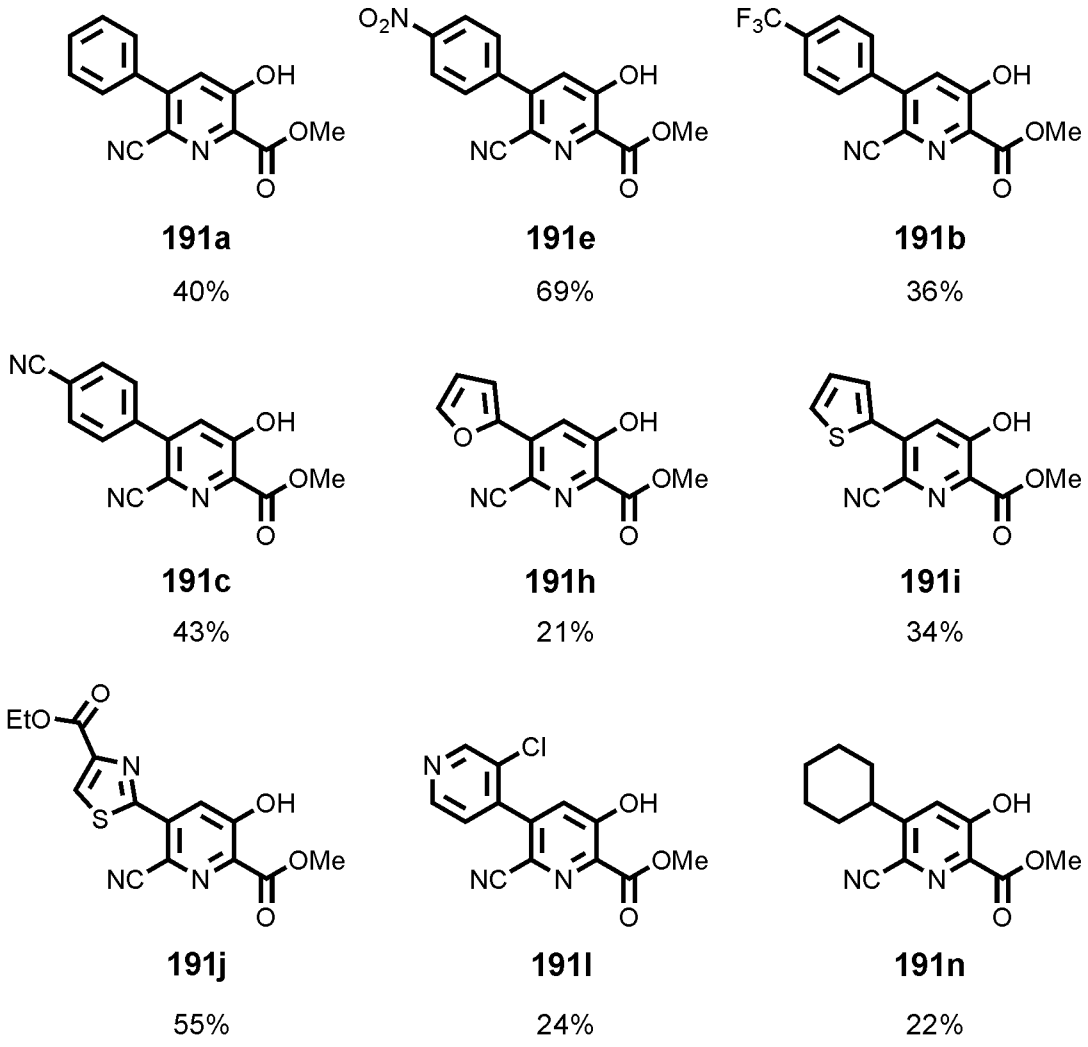


Figure 2-29. A small library of 6-cyanohydroxypyridine obtained from **184** and **121** (150°C, neat, 12h).

The 6-cyanohydroxypyridine **191e** shall be discussed here in detail. The HPLC trace of the reaction mixture showed only one major product (figure 2-30a) and only one pyridine isomer was present in the ^{1}H-NMR after column chromatography on silica gel (Figure 2-30b). In the 2D-NMR (HMBC, figure 2-30c), the 4-H on the pyridine ring showed correlation to 2-C, 3-C, 6-C on the pyridine ring and the 7-C of the phenyl ring, but there was no correlation between 4-H and the cyano group. All the above evidence indicated the 6-cyano-3-hydroxypyridine regioisomer. Evidence for the 5-cyano regioisomer was not found, neither in the crude mixtures (GC-MS, HPLC-MS) nor after purification.

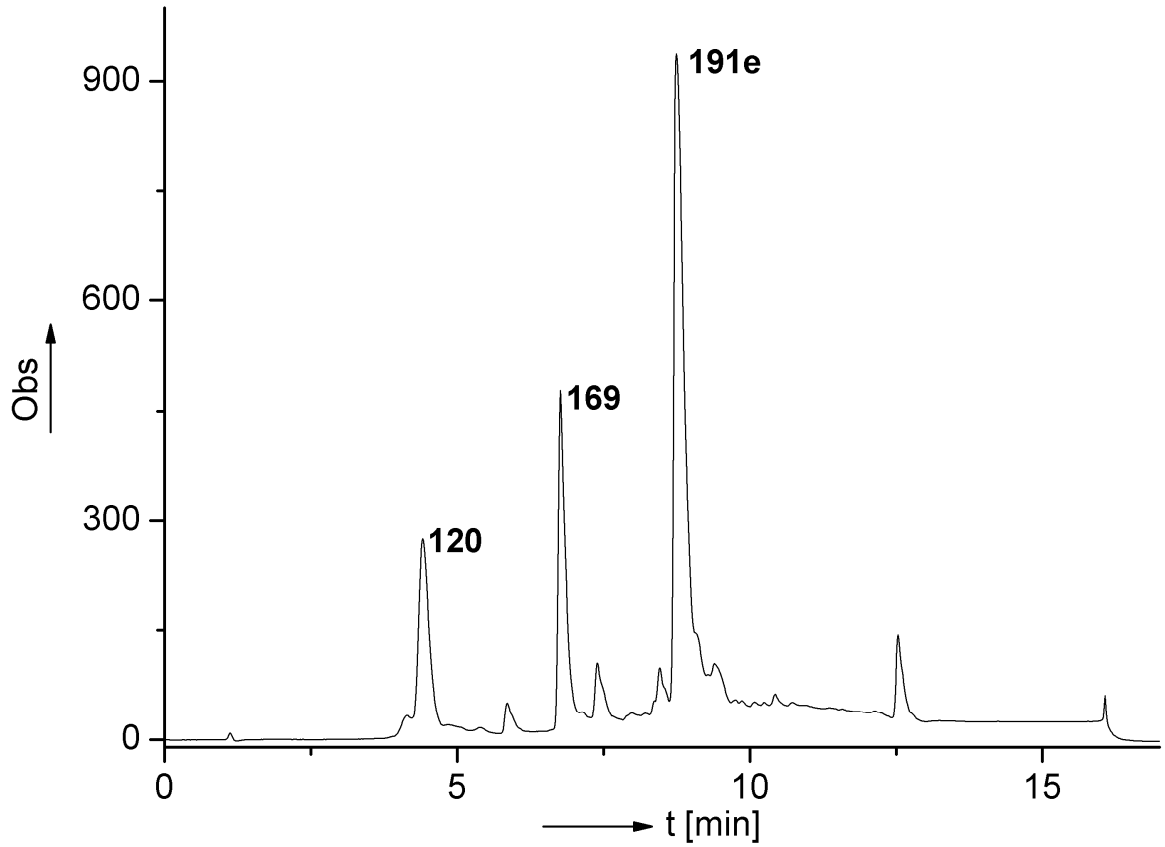


Figure 2-30a. HPLC-trace of crude HDA cycloadditions involving alkene **184e**.

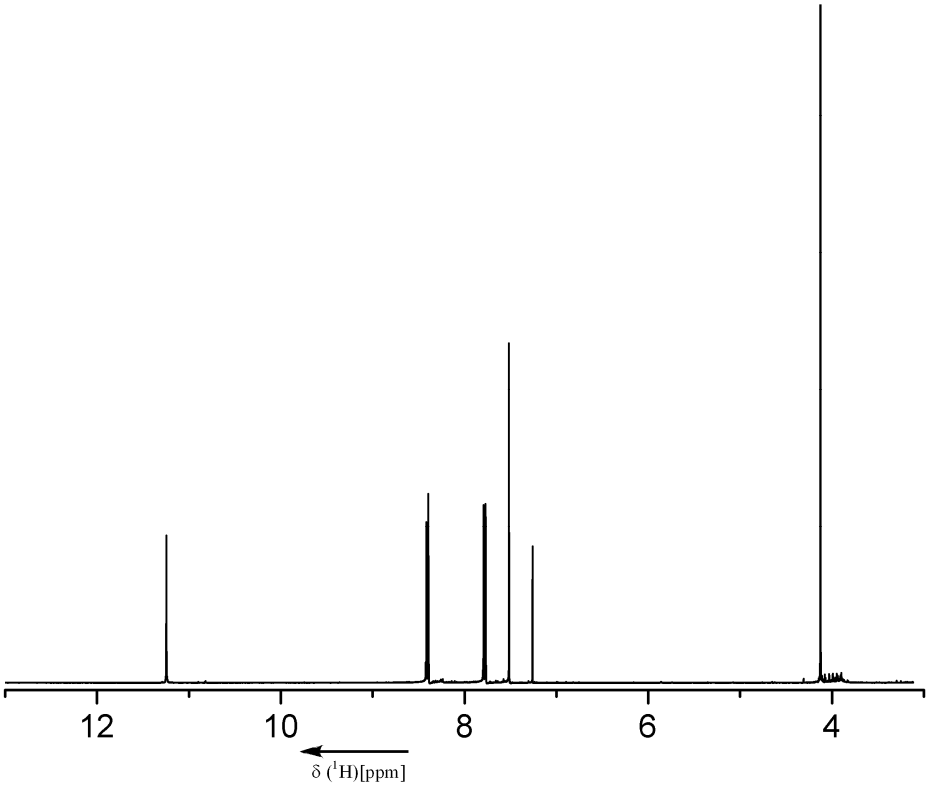


Figure 2-30b. ^{1}H NMR of **191e** showing only one isomer.

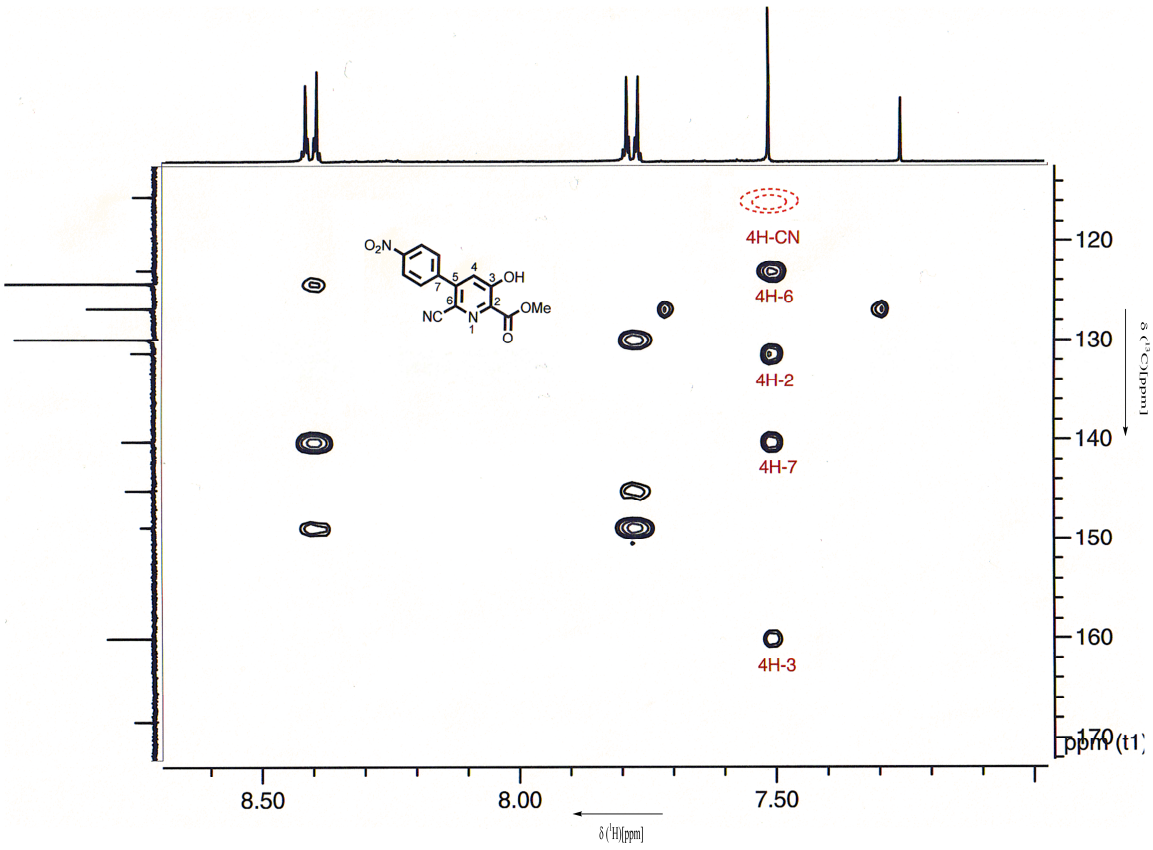
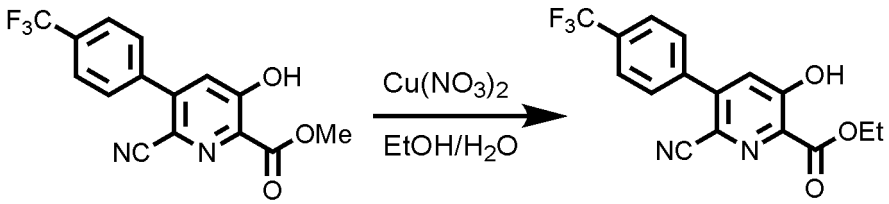


Figure 2-30c. 2D HMBC of **191e** experiment supporting the structural assignment, 27°C, 400 MHz (^{1}H), 100 MHz (^{13}C).

All of the compounds were easily assigned by inference and compoisor. By mixing 6-cyanohydroxypyridine **191b** with copper nitrate in ethanol and water, a single crystal of derivative **194** (figure 2-31a) was obtained. The X-ray structure is shown in figure 2-31b. The cyano substituent is located at 6th position on the pyridine ring, which confirmed the assignments by NMR.



191b **194**

Figure 2-31a. Conditions for crystallizing pyridine **194**.

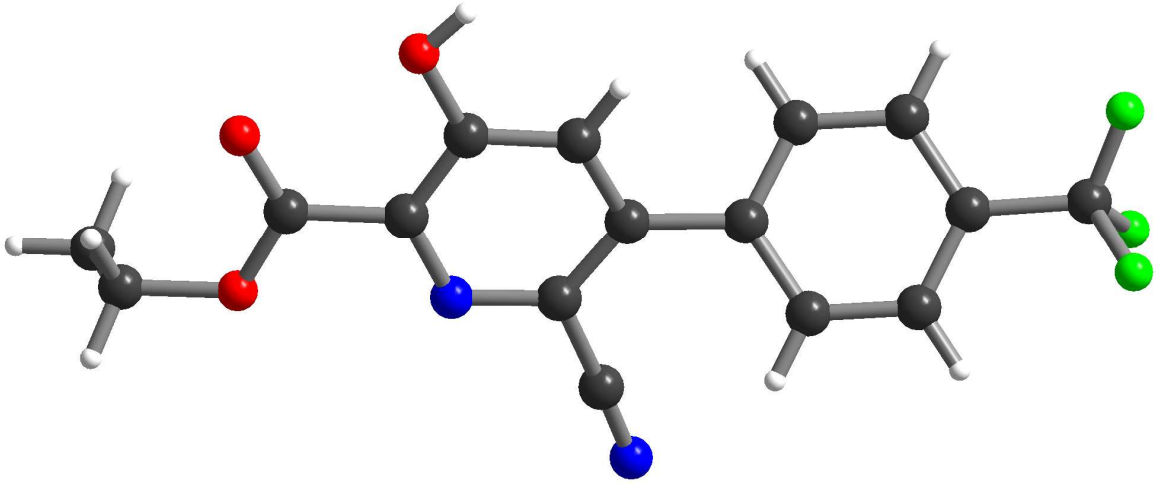
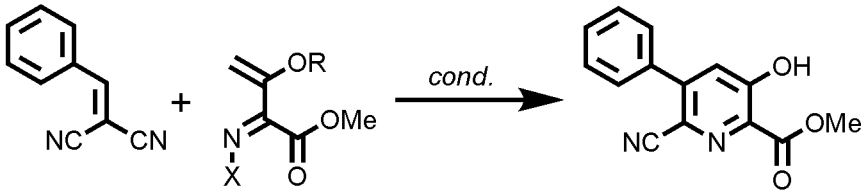


Figure 2-31b. X-ray structure of pyridine **194**.

In order to overcome the moderate conversions, variations of the 1-azadiene were studied. The importance of the activating substituent on the nitrogen atom for cycloaddition efficiency was studied using different *Z*-configured[97] 1-azadienes and unsaturated hydrazone **152** (Table 2-7). Screening reactions with **121-195f** were conducted at 150°C under neat condition in sealed Schlenk tubes. It was found, that *O*-alkylated oximes were superior to *O*-silyl groups (**195** vs **121**, **195a** vs **155**), with OMe giving the best results (**195**). The hydrazone derivative[86,129] **152** did not lead to appreciable formation of pyridine products. The importance of steric factors was evident as an increase in substituent size (**195** vs. **195b**, **195** vs. **195a**, **121** vs. **195f**) always attenuated reactivity. Electron-withdrawing groups on the oxygen atom compromised the productivity (**195d**, **195e**), probably due to the thermal instability of the dienes. Further increasing the temperature led to low yield (entry 11). Probably the diene decomposed under these forcing condition.



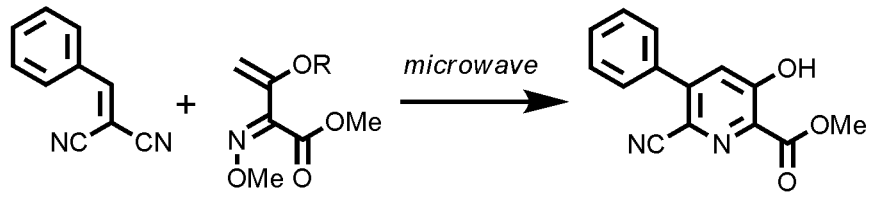
184a **191a**

entry	1-azadiene	X	R	yield[a] of **191**
1	**121**	OTMS	TMS	40%
2	**152**	NMePh	TES	<5%
3	**155**	OTES	TES	20%[b]

4	**195**	**OMe**	**TMS**	**60%**
5	**195a**	OMe	TES	30%
6	**195b**	OMOM	TMS	20%[c]
7	**195c**	OMOM	TES	23%
8	**195d**	OAc	TES	4%
9	**195e**	OMs	TMS	2%
10	**195f**	OPiv	TMS	2%
11	**195a**	OMe	TES	13%[d]

Table 2-7. Variations of 1-azadienes. [a]Reactions at 150°C for 12h, [b]120°C, 60h; [c] 150°C, 7h; [d] 180-190°C, 4h.

Encouraged by the successful 1-azadiene screening, a chemical microwave[130] reactor was employed to improve the transformation efficiency further. As shown in table 2-8, low temperature led to incomplete conversion (entry 1), higher temperature gave better results (entry 2-7), but decomposition of the 1-azadiene was observed when the temperature was raised above 140°C (entry 2-3 vs entry 5-8). The cycloaddition was more dependend on temperature and reaction time than on concentration (entry 1-5). Conversion was cleanest with DMF as the solvent and completed in 60 min at 130°C core temperature (entry 4). The conversion efficiency was slightly improved by excess of 1-azadiene (entry 7 vs entry 10, entry 8 vs entry 9), but increasing the protecting group size on the 1-azadiene decreased the reactivity dramatically (entry 6 vs entry 11, entry 8 vs entry 12). The same was observed in case of normal thermal heating.



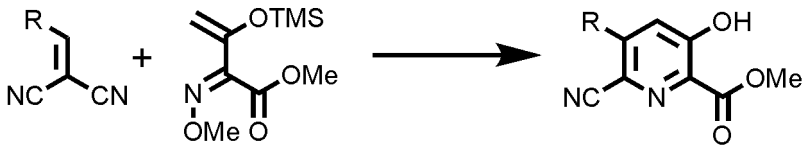
184a **195** (R = TMS) **195a** (R = TES) **191a**

entry	Diene (eq.)	R	Termp. (°C)	Time (min)	[**184a**]	yield[a] of **191a**
1	3	TMS	100	30	0.90 M	58%
2	3	TMS	120	60	0.90 M	86%
3	3	TMS	130	30	0.90 M	82%

4	**3**	**TMS**	**130**	**60**	**0.90 M**	**96%**
5	3	TMS	140	20	0.90 M	79%
6	3	TMS	150	30	0.71 M	62%
7	3	TMS	150	50	0.67 M	61%
8	3	TMS	180	30	0.67 M	48%
9	1.5	TMS	180	30	0.84 M	42%
10	1.5	TMS	150	50	0.84 M	54%
11	3	TES	150	30	0.84 M	44%
12	3	TES	180	30	0.84 M	19%
13	3	TES	180	60	0.84 M	20%

Table 2-8. Condition screened for microwave.

With these optimized conditions, a broad spectrum of substituents was nicely tolerated (table 2-9), and high yields could be achieved. Electron-poor aromatics (**184b**, **184c**, **184d,** 83-97%) transformed excellently, but short reaction times were essential to avoid product decomposition (**184c**, **184b**). Electron-rich aromatics (**184a, 184f**, **184h**, **184s,** 81-96%) performed almost equally well, however, longer reaction times were required for full conversion (**184h**, **184s**). Heterocyclic and alkyl-substituted dicyano alkenes had a wider range in performance (**184h-n**, 47-87%), whereas an alkyl substituent (**184n**) and *ortho*-substituted aromatic ring (**184l-m**) showed reduced reactivity, probably the result of low reactivity and steric hindrance from the ortho position. Interestingly, the 4-nitrophenyl substituted dicyano alkene (**184e**) performed best under normal thermal heating. The alkyne group in dicyano alkene **184g** remained untouched, which in line with the observations made before.[128] No corresponding pyridine product could be formed using methods A or B when free NH groups were present (**184o-q**) in the dicyano alkene, the starting dicyano alkene was fully recovered in these cases (for alkene **184q**, 98% dicyano alkene was recovered after column chromatography on silica gel). Electron rich dicyano alkene **184r** was inert even under forcing conditions.



184 **195** **191**

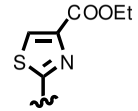
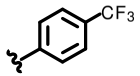
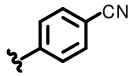
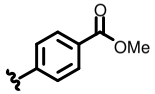
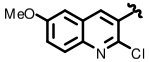
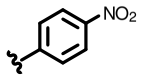
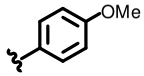
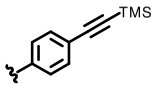
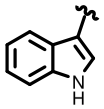
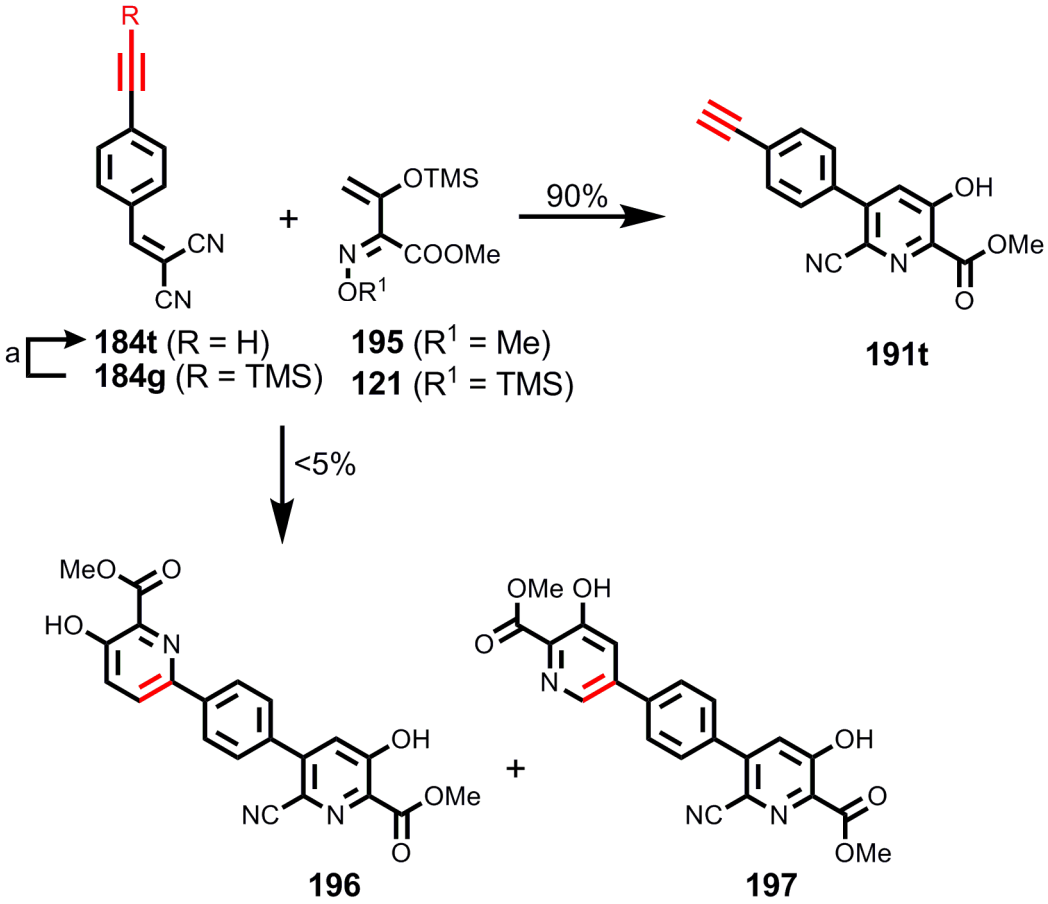
alkene	**R**	pyridine	method A	B	alkene	**R**	pyridine	method A	B
184a		**191a**	60% (12h)	96%	**184j**		**191j**	51% (7h)	87%[a]
184b		**191b**	75% (7h)	82% 95%[a]	**184k**		**191k**	34% (5h)	66%[a]
184c		**191c**	74% (12h)	35% 97%[a]	**184l**		**191l**	--	47%[a]
184d		**191d**	--	83%[a]	**184m**		**191m**	--	64%
184e		**191e**	72% (6h)	40%[a]	**184n**		**191n**	47% (10h)	60%
184f		**191f**	39% (24h)	81%	**184o**		**191o**	0%	0%
184g		**191g**	71% (9h)	--	**184p**		**191p**	0%	0%
184h		**191h**	55% (5h)	80%[a] 87%	**184q**		**191q**	0%	0%
184i		**191i**	71% (5h)	67%[a] 72%	**184r**	OEt	**191r**	0%	0%

Table 2-9. Hydroxypyridines from dicyanoalkenes **184a-r**. method A: the reactions were run with 3eq of **195** at 150°C without solvent for the time indicated; Method B: the reactions were run in a microwave reactor at 130°C for 60 min in DMF as solvent (0.7–0.9 M alkene). [a] Reaction time 30 min in the microwave with method B.

Another challenge was chemoselectivity. What would be the selectivity if a terminal alkyne and a dicyano alkene would be present in the same molecule? Which functional group would be more reactive? To test for this, dicyano alkene **184t** was prepared by desilylation of alkene **184g** (K_2CO_3, MeOH, R.T.).



entry	diene	diene (eq.)	condition	time	yield (**191t**)
1	**121**	3	microwave, 130°C	60min	48%
2	**121**	1.5	microwave, 130°C	60min	46%
3	**121**	3	neat, 150°C	7h	50%
4	**195**	3	neat, 150°C	7h	59%
5	**195**	1.5	microwave, 130°C	60min	78%
6	**195**	**3**	**microwave, 130°C**	**60min**	**90%**

Table 2-10. Chemoselective HDA reaction with **184t**. a) K_2CO_3, MeOH, R.T., 45%.

Normal thermal heating under neat conditions with 1-azadiene **121** and **195** (entry 3-4), microwave irradiation with **121** (entry 1-2) led to formation of hydroxypyridine **191t**, but with moderate efficiency. Notably, when nearly stoichiometric amounts of 1-azadiene (**195**, 1.5 eq) were used under microwave irradiation, the cycloaddition gave good yields (78%), and delivered the 3-hydroxypyridine **191t** in very high chemoselectivity and complete regioselectivity for the dicyanoalkene functional group (table 2-10, entry 5). Pyridine **196** and pyridine **197** were detected as the minor products (less than 5%). Remarkably, even when an excess of 1-azadiene **195** was employed (3 eq), the hydroxypyridine **191t** was isolated with excellent yield (90%) and the chemo- and regioselectivity was not affected (entry 6), which underscores the practical utility of this novel 3-hydroxypyridine synthesis.

2.4.3 Additional investigations on HDA reactions.

Multicomponent reaction[131] are very important methodologies for building up functional scaffolds in a simple operation from easily available starting materials. In order to diversify the HDA reaction, a multicomponent reaction (figure 2-32) was designed and conducted, which yielded the hydroxypyridine **191a** in modest yield. This may be explained by the water generated from the Knoevenagel condensation, which may be promoted the decomposition of 1-azadiene **195**. Future efforts should hence concentrate on additives.

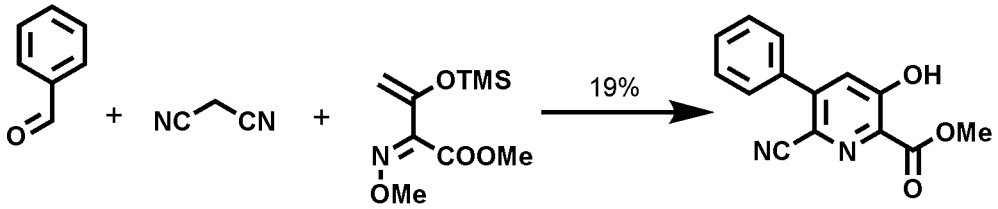
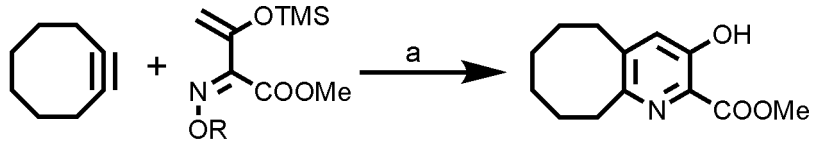


Figure 2-32. Multicomponent HDA formation of 3-hydroxypyridine. Condition: microwave, DMF, 60 min, 19%.

2.5 HDA reaction with cycloalkynes

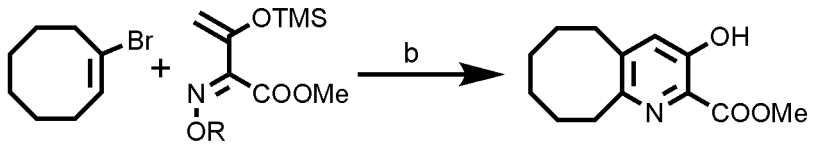
Previously, disubstituted alkynes (without strongly electron-withdrawing substituents) failed to undergo cycloadditions with all 1-azadienes investigated (**121**, **147**, **152**, **154**, **155** and **195**).

To investigate this recalcitrance, strained cycloalkynes were studied. Cyclooctyne **198** has been reported to undergo a [4+2] cycloaddition with an electron deficient diazadiene via inverse electron demand type DA reaction in modest yield (28-34%).[132,133] To study the reactivity of cyclooctyne **198** with electron rich 1-azadienes **121** and **195** via a presumed normal electron demand DA reaction, the cyclooctyne **198** and its precursor **200** were prepared following a reported procedure.[134] In the event, 3-hydroxypyridine **199** was obtained in only moderate yield when the 1-azadiene **195** was used as substrate (figure 2-33). Surprisingly, when the diene **121** was employed, prolonged reaction time was necessary, but an excellent yield was obtained. As before, this observation supports the assumption that the O-silylated 1-azadiene **121** was more suitable for alkyne dienophile. In contrast, in the transformation of bromo-cyclooctene **200**, the reactivity of 1-azadiene **195** was much higher than the reactivity of **121**, but conversion remained low, presumably due to steric hindrance.



198 **121** (R = TMS), **195** (R = Me) **199**

195	3h	40%
121	6h	85%



200 **121** (R = TMS), **195** (R = Me) **199**

195	1h	17%
121	1h	<5%

Figure 2-33. HDA reaction with cyclooctyne and bromo-cyclooctene. a) neat, 150°C; b) microwave, DMF, 130°C;

This result illustrates, that alkyne strain can be used to promote cycloaddition efficiency in HDA reactions, and that alkenes have low intrinsic reactivity towards azddienes such as **121** or **195**.

Benzyne **201** has much higher intrinsic strain than cycloalkynes, and has been frequently applied in cycloadditions.[135] Its combination with 1-azadiene **85** was anticipated to lead to 3-hydroxyquinolines **202**.

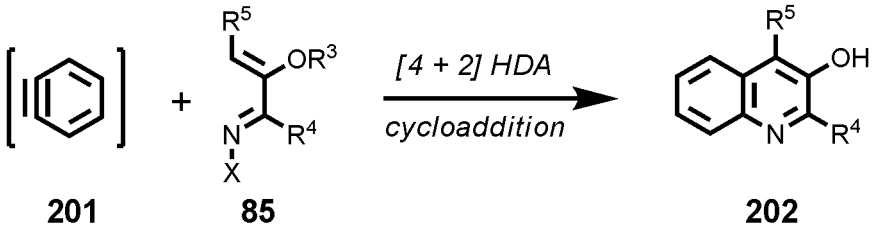
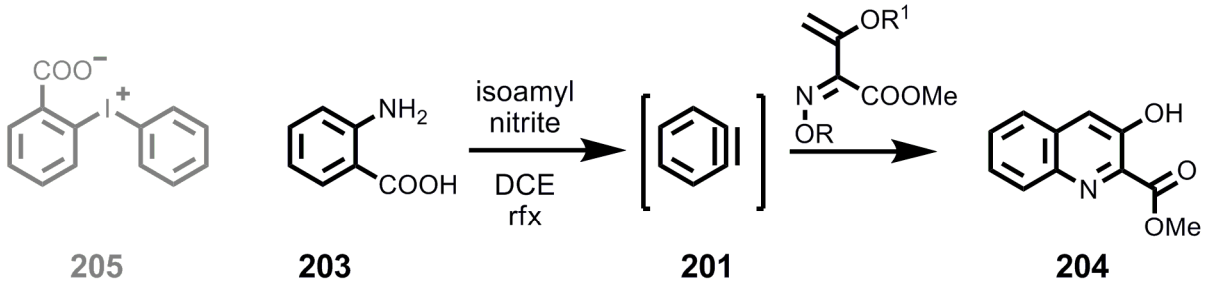


Figure 2-34. HDA reaction with benzynes.

3-Hydroxyquinoline is a key element of decadepsipeptides natural products like sandramycin[136,137] and luzopeptin.[138] Only one direct synthesis of hydoxyquinoline has been reported using a modified Friedländer condensation.[139] The difficulty of this ring construction promoted us to study if this scaffold could be formed by a HDA reaction. To generate benzyne, several methods have been reported.[140-144] However, the silylated 1-azadiene did not allow to utilize fluoride-mediated or basic conditions for benzyne generation.[140] Decomposition of the stable diphenyliodonium-2-carboxylate **205**[145] at high temperature (200°C) *in situ* was not met with success, probably as a result of the thermal instability of the 1-azadienes. Finally, it was found that oxidizing anthranilic acid **203** to generate the benzyne **201** *in situ* could lead to the desired hydroxylquinoline **204** in moderate yield. Further investigation to increase the efficiency of this transformation is warranted.



195 (R = Me, R^1 = TMS)	1h	26%
155 (R = R^1 = TES)	6h	15%

Figure 2-35. HDA reaction with anthranilic acid.

2.6 Mechanistic considerations.

2.6.1 Mechanism study by DFT calculations.

The remarkable regioselectivity of the HDA cycloadditions with the *bis*-nitriles **184** compared to alkynes **129**[128] prompted us to investigate the mechanism of this transformation from first principle quantum mechanics. Earlier computational work in the field concentrated on *E*-1-aza-1,3-butadiene and ethylene as a dienophile in the gas-phase, and on "inverse-electron-demand" type cycloadditions of electron-poor 1-azadienes to vinyl ethers[146] or enamines.[147] In cooperation with Dr. Timo Jacob (Universität Ulm), the "normal-electron-demand" type reactions of **121** with phenylacetylene **84e** (figure 2-36) and of **195** with **184a** (figure 2-37) was evaluated using density functional theory (DFT).

Concerted/asynchronous, singlet and triplet stepwise radicaloid,[148] and stepwise polar mechanisms were considered for the cycloadditions (detailed information can be found in the attachment). An advanced method was applied to determine **M**inimum **E**nergy **C**rossing **P**oints (MECPs) between singlet and triplet states.[149]

For the reaction of **84e** (figure 2-36), a concerted pathway through TS **206** led to **207**. Step-wise processes leading to **207** were not identified. For reactions leading to **209**, the step-wise process for C–C bond formation (**210**) was lower than the concerted barrier (**208**). The MECP linking the closed-shell singlet surface to the open-shell singlet surface (**MECP-1**) was essentially isoenergetic to TS **210**. Diradical intermediates **211** were found metastable, but the MECP linking the open-shell surface of **211** to the closed shell-surface of **209** (**MECP-2**) was prohibitively high in energy (table 2-11).

Pathways leading to 5- and 4-membered rings (**212**, **213**) were studied as well; however, preliminary data on non-fully optimized structures suggested that these processes are prohibitive. Thus, **206** (+35.2 kcal/mol) and **208** (+30.4 kcal/mol) are deemed the most likely processes to reach products **207** and **209**, respectively. Considering the inherent uncertainty of barrier heights and the omission of thermal corrections (≈5 kcal/mol), these results agree well with the experimentally observed moderate selectivity for alkyne cycloadditions.

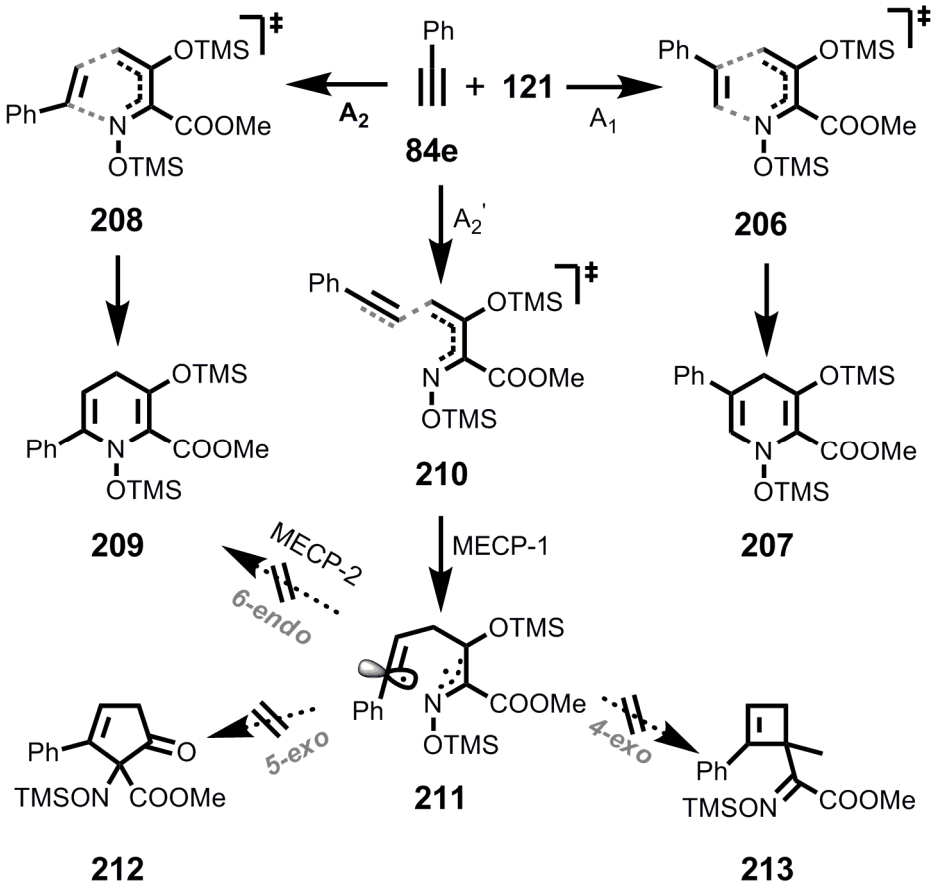


Figure 2-36. Reaction pathways as identified by DFT calculations for alkyne **84e**.

	path A_1(→**207**)		path A_2(→**209**)	
compound	vacuum	solvated	vacuum	solvated
121 + 84e	0	0	0	0
206/208	32.5	35.2	26.9	30.4
210	not identified		23.0	25.3
MECP-1	not calculated		23.5	26.6
211 (singlet)	29.7	32.8	15.8	18.1
211 (triplet)	29.7	32.8	17.2	19.5
MECP-2	not calculated		38.0	39.3
207/209	-36.3	-33.3	-34.5	-31.5

Table 2-11. Overall energetics for HDA reaction with alkyne **84e** (All energies ΔE in kcal/mol)**.**

For the reaction of **184a** (figure 2-37), concerted **214** (+33.9 kcal/mol) and concerted-asynchronous **218** (+21.7 kcal/mol) were the lowest energy pathways. TS calculations leading to the corresponding diradicals either relaxed into Diels-Alder type TS **218** or were ≈10

kcal/mol higher (**217**) than concerted process barriers. In contrast to the study on the reaction of **84e**, the activation barriers **214** and **218** were distinctly different ($\Delta\Delta E^{\ddagger} \approx 10$ kcal/mol), fully consistent with the experimental observation that dicyanoalkenes would give excellent regioselectivity. On the other hand, the net energy gain along the reaction coordinate was found to be small (0 to – 3 kcal/mol). Microscopic reversibility thus suggests that the initial cycloadducts **215** and **219** should be in equilibrium with the starting materials. In a scenario where CN-elimination precedes aromatization, tetrahydropyridine **219** is hence expected to easily convert to dihydropyridine **220** and drive the equilibrium assisted by the adjacent α-N lone pair. This agrees well with the observed regiospecificity, and the inability to convert tetrasubstituted dicyanoalkenes productively (*vide infra*).

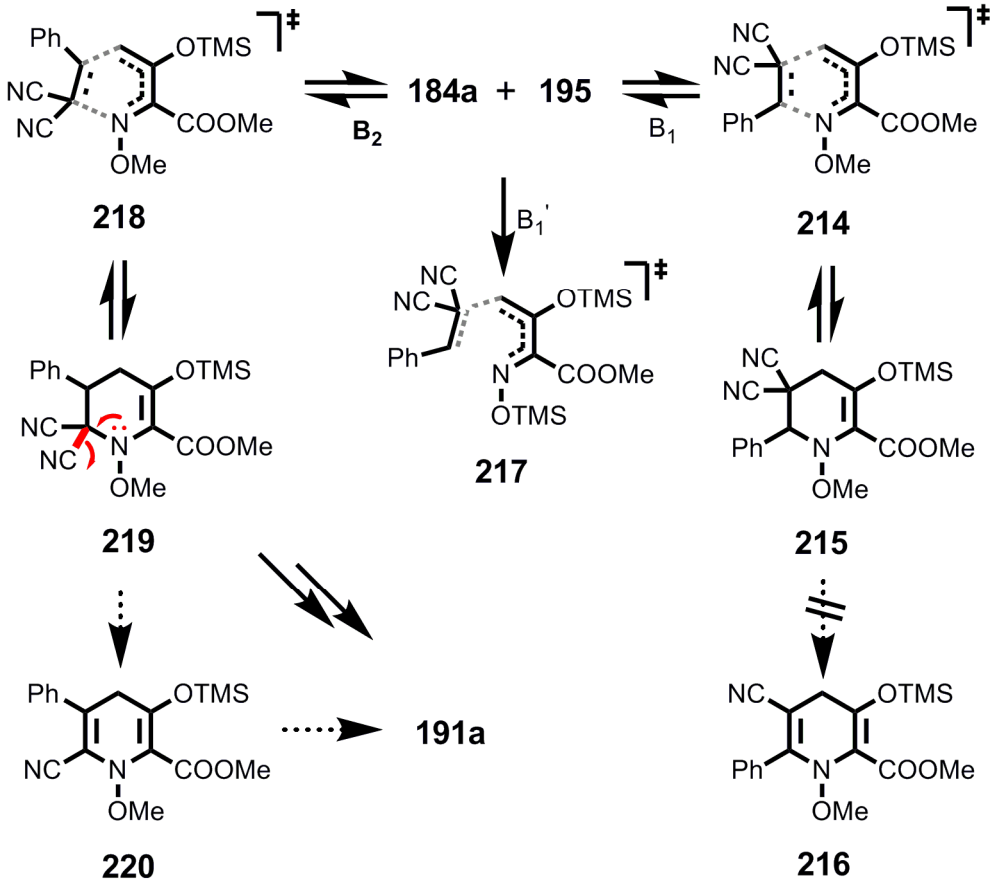


Figure 2-37. Reaction pathways as identified by DFT calculations for dicyanoalkene **184a**.

	path B_1(→**215**)		path B_2(→**219**)	
compound	vacuum	solvated	vacuum	solvated
195 + 184a	0	0	0	0
stepwise TS	41.8	44.5	relaxed to **218**	
concerted TS	32.1	33.9	23.9	21.7

(**214/218**)				
215/219	-2.7	1.0	-3.3	-1.2

Table 2-12. Overall energetics for HDA reactions with alkene **184a** (All energies ΔE in kcal/mol)**.**

Computational evidence for stepwise polar mechanisms was never secured for reactions of **84e** and of **184a**, in line with the neutral reaction conditions and negligible solvent influence on the experimental outcome. In fact, solvation does not appear to play much of a role since vacuum energies led to the same conclusions (table 2-11, 2-12). When comparing the preferred TSs, both **208** and **218** are clearly asynchronous with substantially longer C–N than C–C distances (Figure 2-38). Mulliken charges and **N**atural **B**ond **O**rder (NBO) analysis of **218** both show fairly unpolarized TSs and matching polarities of the 1-azadiene and dienophile, in full accord with the experiment. Notably, the 1-azadiene geometry correlated well with the X-ray crystal structure data (figure 2-17, **141**).[97]

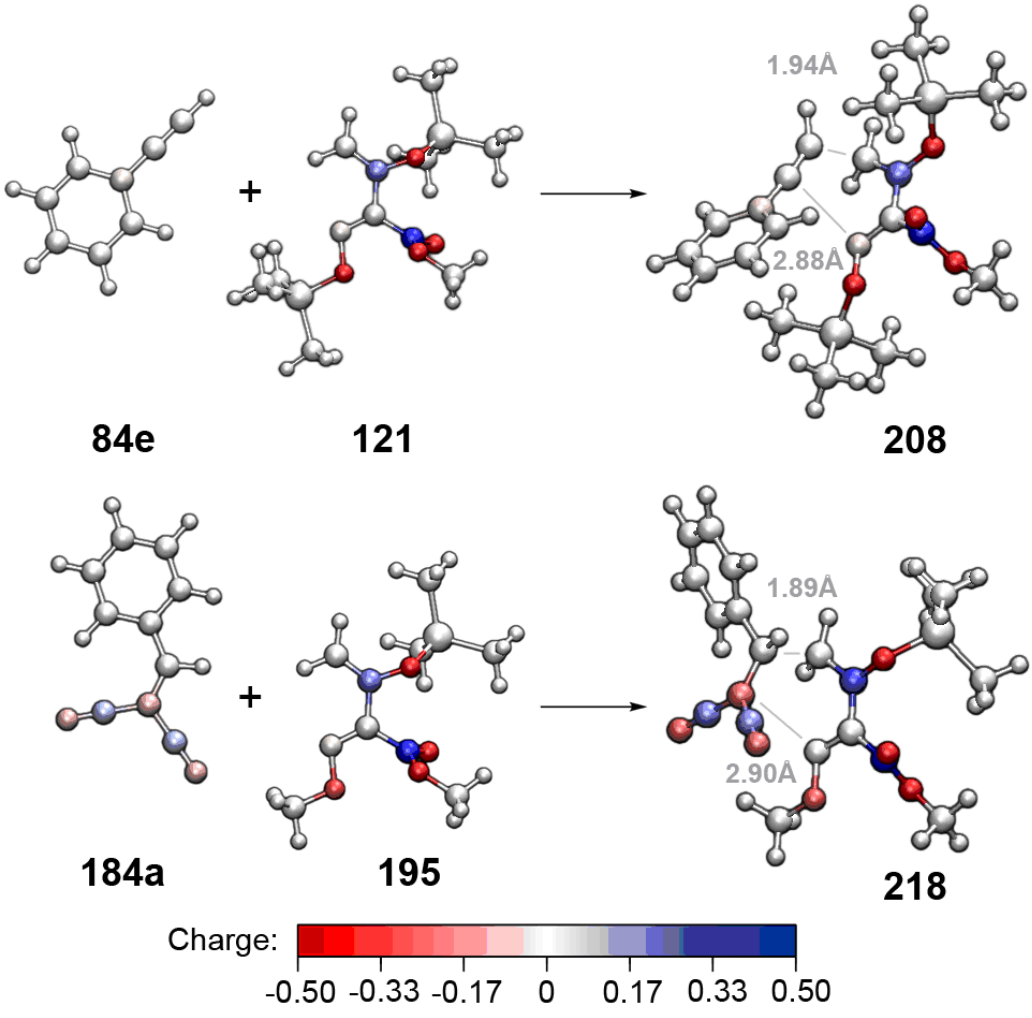
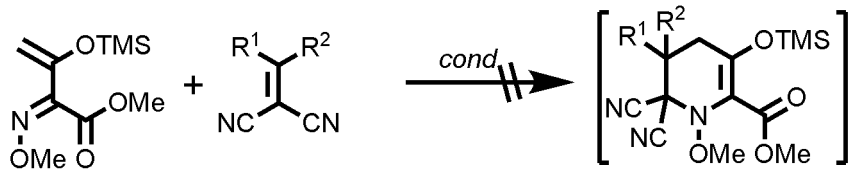


Figure 2-38. Structures of reactants and transition states **208** and **218** with annotated distances and NBO charges (red: –0.50 → blue: +0.50).Graphics were created with VMD,[150] coutesy of Dr. John Keith.

2.6.2 Mechanism study by experimental proof.

In order to prove that there was HCN elimination involved in the proposed mechanism, the HDA reaction of tetrasubstituted dicyanoalkenes **184u**[151] and **184v** were investigated (figure 2-39). The dicyanoalkene **184u** was recovered after heating with **195** for 60 min in microwave. The active tetracyanoalkene **184v** could not be detected any more after the attempted transformations (conventional or microwave), it might have polymerized under the reaction condition. The cycloaddtion product **219a** was not detected in both cases, which indicated HCN elimination was essential for this transformation. These observations support the assumption that the tetrahydropyridine **219** formation might be reversible, and that the final HCN elimination drives the equilibrium to pyridine **191a**, as predicted by theory.[152]



195 **184u** (R^1 = Ph, R^2 = Me) **184v** (R^1 = R^2 = CN) **219a**

Figure 2-39. HDA reaction with tetrasubstituted alkene. Condition: microwave, 130°C, DMF, 60 min.

2.7 Conclusion.

In summary, it could be shown that 1-azadiene hetero-Diels-Alder reactions are well suited to provide diverse 3-hydroxypyridines in good yields and selectivities in one simple operation. For alkynes, the choice of 1-azadiene and dienophile is flexible as long as electronically activated alkynes are employed, and the 1-azadiene is not deactivated further by steric bulk. Good to excellent selectivities are obtained. Alkynyl ketones were found to deliver the 6-isomer with almost perfect regioselectivity. Further exploration with more complex 1-azadiene and dienophile did not meet with success.

Furthermore, it was found that highly functionalized 3-hydroxypyridines can be directly obtained from α,α-dicyanoalkenes **184** with excellent yield, chemoselectivity, and complete regiocontrol. Electron-rich aromatic, electron-deficient aromatic, heteroaromatic and alkyl substituents on dicyanoalkene were well tolerated, and all of them gave complete regioselectivity. A chemical microwave was found to enhance the transformation efficiency with shorter reaction time and lower temperature compared to normal heating. Excellent chemoselectivity for a dicyanoalkene over an alkyne was found.

DFT calculations clearly reported the concerted Diels-Alder-type mechanisms being operative for alkynes **84** and dicyanoalkenes **184** in this novel 1-azadiene cycloaddition, with rather unpolarized transition states. The calculated energy difference between the proposed intermediates were in line with the experimentally observed regioselectivities.

3. Toward a total synthesis of nosiheptide

3.1 Introduction

Nosiheptide **3**[41] (figure 3-1) belongs to the class of thiopeptide antibiotics[5] and is probably the most potent compound ever identified for combatting *S. aureus* (MIC 0.6 - 2.5 nM).[47] Nosiheptide **3** is structurally characterized by a macrocycle (**A**) extending from a hydroxypyridine core featuring three radiant thiazole rings and a rigidifying loop (**B**). The loop (**B**) in **3** consists of a unique indolic acid thioester. The prototypical structure and outstanding potency within the thiopeptide class render nosiheptide **3** an outstanding platform for synthetic investigations. Importantly, to the present date solutions for the total synthesis of nosiheptide have not been reported. Significant synthetic challenges are posed by the 3-hydroxypyridine as well as the dehydroaminoacids together with a thioester in the final target structure.

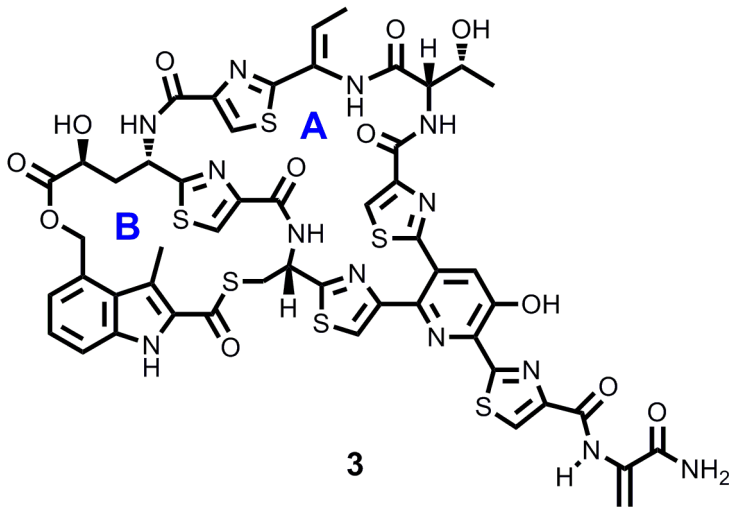


Figure 3-1. Chemical structure of nosiheptide.

3.2 Retrosynthetic analysis and challenges.

Our general retrosynthetic analysis based on considering the structural challenges is shown in figure 3-2. After disconnection of the indolic acid thioester **221**, which can be obtained by a modified Reissert-indole synthesis[153] and Negishi-couping,[154] the peptidic macrocycle **222** (A-ring) with suitable latent functionalities and orthogonal protecting groups remains the key synthetic target.

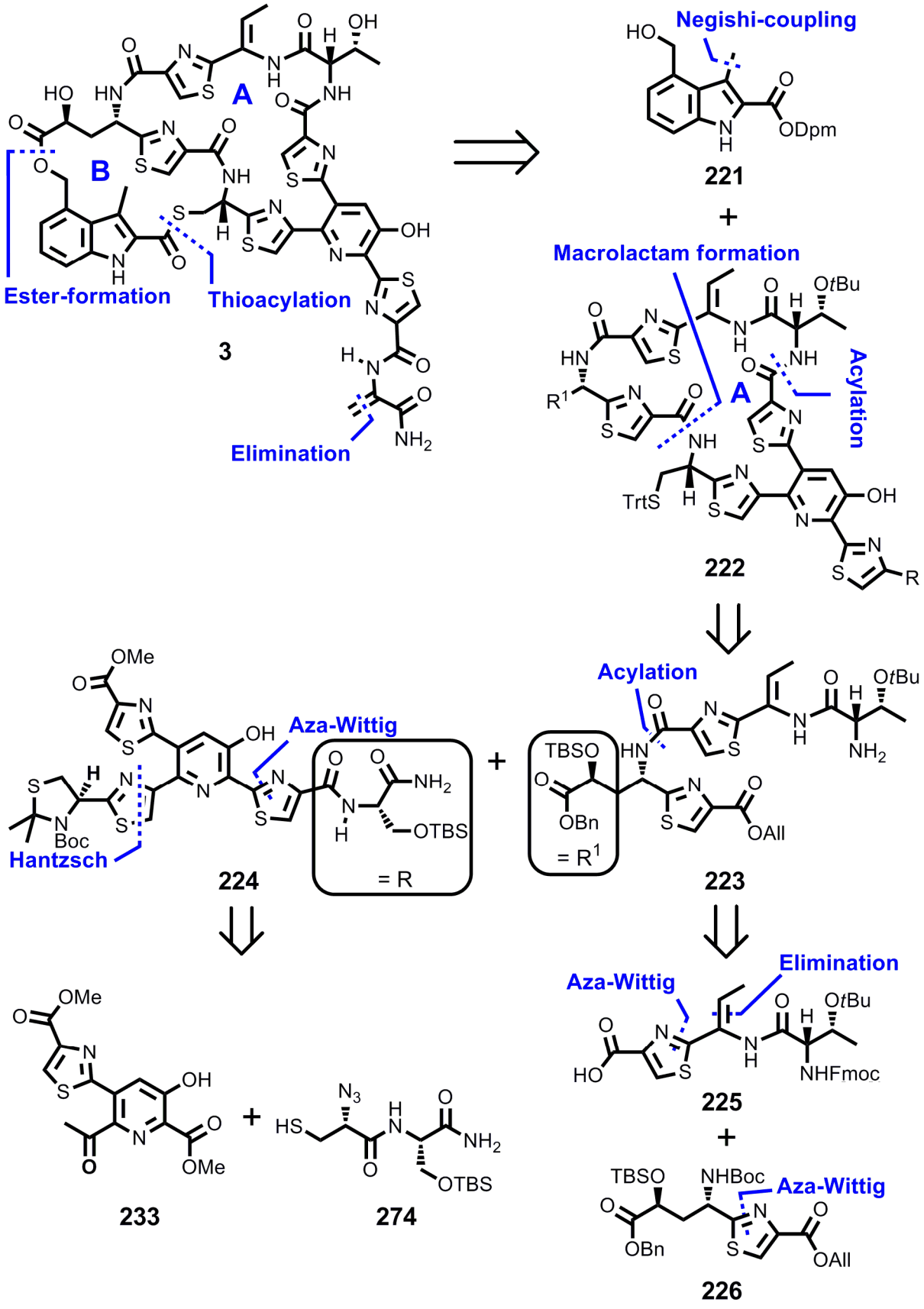


Figure 3-2. Retrosynthetic analysis of nosiheptide.

The A-ring can be further simplified to a peptidic building block **223** and a tris-thiazolylpyridine **224**. The former may be obtained by applying Aza-Wittig reactions,[155] a threonine side chain elimination will lead to the enamine. The latter could arise from 3-hydroxypyridine **233**, which shoud be obtained from a 1-azadiene HDA reaction (chapter 2). A Hantzsch annulation should gave to attach the second thiazole ring, and an aza-Wittig reaction is planned to install the third thiazole. The dipeptide side chain **274** should be available in a straightforward fasion. In the group, the synthesis of peptide building block **223** has been worked out in parallel to this thesis.[55]

3.3 Result and discussion.

3.3.1 HDA reaction with thiazolyl alkyne.

The synthesis began with the preparation of the ethoxycarbony thiazolyl alkyne **167** and methoxycarbonyl substituted alkyne **164** (figure 3-3). Thiazoles **228** and **230** were prepared from thiourea **227** following a reported procedure.[156] Alkyne **232a**[157] was employed for a Sonagashira cross coupling (1% $Pd(PPh_3)_2Cl_2$, 2% CuI, 2 eq. Et_3N, DMF, 55°C, 5h), but very poor yields were found (5%). Further investigations revealed that alkyne **232** could undergo a Sonagashira cross coupling with thiazoles **228** and **230** chemoselectively to give the alcohols **229** and **231** in excellent yields. $Pd(PPh_3)_2Cl_2$ could be replaced by $PdCl_2$ and 2 equivalents of PPh_3, which showed the same catalytic activity. IBX (2-Iodoxybenzoic acid)[158] mediated oxidation then cleanly delivered the ketones **167** or **164** without touching neither the triple bond nor the thiazole ring.

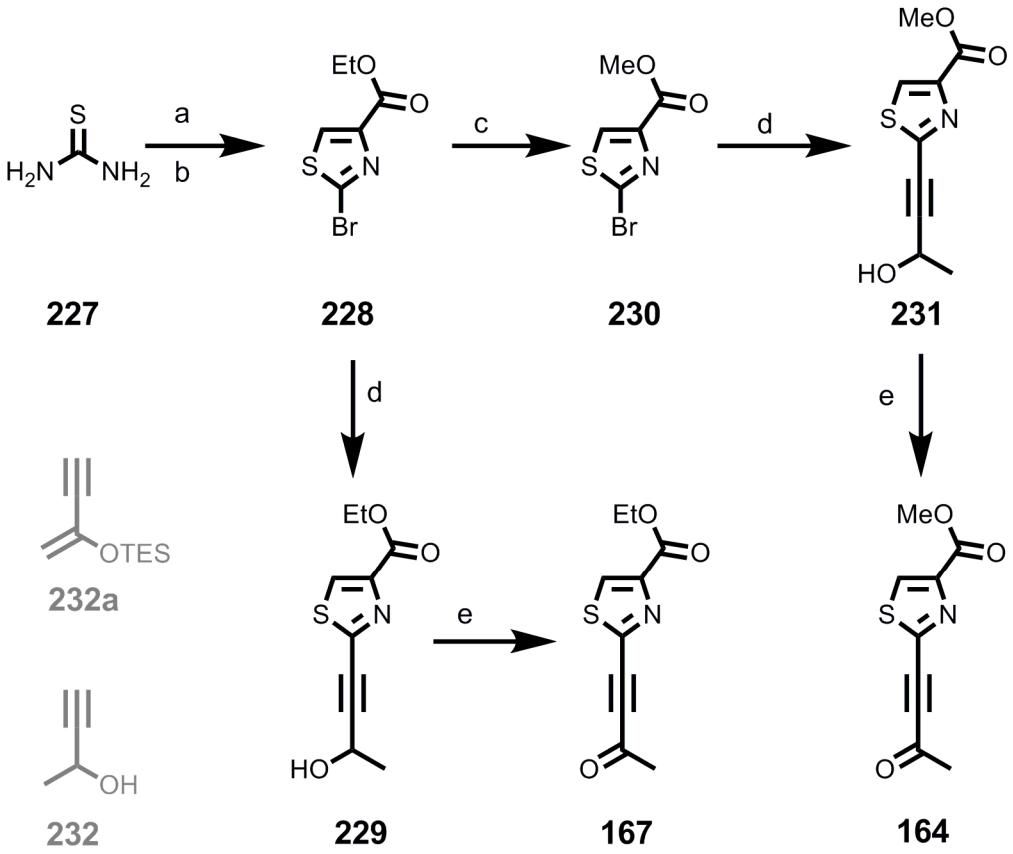
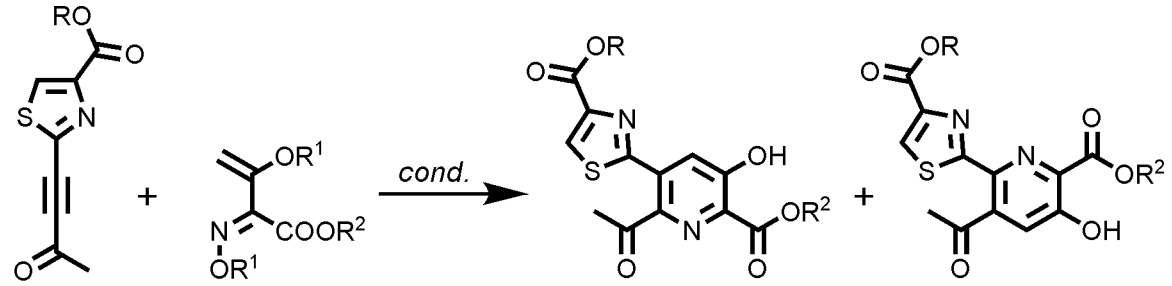


Figure 3-3. Synthesis of the alkynes. a) Bromopyruvate, 100°C, 20 min, 99%; b) 3 eq. $CuSO_4$ x 5 H_2O, 3 eq. NaBr, 1.1 eq. $NaNO_2$, 9 M H_2SO_4, 45%; c) Cat. H_2SO_4, MeOH, 90%; d) **232**, 1% $Pd(PPh_3)_2Cl_2$, 2% CuI, 2 eq. Et_3N, DMF, 80°C, 1h, 91% or **232**, 1% $PdCl_2$, 2% PPh_3, 2% CuI, 2 eq. Et_3N, DMF, 80°C, 1h, 91%; e) IBX, DMSO/THF = 1:1, 0°C ~ R.T., 12h, 97~99%.

With the alkynyl ketones **164** and **167** in hand, the HDA reaction was conducted under different conditions (table 3-1) for optimization. When alkyne **167** was employed neat, the desired hydroxypyridine **233a** (R = Et) was obtained in moderate yield, but it was very difficult to separate from the other isomer **234a** and the dimer of 1-azadiene **121** (table 3-1, entry 1). The double TES protected 1-azadiene **155** helped to depress dimer formation, but unfortunately led to undesired regioselectivity and poor yield (table 3-1, entry 2). In further investigations it was found that alkyne **164** surprisingly led to better yields, and the isolation of the desired hydroxypyridine **233** (R = Me) was much easier in this case (entry 3). Promoted by this observation, different temperatures and solvents were screened. The reaction in overheated toluene (pressure tube) gave the best result (entry 4-8). Unfortunately, a changing the ester on the 1-azadiene (ethyl instead of methyl) retarded the reactivity (entry 6).



167 (R = Et) **121** (R^1 = TMS, R^2 = Me) **233** **234**
164 (R = Me) **155** (R^1 = TES, R^2 = Me)

entry	R	R^1	R2	Condition	yield	Ratio **233/234**
1	Et	TMS	Me	neat, 150°C, 12h	52%	1.4:1
2	Et	TES	Me	neat, 150°C, 12h	45%	1:1.4
3	Me	TMS	Me	neat, 150°C, 12h	62%	1.2:1
4	Me	TMS	Me	xylene, 200°C, 3h	74%	1.6:1
5	Me	TMS	Me	xylene, 180°C, 4h	81%	2.1:1
6	Me	TMS	Et	toluene, 180°C, 3h	56%	2.6:1[a]
7	Me	TMS	Me	DMF, 130°C, 60 min[b]	78%	1.7:1
8	**Me**	**TMS**	**Me**	**toluene, 180°C, 4h**	**83%**	**2:1**

Table 3-1. HDA reaction with thiazolyl alkyne. [a] see regioselective hydrolysis part; [b] microwave irradiation.

The regioisomers **233** and **234** were characterized by 2D NMR (HSQC, HMBC). The 4-H on the pyridine ring in **233** showed no correlation with the 6-ketone; but the 4-H on the pyridine ring in **234** showed strong correlation with the 5-ketone. Confirmation of the exact structure of the cycloaddition products was obtained on a later stage by X-ray crystal structure analysis (*vide infra*).

AgOTf, $Cu(OTf)_2$ and $Zn(OTf)_2$ were studied for their influence on the transformation efficiency in various solvents (xylene, toluene, THF, DCE) with unsatured hydrazone **152**. Interestingly, 20% $Cu(OTf)_2$ delivered the hydroxypyridine **234a** in moderate yield (figure 3-4, 18%). Increasing the amount of $Cu(OTf)_2$ did not lead to better yield, therefore, this procedure was not further investigated.

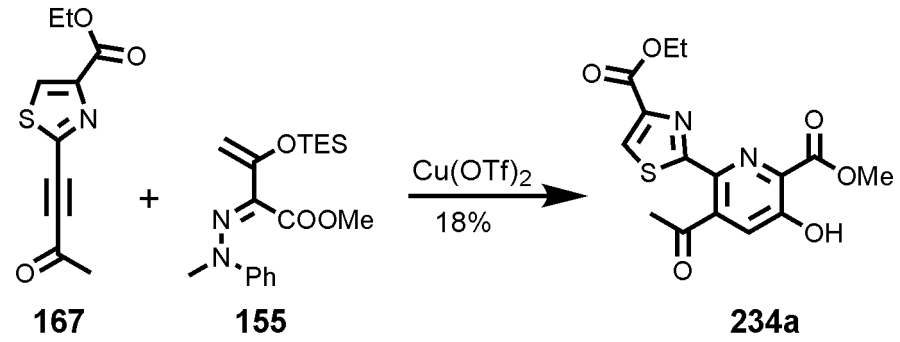


Figure 3-4. $Cu(OTf)_2$ catalyzed HDA reaction of alkyne **167**. Condition: 20% $Cu(OTf)_2$, xylene, 70°C, 12h, 18%.

An attempt of employing TMSOTf to promote a cascade reaction of **164a** to form hydroxypyridine **233** via anticipated oxonium ion **164b** was not met with success (figure 3-5).[159-161]

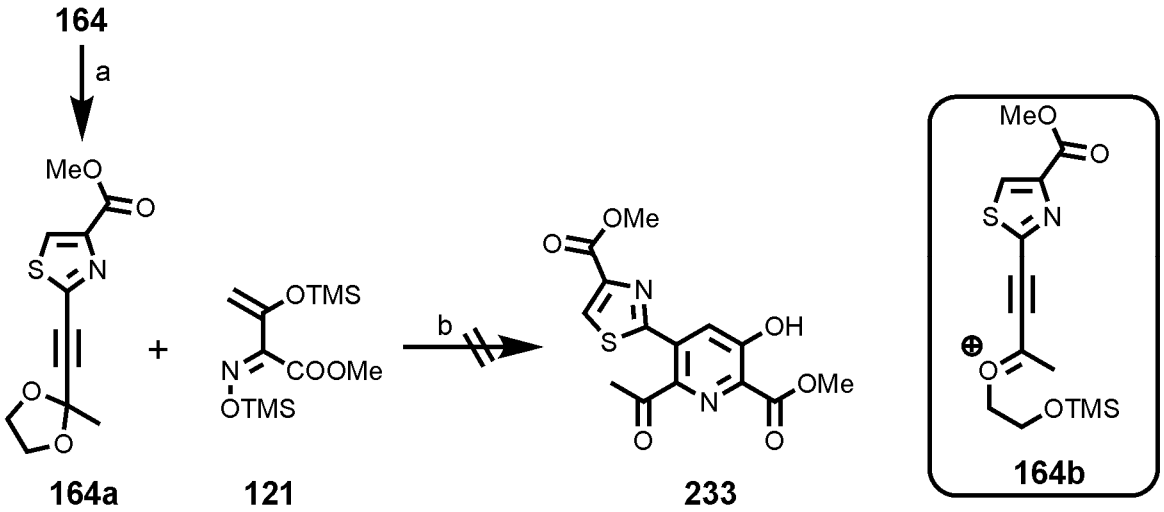
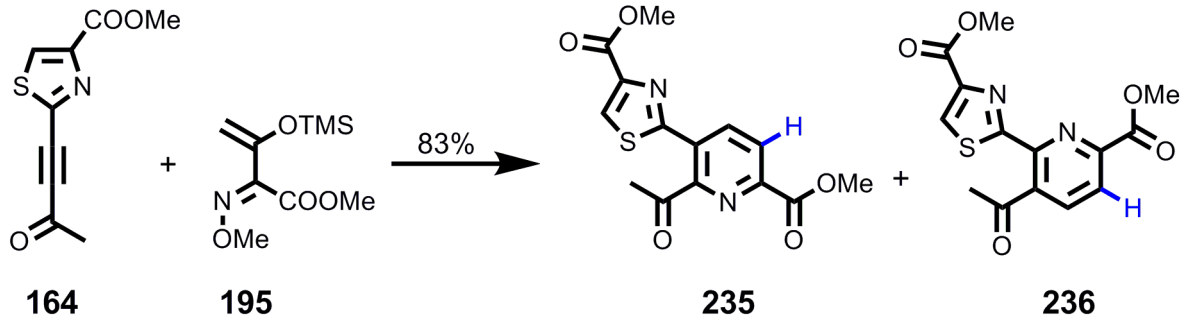


Figure 3-5. TMSOTf catalyzed cascade reaction attempt. a) $HOCH_2CH_2OH$, 10% PTSA, benzene, 110°C, 5h, 37%; b) 30 mol% TMSOTf, THF, R.T., 24h.

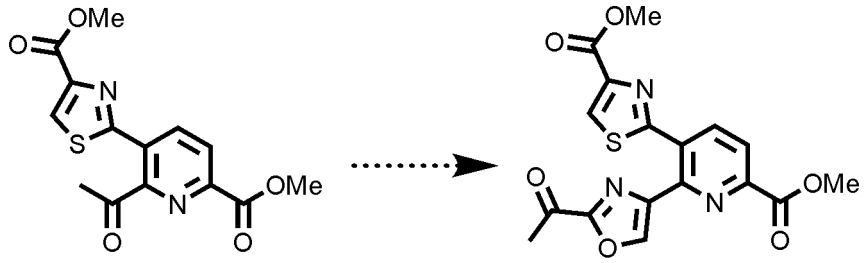
The hetero-Diels-Alder reaction of 1-azadiene **195** with α,α-dicyanoalkene gave clean conversion in excellent yields, chemoselectivity and complete regioselectivity.[152] When the same 1-azadiene **195** was applied to the HDA reaction with alkyne **164** (figure 3-6), interestingly, the pyridine **235** and its isomer **236** were obtained in excellent yields. The loss of the 3-hydroxy group during the reaction was unexpected and remains difficult to explain considering the observed efficiency. To identify the source of the apparent reduction equivalent, future research is necessary.



164 **195** **235** **236**

Figure 3-6. Pyridine formation. Condition: DMF, 130°C, microwave irradiation, 60min, 83%, **235**:**236** = 1.4:1.

However, the unexpected elimination may potentially serve as central pyridine cores of other thiopeptides GE2270A,[162,163] promothiocin A,[164] amythiamicin A,[165-167] microccocin P[168-170] or their analogs in the future. For example, pyridine **235** could be used for the synthesis of dimethyl sulfomycinamate **237**[156,171] by oxazole formation.



235 **237**

Figure 3-7. A potential access to dimethyl sulfomycinamate **237**.

Overall, the thermal cycloaddition of **164** and **121** proved optimal and was used for further studies.

3.3.2 Thiazole annulation.

In order to achieve a thiazole annulation via a Hantzsch reaction, a regioselective α-bromination of the methyl ketone had to be realized. Initially, the hydroxypyridine **233a** was protected and the silyl enol ether **238** was formed in one operation with TIPSOTf. It was found the bromoketone **239** was not stable on silica gel, so *in situ* generated bromoketone **239** had to be used directly in the next step after CH_2Cl_2 extraction. Unfortunately, the thiazole **240** was formed in poor yield and the 4-brominated thiazolyl pyridine **239a** was detected as a major side product (figure 3-8).

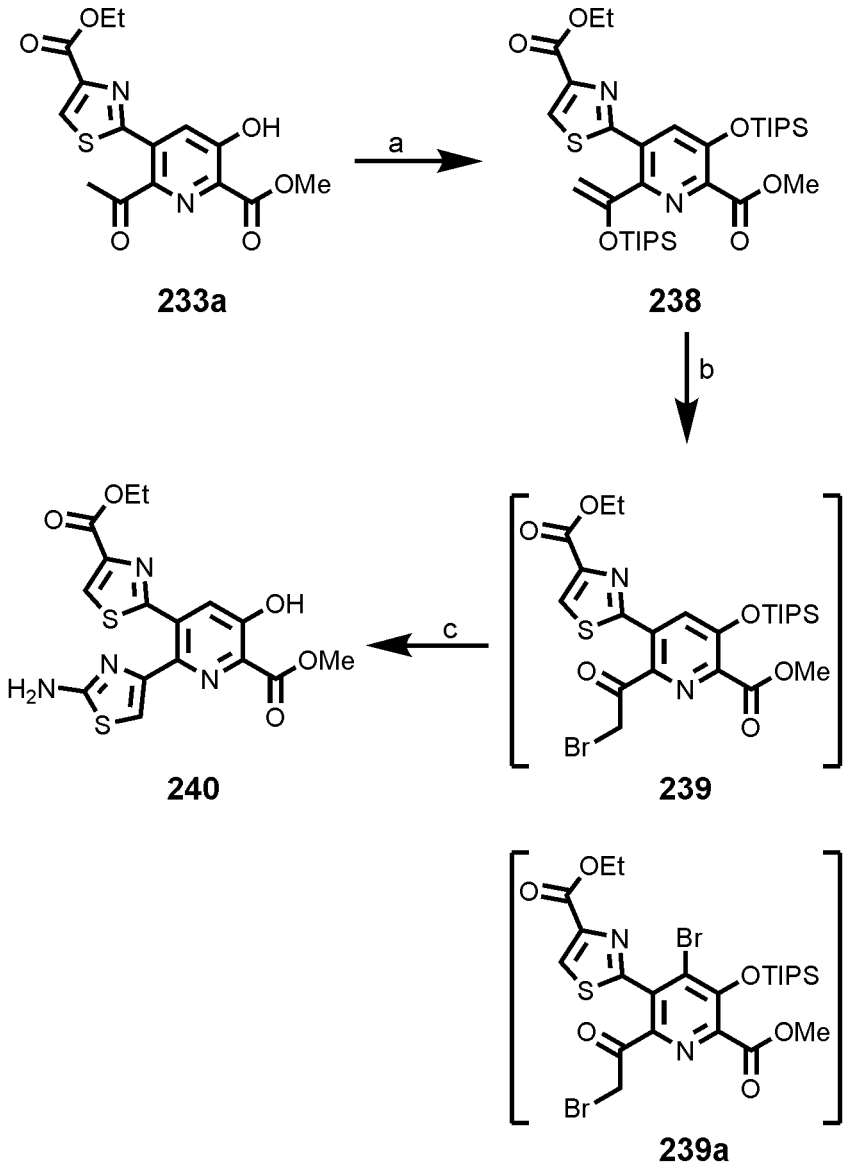
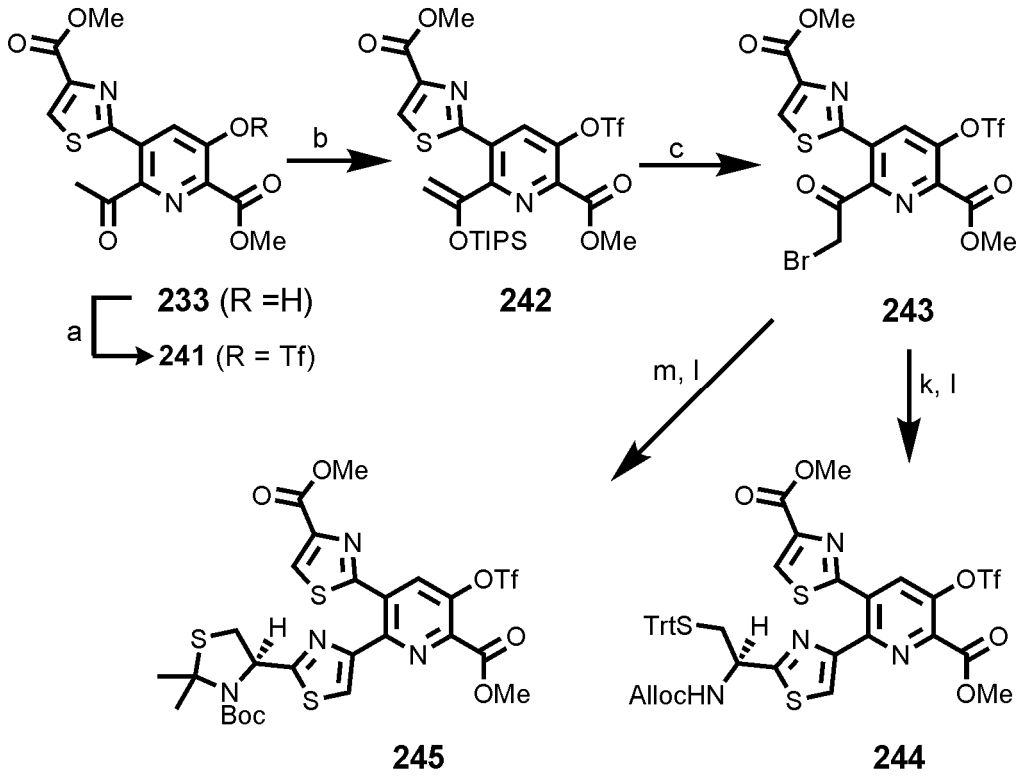


Figure 3-8. Model study toward the Hantzsch annulation. a) TIPSOTf, lutidine, CH_2Cl_2, 0°C ~ R.T., 81%; b) NBS, THF/H_2O = 3:1, R.T.; c) thiourea, EtOH, 26% (over two steps).

Different solvent mixtures were screened for the bromination reaction (THF, THF/pH 7.0 phosphate buffer = 1:1, THF/MeOH/pH 7.0 phosphate buffer = 5:4:1, THF/saturated $NaHCO_3$ = 9:1, etc), but none of the tested solvents allowed selective bromination (NMR of the reaction mixture showed several side products). The bromination reaction in solvent mixture (THF/pH 7.0 phophate buffer = 1:1) indicated doubly and triply brominated products.
Apparently, steric blockade of the 3-hydroxy group by TIPS was not sufficient to suppress electrophilic bromination of the pyridine core.

Based on this observation, further investigation focused on deactivating the 3-hydroxypyridine **233**. It was assumed that triflate formation should be sufficient to suppress the bromination on the pyridine ring. The ketone was then activated as a silylenol ether (**242**) to ensure regioselectivity. As shown in figure 3-9, the bromoketone **243** was obtained regioselectively in excellent yield. Notably, the electron poor pyridine **243** was found to be isolable, indicating a much reduced nucleophilicity of the pyridine nitrogen.This set the stage for a mild Hantzsch reaction.[128] Toward this end, thioamide **248** with orthogonal protecting groups was chosen. Cysteine **246** was protected with trityl[172] and alloc groups[173] to give the cysteine derivative **247**. DCC mediated activation as an OSu ester, followed by amide formation with ammonia gave the amide in excellent yield. Treatment of the amide with Lawesson's reagent delivered the thioamide **248**.alternatively, the thioamide **250** was synthesized following a reported procedure from **246** and acid **249**.[174] After careful experimentation, it was found that the bromoketone **243** had to be used for alkylation of the thioamides immediately. Dehydration with trifluoroacetic anhydride (TFAA) then cleanly delivered the nosiheptide pyridine cores **244** and **245** in good yields.



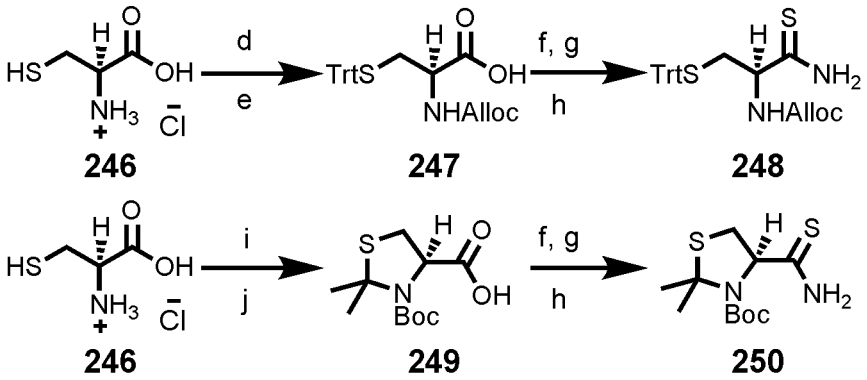


Figure 3-9. Thiazole annulation. a) Tf_2O, NEt_3, CH_2Cl_2, 0°C ~ R.T., 80%; b) TIPSOTf, NEt_3, CH_2Cl_2, 0°C ~ R.T., 99%; c) NBS, THF/pH 7.0 phosphate buffer = 6:1, 97%; d) TrtCl, DMF, R.T., 48h, 66%; e) AllocCl, 2M NaOH, 1h, 99%; f) HOSu, DCC, THF, 0°C ~ R.T., 6h; g) NH_4OH, ethyl acetate, 99%; h) Lawesson's reagent, CH_2Cl_2, R.T., 12h, 74%; i) acetone, reflux, 5h, 99%; j) $(Boc)_2O$, DIPEA, CH_3CN, 58%; f, g) 98%, h) 92%; k) **248**, $KHCO_3$, THF, - 40°C ~ R.T., 48h; l) TFAA, 2,6-lutidine, -20°C, 69%; m) **250**, $KHCO_3$, THF, - 40°C ~ R.T., 48h; l) 60%.

An X-ray structure was obtained of pyridine triflate **241** (figure 3-10). It showed clearly that the acetyl group was located on the 6th position of the pyridine ring, which confirmed our previous assignment by 2D-NMR.

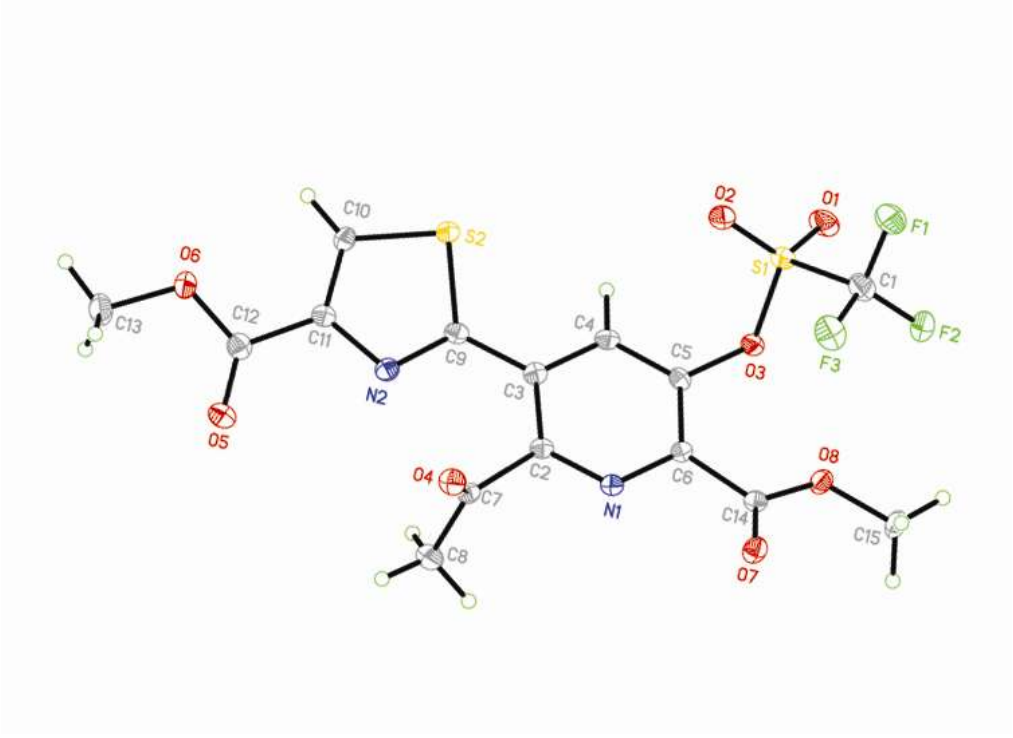
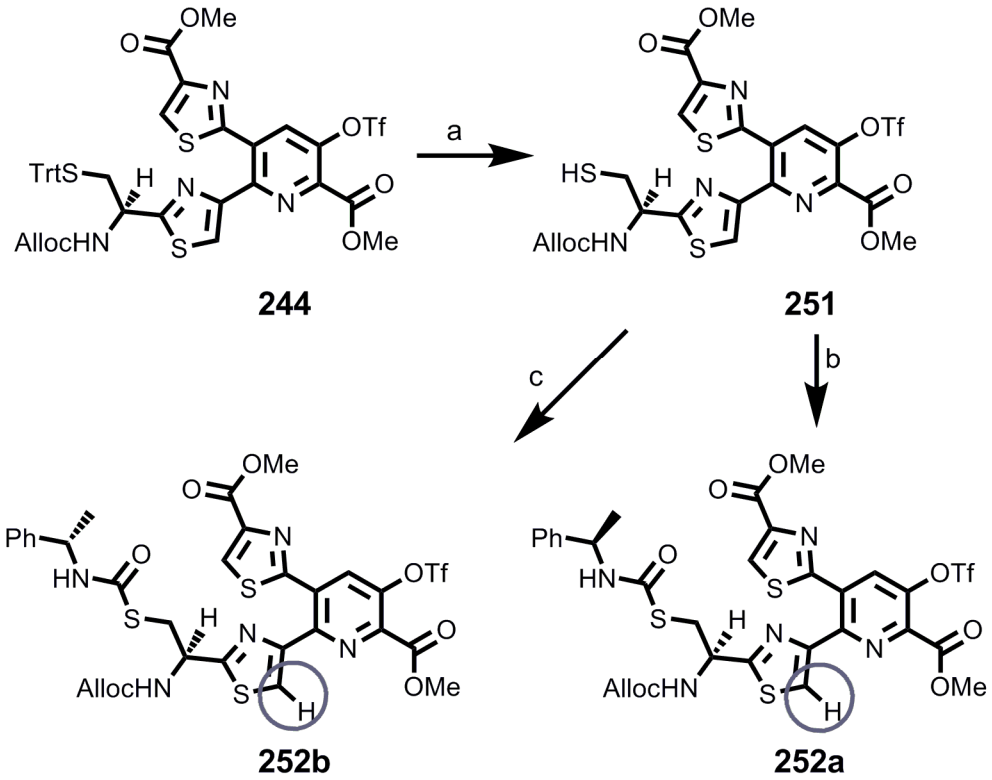


Figure 3-10. X-ray structure of hydroxypyridine **241**.

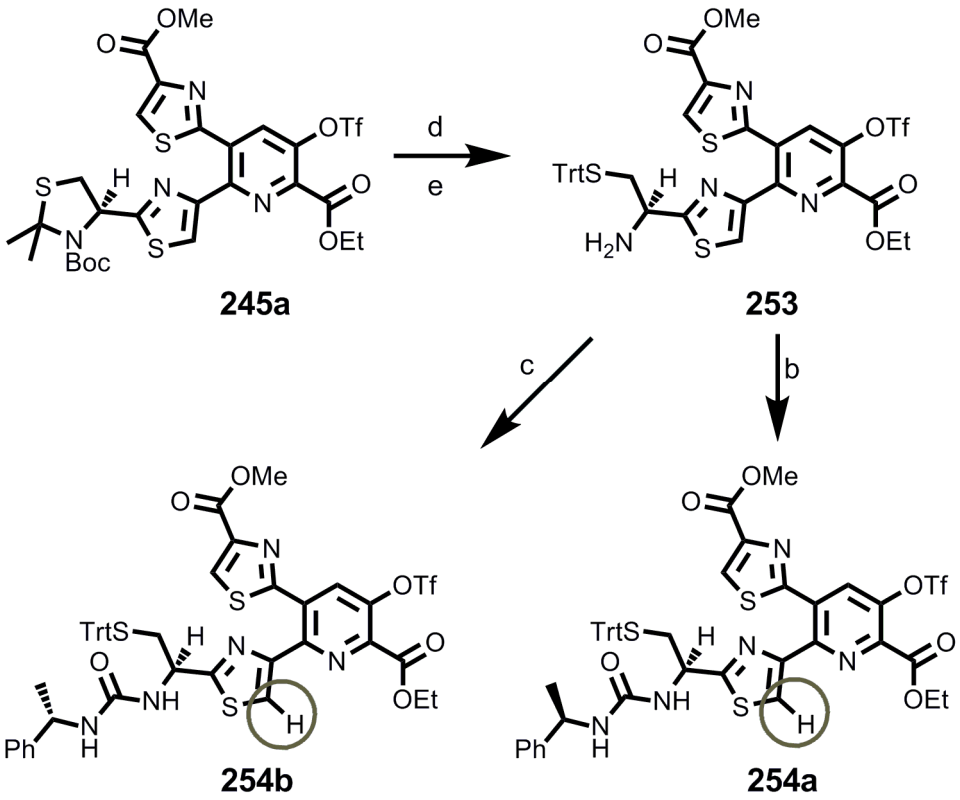
3.3.3 Enantiomeric excess (ee) determination.

The enantiomeric excess (ee) of chiral molecules can be determined by ^{1}H-NMR.[175] The ee of pyridine **244** was determined by trityl-group cleavage and derivatization with (*R*)- and (*S*)-phenylethyl isocyanate (figure 3-11, **A**). After determining the ee of pyridine **244** (60-85%), it was evident that the cysteine derivative racemized potentially during the Hantzsch annulation. A solution was found with the ketal-protected thioamide **250**: the ee of pyridine **245a** was sufficient optically pure (>96% ee) after derivatization (figure 3-11, **B**). A ^{1}H-NMR spectrum of pyridine derivative **254b** is shown in figure 3-11 (**C**). Importantly, conducting the reaction on larger scale (>10 mmol) did not compromise the outcome. It was reported[176] that, compared with other α-amino acids, pseudo-prolines (ketal protected serine, threonin and cysteine derivatives) have, like proline itself, a much lower tendency to reacemize at the α–carbon. The beneficial robustness of the cysteine building block **250** can be tentatively explained by A^{1,3}-strain arguments,[177] which synergistically disfavor a planarized enol(ate) intermediate and hence help to suppress racemization.

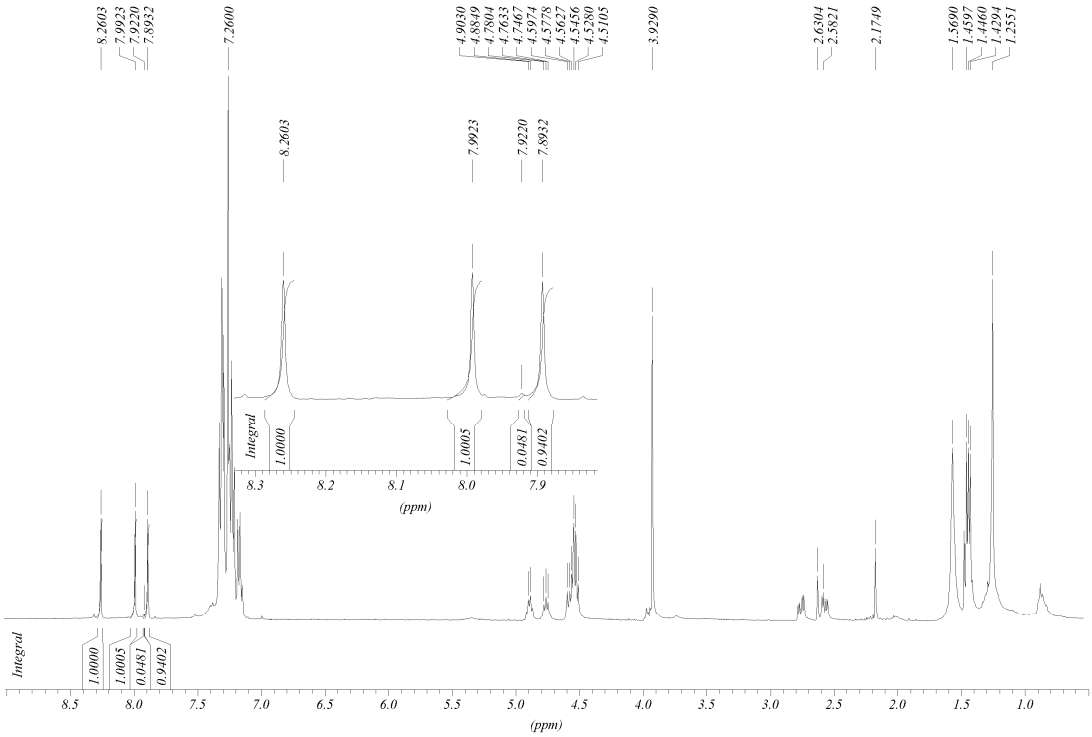
A



B


OMe
OTf
OEt
Boc
TrtS
H_2N
NH
Ph
d
e
c
b
245a
253
254b
254a

C


8.2603
7.9923
7.9220
7.8932
7.2600
4.9030
4.8849
4.7804
4.7633
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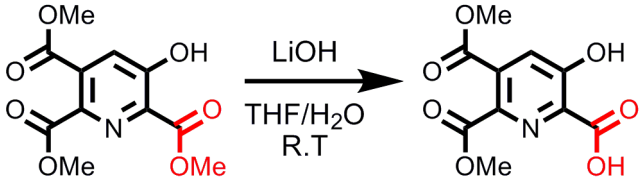
4.5778
4.5627
4.5456
4.5280
4.5105
3.9290
2.6304
2.5821
2.1749
1.5690
1.4597
1.4460
1.4294
1.2551
Integral
1.0000
1.0005
0.0481
0.9402
(ppm)

Figure 3-11. Enantiomeric excess determination. A) ee determination of pyridine **244**; B) ee determination of pyridine **245a**; C) 1H-NMR of **254b**. a) 5% TFA, Et_3SiH, CH_2Cl_2, 30min; b) (*R*)-phenylethyl isocyanate, pyridine, CH_2Cl_2, 10h, 48%; c) (*S*)-phenylethyl isocyanate, pyridine, CH_2Cl_2, 10h, 54%; d) 20% TFA, Et_3SiH, CH_2Cl_2, 1h; e) TrtCl, DMF, 48h, 80% (2 steps).

3.3.4 Regioselective hydrolysis.

To attach the third thiazole ring to hydroxypyridine **244**, a regioselective hydrolysis of a single methyl ester had to be achieved to furnish **258**. To realize this, hydroxypyridine **143** was studied as a model for regioselective hydrolysis. Surprisingly, only one methyl group was cleaved with 2 equivalent of LiOH. ^{1}H-NMR analysis indicated that presumably the methyl ester at 2nd position was hydrolyzed (for confirmation, *vide infra*).



143 **255**

Figure 3-12. Pyridine **143** hydrolysis.

Promoted by this successful transformation, pyridine **244** was treated with 1 equivalent LiOH (figure 3-13). However, three products (**256**, **257** and **258**) were found in this case, and hydroxypyridine **256** was the major product among them. This indicated that the triflate protecting group was highly labile to nucleophilic base.

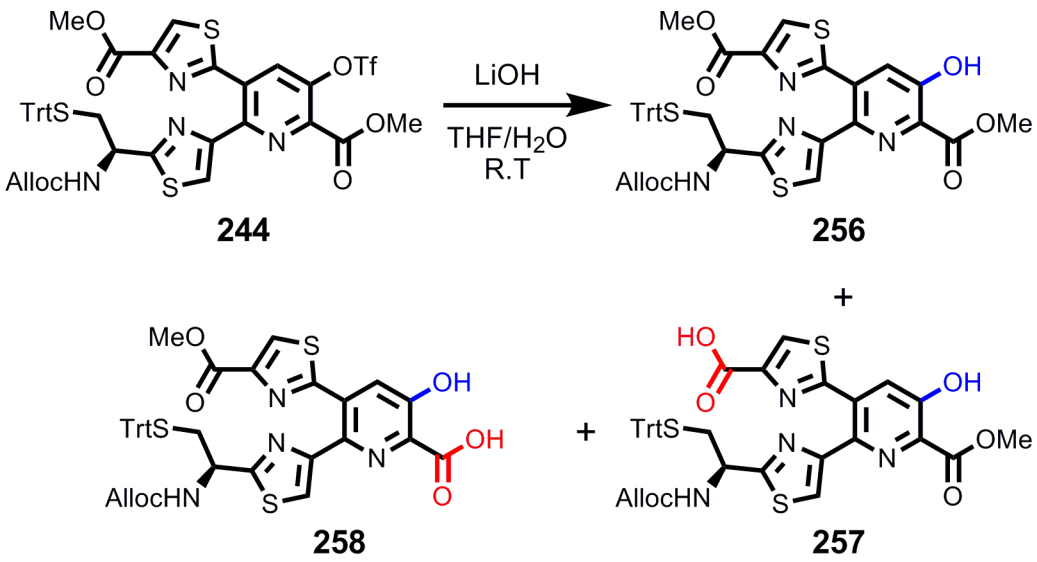


Figure 3-13. Hydrolysis of **244** with LiOH.

In order to differentiate the two methyl esters in **244** and determine the regioselectivity, pyridines **244a** and **245a** were designed and synthesized (figure 3-14). The synthetic route was identical to the pyridines **244** and **245**. Compared to hydroxypyrine **233**, hydroxypyridine **259** was obtained in lower yield, but with slightly better regioselectivity.

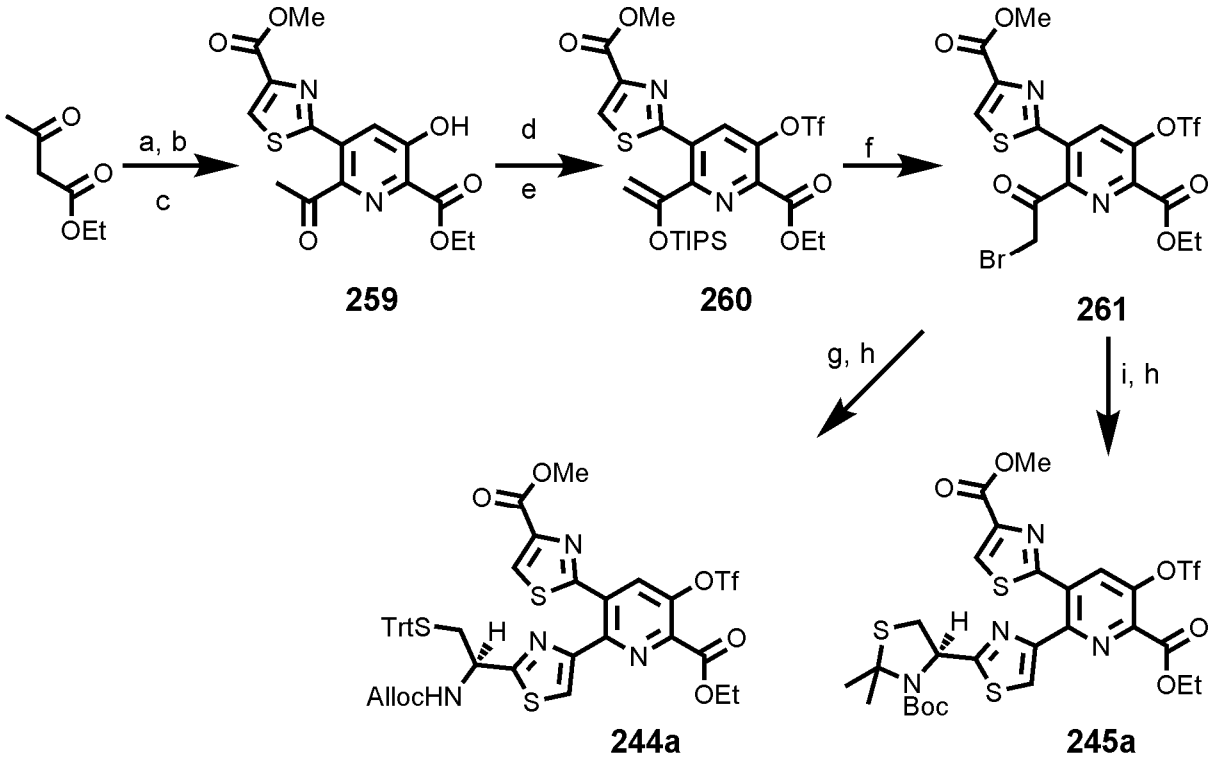
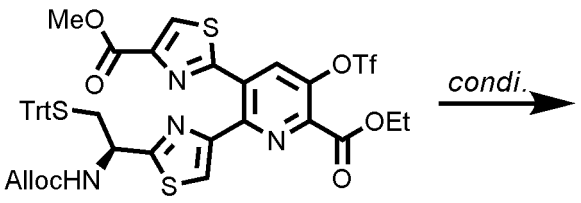


Figure 3-14. Preparation of pyridine **244a** and **245a**. a) $NaNO_2$, CH_3COOH, 0°C ~ R.T., 99%; b) TMSCl, Et_3N, CH_3CN; c) toluene, 180°C, 3h, 56% (**259/259a** = 2.6:1); d) Tf_2O, NEt_3, CH_2Cl_2, 0°C ~ R.T., 33%; e) TIPSOTf, NEt_3, CH_2Cl_2, 0°C ~ R.T., 91%; f) NBS, THF/pH 7.0

phosphate buffer = 6:1; g) **248**, $KHCO_3$, THF, - 40°C ~ R.T., 48h; h) TFAA, 2,6-lutidine, -20°C, 66% (over 3 steps); m) **250**, $KHCO_3$, THF, - 40°C ~ R.T., 48h; l) 60% (over 3 steps).

The non-selective hydrolysis shown in figure 3-13 might be as a result of strong nucleophilic base. Therefore, the hydrolysis of pyridine **244a** was studied at three different pH values (8.5, 9.0, 10; HCO_3^-/CO_3^{2-} buffers were used). It was found that pyridine **244a** was fully converted after 6h at 60°C with no regioselectivity (table 3-2, entry 1-3); fully deprotected pyridine (methyl, ethyl and Tf were cleaved) was observed when the pH was raised (entry 3). Reduced reaction time and lowered reaction temperature increased the ratio of hydroxypyridine **256a** (entry 4-7), but a complete regioselective hydrolysis could not be achieved under these conditions. Another buffer system (dioxane/NH_4OH = 2:1, pH 10) converted the pyridine **244a** to amide **263** in excellent yield, but attempts to form a thioamide (which could potentially be used for Hantzsch annulation to attach the third thiazole) from amide **263** with Lawesson's reagent were not successful. It was found after careful experimentation that pyridine **244a** could be cleanly deprotected to hydroxypyridine **256a** with 2 equivalents *n*-Bu_4NOH in dioxane.[178] The desired pyridine acid **258** was obtained in moderate yield with more *n*-Bu_4NOH (another 2 equivalent).



244a

256a (R^1 = Me, R^2 = H, R^3 = OEt)
257a (R^1 = R^2 = H, R^3 = OEt)
258 (R^1 = Me, R^2 = H, R^3 = OH)
262 (R^1 = R^2 = H, R^3 = OH)
263 (R^1 = Me, R^2 = H, R^3 = NH_2)

entry	condition	products
1	pH 8.5, 60°C, 6h	**256a**:**258** = 3:2
2	pH 9.0, 60°C, 6h	**256a**:**258**:**262** = 2:5:1
3	pH 10.0, 60°C, 6h	**258**:**262** = 1:2
4	pH 10.0, 60°C, 1h	**256a**:**258** = 1.3:1
5	pH 10.0, 60°C, 30min	**256a**:**258** = 3.6:1
6	pH 10.0, 40°C, 30min	**244a**:**256a** = 1:2.4
7	pH 10.0, 40°C, 40min	**244a**:**256a**:**258** = 1:7:1

8	dioxane/NH_4OH[a], 60°C, 90min	78% (**263**)
9	dioxane, *n*-Bu_4NOH, R.T., 40min	50% (**258**)

Table 3-2. Hydrolysis by pH control. [a] aqueous ammonium solution (25-30%).

The low efficiency of pyridine acid **258** formations promoted us to investigate a regioselective hydrolysis. Lewis acids and/or other soft nucleophlic catalyzed/mediated hydrolysis was speculated to enable delevering the pyridine acid **258** specifically.

Mild hydrolysis mediated by lewis acids and iodide using LiI[179] and ZnI_2 were screened, but LiI decomposed the starting pyridine **244** (1.5 eq. LiI, DMF, 120°C); ZnI_2 showed no reactivity under the same condition. Reducing agents ($NaBH_3CN$, $LiBH_4$)[180] showed no selectivity. Copper nitrate had been reported to selectively cleave 2- or 6-esters on pyridine rings by chelation of the N1 nitrogen and the carbonyl group of the ester.[180] In our attempt, the trityl group was chemo-selectively deprotected and formed a disulfide quantatively when copper nitrate was applied (figure 3-15). A radical oxidation pathway might be involved in this transformation.

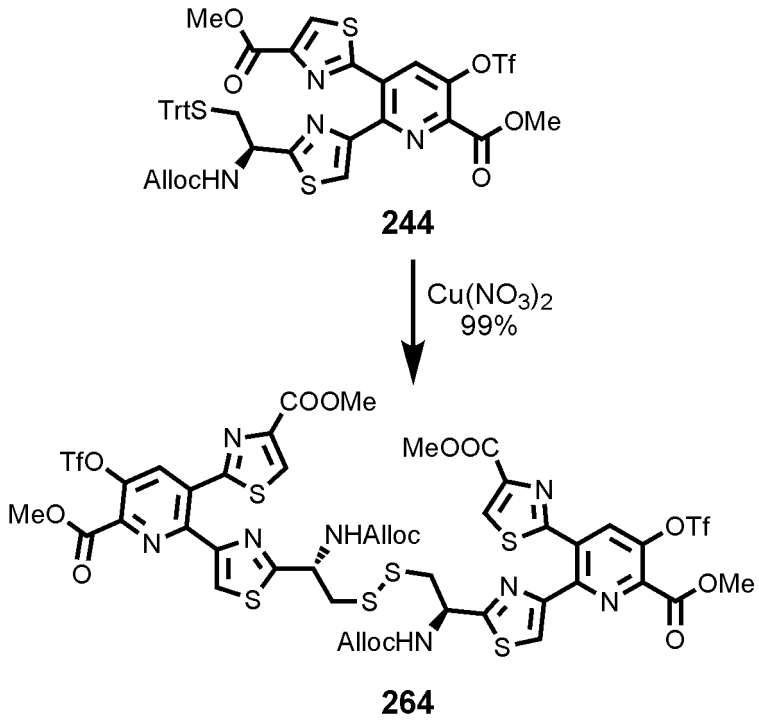


Figure 3-15. Trityl deprotection mediated by $Cu(NO_3)_2$.

These negative observations promoted us to investigate different reaction modes. Instead of the pyridine nitrogen, the free 3-hydroxyl group might direct the hydrolysis as well. To test

for this, pyridine **244** was deprotected with NaOMe to afford hydroxypyridine **256** quantitatively (figure 3-16).

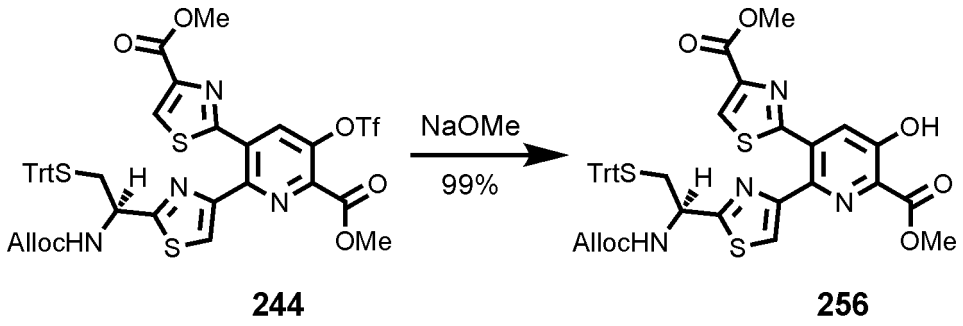
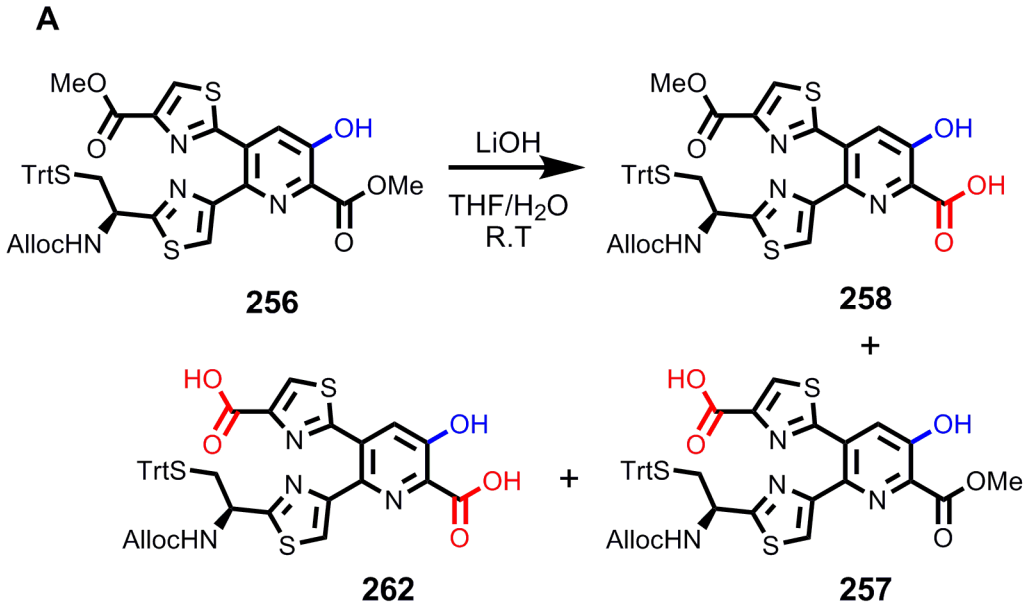


Figure 3-16. 3-Hydroxypyridine formation.

Hydroxypyridine **256** was treated with 2 equivalents of LiOH (figure 3-17, **A**). The HPLC analysis (figure 3-17, **B**) showed almost no regioselectivity: The desired acid **258** was only slightly favored over the other two products (HPLC trace).



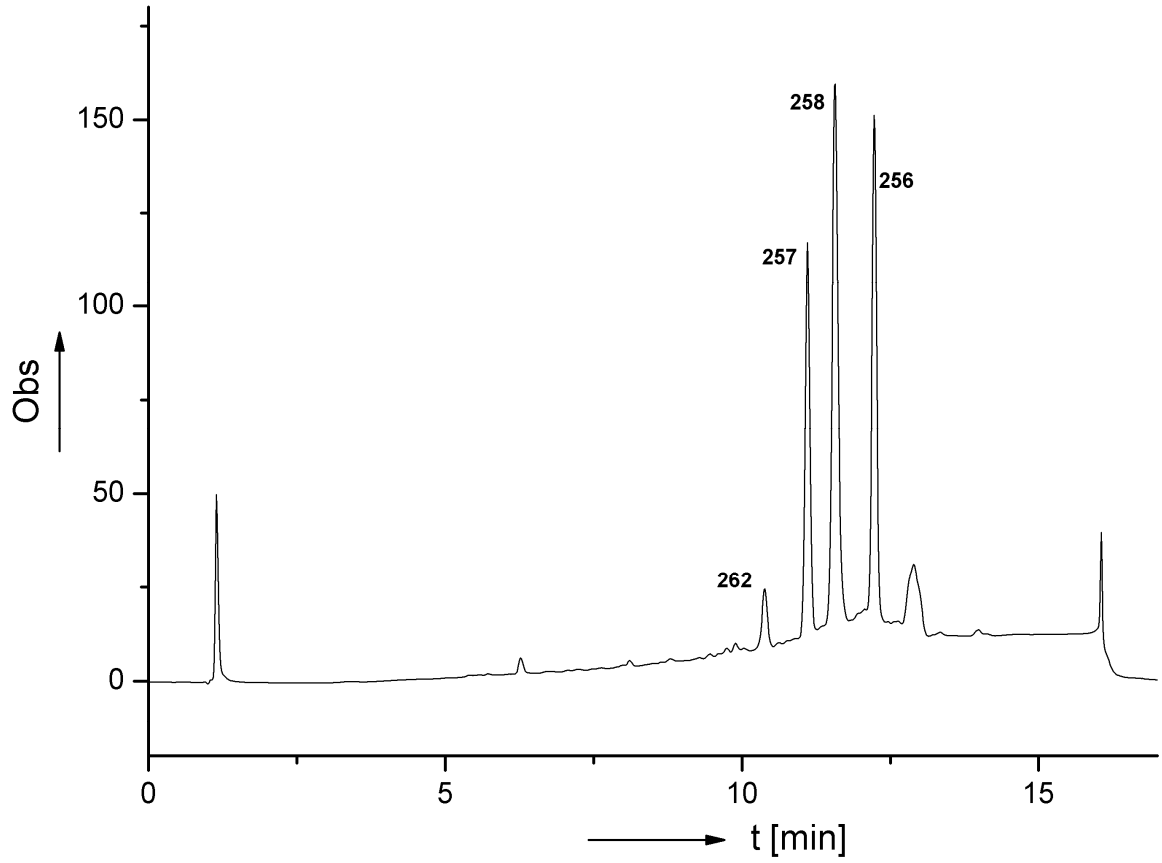
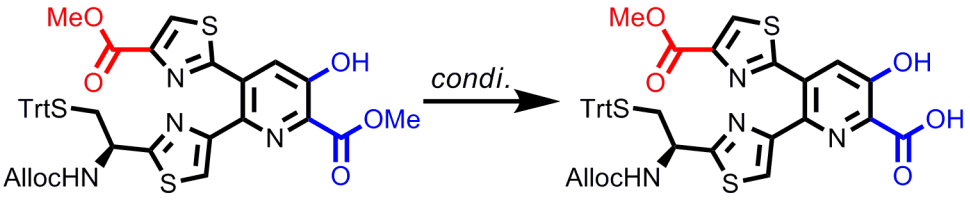


Figure 3-17. Hydroxy directed hydrolysis with LiOH.

A detailed screening for Lewis acid catalyzed regioselectively hydrolysis was then conducted. Results are shown in table 3-3. Initially, bis(tributyltin) oxide (BBTO)[181] was expected to regioselectively mediate the hydrolysis, but it decomposed the starting material and led to many undetectable side products (entry 1); dibutyltin oxide (DBTO) is known to form a dibutylstannylene acetal intermediate with diols, thereby enhancing regioselectivity in ether or ester formations.[182] Theoretically, the DBTO could coordinate with the hydroxyl and carbonyl groups (table 3-3, blue color) and form a dibutylstannylene acetal intermediate. Interestingly, this transformation did work well on small scale (**256** < 20 mg), but decomposition of the hydroxypyridine **256** was observed upon scaling up (entry 2), and the tin reagent was difficult to separate from the product. Interestingly, transesterification (entry 3) occurred when $Ba(OH)_2$ was applied (*vide infra*).



256 **258**

entry	reagent	condition[a]	yield
1	2 eq. BBTO	toluene, 80°C, 24h	decomp.
2	1 eq. DBTO	dioxane/H_2O, 80°C, 24h	decomp.[b]
3	0.5 eq. $Ba(OH)_2$	isopropanol/H_2O = 200:1, R.T.	transesterification
4	1 eq. $Yb(OTf)_3$	dioxane/H_2O, R.T.	no conversion
5	1 eq. $Sc(OTf)_3$	dioxane/H_2O, R.T., 24h	>60% conversion
6	1 eq. $Sc(OTf)_3$	DMSO/H_2O = 100:1, R.T.	slow conversion
7	50% $Sc(OTf)_3$	dioxane/H_2O = 100:1, R.T.	slow conversion
8	50% $Sc(OTf)_3$	dioxane/(s)$NaHCO_3$ = 100:1, R.T.[c]	<10% conversion
9	1 eq. $Sc(OTf)_3$	dioxane/H_2O, 40°C, 3 days	53%
10	1 eq. $Sc(OTf)_3$	dioxane/H_2O, 60°C, 18h	76%[d]
11	**1 eq. $Sc(OTf)_3$**	**dioxane/H_2O, 60°C, 15h**	**92%[e]**
12	5% $Sc(OTf)_3$	dioxane/H_2O, 110°C, 19h	decomp.
13	20% $Sc(OTf)_3$	dioxane/H_2O, 110°C, 7h	slow conversion
14	**5% $Sc(OTf)_3$**	**dioxane/H_2O, pH 8.5, 60°C, 9h**	**93%**

Table 3-3. Regioselective hydrolysis. [a] dioxane/H_2O = 2:1, pH = 4.3 ~ 4.5 without buffer; [b] clean conversion in small scale (<20 mg), decomposition observed when more than 20 mg; [c] 21h, [d] [**256**] = 3.6 mmol/L; [e] [**256**] = 9.1 mmol/L.

Transition metal triflates have been reported to enable ester hydrolysis under forcing conditions, but have been not well explored.[183] Different transition metal triflates were screened. Among them, $Yb(OTf)_3$ did not show any activity in the hydrolysis (entry 4), but $Sc(OTf)_3$ cleanly hydrolyzed the methyl ester at the 2nd position on the pyridine ring at room temperature (entry 5). Reducing the water content, change of the organic solvent, and decreasing amounts of $Sc(OTf)_3$ led to slow conversion (<10%) (entry 6-8); elevating the temperature delivered the desired acid **258** in good yield (entry 9); further increase of temperature and increasing the concentration enhanced the conversion dramatically and showed no side effect on the regioselectivity (entry 10, 11). From these results, hydrolysis

could be achieved with catalytic amount of $Sc(OTf)_3$, but pyridine **256** was decomposed with 5% catalyst at high temperature for long reaction time (entry 12). After examining the pH value of the reaction mixture, it was found that the pH value was 4.3 with 1 equivalent $Sc(OTf)_3$, 4.5 with 50% of $Sc(OTf)_3$, and 5.0 with 5% of $Sc(OTf)_3$. The nucleophilic attack by water might be retarded (entry 12, 13) at these slightly acidic conditions, which might also be the reason that 1 equivalent of $Sc(OTf)_3$ was essential. Adjusting the pH value to 8.5 with saturated $NaHCO_3$ solution, 5% $Sc(OTf)_3$ at 60°C was sufficient to deliver the desired acid **258** in excellent yield and complete regioselectivity.

The regioselectivity of **258** from the $Sc(OTf)_3$ catalyzed hydrolysis was determined by coninjection (analytical HPLC and LC-MS) of pyridine acid **258** from **244a** (table 3-2).

3.3.5 $Sc(OTf)_3$ catalyzed reactions.

In our effort to synthesize the nosiheptide hydroxypyridine acids **258**, Scandium triflate had been found to catalyze ester hydrolysis in a chemo- and regioselective fashion. Interestingly, $Sc(OTf)_3$ catalyzed hydrolysis, transesterification and transamidation is not well explored.[183] Therefore, a range of nucleophiles was tested in this transformation.

As shown in figure 3-18, pyridine monoacid **225**, transamidation product **255c**, transesterification product **255a** and allyl alcohol **255b** could be prepared in a complete chemoselective fashion with excellent yields. Alcohols like phenol and *tert*-butanol did not undergo the transesterification reaction as a result of low activity and steric hindrance. Only hydrolyzed pyridine acid **255** was detected in these cases.

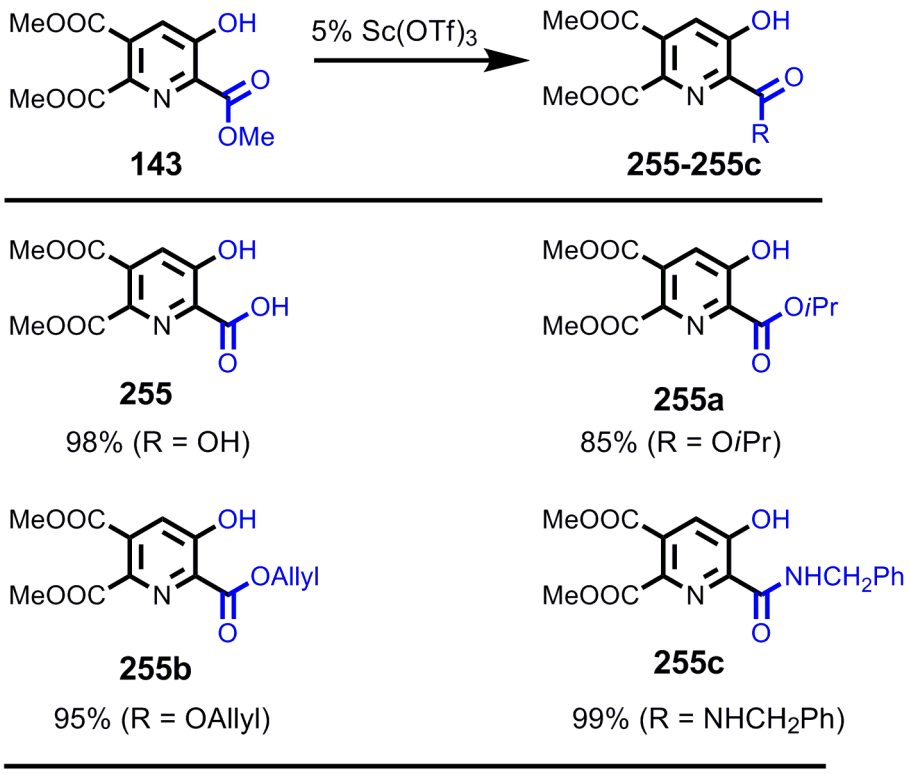
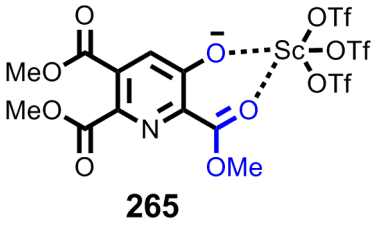


Figure 3-18. $Sc(OTf)_3$ catalyzed reactions.

A plausible transition state **265** is shown in figure 3-19. The 3-hydroxyl group could become deprotonated under slightly basic condition to give a phenolic anion. Scandium triflate could coordinate to the anion and the neighbouring carbonyl group (the hydroxyl and carbonyl group are in the same plane as shown by a crystal structure of **255b**, figure 3-20). Thus should activate the carbonyl group, rendering the methyl ester at the 2nd position more reactive than the others.



265

Figure 3-19. Proposed transition state of $Sc(OTf)_3$ catalyzed reaction.

Further confirmation of this intriguing regioselectivity was obtained by analyzing a crystal structure of hydroxypyridine **255b** (figure 3-20). It clearly showed the transformation occurred at the 2nd position of the pyridine ring, the two methyl esters at 5- and 6-position were not touched.

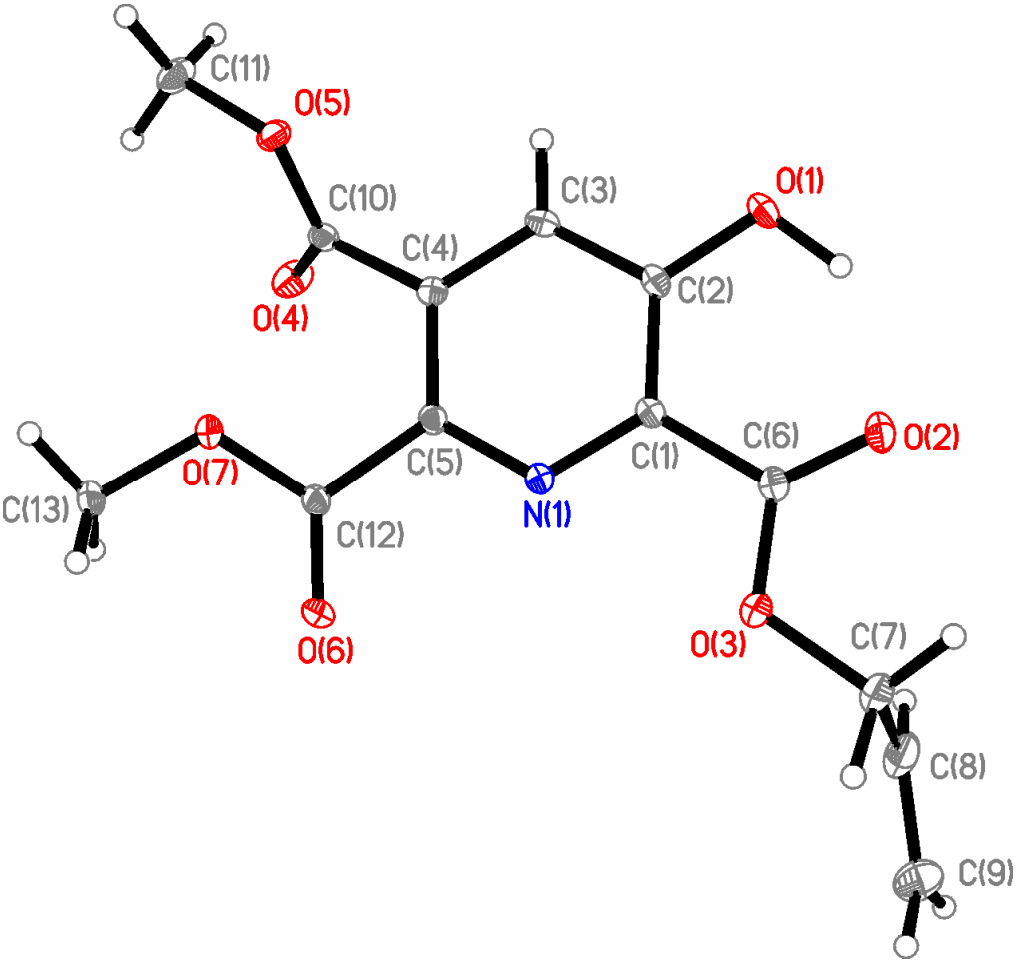


Figure 3-20. X-ray structure of hydroxypyridine **255b**.

3.3.6 Tristhiazolyl pyridine formation.

In order to install the third thiazole ring on the pyridine ring, an aza-Wittig reaction[55,155] seemed promising. To test for this, the dipeptide **272** had to be synthesized (figure 3-21). The TBS protected serine **267** was prepared from **266** by modifying a reported procedure[184] in excellent yield. Subsequent terminal amide formation (→ **268**) and standard Cbz deprotection led to free amine **269** ready for peptide coupling. The cysteine azide **271** was obtained by a modified diazo transfer reaction from **270**.[29] After careful experimentation, it was found that isobutyl chloroformate mediated coupling gave the best conversions to form dipeptide **272** (55%).

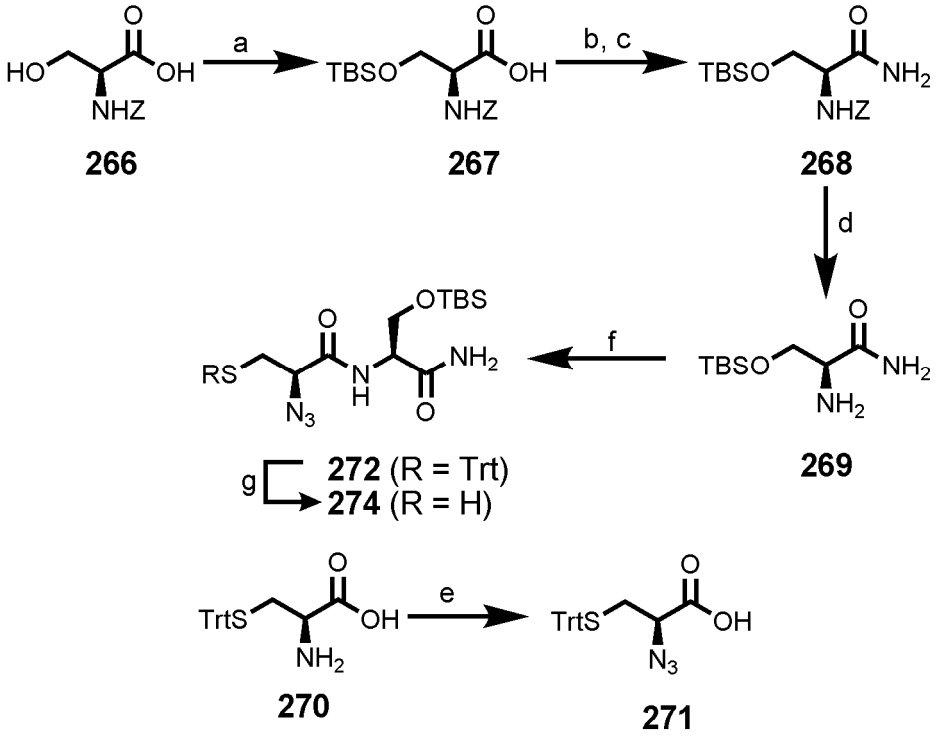


Figure 3-21. Dipeptide formation. a) TBSCl, imidazole, DMF, R.T., 92%; b) HOSu, DCC, THF, 0°C ~ R.T., 16h; c) NH_4OH, ethyl acetate, 0°C, 1h; d) H_2, Pd/C, MeOH, R.T., 12h, 85% (over 3 steps); e) Tf_2O, NaN_3, MeOH/CH_2Cl_2/H_2O, Et_3N, R.T., 12h, 90%; f) **271**, NMM, tBuOC(O)Cl, THF, R.T., 12h, 55%; g) TFA/CH_2Cl_2 = 1:19, 30 min.

The trityl group in **272** was cleaved with 5% TFA in CH_2Cl_2 to deliver free thiol **274**, which was clean enough for thioester formation after the solvent were completely removed. Thiol **274** always needed to be prepared freshly for best results. Simple thioester formation (EDC, HOBt) from **258** was not met with success in this specific case. It was found that pyridine acid **258** could form a cyclic anhydride intermediate **273** with phosgene at low temperature, which could be opened by nucleophilic attack of free thiol **274** if catalytic amounts of DMAP were present. The thioester **275** was unstable to silica gel, therefore, it was directly subjected to an aza-Wittig[155] condensation after work up. Surprisingly, the aza-Wittig reaction worked perfectly in this complex molecule, which even bears a free hydroxyl group at the β-position. After removing the PPh_3, the crude thiazoline **276** could be directly oxidized to give the yellow fluorescent tristhazolyl pyridine **277** with excellent yield (58% over 4 steps) after isolation with normal silica gel column chromatography (figure 3-22).

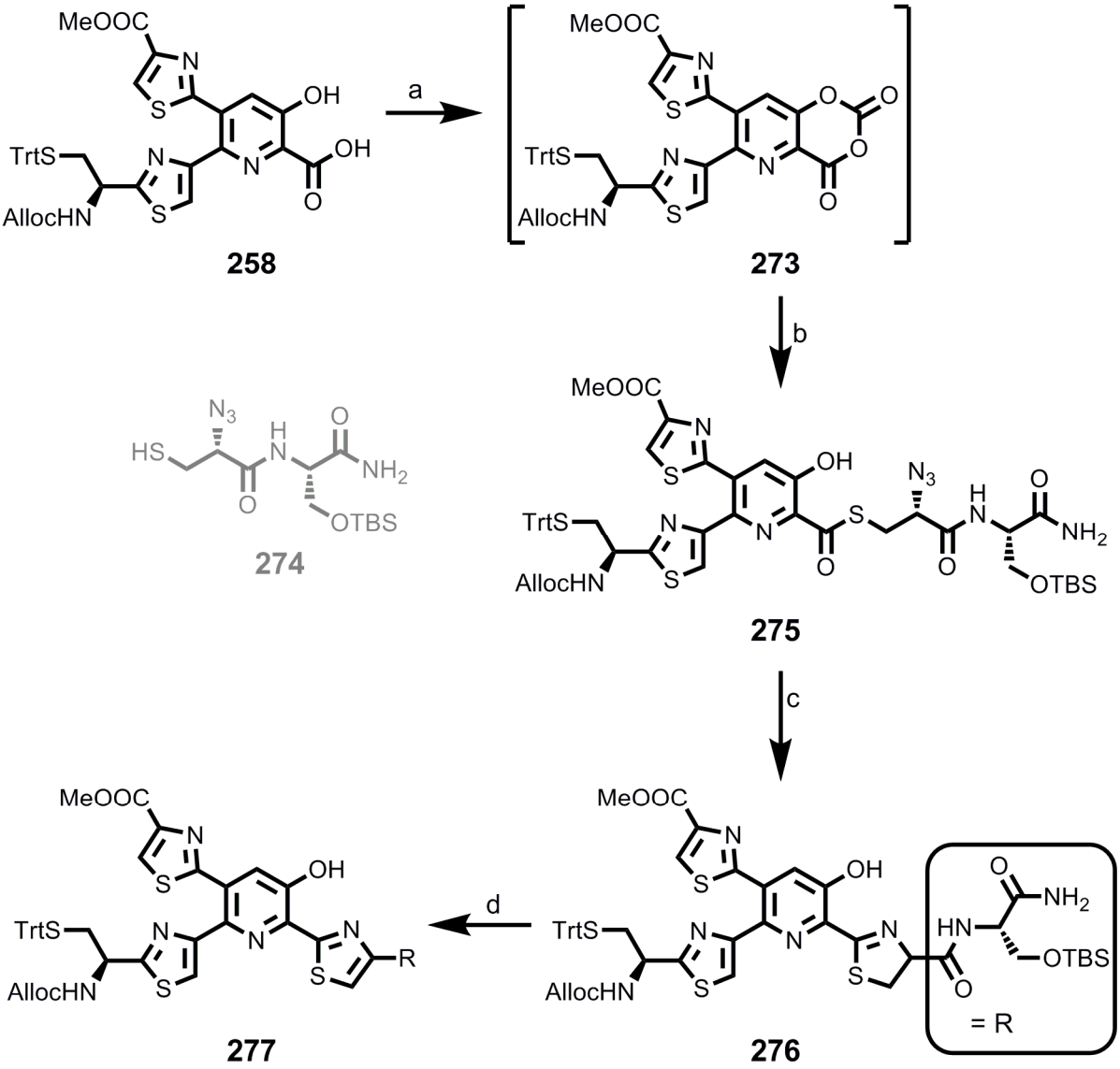
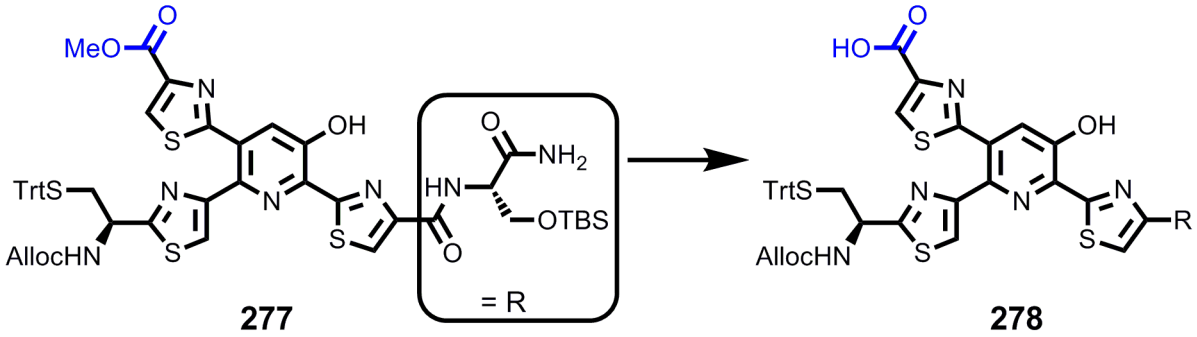


Figure 3-22. Tristhiazolyl pyridine formation. a) $COCl_2$, Et_3N, THF, -40°C ~ 0°C, 4h; b) **274**, DMAP; c) PPh_3, THF; d) $CBrCl_3$, DBU, CH_2Cl_2, - 20°C ~ R.T., 58% (over 4 steps).

3.3.7 Fragment union (generation 1).

Coupling of 277 to peptide building blocks had to be studied next. Initially, pH 12 buffer (THF/H_2O, LiOH) was employed to hydrolyze the methyl ester in **277**, but led to decomposition (table 3-4); further modified conditions gave low conversion. Clean conversion was achieved when applying 4 equivalents of LiOH in THF/H_2O at 0°C. The acid **278** was not stable to silica gel, therefore, it was generated *in situ* and used to the peptide coupling after simple work up to remove the inorganic salt.



entry	condition	conversion
1	THF/LiOH (aq), pH 12, R.T., 12h	decomposition
2	BBTO, DCE, 60°C, 5h	<5%
3	pH 10.0[a], 60°C, 10h	50%
4	2 eq. $Ba(OH)_2$, MeOH/H_2O, R.T., 10h	50%
5	**4 eq. LiOH[b], 0°C ~ R.T., 6h**	**100%**

Table 3-4. Ester hydrolysis of **277**. [a] dioxane/$NaHCO_3$/Na_2CO_3 = 2:1; [b] THF/H_2O = 3:1.

The dithazolyl peptide **279** was prepared by Matthias Riedrich[55] using aza-Wittig reactions.[155] A peptide coupling reaction was attempted with various coupling reagents (figure 3-23), but in all the cases, the acid **278** decomposed, and the starting amine **279** was recovered.

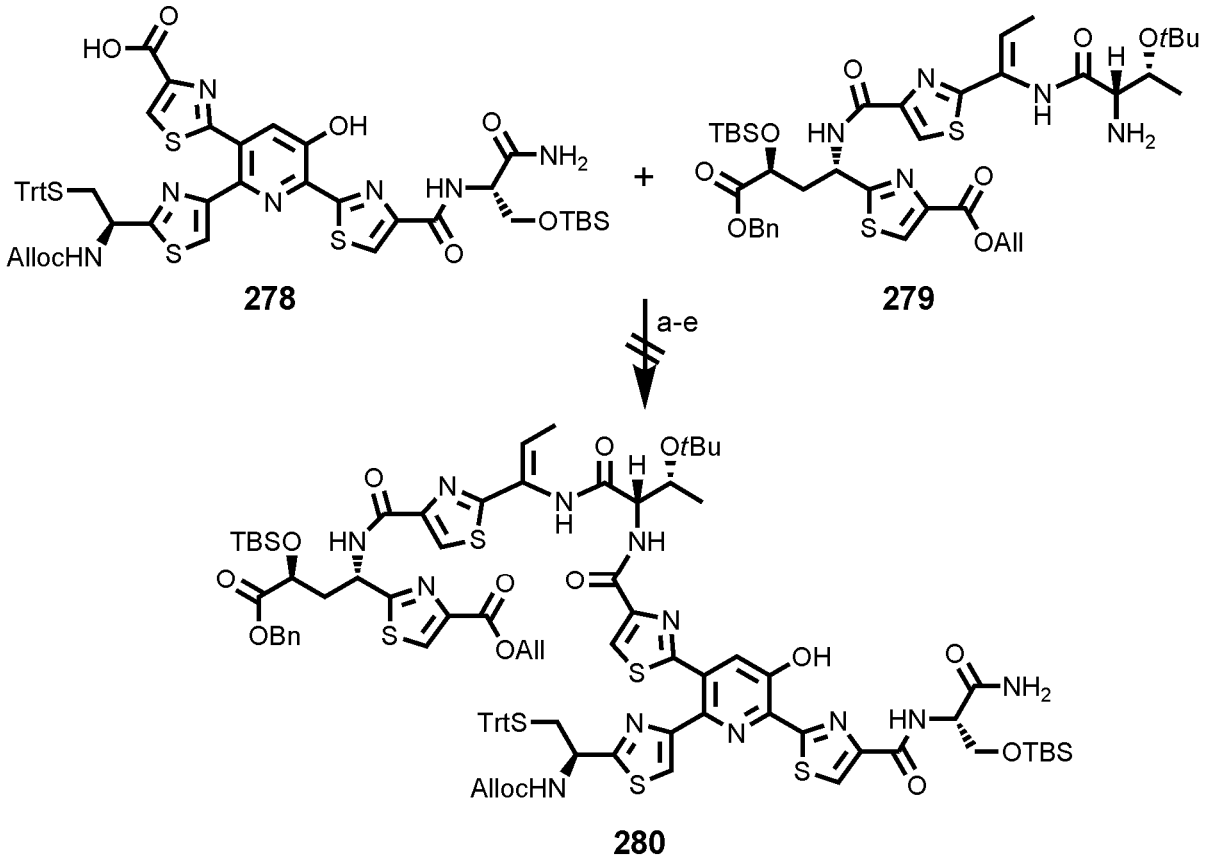


Figure 3-23. Dipeptide formation attempts. a) 1.5 eq. HOBt, 5 eq. TEA, 1.25 eq. EDC, CH_2Cl_2, 0°C ~R.T.; b) 4 eq. HOAt, 2.5 eq. HATU, 3 eq. DIEA, CH_2Cl_2/DMF, R.T.; c) 1.2 eq. HATU, (*cat.* DMAP), DMF, R.T.; d) 1.5 eq. HATU, NMP, 60°C; e) 1.5 eq. PyBOP, DMF, R.T..

The frustrating peptide coupling result promoted us to investigate the reactivity of the acid **278** and amine **279** (figure 3-24). The acid **278** could be fully converted to amide **367** within hours, half conversion was observed in the case of the amine **279**, even with 3 equivalents of HATU (HPLC and LC-MS control). The low reactivity of the amine **279** could be the result of the bulky *tert*-butyl protecting group on the secondary alcohol. Therefore, the *tert*-butyl group was removed to enhance the nucleophilicity of the amine.

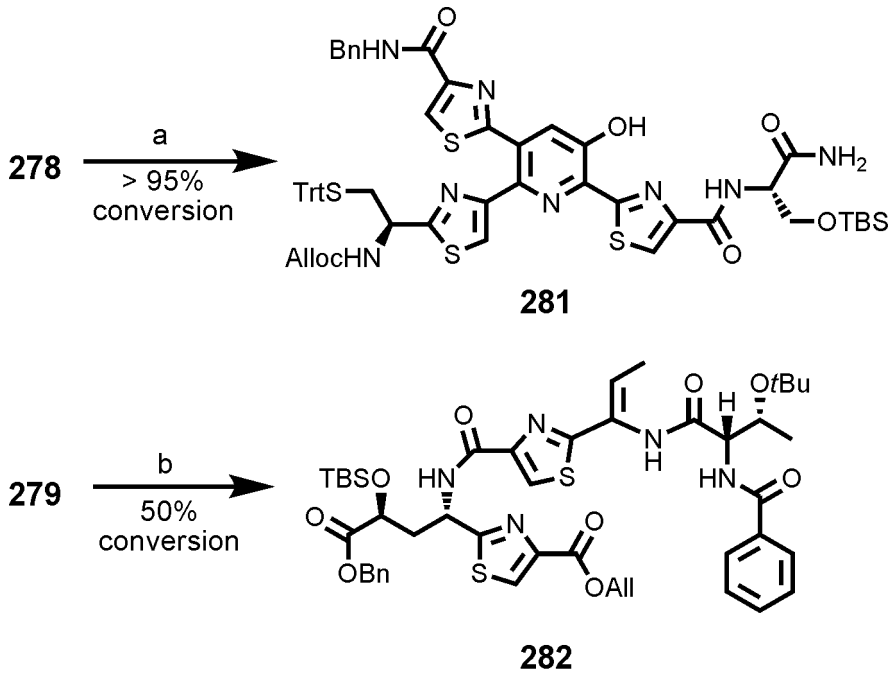


Figure 3-24. Building block reactivity tests. a) 1.2 eq. $BnNH_2$, 1.2 eq. HATU, DMF, R.T., 2h, >95% conversion; b) 3 eq. HATU, 1.6 eq. benzoic acid, 16h, 50% conversion.

3.3.8 Fragment union (generation 2).

As mentioned before, pyridine **244** was partially racemized, therefore it was used as a model system for optimizing the chemistry, including regioselective ester hydrolysis, the aza-Wittig reaction and the peptide coupling. Now enantiopure pyridine **285** (figure 3-25) was synthesized from enantio pure pyridine **245** using the chemistry we developed before. Both

NaOMe and *n*-Bu_4NOH deprotected the triflate quantitively; the Sc-mediated regioselective hydrolysis proceeded cleanly and regioselectively led to the acid **283** ready for one pot thioester formation. The aza-Wittig reaction of crude thioester **284** and subsequent oxidation gave the yellow fluorescent pyridine **285** in excellent yield, and LiOH mediated hydrolysis delivered acid **286** ready for the peptide coupling.

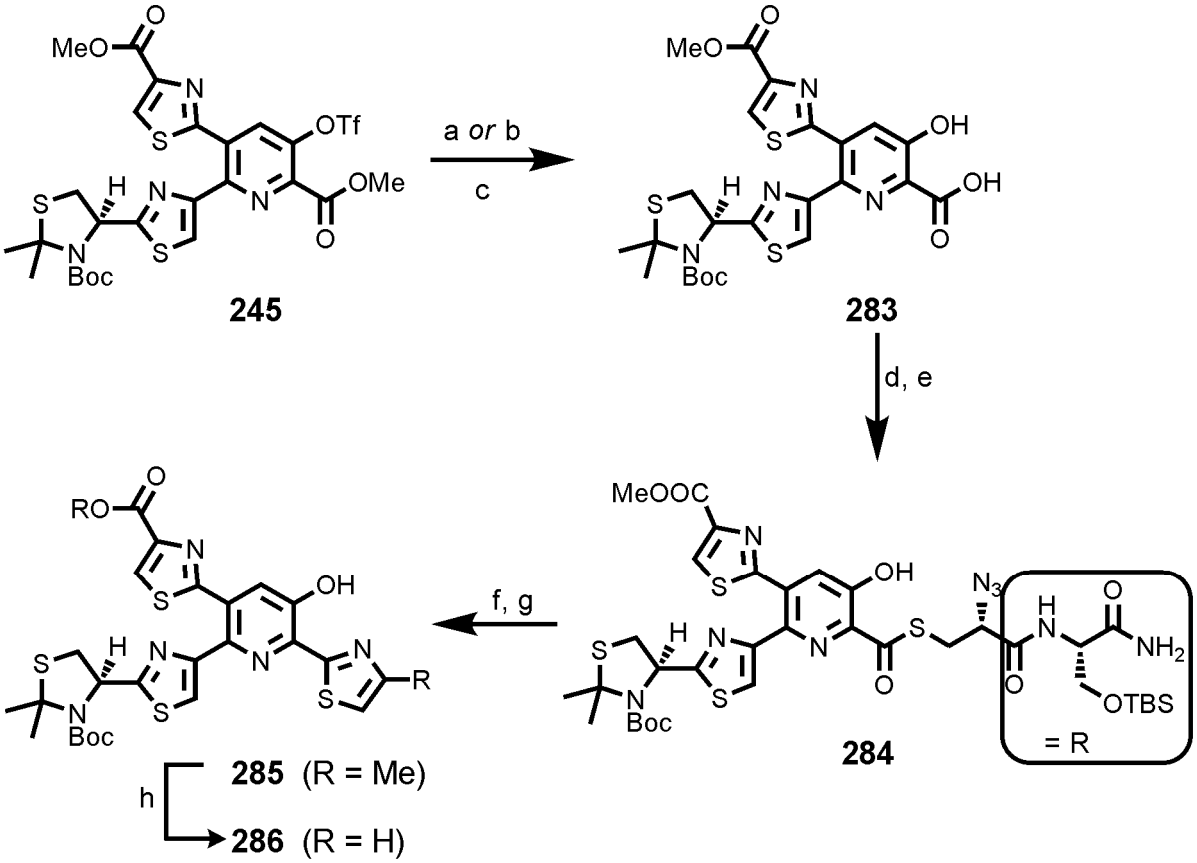
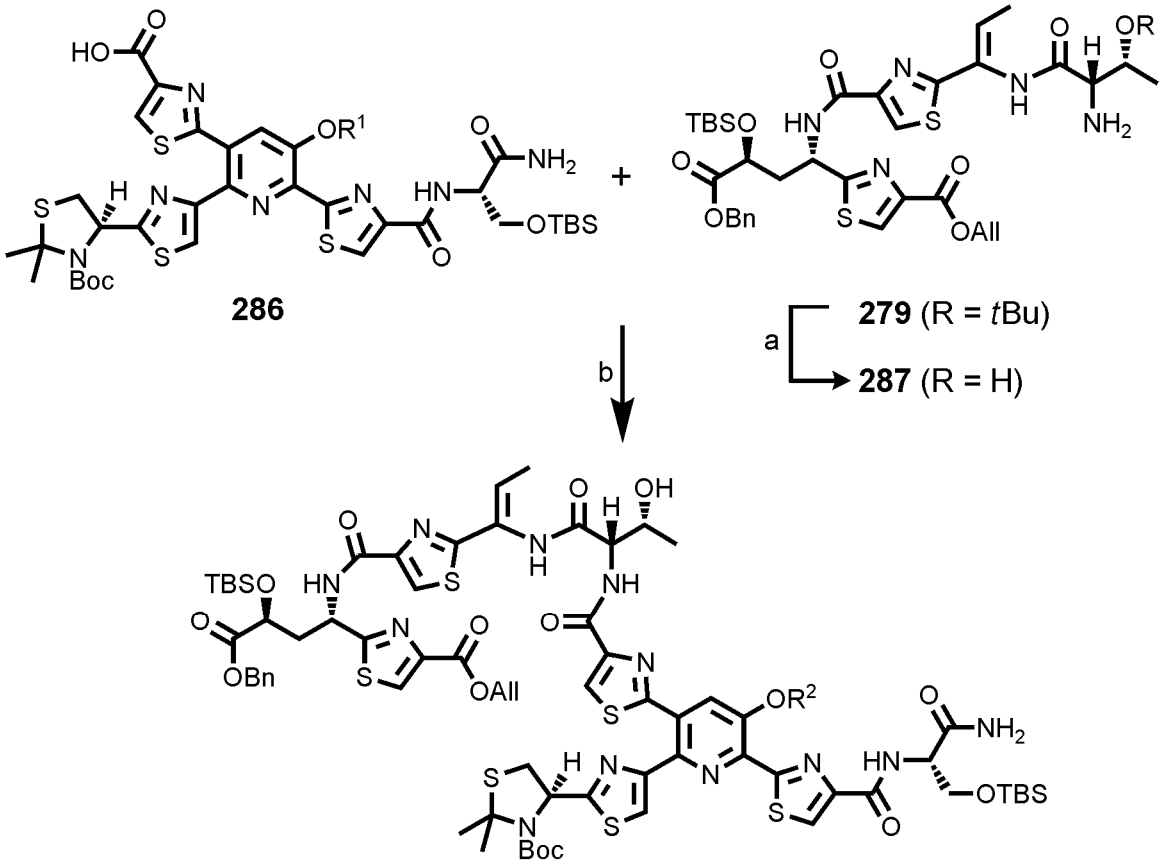


Figure 3-25. Thisthazolyl pyridine formation. a) NaOMe, MeOH, R.T., 99%; b) *n*-Bu_4NOH, dioxane, R.T., 99%; c) 5% $Sc(OTf)_3$, dioxane/H_2O, pH 8.5, 60°C, 90%; d) $COCl_2$, Et_3N, THF, -40°C ~ 0°C, 4h; e) **274**, *cat.* DMAP; f) PPh_3, THF; g) $BrCCl_3$, DBU, CH_2Cl_2, - 20°C ~ R.T., 74% (over 4 steps); h) LiOH, THF/H_2O, 0°C ~ R.T..

The *t*Bu-deprotected amine **287** was prepared by TFA mediated cleavage of the *tert*-butyl group from the threonine residue in **279**. Indeed, now the coupling product **288** could be obtained by HATU mediated activation in DMF, but with rather low yield (table 3-5, entry 1). The low conversion was suspected to be a result of the free acidic hydroxyl group on the pyridine. First, TIPS-group (TIPSOTf, 2,6-lutidine, CH_2Cl_2, 0°C ~ R.T., 83%) was employed to protect the free hydroxyl group. Surprisingly, partially loss of the TIPS group upon treatment with LiOH was observed. However, peptide coupling led to the peptide **288** with acceptable yield, but the TIPS group became fully cleaved during the peptide coupling

reaction (entry 2). A base stable and acid labile MOM protecting group was then introduced (MOMCl, DIPEA, CH_2Cl_2, 58% (90% based on recovered starting material)), which could be orthogonally deprotected with 0.5 ~ 1% TFA. The ester hydrolysis showed a clean single peak in the analytical HPLC trace, and excellent conversion was found in the coupling reaction, however, 50% MOM group was cleaved (entry 3). Other coupling conditions (HATU) led to excellent conversions as well, but partial deprotection could not be suppressed (entry 4). Additives like NMM decreased the efficiency and the ratio of protected product (entry 5).



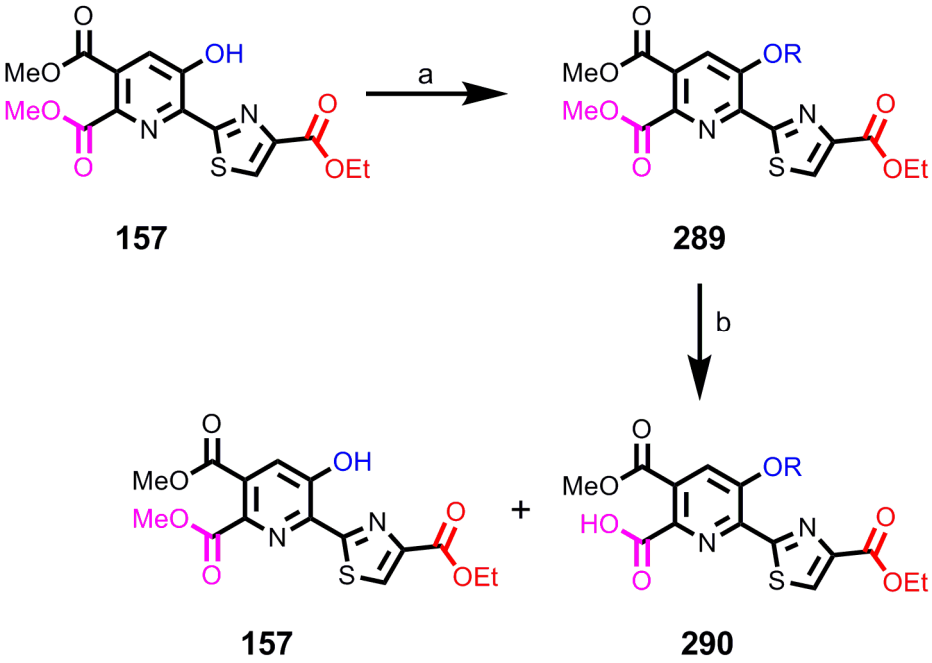
entry	R^1	b	yield	R^2
1	H	1.5 eq. HATU, DMF, R.T., 5h	9%	H
2	TIPS	1.3 eq. PyBOP, DMF, R.T., 17h	39%	H
3	MOM	1.5 eq. PyBOP, DMF, R.T., 17h	88%	MOM/H (1:1)
4	MOM	1.5 eq. HATU, DMF, R.T., 6h	90%	MOM/H (2.5:1)
5	MOM	1.5 eq. HATU, 6 eq. NMM, DMF, R.T., 6h	34%	MOM/H (1:1)

Table 3-5. Peptide coupling with free threonine alcohol. a) 50% TFA in CH_2Cl_2, Et_3SiH, R.T., 30min, 83%.

Therefore in these experiments it turned out to be quite difficult to purify compound **288**. The polarity of the deprotected and protected coupling products **288** were very similar, so normal column chromatography on silica gel could not deliver analytically pure products. Attempts to re-protect the 3-hydroxy group on the pyridine ring in **288** (MOMCl, DIPEA, CH_2Cl_2) as well as attempts to protect the secondary alcohol on the threonine residue with TBSCl or TBSOTf to facilitate the purification were not successful. Carrying the material forward and use $Pd(PPh_3)_4$ catalyzed deprotection of the allyl ester did not give pure products either. This forced us to exam an appropriate protecting group for the 3-hydroxy group, which would tolerate the peptide coupling conditions and enhance the coupling efficiency and compound purification.

3.3.9 Fragment union (generation 3).

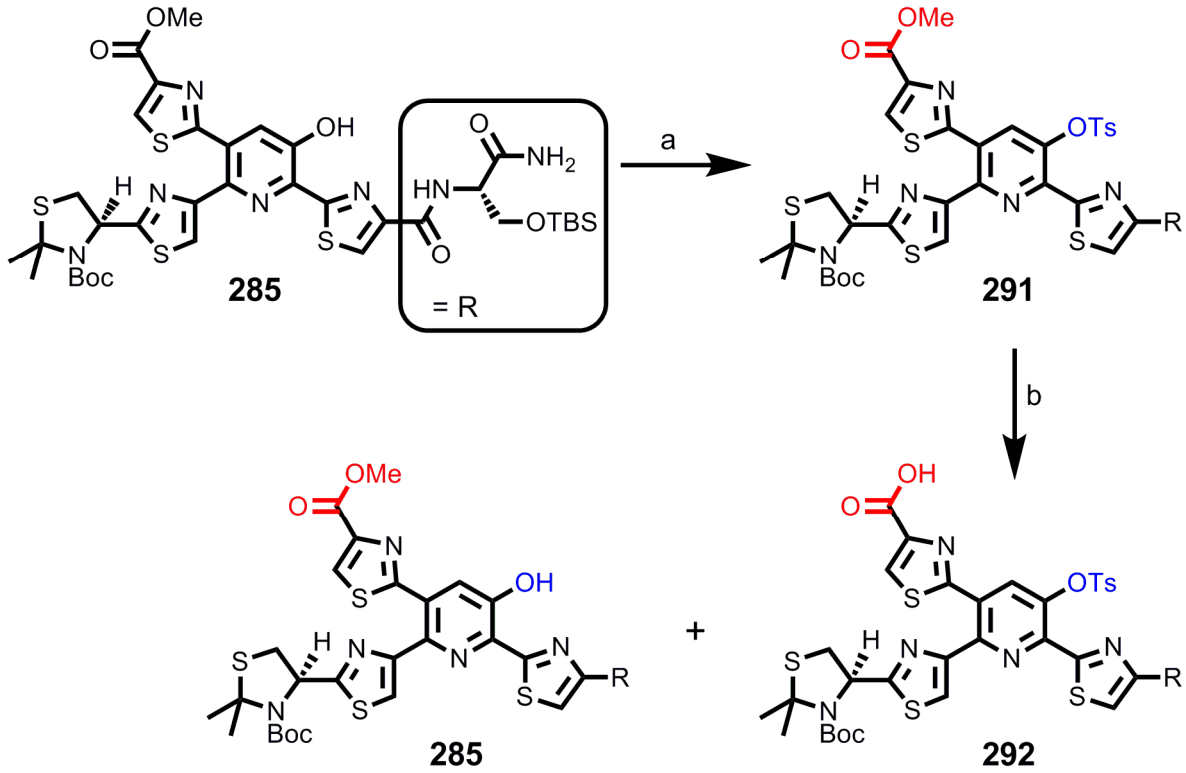
Before, a regioselective bromination could be realized after introducing a deactivating triflate group on the 3-position of the pyridine. However, the triflate group appeared too labile to nucleophilic attack to be used for protection. This promoted us to screen other electron withdrawing groups that could deactivate the pyridine ring, and should be easily removed orthogonally. The hydroxypyridine **157** was selected as a model for these studies (table 3-6). Three pyridines (**289a**, **289b**, **289c**) were obtained in good yield after derivatization with sulfonyl chlorides. When these compounds were treated with 2 equivalents of LiOH in THF/H_2O (1 equivalent of LiOH only gave half conversion), one methyl group was cleaved in case of **289a** (LC-MS); free hydroxypyridine **157** was recovered with pyridine **289b**, and a mixture of **157** and **290** was obtained from pyridine **289c**. Therefore, the activity of the protecting group followed the sequence: Ms > *p*-NO_2Phs > Ts, and the tosyl group was chosen for further studies.



entry	R	yield (**289**)	ratio **157**/**290**
a	Ts	77%	**0:1**
b	Ms	70%	1:0
c	*p*-NO_2-Phs	59%	2:3

Table 3-6. Deactivating protecting group screening. a) 1.2 eq. RCl, 1.2 eq. TEA, 10% DMAP, CH_2Cl_2, 0°C; b) 2 eq. LiOH, THF/H_2O = 3:1, R.T.; *p*-NO_2-Phs: *para*-nitrophenyl sulfonyl.

The pyridine **291** was then synthesized from hydroxypyridine **285** in very good yield. Subsequent hydrolysis with 4 equivalents of LiOH in THF/H_2O resulted in a mixture of the desired acid **292** and detosylated pyridine **285** as a ratio of 1:1 (table 3-7, entry 1); other solvents like MeOH/H_2O favoured detosylation (entry 2); stronger base (CsOH) completely deprotected the tosyl group in a very short reaction time (entry 3); other soft hydrolysis reagents like PhSNa and DBTO very slowly cleaved the tosyl group. Trimethyltin hydroxide (Me_3SnOH) then drew our attention as it was reported as a very mild reagent for ester cleavage.[34] To our delight, trimethyltin hydroxide hydrolyzed the methyl ester selectively, leaving the tosyl group completely untouched. It was found that elevated temperature (80°C) was a key factor, lower temperature decreased the efficiency dramatically (no conversion at 50°C, slow conversion at 60°C). Importantly, the acid **292** was not very stable to silica gel (approximately 30% product loss, and the tosyl group was cleaved with Et_3N deactivated silica). However, acid **292** could be purified using RP-chromatography with acetonitrile as the eluant (C-18 cartridge, 100 mg scale).



Entry	condition b	**285/292**
1	4 eq. LiOH, THF/H_2O, 0°C	1:1
2	4eq. LiOH, MeOH/H_2O, 0°C, 2h	1:0
3	4eq. CsOH, THF/H_2O, 0°C, 4h	1:0
4	PhSNa, DMF, 80°C, 10h	1:0
5	DBTO, dioxane/H_2O, 80°C, 24h	1:0
6	**10 eq. Me_3SnOH, DCE, 80°C, 3h**	**0:1**

Table 3-7. Methyl ester hydrolysis of pyridine **291**. a) TsCl, TEA, 10% DMAP, CH_2Cl_2, 0°C, 2h, 73%.

The peptide coupling reaction between the amine **279** and the acid **292** was then tested with various coupling reagents and conditions [a) HATU, DIPEA, DMF; b) PyBrOP, DIPEA, DMF/CH_2Cl_2; c) DPPA, DIPEA, DMF/CH_2Cl_2; d) HATU, HOAt, DIPEA, DMF], but only starting amine **279** was recovered.

Surprisingly, tosylated coupling product was isolated as the major product (the minor product was **288**) when conducting the peptide coupling reaction between the amine **287** and the acid **279** on small scale (2 mg of acid **292**); fully de-tosylated product **288** was isolated with slightly lager scale (8 mg of acid **292**). Further control experiments showed that the excess of HATU played an important role in deprotecting the tosyl group; less HATU (1.2 eq.) gave the

tosylated coupling product as the major product, but with reduced efficiency; excess HATU (4 eq.) increased the efficiency, but led to detosylated coupling product **288** completely; the ratio of **288** to the tosylated product was 1:1 in one hour; after 2 hours, **288** became major product; a characteristic single peak **288** presented in the analytical HPLC trace and LC-MS after 11 hours at room temperature (figure 3-26).

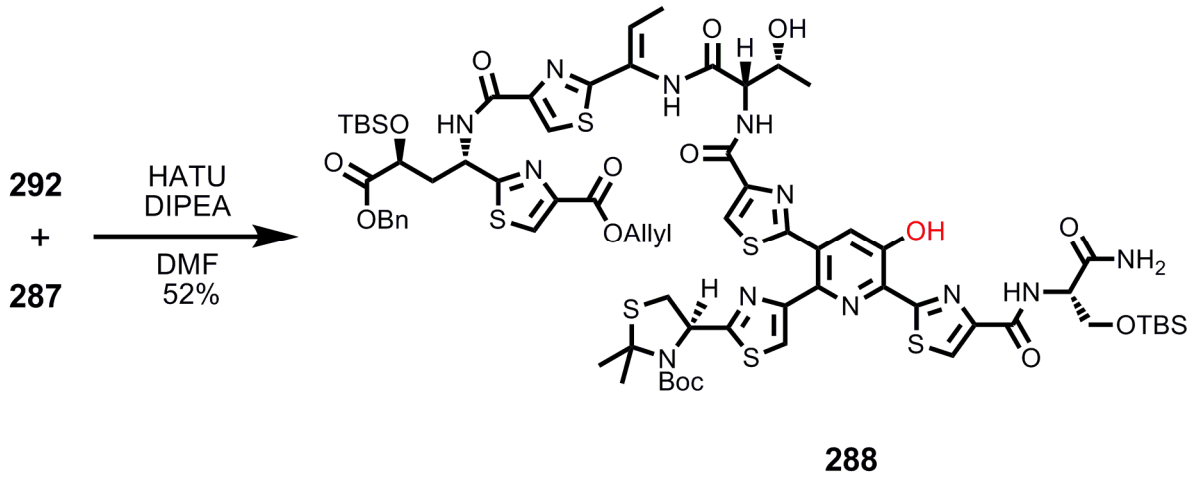


Figure 3-26. Peptide coupling with tosylated acid.

A 2,4,6-trimethylphenylsulfonyl group was then introduced to hydroxypyridine **285** (figure 3-27, **293**) to increase the steric hindrance. Surprisingly, this substrate still led to the hydrolyzed product **288** as monitored by HPLC and LC-MS. This observation implied that HATU or HOAt (which is formed from HATU during the peptide coupling) played an important role in the detosylation reaction, even with bulky protecting group at 3-hydroxy of the pyridine.

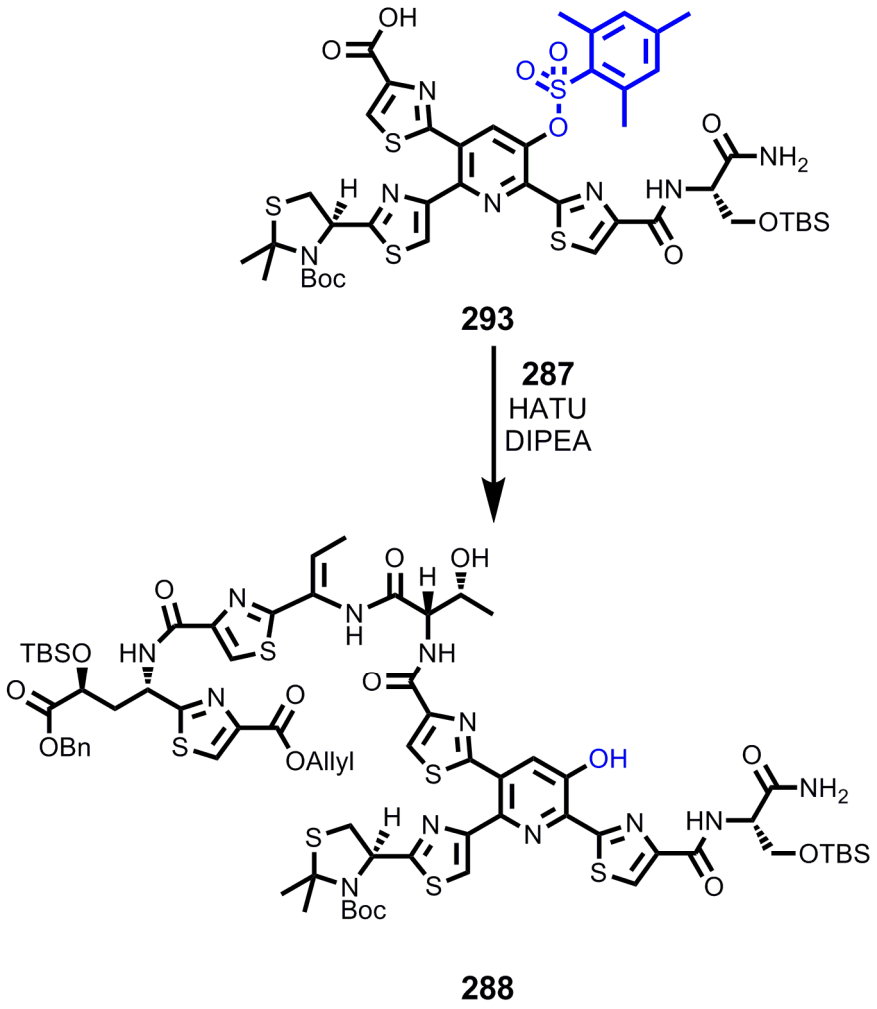


Figure 3-27. Peptide coupling with more bulky sulfonyl ester.

Apparently, HOAt-based coupling reagents could not be used for this coupling reaction. DEPBT (3-(Diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3H)-one) was reported to efficiently couple free amines and acids, and to display low degrees of racemization when compared to other coupling reagents, even in the presence of a free secondary alcohol.[185]
Using DEPBT and solid $NaHCO_3$, the coupling product **294** was formed cleanly (much cleaner than before as shown by HPLC and NMR) in good yield. Most importantly, the tosyl group was left untouched, which facilitated the isolation (figure 3-28).

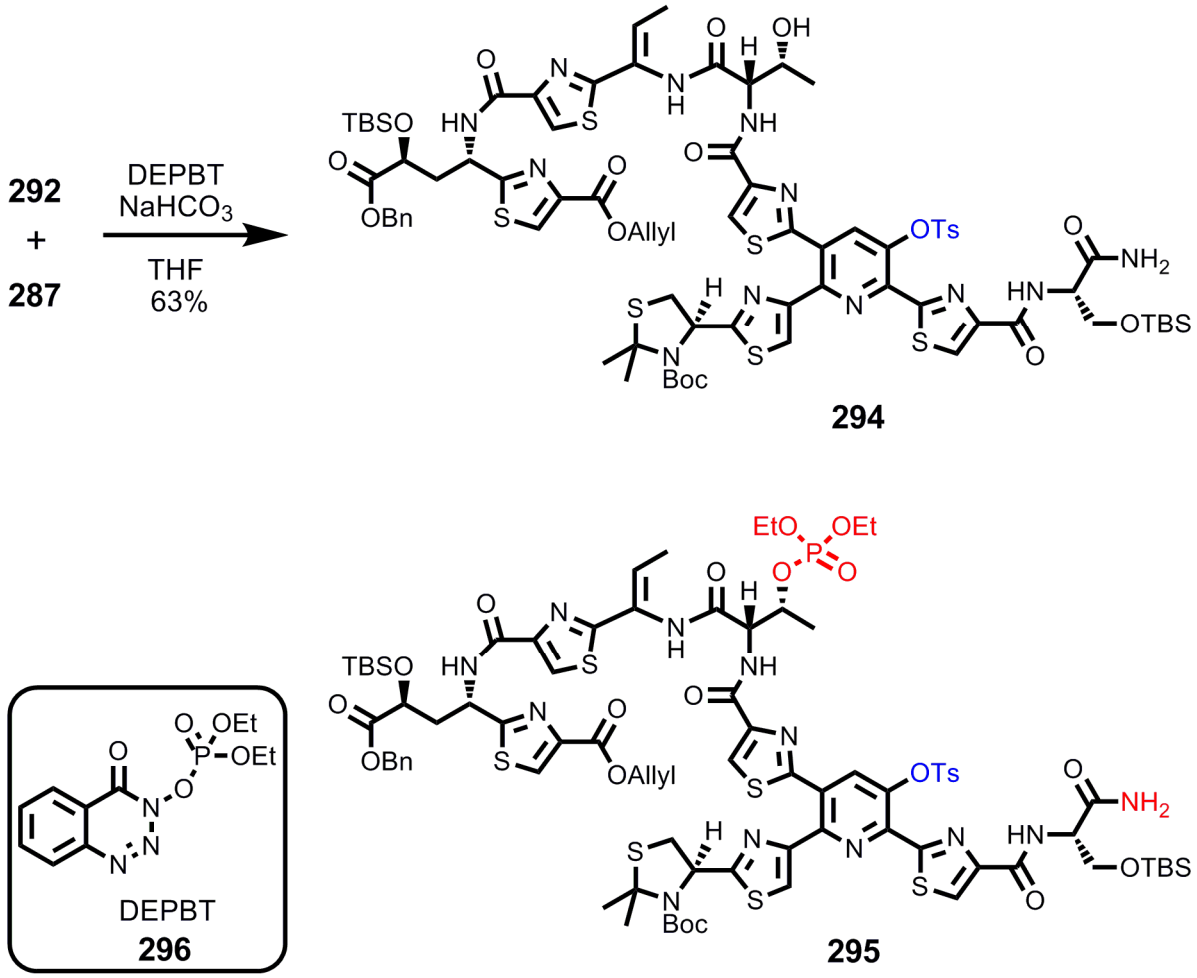


Figure 3-28. DEPBT mediated amide bond formation.

From LC-MS, formation of phosporylated side products (probably **295**) was apparent in minor amounts, but the coupling product **294** was pure enough for further transformations.

A plausible mechanism for DEPBT mediated peptide coupling[186] is shown in figure 3-29. The carboxylate attacks the phosphorus atom of the DEPBT **296**, and the resulting transient intermediate **297** looses diethyl phosphate to form the active ester **298** by rearrangement, which is converted to the amide **299** by nucleophilic attack of the free amine. Secondary alcohols or terminal amides could also be deprotonated and act as nucleophiles to attack the central phosphorous in DEPBT, if they are acidic enough, which can explain the formation of phosphorylated side products.

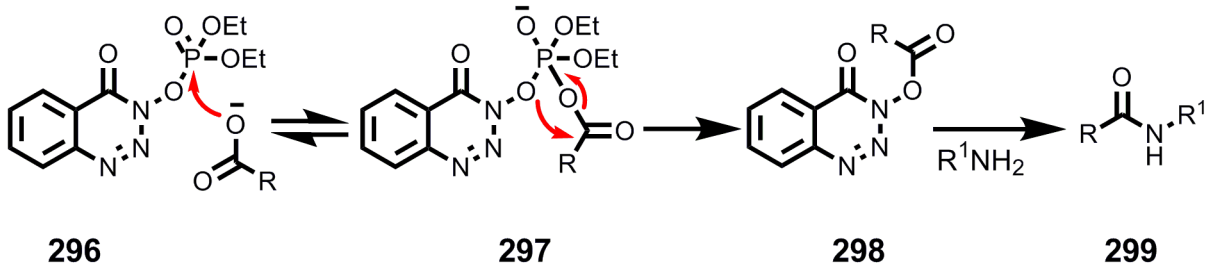


Figure 3-29. A plausible mechanism of DEPBT mediated amide bond formation.

To avoid potential side reactions caused by the secondary alcohol on the threonine residue in coupling product **294**, the alcohol needs to be protected. The attempt to protect the secondary alcohol with TBSOTf failed. Interestingly, the attempt to form acetate **300** was successful with moderate yields (figure 3-30).

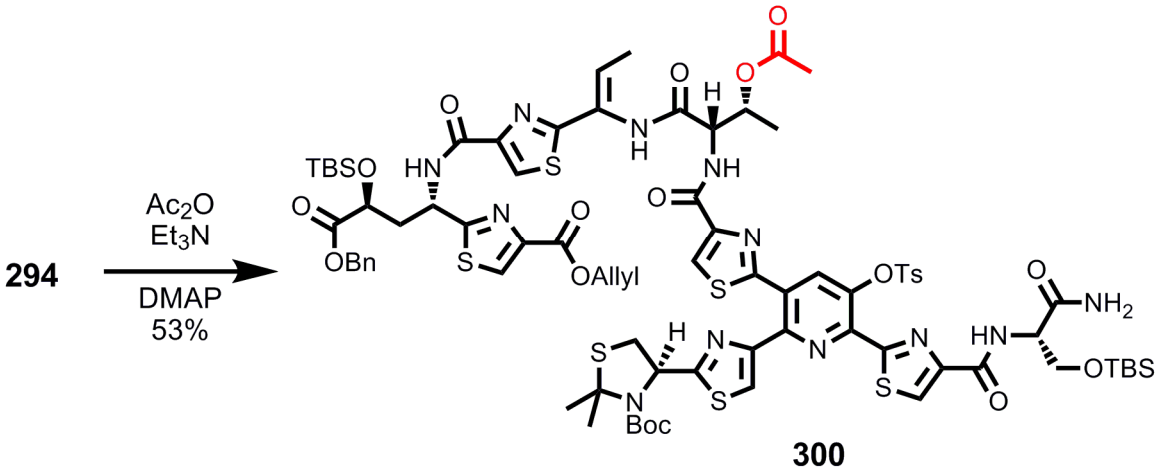


Figure 3-30. Secondary alcohol protection.

Unfortunately, acetate is not well suited as a protecting group due to the presence of a thioester in nosiheptide. Therefore, a direct amide bond formation between free amine **279** (with *t*-butyl ether protection) and acid **292** was evaluated (figure 3-31). Gratifyingly, the coupling reaction proceeded cleanly and afforded the new coupling product **301** in excellent yield (87%). Side products like **295** were not observed in this case, which indicated that the diethylphosphoryl group was located on the secondary alcohol in the side product **295**.

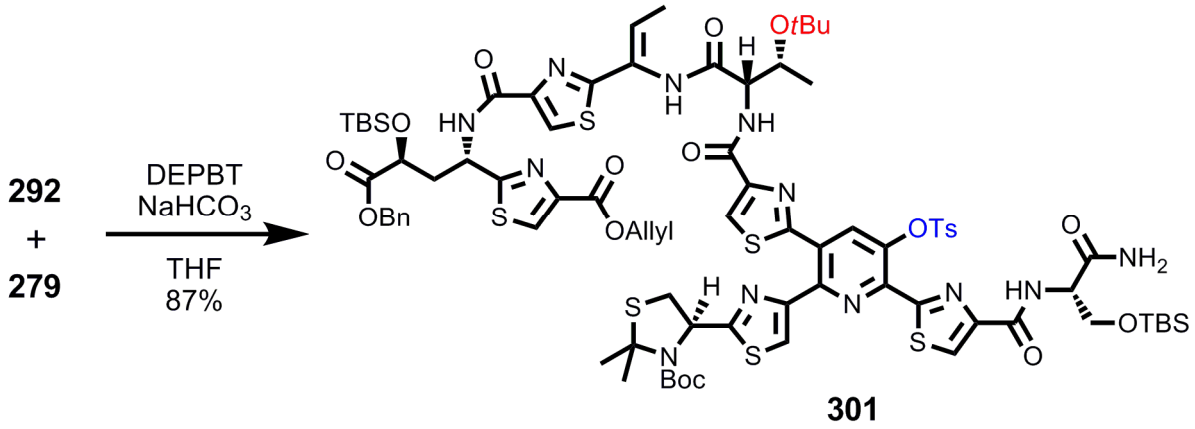


Figure 3-31. DEPBT mediated coupling between **279** and **292**.

3.3.10 Macrocycle formation (generation 1).

With coupling product **301** in hand macrocyclization was the next step (figure 3-32). Pd^0 catalyzed deallylation cleanly gave the corresponding acid, which was converted to the thioester **302** in good yield, which was expected to be a suitable substrate for a ring-closing transthioesterification followed by rearrangement to an cysteine amide bond ("native chemical ligation").[55] The thioester **302** was treated with 10% TFA in CH_2Cl_2 with $PhSiH_3$ as the scavenger to cleave the thioketal, however several products were formed; it was found that TBS, ketal, and *tert*-butyl groups were partially cleaved, only the Boc was completely removed. After removal of the solvent and adjusting the pH to 3.8 with buffer, methoxyamine[187] was employed to cleave the thioketal, but after readjustment of the buffer to pH 9.0 to induce trans-thioesterification and rearrangement to the amide did not lead to macrocycle **304** by "native chemical ligation".

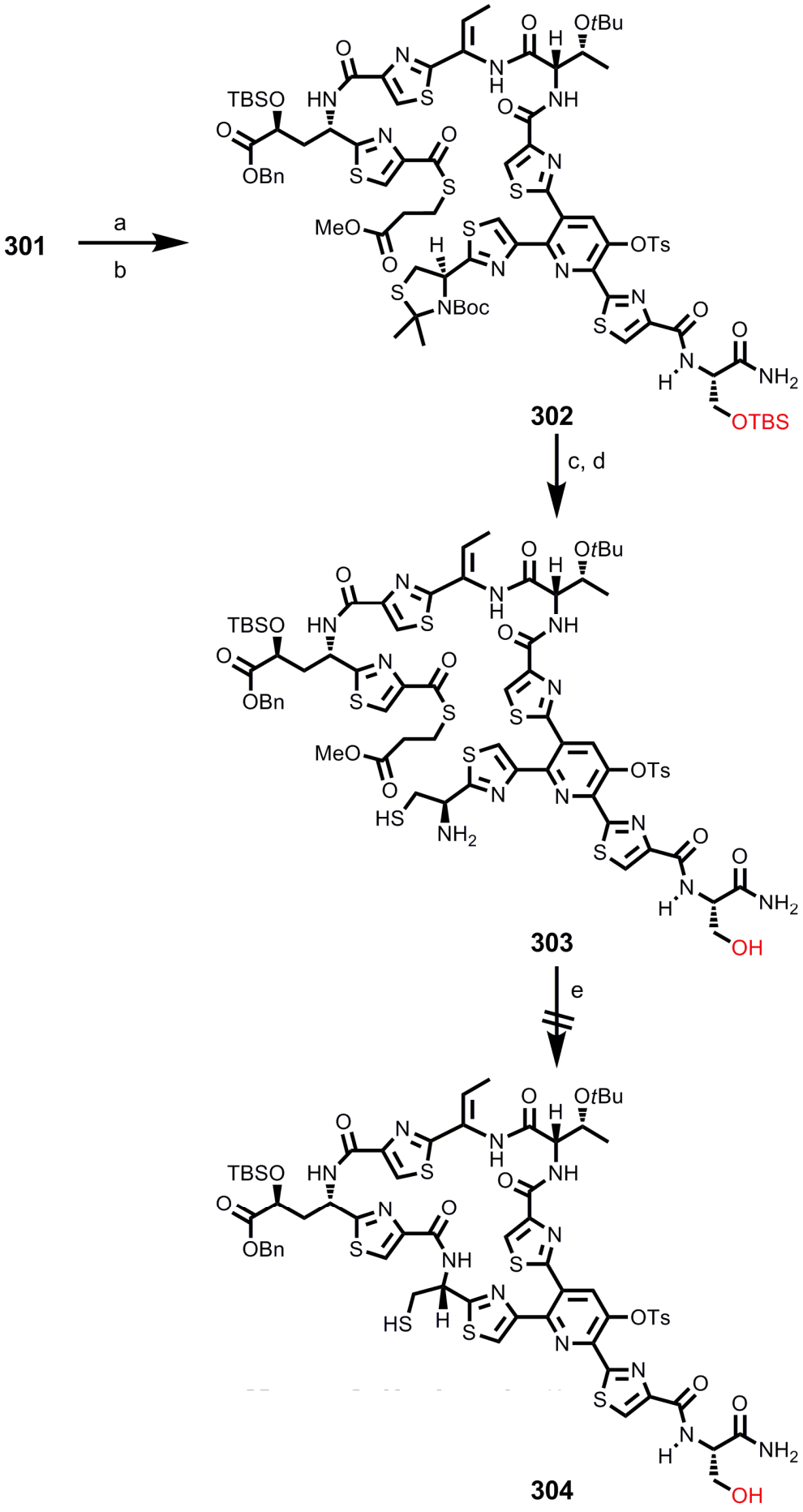

301
a
b
TBSO
HN
OBn
MeO
NBoc
OTs
OtBu
NH
NH2
OTBS
302
c, d
HS
OH
303
e
304

Figure 3-32. Macrocycle formation attempts by native chemical ligation. a) 10% $Pd(PPh_3)_4$, 2 eq. $PhSiH_3$, CH_2Cl_2, 54%; b) 2 eq. EDC, 2 eq. DMAP, 1 eq. PBu_3, CH_2Cl_2, 59%; c) 10% TFA in CH_2Cl_2; d) $MeONH_2$, H_2O; e) 1% PhSH, DMF/pH 9.0 buffer.

3.3.11 Macrocycle formation (generation 2).

A native chemical ligation like ring formation was not successful, probably as a result of the unreacted aromatic acid (thiazolyl acid) and difficulties associated with deprotection. An alternative plan for macrocyle formation was then envisioned (figure 3-33). The problematic ketal could be liberated and reprotected by a trityl group to give amine **305**. A peptide coupling could then deliver peptide **306**, which would be converted to macrocycle **307** after hydrolysis, Fmoc cleavage and DEPBT mediated ring closure.

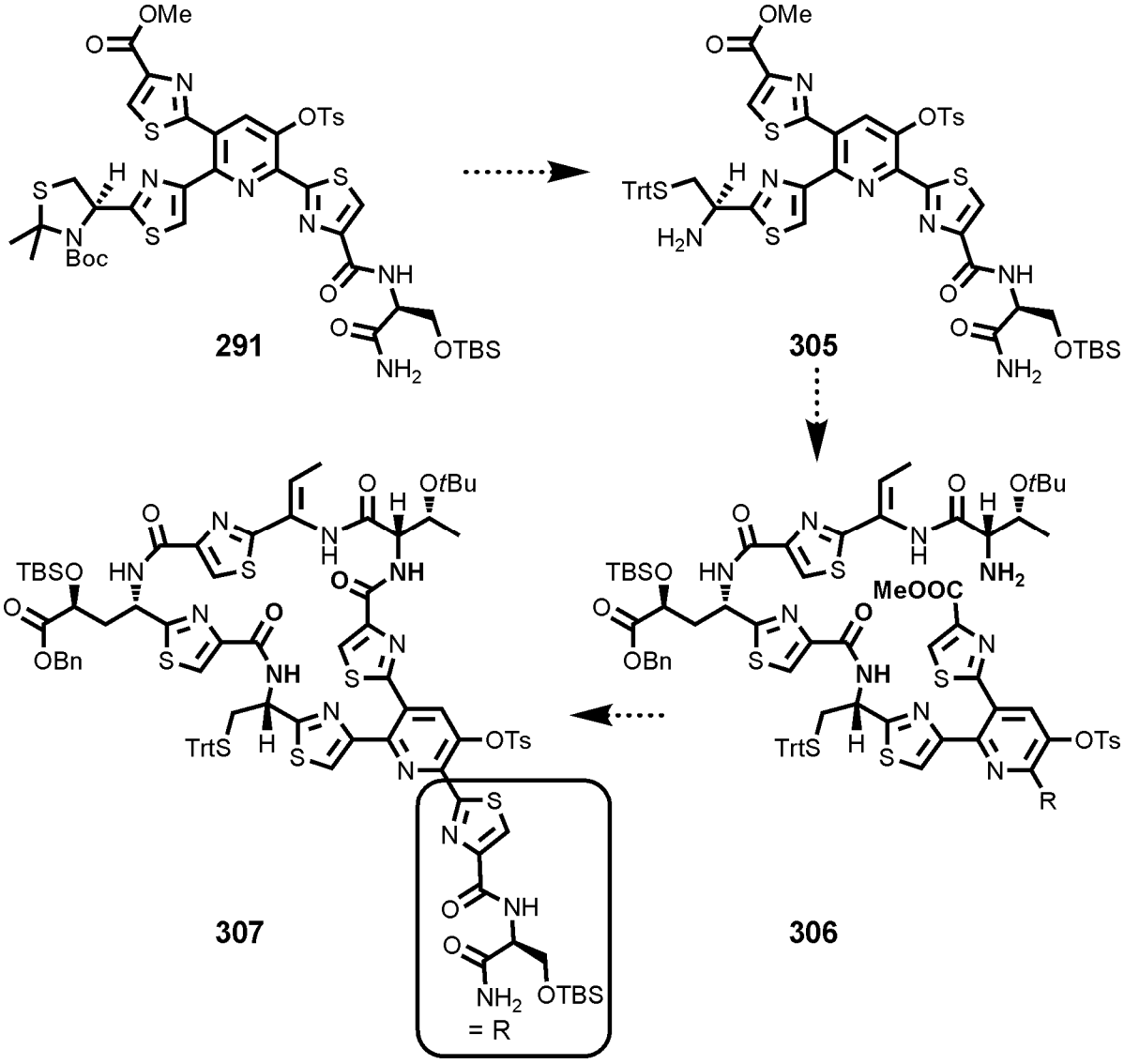


Figure 3-33. Alternative plan for macrocycle formation.

To realize this plan, a chemoselective deprotection of the ketal group in the presence of the TBS ether was necessary. The free alcohol **308** was the major product when pyridine **291** was treated with 10% TFA at 0°C for 2 hours. The desired Boc deprotection product (**311** in table 3-8) was formed in less than 10%, which implied that the primary TBS ether was more acid labile than the Boc group in this case. Increasing the concentration of TFA without scavenger led to Boc and TBS deprotected pyridine **309**. Various conditions were screened, but the thioketal ring could not be removed. Stronger conditions with scavenger led to the fully deprotected product **310** (figure 3-34).

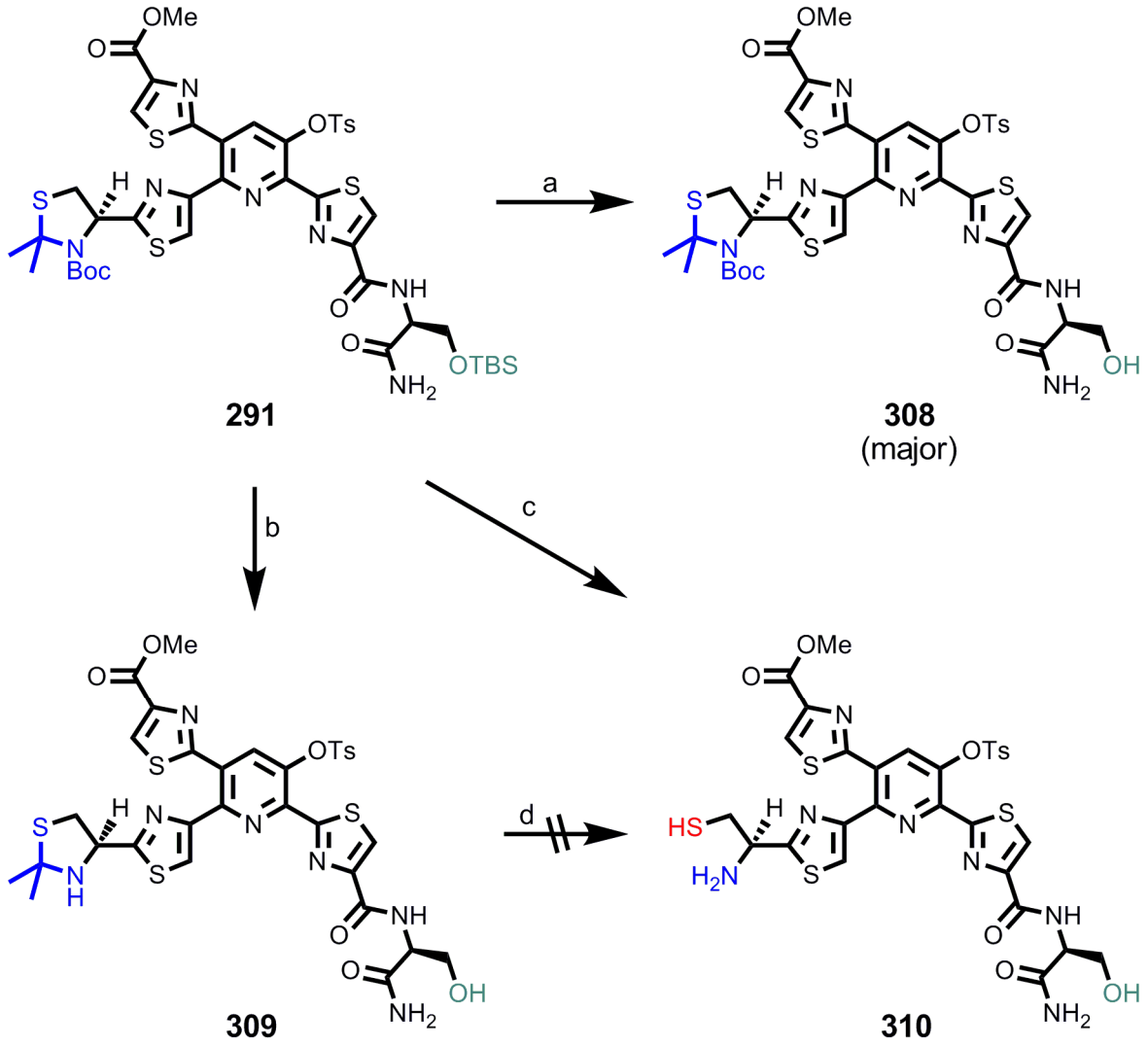
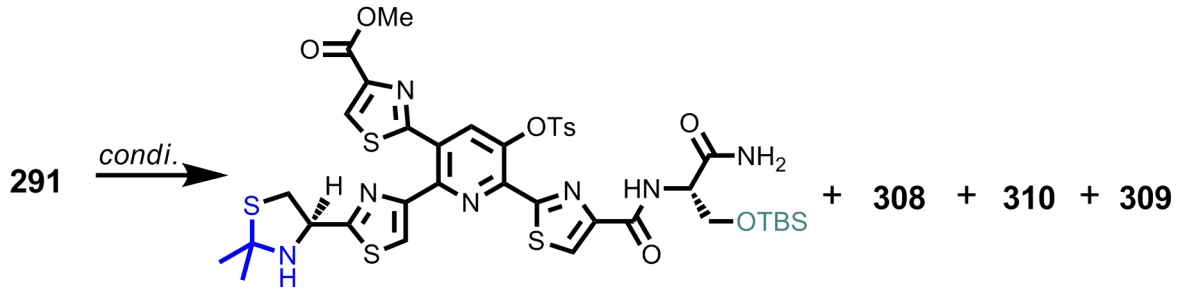


Figure 3-34. Ketal deprotection attempts. a) 10% TFA in CH_2Cl_2, Et_3SiH, 0°C, 2h; b) 20% TFA in CH_2Cl_2; c) 20% TFA in CH_2Cl_2, Et_3SiH, R.T., 1h; d) methoxyamine, pH 3.0 buffer.

In order to suppress the TBS deprotection, a wide range of methods were screened to selectively deprotect the Boc and ketal groups (table 3-8). Lowering the concentration of TFA

and changing the scavenger did not lead to selective cleavage (entry 1). Two different additives were tested to enhance the selectivity (entry 2, 3). $ZnBr_2$[188] selectively deprotected the Boc and TBS group, but it was not reproducible on large scale (>10 mg **291**) (entry 4). TBSOTf,[189] TIPSOTf and TESOTf gave no conversion, but decomposed **291** when large excess was used (>20 eq.) (entry 5-7). PTSA, HCl in dioxane and CAN chemoselectively desilylated **291** (entry 8-10). HCl in ethyl acetate[190] gave a mixure (entry 11). A combination of TMSCl and phenol[191] cleanly converted **291** to fully deprotected **310** (entry 12), but the excess phenol was difficult to remove by chromatography.



311

Entry	condition	product
1	5% TFA, $PhSiH_3$, CH_2Cl_2	mixture[a]
2	$Hg(OOCCF_3)_2$, TFA, $PhSiH_3$, CH_2Cl_2	mixture
3	$AgBF_4$, TFA, anisole, CH_2Cl_2	mixture
4	$ZnBr_2$, CH_2Cl_2	**309**[b]
5	TBSOTf, lutidine, CH_2Cl_2	n.c[c]
6	TIPSOTf, lutidine, CH_2Cl_2	n.c
7	TESOTf, lutidine, CH_2Cl_2	n.c
8	PTSA, MeOH	**308**
9	HCl, dioxane	**308**
10	CAN, CH_3CN	**308**
11	HCl, ethyl acetate	mixture
12	TMSCl, PhOH, CH_2Cl_2	**310**

Table 3-8. Chemoselective deprotection screening. [a] mixture = **308** + **309** + **310**; [b] difficult to reproduce; [c] n.c = no conversion.

In all methods screened, the desired pyridine **311** was only detected as a minor product or not detected. The ketal group was more stable, the TBS ether was more labile than expected. To

explore whether an alternation macrocyclization site would be useful in general, we continued with fully deprotected pyridine **310**.

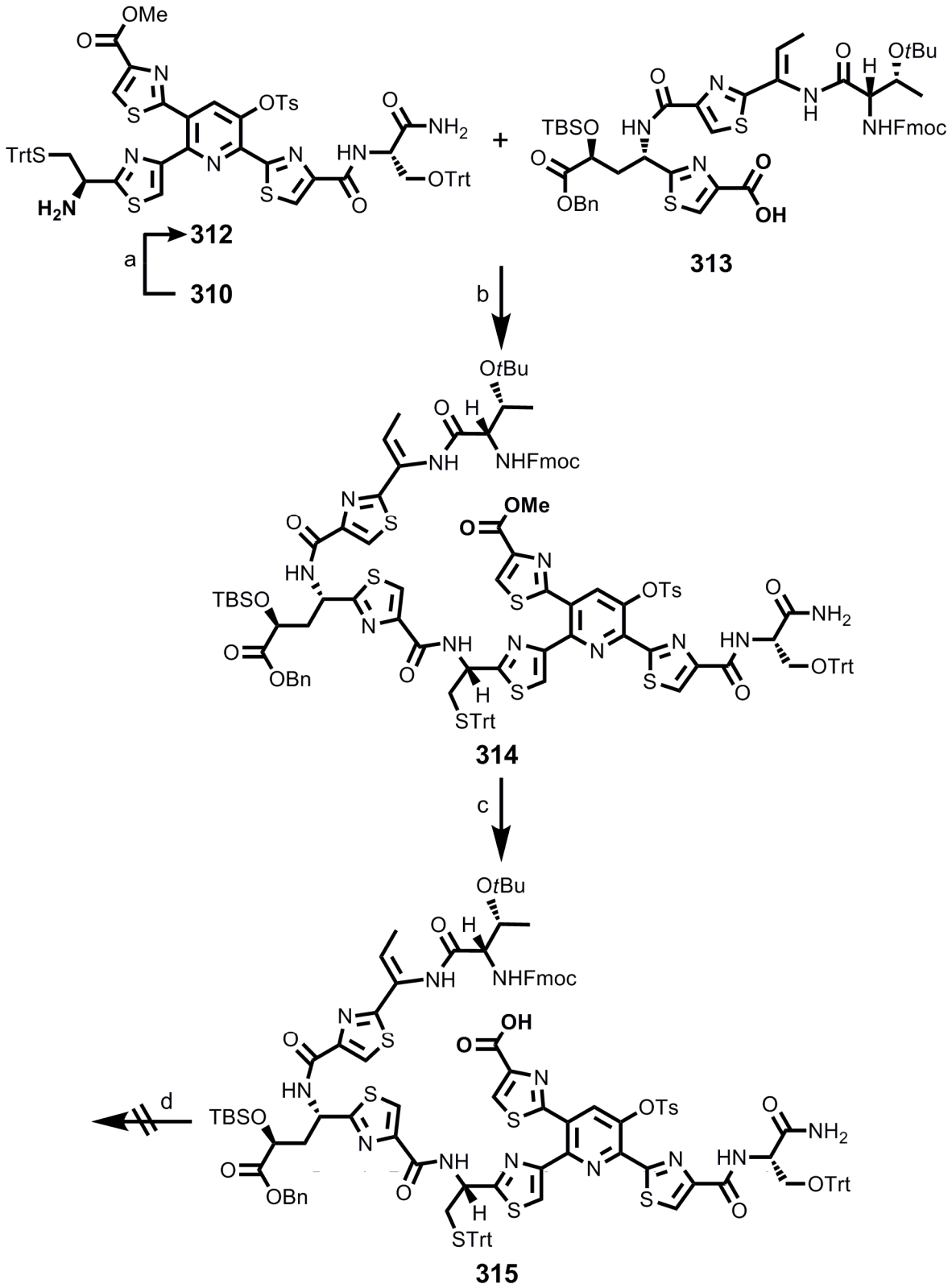


Figure 3-35. Macrocycle formation attempts. a) TrtCl, DMF, 48h, 38% (over 2 steps); b) DEPBT, $NaHCO_3$, THF, 53%; c) Me_3SnOH, DCE, 80°C; d) 5% DBU, CH_2Cl_2.

Double tritylated product **312** was obtained when **310** was treated with trityl chloride. DEPBT mediated peptide coupling between free amine **312** and acid **313**[55] gave **314** in good yield. Me_3SnOH mediated hydrolysis led to acid **315**, which was submitted to peptide coupling conditions after treatment with DBU to deprotect the Fmoc group. Unfortunately, a macrocyclic product could not be observed, even after changing the order of hydrolysis and Fmoc deprotection (figure 3-35).

3.3.12 Fragment union (generation 4).

In order to overcome these difficulties, protecting group exchange was conducted at an earlier stage.

Hydroxypyridine acid **283** was treated with 50% TFA for 1 hour with Et_3SiH as the scavenger. HPLC and LC-MS then showed two products with a ratio about 1:1, and ESI-MS analysis indicated one product was fully deprotected and the other one was still containing the ketal group. Longer reaction time slightly changed the ratio, but did not lead to fully deprotected product (for details, *vide infra*). Nevertheless, when the resulting mixture was treated with trityl chloride in DMF, and the free amine **316** was formed. After Alloc protection, acid **258** was obtained. Using the chemistry developed earlier in this thesis, the macrocycle precursor **318** was obtained in good yield after preparative HPLC (figure 3-36).

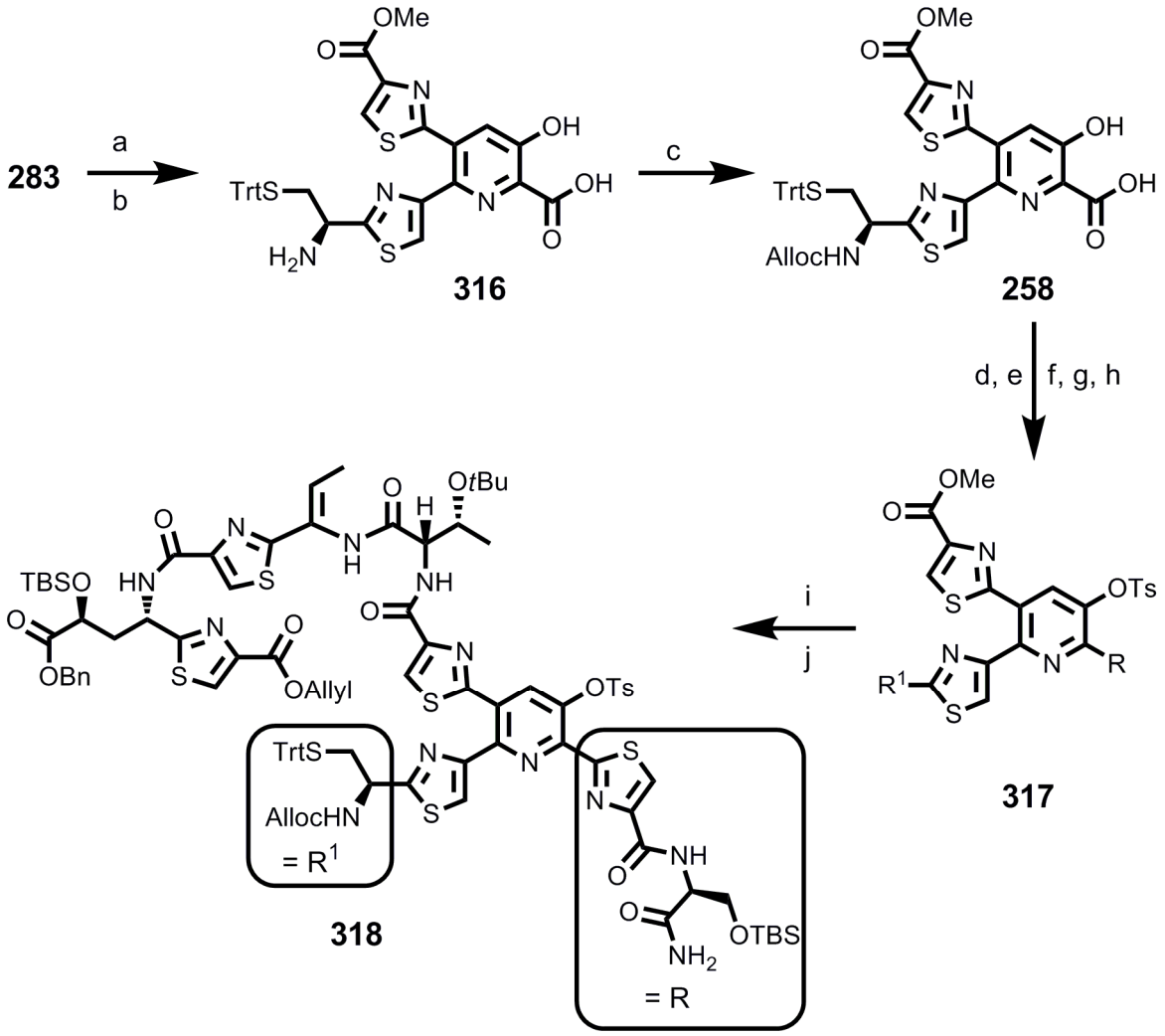


Figure 3-36. Protecting group exchange and fragment union. a) 50% TFA in CH_2Cl_2, Et_3SiH; b) TrtCl, DMF, 12h; c) AllocCl, $NaHCO_3$, THF/H_2O = 5:1, 82% (over 3 steps); d) $COCl_2$, Et_3N, THF, - 40°C ~ 0°C; e) **274**, *cat.* DMAP, THF; f) PPh_3, THF; g) $CBrCl_3$, DBU, CH_2Cl_2, - 20°C ~ R.T., 49% (over 4 steps); h) TsCl, Et_3N, 10% DMAP, CH_2Cl_2; i) Me_3SnOH, DCE, 80°C; j) **279**, DEPBT, $NaHCO_3$, THF, 38% (after preparative HPLC).

3.3.13 Acid catalyzed protecting group exchange

In the protecting exchange transformation, we found the liberation of the cysteine residue to be really slow. When the mixture (fully deprotected and ketal remaining pyridines) was submitted to the tritylation sequence, interestingly, only the product **316** was detected and isolated.

This was investigated further (figure 3-37). Ketal protected **319** was converted to free amine **320** in excellent yields with 1.8% TFA as the catalyst; acid **321** led to trityl protected cysteine

without any additive; the reactivity became really low when the nitrogen position was blocked by the Boc group. Acid **249** could not deliver the cysteine **356** without TFA, slow conversion (HPLC control) was observed with 1.8% TFA as the catalyst.

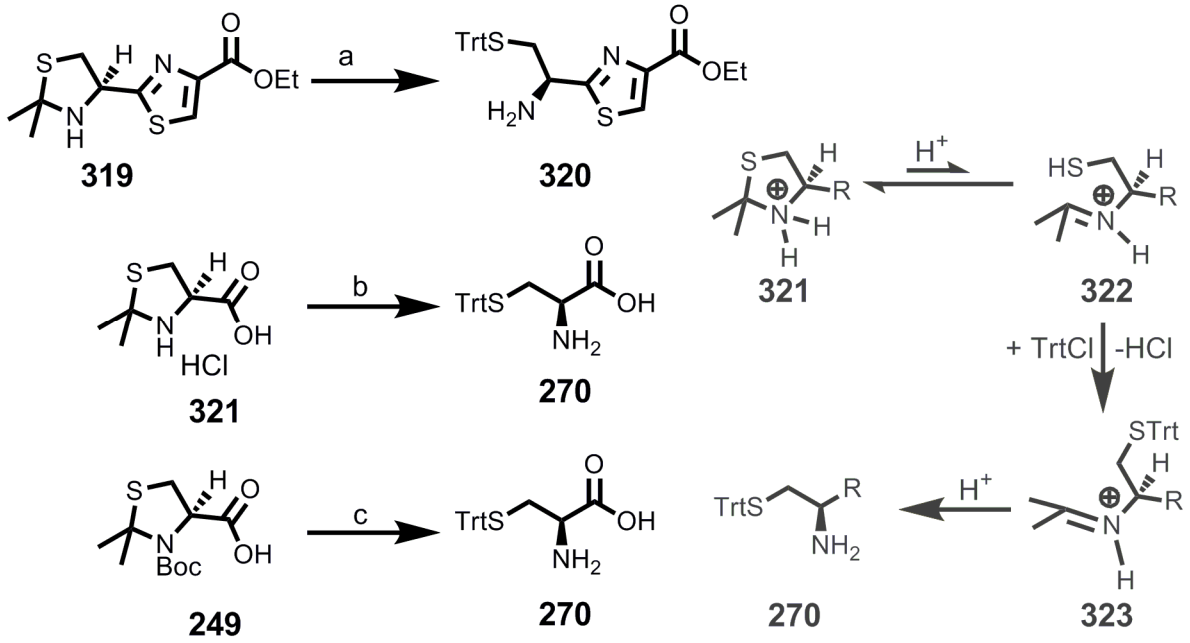


Figure 3-37. Acid catalyzed protecting group exchange. a) 1.8mol% TFA, DMF, TrtCl, R.T., 99%; b) TrtCl, DMF, R.T., 24h; c) 1.8mol% TFA, DMF, TrtCl.

Overall, TrtCl was found to promote thioketal removal. The mechanistic rationale is shown in figure 3-37. Under acidic conditions, protected **321** is in equilibrium with iminum ion **322**, but **321** is much more stable. However, when the free thio in **322** gets captured by trityl chloride the equilibrium is driven to **323**, which can easily release amine **270** by hydrolysis.

3.3.14 Macrocycle formation (generation 3)

With precursor **318** in hand, macrocycle formation was addressed next. The Pd^0 catalyzed deprotection of allyl ester and alloc groups in **318** worked cleanly and gave the macrolactamization precursor. Indeed, after short silica gel column chromatography purification, the macrocycle **307** was formed cleanly in good yield under high dilution conditions (figure 3-38).

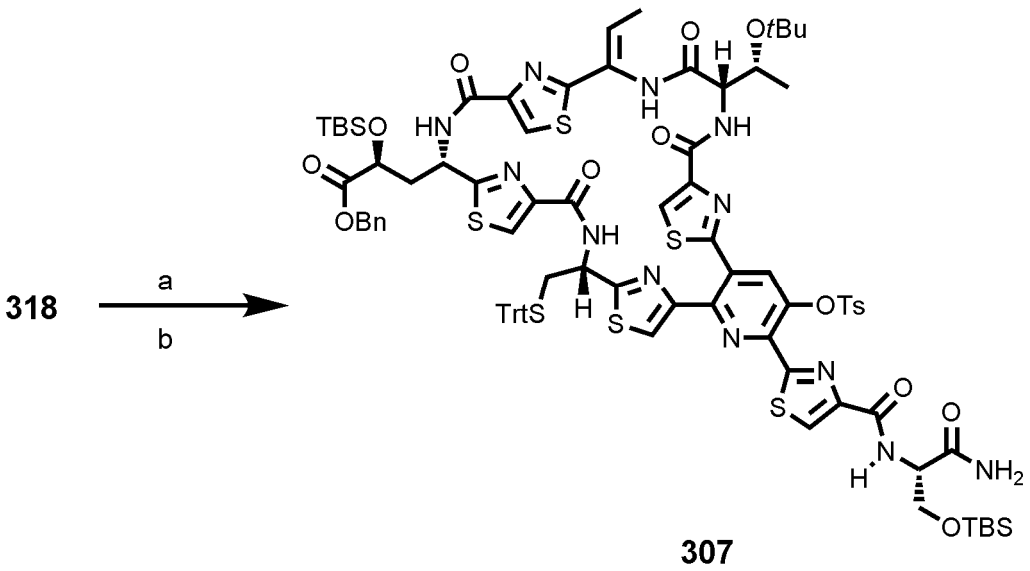


Figure 3-38. Macrocycle formation. a) 20% $Pd(PPh_3)_4$, $PhSiH_3$, CH_2Cl_2, R.T., 20 min; b) HATU, DIPEA, CH_2Cl_2/DMF = 20:1, R.T., 16h, 30-60% (1-2 mg scale).

3.3.15 Macrocycle formation (generation 4).

The TBS ether was partially cleaved when attempted to deprotect the trityl group in **318**, which indicated the TBS ether at the tail part was surprisingly acid sensitive. To overcome this limitation, it was exchanged for a TIPS group to enhance stability against acid and base.[192]

The optimized synthesis of macrocycle **330** is shown in figure 3-39. The preparation of the tail dipeptide **326** followed the sequence as before, and **326** was submitted to an aza-Wittig sequence after trityl deprotection. The resulting hydroxypyridine **327** was tosylated and hydrolyzed to deliver the free acid **328** ready for fragment union with free amine **279**. After purification by prep-HPLC, the peptide **329** furnished macrocycle **330** in excellent yield after parallel deprotection of the allyl and alloc groups and macrolatamization under high dilution conditions using HATU.

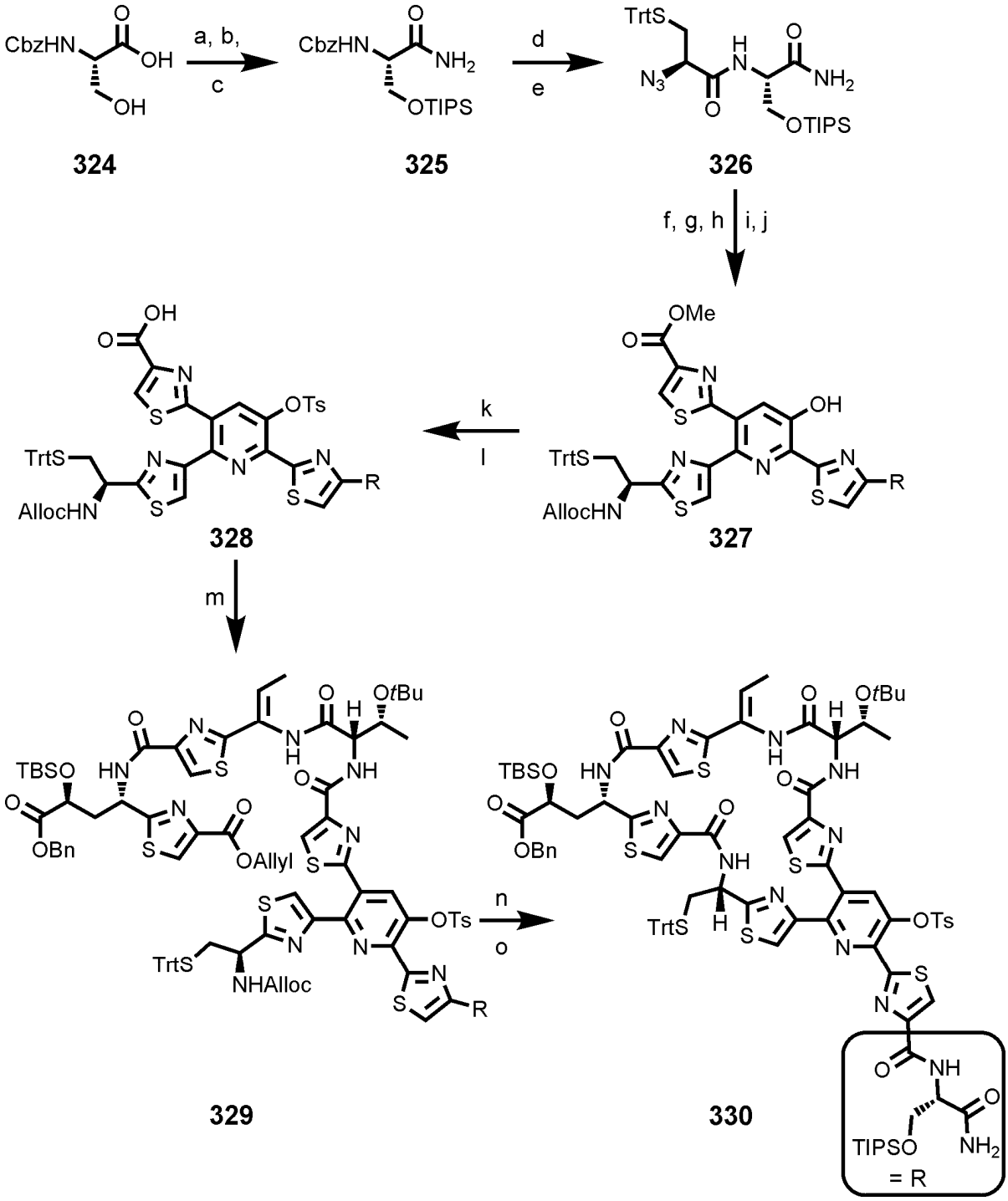


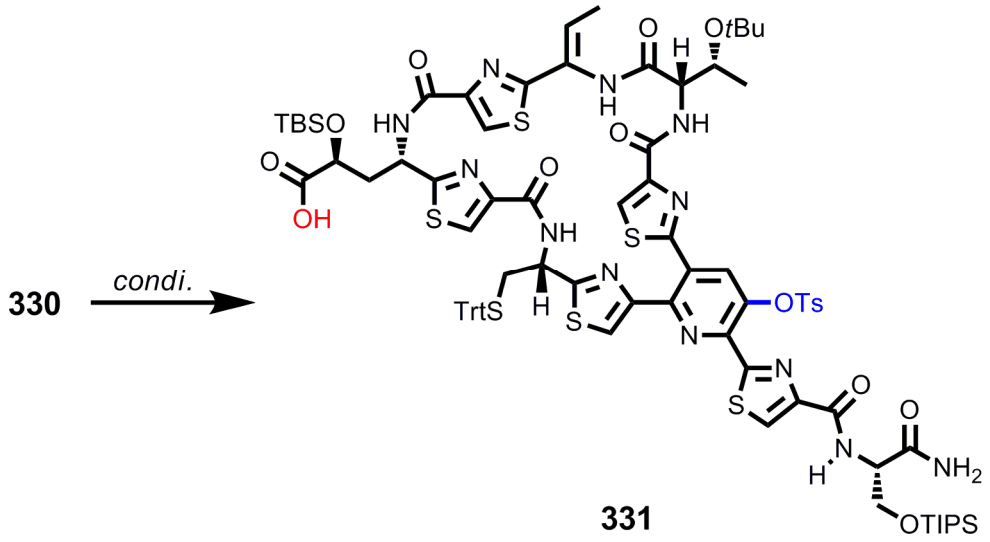
Figure 3-39. Macrocycle **330** formation. a) TIPSCl, imidazole, DMF, R.T., 73%; b) HOSu, DCC, THF, 0°C ~ R.T., 10h; c) NH_4OH, ethyl acetate, 0°C, 1h, 78%; d) H_2, Pd/C, MeOH, R.T., 12h, 99%; e) **271**, NMM, *t*BuOC(O)Cl, THF, -20°C ~ R.T., 16h, 77%; f) 5% TFA in CH_2Cl_2, Et_3SiH, R.T., 30 min; g) $COCl_2$, Et_3N, THF, - 40°C ~ 0°C; h) **258**, cat. DMAP, THF; i) PPh_3, THF; j) $BrCCl_3$, DBU, CH_2Cl_2, - 20°C ~ R.T., 46% (over 4 steps); k) TsCl, Et_3N, 10% DMAP, CH_2Cl_2, 49%; l) Me_3SnOH, DCE, 80°C, 99%; m) **279**, DEPBT, $NaHCO_3$, THF,

47% (after prep-HPLC); n) 20% $Pd(PPh_3)_4$, $PhSiH_3$, CH_2Cl_2, R.T., 20 min, 99%; o) HATU, DIPEA, CH_2Cl_2/DMF = 15:1, R.T., 16h, 56% (after prep-HPLC).

3.3.16 Bis macrocycle formation (generation 1)

After establishing a reliable synthetic route to the A-ring of nosiheptide, installation of the indolic acid B-ring was studied.

Different experiments aimed at hydrolyzing the benzyl ester **330** are shown in table 3-9. Standard basic hydrolysis (K_2CO_3,[193] Me_3SnOH and DABCO[194]) could not cleave the surprisingly robust benzyl group, the tosyl group was cleaved with Me_3SnOH (entry 1-3); hydrolysis catalyzed by Lewis acid (LiBr[195], $AlCl_3$[196], BCl_3[197]) did not give any conversion (entry 4-6); stronger Lewis acid (TMSI[198]) led to decomposition (entry 7). Oxidative benzyl ester cleavage (NBS[199], DDQ[200], $FeCl_3$[201]) was not met success (entry 8-10); Pd-catalyzed reductive debenzylation[202-204] could not deliver the acid **331** and excess palladium led to decomposition (entry 11-14).



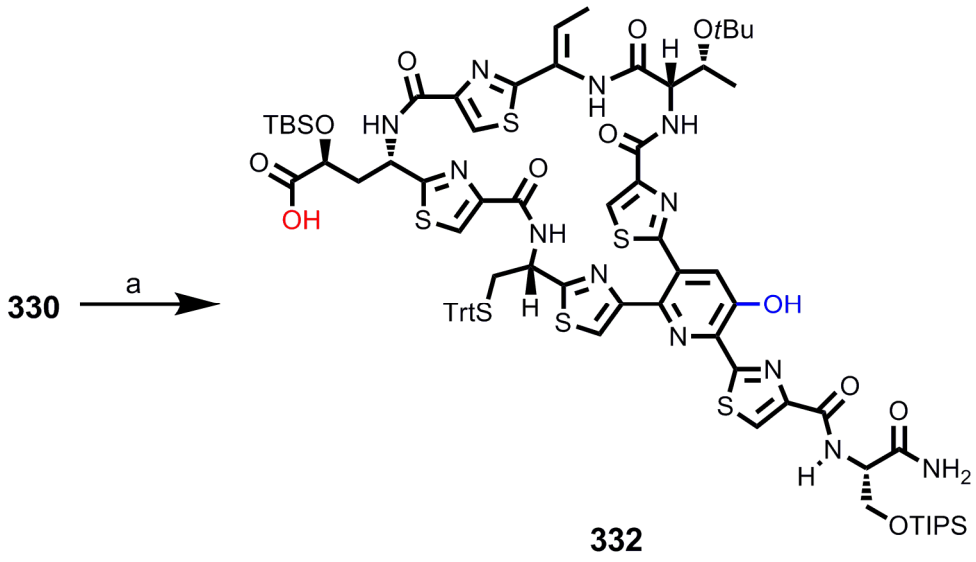
331

Entry	condition	yield
1	K_2CO_3, THF/H_2O, R.T.	n.c
2	Me_3SnOH, DCE, 80°C	detosylated
3	DABCO, toluene, 130°C	decomp.[a]
4	LiBr, Et_3N, THF	n.c
5	$AlCl_3$, anisole, CH_2Cl_2	n.c
6	BCl_3, anisole, CH_2Cl_2	n.c[b]
7	TMSCl, NaI, CH_3CN	decomp.

8	NBS, AIBN, CCl_4, rfx	decomp.
9	DDQ, dioxane, 80°C	n.c
10	$FeCl_3$, CH_2Cl_2	n.c
11	$Pd(OAc)_2$, Et_3SiH, Et_3N, CH_2Cl_2	decomp.[c]
12	Pd black, $HCOONH_4$, EtOH	n.c
13	Pd black, 1,4-hexadiene, EtOH	n.c
14	$Pd(OH)_2$, 1,4-hexadiene, EtOH	n.c

Table 3-9. Conditions screening for benzyl ester deprotection. [a] no conversion after 2 hours, decompose after 6 hours; [b] decomposition when large excess used; [c] no conversion with 20% $Pd(OAc)_2$, decomposition with large excess.

Apparently, the benzyl ester could not be selectively deprotected, but the pyridine **332** was obtained when **330** was treated with NaOH in CH_2Cl_2/MeOH. However, an attempt to *in situ* reprotect the 3-hydroxy group in **332** with tosyl chloride and transform the anticipated mixed anhydride **333** to furnish **334** proved to be not feasible in this case (figure 3-40).



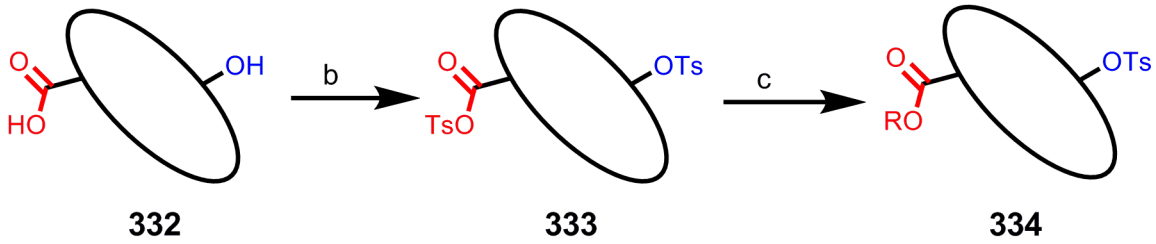


Figure 3-40. *In situ* esterification attempts. a) 2 M NaOH in MeOH, CH_2Cl_2/MeOH = 5:1, R.T.; b) TsCl, Et_3N, Cat. DMAP, CH_2Cl_2; c) ROH.

3.3.17 Bis macrocycle formation (generation 2).

The benzyl ester could not be chemoselectively cleaved, therefore, it was attempted to install the indolic alcohol already at an earlier stage. An alternative retrosynthetic analysis based on this consideration is shown in figure 3-41. The bis macrocycle **335** can be disconnected to **336** retro thioesterification. The indolic macrocycle **336** could be derived from building block **338** after the peptide coupling to **337** and macrolactam formation. Overall, a zipper like assembly may be achieved following this strategy.

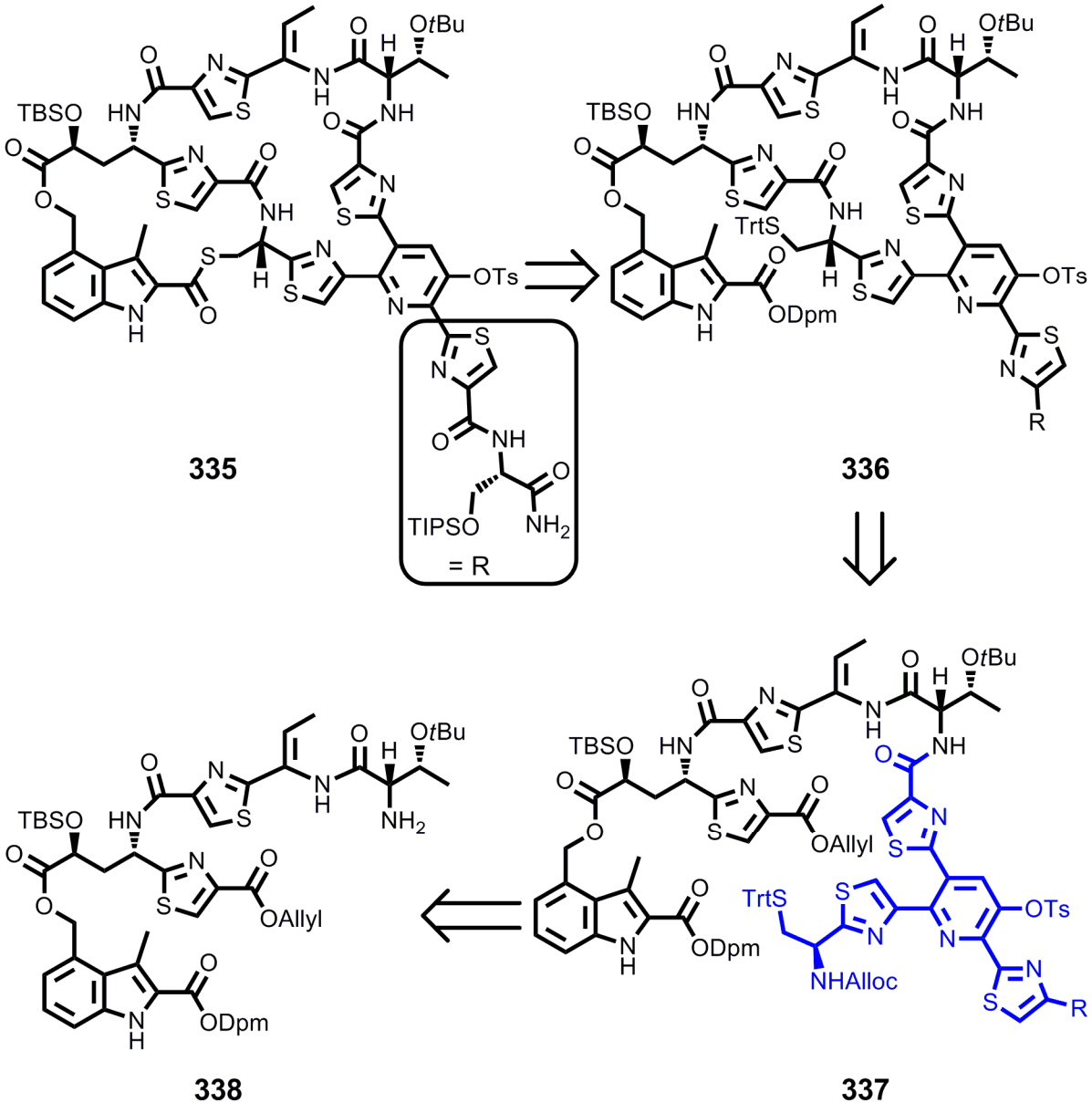


Figure 3-41. Retrosynthetic analysis for macrocycle **335** leading to zipper like annulations.

The free amine **338** could further be traced to glutamate derivative **339**, thiazolyl acid **340** and indolic alcohol **341** (figure 3-42), syntheses of there building blocks have been worked out in the group.[55] The PMB-ester was chosen because of its increased lability towards acid and oxidation reagents.[205]

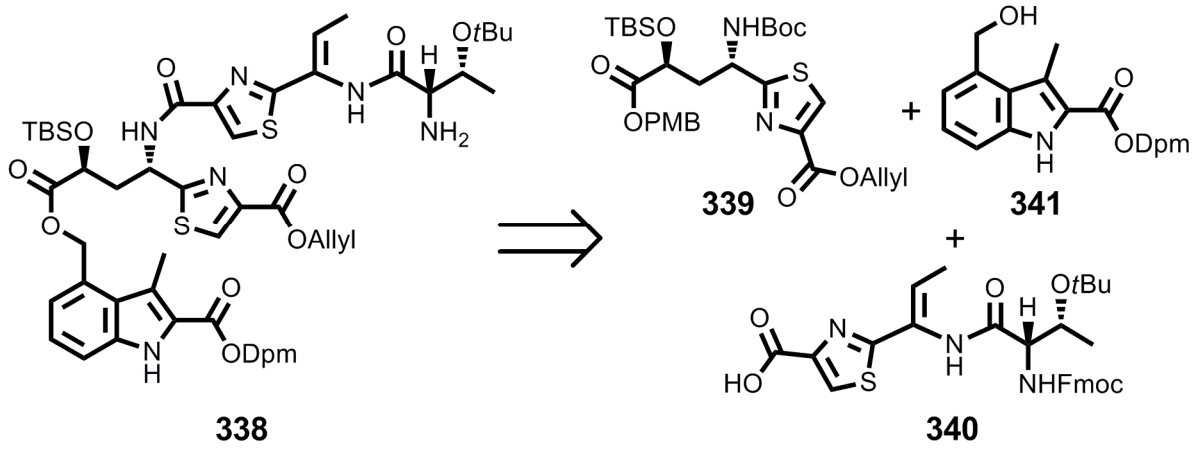
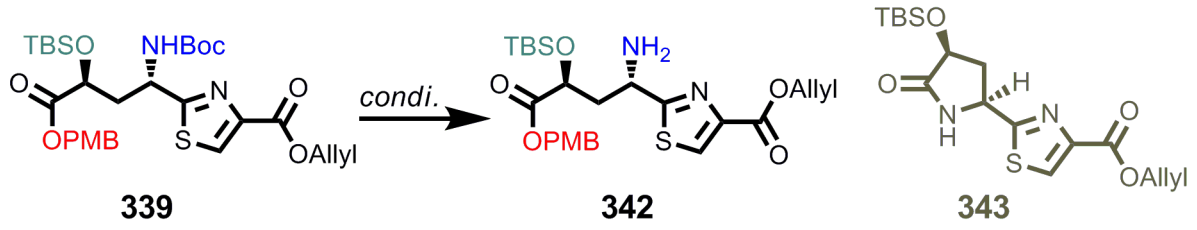


Figure 3-42. Free amine **338** synthetic analysis.

Initially, the glutamate derivative **339** was treated with 30% TFA in CH_2Cl_2. The Boc group was cleanly cleaved, but surprisingly, the PMB ester and the TBS ether became cleaved as well to give the fully deprotected product.[55] Probably, the free acid formation labilizes the neighbouring TBS ether.

Screening of deprotection conditions with Lewis acid revealed that TESOTf chemoselectively deprotected the PMB ester (table 3-10, entry 2); CAN did not cleave any functional group in the molecule (entry 3); $ZnBr_2$ mediated deprotection gave clean Boc-deprotection, but depending on the work up, lactam product **343** was formed rather easily (entry 4). Similar cases have been reported.[60] However, acidic work up yielded the desired free amine **342** (entry 5). It was found that the free amine **342** tended to undergo intra-molecular lactamization after purification, therefore, it was applied to the coupling reaction without further purification.

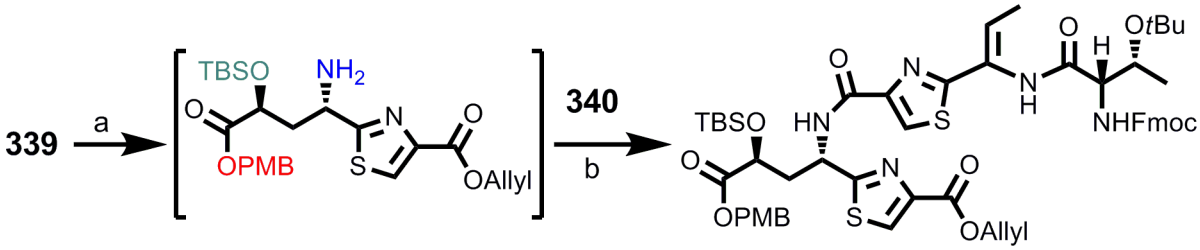


Entry	condition	yield
1	30% TFA in CH_2Cl_2	Boc, PMB, TBS cleaved

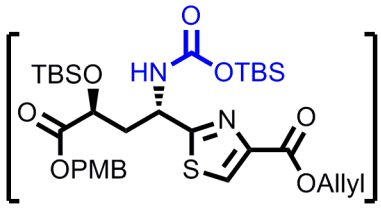
2	TESOTf, lutidine, CH_2Cl_2	PMB cleaved
3	CAN	n.c
4	$ZnBr_2$, CH_2Cl_2	**343**[a]
5	$ZnBr_2$, CH_2Cl_2	**342**[b]

Table 3-10. Boc deprotection. a) filtrate through Celite; b) acidic work up.

After $ZnBr_2$ was removed, the resulting residue from the Boc deprotection was submitted to the coupling conditions. This gave the thiazolyl peptide **344** in moderate yield (table 3-11, entry 1). The conversion efficiency was slightly better when TBSOTf was applied to cleave the Boc group (entry 2). Gratifyingly, amide **344** was obtained in good yield with a stronger coupling reagent and an inorganic base to trap any acid (entry 3). Notably, for best results the anticipated silyloxy carbonyl intermediate **342a** was neither purified nor cleaved to the free amine, but directly submitted to the coupling reaction.



342 **344**



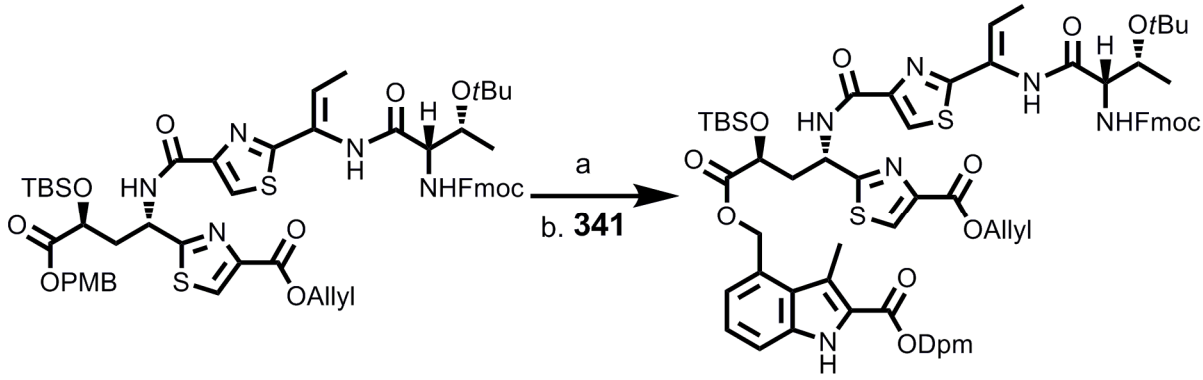
342a

Entry	a	b	yield
1	$ZnBr_2$, CH_2Cl_2	HOBt, EDC, Et_3N, CH_2Cl_2	39%
2	TBSOTf, lutidine, CH_2Cl_2	HOBt, EDC, Et_3N, CH_2Cl_2	43%
3	TBSOTf, lutidine, CH_2Cl_2	HATU, HOAt, $NaHCO_3$, THF	**59%**

Table 3-11. One pot peptide coupling.

It was then found that the PMB ester in **344** was cleanly converted to the corresponding acid under the action of $AlCl_3$ at low temperature. This resulting acid was not stable to silica gel

column chromatography (*vide supra*), and therefore directly taken to the next step. In the following esterification sequence, PyBOP activation did not lead to the ester **345** (table 3-12, entry 1); Yamaguchi and Mitsunobu conditions slowly converted the acid to the ester **345**, but not reaching full conversion even after 48 hours (TLC control) (entry 2, 3). To our delight, DCC mediated[48] esterification delivered the ester **345** in excellent yield when HOAt was applied as an additive (entry 4).



344 **345**

Entry	a[a]	b	yield
1	$AlCl_3$, - 50°C	PyBOP, DIPEA, CH_2Cl_2	0%
2	$AlCl_3$, - 50°C	ArCOCl[b], Et_3N, DMAP, THF	slow
3	$AlCl_3$, - 50°C	DIAD, PPh_3, THF	slow
4	$AlCl_3$, - 50°C	DCC, DMAP, HOAt, CH_2Cl_2	**70%**

Table 3-12. Indolic ester formation. [a] anisole/CH_2Cl_2 = 2:1 as the solvent; [b] ArCOCl = 2,4,6-trichlorobenzoyl chloride.

With peptide **345** in hand, we executed the attempt to build up the bis-macrocycle **336** (figure 3-43). Fmoc deprotection cleanly furnished the free amine **338** ready for fragment union. DEPBT mediated peptide coupling delivered the **337** in excellent yield after prep-HPLC, and palladium catalyzed deprotection cleanly gave the macrolactamization precursor **346**. However, attempts to form the macrocycle **336** using the previously established conditions were surprisingly difficult. Further experimentation should concentrate on optimizing this crucial ring forming reaction.

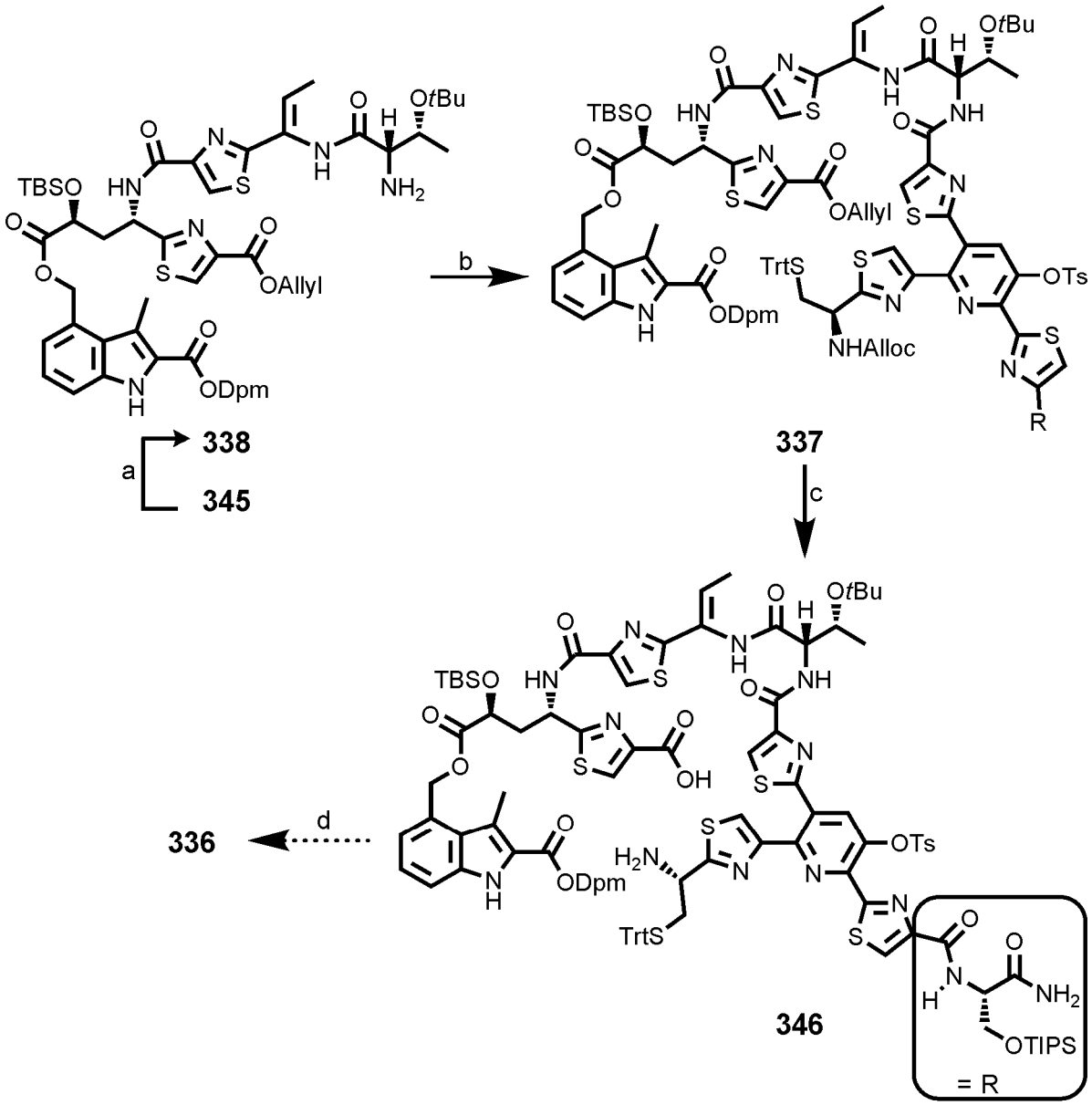


Figure 3-43. Attempted bis-macrocyle formation. a) 1% DBU in CH_2Cl_2, R.T., 5 min, 82%; b) **328**, DEPBT, $NaHCO_3$, THF, 68%; c) 20% $Pd(PPh_3)_4$, $PhSiH_3$, CH_2Cl_2, R.T., 20 min, 63%; d) HATU, DIPEA, CH_2Cl_2/DMF = 15:1.

An alternative plan was pursued, which aimed at building the macrocyle first and then attaching the indole alcohol **341** (figure 3-44). As already shown, PMB ester removal should be feasible. Test experiments showed that the coupling with PMB ester **347** can successfully yield **348**. Here, future experiments must show whether the synthesis can be continued in this way.

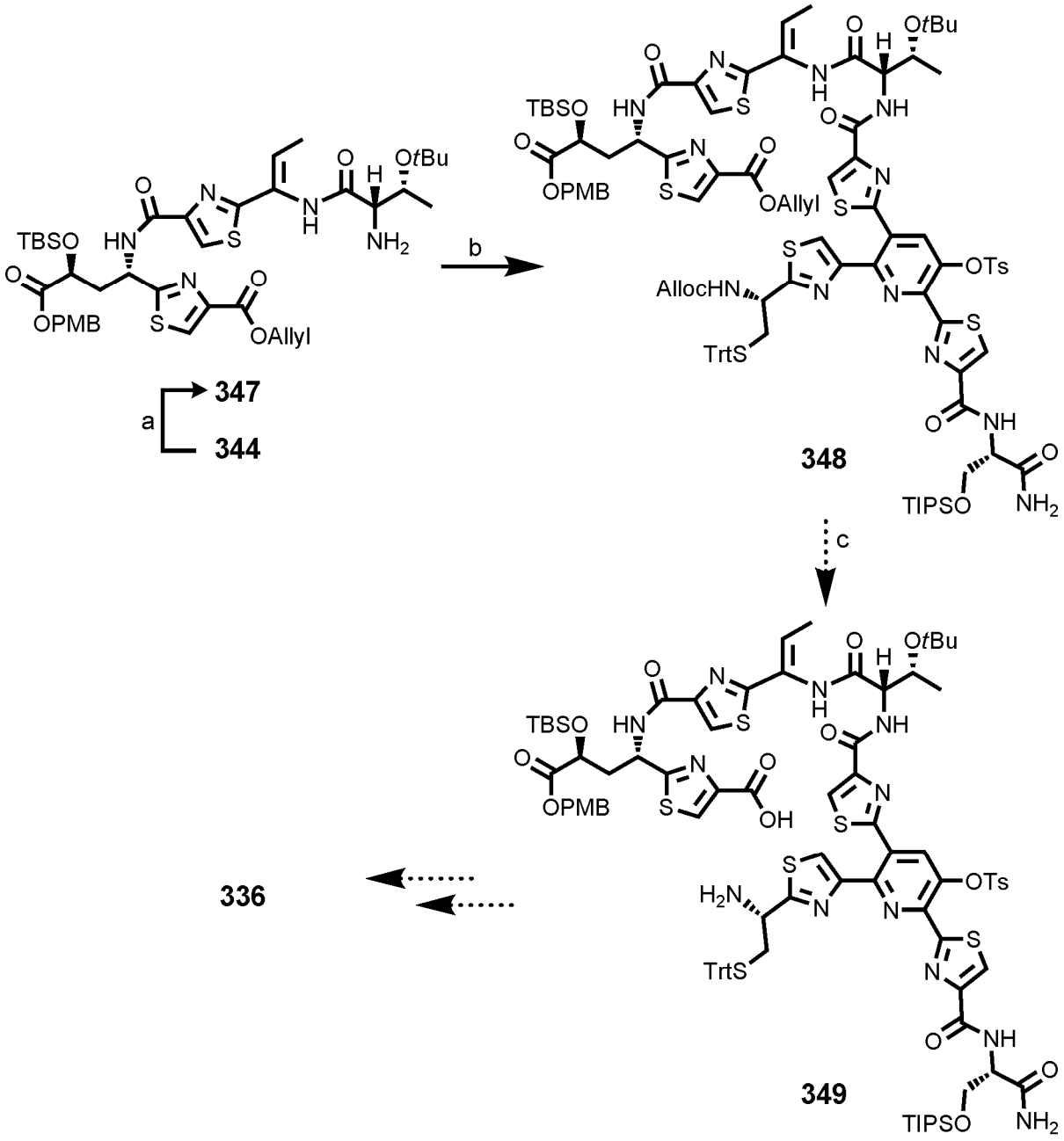


Figure 3-44. Alternative bis macrocyle formation. a) 1% DBU and 1% piperidine in CH_2Cl_2, R.T., 5 min, 88%; b) **328**, DEPBT, $NaHCO_3$, THF, 16% (**347** was recovered); c) 20% $Pd(PPh_3)_4$, $PhSiH_3$, CH_2Cl_2, R.T., 20 min.

3.3.18 Protecting group cleavage.

In order to install the second macrocycle, the trityl group needs to be selectively cleaved (figure 3-45). The free thiol was selectively obtained quantatively by treating **330** with 5% TFA, which was captured by iodoacetamide to give macrocycle **350**.

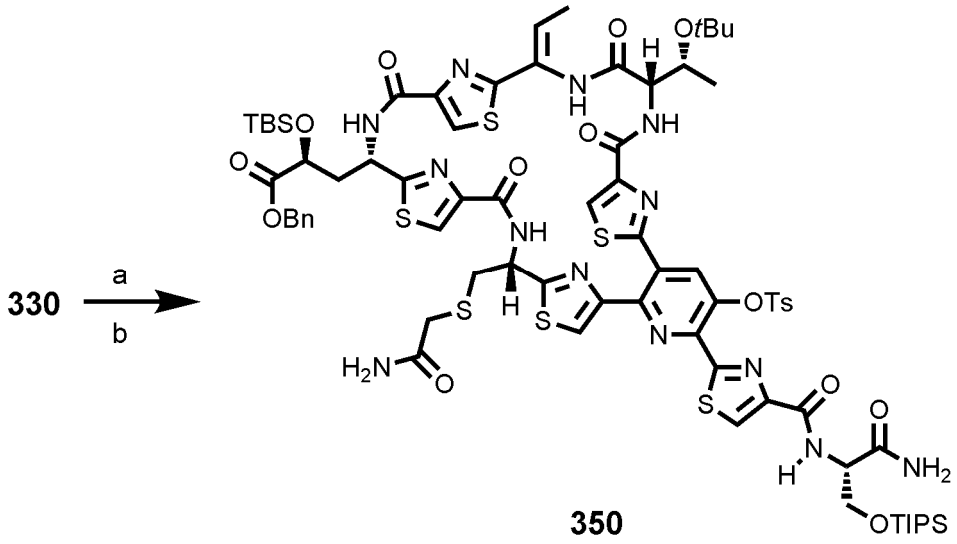


Figure 3-45. Macrocycle deprotection. A) 5% TFA in CH_2Cl_2, 1% Et_3SiH; b) $ICH_2C(O)NH_2$, DMF.

3.3.19 Indolic thioester.

As shown before, we could attach the indolic alcohol to dithazolyl peptide **344**. This left the question how the indolic thioester could be efficiently formed. In order to find suitable conditions for thioester formation, indolic alcohol **341** and dipeptide **326** were chosen as models (figure 3-46).

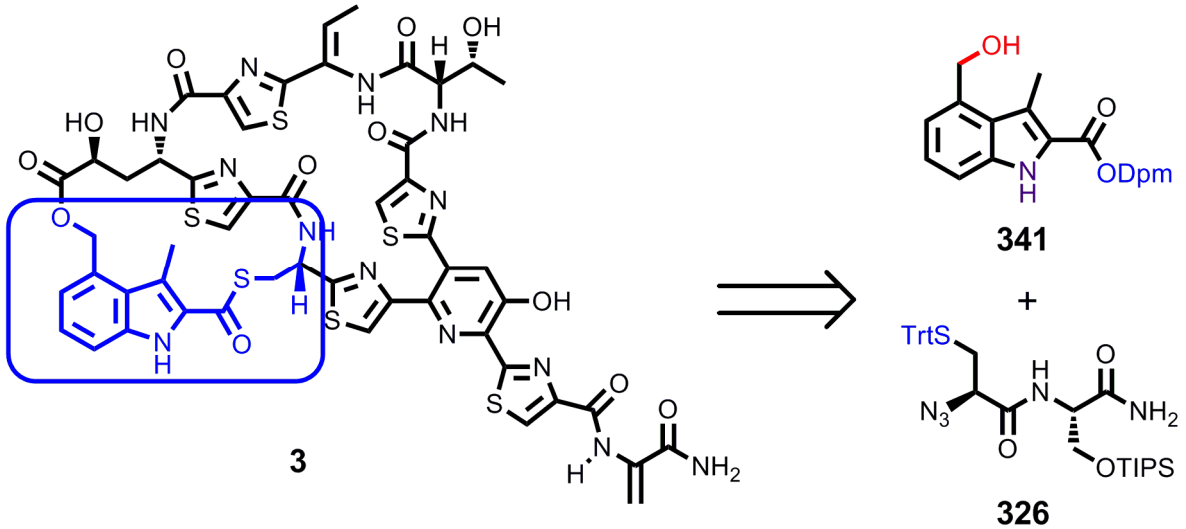


Figure 3-46. Indolic thioester retrosynthetic analysis.

Initially, a more bulky group at 3-position of the indolic acid **351** (prepared ealier by S. Thavam) was applied for screening. Among the conditions screened, PyBOP mediated

coupling gave the best result, DCC as the activating reagent led to slow conversion (figure 3-47, **A**).

Motivated by this fast and clean transformation, thioester **354** was prepared from **341** and **326** in one pot. TFA mediated deprotection and simultaneous dehydration gave **354** in excellent yield. Interestingly, the free alcohol and indole core tolerated all reaction conditions well (figure 3-47, **B**). This indicates that parallel removal of the S-Trt and DPm-ester protecting groups works well, and that thioester formation should be feasible on advanced nosiheptide precursors.

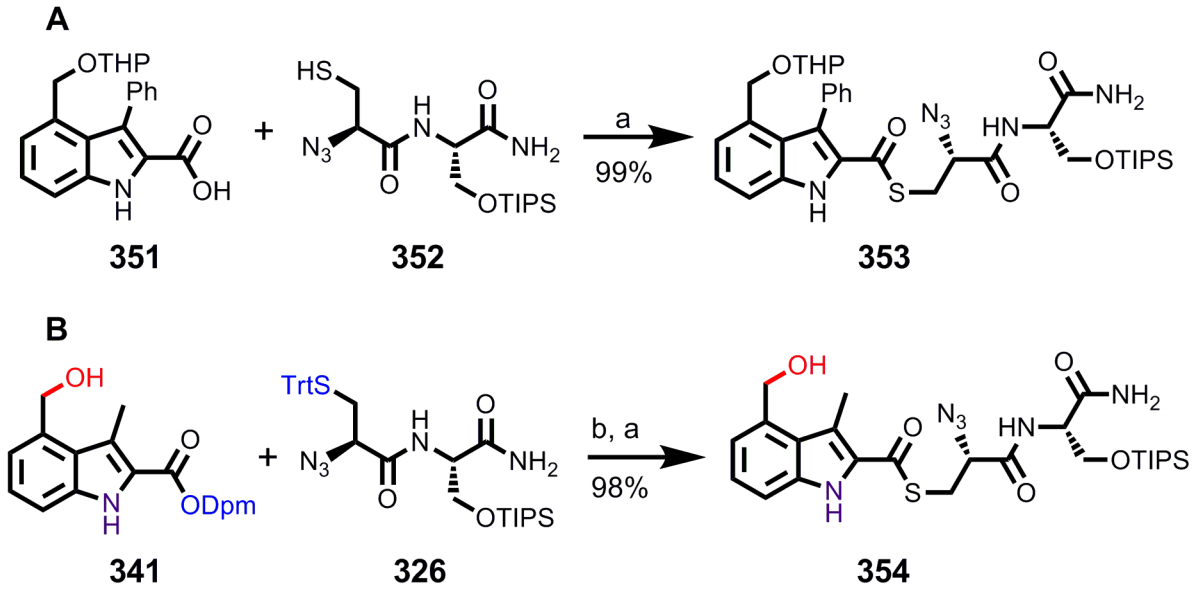


Figure 3-47. Indolic acid thioester formation. a) PyBOP, DIPEA, CH_2Cl_2, R.T., 1h, 99%; b) 5% TFA in CH_2Cl_2, Et_3SiH, R.T..

To make use of these materials, thioesters **353** and **354** was transformed further by aza-Wittig reactions, which delivered thiazoles **355** and **356** cleanly (figure 3-48). This demonstrated again the facility by which aza-Wittig reactions allow to form heterocycles in complex molecules.

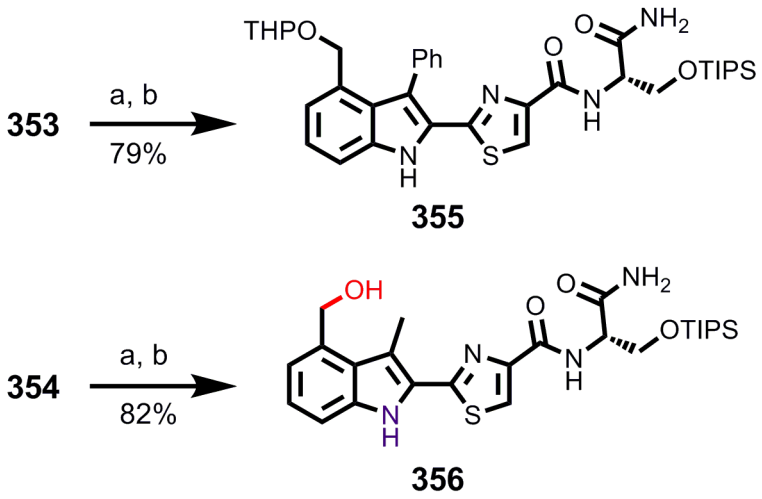


Figure 3-48. Indolic thiazole formation. a) PPh_3, THF; b) $CBrCl_3$, DBU, CH_2Cl_2.

3.4 Conclusion.

The developed HDA reaction with 1-azadiene was successfully applied to construct the central 3-hydroxypyridine core of the nosiheptide. It was found that with elevated pressure and temperature, excellent regioselectivity and yields were achieved. Protecting groups were optimized for installing the second thiazole ring, pseudo-proline like protecting groups led to racemization free Hantzsch reaction. $Sc(OTf)_3$ was found to catalyze the methyl ester hydrolysis with complete regioselectivity under mild conditions, and it was also successfully applied transesterification and transamidation. An aza-Wittig reaction was used to attach the third thiazole ring in excellent yields. Me_3SnOH mediated hydrolysis was found to convert the methyl ester to acid cleanly and quantitatively. DEPBT was identified as an optimal coupling reagent to couple the nosiheptide segments efficiently, and the linear precursor could be transformed to the macrocycle A-ring under highly diluted conditions in excellent yields after Pd^0 catalyzed deprotection of allyl and alloc groups. A benzyl group was difficult to be selectively removed with various conditions screened, but an alternative synthetic route to nosiheptide by attaching the indole ring on an earlier stage was successful. Future work should concentrate on optimizing the crucial macrocycle formation reaction and an realizing the annulation of the indole thioester.

4. Summary.

4.1. De novo synthesis of 3-hydroxypyridines by Hetero-Diels-Alder (HDA) reaction

4.1.1. HDA cycloaddition with alkynes

To achieve a total synthesis of nosiheptide **3**, the 3-hydroxypyridines have to be obtained efficiently with high economy of steps. We have developed a general, flexible access to this important class of heterocycles.

3-hydroxypyridine **88** and its isomer **89** were obtained from alkynes **84** and 1-azadienes **85** by HDA cycloaddition in one operation (figure 4-1).

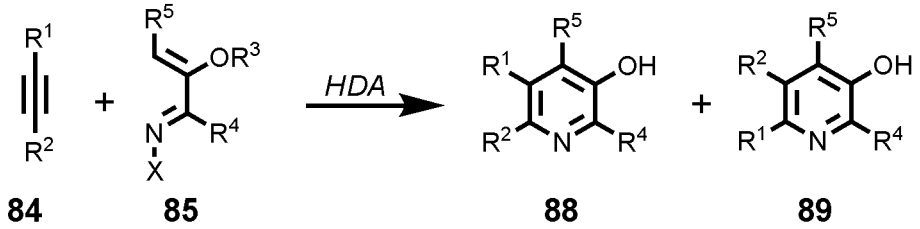


Figure 4-1. HDA cycloaddition with alkynes for 3-hydroxypyridine synthesis.

When screening conditions, alkynes and 1-azadienes, it was found that high temperature and high concentrations were beneficial for effective cycloadditions. Electron-withdrawing groups or a terminal alkyne were facilitated for yield and regioselectivity, and monosubstituted alkynyl ketones were found to deliver the 6-isomer specifically. Sterically hindered 1-azadienes and alkyne dienophiles led to low efficiency. Electron-rich alkynes were inert under these normal $HUMO_{diene}$-controlled HDA conditions.

4.1.2. Regioselective HDA cycloaddition with dicyanoalkenes

In our investigations, it was found that bis-nitriles **188** as alkyne surrogates cyclized to form pyridine **191** after aromatization of tetrahydropyridine intermediates **189** (Figure 4-2). This transformation was found to deliver the 6-cyano-3-hydroxypyridines in a completely regioselective fashion. Best results were obtained with 1-azadine **195** in DMF using microwave heating.

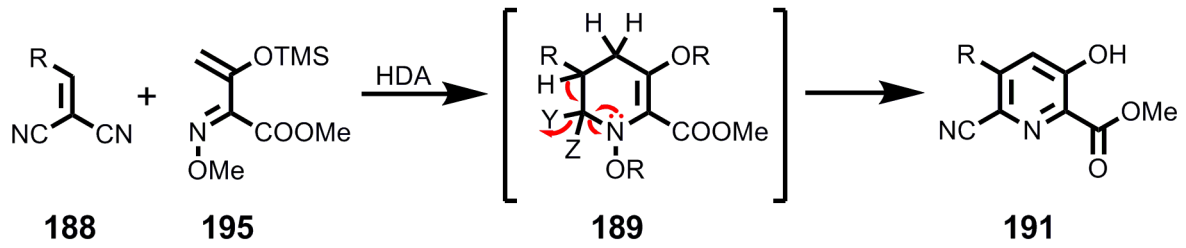


Figure 4-2. Regioselective 3-hydroxypyridine formation with dicyanoalkenes.

A broad variety of substituents are tolerated in this cycloaddition, including electron poor and electron rich aromatics, heteroaromatics, and alkyl substituents. All of them gave complete regioselectivity, electron deficient substituent on alkenes gave better yields. Importantly, 3-hydroxypyridine **191t** was obtained in excellent yield and chemoselectivity for the dicyanoalkene function (Figure 4-3). Therefore, this method holds great promise for target and diversity oriented *de-novo* pyridine synthesis.

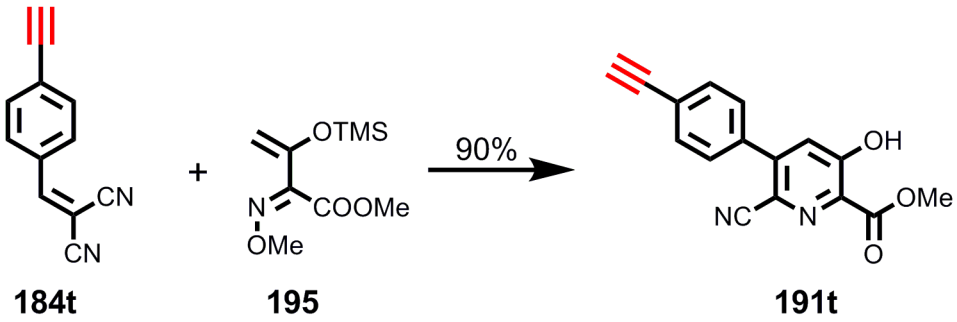


Figure 4-3. Chemoselective 3-hydroxypyridine **191t** formation.

4.1.3. Investigation of the HDA reaction mechanism by DFT calculations

To gain more insight into the driving forces guiding these HDA reactions, the mechanism was studied in collaboration with the group of T. Jacob (Universität Ulm). It could be found by DFT calculations that the HDA reaction in this case can be expected to be concerted via an unpolarized transition state (figure 4-4). Notably, the diene geometry correlated well with X-ray crystal structure data, and the matching polarities of the diene and the dienophile were in full accord with negligible solvent effects in the experiment.

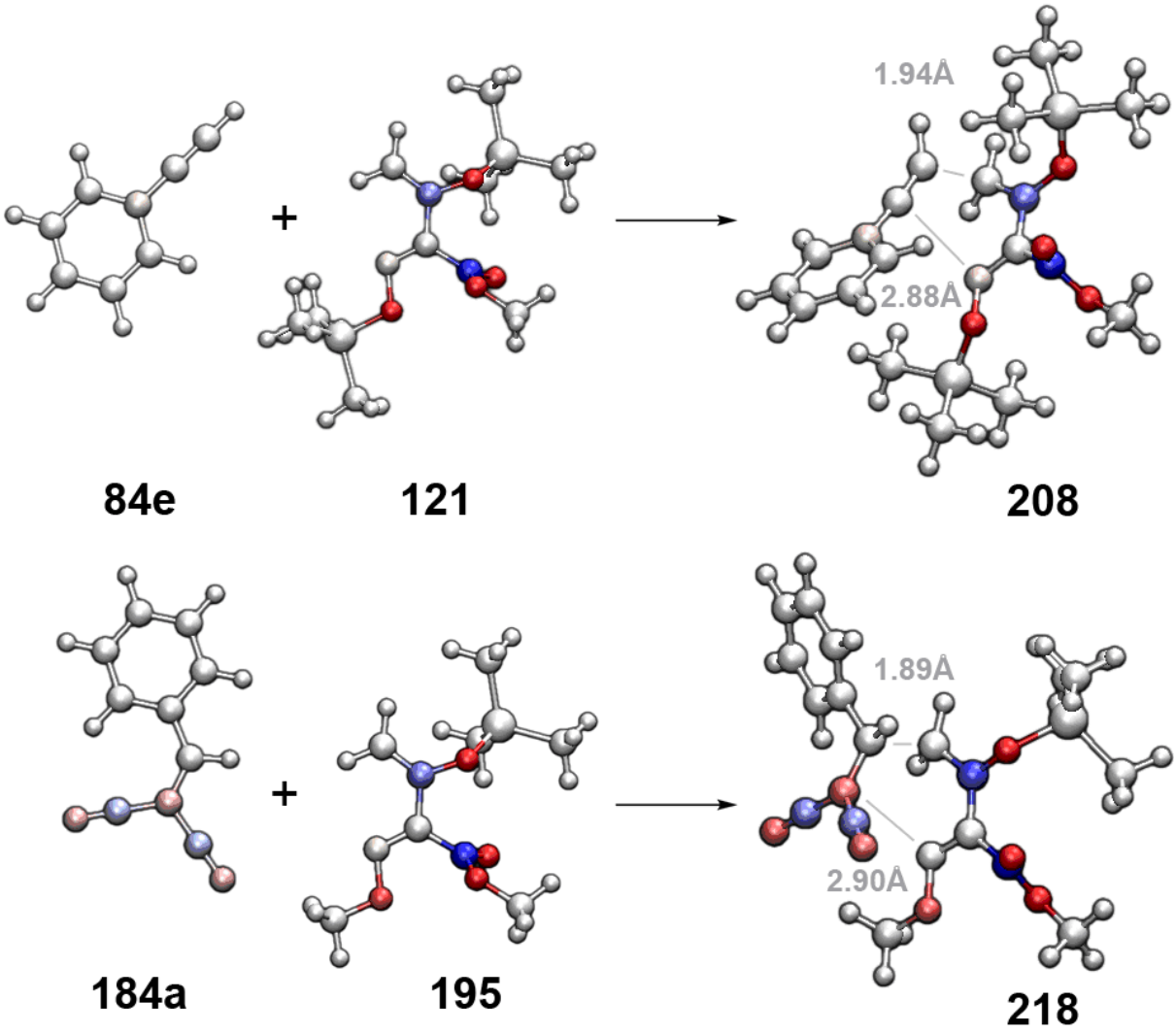


Figure 4-4. Concerted transition states geometries for alkyne and dicyanoalkene cycloadditions.

4.2. Total synthesis of nosiheptide A-ring

The newly developed HDA reaction was applied to synthesize the pyridine **233** in good regioselectivity and yield on multigram scale (figure 4-5). Fully protected pyridine **245** was obtained by annulation of suitably protected cysteine thioamide **250** and bromoketone **243** in a racemization free fashion. 3-Hydroxypyridine acid **283** was obtained using a hydroxyl-directed and $Sc(OTf)_3$ catalyzed regioselective ester hydrolysis in excellent yield under mild conditions. It was found that the ketal protecting group had to be orthoganolly exchanged (**258**) to allow the A-ring formation. A PPh_3 induced aza-Wittig reaction was applied to

smoothly append a thiazole ring to the tris-thiazolyl pyridine **327**. Ts-protection was found essential to enable consequent peptide couplings.

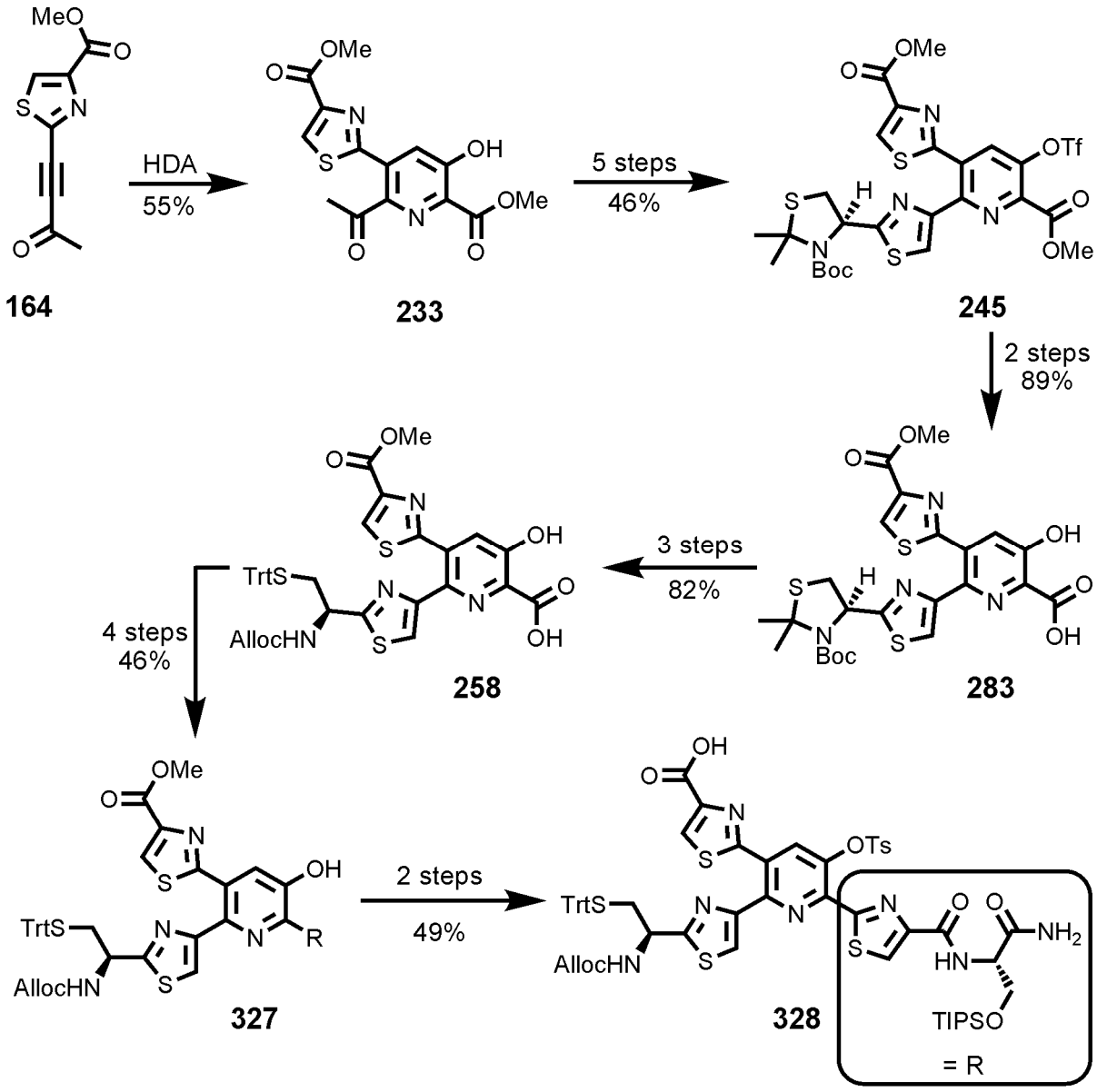


Figure 4-5. Synthesis of pyridine acid **328**.

The coupling product **329** was obtained by DEPBT activated coupling of free amine **279** and pyridine acid **328** in good yield (figure 4-6). The A-ring **330** was efficiently synthesized from **329** after Pd^0 catalyzed allyl and alloc deprotection in highly diluted solution. After trityl removal, macrocycle **330** was derivatized to amide **350**.

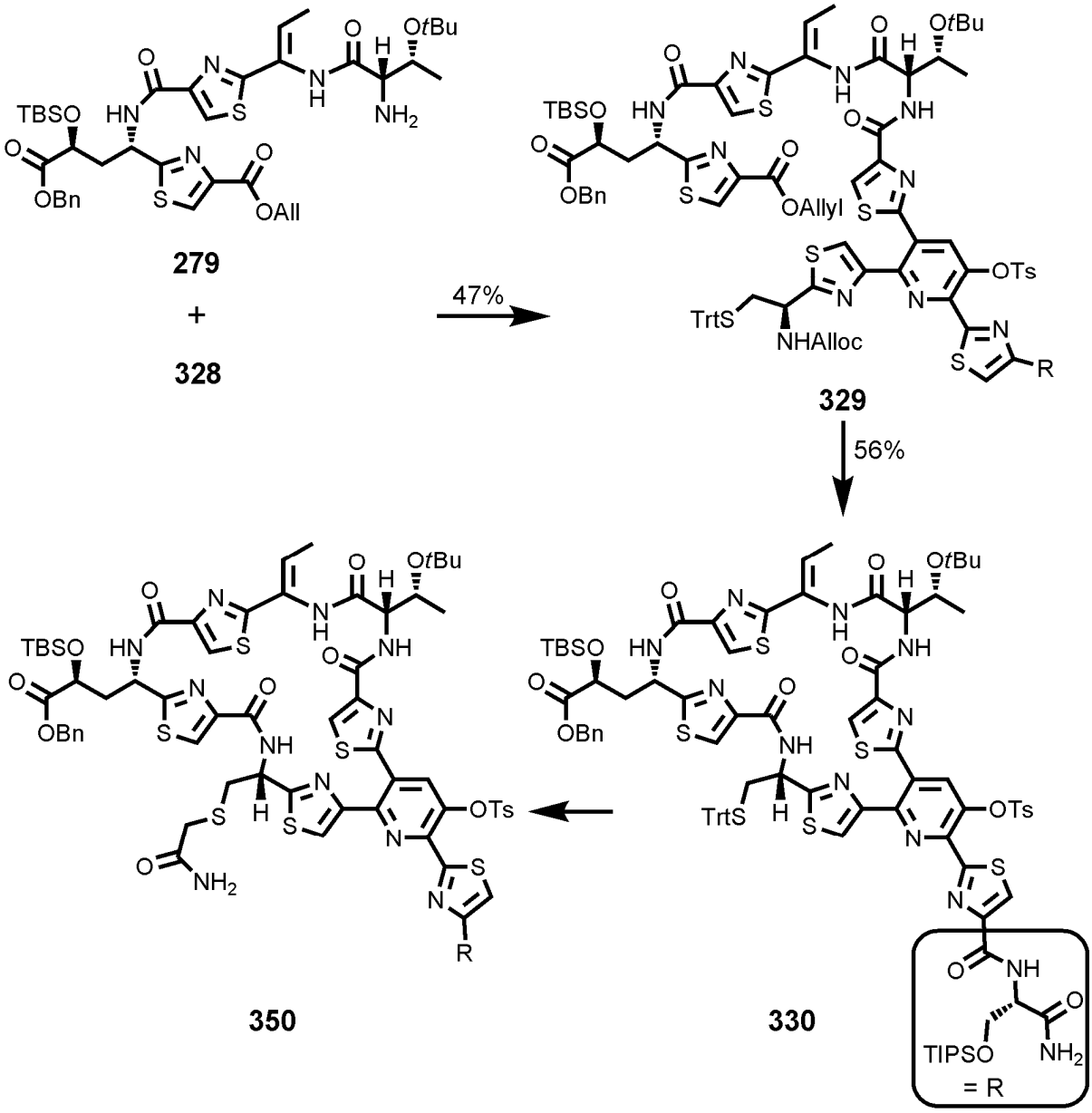


Figure 4-6. Macrolactam formation.

In summary, novel chemistry for the preparation of highly substituted 3-hydroxypyridines has been developed, and building block synthesis, coupling conditions and protecting group patterns suitable for pursuing a total synthesis of nosiheptide have been fully established. A synthesis of the nosiheptide A ring was achieved, featuring full functionalization and orthogonal protection.

Overall, important achievements have been reported here, which should securely facilitate all future undertakings toward the total synthesis of nosiheptide.

5. Experimental section

5.1 General methods

Silica gel flash liquid chromatography:

Purifications were performed using silica gel from J. T. Baker or Merck (particle size 40-60µm) under approximately 0.5 bar pressure.

Nuclear magnetic resonance spectroscopy (NMR):

^{1}H- and ^{13}C-NMR spectra were recorded using a Varian Mercury 400 spectrometer (400MHz (^{1}H) and 100.6MHz (^{13}C)). Chemical shifts are expressed in parts per million (ppm) from internal deuterated solvent standard (CDCl3: δ_H = 7.26 ppm, δ_C = 77.0 ppm; CD_3OD: δ_H = 4.84 ppm, δ_C = 49.05 ppm; DMSO: δ_H = 2.50 ppm, δ_C = 39.43 ppm; CD_3CN: δ_H =1.94 ppm, δ_H = 1.24 ppm). Coupling constants (*J*) are given in Hertz (Hz) and the following notations indicate the multiplicity of the signals: s (singlet), d (doublet), t (triplet), dd (doublet of doublet), m (multiplet), br (broad signal).

Mass spectrometry (Maldi-TOF, ESI-MS and FAB-HR/LR):

Matrix assisted laser desorption ionization time-of-flight (Maldi-TOF) measurements were carried out with a Voyager-DE Pro Biospectrometry Workstation from PerSeptive Biosystems using 2,5-dihydroxybenzoic acid as matrix (unless otherwise stated). Electrospray mass spectrometric analyses (ESI-MS) were performed on a Finnigan LCQ spectrometer. Fast atom bombardment (FAB) mass spectra were recorded on a Finnigan MAT MS 70 spectrometer, using *m*-nitrobenzylalcohol as matrix. Calculated masses were obtained using the software ChemDraw Ultra (CambridgeSoft Corporation) or Xcalibur.

Reversed-phase liquid chromatography – electronspray ionization mass spectrometry (LC-MS):

LC-MS measurements were carried out on a Hewlett Packard HPLC 1100/Finnigan LCQ mass spectrometer system using Nucleodur C18 Gravity, Nucleosyl 100-5 C18 Nautilus (Macherey-Nagel) or Jupiter C4 (Phenomenex) columns and detection at 215 and 254 nm.

Method A: Positive linear gradients of solvent B (0.1% formic acid in acetonitrile) and solvent A (0.1% formic acid in water) were used at 1mL/min flow rate.

Method B: Negative linear gradients of solvent B (10mM NH_4OH in acetonitrile) and solvent A (10mM NH_4OH in water) were used at 1mL/min flow rate.
Method C: Positive linear gradients of solvent B (0.1% formic acid and 5% THF in methanol) and solvent A (0.1% formic acid in water) were used at 1mL/min flow rate.
Method D: Negative linear gradients of solvent B (10mM NH_4OH and 5% THF in methanol) and solvent A (10mM NH_4OH in water) were used at 1mL/min flow rate.

Analytical reversed-phase high performance liquid chromatography (an. HPLC):
Analyses were performed on a Varian prostar system using CC 125/4 Nucleodur C18 Gravity 3 µm and CC 125/4 Nucleodur C4 Gravity columns (Macherey-Nagel), autosampler prostar 410 and UV/Vis detector with Varian prostar 335. Linear gradients were used at 1mL/min flow rate (A: water, B: acetonitrile, C: 2% TFA in water).

Method A (C18_pos1_17min_tfa.meth):

$$85\%A \xrightarrow{1\,\text{min}} 85\%A \xrightarrow{10\,\text{min}} 0\%A \xrightarrow{3\,\text{min}} 0\%A \xrightarrow{3\,\text{min}} 85\%A$$ (5% C in the whole sequence)

Method B (C4_pos5_25min_lu.meth):

$$95\%A \xrightarrow{1\,\text{min}} 95\%A \xrightarrow{10\,\text{min}} 15\%A \xrightarrow{2\,\text{min}} 10\%A \xrightarrow{7\,\text{min}} 10\%A \xrightarrow{2\,\text{min}} 95\%A \xrightarrow{3\,\text{min}} 95\%A$$
(0% C in the whole sequence)

Method D (C4_pos5_25min_lu.meth):

$$95\%A \xrightarrow{1\,\text{min}} 95\%A \xrightarrow{10\,\text{min}} 15\%A \xrightarrow{2\,\text{min}} 10\%A \xrightarrow{7\,\text{min}} 10\%A \xrightarrow{2\,\text{min}} 95\%A \xrightarrow{3\,\text{min}} 95\%A$$
(5% C in the whole sequence)

Preparative reverse-phase high performance liquid chromatography (prep HPLC):
Purification of compounds was performed on an Varian Prostar system using VP 250/21 Nucleodur C4 Gravity 5 µm column (Macherey-Nagel), fraction collector prostar 701 and detection at 220 ~ 240 nm with UV/Vis prostar 340. Linear gradients of solvent A (water) and solvent B (acetonitrile) were used at 20mL/min flow rate.

Method C (Semi_50min_100ACN_lu_new.meth):

(phase A and B)

$$95\%A \xrightarrow{5\,\text{min}} 50\%A \xrightarrow{5\,\text{min}} 40\%A \xrightarrow{10\,\text{min}} 5\%A \xrightarrow{30\,\text{min}} 0\%A$$

Thin layer chromatography (TLC):
TLC was carried out on Merck precoated silica gel plates (60F-254) using ultraviolet light irradiation at 254 nm and 360 nm or the following solutions as developing agents: *Staining*

solution A: molybdatophosphoric acid (25g) and cerium (IV) sulfate (10g) in concentrated sulfuric acid (60mL) and water (to 1000mL);
Staining solution B: (for detection of free amino groups): ninhydrin (300mg) in ethanol (100mL) and acetic acid (3mL).
Staining solution C: $KMnO_4$ (1g), K_2CO_3 (6.6g), 5% NaOH solution (1.7mL) in H_2O (to 100mL).

Gas chromatography – mass spectrometry (GC-MS):
Spectra were obtained from a Hewlett Packard 6890 GC system coupled to a Hewlett Packard 5973 Mass Selective Detector. A HP 5TA capillary column (0.33µm x 25m x 0.2mm) and helium flow rate of 2mL/min were used.
Method A: temperature gradient: 0min (100°C) → 1min (100°C) → 6min (300°C) → 12min (300°C).
Method B: temperature gradient: 0min (50°C) → 2min (50°C) → 8min (300°C) → 12min (300°C).

Optical rotation:
Optical rotations were measured in a Schmidt + Haensch Polartronic HH8 polarimeter at 589 nm. Concentrations are given in g/100mL solvent.

FT-IR:
Fourier transform infrared spectroscopy (FT-IR) spectra were measured in Bruker vector 22 with a diffuse reflectance head A527 from Spectra Tech (KBr as matrix) and a Bruker tensor 27 spectrometer with transmission and attenuated total reflection (ATR) and coupled with infrared microscope from Spectra Tech (neat). The following notations indicate the intensity of the absorption bands: s = strong, m = middle, w = weak, b = broad.

Melting Point:
Melting points were measured in Büchi melting point B-540 with open capillary (uncorrected).

Microwave Irradiation:
Microwave-assisted reactions were performed in a Discover (CEM Corporation) single-mode microwave instrument producing controlled irradiation, using standard sealed microwave glass vials. Reaction temperatures were monitored with an IR sensor on the outside wall of

the reaction vials. Reaction times refer to hold times at the indicated temperatures, not to total irradiation times.

5.2 Abbreviations

Ac	acetyl (CH_3CO)
AIBN	azobisisobutyronitrile
aq.	aqueous
Ar	aromatic
Bn	benzyl ($PhCH_2$)
BOP	(benzotriazol-1-yloxy)tris(dimethylamino)-phosphonium hexafluorophosphate
Bu	butyl
CAN	ceric ammonium nitrate
Cy	cyclohexyl
DBTO	dibutyltin oxide
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N,N*-dicyclohexyl carbodiimide
DCE	1,2-dichloroethane
DEPBT	3-(Diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3H)-one
DIBAL-H	diisobutylaluminiumhydride
DIPEA	*N,N*-diisopropylethylamine
DMAP	*N,N*-dimethylamino pyridine
DMF	*N,N*-dimethyl formamide
DMSO	*N,N*-dimethyl sulfoxide
DPPA	diphenylphosphoryl azide
dppe	1,2-bis(diphenylphosphino)ethane
ee	enantiomeric excess
EI	electron impact
eq.	stoichiometic equivalent
Et	ethyl (CH_3CH_2)
FAB	fast atom bombardment
Fmoc	9-fluorenylmethoxycarbonyl
GC-MS	gas chromatography-mass spectroscopy
h	hour
HFIP	hexafluoroisopropanol
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectroscopy
Hz	hertz

IBX	2-iodoxybenzoic acid
i-Pr	iso-propyl
LC-MS	liquid chromatography-mass spectroscopy
LDA	lithium diisopropylamide
Me	methyl (CH_3)
MEK	methylethylketone
min	minute
mmol	milimole
MOM	methoxy methyl (CH_3OCH_2)
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
n-Bu	normal butyl ($CH_3CH_2CH_2CH_2$)
NMR	nuclear magnetic resonance
NTf_2	bistrifluoromethanesulfonimide
PCC	pyridinium chlorochromate
Ph	phenyl (C_6H_5)
Piv	pivaloyl [$(CH_3)_3CCO$]
PPA	polyphosphoric acid
ppm	parts per million
PTLC	preparative thin layer chromatography
PTSA	*p*-toluenesulfonic acid
Py	pyridine
R_f	retention factor
R.T.	room temperature
TBAF	tetrabutylammonium fluoride
TBTO	bis(tributyltin) oxide
t-Bu	*tert*-butyl [$(CH_3)_3C$]
TBS	*tert*-butyl dimethyl silyl [$(CH_3)_3CSi(CH_3)_2$]
TBDPS	*tert*-butyl diphenyl silyl [$(CH_3)_3CSi(C_6H_5)_2$]
TES	triethyl silyl [$Si(CH_2CH_3)_3$]
Tf	trifluoromethylsulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl [$((CH_3)_2CH)_3Si$]
TLC	thin layer chromatography
TMS	trimethyl silyl [$(CH_3)_3Si$]
t_R	retention time
Trt	trityl (triphenylmethyl)
Ts	*p*-toluenesulfonyl
TS	transition state

$[\alpha]_D^{20}$ specific optical rotation

5.3 Solvents and Reagents

The reagents were purchased from Acros Chimica, Aldrich, Fluka, Merck, Novabiochem, Riedel de Haen, Roth. Deionized water was obtained using a Millipore Q-plus System.

Solvent and reagent purification.
Dichloromethane, acetonitrile, 2,6-lutidine, DIPEA and triethylamine were refluxed and distilled from CaH_2 under argon and stored with KOH. Acetonitrile was stored with molecular sieves 4Å. Xylene was dried with molecular sieves 4Å. Ethanol was refluxed with Mg and I_2 under argon and distilled, then stored with molecular sieves 4Å. Other anhydrous solvents like diethylether, DMF, MeOH, toluene and pyridine were directly purchased from Fluka. Triphenylphosphine (PPh_3) was recrystallized from ethanol. NBS was recrystallized from water. Acetic anhydride was redistilled.

5.4 Preparation of Buffers

pH 2.5 ~ 3.0 phosphate buffer
$NaH_2PO_4 \times H_2O$ (13.8 g) was dissolved in water (1 L), the H_3PO_4 was used to adjust the pH 2.5 ~ 3.0.

pH 7.0 phosphate buffer.
$NaH_2PO_4 \times H_2O$ (58 g) and $Na_2HPO_4 \times 2\ H_2O$ (103 g) were dissolved in water (1 L).

pH 10.0 buffer.
$NaHCO_3$ (84 g) and Na_2CO_3 (106 g) were dissolved in water (1 L).

5.5 Preparation of Common Reagents.

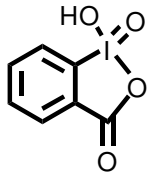
$Co(dppe)Br_2$[206]

$CoBr_2$ (1.0 g, 4.6 mmol) was added to dppe (1.82 g, 4.6 mmol) in anhydrous THF (50 mL), the resulting reaction mixture was stirred for 10h at room temperature. The green precipitate was filtered and washed with pentane (3 x 10 mL). The green solid was dried under high vacuum and gave $Co(dppe)Br_2$ 2.7 g (4.4 mmol, 96%) as a green solid.

$Pd(PPh_3)_4$[104]

$PdCl_2$ (0.5 g, 2.8 mmol) and PPh_3 (3.7 g, 14.1 mmol) were dissolved in DMSO (34 mL), the above mixture was heated up to 140°C (oil bath) for 1h. Hydrazine hydrate (0.54 mL, 11.2 mmol) was added rapidly, whereupon the reaction mixture became homogenous. The oil bath was removed and the reaction mixture was cooled to room temperature using a water bath. Yellow crystals appeared during cooling. The yellow crystals were filtered, washed with ethanol (2 x 2 mL), diethyl ether (2 x 2 mL) and dried under high vacuum to give $Pd(PPh_3)_4$ 3.20 g (2.77 mmol, 99%) as yellow crystalline solid.

IBX (2-Iodoxybenzoic acid)[158]



2-iodobenzoic acid (20 g, 80.6 mmol) was added to a solution of oxone (133 g, 213 mmol) in deionized water (800 mL). The reaction mixture was heated to 70°C and kept at this temperature for 2h. During this time the white solid on the top of the water layer was manually submerged. The reaction mixture was cooled with an ice bath for 30min, the solid was filtered and washed with cold water (3 x 10 mL), dried under high vacuum to afford IBX 21.5g (76.8 mmol, 95%) as a colorless solid.

5.6 General Procedures.

General procedure A (GP A) for the preparation of 1-aza-1,3-butadiene (double TMS protected):

In a Schlenk flask under argon, was placed the α-keto-oxime (60 mmol), NaI (30 mmol), dry triethylamine (122 mmol) and dry acetonitrile (100 mL). The flask was cooled with water,

and TMSCl (122 mmol) was added dropwise. A white solid formed during the addition. The reaction mixture was stirred at room temperature for 12 h under Ar. The precipitate was filtered off, and dry ether (3 x 10 mL) was used to wash the residue. After concentration of the filtrate, the residue was re-dissolved in dry ether (50 mL), and filtered again. The filtrate was concentrated to give a brown oil, which was distilled under high vaccum to yield the 1-aza-1,3-butadiene as colorless oil.

For mono TMS protected 1-azadiene: the same procedure was followed and the reagent reduced to 1.1 equivalents.

General procedure B (GP B) for the preparation of 1-aza-1,3-butadiene (double TES protected):

Triethylsilyl triflate (25 mmol) was added dropwise to a stirred solution of α-keto-oxime (12.5 mmol) and 2,6-lutidine (50 mmol) in dry dichloromethane (15 mL) at 0°C under argon atmosphere. The mixture was allowed to warm to room temperature after 1 h and stirred for 12 h. Saturated NaCl solution (40 mL) was added and the mixture was extracted with dichloromethane (3 x 60 mL). The combined organic extracts were dried with Na_2SO_4, concentrated to dryness and purified by column chromatography on silica gel (ethyl acetate/cyclohexane = 1:12) to give the 1-azadiene as a colorless oil.

For mono TES protected 1-azadiene: the same procedure was followed and the reagent reduced to 1.1 equivalents.

General procedure C (GP C) for the preparation of dicyanoalkene:

The aldehyde (10 mmol) and malonodinitile (10 mmol) was dissolved in a minimum volume of ethanol, NaOH solution (1N, 5 drops) was added to the above stirring solution at room temperature (TLC control). The reaction mixture was filtered and the collected solid was recrystallized from ethanol/H_2O to yield the dicyanoalkene.

General procedure D (GP D) for the preparation of 3-hydroxypyridine:

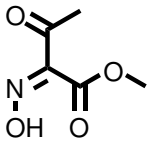
A solution of alkyne or alkyne surrogate (1 mmol) and 1-aza-1,3-butadiene (3 mmol) was heated to 150°C under Ar (TLC control). The reaction mixture was purified by column

chromatography on silica gel (ethyl acetate/cyclohexane or ethyl acetate/light petroleum) to give the title product.

General procedure E (GP E) for the preparation of 3-hydroxypyridine:
A dicyanoalkene (0.25 mmol) and a 1-azadiene (0.75 mmol) were dissolved in DMF (100 µL) in the microwave glass vial under Ar, and the reaction mixture was heated to 130°C for the time given (30 min or 60 min). The reaction mixture was cooled to room temperature, the DMF was removed under vacuum, and the residue was purified by column chromatography on silica gel to yield the title 6-cyano-3-hydroxypyridine.

5.7 Preparation of 1-Azadienes

(*Z*) 2-Hydroxyimino-3-oxo-butyric acid methyl ester (120)[96]



120

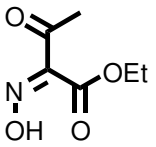
In a three-necked 250 mL flask, fitted with a thermometer, reflux condenser, and an addition funnel, was placed commercial methyl acetoacetate (14.6 mL, 135 mmol), and glacial acetic acid (17 mL). The flask was cooled in an ice-salt bath, and a solution of sodium nitrite (10.3 g, 149 mmol) in water (20 mL) was added over a period of approximately 30 min, thereby keeping the inner temperature below 5°C. The mixture was then stirred for a half hour at room temperature, water (30 mL) was added, and stirring continued for two hours.
The reaction mixture was diluted with water (100 mL), placed in a 500 mL separatory funnel, and extracted with diethyl ether (3 x 100 mL). The ether extracts were combined, washed with water (1 x 100 mL), saturated sodium bicarbonate solution (4 x 50 mL, caution! CO_2 pressure may build up), and brine (50 mL). The ether solution was dried with sodium sulfate and the solvent was evaporated. Purification of the residue by column chromatography (silica gel, 100 g, Et_2O as eluant) gave 16.6 g (0.11 mol, 84%) of oxime **120** as a colorless oil.

TLC: R_f = 0.36 (ethyl acetate/cyclohexane = 1:2).
GC-MS (method A): t_R = 2.54 min, m/Z = 145.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.41 (3H, s, $COCH_3$), 3.90 (3H, s, $COOCH_3$), 9.67 (1H, s, OH).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 25.4 ($CO\underline{C}H_3$), 52.9 ($COO\underline{C}H_3$), 151.0 (C=N), 162.0 ($\underline{C}OOCH_3$), 193.9 ($\underline{C}OCH_3$).

(*Z*) 2-Hydroxyimino-3-oxo-butyric acid ethyl ester (120a)



120a

Ethyl acetoacetate (14.6 mL, 0.1 mol) yielded 15.88 g (0.1 mol, 99%) of oxime **120a** as a colorless glass by following the same procedure as the preparation of oxime **120**.

TLC: R_f = 0.29 (ethyl acetate/cyclohexane = 1:2).

GC-MS (method B): t_R = 5.50 min, m/Z = 159.

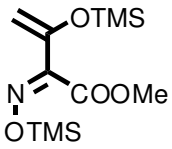
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.35(3H, t, $CH_2\underline{CH_3}$), 2.41 (3H, s, CH_3), 4.38 (2H, dd, $\underline{CH_2}CH_3$), 9.59 (1H, s, OH).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 14.0, 25.4, 62.5, 151.1, 161.7, 193.9.

IR (KBr): $\tilde{\nu}$ = 3333 (b), 2986 (s), 1747 (s), 1726 (s), 1373 (s), 1238 (s), 1075 (s), 1007 (s) cm^{-1}

HRMS (EI): Calc for $C_6H_9NO_4$ $[M]^+$, 159.0526, found: 159.0526.

(*Z*) 2-Methoxycarbonyl-1,3-bis(trimethylsiloxy)-1-aza-1,3-butadiene (121)[89]



121

GP A: oximine **120** (8.7 g, 60 mmol) yielded 15.4 g (53.4 mmol, 89%) of 1-azadiene **121** as a colorless liquid after distillation under high vaccum.

B.p.: 66°C (0.01 mbar).

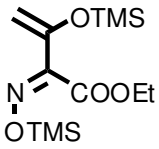
TLC: R_f = 0.73 (ethyl acetate/cyclohexane = 1:2)

GC-MS (method A): t_R = 2.95 min, m/Z = 289.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.20 (18H, s, $Si(CH_3)_3$), 3.81 (3H, s, $COOCH_3$), 4.65 (1H, d, J = 2.0 Hz, CH_2), 4.69 (1H, d, J = 2.0 Hz, CH_2).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = -0.9 (NOTMS), -0.1 (OTMS), 52.0 ($COOCH_3$), 100.8 (CH_2), 148.4 ($C=CH_2$), 154.5 (C=N), 163.7 ($COOCH_3$).

(*Z*) 2-Ethoxycarbonyl-1,3-bis(trimethylsiloxy)-1-aza-1,3-butadiene (121a)



121a

GP A: oxime **120a** (4.77 g, 30 mmol) yielded 7.8 g (25.7 mmol, 86%) of 1-azadiene **121a** as a colorless liquid after distillation under high vaccum.

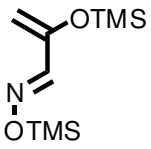
B.p.: 130°C (0.1 mbar).

GC-MS (method B): t_R = 5.83 min, m/Z = 303.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.21 (18H, s, $Si(CH_3)_3$), 1.31 (3H, t, CH_2CH_3), 4.32 (2H, dd, CH_2CH_3), 4.68 (2H, d, J = 6.3 Hz, $C=CH_2$).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = -0.9 (NOTMS), -0.1 (OTMS), 14.1 (CH_2CH_3), 61.3 (CH_2CH_3), 100.8 (CH_2), 148.5 ($C=CH_2$), 154.8 (C=N), 163.3 ($COOCH_3$).

(*E*) 1,3-Bis(trimethylsiloxy)-1-aza-1,3-butadiene (154)[89]



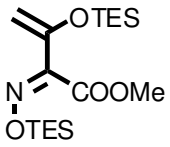
154

TMSCl (3.8 mL, 30 mmol) was added dropwise to a solution of 2-oxopropanal oxime (1.3 g, 14.9 mmol), triethylamine (4.2 mL, 30 mmol) and $ZnCl_2$ (75 mg, 0.55 mmol) in dry benzene (25 mL). The reaction mixture was stirred for 40 min at room temperature and then heated to 40°C for 12 hours under argon. After concentration, the residue was dissolved in dry ether (25 mL), the resulting precipitate was filtered off. The filtrate was concentrated to give a brown

oil, which was distilled under vacuum to give 1.44 g (6.2 mmol, 42%) of 1-azadiene **154** as a colorless oil.

GC-MS (method A): t_R = 2.08 min, m/Z = 231.
^{1}H-NMR (400 MHz, $CDCl_3$): δ = -0.08 (TMS), 4.32 (1H, d, J = 0.6 Hz, CH_2), 4.44 (1H, d, J = 0.6 Hz, CH_2), 7.37 (1H, s, CH).
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = -1.0, -0.8, 103.3, 151.8, 153.1.

(*Z*) 2-Methoxycarbonyl-1,3-bis(triethylsiloxy)-1-aza-1,3-butadiene (155)

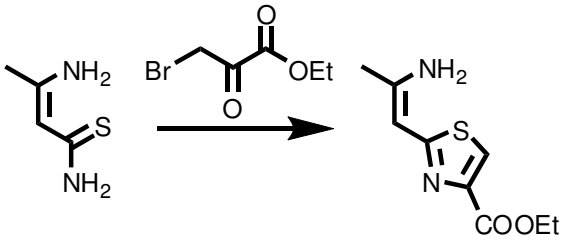


155

GP B: oxime **120** (1.81 g, 12.5 mmol) gave 4.39 g (11.8 mmol, 94%) of 1-azadiene **155** as a colorless oil.

TLC: R_f = 0.84 (ethyl acetate /cyclohexane = 1:2).
GC-MS (method A): t_R = 7.45 min, m/Z = 373 (95%), t_R = 7.39 min, m/Z = 373 (5%).
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.71-0.97 (30H, m, TES), 3.83 (3H, s, COOMe), 4.64 (1H, d, J = 2.0 Hz, C=CH_2), 4.67 (1H, d, J = 2.0 Hz, C=CH_2).
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 4.4 (C-OSi<u>C</u>H_2), 5.0 (N-OSi<u>C</u>H_2), 6.6 (C-OSiCH_2<u>C</u>H_3), 6.7 (N-OSiCH_2<u>C</u>H_3), 52.1 (COO<u>C</u>H_3), 99.6 (C=<u>C</u>H_2), 148.9 (<u>C</u>=CH_2), 154.9 (<u>C</u>-COOMe), 164.1 (<u>C</u>OOMe).
IR (KBr): $\tilde{\nu}$ = 2960 (s), 2736 (s), 1757 (s), 1600 (s), 942 (s) cm^{-1}.
HRMS (EI): Calc for $C_{17}H_{35}NO_4Si_2$ $[M]^+$, 373.2099, found: 373.2105.

(*Z*) 2-(2-Aminoprop-1-enyl)thiazole-4-carboxylic acid ethyl ester (145)

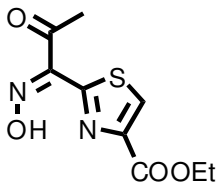


144 **145**

A mixture of 3-aminocrotonic thioamide **144** (1.16g, 10 mmol), ethyl bromopyruvate (1.4 mL, 13 mmol), triethylamine (2.1 mL, 15 mmol) and ethanol (5 mL) was heated to reflux for exactly 20 min (TLC control) and cooled quickly to room temperature. Water (100 mL) was added, the solid precipitate was filtered off and recrystallized from isopropanol (5 mL) to give 1.6 g (7.5 mmol, 76%) of thiazole **145** as a yellow solid.

M. p.: 109-110°C (isopropanol).
TLC: R_f = 0.17 (ethyl acetate/cyclohexane = 1:2).
GC-MS (method B): t_R = 7.21 min, m/Z = 212.
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.38 (3H, t, J = 7.0 Hz, -$CH_2\underline{CH_3}$), 1.99 (3H, s, CH_3), 4.36 (2H, q, J = 7.2 Hz, -$\underline{CH_2}CH_3$), 5.18 (1H, s, CH=C), 6.46 (2H, s, NH_2), 7.70 (1H, s, CH).
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 14.4 ($CH_2\underline{C}H_3$), 22.2 ($\underline{C}H_3$), 61.0 ($\underline{C}H_2CH_3$), 88.3 ($\underline{C}$H=C), 121.2 ($\underline{C}$H), 146.0 ($\underline{C}$-COOEt), 149.6 ($\underline{C}$-NH_2), 161.6 ($\underline{C}$(N)S), 168.8 ($\underline{C}OOCH_2CH_3$).
IR (KBr): $\tilde{\nu}$ = 3410 (s), 3100 (s), 2980 (s), 2903 (m), 1715 (s), 1633 (w), 1219 (s), 800 (s) cm^{-1}.
HRMS (FAB): Calc for $C_9H_{12}N_2O_2S$ $[M]^+$, 212.0619, found: 212.0607.

(*Z*) 2-(1-(Hydroxyimino)-2-oxopropyl)thiazole-4-carboxylic acid ethyl ester (146)



146

Sodium nitrite (0.16g, 2.3 mmol) in water (5 mL) was added dropwise to a cooled thiazole **145** (0.48g, 2.3 mmol) in glacial acetic acid (5 mL) and water (5 mL). The mixture was stirred for 30 min and 2 h at room temperature. Water (100 mL) was added and the mixture was extracted with Et_2O (3 x 50 mL). The ether layers were combined, washed with water (100 mL), saturated sodium bicarbonate (4 x 50 mL) and brine (50 mL). The ether solution was dried with sodium sulfate and concentrated to dryness. Purification by column chromatography (silica gel, 10 g, ethyl acetate/cyclohexane = 1:6) delivered 0.34 g (1.4 mmol, 60%) of oxime **146** as a yellow solid.

M. p.: 120-121°C.

TLC: R_f = 0.33 (ethyl acetate /cyclohexane = 1:2).

GC-MS (method B): t_R = 7.28 min, m/Z = 242.

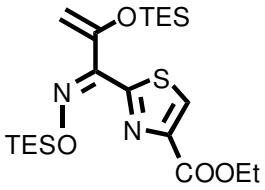
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.40 (3H, t, J = 7.2 Hz, -$CH_2\underline{CH_3}$), 2.61 (3H, s, CH_3), 4.42 (2H, q, J = 7.0 Hz, -$\underline{CH_2}CH_3$), 8.36 (1H, s, CH).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 14.2 ($CH_2\underline{CH_3}$), 24.7 (CH_3), 61.9 ($\underline{CH_2}CH_3$), 130.6 (CH), 143.7 (<u>C</u>-COOEt), 144.5 (CNS), 155.1 (C=N), 159.9 ($\underline{C}OOCH_2CH_3$), 196.5 (C=O).

IR (KBr): $\tilde{\nu}$ = 3100 (s), 2983 (s), 2956 (m), 2529 (b), 1727 (s), 1692 (m), 1227 (s), 857 (s) cm^{-1}.

HRMS (FAB): Calc for $C_9H_{10}N_2O_4S$ $[M]^+$, 242.0361, found: 242.0371.

(*Z*) 2-(4-Ethoxycarbonyl-thiazole-)-1,3-bis(triethylsiloxy)-1-aza-1,3-butadiene (147)



147

GP B: oxime **146** (0.12 g, 0.50 mmol) gave 0.23 g (0.49 mmol, 99%) of 1-azadiene **147** as a light yellow oil.

TLC: R_f = 0.65 (ethyl acetate /cyclohexane = 1:2).

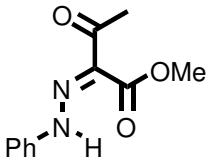
GC-MS (method B): t_R = 9.14 min, m/Z = 470.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.51-1.0 (30H, m, TES), 1.37 (3H, t, J = 7.2 Hz, $CH_2\underline{CH_3}$), 4.39 (2H, q, J = 7.0 Hz, $\underline{CH_2}CH_3$), 4.67 (1H, s, C=CH_2), 4.92 (1H, s, C=CH_2), 8.31 (1H, s, CH).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 4.2 (C-OSi$\underline{C}H_2$), 4.7 (N-OSi$\underline{C}H_2$), 6.4 (C-OSi$CH_2\underline{C}H_3$), 6.5 (N-OSi$CH_2\underline{C}H_3$), 14.2 ($CH_2\underline{C}H_3$), 61.1 ($\underline{C}H_2CH_3$), 98.1 (C=$\underline{C}H_2$), 129.7 (<u>C</u>H), 146.2 (<u>C</u>=CH_2), 151.1(<u>C</u>-COOEt), 152.6 (<u>C</u>(N)OTES), 154.1 (<u>C</u>(N)S), 161.5 ($\underline{C}OOCH_2CH_3$).

IR (KBr): $\tilde{\nu}$ = 2955 (s), 2910 (s), 2877 (s), 1746 (m), 1730 (s), 1715 (m), 1238 (s), 857 (s) cm^{-1}.

2-(Phenylamino)imino-3-oxobutyric acid methyl ester (149)[207]



149

Diazonium solution: a saturated aqueous solution of sodium nitrite (8 g, 116 mmol) was added dropwise to a stirred solution of aniline (9.5 g, 102 mmol) in HCl (5 M, 80 mL) at 0°C, the resulting mixture was kept stirring for 30 min.

A solution of methyl aceto acetate (10.8 mL, 100 mmol) in pyridine (90 mL) was diluted with water until the solution became cloudy and then cooled to 0°C. The diazonium solution was then added dropwise to the solution. During the addition, a yellow precipitate separated. The mixture was poured into ice/water (200 mL), filtered, washed with cold water (3 x 10 mL) and dried under high vacuum to give 19.7 g (89.5 mmol, 90%) of hydrazone **149** as a yellow resin.

TLC: R_f = 0.57 (ethyl acetate/cyclohexane = 1:2).

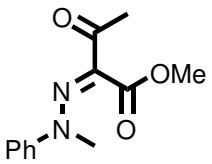
GC-MS (method B): t_R = 6.77 min, m/Z = 220.

^{1}H-NMR (400 MHz, $CDCl_3$) (*E*, *Z* mixture): δ = 2.49 (3H, s, CH_3), 2.59 (3H, s, CH_3), 3.87 (3H, s, -$COOCH_3$), 3.90 (3H, s, -$COOCH_3$), 7.14-7.43 (5H, m, Ph), 12.82 (0.5H, s, NH), 14.85 (0.5H, s, NH).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 26.8, 30.7, 51.98, 52.01, 115.6, 116.4, 125.1, 125.6, 125.8, 126.6, 129.5, 129.6, 141.5, 164.2, 165.4, 194.5, 197.0.

IR (KBr): $\tilde{\nu}$ = 2922 (s), 2845 (s), 2021 (s), 1940 (s), 1866 (s), 1730 (s) cm^{-1}.

2-(Methylphenylamino)imino-3-oxobutyric acid methyl ester (151)



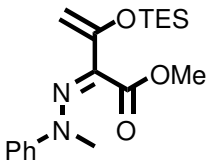
151

NaH (0.22g, 9.2 mmol) was added slowly to a cold (0°C) solution of hydrazone **149** (1.68 g, 7.6 mmol) in DMF (3 mL) and THF (30 mL), and stirred for 30 min. Then MeI (1.4 mL, 23.3 mmol) was added dropwise, stirred for 1 h and slowly warm to room temperature for 4 h

(TLC control). Methanol (2 mL) and water (20 mL) were added, the mixture was extracted with diethyl ether (3 x 60 mL), the extracts were combined and dried with sodium sulfate. Concentration and purification by column chromatography (silica gel, 20 g, ethyl acetate/cyclohexane = 1:10) gave 1.62 g (6.92 mmol, 91%) of methylhydrazone **151** as a yellow oil.

TLC: R_f = 0.47 (ethyl acetate/cyclohexane = 1:2).
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.44 (3H, s, CH_3), 3.52 (3H, s, -N$\underline{C}H_3$), 3.87 (3H, s, -$COOCH_3$), 7.14-7.41 (5H, m, Ph).
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 25.0 (CH_3), 38.3 ($\underline{C}H_3$), 52.5 ($COO\underline{C}H_3$), 117.9 (Ar), 124.5 (Ar), 129.2 (Ar), 131.9 (Ar), 147.2 (C=N), 167.3 ($\underline{C}OOCH_3$), 195.8 (-$C(=O)CH_3$).

2-Methoxycarbonyl-(methylphenylamino)imino-3-triethylsiloxy-1-aza-1,3-butadiene (152)

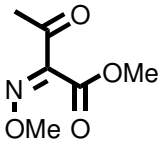


152

GP B: methyl hydrazone **151** (0.23 g, 0.98 mmol) gave 0.28 g (0.80 mmol, 82%) of 1-azadiene **152** as a light yellow oil.

TLC: R_f = 0.84 (ethyl acetate/cyclohexane = 1:2).
GC-MS (method B): t_R = 8.29 min, m/Z =348.
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.70-1.0 (15H, m, TES), 3.32 (3H, s, -$\underline{C}H_3$), 3.77 (3H, s, -$COOCH_3$), 4.43 (1H, s, C=CH_2), 4.74 (1H, s, C=CH_2), 6.94-7.24 (5H, m, Ph).
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 4.8 (C-OSi$\underline{C}H_2$), 6.6 (C-OSi$CH_2\underline{C}H_3$), 39.5 ($\underline{C}H_3$), 52.0 ($COO\underline{C}H_3$), 93.5 (C=$\underline{C}H_2$), 116.5 (Ar), 121.9 (Ar), 128.8 (Ar), 133.8 (Ar), 148.6 ($\underline{C}$=CH_2), 152.8 (C=N), 167.0 ($\underline{C}OOCH_3$).

(*Z*) 2-(Methoxyimino)-3-oxobutyric acid methyl ester (141)



141

Dimethyl sulfate (5.70 mL, 60.0 mmol) was added to a stirred reaction mixture of oxime **120** (7.25 g, 50.0 mmol) and potassium carbonate (3.8 g, 27.5 mmol) in dry acetone (50 mL) at 0°C. The reaction mixture was slowly warmed to room temperature after 2 hours and stirred for another 10 hours (TLC control). The reaction mixture was filtered and the precipitate was rinsed with acetone (3 x 10 mL). The combined filtrates were evaporated to dryness, then dissolved in diethyl ether (100 mL), washed with brine (3 x 40 mL), and dried with sodium sulfate. Concentration and purification by column chromatography (silica gel, 60 g, ethyl acetate/light petroleum = 1:8) gave 7.60 g (47.8 mmol, 96%) of the (*Z*)-2-(methoxyimino)-3-oxobutyric acid methyl ester **141** as a colorless crystalline solid.

M. p.: 62-64°C.

TLC: R_f = 0.46 (ethyl acetate/cyclohexane = 1:2).

GC-MS (method B): t_R = 4.67 min, m/Z = 159.

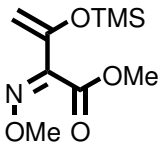
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.38 (3H, s, C(O)CH_3), 3.85 (3H, s, NOCH_3), 4.08 (3H, s, COOCH_3).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 25.1 (C(O)$\underline{C}H_3$), 52.5 (COO$\underline{C}H_3$), 64.4 (NO$\underline{C}H_3$), 149.9 ($\underline{C}$=N), 161.5 ($\underline{C}$OOCH$_3$), 192.7 ($\underline{C}$(O)CH$_3$).

IR (KBr): $\tilde{\nu}$ = 3009 (w), 2951 (w), 1744 (s), 1683 (s), 1596 (s), 1241 (s), 1021 (s), 841 (s) cm^{-1}.

HRMS (EI): Calcd for $C_6H_9NO_4$ $[M]^+$, 159.0532, found: 159.0524.

(*Z*) 2-Methoxycarbonyl-1-methoxy-3-trimethylsiloxy-1-aza-1,3-butadiene (195)



195

GP A: oxime **141** (6.78 g, 42.6 mmol) gave 9.4 g (40.7 mmol, 95%) of 1-azadiene **195** as a colorless oil.

TLC: R_f = 0.62 (ethyl acetate/cyclohexane = 1:2).

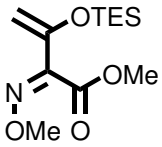
GC-MS (method B): t_R = 5.42 min, m/Z = 231.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.23 (9H, s, TMS), 3.84 (3H, s, $COOCH_3$), 3.94 (3H, s, OCH_3), 4.67 (2H, dd, J = 7.8 Hz, CH_2).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 0, 52.3, 62.7, 100.2, 148.2, 149.5, 163.3.

HRMS (EI): Calcd for $C_9H_{17}NO_4Si$ $[M]^+$, 231.0921, found: 231.0923.

(*Z*) 2-Methoxycarbonyl-1-methoxy-3-triethylsiloxy-1-aza-1,3-butadiene (195a)



195a

GP B: oxime **141** (1.6 g, 10 mmol) gave 2.7 g (9.9 mmol, 99%) of 1-azadiene **195a** as a colorless oil.

TLC: R_f = 0.64 (ethyl acetate/cyclohexane = 1:2).

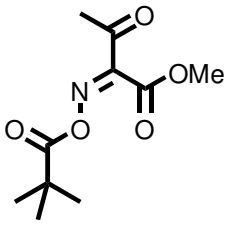
GC-MS (method B): t_R = 6.45 min, m/Z = 273.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.73 (6H, dd, J = 8.2 Hz, TES), 0.99 (9H, t, J = 7.6 Hz, TES), 3.85 (3H, s, $COOCH_3$), 3.95 (3H, s, OCH_3), 4.66 (1H, d, J = 2.3 Hz, CH_2), 4.67 (1H, d, J = 2.3 Hz, CH_2).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 4.8, 6.5, 52.3, 63.0, 99.3, 148.4, 149.5, 163.3.

HRMS (EI): Calcd for $C_{12}H_{23}NO_4Si$ $[M]^+$, 273.1391, found: 273.1394.

(*Z*) 2-(Pivaloyloxyimino)-3-oxo-butyric acid methyl ester (141a)

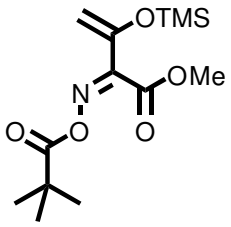


141a

DMAP (0.122 g, 1 mmol) was added to a solution of oxime **120** (1.45 g, 10 mmol), pivalic anhydride (3.04 mL, 15 mmol) and triethylamine (2.78 mL, 20 mmol) in dichloromethane (10 mL) at room temperature. The reaction mixture was stirred for 1h (TLC control). Phosphate buffer (pH 7.0, 1 M, 20 mL) was added and the mixture was extracted with dichloromethane (3 x 30 mL). The combined organic extracts were dried with sodium sulphate and concentrated to dryness. Purification by column chromatography (silica gel, 20 g, ethyl acetate/light petroleum = 1:7) gave 1.79g (7.8 mmol, 78%) of pivalate **141a** as a colorless oil.

TLC: R_f = 0.48 (ethyl acetate/cyclohexane = 1:2).
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.28 (9H, s, Piv), 2.56 (3H, s, CH_3), 3.92 (3H, s, $COOCH_3$).
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 25.9, 26.8, 38.7, 52.9, 154.2, 160.2, 173.1, 192.8.

(*Z*) 2-Methoxycarbonyl-1-pivaloyloxy-3-trimethylsiloxy-1-aza-1,3-butadiene (195f)

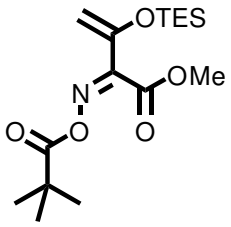


195f

GP A: oxime **141a** (0.95 g, 4.1 mmol) gave 0.42 g (1.4 mmol, 34%) of 1-azadiene **195f** as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.25 (9H, s, TMS), 1.22 (9H, s, Piv), 3.87 (3H, s, $COOCH_3$), 4.84, 4.85 (1H, dd, J = 2.4 Hz, CH_2), 4.92, 4.93 (1H, d, J = 2.4 Hz, CH_2).
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = -0.1, 26.9, 29.8, 52.5, 103.5, 147.3, 156.3, 161.9, 173.5.

(*Z*) 2-Methoxycarbonyl-1-pivaloyloxy-3-triethylsiloxy-1-aza-1,3-butadiene (195g)

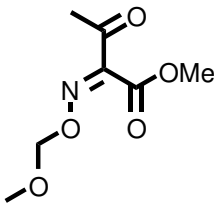


195g

GP B: oxime **141a** (1.0 g, 4.4 mmol) gave 1.34 g (3.9 mmol, 89%) of 1-azadiene **195g** as a colorless oil.

TLC: R_f = 0.58 (ethyl acetate/cyclohexane = 1:2).
GC-MS (method B): t_R = 7.38min, m/Z = 343.
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.49-0.78 (6H, m, TES), 0.91-1.01 (9H, m, TES), 1.24 (9H, s, Piv), 3.89 (3H, s, $COOCH_3$), 4.82 (1H, d, J = 2.4 Hz, CH_2), 4.96 (1H, d, J = 2.4 Hz, CH_2).
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 4.7, 6.4, 6.5, 6.8, 27.0, 38.43, 52.5, 102.0, 147.4, 156.4, 161.9, 173.6.
LRMS (EI): Calcd for $C_{16}H_{29}NO_5Si$ $[M]^+$, 343.18, found: 343.09.

(*Z*) 2-(Methoxymethoxyimino)-3-oxo-butyric acid methyl ester (141b)

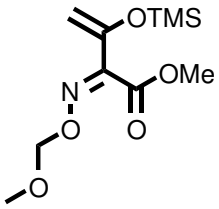


141b

Oxime **120** (1.45 g, 10 mmol), MOMCl (1.14 mL, 15 mmol) and DIPEA (3.48 mL, 20.5 mmol) were dissolved in dichloromethane (10 mL) at 0°C, the reaction mixture was stirred for 1.5 h at this temperature (TLC control). The reaction mixture was diluted with phosphate buffer (pH 7.0, 1 M, 20 mL) and extracted with dichloromethane (3 x 30 mL). The combined organic extracts were dried with sodium sulphate and concentrated to dryness. Purification by column chromatography (silica gel, ethyl acetate/light petroleum = 1:6) gave 1.72 g (9.1 mmol, 91%) of oxime **141b** as a colorless oil.

TLC: R_f = 0.39 (ethyl acetate/cyclohexane = 1:2).
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.43 (3H, s, CH_3), 3.46 (3H, s, $COOCH_3$), 3.89 (2H, s, CH_2), 5.24 (2H, s, CH_2).
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 25.3, 52.7, 56.9, 100.4, 151.5, 161.2, 192.8.

(*Z*) 2-Methoxycarbonyl-1-methoxymethoxy-3-trimethylsiloxy-1-aza-1,3-butadiene (195b)

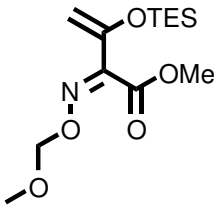


195b

GP A: oxime **141b** (1 g, 5.3 mmol) gave 1.2 g (4.6 mmol, 87%) of 1-azadiene **195b** as a colorless oil.

TLC: R_f = 0.54 (ethyl acetate/cyclohexane = 1:2).
GC-MS (method B): t_R = 5.94 min, m/Z = 261.
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.21 (9H, s, TMS), 3.39 (3H, s, CH_3), 3.84 (3H, s, $COOCH_3$), 4.71 (2H, dd, J = 2.2 Hz, CH_2), 5.11 (2H, s, MOM).
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = -0.1, 52.3, 56.2, 99.1, 100.7, 148.0, 151.3, 162.9.

(*Z*) 2-Methoxycarbonyl-1-methoxymethoxy-3-triethylsiloxy-1-aza-1,3-butadiene (195c)

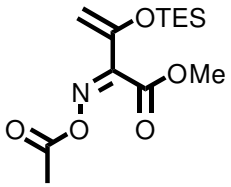


195c

GP B: oxime **141b** (0.63 g, 3.3 mmol) gave 0.97 g (3.2 mmol, 97%) of 1-azadiene **195c** as a colorless oil.

TLC: R_f = 0.51 (ethyl acetate/cyclohexane = 1:2).
GC-MS (method B): t_R = 6.88 min, m/Z = 303.
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.72 (6H, dd, TES), 0.99 (9H, t, TES), 3.41 (3H, s, CH_3), 3.87 (3H, s, $COOCH_3$), 4.69 (1H, d, J = 2.2 Hz, CH_2), 4.73 (1H, d, J = 2.2 Hz, CH_2), 5.13 (2H, s, MOM).
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 4.8, 4.5, 52.3, 56.4, 99.3, 99.7, 148.3, 151.4, 163.1.
HRMS (EI): Calcd for $C_{13}H_{25}NO_5Si$ $[M]^+$, 303.1497, found: 303.1510.

(*Z*) 2-Methoxycarbonyl-1-acetyl-3-triethylsiloxy-1-aza-1,3-butadiene (195d)

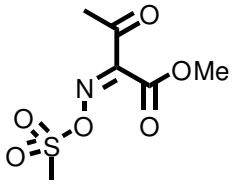


195d

GP B: 2-(actyloxyimino)-3-oxo-butyric acid methyl ester (2.0 g, 10.7 mmol) gave 1.4 g (4.6 mmol, 43%) of 1-azadiene **195d** as a light yellow oil.

TLC: R_f = 0.50 (ethyl acetate/cyclohexane = 1:2).
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.74 (6H, dd, TES), 0.99 (9H, t, TES), 2.18 (3H, s, CH_3), 3.90 (3H, s, $COOCH_3$), 4.82 (1H, d, J = 2.5 Hz, CH_2), 4.95 (1H, d, J = 2.4 Hz, CH_2)

(*Z*) 2-(Mesyloxyimino)-3-oxobutyric acid methyl ester (141d)

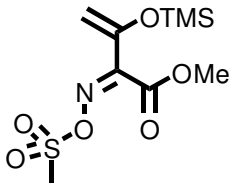


141d

Oxime **120** (1.45 g, 10 mmol), MsCl (0.93 mL, 15 mmol) and DIPEA (3.48 mL, 20.5 mmol) were dissolved in dichloromethane (10 mL) at 0°C, the reaction mixture was stirred for 3 h at this temperature (TLC control). The reaction mixture was diluted with phosphate buffer (pH 7.0, 1 M, 20 mL) and extracted with dichloromethane (3 x 30 mL). The combined organic extracts were dried with sodium sulphate and concentrated to dryness. The resulting crude product **141d** was directly used to next step without purification due to instability on silica gel column.

TLC: R_f = 0.23 (ethyl acetate/cyclohexane = 1:2).
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.25 (3H, s, CH_3), 2.54 (3H, s, $C(O)CH_3$), 3.93 (3H, s, $COOCH_3$).

(*Z*) 2-Methoxycarbonyl-1-mesyl-3-trimethylsiloxy-1-aza-1,3-butadiene (195e)

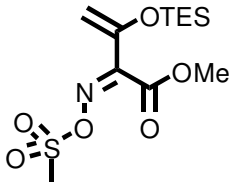


195e

GP A: oxime **141d** (2.9 g, 20 mmol) gave 0.77 g (2.6 mmol, 13% over 2 steps) of 1-azadiene **195e** as a light yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 0.23 (9H, s, TMS), 2.22 (3H, s, CH_3), 3.89 (3H, s, $COOCH_3$), 4.83 (1H, d, J = 2.4 Hz, CH_2), 4.91, 4.92 (1H, d, J = 2.4 Hz, CH_2).

(*Z*) 2-Methoxycarbonyl-1-mesyl-3-triethylsiloxy-1-aza-1,3-butadiene (195h)



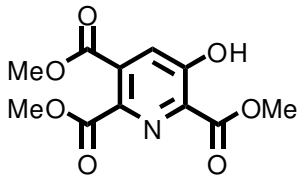
195h

GP B: oxime **141d** (1.45 g, 10 mmol) gave 0.86 g (2.5 mmol, 25% over 2 steps) of 1-azadiene **195h** as a light yellow oil.

TLC: R_f = 0.54 (ethyl acetate/cyclohexane = 1:2).
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.74 (6H, dd, TES), 0.99 (9H, t, TES), 2.18 (3H, s, CH_3), 3.90 (3H, s, $COOCH_3$), 4.82 (1H, d, J = 2.5 Hz, CH_2), 4.95 (1H, d, J = 2.4 Hz, CH_2).
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 4.7, 6.5, 19.4, 52.7, 102.1, 147.4, 155.6, 161.8, 167.4.

5.8 Preparation of 3-hydroxypyridines.

3-Hydroxy-2,5,6-pyridinetricarboxylic acid trimethyl ester (143)



143

GP D: dimethyl acetylenedicarboxylate **142** (0.12 mL, 1 mmol) and 2-methoxycarbonyl-1,3-bis(trimethylsiloxy)-1-aza-1,3-butadiene **121** (1 mL, 3.5 mmol) gave 0.267 g (1 mmol, 99%) of pyridine **143** as a white solid.

M. p.: 124-126°C.

TLC: R_f = 0.27 (ethyl acetate/cyclohexane = 1:2).

GC-MS (method A): t_R = 4.89 min, m/Z = 269.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.95 (3H, s, $COOCH_3$), 3.96 (3H, s, $COOCH_3$), 4.07 (3H, s, $COOCH_3$), 9.67 (1H, s, CH), 11.02 (1H, s, OH).

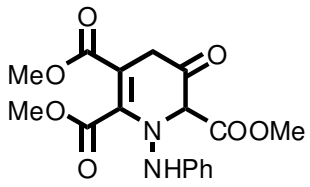
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 53.2 ($COO\underline{C}H_3$), 53.3 ($COO\underline{C}H_3$), 53.7 ($COO\underline{C}H_3$), 127.0 (C_{Ar}), 130.5 (C_{Ar}), 134.0 (C_{Ar}), 139.9 (C_{Ar}), 159.4 (<u>C</u>-OH), 164.9 (<u>C</u>$OOCH_3$), 165.3 (<u>C</u>$OOCH_3$), 168.8 (<u>C</u>$OOCH_3$).

IR (KBr): $\tilde{\nu}$ = 3155 (b), 2846 (s), 1728 (s), 1657 (s), 1555 (s), 1505 (s), 965 (s) cm^{-1}.

HRMS (FAB): Calc for $C_{11}H_{11}NO_7$ $[M + H]^+$, 270.0608, found: 270.0611.

Elemental Analysis: Calcd for $C_{11}H_{11}NO_7$, C, 49.08; H, 4.12; N, 5.20; found: C, 49.3; H, 4.0; N, 5.2.

1-(Phenylamino)-3-oxo-1,2,3,4-tetrahydropyridine-2,5,6-tricarboxylic acid methyl ester (158)



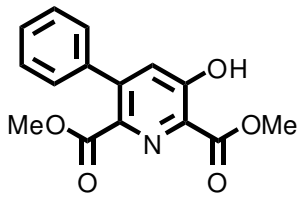
158

TMSCl (0.59 mL, 4.7 mmol) was added dropwise to a solution of hydrazone **149** (0.5 g, 2.3 mmol), NaI (0.2 g, 1.3 mmol), DMAP (0.55 g, 4.5 mmol) and dimethyl acetylenedicarboxylate **142** (0.28 mL, 2.3 mmol) in toluene/acetonitril (10 mL/6 mL). The

resulting reaction mixture was heated to 60°C for 36 hours. Brine (20 mL) was added and the mixture was extracted with dichloromethane (3 x 20 mL). Then combined organic extracts were dried with sodium sulphate and concentrated. Purification by column chromatography (silica gel, 30 g, ethyl acetate/cyclohexane = 1:6 → 1:2) gave 128 mg (0.35 mmol, 16%) of **158** as colorless glass.

TLC: R_f = 0.56 (ethyl acetate/cyclohexane = 3:2).
GC-MS (method A): t_R = 8.38 min, m/Z = 362.
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.98 (1H, dd, J = 7.8 Hz, CH_2), 3.24 (1H, dd, J = 7.4 Hz, CH_2), 3.61 (3H, s, $COOCH_3$), 3.69 (3H, s, $COOCH_3$), 3.96 (3H, s, $COOCH_3$), 4.26 (1H, t, J = 7.6 Hz, CH), 7.15 (1H, s, NH), 7.46-7.52 (5H, m, Ar).
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 33.9, 37.7, 51.9, 52.0, 52.8, 124.3, 126.2, 129.1, 129.3, 129.4, 138.9, 144.2, 165.0, 170.3, 171.4.
ESI-MS: Calc for $C_{17}H_{19}N_2O_7$ $[M + H]^+$, 363.12, found: 363.10.

3-Hydroxy-5-phenylpyridine-2,6-dicarboxylic acid dimethyl ester (160a)



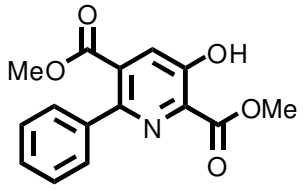
160a

GP D: alkyne **84a** (0.16 g, 1 mmol) yielded 0.2 g (0.7 mmol, 70%) **160a** as a colorless solid.

M. p.: 111-113°C.
TLC: R_f = 0.15 (ethyl acetate/cyclohexane = 1:2).
GC-MS (method A): t_R = 5.43 min, m/Z = 287.
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.63 (3H, s, $COOCH_3$), 4.07 (3H, s, $COOCH_3$), 7.28-7.44 (5H, m, Ar), 8.60 (1H, s, CH), 11.07 (1H, s, OH).
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 52.4 ($COO\underline{C}H_3$), 53.5 ($COO\underline{C}H_3$), 128.0 (Ar), 128.6 (Ar), 128.7 (Ar), 131.2 (<u>C</u>-COOMe), 132.0 (<u>C</u>-COOMe), 132.6(Ar), 139.4(<u>C</u>-Ar), 140.9 (<u>C</u>H), 156.3 (<u>C</u>-OH), 166.0 ($\underline{C}OOCH_3$), 169.6 ($\underline{C}OOCH_3$).
IR (KBr): $\tilde{\nu}$ = 3179 (b), 2957(m), 2919 (m), 2850 (m), 1747 (s), 1685 (s), 1448 (s), 807 (s) cm^{-1}.

HRMS (FAB): Calc for $C_{15}H_{14}NO_5$ $[M + H]^+$, 288.0866, found: 288.0906.

3-Hydroxy-6-phenylpyridine-2,5-dicarboxylic acid dimethyl ester (161a)



161a

GP D: alkyne **84a** (0.16 g, 1 mmol) yielded 66 mg (0.23 mmol, 23%) **161a** as a colorless solid.

M. p.: 108-109°C.

TLC: R_f = 0.37 (ethyl acetate/cyclohexane = 1:2).

GC-MS (method A): t_R = 5.38 min, m/Z = 287.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.71 (3H, s, $COOCH_3$), 4.06 (3H, s, $COOCH_3$), 7.40-7.50 (5H, m, Ph), 7.72 (1H, s, CH), 10.69 (1H, s, OH).

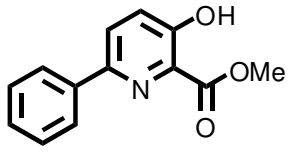
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 52.7 ($COO\underline{C}H_3$), 53.4 ($COO\underline{C}H_3$), 127.7 (<u>C</u>H), 128.3 (Ph), 128.4 (Ph), 128.6 (Ph), 130.7 (<u>C</u>-COOMe), 132.8 (Ph), 138.9 (<u>C</u>-COOMe), 149.9 (<u>C</u>-Ph), 156.9 (<u>C</u>-OH), 167.3 ($\underline{C}OOCH_3$), 169.5 ($\underline{C}OOCH_3$).

IR (KBr): $\tilde{\nu}$ = 3225 (b), 3023 (m), 2957 (m), 1730 (s), 1687 (s), 1455 (s), 798 (s) cm^{-1}.

HRMS (FAB): Calc for $C_{15}H_{14}NO_5$ $[M + H]^+$, 288.0866, found: 288.0845.

Elemental Analysis: Calcd for $C_{15}H_{13}NO_5$, C, 62.72; H, 4.56; N, 4.88; found: C, 62.8; H, 4.9; N, 4.5.

3-Hydroxy-6-phenylpyridine-2-carboxylic acid methyl ester (160e)



160e

GP D: alkyne **84e** (0.11 mL, 1 mmol) yielded 0.15 g (0.66 mmol, 66%) **160e** as a colorless solid.

M. p.: 107-109°C.

TLC: R_f = 0.47 (ethyl acetate/cyclohexane = 1:2).

GC-MS (method B): t_R = 7.13 min, m/Z = 229.

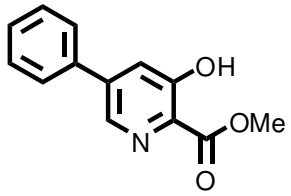
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.07 (3H, s, $COOCH_3$), 7.36-7.39 (1H, m, Ar), 7.42 (1H, d, J = 8.8 Hz, CH), 7.43-7.47 (2H, m, Ar), 7.83 (1H, d, J = 8.8 Hz, CH), 7.92-7.94 (2H, m, Ar), 10.71 (1H, s, OH).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 53.0 ($COO\underline{C}H_3$), 126.6 (C_{Ar}), 126.8 (C_{Ar}), 126.9 (C_{Ar}), 128.7 (C_{Ar}), 128.8 (C_{Ar}), 129.4 (C_{Ar}), 138.3 (C_{Ar}), 149.5 (C_{Ar}), 157.8 ($\underline{C}$-OH), 170.2 ($\underline{C}OOCH_3$).

IR (KBr): $\tilde{\nu}$ = 3092 (b), 2955 (m), 1714 (s), 1694 (s), 1372 (s), 805 (s) cm^{-1}.

HRMS (ESI): Calc for $C_{13}H_{12}NO_3$ $[M+H]^+$, 230.0812, found: 230.0811.

3-Hydroxy-5-phenylpyridine-2-carboxylic acid methyl ester (161e)



161e

GP D: alkyne **84e** (0.11 mL, 1 mmol) yielded 55 mg (0.24 mmol, 24%) **161e** as a colorless solid.

M. p.: 83-86°C.

TLC: R_f = 0.13 (ethyl acetate/cyclohexane = 1:2).

GC-MS (method B): t_R = 7.16 min, m/Z = 229.

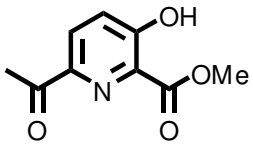
^{1}H-NMR (400 MHz, CD_3CN): δ = 4.00 (3H, s, $COOCH_3$), 7.44-7.51 (3H, m, Ar), 7.54 (1H, d, J = 4.6 Hz, CH), 7.65 (2H, m, Ar), 8.27 (1H, d, J = 4.6 Hz, CH), 11.18 (1H, s, OH).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 53.7 ($COO\underline{C}H_3$), 129.3 (C_{Ar}), 129.6 (C_{Ar}), 130.1 (C_{Ar}), 130.4 (C_{Ar}), 131.5 (C_{Ar}), 135.8 (C_{Ar}), 138.9 (C_{Ar}), 142.1 (C_{Ar}), 157.0 ($\underline{C}$-OH), 171.6 ($\underline{C}OOCH_3$).

IR (KBr): $\tilde{\nu}$ = 2955 (w), 2921 (s), 2852 (s), 1744 (s), 1694 (s), 1245 (s), 863 (s) cm^{-1}.

HRMS (ESI): Calc for $C_{13}H_{12}NO_3$ $[M+H]^+$, 230.0812, found: 230.0810.

6-Acetyl-3-hydroxypyridine-2-carboxylic acid methyl ester (160f)



160f

GP D: alkyne **84f** (0.156 mL, 2 mmol) yielded 0.21 g (1.07 mmol, 54%) **160f** as a colorless solid.

M. p.: 120-122°C.

TLC: R_f = 0.35 (ethyl acetate/cyclohexane = 1:2).

GC-MS (method B): t_R = 6.30 min, m/Z = 195.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.71 (3H, s, $COCH_3$), 4.08 (3H, s, $COOCH_3$), 7.44 (1H, d, J = 8.8 Hz, C<u>H</u>CHCOH), 8.19 (1H, d, J = 8.8 Hz, CHC<u>H</u>COH), 11.11 (1H, s, OH).

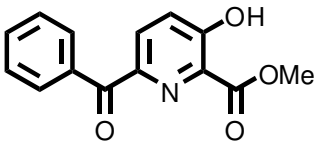
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 25.2 (C(O)<u>C</u>H_3), 53.3 (COO<u>C</u>H_3), 126.6 (<u>C</u>H), 128.0 (C<u>C</u>HCHCOH), 128.6 (<u>C</u>COOMe), 146.0 (<u>C</u>C(O)Me), 161.3 (<u>C</u>-OH), 169.7 (<u>C</u>OOMe), 198.2 (<u>C</u>(O)Me).

IR (KBr): $\tilde{\nu}$ = 3192 (b), 2968 (m), 2925 (m), 2855 (m), 1699 (s), 1681 (s), 1574 (s), 851 (s) cm^{-1}.

HRMS (FAB): Calcd for $C_9H_{10}NO_4$ $[M + H]^+$, 196.0604, found: 196.0587.

Minor isomer **9m**: GC-MS (method B): t_R = 6.55 min, m/Z = 195.

6-Benzoyl-3-hydroxypyridine-2-carboxylic acid methyl ester (160h)



160h

GP D: alkyne **84h** (0.25 g, 1.92 mmol) yielded 0.365 g (1.42 mmol, 74%) **160h** as a light yellow solid.

M. p.: 94-96°C.

TLC: R_f = 0.38 (ethyl acetate/cyclohexane = 1:2).

GC-MS (method B): t_R = 8.09 min, m/Z = 257.

^{1}H-NMR (400 MHz, CD_3CN): δ = 3.92 (3H, s, COOMe), 7.43-7.48 (2H, m, Ar), 7.48 (1H, d, *J* = 8.8 Hz, CH), 7.56-7.61 (1H, m, Ar), 8.05-8.07 (2H, m, Ar), 8.12 (1H, d, *J* = 8.8 Hz, CH), 10.93 (1H, s, OH).

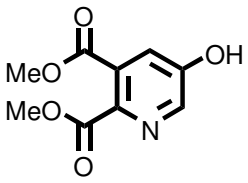
^{13}C-NMR (100.6 MHz, CD_3CN): δ = 53.6 (COO<u>C</u>H$_3$), 127.3 (<u>C</u>H), 128.7 (Ar), 129.3 (<u>C</u>-COOMe), 131.2 (CH), 131.6 (Ar), 133.4 (Ar), 137.1 (Ar), 147.1 (<u>C</u>-C(O)Ar), 160.9 (<u>C</u>-OH), 170.2 (<u>C</u>OOMe), 191.8 (<u>C</u>(O)-Ar).

IR (KBr): $\tilde{\nu}$ = 3067 (s), 2916 (w), 1679 (s), 1577 (s), 1219 (s), 944 (s), 698 (s) cm^{-1}.

HRMS (ESI): Calc for $C_{14}H_{12}NO_4$ $[M + H]^+$, 258.0761, found: 258.0762.

Minor isomer **161h** (9 mg, 1%, determined by NMR), **GC-MS (method B):** t_R = 8.28 min, m/Z = 257.

3-Hydroxypyridine-5,6-dicarboxylic dimethyl ester (156)



156

GP D: alkyne **142** (0.06 mL, 0.5 mmol) yielded 61 mg (0.29 mmol, 58%) **156** as a colorless solid.

M. p.: 133-135°C.

TLC: R_f = 0.12 (ethyl acetate/light petroleum = 1:1).

GC-MS (method A): t_R = 4.85 min, m/Z = 211.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.93 (3H, s, $COOCH_3$), 3.94 (3H, s, $COOCH_3$), 7.47 (1H, d, *J* = 2.7 Hz, CH), 8.32 (1H, d, *J* = 2.5 Hz, CH).

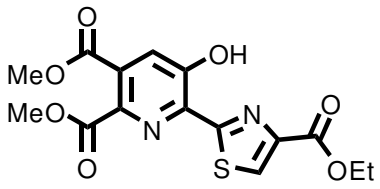
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 52.9 (COO<u>C</u>H$_3$), 53.1 (COO<u>C</u>H$_3$), 122.9 (C_{Ar}), 130.9 (C_{Ar}), 138.2 (C_{Ar}), 139.4 (C_{Ar}), 155.7 (<u>C</u>-OH), 165.9 (<u>C</u>OOCH$_3$), 166.8 (<u>C</u>OOCH$_3$).

IR (KBr): $\tilde{\nu}$ = 3100 (m), 2954 (s), 1644 (s), 1605 (s), 1504 (s), 962 (s) cm^{-1}.

HRMS (FAB): Calcd for $C_9H_{10}NO_5$ $[M + H]^+$, 212.0553, found: 212.0516.

Elemental Analysis: Calcd for $C_9H_9NO_5$, C, 51.19; H, 4.30; N, 6.63; found: C, 51.0; H, 4.4; N, 6.4.

2-(4-(Ethoxycarbonyl)thiazol-2-yl)-3-hydroxypyridine-5,6-dicarboxylic dimethyl ester (157)



157

GP D: alkyne **142** (0.12 mL, 1 mmol) and 1-azadiene **147** (0.30 g, 0.64 mmol) yielded 0.132 g (0.36 mmol, 57%) of **157** as a yellow fluorescent solid.

M. p.: 136-138°C.

TLC: R_f = 0.11 (ethyl acetate/cyclohexane = 1:2).

GC-MS (method B): t_R = 9.88 min, m/Z = 366.

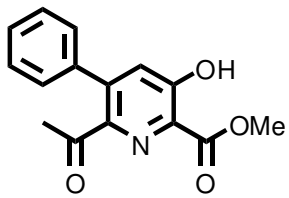
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.43 (3H, t, J = 7.2 Hz, $CH_2\underline{CH_3}$), 3.95 (3H, s, $COOCH_3$), 3.99 (3H, s, $COOCH_3$), 4.44 (2H, q, J = 7.0 Hz, $\underline{CH_2}CH_3$), 7.81 (1H, s, CH), 8.30 (1H, s, CH), 11.94 (1H, s, OH).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 14.3 ($CH_2\underline{C}H_3$), 53.0 ($COO\underline{C}H_3$), 53.1 ($COO\underline{C}H_3$), 61.8 ($\underline{C}H_2CH_3$), 126.4 (C_{Ar}), 129.1 (C_{Ar}), 129.5 (C_{Ar}), 135.6 (C_{Ar}), 141.4 (C_{Ar}), 146.7 (C_{Ar}), 153.8 ($\underline{C}$-OH), 160.2 (C_{Ar}), 165.2 ($\underline{C}OOCH_3$), 165.9 ($\underline{C}OOCH_3$), 168.7 ($\underline{C}$OOEt).

IR (KBr): $\tilde{\nu}$ = 3402 (b), 2960 (s), 2922 (s), 1741 (s), 1726 (s), 1568 (m), 1221 (s), 798 (s) cm^{-1}.

HRMS (FAB): Calcd for $C_{15}H_{15}N_2O_7S$ $[M + H]^+$, 367.0594, found: 367.0629.

6-Acetyl-3-hydroxy-5-phenylpyridine-2-carboxylic acid methyl ester (160b)



160b

GP D: alkyne **84b** (0.5 g, 3.47 mmol) yielded 0.194 g (0.72 mmol, 21%) **160b** as a colorless solid.

M. p.: 136-138°C.

TLC: R_f = 0.24 (ethyl acetate/light petroleum = 1:1).

GC-MS (method B): t_R = 8.29 min, m/Z = 271.

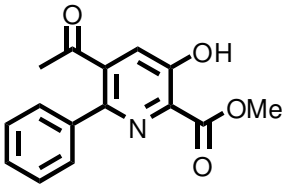
^{1}H-NMR (400 MHz, CD_3CN): δ = 1.99 (3H, s, CH_3), 4.01 (3H, s, $COOCH_3$), 7.33-7.49 (5H, m, Ar), 8.31 (1H, s, CH), 11.04 (1H, s, OH).

^{13}C-NMR (100.6 MHz, CD_3CN): δ = 30.4 ($\underline{C}H_3$), 53.6 ($COO\underline{C}H_3$), 129.2 (C_{Ar}), 129.6 (C_{Ar}), 130.3 (C_{Ar}), 131.9 (C_{Ar}), 133.5 (C_{Ar}), 137.0 (C_{Ar}), 139.6 (C_{Ar}), 141.4 (C_{Ar}), 156.6 ($\underline{C}$-OH), 170.6 ($\underline{C}OOCH_3$), 201.9 ($\underline{C}(O)CH_3$).

IR (KBr): $\tilde{\nu}$ = 3037 (s), 2967 (s), 1746 (s), 1696 (s), 1678 (s), 1397 (s), 1178 (s), 818 (s), 747 (s) cm^{-1}.

HRMS (ESI): Calcd for $C_{15}H_{14}NO_4$ $[M + H]^+$, 272.0917, found: 272.0918.

5-Acetyl-3-hydroxy-6-phenylpyridine-2-carboxylic acid methyl ester (161b)



161b

GP D: alkyne **84b** (0.5 g, 3.47 mmol) yielded 0.198 g (0.73 mmol, 21%) **161b** as a light yellow solid.

M. p.: 101-103°C.

TLC: R_f = 0.41 (ethyl acetate/cyclohexane = 1:2).

GC-MS (method B): t_R = 8.19 min, m/Z =271.

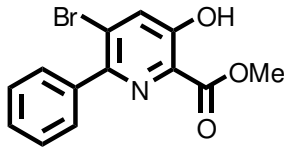
^{1}H-NMR (400 MHz, CD_3CN): δ = 2.21 (3H, s, CH_3), 3.99 (3H, s, $COOCH_3$), 7.44 (5H, s, Ar), 7.51 (1H, s, CH), 10.56 (1H, s, OH).

^{13}C-NMR (100.6 MHz, CD_3CN): δ = 30.4 ($\underline{C}H_3$), 53.8 ($COO\underline{C}H_3$), 126.1 ($\underline{C}$H), 129.4 (Ar), 129.6 (Ar), 129.6 (Ar), 131.3 ($\underline{C}$-COOMe), 139.8 (Ar), 142.3 ($\underline{C}$-CH), 148.9 ($\underline{C}$-Ar), 157.7 ($\underline{C}$-OH), 170.3 ($\underline{C}OOCH_3$), 202.5 ($\underline{C}(O)CH_3$).

IR (KBr): $\tilde{\nu}$ = 2899 (s), 2899 (w), 2850 (w), 1744 (s), 1697 (s), 1201 (s), 849 (s), 809 (s) cm^{-1}.

HRMS (ESI): Calcd for $C_{15}H_{14}NO_4$ $[M + H]^+$, 272.0917, found: 272.0918.

5-Bromo-3-hydroxy-6-phenylpyridine-2-carboxylic acid methyl ester (160c)



160c

GP D: alkyne **84c** (90 mg, 0.497 mmol) yielded 49 mg (0.16 mmol, 32%) **160c** as a colorless solid.

M. p.: 103-104°C.

TLC: R_f = 0.30 (ethyl acetate/cyclohexane = 1:2).

GC-MS (method B): t_R = 7.53 min, m/Z = 307, 308.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.03 (3H, s, $COOCH_3$), 7.42-7.63 (5H, m, Ar), 7.75 (1H, s, CH), 10.69 (1H, s, OH).

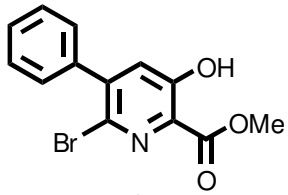
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 53.3 ($COO\underline{C}H_3$), 125.7 (<u>C</u>-Br), 128.0 (Ar), 128.7 (Ar), 129.5 (Ar), 130.8 (Ar), 136.5 (<u>C</u>H), 138.5 (<u>C</u>-COOMe), 150.4 (<u>C</u>-Ar), 157.2 (<u>C</u>-OH), 169.7 ($\underline{C}OOCH_3$).

IR (KBr): $\tilde{\nu}$ = 3171 (b), 2957 (m), 1683 (s), 1504 (m), 1434 (s), 1207 (s), 801 (s) cm^{-1}.

HRMS (FAB): Calcd for $C_{13}H_{10}NO_3{}^{79}Br$ $[M]^+$, 306.9844, found: 306.9843.

Elemental Analysis: Calcd for $C_{13}H_{10}BrNO_3$: C, 50.67; H, 3.27; N, 4.55; found: C, 50.8; H, 3.6; N, 4.2.

6-Bromo-3-hydroxy-5-phenylpyridine-2-carboxylic acid methyl ester (161c)



161c

GP D: alkyne **84c** (90 mg, 0.497 mmol) yielded 25 mg (0.08 mmol, 16%) **161c** as a colorless solid.

M. p.: 100-101°C.

TLC: R_f = 0.19 (ethyl acetate/cyclohexane = 1:2).

GC-MS (method A): t_R = 5.31 min, m/Z = 307, 308.

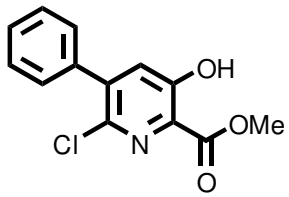
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.07 (3H, s, $COOCH_3$), 7.33-7.51 (5H, m, Ar), 8.48 (1H, s, CH), 11.07 (1H, s, OH).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 53.4 ($COO\underline{C}H_3$), 127.6 (C_{Ar}), 128.4 (C_{Ar}), 128.6 (C_{Ar}), 129.0 (C_{Ar}), 129.2 (C_{Ar}), 133.3 (C_{Ar}), 140.0 (C_{Ar}), 143.4 (C_{Ar}), 157.0 (<u>C</u>-OH), 170.0 (<u>C</u>$OOCH_3$).

IR (KBr): $\tilde{\nu}$ = 3128 (b), 1746 (s), 1681 (s), 1504 (s), 1360 (s), 898 (s), 811 (s) cm^{-1}.

HRMS (FAB): Calcd for $C_{13}H_{10}NO_3{}^{79}Br$ $[M]^+$, 306.9844, found: 306.9882.

6-Chloro-3-hydroxy-5-phenylpyridine-2-carboxylic acid methyl ester (160d)



160d

GP D: alkyne **84d** (70 mg, 0.51 mmol) yielded 46 mg (0.17 mmol, 34%) **160d** as a colorless solid.

M. p.: 108-109°C.

TLC: R_f = 0.28 (ethyl acetate/cyclohexane = 1:2).

GC-MS (method B): t_R = 7.32 min, m/Z = 263.

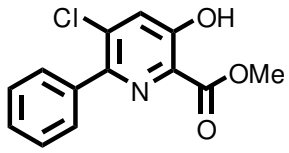
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.08 (3H, s, $COOCH_3$), 7.36-7.51 (5H, m, Ar), 8.36 (1H, s, CH), 11.11 (1H, s, OH).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 53.4 ($COO\underline{C}H_3$), 128.2 (<u>C</u>-Cl), 128.4 (Ar), 129.0 (Ar), 129.5 (Ar), 131.3 (Ar), 136.3 (<u>C</u>-COOMe), 137.7 (<u>C</u>-Ar), 141.2 (<u>C</u>H), 157.1 (<u>C</u>-OH), 169.9 (<u>C</u>$OOCH_3$).

IR (KBr): $\tilde{\nu}$ = 3054 (b), 2923 (m), 1673 (s), 1576 (m), 1397 (s), 913 (s), 812 (s) cm^{-1}.

HRMS (FAB): Calcd for $C_{13}H_{11}NO_3Cl$ $[M + H]^+$, 264.0422, found: 264.0437.

5-Chloro-3-hydroxy-6-phenylpyridine-2-carboxylic acid methyl ester (161d)



161d

GP D: alkyne **84d** (70 mg, 0.51 mmol) yielded 20 mg (0.08 mmol, 15%) **161d** as a colorless solid.

M. p.: 164-165°C.

TLC: R_f = 0.46 (ethyl acetate/cyclohexane = 1:2).

GC-MS (method B): t_R = 7.30 min, m/Z = 263.

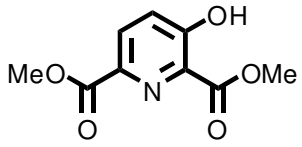
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.04 (3H, s, $COOCH_3$), 7.42-7.67 (5H, m, Ar), 7.54 (1H, s, CH), 10.72 (1H, s, OH).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 53.3 ($COO\underline{C}H_3$), 126.6 (C_{Ar}), 127.4 (C_{Ar}), 128.1 (C_{Ar}), 128.1 (C_{Ar}), 128.8 (C_{Ar}), 129.4 (C_{Ar}), 135.8 (C_{Ar}), 137.2 (C_{Ar}), 157.6 ($\underline{C}$-OH), 169.6 ($\underline{C}OOCH_3$).

IR (KBr): $\tilde{\nu}$ = 3157 (s), 2902 (m), 1683 (s), 1556 (m), 1436 (s), 802 (s) cm^{-1}.

HRMS (FAB): Calcd for $C_{13}H_{11}NO_3Cl$ $[M + H]^+$, 264.0422, found: 264.0445.

3-Hydroxypyridine-2,6-dicarboxylic acid dimethyl ester (160m)



160m

GP D: alkyne **84m** (178 µL, 2.0 mmol) yielded 235 mg (1.11 mmol, 56%) **160m** as a colorless solid.

M. p.: 170°C (decomp.).

TLC: R_f = 0.45 (ethyl acetate/light petroleum = 1:1).

GC-MS (method B): t_R = 6.80 min, m/Z = 211.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.98 (3H, s, COOMe), 4.06 (3H, s, COOMe), 7.47 (1H, d, J = 8.8 Hz, CH), 8.25 (1H, d, J = 8.8 Hz, CH), 11.08 (1H, s, OH).

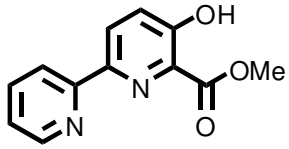
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 53.0 (COO<u>C</u>H$_3$), 53.5 (COO<u>C</u>H$_3$), 126.8 (<u>C</u>H), 129.7 (<u>C</u>-COOMe), 131.1 (CH), 139.7 (<u>C</u>-COOMe), 160.9 (<u>C</u>-OH), 164.5 (<u>C</u>OOMe), 169.4 (<u>C</u>OOMe).

IR (KBr): $\tilde{\nu}$ = 3175 (b), 2916 (w), 1726 (s), 1682 (s), 1210 (s), 900 (s), 860 (s) cm^{-1}.

HRMS (ESI): Calcd for $C_9H_{10}NO_5$ $[M + H]^+$, 212.0554, found: 212.0548.

Minor isomer **9n GC-MS (method B):** t_R = 6.76 min, m/Z = 211.

3-Hydroxy-6,2'-bipyridine-2-dicarboxylic acid methyl ester (160n)



160n

GP D: alkyne **84n** (202 µL, 2.0 mmol) yielded 230 mg (1.0 mmol, 50%) **160n** as a colorless solid.

M. p.: 158-160°C.

TLC: R_f = 0.69 (dichloromethane/MeOH = 10:1).

GC-MS (method B): t_R = 7.32 min, m/Z = 230.

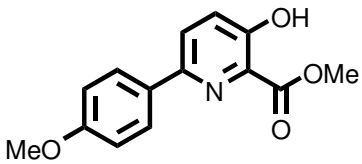
^{1}H-NMR (400 MHz, CD_3CN): δ = 4.01 (3H, s, COOMe), 7.32-7.35 (1H, m, H-C(5')), 7.47 (1H, d, J = 8.8 Hz, CH), 7.83-7.87 (1H, m, H-C(4')), 8.25-8.27 (1H, m, H-C(3')), 8.51 (1H, d, J = 8.8 Hz, CH), 8.59-8.61 (1H, m, H-C(6')), 10.69 (1H, s, OH).

^{13}C-NMR (100.6 MHz, CD_3CN): δ = 53.6, 120.9, 124.5, 127.6, 128.0, 130.3, 138.0, 148.8, 150.1, 155.8, 159.7, 170.9.

IR (KBr): $\tilde{\nu}$ = 1683 (s), 1454 (s), 1181 (s), 853 (s), 808 (s) cm^{-1}.

HRMS (ESI): Calcd for $C_{12}H_{11}N_2O_3$ $[M + H]^+$, 231.0764, found: 231.0764.

6-(4'-Methoxyphenyl)-3-hydroxypyridine-2-dicarboxylic acid methyl ester (160o)



160o

GP D: alkyne **84o** (259 µL, 2.0 mmol) yielded 102 mg (0.39 mmol, 54%) **160o** as a colorless solid based on recovered starting alkyne (150 mg, 1.14 mmol).

M. p.: 95-96°C.

TLC: R_f = 0.43 (ethyl acetate/cyclohexane = 1:2).

GC-MS (method B): t_R = 8.47 min, m/Z = 259.

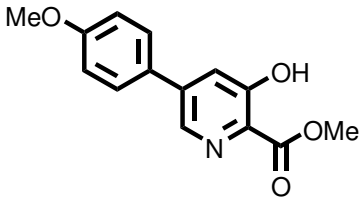
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.85 (3H, s, COOMe), 4.06 (3H, s, COOMe), 6.97-6.99 (2H, m, Ar-H), 7.41 (1H, d, J = 8.8 Hz, CH), 7.80 (1H, d, J = 8.8 Hz, CH), 7.87-7.90 (2H, m, Ar-H), 10.65 (1H, s, OH).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 53.0 (COO<u>C</u>H$_3$), 55.3 (COO<u>C</u>H$_3$), 114.2 (<u>Ar</u>), 126.3 (<u>C</u>H), 126.9 (<u>C</u>H), 127.8 (<u>Ar</u>), 129.1 (<u>C</u>-COOMe), 131.1 (<u>Ar</u>), 149.3 (<u>C</u>-Ar), 157.4 (<u>C</u>-OH), 160.2 (<u>C</u>-OMe), 170.2 (<u>C</u>OOMe).

IR (KBr): $\tilde{\nu}$ = 3175 (b), 2957 (w), 2857 (w), 1683 (s), 1463 (s), 1280 (s), 832 (s), 798 (s) cm^{-1}.

HRMS (ESI): Calcd for $C_{14}H_{14}NO_4$ [M + H$^+$], 260.0917, found: 260.0913.

5-(4'-Methoxyphenyl)-3-hydroxypyridine-2-dicarboxylic acid methyl ester (161o)



161o

GP D: alkyne **84o** (259 µL, 2.0 mmol) yielded 45.9 mg (0.18 mmol, 13%) **161o** as a colorless solid based on recovered starting alkyne (150 mg, 1.14 mmol).

M. p.: 118-120°C.

TLC: R_f = 0.16 (ethyl acetate/light petroleum = 1:1).

GC-MS (method B): t_R = 8.51 min, m/Z = 259.

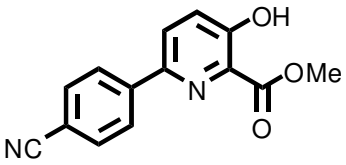
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.86 (3H, s, COOMe), 4.07 (3H, s, COOMe), 6.99-7.01 (2H, m, Ar-H), 7.45 (1H, d, J = 4.6 Hz, CH), 7.61-7.64 (2H, m, Ar-H), 8.29 (1H, d, J = 4.6 Hz, CH), 11.22 (1H, s, OH).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 53.2 (COO<u>C</u>H$_3$), 55.3 (COO<u>C</u>H$_3$), 113.9 (<u>Ar</u>), 126.7 (<u>C</u>$_{Ar}$), 128.9 (<u>C</u>$_{Ar}$), 130.4 (<u>C</u>$_{Ar}$), 130.6 (<u>C</u>$_{Ar}$), 138.3 (<u>C</u>$_{Ar}$), 141.3 (<u>C</u>$_{Ar}$), 156.5 (<u>C</u>-OH), 160.2 (<u>C</u>-OMe), 170.4 (<u>C</u>OOMe).

IR (KBr): $\tilde{\nu}$ = 3175 (b), 2846 (w), 1714 (s), 1694 (s), 1445 (s), 1230 (s), 853 (s), 802 (s) cm^{-1}.

HRMS (ESI): Calcd for $C_{14}H_{14}NO_4$ $[M + H]^+$, 260.0917, found: 260.0915.

6-(4'-Cyanophenyl)-3-hydroxypyridine-2-dicarboxylic acid methyl ester (160q)



160q

GP D: alkyne **84q** (254 mg, 2.0 mmol) yielded 200 mg (0.77 mmol, 47%) **160q** as a colorless solid based on recovered starting alkyne (42 mg, 0.33 mmol).

M. p.: 200°C (decomp.).

TLC: R_f = 0.37 (ethyl acetate/cyclohexane = 1:2).

GC-MS (method B): t_R = 8.60 min, m/Z = 254.

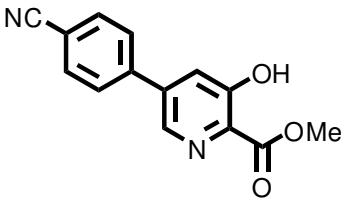
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.08 (3H, s, COOMe), 7.49 (1H, d, J = 8.8 Hz, CH), 7.74-7.76 (2H, m, Ar-H), 7.90 (1H, d, J = 8.8 Hz, CH), 8.06-8.08 (2H, m, Ar-H), 10.80 (1H, s, OH).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 53.2 (COO<u>C</u>H$_3$), 112.2 (<u>C</u>-CN), 118.7 (<u>C</u>N), 127.0 (<u>C</u>H), 127.1 (Ar-C), 127.3 (<u>CH</u>), 129.9 (<u>C</u>-COOMe), 132.6 (Ar-C), 142.3 (Ar-C), 147.0 (<u>C</u>-Ar), 158.5 (<u>C</u>-OH), 169.8 (<u>C</u>OOMe).

IR (KBr): $\tilde{\nu}$ = 3208 (b), 2922 (m), 2224 (s), 1682 (s), 1456 (s), 1181 (s), 831 (s) cm^{-1}.

HRMS (ESI): Calcd for $C_{14}H_{11}N_2O_3$ $[M + H]^+$, 255.0764, found: 255.0762.

5-(4'-Cyanophenyl)-3-hydroxypyridine-2-dicarboxylic acid methyl ester (161q)



161q

GP D: alkyne **84q** (254 mg, 2.0 mmol) yielded 100 mg (0.39 mmol, 24%) **161q** as a colorless solid based on recovered starting alkyne (42 mg, 0.33 mmol).

M. p.: 176°C (decomp.).

TLC: R_f = 0.10 (ethyl acetate/light petroleum = 1:1).

GC-MS (method B): t_R = 8.65 min, m/Z = 254.

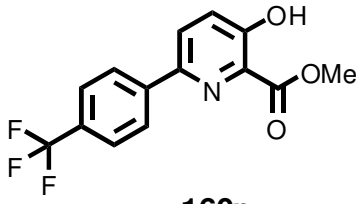
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.09 (3H, s, COOMe), 7.47 (1H, d, J = 4.6 Hz, CH), 7.76 (4H, s, Ar-H), 8.37 (1H, d, J = 4.6 Hz, CH), 11.30 (1H, s, OH).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 53.5 (COO<u>C</u>H$_3$), 112.6 (<u>Ar</u>), 118.4 (<u>C</u>N), 129.0 (<u>C</u>$_{Ar}$), 129.8 (<u>C</u>$_{Ar}$), 130.7 (<u>C</u>-COOMe), 132.2 (<u>C</u>$_{Ar}$), 136.4 (<u>C</u>$_{Ar}$), 139.0 (<u>C</u>$_{Ar}$), 141.4 (<u>C</u>$_{Ar}$), 156.0 (<u>C</u>-OH), 170.1 (<u>C</u>OOMe).

IR (KBr): $\tilde{\nu}$ = 3047 (b), 2923 (w), 2231 (s), 1666 (s), 1427 (s), 1217 (s), 831 (s) cm^{-1}.

HRMS (ESI): Calcd for $C_{14}H_{11}N_2O_3$ $[M + H]^+$, 255.0764, found: 255.0762.

6-(4'-Trifluoromethylphenyl)-3-hydroxypyridine-2-dicarboxylic acid methyl ester (160p)



160p

GP D: alkyne **84p** (326 µL, 2.0 mmol) yielded 270 mg (0.91 mmol, 50%) **160p** as a colorless solid based on recovered starting alkyne (25 mg, 0.15 mmol).

M. p.: 125-127°C.

TLC: R_f = 0.53 (ethyl acetate/cyclohexane = 1:2).

GC-MS (method B): t_R = 7.63 min, m/Z = 297.

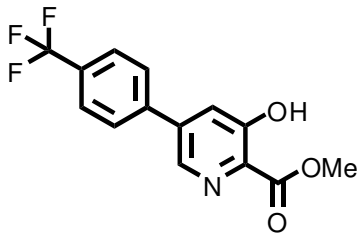
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.08 (3H, s, COOMe), 7.48 (1H, d, J = 8.8 Hz, CH), 7.70-7.72 (2H, m, Ar-H), 7.89 (1H, d, J = 8.8 Hz, CH), 8.04-8.07 (2H, m, Ar-H), 10.77 (1H, s, OH).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 53.2 (COO<u>C</u>H$_3$), 125.8 (<u>C</u>F$_3$), 125.8 (Ar-C), 126.9 (Ar-C), 126.9 (<u>C</u>H), 127.2 (<u>C</u>H), 129.8 (<u>C</u>-COOMe), 130.7 (Ar-C), 141.6 (Ar-C), 146.8 (<u>C</u>-Ar), 158.3 (<u>C</u>-OH), 170.0 (<u>C</u>OOMe).

IR (KBr): $\tilde{\nu}$ = 3079 (b), 2958 (s), 1938 (s), 1693 (s), 1336 (s), 840 (s) cm^{-1}.

HRMS (ESI): Calcd for $C_{14}H_{11}F_3NO_3$ $[M + H]^+$, 298.0686, found: 298.0684.

5-(4'-Trifuoromethylphenyl)-3-hydroxypyridine-2-dicarboxylic acid methyl ester (161p)



161p

GP D: alkyne **84p** (326 µL, 2.0 mmol) yielded 75 mg (0.25 mmol, 13%) **161p** as a colorless solid based on recovered starting alkyne (25 mg, 0.15 mmol).

M. p.: 100-103°C.

TLC: R_f = 0.02 (ethyl acetate/light petroleum = 1:1).

GC-MS (method B): t_R = 7.64 min, m/Z = 297.

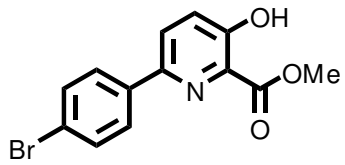
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.07 (3H, s, COOMe), 7.46 (1H, d, J = 4.6 Hz, CH), 7.70-7.76 (4H, m, Ar-H), 8.34 (1H, d, J = 4.6 Hz, CH), 11.25 (1H, s, OH).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 53.3 (COO<u>C</u>H_3), 125.3 (<u>C</u>F_3), 125.4 (Ar-C), 128.1 (<u>C</u>$_{Ar}$), 129.4 (<u>C</u>$_{Ar}$), 130.5 (<u>C</u>$_{Ar}$), 137.1 (<u>C</u>$_{Ar}$), 138.0 (<u>C</u>$_{Ar}$), 138.0 (<u>C</u>$_{Ar}$), 141.4 (<u>C</u>$_{Ar}$), 156.2 (<u>C</u>-OH), 170.1 (<u>C</u>OOMe).

IR (KBr): $\tilde{\nu}$ = 3053 (b), 1671 (s), 1326 (s), 811 (s) cm^{-1}.

HRMS (ESI): Calcd for $C_{14}H_{11}F_3NO_3$ $[M + H]^+$, 298.0686, found: 298.0684.

6-(4'-Bromophenyl)-3-hydroxypyridine-2-dicarboxylic acid methyl ester (160s)



160s

GP D: alkyne **84s** (362 mg, 2.0 mmol) yielded 142.6 mg (0.46 mmol, 24%) **160s** as a colorless solid based on recovered starting alkyne (18 mg, 0.10 mmol).

M. p.: 152-154°C.

TLC: R_f = 0.51 (ethyl acetate/cyclohexane = 1:2).

GC-MS (method B): t_R = 8.56 min, m/Z = 307.

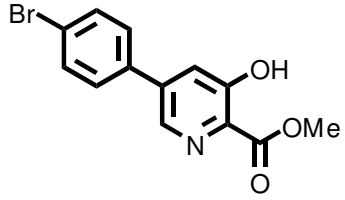
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.06 (3H, s, COOMe), 7.43 (1H, d, J = 7.8 Hz, CH), 7.57 (2H, d, J = 8.6 Hz, 2 x CH), 7.81 (3H, d, J = 8.6 Hz, 2 x CH, CH), 10.72 (1H, s, OH).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 53.1, 123.1, 126.5, 127.1, 128.1, 129.5, 131.9, 137.2, 148.2, 157.9, 170.0.

IR (KBr): $\tilde{\nu}$ = 3226 (b), 2959 (m), 1682 (s), 1457 (s), 1173 (s), 822 (s) cm^{-1}.

HRMS (ESI): Calcd for $C_{13}H_{10}{}^{81}BrNO_3Na$ $[M + Na]^+$, 331.9716, found: 331.9715.

5-(4'-Bromophenyl)-3-hydroxypyridine-2-dicarboxylic acid methyl ester (161s)



161s

GP D: alkyne **84s** (362 mg, 2.0 mmol) yielded 87.6 mg (0.29 mmol, 15%) **161s** as a colorless solid based on recovered starting alkyne (18 mg, 0.10 mmol).

M. p.: 137°C (decomposition).

TLC: R_f = 0.21 (ethyl acetate/light petroleum = 1:1).

GC-MS (method B): t_R = 8.59 min, m/Z = 307.

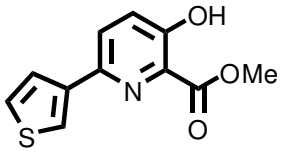
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.09 (3H, s, COOMe), 7.46 (1H, d, J = 4.6 Hz, CH), 7.54 (2H, d, J = 8.8 Hz, 2 x CH), 7.61 (2H, d, J = 8.8 Hz, 2 x CH), 8.33 (1H, d, J = 4.6 Hz , CH), 11.24 (1H, s, OH).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 53.4, 123.4, 129.1, 130.3, 130.7, 131.7, 133.3, 137.6, 141.3, 156.2, 170.2.

IR (KBr): $\tilde{\nu}$ = 3173 (b), 2956 (m), 1745 (s), 1446 (s), 1176 (s), 849 (s) cm^{-1}.

HRMS (ESI): Calcd for $C_{13}H_{10}{}^{79}BrNO_3Na$ $[M+ Na]^+$, 329.9736, found: 329.9737.

6-(Thiophen-3'-yl)-3-hydroxypyridine-2-carboxylic acid methyl ester (160u)



160u

GP D: alkyne **84u** (197 µL, 2.0 mmol) yielded 53.6 mg (0.23 mmol, 12%) **160u** as a colorless solid.

M. p.: 72-74°C.

TLC: R_f = 0.51 (ethyl acetate/cyclohexane = 1:2).

GC-MS (method B): t_R = 7.78 min, m/Z =235.

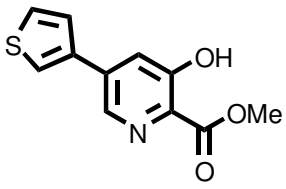
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.05 (3H, s, COOMe), 7.38 (1H, t, J = 4.9 Hz, CH), 7.39 (1H, d, J = 8.8 Hz, CH), 7.63 (1H, dd, J = 4.9 Hz, CH), 7.74 (1H, d, J = 8.6 Hz, CH), 7.79 (1H, dd, J = 3.0 Hz, CH), 10.68 (1H, s, OH).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 53.0, 122.8, 126.1, 126.4, 126.8, 126.9, 129.1, 141.1, 145.9, 157.5, 170.1.

IR (KBr): $\tilde{\nu}$ = 3263 (b), 2957 (m), 1713 (s), 1696 (s), 1471 (s), 1231 (s), 803 (s) cm^{-1}.

HRMS (ESI): Calcd for $C_{11}H_{10}NO_3S$ $[M + H]^+$, 236.0376, found: 236.0374.

5-(Thiophen-3'-yl)-3-hydroxypyridine-2-carboxylic acid methyl ester (161u)



161u

GP D: alkyne **84u** (197 µL, 2.0 mmol) yielded 33.1 mg (0.23 mmol, 7%) **161u** as a colorless solid.

M. p.: 87-89°C.

TLC: R_f = 0.49 (ethyl acetate/light petroleum = 1:1).

GC-MS (method B): t_R = 7.87 min, m/Z = 235.

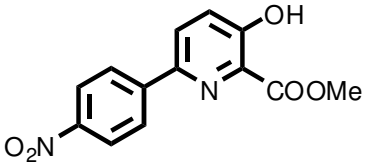
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.08 (3H, s, COOMe), 7.41 (1H, dd, *J* = 5.0 Hz, CH), 7.56 (1H, dd, *J* = 5.1 Hz, CH), 7.63 (1H, d, *J* = 4.7 Hz, CH), 8.07 (1H, dd, *J* = 2.7 Hz, CH), 8.28 (1H, d, *J* = 4.7 Hz, CH), 11.48 (1H, s, OH).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 53.3, 125.6, 127.0, 127.2, 127.4, 130.4, 132.6, 134.3, 141.3, 156.2, 170.4.

IR (KBr): $\tilde{\nu}$ = 3072 (m), 2851 (b), 1733 (s), 1675 (s), 1455 (s), 1208 (s), 813 (s) cm^{-1}.

HRMS (ESI): Calcd for $C_{11}H_{10}NO_3S$ $[M + H]^+$, 236.0376, found: 236.0375.

6-(4'-Nitrophenyl)-3-hydroxypyridine-2-dicarboxylic acid methyl ester (160r)



160r

GP D: alkyne **84r** (294 mg, 2.0 mmol) yielded 220.3 mg (0.80 mmol, 40%) **160r** as a colorless solid.

M. p.: 197-198°C.

TLC: R_f = 0.65 (ethyl acetate/cyclohexane = 1:2).

GC-MS (method B): t_R = 8.99 min, m/Z = 274.

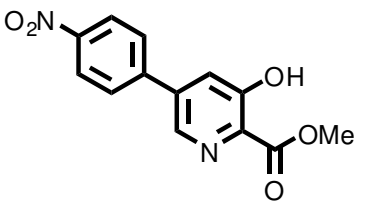
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.09 (3H, s, COOMe), 7.51 (1H, d, *J* = 8.8 Hz, CH), 7.94 (1H, d, *J* = 8.8 Hz, CH), 8.13 (2H, d, *J* = 9.1 Hz, 2 x CH), 8.31 (2H, d, *J* = 9.1 Hz, 2 x CH), 10.83 (1H, s, OH).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 53.3, 124.1, 127.1, 127.3, 127.3, 130.0, 144.1, 146.6, 147.9, 158.6, 169.8.

IR (KBr): $\tilde{\nu}$ = 3252 (b), 2960 (m), 1683 (s), 1463 (s), 1349 (s), 838 (s) cm^{-1}.

HRMS (ESI): Calcd for $C_{13}H_{11}N_2O_5$ $[M + H]^+$, 275.0663, found: 275.0663.

5-(4'-Nitrophenyl)-3-hydroxypyridine-2-dicarboxylic acid methyl ester (161r)



161r

GP D: alkyne **84r** (294 mg, 2.0 mmol) yielded 112.1 mg (0.41 mmol, 21%) **161r** as a colorless solid.

M. p.: 221-222°C.

TLC: R_f = 0.09 (ethyl acetate/light petroleum = 1:1).

GC-MS (method B): t_R = 9.00 min, m/Z = 274.

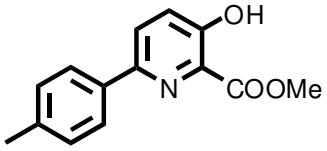
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.09 (3H, s, COOMe), 7.50 (1H, d, *J* = 4.6 Hz, CH), 7.83 (2H, d, *J* = 9.0 Hz, 2 x CH), 8.32 (2H, d, *J* = 9.0 Hz, 2 x CH), 8.38 (1H, d, *J* = 4.6 Hz, CH), 11.32 (1H, s, OH).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 53.5, 123.6, 129.1, 130.1, 130.8, 136.1, 140.9, 141.4, 147.9, 156.0, 170.1.

IR (KBr): $\tilde{\nu}$ = 3150 (b), 2958 (m), 1672 (s), 1511 (s), 1350 (s), 1205 (s), 832 (s) cm^{-1}.

HRMS (EI): Calcd for $C_{13}H_{10}N_2O_5$ $[M]^+$, 274.0584, found: 274.0576.

6-(4'-Methylphenyl)-3-hydroxypyridine-2-dicarboxylic acid methyl ester (160t)



160t

GP D: alkyne **84t** (380 mg, 3.3 mmol) yielded 114.9 mg (0.47 mmol, 15%) **160t** as a colorless solid.

M. p.: 84-86°C.

TLC: R_f = 0.51 (ethyl acetate/cyclohexane = 1:2).

GC-MS (method B): t_R = 7.96 min, m/Z = 243.

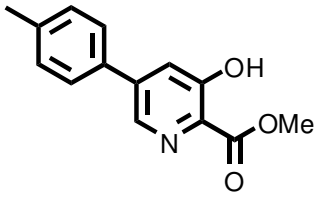
^{1}H-NMR (400 MHz, CD_3CN): δ = 2.37 (3H, s, CH_3), 3.99 (3H, s, $COOCH_3$), 7.27 (2H, d, *J* = 8.0 Hz, 2 x CH), 7.42 (1H, d, *J* = 8.8 Hz, CH), 7.84 (2H, d, *J* = 8.2 Hz, 2 x CH), 7.93 (1H, d, *J* = 8.8 Hz, CH), 10.56 (1H, s, OH).

^{13}C-NMR (100.6 MHz, CD_3CN): δ = 21.2, 53.5, 127.1, 127.3, 127.6, 130.3, 130.3, 136.3, 139.7, 149.6, 158.4, 171.1.

IR (KBr): $\tilde{\nu}$ = 3241 (b), 2957 (m), 1731 (s), 1455 (s), 816 (s) cm^{-1}.

HRMS (EI): Calcd for $C_{14}H_{13}NO_3$ $[M]^+$, 243.0890, found: 243.0899.

5-(4'-Methylphenyl)-3-hydroxypyridine-2-dicarboxylic acid methyl ester (161t)



161t

GP D: alkyne **84t** (380 mg, 3.3 mmol) yielded 42.3 mg (0.17 mmol, 5%) **161t** as a colorless solid.

M. p.: 110-112°C.

TLC: R_f = 0.22 (ethyl acetate/light petroleum = 1:1).

GC-MS (method B): t_R = 8.01 min, m/Z = 243.

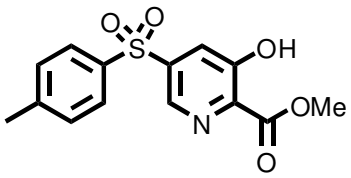
^{1}H-NMR (400 MHz, CD_3CN): δ = 2.39 (3H, s, CH_3), 3.99 (3H, s, COOMe), 7.29 (2H, d, J = 8.0 Hz, 2 x CH), 7.51 (1H, d, J = 4.5 Hz, CH), 7.54 (2H, d, J = 8.2 Hz, 2 x CH), 8.24 (1H, d, J = 4.5 Hz, CH), 11.17 (1H, s, OH).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 21.3, 53.2, 128.9, 129.1, 129.2, 130.1, 131.5, 138.7, 138.9, 141.3, 156.5, 170.4.

IR (KBr): $\tilde{\nu}$ = 3074 (b), 2921 (m), 1674 (s), 1216 (s), 811 (s) cm^{-1}.

HRMS (EI): Calcd for $C_{14}H_{13}NO_3$ $[M]^+$, 243.0890, found: 243.0881.

5-Tosyl-3-hydroxypyridine-2-dicarboxylic acid methyl ester (161v)



161v

GP D: alkyne **84v** (180 mg, 1.0 mmol) yielded 37 mg (0.12 mmol, 12%) **161v** as a light yellow glass. The minor isomer was not detected.

TLC: R_f = 0.34 (ethyl acetate/light petroleum = 1:1).

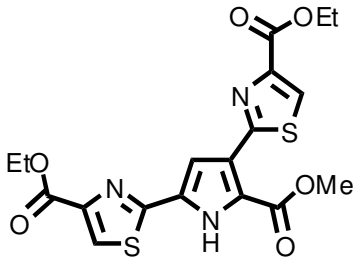
^{1}H-NMR (400 MHz, CD_3CN): δ = 2.42 (3H, s, CH_3), 4.06 (3H, s, COOMe), 7.35 (2H, d, J = 8.0 Hz, 2 x CH), 7.84 (1H, d, J = 1.9 Hz, CH), 7.85 (2H, d, J = 8.4 Hz, 2 x CH), 8.69 (1H, d, J = 2.0 Hz, CH), 10.80 (1H, s, OH).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 21.6, 53.7, 125.5, 128.1, 130.4, 132.7, 136.9, 138.9, 143.4, 145.6, 158.2, 168.8.

IR (KBr): $\tilde{\nu}$ = 3422 (b), 2957 (s), 1686 (s), 1449 (s), 1295 (s), 1211 (s), 1157 (s), 1089 (s), 707 (s) cm^{-1}.

HRMS (ESI): Calcd for $C_{14}H_{14}NO_5S$ $[M + H]^+$, 308.0587, found: 308.0588.

3,5-Bis(4'-(ethoxycarbonyl)thiazol-2'-yl)-pyrrole-2-carboxylic acid methyl ester (168).



168

A mixture of ketone **167** (0.27 g, 1.2 mmol) and unsaturated hydrazone **152** (0.64 g, 1.8 mmol) in toluene (0.5 mL) was heated to 150°C for 11 hours and cooled down to room temperature. Purification by column chromatography (silica gel, 20 g, ethyl acetate/cyclohexane = 1:2) gave 94 mg (0.22 mmol, 36%) of pyrrole **168** as a light yellow solid.

M. p. = 169-171°C.

TLC: R_f = 0.41 (ethyl acetate/light petroleum = 1:1).

LC-MS (method A): t_R = 9.69 min, calcd for $C_{18}H_{18}N_3O_6S_2$ $[M + H]^+$, 436.1, found: 436.0.

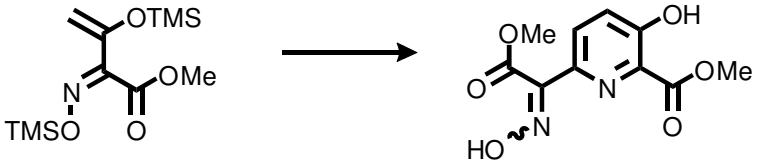
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.43 (6H, t, 2 x $CH_2\underline{C}H_3$), 3.91 (3H, s, $COOCH_3$), 4.44 (4H, dd, 2 x $\underline{C}H_2CH_3$), 7.24 (1H, s, CH), 8.13 (1H, s, CH), 8.17 (1H, s, CH), 10.72 (1H, s, NH).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 14.3, 14.4 ($CH_2\underline{C}H_3$), 52.0 ($COO\underline{C}H_3$), 61.4, 61.5 ($COO\underline{C}H_2CH_3$), 115.8 (CH), 117.8 (<u>C</u>-COOMe), 124.1 (-<u>C</u>-C-COOMe), 126.6 (CH), 127.5 (<u>C</u>-NH), 128.5 (<u>C</u>H), 146.2 (<u>C</u>-C(N)S), 147.2 (<u>C</u>-C(N)S), 157.6 (<u>C</u>-COOEt), 160.2 (<u>C</u>OOMe), 161.1 (<u>C</u>OOEt), 161.4 (<u>C</u>OOEt), 162.3 (<u>C</u>-COOEt).

IR (KBr): $\tilde{\nu}$ = 3506 (s), 2982 (s), 2856 (s), 1732 (s), 1399 (s), 1245 (s), 1212 (s), 763 (s), 520 (s) cm^{-1}.

HRMS (FAB): Calcd for $C_{18}H_{18}N_3O_6S_2$ $[M + H]^+$, 436.0632, found: 436.0656.

Azadiene homodimer 169.



121 **169**

GP D: 1-azadiene **121** (0.6 mL, 2.08 mmol) gave 41 mg (0.16 mmol, 15.5%) of pyridine **169** as a colorless solid.

M. p.: 157-158°C.

TLC: R_f = 0.29 (ethyl acetate/cyclohexane = 1:2).

GC-MS (method B): t_R = 7.74 min, m/Z = 254.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.99 (3H, s, COOMe), 4.0 (3H, s, COOMe), 7.39 (1H, d, J = 8.8 Hz, CH), 7.92 (1H, d, J = 9.0 Hz, CH), 8.62 (1H, br, N-OH), 10.90 (1H, s, OH).

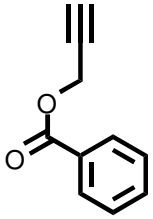
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 52.6 (COO$\underline{C}H_3$), 53.1 (COO$\underline{C}H_3$), 127.0 ($\underline{C}$H), 127.1 ($\underline{C}$H), 129.4 ($\underline{C}$-COOMe), 141.8 ($\underline{C}$-C(N)OH), 151.1 ($\underline{C}$-OH), 159.4 ($\underline{C}$(N)OH), 163.4 ($\underline{C}$OOMe), 169.6 ($\underline{C}$OOMe).

IR (KBr): $\tilde{\nu}$ = 3480 (s), 3457 (s), 3159 (b), 2963 (s), 2922 (s), 1745 (s), 1673 (s), 1469 (s), 1234 (s), 849 (s), 804 (s) cm^{-1}.

HRMS (ESI): Calcd for $C_{10}H_{11}N_2O_6$ $[M + H]^+$, 255.0612, found: 255.0612.

5.9 Preparation of Alkynes.

(2-Propynyl)benzolate (84x)[208]

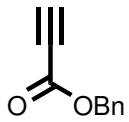


84x

4-(Dimethylamino)-pyridine (244 mg, 2.0 mmol) was added to a stirred reaction mixture of benzoic acid (2.0 g, 16.3 mmol), dicyclohexylcarbodiimide (3.7 g, 17.9 mmol), 2-propynol (1 mL, 17.9 mmol) in dry dichloromethane (30 mL) at room temperature. The reaction mixture was filtered after 1.5 h (TLC control), the precipitate was rinsed with dichloromethane (2 x 10 mL). The combined filtrates were evaporated to dryness. Purification by column chromatography (silica gel, 20 g, dichloromethane/n-hexane = 1:3) gave 2.55 g (15.9 mmol, 98%) of alkyne **84x** as a colorless oil.

TLC: R_f = 0.54 (ethyl acetate/cyclohexane = 1:2).
GC-MS (method B): t_R = 5.60 min, m/Z = 160.
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.52 (1H, t, J = 2.5 Hz, CH), 4.93 (2H, d, J = 2.5 Hz, $COOCH_2$-), 7.43-7.47 (2H, m, Ar-H), 7.56-8.06 (1H, m, Ar-H), 8.07-8.08 (1H, m, Ar-H).
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 52.4 (-$\underline{C}H_2$-), 75.0 (H$\underline{C}$C-), 77.7 (HC$\underline{C}$-), 128.4 (Ar-C), 129.4 (Ar-C), 129.8 (Ar-C), 133.3 (Ar-C), 165.8 (-$\underline{C}$OO-).
IR (KBr): $\tilde{\nu}$ = 3288 (s), 2128 (s), 1728 (s), 814 (s) cm^{-1}.
HRMS (EI): Calcd for $C_{10}H_8O_2$ $[M]^+$, 160.0519, found: 160.0520.

Benzyl propiolate (84w)[209]



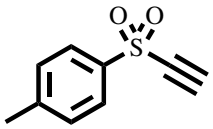
84w

Benzyl bromide (1.9 mL, 16 mmol) was added to the stirred suspension of propargyl alcohol (1 mL, 16 mmol) and potassium carbonate (2.2 g, 16.2 mmol) in acetone (50 mL) at room temperature. The reaction mixture was stirred for 30 min and then heated to 50°C for 5 h (TLC control). After cooling, water (50 mL) was added and the mixture was extracted with diethyl ether (3 x 30 mL). The combined ether extracts were dried with sodium sulphate and concentrated to dryness. Purification by column chromatography (silica gel, 20 g, ethyl acetate/cyclohexane = 1:8) gave 2.1 g (13 mmol, 82%) of benyl propiolate **84w** as a colorless oil.

TLC: R_f = 0.5 (ethyl acetate/cyclohexane = 1:2).
GC-MS (method B): t_R = 5.55 min, m/Z = 160.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.89 (1H, s, CH), 5.23 (2H, s, -CH_2-), 7.38 (5H, s, Ar-H).
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 67.9 (-$\underline{C}H_2$-), 74.5 (H$\underline{C}$C-), 75.0 (HC$\underline{C}$-), 128.5 (Ar-C), 128.6 (Ar-C), 128.7 (Ar-C), 134.5 (Ar-C), 152.5 (-$\underline{C}$OO-).
IR (KBr): $\tilde{\nu}$ = 3257 (s), 2128 (s), 1707 (s), 1400 (b), 757 (s) cm^{-1}.
HRMS (EI): Calcd for $C_{10}H_8O_2$ $[M]^+$, 160.0519, found: 160.0515.

4-ethynylsulfonyltoluene (84v)[210]

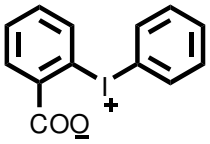


84v

p-Toluenesulfonyl chloride (4.1 g, 21.7 mmol) was added to $AlCl_3$ (2.9 g, 21.7 mmol) in dichloromethane (10 mL), the reaction mixture became sticky oil, and more dichloromethane (10 mL) was added. The clear, light yellow solution was kept for 30 min at room temperature, and transferred slowly via cannular to another flask containing bis-(trimethylsilyl)acetylene (3.3 g, 19.3 mmol) in dichloromethane (10 mL) at 0°C. The reaction mixture turned to dark red, and was stirred for 24 hours at room temperature. The reaction mixure was then added to a mixture of 2N HCl and crushed ice (100 mL). The organic layer was separated, washed with brine (2 x 20 mL), dried with sodium sulphate and concentrated. Purification by column chromatography (silica gel, 40 g, ethyl acetate/light petroleum = 1:10) afforded 1.0 g of pure alkyne **84v** and 2.8 g of a mixture containing alkyne **84v** with a TMS group.

TLC: R_f = 0.42 (ethyl acetate/cyclohexane = 1:2).
GC-MS (method B): t_R = 6.48min, m/Z = 180.
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.48 (3H, s, CH_3), 3.44 (1H, s, C≡CH), 7.39 (2H, d, J = 8.0 Hz, Ph), 7.90 (2H, d, J = 8.2 Hz, Ph).
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 21.8, 80.4, 81.0, 127.7, 130.1, 137.9, 166.0.
HRMS (EI): Calcd for $C_9H_8O_2S$ $[M]^+$, 180.0240, found: 180.0247.

Diphenyliodonium-2-carboxylic acid methyl ester (205)[145]

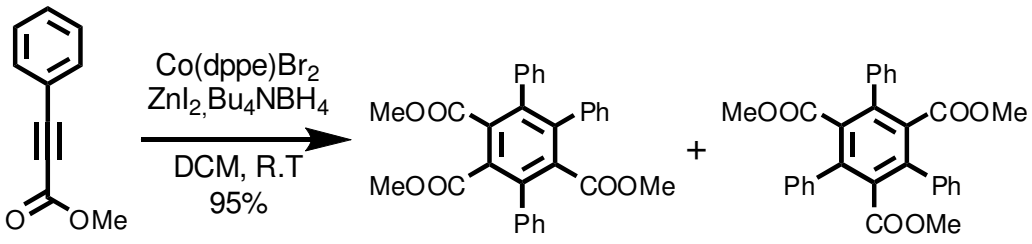


205

Potassium persulfate (5.2 g, 19.2 mmol) was added to a solution of *o*-iodobenzoic acid (4 g, 16.1 mmol) in concentrated sulphuric acid (16 mL) at 0°C. Benzene (4 mL, 45.2 mmol) was added after 30 min. The reaction mixture was stirred for 18h at room temperature. The reaction mixture was poured on ice, adjusted to pH 10 with aqueous NaOH solution (2M) and extracted with chloroform. Concentration of the chloroform extracts gave 5.0 g (15.4 mmol, 96%) of the iodonium carboxylate **205** as a colorless solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.74, 6.76 (1H, d, *J* = 8.2 Hz, CH), 7.36-7.40 (1H, dd, *J* = 4.7, 7.2 Hz, CH), 7.55-7.60 (3H, dd, *J* = 6.8, 7.6 Hz, 3 x CH), 7.73-7.77 (1H, t, *J* = 7.4 Hz, CH), 8.00, 8.01 (2H, d, *J* = 7.6 Hz, 2 x CH), 8.43, 8.44 (1H, *J* = 7.0 Hz, CH).

Hexasubstituted benzene



84a **162** : **163**

93 : 7

Bu_4NBH_4 (12.9 mg, 0.05 mmol) was added slowly to a mixture of $Co(dppe)Br_2$ (30.9 mg, 0.05 mmol), ZnI_2 (47.9 mg, 0.15 mmol) and alkyne **84a** (7.4 mL, 0.5 mmol) in dichloromethane (1 mL) under argon at room temperature. The reaction mixture was stirred for 5h (TLC control). Water (30 mL) was added and the mixture was extracted with dichloromethane (3 x 30 mL). The combined extracts were dried with sodium sulphate and concentrated to dryness. Purification by column chromatography (silica gel, 10 g, ethyl acetate/cyclohexane = 1:15) gave 76.2 mg (0.16 mmol, 95%) of a mixture of the hexasubstituted bezenes **162** and **163** as a colorless solid (**162/163** = 93:7, ratio determined by ^{1}H-NMR).

TLC: R_f = 0.42 (ethyl acetate/cyclohexane = 1:2).

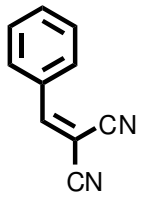
GC-MS (method B): t_R = 12.15 min, m/Z = 480 (major isomer), t_R = 11.76 min, m/Z = 480 (minor isomer)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.17 (3H, s, $COOCH_3$), 3.47 (3H, s, $COOCH_3$), 3.51 (3H, s, $COOCH_3$), 7.03-7.37 (15H, m, Ph).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 51.7, 52.28, 52.31, 127.2, 127.3, 127.5, 127.7, 127.9, 128.0, 128.1, 128.6, 128.8, 129.6, 131.7, 134.1, 134.5, 136.9, 137.2, 137.3, 137.4, 138.1, 139.3, 140.9, 167.7, 167.8, 168.0.

5.10 Preparation of Dicyanoalkenes.

2-Benzylidenemalononitrile (184a)



184a

GP C: aldehyde **192a** (1.02 mL, 10 mmol) gave 1.50 g (9.7 mmol, 97%) of dicyanoalkene **184a** as a colorless solid.

M. p.: 88-90°C (EtOH/H_2O).

TLC: R_f = 0.39 (ethyl acetate/cyclohexane = 1:2).

GC-MS (method B): t_R = 6.06 min, m/Z = 154.

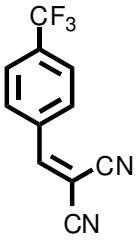
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.54 (2H, t, Ph), 7.64 (1H, t, Ph), 7.78 (1H, s, CH), 7.91 (2H, d, Ph).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 82.8 (CH=<u>C</u>), 112.5, 113.6 (CN), 129.6 (Ph), 130.7 (Ph), 130.9 (Ph), 134.6 (Ph), 159.9 (<u>CH</u>=C).

IR (KBr): $\tilde{\nu}$ = 3033 (s), 2224 (s), 1591 (s), 1218 (s), 678 (s) cm^{-1}.

HRMS (EI): Calcd for $C_{10}H_6N_2$ $[M]^+$, 154.0531, found: 154.0528.

2-(4'-(Trifluoromethyl)benzyliene)malononitrile (184b)



184b

GP C: aldehyde **192b** (1.74 g, 10 mmol) gave 2.04 g (9.2 mmol, 92%) of dicyanoalkene **184b** as a colorless solid.

M. p.: 108-110°C (EtOH/H_2O).

TLC: R_f = 0.48 (ethyl acetate/cyclohexane = 1:2).

GC-MS (method B): t_R = 6.14 min, m/Z = 222.

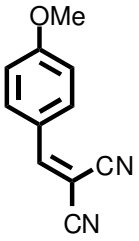
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.80 (2H, d, Ph), 7.86 (1H, s, CH), 8.02 (2H, d, Ph).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 86.0 (CH=<u>C</u>), 111.8, 112.9 (CN), 126.5 (CF_3), 126.5 (Ar), 126.6 (Ar), 130.7 (Ar), 133.7 (Ar), 158.0 (<u>CH</u>=C).

IR (KBr): $\tilde{\nu}$ = 3095 (s), 3036 (s), 2235 (s), 1567 (s), 1222 (s), 837 (s) cm^{-1}.

HRMS (EI): Calcd for $C_{11}H_5F_3N_2$ $[M]^+$, 222.0405, found: 222.0404.

2-(4'-Methoxybenzyliene)malononitrile (184f)



184f

GP C: aldehyde **192f** (1.36 g, 10 mmol) gave 1.55 g (8.4 mmol, 84%) of dicyanoalkene **184f** as a light yellow solid.

M. p.: 115-116°C (EtOH/H_2O).

TLC: R_f = 0.37 (ethyl acetate/cyclohexane = 1:2).

GC-MS (method B): t_R = 7.25 min, m/Z = 184.

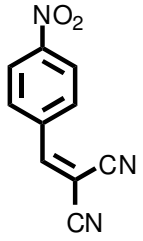
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.91 (3H, s, Me), 7.01 (2H, d, Ph), 7.66 (1H, s, CH), 7.90 (2H, d, Ph).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 55.8, 78.5, 113.3, 114.4, 115.1, 124.0, 133.4, 158.8, 164.8.

IR (KBr): $\tilde{\nu}$ = 3029 (s), 2851 (s), 2222 (s), 1571 (s) 1237 (s), 834 (s) cm^{-1}.

HRMS (EI): Calcd for $C_{11}H_8F_3N_2O$ $[M]^+$, 184.0637, found: 184.0630.

2-(4'-Nitrobenzyliene)malononitrile (184e)



184e

GP C: aldehyde **192e** (0.5 g, 3.3 mmol) gave 0.54 g (2.7 mmol, 82%) of dicyanoalkene **184e** as a light olive colored solid.

M. p.: 157-159°C (EtOH/H_2O).

TLC: R_f = 0.29 (ethyl acetate/cyclohexane = 1:2).

GC-MS (method B): t_R = 7.53 min, m/Z = 199.

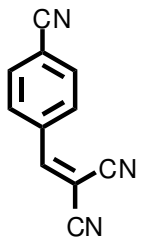
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.89 (1H, s, CH), 8.07 (2H, d, J = 8.6 Hz, Ph), 8.39 (2H, d, J = 8.6 Hz, Ph).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 87.5, 111.6, 112.6, 112.6, 113.3, 135.8, 150.3, 156.8.

IR (KBr): $\tilde{\nu}$ = 3116 (s), 3040 (s), 2232 (s), 1521 (s), 1345 (s), 836 (s) cm^{-1}.

HRMS (EI): Calcd for $C_{10}H_5N_2O_3$ $[M]^+$, 199.0376, found: 199.0368.

2-(4'-Cyanobenzyliene)malononitrile (184c)



184c

GP C: aldehyde **192c** (1.53 g, 11.7 mmol) gave 1.57 g (8.8 mmol, 75%) of dicyanoalkene **184c** as a colorless solid.

M. p.: 153-155°C (EtOH/H_2O).

TLC: R_f = 0.26 (ethyl acetate/cyclohexane = 1:2).

GC-MS (method B): t_R = 7.22 min, m/Z = 179

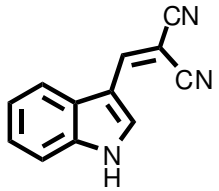
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.83 (1H, s, CH), 7.83 (2H, d, J = 8.5 Hz, Ph), 7.99 (2H, d, J = 8.5 Hz, Ph).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 86.9, 111.6, 112.7, 117.2, 117.2, 130.6, 133.1, 134.2, 157.3.

IR (KBr): $\tilde{\nu}$ = 3049 (s), 2942 (m), 2232 (s), 1589 (s), 1293 (s), 833 (s) cm^{-1}.

HRMS (EI): Calcd for $C_{11}H_5N_3$ $[M]^+$, 179.0478, found: 179.0478.

2-((1'H-indol-3'-yl)methylene)malononitrile (184p)



184p

GP C: aldehyde **192p** (1.47 g, 10.1 mmol) gave 1.40 g (7.3 mmol, 72%) of dicyanoalkene **184p** as a light yellow solid.

M. p.: 228-230°C (EtOH/H_2O).

TLC: R_f = 0.29 (ethyl acetate/cyclohexane = 1:2).

GC-MS (method B): t_R = 8.73 min, m/Z = 193.

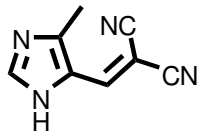
^{1}H-NMR (400 MHz, DMSO): δ =7.26-7.33 (2H, m, 2 x CH), 7.58 (1H, d, J = 7.1 Hz, CH), 8.05 (1H, d, J = 7.1 Hz, CH), 8.53 (1H, s, CH), 8.70 (1H, s, CH), 12.71 (1H, s, NH).

^{13}C-NMR (100.6 MHz, DMSO): δ = 69.1, 110.9, 112.9, 115.8, 115.8, 119.0, 122.5, 123.9, 126.6, 133.2, 136.1, 152.5.

IR (KBr): $\tilde{\nu}$ = 3283 (b), 2945 (m), 2224 (s), 1589 (s), 1236 (s), 741 (s) cm^{-1}.

HRMS (EI): Calcd for $C_{12}H_7N_3$ $[M]^+$, 193.0634, found: 193.0631.

2-((4'-Methyl-1'H-imidazol-5-yl)methylene)malononitrile (184o)



184o

GP C: aldehyde **192o** (1.36 g, 12.4 mmol) gave 1.4 g (8.9 mmol, 72%) of dicyanoalkene **184o** as a colorless solid.

M. p.: 230°C (decomposition) (EtOH/H_2O).

TLC: R_f = 0.28 (ethyl acetate/cyclohexane = 1:2).

GC-MS (method B): t_R = 6.94 min, m/Z = 158

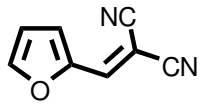
^{1}H-NMR (400 MHz, DMSO): δ = 2.41 (3H, s, CH_3), 7.89 (1H, s, CH), 8.19 (1H, s, CH), 12.92 (1H, bs, NH)

^{13}C-NMR (100.6 MHz, DMSO): δ = 9.3, 71.2, 114.2, 116.1, 132.0, 138.2, 140.9, 149.6.

IR (KBr): $\tilde{\nu}$ = 3223 (b), 3100 (s), 2913 (w), 2234 (s), 2215 (s), 1593 (s), 1335 (s), 827 (s) cm^{-1}.

HRMS (EI): Calcd for $C_8H_6N_4$ $[M]^+$, 158.0587, found: 158.0586.

2-(Furan-2'-ylmethylene)malononitrile (184h)



184h

GP C: aldehyde **192h** (1.66 mL, 20.1 mmol) gave 1.53 g (10.6 mmol, 53%) of dicyanoalkene **184h** as a light pink solid.

M. p.: 71-73°C (EtOH/H_2O).

TLC: R_f = 0.28 (ethyl acetate/cyclohexane = 1:2).

GC-MS (method B): t_R = 5.76 min, m/Z = 144

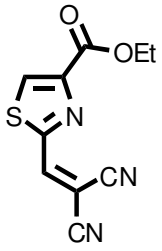
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.72 (1H, dd, J = 1.7 Hz, CH), 7.37 (1H, d, J = 3.7 Hz, CH), 7.51 (1H, s, CH), 7.80 (1H, d, J = 1.7 Hz, CH).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 77.7, 112.5, 113.7, 114.4, 123.4, 143.0, 148.1, 149.5.

IR (KBr): $\tilde{\nu}$ = 3124 (s), 3046 (sb), 2922 (m), 2230 (s), 1608(s), 1297 (s), 768 (s) cm^{-1}.

HRMS (EI): Calcd for $C_8H_4N_2O$ $[M]^+$, 144.0318, found: 144.0311.

2-((4'-Ethoxycarbonyl-thiazole-2'-yl)methylene)malononitrile (184j)



184j

2,2-Diethoxyethanethioamide (1.0 g, 6.1 mmol) and ethyl bromopyruvate (0.7 mL, 5.8 mmol) were dissolved in ethanol (25 mL), and molecular sieves (4Å, 1.0 g) was added to the reaction mixture. The reaction mixture was refluxed for 100 min (TLC control), cooled to room temperature and filtered through a pad of Celite. The filtrate was concentrated to dryness. The crude thiazole was pure enough for next step.

TLC: R_f = 0.4 (ethyl acetate/cyclohexane = 1:2).

Hydrochloric acid (2 M, 3 mL) was added to the above thiazole in acetone (100 mL). The reaction mixture was refluxed for 1h (TLC control), then cooled down to room temperature. The reaction mixture was concentrated to minimum volume, diluted with ethyl acetate (30 mL), washed with brine (3 x 10 mL), dried with sodium sulfate and concentrated. The crude aldehyde **192j** such obtained was pure enough for next step.

TLC: R_f = 0.3 (ethyl acetate/cyclohexane = 1:2).

The crude aldehyde **192j** was converted into the dicyanoalkene following GP C. Recrystallization from EtOH/H_2O gave 0.94 g (4.0 mmol, 66% 3 steps) of **184j** as a colorless solid.

M. p.: 158-160°C (EtOH/H_2O).
TLC: R_f = 0.22 (ethyl acetate/cyclohexane = 1:2).
GC-MS (method B): t_R = 7.62 min, m/Z = 233

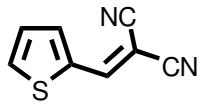
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.43 (3H, t, *J* = 7.1 Hz, CH3), 4.48 (2H, dd, *J* = 7.1 Hz, CH_2), 8.15 (1H, s, CH), 8.56 (1H, s, CH).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 14.2, 62.4, 87.1, 111.4, 112.1, 132.9, 149.8, 150.4, 157.9, 160.1.

IR (KBr): $\tilde{\nu}$ = 3126 (s), 3053 (s), 2990 (m), 2236 (s), 1729 (s), 1227 (s), 770 (s) cm^{-1}.

HRMS (EI): Calcd for $C_{10}H_7N_3O_2S$ $[M]^+$, 233.0253, found: 233.0250.

2-(Thiophene-2'-ylmethylene)malononitrile (184i)



184i

GP C: aldehyde **192i** (1.83 mL, 20.0 mmol) gave 2.93 g (18.3 mmol, 92%) of dicyanoalkene **184i** as a light yellow solid.

M. p.: 96-98°C (EtOH/H_2O).

TLC: R_f = 0.33 (ethyl acetate/cyclohexane = 1:2).

GC-MS (method B): t_R = 6.53 min, m/Z = 160

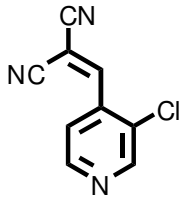
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.28 (1H, dd, *J* = 1.1 Hz, CH), 7.80-7.81 (1H, m, CH), 7.88 (1H, s, CH), 7.89 (1H, t, *J* = 1.1 Hz, CH).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 78.3, 112.9, 113.7, 129.0, 135.4, 136.8, 138.1, 151.0.

IR (KBr): $\tilde{\nu}$ = 3103 (s), 3025 (s), 2976 (m), 2226 (s), 1572 (s), 1408 (s), 725 (s) cm^{-1}.

HRMS (EI): Calcd for $C_8H_4N_2S$ $[M]^+$, 160.0090, found: 160.0091.

2-(3'-Chloropyridin-4'-ylmethylene)malononitrile (184l)



184l

GP C: aldehyde **192l** (0.28 g, 2.0 mmol) gave 0.27 g (1.4 mmol, 71%) of dicyanoalkene **184l** as a colorless solid.

M. p.: 98-100°C (EtOH/H_2O).

TLC: R_f = 0.22 (ethyl acetate/cyclohexane = 1:2).

GC-MS (method B): t_R = 6.45 min, m/Z = 189

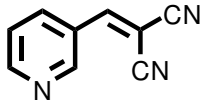
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.91 (1H, d, J = 5.1 Hz, -CH-), 8.16 (1H, s, -CH-), 8.73 (1H, d, J = 5.1 Hz, -CH-), 8.82 (1H, s, -CH-).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 90.6, 110.8, 112.1, 121.6, 131.5, 135.5, 148.9, 151.0, 153.6.

IR (KBr): $\tilde{\nu}$ = 3034 (s), 2930 (m), 2237 (s), 1594 (s), 1398 (s), 831 (s) cm^{-1}.

HRMS (EI): Calcd for $C_9H_4N_3Cl$ $[M]^+$, 189.0088, found: 189.0084.

2-(Pyridin-3'-ylmethylene)malononitrile (184k)



184k

GP C: aldehyde **192k** (1.87 mL, 19.9 mmol) gave 2.72 g (17.5 mmol, 88%) of dicyanoalkene **184k** as a light purple solid.

M. p.: 83-85°C (EtOH/H_2O).

TLC: R_f = 0.13 (ethyl acetate/light petroleum = 1:1).

GC-MS (method B): t_R = 6.37 min, m/Z = 155.

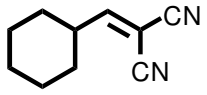
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.50 (1H, dd, J = 4.7 Hz, H-5) 7.83 (1H, s, CH), 8.45 (1H, d, J = 7.8 Hz, H-4), 8.81 (1H, d, J = 3.6 Hz, H-6), 8.88 (1H, s, H-2).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 85.6, 111.9, 112.9, 124.2, 127.0, 135.6, 152.3, 154.5, 156.4.

IR (KBr): $\tilde{\nu}$ = 3033 (s), 2954 (w), 2228 (s), 1591 (s), 1413 (s), 802 (s) cm^{-1}.

HRMS (ESI): Calcd for C_9H6N_3 $[M + H]^+$, 156.0551, found: 156.0551.

2-(Cyclohexylmethylene)malononitrile (184n)



184n

GP C: aldehyde **192n** (0.24 mL, 2.0 mmol) gave 0.128 g (0.8 mmol, 40%) of dicyanoalkene **184n** as a colorless solid.

M. p.: 36-38°C.

TLC: R_f = 0.54 (ethyl acetate/cyclohexane = 1:2).

GC-MS (method B): t_R = 5.90 min, m/Z = 159

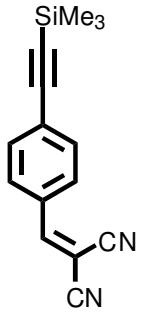
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.18-1.42 (5H, m, -CH2-), 1.70-1.84 (5H, m, -CH2-), 2.67-2.77 (1H, m, -CH-), 7.15 (1H, d, J = 10.5 Hz, CH).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 24.6, 25.1, 30.8, 42.1, 87.8, 110.6, 112.2, 173.6.

IR (KBr): $\tilde{\nu}$ = 3034 (m), 2938 (bs), 2857 (s), 2236 (s), 1607 (s), 1453 (s), 967 (s), 618 (s) cm^{-1}.

HRMS (EI): Calcd for $C_{10}H_{12}N_2$ $[M]^+$, 160.0995, found: 160.0993.

2-(4'-((Trimethylsilyl)ethynyl)benzylidene)malononitrile (184g)



184g

GP C: aldehyde **192g** (3.04 g, 15.0 mmol) gave 3.50 g (14.0 mmol, 93%) of dicyanoalkene **184g** as a light yellow solid.

M. p.: 129-131°C (EtOH/H_2O).

TLC: R_f = 0.63 (ethyl acetate/cyclohexane = 1:2).

GC-MS (method B): t_R = 7.74 min, m/Z = 250.

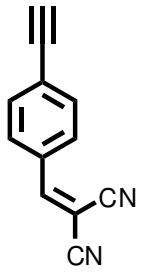
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.27 (9H, s, TMS), 7.58 (2H, d, J = 8.5 Hz, Ph), 7.72 (1H, s, CH), 7.85 (2H, d, J = 8.6 Hz, Ph).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = -0.3, 83.1, 101.0, 103.4, 112.5, 113.6, 129.7, 130.4, 130.5, 132.8, 158.5.

IR (KBr): $\tilde{\nu}$ = 2964 (bw), 2227 (s), 2154 (s), 1588 (s), 1247 (s), 870 (s) cm^{-1}.

HRMS (EI): Calcd for $C_{15}H_{14}N_2Si$ $[M]^+$, 250.0921, found: 250.0917.

2-(4'-Ethynyl-benzylidene)malononitrile (184t)



184t

K_2CO_3 (120 mg, 0.86 mmol) was added to a solution of dicyanoalkene **184g** (100 mg, 0.40 mmol) in MeOH (30 mL), the resulting mixture was stirred for 1.5 h (TLC control). Phosphate buffer (pH 2.5, 30 mL) was added and the mixture was extracted with dichloromethane (3 x 30 mL). The combined extracts were dried with sodium sulphate and concentrated. Purification by column chromatography (silica gel, 20 g, ethyl acetate/light petroleum = 1:12) gave 31.5 mg (0.18 mmol, 45%) of dicyanoalkene **184t** as a colorless solid.

M. p.: 158-160°C.

TLC: R_f = 0.46 (ethyl acetate/cyclohexane = 1:2).

GC-MS (method B): t_R = 6.88 min, m/Z = 178.

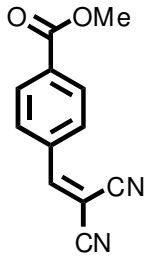
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.36 (1H, s, CCH), 7.60 (2H, d, J = 8.5 Hz, Ph), 7.74 (1H, s, CH), 7.87 (2H, d, J = 8.5 Hz, Ph)

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 82.3, 82.4, 83.6, 112.4, 113.5, 128.5, 130.5, 130.8, 133.1, 158.5.

IR (KBr): $\tilde{\nu}$ = 3261 (s), 2354 (m), 2229 (s), 2101 (s), 1583 (s), 832 (s) cm^{-1}.

HRMS (EI): Calcd for $C_{12}H_6N_2$ $[M]^+$, 178.0525, found: 178.0520.

2-(4'-Methoxycarbonylbenzylidene)malononitrile (184d)



184d

GP C: aldehyde **192d** (1.64 g, 10.0 mmol) gave 2.0 g (9.4 mmol, 94%) of dicyanoalkene **184d** as a colorless solid.

M. p.: 163-165°C (EtOH/H_2O).

TLC: R_f = 0.36(ethyl acetate/cyclohexane = 1:2).

GC-MS (method B): t_R = 7.45 min, m/Z = 212.

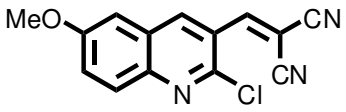
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.97 (3H, s, CH_3), 7.74 (1H, s, CH), 7.96 (2H, d, J = 8.4 Hz, Ph), 8.17 (2H, d, J = 8.4 Hz, Ph).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 52.7, 85.4, 112.0, 113.2, 130.4, 130.5, 134.3, 134.9, 158.5, 165.5.

IR (KBr): $\tilde{\nu}$ = 3037 (s), 2960 (m), 2230 (s), 1713 (s), 1290 (s), 1118 (s), 763 (s) cm^{-1}.

HRMS (EI): Calcd for $C_{12}H_8N_2O_2$ $[M]^+$, 212.0580, found: 212.0573.

2-((2'-Chloro-6'-methoxyquinolin-3'-yl)methylene)malononitrile (184m)



184m

GP C: aldehyde **192m** (1.63 g, 7.4 mmol) gave 1.3 g (4.8 mmol, 66%) of dicyanoalkene **184m** as a light yellow solid.

M. p.: 198-200°C (EtOH/H_2O).

TLC: R_f = 0.4 (ethyl acetate/cyclohexane = 1:2).

GC-MS (method B): t_R = 8.66min, m/Z = 269.

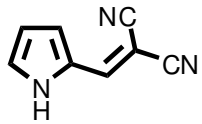
^{1}H-NMR (400 MHz, $CDCl_3$): δ =3.97 (3H, s, CH_3), 7.18 (1H, d, *J* = 2.8 Hz, CH), 7.55 (1H, dd, *J* = 2.8 Hz, CH), 7.94 (1H, d, *J* = 9.2 Hz, CH), 8.35 (1H, d, *J* = 0.7 Hz, CH), 8.90 (1H, s, CH).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 55.9, 86.5, 106.0, 111.9, 112.8, 123.2, 127.3, 127.4, 130.0, 137.9, 145.3, 146.4, 155.1, 159.3.

IR (KBr): $\tilde{\nu}$ = 3010 (s), 2978 (m), 2230 (s), 1574 (s), 1238 (s), 834 (s) cm^{-1}.

HRMS (EI): Calcd for $C_{14}H_8N_3OCl$ $[M]^+$, 269.0350, found: 269.0348.

2-((1'H-pyrrol-2'-yl)methylene)malononitrile (184q)



184q

GP C: aldehyde **192q** (3.1 g, 32.6 mmol) gave 3.74 g (26.2 mmol, 80%) of dicyanoalkene **184q** as a light yellow solid.

M. p.: 128-130°C (EtOH/H_2O).

TLC: R_f = 0.22 (ethyl acetate/cyclohexane = 1:2).

GC-MS (method B): t_R = 6.37 min, m/Z = 143

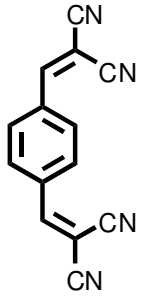
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.49 (1H, dd, *J* = 2.2 Hz, CH), 6.99 (1H, s, CH), 7.30 (1H, s, CH), 7.50 (1H, s, CH), 9.79 (1H, s, NH).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 69.9, 113.3, 114.5, 115.6, 125.5, 126.8, 130.2, 145.9.

IR (KBr): $\tilde{\nu}$ = 3372 (b), 3116 (s), 2226 (s), 1587 (s), 1398 (s), 1050 (s), 776 (s) cm^{-1}.

HRMS (EI): Calcd for $C_8H_5N_3$ $[M]^+$, 143.0478, found: 143.0471.

2,2'-(1,4-Phenylenebis(methan-1-yl-1-ylidene))dimalononitrile (184s)

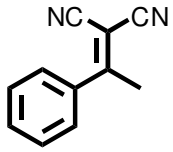


184s

GP C: aldehyde **192s** (1.34 g, 10.0 mmol) gave 2.17 g (9.4 mmol, 94%) of dicyanoalkene **184s** as a colorless solid.

M. p.: 268°C (decomposition) (EtOH/H_2O).
TLC: R_f = 0.19 (ethyl acetate/cyclohexane = 1:2).
GC-MS (method B): t_R = 8.56 min, m/Z = 230.
^{1}H-NMR (400 MHz, DMSO): δ = 8.09 (4H, s, Ph), 8.63 (2H, s, 2 x CH).
^{13}C-NMR (100.6 MHz, DMSO): δ = 84.6, 112.6, 113.7, 130.7, 135.2, 159.7.
IR (KBr): $\tilde{\nu}$ = 3038 (s), 2945 (m), 2232 (s), 1588 (s), 1221 (s), 844 (s) cm^{-1}.
HRMS (EI): Calcd for $C_{14}H_6N_4$ $[M]^+$, 230.0587, found: 230.0589.

2-(1'-Phenylethylidene)malononitrile (184u)

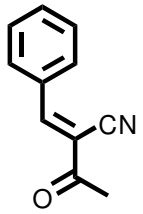


184u

Ammonium acetate (0.5 g, 6.5 mmol) and glacial acetic acid (2 mL) were added to a solution of malononitrile (2.11 g, 32 mmol) and acetophenone (3.27 mL, 28 mmol) in toluene (20 mL) and heated to reflux. The water formed in the reaction was removed by a Dean-Stark trap (TLC control). Removal of the solvent and recrystallization of the resulting residue gave 3.5 g (20.8 mmol, 74%) of dicyanoalkene **184u** as a colorless solid.

M. p.: 84-86°C (EtOH/H_2O).
TLC: R_f = 0.43 (ethyl acetate/cyclohexane = 1:2).
GC-MS (method B): t_R = 6.36 min, m/Z = 168.
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.64 (3H, s, CH_3), 7.48-7.56 (5H, m, Ph).
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 24.2, 84.7, 112.7, 112.7, 127.3, 129.1, 132.2, 135.9, 175.4.
IR (KBr): $\tilde{\nu}$ = 3068 (w), 2228 (s), 1585 (s), 1566 (s), 771 (s) cm^{-1}.
HRMS (EI): Calcd for $C_{11}H_8N_2$ $[M]^+$, 168.0682, found: 168.0675.

(*E/Z*) 2-Benzylidene-3-oxobutanenitrile (188b)[124]

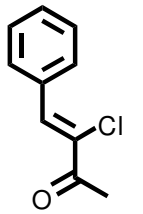


188b

Sodium (0.23 g, 10 mmol) was added slowly to a solution of benzyaldehyde (1.02 mL, 10 mmol) and 5-methylisoxazole (0.81 mL, 10 mmol) in ethanol (10 mL) at room temperature, and the mixture was stirred for 24 h (TLC control). Brine (30 mL) was added and the mixture was extracted with dichloromethane (3 x 30 mL). The combined extracts were dried with sodium sulfate and concentrated. Purification by column chromatography (silica gel, 40 g, ethyl acetate/cyclohexane = 1: 8) gave 0.17 g (0.99 mmol, 10%) of alkene **188b** as a colorless solid.

TLC: R_f = 0.47 (ethyl acetate/cyclohexane = 1:2).
GC-MS (method B): t_R = 6.28 min, m/Z = 171.
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.58 (3H, s, CH_3), 7.49-7.57 (3H, m, Ph), 8.00 (1H, d, Ph), 8.14 (1H, s, CH).
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 27.9, 109.7, 117.2, 129.3, 131.3, 131.5, 133.5, 153.1, 191.1.
IR (KBr): $\tilde{\nu}$ = 3057 (m), 2217 (s), 1698 (s), 1588 (s), 1201 (s), 952 (s) cm^{-1}.
HRMS (EI): Calcd for $C_{11}H_9NO$ $[M]^+$, 171.0679, found: 171.0678.

(*E/Z*) 3-Chloro-4-phenylbut-3-en-2-one (188c)[125]



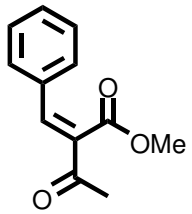
188c

Benzyaldehyde (0.102 mL, 1 mmol) and trichloroacetone (0.113 mL, 1 mmol) were added to a solution of $CrCl_2$ (0.6 g, 5 mmol) in THF (10 mL) at 0°C. The reaction mixture was slowly warmed to room temperature and stirred for 3 hours (TLC control). Water (10 mL) was added

and the mixture was extracted with dichloromethane (3 x 20 mL). The combined extracts were dried with sodium sulfate and concentrated. Purification by column chromatography (silica gel, 20 g, ethyl acetate/cyclohexane = 1: 6) gave 10 mg (0.07 mmol, 5%) of alkene **188c** as a colorless oil.

TLC: R_f = 0.55 (ethyl acetate/cyclohexane = 1:2).
GC-MS (method B): t_R = 5.73 min, m/Z = 145
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.39 (3H, s, CH_3), 6.70, 6.74 (1H, d, E/Z isomer CH), 7.39-7.56 (5H, m, Ph).
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 27.5, 127.2, 128.2, 129.0, 130.5, 134.4, 143.4, 198.3.

(*E/Z*) Methyl 2-benzylidene-3-oxobutanoate (188a)[211]

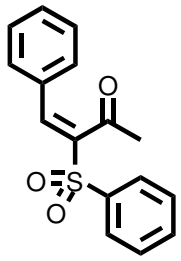


188a

A mixture of benzaldehyde (1.02 mL, 10 mmol), methyl acetoacetate (1.08 mL, 10 mmol) and L-proline (0.23 g, 2 mmol) in methanol (1 mL) was stirred for 24 hours (TLC control). Water (20 mL) was added and the mixture was extracted with dichloromethane (3 x 20 mL). The combined extracts were dried with sodium sulfate and concentrated. Purification by column chromatography (silica gel, 20 g, ethyl acetate/cyclohexane = 1:8) gave 0.86 g (4.2 mmol, 42%) of alkene **188a** as a light yellow oil.

TLC: R_f = 0.50 (ethyl acetate/cyclohexane = 1:2).
GC-MS (method B): t_R = 6.55 min, m/Z = 204.
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.42 (3H, s, CH_3), 3.84 (3H, s, COOMe), 7.39-7.44 (5H, m, Ph), 7.58 (1H, s, CH).
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 26.5, 52.5, 128.9, 129.4, 130.8, 132.9, 134.3, 141.6, 168.2, 194.5.
IR (KBr): $\tilde{\nu}$ = 3004 (w), 2952 (m), 1733 (s), 1668 (s), 1224 (s), 757 (s) cm^{-1}.
HRMS (EI): Calcd for $C_{12}H_{12}O_3$ $[M]^+$, 204.0781, found: 204.0774.

(*E/Z*) 4-Phenyl-3-(phenylsulfonyl)but-3-en-2-one (188d)[212]



188d

The mixture of benzyaldehyde (67 µL, 0.66 mmol), phenylsulfonylacetone (100 mg, 0.50 mmol), piperidine (8 µL, 0.081 mmol) and glacial acetic acid (16 µL, 0.28 mmol) in toluene (10 mL) was refluxed for 3 hours (TLC control). After cooling to room termperature, water (20 mL) was added and the mixture was extracted with dichloromethane (3 x 20 mL). The combined extracts were dried with sodium sulfate and concentrated. Purification by column chromatography (silica gel, 10 g, ethyl acetate/cyclohexane = 1:10) gave 0.12 g (0.42 mmol, 83%) of the alkene **188d** as a colorless solid.

M. p.: 128-129°C.

TLC: R_f = 0.52, 0.62 (ethyl acetate/cyclohexane = 1:2).

GC-MS (method B): t_R = 8.49 min, m/Z = 286.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.29 (3H, s, CH_3), 7.61, 7.63 (1H, d, *E/Z* isomer CH), 7.30-7.95 (10H, m, Ph).

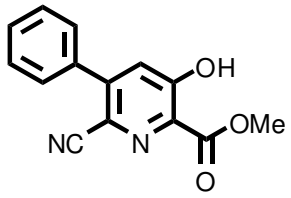
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 31.9, 126.1, 128.4, 128.5, 128.7, 128.8, 128.9, 129.0, 129.08, 129.09, 129.6, 130.2, 131.21, 131.25, 131.4, 133.6, 133.7, 139.5, 140.2, 141.3, 142.0, 148.1, 191.0, 199.4.

IR (KBr): $\tilde{\nu}$ = 2949 (m), 2824 (w), 1724 (s), 1302 (s), 862 (s) cm^{-1}.

HRMS (EI): Calcd for $C_{16}H_{14}O_3S$ $[M]^+$, 286.0658, found: 286.0648.

5.11 Preparation of 6-Cyanopyridines.

6-Cyano-5-phenyl-3-hydroxypyridine-2-carboxylic acid methyl ester (191a)



191a

GP E: dicyanoalkene **184a** (39 mg, 0.25 mmol) gave 62 mg (0.24 mmol, 96%) of hydroxypyridine **191a** as a colorless solid.

M. p.: 173-174°C.

TLC: R_f = 0.25 (ethyl acetate/cyclohexane = 1:2).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.11 (3H, s, $COOCH_3$), 7.48 (1H, s, CH), 7.53-7.61 (5H, m, Ar), 11.13 (1H, s, OH).

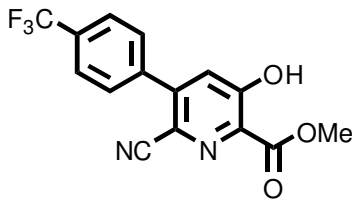
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 53.7, 116.2, 123.5, 126.6, 128.7, 129.1, 130.2, 130.3, 134.2, 147.6, 160.1, 168.7.

IR (neat): $\tilde{\nu}$ = 3133 (b), 3065 (m), 2245 (w), 2228 (s), 1696 (s), 1556 (s), 1456 (s), 1209 (s), 892 (s), 757 (s) cm^{-1}.

HRMS (ESI): Calcd for $C_{14}H_{11}N_2O_3$ $[M + H]^+$, 255.0764; found: 255.0763.

Elemental analysis: Calcd for $C_{14}H_{10}N_2O_3$, C, 66.14; H, 3.96; N, 11.02. Found: C, 65.9; H, 3.9; N, 10.8.

6-Cyano-5-(4'-trifluoromethylphenyl)-3-hydroxypyridine-2-carboxylic acid methyl ester (191b)



191b

GP E: dicyanoalkene **184b** (56.2 mg, 0.25 mmol) gave 77.5 mg (0.24 mmol, 95%) of hydroxypyridine **191b** as a colorless solid.

M. p.: 145-146°C.

TLC: R_f = 0.3 (ethyl acetate/cyclohexane = 1:2).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.12 (3H, s, $COOCH_3$), 7.49 (1H, s, CH), 7.72 (2H, d, J = 8.0 Hz, Ph), 7.81 (2H, d, J = 8.2 Hz, Ph), 11.13 (1H, s, OH).

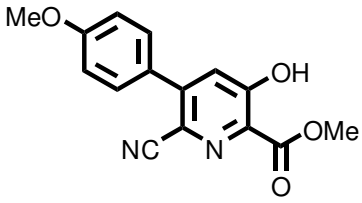
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 53.8, 115.8, 123.3, 126.1, 126.2, 126.2, 126.8, 129.2, 131.0, 132.4, 137.6, 146.0, 160.1, 168.5.

IR (neat): $\tilde{\nu}$ = 3189 (b), 2959 (w), 2233 (m), 1677 (s), 1321 (s), 1114 (s), 1068 (s), 753 (s) cm^{-1}.

HRMS (FAB): Calcd for $C_{15}H_{10}F_3N_2O_3$ $[M+H]^+$, 323.0638; found: 323.0675.

Elemental analysis: Calcd for $C_{15}H_9F_3N_2O_3$, C, 55.91; H, 2.82; N, 8.69. Found: C, 55.9; H, 3.2; N, 8.6.

6-Cyano-5-(4'-methoxyphenyl)-3-hydroxypyridine-2-carboxylic acid methyl ester (191f)



191f

GP E: dicyanoalkene **184f** (46.6 mg, 0.25 mmol) gave 58.5 mg (0.21 mmol, 81%) of hydroxypyridine **191f** as a colorless solid.

M. p.: 187-188°C.

TLC: R_f = 0.31 (ethyl acetate/cyclohexane = 1:2).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.88 (3H, s, OCH_3), 4.10 (3H, s, $COOCH_3$), 7.05 (2H, d, J = 8.8 Hz, Ph), 7.44 (1H, s, CH), 7.56 (2H, d, J = 8.8 Hz, Ph), 11.09 (1H, s, OH).

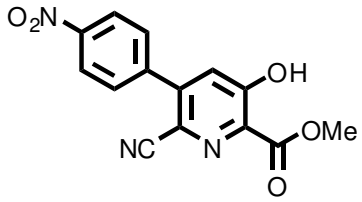
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 53.6, 55.4, 114.7, 116.5, 123.3, 126.0, 126.3, 129.8, 130.2, 147.3, 160.0, 161.3, 168.7.

IR (neat): $\tilde{\nu}$ = 3195 (bw), 2928 (w), 2845 (w), 2230 (m), 1670 (s), 1519 (s), 1434 (s), 1237 (s), 827 (s), 751 (s) cm^{-1}.

HRMS (ESI): Calcd for $C_{15}H_{13}N_2O_4$ $[M+H]^+$, 285.0870, found: 285.0871.

Elemental analysis: Calcd for $C_{15}H_{12}N_2O_4$, C, 63.38; H, 4.25; N, 9.85. Found: C, 63.5; H, 3.9; N, 9.8.

6-Cyano-5-(4'-nitrophenyl)-3-hydroxypyridine-2-carboxylic acid methyl ester (191e)



191e

GP D: dicyanoalkene **184e** (170 mg, 0.85 mmol) gave 180 mg (0.60 mmol, 72%) of hydroxypyridine **191e** as a yellow solid.

M. p.: 170-172°C.

TLC: R_f = 0.23 (ethyl acetate/light petroleum = 1:1).

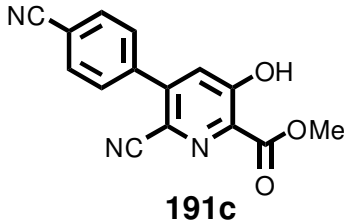
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.13 (3H, s, $COOCH_3$), 7.52 (1H, s, CH), 7.78 (2H, d, J = 8.6 Hz, Ph), 8.41 (2H, d, J = 8.8 Hz, Ph), 11.25 (1H, s, OH).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 53.9, 115.6, 123.1, 124.3, 126.8, 129.9, 131.3, 140.2, 145.1, 148.9, 160.0, 168.4.

IR (neat): $\tilde{\nu}$ = 3251 (b), 2958 (m), 2925 (m), 2855 (m), 2233 (s), 1713 (s), 1694 (s), 1601 (s), 1530 (s), 1435 (s), 1352 (s), 1213 (s), 857 (s) cm^{-1}.

HRMS (ESI): Calcd for $C_{14}H_{10}N_3O_5$ $[M + H]^+$, 300.0615, found: 300.0617.

6-Cyano-5-(4'-cyanophenyl)-3-hydroxypyridine-2-carboxylic acid methyl ester (191c)



191c

GP E: dicyanoalkene **184c** (45.3 mg, 0.25 mmol) gave 68.5 mg (0.25 mmol, 97%) of hydroxypyridine **191c** as a colorless solid.

M. p.: 261°C (decomp.).

TLC: R_f = 0.33 (ethyl acetate/light petroleum = 1:1).

^{1}H-NMR (400 MHz, DMSO): δ = 3.92 (3H, s, $COOCH_3$), 7.59 (1H, s, CH), 7.87 (2H, d, J = 8.2 Hz, Ph), 8.07 (2H, d, J = 8.4 Hz, Ph), 11.81 (1H, s, OH).

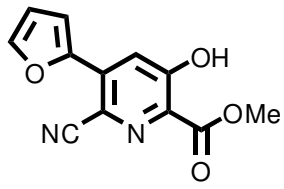
^{13}C-NMR (100.6 MHz, DMSO): δ = 52.7, 112.4, 116.4, 118.2, 120.7, 126.0, 129.8, 132.7, 136.8, 139.0, 143.5, 156.3, 164.6.

IR (neat): $\tilde{\nu}$ = 3246 (b), 2923 (w), 2236 (s), 1697 (s), 1434 (s), 1196 (s), 842 (s), 688 (s) cm^{-1}.

HRMS (ESI): Calcd for $C_{15}H_{10}N_3O_3$ $[M + H]^+$, 280.0717; found: 280.0717.

Elemental analysis: Calcd for $C_{15}H_9N_3O_3$, C, 64.52; H, 3.25; N, 15.05. Found: C, 64.5; H, 3.7; N, 14.8.

6-Cyano-5-(furan-2'-yl)-3-hydroxypyridine-2-carboxylic acid methyl ester (191h)



191h

GP E: dicyanoalkene **184h** (36.5 mg, 0.25 mmol) gave 53.7 mg (0.22 mmol, 87%) of hydroxypyridine **191h** as a colorless solid.

M. p.: 186-187°C.

TLC: R_f = 0.37 (ethyl acetate/cyclohexane = 1:2).

^{1}H-NMR (400 MHz, CDCl$_3$): δ = 4.09 (3H, s, $COOCH_3$), 6.64 (1H, dd, J = 1.8 Hz, furan), 7.63 (1H, d, J = 3.7 Hz, furan), 7.66 (1H, d, J = 1.6 Hz, furan), 7.81 (1H, s, CH), 11.09 (1H, s, OH).

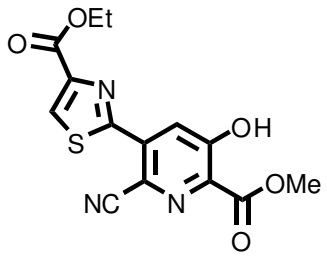
^{13}C-NMR (100.6 MHz, CDCl$_3$): δ = 53.6, 113.1, 114.2, 116.8, 119.0, 121.3, 129.5, 135.3, 145.6, 146.1, 160.2, 168.4.

IR (neat): $\tilde{\nu}$ = 3211 (b), 3136 (m), 2924 (m), 2233 (m), 1690 (s), 1593 (s), 1174 (s), 773 (s), 723 (s) cm^{-1}.

HRMS (ESI): Calcd for $C_{12}H_9N_2O_4$ $[M + H]^+$, 245.0557; found: 245.0557.

Elemental analysis: Calcd for $C_{12}H_8N_2O_4$, C, 59.02; H, 3.30; N, 11.47. Found: C, 58.7; H, 3.1; N, 11.2.

6-Cyano-5-(4'-ethoxycarbonyl-thiazole-2-yl)-3-hydroxypyridine-2-carboxylic acid methyl ester (191j)



191j

GP E: dicyanoalkene **184j** (59.0 mg, 0.25 mmol) gave 73.0 mg (0.22 mmol, 87%) of hydroxypyridine **191j** as a colorless solid.

M. p.: 190-192°C.

TLC: R_f = 0.58 (dichloromethane/MeOH = 10:1).

GC-MS (method B): t_R = 10.04 min, m/Z = 333

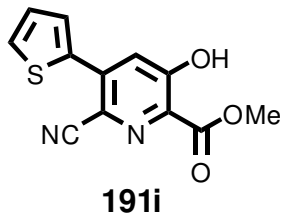
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.44 (3H, t, J = 7.1 Hz, CH_3), 4.12 (3H, s, $COOCH_3$), 4.48 (2H, dd, J = 7.1 Hz, CH_2), 8.23 (1H, s, CH), 8.43 (1H, s, CH), 11.17 (1H, s, OH).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 14.3, 53.9, 62.0, 115.9, 121.4, 126.4, 130.2, 132.0, 137.7, 148.9, 159.4, 160.0, 160.7, 168.2.

IR (KBr): $\tilde{\nu}$ = 3447 (b), 2994 (w), 2231 (m), 1734 (s), 1686 (s), 1220 (s), 903 (s) cm^{-1}.

HRMS (ESI): Calcd for $C_{14}H_{11}N_3O_5SNa$ $[M + Na]^+$, 356.0312, found: 356.0312.

6-Cyano-5-(thiophen-2'-yl)-3-hydroxypyridine-2-carboxylic acid methyl ester (191i)



191i

GP E: dicyanoalkene **184i** (40.5 mg, 0.25 mmol) gave 47.4 mg (0.18 mmol, 72%) of hydroxypyridine **191i** as a colorless solid.

M. p.: 173-174°C.

TLC: R_f = 0.36 (ethyl acetate/cyclohexane = 1:2).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.10 (3H, s, $COOCH_3$), 7.23 (1H, dd, J = 4.0 Hz, thiophene), 7.56 (1H, s, CH), 7.59 (1H, dd, J = 0.8 Hz, thiophene), 7.88 (1H, dd, J = 1.0 Hz, thiophene), 11.10 (1H, s, OH).

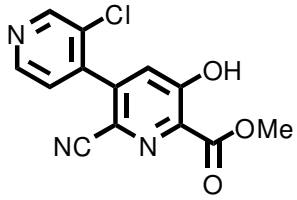
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 53.7, 116.6, 121.6, 125.1, 129.0, 129.7, 129.9, 133.6, 135.1, 139.9, 159.9, 168.5.

IR (neat): $\tilde{\nu}$ = 3111 (b), 3056 (w), 2956 (w), 2231 (m), 1667 (s), 1421 (s), 1204 (s), 698 (s) cm^{-1}.

HRMS (ESI): Calcd for $C_{12}H_9N_2O_3S$ $[M + H]^+$, 261.0328; found: 261.0330.

Elemental analysis: Calcd for $C_{12}H_8N_2O_3S$, C, 55.38; H, 3.10; N, 10.76. Found: C, 55.0; H, 3.3; N, 10.6.

6-Cyano-5-(3'-chloro-pyridine-4'-yl)-3-hydroxypyridine-2-carboxylic acid methyl ester (191l)



191l

GP E: dicyanoalkene **184l** (47.0 mg, 0.25 mmol) gave 33.9 mg (0.12 mmol, 47%) of hydroxypyridine **191l** as a pink solid.

M. p.: 164-166°C.

TLC: R_f = 0.81 (Dichloromethane/MeOH = 10:1).

GC-MS (method B): t_R = 8.60 min, m/Z = 289

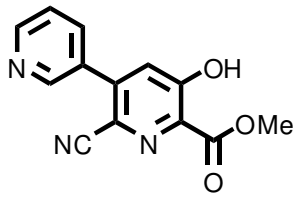
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.12 (3H, s, $COOCH_3$), 7.34 (1H, d, J = 4.7 Hz, CH), 7.46 (1H, s, CH), 8.68 (1H, d, J = 0.7 Hz, CH), 8.81 (1H, s, CH), 11.26 (1H, s, OH).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 53.9, 114.9, 123.8, 124.5, 127.6, 131.5, 140.5, 142.2, 148.3, 150.5, 159.8, 168.4.

IR (KBr): $\tilde{\nu}$ = 3191 (b), 2956 (w), 2236 (s), 1684 (s), 1216 (s), 850 (s) cm^{-1}.

HRMS (ESI): Calcd for $C_{13}H_9N_3O_3Cl$ $[M + H]^+$, 290.0327, found: 290.0328.

6-Cyano-5-(pyridine-3'-yl)-3-hydroxypyridine-2-carboxylic acid methyl ester (191k)



191k

GP E: dicyanoalkene **184k** (39.3 mg, 0.25 mmol) gave 42.5 mg (0.17 mmol, 66%) of hydroxypyridine **191k** as a colorless solid.

M. p.: 198-199°C.

TLC: R_f = 0.58 (CH_2Cl_2/MeOH = 10:1).

^{1}H-NMR (400 MHz, DMSO): δ = 4.01 (3H, s, $COOCH_3$), 7.43 (1H, t, J = 8.1 Hz, H-5'), 7.44 (1H, s, CH), 7.92 (1H, dt, J = 8.0 Hz, H-4'), 8.69 (1H, dd, J = 6.4 Hz, H-6'), 8.72 (1H, d, J = 1.8 Hz, H-2'), 11.12 (1H, s, OH).

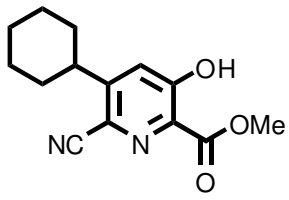
^{13}C-NMR (100.6 MHz, DMSO): δ = 53.5, 115.6, 123.0, 123.5, 126.6, 130.2, 131.1, 136.0, 143.6, 148.6, 150.7, 159.7, 168.0.

IR (neat): $\tilde{\nu}$ = 3201 (b), 3071 (w), 2231 (m), 1681 (s), 1367 (s), 1199 (s), 714 (s) cm^{-1}.

HRMS (ESI): Calcd for $C_{13}H_{10}N_3O_3$ $[M + H]^+$ 256.0717; found: 256.0716.

Elemental analysis: Calcd for $C_{13}H_9N_3O_3$, C, 61.18; H, 3.55; N, 16.46. Found: C, 60.7; H, 4.0; N, 16.9.

6-Cyano-5-cyclohexyl-3-hydroxypyridine-2-carboxylic acid methyl ester (191n)



191n

GP E: dicyanoalkene **184n** (40.5 mg, 0.25 mmol) gave 42.1 mg (0.16 mmol, 60%) of hydroxypyridine **191n** as a colorless solid.

M. p.: 103-104°C.

TLC: R_f = 0.47 (ethyl acetate/cyclohexane = 1:2).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.24-1.50 (6H, m, cyclohexyl), 1.78-1.95 (6H, m, cyclohexyl), 2.95-3.00 (1H, m, cyclohexyl), 4.05 (3H, s, $COOCH_3$), 7.30 (1H, s, CH), 11.00 (1H, s, OH).

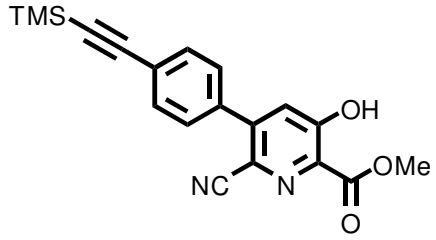
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 25.6, 26.2, 33.1, 41.0, 53.5, 115.5, 123.8, 124.8, 129.5, 154.2, 160.5, 168.7.

IR (neat): $\tilde{\nu}$ = 3152 (b), 2926 (s), 2853 (s), 2229 (m), 1680 (s), 1431 (s), 1228 (s), 740 (s) cm^{-1}.

HRMS (ESI): Calcd for $C_{14}H_{17}N_2O_3$ $[M + H]^+$, 261.1234, found: 261.1234.

Elemental analysis: Calcd for $C_{14}H_{16}N_2O_3$, C, 64.60; H, 6.20; N, 10.76. Found: C, 64.8; H, 6.3; N, 10.5.

6-Cyano-5-(4'-((trimethylsilyl)ethylnyl)phenyl)-3-hydroxypyridine-2-carboxylic acid methyl ester (191g)



191g

GP D: dicyanoalkene **184g** (250 mg, 1 mmol) gave 250 mg (0.71 mmol, 71%) of hydroxypyridine **191g** as a colorless solid.

M. p.: 95-97°C.

TLC: R_f = 0.33 (ethyl acetate/cyclohexane = 1:2).

GC-MS (method B): t_R = 9.94 min, m/Z = 350.

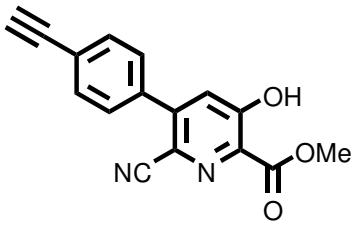
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.27 (9H, s, TMS), 4.10 (3H, s, COOMe), 7.46 (1H, s, CH), 7.54 (2H, d, J = 8.6 Hz, Ph), 7.62 (2H, d, J = 8.6 Hz, Ph), 11.14 (1H, s, OH).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = -0.2, 53.7, 97.2, 103.8, 116.0, 123.3, 125.4, 126.5, 128.5, 130.4, 132.6, 133.8, 146.8, 160.0, 168.0.

IR (KBr): $\tilde{\nu}$ =3159 (w), 2959 (s), 2854 (s), 2232 (s), 2159 (s), 1682 (s), 1231 (s), 866 (s) cm^{-1}.

HRMS (ESI): Calcd for $C_{19}H_{19}N_2O_3Si$ $[M + H]^+$, 351.1160, found: 351.1159.

6-Cyano-5-(4'-ethynylphenyl)-3-hydroxypyridine-2-carboxylic acid methyl ester (191t)



191t

GP E: dicyanoalkene **184t** (23.0 mg, 0.13 mmol) gave 32.3 mg (0.12 mmol, 90%) of hydroxypyridine **191t** as a colorless solid.

M. p.: 227-228°C.

TLC: R_f = 0.58 (ethyl acetate/light petroleum = 1:1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.21 (1H, s, CCH), 4.11 (3H, s, $COOCH_3$), 7.47 (1H, s, CH), 7.57 (2H, d, J = 8.5 Hz, Ph), 7.66 (2H, d, J = 8.5 Hz, Ph), 11.16 (1H, s, OH).

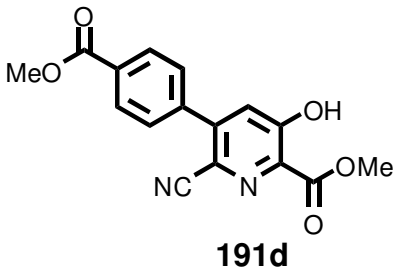
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 53.8, 116.0, 123.3, 124.4, 126.5, 128.7, 130.6, 132.8, 134.3, 146.7, 160.0, 168.6.

IR (neat): $\tilde{\nu}$ = 3264 (s), 3175 (bw), 2959 (w), 2231 (m), 1680 (s), 1432 (s), 1206 (s), 834 (s), 689 (s) cm^{-1}.

HRMS (ESI): Calcd for $C_{16}H_{11}N_2O_3$ $[M + H]^+$, 279.0764; found: 279.0765.

Elemental analysis: Calcd for $C_{16}H_{10}N_2O_3$: C, 69.06; H, 3.62; N, 10.07. Found: C, 68.8; H, 4.0; N, 9.9.

6-Cyano-5-(4'-methoxycarbonyl)phenyl)-3-hydroxypyridine-2-carboxylic acid methyl ester (191d)



191d

GP E: dicyanoalkene **184d** (53.0 mg, 0.25 mmol) gave 64.5 mg (0.21 mmol, 83%) of hydroxypyridine **191d** as a light yellow solid.

M. p.: 144°C (decomposition).

TLC: R_f = 0.15 (ethyl acetate/cyclohexane = 1:2).

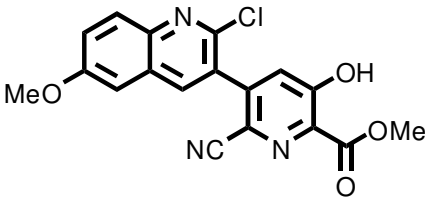
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.97 (3H, s, $COOCH_3$), 4.12 (3H, s, $COOCH_3$), 7.50 (1H, s, CH), 7.67 (2H, d, J = 9.7 Hz, 2 x CH), 8.20 (2H, d, J = 9.7 Hz, 2 x CH), 11.18 (1H, s, OH).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 52.5, 53.8, 115.9, 123.3, 126.8, 128.8, 130.3, 130.8, 131.7, 138.3, 146.5, 160.0, 166.2, 168.6.

IR (KBr): $\tilde{\nu}$ = 2924 (s), 2854 (s), 2233 (m), 1728 (s), 1436 (s), 1283 (s), 859 (s) cm^{-1}.

HRMS (ESI): Calcd for $C_{16}H_{13}N_2O_5$ $[M + H]^+$, 313.0819, found: 313.0820.

5-(2'-Chloro-6'-methoxyquinolin-3'-yl)-6-cyano-3-hydroxypyridine-2-carboxylic acid methyl ester (191m)



191m

GP E: dicyanoalkene **184m** (67.0 mg, 0.25 mmol) gave 59.2 mg (0.16 mmol, 64%) of hydroxypyridine **191m** as a colorless solid.

M. p.: 217°C (decomposition).

TLC: R_f = 0.14 (ethyl acetate/light petroleum = 1:1).

R_f = 0.73 (dichloromethane/MeOH = 10:1).

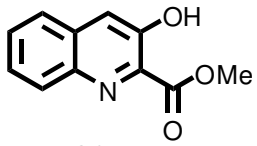
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.95 (3H, s, OCH_3), 4.14 (3H, s, $COOCH_3$), 7.14 (1H, d, J = 2.5 Hz, CH), 7.49 (1H, dd, J = 2.6 Hz, 9.2 Hz, CH), 7.57 (1H, s, CH), 8.00 (1H, d, J = 9.4 Hz, CH), 8.11 (1H, s, CH), 11.25 (1H, s, OH).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 53.9, 55.7, 105.3, 115.3, 124.9, 124.9, 127.3, 127.6, 128.5, 130.0, 131.2, 138.4, 143.7, 144.2, 144.9, 158.9, 159.7, 168.5.

IR (KBr): $\tilde{\nu}$ = 3008 (ws), 2955 (ws), 2230 (s), 1731 (s), 1714 (s), 1693 (s), 1682 (s), 1668 (s), 1661 (s), 1651 (s), 1495 (s), 1227 (s), 913 (s), 799 (s) cm^{-1}.

HRMS (ESI): Calcd for $C_{18}H_{13}N_3O_4Cl$ $[M + H]^+$, 370.0589, found: 370.0591.

3-Hydroxyquinoline-2-carboxylic acid methyl ester (204)



204

Isoamyl nitrite (131 µL, 0.98 mmol) and 1-azadiene **195** (568 mg, 2.5 mmol) were added dropwise at the same time to a suspension of anthranilic acid (113 mg, 0.82 mmol) in DCE (1.5 mL) at reflux. The reaction mixture was refluxed for 1 hour and cooled to room temperature. Phosphate buffer (pH 2.5, 20 mL) was added and the mixture was extracted with dichloromethane (3 x 20 mL). The combined extracts were dried with sodium sulfate and concentrated. Purification by column chromatography (silica gel, 20 g, ethyl acetate/light petroleum = 1:8) gave 56.1 mg (0.28 mmol, 26%) of quinoline **204** as a light yellow solid.

M. p.: 118-122°C.

TLC: R_f = 0.26 (ethyl acetate/cyclohexane = 1:2).

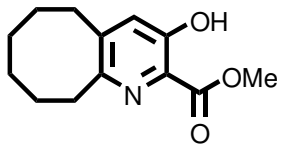
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.15 (3H, s, $COOCH_3$), 7.47 (1H, s, CH), 7.57 (2H, d, J = 8.5 Hz, Ph), 7.66 (2H, d, J = 8.5 Hz, Ph), 11.16 (1H, s, OH).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 53.7, 120.8, 126.3, 127.7, 129.5, 130.4, 132.1, 133.5, 142.6, 153.9, 169.6.

IR (neat): $\tilde{\nu}$ = 3189 (b), 2947 (s), 1701 (s), 1505 (s), 1223 (s), 781 (s) cm^{-1}.

HRMS (ESI): Calcd for $C_{11}H_{10}NO_3$ $[M + H]^+$, 204.0655, found: 204.0655.

3-Hydroxy-cyclooct-1-eno[b]pyridine-2-carboxylic acid methyl ester (199)



199

GP D: cyclooctyne **198** (119.4 mg, 1.11 mmol) gave 220.5 mg (0.94 mmol, 85%) of hydroxypyridine **199** as a colorless solid.

M. p.: 104-108°C.

TLC: R_f = 0.32 (ethyl acetate/cyclohexane = 1:2).

GC-MS (method B): t_R = 7.69min, m/Z = 235.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.38 (4H, t, J = 2.7 Hz, CH_2), 1.71-1.78 (4H, m, J = 4.9 Hz, CH_2), 2.78 (2H, t, J = 6.3 Hz, CH_2), 2.98 (2H, t, J = 6.3 Hz, CH_2), 4.03 (3H, s, $COOCH_3$), 7.09 (1H, s, CH), 10.52 (1H, s, OH).

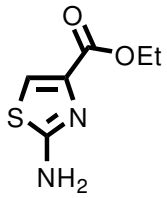
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 25.6, 26.0, 30.9, 31.9, 31.9, 33.8, 53.1, 126.2, 127.0, 144.7, 153.7, 157.6, 170.0.

IR (neat): $\tilde{\nu}$ = 3100 (b), 2928 (s), 1675 (s), 1457 (s), 1224 (s), 728 (s) cm^{-1}.

HRMS (EI): Calcd for $C_{13}H_{17}NO_3$ $[M]^+$, 235.1203, found: 235.1199.

5.12 Preparation of nosiheptide A-ring.

2-Amino-4-thiazolecarboxylic acid ethyl ester (227a)[156]



227a

Ethyl bromopyruvate (90%, 10.0 mL, ~70 mmol) and thiourea (5.5 g, 71.5 mmol) were combined and heated slowly to 100°C (oil bath) and maintained at that temperature for 20 min. The reaction mixture became homogeneous at 70°C, whereupon a rapid, exothermic reaction was observed (careful temperature control was necessary to avoid a violent reaction). After cooling and drying under high vacuum, 12.8 g of a pale brown solid **227a** was obtained which was of sufficient purity to be used directly in the next step. A pure sample was obtained by recrystallization from ethyl acetate as a colorless solid.

TLC: R_f = 0.08 (ethyl acetate/cyclohexane = 1:2).

GC-MS (method B): t_R = 6.61 min, m/Z = 172.

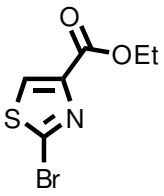
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.29 (3H, t, J = 7.1 Hz, CH_2CH_3), 4.30 (2H, dd, J = 7.1 Hz, CH_2CH_3), 7.63 (1H, s, -CH-).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 14.5 ($CH_2\underline{C}H_3$), 63.7 ($\underline{C}H_2CH_3$), 118.3 ($\underline{C}$H), 132.3 ($\underline{C}$-$COOCH_2CH_3$), 158.3 ($\underline{C}OOCH_2CH_3$), 172.0 ($\underline{C}$-NH_2).

IR (KBr): $\tilde{\nu}$ = 3094 (w), 1731 (s), 1633 (s), 1226 (s), 799 (s) cm^{-1}.

HRMS (EI): Calcd for $C_6H_8N_2O_2S$ $[M]^+$, 172.0301, found: 172.0302.

2-Bromo-4-thiazolecarboxylic acid ethyl ester (228)

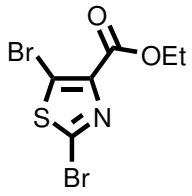


228

To a mixture of crude aminothiazole **227a** (12.8 g, approximately 70 mmol), $CuSO_4$ (34.2 g, 215 mmol), and NaBr (29.5 g, 285 mmol) in sulfuric acid (9 M, 150 mL) cooled with an ice-salt bath at -5 to 0°C (internal temperature) was added a solution (precooled to 0°C) of $NaNO_2$ (5.9 g, 85 mmol) in H_2O (100 mL) dropwise over 60 min. The internal temperature was maintained below 0°C during the addition. After being stirred at 0°C for 1 h, the reaction mixture was gradually warmed to room temperature over 1 h and stirred for another hour. The mixture was then diluted with water (200 mL) and extracted with diethyl ether (5 x 200 mL). The combined ether extracts were dried with sodium sulfate and concentrated. The crude product **228** (12.7 g, colorless powder) was used directly in the next step without purification. An analytical sample was purified by column chromatography.

TLC: R_f = 0.68 (ethyl acetate/cyclohexane = 1:2).
GC-MS (method B): t_R = 6.09 min, m/Z = 237.
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.35 (3H, t, J = 7.1 Hz, CH_2CH_3), 4.36 (2H, dd, J = 7.1 Hz, CH_2CH_3), 8.08 (1H, s, -CH-).
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 14.2 ($CH_2\underline{C}H_3$), 61.7 ($\underline{C}H_2CH_3$), 130.7 ($\underline{C}$H), 136.6 ($\underline{C}$-Br), 147.1 ($\underline{C}$-$COOCH_2CH_3$), 159.9 ($\underline{C}OOCH_2CH_3$).
LC-MS (ESI): t_R = 7.36 min, calcd for $C_6H_7{}^{81}BrNO_2S$ $[M + H]^+$, 237.9, found: 237.9
IR (KBr): $\tilde{\nu}$ = 3420 (w), 3090 (s), 2986 (s), 1715 (s), 1431 (s), 1225 (s), 774 (s) cm^{-1}.
HRMS (EI): Calcd for $C_6H_6NO_2S^{79}Br$ $[M]^+$, 234.9297, found: 234.9300.

2, 5-Dibromo-4-thiazolecarboxylic acid ethyl ester (228a)

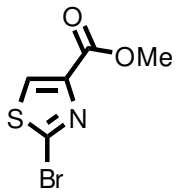


228a

The side product from the preparation of **228**.

TLC: R_f = 0.70 (ethyl acetate/cyclohexane = 1:2).
GC-MS (method B): t_R = 6.79 min, m/Z = 315.
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.37 (3H, t, $CH_2\underline{CH_3}$), 4.39 (2H, dd, $\underline{CH_2}CH_3$).
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 14.1 ($CH_2\underline{C}H_3$), 61.9 ($\underline{C}H_2CH_3$), 118.7 ($\underline{C}$-Br), 135.6 ($\underline{C}$-Br), 143.7 ($\underline{C}$-$COOCH_2CH_3$), 159.5 ($\underline{C}OOCH_2CH_3$).
LC-MS (ESI) (method A): t_R = 8.81 min, calcd for $C_6H_6{}^{81}Br_2NO_2S$ $[M + H]^+$, 315.9, found: 315.8.

2-Bromo-4-thiazolecarboxylic acid methyl ester (230)



230

The crude ethyl ester **228** (12.7 g) was dissolved in methanol (150 mL), and concentrated sulfuric acid (1 mL) was added. The mixture was heated to reflux for 12 h (TLC control). The solvent was evaporated, the residue was diluted with H_2O (150 mL), neutralized with saturated sodium bicarbonate solution, and extracted with dichloromethane (4 x 100 mL). The combined extracts were dried with sodium sulfate and concentrated. Purification by column chromatography (silica gel, 80 g, ethyl acetate/cyclohexane = 1:15) gave 6.5 g methyl ester **230** (29.4 mmol, 49% over three steps) as a colorless solid.

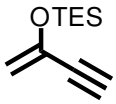
TLC: R_f = 0.55 (ethyl acetate/cyclohexane = 1:2).
GC-MS (method B): t_R = 5.92 min, m/Z = 223.
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.88 (3H, s, CH_3), 8.08 (1H, s, -CH-).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 52.5 ($\underline{C}H_3$), 130.9 ($\underline{C}H$), 136.7 ($\underline{C}$-Br), 146.6 ($\underline{C}$-$COOCH_3$), 160.3 ($\underline{C}OOCH_3$).

IR (KBr): $\tilde{\nu}$ = 3046 (w), 3115 (s), 3004 (m), 2956 (s), 1715 (s), 1444 (s), 1242 (s), 973 (s) cm^{-1}.

HRMS (EI): Calcd for $C_5H_4NO_2SBr$ $[M]^+$, 220.9141, found: 220.9140.

2-Triethylsilyloxy-but-1-ene-3-yne (232a)



232a

Triethylsilyl trifluoromethanesulfonate (1.8 mL, 7.9 mmol) was added dropwise to a stirred solution of 3-butyn-2-one (0.6 mL, 7.7 mmol) and 2,6-lutidine (1.8 mL, 15.5 mmol) in dichloromethane (7 mL) at 0°C. The reaction mixture was stirred at this temperature for 30 min, then slowly warmed to room temperature for another 1h (TLC control). The reaction mixture was quenched with HCl (1M, 10 mL), and extracted with diethyl ether (3 x 20 mL). The combined ether layers were washed with satured NaCl solution (30 mL), dried with sodium sulfate, and concentrated. Purification by column chromatography (silica gel, 40 g, dichloromethane/*n*-pentane = 1:10) gave 1.2 g (6.6 mmol, 85%) of enol ether **232a** as colorless oil.

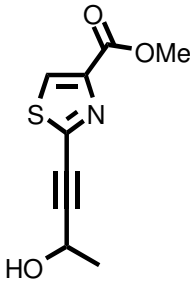
TLC: R_f = 0.5 (dichloromethane/cyclohexane = 1:8).

GC-MS (method B): t_R = 4.63 min, m/Z = 182.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.74, 1.0 (TES), 2.86 (1H, s, CH), 4.74 (2H, s, CH_2).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 5.1, 6.7, 75.3, 81.3, 103.6, 138.9.

2-But-1´-in-3´-olyl-4-thiazolecarboxylic acid methyl ester (231)

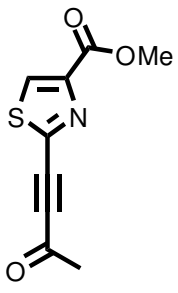


231

To a dry Schlenk flask, $PdCl_2$ (11.7 mg, 0.059 mmol), PPh_3 (34.4 mg, 0.118 mmol), CuI (23.6 mg, 0.118 mmol) and DMF (15 mL) were added under argon, the mixture was stirred for 30 min, then thiazole **230** (1.3 g, 5.9 mmol), 3-Butyn-2-ol (78 µL, 8.8 mmol) and triethylamine (1.8 mL, 12 mmol) were introduced. The mixture was heated to 80°C for 2 h (TLC control). During this time the solution turned dark brown. The mixture was cooled to room temperature, diluted with dichloromethane (50 mL) and filtered through Celite. The pad of Celite was washed with dichloromethane (3 x 10 mL). The combined filtrates were concentrated in vacuum and purified by column chromatography (silica gel, 20 g, ethyl acetate/cyclohexane = 1:4) to give 0.90 g (4.3 mmol, 90%) of alcohol **231** as a colorless solid.

M. p.: 94-95°C.
TLC: R_f = 0.15 (ethyl acetate/cyclohexane = 1:2).
GC-MS (method B): t_R = 7.22 min, m/Z = 211.
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.56 (3H, d, J = 6.7 Hz, CH_3), 2.23 (1H, s, OH), 3.95 (3H, s, $COOCH_3$), 4.77 (1H, dd, J = 6.5 Hz, $CHCH_3$), 8.17 (1H, s, CH).
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 23.6 ($CH\underline{C}H_3$), 52.5 ($\underline{C}H_3$), 58.6 ($\underline{C}HCH_3$), 76.4 (C-$\underline{C}$COH), 96.9 (C$\underline{C}$OH), 128.6 ($\underline{C}$H), 147.2 ($\underline{C}$-CCOH), 148.8 ($\underline{C}$-$COOCH_3$), 161.2 ($\underline{C}OOCH_3$).
IR (KBr): $\tilde{\nu}$ = 3343 (b), 2981 (s), 2486 (s), 2230 (s), 1681 (s), 1248 (s), 928 (s), 771 (s) cm^{-1}.
HRMS (FAB): Calcd for $C_9H_{10}NO_3S$ $[M + H]^+$, 212.0376, found: 212.0416.

2-But-1´-in-3´-onyl-4-thiazolecarboxylic acid methyl ester (164)



164

To a cooled solution (0°C) of thiazolyl alcohol **231** (0.9 g, 4.3 mmol) in dry THF (10 mL) under argon was added dropwise a solution of IBX (1.57 g, 5.59 mmol) in dry DMSO (10 mL). The solution was stirred for 12 h (TLC control), then diluted with water (60 mL) and

extracted with diethyl ether (4 x 50 mL). The combined extracts were dried with sodium sulfate and concentrated to dryness. Purification by column chromatography (silica gel, 10 g, ethyl acetate/cyclohexane = 1:6) gave 0.8 g (3.83 mmol, 99%) ketone **164** as a colorless solid.

M. p.: 159-160°C.

TLC: R_f = 0.39 (ethyl acetate/cyclohexane = 1:2).

GC-MS (method B): t_R = 6.99 min, m/Z = 209.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.44 (3H, s, C(O)CH_3), 3.94 (3H, s, $COOCH_3$), 8.32 (1H, s, CH).

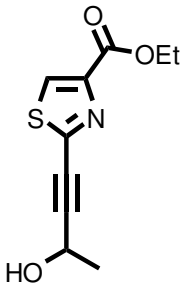
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 32.4 (C(O)<u>C</u>H_3), 52.7 (<u>C</u>H_3), 79.5 (C-<u>C</u>CC(O)CH_3), 90.4 (<u>C</u>C(O)CH_3), 130.9 (<u>C</u>H), 146.2 (<u>C</u>-CC(O)CH_3), 148.2 (<u>C</u>-$COOCH_3$), 160.7 (<u>C</u>$OOCH_3$), 183.1 (<u>C</u>(O)CH_3).

IR (KBr): $\tilde{\nu}$ = 3078 (s), 2204 (s), 1728 (s), 1673 (m), 1453 (s), 1231 (s), 861 (s) cm^{-1}.

HRMS (FAB): Calcd for $C_9H_8NO_3S$ $[M + H]^+$, 210.0219, found: 210.0219.

Elemental analysis: Calcd for $C_9H_7NO_3S$, C, 51.67; H, 3.37; N, 6.69; found: C, 51.7; H, 3.5; N, 6.8.

2-But-1´-in-3´-olyl-4-thiazolecarboxylic acid ethyl ester (229)



229

Using the same procedure as the preparation of thiazolyl alcohol **231**, thiazole **228** (117 mg, 0.50 mmol) yielded 102 mg (0.45 mmol, 91%) of the **229** as a colorless solid.

M. p.: 165°C (decomp.).

TLC: R_f = 0.21 (ethyl acetate/cyclohexane = 1:2).

GC-MS (method B): t_R = 7.39 min, m/Z = 225.

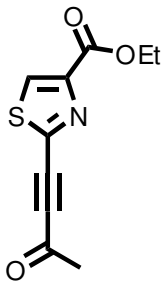
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.35 (3H, t, J = 7.2 Hz, $CH_2\underline{CH_3}$), 1.53 (3H, d, J = 6.7 Hz, CH_3), 3.67 (1H, s, OH), 4.35 (2H, dd, J = 7.0 Hz, $COOCH_3$), 4.79 (1H, dd, J = 6.6 Hz, $\underline{CH}CH_3$), 8.10 (1H, s, CH).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 14.1 ($CH_2\underline{CH_3}$), 23.4 ($CH\underline{C}H_3$), 58.1 ($\underline{CH_2}CH_3$), 61.6 ($\underline{C}HCH_3$), 75.9 (C-$\underline{C}$COH), 97.7 (C$\underline{C}$OH), 128.4 ($\underline{C}$H), 147.2 ($\underline{C}$-CCOH), 148.9 ($\underline{C}$-$COOCH_3$), 160.6 ($\underline{C}OOCH_2CH_3$).

IR (KBr): $\tilde{\nu}$ = 3286 (w), 3091 (s), 2981 (m), 2354 (m), 1723 (s), 1232 (s), 795 (s) cm^{-1}.

HRMS (EI): Calcd for $C_{10}H_{11}NO_3S$ $[M]^+$, 225.0454, found: 225.0459.

2-But-1´-in-3´-onyl-4-thiazolecarboxylic acid ethyl ester (167)



167

Using the same procedure as the preparation of thiazolyl ketone **164**, thiazole **229** (2.3 g, 10.2 mmol) yielded 2.25 g (10.1 mmol, 99%) of the **167** as a colorless solid.

M. p.: 155°C (decomp.).

TLC: R_f = 0.44 (ethyl acetate/cyclohexane = 1:2).

GC-MS (method B): t_R = 7.16 min, m/Z = 223.

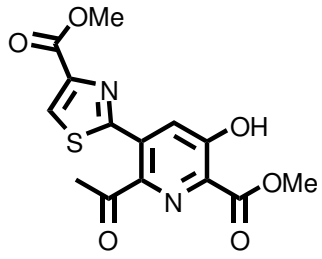
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.37 (3H, t, J = 7.2 Hz, CH_2CH_3), 2.43 (3H, s, $C(O)CH_3$), 4.41 (2H, dd, J = 7.0 Hz, $COOCH_2CH_3$), 8.30 (1H, s, CH).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 14.2 ($CH_2\underline{CH_3}$), 32.4 ($C(O)\underline{C}H_3$), 61.9 ($\underline{C}H_2CH_3$), 79.6 (C-$\underline{C}$CC(O)CH_3), 90.4 ($\underline{C}$C(O)CH_3), 130.7 ($\underline{C}$H), 146.1 ($\underline{C}$-CC(O)CH_3), 148.6 ($\underline{C}$-$COOCH_3$), 160.3 ($\underline{C}OOCH_3$), 183.0 ($\underline{C}(O)CH_3$).

IR (KBr): $\tilde{\nu}$ = 3079 (s), 2203 (s), 1717 (s), 1677 (s), 1233 (s), 1101 (s), 779 (s) cm^{-1}.

HRMS (FAB): Calcd for $C_{10}H_{10}NO_3S$ $[M + H]^+$, 224.0376, found: 224.0376.

5-(4'-(Methoxycarbonyl)thiazol-2'-yl)-6-acetyl-3-hydroxypyridine-2-carboxylic acid methyl ester (233).



233

A solution of thiazolylketone **164** (1.0 g, 4.78 mmol) and 1-azadiene **121** (4.15 g, 14.4 mmol) in toluene (1 mL) was heated to 180°C for 3 h under Ar (CAUTION! Use thick-walled sealed tube!). After cooling to room temperature, the reaction mixture was purified by column chromatography (silica gel, 30 g, ethyl acetate/light petroleum = 1:4) to give 888 mg (2.64 mmol, 55%) of ketone **233** and 447 mg (1.33 mmol, 28%) of its 5-acetyl regioisomer **234** as colorless solids.

M. p.: 217°C (decomp.).

TLC: R_f = 0.06 (ethyl acetate/cyclohexane = 1:2).

GC-MS (method B): t_R = 9.51 min, m/Z = 336.

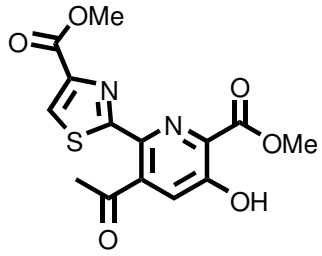
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.70 (3H, s, C(O)CH_3), 3.95 (3H, s, COOCH_3), 4.09 (3H, s, COOCH_3), 7.68 (1H, s, CH), 8.34 (1H, s, CH), 11.02 (1H, s, C-OH).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 27.4 (C(O)$\underline{C}H_3$), 52.5 (COO$\underline{C}H_3$), 53.4 (COO$\underline{C}H_3$), 129.0 ($\underline{C}$H), 129.1 ($\underline{C}$-COOMe), 129.7 ($\underline{C}$H), 134.3 ($\underline{C}$-CH), 145.0 ($\underline{C}$-C(O)Me), 147.1 ($\underline{C}$-COOMe), 159.4 ($\underline{C}$-OH), 161.6 ($\underline{C}$OOMe), 163.3 (C-$\underline{C}$(N)S), 169.1 ($\underline{C}$OOMe), 198.8 ($\underline{C}$(O)CH_3).

IR (KBr): $\tilde{\nu}$ = 3157 (s), 2914 (s), 2854 (s), 1729 (m), 1692 (m), 1461 (s), 1377 (s), 1179 (w), 890 (s) cm^{-1}.

HRMS (FAB): Calcd for $C_{14}H_{13}N_2O_6S$ $[M + H]^+$, 337.0489, found: 337.0515.

6-(4'-(Methoxycarbonyl)thiazol-2'-yl)-5-acetyl-3-hydroxypyridine-2-carboxylic acid methyl ester (234).



234

M. p.: 186°C (decomp.).

TLC: R_f = 0.17 (ethyl acetate/cyclohexane = 1:2).

GC-MS (method B): t_R = 9.41 min, m/Z = 336.

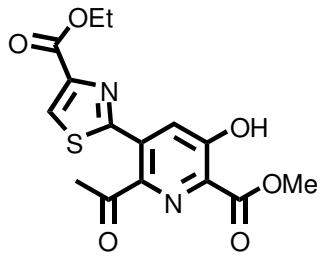
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.64 (3H, s, C(O)CH_3), 3.93 (3H, s, COOCH_3), 4.09 (3H, s, COOCH_3), 7.29 (1H, s, CH), 8.22 (1H, s, CH), 10.91 (1H, s, C-OH).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 30.9 (C(O)$\underline{C}H_3$), 52.4 (COO$\underline{C}H_3$), 53.4 (COO$\underline{C}H_3$), 124.4 ($\underline{C}$H), 129.4 ($\underline{C}$H), 129.5 ($\underline{C}$-COOMe), 138.1 ($\underline{C}$-C(N)S), 142.3 ($\underline{C}$-C(O)Me), 147.6 ($\underline{C}$-COOMe), 159.1 ($\underline{C}$-OH), 161.6 ($\underline{C}$OOMe), 166.5 ($\underline{C}$(N)S), 168.9 ($\underline{C}$OOMe), 201.0 ($\underline{C}$(O)CH_3).

IR (KBr): $\tilde{\nu}$ = 3124 (s), 2958 (w), 2922 (w), 2852 (w), 1743 (s), 1704 (s), 1454 (s), 1216 (s), 808 (s) cm^{-1}.

HRMS (ESI): Calcd for $C_{14}H_{13}N_2O_6S$ $[M + H]^+$, 337.0489, found: 337.0492.

5-(4'-(Ethoxycarbonyl)thiazol-2'-yl)-6-acetyl-3-hydroxypyridine-2-carboxylic acid methyl ester (233a).



233a

Using the same procedure as for the preparation of pyridine **233**, thiazole **167** (0.11 mg, 0.50 mmol) yielded 52.4 mg (0.15 mmol, 30%) **233a** and 36.5 mg (0.10 mmol, 20%) **234a** (total yield, 52%) as colorless solids.

M. p.: 165-168°C.

TLC: R_f = 0.26 (ethyl acetate/light petroleum = 1:1).

GC-MS (method B): t_R = 9.40 min, m/Z = 350.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.41 (3H, t, $CH_2\underline{CH_3}$), 2.71 (3H, s, $C(O)CH_3$), 4.10 (3H, s, $COOCH_3$), 4.44 (2H, dd, $\underline{CH_2}CH_3$), 7.70 (1H, s, CH), 8.32 (1H, s, CH), 11.02 (1H, s, C-OH).

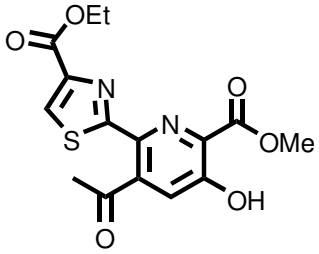
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 14.5 ($CH_2\underline{CH_3}$), 27.7 ($C(O)\underline{C}H_3$), 53.6 ($COO\underline{C}H_3$), 61.8 ($\underline{CH_2}CH_3$), 129.1 (CH), 129.2 (C-COOMe), 129.6 (CH), 134.5 (C-CH), 145.4 (C-C(O)Me), 147.7 (C-COOEt), 159.5 (C-OH), 161.3 (COOEt), 163.3 (C-C(N)S), 169.3 (COOMe), 199.1 ($C(O)CH_3$).

IR (KBr): $\tilde{\nu}$ = 3099 (w), 2958 (s), 1716 (s), 1685 (s), 1550 (m), 1446 (s), 1219 (s), 1097 (s), 892 (s), 754 (s) cm^{-1}.

LC-MS (ESI) (method C): t_R = 8.89 min, calcd for $C_{15}H_{15}N_2O_6S$ $[M + H]^+$, 351.1, found: 350.9.

HRMS (FAB): Calcd for $C_{15}H_{14}N_2O_6SNa$ $[M + Na]^+$, 373.0465, found: 373.0465.

6-(4'-(Ethoxycarbonyl)thiazol-2-yl)-5-acetyl-3-hydroxypyridine-2-carboxylic acid methyl ester (234a)



234a

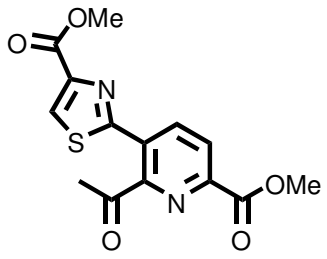
TLC: R_f = 0.34 (ethyl acetate/light petroleum = 1:1).

GC-MS (method B): t_R = 9.36 min, m/Z = 350.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.41 (3H, t, $CH_2\underline{CH_3}$), 2.65 (3H, s, $C(O)CH_3$), 4.08 (3H, s, $COOCH_3$), 4.38 (2H, dd, $\underline{CH_2}CH_3$), 7.28 (1H, s, CH), 8.21 (1H, s, CH), 10.92 (1H, s, C-OH).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 14.2 ($CH_2\underline{CH_3}$), 30.9 ($C(O)\underline{C}H_3$), 53.4 ($COO\underline{C}H_3$), 61.3 ($\underline{CH_2}CH_3$), 124.3 (CH), 129.1 (CH), 129.5 (C-COOMe), 138.1 (C-C(N)S), 142.4 (C-C(O)Me), 147.9 (C-COOEt), 159.1 (C-OH), 161.1 (COOEt), 166.4 (C(N)S), 168.9 (COOMe), 201.0 ($C(O)CH_3$).

5-(4'-(Methoxycarbonyl)thiazol-2-yl)-6-acetyl-pyridine-2-carboxylic acid methyl ester (235)



235

A mixture of alkyne **164** (21 mg, 100 µmol) and 1-azadiene **195** (70 µL, 303 µmol) in DMF (200 µL) was heated to 130°C for 60 minutes in a chemical microwave. The solvent was removed under high vacuum and purification by column chromatography (silica gel, 20 g, ethyl acetate/light petroleum = 1:10 → 1:1) gave 15.6 mg (48.7 µmol, 49%) of pyridine **235** and 11.2 mg (35.0 µmol, 35%) pyridine **236** as colorless solids.

M. p. = 149-153°C.

TLC: R_f = 0.25 (ethyl acetate/light petroleum = 1:1).

GC-MS (method B): t_R = 9.16 min, m/Z = 320.

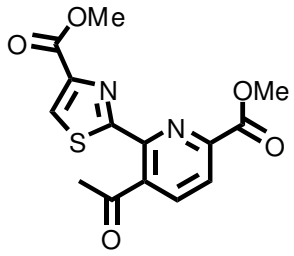
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.79 (3H, s, C(O)CH_3), 3.96 (3H, s, COOCH_3), 4.05 (3H, s, COOCH_3), 8.24 (1H, d, J = 8.2 Hz, CH), 8.28 (1H, d, J = 8.2 Hz, CH), 8.33 (1H, s, CH).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 28.2 (C(O)$\underline{C}H_3$), 52.6 (COO$\underline{C}H_3$), 53.2 (COO$\underline{C}H_3$), 126.4 (CH), 129.7 ($\underline{C}$H), 130.4 ($\underline{C}$-COOMe), 140.1 ($\underline{C}$H), 147.5 ($\underline{C}$-CH), 147.7 ($\underline{C}$-C(O)Me), 154.1 ($\underline{C}$-COOMe), 161.5 ($\underline{C}$OOMe), 163.4 (C-$\underline{C}$(N)S), 164.5 ($\underline{C}$OOMe), 200.4 ($\underline{C}$(O)CH_3).

IR (KBr): $\tilde{\nu}$ = 3144 (s), 2959 (s), 2854 (s), 1751 (s), 1727 (s), 1693 (s), 1223 (s), 1037 (s), 749 (s) cm^{-1}.

HRMS (ESI): Calcd for $C_{14}H_{13}N_2O_5S$ $[M + H]^+$, 321.0540, found: 321.0540.

5-(4'-(Methoxycarbonyl)thiazol-2-yl)-6-acetyl-pyridine-2-carboxylic acid methyl ester (236)



236

M. p. = 159-162°C.

TLC: R_f = 0.34 (ethyl acetate/light petroleum = 1:1).

GC-MS (method B): t_R = 9.12 min, m/Z = 320.

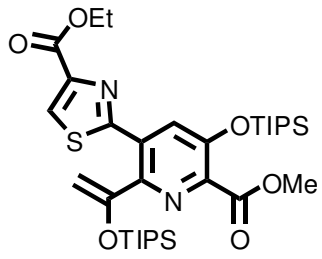
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.65 (3H, s, C(O)CH_3), 3.96 (3H, s, COOCH_3), 4.04 (3H, s, COOCH_3), 7.81 (1H, d, J = 7.8 Hz, CH), 8.18 (1H, d, J = 7.8 Hz, CH), 8.31 (1H, s, CH).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 31.0 (C(O)$\underline{C}H_3$), 52.4 (COO$\underline{C}H_3$), 53.1 (COO$\underline{C}H_3$), 125.6 ($\underline{C}$H), 130.3 ($\underline{C}$H), 136.1 ($\underline{C}$H), 139.0 ($\underline{C}$-COOMe), 146.2 ($\underline{C}$-C(O)Me), 148.0 ($\underline{C}$-COOMe), 161.5 ($\underline{C}$OOMe), 164.3 ($\underline{C}$OOMe), 166.7 ($\underline{C}$(N)S), 202.1 ($\underline{C}$(O)CH_3) (not all the carbon signals could be observed).

IR (KBr): $\tilde{\nu}$ = 3125 (s), 2926 (s), 2854 (s), 1729 (s), 1690 (s), 1321 (s), 1253 (s), 1101 (s), 764 (s) cm^{-1}.

HRMS (ESI): Calcd for $C_{14}H_{13}N_2O_5S$ $[M + H]^+$, 321.0540, found: 321.0539.

5-(4'-Ethoxycarbonyl-thiazol-2-yl)-3-triisopropylsilyloxyl-6-(1-triisopropylsilyloxy-vinyl)-pyridine-2-carboxylic acid methyl ester (238).



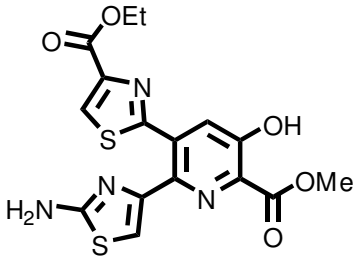
238

Triisopropylsilyl triflate (69 µL, 0.26 mmol) was added dropwise to a stirring solution of ketone **233a** (30 mg, 0.086 mmol) and 2,6-lutidine (60 µL, 0.52 mmol) in dry

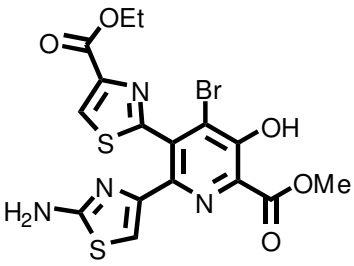
dichloromethane (2 mL) at 0°C under an argon atmosphere. The mixture was allowed to warm to room temperature after 1 h and stirred for another 12 h (TLC control). Saturated NaCl solution (20 mL) was added and the mixture was extracted with dichloromethane (3 x 20 mL). The combined organic extracts were dried with sodium sulfate and concentrated. Purification by column chromatography (silica gel, 10 g, ethyl acetate/cyclohexane = 1:15) gave 46 mg (0.069 mmol, 80%) of enol ether **238** as a yellow oil.

TLC: R_f = 0.85 (ethyl acetate/cyclohexane = 1:2).
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.95-1.12 (TIPS), 1.41 (3H, t, $CH_2\underline{CH_3}$), 3.92 (3H, s, $COOCH_3$), 4.43 (2H, dd, $\underline{CH_2}CH_3$), 4.73 (1H, d, J = 1.4Hz, C=$\underline{CH_2}$), 4.93 (1H, d, J = 1.4 Hz, C=$\underline{CH_2}$), 7.77 (1H, s, CH), 8.27 (1H, s, CH).
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 12.5, 12.7, 14.3, 17.8, 52.4, 61.3, 98.7, 128.3, 129.4, 129.7, 141.9, 147.2, 150.0, 154.7, 161.4, 164.2, 165.6.
IR (KBr): $\tilde{\nu}$ = 2943 (s), 1737 (s), 1629 (s), 1458 (s), 1015 (s), 882 (s) cm^{-1}.
ESI-MS: Calcd for $C_{33}H_{55}N_2O_6SSi_2$ $[M + H]^+$, 663.3, found: 663.5.

6-[2'-Aminothiazol-4-yl]-5-(4'-ethoxycarbonyl-thiazol-2'-yl)-3-hydroxypyridine-2-carboxylic acid methyl ester (240)



240



240a

NBS (102.8 mg, 0.58 mmol) was added to a solution of enol ether **238** (0.31 g, 0.47 mmol) in THF (12 mL) and water (4 mL) at 0°C, the reaction mixture was warmed to room temperature after 2 hours and stirred for another 2 hours (TLC control). Water (20 mL) was added and the mixture was extracted with dichloromethane (3 x 30 mL). The combined extracts were dried with sodium sulfate and concentrated. The resulting crude bromoketone **239** was directly used to next step due to its stability.

The mixture of crude bromoketone **239** was combined with thiourea (71 mg, 0.93 mmol) in DMF (10 mL) and stirred for 48 hours. The reaction was quenched with water (20 mL) and extracted with dichloromethane (3 x 20 mL), the combined extracts were dried with sodium sulfate and concentrated. Purification by column chromatography (silica gel, 30 g, dichloromethane/MeOH = 40:1) gave 48.8 mg (0.12 mmol, 26%) hydroxypyridine **240** as a yellow foam (containing side product **240a**).

TLC: R_f = 0.38 (dichloromethane/MeOH = 10:1).

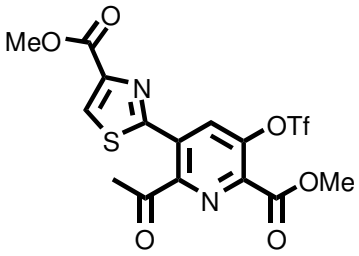
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.42 (3H, t, $CH_2\underline{CH_3}$), 4.05 (3H, s, $COOCH_3$), 4.44 (2H, dd, $\underline{CH_2}CH_3$), 5.41 (2H, br, NH_2), 6.65 (1H, s, CH), 8.01 (1H, s, CH), 8.23 (1H, s, CH), 10.71 (1H, s, OH).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 14.3, 53.4, 61.6, 110.4, 127.8, 129.7, 129.9, 130.0, 134.1, 143.4, 147.2, 157.6, 161.2, 163.8, 168.1, 169.3.

ESI-MS: Calcd for $C_{16}H_{15}N_4O_5S_2$ $[M + H]^+$, 407.1, found: 407.1.

Calcd for $C_{16}H_{15}N_4O_5S_2{}^{81}Br$ $[M + H]^+$, 487.0, found: 487.0.

5-(4'-(Methoxycarbonyl)thiazol-2'-yl)-6-acetyl-3- trifluoromethanesulfonyloxy pyridine-2-carboxylic acid methyl ester (241)



241

To a solution of hydroxypyridine **233** (1.2 g, 3.6 mmol) and triethylamine (1 mL, 7.2 mmol) in dry dichloromethane (40 mL) at 0°C under argon atmosphere was added trifluoromethanesulfonic anhydride (0.9 mL, 5.4 mmol) dropwise over 10 min. The reaction mixture was gradually warmed to room temperature and stirred for 12h. Phosphate buffer (pH 2, 0.50 M, 20 mL) was added and the mixture was extracted with dichloromethane (3 x 50 mL), the extracts were dried with Na_2SO_4, and concentrated. Purification by column chromatography (silica gel, 10 g, ethyl acetate/light petroleum = 1:3) gave 0.81 g (1.7 mmol, 80% based on recovered starting material) pyridineketone **241** as a colorless solid.

M. p.: 126-128°C.

TLC: R_f = 0.22 (ethyl acetate/cyclohexane = 1:2).

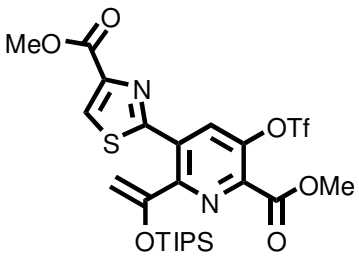
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.78 (3H, s, C(O)CH_3), 3.96 (3H, s, COOCH_3), 4.06 (3H, s, COOCH_3), 8.20 (1H, s, CH), 8.38 (1H, s, CH).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 28.1 (C(O)$\underline{C}H_3$), 52.6 (COO$\underline{C}H_3$), 53.5 (COO$\underline{C}H_3$), 116.9, 120.1 (Tf), 130.6 ($\underline{C}$-C(N)S), 132.4 ($\underline{C}$H), 133.9 ($\underline{C}$H), 141.0 ($\underline{C}$-COOMe), 146.0 ($\underline{C}$-C(O)Me), 147.7 ($\underline{C}$-COOMe), 151.9 ($\underline{C}$-OTf), 160.6 (C-$\underline{C}$(N)S), 161.2 ($\underline{C}$OOMe), 161.9 ($\underline{C}$OOMe), 198.9 ($\underline{C}$(O)CH_3).

IR (KBr): $\tilde{\nu}$ = 3100 (s), 1740 (s), 1716 (s), 1423 (s), 1221 (s), 930 (s), 893 (s), 798 (s) cm^{-1}.

HRMS (FAB): Calcd for $C_{15}H_{12}F_3N_2O_8S_2$ $[M + H]^+$, 468.9982, found: 468.9959.

5-(4'-Methoxycarbonyl-thiazol-2'-yl)-3-trifluoromethanesulfonyloxy-6-(1-triisopropylsilyloxy-vinyl)-pyridine-2-carboxylic acid methyl ester (242)



242

Under argon, triisopropylsilyl triflate (0.68 mL, 2.52 mmol) was added dropwise to a stirred solution of ketone **241** (0.59 g, 1.26 mmol) and triethylamine (0.3 mL, 5.0 mmol) in dry dichloromethane (10 mL) at 0°C under an argon atmosphere. The mixture was allowed to warm to room temperature after 1 h and stirred for 12 h. Saturated NaCl solution (20 mL) was added and the mixture was extracted with dichloromethane (3 x 20 mL). The combined organic extracts were dried with Na_2SO_4 and concentrated. Purification by column chromatography (silica gel, 10 g, ethyl acetate/cyclohexane = 1:12) gave 0.785 g (1.25 mmol, 99%) of enol ether **242** as a yellow oil.

TLC: R_f = 0.84 (ethyl acetate/cyclohexane = 1:2).

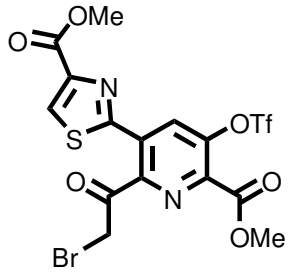
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.87-1.03 (21H, m, TIPS), 3.98 (3H, s, COOCH_3), 4.01 (3H, s, COOCH_3), 4.84 (1H, d, J = 13.7, C=$\underline{CH_2}$), 5.09 (1H, d, J = 18.8, C=$\underline{CH_2}$), 8.27 (1H, s, CH), 8.36 (1H, s, CH).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 12.4, 17.7, 52.6, 53.2, 100.4, 130.4, 130.5, 131.3, 132.6, 141.0, 144.5, 147.2, 153.4, 154.2, 161.4, 162.1, 162.5.

IR (KBr): $\tilde{\nu}$ = 2942 (w), 2857 (w), 1741 (s), 1695 (s), 1434 (s), 1223 (b), 858 (s), 799 (s) cm^{-1}.

HRMS (FAB): Calcd for $C_{24}H_{31}F_3N_2O_8S_2Si$ $[M + H]^+$, 625.1316, found: 625.1291.

6-(2'-Bromo-acetyl)-5-(4''-methoxycarbonyl-thiazol-2''-yl)-3-trifluoromethanesulfonyloxy-pyridine-2-carboxylic acid methyl ester (243)



243

To a solution of enol ether **242** (0.67 g, 1.10 mmol) in THF/0.5 M phosphate buffer (6:1, 14 mL, pH 7) was added NBS (0.23 g, 1.3 mmol) at room temperature, and the reaction mixture was stirred for 30 min (TLC control). The reaction mixture was diluted with phosphate buffer (pH 7, 20 mL), the layers were separated, and the aqueous layer was extracted with dichloromethane (3 x 20 mL). The combined extracts were dried with Na_2SO_4 and concentrated. Purification by column chromatography (silica gel, 10 g, diethyl ether/*n*-pentane = 1:3) yielded 0.583 g (1.07 mmol, 97%) of bromoketone **243** as a colorless solid.

M. p.: 133°C (decomp.).

TLC: R_f = 0.39 (ethyl acetate/cyclohexane = 2:3).

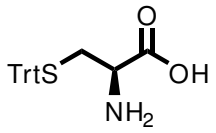
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.99 (3H, s, $COOCH_3$), 4.08 (3H, s, $COOCH_3$), 4.81 (2H, s, CH_2Br), 8.31 (1H, s, CH), 8.40 (1H, s, CH).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 33.1, 52.7, 53.6, 127.8, 130.8, 133.6, 134.1, 146.5, 148.0, 149.4, 156.0, 159.8, 161.2, 161.6, 191.2.

IR (KBr): $\tilde{\nu}$ = 2924 (s), 2854 (s), 1740 (b), 1434 (s), 1222 (s), 800 (s) cm^{-1}.

HRMS (FAB): Calcd for $C_{15}H_{11}{}^{79}BrF_3N_2O_8S_2$ $[M + H]^+$, 546.9087, found: 546.9122.

(*R*)-2-Amino-3-tritylthio-propionic acid (270)[172]



270

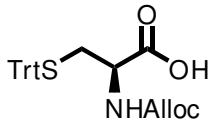
L-Cysteine hydrochloride monohydrate (30.0 g, 190.2 mmol) and trityl chloride (81.0 g, 290.7 mmol) were stirred in DMF (200 mL) for 48 h at room temperature. 10% sodium acetate solution (350 mL) was added, the resulting precipitate was filtered and washed with distilled water (3 x 10 mL). The residue was stirred with acetone (200 mL) at 50°C for 30 min, cooled to room temperature, and filtered. The resulting powder was washed cold acetone (2 x 20 mL) and diethyl ether (2 x 20 mL). After drying with vacuum, 41.2 g (113 mmol, 66%) of trityl cysteine **270** was obtained as a colorless powder.

TLC: R_f = 0.18 (dichloromethane/MeOH = 10:1).

^{1}H-NMR (400 MHz, DMSO): δ = 2.43 (1H, dd, J = 12.5 Hz, -CH_2-), 2.58 (1H, dd, J = 12.5 Hz, -CH_2-), 2.94 (1H, dd, J = 9.0 Hz, -CH-), 7.25-7.34 (15H, m, trityl), 7.52 (2H, d, J = 7.8 Hz, NH_2).

^{13}C-NMR (100.6 MHz, DMSO): δ = 33.4 (-CH_2-), 53.3 (-CH-), 65.9 ($\underline{C}Ph_3$), 126.6, 127.9, 129.0, 144.1(trityl), 167.9 (COOH).

(*R*)-2-Allyloxycarbonylamino-3-tritylthio-propionic acid (247).



247

A vigorously stirred solution of trityl L-cysteine **270** (1.0 g, 2.8 mmol) in 2 M NaOH (1.4 mL, 2.8 mmol) was cooled to 0°C. Allyl chloroformate (0.35 mL, 3.3 mmol) and 2 M NaOH (1.65 mL, 3.3 mmol) were added in portions over a period of 10 min. After being stirred at 0°C for 1h, the reaction mixture was acidified to pH = 2 with 2 M HCl, and extracted with ethyl acetate (3 x 20 mL). The combined organic layers were dried with Na_2SO_4 and concentrated. Purification by column chromatography (silica gel, 20 g, dichloromethane/MeOH = 20:1) gave 1.24 g (2.77 mmol, 99%) of acid **247** as a colorless solid.

M. p.: 119-120°C.

TLC: R_f = 0.25 (dichloromethane/MeOH = 10:1).

^{1}H-NMR (400 MHz, DMSO): δ = 2.38-2.58 (2H, m, CH_2), 3.84 (1H, d, J = 9.0 Hz, $CH_2\underline{CH}$), 4.47 (2H, d, J = 4.7 Hz, $COOCH_2$), 5.18 (1H, d, J = 10.4 Hz, $CH=\underline{CH_2}$), 5.30 (1H, d, J = 17.3 Hz, $CH=\underline{CH_2}$), 5.85-5.93 (1H, m, $\underline{CH}=CH_2$), 7.23-7.35 (15H, m, trityl), 7.50 (1H, d, J = 7.6 Hz, NHCOO).

^{13}C-NMR (100.6 MHz, DMSO): δ = 33.1 ($\underline{C}H_2CH$), 53.4 ($COO\underline{C}H_2$), 64.4 ($\underline{C}Ph_3$), 66.0 ($CH_2\underline{C}H$), 116.9 ($CH=\underline{C}H_2$), 126.7 (Ar), 127.9 (Ar), 129.0 (Ar), 133.4 (Ar), 144.2 ($\underline{C}H=CH_2$), 155.5 ($\underline{C}OOCH_2$), 171.8 ($\underline{C}OOH$).

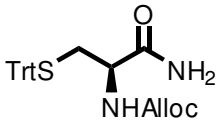
IR (KBr): $\tilde{\nu}$ = 3417 (b), 3061 (s), 2917 (w), 1730 (s), 1714 (s), 1504 (s), 1445 (s), 798 (s), 701 (s) cm^{-1}.

Optical rotation: $[\alpha]_D^{20}$ = + 30.4 (c = 1.0, $CHCl_3$).

HRMS (ESI): Calcd for $C_{26}H_{25}NO_4SNa$ $[M + Na]^+$, 470.1397, found: 470.1397.

Elemental analysis: Calcd for $C_{26}H_{25}NO_4S$: C, 69.78; H, 5.63; N, 3.13; found C, 69.7; H, 6.0; N, 3.0.

(*R*)-2-Allyloxycarbonylamino-3-tritylthio-propionic amide (247a).



247a

To a stirred solution of acid **247** (1.0 g, 2.2 mmol) in THF (10 mL) was added HOSu (0.28 g, 2.4 mmol) and DCC (0.51 g, 2.4 mmol) at 0°C. The reaction mixture was stirred for 1h at 0°C and then for 5h at ambient temperature. The mixture was filtered and concentrated to dryness. The residue was taken up in ethyl acetate (20 mL) and cooled to 0°C, then aqueous 25% NH_4OH solution (0.6 mL) was added dropwise and stirred for 1h. The mixture was diluted with ethyl acetate (20 mL), washed with saturated aqueous $NaHCO_3$ solution (2 x 10 mL) and brine (20 mL), dried with Na_2SO_4 and concentrated. The resulting residue was purified by column chromatography (silica gel, 10 g, ethyl acetate/light petroleum = 1:2) to give 0.99 g (2.2 mmol, 99%) of the primary amide **247a** as a colorless solid.

M. p.: 96-98°C.

TLC: R_f = 0.21 (ethyl acetate/cylohexane = 1:2).

^{1}H-NMR (400 MHz, DMSO): δ = 4.10-4.15 (2H, m, J = 6.8 Hz, CH_2), 4.58 (2H, t, J = 3.7 Hz, $COOCH_2$), 5.27 (1H, d, J = 10.6 Hz, CH=$\underline{CH_2}$), 5.40 (1H, d, J = 17.2 Hz, CH=$\underline{CH_2}$), 5.97-6.04 (1H, m, J = 5.3 Hz, $\underline{CH}$=CH_2), 7.22 (1H, s, $CH_2\underline{CH}$), 7.34 (2H, d, J = 4.1 Hz, NH_2), 7.41-7.42 (15H, m, trityl), 7.48 (1H, d, J = 8.4 Hz, NH).

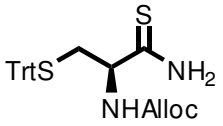
^{13}C-NMR (100.6 MHz, DMSO): δ = 34.0 ($\underline{C}H_2CH$), 53.6 ($COO\underline{C}H_2$), 59.6 ($CH_2\underline{C}H$), 64.5 ($\underline{C}Ph_3$), 116.8 (CH=$\underline{C}H_2$), 126.6 (Ar), 127.9 (Ar), 129.0 (Ar), 130.4 (Ar), 144.2 ($\underline{C}H$=CH_2), 155.3 ($\underline{C}OOCH_2$), 171.8 ($\underline{C}(O)NH_2$).

IR (KBr): $\tilde{\nu}$ = 3317 (b), 3030 (s), 2926 (s), 1682 (s), 1232 (s), 743 (s), 701 (s) cm^{-1}.

Optical rotation: $[\alpha]_D^{20}$ = + 23.8 (c = 1.0, $CHCl_3$).

HRMS (ESI): Calcd for $C_{26}H_{26}N_2O_3SNa$ $[M + Na]^+$, 469.1556, found: 469.1554.

(*R*)-2-Allyloxycarbonylamino-3-tritylthio-propionic thioamide (248).



248

To a stirred solution of the primary amide **247a** (2.74 g, 6.1 mmol) in dichloromethane (20 mL) at 0°C was added Lawesson's reagent (1.49 g, 3.7 mmol). The reaction mixture was stirred at 0°C for 1h and at room temperature for 12h (TLC control), concentrated, and purified by column chromatography (silica gel, 40 g, ethyl acetate/cyclohexane = 1:2) to give 2.08 g (4.5 mmol, 74%) of thioamide **248** as a colorless solid.

M. p.: 124-125°C.

TLC: R_f = 0.28 (ethyl acetate/cyclohexane = 1:2).

^{1}H-NMR (400 MHz, CD_3CN): δ = 2.57-2.69 (2H, m, CH_2), 4.17 (1H, d, J = 5.3 Hz, $CH_2\underline{CH}$), 4.50 (2H, t, J = 1.8 Hz, $COOCH_2$), 5.19 (1H, d, J = 17.2 Hz, CH=$\underline{CH_2}$), 5.30 (1H, d, J = 17.2 Hz, CH=$\underline{CH_2}$), 5.81 (1H, br, NHCOO), 5.87-5.96 (1H, m, $\underline{CH}$=CH_2), 7.23-7.41 (15H, m, trityl), 7.76 (1H, s, NH_2), 8.05 (1H, s, NH_2).

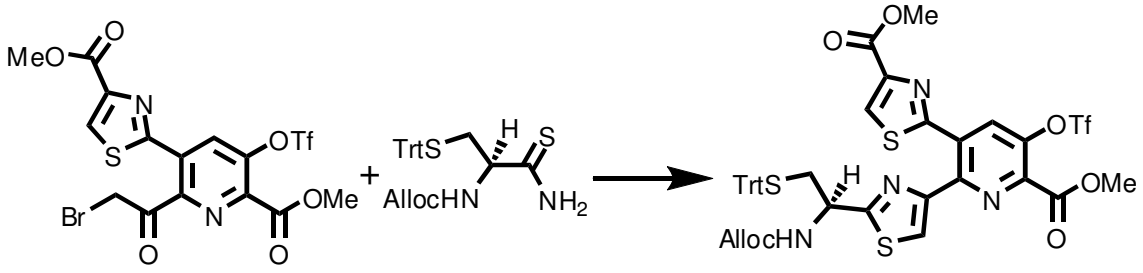
^{13}C-NMR (100.6 MHz, CD_3CN): δ = 37.3 ($\underline{C}H_2CH$), 60.5 ($COO\underline{C}H_2$), 66.2 ($\underline{C}Ph_3$), 67.7 ($CH_2\underline{C}H$), 117.6 (CH=$\underline{C}H_2$), 118.2 (Ar), 127.9 (Ar), 129.0 (Ar), 130.3 (Ar), 134.1 ($\underline{C}H$=CH_2), 145.5 ($\underline{C}OOCH_2$), 207.6 ($\underline{C}(S)NH_2$).

IR (KBr): $\tilde{\nu}$ = 3299 (b), 3196 (b), 2921 (w), 1697 (s), 1651 (s), 1505 (s), 891 (b), 799 (s) cm^{-1}.

Optical rotation: $[\alpha]_D^{20}$ = + 17.3 (c = 1.0, $CHCl_3$).

HRMS (ESI): Calcd for $C_{26}H_{26}N_2O_2S_2Na$ $[M + Na]^+$, 485.1328, found: 485.1325.

(*R*)-6-[2-(1'-Allyoxycarbonylamino-2'-tritylsulfanyl-ethyl)-thiazol-4-yl]-5-(4-methoxycarbonyl-thiazol-2-yl)-3-trifluoromethanesulfonyloxy-pyridine-2-carboxylic acid methyl ester (244)



243 **248** **244**

A suspension of thioamide **248** (0.67 g, 1.5 mmol) and anhydrous $KHCO_3$ (0.29 g, 2.9 mmol) in THF (10 mL) was cooled to – 40°C, and bromoketone **243** (0.51 g, 0.93 mmol) in THF (2 mL) was added dropwise. After stirring for 2h, the reaction mixture was allowed to warm up to ambient temperature, and stirred for 48h. The reaction mixture was filtered under argon and cooled to -20°C. 2,6-Lutidine (1.2 mL, 10.5 mmol) and trifluoroacetic anhydride (0.6 mL, 4.4 mmol) were added slowly and the solution was allowed to stir for 2h. Brine (50 mL) was added, and the mixture was extracted with dichloromethane (3 x 50 mL). The combined organic extracts were dried with Na_2SO_4 and concentrated. Column chromatography (silica gel, 20 g, ethyl acetate/light petroleum = 1:5) gave 0.59 g (0.65 mmol, 69%) of thiazolylpyridine **244** as a yellow microcrystalline solid.

M. p.: 104°C (decomp.).

TLC: R_f = 0.33 (ethyl acetate/cyclohexane = 1:2).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.64-2.86 (2H, m, CH_2CH), 4.02 (3H, s, $COOCH_3$), 4.11 (3H, s, $COOCH_3$), 4.58 (2H, d, J = 5.6 Hz, $COO\underline{CH_2}CH=CH_2$), 4.73 (1H, m. $CH_2\underline{CH}$), 5.13 (1H, m, NH), 5.29 (1H, d, J = 10.0 Hz, $CH=\underline{CH_2}$), 5.36 (1H, d, J = 16.8 Hz, $CH=\underline{CH_2}$), 5.95 (1H, m, $\underline{CH}=CH_2$), 7.28-7.42 (15H, m, trityl), 7.98 (1H, s, CH), 8.15 (1H, s, CH), 8.34 (1H, s, $C\underline{H}$=CNCOOMe).

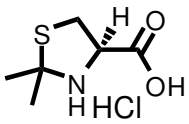
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 36.8, 52.0, 52.6, 53.4, 66.0, 67.5, 118.0, 120.2, 123.2, 127.0, 128.1, 129.5, 130.4, 132.3, 132.5, 133.5, 141.6, 144.3, 144.5, 147.0, 150.2, 151.2, 155.0, 161.4, 162.4, 162.5, 171.1.

IR (KBr): $\tilde{\nu}$ = 2924 (s), 2854 (s), 1731 (s), 1494 (m), 1433 (s), 1217 (s), 886 (s), 796 (s) cm^{-1}.

Optical rotation: $[\alpha]_D^{20}$ = - 2.1 (*c* = 1, $CHCl_3$).

HRMS (FAB): Calcd for $C_{41}H_{34}F_3N_4O_9S_4$ $[M + H]^+$, 911.1155, found: 911.1165.

(*R*)-2,2-Dimethylthiazolidine-4-carboxylic acid (246a)[213]



246a

L-Cysteine hydrochloride monohydrate **246** (10 g, 56.9 mmol) was refluxed in dry acetone (400 mL) under argon for 5 h. The reaction mixture was cooled down to room temperature and concentrated to 150 mL, and the residual slurry was cooled to 0-5°C for 30 min. The resulting crystalline solid was collected by filtration, washed with cold acetone (3 x 20 mL) and dried under high vacuum to give thioaminal hydrochloride **246a** 11.2 g (56.7 mmol, 99%) as a colorless crystals.

M. p.: 176-177°C (acetone).

^{1}H-NMR (500 MHz, DMSO): δ = 1.73 (3H, s, CH_3), 1.74 (3H, s, CH_3), 3.39 (1H, t, *J* = 9.14 Hz -CH_2-), 3.53 (1H, q, *J* = 7.86 Hz, -CH_2-), 4.89 (1H, t, *J* = 8.4 Hz, -CH-).

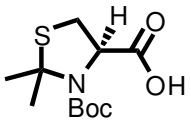
^{13}C-NMR (100.6 MHz, DMSO): δ = 27.1 ($\underline{C}H_3$), 28.6 ($\underline{C}H_3$), 31.4 (-$\underline{C}H_2$-), 60.9 (-$\underline{C}H$-), 71.8 ($\underline{C}(CH_3)_2$), 168.2 ($\underline{C}OOH$).

IR (KBr): $\tilde{\nu}$ = 2905 (w), 2443 (w), 1747 (s), 1556 (m), 1227 (s), 799 (s) cm^{-1}.

Optical rotation: $[\alpha]_D^{20}$ = - 80.7 (*c* = 2, MeOH).

HRMS (ESI): Calcd for $C_6H_{12}NO_2S$ $[M + H]^+$, 162.0583, found: 162.0581.

(*R*)-3-(*tert*-Butoxycarbonyl)-2,2-dimethylthioazolidine-4-carboxylic acid (249)

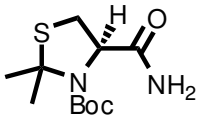


249

To a suspension of amine **246a** (13.7 g, 69 mmol) and di-*tert*-butyl dicarbonate (20 g, 92 mmol) in dry acetonitrile was added DIPEA (13.3 mL, 76 mmol). The suspension was allowed to stir for 48 h. The volatiles were removed in vacuo, and the remaining oil was taken up in ethyl acetate (300 mL), washed with phosphate buffer (pH = 1, 100 mL), water (100 mL) and brine (100 mL). The organic layer was dried with $MgSO_4$ and concentrated. The residue was recrystallized from *n*-hexane to give **249** 10.6 g (41 mmol, 58%) as a colorless solid.

TLC: R_f = 0.56 (dichloromethane/MeOH = 10:1).
^{1}H-NMR (500 MHz, DMSO): δ = 1.35 (*t*Bu), 1.43 (*t*Bu), 1.70 (3H, s, CH_3), 1.75 (3H, s, CH_3), 3.05 (1H, d, J = 11.89 Hz, -CH_2-), 3.35 (1H, q, J = 6.87 Hz, -CH_2-), 4.74 (1H, q, J = 4.49 Hz, -CH-), 12.76 (1H, s, COOH).
^{13}C-NMR (125.8 MHz, DMSO): δ = 27.6 (C($\underline{C}H_3)_3$), 29.3 ($\underline{C}H_3$), 29.8 ($\underline{C}H_3$), 30.7 (-$\underline{C}H_2$-), 65.0 (-$\underline{C}$H-), 70.8($\underline{C}(CH_3)_2$), 79.3 ($\underline{C}$-$(CH_3)_3$), 151.2 ($\underline{C}$OOC-$(CH_3)_3$), 172.0 ($\underline{C}$OOH).
IR (KBr): $\tilde{\nu}$ = 3198 (b), 2979 (s), 2508 (w), 1757 (s), 1678 (s), 1387 (m) 1172 (s), 825 (s) cm^{-1}.
HRMS (ESI): Calcd for $C_{11}H_{20}NO_4S$ $[M + H]^+$, 262.1108, found: 262.1108.
Optical rotation: $[\alpha]_D^{20}$ = -73.4 (c = 1, MeOH).

(*R*)-3-*tert*-Butoxycarbonyl-2,2-dimethylthiazolidine-4-carboxamide (249a)



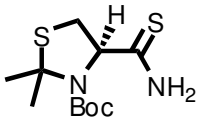
249a

To a stirred solution of Boc-Dmt-OH **249** (10.5 g, 0.04 mol) in THF (200 mL) was added HOSu (5.57 g, 0.048 mol) and DCC (10.08 g, 0.048 mol) at room temperature. The reaction mixture was stirred for 3 h at room temperature, then filtered to remove the resulting colorless precipitate (*N, N'*-dicyclohexylurea), and concentrated to dryness. The residue was redissolved in ethyl acetate (300 mL) and cooled to 0°C, then aqueous NH_4OH solution (4.0

mL) was added dropwise. The reaction mixture was warmed to room temperature after 2 h and kept at this temperature for 10 h (TLC control). The organic layer was washed with saturated aqueous $NaHCO_3$ solution (2 x 100 mL) and brine (100 mL), dried with Na_2SO_4 and concentrated to dryness. The resulting residue was purified (silica gel, 100g, ethyl acetate/light petroleum = 1:1) to give 10.3 g (39.6 mmol, 98%) of amide **249a** as a colorless glass.

TLC: R_f = 0.26 (ethyl acetate/light petroleum = 1:1).
^{1}H-NMR (400 MHz, DMSO): δ = 1.36 (9H, s, $C(CH_3)_3$), 1.70 (3H, s, CH_3), 1.75 (3H, s, CH_3), 2.94 (1H, q, J = 4.05 Hz, -CH_2-), 2.96 (1H, q, J = 7.02 Hz, -CH_2-), 4.55 (1H, br, -CH-), 7.03 (1H, s, $CONH_2$), 7.20 (1H, s, $CONH_2$).
^{13}C-NMR (100.6 MHz, DMSO): δ = 27.9 ($C(\underline{C}H_3)_3$), 28.5 ($\underline{C}H_3$), 30.6 ($\underline{C}H_3$), 33.2 (-$\underline{C}H_2$-), 65.9 (-$\underline{C}$H-), 71.0($\underline{C}(CH_3)_2$), 79.2 ($\underline{C}$-$(CH_3)_3$), 151.4 ($\underline{C}$OOC-$(CH_3)_3$), 172.0 ($\underline{C}ONH_2$).
ESI-MS: Calcd for $C_{11}H_{21}N_2O_3S$ $[M + H]^+$, 261.1, found: 260.8.

(*R*)-3-*tert*-Butoxycarbonyl-2,2-dimethylthiazolidine-4-thiocarboxamide (250)



250

To a stirred solution of amide **249a** (2.1 g, 8.07 mmol) in THF (20 mL) was added Lawesson's reagent (2.0 g, 4.9 mmol) and the reaction mixture was stirred for 12 h at room temperature (TLC control). The reaction mixture was concentrated to dryness and purified by column chromatography (silica gel, ethyl acetate/light petroleum = 1:3) to give 2.04 g (7.4 mmol, 92%) thioamide **250** as a colorless glass.

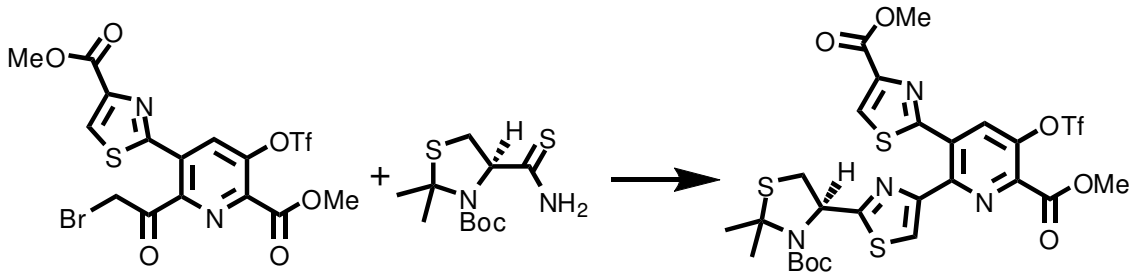
TLC: R_f = 0.84 (ethyl acetate/light petroleum = 1:1).
^{1}H-NMR (400 MHz, CD_3CN): δ = 1.43 (9H, s, $C(CH_3)_3$), 1.74 (3H, s, CH_3), 1.86 (3H, s, CH_3), 3.26 (1H, dd, J = 12.5 Hz, -CH_2-), 3.49 (1H, dd, J = 12.5 Hz, -CH_2-), 5.00 (1H, dd, J = 7.6 Hz, -CH-), 7.73 (1H, s,$CSNH_2$), 8.26 (1H, s, $CSNH_2$).
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 28.3 ($C(\underline{C}H_3)_3$), 28.8 ($\underline{C}H_3$), 33.7 (-$\underline{C}H_2$-), 72.1 (-$\underline{C}$H-), 77.2($\underline{C}(CH_3)_2$), 82.0 ($\underline{C}$-$(CH_3)_3$), 152.7 ($\underline{C}$OOC-$(CH_3)_3$), 207.5 ($\underline{C}SNH_2$).

IR (KBr): $\tilde{\nu}$ = 3416 (b), 2979 (s), 1707 (s), 1616 (m), 1391 (s), 1171 (s), 857 (s), 799 (s) cm^{-1}.

Optical rotation: $[\alpha]_D^{20}$ = - 40.7 (*c* = 0.6, $CHCl_3$).

HRMS (ESI): Calcd for $C_{11}H_{20}N_2O_2S_2$ $[M + Na]^+$, 299.0858, found: 299.0859.

(*R*)-6-(2',2'-Dimethyl-3'-*tert*-butoxycarbonyl-4',5'-dihydro-[2, 4']bithiazolyl-4-yl)-5-(4-methoxycarbonyl-thiazol-2-yl)-3-trifluoromethanesulfonyloxy-pyridine-2-carboxylic acid methyl ester (245)



243 **250** **245**

A suspension of thioamide **250** (2.45 g, 8.9 mmol) and anhydrous $KHCO_3$ (2.4 g, 24 mmol) in THF (100 mL) was cooled to –40°C, and bromoketone **243** (3.2 g, 5.9 mmol) in THF (20 mL) was added dropwise. After stirring for 2h, the reaction mixture was allowed to warm up to room temperature, and stir for 48h. The reaction mixture was filtered under argon and cooled to -20°C. 2,6-Lutidine (7.2 mL, 61.9 mmol) and trifluoroacetic anhydride (4.1 mL, 29 mmol) were added slowly and the solution was allowed to stir for 2h. Brine (100 mL) was added slowly, and the mixture was extracted with dichloromethane (3 x 100 mL). The combined organic extracts were dried with Na_2SO_4 and concentrated. Column chromatography (silica gel, 40 g, ethyl acetate/cyclohexane = 1:5) gave 2.56 g (3.54 mmol, 60%) of thiazolylpyridine **245** as a yellow microcrystalline solid.

M. p.: 108°C (decomp.).

TLC: R_f = 0.35 (ethyl acetate/cyclohexane = 1:2).

^{1}H-NMR (400 MHz, CD_3CN): δ = 1.33 (9H, s, $C(CH_3)_3$), 1.78 (3H, s, CH_3), 1.87 (3H, s, CH_3), 2.80 (1H, dd, *J* = 12.3 Hz, CH_2), 3.41 (1H, dd, *J* = 5.9 Hz, CH_2), 3.88 (3H, s, COOMe), 4.01 (3H, s, COOMe), 5.47 (1H, br, CH), 7.94 (1H, s, CH), 8.30 (1H, s, CCHS), 8.37 (1H, s, CCHS).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 28.4, 29.0, 29.2, 52.9, 53.9, 60.1, 66.1, 108.5, 121.2, 123.8, 132.0, 133.5, 134.1, 142.2, 145.5, 147.8, 151.7, 162.2, 163.5.

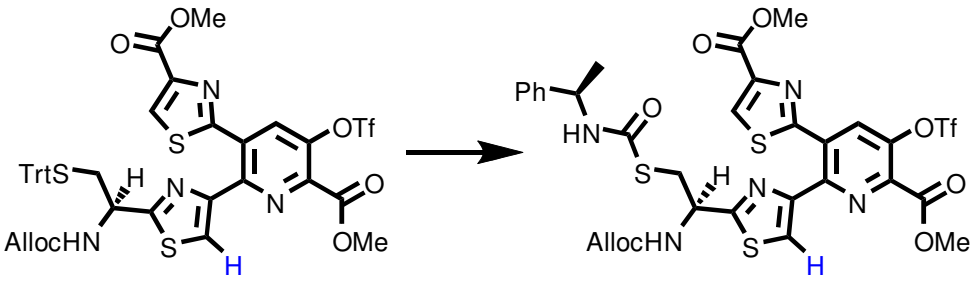
IR (KBr): $\tilde{\nu}$ = 2979 (s), 2928 (s), 1702 (s), 1602 (s), 1432 (s), 1347 (s), 1217 (s), 859 (s), 798 (s) cm^{-1}.

Optical rotation: $[\alpha]_D^{20}$ = - 48.0 (c = 1, $CHCl_3$).

HRMS (FAB): Calcd for $C_{26}H_{28}F_3N_4O_9S_4$ $[M + H]^+$, 725.0686, found: 725.0712.

Enantiomeric excess (ee) determination of pyridine 244.

With (*R*)-phenylethyl isocyanate

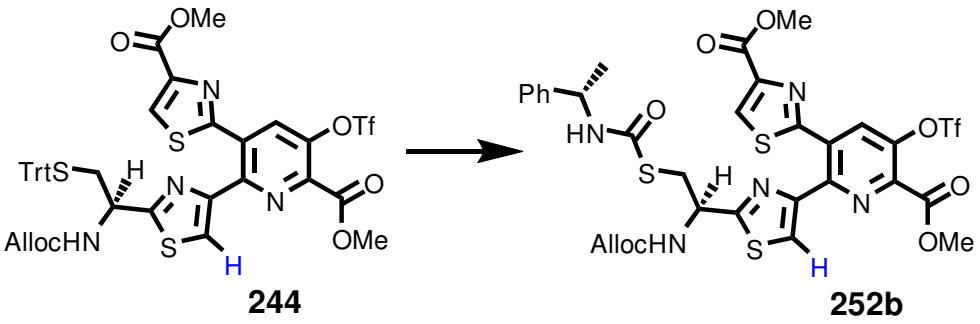


Trifluoroacetic acid (10 µL) was added dropwise to a stirred solution of trityl thioether **244** (9.7 mg, 0.01 mmol) in dry dichloromethane (2 mL) at room temperature, then triethylsilane (6 µL) was added to the reaction mixture. The reaction mixture was stirred for 30 min (TLC control) and concentrated to dryness.

(*R*) Phenylethyl isocyanate (1.8 µL, 0.012 mmol) and pyridine (1 µL) were added to the above residue **251** in dichloromethane (1 mL) at room temperature. The reaction mixture was stirred for 10h (TLC control), quenched by water (1 mL) and diluted by brine (10 mL), extracted with dichloromethane (3 x 10 mL), dried with Na_2SO_4 and concentrated to dryness. Purification by column chromatography (silica gel, ethyl acetate/cyclohexane = 1:3) gave 4.2 mg (0.005 mmol, 48%) of urea **252a** as a colorless solid.

TLC: R_f = 0.21 (ethyl acetate/cyclohexane = 1:2); ee > 85% (from the integration of ^{1}H NMR).

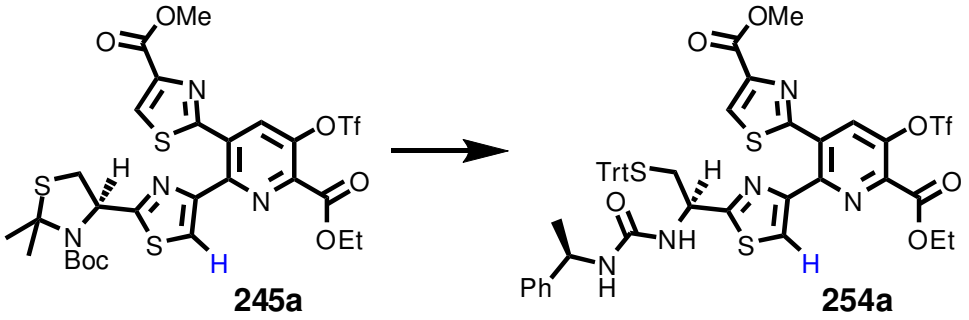
With (*S*)-phenylethyl isocyanate



252b was obtained likewise from (*S*)-phenylethyl isocyanate (54% yield).
colorless solid; ee > 60% (from the integration of ^{1}H NMR).

Enantiomeric excess (e.e.) determination of pyridine 245a.

With (*R*)-phenylethyl isocyanate



Trifluoroacetic acid (0.6 mL) was added dropwise to a stirred solution of thioaminal **245a** (24 mg, 0.03 mmol) in dry dichloromethane (3 mL) at room temperature, then triethylsilane (0.6 mL) was added to the reaction mixture. The reaction mixture was stirred for 1h (TLC control) and concentrated to dryness.

Maldi-MS: Calcd for $C_{19}H_{18}F_3N_4O_7S_4$ $[M + H]^+$, 599.0, found: 599.7.

Trityl chloride (13.6 mg, 0.05 mmol) was added to the above residue in DMF (2 mL) at room temperature and the reaction mixture was stirred for 2 days. The reaction mixture was diluted by dichloromethane (60 mL), washed by 10% sodium acetate solution (2 x 20 mL) and brine (2 x 20 mL), the organic layer was dried with Na_2SO_4 and concentrated to dryness. Purification by column chromatography (silica gel, ethyl acetate/light petroleum = 1:1) gave 18 mg (0.02 mmol, 67%) of the *S*-trityl aminothiol **253**.

TLC: R_f = 0.28 (ethyl acetate/light petroleum = 1:1).

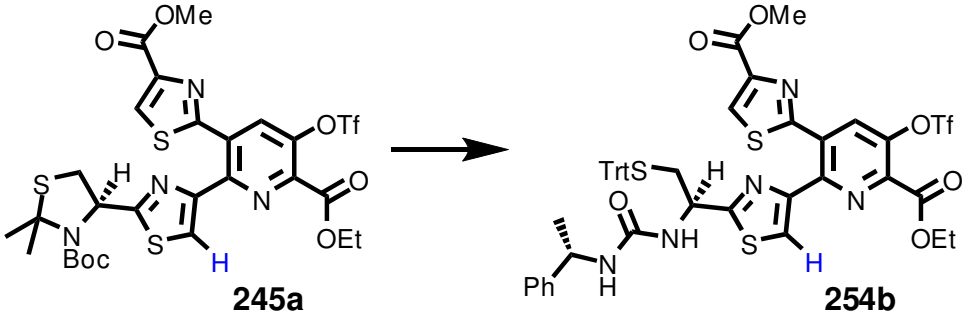
Maldi-MS: Calcd for $C_{38}H_{32}F_3N_4O_7S_4$ $[M + H]^+$, 841.1, found: 842.0.

(*R*) Phenylethyl isocyanate (5 µL, 0.033 mmol) and pyridine (2.7 µL) were added to the *S*-trityl aminothiol **253** (9 mg, 0.01 mmol) in dichoromethane (1 mL) at room temperature. The reaction mixture was stirred for 3 h, quenched with water (1 mL), diluted by brine (10 mL) and extracted with dichloromethane (3 x 10 mL). The organic extracts were dried with Na_2SO_4 and concentrated. Purification by column chromatography (silica gel, ethyl acetate/light petroleum = 1:4) to give 4.0 mg (0.004 mmol, 40%) of the urea **254a** as a colorless solid.

TLC: R_f = 0.37 (ethyl acetate/light petroleum = 1:1).

Maldi-MS: Calcd for $C_{47}H_{40}F_3N_5O_8S_4Na$ $[M + Na]^+$, 1010.2, found: 1010.9; ee > 99% (from the integration of ^{1}H NMR).

With (*S*)-phenylethyl isocyanate

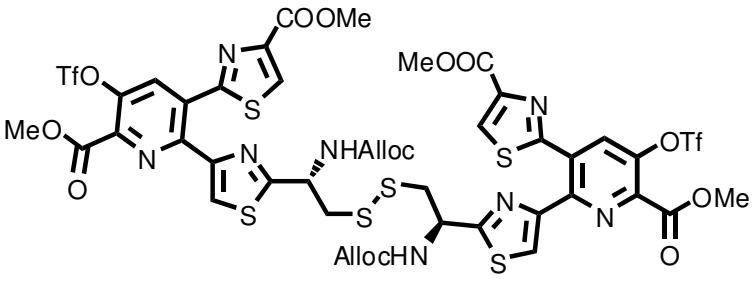


254b was obtained likewise from (*S*)-phenylethyl isocyanate (50% yield) as a colorless solid.

TLC: R_f = 0.37 (ethyl acetate/light petroleum = 1:1).

Maldi-MS: Calcd for $C_{47}H_{40}F_3N_5O_8S_4Na$ $[M + Na]^+$, 1010.2, found: 1010.9. ee > 96% (from the integration of ^{1}H NMR).

Disulfide 264.



264

Copper(II) nitrate trihydrate (14 mg, 57.9 mmol) was added to a solution of pyridine **244** (26 mg, 28.5 mmol) in methanol (10 mL) in a 50 mL round bottom flask equipped with a reflux condenser and a stirring bar. The reaction mixture was refluxed for 80 min, and cooled to room temperature. H_2S (*in situ* generated by concentrated HCl added dropwise to Na_2S) gas was bubbled into the solution. A black precipitate formed in 2 min, and H_2S introduction was continued for 15 min. The black precipitate was filtered off through a plug of celite and washed with dichloromethane (3 x 10 mL). The filtrate was concentrated, diluted with phosphate buffer (pH 2.5, 20 mL) and extracted with dichloromethane (3 x 20 mL). The extracts were dried with sodium sulfate and concentrated. Purification by column chromatography (silica gel, 20 g, ethyl acetate/light petroleum = 1:2) gave 19 mg (14.2 mmol, 99%) of disulfide **264** as a light yellow glass.

TLC: R_f = 0.24 (ethyl acetate/light petroleum = 1:1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.93-2.98 (1H, m, $\underline{CH_2}CH$), 3.12 (1H, s, $\underline{CH_2}CH$), 3.95 (3H, s, $COOCH_3$), 4.06 (3H, s, $COOCH_3$), 4.60 (2H, d, J = 5.7 Hz, $COO\underline{CH_2}CH{=}CH_2$), 5.23 (2H, d, J = 10.0 Hz, $CH_2\underline{CH}$, $CH{=}\underline{CH_2}$), 5.31 (1H, d, J = 17.2 Hz, $CH{=}\underline{CH_2}$), 5.82 (1H, s, NH), 5.86-5.95 (1H, m, $\underline{CH}{=}CH_2$), 8.05 (1H, s, CH), 8.17 (1H, s, CH), 8.36 (1H, s, $C\underline{H}$=CNCOOMe).

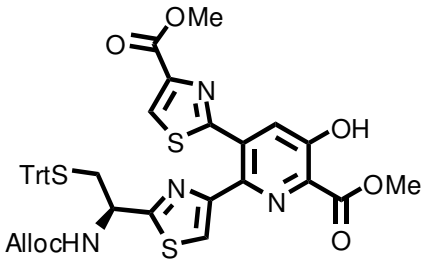
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 29.7, 43.7, 52.7, 53.4, 66.2, 77.2, 118.2, 120.2, 123.8, 130.4, 132.0, 132.4, 133.7, 141.9, 144.3, 147.2, 150.0, 151.2, 155.4, 161.4, 162.3, 162.8.

IR (KBr): $\tilde{\nu}$ = 2942 (w), 2893 (w), 1731 (s), 1715 (s), 1682 (s), 1645 (s), 1221 (s), 887 (s), 797 (s) cm^{-1}.

Optical rotation: $[\alpha]_D^{20}$ = - 14.4 (c = 0.23, $CHCl_3$).

HRMS (ESI): Calcd for $C_{44}H_{36}F_6N_8O_{18}S_8Na$ $[M + Na]^+$, 1356.9710, found: 1356.9715.

(*R*)-6-[2-(1'-Allyoxycarbonylamino-2'-tritylsulfanyl-ethyl)-thiazol-4-yl]-5-(4-methoxycarbonyl-thiazol-2-yl)-3-hydroxypyridine-2-carboxylic acid methyl ester (256)



256

To a solution of pyridine triflate **244** (0.23g, 0.25 mmol) in methanol (20 mL) was added NaOMe (27 mg, 0.6 mmol) at room temperature. The reaction mixture was stirred for 30 min (TLC control) at room temperature. The reaction mixture was diluted phosphate buffer (pH 2.5, 20 mL), extracted with dichloromethane (3 x 50 mL), dried with Na_2SO_4 and concentrated. The residue was purified by column chromatography (silica gel, 10 g, ethyl acetate/cyclohexane = 1:2) to yield 0.177 g (0.228 mmol, 99%) of hydroxypyridine **256** as a light yellow foam.

TLC: R_f = 0.23 (ethyl acetate/cyclohexane = 1:2).

HPLC (method A): t_R = 12.23 min.

LC-MS (ESI) (method A): t_R = 11.53 min, calcd for $C_{40}H_{34}N_4O_7S_3Na$ $[M + Na]^+$, 801.2, found: 801.0.

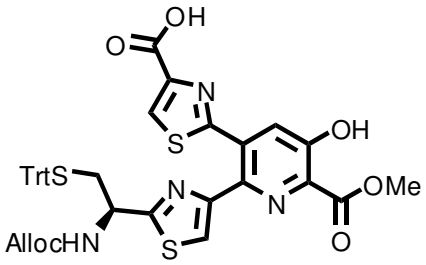
^{1}H-NMR (400 MHz, DMSO): δ = 1.66 (1H, d, J = 5.1 Hz, $\underline{CH_2}CH$), 1.90 (1H, d, J = 9.6 Hz, $\underline{CH_2}CH$), 3.05 (3H, s, $COOCH_3$), 3.08 (3H, s, $COOCH_3$), 3.56 (1H, dd, J = 4.9 Hz, $CH_2\underline{CH}$), 3.68 (2H, d, J = 4.9 Hz, $COO\underline{CH_2}CH{=}CH_2$), 4.37 (1H, d, J = 10.3 Hz, $CH{=}\underline{CH_2}$), 4.48 (1H, d, J = 17.2 Hz, $CH{=}\underline{CH_2}$), 5.05-5.12 (1H, m, $\underline{CH}{=}CH_2$), 6.40-6.50 (15H, m, trityl), 7.07 (1H, s, CH), 7.18 (1H, s, CH), 7.28 (1H, d, J = 8.4 Hz, NH), 7.50 (1H, s, $C\underline{H}$=CNCOOMe), 10.15 (1H, s, OH).

^{13}C-NMR (100.6 MHz, DMSO): δ = 35.4, 52.0, 52.3, 52.5, 64.5, 66.5, 116.9, 121.2, 125.3, 126.7, 127.9, 128.9, 131.1, 131.3, 133.3, 135.5, 141.6, 144.1, 145.3, 151.3, 153.3, 155.2, 160.9, 163.0, 165.6, 171.5.

IR (KBr): $\tilde{\nu}$ = 3391 (w), 2952 (s), 1724 (s), 1681 (m), 1490 (m), 1445 (s), 1317 (s), 1227 (s), 747 (s), 702 (s) cm^{-1}.

HRMS (ESI): Calcd for $C_{40}H_{34}N_4O_7S_3Na$ $[M + Na]^+$, 801.1482, found: 801.1478.

(*R*)-6-[2-(1'-Allyoxycarbonylamino-2'-tritylsulfanyl-ethyl)-thiazol-4-yl]-5-(4-hydroxycarbonyl-thiazol-2-yl)-3-hydroxypyridine-2-carboxylic acid methyl ester (257)



257

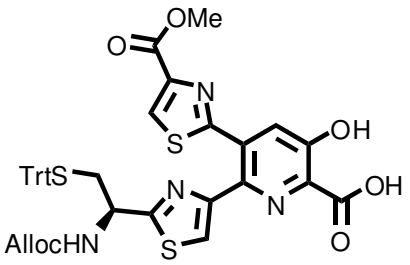
LiOH x H_2O (2.39 mg, 56.9 µmol) was added to hydroxypyridine **256** (22.1 mg, 28.4 µmol) in THF (12 mL) and water (3 mL) at room temperature, and the reaction mixture was stirred for 4 hours. The reaction mixture was quenched with water (20 mL) and extracted with ethyl acetate (3 x 40 mL), the combined extracts were dried with sodium sulfate and concentrated. Purification by preparative HPLC (method C) gave pyridine acid **257** as a light yellow glass. **257** was obtained to differentiate the chemical shift in NMR with acid **258**. Therefore, the yield was not calculated.

HPLC (method A): t_R = 11.1 min.

^{1}H-NMR (400 MHz, CD_3OD): δ = 2.60-2.72 (2H, m, $\underline{CH_2}CH$), 4.03 (3H, s, $COOCH_3$), 4.45 (1H, dd, J = 6.5 Hz, $CH_2\underline{CH}$), 4.53 (2H, d, J = 4.7 Hz, $COO\underline{CH_2}CH{=}CH_2$), 5.18 (1H, d, J = 10.7 Hz, $CH{=}\underline{CH_2}$), 5.31 (1H, d, J = 18.4 Hz, $CH{=}\underline{CH_2}$), 5.89-5.95 (1H, m, $\underline{CH}{=}CH_2$), 7.21-7.37 (15H, m, trityl), 7.83 (1H, s, CH), 8.00 (1H, s, CH), 8.12 (1H, s, $C\underline{H}$=CNCOOMe).

LC-MS (ESI) (method A): t_R = 10.32 min, calcd for $C_{39}H_{32}N_4O_7S_3Na$ $[M + Na]^+$, 787.1, found: 787.0.

(*R*)-6-[2-(1'-Allyoxycarbonylamino-2'-tritylsulfanyl-ethyl)-thiazol-4-yl]-5-(4-methoxycarbonyl-thiazol-2-yl)-3-hydroxypyridine-2-carboxylic acid (258)

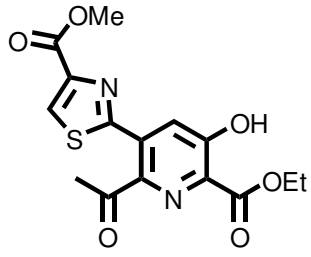


258

A mixture of hydroxypyridine **256** (30 mg, 39 µmol) and $Sc(OTf)_3$ (0.9 mg, 2 µmol) in 1,4-dioxane (2 mL) and water (0.6 mL) was titrated to pH 8.5 with satured $NaHCO_3$ solution (approximately 0.4 mL). The reaction mixture was then heated to 60°C for 8.5 hours (HPLC control). Phosphate buffer (pH 2.5, 30 mL) was added and the mixture was extracted with ethyl acetate (3 x 50 mL), the combined extracts were dried with Na_2SO_4 and concentrated. Purification by column chromatography (silica gel, 10 g, dichloromethane/MeOH = 15:1) yielded 27.8 mg (36 µmol, 93%) of pyridine acid **258** as a light yellow glass.

For characterization see page 272.

5-(4'-(Methoxycarbonyl)thiazol-2'-yl)-6-acetyl-3-hydroxypyridine-2-carboxylic acid ethyl ester (259)



259

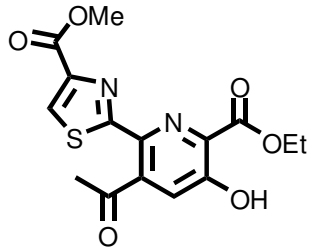
The same procedure as the preparation of pyridine **233** was used. Alkyne **164** (1.83 g, 8.8 mmol) yielded 1.24 g (3.5 mmol, 40%) of hydroxypyridine **259** and 0.48 g (1.4 mmol, 16%) of its isomer **259a** as colorless solids.

TLC: R_f = 0.26 (ethyl acetate/cyclohexane = 2:3).
LC-MS (method A): t_R = 8.03 min, calcd for $C_{15}H_{15}N_2O_6S$ $[M + H]^+$, 351.4, found: 350.8.
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.51 (3H, t, $CH_2\underline{CH_3}$), 2.71 (3H, s, $C(O)CH_3$), 3.96 (3H, s, $COOCH_3$), 4.55 (2H, dd, $\underline{CH_2}CH_3$), 7.67 (1H, s, CH), 8.34 (1H, s, CH), 11.12 (1H, s, C-OH).
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 14.1 ($CH_2\underline{CH_3}$), 27.4 ($C(O)\underline{C}H_3$), 52.5 ($COO\underline{C}H_3$), 62.9 ($\underline{CH_2}CH_3$), 128.0 (<u>C</u>H), 129.0 (<u>C</u>-COOEt), 129.7 (<u>C</u>H), 134.3 (<u>C</u>-CH), 144.8 (<u>C</u>-C(O)Me), 147.0 (<u>C</u>-COOMe), 159.5 (<u>C</u>-OH), 161.6 (<u>C</u>OOMe), 163.5 (C-<u>C</u>(N)S), 168.7 (<u>C</u>OOEt), 198.9 ($\underline{C}(O)CH_3$).

IR (KBr): $\tilde{\nu}$ = 3123 (m), 2992 (m), 1715 (s), 1694 (s), 1682 (s), 1242 (s), 898 (s), 864 (s), 757 (s) cm^{-1}.

HRMS (ESI): Calcd for $C_{15}H_{14}N_2O_6SNa$ $[M + Na]^+$, 373.0465, found: 373.0465.

6-(4'-(Methoxycarbonyl)thiazol-2'-yl)-5-acetyl-3-hydroxypyridine-2-carboxylic acid ethyl ester (259a)



259a

TLC: R_f = 0.34 (ethyl acetate/cyclohexane = 2:3).

GC-MS (method B): t_R = 9.39 min, m/Z = 350.

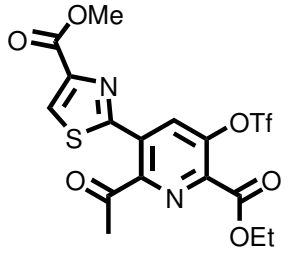
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.51 (3H, t, $CH_2\underline{CH_3}$), 2.64 (3H, s, $C(O)CH_3$), 3.93 (3H, s, $COOCH_3$), 4.55 (2H, dd, $\underline{CH_2}CH_3$), 7.28 (1H, s, CH), 8.22 (1H, s, CH), 11.01 (1H, s, C-OH).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 14.0 ($CH_2\underline{CH_3}$), 30.9 ($C(O)\underline{C}H_3$), 52.4 ($COO\underline{C}H_3$), 62.9 ($\underline{CH_2}CH_3$), 124.3 (<u>C</u>H), 129.4 (<u>C</u>H), 129.8 (<u>C</u>-COOEt), 138.0 (<u>C</u>-C(N)S), 142.1 (<u>C</u>-C(O)Me), 147.6 (<u>C</u>-COOMe), 159.2 (<u>C</u>-OH), 161.7 (<u>C</u>OOMe), 166.7 (<u>C</u>(N)S), 168.5 (<u>C</u>OOEt), 201.2 ($\underline{C}(O)CH_3$).

IR (KBr): $\tilde{\nu}$ = 3118 (s), 1744 (s), 1713 (s), 1682 (s), 1556 (s), 1435 (s), 1212 (s), 1101 (s), 863 (s) cm^{-1}.

HRMS (EI): Calcd for $C_{15}H_{14}N_2O_6S$ $[M]^+$, 350.0567, found: 350.0572.

5-(4'-(Methoxycarbonyl)thiazol-2'-yl)-6-acetyl-3- trifluoromethanesulfonyloxy pyridine-2-carboxylic acid ethyl ester (260a).

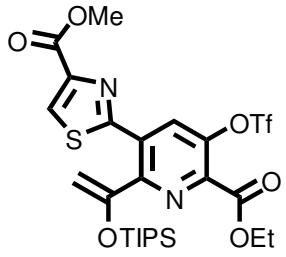


260a

Using the same procedure as the preparation of pyridine **241**. Hydroxypyrine **259** (1.23 g, 3.5 mmol) yielded 0.68 g (1.4 mmol, 40%) of **260a** as a colorless solid.

TLC: R_f = 0.49 (ethyl acetate/cyclohexane = 2:3).
LC-MS (ESI) (method A): t_R = 10.07 min, calcd for $C_{16}H_{14}N_2O_8S_2F_3$ $[M + H]^+$, 483.4, found: 483.0.

5-(4'-Methoxycarbonyl-thiazol-2'-yl)-3-trifluoromethanesulfonyloxy-6-(1-triisopropylsilyloxy-vinyl)-pyridine-2-carboxylic acid ethyl ester (260).

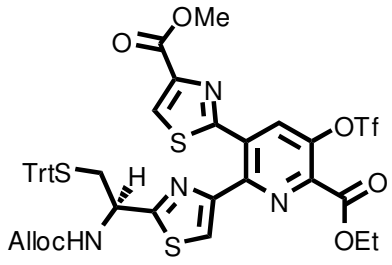


260

The same procedure as the preparation of enol ether **242** was used. Pyridine triflate **260a** (0.15 g, 0.3 mmol) yielded 0.18 g (0.3 mmol, 91%) of enol ether **260** as a light yellow oil, which was directly used in bromination.

TLC: R_f = 0.76 (ethyl acetate/cyclohexane = 1:2).

(*R*)-6-[2-(1'-Allyoxycarbonylamino-2'-tritylsulfanyl-ethyl)-thiazol-4-yl]-5-(4-methoxycarbonyl-thiazol-2-yl)-3-trifluoromethanesulfonyloxy-pyridine-2-carboxylic acid ethyl ester (244a)



244a

The same procedure as the preparation of thiazole **244** was used. Enol ether **260** (0.19 g, 0.3 mmol) yielded 0.18 g (0.2 mmol, 66% over 2 steps) of **244a** as a light yellow foam.

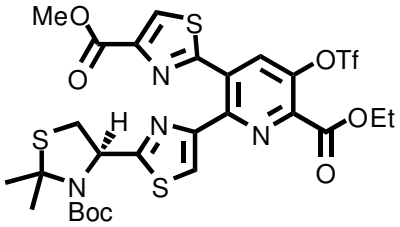
TLC: R_f = 0.48 (ethyl acetate/cyclohexane = 1:2).

HPLC (method A): t_R = 13.1 min.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.65-2.87 (2H, m, $\underline{CH_2}CH$), 3.99 (3H, s, $COOCH_3$), 4.52 (2H, d, J = 4.2 Hz, $COO\underline{CH_2}CH{=}CH_2$), 4.54 (2H, dd, $\underline{CH_2}CH_3$), 4.71 (1H, d, J = 6.3 Hz, $CH_2\underline{CH}$), 5.22 (1H, d, J = 10.2 Hz, $CH{=}\underline{CH_2}$), 5.30 (1H, d, J = 17.6 Hz, $CH{=}\underline{CH_2}$), 5.89 (1H, m, $\underline{CH}{=}CH_2$), 6.86 (1H, d, J = 18.6 Hz, NH), 7.22-7.42 (15H, m, trityl), 7.96 (1H, s, CH), 8.13 (1H, s, CH), 8.31 (1H, s, C$\underline{H}$=CNCOOMe).

LC-MS (ESI) (method A): t_R = 10.07 min, calcd for $C_{42}H_{35}N_4O_9S_4F_3Na$ $[M + Na]^+$, 947.1, found: 947.0.

(*R*)-6-(2',2'-Dimethyl-3'-*tert*-butoxycarbonyl-4',5'-dihydro-[2, 4']bithiazolyl-4-yl)-5-(4-methoxycarbonyl-thiazol-2-yl)-3-trifluoromethanesulfonyloxy-pyridine-2-carboxylic acid ethyl ester (245a)



245a

The same procedure as the preparation of enol ether **245** was used. Enol ether **260** (0.18 g, 0.3 mmol) yielded 0.12 g (0.2 mmol, 60% over two steps) of **245a** as a light yellow foam.

TLC: R_f = 0.49 (ethyl acetate/cyclohexane = 1:2).

LC-MS (ESI) (method A): t_R = 11.85 min, calcd for $C_{27}H_{30}N_4O_9S_4F_3$ $[M + H]^+$, 739.1, found: 738.9.

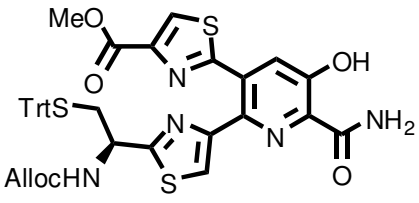
^{1}H-NMR (400 MHz, CD_3CN): δ = 1.33 (9H, s, $C(CH_3)_3$), 1.41 (3H, t, $CH_2\underline{CH_3}$), 1.78 (3H, s, CH_3), 1.87 (3H, s, CH_3), 2.79 (1H, d, J = 12.1 Hz, CH_2), 3.42 (1H, dd, J = 6.3 Hz, CH_2), 3.88 (3H, s, COOMe), 4.49 (2H, dd, $COO\underline{CH_2}CH_3$), 5.48 (1H, br, CH), 7.95 (1H, s, CH), 8.29 (1H, s, CCHS), 8.36 (1H, s, CCHS).

^{13}C-NMR (100.6 MHz, CD_3CN): δ = 14.3, 28.4, 52.9, 63.8, 118.0, 123.8, 131.9, 133.3, 134.0, 142.7, 145.4, 147.7, 147.9, 151.6, 162.2, 163.2, 163.6 (not all the carbon signals can be could be observed due to slow exchanges).

IR (KBr): $\tilde{\nu}$ = 2923 (s), 2853 (s), 1732 (s), 1715 (s), 1682 (s), 1651 (s), 1455 (s), 1179 (s), 889 (s), 799 (s) cm^{-1}.

HRMS (ESI): Calcd for $C_{27}H_{30}F_3N_4O_9S_4$ $[M + H]^+$, 739.0842, found: 739.0844.

(*R*)-6-[2-(1'-Allyoxycarbonylamino-2'-tritylsulfanyl-ethyl)-thiazol-4-yl]-5-(4-methoxycarbonyl-thiazol-2-yl)-3-hydroxypyridine-2-carboxamide (263)



263

A solution of pyridine **244a** (22 mg, 23.8 μmol) in dioxane (2 mL) and aqueous ammonium (25%, 1 mL) was heated to 60°C for 90 minutes (TLC control). The reaction mixture was cooled down to room temperature, diluted with phosphate buffer (pH 2.5, 20 mL) and extracted with ethyl acetate (3 x 40 mL). The combined extracts were dried with sodium sulfate and concentrated. Purification by column chromatography (silica gel, 20 g, dichloromethane/MeOH = 40:1) gave 14 mg (18.3 μmol, 78%) of hydroxypyridine amide **263** as a light yellow glass.

TLC: R_f = 0.64 (dichloromethane/MeOH = 10:1).

HPLC (method A): t_R = 11.7 min.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.54 (2H, dd, J = 4.5 Hz, CH_2), 3.78(3H, s, $COOCH_3$), 4.41 (2H, d, J = 5.3 Hz, $COO\underline{CH_2}CH{=}CH_2$), 4.46 (1H, d, J = 4.8 Hz, CH), 5.05 (1H, d, J = 10.5 Hz, $CH{=}\underline{CH_2}$), 5.19 (1H, d, J = 15.8 Hz, $CH{=}\underline{CH_2}$), 5.77-5.83 (1H, m, $\underline{CH}{=}CH_2$), 6.63 (1H, d, J = 8.0 Hz, NH), 7.11-7.27 (15H, m, trityl), 7.41 (1H, b, NH_2), 7.71 (1H, s, CH), 7.92 (1H, s, CH), 8.06 (1H, s, CH), 8.34 (1H, b, NH_2), 12.62 (1H, s, OH).

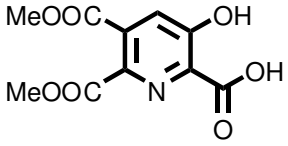
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 33.8, 36.8, 52.5, 66.0, 67.5, 117.9, 120.0, 127.0, 128.1, 128.2, 128.4, 129.5, 129.7, 129.8, 130.0, 132.5, 133.6, 144.3, 146.8, 157.3, 161.6, 164.3, 170.7.

IR (KBr): $\tilde{\nu}$ = 3448 (b), 2926 (s), 2854 (s), 1720 (s), 1686 (s), 1672 (s), 1639 (s), 1253 (s), 1145 (s), 1034 (m), 670 (s) cm^{-1}.

LC-MS (ESI) (method A): t_R = 11.39 min, calcd for $C_{39}H_{33}N_5O_6S_3Na$ $[M + Na]^+$, 786.15, found: 786.10.

HRMS (ESI): Calcd for $C_{39}H_{34}N_5O_6S_3$ $[M + H]^+$, 764.1666, found: 764.1667.

5,6-Di(methoxycarbonyl)-3-hydroxypyridine 2-carboxylic acid (255)



255

The same procedure as the preparation of **258** was used. Hydroxypyridine **143** (110 mg, 0.41 mmol) yielded 102 mg (0.40 mmol, 98%) of pyridine **255** as a colorless foam.

HPLC (method A): t_R = 5.9 min.

^{1}H-NMR (400 MHz, CD_3OD): δ = 3.85 (6H, s, 2 x $COOCH_3$), 7.54 (1H, s, CH).

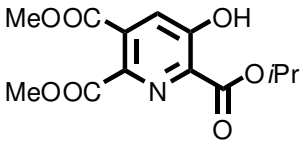
^{13}C-NMR (100.6 MHz, CD_3OD): δ = 53.87, 53.89, 127.2, 135.1, 136.0, 138.5, 161.5, 163.9, 167.2, 167.6.

IR (KBr): $\tilde{\nu}$ = 2958 (s), 1737 (s), 1643 (s), 1572 (s), 1463 (s), 1334 (s), 1262 (s), 1158 (s), 1042 (s), 704 (s) cm^{-1}.

LC-MS (method C): t_R = 8.15 min, calcd for $C_{10}H_{10}NO_7$ $[M + H]^+$, 256.1, found: 255.8.

HRMS (ESI): Calcd for $C_{10}H_{10}NO_7$ $[M + H]^+$, 256.0452, found: 256.0454.

5,6-Bis(methoxycarbonyl)-3-hydroxypyridine-2-carboxylic acid *iso*-propyl ester (255a)



255a

$Sc(OTf)_3$ (0.9 mg, 1.8 umol) was added to hydroxypyridine **143** (14 mg, 0.05 mmol) in isopropanol (2 mL) and H_2O (10 uL). The reaction mixture was heated to 60°C for 6 hours (TLC control), cooled down to room temperature. Phosphate buffer (pH 2.5, 10 mL) was added to the reaction mixture, which was extracted with dichloromethane (3 x 20 mL). The organic extracts were dried with sodium sulfate and concentrated. Purification by column chromatography (silica gel, 10 g, ethyl acetate/light petroleum = 1:6) gave 13.6 mg (0.046 mmol, 85%) **255a** as a colorless glass.

TLC: R_f = 0.40 (ethyl acetate/cyclohexane = 1:2).

LC-MS (method A): t_R = 8.71 min, calcd for $C_{13}H_{16}NO_7$ $[M + H]^+$, 298.1, found: 298.0.

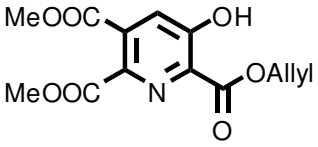
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.48 (6H, d, J = 6.4 Hz, $CH(\underline{CH_3})_2$), 3.94 (3H, s, $COOCH_3$), 3.96 (3H, s, $COOCH_3$), 5.32-5.38 (1H, m, $\underline{CH}(CH_3)_2$), 7.66 (1H, s, CH), 11.25 (1H, s, OH).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 21.6, 53.0, 53.2, 71.8, 126.8, 131.3, 133.3, 140.1, 159.4, 165.3, 165.4, 168.3.

IR (KBr): $\tilde{\nu}$ = 3171 (b), 2991 (s), 2859 (s), 2926 (s), 1747 (s), 1736 (s), 1308 (s), 1211 (s), 1096 (s), 812 (s) cm^{-1}.

HRMS (ESI): Calcd for $C_{13}H_{16}NO_7$ $[M + H]^+$, 298.0921, found: 298.0922.

5,6-Bis(methoxycarbonyl)-3-hydroxypyridine-2-carboxylic acid allyl ester (255b)



255b

Similar procedure to the preparation of **255a** was used. Hydroxypyridine **143** (11 mg, 0.04 mmol) yielded 10.8 mg (0.04 mmol, 95%) of pyridine **255b** as a colorless solid.

M.p.: 73-75°C.

TLC: R_f = 0.40 (ethyl acetate/cyclohexane = 1:2).

GC-MS (method B): t_R = 7.79 min, m/Z = 295.

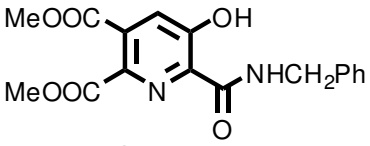
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.95 (3H, s, $COOCH_3$), 3.96 (3H, s, $COOCH_3$), 4.97 (2H, d, J = 6.0 Hz, $\underline{CH_2}CH=CH_2$), 5.37 (2H, dd, J = 10.4, 0.8 Hz, $CH_2CH=\underline{CH_2}$), 5.48 (2H, d, J = 17.2, 1.2 Hz, $CH_2CH=\underline{CH_2}$),6.03-6.13 (1H, m, $CH_2\underline{CH}=CH_2$), 7.68 (1H, s, CH), 11.02 (1H, s, OH).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 29.7, 53.1, 53.2, 67.6, 120.4, 127.0, 130.7, 130.8, 133.7, 140.2, 159.5, 165.1, 165.3, 168.3.

IR (KBr): $\tilde{\nu}$ = 3197 (b), 3070 (s), 2957 (s), 2855(s), 1737 (s), 1686 (s), 1323 (s), 1203 (s), 1154 (s), 801 (s) cm^{-1}.

HRMS (ESI): Calcd for $C_{13}H_{14}NO_7$ $[M + H]^+$, 296.0765, found: 296.0766.

5,6-Bis(methoxycarbonyl)-3-hydroxypyridine-2-carboxylic acid N-benzyl amide (255c)

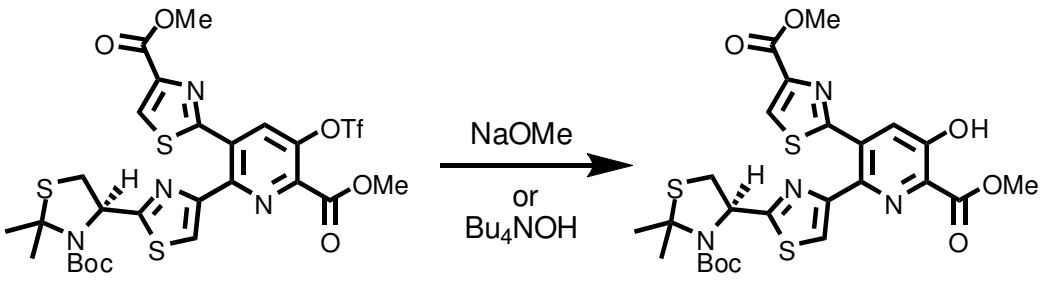


255c

$Sc(OTf)_3$ (1.0 mg, 2.0 umol) was added to hydroxypyridine **143** (11.2 mg, 0.04 mmol) and benzyl amine (8 uL, 0.08 mmol) in dioxane/DIPEA (pH 8.0, 1 mL). The reaction mixture was stirred for 3 hours (TLC control) at room temperature. Phosphate buffer (pH 2.5, 10 mL) was added to the reaction mixture, which was extracted with dichloromethane (3 x 20 mL). The organic extracts were dried with sodium sulfate and concentrated. Purification by column chromatography (silica gel, 10 g, ethyl acetate/light petroleum = 1:4) gave 14.3 mg (0.04 mmol, 99%) **255c** as a light yellow glass.

TLC: R_f = 0.49 (ethyl acetate/light petroleum = 1:1).
LC-MS (method A): t_R = 9.47 min, calcd for $C_{17}H_{17}N_2O_6$ $[M + H]^+$, 345.1, found: 345.0.
^{1}H-NMR (400 MHz, CD_3CN): δ = 3.87 (3H, s, $COOCH_3$), 3.88 (3H, s, $COOCH_3$), 4.59 (1H, d, J = 6.6 Hz, $NH\underline{CH_2}Ph$), 7.28-7.36 (5H, m, Ph), 7.66 (1H, s, CH), 8.75 (1H, b, NH), 12.76 (1H, s, OH).
^{13}C-NMR (100.6 MHz, CD_3CN): δ = 43.3, 53.4, 53.7, 127.5, 128.3, 128.5, 129.5, 133.4, 133.5, 139.1, 139.9, 159.6, 166.27, 166.32, 168.7.
HRMS (ESI): Calcd for $C_{17}H_{17}N_2O_6$ $[M + H]^+$, 345.1081, found: 345.1080.

(*R*)-6-(2',2'-Dimethyl-3'-*tert*-butoxycarbonyl-4',5'-dihydro-[2,4']bithiazolyl-4-yl)-5-(4-methoxycarbonyl-thiazol-2-yl)-3-hydroxypyridine-2-carboxylic acid methyl ester (283a)



245 **283a**

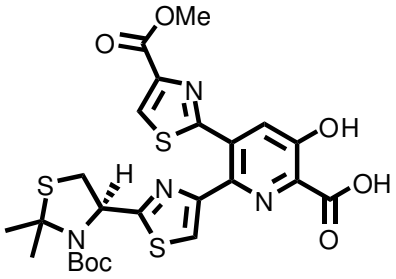
Procedure A: To a solution of pyridine triflate **245** (0.24g, 0.331 mmol) in dioxane (30 mL) was added 10% aqueous Bu_4NOH solution (1.68 mL, 0.6 mmol) dropwise at room temperature, and the resulting reaction mixture was stirred for 5 minutes (TLC control). The

reaction mixture was diluted with phosphate buffer (pH 2, 0.5 M, 20 mL) and extracted with dichloromethane (3 x 50 mL). The combined extracts were dried with Na_2SO_4 and concentrated. Purification by column chromatography (silica gel, 10 g, ethyl acetate/light petroleum = 1:1) yielded 0.195 g (0.329 mmol, 99%) of hydroxypyridine **283a** as a light yellow foam.

Procedure B: To a solution of pyridine triflate **245** (0.24g, 0.3 mmol) in methanol (30 mL) was added NaOMe (36 mg, 0.6 mmol) at room temperature and the reaction mixture was stirred for 30 min (TLC control). The reaction mixture was diluted with phosphate buffer (pH 2, 0.5 M, 20 mL) and extracted with dichloromethane (3 x 50 mL). The combined extracts were dried with Na_2SO_4 and concentrated. Purification by column chromatography (silica gel, 10 g, ethyl acetate/light petroleum = 1:1) gave 0.195 g (0.329 mmol, 99%) of hydroxypyridine **283a** as a light yellow foam.

TLC: R_f = 0.08 (ethyl acetate/cyclohexane = 1:2).
HPLC (method A): t_R = 11.2 min.
^{1}H-NMR (400 MHz, CD_3CD): δ = 1.23 (9H, s, *t*-Bu), 1.77 (3H, s, CH_3), 1.87 (3H, s, CH_3), 2.77, 2.80 (1H, d, J = 12.1 Hz, CH_2), 3.37-3.42 (1H, dd, J = 6.0 Hz, CH_2), 3.86 (3H, s, COOCH3), 4.02 (3H, s, COOCH3), 5.47 (1H, br, CH), 7.69 (1H, s, CH), 7.82 (1H, s, CH), 8.29 (1H, s, CH), 10.65 (1H, s, OH).
^{1}H-NMR (100.6 MHz, CD_3CD): δ = 14.3, 23.3, 24.3, 28.4, 30.3, 32.6, 52.8, 53.9, 121.1, 128.0, 131.4, 134.8, 144.2, 147.6, 158.2, 162.3, 165.0, 170.2 (not all the carbon signals could be observed).
IR (KBr): $\tilde{\nu}$ = 3481 (s), 3199 (b), 2977 (s), 2933 (s), 1695 (s), 1590 (s), 1357 (s), 1170 (s), 1072 (s), 773 (s) cm^{-1}.
LC-MS (ESI) (method A): t_R = 10.47 min, calcd for $C_{25}H_{29}N_4O_7S_3$ $[M + H]^+$, 593.1, found: 593.0.
HRMS (FAB): Calcd for $C_{25}H_{29}N_4O_7S_3$ $[M + H]^+$, 593.1193, found: 593.1180

(*R*)-6-(2',2'-Dimethyl-3'-*tert*-butoxycarbonyl-4',5'-dihydro-[2,4']bithiazolyl-4-yl)-5-(4-methoxycarbonyl-thiazol-2-yl)-3-hydroxypyridine-2-carboxylic acid (283)



283

A solution of hydroxypyridine **283a** (0.16 g, 0.27 mmol) and $Sc(OTf)_3$ (6.4 mg, 0.01 mmol) in dioxane (36 mL) and water (12 mL) was titrated to pH 8.5 with satured $NaHCO_3$ aqueous solution (approximately 1 mL), and heated to 60°C for 8.5 hours (HPLC control). The reaction mixture was diluted by phosphate buffer (pH 2, 0.5 M, 30 mL) and extracted with ethyl acetate (3 x 50 mL). The combined extracts were dried with Na_2SO_4 and concentrated. Purification by column chromatography (silica gel, 20 g, dichloromethane/MeOH = 15:1) yielded 0.14 g (0.24 mmol, 90%) of hydroxypyridine acid **283** as a light yellow solid.

M. p.: 239°C (foaming).

TLC: R_f = 0.43 (dichloromethane/MeOH = 10:1).

HPLC (method A): t_R = 10.16 min.

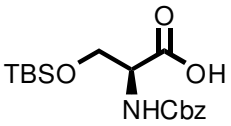
^{1}H-NMR (400 MHz, CD_3OD): δ = 1.11 (9H, s, *t*-butyl), 1.66 (3H, s, CH_3), 1.80 (3H, s, CH_3), 3.10 (1H, d, J = 11.9 Hz, -CH_2-), 3.63 (1H, d, J = 9.1 Hz, -CH_2-), 3.98 (3H, s, $COOCH_3$), 5.94 (1H, d, J = 5.5Hz, -CH-), 6.74 (1H, s, CH), 7.61 (1H, s, CH), 8.71 (1H, s, CH).

IR (KBr): $\tilde{\nu}$ = 3445 (w), 3111 (b), 2978 (s), 1866 (s), 1842 (s), 1823 (s), 1799 (s), 1790 (s), 1769 (s), 1731 (s), 1714 (s), 1696 (s), 1682 (s), 1668 (s), 1660 (s), 1651 (s), 1644 (s), 1393 (s), 1347 (s), 1240 (s), 1168 (s), 949 (s), 798 (s), 666 (s) cm^{-1}.

Optical rotation: $[\alpha]_D^{20}$ = + 125.8 (c = 0.67, $CHCl_3$).

HRMS (ESI): Calcd for $C_{24}H_{27}O_7N_4S_3$ $[M + H]^+$, 579.1036, found: 579.1033.

(*S*)-2-(Benzyloxycarbonylamino)-3-(*tert*-butyldimethylsilyloxy)propanoic acid (267)[184]

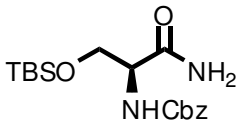


267

Cbz-Serine **266** (9.56 g, 40 mmol), TBDMSCl (6.04 g, 40 mmol) and imidazole (5.44 g, 80 mmol) were dissolved in dry DMF (40 mL) and stirred for 48 hours at room temperature under argon. The reaction mixture was concentrated, suspended in *n*-hexane (100 mL) and extracted with 5% $NaHCO_3$ aqueous solution (3 x 60 mL). The aqueous fraction was acidified to pH 2 with 2 M HCl and extracted with ethyl acetate (3 x 60 mL). The combined extracts were dried with Na_2SO_4 and concentrated. Drying under high vaccum gave 12.94 g (36.8 mmol, 92%) of TBS-serine **267** as a colorless glass.

TLC: R_f = 0.16 (ethyl acetate/cyclohexane = 2:3).
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.047, 0.86 (15H, s, TBS), 3.85 (1H, dd, J = 10.1 Hz, -CH_2-), 4.12 (1H, dd, J = 9.1 Hz, -CH_2-), 4.45 (1H, dd, J = 8.0 Hz, -CH-), 5.14 (2H, s, PhCH_2), 5.79 (1H, d, J = 8.1 Hz, NH), 7.36 (5H, m, Ph).
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = -5.6, 18.2, 25.7 (TBS), 55.6 (CH), 63.3 (CH_2), 67.2 (Ph<u>C</u>H_2), 128.1 (Ph), 128.2 (Ph), 128.5 (Ph), 136.1 (Ph), 156.1 (<u>C</u>OOBz), 174.7 (COOH).
Optical rotation: $[\alpha]_D^{20}$ = + 25.1 (c = 1, $CHCl_3$).
ESI-MS: Calcd for $C_{17}H_{28}NO_5Si$ $[M + H]^+$, 354.2, found: 354.0.

(*S*)-2-(Benzyloxycarbonylamino)-3-(*tert*-butyldimethylsilyloxy)-propanamide (268)



268

To a stirred solution of TBS-serine **267** (12.9 g, 37 mmol) in THF (40 mL) was added HOSu (5.07 g, 44 mmol) and DCC (9.06 g, 44 mmol) at 0°C. The reaction mixture was stirred at ambient temperature for 16 hours, then filtered to remove the resulting colorless precipitate (*N, N'*-dicyclohexylurea), and concentrated. The residue was taken up in ethyl acetate (150 mL) and cooled to 0°C, then aqueous NH_4OH solution (25%, 3.7 mL) was added dropwise. The reaction mixture was stirred for 1 hour (TLC control), filtered, and the solid was rinsed with ethyl acetate (3 x 50 mL). The organic filtrate was washed with saturated aqueous $NaHCO_3$ solution (2 x 100 mL), brine (100 mL), dried with Na_2SO_4 and concentrated. The resulting residue (14.19 g) containing urea could be used directly in next step. An analytical sample was obtained by column chromatography (silica gel, 10 g, ethyl acetate/light petroleum = 1:1) to give the amide **268** as a colorless glass.

TLC: R_f = 0.29 (ethyl acetate/cyclohexane = 2:3).

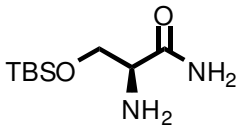
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.08, 0.88 (15H, s, TBS), 3.66 (1H, dd, J = 9.8 Hz, -CH_2-), 4.04 (1H, dd, J = 9.5 Hz, -CH_2-), 4.21 (1H, br, CH), 5.11 (2H, s, PhCH_2-), 5.73 (1H, d, J = 4.8 Hz, NH), 5.96 (1H, s, $CONH_2$), 6.51 (1H, s, $CONH_2$), 7.35 (5H, s, Ph).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = -5.5, 18.1, 25.7 (TBS), 55.6 (CH), 63.0 (Ph$\underline{C}H_2$-), 67.1 (CH_2), 128.1 (Ph), 128.2 (Ph), 128.5 (Ph), 136.0 (Ph), 156.0 ($\underline{C}OOCH_2Ph$), 172.7 ($CONH_2$).

IR (KBr): $\tilde{\nu}$ = 3325 (bs), 2928 (s), 2852 (s), 1667 (s), 1627 (s), 841 (s) cm^{-1}.

ESI-MS: Calcd for $C_{17}H_{29}N_2O_4Si$ $[M + H]^+$, 353.2, found: 353.0.

(*S*)-2-Amino-3-(*tert*-butyldimethylsilyloxy)-propanamide (269)



269

The crude propanamide **268** (14.19 g) was dissolved in dry methanol (200 mL) under argon and Pd/C (0.39 g, 3.7 mmol) was added. The reaction vessel was purged three times with H_2 to remove argon, and the flask was connected to hydrogen balloon. The reaction mixture was stirred for 12 hours (TLC control), and then filtered through Celite, the pad was washed with dichloromethane (3 x 10 mL), the combined filtrates were concentrated and purified by column chromatography (silica gel, 40 g, ethyl acetate/light petroleum = 1:1 then dichloromethane/MeOH = 10:1) to yield 6.77 g (31 mmol, 85% over two steps) of amine **269** as a light yellow sticky oil.

GC-MS (method B): t_R = 6.48 min, m/Z = 218.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.061, 0.88 (15H, s, TBS), 2.11 (2H, br, NH_2), 3.45 (1H, d, J = 4.8 Hz, -CH-), 4.79 (2H, d, J = 5.4 Hz, -CH_2-), 5.91 (1H, s, $CONH_2$), 7.20 (1H, s, $CONH_2$).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = -5.5, 18.2, 25.8 (TBS), 56.5 (CH), 65.1 (CH_2), 176.0 ($CONH_2$).

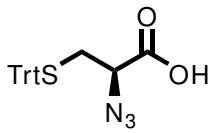
IR (KBr): $\tilde{\nu}$ = 3317 (bs), 2929 (s), 2858 (s), 1681 (s), 1505 (s), 1256 (s), 1099 (s), 837 (s), 780 (s) cm^{-1}.

Optical rotation: $[\alpha]_D^{20}$ = - 14.9 (c = 1, $CHCl_3$).

ESI-MS: Calcd for $C_9H_{23}N_2O_2Si$ $[M + H]^+$, 219.2, found: 219.1.

HRMS (ESI): Calcd for $C_9H_{23}N_2O_2Si$ $[M + H]^+$, 219.1523, found: 219.1523.

(*R*)-2-Azido-3-(tritylthio)propanoic acid (271)



271

Trifluoromethanesulfonic anhydride (15.1 mL, 90.7 mmol) was added dropwise to a mixture of sodium azide (11.8 g, 181.5 mmol) in dichloromethane (30 mL) and water (30 mL) at 0°C with stirring. The reaction mixture was stirred for 2h at this temperature, then saturated $NaHCO_3$ solution (25 mL) was added dropwise (gas evolution). The layers were separated and the aqueous layer was re-extracted with dichloromethane (2 x 15 mL), and the combined organic extracts were washed with saturated $NaHCO_3$ solution (2 x 15 mL). This freshly prepared solution of trifluoromethanesulfonyl azide in dichloromethane was added to a suspension of trityl-cysteine **270** (10.9 g, 30.1 mmol) in MeOH (240 mL) and water (75 mL), followed by triethylamine (16.9 mL, 120.5 mmol) and $CuSO_4 \times 5\ H_2O$ (0.36 g, 1.4 mmol). The reaction mixture became homogenous and was stirred at room temperature for 12h. The volatiles were removed on a rotavap. Equipped with a blast shield. The aqueous phase was acidified to pH = 1 with 0.2 M HCl solution and extracted with ethyl acetate (3 x 100 mL). The combined extracts were dried with sodium sulfate and concentrated. Purification by column chromatography (silica gel, 80 g, ethyl acetate/light petroleum = 1:12 to dichloromethane/MeOH = 40:1) gave 10.5 g (27.0 mmol, 90%) of the azide **271** as a yellow sticky oil.

TLC: R_f = 0.50 (dichloromethane/MeOH = 10:1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.62 (1H, dd, J = 8.2 Hz, -CH_2-), 2.74 (1H, dd, J = 5.7 Hz, CH_2), 3.18 (1H, t, J = 7.6 Hz, -CH-), 7.22-7.47 (15H, m, trityl).

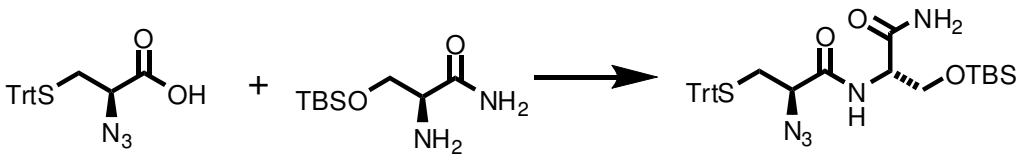
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 33.0 (CH_2), 61.1 (CH), 67.4 ($\underline{C}Ph_3$), 127.0 (Ph), 128.1 (Ph), 129.5 (Ph), 144.1 (Ph), 174.4 (COOH).

IR (KBr): $\tilde{\nu}$ = 3445 (w), 3060 (w), 2116 (s), 1730 (m), 743 (s) cm^{-1}.

Optical rotation: $[\alpha]_D^{20}$ = - 49.1 (c = 1.7, MeOH).

HRMS (ESI): Calcd for $C_{22}H_{18}N_2O_3SSi$ [M - H]$^-$, 388.1125, found: 388.1125.

(2S, 2'*R*)-2-(2'-Azido-3'-tritylthiopropyl)amido-3-*tert*-butyldimethylsilyloxy-propanamide (272).



N-Methyl morpholine (7.9 mL, 71.9 mmol) was added to azido-cysteine **271** (14 g, 36.0 mmol) in THF (300 mL) at -20°C, then isobutyl chloroformate (4.7 mL, 36.0 mmol) was added dropwise to the above reaction mixture, the resulting reaction mixture was stirred for 10 minutes at -20°C, then the free amine **269** (7.9 g, 36.2 mmol) was added to the reaction mixture, stirred at this temperature for another 2 hours, then slowly warm to room temperature and stirred for 12 hours (TLC control). The reaction mixture was filtered, the organic layer was concentrated and dissolved in ethyl acetate (300 mL), washed with phosphate buffer (pH 2, 0.5 M, 100 mL), saturated NaCl solution (100 mL), 5% $NaHCO_3$ (100 mL) and saturated NaCl solution (100 mL). The organic layer was dried with sodium sulfate and concentrated. Purification by column chromatography (silica gel, 80 g, ethyl acetate/light petroleum = 1:4) yielded 10.5 g (17.8 mmol, 49%) of the dipeptide **272** as a colorless foam.

TLC: R_f = 0.37 (ethyl acetate/light petroleum = 1:1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.05, 0.06, 0.86 (15H, s, TBS), 2.67 (1H, dd, J = 7.4 Hz, CH_2), 2.82 (1H, dd, J = 5.6 Hz, CH_2), 2.98 (1H, dd, J = 5.6 Hz, -CHN_3), 3.54 (1H, dd, J = 7.3 Hz, CH_2OTBS), 3.97 (1H, dd, J = 3.8 Hz, CH_2OTBS), 4.30-4.34 (1H, m, -CH-), 5.92 (1H, s, $CONH_2$), 6.44 (1H, s, $CONH_2$), 6.88 (1H, d, J = 6.9 Hz, NH), 7.20-7.28 (15H, m, trityl).

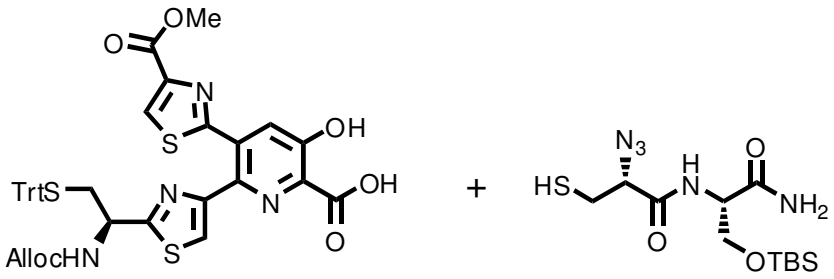
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = -5.5, -5.6, 18.1, 25.7 (TBS), 33.6 (CH_2), 34.4 ($\underline{C}HCONH_2$), 54.0 (CH), 62.3 (CH_2OTBS), 67.2 ($\underline{C}Ph_3$), 127.0 (Ph), 128.1 (Ph), 129.5 (Ph), 144.2 (Ph), 167.9 (CONH), 171.7 ($CONH_2$).

IR (KBr): $\tilde{\nu}$ = 3400 (bw), 3060 (m), 2929 (s), 2117 (s), 1677 (s), 1205 (s), 839 (s) cm^{-1}.

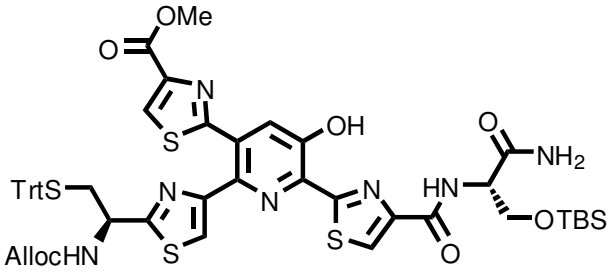
Optical rotation: $[\alpha]_D^{20}$ = + 50.2 (c = 0.4, $CDCl_3$).

HRMS (ESI): Calcd for $C_{31}H_{40}N_5O_3SSi$ $[M + H]^+$, 590.2616, found: 590.2616.

(2'*S*, 1''*R*)-2-{4-[2-(*Tert*-butyl-dimethylsilanyloxy)-1-carbamoyl-ethylcarbamoyl]-thiazol-2-yl}-5-(4-methoxycarbonyl-thiazol-2-yl)-6-(2-[2-(1-allyloxycarbonylamino-2-tritylsulfanyl-ethyl)-thiazol-5-yl]-3-hydroxypyridine (277)



258 **274**



277

Phosgene (240 µL, 20% in toluene) was added dropwise to a mixture of hydroxypyridine acid **258** (0.23 g, 0.39 mmol) and triethyamine (127 µL, 0.91mmol) in THF (40 mL) under argon at -40°C. The reaction mixture was stirred for 2 hours at – 40°C and filtered under argon. The resulting solution was cooled dto -40°C, and the excess of phosgene was removed under vacuum (20 mbar) to give a solution of anhydride **273**.

Trifluoroacetic acid (0.2 mL) and triethylsilane (0.1 mL) were added dropwise to a stirred solution of dipeptide **272** (0.36 g, 0.61 mmol) in dichloromethane (4 mL) at room temperature under argon, the reaction mixture was stirred for 30 minutes (TLC control). Toluene (4 mL) was added to the reaction mixture, and solvents and volatiles were removed under high vacuum. The resulting residue containing free thiol **274** was directly used in the next transformation.

The free thiol **274** in THF (4 mL) was added dropwise to the solution of anhydride **273** at - 40°C, DMAP (4.9 mg, 0.04 mmol) was added to the reaction mixture. The reaction mixture was slowly warmed to room temperature and stirred for 48 hours, diluted with phosphate buffer (pH 2.5, 60 mL) and extracted with dichloromethane (3 x 30 mL). The combined extracts were dried with sodium sulfate and concentrated. The thioester **275** obtained was found to be unstable to silica gel, therefore, it was used directly in the next step.

The crude thioester **275** was dissolved in THF (30 mL) and cooled to -20°C. PPh_3 (162 mg, 0.62 mmol) in THF (2 mL) was added dropwise. The reaction mixture was stirred for 1 hour at this temperature, slowly warmed to room temperature in 1 hour and warmed to 40°C for 20 hours (TLC control). The reaction mixture was concentrated and prepurified (removing the excess PPh_3) by column chromatography (silica gel, 10 g, dichloromethane/EtOH = 1:0 → 20:1) to give the crude thiazoline **276** (containing some triphenylphosphine oxide).

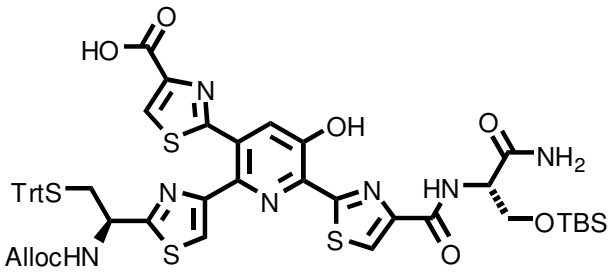
Thiazoline **276** was dissolved in dichloromethane (30 mL) and cooled to -20°C. $BrCCl_3$ (50 µL, 0.5 mmol) and DBU (124 µL, 0.8 mmol) were added dropwise. The reaction mixture was stirred for 1 hour at -20°C and then slowly warm to room temperature in 1 hour, diluted with phosphate buffer (pH 2.5, 40 mL) and extracted with dichloromethane (3 x 30 mL). The combined extracts were dried with sodium sulfate and concentrated. Purification by column chromatography (silica gel, 40 g, dichloromethane/ethanol = 30:1) gave 250 mg (23.8 mmol, 74% over 4 steps) of tristhiazolylpyridine **277** as a yellow foam.

TLC: R_f = 0.68 (dichloromethane/MeOH = 10:1).
^{1}H-NMR (400 MHz, CD_3CN): δ = 0.10, 0.90 (15H, s, TBS), 2.57 (1H, dd, J = 5.4 Hz, CH_2), 2.68 (1H, dd, J = 8.4 Hz, CH_2), 3.87 (3H, s, $COOCH_3$), 3.97 (1H, dd, J = 5.2 Hz, -CH), 4.08 (1H, dd, J = 4.5 Hz, CH), 4.52 (4H, dd, J = 5.7 Hz, $\underline{CH_2}CH=CH_2$, $\underline{CH_2}OTBS$), 5.19 (1H, d, J = 10.4 Hz, -CH=$\underline{CH_2}$), 5.29 (1H, d, J = 10.4 Hz, -CH=$\underline{CH_2}$), 5.90 (1H, dd, J = 4.8 Hz, -$\underline{CH}$=CH_2), 5.97 (1H, s, $CONH_2$), 6.59 (1H, s, $CONH_2$), 7.23-7.36 (15H, m, trityl), 7.81 (1H, s, CH), 7.85 (1H, s, CH), 8.04 (1H, s, CH), 8.29 (1H, s, CH), 10.85 (1H, s, CH).
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = -5.5, -5.6, 14.1, 18.2, 25.8, 29.7, 31.9, 37.0, 52.5, 54.1, 62.5, 65.9, 67.4, 117.8, 120.3, 126.1, 126.9, 127.5, 127.9, 128.0, 129.5, 129.6, 129.7, 129.9, 130.0, 131.0, 134.6, 143.0, 144.4, 146.5, 149.5, 151.4, 160.1, 161.7, 164.9, 169.9, 172.3.
HPLC (method A): t_R = 13.3 min.

LC-MS (ESI) (method A): t_R = 12.2 min, calcd for $C_{51}H_{54}N_7O_8S_4Si$ $[M + H]^+$, 1048.3, found: 1047.7.

LRMS (FAB): Calcd for $C_{51}H_{54}N_7O_8S_4Si$ $[M + H]^+$, 1048.27, found: 1048.27.

(2'*S*, 1''*R*)-2-{4-[2-(*Tert*-butyl-dimethylsilanyloxy)-1-carbamoyl-ethylcarbamoyl]-thiazol-2-yl}-5-(4-hydroxycarbonyl-thiazol-2-yl)-6-(2-[2-(1-allyloxycarbonylamino-2-tritylsulfanyl-ethyl)-thiazol-5-yl]-3-hydroxypyridine



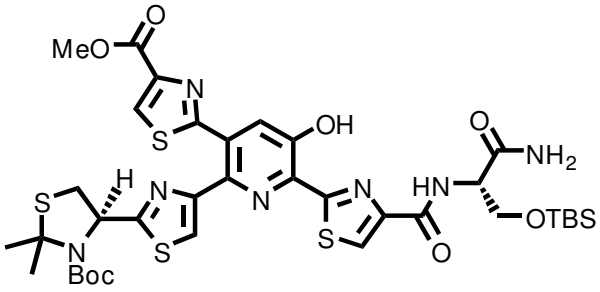
278

Hydroxypyridine **277** (19 mg, 18.1 μmol) was dissolved in THF (4 mL) and water (1.2 mL) at 0°C, LiOH (0.5 M aqueous solution, 152 μL) was added dropwise, and the reaction mixture was stirred at 0°C for 5 hour (HPLC control). 5% $NaHCO_3$ (10 mL) was added to the reaction mixture and extracted with dichloromethane (3 x 20 mL). The combined extracts were dried with sodium sulfate and concentrated. The crude acid **278** was directly used in the next step without purification due to its stability.

HPLC (method A): t_R = 12.4 min.

LC-MS (ESI) (method A): t_R = 12.2 min, calcd for $C_{50}H_{52}N_7O_8S_4Si$ $[M + H]^+$, 1034.25, found: 1033.67.

(2'*S*, 3''*R*)-2-{4-[2-(*Tert*-butyl-dimethylsilanyloxy)-1-carbamoyl-ethylcarbamoyl]-thiazol-2-yl}-6-(2',2'-dimethyl-3'-*tert*-butoxycarbonyl-4',5'-dihydro-[2,4']bithiazolyl-4-yl)-5-(4-methoxycarbonyl-thiazol-2-yl)-3-hydroxypyridine (285)



285

The same procedure as the preparation of hydroxypyrine **277** was used. Pyridine acid **283** (0.23 g, 0.4 mmol) yielded 0.25 g (0.3 mmol, 74%) of **285** as a light yellow foam.

TLC: R_f = 0.44 (dichloromethane/methanol = 10:1).

HPLC (method A): t_R = 12.8 min.

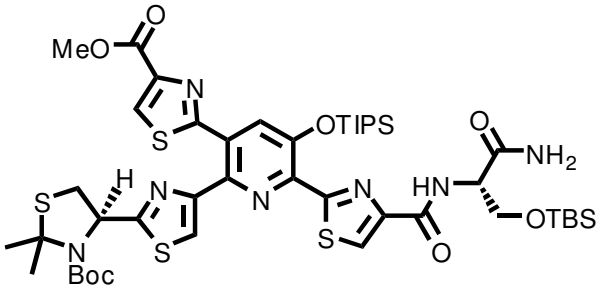
^{1}H-NMR (400 MHz, CD_3CN): δ = 0.09 (6H, s, TBS), 0.90 (9H, s, TBS), 1.32 (9H, s, *t*-Bu), 1.77 (3H, s, CH_3), 1.88 (3H, s, CH_3), 2.79 (1H, d, J = 12.2 Hz, CH_2), 3.40 (1H, dd, J = 6.2 Hz, CH_2), 3.87 (3H, s, $COOCH_3$), 3.97 (1H, dd, J = 5.5 Hz, CH_2), 4.07 (1H, dd, J = 4.5 Hz, CH_2), 4.55 (1H, dd, J = 7.3, 5.1 Hz, CH), 5.47 (1H, br, CH), 6.06 (1H, br, NH_2), 6.66 (1H, br, NH_2), 7.79 (1H, s, CH), 7.81 (1H, s, CH), 7.84 (1H, d, J = 7.6 Hz, NH), 8.26 (1H, s, CH), 8.28 (1H, s, CH), 10.80 (1H, s, OH).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = -5.6, -5.5, 4.2, 6.6, 13.5, 18.2, 23.9, 25.8, 28.3, 52.5, 54.1, 58.7, 62.5, 120.1, 126.0, 127.4, 129.4, 131.0, 134.6, 143.4, 146.7, 149.5, 151.4, 152.0, 160.1, 161.8, 165.2, 170.0, 172.1.

LC-MS (ESI) (method B): t_R = 9.7 min, calcd for $C_{36}H_{46}N_7O_8S_4Si$ $[M - H]^-$, 860.2, found: 860.2.

HRMS (FAB): Calcd for $C_{36}H_{48}N_7O_8S_4Si$ $[M + H]^+$, 862.2216, found: 862.2198.

(2'*S*, 3''*R*)-2-{4-[2-(*Tert*-butyl-dimethylsilanyloxy)-1-carbamoyl-ethylcarbamoyl]-thiazol-2-yl}-6-(2',2'-dimethyl-3'-*tert*-butoxycarbonyl-4',5'-dihydro-[2,4']bithiazolyl-4-yl)-5-(4-methoxycarbonyl-thiazol-2-yl)-3-(triisopropylsilyloxy)pyridine (285b)

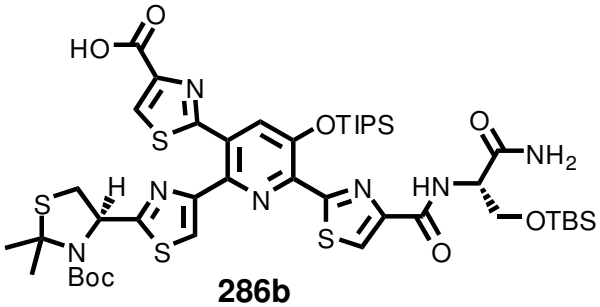


285b

TIPSOTf (8 µL, 29.8 µmol) was added to a mixture of hydroxypyridine **285** (18 mg, 20.9 µmol) and lutidine (7 µL, 60.1 µmol) in dichloromethane (2 mL) at 0°C, the reaction mixture was stirred for 1 hour at this temperature (TLC control). The reaction mixture was diluted with phosphate buffer (pH 2.0, 30 mL) and extracted with dichloromethane (3 x 30 mL). The combined extracts were dried with sodium sulfate and concentrated. Purification by column chromatography (silica gel, 20 g, dichloromethane/MeOH = 40:1) gave 14 mg (13.7 µmol, 66%) of pyridine **285b** as a colorless resin (83% based on recovered starting material).

TLC: R_f = 0.48 (dichloromethane/MeOH = 10:1).
HPLC (method A): t_R = 14.2 min.
Maldi-MS: Calcd for $C_{45}H_{68}N_7O_8S_4Si_2$ $[M + H]^+$, 1018.4, found: 1018.3.

(2'*S*, 3''*R*)-2-{4-[2-(*Tert*-butyl-dimethylsilanyloxy)-1-carbamoyl-ethylcarbamoyl]-thiazol-2-yl}-6-(2',2'-dimethyl-3'-*tert*-butoxycarbonyl-4',5'-dihydro-[2,4']bithiazolyl-4-yl)-5-(4-hydroxycarbonyl-thiazol-2-yl)-3-(triisopropylsilyloxy)pyridine (286b)



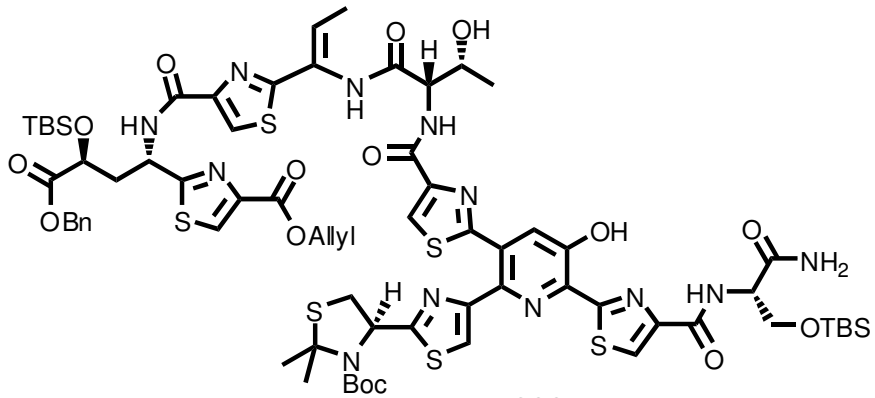
286b

TIPS pyridine **285b** (10 mg, 9.8 µmol) was dissolved in THF (3 mL) and water (0.9 mL) at 0°C, LiOH (0.5 M aqueous solution, 67 µL) was added dropwise, the reaction mixture was stirred at 0°C for 6 hours (HPLC control). 5% $NaHCO_3$ (10 mL) was added to the reaction mixture and extracted with dichloromethane (3 x 20 mL). The combined extracts were dried

with sodium sulfate and concentrated. The crude acid **286b** was directly applied to next step without purification due to its stability.

HPLC (method A): t_R = 12.8 min.
LC-MS (ESI) (method B): t_R = 10.5 min, calcd for $C_{44}H_{64}N_7O_8S_4Si_2$ [M - H]$^-$, 1002.3, found: 1002.3.

(1'S, 3'S, 2''''S, 3''''R)-2-(1-(2-((Z)-1-(2-(2-(2-(4-((S)-1-Carbamoyl-3-(triisopropylsilyloxy)propan-2-ylcarbamoyl)thiazol-2-yl)-6-(2',2'-dimethyl-3'-*tert*-butoxycarbonyl-4',5'-dihydro-[2,4']bithiazolyl-4-yl)-3-(hydroxy)pyridin-5-yl)thiazol-4-carboxamido)-3-hydroxybutanamido)prop-1-enyl)thiazol-4-carboxamido)-4-(benzyloxy)-3-(*tert*-butyldimethylsilyloxy)-4-oxobutyl)thiazol-4-carboxylic acid allyl ester (288)



288

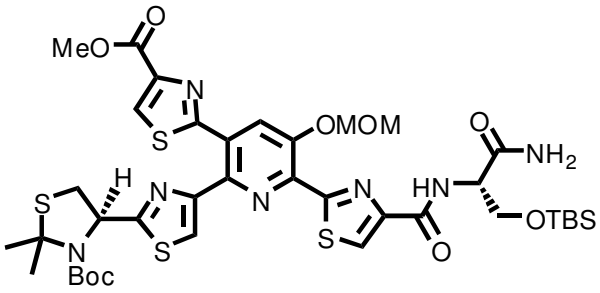
The free amine **287** (12.5 mg, 16.5 μmol) was added to the stirred solution of crude free acid **286b** (10 mg, 10 μmol) and PyBOP (10.7 mg, 20.6 μmol) in anhydrous DMF (3 mL), the reaction mixture was stirred for 17 hr at room temperature (TLC control). The reaction mixture was diluted with pH 7.0 phosphate buffer (10 mL) and extracted with dichloromethane (3 x 10 mL), the combined organic layers were dried with sodium sulfate and concentrated to dryness. Purification by column chromatography (silica gel, 20 g, dichloromethane/MeOH = 40:1) gave 6.1 mg (3.8 μmol, 39%) coupling product **288** as a yellow fluorescent foam.

TLC: R_f = 0.35 (dichloromethane/MeOH = 10:1).
HPLC (method A): t_R = 14.9 min.

LC-MS (ESI) (method B): t_R = 12.2 min, calcd for $C_{70}H_{89}N_{12}O_{15}S_6Si_2$ [M - H]$^-$, 1585.4, found: 1585.4.

Maldi-MS: Calcd for $C_{70}H_{91}N_{12}O_{15}S_6Si_2Na$ [M + H]$^+$, 1587.5, found: 1587.2.

(2'*S*, 3''*R*)-2-{4-[2-(*Tert*-butyl-dimethylsilanyloxy)-1-carbamoyl-ethylcarbamoyl]-thiazol-2-yl}-6-(2',2'-dimethyl-3'-*tert*-butoxycarbonyl-4',5'-dihydro-[2,4']bithiazolyl-4-yl)-5-(4-methoxycarbonyl-thiazol-2-yl)-3-(methoxymethoxy)pyridine (285c)



285c

Hydroxypyridine **285** (26 mg, 30 µmol) was dissolved in dichloromethane (3 mL) at 0°C, MOMCl (5 µL, 66 µmol) and DIPEA (16 µL, 92 µmol) were added subsequently. The reaction was warmed to room temperature after 1 hour and stirred for another 3 hours. The reaction mixture was quenched with water (20 mL) and extracted with dichloromethane (3 x 10 mL), the combined extracts were dried with sodium sulfate and concentrated. Purification by column chromatography (silica gel, 20 g, dichloromethane/MeOH = 30:1) gave 15.7 mg (17 µmol, 58%) of protected pyridine **285c** as a colorless resin (yield: 90% based on recovered starting material **285**: 9.4 mg).

TLC: R_f = 0.52 (dichloromethane/methanol = 10:1).

HPLC (method A): t_R = 12.6 min.

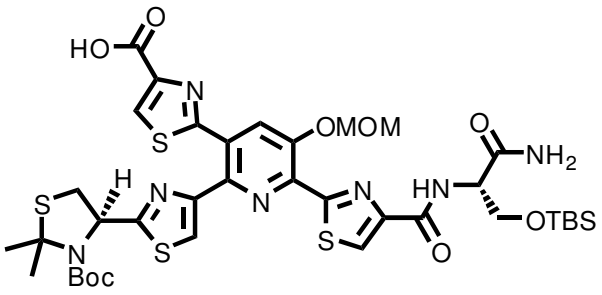
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.13 (3H, s, TBS), 0.16 (3H, s, TBS), 0.92 (9H, s, TBS), 1.25 (9H, s, *t*-Bu), 1.80 (3H, s, CH_3), 1.93 (3H, s, CH_3), 2.92 (1H, b, CH_2), 3.33 (1H, dd, J = 6.1 Hz, CH_2), 3.60 (3H, s, $CH_2O\underline{CH_3}$), 3.74 (1H, t, J = 9.4, 8.4 Hz, CH_2), 3.97 (3H, s, $COOCH_3$), 4.23 (1H, dd, J = 5.5, 4.1 Hz, CH_2), 4.63 (1H, m, CH), 5.44 (1H, b, CH), 5.52 (2H, dd, J = 19.5, 6.7 Hz, $\underline{CH_2}OCH_3$), 5.60 (1H, br, NH_2), 6.64 (1H, br, NH_2), 7.83 (1H, s, CH), 8.05 (1H, s, CH), 8.23 (1H, s, CH), 8.27 (1H, s, CH), 8.37 (1H, d, J = 6.6 Hz, NH).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = -5.5, -5.4, 4.2, 6.7, 13.5, 18.2, 19.6, 23.8, 25.7, 28.3, 29.6, 52.5, 54.3, 57.0, 62.7, 95.3, 119.2, 120.6, 122.4, 126.1, 126.4, 129.4, 129.5, 140.2, 144.6, 146.6, 149.6, 150.7, 152.1, 161.3, 161.8, 165.3, 165.4, 172.2.

LC-MS (ESI) (method A): t_R = 11.98 min, calcd for $C_{38}H_{52}N_7O_9S_4Si$ $[M + H]^+$, 906.3, found: 906.0.

Maldi-MS: Calcd for $C_{38}H_{51}N_7O_9S_4SiNa$ $[M + Na]^+$, 928.2, found: 928.5.

(2'*S*, 3''*R*)-2-{4-[2-(*Tert*-butyl-dimethylsilanyloxy)-1-carbamoyl-ethylcarbamoyl]-thiazol-2-yl}-6-(2',2'-dimethyl-3'-*tert*-butoxycarbonyl-4',5'-dihydro-[2,4']bithiazolyl-4-yl)-5-(4-hydroxycarbonyl-thiazol-2-yl)-3-(methoxymethoxy)pyridine (286c)



286c

MOM pyridine **285c** (21.2 mg, 23 μmol) was dissolved in THF (4 mL) and water (1.2 mL) at 0°C, LiOH (0.5 M aqueous solution, 140 μL) was added dropwise, the reaction mixture was stirred at 0°C for 3 hour (HPLC control). 5% $NaHCO_3$ (10 mL) was added to the reaction mixture and extracted with dichloromethane (3 x 20 mL). The combined extracts were dried with sodium sulfate and concentrated. The crude acid **286c** was directly applied to next step without purification due to its lability.

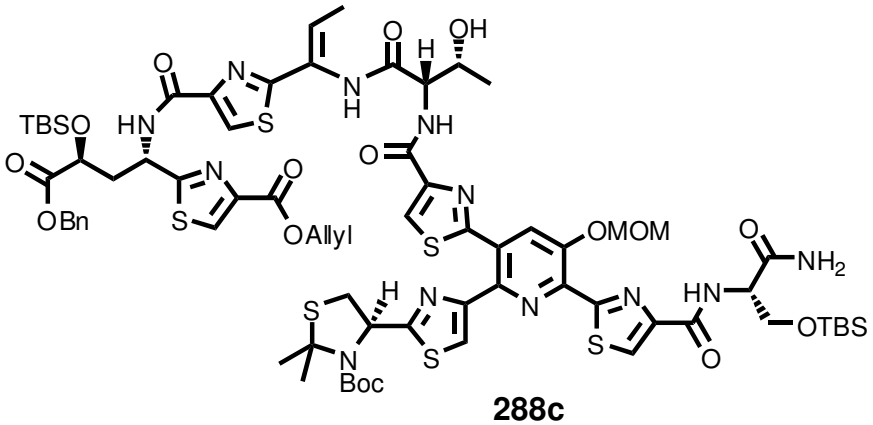
TLC: R_f = 0.11 (dichloromethane/methanol = 10:1).

HPLC (method A): t_R = 11.4 min.

LC-MS (ESI) (method A): t_R = 11.5 min, calcd for $C_{37}H_{50}N_7O_9S_4Si$ $[M + H]^+$, 892.2, found: 892.0.

(1'S,3'S,2''''S,3''''R)-2-(1-(2-((Z)-1-(2-(2-(2-(4-((S)-1-Carbamoyl-3-(triisopropylsilyloxy)propan-2-ylcarbamoyl)thiazol-2-yl)-6-(2',2'-dimethyl-3'-*tert*-butoxycarbonyl-4',5'-dihydro-[2,4']bithiazolyl-4-yl)-3-(methoxymethoxy)pyridin-5-yl)thiazol-4-carboxamido)-3-hydroxybutanamido)prop-1-enyl)thiazol-4-carboxamido)-

4-(benzyloxy)-3-(*tert*-butyldimethylsilyloxy)-4-oxobutyl)thiazol-4-carboxylic acid allyl ester (288c)



288c

Procedure A:

The free amine **287** (15.7 mg, 20.7 μmol) was added to the stirred solution of crude free acid **286c** (15.7 mg, 17.6 μmol) and PyBOP (13.5 mg, 16.5 μmol) in anhydrous DMF (3 mL), the reaction mixture was stirred for 17 hr at room temperature (TLC control). The reaction mixture was diluted with pH 7.0 phosphate buffer (10 mL) and extracted with dichloromethane (3 x 10 mL), the combined organic layers were dried with sodium sulfate and concentrated. Purification by column chromatography (silica gel, 20 g, dichloromethane/MeOH = 40:1) gave 11.3 mg (7.1 μmol) of the MOM deprotected coupling product **288** and 12.8 mg (7.8 μmol) **288c** as a colorless resin (total yield, 88%).

Procedure B:

The free amine **287** (15 mg, 19.8 μmol) was added to the stirred solution of crude free acid **286c** (23 mg, 25.8 μmol) and HATU (14.7 mg, 38.7 μmol) in anhydrous DMF (4 mL) at 0°C, the reaction mixture was slowly warmed to room temperature and stirred for 6 hr at room temperature (TLC control). The reaction mixture was diluted with phosphate buffer (pH 7.0, 10 mL) and extracted with dichloromethane (3 x 20 mL), the combined organic layers were dried with sodium sulfate and concentrated. Purification by column chromatography (silica gel, 20 g, dichloromethane/MeOH = 40:1) gave 8.1 mg (5.1 μmol) coupling product **288** and 20.8 mg (12.7 μmol) **288c** as a colorless resin (total yield, 90%).

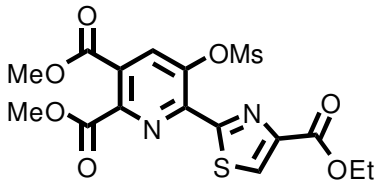
TLC: R_f = 0.54 (dichloromethane/MeOH = 10:1).

HPLC (method A): t_R = 15.8 min.

LC-MS (ESI) (method B): t_R = 12.2 min, calcd for $C_{72}H_{93}N_{12}O_{16}S_6Si_2$ [M - H]$^-$, 1629.5, found: 1629.2.

Maldi-MS: Calcd for $C_{72}H_{94}N_{12}O_{16}S_6Si_2Na$ [M + Na]$^+$, 1653.5, found: 1653.1.

2-(4'-(Ethoxycarbonyl)thiazol-2'-yl)-3-(methylsulfonyloxy)pyridine-5,6-dicarboxylic acid dimethyl ester (289b)



289b

Mesyl chloride (5.1 µL, 66 µmol) was added to pyridine **157** (20 mg, 55 µmol) and triethylamine (9 µL, 64 µmol) in dichloromethane (5 mL) at 0°C, DMAP (0.7 mg, 5.7 µmol) was added. The reaction mixture was allowed to warm to room temperature for 12 hours. The reaction mixture was quenched with phosphate buffer (20 mL) and extracted with dichloromethane (3 x 10 mL). The combined extracts were dried with sodium sulfate and concentrated. Purification by column chromatography (silica gel, 10 g, ethyl acetate/light petroleum = 1:2) gave 17 mg (38 µmol, 70%) mesylated pyridine **289b** as a colorless resin.

TLC: R_f = 0.22 (ethyl acetate/cyclohexane =1:2).

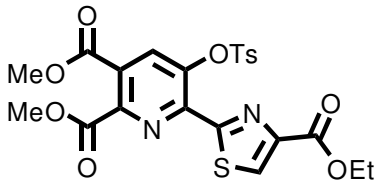
HPLC (method A): t_R = 9.4 min.

^{1}H-NMR (400 MHz, CD_3CN): δ = 1.38 (3H, t, $CH_2\underline{CH_3}$), 3.63 (3H, s, CH_3), 3.93 (3H, s, $COOCH_3$), 3.97 (3H, s, $COOCH_3$), 4.39 (2H, dd, $\underline{CH_2}CH_3$), 8.30 (1H, s, CH), 8.49 (1H, s, CH).

LC-MS (ESI) (method A): t_R = 9.28 min, calcd for $C_{16}H_{17}N_2O_9S_2$ [M + H]$^+$, 445.0, found: 445.0.

HRMS (ESI): Calcd for $C_{16}H_{17}N_2O_9S_2$ [M + H]$^+$, 445.0370, found: 445.0365.

2-(4'-(Ethoxycarbonyl)thiazol-2'-yl)-3-(tosyloxy)pyridine-5,6-dicarboxylic acid dimethyl ester (289a)

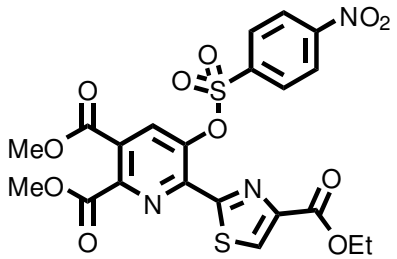


289a

Tosyl chloride (9.4 mg, 49 µmol) was added to pyridine **157** (15 mg, 41 µmol) and triethylamine (7 µL, 50 µmol) in dichloromethane (5 mL) at 0°C, DMAP (0.5 mg, 4.5 µmol) was added. The reaction mixture was allowed to warm to room temperature for 12 hours. The reaction mixture was quenched with phosphate buffer (20 mL) and extracted with dichloromethane (3 x 10 mL). The combined extracts were dried with sodium sulfate and concentrated. Purification by column chromatography (silica gel, 10 g, ethyl acetate/light petroleum = 1:2) gave 16.4 mg (32 µmol, 77%) of tosylated pyridine **289a** as a colorless resin.

TLC: R_f = 0.20 (ethyl acetate/cyclohexane =1:2).
HPLC (method A): t_R = 10.4 min.
^{1}H-NMR (400 MHz, CD_3CN): δ = 1.43 (3H, t, $CH_2\underline{CH_3}$), 2.30 (3H, s, CH_3), 3.95 (3H, s, $COOCH_3$), 3.98 (3H, s, $COOCH_3$), 4.44 (2H, dd, $\underline{CH_2}CH_3$), 7.15 (2H, d, J = 8.0 Hz, 2 x CH), 7.66 (2H, d, J = 8.2 Hz, 2 x CH), 8.32 (1H, s, CH), 8.38 (1H, s, CH).
LC-MS (ESI) (method A): t_R = 9.99 min, calcd for $C_{22}H_{21}N_2O_9S_2$ $[M + H]^+$, 521.1, found: 521.1.
HRMS (ESI): Calcd for $C_{22}H_{21}N_2O_9S_2$ $[M + H]^+$, 521.0683, found: 521.0678.

2-(4'-(Ethoxycarbonyl)thiazol-2'-yl)-3-(4-nitrophenylsulfonyloxy)pyridine-5,6-dicarboxylic acid dimethyl ester (289c)



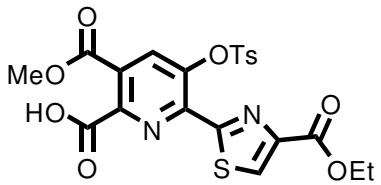
289c

p-Nitrophenylsulfonyl chloride (10.9 mg, 49 µmol) was added to pyridine **157** (15 mg, 41 µmol) and triethylamine (7 µL, 50 µmol) in dichloromethane (5 mL) at 0°C, DMAP (0.5 mg,

4.5 µmol) was added. The reaction mixture was allowed to warm to room temperature for 12 hours. The reaction mixture was quenched with phosphate buffer (20 mL) and extracted with dichloromethane (3 x 10 mL). The combined extracts were dried with sodium sulfate and concentrated. Purification by column chromatography (silica gel, 10 g, ethyl acetate/light petroleum = 1:2) gave 13.3 mg (24 µmol, 59%) of pyridine **289c** as a colorless resin.

TLC: R_f = 0.20 (ethyl acetate/cyclohexane =1:2).
HPLC (method A): t_R = 10.0 min.
^{1}H-NMR (400 MHz, CD_3CN): δ = 1.38 (3H, t, $CH_2\underline{CH_3}$), 3.93 (3H, s, $COOCH_3$), 3.97 (3H, s, $COOCH_3$), 4.38 (2H, dd, $\underline{CH_2}CH_3$), 7.73 (2H, dd, J = 7.7 Hz, 2 x CH), 7.84 (1H, t, J = 7.4 Hz, CH), 8.26 (1H, d, J = 3.9 Hz, CH), 8.28 (1H, s, CH), 8.34 (1H, s, CH).
LC-MS (ESI) (method A): t_R = 9.63 min, calcd for $C_{21}H_{18}N_3O_{11}S_2$ $[M + H]^+$, 552.0, found: 552.0.
HRMS (ESI): Calcd for $C_{21}H_{18}N_3O_{11}S_2$ $[M + H]^+$, 552.0377, found: 552.0372.

2-(4'-(Ethoxycarbonyl)thiazol-2'-yl)-3-(tosyloxy)pyridine-5-methoxycarbonyl-6-carboxylic acid (290a)

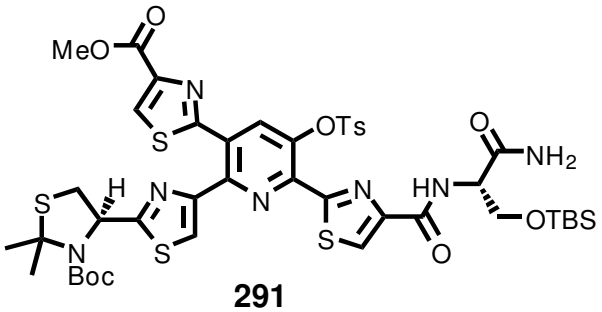


290a

The pyridine **289a** (16.4 mg, 31.5 mmol) was dissolved in THF (3 mL) and water (1 mL) at room temperature, LiOH (0.5 M, 126 µL, 63 mmol) was added dropwise. The reaction mixture was stirred for 3 hours (HPCL control). This reaction was designed to exam the regioselectivity in the hydrolysis, therefore, it was not purified and the yield was not calculated.
The exact acid position was not confirmed, but ESI-MS showed one methyl group was cleaved.

HPLC (method A): t_R = 9.2 min.
LC-MS (ESI) (method A): t_R = 9.63 min, calcd for $C_{21}H_{19}N_2O_9S_2$ $[M + H]^+$, 507.1, found: 507.0.

(2'*S*, 3''*R*)-2-{4-[2-(*Tert*-butyl-dimethylsilanyloxy)-1-carbamoyl-ethylcarbamoyl]-thiazol-2-yl}-6-(2',2'-dimethyl-3'-*tert*-butoxycarbonyl-4',5'-dihydro-[2,4']bithiazolyl-4-yl)-5-(4-methoxycarbonyl-thiazol-2-yl)-3-(tosyloxy)pyridine (291)



291

Tosyl chloride (53 mg, 0.28 mmol) was added to the mixture of hydroxypyridine **285** (200 mg, 0.23 mmol) and triethylamine (39 µL, 0.28 mmol) in dichloromethane (40 mL) at 0°C, and DMAP (3 mg, 0.02 mmol) was added after 5 min. The reaction mixture was stirred for 90 min at 0°C (TLC control), diluted with phosphate buffer (pH 2.5, 50 mL) and extracted with dichloromethane (3 x 40 mL). The combined extracts were dried with sodium sulfate and concentrated. Purification by column chromatography (silica gel, 40 g, dichloromethane/MeOH = 50:1) gave 171.9 mg (0.17 mmol, 73%) of pyridine tosylate **291** as a colorless resin.

TLC: R_f = 0.48 (dichloromethane/methanol = 10:1).

HPLC (method A): t_R = 13.3 min.

^{1}H-NMR (400 MHz, CD_3CN): δ = 0.12 (6H, s, TBS), 0.91 (9H, s, TBS), 1.27 (9H, s, *t*-Bu), 1.78 (3H, s, CH_3), 1.88 (3H, s, CH_3), 2.32 (3H, s, CH_3), 2.70 (1H, d, J = 12.1 Hz, CH_2), 3.42 (1H, dd, J = 6.1 Hz, CH_2), 3.89 (3H, s, $COOCH_3$), 3.97 (1H, dd, J = 5.7 Hz, CH_2), 4.10 (1H, dd, J = 4.4 Hz, CH_2), 4.59 (1H, m, CH), 5.48 (1H, b, CH), 5.98 (1H, b, NH_2), 6.55 (1H, b, NH_2), 7.21 (2H, d, J = 8.2 Hz, 2 x CH), 7.67 (2H, d, J = 8.4 Hz, 2 x CH), 7.98 (1H, s, CH), 8.05 (1H, s, CH), 8.03 (1H, d, J = 13.5 Hz, NH), 8.20 (1H, s, CH), 8.34 (1H, s, CH).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = -5.52, -5.50, 0.97, 4.3, 5.8, 6.7, 14.1, 18.2, 21.7, 25.7, 28.3, 29.7, 52.5, 54.8, 63.1, 122.1, 126.9, 128.3, 128.5, 129.3, 129.5, 130.0, 130.2, 132.9, 134.2, 141.5, 144.2, 146.0, 146.2, 146.8, 149.2, 151.3, 161.1, 161.5, 163.9, 164.7, 172.5.

IR (KBr): $\tilde{\nu}$ = 3439 (bw), 2926 (s), 2855 (s), 1695 (s), 1668 (s), 1651 (s), 1634 (s), 1539 (s), 1505 (s), 1470 (s), 1347 (s), 1247 (s), 1195 (s), 1177 (s), 1107 (s), 837 (m) cm^{-1}.

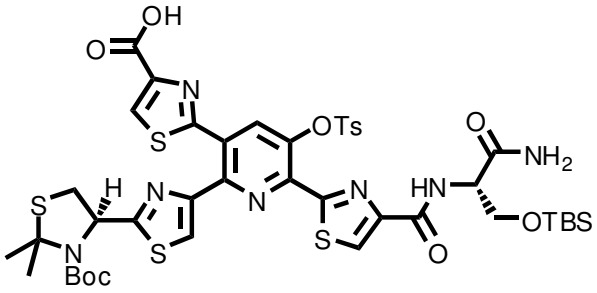
LC-MS (ESI) (method A): t_R = 12.0 min, calcd for $C_{43}H_{54}N_7O_{10}S_5Si$ $[M + H]^+$, 1016.2, found: 1016.0

Maldi-MS: Calcd for $C_{43}H_{53}N_7O_{10}S_5SiNa$ $[M + Na]^+$, 1038.2, found: 1038.0.

HRMS (ESI): Calcd for $C_{43}H_{53}N_7O_{10}S_5SiNa$ $[M + Na]^+$, 1038.2119, found: 1038.2119.

Optical rotation: $[\alpha]_D^{20}$ = - 42.4 (c = 1, $CHCl_3$).

(2'*S*, *3''R*)-2-{4-[2-(*Tert*-butyl-dimethylsilanyloxy)-1-carbamoyl-ethylcarbamoyl]-thiazol-2-yl}-6-(2',2'-dimethyl-3'-*tert*-butoxycarbonyl-4',5'-dihydro-[2,4']bithiazolyl-4-yl)-5-(4-hydroxycarbonyl-thiazol-2-yl)-3-(tosyloxy)pyridine (292)



292

Trimethyltin hydroxide (173.6 mg, 0.96 mmol) was added to a mixture of pyridine tosylate **291** (117 mg, 0.11 mmol) in 1,2-dichloroethane (10 mL). The reaction mixture was heated to 80°C for 4 hours (TLC control), cooled down to room temperature, diluted with phosphate buffer (pH 7.0, 20 mL) and extracted with ethyl acetate (3 x 40 mL). The combined extracts were dried with sodium sulfate and concentrated. Purification by C18 cartridge (CH_3CN as eluant) gave 117 mg (0.11 mmol, 100%) of acid **292** as a yellow foam.

TLC: R_f = 0.20 (dichloromethane/methanol = 10:1).

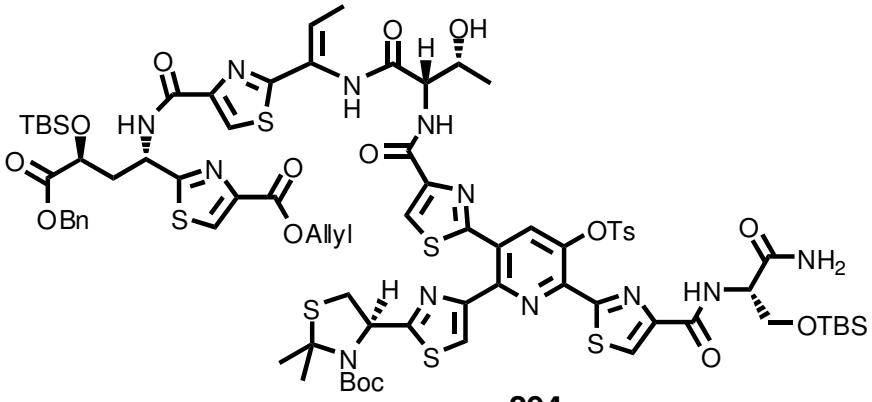
HPLC (method A): t_R = 12.1 min.

^{1}H-NMR (400 MHz, CD_3CN): δ = 0.11 (3H, s, TBS), 0.12 (3H, s, TBS), 0.91 (9H, s, TBS), 1.27 (9H, s, *t*-Bu), 1.78 (3H, s, CH_3), 1.88 (3H, s, CH_3), 2.32 (3H, s, CH_3), 2.83 (1H, d, J = 12.7 Hz, CH_2), 3.42 (1H, dd, J = 6.7 Hz, CH_2), 3.97 (1H, dd, J = 5.7 Hz, CH_2), 4.10 (1H, dd, J = 4.3 Hz, CH_2), 4.57-4.61 (1H, m, CH), 5.49 (1H, b, CH), 6.00 (1H, b, NH_2), 6.56 (1H, b, NH_2), 7.22 (2H, d, J = 8.2 Hz, 2 x CH), 7.68 (2H, d, J = 8.4 Hz, 2 x CH), 7.98 (1H, s, CH), 8.11 (1H, s, CH), 8.06 (1H, d, J = 7.4 Hz, NH), 8.21 (1H, s, CH), 8.34 (1H, s, CH).

LC-MS (ESI) (method A): t_R = 11.2 min, calcd for $C_{42}H_{52}N_7O_{10}S_5Si$ $[M + H]^+$, 1002.2, found: 1002.0.

HRMS (ESI): Calcd for $C_{42}H_{52}N_7O_{10}S_5Si$ $[M + H]^+$, 1002.2143, found: 1002.2173.

(1'S, 3'S, 2''''S, 3''''R)-2-(1-(2-((Z)-1-(2-(2-(2-(4-((S)-1-Carbamoyl-3-(triisopropylsilyloxy)propan-2-ylcarbamoyl)thiazol-2-yl)-6-(2',2'-dimethyl-3'-*tert*-butoxycarbonyl-4',5'-dihydro-[2,4']bithiazolyl-4-yl)-3-(tosyloxy)pyridin-5-yl)thiazol-4-carboxamido)-3-hydroxybutanamido)prop-1-enyl)thiazol-4-carboxamido)-4-(benzyloxy)-3-(*tert*-butyldimethylsilyloxy)-4-oxobutyl)thiazol-4-carboxylic acid allyl ester (294)



294

The free amine **287** (10.2 mg, 13 μmol) was added to a stirred solution of free acid **292** (19 mg, 19 μmol), DEPBT (22.7 mg, 76 μmol) and $NaHCO_3$ (15 mg, 0.18 mmol) in anhydrous THF (0.3 mL), the reaction mixture was stirred for 25 hr at room temperature (TLC control). The reaction mixture was diluted with pH 7.0 phosphate buffer (20 mL) and extracted with dichloromethane (3 x 30 mL). The combined organic extracts were dried with sodium sulfate and concentrated to dryness. Purification by column chromatography (silica gel, 20 g, dichloromethane/MeOH = 40:1) gave 14.7 mg (8 μmol, 63%) of the coupling product **294** as a colorless glass.

TLC: R_f = 0.55 (dichloromethane/MeOH = 10:1).
HPLC (method D): t_R = 14.6 min.
HPLC (method A): t_R = 16.0 min.
^{1}H-NMR (400 MHz, CD_3OD): δ = -0.03 (3H, s, TBS), -0.02 (3H, s, TBS), 0.13 (3H, s, TBS), 0.14 (3H, s, TBS), 0.88 (9H, s, TBS), 0.92 (9H, s, TBS), 1.35 (3H, d, J = 6.2 Hz, CH_3), 1.76 (3H, s, CH_3), 1.88 (3H, s, CH_3), 1.89 (3H, d, J = 7.0 Hz, CH_3), 2.19 (1H, dd, J = 7.4 Hz, CH_2), 2.30 (3H, s, CH_3), 2.41 (1H, d, J = 7.0 Hz, CH_2), 2.61-2.68 (1H, m, CH_2), 2.81 (1H, d,

J = 11.9 Hz, CH_2), 3.39 (1H, dd, *J* = 6.0 Hz, CH), 3.50 (1H, dd, *J* = 6.0, 1.2 Hz, CH_2), 3.62 (1H, dd, *J* = 6.8 Hz, CH_2), 4.08 (1H, dd, *J* = 4.8 Hz, CH), 4.16 (1H, dd, *J* = 4.9 Hz, CH), 4.53 (1H, dd, *J* = 4.3 Hz, CH), 5.14 (2H, d, *J* = 3.3 Hz, $\underline{CH_2}CH=CH_2$), 5.24 (1H, d, *J* = 10.4 Hz, $CH_2CH=\underline{CH_2}$), 5.36 (1H, d, *J* = 15.8 Hz, $CH_2CH=\underline{CH_2}$), 5.47 (1H, d, *J* = 5.2 Hz, CH), 5.50 (2H, s, CH_2Ph), 5.68 (1H, dd, *J* = 4.7 Hz, CH), 5.95-6.03 (1H, m, $CH_2\underline{CH}=CH_2$), 6.78 (1H, dd, *J* = 7.2 Hz, $\underline{CH}CH_3$), 7.28-7.40 (7H, m, Ph, tosyl), 7.72 (2H, d, *J* = 8.2 Hz, tosyl), 8.10 (1H, s, CH), 8.12 (1H, s, CH), 8.14 (1H, s, CH), 8.29 (1H, s, CH), 8.38 (1H, s, CH), 8.44 (1H, s, CH).

LC-MS (ESI) (method A): t_R = 13.3 min, calcd for $C_{77}H_{97}N_{12}O_{17}S_7Si_2$ $[M + H]^+$, 1741.5, found: 1741.9.

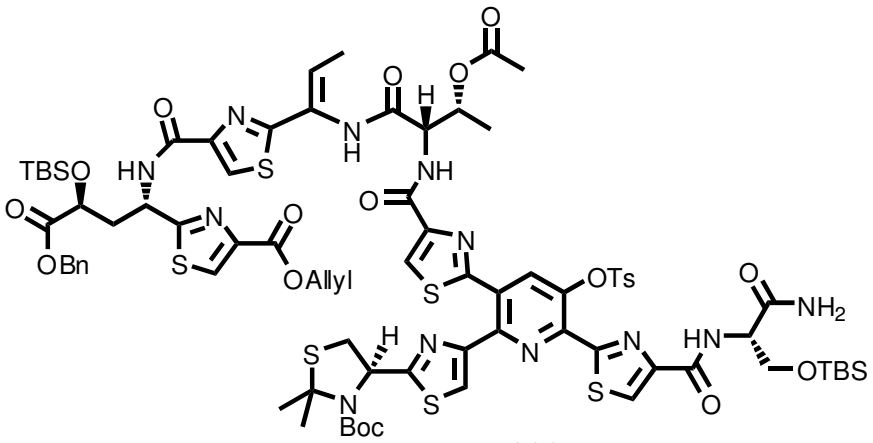
HRMS (ESI): Calcd for $C_{77}H_{97}N_{12}O_{17}S_7Si_2$ $[M + H]^+$, 1741.4673, found: 1741.4684.

MS for the side product 295:

LC-MS (ESI) (method A): t_R = 13.7 min, calcd for $C_{81}H_{105}N_{12}O_{20}S_7Si_2P$ $[M + H]^+$, 1877.5, found: 1878.0.

HRMS (ESI): Calcd for $C_{81}H_{106}N_{12}O_{20}S_7Si_2P$ $[M + H]^+$, 1878.4996, found: 1878.4986.

(1'S,3'S,2''''S,3''''R)-2-(1-(2-((Z)-1-(2-(2-(2-(4-((S)-1-Carbamoyl-3-(triisopropylsilyl-oxy)propan-2-ylcarbamoyl)thiazol-2-yl)-6-(2',2'-dimethyl-3'-*tert*-butoxycarbonyl-4',5'-dihydro-[2,4']bithiazolyl-4-yl)-3-(tosyloxy)pyridin-5-yl)thiazol-4-carboxamido)-3-acetyloxybutanamido)prop-1-enyl)thiazol-4-carboxamido)-4-(benzyloxy)-3-(*tert*-butyldimethylsilyloxy)-4-oxobutyl)thiazol-4-carboxylic acid allyl ester (300)



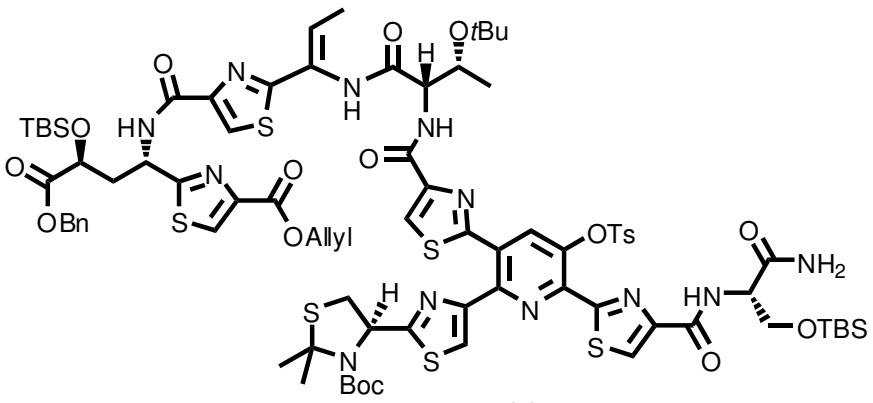
300

DMAP (0.11 mg, 0.9 µmol) was added to a mixture of pyridine **294** (15 mg, 8.6 µmol), acetic anhydride (1.2 µL, 12.7 µmol), triethylamine (1.8 µL, 12.9 µmol) in dichloromethane

(200 µL) at 0°C. The reaction mixture was stirred for 4 hours at this temperature (TLC control), quenched with phosphate buffer (pH 7.0, 10 mL) and extracted with ethyl acetate (3 x 10 mL). The combined extracts were dried with sodium sulfate and concentrated. Purification by column chromatography gave 8.2 mg (4.6 µmol, 53%) of pyridine **300** as a colorless resin.

TLC: R_f = 0.79 (dichloromethane/MeOH = 10:1).
HPLC (method B): t_R = 13.1 min.
^{1}H-NMR (400 MHz, CD_3OD): δ = -0.03 (3H, s, TBS), -0.02 (3H, s, TBS), 0.14 (3H, s, TBS), 0.15 (3H, s, TBS), 0.87 (9H, s, TBS), 0.93 (9H, s, TBS), 1.31 (3H, d, J = 3.7 Hz, CH_3), 1.31 (9H, s, *t*Bu), 1.78 (3H, s, CH_3), 1.84 (3H, d, J = 7.0 Hz, CH_3), 1.90 (3H, s, CH_3), 2.16 (1H, d, J = 7.4 Hz, CH_2), 2.32 (3H, s, CH_3), 2.59-2.68 (1H, m, CH_2), 2.83 (2H, d, J = 11.8, 3.9 Hz, CH_2), 3.43 (1H, dd, J = 6.1 Hz, CH), 3.56 (1H, dd, J = 3.9, 1.9 Hz, CH), 4.08 (1H, dd, J = 5.1 Hz, CH_2), 4.16 (4H, dd, J = 4.5 Hz, 2 x CH, CH_2), 4.54 (1H, t, J = 4.3 Hz, CH), 4.72 (2H, t, J = 4.7 Hz, $\underline{CH_2}CH{=}CH_2$), 5.14 (2H, s, CH_2Ph), 5.28 (1H, d, J = 10.6 Hz, $CH_2CH{=}\underline{CH_2}$), 5.41 (1H, dd, J = 17.2, 1.4 Hz, $CH_2CH{=}\underline{CH_2}$), 5.51 (1H, b, CH), 5.69 (1H, dd, J = 4.9 Hz, CH), 6.01-6.08 (1H, m, $CH_2\underline{CH}{=}CH_2$), 6.80 (1H, dd, J = 7.2 Hz, $\underline{CH}CH_3$), 7.26-7.38 (7H, m, Ph, tosyl), 7.72 (2H, d, J = 8.2 Hz, tosyl), 8.11 (1H, s, CH), 8.15 (1H, s, CH), 8.26 (1H, s, CH), 8.33 (1H, s, CH), 8.36 (1H, s, CH), 8.47 (1H, s, CH).
LC-MS (ESI) (method A): t_R = 11.8 min, calcd for $C_{79}H_{99}N_{12}O_{18}S_7Si_2$ $[M + H]^+$, 1783.5, found: 1783.0.

(1'S,3'S,2''''S,3''''R)-2-(1-(2-((Z)-1-(2-(2-(2-(4-((S)-1-Carbamoyl-3-(triisopropylsilyl-oxy)propan-2-ylcarbamoyl)thiazol-2-yl)-6-(2',2'-dimethyl-3'-*tert*-butoxycarbonyl-4',5'-dihydro-[2,4']bithiazolyl-4-yl)-3-(tosyloxy)pyridin-5-yl)thiazol-4-carboxamido)-3-*tert*-butoxybutanamido)prop-1-enyl)thiazol-4-carboxamido)-4-(benzyloxy)-3-(*tert*-butyldimethylsilyloxy)-4-oxobutyl)thiazol-4-carboxylic acid allyl ester (301)



301

The free amine **279** (9 mg, 11 µmol) was added to the stirred solution of free acid **292** (13.3 mg, 13.3 µmol), DEPBT (15 mg, 0.05 mmol) and $NaHCO_3$ (10 mg, 0.12 mmol) in anhydrous THF (0.3 mL). The reaction mixture was stirred for 16 hr at room temperature (TLC control), then diluted with phosphate buffer (pH 7.0, 20 mL) and extracted with dichloromethane (3 x 30 mL). The combined organic layers were dried with sodium sulfate and concentrated. Purification by column chromatography (silica gel, 20 g, dichloromethane/MeOH = 40:1) gave 17.2 mg (10 µmol, 87%) of the coupling product **301** as a colorless glass.

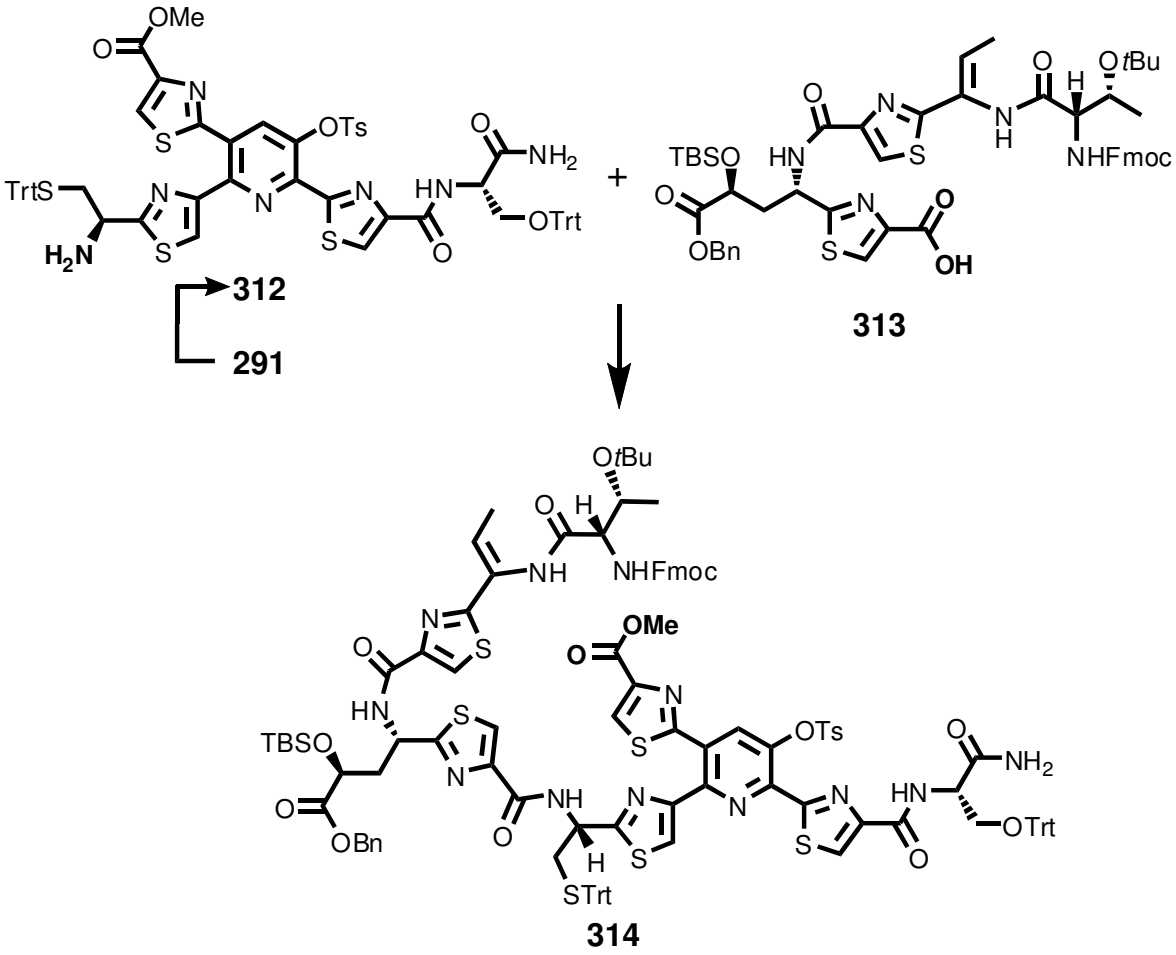
TLC: R_f = 0.46 (dichloromethane/MeOH = 10:1).

HPLC (method B): t_R = 17.2 min.

^{1}H-NMR (400 MHz, CD_3OD): δ = -0.03 (3H, s, TBS), -0.01 (3H, s, TBS), 0.14 (3H, s, TBS), 0.15 (3H, s, TBS), 0.87 (9H, s, TBS), 0.93 (9H, s, TBS), 1.25 (3H, d, J = 3.3 Hz, CH_3), 1.32 (9H, s, *t*Bu), 1.76 (3H, s, CH_3), 1.90 (3H, s, CH_3), 1.91 (3H, d, J = 7.0 Hz, CH_3), 2.15 (1H, d, J = 7.4 Hz, CH_2), 2.32 (3H, s, CH_3), 2.59-2.70 (1H, m, CH_2), 2.79 (1H, d, J = 12.3 Hz, CH_2), 3.38 (1H, dd, J = 6.0 Hz, CH), 4.08 (1H, dd, J = 5.5, 4.9 Hz, CH_2), 4.17 (1H, dd, J = 4.7 Hz, CH_2), 4.30 (1H, dd, J = 6.8, 2.9 Hz, CH), 4.39 (1H, dd, J = 3.9 Hz, CH), 4.53 (1H, t, J = 4.3 Hz, CH), 4.69 (2H, dt, J = 4.7, 3.9 Hz, $\underline{CH_2}CH=CH_2$), 5.12 (2H, s, CH_2Ph), 5.28 (1H, d, J = 10.6 Hz, $CH_2CH=\underline{CH_2}$), 5.41 (1H, dd, J = 17.2, 1.4 Hz, $CH_2CH=\underline{CH_2}$), 5.48 (1H, b, CH), 5.70 (1H, dd, J = 4.7 Hz, CH), 5.99-6.09 (1H, m, $CH_2\underline{CH}=CH_2$), 6.77 (1H, dd, J = 7.0 Hz, $\underline{CH}CH_3$), 7.26-7.37 (7H, m, Ph, tosyl), 7.70 (2H, d, J = 8.2 Hz, tosyl), 8.09 (1H, s, CH), 8.14 (1H, s, CH), 8.18 (1H, s, CH), 8.32 (1H, s, CH), 8.36 (1H, s, CH), 8.46 (1H, s, CH).

LC-MS (ESI) (method A): t_R = 12.5 min, calcd for $C_{81}H_{105}N_{12}O_{17}S_7Si_2$ $[M + H]^+$, 1797.5, found: 1798.8.

(1'S, 3'S, 2''''S, 3''''R)-N-(1-tritylsulfanyl-ethyl)-{2-{4-[2-(trityloxy)-1-carbamoyl-ethylcarbamoyl]-thiazol-2-yl}-5-(4-methoxycarbonyl-thiazol-2-yl)-3-(tosyloxypyridin-6-yl)}-1-thiazol-2-yl 2-(1-(2-((Z)-1-(2-(((9H-Fluoren-9-yl)methoxy)carbonylamino)-3-*tert*-butoxybutanamido)prop-1-enyl)thiazol-4-carboxamido)-3-(*tert*-butyldimethylsilyloxy)-4-(4-methoxybenzyloxy)-4-oxobutyl)thiazol-4-carboxamide (314)



TFA (0.6 mL) and Et_3SiH (0.4 mL) were added to ketal protected pyridine **291** (9 mg, 8.9 µmol) in dichloromethane (3 mL), the resulting reaction mixture was stirred for 90 min (TLC control). After removal of the volatile, the crude pyridine **310** was directly used in next step.

TLC: R_f = 0.26 (dichloromethane/MeOH = 10:1).

HPLC (method D): t_R = 7.9 min.

LC-MS (ESI) (method A): t_R = 6.4 min, calcd for $C_{29}H_{28}N_7O_8S_5$ $[M + H]^+$, 762.1, found: 761.9.

Maldi-MS: Calcd for $C_{29}H_{28}N_7O_8S_5$ $[M + H]^+$, 762.1, found: 762.1.

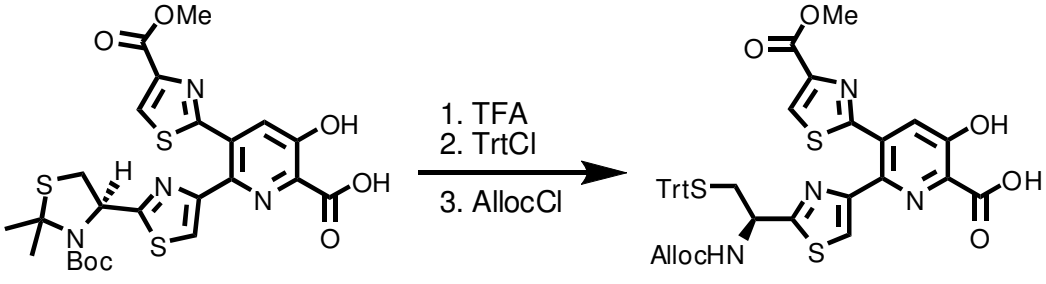
The crude **310** and trityl chloride (3.7 mg, 12.3 µmol) was dissolved in DMF (500 µL), the reaction mixture was stirred for 48 hours. After removal of DMF, the resulting residue was purified by column chromatography (silica gel, 10 g, dichloromethane/MeOH = 30:1) to give 4.2 mg (3.4 µmol, 38% (for 2 steps)) free amine **312** as a colorless glass.

TLC: R_f = 0.46 (dichloromethane/MeOH = 10:1).
HPLC (method D): t_R = 9.9 min.
LC-MS (ESI) (method A): t_R = 9.3 min, calcd for $C_{67}H_{55}N_7O_8S_5Na$ $[M + Na]^+$, 1268.3, found: 1267.9.
Maldi-MS: Calcd for $C_{67}H_{55}N_7O_8S_5Na$ $[M + Na]^+$, 1268.3, found: 1267.9.

The free amine **312** (7.9 mg, 6.3 µmol) was added to the stirred solution of free acid **313** (6.3 mg, 6.3 µmol), DEPBT (7.6 mg, 25.4 µmol) and $NaHCO_3$ (5.1 mg, 60.7 µmol) in anhydrous THF (400 µL), the reaction mixture was stirred for 12 hr at room temperature (TLC control). The reaction mixture was diluted with phosphate buffer (pH 7.0, 10 mL) and extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried with sodium sulfate and concentrated. Purification by column chromatography (silica gel, 10 g, dichloromethane/MeOH = 30:1) gave the coupling product **314** 7.5 mg (3.4 µmol, 54%) as a colorless glass.

TLC: R_f = 0.73 (dichloromethane/MeOH = 10:1).
HPLC (method D): t_R = 18.5 min.
Maldi-MS: Calcd for $C_{118}H_{115}N_{12}O_{17}S_7Si$ $[M + H]^+$, 2223.6, found: 2223.2.

(*R*)-6-[2-(1'-Allyoxycarbonylamino-2'-tritylsulfanyl-ethyl)-thiazol-4-yl]-5-(4-methoxycarbonyl-thiazol-2-yl)-3-hydroxypyridine-2-carboxylic acid (258)



283 **258**

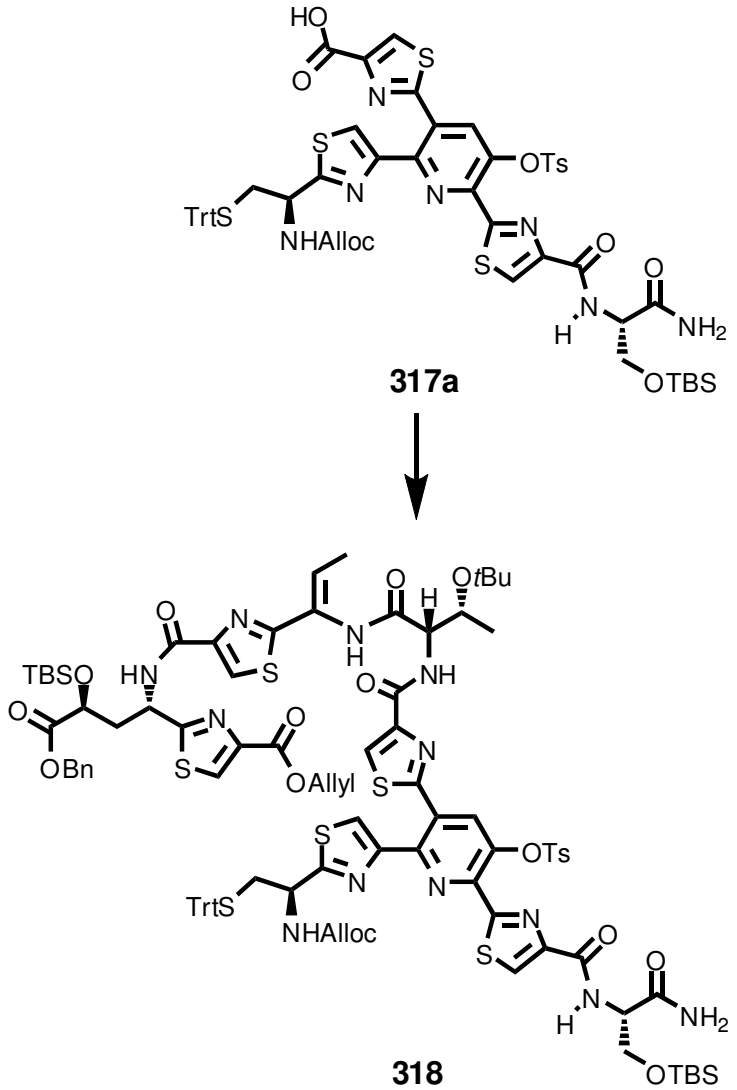
TFA (13 mL) and triethysilane (1 mL) was added dropwise to a solution of hydroxypyridine acid **283** (480 mg, 0.8 mmol) in dichloromethane (13 mL) with stirring. The reaction mixture was stirred for 30 min (HPLC control). The solvent was removed under high vacuum and the residue was directly used in next step without purification.

The above residue was dissolved in DMF (20 mL), and trityl chloride (0.69 g, 2.5 mmol) was added. The reaction mixture was stirred for 14 hours (HPLC control). DMF was removed under reduced pressure. The residue was triturated with *n*-hexane (3 x 10 mL) to remove excess trityl chloride. The resulting amine **316** was pure enough for the next step.

The amine **316** was dissolved in THF (20 mL) and water (4 mL), the reaction mixture was cooled down to 0°C, and $NaHCO_3$ (140 mg, 1.7 mmol) was added. Allyl chloroformate (89 µL, 0.8 mmol) was added dropwise. The reaction mixture was stirred at 0°C for 1h. Another portion of $NaHCO_3$ (140 mg, 1.7 mmol) and ally chloroformate (89 µL, 0.8 mmol) was added. The reaction mixture was stirred for 1 hour (HPLC control). The reaction mixture was diluted with phosphate buffer (pH 2.5, 100 mL) and extracted with ethyl acetate (3 x 50 mL). The combined extracts were dried with sodium sulfate and concentrated. Purification by column chromatography (silica gel, 40 g, dichloromethane/EtOH = 30:1) gave 634 mg (0.8 mmol, 82% over 3 steps) of hydroxypyridine acid **258** as a light yellow foam.

TLC: R_f = 0.18 (dichloromethane/MeOH = 10:1).
HPLC (method A): t_R = 11.5 min.
^{1}H-NMR (400 MHz, DMSO): δ = 2.00 (1H, dd, *J* = 7.9 Hz, CH_2), 2.69 (1H, t, *J* = 9.5 Hz, CH_2), 3.83 (3H, s, $COOCH_3$), 4.32-4.39 (1H, m, CH), 4.48 (2H, d, *J* = 3.8 Hz, $CH_2CH{=}CH_2$), 5.17 (1H, d, *J* = 10.5 Hz, $CH{=}CH_2$), 5.28 (1H, d, *J* = 17.4 Hz, $CH{=}CH_2$), 5.85-5.95 (1H, m, $CH{=}CH_2$), 7.22-7.32 (15H, m, trityl), 7.45 (1H, s, CH), 7.69 (1H, s, CH), 8.03 (1H, d, *J* = 7.3 Hz, NH), 8.22 (1H, s, CH).
IR (KBr): $\tilde{\nu}$ = 3392 (b), 2958 (s), 2927 (s), 2856 (s), 1729 (s), 1681 (s), 1644 (s), 1441 (s), 1417 (s), 1384 (s), 1246 (s), 751 (s) cm^{-1}.
LC-MS (ESI) (method A): t_R = 11.99 min, calcd for $C_{39}H_{32}N_4O_7S_3Na$ $[M + Na]^+$, 787.1, found: 787.0.
HRMS (ESI): Calcd for $C_{39}H_{32}N_4O_7S_3Na$ $[M + Na]^+$, 787.1325, found: 787.1325.
Optical rotation: $[\alpha]_D^{20}$ = - 26.3 (c = 0.08, $CHCl_3$).

(1'S,3'S,2''''S,3''''R)-2-(1-(2-((Z)-1-(2-(2-(2-(4-((S)-1-Carbamoyl-3-(triisopropylsilyl-oxy)propan-2-ylcarbamoyl)thiazol-2-yl)-6-(2-((S)-1-amino-2-(tritylthio)ethyl)thiazol-4-yl)-3-(tosyloxy)pyridin-5-yl)thiazol-4-carboxamido)-3-*tert*-butoxybutanamido)prop-1-enyl)thiazol-4-carboxamido)-4-(benzyloxy)-3-(*tert*-butyldimethylsilyloxy)-4-oxobutyl)thiazol-4-carboxylic acid allyl ester (318)



The free amine **279** (23 mg, 28 μmol) was added to a stirred solution of free acid **317a** (34 mg, 29 μmol), DEPBT (54 mg, 0.18 mmol) and $NaHCO_3$ (30 mg, 0.36 mmol) in anhydrous THF (0.5 mL). The reaction mixture was stirred for 19 hours at ambient temperature (TLC control). The reaction mixture was diluted with phosphate buffer (pH 7.0, 20 mL), extracted with dichloromethane (3 x 30 mL). The combined organic layers were dried with sodium sulfate

and concentrated. Purification by preparative HPLC (method C) gave 21.4 mg (11 μmol, 38%) of the coupling product **318** as a colorless glass.

TLC: R_f = 0.28 (dichloromethane/MeOH = 10:1).

HPLC (method B): t_R = 16.6 min.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = -0.04 (3H, s, TBS), -0.02 (3H, s, TBS), 0.11 (3H, s, TBS), 0.12 (3H, s, TBS), 0.85 (9H, s, TBS), 0.91 (9H, s, TBS), 1.20 (3H, d, J = 6.2 Hz, CH_3), 1.39 (9H, s, *t*Bu), 1.89 (3H, d, J = 7.2 Hz, CH_3), 2.27 (3H, s, CH_3), 2.66 (3H, dd, J = 8.0, 5.2 Hz, CH, CH_2), 2.80 (1H, b, CH), 3.93 (1H, dd, J = 6.0, 3.7 Hz, CH_2), 4.20 (1H, dd, J = 4.1, 3.7 Hz, CH_2), 4.47 (1H, dd,, J = 4.9, 2.9 Hz, CH), 4.44-4.52 (4H, m, 2 x $\underline{CH_2}CH=CH_2$), 4.66 (1H, t, J = 4.6 Hz, CH), 4.76 (1H, t, J = 4.2 Hz, CH), 4.81 (2H, s, CH_2Ph), 5.09 (2H, d, J =8.2 Hz, CH_2), 5.19 (1H, s, NH_2), 5.26 (2H, dd, J = 10.4, 1.3 Hz, $CH_2CH=\underline{CH_2}$), 5.37 (2H, dd, J = 17.2, 1.4 Hz, $CH_2CH=\underline{CH_2}$), 5.55 (1H, s, NH_2), 5.73 (1H, dd, J = 5.3, 3.3 Hz, CH), 5.84-5.92 (1H, m, $CH_2\underline{CH}=CH_2$), 5.94-6.04 (1H, m, $CH_2\underline{CH}=CH_2$), 6.74 (1H, dd, J = 7.2 Hz, $\underline{CH}CH_3$), 7.18-7.36 (22H, m, trityl, Ph, tosyl), 7.79 (2H, d, J = 8.2 Hz, tosyl), 7.83 (1H, s, CH), 7.98 (1H, d, J = 8.8 Hz, NH), 8.03 (1H, s, CH), 8.08 (1H, s, CH), 8.09 (1H, s, CH), 8.12 (1H, d, J = 8.6 Hz, NH), 8.14 (1H, d, J =9.0 Hz, NH), 8.28 (1H, s, CH), 8.46 (1H, d, J = 8.2 Hz, NH), 8.73 (1H, s, CH), 8.83 (1H, s, NH).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = -5.5, -5.0, 1.0, 14.1, 17.4, 18.1, 18.3, 21.6, 25.7, 25.8, 28.3, 29.3, 39.1, 47.7, 54.8, 57.8, 63.1, 65.89, 65.95, 66.4, 66.9, 67.6, 69.3, 76.3, 77.2, 117.9, 118.8, 122.1, 122.2, 123.5, 126.1, 126.4, 126.9, 127.2, 127.68, 127.74, 127.9, 128.0, 128.1, 128.2, 128.3, 128.4, 128.5, 128.6, 129.5, 129.6, 129.7, 129.9, 130.2, 131.8, 132.5, 132.6, 133.0, 135.3, 141.9, 144.1, 144.3, 146.0, 146.8, 148.4, 148.9, 149.5, 151.4, 151.7, 154.95, 155.0, 160.5, 160.58, 160.60, 160.8, 161.1, 163.0, 164.6, 168.1, 170.5, 170.8, 171.7, 172.5, 172.7.

IR (KBr): $\tilde{\nu}$ = 3399 (b), 2927 (s), 2855 (s), 1719 (s), 1671 (s), 1559 (s), 1533 (s), 1509 (s), 1474 (s), 1259 (s), 1196 (s), 1103 (s), 839 (s) cm^{-1}.

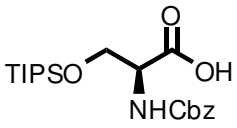
Maldi-MS: Calcd for $C_{96}H_{110}N_{12}O_{17}S_7Si_2Na$ $[M + Na]^+$, 2005.6, found: 2006.0.

LC-MS (ESI) (method A): t_R = 12.4 min, calcd for $C_{96}H_{111}N_{12}O_{17}S_7Si_2$ $[M + H]^+$, 1983.6, found: 1982.7.

HRMS (ESI): Calcd for $C_{96}H_{111}N_{12}O_{17}S_7Si_2$ $[M + H]^+$, 1983.5768, found: 1983.5779.

Optical rotation: $[\alpha]_D^{20}$ = + 8.8 (c = 0.17, $CHCl_3$).

(*S*)-2-(Benzyloxycarbonylamino)-3-(triisopropylsilyloxy)propanoic acid (324a)



324a

The same procedure as the preparation of acid **267** was used. Cbz-serine **324** (10.17 g, 42.6 mmol) yielded 12.2 g (30.9 mmol, 73%) of acid **324a** as a colorless glass.

TLC: R_f = 0.34 (dichloromethane/MeOH = 10:1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.02-1.04 (21H, TIPS), 3.94 (1H, t, J = 5.8, 3.5Hz, -CH-), 4.24 (1H, d, J = 9.4 Hz, -CH_2-), 4.46 (1H, b, -CH_2-), 5.13 (2H, s, Cbz), 5.61 (1H, d, J = 7.6 Hz, NH), 7.36 (5H, s, Ph).

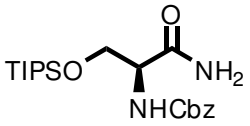
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 11.8 (TIPS), 17.8 (TIPS), 55.5 (CH), 63.7 ($\underline{C}H_2$Ph), 67.2 (-CH_2-), 128.1 (Ph), 128.2 (Ph), 128.5 (Ph), 136.1 (Ph), 156.0 (Cbz), 174.5 (COOH).

IR (KBr): $\tilde{\nu}$ = 3443 (b), 2944 (bs), 2867 (s), 1729 (s), 1505 (s), 1213 (s), 883 (s) cm^{-1}.

Optical rotation: $[\alpha]_D^{20}$ = - 32.7 (c = 0.3, $CHCl_3$).

HRMS (ESI): Calcd for $C_{20}H_{34}NO_5Si$ $[M + H]^+$, 396.2201, found: 396.2193.

(*S*)-2-(Benzyloxycarbonylamino)-3-(triisoproylsilyloxy)-propanamide (325)



325

The same procedure as the preparation of amide **268** was used. Serine acid **324a** (12.2 g, 30.9 mmol) yielded 9.52 g (24.2 mmol, 78%) of amide **325** as a colorless glass.

TLC: R_f = 0.31 (ethyl acetate/light petroleum = 1:1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.06 (21H, TIPS), 3.73 (1H, t, J = 7.8, 9.2Hz, -CH-), 4.14 (1H, d, J = 6.2 Hz, -CH_2-), 4.24 (1H, b, -CH_2-), 5.12 (2H, s, Cbz), 5.74 (1H, s, NH), 5.91 (1H, s, NH), 6.58 (1H, s, NH), 7.30-7.35 (5H, m, Ph).

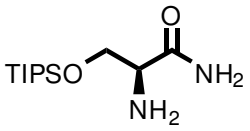
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 11.7, 17.8, 55.5, 63.4, 67.0, 128.1, 128.2, 128.5, 136.1, 156.0, 172.6.

IR (KBr): $\tilde{\nu}$ = 3437 (s), 3294 (b), 2942 (b), 2865 (s), 1695 (s), 1668 (s), 1539 (s), 1128 (s), 883 (s), 680 (s) cm^{-1}.

Optical rotation: $[\alpha]_D^{20}$ = + 39.3 (c = 1.5, $CHCl_3$).

HRMS (ESI): Calcd for $C_{20}H_{35}N_2O_4Si$ $[M + H]^+$, 395.2361, found: 395.2355.

(*S*)-2-Amino-3-(triisoproylsilyloxy)-propanamide (326a)



326a

The same procedure as the preparation of amine **269** was used. Serine amide **325** (11.0 g, 27.9 mmol) yielded 7.25 g (27.9 mmol, 99%) of amine **326a** as a colorless sticky oil.

TLC: R_f = 0.09 (dichloromethane/MeOH = 10:1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.02 (21H, TIPS), 3.44 (1H, t, J = 5.7Hz, -CH-), 3.84 (2H, dd, J = 2.5, 3.5 Hz, -CH_2-), 6.34 (1H, s, NH), 7.19 (1H, s, NH).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 11.8, 17.8, 56.6, 65.5, 176.2.

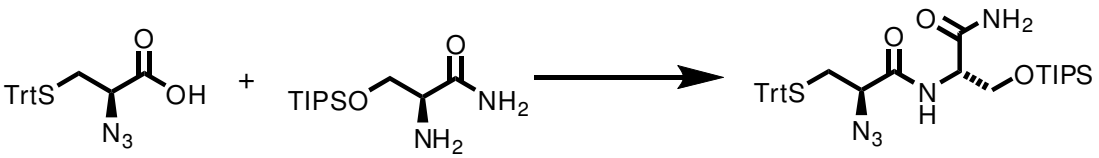
IR (KBr): $\tilde{\nu}$ = 3388 (s), 3183 (b), 2943 (b), 2866 (s), 1681 (s), 1591 (s), 1463(s), 1112 (s), 882 (s), 680 (s) cm^{-1}.

Optical rotation: $[\alpha]_D^{20}$ = - 7.3 (c = 1.1, $CHCl_3$).

LC-MS (method C): t_R = 7.88 min, calcd for $C_{12}H_{29}N_2O_2Si$ $[M + H]^+$, 261.2, found: 260.9.

HRMS (ESI): Calcd for $C_{12}H_{29}N_2O_2Si$ $[M + H]^+$, 261.1993, found: 261.1993.

(2S, 2'*R*)-2-(2'-Azido-3'-tritylthiopropyl)amido-3-triisopropylsilyloxypropanamide (326).



271 **326a** **326**

The same procedure as the preparation of dipeptide **272** was used. Amine **326a** (7.48 g, 28.8 mmol) yielded 14.06 g (22.3 mmol, 77%) of dipeptide **326** as a colorless foam.

TLC: R_f = 0.47 (ethyl acetate/light petroleum = 1:1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.04-1.07 (21H, TIPS), 2.71 (1H, dd, J = 7.2 Hz, -CH_2-), 2.81 (1H, dd, J = 5.4 Hz, -CH_2-), 3.09 (1H, dd, J = 5.5 Hz, CH), 3.65 (1H, dd, J = 8.0Hz, CH_2OTIPS), 4.10 (1H, dd, J = 3.9 Hz, CH_2OTIPS), 4.33-4.38(1H, m, $\underline{CH}CONH_2$), 5.59 (1H, s, $CONH_2$), 6.51 (1H, s, $CONH_2$), 6.95 (1H, d, J = 6.7 Hz, NH), 7.21-7.46 (15H, m, trityl).

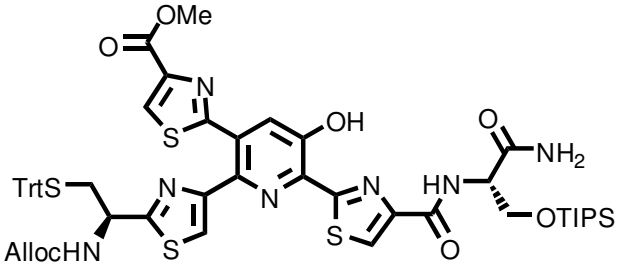
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 11.7, 17.8 (TIPS), 34.4 (-CH_2-), 54.0 ($\underline{CH}CONH_2$), 62.3 (CH), 62.7 ($\underline{C}H_2$OTIPS), 67.1 ($\underline{C}Ph_3$), 126.9 (Ph), 128.1 (Ph), 129.5 (Ph), 144.2 (Ph), 167.9 (CONH), 172.0 ($CONH_2$).

IR (KBr): $\tilde{\nu}$ = 3397 (bw), 3061 (m), 2944 (s), 2868 (s), 2116 (s), 1673 (s), 1506 (s), 882 (s) cm^{-1}.

Optical rotation: $[\alpha]_D^{20}$ = + 61.5 (c = 0.6, $CHCl_3$).

HRMS (ESI): Calcd for $C_{34}H_{45}N_5O_3SSiNa$ $[M + Na]^+$, 654.2905, found: 654.2901.

(2'*S, 1''R*)-2-{4-[2-(Trisisopropylsilanyloxy)-1-carbamoyl-ethylcarbamoyl]-thiazol-2-yl}-5-(4-methoxycarbonyl-thiazol-2-yl)-6-(2-[2-(1-allyloxycaronylamino-2-tritylsulfanyl-ethyl)-thiazol-5-yl]-3-hydroxypyridine (327)



327

The same procedure as the preparation of hydroxypyridine **277** was used. Hydroxypyridine **258** (229 mg, 0.30 mmol) yielded 150 mg (0.14 mmol, 46%) of hydroxypyridine **327** as a light yellow foam.

TLC: R_f = 0.54 (dichloromethane/MeOH =10:1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.09-1.26 (21H, TIPS), 2.20 (1H, dd, J = 7.7 Hz, CH_2), 2.61 (1H, dd, J = 5.7 Hz, CH_2), 3.85 (1H, t, J = 8.2 Hz, CH), 3.96 (3H, s, $COOCH_3$), 4.34 (1H, dd, J = 3.9 Hz, CH), 4.53 (2H, d, J = 5.3 Hz, $\underline{CH_2}$OTIPS), 4.63-4.68 (2H, m, $\underline{CH_2}CH{=}CH_2$), 5.11 (1H, d, J = 7.4 Hz, CH=$\underline{CH_2}$), 5.23 (1H, d, J = 10.4 Hz, CH=$\underline{CH_2}$), 5.56 (1H, b, NH_2), 5.90 (1H, dd, J = 4.3 Hz, $\underline{CH}{=}CH_2$), 6.68 (1H, b, NH_2), 7.19-7.37 (15H, m, trityl), 7.72 (1H, s,

CH), 7.83 (1H, d, *J* = 6.5 Hz, NH), 7.93 (1H, s, CH), 8.06 (1H, s, CH), 8.29 (1H, s, CH), 10.72 (1H, s, OH).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 11.8, 17.9, 22.7, 25.5, 27.2, 31.9, 35.9, 37.0, 52.5, 54.2, 62.9, 65.9, 77.2, 117.9, 126.1, 126.9, 127.6, 128.1, 129.4, 129.6, 129.7, 130.0, 131.1, 134.6, 143.1, 144.4, 149.5, 151.5, 160.1, 161.7, 165.0, 170.0, 171.9.

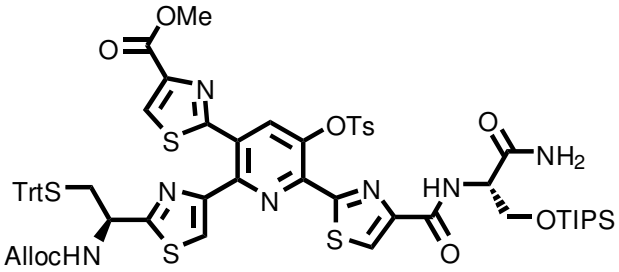
IR (KBr): $\tilde{\nu}$ = 3421 (b), 3059 (w), 2927 (s), 2864 (s), 1724 (s), 1664 (s), 1535 (s), 1492 (s), 1245 (s), 1105 (s), 746 (s), 724 (s) cm^{-1}.

LC-MS (ESI) (method A): t_R = 11.89 min, calcd for $C_{54}H_{60}N_7O_8S_4Si$ $[M + H]^+$, 1090.3, found: 1089.5.

HRMS (ESI): Calcd for $C_{54}H_{59}N_7O_8S_4SiNa$ $[M + Na]^+$, 1112.2969, found: 1112.2967.

Optical rotation: $[\alpha]_D^{20}$ = + 12.8 (c = 0.6, $CHCl_3$).

(2'*S, 1''R*)-2-{4-[2-(Trisisopropylsilanyloxy)-1-carbamoyl-ethylcarbamoyl]-thiazol-2-yl}-5-(4-methoxycarbonyl-thiazol-2-yl)-6-(2-[2-(1-allyloxycaronylamino-2-tritylsulfanyl-ethyl)-thiazol-5-yl]-3-(tosyloxy)-pyridine (327a)



327a

The same procedure as the preparation of pyridine **291** was used. Hydroxypyridine **327** (180 mg, 0.17 mmol) yielded 100 mg (0.08 mmol, 49%) of pyridine tosylate **327a** as a colorless glass.

TLC: R_f = 0.61 (dichloromethane/MeOH = 10:1).

^{1}H-NMR (400 MHz, CD_3CN): δ = 1.08-1.18 (21H, TIPS), 2.32 (3H, s, CH_3), 2.57 (1H, dd, *J* = 5.5 Hz, CH_2), 2.69 (1H, dd, *J* = 8.4 Hz, CH_2), 3.89 (3H, s, $COOCH_3$), 4.03 (1H, dd, *J* = 6.0 Hz, CH), 4.18 (1H, dd, *J* = 4.5 Hz, CH), 4.50 (2H, d, *J* = 5.3 Hz, $\underline{CH_2}$OTIPS), 4.45-4.63 (2H, m, $\underline{CH_2}CH=CH_2$), 5.19 (1H, d, *J* = 10.3 Hz, $CH=\underline{CH_2}$), 5.29 (1H, d, *J* = 17.0 Hz, $CH=\underline{CH_2}$), 5.90 (1H, dd, *J* = 5.7 Hz, $\underline{CH}=CH_2$), 6.00 (1H, b, NH_2), 6.59 (1H, b, NH_2),

7.20-7.36 (17H, m, trityl, Ph), 7.67 (2H, d, *J* = 8.2 Hz, CH), 7.95 (1H, s, CH), 8.05 (1H, d, NH), 8.069 (1H, s, CH), 8.072 (1H, s, CH), 8.19 (1H, s, CH).

^{13}C-NMR (100.6 MHz, CD_3CN): δ = 12.7, 18.3, 21.6, 30.3, 36.7, 52.8, 53.5, 55.2, 55.7, 64.6, 66.2, 68.0, 117.6, 123.8, 127.8, 127.9, 129.0, 129.3, 130.3, 130.7, 130.8, 130.9, 131.5, 132.8, 134.1, 136.0, 142.5, 144.3, 145.5, 147.4, 147.5, 150.0, 152.3, 161.2, 162.3, 164.0, 165.3, 172.6.

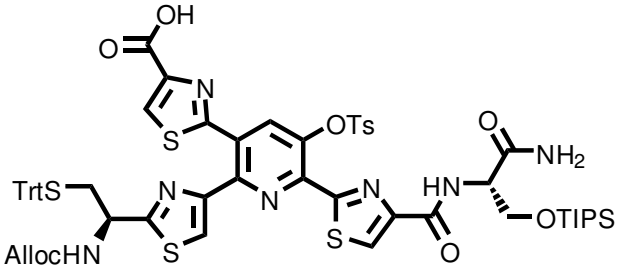
IR (KBr): $\tilde{\nu}$ = 3057 (m), 2927 (s), 2866 (s), 1969 (w), 1897 (w), 1686 (s), 1595 (s), 1465 (s), 1246 (s), 1178 (s), 1119 (s), 922 (s), 748 (s), 722 (s) cm^{-1}.

Optical rotation: $[\alpha]_D^{20}$ = - 12.7 (c = 0.3, $CHCl_3$).

LC-MS (ESI) (method C): t_R = 11.9 min, calcd for $C_{61}H_{66}N_7O_{10}S_5Si$ $[M + H]^+$, 1244.3, found: 1243.6.

HRMS (ESI): Calcd for $C_{61}H_{66}N_7O_{10}S_5Si$ $[M + H]^+$, 1244.3239, found: 1244.3257.

(2'*S, 1''R*)-2-{4-[2-(Trisisopropylsilanyloxy)-1-carbamoyl-ethylcarbamoyl]-thiazol-2-yl}-5-(4-hydroxycarbonyl-thiazol-2-yl)-6-(2-[2-(1-allyloxycaronylamino-2-tritylsulfanyl-ethyl)-thiazol-5-yl]-3-(tosyloxy)-pyridine (328)



328

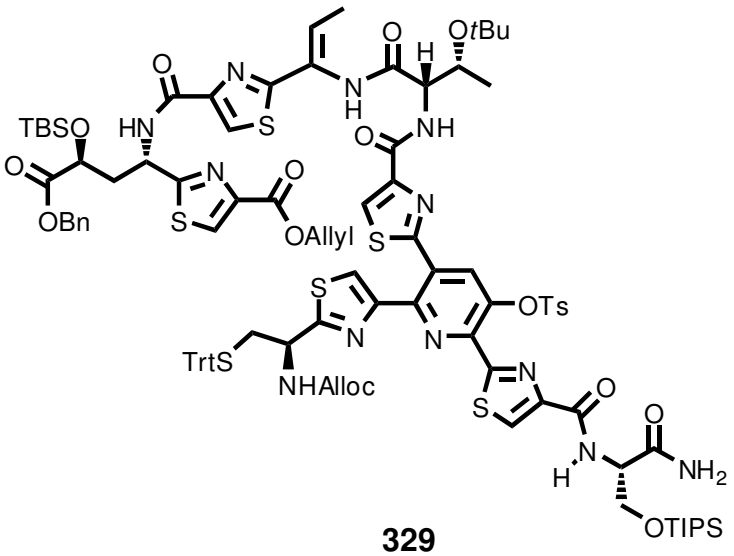
The same procedure as the preparation of pyridine acid **292** was used. Hydroxypyridine **327a** (50 mg, 0.04 mmol) yielded 50 mg (0.04 mmol, 100%) of pyridine acid **328** as a light yellow foam.

TLC: R_f = 0.35 (dichloromethane/MeOH = 10:1).

LC-MS (ESI) (method A): t_R = 12.1 min, calcd for $C_{60}H_{64}N_7O_{10}S_5Si$ $[M + H]^+$, 1230.3, found: 1229.3.

HRMS (ESI): Calcd for $C_{60}H_{64}N_7O_{10}S_5Si$ $[M + H]^+$, 1230.3082, found: 1230.3093.

(1'S,3'S,2''''S,3''''R)-2-(1-(2-((Z)-1-(2-(2-(2-(4-((S)-1-Carbamoyl-3-(triisopropylsilyl-oxy)propan-2-ylcarbamoyl)thiazol-2-yl)-6-(2-((S)-1-amino-2-(tritylthio)ethyl)thiazol-4-yl)-3-(tosyloxy)pyridin-5-yl)thiazol-4-carboxamido)-3-*tert*-butoxybutanamido)prop-1-enyl)thiazol-4-carboxamido)-4-(benzyloxy)-3-(*tert*-butyldimethylsilyloxy)-4-oxobutyl)thiazol-4-carboxylic acid allyl ester (329)



329

The free amine **279** (32 mg, 39 µmol) was added to the stirred solution of free acid **328** (64 mg, 52 µmol), DEPBT (74 mg, 0.25 mmol) and $NaHCO_3$ (40 mg, 0.48 mmol) in anhydrous THF (0.5 mL), the reaction mixture was stirred for 19 hr at room temperature (TLC control). The reaction mixture was diluted with pH 7.0 phosphate buffer (20 mL), extracted with dichloromethane (3 x 30 mL), the combined organic layers were dried with sodium sulfate and concentrated. Purification by column chromatography (silica gel, 20 g, dichloromethane/MeOH = 50:1) gave 69 mg (34 µmol, 87%) of the coupling product **329** as colorless glass. Further purification by preparative HPLC (method C) gave the coupling product 37.7 mg (19 µmol, 47%) as a colorless glass.

TLC: R_f = 0.59 (dichloromethane/MeOH = 10:1).

^{1}H-NMR (400 MHz, CD_3OD): δ = -0.05 (3H, s, TBS), -0.03 (3H, s, TBS), 0.85 (9H, s, TBS), 1.08, 1.10 (21H, TIPS), 1.26 (3H, t, J = 4.6 Hz, CH_3), 1.32 (9H, s, *t*Bu), 1.90 (3H, d, J = 7.2 Hz, CH_3), 2.29 (3H, s, CH_3), 2.65 (3H, dd, J = 8.0, 5.2 Hz, CH, CH_2), 2.73 (1H, dd, J = 9.0, 5.6 Hz, CH), 4.15 (1H, dd, J = 5.2 Hz, CH_2), 4.24 (1H, dd, J = 4.7 Hz, CH_2), 4.37 (1H, dd, J = 4.7, 1.7 Hz, CH), 4.52 (4H, dd, J = 5.3, 2.9 Hz, 2 x $\underline{CH_2}CH=CH_2$), 4.69 (1H, dd, J = 4.6, 3.3 Hz, CH), 4.74 (1H, dd, J = 8.2, 3.0 Hz, CH), 4.79 (2H, d, J =5.4 Hz, CH_2), 5.09

(2H, s, CH_2Ph), 5.17 (1H, d, *J* = 10.3 Hz, $CH_2CH=\underline{CH_2}$), 5.25 (1H, d, *J* = 10.6 Hz, $CH_2CH=\underline{CH_2}$), 5.30 (1H, d, *J* = 17.9 Hz, $CH_2CH=\underline{CH_2}$), 5.38 (1H, dd, *J* = 17.2, 1.4 Hz, $CH_2CH=\underline{CH_2}$), 5.69 (1H, dd, *J* = 5.7, 3.1 Hz, CH), 5.87-5.92 (1H, m, $CH_2\underline{CH}=CH_2$), 5.98-6.05 (1H, m, $CH_2\underline{CH}=CH_2$), 6.80 (1H, dd, *J* = 7.3 Hz, $\underline{CH}CH_3$), 7.15-7.34 (22H, m, trityl, Ph, tosyl), 7.69 (2H, d, *J* = 8.1 Hz, tosyl), 7.99 (1H, s, CH), 8.11 (1H, s, CH), 8.18 (1H, s, CH), 8.25 (1H, s, CH), 8.28 (1H, s, CH), 8.32 (1H, s, CH), 8.49 (1H, d, *J* = 8.0 Hz, NH).

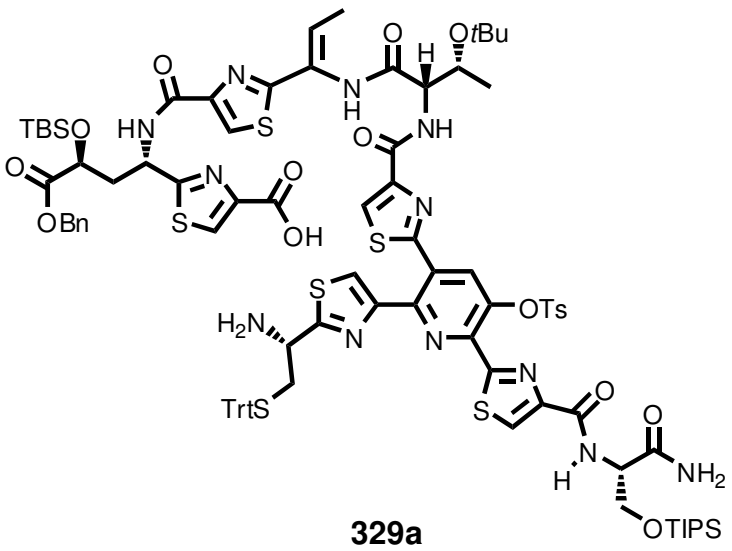
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = -5.4, -5.1, 1.0, 11.8, 14.05, 14.09, 14.11, 14.14, 17.92, 17.94, 21.6, 25.7, 28.3, 29.7, 36.81, 36.82, 39.0, 47.7, 52.0, 54.7, 63.5, 65.89, 65.93, 66.4, 66.9, 67.5, 69.3, 117.9, 118.8, 122.1, 123.5, 126.1, 126.4, 126.9, 127.2, 127.5, 127.69, 127.74, 127.9, 128.09, 128.15, 128.2, 128.4, 128.5, 128.6, 129.5, 129.7, 130.1, 131.8, 132.6, 133.1, 133.66, 133.67, 133.71, 135.3, 135.6, 135.68, 135.70, 137.7, 141.9, 144.26, 144.32, 146.0, 146.8, 148.96, 148.99, 149.6, 151.4, 151.76, 151.78, 156.8, 160.6, 160.8, 161.1, 164.6, 171.7, 172.8.

Maldi-MS: Calcd for $C_{99}H_{116}N_{12}O_{17}S_7Si_2Na$ $[M + Na]^+$, 2047.6, found: 2047.8.

HRMS (ESI): Calcd for $C_{99}H_{118}N_{12}O_{17}S_7Si_2$ $[M + 2H]^{2+}$, 1013.3155, found: 1013.3174.

Optical rotation: $[\alpha]_D^{20}$ = + 4.8 (c = 0.8, $CHCl_3$).

(1'S,3'S,2''''S,3''''R)-2-(1-(2-((Z)-1-(2-(2-(2-(4-((S)-1-Carbamoyl-3-(triisopropylsilyl-oxy)propan-2-ylcarbamoyl)thiazol-2-yl)-6-(2-((S)-1-amino-2-(tritylthio)ethyl)thiazol-4-yl)-3-(tosyloxy)pyridin-5-yl)thiazol-4-carboxamido)-3-*tert*-butoxybutanamido)prop-1-enyl)thiazol-4-carboxamido)-4-(benzyloxy)-3-(*tert*-butyldimethylsilyloxy)-4-oxobutyl)thiazol-4-carboxylic acid (329a)

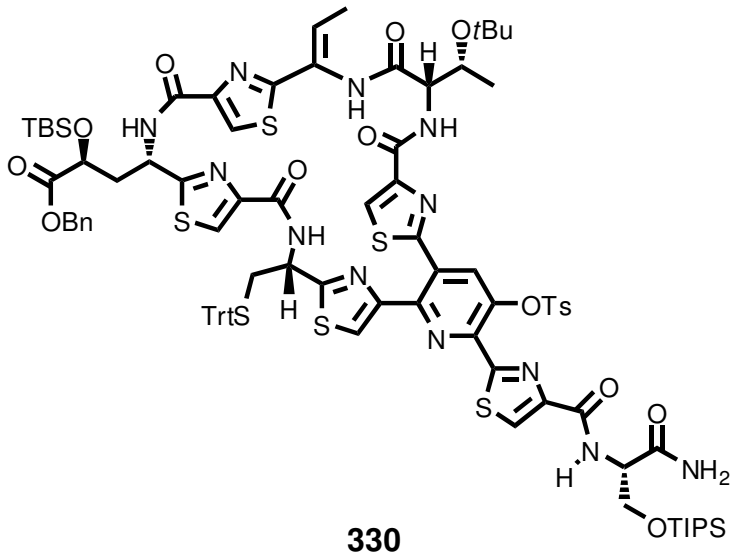


329a

$Pd(PPh_3)_4$ (2.1 mg, 1.8 µmol) in anhydrous dichloromethane (400 µL) was added to a solution of pyridine **329** (17.9 mg, 8.8 µmol) and $PhSiH_3$ (6 µL, 45 µmol) in anhydrous dichloromethane (3 mL) at room temperature. The resulting reaction mixture was stirred for 10 min (TLC control). Toluene (3 mL) was added to the reaction mixture. The solvents and volatiles were removed under reduced pressure. Purification by column chromatography (silica gel, 8 g, dichloromethane/MeOH = 20:1) gave 16.7 mg (8.8 µmol, 99%) of the amino acid **329a** as a yellow resin. The amino acid was not stable upon storage and used directly in the next step after drying.

TLC: R_f = 0.2 (dichloromethane/MeOH = 10:1).
Maldi-MS: Calcd for $C_{92}H_{108}N_{12}O_{15}S_7Si_2Na$ $[M + Na]^+$, 1923.6, found: 1924.0.
HRMS (ESI): Calcd for $C_{92}H_{109}N_{12}O_{15}S_7Si_2$ $[M + H]^+$, 1901.5713, found: 1901.5721.

(1'S, 3'S, 2''''S, 3''''R)-N-(1-tritylsulfanyl-ethyl)-{2-{4-[2-(trityloxy)-1-carbamoyl-ethylcarbamoyl]-thiazol-2-yl}-5-(4-carboxamido-thiazol-2-yl)-3-(tosyloxypyridin-6-yl)}-1-thiazol-2-yl 2-(1-(2-((Z)-1-(3-*tert*-butoxybutanamido)prop-1-enyl)thiazol-4-carboxamido)-3-(*tert*-butyldimethylsilyloxy)-4-(4-methoxybenzyloxy)-4-oxobutyl)thiazol-4-carboxamide (330)



330

The amino acid **329a** (16.7 mg, 8.8 µmol) in dichloromethane (2 mL) was added dropwise in 2 hours by syringe pump to HATU (6.5 mg, 17.1 µmol.) and DIPEA (6 µL, 35 µmol) in dichloromethane (8 mL) and DMF (0.5 mL) at room temperature. The reaction mixture was stirred for another 12 hours. The reaction was diluted with phosphate buffer (pH 7.0, 20 mL)

and extracted with dichloromethane (3 x 20 mL). The combined extracts were dried with sodium sulfate. Purification by preparative HPLC (method C) yielded 9.2 mg (4.9 μmol, 56%) of macrocycle **330** as a colorless glass.

TLC: R_f = 0.56 (dichloromethane/MeOH = 10:1).

^{1}H-NMR (400MHz, DMSO): δ = -0.07 (3H, s, TBS), -0.01 (3H, s, TBS), 0.81 (9H, s, TBS), 1.01, 1.02 (21H, TIPS), 1.23 (9H, s, *t*Bu), 1.33 (3H, d, J = 6.1 Hz, CH_3), 1.79 (3H, d, J = 6.9 Hz, CH$\underline{CH_3}$), 2.00 (2H, dd, J = 7.8 Hz, CH_2), 2.29 (3H, d, J = 6.6 Hz, CH_3), 2.29 (3H, s, CH_3), 2.91 (1H, dd, J = 6.6 Hz, CH), 4.01-4.10 (2H, m, CH_2), 4.22 (1H, dd, J = 5.5 Hz, CH), 4.39 (1H, dd, J = 5.9 Hz, CH), 4.52 (1H, dd, J = 10.0 Hz, CH), 4.61 (1H, d, J = 4.5 Hz, CH), 4.81 (1H, t, J = 7.4 Hz, CH), 5.54 (1H, t, J = 7.0 Hz, CH), 6.45 (1H, dd, J = 6.9 Hz, $\underline{CH}CH_3$), 7.21-7.31 (22H, m, trityl, Ph, tosyl), 7.61 (2H, s, $\underline{CH_2}$Ph), 7.68 (1H, d, J = 8.5 Hz, NH), 7.70 (2H, d, J = 8.6 Hz, tosyl), 7.79 (1H, d, J = 6.5 Hz, NH), 7.97 (2H, d, J = 8.4 Hz, 2 x NH), 8.10 (1H, s, CH), 8.21 (2H, s, 2 x CH), 8.24 (2H, s, 2 x CH), 8.31 (1H, s, NH), 8.42 (1H, s, CH), 9.17 (1H, s, NH_2), 9.68 (1H, s, NH_2).

LC-MS (ESI) (method A): t_R = 13.2 min, calcd for $C_{92}H_{107}N_{12}O_{14}S_7Si_2$ $[M + H]^+$, 1883.6, found: 1883.9.

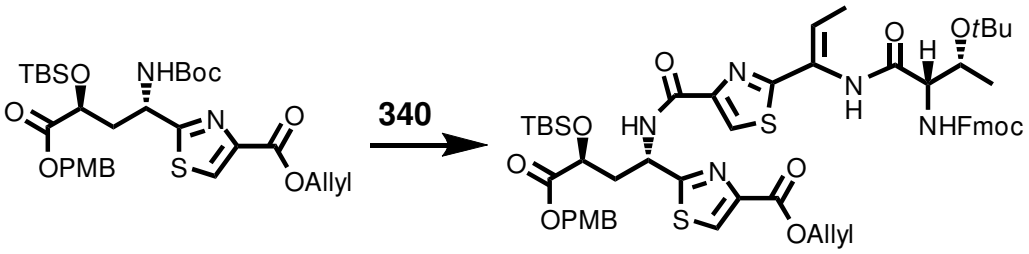
Maldi-MS: Calcd for $C_{92}H_{106}N_{12}O_{14}S_7Si_2Na$ $[M + Na]^+$, 1905.5, found: 1905.9

IR (KBr): $\tilde{\nu}$ = 3447 (b), 2959 (s), 2923 (s), 2856 (s), 1750 (s), 1734 (s), 1717 (s), 1699 (s), 1684 (s), 1670 (s), 1654 (s), 1647 (s), 1637 (s), 1625 (s), 1577 (s), 1570 (s), 1523 (s), 1458 (s), 1262 (s), 1104 (s),799 (s) cm^{-1}.

HRMS (ESI): Calcd for $C_{92}H_{107}N_{12}O_{14}S_7Si_2$ $[M + H]^+$, 1883.5608, found: 1883.5611;
Calcd for $C_{92}H_{108}N_{12}O_{14}S_7Si_2$ $[M + 2H]^{2+}$, 942.2840, found: 942.2852.

Optical rotation: $[\alpha]_D^{20}$ = + 27.3 (c = 0.15, $CHCl_3$).

(1'S, 3'S, 2''''S, 3''''R)-2-(1-(2-((Z)-1-(2-(((9H-Fluoren-9-yl)methoxy)carbonylamino)-3-*tert*-butoxybutanamido)prop-1-enyl)thiazol-4-carboxamido)-3-(*tert*-butyldimethylsilyl-oxy)-4-(4-methoxybenzyloxy)-4-oxobutyl)thiazol-4-carboxylic acid allyl ester (344)



339 **344**

Method A: $ZnBr_2$ (11.5 mg, 51.1 µmol) was added to the solution of Boc protected glutamate **339** (10 mg, 16.1µmol) in dichloromethane (3 mL) at room temperature under stirring. The reaction mixture was stirred for 4 hours (TLC control). The reaction mixture was diluted with dichloromethane (15 mL) and phosphate buffer (pH 2.5, 20 mL), the aqueous phase was extracted with dichloromethane (3 x 20 mL). The combined organic layers were dried with sodium sulfate and concentrated to dryness. The free amine **342** was directly used in next peptide coupling without purification.

TLC: R_f = 0.15 (ethyl acetate/cyclohexane =1:2).
Maldi-MS: Calcd for $C_{25}H_{37}N_2O_6SSi$ $[M + H]^+$, 521.2, found: 521.2

The free amine **342**, acid **340** (9.1 mg, 16.1 µmol), HOBt anhydrous (3.3 mg, 24.4 µmol), triethylamine (7 uL, 50.1 µmol) were dissolved in dichloromethane (1 mL) at 0°C. The reaction mixture was stirred for 15 min at this temperature. EDC (3.9 mg, 20.3 µmol) was added to the above reaction mixture. The reaction mixture was slowly warmed to room temperature and stirred for 12 h (TLC control). The reaction mixture was diluted with dichloromethane (20 mL) and phosphate buffer (pH 2.5, 20 mL), and the aqueous phase was extracted with dichloromethane (3 x 30 mL). The combined organic layers were dried with sodium sulfate and concentrated. Purification by column chromatography (silica gel, 10 g, ethylacetate/light petroleum = 1:2) gave 6.7 mg (6.3 µmol, 39%) of the thiazolyl dipeptide **344** as colorless foam.

Method B: Glutamate **339** (10 mg, 16.1 µmol) and 2,6-lutidine (40 µL, 345.4 µmol) were dissolved in dichloromethane (1 mL) and cooled to 0°C. TBSOTf (40 µL, 174.0 µmol) was added dropwise. The reaction mixture was stirred for 12 h (TLC control). The solvent and the volatiles were removed under high vacuum.

The crude product was dissolved in THF (1 mL) under argon at 0°C, and acid **340** (8 mg, 14.2 µmol), HOAt (7.7 mg, 56.6 µmol), HATU (13.5 mg, 35.5 µmol) were added to the reaction mixture. $NaHCO_3$ (3.6 mg, 42.9 µmol) was added after 15min. The reaction mixture was stirred at ambient temperature for 12h. The reaction mixture was diluted with phosphate buffer (pH 2.5, 10 mL) and extracted with dichloromethane (3 x 10 mL). The combined extracts were dried with sodium sulfate and concentrated. Purification by column

chromatography (silica gel, 10 g, ethyl acetate/light petroleum = 1:2) gave 9 mg (8.4 µmol, 59%) of the thiazolyl dipeptide **344** as colorless foam.

TLC: R_f = 0.45 (ethyl acetate/light petroleum =1:1).

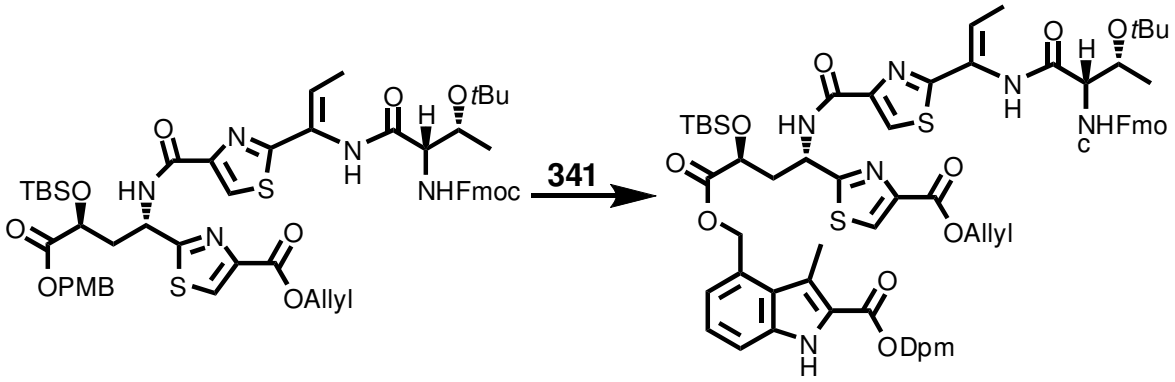
^{1}H-NMR (400 MHz, $CDCl_3$): δ = -0.03 (3H, s, TBS), -0.02 (3H, s, TBS), 0.86 (9H, s, TBS), 1.18 (3H, d, J = 6.2 Hz, CH_3), 1.33 (9H, s, *t*Bu), 1.86 (3H, d, J = 7.3 Hz, CH_3), 2.58-2.70 (2H, m, CH_2), 3.79 (3H, s, OCH_3), 4.23 (1H, t, J = 6.8 Hz, CH), 4.29 (1H, t, J = 4.6 Hz, Fmoc), 4.43 (3H, t, J = 5.5 Hz, CH, Fmoc), 4.83 (2H, d, J = 5.9 Hz, CH_2Ph), 5.03 (2H, dd, J = 6.0 Hz, $\underline{CH_2}CH=CH_2$), 5.28 (1H, d, J = 10.6 Hz, $CH_2CH=\underline{CH_2}$), 5.39 (1H, dd, J = 17.2, 1.3 Hz, $CH_2CH=\underline{CH_2}$), 5.69-5.75 (1H, m, CH), 5.96-6.06 (2H, m, $CH_2\underline{CH}=CH_2$, Fmoc-NH), 6.69 (1H, dd, J = 7.2 Hz, $\underline{CH}CH_3$), 6.86 (2H, d, J = 8.6 Hz, Fmoc), 7.30 (4H, dd, J = 8.6, 1.3 Hz, Fmoc), 7.39 (2H, t, J = 7.6 Hz, Fmoc), 7.60 (2H, d, J = 7.5 Hz, PMB), 7.76 (2H, d, J = 7.4 Hz, PMB), 7.92 (1H, d, J = 8.8 Hz, NH), 8.03 (1H, s, CH), 8.09 (1H, s, CH), 8.65 (1H, s, NH).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = -5.4, -5.0, 14.1, 17.0, 18.2, 25.7, 28.3, 29.7, 39.0, 47.2, 47.7, 55.3, 58.9, 65.9, 66.7, 66.8, 67.0, 69.3, 76.2, 77.3, 113.9, 118.8, 120.0, 123.5, 125.1, 126.4, 127.1, 127.5, 127.7, 127.8, 128.0, 130.5, 131.9, 141.3, 141.3, 143.6, 143.8, 146.8, 149.5, 156.0, 159.8, 160.6, 160.9, 167.0, 167.9, 168.2, 171.7, 172.8, 178.7.

IR (KBr): $\tilde{\nu}$ = 3398 (w), 3316 (w), 2929 (s), 2856 (w), 1725 (s), 1696 (s), 1246 (s), 814 (s) cm^{-1}

HRMS (ESI): Calcd for $C_{55}H_{67}N_5O_{11}S_2SiNa$ $[M + Na]^+$, 1088.3940, found: 1088.3944.

(1'S, 3'S, 2''''S, 3''''R)-2-(1-(2-((Z)-1-(2-(((9H-Fluoren-9-yl)methoxy)carbonylamino)-3-*tert*-butoxybutanamido)prop-1-enyl)thiazol-4-carboxamido)-3-(*tert*-butyldimethylsilyl-oxy)-4-((2-(diphenylmethoxycarbonyl)-3-methyl-1H-indol-4-yl)methyl)-4-oxobutyl)thia-zol-4-carboxylic acid allyl ester (345)



344 **345**

$AlCl_3$ (10.1 mg, 75.9 µmol) was added to a solution of PMB ester **344** (27 mg, 25.3 µmol) in anisole (2 mL) and dichoromethane (1 mL) at -50°C. The reaction mixture was stirred for 20 min (TLC control) at this temperature. The reaction mixture was diluted with phosphate buffer (pH 7.0, 20 mL) and extracted with dichloromethane (3 x 20 mL). The combined organic extracts were dried with sodium sulfate and concentrated to dryness. The crude acid was directly used to next step due to the inherent lability of the TBS ether group.

TLC: R_f = 0.32 (dichloromethane/MeOH =25:1).
LC-MS (ESI) (method A): t_R = 10.83 min, calcd for $C_{41}H_{45}N_5O_{10}S_2$ [M-TBS+ H^+], 831.3, found: 831.8. t_R = 12.17 min, calcd for $C_{47}H_{59}N_5O_{10}S_2Si$ $[M]^+$, 945.4, found: 945.9
HRMS (ESI): Calcd for $C_{41}H_{45}N_5O_{10}S_2Na$ $[M\text{-TBS} + H + Na]^+$, 854.2500, found: 854.2496.

DCC (6.3 mg, 30.6 µmol) was added slowly to a stirred solution of the crude acid in dichloromethane (1 mL) at 0°C under argon. After 15 min, the indolic alcohol **341** (11.2 mg, 30.2µmol), DMAP (0.3 mg, 2.5 µmol), and HOAt (0.4 mg, 3.0 µmol) were added. The reaction mixture was stirred for 24 h, diluted with phosphate buffer (pH 7.0, 20 mL), and extracted with dichloromethane (3 x 30 mL). The combined extracts were dried with sodium sulfate and concentrated. Purification by column chromatography (silica gel, 10 g, ethyl acetate/light petroleum = 1:3) gave 23 mg (17.7 µmol, 70%) of **345** as a colorless glass.

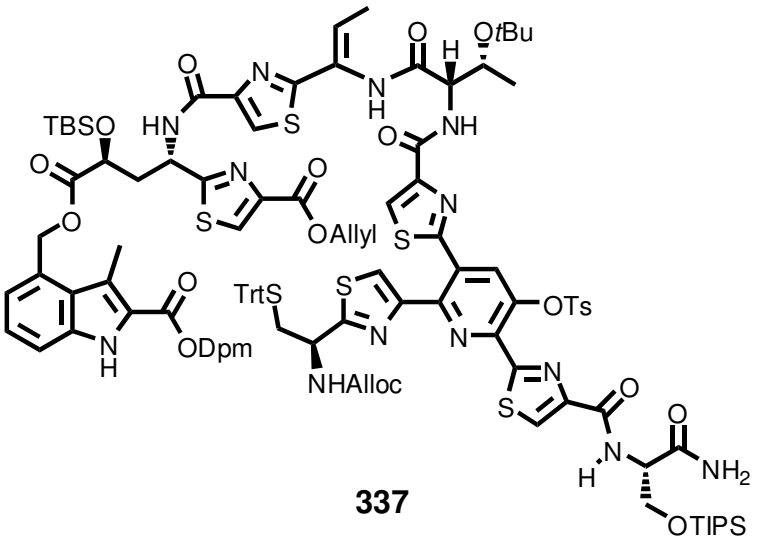
TLC: R_f = 0.14 (ethyl acetate/light petroleum =1:1).
^{1}H-NMR (400 MHz, $CDCl_3$): δ = -0.08 (3H, s, TBS), -0.03 (3H, s, TBS), 0.83 (9H, s, TBS), 1.17 (3H, d, J = 5.3 Hz, CH_3), 1.30 (9H, s, *t*Bu), 1.83 (3H, d, J = 7.2 Hz, CH_3), 2.61-2.74 (2H, m, CH_2), 2.82 (3H, s, CH_3), 4.12 (1H, dd, J = 7.2 Hz, CH), 4.22 (1H, t, J = 6.9 Hz, Fmoc),

4.41 (2H, d, *J* = 6.9 Hz, Fmoc), 4.48 (1H, dd, *J* = 4.7, 3.0 Hz, CH), 4.80 (2H, d, *J* = 5.7 Hz, -CH_2OOC-), 5.27 (2H, dd, *J* = 17.2, 10.5 Hz, $\underline{CH_2}CH=CH_2$), 5.44 (1H, d, *J* = 12.3 Hz, $CH_2CH=\underline{CH_2}$), 5.59 (1H, d, *J* = 12.3 Hz, $CH_2CH=\underline{CH_2}$), 5.69-5.75 (1H, m, CH), 5.94-6.04 (2H, m, $CH_2\underline{CH}=CH_2$, Fmoc-NH), 6.64 (1H, dd, *J* = 7.2 Hz, $\underline{CH}CH_3$), 7.16 (1H, s, Dpm), 7.11-7.76 (21H, m, Dpm, indole, Fmoc), 7.91 (1H, d, *J* = 8.8 Hz, NH), 7.99 (1H, s, CH), 8.06 (1H, s, CH), 8.64 (1H, s, NH), 8.88 (1H, s, NH).

LC-MS (ESI) (method A): t_R = 13.6 min, calcd for $C_{71}H_{79}N_6O_{12}S_2Si$ $[M + H]^+$, 1299.5, found: 1299.0

HRMS (ESI): Calcd for $C_{71}H_{78}N_6O_{12}S_2SiNa$ $[M + Na]^+$, 1321.4781, found: 1321.4792.

(1'S,3'S,2''''S,3''''R)-2-(1-(2-((Z)-1-(2-(2-(2-(4-((S)-1-Carbamoyl-3-(triisopropylsilyl-oxy)propan-2-ylcarbamoyl)thiazol-2-yl)-6-(2-((S)-1-amino-2-(tritylthio)ethyl)thiazol-4-yl)-3-(tosyloxy)pyridin-5-yl)thiazol-4-carboxamido)-3-*tert*-butoxybutanamido)prop-1-enyl)thiazol-4-carboxamido)-4-((2-(diphenylmethoxycarbonyl)-3-methyl-1H-indol-4-yl)methyl)-3-(*tert*-butyldimethylsilyloxy)-4-oxobutyl)thiazol-4-carboxylic acid allyl ester (337)



337

DBU (20 µL) was added to a mixture of peptide **345** (23 mg, 17.7 µmol) in dichloromethane (2 mL) at room temperature. The reaction mixture was stirred for 5 min (TLC control). After removed the volatiles, the residue was purified by column chromatography (silica gel, 20 g, dichloromethane/MeOH = 30:1) gave 15.6 mg (14.5 µmol, 82%) free amine **338** as a colorless resin.

LC-MS (ESI) (method A): t_R = 9.3 min, calcd for $C_{56}H_{69}N_6O_{10}S_2Si$ $[M + H]^+$, 1077.4, found: 1077.2

Maldi-MS: Calcd for $C_{56}H_{68}N_6O_{10}S_2SiNa$ $[M + Na]^+$, 1099.4, found: 1099.2.

The free amine **338** (15.6 mg, 14.5 μmol) was added to a stirred solution of free acid (20 mg, 16.3 μmol), DEPBT (47 mg, 0.157 mmol) and $NaHCO_3$ (26 mg, 0.31 mmol) in anhydrous THF (1 mL). The reaction mixture was stirred for 24 hr at room temperature (TLC control). The reaction mixture was diluted with pH 7.0 phosphate buffer (20 mL), extracted with dichloromethane (3 x 30 mL), the combined organic layers were dried with sodium sulfate and concentrated to dryness. Purification by preparative HPLC (method C) gave 22.6 mg (9.9 μmol, 68%) of the coupling product **337** as a colorless glass.

TLC: R_f = 0.59 (dichloromethane/MeOH = 10:1).

HPLC (method B): t_R = 19.83 min.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = -0.10 (3H, s, TBS), -0.05 (3H, s, TBS), 0.82 (9H, s, TBS), 1.08 (21H, TIPS), 1.19 (3H, d, J = 6.5 Hz, CH_3), 1.26 (9H, s, *t*Bu), 1.86 (3H, d, J = 7.2 Hz, CH_3), 2.10 (1H, d, J = 7.6 Hz, CH), 2.26 (3H, s, CH_3), 2.58-2.67 (3H, dd, J = 8.0, 2.8 Hz, CH, CH_2), 2.80 (3H, s, CH_3), 4.01 (2H, dd, J = 10.9, 9.2 Hz, CH_2), 4.29 (2H, dd, J = 5.8, 4.2 Hz, CH_2), 4.42 (1H, dd, J = 5.0 Hz, CH), 4.47 (4H, dd, J = 7.3 Hz, 2 x $\underline{CH_2}CH=CH_2$), 4.64 (1H, br, CH), 4.77 (2H, t, J = 6.8, 5.5 Hz, CH_2), 4.87 (1H, dd, J = 6.5 Hz, CH), 5.24 (1H, d, J = 10.4 Hz, $CH_2CH=\underline{CH_2}$), 5.34 (1H, d, J = 6.8 Hz, $CH_2CH=\underline{CH_2}$), 5.36 (1H, d, J = 10.2 Hz, $CH_2CH=\underline{CH_2}$), 5.43 (1H, d, J = 12.3 Hz, $CH_2CH=\underline{CH_2}$), 5.55 (2H, s, CH_2), 5.58 (1H, s, $C(O)NH_2$), 5.70 (1H, dd, J = 8.4, 5.3 Hz, CH), 5.83-5.91 (1H, m, $CH_2\underline{CH}=CH_2$), 5.92-6.01 (1H, m, $CH_2\underline{CH}=CH_2$), 6.48 (1H, s, $C(O)NH_2$), 6.70 (1H, dd, J = 7.2 Hz, $\underline{CH}CH_3$), 7.00-7.42 (29H, m, trityl, tosyl, indole), 7.77 (2H, d, J = 8.2 Hz, tosyl), 7.81 (1H, d, J = 5.7 Hz, NH), 7.98 (1H, d, J = 9.2 Hz, NH), 8.00 (1H, s, CH), 8.05 (1H, s, CH), 8.09 (1H, s, CH), 8.13 (1H, s, CH), 8.22 (1H, s, CH), 8.30 (1H, s, CH), 8.54 (1H, d, J = 8.4 Hz, NH), 8.73 (1H, s, NH), 8.96 (1H, s, NH).

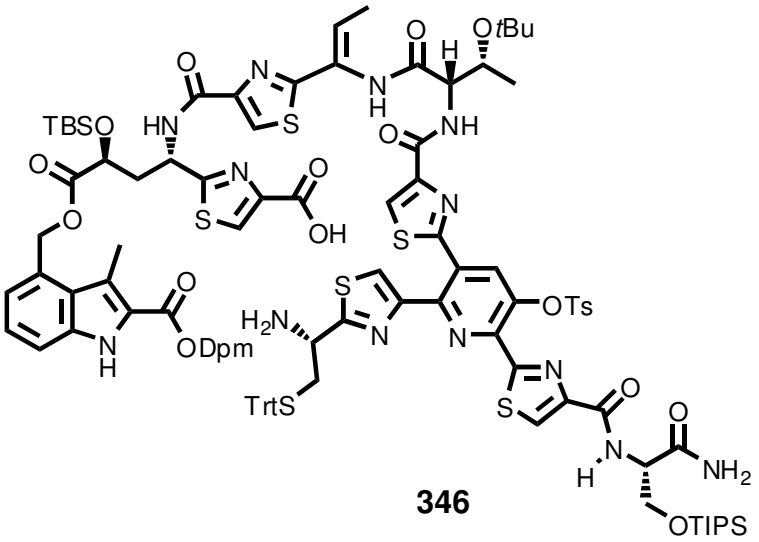
IR (KBr): $\tilde{\nu}$ = 3442 (b), 2925 (s), 2855 (s), 1731 (s), 1714 (s), 1695 (s), 1681 (s), 1668 (s), 1660 (s), 1651 (s), 1644 (s), 1633 (s), 1614 (s), 1574 (s), 1567 (s), 1556 (s), 1539 (s), 1434 (s), 1263 (s), 1104 (s), 797 (s) cm^{-1}.

Maldi-MS: Calcd for $C_{116}H_{129}N_{13}O_{19}S_7Si_2$ $[M + Na]^+$, 2310.7, found: 2310.5.

HRMS (ESI): Calcd for $C_{116}H_{131}N_{13}O_{19}S_7Si_2$ $[M + 2H]^{2+}$, 1144.8628, found: 1144.8637.

Optical rotation: $[\alpha]_D^{20}$ = - 8.0 (c = 0.1, $CHCl_3$).

(1'S,3'S,2''''S,3''''R)-2-(1-(2-((Z)-1-(2-(2-(2-(4-((S)-1-Carbamoyl-3-(triisopropylsilyl-oxy)propan-2-ylcarbamoyl)thiazol-2-yl)-6-(2-((S)-1-amino-2-(tritylthio)ethyl)thiazol-4-yl)-3-(tosyloxy)pyridin-5-yl)thiazol-4-carboxamido)-3-*tert*-butoxybutanamido)prop-1-enyl)thiazol-4-carboxamido)-4-((2-(diphenylmethoxycarbonyl)-3-methyl-1H-indol-4-yl)methyl)-3-(*tert*-butyldimethylsilyloxy)-4-oxobutyl)thiazol-4-carboxylic acid allyl ester (346)

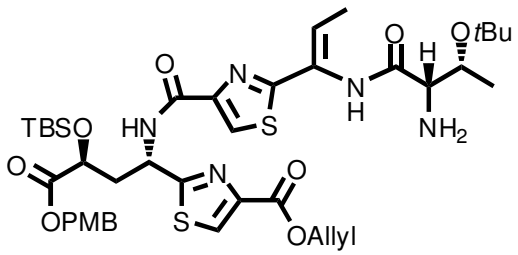


346

$Pd(PPh_3)_4$ (0.2 mg, 0.2 µmol) in anhydous dichloromethane (200 µL) was added to a solution of pyridine **337** (2.0 mg, 0.9 µmol) and $PhSiH_3$ (0.5 µL, 3.8 µmol) in anhydrous dichloromethane (1 mL) at room temperature. The resulting reaction mixture was stirred for 10 min (TLC control). Toluene (2 mL) was added to the reaction mixture. The solvents and volatiles were removed under reduced pressure. Purification by column chromatography (silica gel, 6 g, dichloromethane/MeOH = 20:1) gave 1.2 mg (0.6 µmol, 63%) of the amino acid **346** as a yellow resin.

TLC: R_f = 0.18 (dichloromethane/MeOH = 10:1).
Maldi-MS: Calcd for $C_{109}H_{121}N_{13}O_{17}S_7Si_2Na$ $[M + Na]^+$, 2186.7, found: 2186.4.

(1'S, 3'S, 2''''S, 3''''R)-2-(1-(2-((Z)-1-(2-Amino-3-*tert*-butoxybutanamido)prop-1-enyl)-thiazol-4-carboxamido)-3-(*tert*-butyldimethylsilyloxy)-4-(4-methoxybenzyloxy)-4-oxobutyl)thiazol-4-carboxylic acid allyl ester (347)

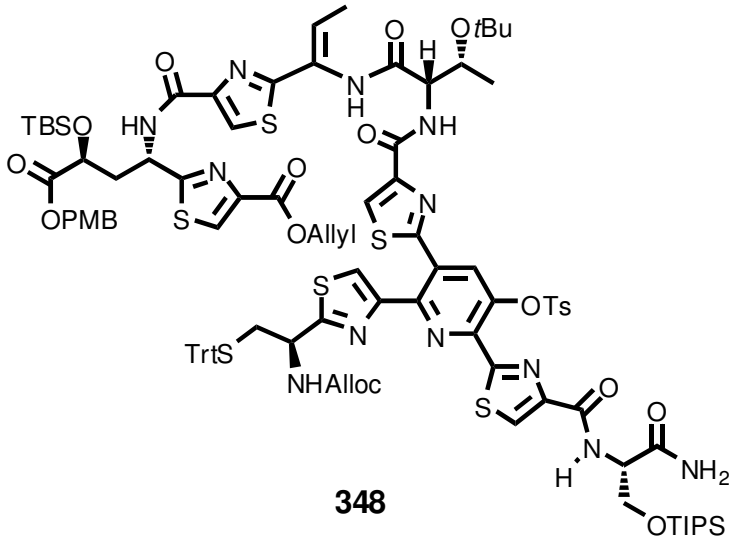


347

DBU (40 µL) and piperidine (40 µL) were added to a mixture of peptide **344** (24 mg, 22.5 µmol) in dichloromethane (4 mL) at room temperature. The reaction mixture was stirred for 20 min (TLC control) and concentrated under high vacuum.The residue was purified by column chromatography (silica gel, 20 g, dichloromethane/MeOH = 30:1) to give 16.8 mg (19.9 µmol, 88%) of free amine **347** as a colorless resin.

TLC: R_f = 0.47 (dichloromethane/MeOH = 10:1).
LC-MS (ESI) (method A): t_R = 7.77 min, calcd for $C_{40}H_{58}N_5O_9S_2Si$ $[M + H]^+$, 844.3, found: 844.0
HRMS (ESI): Calcd for $C_{40}H_{57}N_5O_9S_2SiNa$ $[M + Na]^+$, 866.3259, found: 866.3257.

(1'S,3'S,2''''S,3''''R)-2-(1-(2-((Z)-1-(2-(2-(2-(4-((S)-1-Carbamoyl-3-(triisopropylsilyl-oxy)propan-2-ylcarbamoyl)thiazol-2-yl)-6-(2-((S)-1-amino-2-(tritylthio)ethyl)thiazol-4-yl)-3-(tosyloxy)pyridin-5-yl)thiazol-4-carboxamido)-3-*tert*-butoxybutanamido)prop-1-enyl)thiazol-4-carboxamido)-4-(4-methoxybenzyloxy)-3-(*tert*-butyldimethylsilyloxy)-4-oxobutyl)thiazol-4-carboxylic acid allyl ester (348)



348

The free amine **347** (15.1 mg, 17.9 μmol) was added to a stirred solution of free acid **328** (22 mg, 17.9 μmol), DEPBT (25 mg, 83.6 μmol) and $NaHCO_3$ (14 mg, 0.17 mmol) in anhydrous THF (1 mL), the reaction mixture was stirred for 20 hr at room temperature (TLC control). The reaction mixture was diluted with pH 7.0 phosphate buffer (10 mL), extracted with dichloromethane (3 x 20 mL). The combined organic layers were dried with sodium sulfate and concentrated. Purification by preparative HPLC (method C) gave 6 mg (2.9 μmol, 16%) of the coupling product **348** as a colorless glass (**347** was recovered).

TLC: R_f = 0.63 (dichloromethane/MeOH = 10:1).

^{1}H-NMR (400 MHz, CD_3OD): δ = -0.06 (3H, s, TBS), -0.04 (3H, s, TBS), 0.85 (9H, s, TBS), 1.09, 1.10 (21H, TIPS), 1.26 (3H, d, *J* = 4.5 Hz, CH_3), 1.33 (9H, s, *t*Bu), 1.90 (3H, d, *J* = 7.2 Hz, CH_3), 2.14 (1H, d, *J* = 7.4 Hz, CH), 2.29 (3H, s, CH_3), 2.61 (2H, dd, *J* = 8.0, 2.8 Hz, CH_2), 2.72 (1H, dd, *J* = 6.5 Hz, CH), 3.76 (3H, s, OCH_3), 4.16 (1H, dd, *J* = 5.0 Hz, CH_2), 4.25 (1H, dd, *J* = 4.6 Hz, CH_2), 4.38 (1H, dd, *J* = 5.5 Hz, CH), 4.50 (4H, dd, *J* = 5.3, 2.9 Hz, 2 x $\underline{CH_2}CH=CH_2$), 4.69 (1H, dd, *J* = 4.6, 3.3 Hz, CH), 4.75 (1H, dd, *J* = 3.3 Hz, CH), 4.78-4.84 (2H, m, CH_2), 5.02 (2H, s, CH_2Ph), 5.18 (1H, d, *J* = 10.0 Hz, $CH_2CH=\underline{CH_2}$), 5.26 (1H, d, *J* = 10.3 Hz, $CH_2CH=\underline{CH_2}$), 5.30 (1H, d, *J* = 17.9 Hz, $CH_2CH=\underline{CH_2}$), 5.39 (1H, d, *J* = 17.2 Hz, $CH_2CH=\underline{CH_2}$), 5.68 (1H, dd, *J* = 9.4, 5.4 Hz, CH), 5.86-5.95 (1H, m, $CH_2\underline{CH}=CH_2$), 5.97-6.07 (1H, m, $CH_2\underline{CH}=CH_2$), 6.82 (1H, dd, *J* = 10.2, 8.6 Hz, $\underline{CH}CH_3$), 7.16-7.34 (22H, m, trityl, Ph, tosyl), 7.70 (2H, d, *J* = 8.0 Hz, tosyl), 8.00 (1H, s, CH), 8.11 (1H, s, CH), 8.18 (1H, s, CH), 8.26 (1H, s, CH), 8.29 (1H, s, CH), 8.34 (1H, s, CH), 8.50 (1H, d, *J* = 8.2 Hz, NH).

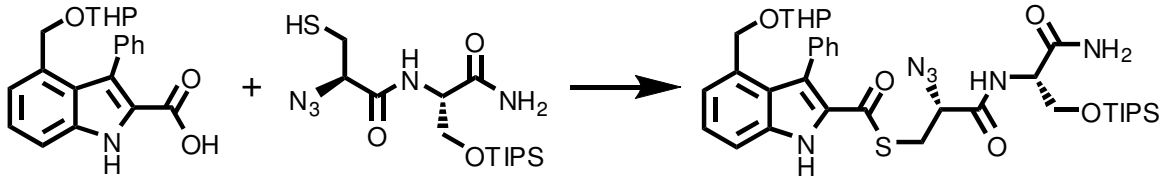
IR (KBr): $\tilde{\nu}$ = 3446 (b), 2925 (s), 2855 (s), 1716 (s), 1669 (s), 1539 (s), 1471 (s), 1405 (s), 1318 (s), 1250 (s), 1195 (s), 1104 (b), 1036 (m), 669 (s) cm^{-1}.

Maldi-MS: Calcd for $C_{100}H_{118}N_{12}O_{18}S_7Si_2Na$ $[M + Na]^+$, 2077.6, found: 2078.2.

HRMS (ESI): Calcd for $C_{100}H_{120}N_{12}O_{18}S_7Si_2$ $[M + 2H]^{2+}$, 1028.3208, found: 1028.3219.

Optical rotation: $[\alpha]_D^{20}$ = - 1.5 (c = 0.2, $CHCl_3$).

(2*S*, 2'*R*)-(3-Phenyl-4-((tetrahydro-2*H*-pyran-2-yloxy)methyl)-1*H*-indol-2''-yl)-2'-azido-3'-thiopropionyl)-2-triisopropylsilanyloxyethyl-2-aminopropanoic amide (353)



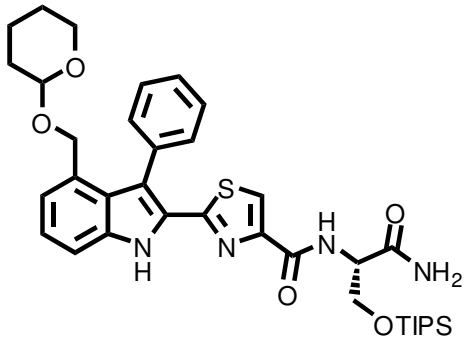
351 **352** **353**

Trifluoroacetic acid (0.2 mL) and triethylsilane (0.1 mL) were added dropwise to a stirred solution of dipeptide **326** (5.2 mg, 8.2 µmol) in dichloromethane (4 mL) at room temperature under argon (TLC control). Toluene (4 mL) was added to the reaction mixture and the volatiles were removed in vacuo. The resulting thiol **352** was pure enough for next step.

PyBOP (4.3 mg, 8.3 µmol) was added to a mixture of the crude free thio **352**, indolic acid **351** (2.4 mg, 6.8 µmol) and DIPEA (2.3 µL, 13.5 µmol) in dichloromethane (500 µL) at room temperature, the reaction mixture was stirred for 1 hour (TLC control). The reaction mixture was diluted with phosphate buffer (pH 3.0, 10 mL) and extracted with dichloromethane (3 x 10 mL), the combined extracts were dried with sodium sulfate and concentrated. Purification by column chromatography (silica gel, 10 g, ethyl acetate/light petroleum = 1:2) gave 4.9 mg (6.7 µmol, 99%) of thioester **353** as a light yellow resin.

TLC: R_f = 0.40 (ethyl acetate/light petroleum = 1:1).
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.04-1.26 (21H, TIPS), 1.43-1.56 (5H, m, THP), 1.72-1.78 (1H, m, THP), 3.16 (1H, d, J = 7.9 Hz, CH_2), 3.36 (1H, dd, J = 6.0, 3.1 Hz, CH_2), 3.55-3.77 (4H, m, CH_2, THP), 3.94 (1H, dd, J = 3.3 Hz, THP), 4.07-4.11 (2H, m, 2 x CH), 4.15 (1H, d, J = 12.0 Hz, CH_2Ph), 4.42 (1H, d, J = 12.0 Hz, CH_2Ph), 5.62 (1H, s, NH_2), 6.59 (1H, s, NH_2), 7.18 (1H, d, J = 6.8 Hz, NH), 7.28-7.44 (8H, m, 3 x CH, Ph), 9.40 (1H, s, NH).
Maldi-MS: Calcd for $C_{36}H_{50}N_6O_6SSiNa$ $[M + Na]^+$, 745.3, found: 745.2.

(*S*)-1'-Carbamoyl-2'-triisopropylsilanyloxy-ethyl 4''-((tetrahydro-2'''*H*-pyran-2'''-yloxy)methyl-3''-phenyl-1''H-indol-2'-yl)-thiazole-4-carbamide (355)



355

PPh_3 (3.5 mg, 13.4 µmol) was added to a solution of **353** (4.9 mg, 6.7 µmol) in THF (2 mL) at -20°C, the reaction mixture was stirred for 1 hour at this temperature, warmed to room temperature and then heated up to 40°C for 20 hours. The reaction mixture was cooled to room temperature and concentrated. Excess of PPh_3 was removed by column chromatography (silica gel, 5 g, ethyl acetate/light petroleum = 1:6), the resulting crude thiazoline was directly used in the next step.

DBU (1.5 µL, 10.1 µmol) was added dropwise to a mixture of crude thiazoline and $BrCCl_3$ (2 mg, 10.1 µmol) in dichloromethane (2 mL) at -20°C. The reaction mixture was stirred for 1 h and warmed to room temperature for 1 h. The reaction mixture was diluted with phosphate buffer (pH 3.0, 10 mL) and extracted with dichloromethane (3 x 10 mL). The combined extracts were dried with sodium sulfate and concentrated. Purification by column chromatography (silica gel, 5 g, ethyl acetate/light petroleum = 1:4) gave 3.6 mg (5.3 µmol, 79% over 2 steps) of thiazole **355** as a light yellow glass.

TLC: R_f = 0.30 (ethyl acetate/light petroleum = 1:1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.12-1.26 (21H, TIPS), 1.41-1.61 (5H, m, THP), 1.72-1.78 (1H, m, THP), 3.37 (1H, dd, J = 6.3, 3.9 Hz, THP), 3.72 (1H, dd, J = 9.0, 3.1 Hz, CH_2), 3.84 (1H, t, J = 8.4 Hz, CH_2), 3.94 (1H, d, J = 3.3 Hz, THP), 4.27 (1H, d, J = 11.6 Hz, CH_2Ph), 4.36 (1H, dd, J = 9.4, 3.3 Hz, CH), 4.52 (1H, d, J = 11.6 Hz, CH_2Ph), 4.63-4.68 (1H, m, THP), 5.56 (1H, s, NH_2), 6.65 (1H, s, NH_2), 7.18 (1H, d, J = 7.0 Hz, CH), 7.32 (1H, t, J = 8.1 Hz, CH), 7.43-7.55 (5H, m, Ph), 7.68 (1H, dd, J = 7.4, 4.3 Hz, CH), 7.86 (1H, s, CH), 8.23 (1H, d, J = 6.9 Hz, NH), 9.31 (1H, s, NH).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 11.8, 18.0, 25.4, 29.7, 30.5, 54.1, 61.8, 63.0, 66.4, 77.2, 98.0, 111.3, 119.8, 121.8, 123.6, 124.7, 126.5, 128.3, 128.4, 128.7, 129.0, 129.1, 131.2, 131.3, 131.4, 131.5, 131.9, 132.1, 132.2, 134.7, 136.1, 148.4, 159.3, 161.0, 172.5.

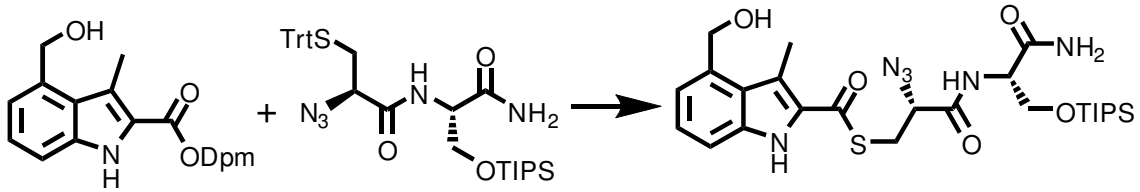
IR (KBr): $\tilde{\nu}$ = 3446 (bs), 2928 (s), 2866 (s), 1661 (s), 1540 (s), 1466 (s), 1411 (s), 1119 (s), 1076 (s), 1022 (s), 906 (s) cm^{-1}.

LC-MS (method C): t_R = 12.15 min, calcd for $C_{36}H_{49}N_4O_5SSi$ $[M + H]^+$, 677.3, found: 677.0.

HRMS (ESI): Calcd for $C_{36}H_{49}N_4O_5SSi$ $[M + H]^+$, 677.3187, found: 677.3186.

Optical rotation: $[\alpha]_D^{20}$ = + 23.3 (c = 0.15, $CHCl_3$).

(2*S*, 2'*R*)-(3'''-Methyl-4'''-hydroxylmethyl-1'''*H*-indol-2''-yl)-2'-azido-3'-thiopropionyl)-2-triisopropylsilanyloxyethyl-2-aminopropanoic amide (354)



341 **326** **354**

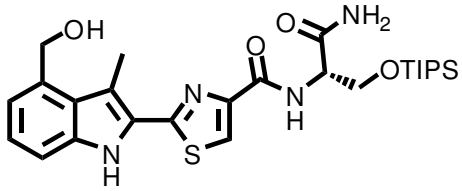
Trifluoroacetic acid (0.1 mL) and triethylsilane (0.1 mL) were added dropwise to a stirred solution of dipeptide **326** (12.8 mg, 20.3 µmol) and hydroxyindole **341** (7.5 mg, 20.2 µmol) in dichloromethane (2 mL) at room temperature under argon (TLC control). Toluene (4 mL) was added to the reaction mixture, and the volatiles were removed in vacuo. The resulting residue was directly used for the next step.

PyBOP (12.6 mg, 24.2 µmol) was added to the mixture of the crude products and DIPEA (6.8 µL, 39.9 µmol) in dichloromethane (1 mL) at room temperature, and the mixture was stirred for 1 hour (TLC control). The reaction mixture was diluted with phosphate buffer (pH 3.0, 10 mL) and extracted with dichloromethane (3 x 10 mL). The combined extracts were dried with sodium sulfate and concentrated. Purification by column chromatography (silica gel, 10 g, ethyl acetate/light petroleum = 1:2) gave 11.4 mg (19.8 µmol, 98%) of thioester **354** as a light yellow resin.

TLC: R_f = 0.56 (ethyl acetate/light petroleum = 1:1).

Maldi-MS: Calcd for $C_{26}H_{41}N_6O_5SSi$ $[M + H]^+$, 577.3, found: 578.2.

(*S*)-1'-Carbamoyl-2'-triisopropylsilanyloxy-ethyl 4''-(hydroxymethyl-3''-methyl-1''*H*-indol-2'-yl)-thiazole-4-carbamide (356)



356

A similar procedure to the preparation of thiazole **355** was used. Thioester **354** (11.4 mg, 19.8 μmol) gave 8.6 mg (16.2 μmol, 82% over two steps) of thiazole **356** as a colorless glass.

TLC: R_f = 0.09 (ethyl acetate/light petroleum = 1:1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.12-1.26 (21H, TIPS), 2.83 (3H, s, CH_3), 3.86 (1H, dd, J = 7.8, 1.5 Hz, CH_2), 4.37 (1H, dd, J = 9.6, 3.7 Hz, CH_2), 4.67-4.71 (1H, m, CH), 5.09 (2H, s, CH_2OH), 5.35 (1H, t, J = 5.7 Hz, OH), 5.62 (1H, s, NH_2), 6.67 (1H, s, NH_2), 7.38 (1H, d, J = 8.2 Hz, CH), 7.61 (1H, dd, J = 7.6, 3.1 Hz, CH), 7.74-7.80 (1H, m, CH), 8.17 (1H, s, CH), 8.26 (1H, d, J = 6.8 Hz, NH), 9.15 (1H, s, NH).

IR (KBr): $\tilde{\nu}$ = 3445 (bs), 2923 (s), 2856 (s), 1790 (s), 1769 (s), 1651 (s), 1645 (s), 1261 (s), 1109 (s), 798 (s) cm^{-1}.

LC-MS (method C): t_R = 11.11 min, calcd for $C_{26}H_{39}N_4O_4SSi$ $[M + H]^+$, 531.3, found: 530.9.

HRMS (ESI): Calcd for $C_{26}H_{39}N_4O_4SSi$ $[M + H]^+$, 531.2456, found: 531.2451.

Optical rotation: $[\alpha]_D^{20}$ = + 30.0 (c = 0.04, $CHCl_3$).

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7. Supporting information.

7.1 Calculation details

Computational data reported in this study were obtained with the Jaguar program-suite version 7.0.[214] Simulations involved full molecular systems with no atom or fragment substitutions. Calculations on closed-shell and open-shell species used the restricted and unrestricted forms of the B3LYP hybrid exchange-correlation functional.[215-217] Molecular geometries were first optimized with a mixed basis set involving 6-31G** on the six atoms involved in the Hetero-Diels-Alder reaction and Si atoms, while all other atoms were treated with the 'midi!' basis set,[218] which contains a minimal but sufficient number of polarization functions for reliable geometry optimizations. Stable intermediates and transition states were confirmed with zero and one imaginary vibrational frequencies, respectively, from this level of calculation. From these geometries, molecular species were further optimized with the 6-31G** basis set on all atoms. Subsequently single point energies were calculated with the 6-311G**+ basis set. Solvation energies were obtained by Jaguar's Poisson-Boltzmann implicit solvation program[219,220] with the 6-311G** basis set and using default parameters for DMF: dielectric constant = 36.7, probe radius = 2.49Å. Since qualitative differences in barriers were not found between gas phase and solvated calculations, solvent-optimized structures were not investigated further.

Crucial to the understanding of these mechanisms was the detection of minimum energy crossing points (MECP) for step-wise reactions.[149] By self-consistently optimizing structures according to both energies and a hybrid gradient of singlet and triplet states, MECPs were found. mPW1PW91/6-31G** and PBE0/6-31G** control calculations were undertaken from B3LYP/6-31G** geometries to ensure that B3LYP calculations could be trusted for these systems. These data provided confidence in our calculations, as easily distinguishable trends were found (Table S1), and suggested qualitative agreement across three functionally different hybrid density functionals. Lastly, NBO calculations were run with NBO 5.0 (Glendening, E. D., Badenhoop, J. K., Reed, A. E., Carpenter, J. E., Bohmann, J. A., Morales, C. M., Weinhold, F. *NBO 5.0*, Theoretical Chemistry Institute, University of Wisconsin, Madison, WI **2001**; http://www.chem.wisc.edu/~nbo5).

Compound	Path A1 B3LYP	Path A1 mPW1PW91	Path A1 PBE0	Path A2 B3LYP	Path A2 mPW1PW91	Path A2 PBE0
121 + 84e	0.0	0.0	0.0	0.0	0.0	0.0
202/208	27.5	24.2	22.1	21.1	18.8	16.4
210	Not identified			19.8	17.2	15.6
	Path B1 B3LYP	Path B1 mPW1PW91	Path B1 PBE0	Path B2 B3LYP	Path B2 mPW1PW91	Path B2 PBE0
195 + 184a	0.0	0.0	0.0	0.0	0.0	0.0
2214/218	29.1	23.4	21.1	21.1	16.9	14.8

Table 6-1. Control calculations on selected structures. All geometries were obtained on the B3LYP/6-31G** level.

Absolute energies and optimized geometries of computed structures

Escf = single-point energy obtained from B3LYP/6-311G**+

Esolv = single-point solvation energy obtained from B3LYP/6-311G**

ZPE, Htot, Stot = thermodynamic terms obtained from B3LYP/(6-31G**|midi!)

121.

Escf = -1368.021173 au

Esolv = -0.012100153 au

ZPE = 206.245 kcal/mol

Htot = 29.2152 kcal/mol

Stot = 122.623 cal/mol*K

N1	-2.4068743629	-0.3042777251	-0.3407848758
C2	-1.2449373178	-0.5207354168	-0.8400739413
C3	-0.1248915381	-0.9683081601	0.0254286023
C4	-0.2761679319	-1.3650645279	1.2960499421
Si5	-4.8822059499	0.4088176106	-0.6504022055
C6	-4.7548615451	1.7950419766	0.6118006414
O7	-3.3288142743	0.0962606727	-1.3155033779
C8	-0.9462820815	-0.2750142998	-2.3062091926
O9	-0.4556656775	0.7475423498	-2.7326451992
O10	1.0722350712	-0.9899229185	-0.6365437004
Si11	2.3453728444	0.1317695848	-0.4753082092
C12	3.4554315748	-0.4109042380	0.9467398894
O14	-1.2935790577	-1.3277066357	-3.0564829815

C15	-1.0725207684	-1.1735827602	-4.4715191394
C16	-5.5573396212	-1.1677587155	0.1187020637
C17	3.2494058000	0.0299962441	-2.1165664181
C18	1.6412591837	1.8459953611	-0.1638560218
C19	-5.8708011685	0.9282430100	-2.1607700038
H20	0.5735287312	-1.7048057178	1.8756054069
H21	-1.2570726832	-1.3630482403	1.7530450686
H22	-6.5550430651	-1.0055681884	0.5424805893
H23	-5.6340231694	-1.9662337291	-0.6266070118
H24	-4.9032531753	-1.5205064760	0.9220158186
H25	-6.9054185856	1.1632509583	-1.8861942169
H26	-5.4390832921	1.8183161331	-2.6293785538
H27	-5.8971211234	0.1319820267	-2.9115075477
H28	-5.7340350729	2.0222878510	1.0482932575
H29	-4.0780341306	1.5189443506	1.4258756189
H30	-4.3707379778	2.7114840851	0.1519218755
H31	-1.4152089158	-2.1037986900	-4.9230214931
H32	-1.6432513743	-0.3246153847	-4.8545956100
H33	-0.0115656012	-1.0131941905	-4.6770061731
H34	2.4440203432	2.5909648118	-0.1209366988
H35	0.9536737371	2.1236883990	-0.9682501011
H36	1.0942043772	1.8921504480	0.7834060714
H37	4.3278263576	0.2474171495	1.0317646794
H38	2.9255475150	-0.3797276661	1.9047134570
H39	3.8208296330	-1.4321740281	0.7971306940
H40	4.1333718507	0.6770026492	-2.1235327482
H41	3.5803329495	-0.9925261631	-2.3258910661
H42	2.5896930917	0.3480585246	-2.9296067148

84e.

Escf = -308.4767775 au

Esolv = -0.008472285 au

ZPE = 69.391 kcal/mol

Htot = 3.948 kcal/mol

Stot = 55.3196 cal/mol*K

C1	-1.2619619877	-0.0004569264	-0.7581515360
C2	-2.3053351050	-0.0006620477	-1.3717757244
C3	-0.0295450725	-0.0004175728	-0.0317634645
C4	-0.0311090573	-0.0004990884	1.3753702518
C5	1.1703447394	-0.0004411302	2.0787818658
C6	2.3872101854	-0.0006226752	1.3936940601
C7	2.3980040701	-0.0006536391	-0.0027135736
C8	1.2011476781	-0.0003748355	-0.7139634068
H9	-0.9792905710	-0.0005069879	1.9034153423

H10	1.1570701778	-0.0002495659	3.1649388267
H11	3.3227886992	-0.0007481406	1.9455341972
H12	3.3421658718	-0.0009124403	-0.5397788677
H13	1.2045493414	-0.0002782921	-1.7992390502
H14	-3.2230472087	-0.0007952645	-1.9115011299

206.

Escf = -1676.446141 au

Esolv = -0.016324988 au

ZPE = 275.73 kcal/mol

Htot = 22.574 kcal/mol

Stot = 145.611 cal/mol*K

N1	-5.1269444817	-2.3445207449	-0.1016205157
C2	-3.8722003135	-1.9081828530	-0.0181973064
C3	-3.5976573987	-0.9247316231	0.9612323026
C4	-4.6454969921	-0.4236591908	1.7102077131
C5	-5.5410246292	-2.2648333365	2.6843582709
C6	-5.6913876909	-3.0695913240	1.7401619800
H7	-5.9990608096	-3.9952819975	1.2984167603
C8	-5.6309569571	-1.9712553594	4.0996080334
C9	-5.0916532766	-2.8771272993	5.0339161339
C10	-5.1872709859	-2.6304019515	6.4011512726
C11	-5.8311496702	-1.4833751664	6.8684249081
C12	-6.3761433672	-0.5819304178	5.9523018572
C13	-6.2715843534	-0.8161160529	4.5830175238
H14	-6.6979369514	-0.1093554427	3.8778937521
H15	-6.8829838973	0.3119394196	6.3051014945
H16	-5.9085420108	-1.2943704530	7.9348865523
H17	-4.7617844363	-3.3414598690	7.1038711578
H18	-4.6035459985	-3.7765214175	4.6718786524
H19	-5.6232314687	-0.3717025304	1.2516632807
H20	-4.4405808125	0.2608502632	2.5252705920
O21	-2.2874632006	-0.6095360333	1.1947946637
Si22	-1.2781266360	-1.0484745075	2.4915997964
C23	-1.5078647899	-2.8578873636	2.9380060075
C24	-1.6595880787	0.0485096254	3.9760360650
C25	0.4467641198	-0.7031743006	1.8339868611
H26	0.6675102912	-1.3444357730	0.9751414503
H27	0.5485129748	0.3385003153	1.5124625474
H28	1.2053922424	-0.8936361611	2.6012511410
H29	-1.5975481566	1.1112711415	3.7177748684
H30	-0.9431478871	-0.1400719841	4.7838694453
H31	-2.6602674508	-0.1473137343	4.3760442234
H32	-0.7567403555	-3.1663633016	3.6750492001

H33	-2.4954685478	-3.0371503538	3.3737602722
H34	-1.4105857119	-3.4890020412	2.0507822079
C35	-2.7575375871	-2.5576015205	-0.8027427621
O36	-1.9767667702	-3.3730079572	-0.3647140435
O37	-2.7284751320	-2.0914131434	-2.0644574421
C38	-1.6953886937	-2.6480974804	-2.8983437466
H39	-1.8068328361	-2.1612121227	-3.8670786723
H40	-0.7097996234	-2.4412727543	-2.4749914522
H41	-1.8219555483	-3.7291483183	-2.9921756871
O42	-5.2104469363	-3.4376825354	-1.0007716697
Si43	-6.5895924960	-3.3490329005	-2.0158568672
C44	-8.1569008911	-3.4442385851	-0.9789000264
H45	-9.0467458003	-3.3249939503	-1.6070528238
H46	-8.1736873907	-2.6557868995	-0.2201689933
H47	-8.2393580983	-4.4080682512	-0.4652604966
C48	-6.3900382396	-4.8686721143	-3.1036572868
H49	-5.4720182398	-4.8131197609	-3.6972436434
H50	-7.2327194176	-4.9641189502	-3.7979026756
H51	-6.3466487532	-5.7833425881	-2.5033488396
C52	-6.5238660144	-1.7595550497	-3.0167707434
H53	-7.3241631838	-1.7264077716	-3.7642462063
H54	-5.5652082699	-1.6726083002	-3.5379896803
H55	-6.6292695050	-0.8831624250	-2.3698423552

208.

Escf = -1676.455155 au

Esolv = -0.01493804 au

ZPE = 275.898 kcal/mol

Htot = 20.867 kcal/mol

Stot = 145.877 cal/mol*K

C1	-0.3195099725	1.3348363015	1.0298577123
C2	-0.1690331611	0.9254382739	-0.2983629537
C3	-1.3284189698	0.5747907917	-1.0550108582
N4	-2.5061395619	0.7534270408	-0.5076051702
C5	-1.9261971469	-0.8268249602	1.8238993138
C6	-0.8472710509	-0.2330167021	2.0443140018
C7	-4.3878718257	-3.2564621006	0.4390310308
C8	-3.2548232466	-2.4583583988	0.5517496376
C9	-3.1034054299	-1.5849570113	1.6562589524
C10	-4.1402408427	-1.5274754766	2.6183484492
C11	-5.2728732594	-2.3218615891	2.4849722318
C12	-5.4017959729	-3.1940762581	1.3995654732
O13	1.0411281472	0.6797996227	-0.8760636869
Si14	2.2352854024	-0.4814144612	-0.5261657476

C15	3.2142016008	0.0696765024	0.9899997850
O16	-3.5158458629	0.2085024391	-1.3088660359
Si17	-4.9943919091	1.0788928313	-1.2372877637
C18	-5.5632704429	1.3147511353	0.5367506638
C19	-1.1799333090	-0.1153472180	-2.3917293633
O20	-1.4099866580	0.7317003555	-3.4068238025
C21	-1.3271291321	0.1525128963	-4.7214182465
O22	-0.8909340975	-1.2852472365	-2.5311373389
C23	1.4614496338	-2.1690881163	-0.2444633394
C24	3.3224103150	-0.4550533234	-2.0563824635
C25	-4.7407481600	2.7399380132	-2.0866882056
C26	-6.1606442061	-0.0297984525	-2.2072473587
H27	0.5747805073	1.6683074852	1.5482887153
H28	-1.2176715496	1.8942803185	1.2619358047
H29	-6.5028543112	1.8795780276	0.5663091219
H30	-5.7252534099	0.3529844328	1.0319279530
H31	-4.8173101442	1.8675905112	1.1149496644
H32	-7.1594296778	0.4159783190	-2.2746209646
H33	-5.7986719091	-0.1967592551	-3.2269025941
H34	-6.2585831960	-1.0049878376	-1.7200231495
H35	-5.6767881962	3.3078354143	-2.1381645758
H36	-4.0101163261	3.3473378414	-1.5425962247
H37	-4.3674910302	2.6070864916	-3.1075565589
H38	-1.5393631049	0.9669695149	-5.4136119911
H39	-0.3284223897	-0.2534654422	-4.8998584393
H40	-2.0614077300	-0.6490810718	-4.8313601267
H41	4.0619103428	-0.6035562170	1.1637577794
H42	3.6138361200	1.0809423899	0.8607858530
H43	2.6033600195	0.0633919173	1.8988974507
H44	2.2398299005	-2.9303230117	-0.1152580852
H45	0.8276815092	-2.1788144793	0.6479239052
H46	0.8350721071	-2.4476956738	-1.0966634650
H47	4.1803745592	-1.1263248982	-1.9421359062
H48	2.7581031466	-0.7785475697	-2.9360934105
H49	3.7068792099	0.5517591019	-2.2520321537
H50	-4.0324909619	-0.8622136244	3.4687272140
H51	-6.0566496336	-2.2680060526	3.2356247291
H52	-6.2848479305	-3.8192971546	1.3037090019
H53	-4.4850164727	-3.9270682924	-0.4102917548
H54	-2.4808317898	-2.4889306891	-0.2080646949
H55	0.0129087991	-0.3683734883	2.6797603697

210 (A2 reaction).

Escf = -1676.460783 au

Esolv = -0.017079452 au

ZPE = 275.824 kcal/mol

Htot = 20.982 kcal/mol

Stot = 130.929 cal/mol*K

C1	-1.9157751783	1.4826507461	1.2227768798
C2	-1.1801584126	1.1359178902	0.0376500691
C3	-1.8583731798	0.7809595344	-1.1619947492
N4	-3.1692654298	0.8392764198	-1.1955112633
C5	-2.5428364946	-0.3350531053	2.9537892531
C6	-2.7289551443	0.1226022237	1.7857762871
C7	-2.3547120904	-0.3969268070	6.6625998446
C8	-2.7775362474	-0.0838294652	5.3800448190
C9	-2.1271262304	-0.6463035327	4.2465367653
C10	-1.0492286362	-1.5477001936	4.4724339703
C11	-0.6494777158	-1.8581237188	5.7630954154
C12	-1.2924881683	-1.2850761654	6.8660214903
O13	0.1509153379	0.8535429260	0.0793798377
Si14	1.4489905961	1.8930566332	0.4435928845
C15	1.1497654036	3.5467712764	-0.4019592488
O16	-3.6535573685	0.4886891372	-2.4631576595
Si17	-5.3647055382	0.5150408834	-2.5552942881
C18	-6.0811263758	-0.7941462746	-1.4114297206
C19	-1.0541048150	0.2788687249	-2.3431263469
O20	-0.5111421915	1.3066964848	-3.0307602130
C21	0.2427011836	0.9224727327	-4.1956334570
O22	-0.9152832857	-0.8840685927	-2.6335503009
C23	1.6226369446	2.1033518508	2.3073593233
C24	2.9424485646	0.9969221205	-0.2556291505
C25	-5.9971435752	2.2311842704	-2.1152887232
C26	-5.6793960960	0.1002840261	-4.3601845169
H27	-1.2964148829	1.8469818053	2.0376105685
H28	-2.7473041460	2.1585873788	1.0205950359
H29	-7.1730498096	-0.8362030775	-1.4975551342
H30	-5.6861078681	-1.7854101863	-1.6563791255
H31	-5.8359673793	-0.5842114295	-0.3659155032
H32	-6.7538738031	0.0737425616	-4.5732531884
H33	-5.2254879295	0.8443705909	-5.0223587718
H34	-5.2620956643	-0.8780109227	-4.6185009498
H35	-7.0908067232	2.2753710701	-2.1721093184
H36	-5.7001989886	2.5070360156	-1.0991866722
H37	-5.5943617604	2.9852924337	-2.7991316051
H38	0.5971342890	1.8537849205	-4.6367949092
H39	1.0832694559	0.2829411673	-3.9160277459
H40	-0.3938928099	0.3812334493	-4.8990830220
H41	0.2873946713	4.0682106565	0.0265609405
H42	2.0208596664	4.2027385817	-0.2983285285
H43	0.9518870648	3.4034035852	-1.4685068991
H44	2.5643964316	2.6113409916	2.5448661727
H45	0.8124894264	2.7011254915	2.7381588462
H46	1.6305128680	1.1344054159	2.8169114468

H47	3.8665134028	1.5466873769	-0.0462388199
H48	3.0401614522	-0.0015451894	0.1823489802
H49	2.8590455889	0.8776097365	-1.3400999491
H50	-0.5480291108	-1.9883534501	3.6167950711
H51	0.1748672790	-2.5491561170	5.9160113804
H52	-0.9705683276	-1.5296695805	7.8735126388
H53	-2.8582797706	0.0492957469	7.5155205556
H54	-3.6074817863	0.5976823232	5.2230211772
H55	-3.3925520461	-0.2007441873	0.9806130579

MECP-1.

Escf = -1676.460525 au

Esolv = -0.015546449 au

(frequencies with the hybrid density matrix were not computed)

C1	-1.9258438300	1.4702060100	1.2318738700
C2	-1.1825475700	1.1290432400	0.0358135700
C3	-1.8576971500	0.7791560300	-1.1619289700
N4	-3.1717016700	0.8398006900	-1.1965685900
C5	-2.5379487800	-0.3298693500	2.9525410300
C6	-2.7187461700	0.1379915300	1.7813269100
C7	-2.3559657600	-0.3971813000	6.6613949600
C8	-2.7792510500	-0.0839642200	5.3790302100
C9	-2.1275825800	-0.6452205600	4.2427637700
C10	-1.0491132800	-1.5487043100	4.4705265200
C11	-0.6500430600	-1.8588312600	5.7614178700
C12	-1.2929309300	-1.2854891100	6.8654942400
O13	0.1484710500	0.8583028800	0.0797624600
Si14	1.4500028000	1.8946050500	0.4442607600
C15	1.1504650400	3.5476460000	-0.4019944100
O16	-3.6539429800	0.4893599800	-2.4629027100
Si17	-5.3655860500	0.5151982100	-2.5556573000
C18	-6.0814319500	-0.7942305900	-1.4113904400
C19	-1.0543636400	0.2785126700	-2.3437607600
O20	-0.5109532400	1.3066565600	-3.0313088300
C21	0.2425392800	0.9224413200	-4.1956007000
O22	-0.9149128700	-0.8842754700	-2.6360511500
C23	1.6231737000	2.1034579000	2.3082555000
C24	2.9422286900	0.9968727400	-0.2554632000
C25	-5.9974776200	2.2315543400	-2.1154352500
C26	-5.6797761700	0.1003717600	-4.3607679900
H27	-1.2994583400	1.8443710700	2.0386869400
H28	-2.7416008600	2.1647956000	1.0216489200
H29	-7.1735686800	-0.8364136400	-1.4973637900
H30	-5.6861364900	-1.7855225900	-1.6565048500
H31	-5.8356788800	-0.5840096600	-0.3659267700

H32	-6.7544008400	0.0735226800	-4.5740606300
H33	-5.2255902000	0.8447098000	-5.0228573300
H34	-5.2621613400	-0.8780082600	-4.6188048900
H35	-7.0912231700	2.2758879000	-2.1720413500
H36	-5.6999012600	2.5070396100	-1.0990822000
H37	-5.5943123300	2.9857562100	-2.7994094700
H38	0.5973166900	1.8538124000	-4.6370899200
H39	1.0834832100	0.2825735900	-3.9164188900
H40	-0.3937301400	0.3807855100	-4.8995486600
H41	0.2874959200	4.0682512900	0.0267767900
H42	2.0213839100	4.2045899800	-0.2988053300
H43	0.9520533400	3.4031856600	-1.4687789900
H44	2.5650286400	2.6116302300	2.5463729200
H45	0.8126780500	2.7010167900	2.7381645000
H46	1.6304299400	1.1341171700	2.8173869000
H47	3.8668923200	1.5466355500	-0.0464470800
H48	3.0398323800	-0.0017735400	0.1827482600
H49	2.8587503100	0.8774219600	-1.3402828900
H50	-0.5466990300	-1.9895592800	3.6152746300
H51	0.1746716900	-2.5497296100	5.9149585100
H52	-0.9707849900	-1.5298733900	7.8733186900
H53	-2.8588912400	0.0495340500	7.5149788300
H54	-3.6091074900	0.5982471100	5.2230889500
H55	-3.3902804700	-0.2065081000	0.9897109500

211 (singlet)

Escf = -1676.472784 au

Esolv = -0.016877075 au

ZPE = 276.131 kcal/mol

Htot = 22.966 kcal/mol

Stot = 148.844 kcal/mol

211 (triplet)

Escf = -1676.470617 au

Esolv = -0.016867637 au

ZPE = 276.131 kcal/mol

Htot = 22.966 kcal/mol

Stot = 148.844 kcal/mol

C1	-0.6510527811	1.5978365381	1.4199011583
C2	-0.5252218810	1.3046569946	-0.0519179390
C3	-1.6214332140	1.1375021492	-0.8931556590
N4	-2.8618636094	1.2602998418	-0.4051966471
C5	-1.1108101410	-0.2868785848	3.0160350120
C6	-0.2835091576	0.3766419183	2.2586049119
C7	-3.5014360602	-2.9001438347	4.0879028470
C8	-2.6779187342	-2.1421746485	3.2751663649
C9	-1.9305653739	-1.0444168069	3.8163132668
C10	-2.0735202726	-0.7668947424	5.2150001338
C11	-2.9028738644	-1.5421171267	6.0050097687
C12	-3.6237227833	-2.6127550523	5.4555635369
O13	0.7065682830	1.0552943988	-0.5630323899
Si14	2.0964130192	2.0299504780	-0.6785222188
C15	3.0320922228	1.3148857195	-2.1387073811
O16	-3.7981387586	1.1246605092	-1.4340591765
Si17	-5.3864920323	0.8768019391	-0.8313751484
C18	-5.4402310626	-0.7457119854	0.1155161370
C19	-1.3920997687	0.7461333883	-2.3370055376
O20	-1.0377581390	1.8151238862	-3.0847616434
C21	-0.8425714048	1.5331681392	-4.4827184379
O22	-1.5125339296	-0.3737656612	-2.7723594441
C23	1.5645076760	3.8083732803	-0.9803194075
C24	3.1194015455	1.8664356805	0.8949286225
C25	-5.8855832239	2.3298500514	0.2522884666
C26	-6.4136905867	0.7951682081	-2.4027186521
H27	0.0145393879	2.4328573581	1.6845860350
H28	-1.6763094040	1.9027943217	1.6318692107
H29	-6.4507018029	-0.9566677874	0.4838254102
H30	-5.1348282618	-1.5787949685	-0.5262504404
H31	-4.7662747802	-0.7207898779	0.9773232017
H32	-7.4708692777	0.6261142522	-2.1685218186
H33	-6.3425118904	1.7266760483	-2.9734265729
H34	-6.0793262116	-0.0220531422	-3.0495204629
H35	-6.8955084423	2.1918319761	0.6548939144
H36	-5.1966990254	2.4377498691	1.0951274093
H37	-5.8739076918	3.2663821328	-0.3147818640
H38	-0.5834697778	2.4870172441	-4.9418753309
H39	-0.0379452010	0.8066246986	-4.6205235294
H40	-1.7587758715	1.1312532752	-4.9214695760
H41	3.9936901520	1.8208510386	-2.2799760469
H42	3.2328253837	0.2491150993	-1.9890829637
H43	2.4559225166	1.4190171119	-3.0632186206
H44	2.4285437075	4.4413531388	-1.2118079863
H45	0.8683090701	3.8579297008	-1.8235745407
H46	1.0625755611	4.2403495972	-0.1082817614
H47	4.0596652767	2.4224145852	0.7999568620
H48	2.5960236862	2.2533939990	1.7750938536
H49	3.3742950516	0.8192451940	1.0900090704
H50	-1.5161112513	0.0603580081	5.6424070380

H51	-2.9946412167	-1.3170257678	7.0640191033
H52	-4.2714380418	-3.2152110255	6.0848143936
H53	-4.0576740469	-3.7288193704	3.6586244489
H54	-2.5816200700	-2.3668376164	2.2179907354
H55	0.7537488159	0.0387970750	2.1631454799

MECP-2

Escf = -1676.437403 au

Esolv = -0.018568271 au

(frequencies with the hybrid density matrix were not computed)

C1	-0.5222416700	-2.1116327300	1.3429083100
C2	-0.4733550500	-0.8205848200	2.0794262300
C3	0.6832202200	-0.4858352800	2.7817254900
N4	1.6766724900	-1.4052347100	2.6994370300
C5	1.6649378000	-1.8305695900	0.0837665500
C6	0.4010298000	-2.1381119000	0.0955721600
C7	4.6039594800	-0.2023429300	-1.5027420500
C8	3.3092347500	-0.4098737500	-1.0507713400
C9	2.9434007900	-1.6410400000	-0.4337281500
C10	3.9417657700	-2.6523916200	-0.3166807500
C11	5.2308842500	-2.4216257300	-0.7702597300
C12	5.5776228800	-1.1991596500	-1.3571670700
O13	-1.5507398000	-0.0034517700	2.0868830900
Si14	-2.2792265800	0.8340910700	0.7935495500
C15	-3.3189720600	2.1390971400	1.6495767800
O16	2.7768119400	-1.1981572400	3.4958542200
Si17	4.0130837300	-0.0309096900	3.6576805800
C18	4.0214221400	0.5775990100	5.4384104800
C19	0.6979842200	0.7181260800	3.6758335000
O20	0.4226490100	1.8589633500	2.9994091900
C21	0.3204600700	3.0410999500	3.8117400500
O22	0.9160183700	0.6898524500	4.8673550400
C23	-0.9561849400	1.5727700000	-0.3210823900
C24	-3.3737259500	-0.3517594800	-0.1778941100
C25	5.6176975100	-0.9514803000	3.3268979200
C26	3.8179927300	1.3769270500	2.4232158400
H27	-0.1871863200	-2.9152161600	2.0103906600
H28	-1.5483295900	-2.3297590700	1.0413792900
H29	4.9008923000	1.2102049500	5.6092810500
H30	3.1210709200	1.1454050500	5.6802085200
H31	4.0768596100	-0.2649293900	6.1360208500
H32	4.6868058900	2.0391575700	2.5164679300
H33	3.7993464300	0.9958699200	1.3976021100
H34	2.9189647900	1.9781549800	2.5763726800
H35	6.4764559400	-0.3017303800	3.5342673200

H36	5.7010142400	-1.8306694300	3.9742233000
H37	5.6823794200	-1.2870106600	2.2875250500
H38	0.0340929900	3.8380178600	3.1260497100
H39	-0.4351662500	2.9030774400	4.5881745300
H40	1.2801022800	3.2670582700	4.2828200800
H41	-3.9012108800	2.7218488200	0.9276257900
H42	-4.0201422100	1.6739527700	2.3503030700
H43	-2.6896991000	2.8319205600	2.2164257500
H44	-1.4148396900	2.1166853100	-1.1549942100
H45	-0.3146662400	2.2654385100	0.2311805800
H46	-0.3158261000	0.7917240600	-0.7445159600
H47	-3.9788333900	0.1986088400	-0.9072588700
H48	-2.7891934300	-1.0944014200	-0.7308588300
H49	-4.0592143900	-0.8880701200	0.4866244200
H50	3.6800662700	-3.6000132900	0.1433160400
H51	5.9797951900	-3.2022777900	-0.6666884300
H52	6.5932213300	-1.0221369700	-1.6953455700
H53	4.8605250300	0.7429941700	-1.9697124300
H54	2.5555792600	0.3631474400	-1.1659415200
H55	-0.0917234000	-2.4668376700	-0.8256540600

207.

Escf = -1676.552918 au

Esolv = -0.01226449 au

ZPE = 280.623 kcal/mol

Htot = 21.416 kcal/mol

Stot = 13.269 cal/mol*K

C1	-0.1933928884	-1.3051189527	1.3321071731
C2	-0.0455516677	-0.4974145344	0.0668837840
C3	-1.1469666018	0.0677784229	-0.5082027969
N4	-2.4577876548	-0.2120182549	-0.0093576671
C5	-2.5488540112	-0.5435414657	1.3835369280
C6	-1.4899324337	-1.0438200775	2.0356107339
C7	-5.5751877127	-0.7706740790	3.6583956242
C8	-4.3734114629	-1.0860456524	3.0272508320
C9	-3.8547130040	-0.2570837851	2.0215247318
C10	-4.5775770813	0.8886592707	1.6539117352
C11	-5.7775195878	1.2039119035	2.2876376808
C12	-6.2808683716	0.3762228309	3.2923895535
O13	1.2250358079	-0.3133416782	-0.2914185082
Si14	2.2136793277	-0.6259687739	-1.6565680934
C15	3.4708284522	-1.8619345166	-0.9854658445
O16	-2.9752095486	-1.4231611487	-0.6994592305
Si17	-4.1271778026	-1.3010559357	-1.9457660295

C18	-4.9832264317	-2.9780531036	-1.8633235204
C19	-1.0454841817	1.0692784615	-1.5844082440
O20	-2.2119589454	1.7272108018	-1.8035581715
C21	-2.1441021527	2.7612270869	-2.7974809929
O22	-0.0323764620	1.3347628547	-2.2139615004
C23	1.2367571461	-1.4263401968	-3.0474255165
C24	3.0906466671	0.9612800665	-2.1310517022
C25	-5.3637484293	0.0937782776	-1.7020250034
C26	-3.2714539229	-1.1220970167	-3.6205812576
H27	-0.0826395658	-2.3744747459	1.0893178181
H28	0.6638515567	-1.0605858734	1.9704835683
H29	-5.7117058935	-3.0872500389	-2.6748331480
H30	-4.2634570506	-3.7987458701	-1.9489357201
H31	-5.5148932483	-3.0972043021	-0.9138198549
H32	-4.0015730430	-1.1955232650	-4.4358330259
H33	-2.7626851100	-0.1588044114	-3.7178408601
H34	-2.5279904884	-1.9116903159	-3.7705791194
H35	-6.0816684014	0.1015357851	-2.5308583488
H36	-5.9227165112	-0.0191783365	-0.7692266270
H37	-4.8576325080	1.0623161004	-1.6799823628
H38	-3.1506940333	3.1761183688	-2.8559112611
H39	-1.4283287606	3.5328231368	-2.5034912252
H40	-1.8412128154	2.3537661062	-3.7652501229
H41	4.2218760564	-2.1089256617	-1.7445252195
H42	3.9985747812	-1.4570663606	-0.1155496303
H43	2.9910408344	-2.7975674872	-0.6784011461
H44	1.9265339602	-1.8507603619	-3.7861509718
H45	0.6123025969	-2.2455979837	-2.6737525150
H46	0.5905610924	-0.7030680774	-3.5473966676
H47	3.8503594540	0.7642274709	-2.8965733890
H48	2.3816721416	1.6949357489	-2.5174301725
H49	3.6003770873	1.3939947447	-1.2632440746
H50	-4.1804864886	1.5244893297	0.8701233648
H51	-6.3211128959	2.0986898242	1.9968397781
H52	-7.2197322885	0.6197538033	3.7818879008
H53	-5.9678787809	-1.4280647612	4.4289291766
H54	-3.8416959355	-1.9939445908	3.2967310922
H55	-1.5425839154	-1.2266351163	3.1045819893

209.

Escf = -1676.555791 au

Esolv = -0.015824897 au

ZPE = 280.473 kcal/mol

Htot = 21.66 kcal/mol

Stot = 139.957 cal/mol*K

N1	-4.9768301863	-2.2862815145	0.3636097768
C2	-3.6350204933	-1.8202796700	0.4448854645
C3	-3.1673453112	-1.2194581229	1.5686926187
C4	-4.0210762302	-0.9992216386	2.7878226677
C5	-5.3847302434	-1.6341628749	2.6819678991
C6	-5.7448895512	-2.2401515227	1.5361830294
H7	-6.7171390210	-2.7009763219	1.4159803737
C8	-6.3042705848	-1.5526799862	3.8388366291
C9	-7.3333901292	-2.4952135933	4.0306322326
C10	-8.2033108153	-2.4027648417	5.1111113904
C11	-8.0642136436	-1.3731845709	6.0448424728
C12	-7.0386213374	-0.4443288850	5.8845259503
C13	-6.1679746445	-0.5350706115	4.7989369091
H14	-5.3843104078	0.2080697444	4.6930793853
H15	-6.9130823752	0.3588027505	6.6053149781
H16	-8.7414471614	-1.3043488207	6.8910441572
H17	-8.9857726938	-3.1464743144	5.2338728483
H18	-7.4372201722	-3.3260807528	3.3396871256
H19	-4.0866814637	0.0904031248	2.9356501187
H20	-3.4889796568	-1.3706697606	3.6771159424
O21	-1.9689666178	-0.6019814192	1.6318758936
Si22	-0.4288606015	-1.1858735371	2.0797706498
C23	-0.4117257250	-3.0646510373	2.0679058333
C24	-0.1138649111	-0.5396215557	3.8238685842
C25	0.7930962860	-0.4290741280	0.8769659589
H26	0.5817858369	-0.7754765720	-0.1375170747
H27	0.7280699041	0.6640679687	0.8879257750
H28	1.8219074948	-0.7048949639	1.1355623166
H29	-0.2046831303	0.5510058178	3.8634501287
H30	0.8957905662	-0.8011547574	4.1612205169
H31	-0.8214214777	-0.9598284171	4.5470500389
H32	0.5665367243	-3.4348372435	2.3960791156
H33	-1.1655206758	-3.4838930028	2.7430936823
H34	-0.6060937752	-3.4412364740	1.0609102826
C35	-2.8198382914	-1.8839460916	-0.7916109915
O36	-1.6050320949	-1.9563714530	-0.8276790705
O37	-3.5710350025	-1.8213179944	-1.9167007032
C38	-2.8238042522	-1.8625158665	-3.1427349639
H39	-3.5670352201	-1.8251011815	-3.9392453506
H40	-2.1473177214	-1.0070742113	-3.2104229361
H41	-2.2356554396	-2.7811855452	-3.2073685022
O42	-4.9709582463	-3.6578058092	-0.1430045015
Si43	-6.1219450561	-4.0475229473	-1.3481134187
C44	-7.4661127757	-5.0988789509	-0.5383992982
H45	-8.1628218577	-5.4884204932	-1.2900554611
H46	-8.0549840826	-4.5249072024	0.1856664086
H47	-7.0336523019	-5.9555269575	-0.0106573241
C48	-5.1862516879	-5.0986097293	-2.5973103824
H49	-4.4288384925	-4.5104147311	-3.1235262770

H50	-5.8674678590	-5.5220761181	-3.3442294163
H51	-4.6767841845	-5.9316544548	-2.1020182870
C52	-6.8816181049	-2.5137542272	-2.1248222948
H53	-7.5291200106	-2.7971820071	-2.9629904289
H54	-6.1047700948	-1.8394103413	-2.4918114419
H55	-7.4906479662	-1.9571160862	-1.4058451616

195.

Escf = -998.5603439 au

Esolv = -0.013067671 au

ZPE = 160.106 kcal/mol

Htot = 22.4788 kcal/mol

Stot = 103.278 cal/mol*K

N1	-0.0039742847	0.0747551811	-0.0049764203
C2	-0.0578067791	-0.0034327500	1.2760452938
C3	1.1942623375	-0.0689314744	2.0717806208
C4	2.4185805669	-0.1293205157	1.5311975962
O5	-1.2700125682	0.0926503850	-0.5797261032
C6	-1.3654176587	-0.1011874786	2.0359223249
O7	-1.7850651633	-1.1307929314	2.5187856791
O8	0.9522803352	-0.0147898145	3.4160169241
Si9	1.2572931612	-1.2320157783	4.5691874223
C10	3.0120046081	-1.0371617830	5.2272586732
O11	-1.9875074656	1.0819884712	2.0999068711
C12	-3.2557216214	1.0748195671	2.7822750037
C13	-0.0029726411	-0.8967623811	5.9191955372
C14	1.0093829999	-2.9167861404	3.7764725462
H15	3.3039287693	-0.1317433297	2.1550716253
H16	2.5354093252	-0.1551087806	0.4558119553
H17	-3.6202175623	2.1000630760	2.7304592760
H18	-3.9501090415	0.3923247956	2.2869867457
H19	-3.1288575891	0.7633457312	3.8217559113
H20	1.1196505044	-3.7158083503	4.5182707916
H21	0.0072900003	-2.9821104866	3.3421002443
H22	1.7367540647	-3.0980546647	2.9790354686
H23	3.1988382324	-1.7416059110	6.0460742376
H24	3.7603976300	-1.2301047259	4.4515051077
H25	3.1799437272	-0.0261576157	5.6125325673
H26	0.1217933466	-1.5883313396	6.7596155575
H27	0.0919465797	0.1227738334	6.3069146140
H28	-1.0173490904	-1.0192821812	5.5270079633
C29	-1.1410414711	0.1942948316	-1.9967177622
H30	-2.1628790002	0.1878448174	-2.3807893194
H31	-0.6419416085	1.1267068654	-2.2797870298

H32	-0.5842177562	-0.6568103852	-2.4018266252

184a.

Escf = -494.2556917 au

Esolv = -0.018479417 au

ZPE = 83.573 kcal/mol

Htot = 7.879 kcal/mol

Stot = 69.1075 cal/mol*K

C1	-1.4059583453	0.5797022385	-0.1148708337
C2	-1.8484472480	1.3032439722	-1.1861717156
C3	1.1116599938	0.9288071925	-0.1013785405
C4	-0.0736057935	0.3741127732	0.4272407165
C5	0.0207423882	-0.4478516032	1.5709658206
C6	1.2479871898	-0.7087790563	2.1678915873
C7	2.4104592700	-0.1524104847	1.6325574168
C8	2.3358556399	0.6635589283	0.5002568572
H9	-0.8843831502	-0.8813815681	1.9875536161
H10	1.2988182044	-1.3434913753	3.0469629794
H11	3.3722752352	-0.3531737773	2.0948956252
H12	3.2397101672	1.0962717173	0.0831990732
H13	1.0795700103	1.5635244432	-0.9776288427
C14	-3.2510834300	1.3202741407	-1.4866265736
H15	-2.1942447769	0.0651795652	0.4294511616
C16	-1.0218971563	2.0715949334	-2.0668836794
N17	-0.3708283267	2.7028957817	-2.7960900003
N18	-4.3895801518	1.3305543586	-1.7257408487

stepwise (195 + 184a)

Escf = -1492.749435 au

Esolv = -0.027209847 au

ZPE = 242.894 kcal/mol

Htot = 21.205 kcal/mol

Stot = 139.555 cal/mol*K

C1	-0.4518986662	0.6716825725	-0.2388180839
C2	-0.4569253805	0.9103089228	1.1898341355
N3	2.8252116819	0.3407456542	-2.2138687418
C4	0.6796344686	-0.6652284495	-0.6320059792

C5	0.8234141719	-0.9098125241	-2.0314617214
C6	1.8969710356	-0.3477553434	-2.8157385168
O7	3.7750082974	0.8048725419	-3.0949808935
C8	4.6427319708	1.7201300698	-2.4187165651
C9	1.8954521573	-0.5659540852	-4.3174090142
O10	1.1276711779	-0.0352578186	-5.0825186922
O11	2.8609794268	-1.4337171072	-4.6765188079
C12	3.0041101311	-1.6335499210	-6.0970740144
O13	-0.1775730922	-1.4780596080	-2.7158654462
Si14	-0.6896777862	-3.0727826965	-3.0610259710
C15	-1.5441756402	-2.9150381982	-4.7180021227
C16	0.8464681928	-4.1593577830	-3.1358795999
C17	-1.8678186040	-3.6390055445	-1.7128697723
C18	-0.9895619481	0.0682674032	2.2074039546
C19	-0.7398963752	0.4217742542	3.5637475217
C20	-1.2124091788	-0.3490653325	4.6120901686
C21	-1.9465850778	-1.5143606511	4.3583172133
C22	-2.2048701370	-1.8852935183	3.0368336450
C23	-1.7449057890	-1.1143413986	1.9762251426
H24	-1.9995238618	-1.4122077987	0.9671014650
H25	-2.7830515187	-2.7815455610	2.8296584779
H26	-2.3157710586	-2.1201657021	5.1802637305
H27	-1.0072381796	-0.0476489906	5.6354934336
H28	-0.1660901141	1.3212027290	3.7699068171
H29	-2.7054277134	-2.9411213409	-1.6172181665
H30	-1.3712647762	-3.7144129609	-0.7393108077
H31	-2.2764305746	-4.6282837620	-1.9502061364
H32	1.2759055706	-4.3182255421	-2.1409006200
H33	0.5971951581	-5.1450052721	-3.5452333794
H34	1.6219840617	-3.7164877057	-3.7686104014
H35	-1.8971507860	-3.8876830425	-5.0779783347
H36	-0.8663879191	-2.4937240410	-5.4668319910
H37	-2.4083041912	-2.2476533171	-4.6431796654
H38	2.0817391266	-2.0318442743	-6.5257669667
H39	3.2449175958	-0.6880370378	-6.5877558852
H40	3.8207916972	-2.3454783753	-6.2100120794
H41	4.0674477360	2.5487919476	-1.9962148405
H42	5.3304589091	2.0841106579	-3.1830485738
H43	5.1969775286	1.2106336820	-1.6237980546
H44	0.1958041027	-1.4720838163	-0.0809622148
H45	0.1806377227	1.7251155587	1.5168400630
N46	0.4124503322	2.8073196707	-1.5024755959
C47	0.0231571058	1.8611978174	-0.9549884177
N48	-2.7793740292	-0.0445724278	-1.2353022355
C49	-1.7434144201	0.2606412003	-0.8088830952
H50	1.6038715183	-0.3392135213	-0.1639437067

concerted (214)

Escf = -1492.764868 au

Esolv = -0.028632711 au

ZPE = 244.557 kcal/mol

Htot = 20.597 kcal/mol

Stot = 134.897 cal/mol*K

c1	0.0000000000	0.0000000000	0.0000000000
c2	0.0000000000	0.0000000000	1.4500530133
n3	1.7947106022	0.0000000000	2.0785568383
c4	2.1694259675	-0.2691541665	-0.5340431178
c5	2.7358302546	0.8374957702	0.0959421172
c6	2.5491466010	0.9447485899	1.4855634762
o7	1.6740511276	0.2716255472	3.4585204162
c8	2.0557231508	-0.8861300047	4.2103233062
c9	2.9121846343	2.2177062252	2.2078683251
o10	2.0905263504	3.0292424741	2.5645994347
o11	4.2373043282	2.3314488969	2.3790757330
c12	4.6671657406	3.5508836063	3.0174397426
o13	3.2286514325	1.9251200137	-0.5384641450
si14	3.8593029332	2.1547072989	-2.1083159118
c15	4.5408300901	3.8993378482	-2.0264431410
c16	5.2179662292	0.8838716465	-2.4038389720
c17	2.4967715829	2.0243241998	-3.3960848128
c18	-0.6432225322	-1.0951745541	2.2204081607
c19	-1.5109520073	-0.7415331443	3.2637443089
c20	-2.1683812140	-1.7192292536	4.0074346668
c21	-1.9571977196	-3.0686692950	3.7270865281
c22	-1.0805450736	-3.4333957389	2.7035474382
c23	-0.4263547444	-2.4572973791	1.9550747898
h24	0.2511457321	-2.7606561381	1.1659232216
h25	-0.9081245386	-4.4829509441	2.4824259779
h26	-2.4707741340	-3.8326585591	4.3028163256
h27	-2.8453068307	-1.4254066978	4.8042242336
h28	-1.6747502446	0.3094895360	3.4856807936
h32	1.5992031445	2.5585659932	-3.0701529257
h33	2.2079232056	0.9898729858	-3.6084458020
h34	2.8334252936	2.4671937541	-4.3410461556
h35	4.8427696303	-0.1435509088	-2.3474693458
h36	5.6558540817	1.0179218263	-3.3992147253
h37	6.0219868152	0.9859556785	-1.6681414335
h38	4.9900323477	4.1898259955	-2.9826162113
h39	5.3080315339	3.9908132204	-1.2513961833
h40	3.7440697272	4.6149707804	-1.8000165149
h41	4.3752646251	4.4163084182	2.4184164444
h42	4.2213974897	3.6388981387	4.0102792791
h43	5.7521060373	3.4775847908	3.0862948172
h44	1.4579190566	-1.7572758663	3.9323745451

h45	1.8644216296	-0.6185569188	5.2514282517
h46	3.1212896245	-1.1048367558	4.0731533252
H44	2.1299588085	-0.3365541823	-1.6148303577
H45	-0.2050702241	0.9826751552	1.8654495956
N47	-0.3678728291	2.2916531661	-1.1696659642
C48	-0.2069794549	1.2636222988	-0.6477774792
N48	-0.8202878490	-2.0159819666	-1.4163840098
C49	-0.4764314223	-1.1194032830	-0.7583743775
H50	2.1448579475	-1.2017742433	0.0135446953

concerted (218)

Escf = -1492.777972 au

Esolv = -0.034961266 au

ZPE = 243.795 kcal/mol

Htot = 21.052 kcal/mol

Stot = 138.981 cal/mol*K

c1	0.0000000000	0.0000000000	0.0000000000
c2	0.0000000000	0.0000000000	1.4500530133
n3	1.7947106022	0.0000000000	2.0785568383
c4	2.1694259675	-0.2691541665	-0.5340431178
c5	2.7358302546	0.8374957702	0.0959421172
c6	2.5491466010	0.9447485899	1.4855634762
o7	1.6740511276	0.2716255472	3.4585204162
c8	2.0557231508	-0.8861300047	4.2103233062
c9	2.9121846343	2.2177062252	2.2078683251
o10	2.0905263504	3.0292424741	2.5645994347
o11	4.2373043282	2.3314488969	2.3790757330
c12	4.6671657406	3.5508836063	3.0174397426
o13	3.2286514325	1.9251200137	-0.5384641450
si14	3.8593029332	2.1547072989	-2.1083159118
c15	4.5408300901	3.8993378482	-2.0264431410
c16	5.2179662292	0.8838716465	-2.4038389720
c17	2.4967715829	2.0243241998	-3.3960848128
c18	-0.6432225322	-1.0951745541	2.2204081607
c19	-1.5109520073	-0.7415331443	3.2637443089
c20	-2.1683812140	-1.7192292536	4.0074346668
c21	-1.9571977196	-3.0686692950	3.7270865281
c22	-1.0805450736	-3.4333957389	2.7035474382
c23	-0.4263547444	-2.4572973791	1.9550747898
h24	0.2511457321	-2.7606561381	1.1659232216
h25	-0.9081245386	-4.4829509441	2.4824259779
h26	-2.4707741340	-3.8326585591	4.3028163256
h27	-2.8453068307	-1.4254066978	4.8042242336
h28	-1.6747502446	0.3094895360	3.4856807936

h32	1.5992031445	2.5585659932	-3.0701529257
h33	2.2079232056	0.9898729858	-3.6084458020
h34	2.8334252936	2.4671937541	-4.3410461556
h35	4.8427696303	-0.1435509088	-2.3474693458
h36	5.6558540817	1.0179218263	-3.3992147253
h37	6.0219868152	0.9859556785	-1.6681414335
h38	4.9900323477	4.1898259955	-2.9826162113
h39	5.3080315339	3.9908132204	-1.2513961833
h40	3.7440697272	4.6149707804	-1.8000165149
h41	4.3752646251	4.4163084182	2.4184164444
h42	4.2213974897	3.6388981387	4.0102792791
h43	5.7521060373	3.4775847908	3.0862948172
h44	1.4579190566	-1.7572758663	3.9323745451
h45	1.8644216296	-0.6185569188	5.2514282517
h46	3.1212896245	-1.1048367558	4.0731533252
H44	2.1299588085	-0.3365541823	-1.6148303577
H45	-0.2050702241	0.9826751552	1.8654495956
N47	-0.3678728291	2.2916531661	-1.1696659642
C48	-0.2069794549	1.2636222988	-0.6477774792
N48	-0.8202878490	-2.0159819666	-1.4163840098
C49	-0.4764314223	-1.1194032830	-0.7583743775
H50	2.1448579475	-1.2017742433	0.0135446953

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Escf = -1492.820354 au

Esolv = -0.025702215 au

ZPE = 247.386 kcal/mol

Htot = 18.926 kcal/mol

Stot = 190.257 cal/mol*K

N1	0.0359894166	0.0336034397	-0.1863084850
C2	0.0456675062	-0.2314259579	1.2234979044
C3	1.2035182418	-0.4909025383	1.8901022032
O4	-0.3308474507	-1.1843668814	-0.8805803232
C5	-1.5150161862	-0.9647279096	-1.6684552376
H6	-1.7402869063	-1.9451566579	-2.0965334162
H7	-2.3327513159	-0.6202905669	-1.0343526399
H8	-1.3290477081	-0.2493048090	-2.4739959179
C9	-1.3229224125	-0.1321807136	1.8039830208
O10	-2.2979015217	0.2141524319	1.1662318715
O11	-1.4032135699	-0.4839757436	3.1086481487
C12	-2.7194634549	-0.3626261193	3.6762807808
H13	-2.6195977924	-0.6789924237	4.7146494031
H14	-3.0666972811	0.6716960741	3.6225101693
H15	-3.4305520744	-1.0001084499	3.1456998320

C16	1.3490516893	0.4530777382	-0.7325819405
C17	2.4760116374	-0.5665013979	-0.3288839124
H18	2.0657132221	-1.5209179905	-0.6711250896
C19	2.5428360248	-0.5802437832	1.2012267787
H20	3.1535449386	0.2480865380	1.5796891551
H21	3.0482506475	-1.4952626726	1.5301129660
N22	1.8908549792	2.8611325601	0.2046882449
C23	1.6337323288	1.8110454968	-0.2147055675
N24	1.1897954928	0.6211606312	-3.3587833261
C25	1.2422973678	0.5437903727	-2.2037652760
O26	1.2817696857	-0.5509810937	3.2300748488
Si27	1.4586352721	-1.8545719653	4.3125970763
C28	0.4791002501	-3.3276506131	3.6774610287
H29	0.8434783367	-3.6649329589	2.7006254213
H30	0.5646850472	-4.1734248439	4.3692100009
H31	-0.5791807396	-3.0756948935	3.5695990916
C32	0.8179028143	-1.1907747314	5.9435156993
H33	-0.2328244779	-0.8996159775	5.8597171668
H34	0.9046199709	-1.9415491759	6.7366932382
H35	1.3854985752	-0.3076464610	6.2547921175
C36	3.2855950192	-2.2935757842	4.4568115577
H37	3.4340468547	-3.0347952677	5.2502394880
H38	3.6890618432	-2.7233226455	3.5336767726
H39	3.8876235328	-1.4147810828	4.7092929255
C40	6.2700493954	-0.0077839432	-2.3328940088
C41	5.4138109975	-1.0438991591	-2.7042020275
C42	4.1960977079	-1.2112207456	-2.0476326125
C43	3.8131375119	-0.3505050728	-1.0110431503
C44	4.6813968221	0.6890910342	-0.6473142170
C45	5.8989898041	0.8581105025	-1.3044820668
H46	7.2191396707	0.1262248536	-2.8432299590
H47	5.6908693547	-1.7214662183	-3.5062725114
H48	3.5299195979	-2.0165433460	-2.3463888266
H49	4.4082974535	1.3829542915	0.1413559216
H50	6.5571305728	1.6711847271	-1.0122649950

219.

Escf = -1492.821248 au

Esolv = -0.028300892 au

ZPE = 247.591 kcal/mol

Htot = 18.835 kcal/mol

Stot = 189.333 cal/mol*K

N1	0.5565515071	-0.1669321124	-0.2721119407
C2	0.4298143117	-0.1980693827	1.1473758658

C3	1.5048575145	-0.2679502996	1.9726824036
O4	-0.0357052889	-1.3768977760	-0.7966450632
C5	-1.0924388071	-1.0503311381	-1.7121422662
H6	-1.4789531387	-2.0195248403	-2.0389151696
H7	-1.8711311179	-0.4748996442	-1.2090428093
H8	-0.7145519411	-0.4979421637	-2.5769399591
C9	-0.9866751238	-0.0323713568	1.5934504336
O10	-1.8490833620	0.4911445328	0.9175452064
O11	-1.2354646010	-0.5440580721	2.8194660376
C12	-2.5915083095	-0.3802013173	3.2709701157
H13	-2.6293248600	-0.8435916263	4.2566514995
H14	-2.8509432976	0.6793155902	3.3334539482
H15	-3.2863191810	-0.8734987107	2.5873258097
C16	2.9663501884	-0.8807875351	-0.0092006222
C17	1.9098352521	0.0099075921	-0.7931241471
H18	2.1838473428	1.0314597641	-0.5079070294
C19	2.9180069265	-0.3954173515	1.4628424835
H20	3.4222727548	0.5762295491	1.5313850849
H21	3.4803434831	-1.0820714830	2.1008171923
N22	2.5033827521	-3.4722674012	0.0312183039
C23	2.6762077608	-2.3267591299	-0.0355092983
N24	5.3920370822	-0.4490314336	-0.9291991418
C25	4.3181826105	-0.6630694057	-0.5454022859
O26	1.4282163004	-0.0850414596	3.3093133094
Si27	1.5969614119	-1.2502648254	4.5524477997
C28	0.9671327089	-2.9114926585	3.9452617281
H29	1.5194824472	-3.2646870570	3.0675371832
H30	1.0743088357	-3.6701818791	4.7289333278
H31	-0.0879690565	-2.8485192687	3.6664728165
C32	0.6007163027	-0.5508369277	5.9776737005
H33	-0.4522873153	-0.4441447040	5.7030090625
H34	0.6615630409	-1.2018935930	6.8567670570
H35	0.9743253727	0.4369254175	6.2668722797
C36	3.4160725380	-1.3638402898	5.0365135813
H37	3.5240796838	-1.9683342858	5.9447045934
H38	4.0315071365	-1.8357973799	4.2632741109
H39	3.8377029566	-0.3753124379	5.2465572600
C40	2.2504133518	-0.0979298718	-5.1022608296
C41	2.2365382947	1.1139798701	-4.4136055247
C42	2.1186356811	1.1227649778	-3.0248886441
C43	2.0076762131	-0.0733010625	-2.3056108788
C44	2.0197073694	-1.2869773076	-3.0062726611
C45	2.1417466270	-1.2953477462	-4.3948163436
H46	2.3484838425	-0.1101762341	-6.1838305727
H47	2.3242367835	2.0520508215	-4.9535519552
H48	2.1139079458	2.0708221914	-2.4930745366
H49	1.9187311304	-2.2256104298	-2.4753377224
H50	2.1514461515	-2.2433973072	-4.9244481019

7.2 Data for single crystals

7.2.1 Cyanopyridine **194**

7.2.1.1 Crystal data and structure refinement

Identification code	JYLu1
Empirical formula	$C_{16}H_{11}F_3N_2O_3$
Formula weight	336.27
Temperature	173 K
Wavelength	MoKa 0.71073 Å
Crystal system, space group	Monoclinic, P21/n (No. 14)
Unit cell dimensions	a = 14.1687(16) Å, α = 90°
	b = 6.9866(9) Å, β = 96.257(6)°
	c = 31.257(3) Å, γ = 90°
Volume	3075.7(6) $Å^3$
Z, Calculated density	8, 1.452 g/cm^3
Absorption coefficient	0.125 mm^{-1}
F(000)	1376
Crystal size	0.20 x 0.30 x 0.50 mm
θ range for data collection	2.6 to 25.4 °
Limiting indices	$-17 \le h \le 17$, $-8 \le k \le 8$, $-37 \le l \le 37$
Reflections collected / unique	40932 / 5622, [R(int) = 0.051]
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5622 / 0 / 465
Goodness-of-fit on F^2	0.915
Final R indices [I>2σ(I)]	$R_1 = 0.0406$, $wR_2 = 0.0658$
R indices (all data)	$R_1 = 0.1941$, $wR_2 = 0.0831$
Maximum and Average Shift/Error	0.00, 0.00

$R_1 = \Sigma \, ||F_o| - |F_c|| / \Sigma |F_o|$. $wR_2 = [\Sigma[w(F_o^2 - F_c^2)^2] / \Sigma[w(F_o^2)^2]]^{1/2}$

7.2.1.2 Atomic coordinates and equivalent isotropic displacement parameters.

Atom	x	Y	z	U(eq)
*F1A	-0.0932(11)	-0.7858(11)	0.2236(7)	0.115(7)
*F2A	-0.1317(11)	-0.625(2)	0.2750(3)	0.091(6)
*F3A	-0.2129(9)	-0.602(3)	0.2164(6)	0.134(8)
O1	0.10808(17)	0.4390(3)	0.12740(9)	0.0438(11)
O2	0.28731(18)	0.5467(3)	0.12523(8)	0.0444(11)
O3	0.40251(19)	0.3609(3)	0.15923(8)	0.0424(11)
N1	0.2808(2)	0.0942(4)	0.17688(9)	0.0344(11)
N2	0.3059(2)	-0.3342(4)	0.22361(11)	0.0499(16)
C1	0.0557(3)	-0.1676(5)	0.19513(13)	0.0367(16)
C2	-0.0234(3)	-0.2274(5)	0.16825(13)	0.0438(17)
C3	-0.0825(3)	-0.3690(5)	0.18097(13)	0.0456(17)
C4	-0.0625(3)	-0.4535(5)	0.22117(13)	0.0432(17)
C5	0.0157(3)	-0.3972(5)	0.24860(12)	0.0463(17)
C6	0.0738(3)	-0.2536(5)	0.23547(13)	0.0420(17)

C7	0.1208(3)	-0.0198(5)	0.18138(11)	0.0340(16)
C8	0.2199(3)	-0.0362(5)	0.18793(11)	0.0341(16)
C9	0.2449(3)	0.2543(5)	0.15747(12)	0.0322(16)
C10	0.1475(3)	0.2830(5)	0.14811(12)	0.0380(17)
C11	0.0846(3)	0.1453(5)	0.16071(11)	0.0372(16)
C12	0.3129(3)	0.4021(6)	0.14542(12)	0.0393(17)
C13	0.4716(3)	0.5069(5)	0.15061(13)	0.0511(17)
C14	0.5683(3)	0.4374(5)	0.16852(14)	0.072(2)
C15	0.2669(3)	-0.2046(5)	0.20825(13)	0.0393(17)
C16	-0.1268(5)	-0.6114(9)	0.2337(3)	0.064(3)
*F3	-0.196(2)	-0.533(3)	0.2536(16)	0.203(18)
*F1	-0.162(3)	-0.712(4)	0.2048(5)	0.141(12)
*F2	-0.0870(14)	-0.713(4)	0.2640(9)	0.108(12)
F1'	0.75429(19)	-0.1633(5)	0.12185(13)	0.177(2)
F2'	0.7804(2)	0.1284(5)	0.11217(11)	0.1251(18)
F3'	0.77268(19)	-0.0608(4)	0.06123(11)	0.1103(16)
O1'	0.12421(17)	-0.1957(3)	0.07739(9)	0.0427(10)
O2'	-0.02124(18)	0.0185(3)	0.05474(8)	0.0485(11)
O3'	0.00080(18)	0.3093(3)	0.02563(8)	0.0415(11)
N1'	0.1882(2)	0.2708(4)	0.03680(9)	0.0345(12)
N2'	0.3718(2)	0.5607(4)	0.02333(11)	0.0520(16)
C1'	0.4347(3)	0.0742(5)	0.07029(12)	0.0350(16)
C2'	0.4719(3)	-0.0186(5)	0.10788(12)	0.0400(17)
C3'	0.5678(3)	-0.0469(5)	0.11695(13)	0.0452(17)
C4'	0.6285(3)	0.0156(5)	0.08840(15)	0.0461(17)
C5'	0.5942(3)	0.1137(5)	0.05151(14)	0.0482(17)
C6'	0.4974(3)	0.1431(5)	0.04270(13)	0.0421(16)
C7'	0.3310(3)	0.0889(5)	0.06110(11)	0.0326(16)
C8'	0.2826(3)	0.2528(5)	0.04344(12)	0.0347(16)
C9'	0.1353(3)	0.1229(5)	0.04793(12)	0.0342(16)
C10'	0.1764(3)	-0.0461(5)	0.06539(12)	0.0349(16)
C11'	0.2741(3)	-0.0619(5)	0.07140(11)	0.0328(16)
C12'	0.0299(3)	0.1440(6)	0.04315(13)	0.0404(17)
C13'	-0.1010(3)	0.3506(5)	0.02334(12)	0.0447(17)
C14'	-0.1185(3)	0.4809(5)	0.06020(12)	0.0614(17)
C15'	0.3343(3)	0.4246(5)	0.03215(12)	0.0393(17)
C16'	0.7333(4)	-0.0224(9)	0.09748(19)	0.078(3)

7.2.1.3 (An)isotropic displacement parameters

	U11	U22	U33	U23	U13	U12
F1A	0.157(11)	0.046(4)	0.163(16)	-0.002(6)	0.110(10)	-0.016(5)
F2A	0.110(13)	0.117(10)	0.050(6)	-0.001(5)	0.022(7)	-0.059(8)
F3A	0.058(7)	0.139(16)	0.192(18)	0.099(13)	-0.044(8)	-0.049(7)
O1	0.0481(19)	0.0333(17)	0.0498(19)	0.0073(14)	0.0042(16)	0.0069(14)
O2	0.055(2)	0.0327(16)	0.0444(19)	0.0113(14)	0.0009(16)	0.0011(15)
O3	0.0378(19)	0.0384(17)	0.0504(19)	0.0052(14)	0.0023(15)	-0.0055(15)
N1	0.038(2)	0.0305(19)	0.034(2)	0.0005(16)	0.0003(17)	0.0000(18)
N2	0.061(3)	0.037(2)	0.053(3)	0.0083(19)	0.012(2)	0.0103(19)
C1	0.038(3)	0.033(2)	0.039(3)	0.000(2)	0.004(2)	0.005(2)

C2	0.048(3)	0.040(3)	0.042(3)	0.006(2)	-0.002(3)	0.003(2)
C3	0.038(3)	0.053(3)	0.044(3)	0.000(2)	-0.004(2)	-0.004(2)
C4	0.046(3)	0.035(3)	0.048(3)	0.008(2)	0.003(3)	-0.006(2)
C5	0.052(3)	0.046(3)	0.039(3)	0.010(2)	-0.003(2)	-0.002(2)
C6	0.044(3)	0.038(3)	0.042(3)	0.002(2)	-0.004(2)	-0.005(2)
C7	0.041(3)	0.031(2)	0.029(3)	-0.0027(19)	0.000(2)	0.005(2)
C8	0.043(3)	0.027(2)	0.031(3)	0.0032(19)	-0.002(2)	0.000(2)
C9	0.035(3)	0.030(2)	0.032(3)	-0.002(2)	0.005(2)	0.002(2)
C10	0.051(3)	0.031(3)	0.031(3)	-0.002(2)	0.000(2)	0.008(2)
C11	0.037(3)	0.034(2)	0.040(3)	0.003(2)	0.001(2)	0.006(2)
C12	0.045(3)	0.038(3)	0.035(3)	-0.009(2)	0.005(2)	-0.005(2)
C13	0.046(3)	0.043(3)	0.065(3)	0.005(2)	0.009(3)	-0.010(2)
C14	0.050(3)	0.047(3)	0.118(5)	-0.004(3)	0.007(3)	-0.007(2)
C15	0.048(3)	0.035(3)	0.036(3)	-0.004(2)	0.010(2)	-0.005(2)
C16	0.063(5)	0.065(4)	0.064(5)	0.014(4)	0.006(4)	-0.007(4)
F3	0.12(2)	0.097(12)	0.42(5)	0.05(2)	0.16(3)	-0.011(12)
F1	0.23(3)	0.11(2)	0.069(9)	0.022(11)	-0.042(16)	-0.13(2)
F2	0.079(12)	0.113(18)	0.13(3)	0.073(18)	0.001(11)	-0.037(10)
F1'	0.046(2)	0.223(4)	0.262(5)	0.191(4)	0.020(2)	0.039(2)
F2'	0.046(2)	0.127(3)	0.194(4)	-0.052(3)	-0.024(2)	-0.0036(19)
F3'	0.057(2)	0.123(3)	0.153(3)	0.001(2)	0.021(2)	0.0196(18)
O1'	0.0377(18)	0.0363(16)	0.054(2)	0.0035(14)	0.0048(17)	-0.0027(14)
O2'	0.0369(19)	0.0410(17)	0.068(2)	0.0116(15)	0.0071(16)	-0.0006(15)
O3'	0.0332(18)	0.0384(18)	0.052(2)	0.0038(14)	0.0012(15)	0.0055(14)
N1'	0.034(2)	0.031(2)	0.038(2)	0.0027(16)	0.0024(18)	0.0033(17)
N2'	0.052(3)	0.037(2)	0.069(3)	0.010(2)	0.016(2)	0.0009(19)
C1'	0.039(3)	0.026(2)	0.040(3)	0.003(2)	0.004(2)	0.002(2)
C2'	0.040(3)	0.036(3)	0.045(3)	0.005(2)	0.009(2)	-0.003(2)
C3'	0.043(3)	0.039(3)	0.053(3)	0.014(2)	0.003(3)	0.001(2)
C4'	0.031(3)	0.038(3)	0.069(3)	0.009(2)	0.004(3)	0.004(2)
C5'	0.040(3)	0.047(3)	0.059(3)	0.017(2)	0.012(2)	0.004(2)
C6'	0.044(3)	0.034(2)	0.048(3)	0.009(2)	0.004(2)	0.005(2)
C7'	0.037(3)	0.028(2)	0.033(3)	0.0014(19)	0.005(2)	0.005(2)
C8'	0.042(3)	0.030(2)	0.032(3)	-0.0023(19)	0.004(2)	-0.002(2)
C9'	0.040(3)	0.029(2)	0.033(3)	-0.001(2)	0.001(2)	0.003(2)
C10'	0.038(3)	0.027(2)	0.040(3)	-0.001(2)	0.005(2)	0.000(2)
C11'	0.041(3)	0.025(2)	0.032(3)	0.0035(19)	0.002(2)	0.005(2)
C12'	0.040(3)	0.044(3)	0.036(3)	-0.001(2)	-0.001(2)	0.008(2)
C13'	0.033(3)	0.043(3)	0.056(3)	0.006(2)	-0.004(2)	0.001(2)
C14'	0.048(3)	0.071(3)	0.066(3)	-0.010(3)	0.010(3)	0.014(3)
C15'	0.037(3)	0.037(3)	0.044(3)	0.001(2)	0.005(2)	0.015(2)
C16'	0.053(4)	0.106(5)	0.077(5)	0.022(4)	0.014(4)	-0.002(4)

7.2.1.4 Bond Distances (Angstrom)

F1-C16	1.21(3)	C2-C3	1.382(5)	N1-C8	1.326(5)	C14-H14B	0.9800
F1A-C16	1.358(12)	C3-C4	1.389(6)	N1-C9	1.346(5)	C14-H14C	0.9800
F2-C16	1.27(3)	C4-C5	1.382(6)	N2-C15	1.139(5)	C14-H14A	0.9800
F2A-C16	1.304(13)	C4-C16	1.509(8)	N1'-C8'	1.337(5)	C1'-C6'	1.390(6)
F3-C16	1.34(3)	C5-C6	1.388(5)	N1'-C9'	1.344(5)	C1'-C7'	1.470(6)

F3A-C16	1.281(16)	C7-C8	1.401(6)	N2'-C15'	1.138(5)	C1'-C2'	1.394(5)
F1'-C16'	1.260(7)	C7-C11	1.392(5)	C1-C7	1.479(5)	C2'-C3'	1.372(6)
F2'-C16'	1.304(7)	C8-C15	1.463(5)	C1-C2	1.390(6)	C3'-C4'	1.376(6)
F3'-C16'	1.344(7)	C9-C12	1.489(6)	C1-C6	1.395(6)	C4'-C16'	1.505(7)
O1-C10	1.357(4)	C9-C10	1.394(6)	C4'-C5'	1.383(6)	C3'-H3'A	0.9500
O2-C12	1.225(5)	C10-C11	1.397(5)	C5'-C6'	1.385(6)	C5'-H5'A	0.9500
O3-C13	1.459(5)	C13-C14	1.503(6)	C7'-C11'	1.386(5)	C6'-H6'A	0.9500
O3-C12	1.327(5)	C2-H2A	0.9500	C7'-C8'	1.416(5)	C11'-H11'	0.9500
O1-H1	0.8400	C3-H3A	0.9500	C8'-C15'	1.469(5)	C13'-H13C	0.9900
O1'-C10'	1.357(4)	C5-H5A	0.9500	C9'-C10'	1.401(5)	C13'-H13D	0.9900
O2'-C12'	1.218(5)	C6-H6A	0.9500	C9'-C12'	1.492(6)	C14'-H14D	0.9800
O3'-C13'	1.465(5)	C11-H11A	0.9500	C10'-C11'	1.381(6)	C14'-H14E	0.9800
O3'-C12'	1.325(5)	C13-H13B	0.9900	C13'-C14'	1.510(5)	C14'-H14F	0.9800
O1'-H1'	0.8400	C13-H13A	0.9900	C2'-H2'A	0.9500		

7.2.1.5 Bond Angles (Degrees)

C12-O3-C13	115.2(3)	C2'-C1'-C6'	118.4(4)	C4-C3-H3A	120.00
C10-O1-H1	110.00	C1'-C2'-C3'	121.1(4)	C6-C5-H5A	121.00
C12'-O3'-C13'	116.9(3)	C2'-C3'-C4'	119.7(4)	C4-C5-H5A	121.00
C10'-O1'-H1'	110.00	C3'-C4'-C16'	119.7(4)	C5-C6-H6A	119.00
C8-N1-C9	117.6(3)	C5'-C4'-C16'	119.6(4)	C1-C6-H6A	119.00
C8'-N1'-C9'	117.7(3)	C3'-C4'-C5'	120.7(4)	C10-C11-H11A	120.00
C2-C1-C6	118.3(4)	C4'-C5'-C6'	119.3(4)	C7-C11-H11A	120.00
C6-C1-C7	120.3(4)	C1'-C6'-C5'	120.8(4)	C10'-C9'-C12'	119.4(4)
C2-C1-C7	121.4(3)	C1'-C7'-C8'	124.4(3)	N1'-C9'-C10'	121.9(4)
C1-C2-C3	121.0(4)	C1'-C7'-C11'	119.7(3)	O1'-C10'-C11'	118.0(3)
C2-C3-C4	119.6(4)	C8'-C7'-C11'	115.9(4)	C9'-C10'-C11'	119.2(4)
C3-C4-C16	118.4(5)	N1'-C8'-C15'	113.7(3)	O1'-C10'-C9'	122.8(4)
C5-C4-C16	120.9(5)	C7'-C8'-C15'	121.4(4)	C7'-C11'-C10'	120.5(3)
C3-C4-C5	120.7(4)	N1'-C8'-C7'	124.8(3)	O2'-C12'-O3'	125.6(4)
C4-C5-C6	118.9(4)	N1'-C9'-C12'	118.6(3)	O3'-C12'-C9'	113.0(3)
C1-C6-C5	121.5(4)	O3'-C13'-H13D	110.00	O2'-C12'-C9'	121.4(4)
C8-C7-C11	116.6(3)	C14'-C13'-H13C	110.00	O3'-C13'-C14'	108.9(3)
C1-C7-C11	120.2(4)	C14'-C13'-H13D	110.00	N2'C15'-C8'	177.9(4)
C1-C7-C8	123.2(3)	H13C-C13'-H13D	108.00	F1'-C16'-F3'	105.2(5)
N1-C8-C15	112.8(4)	C13'-C14'-H14D	110.00	F1'-C16'-C4'	114.5(5)
C7-C8-C15	122.1(3)	C7-C11-C10	119.2(4)	F1'-C16'-F2'	109.9(5)
N1-C8-C7	125.2(3)	O2-C12-O3	124.4(4)	F2'-C16'-C4'	112.4(5)
C10-C9-C12	120.0(3)	O3-C12-C9	113.0(3)	F3'-C16'-C4'	111.6(4)
N1-C9-C10	122.1(3)	O2-C12-C9	122.6(4)	F2'-C16'-F3'	102.4(4)
N1-C9-C12	117.9(4)	O3-C13-C14	107.9(3)	C1'-C2'-H2'A	119.00
O1-C10-C9	124.2(3)	N2-C15-C8	178.0(4)	C3'-C2'-H2'A	120.00
C9-C10-C11	119.3(3)	F1A-C16-F3A	106.8(13)	C2'-C3'-H3'A	120.00
O1-C10-C11	116.5(4)	F1A-C16-C4	111.0(8)	C4'-C3'-H3'A	120.00
O3-C13-H13A	110.00	F1-C16-C4	116.3(16)	C4'-C5'-H5'A	120.00
C14-C13-H13B	110.00	F1A-C16-F2A	102.9(12)	C6'-C5'-H5'A	120.00
C14-C13-H13A	110.00	F3-C16-C4	108.4(11)	C1'-C6'-H6'A	120.00
O3-C13-H13B	110.00	F1-C16-F2	110.3(19)	C5'-C6'-H6'A	120.00
H13A-C13-H13B	108.00	F1-C16-F3	109(3)	C7'-C11'-H11'	120.00

C13-C14-H14C	109.00	F2-C16-F3	100(2)	C10'-C11'-H11'	120.00
C13-C14-H14B	109.00	F3A-C16-C4	115.3(11)	O3'-C13'-H13C	110.00
H14B-C14-H14C	109.00	F2A-C16-C4	114.1(8)	C13'-C14'-H14E	109.00
H14A-C14-H14B	109.00	F2-C16-C4	111.8(12)	C13'-C14'-H14F	110.00
C13-C14-H14A	110.00	F2A-C16-F3A	105.7(12)	H14D-C14'-H14E	109.00
H14A-C14-H14C	109.00	C3-C2-H2A	119.00	H14D-C14'-H14F	109.00
C2'-C1'-C7'	118.4(4)	C1-C2-H2A	120.00	H14E-C14'-H14F	109.00
C6'-C1'-C7'	123.2(3)	C2-C3-H3A	120.00		

7.2.1.6 Torsion Angles (Degrees)

C13-O3-C12-O2	2.9(5)	C12-C9-C10-C11	-178.2(3)
C13-O3-C12-C9	-176.4(3)	N1-C9-C12-O2	175.2(3)
C12-O3-C13-C14	179.7(3)	N1-C9-C12-O3	-5.5(5)
C13'-O3'-C12'-C9'	-174.4(3)	C10-C9-C12-O2	-4.0(6)
C12'-O3'-C13'-C14'	99.1(3)	C10-C9-C12-O3	175.3(3)
C13'-O3'-C12'-O2'	5.4(6)	O1-C10-C1-C7	178.8(3)
C9-N1-C8-C7	-0.7(5)	C9-C10-C11-C7	-1.6(5)
C9-N1-C8-C15	179.3(3)	C6'-C1'-C2'-C3'	-2.0(5)
C8-N1-C9-C10	-1.5(5)	C7'-C1'-C2'-C3'	176.1(3)
C8-N1-C9-C12	179.4(3)	C2'-C1'-C6'-C5'	2.5(5)
C9'-N1'-C8'-C7'	0.4(5)	C7'-C1'-C6'-C5'	-175.5(3)
C8'-N1'-C9'-C12'	176.6(3)	C2'-C1'-C7'-C8'	140.4(4)
C9'-N1'-C8'-C15'	-177.4(3)	C2'-C1'-C7'-C11'	-37.1(5)
C8'-N1'-C9'-C10'	-0.8(5)	C6'-C1'-C7'-C8'	-41.7(5)
C6-C1-C2-C3	-0.3(6)	C6'-C1'-C7'-C11'	140.8(4)
C7-C1-C2-C3	178.4(4)	C1'-C2'-C3'-C4'	-0.6(6)
C2-C1-C6-C5	0.9(6)	C2'-C3'-C4'-C5'	2.7(6)
C7-C1-C6-C5	-177.8(4)	C2'-C3'-C4'-C16'	-177.6(4)
C2-C1-C7-C8	-135.3(4)	C3'-C4'-C5'-C6'	-2.2(6)
C6-C1-C7-C8	43.4(5)	C16'-C4'-C5'-C6'	178.1(4)
C6-C1-C7-C11	-136.9(4)	C3'-C4'-C16'-F1'	24.0(7)
C2-C1-C7-C11	44.5(5)	C3'-C4'-C16'-F2'	-102.3(5)
C1-C2-C3-C4	-0.2(6)	C3'-C4'-C16'-F3'	143.3(4)
C2-C3-C4-C16	-178.4(4)	C5'-C4'-C16'-F1'	-156.3(4)
C2-C3-C4-C5	0.2(6)	C5'-C4'-C16'-F2'	77.4(6)
C3-C4-C16-F1A	93.0(11)	C5'-C4'-C16'-F3'	-37.0(6)
C16-C4-C5-C6	178.9(4)	C4'-C5'-C6'-C1'	-0.4(6)
C3-C4-C5-C6	0.4(6)	C1'-C7'-C8'-N1'	-176.8(3)
C3-C4-C16-F2A	-151.3(8)	C1'-C7'-C8'-C15'	0.8(6)
C3-C4-C16-F3A	-28.7(12)	C11'-C7'-C8'-N1'	0.8(5)
C5-C4-C16-F1A	-85.6(12)	C11'-C7'-C8'-C15'	178.4(3)
C5-C4-C16-F2A	30.1(10)	C1'-C7'-C11'-C10'	176.1(3)
C5-C4-C16-F3A	152.8(11)	C8'-C7'-C11'-C10'	-1.6(5)
C4-C5-C6-C1	-1.0(6)	N1'-C9'-C10'-O1'	179.0(3)
C1-C7-C8-N1	-178.7(3)	N1'-C9'-C10'-C11'	0.0(6)
C11-C7-C8-C15	-178.4(3)	C12'-C9'-C10'-O1'	1.7(6)
C1-C7-C8-C15	1.4(5)	C12'-C9'-C10'-C11'	-177.4(3)
C11-C7-C8-N1	1.6(5)	N1'-C9'-C12'-O2'	-176.3(3)
C1-C7-C11-C10	179.9(3)	N1'-C9'-C12'-O3'	3.6(5)

C8-C7-C11-C10	-0.3(5)	C10'-C9'-C12'-O2'	1.2(6)
C12-C9-C10-O1	1.3(6)	C10'-C9'-C12'-O3'	-179.0(3)
N1-C9-C10-O1	-177.8(3)	O1'-C10'-C11'-C7'	-177.8(3)
N1-C9-C10-C11	2.6(6)	C9'-C10'-C11'-C7'	1.3(5)

7.2.2 6-Acetylpyridine **241**

7.2.2.1 Crystal data and structure refinement

Identification code	JYLu2
Empirical formula	$C_{15}H_{11}F_3N_2O_8S_2$
Formula weight	468.40
Temperature	173 K
Wavelength	MoKa 0.71073 Å
Crystal system, space group	Orthorhombic, Pca21 (No. 29)
Unit cell dimensions	a = 15.2539(8) Å, α = 90°
	b = 5.3350(3) Å, β = 90°
	c = 22.2743(10) Å, γ = 90°
Volume	1812.67(16) $Å^3$
Z, Calculated density	4, 1.716 g/cm^3
Absorption coefficient	0.374 mm^{-1}
F(000)	952
Crystal size	0.10 x 0.10 x 0.10 mm
θ range for data collection	2.7 to 27.5 °
Limiting indices	$-19 \le h \le 19$, $-6 \le k \le 6$, $-28 \le l \le 28$
Reflections collected / unique	3752 / 3752, [R(int) = 0.000]
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3752 / 1 / 274
Goodness-of-fit on F^2	1.027
Final R indices [I>2σ(I)]	$R_1 = 0.0271$, $wR_2 = 0.0491$
R indices (all data)	$R_1 = 0.0619$, $wR_2 = 0.0543$
Maximum and Average Shift/Error	0.00, 0.00

$R_1 = \Sigma \, ||F_o| - |F_c|| / \Sigma |F_o|$. $wR_2 = [\Sigma[w(F_o^2 - F_c^2)^2] / \Sigma[w(F_o^2)^2]]^{1/2}$

7.2.2.2 Atomic coordinates and equivalent isotropic displacement parameters.

Atom	x	y	z	U(eq)
S1	0.65429(5)	0.48085(12)	0.34133(3)	0.0282(2)
S2	0.75232(5)	1.16564(12)	0.16754(3)	0.0274(2)
F1	0.59160(12)	0.5121(3)	0.44768(7)	0.0501(7)
F2	0.54644(11)	0.1857(3)	0.39997(7)	0.0423(6)
F3	0.49403(11)	0.5483(3)	0.37779(8)	0.0451(6)
O1	0.72135(12)	0.3082(3)	0.35614(8)	0.0375(7)
O2	0.66725(13)	0.7432(3)	0.33967(8)	0.0361(6)
O3	0.61026(11)	0.3846(3)	0.28117(8)	0.0248(6)
O4	0.42190(12)	1.2156(3)	0.12803(8)	0.0309(7)
O5	0.60661(14)	1.5262(4)	-0.00739(9)	0.0447(7)
O6	0.72966(12)	1.7274(4)	0.02056(8)	0.0342(7)
O7	0.33998(12)	0.4256(3)	0.24744(8)	0.0297(6)
O8	0.45001(12)	0.1820(3)	0.27951(8)	0.0280(6)

N1	0.45414(13)	0.7016(4)	0.18203(9)	0.0216(7)
N2	0.62408(14)	1.2083(4)	0.09347(9)	0.0255(8)
C1	0.56472(19)	0.4266(5)	0.39482(14)	0.0363(10)
C2	0.50688(16)	0.8630(4)	0.15494(11)	0.0207(8)
C3	0.59645(15)	0.8873(4)	0.16882(12)	0.0226(8)
C4	0.63026(16)	0.7238(5)	0.21168(11)	0.0244(9)
C5	0.57393(17)	0.5572(5)	0.23932(11)	0.0224(8)
C6	0.48638(16)	0.5461(5)	0.22395(12)	0.0213(8)
C7	0.45899(16)	1.0295(5)	0.10982(12)	0.0238(8)
C8	0.45114(19)	0.9346(5)	0.04698(13)	0.0332(10)
C9	0.65086(16)	1.0790(5)	0.14017(11)	0.0226(8)
C10	0.75914(18)	1.3900(4)	0.11346(11)	0.0250(9)
C11	0.68634(16)	1.3842(5)	0.07823(12)	0.0232(8)
C12	0.66785(19)	1.5492(5)	0.02578(12)	0.0294(10)
C13	0.7174(2)	1.8969(5)	-0.03013(13)	0.0407(11)
C14	0.41619(18)	0.3800(5)	0.25078(12)	0.0234(9)
C15	0.38516(18)	0.0233(5)	0.30928(13)	0.0317(9)

7.2.2.3 (An)isotropic displacement parameters

	U11	U22	U33	U23	U13	U12
S1	0.0266(3)	0.0320(4)	0.0260(3)	0.0009(3)	-0.0043(4)	-0.0019(3)
S2	0.0208(3)	0.0313(3)	0.0301(3)	0.0049(3)	-0.0040(3)	-0.0039(3)
F1	0.0622(13)	0.0637(12)	0.0244(9)	-0.0039(8)	-0.0004(9)	-0.0116(9)
F2	0.0495(11)	0.0379(10)	0.0396(10)	0.0093(8)	0.0015(8)	-0.0099(8)
F3	0.0377(10)	0.0556(12)	0.0419(10)	0.0038(9)	0.0077(9)	0.0127(9)
O1	0.0267(11)	0.0462(12)	0.0397(12)	0.0045(9)	-0.0089(9)	0.0077(9)
O2	0.0461(13)	0.0318(10)	0.0305(10)	-0.0016(9)	-0.0087(10)	-0.0090(9)
O3	0.0237(10)	0.0251(10)	0.0256(10)	0.0015(8)	-0.0049(9)	0.0002(8)
O4	0.0312(11)	0.0256(11)	0.0360(12)	-0.0011(9)	-0.0029(9)	0.0065(9)
O5	0.0428(12)	0.0488(13)	0.0425(13)	0.0128(10)	-0.0184(12)	-0.0088(11)
O6	0.0332(11)	0.0364(12)	0.0329(11)	0.0106(9)	-0.0005(9)	-0.0068(9)
O7	0.0203(10)	0.0289(11)	0.0398(12)	0.0060(8)	0.0023(9)	0.0012(9)
O8	0.0236(10)	0.0260(10)	0.0345(11)	0.0049(9)	0.0004(9)	-0.0032(8)
N1	0.0205(11)	0.0214(12)	0.0228(13)	-0.0018(9)	-0.0009(9)	0.0009(10)
N2	0.0215(12)	0.0276(13)	0.0274(14)	0.0004(10)	0.0005(10)	-0.0015(10)
C1	0.0368(18)	0.0438(19)	0.0282(17)	0.0016(14)	-0.0011(14)	0.0017(15)
C2	0.0196(13)	0.0219(14)	0.0207(15)	-0.0048(11)	0.0007(11)	0.0010(11)
C3	0.0231(13)	0.0221(14)	0.0226(14)	-0.0050(12)	0.0021(14)	0.0016(11)
C4	0.0196(15)	0.0285(16)	0.0250(14)	-0.0032(12)	-0.0022(12)	-0.0003(12)
C5	0.0229(14)	0.0242(15)	0.0201(15)	0.0005(11)	-0.0013(11)	0.0040(12)
C6	0.0210(14)	0.0209(15)	0.0220(14)	-0.0009(11)	-0.0002(12)	-0.0006(12)
C7	0.0158(13)	0.0276(16)	0.0279(15)	0.0029(13)	-0.0005(12)	-0.0042(12)
C8	0.0365(16)	0.0343(19)	0.0287(16)	-0.0018(12)	-0.0049(14)	0.0026(14)
C9	0.0178(13)	0.0267(15)	0.0234(14)	-0.0029(11)	-0.0001(12)	0.0034(12)
C10	0.0228(15)	0.0251(15)	0.0271(15)	0.0020(11)	0.0037(12)	-0.0020(12)
C11	0.0226(14)	0.0249(14)	0.0220(14)	-0.0038(11)	0.0004(12)	0.0020(12)
C12	0.0281(16)	0.0331(19)	0.0271(16)	0.0005(12)	0.0030(13)	0.0023(14)
C13	0.0435(19)	0.0433(19)	0.0353(18)	0.0131(14)	0.0017(15)	-0.0006(15)
C14	0.0240(16)	0.0238(15)	0.0224(14)	-0.0032(12)	-0.0020(12)	-0.0005(13)

C15	0.0288(16)	0.0302(16)	0.0362(16)	0.0088(13)	0.0059(13)	-0.0064(13)

7.2.2.4 Bond distances (Angstrom)

S1-O1	1.4155(19)	O7-C14	1.190(3)	C7-C8	1.493(4)
S1-O2	1.4140(17)	O8-C14	1.339(3)	C10-C11	1.360(4)
S1-O3	1.5844(19)	O8-C15	1.461(3)	C11-C12	1.490(4)
S1-C1	1.836(3)	N1-C2	1.324(3)	C4-H4A	0.9500
S2-C9	1.726(3)	N1-C6	1.342(3)	C8-H8A	0.9800
S2-C10	1.701(2)	N2-C9	1.313(3)	C8-H8B	0.9800
F1-C1	1.328(3)	N2-C11	1.378(3)	C8-H8C	0.9800
F2-C1	1.320(3)	C2-C3	1.407(3)	C10-H10A	0.9500
F3-C1	1.315(3)	C2-C7	1.527(4)	C13-H13A	0.9800
O3-C5	1.423(3)	C3-C4	1.392(4)	C13-H13B	0.9800
O4-C7	1.213(3)	C3-C9	1.464(3)	C13-H13C	0.9800
O5-C12	1.197(4)	C4-C5	1.381(4)	C15-H15A	0.9800
O6-C12	1.344(3)	C5-C6	1.380(4)	C15-H15B	0.9800
O6-C13	1.459(3)	C6-C14	1.513(4)	C15-H15C	0.9800

7.2.2.5 Bond angles (Degrees)

O1-S1-O2	123.31(12)	N1-C6-C5	120.0(2)
O1-S1-O3	107.01(10)	N1-C6-C14	112.2(2)
O1-S1-C1	106.50(12)	C5-C6-C14	127.7(2)
O2-S1-O3	110.97(10)	O4-C7-C2	118.6(2)
O2-S1-C1	106.09(12)	O4-C7-C8	123.6(2)
O3-S1-C1	100.51(12)	C2-C7-C8	117.3(2)
C9-S2-C10	89.61(13)	S2-C9-N2	114.70(19)
S1-O3-C5	120.63(15)	S2-C9-C3	122.78(19)
C12-O6-C13	114.6(2)	N2-C9-C3	122.4(2)
C14-O8-C15	114.4(2)	S2-C10-C11	110.03(19)
C2-N1-C6	119.8(2)	N2-C11-C10	115.9(2)
C9-N2-C11	109.8(2)	N2-C11-C12	117.7(2)
S1-C1-F1	106.95(19)	C10-C11-C12	126.4(2)
S1-C1-F2	111.54(19)	O5-C12-O6	124.5(2)
S1-C1-F3	110.2(2)	O5-C12-C11	124.8(3)
F1-C1-F2	108.8(2)	O6-C12-C11	110.7(2)
F1-C1-F3	109.9(2)	O7-C14-O8	124.6(2)
F2-C1-F3	109.4(2)	O7-C14-C6	123.2(2)
N1-C2-C3	123.4(2)	O8-C14-C6	112.2(2)
N1-C2-C7	112.8(2)	C3-C4-H4A	121.00
C3-C2-C7	123.8(2)	C5-C4-H4A	121.00
C2-C3-C4	116.9(2)	C7-C8-H8A	109.00
C2-C3-C9	121.3(2)	C7-C8-H8B	109.00
C4-C3-C9	121.8(2)	C7-C8-H8C	109.00
C3-C4-C5	118.6(2)	H8A-C8-H8B	109.00
O3-C5-C4	117.8(2)	H8A-C8-H8C	109.00
O3-C5-C6	120.8(2)	H8B-C8-H8C	109.00
C4-C5-C6	121.3(2)	S2-C10-H10A	125.00
C11-C10-H10A	125.00	O8-C15-H15A	109.00

O6-C13-H13A	109.00	O8-C15-H15B	109.00
O6-C13-H13B	110.00	O8-C15-H15C	109.00
O6-C13-H13C	109.00	H15A-C15-H15B	109.00
H13A-C13-H13B	109.00	H15A-C15-H15C	109.00
H13A-C13-H13C	109.00	H15B-C15-H15C	109.00
H13B-C13-H13C	109.00		

7.2.2.6 Torsion Angles (Degrees)

O1-S1-O3-C5	-149.14(17)	N1-C2-C3-C9	-176.2(2)
O2-S1-O3-C5	-12.1(2)	C7-C2-C3-C4	179.0(2)
C1-S1-O3-C5	99.83(19)	C7-C2-C3-C9	0.1(4)
O1-S1-C1-F1	71.63(19)	N1-C2-C7-O4	83.7(3)
O1-S1-C1-F2	-47.3(2)	N1-C2-C7-C8	-88.6(3)
O1-S1-C1-F3	-169.01(18)	C3-C2-C7-O4	-93.0(3)
O2-S1-C1-F1	-61.3(2)	C3-C2-C7-C8	94.7(3)
O2-S1-C1-F2	179.79(19)	C2-C3-C4-C5	-2.6(4)
O2-S1-C1-F3	58.0(2)	C9-C3-C4-C5	176.3(2)
O3-S1-C1-F1	-176.95(17)	C2-C3-C9-S2	164.3(2)
O3-S1-C1-F2	64.2(2)	C2-C3-C9-N2	-11.8(4)
O3-S1-C1-F3	-57.6(2)	C4-C3-C9-S2	-14.6(3)
C10-S2-C9-N2	0.4(2)	C4-C3-C9-N2	169.3(2)
C10-S2-C9-C3	-176.1(2)	C3-C4-C5-O3	177.5(2)
C9-S2-C10-C11	-0.7(2)	C3-C4-C5-C6	1.9(4)
S1-O3-C5-C4	64.1(3)	O3-C5-C6-N1	-176.5(2)
S1-O3-C5-C6	-120.3(2)	O3-C5-C6-C14	6.2(4)
C13-O6-C12-O5	-0.3(4)	C4-C5-C6-N1	-1.0(4)
C13-O6-C12-C11	179.4(2)	C4-C5-C6-C14	-178.4(3)
C15-O8-C14-O7	-1.9(4)	N1-C6-C14-O7	-18.7(4)
C15-O8-C14-C6	176.6(2)	N1-C6-C14-O8	162.8(2)
C6-N1-C2-C3	-1.9(4)	C5-C6-C14-O7	158.8(3)
C6-N1-C2-C7	-178.5(2)	C5-C6-C14-O8	-19.7(4)
C2-N1-C6C5	0.9(4)	S2-C10-C11-N2	1.0(3)
C2-N1-C6-C14	178.7(2)	S2-C10-C11-C12	-179.5(2)
C11-N2-C9-S2	0.1(3)	N2-C11-C12-O5	-7.0(4)
C11-N2-C9-C3	176.6(2)	N2-C11-C12-O6	173.3(2)
C9-N2-C11-C10	-0.7(3)	C10-C11-C12-O5	173.5(3)
C9-N2-C11-C12	179.7(2)	C10-C11-C12-O6	-6.2(4)
N1-C2-C3-C4	2.7(4)		

7.2.3 Methoxyoxime **141**.

7.2.3.1 Crystal data and structure refinement

Identification code	JYLu3
Empirical formula	$C_6H_9NO_4$
Formula weight	159.14
Temperature	293(2) K
Wavelength	MoKa 0.71073 Å

Crystal system, space group	Orthorhombic, Pna21 (No. 33)
Unit cell dimensions	a = 8.3410(17) Å, α = 90°
	b = 13.410(3) Å, β = 90°
	c = 7.2900(15) Å, γ = 90°
Volume	815.4(3) $Å^3$
Z, Calculated density	4, 1.296 g/cm^3
Absorption coefficient	0.110 mm^{-1}
F(000)	336
Crystal size	0.20 x 0.20 x 0.20 mm
θ range for data collection	3.9 to 26.4 °
Limiting indices	$-10 \le h \le 10$, $-16 \le k \le 16$, $0 \le l \le 9$
Reflections collected / unique	3104 / 899, [R(int) = 0.045]
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	899 / 1 / 104
Goodness-of-fit on F^2	1.092
Final R indices [I>2σ(I)]	$R_1 = 0.0273$, $wR_2 = 0.0530$
R indices (all data)	$R_1 = 0.0677$, $wR_2 = 0.0570$
Maximum and Average Shift/Error	0.00, 0.00
Absolute structure parameter	-2.3(15)
Extinction coefficient	0.087(6)

$R_1 = \Sigma \, ||F_o| - |F_c|| / \Sigma |F_o|$. $wR_2 = [\Sigma[w(F_o^2 - F_c^2)^2] / \Sigma[w(F_o^2)^2]]^{1/2}$

7.2.3.2 Atomic coordinates and equivalent isotropic displacement parameters.

Atom	x	y	z	U(eq)
O1	0.14686(19)	0.12432(11)	0.8457(2)	0.0633(6)
O2	0.1931(2)	0.03995(12)	0.4285(2)	0.0784(7)
O3	0.4017(2)	0.23981(12)	0.3446(3)	0.0923(8)
O4	0.4114(2)	0.03491(11)	0.6049(2)	0.0634(6)
N1	0.19750(19)	0.20788(12)	0.7495(3)	0.0535(7)
C1	0.2847(3)	0.07762(15)	0.5349(3)	0.0521(8)
C3	0.2673(2)	0.18321(15)	0.5998(3)	0.0463(7)
C5	0.3291(3)	0.26405(17)	0.4804(3)	0.0557(9)
C7	0.0702(3)	0.15466(19)	1.0136(3)	0.0749(10)
C8	0.4383(4)	-0.06865(16)	0.5537(3)	0.0821(11)
C9	0.3008(3)	0.37018(15)	0.5307(4)	0.0674(9)

7.2.3.3 (An)isotropic displacement parameters

	U11	U22	U33	U23	U13	U12
O1	0.0881(11)	0.0498(9)	0.0519(9)	0.0002(9)	0.0208(9)	-0.0045(8)
O2	0.0868(13)	0.0657(11)	0.0828(13)	-0.0202(11)	-0.0205(12)	0.0028(9)
O3	0.1322(17)	0.0691(12)	0.0755(13)	-0.0068(11)	0.0492(14)	-0.0101(10)
O4	0.0676(10)	0.0551(9)	0.0675(10)	-0.0037(9)	-0.0078(9)	0.0137(8)
N1	0.0625(12)	0.0471(11)	0.0510(12)	0.0004(10)	0.0046(12)	-0.0028(9)
C1	0.0601(14)	0.0494(13)	0.0467(14)	-0.0023(13)	0.0041(14)	-0.0018(13)
C3	0.0483(12)	0.0491(13)	0.0415(12)	-0.0037(12)	-0.0001(12)	0.0010(10)
C5	0.0615(16)	0.0567(15)	0.0490(14)	-0.0008(13)	0.0063(13)	-0.0031(12)
C7	0.0981(19)	0.0731(17)	0.0535(16)	-0.0040(14)	0.0276(15)	-0.0063(16)
C8	0.1075(19)	0.0597(17)	0.079(2)	0.0008(15)	0.0040(16)	0.0278(14)

C9	0.0773(15)	0.0517(14)	0.0732(17)	0.0009(15)	0.0087(13)	-0.0057(13)

7.2.3.4 Bond distances (Angstrom)

O1-N1	1.388(2)	C1-C3	1.500(3)	C8-H8A	0.9600
O1-C7	1.440(3)	C3-C5	1.483(3)	C8-H8B	0.9600
O2-C1	1.200(3)	C5-C9	1.489(3)	C8-H8D	0.9600
O3-C5	1.205(3)	C7-H7A	0.9600	C9-H9A	0.9600
O4-C1	1.306(3)	C7-H7B	0.9600	C9-H9B	0.9600
O4-C8	1.455(3)	C7-H7C	0.9600	C9-H9D	0.9600
N1-C3	1.280(3)				

7.2.3.5 Bond angles (Degrees)

N1-O1-C7	109.67(16)	H7A-C7-H7B	109.00
C1-O4-C8	116.30(19)	H7A-C7-H7C	109.00
O1-N1-C3	111.13(16)	H7B-C7-H7C	109.00
O2-C1-O4	125.7(2)	O4-C8-H8A	109.00
O2-C1-C3	122.7(2)	O4-C8-H8B	109.00
O4-C1-C3	111.66(18)	O4-C8-H8D	109.00
N1-C3-C1	123.83(19)	H8A-C8-H8B	110.00
N1-C3-C5	118.00(18)	H8A-C8-H8D	110.00
C1-C3-C5	118.12(18)	H8B-C8-H8D	109.00
O3-C5-C3	117.4(2)	C5-C9-H9A	109.00
O3-C5-C9	122.7(2)	C5-C9-H9B	109.00
C3-C5-C9	120.0(2)	C5-C9-H9D	109.00
O1-C7-H7A	109.00	H9A-C9-H9B	110.00
O1-C7-H7B	109.00	H9A-C9-H9D	109.00
O1-C7-H7C	110.00	H9B-C9 -H9D	110.00

7.2.3.6 Torsion Angles (Degrees)

C7-O1-N1-C3	179.55(17)	O4-C1-C3-N1	-85.8(2)
C8-O4-C1-O2	-2.7(3)	O4-C1-C3-C5	96.6(2)
C8-O4-C1-C3	178.87(18)	N1-C3-C5-O3	176.3(2)
O1-N1-C3-C1	2.5(3)	N1-C3-C5-C9	-3.5(3)
O1-N1-C3-C5	-179.91(17)	C1-C3-C5-O3	-5.9(3)
O2-C1-C3-N1	95.7(3)	C1-C3-C5-C9	174.2(2)
O2-C1-C3-C5	-81.9(3)		

7.2.4 Pyridine **255b**

7.2.4.1 Crystal data and structure refinement

Identification code	JYLu4
Empirical formula	$C_{13}H_{13}NO_7$
Formula weight	295.24
Temperature	150(2)K
Wavelength	MoKa 0.71073 Å

Crystal system, space group	Monoclinic, P2(1)/n (No. 14)
Unit cell dimensions	a = 5.1062(3) Å, α = 90° b = 14.7400(7)Å, β = 91.303(5)° c = 18.0416(10) Å, γ = 90°
Volume	1357.56(13) Å^3
Z, Calculated density	4, 1.445 g/cm^3
Absorption coefficient	0.119 mm^{-1}
F(000)	616
Crystal size	0.20 x 0.20 x 0.20 mm
θ range for data collection	2.3 to 28.9 °
Limiting indices	$-6 \le h \le 6$, $-19 \le k \le 19$, $23 \le l \le 22$
Reflections collected / unique	13582 / 3244, [R(int) = 0.038]
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3244 / 0 / 193
Goodness-of-fit on F^2	1.228
Final R indices [I>2σ(I)]	$R_1 = 0.0532$, $wR_2 = 0.1305$
R indices (all data)	$R_1 = 0.0928$, $wR_2 = 0.1358$
Maximum and Average Shift/Error	0.00, 0.00

$R_1 = \Sigma \, ||F_o| - |F_c|| / \Sigma |F_o|$. $wR_2 = [\Sigma[w(F_o^2 - F_c^2)^2] / \Sigma[w(F_o^2)^2]]^{1/2}$

7.2.4.2 Atomic coordinates and equivalent isotropic displacement parameters.

Atom	x	y	z	U(eq)
O1	-0.6978(3)	0.93844(9)	0.41167(9)	0.0375(6)
O2	-0.8584(3)	1.07952(10)	0.48912(9)	0.0402(6)
O3	-0.6588(3)	1.21410(10)	0.47434(9)	0.0433(6)
O4	-0.2039(3)	1.03617(11)	0.15177(9)	0.0400(6)
O5	0.0514(3)	0.94155(9)	0.21860(8)	0.0302(5)
O6	-0.1268(3)	1.27373(10)	0.27138(10)	0.0426(6)
O7	0.1347(3)	1.15808(9)	0.24046(8)	0.0302(5)
N1	-0.3777(3)	1.15143(11)	0.36428(9)	0.0259(6)
C1	-0.5332(4)	1.09217(13)	0.39859(11)	0.0245(7)
C2	-0.5482(4)	1.00011(14)	0.37834(11)	0.0257(7)
C3	-0.3997(4)	0.97101(14)	0.31902(12)	0.0273(7)
C4	-0.2471(4)	1.03253(13)	0.28216(11)	0.0220(6)
C5	-0.2372(4)	1.12270(13)	0.30786(11)	0.0236(6)
C6	-0.7001(5)	1.12732(15)	0.45863(12)	0.0315(8)
C7	-0.8202(6)	1.25480(16)	0.53158(14)	0.0454(10)
C8	-1.0473(5)	1.3007(2)	0.49604(14)	0.0481(10)
C9	-1.1099(6)	1.38626(18)	0.50882(14)	0.0515(10)
C10	-0.1298(4)	1.00505(13)	0.21017(12)	0.0245(7)
C11	0.1622(6)	0.90708(17)	0.15072(13)	0.0419(9)
C12	-0.0738(4)	1.19409(14)	0.27206(12)	0.0257(7)
C13	0.2899(5)	1.21968(15)	0.19640(13)	0.0369(8)

7.2.4.3 (An)isotropic displacement parameters

	U11	U22	U33	U23	U13	U12
O1	0.0451(11)	0.0268(8)	0.0412(10)	0.0045(7)	0.0146(8)	-0.0090(8)
O2	0.0428(11)	0.0385(9)	0.0402(10)	-0.0003(7)	0.0189(9)	-0.0098(8)

O3	0.0553(12)	0.0308(9)	0.0450(10)	-0.0048(7)	0.0266(9)	-0.0007(8)
O4	0.0473(11)	0.0468(10)	0.0258(9)	0.0022(7)	-0.0035(8)	0.0176(9)
O5	0.0347(9)	0.0280(8)	0.0282(9)	0.0010(6)	0.0055(7)	0.0076(7)
O6	0.0403(11)	0.0216(8)	0.0668(12)	-0.0004(7)	0.0204(9)	-0.0045(7)
O7	0.0279(9)	0.0290(8)	0.0343(9)	0.0021(6)	0.0110(7)	-0.0019(7)
N1	0.0258(10)	0.0231(9)	0.0290(10)	-0.0005(7)	0.0056(8)	-0.0030(8)
C1	0.0247(12)	0.0237(11)	0.0251(12)	0.0012(8)	0.0026(10)	-0.0021(9)
C2	0.0265(12)	0.0258(11)	0.0249(12)	0.0066(9)	0.0022(10)	-0.0038(10)
C3	0.0319(13)	0.0192(10)	0.0307(12)	0.0003(9)	-0.0017(11)	-0.0015(10)
C4	0.0219(11)	0.0217(10)	0.0222(11)	0.0009(8)	-0.0029(9)	0.0007(9)
C5	0.0207(11)	0.0247(10)	0.0255(12)	0.0012(9)	0.0015(10)	-0.0010(9)
C6	0.0340(14)	0.0313(12)	0.0296(13)	0.0036(10)	0.0067(11)	-0.0010(11)
C7	0.0567(19)	0.0414(14)	0.0391(16)	-0.0028(11)	0.0223(14)	0.0031(13)
C8	0.0336(16)	0.0660(19)	0.0451(16)	-0.0193(13)	0.0104(13)	-0.0068(14)
C9	0.061(2)	0.0511(17)	0.0419(16)	-0.0095(13)	-0.0100(14)	0.0065(14)
C10	0.0234(12)	0.0208(10)	0.0292(13)	-0.0002(9)	-0.0011(10)	-0.0017(9)
C11	0.0505(17)	0.0429(14)	0.0328(14)	-0.0016(10)	0.0126(12)	0.0167(12)
C12	0.0241(12)	0.0247(11)	0.0285(12)	-0.0042(9)	0.0038(10)	-0.0058(10)
C13	0.0320(14)	0.0379(13)	0.0414(15)	-0.0033(11)	0.0166(12)	-0.0091(11)

7.2.4.4 Bond distances (Angstrom)

O1-C2	1.339(3)	N1-C5	1.328(3)	C7-H7A	0.9900
O2-C6	1.214(3)	C1-C2	1.407(3)	C7-H7B	0.9900
O3-C6	1.326(3)	C1-C6	1.487(3)	C8-H8	0.9500
O3-C7	1.464(3)	C2-C3	1.393(3)	C9-H9A	0.9500
O4-C10	1.202(3)	C3-C4	1.377(3)	C9-H9B	0.9500
O5-C10	1.323(2)	C4-C5	1.408(3)	C11-H11A	0.9800
O5-C11	1.452(3)	C4-C10	1.498(3)	C11-H11B	0.9800
O6-C12	1.205(3)	C5-C12	1.498(3)	C11-H11C	0.9800
O7-C12	1.330(3)	C7-C8	1.476(4)	C13-H13A	0.9800
O7-C13	1.454(3)	C8-C9	1.323(4)	C13-H13B	0.9800
O1-H1	0.8400	C3-H3	0.9500	C13-H13C	0.9800
N1-C1	1.341(3)				

7.2.4.5 Bond angles (Degrees)

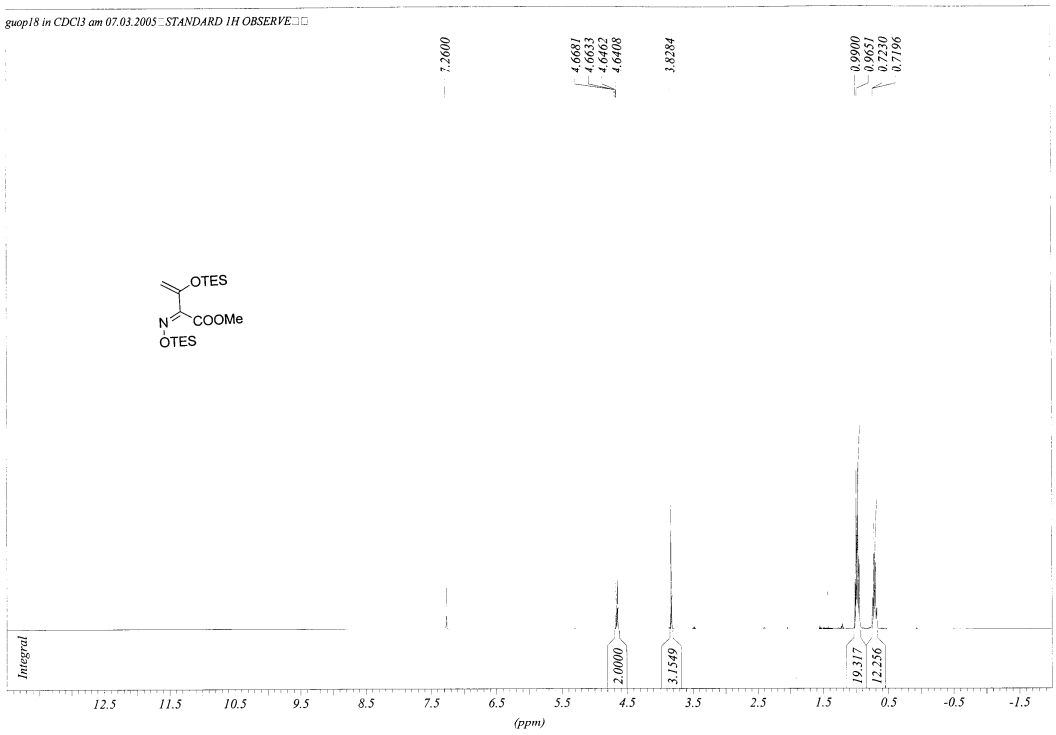
C6-O3-C7	117.17(18)	O7-C12-C5	111.32(17)
C10-O5-C11	115.82(17)	O6-C12-O7	124.51(19)
C12-O7-C13	115.91(16)	C2-C3-H3	120.00
C2-O1-H1	110.00	C4-C3-H3	120.00
C1-N1-C5	118.81(17)	O3-C7-H7A	110.00
N1-C1-C2	122.52(18)	O3-C7-H7B	110.00
N1-C1-C6	117.68(17)	C8-C7-H7A	110.00
C2-C1-C6	119.78(18)	C8-C7-H7B	110.00
O1-C2-C3	117.52(18)	H7A-C7-H7B	108.00
C1-C2-C3	117.97(19)	C7-C8-H8	118.00
O1-C2-C1	124.51(18)	C9-C8-H8	118.00
C2-C3-C4	119.48(19)	C8-C9-H9A	120.00
C3-C4-C5	118.63(19)	C8-C9-H9B	120.00

C3-C4-C10	118.85(18)	H9A-C9-H9B	120.00
C5-C4-C10	121.90(17)	O5-C11-H11A	109.00
N1-C5-C12	114.98(17)	O5-C11-H11B	109.00
C4-C5-C12	122.49(18)	O5-C11-H11C	109.00
N1-C5-C4	122.51(18)	H11A-C11-H11B	109.00
O2-C6-O3	124.6(2)	H11A-C11-H11C	110.00
O3-C6-C1	113.64(19)	H11B-C11-H11C	109.00
O2-C6-C1	121.8(2)	O7-C13-H13A	109.00
O3-C7-C8	109.3(2)	O7-C13-H13B	109.00
C7-C8-C9	123.5(2)	O7-C13-H13C	109.00
O4-C10-C4	122.17(18)	H13A-C13-H13B	109.00
O5-C10-C4	112.59(17)	H13A-C13-H13C	109.00
O4-C10-O5	125.2(2)	H13B-C13-H13C	109.00
O6-C12-C5	124.16(19)		

7.2.4.6 Torsion Angles (Degrees)

C7-O3-C6-O2	-1.2(3)	C6-C1-C2-C3	176.41(19)
C7-O3-C6-C1	178.44(19)	N1-C1-C6-O2	175.2(2)
C6-O3-C7-C8	-95.4(2)	N1-C1-C6-O3	-4.5(3)
C11-O5-C10-O4	-1.1(3)	C2-C1-C6-O2	-3.0(3)
C11-O5-C10-C4	176.12(18)	C2-C1-C6-O3	177.28(19)
C13-O7-C12-O6	-6.4(3)	O1-C2-C3-C4	178.70(19)
C13-O7-C12-C5	172.83(17)	C1-C2-C3-C4	-0.6(3)
C5-N1-C1-C2	1.7(3)	C2-C3-C4-C5	2.8(3)
C5-N1-C1-C6	-176.46(18)	C2-C3-C4-C10	-168.38(19)
C1-N1-C5-C4	0.6(3)	C3-C4-C5-N1	-2.9(3)
C1-N1-C5-C12	178.80(17)	C3-C4-C5-C12	179.11(19)
N1-C1-C2-O1	179.05(19)	C10-C4-C5-N1	167.98(19)
N1-C1-C2-C3	-1.7(3)	C10-C4-C5-C12	-10.0(3)
C6-C1-C2-O1	-2.9(3)	C3-C4-C10-O4	109.5(2)

7.3 NMR spectra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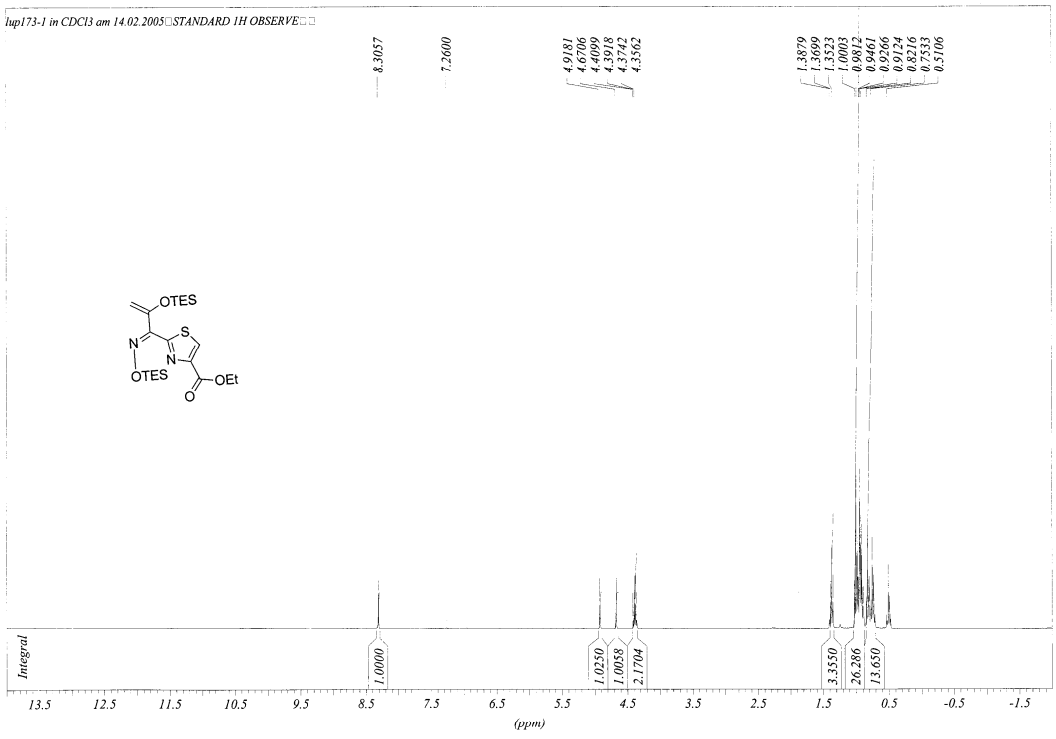
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0.5106
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S
N
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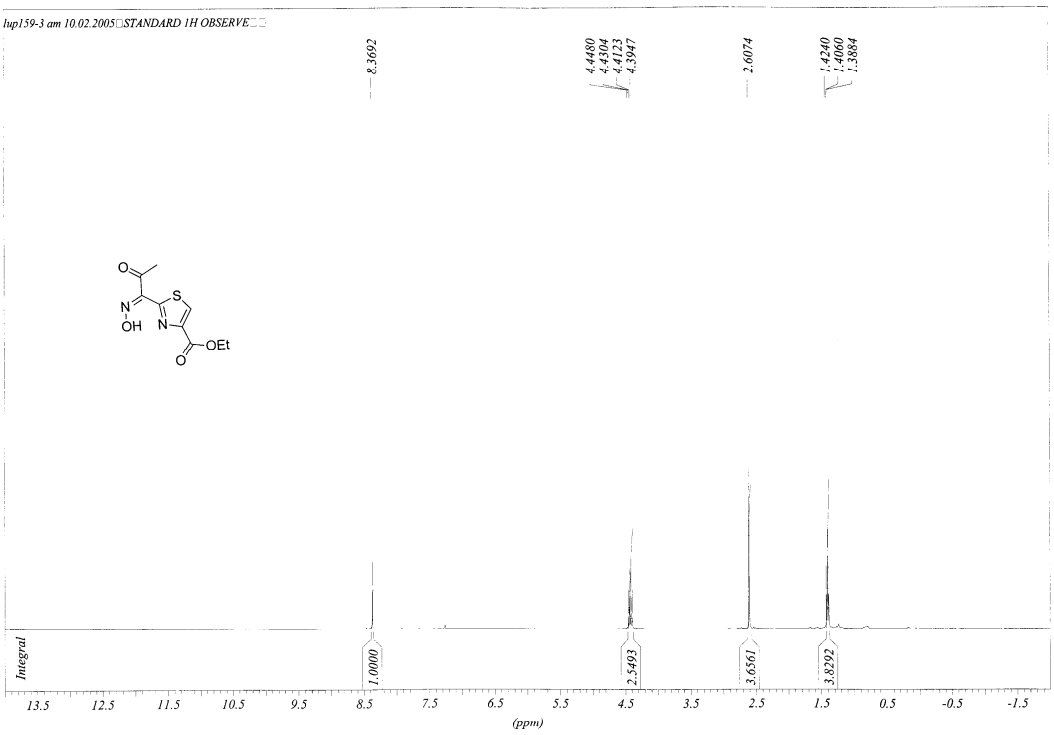
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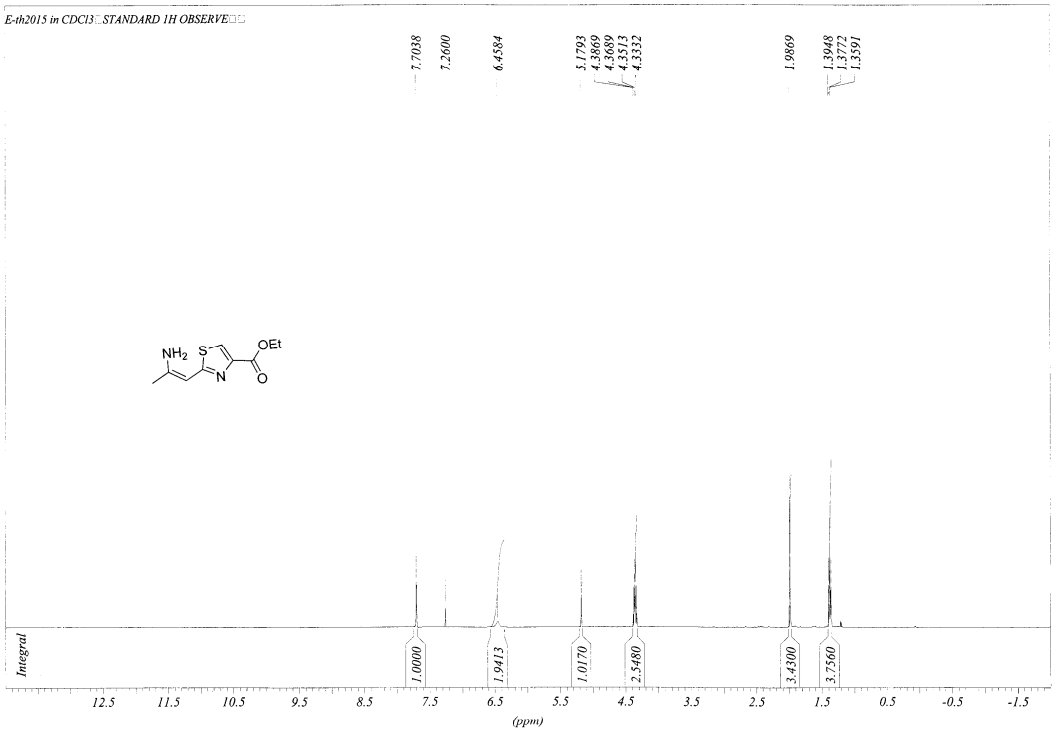
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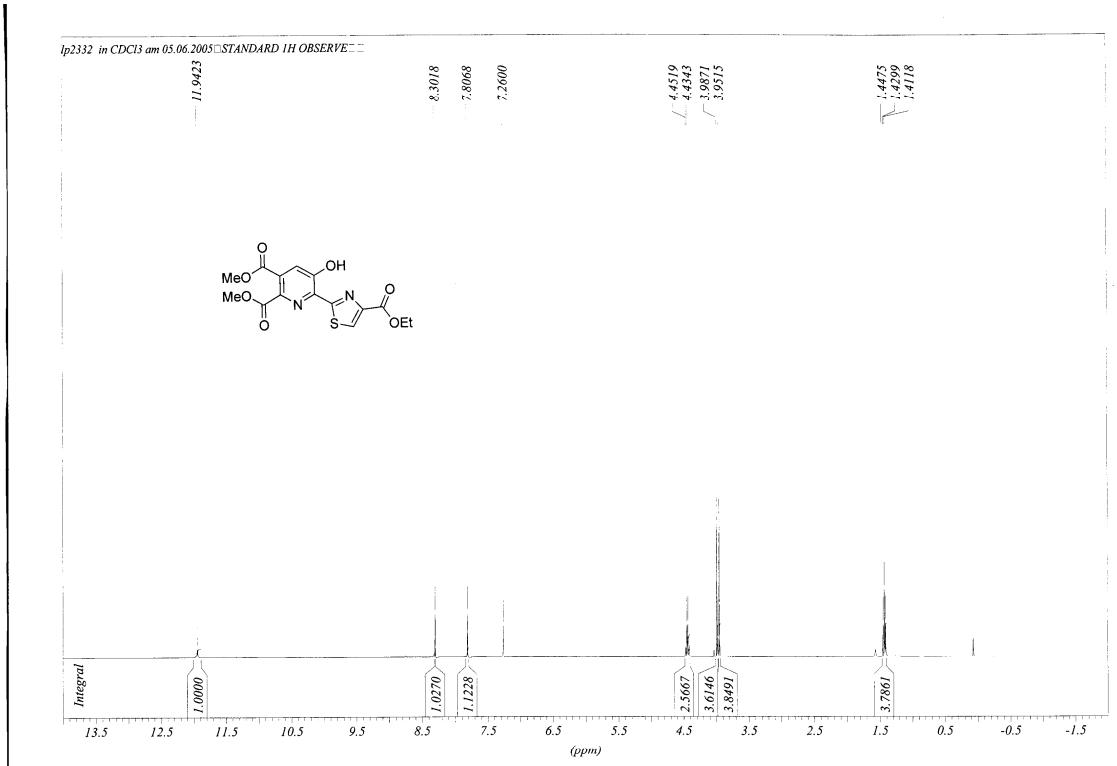
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MeO
OH
N
N
S
O
OEt
Integral
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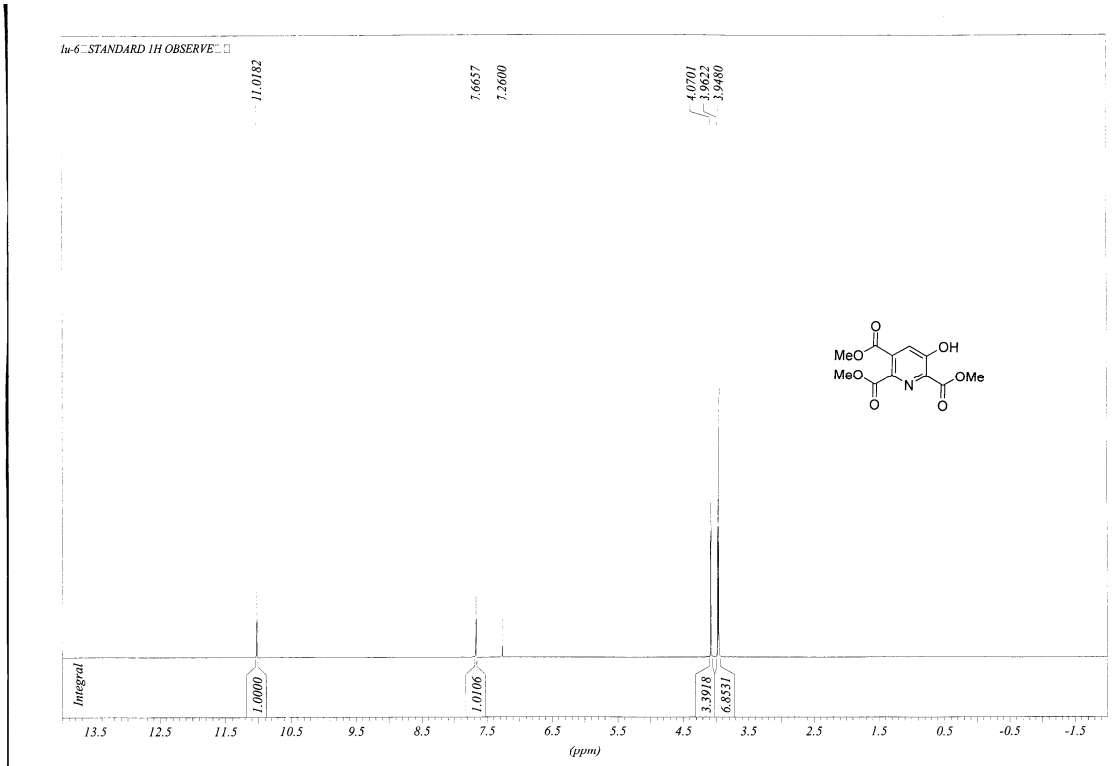
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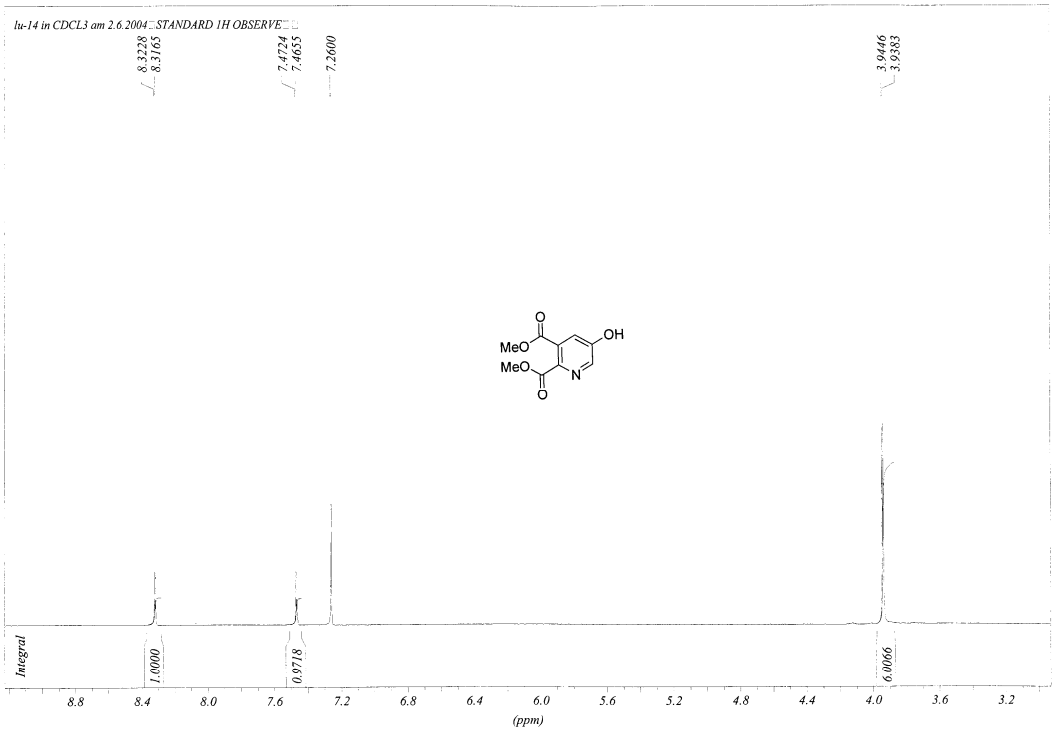
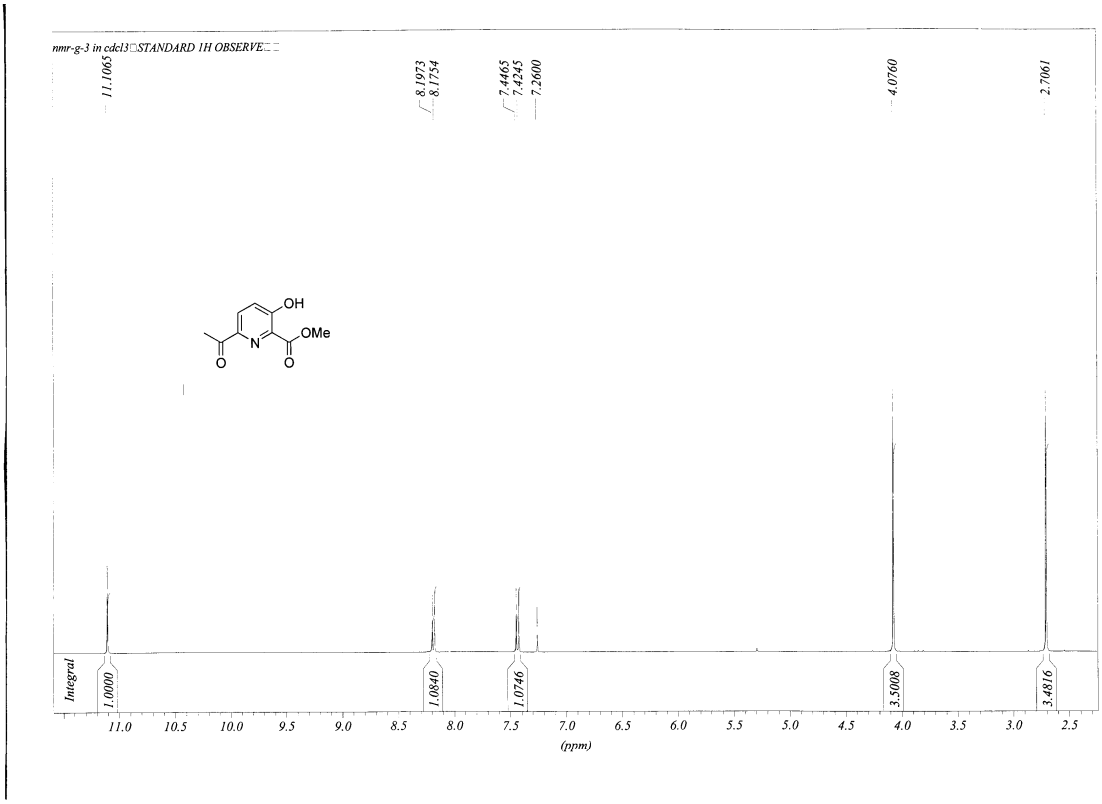
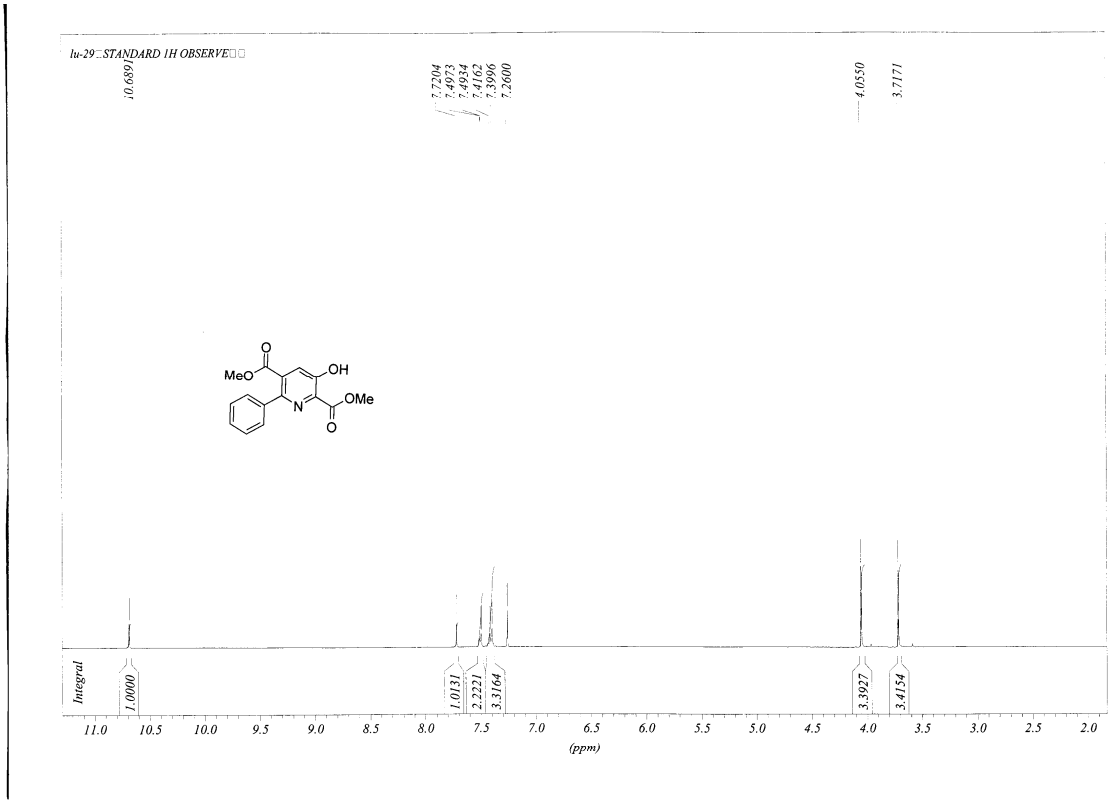
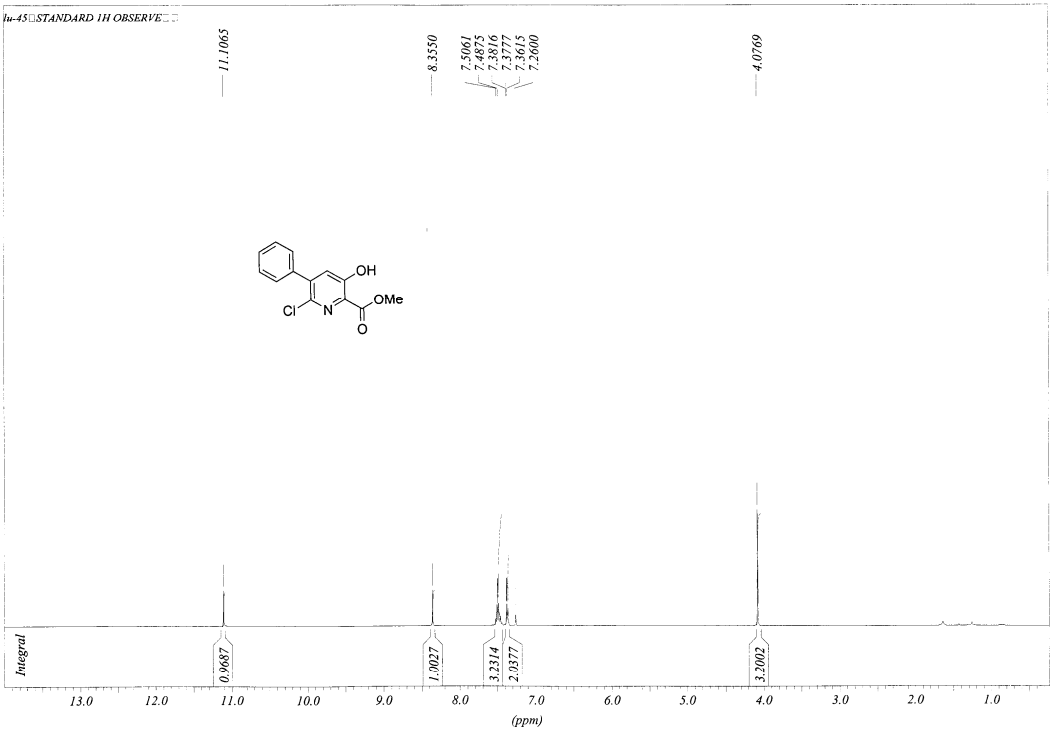
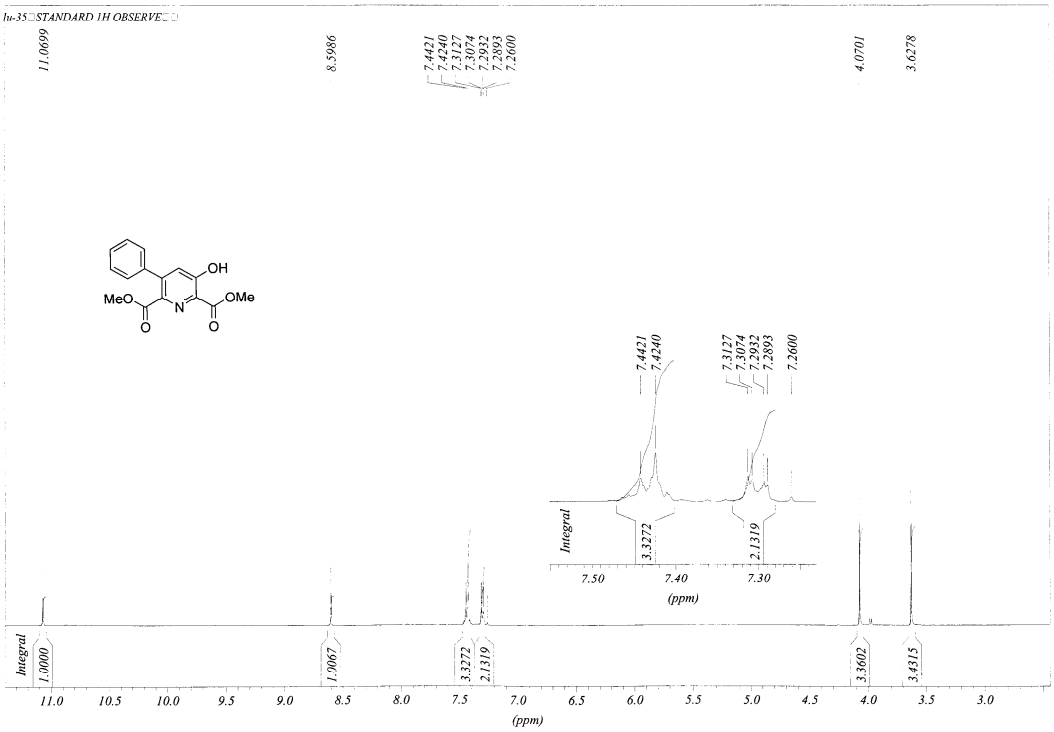
3.3918
6.8531
13.5 12.5 11.5 10.5 9.5 8.5 7.5 6.5 5.5 4.5 3.5 2.5 1.5 0.5 -0.5 -1.5
(ppm)

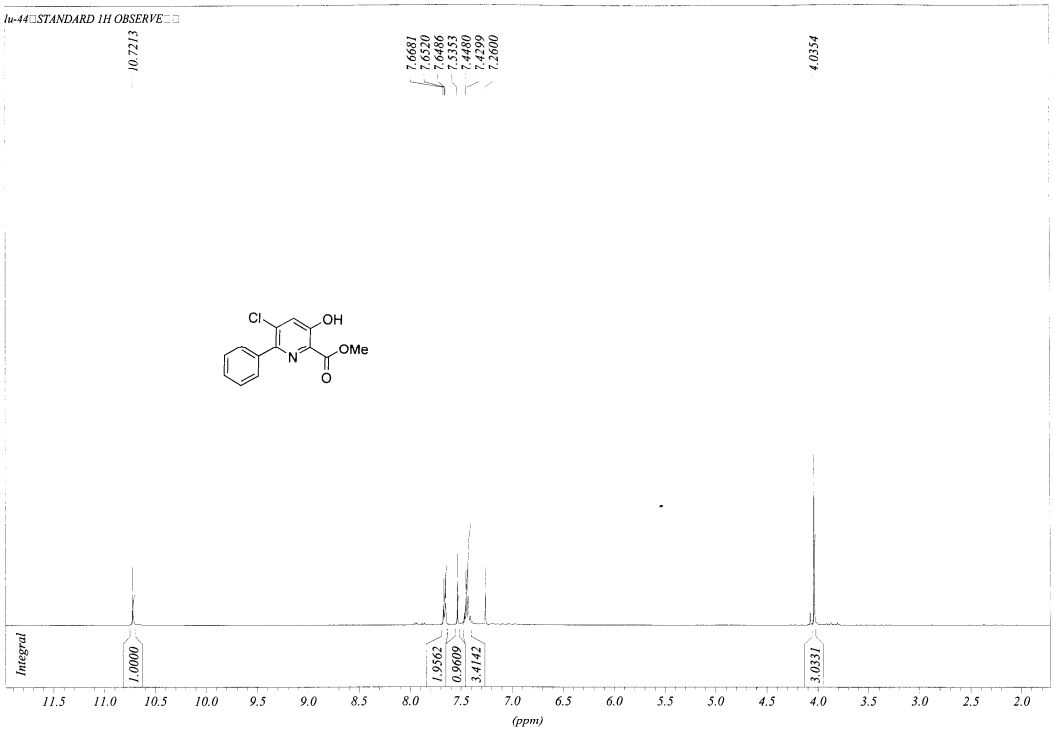

lu-14 in CDCL3 am 2.6.2004 STANDARD 1H OBSERVE
8.3228
8.3165
7.4724
7.4655
7.2600
3.9446
3.9383
MeO
MeO
O
OH
N
Integral
1.0000
0.9718
6.9066
8.8 8.4 8.0 7.6 7.2 6.8 6.4 6.0 5.6 5.2 4.8 4.4 4.0 3.6 3.2
(ppm)

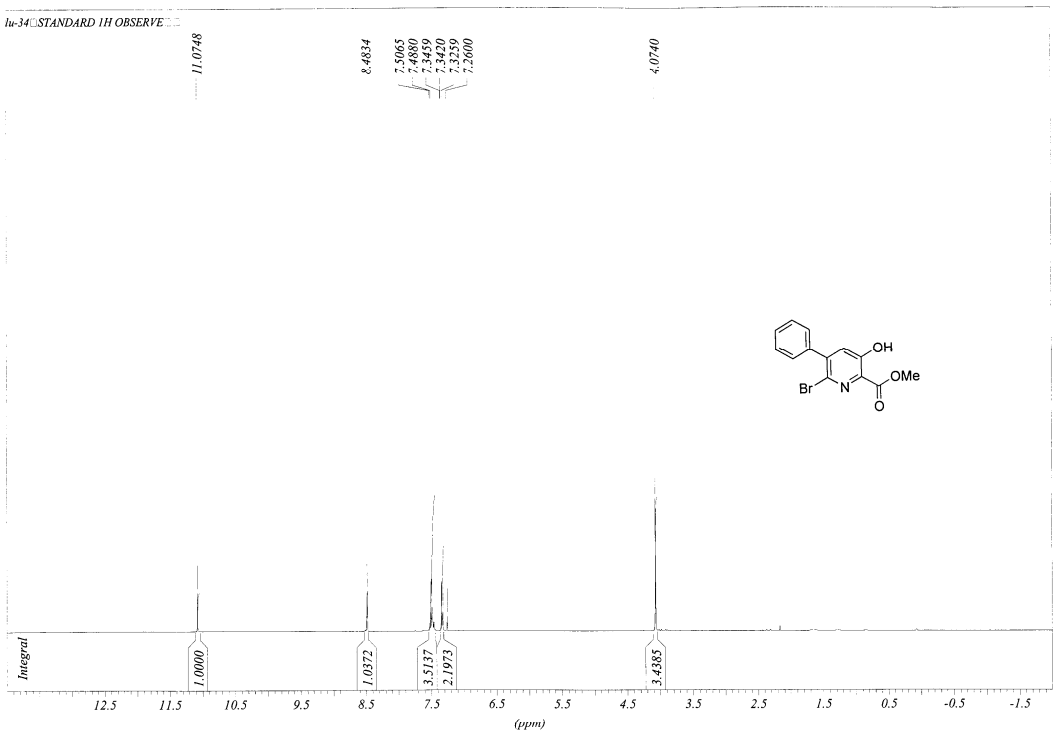

nmr-g-3 in cdcl3 STANDARD 1H OBSERVE
11.1065
8.1973
8.1754
7.4465
7.4245
7.2600
4.0760
2.7061
OH
OMe
N
O
O
Integral
1.0000
1.0840
1.0746
3.5008
3.4816
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5
(ppm)

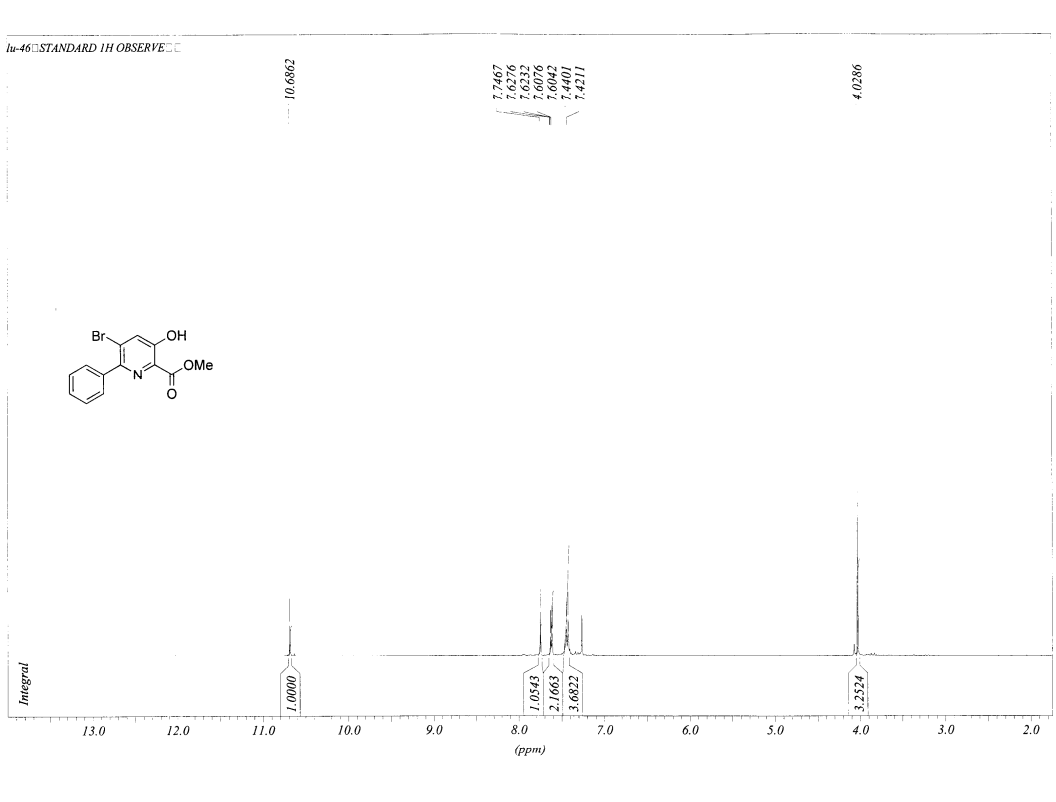

lu-29□STANDARD 1H OBSERVE□□
10.6891
7.7204
7.4973
7.4934
7.4162
7.3996
7.2600
4.0550
3.7171
MeO
O
OH
N
OMe
O
Integral
1.0000
1.0131
2.2221
3.3164
3.3927
3.4154
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
(ppm)

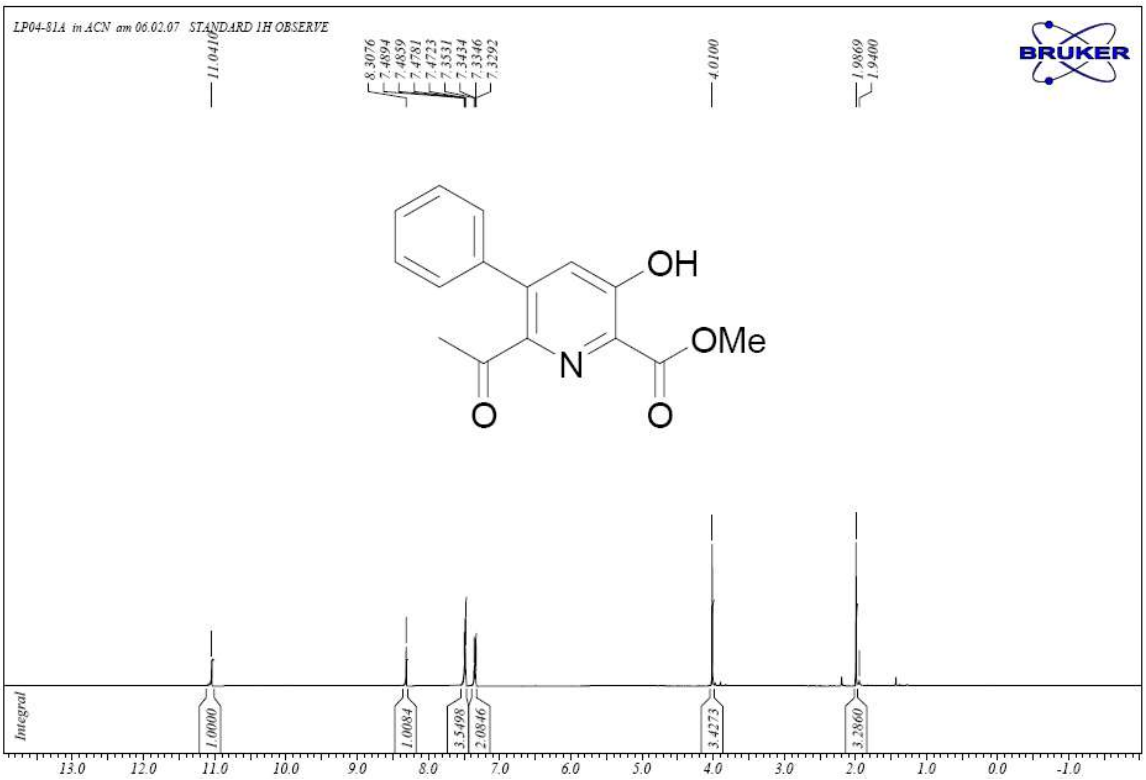

lu-45□STANDARD 1H OBSERVE□□
11.1065
8.3550
7.5061
7.4875
7.3816
7.3777
7.3615
7.2600
4.0769
OH
Cl
N
OMe
O
Integral
0.9687
1.0027
3.2314
2.0377
3.2002
13.0
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
(ppm)

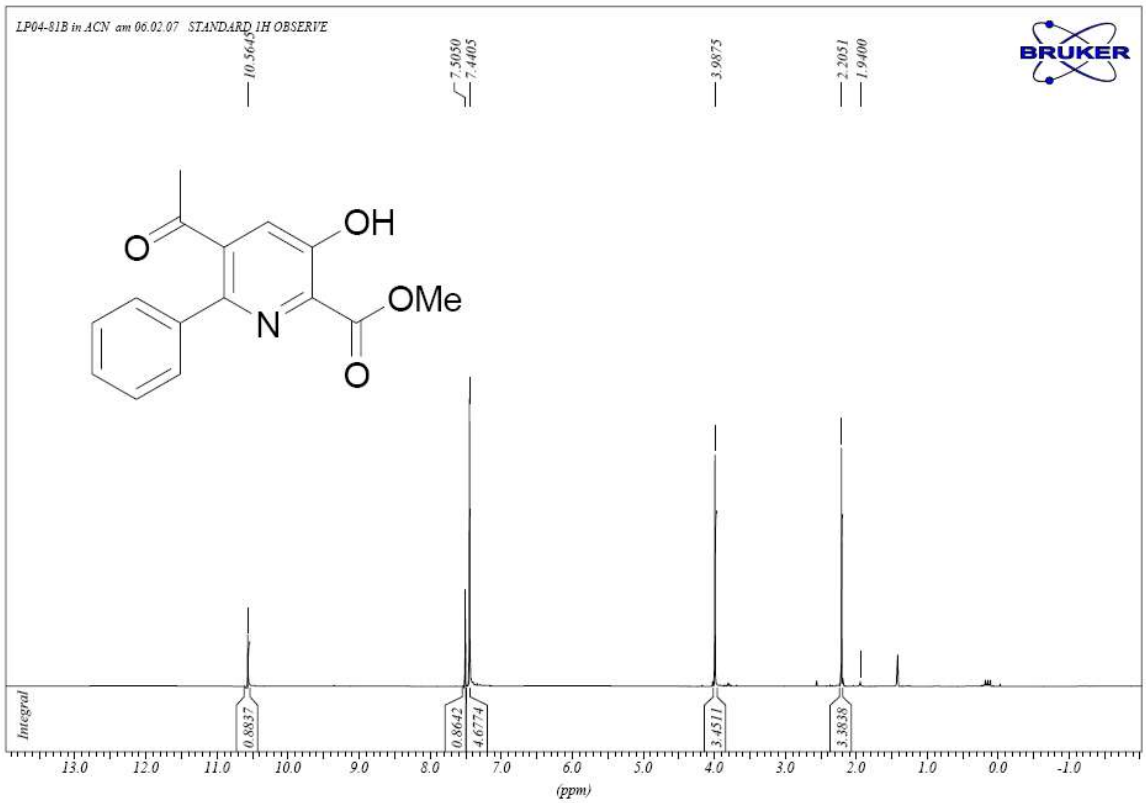

lu-35□STANDARD 1H OBSERVE□□
11.0699
8.5986
7.4421
7.4240
7.3127
7.3074
7.2932
7.2893
7.2600
4.0701
3.6278
OH
MeO
N
OMe
O
O
Integral
3.3272
2.1319
7.50
7.40
7.30
(ppm)
Integral
1.0000
1.9067
3.3272
2.1319
3.3602
3.4315
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
(ppm)

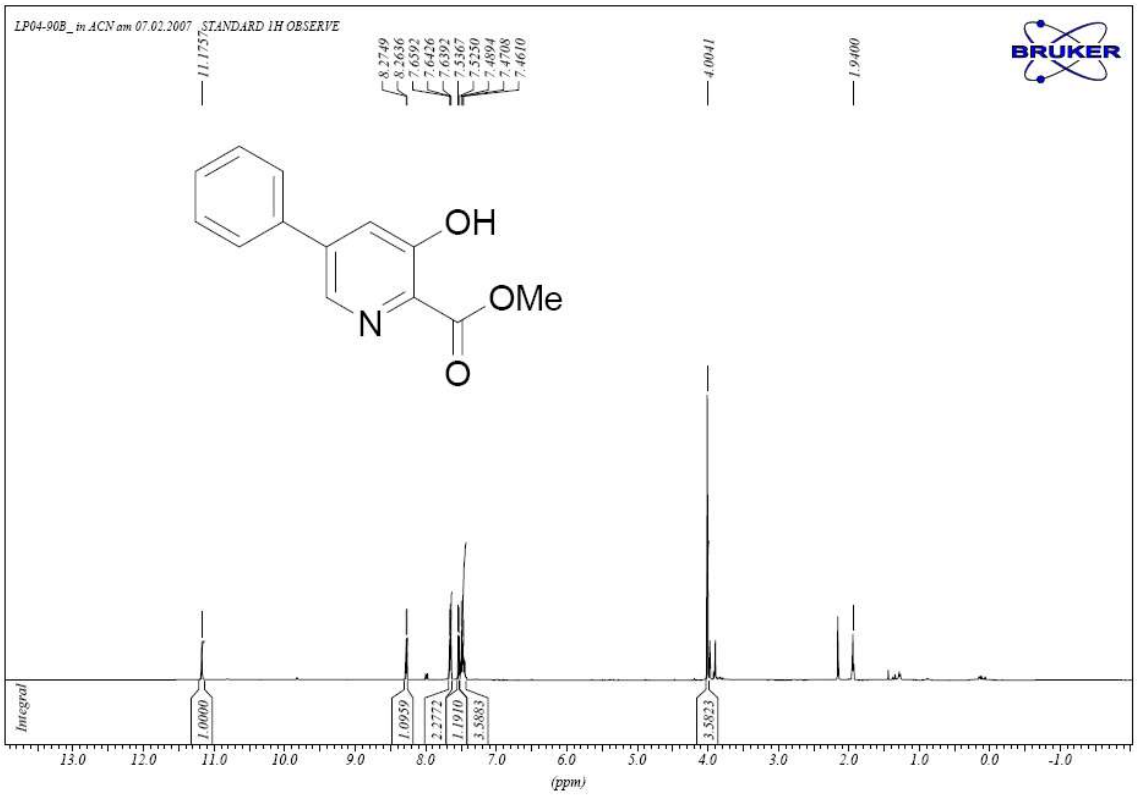

lu-44□STANDARD 1H OBSERVE□□
10.7213
7.6681
7.6520
7.6486
7.5353
7.4480
7.4299
7.2600
4.0354
Cl
OH
N
OMe
O
Integral
1.0000
1.9562
0.9609
3.4142
3.0331
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
(ppm)

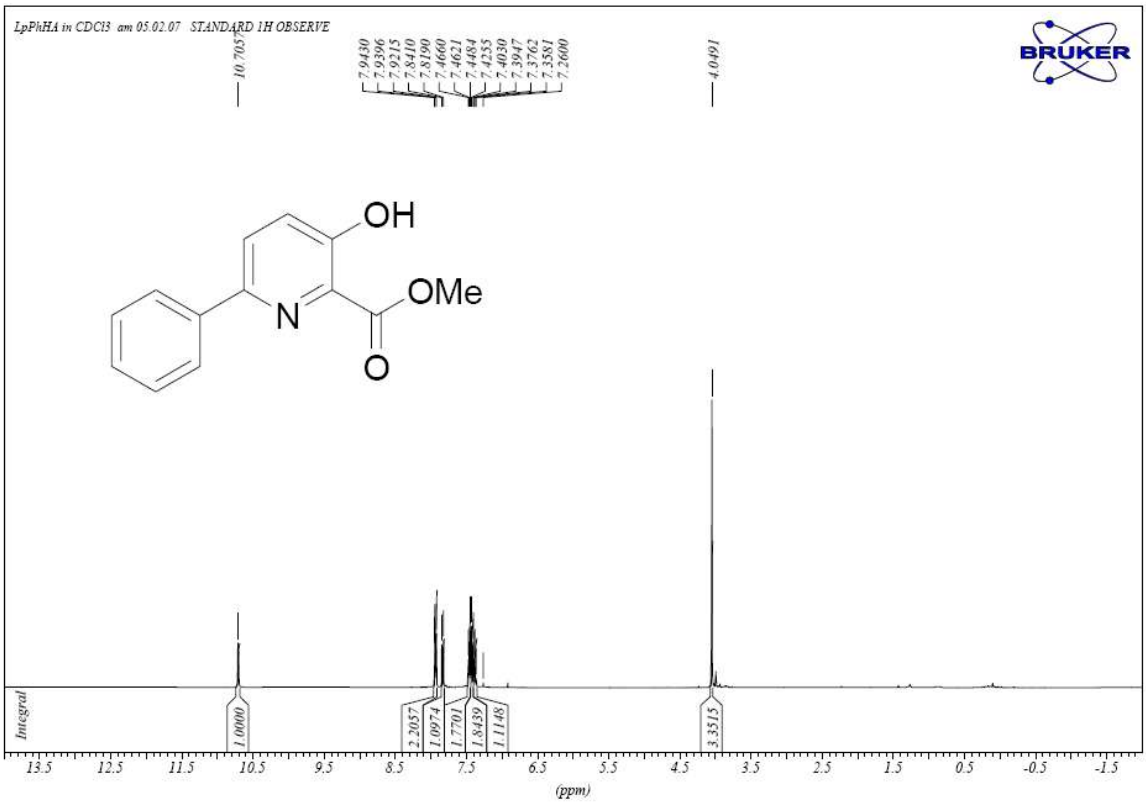

lu-34□STANDARD 1H OBSERVE□□
11.0748
8.4834
7.5065
7.4880
7.3459
7.3420
7.3259
7.2600
4.0740
OH
OMe
Br
N
O
Integral
1.0000
1.0372
3.5137
2.1973
3.4385
12.5
11.5
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
-1.5
(ppm)

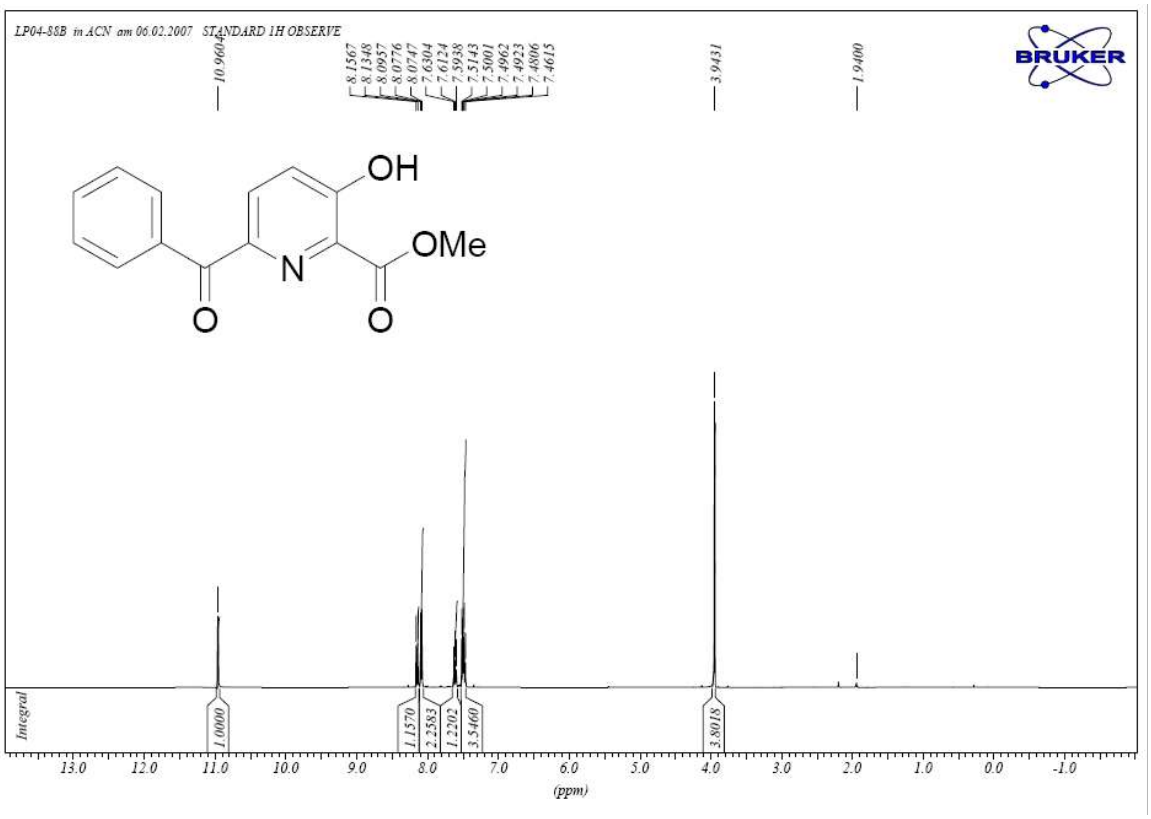

lu-46□STANDARD 1H OBSERVE□□
10.6862
7.7467
7.6276
7.6232
7.6076
7.6042
7.4401
7.4211
4.0286
Br
OH
OMe
N
O
Integral
1.0000
1.0543
2.1663
3.6822
3.2524
13.0
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
(ppm)

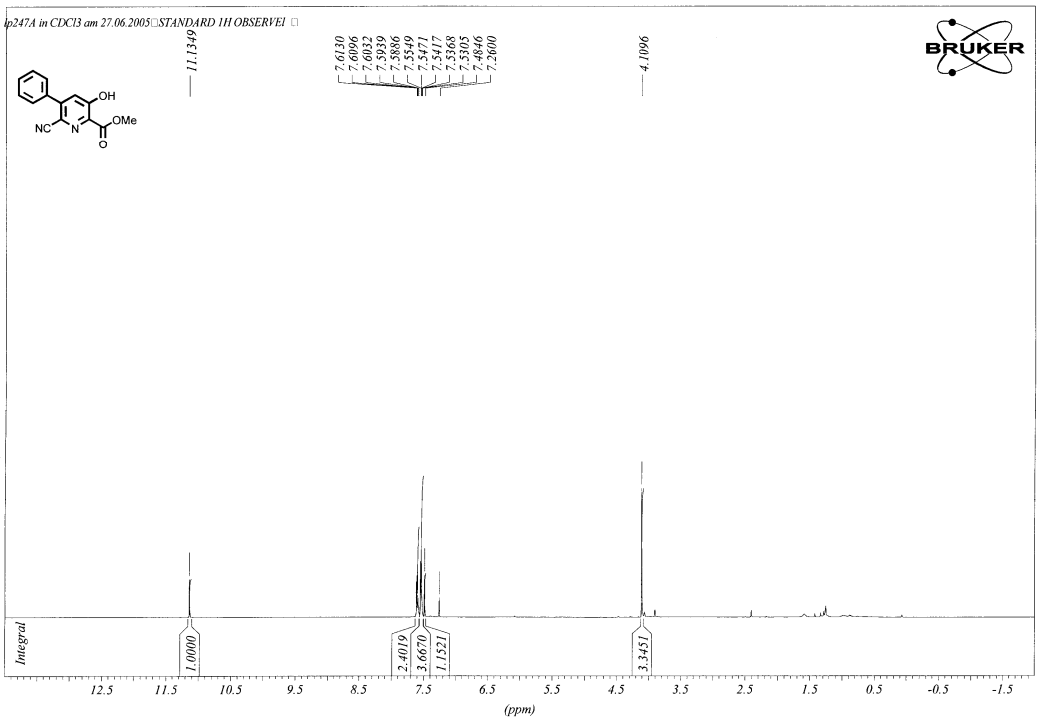

LP04-81A in ACN am 06.02.07 STANDARD 1H OBSERVE
11.0410
8.3076
7.4894
7.4839
7.4781
7.4723
7.3531
7.3434
7.3346
7.3292
4.0100
1.9869
1.9400
BRUKER
OH
OMe
N
O
O
Integral
1.0000
1.0084
3.5498
2.0846
3.4273
3.2860
13.0
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
-1.0

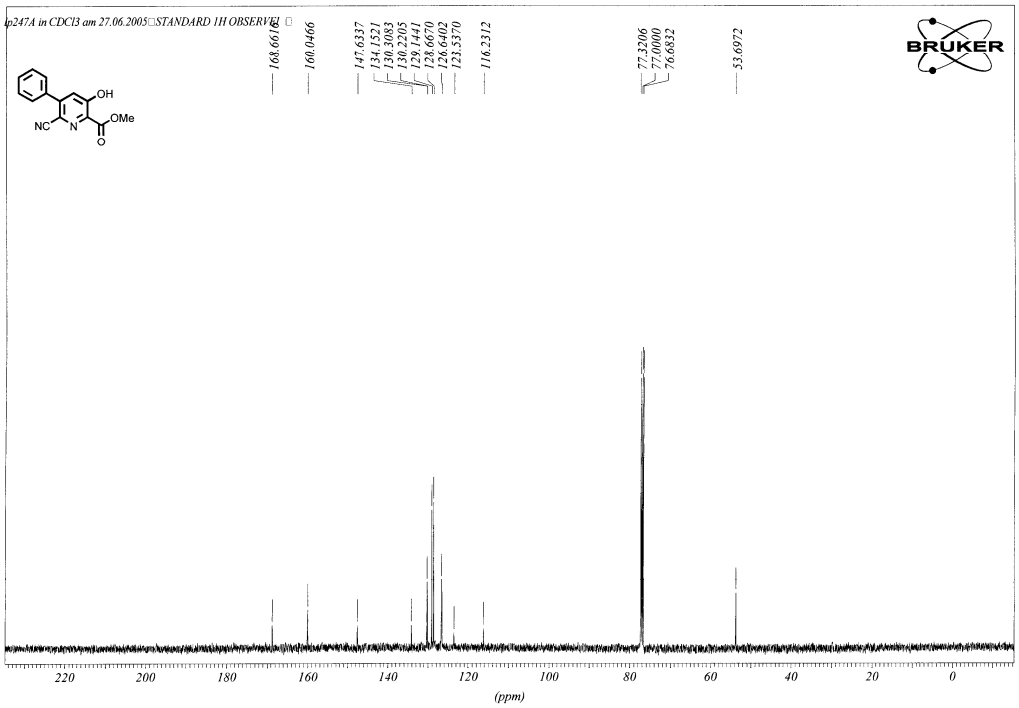

LP04-81B in ACN am 06.02.07 STANDARD 1H OBSERVE
10.5645
7.5050
7.4405
5.9875
2.2051
1.9400
BRUKER
O
OH
OMe
N
O
Integral
0.8837
0.8642
4.6774
3.4511
3.3838
13.0
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
-1.0
(ppm)

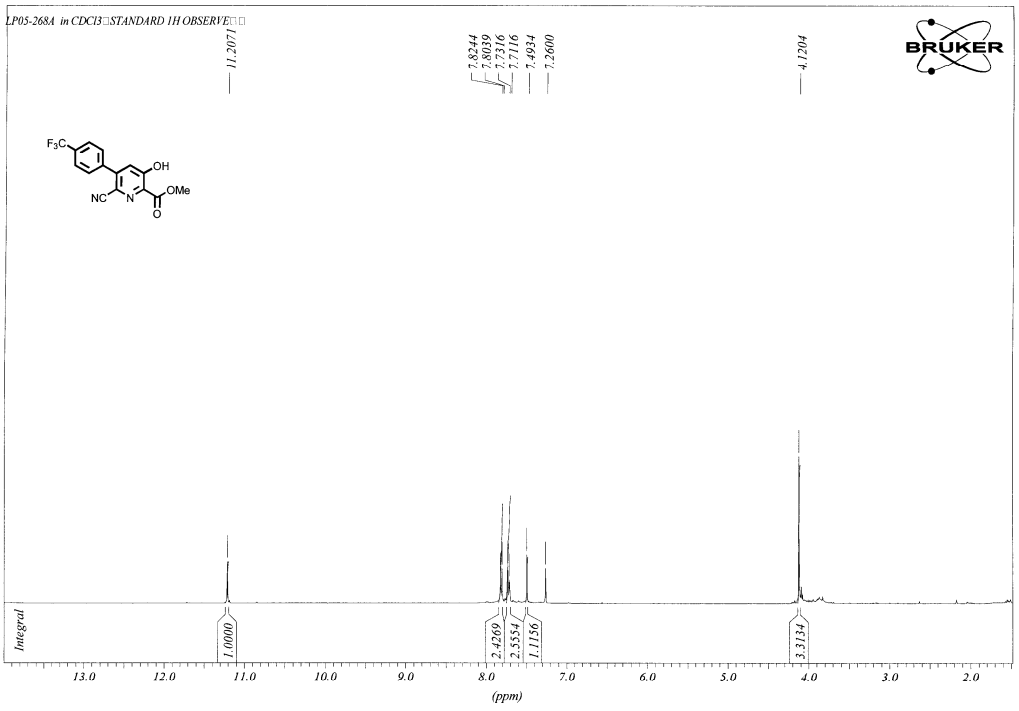

LP04-90B_ in ACN am 07.02.2007 STANDARD 1H OBSERVE
11.1757
8.2749
8.2636
7.6592
7.6426
7.6392
7.5367
7.5250
7.4894
7.4708
7.4610
4.0041
1.9400
OH
OMe
N
O
Integral
1.0000
1.0959
2.2772
1.1910
3.5883
3.5823
(ppm)

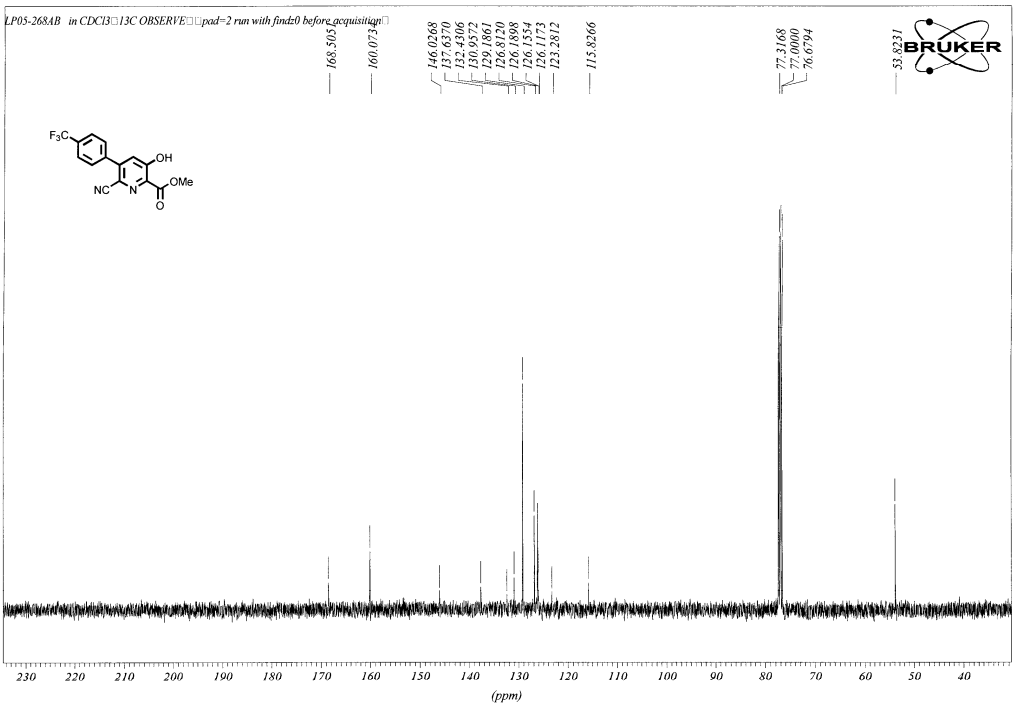

LpPhHA in CDCl3 am 05.02.07 STANDARD 1H OBSERVE
10.7057
7.9430
7.9396
7.9215
7.8410
7.8190
7.4660
7.4621
7.4484
7.4255
7.4030
7.3947
7.3762
7.3581
7.2600
4.0491
OH
OMe
N
O
Integral
1.0000
2.2057
1.0974
1.7701
1.8439
1.1148
3.3515
(ppm)

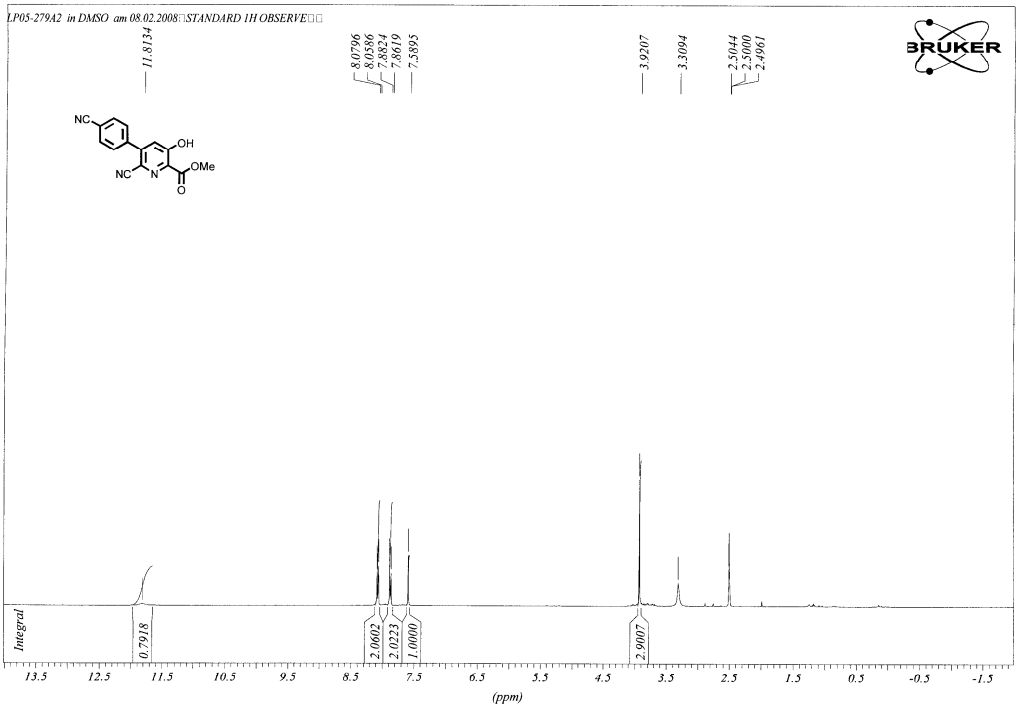

LP04-88B in ACN am 06.02.2007 STANDARD 1H OBSERVE
BRUKER
OH
OMe
N
O
O
(ppm)

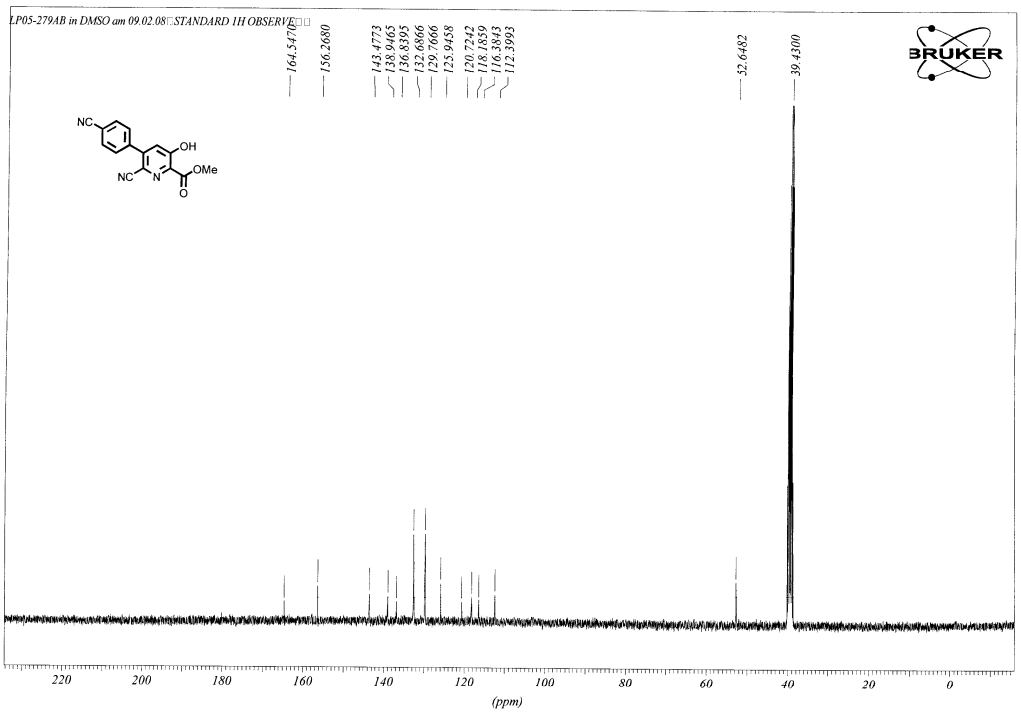

BRUKER
OH
OMe
NC
N
O
(ppm)

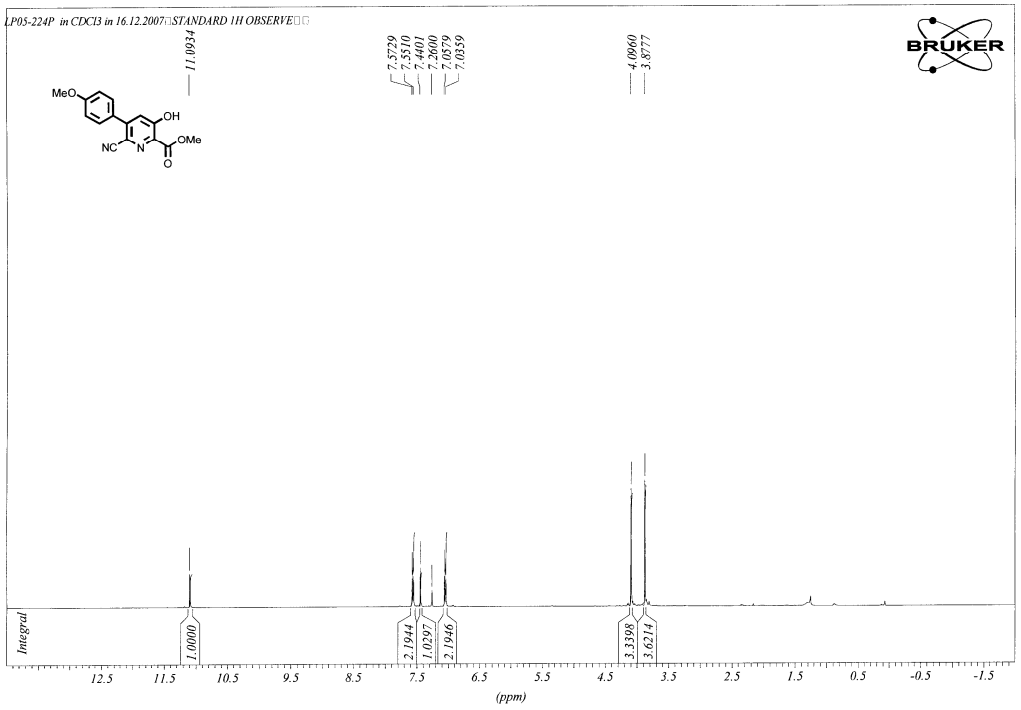

lp247A in CDCl3 am 27.06.2005 STANDARD 1H OBSERVE
168.6616
160.0466
147.6337
134.1521
130.3083
130.2205
129.1441
128.6670
126.6402
123.5370
116.2312
77.3206
77.0000
76.6832
53.6972
OH
NC
N
OMe
O
BRUKER
220
200
180
160
140
120
100
80
60
40
20
0
(ppm)

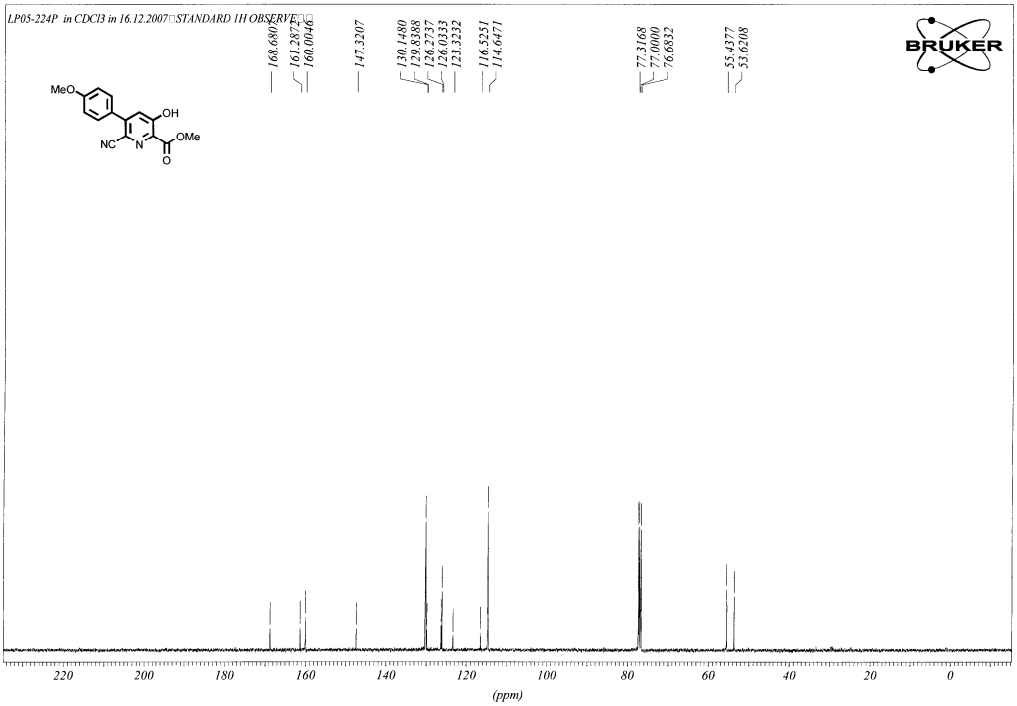

LP05-268A in CDCl3 STANDARD 1H OBSERVE
11.2071
7.8244
7.8039
7.7316
7.7116
7.4934
7.2600
4.1204
F3C
OH
NC
N
OMe
O
BRUKER
Integral
1.0000
2.4269
2.5554
1.1156
3.3134
13.0
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
(ppm)

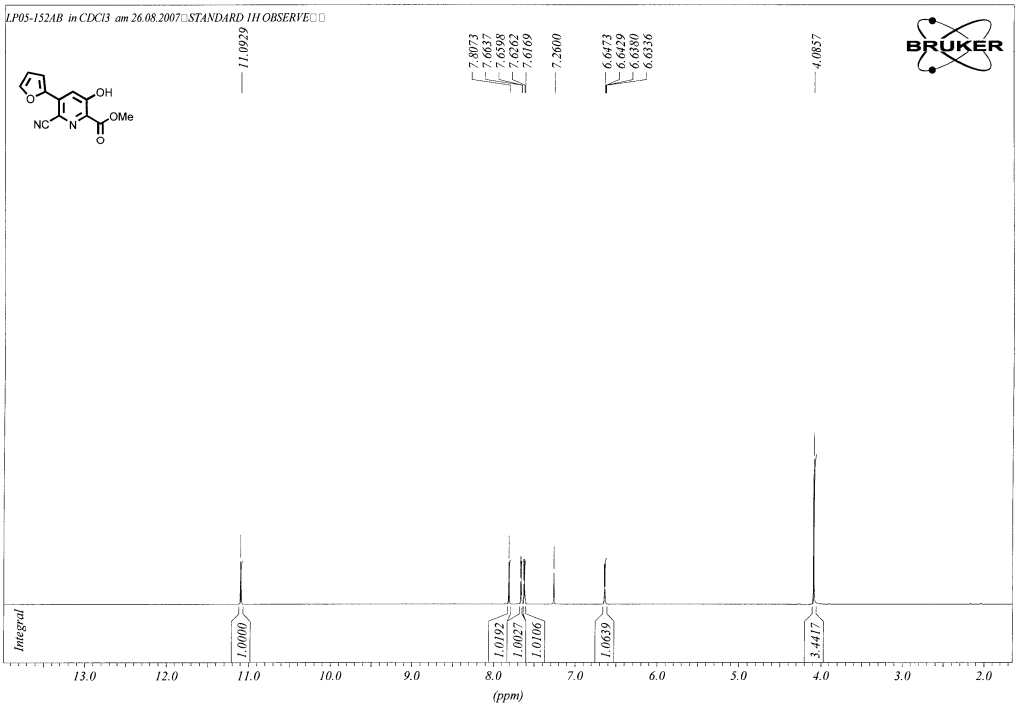

LP05-268AB in CDCl3 13C OBSERVE pad=2 run with findz0 before acquisition
168.5055
160.0734
146.0268
137.6370
132.4106
130.9572
129.1861
126.8120
126.1898
126.1554
126.1173
123.2812
115.8266
77.3168
77.0000
76.6794
53.8231
BRUKER
F3C
OH
NC
N
OMe
O
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40
(ppm)

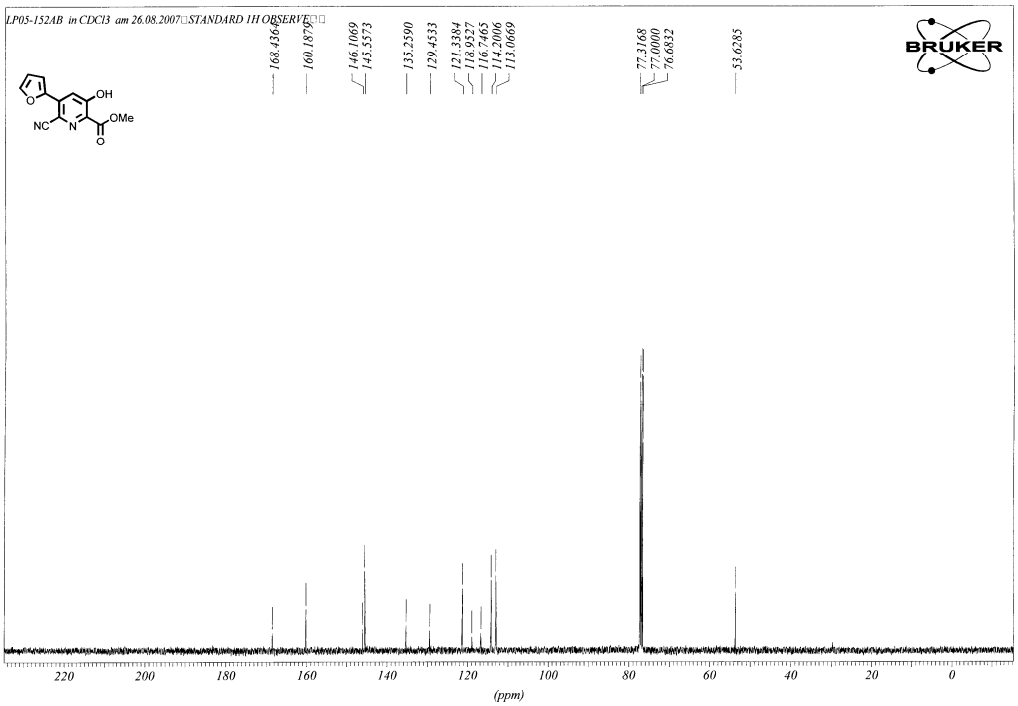

LP05-279A2 in DMSO am 08.02.2008 STANDARD 1H OBSERVE
11.8134
8.0796
8.0586
7.8824
7.8619
7.5895
3.9207
3.3094
2.5044
2.5000
2.4961
BRUKER
NC
OH
NC
N
OMe
O
Integral
0.7918
2.0602
2.0223
1.0000
2.9007
13.5 12.5 11.5 10.5 9.5 8.5 7.5 6.5 5.5 4.5 3.5 2.5 1.5 0.5 -0.5 -1.5
(ppm)

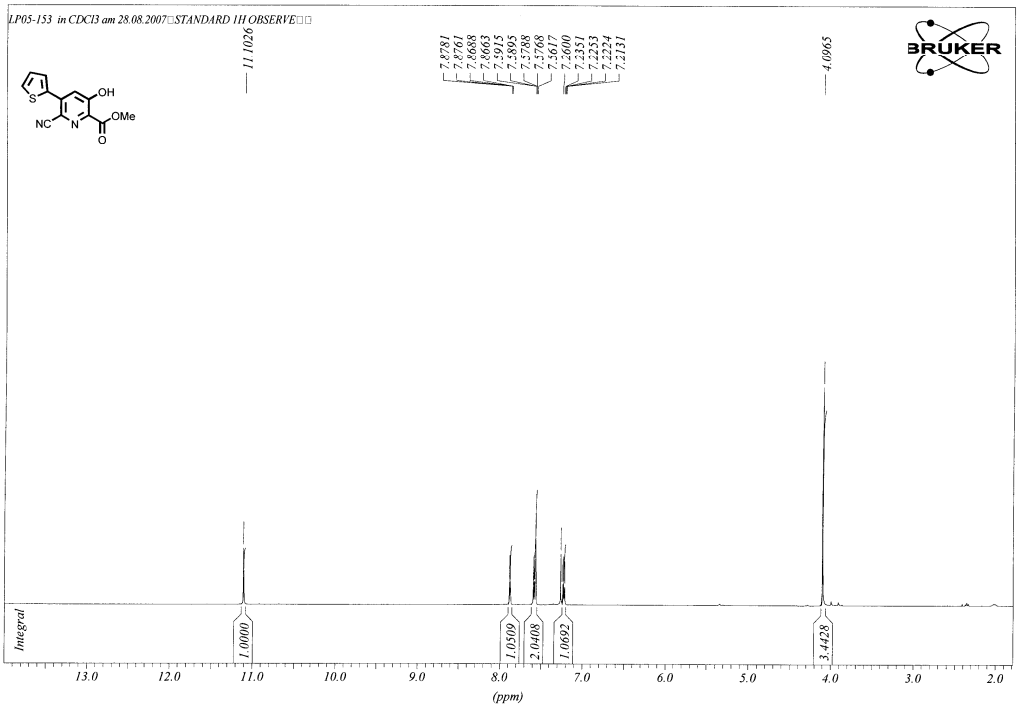

LP05-279AB in DMSO am 09.02.08 STANDARD 1H OBSERVE
164.5470
156.2680
143.4773
138.9465
136.8395
132.6866
129.7666
125.9458
120.7242
118.1859
116.3843
112.3993
52.6482
39.4300
BRUKER
NC
OH
NC
N
OMe
O
220
200
180
160
140
120
100
80
60
40
20
0
(ppm)

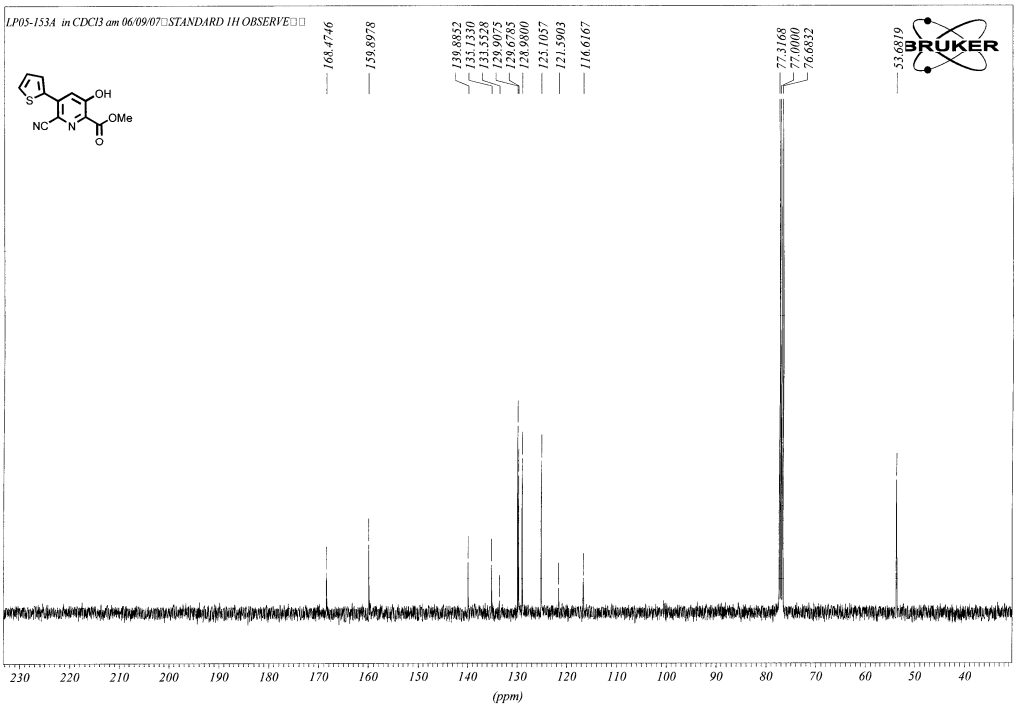

LP05-224P in CDCl3 in 16.12.2007 STANDARD 1H OBSERVE
11.0934
7.5729
7.5510
7.4401
7.2600
7.0579
7.0359
4.0960
3.8777
BRUKER
MeO
OH
NC
N
OMe
O
Integral
1.0000
2.1944
1.0297
2.1946
3.3398
3.6214
12.5
11.5
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
-1.5
(ppm)

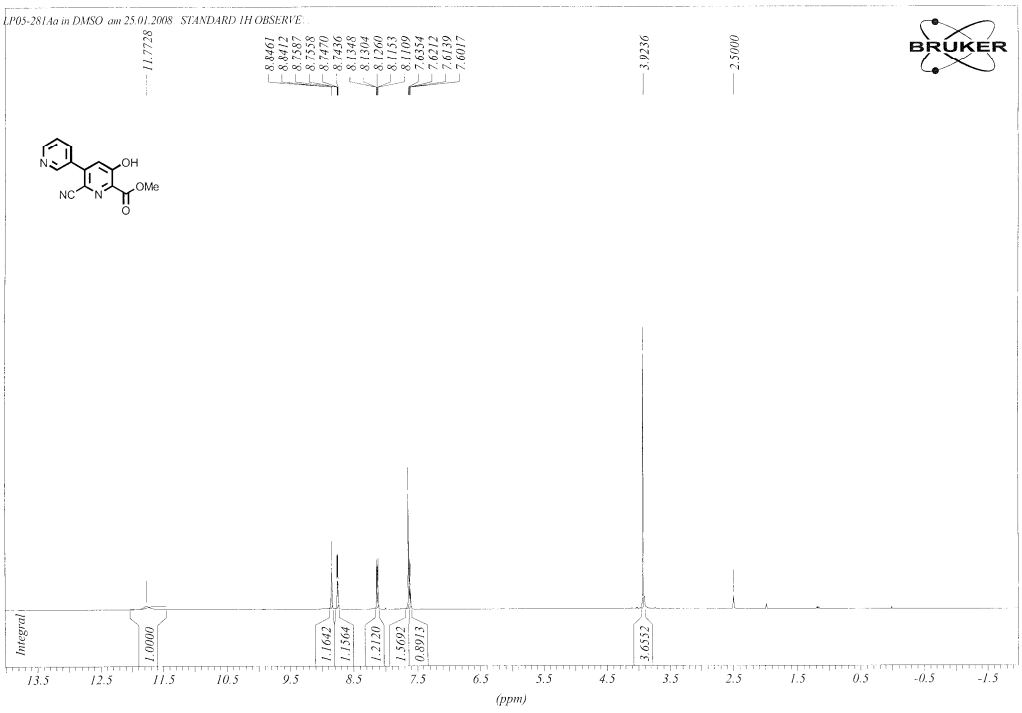

LP05-224P in CDCl3 in 16.12.2007 STANDARD 1H OBSERVE
168.6807
161.2874
160.0046
147.3207
130.1480
129.8388
126.2737
126.0333
121.3232
116.5251
114.6471
77.3168
77.0000
76.6832
55.4377
53.6208
BRUKER
MeO
OH
NC
N
OMe
O
220
200
180
160
140
120
100
80
60
40
20
0
(ppm)

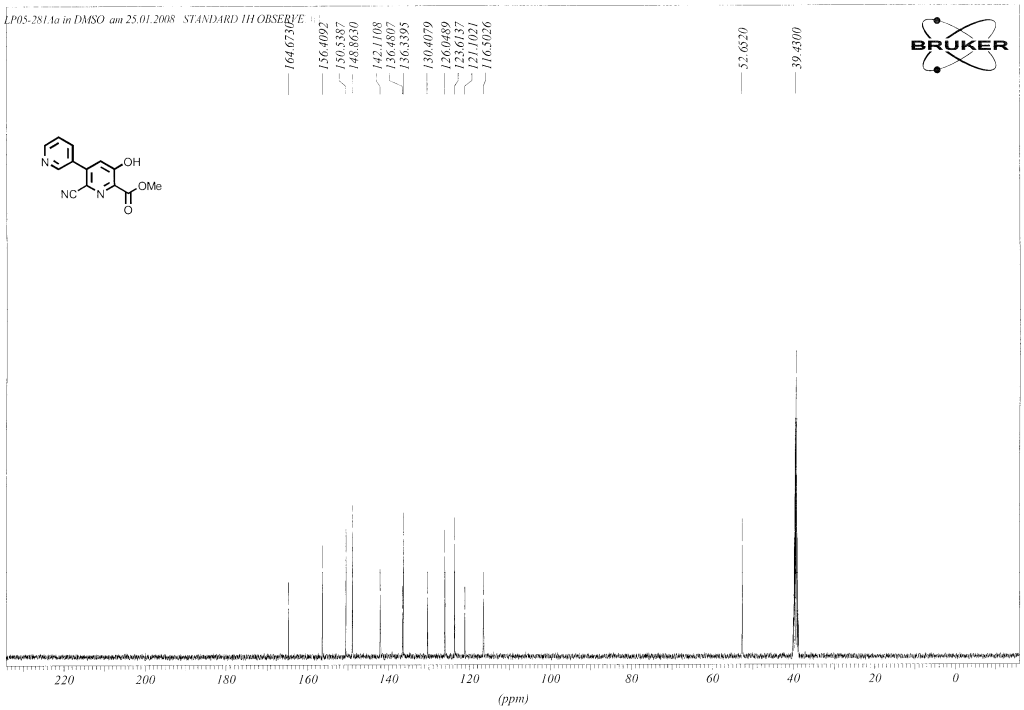

LP05-152AB in CDCl3 am 26.08.2007 STANDARD 1H OBSERVE
11.0929
7.8073
7.6637
7.6598
7.6262
7.6169
7.2600
6.6473
6.6429
6.6380
6.6336
4.0857
BRUKER
OH
NC
N
OMe
O
Integral
1.0000
1.0192
1.0027
1.0106
1.0639
3.4417
13.0
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
(ppm)

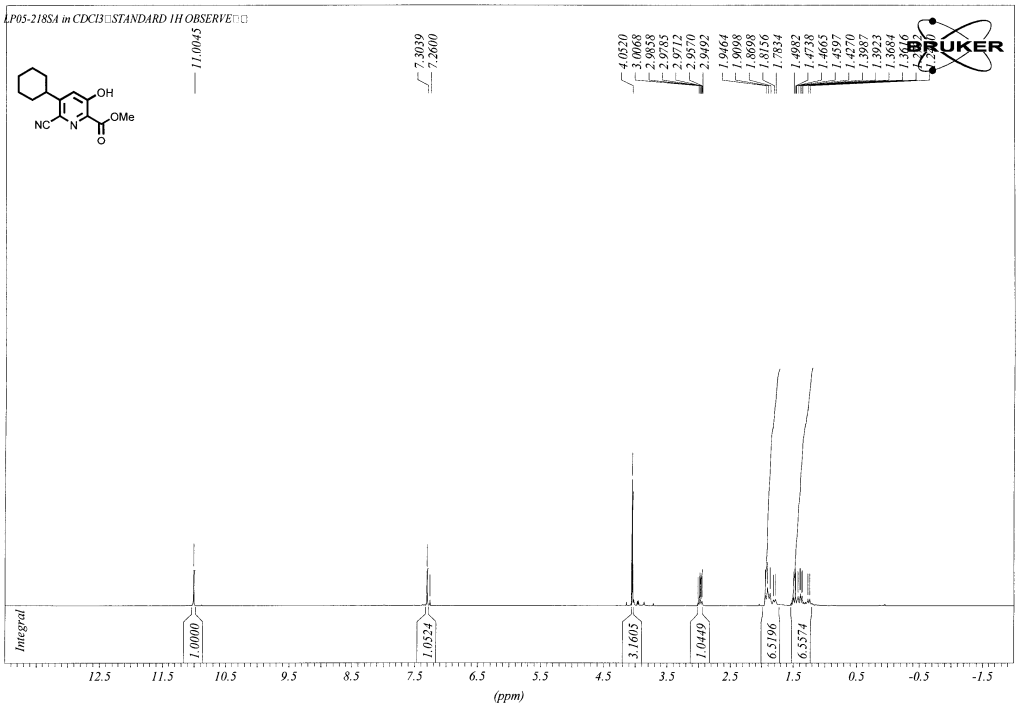

LP05-152AB in CDCl3 am 26.08.2007 STANDARD 1H OBSERVE
168.4367
160.1877
146.1069
145.5573
135.2590
129.4533
121.3384
118.9527
116.7465
114.2006
113.0669
77.3168
77.0000
76.6832
53.6285
BRUKER
OH
NC
N
OMe
O
220
200
180
160
140
120
100
80
60
40
20
0
(ppm)

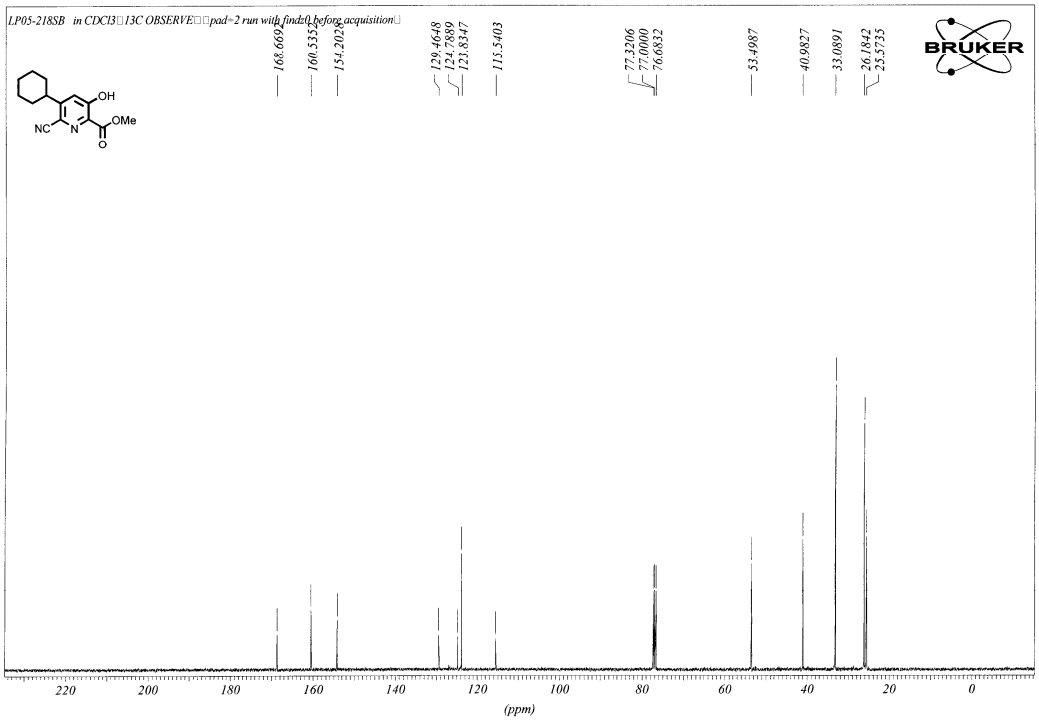

LP05-153 in CDCl3 am 28.08.2007 STANDARD 1H OBSERVE
11.1026
7.8781
7.8761
7.8688
7.8663
7.5915
7.5895
7.5788
7.5768
7.2617
7.2600
7.2351
7.2253
7.2224
7.2131
4.0965
BRUKER
OH
NC
N
OMe
O
Integral
1.0000
1.0509
2.0408
1.0692
3.4428
13.0
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
(ppm)

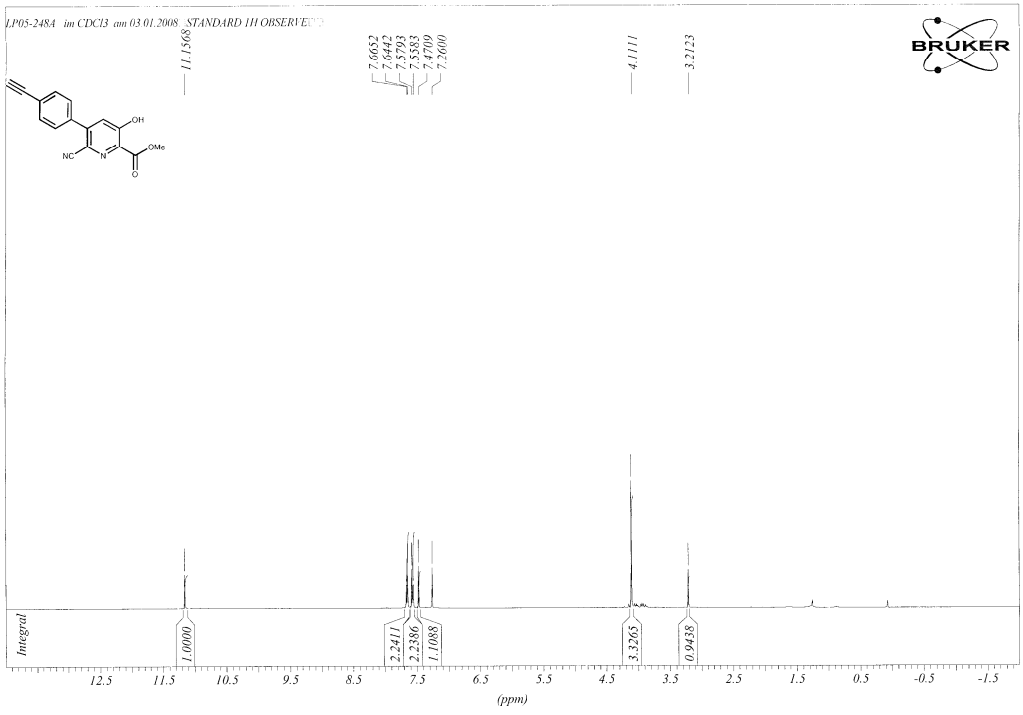

LP05-153A in CDCl3 am 06/09/07□STANDARD 1H OBSERVE□□
168.4746
158.8978
139.8852
133.1330
131.5528
129.9075
129.6785
128.9800
123.1057
121.5903
116.6167
77.3168
77.0000
76.6832
53.6819
BRUKER
OH
NC
N
OMe
O
S
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40
(ppm)

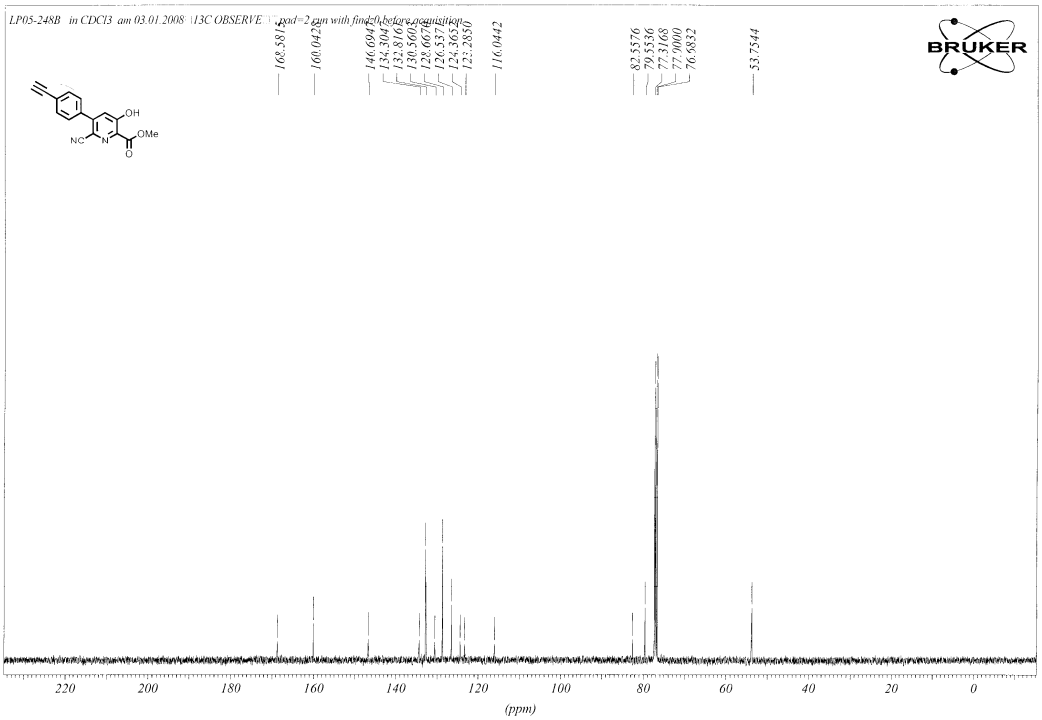

LP05-281Aa in DMSO am 25.01.2008 STANDARD 1H OBSERVE
11.7728
8.8461
8.8412
8.7587
8.7558
8.7470
8.7436
8.1348
8.1304
8.1260
8.1153
8.1109
7.6554
7.6212
7.6139
7.6017
3.9236
2.5000
BRUKER
OH
NC
N
OMe
O
Integral
1.0000
1.1642
1.1564
1.2120
1.5692
0.8913
3.6552
13.5 12.5 11.5 10.5 9.5 8.5 7.5 6.5 5.5 4.5 3.5 2.5 1.5 0.5 -0.5 -1.5
(ppm)

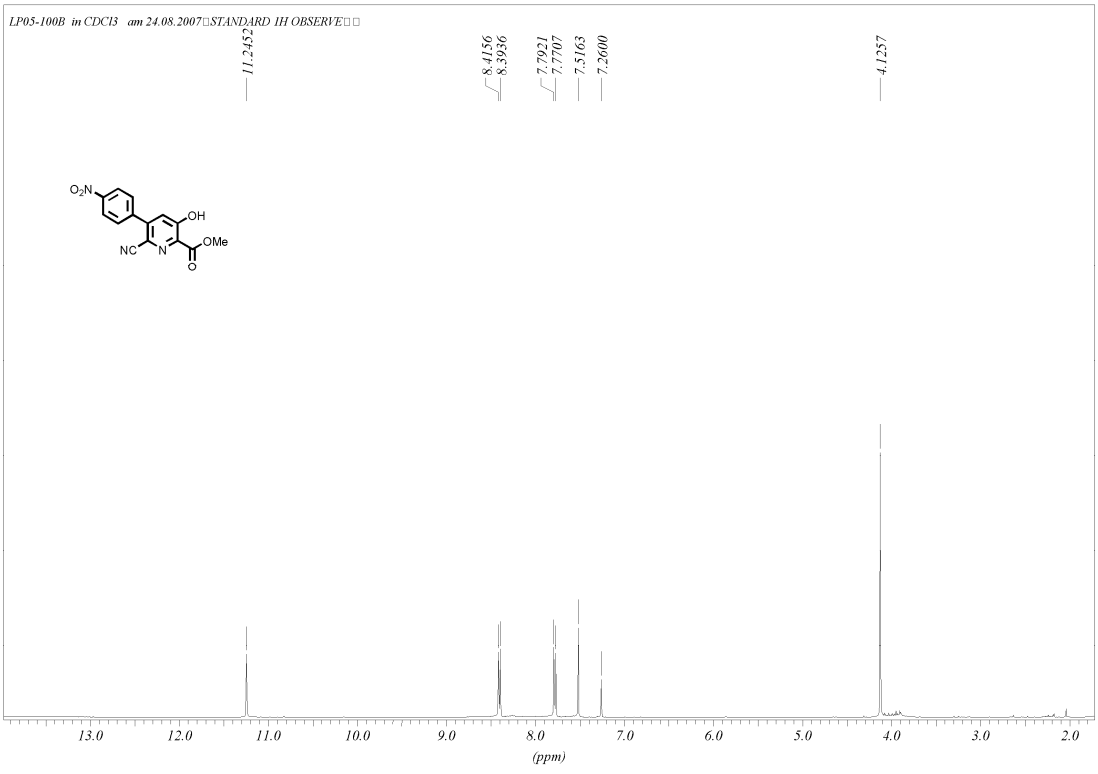

LP05-281Aa in DMSO am 25.01.2008 STANDARD 1H OBSERVE
164.6730
156.4092
150.5387
148.8630
142.1108
136.4807
136.3395
130.4079
126.0489
123.6137
121.1021
116.5926
52.6520
39.4300
BRUKER
OH
OMe
NC
N
O
220
200
180
160
140
120
100
80
60
40
20
0
(ppm)

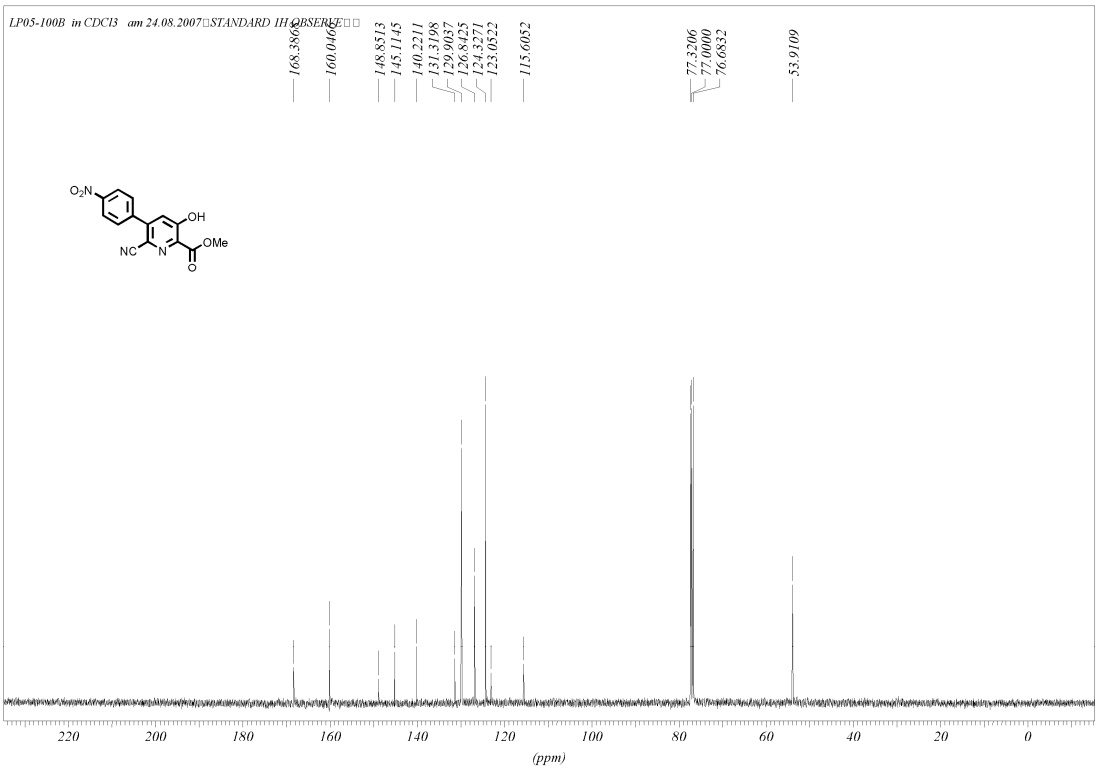

LP05-218SA in CDCl3 STANDARD 1H OBSERVE
11.0045
7.3039
7.2600
4.0520
3.0068
2.9858
2.9785
2.9712
2.9570
2.9492
1.9464
1.9098
1.8698
1.8536
1.7834
1.4982
1.4738
1.4665
1.4597
1.4270
1.3987
1.3923
1.3684
BRUKER
OH
OMe
NC
N
O
Integral
1.0000
1.0524
3.1605
1.0449
6.5196
6.5574
12.5
11.5
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
-1.5
(ppm)

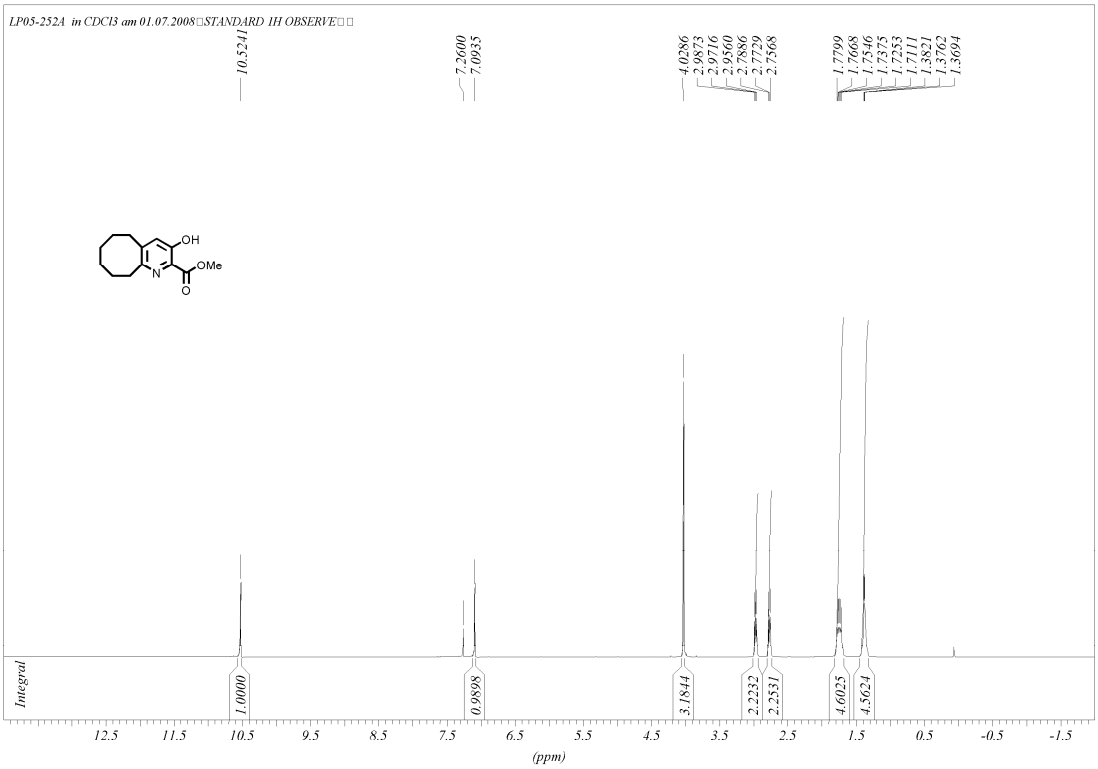

LP05-218SB in CDCl3 13C OBSERVE pad=2 run with findzl before acquisition
168.6692
160.5352
154.2026
129.4648
124.7889
123.8347
115.5403
77.3206
77.0000
76.6832
53.4987
40.9827
33.0891
26.1842
25.5735
BRUKER
OH
NC
N
OMe
O
220
200
180
160
140
120
100
80
60
40
20
0
(ppm)

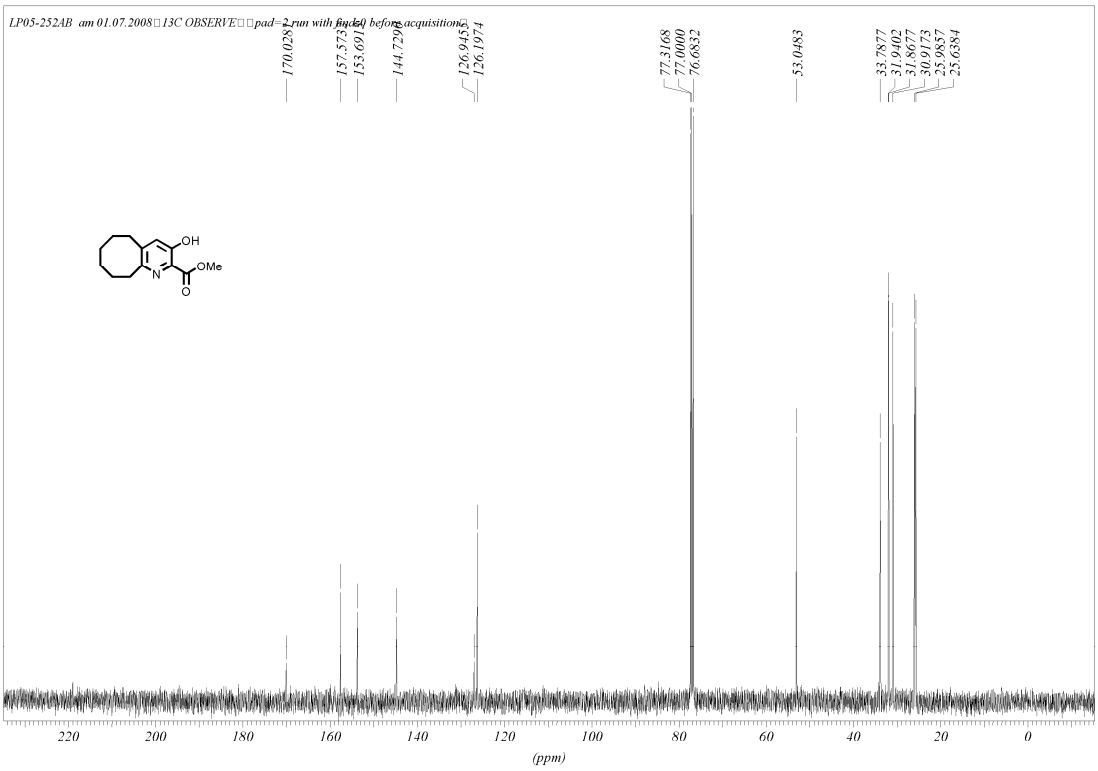

LP05-248A im CDCl3 ann 03.01.2008 STANDARD 1H OBSERVE
1.1568
7.6652
7.6442
7.5793
7.5583
7.4709
7.2600
4.1111
3.2123
BRUKER
OH
NC
N
OMe
O
Integral
1.0000
2.2411
2.2386
1.1088
3.3265
0.9438
12.5
11.5
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
-1.5
(ppm)

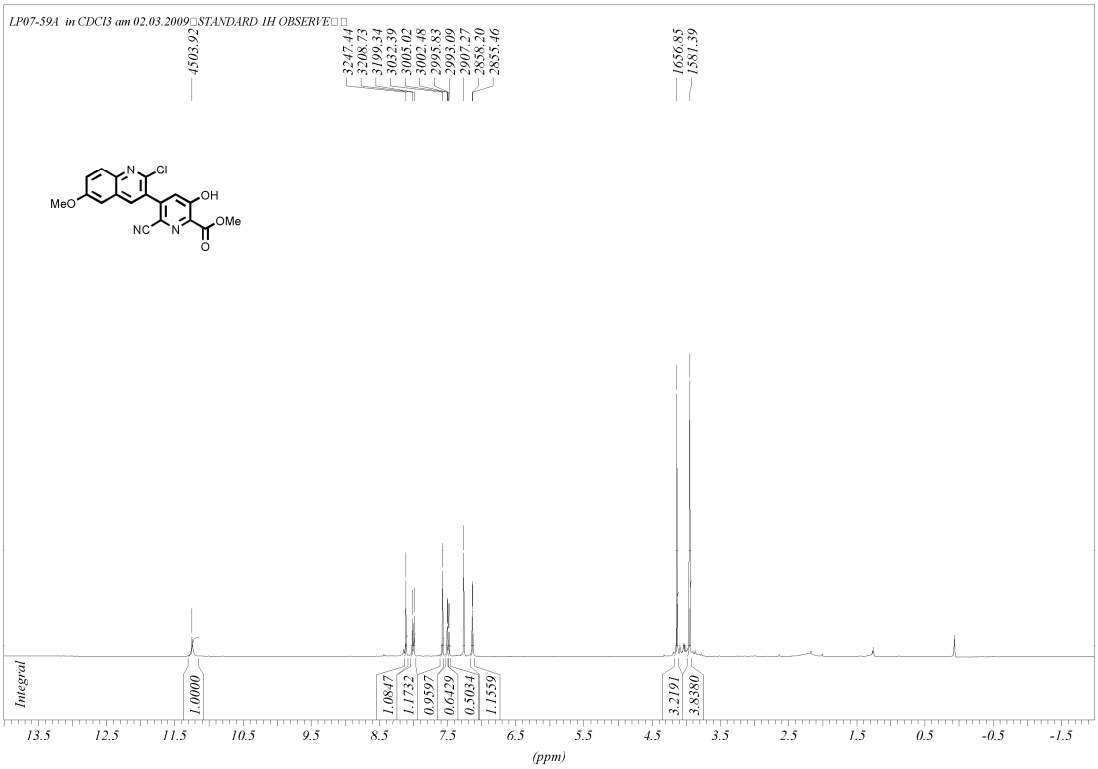

LP05-248B in CDCl3 am 03.01.2008 13C OBSERVE
168.5815
160.0425
146.6947
134.3044
132.8164
130.5602
128.6678
126.5377
124.3653
122.2850
116.0442
82.5576
79.5536
77.3168
77.0000
76.6832
53.7544
OH
OMe
NC
N
O
220
200
180
160
140
120
100
80
60
40
20
0
(ppm)

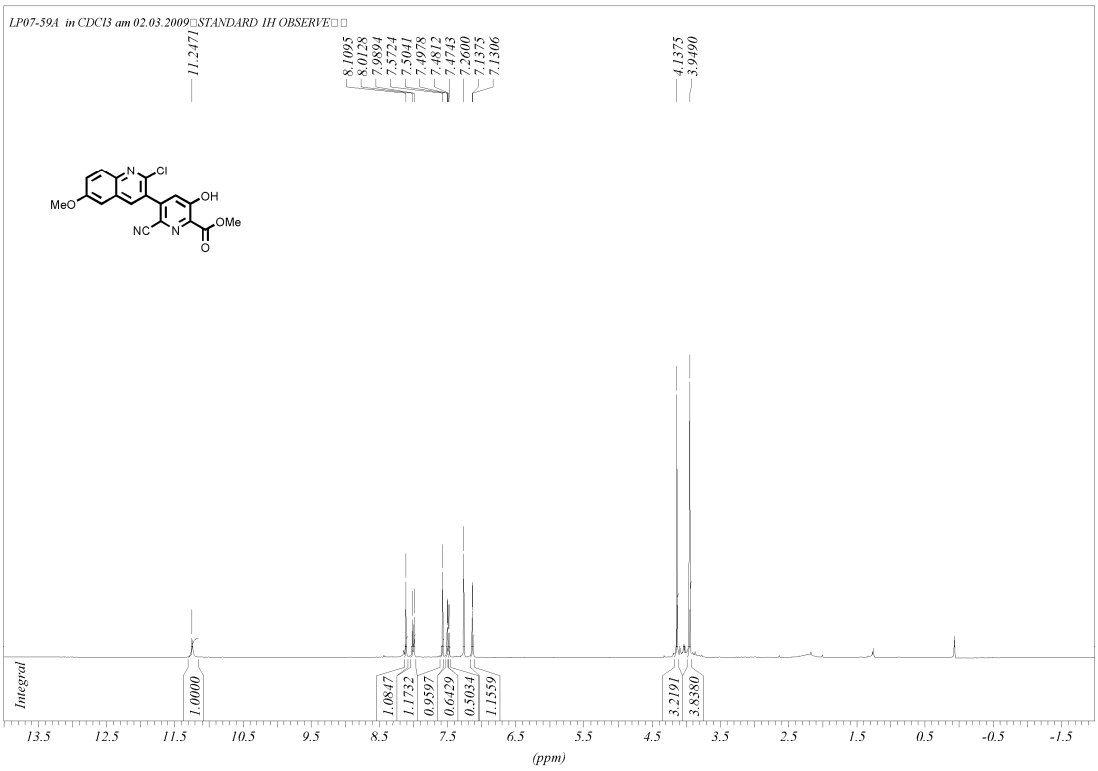

LP05-100B in CDCl3 am 24.08.2007 STANDARD 1H OBSERVE
11.2452
8.4156
8.3936
7.7921
7.7707
7.5163
7.2600
4.1257
O2N
OH
OMe
NC
N
O
13.0
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
(ppm)

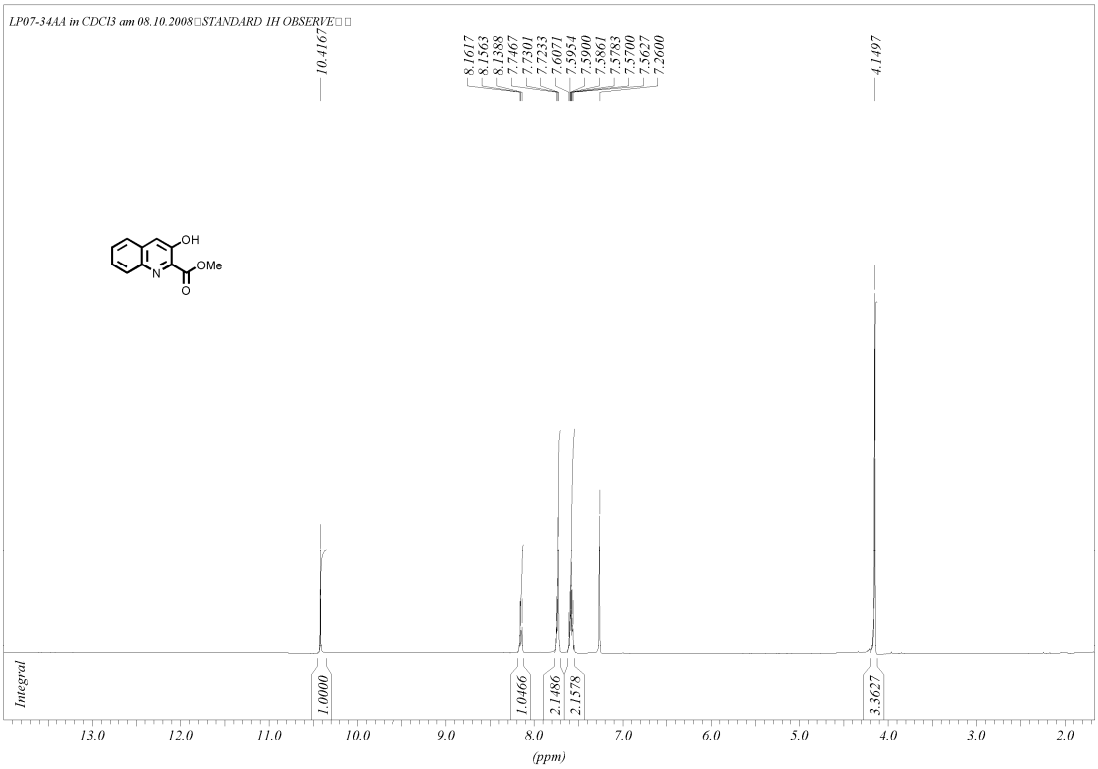

LP05-100B in CDCl3 am 24.08.2007 STANDARD 1H OBSERVE
168.3865
160.0466
148.8513
145.1145
140.2211
131.3198
129.9037
126.8425
124.3271
123.0522
115.6052
77.3206
77.0000
76.6832
53.9109
O2N
OH
NC
N
OMe
O
220
200
180
160
140
120
100
80
60
40
20
0
(ppm)

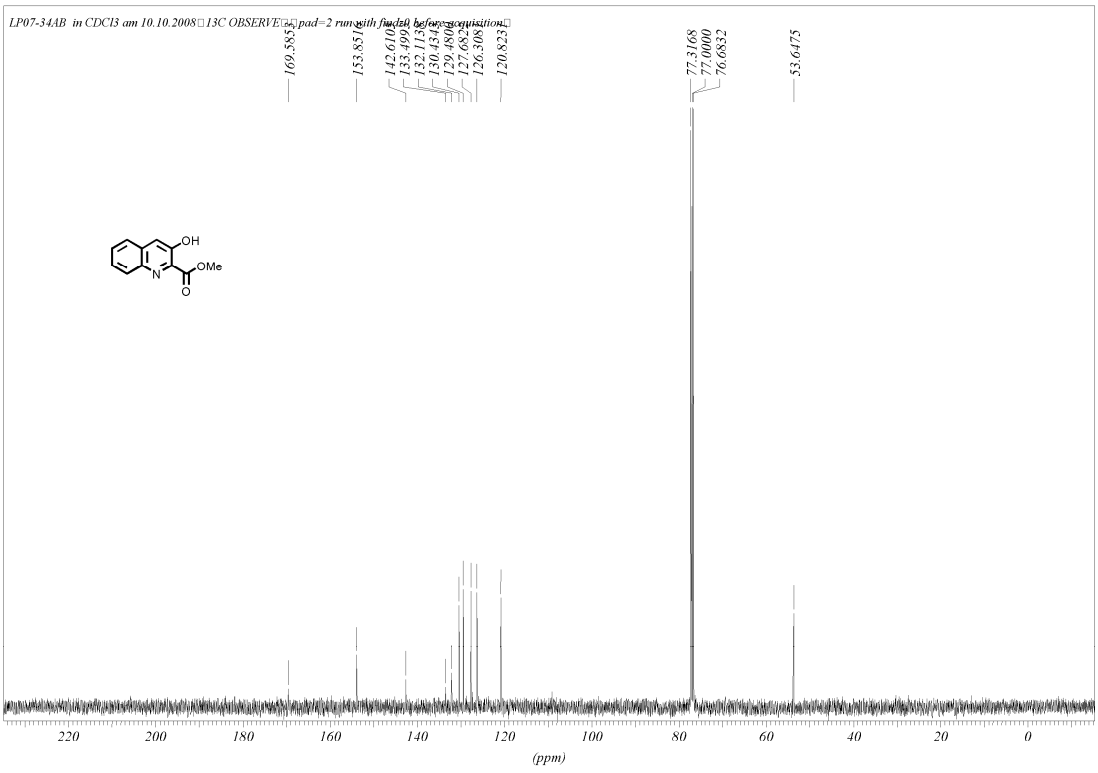

LP05-252A in CDCl3 am 01.07.2008 STANDARD 1H OBSERVE
10.5241
7.2600
7.0935
4.0286
2.9873
2.9716
2.9560
2.7886
2.7729
2.7568
1.7799
1.7668
1.7546
1.7375
1.7253
1.7111
1.3821
1.3762
1.3694
OH
N
OMe
O
Integral
1.0000
0.9898
3.1844
2.2232
2.2531
4.6025
4.5624
12.5
11.5
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
-1.5
(ppm)

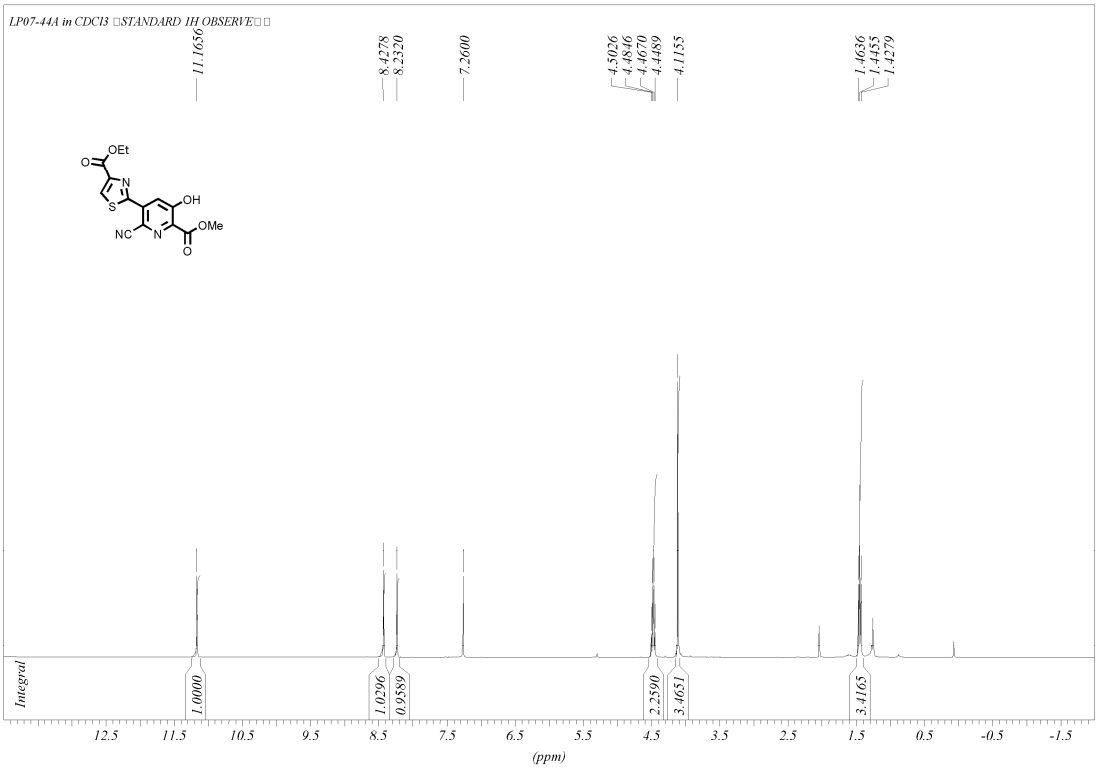

LP05-252AB am 01.07.2008 13C OBSERVE pad=2 run with hydrol before acquisition
170.0281
157.5736
153.6915
144.7296
126.9451
126.1974
77.3168
77.0000
76.6832
53.0483
33.7877
31.9402
31.8677
30.9173
25.9857
25.6384
OH
OMe
N
O
220
200
180
160
140
120
100
80
60
40
20
0
(ppm)

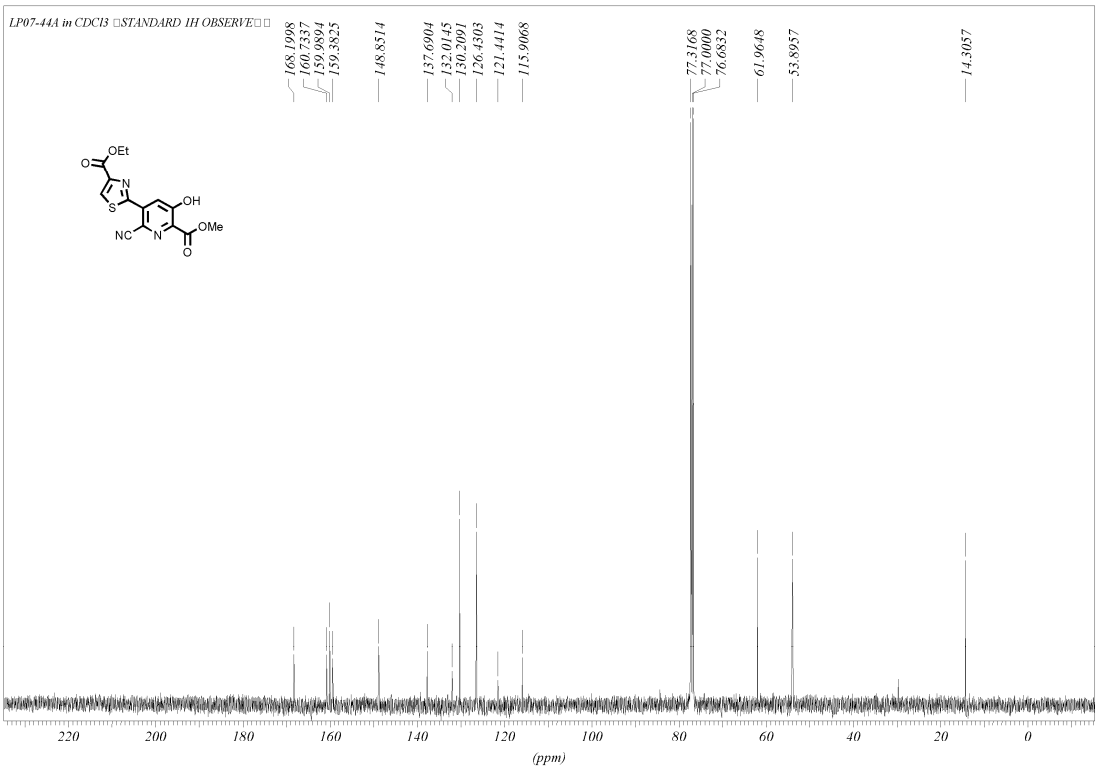

LP07-59A in CDCl3 am 02.03.2009 STANDARD 1H OBSERVE
4503.92
3247.44
3208.73
3199.34
3032.39
3005.02
3002.48
2993.83
2993.09
2907.27
2858.20
2855.46
1656.85
1581.39
Cl
N
MeO
OH
NC
N
OMe
O
Integral
1.0000
1.0847
1.1732
0.9597
0.6429
0.5034
1.1559
3.2191
3.8380
13.5
12.5
11.5
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
-1.5
(ppm)

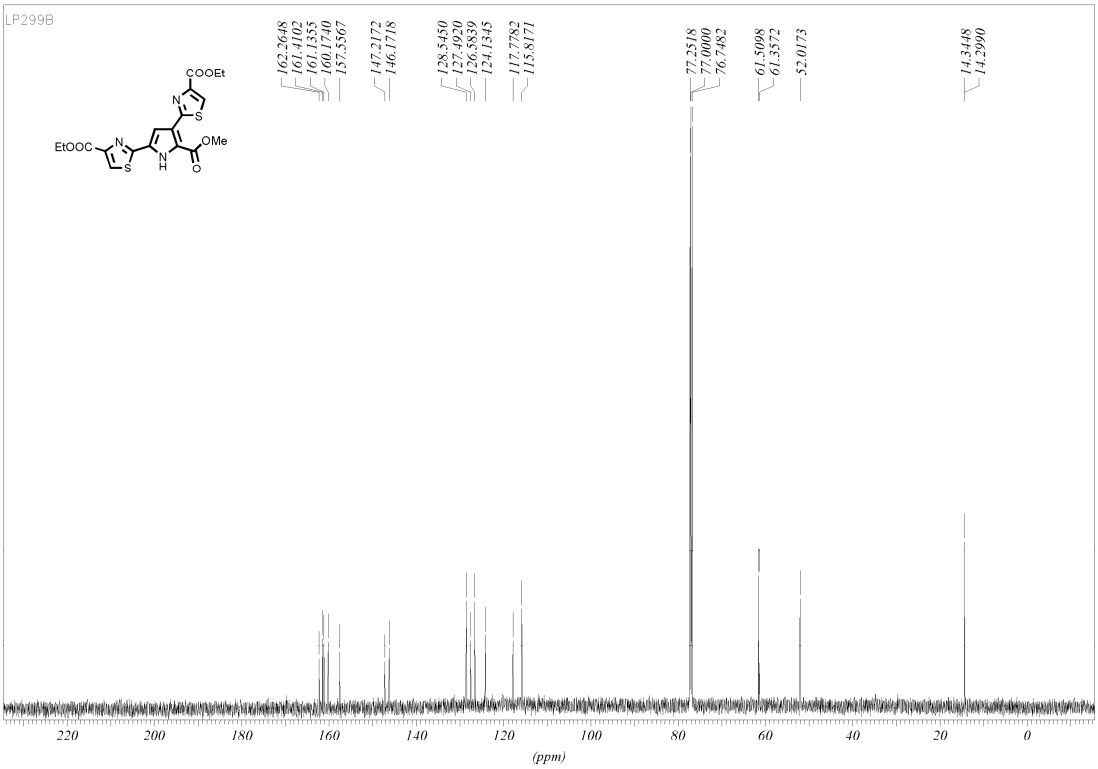

LP07-59A in CDCl3 am 02.03.2009 STANDARD 1H OBSERVE
11.2471
8.1095
8.0128
7.9894
7.5724
7.5041
7.4978
7.4812
7.4743
7.2600
7.1375
7.1306
4.1375
3.9490
Cl
N
MeO
OH
NC
N
OMe
O
Integral
1.0000
1.0847
1.1732
0.9597
0.6429
0.5034
1.1559
3.2191
3.8380
13.5
12.5
11.5
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
-1.5
(ppm)

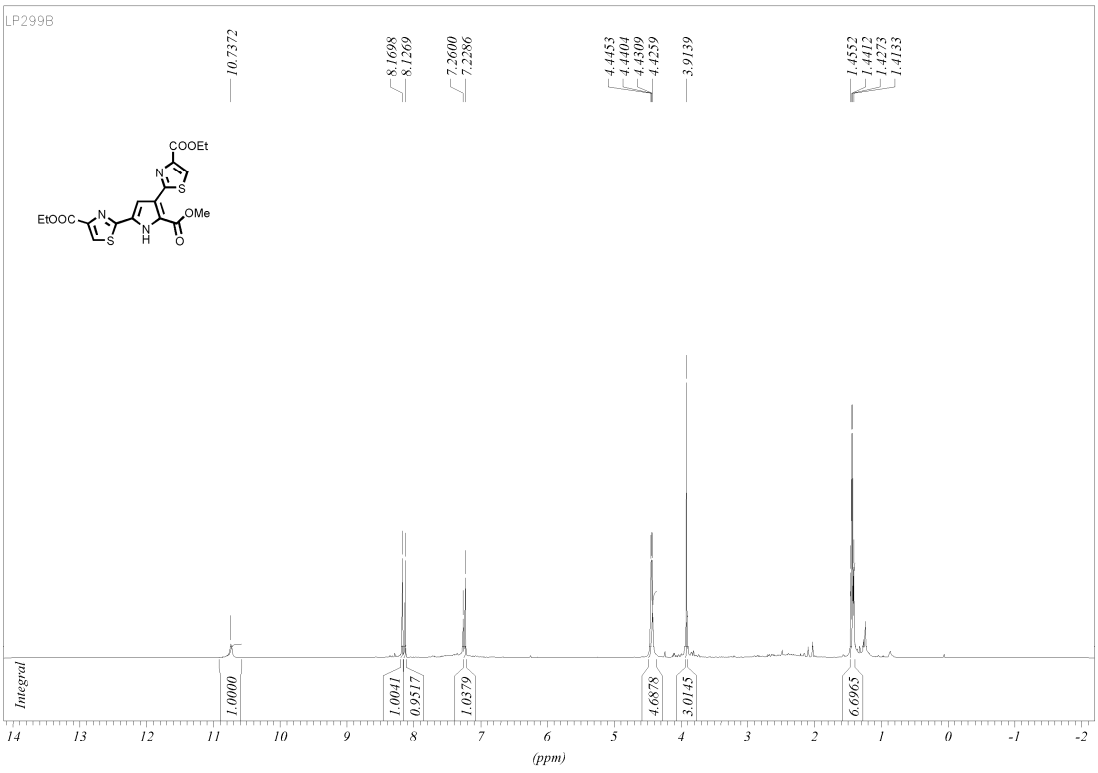

LP07-34AA in CDCl3 am 08.10.2008 STANDARD 1H OBSERVE
10.4167
8.1617
8.1563
8.1388
7.7467
7.7301
7.7233
7.6071
7.5954
7.5900
7.5861
7.5783
7.5700
7.5627
7.2600
4.1497
OH
N
OMe
O
Integral
1.0000
1.0466
2.1486
2.1578
3.3627
13.0
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
(ppm)

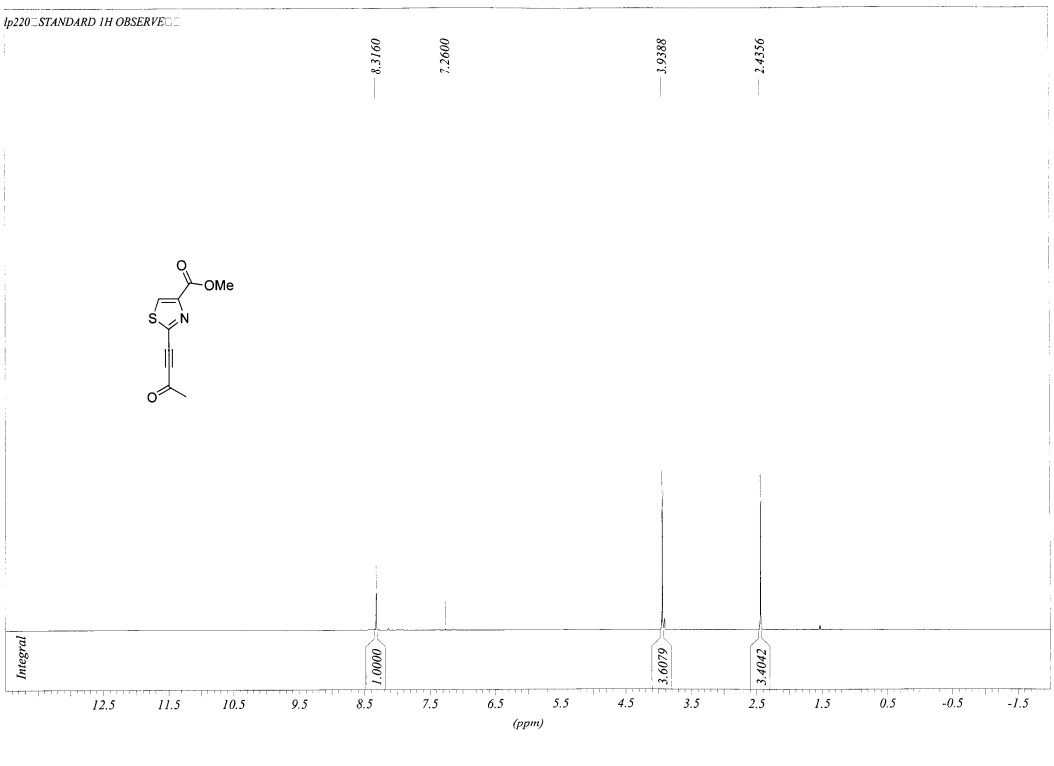

LP07-34AB in CDCl3 am 10.10.2008 13C OBSERVE
169.5853
153.8516
142.6105
133.4999
132.1135
130.4344
129.4806
127.6825
126.5085
120.8233
77.3168
77.0000
76.6832
53.6475
OH
OMe
N
O
220
200
180
160
140
120
100
80
60
40
20
0
(ppm)

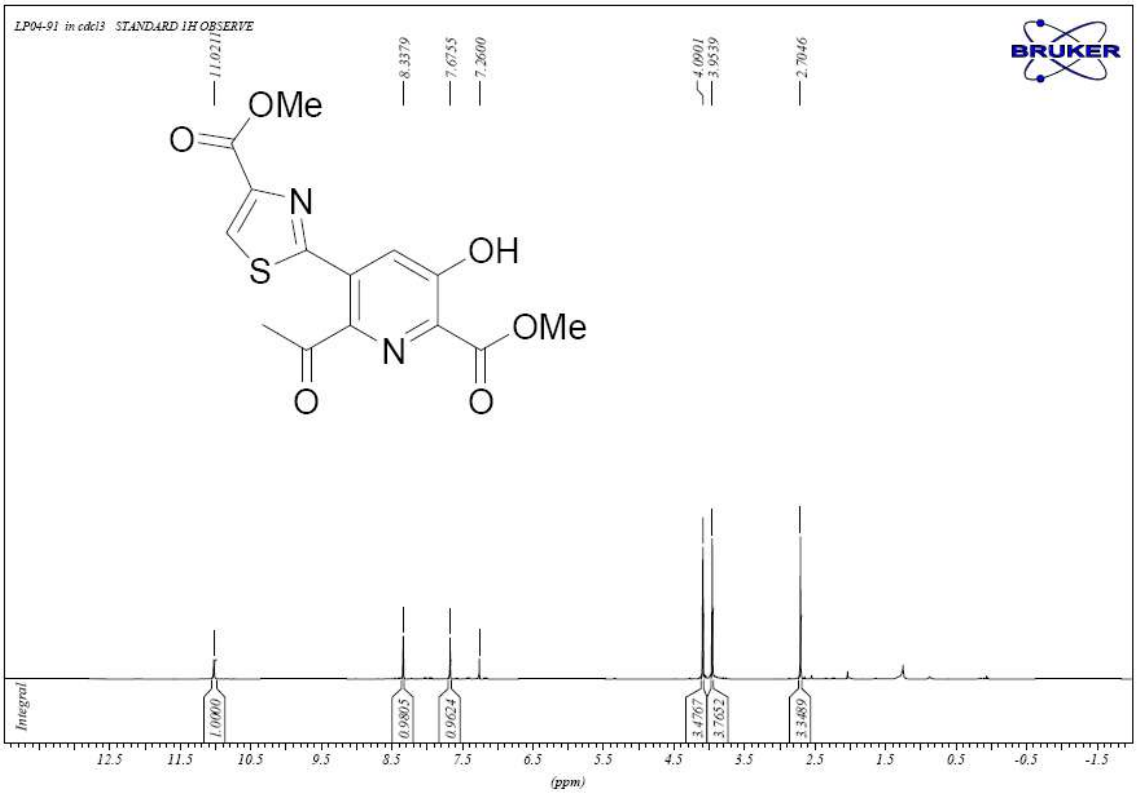

LP07-44A in CDCl3 STANDARD 1H OBSERVE
11.1656
8.4278
8.2320
7.2600
4.5026
4.4846
4.4670
4.4489
4.1155
1.4636
1.4455
1.4279
OEt
O
N
S
NC
OH
OMe
Integral
1.0000
1.0296
0.9589
2.2590
3.4651
3.4165
12.5
11.5
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
-1.5
(ppm)

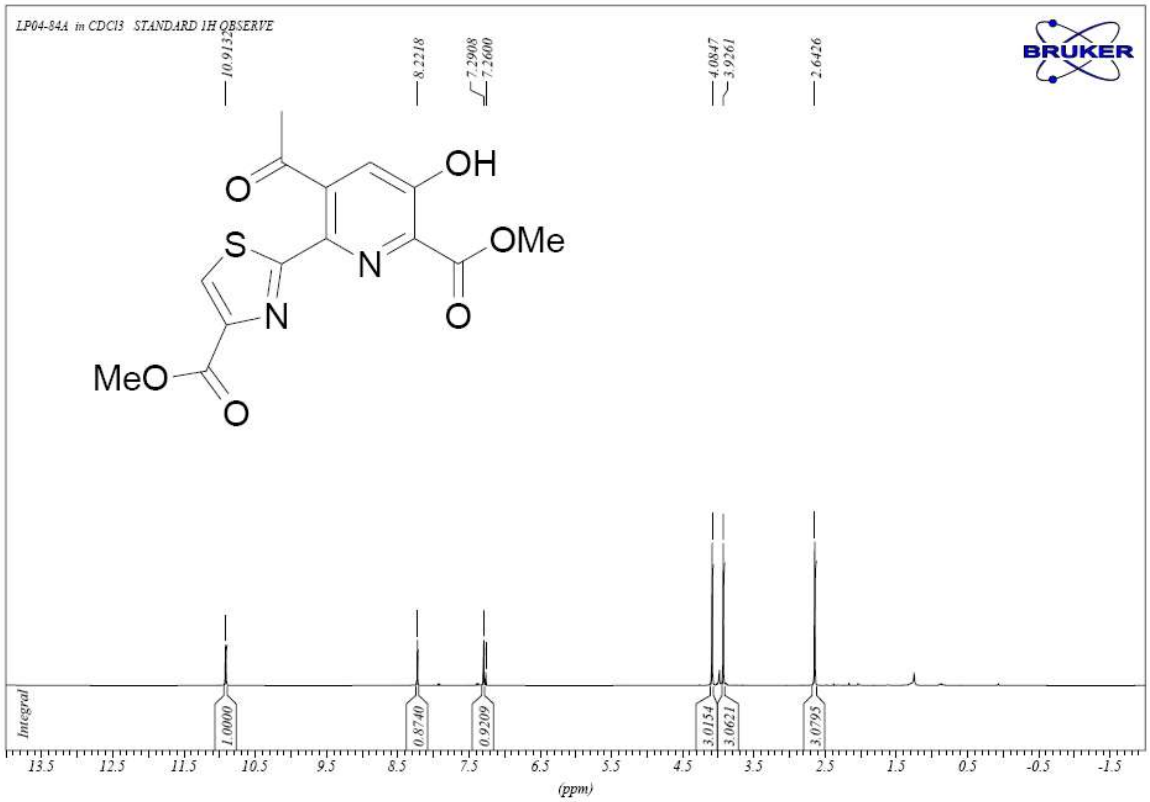

LP07-44A in CDCl3 □STANDARD 1H OBSERVE□□
168.1998
160.7337
159.9894
159.3825
148.8514
137.6904
132.0145
130.2091
126.4303
121.4414
115.9068
77.3168
77.0000
76.6832
61.9648
53.8957
14.3057
OEt
OH
OMe
NC
220
200
180
160
140
120
100
80
60
40
20
0
(ppm)

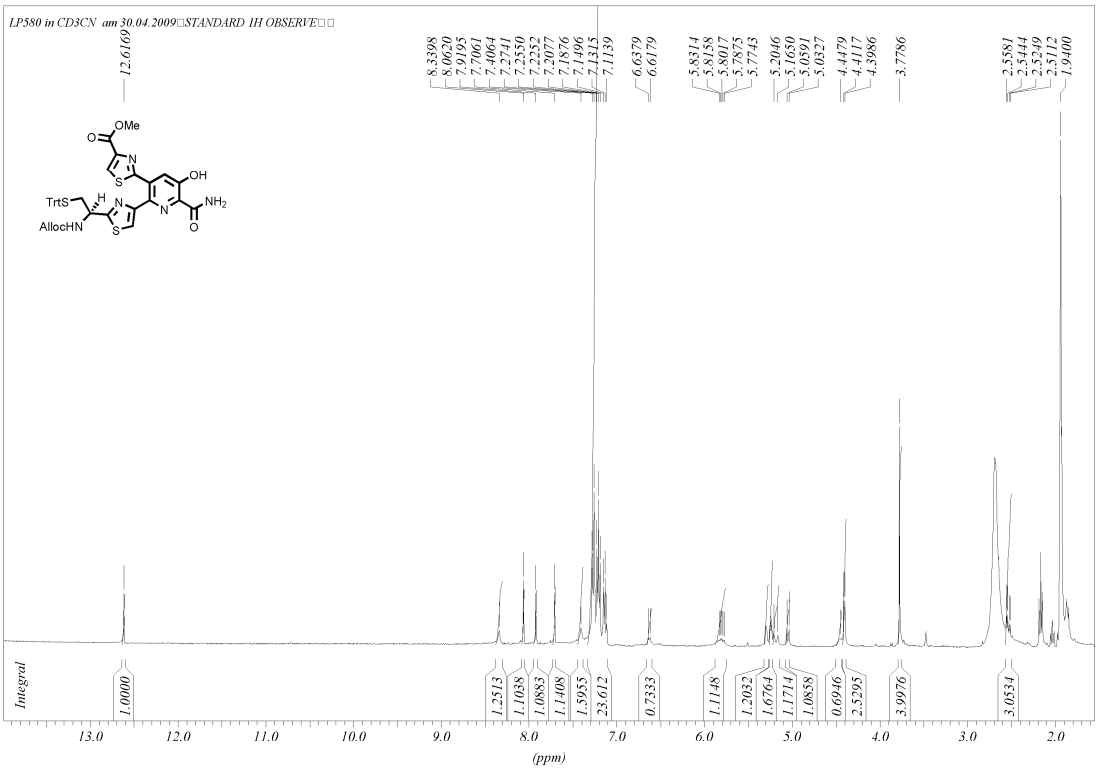

LP299B
162.2648
161.4102
161.1355
160.1740
157.5567
147.2172
146.1718
128.5450
127.4920
126.5839
124.1345
117.7782
115.8171
77.2518
77.0000
76.7482
61.5098
61.3572
52.0173
14.3448
14.2990
COOEt
EtOOC
OMe
220
200
180
160
140
120
100
80
60
40
20
0
(ppm)

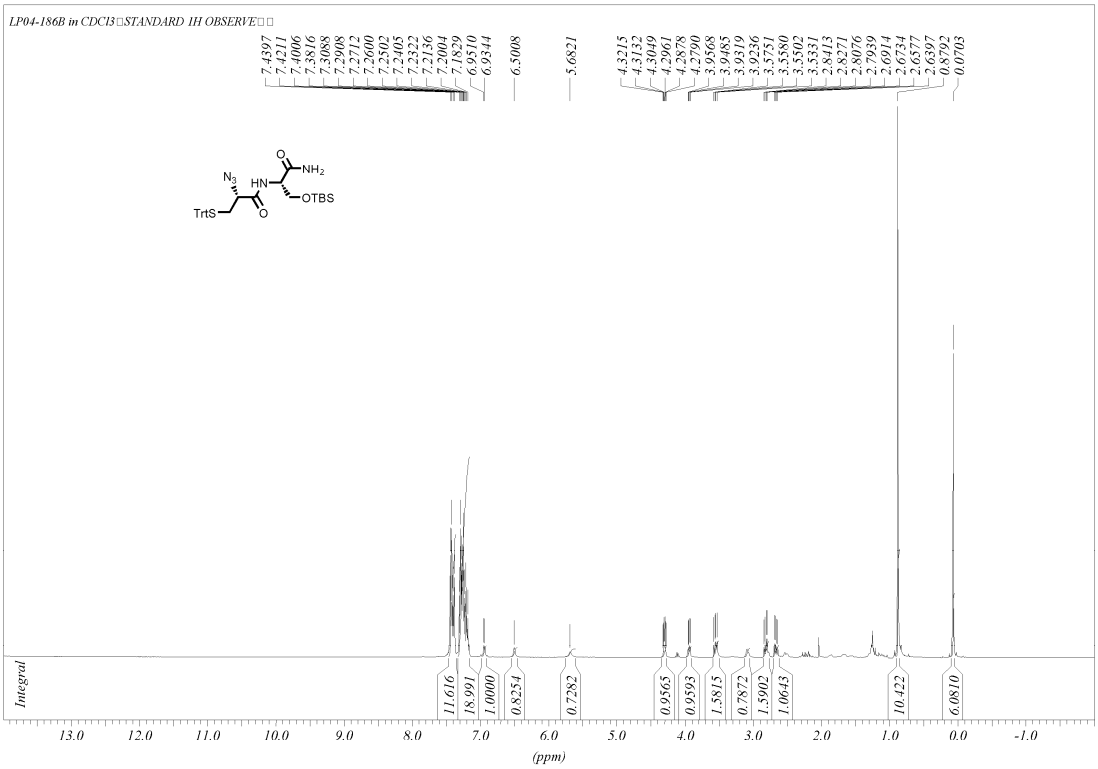

LP299B
10.7372
8.1698
8.1269
7.2600
7.2286
4.4453
4.4404
4.4309
4.4259
3.9139
1.4552
1.4412
1.4273
1.4133
COOEt
EtOOC
OMe
Integral
1.0000
1.0041
0.9517
1.0379
4.6878
3.0145
6.6965
(ppm)

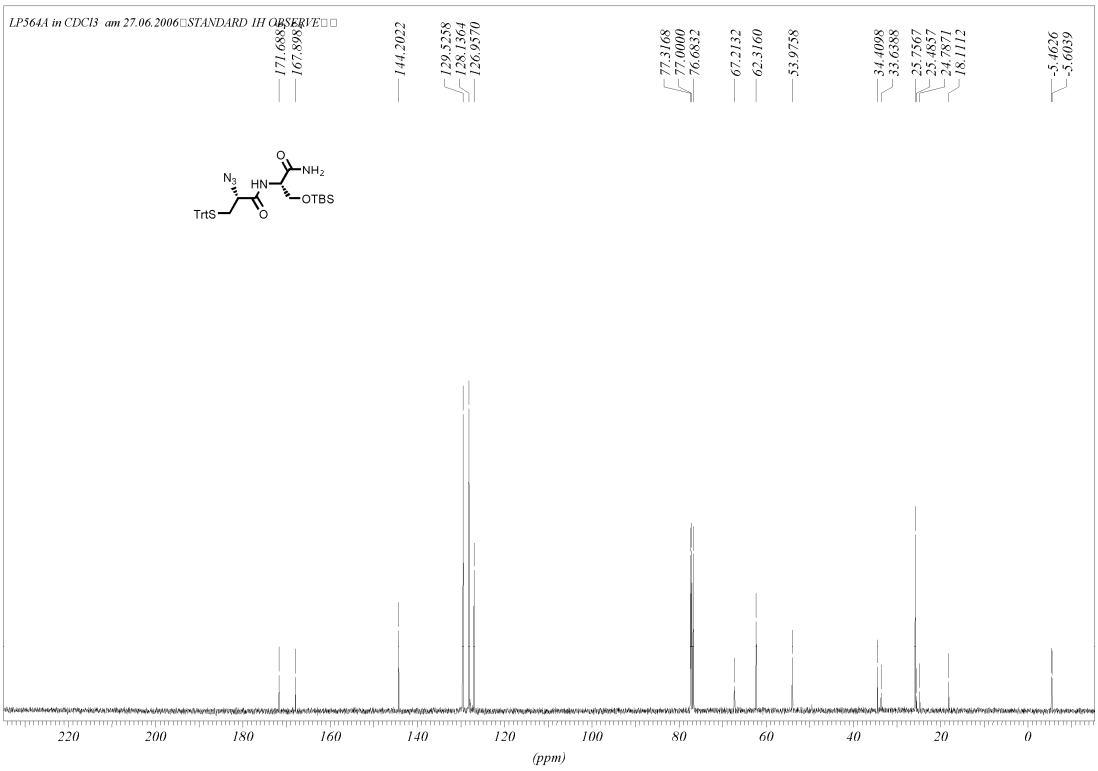

lp220□STANDARD 1H OBSERVE□□
8.3160
7.2600
3.9388
2.4356
OMe
Integral
1.0000
3.6079
3.4042
(ppm)

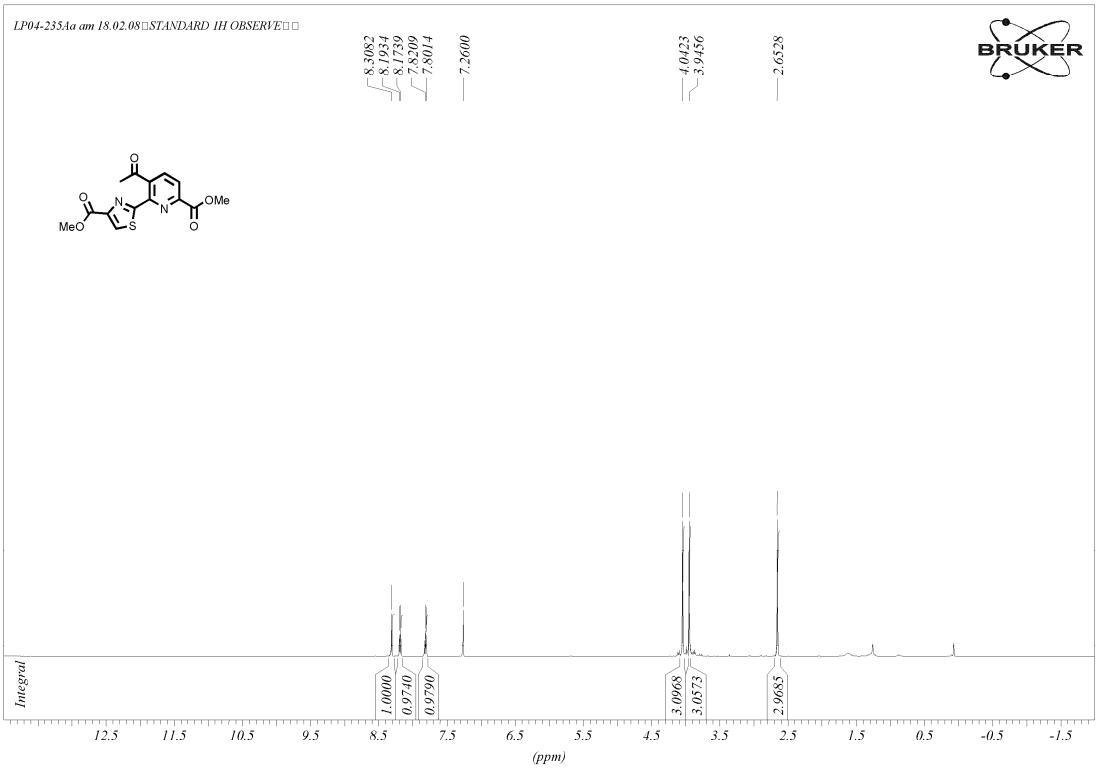

LP04-91 in cdcl3 STANDARD 1H OBSERVE
11.0211
8.3379
7.6755
7.2600
4.0901
3.9539
2.7046
OMe
O
N
S
OH
OMe
N
O
O
Integral
1.0000
0.9805
0.9624
3.4767
3.7652
3.3489
12.5
11.5
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
-1.5
(ppm)

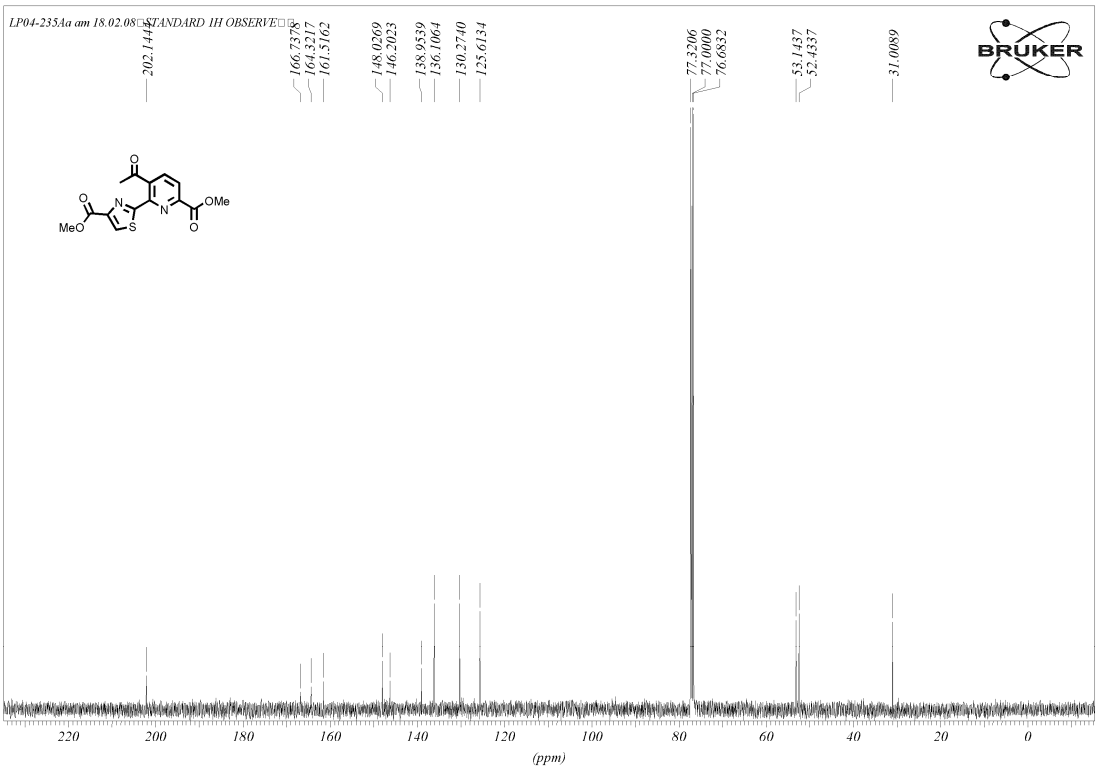

LP04-84A in CDCl3 STANDARD 1H OBSERVE
10.9132
8.2218
7.2908
7.2600
4.0847
3.9261
2.6426
O
OH
S
N
OMe
N
O
MeO
O
Integral
1.0000
0.8740
0.9209
3.0154
3.0621
3.0795
13.5
12.5
11.5
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
-1.5
(ppm)

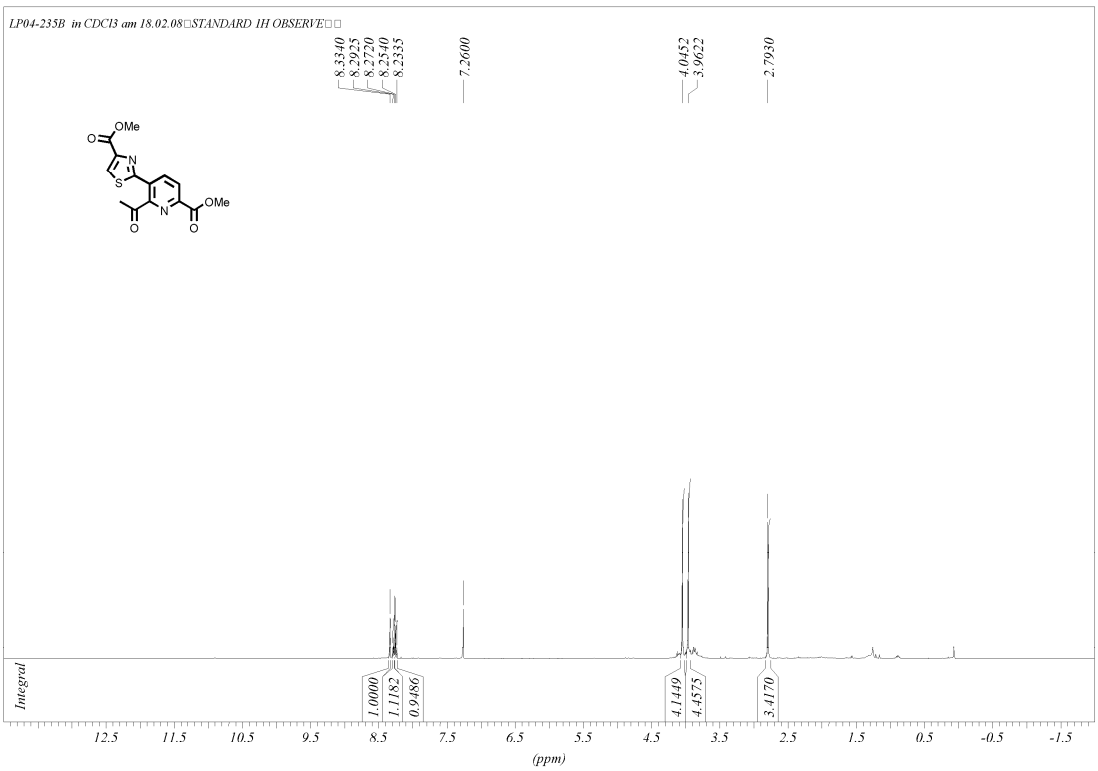

LP580 in CD3CN am 30.04.2009□STANDARD 1H OBSERVE□□
12.6169
8.3398
8.0620
7.9195
7.7061
7.4064
7.2741
7.2550
7.2252
7.2077
7.1876
7.1496
7.1345
7.1139
6.6379
6.6179
5.8314
5.8158
5.8017
5.7875
5.7743
5.2046
5.1650
5.0591
5.0327
4.4479
4.4117
4.3986
3.7786
2.5581
2.5444
2.5249
2.5112
1.9400
OMe
OH
NH2
TrtS
AllocHN
Integral
1.0000
1.2513
1.1038
1.0883
1.1408
1.5955
23.612
0.7333
1.1148
1.2032
1.6764
1.1714
1.0858
0.6946
2.5295
3.9976
3.0534
(ppm)

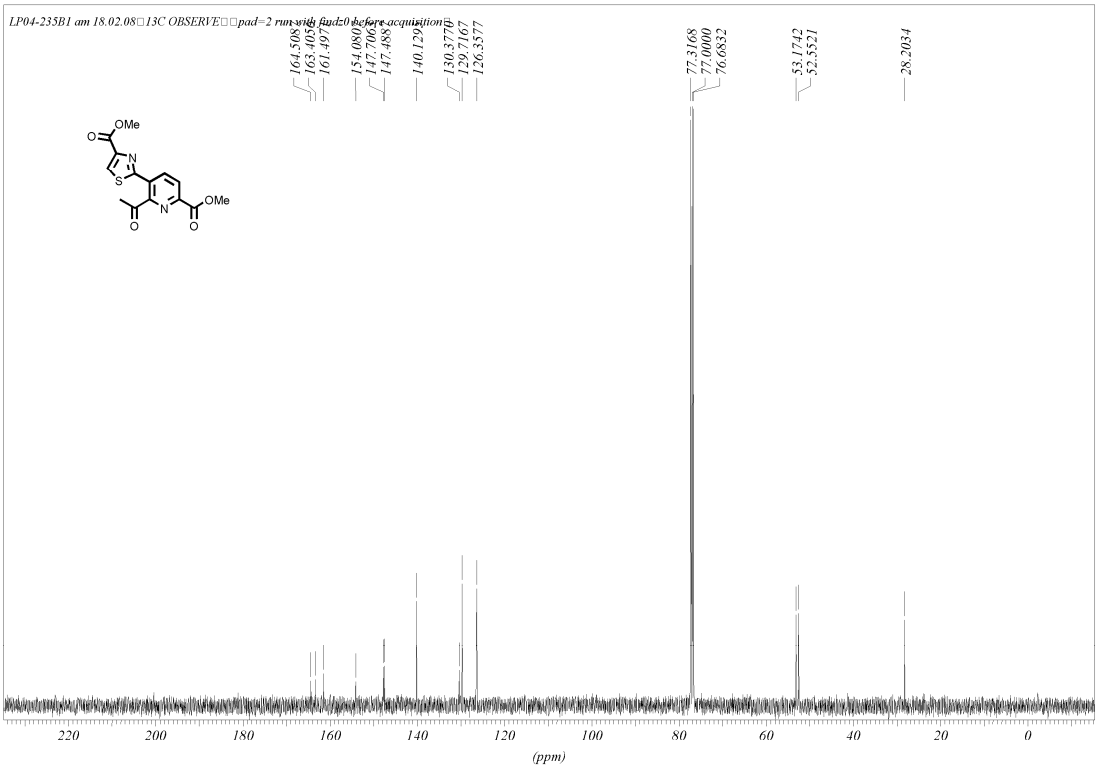

LP04-186B in CDCl3□STANDARD 1H OBSERVE□□
7.4397
7.4211
7.4006
7.3816
7.3088
7.2908
7.2712
7.2600
7.2502
7.2405
7.2322
7.2136
7.2004
7.1829
6.9510
6.9344
6.5008
5.6821
4.3215
4.3132
4.3049
4.2961
4.2878
4.2790
3.9568
3.9485
3.9319
3.9236
3.5751
3.5580
3.5502
3.5331
2.8413
2.8271
2.8076
2.7939
2.6914
2.6734
2.6577
2.6397
0.8792
0.0703
NH2
N3
HN
OTBS
TrtS
Integral
11.616
18.991
1.0000
0.8254
0.7282
0.9565
0.9593
1.5815
0.7872
1.5902
1.0643
10.422
6.0810
(ppm)

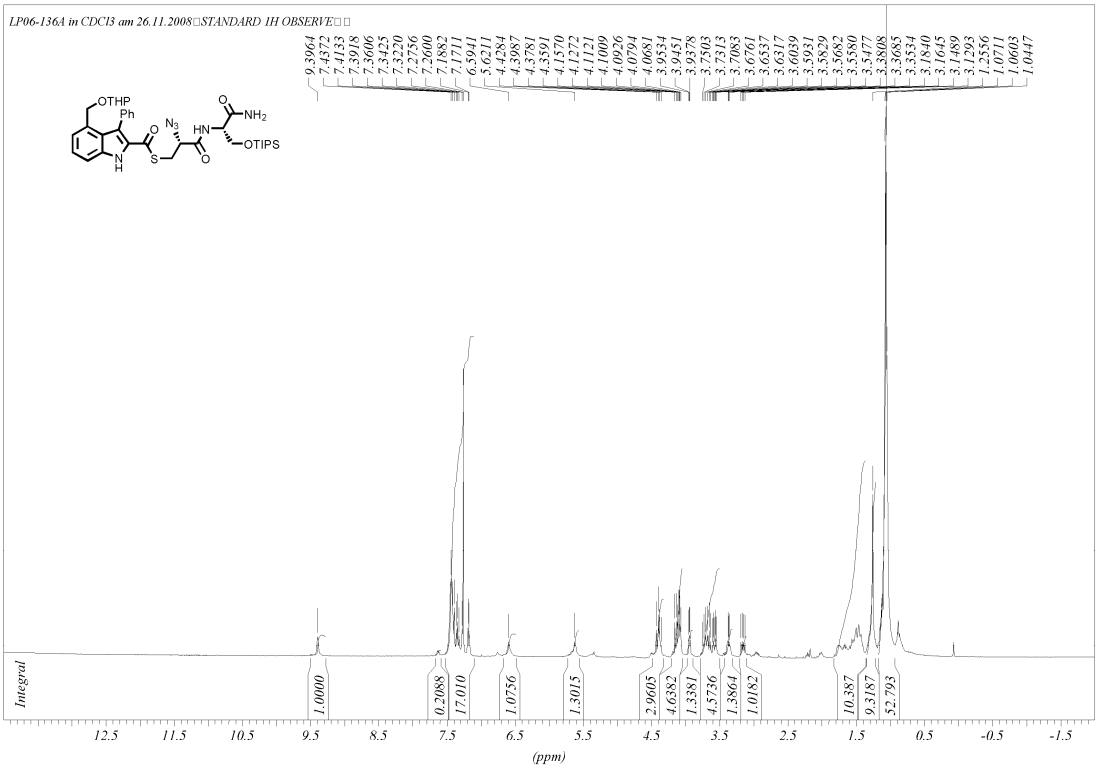

LP564A in CDCl3 am 27.06.2006 STANDARD 1H OBSERVE
171.6885
167.8982
144.2022
129.5258
128.1364
126.9570
77.3168
77.0000
76.6832
67.2132
62.3160
53.9758
34.4098
33.6388
25.7567
25.4857
24.7871
18.1112
-5.4626
-5.6039
O
NH2
N3
HN
OTBS
TrtS
O
220
200
180
160
140
120
100
80
60
40
20
0
(ppm)

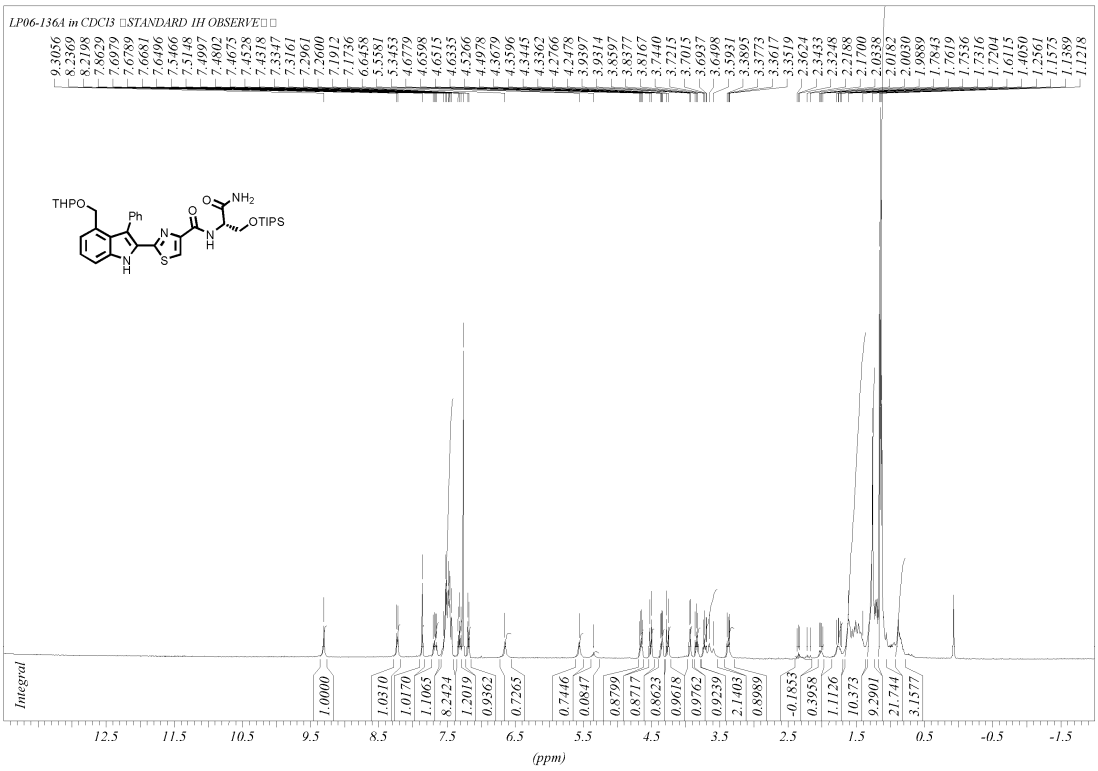

LP04-235Aa am 18.02.08 STANDARD 1H OBSERVE
8.3082
8.1934
8.1739
7.8209
7.8014
7.2600
4.0423
3.9456
2.6528
BRUKER
O
O
N
S
N
OMe
MeO
O
Integral
1.0000
0.9740
0.9790
3.0968
3.0573
2.9685
12.5
11.5
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
-1.5
(ppm)

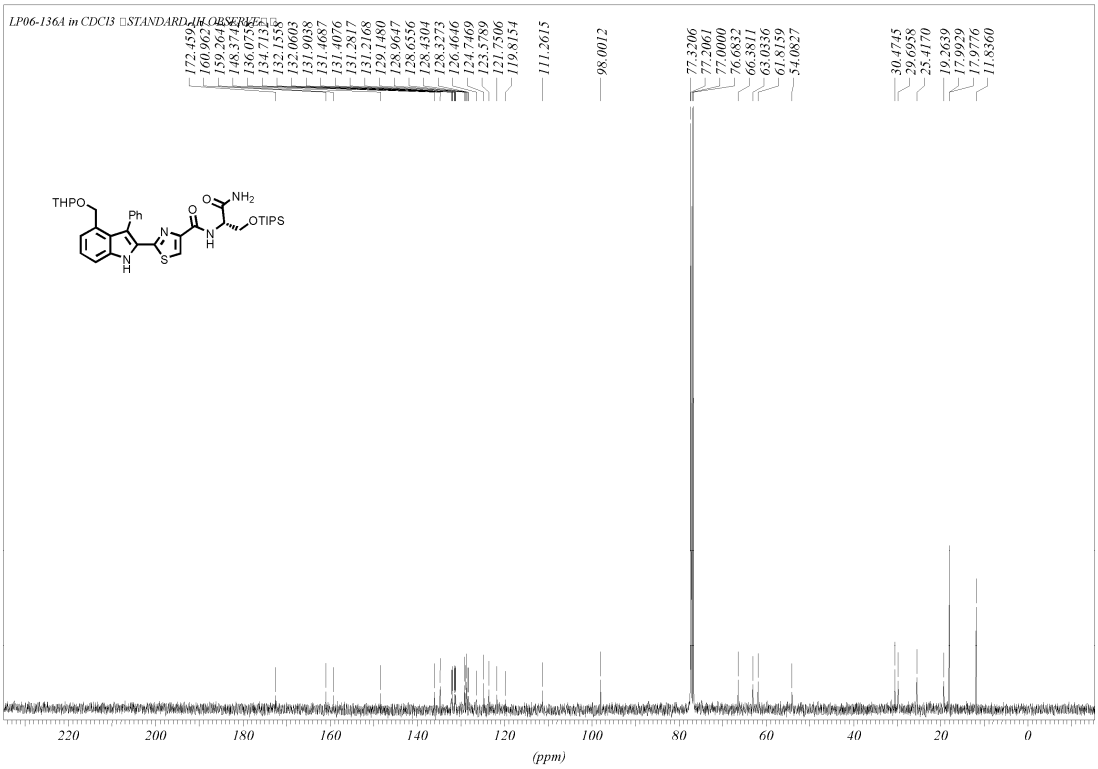

LP04-235Aa am 18.02.08□STANDARD 1H OBSERVE□□
202.1444
166.7376
164.3217
161.5162
148.0269
146.2023
138.9539
136.1064
130.2740
125.6134
77.3206
77.0000
76.6832
53.1437
52.4337
31.0089
BRUKER
(ppm)

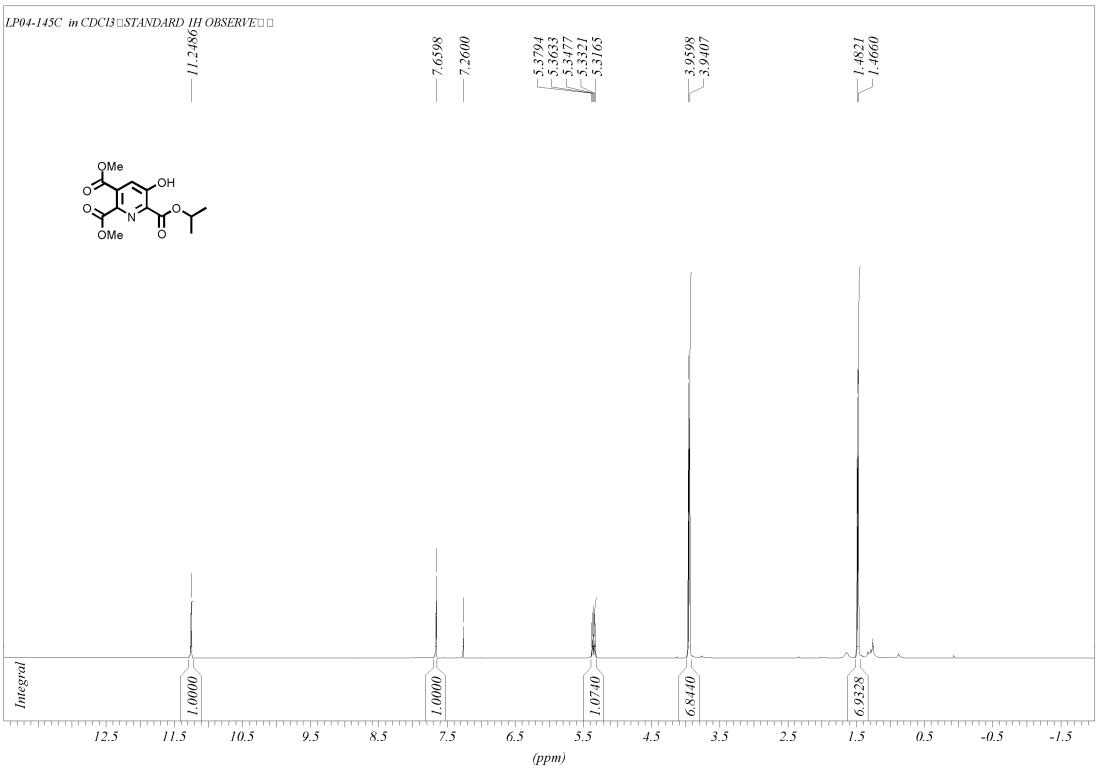

LP04-235B in CDCl3 am 18.02.08□STANDARD 1H OBSERVE□□
8.3340
8.2925
8.2720
8.2540
8.2335
7.2600
4.0452
3.9622
2.7930
Integral
1.0000
1.1182
0.9486
4.1449
4.4575
3.4170
(ppm)

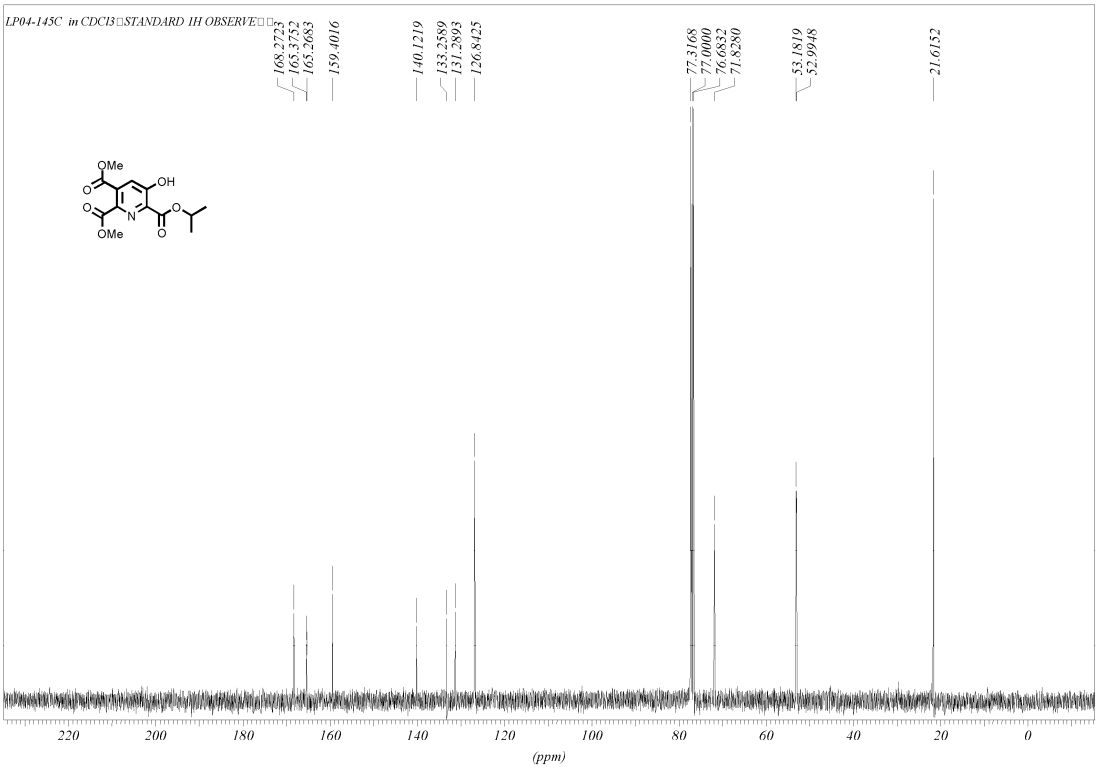

LP04-235B1 am 18.02.08□13C OBSERVE□□pad=2 run with fudr=0 before acquisition
164.508
163.405
161.497
154.080
147.706
147.488
140.129
130.377
129.716
126.357
77.3168
77.0000
76.6832
53.1742
52.5521
28.2034
OMe
OMe
(ppm)

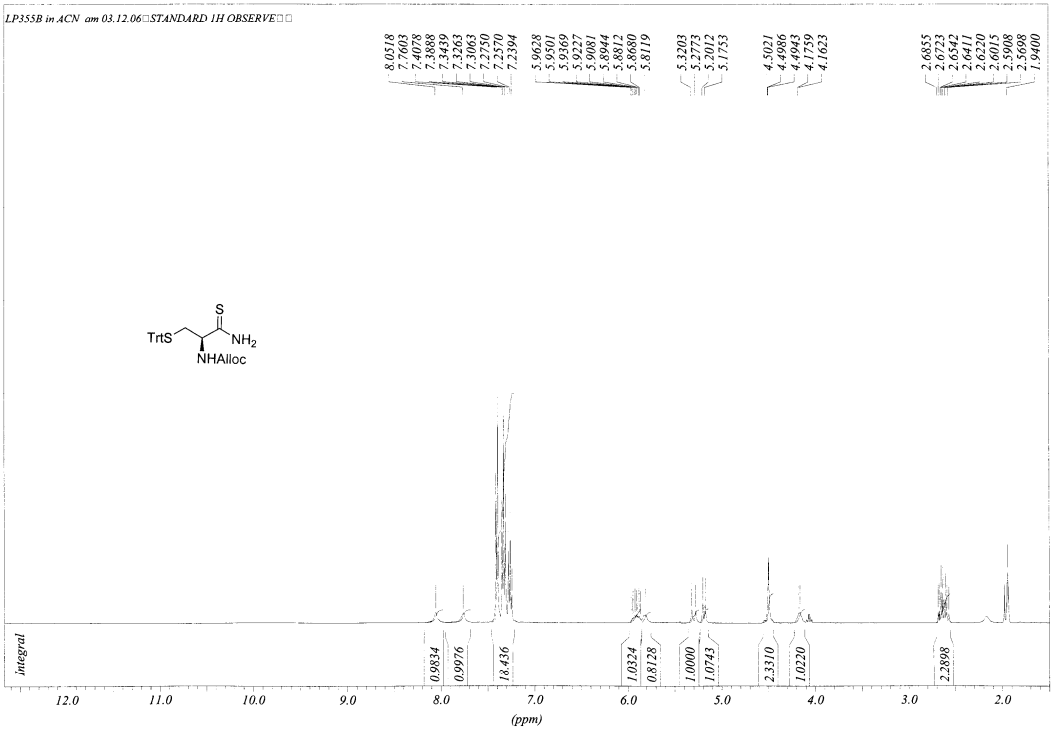

LP06-136A in CDCl3 am 26.11.2008□STANDARD 1H OBSERVE□□
9.3964
7.4372
7.4133
7.3918
7.3606
7.3425
7.3220
7.2756
7.2600
7.1882
7.1711
6.5941
5.6211
4.4284
4.3987
4.3781
4.3591
4.1570
4.1272
4.1121
4.1000
4.0926
4.0794
4.0681
3.9534
3.9451
3.9378
3.7503
3.7313
3.7083
3.6761
3.6537
3.6317
3.6039
3.5931
3.5829
3.5682
3.5580
3.5477
3.3808
3.3685
3.3534
3.1840
3.1645
3.1489
3.1293
1.2556
1.0711
1.0603
1.0447
OTHP
Ph
N3
O
NH2
HN
OTIPS
Integral
1.0000
0.2088
17.010
1.0756
1.3015
2.9605
4.6382
1.3381
4.5736
1.3864
1.0182
10.387
9.3187
52.793
(ppm)

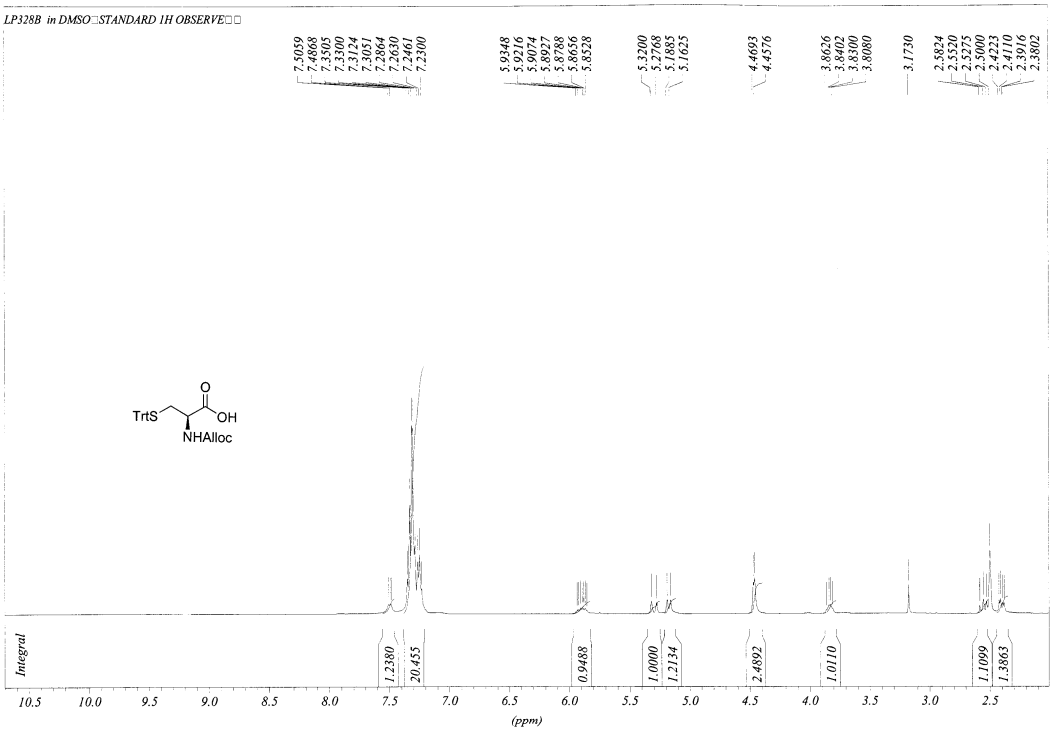

LP06-136A in CDCl3 □STANDARD 1H OBSERVE□□
THPO
Ph
N
O
NH2
N
H
S
OTIPS
Integral
(ppm)

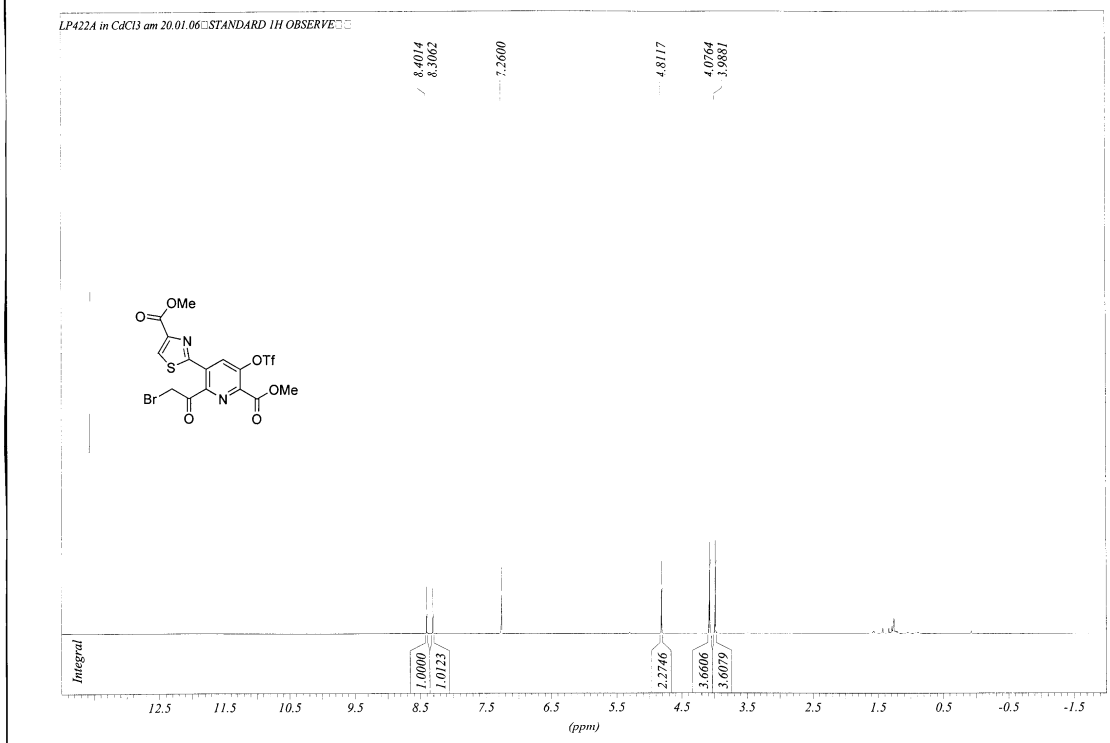

LP06-136A in CDCl3 □STANDARD 1H OBSERVE□□
THPO
Ph
N
O
NH2
N
H
S
OTIPS
(ppm)

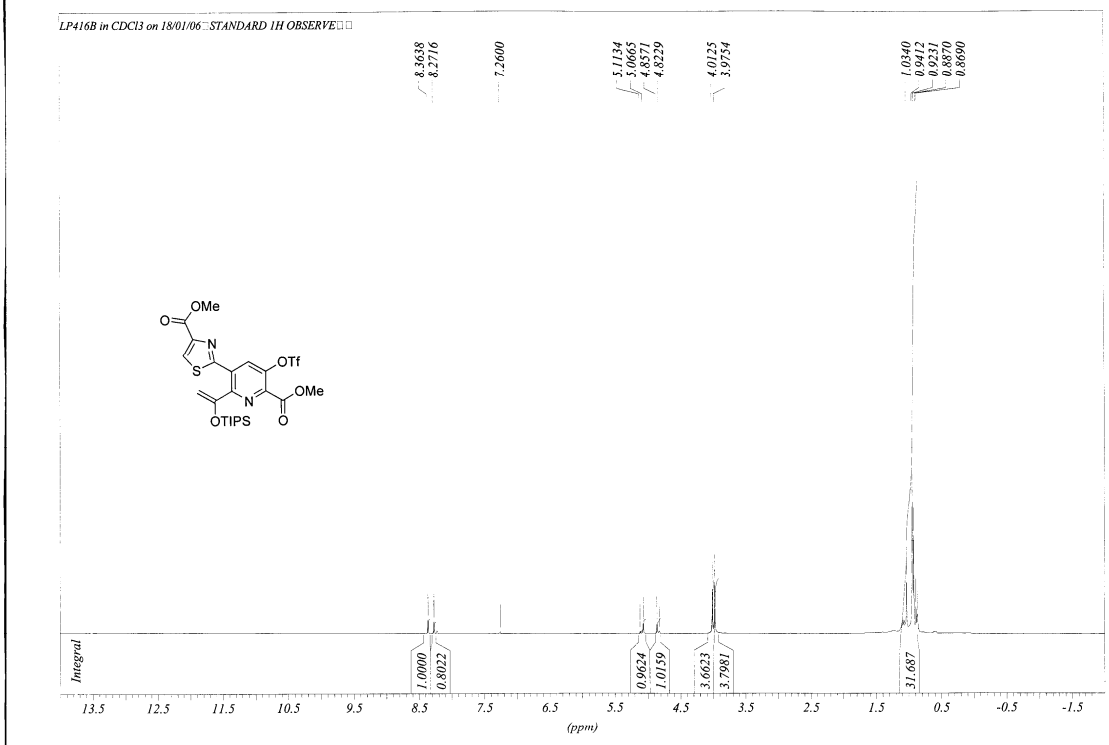

LP04-145C in CDCl3 STANDARD 1H OBSERVE
11.2486
7.6598
7.2600
5.3794
5.3633
5.3477
5.3321
5.3165
3.9598
3.9407
1.4821
1.4660
OMe
OH
O
N
OMe
Integral
1.0000
1.0000
1.0740
6.8440
6.9328
12.5
11.5
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
-1.5
(ppm)

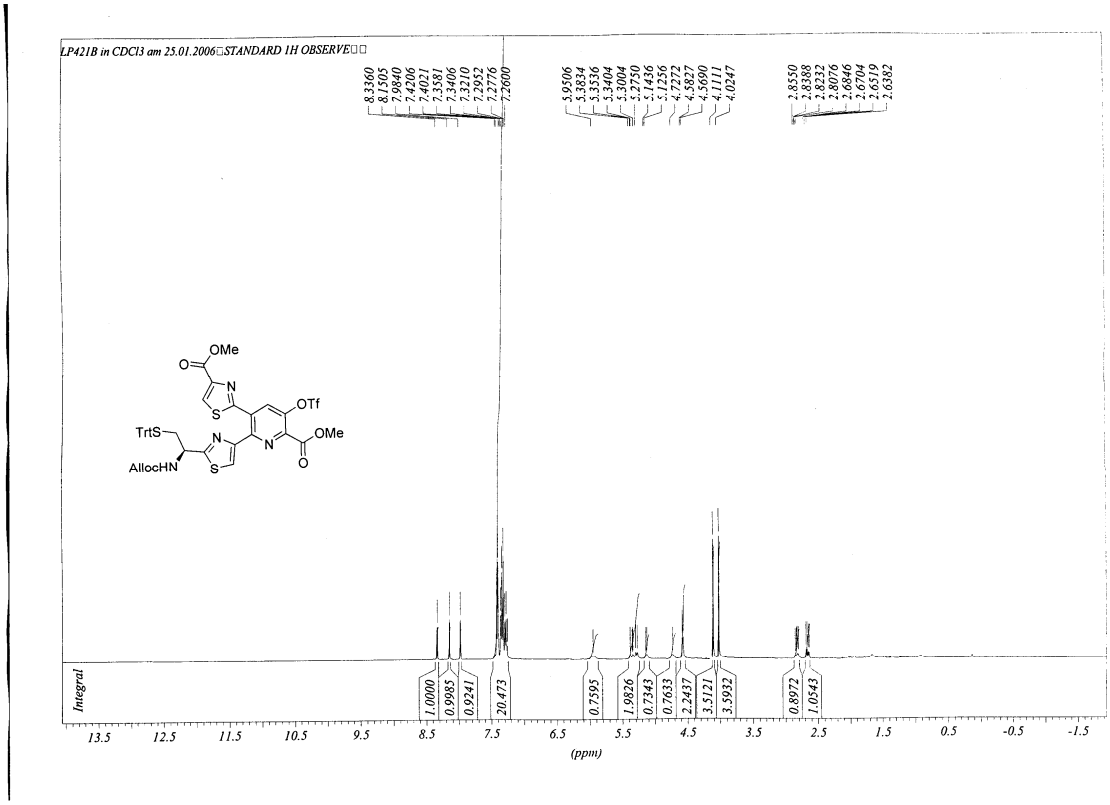

LP04-145C in CDCl3 STANDARD 1H OBSERVE
168.2723
165.3752
165.2683
159.4016
140.1219
133.2589
131.2893
126.8425
77.3168
77.0000
76.6832
71.8280
53.1819
52.9948
21.6152
OMe
OH
O
N
OMe
220
200
180
160
140
120
100
80
60
40
20
0
(ppm)

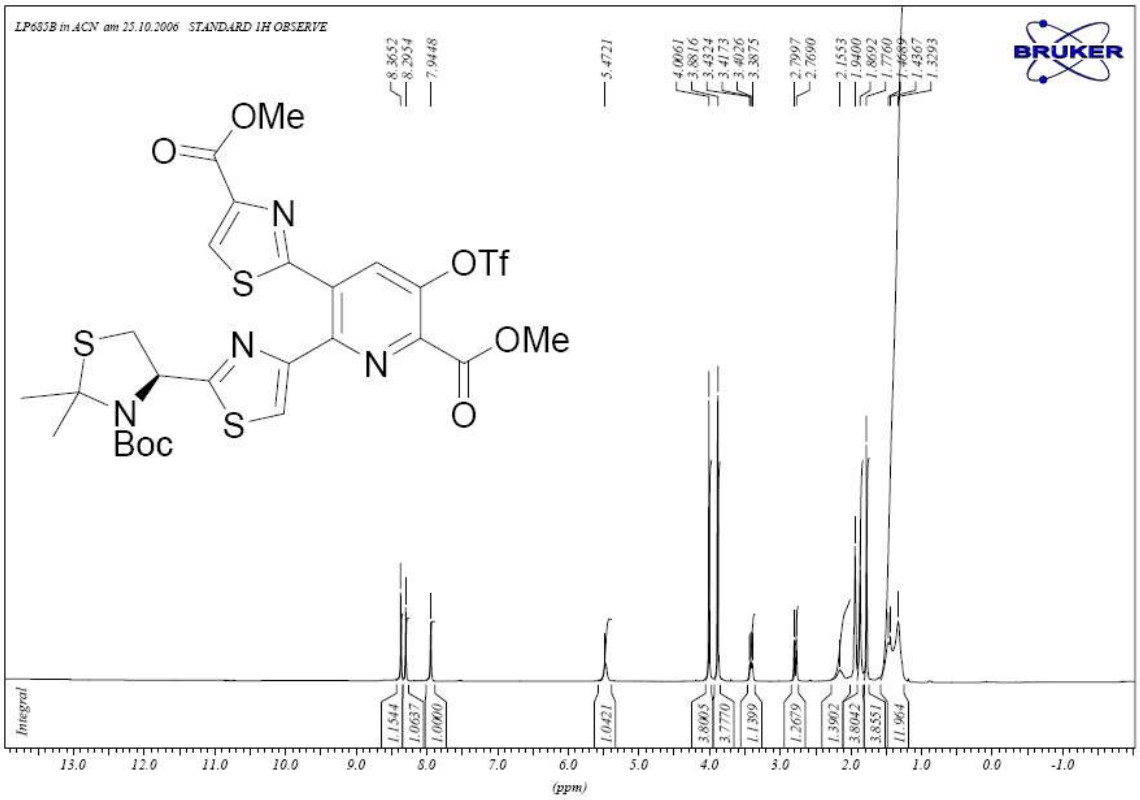

LP355B in ACN am 03.12.06□STANDARD 1H OBSERVE□□
TrtS
S
NH2
NHAlloc
integral
(ppm)

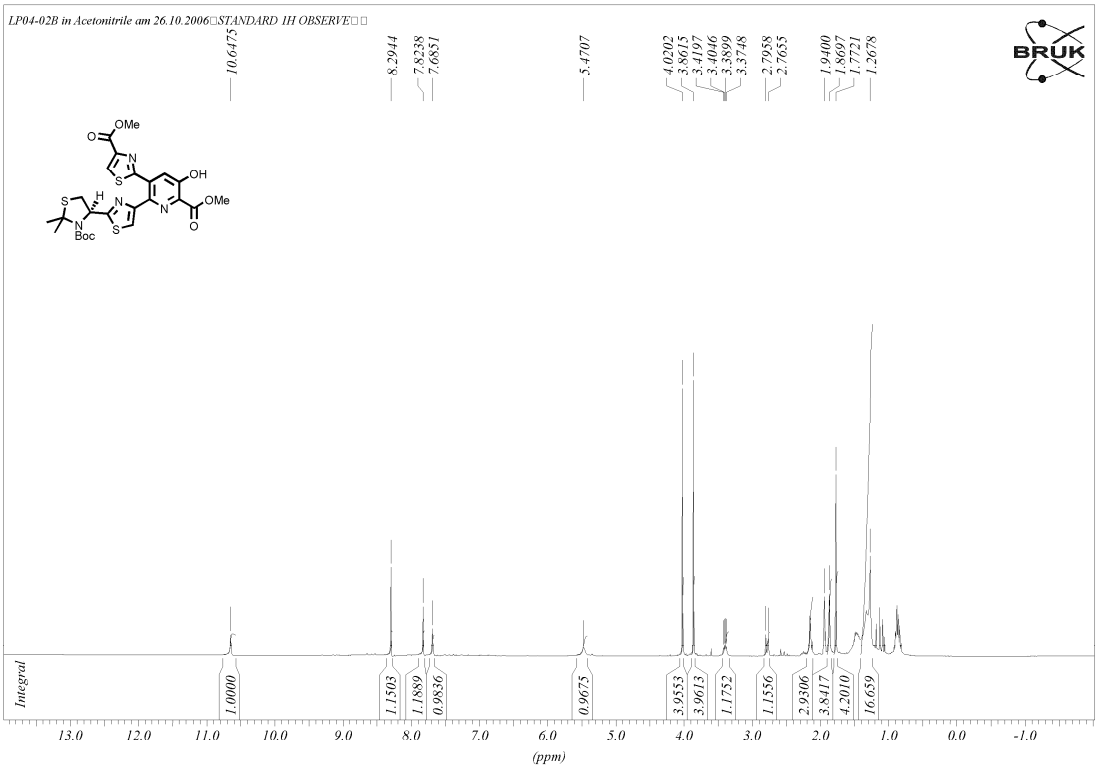

LP328B in DMSO□STANDARD 1H OBSERVE□□
TrtS
O
OH
NHAlloc
Integral
(ppm)

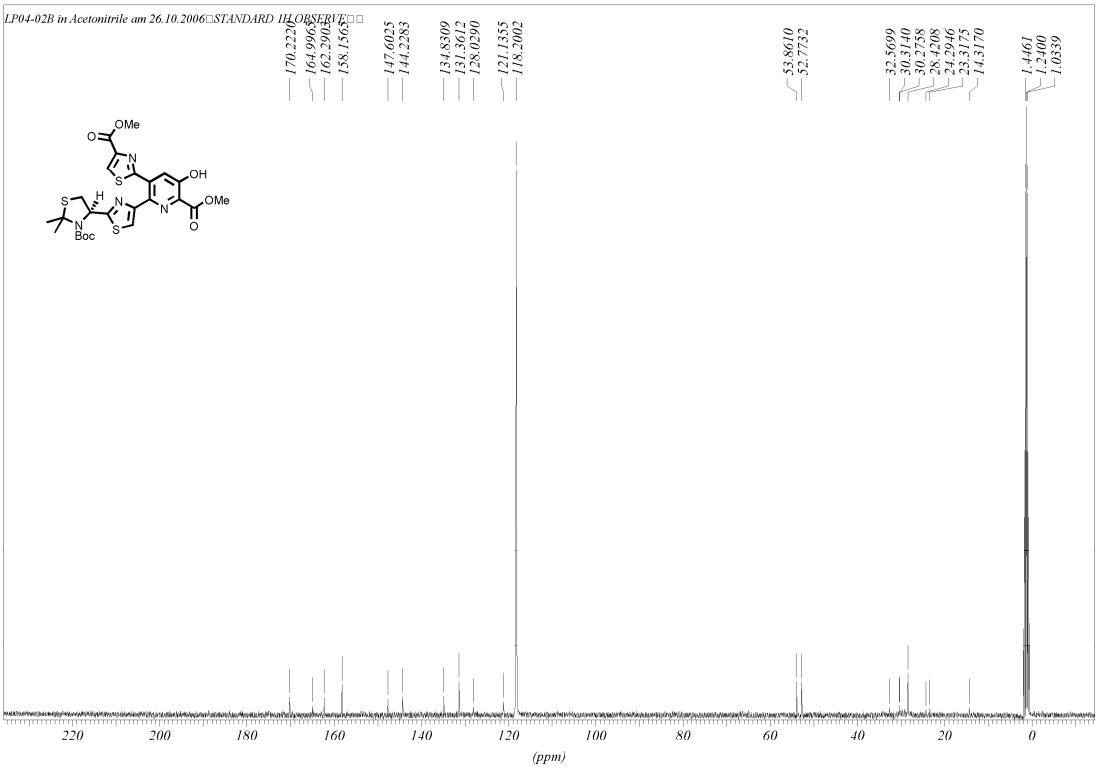

LP422A in CdCl3 am 20.01.06□STANDARD 1H OBSERVE□□
8.4014
8.3062
7.2600
4.8117
4.0764
3.9881
OMe
O
N
S
OTf
Br
N
OMe
O
O
Integral
1.0000
1.0123
2.2746
3.6606
3.6079
12.5
11.5
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
-1.5
(ppm)

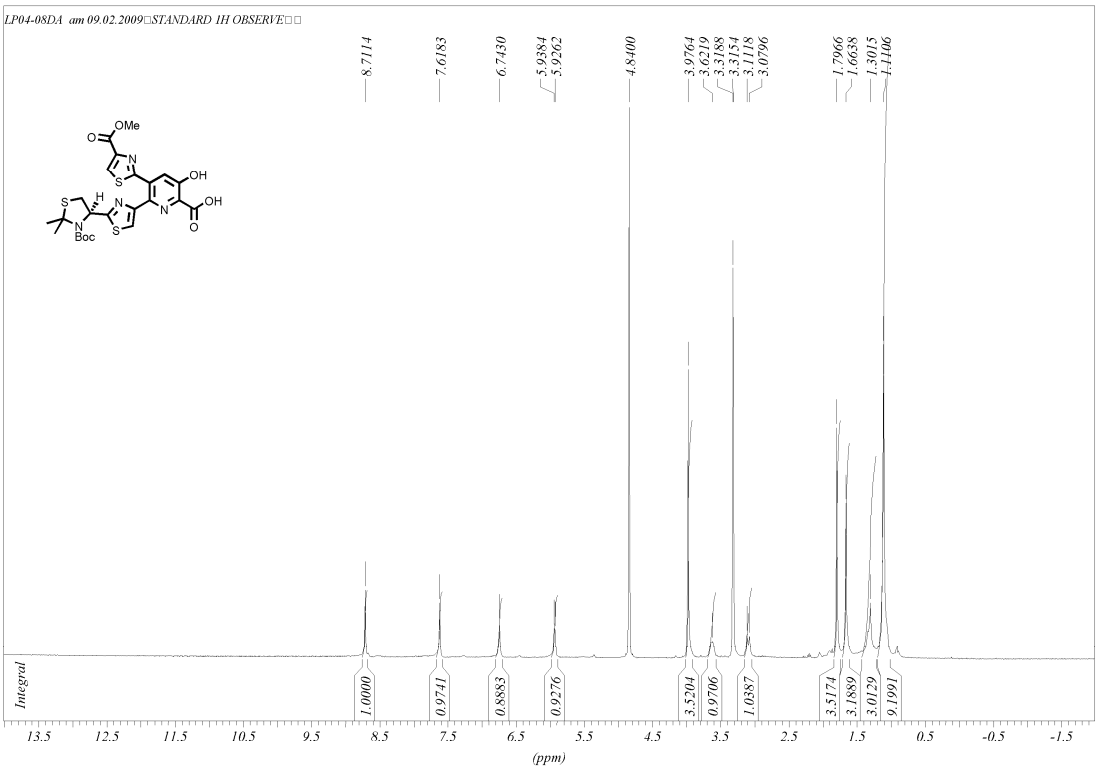

LP416B in CDCl3 on 18/01/06□STANDARD 1H OBSERVE□□
8.3638
8.2716
7.2600
5.1134
5.0665
4.8577
4.8229
4.0125
3.9754
1.0340
0.9412
0.9231
0.8870
0.8690
OMe
O
N
S
OTf
OMe
N
OTIPS
O
Integral
1.0000
0.8022
0.9624
1.0159
3.6623
3.7981
31.687
13.5
12.5
11.5
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
-1.5
(ppm)

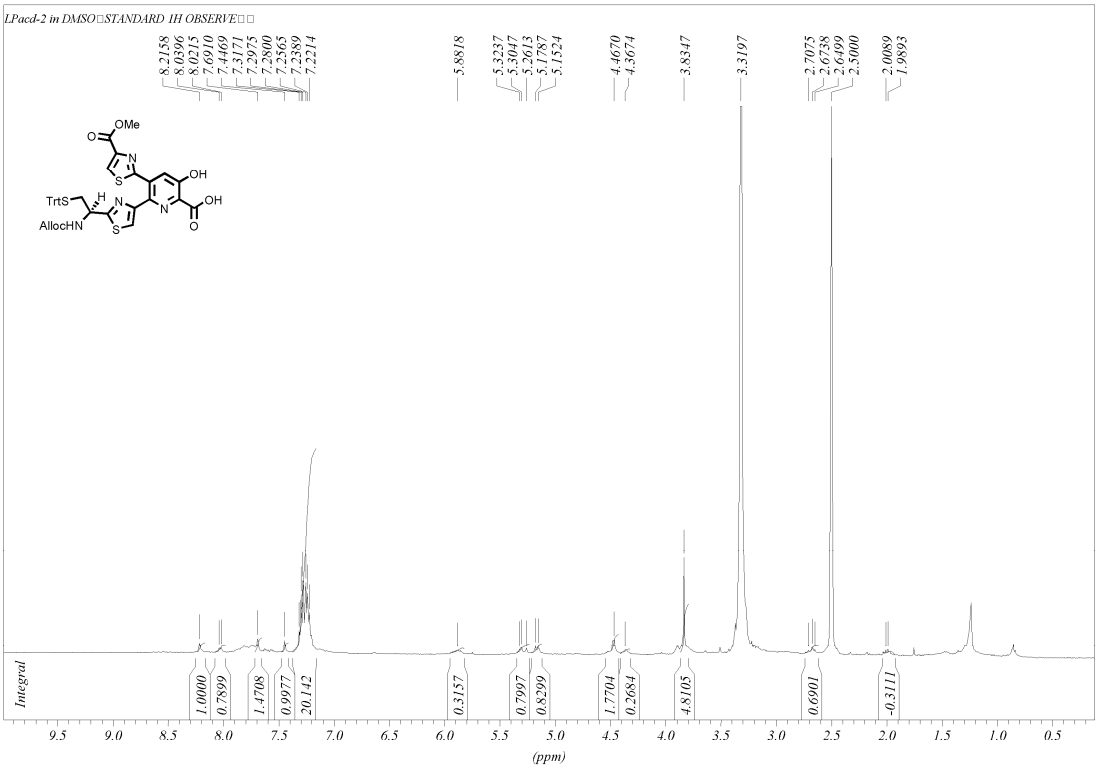

LP421B in CDCl3 am 25.01.2006 STANDARD 1H OBSERVE
OMe
OTf
TrtS
AllocHN
OMe
Integral
(ppm)

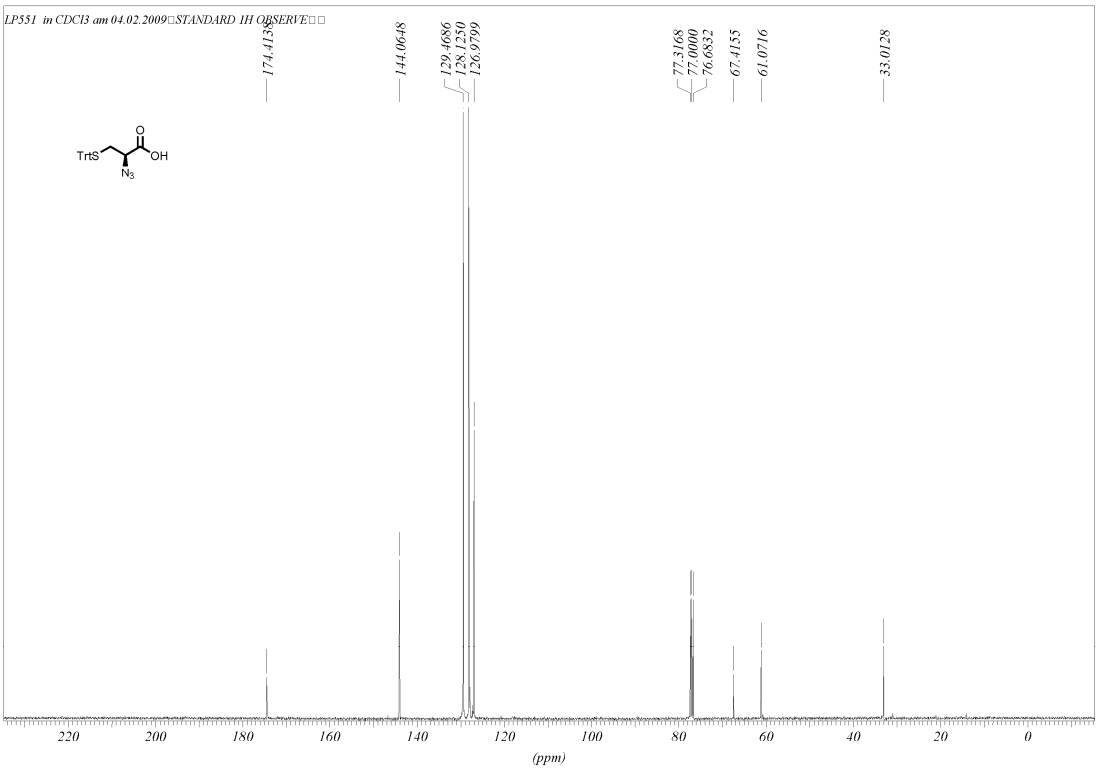

LP685B in ACN am 25.10.2006 STANDARD 1H OBSERVE
BRUKER
OMe
OTf
OMe
Boc
Integral
(ppm)

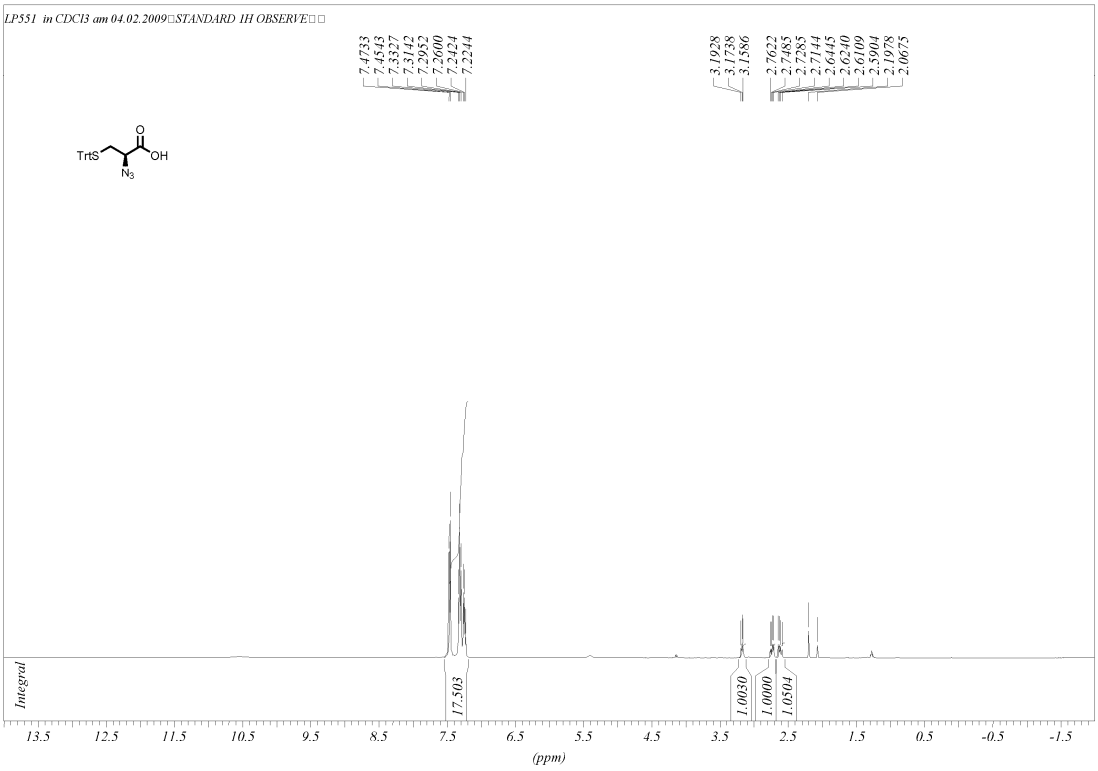

LP04-02B in Acetonitrile am 26.10.2006□STANDARD 1H OBSERVE□□
10.6475
8.2944
7.8238
7.6851
5.4707
4.0202
3.8615
3.4197
3.4046
3.3899
3.3748
2.7958
2.7655
1.9400
1.8697
1.7221
1.2678
BRUK
OMe
OH
OMe
Boc
Integral
1.0000
1.1503
1.1889
0.9836
0.9675
3.9553
3.9613
1.1752
1.1556
2.9306
3.8417
4.2010
16.659
13.0
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
-1.0
(ppm)

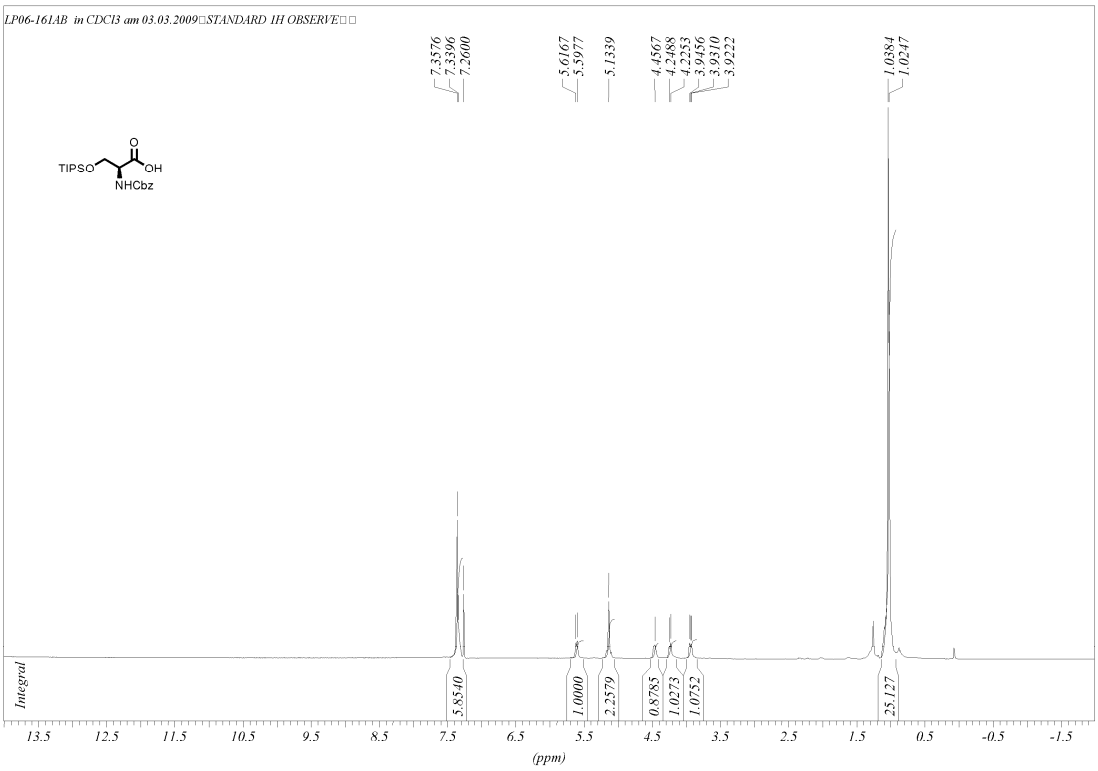

LP04-02B in Acetonitrile am 26.10.2006□STANDARD 1H OBSERVE□□
170.2220
164.9963
162.2902
158.1563
147.6025
144.2283
134.8309
131.3612
128.0290
121.1355
118.2002
53.8610
52.7732
32.5699
30.3140
30.2758
28.4208
24.2946
23.3175
14.3170
1.4461
1.2400
1.0339
OMe
OH
OMe
Boc
220
200
180
160
140
120
100
80
60
40
20
0
(ppm)

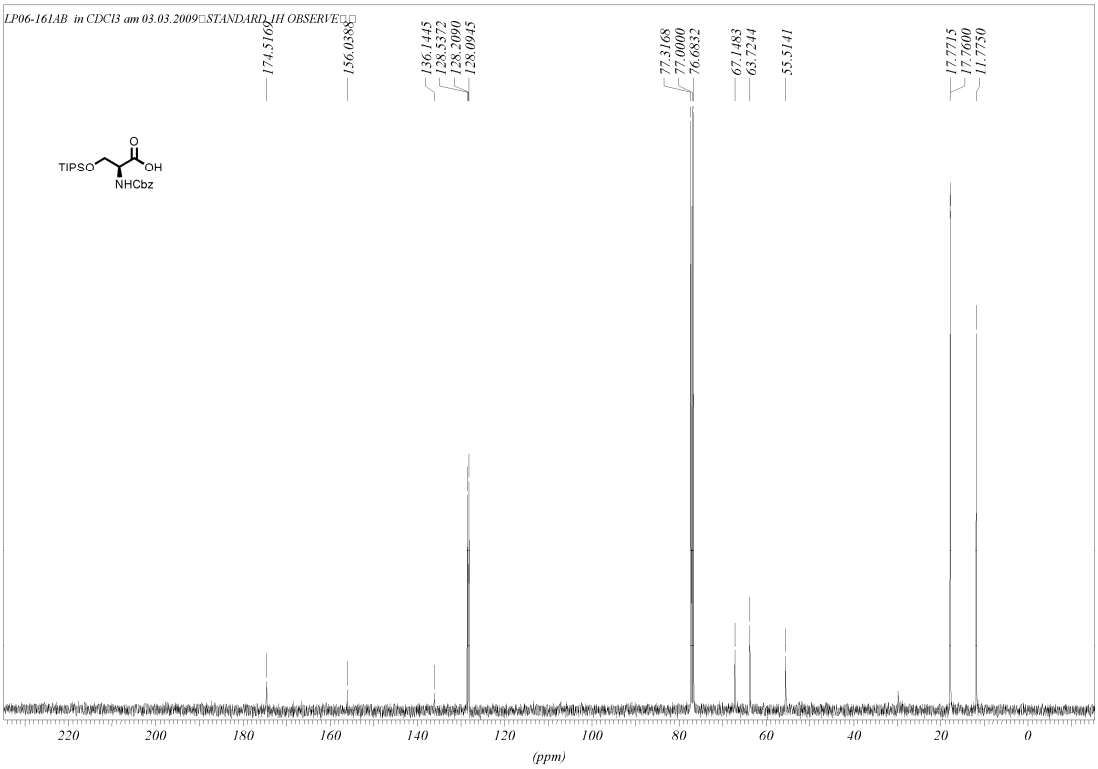

LP04-08DA am 09.02.2009□STANDARD 1H OBSERVE□□
8.7114
7.6183
6.7430
5.9384
5.9262
4.8400
3.9764
3.6219
3.3188
3.3154
3.1118
3.0796
1.7966
1.6638
1.3015
1.1106
OMe
OH
OH
Boc
Integral
1.0000
0.9741
0.8883
0.9276
3.5204
0.9706
1.0387
3.5174
3.1889
3.0129
9.1991
(ppm)

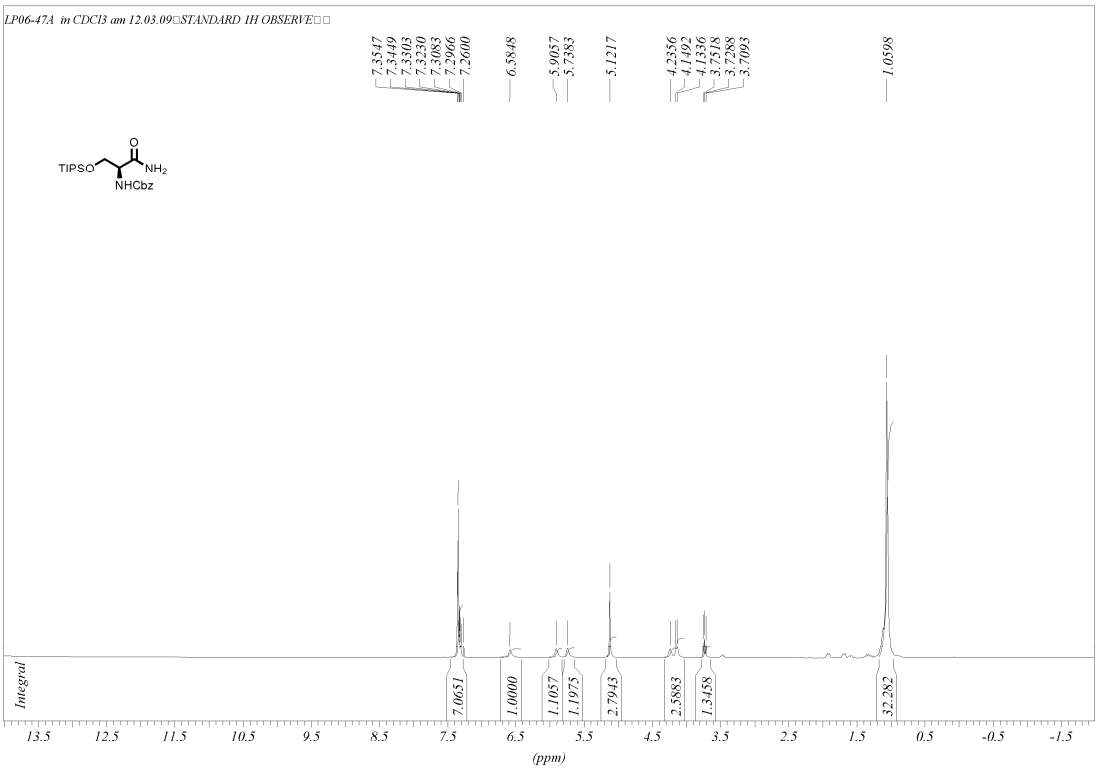

LPacd-2 in DMSO□STANDARD 1H OBSERVE□□
8.2158
8.0396
8.0215
7.6910
7.4469
7.3171
7.2975
7.2800
7.2565
7.2389
7.2214
5.8818
5.3237
5.3047
5.2613
5.1787
5.1524
4.4670
4.3674
3.8347
3.3197
2.7075
2.6738
2.6499
2.5000
2.0089
1.9893
OMe
OH
OH
TrtS
AllocHN
Integral
1.0000
0.7899
1.4708
0.9977
20.142
0.3157
0.7997
0.8299
1.7704
0.2684
4.8105
0.6901
-0.3111
(ppm)

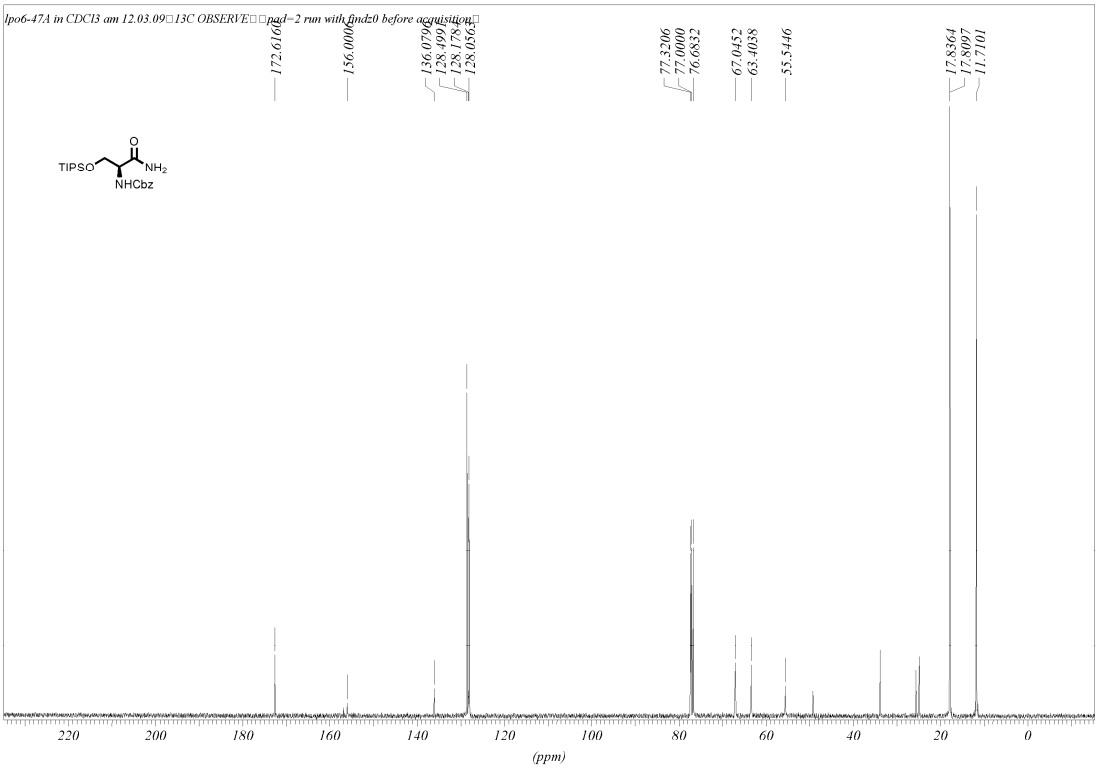

LP551 in CDCl3 am 04.02.2009□STANDARD 1H OBSERVE□□
174.4136
144.0648
129.4686
128.1250
126.9799
77.3168
77.0000
76.6832
67.4155
61.0716
33.0128
TrtS
O
OH
N3
220
200
180
160
140
120
100
80
60
40
20
0
(ppm)

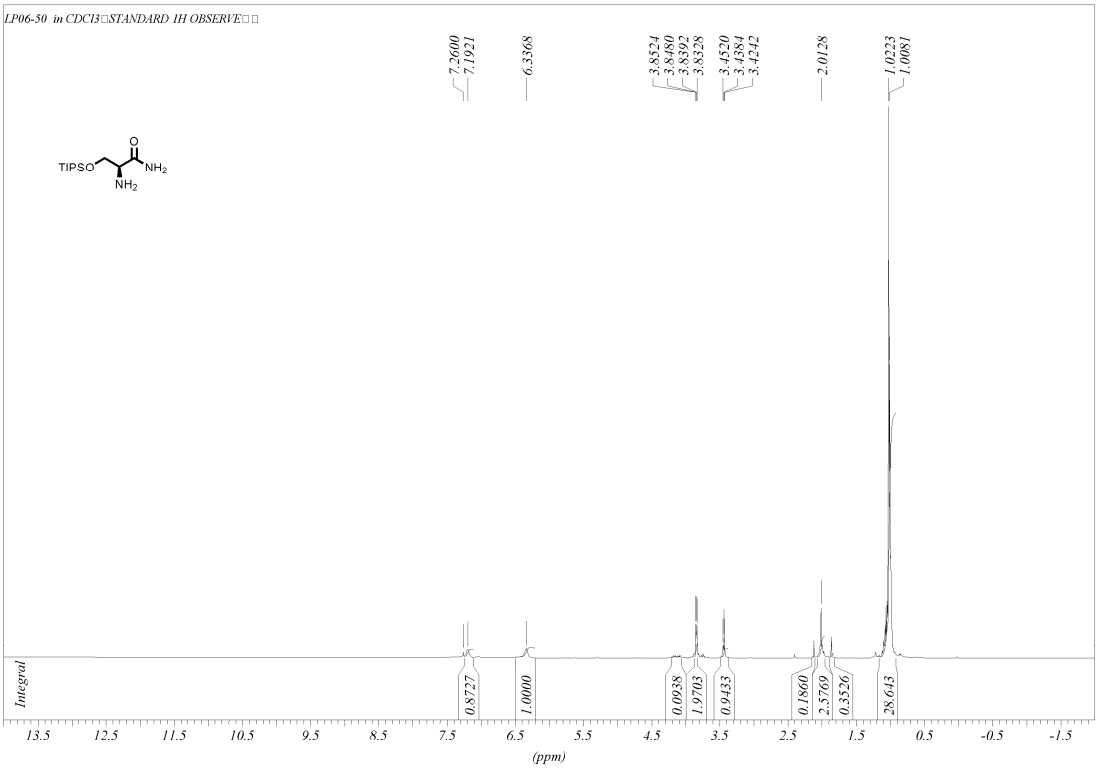

LP551 in CDCl3 am 04.02.2009□STANDARD 1H OBSERVE□□
7.4733
7.4543
7.3327
7.3142
7.2952
7.2600
7.2424
7.2244
3.1928
3.1738
3.1586
2.7622
2.7485
2.7285
2.7144
2.6445
2.6240
2.6109
2.5904
2.1978
2.0675
TrtS
O
OH
N3
Integral
17.503
1.0030
1.0000
1.0504
13.5
12.5
11.5
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
-1.5
(ppm)

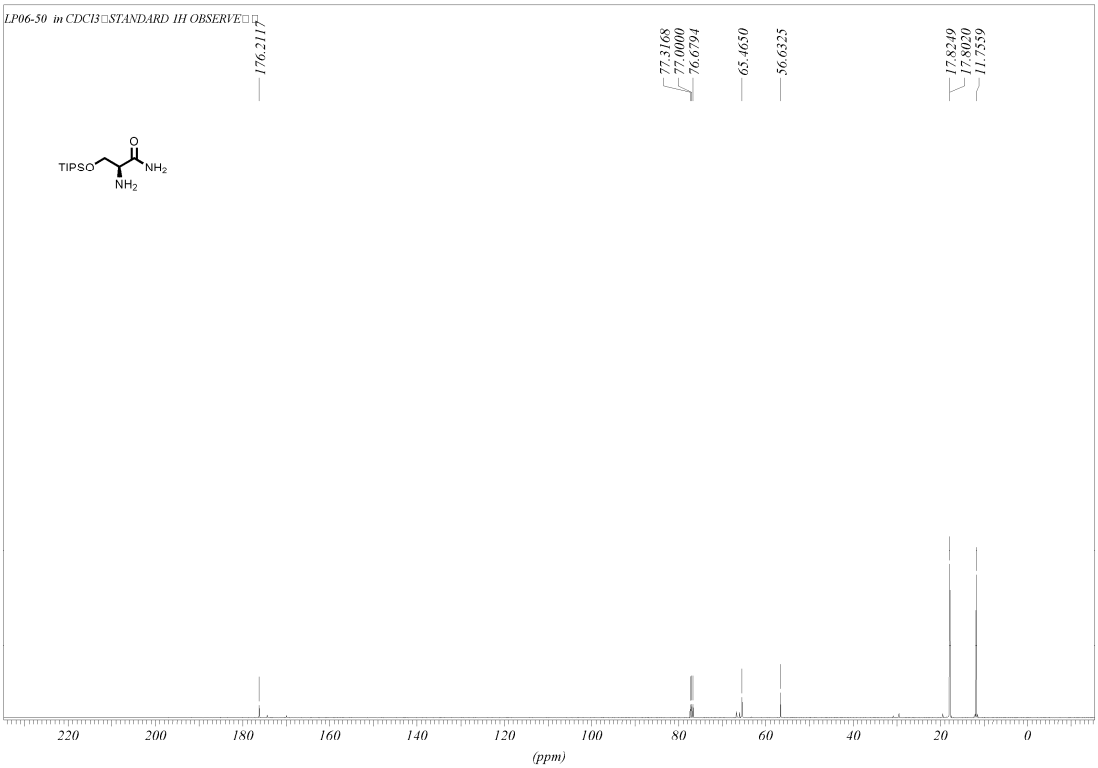

LP06-161AB in CDCl3 am 03.03.2009□STANDARD 1H OBSERVE□□
7.3576
7.3396
7.2600
5.6167
5.5977
5.1339
4.4567
4.2488
4.2253
3.9456
3.9310
3.9222
1.0384
1.0247
TIPSO
OH
NHCbz
Integral
5.8540
1.0000
2.2579
0.8785
1.0273
1.0752
25.127
13.5
12.5
11.5
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
-1.5
(ppm)

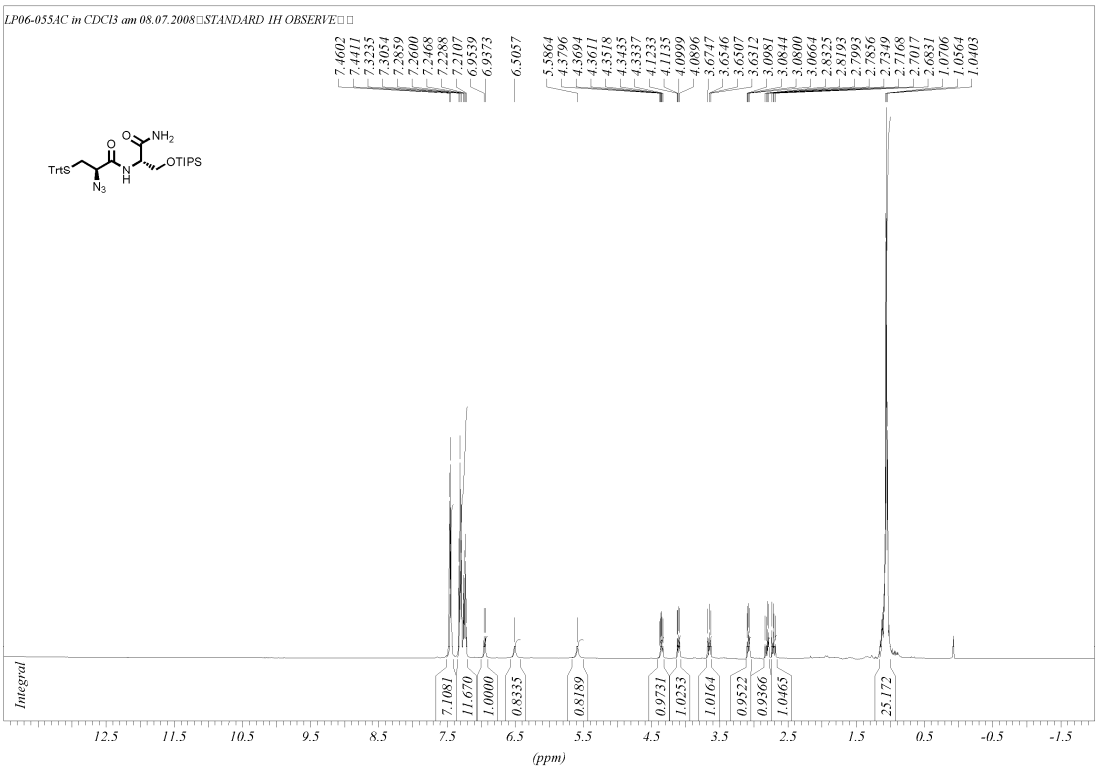

LP06-161AB in CDCl3 am 03.03.2009□STANDARD 1H OBSERVE□□
174.5162
156.0388
136.1445
128.5372
128.2090
128.0945
77.3168
77.0000
76.6832
67.1483
63.7244
55.5141
17.7715
17.7600
11.7750
TIPSO
OH
NHCbz
220
200
180
160
140
120
100
80
60
40
20
0
(ppm)

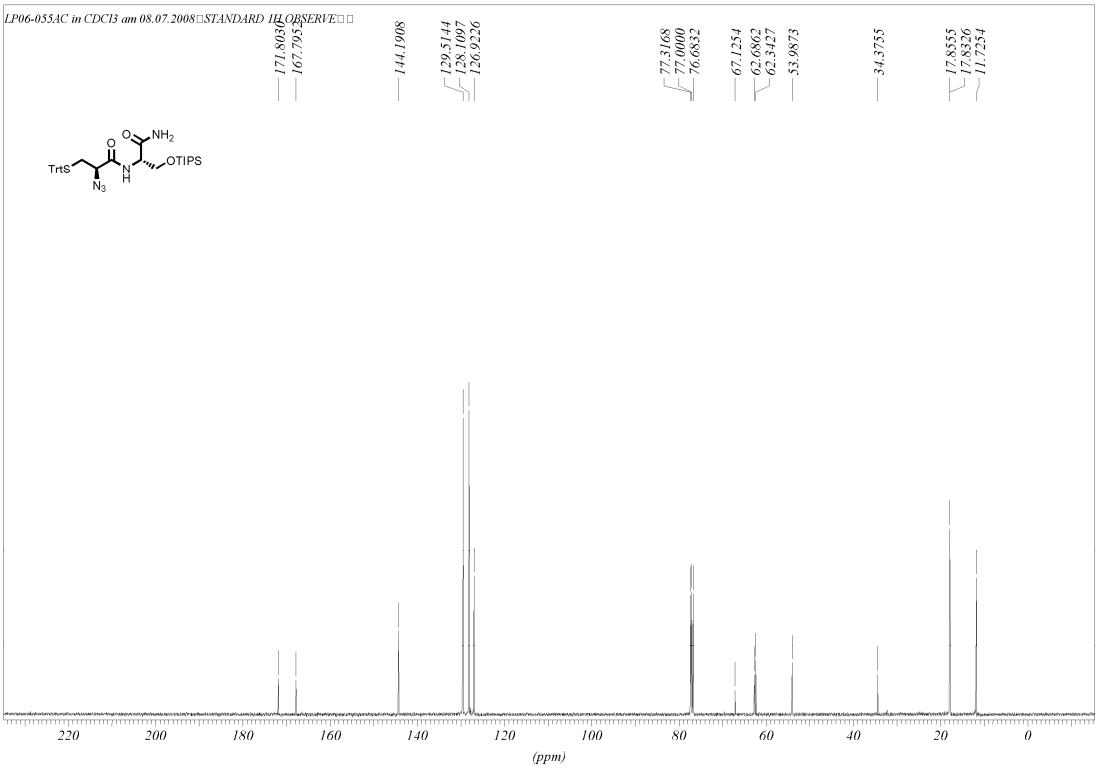

LP06-47A in CDCl3 am 12.03.09□STANDARD 1H OBSERVE□□
7.3547
7.3449
7.3303
7.3230
7.3083
7.2966
7.2600
6.5848
5.9057
5.7383
5.1217
4.2356
4.1492
4.1336
3.7518
3.7288
3.7093
1.0598
TIPSO
NH2
NHCbz
Integral
7.0651
1.0000
1.1057
1.1975
2.7943
2.5883
1.3458
32.282
13.5
12.5
11.5
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
-1.5
(ppm)

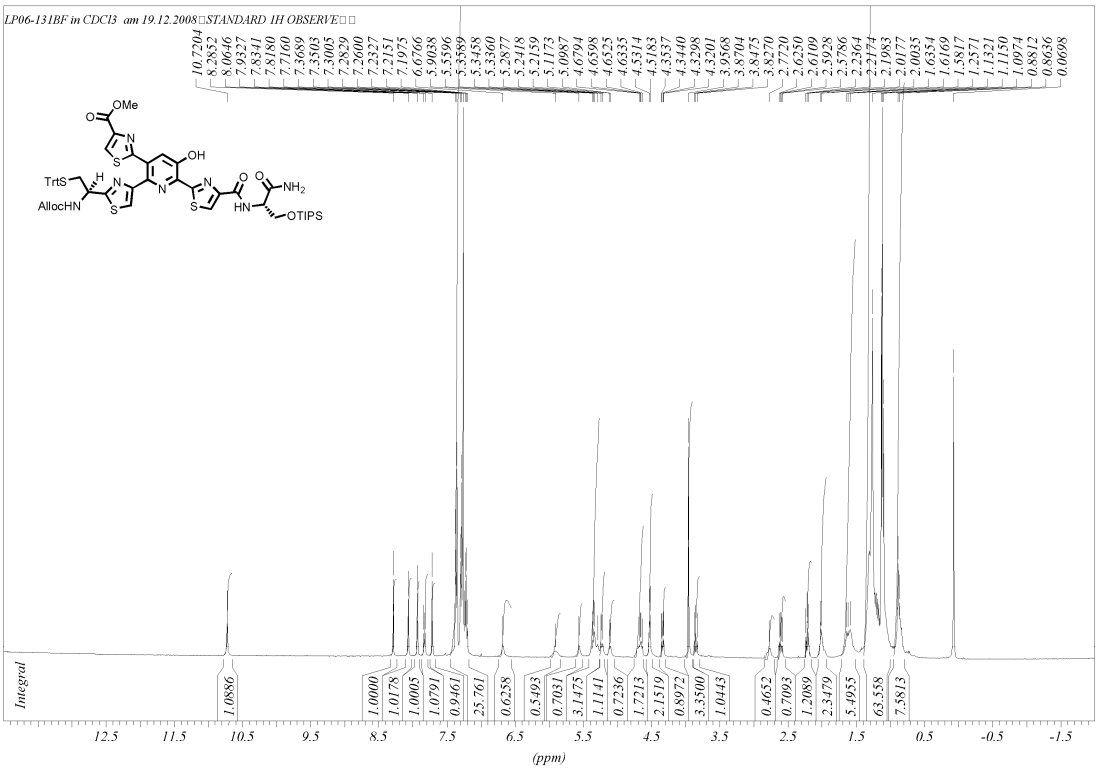

lpo6-47A in CDCl3 am 12.03.09□13C OBSERVE□□pad=2 run with fndz0 before acquisition□
172.6160
156.0000
136.0796
128.4991
128.1784
128.0563
77.3206
77.0000
76.6832
67.0452
63.4038
55.5446
17.8364
17.8097
11.7101
TIPSO
NH2
NHCbz
220
200
180
160
140
120
100
80
60
40
20
0
(ppm)

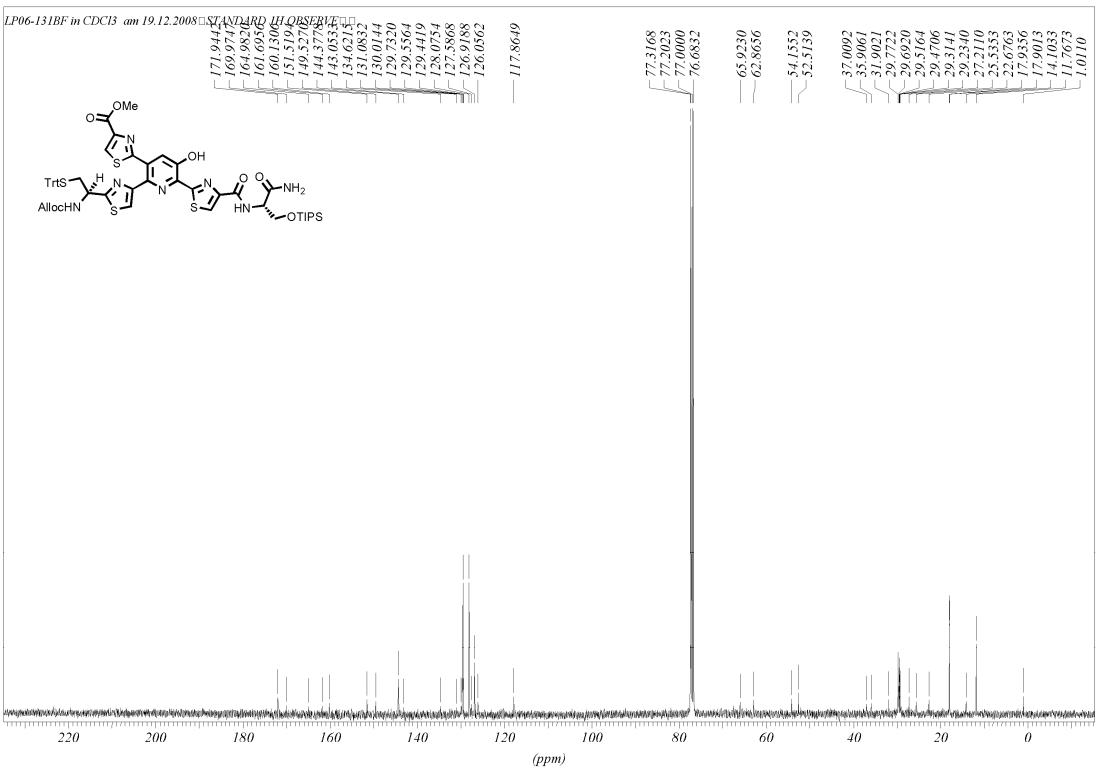

LP06-50 in CDCl3□STANDARD 1H OBSERVE□□
7.2600
7.1921
6.3368
3.8524
3.8480
3.8392
3.8328
3.4520
3.4384
3.4242
2.0128
1.0223
1.0081
TIPSO
NH2
NH2
Integral
0.8727
1.0000
0.0938
1.9703
0.9433
0.1860
2.5769
0.3526
28.643
13.5 12.5 11.5 10.5 9.5 8.5 7.5 6.5 5.5 4.5 3.5 2.5 1.5 0.5 -0.5 -1.5
(ppm)

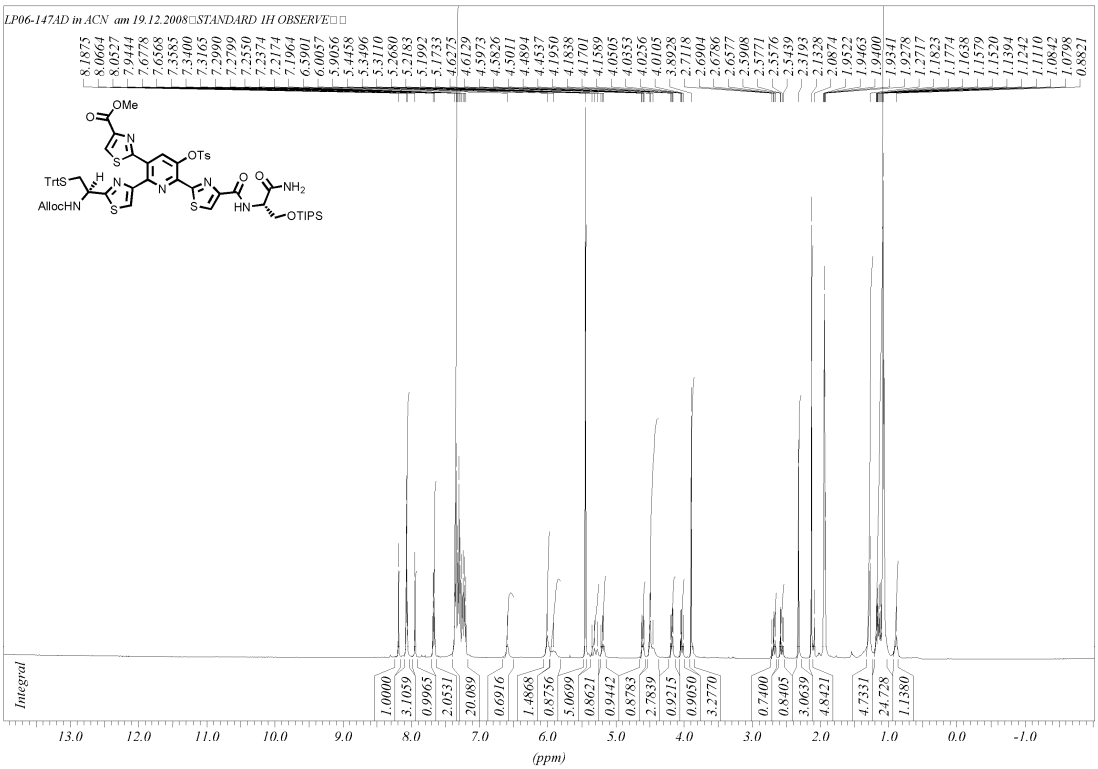

LP06-50 in CDCl3□STANDARD 1H OBSERVE□□
176.2117
77.3168
77.0000
76.6794
65.4650
56.6325
17.8249
17.8020
11.7559
TIPSO
NH2
NH2
220 200 180 160 140 120 100 80 60 40 20 0
(ppm)

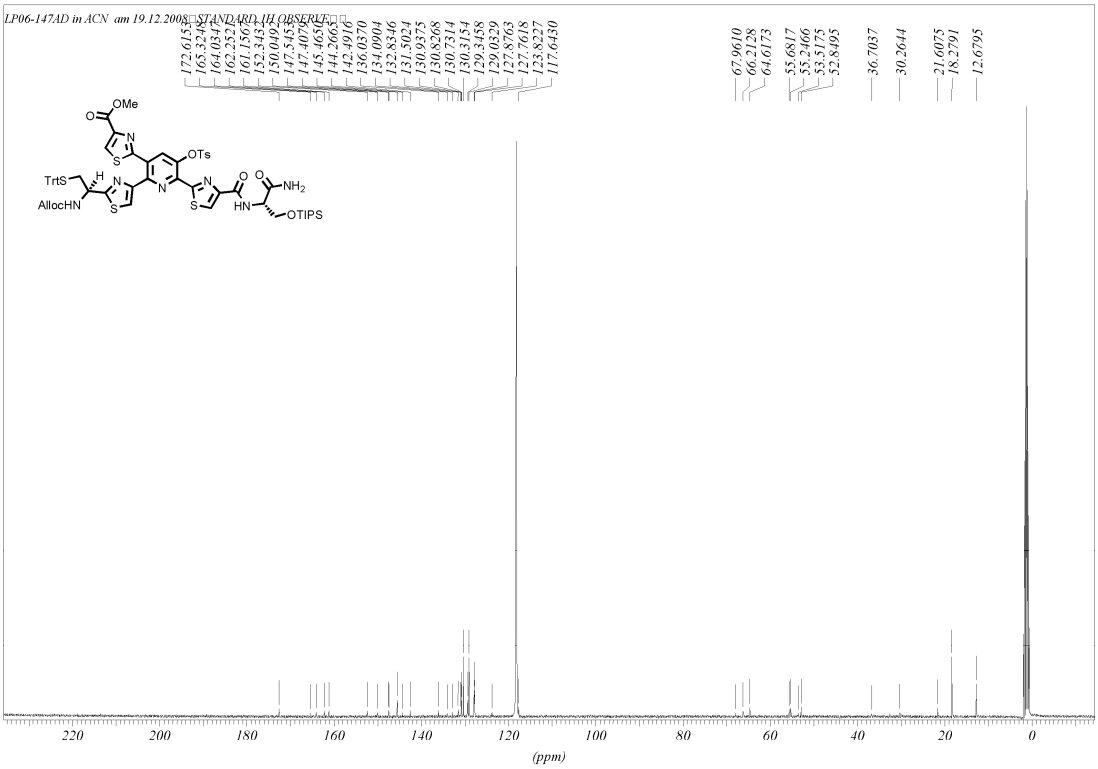

LP06-055AC in CDCl3 am 08.07.2008 STANDARD 1H OBSERVE
7.4602
7.4411
7.3235
7.3054
7.2859
7.2600
7.2468
7.2288
7.2107
6.9539
6.9373
6.5057
5.5864
4.3796
4.3694
4.3611
4.3518
4.3435
4.3337
4.1233
4.1135
4.0999
4.0896
3.6747
3.6546
3.6507
3.6312
3.0981
3.0844
3.0800
3.0664
2.8325
2.8193
2.7993
2.7856
2.7349
2.7168
2.7017
2.6831
1.0706
1.0564
1.0403
TrtS
OTIPS
Integral
7.1081
11.670
1.0000
0.8335
0.8189
0.9731
1.0253
1.0164
0.9522
0.9366
1.0465
25.172
12.5
11.5
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
-1.5
(ppm)

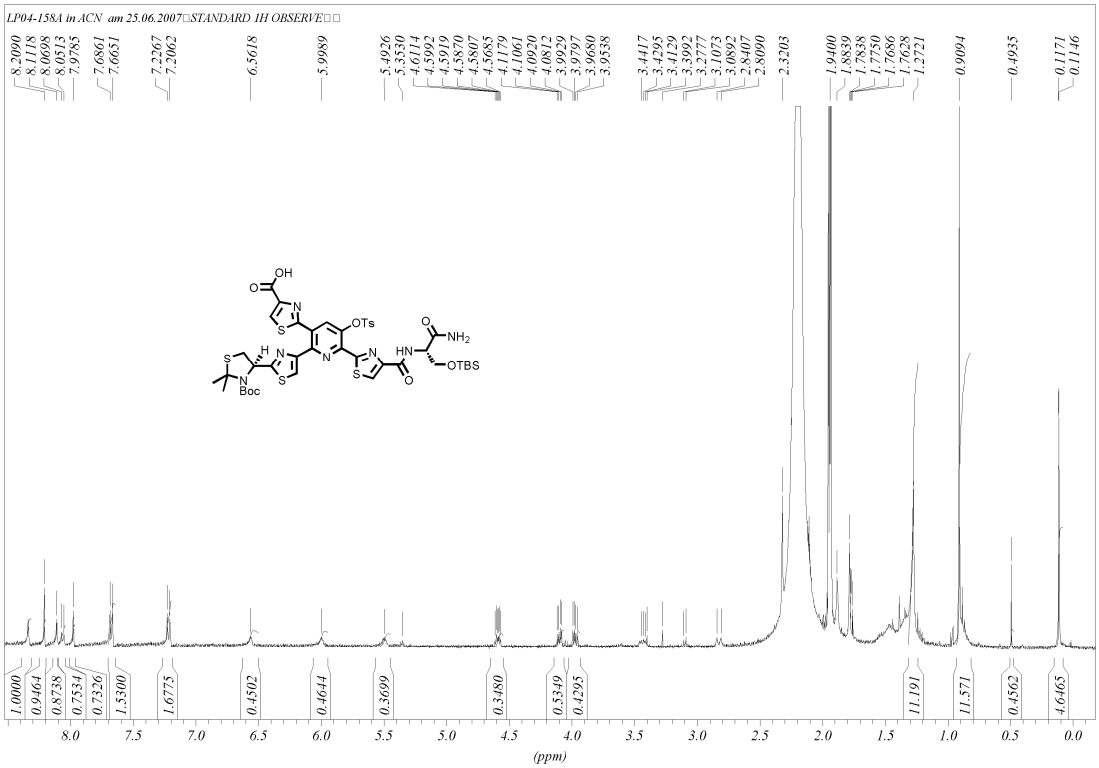

LP06-055AC in CDCl3 am 08.07.2008 STANDARD 1H OBSERVE
171.8030
167.7952
144.1908
129.5144
128.1097
126.9226
77.3168
77.0000
76.6832
67.1254
62.6862
62.3427
53.9873
34.3755
17.8555
17.8326
11.7254
TrtS
OTIPS
220
200
180
160
140
120
100
80
60
40
20
0
(ppm)

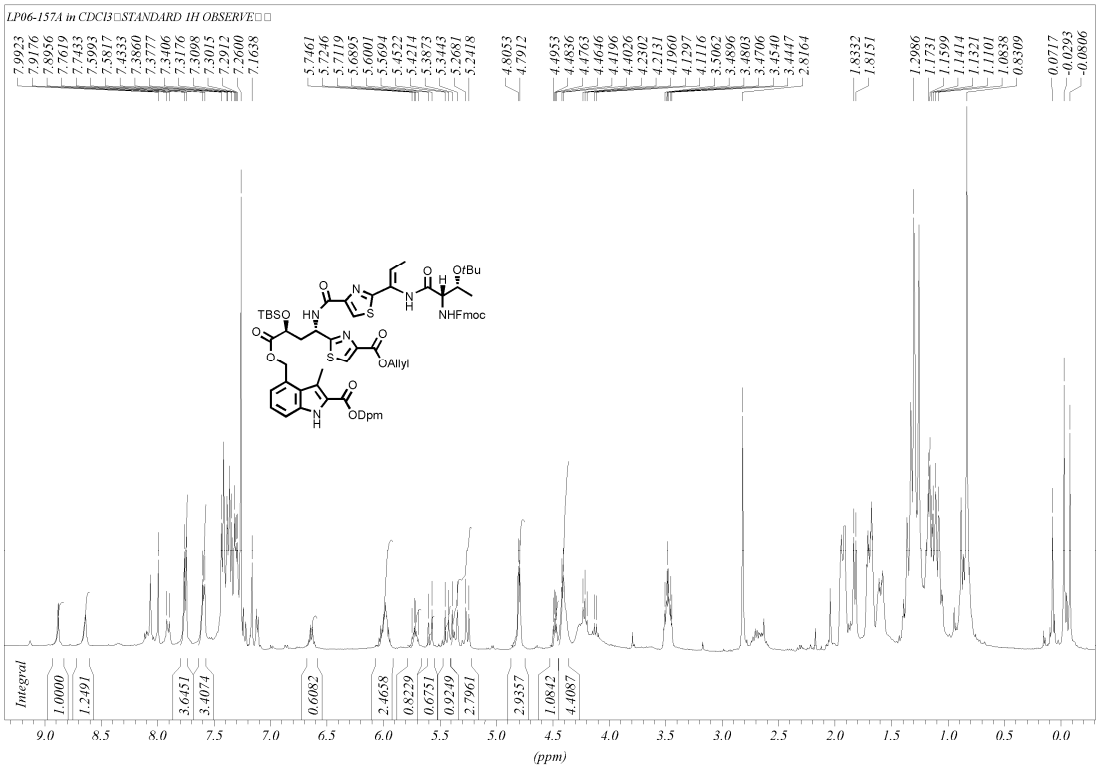

LP06-131BF in CDCl3 am 19.12.2008 STANDARD 1H OBSERVE
OMe
OH
TrtS
AllocHN
OTIPS
NH2
Integral
(ppm)

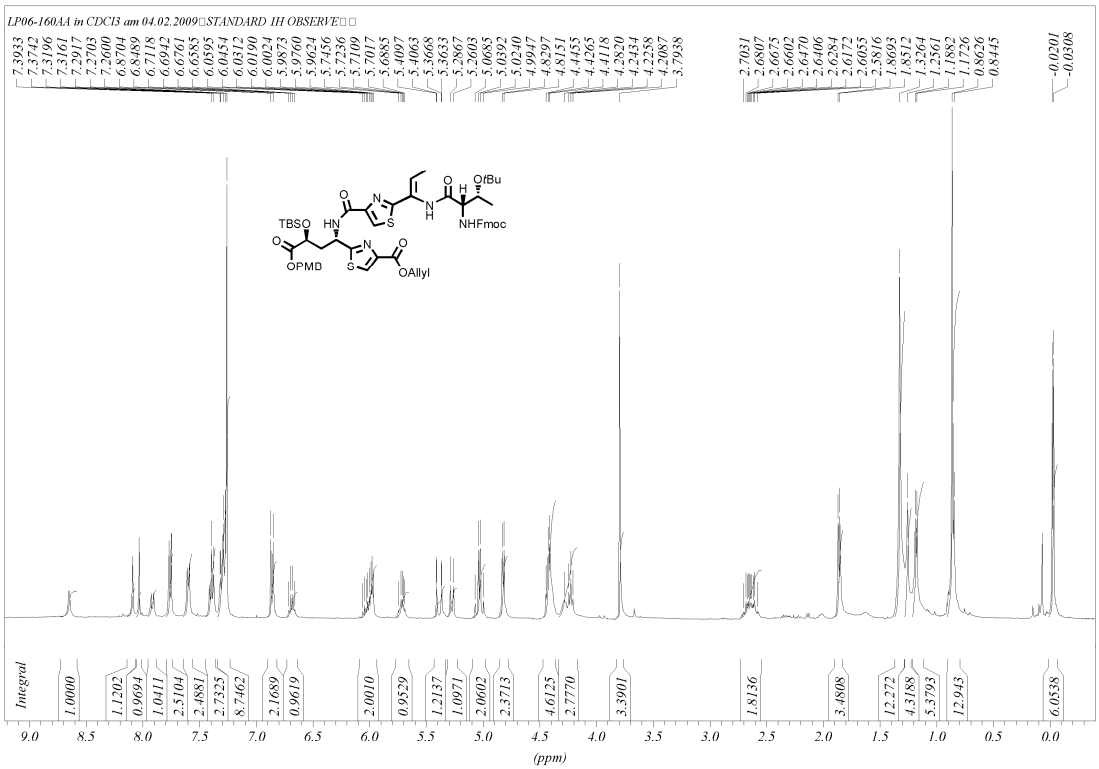

LP06-131BF in CDCl3 am 19.12.2008 STANDARD 1H OBSERVE
OMe
OH
TrtS
AllocHN
OTIPS
NH2
(ppm)

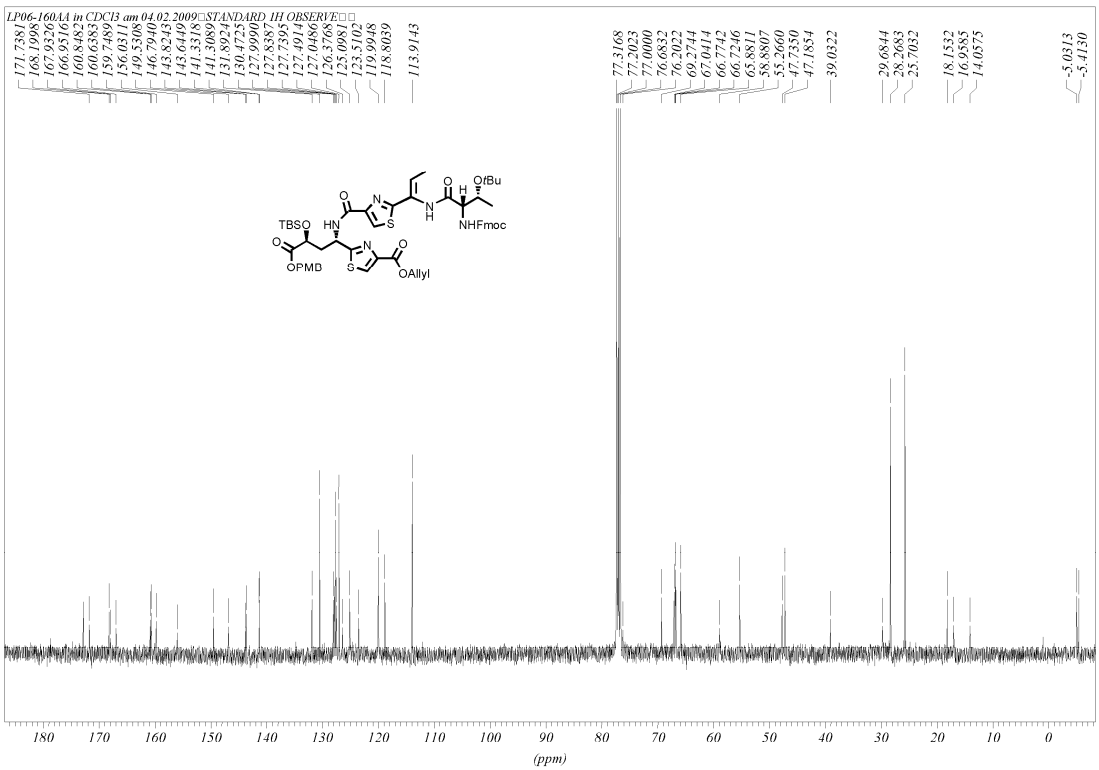

LP06-147AD in ACN am 19.12.2008 STANDARD 1H OBSERVE
Integral
(ppm)

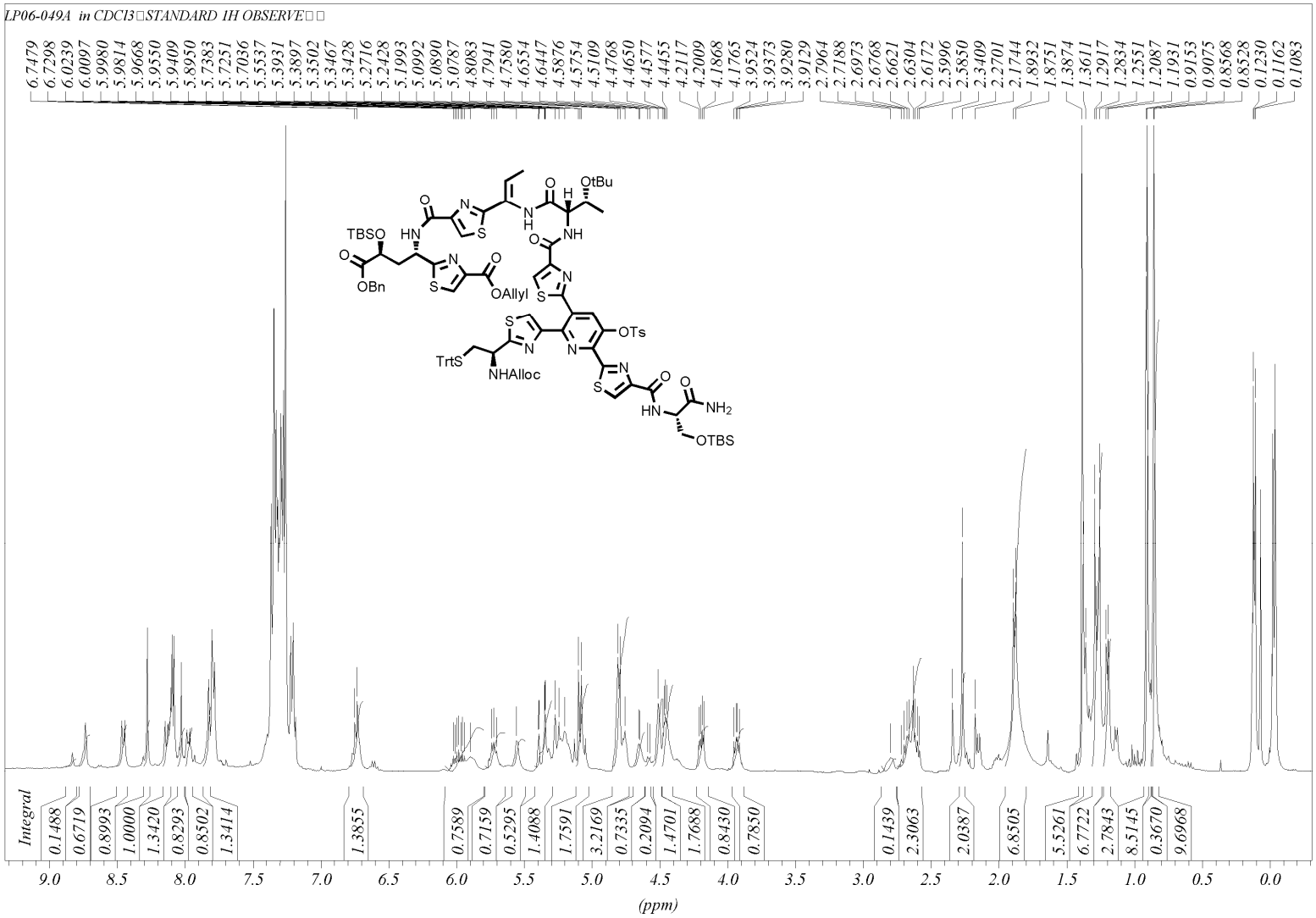

LP06-147AD in ACN am 19.12.2008 STANDARD 1H OBSERVE
(ppm)

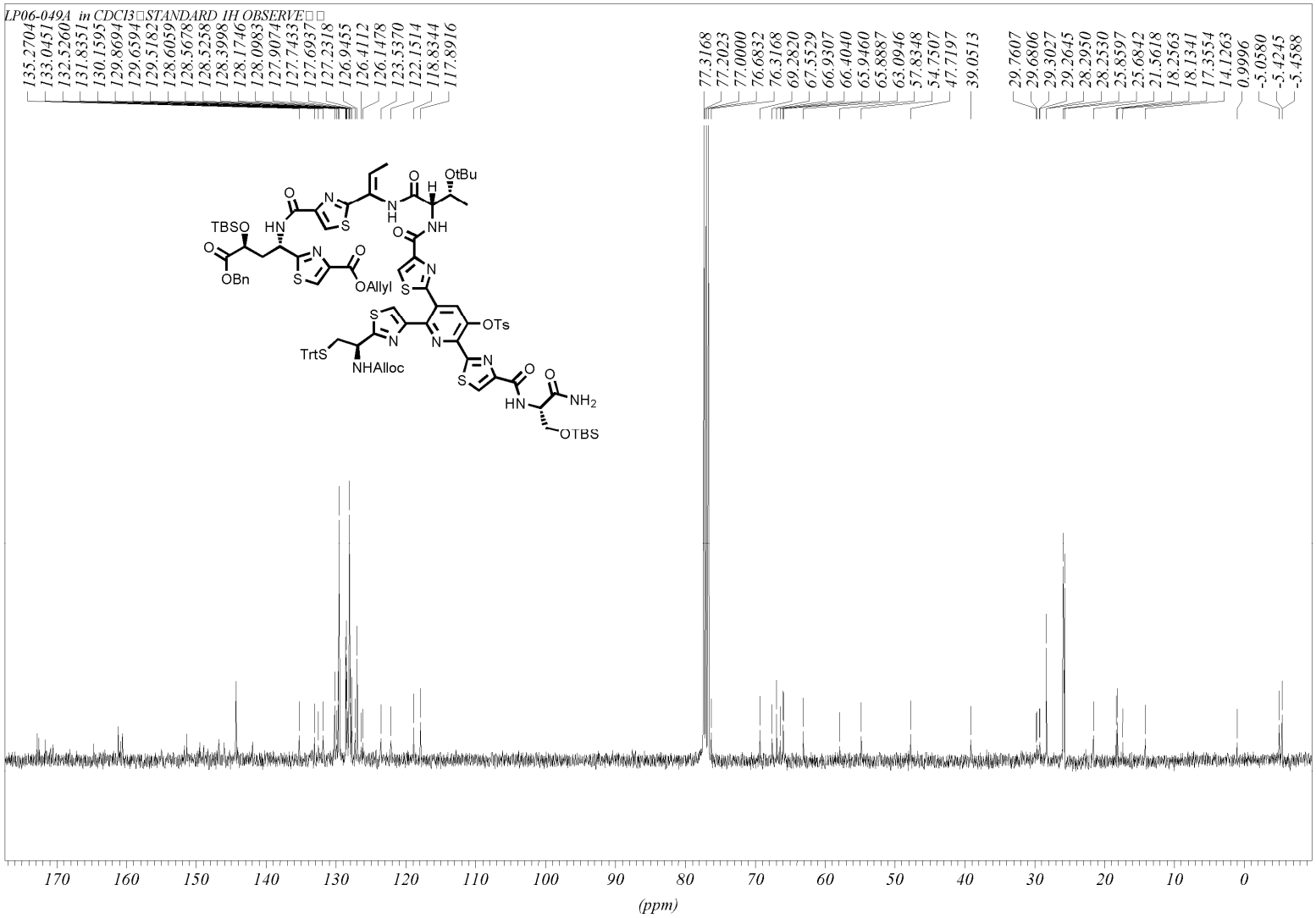

LP04-158A in ACN am 25.06.2007□STANDARD 1H OBSERVE□□
(ppm)

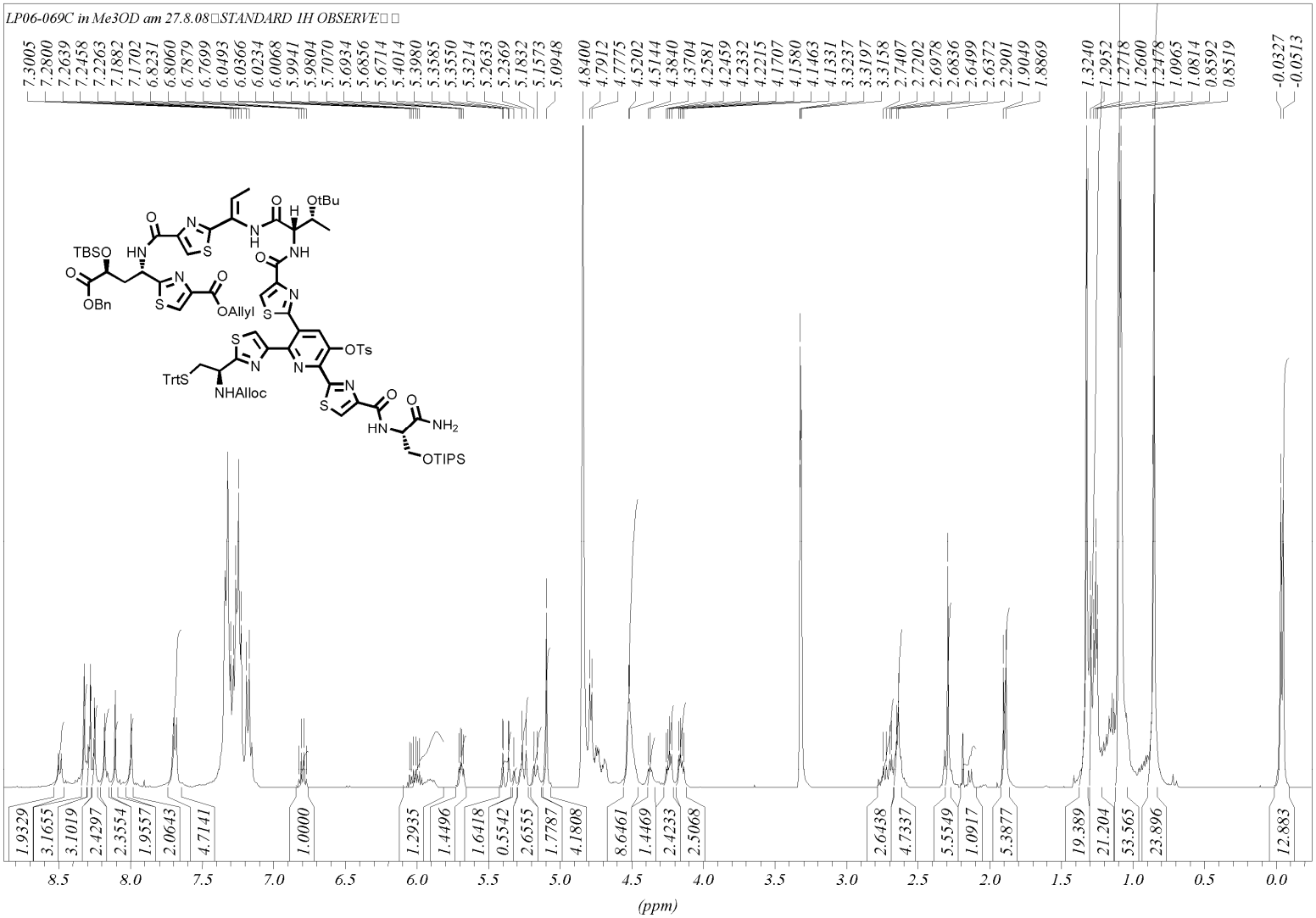

LP06-157A in CDCl3□STANDARD 1H OBSERVE□□
Integral
(ppm)

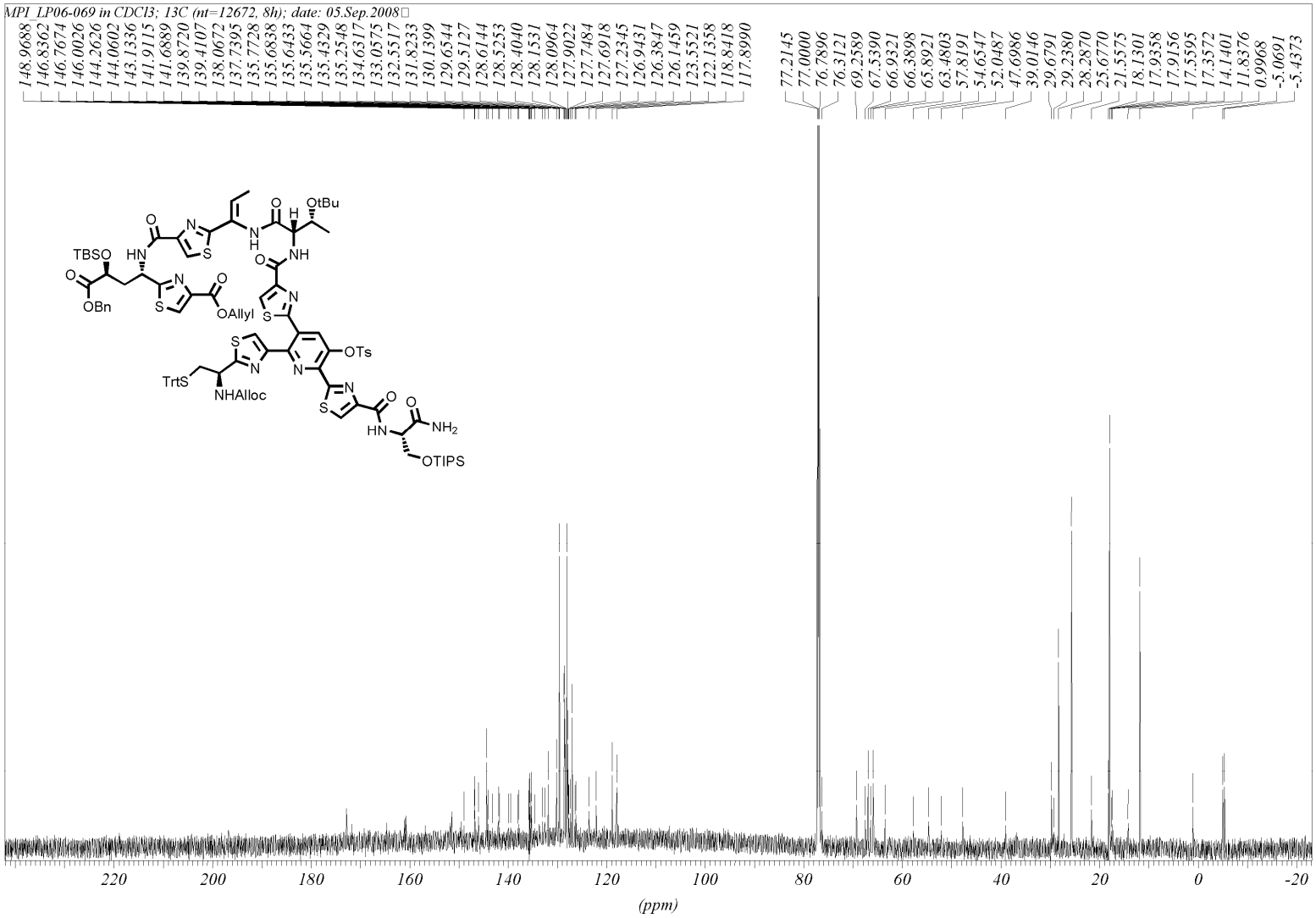

LP06-160AA in CDCl3 am 04.02.2009□STANDARD 1H OBSERVE□□
7.3933 7.3742 7.3196 7.3161 7.2917 7.2703 7.2600 6.8704 6.8489 6.7118 6.6942 6.6761 6.6585 6.6595 6.6454 6.6312 6.6190 6.6024 5.9873 5.9760 5.9624 5.7456 5.7236 5.7109 5.7017 5.6885 5.4097 5.4063 5.3668 5.3633 5.2867 5.2603 5.0685 5.0392 5.0240 4.9947 4.8297 4.8151 4.4455 4.4265 4.4118 4.2820 4.2434 4.2258 4.2087 3.7938
2.7031 2.6807 2.6675 2.6602 2.6470 2.6406 2.6284 2.6172 2.6055 2.5816 1.8693 1.8512 1.3264 1.2561 1.1882 1.1726 0.8626 0.8445
-0.0201 -0.0308
OfBu
NHFmoc
TBSO
HN
OPMB
OAllyl
Integral
1.0000 1.1202 0.9694 1.0411 2.5104 2.4881 2.7325 8.7462 2.1689 0.9619 2.0010 0.9529 1.2137 1.0971 2.0602 2.3713 4.6125 2.7770 3.3901 1.8136 3.4808 12.272 4.3188 5.3793 12.943 6.0538
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
(ppm)

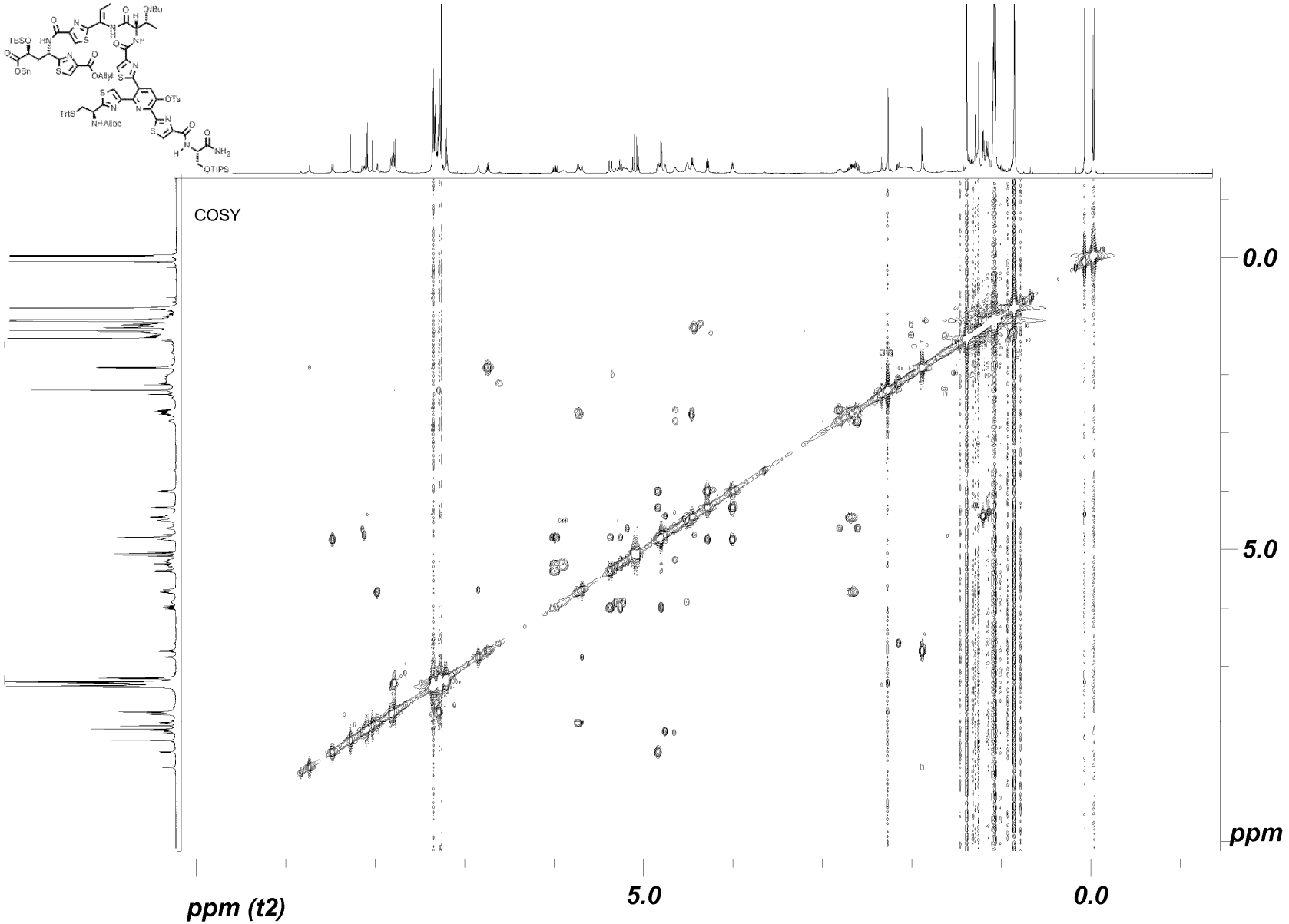

LP06-160AA in CDCl3 am 04.02.2009□STANDARD 1H OBSERVE□□
171.7381 168.1996 167.9326 166.9516 160.8482 160.6385 159.7489 156.0311 149.5306 146.7940 143.8243 143.6449 141.3318 141.3089 131.8927 130.4722 127.9990 127.8887 127.7391 127.4911 127.0480 126.3765 125.0981 123.5102 119.9948 118.8039 113.9143
77.3168 77.2023 77.0000 76.6832 76.2022 69.2744 67.0414 66.7742 66.7246 65.8811 58.8807 55.2660 47.7350 47.1854 39.0322
29.6844 28.2683 25.7032
18.1532 16.9585 14.0575
-5.0313 -5.4150
OfBu
NHFmoc
TBSO
HN
OPMB
OAllyl
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
(ppm)

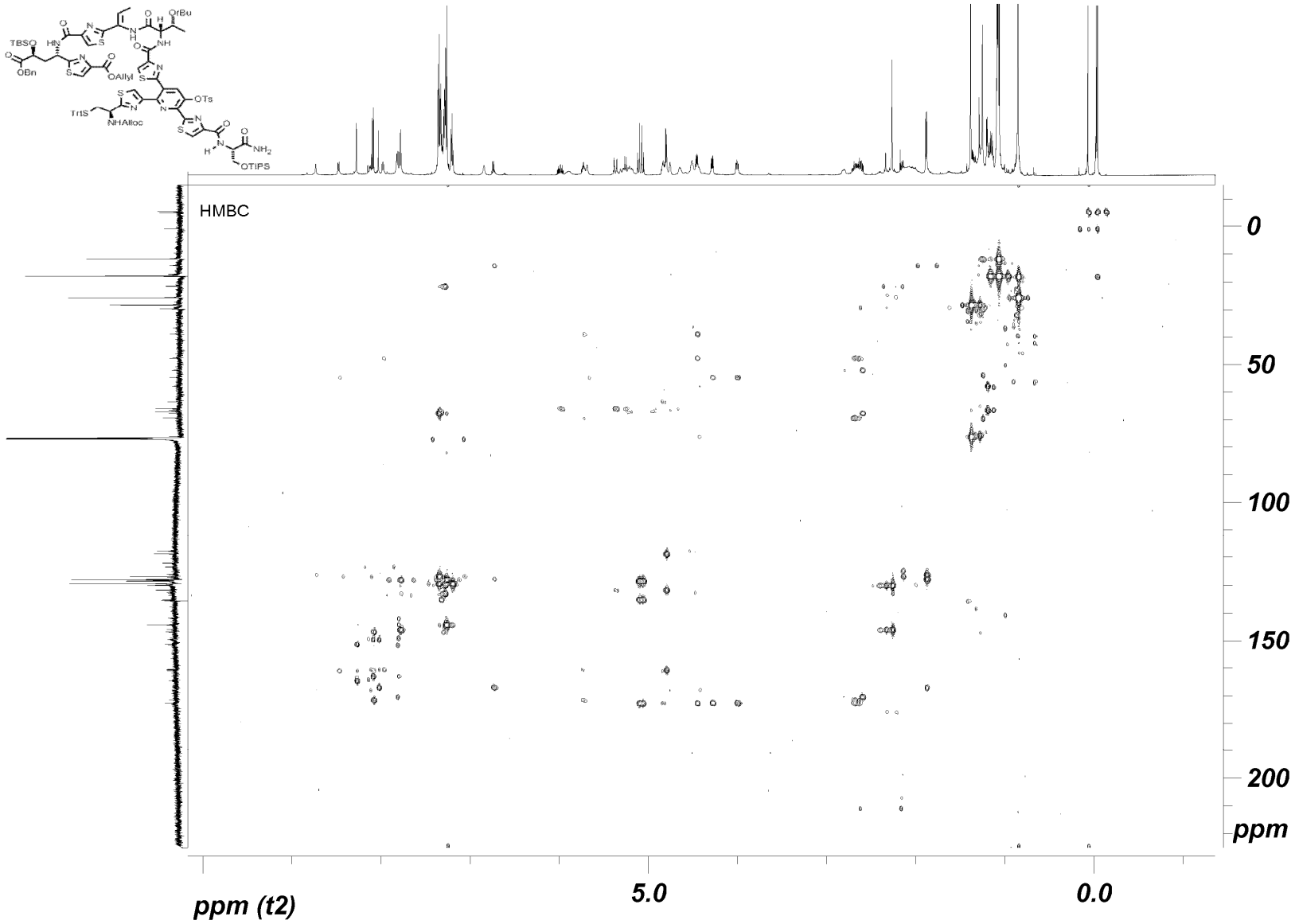

LP06-049A in CDCl3 STANDARD 1H OBSERVE
6.7479 6.7298 6.0239 6.0097 5.9980 5.9814 5.9668 5.9550 5.9409 5.8950 5.7383 5.7251 5.7036 5.5537 5.3931 5.3897 5.3502 5.3467 5.3428 5.2716 5.2428 5.1993 5.0992 5.0890 5.0787 4.8083 4.7941 4.7580 4.6554 4.6447 4.5876 4.5754 4.5109 4.4768 4.4650 4.4577 4.4455 4.2117 4.2009 4.1868 4.1765 3.9524 3.9373 3.9280 3.9129 2.7964 2.7188 2.6973 2.6768 2.6621 2.6304 2.6172 2.5996 2.5850 2.3409 2.2701 2.1744 1.8932 1.8751 1.3874 1.3611 1.2917 1.2834 1.2551 1.2087 1.1931 0.9153 0.9075 0.8568 0.8528 0.1230 0.1162 0.1083
OtBu
TBSO
HN
OBn
OAllyl
OTs
TrtS
NHAlloc
NH2
OTBS
Integral
0.1488 0.6719 0.8993 1.0000 1.3420 0.8293 0.8502 1.3414 1.3855 0.7589 0.7159 0.5295 1.4088 1.7591 3.2169 0.7335 0.2094 1.4701 1.7688 0.8430 0.7850 0.1439 2.3063 2.0387 6.8505 5.5261 6.7722 2.7843 8.5145 0.3670 9.6968
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
(ppm)

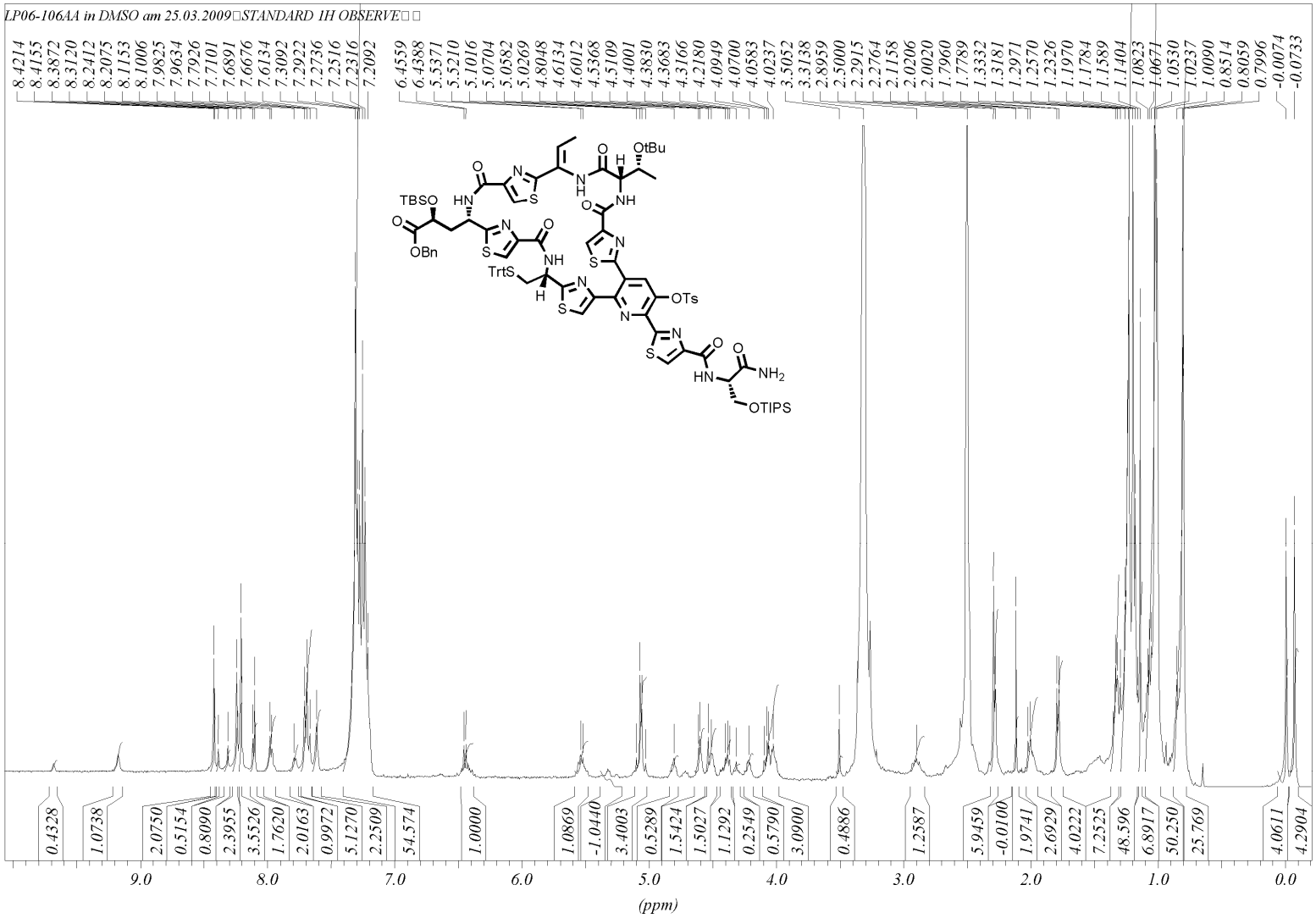

LP06-049A in CDCl3 STANDARD 1H OBSERVE
135.2704
133.0451
132.5260
131.8351
130.1595
129.8694
129.6594
129.5182
128.6059
128.5678
128.5258
128.3998
128.1746
128.0983
127.9074
127.7433
127.6937
127.2318
126.9455
126.4112
126.1478
123.5370
122.1514
118.8344
117.8916
77.3168
77.2023
77.0000
76.6832
76.3168
69.2820
67.5529
66.9307
66.4040
65.9460
65.8887
63.0946
57.8348
54.7507
47.7197
39.0513
29.7607
29.6806
29.3027
29.2645
28.2950
28.2530
25.8597
25.6842
21.5618
18.2563
18.1341
17.3554
14.1263
0.9996
-5.0580
-5.4245
-5.4588
OtBu
TBSO
HN
OBn
OAllyl
OTs
TrtS
NHAlloc
NH2
OTBS
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
(ppm)

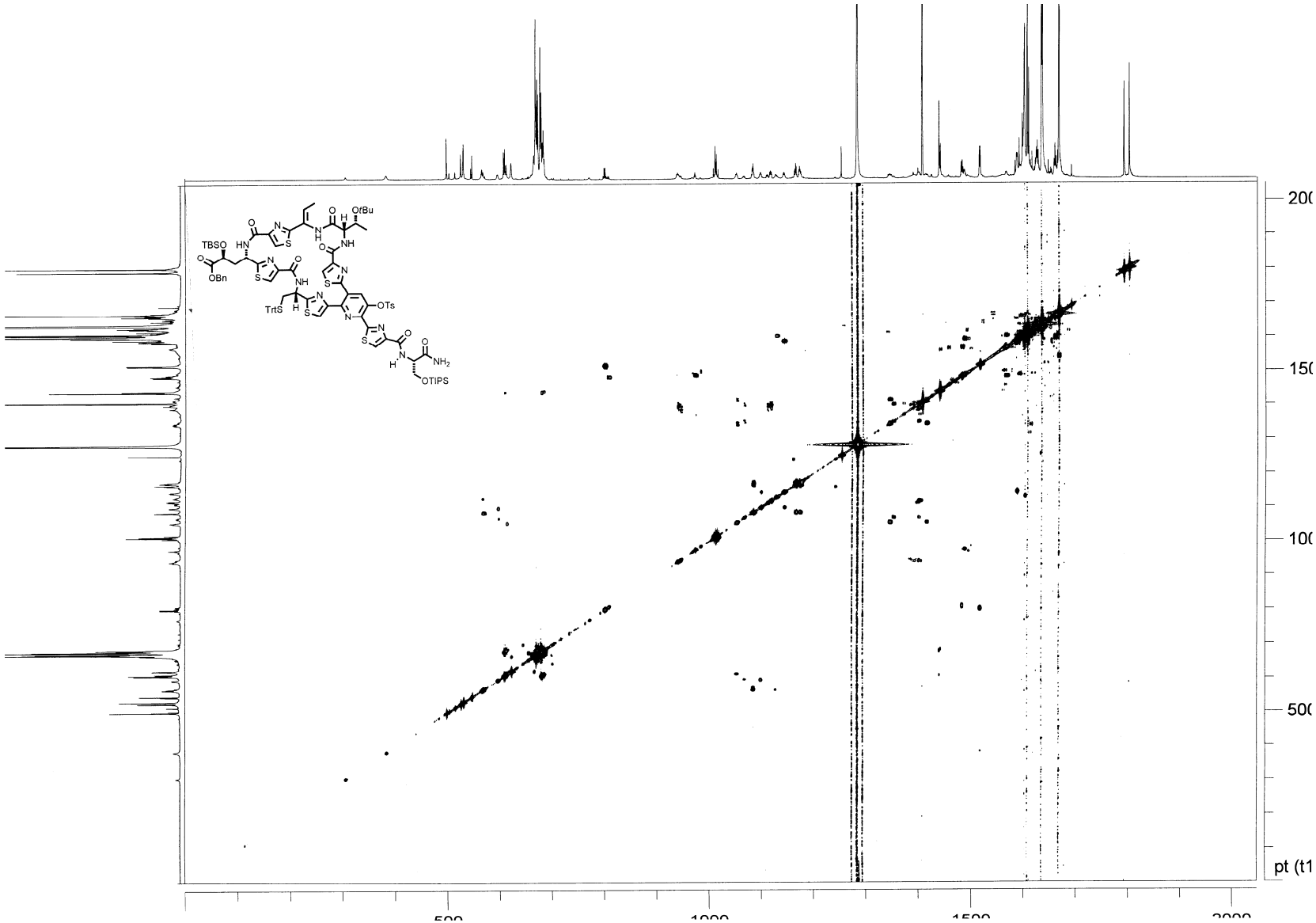

LP06-069C in Me3OD am 27.8.08□STANDARD 1H OBSERVE□□
7.3005 7.2800 7.2639 7.2458 7.2263 7.1882 7.1702 6.8231 6.8060 6.7879 6.7699 6.0493 6.0366 6.0234 6.0068 5.9941 5.9804 5.7070 5.6934 5.6856 5.6714 5.4014 5.3980 5.3585 5.3550 5.3214 5.2633 5.2369 5.1832 5.1573 5.0948
4.8400 4.7912 4.7775 4.5202 4.5144 4.3840 4.3704 4.2381 4.2459 4.2332 4.2215 4.1707 4.1580 4.1463 4.1331 3.3237 3.3197 3.3158 2.7407 2.7202 2.6978 2.6836 2.6499 2.6372 2.2901 1.9049 1.8869
1.3240 1.2952 1.2718 1.2600 1.2478 1.0965 1.0814 0.8592 0.8519
-0.0327 -0.0513
TBSO
OBn
OAllyl
OtBu
OTs
TrtS
NHAlloc
OTIPS
NH2
1.9329 3.1655 3.1019 2.4297 2.3554 1.9557 2.0643 4.7141 1.0000 1.2935 1.4496 1.6418 0.5542 2.6555 1.7787 4.1808 8.6461 1.4469 2.4233 2.5068 2.6438 4.7337 5.5549 1.0917 5.3877 19.389 21.204 53.565 23.896 12.883
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
(ppm)

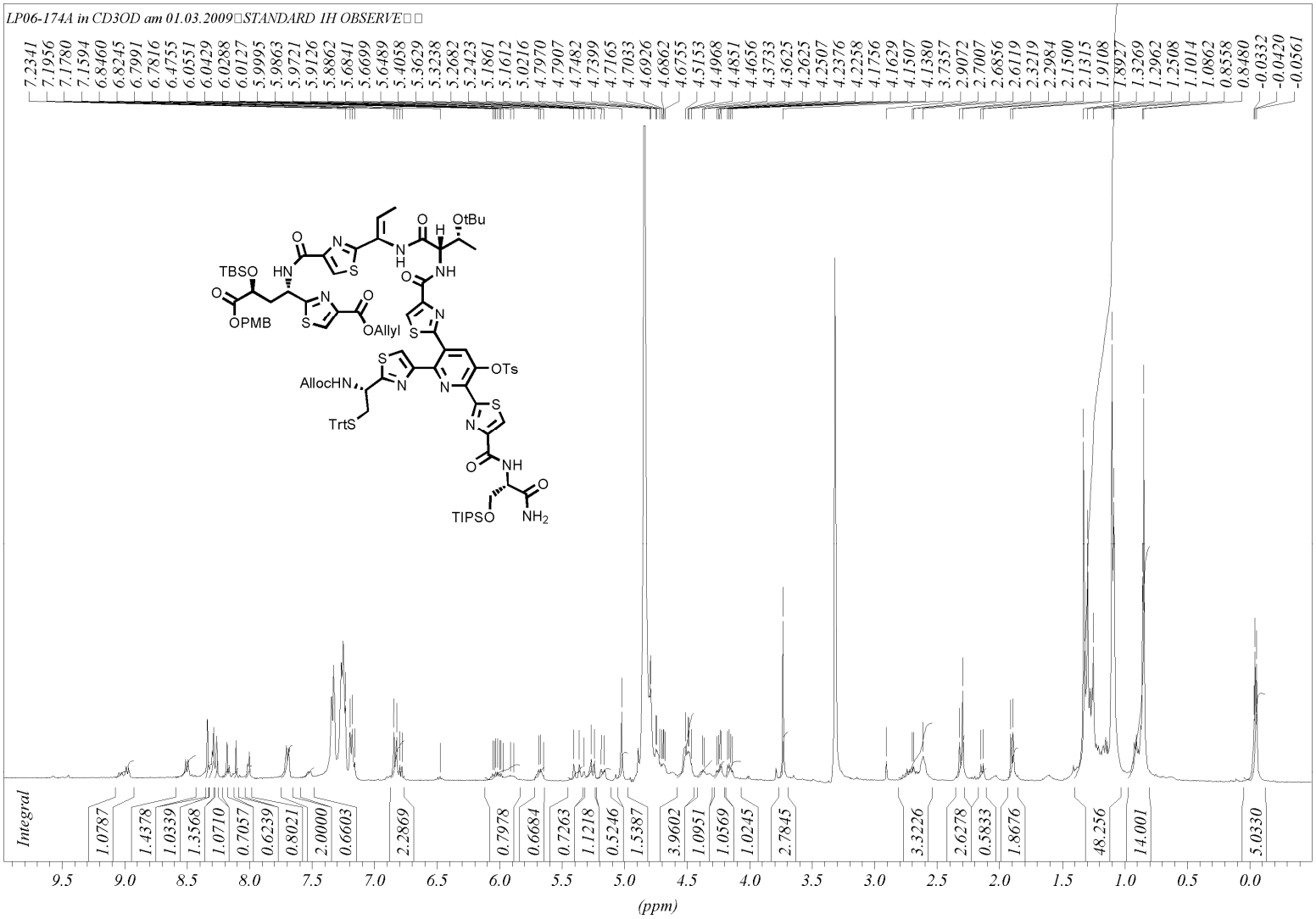

MPI_LP06-069 in CDCl3; 13C (nt=12672, 8h); date: 05.Sep.2008
148.9688
146.8362
146.7674
146.0026
144.2626
144.0602
143.1336
141.9115
141.6889
139.8720
139.4107
138.0672
137.7395
135.7728
135.6838
135.6433
135.5664
135.4329
135.2548
134.6317
133.0575
132.5517
131.8233
130.1399
129.6544
129.5127
128.6144
128.5253
128.4040
128.1531
128.0964
127.9022
127.7484
127.6918
127.2345
126.9431
126.3847
126.1459
123.5521
122.1358
118.8418
117.8990
77.2145
77.0000
76.7896
76.3121
69.2589
67.5390
66.9321
66.3898
65.8921
63.4803
57.8191
54.6547
52.0487
47.6986
39.0146
29.6791
29.2380
28.2870
25.6770
21.5575
18.1301
17.9358
17.9156
17.5595
17.3572
14.1401
11.8376
0.9968
-5.0691
-5.4373
OtBu
TBSO
HN
OBn
OAllyl
OTs
TrtS
NHAlloc
NH2
OTIPS
220
200
180
160
140
120
100
80
60
40
20
0
-20
(ppm)

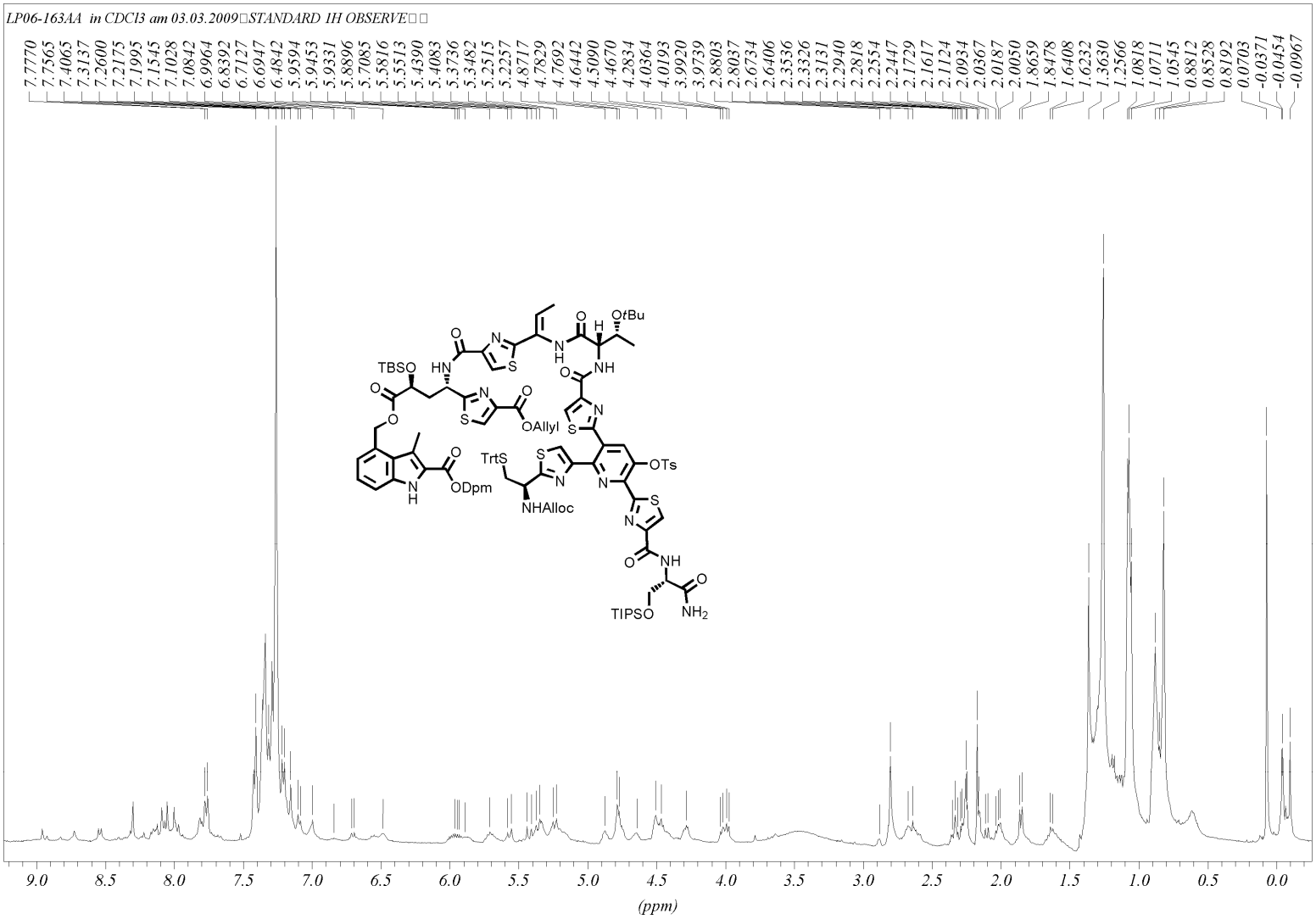

COSY
ppm (t2)
5.0
0.0
5.0
0.0
ppm


HMBC
0
50
100
150
200
ppm
ppm (t2)
5.0
0.0


LP06-106AA in DMSO am 25.03.2009 STANDARD 1H OBSERVE
8.4214 8.4155 8.3872 8.3120 8.2412 8.2075 8.1153 8.1006 7.9825 7.9634 7.7926 7.7101 7.6891 7.6676 7.6134 7.3092 7.2922 7.2736 7.2516 7.2316 7.2092
6.4559 6.4388 5.5371 5.5210 5.1016 5.0704 5.0582 5.0269 4.8048 4.6134 4.6012 4.5368 4.5109 4.4001 4.3830 4.3683 4.3166 4.2180 4.0949 4.0700 4.0583 4.0237
3.5052 3.3138 2.8959 2.5000 2.2915 2.2764 2.1158 2.0206 2.0020 1.7960 1.7789 1.3332 1.3181 1.2971 1.2570 1.2326 1.1970 1.1784 1.1589 1.1404 1.0823 1.0671 1.0530 1.0237 1.0090 0.8514 0.8059 0.7996 -0.0074 -0.0733
OtBu
TBSO
OBn
TrtS
OTs
NH2
OTIPS
0.4328 1.0738 2.0750 0.5154 0.8090 2.3955 3.5526 1.7620 2.0163 0.9972 5.1270 2.2509 54.574 1.0000 1.0869 -1.0440 3.4003 0.5289 1.5424 1.5027 1.1292 0.2549 0.5790 3.0900 0.4886 1.2587 5.9459 -0.0100 1.9741 2.6929 4.0222 7.2525 48.596 6.8917 50.250 25.769 4.0611 4.2904
9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0 0.0
(ppm)


TBSO
OBn
HN
OfBu
NH
TrtS
OTs
NH2
OTIPS
200
150
100
500
pt (t1


LP06-174A in CD3OD am 01.03.2009 STANDARD 1H OBSERVE
7.2341
7.1956
7.1780
7.1594
6.8460
6.8245
6.7991
6.7816
6.4755
6.0551
6.0429
6.0288
6.0127
5.9995
5.9863
5.9721
5.9126
5.8862
5.6841
5.6699
5.6489
5.4058
5.3629
5.3238
5.2682
5.2423
5.1861
5.1612
5.0216
4.7970
4.7907
4.7482
4.7399
4.7165
4.7033
4.6926
4.6862
4.6755
4.5153
4.4968
4.4851
4.4636
4.3733
4.3625
4.2625
4.2507
4.2376
4.2258
4.1756
4.1629
4.1507
4.1380
3.7357
2.9072
2.7007
2.6856
2.6119
2.3219
2.2984
2.1500
2.1315
1.9108
1.8927
1.3269
1.2962
1.2508
1.1014
1.0862
0.8558
0.8480
-0.0332
-0.0420
-0.0561
OtBu
TBSO
HN
OPMB
OAllyl
OTs
AllocHN
TrtS
TIPSO
NH2
Integral
1.0787
1.4378
1.0339
1.3568
1.0710
0.7057
0.6239
0.8021
2.0000
0.6603
2.2869
0.7978
0.6684
0.7263
1.1218
0.5246
1.5387
3.9602
1.0951
1.0569
1.0245
2.7845
3.3226
2.6278
0.5833
1.8676
48.256
14.001
5.0330
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
(ppm)


LP06-163AA in CDCl3 am 03.03.2009□STANDARD 1H OBSERVE□□
7.7770
7.7565
7.4065
7.3137
7.2600
7.2175
7.1995
7.1545
7.1028
7.0842
6.9964
6.8392
6.7127
6.6947
6.4842
5.9594
5.9453
5.9331
5.8896
5.7085
5.5816
5.5513
5.4390
5.4083
5.3736
5.3482
5.2515
5.2257
4.8717
4.7829
4.7692
4.6442
4.5090
4.4670
4.2834
4.0364
4.0193
3.9920
3.9739
2.8803
2.8037
2.6734
2.6406
2.3536
2.3326
2.3131
2.2940
2.2818
2.2554
2.2447
2.1729
2.1617
2.1124
2.0934
2.0367
2.0187
2.0050
1.8659
1.8478
1.6408
1.6232
1.3630
1.2566
1.0818
1.0711
1.0545
0.8812
0.8528
0.8192
0.0703
-0.0371
-0.0454
-0.0967
TBSO
HN
OtBu
NH
OAllyl
TrtS
OTs
ODpm
NHAlloc
TIPSO
NH2
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
(ppm)