MAX-PLANCK-INSTITUT FÜR KOHLENFORSCHUNG

technische universität dortmund

Total Syntheses of Keramaphidin B and Nominal Njaoamine I

&

Studies towards the Total Synthesis of Providencin

Dissertation

Zur Erlangung des akademischen Grades eines

Doktors der Naturwissenschaften

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vorgelegt von

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geboren am 22.01.1995 in Neustadt am Rübenberge

Mülheim an der Ruhr, Mai 2023

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1. Berichterstatter: Prof. Dr. Alois Fürstner

2. Berichterstatter: Prof. Dr. Norbert Krause

Die vorliegende Arbeit entstand unter der Anleitung von Prof. Dr. Alois Fürstner in der Zeit von Oktober 2019 bis Mai 2023 am Max-Planck-Institut für Kohlenforschung in Mülheim an der Ruhr. Teile dieser Arbeit wurden bereits veröffentlicht:

Z. Meng‡, S.M. Spohr‡, S. Tobegen, C. Farès, A. Fürstner, *J. Am. Chem. Soc.* **2021**, *143*, 14402-14414. (‡contributed equally)

S.M. Spohr, A. Fürstner, *Org. Lett.* **2023**, *25*, 1536-1540.

Die praktischen Arbeiten erfolgten zum Teil in Zusammenarbeit mit Dr. Zhanchao Meng. Die beschriebenen Ergebnisse bilden eine vollständige Darstellung dieser gemeinsamen Arbeiten. Die von diesem Mitarbeiter alleinverantwortlich erzielten Ergebnisse wurden als solche an entsprechender Stelle gekennzeichnet.

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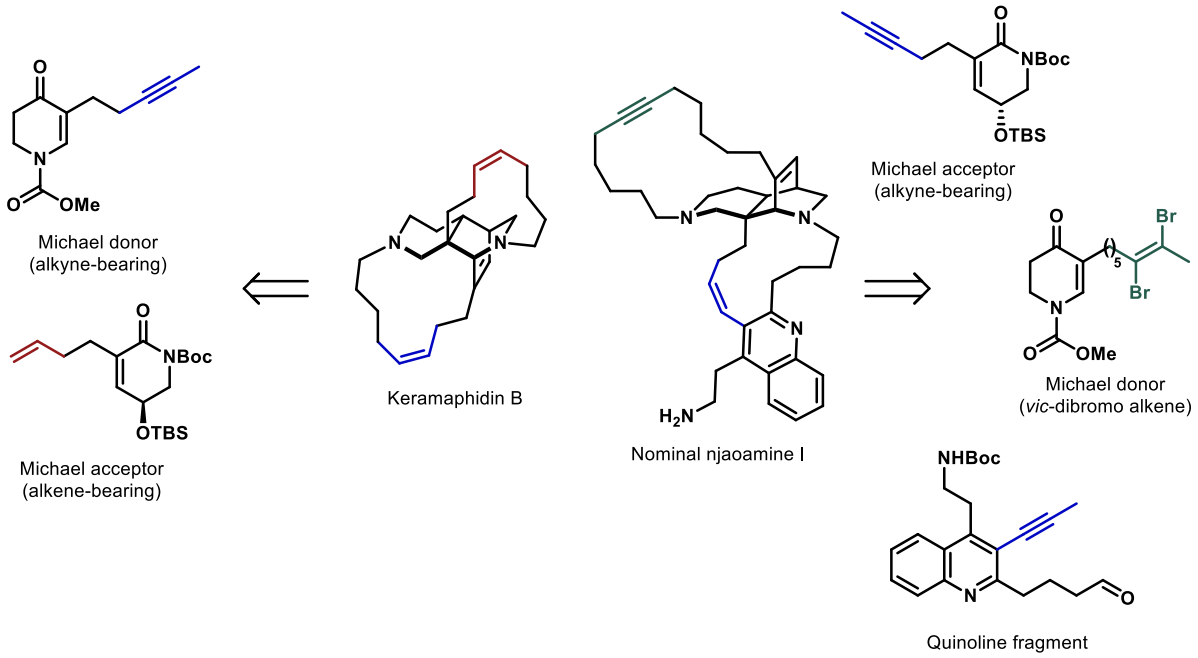
Abschließend möchte ich meinen Eltern und Geschwistern für die bedingungslose Unterstützung danken.

Abstract:

After the discovery of manzamine A, a macrocyclic marine alkaloid, Baldwin and Whitehead proposed the biogenesis of a whole class of natural products arising from partly reduced alkylpyridine derivatives. Although manzamine A was quickly conquered by total synthesis around the turn of the millennium, a family of alkaloids emerging early in the biogenesis of these natural products remained elusive. In a total synthesis campaign, alkaloids of the ingenamine estate were targeted, pursuing an approach purely based on chemical logic. Therein, a Michael/Michael cascade was developed forging the common tricyclic core in diastereoselective fashion. Furthermore, the transformation proved highly flexible concerning the introduction of requisite handles for macrocyclization.

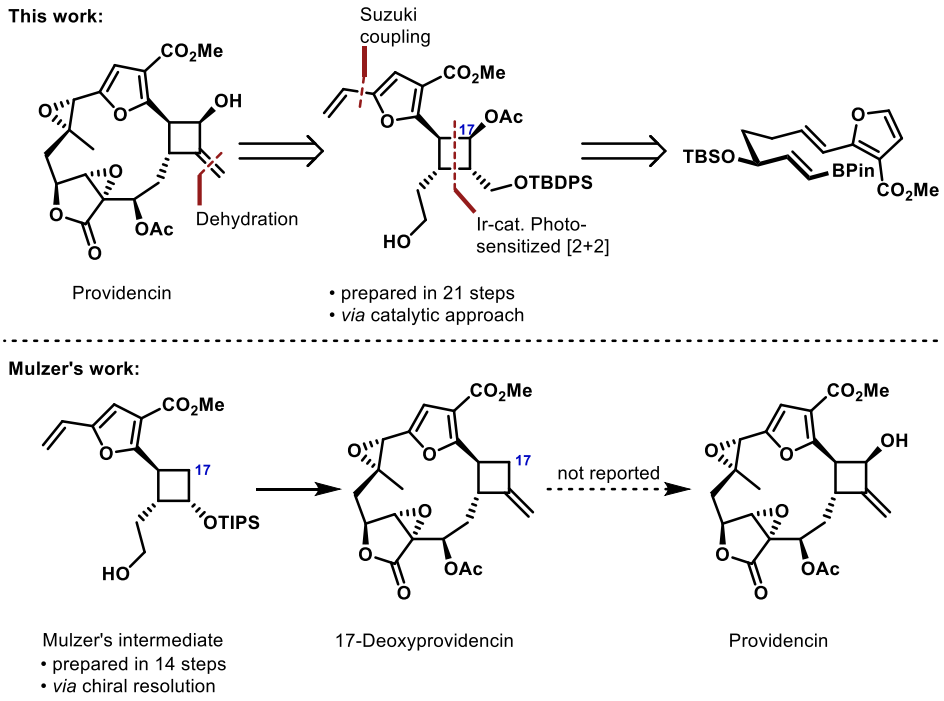


For the total synthesis of keramaphidin B the macrocyclization strategy relied on the use of ring-closing alkyne metathesis (RCAM) for the 13-membered macrocycle and ring-closing olefin metathesis (RCM) for the 11-membered macrocycle. While the RCAM proved highly reliable, the RCM reaction had to be optimized carefully. Eventually, however, the inaugural total synthesis of keramaphidin B was accomplished in 19 steps along the longest linear sequence (LLS) and 0.93% overall yield.

As the more recently discovered njaoamines carry an additional Lewis basic amine functionality in the quinoline annulated to one of the macrocycles, the use of RCM became less inviting. After the identification of *vic*-dibromoalkenes as sufficient alkyne surrogates, nominal njaoamine I was synthesized employing two subsequent RCAMs in 21 steps LLS and 1.14% overall yield. The total synthesis revealed a positional misassignment of the triple bond in the 17-membered macrocycle, which was revised by an in-depth NMR study.

Furanocembranoids are a diverse family of diterpenes. Their macrocyclic framework features, in most cases, a furan and butenolide moiety of some sort. One of the most intriguing molecules found within this class is providencin. Apart from its highly oxygenated nature it is recognized easily by the *trans*-fused cyclobutane bearing an allylic alcohol and an exocyclic methylene unit. Despite numerous efforts to bring this target down by total synthesis, providencin remains elusive. In particular the exceptionally high ring-strain of the macrocycle and the highly functionalized cyclobutane represent major challenges in an attempted synthesis.

Herein, a new route towards the cyclobutane sector of providencin was established, which was used to evaluate the application of RCAM in the context of macrocyclization. At the centerpiece, an Ir-catalyzed photosensitized [2+2] cycloaddition was harnessed to build the furanyl-cyclobutanol fragment. Stereochemical relay of a neighboring stereocenter onto the cyclobutane rendered this approach asymmetric. Furthermore, this handle served as the linchpin to open the thus constructed bicycle *via* oxidative cleavage. Subsequent functionalization of the furan with a highly electrophilic hypoiodite reagent opened entry into a 2-iodofuran paramount for coupling requisite handles for macrocyclization.

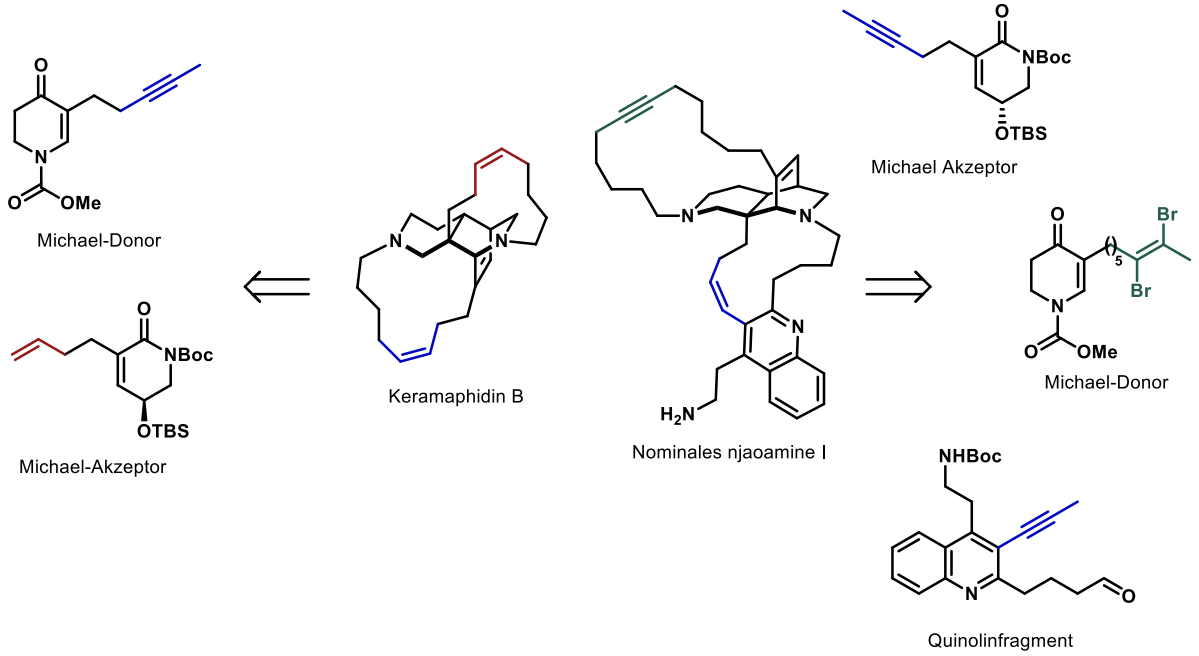


At this stage, Suzuki coupling was found to be optimal and an alkyne-bearing *E*-olefinic fragment could be introduced into the molecule. After accessing a viable diyne it became clear that the macrocycle was too strained to be forged by RCAM, because this reaction is largely entropically driven.

These setbacks notwithstanding, a Suzuki coupling could be carried out with potassium vinyltrifluoroborate giving rise to an intermediate, which is expected to be elaborated into providencin *via* a literature known route previously established in the group of Mulzer.

Inhalt:

Nach der Entdeckung von Manzamine A, einem macrocyclischen, marinen Alkaloid, schlugen Baldwin und Whitehead die Biosynthese einer gesamten Klasse an Naturstoffen vor, welche sich von teilweise reduzierten Alkylpyridin Derivaten ableiten. Obwohl Manzamine A um die Jahrtausendwende durch Totalsynthesen zugänglich gemacht wurde, blieben andere Alkaloide, welche im Biosyntheseweg deutlich früher angesiedelt sind, unerreicht. Diese Alkaloide der Ingenamine Familie wurden in dieser Arbeit durch eine Strategie basierend auf chemischer Logik anvisiert. Dazu wurde eine Michael/Michael-Kaskadenreaktion entwickelt, welche das tricyclische Zentralfragment diastereoselektiv aufbaut. Des Weiteren zeigte sich eine hohe Toleranz dieser Transformation gegenüber der Mitführung von unterschiedlichen Verknüpfungselementen zur Makrocyclisierung.

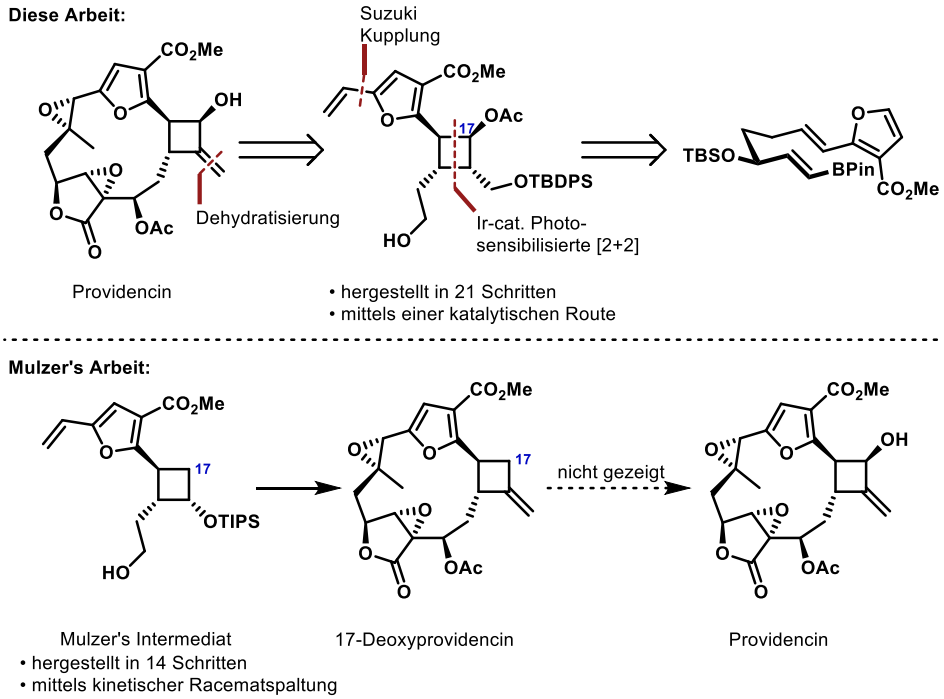


In der Totalsynthese von Keramaphidin B wurden zwei verschiedene Strategien zur Makrocyclisierung der beiden Ringe verfolgt. So wurden der 13-gliedrige Ring mittels ringschließender Alkinmetathese (RCAM) und der 11-gliedrige Makrocyclus mithilfe von ringschließender Olefinmetathese (RCM) cyclisiert. Während sich die RCAM als höchst zuverlässig herausstellte, musste die RCM sorgfältig optimiert werden. Letztlich konnte Keramaphidin B jedoch in 19 Schritten und 0.93% Gesamtausbeute synthetisiert werden.

Da das im 13-gliedrigen Makrocyclus von Njaoamine eingegliederte Quinolin ein weiteres Lewis-basisches Stickstoffatom aufweist, sahen wir von der Verwendung einer RCM zum Aufbau dieses Ringsystems ab. Nachdem *vic*-Dibromoalkene als hinreichende Alkinschutzgruppe befunden wurden, konnte nominales Njaoamine I durch den Einsatz zweier aufeinanderfolgender ringschließender Alkinmetathesen in 21 Schritten und 1.14% Gesamtausbeute synthestisiert werden. Die fehlzugeordnete Position des Alkins im 17-gliedrigen Makrocyclus konnte durch detaillierte NMR-Studien neu zugewiesen werden.

Die Furanocembranoide sind eine diverse Familie an Diterpenen. Eines der wohl interessantesten Moleküle dieser Klasse ist vermutich Providencin. Neben der hoch oxidierten Natur des Grundgerüsts sticht es durch ein *trans*-anneliertes Cyclobutan mit einem allylischen Alkohol und einer exocyclischen Methyleneinheit ins Auge. Trotz zahlreicher Versuche Providencin zu synthetisieren, wurde bisher keiner dieser Versuche erfolgreich abgeschlossen.

In dieser Arbeit wurde eine neue Route zum Cyclobutanfragment Providencins etabliert, welche genutzt werden konnte, um die Applikation von Alkinmetathese zum Ringschluss zu testen. Als Schlüsselschritt zur Herstellung des Furanyl-Cyclobutanolfragments fungierte eine Ir-katalysierte photosensibilisierte [2+2] Cycloaddition. Darin wurde ein benachbartes, enantioselektiv eingeführtes Stereozentrum genutzt, um die Stereoinformation auf das Cyclobutan zu übertragen und die Synthese somit asymmetrisch durchführen zu können. Des Weiteren konnte die so eingeführte funktionelle Gruppe als Knotenpunkt dienen, um den vorher aufgebauten Bicyclus oxidativ zu öffnen. Funktionalisierung des Furans mittels eines hoch elektrophilen Hypoiodit-Reagenzes eröffnete den Weg zu einem 2-Iodfuran, welches zentrale Bedeutung für die Kupplung anderer Fragmente trägt.



So konnte ein *E*-konfiguriertes Olefin mittels Suzuki Kupplung eingeführt werden, welches ein Alkin für eine mögliche RCAM mitträgt. Jedoch konnten die synthetisierten Diine nicht mittels der weitgehend entropie-getriebenen RCAM cyclisiert werden, was auf die große Ringspannung des Makrocyclus zurückgeführt wurde.

Trotz dieser Rückschläge konnte mithilfe einer Suzuki Kupplung mit Kaliumvinyl-trifluoroborate ein Intermediat erschlossen werden, welches durch die Verfolgung einer literaturbekannten Syntheseroute der Mulzer Gruppe Providencin ergeben sollte.

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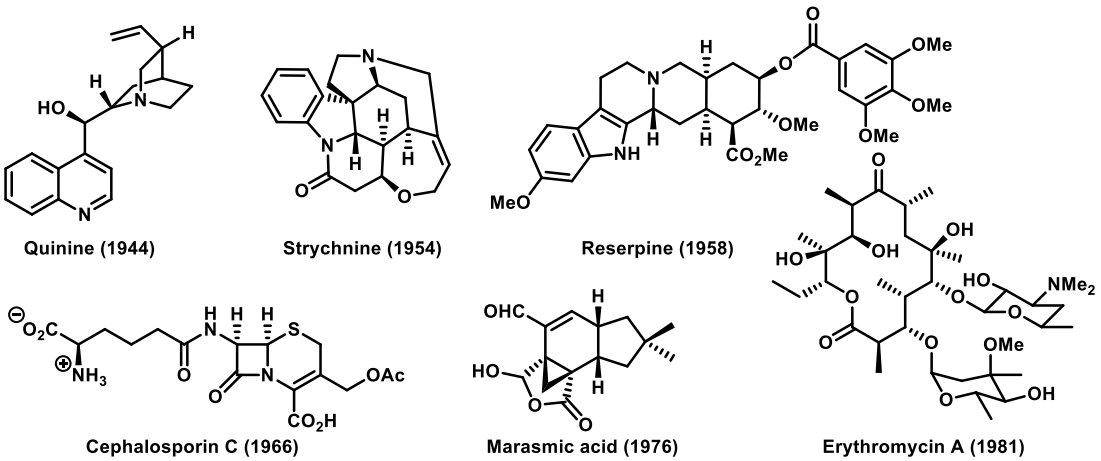
1. Introduction

The field of total synthesis emerged in 1828 by the serendipitous discovery of Wöhler, who was surprised to find that isocyanic acid and ammonia, under certain conditions, converted into urea.[1] Later in 1845 Kolbe disclosed the formation of acetic acid from its elements. In this publication he coined the term synthesis (dt. "Synthese") to describe the assembly of a chemical compound from other substances.[2] Numerous heroic efforts followed,[3,4] but it was not until the 20th century, that Robert B. Woodward elevated the field to new heights.

Woodward became assistant professor at Harvard University in 1937 at the age of 20. During a period when total synthesis primarily served for the structural elucidation of natural products, Woodward conquered the most complex molecular architectures of the time. His artistic syntheses featured the novel use of ring systems to control stereochemical elements, or unveil functional groups by ring-cleavage. His implementation of mechanistic rationale to predict reaction outcomes was unprecedented and in the case of pericyclic reactions led to the development of the Woodward-Hoffman rules, together with Roald Hoffmann (Chemistry Nobel Prize 1981). In 1965, R.B. Woodward received the chemistry Nobel Prize for the art of organic synthesis. Some of his group's most notable achievements are shown in Figure 1.1., with quinine as their first synthetic target in 1944,[5,6] strychnine (1954),[7] reserpine (1958),[8] cephalosporin C (1966),[9] marasmic acid (1976)[10] and erythromycin A[11–13] as their last in 1981.[14]

Figure 1.1. Selected syntheses by the Woodward group (1944-1981).

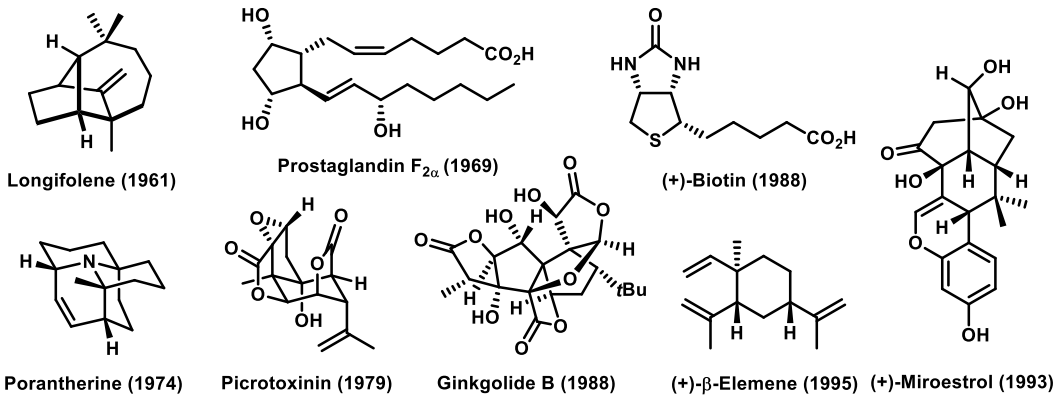


The advent of new analytical techniques throughout the 20th century (FT-NMR[15–17], X-Ray diffraction, etc.) was followed by an avalanche of new natural products and hence new synthetic targets. Simultaneously, however, a new player arrived on scene, who would change the field of total synthesis drastically.

In 1959, Elias J. Corey moved to Harvard University as a full professor at the age of 31. As such, he would build his research program on a logical approach towards total synthesis, paired with the development of methodologies that would fill voids in chemical space needed to engage new classes of molecules. The total synthesis of longifolene in 1961 was the first to be devised by using the principles of retrosynthetic analysis:[18] a concept which simplifies a target molecule in iterative fashion, until a commercially available starting material is identified.[19] In the following years, the concept enabled students to be taught the "logic of synthesis", changing the perception of the field from that of an art form into that of a precise science. Notably, the offspring from his synthetic ventures might even be more impressive. The development of various protecting groups (for example: silyl ethers,[20–22] allyl ether[23] or the MEM group[24]), new reagents such as pyridinium chlorochromate,[25] named reactions for novel functional group transformations as the Corey-Seebach,[26] Corey-Chaykovsky,[27] Corey-Fuchs,[28] or enantioselective methodologies as the Corey-Bakshi-Shibata-reduction[29,30] certainly changed the art of synthesis we practice today. Corey was awarded the 1990 Nobel Prize in chemistry for his development of the theory and methodology of organic synthesis.[14]

Selected total syntheses by the Corey group in the time from 1961 to 1993 are shown in Figure 1.2., starting with the racemic synthesis of longifolene (1961),[18] prostaglandin $F_{2\alpha}$ (1969),[31] porantherine (1974),[32] picrotoxinin (1979),[33] ginkgolide B (1988),[34] the enantioselective total synthesis of (+)-biotin (1988),[35] (+)-miroestrol (1993)[36] and (+)-β-elemene (1995)[37].

Figure 1.2. Selected syntheses by the Corey group (1961-1993).



Especially, the fall of ginkgolide B bears witness of the notion that a new era was entered, in which any given target molecule, regardless of its complexity, might be conquered by total synthesis.

Entering the 1990s, however, new molecular architectures were discovered that would, yet again, challenge chemists to achieve their synthesis. New concepts, as atom economy[38,39] arose, driving the development of new methodologies to reduce chemical waste, which would accumulate in a poorly planned syntheses. Additionally, organic chemists started to use their

expertise to probe daunting biological hypotheses interweaving the field with biology and medicine.[40,41]

In the 21st century, the field of total synthesis has reached an awe-inspiring level. More complex targets are being synthesized, with the aim to become more efficient in regards of step and redox economy.[42–46] Total synthesis has matured from an art form that targeted molecular architectures to show they could be synthesized, to an exact, practical science that strives for an ideal synthesis of any given compound, regardless of its complexity.[47–49]

Incidentally, it provides students with the most rigorous training. Individuals that pursue a natural product will eventually be presented with challenges that demand ingenuity, perseverance and the highest experimental skill. Furthermore, an organic chemist sees a certain beauty in complex molecules. Thus, a well-executed total synthesis may be compared with a painting in arts. The composition of different brushstrokes defines a painting, just like an original sequence of synthetic transformations defines a total synthesis.

2. A Unified Approach to Polycyclic Alkaloids of the Ingenamine Estate

2.1 Introduction

In 1986 manzamine A (**7**) a novel antitumor alkaloid was isolated from an Okinawan sponge (*Haliclona sp.*) in Japan.[50] The alkaloid's structure was unprecedented in nature and its biogenesis remained a mystery for half a decade. Eventually Baldwin and Whitehead proposed a biogenetic pathway that would not only rationalize the origin of manzamine A (**7**), but also predict a class of alkaloids belonging to its biosynthesis which would be isolated after this postulate was made.[51–54]

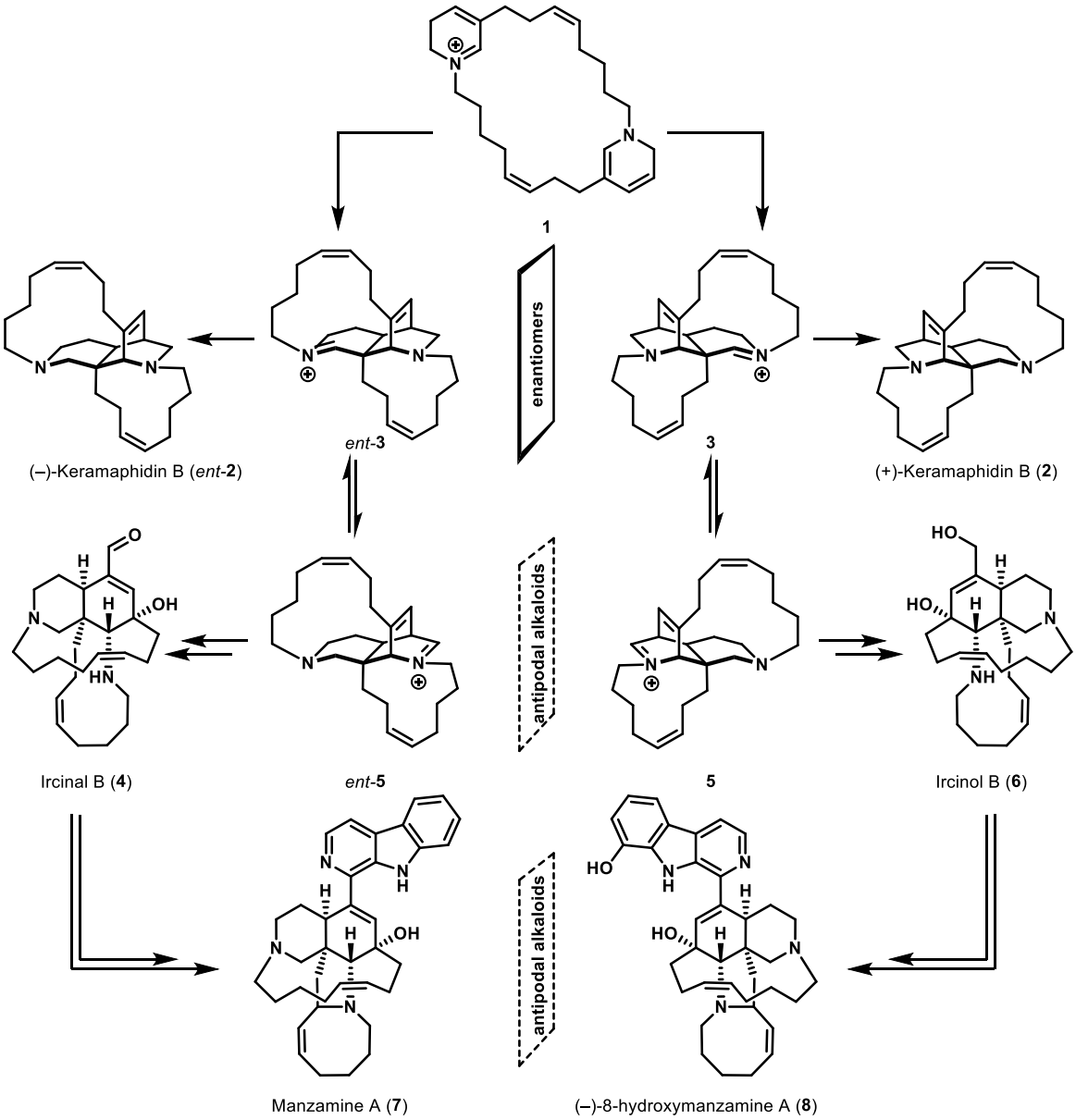
In their theorem (Figure 2.1), they propose a bis-dihydropyridine intermediate (**1**), which undergoes a transannular [4+2] cycloaddition forging a pentacyclic iminium ion (**3**). If this iminium species (**3**) is reduced, keramaphidin B (**2**) can be isolated. In case of a redox exchange within the molecule another iminium intermediate (**5**) is formed, which upon hydrolysis reveals the core structure of the ircinals, ircinols and manzamines among other natural products.

Interestingly, in this class of natural products, enantiomeric species have been isolated, depending on the synthesizing organism. This rare phenomenon was first observed, when ircinol A and B (**6**) were allegedly found to exhibit an antipodal configuration of the corresponding core structure, if compared to the ircinals and manzamines. Since then more alkaloids of this genus were found as enantiomeric congeners like keramaphidin B (**2**) or manzamine F.[55–57] While it is rare that both enantiomeric forms of a natural product can be isolated from the same organism, it is widely accepted that the synthesis of manzamine alkaloids is a result of a symbiotic relationship of these sponges with certain microorganisms. However, efforts to elucidate the biosynthesis of these alkaloids remains challenging, since identification and culturing of bacterial isolates from manzamine-producing sponges are challenging.[55]

Due to their intriguing chemical structure and biological activity, the family of manzamine natural products has received widespread attention in the chemical community over the years. This attention resulted in hallmark syntheses by Winkler *et al.* in 1998 and Martin *et al.* in 2002, each targeting manzamine A (**7**), ircinal A and ircinol A.[58,59] Furthermore these authors were able to provide evidence that ircinal A and ircinol A are in fact of the same enantiomeric series, contrary to what was originally proposed by Kobayashi *et al*.[53] While natural products that originate in the Baldwin-Whitehead pathway (e.g. keramaphidin B (**2**)) had been targets of biomimetic studies by Baldwin *et al*.[60,61] early on, all purely synthetic approaches failed to provide any of these compounds, until a foray by Fürstner *et al.* ultimately provided (nominal)

xestocyclamine A (**11**).[62] The isolation and structure of some of these alkaloids is discussed in the following chapter.

Figure 2.1. Illustration of the Baldwin-Whitehead postulate in the context of the biosynthesis of keramaphidin B (**2**), ircinal B (**4**), ircinol B (**6**), manzamine A (**7**) and (−)-8-hydroxymanzamine A (**8**).



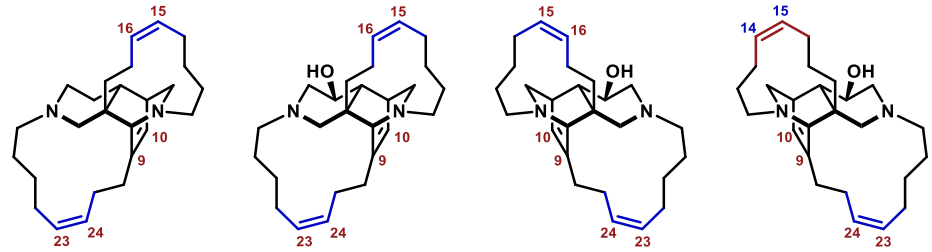
2.1.1 Isolation and Structure

With the aim of investigating biogenetic siblings of ircinals A and B (**4**), Kobayashi *et al.* successfully isolated keramaphidin B (**2**) (Scheme 2.2).[51,54] Methanol extracts of *Amphimedon sp.*, collected in the waters of Kerama Island in Okinawa (Japan), were partitioned between ethyl acetate and water. The ethyl acetate soluble material was subjected to chromatography furnishing keramaphidin B (**2**) in 0.003% yield (referring to wet weight of the sponge). Besides **2**, the literature known alkaloids ircinal A and B (**6**), as well as manzamines

A (**7**), B, G and H were isolated as minor components. Structural elucidation was initiated *via* extensive 2D-NMR studies, unveiling a 1,4-etheno-bridged 2,7-diazadecalin core and one unsaturation within the 11- and 13-membered macrocycles each. The two disubstituted $\Delta^{15(16)}$ and $\Delta^{23(24)}$ double bonds were assigned as *Z*-configured. These features were confirmed by single crystal X-Ray analysis of a suitable sample grown in acetonitrile, leading to the structure of **2** shown in Figure 2.2. Keramaphidin B showed cytotoxic activity against P388 murine leukemia and KB human epidermoid carcinoma cells with IC_{50}-values in the low µg/mL regime.

While isolated in the presence of the ircinals and manzamines A (**7**), B, G and H, Kobayashi *et al.* reported keramaphidin B (**2**) as a racemate. Later, however, they discovered that despite the crystals grown for X-ray studies being racemic, the mother liquor itself seemed to contain one of the enantiomers in excess.

Figure 2.2. Selected pentacyclic alkaloids isolated from *Amphimedon sp.* (keramaphidin B), *Xestospongia ingens* (keramaphidin B and ingenamine) and *Xestospongia sp.* (xestocyclamine A) thought to derive from similar pathways.



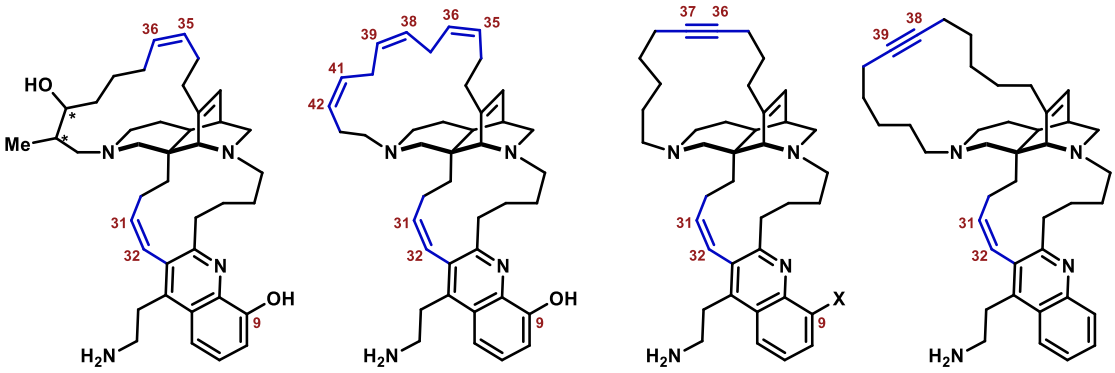
This supposition was then further investigated and chiral phase HPLC analysis revealed that the mother liquor was indeed a 20:1 mixture of (+)-keramaphidin B (major enantiomer, **2**) and (−)-keramaphidin B (minor enantiomer, *ent*-**2**).[63] Interestingly, once the absolute configuration of (+)-keramaphidin B (**2**) was determined *via* derivatization to the corresponding Mosher esters, it became clear that (+)-**2** had the opposite absolute configuration to manzamine A (**7**). This conclusion was supported by the isolation of enantiopure (+)-keramaphidin B (**2**) from *Xestospongia ingens* collected by Andersen *et al.* in Papua New Guinea.[56]

Besides (+)-**2**, a closely related family of natural products was described, namely the ingenamine alkaloids. Ingenamine (**9**) itself only differs from **2** by the presence of an alcohol in the non-bridged section of the tetracyclic core and represents the first example of the second class of marine alkaloids foreseen by the Baldwin-Whitehead proposal, when it was first isolated in a bioassay guided fractionation approach by Andersen *et al.* in 1994.[64] As with keramaphidin B (**2**), it is in the enantiomeric series to manzamine A (**7**), as are all other members of the ingenamine family. **2** showed cytotoxic activity *in vitro* against murine leukemia P388 (ED_{50} = 1 µg/mL).

Nominal xestocyclamine A (**11**), isolated from *Xestospongia sp.* in Papua New Guinea, was reported by Crews *et al.* in 1993.[65] A year after disclosing the first structural proposition, the team revised the initial structure upon extensive 1D- and 2D-NMR analysis to **11**, bearing a $\Delta^{14(15)}$ unsaturation in the 11-membered macrocycle and therefore making it a positional isomer of ingenamine (**9**).[66] Moreover, **11** is levorotatory, suggesting it might be antipodal to the ingenamines and (+)-keramaphidin B (**2**). In a total synthesis effort targeting (nominal) xestocyclamine A (**11**), Fürstner *et al.* shed light on these assumptions and provided evidence that **11** is not a positional isomer of ingenamine (**9**), but the true enantiomer **10**.[62] While it is moderately potent against protein kinase C (IC_{50} = 4 µg/mL), it also showed activity in a whole cell IL-1 release assay with an IC_{50} of 1 µM. As it appears to be inactive against other cancer-relevant targets, as Protein Tyrosine Kinase (PTK) and Inosine Monophosphate Dehydrogenase (IMPDH), it might be selective.[65]

Since these breakthrough discoveries in the 1990s, a plethora of related natural products have been added to the family of these alkaloids.[67,68] Isolated from the extracts of *Reniera sp.* and *Neopetrosia sp.* collected off the Tanzania coast line, the njaoamines display a close structural relationship to ingenamine (**9**) and keramaphidin B (**2**). Sharing the same tricyclic core, they mainly differ in size and degree of unsaturation of the macrocycles as well as the tryptamine-derived quinoline moiety attached to the 13-membered ring. Furthermore, a variable oxidation pattern can be observed on the quinoline nucleus. Their absolute configuration was assumed to be analogous to ingenamine (**9**) and (+)-keramaphidin B (**2**), due to their close biosynthetic relationship. In the light of previous work,[62] a total synthesis of these natural products would provide compelling evidence for their absolute configuration [69–71]

Figure 2.3. Selected members of the njaoamine family isolated from *Reniera sp.* in Tanzania.



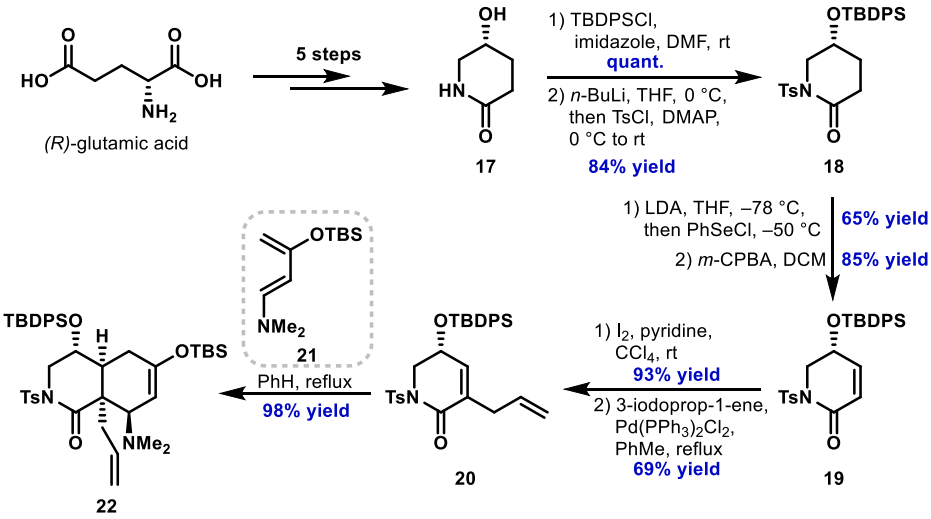
This family of natural products shows interesting anticancer activity; for example njaoamine I (**16**) was tested against MDA-MB-231 breast-, HT-29 colon- and NSLC A-549 lung-cancer cell lines showing GI_{50}-values in the micromolar range. Additionally, **16** was tested in an enzymatic topoisomerase 1 (Top1) assay with human recombinant enzyme, where even at the

highest concentration tested (100 µM) no inhibition was induced. Neither inhibition of PD-1 (Programmed Cell Death Protein 1) nor the interaction with its natural ligand PD-L1 could be observed even at the highest concentration tested (100 µM). These results notwithstanding, the njaoamines are an important sub-class within the family of ingenamine alkaloids, diversifying both the chemical space and biological activity profile of these alkaloids.

2.1.2 Literature Review

In the following chapter synthetic approaches towards alkaloids of the ingenamine estate are reviewed and the current state-of-the-art in the total synthesis of these intriguing targets is discussed.

As the first total syntheses of manzamine A (**7**), ircinal A and (*ent*-)ircinol A were published around the turn of the millennium by Winkler and Martin *et al.* respectively,[58,59] the Danishefsky group reported on their quest targeting nominal xestocyclamine A (**11**).[72] In a forward sense, Danishefsky's approach commences from literature known oxopiperidine **17**, which was prepared in 5 steps from *(R)*-glutamic acid (Scheme 2.1).[73] Protection of the stereodefined alcohol as a TBDPS-ether and *N*-tosylation of the lactam gave **18** in good yield. Conversion to the α,β-unsaturated analogue **19** was achieved by elimination of the preformed selenoxide upon treatment with *m*-CPBA in 55% yield over two steps.

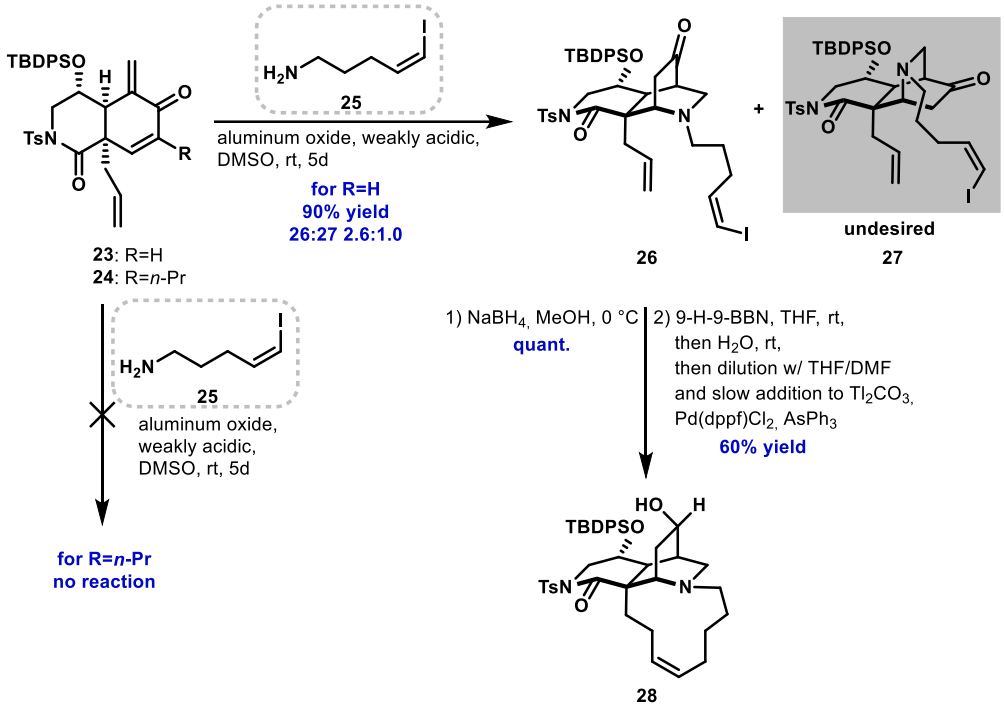


Scheme 2.1. Bicycle formation in Danishefsky's approach towards xestocylamine A (**11**), starting from *(R)*-glutamic acid.[72]

Next the α-position of lactam **19** was functionalized with iodine and pyridine in carbon tetrachloride, giving rise to the α-iodo lactam, which could be coupled with 3-iodo-prop-1-ene providing **20**. To access the 1,4-etheno-bridged 2,7-diazadecalin, their strategy relied on a Diels-Alder reaction of dienophile **20** with Rawal-Kozmin diene[74–76] **21**, forging bicycle **22** and setting three important stereocentres, as the reaction proceeded with *endo*-selectivity. Notably other dienes were not reactive enough to engage **20** in a [4+2]-cycloaddition.[72] After a series

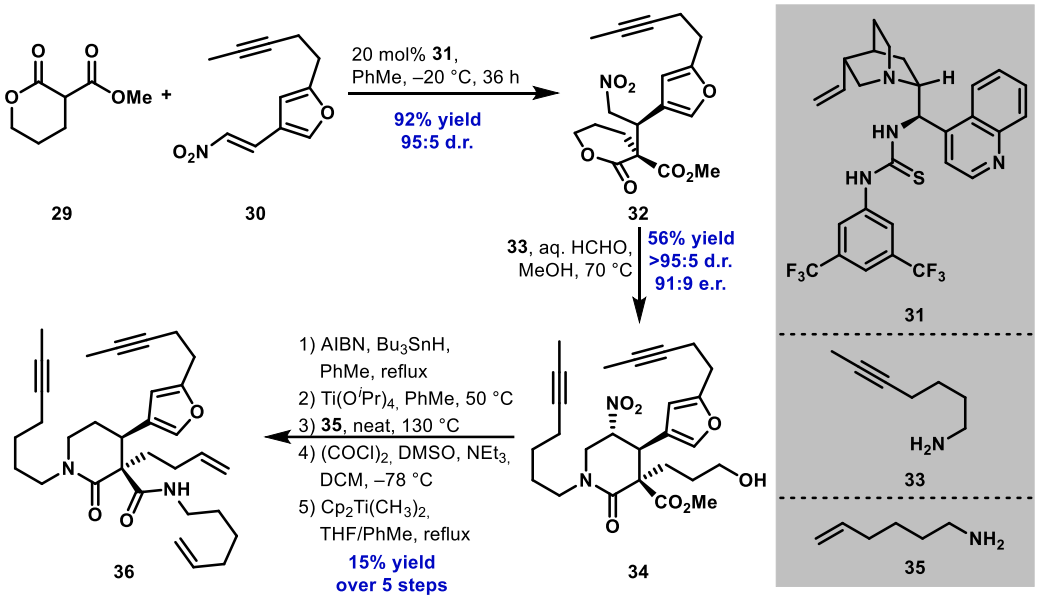
of functional group manipulations on the Diels-Alder adduct **22**, dienone **23** was susceptible to a double 1,4-addition with primary amine **25**, releasing tricycle **26**, albeit with poor facial selectivity. For ring-closure of the 11-membered macrocycle they harnessed *boron*-alkyl Suzuki methodology.[72]

When substitution was installed to give Michael acceptor **24**, the Michael/Michael cascade did not proceed, probably due to an unfavorable 1,3-allylic interaction in the primary addition product. Additional destabilizing interactions between the propyl- and either the iodoalkenyl- or allyl-group cannot be ruled out.[77] To date, no additional reports by the Danishefsky group on progress towards (nominal) xestocyclamine A (**11**) have been published.



Scheme 2.2. Michael/Michael cascade and alkyl-Suzuki coupling forging the 11-membered macrocycle.[72,77]

Later, both Fukuyama *et al.*[78] and Dixon *et al.*[79] published their approaches towards manzamine natural products, with the Dixon group also showing interest in biogenetically related compounds.[80] In 2016, Dixon *et al.* disclosed their approach towards keramaphidin B (**2**) (Scheme 2.3).[81]



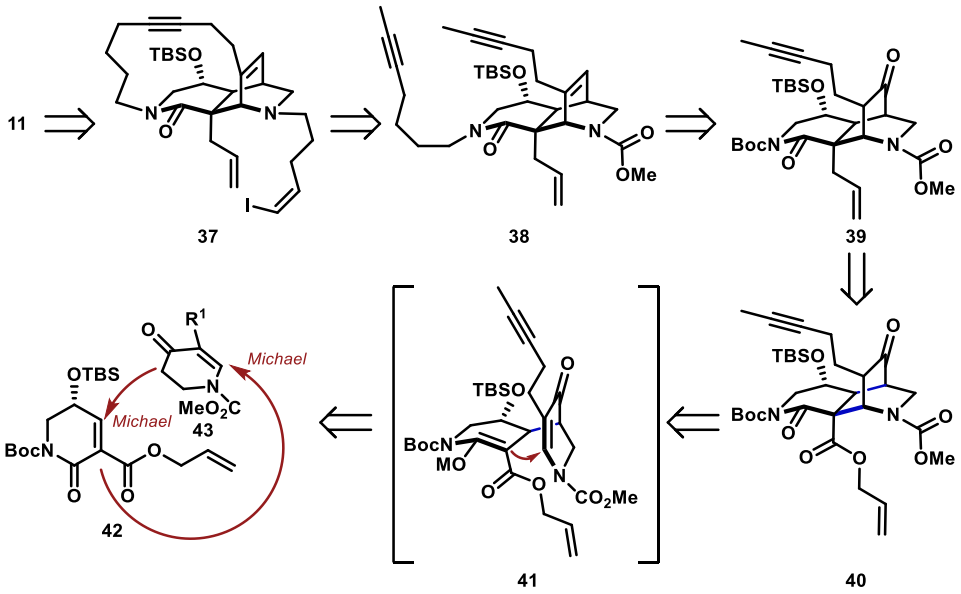
Scheme 2.3. Summary of Dixon's approach towards keramaphidin B (**2**).[81]

δ-Valerolactone **29** and furanyl nitroolefin **30**, both readily synthesized on gram-scale, reacted in an organocatalyzed Michael addition with cinchonine-derived bifunctional thiourea **31**. This transformation sets two important stereocentres, necessary to selectively build the 2,7-diazadecalin core later. Treating lactone **32** with hept-5-yn-1-amine **33** and formaldehyde in boiling methanol furnished lactam **34** in moderate yield as a single diastereomer. Albeit essential for previous steps, the nitro-group in lactam **34** had to be cleaved off in order to generate the δ-unsubstituted oxopiperidine. This manipulation was achieved in good yield by usage of AIBN and tributyltin hydride in refluxing toluene. In order to install handles for an olefin metathesis, lactonization with titanium tetraisopropoxide, lactone opening with hex-5-en-1-amine **35**, Swern oxidation of the resulting primary alcohol and olefination employing Petasis reagent were carried out to produce the bis-alkene **36** in 15% yield over 5 steps. Despite having all the necessary handles for an olefin and alkyne metathesis installed, no additional results were disclosed from this approach.[81]

A key challenge in synthesizing alkaloids of the ingenamine estate, appears to be generating the tricyclic core in a way that tolerates the requisite synthetic handles for macrocyclisation. In summary, Danishefsky's approach provides a powerful macrocyclization strategy for the 11-membered ring; yet shortcomings in permitting necessary substitution in their Diels-Alder/double Michael strategy prevented them from installing the appropriate handles for further elaboration. The same applies to Dixon's approach: although their synthesis installs the corresponding alkyne and olefin linchpins for upcoming macrocyclization events, the approach falls short at generating the tricyclic core motif of keramaphidin B (**2**).[81]

Considering our group's background in both olefin and alkyne metathesis, the ingenamine alkaloids present a prime target to highlight our macrocyclization methodology. This fact

notwithstanding, a new strategy towards the synthesis of the 1,4-etheno-bridged 2,7-diazadecalin core had to be developed, which would allow for necessary functionalities to be installed. A first generation total synthesis of xestocyclamine A by our group is discussed in the following section.[62]

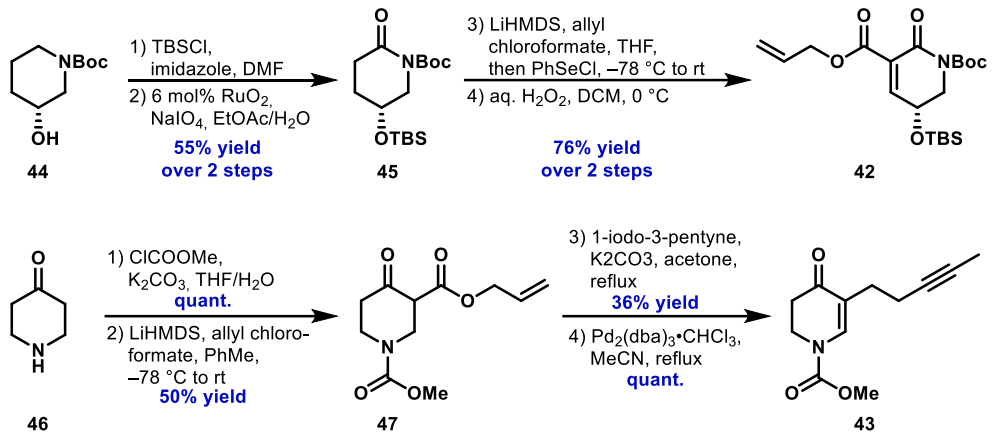


Scheme 2.4. Retrosynthetic analysis of a first-generation approach towards nominal Xestocyclamine A (**11**) by Fürstner *et al.*[62]

The synthetic blueprint relies partially on literature precedent by Danishefsky *et al.*[72], where the *B*-alkyl Suzuki methodology was used to forge the 11-membered macrocycle. Since RCAM is orthogonal to all kinds of double bonds, these strategies would perfectly complement each other. The handles for these transformations would ideally be preinstalled before the tricyclic core is assembled. This boundary condition cannot be met *via* [4+2] cycloaddition as outlined above. Ultimately, the chosen methodology needed to set four consecutive stereocentres, ideally in an enantioselective fashion.

Regarding the construction of the tricyclic core, a Michael/Michael cascade was determined feasible, as a close literature precedent by Passarella *et al.*[82] existed. In general, sequential 1,4-additions represent a powerful tool for generating complex structures with high efficiency regarding stereoselectivity.[83–85] The stereocenter included in Michael acceptor **42** was anticipated to steer the stereochemical course of the cascade reaction, because the tricycle **40** is found in its thermodynamically most favorable conformation, when the silyl ether is oriented in the equatorial position. Pd-catalyzed decarboxylative allylation[86,87] on intermediate **40** was expected to deliver the allyl-substituent to the core scaffold with stereoretention. Reduction of the ketone **39** and dehydration of the resulting alcohol was thought to deliver the unsaturation within the bridged bicycle. Next RCAM on diyne **38** would close the 13-membered ring, and the iodo-alkene of **37** would be installed via reductive amination after carbamate cleavage.

Finally *B*-alkyl Suzuki-cross coupling, would forge the *Z*-olefin within the 11-membered macrocycle and reduction of the resulting lactam would give rise to nominal xestocyclamine A (**11**).[62,66]



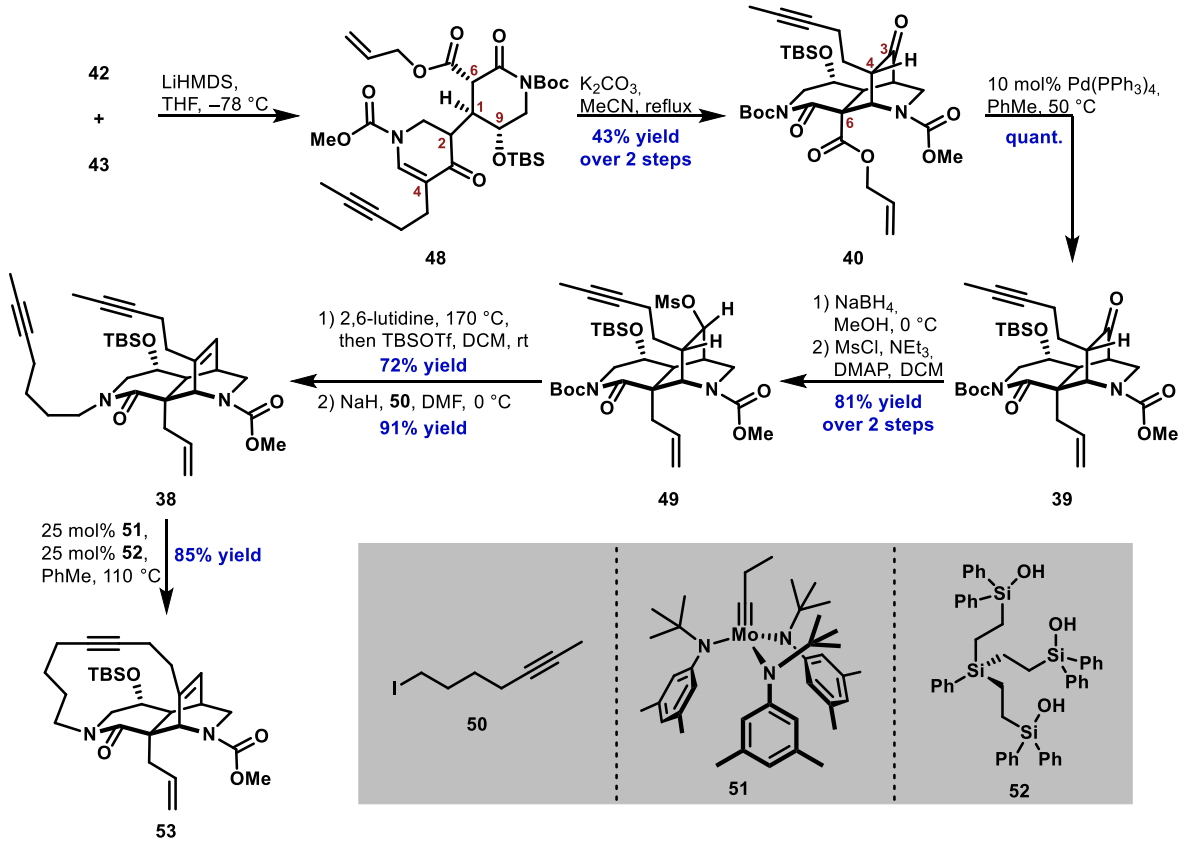
Scheme 2.5. Syntheses of Michael acceptor **42** and Michael donor **43**.[62]

As the literature-known route towards Michael acceptor **42** would require nine steps from (*R*)-glutamic acid, a new route was envisaged.[73,88] This route commences with *O*-silylation of commercially available enantioenriched alcohol **44** and subsequent regioselective C-H oxidation with catalytic RuO_2 using stoichiometric amounts of $NaIO_4$ as the terminal oxidant, furnishing piperidinone **45** in 55% yield over two steps with essentially perfect preservation of stereochemistry (>99% ee). Subsequent addition of allyl chloroformate and phenylselenyl chloride to the lithium enolate of **45**, generated with excess LiHMDS, gave rise to a selenide intermediate. Treatment with H_2O_2 triggered elimination of the *in situ* generated selenoxide, producing the Michael acceptor **42**.

For the preparation of the prime Michael donor **43**, 4-piperidone **46** was *N*-protected as the methyl carbamate and acylated *via* a lithium enolate with allyl chloroformate. Next the β-ketoester **47** was alkylated with 1-iodo-3-pentyne, employing potassium carbonate in acetone at reflux. The relatively low yield of the alkylation, was attributed to decomposition upon ring-opening of the enolate with expulsion of the carbamate unit. Finally, **43** was obtained via a Pd-catalyzed decarboxylative dehydrogenation, which proceeded in excellent yield and regioselectivity. Notably, this methodology, first pioneered by Tsuji *et al.*,[89,90] provided the best results, when no additional ligand was present.

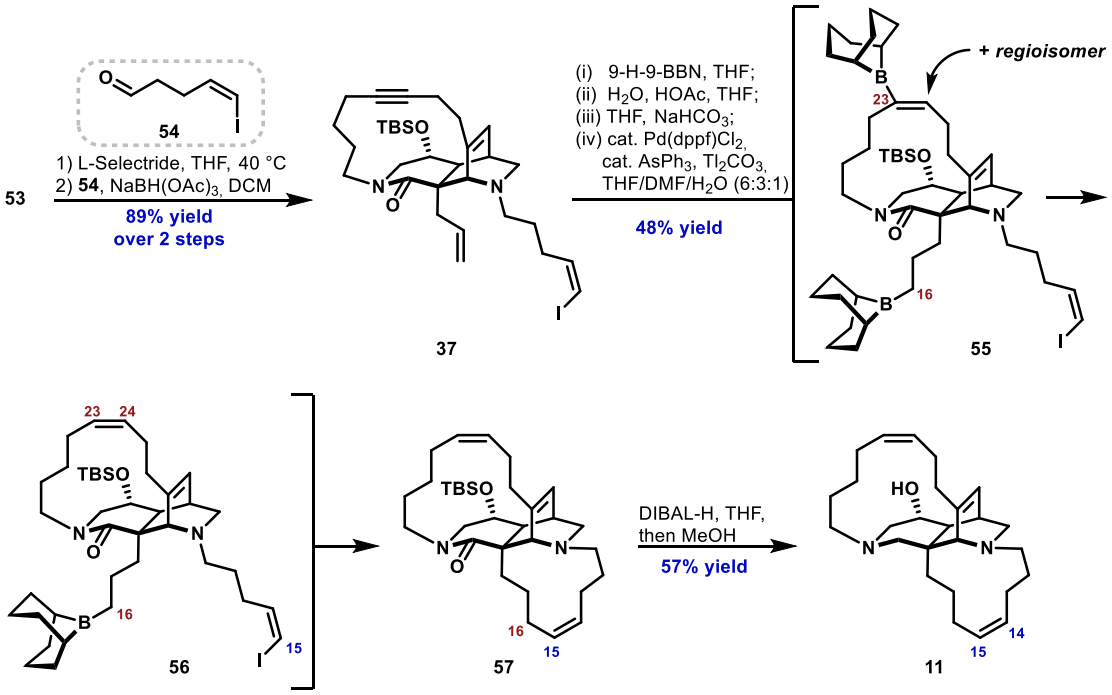
With both Michael acceptor **42** and donor **43** available at gram scale, the cascade reaction itself was examined. In presence of LiHMDS, the lithium-derived enolate of the 1,3-dicarbonyl unit turned out as a formidable leaving group, causing the second step of the cascade to be reversible. While the stereocenter generated at C-1 of the Michael adduct **48** was set with excellent stereocontrol, the C-2 stereochemistry on **48** could not be influenced. Once potassium carbonate was identified as an appropriate base for mediating the intramolecular Michael

addition in a second pot and the C-2 isomeric product could be separated at this point, this two-step approach was deemed as an efficient entry into the tricyclic core of **40**.



Scheme 2.6. Michael/Michael cascade, elimination and RCAM sequence.[62]

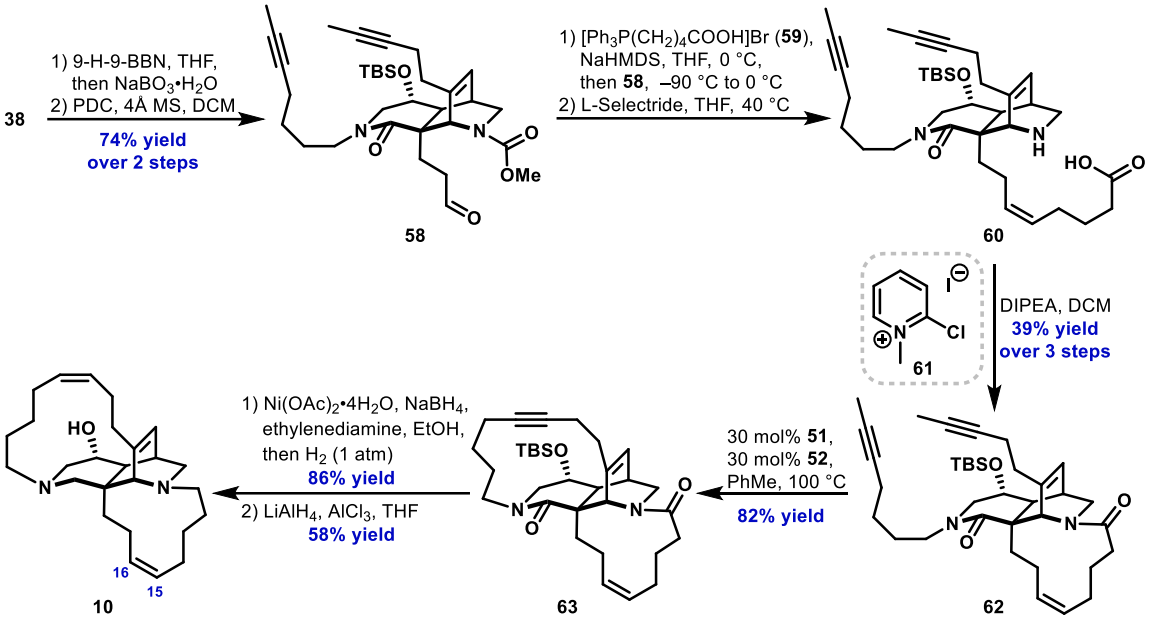
With all critical stereocentres on the core of xestocyclamine A (**11**) established, the stage was set for the installation of the allyl-substituent on C-6 of **40**. This transformation was accomplished under Pd catalysis in toluene at slightly elevated temperature. The observation of the formation of a single diastereomer in perfect yield underlines the rigidity of the built-up core structure. Ketone **39** was then reduced stereoselectively with sodium borohydride and the resulting alcohol was converted to mesylate **49**. After extensive experimentation it was found that reaction of mesylate **49** at 170 °C in neat 2,6-lutidine, furnished the desired olefin with concomitant *N*-Boc and partial TBS cleavage. In any way, TBS-reprotection of the secondary alcohol after the elimination proceeded smoothly using TBSOTf at 0 °C. The lactam was alkylated with 7-iodo-2-heptyne **50** affording diyne **38**. Next, ring closing alkyne metathesis was performed utilizing the two-component catalyst system of Mo complex **51** and trisilanol ligand **52**.[91,92] The 13-membered macrocyclic product **53** could be isolated in good yield after ten minutes reaction time. With the structure of cycloalkyne **53** confirmed by single crystal X-ray diffraction, substrate **37** had to be prepared for the following alkyl Suzuki macrocyclization (Scheme 2.7). Therefore the methyl carbamate was cleaved by means of L-Selectride and the free amine subjected to reductive amination conditions with aldehyde **54**.



Scheme 2.7. Total synthesis endgame for nominal xestocyclamine A (**11**) by Fürstner *et al.*[62]

Differing to the model study by Danishefsky *et al.*[72] compound **37** bears an additional triple-bond and an internal trisubstituted olefin. With an excess of 9-H-9-BBN, hydroboration of the terminal olefin as well as of the cycloalkyne was observed, while the trisubstituted alkene remained intact. Treatment of this intermediate **55** with dilute acetic acid resulted in protonation of the alkenylborane furnishing the $\Delta^{23(24)}$ *Z*-olefin **56**.[93] Since the alkyl borane and the *Z*-iodoalkene moieties were unaffected, subsequent quench of residual acid with sodium bicarbonate and slow addition of the resulting mixture into a solution of catalytic $Pd(dppf)Cl_2$, $AsPh_3$ and Tl_2CO_3 in $THF/DMF/H_2O$ initiated the ring-closing alkyl Suzuki reaction. This semireduction/alkyl Suzuki sequence furnished diene **57** as the bis-*Z*-isomer in a reproducible manner. Finally lactam reduction and silyl cleavage were effected by DIBAL-H in THF, revealing nominal xestocyclamine A (**11**).[62]

With an indisputable proof of the constitution and stereochemistry of the synthetic material, a structural misassignment was recognized, since the NMR data of neither the free base nor the **11** dihydrochloride salt aligned with that reported in the isolation paper.[66] Revisiting the biosynthesis of xestocyclamine A in the light of ingenamine (**9**) and keramaphidin B (**2**), an error in the assignment of the position of $\Delta^{14(15)}$-olefin seemed most likely. However, to ultimately proof this theory, a synthetic sample of the isomeric $\Delta^{15(16)}$-olefinic material was required.



Scheme 2.8. Total synthesis endgame for revised xestocyclamine A (**10**).[62]

In pursuance of actual xestocyclamine A (**10**), diyne **38** was chosen as an appropriate entry point to divert the synthesis (Scheme 2.8). Initially, chemoselective hydroboration of the terminal alkene was achieved with 9-H-9-BBN in THF followed by oxidative work-up and oxidation of the resulting alcohol provided aldehyde **58** in good yield.[94] Wittig olefination, employing the commercially available phosphonium salt **59**, revealed the $\Delta^{15(16)}$-*Z*-olefin and cleavage of the *N*-carbamate furnished cyclization precursor **60**. Mukaiyama's reagent **61** then mediated the macrolactamization event to give diyne **62** in 39% yield over three steps.[95,96] The subsequent RCAM readily provided pentacycle **63**. Finally nickel boride effected the semireduction of the alkyne and *in situ* generated AlH_3 reduced both amides, while cleaving the silyl ether.[97] With an X-ray structure of synthetic (*ent*)-ingenamine **10** leaving no doubt about its structural integrity, the NMR spectra in [D_4]-MeOH were found to match the freebase isolated ingenamine.[62,98] With the structure of xestocyclamine A (**11**) resolved, the levorotatory rotation of synthetic and natural xestocyclamine A (**10**) led to the conclusion that xestocyclamine A (**10**) is the enantiomer of ingenamine (**9**).[62]

Consequently a second-generation synthesis of ingenamine (**9**) and its sibling keramaphidin B (**2**) as early intermediates in the Baldwin-Whitehead pathway would shed more light on the natural products Baldwin and Whitehead proposed almost 30 years ago.[51] If successful, the underlying strategy might also give access to the njaoamines as new biologically active members of this family. With these goals in mind, ingenamine (**9**), keramaphidin B (**2**) and (nominal) njaoamine I (**16**) were chosen as targets for an adapted approach.

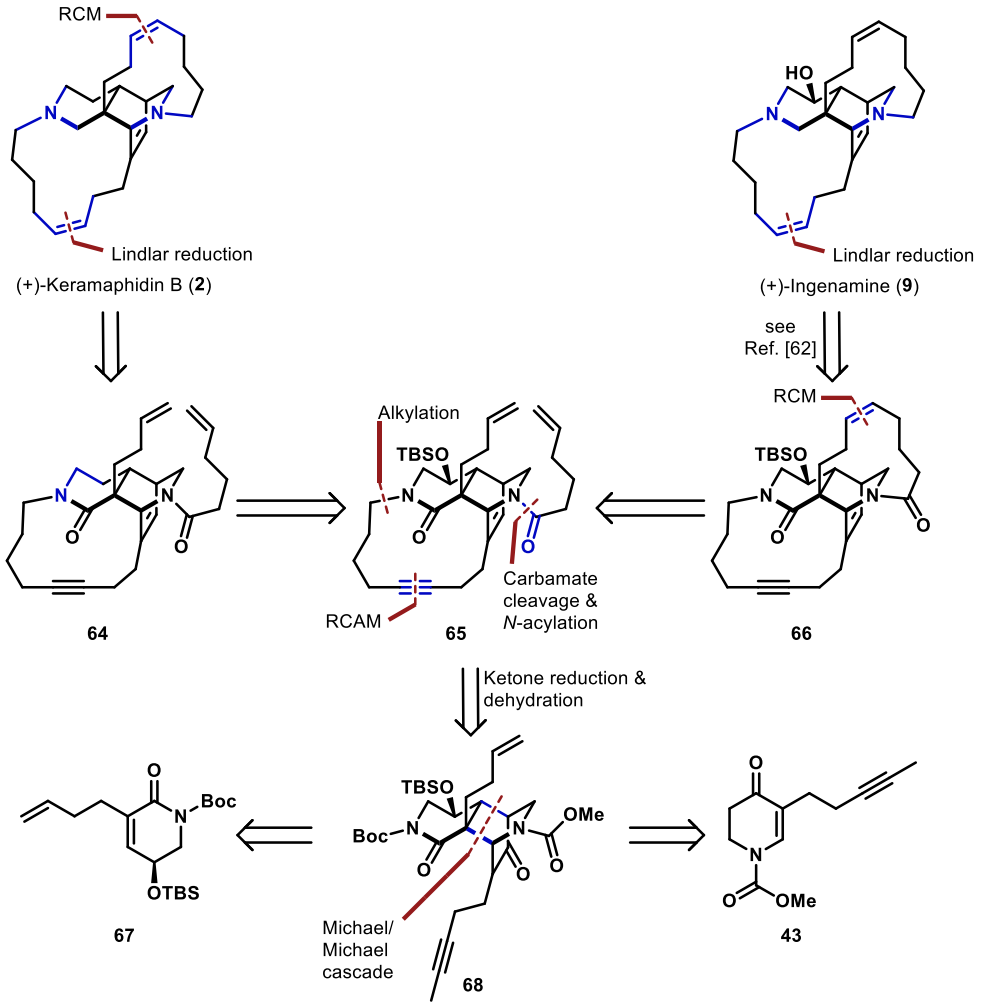
2.2 Second Generation Approach towards Ingenamine and Total Synthesis of Keramaphidin B

The retrosynthetic analysis was devised in collaboration with Dr. Zhanchao Meng.

At the outset of the second-generation approach towards (+)-ingenamine (**9**) and (+)-keramaphidin B (**2**), a few chemical, tactical and strategic issues from the first-generation synthesis had to be addressed. First, both Michael donor **43** and Michael acceptor **42** were prepared on multigram scale, however, their syntheses proceeded only in moderate yields. Secondly, a redesign of the Michael acceptor **42** was deemed necessary, since the resulting enolate formed after the first Michael addition step **41** was too stable, rendering the second Michael addition step reversible. Thirdly, in the light of biological testing, an entry into the correct enantiomeric series would be desirable. Penultimately, flexible introduction of substituents, other than allyl, at the C6-bridgehead would drastically improve the scope of the synthesis. Finally, a larger set of chemically orthogonal macrocyclization strategies would render the synthetic blueprint more comprehensive.

2.2.1 Retrosynthetic Analysis

With these caveats in mind, we set out to tackle as many of these problems as possible, while preserving the reliability of the successful strategic transformations in the first-generation synthesis.[62] As the *B*-alkyl Suzuki reaction would require a vinyl handle at the C6-bridgehead, in order to install the $\Delta^{15(16)}$-olefin, a different cyclization strategy was preferable. Albeit not strictly orthogonal to alkynes, olefin metathesis has been successfully applied in macrocyclizations to form 11-membered rings.[99–101] Additionally, the requisite alkene moiety could be easily installed on the Michael acceptor **67** *via* alkylation. The absence of a 1,3-dicarbonyl unit in **67** would in turn decrease the stabilization of the enolate after the first 1,4-addition step. This small detail, in combination with a well matched base, was envisioned to render the Michael/Michael sequence into a true cascade reaction (Scheme 2.9). The deoxygenated core of keramaphidin B (**2**) was anticipated to arise from a dehydration of the masked alcohol in **65** and subsequent reduction of the thus formed enamide, diverting the synthesis between keramaphidin B (**2**) and ingenamine (**9**) at this stage. In general, keramaphidin B (**2**) would be accessed *via* reduction of a bis-amide in combination with RCM on the deoxygenated core **64**. Silyl cleavage and dehydration followed by reduction of the resulting enamide, traces back to the ingenamine core of **65**. *En route* to ingenamine (**9**) this intermediate would be subjected to RCM intercepting the pentacycle accessed in our first-generation approach, therefore completing a formal synthesis of the target. The central intermediate **65** would be formed *via N*-acylation after carbamate cleavage, following the RCAM of the diyne substrate arising from *N*-alkylation of the amide, which in turn stems from the previously applied elimination sequence exercised on ketone **68**. This compound leads back to the requisite Michael acceptor **67** and donor **43**, which can be merged in a 1,4-addition cascade.



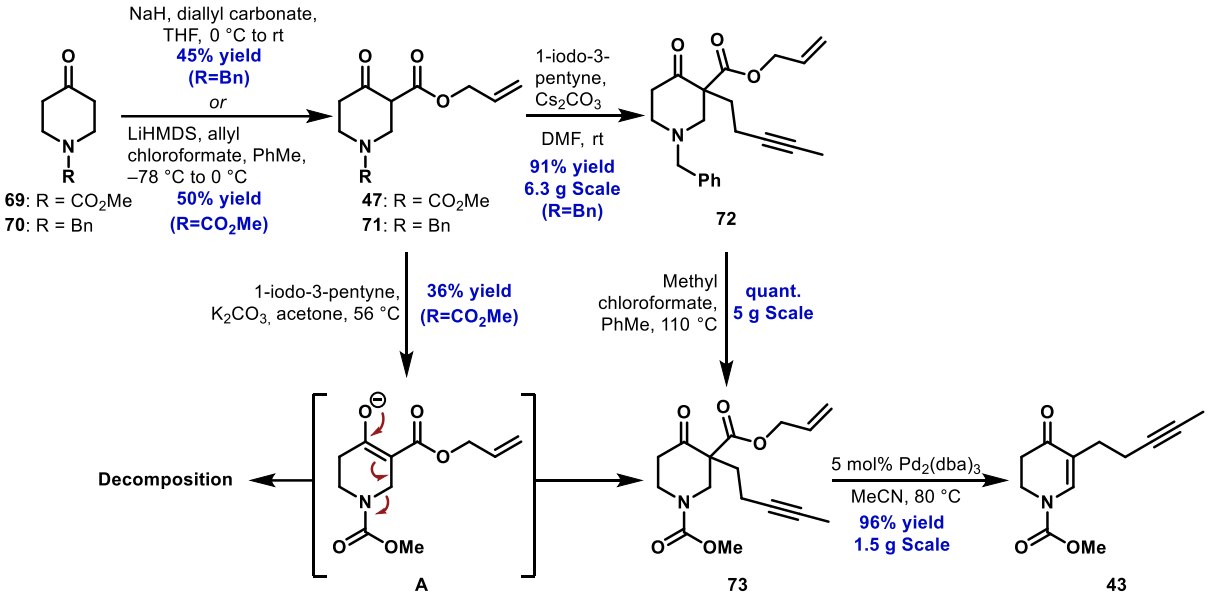
Scheme 2.9. Retrosynthetic analysis of keramaphidin B (**2**) and ingenamine (**9**).

2.2.2 Synthesis of the Michael Donor

In the first-generation approach towards Michael donor **43**, the *N*-methylcarbamate group was preinstalled on piperidone **46**. Although this route ultimately provided building block **43** on scale, this approach was found to be suboptimal, since the alkylation of β-ketoester **47** proceeded in rather low yield (Scheme 2.10).

It was envisaged that **A** could expel the *N*-residue adjacent to the enolate, for the leaving group properties of this terminus. If this were true, a more electron rich *N*-protecting group (e.g. benzyl) might alleviate this problem. The assumption was tested, when commercially available *N*-benzyl protected piperidone **70** was transformed into β-ketoester **71** *via* a literature known procedure.[102] Gratifyingly, the alkylation with 1-iodo-3-pentyne and caesium carbonate as base now proceeded in high yields on scale. The *N*-benzyl group was swiftly exchanged for the previously used methyl carbamate by treatment with methyl chloroformate in refluxing toluene, taking advantage of the electron-rich nature of the benzyl substituted nitrogen atom. The final palladium-catalyzed decarboxylative dehydrogenation furnished the

target molecule **43** with excellent regioselectivity for the internal double bond and very good yield.

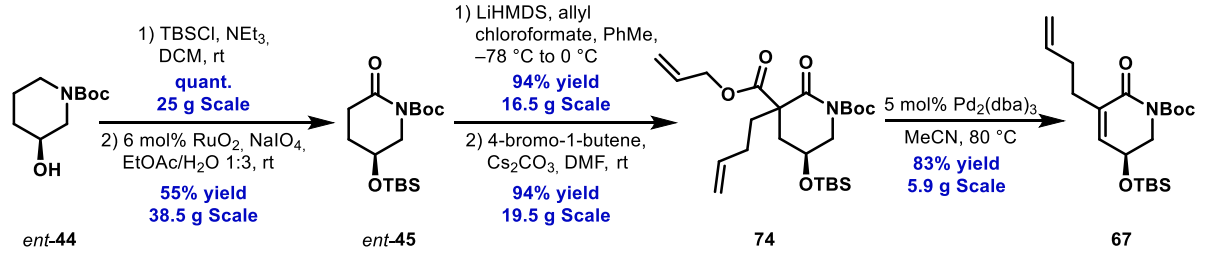


Scheme 2.10. Revised synthesis of Michael donor **43**.[62]

With this revised sequence, building blocks (and potential analogues) of **43** can be accessed in an efficient manner with great flexibility regarding the side chain. The route has proven to be reliable and scalable on different systems (*vide infra*).

2.2.3 Synthesis of the Michael Acceptor

As in the previous approach, the synthesis of Michael acceptor **67** starts with commercially available enantiopure *N*-Boc hydroxypiperidine *ent*-**44**, which after *O*-silylation and regioselective C-H oxidation with catalytic RuO_2 and $NaIO_4$ gave siloxypiperidone **45** on decagram scale.[103] As this approach targets alkaloids of the dextrorotatory ingenamine estate, the enantiomeric entry to our previous approach was chosen.[62] Siloxypiperidone *ent*-**45** was acylated with allyl chloroformate and the resulting 1,3-dicarbonyl compound alkylated with 4-bromo-1-butene, in order to install the requisite handle for the planned RCM.



Scheme 2.11. Revised synthesis of Michael acceptor **67**.

In the first foray a stoichiometric selenation/selenoxide elimination had been employed to install the α,β-unsaturated lactam, since the preceding Michael acceptor was more

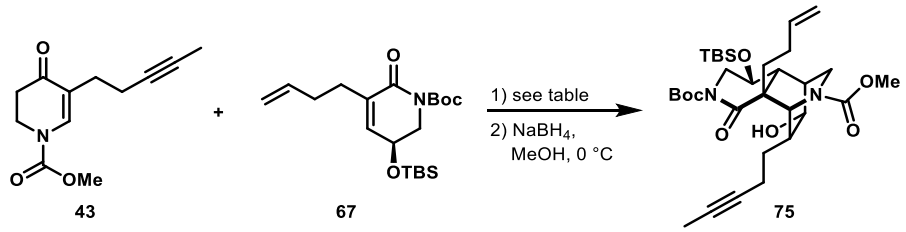
electrophilic and therefore more sensitive to forcing reaction conditions (Scheme 2.5). Since the second foray targets a much less electrophilic intermediate, Michael acceptor **67** could be formed *via* Tsuji's Pd-catalyzed decarboxylative dehydrogenation in good yield.[89,90]

With both building blocks for the Michael/Michael sequence available on gram scale, it was time to test whether the redesign of the Michael acceptor in the form of compound **67** would destabilize the enolate arising in the cascade to a sufficient degree to render that step irreversible.

2.2.4 Michael/Michael Cascade and RCAM

The starting point of the initial screening for the Michael/Michael cascade was adopted from a literature report.[82] Therein, LiHMDS gave good results, while a slightly stronger base such as LDA showed no product formation at all. Gratifyingly, the system described herein produced the cascade product with LiHMDS as base, after which subsequent reduction of the ketone gave tricycle **75** as a single diastereomer, albeit in modest yield (Entry 1). This result indicated that the redesign of the Michael acceptor (**67**) to generate a less stabilized enolate upon 1,4-addition indeed rendered the intramolecular addition step irreversible and turned the sequence into a true reaction cascade. Although DMPU seemed to accelerate the reaction initially, no improvement in yields was observed (Entry 2).

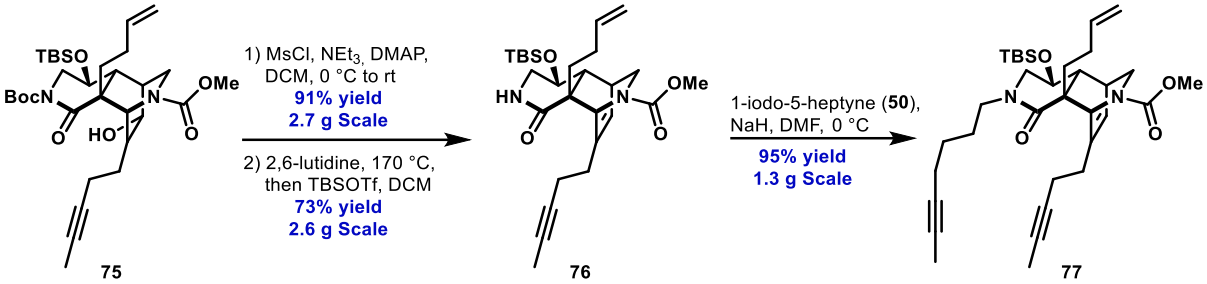
Table 2.1. Screening conditions for the Michael/Michael cascade.



Entry[a]	Base	T[b] / °C	Additive	Time / d	Yield (o2s)
1	LiHMDS	−50 → rt	-	2	26%
2	LiHMDS	−50 → rt	DMPU	2	27%
3	LiHMDS	−50 → −10	-	2	30%
4	NaO*t*Bu	−50 → rt	-	1	40%
5	LiO*t*Bu	−50 → rt	-	1	50%
6	LiO*t*Bu	−50 → rt	DMPU	1	41%
7[c]	LiO*t*Bu	−50 → rt	-	2	50%
8[c,d,e]	**LiO*t*Bu**	**−50 → rt**	**-**	**1**	**53%**

[a] All reactions were performed in THF (0.1 M), ratio of **43**:**67** = 1:1; before workup Boc_2O (2 eq.) and DMAP (2 eq.) were added. [b] Temperature gradient was run over 3h. [c] Ratio of **43**:**67** = 1.2:1. [d] Scale-up to 740 mg of **43**. [e] Temperature gradient was run over 5 h.

Quenching the reaction at a lower temperature (−10 °C), which had beneficial effects in the report by Passarella and co-workers,[82] did not have great influence in our case (Entry 3). However, changing to sodium *tert*-butoxide as base caused a slight but noteworthy increase in yield (Entry 4). Another constructive adjustment was changing the cation of the *tert*-butoxide base from sodium to lithium, which now furnished tricycle **75** in 50% yield over two steps. Interestingly, with LiO^{t}Bu as base, complete *N*-Boc cleavage was observed after one day, necessitating reprotection before workup. With LiHMDS this cleavage was only found to proceed partially and it might be argued that *N*-Boc cleavage on the cascade product might render a potential retro-Michael unlikely, since the thus formed enolate is further destabilized. Besides, added DMPU now reduced the yield (Entry 6) and a longer reaction time paired with a slight excess of donor **43** (Entry 7) did not improve the outcome of the cascade reaction either. Finally the optimized conditions (Entry 8) furnished cascade product **75**, with LiO^{t}Bu as base, a slight excess of Michael donor and a one day reaction time, in a reproducible 53% yield over two steps (740 mg scale, single largest batch).

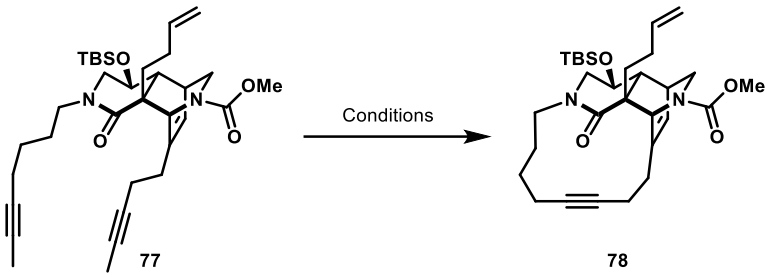


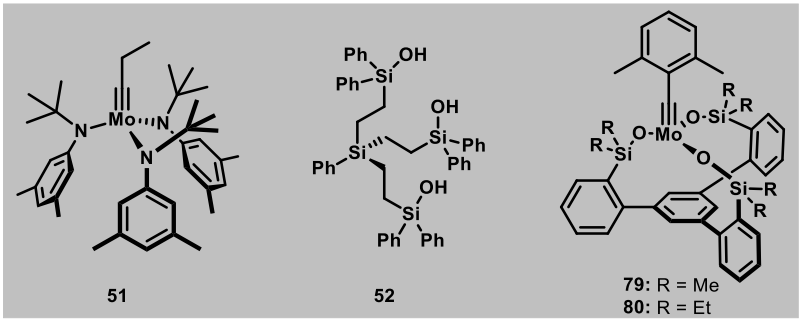
Scheme 2.11. Base induced elimination of mesylate and elaboration towards RCAM precursor **77**.

After the access to tricycle **75** was established, the substrate could be elaborated towards the RCAM step. Along these lines, the mesylate derived from **75** was eliminated under harsh conditions at 170 °C in 2,6-lutidine. Thorough drying of the intermediate mesylate in high vacuum was required prior to the next step to obtain reproducible yields. Concomitant *N*-Boc cleavage provided lactam **76**, which could readily be converted into diyne **77** by alkylation with 1-iodo-5-heptyne (**50**) (Scheme 2.11).

When diyne **77** was treated with the premixed two-component system of Mo complex **51** and trisilanol ligand **52** at elevated temperature in toluene, ring closure occurred to give **78** in 79% yield (Table 2.2, Entry 1).[91] With a new molybdenum alkylidyne complex **79** available in our laboratory, this structurally well-defined complex was tested for RCAM on diyne **77**.[104,105] While a low catalyst loading of 10 mol% only provided the cycloalkyne **78** in moderate yield (Entry 2), an increase to 20 mol% of **79** could alleviate this inconvenience and provide **78** in good yields on scale (Entry 3). Interestingly, the analogous ethyl-derivative **80** resulted in a significant drop in yield while operating at higher catalyst loading. This result illustrates the dramatic effect of different substituents at *silicon* on the tripodal catalysts of type **79**.

Table 2.2. Catalyst screening for RCAM.





Entry[a]	Catalyst	T / °C	Solvent	Yield
1	25 mol% **51** 30 mol% **52**	100	PhMe	79%
2	10 mol% **79**	110	PhMe	63%
3[b]	**20 mol% 79**	**110**	**PhMe**	**83%**
4	30 mol% **80**	110	PhMe	39%

[a] All reactions were performed in PhMe (2 mM), in presence of 5Å MS. [b] 1.3 g scale.

The constitution and stereochemical integrity of **78** was unambiguously established by X-ray diffraction of a sample grown in acetone.

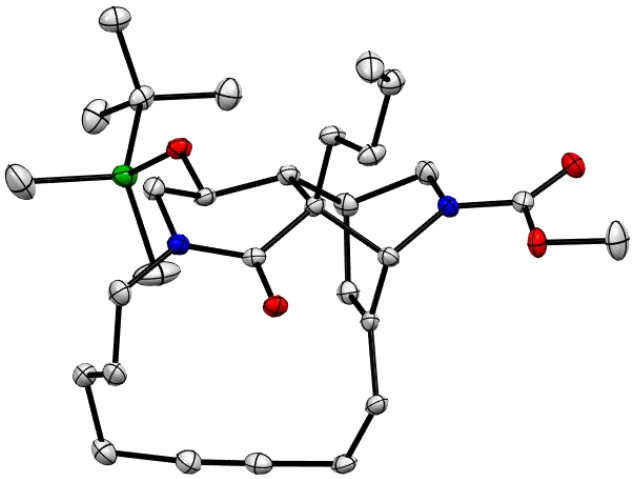
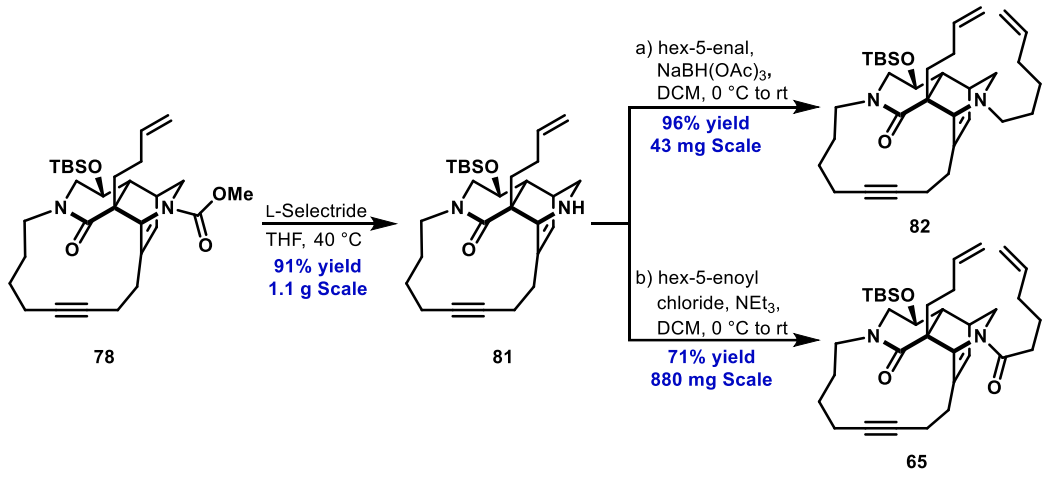


Figure 2.3. Structure of cycloalkyne **78** in the solid state.

2.2.5 Endgame and Completion of the Total Synthesis

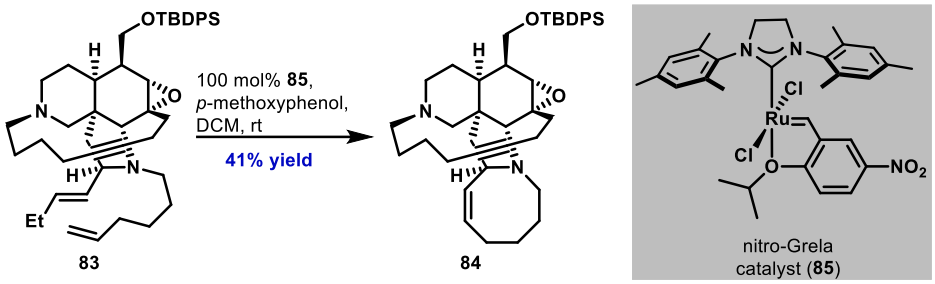
With a concise, efficient and scalable access to cycloalkyne **78** established, it was time for further elaboration towards the second macrocyclization event. To this end, compound **78** was treated with L-Selectride in THF at elevated temperature (40 °C) to afford reductive cleavage of the *N*-methylcarbamate. Thus formed, the secondary amine **81** was engaged in the installation of two different olefinic handles (Scheme 2.12). Reductive amination with hex-5-enal and sodium triacetoxyborohydride gave tertiary amine **82** in nearly perfect yield, while treatment of **81** with pregenerated hex-5-enoyl chloride formed amide **65** in good yields.



Scheme 2.12. Syntheses of amine **82** and amide **65**, *via* secondary amine **81**.

With dienes **82** and **65** in hand, we turned our attention towards the upcoming RCM. Albeit its widespread application in natural product synthesis in general,[106,107] accessing 11-membered rings *via* RCM is rather rare and the yields are in many cases moderate.[99–101,108–121] The main driving force of RCM is the reaction entropy (ΔS_r), since a diene substrate is converted into a cyclic olefin and ethylene, which evaporates under the reaction conditions. It is for this reason, that large enthalpic barriers cannot be overcome ($\Delta G_r > 0$). Additionally, the chemical and physical attributes of 11-membered rings largely originate from transannular and angle strain, imposing another hurdle for ring closure in the transition state.[122]

On top of these intrinsic aspects, the potential cross-reactivity of standard olefin metathesis catalysts with our preinstalled cycloalkyne in **82**/**65** needed to be considered. Since metal carbenes can react with both olefinic- and acetylenic-π-systems, a potential crossover would also be possible here. Although this would be detrimental to our strategy, it was hypothesized that the rigid tricyclic core separates the olefins and the cycloalkyne enough in space, which alleviates the risk of such an event. Furthermore the total synthesis of manzamine A (**7**) by Fukuyama *et al*.[123] provides precedent, affording ring closure of an 8-membered cycloalkene in the presence of a 13-membered cycloalkyne using the Ru-carbene complex **85** (Scheme 2.13).



Scheme 2.13. RCM in the total synthesis of manzamine A (**7**) by Fukuyama *et al*.[123]

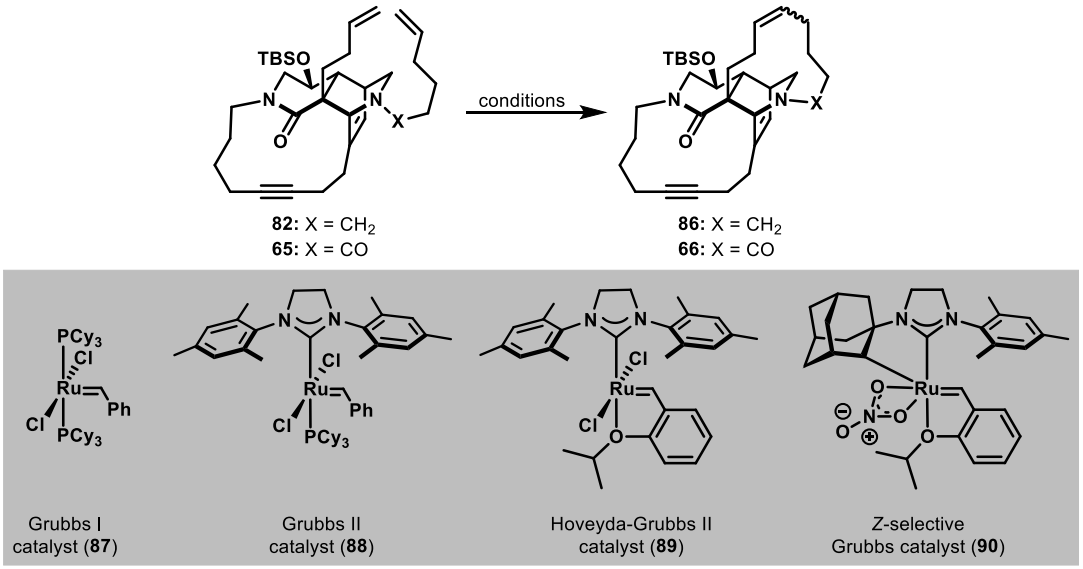
Notably, Fukuyama *et al*.[123] encountered both participation of the tertiary amine and the alkyne in their RCM reactions. After optimization they found that stoichiometric amounts of nitro-substituted derivative of the Hoveyda-Grubbs II class of catalysts **85** developed by Grela *et al*.[124] in the presence of *p*-methoxyphenol[125] generates product **84** in moderate yield at room temperature. The phenol additive has been shown to increase TON especially in the case of Grubbs I catalyst **87**.[124,125]

The screening was initiated with tertiary amine **82** and Grubbs I catalyst **87** in dichloromethane (Entry 1). Surprisingly, there was no reaction with neither the free base nor the protonated amine of **82**. Switching to the second-generation catalyst **88** generated small quantities of dimeric products (Entry 2), however more forcing conditions in boiling toluene led to decomposition of the starting material (Entry 3). These results suggest that the conformational preorganization enforced by the tricyclic core is negated by the high degree of flexibility from the tertiary amine. Additionally, free amines remain challenging functional groups in the context of RCM in natural product syntheses, since they are often observed to shut down catalytic activity in the case of Ru-carbene catalysts.[106]

Gratifyingly, when amide **65** was reacted with Grubbs I catalyst **87** (30 mol%) in dichloromethane at 40 °C, the cyclic product **66** was obtained in low yields, although as a 1:1 mixture of *E*/*Z* isomers (Entry 4). Stoichiometric quantities of **87**, now furnished cycloalkene **66** in moderate yield, slightly favoring the formation of the *E*-isomer of **66** (Entry 5). The initiation of Ru-carbene **87** highly varies with the chosen solvent.[126] Therefore, chlorinated solvents can give drastically different reaction profiles, compared with non-chlorinated solvents and vice-versa. Grubbs I catalyst **87** in toluene at elevated temperature provided **66** in very good yield, although the high temperatures now favored the *E*- over the *Z*-Isomer (Entry 6).

The catalyst loading could be decreased to sub-stoichiometric amounts by slow addition of the catalyst in toluene (Entry 7). The best result was obtained, when the concentration was increased (1 mM) and the catalyst was slowly added over a period of three hours as a solution in toluene (Entry 8).

Table 2.3. Condition screening for second macrocyclization via RCM.

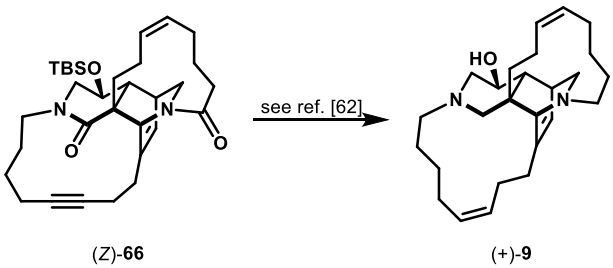


Entry[a]	X	Catalyst	Solvent	T / °C	Yield	*E*:*Z* ratio	Comment
1[b]	CH_2	**87** (50 mol%)	DCM	40	-	-	no reaction
2	CH_2	**88** (30 mol%)	DCM	40	-	-	low conversion to dimer
3	CH_2	**89** (30 mol%)	PhMe	110	-	-	decomposition
4	C=O	**87** (30 mol%)	DCM	40	22%	50:50	-
5	C=O	**87** (100 mol%)	DCM	40	55%	55:45	-
6	C=O	**87** (100 mol%)	PhMe	100	94%	64:36	-
7[c]	C=O	**87** (50 mol%)	PhMe	100	73%	60:40	-
8[c,d]	**C=O**	**87 (50 mol%)**	**PhMe**	**100**	**97%**	**60:40**	**-**
9	C=O	**89** (100 mol%)	PhMe	100	-	-	decomposition
10	C=O	**90** (100 mol%)	1,2-DCE	83	-	-	no reaction
11[c,d,e]	C=O	**87** (50 mol%)	PhMe	100	33%	66:34	-

[a] All reactions were performed at a concentration of 0.5 mM and 10 mg scale, unless noted otherwise. *E*:*Z*-ratios were determined by crude ^{1}H-NMR. [b] CSA as additive. [c] Slow addition of catalyst in PhMe over 3 h. [d] The reaction was run at 1 mM concentration. [e] 270 mg scale.

Due to competitive decomposition of the first-generation Grubbs catalyst **87** and the necessity for elevated temperatures, the second-generation Hoveyda-Grubbs catalyst **89** was tested (Entry 9). Bearing a chelating isopropoxy-group covalently bound to the benzylidene moiety instead of a labile phosphine ligand, this catalyst possesses remarkable stability towards water and air. Similar to our previous results with tertiary amine **82** and catalyst **89** (Entry 3) however, treatment of amide **65** with the latter only resulted in decomposition of the diene substrate (Entry 9). Furthermore, the *Z*-selective Grubbs catalyst **90** was employed in order to correct the lack of stereoselectivity, observed in all previous iterations.[127] Unfortunately,

complex **90** proved unreactive towards amide **65** (Entry 10). Attempted scale-up using the refined conditions (Entry 8), showed problems in reproducibility, when pentacycle **66** was isolated in poor yields and in favor of the undesired *E*-Isomer (Entry 11). Nevertheless, compound **66** could be accessed in sufficient quantities to perform HPLC separation of the stereoisomers arising from RCM, providing (*Z*)-**66** and hence intercepting our previous route towards (+)-ingenamine (**9**).[62]



(*Z*)-**66** (+)-**9**

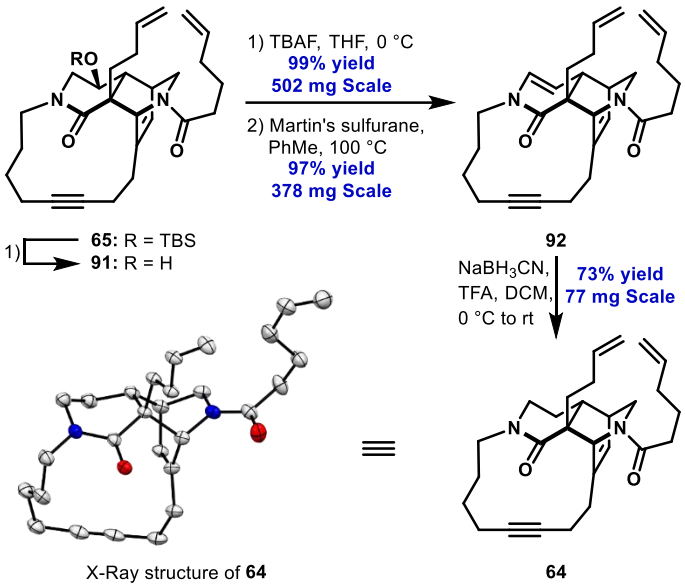
Scheme 2.14. Interception of our previous route towards (+)-ingenamine (**9**).

Therein, pentacycle *(Z)*-**66** is treated with nickel boride[97] to afford semihydrogenation of the alkyne, followed by reduction of the remaining amide groups with excess AlH_3, generated *in situ* from $LiAlH_4$ and $AlCl_3$ (Scheme 2.14). Concomitant cleavage of the silyl ether furnishes ingenamine (**9**).[62]

While the TBS ether plays a quintessential role in inducing chirality in the Michael/Michael cascade and therefore relays its stereochemical information onto four stereocenters of the tricyclic core, an approach towards keramaphidin B (**2**) would now ask for a removal of this critical substituent. The efforts towards keramaphidin B (**2**) were diverted at the stage of diene **65**, when it was found that alcohol **91**, which was afforded after silyl cleavage, swiftly succumbs to dehydration with Martin's sulfurane at elevated temperature in toluene (Scheme 2.15).[128] The resulting enamide was subsequently reduced with sodium cyanoborohydride and trifluoroacetic acid, giving rise to compound **64**, bearing the desired oxidation state at C-9 of keramaphidin B (**2**).[129,130] At this time, the stage was set for yet another RCM attempt. In line with our previous results, Grubbs I catalyst **87** was envisaged to mediate this transformation. With the crystal structure of diene **64** at our disposal, the structural preorganization was illustrated by the pendant 5-hexenamide and the butenyl group coming off the rigid tricyclic core both pointing upwards, away from the cycloalkyne. Although the conformation in solution might differ from the structure in the solid state, no competing ene/yne crossover was observed.

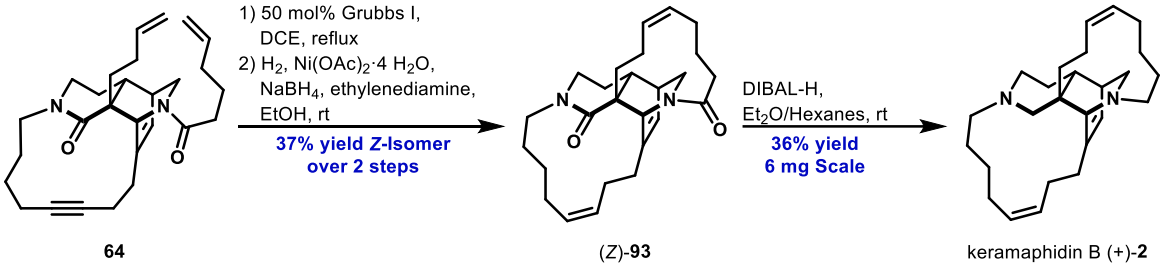
In practical terms, treatment of diene **64** with Grubbs I catalyst (50 mol%) in boiling 1,2-DCE was necessary to afford ring closure (Scheme 2.16). The product was obtained in 83% yield as a 1:1 mixture of double bond isomers. The reaction in toluene favored the undesired *E*-isomer (66:34 *E*:*Z*-isomeric ratio), and is also being inferior in terms of yield (55% yield). Additionally, the RCM in 1,2-DCE was scalable and showed a high degree of reproducibility. After

semihydrogenation of the alkyne with nickel-boride[97] the *E*-isomer was separated *via* flash chromatography and the resulting (*Z*)-bislactam **93** was reduced with DIBAL-H in a mixture of diethylether and hexanes yielding keramaphidin B (**2**).



Scheme 2.15. Dehydration/reduction sequence and X-ray structure of compound **64** in the solid state.

Although discrepancies between the NMR data acquired in methanol-d_4 and the previously reported data by Anderson *et al.*[56,98] suggested a different protonation state, our synthetic sample of (+)-**2** measured in $CDCl_3$ showed an almost perfect agreement of the spectral properties reported by Kobayashi *et al.*[54]



Scheme 2.16. Endgame in the total synthesis of keramaphidin B (**2**).

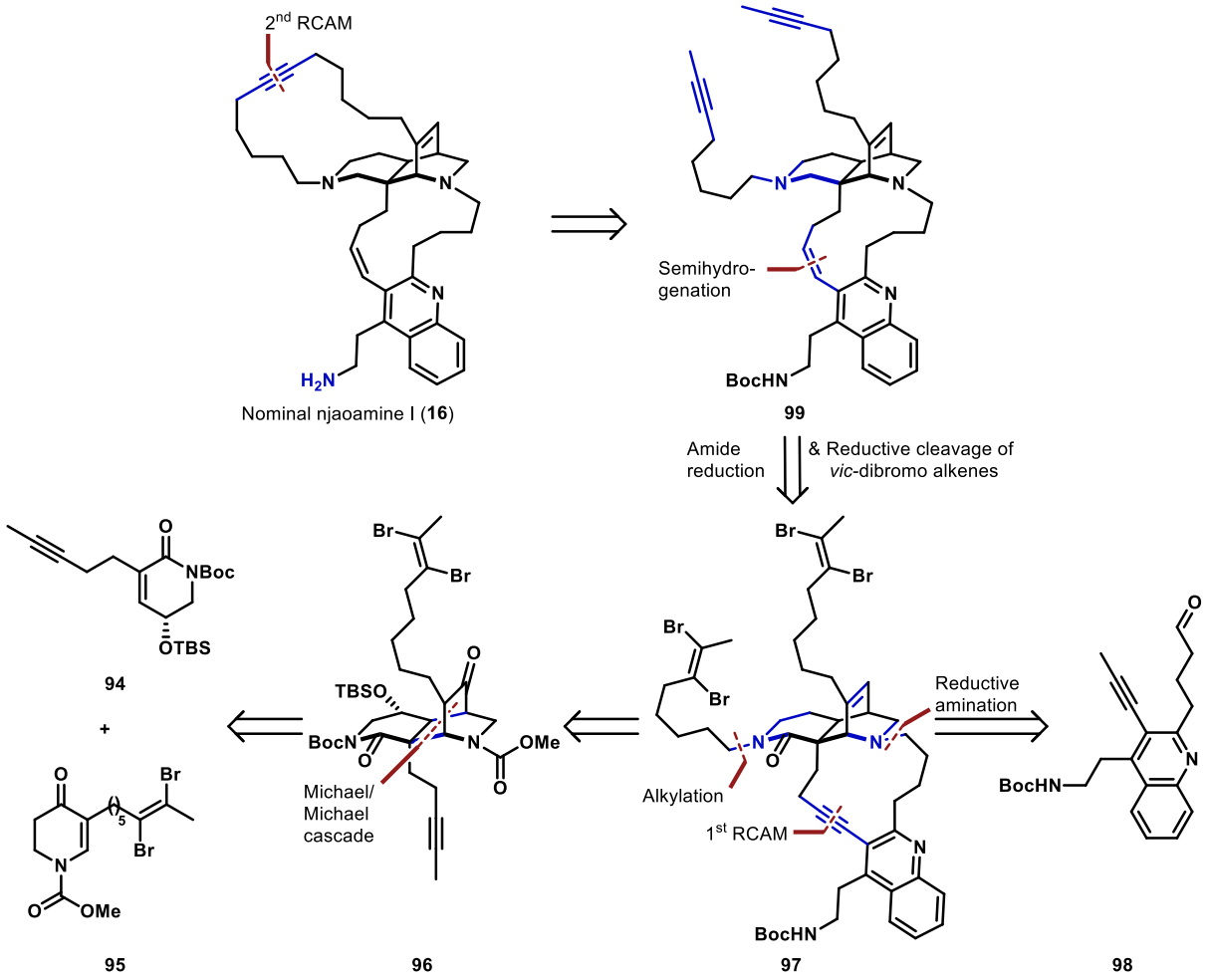
2.3 Total Synthesis of Nominal Njaoamine I

*The total synthesis of nominal njaoamine I (**16**) was carried out in cooperation with Dr. Zhanchao Meng. The NMR studies supporting the structural revision of njaoamine I were carried out by Sandra Tobegen and Dr. Christophe Farès.*

By virtue of the advancements made through the second-generation approach of ingenamine (**9**), as well as the inaugural total synthesis of keramaphidin B (**2**), an extension of our synthetic program towards more complex targets was tempting. The njaoamine family of natural products (see chapter 2.1.1) provides a stringent testing ground, as one of the macrocycles is annulated to a functionalized quinoline bearing two additional basic nitrogen atoms. (Nominal) njaoamine I (**16**) was chosen as the target compound, since the intact triple bond in the peripheral ring seemed tempting for a late-stage RCAM. A failed first foray[131] will not be covered in the following section, however the considerations following from this approach will be discussed in the retrosynthetic analysis.

2.3.1 Retrosynthetic Analysis

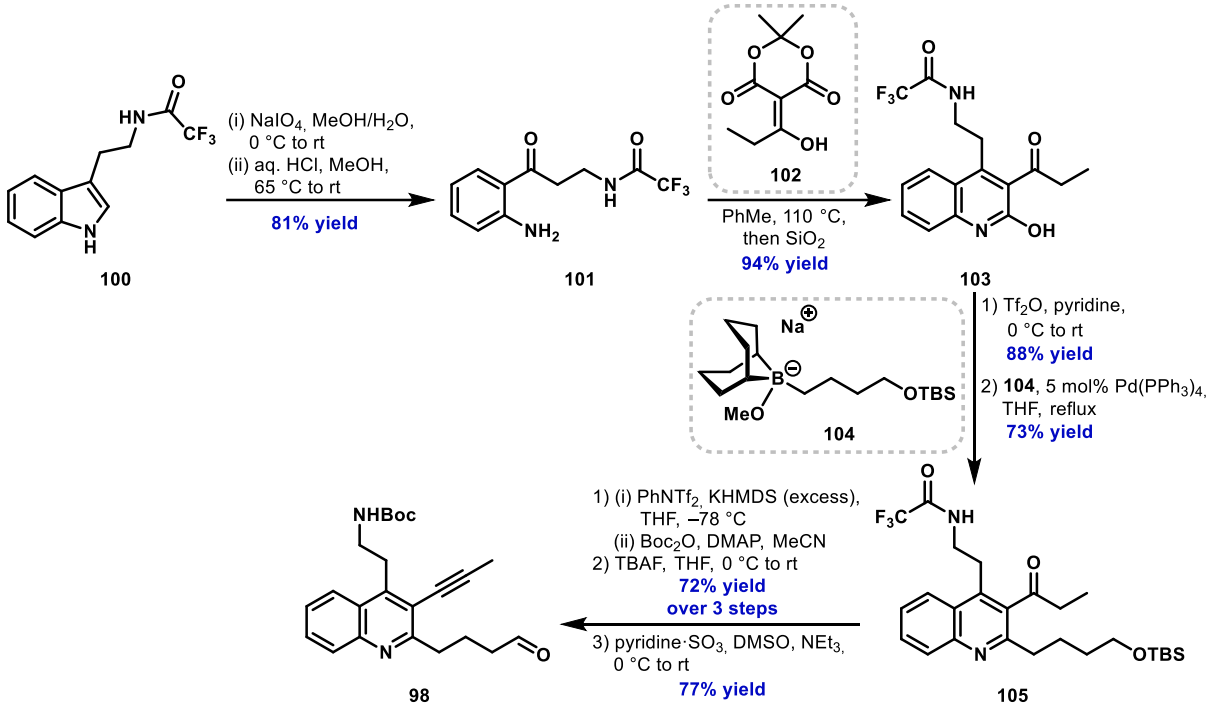
The macrocyclization strategy in an approach towards (nominal) njaoamine I (**16**) had to be selected carefully. Since RCM had been troublesome in the presence of basic amine functionalities *en route* to keramaphidin B (**2**) (see chapter 2.2.5) and the respective natural product additionally bears a quinoline and a primary amine, this transformation was excluded from the analysis at the start. With the alkyne in the periphery of the 17-membered ring inviting the use of RCAM, this strategy would require either a methodology completely orthogonal to alkynes, or the masking of the respective alkynes in order to carry out two subsequent RCAMs. Although a cross-coupling strategy, as used in the synthesis of xestocyclamine A (**11**),[62] was also a viable option, the choice fell on the use of two consecutive RCAMs (Scheme 2.17). Most common protecting groups for alkynes did not meet the boundary criteria, as they would have to withstand basic, acidic, oxidative, different reductive conditions, and fluoride. Eventually, *vic*-dibromoalkenes were selected,[132,133] knowing that the halide atoms could be inimical for the Pd-catalyzed Tsuji dehydrogenation and the required semireduction of the alkyne over a (noble) metal catalyst. Therefore, a late-stage RCAM would forge the 17-membered ring, revealing (nominal) njaoamine I (**16**) after *N*-Boc cleavage. The diyne **99** results from reductive cleavage of the corresponding *vic*-dibromides, semi-hydrogenation of the cycloalkyne **97** to the corresponding *cis*-olefin and amide reduction. As discussed, cycloalkyne **97** arises from cleavage of the methyl-carbamate, followed by reductive amination with the requisite quinoline fragment **98** and RCAM. The previously employed dehydration/reduction- and reduction/elimination-sequence would install the core, which shows similarities to keramaphidin B (**2**). Retrosynthetically this would trace back to the Michael cascade product **96**. The required building blocks **94** and **95** would be synthesized as previously described (see chapter 2.2.2 and 2.2.3).



Scheme 2.17. Retrosynthetic analysis of nominal njaoamine I (**16**).

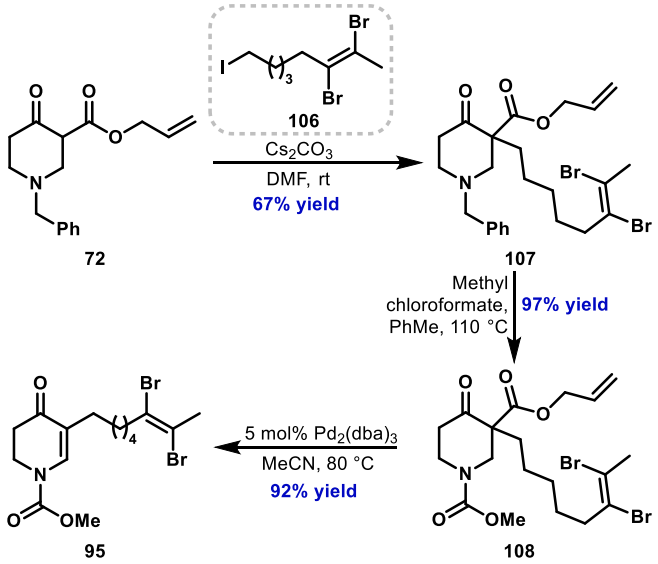
2.3.2 Synthesis of the Building Blocks

The synthesis of the quinoline fragment **98** commences with oxidative cleavage of the C2-C3 bond of *N*-trifluoroacetylated tryptamine **100** and subsequent hydrolysis of the resulting formamide (Scheme 2.18). Aniline **101** undergoes a Dieckmann-type condensation with **102** to give hydroxyquinoline **103** on scale.[134] Treatment of **103** with triflic anhydride in pyridine furnishes the corresponding triflate, which was employed in a Suzuki cross coupling with borate **104**. The latter was generated *via* hydroboration of TBS-protected 3-butene-1-ol with 9-H-9-BBN and formation of the ate-complex after addition of stoichiometric amounts of sodium methanolate.[135–137] The enolate derived from ketone **105** can be trapped with phenyl triflimide and succumbed to spontaneous elimination with excess KHMDS.[138] Quenching with Boc_2O and subsequent addition of NH_4Cl interchanged the protecting groups at the primary amine. Cleavage of the silyl ether using TBAF and oxidation of the primary alcohol under Parikh-Doering conditions furnished aldehyde **98** in good yield.[139]



Scheme 2.18. Synthesis of the quinoline fragment **98**.

The Michael acceptor **94**, required for the Michael/Michael cascade was synthesized in analogy to the route shown in chapter 2.2.3. Instead of 4-bromo-1-butene, 1-iodo-3-pentyne was employed in the alkylation of the β-ketoester derived from **45**.



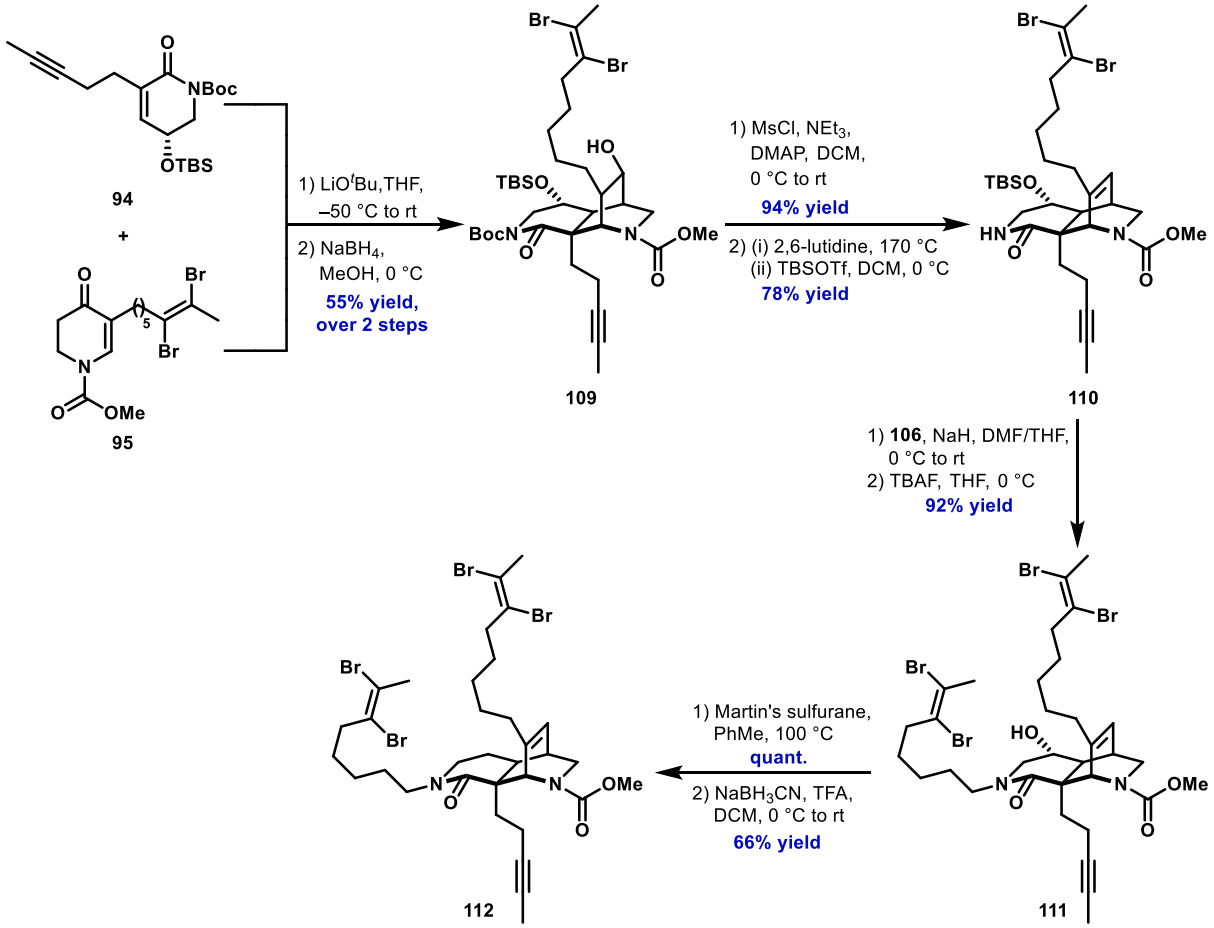
Scheme 2.19. Synthesis of the Michael donor **95**.

In terms of the Michael donor **95**, the adaptation was slightly more elaborate (Scheme 2.19). The *vic*-dibromide alkyne surrogate **106** was united with β-ketoester **72** *via* alkylation and the resulting *N*-benzyl protected piperidone **107** reacted with methylchloroformate in boiling toluene to give the desired *N*-methyl carbamate protected piperidone **108**.

In this case, the Pd-catalyzed Tsuji dehydrogenation proceeded smoothly, as no competing reactivity of the *vic*-dibromides was observed. Since this process is catalyzed by $Pd_2(dba)_3$ in the absence of any external ligand, the Pd species in solution seems to lack the required electron density to engage the alkenyl halides.

2.3.3 Completion of the Total Synthesis

With all building blocks in hand, the goal was set to reach the first RCAM event. In practical terms, the previously optimized route towards the core structure of keramaphidin B (**2**) proved highly reliable.



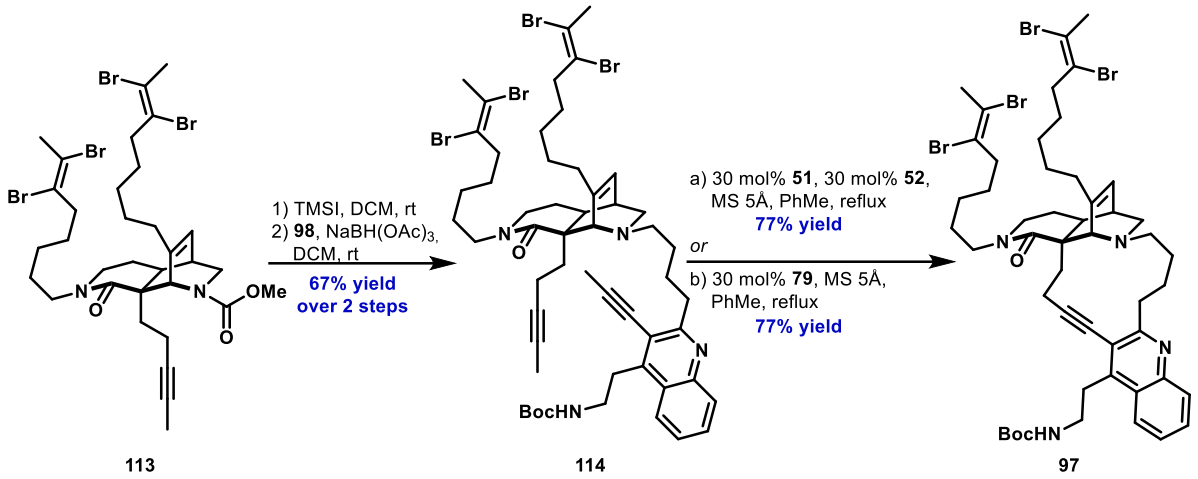
Scheme 2.20. Elaboration of the njaoamine I core.

The base mediated Michael/Michael cascade, followed by reduction of the ketone with $NaBH_4$, furnished alcohol **109**, as a single diastereomer in good yield. The harsh conditions (170 °C, 5 d) used for unveiling the etheno-bridge on the core did not harm the *vic*-dibromides and provided lactam **110** in reproducible fashion, when the starting material was vigorously dried. *N*-Alkylation of the free amide, fluoride mediated cleavage of the silyl ether and dehydration of the resulting alcohol **111** with Martin's sulfurane proceeded without problems. Only the

reduction of the enamide with excess $NaBH_3CN$/TFA had to be quenched as soon as full conversion of the starting material was observed, as otherwise decomposition occured.

Although the *N*-methyl carbamate had been a reliable protecting group previously, problems with the reductive cleavage were encountered in the presence of the *vic*-dibromides. When L-Selectride was used, extensive reduction of the *vic*-dibromo olefins was observed, leaving no choice but to search for another reagent capable of carbamate cleavage. After some experimentation it was found, that TMSI[140] served this purpose and revealed the *N*-terminus for the following reductive amination. HBr in acetic acid did also mediate this transformation, however the yields were low and hydrobromination of the free alkyne was detectable. Trace amounts of HI, from hydrolysis of TMSI, were deemed equally problematic. Consequently, fresh TMSI was used directly upon receipt from the vendor.

Merger of the free amine and aldehyde **98** in a reductive amination reaction furnished diyne **114** ready for the first macrocyclization event (Scheme 2.21). As expected the RCAM worked well, regardless whether the two-component system (**51**/**52**)[91] or the structurally well-defined Mo-complex **79**[104,105] was employed. The *vic*-dibromoalkenes did not interfere with the Mo-catalyzed RCAM, nor did they get damaged. Since this functional group had not been tested previously in context of alkyne metathesis, it can now be added to the list of functional groups compatible with the Mo-alkylidynes.

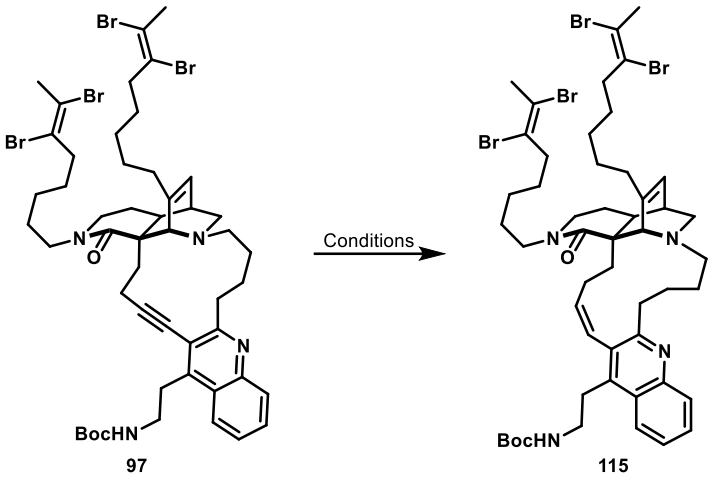


Scheme 2.21. Synthesis of diyne **114** and first macrocyclization event.

With cycloalkyne **97** in hand, investigations for the semi-hydrogenation of the newly formed triple bond were initiated. This represented another crucial step in the strategy, as it would show, whether the *vic*-dibromoalkenes can withstand the noble metal catalyzed reaction. The Cu-NHC catalyzed process developed by Lalic *et al.*[141] only provided olefin **115** in minute amounts (Table 2.4, entry 1). When a hydroboration/protodeborylation strategy, similar to the first generation synthesis of nominal xestocyclamine A (**11**),[62] was employed with dicyclohexylborane, as the reagent, only decomposition was observed. It may be noted, that

substrate **97** bears a quinoline moiety, which is known to be a potential poison for heterogeneous catalyst systems.[142] Gratifyingly, heterogeneous hydrogenation over unpoisoned Pd/$CaCO_3$ in THF served its purpose and provided the *Z*-olefin **115** in moderate yields. Although superstoichiometric quantities of the Pd species had to be used, these conditions turned out as an almost singular hit in the reaction screening. With other solvents as EtOAc (Entry 4) or toluene (Entry 5) the $CaCO_3$ supported Pd species was rendered unreactive towards alkyne **97**. Finally, we intended to poison Pd/C by using pyridine as the reaction solvent (Entry 6), however this hydrogenation attempt resulted in extensive overreduction of the *vic*-dibromoalkenes.

Table 2.4. Condition screening for the semi-hydrogenation of alkyne **97**.

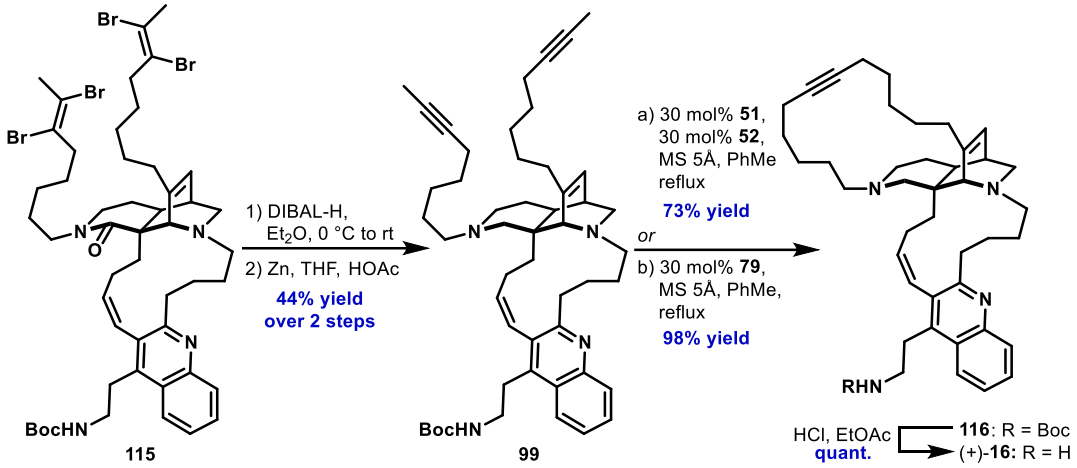


97 115

Entry	Catalyst/Reagent	Solvent	Result
1	IPrCuCl, NaO*t*Bu, PMHS, *t*BuOH	PhMe	<10% yield
2	Cy_2BH	THF	decomposition
3	**H_2, Pd/$CaCO_3$ (2.0 eq.)**	**THF**	**52% yield**
4	H_2, Pd/$CaCO_3$ (1.5 eq.)	EtOAc	no reaction
5	H_2, Pd/$CaCO_3$ (1.5 eq.)	PhMe	no reaction
6	H_2, Pd/C	Pyridine	overreduction

Next, studies towards the selective reduction of the amide embedded in the core of the molecule were initiated. Only after considerable experimentation it was found, that DIBAL-H in Et_2O was selective in reducing solely the amide (Scheme 2.22). The choice of the solvent was critical and the reaction time had to be monitored carefully, in order to avoid reduction of the C–Br bonds. The endgame of the total synthesis turned out to be a little more straightforward. Unmasking of the alkynes with Zn-dust in a protic medium proceeded smoothly.[132,133] In line with previous results, the following RCAM on **99** furnished the 17-membered macrocycle **116** with both the two-component system comprised of **51** (30 mol%) and **52** (30 mol%), as well as

with the well defined "canopy" catalyst **79** (30 mol%). Notably, the latter provided cycloalkyne **116** in essentially quantitative yield, which marks the success of alkyne metathesis employing silanolate ligated high-valent molybdenum alkylidynes of type **79**. Neither the presence of two tertiary amines and a quinoline, nor a Lewis-basic carbamate group masking a primary amine terminus compromises the reactivity. When put in perspective with the RCM of **82** bearing a single tertiary amine, which shut down any reactivity of the Grubbs-type ruthenium carbenes, regardless of the protonation state, this result is remarkable.



Scheme 2.22. Synthesis of diyne **99** and final macrocyclization event.

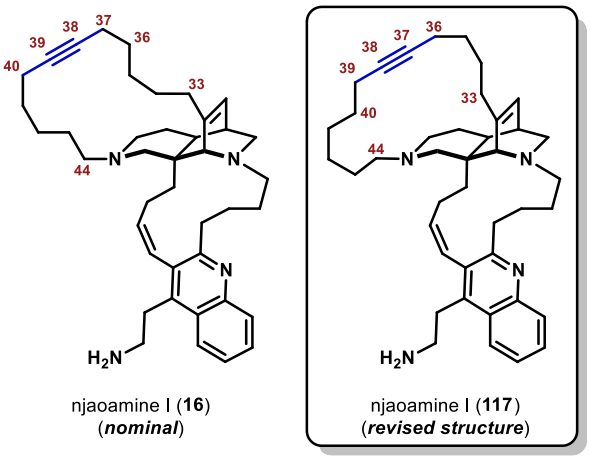
Ultimately, cleavage of the *N*-*tert*-butyloxycarbonate group with HCl in 1,4-dioxane/EtOAc[143] furnished the structure, which had been proposed as njaoamine I (**16**) by the isolation team.[71] Surprisingly, however, the analytical and spectral data gathered from our synthetic sample (**16**) showed small but significant deviations from the tabulated NMR data from the isolated natural product.[71] A comparison with an authentic sample, generously made available by the isolation team, confirmed the suspicion that, although the differences are extremely subtle and the compounds were indistinguishable by HPLC analysis, the discrepancy was indeed non-neglible. The differences were surmised to most likely originate from the positioning of the triple bond in the 17-membered macrocycle. To test this hypothesis, an in-depth study into the origin of the mismatch was initiated.

2.3.4 Structural Revision of Njaoamine I

In order to investigate the positional misassignment of the alkyne in the macrocycle, the 12-carbon chain in the northern part of the molecule had to be reassigned unambiguously. A challenging task, considering the high dilution of **117** in pyridine-d_5, which rendered heteronuclear long-range coupling experiments, primarily HMBC, impractical. Furthermore, the assignment was obstructed by limited resolution, especially crucial in the region between 1.1 and 1.7 ppm where 20 methylene protons (14 of the 12-carbon fragment under investigation) and one methine proton resonate. Additionally, the assignment of two ^{13}C-NMR

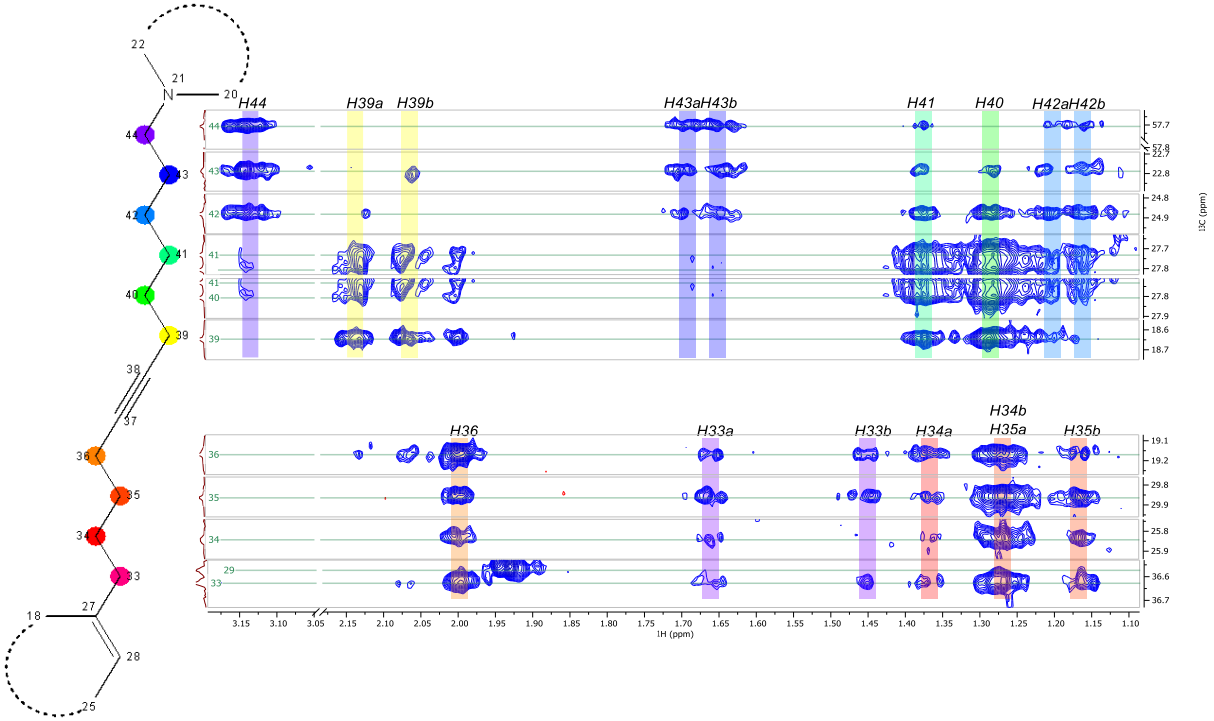
signals at 27.7 and 27.8 ppm proved challenging and could only be distinguished by very high-resolution multidimensional experiments.

Figure 2.4. Comparison of nominal njaoamine I (**16**) and the revised structure of njaoamine I (**117**).



At first, all ^{1}H-signals of the 10 methylene groups belonging to the 12-carbon chain in question, were identified in a high resolution HSQC experiment. Secondly, the methylene chain was surveyed through $^{3}J_{HH}$ in a CLIP-COSY experiment[144] linking the chain-terminating methylenes H44 and H33 to their respective propargylic CH_2-groups flanking the alkyne.

Figure 2.5. HSQC-TOCSY experiment of actual njaoamine I (**117**) shown as ordered strips correlating each ^{13}C-atom to the respective ^{1}H-signals within their associated spin-system.

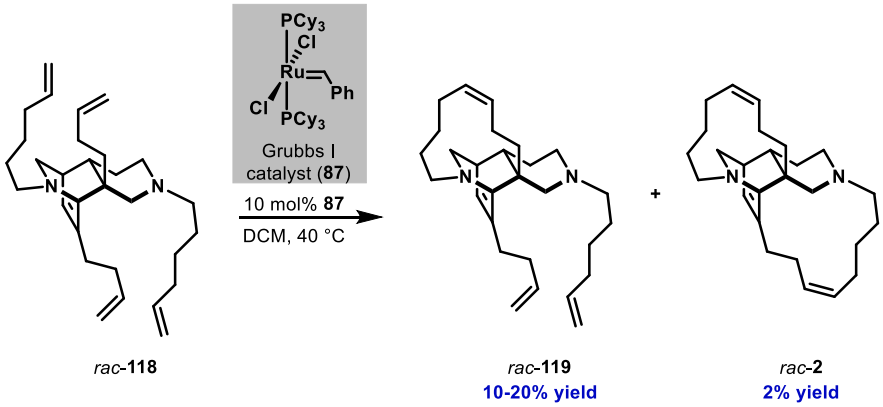


Especially in the center of the aliphatic chains, ambiguity persisted. Finally, a long, high-resolution HSQC-TOCSY experiment correlated all ^{13}C signals with the proton signals within their associated spin system. This supported the supposition, that the alkyne was indeed positioned at the C37-C38 position (Figure 2.5). As the same pattern of correlations was observable in a 1D ^{1}H-TOCSY, selectively irradiating the terminal methylene protons at H44 and H33, along with the methylene protons H39 and H36, the revised structure of njaoamine I (**117**) (Figure 2.4) could be confidently proposed.

Additionally, the observed specific optical rotation of our synthetic njaoamine I (**16**) is worth a comment. Although actual njaoamine I (**117**) and our synthetic nominal njaoamine I (**16**) are isomeric to each other, their observed dextrorotatory nature suggests them being compounds of the same enantiomeric series as xestocyclamine A (**10**). This stands in contrast to the depiction in the isolation paper[71], which insinuates (+)-**117** to have the same absolute configuration as ingenamine (**9**).

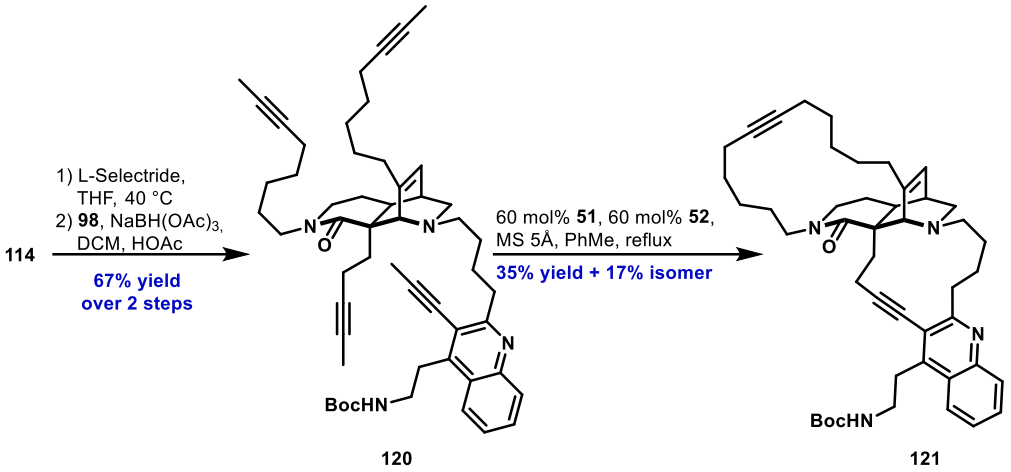
2.3.5 Concerted Macrocyclization Event

In attempts to elucidate the biosynthetic pathway of keramaphidin B (**2**), Baldwin *et al.*[60,61] carried out synthetic studies trying to emulate the formation of the tricyclic core by Diels-Alder reaction (Chapter 2.1). Moreover, they generated a tetra-ene substrate, which allowed them to attempt the concurrent formation of the two macrocycles. These efforts met with minimal success, when keramaphidin B (*rac*-(**2**)) was only observed in minute amounts (1-2% yield). It was for this exact reason, that we pursued a stepwise approach in all our macrocyclization strategies.



Scheme 2.23. Baldwin and Whitehead's attempt of concurrent RCM reaction on the keramaphidin B (**2**) scaffold.[61]

The fact, however, that a RCAM/RCM sequence could be executed *en route* to **2** and no competing ene/yne-crossover was observed, insinuated that there was a favorable bias towards the formed macrocycles. If there was indeed a structural preorganization of the pendant side-chains, a concerted macrocyclization event might be feasible with our system.



Scheme 2.24. Double RCAM of tetrayne **120**.

Since clean reduction of the *vic*-dibromoalkenes was found when L-selectride was employed for reductive cleavage of the methyl carbamate **114**, advantage was taken of this transformation for the synthesis of the projected tetra-yne **120** (Scheme 2.24). The latter was afforded after reductive amination of the secondary amine with quinoline aldehyde **98**. The concerted RCAM worked equally well with both the two component system **51** (60 mol%), **52** (60 mol%) and the well defined canopy catalyst **79** (30 mol%). Unfortunately, purification issues were encountered, since the silanolate ligand co-eluted with the desired biscycloalkyne **121**, resulting in impeded material recovery of 35%. This technical issue notwithstanding, the herein (yet unoptimized) result opens up new avenues for the target-oriented synthesis with RCAM. Since the chemoselective functionalization of the C31≡C32 alkyne without touching the more accessible C36≡C37 triple bond in **121** was practically impossible, the synthetic use of the concurrent RCAM was limited in our context.

2.4 Summary and Outlook

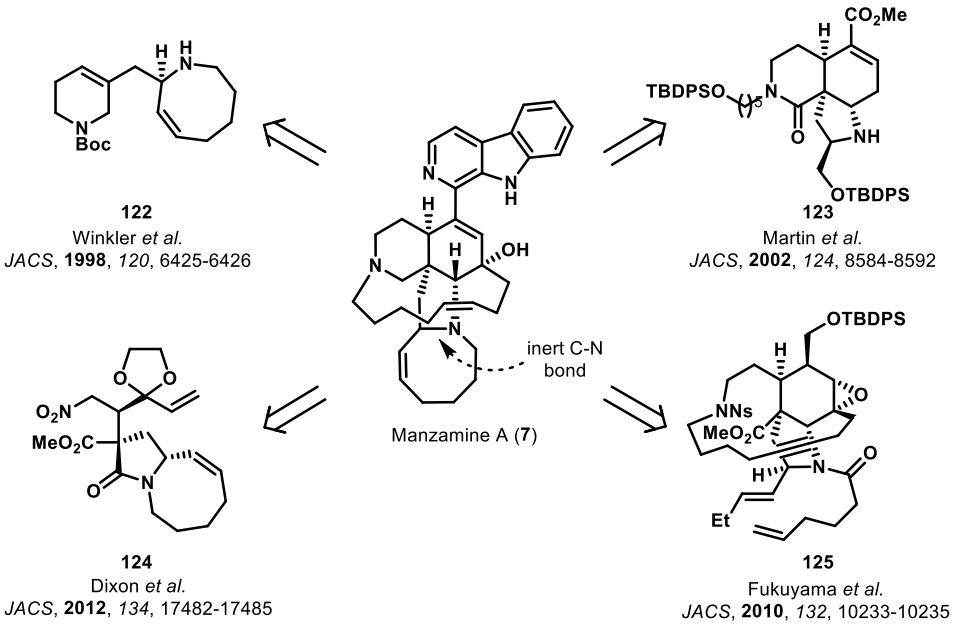
In a second-generation approach towards ingenamine (**9**) several improvements were implemented into the synthetic blueprint. First, the synthesis of the required building blocks for the Michael/Michael cascade was optimized concerning versatility, scalability and productivity. Conditions were found to successfully construct the tricyclic core of alkaloids of the ingenamine estate from these two building blocks in a single step with full diastereoselectivity. Access was thus extended to the non-hydroxylated core of keramaphidin B (**2**) and the njaoamines **12**-**16**. Two macrocyclization strategies were applied constructing the 11- and 13-membered rings of ingenamine (**9**) and keramaphidin B (**2**), as well as the 13- and 17-membered macrocycles of nominal njaoamine I (**16**). In particular, the RCAM/RCM strategy applied in the total synthesis of keramaphidin B (**2**) showcased the necessity of orthogonal metathesis based methodologies, when the most pressing drawbacks of Ru-catalyzed olefin metathesis became apparent (functional group tolerance towards basic amines and stereoselectivity). In the light of these challenges, the performance of RCAM in all of these settings becomes more impressive. Particularly the well-defined metathesis active Mo-alkylidyne complex **79** was put through a number of challenging transformations, attesting to a remarkable and enabling functional group tolerance. These examples challenge the orthodoxy that highly functionalized compounds impede high-valent early transition metal catalysts.

The inaugural total synthesis of keramaphidin B (**2**), a molecule central in the biosynthetic pathway first proposed by Baldwin and Whitehead *et al*.[51] thirty years ago, and especially the conquest of (nominal) njaoamine I (**16**) leading to a structural reassignment, advocates for the integral role of total synthesis in the realm of natural products.

The concerted use of RCAM might inspire future synthetic strategies, if the target provides sufficient conformational preorganization and the thus formed triple bonds can be functionalized in parallel. An intriguing target is present in njaoamine C,[69] since this natural product bears two Z-olefins within its macrocycles and a double semi-hydrogenation is feasible.

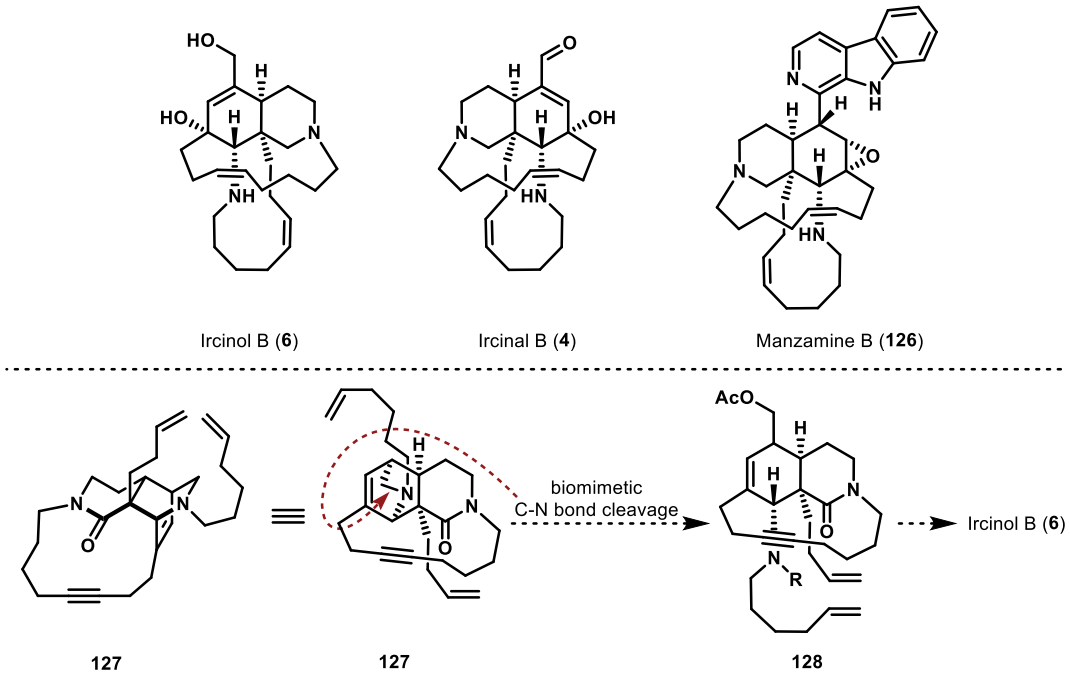
Interestingly, a literature survey reveals another synthetic gap in the manzamine estate. Whereas manzamine A (**7**) and its biogenetic precursors ircinal A and ircinol A were the first members of this class to be targeted by several groups over the years,[58,59,79,123] manzamine B (**7**), ircinol B (**6**) and ircinal B (**4**) have been completely left out of the picture. Although seemingly less complex, due to the absence of a C-N bond, almost all total syntheses rely on this stereodefining element early in their synthesis (see scheme 2.22.). Winkler and Axten, harness the 8-membered ring, as their stereodefining element,[58] while Martin *et al*.[59] rely on the 5-membered ring in their Diels-Alder disconnection building up the central 6,6,5-tricycle. In Fukuyama's approach the respective C-N bond is introduced rather late, possibly

amendable to target the aforementioned natural products **126**, **4** and **6**.[123] However, Dixon's strategy completely relied on the formation of the 5,8-bicycle at the start of the synthesis.[79]



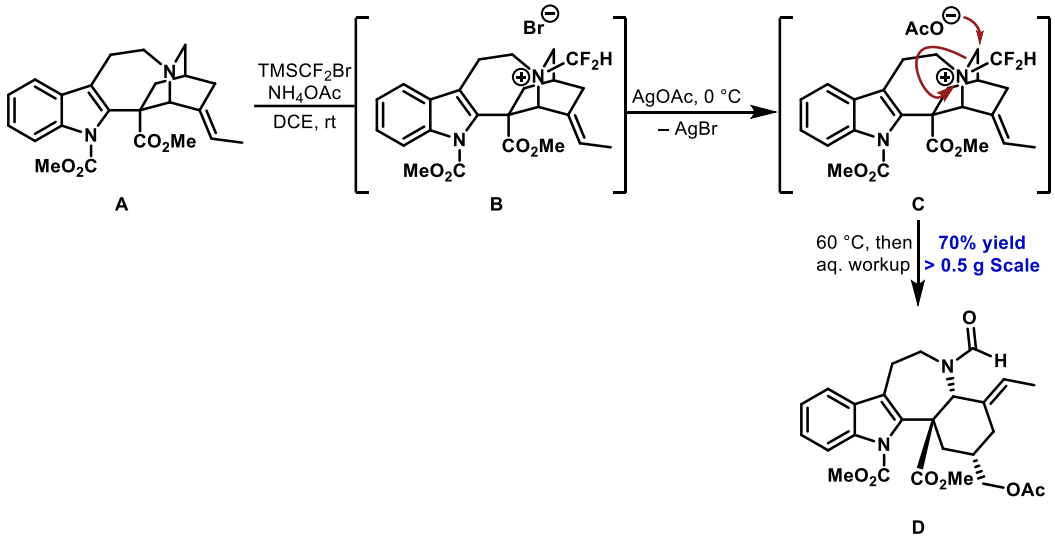
Scheme 2.25. Summary of synthetic efforts towards manzamine A (**7**).

Albeit fit to purpose in targeting manzamine A (**7**), these strategies do not allow an easy strategic switch towards the natural products in the realm of manzamine B (**126**),[52,53,145] due to the inert nature of the indicated C-N bond.



Scheme 2.26. Unconquered natural products of the manzamine estate and a possible biomimetic entry along intermediate **127**.

Since our strategy builds on the synthesis of the etheno-bridged diazadecalin core, a ring-opening might be a feasible entry to the core scaffold of the manzamine B (**126**) family. If tetracycle **127**, closely related to previously prepared substrates **64** and **82**, is activated at the tertiary amine, nucleophilic attack by an acetate at the adjacent α-carbon atom might be regioselective, when the reaction is releasing strain of the tricyclic core. A viable synthetic equivalent of this disconnection is precedented in the work from Han *et al.* (Scheme 2.27).[146]



Scheme 2.27. Biopatterned reorganization of a catharantine scaffold (**A**) towards the chippiine/dippinine-type frameworks, adopted from Han *et al*.[146]

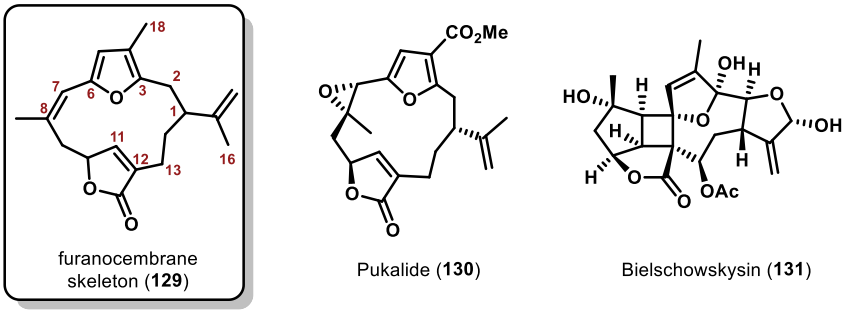
This approach takes advantage of the instability of certain difluoromethylated ammonium salts (**B** or **C**), which were accessed through *in-situ* generated difluorocarbene in presence of a tertiary amine (**A**). These semistable adducts can undergo C-N bond cleavage, when the associated anion attacks the α-position of the cyclic ammonium cation (**C**). In order to implement different nucleophiles, the authors utilized an anion exchange strategy, which takes advantage of the high affinity of silver(I) species towards halide anions (**B** → **C**). After aqueous workup, the reorganized *N*-formamide protected product (**D**) was obtained in good yield.[146]

3. Studies towards the Total Synthesis of Providencin

3.1 Introduction

The biomass in coral reef environments is largely dominated by gorgonian and soft corals. While reefs in the Indo-Pacific region are populated by soft corals (especially *Sinularia sp.*), the predominant species in the northwestern Atlantic ocean and the Caribbean Sea are gorgonian corals. These "sea plumes", named after the feather-like appearance of their branches, seem to have very few predators, such as fish or other competing reef organisms. This observation can be explained by certain metabolites, which act as chemical defense compounds and are known as the cembranoids. The most well-studied class of cembranoids from corals might be represented in the so-called furanocembranoids (Figure 3.1).[147]

Figure 3.1. General furanocembranoid skeleton and representative examples.



This class of natural products presents itself with a 14-membered ring, embedding a furan from C3 to C6 and a butenolide unit from C10 to C12. Generally, the metabolites can be highly oxidized bearing almost all possible oxidations states at C18 (except for CH_2OH), epoxidations in the C7-C8 and the C11-C12 positions, acetoxylation at C13 and oxidation at C2 and/or C16. Notably, in natural products with the *trans*-configuration between C7 and C8, an epoxide at this position is observed in most cases.[148]

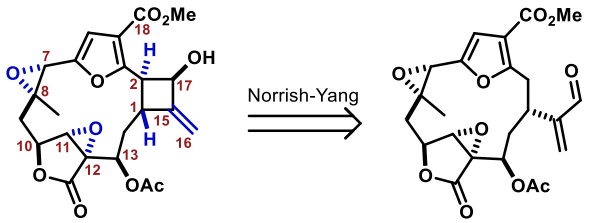
The first member of this family to be characterized in 1975 by Scheuer *et al*.[149] was pukalide (**130**) from *Sinularia abrupta*. The diverse and rich chemistry of furans is reflected in several rearranged natural products,[147,150] culminating in arguably one of the most complex molecular architectures in bielschowskysin (**131**), isolated from *Pseudopterogorgia kallos* in 2004.[151] Although most metabolites of this gorgonian octocoral are not oxidized at C18,[152] an exception was found in providencin (**132**) a natural product isolated in 2003.[153] The isolation and structure of the aforementioned furanocembranoid is described in the following section.

3.1.1 Isolation and Structure

Specimen of *Pseudopterogorgia kallos* were collected near Providencia Island in the southwestern Caribbean sea. The dried material was homogenized in a mixture of dichloromethane and methanol, before it was concentrated *in vacuo*. Partitioning between

hexane, chloroform and ethyl acetate, with subsequent purification of the chloroform-soluble material *via* size-exclusion chromatography, yielded providencin (**132**, 20 mg, 0.012% dry weight). The chemical structure was elucidated with the help of different 1D- and 2D-NMR experiments, while X-Ray diffraction of a suitable single crystal grown in methanol/chloroform (9:1 *v*/*v*) provided proof. It is dextrorotatory (α_D^{20} = +7.9°, *c* = 1.2 in $CHCl_3$), however, the absolute configuration of the natural product remains unknown.[153]

Figure 3.2. Structure of providencin (**132**) and its proposed biogenetic precursor bipinnatin E (**133**).



Providencin (**132**) Bipinnatin E (**133**)

The diterpene features a bicyclo[12.2.0] hexadecane ring system with a *trans*-fused cyclobutane at C1-C2. An *exo*-methylene moiety (C15-C16) and an allylic alcohol at C17 decorate the cyclobutane unit, while the C7-C8 *E*-alkene and the C11-C12 position of the butenolide are epoxidized. Another attribute of highly oxidized furanocembranoid members is the acetoxylation at C13. Interestingly, the C18 terminus of the furan unit (C3-C6) is oxidized and subsides as the methyl ester, which is unusual for a metabolite extracted from *Pseudopterogorgia kallos*.[153]

Biosynthetically, providencin (**132**) was proposed to arise through a Norrish-Yang cyclization from bipinnatin E (**133**).[154,155] This hypothesis is supported by model studies carried out by Pattenden *et al.*,[156] who could show that irradiation of a structurally simplified substrate indeed furnished the cyclobutanol, albeit in low yields.

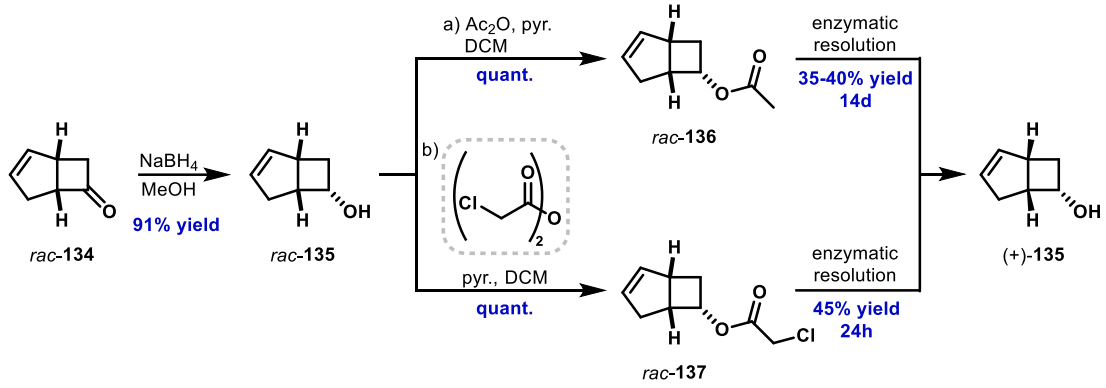
Beyond the intriguing chemical architecture, providencin was tested for biological activities in various cell assays. Therein, it showed modest cytotoxicity *in vitro* against MCF7 breast cancer, NCI-H460 non-small cell lung cancer and SF-268 CNS cancer cells.[153]

Overall, providencin (**132**) has been at the top of the list for synthetic chemists, ever since its discovery in 2003. In particular, the tetrasubstituted cyclobutane sub-unit attracted a lot of attention, since it appears as a unique feature of this particular natural product. A short overview of the literature tackling this highly oxidized marine diterpene is provided in the following section.

3.1.2 Literature Review

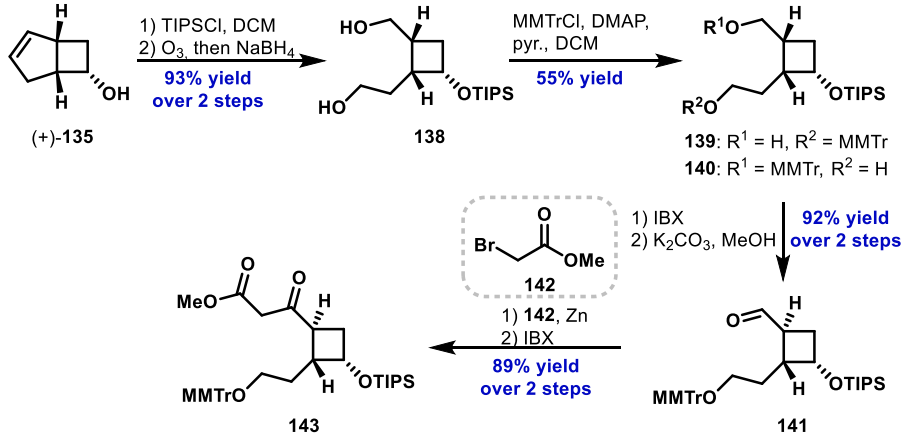
In 2007, Mulzer *et al.* reported their initial work targeting providencin (**132**).[157] Regarding the cyclobutane section of the natural product, they identified racemic bicycloheptenone (**134**) as their starting point (Scheme 3.1). Diastereoselective reduction of **134** furnishes alcohol *rac*-**135**,

which can be diverted into acetate *rac*-**136** (pathway a), or chloroacetate *rac*-**137** (pathway b). The enzymatic resolutions are both satisfactory in terms of yield and enantioselectivity, however, acetate *rac*-**136** only converts slowly over two weeks, while chloroacetate shows favorable kinetics reaching its endpoint in 24 hours.[158]



Scheme 3.1. Synthesis of enantioenriched bicycloheptenol **135** *via* enzymatic resolution.[158]

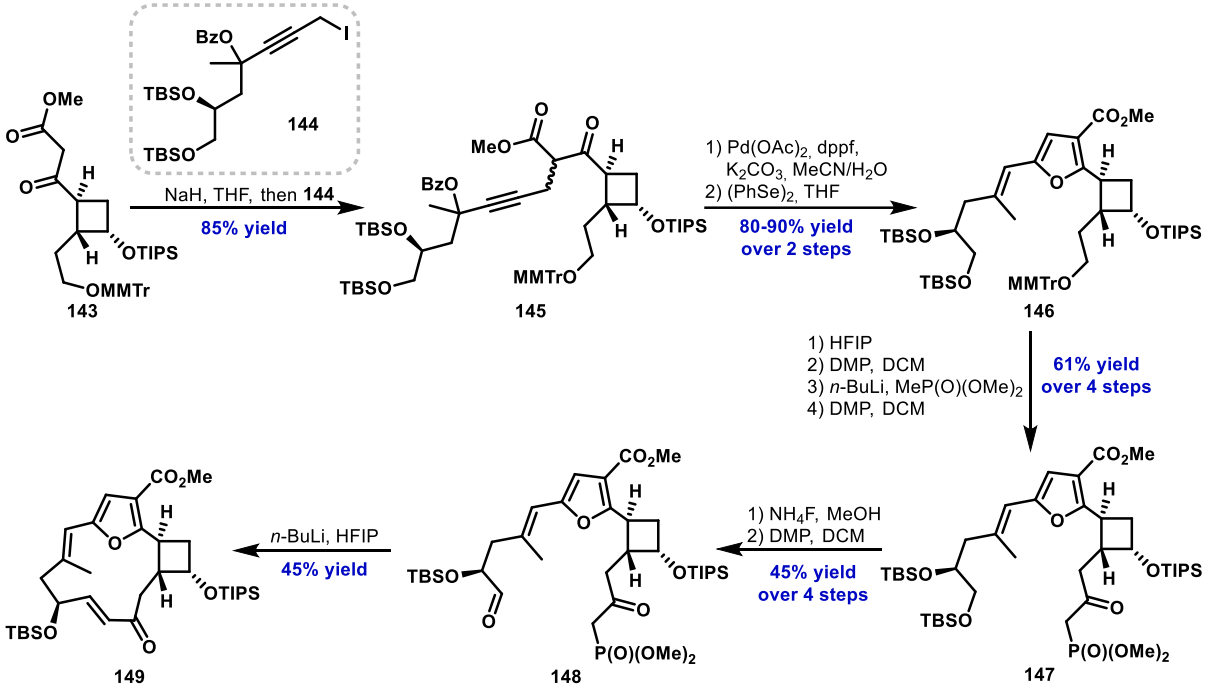
With the enantioenriched cyclobutanol in hand, they set out to install the furan moiety (Scheme 3.2). In practical terms, *O*-silylation of (+)-**135** followed by ozonolysis and *in situ* reduction of the bis-aldehyde gave diol **138** in good yields.[158] Selective tritylation using monomethoxytrityl chloride (MMTrCl) gave a separable mixture of mono-protected alcohols **139** and **140**. The desired alcohol **139** was oxidized to the aldehyde by means of IBX, which, upon treatment with catalytic potassium carbonate in methanol, results in epimerization, yielding the now *trans*-configured cyclobutyl-aldehyde **141**.[158] Reformatsky reaction with bromoacetate **142** and subsequent oxidation reveals the β-ketoester **143** in very good yield.



Scheme 3.2. Synthesis of the enantioenriched β-ketoester **143**.[158]

Next, deprotonation followed by alkylation with propargyl iodide **144** furnished alkyne **145** as a mixture of diastereomers (Scheme 3.3). Pd-mediated Wipf cyclization[159] afforded furan **146** as a 1:1 mixture of *E*-/*Z*-isomers, which were equilibrated to the desired *E*-isomer through a radical addition/elimination pathway with diphenyl diselenide.[158] Subsequent MMTr

cleavage in HFIP and introduction of the phosphonate moiety for an intramolecular HWE reaction was achieved over four steps. Deprotection of the primary TBS ether with ammonium fluoride in methanol and oxidation to the aldehyde gave macrocyclization precursor **148** in moderate yields. The olefination proceeded well, with *n*-butyllithium in HFIP at high dilution, considering the extraordinarily high ring strain presumably exhibited by the *trans*-fused cyclobutane and the *E*-configured C7-C8 olefin.



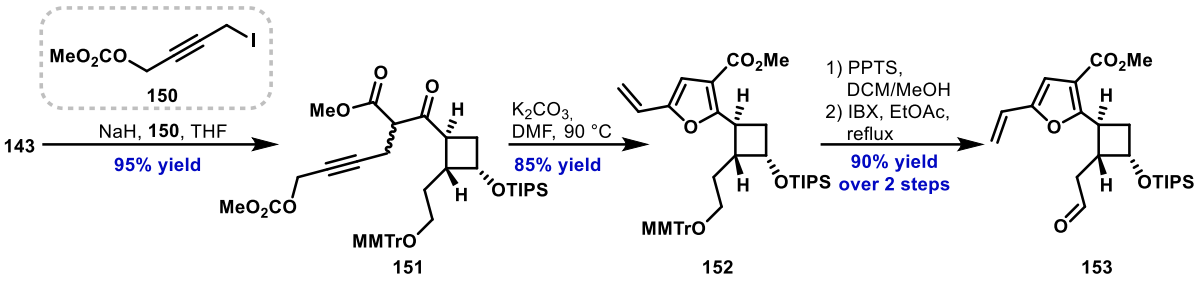
Scheme 3.3. Furan formation and macrocyclization *via* HWE olefination.[158]

Despite disclosing this late-stage intermediate in combination with the proposal of an endgame-strategy, no further work was published by Mulzer *et al.* pursuing this approach.

Instead, a different strategy was engaged in which the macrocyclization event was changed from the intramolecular HWE olefination to an olefin metathesis. Furthermore, the site at which the ring closure was going to be carried out was revised to the C7-C8 alkene. In practical terms, this approach was deemed to be more convergent and allowed for the preparation of more simplified fragments. Although already mentioned in their 2009 publication on synthetic efforts towards providencin (**132**), it took another five years until the total synthesis of 17-deoxyprovidencin (**160**) was disclosed.[160]

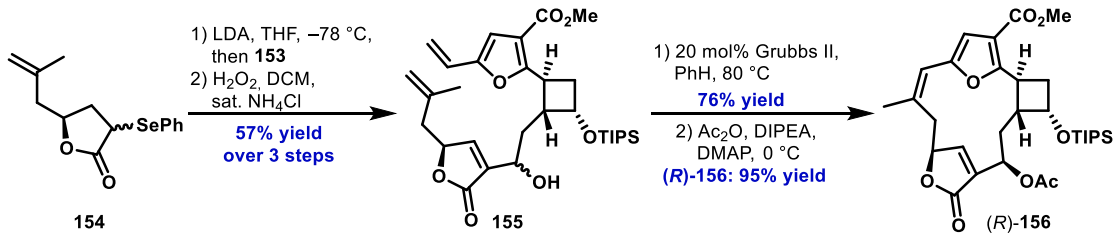
In similar fashion to the first-generation approach, the synthesis of the furan fragment commenced with enantioenriched β-ketoester **143**, generated *via* enzymatic resolution (Scheme 3.1). At this point, alkylation of **143** with simple propargyl iodide **150** furnished alkyne **151**, which was cyclized under base catalysis to give furan **152** (Scheme 3.4).

Detritylation under acidic conditions and oxidation of the resulting primary alcohol by IBX in boiling EtOAc, gave rise to the vinyl furan fragment **153**.[160]



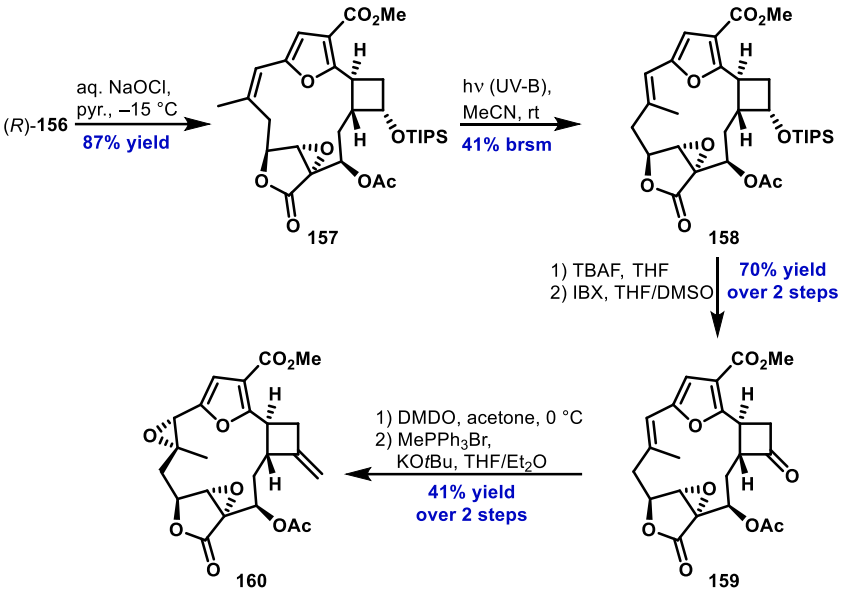
Scheme 3.4. Synthesis of the vinyl furan fragment **153**.[160]

Selenolactone **154**, synthesized from *(R)*-glycidyl tosylate in four steps, was deprotonated with LDA at cryogenic temperatures and treated with aldehyde **153**, generating the aldol product (Scheme 3.4). The latter was oxidized with aqueous hydrogen peroxide, to mediate selenoxide elimination, thereby forging the butenolide **155** as a mixture of diastereomers (dr 1.5:1).[160] This mixture was treated with catalytic amounts (20 mol%) of Grubbs II catalyst (**88**) in refluxing benzene, affording the unsaturated macrocycle exclusively, as the undesired *Z*-isomer. Separation of the C13-diastereomers and subsequent acetylation of the secondary alcohol produced bis-olefin **156**.



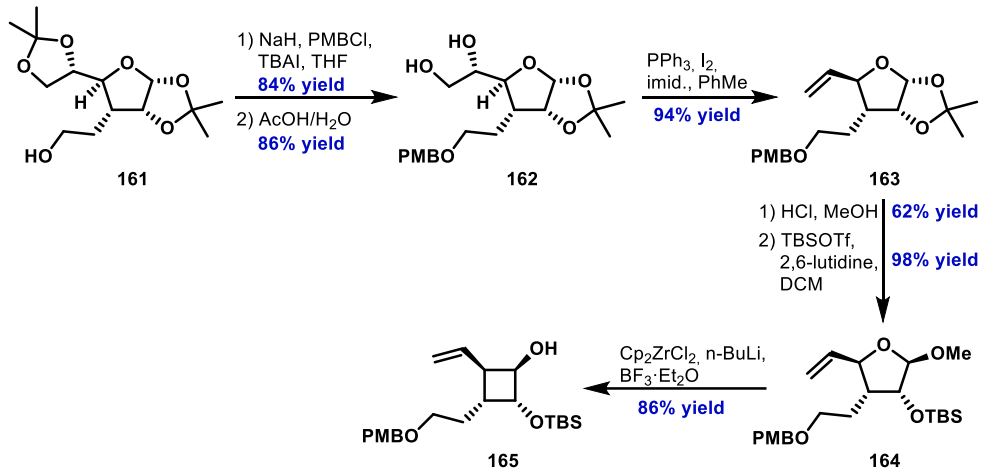
Scheme 3.4. Fragment coupling and subsequent RCM.[160]

Epoxidation at the butenolide subunit proceeded smoothly when *(R)*-**156** was treated with sodium hypochlorite in pyridine (Scheme 3.5). At this stage, the *Z*-olefin **157** was isomerized under irradiation with UV-B light resulting in a separable mixture of *E*-/*Z*-isomers in low yield.[160] The E-isomer **158** was desilylated with TBAF, revealing the secondary alcohol, which was oxidized to the corresponding ketone **159**. Only this intermediate succumbed to epoxidation with DMDO in diastereoselective fashion, while a final Wittig olefination furnished 17-deoxyprovidencin (**160**).[160]



Scheme 3.5. Photoinduced *E*-/*Z*-isomerization and endgame towards 17-deoxyprovidencin (**160**).[160]

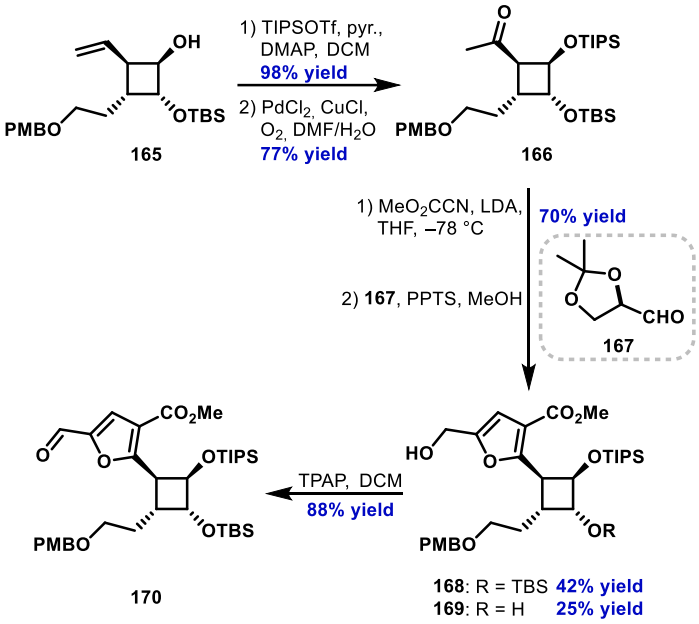
This heroic effort by Mulzer and coworkers represents the most advanced foray towards providencin (**132**). To this date, however, no further attempts were disclosed moving from 17-deoxyprovidencin (**160**) to actual providencin (**132**).



Scheme 3.6. Cyclobutane formation *via* oxygen atom excision from furanoside **164**.[161]

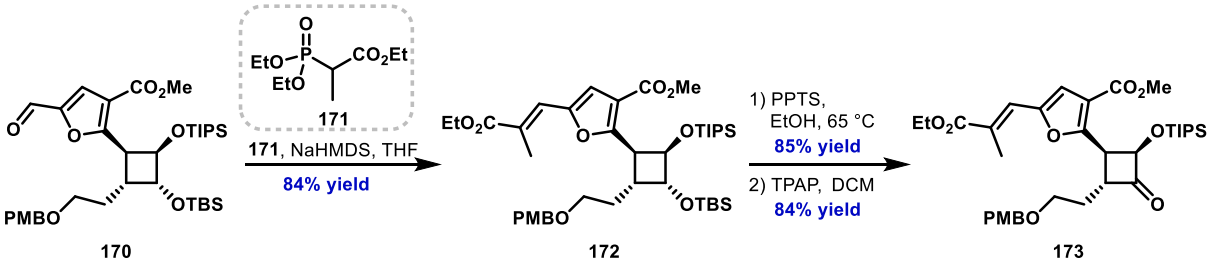
In 2009, White *et al.* disclosed their take on providencin (**132**). Starting from the chiral pool, specifically D-glucose, bis-acetonide **161** was synthesized in four steps.[162,163] Standard protecting group manipulations gave rise to diol **162**, which under treatment with triphenylphosphine, iodine and base transforms to olefin **163** (Scheme 3.6). Acetonide cleavage in acidic methanol, followed by TBS protection furnished methyl-furanoside **164**. *In situ* generated dicyclopentadienyl zirconium(II) mediates a stereoretentive oxygen atom abstraction, producing cyclobutanol **165** in good yield.[164]

After protection of the secondary alcohol as the TIPS ether, Wacker-Tsuji oxidation[165] revealed the methyl ketone **166**, from the vinyl handle formed in the cyclobutane formation (Scheme 3.7). Ketone **166** was reacted with LDA and the resulting enolate trapped with methylcyanoformate. The resulting β-ketoester was treated with D-glyceraldehyde acetonide **167** under acidic conditions, converting slowly into a mixture of silylated (**168**) and desilylated products (**169**) after the initial Knoevenagel condensation. Ley-Griffith oxidation[166] of benzylic alcohol **168** furnished aldehyde **170** in good yield.[164]



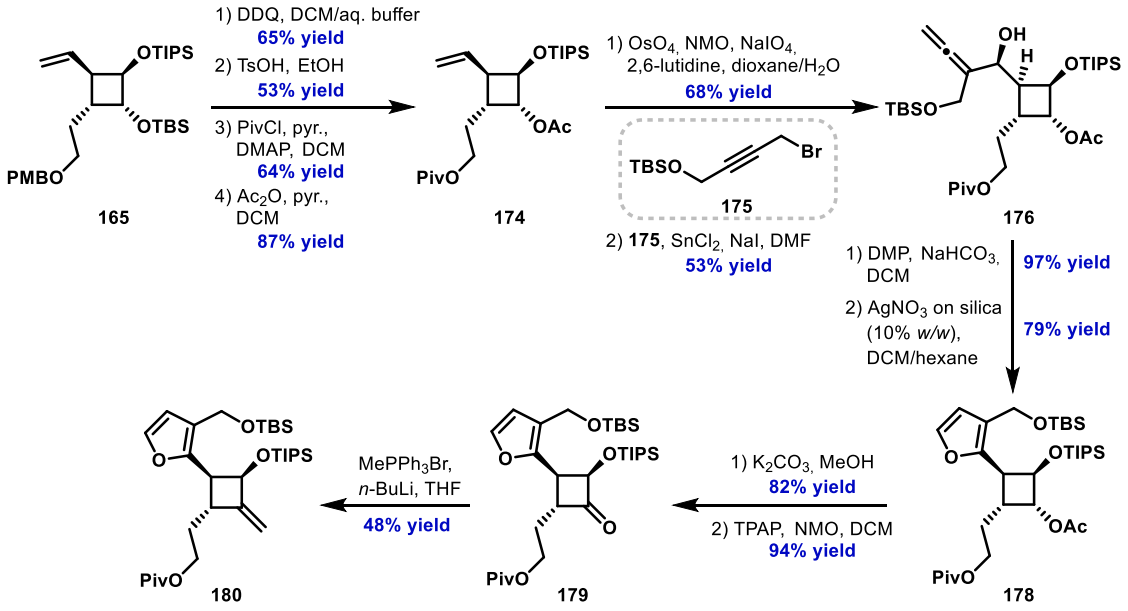
Scheme 3.7. Further elaboration of the cyclobutane fragment **165** in White's approach.[164]

To this end, HWE olefination with phosphonate **171** produced ester **172** in high *E*-selectivity (Scheme 3.8). This route, however, was abandoned after it was found that TBS cleavage with PPTS at elevated temperatures in ethanol and final oxidation of the secondary alcohol to the ketone resulted in a substrate which could not be moved forward. Problems of distinguishing the different ester moieties and *exo*-methylene installation forced the authors to pursue a different approach.[161]



Scheme 3.8. Synthesis of the final intermediate **173** in White's first-generation approach.[164]

In practical terms, intermediate **165** was selected as the starting point for the second-generation approach. A laborious sequence of protecting group manipulations led to acetate **174**, which undergoes oxidative cleavage of the alkene in presence of sodium periodate and catalytic amounts of osmium tetroxide (Scheme 3.9).[167]

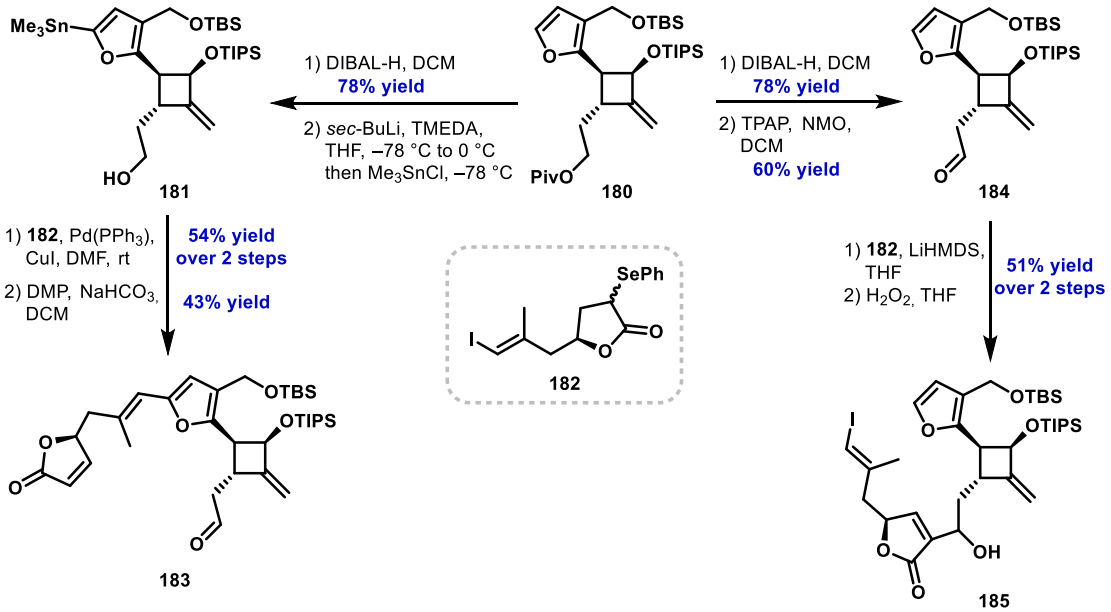


Scheme 3.9. Synthesis of a modified cyclobutane fragment **180** in a second-generation approach.[167]

Reaction of this aldehyde with propargyl bromide **175** in presence of stannous chloride gave the allenic alcohol **176** as a single diastereomer. Following oxidation to the corresponding ketone, silver nitrate on silica mediated the cyclization to the furan, a procedure by Marshall and coworkers.[168,169] Furan **178** undergoes acetate cleavage and subsequent oxidation with Ley's reagent to furnish ketone **179**. This building block, as similar as it seemed to the first-generation intermediate **173**, succumbed to methylenation with the corresponding Wittig salt and *n*-butyl lithium as base. The authors eventually concluded that the failed methylenation at the stage of the former ketone intermediate **173** must not be attributed to the substituents on the cyclobutane, but rather to the furan moiety.[167]

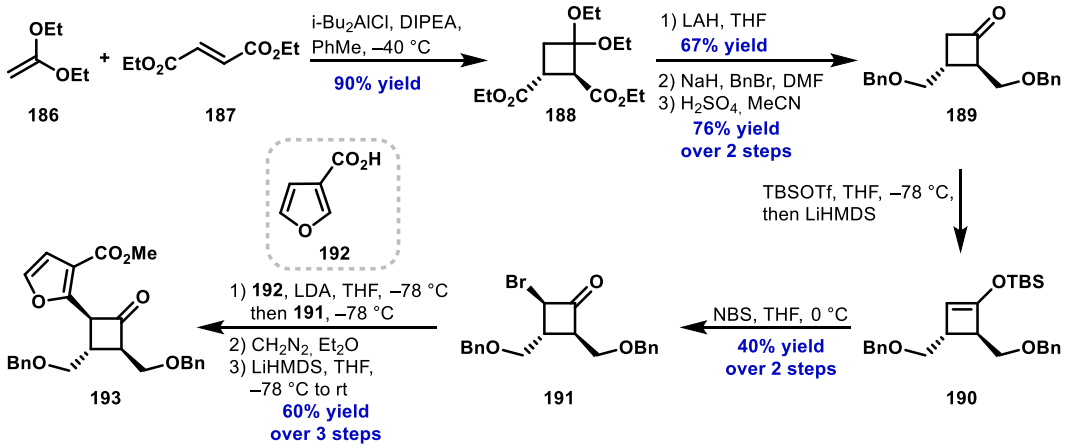
At this stage, two distinct pathways were investigated (Scheme 3.10). Reductive cleavage of the pivalate and subsequent oxidation furnished aldehyde **184**. Next, treatment of fragment **182** with LiHMDS and oxidative selenide elimination gave the aldol product **185**. Unfortunately, all attempts to cyclize **185** *via* C-H activation on the furan led to decomposition of the substrate. Therefore, a second pathway was tested, in which pivalate cleavage was followed by functionalizing the furan through deprotonation in the 2-position and quenching of the corresponding anion with trimethyltin chloride. Stille cross-coupling with alkenyl iodide **182** afforded the selenide product, but, all attempts to oxidize the primary alcohol in presence of the phenylselenide substituent led to oxidative elimination. This unexpected

pitfall forced the authors to abandon the attempted total synthesis of providencin (**132**) along the lines investigated.[167]



Scheme 3.10. Attempted endgame of White's second-generation approach towards providencin (**132**).[167]

Apart from these in-depth studies by the groups of Mulzer[157,158,160] and White[164,167], another effort was undertaken by Wood *et al.*[170], who disclosed a short, but racemic, route towards a viable cyclobutane fragment in 2011. Therein, diethyl ketene acetal **186** was reacted with diethyl fumarate **187** in presence of diisobutyl aluminium chloride in toluene at cryogenic temperatures, affording the [2+2]-cycloaddition product **188** (Scheme 3.11).



Scheme 3.11. Wood's synthesis of the furanyl-cyclobutanone fragment **193**.[170]

Exhaustive reduction employing lithium aluminium hydride, followed by double benzyl protection and acetal hydrolysis gave rise to cyclobutanone **189**. Formation of the silyl enol ether **190** and subsequent trapping with NBS produced bromo ketone **191** as a mixture of

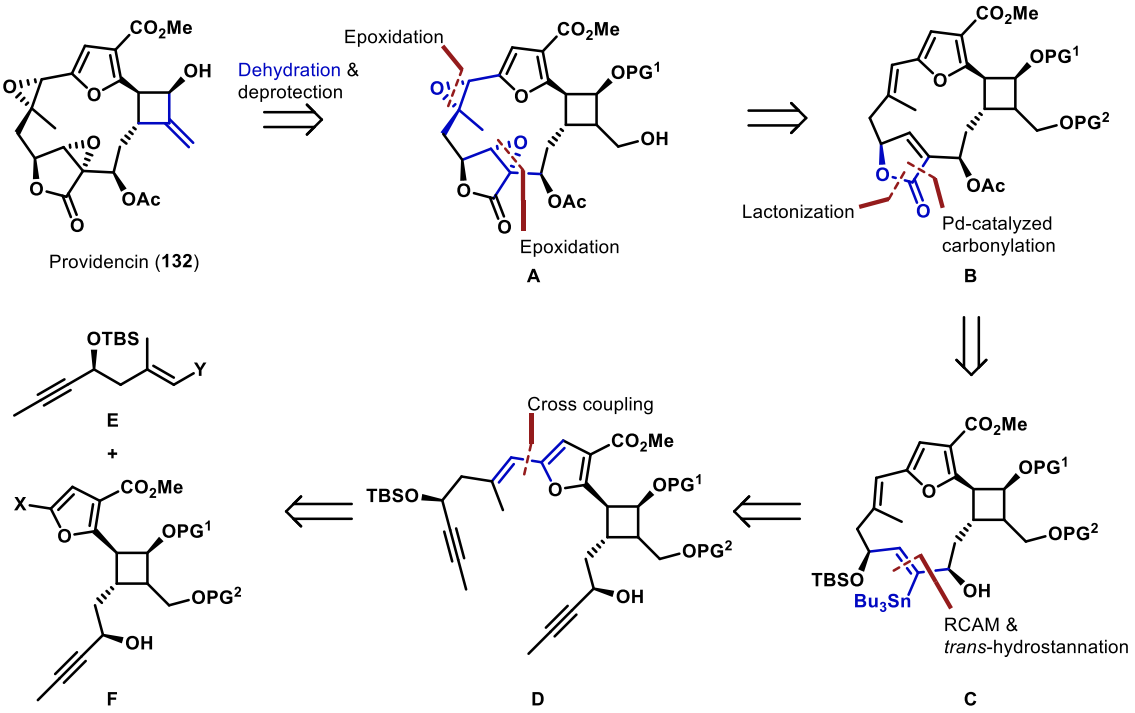
diastereomers (dr 6:1). The installation of the furan was anticipated to proceed *via* the 1,2-addition product of ketone **191**. In practical terms, 3-furoic acid (**192**) is deprotonated and attacks the ketone forming a tertiary alcohol as evidenced in NMR studies. This intermediate can be reacted with diazomethane to form the methyl ester, which after treatment with base undergoes a 1,2-shift with displacement of bromine, to furnish furanyl-cyclobutanone fragment **193**. Despite this concise entry into a possible synthesis of providencin (**132**), no further developments along these lines have been disclosed since.

3.2 Towards the Total Synthesis of Providencin *via* a Ring Closing Alkyne Metathesis Approach

To this day, the furanocembranoid providencin (**132**) remains an elusive target in natural product synthesis. Intrigued by previous heroic efforts from Mulzer[157,158,160] and White[161,167], a retrosynthetic analysis of **132** was devised, which tries to address the shortcomings of earlier approaches, to eventually conquer this puzzling diterpene. It was conjectured that the use of RCAM at the centerpiece of the retrosynthesis might resolve the major challenge of macrocyclization in this highly strained system. Previous studies on the total synthesis of lactimidomycin revealed the advantages of RCAM over RCM, when the ring strain can be attributed to transannular interactions rather than angle strain.[171–174] With this caveat in mind, a synthetic program towards providencin (**132**) was initiated, ideally going through a versatile intermediate.

3.2.1 Retrosynthetic Analysis

Since the installation of the *exo*-methylene group in **132**, was shown to be highly sensitive to substituents on the furan, when installed from the corresponding ketone,[161,167] we anticipated to reveal this functionality by means of a formal late-stage dehydration (Scheme 3.12). Final deprotection on the C17 alcohol would then afford providencin (**132**). Intermediate **A** was envisaged to arise from stepwise epoxidation, as previously described in Mulzer's effort.[160] In an ideal setting the C16-OH, serving as the handle for exo-methylene installation, should be orthogonally protected to the C17-OH.

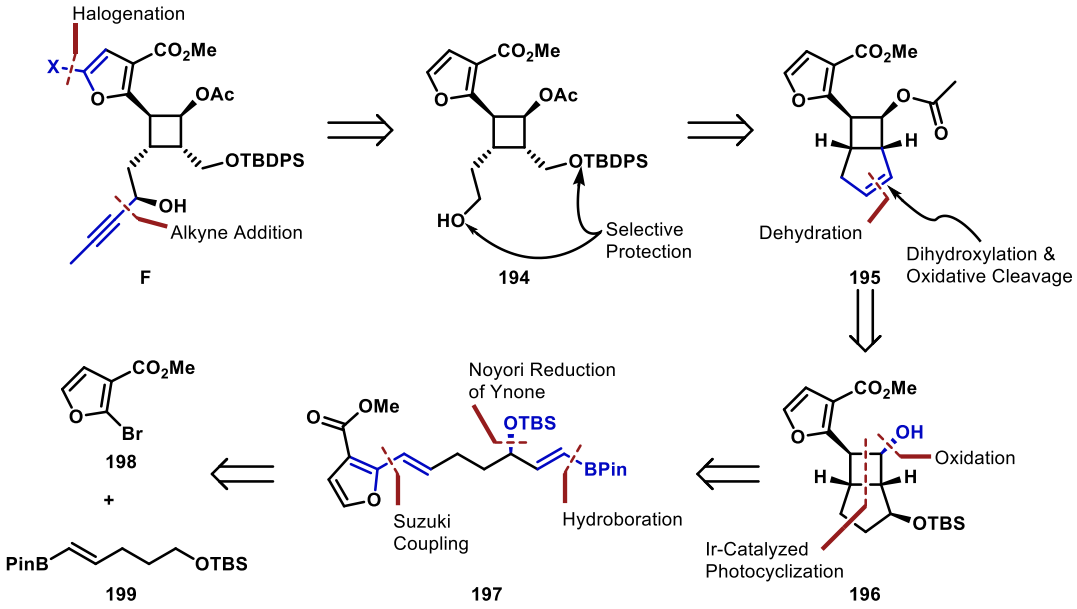


Scheme 3.12. Retrosynthetic analysis of providencin (**132**).

Although these hydroxy groups should be distinguishable due to their primary- and secondary substitution, an orthogonal protection strategy seemed to be the more sensible option. Butenolide **B** was planned to be assembled through carbonylation of the corresponding alkenyl stannane,[92,175] which after desilylation should readily cyclize to produce the butenolide unit. Alkenyl stannane **C** could arise from *trans*-hydrostannation of the corresponding mono-protected butyne-1,4-diol subunit.[176,177] Macrocylization *via* RCAM of the corresponding bis-propargylic compound **D** would forge the precursor of **C**. Cross-coupling of furan building block **F** and properly functionalized enyne fragment **E** were anticipated to allow access to **D**.

The fragment coupling was especially well precedented in the literature, since both Negishi and Stille cross couplings were extensively used to assemble the carbon skeletons of various furanocembranoids.[178–181]

In terms of fragment **E**, our own group had established a racemic route to similar building block in the total synthesis of manshurolide.[91] Along these lines, the route was expected to allow certain modifications that would render the synthesis asymmetric. Particularly the asymmetric propargylation by Carreira *et al.* was deemed promising in this setting.[182]

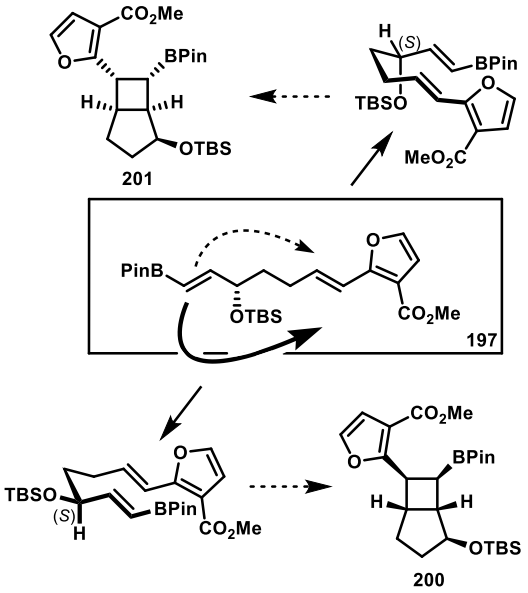


Scheme 3.13. Retrosynthetic analysis of the furanyl-cyclobutanol fragment.

The cyclobutane containing fragment **F**, however, turned out more involved (Scheme 3.13). Since the direct enantioselective access to cyclobutanes is extremely challenging, only a few appropriate methodologies could be found in the literature. At the start of the synthetic campaign, two routes were considered, employing either an enantioselective allenoate-alkene [2+2] cycloaddition developed by Brown *et al.*[183–187] or a photosensitzed [2+2] cycloaddition developed by Yoon *et al.*[188,189]. Although, the first approach could generate the cyclobutane in

enantioselective fashion, the introduction of the desired oxidation state at C17 was not well precedented by using that strategy. Additionally, the intrinsic instability and sensitivity of the prerequisite alkynoates were expected to be potential troublemakers.

On the other hand, Yoon *et al.* could introduce the hydroxyl function into their cyclobutane scaffolds *via* oxidation of the secondary pinacol boronic esters, however, no enantioselective access to the cyclobutanes was developed.[189] This fact notwithstanding, the substrate scope contained heterocycles, including furans, making it the prime candidate in the setting of providencin. Furthermore, a relay of stereoinformation from a distant chiral center, onto the cyclobutane upon diastereoselective ring formation was envisaged to circumvent the lack of options for introducing chirality directly. Thus, it was conjectured that fragment **F** could arise from oxidative cleavage of cyclopentene **195**, followed by differentiation of the resulting primary alcohols (Scheme 3.13). The alkene moiety would be introduced through the dehydration of an enantioenriched secondary alcohol in **196**, serving the purpose of rendering this route enantioselective.



Scheme 3.14. Possible conformers of **197** in the [2+2] cycloaddition step.

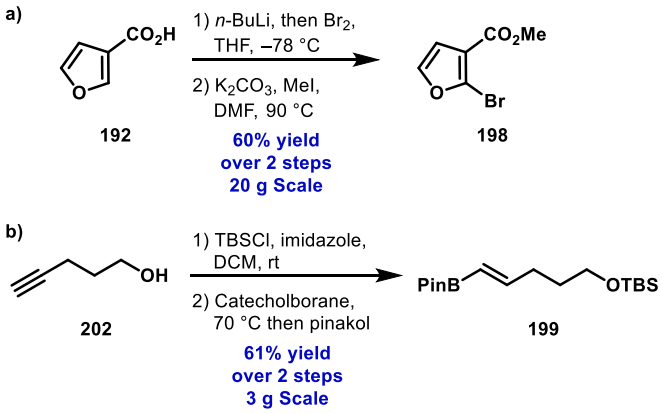
It was presumed, that the photosensitized [2+2] cycloaddition could proceed with facial selectivity, because the two possible pseudochairlike transition states resulting from folding of linear alkenyl boronate **197** exhibit either an axial- or equatorial-oriented TBS-ether, producing two distinct diastereomers. However, this stereochemical model is significantly simplified and excludes the possibility of other half-chair conformers of the open-chain cyclopentane section in the transition state.[190]

Cyclobutanes **200/201** can be traced back to alkenylboronate **197**, which in turn was envisaged to be produced *via* hydroboration of a terminal alkyne. The critical stereocenter was projected to be introduced *via* Noyori transfer hydrogenation of the corresponding TMS-capped

ynone.[191,192] A Suzuki coupling merges bromofuran **198** and alkenyl boronic ester **199**, before the TBS ether is deprotected, oxidized and treated with deprotonated trimethylsilylacetylene.

3.2.2 Synthesis of the Furanyl-Cyclobutanol Fragment

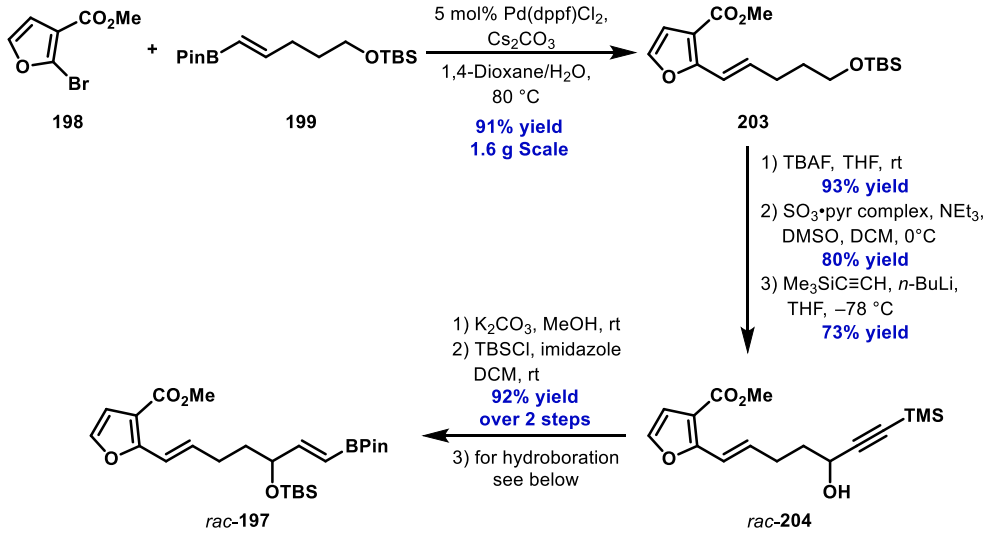
Reduced to practice, commercially available 3-furoic acid (**192**) was transformed into 2-bromofuran-3-carboxylic acid via a literature procedure.[193] The crude material was subjected to methyl iodide and potassium carbonate in DMF at elevated temperature, affording the crude methyl 2-bromofuran-3-carboxylate (**198**), which was purified by flash chromatography yielding the desired furan building block in 60% yield over two steps and a single chromatographic purification step on decagram scale (Scheme 3.15). The coupling partner was prepared *via* *O*-silylation of **202**, followed by hydroboration in neat catecholborane and subsequent pinacol-for-catechol exchange. The alkenyl boronate **199** was isolated in 61% yield over 2 steps.[194]



Scheme 3.15. Syntheses of the Suzuki coupling precursors **198** and **199**.

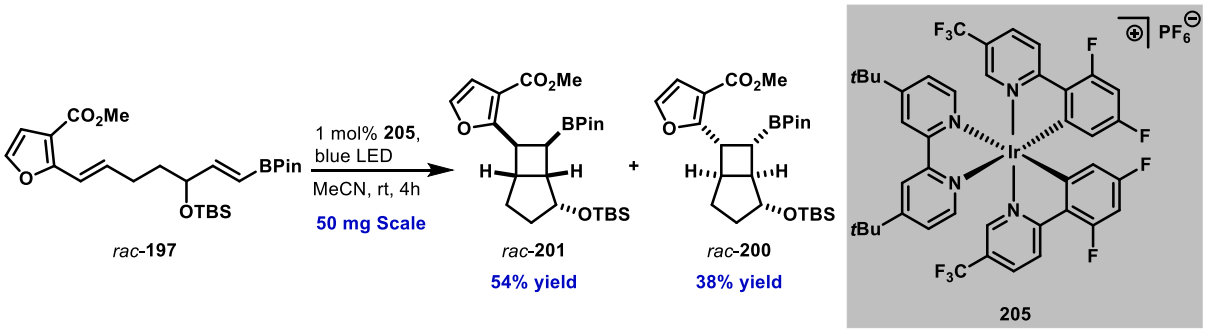
The Suzuki coupling proceeded smoothly under standard conditions, giving access to the alkenylfuran **203** in good yield on gram scale (Table 3.1). To prove the feasibility of this approach, we initiated our first foray towards the [2+2] cycloaddition in a racemic manner. Thus, desilylation of the TBS-ether, Parikh-Doering oxidation[139] of the primary alcohol and lithium acetylide addition into the aldehyde furnished propargyl alcohol **204** in reproducible fashion. Next, TMS-cleavage and *O*-silylation with TBSCl gave the terminal alkyne, ready for hydroboration. Although the hydroboration proceeded in low yields when Wang's conditions[195] were employed using catalytic Schwartz reagent, recourse to the 9-H-9-BBN catalyzed hydroboration of the terminal alkyne, known as the Arase-Hoshi conditions,[196–198] furnished the desired alkenyl boronate *rac*-**197** in good yield.

Table 3.1. Racemic synthesis of the [2+2] cycloaddition precursor *rac*-**197**.



Entry	Catalyst	Reagents	Solvent	T / °C	Yield
1	10 mol% Cp_2ZrHCl	HBPin, NEt_3	-	60 °C	33%
2	**10 mol% 9-H-9-BBN**	**HBPin**	**THF**	**60 °C**	**80%**

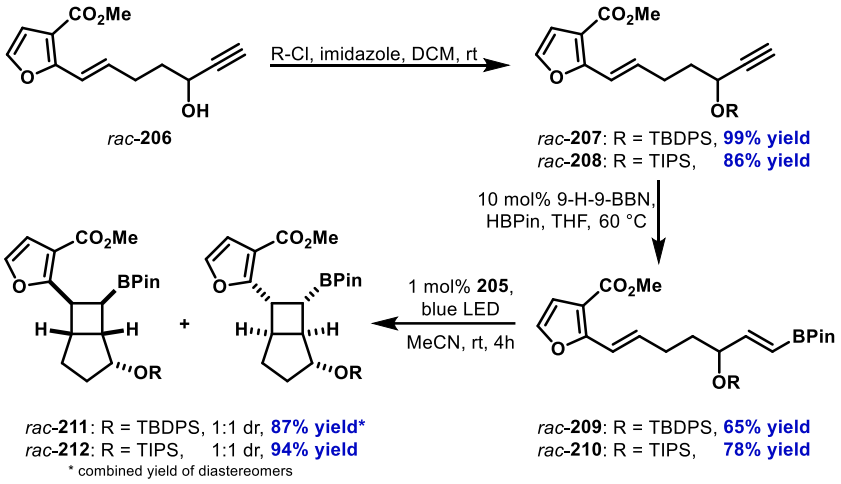
At this stage alkenyl boronate **197** was ready to be cyclized in presence of photocatalyst **205** (Scheme 3.16) under conditions previously described by Yoon *et al.*[188,189]. Treatment with the Ir-catalyst **205** in carefully degassed acetonitrile accomplished the [2+2] cycloaddition in impressive fashion, yielding a diastereomeric mixture (1.6:1 dr) of cyclobutanes *rac*-**201** and *rac*-**200** in a combined yield of 92%.



Scheme 3.16. Photosensitized intramolecular [2+2] cycloaddition of furan *rac*-**197**.

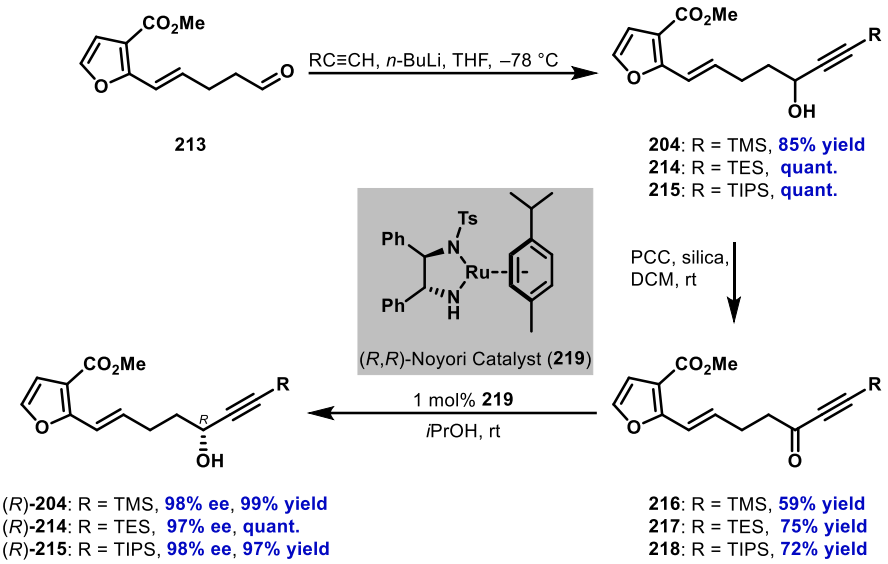
NOE-studies of the separated diastereomers showed that the isomers are enantiomeric regarding all the substituents on the cyclobutane. Although we had hoped, that the TBS-ether might induce higher levels of diastereoinduction (Scheme 3.14), the fact that the absolute configuration of providencin (**132**) remains elusive, necessitated access to both enantiomers of the furanyl-cyclobutanol fragment. To test whether higher levels of stereoinduction could be achieved when bulkier silyl ethers are installed at the stage of the propargyl alcohol **206**, TIPS-

and TBDPS-protected **209** and **210** were targeted (Scheme 3.17). Silyl protection under standard conditions furnished terminal alkynes **207** and **208**, which readily succumbed to hydroboration using Arase and Hoshi's procedure.[196] The photocycloaddition proceeded smoothly, although no superior diastereoselectivity was observed for adducts **211** and **212**. Interestingly, the stereoselectivity compared to the TBS-ether **197** is actually slightly worse (1:1 dr). With these results in hand, the synthesis was intended to be pushed forward with TBS-ether **197**, since it is the most simple of the three protecting groups and worked equally well, if not somewhat better than the others.



Scheme 3.17. Synthesis of different silyl-protected alcohols for [2+2] cycloaddition.

With a route towards the cyclobutane core established, the efforts turned to rendering the synthesis asymmetric. As indicated in the retrosynthetic analysis (see scheme 3.13) it was envisaged to introduce the critical stereocenter *via* Noyori's transfer hydrogenation of a silyl-capped ynone.[191,192] In order to test the influence of the silyl-cap on the enantioselectivity of the Noyori reduction, three easily accessible ynones were prepared (Scheme 3.18). Starting from aldehyde **213**, addition of the corresponding lithium acetylides afforded the TES- and TIPS-capped propargylic alcohols **214** and **215** respectively in quantitative yields. Due to partial TMS cleavage, the TMS-capped propargylic alcohol **204** was isolated in only 85% yield. Oxidation of the propargylic alcohols with PCC[25] furnished the corresponding ynones **216**-**218** in moderate yields. With access to the ynones secured, the transfer hydrogenation, using Noyori's Ru-cymene complex (*R,R*)-**219**, resulted in excellent enantioinduction for all silyl-capped derivatives, while delivering the enantioenriched alcohols *(R)*-**204**, *(R)*-**214** and *(R)*-**215** in near quantitative yields.

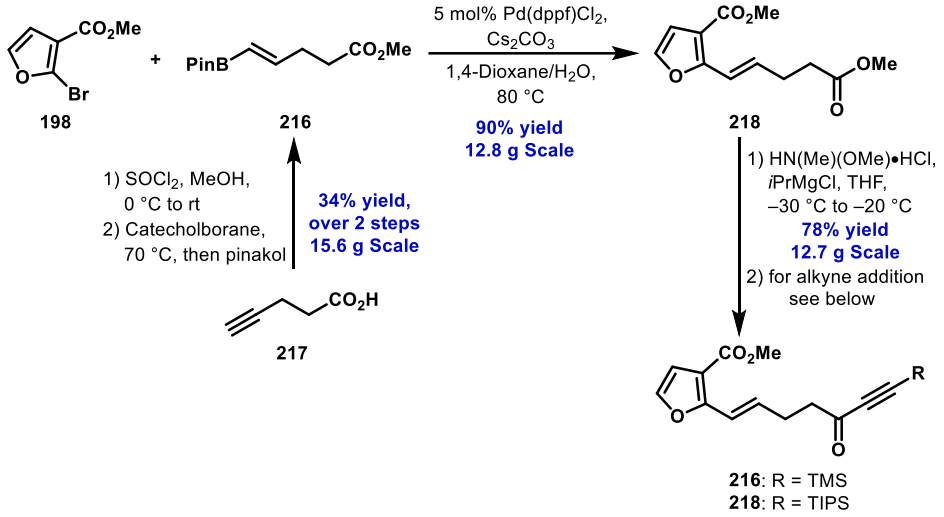


Scheme 3.18. Examination of the influence of different silyl-capped ynones on Noyori's transfer hydrogenation.

As the current route from alkene **203** to enantioenriched alkenyl boronic ester **197** comprised of three silyl group manipulations and two oxidation steps, a change in the starting material was envisaged in order to improve the atom and redox economy in our first scale-up. The synthesis of the corresponding alkenyl boronate **216** proceeded similarly to our previous fragment **199** (Table 3.2). The yield was slightly diminished, due to increased instability of the pinacol boronic ester **216** towards silica. For further improvements to this short sequence, recourse to the Epin-boronic ester[199] for increased stability towards silica gel should be considered.

The Suzuki coupling of bromofuran **198** and thus formed boronic ester **216** produced ester **218** in good yield on decagram scale. The Weinreb amide was selectively formed from the alkyl ester, ready for addition of the carbon nucleophile. While the addition of the organolithium arising from trimethylsilyl acetylene was accompanied by serious amounts of the desilylated alkynoate (Table, 3.2, Entry 1), the TMS-cleavage could be reduced by using EtMgCl as a base (Entry 2).

Table 3.2. Alkynoate synthesis *via* the Weinreb amide **218**.

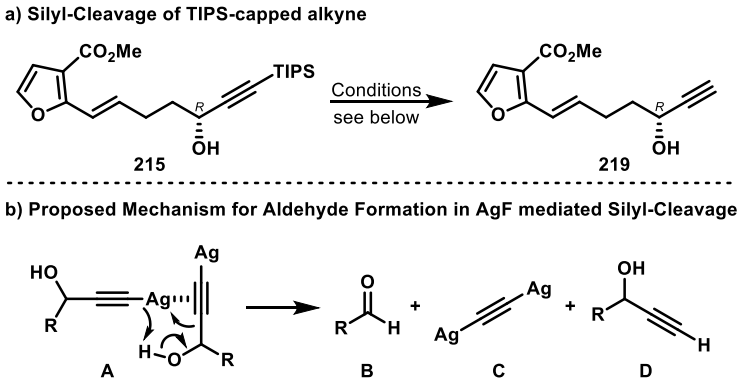


Entry	Alkyne	Base	T / °C	Solvent	Yield
1	$Me_3SiC{\equiv}CH$	*n*-BuLi	−78 to rt	THF	55%
2	$Me_3SiC{\equiv}CH$	EtMgCl	0 to rt	THF	76%
3	$iPr_3SiC{\equiv}CH$	*n*-BuLi	−78 to rt	THF	99%

This inconvenience could be completely circumvented when triisopropyl acetylene was deprotonated with *n*-butyllithium and the corresponding nucleophile added into the Weinreb amide derived from ester **218** (Entry 3). In this case no cleavage of the bulkier silyl cap was observed.

Surprisingly, TBAF mediated cleavage of the TIPS-group was quite low yielding (Table 3.3, Entry 1). When conditions using silver fluoride, originally reported by Kim *et al*.[200] were employed, copious amounts of the aldehyde were detected (Table 3.3, Entry 2). The formation of aldehyde **213** from propargyl alcohol **215** might be explained *via* a fragmentation first observed in steroid systems by Gardi *et al*.[201] Therein, silver acetylide produced after silyl-cleavage abstracts a proton of the propargylic alcohol (**A**) and thereupon aldehyde (**B**) and silver acetylide (**C**) are generated (Table 3.3). The formation of the latter presumably represents the driving force of this reaction.[202] Although the scope in Kim's study contains a propargylic alcohol, this fragmentation does not appear to be operative in their case.[200]

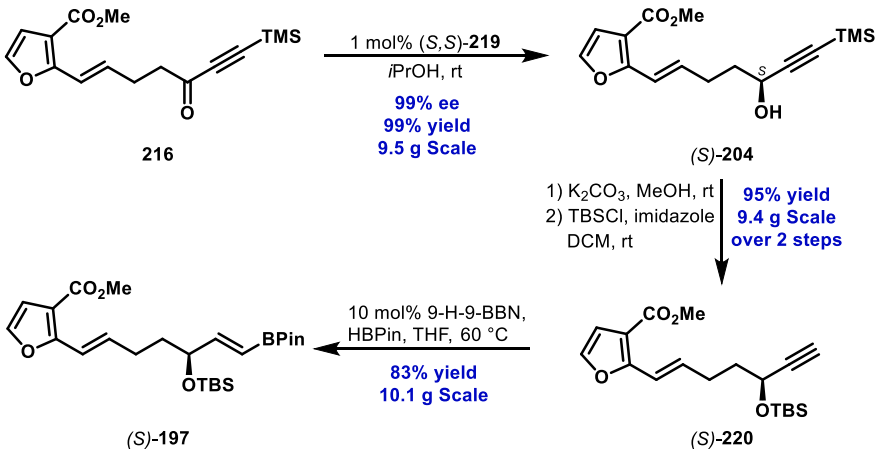
Table 3.3. Attempted silyl cleavage on TIPS-capped alkyne **215** (a) and proposed mechanism for AgF-mediated aldehyde fragmentation.



Entry	Reagent	T / °C	Solvent	Comment
1	TBAF	0 °C	THF	48% yield
2	AgF	rt	MeCN	3.8:1 **219**:**213**[a]

[a] Ratio determined by ^{1}H NMR.

With these results in hand, the trimethylsilyl-capped alkynoate **216** was pushed forward. As expected, Noyori transfer hydrogenation was perfectly transferable to multigram scale and provided alcohol (*S*)-**204** in practically perfect optical purity and quantitative yield (Scheme 3.19).[191,192] Cleavage of the silyl cap under basic conditions followed by standard TBS-protection furnished terminal alkyne **220** in very good yields over two steps. Arase and Hoshi's conditions for hydroboration produced alkenyl boronic ester *(S)*-**197** on decagram scale in a highly reproducible fashion.[196,198]

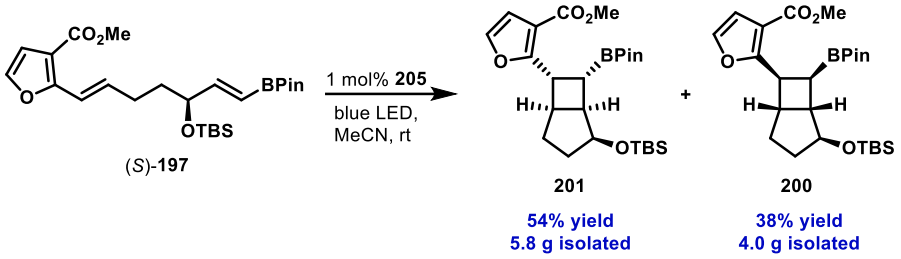


Scheme 3.19. Scale-up of the enantioselective route towards alkenyl boronic ester *(S)*-**197**.

Next, the scale-up of the photosensitized [2+2] cycloaddition was investigated. Since blue light is absorbed by neither glass nor water, the reaction was run in a water cooled, jacketed vessel to ensure sufficient heat transfer. Assuring efficient convection should mitigate long reaction

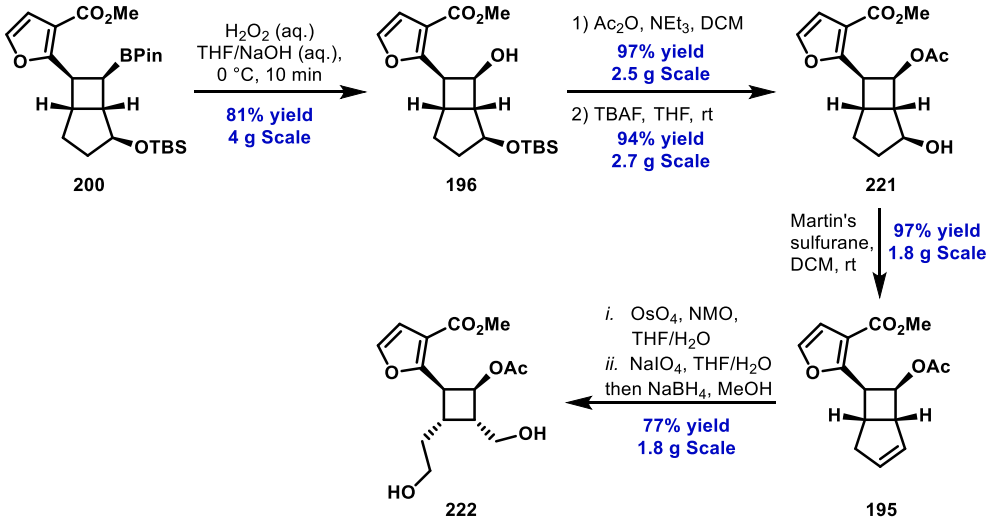
times, arising from inefficient light penetration in the larger reaction container. Reduced to practice, a solution of *(S)*-**197** accompanied by Ir-catalyst **205** in carefully degassed MeCN was irradiated with a blue LED (Scheme 3.20), thus resulting in the formation of cycloadducts **200** and **201**, which were easily separated by flash chromatography at decagram scale.

The modest diastereoselectivity (dr 1.5:1) of the transformation notwithstanding, it is worth mentioning, that the resulting products **200** and **201** are "quasi-enantiomers" regarding the cyclobutane subunit. As they are separable by flash chromatography, they should allow access to both enantiomers of fragment **195** (Scheme 3.13), which is desirable since the absolute configuration of providencin (**132**) remains unknown.



Scheme 3.20. Scale-up of the photosensitized [2+2] cycloaddition with enantioenriched alkenyl boronic ester *(S)*-**197**.

Reaction of **200**/**201** with sodium perborate resulted in slow decomposition of the substrates. Conditions using aqueous hydrogen peroxide in a biphasic mixture of THF and aqueous NaOH, however, delivered the desired secondary alcohol **196** in good yield (Scheme 3.21).[189] Acetylation of the secondary alcohol **196** preceded desilylation with TBAF revealing the hydroxy group attached to the five-membered ring in **221**.

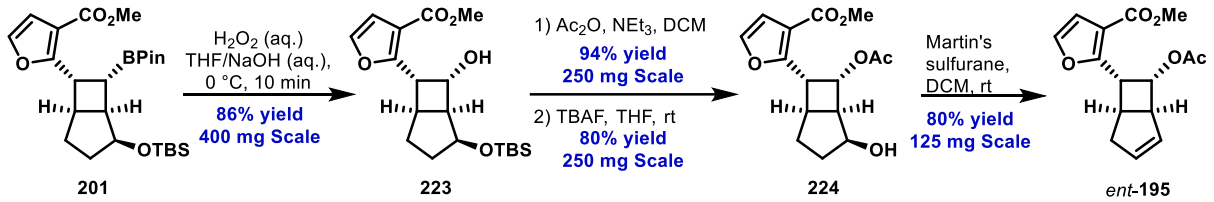


Scheme 3.21. Elaboration of the minor diastereomer **200** arising from the [2+2] cycloaddition.

The acetate was identified as a viable protecting group, as it is easily cleaved under basic and reductive conditions, while displaying full compatibility with Pd-mediated transformations; moreover it is orthogonal to silyl protecting groups. Alternatively, a MOM-ether might be introduced, having the advantage of tolerating strongly basic conditions and strong nucleophiles.

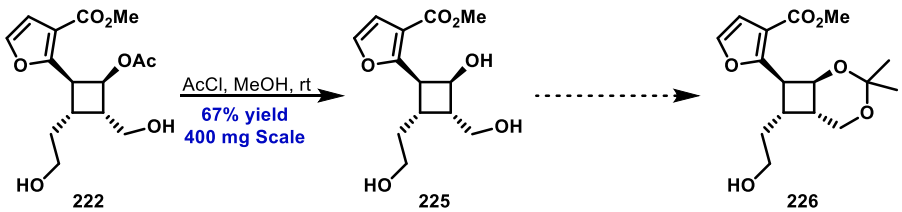
With the stage set for the dehydration event, it was found that Martin's sulfurane, without external base, was optimal to afford olefin **195** in excellent yield. Although ozonolysis led to full decomposition of the substrate, OsO_4-catalyzed dihydroxylation, followed by periodate cleavage and *in situ* reduction of the bis-aldehyde worked exceptionally well and provided diol **222** on gram scale.

Parallel to the minor diastereomer **200**, the major diastereomer **201**, arising in the [2+2] cycloaddition, was converted to cycloolefin *ent*-**195** (Scheme 3.22). Noticeable are the diminished yields at the stage of TBS-cleavage and dehydration of the respective alcohol. These observations might be explained by the orientation of the C16-OH group, as it points into the concave face of the *cis*-fused bicycle, shielding it from the attack of fluoride in the desilylation as well as the attack onto Martin's sulfurane in the dehydration. As these reactions are accompanied by decomposition at longer reaction times, the yields are lower, when compared to the diastereomeric series.



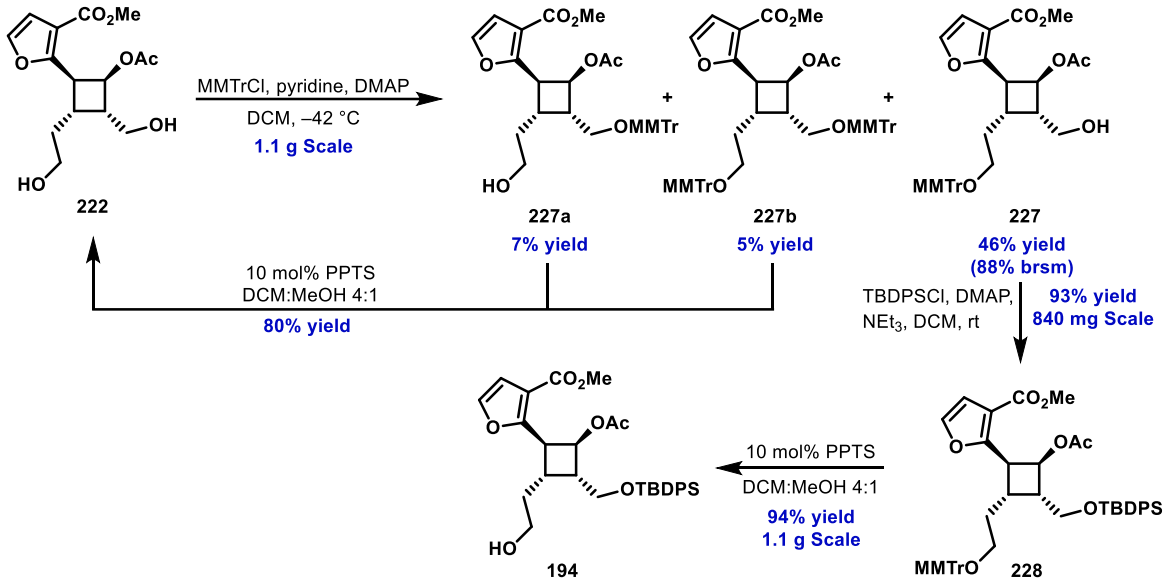
Scheme 3.22. Elaboration of the major diastereomer **201** arising in the [2+2] cycloaddition.

The deprotection of acetate **222** could be afforded by means of *in situ* generated HCl, from AcCl in MeOH (Scheme 3.23). As triol **225** now consisted of a 1,3-diol moiety, it was conjectured that the latter might be selectively masked by a thermodynamically formed acetonide. Unfortunately, the *trans*-configured acetonide **226** turned out as highly sensitive, which led us to abandon this approach.



Scheme 3.23. Acetate cleavage and projected acetonide protection of the 1,3-diol in **225**.

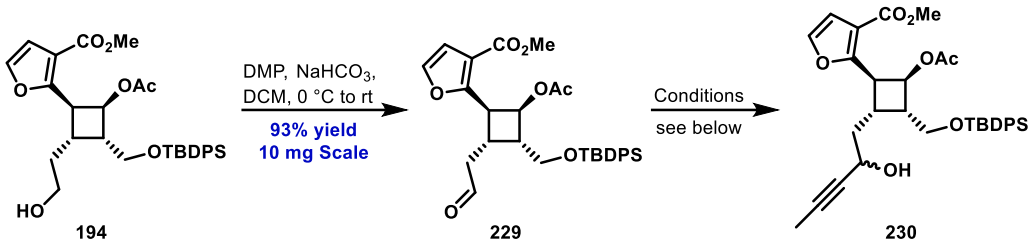
Due to the high polarity of triol **225**, resulting in complicated compound handling and low yields when the triol had to be recovered, diol **222** was moved forward. To this end, selective tritylation of the less sterically demanding primary alcohol gave the desired monomethoxytrityl-protected cyclobutane **227** (Scheme 3.24), along with the undesired mono- and bis-protected cyclobutanes **227a** and **227b** respectively. The latter two were recycled to diol **222** after separation through flash chromatography. Protection of the remaining primary alcohol of **227** with TBDPSCl gave fully protected building block **228**, which upon treatment with catalytic amounts of PPTS in a mixture of DCM and MeOH delivered the orthogonally protected cyclobutane **194**.



Scheme 3.24. Selective tritylation of **222** and following protecting group manipulations.

Oxidation with Dess-Martin periodinane furnished the aldehyde **229** in satisfying yield and purity (Table 3.4). The alkynylation was tested with both lithium- and magnesium-derived species (Entry 1 and 2 respectively), where the latter proved to be superior. Further functionalization of furan **230** *via* electrophilic bromination with NBS in various solvents or with the aid of sulfonyl hypoiodite generated from AgOMs and I_2 in MeCN failed,[203] as decomposition of the substrate was observed.

Table 3.4. Towards the coupling precursor (Scheme 3.12).

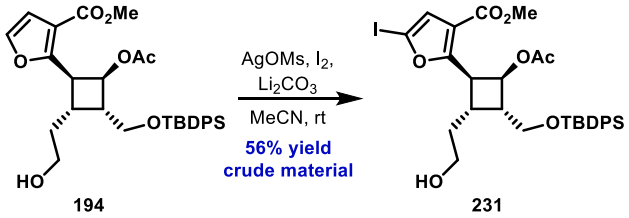


Entry	Reagent	T / °C	Solvent	Yield
1	$H_3CC{\equiv}CLi$	− 78	THF	18% (dr 1.5:1)[a]
2	$H_3CC{\equiv}CMgBr$	− 40 to − 20	THF	59% (dr 1.5:1)[a]

[a] Ratio determined by ^{1}H NMR.

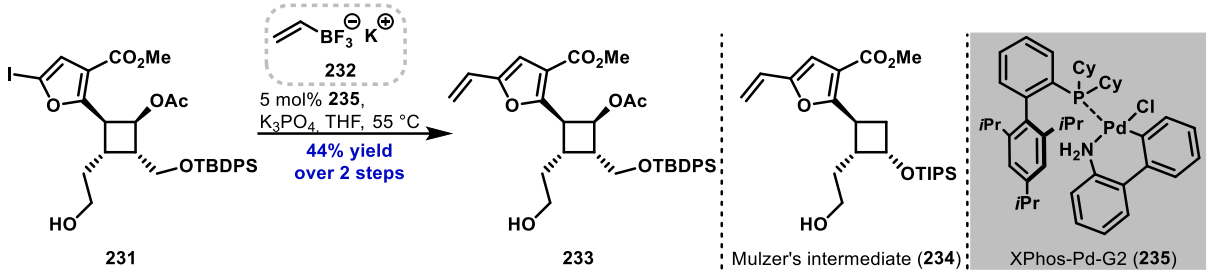
Deprotonation at the 2-position of the furan and subsequent trapping of the carbanion was not attempted, because the acetate in **230** was known to be sensitive to strong bases necessary to abstract the most acidic proton of the furan moiety.

The crude NMR spectra indicated involvement of the triple bond, which led us to investigate the functionalization of the furan, before the alkyne was installed. After a considerable amount of experimentation it was found, that Ritter's method[203] in combination with a modified workup procedure provided iodofuran **231** (Scheme 3.25). The modified procedure, consisted of an aqueous work up with sodium thiosulfate prior to concentration of the substrate, in order to render the unreacted hypoiodite reagent harmless, as significant decomposition was observed otherwise.



Scheme 3.25. Successful iodination of furan **194** using Ritter's conditions.[203]

Subsequently, coupling of vinyltrifluoroborate salt **232** to this fragment was attempted (Scheme 3.26). This would not only give the proof-of-concept that a viable building block for cross-coupling was prepared, but also strategically intercept Mulzer's route to providencin (**132**). Adopting the literature route, which allowed intermediate **234** to be converted into 17-deoxyprovidencin (**160**), should allow entry for our vinyl furan **233** to be elaborated into actual providencin (**132**).

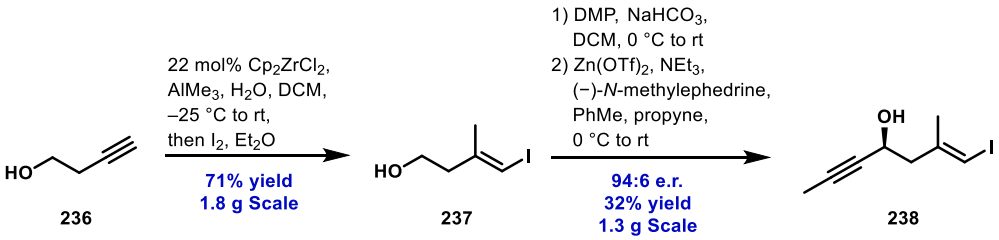


Scheme 3.26. Suzuki coupling of vinyltrifluoroborate salt **232** with iodofuran **231** and the corresponding intermediate in Mulzer's synthesis of 17-deoxyprovidencin (**160**).[160]

Finally, with an enantioselective access to iodofuran **231** established and the first coupling reaction performed, our attention turned towards a properly functionalized alkenyl building block, to pursue the RCAM strategy towards providencin (**132**).

3.2.3 Synthesis of the Western Fragment

For the synthesis of the western fragment, an approach was selected, which was very well precedented by work from our own group. Specifically, in the synthesis of manshurolide, a MAP-kinase inhibitor, 3-butyn-1-ol (**236**) was converted into alkenyl iodide **238** in three steps.[91] Although this sequence was carried out in racemic fashion, employing an asymmetric propynylation step developed by Carreira *et al*.[182] might allow access to the enantioenriched material.

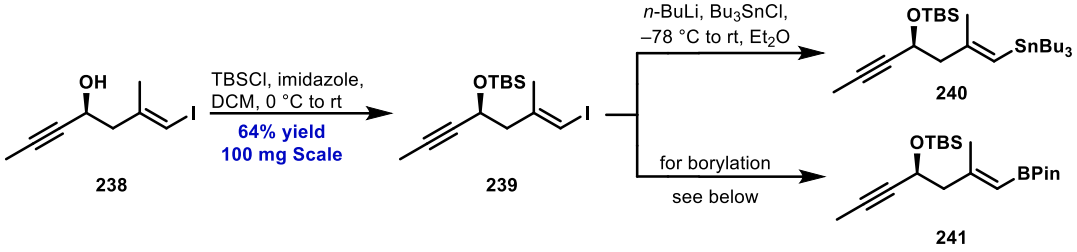


Scheme 3.27. Synthesis of enantioenriched alcohol **238** *via* Carreira's alkynylation.

In practice, Zr-mediated carbometalation of 3-butyn-1-ol (**236**) provided *(E)*-alkenyl iodide **237** in good yield and excellent regioselectivity (Scheme 3.27). Gratifyingly, Carreira's alkynylation using propyne delivered propargyl alcohol **238** in good enantioselectivity, though in poor yield.

With the literature known compound **238** in hand, TBS-protection preceded the attempt to synthesize the corresponding alkenyl stannane **240** (Table 3.5). Although crude NMR showed signals arising from the desired stannane, every purification of the highly acid sensitive molecule resulted in quantitative protodestannylation. Therefore, the focus was put towards alkenyl boronic ester **241**.

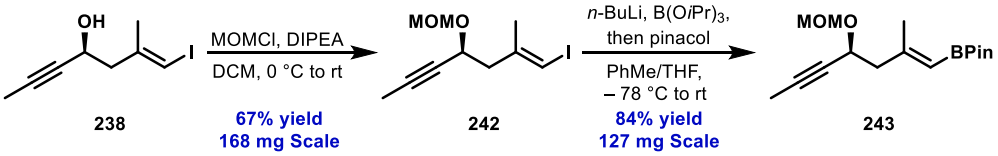
Table 3.5. Derivatization of alkenyl iodide **239** into viable coupling partners.



Entry	Reagents	T / °C	Solvent	Yield
1	$Pd(PPh_3)Cl_2$, PPh_3, B_2Pin_2, KOPh	50	PhMe	10-40%
2	$Pd(dppf)Cl_2$, B_2Pin_2, KOAc	80	DMSO	0%
3	*n*-BuLi, $B(OiPr)_3$, pinacol	−78 to rt	PhMe/THF	95%

First, classic Miyaura borylation conditions were employed, resulting in irreproducible yields ranging from 10 to 40% (Table 3.5, Entry 1).[204,205] Another palladium-catalyzed protocol was attempted, however, at this time full decomposition of the substrate was observed (Entry 2).[206] Only recourse to lithium-halogen exchange followed by trapping with triisopropylborate and addition of pinacol delivered the boronic ester **241** in reproducible fashion (Entry 3).[207]

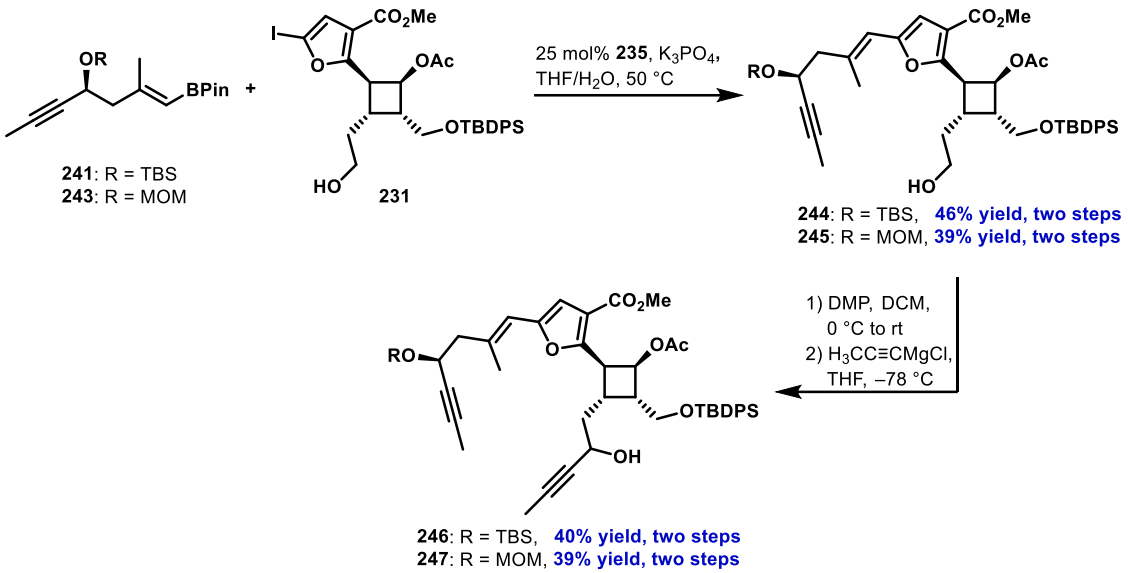
The 1,4-butyne-diol moiety is arguably one of the hardest motifs to build through alkyne metathesis. Additionally, the mono-TBS-protected subunit was unprecedented, so we also planned to target a MOM-protected building block **243**, which in turn would give us a well-precedented scaffold previously built by RCAM.[91] In practical terms, fragment **242** bearing a MOM- instead of a TBS-ether was synthesized from enantioenriched alcohol **238** *via* the previously established route (Scheme 3.28).



Scheme 3.28. Synthesis of MOM-protected western fragment **243**.

3.2.4 Fragment Coupling and Attempted Ring Closing Alkyne Metathesis

Finally, the Suzuki coupling with the originally targeted fragments **241/243** and **231** could be tested. Using Buchwald's 2nd generation XPhos-Pd-precatalyst **235**,[208] the fragment merger provided the desired products **244** and **245**, from both the TBS- and MOM-protected western fragments (Scheme 3.29). A high catalyst loading was necessary to ensure full conversion, which might be explained through impurities resulting from the crude iodofuran **231** or decomposition products formed at higher temperatures during the course of the reaction.



Scheme 3.29. Fragment coupling and further elaboration into diyne **246/247**.

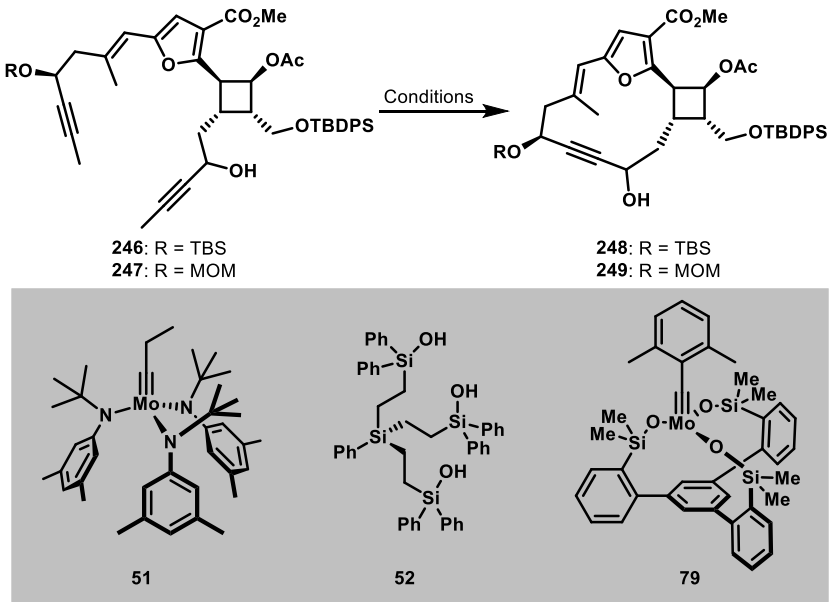
In any case, unreacted alkenyl boronic ester **241/243** could always be reisolated after the reaction, indicating degradation of the iodofuran fragment **231**. Based on these observations the mediocre yields can probably be attributed to the high instability of iodofuran **231**, notwithstanding that a thorough optimization of reaction conditions might increase the yield. Notably, the Suzuki coupling as carried out herein is unprecedented for furanocembranoids, where a large portion of synthetic literature has used Stille couplings from the corresponding stannylfurans or Negishi coupling *via* the appropriate organozinc compounds.[178,180,181,209]

At the stage of alcohol **244/245**, DMP mediated oxidation of the primary alcohol, followed by addition of 1-propynylmagnesium bromide, furnished diynes **246/247** over two steps. Slight degradation was observed during the Grignard reaction, probably arising from the base-labile acetate present in the molecule.

At last, it was time to test the ring-closing alkyne metathesis on the respective diynes **246** and **247**. First we probed whether TBS-ether **246** would succumb to macrocyclization *via* RCAM in presence of Mo-alkylidyne **79** (Table 3.6, Entry 1).[104,105] The starting material was quickly consumed in refluxing toluene; however, the crude reaction mixture was mainly composed of ill-defined oligomers giving broad signals in ^{1}H-NMR. After checking if the starting material was stable at the high temperature needed to achieve RCAM in strained systems, it was speculated, that the TBS-ether was too sterically demanding and therefore might hinder ring closure. Anyhow, MOM-ether **247** was also uncompliant in forming the 14-membered macrocycle with complex **79** and only returned an intractable mixture (Entry 2). As a last resort, we turned our hopes to the two component catalyst system consisting of complex **51** and silanolate ligand **52**.[91] Disconcertingly, this last line in RCAM catalytic systems also failed to afford any cyclized product (Entry 3).

Ultimately, no further experiments were performed, as it was concluded, that a RCAM macrocylization strategy with the pre-installed furan was not a viable approach towards the synthesis of providencin (**132**). Since strategies that pursued macrocyclization in advance of furan formation had been investigated previously,[210] we were aware of the difficulties arising from selective formation of the *E*-alkene between C7 and C8 within the macrocycle. The putative advantage of our strategy lay in forming the *E*-olefin prior to macrocyclization. Attempts to epoxidize the C7=C8 olefin, releasing some of the strain embedded in the sp^2-hybridized bond in conjugation with the aromatic furan were met with failure. In order to investigate whether the strain of the *trans*-fused cyclobutane unit was the problematic structural element for the RCAM step, a synthesis of a model substrate was planned, which excluded this strain-increasing-element and substituted it with an alkyl chain for simplicity. The synthesis and behavior of these model compounds in RCAM is discussed in the following section.

Table 3.6. Attempted macrocyclization of **246**/**247** by RCAM.



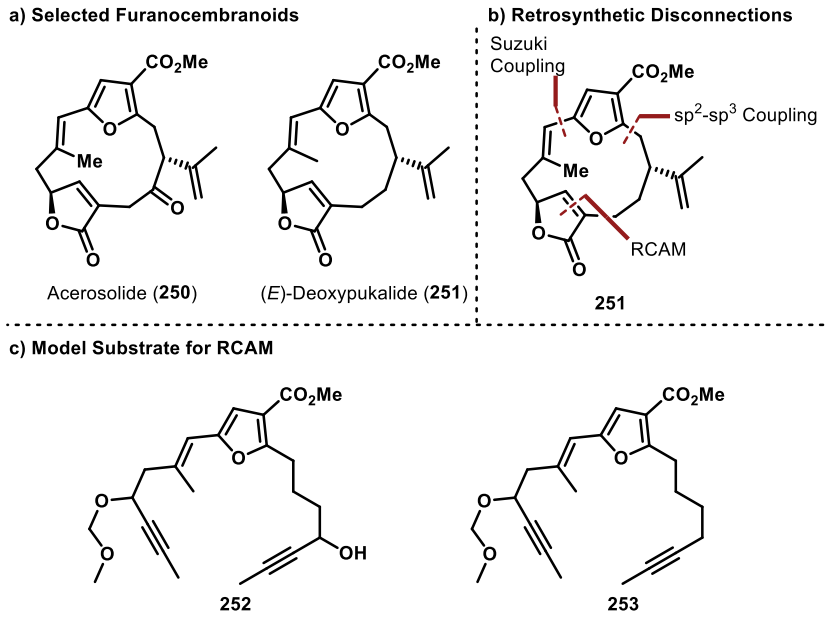
Entry[a]	Substrate	Catalyst	T / °C	Comment
1	**246**	40 mol% **79**	110	Complex mixture of oligomers at full conversion of starting material
2	**247**	30 mol% **79**	110	"
3	**247**	25 mol% **51** 30 mol% **52**	110	"

[a] All reactions were performed in PhMe (2 mM), in presence of 5Å MS.

3.2.5 Synthesis of a Model System and Application in Ring Closing Alkyne Metathesis

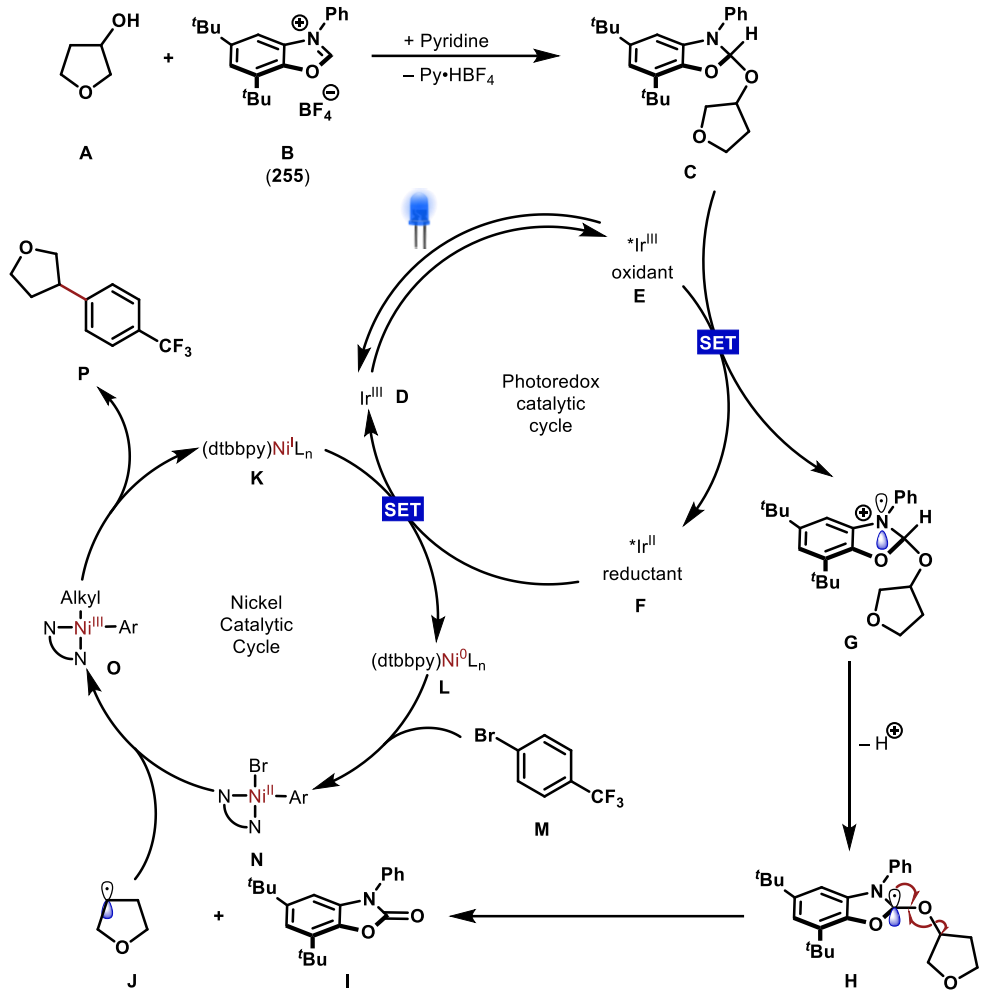
With the primary focus set on the synthesis of simplified diynes **252** and **253** (Scheme 3.30), we focused on the strategic introduction of the alkyl substituent *via* a sp^2-sp^3-coupling, replacing the fused cyclobutane unit. In the case of a productive RCAM event on these substrates, this strategy would directly allow entry into syntheses of acerosolide (**250**) or *(E)*-deoxypukalide (**251**).[211,212]

To this end, a classic Negishi coupling[213,214] of an alkyl iodide precursor might be envisioned, however, modern methods arising from the field of photoredox catalysis[215,216] might also open entry into 2-alkyl furans. Intrigued by the direct deoxygenative sp^2-sp^3-coupling of alcohols with halo arenes developed by Macmillan *et al*.[216], investigations were started to evaluate the feasibility of this methodology in our setting.



Scheme 3.30. (a) Selected furanocembranoids, (b) major strategic retrosynthetic disconnections for **251** and (c) targeted model substrates **252**/**253** for RCAM.

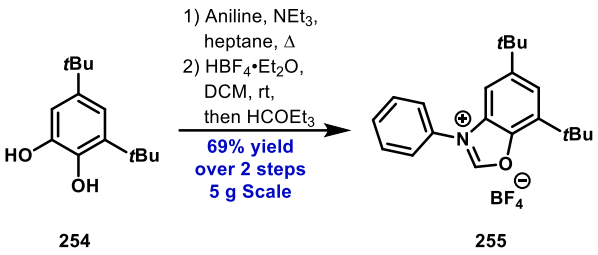
Mechanistically the coupling reaction mentioned above initiates by addition of the alcohol **A** to the benzoxazolium salt **B**, accompanied by the loss of a pyridinium salt (Scheme 3.31) to give adduct **C**. A long-lived excited triplet state Ir(III)-complex **E** is known to be generated from the parent photocatalyst **D** under irradiation with blue light. Adduct **C** is oxidized by **E** in a single electron transfer, generating a radical cation intermediate of type **G**. Deprotonation of the now weakened C-H bond adjacent to the *N*-centered radical gives rise to the α-amino radical **H**. This radical, adjacent to three heteroatoms, readily undergoes β-scission to leave behind the aromatized carbamate byproduct **I** as well as the deoxygenated carbon centered radical **J**. The gain in aromaticity of the former was anticipated to provide the necessary thermodynamic driving force for the alcohol C-O bond homolysis.



Scheme 3.31. Proposed mechanism for the deoxygenative arylation by MacMillan *et al.*[216]

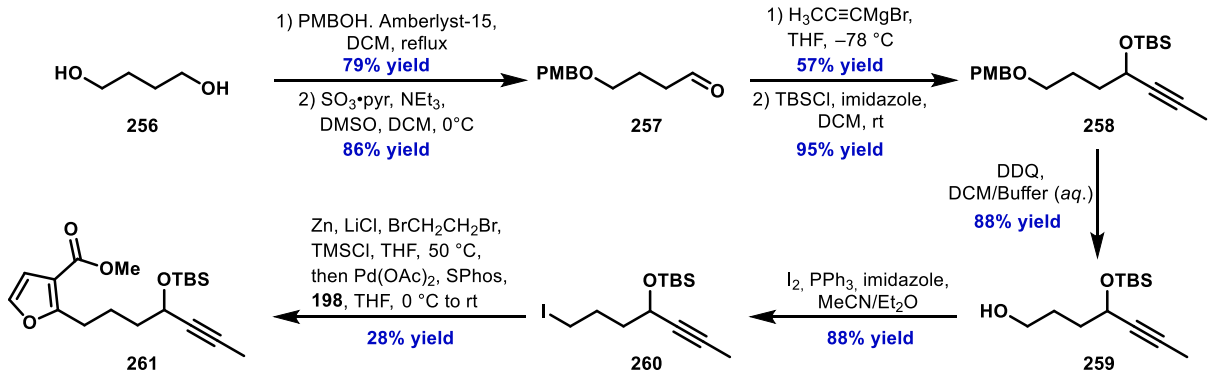
In the nickel-catalytic cycle, the Ni(0)-species **L** arises from two consecutive SET events with reduced photocatalyst **F** and subsequently reacts with aryl bromide **M** to give the oxidative addition Ni(II)-complex **N**. Entering the nickel catalytic cycle, the alkyl radical **J** traps the Ni(II)-species **N** to yield the Ni(III)-intermediate **O**, which after reductive elimination with formation of the C-C coupled product **P** releases the final Ni(I)-complex **K**. A final SET-event oxidizing the Ir(II)-species **F** and reducing the Ni(0)-complex **L** closes both catalytic cycles.[216]

In practical terms, synthesis of the required NHC precursor was carried out in two steps following the literature procedure (Scheme 3.32).[216] The synthesis of a potential coupling partner commenced with 1,4-butanediol (**256**), which was protected as the mono PMB-ether under acidic conditions (Scheme 3.33). Oxidation of the remaining primary alcohol under Parikh-Doering conditions preceded addition of 1-propinylmagnesium bromide giving rise to propargyl alcohol **258**. Standard functional group manipulations eventually led to primary alcohol **259**, which can either be used in the MacMillan-type coupling, or alternatively in an Appel reaction to produce primary iodide **260**.



Scheme 3.32. Synthesis of the benzoxazolium salt **255**.

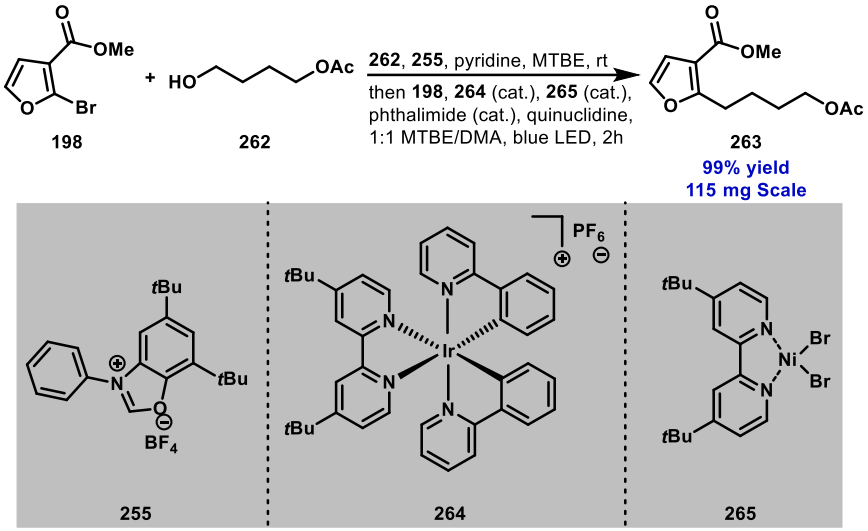
With an efficient access to the primary alkyl iodide in hand, a Negishi-coupling was investigated.[213,214] Alkyl iodide **260** was transformed into the corresponding alkyl zinc species according to Knochel's procedure,[217] and subsequently cross-coupled with the bromofuran **261** under palladium catalysis.



Scheme 3.33. Synthesis of alkyliodide **260** and Negishi coupling with bromofuran **198**.

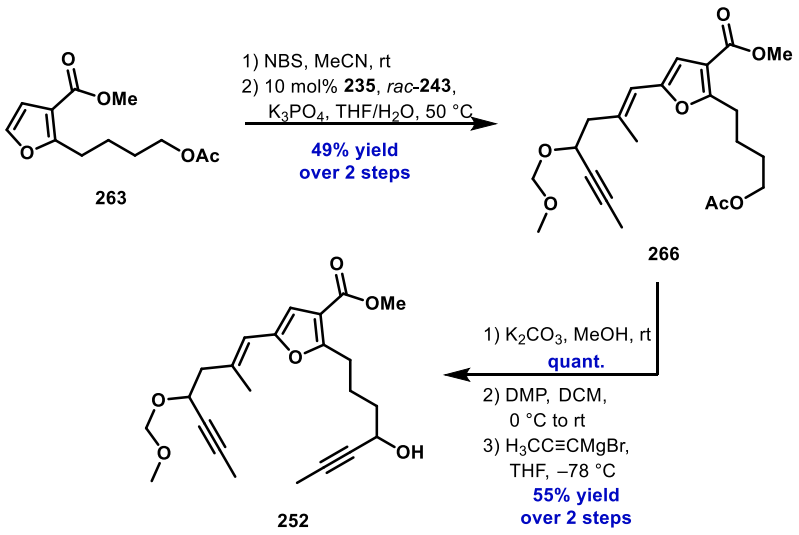
Since the zinc insertion required elevated temperatures, the low yield was assigned to a probable 5-*exo*- or 6-*endo*-dig cyclization onto the alkyne. The radical generated from the NHC-adduct in MacMillan's coupling reaction[216] would most likely also favor this detrimental cyclization pathway. Therefore the unsaturated alcohol **259** was ruled out as a potential substrate. Halogenation of furan **261** using Ritter's hypoiodite reagent[203] or NBS in various solvents failed and this route was abandoned.

With these limitations in mind, primary alcohol **262** was subjected to coupling conditions with NHC-precursor **255** and bromofuran **198** (Scheme 3.34). Furthermore phthalimide was employed, since an additive mapping study had found beneficial effects in Ni(dtbbpy)Br_2 (**265**) -catalyzed couplings, especially those involving electron-rich aryl halides.[218] To our delight, the coupling reaction proceeded exceedingly well, providing the acetate-protected product **263** in quantitative yield. These results suggest that this specific coupling methodology might be used, if a synthetic program is set up for the synthesis of furanocembranoids as **250** and **251**.



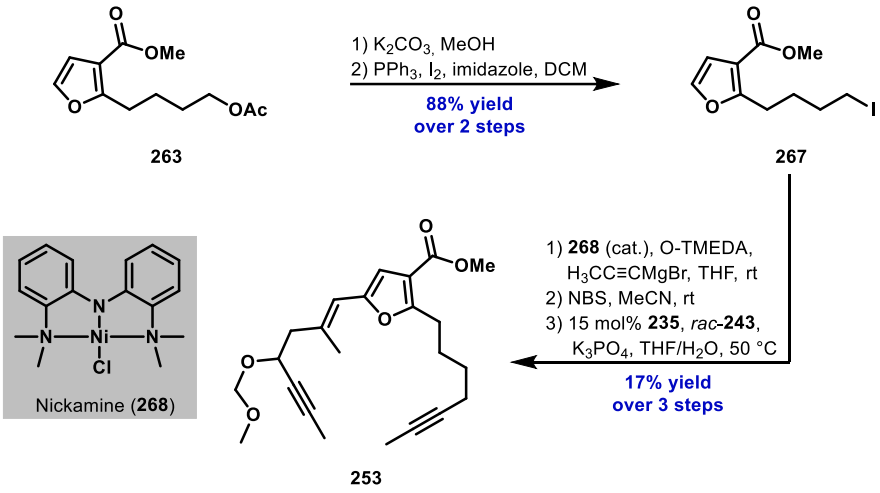
Scheme 3.34. Deoxygenative arylation of primary alcohol **262** with bromofuran **198**.[216]

At the stage of compound **263**, iodination using Ritter's conditions[203] did not give a clean reaction profile; however, NBS in MeCN cleanly delivered the corresponding bromofuran (Scheme 3.35). The Suzuki coupling of the latter with *rac*-**243** provided access to acetate **266**. Methanolysis of the protecting group revealed the primary alcohol, which after oxidation and addition of 1-propynyl magnesium bromide furnished diyne **252**. Interestingly, when the deacetylation was carried out first on **263**, subsequent bromination of the furan led to complete decomposition within minutes. It is likely, that the free alcohol may cyclize onto the oxocarbenium ion (also known as a Wheland intermediate),[219] which is transiently formed in the electrophilic aromatic bromination and opens up deleterious reaction pathways. Thus far, it has been found that either alkynes or free alcohols, which are capable of cyclizing onto the furan, are problematic in electrophilic halogenation reactions in our furan systems.



Scheme 3.35. Suzuki coupling and final steps towards model substrate **252**.

To make the deoxygenated model substrate **253**, the acetate-protected coupling product **263** was deprotected with K_2CO_3 in methanol (Scheme 3.36). Next, an Appel reaction furnished the primary alkyl iodide **267**, which serves as a linchpin to install the alkyne in the alkyl chain. A methodology using Nickel-complex **268** and 1-propynylmagnesium bromide in presence of bis[2-(*N*,*N*-dimethylaminoethyl)]ether (*O*-TMEDA) worked well.[220] Gratifyingly, electrophilic bromination of the furan with NBS was successful despite the presence of the alkyne. Ultimately, the Suzuki coupling furnished propargyl ether **253**, in 17% yield over three steps.



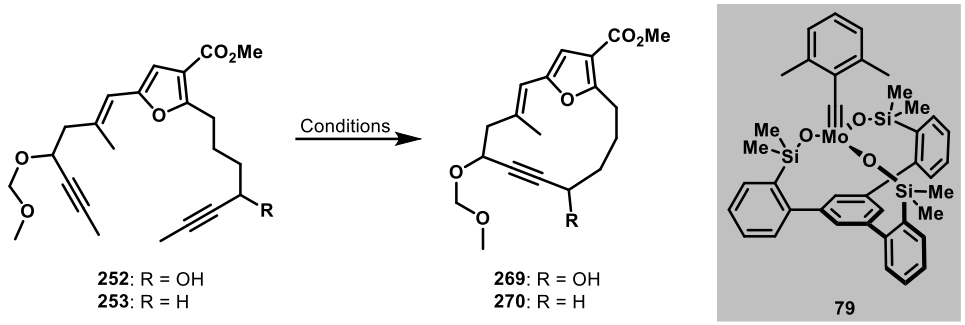
Scheme 3.36. Synthesis of the mono propargylic diyne **253**.

With diynes **252** and **253** in hand, their behavior in RCAM was tested (Table 3.7). First, diyne **252** was subjected to Mo-alkylidyne **79** in boiling toluene (Entry 1), at which point surprisingly, the exact same outcome as with cyclobutane containing diyne **246/247** was observed. Apparently, the *E*-configured olefin conjugated to the furan moiety presents an insurmountable strain-energy barrier for a RCAM-based macrocyclization strategy.

It must be reiterated that the 1,4-butyne dioxy unit comprises one of the most challenging substrates in RCAM. The reasons for this are unclear. One possibility is that, in some systems, the RCAM reaction initially forms oligomeric species, which then de-polymerize to yield monomeric macrocycles in an entropically-driven process; this would be analogous to some olefin metathesis mechanisms. If so, 1,4-dioxybut-2-yne subunits formed by an initial oligomerisation may be to sterically and/or electronically deactivated to engage in de-polymerization. However, in the C-X deoxy system **253**, the reaction yielded dimeric macrocyclic products (Entry 2); this implies that the enthalpic gain entailed in forming the strained monomeric macrocycle is not sufficiently offset by the entropic gain of monomer formation.

With these results in hand any further attempts to target *(E)*-configured furanocembranoids *via* RCAM were abandoned.

Table 3.7. Attempted RCAM on the model compounds **252** and **253**.



252: R = OH
253: R = H

269: R = OH
270: R = H

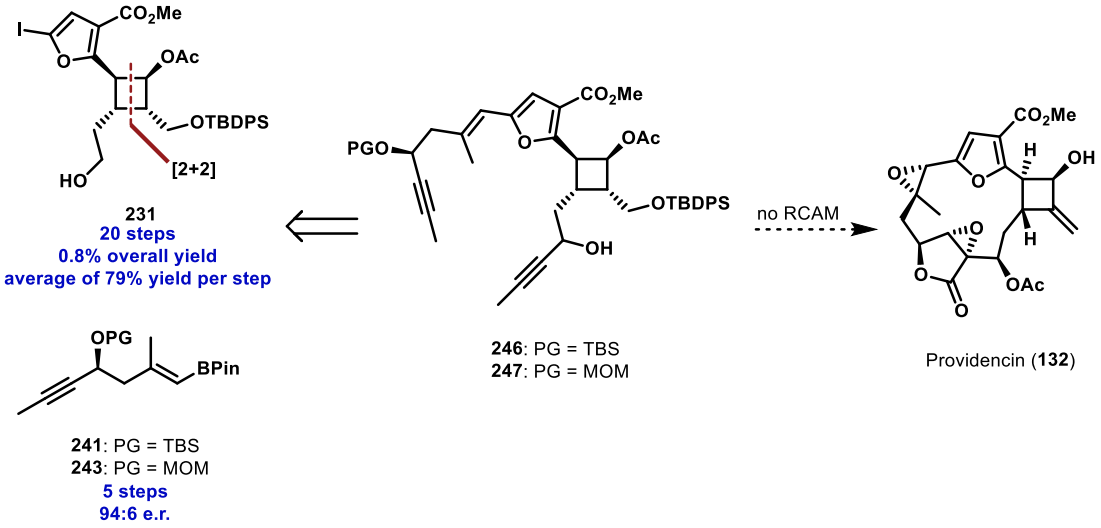
79

Entry[a]	Substrate	Catalyst	T / °C	Comment
1	**252**	30 mol% **79**	110	Complex mixture of oligomers at full conversion of starting material
2	**253**	30 mol% **79**	110	37% yield of dimers

[a] All reactions were performed in PhMe (2 mM), in presence of 5Å MS.

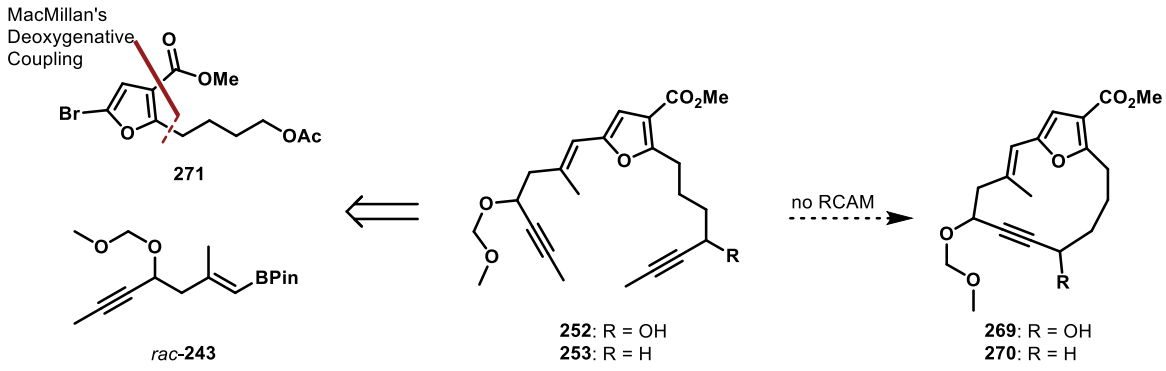
3.3 Summary and Outlook

A new approach was taken in order to conquer providencin (**132**), an intriguing marine diterpene.[153] Basing on the heroic efforts by Mulzer and White, a new strategy was envisaged, in which the macrocylization would have been effected by RCAM (Scheme 3.37), thereby allowing full control over the geometry of the C7-C8 olefin. For fragment **231**, the enantioinduction harnessed Noyori's powerful transfer hydrogenation,[191] while Yoon's energy-transfer catalysis served as the key strategic disconnection.[189] The robustness of this approach is demonstrated by the fact that most steps could be carried out on gram-scale. In the late stages, towards the cyclobutane building block **231**, an electrophilic functionalization of the furan set the stage for a Suzuki coupling with a properly functionalized alkene.



Scheme 3.37. Summary of the RCAM approach towards providencin (**132**).

For the alkene coupling partner, Carreira's alkynylation[182] set the stereocenter with good enantioselectivity and a simple lithium-halogen exchange followed by trapping with the respective borate furnished alkenyl boronic esters **241/243**.

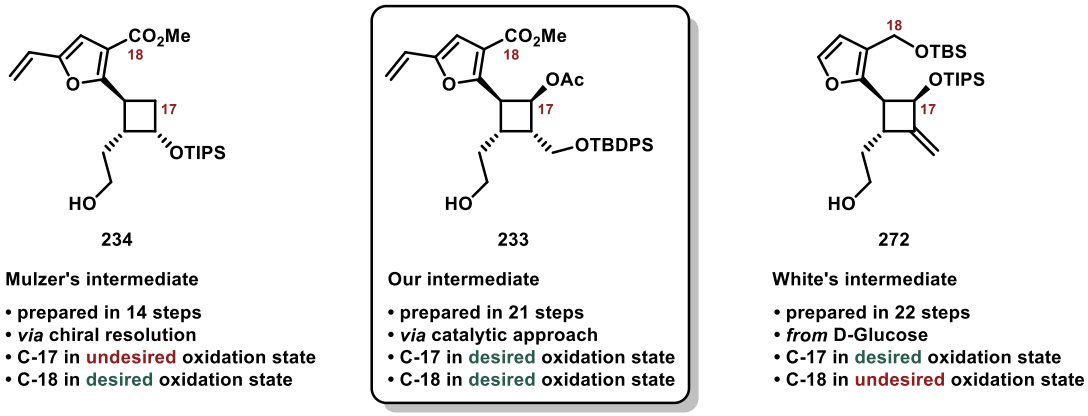


Scheme 3.38. Summary of the RCAM approach towards simplified model substrates.

Arriving at the climax of the synthetic proposal, it was surprising to find, that none of the most active alkyne metathesis catalysts was able to close the macrocycle. Neither the TBS-protected nor the MOM-protected diyne succumbed to the Mo-alkylidyne catalysts, but rather returned intractable mixtures of oligomers.

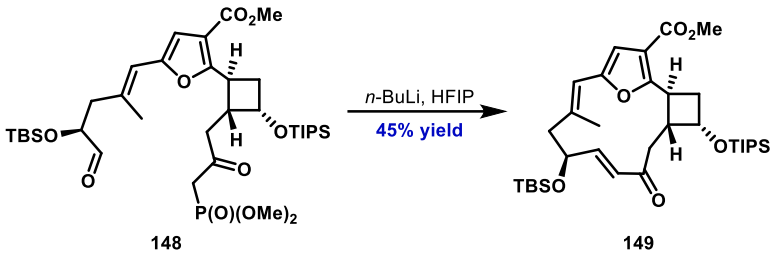
Startled by these results, our attention was turned towards a model substrate to investigate the likely cause of this failure. As the *trans*-fused cyclobutane in **132**, might be viewed as one of the strain-inducing elements in the macrocycle of **132**, removal of this moiety altogether was envisaged. In the synthesis of the model substrates (Scheme 3.38), MacMillan's deoxygenative cross-coupling worked exceedingly well and opened entry towards the diyne substrates **252** and **253**, after Suzuki-coupling of the bromofuran **271** and alkenyl boronic ester **243**. Yet these diynes also did not yield to RCAM and rather returned mixtures of oligomers or dimers. The *E*-configured olefin in conjugation with the furan is hence sufficient to render macrocylizations by RCAM unfeasible.

Notwithstanding this setback, the cyclobutane fragment **231** served as a versatile linchpin in accessing vinylfuran **233**. This intermediate might allow entry to providencin (**132**), when subjected to the strategy exercised by Mulzer *et al*.[160] Advantageously, this building block bears all functionalities found in Mulzer's intermediate **234**, but in addition already carries the desired oxidation state at C17, thus addressing the Achilles' heel of Mulzer's campaign (Scheme 3.39).



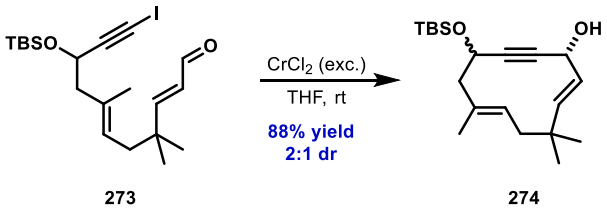
Scheme 3.39. Comparison of different synthetic intermediates in approaches towards providencin (**132**).[160,167]

In retrospect, the HWE macrocyclization in Mulzer's first-generation approach (Scheme 3.40) becomes more impressive. Therein, ring closure was afforded in acceptable yields, with both the *trans*-fused cyclobutane unit and the *E*-configured C7=C8 alkene preinstalled.[158] Since the HWE olefination forges a highly thermodynamically favorable P=O double bond, it may be possible to achieve macrocyclization, if a reaction is chosen, which intrinsically possesses a large enthalpic gain.



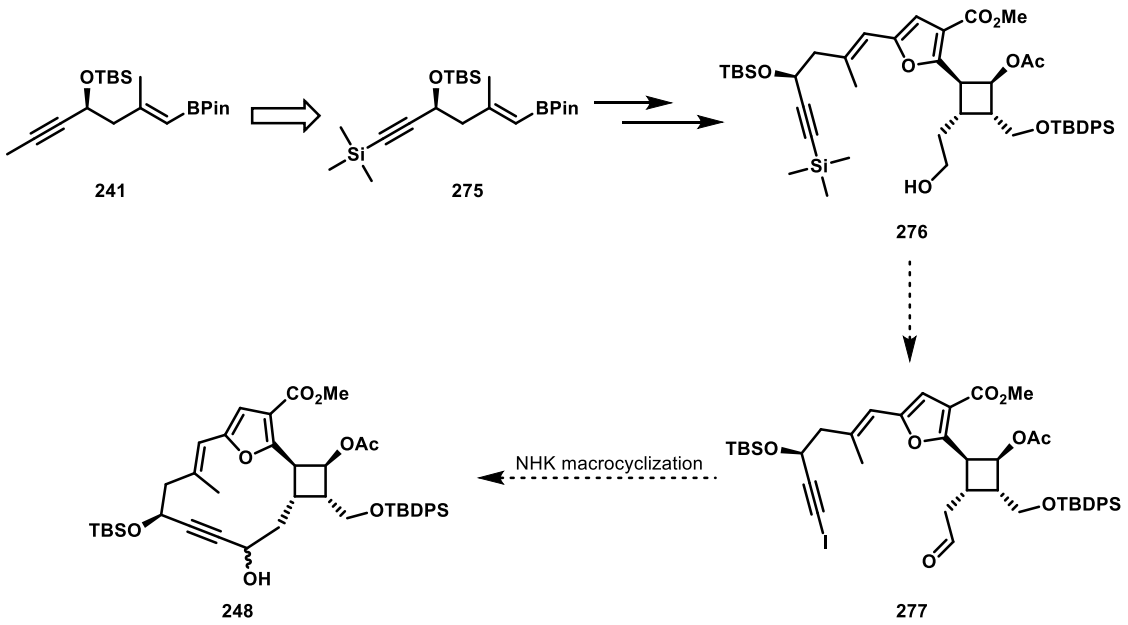
Scheme 3.40. Successful HWE ring-closing olefination in Mulzer's abandoned first-generation approach towards providencin (**132**).[158]

Another extremely versatile reaction, which engenders a large enthalpic gain, is the NHK-reaction. Interestingly, literature precedent could be found from Malacria *et al*.[221] (Scheme 3.41). The intramolecular NHK reaction of alkynyl iodide **273** and an aldehyde forges the 11-membered ring system of **274**. Intriguingly, this macrocycle bears the exact same monoprotected butyne-1,4-dioxo subunit, which was targeted in our approach *via* RCAM. In this system, slow addition of the substrate into a suspension of chromium dichloride was necessary to favor the intramolecular pathway and the reaction gave only mediocre diastereoselectivity.



Scheme 3.41. Literature precedent of a NHK-macrocyclization by Malacria *et al*.[221]

Despite the higher probability of actual ring closure employing the NHK reaction, achieving the desired diastereoselectivity might be challenging; a downside, which would have been circumvented in the RCAM approach. Another convenient feature of this conceivable strategic change, is the compatibility with the previously used methods. Strategically, the methyl cap of alkyne **241** can be substituted for a TMS-group as in **275**, which should largely be compatible with all subsequent transformations (Scheme 3.42). After fragment coupling, silver-mediated TMS cleavage[222] followed by alkyne iodination[223] and oxidation of the primary alcohol should give rise to compound **277**, which has a compelling similarity with literature known substrate **273** in proximity of the alkyne.



Scheme 3.42. Possible NHK macrocyclization *en route* to providencin (**132**).

Gratifyingly, the NHK route intercepts our previous effort at an intermediate, which was anticipated *via* the RCAM route. The major strategic deviation of this route from our previous one is to use a more strongly enthalpically driven process to close the presumably strained macrocycle. However, as an investigation therein would be a departure from our goal of developing an RCAM-based approach towards providencin (**132**), it constitutes a future frontier of synthetic chemistry with respect to this thesis.

4. Experimental Section

4.1 A Unified Approach to Polycyclic Alkaloids of the Ingenamine Estate

Unless stated otherwise, all reactions were carried out in flame-dried glassware using anhydrous solvents under argon atmosphere. The solvents were purified by distillation over the following drying agents and were transferred under argon: THF, Et_2O (Mg/anthracene); MeCN, 2,6-lutidine, CH_2Cl_2, DCE (CaH_2); toluene (Na/K alloy); MeOH (Mg, stored over MS 3 Å). DMSO, DMF, NEt_3, pentane and pyridine were dried by an adsorption solvent purification system based on molecular sieves. Thin layer chromatography (TLC): Macherey-Nagel precoated plates (POLYGRAM®SIL/UV254). Detection was achieved under UV-Light (254 nm) and by staining with either acidic *p*-anisaldehyde, cerium ammonium molybdenate or basic $KMnO_4$ solution. Flash chromatography: Merck silica gel 60 (40–63 μm) with predistilled or HPLC grade solvents. NMR: Spectra were recorded on Bruker AV 400, AV 500, AVIII 600 or AVneo 600 spectrometers in the solvents indicated; chemical shifts (δ) are given in ppm relative to TMS, coupling constants (*J*) in Hz. The solvent signals were used as references and the chemical shifts converted to the TMS scale ($CDCl_3$: δ_C = 77.00 ppm; residual $CHCl_3$ in $CDCl_3$: δ_H = 7.26 ppm; CD_3OD: δ_C = 49.00 ppm, residual CD_2HOD in CD_3OD: δ_H = 3.31 ppm; $(CD_3)_2SO$: δ_C = 39.52 ppm, residual CD_2HSOCD_3 in $(CD_3)_2SO$: δ_H = 2.50 ppm); all spectra were recorded at 25 °C. Multiplicities are indicated by the following abbreviations: s: singlet, d: doublet, t: triplet, q: quartet, p: pentet, h: hextet, hept: heptet, m: multiplet, br: broad signal. ^{13}C NMR spectra were recorded in ^{1}H-decoupled manner and the values of the chemical shifts are rounded to one decimal point. Signal assignments were established using HSQC, HMBC, COSY, NOESY and other 2D experiments. IR: Spectra were recorded on an Alpha Platinum ATR instrument (Bruker), wavenumbers ($\tilde{\nu}$) in cm-1. MS (ESI-MS): Finnigan MAT 8200 (70 eV), ESI-MS: ESQ3000 (Bruker), accurate mass determinations: Bruker APEX III FTMS (7 T magnet) or Mat 95 (Finnigan). Optical rotations ($[\alpha]_D$) were measured with an A-Krüss Otronic Model P8000-t polarimeter at a wavelength of 589 nm. Preparative LC was performed with an Agilent 1260 infinity prep system (fraction collector G7159 B + G7166A, diode array detector G7115A); stationary phase and conditions for each compound are specified below.

Molecular sieves (5 Å) were activated at 150 °C for 24 h in high vacuum (1×10^{-3} mbar) and stored under argon.

Unless stated otherwise, commercially available compounds (Alfa Aesar, Aldrich, TCI, Strem Chemicals, ChemPUR) were used as received. The following compounds were prepared according to the cited literature: 5-iodopent-2-yne,[224] 7-iodohept-2-yne (**50**)[62] and molybdenum alkylidyne complex **79/80**.[105]

4.1.1 Supporting Crystallographic Information

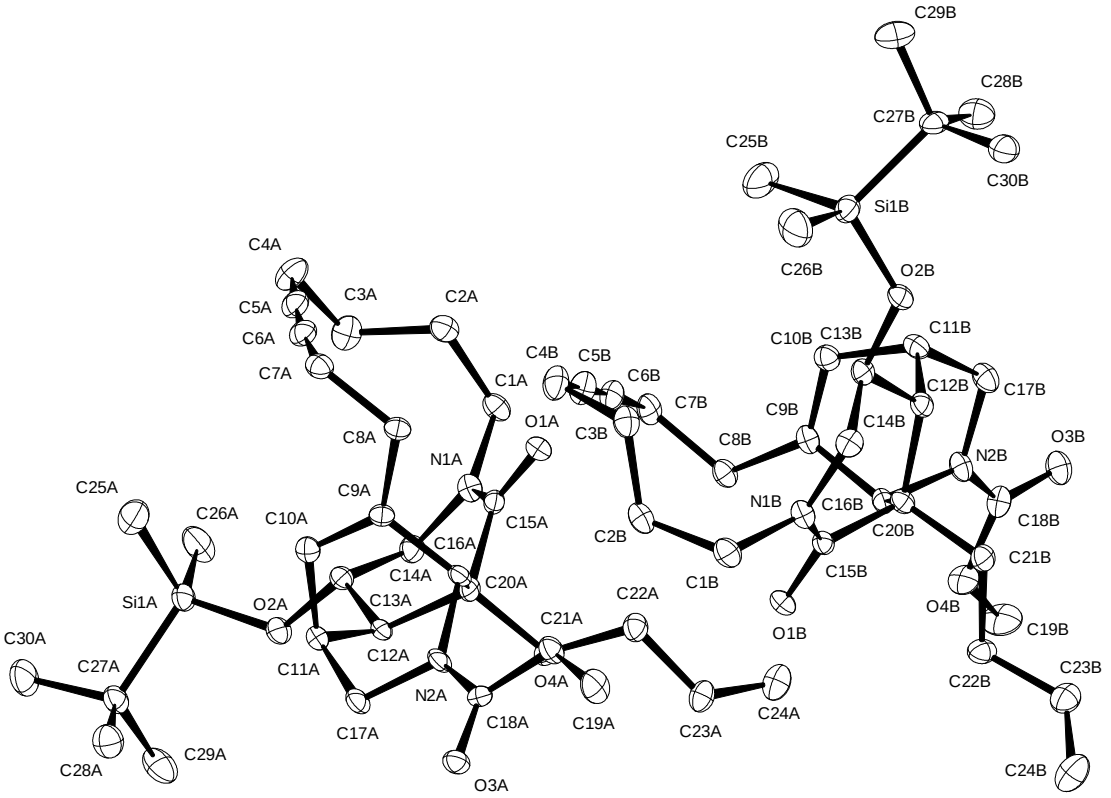


Figure 4.1. Molecular structure of the two independent molecules of cycloalkyne **78** in the solid state; atomic displacement ellipsoids are shown at the 50% probability level, H-atoms omitted for clarity

X-ray Crystal Structure Analysis of Compound 78: $C_{30}H_{46}N_2O_4Si$, M_r = 526.78 g · mol^{-1}, colorless needle, crystal size 0.140 x 0.034 x 0.025 mm^3, monoclinic, space group $P2_1$ [4], a = 15.6435(7) Å, b = 8.6081(4) Å, c = 23.3896(10) Å, β = 109.531(2)°, V = 2968.4(2) Å^3, T = 100(2) K, Z = 4, D_{calc} = 1.179 g · cm^3, λ = 0.71073 Å, μ(*Mo-K*$_\alpha$) = 0.115 mm^{-1}, analytical absorption correction (T_{min} = 0.99, T_{max} = 1.00), Bruker-AXS Kappa Mach3 APEX-II diffractometer with a Iμs microsource, 1.381 < θ < 32.467°, 106114 measured reflections, 20839 independent reflections, 16939 reflections with $I > 2\sigma(I)$, R_{int} = 0.0706, S = 1.031, 680 parameters, absolute structure parameter = 0.02(3), residual electron density +0.4 (1.12 Å from H3AA) / –0.4 (0.13 Å from Si1A) e · Å^{-3}.

The structure was solved by *SHELXT* and refined by full-matrix least-squares (*SHELXL*) against F^2 to R_1 = 0.049 [$I > 2\sigma(I)$], wR_2 = 0.107. **CCDC-2081190**.

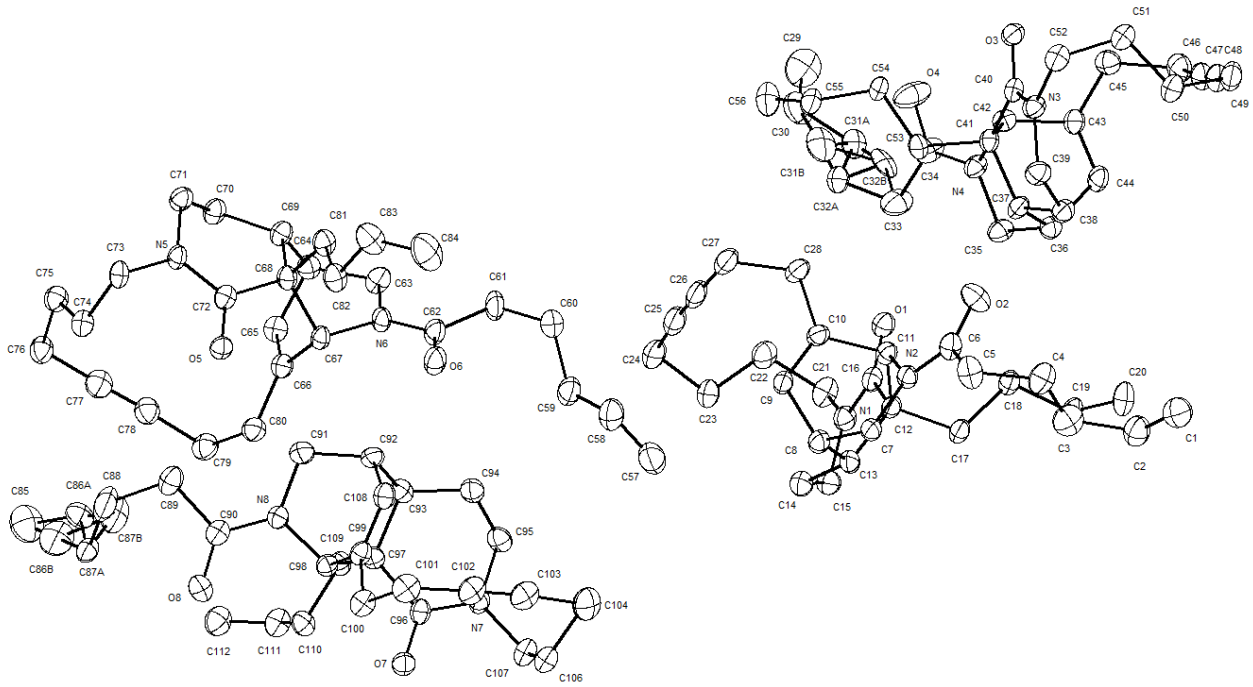


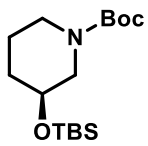
Figure 4.2. Molecular structure of the four independent molecules of compound **64** in the solid state; atomic displacement ellipsoids are shown at the 50% probability level, H-atoms omitted for clarity

X-ray Crystal Structure Analysis of Compound 64: $C_{28}H_{38}N_2O_2$, $M_r = 434.60$ g · mol^{-1}, colorless plate, crystal size 0.180 x 0.155 x 0.111 mm^3, triclinic, space group *P1* [2], $a = 11.7256(5)$ Å, $b = 13.3258(6)$ Å, $c = 15.6551(7)$ Å, $\alpha = 89.927(2)°$, $\beta = 89.955(2)°$, $\gamma = 83.357(2)°$, $V = 2429.73(19)$ Å^3, $T = 100(2)$ K, $Z = 4$, $D_{calc} = 1.188$ g · cm^3, $\lambda = 1.54178$ Å, $\mu(Cu\text{-}K_\alpha) = 0.576$ mm^{-1}, analytical absorption correction ($T_{min} = 0.92$, $T_{max} = 1.00$), Bruker AXS Enraf-Nonius KappaCCD diffractometer with a FR591 rotating Cu-anode X-ray source, $2.823 < \theta < 72.989°$, 105618 measured reflections, 18363 independent reflections, 17486 reflections with $I > 2\sigma(I)$, $R_{int} = 0.0426$, $S = 1.145$, 1190 parameters, absolute structure parameter = –0.09(6), residual electron density +0.2 (0.71 Å from H33B) / –0.2 (0.86 Å from C108) e · Å^{-3}.

The structure was solved by *SHELXT* and refined by full-matrix least-squares (*SHELXL*) against F^2 to $R_1 = 0.040$ [$I > 2\sigma(I)$], $wR_2 = 0.093$. **CCDC-2081189**.

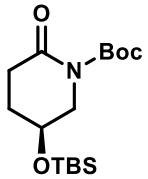
4.1.2 Second Generation Approach towards Ingenamine and Total Synthesis of Keramaphidin B

***tert*-Butyl (*S*)-3-((*tert*-butyldimethylsilyl)oxy)piperidine-1-carboxylate** (*ent*-**44**).

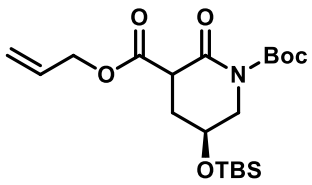


4-Dimethylamino-pyridine (8.3 g, 68.3 mmol) and triethylamine (17.3 mL, 124.22 mmol) were added to a stirred solution of (*S*)-1-Boc-3-hydroxypiperidine (25.00 g, 124.22 mmol) in dichloromethane (250 mL) at room temperature. After 5 min, *tert*-butyldimethylsilylchloride (20.03 g, 132.91 mmol) was added and the resulting mixture stirred for 4 h at room temperature. Next, the mixture was poured into ice-cooled water (100 mL), which was extracted with CH_2Cl_2 (3 x 250 mL). The combined organic phases were washed with brine (50 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography on silica (hexanes/EtOAc, 10:1), providing the title compound as a colorless oil (39.09 g, quant.). $[\alpha]_D^{25}$ = +14.7° (c = 1.0, $CHCl_3$)[103]; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.91 – 3.73 (m, 1H), 3.68 (dt, *J* = 13.3, 3.7 Hz, 1H), 3.59 (dp, *J* = 8.3, 4.0 Hz, 1H), 2.89 (tt, *J* = 10.0, 3.3 Hz, 1H), 2.80 (t, *J* = 9.7 Hz, 1H), 1.90 – 1.78 (m, 1H), 1.77 – 1.64 (m, 1H), 1.63 – 1.57 (m, 1H), 1.45 (s, 10H), 0.88 (s, 9H), 0.07 (d, *J* = 3.4 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 154.8, 79.3, 67.1, 51.1, 43.6, 33.9, 28.4, 25.8, 23.1, 18.1, –4.8; IR (film): $\tilde{\nu}$ = 2930, 2886, 2857, 1697, 1465, 1421, 1391, 1365, 1278, 1254, 1239, 1176, 1154, 1099, 1041, 981, 904, 873, 858, 837, 775 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{16}H_{33}NO_3SiNa$ [M+Na$^+$]: 338.21219, found: 338.21235.

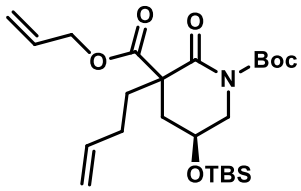
***tert*-Butyl (*S*)-5-((*tert*-butyldimethylsilyl)oxy)-2-oxopiperidine-1-carboxylate** (*ent*-**45**).



Ruthenium(IV) oxide hydrate (974 mg, 7.31 mmol) was added to a solution of piperidine *ent*-**44** (38.50 g, 122.02 mmol) and $NaIO_4$ (121.88 g, 569.83 mmol) in EtOAc/H_2O (1.62 L, 1:3). The resulting mixture was vigorously stirred in a flask open to air at room temperature for 1.5 h. The organic phase was separated and the aqueous layer extracted with EtOAc (3 x 300 mL). The combined organic extracts were stirred with isopropanol (20 mL) for 3 h to decompose any remaining catalyst before they were filtered. The filtrate was washed with brine (100 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography on silica (hexanes/EtOAc, 20:1 to 10:1), furnishing the title compound as a white solid (22.10 g, 55% yield). M.p. = 36.3-37.2 °C; $[\alpha]_D^{25}$ = +8.2° (c = 1.0, $CHCl_3$)[103]; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.19 – 4.10 (m, 1H), 3.69 – 3.58 (m, 2H), 2.71 (ddd, *J* = 17.2, 9.1, 6.7 Hz, 1H), 2.42 (dt, *J* = 17.2, 6.2 Hz, 1H), 1.95 (dddd, *J* = 13.2, 9.0, 6.4, 3.9 Hz, 1H), 1.82 (ddtd, *J* = 13.6, 6.8, 5.7, 1.2 Hz, 1H), 1.51 (s, 9H), 0.87 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.9, 152.5, 82.9, 64.4, 52.4, 31.1, 29.0, 28.0, 25.7, 18.0, –4.9; IR (film): $\tilde{\nu}$ = 2954, 2931, 2895, 2857, 1773, 1716, 1472, 1391, 1368, 1346, 1296, 1251, 1151, 1114, 1087, 1061, 1020, 984, 938, 881, 836, 777, 702 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{16}H_{31}NO_4SiNa$ [M+Na$^+$]: 352.19146, found: 352.19136.

3-Allyl 1-(*tert*-butyl) (5*S*)-5-((*tert*-butyldimethylsilyl)oxy)-2-oxopiperidine-1,3-dicarboxylate (S1). 

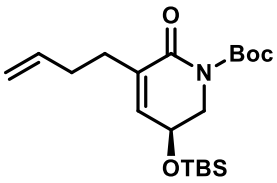
LiHMDS (1 M in THF, 19.21 g, 114.82 mmol) was added dropwise to a solution of oxopiperidine *ent*-**45** (16.45 g, 49.92 mmol) in anhydrous THF (250 mL) at –78 °C. The mixture was stirred at –78 °C for 1 h, before allyl chloroformate (5.6 mL, 52.42 mmol) was added. The resulting yellow solution was stirred for 25 min at –78 °C before the reaction was quenched with sat. aq. NH_4Cl solution (50 mL) and the mixture warmed to ambient temperature. The aqueous phase was diluted with H_2O (100 mL) and extracted with EtOAc (3 x 300 mL). The combined extracts were washed with brine (100 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica (hexanes/EtOAc, 5:1), furnishing the title compound as a white solid (19.45 g, 94% yield). M.p. = 49.4-50.3 °C. $[\alpha]_D^{25}$ = +15.0° (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, mixture of diastereomers) δ = 5.93 (ddtd, *J* = 17.2, 10.5, 5.7, 2.0 Hz, 1H), 5.35 (dp, *J* = 17.2, 1.5 Hz, 1H), 5.25 (ddt, *J* = 10.5, 2.1, 1.2 Hz, 1H), 4.73 – 4.61 (m, 2H), 4.30 – 4.21 (m, 0.7H, major), 4.13 (tdd, *J* = 6.4, 5.6, 3.7 Hz, 0.3H, minor), 3.84 – 3.78 (m, 0.7H, major), 3.77 – 3.63 (m, 1.7H, major), 3.60 (ddd, *J* = 13.2, 3.9, 0.9 Hz, 0.3H, minor), 3.46 (dd, *J* = 10.0, 7.3 Hz, 0.3H, minor), 2.37 – 2.19 (m, 1.3H), 2.09 (dddd, *J* = 13.6, 6.4, 4.6, 1.6 Hz, 0.7H, major), 1.51 (d, *J* = 1.7 Hz, 9H), 0.87 (d, *J* = 1.6 Hz, 9H), 0.12 – 0.04 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$, mixture of diastereomers): δ = 169.6, 168.8, 166.9, 166.9, 152.5, 152.2, 131.6, 131.6, 118.7, 118.6, 83.5, 83.4, 66.1, 64.3, 63.2, 52.2, 51.3, 49.5, 48.0, 33.4, 32.8, 27.9, 25.6, 17.9, –4.8, –4.9, –5.0, –5.1; IR (film): $\tilde{\nu}$ = 2955, 2932, 2896, 2857, 1776, 1746, 1722, 1472, 1391, 1369, 1296, 1255, 1147, 1103, 1030, 1005, 970, 927, 838, 810, 778 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{20}H_{35}NO_6SiNa$ [M+Na$^+$]: 436.21259, found: 436.21242.

3-Allyl 1-(*tert*-butyl) (5*S*)-3-(but-3-en-1-yl)-5-((*tert*-butyldimethylsilyl)oxy)-2-oxopiperidine-1,3-dicarboxylate (74). 

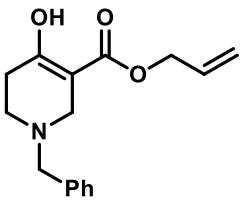
4-Bromobut-1-ene (7.2 mL, 70.62 mmol) and caesium carbonate (24.54 g, 75.32 mmol) were added to a solution of compound **S1** (19.47 g, 47.08 mmol) in anhydrous DMF (47 mL) at room temperature. The mixture was vigorously stirred for 16 h before the reaction was quenched with sat. aq. NH_4Cl (10 mL) and the mixture was extracted with EtOAc (3 x 200 mL). The combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography (hexanes/*tert*-butyl methyl ether, 5:1), furnishing the title compound as a colorless oil (20.60 g, 94% yield). $[\alpha]_D^{25}$ = +3.8° (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, mixture of diastereomers): δ = 5.95 – 5.72 (m, 2H), 5.34 (ddq, *J* = 17.2, 4.4, 1.5 Hz, 1H), 5.23 (ddq, *J* = 11.0, 8.5, 1.3 Hz, 1H), 5.03 (dp, *J* = 17.1, 1.7 Hz, 1H), 4.96 (dt, *J* = 10.1, 1.6 Hz, 1H), 4.70 – 4.56 (m, 2H), 4.20 (dtd, *J* = 7.0, 5.9, 3.8 Hz, 0.5H), 4.14 – 4.05 (m, 0.5H), 3.83 (ddd, *J* = 13.1, 4.4, 1.1 Hz, 0.5H), 3.72 (dd, *J* = 13.3, 5.9 Hz, 0.5H), 3.54 – 3.39 (m, 1H), 2.63 (ddd, *J* = 13.9, 5.8, 1.1 Hz, 0.5H), 2.48 (ddd, *J* = 13.9, 6.5, 0.9 Hz, 0.5H), 2.23 – 1.90 (m, 4H), 1.70 (dd, *J* = 13.9, 7.1 Hz, 0.6H), 1.52 (s, 9.4H), 0.87 (d, *J* = 4.4 Hz, 9H), 0.13 – 0.03 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$, mixture of diastereomers): δ = 171.3, 171.3, 169.8, 169.2, 152.7, 152.6,

137.6, 137.5, 131.4, 131.2, 119.0, 118.4, 115.1, 83.1, 83.1, 66.2, 66.0, 64.0, 63.9, 55.5, 54.7, 51.2, 51.0, 38.8, 35.8, 35.4, 29.0, 28.6, 27.9, 25.7, 25.6, 18.1, 17.9, –4.8, –4.8, –5.0; IR (film): $\tilde{\nu}$ = 2955, 2931, 2897, 2858, 1777, 1723, 1642, 1472, 1462, 1392, 1368, 1302, 1256, 1151, 1126, 985, 914, 870, 838, 810, 778 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{24}H_{41}NO_6SiNa$ [M+Na^+]: 490.25954, found: 490.25960.

***tert*-Butyl (*S*)-5-(but-3-en-1-yl)-3-((*tert*-butyldimethylsilyl)oxy)-6-oxo-3,6-dihydropyridine-1(2*H*)-carboxylate (67).** $Pd_2(dba)_3{\cdot}CHCl_3$ (1.11 g, 1.07 mmol) was added to a solution of compound **74** (10.00 g, 21.38 mmol) in anhydrous MeCN (86 mL). The mixture was stirred at 80 °C for 30 min. The crude mixture was filtered through a plug of Celite, which was carefully washed with *tert*-butyl methyl ether. The combined filtrates were concentrated in vacuo and the resulting crude material was purified by flash chromatography on silica (toluene, then hexane/*tert*-butyl methyl ether, 10:1) to furnish the title compound as a colorless oil (6.77 g, 83% yield). $[\alpha]_D^{25}$ = +62.6° (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.38 (dq, *J* = 3.4, 1.1 Hz, 1H), 5.79 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 5.05 – 4.94 (m, 2H), 4.43 (dddt, *J* = 8.0, 4.7, 3.3, 1.3 Hz, 1H), 3.88 (ddd, *J* = 12.8, 4.8, 1.1 Hz, 1H), 3.65 (dd, *J* = 12.8, 7.9 Hz, 1H), 2.38 (ddt, *J* = 8.5, 5.8, 1.3 Hz, 2H), 2.29 – 2.18 (m, 2H), 1.54 (s, 9H), 0.89 (s, 9H), 0.10 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 163.8, 152.8, 141.0, 137.7, 135.3, 115.2, 83.1, 63.8, 50.7, 32.3, 29.6, 28.1, 25.7, 18.1, –4.7, –4.7; IR (film): $\tilde{\nu}$ = 2955, 2930, 2889, 2858, 1768, 1716, 1651, 1472, 1389, 1368, 1337, 1303, 1256, 1194, 1149, 1091, 1034, 1005, 980, 954, 913, 876, 837, 810, 778 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{20}H_{35}NO_4SiNa$ [M+Na^+]: 404.22276, found: 404.22262.

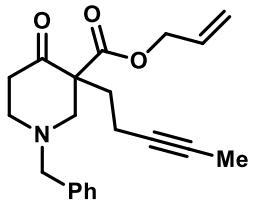


Allyl 1-benzyl-4-hydroxy-1,2,5,6-tetrahydropyridine-3-carboxylate (71). NaH (3.07 g, 127.81 mmol) was transferred into a Schlenk flask before anhydrous THF (54 mL) was added. The mixture was cooled to 0 °C and a solution of 1-benzyl-4-piperidone **70** (9.5 mL, 51.12 mmol) in THF (16.6 mL) was added dropwise. Once the addition was complete, the mixture was warmed to room temperature before diallyl carbonate (11.0 mL, 76.68 mmol) was added. The resulting mixture was stirred at room temperature for 18 h before sat. aq. NH_4Cl (30 mL) was carefully added to quench the reaction. The aqueous phase was diluted with H_2O (5 mL) and extracted with EtOAc (3 x 150 mL). The combined extracts were washed with brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica (hexanes/EtOAc, 5:1), furnishing the title compound as a colorless oil (6.35 g, 45% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.93 (s, 0.7H), 7.37 – 7.27 (m, 5H), 5.91 (dddt, *J* = 17.2, 10.4, 9.1, 5.6 Hz, 1H), 5.38 – 5.19 (m, 2H), 4.73 – 4.56 (m, 2H), 3.65 (d, *J* = 2.5 Hz, 2H), 3.50 (ddd, *J* = 7.9, 5.0, 1.3 Hz, 0.25H), 3.24 (t, *J* = 1.8 Hz, 1.5H), 3.08 (ddd, *J* = 11.6, 7.8, 1.2 Hz, 0.25H), 2.96 (ddd, *J* = 11.7, 5.0, 1.7 Hz, 0.25H), 2.84 (dddd, *J* = 11.7, 6.3, 5.6, 1.7 Hz, 0.25H), 2.75 (dddd, *J* = 11.3, 8.1, 4.8, 1.2 Hz, 0.25H), 2.64 – 2.50 (m, 2H), 2.41 (td, *J* = 5.9, 3.1 Hz, 1.5H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 203.9, 170.7, 170.6, 168.5, 137.8, 132.0, 131.6, 129.0, 128.8, 128.4, 128.4, 127.4, 127.3, 118.7, 118.1, 96.7, 65.8, 64.8, 62.0, 61.6, 56.6, 55.1, 53.1, 50.0, 48.5, 40.8, 29.4;



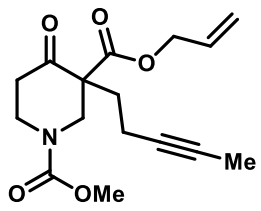
IR (film): $\tilde{\nu}$ = 3063, 3028, 2935, 2808, 2764, 1743, 1720, 1664, 1622, 1495, 1453, 1418, 1403, 1367, 1350, 1302, 1285, 1233, 1212, 1193, 1168, 1126, 1078, 1052, 1028, 994, 972, 934, 815, 742, 699 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{16}H_{20}NO_3$ [M+H$^+$]: 274.14377, found: 274.14376.

Allyl 1-benzyl-4-oxo-3-(pent-3-yn-1-yl)piperidine-3-carboxylate (72). 5-Iodopent-2-yne



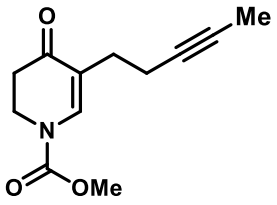
(14.72 g, 58.06 mmol)[224] and caesium carbonate (19.67 g, 60.38 mmol) were added in three portions (1:1:0.5) to a solution of compound **71** (6.35 g, 23.22 mmol) in anhydrous DMF (24 mL) at room temperature (the second and third portion were added after 30 min and 1h, respectively). The mixture was stirred for 3 h, before the reaction was quenched with sat. aq. NH_4Cl (15 mL). The aqueous phase was extracted with EtOAc (3 x 250 mL), the combined organic extracts were washed with brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica (hexanes/EtOAc, 5:1) to give the title compound as a colorless oil (7.15 g, 91% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29 – 7.20 (m, 5H), 5.82 (ddt, *J* = 17.2, 10.4, 5.8 Hz, 1H), 5.32 – 5.14 (m, 2H), 4.58 (qdt, *J* = 13.1, 5.8, 1.4 Hz, 2H), 3.52 (d, *J* = 1.9 Hz, 2H), 3.36 (dd, *J* = 11.6, 2.6 Hz, 1H), 2.92 (dtd, *J* = 12.8, 5.9, 3.5 Hz, 1H), 2.79 (ddd, *J* = 16.0, 12.3, 6.6 Hz, 1H), 2.39 – 2.28 (m, 2H), 2.28 – 2.12 (m, 2H), 2.04 – 1.86 (m, 2H), 1.76 – 1.68 (m, 1H), 1.67 (t, *J* = 2.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 205.8, 170.9, 137.7, 131.5, 128.8, 128.3, 127.4, 118.9, 78.3, 75.9, 65.9, 61.8, 61.1, 60.7, 53.4, 40.5, 31.7, 14.5, 3.5; IR (film): $\tilde{\nu}$ = 3028, 2957, 2919, 2807, 1717, 1649, 1495, 1453, 1423, 1348, 1316, 1227, 1186, 1121, 1076, 1059, 1029, 1000, 971, 936, 742, 699 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{21}H_{26}NO_3$ [M+H$^+$]: 340.19072, found: 340.19053.

3-Allyl 1-methyl 4-oxo-3-(pent-3-yn-1-yl)piperidine-1,3-dicarboxylate (73). Methyl



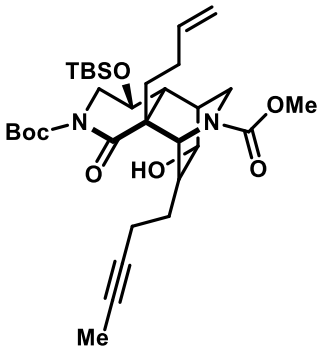
chloroformate (5.7 mL, 73.65 mmol) was added to a solution of compound **72** (5.00 g, 14.73 mmol) in toluene (21 mL). The reaction was stirred at 100 °C for 14 h. The mixture was cooled to room temperature and concentrated *in vacuo.* The residue was purified by flash chromatography on silica (hexanes/EtOAc, 3:1 to 2:1), furnishing the title compound as a yellow oil (4.52 g, quant.). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.86 (ddt, *J* = 16.5, 9.9, 5.8 Hz, 1H), 5.36 – 5.20 (m, 2H), 4.65 – 4.50 (m, 3H), 4.27 – 3.93 (br, 1H), 3.73 (s, 3H), 3.39 (br, 1H), 3.22 (d, *J* = 13.7 Hz, 1H), 2.68 (ddd, *J* = 14.1, 9.8, 6.3 Hz, 1H), 2.48 (dt, *J* = 14.7, 4.7 Hz, 1H), 2.28 – 2.02 (m, 3H), 1.86 (br, 1H), 1.76 – 1.68 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 203.9, 169.4, 155.6, 131.1, 119.3, 77.8, 76.5, 66.3, 60.6, 53.1, 50.1, 43.6, 39.6, 31.1, 14.3, 3.4; IR (film): $\tilde{\nu}$ = 2956, 2920, 2860, 1699, 1650, 1447, 1474, 1413, 1375, 1264, 1238, 1220, 1189, 1130, 1067, 1028, 995, 935, 876, 767, 528 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{16}H_{21}NO_5Na$ [M+Na$^+$]: 330.13119, found: 330.13101.

Methyl 4-oxo-5-(pent-3-yn-1-yl)-3,4-dihydropyridine-1(2*H*)-carboxylate (43).



$Pd_2(dba)_3{\cdot}CHCl_3$ (668 mg, 0.73 mmol) was added to a solution of compound **73** (4.49 g, 14.60 mmol) in anhydrous MeCN (59 mL). The mixture was stirred at 80 °C for 30 min before it was cooled to ambient temperature and filtered through a plug of Celite, which was carefully washed with *tert*-butyl methyl ether. The combined filtrates were concentrated in vacuo and the resulting crude material was purified by flash chromatography on silica (hexane/EtOAc, 3:1 to 1:1) to give the title compound as a white solid (3.10 g, 96% yield). M.p. = 69.8-70.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.77 (br, 1H), 3.98 (t, *J* = 7.3 Hz, 2H), 3.85 (s, 3H), 2.57 – 2.51 (m, 2H), 2.35 – 2.28 (m, 2H), 2.24 (dddd, *J* = 7.7, 6.1, 2.9, 2.1 Hz, 2H), 1.74 (t, *J* = 2.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 192.8, 153.4, 140.9, 117.3, 78.4, 76.6, 53.9, 42.6, 35.8, 26.9, 18.7, 3.4; IR (film): $\tilde{\nu}$ = 2956, 2919, 2857, 1722, 1662, 1615, 1440, 1399, 1369, 1322, 1300, 1245, 1204, 1174, 1122, 1077, 1049, 1017, 969, 927, 909, 868, 767, 666, 512, 484, 438 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{12}H_{15}NO_3Na$ [M+Na$^+$]: 244.09441, found: 244.09442.

Compound 75. A solution of Li*O*t*Bu* (223 mg, 2.89 mmol) in THF (6 mL) was added dropwise

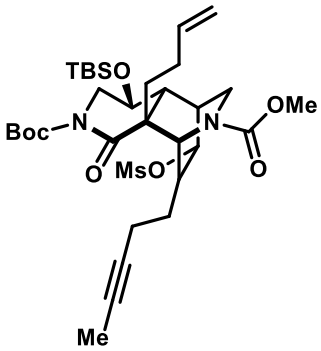


to a solution of compound **43** (617 mg, 2.79 mmol) in anhydrous THF (11 mL) at –50 °C. The resulting red solution was stirred for 10 min before a solution of compound **67** (887 mg, 2.33 mmol) in THF (5 mL) was added. The mixture was warmed to room temperature over the course of 5 h and stirring was continued for another 16 h. Next, 4-dimethyl-aminopyridine (568 mg, 4.65 mmol) and di-*tert*-butyl dicarbonate (1.1 mL, 4.65 mmol) were added and the resulting mixture was stirred for 1 h. sat. aq. NH_4Cl (10 mL) was carefully introduced to quench the reaction. The aqueous phase was extracted with EtOAc (3 x 150 mL) and the combined extracts were washed with brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by flash chromatography on silica (hexane/*tert*-butyl methyl ether, 10:1; then hexane/EtOAc, 10:1), furnishing compound **68** as a white foam which was used in the next step without further purification.

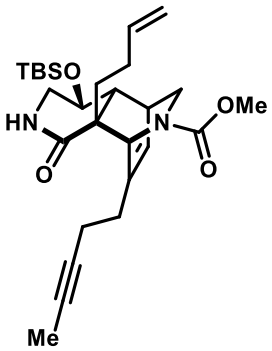
$NaBH_4$ (356 mg, 9.42 mmol) was added in portions to a solution of **68** in methanol (15.9 mL) at 0 °C. The mixture was stirred for 20 min, before the reaction was quenched with sat. aq. NH_4Cl (5 mL) at this temperature. The aqueous phase was extracted with EtOAc (3 x 100 mL) and the combined extracts were washed with brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica (pentane/*tert*-butyl methyl ether, 3:1) to furnish the title compound as a white foam (742 mg, 53% yield over 2 steps). $[\alpha]_D^{25}$ = –66.9° (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers): δ = 5.76 – 5.60 (m, 1H), 5.00 – 4.83 (m, 2H), 4.49 (tdd, *J* = 10.6, 4.1, 2.2 Hz, 1H), 4.32 (s, 0.3H, minor), 4.20 (s, 0.7H, major), 4.10 (ddd, *J* = 12.4, 4.2, 1.8 Hz, 1H), 3.68 (s, 3H), 3.66 – 3.61 (m, 1H), 3.31 (ddd, *J* = 20.7, 11.4, 3.0 Hz, 1H), 3.18 – 3.05 (m, 2H), 2.44 – 2.01 (m, 5H), 2.00 – 1.84 (m, 1H), 1.82 – 1.56

(m, 8H), 1.52 (s, 10H), 0.88 (s, 9H), 0.10 (d, J = 3.3 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$, mixture of rotamers): δ = 172.2, 172.1, 156.7, 156.6, 151.8, 151.7, 137.9, 137.4, 115.0, 114.7, 83.3, 83.2, 79.1, 78.9, 76.5, 76.4, 75.5, 75.3, 67.7, 67.7, 52.7, 52.6, 52.6, 52.5, 52.4, 52.1, 52.1, 51.6, 50.0, 49.9, 48.1, 46.2, 46.0, 40.2, 39.8, 34.3, 34.2, 32.3, 32.3, 28.3, 28.1, 28.0, 25.8, 17.9, 16.4, 16.4, 3.4, –4.5, –4.5, –4.6; IR (film): $\tilde{\nu}$ = 3493, 2952, 2930, 2885, 2857, 1766, 1707, 1681, 1641, 1453, 1394, 1369, 1338, 1298, 1256, 1190, 1156, 1125, 1074, 1005, 914, 865, 839, 779 cm^{-1}. HRMS (ESI): m/z calcd. for $C_{32}H_{52}N_2O_7SiNa$ [M+Na$^+$]: 627.34360, found: 627.34354.

Compound S2. Triethylamine (9.7 mL, 69.64 mmol), 4-dimethylaminopyridine (1.36 g, 11.16 mmol) and methanesulfonyl chloride (2.14 mL, 27.68 mmol) were successively added to a solution of compound **75** (2.70 g, 4.46 mmol) in CH_2Cl_2 (22 mL) at 0 °C. The mixture was warmed to room temperature after 5 min and stirred for 1 h. The reaction was quenched with sat. aq. $NaHCO_3$ (20 mL) and the aqueous phase extracted with *tert*-butyl methyl ether (3 x 250 mL). The combined organic extracts were washed with brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica (hexane/EtOAc, 5:1 to 4:1), furnishing the title compound as a white foam (2.79 g, 91% yield). $[\alpha]_D^{25}$ = –30.7° (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers): δ = 5.68 (dtt, J = 17.0, 10.5, 6.5 Hz, 1H), 5.01 – 4.86 (m, 2H), 4.52 – 4.27 (m, 2H), 4.26 – 4.14 (m, 2H), 3.71 (d, J = 4.8 Hz, 3H), 3.38 (ddd, J = 10.9, 8.3, 2.6 Hz, 1H), 3.30 – 3.12 (m, 2H), 3.04 (d, J = 5.0 Hz, 4H), 2.59 (dp, J = 17.1, 2.6 Hz, 1H), 2.48 – 2.03 (m, 3H), 2.02 – 1.83 (m, 1H), 1.83 – 1.59 (m, 7H), 1.52 (s, 9H), 0.88 (d, J = 0.9 Hz, 9H), 0.14 (d, J = 6.1 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$, mixture of rotamers) δ = 171.2, 171.1, 156.5, 156.4, 151.4, 151.3, 137.5, 137.0, 115.3, 115.0, 84.6, 84.3, 83.6, 83.5, 78.5, 78.1, 76.3, 76.2, 67.8, 67.7, 52.9, 52.2, 51.8, 51.6, 50.3, 49.8, 49.3, 49.2, 48.0, 42.8, 42.8, 40.0, 39.5, 38.8, 38.7, 34.0, 33.8, 31.8, 31.7, 28.3, 28.1, 28.0, 25.8, 17.9, 16.1, 16.0, 3.5, 3.5, –4.3, –4.3, –4.5, –4.6; IR (film): $\tilde{\nu}$ = 2953, 2931, 2857, 1770, 1704, 1641, 1450, 1389, 1366, 1338, 1297, 1256, 1176, 1155, 1125, 1096, 1051, 994, 964, 941, 897, 838, 779, 754, 686, 666, 527 cm^{-1}. HRMS (ESI): m/z calcd. for $C_{33}H_{54}N_2O_9SSiNa$ [M+Na$^+$]: 705.32115, found: 705.32108.

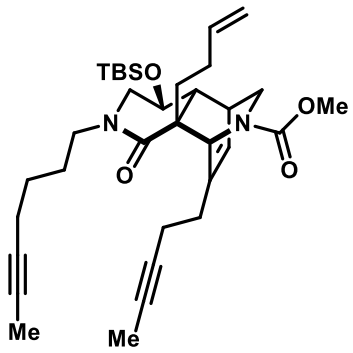


Compound 76. A solution of mesylate **S2** (2.616 g, 3.83 mmol) in 2,6-lutidine (21 mL) was stirred at 170 °C for 5 d. The mixture was cooled to 0 °C before CH_2Cl_2 (22 mL) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (3.52 mL, 15.32 mmol) were added. Stirring was continued at room temperature for 45 min before sat. aq. $NaHCO_3$ (5 mL) was added at 0 °C. Next, the mixture was poured into a solution of HCl (2 M, 45 mL), which was vigorously stirred for 15 min. The aqueous phase was extracted with EtOAc (3 x 200 mL), the combined organic extracts were washed with sat. aq. $NaHCO_3$ (50 mL) and brine (25 mL), before they

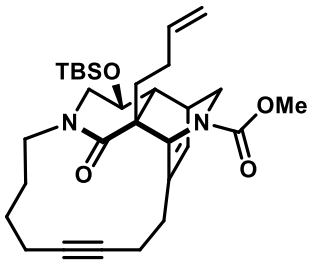


were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica (CH_2Cl_2/*tert*-butyl methyl ether, 6:1), furnishing the title compound as a white foam (1.357 g, 73% yield). $[\alpha]_D^{25}$ = –69.4° (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers): δ = 6.43 (d, *J* = 6.2 Hz, 0.3H, minor), 6.37 (d, 0.7H, major), 5.94 (dd, *J* = 10.2, 6.6 Hz, 1H), 5.72 (dddd, *J* = 16.7, 13.0, 10.2, 6.0 Hz, 1H), 5.04 – 4.86 (m, 2.3H, minor), 4.80 (d, *J* = 1.6 Hz, 0.7H, major), 3.69 (s, 2H), 3.66 (s, 1H), 3.37 (tdd, *J* = 9.4, 5.0, 1.7 Hz, 1H), 3.22 – 2.92 (m, 4H), 2.84 – 2.72 (m, 1H), 2.48 – 2.14 (m, 5H), 2.14 – 1.96 (m, 1H), 1.77 – 1.55 (m, 6H), 0.89 (s, 9H), 0.08 (d, *J* = 16.6 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$, mixture of rotamers): δ = 173.5, 173.5, 156.1, 156.1, 146.6, 145.9, 138.3, 137.8, 125.6, 125.1, 114.8, 114.5, 78.5, 78.1, 75.9, 75.5, 70.9, 70.8, 54.3, 54.2, 52.8, 52.5, 52.4, 52.3, 51.5, 51.5, 47.2, 47.0, 45.6, 39.8, 39.5, 33.7, 33.4, 33.2, 33.1, 28.6, 28.3, 25.6, 17.8, 16.9, 16.8, 3.4, 3.4, –4.3, –4.4, –4.8, –4.8; IR (film): $\tilde{\nu}$ = 3209, 3075, 2953, 2929, 2896, 2857, 1702, 1667, 1448, 1389, 1345, 1329, 1300, 1273, 1257, 1220, 1191, 1120, 1091, 1006, 956, 913, 873, 838, 776, 685 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{27}H_{42}N_2O_4SiNa$ [M+Na$^+$]: 509.28061, found: 509.28065.

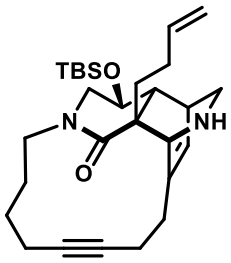
Compound 77. A solution of amide **76** (1.357 g, 2.79 mmol) in DMF (2 mL) and 7-iodohept-2-yne **50** (2.166 g, 9.76 mmol)[62] were successively added to a mixture of NaH (1.003 g, 41.81 mmol) in DMF (25 mL) at 0 °C. The mixture was stirred for 30 min before sat. aq. NH_4Cl (5 mL) was carefully added. The aqueous phase was diluted with H_2O (5 mL) and extracted with EtOAc (3 x 100 mL). The combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica (pentane/*tert*-butyl methyl ether, 4:1), furnishing the title compound as a colorless oil (1.545 g, 95% yield). $[\alpha]_D^{25}$ = –54.7° (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers): δ = 5.92 (t, *J* = 7.7 Hz, 1H), 5.73 (dddt, *J* = 16.8, 13.2, 10.2, 6.5 Hz, 1H), 5.04 – 4.85 (m, 3H), 3.71 (s, 2H, major), 3.66 (s, 1H, minor), 3.38 (dt, *J* = 13.8, 7.0 Hz, 1H), 3.34 – 3.21 (m, 2H), 3.21 – 3.11 (m, 2H), 3.03 (dd, *J* = 10.5, 2.8 Hz, 0.7H, major), 2.99 – 2.92 (m, 1.3H, minor), 2.81 – 2.70 (m, 1H), 2.47 – 2.08 (m, 7H), 2.08 – 1.95 (m, 1H), 1.75 (t, *J* = 2.5 Hz, 3H), 1.71 (t, *J* = 2.3 Hz, 3H), 1.69 – 1.47 (m, 5H), 1.45 – 1.33 (m, 2H), 0.91 (s, 9H), 0.10 (d, *J* = 11.7 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$, mixture of rotamers): δ = 170.4, 156.2, 156.1, 147.0, 146.3, 138.5, 138.1, 125.2, 124.6, 114.6, 114.3, 78.6, 78.6, 78.5, 78.3, 75.9, 75.8, 75.4, 70.7, 70.6, 54.8, 54.7, 53.1, 52.9, 52.4, 52.3, 52.1, 52.0, 51.0, 47.1, 46.9, 46.9, 40.0, 39.7, 33.7, 33.4, 33.1, 33.0, 28.7, 28.4, 26.6, 26.6, 25.9, 25.7, 18.4, 18.3, 17.8, 16.8, 16.8, 3.4, 3.4, –4.3, –4.4, –4.8, –4.8; IR (film): $\tilde{\nu}$ = 2951, 2928, 2857, 1701, 1645, 1446, 1389, 1347, 1328, 1299, 1259, 1190, 1161, 1104, 1088, 1049, 1005, 956, 908, 871, 837, 811, 776 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{34}H_{52}N_2O_4SiNa$ [M+Na$^+$]: 603.35886, found: 603.35906.



Compound 78. A solution of the molybdenum complex **79** (351 mg, 0.45 mmol)[105] in toluene (10 mL) was added dropwise to a suspension comprising diyne **77** (1.310 g, 2.26 mmol) and powdered MS (5 Å, 30 g) in toluene (1.17 L) at reflux temperature. After stirring for 10 min, EtOH (10 mL) was added, the mixture was cooled to room temperature and filtered through a short pad of Celite, which was carefully rinsed with EtOAc. The combined filtrates were concentrated *in vacuo* and the residue was purified by flash chromatography on silica (toluene/EtOAc, 8:1), furnishing the title compound as a white solid (983 mg, 83% yield). M.p. = 163.9-165.1 °C; $[\alpha]_D^{25}$ = –102.4° (c = 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers): δ = 6.00 – 5.89 (m, 1H), 5.73 (dddt, *J* = 16.8, 13.1, 10.1, 6.5 Hz, 1H), 5.04 – 4.80 (m, 3H), 4.04 – 3.92 (m, 1H), 3.72 – 3.59 (m, 4H), 3.39 (dd, *J* = 12.3, 10.6 Hz, 1H), 3.19 (dd, *J* = 10.5, 2.0 Hz, 1H), 3.06 – 2.89 (m, 2H), 2.89 – 2.77 (m, 1H), 2.70 – 2.51 (m, 1H), 2.47 – 2.03 (m, 8H), 1.92 (ddt, *J* = 16.3, 13.2, 3.1 Hz, 1H), 1.74 – 1.51 (m, 4H), 1.40 – 1.27 (m, 1H), 1.27 – 1.08 (m, 1H), 0.89 (s, 9H), 0.09 (d, *J* = 25.2 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$, mixture of rotamers): δ = 170.0, 170.0, 156.3, 146.0, 145.2, 138.6, 138.2, 123.4, 122.9, 114.6, 114.3, 81.0, 80.9, 79.3, 79.2, 70.4, 70.3, 55.2, 54.7, 54.7, 54.5, 54.2, 52.4, 52.4, 52.1, 52.0, 50.6, 47.2, 47.0, 39.8, 39.5, 33.9, 33.6, 32.2, 32.1, 28.7, 28.5, 26.2, 26.1, 25.7, 18.7, 17.8, 14.1, –4.2, –4.2, –4.6, –4.7; IR (film): $\tilde{\nu}$ = 2953, 2928, 2857, 1699, 1640, 1449, 1423, 1390, 1350, 1319, 1262, 1218, 1190, 1170, 1157, 1140, 1103, 1085, 1051, 1006, 955, 909, 870, 836, 809, 775, 754, 723, 712, 683, 665, 442 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{30}H_{46}N_2O_4SiNa$ [M+Na$^+$]: 549.31191, found: 549.31220.



Compound 81. L-Selectride (1 M in THF, 8.28 mL, 8.28 mmol) was added to a solution of carbamate **78** (1.090 g, 2.07 mmol) in THF (19 mL). The mixture was stirred at 40 °C for 16 h. Next, the mixture was cooled to 0 °C before MeOH (5 mL) was carefully added. The solution was concentrated *in vacuo* and the residue was purified by flash chromatography on silica (CH_2Cl_2/MeOH, 95:5 to 90:10), furnishing the title compound as a yellow oil (878 mg, 91% yield). $[\alpha]_D^{25}$ = –45.5° (c = 0.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.97 (dd, *J* = 6.8, 2.1 Hz, 1H), 5.84 (ddt, *J* = 16.8, 10.2, 6.4 Hz, 1H), 5.05 (dq, *J* = 17.1, 1.7 Hz, 1H), 4.94 (dq, *J* = 10.2, 1.3 Hz, 1H), 4.04 – 3.92 (m, 1H), 3.86 (s, 1H), 3.65 (ddd, *J* = 10.6, 8.8, 4.5 Hz, 1H), 3.38 (dd, *J* = 12.2, 10.6 Hz, 1H), 2.99 – 2.85 (m, 2H), 2.77 (dd, *J* = 7.0, 2.4 Hz, 1H), 2.62 – 2.07 (m, 10H), 1.95 (dddd, *J* = 22.0, 19.4, 12.6, 4.1 Hz, 2H), 1.72 (ddd, *J* = 13.7, 11.3, 5.5 Hz, 1H), 1.66 – 1.52 (m, 2H), 1.34 (tq, *J* = 12.3, 3.4 Hz, 1H), 1.28 – 1.11 (m, 2H), 0.90 (s, 9H), 0.10 (d, *J* = 25.8 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 170.6, 146.2, 138.5, 122.6, 114.5, 81.2, 79.2, 70.4, 55.6, 55.2, 54.3, 50.7, 50.6, 45.1, 39.7, 33.4, 31.9, 28.8, 26.3, 26.2, 25.7, 18.8, 17.9, 14.2, –4.2, –4.6; IR (film): $\tilde{\nu}$ = 2952, 2927, 2856, 1638, 1484, 1452, 1422, 1388, 1357, 1327, 1258, 1171, 1141, 1092, 1006, 924, 910, 868, 836, 804, 775, 750, 678, 664, 439 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{28}H_{45}N_2O_2Si$ [M+H$^+$]: 469.32448, found: 469.32463.

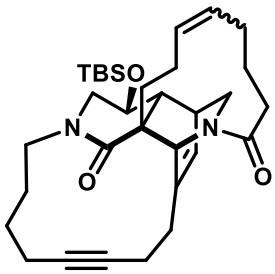


Compound 82. $NaBH(OAc)_3$ (39.0 mg, 0.18 mmol) was added to a solution of secondary amine **81** (43.2 mg, 0.09 mmol) and 5-hexenal (40.7 mg, 0.42 mmol) in CH_2Cl_2 (0.9 mL) and the resulting mixture was stirred at ambient temperature for 3 h. The mixture was diluted with CH_2Cl_2 (5 mL) and the reaction quenched with sat. aq. $NaHCO_3$ (5 mL). The aqueous phase was extracted with EtOAc (3 x 20 mL), the combined organic fractions were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography on silica (hexane/EtOAc, 8:1), furnishing the title compound as a colorless oil (48.5 mg, 96% yield). $[\alpha]_D^{25}$ = –24.4° (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.94 (d, *J* = 4.6 Hz, 1H), 5.87 – 5.71 (m, 2H), 4.99 (ddq, *J* = 17.2, 10.4, 1.7 Hz, 2H), 4.94 – 4.87 (m, 2H), 4.04 – 3.91 (m, 1H), 3.65 – 3.53 (m, 2H), 3.35 (dd, *J* = 12.1, 10.6 Hz, 1H), 2.96 (dd, *J* = 9.6, 2.0 Hz, 1H), 2.89 (dd, *J* = 12.1, 4.5 Hz, 1H), 2.58 (ttd, *J* = 8.8, 6.9, 1.8 Hz, 2H), 2.42 (dt, *J* = 11.5, 7.2 Hz, 1H), 2.33 (ddt, *J* = 12.3, 7.9, 4.2 Hz, 4H), 2.26 – 2.00 (m, 8H), 1.90 (ddq, *J* = 15.9, 12.8, 3.0 Hz, 1H), 1.77 (dd, *J* = 9.5, 2.7 Hz, 1H), 1.72 – 1.51 (m, 2H), 1.52 – 1.25 (m, 6H), 1.18 (qd, *J* = 12.2, 3.0 Hz, 1H), 0.89 (s, 9H), 0.09 (d, *J* = 24.2 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.36, 143.24, 139.22, 139.05, 121.67, 114.19, 113.91, 81.22, 79.09, 70.75, 61.86, 57.68, 54.48, 54.37, 54.05, 52.04, 50.55, 39.35, 34.31, 33.65, 28.92, 27.96, 26.47, 26.20, 26.13, 25.73, 18.82, 17.86, 14.28, -4.25, -4.61; IR (film): $\tilde{\nu}$ = 2929, 2881, 2857, 1642, 1482, 1451, 1419, 1357, 1328, 1287, 1257, 1171, 1157, 1123, 1086, 1042, 1065, 1006, 997, 925, 908, 870, 836, 775, 804 cm^{-1}. HRMS (ESI): *m/z* calcd. for $C_{34}H_{55}N_2O_2Si$ [M+H$^+$]: 551.40273, found: 551.40310.

Compound 65. DMF (2 drops) and oxalyl chloride (0.18 mL, 2.06 mmol) were added to a solution of 5-hexenoic acid (0.20 mL, 1.72 mmol) in CH_2Cl_2 (5.5 mL) at 0 °C. The mixture was warmed to room temperature and stirred for 2 h. The resulting solution was added to a solution of amine **81** (878 mg, 1.87 mmol) and triethylamine (1.3 mL, 9.37 mmol) in CH_2Cl_2 (10 mL) at 0 °C. After 5 min, the mixture was warmed to room temperature and stirred for 1 h. sat. aq. $NaHCO_3$ (5 mL) was added and the aqueous phase extracted with EtOAc (3 x 100 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica (hexane/EtOAc, 4:1 to 3:1) to give the title compound as a white foam (756 mg, 71% yield). $[\alpha]_D^{25}$ = –103.0° (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers): δ = 6.03 – 5.92 (m, 1H), 5.85 – 5.63 (m, 2H), 5.50 (d, *J* = 1.5 Hz, 0.4H, minor), 5.07 – 4.85 (m, 4H), 4.61 (d, *J* = 1.5 Hz, 0.6H, major), 4.01 (dt, *J* = 9.6, 3.0 Hz, 1H), 3.68 (dtd, *J* = 10.6, 8.8, 4.6 Hz, 1H), 3.41 (ddd, *J* = 12.3, 10.7, 5.1 Hz, 1H), 3.30 (dd, *J* = 9.5, 2.0 Hz, 0.4H, minor), 3.22 – 3.12 (m, 1.2H, major/major), 3.06 (dd, *J* = 9.5, 2.8 Hz, 0.4H, minor), 3.00 – 2.85 (m, 2H), 2.72 – 2.52 (m, 1H), 2.46 – 1.87 (m, 13H), 1.83 – 1.51 (m, 6H), 1.44 – 1.11 (m, 2H), 0.91 (d, *J* = 0.8 Hz, 9H), 0.11 (d, *J* = 27.2 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$, mixture of rotamers): δ = 172.2, 171.9, 170.2, 169.9, 146.4, 144.4, 138.6, 138.2, 138.0, 137.4, 124.2, 122.8, 115.2, 115.1, 114.3, 81.0, 80.8, 79.5, 79.3, 70.4, 69.9, 58.2, 55.0, 54.3, 54.2, 53.4, 52.5, 52.1,

51.8, 50.7, 50.5, 48.1, 46.5, 40.0, 39.6, 34.2, 33.6, 33.3, 33.3, 33.0, 33.0, 32.9, 32.3, 32.3, 32.2, 29.0, 28.5, 26.3, 26.2, 26.1, 25.7, 24.3, 23.9, 18.8, 18.7, 17.9, 14.2, 14.1, –4.2, –4.2, –4.6, –4.6; IR (film): $\tilde{\nu}$ = 2952, 2928, 2857, 1645, 1472, 1484, 1452, 1415, 1358, 1326, 1299, 1260, 1170, 1141, 1120, 1086, 1005, 910, 871, 837, 809, 776 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{34}H_{52}N_2O_3SiNa$ [M+Na^+]: 587.36394, found: 587.36424.

Compound 66. A solution of benzylidene-bis(tricyclohexylphosphino)-dichlororuthenium **87**



("first generation" Grubbs catalyst, 7.3 mg, 0.009 mmol) in toluene (2 mL) was slowly added to a solution of compound **65** (10 mg, 0.018 mmol) in toluene (16 mL) at 100 °C over the course of 2.5 h. After the addition was complete, stirring was continued at 100 °C for another 2 h before a solution of potassium 2-isocyanoacetate (19 mg, 0.154 mmol) in MeOH (3 mL) was added at 100 °C. The mixture was cooled to room temperature and stirred for an additional 30 min, before it was concentrated *in vacuo.* The residue was purified by flash chromatography on silica (hexane/EtOAc, 2:1 to 1:1), furnishing the title compound as a mixture of olefin isomers (9.2 mg, 97% yield, *E*-/*Z*-ratio 60:40) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$, mixture of *E*-/*Z*-Isomers ca. 60:40): δ 5.98 (dd, *J* = 15.7, 6.9 Hz, 1H, major/minor), 5.91 – 5.84 (m, 0.6H, major), 5.59 (s, 0.4H, minor), 5.51 – 5.40 (m, 0.6H, major), 5.32 (td, *J* = 10.3, 5.2 Hz, 0.4H, minor), 5.08 (d, *J* = 1.6 Hz, 0.6H, major), 4.99 (d, *J* = 1.5 Hz, 0.4H, minor), 4.01 (dt, *J* = 9.7, 2.8 Hz, 1H, major/minor), 3.74 – 3.62 (m, 1H, major/minor), 3.39 (ddd, *J* = 12.3, 10.5, 3.4 Hz, 1H, major/minor), 3.27 – 3.08 (m, 2H, major/minor), 2.98 (ddd, *J* = 12.4, 4.4, 2.5 Hz, 1H, major/minor), 2.84 (dq, *J* = 5.4, 2.4 Hz, 1H, major/minor), 2.77 – 2.55 (m, 1H, major/major/minor), 2.46 – 2.23 (m, 7H, major/minor), 2.22 – 2.04 (m, 4H, major/minor), 2.01 – 1.96 (m, 1H, major/minor), 1.90 (td, *J* = 15.3, 14.9, 3.8 Hz, 3H, major/minor), 1.83 – 1.75 (m, 1H, major/minor), 1.66 – 1.51 (m, 3H, major/minor), 1.38 (dddd, *J* = 15.5, 11.2, 7.6, 3.6 Hz, 1H, major/minor), 1.22 – 1.12 (m, 1H, major/minor), 0.91 (d, *J* = 0.9 Hz, 9H, major/minor), 0.14 (s, 3H, major/minor), 0.08 (s, 3H, major/minor); HRMS (ESI): *m*/*z* calcd. for $C_{32}H_{48}N_2O_3SiNa$ [M+Na^+]: 559.33209, found: 559.33264.

The isomer mixture was separated by preparative HPLC (two consecutive Multochrom 100-3 Si columns, 250 mm x 20 mm, iso-hexane/isopropanol 95:5, 20 mL/min, λ = 220 nm, t_R (*Z*-Isomer) = 31.0 min). The pure *Z*-isomer analyzed as follows: ^{1}H NMR (600 MHz, $CDCl_3$): δ = 5.95 (d, *J* = 6.6 Hz, 1H), 5.60 (s, 1H), 5.31 (td, *J* = 10.5, 5.4 Hz, 1H), 4.98 (s, 1H), 4.04 – 3.98 (m, 1H), 3.66 (ddd, *J* = 10.1, 8.7, 4.3 Hz, 1H), 3.39 (dd, *J* = 12.3, 10.5 Hz, 1H), 3.22 (dd, *J* = 11.5, 1.5 Hz, 1H), 3.12 (dd, *J* = 12.0, 3.0 Hz, 1H), 2.98 (dd, *J* = 12.3, 4.3 Hz, 1H), 2.83 (dd, *J* = 6.7, 2.6 Hz, 1H), 2.71 (ddd, *J* = 14.3, 12.1, 2.4 Hz, 1H), 2.62 (ddt, *J* = 15.4, 13.6, 2.2 Hz, 1H), 2.44 – 2.32 (m, 4H), 2.31 – 2.26 (m, 1H), 2.26 – 2.17 (m, 2H), 2.16 – 2.03 (m, 4H), 1.98 – 1.84 (m, 3H), 1.79 (s, 1H), 1.70 – 1.56 (m, 3H), 1.43 – 1.31 (m, 1H), 1.23 – 1.12 (m, 1H), 0.90 (s, 9H), 0.13 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 173.3, 170.3, 145.1, 130.0, 129.6, 123.6, 80.7, 79.4, 70.4, 58.2, 55.6,

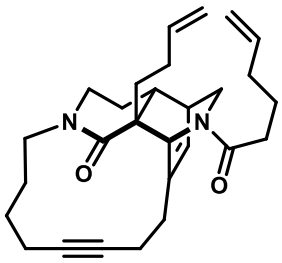
54.3, 52.3, 50.9, 47.7, 38.3, 33.2, 31.8, 30.6, 26.3, 26.1, 25.9, 25.7, 25.4, 22.8, 18.8, 17.9, 14.2, –4.3, –4.6.

Compound 91. Tetrabutylammonium fluoride (1 M in THF, 1.78 mL, 1.78 mmol) was added to a solution of TBS-ether **65** (502 mg, 0.89 mmol) in THF (50 mL) at 0 °C. The solution was stirred for 20 min before sat. aq. NH_4Cl (15 mL) was added. The aqueous phase was extracted with EtOAc (3 x 100 mL) and the combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica (hexane/EtOAc, 1:2 to pure EtOAc), furnishing the title compound as a white foam (400 mg, quant.). $[\alpha]_D^{25} = -134.2°$ (c = 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers): δ = 6.10 – 6.00 (m, 1H), 5.84 – 5.63 (m, 2H), 5.47 (d, *J* = 1.6 Hz, 0.4H, minor), 5.06 – 4.86 (m, 4H), 4.60 (d, *J* = 1.5 Hz, 0.6H, major), 3.99 (ddt, *J* = 12.3, 5.7, 2.7 Hz, 1H), 3.81 – 3.66 (m, 1H), 3.45 (ddd, *J* = 12.2, 10.8, 5.8 Hz, 1H), 3.32 (dd, *J* = 9.3, 1.7 Hz, 0.4H, minor), 3.22 – 3.02 (m, 4.6H, major), 2.69 – 2.51 (m, 1H), 2.46 – 2.33 (m, 4H), 2.33 – 1.99 (m, 8H), 1.90 (ddd, *J* = 16.7, 13.2, 3.0 Hz, 1H), 1.80 – 1.68 (m, 3H), 1.68 – 1.52 (m, 3H), 1.36 (tdd, *J* = 14.9, 11.3, 6.7 Hz, 1H), 1.23 – 1.06 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$, mixture of rotamers): δ = 172.3, 172.1, 170.3, 170.0, 145.9, 144.2, 138.4, 138.1, 137.9, 137.3, 124.5, 123.2, 115.3, 115.3, 115.1, 114.6, 81.0, 80.8, 79.7, 79.5, 69.3, 68.9, 58.4, 54.4, 54.2, 52.8, 52.6, 52.1, 51.9, 50.7, 50.5, 48.1, 46.7, 40.0, 39.7, 34.2, 33.7, 33.3, 33.2, 33.0, 32.3, 29.1, 28.6, 26.3, 26.2, 26.1, 24.3, 23.9, 18.9, 18.8, 14.1, 14.1; IR (film): $\tilde{\nu}$ = 3364, 2924, 2863, 1635, 1612, 1487, 1418, 1356, 1326, 1264, 1236, 1167, 1137, 1116, 1063, 1034, 996, 911, 831, 812, 751, 685, 665, 646, 579, 443 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{28}H_{38}N_2O_3Na$ [M+Na$^+$]: 473.27746, found: 473.27731.

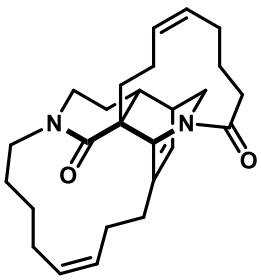
Compound 92. Martin's sulfurane (1.41 g, 2.10 mmol) was added to a mixture of alcohol **91** (378 mg, 0.84 mmol) in toluene (38 mL) at room temperature. The mixture was stirred at 100 °C for 1 h before it was cooled to room temperature and sat. aq. $NaHCO_3$ (10 mL) was added. The aqueous phase was extracted with EtOAc (3 x 100 mL) and the combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography on silica (toluene/EtOAc, 8:1 to 4:1) to furnish the title compound as a colorless oil (351 mg, 97% yield). $[\alpha]_D^{25} = -121.3°$ (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers): δ = 6.25 – 6.11 (m, 1H), 5.87 – 5.64 (m, 3H), 5.41 (d, *J* = 1.6 Hz, 0.3H, minor), 5.06 – 4.85 (m, 4H), 4.79 (ddd, *J* = 19.5, 8.1, 4.9 Hz, 1H), 4.52 (d, *J* = 1.5 Hz, 0.7H, major), 4.16 (dt, *J* = 14.0, 2.7 Hz, 1H), 3.33 – 3.24 (m, 1H), 2.88 – 2.79 (m, 1H), 2.73 (tt, *J* = 6.4, 1.8 Hz, 1H), 2.61 – 2.31 (m, 5H), 2.31 – 1.95 (m, 10H), 1.92 – 1.64 (m, 3H), 1.58 – 1.33 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$, mixture of rotamers): δ = 172.4, 169.1, 169.1, 145.9, 144.1, 138.3, 138.2, 138.0, 137.7, 130.8, 130.5, 125.0, 123.5, 115.2, 115.0, 114.9, 114.5, 105.2, 104.4, 81.4, 81.2, 80.9, 80.7, 59.4, 54.5, 53.5, 53.3, 50.4, 49.2, 48.7, 48.7, 44.6, 43.9, 41.0, 40.8, 37.9, 37.2, 33.4, 33.3, 33.2, 33.0, 32.5, 29.2, 29.1,

27.0, 26.7, 24.2, 23.8, 18.6, 18.6, 14.3; IR (film): $\tilde{\nu}$ = 3072, 2920, 2862, 1639, 1450, 1408, 1398, 1355, 1330, 1308, 1263, 1230, 1197, 1167, 1150, 1132, 1068, 1044, 1026, 995, 910, 852, 825, 750, 724, 695, 646, 608, 591, 434 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{28}H_{36}N_2O_2Na$ [M+Na$^+$]: 455.26690, found: 455.26713.

Compound 64. $NaBH_3CN$ (56 mg, 0.89 mmol) and trifluoroacetic acid (0.14 mL, 1.78 mmol) were successively added to a solution of compound **92** (77 mg, 0.18 mmol) in CH_2Cl_2 (7 mL) at 0 °C. The mixture was then stirred at room temperature for 1 h. Next, sat. aq. $NaHCO_3$ (5 mL) was added and the resulting mixture was vigorously stirred for 45 min. The aqueous phase was extracted with EtOAc (3 x 50 mL), the combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude material was purified by flash chromatography (hexane/EtOAc, 2:1 to 1:1) to give the title compound as a white solid (57 mg, 73% yield). M.p. = 86.2-86.9 °C; $[\alpha]_D^{25}$ = –153.0° (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers): δ = 6.04 – 5.93 (m, 1H), 5.85 – 5.61 (m, 2H), 5.49 (d, *J* = 1.5 Hz, 0.34H, minor), 5.07 – 4.83 (m, 4H), 4.61 (d, *J* = 1.5 Hz, 0.66H, major), 4.03 (dt, *J* = 12.9, 3.1 Hz, 1H), 3.47 (tdd, *J* = 12.7, 5.4, 2.1 Hz, 1H), 3.29 (dd, *J* = 9.3, 2.1 Hz, 0.34H, minor), 3.21 (dd, *J* = 11.8, 2.0 Hz, 0.66H, major), 3.11 – 2.95 (m, 2H), 2.72 – 2.53 (m, 2H), 2.45 – 2.15 (m, 8H), 2.15 – 1.80 (m, 7H), 1.80 – 1.10 (m, 8H); ^{13}C NMR (101 MHz, $CDCl_3$, mixture of rotamers) δ = 172.1, 171.8, 170.7, 170.4, 145.7, 143.7, 138.7, 138.3, 138.0, 137.6, 124.0, 122.6, 115.2, 115.0, 115.0, 114.2, 81.0, 80.8, 79.8, 79.6, 58.3, 52.6, 51.6, 51.5, 50.7, 50.5, 48.5, 48.2, 48.1, 47.1, 46.0, 44.3, 39.9, 39.7, 37.2, 36.7, 33.3, 33.2, 32.9, 32.4, 32.4, 30.0, 29.6, 29.2, 28.7, 26.4, 26.3, 26.3, 26.2, 24.3, 23.9, 18.9, 18.8, 14.1, 14.1; IR (film): $\tilde{\nu}$ = 3073, 2924, 2859, 1632, 1489, 1451, 1415, 1355, 1342, 1310, 1279, 1229, 1164, 1145, 1109, 1021, 997, 910, 809, 753, 661, 432 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{28}H_{39}N_2O_2$ [M+H$^+$]: 435.30060, found: 435.30068.

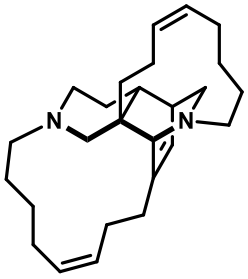


Compound 93. A solution of benzylidene-bis(tricyclohexylphosphino)-dichlororuthenium **87** (Grubbs first generation catalyst, 14.2 mg, 0.018 mmol) in 1,2-dichloroethane (2 mL) was slowly added to a refluxing solution of diene **64** (30 mg, 0.069 mmol) in 1,2-dichloroethane (140 mL) over 10 min. Stirring was continued at reflux temperature for 2 h before a second batch of benzylidene-bis(tricyclohexylphosphino)-dichlororuthenium (14.2 mg, 0.018 mmol) was slowly added as a solution in 1,2-dichloroethane (2 mL) over 10 min. After stirring for another 2 h, a solution of potassium 2-isocyanoacetate (19 mg, 0.154 mmol) in MeOH (3 mL) was added at reflux temperature. The mixture was cooled to room temperature and stirred for an additional 30 min. All volatile materials were evaporated *in vacuo* and the residue was purified by flash chromatography on silica (hexane/EtOAc, 1:1 to pure EtOAc) to furnish the cycloolefin as a mixture of olefin isomers.



$NaBH_4$ (10 mg, 0.267 mmol) was added to a vigorously stirred solution of $Ni(OAc)_2 \cdot 4\ H_2O$ (60 mg, 0.241 mmol) in EtOH (3 mL) at room temperature. The resulting black suspension was vigorously stirred for 1 h before ethylenediamine (65 µL, 0.968 mmol) was introduced. After stirring for another 30 min, the mixture was added to a flask purged with hydrogen containing the cycloalkyne. Stirring was continued for 4 h under a hydrogen atmosphere, before the suspension was filtered through a plug of silica, which was carefully rinsed with EtOAc. The combined filtrates were evaporated and the crude product was purified by flash chromatography on silica (hexane/EtOAc, 1:1 to pure EtOAc) to provide the title compound in isomerically pure form as a white amorphous solid (10.4 mg, 37% yield over 2 steps). $[\alpha]_D^{25}$ = –56.5° (c = 0.4, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 5.87 (dd, *J* = 6.5, 1.7 Hz, 1H), 5.54 – 5.40 (m, 2H), 5.40 – 5.29 (m, 2H), 4.99 (s, 1H), 4.37 (dt, *J* = 13.8, 7.8 Hz, 1H), 3.23 (dd, *J* = 11.8, 1.9 Hz, 1H), 3.14 – 3.08 (m, 2H), 3.05 (dd, *J* = 11.8, 2.9 Hz, 1H), 2.77 (ddd, *J* = 14.4, 11.7, 2.5 Hz, 1H), 2.60 – 2.54 (m, 2H), 2.50 (dtd, *J* = 14.9, 9.2, 6.5 Hz, 1H), 2.31 – 2.21 (m, 3H), 2.20 – 2.10 (m, 5H), 2.06 – 1.98 (m, 2H), 1.95 – 1.87 (m, 2H), 1.78 (ddd, *J* = 9.1, 6.4, 2.2 Hz, 1H), 1.76 – 1.62 (m, 3H), 1.57 – 1.50 (m, 2H), 1.50 – 1.43 (m, 1H), 1.39 (ddq, *J* = 13.9, 11.5, 5.7 Hz, 1H), 1.10 (dddd, *J* = 21.5, 11.8, 8.0, 5.1 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ = 173.1, 171.2, 145.3, 130.7, 130.4, 130.1, 128.4, 126.3, 58.5, 51.2, 47.9, 45.6, 44.2, 42.7, 39.7, 36.6, 33.8, 31.0, 28.9, 27.2, 26.7, 25.8, 25.6, 24.8, 24.2, 21.8; IR (film): $\tilde{\nu}$ = 3003, 2927, 2859, 1625, 1488, 1443, 1416, 1342, 1327, 1276, 1230, 1203, 1162, 923, 728, 665, 644 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{26}H_{37}N_2O_2$ [M+H$^+$]: 409.28495, found: 409.28469.

(+)-Keramaphidin B ((+)-2). DIBAL-H (1 M in hexane, 0.15 mL, 0.15 mmol) was added to a solution of bislactam **93** (6.0 mg, 0.015 mmol) in diethyl ether (0.15 mL). The mixture was stirred at rt for 3.5 h, before it was cooled to 0 °C and diluted with CH_2Cl_2 (1 mL). Next, sat. aq. Rochelle's salt solution (0.5 mL) was carefully added and the mixture was vigorously stirred for 1 h. The aqueous phase was extracted with CH_2Cl_2 (3 x 15 mL), the combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by preparative HPLC (YMC Triart C18, 5 µm, 150 mm x 10 mm, methanol:20 mM NH_4HCO_3 pH 9.0 = 85:15, 4.7 mL/min, λ = 210 nm, t_R = 4.0 min) to afford the title compound as a white amorphous solid (2.1 mg, 38% yield). $[\alpha]_D^{20}$ = +27.0° (c = 0.20, MeOH); For ^{1}H- and ^{13}C-NMR Data see Tables S3-S7. IR (film): $\tilde{\nu}$ = 3005, 2920, 2851, 1486, 1460, 1340, 1317, 1299, 1275, 1220, 1207, 1174, 1130, 1103, 1048, 989, 933, 908, 819, 764, 721, 685, 666, 461 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{26}H_{41}N_2$ [M+H$^+$]: 381.32642, found: 381.32671.



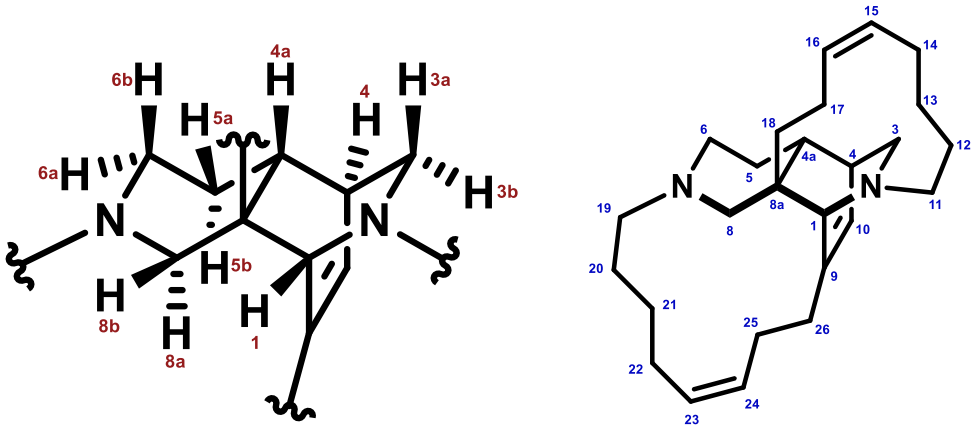


Figure 4.3. Numbering scheme for Keramaphidin B (**2**) adopted from Kobayashi *et al*.[54]

Table 4.1. Comparison of ^{1}H NMR ([D$_4$]-MeOH) data of synthetic Keramaphidin B with isolated Keramaphidin B[56] (numbering scheme as shown in figure 4.3).

Position	Original Assignment[56]	^{1}H NMR Synthetic δ (ppm), *J* (Hz)	^{1}H NMR Isolated[56] δ (ppm), *J* (Hz)
1	1	3.12, d	3.18, br s
3a	3	2.87 (dd, *J* = 9.1, 2.0)	2.89 (dd, *J* = 9.2, 1.9)
3b	3	1.67, (dd, *J* = 9.1, 2.8)	1.68 (dd, *J* = 9.2, 2.6)
4	4	2.25, m	2.30, m
4a	4a	0.90, (ddd, *J* = 12.4, 5.8, 2.4)	0.98 (ddd, *J* = 12.5, 5.5, 2.1)
5a	5	1.20 (tdd, *J*=13.7, 12.4, 4.1)	1.23 (qd, *J*=14.0, 4.1)
5b	5	1.36, (pd, *J* = 13.5, 3.2, 2.8, 2.0)	1.50, m
6a	6	2.68 (dt, *J* = 12.9, 4.1, 2.8)	2.88, m
6b	6	2.76 (td, *J* = 13.8, 13.0, 2.7)	2.97 (td, *J* = 13.5, 2.6)
8a	8	2.09, m	2.16 (d, *J*=11.6)
8b	8	2.34, m	2.70 (d, *J*=11.6)
10	10	5.85 (d, *J*= 6.4)	5.91 (d, *J* = 6.4)
11	11	2.21, m	2.21, (ddd, *J* = 12.5, 5.2, 1.2)
		2.98 (td, *J*= 12.6, 5.0)	2.99 (td, J = 12.5, 5.2)
12	12	1.27, m	1.27, m
		1.48, m	1.53, m
13	13	1.52, m	1.50, m
		1.58, m	1.61, m
14	14	1.55, m	1.56, m
		2.42, m	2.41, m
15	15	5.65, m	5.65, m
16	16	5.64, m	5.65, m
17	17	1.75, m	1.76, m
		2.35, m	2.38, m

18	18	1.67, m	1.75, m
		1.77, m	1.75, m
19	19	2.24, m	2.52, (ddd, *J* = 13.5, 7.5, 2.5)
		3.06, (ddd, J = 13.8, 8.2, 6.8)	3.24, (dt, *J* = 13.5, 7.5)
20	20	1.44, m	1.49, m
		1.61, m	1.73, m
21	21	1.35, m	1.44, m
		1.49, m	1.52, m
22	22	1.98, m	2.02 (br d, *J*=15.2)
		2.22, m	2.26, m
23	23	5.24 (tt, *J*=10.8, 2.7)	5.28 (tt, J=10.8, 2.8)
24	24	5.38, m	5.41, m
25	25	2.09, m	2.11, m
		2.36, m	2.35, m
26	26	2.35, m	2.38, m
		2.29, (ddd, *J* = 10.8, 6.1, 1.5)	2.31, m

Table 4.2. Comparison of ^{13}C NMR data ([D_4]-MeOH) of synthetic Keramaphidin B with those of isolated Keramaphidin B[56] (numbering scheme as shown in figure 4.3).

Position	Original Assignment[56]	^{13}C NMR Synthetic δ (ppm)	^{13}C NMR Isolated[56] δ (ppm)	Δδ (ppm)
20	20	21.5	20.9	+0.6
17	17	21.8	21.6	+0.2
14	14	23.8	23.8	0
22	22	26.1	26.1	0
25	25	26.6	26.5	+0.1
12	5	27.2	26.8	+0.4
13	12	27.5	27.1	+0.4
21	21	27.7	27.1	+0.6
5	13	28.0	27.5	+0.5
26	26	37.9	37.6	+0.3
4	4	39.1	38.8	+0.3
18	18	42.3	41.8	+0.5
4a	4a	44.9	44.1	+0.8
8a	8a	45.9	45.0	+0.9
6	6	48.5	48.8	-0.3
8	8	51.0	50.8	+0.2
3	3	54.6	54.3	+0.3
11	11	55.2	55.1	+0.1
19	19	57.1	56.9	+0.2

1	1	65.3	64.6	+0.7
10	10	124.3	125.0	-0.7
15	16	131.5	131.0	+0.5
16	23	132.4	132.6	-0.2
23	15	132.6	132.8	-0.2
24	24	133.3	133.4	-0.1
9	9	143.0	142.8	+0.2

Table 4.3. Comparison of the ^{13}C NMR ([D_4]-MeOH) data of synthetic Keramaphidin B with those of a sample of Keramaphidin B prepared by Baldwin *et al.*,[225] which had been doped with authentic material provided by Kobayashi *et al*.[54] (numbering scheme as shown in figure 4.3).

Position	^{13}C NMR Synthetic δ (ppm)	^{13}C NMR (literature) δ (ppm)	Δδ (ppm)
20	21.5	21.3	+0.2
17	21.8	21.7	+0.1
14	23.8	23.8	0
22	26.1	26.1	0
25	26.6	26.5	+0.1
12	27.2	27.1	+0.1
13	27.5	27.5	0
21	27.7	-	-
5	28.0	-	-
26	37.9	37.8	+0.1
4	39.1	39.0	+0.1
18	42.3	42.1	+0.2
4a	44.9	44.7	+0.2
8a	45.9	-	-
6	48.5	48.8	-0.3
8	51.0	50.9	+0.1
3	54.6	54.5	+0.1
11	55.2	55.2	0
19	57.1	57.0	+0.1
1	65.3	65.0	+0.3
10	124.3	124.5	-0.2
15	131.5	131.3	+0.2
16	132.4	132.6	-0.2
23	132.6	132.6	0
24	133.3	133.3	0
9	143.0	142.9	+0.1

Table 4.4. Comparison of ^{1}H NMR ($CDCl_3$) data of synthetic Keramaphidin B with those of the isolated sample fo Keramaphidin B[54] (numbering scheme as shown in figure 4.3).

Position	Original Assignment[54]	^{1}H NMR Synthetic δ (ppm), *J* (Hz)	^{1}H NMR Isolated[54] δ (ppm), *J* (Hz)
1	1	3.01, s	3.01, s
3a	3	2.85 (dd, *J* = 9.1, 2.1)	2.86 (dd, *J* = 8.5, 1.5)
3b	3	1.64 (dd, *J* = 9.1, 2.7)	1.64 (dd, *J* = 9.0, 2.3)
4	4	2.20, m	2.22, m
4a	4a	0.91, m	0.93 (ddd, *J* = 11.6, 5.6, 1.9)
5a	5	1.16 (qd, *J* = 13.0, 4.6)	1.17 (ddd, *J* =13.0, 8.7, 4.4)
5b	5	1.30, m	1.36, m
6a	6	2.62 (d, *J*= 12.2)	2.63 (dt, *J* = 12.3, 3.6)
6b	6	2.67 (t, *J* = 12.4)	2.75, m
8a	8	2.07, m	2.08 (d, *J* = 10.7)
8b	8	2.12, m	2.23 (d, *J* = 12.3)
10	10	5.79 (d, *J* = 6.5)	5.81
11	11	2.22, m	2.23, m
	3	2.88 (dd, *J* = 12.6, 5.2)	2.91 (dd, *J* = 20.7, 9.7)
12	12	1.25, m	1.24, m
		1.45, m	1.45, m
13	13	1.49, m	1.46, m
		1.58, m	1.58, m
14	14	1.58, m	1.57, m
		2.34, m	2.35, m
15	16	5.70 (td, *J* = 10.4, 9.7, 6.3)	5.69 (ddd, *J* = 13.6, 10.1, 6.3)
16	15	5.64 (td, *J* = 10.4, 5.1)	5.64 (ddd, *J* = 13.6, 10.1, 5.2)
17	17	1.73, br s	1.78, m
		2.28, m	2.27, m
18	18	1.62, m	1.61, m
		1.86 (td, *J*= 12.1, 7.6)	1.88 (dt, *J* = 12.3, 7.6)
19	19	2.16, m	2.24, m
		3.05, br s	3.07, m
20	20	1.30, m	1.34, m
		1.54, m	1.55, m
21	21	1.29, m	1.32, m
		1.46, m	1.48, m
22	22	1.95 (d, *J* = 15.1)	1.96 (br d, *J*= 15.2)
		2.16, m	2.14, m
23	23	5.23 (tt, *J* = 10.8, 3.1)	5.24 (br d, *J* = 10.8)
24	24	5.35, m	5.36 (br d, *J* = 10.8)

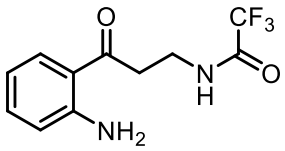
25	25	2.10, m	2.12, m
		2.28, m	2.29, m
26	26	2.23, m	2.25, m
		2.32, m	2.33, m

Table 4.5. Comparison of ^{13}C NMR ($CDCl_3$) data of synthetic Keramaphidin B with those of isolated Keramaphidin B[54] (numbering scheme as shown in figure 4.3).

Position	Original Assignment[54]	^{13}C NMR Synthetic δ (ppm)	^{13}C NMR Isolated[54] δ (ppm)	Δδ (ppm)
17	17	21.0	21.0	0
20	20	21.2	21.1	+0.1
14	14	22.9	22.9	0
22	22	24.9	25.0	-0.1
25	25	25.5	25.6	-0.1
12	12	26.1	26.1	0
13	13	26.4	25.6	+0.8
21	21	27.3	27.2	+0.1
5	5	27.8	27.6	+0.2
26	26	37.0	37.0	0
4	4	37.9	38.0	-0.1
18	18	41.6	41.6	0
4a	4a	43.4	43.3	+0.1
8a	8a	45.2	45.1	+0.1
6	6	47.4	47.4	0
8	8	50.7	50.8	-0.1
3	3	53.6	53.6	0
11	11	54.0	54.1	-0.1
19	19	56.2	56.2	0
1	1	64.3	64.3	0
10	10	122.5	122.6	-0.1
15	16	130.9	130.9	0
16	15	131.2	131.2	0
23	23	131.5	131.5	0
24	24	132.0	132.0	0
9	9	141.7	141.8	-0.1

4.1.3 Total Synthesis of Nominal Njaoamine I

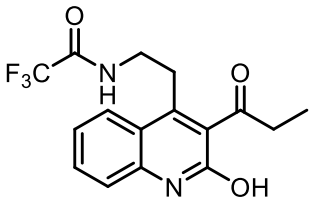
***N*-(3-(2-Aminophenyl)-3-oxopropyl)-2,2,2-trifluoroacetamide (101).** Trifluoroacetic acid anhydride (9.5 mL, 68.3 mmol) was slowly added to a solution of tryptamine (8.0 g, 50.0 mmol) in CH_2Cl_2 (300 mL) at 0 °C. After stirring for 2h at this temperature, H_2O (50 mL) was added to terminate the reaction. The mixture was extracted with CH_2Cl_2 (3 x 500 mL), the combined extracts were dried over anhydrous Na_2SO_4, the solvent was removed under vacuum, and the crude product was used in the next step without further purification.



The crude product was dissolved in MeOH (800 mL) and the solution was added dropwise to a solution of $NaIO_4$ (54.8 g, 256 mmol) in H_2O (800 mL) at 0 °C. The ice bath was removed and stirring continued at ambient temperature for 24 h. The mixture was poured into H_2O (500 mL), the aqueous layer was extracted with CH_2Cl_2 (3 x 800 mL), and the combined organic phases were washed with brine and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated to provide the crude product, which was directly used in the next step.

conc. HCl (6.4 mL, 80.0 mmol) was added dropwise to a solution of this crude material in MeOH (640 mL). The mixture was stirred at reflux temperature for 1 h before it was cooled to room temperature and aq. K_2CO_3 (1 M, 76 mmol) was added until a pH ≈ 6 was reached. The yellow residue was poured into H_2O (80 mL), the aqueous phase was extracted with CH_2Cl_2 (3 x 500 mL), the combined extracts were dried over anhydrous Na_2SO_4 and filtered. After removing the solvent, the residue was purified by flash chromatography on silica gel (CH_2Cl_2/*tert*-butyl methyl ether, 20:1) to afford the title compound as a yellow solid (13.1 g, 81% over 3 steps). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67–7.63 (m, 1H), 7.30 (ddd, *J* = 8.6, 7.1, 1.5 Hz, 1H), 7.20 (s, 1H), 6.66 (td, *J* = 8.2, 1.0 Hz, 2H), 6.29 (s, 2H), 3.80–3.73 (m, 2H), 3.25 (dd, *J* = 6.0, 5.0 Hz, 2H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 200.5, 150.5, 135.1, 130.9, 117.5, 117.3, 117.1, 116.1, 114.4, 37.6, 34.9 ppm; ^{19}F NMR (282 MHz, $CDCl_3$) δ = –76.1 ppm; IR (film) $\tilde{\nu}$ = 3468, 3348, 1708, 1616, 1550, 1452, 1204, 1159, 971, 750 cm^{-1}; MS (EI)*: m/z* (%): 120 (100), 260 (32.9); HRMS (ESI): *m/z:* calcd. for $C_{11}H_{11}N_2O_3F$ [M^+]: 260.07671, found: 260.07733.

2,2,2-Trifluoro-*N*-(2-(2-hydroxy-3-propionylquinolin-4-yl)ethyl)acetamide (103). Compound **102** (5.50 g, 27.5 mmol)[226] was added to a solution of compound **101** (4.78 g, 18.4 mmol) in toluene (60 mL) at ambient temperature. The resulting mixture was stirred at reflux temperature for 2 h before it was cooled to ambient temperature and directly loaded on silica filled into a flash column. After a contact time of 24 h, the product was eluted (hexanes/acetone, 3:1 to 0:1) to provide the tilte compound as a yellow solid (5.89 g, 94%). ^{1}H NMR (400 MHz, [D$_4$]-MeOH): δ = 8.07 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.61 (ddd, *J* = 8.4, 7.1, 1.3 Hz, 1H), 7.42– 7.31 (m, 2H), 3.58 (dd, *J* = 8.5, 6.5 Hz, 2H), 3.07-3.02 (m, 2H), 2.92 (q, *J* = 7.2 Hz, 2H), 1.18 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (101 MHz, [D$_4$]-MeOH): δ = 208.1, 162.1, 146.9, 139.8, 134.8, 132.7 126.6, 124.4, 120.3, 119.0, 117.4, 116.1, 40.9,



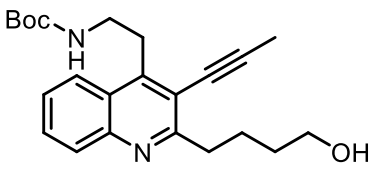
37.9, 29.8, 7.9 ppm; ^{19}F NMR (282 MHz, MeOD): δ = –77.4 ppm; IR (film) $\tilde{\nu}$ = 3307, 2942, 2883, 1701, 1652, 1563, 1187, 1152, 757 cm^{-1}; MS (EI)*: m/z* (%): 212 (100), 340 (12); HRMS (ESI): *m/z:* calcd. for $C_{16}H_{15}F_3N_2O_3$ [M^+]: 340.10293, found: 340.10283.

2,2,2-Trifluoro-N-(2-(2-hydroxy-3-propionylquinolin-4-yl)ethyl)acetamide (S3). Tf_2O (2.3 mL, 13.7 mmol) was added to a solution of compound **103** (3.18 g, 9.30 mmol) in pyridine (50.0 mL) at 0 °C. After 10 min, the cooling bath was removed and the mixture stirred at ambient temperature for 12 h. The mixture was poured into H_2SO_4 (2 M, 400 mL) at 0 °C, the aqueous phase was extracted with EtOAc (3 x 500 mL), and the combined organic layers were washed with brine and dried over $MgSO_4$. After filtration and evaporation of the solvent, the crude product was purified by flash chromatography on silica gel (CH_2Cl_2/*tert*-butyl methyl ether, 40:1) to provide the title compound as a yellow solid material (3.88 g, 88%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.21 (dd, *J* = 8.6, 0.8 Hz, 1H), 8.07 (ddd, *J* = 8.4, 1.4, 0.6 Hz, 1H), 7.87 (ddd, *J* = 8.4, 7.0, 1.4 Hz, 1H), 7.79–7.66 (m, 2H), 3.74 (td, *J* = 6.9, 5.1 Hz, 2H), 3.28 (t, *J* = 7.0 Hz, 2H), 2.95 (q, *J* = 7.3 Hz, 2H), 1.27 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 204.7, 158.5, 158.1, 157.7, 157.4, 149.3, 147.6, 145.5, 132.3, 129.8, 128.9, 126.1, 125.8, 124.3, 120.1, 117.0, 116.9, 114.2, 40.2, 38.3, 28.5, 7.9 ppm; ^{19}F NMR (282 MHz, $CDCl_3$) δ = –72.4, –76.0 ppm; IR (film) $\tilde{\nu}$ = 3342, 2955, 1703, 1563, 1420, 1178, 1121, 997, 760 cm^{-1}; MS (ESI)*: m/z*: 473 [*M*+H$^+$], 495 [*M*+Na$^+$]; HRMS (ESI): *m/z:* calcd. for $C_{17}H_{14}F_6N_2O_5SNa$ [*M*+Na$^+$]: 495.04199, found: 495.04193.

***N*-(2-(2-(4-((*tert*-butyldimethylsilyl)oxy)butyl)-3-propionylquinolin-4-yl)ethyl)-2,2,2-trifluoroacetamide (105).** Neat (but-3-en-1-yloxy)(tert-butyl)dimethylsilane (8.0 mL, 29.1 mmol)[227] was added to a solution of 9-H-9-BBN (0.5 M in THF, 31.6 mL, 15.8 mmol) at ambient temperature. After stirring at this temperature for 12 h, the solution was warmed to 40 °C and stirring was continued for another 6 h before the mixture was cooled to ambient temperature. MeONa (821 mg, 15.2 mmol) was added and the resulting mixture was stirred for 1 h at ambient temperature. $Pd(PPh_3)_4$ (475 mg, 0.411 mmol) and triflate **S3** (3.88 g, 8.21 mmol) were successively added to this solution. The resulting mixture was stirred at 80 °C for 15 h before it was cooled to ambient temperature. The mixture was diluted with *t*ert-butyl methyl ether (3 x 100 mL) and washed with brine, the organic phase was dried with Na_2SO_4, the solvent was evaporated under vacuum, and the crude product was purified by flash chromatography on silica gel (hexanes/EtOAc, 10:1 to 4 :1) to afford the title compound as a yellow oil (3.08 g, 73%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.08 (ddd, *J* = 8.5, 1.3, 0.6 Hz, 1H), 8.04 (ddd, *J* = 8.5, 1.4, 0.6 Hz, 1H), 7.75 (ddd, *J* = 8.4, 6.9, 1.3 Hz, 1H), 7.69 (s, 1H), 7.60 (ddd, *J* = 8.3, 6.9, 1.3 Hz, 1H), 3.68 (td, *J* = 6.6, 4.8 Hz, 2H), 3.63 (t, *J* = 6.4 Hz, 2H), 3.16 (s, 2H), 2.86–2.79 (m, 4H), 1.94–1.81 (m, 2H), 1.63–1.53 (m, 2H), 1.27 (t, *J* = 7.2 Hz, 3H), 0.88 (s, 9H), 0.03 (s, 6H) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ = 211.4, 157.9, 157.5, 156.5, 147.9, 138.9, 135.5, 130.2, 130.0, 127.2, 124.4, 123.3, 114.2, 62.7, 40.1, 39.2, 37.0, 32.6, 27.8, 26.0, 25.9, 18.3, 8.0, –5.4ppm; ^{19}F NMR (282 MHz, $CDCl_3$): δ = –75.9 ppm; IR (film) $\tilde{\nu}$ = 3309, 2931, 2858, 1703, 1208, 1160, 835, 762 cm^{-1}; MS (ESI)*: m/z*: 511 [*M*+H$^+$], 533 [*M*+Na$^+$]; HRMS (ESI): *m/z:* calcd. for $C_{26}H_{37}N_2O_3F_3SiNa$ [*M*+Na$^+$]: 533.24178, found: 533.24155.

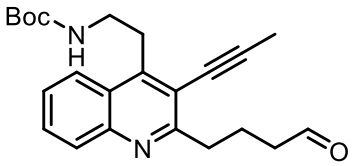
***tert*-Butyl (2-(2-(4-hydroxybutyl)-3-(prop-1-yn-1-yl)quinolin-4-yl)ethyl)carbamate (S4).**



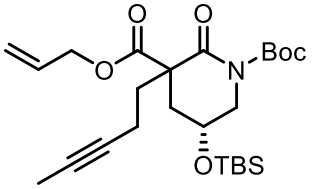
KHMDS (1.0 M in THF, 31.7 mL, 31.7 mmol) was added to a solution of compound **105** (3.08 g, 6.03 mmol) and $PhNTf_2$ (3.39 g, 9.49 mmol) in THF (40 mL) at –78 °C. After stirring at this temperature for 1 h, the reaction was quenched with sat. aq. $NaHCO_3$ (10 mL). The aqueous layer was extracted with EtOAc (3 x 100 mL), and the combined extracts were washed with brine and dried with anhydrous Na_2SO_4. After filtration and evaporation of the solvent, the crude material was dissolved in CH_3CN (30 mL). DMAP (3.10 g, 25.4 mmol) and Boc_2O (5.34 g, 24.5mmol) were successively added at 0 °C, the cooling bath was removed after 5 min, and the mixture stirred at ambient temperature for 2 h before the reaction was quenched with sat. aq. NH_4Cl (30 mL). The resulting mixture was stirred for 5 h before it was extracted with *t*ert-butyl methyl ether (3 x 100 mL). The combined organic layers were washed with brine, dried with anhydrous $MgSO_4$, filtered and the solvent was evaporated. The residue was purified by flash chromatography on silica gel (hexanes/*tert*-butyl methyl ether, 8:1 to 2:1).

TBAF (1.0 M in THF, 24.0 mL, 24.0 mmol) was added to a solution of the product thus obtained in THF (10 mL) at 0 °C. The mixture was then stirred at ambient temperature for 1 h before the reaction was quenched with sat. aq. NH_4Cl (50 mL). The aqueous layer was extracted with EtOAc (4 x 100 mL), the combined organic phases were washed with brine, dried with anhydrous Na_2SO_4 and filtered. After evaporation of the solvent, the residue was purified by flash chromatography on silica (hexanes/acetone, 8:1 to 1:1) to afford the title compound as a yellow oil (1.66 g, 72%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06 (d, *J* = 8.4 Hz, 1H), 7.99 (dd, *J* = 8.4, 1.3 Hz, 1H), 7.64 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.51 (ddd, *J* = 8.3, 6.9, 1.3 Hz, 1H), 4.69 (s, 1H), 3.69 (t, *J* = 6.3 Hz, 2H), 3.48 (d, *J* = 2.8 Hz, 5H), 3.20 (t, *J* = 7.3 Hz, 2H), 2.87 (s, 1H), 2.21 (s, 3H), 2.08 – 1.89 (m, 2H), 1.83 – 1.55 (m, 1H), 1.42 (s, 9H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 162.6, 155.9, 147.4, 145.7, 129.4, 129.1, 126.4, 125.7, 123.8, 117.7, 95.9, 79.3, 75.8, 62.3, 40.4, 36.8, 32.3, 30.9, 28.4, 24.1, 4.8 ppm; IR (film) $\tilde{\nu}$ = 3322, 2933, 1691, 1498, 1365, 1252, 1170, 1072, 761 cm^{-1}; MS (ESI)*: m/z*: 383 [*M*+H$^+$], 405 [*M*+Na$^+$]; HRMS (ESI): *m/z:* calcd. for $C_{23}H_{31}N_2O_3$ [*M*+H$^+$]: 383.23292, found: 383.23288.

***tert*-Butyl (2-(2-(4-oxobutyl)-3-(prop-1-yn-1-yl)quinolin-4-yl)ethyl)carbamate (98).** Sulfur trioxide pyridine complex (750 mg, 4.71 mmol) was added to a solution of anhydrous Et_3N (1.3 mL, 9.32 mmol), alcohol **S4** (604 mg, 40.8 mg) and DMSO (0.56 mL, 7.88 mmol) in CH_2Cl_2 (6.3 mL) at 0 °C. After 10 min, the cooling bath was removed and stirring was continued at ambient temperature for 3 h before sat. aq. $NaHCO_3$ (2.0 mL) was added. The aqueous layer was extracted with EtOAc (3 x 30 mL), and the combined organic phases were dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (hexanes/acetone, 6:1 to 3:1) to afford the title compound as a yellow oil (461 mg, 77%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.79 (t, *J* = 1.7 Hz, 1H), 8.05 (d, *J* = 8.4 Hz, 1H), 7.98 (dd, *J* = 8.4, 1.3 Hz, 1H), 7.64 (ddd, *J* = 8.3, 6.8, 1.4 Hz, 1H), 7.51 (ddd, *J* = 8.3, 6.9, 1.3 Hz, 1H), 4.73 (s, 1H), 3.47 (d, *J* = 2.8 Hz, 4H), 3.25–3.03 (m, 2H), 2.57 (td, *J* = 7.2, 1.8 Hz, 2H), 2.32–2.15 (m, 5H), 1.42 (s, 9H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 202.5, 161.7, 155.9, 147.3, 146.0, 129.4, 129.3, 126.4, 125.7, 123.8, 117.7, 96.0, 75.7, 43.4, 40.3, 36.7, 30.8, 28.4, 21.1, 4.7 ppm; IR (film) $\tilde{\nu}$ = 3368, 2977, 2936, 1713, 1498, 1367, 1250, 872, 764 cm^{-1}; MS (ESI): *m*/*z*: 381 [*M*+H$^+$]; HRMS (ESI): *m*/*z:* calcd. for $C_{23}H_{29}N_2O_3$ [*M*+H$^+$]: 381.21727, found: 381.21717.



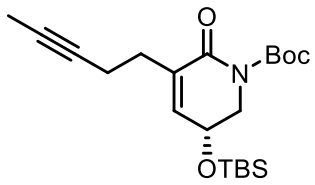
3-Allyl 1-(*tert*-butyl) (5*R*)-5-((*tert*-butyldimethylsilyl)oxy)-2-oxo-3-(pent-3-yn-1-yl)piperidine-1,3-dicarboxylate (S5). LiHMDS (1 M in THF, 26.7 ml, 26.7 mmol) was slowly added to a solution of *ent*-**45** (3.83 g, 11.6 mmol) in anhydrous THF (58 ml) at –78 °C. The mixture was stirred for 1 h before allyl chloroformate (1.3 ml, 12.2 mmol) was added. After 30 min, the reaction was quenched with sat. aq. NH_4Cl (10 mL). The aqueous layer was extracted with EtOAc (3 x 200 mL) and the combined organic phases were washed with brine (20 mL), dried over Na_2SO_4 and filtered. After evaporation of the solvent, the residue was purified by flash chromatography on silica (hexanes/EtOAc, 5 :1 to 3:1) to provide a yellow oil.



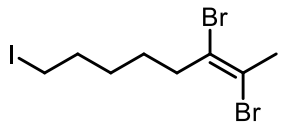
Cs_2CO_3 (7.66 g , 23.5 mmol) was added to a solution of this compound and 5-iodopent-2-yne (4.5 g, 23.2 mmol)[224] in DMF (20.0 mL) at ambient temperature. The mixture was stirred for 12 h before the reaction was quenched with sat. aq. NH_4Cl (10 mL). The resulting solution was extracted with EtOAc (3 x 50 mL). The combined extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica (hexane/EtOAc, 1:10) to afford the title product as a white solid material (5.17 g, 93%). $[\alpha]_D^{20}$ = –10.2° (c = 1.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.99–5.73 (m, 1H), 5.42–5.27 (m, 1H), 5.25–5.16 (m, 1H), 4.68–4.52 (m, 2H), 4.20–4.04 (m, 1H), 3.83–3.69 (m, 1H), 3.51–3.37 (m, 1H), 2.68–2.41 (m, 1H), 2.31–1.96 (m, 5H), 1.80–1.66 (m, 3H), 1.49 (s, 9H), 0.89–0.79 (m, 9H), 0.09 – –0.03 (m, 6H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.0, 170.9, 169.4, 168.9, 152.7, 152.5, 131.3, 131.1, 119.0, 118.4, 83.1, 83.1, 78.2, 78.1, 76.2, 76.2, 66.2, 66.0, 63.9, 63.8, 55.2, 54.4, 51.1, 50.9, 38.7, 38.6, 35.8, 35.4, 27.9, 25.6, 25.6, 18.0, 17.9, 14.7, 14.4, 3.4, 3.4, –4.8, –4.9,

–5.04, –5.00 ppm; IR (film) $\tilde{\nu}$ = 2926, 2856, 1717, 1376, 1300, 1254, 1147, 1092, 836, 777 cm^{-1}; MS (ESI): *m/z*: 502 [*M*+Na$^+$]; HRMS (ESI): *m/z:* calcd. for $C_{25}H_{41}NO_6SiNa$ [*M*+Na$^+$]: 502.2595, found: 502.2597.

***tert*-Butyl (*R*)-3-((*tert*-butyldimethylsilyl)oxy)-6-oxo-5-(pent-3-yn-1-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate (94).** $Pd_2(dba)_3 \cdot CHCl_3$ (974 mg, 0.941 mmol) was added to a solution of compound **S5** (9.03 g, 18.8 mmol) in CH_3CN (76 mL) at ambient temperature. The mixture was stirred at 80 °C for 30 min before it was cooled to ambient temperature and filtered through a pad of Celite. The filtrate was evaporated and the residue was purified by chromatography on silica (hexanes/CH_2Cl_2, 1:1 to 1:4 to remove the dba, then the elutant was changed to hexanes/*tert*-butyl methyl ether, 4:1) to afford the title compound as a colorless oil (5.84 g, 79%). $[\alpha]_D^{20}$ = +56.3° (c = 0.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.51–6.48 (m, 1H), 4.50–4.44 (m, 1H), 3.91 (ddd, *J* = 12.8, 4.9, 1.2 Hz, 1H), 3.64 (dd, *J* = 12.8, 8.2 Hz, 1H), 2.57–2.36 (m, 2H), 2.32 (ddddd, *J* = 6.3, 5.3, 3.8, 2.6, 1.0 Hz, 2H), 1.75 (t, *J* = 2.5 Hz, 3H), 1.54 (s, 9H), 0.89 (s, 9H), 0.11 (s, 6H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 163.6, 152.7, 142.1, 134.0, 83.1, 78.3, 63.9, 50.7, 29.9, 28.1, 25.7, 18.1, 17.9, 3.4, –4.7, –4.7 ppm; IR (film) $\tilde{\nu}$ = 2930, 2857, 1715, 1368, 1301, 1255, 1093, 837, 778 cm^{-1}; MS (ESI): *m/z*: 416 [*M*+Na$^+$]; HRMS (ESI): *m/z:* calcd. for $C_{21}H_{35}NO_4SiNa$ [*M*+Na$^+$]: 416.22276, found: 416.22272.



(*E*)-2,3-Dibromo-8-iodooct-2-ene (106). Bromine (5.2 mL, 101.5 mmol) was added to a solution of oct-6-yn-1-ol (10.6 g, 84.0 mmol) in CH_2Cl_2 (420 mL) at 0 °C. After stirring for 20 min at this temperature, the reaction mixture was poured into a solution of sat. aq. Na_2SO_3 (500 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 500 mL), the combined organic layers were washed with brine, dried with anhydrous $MgSO_4$ and filtered, and the solvent was evaporated. The crude dibromide **60** thus obtained was used in the next step without further purification.



Iodine (25.6 g, 100.9 mmol) was added to a vigorously stirred solution of PPh_3 (26.5 g, 101.0 mmol) and imidazole (6.88 g, 101.1 mmol) in CH_2Cl_2 (280 mL) at 0 °C. After stirring at this temperature for 30 min, a solution of the crude dibromide in CH_2Cl_2 (50 mL) was added and the resulting mixture was stirred for 2 h before the reaction was quenched with aq. sat. $Na_2S_2O_3$ (200 mL). The aqueous phase was extracted with CH_2Cl_2 (2 x 300 mL), the combined extracts were dried over Na_2SO_4 and evaporated. The residue was purified by chromatography on silica (pentane) to afford the title compound as a colorless oil (33.0 g, 99%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.20 (t, *J* = 7.1 Hz, 2H), 2.67 (t, *J* = 7.5 Hz, 2H), 2.42 (d, *J* = 1.1 Hz, 3H), 1.86 (ddd, *J* = 13.0, 7.9, 6.5 Hz, 2H), 1.65–1.55 (m, 2H), 1.48–1.38 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 121.6, 115.6, 40.3, 33.2, 29.3, 28.8, 26.3, 6.7 ppm; IR (film) $\tilde{\nu}$ = 2929, 2857, 1453, 1428, 1375, 1349, 1298, 1267, 1204, 1165, 1104, 1069, 1030, 957, 723, 615, 505 cm^{-1}; MS (EI): *m/z* (%):107 (100), 213 (43), 396 (4); HRMS (ESI): *m/z:* calcd. for $C_8H_{13}IBr_2$ [*M*$^+$]: 393.84235, found: 393.84232.

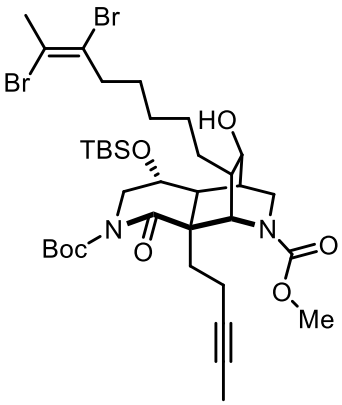
Allyl (*E*)-1-benzyl-3-(6,7-dibromooct-6-en-1-yl)-4-oxopiperidine-3-carboxylate (107). Cs_2CO_3 (27.2 g, 83.5 mmol) was added to a solution of compound **71** (14.5 g, 53.0 mmol) and iodide **106** (33.0 g, 83.4 mmol) in DMF (128 mL) at ambient temperature. The mixture was stirred for 12 h before the reaction was quenched with sat. aq. NH_4Cl (10 mL). The resulting mixture was extracted with EtOAc (3 x 300 mL), and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica (EtOAc/hexanes, 1:8) to afford the title compound as a colorless oil (19.1 g, 67%).^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.14 (m, 5H), 5.89 (ddt, *J* = 17.3, 10.4, 5.8 Hz, 1H), 5.38–5.20 (m, 2H), 4.76–4.51 (m, 2H), 3.64–3.51 (m, 2H), 3.41 (dd, *J* = 11.5, 2.6 Hz, 1H), 2.98 (dtd, *J* = 12.6, 5.2, 2.7 Hz, 1H), 2.91–2.76 (m, 1H), 2.66–2.58 (m, 2H), 2.49–2.32 (m, 5H), 2.25 (d, *J* = 11.6 Hz, 1H), 1.87–1.72 (m, 1H), 1.61–1.46 (m, 3H), 1.45–1.34 (m, 1H), 1.33–1.22 (m, 2H), 1.17–1.05 (m, 1H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 205.9, 171.2, 137.7, 131.6, 128.7, 128.1, 127.2, 121.8, 118.6, 115.1, 65.5, 61.7, 61.1, 61.0, 53.4, 40.4, 40.3, 31.9, 28.7, 28.6, 26.9, 24.1 ppm; IR (film) $\tilde{\nu}$ = 3027, 2927, 2859, 2805, 1716, 1649, 1494, 1454, 1348, 1318, 1221, 1195, 1160, 1122, 1073, 1027, 972, 997, 931, 820, 734, 698, 616, 554, 501, 462 cm^{-1}; MS (ESI)*: m/z*: 540 [*M*+H$^+$]; 562 [*M*+Na$^+$]; HRMS (ESI): *m/z:* calcd. for $C_{24}H_{32}NO_3Br_2$ [*M*+H$^+$]: 540.07369, found: 540.07475.

3-Allyl 1-methyl (*E*)-3-(6,7-dibromooct-6-en-1-yl)-4-oxopiperidine-1,3-dicarboxylate (108). Methyl chloroformate (13.6 mL, 176 mmol) was added to a solution of **107** (19.1 g, 35.3 mmol) in toluene (35 mL) at ambient temperature. The mixture was stirred at 100 °C for 6 h before it was directly loaded on a column of silica. The product was eluted with hexanes/EtOAc (5:1 to 1:1) to provide the desired product as a colorless oil (17.4 g, 97%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.87 (ddt, *J* = 16.5, 10.5, 5.9 Hz, 1H), 5.37–5.18 (m, 2H), 4.62 (d, *J* = 5.8 Hz, 2H), 4.58–4.47 (m, 1H), 4.11 (s, 1H), 3.74 (s, 3H), 3.39 (s, 1H), 3.22–3.08 (m, 1H), 2.72–2.60 (m, 3H), 2.47 (dt, *J* = 14.6, 4.8 Hz, 1H), 2.40 (s, 3H), 1.91–1.80 (m, 1H), 1.58 (td, *J* = 19.4, 14.8, 8.4 Hz, 3H), 1.31 (dt, *J* = 13.3, 6.9 Hz, 4H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 204.3, 169.8, 155.7, 131.3, 121.8, 119.2, 115.4, 66.1, 61.2, 53.1, 50.2, 43.7, 40.3, 39.7, 31.5, 28.7, 28.6, 27.0, 24.0 ppm; IR (film) $\tilde{\nu}$ = 2930, 2860, 1703, 1650, 1448, 1412, 1376, 1308, 1272, 1236, 1192, 1132, 1073, 994, 933, 767, 616 cm^{-1}; MS (ESI)*: m/z*: 508 [*M*+H$^+$]; 530 [*M*+Na$^+$]; HRMS (ESI): *m/z:* calcd. for $C_{19}H_{28}NO_5Br_2$ [*M*+H$^+$]: 508.03290, found: 508.03322.

Methyl (*E*)-5-(6,7-dibromooct-6-en-1-yl)-4-oxo-3,4-dihydropyridine-1(2*H*)-carboxylate (95). $Pd_2(dba)_3$ (859 mg, 0.938 mmol) was added to a solution of compound **108** (9.54 g, 18.7 mmol) in CH_3CN (94 mL). The mixture was stirred at 80 °C for 30 min before it was cooled to ambient temperature and filtered through a pad of Celite, rinsing with *tert*-butyl methyl ether (100 mL). The combined filtrates

were evaporated and the residue was purified by flash chromatography on silica (hexanes/EtOAc, 4:1 to 1:1) to afford the title compound as a colorless oil (7.22 g, 92%).^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.66 (s, 1H), 3.98 (t, *J* = 7.3 Hz, 2H), 3.85 (d, *J* = 1.0 Hz, 3H), 2.72–2.62 (m, 2H), 2.59–2.48 (m, 2H), 2.41 (d, *J* = 1.1 Hz, 3H), 2.17 (t, *J* = 7.6 Hz, 2H), 1.62–1.53 (m, 2H), 1.50–1.40 (m, 2H), 1.33 (tt, *J* = 10.2, 4.3 Hz, 2H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 193.2, 122.0, 115.2, 53.9, 42.6, 40.5, 36.0, 29.0, 28.8, 28.2, 27.2, 27.2 ppm; IR (film) $\tilde{\nu}$ = 2926, 2857, 1723, 1665, 1617, 1439, 1398, 1370, 1322, 1301, 1243, 1204, 1153, 1122, 1061, 1048, 1006, 974, 917, 766, 668, 615, 511 cm^{-1}; MS (ESI)*: m/z*: 422 [*M*+H$^+$], 444 [*M*+Na$^+$]; HRMS (ESI): *m/z:* calcd. for $C_{15}H_{22}NO_3Br_2$ [*M*+H$^+$]: 421.99612, found: 421.99593.

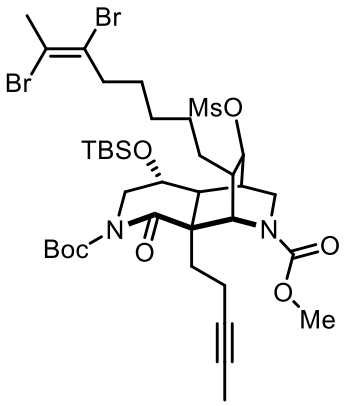
Compound 109. The Michael donor **95** (4.50 g, 10.6 mmol) was dissolved in THF (35 mL) and the solution cooled to –50 °C before a solution of Li*O*t*Bu (854 mg, 10.7 mmol) in THF (18 mL) was added dropwise. After the addition was complete, stirring was continued for 10 min at –50 °C. Then, a solution of the Michael acceptor **94** (3.27 g, 8.89 mmol) in THF (17 mL) was added dropwise at –50 °C. The reaction was warmed to 25 °C over the course of 5 h and then stirred at that temperature for another 16 h. DMAP (1.63 g, 13.3 mmol) and Boc_2O (1.63 g, 13.3 mmol) were added and stirring continued for 1 h before the reaction was quenched with sat. aq. NH_4Cl solution (20 mL). The aqueous phase was extracted with EtOAc (3 x 100 mL), the combined extracts were washed with brine, dried over magnesium sulfate and filtered. After removal of the organic solvents in vacuum, the crude material was purified by flash chromatography on silica (hexanes/EtOAc, 10:1 to 6:1) to afford the desired product.



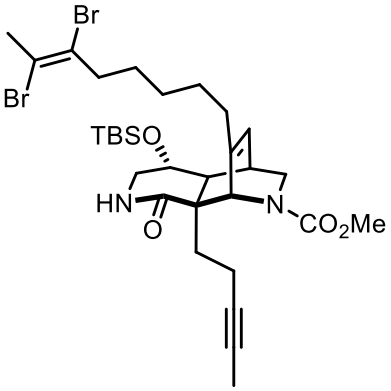
$NaBH_4$ (1.0 g, 26.4 mmol) was added in portions to a solution of this product in MeOH (35.0 mL) at 0 °C. The mixture was stirred at this temperature for 30 min before the reaction was quenched with sat. aq. NH_4Cl (10 mL). The resulting mixture was extracted with EtOAc (3 x 50 mL), the combined organic phases were washed with brine (10 mL), dried over $MgSO_4$ and filtered. After evaporation of the solvent, the crude product was purified by flash chromatography on silica gel (hexanes/EtOAc, 8:1 to 4:1) to afford the title product as a white solid (3.98 g, 55%). $[\alpha]_D^{20}$ = +48.0° (c = 1.0 , $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers, 2.3:1) : δ = 4.46 (tdd, *J* = 10.6, 4.1, 1.8 Hz, 1H), 4.27 (s, 0.3H, minor), 4.18 (s, 0.7H, major), 4.09 (dd, *J* = 12.5, 4.1 Hz, 1H), 3.70 (dd, *J* = 2.5, 1.1 Hz, 3H), 3.57 – 3.49 (m, 1H), 3.30 (ddd, *J* = 22.5, 11.5, 2.8 Hz, 1H), 3.17 – 3.03 (m, 2H), 2.67 – 2.58 (m, 2H), 2.39 (dd, *J* = 2.6, 1.1 Hz, 3H), 2.35 – 2.25 (m, 1H), 2.25 – 2.11 (m, 1H), 1.98 (dtt, *J* = 16.5, 8.5, 4.0 Hz, 1H), 1.84 – 1.58 (m, 8H), 1.58 – 1.23 (m, 17H), 0.87 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.6, 156.8, 156.5, 151.5, 151.4, 122.2, 122.0, 115.2, 115.1, 83.4, 83.3, 78.5, 77.9, 76.2, 76.0, 75.8, 75.5, 67.8, 67.7, 52.7, 52.5, 52.2, 52.1, 51.8, 51.3, 50.8, 49.7, 48.0, 46.2, 46.0, 40.4, 40.1, 39.8, 34.6, 34.5, 33.2, 32.9, 28.7, 28.7, 28.6, 28.0, 27.2, 27.2, 26.5, 26.4, 25.7, 17.9, 13.8, 13.8, 3.5, 3.4, –4.4, –4.5; IR (film) $\tilde{\nu}$ =

3502, 2951, 2929, 2884, 2857, 1766, 1703, 1680, 1454, 1393, 1369, 1339, 1296, 1255, 1191, 1156, 1122, 1067, 991, 939, 865, 838, 808, 779, 756, 685, 671, 666 cm^{-1}; MS (ESI)*: m/z*: 839 [*M*+Na^+]; HRMS (ESI): *m/z:* calcd. for $C_{36}H_{58}N_2O_7SiBr_2Na$ [*M*+Na^+]: 839.22725, found: 839.22744.

Compound S6. Et_3N (1.6 mL, 11.5 mmol), DMAP (474 mg, 3.88 mmol) and MsCl (0.75 mL, 9.69 mmol) were successively added to a solution of alcohol **109** (3.18 g, 3.88 mmol) in CH_2Cl_2 (16.0 mL) at 0 °C. After 5 min, the cooling bath was removed and the mixture stirred at ambient temperature for 2 h before sat. aq. $NaHCO_3$ (10 mL) was added. The aqueous layer was extracted with EtOAc (3 x 50 mL), the combined extracts were washed with brine (5 mL), dried over $MgSO_4$ and filtered, and the solvent was evaporated in vacuum. The residue was purified by flash chromatography on silica gel (hexanes/EtOAc, 4:1 to 2:1) to afford the title compound as a white solid (3.28 g, 94%). $[\alpha]_D^{20}$ = +29.4° (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers, 2:1): δ = 4.42–4.29 (m, 2H), 4.23–4.15 (m, 2H), 3.75 (s, 2H, major), 3.73 (s, 1H, minor), 3.40 (td, *J* = 11.8, 2.7 Hz, 1H), 3.28–3.16 (m, 2H), 3.02–2.99 (m, 3H), 2.67–2.56 (m, 3H), 2.40 (dt, *J* = 3.2, 1.0 Hz, 3H), 2.22 (dddd, *J* = 16.3, 9.6, 6.2, 2.8 Hz, 1H), 2.08–1.99 (m, 1H), 1.97–1.89 (m, 1H), 1.87–1.81 (m, 2H), 1.73 (h, *J* = 2.5 Hz, 4H), 1.60–1.56 (m, 3H), 1.53 (s, 10H), 1.43–1.24 (m, 4H), 0.89 (s, 9H), 0.15 (s, 3H), 0.14 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.9, 156.6, 156.5, 151.1, 151.0, 122.1, 121.9, 115.3, 85.1, 84.8, 83.8, 83.7, 78.2, 77.6, 76.1, 75.8, 67.8, 67.7, 52.9, 51.8, 51.7, 51.6, 51.5, 50.3, 49.8, 49.2, 48.1, 43.5, 43.4, 40.5, 40.4, 40.0, 39.6, 38.7, 38.6, 34.0, 33.8, 32.2, 31.9, 28.8, 28.5, 28.4, 28.0, 27.2, 27.1, 26.1, 26.1, 25.8, 17.9, 13.9, 3.5, 3.4, –4.2, –4.5 ppm; IR (film) $\tilde{\nu}$ = 2931, 2858, 1770, 1704, 1449, 1389, 1367, 1340, 1298, 1256, 1177, 1155, 1125, 1065, 991, 962, 941, 899, 838, 779, 754, 666, 617, 526, 490 cm^{-1}; MS (ESI)*: m/z*: 917 [*M*+Na^+]; HRMS (ESI): *m/z:* calcd. for $C_{37}H_{60}N_2O_9SiBr_2Na$ [*M*+Na^+]: 917.20480, found: 917.20512.



Compound 110. *Note: To assure reproducibility, the starting material should be stirred and dried under high vacuum for 2 d until it has turned into a fine power.*

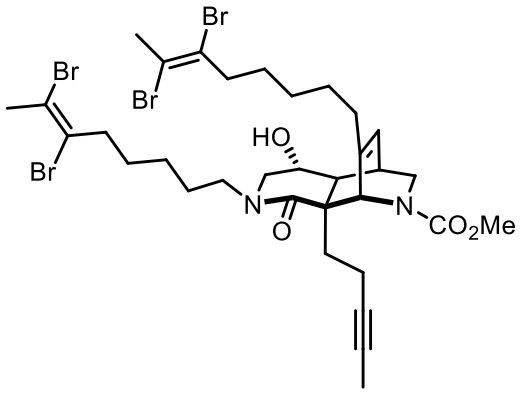


Mesylate **S6** (2.28 g, 2.54 mmol) was dissolved in 2,6-lutidine (12.7 mL) and the resulting solution was stirred at 170 °C (bath temperature) for 5 d. The mixture was then cooled to ambient temperature and diluted with CH_2Cl_2 (6.0 mL).

TBSOTf (2.9 mL, 12.6 mmol) was added to this solution at 0 °C. After 5 min, the cooling bath was removed and the mixture stirred at ambient temperature for 3 h. sat. aq. $NaHCO_3$ (10 mL) was added at 0 °C, followed, after 5 min, by careful addition of HCl (2 M, 40 mL). After stirring for 10 min, the mixture was extracted with EtOAc (3 x 100 mL), the combined organic phases were washed with sat. aq. $NaHCO_3$ (5 mL) and

dried with $MgSO_4$. After filtration and evaporation of the solvent in vacuum, the residue was purified by flash chromatography on silica gel (hexanes/EtOAc, 8:1 to 4:1) to afford the title product as a yellow solid (1.40 g, 78%). $[\alpha]_D^{20}$ = +30.0° (c = 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, mixture of rotamers, ca. 2:1): δ = 5.93–5.82 (m, 1H), 5.80–5.65 (m, 1H), 4.87 (d, *J* = 1.6 Hz, 0.34H, minor), 4.75 (d, *J* = 1.5 Hz, 0.66H, major), 3.73 (s, 2H), 3.68 (s, 1H), 3.35 (td, *J* = 9.4, 4.7 Hz, 1H), 3.20–3.09 (m, 2H), 3.08–2.91 (m, 2H), 2.79–2.70 (m, 1H), 2.66–2.58 (m, 2H), 2.42–2.37 (m, 3H), 2.33 – 2.08 (m, 4H), 1.86 (dq, *J* = 10.7, 5.3 Hz, 2H), 1.74 (t, *J* = 2.5 Hz, 3H), 1.69–1.60 (m, 2H), 1.59–1.48 (m, 2H), 1.44–1.35 (m, 1H), 1.30–1.22 (m, 2H), 0.89 (s, 9H), 0.10 (s, 3H), 0.06 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.6, 156.0, 156.0, 148.4, 147.6, 124.3, 123.7, 122.1, 122.0, 115.2, 115.1, 79.0, 78.5, 75.7, 75.4, 70.8, 70.7, 54.3, 54.2, 52.9, 52.6, 52.5, 51.4, 51.3, 47.3, 47.1, 45.6, 40.6, 40.6, 39.9, 39.7, 33.6, 33.6, 33.3, 28.7, 28.0, 27.9, 27.2, 27.1, 27.0, 26.6, 26.4, 25.7, 17.8, 14.1, 3.5, 3.4, –4.3, –4.3, –4.8 ppm; IR (film) $\tilde{\nu}$ = 2950, 2928, 2857, 1699, 1664, 1446, 1386, 1339, 1299, 1273, 1254, 1216, 1190, 1120, 1107, 1064, 1006, 981, 955, 927, 876, 836, 814, 774, 708, 685, 660, 616 cm^{-1}; MS (ESI): *m*/*z*: 699 [*M*+H^+], 721 [*M*+Na^+]; HRMS (ESI): *m*/*z:* calcd. for $C_{29}H_{46}N_5O_3SiBr_2Na$ [*M*+Na^+]: 721.16291, found: 721.16321.

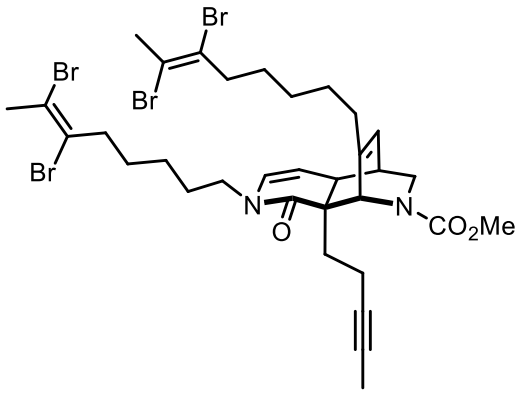
Compound 111. NaH (254 mg, 10.6 mmol) was added to a solution of compound **110** (1.40 g, 1.99 mmol) and iodide **106** (0.75 mL, 2.38 mmol) in DMF/THF (10 mL, 1:1) at 0 °C. After stirring at this temperature for 1 h, the mixture was poured into a solution of sat. aq. NH_4Cl (20 mL). The resulting mixture was extracted with EtOAc (3 x 50 mL), the combined organic phases were washed with brine, dried over $MgSO_4$ and filtered. After evaporation of the solvent in vacuum, the residue was purified by flash chromatography on silica gel (hexanes/*tert*-butyl methyl ether, 8:1 to 4:1) to afford product **111** as a colorless oil.



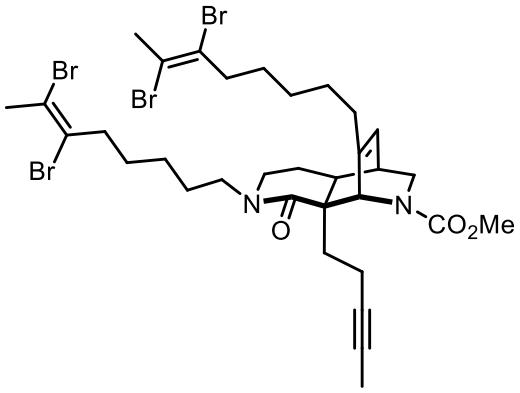
This compound was dissolved in THF (4.2 mL) and TBAF (1 M in THF, 4.0 mL, 4.0 mmol) was added. The resulting mixture was stirred at ambient temperature for 1 h before the reaction was quenched with sat. aq. NH_4Cl (5.0 mL). The resulting mixture was extracted with EtOAc (3 x 10 mL), the combined organic phases were washed with brine and dried over Na_2SO_4. After filtration and evaporation of the solvent in vacuum, the crude material was purified by flash chromatography on silica gel (hexanes/acetone, 15:1 to 4:1) to afford the title compound as a yellow oil (1.56 g, 92%). $[\alpha]_D^{20}$ = +36.7° (c = 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, mixture of rotamers, ca. 2:1): δ = 5.92–5.77 (m, 1H), 4.89 (s, 0.4H, minor), 4.78 (s, 0.6H, major), 3.72 (s, 2H, major), 3.66 (s, 1H, minor), 3.44–3.23 (m, 3H), 3.21–3.09 (m, 3H), 3.03–2.82 (m, 2H), 2.70–2.56 (m, 5H), 2.43–2.36 (m, 6H), 2.31–2.04 (m, 4H), 1.92–1.81 (m, 1H), 1.73 (q, *J* = 2.8 Hz, 4H), 1.62–1.54 (m, 4H), 1.51–1.42 (m, 4H), 1.31–1.16 (m, 4H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ =

169.9, 169.9, 156.1, 156.1, 148.2, 147.4, 124.3, 123.7, 122.1, 121.9, 121.7, 121.7, 115.5, 115.4, 115.2, 115.1, 79.1, 78.6, 75.7, 75.5, 69.6, 69.5, 53.8, 53.8, 53.4, 53.1, 52.6, 52.5, 51.9, 51.8, 51.1, 47.6, 47.5, 47.3, 47.0, 40.6, 40.5, 40.3, 40.3, 39.8, 39.5, 33.7, 33.5, 33.4, 28.7, 28.0, 27.9, 27.2, 27.2, 27.1, 27.1, 27.0, 26.6, 26.4, 25.5, 25.4, 14.2, 3.6, 3.5 ppm; IR (film) $\tilde{\nu}$ = 3400, 2926, 2858, 1700, 1678, 1645, 1617, 1487, 1448, 1391, 1340, 1261, 1192, 1159, 1113, 1066, 971, 955, 816, 766, 714, 616, 582 cm^{-1}; MS (ESI): *m/z*: 851 [*M*+H^+], 873 [*M*+Na^+]; HRMS (ESI): *m/z:* calcd. for $C_{33}H_{45}N_2O_4Br_4$ [M^+]: 849.01188, found: 849.01244.

Compound S7. Martin's sulfurane (1.48 g, 2.20 mmol) was added to a solution of compound **111** (1.18 g, 1.38 mmol) in toluene (7.0 mL) at 100 °C. After stirring at this temperature for 20 min, the mixture was cooled to ambient temperature and directly loaded on silica. The product was eluted with hexanes/EtOAc (8:1 to 4:1) to afford the title compound as a colorless oil (1.16 g, quant.). $[\alpha]_D^{20}$ = +15.9° (c = 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, mixture of rotamers, ca. 2:1): δ = 5.97 (td, *J* = 6.4, 3.2 Hz, 1H), 5.72 (dd, *J* = 8.1, 1.3 Hz, 1H), 4.96–4.76 (m, 2H), 3.74 (s, 2H, major), 3.69 (s, 1H, minor), 3.50 (dddd, *J* = 13.8, 7.9, 6.0, 2.8 Hz, 1H), 3.27–3.18 (m, 1H), 3.09 (dddd, *J* = 13.3, 8.2, 6.7, 3.3 Hz, 1H), 2.84 (ddd, *J* = 25.0, 10.1, 2.4 Hz, 1H), 2.69–2.53 (m, 5H), 2.43–2.38 (m, 6H), 2.32–2.25 (m, 1H), 2.22–1.97 (m, 5H), 1.74 (q, *J* = 2.6 Hz, 3H), 1.65–1.42 (m, 8H), 1.39–1.19 (m, 5H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 168.5, 156.3, 156.2, 147.5, 146.7, 127.9, 127.7, 125.7, 125.1, 122.1, 122.0, 121.7,121.7, 115.6, 115.5, 115.3, 106.9, 106.6, 78.6, 78.5, 75.7, 75.6, 56.2, 55.9, 53.2, 52.6, 52.5, 48.2, 47.1, 44.0, 44.0, 41.0, 40.6, 40.5, 40.4, 40.4, 37.6, 37.3, 34.0, 28.8, 28.8, 28.1, 28.1, 27.9, 27.9, 27.2, 27.1, 27.1, 27.0, 26.6, 25.5, 25.4, 15.0, 3.5 ppm; IR (film) $\tilde{\nu}$ = 2927, 2858, 1700, 1648, 1447, 1390, 1414, 1338, 1274, 1257, 1232, 1191, 1152, 1107, 1067, 973, 951, 847, 766, 730, 702, 617, 590 cm^{-1}; MS (ESI): *m/z*: 833 [*M*+H^+], 855 [*M*+Na^+]; HRMS (ESI): *m/z:* calcd. for $C_{33}H_{44}N_2O_3Br_4Na$ [*M*+Na^+]: 854.99781, found: 854.99776.

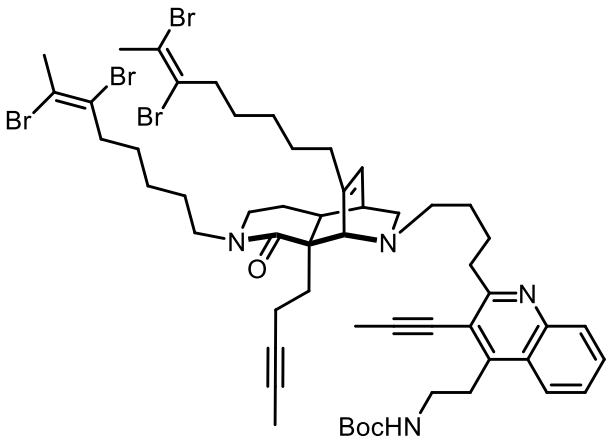


Compound 112. $NaBH_3CN$ (368 mg, 5.86 mmol) was added to a solution of compound **S7** (1.0 g, 1.20 mmol) in CH_2Cl_2 (60 m) at 0 °C. TFA (0.91mL, 11.9 mmol) was slowly added at 0 °C. After stirring for 10 min, the cooling bath was removed and the mixture stirred at ambient temperature for 50 min before the reaction was quenched with sat. $NaHCO_3$ (5.0 mL). [*Note: the reaction is seriously time-dependent: any longer reaction time will cause a sharp decrease in yield*]



The resulting mixture was extracted with CH_2Cl_2 (3 x 300 mL), the combined organic phases were washed with brine, dried over Na_2SO_4, and filtered. After evaporation of the solvent in vacuum, the residue was purified by flash chromatography on silica (hexanes/EtOAc, 8:1 to 4:1) to afford the title product as a colorless oil (664 mg, 66%). $[\alpha]_D^{20}$ = +30.8° (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers, ca. 2:1): δ = 5.85 (t, *J* = 7.9 Hz, 1H), 4.86 (d, *J* = 1.5 Hz, 0.35H, minor), 4.75 (d, *J* = 1.5 Hz, 0.65H, major), 3.73 (s, 2H), 3.68 (s, 1H), 3.41–3.30 (m, 1H), 3.28–3.14 (m, 3H), 3.13–3.04 (m, 1H), 2.91 (ddd, *J* = 29.8, 10.1, 2.6 Hz, 1H), 2.69–2.58 (m, 4H), 2.55–2.45 (m, 1H), 2.41 (dq, *J* = 2.8, 1.8, 1.4 Hz, 6H), 2.31–2.15 (m, 2H), 2.12–2.02 (m, 2H), 2.00–1.89 (m, 2H), 1.81 (dd, *J* = 9.1, 6.8 Hz, 1H), 1.74 (t, *J* = 2.5 Hz, 3H), 1.69–1.60 (m, 2H), 1.56–1.32 (m, 8H), 1.31–1.22 (m, 4H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.4, 170.3, 156.2, 156.2, 147.3, 146.6, 124.1, 123.5, 122.2, 122.0, 121.8, 121.8, 115.4, 115.4, 115.2, 79.3, 78.9, 75.4, 75.3, 54.3, 54.2, 52.6, 52.4, 52.0, 51.9, 48.2, 48.0, 47.8, 47.7, 45.2, 45.1, 44.9, 44.9, 40.6, 40.6, 40.4, 40.4, 39.5, 39.4, 37.2, 36.8, 33.7, 33.6, 29.8, 28.8, 28.0, 27.9, 27.3, 27.2, 27.2, 27.1, 27.1, 27.0, 26.6, 26.4, 25.6, 25.6, 14.5, 14.4, 3.6, 3.5 ppm; IR (film) $\tilde{\nu}$ = 2928, 2858, 1699, 1634, 1487, 1447, 1389, 1338, 1275, 1231, 1210, 1190, 1159, 1110, 1068, 970, 767, 616 cm^{-1}; MS (ESI): *m/z*: 835 [*M*+H$^+$], 857 [*M*+Na$^+$]; HRMS (ESI): *m/z:* calcd. for $C_{33}H_{46}N_2O_3Br_4Na$ [*M*+Na$^+$]: 857.01346, found: 857.01264.

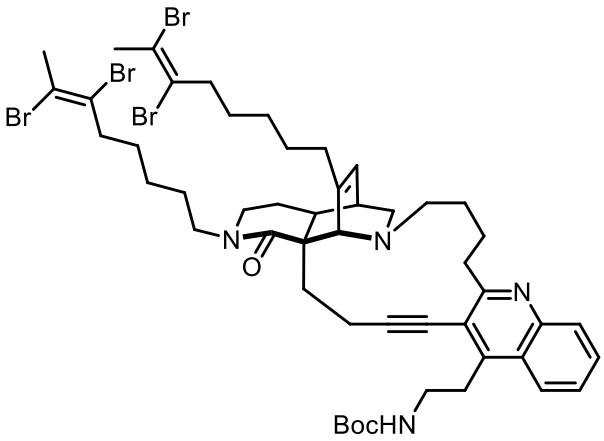
Compound 114. A solution of TMSI (0.13 mL, 0.914 mmol) in CH_2Cl_2 (2.0 mL) was added to a solution of compound **112** (700 mg, 0.835 mmol) in CH_2Cl_2 (17 mL). The resulting mixture was stirred for 1 d at ambient temperature before the reaction was quenched with MeOH (2.0 mL) and sat. aq. $NaHCO_3$ (5.0 mL) at 0 °C. After removal of the solvents, the crude mixture was loaded on an amino cartridge (Agilent, Bond Elut-NH_2, 500 mg, 3 mL, 40 μm, pre-equilibrated with MeOH, H_2O, MeOH (volume of ca. one column length each)) and the amine product was eluted with MeOH to provide a white solid [*purification on silica gel with basic eluent gave much lower yields*].



A solution of aldehyde **98** (476 mg, 1.25 mmol) in CH_2Cl_2 (3 mL) was added to a solution of the amine in CH_2Cl_2 (2 mL). After stirring for 10 min at ambient temperature, $NaBH(OAc)_3$ (230 mg, 1.09 mmol) was added and stirring was continued for 1 h. The reaction was quenched with sat. aq. $NaHCO_3$ (0.5 mL). After removing the solvent in high vacuum, the crude material was subjected to preparative HPLC (Kromasil-5-C18, 5 μm, 150 mm × 30 mm, MeOH, 35 mL/min, λ = 220 nm, t = 9.2 min) to afford the title compound as a brownish solid (642 mg, 67%). $[\alpha]_D^{20}$ = –15.0° (c = 1.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 8.4 Hz, 1H), 7.91 (dd, *J* = 8.5, 1.2 Hz, 1H), 7.54 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.40 (ddd, *J* = 8.3, 6.8, 1.3 Hz,

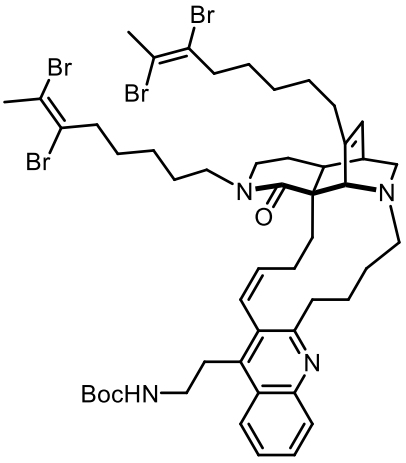
1H), 5.74 (d, *J* = 6.4 Hz, 1H), 4.64 (s, 1H), 3.40 (d, *J* = 3.2 Hz, 4H), 3.30 (s, 1H), 3.23 (dt, *J* = 13.2, 7.4 Hz, 1H), 3.07 (dt, *J* = 16.1, 7.4 Hz, 4H), 3.00–2.84 (m, 2H), 2.62–2.48 (m, 4H), 2.45–2.34 (m, 1H), 2.31 (dd, *J* = 9.2, 1.0 Hz, 6H), 2.15 (s, 5H), 2.08–1.86 (m, 5H), 1.85–1.67 (m, 4H), 1.60 (d, *J* = 8.3 Hz, 2H), 1.57 (d, *J* = 2.4 Hz, 3H), 1.47 (h, *J* = 7.5 Hz, 6H), 1.39–1.32 (m, 12H), 1.29–1.14 (m, 6H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.8, 163.2, 155.9, 147.0, 146.1, 144.6, 129.4, 129.2, 126.2, 125.7, 123.8, 122.4, 122.1, 121.9, 117.7, 115.4, 115.1, 95.6, 79.8, 79.2, 76.1, 74.9, 62.5, 58.0, 55.6, 52.2, 47.7, 45.3, 44.1, 40.6, 40.4, 39.1, 37.9, 35.0, 30.8, 29.7, 28.8, 28.8, 28.4, 28.4, 27.4, 27.2, 27.2, 26.8, 26.4, 25.7, 14.7, 4.9, 3.5 ppm; IR (film) $\tilde{\nu}$ = 3328, 2928, 2857, 1708, 1628, 1453, 1251, 1171, 759 cm^{-1}; MS (ESI)*: m*/z: 1141 [*M*+H$^+$], 1163 [*M*+Na$^+$]; HRMS (ESI): *m*/*z:* calcd. for $C_{54}H_{73}Br_4N_4O_3$ [*M*+H$^+$]: 1141.24112, found: 1141.24199.

Compound 97. A flame-dried two-necked flask connected to a reflux condenser was charged

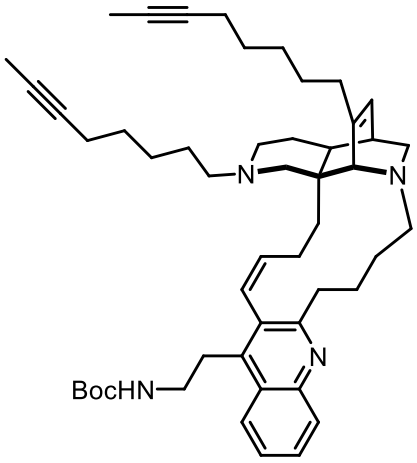


with activated molecular sieve powder (5 Å, 1.5 g) and toluene (20 mL). The suspension was purged with argon at room temperature for 30 min. The mixture was then heated to 110 °C for 30 min and a solution of diyne **114** (50.6 mg, 0.044 mmol) in toluene (2 mL) was added. Next, a solution of the Mo-catalyst **79** (9.8 mg, 0.013 mmol)[105] in toluene (0.5 mL) was added dropwise and stirring was continued at 110 °C for 15 min. Ethanol (5 mL) was added to quench the reaction. The mixture was cooled to room temperature and filtered through a plug of Celite, which was carefully rinsed with EtOAc. The combined filtrates were evaporated *in vacuo* and the residue was purified by preparative HPLC (Kromasil-5-C18, 5 μm, 150 mm × 30 mm, MeOH, 35 mL/min, λ = 254 nm, t = 11.5 min) to afford the title compound a white solid (37.1 mg, 77%) as. $[\alpha]_D^{20}$ = –30.9° (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06 (d, *J* = 8.4 Hz, 1H), 7.99 (dd, *J* = 8.5, 1.2 Hz, 1H), 7.62 (ddd, *J* = 8.3, 6.9, 1.3 Hz, 1H), 7.49 (ddd, *J* = 8.3, 6.8, 1.3 Hz, 1H), 5.84 (dd, *J* = 6.4, 1.8 Hz, 1H), 4.82 (s, 1H), 3.72 (d, *J* = 1.6 Hz, 1H), 3.64–3.41 (m, 7H), 3.29 (td, *J* = 12.4, 2.1 Hz, 1H), 3.09–2.97 (m, 3H), 2.93 (dd, *J* = 9.3, 2.1 Hz, 1H), 2.81 (td, *J* = 11.9, 2.4 Hz, 1H), 2.74–2.56 (m, 6H), 2.55–2.45 (m, 1H), 2.43 (d, *J* = 0.9 Hz, 3H), 2.41 (d, *J* = 0.9 Hz, 3H), 2.33–2.19 (m, 4H), 2.17–2.08 (m, 1H), 1.96 (ddd, *J* = 13.7, 10.4, 5.6 Hz, 1H), 1.86 (ddd, *J* = 13.4, 5.6, 2.4 Hz, 1H), 1.75–1.66 (m, 3H), 1.58 (dtd, *J* = 16.2, 9.1, 8.2, 3.2 Hz, 7H), 1.48 (dd, *J* = 7.9, 2.1 Hz, 2H), 1.43 (s, 9H), 1.37 (qt, *J* = 7.2, 4.0 Hz, 2H), 1.32–1.21 (m, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.9, 164.3, 156.0, 146.3, 146.1, 145.5, 129.2, 129.1, 126.2, 125.8, 123.9, 122.2, 121.9, 117.8, 115.5, 115.1, 102.2, 79.1, 76.3, 60.8, 55.3, 54.3, 52.5, 47.6, 46.9, 45.3, 40.7, 40.5, 40.4, 38.6, 37.5, 37.0, 35.0, 30.8, 30.4, 28.8, 28.8, 28.4, 28.4, 27.8, 27.4, 27.4, 27.2, 26.7, 25.5, 25.1, 13.5 ppm; IR (film) $\tilde{\nu}$ = 3339, 2928, 2855, 1705, 1630, 1450, 1169, 1070, 756, 617 cm^{-1}; MS (ESI)*: m*/*z*: 1086 [*M*+H$^+$]; HRMS (ESI): *m*/*z:* calcd. for $C_{50}H_{67}Br_4N_4O_3$ [*M*+H$^+$]: 1087.19417, found: 1087.19495.

Compound 115. Pd/$CaCO_3$ (5 mol% *w/w*, *unpoisoned*, 704 mg, 0.331 mmol) was added to solution of compound **97** (180 mg, 0.165mmol) in THF (18 mL) at ambient temperature. After stirring for 2 h, the suspension was filtered through a pad of Celite® and the filtrate was concentrated. The crude product was subjected to purification by preparative HPLC (Kromasil-5-C18, 5 μm, 150 mm × 30 mm, MeOH, 35 mL/min, λ = 254 nm, t = 8.6 min) to afford the title compound as a white solid (94.0 mg, 52%). $[\alpha]_D^{20}$ = +4.8° (c = 0.24, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.08–8.00 (m, 2H), 7.65 (t, *J* = 7.0 Hz, 1H), 7.54 (s, 1H), 6.41 (d, *J* = 11.0 Hz, 1H), 5.88–5.81 (m, 1H), 5.79–5.74 (m, 1H), 4.56 (s, 1H), 3.41 (d, *J* = 9.2 Hz, 1H), 3.33–3.10 (m, 9H), 3.02–2.87 (m, 3H), 2.62 (t, *J* = 7.5 Hz, 2H), 2.52 (t, *J* = 7.2 Hz, 2H), 2.41–2.40 (m, 3H), 2.37 (s, 3H), 2.34–2.26 (m, 2H), 2.21 (t, *J* = 12.7 Hz, 1H), 2.15–2.13 (m, 1H), 1.99–1.88 (m, 3H), 1.86–1.73 (m, 3H), 1.71–1.64 (m, 2H), 1.61 (d, *J* = 11.5 Hz, 1H), 1.60–1.52 (m, 3H), 1.50–1.37 (m, 13H), 1.33–1.21 (m, 4H), 1.20 – 1.11 (m, 4H), 1.07 (d, *J* = 13.0 Hz, 1H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$): δ = 171.7, 159.9, 155.8, 146.7, 145.2, 135.7, 130.3, 129.3, 128.6, 126.2, 125.9, 124.5, 124.2, 123.1, 122.2, 121.9, 115.4, 115.0, 79.1, 56.9, 55.5, 54.8, 52.5, 47.4, 46.6, 45.2, 41.6, 40.5, 40.4, 38.5, 37.3, 37.0, 35.1, 30.7, 28.8, 28.7, 28.4, 28.1, 27.3, 27.3, 27.1, 26.5, 26.3, 25.6, 25.2, 24.4 ppm; IR (film) $\tilde{\nu}$ = 2959, 2852, 1253, 1116, 1082, 869, 612 cm^{-1}; MS (ESI)*: m/z*: 1089 [*M*+H$^+$]; HRMS (ESI): *m/z:* calcd. for $C_{50}H_{69}Br_4N_4O_3$ [*M*+H$^+$]: 1089.21116, found: 1089.21061.



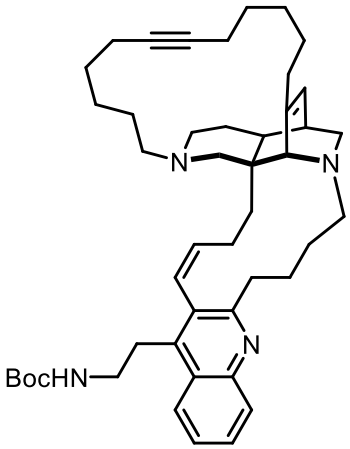
Compound 99. DIBAL-H (1.0 M in hexane, 0.4 mL, 0.40 mmol) was added to a solution of **115** (64.0 mg, 0.0586 mmol) in Et_2O (0.4 mL) at 0 °C. After 5 min, the cooling bath was remved and the mixture stirred at 20 °C for 80 min [*Note: The reaction time should be strictly followed; longer reaction times will result in serious over-reduction of the vicinal dibromide*].



The mixture was diluted with *tert*-butyl methyl ether (2.0 mL) at 0 °C and the reaction quenched with sat. Rochelle's salt solution (0.4 mL). The resulting mixture was vigorously stirred for 5 h. DDQ (13.3 mg/mL) was added to the mixture until the color became brown. The mixture was then filtered through a cartridge (Agilent, Bond Elut-NH_2, 500 mg, 3 mL, 40 μm, pre-equilibrated with of MeOH, H_2O, MeOH (volume of ca. one column length each)), eluting with MeOH. Evaporation of the solvent provided a white solid which was subjected to preparative HPLC (Kromasil-5-C18, 5 μm, 150 mm × 30 mm, MeOH/20 mmol NH_4HCO_3 PH 9 = 98:2, 35 mL/min, λ = 254 nm, t = 29 min) to provide the corresponding amine product as a yellow solid material.

Zn powder (44.0 mg, 0.673 mmol) was added to a solution of this compound in THF/HOAc (1.05 mL, 20:1) at ambient temperature. The mixture was stirred for 1 h before the reaction was carefully quenched with sat. aq. $NaHCO_3$ (0.2 mL). The resulting mixture was passed through a cartridge (Agilent, Bond Elut-NH_2, 500 mg, 3 mL, 40 μm (pre-equilibrated with MeOH, H_2O, MeOH (volume of one column length each); the product was eluted with MeOH to provide a white solid after evaporation of the solvent. The crude material was subjected to preparative HPLC (Kromasil-5-C18, 5 μm, 150 mm × 30 mm, MeOH/ 20 mmol NH_4HCO_3 pH 9 = 98:2, 35 mL/min, λ = 254 nm, t = 7.8 min) to afford the title compound as a white solid (19.7 mg, 44 %). $[\alpha]_D^{20}$ = +210° (c = 0.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.21–8.13 (m, 1H), 8.06 (dd, *J* = 8.4, 1.3 Hz, 1H), 7.67 (ddd, *J* = 8.3, 6.8, 1.3 Hz, 1H), 7.55 (t, *J* = 7.6 Hz, 1H), 6.44 (d, *J* = 10.9 Hz, 1H), 5.94 (t, *J* = 10.9 Hz, 1H), 5.79–5.69 (m, 1H), 4.62 (s, 1H), 3.44–3.16 (m, 5H), 2.99 (d, *J* = 8.7 Hz, 1H), 2.88 (td, *J* = 12.9, 4.6 Hz, 1H), 2.82–2.74 (m, 1H), 2.45–2.22 (m, 6H), 2.12 (tt, *J* = 7.1, 2.6 Hz, 2H), 2.10–2.00 (m, 4H), 1.99–1.89 (m, 2H), 1.81 (s, 2H), 1.78 (t, *J* = 2.5 Hz, 4H), 1.74 (t, *J* = 2.5 Hz, 4H), 1.70–1.64 (m, 4H), 1.44 (s, 9H), 1.39–1.31 (m, 9H), 1.30–1.18 (m, 6H), 1.00 (dd, *J* = 12.0, 5.9 Hz, 2H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 160.5, 155.8, 146.8, 142.9, 136.4, 130.6, 129.7, 128.4, 126.2, 125.8, 124.1, 123.5, 121.6, 79.3, 79.3, 75.5, 75.3, 59.3, 57.1, 56.2, 55.8, 50.2, 49.8, 45.8, 42.9, 40.4, 38.7, 37.7, 36.5, 36.3, 29.0, 28.9, 28.5, 28.4, 27.3, 27.0, 26.8, 26.3, 26.0, 25.4, 23.7, 18.8, 18.6, 3.5, 3.4 ppm; IR (film) $\tilde{\nu}$ = 3315, 2930, 1562, 1406, 1023, 762, 649 cm^{-1}; MS (ESI)*: m/z*: 759 [*M*+H$^+$]; HRMS (ESI): *m/z:* calcd. for $C_{50}H_{71}N_2O_4$ [*M*+H$^+$]: 759.55715, found: 759.55745.

Compound 116. A flame-dried two-necked flask connected to a reflux condenser was charged



with activated powdered molecular sieves (5 Å, 200 mg) and toluene (4 mL). The suspension was purged with argon at room temperature for 15 min. After the purging had been stopped, the mixture was heated to 110 °C for 30 min before a solution of diyne **99** (7 mg, 0.009 mmol) in toluene (0.5 mL) was added, followed by dropwise addition of a solution of the Mo-complex **79** (2.0 mg, 0.003 mmol)[105] in toluene (0.4 mL). The resulting suspension was stirred at 110 °C for 20 min. Ethanol (1 mL) was added to quench the reaction and the crude mixture was cooled to room temperature and filtered through a plug of Celite, which was carefully rinsed with EtOAc. The solvent was evaporated in vacuo and the crude product was purified by preparative HPLC (Kromasil-5-C18, 5 μm, 150 mm × 30 mm, MeOH/20 mmol NH_4HCO_3 pH 9 = 98:2, 35 mL/min, λ = 230 nm, t = 7.6 min) to afford the title compound as a white solid (6.4 mg, 98%). $[\alpha]_D^{20}$ = +23.0° (c = 0.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.17 (d, *J* = 8.4 Hz, 1H), 8.05 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.68–7.63 (m, 1H), 7.55 (t, *J* = 7.6 Hz, 1H), 6.43 (dd, *J* = 10.9, 2.2 Hz, 1H), 5.95 (t, *J* = 10.7 Hz, 1H), 5.77 (d, *J* = 6.5 Hz, 1H), 4.57 (s, 1H), 3.36 (d, *J* = 17.3 Hz, 2H), 3.23 (pd, *J* = 9.2, 4.2 Hz, 3H), 3.00 (dd, *J* = 8.8, 2.2 Hz, 1H), 2.86 (ddd, *J* = 24.4, 12.3, 3.6 Hz, 2H), 2.55 (d, *J* = 10.9 Hz, 2H), 2.42 (d, *J* = 12.7 Hz, 1H), 2.37–2.25 (m, 3H), 2.17–2.05 (m, 5H), 2.03–1.97 (m, 3H), 1.96–1.85 (m, 3H), 1.82–1.62 (m, 5H), 1.52–1.39 (m, 15H), 1.38–1.26

(m, 8H), 1.26–1.13 (m, 1H), 1.07–0.93 (m, 2H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 160.5, 155.8, 146.8, 142.9, 136.3, 130.6, 129.7, 128.4, 126.3, 125.8, 124.2, 123.6, 120.5, 80.6, 80.2, 79.2, 59.4, 57.3, 56.8, 55.8, 49.6, 49.3, 45.6, 42.9, 40.4, 38.7, 37.5, 36.8, 36.4, 29.0, 28.4, 27.9, 27.7, 27.5, 27.4, 27.1, 26.4, 25.4, 24.6, 23.7, 18.2, 17.8 ppm; IR (film) $\tilde{\nu}$ = 2926, 2857, 1703, 1455, 1365, 1171, 758, 678 cm^{-1}; MS (ESI)*: m/z*: 705 [*M*+H$^+$]; HRMS (ESI): *m/z:* calcd. for $C_{46}H_{65}N_4O_2$ [*M*+H$^+$]: 705.51020, found: 705.51087.

Nominal Njaoamine I ((+)-16). HCl (0.48 mmol, 120 μL, 4 M in 1,4-dioxane) was added dropwise to a solution of compound **71** (9.0 mg, 12.8 μmol) in EtOAc (0.42 mL) and H_2O (80 μL) at 0 °C. The resulting solution was stirred for 2 h at this temperature. The solvent was evaporated in high vacuum to provide the HCl salt of njaoamine I. The HCl salt was passed through an amino cartridge (pre-equilibrated with MeOH, H_2O, MeOH (three volumes of three column length each)), eluting the product with MeOH. After evaporation of the solvent, the free amine was subjected to preparative HPLC (150 mm YMC Triart C18 5 μm, 10.0 mm i.D., Methanol/0.1% TFA in H_2O = 55:45, 4.7 mL/min, λ = 220 nm, t = 1.6 min) to afford the title compound as a white solid (8.6 mg, quant.). $[\alpha]_D^{20}$ = +69.3° (c = 0.2, $CHCl_3$); for the ^{1}H NMR and ^{13}C NMR data, see Table 4.6; IR (film) ν = 2936, 1677, 1202, 1182, 1133, 938, 761, 708 cm^{-1}; MS (ESI)*: m/z*: 605 [*M*+H$^+$]; HRMS (ESI): *m/z:* calcd. for $C_{41}H_{57}N_4$ [*M*+H$^+$]: 605.45777, found: 605.45765.

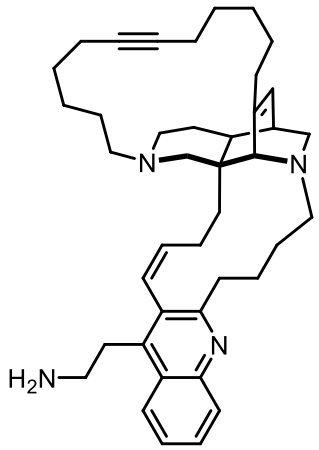
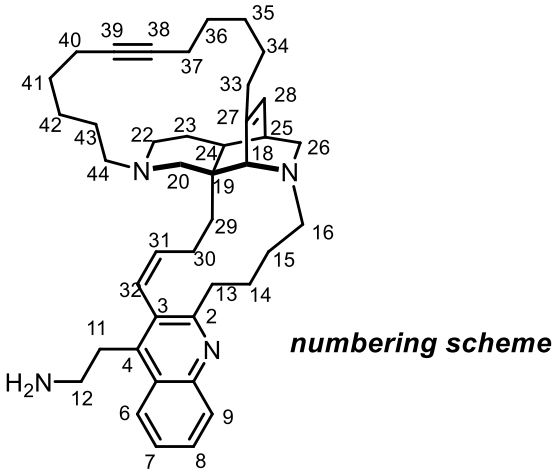


Table 4.6. Summary of all chemical shifts and correlations for the synthetic nominal njaoamine I (**(+)-16**)



nominal Njaoamine I (**16**)

Atom	δ (ppm)	J	COSY	HSQC	HMBC	NOESY
1 N						
2 C	160.59				13a, 13b	
3 C	131.26				11a, 11b, 13b, 31	
4 C	141.84				6, 11a, 11b	
5 C	126.69				6, 7, 9, 11a, 11b	
6 C	124.96			6	8	
H	8.25	8.3(7)	7	6	4, 5, 8, 10	7, 11a, 11b, 12b
7 C	126.88			7	9	
H	7.44	6.8(8), 8.3(6)	6, 8	7	5, 9	6
8 C	129.34			8	6	
H	7.63	8.3(9), 6.8(7)	7, 9	8	6, 10	9
9 C	130.35			9	7	
H	8.31	8.3(8)	8	9	5, 7	8
10 C	147.78				6, 8	
11 C	28.44			11a, 11b	12a, 12b	
Ha	3.85	12.3(12a), 5.6(12b), 12.3(11b)	11b, 12a, 12b	11	3, 4, 5, 12	6, 11b
Hb	3.68	12.3(11a), 4.8(12a), 12.2(12b)	11a, 12a, 12b	11	3, 4, 5	6, 11a, 32
12 C	39.72			12a, 12b	11a	
Ha	3.59	12.2(12b), 12.3(11a), 4.8(11b)	11a, 11b	12	11	
Hb	3.53	12.2(12a), 5.6(11a), 12.2(11b)	11a, 11b	12	11	6
13 C	39.14			13a, 13b		
Ha	3.26	12.9(13b), 12.8(14?), 4.8(14?)	13b, 14a	13	2, 15	32

Hb	3.14	12.9(13a)	13a, 14a, 14b	13	2, 3, 14	
14 C	26.29			14a, 14b	13b, 16a	
Ha	2.42		13a, 13b, 14b, 15a, 15b	14		14b
Hb	1.60		13b, 14a	14		14a, 16a
15 C	27.32			15a, 15b	13a	
Ha	1.52		14a, 16a	15		
Hb	1.43		14a, 16a, 16b	15		18
16 C	56.51			16a, 16b	18, 26b	
Ha	2.42	12.7(16b)	15a, 15b, 16b	16	14	14b, 16b, 18
Hb	2.02	12.7(16a), 12.7(15?), 3.1(15?)	15b, 16a	16		16a
17 N						
18 C	57.09			18	26a, 28, 29b	
H	2.72			18	16, 19, 20, 24, 25, 26, 27, 28, 29, 33	15b, 16a, 20a, 29b, 33b
19 C	44.12				18, 20a, 23a, 25, 29a	
20 C	49.84			20a, 20b	18, 29a, 44a	
Ha	3.47	12.4(20b)	20b	20	19, 22, 24	18, 20b
Hb	2.19	12.4(20a)	20a	20	29, 44	20a, 23b
21 N	-353.20		22b			
22 C	49.25			22a, 22b	20a, 44a	
Ha	3.59		22b, 23b	22		22b, 24
Hb	3.07		22a, 21	22		22a, 23b
23 C	24.46			23a, 23b	24	
Ha	1.60		23b, 24	23	19	23b, 24
Hb	1.17		22a, 23a	23	25	20b, 22b, 23a, 28
24 C	41.79			24	18, 20a, 26a, 26b	
H	1.17		23a	24	23, 25, 28, 29	22a, 23a, 25, 26a, 29a
25 C	37.20			25	18, 23b, 24, 26a, 26b, 28	
H	2.12	6.5(28), 2.3(26b)	26a, 26b, 28	25	19, 27, 28	24, 26a, 26b, 28
26 C	57.37			26a, 26b	18	
Ha	3.07	9.0(26b)	25, 26b	26	18, 24, 25, 28	24, 25, 26b
Hb	1.75	9.0(26a), 2.3(25)	25, 26a	26	16, 24, 25, 28	25, 26a
27 C	143.16				18, 25	
28 C	122.12			28	18, 24, 25, 26a, 26b	
H	5.84	6.5(25)	25	28	18, 25, 33	23b, 25, 34a, 34b
29 C	36.64			29a, 29b	18, 20b, 24, 31	
Ha	2.33	12.4(29b), 12.4(15?)	29b, 30a, 30b	29	19, 20, 30, 31	24, 29b, 30b
Hb	1.96	12.4(29a)	29a, 30a	29	18, 30, 31	18, 29a
30 C	24.04			30a, 30b	29a, 29b, 31, 32	
Ha	2.83		29a, 29b, 30b	30		31

Hb	1.96		29a, 30a, 31	30	31, 32	29a, 31
31 C	136.89			31	29a, 29b, 30b	
H	6.07	11.1(32)	30b, 32	31	3, 29, 30	30a, 30b
32 C	124.94			32	30b	
H	6.46	11.1(31)	31	32	30	11b, 13a
33 C	36.74			33a, 33b	18, 28	
Ha	1.83		33b	33		
Hb	1.40		33a	33	34, 35	18
34 C	24.98			34a, 34b	33b, 36	
Ha	1.40			34		28
Hb	1.21			34		28
35 C	28.01			35a, 35b	33b, 36	
Ha	1.33			35		
Hb	1.21			35	36	
36 C	28.15			36	35b, 37	
H2	1.27			36	34, 35, 37, 38	
37 C	18.33			37	36	
H2	2.10			37	36, 38	
38 C	81.38				36, 37	
39 C	80.52				40, 41a, 41b	
40 C	17.80			40	41a, 41b	
H2	2.10			40	39	
41 C	27.09			41b	42a, 42b, 43a, 43b	
Ha	1.41				39, 40, 42, 43	
Hb	1.31			41	39, 40, 42, 43	
42 C	25.64			42a, 42b	41a, 41b, 43a, 43b	
Ha	1.39			42	41	
Hb	1.38			42	41	
43 C	22.59			43a	41a, 41b, 44a, 44b	
Ha	1.81	11.8(44b)	44a, 44b	43	41, 42, 44	
Hb	1.77	5.0(44b)	44a, 44b	44	41, 42	
44 C	59.31			43b, 44a, 44b	20b, 43a	
Ha	3.23	11.9(44b)	43a, 43b, 44b	44	20, 22, 43	44b
Hb	2.98	11.9(44a), 11.8(43a), 5.0(43b)	43a, 43b, 44a	44	43	44a

Table 4.7. Comparison of the ^{13}C and ^{1}H chemical shifts of the isolated natural product njaoamine I and synthetic compound (+)-**16**; significant shift differences are highlighted.

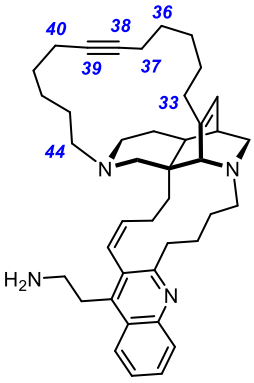
	Fragment A					
	Njaomine I (117)		**Synthetic (+)-16**			
	δC	δH	δC	δH	◎◎δC|	◎◎δH|
2 C	160.50		160.59		0.04	
3 C	131.20		131.26		0.07	
4 C	142.40		141.84		0.69	
5 C	126.60		126.69		0.04	
6 C	124.90		124.96		0.07	
H		8.25		8.25		0.02
7 C	127.00		126.88		0.25	
H		7.42		7.44		0.00
8 C	129.50		129.34		0.29	
H		7.59		7.63		0.02
9 C	129.90		130.35		0.32	
H		8.28		8.31		0.01
10 C	147.20		147.78		0.45	
11 C	28.40		28.44		0.09	
Ha		3.83		3.85		0.00
Hb		3.68		3.68		0.02
12 C	39.70		39.72		0.11	
Ha		3.55		3.59		0.02
Hb		3.55		3.53		0.04
13 C	38.70		39.14		0.31	
Ha		3.22		3.26		0.02
Hb		3.15		3.14		0.03
14 C	26.10		26.29		0.06	
Ha		2.40		2.42		0.00
Hb		1.57		1.60		0.01
15 C	27.50		27.32		0.31	
Ha		1.39		1.52		0.11
Hb		1.39		1.43		0.02
16 C	56.30		56.51		0.08	
Ha		2.39		2.42		0.01
Hb		1.99		2.02		0.01
29 C	36.30		36.64		0.21	
Ha		2.28		2.33		0.03
Hb		1.92		1.96		0.02
30 C	24.10		24.04		0.19	
Ha		2.78		2.83		0.03
Hb		1.93		1.96		
31 C	136.90		136.89		0.14	
H		6.07		6.07		0.02
32 C	124.70		124.94		0.11	
H		6.45		6.46		0.01
	Fragment B					
	Njaomine I (117)		**synth. Njaomine I (+)-16**			
	δC	δH	δC	δH	◎◎δC|	◎◎δH|
18 C	57.10		57.09		0.14	

H		2.65		2.72		0.05
19 C	43.80		44.12		0.19	
20 C	49.10		49.84		0.61	
Ha		3.32		3.47		0.13
Hb		2.25		2.19		0.08
22 C	48.10		49.25		1.02	
Ha		3.50		3.59		0.07
Hb		3.10		3.07		0.05
23 C	25.10		24.46		0.77	
Ha		1.60		1.60		0.02
Hb		1.13		1.17		0.02
24 C	41.20		41.79		0.46	
H		1.12		1.17		0.03
25 C	37.20		37.20		0.13	
H		2.05		2.12		0.05
26 C	57.10		57.37		0.14	
Ha		3.04		3.07		0.01
Hb		1.72		1.75		0.01
27 C	143.00		143.16		0.03	
28 C	122.60		122.12		0.61	
H		5.80		5.84		0.02
	Fragment C					
	Njaomine I (117)		**synth. Njaomine I (+)-16**			
	δC	δH	δC	δH	◎◎δC|	◎◎δH|
33 C	36.40		36.74		0.21	
Ha		1.68		1.83		0.13
Hb		1.38		1.40		0.00
34 C	25.60		24.98		0.75	
Ha		1.45		1.40		0.07
Hb		1.27		1.21		0.08
35 C	24.60		28.01		3.28	
Ha		1.21		1.33		0.10
Hb		1.21		1.21		0.02
36 C	27.60		28.15		0.42	
Ha		1.30		1.27		0.05
Hb		1.30		1.27		0.05
37 C	18.40		18.33		0.20	
Ha		2.14		2.10		0.06
Hb		2.08		2.10		0.00
38 C	80.60		81.38		0.65	
39 C	81.50		80.52		1.11	
40 C	18.90		17.80		1.23	
Ha		2.00		2.10		0.08
Hb		2.00		2.10		0.08
41 C	29.70		27.09		2.74	
Ha		1.27		1.41		0.12
Hb		1.17		1.31		0.12
42 C	25.20		25.64		0.31	
Ha		1.41		1.39		0.04
Hb		1.26		1.38		0.10
43 C	22.50		22.59		0.04	
Ha		1.69		1.81	0.00	0.10

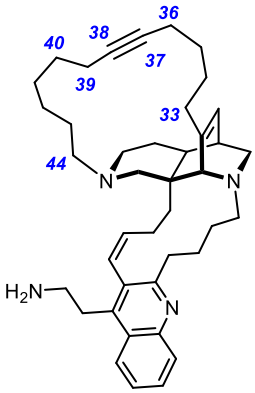
Hb		1.69		1.77	0.00	0.06
44 C	57.50		59.31		1.68	
Ha		3.16		3.23		0.05
Hb		3.16		2.98		0.20

4.1.4 Structural Revision of Njaoamine I

Table 4.8. Revised set of chemical shifts and correlations for the natural product njaoamine I (**117**).



njaoamine I (**16**)
(***nominal***)



njaoamine I (**117**)
(***revised assignment***)

Atom	δ (ppm)	J	COSY	TOCSY	HSQC	HMBC	ROESY
1 N							
2 C	160.84					13a, 13b	
3 C	131.40					11a, 11b, 13b, 31	
4 C	141.95					11a, 11b	
5 C	126.83					7, 9, 11a, 11b	
6 C	125.05				6	8	
H	8.26	8.4(7)	7		6	8, 10	11a, 11b, 12b
7 C	127.05				7	9	
H	7.42	8.4(6), 6.9(8)	6, 8		7	5, 9	
8 C	129.50				8	6	
H	7.60	6.9(7)	7		8	6, 10	
9 C	130.60				9	7	
H	8.29				9	5, 7	
10 C	147.95					6, 8	
11 C	28.60				11a, 11b		
Ha	3.85	5.4(12a), 12.2(12b), 12.5(11b)	11b, 12a, 12b	11b, 12a	11	3, 4, 5, 12	6, 11b
Hb	3.71	12.5(11a), 12.0(12a), 4.5(12b)	11a, 12a	11a, 12a	11	3, 4, 5, 12	6, 11a, 32
12 C	39.94				12a	11a, 11b	

Ha	3.59	12.5(12b), 5.4(11a), 12.0(11b)	11a, 11b, 12b	11a, 11b	12		
Hb	3.53	12.5(12a), 12.2(11a), 4.5(11b)	11a, 12a				6
13 C	39.29				13a, 13b		
Ha	3.23	12.9(13b), 3.7(14?), 3.7(14?)	13b, 14a, 14b	13b, 14a, 14b, 15a, 15b, 16a, 16b	13	2	14a, 14b
Hb	3.12	12.9(13a)	13a, 14a, 14b	13a, 14a, 14b, 15a, 15b, 16a, 16b	13	2, 3, 14	14b, 32
14 C	26.39				14a, 14b	13b, 16a	
Ha	2.40		13a, 13b, 14b, 15a, 15b	13a, 13b, 16a, 16b	14		13a, 14b, 15a, 29a
Hb	1.57		13a, 13b, 14a, 15a, 15b	13a, 13b, 15b, 16a, 16b	14		13a, 13b, 14a, 16b
15 C	27.45				15a, 15b		
Ha	1.48		14a, 14b, 15b, 16a, 16b	13a, 13b, 16a, 16b	15		14a, 16b, 18
Hb	1.40		14a, 14b, 15a, 16a, 16b	13a, 13b, 14b, 16a, 16b	15		16a, 18
16 C	56.59				16a, 16b	18, 26b	
Ha	2.37		15a, 15b, 16b	13a, 13b, 14a, 14b, 15a, 15b, 16b	16	14	15b, 16b, 18, 26b
Hb	1.98		15a, 15b, 16a	13a, 13b, 14a, 14b, 15a, 15b, 16a	16		14b, 15a, 16a, 26b
17 N							
18 C	57.38				18	26a, 29b	
H	2.67			25, 26a, 26b, 28	18	16, 19, 24, 26, 27, 28, 29, 33	15a, 15b, 16a, 20a, 20b, 29b, 33a, 33b, 34a
19 C	44.07					18, 20a, 20b, 23a, 25	
20 C	49.32				20a, 20b	29a	
Ha	3.32	12.5(20b)	20b	20b	20	19, 22, 24, 29	18, 20b, 29b, 30a
Hb	2.23	12.5(20a)	20a	20a	20	19, 29, 44	18, 20a, 24, 28, 43b, 44
21 N							
22 C	48.30				22a, 22b	20a, 44	
Ha	3.51		22b, 23a, 23b	22b, 23a, 23b, 24, 25	22		22b, 23a, 23b, 29b
Hb	3.08		22a, 23a, 23b	22a, 23a, 23b, 24	22		22a, 23b
23 C	25.32				23a, 23b	24	

Ha	1.59		22a, 22b, 24	22a, 22b, 23b	23	19	22a, 23b, 24, 25
Hb	1.12		22a, 22b, 24	22a, 22b, 23a	23		22a, 22b, 23a, 25, 28
24 C	41.46				24	18, 20a, 26a, 26b	
H	1.11		23a, 23b, 25	22a, 22b, 25, 28	24	23, 28, 29	20b, 23a, 25, 26a, 29a, 29b
25 C	37.45				25	26a, 26b, 28	
H	2.06	7.0(28)	24, 26a, 26b, 28	18, 22a, 24, 26a, 28	25	19, 27	23a, 23b, 24, 26a, 26b, 28
26 C	57.38				26a, 26b	18, 28	
Ha	3.03	9.0(26b)	25, 26b	18, 25, 28	26	18, 24, 25, 28	24, 25, 26b, 29a, 30a
Hb	1.71	9.0(26a)	25, 26a	18, 28	26	16, 24, 25	16a, 16b, 25, 26a, 28
27 C	143.28					18, 25, 33b	
28 C	122.77				28	18, 24, 26a, 33b	
H	5.78	7.0(25)	25	18, 24, 25, 26a, 26b	28	25, 26	20b, 23b, 25, 26b, 34a, 34b, 35a
29 C	36.57				29a, 29b	18, 20a, 20b, 24, 31	
Ha	2.28		29b, 30a, 30b	30a, 31, 32	29	20, 30, 31	14a, 24, 26a, 29b, 31
Hb	1.93		29a, 30a, 30b	30b, 31, 32	29	18, 30, 31	18, 20a, 22a, 24, 29a, 30a, 31
30 C	24.29				30a, 30b	29a, 29b, 31, 32	
Ha	2.79		29a, 29b, 31	29a, 30b, 32	30		20a, 26a, 29b, 30b, 31
Hb	1.93	8.7(31)	29a, 29b, 31	29b, 30a, 31, 32	30		30a, 31
31 C	137.03				31	29a, 29b	
H	6.06	8.7(30b), 11.0(32)	30a, 30b, 32	29a, 29b, 30b, 32	31	3, 29, 30	29a, 29b, 30a, 30b
32 C	125.11				32		
H	6.45	11.0(31), 2.5(?)	31	29a, 29b, 30a, 30b, 31	32	30	11b, 13b
33 C	36.63				33a, 33b	18	
Ha	1.66		33b, 34a, 34b	33b, 34a, 34b, 35a, 35b, 36	33		18, 33b, 34a, 34b
Hb	1.37		33a, 34a, 34b	33a, 34a, 34b, 35a, 35b, 36	33	27, 28	18, 33a, 36
34 C	25.84				34a, 34b		

Ha	1.45		33a, 33b, 34b, 35a, 35b	33a, 33b, 34b, 35a, 35b, 36	34		18, 28, 33a, 35a, 35b
Hb	1.27		33a, 33b, 34a	33a, 33b, 34a, 35b, 36	34		28, 33a
35 C	29.86				35a, 35b		
Ha	1.27		34a, 35b, 36	33a, 33b, 34a, 35b, 36	35		28, 34a, 36, 39a
Hb	1.16		34a, 35a, 36	33a, 33b, 34a, 34b, 35a, 36	35		34a, 36
36 C	19.17				36		
H2	2.00		35a, 35b	33a, 33b, 34a, 34b, 35a, 35b	36		33b, 35a, 35b
37 C	81.73						
38 C	80.84					39b	
39 C	18.65				39a, 39b		
Ha	2.14		39b, 40	39b, 40, 41, 42a, 42b, 43a, 43b, 44	39		35a, 40
Hb	2.06		39a, 40	39a, 40, 41, 43a, 43b, 44	39	38	40
40 C	27.81				40		
H2	1.29		39a, 39b, 41	39a, 39b, 41, 42a, 42b, 43a, 43b, 44	40		39a, 39b, 43a
41 C	27.73				41	42a, 42b, 43a, 43b	
H2	1.37		40, 42a, 42b	39a, 39b, 40, 42a, 42b, 43a, 43b, 44	41		42b, 43b
42 C	24.88				42a, 42b	43a, 43b	
Ha	1.21		41, 43a, 43b	39a, 40, 41, 42b, 44	42	41, 43, 44	
Hb	1.16		41, 43a, 43b	39a, 40, 41, 42a, 44	42	41, 43, 44	41, 43a, 43b
43 C	22.79				43a, 43b	42a, 42b, 44	
Ha	1.69		42a, 42b, 43b, 44	39a, 39b, 40, 41, 43b, 44	43	41, 42	40, 42b
Hb	1.64		42a, 42b, 43a, 44	39a, 39b, 40, 41, 43a, 44	43	41, 42	20b, 41, 42b
44 C	57.71				44	20b, 42a, 42b	
H2	3.14		43a, 43b	39a, 39b, 40, 41, 42a, 42b, 43a, 43b	44	22, 43	20b

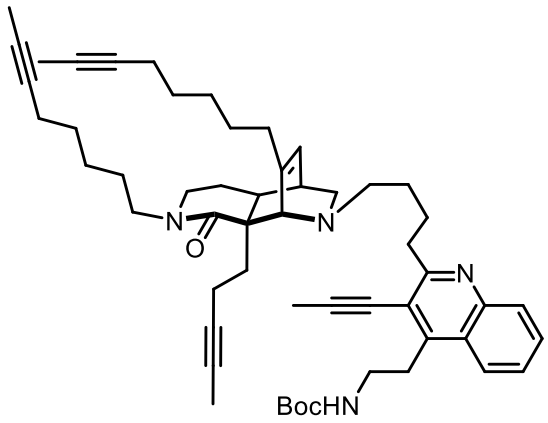
If compared to the original publication,[71] seven ^{13}C NMR signals were reassigned in the following way:

- peak at 29.86 ppm was originally assigned to C41 (29.7 ppm), is now assigned to **C35**
- peak at 19.17 ppm was originally assigned to C40 (18.9 ppm), is now assigned to **C36**
- peak at 81.73 ppm was originally assigned to C39 (81.5 ppm), is now assigned to **C37**
- peak at 18.65 ppm was originally assigned to C37 (18.4 ppm), is now assigned to **C39**

- peak at 27.81 ppm was originally assigned to C36 (27.6 ppm), is now assigned to **C40**
- peak at 24.88 ppm was originally assigned to C35 (24.6 ppm), is now assigned to **C42**

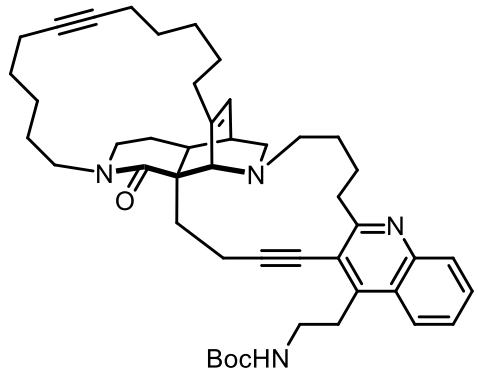
4.1.5 Concerted Macrocyclization Event

Compound 120. L-Selectride (1 M in THF, 1.5 mL, 1.5 mmol) was added to a solution of compound **114** (250 mg, 0.114 mmol) in THF (0.2 mL). The reaction was stirred at 40 °C for 12 h before it was quenched by cautious addition of MeOH (0.5 mL) at 0 °C. The resulting mixture was loaded onto an amino cartridge (pre-equilibrated with MeOH, H_2O, MeOH (volume of three column length each)) and then eluted with MeOH/H_2O (90:10) to provide a white solid.



HOAc (0.02 mL, 0.349 mmol) was added to a solution of this secondary amine and aldehyde **98** (320 mg, 0.841 mmol) in CH_2Cl_2 (1.2 mL) at ambient temperature. After stirring for 30 min at this temperature, $NaBH(OAc)_3$ (84 mg, 0.396 mmol) was added and stirring was continued for 3 h. The reaction was quenched with sat. aq. $NaHCO_3$ (0.5 mL). After removing the solvent under argon, the crude product was then subjected to preparative HPLC (Kromasil-5-C18, 5 μm, 150 mm × 30 mm, MeOH:H_2O = 95:5, 35 mL/min, λ = 254 nm, t = 4.2 min) to afford the title compound as a white solid (165 mg, 67%). $[\alpha]_D^{20} = -23.4°$ (c = 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.05 (d, *J* = 8.4 Hz, 1H), 8.00 (dd, *J* = 8.5, 1.3 Hz, 1H), 7.62 (ddd, *J* = 8.3, 6.9, 1.4 Hz, 1H), 7.49 (ddd, *J* = 8.3, 6.8, 1.3 Hz, 1H), 5.82 (dd, *J* = 6.5, 1.8 Hz, 1H), 4.72 (s, 1H), 3.49 (d, *J* = 2.9 Hz, 4H), 3.37 (d, *J* = 1.7 Hz, 1H), 3.31 (dt, *J* = 13.2, 7.2 Hz, 1H), 3.20–3.10 (m, 4H), 3.03 (ddd, *J* = 20.0, 7.8, 3.1 Hz, 2H), 2.49 (ddd, *J* = 11.5, 8.6, 7.0 Hz, 1H), 2.29–2.21 (m, 4H), 2.20–2.02 (m, 10H), 2.02–1.97 (m, 1H), 1.95–1.88 (m, 1H), 1.88–1.78 (m, 3H), 1.78–1.74 (m, 6H), 1.72–1.67 (m, 2H), 1.64 (dd, *J* = 5.8, 3.4 Hz, 6H), 1.48–1.40 (m, 14H), 1.39–1.28 (m, 6H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.8, 163.3, 156.0, 147.1, 146.1, 144.7, 129.5, 129.2, 126.2, 125.9, 123.8, 122.3, 117.7, 95.6, 79.8, 79.4, 79.2, 79.1, 76.1, 75.5, 75.3, 74.9, 62.5, 58.0, 55.6, 52.2, 47.7, 45.3, 44.2, 40.4, 39.1, 37.9, 35.0, 30.8, 29.7, 29.1, 28.8, 28.8, 28.7, 28.4, 27.0, 26.8, 26.2, 26.1, 18.7, 18.6, 14.7, 4.9, 3.5, 3.5 ppm; IR (film) $\tilde{\nu}$ = 3319, 2929, 2857, 1708, 1627, 1568, 1496, 1436, 1404, 1390, 1365, 1272, 1251, 1170, 1074, 1027, 957, 871, 759, 666, 593cm^{-1}; MS (ESI)*: m/z*: 825 [*M*+H$^+$], 847 [*M*+Na$^+$]; HRMS (ESI): *m/z:* calcd. for $C_{54}H_{73}N_4O_3$ [*M*+H$^+$]: 825.56772, found: 825.56785.

Compound 121. A flame-dried two-necked flask connected to a reflux condenser was charged



with activated 5 Å molecular sieves (powder, 400 mg) and toluene (11 mL). The suspension was purged with argon at room temperature for 30 min. Next, the mixture was stirred at 110 °C for 30 min before a solution of tetrayne **120** (20.0 mg, 0.024 mmol) in toluene (0.9 mL) was added. In a separate flame-dried Schlenk tube under argon, Mo-complex **51** (9.7 mg, 0.015 mmol) was dissolved in toluene (0.5 mL) and transferred via syringe into another Schlenk tube containing the trisilanol **52** (12.4 mg, 0.016 mmol). The resulting mixture was stirred for 30 s, before it was added dropwise to the suspension of the substrate and the molecular sieves in toluene at 110 °C. The mixture was stirred at 110 °C for 30 min, before the reaction was quenched by the addition of ethanol (1 mL). The mixture was cooled to room temperature and filtered through a plug of Celite, which was carefully rinsed with EtOAc. The combined filtrates were evaporated *in vacuo* and the residue purified by preparative HPLC (Kromasil-5-C18, 5 µm, 150 mm × 30 mm, MeOH, 35 mL/min, λ = 230 nm, major product, t = 4.8 min; minor product, t = 4.0 min) to afford the title compound **121** (6.1 mg, 35% yield) and an isomer (3.0 mg, 17% yield) as a white solid each. Analytical and spectral data of compound **121**: $[\alpha]_D^{20}$ = –7.3° (c = 0.31, $CHCl_3$); ^{1}H NMR (600 MHz, [D_4]-MeOH): δ = 8.18 (d, *J* = 8.4 Hz, 1H), 7.93 (d, *J* = 8.5 Hz, 1H), 7.69 (ddd, *J* = 8.3, 6.9, 1.3 Hz, 1H), 7.57 (t, *J* = 7.6 Hz, 1H), 5.94–5.85 (m, 1H), 3.95 (ddd, *J* = 13.1, 8.7, 5.9 Hz, 1H), 3.66 (d, *J* = 1.7 Hz, 1H), 3.55–3.48 (m, 1H), 3.49–3.40 (m, 3H), 3.37 (t, *J* = 7.2 Hz, 1H), 3.26 (t, *J* = 12.5 Hz, 1H), 3.22–3.17 (m, 1H), 2.99 (dd, *J* = 18.4, 4.5 Hz, 1H), 2.93 (dd, *J* = 9.5, 2.1 Hz, 1H), 2.84 (t, *J* = 11.9 Hz, 1H), 2.68 – 2.60 (m, 1H), 2.59–2.48 (m, 3H), 2.40–2.31 (m, 3H), 2.25–2.11 (m, 6H), 2.09–2.02 (m, 1H), 1.92 (ddd, *J* = 9.8, 6.8, 3.5 Hz, 1H), 1.79 (dd, *J* = 9.6, 2.6 Hz, 1H), 1.76–1.64 (m, 3H), 1.63–1.57 (m, 2H), 1.55–1.49 (m, 3H), 1.49–1.41 (m, 5H), 1.41–1.34 (m, 9H), 1.31–1.22 (m, 2H), 1.19–1.16 (m, 2H) ppm; ^{13}C NMR (126 MHz, [D_4]-MeOH): δ = 174.3, 165.6, 158.4, 149.1, 146.7, 146.0, 130.7, 129.0, 127.7, 127.2, 125.4, 122.4, 119.3, 103.8, 81.9, 80.4, 80.0, 76.6, 62.9, 56.3, 54.9, 53.5, 45.0, 41.2, 38.9, 38.6, 38.3, 36.7, 32.1, 31.4, 30.2, 28.9, 28.8, 28.8, 28.7, 28.4, 28.4, 26.3, 25.4, 19.6, 18.7, 14.0 ppm; IR (film) $\tilde{\nu}$ = 2930, 2850, 1705, 1634, 1423, 1159, 759 cm^{-1}; MS (ESI)*: m/z*: 717 [*M*+H$^+$]; HRMS (ESI): *m/z:* calcd. for $C_{46}H_{61}N_4O_3$ [*M*+H$^+$]: 717.47382, found: 717.47373.

4.2 Studies towards the Total Synthesis of Providencin

Unless stated otherwise, all reactions were carried out in flame-dried glassware using anhydrous solvents under an argon atmosphere. The following solvents were purified by distillation over the indicated drying agents and were transferred under an argon atmosphere: THF, Et_2O (Mg/anthracene); MeCN, 2,6-lutidine, CH_2Cl_2, DCE (CaH_2); toluene (Na/K alloy); MeOH (Mg; stored over MS 3 Å). DMSO, DMF, NEt_3, pentane and pyridine were dried by an adsorption solvent purification system based on molecular sieves. Molecular sieves (5 Å) were activated at 150 °C for 24 h in high vacuum (1×10^{-3} mbar) and stored under argon.

Thin layer chromatography (TLC): Macherey-Nagel precoated plates (POLYGRAM®SIL/UV254); detection was achieved under UV-Light (254 nm) and by staining with either acidic *p*-anisaldehyde, cerium ammonium molybdenate or basic $KMnO_4$ solution. Flash chromatography: Merck silica gel 60 (40–63 μm) with predistilled or HPLC grade solvents. Preparative LC was performed with an Agilent 1260 infinity prep system (fraction collector G7159 B + G7166A, diode array detector G7115A); stationary phase and conditions for each compound are specified below.

NMR: Spectra were recorded on Bruker AV 400, AV 500, AVIII 600 or AVneo 600 spectrometers in the solvents indicated; chemical shifts (δ) are given in ppm relative to TMS, coupling constants (*J*) in Hz. The solvent signals were used as references and the chemical shifts converted to the TMS scale ($CDCl_3$: δ_C = 77.00 ppm; residual $CHCl_3$ in $CDCl_3$: δ_H = 7.26 ppm; CD_2Cl_2: δ_C = 53.84 ppm; residual $CDHCl_2$ in CD_2Cl_2: δ_H = 5.32 ppm; CD_3OD: δ_C = 49.00 ppm, residual CD_2HOD in CD_3OD: δ_H = 3.31 ppm; $(CD_3)_2SO$: δC = 39.52 ppm, residual CD_2HSOCD_3 in $(CD_3)_2SO$: δ_H = 2.50 ppm); all spectra were recorded at 25 °C. Multiplicities are indicated by the following abbreviations: s: singlet, d: doublet, t: triplet, q: quartet, p: pentet, h: hextet, hept: heptet, m: multiplet, br: broad signal. ^{13}C NMR spectra were recorded in ^{1}H-decoupled manner and the values of the chemical shifts are rounded to one decimal point. Signal assignments were established using HSQC, HMBC, COSY, NOESY and other 2D experiments.

IR: Spectra were recorded on an Alpha Platinum ATR instrument (Bruker); wavenumbers ($\tilde{\nu}$) in cm^{-1}.

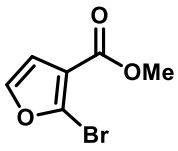
MS (ESI-MS): Finnigan MAT 8200 (70 eV), ESI-MS: ESQ3000 (Bruker), accurate mass determinations: Bruker APEX III FTMS (7 T magnet) or Mat 95 (Finnigan).

Optical rotations ($[\alpha]_D$) were measured with an A-Krüss Otronic Model P8000-t polarimeter at a wavelength of 589 nm.

Unless stated otherwise, all compounds were commercially available (Alfa Aesar, Aldrich, TCI, Strem Chemicals, ChemPUR) and used as received.

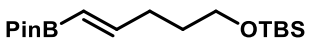
4.2.1 Towards the Total Synthesis of Providencin *via* Ring Closing Alkyne Metathesis

Methyl 2-bromofuran-3-carboxylate (198). An oven-dried 2 L jacketed vessel equipped with a dropping funnel was charged with 3-furoic acid (**192**) (19.73 g, 176 mmol) and THF (800 mL). The resulting solution was cooled to –78 °C before *n*-BuLi (1.6 M in hexanes, 231 mL, 370 mmol) was added dropwise over 2 h. Once the addition was complete, stirring was continued for another 2 h at –78 °C. Next, bromine (9.9 mL, 194 mmol) was added dropwise at this temperature and the resulting mixture was stirred for another 2 h. HCl (1 M, 100 mL) was added and the mixture warmed to rt. The resulting mixture was concentrated *in vacuo* until approximately 100 mL were left before it was diluted with additional HCl (1 M, 200 mL). The aqueous phase was extracted with EtOAc (3 x 350 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The resulting crude 2-bromo-3-carboxylic acid was used in the next step without further purification.



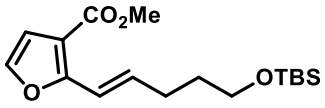
A 1 L round bottom flask equipped with a reflux condenser was charged with this crude material (27.5 g, 144 mmol) and DMF (440 mL). Potassium carbonate (60 g, 432 mmol) was added and the resulting mixture heated to 90 °C for 1.5 h. Next, iodomethane (17.9 mL, 288 mmol) was added and stirring continued for another 12 h at 90 °C. After reaching ambient temperature, water (200 mL) was added. The aqueous phase was extracted with Et_2O (3 x 400 mL) and the combined organic extracts were washed with water (200 mL), brine (100 mL) and dried over sodium sulfate. Concentration *in vacuo* furnished a residue, which was purified by flash chromatography on silica (pentane/*tert*-butyl methyl ether, 9:1) to give the title compound as a white solid (21.4 g, 59% yield over 2 steps). The spectral data are in accordance with the literature.[193] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43 (d, *J* = 2.2 Hz, 1H), 6.76 (d, *J* = 2.1 Hz, 1H), 3.86 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 162.3, 144.3, 129.0, 117.3, 112.7, 51.8. HRMS (EI): *m*/*z* calcd. for $C_6H_5O_3Br$ [M^+]: 203.9416, found: 203.9416.

Compound 199. Catecholborane (1.9 mL, 18 mmol) was added over 1 h to a stirred solution of *tert*-butyl(dimethyl)(pent-4-ynyloxy)silane[194] (3.0 g, 15 mmol) at room temperature. The resulting mixture was then stirred at 70 °C for 12 h before it was cooled to room temperature. Pinacol (2.5 g, 21 mmol) was added as a solid and the resulting mixture was vigorously stirred for 3 h at room temperature. The mixture was diluted with Et_2O (500 mL) and the organic phase washed with NaOH (1 M, 2 x 100 mL) and brine (100 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography on silica (pentane:Et_2O, 40:1), furnishing the title compound as a colorless oil (3.0 g, 61% yield). The spectral data are in accordance with the literature.[194] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.64 (dt, *J* = 17.9, 6.4 Hz, 1H), 5.44 (dt, *J* = 18.0, 1.6 Hz, 1H), 3.61 (t, *J* = 6.4 Hz, 2H), 2.20 (dtd, *J* = 9.4, 6.5, 1.6 Hz, 2H), 1.64 (ddt, *J* = 8.6, 7.5, 6.4 Hz, 2H), 1.26 (s, 12H), 0.88 (s, 9H), 0.03 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ =

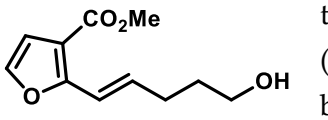


154.2, 83.0, 62.6, 32.1, 31.3, 25.9, 24.8, 18.3, –5.3. HRMS (ESI): *m*/*z* calcd. for $C_{17}H_{36}O_3BSi$ [M+H$^+$]: 327.2521, found: 327.2517.

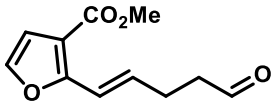
Compound 203. 1,4-Dioxane (11 mL) and degassed water (1 mL) were added to a flask charged with methyl 2-bromofuran-3-carboxylate **198** (1.6 g, 7.8 mmol), boronate **199** (2.8 g, 8.6 mmol), Pd(dppf)Cl_2 (285 mg, 0.39 mmol, 0.05 eq.) and Cs_2CO_3 (5.6 g, 17.2 mmol). The resulting mixture was stirred at 85 °C for 2 h before it was cooled to room temperature. The mixture was diluted with water (30 mL) and the aqueous phase extracted with Et_2O (3 x 100 mL). The combined extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography on silica (hexane:MTBE, 20:1) to give the title compound as a colorless oil (2.3 g, 91% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23 (d, *J* = 2.0 Hz, 1H), 6.95 (dt, *J* = 16.0, 1.5 Hz, 1H), 6.67 (d, *J* = 2.0 Hz, 1H), 6.52 (dt, *J* = 16.0, 7.1 Hz, 1H), 3.83 (s, 3H), 3.66 (t, *J* = 6.3 Hz, 2H), 2.38 – 2.27 (m, 2H), 1.76 – 1.65 (m, 2H), 0.90 (s, 9H), 0.05 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.1, 157.0, 140.7, 135.9, 117.9, 112.2, 111.4, 62.4, 51.4, 32.1, 29.5, 25.9, 18.3, –5.3. IR (film): $\tilde{\nu}$ = 2952, 2930, 2857, 2887, 1719, 1653, 1569, 1509, 1471, 1463, 1439, 1409, 1388, 1361, 1301, 1257, 1197, 1164, 1139, 1098, 1054, 1034, 1006, 971, 940, 893, 836, 812, 776, 740, 662 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{17}H_{28}O_4NaSi$ [M+Na$^+$]: 347.1649, found: 347.1649.



Compound S8. Tetrabutylammonium fluoride (1 M in THF, 14.0 mL, 14.0 mmol) was added to a stirred solution of silyl ether **203** (2.28 g, 7.03 mmol) in THF (17 mL) at 0 °C. The mixture was stirred at room temperature for 1 h before the reaction was quenched with sat. aq. NH_4Cl (15 mL). The aqueous phase was extracted with EtOAc (3 x 100 mL), the combined extracts were dried over Na_2SO_4 and concentrated, and the residue was purified by flash chromatography on silica (hexanes:EtOAc, 1:1) to give the title compound as a yellow oil (1.28 g, 87% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.24 (d, *J* = 2.0 Hz, 1H), 7.01 – 6.95 (m, 1H), 6.67 (d, *J* = 2.0 Hz, 1H), 6.52 (dt, *J* = 16.0, 7.2 Hz, 1H), 3.83 (s, 3H), 3.71 (t, *J* = 6.5 Hz, 2H), 2.36 (qd, *J* = 7.3, 1.6 Hz, 2H), 1.82 – 1.72 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.1, 156.8, 140.8, 135.3, 118.2, 112.4, 111.4, 62.3, 51.5, 31.9, 29.4. IR (film): $\tilde{\nu}$ = 2952, 2931, 2889, 2857, 1823, 1779, 1718, 1654, 1603, 1569, 1509, 1462, 1440, 1409, 1379, 1361, 1304, 1257, 1199, 1164, 1138, 1098, 1054, 1034, 972, 940, 893, 837, 813, 777, 753 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{11}H_{14}O_4Na$ [M+Na$^+$]: 233.0784, found: 233.0786.

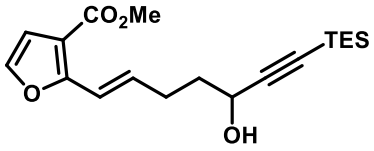


Compound 213. Sulfur trioxide pyridine complex (2.9 g, 18.1 mmol) was added to a solution of anhydrous Et_3N (4.2 mL, 30.2 mmol), alcohol **S8** (1.27 g, 6.0 mg) and DMSO (3.0 mL, 42 mmol) in CH_2Cl_2 (3 mL) at 0 °C. The mixture was stirred for 30 min, before sat. aq. $NaHCO_3$ (20 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3 x 80 mL), and the combined organic phases were dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (pentane:MTBE, 3:1) to afford the title compound as a colorless oil (1.18 g, 94%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.83 (t, *J* = 1.3



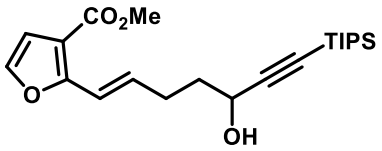
Hz, 1H), 7.24 (d, *J* = 2.0 Hz, 1H), 6.99 (dt, *J* = 16.1, 1.5 Hz, 1H), 6.67 (d, *J* = 2.0 Hz, 1H), 6.49 (dt, *J* = 16.0, 6.7 Hz, 1H), 3.84 (s, 3H), 2.69 – 2.63 (m, 2H), 2.63 – 2.56 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 201.2, 164.0, 156.3, 141.1, 133.1, 118.8, 112.9, 111.5, 51.5, 42.9, 25.4. HRMS (ESI): *m/z:* calcd. for $C_{11}H_{12}O_4Na$ [*M*+Na$^+$]: 231.0628, found: 231.0629.

Compound *rac*-**214.** Aldehyde **213** (156 mg, 0.75 mmol) was slowly added to a solution of



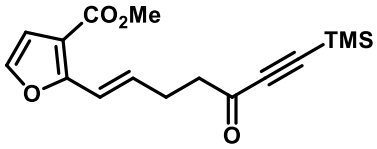
triethylsilylacetylene (0.12 mL, 0.68 mmol) and *n*-BuLi (1.6 M in hexanes, 0.45 mL) in THF (3.5 mL) at –78 °C. The mixture was allowed to warm to room temperature, quenched with sat. aq. NH_4Cl (5 mL) and diluted with water (3 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL), the combined extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography on silica (hexanes:MTBE, 5:1), furnishing the title compound as a colorless oil (243 mg, quant.). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.24 (d, *J* = 1.9 Hz, 1H), 6.98 (dt, *J* = 16.0, 1.6 Hz, 1H), 6.68 (d, *J* = 1.9 Hz, 1H), 6.52 (dt, *J* = 16.0, 7.2 Hz, 1H), 4.45 (t, *J* = 6.5 Hz, 1H), 3.83 (s, 3H), 2.46 (qd, *J* = 7.4, 1.6 Hz, 2H), 1.98 – 1.83 (m, 2H), 0.99 (t, *J* = 7.9 Hz, 9H), 0.60 (q, *J* = 7.8 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.0, 156.7, 140.8, 134.8, 118.4, 112.5, 111.4, 107.5, 87.3, 62.3, 51.4, 36.9, 28.7, 7.4, 4.2. IR (film): $\tilde{\nu}$ = 3427, 2954, 2912, 2875, 1718, 1652, 1568, 1509, 1441, 1412, 1380, 1303, 1263, 1236, 1198, 1161, 1139, 1105, 1053, 1034, 1017,972, 892, 736, 599 cm^{-1}. HRMS (ESI): *m/z* calcd. for $C_{19}H_{28}O_4SiNa$ [M+Na$^+$]: 371.1649, found: 371.1654.

Compound *rac*-**215.** Aldehyde **213** (156 mg, 0.75 mmol) was slowly added to a solution of



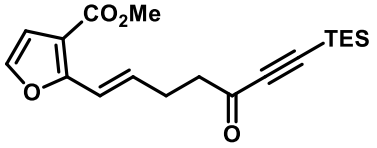
triisopropylsilylacetylene (0.15 mL, 0.68 mmol) and *n*-BuLi (1.6 M in hexanes, 0.45 mL) in THF (3.5 mL) at –78 °C. The mixture was allowed to warm to room temperature, quenched with sat. aq. NH_4Cl (5 mL) and diluted with water (3 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL), the combined extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography on silica (hexanes:MTBE, 5:1), furnishing the title compound as a colorless oil (282 mg, quant.). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, *J* = 2.0 Hz, 1H), 6.98 (dt, *J* = 16.0, 1.5 Hz, 1H), 6.68 (d, *J* = 2.0 Hz, 1H), 6.52 (dt, *J* = 16.0, 7.2 Hz, 1H), 4.46 (t, *J* = 6.4 Hz, 1H), 3.83 (s, 3H), 2.47 (qd, *J* = 7.6, 1.6 Hz, 2H), 1.99 – 1.84 (m, 2H), 1.07 (d, *J* = 2.1 Hz, 21H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.0, 156.6, 140.9, 134.8, 118.4, 112.5, 111.5, 108.3, 86.1, 62.3, 51.4, 37.08, 28.8, 18.6, 11.1. IR (film): $\tilde{\nu}$ = 3428, 2943, 2891, 2864, 1718, 1653, 1568, 1509, 1462, 1441, 1410, 1384, 1366, 1303, 1263, 1198, 1159, 1139, 1105, 1053, 1034, 1016, 998, 971, 942, 919, 883, 782, 739, 677, 576, 599 cm^{-1}. HRMS (ESI): *m*/z calcd. for $C_{22}H_{34}O_4SiNa$ [M+Na$^+$]: 413.2118, found: 413.2118.

Compound 216 (*via rac*-**204**). PCC (186 mg, 0.86 mmol) was added to a mixture of alcohol *rac*-



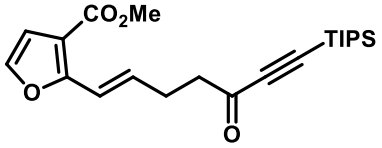
204 (132 mg, 0.43 mmol) and silica (200 mg) in CH_2Cl_2 (3 mL) at room temperature. The mixture was stirred for 4 h, before it was filtered through a pad of Celite and subsequently concentrated *in vacuo*. The residue was purified by flash chromatography on silica (pentane:Et_2O, 9:1), furnishing the title compound as a colorless oil (77 mg, 59% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.24 (d, *J* = 2.0 Hz, 1H), 6.98 (dt, *J* = 16.0, 1.6 Hz, 1H), 6.67 (d, *J* = 2.0 Hz, 1H), 6.47 (dt, *J* = 16.0, 6.9 Hz, 1H), 3.83 (s, 3H), 2.80 – 2.73 (m, 2H), 2.65 – 2.57 (m, 2H), 0.24 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 186.3, 164.0, 156.4, 141.0, 133.0, 118.8, 112.8, 111.4, 101.7, 98.5, 51.5, 44.2, 27.1, -0.8. IR (film): $\tilde{\nu}$ = 2956, 1715, 1675, 1569, 1508, 1439, 1409, 1303, 1252, 1197, 1163, 1137, 1113, 1081, 1047, 1033, 972, 940, 844, 760, 705, 599 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{16}H_{20}O_4SiNa$ [M+Na$^+$]: 327.1023, found: 327.1024.

Compound 217. PCC (280 mg, 1.30 mmol) was added to a mixture of alcohol rac-**214** (227 mg,



0.65 mmol) and silica (300 mg) in CH_2Cl_2 (5 mL) at room temperature. The mixture was stirred for 4 h, before it was filtered through a pad of Celite and subsequently concentrated *in vacuo*. The residue was purified by flash chromatography on silica (pentane:Et_2O, 9:1), furnishing the title compound as a colorless oil (170 mg, 75% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23 (d, *J* = 2.0 Hz, 1H), 6.98 (dt, *J* = 16.0, 1.6 Hz, 1H), 6.67 (d, *J* = 1.9 Hz, 1H), 6.47 (dt, *J* = 16.0, 7.0 Hz, 1H), 3.83 (s, 3H), 2.81 – 2.74 (m, 2H), 2.66 – 2.58 (m, 2H), 1.01 (t, *J* = 7.9 Hz, 9H), 0.67 (q, *J* = 7.9, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 186.3, 164.0, 156.4, 141.0, 133.1, 118.8, 112.8, 111.4, 103.0, 96.8, 51.4, 44.5, 27.2, 7.3, 3.8. IR (film): $\tilde{\nu}$ = 2956, 2912, 2876, 1716, 1675, 1569, 1508, 1439, 1410, 1302, 1263, 1196, 1162, 1137, 1110, 1081, 1047, 1032, 1018, 971, 941, 893, 868, 814, 798, 779, 727, 677, 599, 566 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{19}H_{27}O_4Si$ [M+H$^+$]: 347.1673, found: 347.1675.

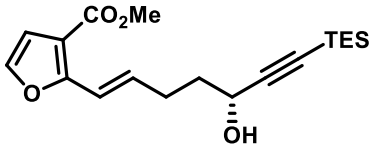
Compound 218. PCC (289 mg, 1.34 mmol) was added to a mixture of alcohol *rac*-**215** (262 mg,



0.67 mmol) and silica (300 mg) in CH_2Cl_2 (5 mL) at room temperature. The mixture was stirred for 4 h, before it was filtered through a pad of Celite and subsequently concentrated *in vacuo*. The residue was purified by flash chromatography on silica (pentane:Et_2O, 9:1), furnishing the title compound as a colorless oil (187 mg, 72% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23 (d, *J* = 2.0 Hz, 1H), 6.98 (dt, *J* = 16.0, 1.6 Hz, 1H), 6.67 (d, *J* = 2.0 Hz, 1H), 6.48 (dt, *J* = 16.0, 7.0 Hz, 1H), 3.83 (s, 3H), 2.81 – 2.74 (m, 2H), 2.67 – 2.59 (m, 2H), 1.10 (d, *J* = 4.2 Hz, 21H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 186.2, 163.9, 156.3, 141.0, 133.1, 118.9, 112.8, 111.5, 103.9, 96.3, 51.4, 44.7, 27.3, 18.4, 10.9. IR (film): $\tilde{\nu}$ = 2945, 2893, 2866, 1718, 1677, 1569, 1508, 1462, 1439, 1409, 1385, 1366, 1303, 1263, 1197, 1164, 1137, 1111, 1072, 1047, 1033, 997, 972, 941, 921, 882, 814, 797, 780, 745, 679, 599, 583 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{22}H_{33}O_4Si$ [M+H$^+$]: 389.2143, found: 389.2142.

Methyl (*R*,*E*)-2-(5-hydroxy-7-(triethylsilyl)hept-1-en-6-yn-1-yl)furan-3-carboxylate (214).



Ru(*p*-cymene)[(*R*,*R*)-Ts-DPEN] (*R*,*R*-**219**) (0.7 mg, 0.001 mmol, 0.01 eq.) was added to *i*-PrOH (0.7 mL) and the mixture vigorously stirred until a faint orange solution had formed. A solution of ynone **217** (40 mg, 0.12 mmol) in *i*-PrOH (0.1 mL) was added dropwise, causing a color change to bright pink. The mixture was stirred for 1 h at room temperature before it was concentrated *in vacuo*. The residue was purified by flash chromatography on silica (pentane:*tert*-butyl methyl ether, 4:1) to afford the title compound as a colorless oil (40 mg, quant., 97% ee). Spectral data matched the racemic sample *rac*-**214**.

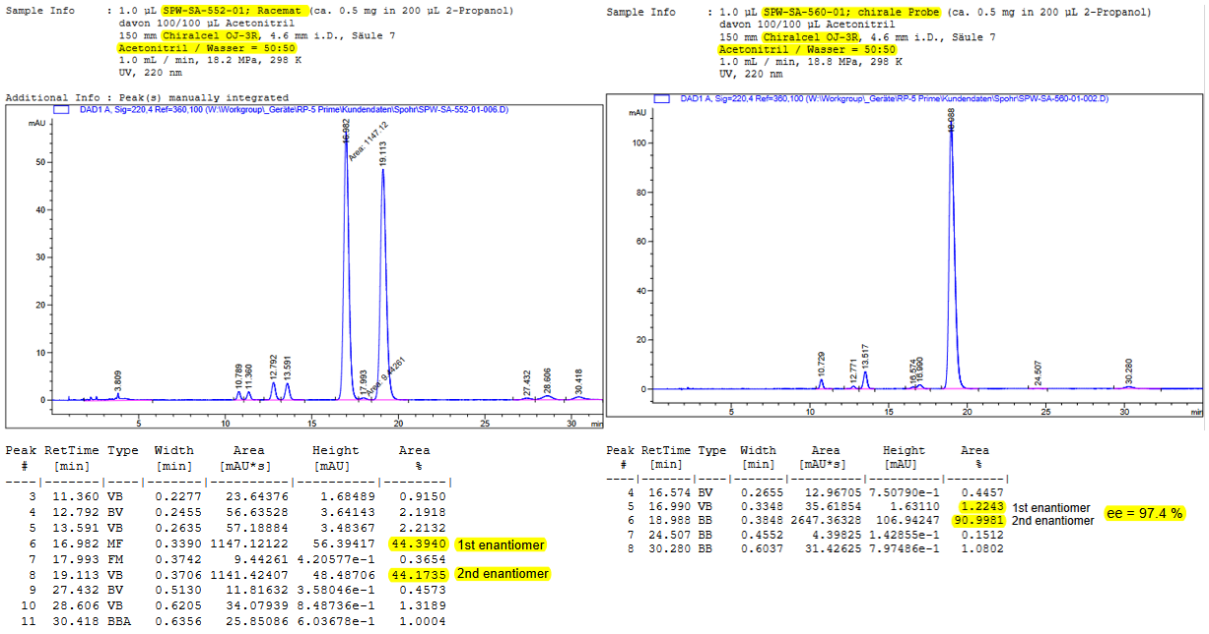
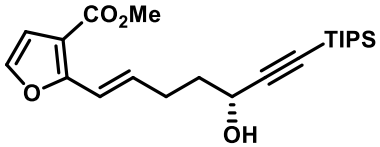


Figure 4.4. HPLC-traces of *rac*-**214** (left) and enantioenriched **214** (right): t_R = 16.99 min (minor enantiomer) and 18.99 min (major enantiomer) (Chiralcel OJ-3R column, λ = 220 nm, isocratic elution 50:50 acetonitrile/water, flow-rate = 1.0 mL/min).

Methyl (*R*,*E*)-2-(5-hydroxy-7-(triisopropylsilyl)hept-1-en-6-yn-1-yl)furan-3-carboxylate (215).



Ru(*p*-cymene)[(*R*,*R*)-Ts-DPEN] (*R*,*R*-**219**) (0.7 mg, 0.001 mmol, 0.01 eq.) was added to *i*-PrOH (0.7 mL) and the mixture vigorously stirred until a faint orange solution had formed. A solution of ynone **218** (45 mg, 0.12 mmol) in *i*-PrOH (0.1 mL) was added dropwise, causing a color change to bright pink. The mixture was stirred for 1 h at room temperature before it was concentrated *in vacuo*. The residue was purified by flash chromatography on silica (pentane:*tert*-butyl methyl ether, 4:1) to afford the title compound as a colorless oil (43 mg, 97% yield, 98% ee). Spectral data matched the racemic sample *rac*-**215**.

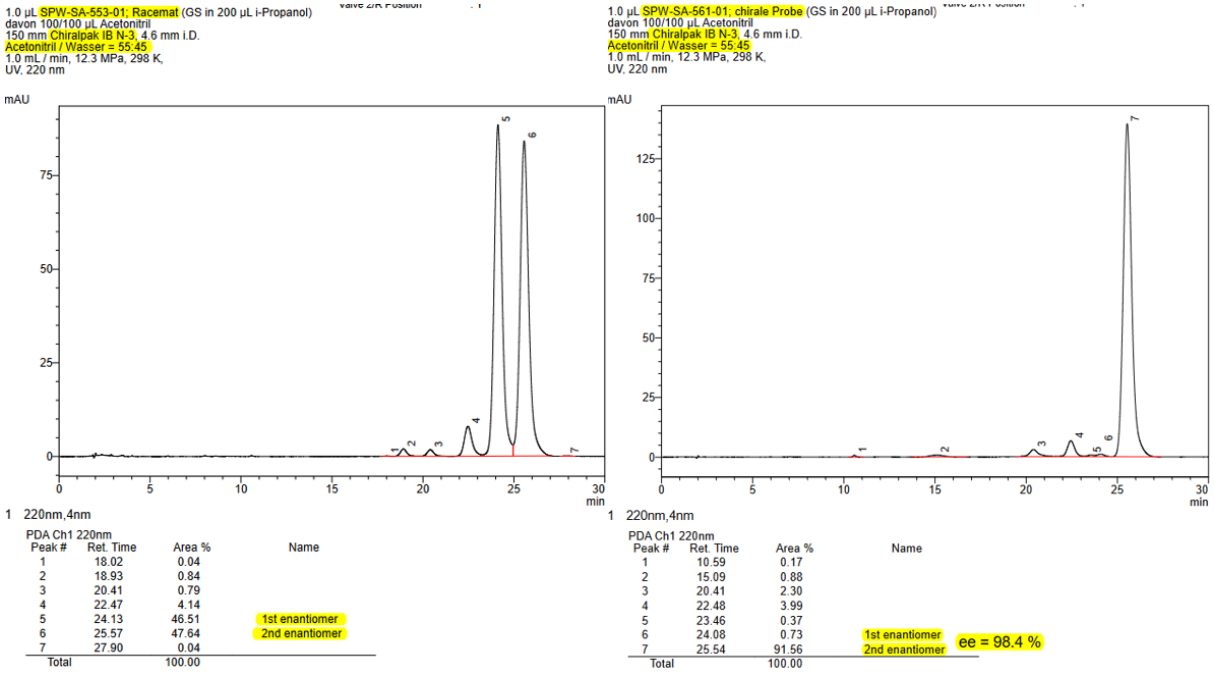
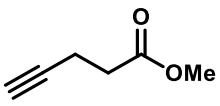


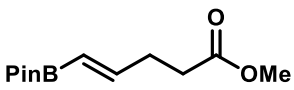
Figure 4.5. HPLC-traces of *rac*-**215** (left) and enantioenriched **215** (right): t_R = 24.08 min (minor enantiomer) and 25.54 min (major enantiomer) (Chiralcel IB-N3 column, λ = 220 nm, isocratic elution 55:45 acetonitrile/water, flow-rate = 1.0 mL/min).

Methyl pent-4-ynoate (S9). Thionyl chloride (21.3 mL, 293 mmol) was added over 30 min to a



stirred solution of pent-4-ynoic acid (**217**) (25 g, 255 mmol) in methanol (200 mL) at 0 °C. The resulting mixture was stirred for 2 h at room temperature before it was concentrated. The residue was dissolved in CH_2Cl_2 (300 mL) and the solution was successively washed with water (50 mL), sat. aq. $NaHCO_3$ (50 mL) and water (50 mL). The organic phase was dried over $MgSO_4$ and concentrated *in vacuo* (heating: 40 °C, pressure: > 250 mbar) to provide the title compound as a brown oil (22.7 g, 79% yield). The spectral data are in accordance with the literature.[228] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.70 (s, 3H), 2.61 – 2.53 (m, 2H), 2.53 – 2.47 (m, 2H), 1.97 (t, *J* = 2.5 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.2, 82.4, 69.0, 51.8, 33.1, 14.3.

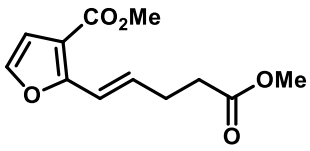
Methyl (*E*)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pent-4-enoate (216).



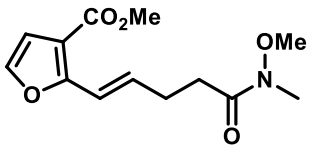
Catecholborane (17.8 mL, 167 mmol) was added over 1 h to a stirred solution of methyl pent-4-ynoate **S9** (15.6 g, 139 mmol) at room temperature. The resulting mixture was then stirred at 70 °C for 12 h before it was cooled to room temperature. Pinacol (23.0 g, 195 mmol) was added as a solid and the resulting mixture was vigorously stirred for 3 h at room temperature. The mixture was diluted with Et_2O (500 mL) and the organic phase washed with NaOH (1 M, 2 x 100 mL) and brine (100 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography on silica (pentane:Et_2O, 40:1), furnishing the title compound as a colorless oil (11.4 g, 34% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.61 (dt, *J*

= 18.0, 5.8 Hz, 1H), 5.46 (dt, *J* = 18.0, 1.6 Hz, 1H), 3.67 (s, 3H), 2.52 – 2.41 (m, 4H), 1.26 (s, 12H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 173.3, 151.6, 83.1, 51.6, 32.5, 30.5, 24.8; IR (film): $\tilde{\nu}$ = 2979, 1740, 1640, 1438, 1398, 1362, 1322, 1268, 1212, 1165, 1144, 1112, 1004, 971, 896, 850 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{12}H_{21}O_4B$ [M$^+$]: 240.1527, found: 240.1529.

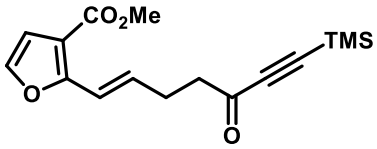
Methyl (*E*)-2-(5-methoxy-5-oxopent-1-en-1-yl)furan-3-carboxylate (218). 1,4-Dioxane (85 mL) and degassed water (8.5 mL) were added to a flask charged with methyl 2-bromofuran-3-carboxylate **198** (12.15 g, 59.25 mmol), boronate **216** (15.65 g, 65.18 mmol), $Pd(dppf)Cl_2$ (2.17 g, 2.96 mmol, 0.05 eq.) and Cs_2CO_3 (42.47 g, 130.36 mmol). The resulting mixture was stirred at 85 °C for 4 h before it was cooled to room temperature. The mixture was diluted with water (100 mL) and the aqueous phase extracted with Et_2O (3 x 250 mL). The combined extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography on silica (pentane:Et_2O, 4.5:1) to give the title compound as a colorless oil (12.70 g, 90% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.24 (d, *J* = 2.0 Hz, 1H), 6.99 (dt, *J* = 16.1, 1.6 Hz, 1H), 6.67 (d, *J* = 2.0 Hz, 1H), 6.48 (dt, *J* = 16.0, 6.8 Hz, 1H), 3.83 (s, 3H), 3.70 (s, 3H), 2.63 – 2.55 (m, 2H), 2.51 (ddd, *J* = 8.6, 6.5, 1.7 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 173.1, 164.0, 156.4, 141.0, 133.4, 118.7, 112.8, 111.5, 51.7, 51.5, 33.3, 28.2; IR (film): $\tilde{\nu}$ = 2953, 1735, 1713, 1655, 1569, 1508, 1437, 1410, 1364, 1303, 1260, 1195, 1156, 1093, 1050, 1032, 971, 941, 893, 846, 808, 780, 746, 600, 564 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{12}H_{14}O_5$ [M$^+$]: 238.0835, found: 238.0836.



Methyl (*E*)-2-(5-(methoxy(methyl)amino)-5-oxopent-1-en-1-yl)furan-3-carboxylate (S10). *N*,*O*-Dimethylhydroxylamine hydrochloride (6.24 g, 63.97 mmol) was added to stirred solution of ester **218** (12.70 g, 53.31 mmol) in THF (450 mL). The resulting mixture was cooled to –78 °C before *i*-PrMgCl (2 M in THF, 64 mL, 127.94 mmol) was added dropwise over the course of 1 h. The mixture was warmed to –50 °C and stirred at this temperature for 30 min before the reaction was quenched with sat. aq. NH_4Cl (150 mL). After reaching room temperature, the aqueous layer was extracted with Et_2O (3 x 250 mL) and the combined extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography on silica (pentane:Et_2O, 1:2) to give the title compound as a pale yellow oil (11.09 g, 78% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23 (d, *J* = 1.9 Hz, 1H), 6.99 (dt, *J* = 16.0, 1.4 Hz, 1H), 6.67 (d, *J* = 2.0 Hz, 1H), 6.60 – 6.50 (m, 1H), 3.83 (s, 3H), 3.69 (s, 3H), 3.19 (s, 3H), 2.66 – 2.56 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.0, 156.7, 140.9, 134.5, 118.4, 112.6, 111.4, 61.3, 51.4, 32.2, 31.2, 30.3, 27.9; IR (film): $\tilde{\nu}$ = 2952, 1715, 1660, 1569, 1509, 1440, 1413, 1386, 1305, 1264, 1198, 1162, 1138, 1049, 1033, 994, 973, 747 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{13}H_{18}O_5N$ [M+H$^+$]: 268.1179, found: 268.1181.

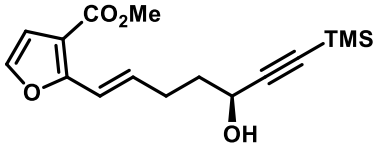


Methyl (*E*)-2-(5-oxo-7-(trimethylsilyl)hept-1-en-6-yn-1-yl)furan-3-carboxylate (216). EtMgCl



(2 M in THF, 22.4 mL, 44.8 mmol) was added dropwise to a stirred solution of trimethylsilylacetylene (6.3 mL, 44.8 mmol) in THF (200 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 1 h and at room temperature for 30 min. The mixture was then cooled to 0 °C and added to a solution of Weinreb amide **S10** (10.89 g, 40.74 mmol) in THF (50 mL) at 0 °C via cannula. After stirring at 0 °C for 5 min and at room temperature for 1 h, the reaction was quenched with sat. aq. NH_4Cl (100 mL). The aqueous phase was extracted with Et_2O (3 x 250 mL), the combined extracts were washed with brine (100 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography on silica (pentane:Et_2O, 9:1), furnishing the title compound as a colorless oil (9.48 g, 76% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.24 (d, *J* = 2.0 Hz, 1H), 6.98 (dt, *J* = 16.0, 1.6 Hz, 1H), 6.67 (d, *J* = 2.0 Hz, 1H), 6.47 (dt, *J* = 16.0, 6.9 Hz, 1H), 3.83 (s, 3H), 2.77 (td, *J* = 7.2, 0.8 Hz, 2H), 2.65 – 2.57 (m, 2H), 0.24 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 186.3, 164.0, 156.4, 141.0, 133.1, 118.8, 112.8, 111.4, 101.8, 98.5, 51.5, 44.2, 27.1, –0.8; IR (film): $\tilde{\nu}$ = 2956, 1715, 1675, 1569, 1508, 1439, 1409, 1303, 1252, 1197, 1163, 1137, 1113, 1081, 1047, 1033, 972, 940, 844, 760, 705, 599 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{16}H_{20}O_4SiNa$ [M+Na$^+$]: 327.1023, found: 327.1024.

Methyl (*S*,*E*)-2-(5-hydroxy-7-(trimethylsilyl)hept-1-en-6-yn-1-yl)furan-3-carboxylate (*S*-204).



Ru(*p*-cymene)[(*S*,*S*)-Ts-DPEN] (*S*,*S*-**219**) (187 mg, 0.31 mmol, 0.01 eq.) was added to *i*-PrOH (200 mL) and the mixture vigorously stirred until a faint orange solution had formed. A solution of ynone **216** (9.48 g, 31.14 mmol) in *i*-PrOH (20 mL) was added dropwise, causing a color change to bright pink. The mixture was stirred for 1 h at room temperature before it was concentrated *in vacuo*. The residue was purified by flash chromatography on silica (pentane:*tert*-butyl methyl ether, 4:1) to afford the title compound as a colorless oil (9.39 g, 99% yield, 99% ee). $[\alpha]_D^{20}$ = +34.8° (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): = 7.28 – 7.20 (m, 1H), 7.03 – 6.94 (m, 1H), 6.69 – 6.64 (m, 1H), 6.58 – 6.45 (m, 1H), 4.46 – 4.38 (m, 1H), 3.85 – 3.81 (m, 2H), 2.49 – 2.39 (m, 2H), 1.93 – 1.84 (m, 2H), 1.79 – 1.71 (m, 1H), 0.20 – 0.15 (m, 9H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.1, 156.7, 140.9, 134.7, 118.4, 112.5, 111.4, 106.2, 90.0, 62.2, 51.5, 36.7, 28.7, –0.2; IR (film): $\tilde{\nu}$ = 3427, 2954, 1717, 1653, 1568, 1509, 1441, 1410, 1304, 1250, 1198, 1161, 1139, 1105, 1053, 1035, 971, 942, 892, 843, 760 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{16}H_{22}O_4SiNa$ [M+Na$^+$]: 329.1179, found: 329.1183.

The racemic sample *rac*-**204** was prepared by the following procedure: Aldehyde **213** (1.18 g, 5.7 mmol) was slowly added to a solution of trimethylsilylacetylene (0.73 mL, 5.16 mmol) and *n*-BuLi (1.6 M in hexanes, 3.3 mL) in THF (26 mL) at –78 °C. The mixture was allowed to warm to room temperature and subsequently quenched with sat. aq. NH_4Cl (20 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 80 mL), the combined extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography on silica

(hexanes:MTBE, 3:1), furnishing the title compound as a colorless oil (1.4 g, 89% yield). Spectral data matched with the enantioenriched sample *(S)*-**204** above.

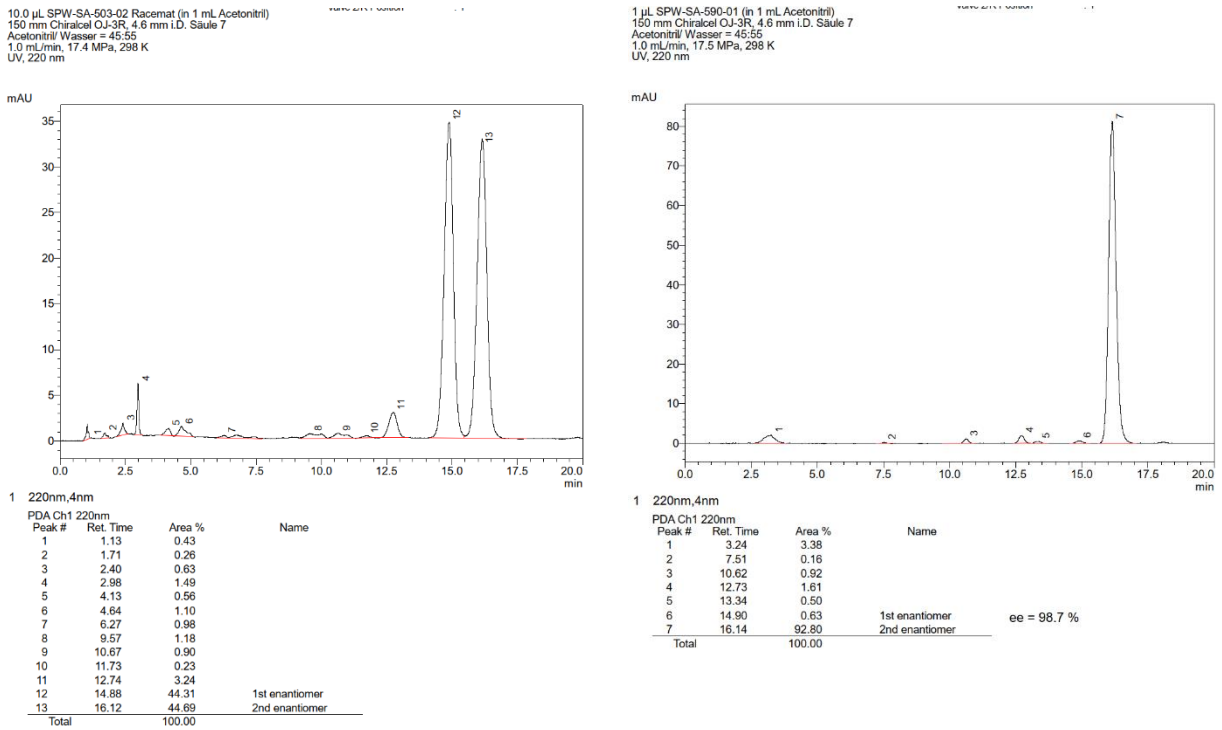
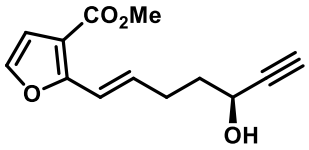
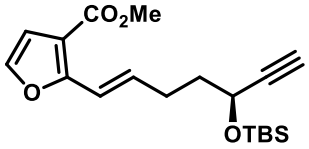


Figure 4.6. HPLC-traces of *rac*-**204** (left) and enantioenriched *(S)*-**204** (right): t_R = 14.90 min (minor enantiomer) and 16.14 min (major enantiomer) (Chiralcel OJ-3R column, λ = 220 nm, isocratic elution 45:55 acetonitrile/water, flow-rate = 1.0 mL/min)

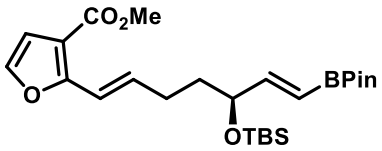
Methyl (*S*,*E*)-2-(5-hydroxyhept-1-en-6-yn-1-yl)furan-3-carboxylate (219). Potassium carbonate (12.7 g, 91.88 mmol) was added to a stirred solution of alcohol *(S)*-**204** (9.39 g, 30.66 mmol) in methanol (136 mL) and the resulting yellow mixture was stirred for 30 min at room temperature. The reaction was quenched upon addition of sat. aq. NH_4Cl (50 mL) and water (80 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 200 mL) and the combined extracts were dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography on silica (hexanes:*tert*-butyl methyl ether, 2:1), providing the title compound as a colorless oil (7.01 g, 98% yield). $[\alpha]_D^{20}$ = +21.9° (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.24 (d, *J* = 2.0 Hz, 1H), 7.03 – 6.96 (m, 1H), 6.67 (d, *J* = 2.0 Hz, 1H), 6.50 (dt, *J* = 16.0, 7.1 Hz, 1H), 4.44 (td, *J* = 6.5, 2.1 Hz, 1H), 3.83 (s, 3H), 2.50 (d, *J* = 2.1 Hz, 1H), 2.46 (qd, *J* = 7.1, 1.3 Hz, 2H), 1.98 (br s, 1H), 1.95 – 1.87 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.1, 156.7, 140.9, 134.5, 118.6, 112.5, 111.4, 84.4, 73.4, 61.6, 51.5, 36.6, 28.5; IR (film): $\tilde{\nu}$ = 3436, 3292, 2952, 1710, 1652, 1568, 1509, 1440, 1409, 1304, 1263, 1199, 1160, 1137, 1103, 1051, 1033, 971, 939, 892, 747, 661, 600, 569 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{13}H_{14}O_4Na$ [M+Na$^+$]: 257.0784, found: 257.0786.



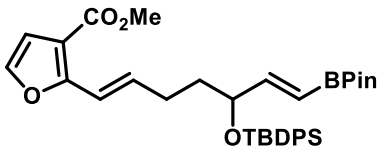
Methyl (*S*,*E*)-2-(5-((*tert*-butyldimethylsilyl)oxy)hept-1-en-6-yn-1-yl)furan-3-carboxylate (220). 

Imidazole (2.24 g, 32.87 mmol) and *tert*-butyldimethylsilyl chloride (4.95 g, 32.87 mmol) were added to a stirred solution of alcohol **219** (7.00 g, 29.88 mmol) in CH_2Cl_2 (80 mL), and the resulting mixture was stirred for 16 h at room temperature. The reaction was quenched with sat. aq. $NaHCO_3$ (40 mL) and the aqueous phase was extracted with CH_2Cl_2 (3 x 150 mL). The combined extracts were dried over Na_2SO_4 and concentrated, and the residue was purified by flash chromatography on silica (pentane:*tert*-butyl methyl ether, 9:1) to afford the title compound as a colorless oil (10.13 g, 97% yield). $[\alpha]_D^{20}$ = –13.1° (c = 2.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.24 (d, *J* = 2.0 Hz, 1H), 6.97 (dt, *J* = 16.0, 1.5 Hz, 1H), 6.67 (d, *J* = 2.0 Hz, 1H), 6.51 (dt, *J* = 16.0, 7.1 Hz, 1H), 4.41 (td, *J* = 6.2, 2.1 Hz, 1H), 3.84 (s, 3H), 2.46 – 2.38 (m, 3H), 1.91 – 1.83 (m, 2H), 0.91 (s, 9H), 0.13 (d, *J* = 11.2 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.1, 156.8, 140.8, 135.1, 118.2, 112.4, 111.4, 85.2, 72.5, 62.1, 51.4, 37.7, 28.6, 25.8, 18.2, –4.6, –5.1; IR (film): $\tilde{\nu}$ = 2952, 2930, 2886, 2857, 1717, 1654, 1569, 1509, 1471, 1462, 1439, 1410, 1361, 1302, 1259, 1197, 1161, 1139, 1088, 1054, 1035, 1005, 970, 941, 893, 837, 811, 778, 740, 661, 631, 599 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{19}H_{29}O_4Si$ [M+H$^+$]: 349.1829, found: 349.1830.

Methyl 2-((*S*,1*E*,6*E*)-5-((*tert*-butyldimethylsilyl)oxy)-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hepta-1,6-dien-1-yl)furan-3-carboxylate (197). A solution of pinacol borane (6.3 mL, 43.47 mmol) and 9-borabicyclo[3.3.1]nonane (9-H-9-BBN, 353 mg, 0.1 eq.) in THF (3 mL) was added to a stirred solution of alkyne **220** (10.10 g, 28.98 mmol) in THF (60 mL). The resulting mixture was stirred at 60 °C for 16 h before the reaction was cautiously quenched at room temperature upon dropwise addition of sat. aq. NH_4Cl (20 mL). The aqueous phase was diluted with water (100 mL) and extracted with EtOAc (3 x 200 mL). The combined extracts were washed with brine (100 mL), dried over Na_2SO_4 and concentrated, and the residue was purified by flash chromatography on silica (hexanes:*tert*-butyl methyl ether, 15:1) to provide the title compound as a colorless oil (11.40 g, 83% yield). $[\alpha]_D^{20}$ = +18.3° (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.22 (d, *J* = 1.9 Hz, 1H), 6.93 (dt, *J* = 16.0, 1.6 Hz, 1H), 6.66 (d, *J* = 1.9 Hz, 1H), 6.60 – 6.45 (m, 2H), 5.62 (dd, *J* = 18.0, 1.5 Hz, 1H), 4.24 (qd, *J* = 5.8, 1.6 Hz, 1H), 3.83 (s, 3H), 2.30 (dddd, *J* = 8.7, 7.4, 6.3, 1.6 Hz, 2H), 1.68 (ddd, *J* = 9.7, 7.9, 5.9 Hz, 2H), 1.27 (s, 12H), 0.90 (s, 9H), 0.03 (d, *J* = 9.3 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.1, 157.0, 155.5, 140.7, 136.1, 117.8, 112.2, 111.4, 83.1, 73.4, 51.4, 36.5, 28.4, 25.9, 24.8, 24.7, 18.2, –4.4, –4.9; IR (film): $\tilde{\nu}$ = 2977, 2952, 2930, 2857, 1718, 1642, 1569, 1508, 1471, 1463, 1439, 1390, 1364, 1339, 1320, 1259, 1196, 1145, 1086, 1053, 1035, 999, 971, 941, 918, 895, 836, 810, 776, 739, 671, 666 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{25}H_{41}O_6BSiNa$ [M+Na$^+$]: 499.2657, found: 499.2661.

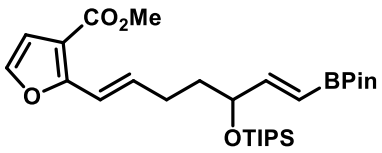


Compound 209. Imidazole (32 mg, 0.47 mmol) and *tert*-butyldiphenylsilyl chloride (129 mg, 0.47 mmol) were added to a stirred solution of *rac*-**206** (100 mg, 0.43 mmol) in CH_2Cl_2 (1.2 mL), and the resulting mixture was stirred for 16 h at room temperature. The reaction was quenched with sat. aq. $NaHCO_3$ (2 mL) and the aqueous phase was extracted with CH_2Cl_2 (3 x 30 mL). The combined extracts were dried over Na_2SO_4 and concentrated, and the residue was purified by flash chromatography on silica (hexane:*tert*-butyl methyl ether, 20:1) to afford the silyl ether as a colorless oil (199 mg, 99% yield).



A solution of pinacol borane (0.09 mL, 0.60 mmol) and 9-borabicyclo[3.3.1]nonane (9-H-9-BBN, 4.9 mg, 0.1 eq.) in THF (0.4 mL) was added to a stirred solution of alkyne **207** (190 mg, 0.40 mmol) in THF (0.5 mL). The resulting mixture was stirred at 60 °C for 16 h before the reaction was diluted with MTBE (4 mL) and cautiously quenched at room temperature upon dropwise addition of sat. aq. NH_4Cl (4 mL). The aqueous phase was diluted with water (20 mL) and extracted with EtOAc (3 x 50 mL). The combined extracts were washed with brine (20 mL), dried over Na_2SO_4 and concentrated, and the residue was purified by flash chromatography on silica (hexanes:*tert*-butyl methyl ether, 15:1) to provide the title compound as a colorless oil (155 mg, 64% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.70 – 7.59 (m, 4H), 7.42 – 7.29 (m, 6H), 7.21 (d, *J* = 2.0 Hz, 1H), 6.82 (dt, *J* = 16.0, 1.5 Hz, 1H), 6.66 (d, *J* = 1.9 Hz, 1H), 6.54 (dd, *J* = 18.0, 5.3 Hz, 1H), 6.32 (dt, *J* = 16.0, 7.1 Hz, 1H), 5.54 (dd, *J* = 18.0, 1.4 Hz, 1H), 4.36 – 4.25 (m, 1H), 3.83 (s, 3H), 2.30 – 2.08 (m, 2H), 1.65 – 1.54 (m, 2H), 1.26 (s, 12H), 1.07 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.1, 156.9, 154.5, 140.6, 136.0, 135.95, 135.86, 129.6, 129.5, 127.5, 127.4, 117.7, 112.1, 111.4, 83.1, 74.3, 51.4, 36.0, 27.7, 27.1, 24.8, 24.7, 19.4. IR (film): $\tilde{\nu}$ = 2975, 2932, 2892, 2857, 2174, 1718, 1643, 1568, 1509, 1472, 1463, 1440, 1428, 1391, 1368, 1339, 1322, 1265, 1239, 1196, 1146, 1111, 1056, 1082, 1037, 971, 998, 939, 895, 850, 823, 772, 741, 703, 652, 630, 613, 622, 531, 507, 486, 460, 430 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{35}H_{45}O_6BSiNa$ [M+Na$^+$]: 623.2971, found: 623.2974.

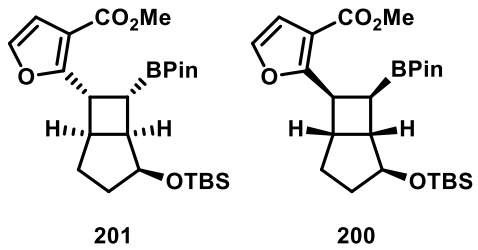
Compound 210. Imidazole (32 mg, 0.47 mmol) and triisopropylsilyl chloride (0.1 mL, 0.47 mmol) were added to a stirred solution of *rac*-**206** (100 mg, 0.43 mmol) in CH_2Cl_2 (1.2 mL), and the resulting mixture was stirred for 16 h at room temperature. The reaction was quenched with sat. aq. $NaHCO_3$ (2 mL) and the aqueous phase was extracted with CH_2Cl_2 (3 x 30 mL). The combined extracts were dried over Na_2SO_4 and concentrated, and the residue was purified by flash chromatography on silica (hexane:*tert*-butyl methyl ether, 20:1) to afford the silyl ether as a colorless oil (143 mg, 86% yield).



A solution of pinacol borane (0.075 mL, 0.52 mmol) and 9-borabicyclo[3.3.1]nonane (9-H-9-BBN, 4.2 mg, 0.1 eq.) in THF (0.4 mL) was added to a stirred solution of alkyne **208** (135 mg, 0.35 mmol) in THF (0.5 mL). The resulting mixture was stirred at 60 °C for 16 h before the reaction was diluted with MTBE (4 mL) and cautiously quenched at room temperature upon

dropwise addition of sat. aq. NH_4Cl (4 mL). The aqueous phase was diluted with water (20 mL) and extracted with EtOAc (3 x 50 mL). The combined extracts were washed with brine (20 mL), dried over Na_2SO_4 and concentrated, and the residue was purified by flash chromatography on silica (hexanes:*tert*-butyl methyl ether, 9:1) to provide the title compound as a colorless oil (140 mg, 78% yield). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.22 (d, *J* = 2.0 Hz, 1H), 6.92 (dt, *J* = 16.0, 1.6 Hz, 1H), 6.66 (d, *J* = 2.0 Hz, 1H), 6.62 – 6.43 (m, 2H), 5.62 (dd, *J* = 18.0, 1.4 Hz, 1H), 4.39 (qd, *J* = 5.5, 1.4 Hz, 1H), 3.83 (s, 3H), 2.41 – 2.18 (m, 2H), 1.85 – 1.68 (m, 2H), 1.27 (d, *J* = 2.7 Hz, 12H), 1.05 (d, *J* = 2.5 Hz, 21H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.1, 157.0, 155.5, 140.7, 136.2, 117.7, 112.1, 111.4, 83.2, 73.9, 51.4, 36.6, 27.8, 24.8, 24.6, 18.1, 12.4. HRMS (ESI): *m/z* calcd. for $C_{28}H_{47}O_6BSiNa$ [M+Na$^+$]: 541.3127, found: 541.3135.

Cyclobutanes 201 and 200. The iridium complex **205** (252 mg, 0.22 mmol, 0.01 eq.) was added to a stirred solution of alkenyl boronic ester *(S)*-**197** (10.70 g, 22.46 mmol) in dry and degassed (three freeze-pump-thaw cycles) MeCN (500 mL) in a 1L-jacketed vessel, which was connected to a stream of cooling water (T ≈ 14 °C). The mixture was irradiated with a blue LED bulb (Hepatochem, 475 nm) for 4 h (see Figure 4.7 for the reaction setup). The mixture was then concentrated *in vacuo* and the resulting residue purified by flash chromatography on fine silica (hexanes:EtOAc, 17:1) to furnish the diastereomeric products **201** (5.82 g, 54% yield) and **200** (4.03 g, 37% yield) as a colorless oil each.



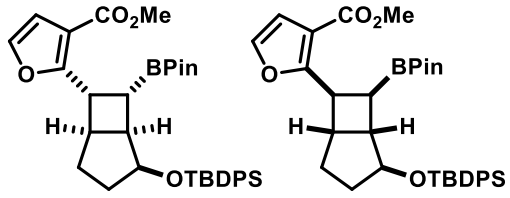
201 200

Figure 4.7. Reaction setup for the photosensitized [2+2] cycloaddition.

Analytical and spectroscopic data of **201**: $[\alpha]_D^{20}$ = –69.1° (c = 1.0, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$): δ = 7.26 (d, *J* = 2.0 Hz, 1H), 6.63 (d, *J* = 1.9 Hz, 1H), 4.22 (ddd, *J* = 10.0, 7.3, 6.3 Hz, 1H), 3.93 (ddd, *J* = 11.7, 4.8, 0.9 Hz, 1H), 3.79 (s, 3H), 2.93 (tdd, *J* = 6.6, 3.5, 1.1 Hz, 1H), 2.85 (q, *J* = 7.0 Hz, 1H), 2.46 (ddd, *J* = 11.6, 6.2, 1.2 Hz, 1H), 2.03 (tdd, *J* = 12.3, 10.0, 8.1 Hz, 1H), 1.93 – 1.85 (m, 1H), 1.64 – 1.57 (m, 2H), 1.11 (s, 6H), 1.04 (s, 6H), 0.87 (s, 9H), 0.05 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 165.0, 164.4, 139.8, 112.3, 111.0, 82.8, 75.4, 51.2, 40.7, 39.2, 36.7, 32.2, 28.9, 25.9, 25.0, 24.6, 18.2, –4.85, –4.89; IR (film): $\tilde{\nu}$ = 2951, 2930, 2885, 2856, 1719, 1595, 1519, 1462, 1441, 1410, 1379, 1323, 1305, 1283, 1250, 1194, 1164, 1142, 1106, 1051, 1032, 1007, 987, 959, 940, 907, 875, 853, 836, 804, 775, 734, 669, 602 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{25}H_{41}O_6BSiNa$ [M+Na^+]: 499.2657, found: 499.2659.

Analytical and spectroscopic data of **200**: $[\alpha]_D^{20}$ = +60.3° (c = 1.0, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$): δ = 7.28 (d, *J* = 2.0 Hz, 1H), 6.62 (d, *J* = 2.0 Hz, 1H), 4.00 (d, *J* = 3.9 Hz, 1H), 3.82 (ddd, *J* = 11.4, 4.8, 1.0 Hz, 1H), 3.78 (s, 3H), 3.20 – 3.15 (m, 1H), 2.75 (t, *J* = 7.0 Hz, 1H), 2.17 (tdd, *J* = 13.1, 7.0, 4.0 Hz, 1H), 1.96 (tt, *J* = 12.9, 7.0 Hz, 1H), 1.83 – 1.77 (m, 1H), 1.72 (ddd, *J* = 11.4, 6.7, 1.2 Hz, 1H), 1.59 (dd, *J* = 12.8, 6.9 Hz, 1H), 1.11 (s, 6H), 1.05 (s, 6H), 0.86 (s, 9H), 0.04 (d, *J* = 1.5 Hz, 6H); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 164.9, 164.3, 139.9, 112.2, 111.0, 82.9, 79.2, 51.2, 45.1, 41.3, 35.4, 33.7, 30.4, 25.9, 25.0, 24.4, 18.2, –4.8, –4.8; IR (film): $\tilde{\nu}$ = 2953, 2929, 2886, 2856, 1720, 1595, 1519, 1462, 1440, 1410, 1377, 1319, 1252, 1195, 1165, 1143, 1109, 1057, 1020, 973, 940, 891, 880, 854, 835, 808, 776, 734, 666 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{25}H_{42}O_6BSi$ [M+H^+]: 477.2838, found: 477.2839.

Cyclobutanes 211-a and 211-b. The iridium complex **205** (2.4 mg, 0.002 mmol, 0.01 eq.) was added to a stirred solution of alkenyl boronic ester *rac*-**209** (130 mg, 0.22 mmol) in dry and degassed (three freeze-pump-thaw cycles) MeCN (5 mL) in a 25 mL-jacketed vessel, which was connected to a stream of cooling water (T ≈ 14 °C). The mixture was irradiated with a blue LED bulb (Hepatochem, 475 nm) for 4 h. The mixture was then concentrated *in vacuo* and the resulting residue purified by flash chromatography on fine silica (hexanes:EtOAc, 15:1) to furnish the diastereomeric products **211-a** (59 mg, 45% yield) and **211-b** (55 mg, 42% yield) as a colorless oil each.



211-a 211-b

Analytical and spectroscopic data of **211-a**:

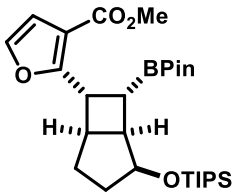
^1H NMR (400 MHz, $CDCl_3$): δ = 7.78 – 7.69 (m, 4H), 7.46 – 7.33 (m, 6H), 7.27 (d, *J* = 2.0 Hz, 1H), 6.65 (d, *J* = 2.0 Hz, 1H), 4.19 (dt, *J* = 10.0, 6.6 Hz, 1H), 4.02 (ddd, *J* = 11.6, 4.6, 0.8 Hz, 1H), 3.81 (s, 3H), 2.95 (q, *J* = 7.0 Hz, 1H), 2.85 (td, *J* = 7.0, 4.6 Hz, 1H), 2.72 (ddd, *J* = 11.7, 6.3, 1.2 Hz, 1H), 2.15 (tdd, *J* = 12.8, 10.0, 7.0 Hz, 1H), 1.81 (dt, *J* = 12.4, 6.3 Hz, 1H), 1.54 (dd, *J* = 13.3, 6.8 Hz, 1H), 1.44 (tt, *J* = 13.3, 6.7 Hz, 1H), 1.15 (s, 6H), 1.06 (s, 6H), 1.04 (s, 9H).^{13}C NMR (101 MHz, $CDCl_3$) δ 165.0, 164.3, 139.8, 135.8, 135.8, 134.6, 134.2, 129.4, 129.4, 127.4, 127.4, 112.3, 110.9, 82.8, 76.2,

51.2, 40.5, 39.1, 36.5, 31.7, 28.9, 26.9, 25.0, 24.6, 19.2. IR (film): $\tilde{\nu}$ = 2953, 2857, 1717, 1594, 1471, 1462, 1441, 1427, 1411, 1378, 1323, 1305, 1284, 1251, 1194, 1164, 1142, 1105, 1051, 1031, 1007, 907, 871, 854, 840, 821, 786, 731, 701, 610, 503, 488 cm^{-1}. HRMS (ESI): *m/z* calcd. for $C_{35}H_{45}O_6BSiNa$ [M+Na^+]: 623.2971, found: 623.2971.

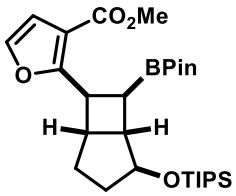
Analytical and spectroscopic data of **211-b**:

^1H NMR (400 MHz, $CDCl_3$): δ = 7.69 – 7.64 (m, 4H), 7.44 – 7.32 (m, 6H), 7.28 (d, *J* = 2.0 Hz, 1H), 6.63 (d, *J* = 2.0 Hz, 1H), 4.13 (d, *J* = 2.4 Hz, 1H), 3.80 (ddd, *J* = 11.5, 4.5, 1.0 Hz, 1H), 3.76 (s, 3H), 3.25 (q, *J* = 6.1 Hz, 1H), 2.96 (t, *J* = 7.0 Hz, 1H), 2.18 – 2.01 (m, 2H), 1.90 – 1.78 (m, 1H), 1.70 – 1.56 (m, 2H), 1.09 (s, 6H), 1.05 (s, 9H), 1.03 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.7, 164.3, 139.9, 135.7, 134.8, 134.7, 129.4, 129.3, 127.5, 127.4, 112.3, 111.0, 82.8, 79.9, 51.2, 45.0, 41.3, 35.3, 33.4, 30.5, 27.0, 25.0, 24.5, 19.2. IR (film): $\tilde{\nu}$ = 2959, 2930, 2857, 1718, 1593, 1471, 1440, 1428, 1410, 1377, 1318, 1246, 1194, 1165, 1142, 1107, 1056, 1020, 972, 940, 910, 880, 854, 822, 786, 734, 702, 687, 611, 506, 488 cm^{-1}. HRMS (ESI): *m/z* calcd. for $C_{35}H_{45}O_6BSiNa$ [M+Na^+]: 623.2971, found: 623.2969.

Cyclobutanes 212-a and 212-b. The iridium complex **205** (2.8 mg, 0.003 mmol, 0.01 eq.) was added to a stirred solution of alkenyl boronic ester *rac*-**210** (130 mg, 0.25 mmol) in dry and degassed (three freeze-pump-thaw cycles) MeCN (6 mL) in a 25 mL-jacketed vessel, which was connected to a stream of cooling water (T ≈ 14 °C). The mixture was irradiated with a blue LED bulb (Hepatochem, 475 nm) for 4 h. The mixture was then concentrated *in vacuo* and the resulting residue purified by flash chromatography on silica (hexanes:EtOAc, 15:1) to furnish an inseparable mixture of diasteomers **212-a/212-b** (122 mg, 94% yield). ^1H NMR (400 MHz, $CDCl_3$, mixture of diastereomers): δ = 7.28 (d, *J* = 2.0 Hz, 0.5H), 7.26 (d, *J* = 2.4 Hz, 0.5H), 6.63 (t, *J* = 2.2 Hz, 1H), 4.33 (dt, *J* = 9.9, 6.6 Hz, 0.5H), 4.09 (d, *J* = 3.8 Hz, 0.5H), 3.99 – 3.92 (m, 0.5H), 3.83 (ddd, *J* = 11.5, 4.9, 1.1 Hz, 0.5H), 3.79 (s, 1.5H), 3.78 (s, 1.5H), 3.20 (td, *J* = 7.1, 4.7 Hz, 0.5H), 3.01 – 2.87 (m, 1H), 2.83 (t, *J* = 6.9 Hz, 0.5H), 2.58 – 2.49 (m, 0.5H), 2.18 (tdd, *J* = 13.0, 6.9, 3.9 Hz, 0.5H), 2.11 – 2.06 (m, 0.5H), 2.03 – 1.92 (m, 1H), 1.87 (dd, *J* = 12.9, 6.6 Hz, 0.5H), 1.72 (ddd, *J* = 11.4, 6.7, 1.2 Hz, 0.5H), 1.66 – 1.53 (m, 1.5H), 1.11 (s, 3H), 1.10 (s, 3H), 1.07 – 1.01 (m, 27H). ^{13}C NMR (101 MHz, $CDCl_3$, mixture of diastereomers): δ = 165.0, 164.9, 164.3, 139.9, 139.8, 112.3, 112.2, 111.04, 110.96, 82.9, 82.7, 79.3, 75.4, 51.3, 51.2, 45.3, 41.3, 40.5, 39.2, 36.6, 35.2, 33.9, 32.4, 30.5, 28.9, 25.00, 24.96, 24.7, 24.4, 18.1, 18.1, 18.0, 12.1. HRMS (ESI): *m/z* calcd. for $C_{28}H_{47}O_6BSiNa$ [M+Na^+]: 541.3127, found: 541.3132.

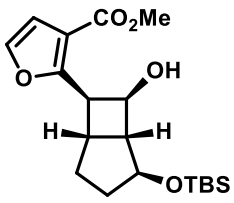


212-a

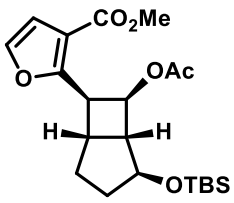


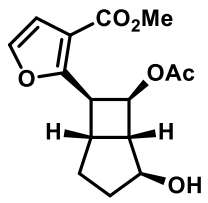
212-b

Methyl 2-((1*R*,2*S*,5*S*,6*R*,7*S*)-2-((*tert*-butyldimethylsilyl)oxy)-7-hydroxybicyclo[3.2.0]heptan-6-yl)-furan-3-carboxylate (196). A mixture (40 mL, 2:1 *v*/*v*) of aq. NaOH (2 M) and H_2O_2 (35% *w*/*w*) was added to a stirred solution of boronic ester **200** (4.01 g, 8.42 mmol) in THF (40 mL) at 0 °C and the resulting mixture was vigorously stirred at this temperature for 30 min. The reaction was carefully quenched with sat. aq. NH_4Cl (20 mL) and the mixture diluted with EtOAc (100 mL). The aqueous phase was extracted with EtOAc (3 x 150 mL), the combined extracts were washed with brine (50 mL), dried over Na_2SO_4 and concentrated *in vacuo*, and the residue was purified by flash chromatography on silica (hexanes:*tert*-butyl methyl ether, 3:1) to give the title compound as an amorphous white solid (2.58 g, 81% yield). $[\alpha]_D^{20}$ = +85.7° (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37 (d, *J* = 2.0 Hz, 1H), 6.69 (d, *J* = 2.0 Hz, 1H), 4.23 (t, *J* = 2.2 Hz, 1H), 4.04 (ddd, *J* = 7.9, 4.1, 0.8 Hz, 1H), 3.84 – 3.77 (m, 4H), 3.24 (td, *J* = 7.8, 4.8 Hz, 1H), 2.66 (ddt, *J* = 8.0, 4.0, 1.1 Hz, 1H), 2.06 – 1.94 (m, 1H), 1.87 – 1.79 (m, 2H), 1.61 – 1.52 (m, 1H), 0.87 (s, 9H), 0.06 (d, *J* = 1.8 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 165.0, 160.8, 141.2, 114.2, 111.0, 76.6, 69.8, 56.7, 51.5, 43.2, 36.2, 34.8, 29.1, 25.8, 18.1, –4.67, –4.72; IR (film): $\tilde{\nu}$ = 2953, 2929, 2887, 2856, 1716, 1593, 1518, 1471, 1462, 1441, 1407, 1360, 1340, 1312, 1253, 1199, 1144, 1082, 1059, 1032, 1006, 940, 887, 835, 812, 772, 736 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{19}H_{30}O_5SiNa$ [M+Na$^+$]: 389.1754, found: 389.1759.

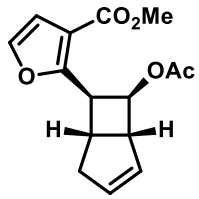


Methyl 2-((1*R*,2*S*,5*S*,6*R*,7*S*)-7-acetoxy-2-((*tert*-butyldimethylsilyl)oxy)bicyclo[3.2.0]heptan-6-yl)-furan-3-carboxylate (S11). 4-Dimethylaminopyridine (72 mg, 0.59 mmol), triethylamine (2.89 mL, 20.74 mmol) and acetic anhydride (1.96 mL, 20.74 mmol) were added to a stirred solution of alcohol **196** (2.53 g, 6.92 mmol) in CH_2Cl_2 (63 mL) at 0 °C. The mixture was stirred at room temperature for 1 h before the reaction was quenched with sat. aq. $NaHCO_3$ (30 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 100 mL), the combined extracts were dried over Na_2SO_4 and concentrated, and the residue was purified by flash chromatography on silica (hexanes:*tert*-butyl methyl ether, 9:1) to provide the title compound as a colorless oil (2.74 g, 97% yield). $[\alpha]_D^{20}$ = +59.8° (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37 (d, *J* = 2.0 Hz, 1H), 6.67 (d, *J* = 2.0 Hz, 1H), 4.76 (ddd, *J* = 8.2, 4.3, 0.8 Hz, 1H), 4.32 – 4.26 (m, 1H), 4.10 (ddd, *J* = 8.1, 4.7, 1.4 Hz, 1H), 3.79 (s, 3H), 3.30 (td, *J* = 7.7, 4.6 Hz, 1H), 2.82 – 2.73 (m, 1H), 2.05 – 1.82 (m, 3H), 1.78 (s, 3H), 1.62 (dd, *J* = 12.2, 6.1 Hz, 1H), 0.87 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 169.7, 164.1, 159.2, 141.1, 114.5, 110.8, 76.3, 70.4, 53.4, 51.4, 40.5, 37.0, 34.7, 29.1, 25.8, 20.5, 18.0, –4.77, –4.79; IR (film): $\tilde{\nu}$ = 2954, 2931, 2893, 2857, 1742, 1722, 1598, 1518, 1472, 1462, 1440, 1407, 1363, 1340, 1313, 1291, 1233, 1196, 1158, 1143, 1073, 1056, 1026, 940, 886, 837, 809, 776, 738 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{21}H_{32}O_6SiNa$ [M+Na$^+$]: 431.1860, found: 431.1865.



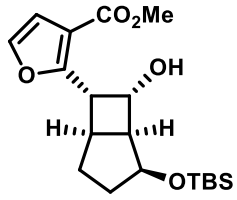
Methyl 2-((1*S*,2*S*,5*S*,6*R*,7*S*)-7-acetoxy-2-hydroxybicyclo[3.2.0]heptan-6-yl)furan-3-carboxylate (221). 

Tetrabutylammonium fluoride (1 M in THF, 8.05 mL, 8.05 mmol) was added to a stirred solution of silyl ether **S11** (2.74 g, 6.71 mmol) in THF (70 mL) at 0 °C. The mixture was stirred at room temperature for 5 h before the reaction was quenched with sat. aq. NH_4Cl (30 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 100 mL), the combined extracts were dried over Na_2SO_4 and concentrated, and the residue was purified by flash chromatography on silica (hexanes:EtOAc, 1:1) to give the title compound as a yellow oil (1.85 g, 94% yield). $[\alpha]_D^{20}$ = +58.5° (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38 (d, *J* = 2.0 Hz, 1H), 6.68 (d, *J* = 1.9 Hz, 1H), 4.82 (ddd, *J* = 8.1, 4.2, 0.8 Hz, 1H), 4.40 (d, *J* = 3.4 Hz, 1H), 4.14 (ddd, *J* = 8.1, 4.8, 1.4 Hz, 1H), 3.79 (s, 3H), 3.37 (ddd, *J* = 8.1, 6.0, 4.6 Hz, 1H), 2.89 – 2.83 (m, 1H), 2.09 – 1.92 (m, 3H), 1.79 (s, 3H), 1.73 – 1.68 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 169.7, 164.0, 158.8, 141.2, 114.6, 110.8, 76.1, 70.3, 53.1, 51.4, 40.5, 37.0, 34.3, 28.9, 20.5; IR (film): $\tilde{\nu}$ = 3449, 2952, 1739, 1720, 1596, 1518, 1441, 1407, 1375, 1339, 1310, 1292, 1234, 1198, 1158, 1063, 1035, 984, 935, 862, 805, 744, 605 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{15}H_{18}O_6Na$ [M+Na$^+$]: 317.0995, found: 317.0997.

Methyl 2-((1*R*,5*S*,6*R*,7*S*)-7-acetoxybicyclo[3.2.0]hept-2-en-6-yl)furan-3-carboxylate (195). 

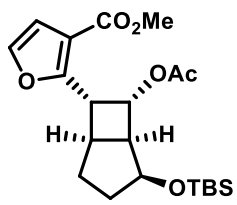
A solution of Martin's sulfurane (6.26 g, 9.31 mmol) in CH_2Cl_2 (10 mL) was added to a stirred solution of alcohol **221** (1.83 g, 6.21 mmol) in CH_2Cl_2 (80 mL) and the resulting mixture was stirred for 5 h at ambient temperature before the reaction was quenched upon addition of sat. aq. $NaHCO_3$ (40 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 100 mL), the combined organic layers were dried over Na_2SO_4 and concentrated, and the residue was purified by flash chromatography on silica (hexanes:*tert*-butyl methyl ether, 8:1) to furnish the title compound as a yellow oil (1.66 g, 97% yield). $[\alpha]_D^{20}$ = +46.7° (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36 (d, *J* = 2.0 Hz, 1H), 6.68 (d, *J* = 2.0 Hz, 1H), 5.88 (s, 2H), 5.11 (dd, *J* = 6.8, 1.6 Hz, 1H), 4.22 (td, *J* = 7.1, 1.5 Hz, 1H), 3.79 (s, 3H), 3.63 – 3.55 (m, 1H), 3.34 – 3.27 (m, 1H), 2.69 – 2.58 (m, 1H), 2.36 (ddd, *J* = 17.2, 3.6, 1.3 Hz, 1H), 1.86 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.0, 164.0, 158.7, 141.1, 133.0, 129.7, 114.1, 111.0, 76.6, 51.5, 51.4, 42.5, 39.4, 36.9, 20.7; IR (film): $\tilde{\nu}$ = 2952, 2845, 1738, 1717, 1596, 1516, 1440, 1409, 1372, 1353, 1330, 1293, 1233, 1197, 1165, 1141, 1106, 1067, 1033, 950, 915, 876, 799, 753, 723, 603 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{15}H_{16}O_5Na$ [M+Na$^+$]: 299.0889, found: 299.0891.

Methyl 2-((1*S*,2*S*,5*R*,6*S*,7*R*)-2-((*tert*-butyldimethylsilyl)oxy)-7-hydroxybicyclo[3.2.0]heptan-6-yl)furan-3-carboxylate (223). A mixture (2:1 *v*/*v*, 4 mL) of aq. NaOH (2 M) and aq. H_2O_2 (35% *w*/*w*) was added to a stirred solution of boronic ester **201** (400 mg, 0.84 mmol) in THF (4 mL) at 0 °C. The resulting mixture was vigorously stirred at this temperature for 30 min before the reaction was carefully quenched with sat. aq. NH_4Cl (5 mL). The mixture was diluted with

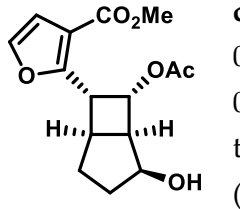


EtOAc (20 mL), the aqueous phase was extracted with EtOAc (3 x 100 mL), and the combined extracts were washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography on silica (hexanes:*tert*-butyl methyl ether, 7:1) to give the title compound as an amorphous white solid (264 mg, 86% yield). $[\alpha]_D^{20}$ = –104.4° (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35 (d, *J* = 2.0 Hz, 1H), 6.69 (d, *J* = 1.9 Hz, 1H), 4.66 (dd, *J* = 7.8, 3.3 Hz, 1H), 4.28 – 4.20 (m, 1H), 3.87 (ddd, *J* = 7.9, 5.3, 1.4 Hz, 1H), 3.82 (s, 3H), 3.15 – 3.07 (m, 1H), 2.62 (tdd, *J* = 7.9, 3.4, 1.4 Hz, 1H), 2.03 – 1.87 (m, 2H), 1.80 (tdd, *J* = 12.3, 9.7, 7.1 Hz, 1H), 1.72 – 1.53 (m, 2H), 0.90 (s, 9H), 0.07 (d, *J* = 2.9 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 165.0, 160.9, 141.0, 114.0, 111.0, 74.1, 66.6, 51.5, 50.7, 44.4, 35.9, 33.4, 28.0, 25.9, 18.2, –4.77, –4.84; IR (film): $\tilde{\nu}$ = 3488, 2953, 2930, 2884, 2857, 1718, 1593, 1518, 1462, 1441, 1407, 1361, 1341, 1305, 1252, 1198, 1163, 1113, 1064, 1050, 1034, 1007, 939, 907, 872, 837, 802, 777, 736, 671, 667 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{19}H_{30}O_5SiNa$ [M+Na$^+$]: 389.1754, found: 389.1758.

Methyl 2-((1*S*,2*S*,5*R*,6*S*,7*R*)-7-acetoxy-2-((*tert*-butyldimethylsilyl)oxy)bicyclo[3.2.0]heptan-6-yl)furan-3-carboxylate (S12). 4-Dimethylaminopyridine (7 mg, 0.058 mmol), triethylamine (0.28 mL, 2.04 mmol) and acetic anhydride (0.19 mL, 2.04 mmol) were added to a stirred solution of alcohol **223** (249 mg, 0.68 mmol) in CH_2Cl_2 (6 mL) at 0 °C. The mixture was stirred at room temperature for 1 h before the reaction was quenched upon addition of sat. aq. $NaHCO_3$ (5 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL), the combined organic layers were dried over Na_2SO_4 and concentrated, and the residue was purified by flash chromatography on silica (hexanes:*tert*-butyl methyl ether, 9:1) to provide the title compound as a colorless oil (262 mg, 94% yield). $[\alpha]_D^{20}$ = –67.0° (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35 (d, *J* = 1.9 Hz, 1H), 6.67 (d, *J* = 1.9 Hz, 1H), 5.46 (dd, *J* = 7.8, 3.7 Hz, 1H), 4.29 – 4.20 (m, 2H), 3.81 (s, 3H), 3.16 – 3.07 (m, 1H), 2.87 (tdd, *J* = 8.0, 3.7, 1.4 Hz, 1H), 2.00 – 1.84 (m, 2H), 1.73 (s, 3H), 1.66 (td, *J* = 6.1, 3.8 Hz, 2H), 0.86 (s, 9H), 0.04 (d, *J* = 12.7 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 169.4, 163.9, 159.1, 141.0, 114.6, 111.0, 73.8, 68.0, 51.4, 47.1, 42.3, 36.8, 33.3, 27.9, 25.7, 20.3, 18.1, –4.9, –5.0; IR (film): $\tilde{\nu}$ = 2954, 2931, 2857, 1746, 1722, 1598, 1518, 1463, 1443, 1407, 1362, 1340, 1304, 1284, 1232, 1197, 1160, 1133, 1115, 1054, 1033, 938, 892, 872, 837, 805, 777, 739, 669, 603 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{21}H_{32}O_6SiNa$ [M+Na$^+$]: 431.1860, found: 431.1861.

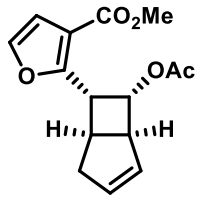


Methyl 2-((1*R*,2*S*,5*R*,6*S*,7*R*)-7-acetoxy-2-hydroxybicyclo[3.2.0]heptan-6-yl)furan-3-carboxylate (224). Tetrabutylammonium fluoride (1 M in THF, 0.72 mL, 0.72 mmol) was added to a stirred solution of silyl ether **S12** (246 mg, 0.60 mmol) in THF (6 mL) at 0 °C. The resulting mixture was stirred at room temperature for 5 h before the reaction was quenched with sat. aq. NH_4Cl (5 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL), the combined organic layers were dried over Na_2SO_4 and concentrated, and the residue was purified by flash chromatography on silica (hexanes:EtOAc, 1:1) to afford the title compound as a yellow oil (142 mg, 80% yield). $[\alpha]_D^{20}$ = –134.1° (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$):



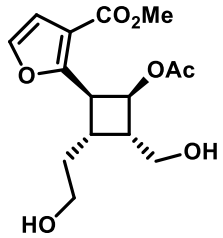
δ = 7.37 (d, *J* = 2.0 Hz, 1H), 6.70 (d, *J* = 2.0 Hz, 1H), 5.22 (dd, *J* = 8.6, 4.3 Hz, 1H), 4.29 – 4.19 (m, 2H), 3.81 (s, 3H), 3.19 – 3.10 (m, 1H), 2.97 – 2.89 (m, 1H), 2.17 – 2.09 (m, 1H), 1.94 – 1.84 (m, 4H), 1.83 – 1.64 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.5, 164.2, 158.7, 141.2, 114.7, 110.8, 73.6, 68.0, 51.4, 49.1, 40.9, 36.6, 33.1, 28.1, 20.9; IR (film): $\tilde{\nu}$ = 3467, 2954, 2869, 1819, 1717, 1596, 1518, 1442, 1405, 1376, 1338, 1304, 1235, 1197, 1160, 1133, 1085, 1053, 1034, 942, 886, 805, 752, 604 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{15}H_{18}O_6Na$ [M+Na$^+$]: 317.0995, found: 317.0993.

Methyl 2-((1*S*,5*R*,6*S*,7*R*)-7-acetoxybicyclo[3.2.0]hept-2-en-6-yl)furan-3-carboxylate (*ent*-195).



A solution of Martin's sulfurane (428 mg, 0.64 mmol) in CH_2Cl_2 (2 mL) was added to a stirred solution of alcohol **224** (125 g, 0.42 mmol) in CH_2Cl_2 (4 mL). The resulting mixture was stirred for 5 h before the reaction was quenched with sat. aq. $NaHCO_3$ (4 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL), the combined extracts were dried over Na_2SO_4 and concentrated, and the residue was purified by flash chromatography on silica (hexanes:*tert*-butyl methyl ether, 8:1) to provide the title compound as a yellow oil (94 mg, 80% yield). $[\alpha]_D^{20}$ = –47.7° (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36 (d, *J* = 2.0 Hz, 1H), 6.68 (d, *J* = 2.0 Hz, 1H), 5.88 (s, 2H), 5.11 (dd, *J* = 6.7, 1.5 Hz, 1H), 4.22 (td, *J* = 7.1, 1.5 Hz, 1H), 3.79 (s, 3H), 3.62 – 3.56 (m, 1H), 3.34 – 3.28 (m, 1H), 2.70 – 2.57 (m, 1H), 2.36 (ddd, *J* = 17.3, 3.7, 1.3 Hz, 1H), 1.86 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.0, 164.0, 158.7, 141.1, 133.0, 129.7, 114.1, 111.0, 76.6, 51.5, 51.4, 42.5, 39.4, 36.9, 20.7; IR (film): $\tilde{\nu}$ = 2952, 2845, 1737, 1715, 1595, 1516, 1440, 1409, 1372, 1353, 1330, 1292, 1230, 1195, 1164, 1140, 1106, 1066, 1032, 950, 915, 876, 831, 860, 799, 751, 721, 603 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{15}H_{20}NO_5$ [M+NH$_4^+$]: 294.1336, found: 294.1337.

Methyl 2-((1*R*,2*S*,3*S*,4*S*)-2-acetoxy-4-(2-hydroxyethyl)-3-(hydroxymethyl)cyclobutyl)furan-3-carboxylate (222).

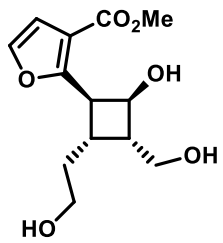


N-Methylmorpholine *N*-oxide (2.09 g, 17.92 mmol) and OsO_4 (4 wt% in water, 0.76 mL, 0.12 mmol, 0.01 eq.) were added to a stirred solution of olefin **195** (1.65 g, 5.97 mmol) in a mixture (10:1 *v*/*v*, 30 mL) of THF/H_2O at room temperature. The mixture was stirred for 3 d before sat. aq. Na_2SO_3 (10 mL) and *tert*-butyl methyl ether (50 mL) were added. The aqueous phase was extracted with *tert*-butyl methyl ether (3 x 150 mL), the combined extracts were washed with brine (50 mL), dried over Na_2SO_4 and concentrated, and the resulting crude diol was used in the next step without further purification.

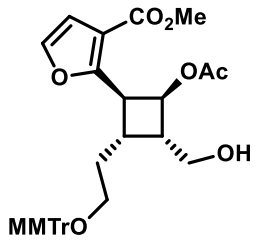
Sodium periodate (1.53 g, 7.17 mmol) was added to a stirred solution of this diol (1.85 g, 5.97 mmol) in THF (38 mL) and water (8 mL). The resulting mixture was vigorously stirred at room temperature for 30 min before it was cooled to 0 °C. Methanol (115 mL) was added and stirring continued for 15 min at 0 °. Sodium borohydride (904 mg, 23.89 mmol) was introduced and the mixture stirred for 30 min at 0 °C. The mixture was poured into a mixture of sat. aq. NH_4Cl (50 mL) and EtOAc (100 mL). After vigorous stirring for 30 min, the aqueous phase was extracted with EtOAc (3 x 250 mL). The combined extracts were washed with sat. aq. $Na_2S_2O_3$ (50 mL) and brine (50 mL) before they were concentrated *in vacuo*. The residue was purified

by flash chromatography on silica (CH_2Cl_2:MeOH, 95:5) to give the title compound as a colorless oil (1.44 g, 77% yield over 2 steps). $[\alpha]_D^{20}$ = +55.2° (c = 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34 (d, *J* = 2.0 Hz, 1H), 6.68 (d, *J* = 2.0 Hz, 1H), 5.10 (ddd, *J* = 8.0, 5.4, 1.0 Hz, 1H), 4.30 (ddd, *J* = 8.0, 6.6, 1.1 Hz, 1H), 3.85 (d, *J* = 7.1 Hz, 2H), 3.80 (s, 3H), 3.70 (ddd, *J* = 10.9, 6.0, 5.0 Hz, 1H), 3.58 (ddd, *J* = 10.6, 8.4, 5.3 Hz, 1H), 3.15 – 3.03 (m, 1H), 2.90 (dtdd, *J* = 10.1, 7.0, 5.4, 1.1 Hz, 1H), 2.69 (s, 2H), 2.04 – 1.93 (m, 1H), 1.87 (s, 3H), 1.72 (ddt, *J* = 13.7, 8.4, 5.2 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.0, 164.1, 158.6, 141.3, 114.6, 110.9, 71.9, 61.6, 60.6, 51.5, 45.3, 40.8, 33.9, 32.4, 20.7; IR (film): $\tilde{\nu}$ = 3403, 2952, 2875, 1717, 1596, 1518, 1442, 1408, 1372, 1309, 1286, 1236, 1199, 1161, 1134, 1108, 1046, 751, 604 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{15}H_{20}O_7Na$ [M+Na$^+$]: 335.1101, found: 335.1101.

Methyl 2-((1*R*,2*S*,3*S*,4*S*)-2-hydroxy-4-(2-hydroxyethyl)-3-(hydroxymethyl)cyclobutyl)furan-3-carboxylate (225). Acetyl chloride (0.27 mL, 3.84 mmol) was added to a stirred solution of diol **222** (400 mg, 1.28 mmol) in methanol (13 mL). The resulting mixture was stirred for 4 h at room temperature before it was concentrated *in vacuo*. The residue was purified by flash chromatography on silica (CH_2Cl_2:MeOH, 90:10) to afford the title compound as a colorless oil (234 mg, 67% yield). $[\alpha]_D^{20}$ = +45.9° (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35 (d, *J* = 2.0 Hz, 1H), 6.68 (d, *J* = 2.0 Hz, 1H), 4.37 (dd, *J* = 7.6, 5.3 Hz, 1H), 3.99 (t, *J* = 7.0 Hz, 1H), 3.90 – 3.77 (m, 5H), 3.72 (dt, *J* = 10.5, 5.2 Hz, 1H), 3.60 (ddd, *J* = 10.5, 8.6, 5.0 Hz, 1H), 3.15 (s, 3H), 3.07 – 2.96 (m, 1H), 2.74 (tt, *J* = 9.2, 5.7 Hz, 1H), 1.98 (ddt, *J* = 14.0, 8.2, 4.0 Hz, 1H), 1.69 (ddt, *J* = 13.9, 7.4, 5.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.8, 160.2, 141.4, 114.4, 110.9, 70.3, 61.9, 60.8, 51.6, 47.5, 43.5, 33.2, 32.5; IR (film): $\tilde{\nu}$ = 3366, 2949, 2878, 1712, 1592, 1519, 1442, 1409, 1310, 1257, 1200, 1162, 1132, 1088, 1033, 740, 603 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{13}H_{18}O_6Na$ [M+Na$^+$]: 293.0995, found: 293.0995.



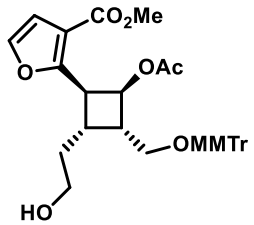
Methyl 2-((1*R*,2*S*,3*S*,4*S*)-2-acetoxy-3-(hydroxymethyl)-4-(2-((4-methoxyphenyl)diphenyl-methoxy)-ethyl)cyclobutyl)furan-3-carboxylate (227). 4-Dimethylaminopyridine (22 mg, 0.18 mmol, 0.05 eq.) and pyridine (0.23 mL, 2.83 mmol, 0.8 eq.) were added to a stirred solution of diol **222** (1.10 g, 3.54 mmol) in CH_2Cl_2 (31 mL). The mixture was cooled to –42 °C using an acetonitrile/dry-ice cooling bath before a solution of 4-monomethoxytrityl chloride (765 mg, 2.48 mmol) in CH_2Cl_2 (6 mL) was added dropwise. Stirring was continued for 2 h at –42 °C before the reaction was quenched with sat. aq. NH_4Cl (10 mL). After reaching room temperature, the aqueous phase was extracted with CH_2Cl_2 (3 x 100 mL), the combined extracts were dried over $MgSO_4$ and concentrated, and the residue was purified by flash chromatography on silica (hexanes:EtOAc, 2:1 to pure EtOAc) to furnish the title compound **227** as a white foam (950 mg, 46% yield), undesired mono-protected product **S13** as a white foam (144 mg, 7% yield), bis-protected



product as a yellow oil **S14** (165 mg, 5% yield), and recovered starting material **222** as a colorless oil (355 mg, 32% yield).

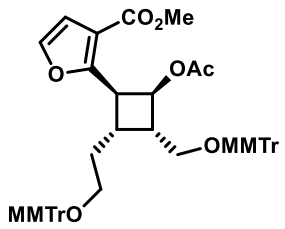
Analytical and spectroscopic data of **227**: $[\alpha]_D^{20}$ = –23.2° (c = 1.0, MeOH); ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.33 (dtd, *J* = 5.9, 3.2, 1.5 Hz, 5H), 7.27 – 7.15 (m, 8H), 6.79 – 6.73 (m, 2H), 6.66 (d, *J* = 2.0 Hz, 1H), 5.10 (ddd, *J* = 8.3, 5.5, 1.0 Hz, 1H), 4.23 (ddd, *J* = 8.0, 6.4, 1.3 Hz, 1H), 3.85 – 3.73 (m, 5H), 3.71 (s, 3H), 3.27 – 3.18 (m, 1H), 3.07 – 2.93 (m, 2H), 2.88 – 2.76 (m, 1H), 2.19 (dd, *J* = 6.8, 4.3 Hz, 1H), 2.01 – 1.91 (m, 1H), 1.84 (s, 3H), 1.72 (ddt, *J* = 13.8, 10.9, 5.4 Hz, 1H); ^{13}C NMR (101 MHz, CD_2Cl_2): δ = 171.5, 164.1, 159.0, 158.9, 145.2, 145.1, 141.6, 136.1, 130.6, 128.7, 128.6, 128.1, 127.09, 127.07, 115.0, 113.3, 111.2, 86.5, 72.6, 61.9, 61.3, 55.5, 51.5, 45.8, 41.0, 33.5, 30.6, 21.0; IR (film): $\tilde{\nu}$ = 3502, 2950, 2872, 2838, 1717, 1604, 1510, 1490, 1445, 1412, 1371, 1301, 1248, 1197, 1179, 1158, 1133, 1113, 1061, 1033, 954, 902, 831, 796, 766, 749, 728, 708, 633, 603, 586, 545 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{35}H_{36}O_8Na$ [M+Na$^+$]: 607.2302, found: 607.2307.

Analytical and spectroscopic data of **227a**: $[\alpha]_D^{20}$ = –14.3° (c = 1.0, MeOH); ^{1}H NMR (400 MHz,



CD_2Cl_2): δ = 7.47 (dt, *J* = 8.2, 1.3 Hz, 4H), 7.39 (d, *J* = 2.0 Hz, 1H), 7.37 – 7.29 (m, 6H), 7.27 – 7.16 (m, 2H), 6.89 – 6.84 (m, 2H), 6.68 (d, *J* = 2.0 Hz, 1H), 5.27 (dd, *J* = 7.8, 4.7 Hz, 1H), 4.30 (dd, *J* = 7.8, 5.1 Hz, 1H), 3.80 (s, 3H), 3.77 (s, 3H), 3.52 – 3.37 (m, 2H), 3.32 – 3.27 (m, 2H), 3.08 – 3.00 (m, 2H), 1.83 (s, 3H), 1.76 – 1.66 (m, 1H), 1.57 – 1.50 (m, 1H); ^{13}C NMR (101 MHz, CD_2Cl_2): δ = 170.1, 164.3, 159.4, 159.1, 145.1, 145.0, 141.7, 135.9, 130.8, 128.8, 128.24, 128.22, 127.3, 114.9, 113.5, 111.2, 86.9, 71.8, 61.7, 61.3, 55.6, 51.7, 43.0, 41.9, 33.8, 33.4, 20.8; IR (film): $\tilde{\nu}$ = 3420, 2949, 2909, 2868, 2837, 1737, 1717, 1598, 1509, 1490, 1444, 1411, 1371, 1300, 1233, 1197, 1179, 1155, 1133, 1114, 1071, 1032, 901, 832, 795, 748, 728, 708, 669, 632, 592, 546 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{35}H_{36}O_8Na$ [M+Na$^+$]: 607.2302, found: 607.2305.

Analytical and spectroscopic data of **227b**: $[\alpha]_D^{20}$ = –16.2° (c = 1.0, MeOH); ^{1}H NMR (400 MHz,



CD_2Cl_2): δ = 7.46 (dq, *J* = 6.7, 1.2 Hz, 4H), 7.35 (d, *J* = 1.9 Hz, 1H), 7.34 – 7.27 (m, 10H), 7.26 – 7.12 (m, 10H), 6.86 – 6.81 (m, 2H), 6.75 – 6.70 (m, 2H), 6.67 (d, *J* = 2.0 Hz, 1H), 5.27 (ddd, *J* = 7.9, 5.9, 1.0 Hz, 1H), 4.21 (ddd, *J* = 8.0, 6.1, 1.1 Hz, 1H), 3.78 (s, 3H), 3.76 (s, 3H), 3.69 (s, 3H), 3.25 (d, *J* = 6.7 Hz, 2H), 3.20 (dq, *J* = 10.7, 5.4 Hz, 1H), 3.06 – 2.96 (m, 1H), 2.95 – 2.82 (m, 2H), 1.82 (m, 4H), 1.54 (m, 1H); ^{13}C NMR (101 MHz, CD_2Cl_2): δ = 170.0, 164.1, 159.3, 159.1, 158.9, 145.3, 145.2, 145.13, 145.07, 141.5, 136.2, 136.0, 130.8, 130.5, 128.8, 128.7, 128.6, 128.2, 128.0, 127.2, 127.04, 127.01, 115.0, 113.4, 113.2, 111.3, 86.8, 86.4, 78.0, 71.7, 61.9, 61.8, 55.6, 55.5, 51.5, 42.9, 42.0, 33.6, 30.7, 20.8; IR (film): $\tilde{\nu}$ = 2972, 2908, 2870, 1741, 1720, 1606, 1510, 1491, 1463, 1446, 1412, 1364, 1300, 1250, 1232, 1200,1180, 1155, 1134, 1115, 1080, 1034, 989, 936, 901, 850, 831, 796, 766, 748, 727, 707, 672, 665, 633, 614, 586, 545, 464 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{55}H_{52}O_9Na$ [M+Na$^+$]: 879.3503, found: 879.3500.

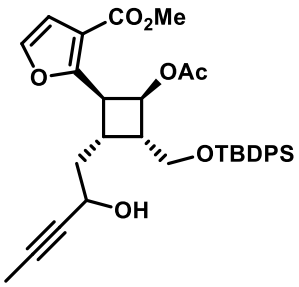
Recycling of 227a+227b to 222. Pyridinium *p*-toluenesulfonate (10 mg, 0.04 mmol, 0.1 eq.) was added to a stirred solution of **227a** (119 mg, 0.20 mmol) and **227b** (165 mg, 0.19 mmol) in CH_2Cl_2/MeOH (4:1 *v*/*v*, 4 mL) at room temperature. The resulting mixture was stirred for 4 h, before the reaction was quenched with sat. aq. $NaHCO_3$ (2 mL) and water (2 mL). The aqueous phase was extracted with Et_2O (3 x 50 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated, and the residue was purified by flash chromatography on silica (EtOAc) to give product **222** as a colorless oil (99 mg, 80% yield).

Methyl 2-((1*R*,2*S*,3*S*,4*S*)-2-acetoxy-3-(((*tert*-butyldiphenylsilyl)oxy)methyl)-4-(2-((4-methoxy-phenyl)diphenylmethoxy)ethyl)cyclobutyl)furan-3-carboxylate (228). 4-Dimethylaminopyridine (9 mg, 0.07 mmol, 0.05 eq.), triethylamine (1.4 mL, 10.06 mmol) and *tert*-butyldiphenylsilyl chloride (0.56 mL, 2.16 mmol) were added to a stirred solution of alcohol **227** (840 mg, 1.44 mmol) in CH_2Cl_2 (17 mL). The resulting mixture was stirred for 2 d at room temperature before the reaction was quenched with sat. aq. $NaHCO_3$ (10 mL). The mixture was diluted with CH_2Cl_2 (20 mL), the aqueous phase was extracted with CH_2Cl_2 (3 x 100 mL), the combined organic layers were dried over $MgSO_4$ and concentrated, and the residue was purified by flash chromatography on silica (hexanes:EtOAc, 4:1) to provide the title compound as a colorless oil (1.10 g, 93% yield). $[\alpha]_D^{20}$ = –8.1° (c = 1.0, MeOH); ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.69 (dt, *J* = 8.1, 1.6 Hz, 4H), 7.47 – 7.37 (m, 6H), 7.32 (ddt, *J* = 4.6, 3.2, 1.6 Hz, 5H), 7.25 – 7.13 (m, 8H), 6.77 – 6.72 (m, 2H), 6.66 (d, *J* = 2.0 Hz, 1H), 5.31 – 5.27 (m, 1H), 4.24 (ddd, *J* = 7.9, 6.5, 1.1 Hz, 1H), 3.87 (qd, *J* = 10.7, 6.2 Hz, 2H), 3.76 (s, 3H), 3.69 (s, 3H), 3.29 – 3.19 (m, 1H), 3.05 – 2.85 (m, 3H), 2.10 – 1.99 (m, 1H), 1.82 (h, *J* = 5.5 Hz, 1H), 1.78 (s, 3H), 1.08 (s, 9H); ^{13}C NMR (101 MHz, CD_2Cl_2): δ = 170.0, 164.1, 159.2, 158.9, 145.4, 145.2, 141.5, 136.3, 136.1, 136.0, 134.0, 133.9, 130.6, 130.1, 128.7, 128.6, 128.1, 128.0, 127.1, 127.0, 115.0, 113.3, 111.3, 86.4, 71.4, 62.4, 61.9, 55.5, 51.5, 44.5, 41.8, 33.9, 30.9, 27.1, 20.7, 19.5; IR (film): $\tilde{\nu}$ = 3069, 2952, 2931, 2858, 1740, 1719, 1603, 1510, 1489, 1463, 1445, 1428, 1412, 1390, 1372, 1302, 1233, 1195, 1180, 1156, 1112, 1089, 1066, 1034, 954, 901, 826, 796, 766, 743, 704, 632, 613, 586, 505 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{51}H_{54}O_8SiNa$ [M+Na$^+$]: 845.3480, found: 845.3474.

Methyl 2-((1*R*,2*S*,3*S*,4*S*)-2-acetoxy-3-(((*tert*-butyldiphenylsilyl)oxy)methyl)-4-(2-hydroxy-ethyl)cyclo-butyl)furan-3-carboxylate (194). Pyridinium *p*-toluenesulfonate (33 mg, 0.13 mmol, 0.1 eq.) was added to a stirred solution of furan **228** (1.09 g, 1.32 mmol) in a mixture of CH_2Cl_2/MeOH (4:1 *v*/*v*, 27 mL). The solution was stirred for 5 h at room temperature before the reaction was quenched upon addition of sat. aq. $NaHCO_3$ (10 mL). The mixture was diluted with water (10 mL), the aqueous phase was extracted with Et_2O (3 x 100 mL), the combined extracts were dried over $MgSO_4$ and concentrated, and the residue was purified by flash chromatography on silica

(hexanes:EtOAc, 3:1) to give the title compound as a colorless oil (683 mg, 94% yield). $[\alpha]_D^{20}$ = –3.6° (c = 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.72 – 7.64 (m, 4H), 7.47 – 7.36 (m, 6H), 7.34 (d, *J* = 1.9 Hz, 1H), 6.68 (d, *J* = 1.9 Hz, 1H), 5.29 (dd, *J* = 7.7, 5.5 Hz, 1H), 4.35 – 4.29 (m, 1H), 3.94 – 3.81 (m, 2H), 3.79 (s, 3H), 3.67 – 3.52 (m, 2H), 3.11 (tt, *J* = 10.0, 6.3 Hz, 1H), 2.95 – 2.85 (m, 1H), 1.97 (ddt, *J* = 13.8, 7.6, 6.2 Hz, 1H), 1.82 (s, 3H), 1.80 – 1.73 (m, 1H), 1.08 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 169.8, 164.0, 158.8, 141.1, 135.7, 133.3, 133.2, 129.8, 127.7, 114.6, 111.0, 71.2, 61.9, 61.3, 51.5, 44.1, 41.4, 33.7, 33.0, 26.9, 20.5, 19.2; IR (film): $\tilde{\nu}$ = 3466, 2953, 2932, 2859, 1740, 1720, 1597, 1518, 1472, 1443, 1428, 1391, 1372, 1307, 1284, 1235, 1197, 1160, 1133, 1111, 1087, 1048, 939, 823, 799, 742, 704, 612, 505, 491 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{31}H_{38}O_7SiNa$ [M+Na^+]: 573.2279, found: 573.2277.

Compound 230. Sodium bicarbonate (8 mg, 0.09 mmol) and Dess-Martin-periodinane (12 mg, 0.03 mmol) were added to a solution of alcohol **194** (10 mg, 0.02 mmol) in CH_2Cl_2 (0.5 mL) at 0 °C. The resulting mixture was stirred at this temperature for 1.5 h before it was diluted with CH_2Cl_2 (3 mL). The reaction was quenched with a mixture of sat. aq. $Na_2S_2O_3$/$NaHCO_3$ (1:1 *v*/*v*, 3 mL) and the resulting mixture was vigorously stirred for 30 min. The aqueous phase was diluted with water (2 mL) and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (3 x 20 mL), dried over $MgSO_4$ and concentrated to give the desired aldehyde **229** as a colorless oil (9 mg, 93% yield). The crude aldehyde thus formed was used in the next step without further purification.



1-Propinylmagnesium bromide (0.5 M in THF, 0.07 mL, 0.03 mmol) was added dropwise to a stirred solution of this crude aldehyde **229** (19 mg, 0.03 mmol) in THF (0.4 mL) at –78 °C. The resulting mixture was stirred for 10 min at –78 °C before the reaction was quenched with sat. aq. NH_4Cl (1 mL). After reaching room temperature, the mixture was diluted with *tert*-butyl methyl ether (10 mL) and water (3 mL). The aqueous phase was extracted with *tert*-butyl methyl ether (3 x 20 mL), the combined organic layers were washed with brine (4 mL), dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography on silica (hexanes:MTBE, 2:1) to provide the title compound as a colorless oil (12 mg, 59% yield). ^1H NMR (400 MHz, $CDCl_3$, mixture of diastereomers): δ = 7.72 – 7.66 (m, 4H), 7.48 – 7.37 (m, 6H), 7.34 (d, *J* = 2.0 Hz, 1H), 6.68 (t, *J* = 2.1 Hz, 1H), 5.34 – 5.24 (m, 1H), 4.41 – 4.27 (m, 2H), 3.94 – 3.81 (m, 2H), 3.78 (d, *J* = 1.1 Hz, 3H), 3.35 – 3.21 (m, 1H), 2.88 (ttd, *J* = 6.9, 5.2, 3.2 Hz, 1H), 2.10 (ddd, *J* = 13.9, 7.3, 5.2 Hz, 1H), 1.95 (ddd, *J* = 13.7, 9.3, 5.8 Hz, 1H), 1.81 (s, 3H), 1.76 (d, *J* = 2.1 Hz, 1H, minor diastereomer), 1.73 (d, *J* = 2.1 Hz, 2H, major diastereomer), 1.09 (d, *J* = 1.4 Hz, 9H). ^{13}C NMR (101 MHz, $CDCl_3$, mixture of diastereomers): δ = 169.8, 164.0, 158.6, 141.14, 141.08, 135.69, 135.66, 133.25, 133.18, 133.16, 133.13, 129.8, 129.7, 127.7, 114.5, 111.05, 111.02, 81.3, 81.1, 80.2, 79.8, 71.35, 71.32, 61.88, 61.86, 61.4, 61.3, 51.4, 51.4, 44.2, 41.7, 41.4, 38.5, 38.4, 33.2, 33.0, 26.9, 20.5, 19.2, 3.4. IR (film): $\tilde{\nu}$ = 3467, 3071, 3049, 2953, 2931, 2857, 1739, 1719, 1596,

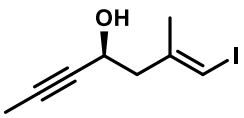
1518, 1472, 1443, 1428, 1390, 1373, 1305, 1233, 1196, 1158, 1135, 1046, 1109, 1008, 937, 912, 889, 823, 803, 739, 703, 610, 505, 491 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{34}H_{40}O_7SiNa$ [$M+Na^+$]: 611.2435, found: 611.2435.

Methyl 2-((1*R*,2*S*,3*S*,4*S*)-2-acetoxy-3-(((*tert*-butyldiphenylsilyl)oxy)methyl)-4-(2-hydroxyethyl)cyclo-butyl)-5-vinylfuran-3-carboxylate (233). Lithium carbonate (2 mg, 0.03 mmol), AgOMs (12 mg, 0.06 mmol) and iodine (15 mg, 0.06 mmol) were successively added to a stirred solution of furan **194** (15 mg, 0.03 mmol) in acetonitrile (0.4 mL) at room temperature. The resulting mixture was stirred for 10 min before it was diluted with EtOAc (10 mL) and sat. aq. $Na_2S_2O_3$/$NaHCO_3$ (1:1 *v*/*v*, 10 mL). The biphasic mixture was vigorously stirred for 10 min until full decolorization and a homogenous solution was observed. The aqueous phase was diluted with water (5 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$ and concentrated. The crude iodofuran **231** thus formed was used in the next step without further purification.

The commercial palladium complex XPhos-Pd-G2 (**235**) (3 mg, 0.004 mmol) was added to a stirred solution of iodofuran **231** (18 mg, 0.027 mmol) and potassium (ethenyl)trifluoroborate (**232**) (7 mg, 0.05 mmol) in a mixture of THF (1 mL) and aqueous K_3PO_4 (3 M, 0.1 mL). The resulting mixture was stirred for 6 h at 55 °C before Et_2O (20 mL) and water (5 mL) were added. The aqueous phase was extracted with Et_2O (3 x 70 mL), the combined organic layers were washed with brine (10 mL), dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography on silica (hexanes:EtOAc, 3:1) to afford the title compound as a brown oil (6.8 mg, 44% yield over 2 steps). $[\alpha]_D^{20}$ = –84.6° (c = 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.72 – 7.67 (m, 4H), 7.48 – 7.38 (m, 6H), 6.54 – 6.44 (m, 2H), 5.76 – 5.68 (m, 1H), 5.30 – 5.21 (m, 2H), 4.32 (ddd, *J* = 7.8, 6.7, 1.1 Hz, 1H), 3.98 – 3.83 (m, 2H), 3.76 (s, 3H), 3.64 – 3.49 (m, 2H), 3.11 (tddd, *J* = 9.9, 6.6, 5.7, 1.0 Hz, 1H), 2.98 – 2.87 (m, 1H), 2.02 – 1.91 (m, 1H), 1.85 – 1.73 (m, 4H), 1.08 (s, 9H); ^{13}C NMR (101 MHz, CD_2Cl_2): δ = 170.2, 164.2, 158.8, 152.0, 136.1, 136.0, 133.9, 133.8, 130.1, 128.1, 124.8, 116.3, 113.4, 108.9, 71.5, 62.4, 61.5, 51.7, 44.6, 41.9, 34.5, 33.6, 27.0, 20.8, 19.5; IR (film): $\tilde{\nu}$ = 3463, 3071, 2952, 2932, 2858, 1740, 1719, 1643, 1591, 1538, 1472, 1442, 1428, 1411, 1373, 1298, 1229, 1111, 1068, 980, 939, 906, 823, 781, 741, 703, 611, 505, 491 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{33}H_{40}O_7SiNa$ [$M+Na^+$]: 599.2435, found: 599.2435.

(*E*)-4-Iodo-3-methylbut-3-en-1-ol (237). This compound was prepared according to the literature procedure.[229] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.02 (q, *J* = 1.2 Hz, 1H), 3.72 (t, *J* = 6.3 Hz, 2H), 2.48 (td, *J* = 6.3, 1.1 Hz, 2H), 1.88 (d, *J* = 1.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 144.6, 76.9, 60.1, 42.4, 23.8; HRMS (ESI): *m*/*z* calcd. for C_5H_9OI [M^+]: 211.9692, found: 211.9694.

(*S*,*E*)-1-Iodo-2-methylhept-1-en-5-yn-4-ol (238). Sodium bicarbonate (5.35 g, 63.67 mmol) and



Dess-Martin periodinane (6.75 g, 15.92 mmol) were added to a solution of alcohol **237** (1.35 g, 6.37 mmol) in CH_2Cl_2 (50 mL) at 0 °C. The resulting mixture was stirred at room temperature for 1 h before it was cooled to 0 °C and a mixture of sat. aq. $Na_2S_2O_3$/$NaHCO_3$ (1:1 *v*/*v*, 50 mL) was added. The resulting mixture was vigorously stirred for 30 min before it was diluted with water (100 mL) and extracted with CH_2Cl_2 (3 x 150 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (3 x 150 mL), dried over $MgSO_4$ and concentrated *in vacuo* (Caution: the aldehyde is volatile! The temperature must be kept at 20 °C and the pressure > 250 mbar). The crude aldehyde was used in the next step without further purification.

Triethylamine (1.85 mL, 13.29 mmol) was added to a rigorously stirred suspension of $Zn(OTf)_2$ (4.60 g, 12.65 mmol) and (1*R*,2*S*)-(–)-*N*-methylephedrine (2.38 g, 13.29 mmol) in toluene (43 mL). The resulting mixture was stirred for 2 h at room temperature before it was cooled to 0 °C and liquid propyne (4 mL, 98.7 mmol) was added via cannula. After stirring for another 45 min at room temperature, a solution of the crude aldehyde (1.33 g, 6.33 mmol) in toluene (6 mL) was slowly added over the course of 4 h. Once the addition was complete, stirring was continued for 16 h before the reaction was quenched with sat. aq. NH_4Cl (30 mL). The mixture was diluted with water (30 mL), the aqueous phase was extracted with Et_2O (3 x 150 mL), the combined extracts were washed with brine (50 mL), dried over $MgSO_4$ and concentrated (T ≥ 20 °C; the compound is heat sensitive!), and the residue was purified by flash chromatography on silica (pentane:Et_2O, 4:1) to provide the title compound as a yellow oil (512 mg, 32% yield, 88% ee). The characterization data are in accordance with the literature.[91] $[\alpha]_D^{20}$ = –12.9° (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.08 (q, *J* = 1.1 Hz, 1H), 4.48 – 4.43 (m, 1H), 2.64 – 2.51 (m, 2H), 1.91 (d, *J* = 1.1 Hz, 3H), 1.84 (d, *J* = 2.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 143.5, 81.9, 79.4, 78.4, 60.6, 47.6, 24.3, 3.5. HRMS (ESI): *m*/*z* calcd. for $C_8H_{12}OI$ [M+H$^+$]: 250.9927, found: 250.9927.

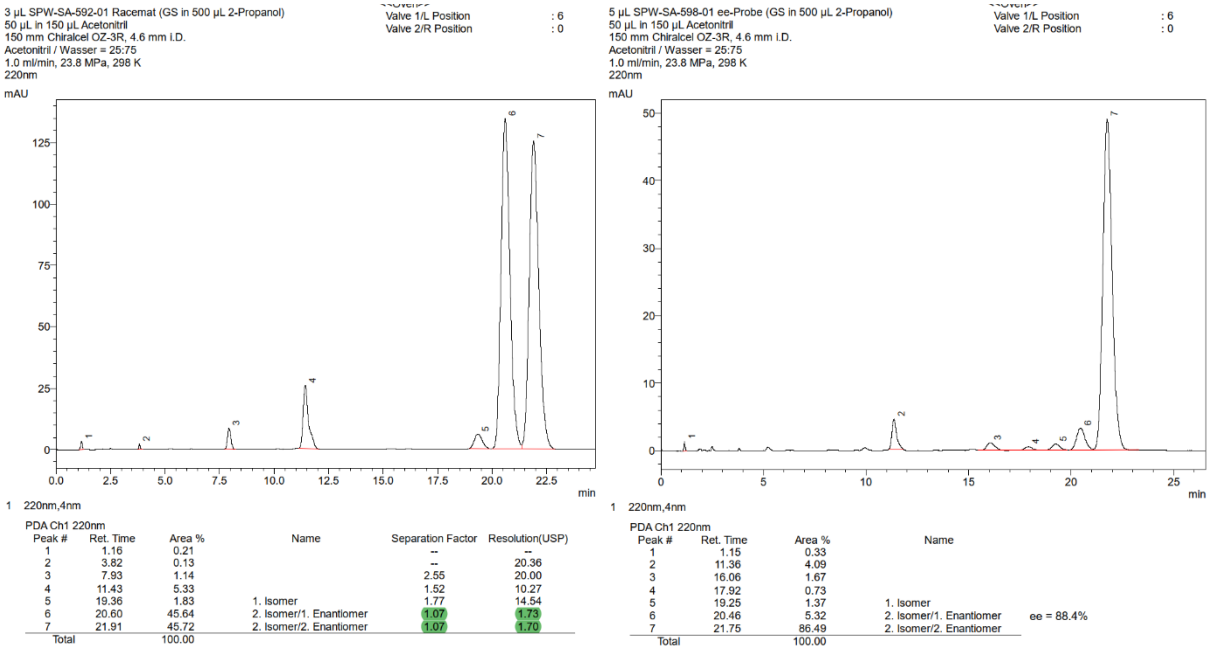
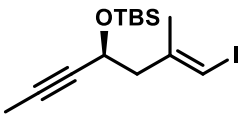
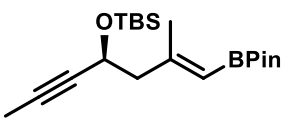


Figure 4.8. HPLC-traces of rac-**238**[91] (left) and enantioenriched **238** (right): t_R = 20.46 min (minor enantiomer) and 21.75 min (major enantiomer) (Chiralcel OZ-3R column, λ = 220 nm, isocratic elution 25:75 acetonitrile/water, flow-rate = 1.0 mL/min).

(*S*,*E*)-*tert*-butyl((1-iodo-2-methylhept-1-en-5-yn-4-yl)oxy)dimethylsilane (239). Imidazole (30 mg, 0.44 mmol) and *tert*-butyldimethylsilyl chloride (66 mg, 0.44 mmol) were added to a stirred solution of alcohol **238** (100 mg, 0.40 mmol) in CH_2Cl_2 (1.1 mL), and the resulting mixture was stirred for 16 h at room temperature. The reaction was quenched with sat. aq. $NaHCO_3$ (5 mL) and the aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL). The combined extracts were dried over Na_2SO_4 and concentrated, and the residue was purified by flash chromatography on silica (pentane:*tert*-butyl methyl ether, 60:1) to afford the title compound as a colorless oil (96 mg, 66% yield). The spectral data are in accordance with the literature.[91] $[\alpha]_D^{20}$ = –35.4° (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.99 (h, *J* = 1.1 Hz, 1H), 4.40 (ddq, *J* = 7.4, 5.3, 2.1 Hz, 1H), 2.61 – 2.44 (m, 2H), 1.86 (d, *J* = 1.2 Hz, 3H), 1.81 (d, *J* = 2.1 Hz, 3H), 0.88 (s, 9H), 0.09 (d, *J* = 11.5 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 143.8, 80.8, 80.1, 78.2, 61.5, 48.4, 25.7, 24.4, 18.2, 3.5, –4.6, –5.1. HRMS (ESI): *m*/*z* calcd. for $C_{14}H_{25}O_1ISiNa$ [M+Na$^+$]: 387.0612, found: 387.0613.



Compound 241. *n*-BuLi (1.6 M in hexanes, 0.11 mL, 0.18 mmol) was added dropwise to a stirred solution of alkenyl iodide **239** (50 mg, 0.14 mmol) and triisopropyl borate (0.04 mL, 0.18 mmol) in a mixture of THF (0.2 mL) and toluene (0.9 mL) at –78 °C. The resulting mixture was rigorously stirred for 40 min at –78 °C before pinacol (24 mg, 0.21 mmol) was added as a solid. The mixture was warmed to room temperature and stirring was continued for an additional 16 h. Et_2O (50 mL)



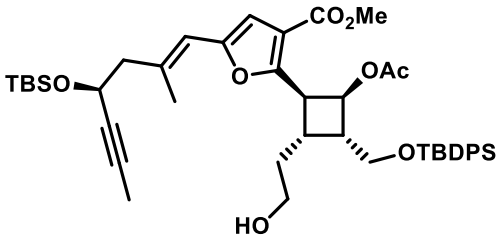
was added and the organic phase was washed with sat. aq. NH_4Cl (10 mL), water (10 mL), brine (10 mL), dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography on silica (pentane:Et_2O, 20:1) to give the title compound as a colorless oil (47 mg, 95% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.18 (q, *J* = 1.0 Hz, 1H), 4.44 (ddq, *J* = 7.5, 6.2, 2.0 Hz, 1H), 2.49 – 2.37 (m, 2H), 2.01 (d, *J* = 1.0 Hz, 3H), 1.81 (d, *J* = 2.1 Hz, 3H), 1.25 (s, 12H), 0.88 (s, 9H), 0.09 (d, *J* = 9.9 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 158.4, 82.6, 80.8, 80.3, 62.4, 51.3, 25.8, 24.8, 21.8, 18.3, 3.5, –4.6, –5.1. IR (film): $\tilde{\nu}$ = 2978, 2957, 2929, 2857, 1641, 1472, 1441, 1402, 1386, 1369, 1349, 1319, 1283, 1257, 1215, 1143, 1084, 1050, 1031, 1005, 971, 941, 900, 869, 852, 836, 811, 777, 663 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{20}H_{37}O_3BSiNa$ [M+Na$^+$]: 387.2508, found: 387.2500.

(*S*,*E*)-1-Iodo-4-(methoxymethoxy)-2-methylhept-1-en-5-yne (242). *N*,*N*-Diisopropylethylamine (0.94 mL, 5.39 mmol) and chloromethyl methyl ether (0.21 mL, 2.70 mmol) were added to a stirred solution of alcohol **238** (168 mg, 0.67 mmol) in CH_2Cl_2 (1.9 mL) at 0 °C. The resulting mixture was stirred at room temperature for 16 h before the reaction was quenched with sat. aq. $NaHCO_3$ (3 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL), the combined extracts were dried over $MgSO_4$ and concentrated, and the residue was purified by flash chromatography on silica (pentane:Et_2O, 60:1) to afford the title compound as a colorless oil (133 mg, 67% yield). $[\alpha]_D^{20}$ = –57.8° (c = 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 6.06 (q, *J* = 1.1 Hz, 1H), 4.88 (d, *J* = 6.8 Hz, 1H), 4.51 (dd, *J* = 6.8, 0.5 Hz, 1H), 4.43 – 4.36 (m, 1H), 3.30 (s, 3H), 2.66 – 2.50 (m, 2H), 1.89 (d, *J* = 1.1 Hz, 3H), 1.83 (d, *J* = 2.1 Hz, 3H); ^{13}C NMR (101 MHz, CD_2Cl_2): δ = 144.3, 94.2, 82.7, 78.1, 77.4, 64.3, 55.9, 45.8, 24.5, 3.6; IR (film): $\tilde{\nu}$ = 2949, 2918, 2888, 2849, 2822, 1439, 1377, 1346, 1277, 1226, 1148, 1096, 1060, 1027, 969, 947, 919, 761, 671 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{10}H_{15}O_2INa$ [M+Na$^+$]: 317.0009, found: 317.0011.

(*S*,*E*)-2-(4-(Methoxymethoxy)-2-methylhept-1-en-5-yn-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (243). *n*-BuLi (1.6 M in hexanes, 0.35 mL, 0.56 mmol) was added dropwise to a stirred solution of alkenyl iodide **242** (127 mg, 0.43 mmol) and triisopropyl borate (0.13 mL, 0.56 mmol) in a mixture of THF (0.7 mL) and toluene (2.7 mL) at –78 °C. The resulting mixture was stirred for 40 min at –78 °C before pinacol (77 mg, 0.65 mmol) was added as a solid. The mixture was warmed to room temperature and stirring was continued for an additional 16 h. Et_2O (50 mL) was added and the organic phase was washed with sat. aq. NH_4Cl (10 mL), water (10 mL), brine (10 mL), dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography on silica (pentane:Et_2O, 20:1 to 10:1) to give the title compound as a colorless oil (107 mg, 84% yield). $[\alpha]_D^{20}$ = –97.4° (c = 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 5.16 (q, *J* = 1.1 Hz, 1H), 4.89 (d, *J* = 6.7 Hz, 1H), 4.52 (dd, *J* = 6.8, 0.5 Hz, 1H), 4.43 (ddt, *J* = 9.4, 6.3, 2.1 Hz, 1H), 3.30 (s, 3H), 2.54 – 2.40 (m, 2H), 2.01 (d, *J* = 1.0 Hz, 3H), 1.83 (d, *J* = 2.1 Hz, 3H), 1.24 (s, 12H); ^{13}C NMR (101 MHz, CD_2Cl_2): δ = 158.0, 94.2, 83.0, 82.1, 78.0, 64.9, 55.8, 48.8, 25.0, 21.5, 3.6; IR (film): $\tilde{\nu}$ =

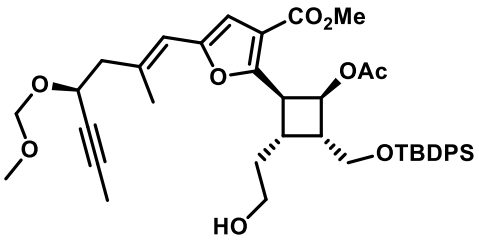
2978, 2923, 1640, 1441, 1401, 1370, 1350, 1319, 1283, 1262, 1214, 1144, 1098, 1064, 1030, 970, 919, 853 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{16}H_{27}O_4BNa$ [M+Na^+]: 317.1894, found: 317.1896.

Compound 244. Lithium carbonate (9 mg, 0.13 mmol), AgOMs (48 mg, 0.24 mmol) and iodine (60 mg, 0.24 mmol) were successively added to a stirred solution of furan **194** (65 mg, 0.12 mmol) in acetonitrile (1.6 mL) at room temperature. The resulting mixture was stirred for 10 min before EtOAc (10 mL) and a mixture of sat. aq. $Na_2S_2O_3$:$NaHCO_3$ (1:1 *v*/*v*, 10 mL) were added. The biphasic mixture was vigorously stirred for 10 min until full decolorization and a homogenous solution was observed. The aqueous phase was diluted with water (5 mL) and extracted with EtOAc (3 x 70 mL). The combined extracts were washed with brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude iodofuran **231** was used in the next step without further purification.



The commercial palladium complex XPhos-Pd-G2 (**235**) (12.5 mg, 0.016 mmol, 0.15 eq.) was added to a stirred solution of **231** (72 mg, 0.11 mmol) and boronic ester **241** (42 mg, 0.12 mmol) in a mixture of THF (0.8 mL) and aqueous K_3PO_4 (3 M, 0.1 mL) at room temperature. The resulting mixture was stirred for 1.5 h at 50 °C before it was diluted with Et_2O (20 mL) and water (5 mL). The aqueous phase was extracted with Et_2O (3 x 70 mL), the combined organic layers were washed with brine (10 mL), dried over $MgSO_4$ and concentrated, and the residue was purified by flash chromatography on silica (hexanes:EtOAc, 3:1) to afford the title compound as a brown oil (37 mg, 42% yield over 2 steps). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.70 – 7.65 (m, 4H), 7.47 – 7.37 (m, 6H), 6.44 (s, 1H), 6.10 (s, 1H), 5.27 (ddd, *J* = 7.8, 5.5, 0.9 Hz, 1H), 4.48 (tt, *J* = 5.6, 2.1 Hz, 1H), 4.30 (ddd, *J* = 7.6, 6.4, 1.0 Hz, 1H), 3.93 – 3.81 (m, 2H), 3.78 (s, 3H), 3.69 – 3.51 (m, 2H), 3.07 (tt, *J* = 9.9, 6.1 Hz, 1H), 3.00 – 2.88 (m, 1H), 2.60 – 2.41 (m, 2H), 2.05 (d, *J* = 1.2 Hz, 3H), 2.01 – 1.92 (m, 1H), 1.82 (d, *J* = 2.1 Hz, 3H), 1.81 (s, 3H), 1.79 – 1.72 (m, 1H), 1.07 (s, 9H), 0.88 (s, 9H), 0.10 (d, *J* = 14.1 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 169.9, 164.2, 156.9, 152.0, 135.6, 135.6, 135.5, 133.3, 133.2, 129.8, 127.7, 116.4, 115.7, 108.4, 80.7, 80.6, 71.2, 62.1, 61.9, 61.4, 51.4, 50.1, 44.2, 41.4, 33.9, 33.0, 26.8, 25.8, 20.6, 19.4, 19.2, 18.2, 3.5, –4.6, –5.1. IR (film): $\tilde{\nu}$ = 3523, 3071, 3048, 2953, 2931, 2894, 2857, 1742, 1719, 1597, 1549, 1472, 1462, 1442, 1429, 1389, 1362, 1234, 1111, 1077, 1007, 938, 837, 778, 741, 704, 612, 505, 490 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{45}H_{62}O_8SiNa$ [M+Na^+]: 809.3875, found: 809.3874.

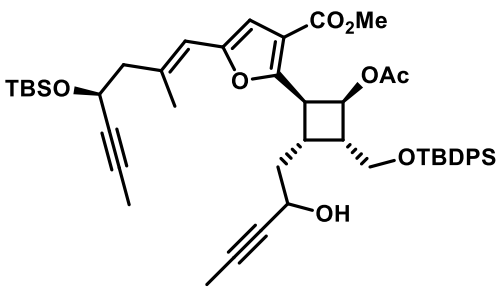
Methyl 2-((1*R*,2*S*,3*S*,4*S*)-2-acetoxy-3-(((*tert*-butyldiphenylsilyl)oxy)methyl)-4-(2-hydroxyethyl)cyclo-butyl)-5-((*S*,*E*)-4-(methoxymethoxy)-2-methylhept-1-en-5-yn-1-yl)furan-3-carboxylate (245).



Lithium carbonate (29 mg, 0.40 mmol), AgOMs (162 mg, 0.80 mmol) and iodine (203 mg, 0.80 mmol) were successively added to a stirred solution of furan **194** (200 mg, 0.36 mmol) in acetonitrile (4.8 mL) at room temperature. The resulting mixture was stirred for 10 min before EtOAc (10 mL) and a mixture of sat. aq. $Na_2S_2O_3$:$NaHCO_3$ (1:1 *v*/*v*, 10 mL) were added. The biphasic mixture was vigorously stirred for 10 min until full decolorization and a homogenous solution was observed. The aqueous phase was diluted with water (5 mL) and extracted with EtOAc (3 x 70 mL). The combined extracts were washed with brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude iodofuran **231** was used in the next step without further purification.

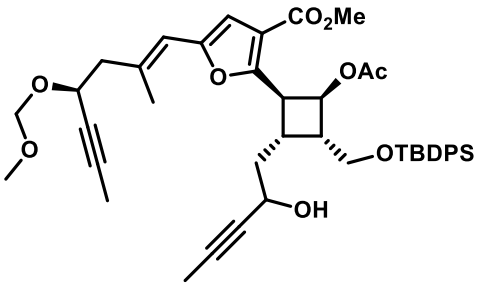
The commercial palladium complex XPhos-Pd-G2 (**235**) (47 mg, 0.06 mmol, 0.25 eq.) was added to a stirred solution of **231** (200 mg, 0.24 mmol) and boronic ester **243** (76 mg, 0.26 mmol) in a mixture of THF (1.8 mL) and aqueous K_3PO_4 (3 M, 0.2 mL) at room temperature. The resulting mixture was stirred for 4 h at 50 °C before it was diluted with Et_2O (20 mL) and water (5 mL). The aqueous phase was extracted with Et_2O (3 x 70 mL), the combined organic layers were washed with brine (10 mL), dried over $MgSO_4$ and concentrated, and the residue was purified by flash chromatography on silica (hexanes:EtOAc, 3:1 to 2:1) to afford the title compound as a brown oil (97 mg, 39% yield over 2 steps). $[\alpha]_D^{20}$ = –48.7° (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.71 – 7.65 (m, 4H), 7.48 – 7.36 (m, 6H), 6.46 (s, 1H), 6.15 (d, *J* = 1.4 Hz, 1H), 5.27 (ddd, *J* = 7.8, 5.6, 0.9 Hz, 1H), 4.92 (d, *J* = 6.8 Hz, 1H), 4.54 (d, *J* = 6.8 Hz, 1H), 4.48 (ddq, *J* = 8.1, 6.2, 2.1 Hz, 1H), 4.31 (ddd, *J* = 7.5, 6.3, 0.9 Hz, 1H), 3.95 – 3.82 (m, 2H), 3.76 (s, 3H), 3.59 – 3.46 (m, 2H), 3.30 (s, 3H), 3.05 (tt, *J* = 9.9, 5.9 Hz, 1H), 2.95 (dtd, *J* = 10.5, 6.3, 5.2 Hz, 1H), 2.62 – 2.49 (m, 2H), 2.09 (d, *J* = 1.2 Hz, 3H), 2.01 – 1.90 (m, 1H), 1.83 (d, *J* = 2.1 Hz, 3H), 1.82 – 1.71 (m, 4H), 1.07 (s, 9H); ^{13}C NMR (101 MHz, CD_2Cl_2): δ = 170.1, 164.4, 157.6, 152.3, 135.99, 135.97, 135.7, 133.80, 133.75, 130.1, 128.1, 116.4, 116.1, 108.9, 94.1, 82.4, 77.7, 71.5, 64.8, 62.3, 61.5, 55.7, 51.7, 47.5, 44.6, 41.7, 34.2, 33.5, 27.0, 20.7, 19.4, 19.2, 3.6; IR (film): $\tilde{\nu}$ = 3503, 3071, 3047, 2930, 2858, 1741, 1718, 1597, 1549, 1442, 1428, 1377, 1233, 1149, 1110, 1058, 1031, 975, 939, 919, 823, 778, 742, 704, 611, 505, 491 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{41}H_{52}O_9SiNa$ [M+Na$^+$]: 739.3272, found: 739.3275.

Compound 246. Sodium bicarbonate (40 mg, 0.48 mmol) and Dess-Martin-periodinane (40 mg, 0.09 mmol) were added to a solution of alcohol **244** (25 mg, 0.03 mmol) in CH_2Cl_2 (0.9 mL) at 0 °C. The resulting mixture was stirred at this temperature for 3.5 h before it was diluted with CH_2Cl_2 (3 mL). The reaction was quenched with a mixture of sat. aq. $Na_2S_2O_3$/$NaHCO_3$ (1:1 *v*/*v*, 3 mL) and the resulting mixture was vigorously stirred for 30 min. The aqueous phase was diluted with water (2 mL) and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (3 x 20 mL), dried over $MgSO_4$ and concentrated. The crude aldehyde thus formed was used in the next step without further purification.



1-Propinylmagnesium bromide (0.5 M in THF, 0.12 mL, 0.06 mmol) was added dropwise to a stirred solution of this crude aldehyde (24 mg, 0.03 mmol) in THF (1.5 mL) at –78 °C. The resulting mixture was stirred for 10 min at –78 °C before the reaction was quenched with sat. aq. NH_4Cl (1 mL). After reaching room temperature, the mixture was diluted with *tert*-butyl methyl ether (10 mL) and water (3 mL). The aqueous phase was extracted with *tert*-butyl methyl ether (3 x 20 mL), the combined organic layers were washed with brine (4 mL), dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography on silica (hexanes:MTBE, 2:1) to provide the title compound as a faint yellow oil (12 mg, 40% yield over 2 steps). ^{1}H NMR (400 MHz, CD_2Cl_2, mixture of diastereomers): δ = 7.74 – 7.65 (m, 4H), 7.50 – 7.35 (m, 6H), 6.44 (d, *J* = 2.3 Hz, 1H), 6.15 – 6.10 (m, 1H), 5.31 – 5.24 (m, 1H), 4.51 (dtd, *J* = 7.2, 4.0, 2.1 Hz, 1H), 4.36 (ddd, *J* = 7.8, 6.7, 1.1 Hz, 1H), 4.29 (s, 1H), 3.89 (qdd, *J* = 10.9, 6.2, 2.8 Hz, 2H), 3.76 (s, 3H), 3.28 – 3.18 (m, 1H), 2.93 (dddd, *J* = 10.9, 8.0, 5.4, 1.2 Hz, 1H), 2.54 – 2.43 (m, 2H), 2.08 (d, *J* = 1.3 Hz, 3H), 2.06 – 2.02 (m, 1H), 1.94 (ddt, *J* = 13.9, 11.0, 5.7 Hz, 1H), 1.81 (d, *J* = 2.1 Hz, 3H), 1.79 (d, *J* = 1.0 Hz, 3H), 1.74 (d, *J* = 2.1 Hz, 0.7H, minor diastereomer), 1.72 (d, *J* = 2.1 Hz, 2.3H, major diastereomer), 1.08 (s, 9H), 0.88 (s, 9H), 0.10 (d, *J* = 14.2 Hz, 6H). ^{13}C NMR (101 MHz, CD_2Cl_2, mixture of diastereomers): δ = 170.1, 164.43, 164.40, 157.41, 157.37, 152.5, 152.4, 136.07, 136.05, 136.01, 135.96, 133.83, 133.78, 133.75, 130.1, 128.1, 116.73, 116.70, 116.09, 116.06, 108.8, 108.7, 81.4, 81.2, 81.0, 80.6, 80.3, 71.7, 71.6, 62.54, 62.50, 62.4, 61.8, 61.6, 51.6, 50.5, 44.7, 42.1, 38.9, 33.8, 30.1, 28.7, 27.0, 25.9, 20.8, 19.6, 19.5, 18.5, 3.6, 3.5, –4.4, –5.0. HRMS (ESI): *m*/*z* calcd. for $C_{48}H_{64}O_8Si_2Na$ [M+Na$^+$]: 847.4032, found: 847.4029.

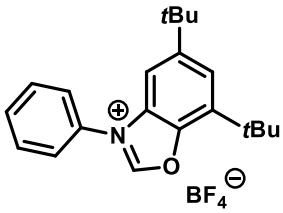
Methyl 2-((1*R*,2*S*,3*S*,4*S*)-2-acetoxy-3-(((*tert*-butyldiphenylsilyl)oxy)methyl)-4-(2-hydroxy-pent-3-yn-1-yl)cyclobutyl)-5-((*S*,*E*)-4-(methoxy-methoxy)-2-methyl-hept-1-en-5-yn-1-yl)furan-3-carboxylate (247). Sodium bicarbonate (35 mg, 0.42 mmol) and Dess-Martin-periodinane (36 mg, 0.08 mmol) were added to a solution of alcohol **245** (20 mg, 0.03 mmol) in CH_2Cl_2 (0.8 mL) at 0 °C. The resulting mixture was stirred at this temperature for 3.5 h before it was diluted with CH_2Cl_2 (3 mL). The reaction was quenched with a mixture of sat. aq. $Na_2S_2O_3$/$NaHCO_3$ (1:1 *v*/*v*, 3 mL) and the resulting mixture was vigorously stirred for 30 min. The aqueous phase was diluted with water (2 mL) and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (3 x 20 mL), dried over $MgSO_4$ and concentrated. The crude aldehyde thus formed was used in the next step without further purification.



1-Propinylmagnesium bromide (0.5 M in THF, 0.13 mL, 0.07 mmol) was added dropwise to a stirred solution of this crude aldehyde (19 mg, 0.03 mmol) in THF (1.3 mL) at –78 °C. The resulting mixture was stirred for 10 min at –78 °C before the reaction was quenched with sat. aq. NH_4Cl (1 mL). After reaching room temperature, the mixture was diluted with *tert*-butyl methyl ether (10 mL) and water (3 mL). The aqueous phase was extracted with *tert*-butyl methyl ether (3 x 20 mL), the combined organic layers were washed with brine (4 mL), dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography on silica (hexanes:EtOAc, 3:1) to provide the title compound as a faint yellow oil (7.8 mg, 39% yield over 2 steps). $[\alpha]_D^{20}$ = –68.0° (c = 0.25, $CHCl_3$); ^{1}H NMR (400 MHz, CD_2Cl_2, mixture of diastereomers): δ = 7.69 (dt, *J* = 7.9, 1.5 Hz, 4H), 7.48 – 7.37 (m, 6H), 6.46 (d, *J* = 2.1 Hz, 1H), 6.16 (dt, *J* = 1.4, 0.7 Hz, 1H), 5.30 – 5.23 (m, 1H), 4.92 (d, *J* = 6.8 Hz, 1H), 4.54 (d, *J* = 6.8 Hz, 1H), 4.48 (tt, *J* = 6.0, 2.1 Hz, 1H), 4.40 – 4.33 (m, 1H), 4.28 (s, 1H), 3.95 – 3.81 (m, 2H), 3.75 (s, 3H), 3.30 (d, *J* = 0.7 Hz, 3H), 3.28 – 3.18 (m, 1H), 2.96 – 2.85 (m, 1H), 2.63 – 2.49 (m, 2H), 2.10 (d, *J* = 1.4 Hz, 3H), 2.08 – 2.01 (m, 1H), 2.01 – 1.89 (m, 1H), 1.83 (d, *J* = 2.0 Hz, 3H), 1.79 (d, *J* = 1.4 Hz, 3H), 1.74 (d, *J* = 2.1 Hz, 1H, minor isomer), 1.72 (d, *J* = 2.1 Hz, 2H, major isomer), 1.08 (d, *J* = 0.7 Hz, 9H); ^{13}C NMR (101 MHz, CD_2Cl_2, mixture of diastereomers): δ = 170.1, 164.3, 157.44, 157.39, 152.29, 152.25, 136.03, 136.01, 135.7, 135.6, 133.73, 133.68, 133.64, 130.1, 128.1, 116.44, 116.39, 116.0, 108.93, 108.90, 94.1, 82.4, 81.4, 81.2, 80.6, 80.3, 77.7, 71.8, 71.7, 64.78, 64.76, 62.3, 61.7, 61.5, 55.8, 51.6, 47.5, 44.6, 41.9, 41.7, 38.8, 33.8, 27.0, 20.7, 19.4, 19.2, 3.6, 3.5; IR (film): $\tilde{\nu}$ = 3466, 3071, 2952, 2930, 2857, 1740, 1717, 1597, 1548, 1471, 1441, 1428, 1376, 1232, 1148, 1106, 1058, 1029, 938, 919, 823, 779, 742, 704, 612, 505, 490 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{44}H_{54}O_9SiNa$ [M+Na$^+$]: 777.3429, found: 777.3420.

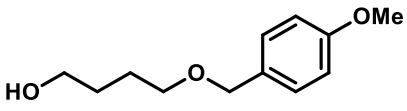
4.2.2 Synthesis of a Model System and Application in Ring Closing Alkyne Metathesis

Compound 255. This compound was prepared according to the literature procedure.[216] The



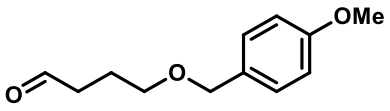
product was isolated as a white solid (6.1 g, 15.5 mmol, 69% yield over 2 steps). The spectral data are in accordance with the literature.[216] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.20 (s, 1H), 7.86 – 7.79 (m, 2H), 7.76 – 7.72 (m, 3H), 7.71 (d, *J* = 1.8 Hz, 1H), 7.37 (d, *J* = 1.8 Hz, 1H), 1.58 (s, 9H), 1.37 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 155.3, 153.8, 146.1, 138.2, 132.3, 131.0, 129.9, 129.1, 125.1, 125.1, 107.8, 35.9, 35.0, 31.4, 29.8.

4-((4-Methoxybenzyl)oxy)butan-1-ol (S13). Amberlyst-15 resin (10% w/w, 500 mg) was added



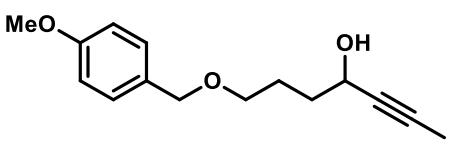
to a mixture of 1,4-butandiol (4.9 mL, 55.5 mmol) and p-anisyl alcohol (8.4 g, 61.0 mmol) in CH_2Cl_2 (240 mL). The mixture was heated to reflux for 3 h, before the solid components were filtered off and the filtrate was dried over Na_2SO_4. The organic filtrate was concentrated in vacuo and the residue was purified by flash chromatography on silica (hexane:EtOAc, 1:1), to provide the title compound as a colorless oil. The spectral data are in accordance with the literature.[230] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29 – 7.21 (m, 2H), 6.91 – 6.85 (m, 2H), 4.45 (s, 2H), 3.80 (s, 3H), 3.63 (t, *J* = 5.8 Hz, 2H), 3.49 (t, *J* = 5.8 Hz, 2H), 2.21 (d, *J* = 2.8 Hz, 1H), 1.75 – 1.61 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.2, 130.1, 129.3, 113.8, 72.7, 70.0, 62.7, 55.2, 30.2, 26.8. HRMS (ESI): *m*/*z* calcd. for $C_{12}H_{18}O_3$ [M^+]: 210.1250, found: 210.1251.

4-((4-Methoxybenzyl)oxy)butanal (257). Sulfur trioxide pyridine complex (11.4 g, 71.4 mmol)



was added to a solution of anhydrous Et_3N (16.6 mL, 119 mmol), 4-((4-methoxybenzyl)oxy)butan-1-ol (**S15**) (5.0 g, 23.8 mmol) and DMSO (11.8 mL, 166 mmol) in CH_2Cl_2 (12 mL) at 0 °C. The mixture was stirred at 0 °C for 1 h before sat. aq. $NaHCO_3$ (50 mL) was added. The aqueous layer was extracted with EtOAc (3 x 200 mL), and the combined organic phases were dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (pentane:Et_2O, 2:1) to afford the title compound as a colorless oil (4.26 g, 86% yield). The spectral data are in accordance with the literature.[231] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.77 (t, *J* = 1.6 Hz, 1H), 7.26 – 7.21 (m, 2H), 6.91 – 6.85 (m, 2H), 4.41 (s, 2H), 3.80 (s, 3H), 3.48 (t, *J* = 6.1 Hz, 2H), 2.53 (td, *J* = 7.1, 1.6 Hz, 2H), 1.93 (tt, *J* = 7.1, 6.1 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 202.3, 159.2, 130.3, 129.2, 113.8, 72.6, 68.8, 55.2, 41.0, 22.5. HRMS (ESI): *m*/*z* calcd. for $C_{12}H_{16}O_3$ [M^+]: 208.1094, found: 208.1094.

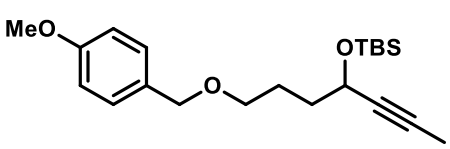
7-((4-Methoxybenzyl)oxy)hept-2-yn-4-ol (S14). 1-Propinylmagnesium bromide (0.5 M in



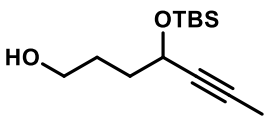
THF, 81 mL, 40.5 mmol) was added dropwise to a stirred solution of 4-((4-methoxybenzyl)oxy)butanal (**257**) (4.2 g, 20 mmol) in THF (50 mL) at –78 °C. The resulting mixture was stirred for 20 min at –78 °C before the reaction was

quenched with sat. aq. NH_4Cl (40 mL). After reaching room temperature, the mixture was diluted with EtOAc (50 mL) and water (20 mL). The aqueous phase was extracted with EtOAc (3 x 200 mL), the combined organic layers were washed with brine (100 mL), dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography on silica (hexanes:EtOAc, 2:1) to provide the title compound as a colorless oil (2.9 g, 57% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30 – 7.22 (m, 2H), 6.91 – 6.84 (m, 2H), 4.45 (d, *J* = 2.0 Hz, 2H), 4.37 (tt, *J* = 6.1, 2.2 Hz, 1H), 3.80 (s, 3H), 3.54 – 3.45 (m, 2H), 1.83 (d, *J* = 2.1 Hz, 3H), 1.88 – 1.70 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.2, 130.2, 129.3, 113.8, 80.8, 80.3, 72.6, 69.8, 62.4, 55.2, 35.5, 25.6, 3.5. IR (film): $\tilde{\nu}$ = 3399, 2919, 2858, 1612, 1586, 1513, 1457, 1362, 1302, 1247, 1175, 1147, 1095, 1033, 953, 820, 590, 518 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{15}H_{20}O_3Na$ [M+Na$^+$]: 271.1305, found: 271.1302.

***tert*-Butyl((7-((4-methoxybenzyl)oxy)hept-2-yn-4-yl)oxy)dimethylsilane (238).** Imidazole (657 mg, 9.67 mmol) and *tert*-butyldimethylsilyl chloride (1.45 g, 9.67 mmol) were added to a stirred solution of alcohol **S16** (2.0 g, 8.05 mmol) in CH_2Cl_2 (40 mL), and the resulting mixture was stirred for 16 h at room temperature. The reaction was quenched with sat. aq. $NaHCO_3$ (50 mL) and the aqueous phase was extracted with CH_2Cl_2 (3 x 150 mL). The combined extracts were dried over Na_2SO_4 and concentrated, and the residue was purified by flash chromatography on silica (hexanes:*tert*-butyl methyl ether, 8:1) to afford the title compound as a colorless oil (2.77 g, 95% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29 – 7.23 (m, 2H), 6.91 – 6.85 (m, 2H), 4.43 (s, 2H), 4.33 (ddt, *J* = 6.1, 4.1, 2.1 Hz, 1H), 3.80 (s, 3H), 3.50 – 3.43 (m, 2H), 1.81 (d, *J* = 2.1 Hz, 3H), 1.78 – 1.66 (m, 4H), 0.89 (s, 9H), 0.10 (d, *J* = 10.4 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.1, 130.7, 129.2, 113.7, 80.9, 80.0, 72.4, 69.9, 63.0, 55.3, 35.6, 25.8, 25.6, 18.2, 3.5, −4.5, −5.0. IR (film): $\tilde{\nu}$ = 2953, 2929, 2855, 1613, 1586, 1512, 1463, 1443, 1407, 1389, 1360, 1301, 1247, 1207, 1172, 1149, 1095, 1071, 1037, 1006, 979, 939, 890, 834, 776, 714, 668, 574, 517 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{21}H_{34}O_3SiNa$ [M+Na$^+$]: 385.2169, found: 385.2166.

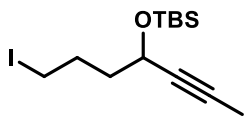


4-((*tert*-Butyldimethylsilyl)oxy)hept-5-yn-1-ol (259). 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (4.26 g, 18.8 mmol) was added to a solution of *tert*-butyl((7-((4-methoxybenzyl)oxy)hept-2-yn-4-yl)oxy)dimethylsilane (**238**) (2.27 g, 6.26 mmol) in CH_2Cl_2/aq. phosphate buffer (pH 7, 55 mL, 5:1 *v*/*v*) at 0 °C. The mixture was vigorously stirred at room temperature for 30 min. The reaction was quenched with sat. aq. $NaHCO_3$ (50 mL), diluted with water (300 mL) and the aqueous phase was extracted with CH_2Cl_2 (3 x 200 mL). The combined extracts were dried over Na_2SO_4 and concentrated, and the residue was purified by flash chromatography on silica (hexanes:*tert*-butyl methyl ether, 2:1) to afford the title compound as a colorless oil (1.33 g, 88% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.41 (qt, *J* = 3.5, 1.4 Hz, 1H), 3.72 – 3.59 (m, 2H), 1.82 (d, *J* = 2.1 Hz, 3H), 1.79 – 1.67 (m, 4H), 0.90 (s, 9H), 0.12 (d, *J* = 8.2 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ =

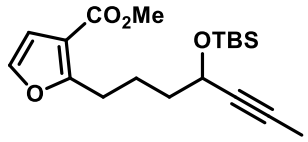


80.6, 80.4, 63.0, 62.7, 35.4, 28.4, 25.8, 18.2, 3.5, –4.5, –5.1. IR (film): $\tilde{\nu}$ = 3350, 2953, 2929, 2885, 2857, 1472, 1463, 1445, 1389, 1361, 1341, 1252, 1144, 1098, 1056, 1006, 975, 939, 918, 884, 835, 815, 776, 716, 666 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{13}H_{26}O_2SiNa$ [M+Na$^+$]: 265.1594, found: 265.1591.

***tert*-Butyl((7-iodohept-2-yn-4-yl)oxy)dimethylsilane (260).** Iodine (344 mg, 1.36 mmol) was added to a vigorously stirred solution of PPh_3 (356 mg, 1.36 mmol) and imidazole (168 mg, 2.47 mmol) in a mixture of Et_2O (1.7 mL) and MeCN (0.7 mL) at 0 °C. After stirring at this temperature for 10 min, 4-((*tert*-butyldimethylsilyl)oxy)hept-5-yn-1-ol (**259**) (299 mg, 1.23 mmol) was added and the resulting mixture was stirred for 30 min before the reaction was quenched with sat. aq. $Na_2S_2O_3$ (5 mL). The aqueous phase was extracted with CH_2Cl_2 (2 x 50 mL), the combined extracts were dried over Na_2SO_4 and evaporated. The residue was purified by chromatography on silica (pentane:Et_2O, 10:1) to afford the title compound as a colorless oil (385 mg, 88% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.36 (tq, *J* = 6.2, 2.1 Hz, 1H), 3.22 (t, *J* = 7.0 Hz, 2H), 2.03 – 1.93 (m, 2H), 1.82 (d, *J* = 2.1 Hz, 3H), 1.76 – 1.69 (m, 2H), 0.90 (s, 9H), 0.11 (d, *J* = 9.2 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 80.5, 80.4, 62.1, 39.5, 29.4, 25.8, 18.2, 6.8, 3.5, –4.5, –5.0. IR (film): $\tilde{\nu}$ = 2954, 2928, 2885, 2856, 1471, 1462, 1442, 1389, 1360, 1342, 1253, 1225, 1172, 1087, 1006, 970, 941, 837, 777, 667 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{13}H_{26}OISi$ [M+H$^+$]: 353.0792, found: 353.0789.



Methyl 2-(4-((*tert*-butyldimethylsilyl)oxy)hept-5-yn-1-yl)furan-3-carboxylate (261). Anhydrous LiCl (46 mg, 1.08 mmol) and zinc powder (106 mg, 1.62 mmol) were suspended in THF (7 mL), before 1,2-dibromoethane (3 drops) and TMSCl (3 drops) were added. Next, *tert*-butyl((7-iodohept-2-yn-4-yl)oxy)dimethyl-silane (**260**) (380 mg, 1.08 mmol) was added and the resulting mixture heated to 50 °C for 4 h. After cooling to room temperature this mixture was filter-cannulated into a flask containing $Pd(OAc)_2$ (10 mg, 0.04 mmol), SPhos (35 mg, 0.08 mmol) and methyl 2-bromofuran-3-carboxylate (**198**) (196 mg, 0.86 mmol) in THF (7 mL) at 0 °C. The mixture was warmed to room temperature and stirred for 16 h, before the reaction was quenched with sat. aq. NH_4Cl (15 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL), the combined extracts were dried over Na_2SO_4 and evaporated. The residue was purified by chromatography on silica (hexanes: *tert*-butyl methyl ether, 3:1) to afford the title compound as a colorless oil (86 mg, 28% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.24 (d, *J* = 2.0 Hz, 1H), 6.63 (d, *J* = 2.0 Hz, 1H), 4.32 (tq, *J* = 6.3, 2.1 Hz, 1H), 3.81 (s, 3H), 3.01 (t, *J* = 7.4 Hz, 2H), 1.88 – 1.74 (m, 5H), 1.69 – 1.61 (m, 2H), 0.89 (s, 9H), 0.10 (d, *J* = 8.5 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.4, 162.8, 140.5, 113.0, 110.6, 80.7, 80.1, 62.8, 51.3, 38.2, 27.1, 25.8, 23.6, 18.2, 3.5, –4.5, –5.0. IR (film): $\tilde{\nu}$ = 2952, 2929, 2857, 1721, 1602, 1520, 1472, 1462, 1440, 1405, 1390, 1361, 1339, 1305, 1251, 1198, 1156, 1134, 1096, 1034, 1006, 940, 894, 837, 804, 777, 739, 666 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{19}H_{30}O_4SiNa$ [M+Na$^+$]: 373.1806, found: 373.1803.



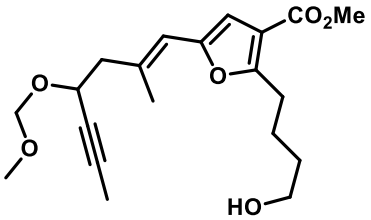
Methyl 2-(4-acetoxybutyl)furan-3-carboxylate (263). 4-Acetoxy-1-butanol[232] (115 mg, 0.87 mmol) was added to a suspension of NHC-**255** (316 mg, 0.80 mmol) in MTBE (4 mL). The mixture was stirred for 5 min, before pyridine (65 µL, 0.80 mmol) was added dropwise. After another 10 min of stirring at room temperature, this solution was added through a filter-cannula to a flask containing ArBr **198** (114 mg, 0.5 mmol), Ir complex **264** (6.8 mg, 0.007 mmol), Ni complex **265** (18 mg, 0.037 mmol), quinuclidine (97 mg, 0.87 mmol) and phthalimide (16 mg, 0.11 mmol) in *N*,*N*-dimethylacetamide (5 mL). The resulting mixture was purged with argon for 15 min, before the flask was sealed and irradiated with a blue LED bulb (Hepatochem, 475 nm) for 2 h. Next, the mixture was diluted with an aq. KH_2PO_4/Na_2HPO_4 solution (0.05 M, 20 mL), water (50 mL) and EtOAc (40 mL). The aqueous phase was extracted with EtOAc (3x 100 mL), the combined organic fractions were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica (hexanes: *tert*-butyl methyl ether, 4:1) to afford the title compound as a colorless oil (119 mg, 99% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25 (d, *J* = 2.0 Hz, 1H), 6.63 (d, *J* = 2.0 Hz, 1H), 4.08 (t, *J* = 6.4 Hz, 2H), 3.82 (s, 3H), 3.03 (t, *J* = 7.3 Hz, 2H), 2.04 (d, *J* = 0.7 Hz, 3H), 1.81 – 1.71 (m, 2H), 1.71 – 1.61 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.1, 164.3, 162.5, 140.6, 113.2, 110.6, 64.1, 51.3, 28.0, 27.0, 24.3, 21.0. IR (film): $\tilde{\nu}$ = 2953, 1737, 1720, 1600, 1520, 1440, 1403, 1390, 1366, 1305, 1242, 1199, 1159, 1133, 1111, 1034, 943, 894, 802, 745, 606 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{12}H_{16}O_5$ [M$^+$]: 240.0992, found: 240.0990.

Compound 268. NBS (42 mg, 0.23 mmol) was added to a stirred solution of furan **263** (63 mg, 0.21 mmol) in acetonitrile (2 mL) at 0 °C. The resulting mixture was stirred for 30 min at room temperature, before *tert*-butyl methyl ether (10 mL) and a mixture of sat. aq. $Na_2S_2O_3$:$NaHCO_3$ (1:1 *v*/*v*, 10 mL) were added. The biphasic mixture was vigorously stirred for 10 min. The aqueous phase was extracted with *tert*-butyl methyl ether (3 x 50 mL). The combined extracts were washed with brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude bromofuran **271** was used in the next step without further purification.

The commercial palladium complex XPhos-Pd-G2 (**235**) (17 mg, 0.021 mmol, 0.10 eq.) was added to a stirred solution of the bromofuran **271** (68 mg, 0.21 mmol) and *rac*-**243** (69 mg, 0.23 mmol) in a mixture of THF (1.6 mL) and aqueous K_3PO_4 (3 M, 0.1 mL) at room temperature. The resulting mixture was stirred for 2.5 h at 50 °C before it was diluted with Et_2O (20 mL) and water (5 mL). The aqueous phase was extracted with Et_2O (3 x 70 mL), the combined organic layers were washed with brine (10 mL), dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography on silica (hexanes:EtOAc, 4:1) to afford the title compound as a brown oil (42 mg, 49% yield over 2 steps). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.43 (s, 1H), 6.14 – 6.10 (m, 1H), 4.95 (d, *J* = 6.8 Hz, 1H), 4.57 (d, *J* = 6.8 Hz, 1H), 4.47 (ddq, *J* = 8.0, 6.1, 2.1 Hz, 1H), 4.08 (t, *J* = 6.4 Hz, 2H), 3.81 (s, 3H), 3.33 (s, 3H), 3.02 (t, *J* = 7.2 Hz, 2H), 2.63 – 2.47 (m, 2H), 2.04

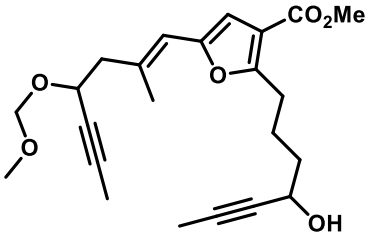
(s, 3H), 2.02 (d, *J* = 1.2 Hz, 3H), 1.84 (d, *J* = 2.1 Hz, 3H), 1.81 – 1.63 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.1, 164.4, 160.6, 151.3, 134.9, 116.3, 114.4, 108.2, 93.9, 82.2, 64.6, 64.1, 55.6, 51.3, 47.1, 28.1, 27.1, 24.3, 21.0, 19.0, 3.6. IR (film): $\tilde{\nu}$ = 2951, 1738, 1718, 1601, 1553, 1440, 1385, 1366, 1236, 1149, 1097, 1060, 1030, 972, 919, 778 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{22}H_{30}O_7Na$ [M+Na$^+$]: 429.1884, found: 429.1879.

Compound S15. Potassium carbonate (4 mg, 0.026 mmol) was added to a solution of acetate



268 (9 mg, 0.02 mmol) in MeOH (0.5 mL) at 0 °C. The resulting mixture was stirred for 1 h at room temperature before it was diluted with EtOAc (5 mL) and sat. aq. NH_4Cl (5 mL). The aqueous phase was extracted with EtOAc (3 x 20 mL), the combined organic layers were washed with brine (10 mL), dried over $MgSO_4$ and concentrated furnishing the product as a colorless oil (8 mg, quant.). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.43 (s, 1H), 6.14 – 6.08 (m, 1H), 4.95 (d, *J* = 6.8 Hz, 1H), 4.57 (d, *J* = 6.8 Hz, 1H), 4.47 (ddq, *J* = 8.0, 6.1, 2.1 Hz, 1H), 3.81 (s, 3H), 3.67 (t, *J* = 6.4 Hz, 2H), 3.33 (s, 3H), 3.01 (t, *J* = 7.5 Hz, 2H), 2.55 (qdd, *J* = 13.8, 6.8, 1.1 Hz, 2H), 2.01 (d, *J* = 1.2 Hz, 3H), 1.84 (d, *J* = 2.1 Hz, 3H), 1.81 – 1.72 (m, 2H), 1.67 – 1.55 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.5, 161.1, 151.2, 134.8, 116.3, 114.2, 108.2, 93.9, 82.2, 77.4, 64.6, 62.4, 55.6, 51.3, 47.1, 31.9, 27.1, 24.1, 19.0, 3.6. IR (film): $\tilde{\nu}$ = 3476, 2947, 1716, 1600, 1553, 1440, 1383, 1281, 1227, 1149, 1094, 1057, 1028, 973, 919, 813, 778 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{20}H_{28}O_6Na$ [M+Na$^+$]: 387.1778, found: 387.1775.

Compound 252. Sodium bicarbonate (92 mg, 1.1 mmol) and Dess-Martin-periodinane (139 mg,

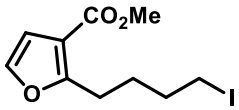


0.33 mmol) were added to a solution of alcohol **S15** (40 mg, 0.11 mmol) in CH_2Cl_2 (3 mL) at 0 °C. The resulting mixture was warmed to room temperature and stirred for 30 min before it was diluted with CH_2Cl_2 (5 mL). The reaction was quenched with a mixture of sat. aq. $Na_2S_2O_3$/$NaHCO_3$ (1:1 *v*/*v*, 5 mL) and the resulting mixture was vigorously stirred for 30 min. The aqueous phase was diluted with water (5 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (3 x 20 mL), dried over $MgSO_4$ and concentrated. The crude aldehyde thus formed was used in the next step without further purification.

1-Propinylmagnesium bromide (0.5 M in THF, 0.41 mL, 0.20 mmol) was added dropwise to a stirred solution of this crude aldehyde (37 mg, 0.10 mmol) in THF (1.3 mL) at –78 °C. The resulting mixture was stirred for 10 min at –78 °C before the reaction was quenched with sat. aq. NH_4Cl (1 mL). After reaching room temperature, the mixture was diluted with *tert*-butyl methyl ether (10 mL) and water (3 mL). The aqueous phase was extracted with *tert*-butyl methyl ether (3 x 20 mL), the combined organic layers were washed with brine (4 mL), dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography on silica

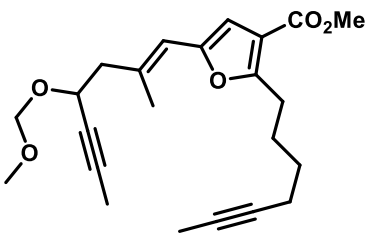
(hexanes:EtOAc, 3:1) to provide the title compound as a faint yellow oil (22.7 mg, 55% yield over 2 steps). ^{1}H NMR (400 MHz, $CDCl_3$, mixture of diastereomers): δ = 6.43 (s, 1H), 6.12 (dd, *J* = 1.3, 0.6 Hz, 1H), 4.95 (d, *J* = 6.8 Hz, 1H), 4.57 (d, *J* = 6.8 Hz, 1H), 4.47 (ddq, *J* = 8.0, 6.1, 2.1 Hz, 1H), 4.37 (tq, *J* = 6.4, 2.1 Hz, 1H), 3.81 (s, 3H), 3.34 (s, 3H), 3.03 (td, *J* = 7.3, 1.3 Hz, 2H), 2.64 – 2.47 (m, 2H), 2.02 (d, *J* = 1.2 Hz, 3H), 1.91 – 1.78 (m, 8H), 1.75 – 1.67 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$, mixture of diastereomers): δ = 164.5, 160.8, 151.3, 134.8, 116.3, 114.3, 108.2, 93.9, 82.2, 81.2, 80.1, 77.4, 64.6, 62.4, 55.6, 51.3, 47.1, 37.3, 27.1, 23.6, 19.0, 3.6. IR (film): $\tilde{\nu}$ = 3474, 2950, 2921, 2854, 1717, 1600, 1553, 1440, 1384, 1340, 1228, 1149, 1088, 1058, 1028, 964, 919, 778 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{23}H_{30}O_6Na$ [M+Na$^+$]: 425.1934, found: 425.1936.

Methyl 2-(4-iodobutyl)furan-3-carboxylate (269). Potassium carbonate (50 mg, 0.36 mmol) was added to a solution of acetate **263** (72 mg, 0.30 mmol) in MeOH (7 mL) at 0 °C. The resulting mixture was stirred for 1 h at room temperature before it was diluted with EtOAc (5 mL) and sat. aq. NH_4Cl (5 mL). The aqueous phase was extracted with EtOAc (3 x 20 mL), the combined organic layers were washed with brine (10 mL), dried over $MgSO_4$ and concentrated furnishing the product as a colorless oil (60 mg, 0.30 mmol). The crude product was used in the next step without further purification.



Iodine (115 mg, 0.45 mmol) was added to a vigorously stirred solution of PPh_3 (119 mg, 0.45 mmol) and imidazole (51 mg, 0.76 mmol) in a CH_2Cl_2 (2.2 mL) at 0 °C. After stirring at this temperature for 10 min, the above prepared alcohol (60 mg, 0.30 mmol) was added and the resulting mixture was stirred for 30 min before the reaction was quenched with sat. aq. $Na_2S_2O_3$ (5 mL). The aqueous phase was extracted with CH_2Cl_2 (2 x 50 mL), the combined extracts were dried over Na_2SO_4 and evaporated. The residue was purified by chromatography on silica (pentane:Et_2O, 8:1) to afford the title compound as a colorless oil (82 mg, 88% yield over 2 steps). ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.28 (d, *J* = 2.0 Hz, 1H), 6.63 (d, *J* = 2.0 Hz, 1H), 3.79 (s, 3H), 3.22 (t, *J* = 6.8 Hz, 2H), 3.02 (t, *J* = 7.2 Hz, 2H), 1.91 – 1.72 (m, 4H). ^{13}C NMR (101 MHz, CD_2Cl_2): δ = 164.5, 162.6, 141.1, 113.7, 110.9, 51.6, 33.2, 29.1, 26.6, 6.8. IR (film): $\tilde{\nu}$ = 2948, 1717, 1601, 1519, 1438, 1404, 1302, 1199, 1160, 1132, 1079, 1055, 1033, 994, 941, 894, 803, 782, 740, 604 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{10}H_{13}O_3I$ [M$^+$]: 307.9904, found: 307.9907.

Compound 253. 1-Propinylmagnesium bromide (0.5 M in THF, 1.0 mL, 0.49 mmol) was added to a mixture of methyl 2-(4-iodobutyl)furan-3-carboxylate **267** (75 mg, 0.24 mmol) and the Ni complex **268** (4.2 mg, 0.01 mmol) in 2-(dimethylamino)-ethylether (0.14 mL) and THF (0.75 mL). The resulting mixture was stirred for 4 h at room temperature. The reaction was quenched upon addition of water (10 mL) and aq. HCl (1 M, 1 mL). The aqueous phase was extracted with *tert*-butyl methyl ether (3x 50 mL) and the combined organic extracts were dried over Na_2SO_4 and



concentrated in vacuo. The residue was purified by chromatography on silica (pentane:Et_2O, 20:1) to afford the title compound as a colorless oil.

NBS (35 mg, 0.20 mmol) was added to a stirred solution of the above prepared furan (29 mg, 0.13 mmol) in acetonitrile (1.3 mL) at 0 °C. The resulting mixture was stirred for 30 min at room temperature, before *tert*-butyl methyl ether (10 mL) and a mixture of sat. aq. $Na_2S_2O_3$:$NaHCO_3$ (1:1 *v*/*v*, 10 mL) were added. The biphasic mixture was vigorously stirred for 10 min. The aqueous phase was extracted with *tert*-butyl methyl ether (3 x 50 mL). The combined extracts were washed with brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude bromofuran was used in the next step without further purification.

The commercial palladium complex XPhos-Pd-G2 (**235**) (11 mg, 0.015 mmol) was added to a stirred solution of the bromofuran (30 mg, 0.1 mmol) and *rac*-**243** (44 mg, 0.15 mmol) in a mixture of THF (1.0 mL) and aqueous K_3PO_4 (3 M, 0.2 mL) at room temperature. The resulting mixture was stirred for 2.5 h at 50 °C before it was diluted with Et_2O (20 mL) and water (5 mL). The aqueous phase was extracted with Et_2O (3 x 70 mL), the combined organic layers were washed with brine (10 mL), dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography on silica (pentane:Et_2O, 9:1) to afford the title compound as a yellow oil (16 mg, 17% yield over 3 steps). ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 6.43 (s, 1H), 6.10 (dd, *J* = 1.3, 0.7 Hz, 1H), 4.91 (d, *J* = 6.7 Hz, 1H), 4.53 (dd, *J* = 6.8, 0.5 Hz, 1H), 4.49 – 4.41 (m, 1H), 3.79 (s, 3H), 3.30 (s, 3H), 2.98 (t, *J* = 7.5 Hz, 2H), 2.60 – 2.46 (m, 2H), 2.14 (tq, *J* = 7.3, 2.5 Hz, 2H), 2.02 (d, *J* = 1.2 Hz, 3H), 1.83 (d, *J* = 2.1 Hz, 3H), 1.80 – 1.71 (m, 5H), 1.53 – 1.45 (m, 2H). ^{13}C NMR (101 MHz, CD_2Cl_2): δ = 164.6, 161.4, 151.6, 135.4, 116.5, 114.7, 108.6, 94.2, 82.4, 79.0, 77.8, 75.8, 64.9, 55.8, 51.5, 47.5, 28.9, 27.5, 27.4, 19.2, 18.7, 3.6, 3.5. IR (film): $\tilde{\nu}$ = 2947, 2921, 2859, 1717, 1600, 1553, 1439, 1383, 1333, 1225, 1149, 1086, 1058, 1029, 971, 919, 853, 814, 777 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{23}H_{30}O_5Na$ [M+Na^+]: 409.1985, found: 409.1987.

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6. Appendix

In the two initial reports describing the isolation of (+)-keramaphidin B (**2**), the Kobayashi group obtained NMR data in $CDCl_3$,[54] while the Andersen group reported their data in [D_4]-MeOH.[56,98] Although our synthetic sample of (+)-**2** was in very good agreement with the publication from Kobayashi *et al.*,[54] the spectra of the same sample recorded in [D_4]-MeOH were showing small, but noticeable, deviations from the spectra generated by Andersen *et al.*[56] Therefore, our coherent dataset of ^{1}H- and ^{13}C-spectra of synthetic (+)-**2** measured in both [D_4]-MeOH and CDCl3 is shown below (Figure 6.1-6.4).

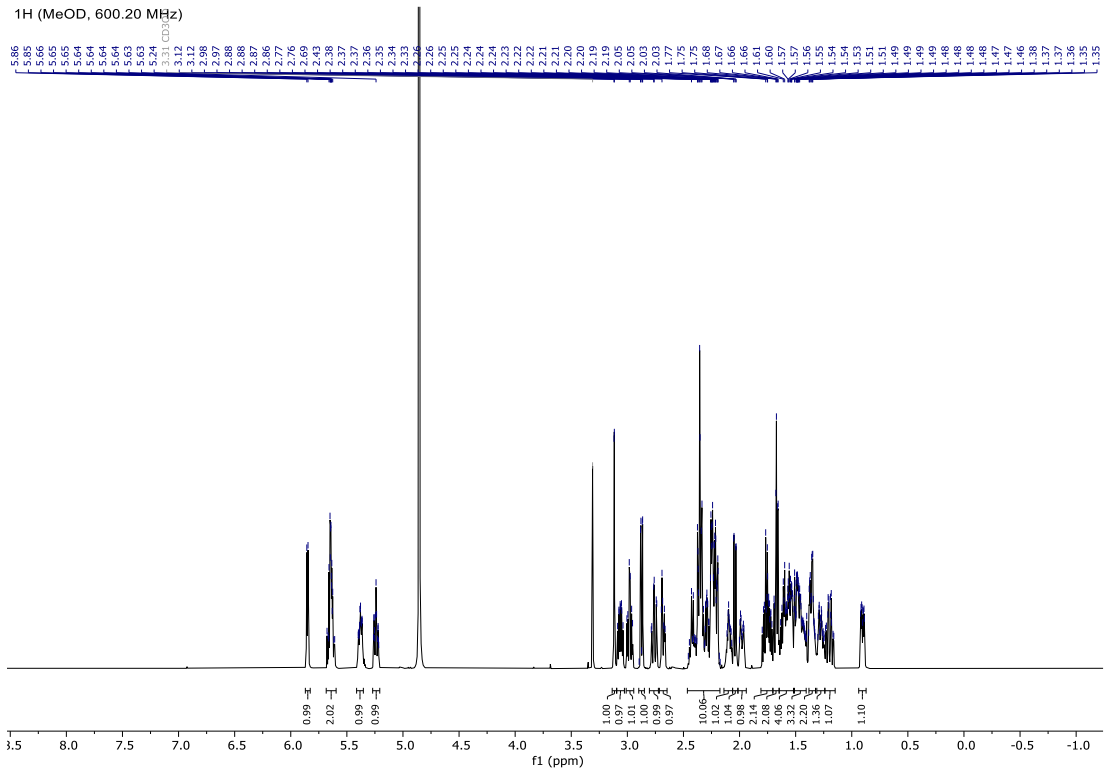

Figure 6.1: ^{1}H NMR Spectrum of Keramaphidin B (+)-**2** ([D_4]-MeOH).

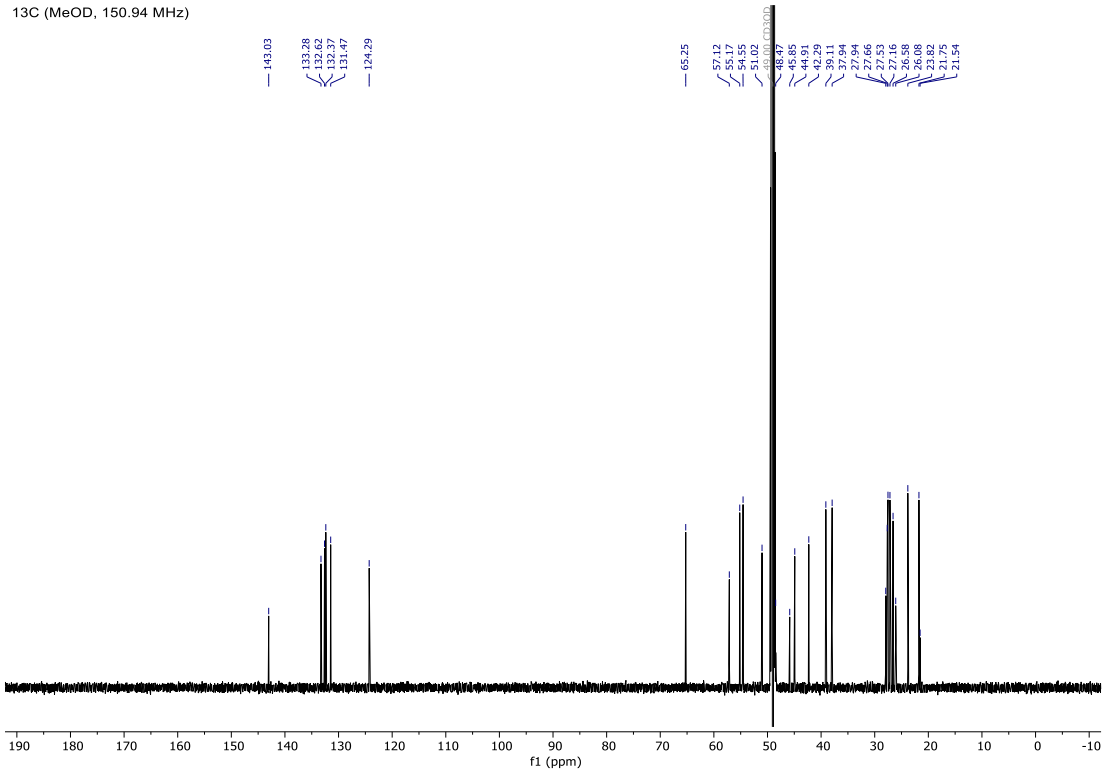

Figure 6.2: ^{13}C NMR Spectrum of Keramaphidin B (+)-**2** ([D_4]-MeOH).

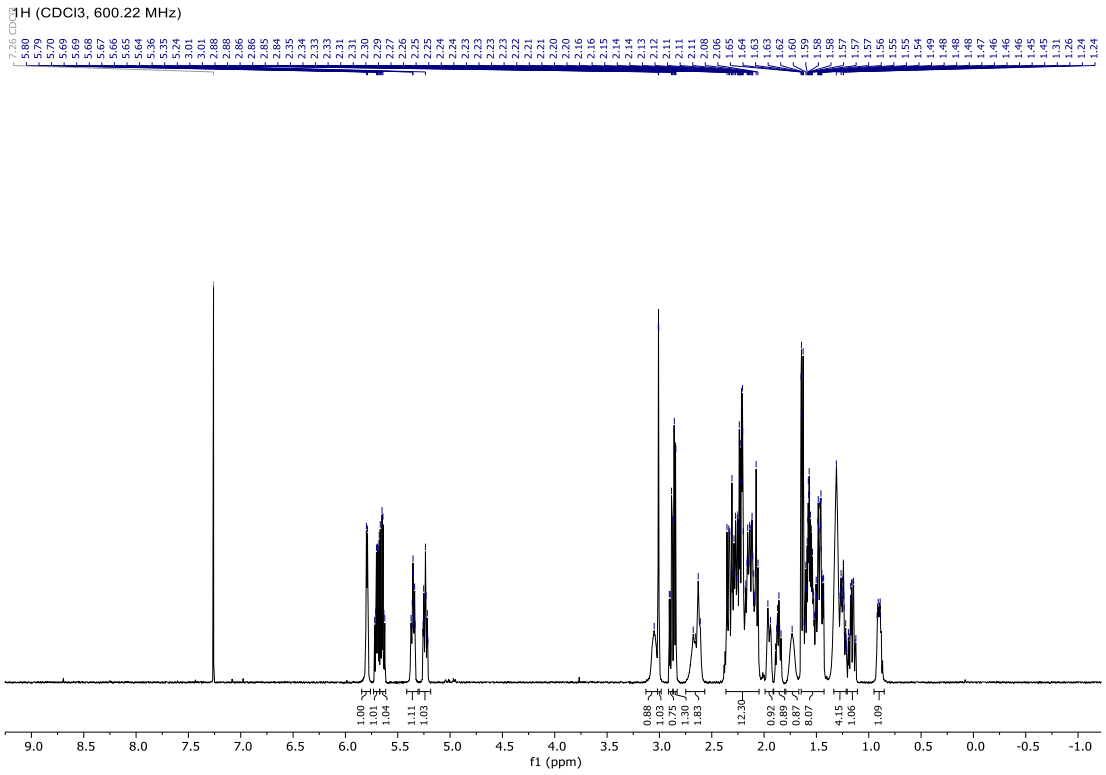

Figure 6.3: ^{1}H NMR of Keramaphidin B (+)-**2** ($CDCl_3$).

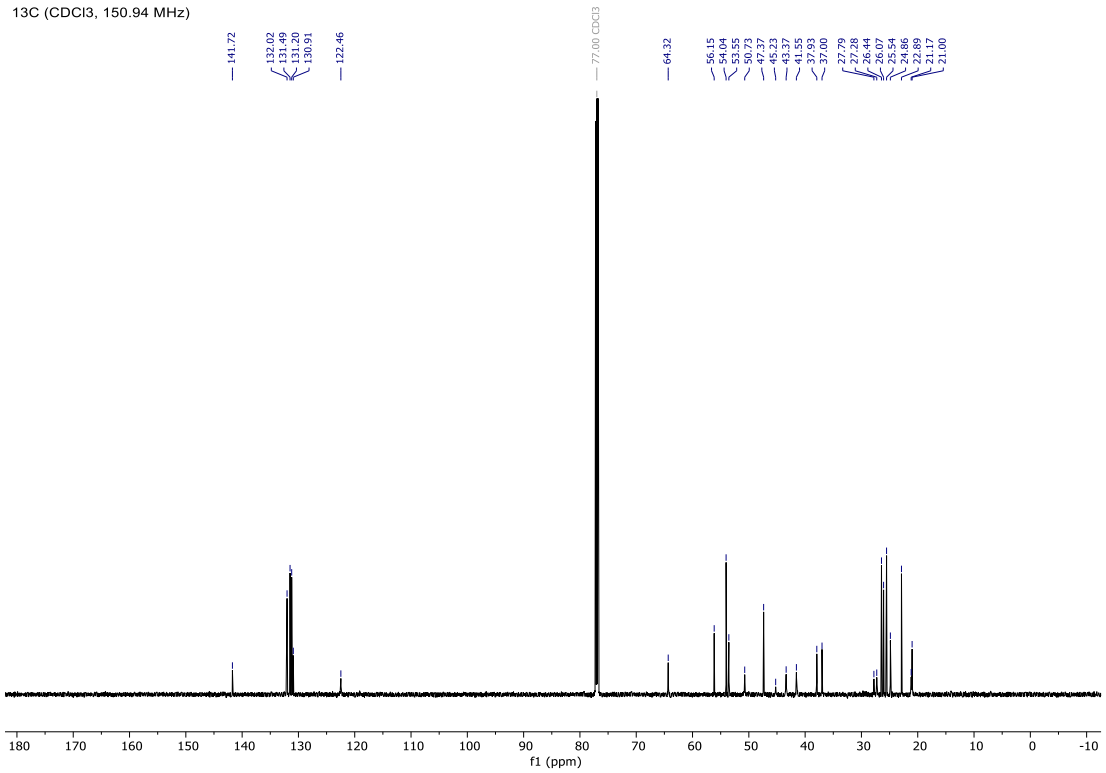

Figure 6.4: ^{13}C NMR of Keramaphidin B (+)-**2** ($CDCl_3$).