Formale Totalsynthese von Kendomycin

&

Totalsynthese eines Marinen 4-Pyrons

Dissertation

zur Erlangung des akademischen Grades eines

Doktors der Naturwissenschaften

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vorgelegt von

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Hiermit versichere ich, dass ich die eingereichte Dissertation selbständig verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel benutzt sowie Zitate kenntlich gemacht habe.

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Die vorliegende Arbeit entstand unter Anleitung von Herrn Prof. Dr. Alois Fürstner in der Zeit von November 2011 bis März 2015 am Max-Planck-Institut für Kohlenforschung in Mülheim an der Ruhr. Teile dieser Arbeit wurden in folgenden Beiträgen veröffentlicht:

- „Formal Total Synthesis of Kendomycin by Way of Alkyne Metathesis/Gold Catalysis“

  L. Hoffmeister, P. Persich, A. Fürstner, *Chem. Eur. J*. **2014,** *20*, 4396.

- „Total Synthesis of an Exceptional Brominated 4-Pyrone Derivative of Algal Origin: An Exercise in Gold Catalysis and Alkyne Metathesis“

  L. Hoffmeister, T. Fukuda, G. Pototschnig, A. Fürstner, *Chem. Eur. J*. **2015**, *21*, 4529.

Die praktischen Arbeiten entstanden teilweise in Zusammenarbeit mit Peter Persich und Gaelle Valot (Kapitel 3) sowie Tsutomu Fukuda, Gerit Pototschnig und Jennifer Lenartowicz (Kapitel 4). Die beschriebenen Ergebnisse bilden eine vollständige Darstellung dieser gemeinsamen Arbeiten. Die von den Mitarbeitern alleinverantwortlich erzielten Ergebnisse wurden als solche an entsprechender Stelle gekennzeichnet.

1. Berichterstatter: **Herr Prof. Dr. Alois Fürstner**

2. Berichterstatter: **Herr Prof. Dr. Norbert Krause**

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Meiner Familie

Zusammenfassung

Formale Totalsynthese von Kendomycin mittels Alkinmetathese/Goldkatalyse

Kendomycin **1** [(**–**)-TAN 2162] tritt als natürliches Stoffwechselprodukt von *Streptomyces violaceoruber* auf. Das vielfältige biologische Profil umfasst Aktivität als Endetholinrezeptor-Agonist, Antiosteoporotikum und eine bemerkenswerte antibakterielle und zytotoxische Wirkung. Der polyketidische 18-gliedrige Carbozyklus besteht aus einem *para*-Chinonmethid-Grundgerüst und einem hochsubstituierten Tetrahydropyranring. Die vielseitigen pharmakologischen Eigenschaften und die faszinierende Struktur des Kendomycins veranlassten bereits zahlreiche andere Forschungsgruppen, Bemühungen hinsichtlich einer Totalsynthese zu unternehmen.

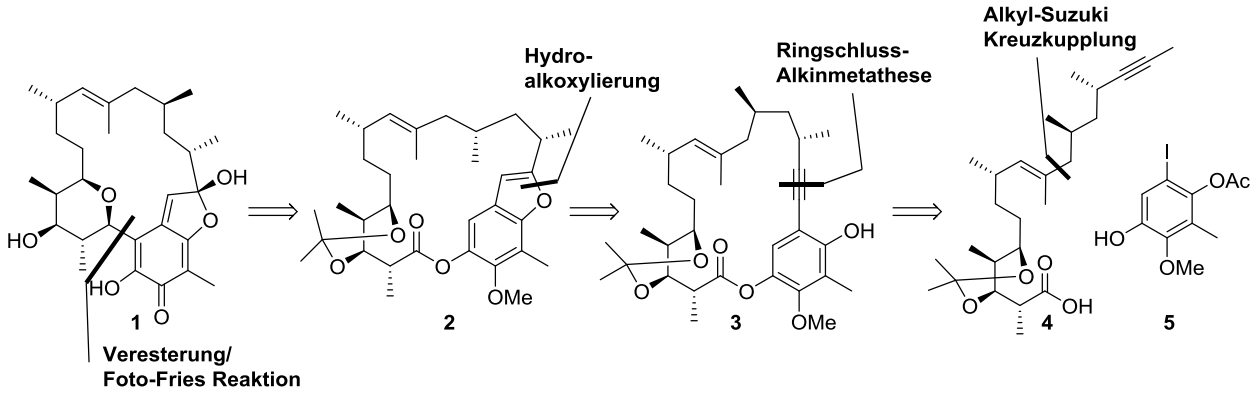


Abbildung 1: Retrosynthetische Analyse des Polyketids Kendomycin **1**.

Eine Ringschluss-Alkinmetathese (RCAM) und die direkte postmetathetische Umsetzung des Alkinmakrozyklus zum Benzofuran mittels π-Säureaktivierung sollten die Schlüsselschritte der hier vorgestellten Totalsynthese darstellen.

Das benötigte polyketidische Fragment **4** (12 Stufen) konnte mittels einer Alkyl-Suzuki-Kupplung zwischen einem Alkenyliodid und einem Alkyliodid aufgebaut und anschließend mit Phenol **5** (3 Stufen) verestert werden. Unter Verwendung einer weiteren Variante der Suzuki-Miyaura Kupplung wurde das zweite Alkin eingeführt und der Alkinmetathese-Vorläufer erhalten. Der Ringschluss des erhaltenen Dialkins erfolgte unter milden Bedingungen in Anwesenheit eines Molybdän-Alkylidinkatalysators. Nach Abspaltung der Acetatschutzgruppe wurde der Heterozyklus in Anwesenheit eines elektrophilen Goldkomplexes gebildet, während z.B. einfache Platin(II)- oder Gold(I/III)chloride keinen Erfolg brachten. Weiterhin konnte durch Foto-Fries Umlagerung eine Ringkontraktion herbeigeführt werden, durch die das gewünschte hexasubstituierte Cyclophan erhalten wurde. Die anschließenden Redoxschritte und

Schutzgruppenmanipulationen führten in Analogie zur Literatur zum angestrebten Naturstoff **1**.

Totalsynthese eines halogenierten marinen 4-Pyron-Derivats

Im weiteren Verlauf der Doktorarbeit sollte ein aus roten Algen der Spezies *Phacelocarpus labillardieri* isolierter 4-Pyron-haltiger makrozyklischer Naturstoff synthetisiert werden. Erste biologische Tests zeigten eine Inhibition der Phospholipase A_2 bei mikromolarer Konzentration (IC_{50} < 4,4 μM).

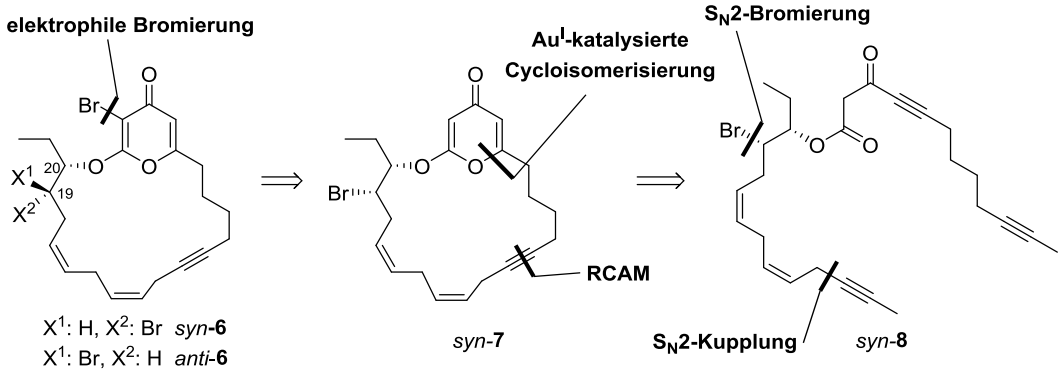


Abbildung 2: Retrosynthetische Strategie für den marinen Naturstoffs **6**.

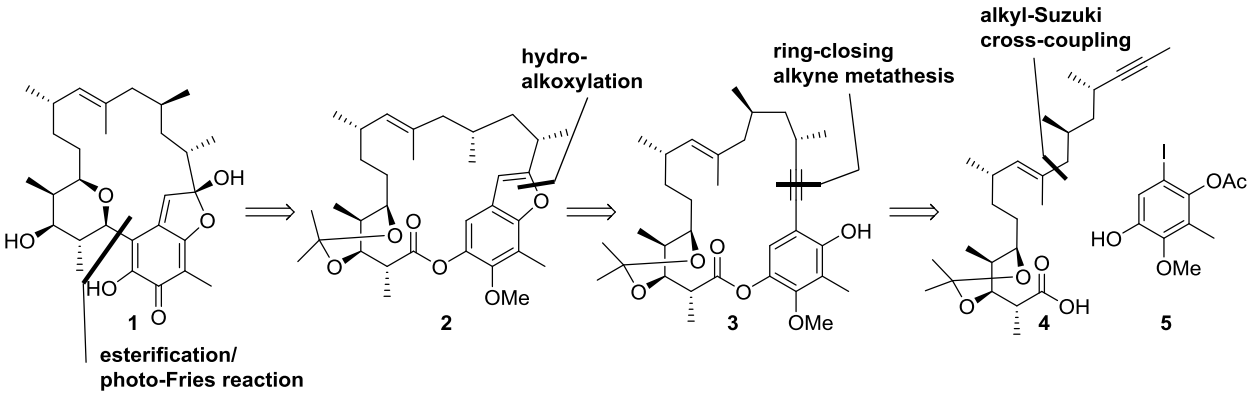
Der polyungesättigte Metabolit **6** gehört einer interessanten und seltenen Verbindungsklasse an, die sich durch ein dibromiertes Molekülskelett mit einem Ketenacetal als einzigartiges Strukturmotiv auszeichnet. Zur Aufklärung der bis dahin unbekannten relativen Stereochemie sollten zwei mögliche Diastereomere *syn*-**6** und *anti*-**6** synthetisiert werden.

Der Schlüsselschritt der Synthese sollte eine π-Säure-katalysierte Cycloisomerisierung des entsprechenden β-Ketoesters zum 4-Pyron sein, gefolgt von einer RCAM zum Aufbau des Cycloalkins. Dazu wurde zunächst das entsprechende Alkoholfragment (8 Stufen) unter Inversion an C19 bromiert und nach Entschützung mit einer β-Ketosäure (6 Stufen) verestert. Die Pyronsynthese sowie die darauffolgende Makrozyklisierung mittels Alkinmetathese verliefen problemlos. Die finale Bromierung am 4-Pyron konnte erfolgreich unter elektrophilen Bromierungsbedingungen durchgeführt werden. Jedoch konkurrierte diese in deutlichem Maße mit einer *cis*/*trans*-Isomerisierung der (*Z*)-Olefine. Ausgehend von einem späten Intermediat konnte durch doppelte Inversion die diastereomere Verbindung *anti*-**6** hergestellt werden. Ein Vergleich der NMR-spektroskopischen Daten von *syn*-**6** und *anti*-**6** ergab, dass die Substituenten an C19 – C20 im Naturstoff *syn* zueinander stehen. Somit konnte die relative Stereochemie des Naturstoffs ermittelt werden.

Summary

Formal Total Synthesis of Kendomyicn via Ring-Closing Alkyne Metathesis

Kendomycin **1** [(**–**)-TAN 2162] occurs as a metabolite of the species *Streptomyces violaceoruber.* The multifarious biological profile of this compound comprises activity as endetholin receptor agonist, exeptional antiosteoporotic and antibiotic properties and a remarkable cytotoxicity. The polyketidic 18-membered macrocycle exhibits a *para*-quinone methide core and a highly substituted tetrahydropyran. The versatile pharmacological activity and the unique structural features have prompted several research groups to pursue a synthesis of kendomycin **1**.



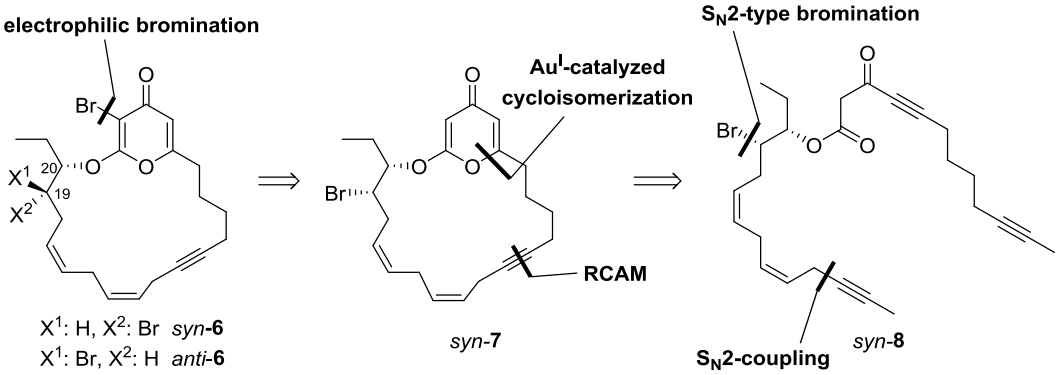
Scheme 1: Retrosynthetic analysis of kendomycin **1**.

A ring-closing alkyne metathesis (RCAM) and a subsequent postmetathetic transformation of the cycloalkyne to the benzofuran by π-acid catalyzed hydroalkoxylation were designed to be the key steps of our total synthesis.

The required polyketide fragment **4** (12 steps) was constructed by an alkyl-Suzuki cross-coupling of a vinyl iodide and an alkyl iodide. The resulting fragment was esterified with phenol **5** (3 steps) before the second alkyne was introduced by another variant of the Suzuki-Miyaura coupling to yield the RCAM precursor. Ring-closure of the obtained diyne was achieved under mild conditions using a molybdenum alkylidyne catalyst. After deprotection of the phenol group, the heterocycle was quickly formed in the presence of catalytic amounts of an electrophilic gold-catalyst, whereas it could not be assembled by simple platinum(II)- oder gold(I/III) chlorides. Furthermore, a ring-contraction by photo-Fries rearrangement gave the desired hexasubstituted cyclophane. Finally, the natural product was obtained after the remaining redox and protecting group manipulations had been carried out according to a literature precedent.

Total Synthesis of a Polyunsaturated, Marine 4-Pyrone Derivative

In the further course of this PhD thesis, the marine 4-pyrone derivative **6** from the red alga of the species *Phacelocarpus labillardieri* was selected for a total synthesis. This compound displayed an impressive inhibitory activity of the phospholipase A_2 in preliminary biological tests (IC_{50} < 4,4 μM).



Scheme 2: Retrosynthetic strategy for the marine natural product **6**.

The polyunsaturated metabolite **6** is a representative of a family of compounds that exhibit a dibrominated, keteneacetal-comprising macrocycle as an extraordinary structural feature. The unknown relative configuration of **6** was to be elucidated by the total syntheses and comparison of the two possible diastereomers *syn*-**6** and *anti*-**6**.

The key transformation of the synthesis was a π-acid catalyzed cycloisomerization of a corresponding β-ketoester to the 4-pyrone and a RCAM to construct the cycloalkyne. At first, the required alcohol fragment (8 steps) was brominated at C19 with inversion of configuration, deprotected and esterified with the corresponding β-ketoacid (6 steps). The formation of the 4-pyrone and the subsequent macrocyclization by RCAM proceeded very efficiently. At last, the second bromine atom on the 4-pyrone was installed under electrophilic bromination conditions. However, the desired bromination competed significantly with the *cis*/*trans* isomerization of the (*Z*)-olefins. Starting from a late-stage intermediate of the alcohol fragment, the diastereomeric compound *anti*-**6** was prepared by twofold inversion of the stereogenic center at C19. By comparison of the NMR data of *syn*- and *anti*-**6** to the data of the natural product, the relative configuration of the substituents at C19 and C20 was determined to be *syn*. Thus, the relative stereochemistry of the natural product **6** was elucidated.

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Formal Total Synthesis of Kendomycin

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Total Synthesis of a Marine 4-Pyrone

Content

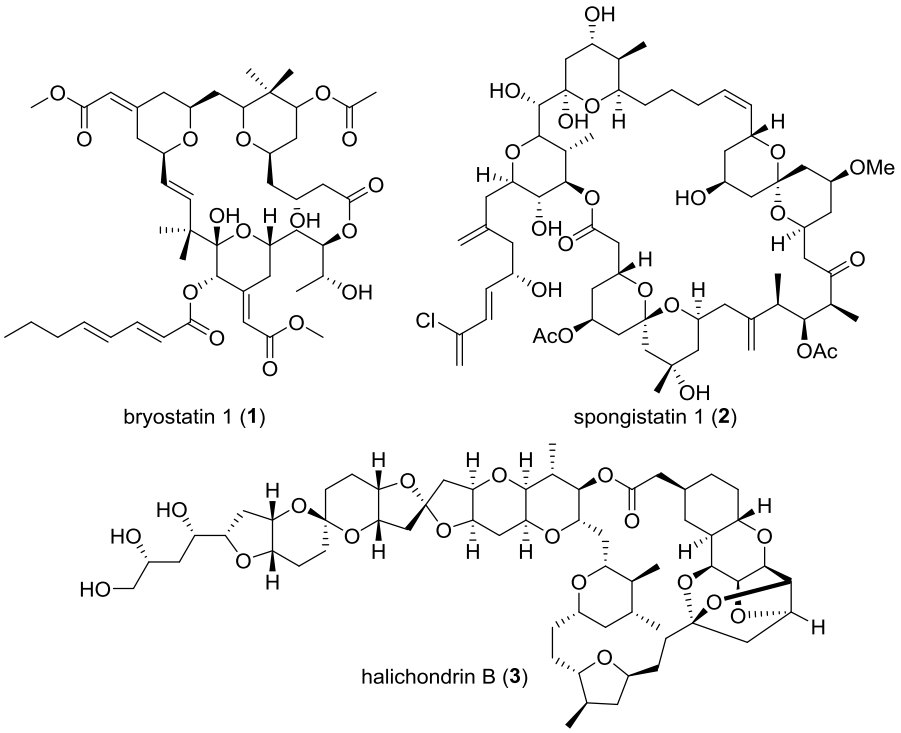
1. Introduction

1.1. Natural Product Synthesis

"There is excitement, adventure, and challenge, and there can be great art in organic synthesis."[1]

With these words Robert B. Woodward describes to the point what has driven generations of synthetic organic chemists to pursue the synthesis of more or less complex organic molecules. Of course, the reasons and motivations behind each and every synthetic endeavor are manifold. The most important drivers will be elucidated in the following.

Natural products from bacteria, fungi and plants fulfil different tasks in their natural surroundings, for example as repellents in defense mechanisms. Frequently, a strong biological activity is observed even towards completely unrelated targets. A few natural products have found direct application as drugs but, in fact, a great number of compounds has served as chemical leads for pharmaceutical and agrochemical agents.



Scheme 1: Highly cytotoxic marine natural products prepared by total synthesis: bryostatin 1 (**1**), (+)-spongistatin 1 (**2**) and halochondrin B (**3**).[2]

In many cases however, a new compound is isolated in low yield from its natural source and often the natural supply of the producing organisms is limited. This is how organic synthesis comes into play as a powerful and versatile tool to provide a reliable amount of material that

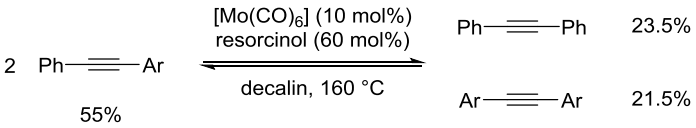
is sufficient for a complete analysis of the biological properties and even for the application as a drug. For example, the highly cytotoxic marine natural products **1**–**3** (scheme 1), which serve as chemical leads, can only be provided by total synthesis in the large amounts of material that are necessary to study their structure-activity relationship.[2]

Furthermore, natural product synthesis has also become a driver for the development of new methods. As synthetic organic chemists have taken the challenge to make bigger and more complex molecules in the course of time, they have perpetually revealed new synthetic questions and, in the search for answers, novel strategies and transformations were established. In this way, organic synthesis and methodology development make a synergy that propels chemical research.

1.2. Ring-Closing Alkyne Metathesis (RCAM)

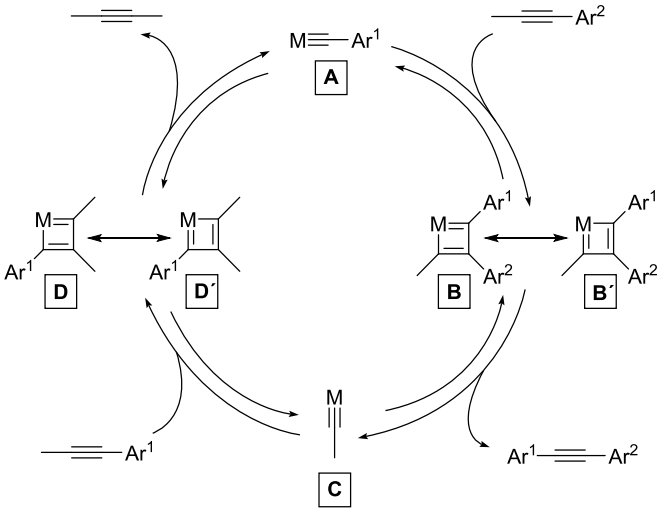
Ring-closing alkyne metathesis (RCAM) is one of the key technologies that were applied in the course of this PhD thesis. Therefore, a short summary containing the underlying principles of this method will be described in the following.

Alkyne metathesis has its origin in the intermolecular alkyne homo- or cross metathesis variants (ACM). In 1974, Mortreux and Blanchard observed that a mixture of [$Mo(CO_6)$] and resorcinol was catalytically active in scrambling the substituents of acetylene derivatives.[3]



Scheme 2: Alkyne metathesis with a [$Mo(CO)_6$]-resorcinol catalyst.[3]

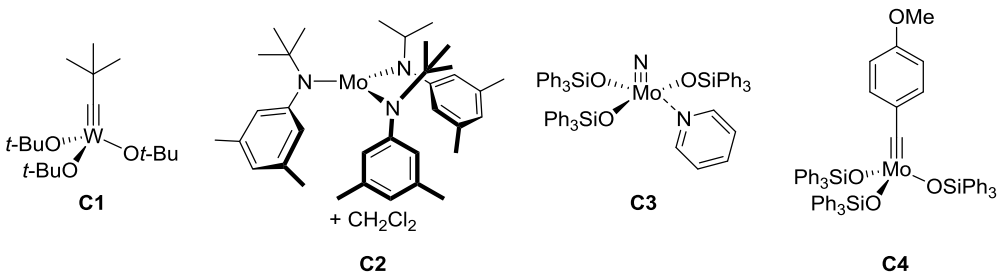
Even though the experimental procedure was simple and practical, the applicability of the reaction suffered from the forcing conditions prohibiting functional group tolerance. At the required reaction temperature of 160 °C the phenolic groups of the ligand are non-innocent bystanders. Shortly after the initial discovery, the mechanism of alkyne metathesis was proposed by Katz and McGinnis.[4] The reaction follows the basic logic of the Chauvin cycle that is commonly accepted for olefin metathesis (scheme 3).[5] Below, the mechanism will be illustrated by an example with two methyl-capped alkyne derivatives as substrates.



Scheme 3: Mechanism of alkyne metathesis as proposed by Katz and McGinnis.[4] For clarity, the ancillary ligands were removed from the metal center.

The principle of microscopic reversibility is underlying the course of the process. A metal alkylidyne species **A** undergoes a formal [2+2]-cycloaddition to form a metallacyclobutadiene that can be described by two resonance structures **B** and **B´**. By cycloreversion the new acetylene species is released and a metal alkylidyne **C** is formed that repeats the same steps to complete the catalytic cycle. Butyne is released as a byproduct in this reaction.

This mechanistic proposal was validated early on by different observations made by Schrock and coworkers.[6] Apart from the high-valent complexes of molybdenum, the rhenium and tungsten alkylidynes were found to be catalytically active. However, broad applications were missing for several decades.[7] It was only in 1998 that research around this methodology was accelerated as the intramolecular version - the ring-closing alkyne metathesis - was identified as a method for the construction of macrocyclic frameworks.[7-8]



Scheme 4: Overview of different types of alkyne metathesis catalysts.

As Fischer carbyne complexes were found to be generally inactive in alkyne metathesis, the development and improvement of the catalysts focused on Schrock alkylidynes. In these

complexes, the metal is usually in its highest oxidation state and the alkylidyne is considered a trianionic ligand. The metal-carbon triple bond is not strongly polarized; however, a distinct nucleophilicity of the α-carbon is observed.

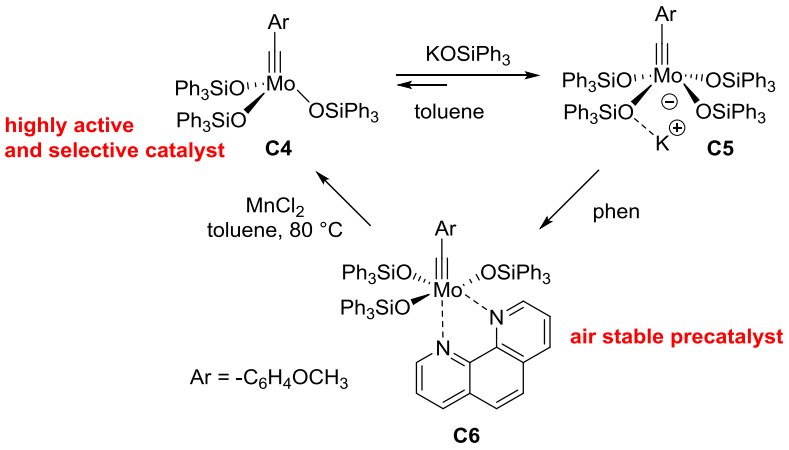
The first well-defined alkyne metathesis catalyst was the tris(*tert*-butoxy) tungsten neopentylidyne **C1** which was reported by Schrock *et al*.[9] The complex is reasonably stable as the bulky *tert*-butoxy groups prevent dimerization and decomposition. The highly Lewis acidic property of the tungsten center somewhat limits the scope, as amines, thioesters or acid labile functional groups are not tolerated.

Another benchmark catalyst was developed by Cummins and coworkers. The tris(amido) molybdenum complex **C2** was originally established for the cleavage of nitrogen.[10] Yet, it was discovered that it reacts with dichloromethane to give a catalytically active species.[11] This precatalyst system was frequently applied because it displays good functional group tolerance towards polar substituents such as basic amines. A drawback of this catalyst is its exceptional lability towards oxidation and hydrolysis.

Furthermore, some nitride complexes should be mentioned.[12] An effective representative of the class is **C3** which is depicted as the stabilized pyridine adduct (scheme 4). This kind of molybdenum nitride species also serves as precatalyst for alkyne metathesis and attracted some attention for its considerable functional group tolerance.[13]

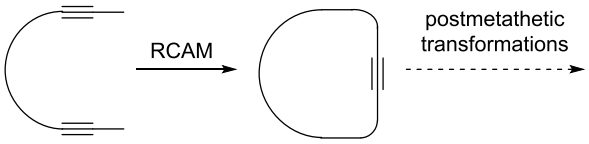
More recently, the Fürstner group[13b, 13c] developed a new catalyst system **C4** (scheme 4) based on triphenylsilanolate ligands which seemed to be an excellent match for the molybdenum core. Furthermore, the Lewis acidity of the metal center is adjusted such that the species remains highly reactive, yet is even more functional group tolerant.

A scalable, safe and reliable procedure was described for the preparation of **C4**.[13c] An interesting feature of the molybdenum alkylidyne **C4** is that it can be rendered air-stable by complexation with 1,10-phenanthroline. The re-activation of the catalyst by removal of the extra ligand can be achieved by treatment with metal salts such as $MnCl_2$ or $ZnCl_2$. Overall, this system is user-friendly and applicable to many functionalized substrates.



Scheme 5: Tris(triphenylsilanolate) molybdenum alkylidyne catalyst developed by Fürstner *et al*.[13b, 13c]

A priori, all steps of an alkyne metathesis reaction are reversible. In order to support product formation, the butyne needs to be removed from the equilibrium. Formerly, this was achieved by either heating of the reaction solution or application of low-pressure. A seminal discovery by the Fürstner group was the use of 5 Å molecular sieves for trapping the butyne, thus making the last step of the catalytic cycle irreversible.



Scheme 6: RCAM as an entry to structurally diversity.

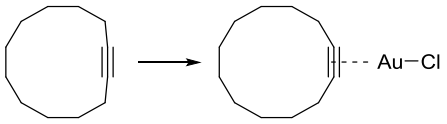
As discussed before, the alkyne metathesis has gained importance especially in the intramolecular version. Today, ring-closing alkyne metathesis (RCAM) is on the rise[7] as a powerful tool in organic synthesis. The resulting cycloalkynes are predestined for further postmetathetic transformations because triple bonds are versatile precursors and therefore valuable species. Initially, the newly formed triple bond was subjected to hydrogenation to access *cis*-olefins selectively. Alkynes also offer a handle for hydrometalation or carbometalation, and intramolecular reactions such as hydroalkoxylations, enyne reactions and cycloadditions are further possible options.

Meanwhile, a range of natural products has been successfully prepared by RCAM in combination with adequate postmetathetic modifications. Thus, RCAM has become a C-C bond-forming tool that has enabled new disconnections for the formation of structurally diverse motifs.

1.3. π–Acid Catalysis with Gold

The second key technology that is at the focal point of this work is π-acid-catalysis with gold. As gold basically does not play a role in classic redox-catalysis, this metal did not attract much attention of organic chemists until π-acid catalysis was gaining importance at the beginning of this century. Thus, gold-catalysis is still an adolescent field.[14]

Due to the strong relativistic effect, late transition metals such as gold and platinum exhibit special properties. These late elements of the sixth period display a significant contraction of the s-orbitals because of the increased positive charge at the atom nucleus. This leads to an expansion of the d- and f-orbitals which are consequentially diffuse and polarizable. This fact is reflected by the soft character of these metals, e.g. gold (I). In accordance with the HSAB concept,[15] the soft gold cation shows a strong preference to interact with soft π-systems such as triple bonds. They can be activated selectively by a gold (I) complex for attack by a nucleophile (intermediate **I**, scheme 9). This mode of action results in a formal *trans*-addition as first described for Pt (II).[16] However, investigations using Au (I) followed quickly and gained particular popularity.[14a, 17]

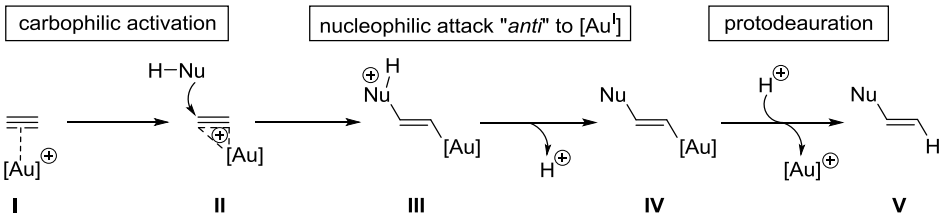


Φ = 176°
d = 1.196 Å

Φ = 168°
d = 1.225 Å

Scheme 8: Polarization of a triple bond by an electrophilic gold (I) species.[18]

The neutral gold complex (LAuCl) bearing for example a phosphine or an N-heterocyclic carbene as ligand L can be activated with silver salts (e.g. $AgBF_4$, $AgNTf_2$) to form a cationic species that can coordinate to π-systems. A computer-based analysis indicated a predominant contribution of a σ-binding interaction by the donation of electron density of the π-bond of the acetylene into the empty d_{z^2}-orbital of the metal center. A weaker but still significant backdonation is made by an occupied d-orbital of the gold atom into the π*-orbital of the alkyne. Certainly, electrostatic interactions also play an important role in these binding interactions.[19] The effect of a simple AuCl-complex on an acetylene group is evidenced by the increased bond length and the contorted bond angle that correspond to the reduced triple bond character (scheme 8).



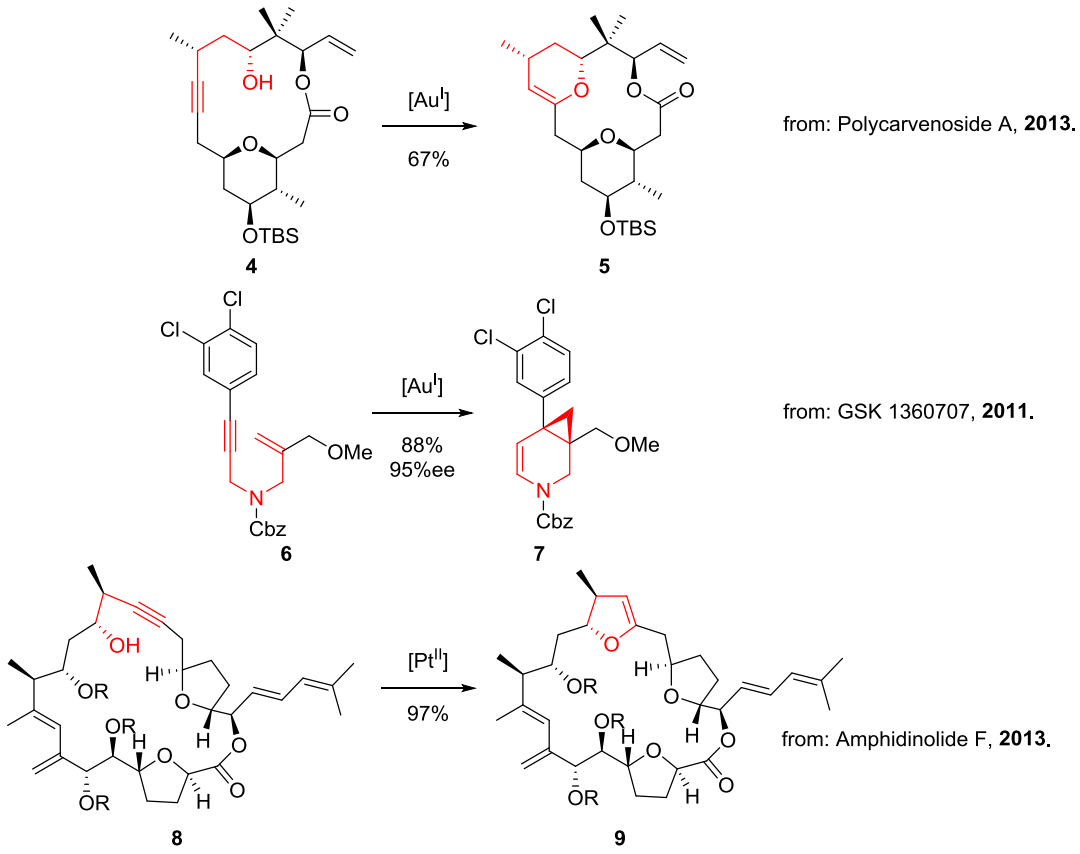
Scheme 9: Gold (I) can activate triple bonds for nucleophilic attack.

Computational studies suggest that a “slippage” of the metal complex along the π-system contributes to the activation.[20] After attack of the nucleophile a proton is usually transferred and finally the product **V** is released by proto-deauration (scheme 9). There are two things to note about this mechanism: First of all, the intermediate gold species are drawn as only one resonance extreme. It was also shown that in some cases the binding mode can be more accurately described by a carbenoid species.[14b, 17a, 17d, 21] Secondly, an important observation was the positive influence of protic solvents[22] which are assumed to promote the proto-deauration of intermediate **IV** which is also prone to undergo diauration – a pathway that infringes on the catalytic cycle.

To underline the increasing number of applications of π-acid catalysis, the following three examples were chosen (scheme 10): The first example is an excerpt from the formal total synthesis of polycarvenoside A.[23] One of the key transformation is a transannular hydroalkoxylation which is based on an electrophilic gold-catalyst.

The second example depicts a sequence from the synthesis of the antidepressant candidate GSK 13600707.[24] A gold-(I)-complex bearing a chiral phosphoramidite ligand is used to induce an asymmetric enyne cylcoisomerization that forms a cyclopropane ring with excellent enantioselectivity.

The third precedent showcases the key step of the total synthesis of amphidinolide F.[25] A platinum-(II)-catalyzed 5-*endo*-dig cyclization furnished a dihydrofuran, which was the gateway for the preparation of a 1,4-diketone moiety present in this target (scheme 10).



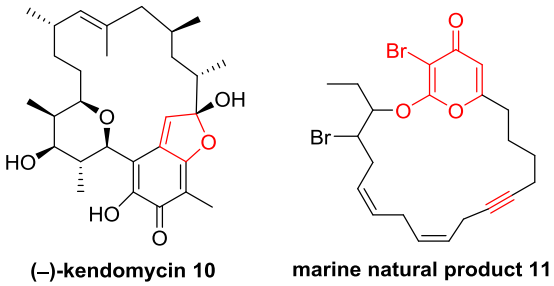
Scheme 10: Three examples for recent applications of π-acid catalysis.[23-25]

In conclusion, π-acid catalysis can be used to generate great structural complexity starting from alkynes. Furthermore, as can be seen in scheme 10, the inherent soft character of the Lewis acidic catalysts ensures compatibility with many functional groups. The highly sophisticated exercises by numerous research groups[14, 17, 21] highlight the broad spectrum of mechanistically different transformations that are enabled by π-acid catalysts, in some cases even with excellent asymmetric induction.[24, 26]

The gold-catalyzed preparation of pyrone-derivatives is another exciting application. However as this topic specifically coheres with the second project of this PhD thesis, a detailed discussion will be given in chapter **4**.

2. Aims and Scope

The work presented in this PhD thesis can be seen against the backdrop of the growing confidence in RCAM as a key operation in natural product synthesis and the application of this methodology in concert with a postmetathetic modification based on gold-catalysis. Two target structures were chosen that we considered suitable for the application of these methods.



(–)-kendomycin 10 **marine natural product 11**

Scheme 11: Natural products that were to be synthesized via RCAM and π-acid catalysis with gold (I).

A common goal of both synthetic endeavors was to find highly convergent and efficient routes for the preparation of the natural compounds. First of all, the macrocyclic polyketide (−)-kendomycin (**10**) was identified as a prime target to employ our recently developed RCAM catalyst for the ring-closure. The highly functionalized and sterically congested compound should challenge the molybdenum alkylidyne complex in terms of functional group tolerance and steric bulk. The formed cycloalkyne should offer a handle for the envisioned gold-catalyzed construction of the benzofuran unit.

Secondly, a dibrominated marine natural product **11** was selected. This macrocyclic molecule contains an immanent acetylene group that we identified as a predestined site of disconnection by RCAM. In the context of a highly sensitive skipped diene/yne moiety, the compatibility of **C4** would be put to test. Furthermore, this highly functionalized 2-alkoxy-3-bromo-4-pyrone was an unprecedented motif that could be constructed from an acetylenic precursor using a π-acid catalyst.

These two synthesis projects were therefore chosen to challenge the scope of ring-closing alkyne metathesis and validate the performance of our state-of-the-art catalyst. Moreover, the scope of π-acidic gold-catalysts should be extended by elaborating internal alkynes into complex heterocyclic structures.

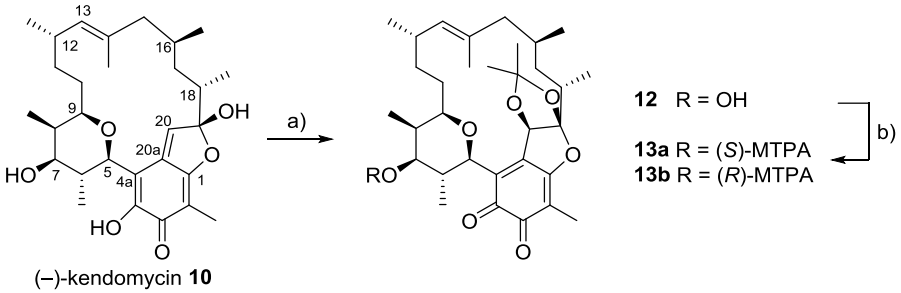
3. Formal Total Synthesis of (–)-Kendomycin

3.1. Introduction

3.1.1. Structure

Kendomycin [(−)-TAN 2162] (**10**) has been a highly pursued target molecule of synthetic organic and medicinal chemists.[27] This interest can most likely be explained by the impressive biological profile as well as the highly intriguing structural motifs. Kendomycin is a densely functionalized 18-membered oxa-bridged macrocylic polyketide that features a unique quinone methide chromophore with a *C*-glycosidic linkage to a highly substituted tetrahydropyran. The pentasubstituted quinoid is embedded in an *ansa*-backbone that is decorated with nine stereogenic centers, one of them being a lactol, and a trisubstituted (*E*)-double bond.

3.1.2. Isolation & Structure Validation



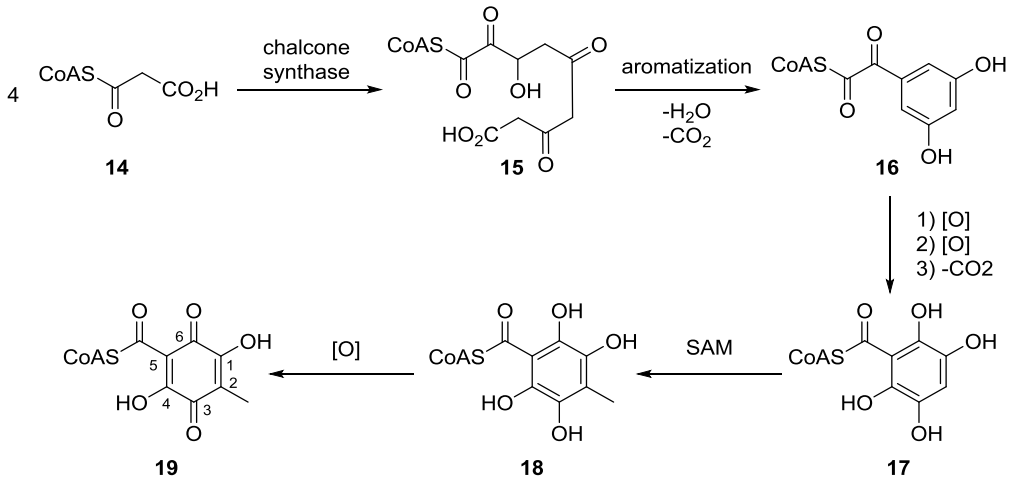
Scheme 12: (−)-Kendomycin (**10**); derivatization to Mosher esters (**13a** and **13b**): a) $FeCl_3$, acetone, rt, 26%; b) (*R*)-MTPA for **13a** or (*S*)-MTPA for **13b**, DMAP, CH_2Cl_2, pyridine.[28]

(−)-Kendomycin (**10**) was first isolated in 1996 from two different *Streptomyces* species by scientists at Takeda Chemical Industries Ltd.[29] and was re-isolated in 2000 from *Streptomyces violaceoruber* (strain 3844-33C) by Zeeck and coworkers.[28] The strain used to produce kendomycin was grown in a medium of soybean (2%), mannitol (2%), agar (1.5%) and deionized water. The seed culture was fermented and the fermentation broth was extracted, concentrated and filtered. After evaporation of the solvent, the crude product was recrystallized from CH_2Cl_2 and was subsequently chromatographed. This process has so far produced multi-gram quantities of the intensely yellow natural product.[30] The previously reported structure and relative configuration[29a, 29b] were confirmed by 2D-NMR experiments and single crystal X-ray diffraction. At the same time, the previously reported ^{13}C NMR assignments were corrected. For clarification of the absolute configuration of the

ansa-chain, kendomycin was derivatized by introduction of an acetal at C19/C20 to give kendomycin acetonide **12**. The single remaining unprotected hydroxyl function at C7 was then used for Mosher´s ester analysis.[31] The C7-center was identified to be *S*-configured thus defining the absolute stereochemistry of **10**.[28]

3.1.3. Elucidation of the Biosynthetic Pathway

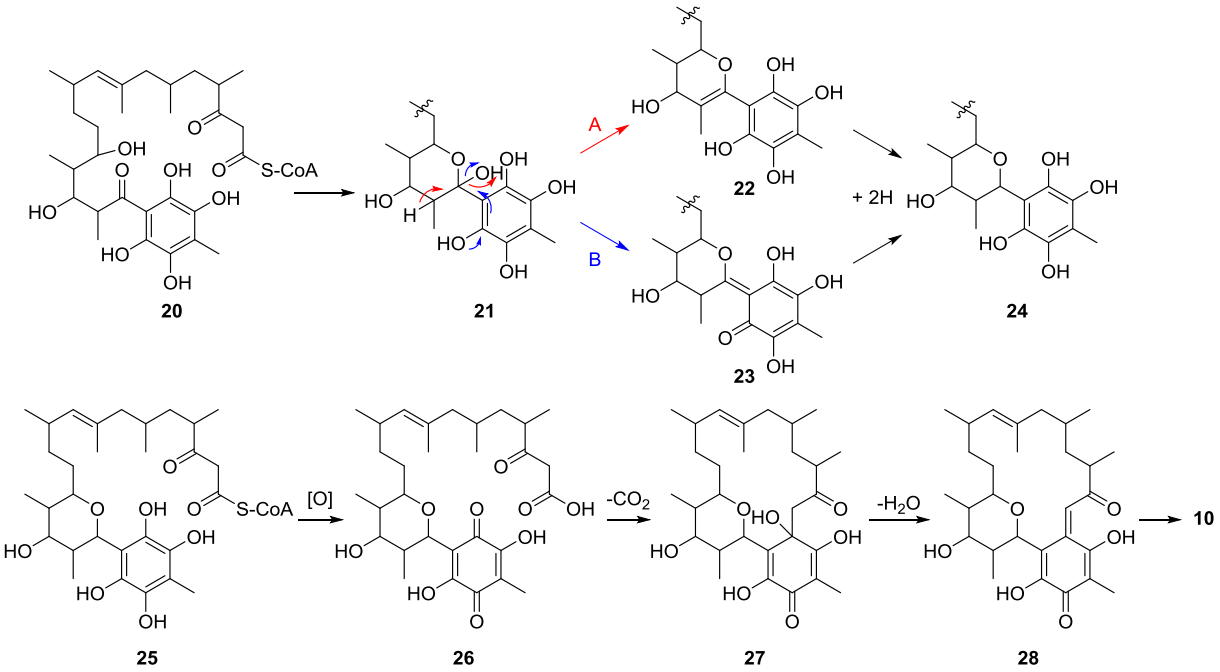
Polyketides usually originate from decarboxylative condensation reactions of malonyl-CoA **14**. Bode and Zeeck (scheme 13)[28] proposed a bacterial type I polyketide pathway for the formation of the aliphatic chain of kendomycin (**10**). The ancestry of the quinone methide core, however, presented a fascinating biosynthetic question. Müller and coworkers clarified the isssue later using gene expression experiments.[32] In fact, the origin of every oxygen atom was ascertained by extensive isotope labeling experiments (^{13}C, ^{18}O). Feeding studies revealed that most oxygen atoms are introduced via acetate (C1), malonate (C3) or methylmalonate units (C7, C9, C19). Only the oxygen atom at C4 derives from molecular oxygen. The C2-methyl group on the chromophore did not exhibit a label in any of the conducted studies, pointing to the involvement of a one-carbon donor (e.g. SAM = S-adenosyl methionine) in the course of forming this methyl substituent.



Scheme 13: Zeeck´s hypothesis regarding the biogenetic origin of (−)-kendomycin´s chromophore.[30]

^{13}C-labeling experiments indicated that the biosynthesis of the ansa chain proceeds from C5 to C20. Hydroquinone **18** or quinone **19** were identified as starter units. These are constructed from acetate and malonate building blocks and loaded onto polyketide synthases (PKS). The β-keto thioester intermediates undergo oxidation/reduction sequences to form the acyclic precursor **16**, which cyclizes under release of CO_2. Reaction with additional oxidases and a methyl transferase completes the substitution pattern of the

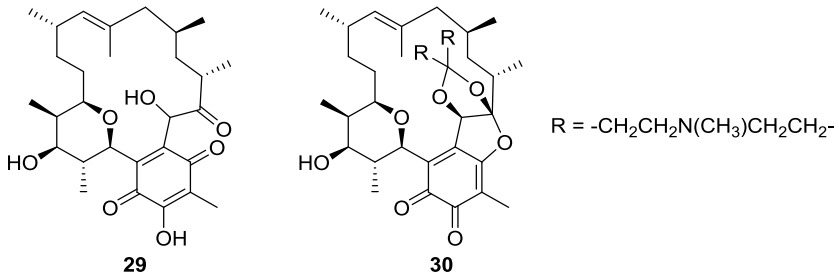
chromophore. Chain elongation is assumed to proceed via typical malonic/methylmalonic acid thioesters and the derived β-keto thioesters.



Scheme 14: Top: two possible biosynthetic pathways for tetrahydropyrane formation; bottom: putative aldol-type macrocyclization.

It remains unclear whether the tetrahydropyranyl ring is closed before or after the macrocyclization and two different pathways for the reductive cyclization have been discussed. Path A is based on a dehydration mechanism forming a double bond at C5-C6. In path B the phenolic hydroxy group participates by forming an *ortho*-quinone methide with a double bond at C4a-C5 as dehydration takes place. Both routes have a subsequent reduction step in common. The macrocyclization at C20-C20a is proposed to resemble an aldol-type condensation. Following cleavage of the enzyme-polyketide complex, decarboxylation generates a nucleophilic site that attacks the quinone. Dehydration gives the aldol condensation product and hemiacetal formation establishes kendomycin (**10**). This proposed pathway is supported by the biosynthetic data of related polyketide macrolides.[33]

3.1.4. Biological Activity



Scheme 15: Hydrolysis product of kendomycin (**29**) and piperidone ketal derivative **30**.

Kendomycin was initially reported as a potent endothelin receptor agonist and displays antiosteoporotic properties. Upon its reisolation by Zeeck and coworkers, diverse antibiotic activity against Gram-positive and Gram-negative bacteria (e.g. multiresistant *Staphylococcus aureus* strains) and a strong cytotoxicity against human stomach adenocarcinoma (HMO2), hepatocellular carcinoma (HEP G2) and breast adeno-carcinoma (MCF7) cell lines were observed. In part, an increased growth inhibition (GI_{50} <0.1 μM) similar to state-of-the-art drugs such as doxorubicin and cisplatin was found.[30] Remarkably, the acetonide derivative **12** exhibited similar cytotoxic properties in in vitro cell assays with three human tumor cell lines (HMO2, HEP G2, MCF7, GI_{50} < 1 μM).[28] The potent cytotoxic effects were initially attributed to an impairment of the ubiquitin proteasome system, but the exact mode of action remained unclear. In later studies, Janssen *et al.*[34] reported that kendomycin (**10**) disrupts the protein-protein interaction of the anti-apoptotic enzymes B-cell lymphoma-extra large (Bcl-xl) and Bak peptides.[35]

Table 1: Selected biological data of kendomycin (**10**) and some active derivatives **12**, **29**-**30**.[34]

	Bcl xL-inhibition		cytotoxicity
	IC_{50} (μM)	E_{max} (%)[a)]	IC_{50} (μM)
10	12.3	70	16
12	9.5	22	14
29	230	35	25
30	5.0	66	14

a) Maximal effect in a fluorescence polarization assay measuring displacement of a fluorescently labeled Bak peptide from a GST-Bcl-xl fusion protein.

Apart from the natural product and the derived acetonide **12**, a congener **29** produced by hydrolysis of the hemiacetal, as well as a piperidone ketal **30** were subjected to biological

testing (scheme 15). Except for the hydrolysis product, all compounds were found to exhibit a significant effect on Bcl-xl[35] and displayed cytotoxicities within the same range. However, there seems to be no clear evidence for the correlation of enzyme inhibition and cytotoxic effects (table 1).[34]

Recent systematic biochemical studies of the kendomycin-proteasome interactions in wild-type and mutant yeast 20S proteasome in vitro and in vivo indicated a novel mechanism that is still not fully understood.[28, 32, 34] The 20S proteasome core particle (CP) is an enzyme with multicatalytic activity that, in general, promotes protein turnover in cells. The catalytically active sites of the proteasome are defined by the N-terminal threonines in the β1, β2, and β5 subunits at the inner cavity of a barrel-like structure. Although a large number of CP inhibitors (such as bortezomib[36] or carfilzomib[37]) emerged from synthetic and natural sources, their activity is compromised by side effects and toxicity by off-target binding.[38] These drugs share a common mode of action, namely locking the substrate binding channel and inducing a conformational change of the active site of the protein and a subsequent covalent bond formation with Thr1.

With this information, Groll and coworkers[39] set out to search for CP inhibitors of natural origin with hitherto unknown mode of action. An investigation of several compounds that were reported as active inhibitors before, only kendomycin passed the first tests. The *ansa*-compound displayed a reproducible *in vitro* proteasome inhibition of yβ1 (24.0%), yβ2 (23.5%) and yβ5 (15.3%) catalytic activities at 200 μM in the presence of sodium dodecyl sulfate (SDS). This observation was consistent with earlier studies indicating that the CP of leukemic monocyte lymphoma cells (IC_{50} = 0.8 μM) were targets of kendomycin, as the natural product reduced the proteasome activity to 25% in the presence of small amounts of SDS.[32] Furthermore, detailed investigations of the proteasome-ligand complex revealed a significant proteasomal β5 inhibitory activity at a reported IC_{50} value of 67.9 μM. However, in the absence of SDS, kendomycin was noneffective. Detergents such as SDS are frequently used in in vitro assays to open the proteolytic chamber of the CP in order to promote substrate binding and product release. Therefore, it was assumed that a CP mutant (α3ΔN) that is lacking the first nine N-terminal amino acids and thus diplaying a permanently open gate structure would render SDS unnecessary. Surprisingly, kendomycin´s inhibitory activity was found to be attributed to small amounts of the detergent and unrelated to the substrate

binding channel. These findings indicated that a non-conventional binding mode must be operative.

Furthermore, crystals of the proteasome-kendomycin complex were diffracted. The obtained data supported the previous conclusion, as the natural product was identified on the surface rather than in the binding pocket. Interestingly, kendomycin (**10**) was found to be covalently bound to the reactive methide at C20 via β2–His141N. After mutagenesis of sections of the binding pocket (β2-H141A), the ligand was absent, even though inhibition of β5 activity was undiminished. Moreover, HeLa cells (derived from cervical cancer cells) were incubated with kendomycin and it was observed that the viability curve superimposes the IC_{50} curve, leading to the conclusion that the detected IC_{50} values in vivo cannot be attributed to impairment of the proteasome activity, but rather to the highly cytotoxic properties of kendomycin.

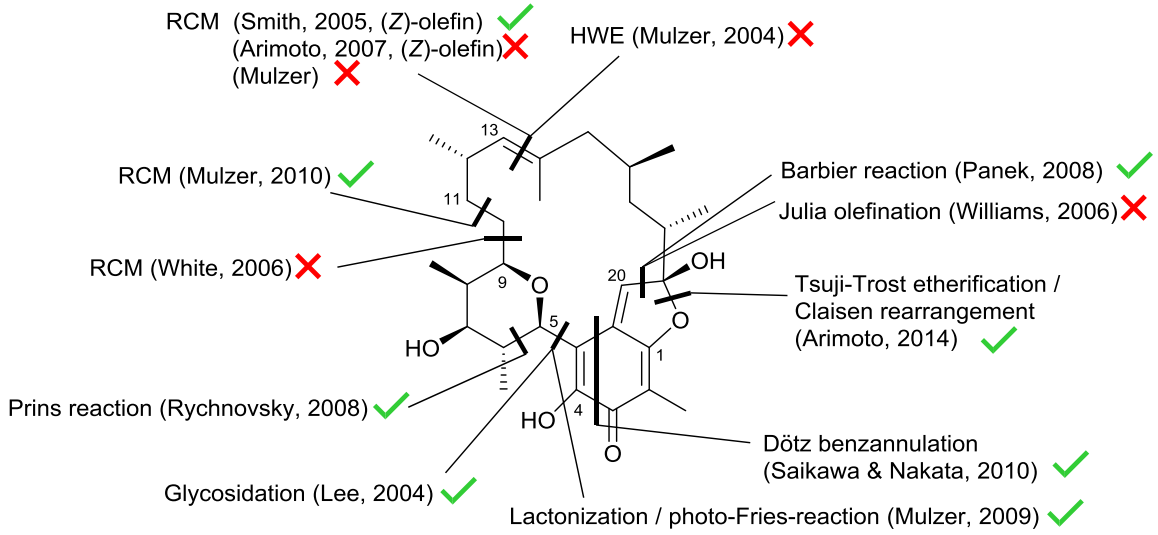
In conclusion, the correct target of kendomycin (**10**) could not yet be identified, even when complementary and orthogonal assay techniques were applied in concert.[39a, 40] A polypharmacological mode of action was suggested to be responsible for the rapid kendomycin-mediated apoptosis.[28, 32, 34]

3.2. Preceding Synthetic Studies

18 years after its first isolation, (−)-kendomycin (**10**) remains an attractive target for synthetic organic chemists. The structural features of this unique ansamycin compound have attracted no less than eight different research groups so far. Six total syntheses (Lee,[41] Smith,[42] Panek,[43] Mulzer (2x),[44] Saikawa and Nakata[45]), two formal syntheses (Rychnovsky)[46] and several fragment syntheses (Mulzer,[47] Arimoto,[48] Panek,[49] White,[50] Williams[51]) were published prior to our work, and one total synthesis was reported briefly thereafter by Arimoto and Uemura.[52] A survey of the synthetic efforts preceding this PhD thesis is presented here. For the sake of brevity, emphasis is put on the key transformations and fragments. Synthetic elaborations published after the completion of this project will not be discussed.

Many synthetic approaches mimic a biogenetic pathway with regard to the *ansa*-chain. Therefore, the majority of the reported syntheses resorted to similar fragment disconnections. Hence, a highly functionalized aromatic unit was commonly linked to a more or less advanced polyketide chain. Interestingly, synthetic efforts towards the latter relied

essentially on auxiliary-assisted aldol and alkylation chemistry. Moreover, the challenging macrocyclization to the all-carbon 18-membered ring and formation of the densely substituted tetrahydropyranyl unit were late stage transformations in all reported syntheses. Oxidation to the quinoid motif was carried out in the final steps in order to avoid issues that could potentially arise from the highly electrophilic C20 methide.

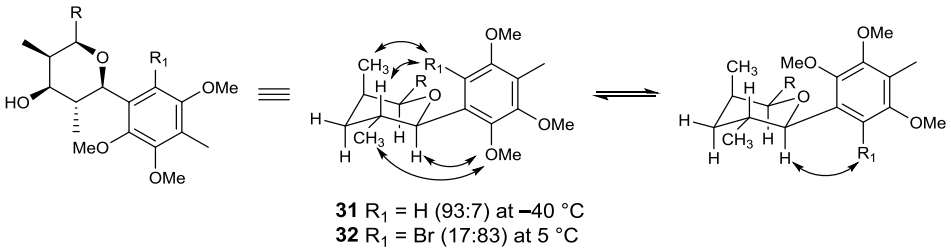


Scheme 16: Overview of previous retrosynthetic disconnections in completed and uncompleted syntheses.

Scheme 16 indicates that certain disconnections were more often selected for macrocyclization than others. A frequent choice was the ring-closing olefin metathesis (RCM) at the C13-C14 double bond.[53] This disconnection was attempted early on by Mulzer *et al.*[47d] and later on by the research groups of Smith[42] and Arimoto.[54] However, these approaches either failed to give the macrocycle or led to the undesired (*Z*)-olefin which had to be inverted to the (*E*)-olefin via several additional steps. In another approach, which was designed to circumvent this problem, the disconnection at the nonstereogenic C10-C11 bond was selected for RCM. In this case, the resulting double had to be reduced by hydrogenation (scheme 16).[44b, 55]

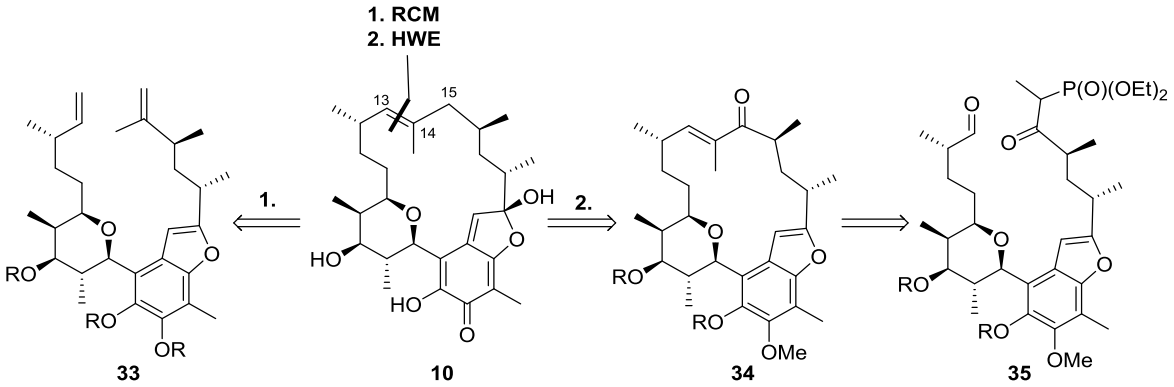
In general, disconnections for macrocyclization placed adjacent to the chromophore have been more successful, as in the examples of Panek[43] (Barbier reaction), Arimoto[52] (Tsuji-Trost etherification) and Lee[41] (glycosidation). On one occasion, the aromatic core was built up de novo by Saikawa and Nakata[45] (Dötz benzannulation), as the macrocyclic framework was closed. Rychnovsky *et al.*[46a] employed a Prins cyclization, thus constructing the tetrahydropyran and the macrocycle at the same time. The above syntheses featured widely varying efficiency.

3.2.1. Early Studies and Total Syntheses by Mulzer and Coworkers



Scheme 17: A distinct atropisomerism about the *C*-glycosidic bond was observed for the substrate depicted above; NOEs are depicted for R_1 = H.[47a]

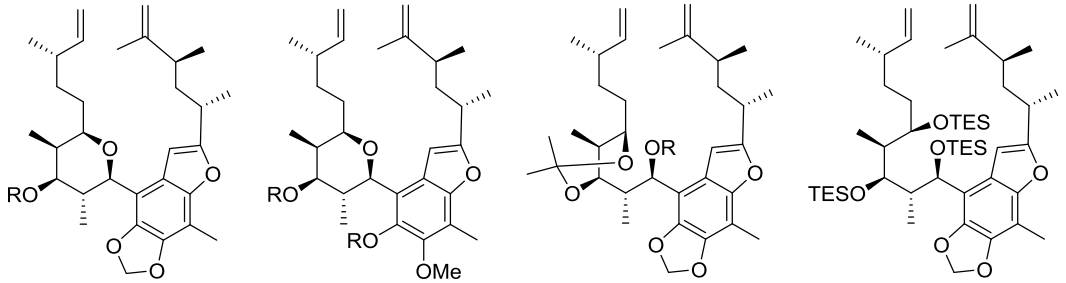
Mulzer´s strategy to form the ansa chain was especially influential on later endeavors. An interesting aspect first observed by Mulzer *et al.* was the rotational limitation about the *C*-glycosidic C4a-C5 bond in two acyclic intermediates **31** and **32** that had the tetrahydropyran next to the arene already in place. In both compounds, rotation about the C4a-C5 single bond was restricted. In case of **31**, temperature dependant NMR studies revealed an equilibrium of two atropisomers with broadened signals at ambient temperature that could be resolved into separate sharp signals at −40 °C. In the case of the brominated compound **32**, two separable rotamers were observed, showing that an increased rotational barrier might exist.[47a] This phenomenon would resurface in some of the succeeding syntheses.



Scheme 18: Initial disconnection approach by Mulzer and coworkers.

The initial synthetic plan of Mulzer and coworkers was centered on a RCM at the C13-C14 olefinic bond (scheme 18). Anticipating the complications in the key macrocyclization step that could arise from the above mentioned atropisomerism, several substrates were prepared. Dienes containing the tetrahydropyran moiety and a dioxole protecting group on the arenes **36** and **37** gave only complex mixtures under metathesis conditions. Modifications that were assumed to decrease the rigidity about the C4a-C5 bond, such as acyclic protecting groups on the aromatic core (**38**, **39** and **40**), as well as derivatives

containing a free (**41** or protected **42** and **43**) benzylic alcohol in place of the rigid THP ring were examined. However, all attempts to achieve ring closure led to dimerization and oligomerization. Since the open-chain representatives **41**-**43** gave the same result as the THP-containing substrates, an underlying negative impact of the planar and rigid benzofuran unit was presumed.[47d]



36 R = H
37 R = Ac

38 R = H
39 R = MOM
40 R = Ac

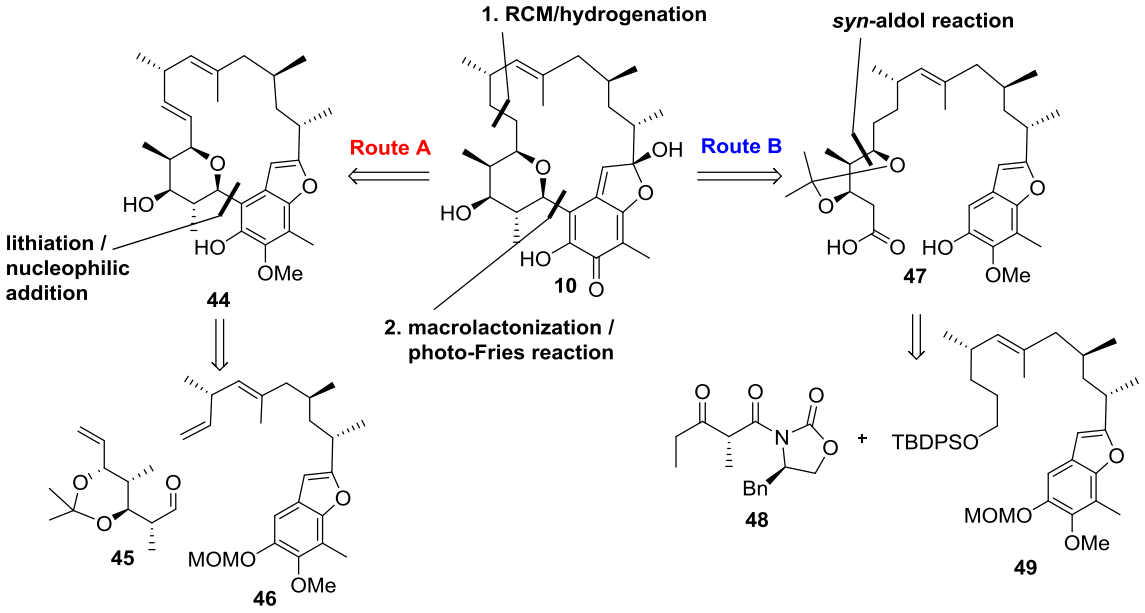
41 R = H
42 R = Ac

43

Scheme 19: Dienes surveyed for the RCM at C13-C14 by Mulzer. Substrates existed as various mixtures of atropisomers.

Nevertheless, the macrocyclization at the C13-C14 double bond was achieved in a later approach utilizing an intramolecular Horner-Wadsworth-Emmons olefination (scheme 18). While the designed key transformation proceed smoothly, deoxygenation at C15 resulted in significant isomerization of the double bond under various conditions.[44b]

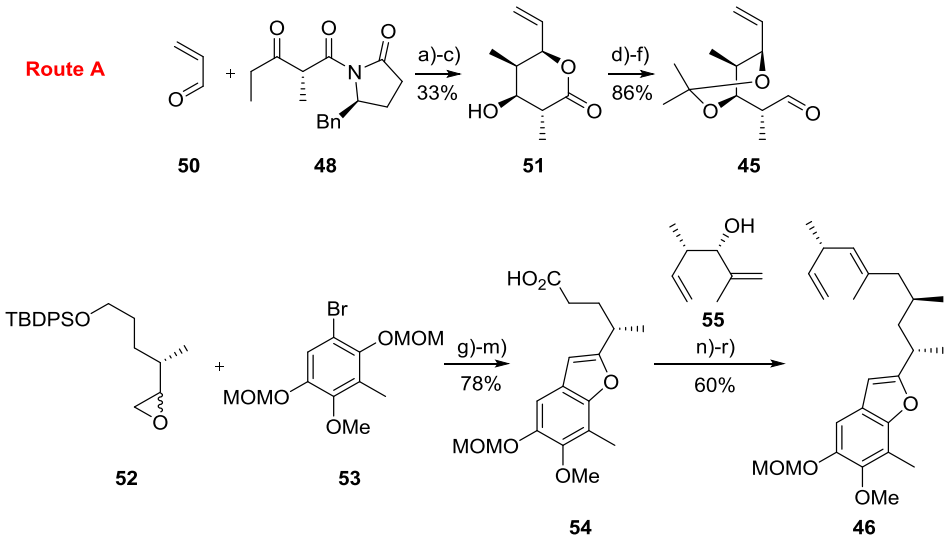
3.2.2. Mulzer´s Total Syntheses of (−)-Kendoymcin by RCM and Photo-Fries Reaction



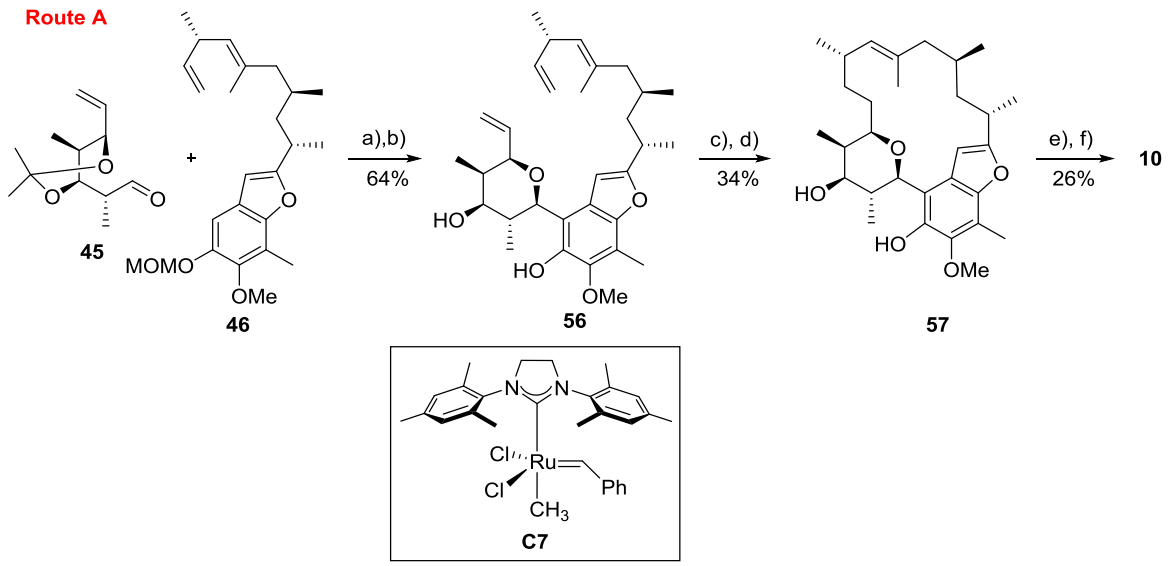
Scheme 20: RCM and macrolactonization/photo-Fries route by Mulzer *et al*.[44a]

The Mulzer group later reported two total syntheses of kendomycin (**10**) predicated on a different retrosynthetic analysis.[44a] RCM was planned at the C10-C11 bond of diene **44**, followed by selective hydrogenation. The precursor was assembled by deprotonation and nucleophilic addition of benzofuran **46** to aldehyde **45**. Furthmore, the *C*-glycosidic bond at C4a-C5 was chosen for the first disconnection. In this case, the macrocycle was built up by macrolactonization to give a metacyclophane, followed by *ortho*-Fries rearrangement, which adjusted the correct substitution pattern of the arene.

Route A The synthesis of the northwestern fragment started with an Evans *syn*-aldol reaction[56] of acrolein **50**, followed by an *anti*-selective reduction with sodium triacetoxyborhydride[57] and hydrolytic cleavage of the auxiliary to give δ-lactone **51**. 1,3-Diol protection as an acetonide followed by a reduction/oxidation sequence furnished aldehyde **45**. The eastern counterpart was prepared starting from aryl bromide **53** with a copper-mediated epoxide opening of diastereomeric **52**. An oxidation/condensation sequence then provided the benzofuran. The free phenol at C4 was reprotected as a MOM-ether. Further elaboration of the fragment was accomplished by silyl-ether cleavage, stepwise oxidation of the primary alcohol to the carboxylic acid **54** and esterification with alcohol **55**. The obtained intermediate was rearranged using an Ireland-Claisen protocol[58] to the extended alkene **46**.



Scheme 21: Synthesis of the northwestern and eastern fragment of Mulzer´s C10-C11 RCM approach. Conditions: a) $Sn(OTf)_2$; b) $Me_4NBH(OAc)_3$; c) LiOH, H_2O_2; d) $Me_2C(OMe)_2$, CSA; e) $LiAlH_4$; f) py·SO_3, DMSO; g) Mg, CuI; h) $(COCl)_2$, DMSO, Et_3N; i) TfOH, toluene, Δ; j) MOMCl, NaH; k) TBAF; l) IBX; m) $NaClO_2$; n) EDCI·HCl, DMAP, **55**; o) LDA, TBSCl, Δ; p) $LiAlH_4$, q) MsCl; r) $LiAlH_4$.[44a]

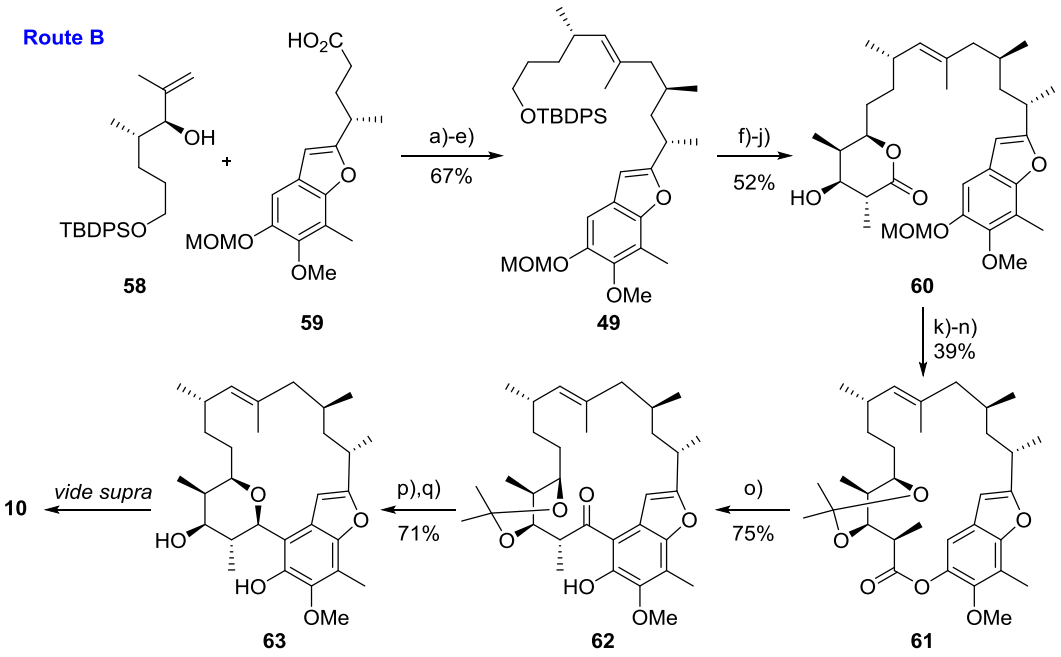


Scheme 22: Mulzer´s total synthesis of (−)-kendomycin (**10**) by RCM. Conditions: a) *n*-BuLi, TMEDA; b) HCl (3 N), MeOH; c) Grubb´s II catalyst **C7**;[59] d) $N_2(COOK)_2$, AcOH; e) DDQ; f) 1% HCl, MeCN.[44a]

The RCM precursor was synthesized by *ortho*-lithiation of benzofuran **46** and addition to aldehyde **45**. Notably, this is one of the rare examples in which the single remaining position on the arene was functionalized by deprotonation. Attempts at utilizing substrates without the benzofuran motif failed. The ensuing RCM proceeded successfully (62% yield) even with the tetrahydropyran in place. This was somewhat unexpected as similar substrates such as **38** did not undergo RCM, presumably due to atropisomerism that sequestered the diene in an unreactive conformation. The newly formed double bond at C10-C11 was reduced in the next step. This total synthesis was finally concluded with an oxidation of the arene to the *ortho*-quinone and a 1,6-addition of H_2O, following the biomimetic pathway.[44a]

Route B In a second approach, Mulzer *et al.* placed the disconnection at the *C*-glycosidic bond. Therefore, the required acyclic precursor **47** was assembled as depicted below (scheme 20). Alcohol **58** and carboxylic acid **59** were known intermediates from previous studies (see 3.2.2.). Esterification of these fragments under Steglich conditions was followed by a sequence of Ireland-Claisen rearrangment/reduction of the resulting acid. Then, deoxygenative manipulations were analogously conducted as before. The Ireland-Claisen route effectively crafted the northern part of the alkyl chain and avoids the difficulties associated with either the RCAM or HWE disconnection at C13-C14. However, a major drawback of this procedure was the laborious deoxygenation that involved three extra steps on an advanced intermediate. The lower part of the northwestern fragment was then

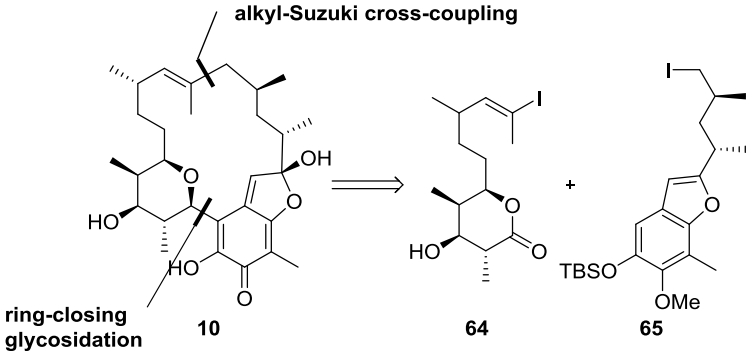
elaborated by silyl-ether cleavage and IBX-oxidation followed by a *syn*-aldol/*anti*-reduction and hydrolytic cleavage of the auxiliary (*cf*. chapter **3.2.2.**).



Scheme 23: Mulzer´s formal total synthesis of kendomycin by lactonization/photo-Fries reaction. Conditions: a) EDCI, DMAP; b) LDA, TBSCl, Δ; c) $LiAlH_4$; d) MsCl; e) $LiAlH_4$; f) TBAF; g) IBX; h) **48**, $Sn(OTf)_2$; i) $NMe_4NBH(OAc)_3$; j) LiOH, H_2O_2; k) HCl; l) $Me_2C(OMe)_2$, CSA; m) LiOH; n) EDCI, DMAP, DMAP·HCl; o) hν (254 nm); p) $NaBH_4$; then HCl; q) *p*-TsOH.[44a]

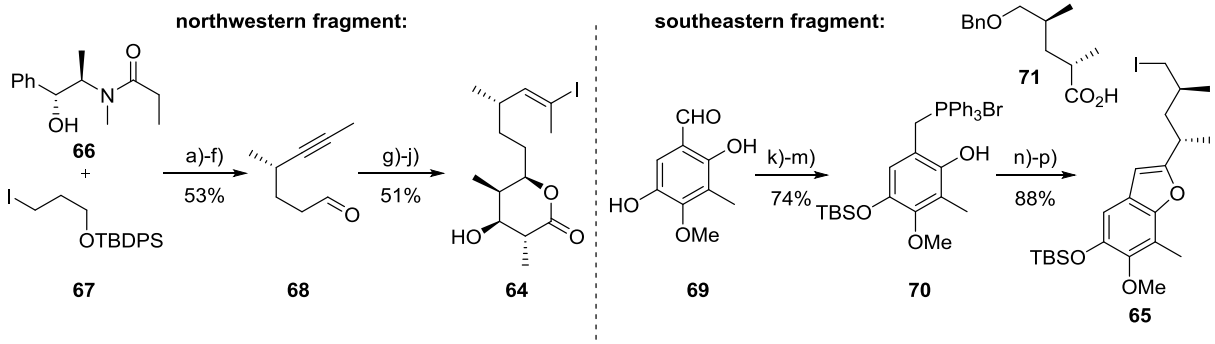
Upon 1,3-diol protection, δ-lactone **60** was opened to the ester which was saponified before macrolactonization under modified Keck-conditions proceeded in moderate yield. The macrolactone **61** was irradiated to undergo an *ortho*-selective Fries rearrangement to ketone **62**. This methodology seemed to be beneficial as macrocyclization and introduction of the sixth substituent on the chromophore were two hurdles overcome at once. Furthmore, installation of the tetrahydropyran was postponed until after the macrocyclization to avoid atropisomerism. Ketone **62** was eventually reduced and the THP-moiety was formed upon acidic work-up. Compound **63** converges with the previously described route to kendomycin (**10**). In summary, the Mulzer group disclosed two successful synthetic approaches to (−)-kendomycin (**10**).

3.2.3. Lee´s Total Synthesis of (−)-Kendomycin by Glycosidation



Scheme 24: Retrosynthetic analysis of (−)-kendomycin (**10**) by Lee *et al*.[41]

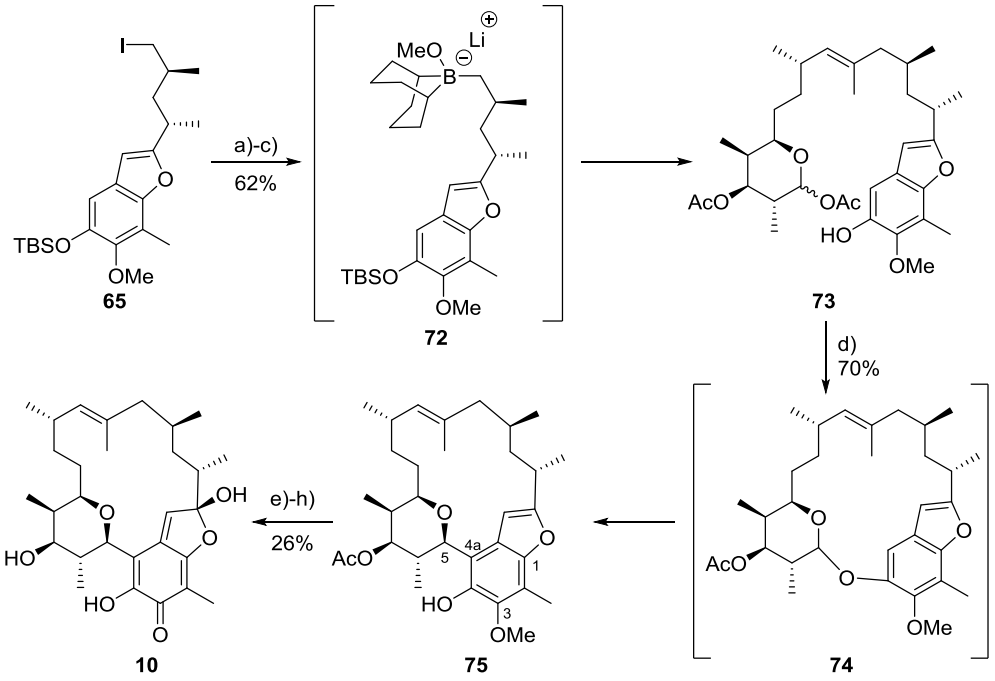
In 2004, a few years after Mulzer *et al.* published the first fragment synthesis,[47a, 47c] Lee and coworkers were first to report a total synthesis of (−)-kendomycin (**10**). A glycosidation at the C4a-C5 bond was selected for ring closure, thus avoiding the trouble that could potentially arise from conformational restrictions about this bond. Further retrosynthetic analysis led to an alkyl-Suzuki cross-coupling of **64** and **65**, two fragments of similar size that allowed for a convergent buildup of the macrocycle.



Scheme 25: Lee´s synthesis of the northwestern and southeastern fragment of (−)-kendomycin (**10**). Conditions: a) LDA, LiCl; b) $LiAlH(OEt)_3$; then TFA, HCl (1 N); c) CBr_4, PPh_3, Zn; d) *n*-BuLi, MeI; e) TBAF; f) DMP; g) $Sn(OTf)_2$, **48**, Et_3N; h) $NaBH(OAc)_3$, AcOH; i) DBU; j) cat. $Pd(OAc)_2$, PCy_3, *n*-Bu_3SnH; then I_2; k) TBSCl, imidazole; l) DIBAl-H; m) PPh_3·HBr; n) **71**, DCC, DMAP, Et_3N, Δ; o) Pd/C, H_2; p) I_2, PPh_3, imidazole.

The synthesis of the western unit **64** started with a Myers´ alkylation of amide **66** with iodide **67**. After cleavage of the chiral auxiliary, the resulting aldehyde was elaborated into the corresponding alkyne. Removal of the silyl-ether followed by Dess-Martin oxidation resulted in aldehyde **68** that was subjected to a *syn*-aldol reaction with β-ketoimide **48**. A diastereoselective hydride reduction to the 1,3-*anti*-diol and treatment with base constructed the δ-lactone moiety. The alkyne was first transformed into an alkenyl stannane that was reacted with molecular iodine to give the alkenyl iodide **64**. The synthetic path for

the eastern fragment commenced with known 1,4-hydroquinone **69** that readily underwent selective monosilylation of the less-hindered phenol group. After reduction of the aldehyde, the resulting benzylic alcohol was subsequently converted to phosphonium bromide **69**. The remaining phenol was then esterified with carboxylic acid **71**, and the resulting ester underwent an intramolecular Wittig reaction at elevated temperature to give the benzofuran. Consecutive hydrogenolytic cleavage of the benzyl ether and an Appel-type reaction completed the synthesis of fragment **65**.

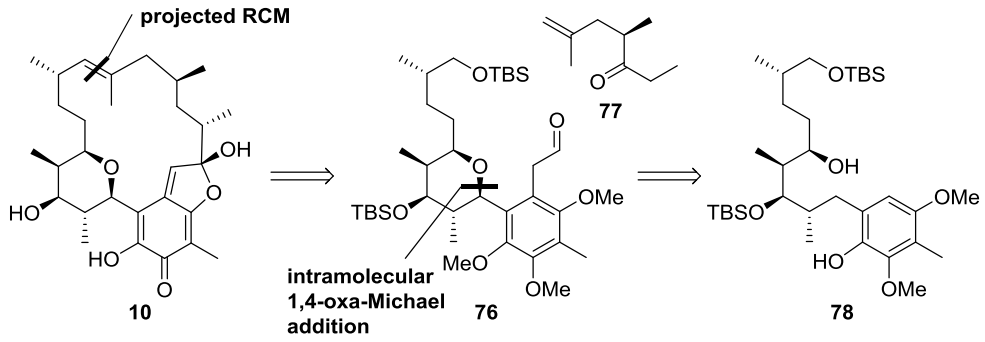


Scheme 26: Macroglycosidation approach by Lee and coworkers. Conditions: a) **65**, *t*-BuLi, 9-(MeO)-9-BBN, THF; cat. $PdCl_2$(dppf), K_3PO_4 (3 M), **64**; b) DIBAl-H,; then Ac_2O, pyridine; c) TBAF; d) $SnCl_4$, 4 Å MS; e) MeONa/MeOH; f) TESOTf, Et_3N; g) IBX; h) aq. HF, MeCN.

The synthesis of the macrocyclization precursor involved a sp^2-sp^3 cross-coupling variant of the Suzuki-Miyaura reaction using borate-complex **72** that was generated *in situ* from alkyl iodide **65** by lithium/halogen exchange and introduction of 9-(MeO)-9-BBN. Under Pd-catalyzed conditions, coupling with alkenyl iodide **64** proceeded successfully. The δ-lactone was then elaborated into a glycosyl donor, paving the way for macrocyclization. However, direct *C*-glycosidation under Friedel-Crafts conditions failed. Instead, the TBS-ether at C4 was cleaved allowing for initial formation of an *O*-glycoside **74** that subsequently rearranged to the *C*-glycoside **75** in respectable yield. Finally, exposure to IBX triggered demethylation at C3 and oxidation to the *ortho*-quinone that subsequently underwent 1,6-addition of H_2O across the benzofuran domain in the presence of aqueous hydrofluoric acid (scheme 26).

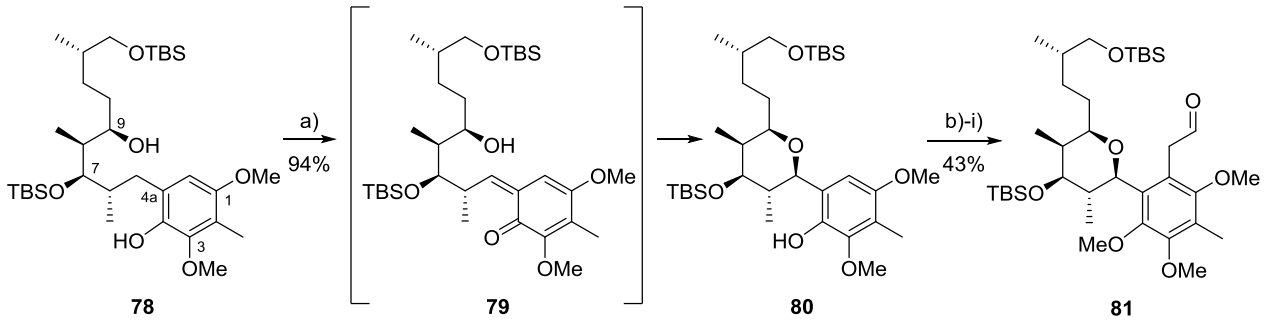
The natural product **10** was therefore constructed by a relatively short total synthesis in 20 linear steps. This very elegant approach is accentuated by an efficient *C*-macroglycosidation as well as an Suzuki-Miyaura reaction at the C14-C15 bond, imparting the adjacent (*E*)-olefin in high stereochemical integrity.

3.2.4. Contributions by the Arimoto Group



Scheme 27: Early proposal for the tetrahydropyran synthesis by Arimoto and Uemura.[48]

The initial synthetic forays by Arimoto and coworkers were published shortly after Lee reported the first total synthesis in 2004. As later results (2007) of Arimoto focus on a macrocyclization approach via RCM at the C13-C14 double bond[54] and as this strategy was discussed at length in chapter **3.2.2.**, merely the construction of the tetrahydopyran moiety will be outlined here.

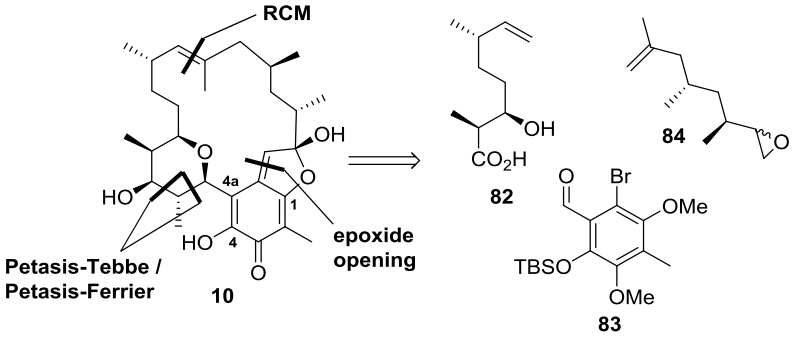


Scheme 28: Arimoto´s synthesis of the tetrahydropyran and construction of the hexasubstituted arene **81**. Conditions: a) Ag_2O; b) $(CF_3COO)IPh$, K_2CO_3; c) $Na_2S_2O_3$; d) allyl bromide, K_2CO_3, Δ; e) *N,N*-dimethylaniline, Δ; f) MeI, K_2CO_3, Δ; g) OsO_4, NMO, Δ; h) $NaIO_4$.[48, 54]

Compound **78** was a key intermediate in Arimoto´s early efforts to construct the aryl-glycoside domain. The introduction of the stereogenic center at C5 was effected by an astute maneuver. The arene was devised to be oxidized to an *ortho*-quinone methide that would be predisposed for an intramolecular 1,4-addition of the free alcohol at C9. In fact, this plan

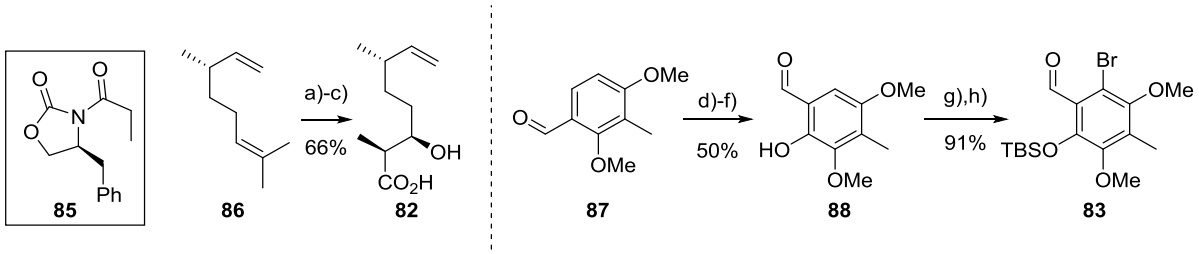
came to fruition when Ag_2O was employed as oxidant to give tetrahydropyran **80** in 94% yield. Another interesting aspect of Arimoto´s strategy is the introduction of the sixth substituent of the arene by Claisen rearrangement. First, the methyl ether at C1 had to be removed. Notably methyl ethers had been used extensively[41-43, 46-47, 49-51] as phenol protecting groups due to their stability, even though this protecting group can cause severe trouble if cleavage has to be carried out on advanced intermediates that bear acid-labile groups. One solution to this challenge was a oxidation/reduction sequence that proceeded via a *para*-quinone. Then, allylation followed by Claisen rearrangement established the hexasubstituted aromatic ring. The terminal olefin was sequentially exposed to OsO_4/$NaIO_4$ producing aldehyde **81**. Although the described synthetic path did not result in a total synthesis, Arimoto et al. reported creative solutions to at least two of the major obstacles, that is the formation of the fully substituted THP unit and the installation of the sixth substituent on the arene.

3.2.5. Smith´s Total Synthesis of (−)-Kendomycin by RCM



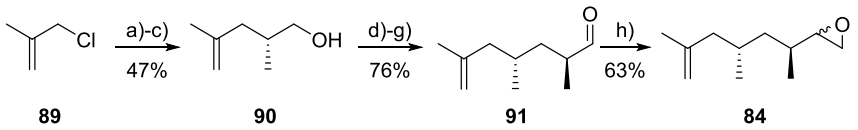
Scheme 29: RCM-based retrosynthesis by Smith and coworkers.[42]

Despite the discouraging literature precedents,[47d, 54] Smith *et al.* set out to attempt a RCM at the C13-C14 bond. Initially, the C4 hydroxyl group was protected as a bulky *tert*-butyldimethylsilyl (TBS) ether which locked the desired synclinal rotamer. Thus, the two terminal olefins would be brought in closer proximity as needed for an effective RCM. Additionally, a sequential Petasis-Tebbe olefination/Petasis-Ferrier rearrangement was implemented in building up the *cis*-2,6-tetrahydrofuran domain.[42]



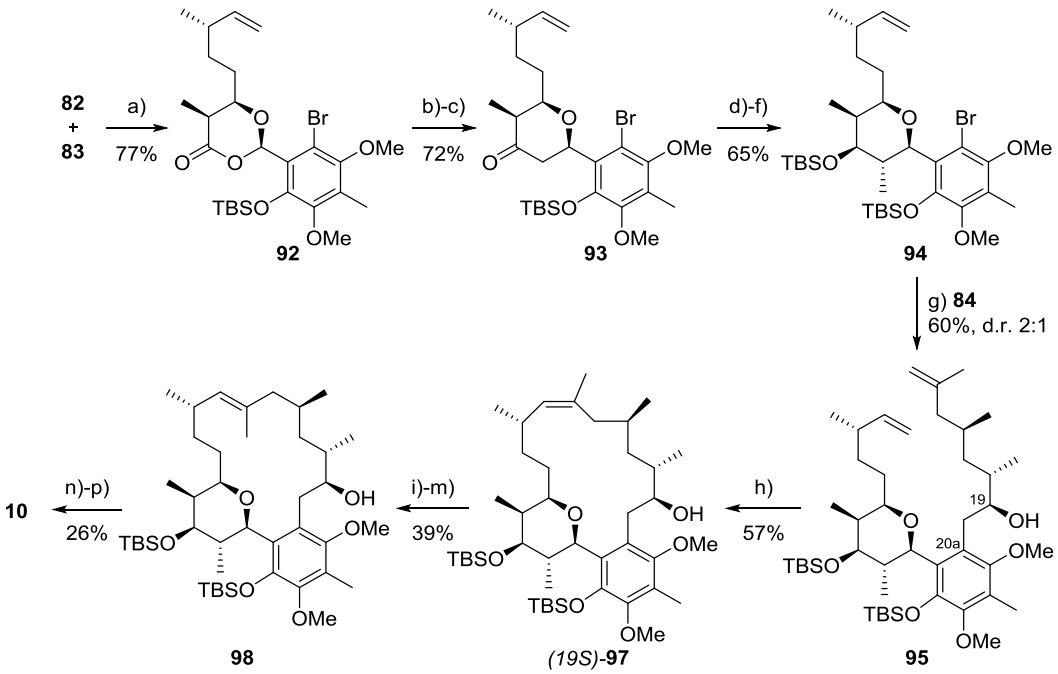
Scheme 30: Synthesis of the northwestern fragment **82** and arene **83** by Smith and coworkers. Conditions: a) O_3; Me_2S; b) **85**, Et_2BOTf, *i*-Pr_2Net; c) LiOH, H_2O_2; d) *m*-CPBA, *p*-TsOH; e) K_2CO_3; f) HMTA, AcOH; g) Br_2, K_2CO_3; h) TBSCl, *i*-Pr_2NEt.[42]

The forward synthesis of the northwestern fragment started from (+)-β-citronellene **86** (scheme 30). Ozonolysis of the more electron-rich double bond followed by reductive work-up yielded the corresponding aldehyde that was elaborated into the β-hydroxy acid **82** by a boron-mediated *syn*-aldol reaction[56] with **85** and cleavage of the oxazolidinone. On the other hand, the fully functionalized arene **83** was constructed in five steps from commercial aldehyde **87**. Baeyer-Villiger oxidation, hydrolysis of the phenol and *ortho*-formylation under Duff conditions[60] established intermediate **88** that was readily brominated. Finally, silylation of the hydroxyl group furnished **83**.



Scheme 31: Synthesis of the eastern fragment **84** by Smith *et al*. Conditions: a) NaI; b) **85**, LDA; c) $LiBH_4$; d) PPh_3, I_2, imidazole; e) **66**, LDA, LiCl; f) LDA, $BH_3{\cdot}NH_3$; g) $SO_3{\cdot}$pyridine, DMSO; h) CH_2Br_2, *n*-BuLi.[42]

For the extension of aryl bromide **83**, epoxide **84** was designed as adequate coupling partner. However as inconspicuous this segment might look, it turned out to be a tedious task to install the two stereogenic centers selectively. Notably, this problem was encountered by all parties who followed this synthetic plan. The route began with a Finkelstein reaction of chloride **89**. The iodide then underwent an asymmetric alkylation to a chiral imide enolate derived from **85**. Reductive cleavage then liberated alcohol **90**, which was transformed into the corresponding iodide under Appel-type conditions. A second alkylation utilizing Myer´s amide **66** furnished the second stereogenic center in an *anti*-relationship. Finally, epoxide **84** was provided by a $BH_3{\cdot}NH_3$ reduction/Parikh-Doering oxidation sequence followed by a Matteson epoxidation.[61]

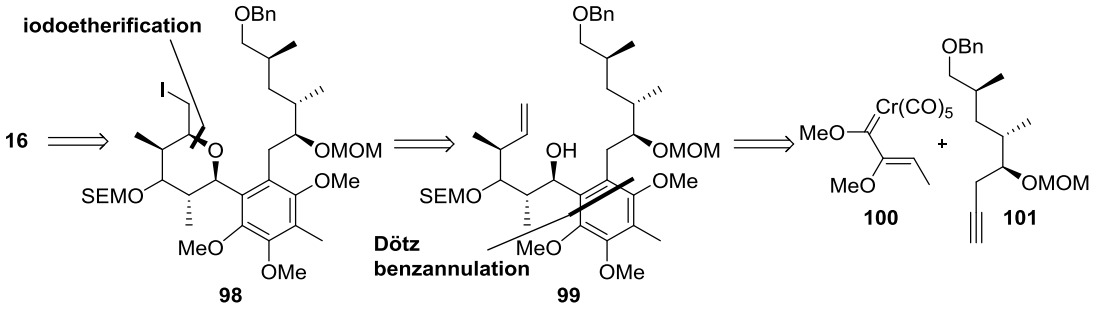


Scheme 32: Fragment assembly and endgame by Smith. Conditions: a) *i*-PrOTMS, TMSOTf; b) Cp_2TiMe_2; c) Me_2AlCl; d) LiHMDS, MeI; e) $NaBH_4$; f) TBSOTf, 2,6-lutidine; g) *t*-BuLi, **84**; then BF_3OEt_2; h) Grubb´s II catalyst **C7**[59, 62]; i) TESOTf, DMAP, 2,6-lutidine; j) OsO_4, pyridine; k) MsCl, pyridine; l) $BnNMe_3OH$, MeOH; m) WCl_6, *n*-BuLi; n) PPTS; o) DMP, pyridine; p) aq. HF, MeCN.[42]

The joining of the prepared fragments began with condensation of aldehyde **83** and β-hydroxy acid **82** by converting the latter into the bis-TMS protected derivative. Exposure to the aldehyde in presence of TMSOTf then provided dioxanone **92**. Smith *et al*. applied a Petasis-Tebbe methylenation[63] as method to install the tetrahydropyran unit. The formed enol acetal was then rearranged to the tetrahydropyranone **93** under Petasis-Ferrier conditions.[64] Formation of the kinetic enolate with LiHMDS resulted in a diastereoselective α-methylation in the equatorial position, thus completing the substitution pattern around the THP-moiety. The ketone in **93** was diastereoselectively reduced and the resulting alcohol was TBS-protected. Introduction of the eastern alkyl chain was attained by lithium/halogen exchange of bromide **93** followed by a $BF_3{\cdot}OEt_2$-mediated epoxide opening of **84**. The alcohol **95** was obtained in a 2:1 diastereomeric ratio. With diene **95** in hand the stage was set for the key RCM step that would establish the macrocycle. Surprisingly, application of Grubbs´ II generation catalyst **C7**[59, 62] led to full conversion of the major diastereomer (*19S*)-**97** to the macrocycle. However, the undesired (*Z*)-isomer was formed exclusively. Conversion to the (*E*)-olefin was only accomplished by a lengthy four-step sequence. The free alcohol at C19 was protected and the undesired (*Z*)-configured double bond *cis*-dihydroxylated to give a single isomer of the diol that was selectively mesylated at the less

hindered C13 position. Treatment with benzyltrimethylammonium hydroxide gave the *trans*-epoxide and liberated the C4 phenol from the TBS-group. Finally a Sharpless deoxygenation[65] procedure utilizing WCl_6 and *n*-butyllithium yielded the required (*E*)-olefin **98**. Other attempts exploiting radical conditions for the equilibration of the double bond configuration or the Vedejs´ isomerization[66] by selectively opening a *cis*-epoxide failed and resulted in either migration of the double bond or decomposition of the material. The remaining oxidation/1,6-addition endgame essentially resembled that of Lee and coworkers[41] and concluded the second total synthesis of (−)-kendomycin (**10**) in 21 steps in the longest linear sequence.

3.2.6. Contributions by the White Group

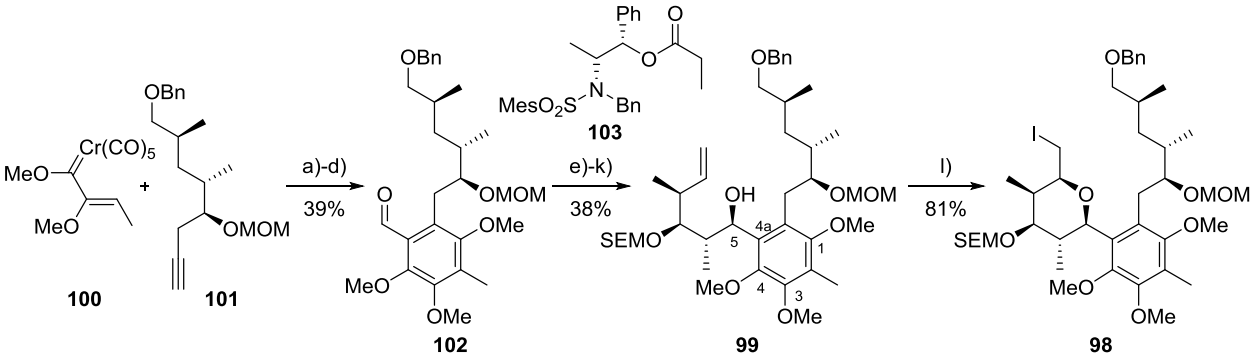


Scheme 33: White *et al.*´s retrosynthetic sketch comprising a Dötz benzannulation and an iodoetherification to construct the THP-unit.[50]

The White group was first to report a synthetic entry to the aryl-glycoside domain of (−)-kendomycin (**10**) by developing a *de novo* synthesis of the aromatic core via a Dötz reaction. Furthermore, an iodoetherification was proposed to construct the tetrahydropyran unit (scheme 33). In the following, only the key transformations will be emphasized.

In a forward sense, the Fischer alkenylchromium carbene **100** was reacted with the terminal alkyne of **101.** The product of CO insertion was obtained as a single regioisomer. Methylation of the free phenol and electrophilic bromination at the C4a position followed by formylation furnished the fully substituted aromatic fragment **102**. The aldehyde was used as a handle for the elongation of the western segment. A boron-mediated Masamune aldol reaction with propionate **103** gave the corresponding β-hydroxyester. Silylation of the benzylic alcohol at C5, cleavage of the auxiliary under reductive conditions and Ley oxidation yielded an aldehyde that was then used as a substrate for a (−)-$(Ipc)_2$BOMe-promoted Brown crotylation.[67] The subsequent protecting group replacement gave compound **99**. Treatment

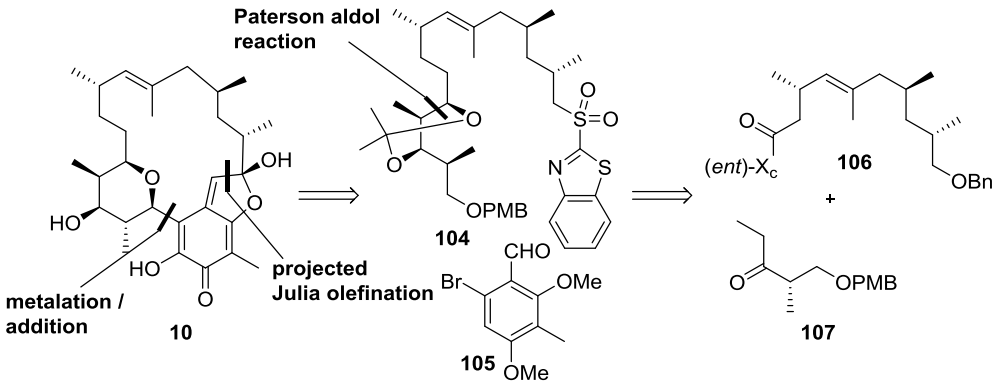
with iodine in the presence of $NaHCO_3$ results in the formation of an iodonium intermediate that was opened by the C5-alcohol in a *6-exo-trig* cyclization providing tetrahydropyran **98** in good yield.



Scheme 34: Intermolecular Dötz benzannulation and iodoetherification by White *et al*. Conditions: a) Δ; b) MeI, K_2CO_3; c) NBS; d) *t*-BuLi, DMF; e) **103**, Cy_2BOTf, Et_3N; f) TESOTf, *i*-Pr_2NEt; g) DIBAl-H; h) TPAP, NMO; i) *trans*-2-butene, *n*-BuLi, *t*-BuOK, (−)-$(Ipc)_2BOMe$, $BF_3{\cdot}Et_2O$; then NaOH, H_2O_2; j) SEMCl, TBAI, 2,6-lutidine, DMAP; k) TBAF; l) I_2, $NaHCO_3$.

Further studies of the White group demonstrated that the cyclization could also be triggered by alkoxymercuration.[55a] However, all attempts to either elaborate the obtained iodide or to oxidatively cleave the corresponding mercury species failed. Altogether, White *et al.* reported a fascinating entry to the aromatic core of (−)-kendomycin (**10**) by Dötz benzannulation. The pursued iodoetherification tactic was successful, yet, the further elaboration of the obtained iodide failed.

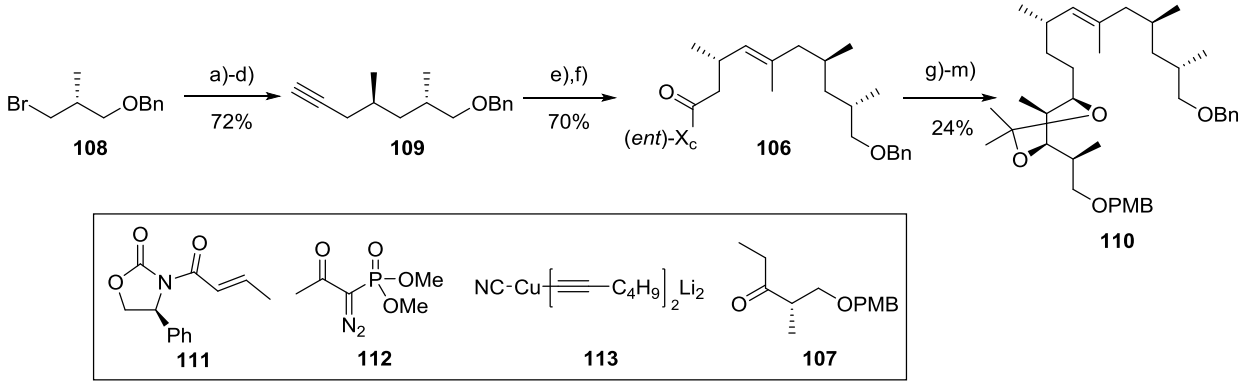
3.2.7. Contributions to the Synthesis of the *ansa*-Chain by Williams and Coworkers



Scheme 35: Williams´ approach to the *ansa* chain of (−)-kendomycin (**10**).[51]

Interestingly, Williams and coworkers chose a linear entry to establish the polyketide chain of (−)-kendomycin (**10**) starting with the C15-C19 fragment. This approach differs clearly in

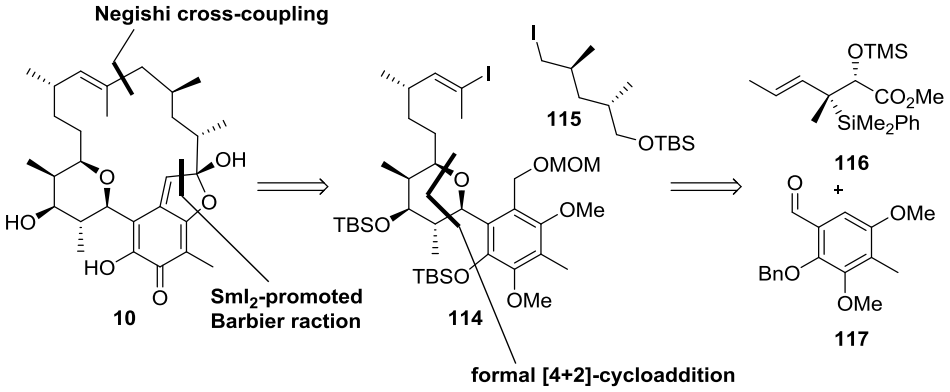
this aspect from the work of all competitors. An intramolecular variant of the Julia olefination was projected to close the macrocycle. Furthermore, the polyketide chain **104** should be linked to the aromatic core by consecutive metalation/addition of aryl bromide **105**. This strategy was designed to avoid atropisomeric mixtures by late-stage introduction of the chromophore.



Scheme 36: Williams´ synthesis of the *ansa* skeleton. Conditions: a) Mg, **108**, $CuBr{\cdot}SMe_2$, $BF_3{\cdot}Et_2O$; then oxazolidinone **111**; b) $LiBH_4$; c) $(COCl)_2$, Et_3N, DMSO; d) **112**, K_2CO_3; e) cat. Cp_2ZrCl_2, $AlMe_3$; f) **113**; then (*ent*)-**111**; g) $LiBH_4$; h) TsCl, pyridine; i) NaCN, DMSO; j) DIBAl-H; k) **107**, (−)-$(Ipc)_2BOTf$, Et_3N; l) $Me_4NBH(OAc)_3$; m) 2,2-dimethoxypropane, PPTS.

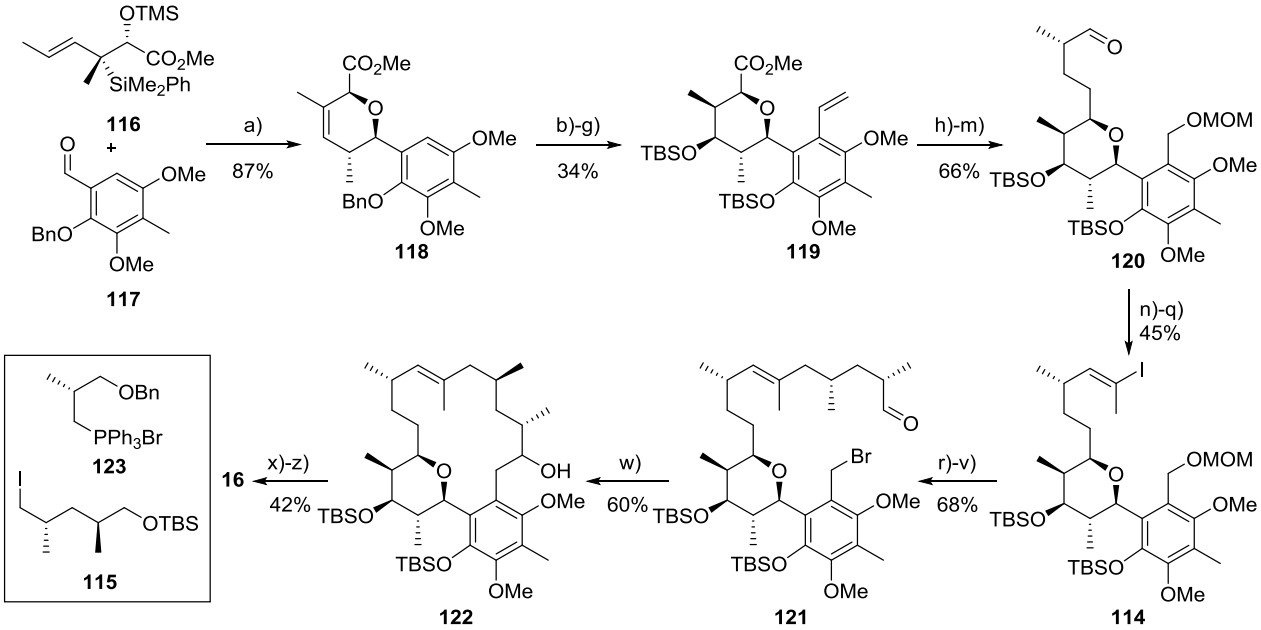
The forward route began with a diastereoselective 1,4-addition of the Yamamoto-type organocopper species derived from bromide **108** onto enoyl oxazolidinone **111**. After cleavage of the auxiliary and Swern oxidation, the obtained aldehyde was elongated to the terminal alkyne **109** under Ohira-Bestmann conditions. The trisubstituted double bond was then constituted by Negishi´s carboalumination followed by transmetalation of aluminum to copper with **113** and subsequent conjugate addition to (*ent*)-**111**. Cleavage of the auxiliary and C_1-homologation using a standard protocol provided the corresponding aldehyde. Ketone **107** was treated with Et_3N and (−)-$(Ipc)_2BOTf$ to form the (*Z*)-enolate selectively before the previously described aldehyde was introduced. The Paterson aldol reaction[68] established the β-hydroxyketone in good diastereoselectivity (*dr* 9:1), which was selectively reduced to the 1,3-*anti*-diol using triacetoxy borohydride. This synthetic route offers a concise access to the fully functionalized *ansa* chain **110**.

3.2.8. Panek´s Total Synthesis of (−)-Kendomycin by an Intramolecular Barbier Reaction



Scheme 37: Panek´s retrosynthetic projection based on an intramolecular Barbier reaction.[43]

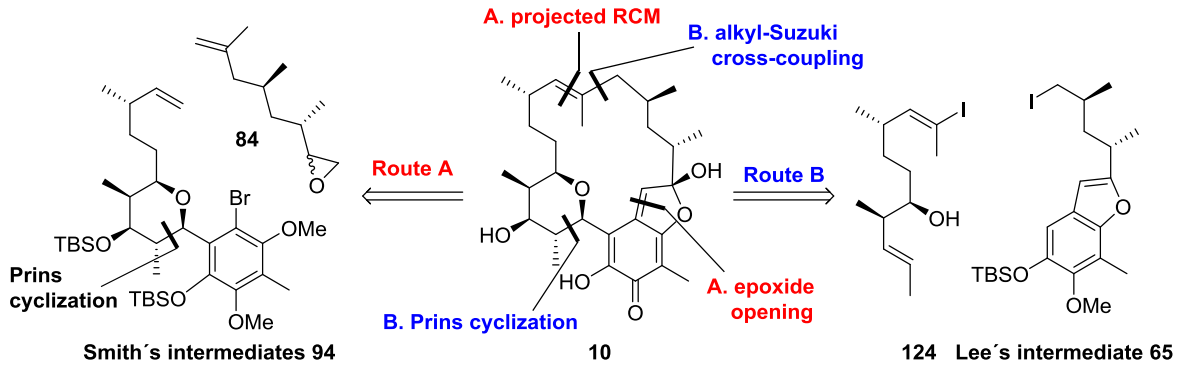
Panek and coworkers relied on a SmI_2-mediated Barbier reaction as key transformation to construct the macrocycle. Moreover, the junction of the aryl and tetrahydropyranyl units was achieved by a Lewis acid-promoted formal [4+2]-cycloaddition of crotylsilane **116** and aldehyde **117**. Notably, the quarternary crotylsilane **116** could be prepared by epoxide opening of the corresponding epoxysilane with an organocuprate.[49]



Scheme 38: Panek´s SmI_2-promoted Barbier macrocyclization approach. Conditions: a) TMSOTf; b) *m*-CPBA; c) K_2CO_3, MeOH; d) H_2, PtO_2, MeOH; e) TBSOTf, 2,6-lutidine; f) Br_2, propylene oxide; g) $Pd(PPh_3)_4$, (*n*-Bu)$_3$Sn(vinyl); h) O_3; then $NaBH_4$; i) MOMCl, 2,6-lutidine; j) DIBAl-H; k) *n*-BuLi, **123**; l) Raney-Ni, H_2, EtOH; m) $(COCl)_2$, Et_3N, DMSO; n) CBr_4, Zn, PPh_3; o) *n*-BuLi; then MeI; p) (*n*-Bu)$_3$SnH, PCy_3, $Pd(OAc)_2$; q) NIS; r) *t*-BuLi, **115**, $ZnCl_2$, $Pd(PPh_3)_4$; s) $MgBr_2$, EtSH; t) PPh_3, Br_2; u) CSA; v) $(COCl)_2$, Et_3N, DMSO; w) SmI_2; x) TBAF; y) DMP; z) aq. HF, MeCN.[49]

After the efficient preparation of dihydropyran **118** by the above mentioned formal [4+2]-cycloaddition, a substrate-controlled epoxidation with *m*-CPBA gave the β-epoxide. Epoxide opening under basic conditions led to double bond migration to the C8-C9 position (scheme 38). Hydrogenation and silyl-protection delivered the tetrahydropyran which was ready for further chain elongation. However, functionalization of the aromatic domain was carried out first since the necessary conditions would have jeopardized the trisubstituted double bond at C13-C14 in later intermediates. Thus, the C20a position was brominated and subsequently converted to a styrene derivative **119** by Stille cross-coupling using tri-*n*-butylvinyltin. Ozonolysis with a reductive work-up gave the benzyl acohol that was finally masked as MOM-ether. Turning towards the western alkyl skeleton, Panek *et al.* placed reliable chemistry in their service. The methyl ester **119** was thus transformed into aldehyde **111**, which represented the precursor for the key transformation. Panek´s approach towards the macrocyclization event resorted to a SmI_2-promoted intramolecular Barbier reaction which gave the carbocycle **122** in moderate yield. After global deprotection, the endgame closely resembled the previously reported protocols. A total of 32 linear steps makes Panek´s synthetic strategy for (−)-kendomycin one of the longest.

3.2.9. Two Formal Total Syntheses of (−)-Kendomycin by Rychnovsky and Coworkers

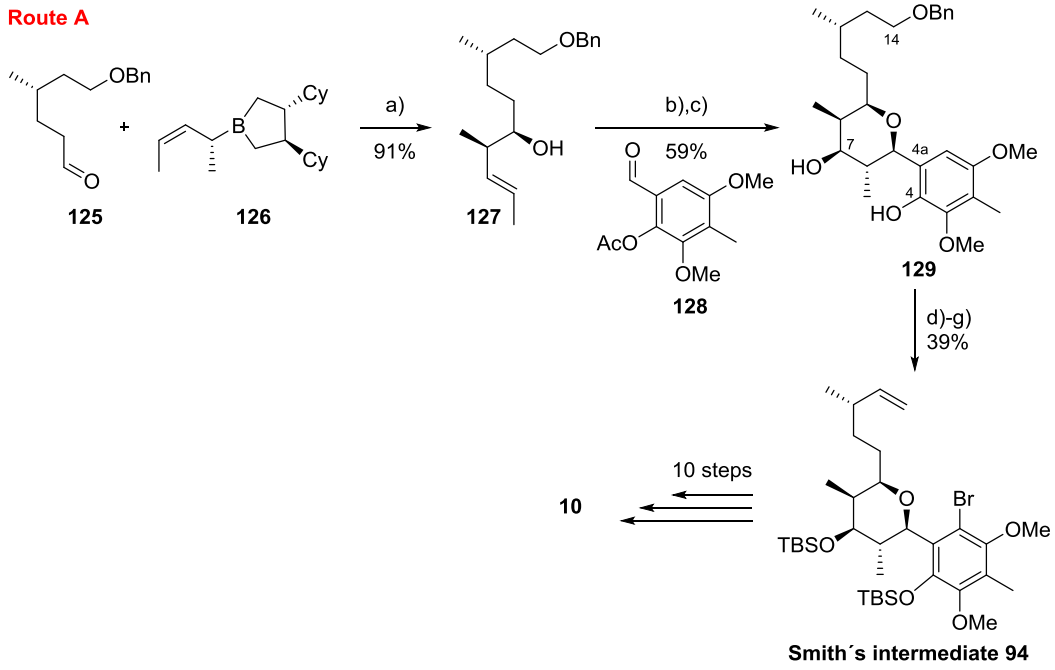


Scheme 39: Theoretical disconnections by Rychnovsky *et al.*[46]

The Rychnovsky group developed two formal syntheses of (−)-kendomycin (**10**). In the first instance, RCM in concert with an epoxide opening was proposed to introduce the eastern fragment. However, this design overlapped with results that Smith and coworkers[42] published prior to completion of Rychnovsky´s work. Thus, Rychnovsky´s first synthetic route ended in a formal synthesis at intermediates **84** and **94** previously used by Smith[42] (scheme 39). In any case, it was demonstrated that a Prins cyclization could furnish the sterically

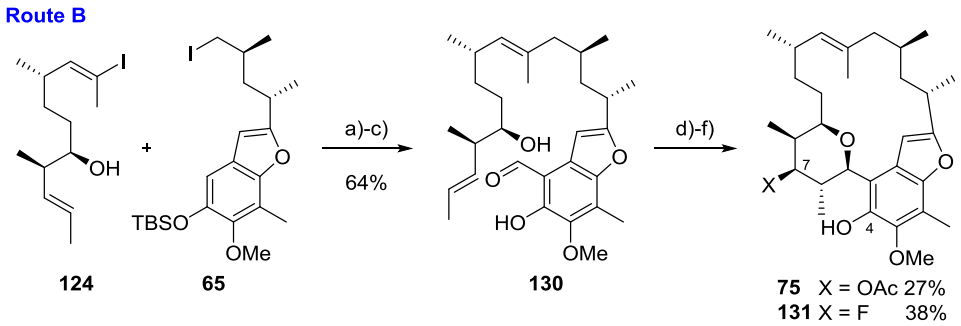
congested tetrahydropyran ring by a Lewis acid-mediated addition of the aldehyde **128** to the corresponding alkene **129**.

In their second synthetic approach, Rychnovsky *et al*. avoided the RCM en route to **10**. The well-proven Prins reaction was instead chosen as the method of choice for macrocylization.



Scheme 40: Synthesis of Smith´s intermediate **94** by Rychnovsky´s Prins cyclization strategy (Route A). Conditions: a) *n*-hexane; then NaOH, H_2O_2; b) $BF_3{\cdot}Et_2O$; c) DIBAl-H; d) Br_2; e) TBSOTf, 2,6-lutidine; f) H_2, Pd/C; g) 2-NO_2-C_6H_4-SeCN, PBu_3; then H_2O_2.[46]

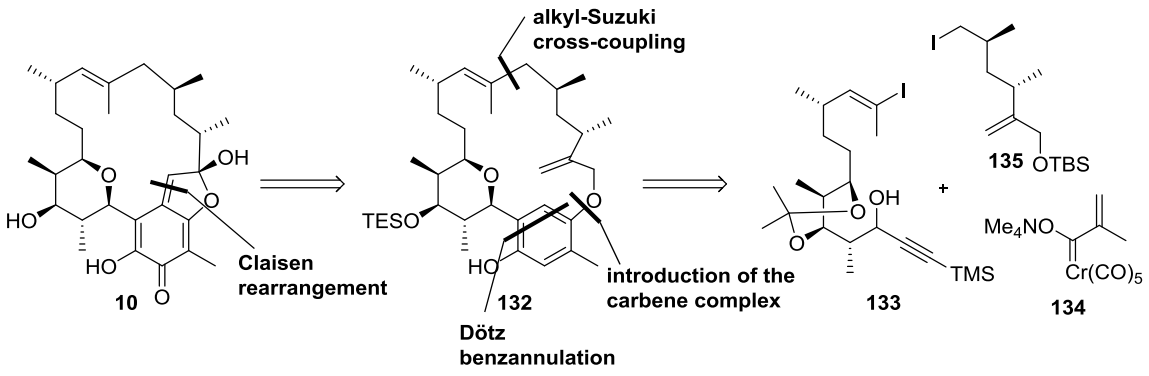
Route A Aldehyde **125** was advanced by allylation using Hoffmann´s borane **126**, to give homoallylic alcohol **127**. Treatment with aldehyde **128** in the presence of $BF_3{\cdot}Et_2O$ furnished the desired tetrahydropyran via an oxonium intermediate. After reductive cleavage of the phenolic acetate, the sixth position of the arene was brominated. Furthermore, both free hydroxyl groups (at C4 and C7) were protected as *tert*-butyldimethylsilyl ethers before the alkyl-benzyl ether at C14 was cleaved hydrolytically. The liberated primary alcohol was transformed into a leaving group and eliminated to give the desired terminal alkene. In summary, Rychnovsky´s first approach gave a straightforward access to the critical THP-aryl moiety. A highly diastereoselective formation of two stereogenic centers in the course of the Prins reaction permitted the rapid fragment assembly.



Scheme 41: Formal total synthesis by Rychnovsky employing an intramolecular Prins cyclization (Route B). Conditions: a) *t*-BuLi, 9-(MeO)-9-BBN, THF, aq. K_3PO_4, $PdCl_2$(dppf); b) TBAF; c) HMTA, H_2O; d) $PhSO_2Cl$, *i*-$PrNEt_2$; e) AcOH, $BF_3{\cdot}Et_2O$; f) KOH, EtOH.[46]

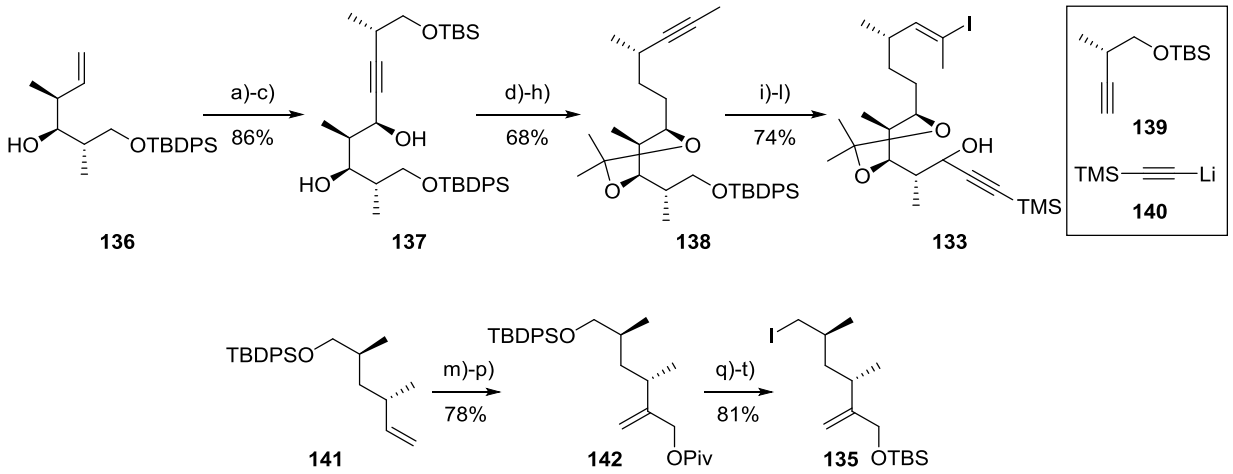
Route B In their second and more sophisticated synthetic venture, Rychnovsky *et al*. relied on an alkyl-Suzuki cross-coupling for linking the western and eastern piece of (−)-kendomycin (**10**). This strategy had been proven to be effective by Lee and coworkers[41] on similar substrates. Next, the silyl ether was cleaved and the free hydroxy-function at C4 exerted an *ortho*-directing effect in the following aromatic formylation with hexamine[60] providing the Prins cyclization precursor **130**. However, the Prins cyclization did not proceed. This outcome was somehow anticipated as earlier results showed that an electron-withdrawing group on the phenol was mandatory to activate the aldehyde for electrophilic attack.[46b] After benzenesulfonylation, the $BF_3{\cdot}E_2O$-promoted Prins cyclization proceeded with remarkable efficiency in 81% yield, albeit 59% of the obtained material was the C7-fluorinated macrocycle. Finally, hydrolysis of the sulfonyl and the acetate group gave the desired kendomycin skeleton in nearly quantitative yield together with the fluorinated congener. Compound **75** converged with the total synthesis of Lee *et al.*[41]

3.2.10. Saikawa´s and Nakata´s Total Synthesis of (−)-Kendomycin by Dötz Benzannulation



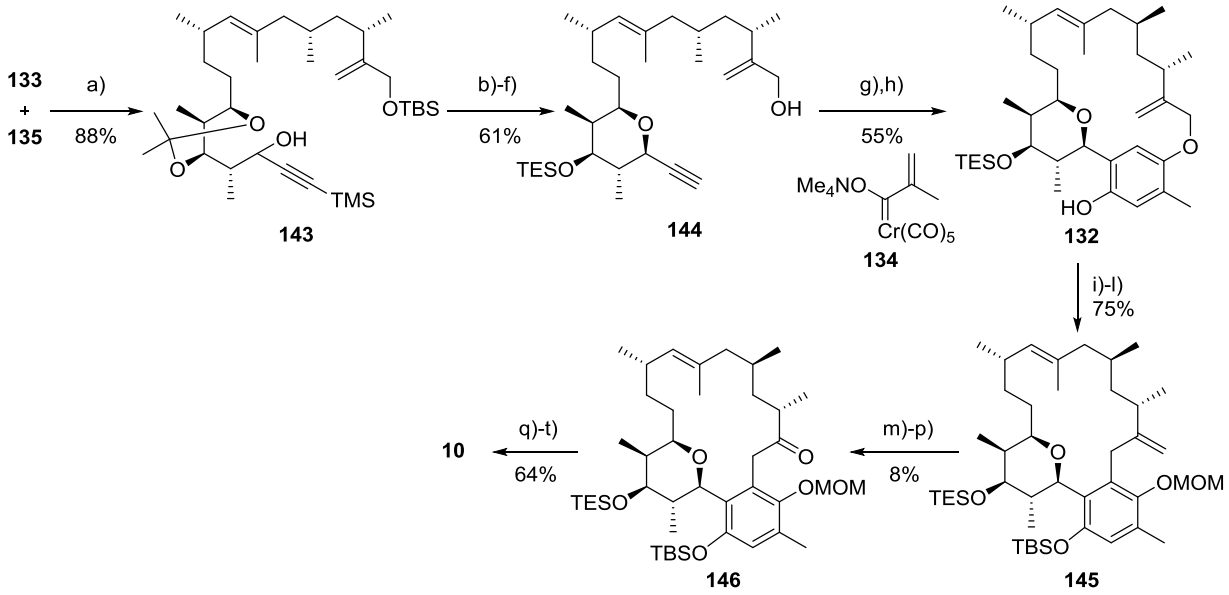
Scheme 42: Retrosynthetic map of (−)-kendomycin (**10**) including a Dötz benzannulation.[45]

Saikawa and Nakata published the sixth total synthesis of (−)-kendomycin (**10**) in 2010. Their efforts center around a ring-closing intramolecular Dötz benzannulation followed by a Claisen rearrangement as entry to the aryl-glycoside unit. The precursor bearing the required synthetic handles for the Dötz reaction was assembled by the previously used alkyl-Suzuki cross-coupling at C14-C15.



Scheme 43: Syntheses of the western and eastern fragment (**133** and **135**). Conditions: a) TESOTf, *i*-Pr_2NEt; b) O_3/O_2; c) **139**, *n*-BuLi, HMPA/THF; d) CSA, $CH(OMe)_3$; e) $N_2H_4{\cdot}H_2O$, aq. H_2O_2; f) DMP; g) CBr_4, PPh_3; h) *n*-BuLi; then MeI; i) Cp_2ZrHCl; then I_2; j) TBAF, AcOH,; k) DMP; l) **140**; m) OsO_4, NMO, H_2O/*t*-BuOH/THF; n) PivCl, Et_3N; o) PCC, NaOAc; p) Ph_3PCH_3Br, LiHMDS; q) TBAF; r) PPh_3, I_2, imidazole; s) DIBAl-H; t) TBSCl, imidazole.[45]

The synthesis of the northwestern segment commenced with silylation of the known homoallylic alcohol **136**.[69] Ozonolysis of the terminal olefin and nucleophilic addition of the lithiated acetylene **139** into the resulting aldehyde yielded alkyne **137**. Reduction of the triple bond to the aliphatic chain using diimide preceeded elaboration of the northern terminus to the methyl-capped alkyne. The 1,3-diol was protected as an acetonide before hydrozirconation/iodination completed the fragment for the envisaged cross-coupling chemistry. After desilylation and Dess-Martin oxidation, treatment with lithium trimethylsilylacetylide resulted in the northwestern fragment **133**. For the eastern unit, Saikawa *et al*. resorted to compound **141**. Dihydroxylation, chemoselective pivaloylation of the formed primary alcohol and sequential oxidation of the secondary alcohol using Corey´s pyridinium chlorochromate,[70] followed by a Wittig olefination yielded intermediate **142** with an *exo* methylene group. Desilylation, iodination and a protecting group interconversion provided alkyl iodide **135**.



Scheme 44: Saikawa´s and Nakata´s Dötz benzannulation approach. Conditions: a) **135**, *t*-BuLi, −78 °C, 9-(MeO)-9-BBN, THF; then aq. K_3PO_4, $PdCl_2$(dppf), **133**; b) DMP; c) CSA; d) Et_3SiH, $BF_3{\cdot}Et_2O$; e) TESOTf, 2,6-lutidine; f) TBAF; g) **134**, AcBr; h) 50 °C, toluene; i) TBSOTf, 2,6-lutidine; j) Ac_2O, DMAP, *N,N*-dimethylaniline, Δ; k) DIBAl-H; l) MOMCl, *i*-Pr_2NEt, TBAI; m) OsO_4, NMO, *t*-BuOH/THF/H_2O; n) O_3/O_2; o) $CS(imid)_2$, Δ; p) $P(OEt)_3$; q) TBAF; r) IBX; s) SiO_2; t) aq. HF, MeCN.[45]

As expected, the two major fragments **133** and **135** could be successfully linked by an alkyl-Suzuki reaction. Oxidation of the propargylic alcohol and transacetalization under acidic conditions constructed the δ-lactol ring which was reduced to the desired THP-ring. In the presence of acetic acid, the complex **134** forms the necessary acetoxychromium carbene species. Attack of alcohol **144** led to Dötz benzannulation through insertion of the terminal alkyne into the Fischer carbene complex followed by cyclization under CO-insertion between C3 and C4a, thus forming the resulting oxametacyclophane **132**. The product was rearranged in a [3,3´]-sigmatropic fashion at elevated temperature. After construction of the *ansa* skeleton the superfluous *exo* methylene moiety in **145** was removed to liberate ketone **146**. The still missing oxygen functionality on the arene was introduced after deprotection of the phenol at C4 by *ortho*-selective IBX oxidation giving rise to the *ortho*-quinone. Quinone methide formation occured smoothly during preparative thin layer chromatography (TLC) on silica. Desilylation gave the natural product. In summary, Saikawa and Nakata reported a highly convergent entry to the ansamycin **10**. Concurrent macrocylization/benzannulation furnished the pentasubstituted arene and the critical aryl-glycoside pattern in a very elegant way. As a drawback of this strategy, the superfluous methylene unit in **145** had to be removed in a five-step detour that involved the protection of the alcohol at C4 and masking

of the internal olefin, ozonolysis of the *exo* double bond followed by regeneration of the C13-C14 double bond and deprotection of the hydroxyl group. In this way, the advanced material was depleted significantly.

3.2.11. Conclusion

Over the last one and a half decades, a variety of synthetic endeavors towards the intriguing cyclophanic polyketide (−)-kendomycin (**10**) have emerged. Mulzer *et al*. delivered the first and most comprehensive studies. Specifically, their early investigations concerning the densely substituted THP ring and the atropisomerism about the C4a-C5 bond observed for sterically congested substrates were seminal. The Lee group was first to report a total synthesis of kendomycin in 2004. Their glycosidation approach was highly efficient and elegant, raising the bar early on. Interestingly, RCM was invoked extensively as method of choice for macrocyclization (Mulzer, Smith, White and Arimoto), in which the trisubstituted double bond, as well as several other bonds were selected for the disconnection. Although olefin metathesis in general allowed access to the macrocyclic intermediates, the process was significantly compromised by the stereochemical outcome, as exclusively the undesired (*Z*)-olefin was formed at C13-C14. These results demonstrate that Grubbs catalysts[59] are reaching limitations when applied to sterically encumbered and strained macrolides and inherently (*E*)-selective olefin metathesis catalysts are so far unknown.[71]

In conclusion (−)-kendomycin holds an exceptional macrolide structure which entails a number of synthetic challenges and triggered a broad spectrum of synthetic approaches that nourished the development and improvement of synthetic methodologies.

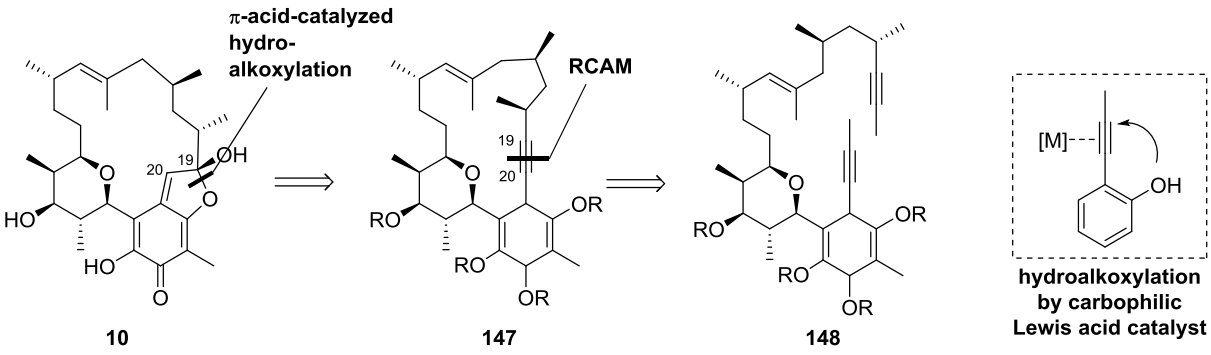
3.3. Retrosynthetic Analysis of Kendomycin: The Key Steps

It was in light of the previous synthetic work towards (−)-kendomycin (**10**) described in **3.2.**, that we envisaged a new approach emloying RCAM for the crucial macrocyclization event. As recent advances in catalyst design had led to a generation of highly active, functional group tolerant and more stable catalysts, (chapter **1.2.**) we foresaw that

(1) RCAM was an excellent tool to close the macrocycle, avoiding any complications deriving from isomer mixtures.

(2) The cycloalkyne would be a valuable substrate for post-metathetic transformations.

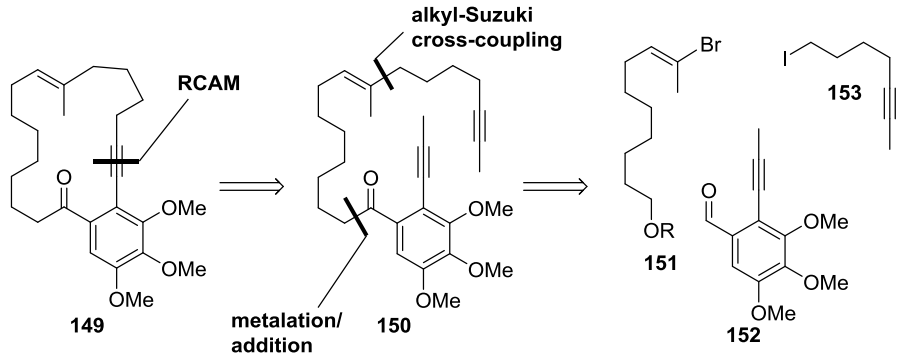
In our retrosynthetic analysis, we chose to place the RCAM disconnection at the C19-C20 bond, expecting that this strategy would give us a handle for the construction of the benzofuran-derived chromophore (scheme 45). It is known that *ortho*-hydroxyphenyl acetylenes undergo *5-endo-dig* cyclizations under basic[46a] or Lewis acidic[17, 21j-l] conditions.



Scheme 45: Our retrosynthetic considerations were based on RCAM and hydroalkoxylation.

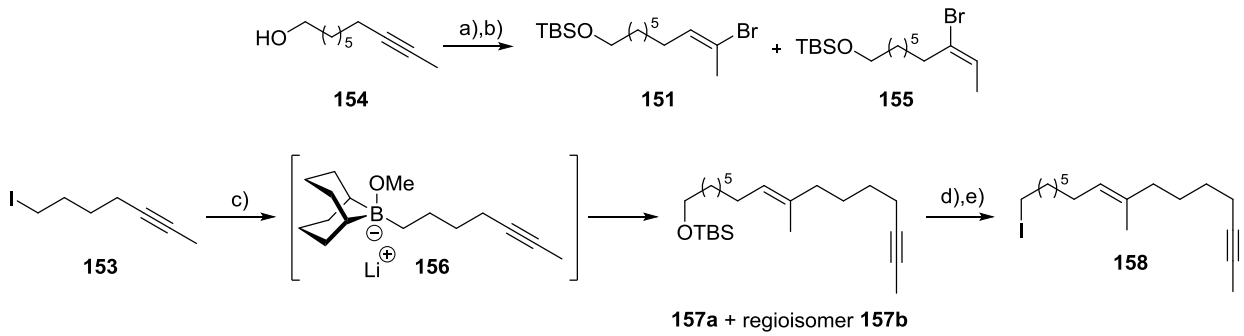
Flexible and sterically unshielded dialkynes of various chain lengths have been efficiently metathesized in the past using the highly-active molybdenum alkylidyne catalysts (**C2**-**C5**, chapter **1.2.**).[7] In the kendomycin case, our proposed target structure for the RCAM product features an 18-membered cycloalkyne **147**. The ring size itself was not expected to be a hurdle. However, limitations were anticipated due to the *ortho*-disubstituted aryl acetylene on the one hand and the α-branched alkyne on the other hand that could obstruct substrate binding to the catalyst with its three bulky triphenylsilanolate ligands. Furthermore, the conformational isomerism about the C4a-C5 glycosidic bond might impede the projected ring closure. Thus, (−)-kendomycin (**10**) represents a sterically demanding target molecule that would put our RCAM catalysts to the test.

3.4. Model Studies for the RCAM



Scheme 46: Structure and retrosynthetic analysis of an RCAM model (**149**).

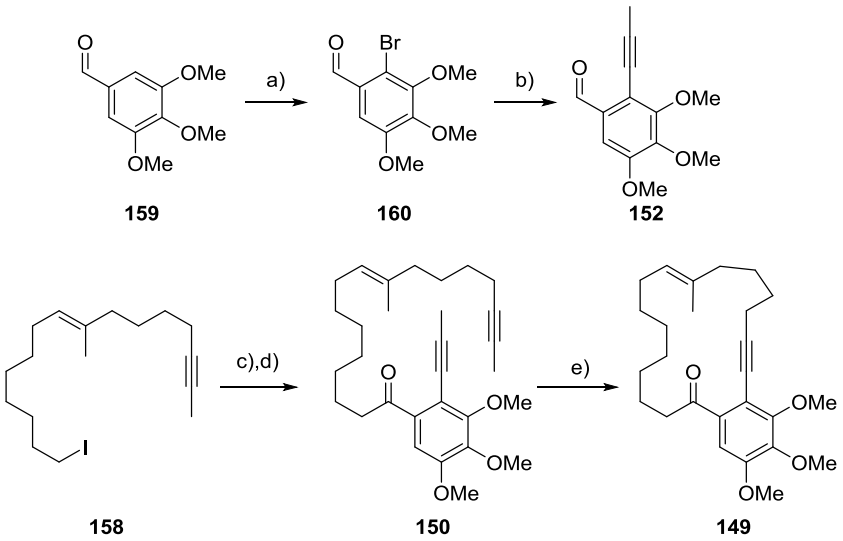
In order to assess the chances of the intended RCAM, preliminary studies were conducted on a model substrate. To this end, diyne **150** was selected as metathesis precursor. The compound was chosen to mimic the correct ring size of the macrocycle and the steric hindrance next to the reacting alkyne. Moreover, a total of three alkoxy-substituents would presumably render this alkyne electron-rich, similar to the fully functionalized diyne **148**. Model compound **150** was to be prepared from three simple fragments by Suzuki cross-coupling of alkenyl bromide **151** and iodide **153**, followed by bromine/lithium exchange and nucleophilic addition to aldehyde **152**.



Scheme 47: Forward synthesis of the aliphatic chain for a model substrate. Conditions: a) TBSCl, imidazole, THF, rt, 88%; b) Cp_2ZrHCl, THF, rt; then NBS, 0 °C to rt, 90% (**151**:**155**, 2.5:1); c) **153**, *t*-BuLi, 9-(MeO)-9-BBN, THF, −78 °C to rt; then $PdCl_2(dppf)\cdot CH_2Cl_2$, K_3PO_4, **151**:**155** (2.5:1), 50 °C, 80% (**157a**:**157b**, 8:1); d) TBAF, THF, rt, 83%; e) PPh_3, imidazole, I_2, $MeCN/Et_2O$, 0 °C to rt, 99%.

The preparation of the aliphatic chain was achieved in an efficient five step sequence. It starts with silylation of the known alcohol **154**.[72] Hydrozirconation of the alkyne under conditions developed by Schwartz *et al*.[73] gave the alkenyl zirconium species that was trapped with *N*-bromosuccinimide (NBS). The resulting alkenyl bromide was obtained as a 2.5:1 mixture of regioisomers. For the consequent cross-coupling, the known iodide **153**[72] was converted to the ate-complex **156** via successive halogen/lithium exchange and transmetalation to boron, which readily underwent the alkyl-Suzuki coupling in presence of 10 mol% of $PdCl_2(dppf)$. To our satisfaction, the major regioisomer reacted preferentially and the ratio was improved to 8:1 in the product mixture. The efficiency of this 9-(MeO)-9-BBN-variant of the Suzuki cross-coupling had previously been used for numerous advanced and highly functionalized substrates.[41, 45-46, 74] Due to its robustness, this method was later also chosen for the fully elaborated polyketide fragment. Desilylation with TBAF and iodination in an Appel-type reaction with molecular iodine occurred smoothly, providing the model fragment **158** in excellent yield. The aromatic segment was prepared in a two-step protocol

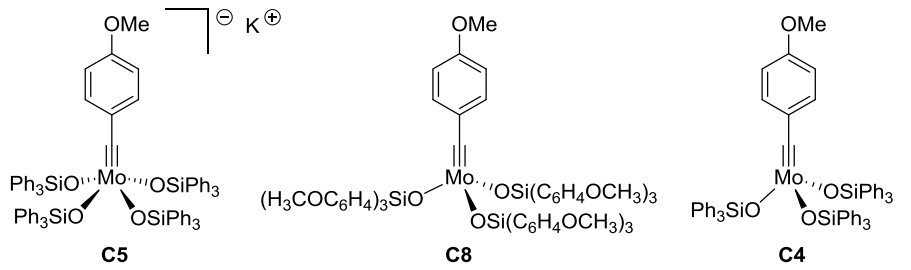
from the commercially available aldehyde **159** (scheme 48). Electrophilic bromination with NBS followed by another variant of the Suzuki-Miyaura cross-coupling with sodium propyne and $B(OMe)_3$ gave the desired arene **152**.[74]



Scheme 48: Fragment assembly of diyne **150** and ring closure. Conditions: a) NBS, MeCN, 50 °C, 95%; b) sodium propyne, $B(OMe)_3$, THF; then **160**, $PdCl_2$(dppf) (10 mol%), Δ, 59%; c) **158**, *t*-BuLi, Et_2O, −78 °C; then **152**, −78 °C to rt, 88%; d) DMP, CH_2Cl_2, 0 °C, 71%; e) for conditions see table 2.

Alkyl iodide **158** was then subjected to halogen/lithium exchange. Treatment of the resulting intermediate with aldehyde **152** gave the benzylic alcohol in 88% yield. After Dess-Martin oxidation, the substrate **150** was ready for the upcoming RCAM. A small screening was conducted that allowed three of the alkyne metathesis catalysts toward ring-closure of **150** to be compared (table 2). To our delight, the diyne participated well in the RCAM when treated with catalytic amounts of **C5** in the presence of 5 Å molecular sieves. The macrocycle was formed at room temperature in 83% yield together with small amounts of an open dimer (table 2, entry 1). After decreasing the concentration to 0.001 M the monomeric cycloalkyne was obtained exclusively in 90% yield (table 2, entry 2). In comparison, catalyst **C8**, adorned with three trianisol silanolate ligands, generated the product in only moderate yield. However, the chromatographic separation of the polar silanol ligands from the desired product was easier in this case. The neutral alkylidyne complex **C4** gave excellent results similar to **C5** (table 2 entry 4). Thus, the *ortho*-disubstitution at the southern aryl alkyne did not constrain the coordination of the molybdenum species. In fact, all test reactions were exceedingly productive. Nevertheless, a potential influence of the tetrahydropyran ring on the steric and conformational situation of the substrate could not be evaluated with this model **150**.

Table 2: Catalyst screening for the RCAM on model substrate **150**.

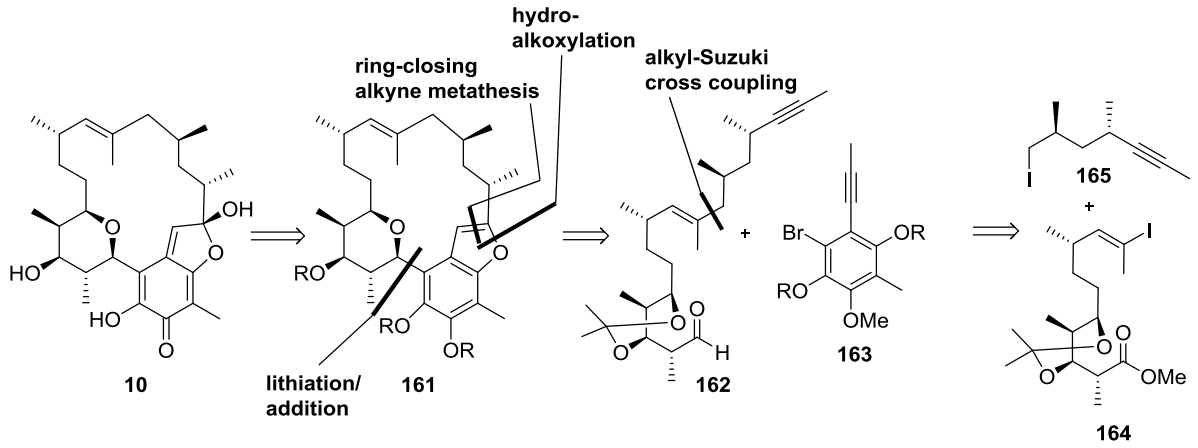


entry	catalyst	conditions	yield (%)
1	**C5** (30 mol%)	toluene (0.02 M), MS 5Å, 1.5 h, rt	83 (traces of open dimer)
2	**C5** (5+5+10 mol%)	toluene (0.001 M), MS 5Å, 6 h, rt	90
3	**C8** (20 mol%)	toluene (0.001 M), MS 5Å, 2 h, rt	71
4	**C4** (20 mol%)	toluene (0.001 M), MS 5Å, 1 h, rt	92

The promising outcome reassured us of the potential for a RCAM approach for the total synthesis of (−)-kendomycin (**10**). In the following section, our synthetic strategy will be discussed in detail.

3.5. Retrosynthetic Analysis of (−)-Kendomycin: Fragment Assembly & Synthesis of a RCAM Precursor

Building on the information gathered in the model studies, we then evaluated the preparation of possible fragments. A reasonable route was identified and is illustrated below.



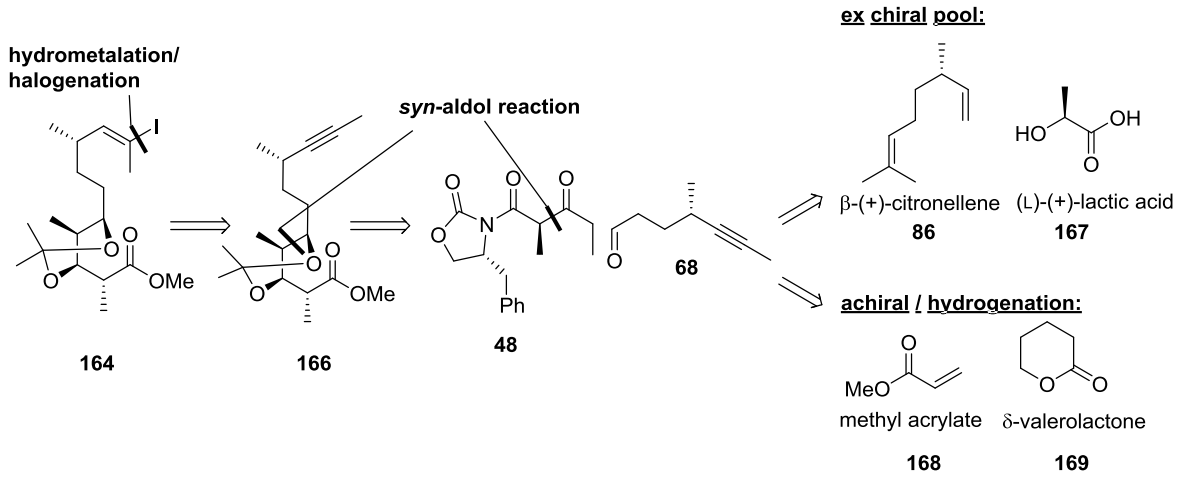
Scheme 49: Disconnection approach by lithiation/addition and alkyl-Suzuki cross-coupling.

The construction of the quinone methide core was planned to proceed via a 1,6-addition and an oxidation to the *ortho*-quinone of the corresponding benzofuran **161**, as previously reported.[41, 44] The retrosynthetic analysis begins with the macrocyclization by RCAM and a

noble metal-promoted hydroalkoxylation[75] to form the benzofuran **161**, which represents a known late-stage intermediate[27] en route to **10**. After careful consideration of the required fragments, a hexasubstituted arene **163** was proposed that would be linked to the polyketide chain via halogen/metal exchange and nucleophilic addition to aldehyde **162**. This strategy would afford a direct and efficient fragment assembly; however, preparation of the hexasubstituted arene was deemed to be difficult.

3.6. Forward Synthesis: The Lithiation/Addition Approach

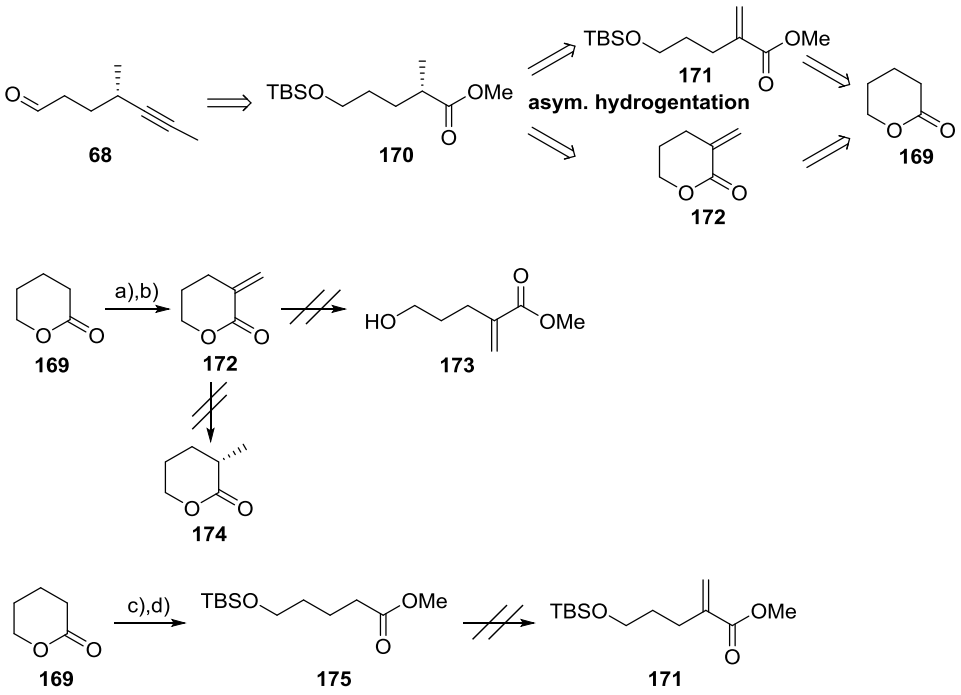
3.6.1. Synthesis of the Northwestern Polyketide Fragment



Scheme 50: Retrosynthetic plan for the northwestern fragment **164**.

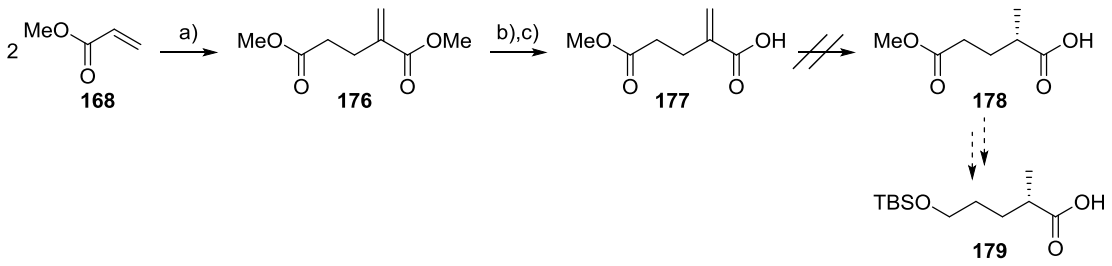
In pursuing an efficient synthesis of the three major fragments, the focus was laid on pragmatic and reliable chemistry. The northwestern polyketide fragment was considered as a product of two *syn*-aldol reactions of two propionate entities and the known aldehyde **68**.[41] The methyl-capped alkyne **166** was to be converted to the alkenyl iodide **164** by sequential hydrometalation and metal/iodine exchange. For aldehyde **68**, several different options were considered. On one hand, simple ex chiral pool compounds might be used. For instance β-(+)-citronellene (**86**) or (L)-(+)-lactic acid (**167**) could deliver the stereogenic center. On the other hand, cheap achiral starting materials such as methyl acrylate (**168**) and δ-valerolactone (**169**) could be converted to the desired chiral aldehyde via an asymmetric hydrogenation. We probed variants based on achiral starting materials first, as these would permit us to synthesize the aldehyde **68** in a few scalable steps. It was proposed that δ-valerolactone **169** could either be directly converted to the α,β-unsaturated lactone **172** or to the linear α,β-unsaturated ester **171** after lactone opening. An asymmetric 1,4-reduction

would define the stereogenic center at the α-position to the carbonyl, which could then be elaborated to the required alkyne.



Scheme 51: Attempted synthesis of aldehyde **68** starting from δ-valerolactone (**169**). Conditions: a) NaH, THF, diethyl oxalate, EtOH; b) K_2CO_3, H_2CO, rt, 82% over two steps; c) DOWEX® 50W X8, MeOH, reflux, 87%; d) TBSCl, imidazole, THF, 0 °C to rt, 95%.

The α-methylenation of simple δ-lactones was described by Tanaka and Yamashita in 1978[76] and their protocol could be successfully reproduced. The two-step procedure proceeds presumably via the formation of a hydroxymethylene derivative by aldol-type condensation with formaldehyde that yielded under a deformylation/elimination-type process the *exo*-methylenated lactone **172** (scheme 51). All attempts to open this cyclic system to the methyl ester **173** resulted in decomposition. Furthermore, attempted direct asymmetric reduction of the *exo* double bond failed. Therefore, the order of steps was reversed. Methanolysis of the δ-lactone in the presence of an ion exchange resin and TBS-protection of the primary alcohol provided methyl ester **175** in excellent yield. However, all attempts to introduce the methylene group on the acyclic substrate with the method described above for the δ-lactone or using Eschenmoser´s salt[77] were met with failure (scheme 51). However, α-methylenated pentanoic diesters such as **176** (scheme 52) could be prepared by dimerization of inexpensive methyl acrylate **168** as reported by Jenner *et al*.[78]

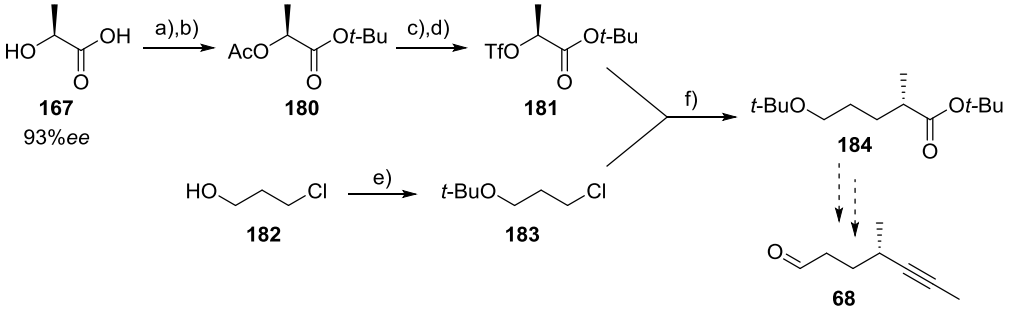


Scheme 52: Synthetic approach based on dimerization of methyl acrylate and asymmetric hydrogenation. Conditions: a) *n*-Bu_3P, hydroquinone, 50 °C, 23%; b) LiOH, THF/H_2O (3:1), 0 °C, 85%; c) CSA, MeOH, rt, 88%.

The phosphine-catalyzed Rauhut-Currier reaction[79] gave dimethyl diester **176** in 23% yield along with polymeric byproducts. Saponification of both ester groups and esterification with methanol catalyzed by camphersulfonic acid selectively furnished the monoester **177**. However, the projected asymmetric hydrogenation using Noyori´s Ru-(*S*)-BINAP dicarboxylate system[80] resulted in decomposition of the material at various temperatures and hydrogen pressures.

Turning towards chiral starting materials, our next synthetic advance was inspired by the work of the Breit group who described a zinc-catalyzed enantiospecific sp^3-sp^3 cross-coupling of α-triflyl esters and Grignard reagents.[81] This methology starts from cheap (L)-(+)-lactic acid and features some advantages compared to variants that rely on chiral auxiliaries or chiral bases which are expensive and often difficult to prepare.

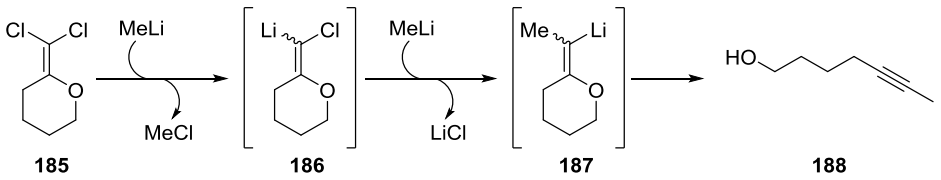
The underlying principle of this transformation is the conversion of the hydroxyl group to a triflate leaving group followed by coupling with a Grignard reagent under complete inversion of the configuration. Therefore, triflate **181** was prepared in a literature-known four-step sequence from (L)-(+)-lactic acid (**167**).[82]



Scheme 53: Synthesis of (*S*)-2-methylpentanoate (**184**) as key intermediate en route to aldehyde **68**. Conditions: a) AcCl, AcOH, 0 °C to rt, 51%; b) *t*-BuOH, DMAP, DCC, CH_2Cl_2, 0 °C to rt, 78%; c) ethane-1,2-diamine, cyclohexane, Δ, 64%; d) 2,6-lutidine, Tf_2O, CH_2Cl_2, 0 °C, 85%; e) isobutene, cat. H_2SO_4, CH_2Cl_2, rt, 75%; f) **183**, Mg, THF, Δ; then $ZnCl_2$ (5 mol%), THF, 0 °C; then **181**, 66%.

Acetylation of the hydroxyl group preceded *tert*-butyl ester formation under Steglich conditions. Chemoselective cleavage of the acetate using ethylenediamine and triflation of the resulting free hydroxyl-group furnished **181**. For the intended coupling, chloro-alcohol **182** was identified as an adequate C_3-source for the Grignard reagent. A *tert*-butyl group was chosen as suitable protecting group because it can be installed and removed with ease and it is also reasonably stable under the harsh conditions of the Grignard formation.[83] In fact, treatment of alcohol **182** with *iso*-butene and catalytic amounts of sulfuric acid triggered the *tert*-butyl ether formation in respectable yield. After formation of the corresponding Grignard reagent, a catalytic amount of $ZnCl_2$ and **181** were added. The reaction proceeded under clean conversion in moderate 66% yield (scheme 53). Even upon careful considerations of the experimental setup, the yield could not be improved. Presumably, some magnesium species, as sideproducts from the Grignard formation, led to decomposition of the triflate coupling partner. Notably, the reaction failed when the *t*-butyl-ether was replaced by a TBS-ether; the silyl group likely underwent a *retro*-[1,4]-Brook rearrangment[84] instead of giving the respective Grignard reagent. This scalable five-step sequence delivered several grams of ester **184**. With this material in hand, the upcoming introduction of the methyl-capped alkyne was considered.

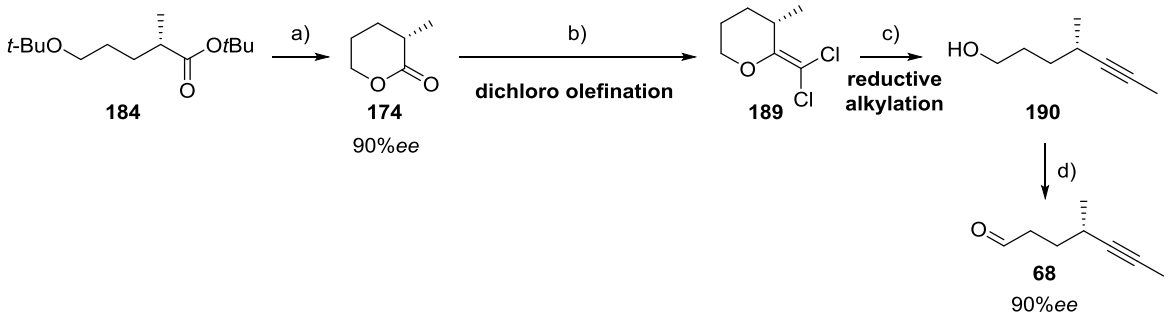
Since RCAM has evolved into a powerful tool, there is a need for new methods that would allow access to the required methyl-capped acetylene substrates. It was in this context that the Fürstner group discovered a new method for the preparation of alkynes from lactones. The Wittig-type reaction of lactones with phopsphorus ylides to give the corresponding dichloro olefin **185** was a known process.[85] It was found that treatment of this dichloro species with lithium reagents (BuLi, MeLi) provoked a reductive alkylation to give internal acetylenes.[86] Furthermore, it was observed that the addition of catalytic amounts of $Cu(acac)_2$ accelerated the reaction significantly.[86b, 87]



Scheme 54: Proposed mechanistic pathway for the reductive alkylation of dichloro olefin **185**.[87]

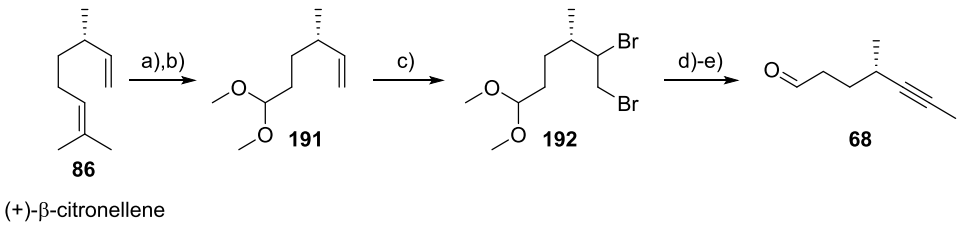
Alkyne formation is thought to start with metal/halogen exchange upon treatment of **185** with methyllithium to generate vinylidene **186** and methyl chloride as side product.[87]

Another equivalent of methyllithium reacts with **186** to an alkenyllithium **187** that yields the alkyne **188** by reductive elimination.



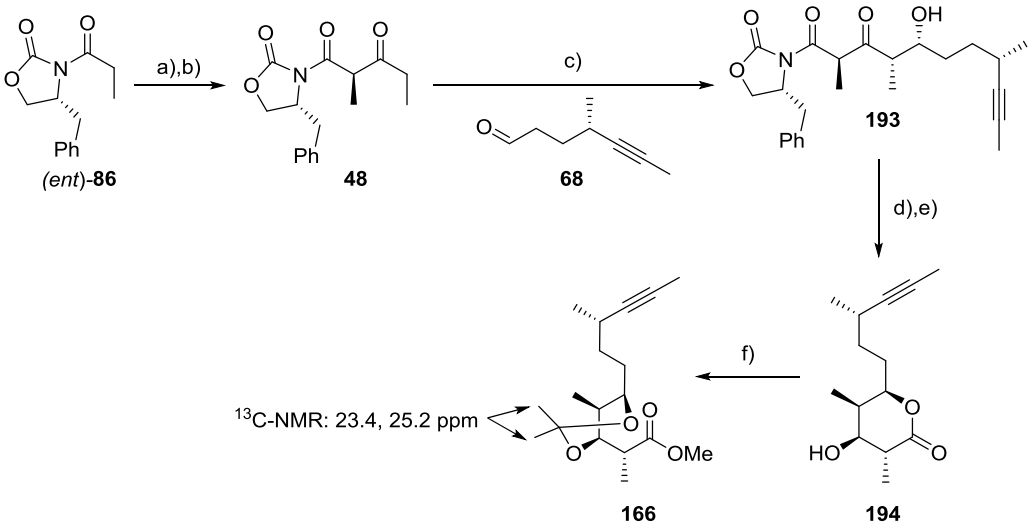
Scheme 55: Introduction of the methyl-capped alkyne via dichloro olefination. Conditions: a) TFA, CH_2Cl_2, rt, 66%, 90%ee; b) CCl_4, PPh_3, THF, Δ, 71%; c) MeLi, Et_2O, $Cu(acac)_2$ (10 mol%), rt, 92%; d) $[Cu(MeCN)_4]BF_4$ (5 mol%), bipyridine (5 mol%), TEMPO (5 mol%), NMI (10 mol%), MeCN, rt, 96%.

In an attempt to apply this methodology to kendomycin, the *tert*-butyl protecting groups on ester **184** were cleaved in the presence of TFA to furnish the δ-lactone **174** immediately. This compound could be stored at 5 °C for a few days but gradually degraded, presumably by polymerization. Treatment of **174** with CCl_4 and PPh_3 effected the dichloro olefination in acceptable yield. The resulting dichloro olefin **189** was opened to the desired alkyne **190** by addition of methyllithium and a catalytic amount of $Cu(acac)_2$. The product **190** was obtained in excellent yield. The remaining oxidation to the aldehyde **68** was performed in virtually quantitative yield using a convenient protocol developed by Stahl and coworkers.[88] To our delight, the stereochemical integrity of the material was preserved throughout the sequence starting from L-(+)-lactic acid (**167**), with only minor erosion of the *enantiomeric excess* during the Breit-coupling.[81] This entry delivered chiral aldehyde **68** in multigram quantities in a good overall yield. However, the nine-step procedure seemed somewhat lengthy for this small fragment.



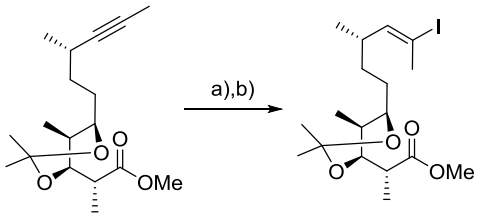
Scheme 56: Alternative approach towards aldehyde **68** starting from (+)-β-citronellene (**86**). Conditions: a) O_3, CH_2Cl_2, −78 °C; then Me_2S; b) $HC(OMe)_3$, K10 montmorrilonite, 75% over 2 steps; c) 4-dimethylaminopyridinium bromide perbromide, DMAP, CH_2Cl_2, 87%; d) LiHMDS, THF, 90%; e) *n*-BuLi, MeI, THF/DMPU; then aq. HCl, 95%.

In 2003, Fürstner *et al*. reported a synthesis of latrunculin B, in which aldehyde **68** had been prepared from β-(+)-citronellene.[89] Specifically, aldehyde **68** could be prepared in a scalable five-step sequence that started with an ozonolysis of the more electron-rich double bond in **86**, reductive work-up and acetalization of the resulting aldehyde. Bromination provided dibromide **192** which was exposed to LiHMDS to give the terminal alkyne via a double elimination process. Treatment with *n*-butyllithium and methyl iodide gave the targeted aldehyde **68** upon acidic work-up. An overall yield of 56% seemed difficult to improve upon in terms of efficiency.



Scheme 57: Synthesis of the C5-C14 fragment **166**. Conditions: a) *n*-Bu_2BOTf, Et_3N, CH_2Cl_2, −78 °C, then propanal, 0 °C, 92%; b) SO_3·pyridine, DMSO, Et_3N, CH_2Cl_2, −10 °C, 83%; c) $Sn(OTf)_2$, Et_3N, **68**, CH_2Cl_2, −78 °C, 57%; d) $Me_4NBH(OAc)_3$, MeCN/AcOH (1.7:1), −50 °C to −10 °C, 80%; e) LiOH, H_2O_2, THF/H_2O (3:1), rt, 99%; f) 2,2-dimethoxypropane, CSA, rt, 90%.

The synthesis of the northwestern fragment continued with the preparation of known β-ketoimide **48** that was prepared via boron-mediated *syn*-aldol reaction[56b] of (*ent*)-**85** with propanal and a Parikh-Doering oxidation[90] of the resulting β-hydroxyimide. In accordance to Mulzer´s strategy[47d], a tin-aldol reaction of β-ketoimide **48** and aldehyde **68** yielded compound **193** in acceptable yield. Using the highly diastereoselective Evans-Saksena reduction the 1,3-*anti*-diol was obtained[57a] which, upon hydrolytic cleavage of the Evans auxiliary, cyclized to the δ-lactone **194** in quantitative yield. Lee´s total synthesis featured this compound as a common intermediate.[41] However in our approach, the lactone formation was inconsequential as it was re-opened in the next step. Treatment of **194** with 2,2-dimethoxypropane in the presence of a catalytic amount of CSA furnished the methyl ester and simultaneously installed the acetonide protecting group on the 1,3-*anti*-diol.



166 164

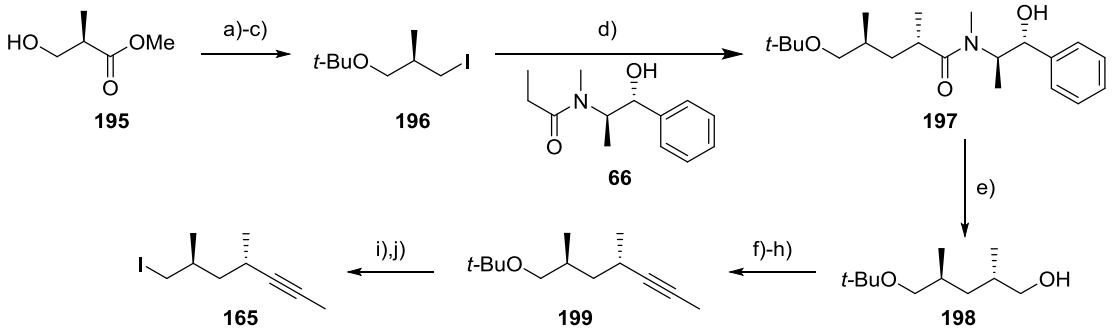
Scheme 58: Silylcupration and Si/I-exchange. Conditions: a) $LiSiMe_2Ph$, CuCN, THF, −78 °C to 0 °C, 93%; b) NIS, 2,6-lutidine, HFIP, 0 °C, 97%.

For completion of the alkenyl iodide fragment **164**, a hydrometalation and subsequent metal/halogen-exchange was required. Initial attempts were focused on a one-pot procedure using Schwartz´s reagent for hydrozirconation. However, the yields varied from 40-60% depending on the batch of Cp_2ZrHCl used. Since the freshly prepared zirconium reagent did not give a satisfactory result, we next tried a hydrostannylation with *n*-Bu_3SnH but the alkenyl stannane was obtained in only moderate yield. A close literature survey revealed a silylcupration as described by Fleming *et al.* to be a viable alternative.[91] In accordance to the literature, the alkenyl silane was formed in high regioselectivity and silicon/iodine-exchange occurred almost quantitatively. This two-step procedure for the formation of the alkenyl iodide turned out to be a very reliable and robust operation. In conclusion, we developed an efficient eleven-step synthesis of the fragment **164** that delivered the material on a half-gram scale.

3.6.2. Synthesis of the Eastern Fragment (C15-C19)

The synthesis of the polyketide fragment **165** was developed and carried out by Dr. Peter Persich.[92] The strategy was based on the use of the ex chiral pool (*R*)-Roche ester (**195**) as starting material and a diastereoselective Myers alkylation[93] which would define the second stereogenic center (scheme 59).

The forward path starts with a sequential *tert*-butylation of (*R*)-Roche ester (**195**), reduction of the ester and an Appel-type iodination. Subsequent alkylation of the Myers pseudoephedrine derivative **66**[93] delivered amide **197** with high diastereoselectivity. Reductive cleavage of the auxiliary yielded the alcohol **198**.



Scheme 59: Diastereoselective alkylation-based entry to the eastern polyketide fragment **165**. Conditions: a) isobutene, H_2SO_4, CH_2Cl_2, rt, 92%; b) $LiAlH_4$, THF, −78 °C, 80%; c) I_2, PPh_3, imidazole, Et_2O/MeCN, rt, 88%; d) **66**, LDA, LiCl, THF, −78 °C; then **196**, −78 °C to 0 °C, 96%; e) LDA, $BH_3{\cdot}NH_3$, THF, 0 °C, 96%; f) TPAP, NMO, MS 4 Å, CH_2Cl_2, 0 °C to rt, 72%; g) CBr_4, PPh_3, Zn, CH_2Cl_2, rt, 68%; h) *n*-BuLi, MeI, THF, −78 °C to rt, 99%; i) TFA, CH_2Cl_2, rt; then KOH, MeOH/H_2O, rt, 88%; j) I_2, PPh_3, imidazole, Et_2O/MeCN, rt, 88%.[92]

Initial studies for the construction of the methyl-capped alkyne focused on exploiting a dichloro olefination/reductive alkylation sequence as successfully applied in the synthesis of the northwestern fragment **164**. However, considerable epimerization of the stereogenic center in α-position was observed which rendered this entry ineffective for the eastern fragment of kendomycin (**10**). Instead, the internal acetylene **199** was introduced via an alternative route utilizing the well-established Corey-Fuchs reaction[94] preceded by a Ley-Griffith oxidation.[95] **199** provided alkyl iodide **165** after acidic cleavage of the *tert*-butyl group and iodination.

Thus, the eastern fragment **165** could be prepared on a multigram scale in high stereochemical purity.[96]

3.6.3. Synthesis of the Aromatic Core

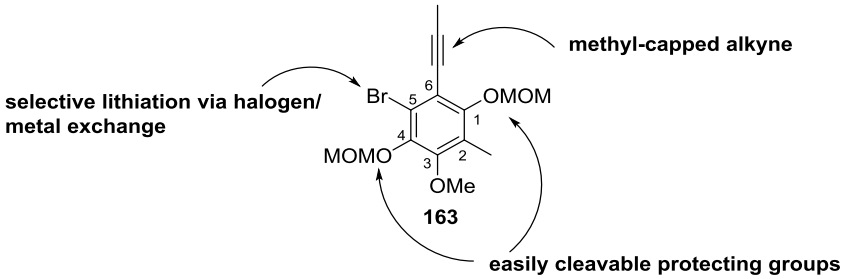
3.6.3.1. Preliminary Considerations

Parts of this chapter describe results obtained by Dr. Peter Persich or derive from a collaboration with Dr. Gaëlle Valot. Where applicable, this will be noted specifically.

The necessary aromatic fragment (scheme 60) needs to feature:

(1) a methyl-capped acetylene substituent in the 6-position for the desired RCAM,
(2) a bromine-atom in 5-position as requisite for the lithiation/addition that would link to the polyketide fragment to **163**

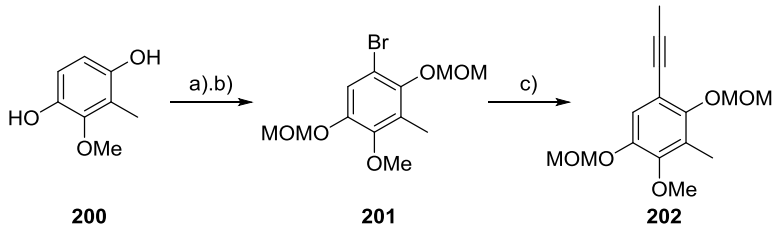
(3) a base-stable and acid-labile protecting groups at the 1- and 4-position that could easily be removed after RCAM



Scheme 60: Design of the aromatic fragment **163**.

According to observations by Lee[41] and Mulzer,[44] the methyl ether in the 3-position seemed to act as a stabilizing anchor for the triphenolic motif and could be removed without difficulty in the course of the late-stage oxidation with IBX. Notably, a methyl ether at C1 had been removed successfully as well.[42] Our initial protecting group strategy relied on a methyl group at the C3 phenol and easily cleavable MOM-ethers at the C1 and C4 phenolic positions.

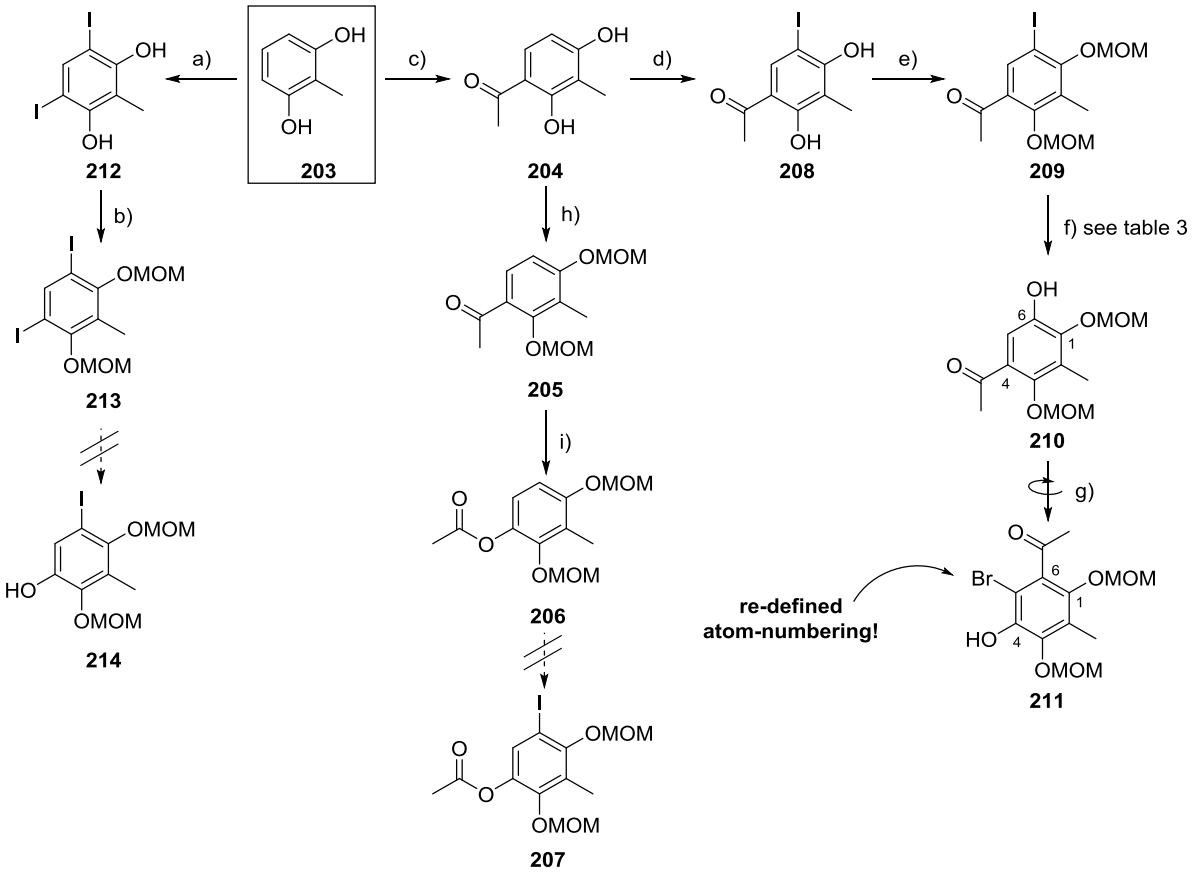
In preliminary studies, a pentasubstituted arene **202** could be obtained by MOM-protection of the commercially available 1,4-diol **200**. NBS-bromination was fully selective for the C6-position as the overall directing effect of the triphenolic system renders this position most electron-rich. The introduction of the alkyne was then achieved in excellent yield by applying a trimethylborate-variant of the Suzuki-Miyaura cross-coupling.[74]



Scheme 61: Synthesis of a pentasubstituted arene. Conditions: a) NaH, DMF, 0 °C to rt; then MOMCl, DMF, 0 °C to rt, 95%; b) NBS, MeCN, 0 °C, 68%; c) sodium propyne, $B(OMe)_3$, THF; then **201**, $PdCl_2(dppf)\cdot CH_2Cl_2$, 65 °C, 99%.

However, subsequent functionalization of the C5-position failed because attempted direct bromination and deprotonation addressed the alkyne and the benzylic position faster than the desired aromatic position. This observation led to the conclusion that the bromine atom had to be introduced before the alkyne was installed.

3.6.3.2. Composition of the 1,3,4-Triphenolic Substitution Pattern by Baeyer-Villiger Oxidation[97]



Scheme 62: Installation of the triphenolic motif in the presence of MOM-ether protecting groups. Conditions: a) NIS, AcOH, cat. H_2SO_4, rt, 96%; b) NaH, DMF, 0 °C to rt; then MOMCl, 0 °C to rt, 51%; c) $BF_3{\cdot}Et_2O$, rt to 70 °C; then Ac_2O, rt to 80 °C, 84%; d) NIS, AcOH, cat. H_2SO_4, rt, 93%; e) MOMCl, DBU, acetone, Δ, 60%; f) $Pd(dba)_2$ (10 mol%), *t*-BuXPhos (20 mol%), KOH, 1,4-dioxane/H_2O (3:1), Δ, 71%; g) Br_2, *t*-$BuNH_2$, CH_2Cl_2, −100 °C, 16%; h) NaH, DMF, 0 °C to rt; then MOMCl, 0 °C to rt; i) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, rt, 95% over two steps.

In further studies, the synthesis of different 1,3,4-trihydroxybenzene derivatives was explored. The pivotal question was how the bromo-substituent at C5 could be introduced without affecting the substituents that were already in place. Furthermore, we decided that a halide or a carbonyl at C6 could serve as a handle to introduce the acetylene later on. In this context, 2-methylresorcinol **203** was identified as the universal starting material. Friedel-Crafts acylation gave selectively the monoacylated compound **204** that was converted to ester **206** in high yield by MOM-diprotection and Bayer-Villiger oxidation. However, attempts to introduce an iodine-atom at C6 failed as both MOM-ethers were partially cleaved under the acidic conditions, giving a complex mixture. In contrast, iodination worked surprisingly well in case of the unprotected bisphenolic substrate **204**. It occured exclusively

at the C6-position, which can be explained by the strong overall directing effect of the hydroxyl-groups. MOM-protection of **208** proceeded in acceptable yield. Unfortunately, a Baeyer-Villiger oxidation of the ketone worked neither with the bisphenolic compound **208** nor the MOM-protected substrate **209**. As an alternative elaboration of aryl iodide **209**, we envisaged a hydroxylation at C6, which would offer two new synthetic perspectives:

(1) The newly installed OH-group at C6 in **210** could be converted to a triflate later on and thus provide an option to install the alkyne by cross-coupling.

(2) For reasons of symmetry, the substituents at C4 and C6 could be "formally exchanged" by re-defining the atom-numbering. Thus, the OH-group would be located at C4 thus completing the required triphenolic substitution pattern. Accordingly, the methyl ketone would become the substituent at C6 and could potentially be transformed to the *gem*-dihaloalkene and undergo a Fritsch-Buttenberg-Wiechell[98] rearrangement to give **211**.

In fact, an I/OH-exchange was observed when aryl iodide **209** was treated with excess potassium hydroxide in presence of a $Pd(dba)_2$ and a Buchwald ligand (*t*-BuXPhos).[99] The product **210** was obtained in good yield when 20.0 equivalents of the hydroxide were used (compare entry 4 and 5, table 3). Other hydroxylation methods using copper-(I)-catalysts[100] or via borylation[101] failed for this substrate (entry 1,2 and 3, table 3).

Table 3: Optimization of the Pd-catalyzed hydroxylation of aryl iodide **208**.

entry	conditions	result
1	CuI, 8-quinolinol-*N*-oxide, $CsOH{\cdot}H_2O$, DMSO/H_2O, 100 °C[100b]	no conversion
2	CuI, 1,10-phenanthroline, KOH, DMSO/H_2O, 100 °C[100a]	no conversion
3	$(Bpin)_2$, $Pd(OAc)_2$, SPhos, K_3PO_4, 1,4-dioxane, 80 °C[102]	s.m. traces of protodeiodination[a)]
4	$Pd(dba)_2$, *t*-BuXPhos, 2.0 eq. KOH, 1,4-dioxane/H_2O, 80 °C[101]	full conversion: 20% **210** & 58% deiodination[a)]
5	$Pd(dba)_2$, *t*-BuXPhos, 20.0 eq. KOH, 1,4-dioxane/H_2O, 80 °C	71%[b)] **210**

a) GC-MS analysis; b) Isolated yield.

Bromination of **210** seemed promising as a free OH-group at C4 should be able to direct the bromination to the *ortho*-position.[103] Yet, the halogenation was somewhat slow, whereas

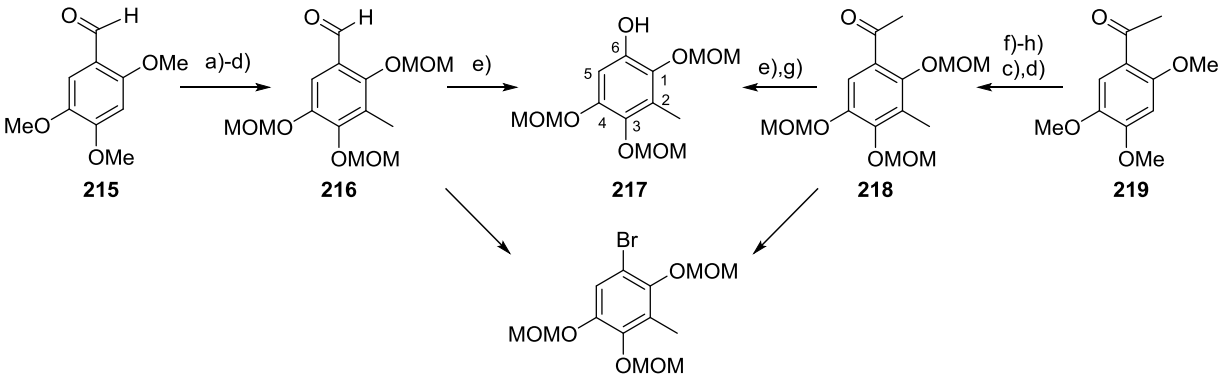
MOM-cleavage occurred very fast in presence of NBS or Br_2. Finally, the desired product **211** was obtained when bromine was introduced as a very dilute precooled solution to the substrate at −100 °C. Nevertheless, the yield remained very poor (16%), and this approach was therefore abandoned.

Based on the success in the hydroxylation of aryl iodide **208**, we derived a strategy in which the symmetric diiodo compound **211** was subjected to the previously applied conditions (conditions of entry 5, table 3). However, the material decomposed to a complex mixture.

3.6.3.3. A Trihydroxybenzene-Based Synthesis of the Aromatic Fragment[92]

As the construction of trihydroxybenzene motif in combination with halogenation at C5 and C6 failed, starting materials were surveyed that already contained the trihydroxyl motif. The tetrasubstituted arenes **215** and **219** were considered as advanced starting points.[92] After methylation at the 2-position and protecting group manipulations, aldehyde **216** and ketone **218** were subjected to different bromination conditions. To our surprise, the electrophilic attack occurred in both cases exclusively at C6 by substitution of the carbonyl group.

Baeyer-Villiger oxidation and hydrolysis of **216** and **218** gave the common intermediate **217** which was then tested in the bromination using different brominating reagents. However, the desired transformation did not take place and only MOM-cleavage was observed.[92]

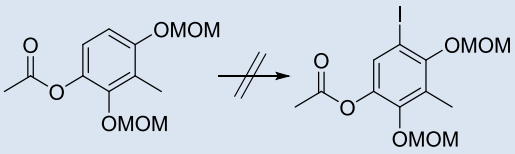
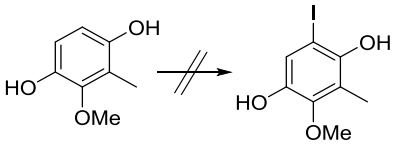
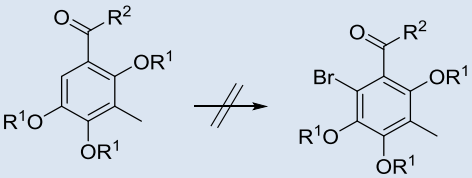
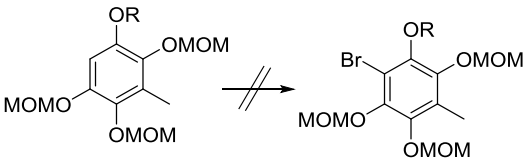


Scheme 63: Attempted synthesis of the hexafunctionalized aromatic core starting from the triphenolic derivatives **215** and **219**. Conditions: a) $HC(OMe)_3$, NH_4Cl, EtOH; b) *n*-BuLi, TMEDA, MeI, THF, −78 °C, 53% over two steps; c) BBr_3, CH_2Cl_2, rt; d) NaH, THF, 0 °C to rt; then MOMCl, 36% over two steps; e) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, rt; then KOH, MeOH, rt, 74% (**216**) and 90% (**218**); f) ethylene glycol, *p*-TsOH·H_2O, toluene, Δ; g) *n*-BuLi, TMEDA, THF, −78 °C to 0 °C; then MeI, 22% over two steps; h) LiCl, H_2O, DMSO, 120 °C, 89%; g) KOH, MeOH, rt, 74%.[92]

3.6.3.4. Strategies Towards the Southern Aromatic Core: Lessons Learned

It was not entirely suprising that the synthesis of **163** was anything but trivial, and we probed numerous pathways to construct the depicted aromatic fragment (scheme 60). From one dead end to another, however, our understanding of the reactivity of the precursors grew. Finally, we came up with a detailed analysis of the failed attempts which can be summarized as shown in table 4.

Table 4: Overview of failed functionalizations of the triphenolic core.

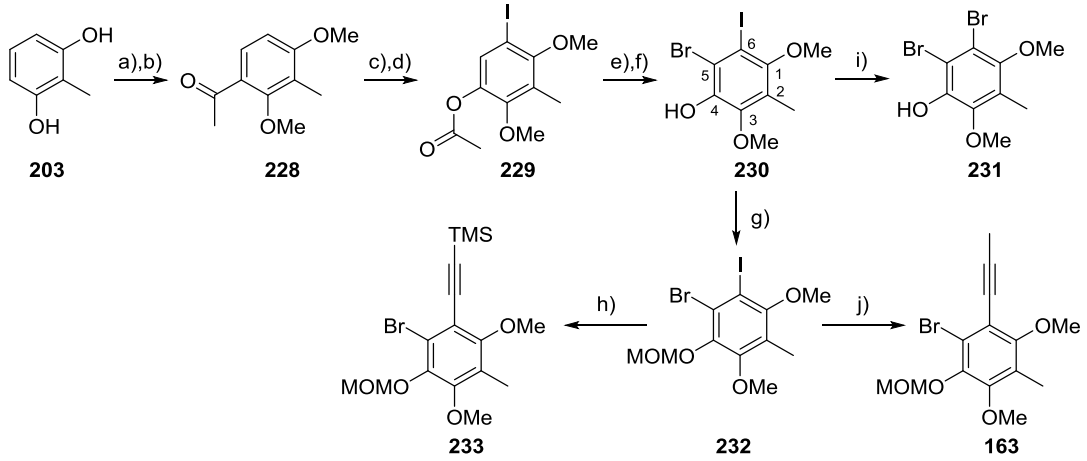
entry	objective	result
1	 **206** **207**	The iodination at the 6-position does not work in presence of the labile MOM-ethers.
2	 **200** **220**	For iodination at the 6-position the *para* OH-groups at C1 and C4 have to be protected to prevent oxidation to the *para*-quinone.
3	 **215** R^1: Me; R^2: H **219** R^1: Me; R^2: Me **216** R^1: MOM; R^2: H **218** R^1: MOM; R^2: Me **221** R^1: Me; R^2: H **222** R^1: Me; R^2: Me **223** R^1: MOM; R^2: H **224** R^1: MOM; R^2: Me	The highly electron-rich arene is very reactive in electrophilic aromatic substitution reactions. The overall mesomeric effect of the hydroxyl-groups directs electrophilic attacks to the C6-position. Even poor leaving groups are substituted.[92]
4	 **217** R: H **225** R: allyl **226** R: H **227** R: allyl	For bromination at C5, the OH-group at C4 has to be free in order to induce an *ortho*-directing effect; the hydroxyl-groups at C1 and C3 have to be protected.

3.6.3.5. Synthesis of the Aromatic Fragment via a Selective Deprotection Strategy

With these conclusions in mind we set out for an approach that would allow us to differentiate the hydroxyl group at C4 from those at C1 and C3, so that a bromine-atom could be introduced in an *ortho*-directed fashion as a sixth substituent. Furthermore, the introduction of methyl ethers on the C1 and C3 OH-groups should increase the stability of the relevant intermediates and prevent unwanted *para*- or *ortho*-quinone formation. This sequence also started with 2-methylresorcinol (**203**), which was first acylated under Friedel-Crafts conditions and then methylated to give compound **228**. Baeyer-Villiger oxidation of the ketone **228** was performed in good yield completing the triphenolic motif. To our delight the iodination at C6 - using NIS and catalytic amounts of sulfuric acid - gave **229** in excellent yields. In comparison to the attempted iodination of **206**, no deprotection or any other side products were oberserved.

The present protecting group set in **229** allowed for a selective deprotection at C4 which paved the way for functionalization at C5. In the event, the bromination with NBS in polar aprotic acetonitrile proceeded smoothly, providing the hexasubstituted arene **230** in satisfactory yield. As the phenolic group at C4 had to be protected for the following transformations, we decided to change the methyl ether to a MOM-ether, which would be easier to cleave at the end. For the deprotection, oxidative and Lewis acidic conditions were tested; however, the material decomposed in all cases.

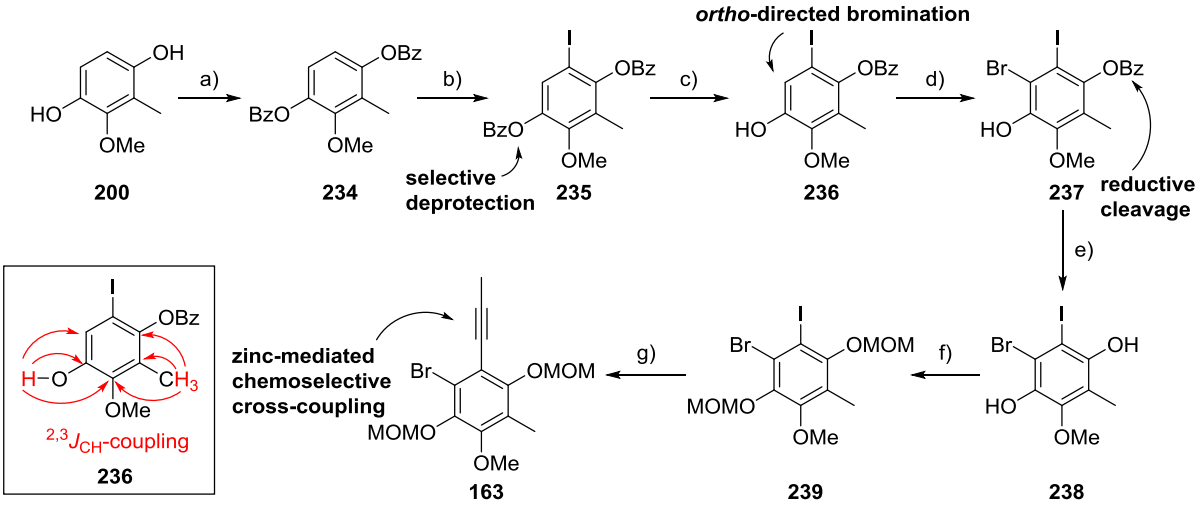
In order to explore the introduction of the alkyne we continued with **230**. Thus, a MOM-ether was installed at C4, giving compound **232** which was considered suitable for the introduction of the acetylene at C6. In earlier studies, a variant of the Suzuki-Miyaura cross-coupling reaction with sodium propyne and trimethylborate was successfully applied to the pentasubstituted substrate **201**. Subjecting the dihalo compound **232** to these conditions, good yields were only obtained when the bulky Buchwald ligand *t*-BuXPhos was present. The alkyne could alternatively be introduced by Sonogashira cross-coupling with TMS-protected acetylene at elevated temperature. The attempted Sonogashira-coupling with propyne failed. Again, the cleavage of the methyl-ether at C1 in **233** was investigated. However, the material seemed to be too sensitive to survive the required reaction conditions.[104]



Scheme 64: Installation of the triphenolic substitution pattern in the presence of methyl ether protecting groups. Conditions: a) $BF_3{\cdot}Et_2O$, rt to 70 °C; then Ac_2O, rt to 80 °C, 84%; b) Me_2SO_4, K_2CO_4, acetone, rt, 93%; c) *p*-TsOH, *m*-CPBA, CH_2Cl_2, rt, 70%; d) AcOH, cat. H_2SO_4, NIS, rt; e) KOH, MeOH/H_2O, rt, 87% over two steps; f) NBS, MeCN, −40 °C, 62%; g) NaH, THF, rt; then MOMCl, 0 °C to rt, 84%; h) $PdCl_2(PPh_3)_2$ (20 mol%), Et_3N, CuI, TMS-acetylene (6.0 eq.), 70 °C, 62% (for further details regarding the optimization of the cross-coupling reaction see experimental section); i) BBr_3, CH_2Cl_2, −78 °C, 56%; j) $B(OMe)_3$, propinyl sodium, *t*-BuXPhos, $PdCl_2(PPh_3)_2$ (20 mol%), Δ, 83%.[104]

The hurdle of the methyl ether cleavage was considered too risky to be left until after the fragment assembly. Therefore, the protecting group strategy for the aryl component **163** was revised once again:[96]

The known 1,4-hydroquinone **200** was converted to the dibenzoate **234**. Following the overall strategy described before, the iodination was conducted employing the established procedure which gave iodide **235** regioselectively in high yield. Under basic conditions, the sterically less hindered benzoate was hydrolyzed whereas the sterically more hindered benzoate at C1 remained intact. The structure of mono-benzoate **236** was confirmed by 2D-NMR spetroscopy (scheme 65). The remaining benzoate in **236** was stable during an *ortho*-directed bromination with NBS. Then, the benzoate at C1 was readily cleaved with DIBAl-H and the rather unstable dihalogenated 1,4-hydroquinone **238** was directly converted to the bis-MOM ether **239**. Finally, the chemoselective cross-coupling reaction at the *ortho*-disubstituted iodide was tested. Preceding investigations (scheme 64) indicated that this transformation would not be trivial; nevertheless, an extensive screening of catalysts, ligands and reagents revealed that the desired product **163** was formed in a mild Negishi-coupling.[96]



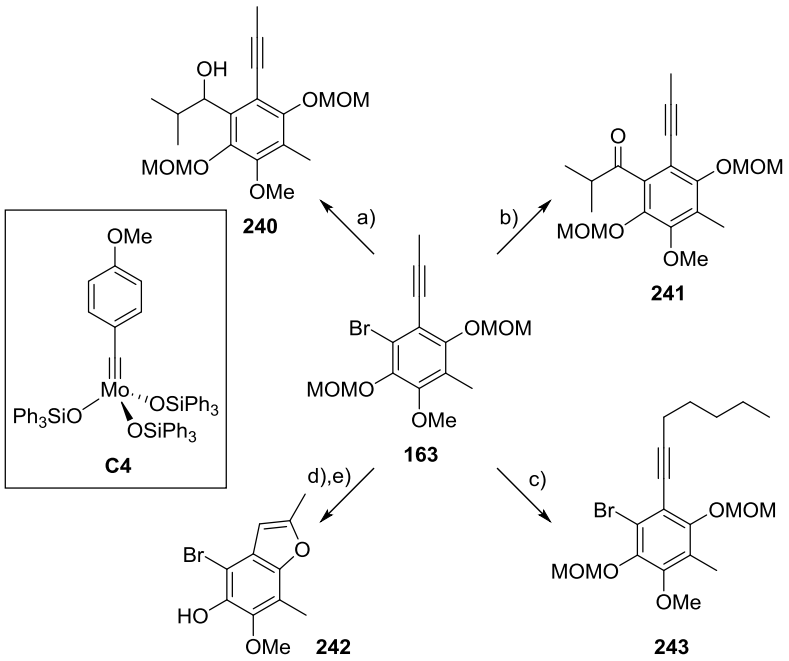
Scheme 65: Revised route for the hexasubstituted arene **163**. Conditions: a) BzCl, Et_3N, THF, 0 °C, 89%; b) NIS, cat. H_2SO_4, AcOH, rt, 94%; c) KOH, MeOH, rt, 80%; d) NBS, MeCN, −10 °C, 49-81%; e) DIBAl-H, CH_2Cl_2, −78 °C; f) MOMCl, DBU, acetone, rt, 61% over two steps; g) $BrMgCCCH_3$, $ZnCl_2$, THF; then **239**, $Pd(PPh_3)_4$ (2x20 mol%), Δ, 82%.[96]

In conclusion, an efficient and reliable route to the desired aromatic fragment was achieved. The key requirements turned out to be a selective deprotection of a C4 benzoate. The resulting hydroxyl group at C4 was then used to direct the bromination to the C5-position, against the overall electronic effects of the triphenolic system which renders the C6-position most nucleophilic. With reasonable amounts of **163** in hand, its usefulness in the prospected transformations was evaluated.

3.6.4. Further Model Studies Towards the Total Synthesis of Kendomycin

In order to determine the utility of arene **163**, the compound was subjected to several tests. The assessment started with the installation of the polyketide chain. To this end, aryl bromide **163** was treated with *n*-BuLi to induce a halogen/lithium-exchange and isobutyraldehyde or the corresponding Weinreb amide were subsequently added. The benzylic alcohol **240** was obtained in almost quantitative yield, whereas in case of the Weinreb amide, poor results were observed, presumably due to the greater steric hindrance around the carbonyl. Moreover, **163** was tested in an alkyne cross metathesis reaction with 2-octyne. In the presence of the molybdenum alkylidyne catalyst **C4** the cross metathesis product **243** was formed at elevated temperature in moderate yields. Thus, the alkyne site seemed to be accessible for the RCAM catalyst despite the two *ortho* substituents. At last, the MOM-ethers were removed under acidic conditions to test the hydroalkoxylation. In

fact, the benzofuran **242** was formed in good yield when **163** was exposed to catalytic amounts of $PtCl_2$.[96]

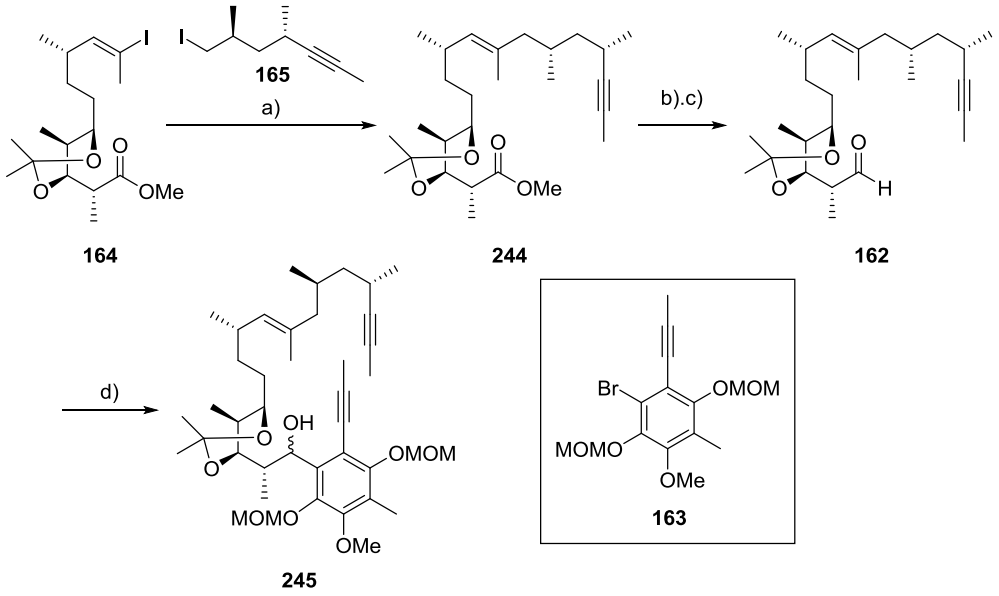


Scheme 66: Model reactions with aromatic substrate **163**. Conditions: a) *n*-BuLi, isobutyraldehyde, THF, −78 °C to 0 °C, 96%; b) *n*-BuLi, *i*-PrC(O)N(OMe)Me, THF, −78 °C to 0 °C, 37%; c) 2-octyne, **C4** (18 mol%), MS 5 Å, rt to 100 °C, 54%; d) *p*-TsOH·H_2O, MeOH, rt; e) $PtCl_2$ (20 mol%), toluene, 82% over two steps.[96]

Arene **163** passed all test reactions successfully, suggesting that the compound is a suitable choice for further synthetic manipulations en route to Kendomycin (**10**).

3.6.5. Fragment Assembly via Lithiation/Addition & RCAM Studies

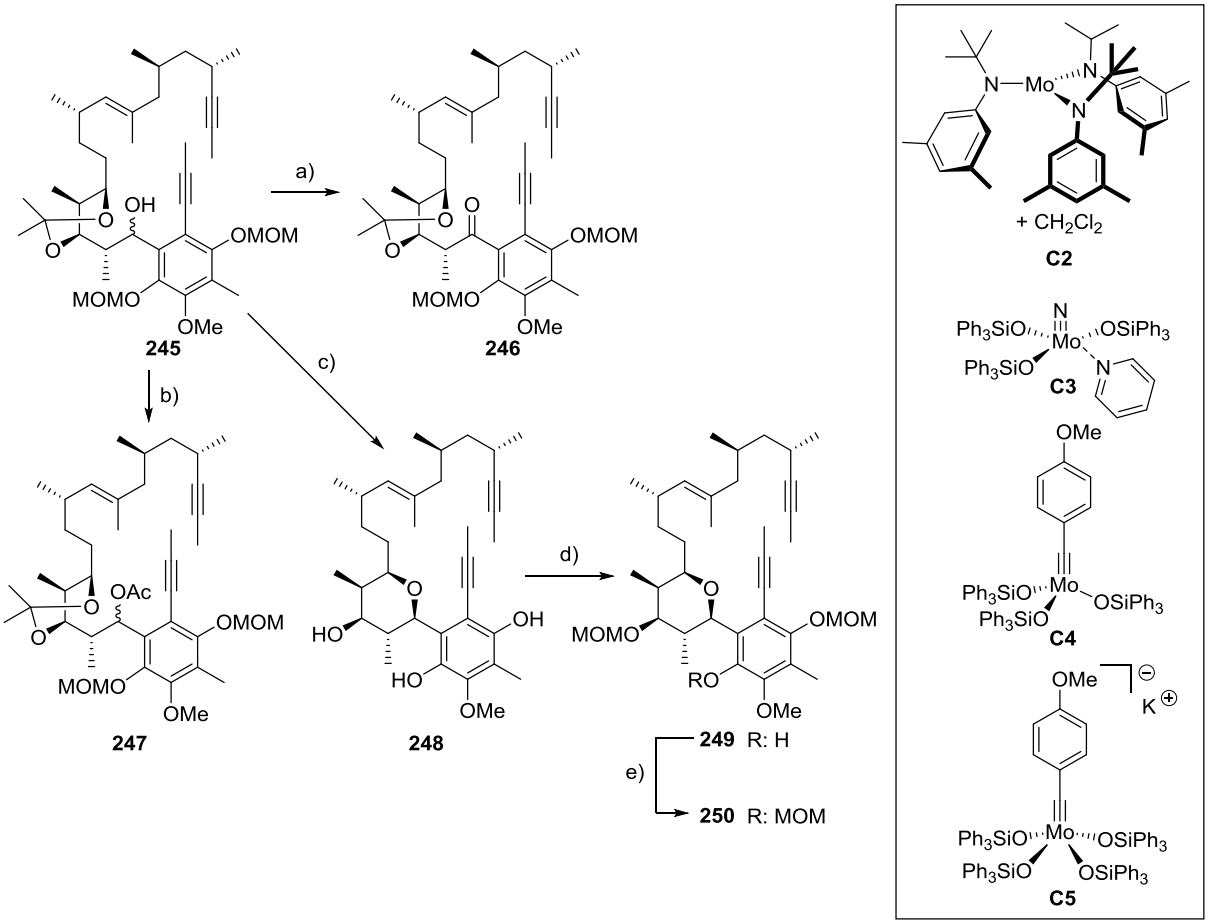
The assembly of the fragments started with the linkage of the polyketide fragments **164** and **165** (scheme 67) via an alkyl-Suzuki cross-coupling[74] that furnished the polyketide chain in quantitative yield. The ester **244** was then converted to aldehyde **162** by a two-step procedure via the corresponding Weinreb amide. The use of the aldehyde **162** in the connection of the aryl fragments seemed a better choice, as yields were higher than with the Weinreb amide in the test reactions (scheme 66). Treatment of aryl bromide **163** with *n*-butyllithium resulted in bromine/lithium exchange; upon addition of aldehyde **162**, the diyne **245** was formed in over 70% yield. Compound **245** served as starting material for the synthesis of several RCAM precursors.[92]



Scheme 67: Assembly of the fragments by alkyl-Suzuki cross-coupling and a lithiation/addition reaction. Conditions: a) **165**, *t*-BuLi, Et_2O, −78 °C; then 9-(MeO)-9-BBN, THF, −78 °C to rt; then aq. K_3PO_4, $PdCl_2$(dppf) (10 mol%), **164**, DMF, rt, 99%; b) *i*-PrMgCl, HN(OMe)Me·HCl, THF, −25 °C to rt, 78%; c) DIBAl-H, THF, −78 °C; d) **163**, *n*-BuLi, THF, −78 °C; then **162**, −78 °C to rt, 70% over 2 steps.[96]

The benzylic alcohol in diyne **245** was considered a possible source of troubles in the metathesis reaction, as the OH-group might coordinate to the catalyst. Thus, **245** was oxidized to the ketone **246**, or protected with an acetate as in **247**. Furthermore, it remained unclear if the acetonide would add extra rigidity to the polyketide chain that might impact on the outcome of the RCAM. Therefore, the acetonide-group was removed under acidic conditions to give tetrahydropyran **248**. However the MOM-ethers were cleaved as well and two phenolic and the secondary alcohol on the THP had to be protected in two separate steps. Notably, the fully protected substrate **250** was obtained as a mixture of two

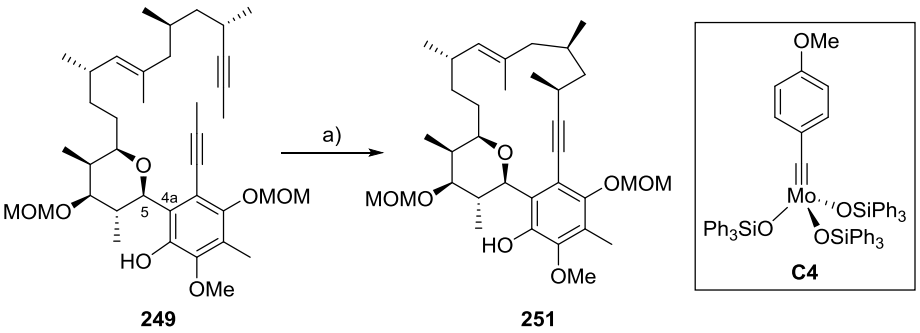
atropisomers. These simple modifications delivered six different substrates for the upcoming ring closure.[96]



Scheme 68: Synthesis of different RCAM precursors **246**-**250**. Conditions: a) DMP, CH_2Cl_2, rt, 97%; b) Ac_2O, DMAP, pyridine, rt, 55%; c) HCl (2 N), MeOH, rt, 77%; d) MOMCl, *i*-Pr_2EtN, CH_2Cl_2, rt, 73%; e) MOMCl, DBU, acetone, rt, 68%.[96]

Next, diynes **245**-**250** were submitted to the RCAM conditions using our highly active alkyne metathesis catalysts **C2**, **C3**, **C4** and **C5**. Remarkably, none of the substrates showed any reactivity in alkyne metathesis below 100 °C. Raising the temperature led to formation of the corresponding methoxybenzylidyne cross metathesis products (in case of **246** and **249**) or open dimers **246**, **247**, **249** and **250** in which the alkyne of the alkyl chain reacted exclusively and the acetylene next to the arene appeared to be completely inert. In the case of **245**, elimination of the alcohol was observed, whereas **248** did not undergo any metathesis reaction. Only the di-MOM protected substrate **249** reacted to the desired macrocycle in up to 62% yield when very harsh conditions were apllied using an increased catalyst loading (2 x 30 mol%) of **C4**, reflux temperature and a high dilution (0.1 μM). However, this result was

not well reproducible. The application of RCAM to this class of substrates was therefore considered impractical.[92]



Scheme 69: Most promising substrate in the RCAM. Conditions: a) **C4** (2 x 30 mol%), MS 5 Å, toluene, *c* = 0.1 μM, Δ, 18-62%.[96]

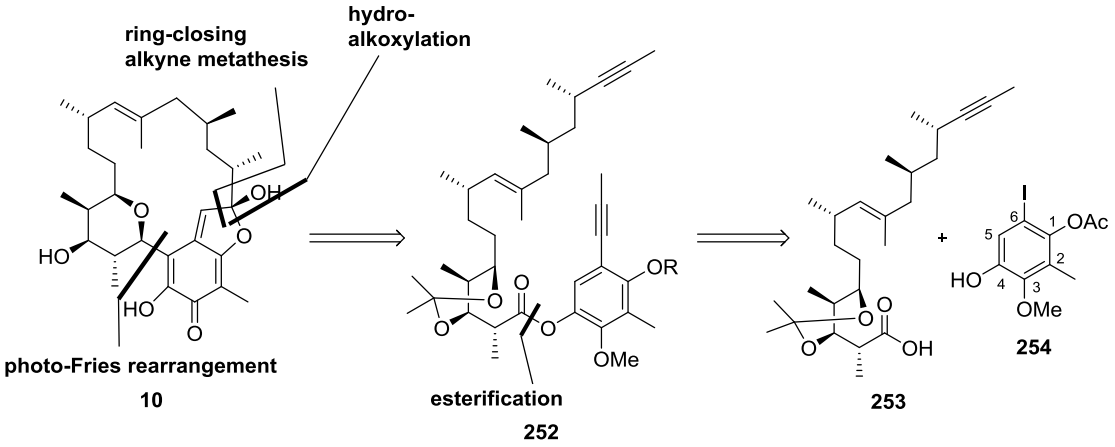
The problems encountered in the alkyne metathesis of substrates **245**-**250** was rationalized by the vastly different reactivity of the two alkynes. As a consequence, the less-hindered acetylene at the polyketide chain reacted whereas the sterically more encumbered one at the arene did not.[96] However, the issue cannot solely be attributed to the two *ortho*-substituents next to the alkyne since the model substrate **150** also bore the *ortho*-disubstitution pattern and was metathesized without difficulty at ambient temperature. Rather, the rotational freedom about the aryl-glycosidic bond must determine whether a reactive conformation can be adopted. Interestingly, subtle structural changes appear to be responsible for the occurence of the atropisomerism. For example, the steric demand of the substituent at C4 is crucial because large protecting groups can presumably function as a steric lock for the rotation about the C4a-C5 bond.

All in all, it must be assumed that the overall outcome of the RCAM reactions was a result of several steric effects.

3.6.6. Revision of the Aromatic Fragment: The Photo-Fries Approach

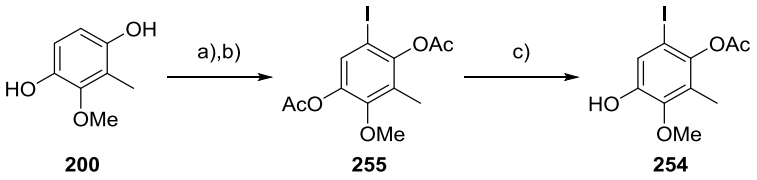
Bypassing the problems arising from an *ortho*-disubstituted acetylene and the frequently recurring atropisomeric rigidity about the *C*-glycosidic bond that likely obstructed the RCAM, a revised route towards the macrocycle of kendomycin based on a pentasubstituted aromatic core **252** was pursued. Based on this strategy, the RCAM product would yield a metacyclophane. The construction of the hexasubstituted arene via a photo-Fries reaction was planned as a post-metathetic transformation. The diyne **252** should be assembled by esterification of phenol **254** and acid **253**. The latter could be derived from the same methyl

ester **244** that had already been used in the preceding approach (chapter **3.6.5.**). This underlines the flexibility of the strategy with regards to the polyketide fragment.



Scheme 70: Retrosynthetic analysis based on an *ortho*-monosubstituted alkyne in the RCAM precursor.

For the synthesis of the aromatic unit we sought to implement the previously used selective deprotection approach, as it was necessary to differentiate between the C1 and C4 hydroxy-group in the esterification step with the polyketide chain **253**. Furthermore, the introduction of the alkyne by cross-coupling was planned to occur after the connection of the fragments. The order of the steps was reasoned in the way that the selective deprotection would only work if the hydroxyl group at C1 is neighbored by a sterically shielding iodine-atom. Moreover, the cross-coupling reaction was expected to be impaired if an unprotected phenolic group was present. Therefore the aromatic fragment should bear an iodine-atom at C6 and the free OH-group at C4 for the esterification.

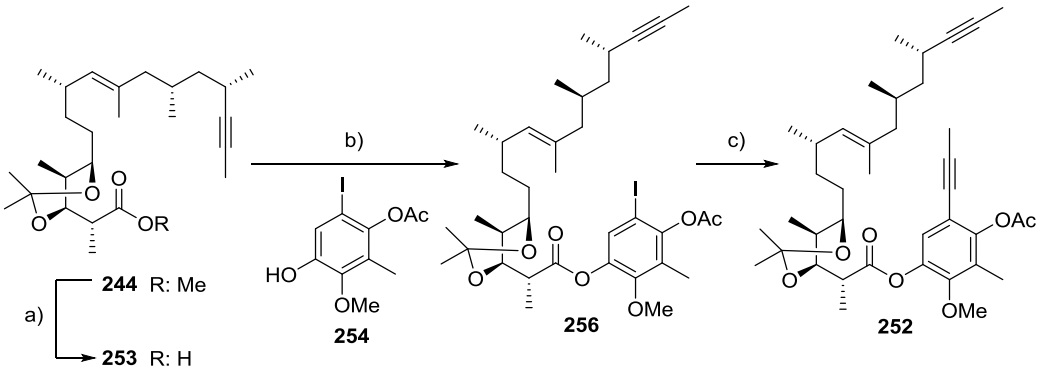


Scheme 71: a) AcCl, Et_3N, THF, −78 °C to rt, 90%; b) NIS, cat. H_2SO_4, AcOH, rt, 99%; c) K_2CO_3, MeOH, H_2O, 0 °C, 97%.

The 1,4-hydroquinone **200** was therefore converted into the corresponding diacetate, which was then iodinated under the previously established conditions with NIS and a catalytic amount of sulfuric acid. Iodide **255** was isolated in basically quantitative yield. To our delight, a selective saponification of the C4 acetate proceeded under mild conditions in analogy to the benzoate case (chapter **3.6.3.5.**). In this way, the required aromatic core was obtained in only three efficient steps in 86% overall yield.

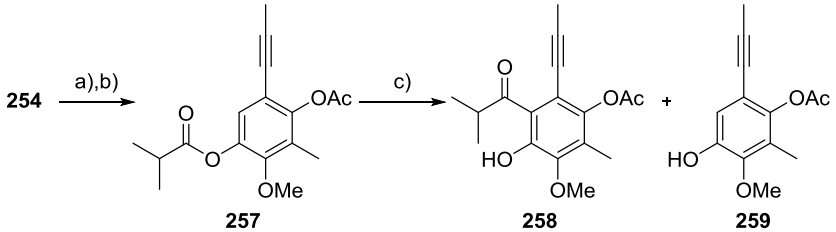
3.6.7. RCAM, Gold-Catalyzed Hydroalkoxylation & Endgame

For fragment assembly, the methyl ester **244** was saponified to acid **253**, which was subsequently esterified with phenol **254** under Steglich conditions. Next, the yet missing alkyne was introduced by Suzuki-Miyaura cross-coupling, in which sodium propyne was transmetalated with trimethylborate. It was observed that the Pd-catalyzed reaction was promoted by Buchwald´s *t*-BuXPhos ligand. With less bulky ligands such as JohnPhos or triphenylphosphine, the reaction time was much longer (up to 16 h) and the yields only moderate.



Scheme 72: Fragment assembly by esterification and introduction of the second alkyne. Conditions: a) LiOH, THF/MeOH/H_2O, rt, 80%; b) **254**, DMAP, DCC, CH_2Cl_2, 0 °C to rt, 77%; c) sodium propyne, $B(OMe)_3$, THF, rt; then $PdCl_2(PPh_3)_2$ (10 mol%), *t*-BuXPhos, THF, 70°C, 78%.

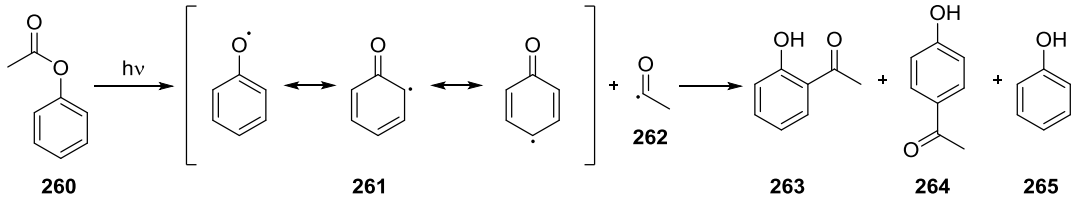
In order to preserve the precious advanced material, initial studies towards the photo-Fries rearrangement were conducted on a model substrate **257**. This was prepared in two steps from phenol **254** by esterification with isobutyric acid under Steglich conditions followed by the introduction of the alkyne at C6 by Suzuki cross-coupling (scheme 73).



Scheme 73: Photo-Fries rearrangement on a model substrate. Conditions: a) DMAP, DCC, isobutyric acid, CH_2Cl_2, rt, 79%; b) sodium propyne, $B(OMe)_3$, THF, rt; then $PdCl_2(PPh_3)_2$ (10 mol%), *t*-BuXPhos, THF, 70 °C, 85%, c) hν (450 W, medium pressure mercury gas lamp), EtOH, −20 °C, 78%.

The photo-Fries reaction[105] is the photochemical version of the Fries reaction[106] that normally proceeds via formation of an acyl cation in the presence of Lewis acids such as AlX_3, (X: Cl, Br or I), BF_3, $TiCl_4$ or $SnCl_4$. The photo-Fries reaction is believed to proceed via

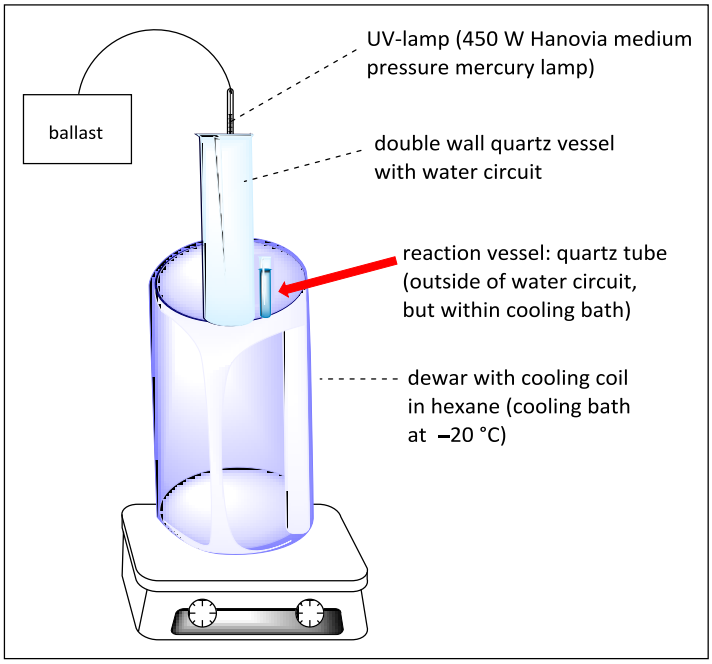
formation of an acyl-radical that is transferred to the *ortho*- or *para*-position. The aromaticity is regained by tautomerization of the product.



Scheme 74: General mechanism of a photo-Fries rearrangement.[105]

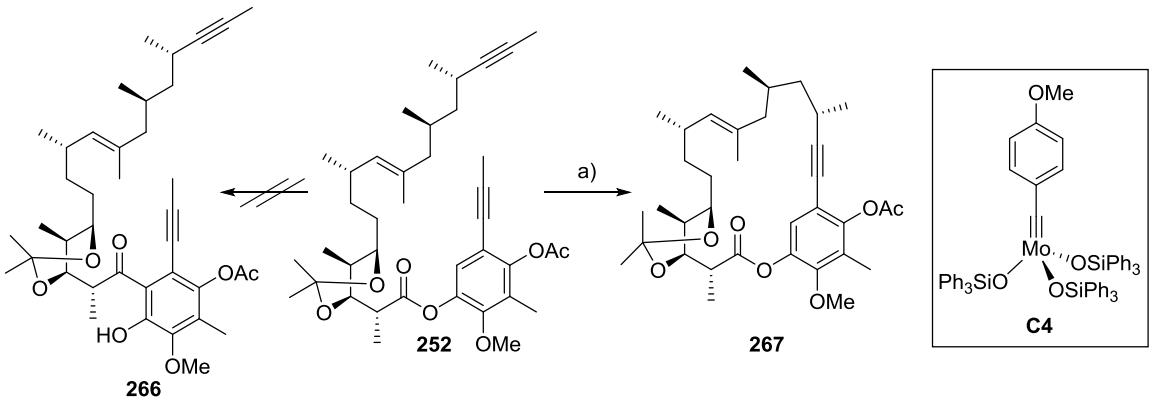
The setup for the photochemical reaction was based on a standard laboratory reactor that consisted of a vertically arranged set of an inner cooling well and an outer immersion well made of quartz. The UV lamp was inserted in a quartz tube that was positioned in the center of the reactor. On small scale, the reaction vessel was a short quartz tube that was attached to the quartz reactor. In our initial attempts, the model substrate **257** was irradiated at ambient temperature using a 125 W high pressure mercury gas lamp. Ethanol and cyclohexane were tested as solvents for their good permeability even for wavelengths as short as 204 nm.[107] However, only starting material was obtained in both cases even after 48 h of irradiation. It was supposed that the intensity of the emitted light of the 125 W lamp might not be high enough. Therefore, a 450 W medium pressure mercury gas lamp entailing the same continuous spectrum in much higher intensity was used instead. For the change of the lamp however, the setup had to be altered. As the 450 W UV lamp was also a strong heat source, the whole reactor had to be additionally placed in an external cooling bath (−20 °C) (scheme 75). Under these conditions, clean conversion of ester **257** to the ketone **258** was observed. The desired product was obtained in 78% yield along with traces of a byproduct **259** that was presumably the result of simple homolytic cleavage of the acyl group. The obtained results indicated that the transformation strongly depended on the light source and the setup.

Diyne **252** was then irradiated using the setup mentioned above. However, applying different reaction temperatures, solvents and UV irradiation sources (125 W, 450 W UV lamps) merely gave the undesired phenol byproduct along with complex mixtures. We supposed that a macrocyclic ester would be a better substrate as the acyl radical could be transferred in an intramolecular fashion and a greater proximity of the two radical species would be enforced.



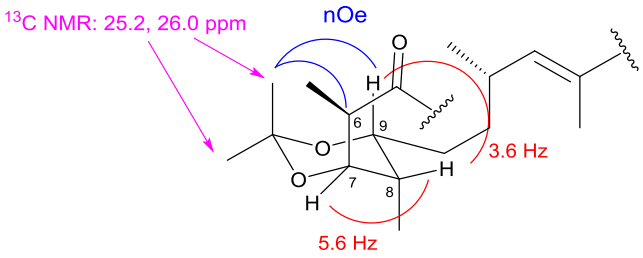
Scheme 75: Experimental setup of the photochemical transformation.

Hence, the undesired simple cleavage of the acyl group should be less favored. Thus, we commenced to investigate the key feature of the synthesis: the ring-closing alkyne metathesis. To our delight, the macrocyclization proceeded efficiently under very mild conditions in 95% yield. Only 5 mol% of the reactive alkylidyne complex **C4** were necessary to promote the RCAM even at ambient temperature. This result showcases the clear difference between diyne **252** and the previously used hexasubstituted substrates **245**-**250**. The ring strain in cycloalkyne **267** is presumably higher than in the *ortho*-cyclophane **251**. Nevertheless, this effect appears to be insignificant in comparison to the influence of steric bulk and the ensuing conformational rigidity of the *ortho*-disubstituted compounds **245**-**250**.



Scheme 76: Formation of the cycloalkyne **267** using molybdenum alkylidyne complex **C4**. Conditions: a) **C4** (5 mol%), MS 5 Å, toluene, rt, 95%.

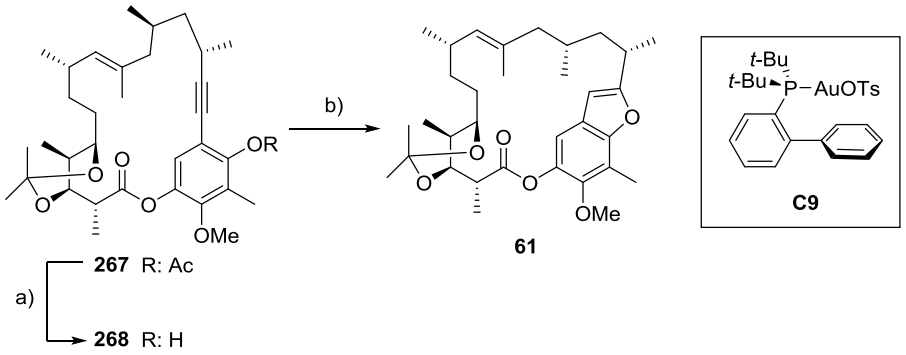
The conformational constraint of the macrocycle was exploited for a conformational analysis and a review of the stereochemistry of the 1,3-diol. All atoms were assigned on the basis of 2D NMR studies. The carbon shifts of the acetonide were closely examined as they correlate to the relative stereochemistry of the 1,3-diol. In 1990, Rychnovsky[108] and Evans[109] independently reported that for propionate-derived polyols the carbon resonances of the methyl-groups were found at 19 and 30 ppm for 1,3-*syn* diols and between 24-25 ppm for 1,3-*anti* diols. In the depicted case, the carbon shifts were observed to be 25.2 and 26.0 ppm, supporting the presence of an 1,3-*anti* diol. Furthermore, NOESY experiments displayed an interaction of the proton at C9 and at C6 with the axial CH_3-group of the acetonide. This observation suggests a 1,3-diaxial relationship of these substituents. The coupling constants of the protons at C7/C8 indicate a 1,2-di-equatorial orientation and a 1,2-*syn* relation for the protons at C8/C9. As a result, the relative configuration of all substituents around the six-membered ring was assigned.



Scheme 77: NOE-experiments of the macrocyclic compound **267** confirmed the *anti*-relationship of the 1,3-diol.

With cycloalkyne **267** in hand, we attempted the construction of the benzofuran, which represents the second key transformation in this synthesis. The acetate at C1 was hydrolyzed under mildly basic conditions which revealed the precursor for the desired heterocycle formation (scheme 78). Platinum-catalyzed hydroalkoxylations are known entries to benzofurans.[75a] However, treatment with $PtCl_2$ did not deliver the cyclization product; even at elevated temperature the starting material was recovered. The cationic gold-complex $[(PPh_3)Au]OTf$ (entry 2 and 3, table 5) merely effected the cleavage of the acid labile acetonide group, which likely indicated the presence of traces of triflic acid. In order to cirmcumvent this problem, the corresponding tosylate species was tested. Yet, only small amounts of the desired product along with decomposition products were formed after a prolonged reaction time. Next, two gold tosylate complexes with Buchwald´s *t*-BuXPhos and JohnPhos ligands were prepared. The biarylmonophosphine ligands were expected to stabilize the Au^I-complexes and render the cationic gold more carbophilic. Indeed, in the

presence of 10 mol% of [JohnPhosAu]OTs (**C9**) the desired benzofuran was generated quantitatively. The phosphine ligand had to be removed by HPLC separation to give the product in 79% yield (entry 4, table 5). In comparison, the use of the bulkier *t*-BuXPhos ligand gave only poor results (entry 5, table 5). Benzofuran **61** intercepts the total synthesis of kendomycin (**10**) reported by Mulzer *et al*.[44a]

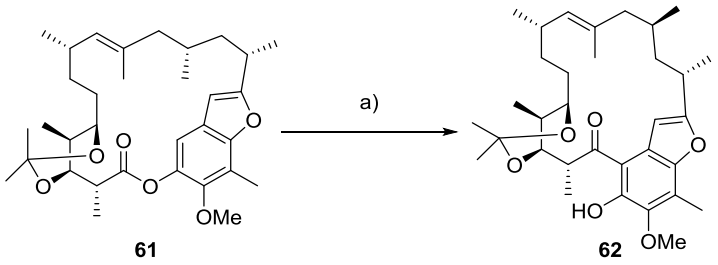


Scheme 78: Au^{I}-catalyzed hydroalkoxylation. Conditions: a) K_2CO_3, MeOH, 0 °C, 86%; b) [Johnphos Au]OTs (**C9**), CH_2Cl_2, rt, 74%.

Table 5: Investigation of the noble-metal-catalyzed hydroalkoxylation of **268**.

entry	catalyst (mol%)	conditions	results
1	$PtCl_2$ (10)	toluene, reflux	sm recovered
2	[(PPh_3)Au]OTf (10)	CH_2Cl_2, rt	full conversion, cleavage of acetonide, further decomposition
3	[(PPh_3)Au]OTs (10)	CH_2Cl_2, rt	5% **61**, very slow reaction, formation of further byproducts
4	[JohnPhosAu]OTs (10)	CH_2Cl_2, rt	full conversion to **61** by ^{1}H NMR, 79% isolated yield after HPLC separation
5	[*t*-BuXPhosAu]OTs (10)	CH_2Cl_2, rt	15% **61** after 2 d, slow decomposition

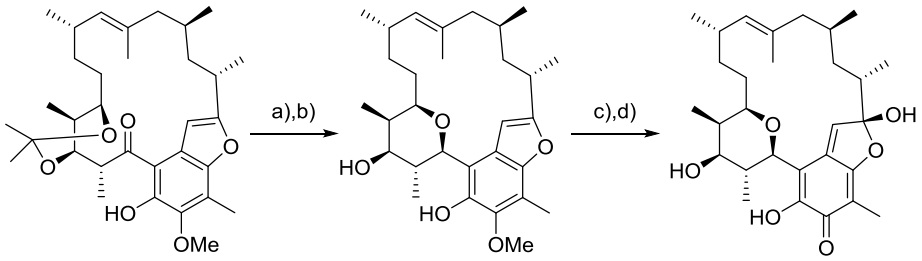
For the completion of the synthesis the remaining transformations were conducted according to the literature.[41, 44a] Thus, we set out to approach the ring contraction. The setup that had been found successful for the model substrate **257** led to complete decomposition of the substrate if the 450 W unit was applied. Upon return to the original setup with the 125 W UV lamp, the reaction proceeded smoothly at ambient temperature to give the hexasubstituted aromatic core in 85% yield. The spectroscopic data of **61** and **62** were in excellent agreement with those reported in the literature.[41, 44a] The remaining steps were repeated on very small scale in analogy to the known protocols.[44a]



61 62

Scheme 79: Photo-Fries rearrangement. Conditions: a) hν (125 W, high pressure mercury gas lamp), cyclohexane, rt, 85%.

Ketone **62** was reduced to the benzylic alcohol and upon treatment with hydrochloric acid, the acetonide was hydrolyzed and the tetrahydropyran **63** formed in 89% yield over the two transformations (scheme 80). Compound **63** was treated sequentially with DDQ and dilute hydrochloric acid to furnish the hemiacetal of kendomycin (**10**). The analytical and spectroscopic data of all known precursors matched the literature. However, the full characterization of the natural product was not attempted.



62 63 10

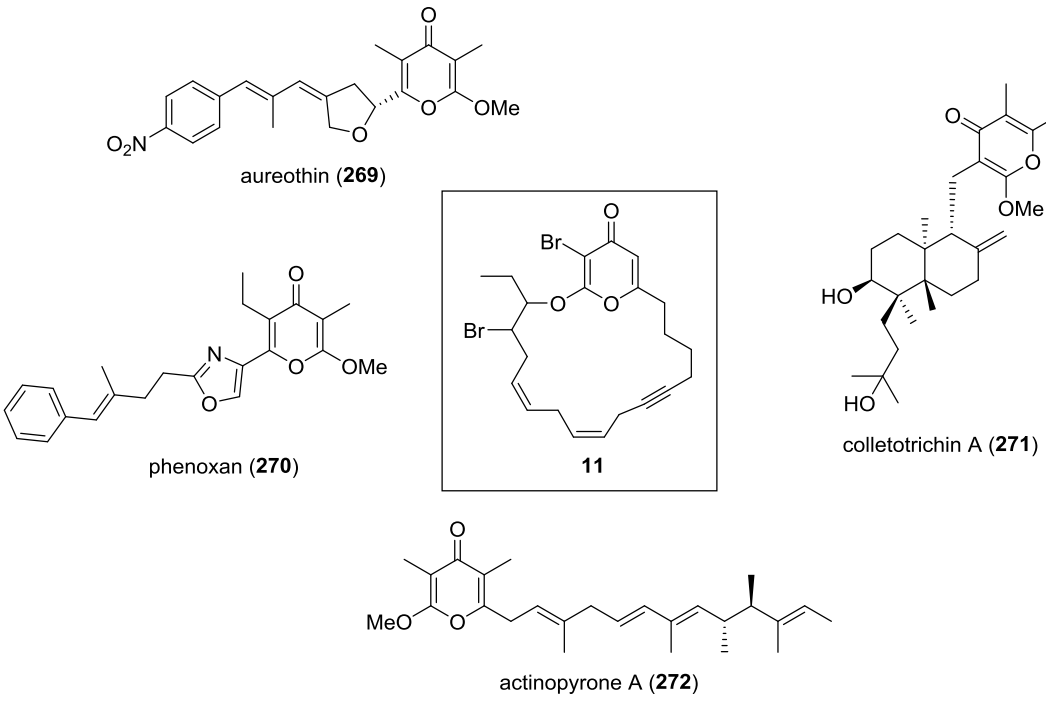
Scheme 80: Formation of the tetrahydropyran and oxidative endgame. Conditions: a) $NaBH_4$, MeOH, rt; then HCl (0.5 N); b) HCl (2.0 N), MeOH, rt, 89% over two steps; c) DDQ, CH_2Cl_2/H_2O (10:1), rt; d) 1% HCl, MeCN.

In summary, a highly convergent formal total synthesis of the macrocyclic natural product kendomycin (**10**) is described. In the course of our studies, it was demonstrated that the RCAM of sterically encumbered diynes **245**-**250** was impractical, even though the cross-metathesis of an *ortho*-disubstituted arene **163** had been successful.[92] In contrast, the RCAM with a pentasubstituted arene proceeded smoothly to yield the metacyclophane **267** that was converted to Mulzer´s benzofuran **61**[44a] in a postmetathetic transformation with a highly carbophilic gold-catalyst **C9**. In analogy to literature precedent[44a], the construction of the fully functionalized aromatic core was achieved by a photo-Fries rearrangement.[110]

4. Total Synthesis of a 4-Pyrone Marine Natural Product

4.1. Isolation & Structure

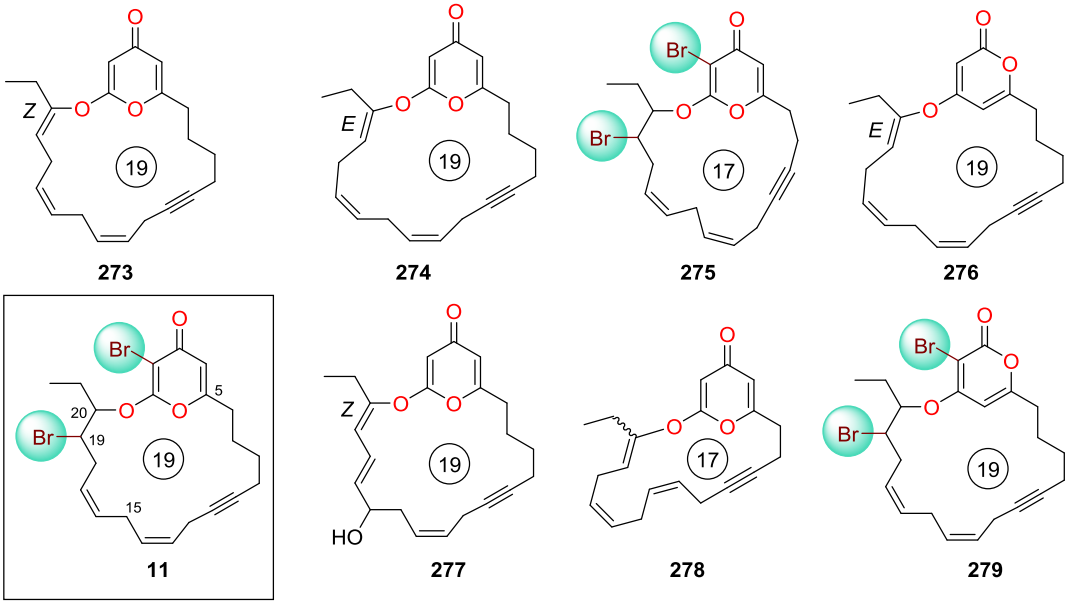
Over the last decades, a few 4-pyrone-containing marine natural products have been isolated from different species such as algae and fungi: A predominant number of these compounds exhibit exotic structural motifs that are mostly accompanied by a versatile and powerful biological activity. In particular, some of the 2-alkoxy-substituted 4-pyrones were discovered to feature antiviral, antibacterial and cytotoxic properties.[111] These compounds have therefore attracted considerable attention of synthetic organic and medicinal chemists. In contrast to other depicted 2-alkoxy-4-pyrones, compound **11** has escaped total synthesis so far. We found the dibrominated, polyunsaturated framework synthetically most interesting. Because of the embedment of the exceptional pyrone motif into a macrocyclic skeleton, pyrone **11** was identified as an exquisite candidate for the application of RCAM and π-acid catalysis. Therefore, we selected **11** to be the target of a total synthesis.



Scheme 81: Natural products isolated from marine animals and algae that contain a 4-pyrone motif.[111-112]

The marine metabolite **11** was first isolated by Kazlauskas and coworkers[112b] in 1982 from the red alga *Phacellocarpus labillardieri* that was originally collected at the southern Tasmanian coastline and re-isolated four years later at Flinders Reef (near Melbourne) by Fenical *et al*.[113] The sample gathered by Fenical was immediately freeze-dried after

collection. The raw material was then extracted and chromatographed on silica gel to give the dihalogenated 4-pyrone **11** in 0.7% yield based on dry algae.



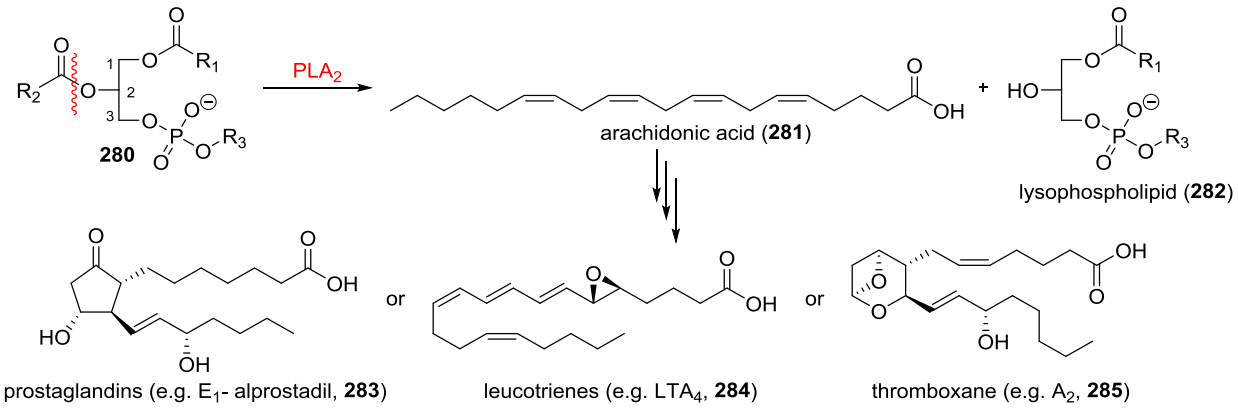
Scheme 82: 4- and 2-pyrone natural products isolated from the same algal origin.[112b, 113]

Several structurally related 2- and 4-pyrone-containing macrolides were isolated from the same algae (scheme 82). Presumably, the reported compounds were the first ketene-acetal-linked macrocycles extracted from natural sources. The 19- or 17-membered macrocyclic scaffolds are polyunsaturated, most of them displaying a 1,4-diene-6-yne. Moreover, the three representatives **11**, **275** & **279** were found to be dihalogenated, displaying a brominated 4-pyrone and a homoallylic bromide function which presumably holds latent non-classical carbocation reactivity.[114] Furthermore, the five macrolides **273**, **274**, **276**, **277**, & **278** bear an uncommon enol-ether in the macrocyclic scaffold which links the polyunsaturated chain to the heterocycle. The relative and absolute configurations of the two stereogenic centers at C19 and C20 was not elucidated by the isolation teams.

4.2. Biological Activity

In 1982, Kazlauskas *et al*. reported a neuromuscular blocking activity of the crude dichloromethane extracts that stimulated some interest in this class of compounds.[112b] In general however, biological data of this unorthodox class of marine compounds are extremely scarce. In a broad survey of numerous algal metabolites, Mayer *et al*. observed a considerable inhibition of bee venom phospholipase A_2 (PLA_2) by **11** in the micromolar range.[115] In fact, their report was the first describing bee venom inhibition in an in vitro

system by pure compounds isolated from marine algae. The dibrominated enol-ether **11** displayed a strong inhibitory activity with 93% inhibition at a 4.4 μM concentration. Even though bee venom phospholipase itself might not appear to be the most fascinating target, it served as an initial model system. Phospholipases A_2 are enzymes with a ubiquitous lipolytic activity and can be found in various cell types. These enzymes essentially hydrolyze the 2-acyl ester bond of 1,2-diacyl-sn-3 glycerophosphatides[116] liberating arachidonic acid and the corresponding lysophospholipid (scheme 83). Arachidonic acid is subsequently metabolized by further enzymatic processes to bioactive eicosanoids (e.g. prostaglandins, leucotrienes or thromboxanes). Therefore, PLA_2 plays a major role in essential physiological processes such as phospholipid turnover or in the regulatory mechanism controlling inflammatory responses. The mode of action can either be direct or indirect; the latter refers to the subsequent biochemical transformations of arachidonic acid and lysophospholipids which are products of the primary process.



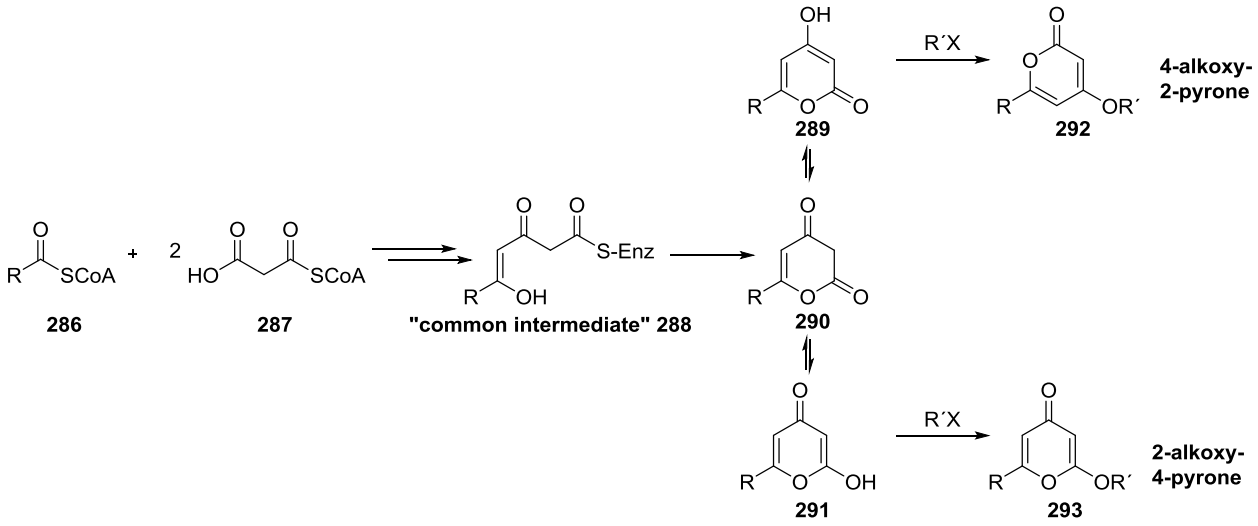
Scheme 83: Release of arachidonic acid from glycerol. Further metabolization of the fatty acid to eicosanoids (e.g. prostaglandins, leucotrienes or thromboxanes).

The crucial role of PLA_2 in the above mentioned metabolisms has prompted many researchers to undertake substantial research on PLA_2 inhibitors which could potentially render novel therapies for diseases that correlate with the enzyme activity such as septic shock, pancreatitis, rheumatoid arthritis etc. However, most of the previously examined candidates were limited in their in vitro potency and in vivo pharmacological activity.[115]

Although, preliminary biological investigations of the 4-pyrone **11** were promising and indicated a potential for several therapeutic applications, further research has to show whether **11** and its congeners inhibit other PLA_2 enzymes as well, especially mammalian types, and might therefore be relevant for future pharmacological studies.

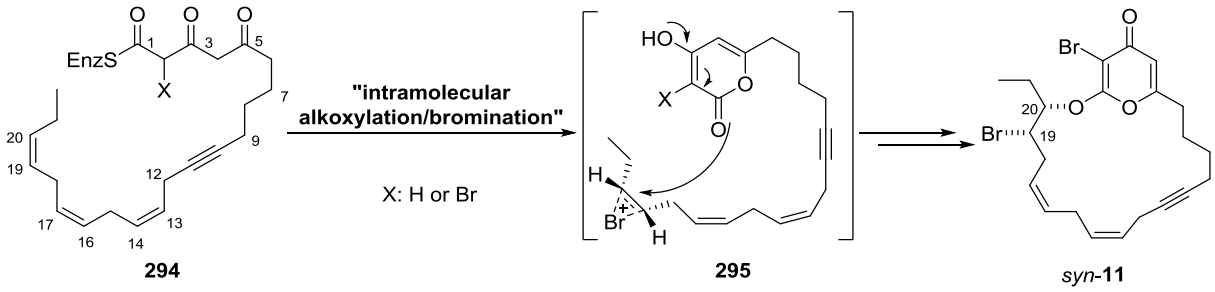
4.3. Biosynthetic Hypothesis

The coexistence of 2- and 4-pyrone-containing natural products in the same species of alga points to an acyclic enol of type **288** as the common intermediate. This 1,3-dicarbonyl could cyclize via enolization to **290** that tautomerizes to two different enol forms. These would be trapped by alkylation of the resulting hydroxyl-group as the 2-alkoxy-4-pyrone **293** or the corresponding 4-alkoxy-2-pyrone **292**.[113]



Scheme 84: Biosynthetic hypothesis by Fenical *et al*.[113]

Although the chosen target **11** was re-isolated several times and the overall structure was repeatedly confirmed, the stereogenic center at the bromohydrin function (C19 and C20) remained unassigned. At the beginning of our synthetic venture, we selected the *syn*-configured isomer which we believed more likely to possess the correct relative configuration.



Scheme 85: Hypothesized biogenetic rationale for the bromohydrin in *syn*-**11**.

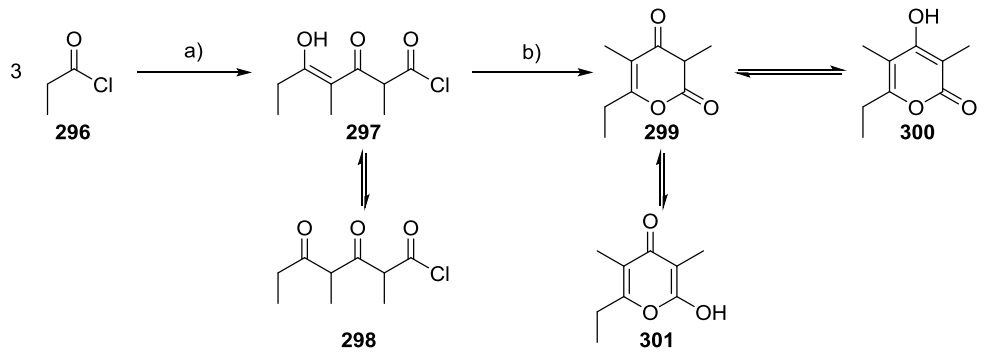
The polyunsaturated chain is believed to derive from an omega-3 fatty acid derivative which carries an unusual acetylenic group and is basically extended by two acetyl units presumably via a polyketide pathway. In the depicted scenario, the hypothesized acyclic precursor would

initially form a 4-hydroxy-2-pyrone **295**. The carboxyl group could undergo an intramolecular attack onto the most distal (*Z*)-alkene that is activated by a bromonium equivalent whereupon the heterocycle tautomerizes to the 2-alkoxy-4-pyrone. The resulting product would be *syn*-configured. The proposed pathway is consistent with the biosynthetic mechanism that is proposed for halogenations by haloperoxidases and O_2-dependent halogenases.[117] The normally prevailing halogen anions (X^-) are converted to more active halogenating species (e.g. of the type −OX) that promote C–X-bond formation. It is noteworthy that we are not able to decide whether the second bromine atom is introduced on the β-ketoester stage or after the 4-pyrone cyclization since there are no biosynthetic references up to date. However, with these available biosynthetic notions in mind we advanced our synthetic plan and decided to address the *syn*-configured isomer first.

4.4. An Overview of Methods for the Synthesis of 2- and 4-Pyrones

4.4.1. Traditional Protocols

Simple synthetic and natural 4-pyrone-containing compounds have been prepared using an array of methods that were mostly based on rather drastic conditions.[118] The first approach was reported by Wedekind and Häussermann in 1908.[118a] They observed the formation of trimeric condensation products from acid chlorides when treated with trimethylamine or pyridine as base. These β,δ-diketoacid chlorides were partially prevailing as their enol-tautomers that could be cyclized in the presence of dilute sulfuric acid under loss of HCl (scheme 86).

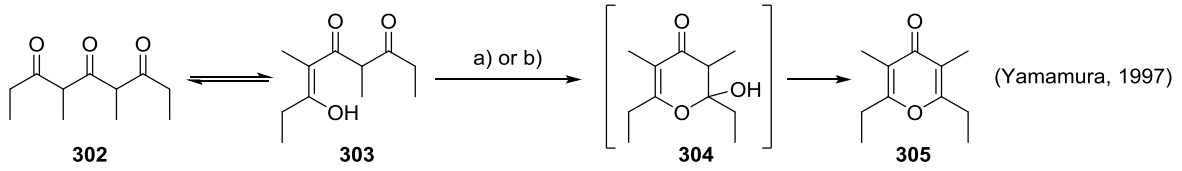


Scheme 86: Early reports of pyrone-derivatives by Wedekind and Häussermann.[118a] Conditions: a) Et_3N; b) H_2SO_4, quant over two steps.

The observed pyronone **299** was presumably obtained as a mixture of two tautomeric forms: the 4-hydroxy-2-pyrone **300** and the 2-hydroxy-4-pyrone **301** (*cf.* chapter **4.2.**). A clear

drawback of these methods is that acid-labile groups and sensitive stereogenic centers are compromised since strong acids and/or elevated temperatures are usually required to provide the 2-alkoxy-4-pyrone of the type **300**.

More selective and substantially milder methods for the synthesis of alkyl-substituted 4-pyrones were reported by Yamamura and coworkers.[112c] Two procedures were described using either a mixture of DMSO and oxalyl chloride or alternatively $Ph_3P{-}CCl_4$ as Lewis-acidic reagents that activate one of the carbonyl groups of the enolized triketone **303** for attack of the enol oxygen. The elimination of H_2O from the resulting dihydropyrone is presumably promoted by the electrophilic reagent as well (scheme 87).

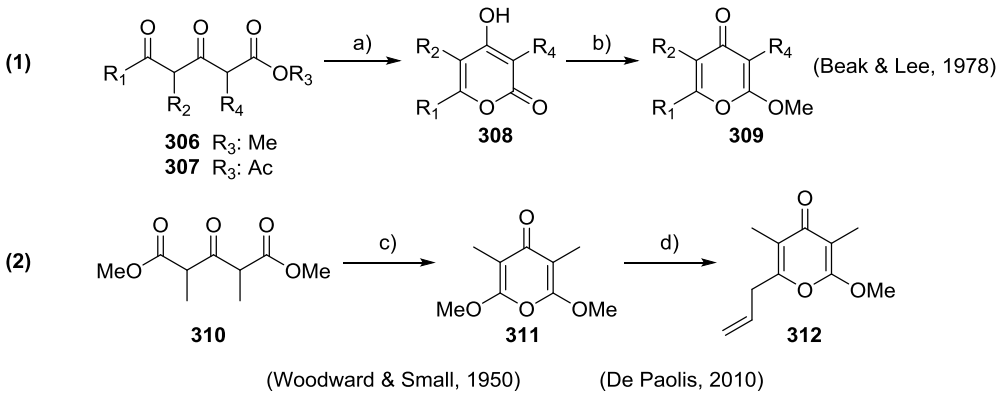


302 **303** **304** **305**

Scheme 87: Synthetic methods for the synthesis of 4-pyrone. Conditions: a) DMSO, $(COCl)_2$, CH_2Cl_2, −30 °C, 69%; b) PPh_3, CCl_4, THF, rt, 78%.[112c]

Due to the fact that the 2- and 4-pyrones can easily undergo interconversion via a pyronone intermediate as previously mentioned, most syntheses of 2-methoxy-4-pyrone-derivatives were based on the methylation of the predominant 4-hydroxy-2-pyrones obtained from either β,δ-diketo anhydrides **307** or β,δ-diketo esters **306**.[119] Standard methylating agents such as dimethyl sulfate,[119c, 120] methyl iodide[121] or trimethyloxonium tetrafluoroborate[122] have been employed, yet result in poor selectivity leading to mixtures of 2- and 4-pyrones. Beak and Lee[119f, 123] developed a method applying methyl fluorosulfonate which exhibits a remarkable preference for methylation of the oxygen at C2, albeit a large excess of the highly toxic reagent is required (scheme 88).

Another protocol was published by De Paolis and coworkers in 2010.[124] Their strategy avoided the problem of chemoselective methylation by exploiting the desymmetrization of the symmetric and therefore readily available 2,6-dimethoxy-3,5-dimethyl-4-pyrone (**311**).[125] Conjugate addition of a nucleophile – for example an allyl tin species – and subsequent elimination of methoxide yielded the corresponding 2-methoxy-dimethyl-4-pyrone derivative **312** (scheme 88).



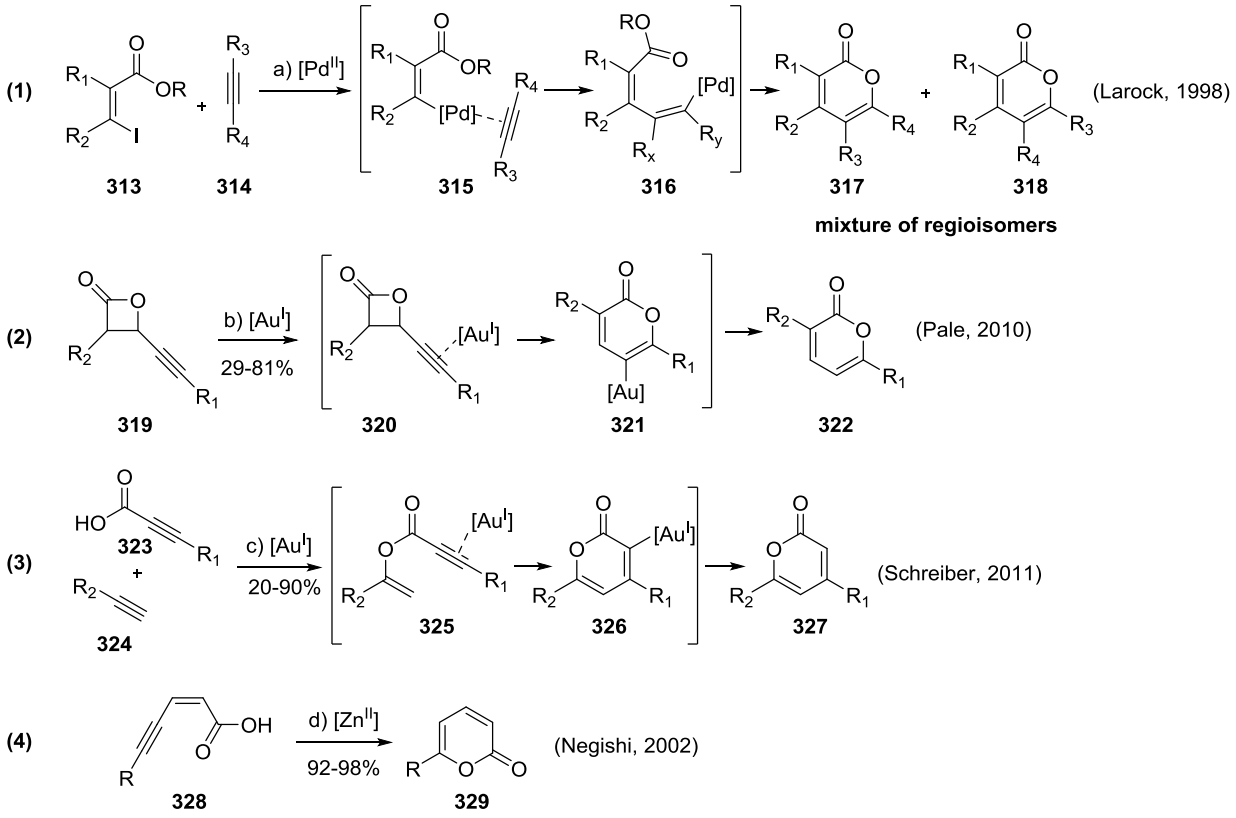
Scheme 88: Literature examples for the synthesis of 2-alkoxy-4-pyrones. Conditions: a) DBU, C_6H_6, Δ, 86%; b) $MeOSO_2F$, CH_2Cl_2, rt, 89%; c) H_2SO_4/SO_3, rt, 60%; d) *n*-Bu_3Sn(allyl), *n*-BuLi, THF, Δ, 65%.[122-125]

Several different nucleophiles could be introduced in this way providing a broad substrate scope. Nevertheless, this method holds an inherent disadvantage, since one of the two alkoxy groups is sacrificed in the reaction. This fact renders the method useless for the preparation of compounds that bear a more complex alkoxy substituent, as it is the case for 4-pyrone **11**.

4.4.2. Transition Metal Catalysis-Based Methods

Within the last two decades, a few transition-metal-catalyzed methods were reported for the preparation of 2-pyrones. Interestingly, these protocols comprised cycloaddition and annulation reactions at which usually one or two of the carbonyl groups were replaced by alkynes as carbonyl equivalents. The triple bonds were activated by different carbophilic transition-metal catalysts – also referred to as π-acid catalysts – for carbo- or alkoxymetalation reactions. Mild reaction conditions and therefore a broader scope speak for these catalyzed versions.

In 1998, Larock[126] described a Pd-catalyzed cascade reaction of β-iodopropenoates **313** and alkynes **314** (scheme 89). According to the proposed mechanism, the sequence starts with the oxidative addition of a alkenyl halide to palladium (0) to give a alkenylpalladium species **315** that coordinates to the alkyne before undergoing an insertion that forms another alkenyl palladium species **316**. After attack of the carbonyl oxygen onto the palladium, a seven-membered ring is formed that contracts to the 2-pyrone by reductive elimination.



Scheme 89: Transition metal-catalyzed methods for the formation of 2-pyrones. Conditions: a) $Pd(OAc)_2$ (5 mol%), Na_2CO_3, LiCl, DMF, 100 °C; b) [(*p*-$CF_3C_6H_4)_3PAu$]OTf (5 mol%), CH_2Cl_2, Δ; c) $[Ph_3PAu]Cl$ (5 mol%), AgOTf, CH_2Cl_2, rt; d) $ZnBr_2$ (5-10 mol%), THF, rt. [126-127]

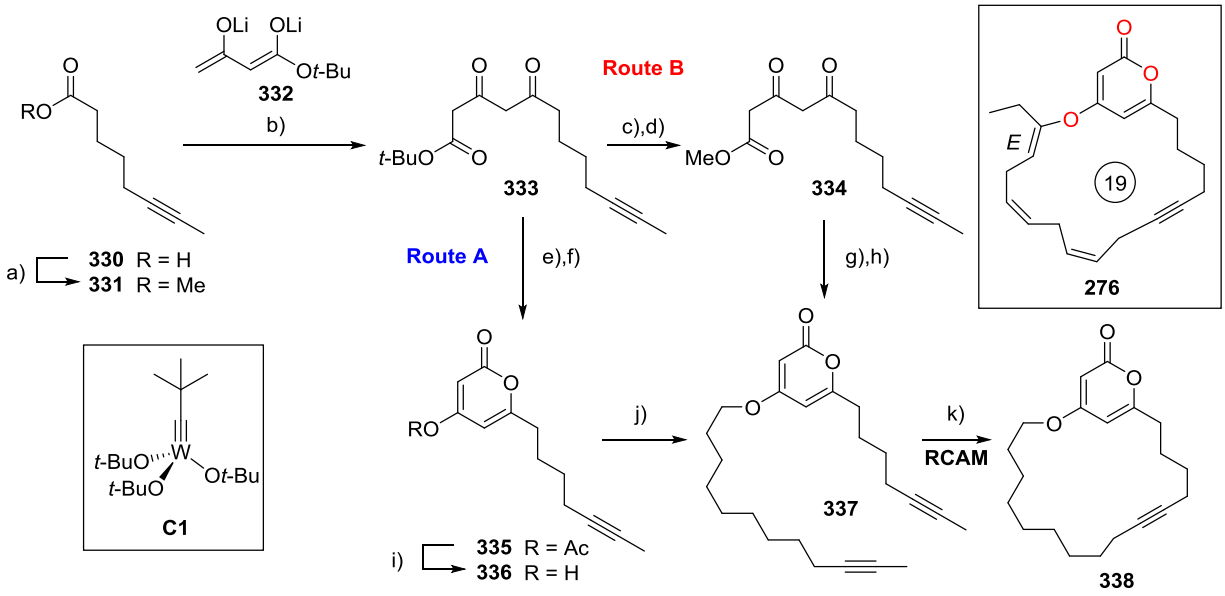
Furthermore, in the emerging field of π-acid catalysis, gold (I) and platinum (II) have gained considerable importance, especially in the synthesis of heterocycles.[16a, 17a, 21a, 26a] The large gold cation is "soft" and polarizable, displaying a higher affinity to the π-bond of the substrate than a proton (*cf.* chapter **1.2.**). The carbophilicity of gold (I) has been employed by Pale *et al*.[127a] for the preparation of 2-pyrones from β-alkynylpropiolactones **319** (scheme 89). Presumably, formation of a π-complex triggers a 1,3-oxygen shift. A two-component Au^I-catalyzed cascade reported by Schreiber and coworkers[127b, 128] is based on sequential activation of propiolic acid **323** and terminal acetylene derivative **324** to give alkenyl propiolate intermediate **325** that undergoes a 6-*endo*-cyclization yielding a cyclic oxonium species **326**. Deprotonation and protodeauration give rise to the 2-pyrone derivatives **327** (scheme 89). Another entry to this class of substrates was reported by Negishi *et al*.[127c] who managed to synthesize a small range of 2-pyrones from (*Z*)-enynoic acid derivatives **328** with catalytic amounts of $ZnBr_2$.

Among the reported examples (scheme 89) for the synthesis of 2-pyrones, gold (I)-catalysts seem to stand out as they can be easily modified by choice of the ancillary ligand. The

exceptional π-acidity displayed by the metal center often allowed the reactions to proceed at ambient temperature. However, to the best of the author´s knowledge, the noble-metal catalyzed direct synthesis of 4-pyrones has only been mentioned once in the literature (see chapter **4.4.3.**).[129]

4.5. Preceding Studies of the Fürstner Group on Macrocyclic Pyrone Derivatives

Foregoing synthetic investigations[130] of the Fürstner group targeted the 4-alkoxy-2-pyrone natural product **276** that was isolated together with the dibrominated 2-alkoxy-4-pyrone **11**. In a model study,[131] the metacyclophane skeleton of **338** – omitting further sites of unsaturation – was synthesized to test the two envisioned cyclizations (scheme 90). The unusual triple bond motif in the macrocyclic frame represents an obvious handle for RCAM. Moreover, a biomimetic approach for the construction of the 2-pyrone was chosen.[111a, 132] The required substrate was identified to be either β,δ-diketo ester **333** or **334** which were prepared from octynoic acid **330** by esterification and Claisen condensation with dianion **332**.[133]

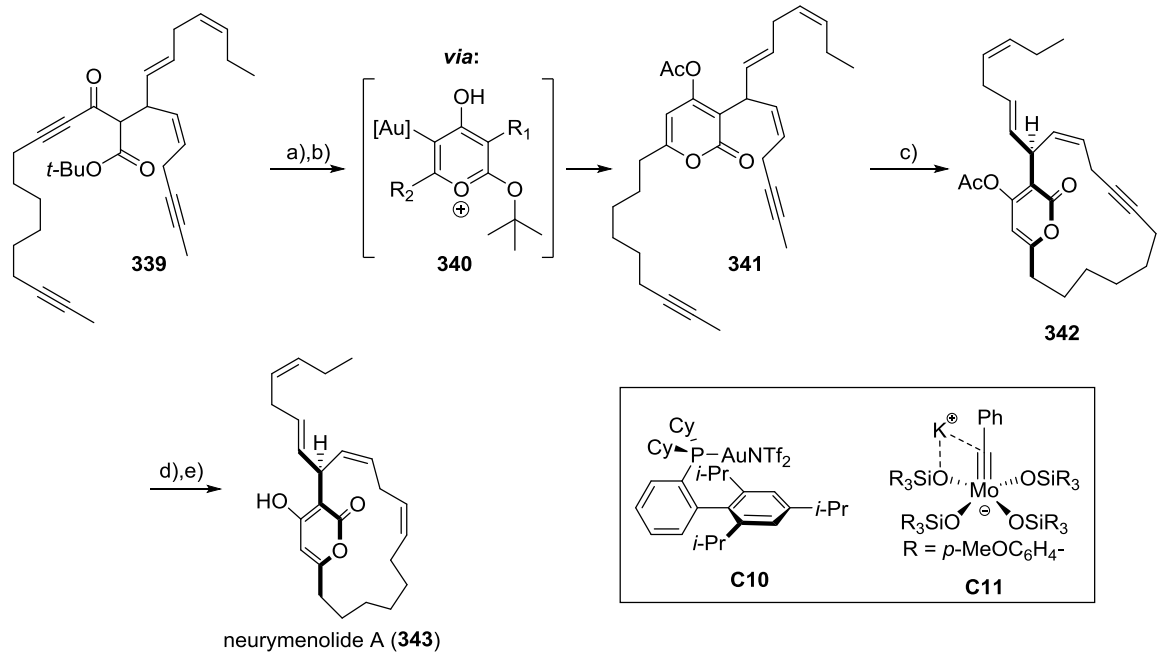


Scheme 90: Model studies for the synthesis of a 4-alkoxy-2-pyrone natural product by Fürstner *et al*. Conditions: a) $TMSCHN_2$, pentane/MeOH, 85%; b) **332**, TMEDA, THF; then *n*-BuLi, 0 °C, 58%; c) TFA, CH_2Cl_2; d) $TMSCHN_2$, MeOH, 71% over two steps; e) TFA, CH_2Cl_2; f) Ac_2O; g) DBU, toluene, Δ; h) 12-bromo-2-dodecyne, MeCN, 53% over two steps; i) K_2CO_3, cat. MeOH, 70% over three steps; j) 12-bromo-2-dodecyne, Et_3N, MeCN, 56% k) **C1** (16 mol%), toluene, 80 °C, 84%.[131]

The 2-pyrone was assembled via two routes: either from the free acid in the presence of acetic anhydride (Route A) or after a hydrolysis/esterification sequence to the methyl ester

334 in the presence of DBU (Route B). However, the question whether these conditions would be tolerated by the fully functionalized sidechains remained unanswered. The second alkyne was subsequently introduced by *O*-alkylation yielding the RCAM precursor **337** which smoothly underwent the formation of cycloalkyne **338** in the presence of catalytic amounts of Schrock´s tungsten alkylidyne complex **C1**. Thus, RCAM had proven to be a suitable tool for the construction of the 2-pyrone-containing macrocycle.[131]

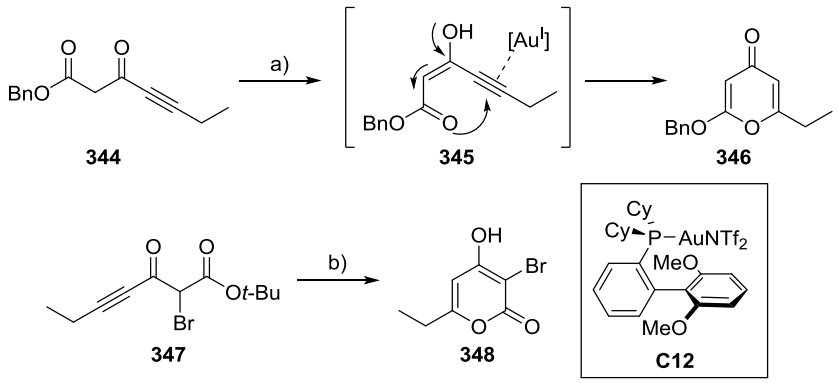
In another work, Fürstner *et al*.[129] reported the total synthesis of neurymenolide A (**343**, scheme 91), an algal metabolite that features similar structural elements as 4-pyrone **11** and 2-pyrone **276**. The 4-hydroxy-2-pyrone of **343** is embedded in a *para*-cyclophane scaffold that displays several non-conjugated unsaturated sites. These characteristics adumbrated the challenges that were encountered during the synthetic endeavor. Interestingly, some of the conclusions made during the course of this project were helpful for the projected synthesis of the 4-pyrone **11**. The construction of the 4-alkoxy-2-pyrone **341** from a γ,δ-unsaturated β-ketoester **339** was conducted using the [XPhosAu]NTf_2 complex **C10**. Key to success was the cleavage of the *tert*-butyl group off the pyronium intermediate **340** to liberate the 2-pyrone.



Scheme 91: Synthesis of the 4-alkoxy-2-pyrone neuromenolide A (**343**) by Fürstner *et al*. Conditions: a) **C10** (5 mol%), $MeNO_2$/AcOH; b) Ac_2O, Et_3N, CH_2Cl_2, 0 °C, 73% over two steps; c) **C11** (5 mol%), MS 5 Å, toluene, 88%; d) Lindlar catalyst, quinoline (cat.), H_2 (1 atm), 84%; e) K_2CO_3, MeOH, 0 °C.[129]

The triple bond in conjugation to the carbonyl group can in fact be considered most electron-deficient which would – contrary to the experimental outcome – result in a decreased affinity to the electrophilic gold catalyst **C10**. It is believed that the catalyst is essentially able to interact with all six unsaturated sites; however, only one interaction is consequential. In a further exciting observation, the stereochemical integrity of the (*Z*)-configured double bonds was found uncompromised under the mentioned conditions. After having constructed the heterocyclic core of neurymenolide A (**343**) the macrocycle was closed by RCAM using the molybdenum alkylidyne **C11**.[7, 13c] Finally, the total synthesis of **343** was completed in two subsequent steps by semi-reduction of the alkyne and acetate cleavage (scheme 91).

Fürstner *et al*. were also able to show that replacement of the *tert*-butyl group on the ester by a benzyl group could direct the reaction pathway towards the formation of the 2-hydroxy-4-pyrone **346** (scheme 92).[129] The 4-pyrone was furnished with exceptional ease using only 1 mol% of the [SPhosAu]NTf_2 **C12**. Moreover, it was demonstrated for the *tert*-butylated substrates that α-brominated β-ketoesters **347** cyclize readily to the corresponding 4-hydroxy-2-pyrone **348** (scheme 92).[129]



Scheme 92: Gold-catalyzed 4-pyrone synthesis by Fürstner *et al*. Conditions: a) **C12** (1 mol%), AcOH, 94%; b) **C12** (1 mol%), HOAc, 82%.[129]

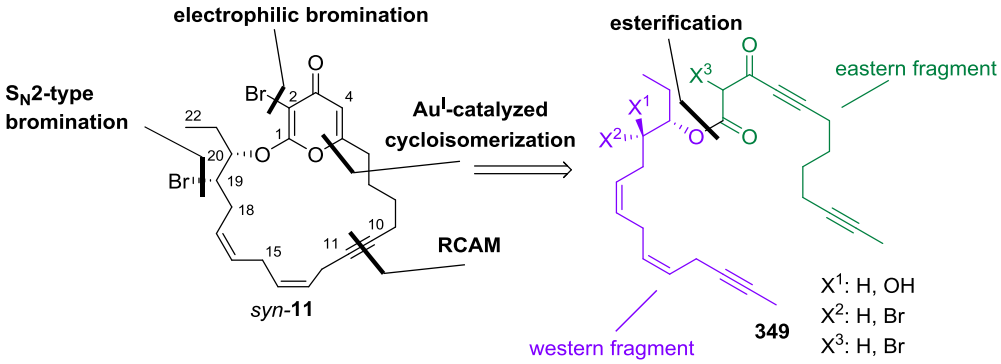
The seminal achievements on synthesizing a 4-pyrone and a halogenated 2-pyrone prompted us to envisage the total synthesis of the marine metabolite **11**. In addition, one successful RCAM was presented. Collectively, the precedents encouraged us to pursue a total synthesis comprising these key transformations.

4.6. Total Synthesis of a 4-Pyrone Natural Product

4.6.1. Preliminary Considerations

The compounds bearing the skipped diene/yne moiety were expected to be rather fragile as the energy barrier for the migration of the double bonds into conjugation was assumed to be low. Additionally, the internal alkyne on the rim of the macrocycle would require a differentiated synthetic approach to secure the selective construction of all sites of unsaturation side by side. Furthermore, the acetylenic unit in the lipophilic tether would serve as gateway for closing the polyunsaturated backbone. Of course, RCAM was the method of choice for this endeavor (scheme 93).

The selective construction of a 2-alkoxy-4-pyrone should be triggered by a gold-catalyzed activation of an oxo-alkynoate. This acyclic precursor **349** would allow a disconnection at the ester function yielding two similarly sized fragments: the eastern β-ketoacid fragment and the western alcohol fragment (scheme 93).



Scheme 93: General disconnection analysis of *syn*-**11**.

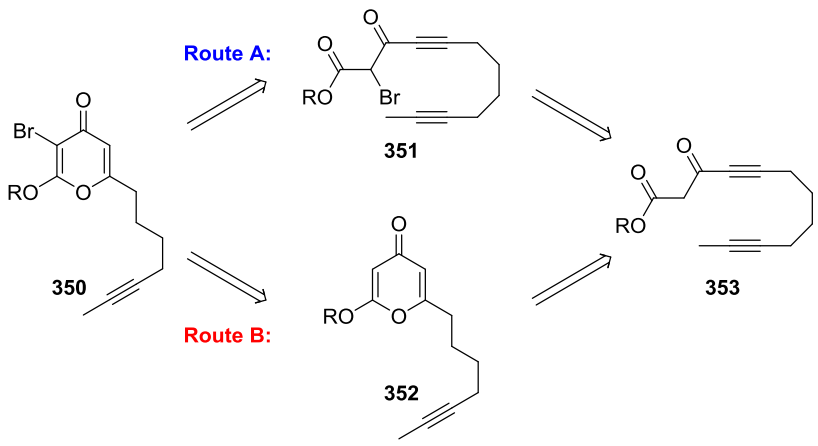
On the basis of the proposal for the relative configuration of the two stereogenic centers (chapter **4.2.**), the *syn*-diastereomer of **11** was chosen as primary target for our synthetic efforts. Based on our hypothesis that the *syn*-bromohydrin presumably derived from an electrophilic activation of a (*Z*)-olefin by a bromonium equivalent, we planned to introduce the bromine atom at C19 by a nucleophilic substitution reaction of the corresponding 1,2-*anti*-diol. Furthermore, the introduction of the bromine atom on the 4-pyrone had to be considered. The ketene-acetal side of the heterocycle appeared sufficiently electron-rich and the directing effect of the enol ether should render the C2-position reasonably reactive for a regioselective electrophilic bromination. However, compounds of the type **349** bear several delicate sites of unsaturation along the lipophilic chain and treatment with an electrophilic species should be exercised with extreme caution.

Having defined the key steps of the synthesis, the question regarding the order of these transformations – especially with respect to the installation of the bromine atoms – remained.

It needs to be mentioned that some valuable groundwork of the projected total synthesis was compiled by coworkers of the Fürstner group. Dr. Tsutomu Fukuda[134] elaborated the initial synthetic strategy for the synthesis of β-keto-acid fragment and the diol-fragment. Attempts to complete the synthesis of *syn*-**11** were focused on the late-stage introduction of both bromine atoms. Furthermore, Dipl.-Chem. Gerit Pototschnig[135] contributed to this work by conducting model studies for the late-stage bromination on 1,2-*anti*-diol derivatives. The respective work will be referenced in the course of this chapter.

4.6.2. Model Studies for the Electrophilic Bromination of the 4-Pyrone

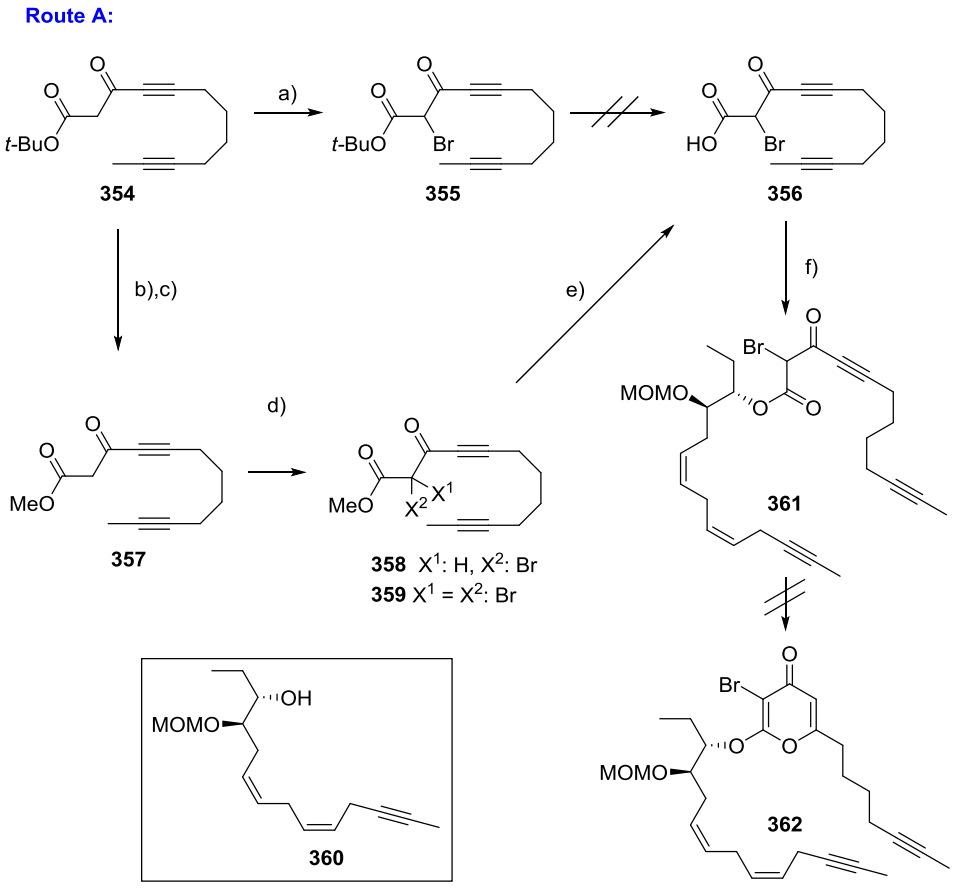
For the examination of a suitable strategy for the 4-pyrone synthesis, two different routes were considered. Because previous results documented that simple α-halogenated oxo-alkynoates can be cyclized to 4-pyrones,[129] an early bromination of the β-ketoester **353** was taken into account (Route A). On the other hand, the late-stage bromination of the 4-pyrone moiety was evaluated. Therefore, reagents were to be tested on a simple 2-alkoxy-4-pyrone of the type **352**, which could be obtained in one step from the corresponding β-ketoester **353** (Route B).



Scheme 94: Route A: Cyclization of a brominated β-ketoester **351**. Route B: Bromination of the 4-pyrone **352**.

Bromination of β-ketoester **354** was tested applying NBS as standard brominating reagent. The α-brominated product **355** was isolated in 55% yield (scheme 95). However, efforts to remove the *tert*-butyl group failed since the reaction competed with an extremely fast decarboxylation to an α-bromoketone. Reversing the order of the steps by cleaving the *tert*-

butyl group prior to bromination also was met with failure as the labile β-ketoacid decomposed under the bromination conditions. The limited options for its cleavage are a detriment of the *tert*-butyl group, as only concentrated TFA worked well. Alternatively, we set out to prepare the equivalent methyl ester **357** from **354** by cleavage of the *tert*-butyl group and subsequent methyl ester formation with trimethylsilyl diazomethane. Methyl ester **357** was then treated with one equivalent of NBS in the presence of an amine base.[136] In this case, an almost equimolar mixture of the monobrominated product **358**, the dibrominated product **359** and the starting material **357** was obtained which could be separated by flash chromatography. Saponification of the monobrominated β-ketoester **358** was achieved with a moderate 52% yield. The compound **356** partially decomposed upon purification.

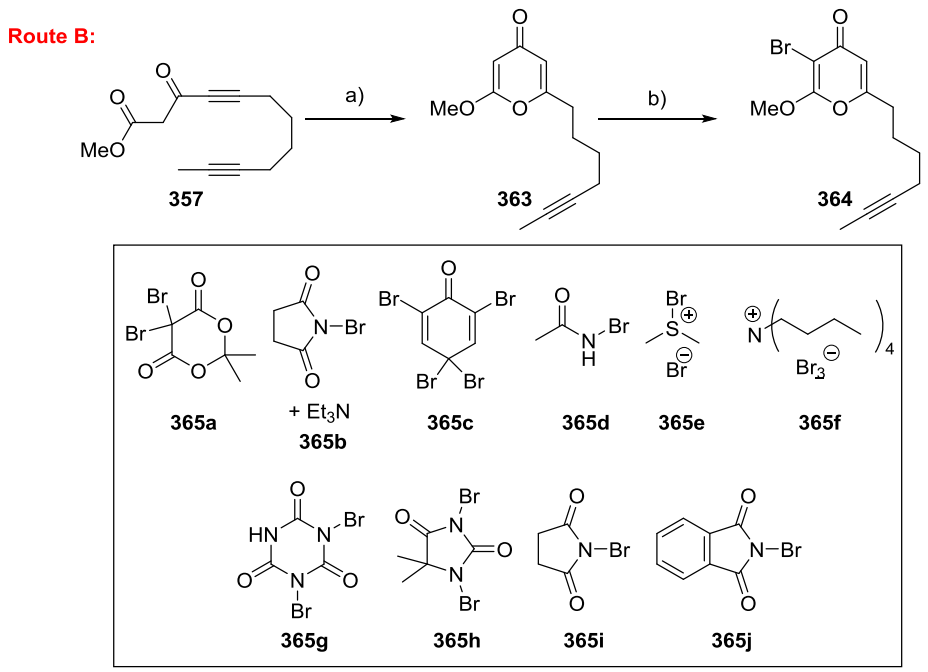


Scheme 95: Investigation of the bromination of the β-ketoesters **354** and **357**. Conditions: a) NBS, 2,6-lutidine, acetone, 0 °C, 96%; b) TFA, CH_2Cl_2 (1:1), rt, 55%; c) $TMSCH_2N_2$, MeOH, CH_2Cl_2, 0 °C, 40-70%; d) NBS, 2,6-lutidine, acetone, 0 °C to rt, **358** (26%), **359** (21%), **357** (28%); e) NaOH, THF/MeOH/H_2O (1:1:1), 0 °C to rt, 52%, f) **360**, DMAP (10 mol%), DCC, CH_2Cl_2, 0 °C, 46%.

Nevertheless, the little material was subjected to an esterification with alcohol fragment **360**. The experimental data indicated the formation of the desired ester **361** that was

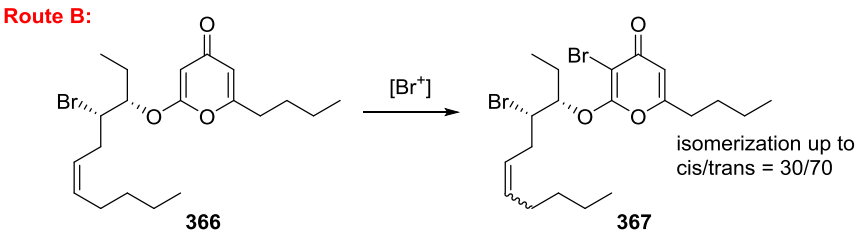
directly treated with [SPhosAu]NTf_2 **C12** to test if the desired 2-alkoxy-3-bromo-4-pyrone **362** would be formed. Unfortunately, the cyclization product was not observed even after extended reaction times upon increasing the catalyst loading. Therefore, this entry to the 3-bromo-4-pyrone was abandoned.

The late-stage bromination of the 4-pyrone seemed to be the only sensible alternative and a careful investigation would be worth all the effort. Therefore, the 2-methoxy-4-pyrone **363** was prepared from the previously described methyl oxo-alkynoate **357** and served as a model substrate for testing a number of electrophilic brominating reagents (**365a**-**j**). The efficiency of these reagents was compared in a screening experiment. To this end, a solution of the 4-pyrone **363** in tetrahydrofuran was treated with one equivalent of the corresponding reagent and the NMR-spectroscopic data of the resulting mixture were compared. Reagents **365a-f** caused several side reactions. However, in most cases moderate amounts of the desired 2-methoxy-3-bromo-4-pyrone **364** were observed among other polybrominated and degradation products. In contrast, reagents **365g**-**j** led to a relatively clean formation of the desired brominated product with only trace impurities. In conclusion, the four reagents **365g**-**j** were found to trigger a reasonably selective electrophilic bromination on the 3-position of the 4-pyrone.



Scheme 96: Model studies for the electrophilic bromination of the 4-pyrone. Conditions: a) [SPhosAu]NTf_2 **C12** (5 mol%), MeCN/AcOH (4:1), rt, 83%; b) [Br^+] (**365a**-**365i**), THF, rt.

In further studies, the electrophilic bromination with NBS was tested on substrate **366**[135] comprising a (*Z*)-olefin. In this case, the bromination proceeded well, but the single (*Z*)-configured double bond in product **367** was isomerized to a significant extent. Lowering the temperature only stopped the bromination whereas the competing isomerization was still observed. It occurred to us that an even greater hurdle would be faced in case of the fully functionalized substrate which would offer ample opportunities for isomerization and further side reactions.

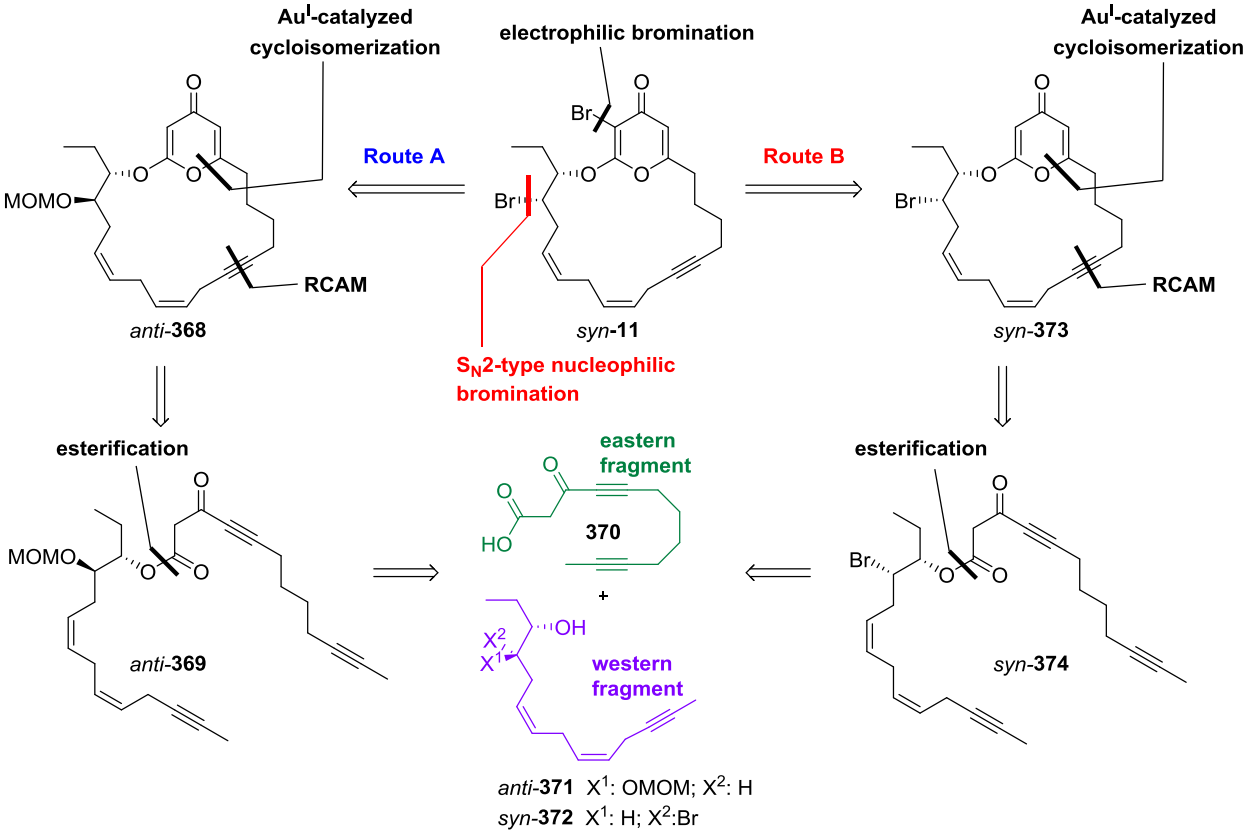


Scheme 97: Studies of the electrophilic bromination on a model substrate.

The results of our model studies suggested that serious difficulties were to be expected for the introduction of the second bromine atom. Yet, in absence of sensible alternatives, the bromination as the final step of the synthesis seemed inevitable.

4.6.3. Total Synthesis of a 4-Pyrone Natural Product: Retrosynthetic Analysis

In the foregoing model studies, the cyclization of the α-halogenated β-ketoester **361** to the corresponding 4-pyrone failed (scheme 95); therefore, the installation of this bromine functionality was placed late in the planned synthetic strategy. For the introduction of the second bromine atom two alternative routes were identified:



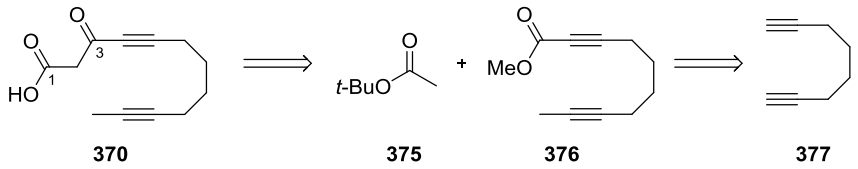
Scheme 98: Retrosynthetic analysis of *syn*-**11**.[134]

Route A: The introduction of both bromine atoms was envisioned as the first retrosynthetic disconnection leading back to homoallylic alcohol *anti*-**368**. The ring-closing triple bond metathesis was projected after the formation of the 4-pyrone from the γ,δ-unsaturated β-ketoester *anti*-**369**. This ester should be obtained from alcohol *anti*-**371** and β-ketoacid **370**.

Route B: Again, the installation of the bromine atom at the 4-pyrone was scheduled late-stage. The bromine atom in the side chain though was to be introduced to the alcohol fragment *syn*-**372** before the construction of the macrocycle and the 4-pyrone moiety.

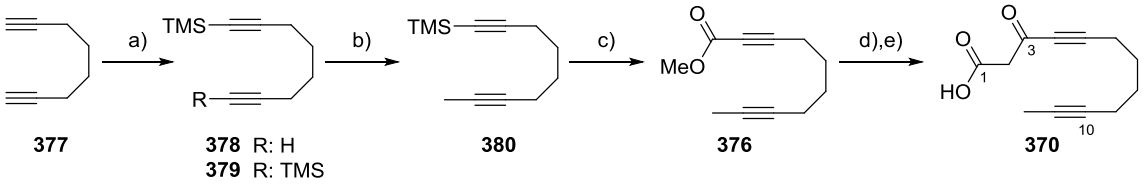
4.6.4. Synthesis of the Eastern β-Ketoacid Fragment

The β-ketoacid **370** relates to a methyl alkynoate **376** via a Claisen condensation with *tert*-butyl acetate **375**.



Scheme 99: Retrosynthetic analysis of β-ketoacid **370**.

The preparation of the β-ketoacid **370** was straightforward. It began with the silylation of 1,7-octadiyne (**377**) to give the monosilylated compound **378** as major product along with the disilylated **379**.[137] After methylation of the remaining terminal alkyne, the direct transformation to the methyl ester **376** was accomplished by subsequent treatment with methyllithium and chloroformate.[138] Finally, a β-ketoester was formed by Claisen condensation of **376** with *t*-butyl acetate (**375**); the product was treated with TFA to give acid **370** (scheme 100). Notably, **370** was very sensitive and decomposed at ambient temperature within hours. Therefore, it had to be prepared promptly before the fragment coupling.

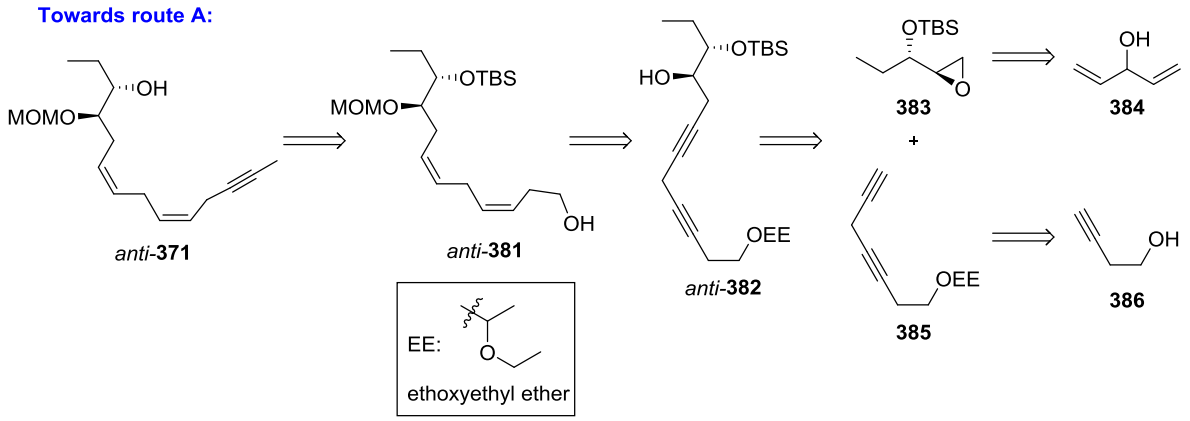


Scheme 100: Synthesis of the β-ketoacid **370** from 1,7-octadiyne (**377**). Conditions: a) LiHMDS, THF, −78 °C; then TMSCl, −78 °C to rt, 52% (**378**), 17% (**379**); b) *n*-BuLi, THF, −78 °C; then MeI, −78 °C to rt, 91%; c) MeLi, THF, −78 °C to 0 °C; then $ClCO_2Me$, −78 °C to rt, 86%; d) *t*-BuOAc (**375**), LDA, THF, −78 °C; then **376**, 87%; e) TFA, CH_2Cl_2, rt, 99%.[134]

By this means, the C1-C10 fragment **370** was synthesized in five efficient steps in 35% overall yield. It could be shown that the sequence initially described by Dr. Fukuda is scalable to gram quantities.

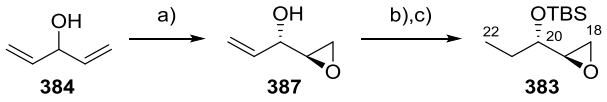
4.6.5. Synthesis of the Western 1,2-Diol Fragment (Route A)

The triply unsaturated alcohol *anti*-**371** can be further disconnected by a Corey-Fuchs reaction that would introduce the methyl-capped alkyne. The diene *anti*-**381** was traced back to the skipped diyne unit *anti*-**385** by way of semihydrogenation.



Scheme 101: Retrosynthetic analysis of the western 1,2-*anti*-diol fragment.

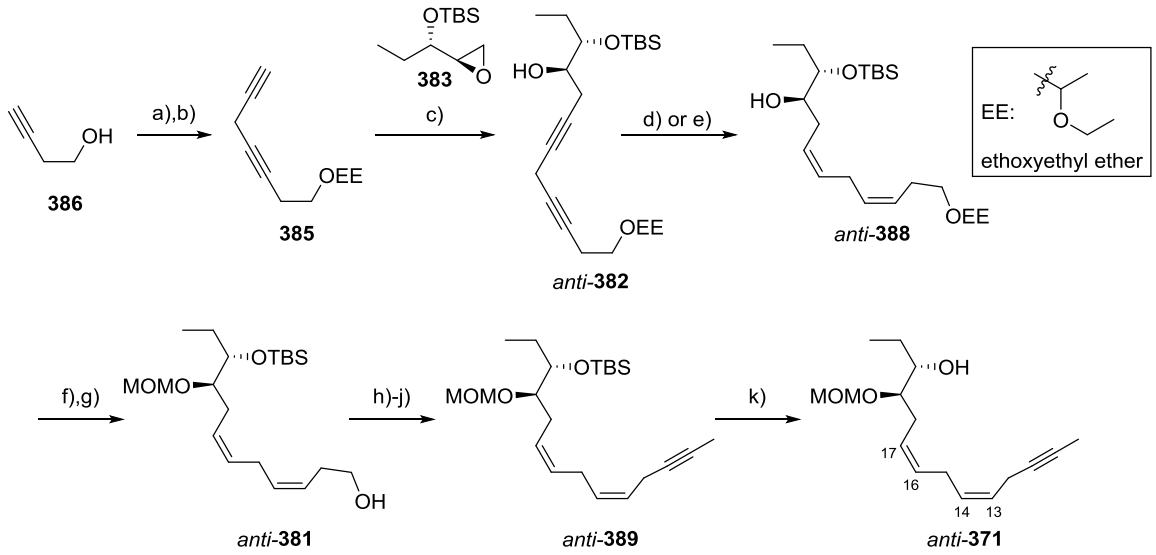
The stereogenic centers in the targeted 1,2-*anti* diol **382** were to be defined by an asymmetric Katsuki-Sharpless epoxidation and a diastereoselective epoxide opening with a diacetylenic unit **385** and epoxide **383**. The latter was prepared in three steps from 1,4-pentadien-3-ol (**384**) which was epoxidized using 13 mol% of (+)-DIPT, 10 mol% of Ti(O*i*-Pr)$_4$ and cumene hydroperoxide as oxidant. A close monitoring of the temperature during addition of the reagents was crucial for securing good yields. Alcohol **387** was then protected as *tert*-butylsilyl ether and the remaining terminal olefin was subsequently hydrogenated over palladium on charcoal to give the C18-C22 fragment **383** in excellent yield. Due to the simple and reliable protocols, the epoxide **383** was obtained in up to 7.6 grams by this route.



Scheme 102: Synthesis of epoxide **383** by asymmetric epoxidation. Conditions: a) (+)-DIPT (13 mol%), Ti(O*i*-Pr)$_4$ (10 mol%), cumene hydroperoxide, CH_2Cl_2, MS 4 Å, −35 °C, 82%; b) TBSCl, imidazole, DMF, 0 °C to rt, 90%; c) H_2, Pd/C, EtOAc, rt, 95%.

The synthesis of the skipped diyne **385** commenced with commercially available 3-butyn-1-ol (**386**). Protection of the primary alcohol as ethoxyethyl ether and a copper-(I)-mediated coupling with propargyl bromide established the skipped diyne in 82% yield (scheme 103). Next, epoxide **383** was to be opened selectively at the sterically less hindered side. For this

purpose, **385** was deprotonated at the terminal alkyne site and formation of a BF_3-adduct was then followed by slow addition of epoxide **383** at −78 °C to give the homopropargylic alcohol *anti*-**382**. As an excess of three equivalents of diyne **385** was required to reach full conversion of the epoxide, the yield suffered from the formation of several byproducts that made the isolation of the delicate product somewhat laborious. Compounds **385** and *anti*-**382** proved to be extremely sensitive and decomposed noticeably within one day, even if stored at −20 °C. Directly after preparation, the skipped diyne *anti*-**382** was reduced to the respective skipped diene *anti*-**388** by using either a nickel boride catalyst[134] or Lindlar´s catalyst[135] for the chemoselective semihydrogenation. The diene *anti*-**388** appeared to be slightly more stable as its precursor and could be stored in the freezer in a matrix of benzene glass. This procedure was employed for all subsequent intermediates since the skipped diene, specifically at the C13-C14 π-system was observed to isomerize at ambient temperature to the thermodynamically more stable (*E*)-alkene.



Scheme 103: Synthesis of the skipped diene/yne fragment *anti*-**371**. Conditions: a) ethyl vinyl ether, *p*-TsOH·H_2O, rt, 90%; b) EtMgBr, THF, 45 °C; then CuCl (5 mol%), 50 °C; then propargyl bromide, 60 °C, 82%; c) *n*-BuLi, Et_2O, −78 °C; then BF_3·Et_2O, −78 °C; then **383**, −78 °C, 59%; d) H_2 (1 atm), P-2 Ni, ethylenediamine, EtOH, rt, 74%; e) H_2 (1 atm), Pd (5% on $CaCO_3$, unpoisened, reduced), quinoline, CH_2Cl_2, rt, 87%; f) MOMCl, NaI, *i*-Pr_2EtN, CH_2Cl_2, 35 °C, 90%; g) PPTS, MeOH, 30 °C, 90%; h) DMP, CH_2Cl_2, rt; i) PPh_3, CBr_4, THF, −78 °C 85% over two steps; j) *n*-BuLi, THF, −78 °C; then MeOTf, −78 °C, 79%; k) TBAF, AcOH, THF, 40 °C, 85%.

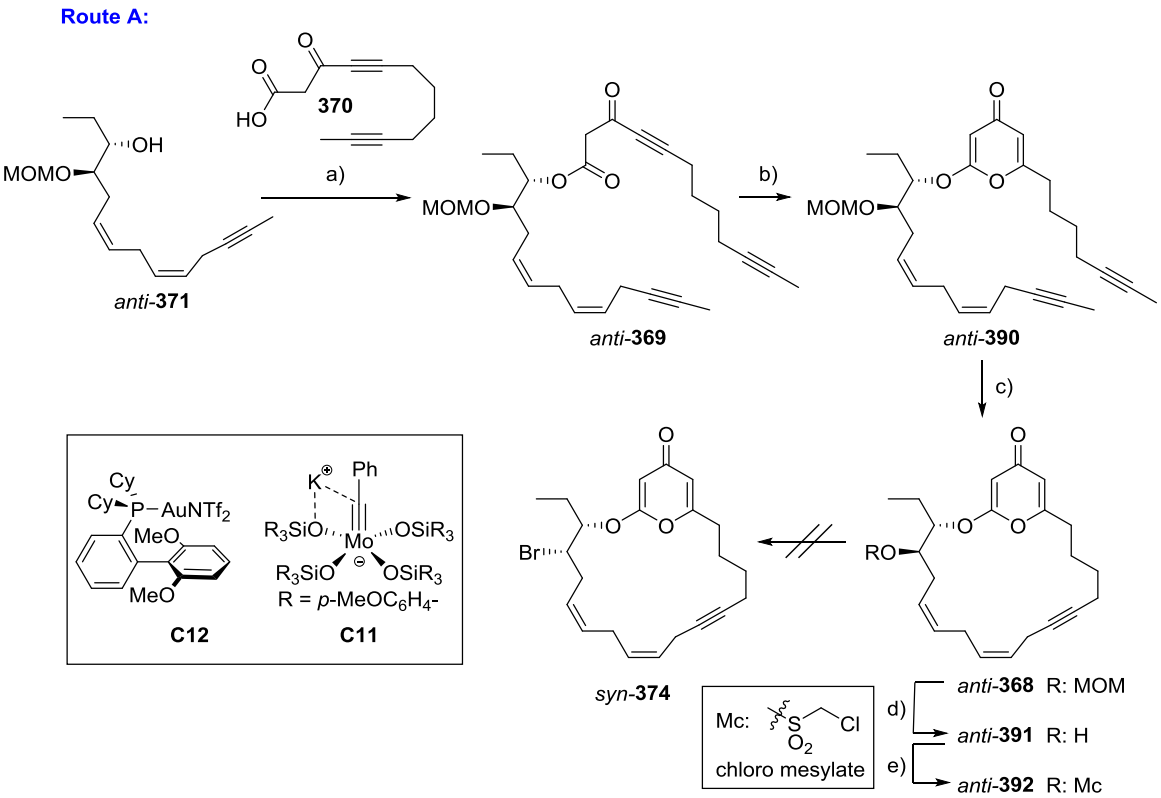
The synthetic sequence was continued with orthogonal protection of the secondary alcohol as MOM-ether using standard conditions. The primary alcohol was then exposed to pyridinium *p*-toluenesulfonate to cleave the acetal group. Treatment of the alcohol *anti*-**381** with Dess-Martin periodinane (DMP) followed by a Corey-Fuchs reaction delivered the

methyl-capped alkyne *anti*-**389** on gram-scale (scheme 103). For the selective removal of the TBS ether, the substrate was stirred for several days at 40 °C in the presence of excess TBAF.[134]

4.6.6. Assembly of the Fragments and Formation of the Macrocycle (Route A)

The esterification of *anti*-**371** and the β-ketoacid **370** under Steglich conditions employed DCC and a catalytic amount of DMAP. The oxo-alknyoate *anti*-**369** was obtained in excellent yield. The material was a mixture of keto/enol tautomers and turned out to be less stable than the preceding alcohol fragment. Thus, β-ketoester *anti*-**369** was immediately engaged in the next step. The 4-pyrone *anti*-**390** was formed under mild conditions as the exclusive product when exposed to 5 mol% of [SPhosAu]NTf_2 (**C12**). Acetic acid was used as co-solvent as it was demonstrated that it would enhance the reaction rate by accelerating the protodeauration step. In this way, a potential diauration was essentially suppressed.[129] The projected RCAM proceeded smoothly with 10 mol% of ate-complex **C11** giving the cycloalkyne *anti*-**368** in 90% yield. At this stage, the synthetic efforts were directed toward the installation of the missing bromine atoms. The S_N2 reaction at the side of the lipophilic backbone was studied first. Thus, the MOM-ether had to be removed. After an extensive screening of reagents that mostly caused decomposition of the fragile material, it was found that $AlCl_3$ could cleave the ether without compromising the stereochemical integrity of the *anti*-diol or the non-conjugated (*Z*)-olefins. Interestingly, the deprotection was only successful if a large excess of anisol was added. Presumably, anisol ligates the metal center and thus tempers the Lewis acidity sufficiently for a clean reaction to take place. With the free alcohol *anti*-**391** in hand, the bromination was investigated. The use of $P(octyl)_3$ and CBr_4, conditions previously reported by Crimmins[139] and Murai[140] for the substitution of a secondary homoallylic alcohol by a bromide, failed in case of *anti*-**391** (scheme 104). Moreover, the chloromesylate *anti*-**392**, which was expected to exhibit a reasonable leaving group ability, was subjected to the bromination conditions but this substrate also failed to give the corresponding brominated product.[134]

In summary, all attempts to brominate the sidechain on the advanced intermediates were met with failure and the scarcity of the delicate advanced material did not allow for a broader screening of reaction conditions.[134]

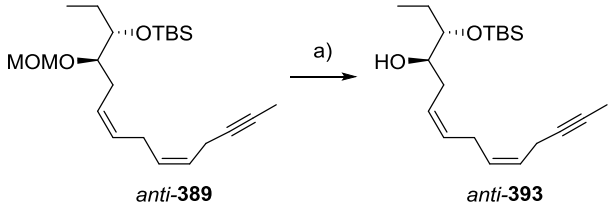


Scheme 104: Fragment assembly and formation of the cycloalkyne *anti*-**392** (Route A). Conditions: a) **370**, DMAP, DCC, CH_2Cl_2, 0 °C, 90%; b) **C12** (5 mol%), MeCN/AcOH (5:1), rt, 86%; c) **C11** (5 mol%), toluene, MS 5 Å, rt, 90%; d) $AlCl_3$, ansiol, CH_2Cl_2, −78 °C to −50 °C, 90%; e) McCl, LiBr, THF, rt, 35%.[134]

Finally, the discussed strategy was abandoned as it seemed too risky to leave this challenging transformation for the end of the synthesis. In the following, the bromination was pursued with an earlier intermediate that was available in bigger amounts.

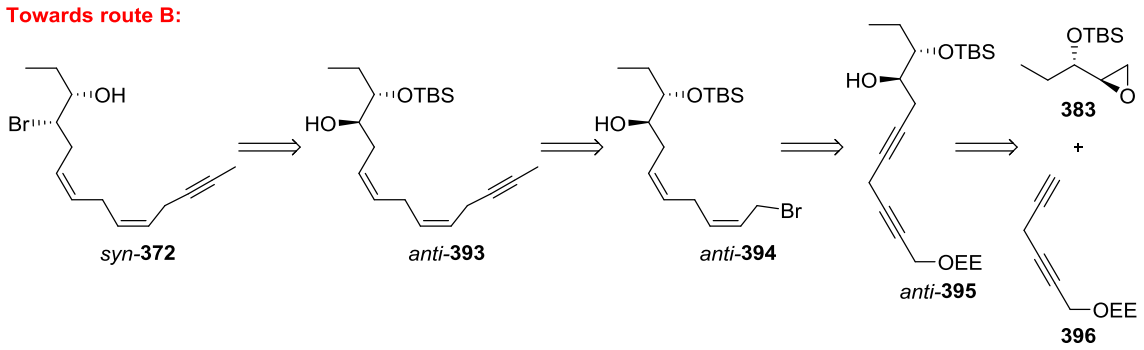
4.6.7. Revised Strategy for the Western Alcohol Fragment (Route B)

In the revised approach, alcohol *anti*-**393** was identified as appropriate substrate for the nucleophilic substitution reaction with a bromide. Two entries to compound *anti*-**393** were considered . Firstly, the bis-protected *anti*-diol **389** could be converted to alcohol *anti*-**393** by selective cleavage of the MOM-ether using dimethylboron bromide.[141]



Scheme 105: Selective cleavage of the MOM-ether. Conditions: a) Me_2BBr, CH_2Cl_2, −78 °C, 86%.

Secondly, a shorter alternative preparation of the skipped diene/yne was pursued, since the preceding approach for the synthesis of alcohol *anti*-**393** was deemed somewhat lengthy with eleven steps in the linear sequence. It was presumed that the appending alkyne in *anti*-**393** could also be installed by a copper-mediated coupling of an allylic bromide *anti*-**394** with a propynyl Grignard instead of by the previously employed Corey-Fuchs chemistry. This disconnection would lead back to a propargylic alcohol *anti*-**395** that is by one carbon atom shorter than its equivalent in the previous retrosynthesis (scheme 101). Furthermore, the protection of the homoallylic alcohol might be avoided on this route.

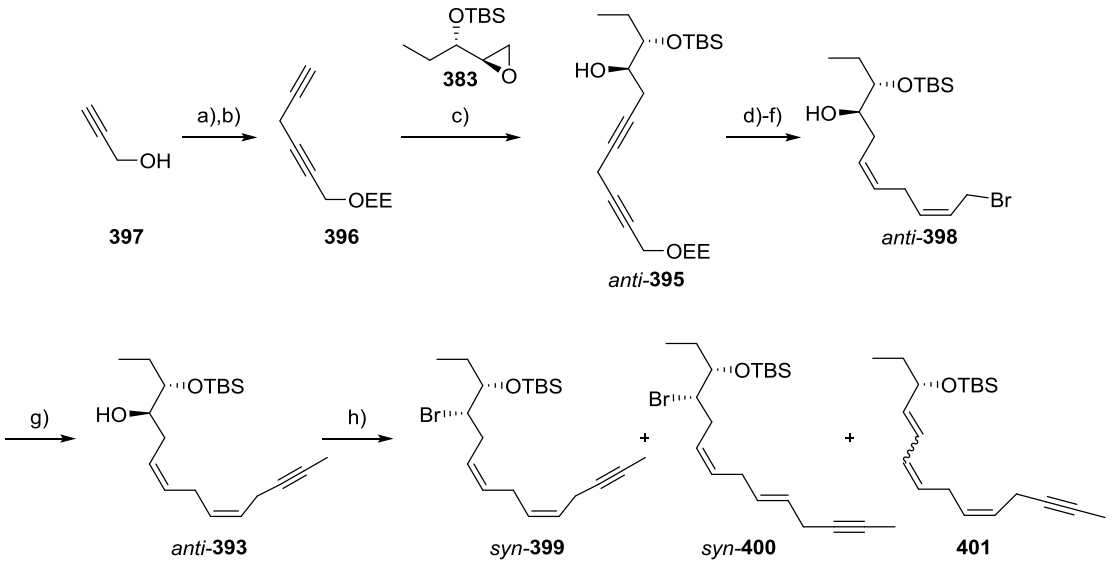


Scheme 106: Retrosynthetic analysis for the western alcohol fragment *anti*-**372** (route B).

The forward synthesis of the 1,2-*anti*-diol **393** started with the protection of the propargylic alcohol **397** as ethoxyethyl ether. The coupling with ethynylmagnesium bromide in the presence of catalytic amounts of copper (I) chloride furnished the skipped diyne **396**. The lipophilic fragment was elaborated by BF_3-mediated epoxide opening with **383**. After cleavage of the acetal in almost quantitative yield, the diyne *anti*-**395** was subjected to semihydrogenation. We resorted to nickel boride in methanol for the chemoselective reduction as these conditions had been established before.[134] Strict monitoring of the reaction mixture allowed us to isolate the diene in 79% yield along with only trace amounts of over-reduced byproducts. Next, the primary alcohol was converted to the corresponding bromide *anti*-**398** under Appel conditions. The desired product was obtained in excellent yield, provided that the temperature was kept at 0 °C. The resulting highly sensitive allylic bromide *anti*-**398** was immediately submitted to the next step.

Our motivation to try the direct coupling of *anti*-**398** with a propynyl Grignard was inspired by preliminary studies in our group.[129] To our delight, the projected copper-mediated coupling of *anti*-**398** proceeded surprisingly well. The formation of an undesired S_N2'product

was not observed at −15 °C. In conclusion, alcohol *anti*-**393** was formed in 29% overall yield via an efficient and scalable eight-step sequence from 1,4-pentadien-3-ol **384**.



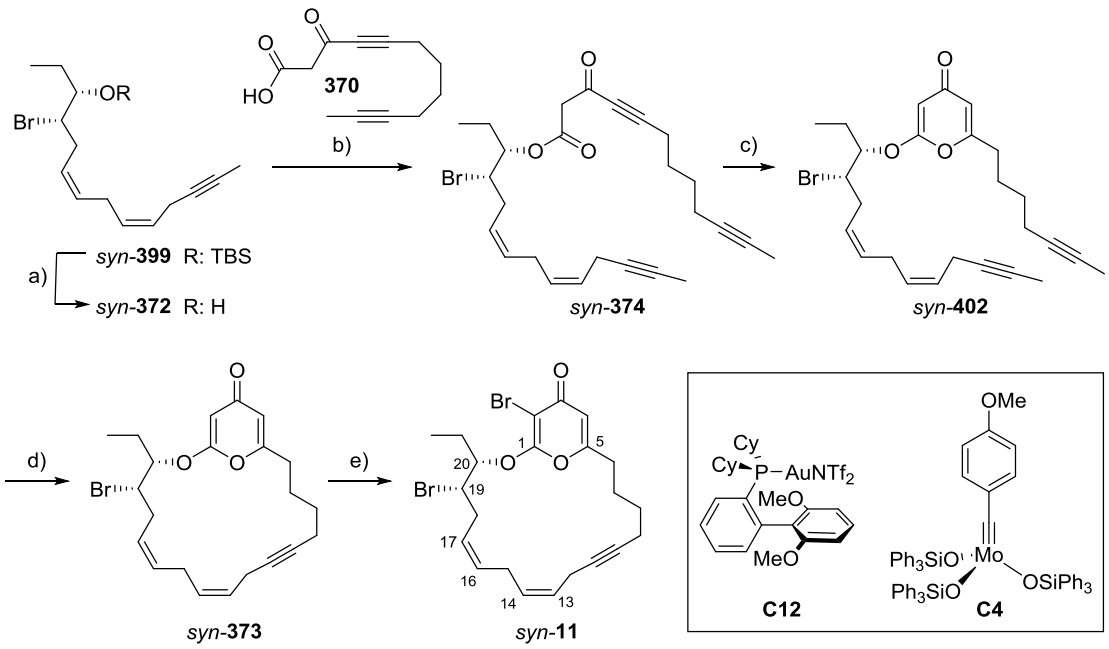
Scheme 107: Revised synthesis and bromination of the 1,2-diol *anti*-**393**. Conditions: a) ethyl vinyl ether, *p*-TsOH·H_2O (10 mol%), 0 °C, 84%; b) EtMgBr, THF, 45 °C; then CuCl (5 mol%), propargyl bromide, 60 °C, 68%; c) *n*-BuLi, THF, −78 °C; then $BF_3{\cdot}OEt_2$; then **383**, −78 °C, 72%; d) PPTS, MeOH, 30 °C, 98%; e) H_2 (1 atm), P2-Ni (25 mol%), EtOH, 79%; f) CBr_4, PPh_3, CH_2Cl_2, 0 °C, 91%; g) propynylmagnesium bromide, CuI (50 mol%), THF, −15 °C to −10 °C, 81%; h) CBr_4, PPh_3, toluene, 65 °C, *syn*-**399** (60%), *syn*-**400** (~12%), **401** (~11%).

Having *anti*-diol **393** in hand, we next scrutinized the bromination with PPh_3 and CBr_4. At ambient temperature, merely the isomerization of the double bonds was triggered. Interestingly, the desired product was formed when the temperature was elevated. However, a complex mixture of isomerization and elimination products was obtained. Considerate optimization finally led to a reliable protocol for the bromination. The starting material and the reagents were mixed at 0 °C and the solution was directly placed in a pre-heated oil bath. It was found that a temperature of 65 °C was necessary for the reaction to proceed. Additionally, the reaction time was kept as short as possible to reduce the amount of byproducts. In this way, bromide *syn*-**399** was isolated in reproducible 60% yield along with around 12% of the isomerized (*Z*),(*E*)-configured bromide *syn*-**400** and 11% of the elimination product **401** (scheme 107).

The same delicacy of the material was observed throughout the synthesis. Therefore, compound **396** and its successors were treated with utmost care by storing the material only for a short time and keeping all intermediates that contain a skipped diyne or diene/yne motif at −20 °C in benzene glass.

4.6.8. Completion of the Total Synthesis of *syn*-11 (Route B)

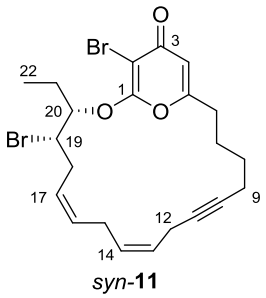
With the brominated fragment *syn*-**399** and acid **370** in hand, we approached the remaining steps of the synthesis again. At first, the alcohol function in *syn*-**399** was unmasked for the upcoming esterification. Hydrofluoric acid buffered with pyridine was found to cleave the silyl ether at 0 °C without compromising the stereochemical integrity of the material. The obtained alcohol *syn*-**372** was then esterified with **370** using the previously established conditions. β-Ketoester *syn*-**374** was obtained in good yield as mixture of keto/enol-tautomers. The ester was found to be extremely unstable and was therefore immediately subjected to the [Au^{I}]-catalyzed cyclization. The 4-pyrone *syn*-**402** was furnished in the presence of acetic acid by 3 mol% of **C12** in 97% yield. Hence, the way was cleared for the macrocyclization by RCAM using molybdenum alkylidyne **C4**[13c] which furnished the macrocycle *syn*-**373** with ease.



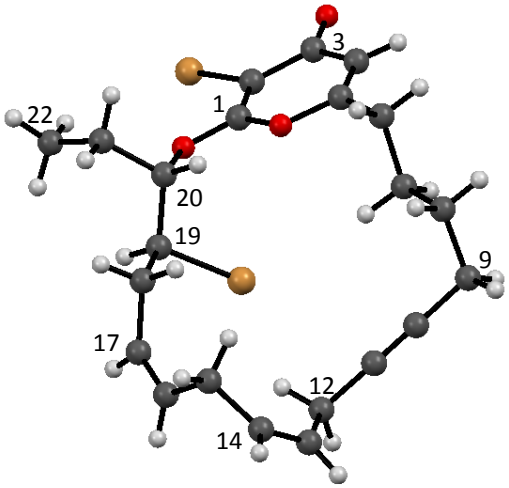
Scheme 108: Fragment assembly and completion of the total synthesis of *syn*-**11**. Conditions: a) HF·pyridine, THF, 0 °C, 83%; b) **370**, DCC, DMAP (30 mol%), CH_2Cl_2, 0 °C, 70%; c) **C12** (3 mol%), MeCN/AcOH (4:1), 97%; d) **C4** (5 mol%), MS 5 Å, toluene, rt, 82%; e) NBS, THF, rt, 40%.

At this stage, the first bromine atom had been successfully installed in the homoallylic position of the lipophilic tether. By careful handling of the isolated brominated intermediates and close monitoring of the reactants during the transformations, it was possible to arrive at the monobrominated cycloalkyne *syn*-**373** (scheme 108).

Finally, we ventured to try the electrophilic bromination of delicate *syn*-**373**. To our delight, the dibrominated compound could be obtained, when freshly recrystallized NBS was added in one portion to a solution of *syn*-**373** in THF. Again, it was observed that the reaction proceeded much cleaner at ambient temperature than at 0 °C. Yet, the (*Z*)/(*E*)-isomerization took place to a certain degree. Under close monitoring, we were contented with receiving the product *syn*-**11** in well reproducible 40% yield. In this way, ten milligrams of *syn*-**11** were prepared that allow for further evaluation of the biological properties.



syn-**11**



Picture 109: Structure of *syn*-**11** in the solid state. Co-crystallized MeCN was removed for simplicity. The complete crystallographic data can be found in the appendix.

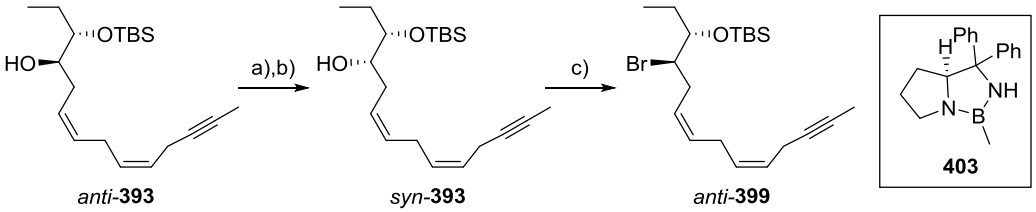
Crystals of *syn*-**11** could be grown.[112b] The X-ray data confirmed the proposed configuration at the stereogenic centers. Apart from the essentially linear alkyne (177.8° and 179.6°), it can be seen that the two (*Z*)-alkenes are not in plane but contorted. This fact likely explains why a migration of the alkenes into conjugation was never observed. Furthermore, an overlap of the π-sytem of the acetylenic bond with the π-system of the vicinal alkene could explain the preferential (*E*)/(*Z*)-isomerization at the C13-C14 double bond. Surprisingly, the dihedral angle (179.1°) of the protons at the bromohydrin junction shows an antiperiplanar orientation which indicates that the conformation in the solid state differs considerably from the one in solution where the coupling constant ($^3J_{H,H}$ = 4.6 Hz) of the respective protons suggests a synclinal orientation (*cf*. appendix).

Finally, the obtained analytical and spectroscopic data were compared to the literature. It must be noted that the reported NMR data were not very detailed, as only the median was given for the multiplets and the coupling constants were rounded to one digit after the

comma. However, the ^{13}C NMR data of *syn*-**11** agree very well with the reported data of the natural product (see table 14 in the appendix). The ^{1}H NMR data match too, except for the shifts of the vinyl protons as well as the proton at C20 which differ by 0.07 – 0.27 ppm. For the protons at the stereogenic centers at C19 and C20, a coupling constant of $^{3}J_{H,H}$ = 4.6 Hz was observed which is in line with the 5 Hz reported for the natural product. The overall match of the data sets was therefore sufficient to propose *syn*-**11** to represent the marine metabolite which is in accordance to our biosynthetic hypothesis. For further validation, we decided to prepare *anti*-**11** since our synthetic route allowed its preparation by a few modifications starting from the advanced intermediate *anti*-**393** (chapter **4.7.1.**).

4.7. Total Synthesis of *anti*-11

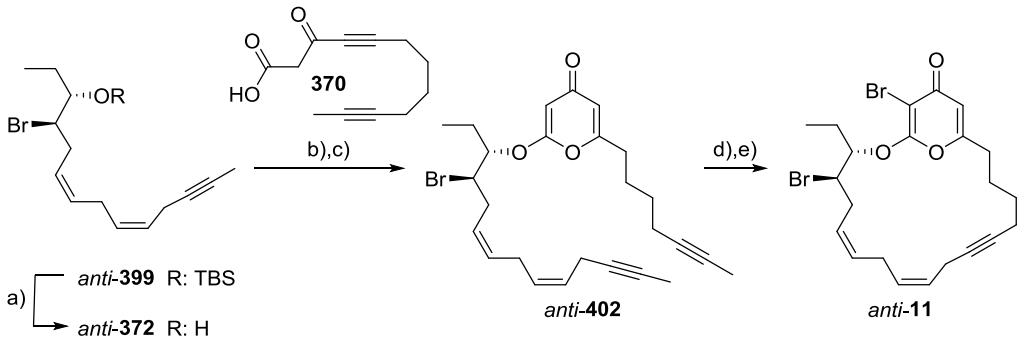
The *anti*-configured diastereomer of **11** was prepared in analogy to *syn*-**11**. For the sake of brevity and convenience the inversion of the stereogenic center at C19 was achieved by an oxidation/reduction sequence. Alcohol *anti*-**393** was treated with DMP to give the corresponding ketone which was reduced to alcohol *syn*-**393** in a diastereoselective fashion using (*S*)-(−)-2-methyl-CBS-oxazaborolidine (**403**) and catecholborane as hydride source.[142] Eventually, the product was obtained in 82% yield with excellent diastereoselectivity. The obtained alcohol *syn*-**393** was then subjected to the same bromination conditions as described for the *anti*-diastereomer to give the S_N2-product *anti*-**399** in acceptable yield.



Scheme 110: Twofold inversion of the 1,2-*anti* diol (**393**) to 1,2-*anti* configured bromide **399**. Conditions: a) DMP, CH_2Cl_2, 0 °C to rt; b) (*S*)-(−)-2-methyl-CBS-oxazaborolidine (**403**), toluene, rt; then catecholborane, −78 °C, 81% over two steps; c) CBr_4, PPh_3, toluene, 65 °C, 55%.

Next, the TBS-ether was removed, the resulting alcohol *anti*-**372** was esterified with acid **370** and the corresponding β-ketoester was treated with [SPhosAu]NTf_2 (**C12**) to form the 2-alkoxy-4-pyrone *anti*-**402**. The dibrominated cycloalkyne *anti*-**11** was established by treatment of *anti*-**402** with 5 mol% of the molybdenum alkylidyne complex **C4** and subsequent NBS-bromination. The previously established procedures worked very well on the diastereomeric compounds and the yields varied only marginally.

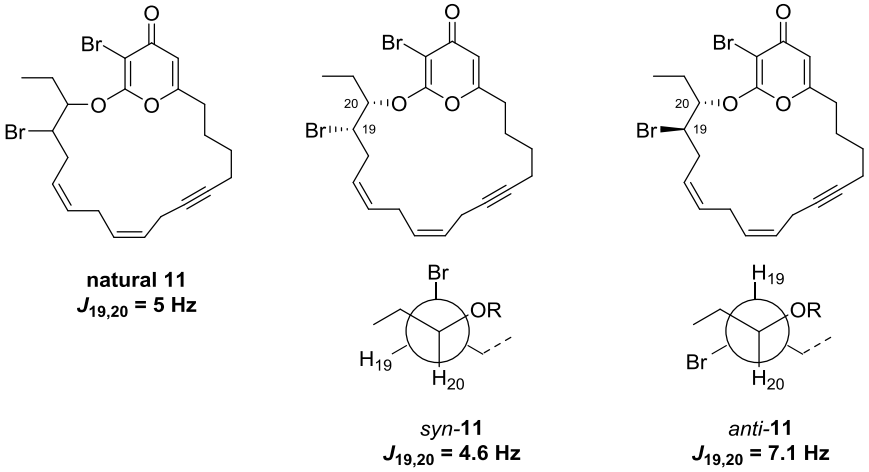
Notably, during earlier studies concerning the 2-pyrone model **276** (chapter **4.5.**) an alternative entry to alcohol fragment *anti*-**393**. This entry would win in the overall step count.[143]



Scheme 111: Fragment assembly, key cyclizations and late-stage bromination. Conditions: a) HF·pyridine, THF, 0 °C to rt, 55%; b) **370**, DCC, DMAP (30 mol%), CH_2Cl_2, 0 °C, 78%; c) **C12** (3 mol%), MeCN/AcOH (5:1), rt, 84%; d) **C4** (5 mol%), MS 5 Å, toluene, rt, 80%; e) NBS, THF, rt, 40%.

The spectroscopic data of *anti*-**11** deviated distinctly from the data of natural **11** (see table 15 in the appendix). Therefore, the unique algal metabolite **11** was confirmed to feature a relative *syn*-configuration[144] which is consistent with our biosynthetic proposal (chapter **4.2.**).

4.8. Structure Elucidation and Conclusion



Scheme 112: Observed coupling constants and the corresponding Newman projections of synthetic compounds *syn*-**11** & *anti*-**11**.

In summary, the 4-pyrone marine metabolite *syn*-**11** was prepared by a 14-step total synthesis in 3.2% overall yield. All materials passed through were found to be highly delicate. This fact made the use of mild and efficient methods absolutely necessary. Therefore, we employed a π-acidic gold-catalyst for the construction of the 2-alkyoxy-4-pyrone.

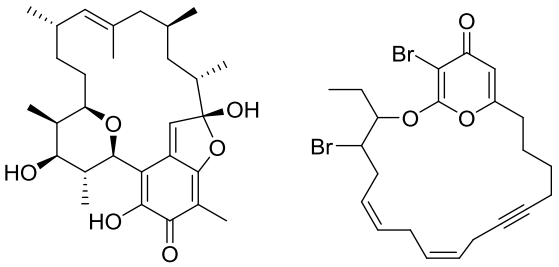
Furthermore, the formation of the cycloalkyne was achieved by ring-closing alkyne metathesis using our molybdenum alkylidyne catalyst. Both transformations were highly chemo- and regioselective and furnished the corresponding products at ambient temperature. Our results therefore demonstrate that gold-catalysis and RCAM are not only extremely efficient but even highly compatible with a fragile skipped diene/yne motif.

The *anti*-configured diastereomer *anti*-**11** was prepared by a diastereoselective inversion of configuration of an advanced intermediate. The comparison of the reported NMR data to the data of the synthetic stereoisomers *syn*-**11** and *anti*-**11** revealed the relative configuration of the natural 4-pyrone.

A virtually perfect fit of the carbon shifts and the characteristic coupling constant of the protons at C19-C20 in case of the *syn*-isomer and significant deviations in case of *anti*-**11** render the assignment of the relative configuration unambiguous. Furthermore, the X-ray diffraction of *syn*-**11** confirmed the proposed relative stereochemistry.[145]

5. Summary & Conclusions

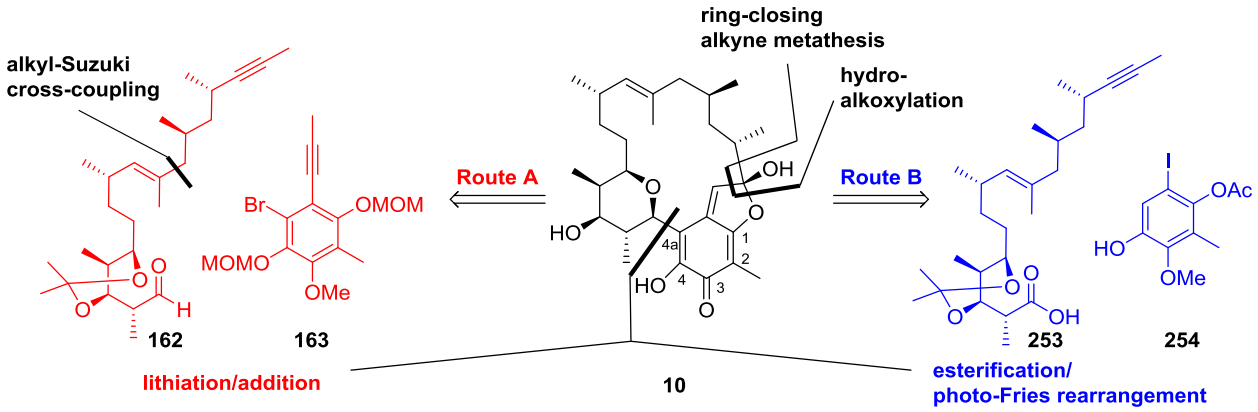
The objective of this thesis were two total syntheses based on the combined application of ring-closing alkyne metathesis (RCAM) and π-acid catalysis as key methodologies. RCAM has been spotlighted in recent synthetic endeavors to be a highly effective tool for the construction of macrocyclic natural products.[7] However, the obtained cycloalkyne motifs have been mainly engaged in semihydrogenations.[146] To date, only few examples are known that describe postmetathetic transformations leading to heterocyclic motifs, and thus leaving ample opportunities for further exploration. Complex heterocyclic fragments, whose derivation from an alkyne is not obvious, could potentially be established in this way. In the course of this thesis, the use of π-acid catalysts, particularly gold-catalysts, was identified as a potent strategy for the activation and the consequent functionalization of alkynes in general and cycloalkynes in particular. With this duet of methods in mind, the antibiotic macrolide (−)-kendomycin (**10**) and the polyunsaturated brominated marine natural product **11** were selected as targets for total synthesis (scheme 113). Both compounds were chosen for their potentially interesting biological profiles and their unique structural features.



Scheme 113: Natural products selected for total syntheses.

Kendomycin (**10**) is a highly versatile bacterial metabolite which displays a broad antibiotic and strong cytotoxic activity. Apart from its impressive biological profile, kendomycin features intriguing structural motifs such as a unique quinone methide chromophore with a linkage to a highly substituted tetrahydropyran and a polyketide scaffold completing the 16-membered carbocycle. The macrocyclic rim is decorated with nine stereogenic centers. These biological and structural properties have motivated a number of synthetic organic chemists to pursue a total synthesis of kendomycin.

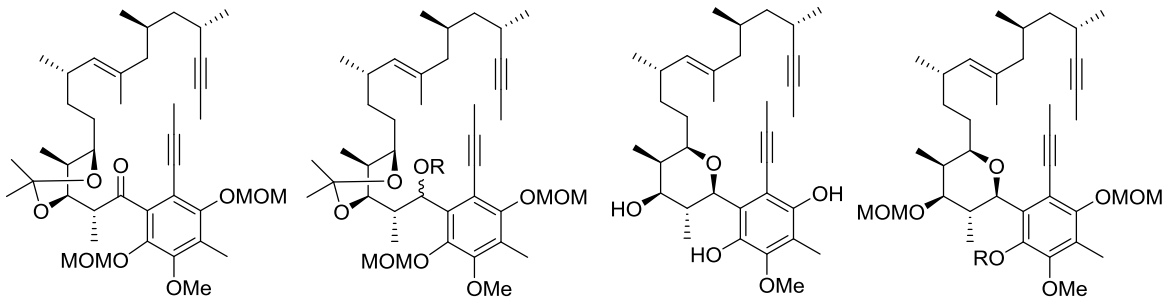
The objective of this work was the development of a novel synthetic route for kendomycin (**10**) enabled by the two above mentioned key processes.



Scheme 114: Disconnection approach by lithiation/addition (route A) and esterification/photo-Fries rearrangement (route B).

Our strategy was based on two highly convergent synthetic routes that were traced back to a polyketide chain **162** or **253** and the aromatic fragments **163** or **254**. The design rendered the building blocks highly flexible: the polyketide chains **162** and **253** (scheme 114) could be used in route A and B by simple derivatization of a common methyl ester progenitor. The syntheses of the two aromatic fragments **163** and **254** were based on a selective deprotection approach of the phenol at C4 which paved the way for the installation of the correct substitution pattern.

On route A, a number of potential substrates for the RCAM were prepared. However, the reaction was found to be unfeasible. This outcome was attributed to two effects: the steric hindrance at the *ortho*-disubstituted aryl alkynes and presumably a rotational limitation about the *C*-glycosidic bond which could lock the two diynes in an unreactive conformation (scheme 115). Thus, route A was abandoned.[96] A brief summary of the successful route B will be given in the following.



246

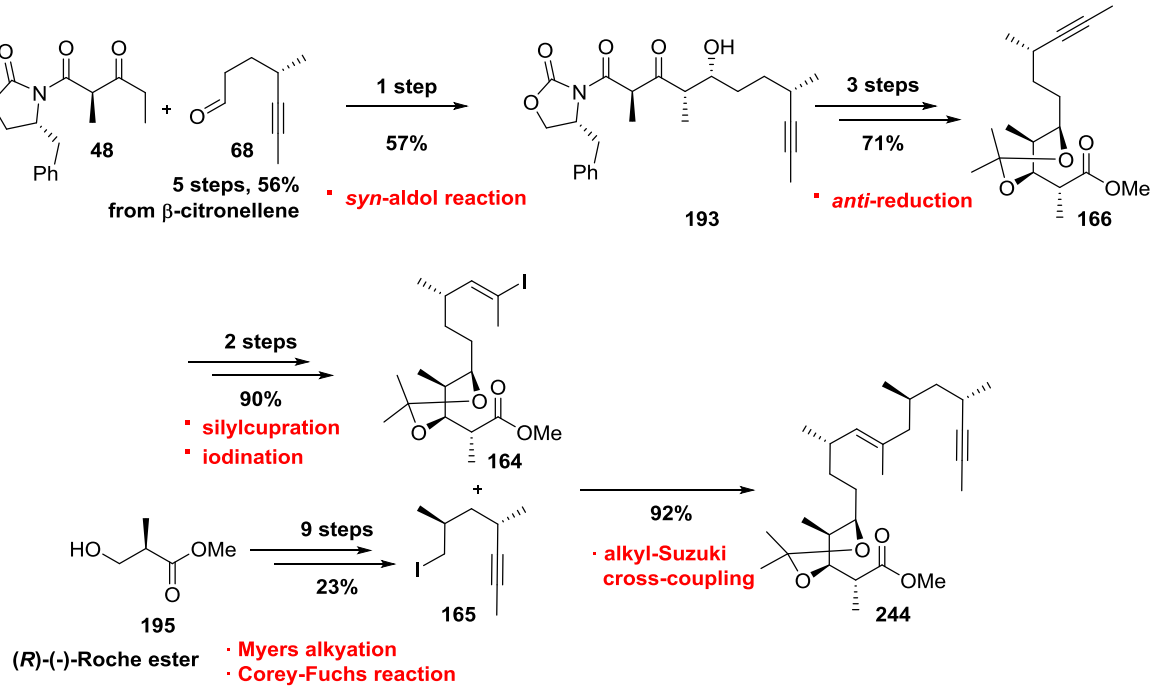
245 R: H
247 R: Ac

248

249 R: H
250 R: MOM

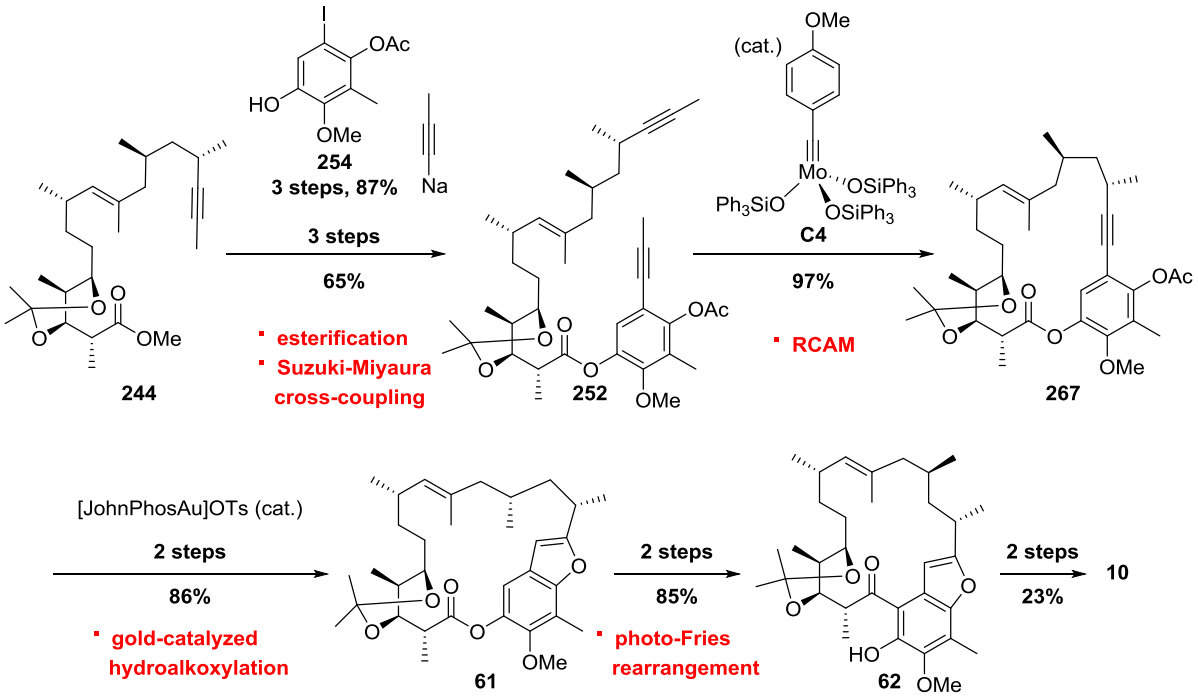
Scheme 115: Substrates that failed to give the RCAM product.

Methyl ester **244** was prepared from aldehyde **68** which could be obtained from either (L)-(+)-lactic acid or β-citronellene (scheme 116). Compound **68** participated in a *syn*-aldol reaction with β-ketoimide **48** to give the aldol **193**. Further transformations that were derived from literature precedents[41, 44a, 147] yielded alkyne **166**, which was converted to an alkenyl iodide **164** by a highly efficient silylcupration/iodination sequence. The coupling partner **165** for an alkyl-Suzuki cross-coupling was prepared from (*R*)-(−)-Roche ester **195** in a few robust operations.[96]



Scheme 116: Synthesis of the polyketide chain **244**.

Methyl ester **244** was saponified, linked to the arene **254** and the resulting ester adorned with an acetylene unit at the aromatic core (scheme 117). Diyne **252** represents the substrate for the envisioned RCAM. The triple bond metathesis with **C4** proceeded under mild conditions furnishing the metacyclophane **267**. The benzofuran moiety was formed by hydroalkoxylation of the cycloalkyne using an electrophilic gold-catalyst that was able to overcome the inherent ring strain. Benzofuran **61** intercepts the total synthesis of kendomycin (**10**) by Mulzer *et al.*[44a, 147] Using a photo-Fries rearrangement, the correct connectivity of the all-carbon macrocycle was put in place. Eventually, the completion of the synthesis was achieved according to the literature protocol.[44a, 147]



Scheme 117: Fragment assembly, RCAM and construction of the benzofuran moiety by π-acid catalysis.

With 22 steps in the longest linear sequence, this synthesis represents one of the shortest entries to the densely substituted polyketide **10** (*cf*. table 6).[110] An overall yield of 2.0% over the longest linear sequence highlights the efficiency of this entry.

Table 6: Synthetic approaches and their efficiency by comparison.

Total Syntheses	Macrocylization event	lls[a]	Overall yield
Lee (2004)	Macro-glycosidation	20	2.0%
Smith (2006)	RCM	21	0.5%
Panek (2008)	Barbier reaction	32	1.5%
Rychnovsky (2008)	Prins cyclization	20	–[b]
Mulzer (1. 2009)	RCM	23	1.0%
Mulzer (2. 2009)	Lactonization/ Photo-Fries	29	0.4%
Saikawa (2010)	Dötz benzannulation	32	0.2%
Our work (2014)	RCAM/gold-catalysis	22	2.0%

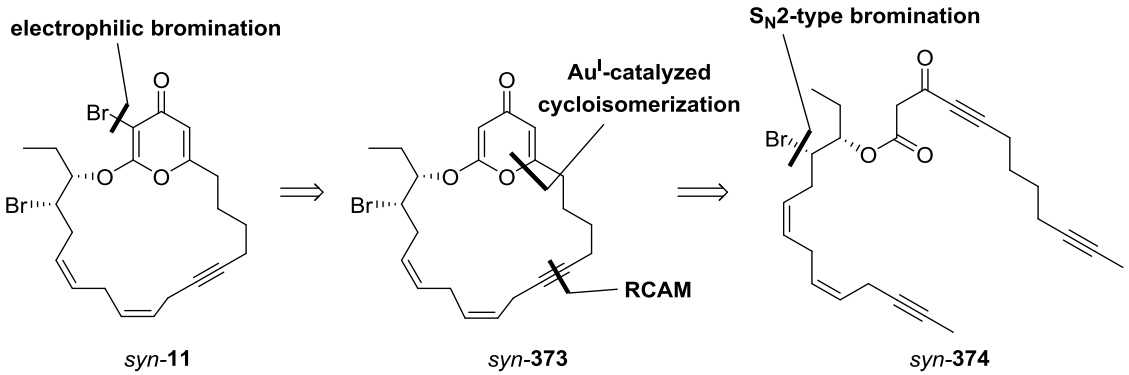
a) Longest linear sequence; b) Formal total synthesis.

In the further course of this PhD thesis, a total synthesis of the highly unusual polyunsaturated marine natural product **11** was pursued. In contrast to the previously discussed compound **10**, this target did not gather much attention after its isolation.[112b, 113]

4-Pyrone **11** is a marine metabolite of algal origin. Initial examination of the biological properties revealed a promising inhibitory activity of 93% for bee venom phospholipase A_2. The structural features of this marine natural product are a unique brominated 2-alkoxy-4-pyrone that is linked by a ketene acetal to the lipophilic tether; a skipped diene/yne motif decorates the macrocycle. Furthermore, a homoallylic bromine augurs for a latent non-classical carbon cation reactivity. These structural attributes all forecast the delicacy of the natural product and its precusors. The relative stereochemistry of **11** was not assigned by the isolation teams and had to be elucidated.

The 4-pyrone **11** was thought to have its biogenetic origin likely from a polyunsaturated fatty acid. In accordance with the literature, we assumed the stereogenic bromohydrin entity to derive from the attack of a nucleophile (the pyrone or its precursor) onto a (*Z*)-alkene which is activated by a bromonium cation equivalent.[117a] Therefore, we deliberately chose *syn*-**11** as our prime target at the outset of the projected synthesis.

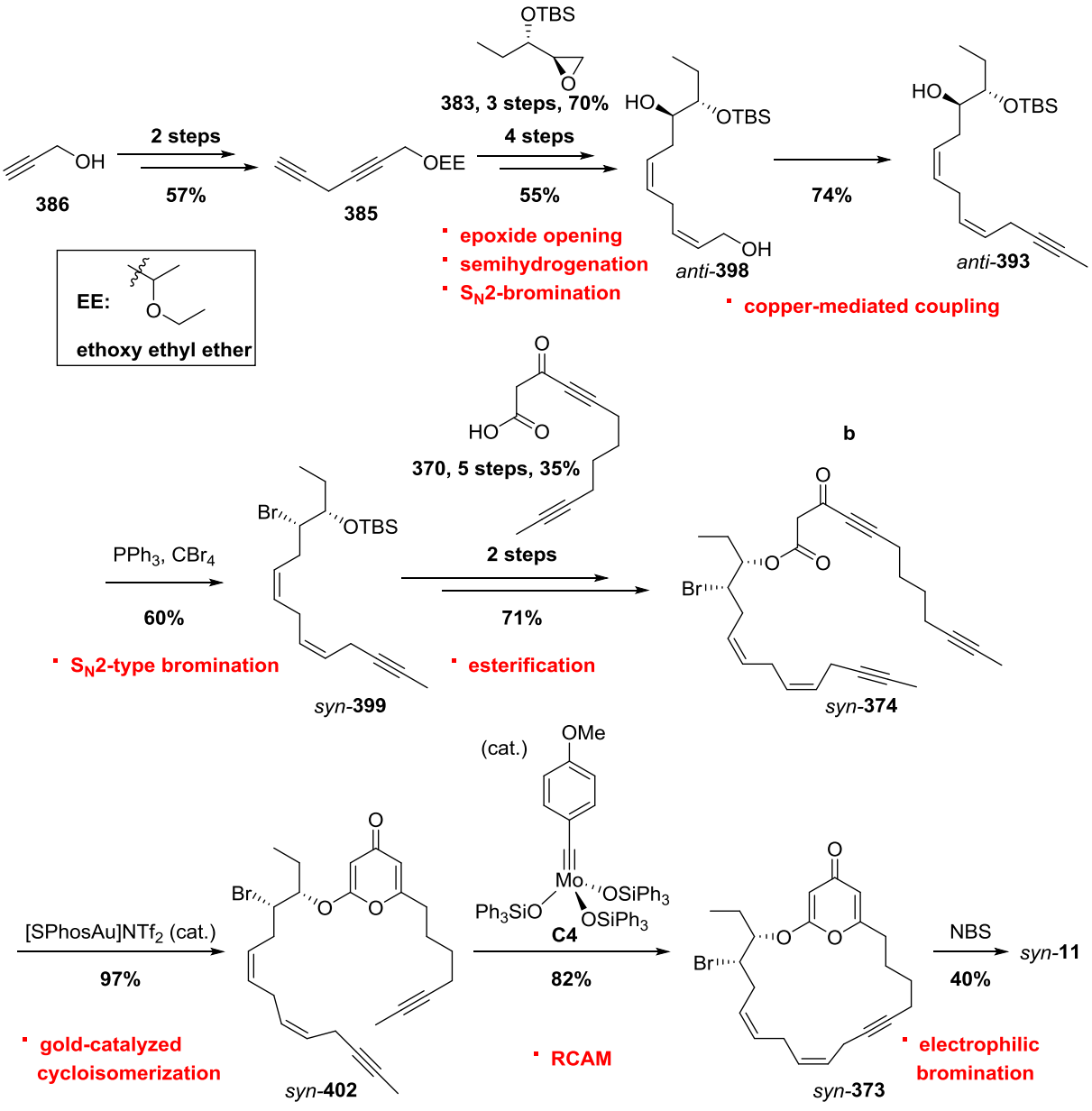
The unusual 2-alkoxy-3-bromo-4-pyrone, embedded in the rim of the macrolide structure, was identified as a motif to be installed through a gold-catalyzed cycloisomerization. The cycloalkyne represented an obvious target for the application of RCAM. With regard to the sensitivity of the material, the installation of the bromine atoms was considered a major challenge.



Scheme 118: Retrosynthetic disconnections of the marine metabolite *syn*-**11**.

Building on prior intelligence,[134-135] β-ketoester *syn*-**374** was chosen as the key intermediate in the ultimately successful approach. It was derived from the previously described acid **370** and a revised alcohol fragment *syn*-**399** (scheme 119). The synthetic route started with the formation of a skipped diyne **385** that was engaged in an epoxide opening with **383**.[134] Next, the methyl-capped alkyne was introduced via copper-mediated coupling of an allyl

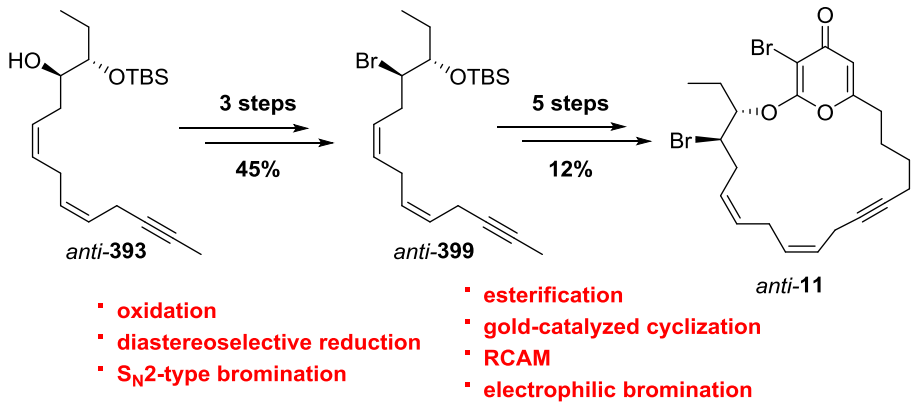
bromide with a propynyl Grignard. The bromination at the homoallylic position could be achieved in a S_N2-type reaction under Appel conditions. After deprotection of *syn*-**399**, the alcohol and the acid fragment **370** were finally linked by esterification giving the β-ketoester *syn*-**374**. Using the previously established conditions,[134] the gold-catalyzed cycloisomerization followed by RCAM provided the macrocyclic 4-pyrone derivative *syn*-**373**. Finally, *syn*-**11** was obtained by electrophilic bromination. The delicacy of the synthetic material was manifest throughout the entire synthesis, and utmost care had to be taken in handling and storing of virtually all compounds during the entire synthesis. The analytical data of the natural product and *syn*-**11** were in very good agreement.



Scheme 119: Fragment assembly & synthesis of *syn*-**11**.

In order to eliminate any uncertainties concerning the relative configuration, the *anti*-configured diastereomer was prepared starting from alcohol *anti*-**393** (scheme 120). Bromide *anti*-**399** was obtained after inversion of the corresponding stereocenter and an Appel-type bromination. Subsequent conversion of *anti*-**399** to *anti*-**11** was conducted in analogy to the synthesis of *syn*-**11** via π-acid catalyzed 4-pyrone formation, RCAM and electrophilic bromination.

The NMR data of *anti*-**11** showed major deviations from the data of the isolated material which supported the initial biosynthetic hypothesis, according to which a *syn*-configuration was suspected.



Scheme 120: Synthesis of *anti*-**11**.

In conclusion, a formal total synthesis of the densely functionalized and synthetically challenging kendomycin (**10**) was successfully completed. A diverse portfolio of reactions, transition-metal catalyzed transformations in particular, were applied and improved along the way. Once again, RCAM has proven to be a valuable synthetic tool for the synthesis of highly complex compounds such as the sterically demanding orthocyclophane in kendomycin. Limitations were only met with substrates containing *ortho*-di-substituted aryl alkynes. The price to be paid to avoid this obstacle was a detour via a metacyclophane derivative, which underwent RCAM in high yield. The all-carbon skeleton of the macrocycle was set in place by a photo-Fries shift. Finally the benzofuran motif was established employing a gold-catalyst which smoothly mediated the reaction and allowed the ring strain to be overcome.

Furthermore, a 14-step total synthesis of the exceptionally delicate marine natural product *syn*-**11** was described. In the course of this work, a 2-alkoxy-4-pyrone was prepared by a

gold-catalyzed cycloisomerization reaction. It was demonstrated that this methodology is advancing to a level of maturity and reliability that should further encourage implementation in synthetic planning, even as a late-stage transformation. Moreover, formation of the cycloalkyne by RCAM proceeded with great efficiency, showcasing the compatibility of this method with very sensitive functional groups such as skipped dienes or enynes. Finally, after preparation of *syn*- and *anti*-**11**, the correct relative stereochemistry was identified to be *syn*, supporting our intitial proposal for the biosynthetic origin of the bromohydrin moiety.

6. Experimental Procedures

6.1. General Experimental Details

All reactions were carried out under argon in flame-dried glassware unless H_2O was used as solvent. The following solvents were purified by distillation over the drying agents indicated and were transferred under Ar: THF, Et_2O (Mg/anthracene), CH_2Cl_2, DMSO (CaH_2), pentane, hexane, toluene (Na/K), MeOH (Mg, stored over MS 3 Å), DMF (MS 4 Å), DMSO (distilled over CaH_2, stored over MS 4 Å). 1,4-Dioxane, DMF, MeCN, Et_3N and pyridine were dried by an adsorption solvent purification system based on molecular sieves. DBU, diisopropylamine (CaH_2), (n-Bu)$_2$BOTf, propanal, $B(OMe)_3$ and acetyl chloride were distilled under argon prior to use. NBS and NIS were freshly recrystallized from H_2O prior to use. All other commercially available compounds (Aldrich, Alfa Aesar, Fluka, TCI, Lancaster) were used as received. The following compounds were prepared according to the cited protocol by myself or within the department of Prof. Fürstner: Cp_2ZrHCl,[148] Me_2BBr,[141, 149] Dess-Martin periodinane,[150] $LiSiMe_2Ph$,[91] oxazolidinone **403**,[56a] **C4** (neutral-complex),[13b] **C5** (ate-complex),[13b] [JohnPhosAu]OTs **C9**[151] and [SPhosAu]NTf_2 **C12**.[151-152]

Compounds and fragments **163**, **165**, **217** and **245 – 251** were prepared by Dr. Peter Persich.[96] The syntheses of **370**, *anti*-**371**, **383** and *anti*-**391** were initially described by Dr. Tsutomu Fukuda.[134]

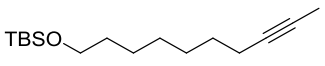
Thin layer chromatography (TLC) was performed on Macherey-Nagel precoated plates (POLYGRAM®SIL/UV254). Detection was achieved under UV light (254 nm) and by staining with either cerium ammonium nitriate (CAN), basic $KMnO_4$ or acidic vanilin solution. Flash chromatography was performed with Merck silica gel 60 (40–63 µm) or Florisil (60-100 mesh). The analytical measurements by gas chromatography were conducted with a Hewlett Packard HP 6890 device with a HP 5973 (GC/MS) detector. Analytical and preparative high pressure liquid chromatography (HPLC) was performed in parts in cooperations with Roswitha Leichtweiß. The measurements and separations of samples were executed with devices LCMS-2010 and LCMS-2020 (Shimadzu). Analysis of samples was effected by a diode array detector and mass spectroscopic analysis. X-ray diffraction was performed in the department “Chemische Kristallographie” in the Max-Planck-Institut für Kohlenforschung under the guidance of Prof. Christian W. Lehmann. Measurements were conducted using a Bruker-AXS X8 Proteum Diffractometer.

NMR spectra were recorded on Bruker DPX 300, AMX 300, AV 400, AV 500 or AVIII 600 spectrometer 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 ($CDCl_3$: $\delta_H \equiv 7.24$ ppm, $\delta_C \equiv 77.0$ ppm; CD_2Cl_2: $\delta_H \equiv 5.32$ ppm, $\delta_C \equiv 53.8$ ppm; C_6D_6: $\delta_H \equiv 7.15$ ppm, $\delta_C \equiv 128.0$ ppm; [D_6]-DMSO: $\delta_H \equiv 2.50$ ppm, $\delta_C \equiv 39.52$ ppm). Multiplets are indicated by the following abbreviations: s: singlet, d: doublet, t: triplet, q: quartet, quint: quintet, hept: heptet, m: multiplet. The abbreviation "br" indicates a broad signal. ^{13}C NMR were recorded in [^1H]-decoupled mode and the values of the chemical shifts are rounded to one digit after the decimal point. All spectra from the 500 MHz and 600 MHz spectrometers were acquired by the NMR department under guidance of Dr. Christophe Farès at the Max-Plank-Institut für Kohlenforschung. The assignments are based upon 1D and 2D spectra recorded using the following pulse sequences from the Bruker standard pulse program library: DEPT; COSY (*cosygpqf* and *cosydqtp*); HSQC (*hsqcedetgpsisp2.2*) optimized for $^1J_{C,H}$ = 145 Hz; HMBC (*hmbcetgpl3nd*) for correlations via $^nJ_{C,H}$; HSQC-TOCSY (*invietgsml*) using an MLEV17 mixing time of 120 ms; NOESY (noesygpph). The IR spectra were recorded on the Spectrum One (Perkin-Elmer) spectrometer and the Alpha Platinum ATR (Bruker) at room temperature, wavenumbers ($\tilde{\nu}$) are given in cm^{-1}. Mass spectrometric samples were measured by the department for mass spectrometry at the Max-Planck-Institut für Kohlenforschung. The following equipment was used: MS (EI): Finnigan MAT 8200 (70 eV), ESI-MS: ESQ3000 (Bruker), accurate mass determinations: Bruker APEX III FT-MS (7 T magnet) or Mat 95 (Finnigan). Optical rotations were measured with a Perkin-Elmer Model 343 polarimeter at a wavelength of 589 nm; they are given as specific optical rotations with exact temperature, concentration (c/(10 mg/mL)) and solvent.

6.2. Formal Total Synthesis of Kendomycin

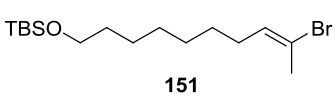
6.2.1. Synthesis of a Model for the Ring-Closing Alkyne Metathesis

Silyl Ether 404. Alkynol **154** (2.00 g, 13.0 mmol) was dissolved in THF (4 mL) and the solution stirred at 0 °C. Subsequently, a solution of TBSCl in THF (7.78 mL, 15.6 mmol, 2.0 M) and imidazole (2.21 g, 32.4 mmol) were added. The mixture was then allowed to warm to ambient temperature and the reaction was monitored by thin layer chromatography. After 4 h the mixture was diluted with EtOAc and

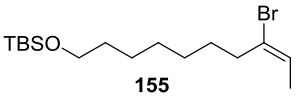


the organic phase was washed with H_2O (3 x 5 mL) and brine (5 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, pentane 100% → pentane/EtOAc, 8/2) to yield the desired silyl ether **404** as a colorless oil (3.07 g, 88%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.59 (t, 2H, *J* = 6.5 Hz), 2.13 – 2.08 (m, 2H), 1.77 (t, 3H, *J* = 2.4 Hz), 1.53 – 1.43 (m, 4H), 1.40 – 1.29 (m, 6H), 0.89 (s, 9H), 0.04 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 79.5, 75.5, 63.4, 33.0, 29.2, 29.1, 29.0, 26.1 (3C), 25.9, 18.9, 18.5, 3.3, 5.1 ppm (2C); IR (film): $\tilde{\nu}$ = 2929, 2857, 1471, 1463, 1387, 1361, 1254, 1098, 1005, 938, 832, 812, 773, 712, 661 cm^{-1}; GC-MS: t_R (70_20) = 8.4 min; MS (EI) m/z (%): 267 (12), 211 (35), 135 (52), 109 (32), 75 (100); HRMS (ESI): *m/z*: calcd. for $C_{16}H_{32}OSiNa$ [*M*+Na^+]: 291.2117, found 291.2115.

Alkenyl Bromides 151 and 155. Cp_2ZrHCl (2.97 g, 11.6 mmol) was added to a solution of



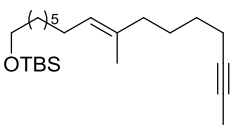
151



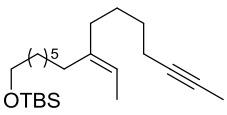
155

alkyne **404** (3.71 g, 13.0 mmol) in THF (25 mL). After stirring for 2 h, the white suspension turned slightly red and NBS (3.02 g, 17.0 mmol) was added slowly as a solution in THF (20 mL). The mixture was stirred for 3 h at ambient temperature and the color changed from red to yellow. For work-up, the solvent was removed and the crude material was purified by flash chromatography (SiO_2, hexanes 100%). The title compound was isolated as a mixture of regioisomers (4.08 g, 90%, **151**:**155** = 2.5:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.83 (tq, 1H, *J* = 7.6, 1.3 Hz), 3.59 (t, 2H, *J* = 6.6 Hz), 2.20 (d, 3H, *J* = 1.3 Hz), 2.00 (dt, 2H, *J* = 7.7, 7.6 Hz), 1.55 – 1.46 (m, 4H), 1.38 – 1.29 ppm (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 132.6, 119.2, 63.4, 33.0, 29.8, 29.4, 29.2, 29.1, 28.7, 26.1 (3C), 25.9, 25.3, −5.1 ppm (2C); IR (film): $\tilde{\nu}$ = 2927, 2855, 1717, 1649, 1430, 1377, 1121, 1056, 817, 723 cm^{-1}; GC-MS: t_R (70_20) = 8.4 min; m/z (%): 349 (10), 291 (15), 169 (22), 137 (32), 109 (27), 95 (100), 81 (77); MS (EI) *m/z* (%): 293 (5), 291 (5), 167 (5), 139 (7), 137 (27), 109 (13), 96 (8), 95 (100), 81 (89), 75 (24), 73 (12), 69 (16), 67 (22), 55 (33), 53 (8), 41 (13); HRMS (CI): *m/z*: calcd. for $C_{16}H_{34}OBrSi$ [*M*+H^+]: 349.1560, found 349.1562.

Silyl Ether 157a and 157b. A solution of alkyl iodide **153** (400 mg, 1.80 mmol) in Et_2O (6.6 mL) was cooled to −78 °C before *t*-butyllithium (2.17 mL, 3.69 mmol, 1.7 M) was added and the solution was stirred for 10 min. Subsequently, 9-MeO-9-BBN (5.40 mL, 5.40 mmol) and THF (6.6 mL) were added dropwise. After stirring for 30 min at −78 °C, the white slurry



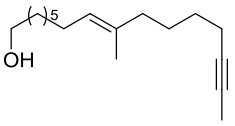
157a



157b

was allowed to warm to ambient temperature and stirring was continued for 2 h. After formation of the borate species[153] the alkenyl bromide was added as a mixture of regioisomers (**151** and **155**) (588 mg, 1.69 mmol) in DMF (7 mL). K_3PO_4 (1.91 g, 9.00 mmol) and $PdCl_2(dppf)\cdot CH_2Cl_2$ (66 mg, 5 mol%) were then subsequently introduced. The mixture was stirred for 15 min at ambient temperature and then for 1 h at 50 °C. For work-up, the reaction mixture was filtered through a pad of Celite, the filtrate was evaporated under reduced pressure and the residue was purified by flash chromatography (SiO_2, hexanes 100% $\rightarrow$ hexanes/EtOAc, 95/5) to afford the desired title compound as a mixture of regiosiomers (492 mg, 80%, **157a**:**157b** = 8:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.12 (tq, 1H, *J* = 7.3, 1.3 Hz), 3.59 (t, 2H, *J* = 6.6 Hz), 2.00 – 1.94 (m, 4H), 1.77 (t, 3H, *J* = 2.6 Hz), 1.58 – 1.57 (m, 3H), 1.53 – 1.42 (m, 6H), 1.34 – 1.27 (m, 10H), 0.89 (s, 9H), 0.04 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 134.2, 125.0, 79.5, 75.5, 63.5, 39.3, 33.1, 30.0, 29.6, 29.5, 29.0, 28.8, 28.1, 27.3, 26.1 (3C), 26.0, 18.8, 16.0, 3.6, 5.1 ppm (2C); IR (film): $\tilde{\nu}$ = 2857, 1712, 1462, 1361, 1251, 1219, 1152, 1094, 1006, 938, 866, 834, 779, 671 cm^{-1}; GC-MS: t_R (70_20) = 8.4 min; MS (EI) m/z (%): 364 (11), 307 (35), 149 (26), 119 (12), 75 (100).

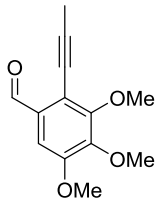
Alcohol 405. A solution of TBAF in THF (4.30 mL, 4.29 mmol, 1.0 M) was added dropwise to silyl ethers **157a** and **157b** (8:1) (390 mg, 1.07 mmol) in THF (10 mL). The pale yellow solution was stirred for 1 h before H_2O was added. The aqueous phase was extracted with EtOAc and the combined organic phases were dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (SiO_2, pentane/EtOAc, 4/1) to give alcohol **405** as a colorless oil (268 mg, 83%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.10 (tq, 1H, *J* = 7.2, 1.2 Hz), 3.80 (br s, 1H), 3.62 (t, 2H, *J* = 6.9 Hz), 2.14 – 2.08 (m, 2H), 1.99 – 1.93 (m, 4H), 1.77 (t, 3H, *J* = 2.5 Hz), 1.58 – 1.55 (m, 3H), 1.55 – 1.52 (m, 2H), 1.46 – 1.41 (m, 4H), 1.36 – 1.28 ppm (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.4, 124.4, 79.0, 75.0, 62.7, 38.8, 32.4, 29.0, 28.9, 28.3, 27.5, 26.8, 25.4, 25.3, 18.3, 15.4, 3.1 ppm; IR (film): $\tilde{\nu}$ = 2934, 1733, 1478, 1390, 1233, 1155, 1092, 1065, 1044, 965 cm^{-1}; GC-MS: t_R (70_20) = 10.5 min; MS (EI) *m/z* (%): 250 (29), 235 (14), 221 (11), 163 (19), 150 (19), 149 (100), 147 (11), 136 (39), 135 (76), 133 (14), 123 (21), 122 (24), 121 (74), 119 (19), 109 (21), 108 (24), 107 (94), 95 (60), 93 (92), 91 (29), 83 (13), 81 (69), 67 (56), 55 (80).



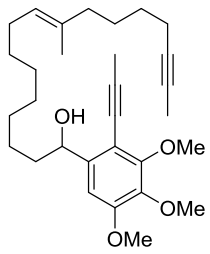
Iodide 158. PPh_3 (236 mg, 0.90 mmol), imidazole (62.0 mg, 0.90 mmol) and iodine (228 mg, 0.90 mmol) were added to a solution of alcohol **405** (150 mg, 0.60 mmol) in MeCN/Et_2O (1:2, 6 mL) at 0 °C. The mixture was allowed to warm to ambient temperature and was stirred for 2 h. For work-up, the mixture was filtered through a pad of Celite which was rinsed with hexanes/EtOAc (7:3). The organic phase was washed with $Na_2S_2O_3$ solution and brine, dried over Na_2SO_4, and the solvent was evaporated. The crude material was purified by flash chromatography (SiO_2, pentane 100%) to afford iodide **158** as a single isomer (214 mg, 99%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.10 (tq, 1H, *J* = 7.1, 1.2 Hz), 3.18 (t, 2H, *J* = 7.1 Hz), 2.14 – 2.09 (m, 2H), 2.00 – 1.94 (m, 4H), 1.85 – 1.78 (m, 2H), 1.78 (t, 3H, *J* = 2.6 Hz), 1.57 (br s, 3H), 1.47 – 1.42 (m, 4H), 1.40 – 1.34 (m, 2H), 1.33 – 1.28 ppm (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 134.9, 124.8, 79.5, 75.5, 39.3, 30.6, 29.9, 29.2, 28.7, 28.6, 27.9, 27.5, 27.2, 18.8, 16.0, 7.6, 3.7 ppm; IR (film): $\tilde{\nu}$ = 3074, 2946, 2830, 2547, 1768, 1688, 1596, 1573, 1471, 1417, 1372, 1291, 1261, 1214, 1176, 1137, 1074, 1060, 1001, 896, 849, 821, 807, 747, 718 cm^{-1}; MS (EI) *m/z* (%): 360 (27), 345 (25), 331 (17), 163 (11), 150 (15), 149 (100), 136 (38), 135 (51), 122 (12), 121 (50), 108 (14), 107 (57), 95 (28), 94 (10), 93 (54), 81 (37), 79 (31), 69 (12), 67 (28), 55 (15), 53 (17), 41 (29); HRMS (EI): *m/z*: calcd. for $C_{17}H_{29}I$ [M^+]: 360.1312, found 360.1314.

Bromide 160. Commercially available 3,4,5-trimethoxybenzaldehyde (**159**) (1.88 g, 6.85 mmol) was dissolved in MeCN (20 mL) and the solution treated with NBS (1.34 g, 7.54 mmol). After stirring for 1 h at ambient temperature the reaction mixture was concentrated and the crude material subjected to flash chromatography (SiO_2, pentane/EtOAc, 85/15) to afford aryl bromide **160** as a colorless crystalline solid (1.79 g, 95%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.29 (s, 1H), 7.30 (s, 1H), 3.98 (s, 3H), 3.91 (s, 3H), 3.90 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.3, 153.1, 150.8, 148.8, 128.8, 115.8, 107.5, 61.4, 61.3, 56.4 ppm; IR (film): $\tilde{\nu}$ = 3349, 3080, 3001, 2940, 2864, 1738, 1684, 1577, 1562, 1470, 1448, 1425, 1403, 1381, 1325, 1284, 1241, 1196, 1103, 1043, 1000, 858, 816, 773, 725, 643, 584, 522, 410 cm^{-1}; GC-MS: t_R (70_20) = 9.6 min; MS (EI) *m/z* (%): 276 (39), 274 (40), 261 (10), 259 (10), 197 (11), 196 (100), 181 (50), 125 (24), 110 (17), 95 (10), 93 (13); HRMS (EI): *m/z*: calcd. for $C_{10}H_{11}O_4Br$ [M^+]: 273.9840, found 273.9841.

Alkyne 152. Trimethylborate (1.30 mL, 11.5 mmol) was slowly added to a suspension of sodium propyne (722 mg, 11.5 mmol) in THF (75 mL) until a clear solution was produced that was stirred for 10 min at ambient temperature before $PdCl_2(ddpf)\cdot CH_2Cl_2$ (559 mg, 10 mol%) and aryl bromide **160** (1.79 g, 7.64 mmol) were added. The dark red mixture was refluxed for 5 h. After completion of the reaction, the yellow solution was filtered through a pad of Celite, concentrated and the residue purified by flash chromatography (SiO_2, hexanes/EtOAc, 7/3) to yield aryl alkyne **152** as a yellow oil (1.06 g, 59%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.40 (s, 1H), 7.21 (s, 1H), 3.95 (s, 3H), 3.94 (s, 3H), 3.90 (s, 3H), 2.16 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.3, 154.6, 153.4, 147.7, 132.2, 116.8, 105.0, 96.3, 70.9, 61.5, 61.3, 56.3, 5.9 ppm; IR (film): $\tilde{\nu}$ = 2991, 2935, 2861, 1685, 1584, 1482, 1459, 1430, 1408, 1390, 1329, 1295, 1264, 1222, 1182, 1191, 1136, 1084, 1049, 988, 966, 920, 839, 754, 689 cm^{-1}; MS (EI) *m/z* (%): 234 (90), 233 (32), 220 (12), 219 (100), 204 (12), 203 (17), 189 (14), 188 (17), 176 (22), 175 (16), 173 (14), 161 (16), 148 (17), 144 (10), 133 (10), 115 (10), 105 (11), 103 (11), 91 (11); HRMS (ESI): *m/z*: calcd. for $C_{13}H_{24}O_4Na$ [*M*+Na$^+$]: 257.0786, found 257.0784.

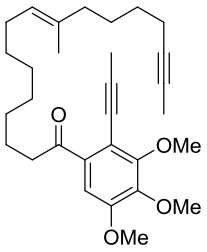


Alcohol 406. At −78 °C *t*-butyllithium (70 μL, 0.12 mmol, 1.7 M) was added to a solution of alkyl iodide **158** (42 mg, 0.12 mmol) in Et_2O (0.95 mL). After 10 min at −78 °C, a solution of aldehyde **152** (18 mg, 78 μmol) in Et_2O (0.25 mL) was added dropwise. After further 15 min at −78 °C, the solution was allowed to warm to rt and stirring was continued for 20 min. The reaction was quenched by addition of aqueous HCl (2 mL, 2.0 M) and H_2O (3 mL) and the aqueous phase was extracted with EtOAc (3 x 10 mL). The combined organic phases were dried over Na_2SO_4 and concentrated, and the crude material was purified by flash chromatography (SiO_2, hexanes/EtOAc, 7/3) to afford the title compound **406** as a colorless oil (32 mg, 88%). ^{1}H NMR (400 MHz, CD_3OD): δ = 6.93 (s, 1H), 5.14 (tq, 1H, *J* = 7.2, 1.3 Hz), 5.07 (dd, 1H, *J* = 8.1, 4.7 Hz), 5.00 (br, 1H), 3.89 (s, 3H), 3.88 (s, 3H), 3.81 (s, 3H), 2.12 – 2.07 (m, 2H), 2.11 (s, 3H), 2.04 – 1.98 (m, 4H), 1.74 (t, 3H, *J* = 2.6 Hz), 1.74 – 1.68 (m, 2H), 1.61 – 1.59 (m, 3H), 1.51 – 1.42 (m, 4H), 1.40 – 1.32 ppm (m, 10H); ^{13}C NMR (100 MHz, CD_3OD): δ = 155.5, 154.7, 145.6, 141.9, 135.8, 126.0, 105.7, 94.0, 79.7, 74.1, 73.3, 72.2, 61.6, 61.4, 56.6, 56.4, 40.2, 39.7, 37.5, 30.9, 30.5, 30.3, 29.7, 28.8, 28.1, 26.9, 19.3, 15.9, 4.3, 3.1 ppm;

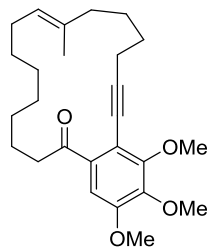


IR (film): $\tilde{\nu}$ = 2924, 2854, 1460, 1331, 1253, 1066, 837, 782, 723, 699, 646, 565, 495 cm^{-1}; MS (ESIpos) *m*/*z* (%): 491 (*M*+Na^+, 100).

Diyne 150. Compound **406** (38 mg, 80 μmol) was dissolved in CH_2Cl_2 (1.3 mL) and the solution was treated with Dess-Martin periodinane (51 mg, 0.12 mmol) at 0 °C. After 1 h, the reaction was quenched by addition of an aqueous solution of $NaHCO_3$/$Na_2S_2O_3$ (1:1). The phases were separated, the aqueous phase was extracted with CH_2Cl_2, the organic layers were washed with brine, dried over $MgSO_4$ and the solvent was evaporated. The residue was purified by flash chromatography (SiO_2, hexanes/EtOAc, 7/3) to give ketone **150** as a colorless oil (27 mg, 71%). ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 6.87 (s, 1H), 5.13 (tq, 1H, *J* = 7.2, 1.1 Hz), 3.90 (s, 3H), 3.86 (s, 6H), 3.05 (t, 2H, *J* = 7.5 Hz), 2.13 – 2.08 (m, 2H), 2.11 (s, 3H), 2.02 – 1.95 (m, 4H), 1.75 (t, 3H, *J* = 2.5 Hz), 1.69 – 1.63 (m, 2H), 1.58 (s, 3H), 1.57 – 1.52 (m, 2H), 1.47 – 1.40 (m, 4H), 1.38 – 1.28 ppm (m, 6H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 204.0, 155.7, 153.7, 145.2, 139.0, 135.3, 125.4, 110.4, 107.6, 95.1, 79.7, 75.7, 74.5, 61.6, 61.4, 56.6, 42.9, 39.7, 30.5, 30.3, 30.0, 29.8, 29.3, 28.4, 27.7, 25.1, 19.1, 16.1, 5.1, 3.7 ppm; IR (film): $\tilde{\nu}$ = 2926, 2854, 1732, 1591, 1488, 1461, 1332, 1236, 1196, 1128, 1015, 796 cm^{-1}; MS (ESIpos) *m*/*z* (%): 489 (*M*+Na^+, 100).



Cycloalkyne 149. Diyne **150** (15 mg, 32 μmol) was stirred with MS 5 Å (100 mg) in toluene (32 mL) for 30 min before a solution of alkylidyne **C4** (8.7 mg, 20 mol%) in toluene (1 mL) was added. After stirring for 1 h at ambient temperature, the reaction was completed and the mixture was filtered through a pad of Celite. The solvent was evaporated and the residue was purified by preparative thin layer chromatography (SiO_2, hexanes/MTBE, 7/3) to afford cycloalkyne **149** as a colorless oil (12 mg, 92%). ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 6.83 (s, 1H), 5.13 (tq, 1H, *J* = 7.4, 1.2 Hz), 3.89 (s, 3H), 3.85 (s, 6H), 2.96 (t, 2H, *J* = 7.5 Hz), 2.46 – 2.42 (m, 2H), 2.07 – 2.01 (m, 4H), 1.67 – 1.60 (m, 2H), 1.46 – 1.42 (m, 2H), 1.41 – 1.33 (m, 4H), 1.31 – 1.26 ppm (m, 6H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 203.9, 155.8, 153.5, 145.0, 139.1, 134.8, 126.5, 107.1, 99.3, 88.8, 74.7, 61.6, 61.4, 56.6, 42.8, 39.6, 30.3, 29.4, 28.7, 28.4, 28.1, 27.6, 27.3, 24.2, 20.7, 15.8 ppm; IR (film): $\tilde{\nu}$ = 3068, 3048, 2928, 2854, 1704, 1608, 1589, 1513, 1486, 1463, 1428, 1284, 1247, 1172, 1117, 1028, 997, 832, 710, 698 cm^{-1}; MS



(ESIpos) *m/z* (%): 435 (*M*+Na^+, 100); HRMS (ESI): *m/z*: calcd. for $C_{26}H_{36}O_4Na$ [*M*+Na^+]: 435.2509, found 435.2506.

6.2.2. Early Approaches to the C9–C14-Fragment

Lactone 172. δ-Valerolactone (**169**) (122 mg, 1.22 mmol) and diethyl oxalate (1.60 mL, 11.7 mmol) were dissolved in THF (8.5 mL) and the solution was cooled to 0 °C before it was added to a suspension of NaH (48 mg, 2.0 mmol) in THF (6.4 mL) at 0 °C. Ethanol (320 μL) was then added and the reaction mixture was allowed to warm to ambient temperature. After 4 h, the mixture was cooled to 0 °C and a solution of K_2CO_3 (693 mg, 5.02 mmol) in H_2O (1.0 mL) followed by paraformaldehyde (1.24 mL, 16.7 mmol, 37%) was added. After 15 min, the mixture was allowed to warm to 5 °C before brine (5 mL) was added. The aqueous phase was extracted with MTBE, the organic layers were washed with brine, dried over $MgSO_4$ and concentrated. The crude material was purified by flash chromatography (SiO_2, pentane/EtOAc, 3/2) to afford title compound **172** as a colorless oil (112 mg, 82%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.38 (q, 1H, *J* = 1.9 Hz), 5.52 (q, 1H, *J* = 1.9 Hz), 4.40 – 4.31 (t, 2H, *J* = 6.1 Hz), 2.63 (ddt, 2H, *J* = 8.1, 6.1, 3.1 Hz), 1.98 – 1.84 ppm (m, 2H). IR (film): $\tilde{\nu}$ = 2935, 1796, 1737, 1470, 1446, 1368, 1277, 1212, 1178, 1152, 1124, 1074, 1042, 1028, 1000, 961, 859, 788, 740, 706 cm^{-1}; GC-MS: t_R (70_20) = 4.9 min; MS (EI) m/z (%): 112 (90), 84 (100), 67 (24), 54 (98).

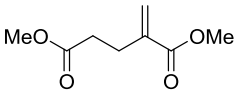
Alcohol 407 and Silyl Ether 175. DOWEX® 50Wx8 (14 mg) was added to a solution of δ-valerolactone (**169**) (1.00 g, 10.0 mmol) in methanol (52 mL). The mixture was stirred at reflux temperature for 4 h before it was filtered through a pad of Celite and the solvent was evaporated. The obtained colorless oil was subjected to the next step without further purification.

407 **175**

Alcohol **407** (1.16 g, 10.0 mmol) was dissolved in THF (20 mL) and the solution was cooled to 0 °C before TBSCl (1.96 g, 13.0 mmol) and imidazole (1.70 g, 25.0 mmol) were added. After warming to rt, the mixture was stirred for 4 h. The yellow suspension was filtered trough a pad of Celite to remove imidazole and salts. Then the sovent was removed under reduced pressure. The crude material was purified by flash chromatography (SiO_2, hexanes/EtOAc, 9/1) to afford TBS-ether **175** as a colorless oil (2.34 g, 95% over 2 steps). ^{1}H NMR (400 MHz,

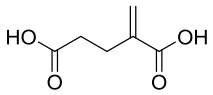
$CDCl_3$): δ = 3.63 (s, 3H), 3.58 (t, 2H, *J* = 6.3 Hz), 2.30 (t, 2H, *J* = 7.5 Hz), 1.72 – 1.59 (m, 2H), 1.56 – 1.44 (m, 2H), 0.85 (s, 9H), 0.00 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.2, 62.7, 51.6, 33.9, 32.2, 26.0 (3C), 21.5, 18.5, −5.3 ppm (2C); IR (film): $\tilde{\nu}$ = 2953, 2930, 2858, 1741, 1472, 1463, 1436, 1388, 1361, 1250, 1198, 1164, 1093, 1006, 972, 938, 872, 833, 773, 715, 661 cm^{-1}; MS (EI) *m/z* (%): 245 (1), 215 (10), 191 (3), 189 (59), 158 (8), 157 (64), 115 (12), 113 (12), 101 (7), 90 (8), 89 (100), 75 (26), 73 (25), 59 (15), 55 (13); HRMS (ESIpos): *m/z*: calcd. for $C_{12}H_{26}O_3SiNa$ [*M*+Na^+]: 269.1543, found 269.1543.

Diester 176. In a pressure tube methyl acrylate (**168**) (0.96 g, 11.2 mmol) was treated with



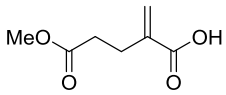
n-Bu_3P (0.14 mL, 5 mol%) and hydroquinone (25 mg, 2 mol%). The mixture was stirred for 24 h at 50 °C in the sealed tube. The resulting yellow solution was poured into aqueous HCl (4.0 M) to remove the phosphine and the aqueous phase was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were washed with aqueous $NaHCO_3$ (15 mL), H_2O (15 ml) and brine (10 mL), dried over $MgSO_4$ and concentrated to afford the title compound **176** as a colorless oil (441 mg, 23%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.95 (d, 1H, *J* = 1.2 Hz), 5.39 (d, 1H, *J* = 1.2 Hz), 3.53 (s, 3H), 3.44 (s, 3H), 2.48 – 2.36 (m, 2H), 2.31 ppm (dd, 2H, *J* = 8.0, 1.0 Hz).; IR (film): $\tilde{\nu}$ = 2954, 1720, 1631, 1436, 1378, 1332, 1307, 1256, 1196, 1159, 1139, 1048, 990, 954, 884, 832, 818, 759, 688 cm^{-1}; GC-MS: t_R (70_20) = 5.5 min; MS (EI) m/z (%): 172 (5), 140 (78), 125 (2), 112 (100), 97 (16), 81 (35).

Diacid 408. A solution of $LiOH{\cdot}H_2O$ (645 mg, 15.4 mmol) in H_2O (1.0 mL) was added to



diester **176** (441 mg, 2.56 mmol) in THF (3.0 mL) at 0 °C. After 24 h the reaction mixture was acidified with aqueous HCl (2.0 M), extracted with EtOAc (3 x 20 mL) and dried over $MgSO_4$. The solvent was evaporated to yield diacid **408** as a colorless crystalline solid (315 mg, 85%). ^{1}H NMR (400 MHz, CD_3OD): δ = 12.41 (br s, 1H), 10.02 (br, 1H), 6.18 (s, 1H), 5.60 (s, 1H), 2.61 – 2.55 (m, 2H), 2.50 – 2.46 ppm (m, 2H); ^{13}C NMR (100 MHz, CD_3OD): δ = 175.1, 168.7, 139.1, 125.5, 32.6, 26.9 ppm.

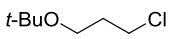
Methyl Ester 177. A solution of compound **408** (275 mg, 1.91 mmol) in methanol (5.5 mL)



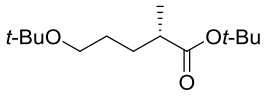
was treated with camphorsulfonic acid (89 mg, 0.38 mmol). After stirring for 1 h, the mixture was filtered through a pad of Celite and the solvent

was evaporated. The residue was purified by flash chromatography (SiO_2, pentane/EtOAc, 1/1) to give monoester **177** as a colorless oil (266 mg, 88%). ^{1}H NMR (400 MHz, CD_3OD): δ = 6.17 – 6.16 (m, 1H), 5.63 (d, 1H, *J* = 1.3 Hz), 5.33 (br, 1H), 3.64 (s, 3H), 2.61 – 2.56 (m, 2H), 2.54 – 2.50 ppm (m, 2H); ^{13}C NMR (100 MHz, CD_3OD): δ = 174.8, 169.7, 140.8, 126.4, 52.1, 33.8, 28.3 ppm; IR (film): $\tilde{\nu}$ = 2954, 2356, 2267, 2076, 1735, 1690, 1629, 1438, 1360, 1272, 1198, 1171, 1027, 985, 951, 887, 824, 752, 683 cm^{-1}; MS (neg. ESI) *m/z* (%): 157 (*M*–H$^+$, 100).

***tert*-Butyl Ether 183.** A solution of 3-chloropropan-1-ol (**182**) (25.0 mL, 299 mmol) in CH_2Cl_2 (625 mL) was treated dropwise with sulfuric acid (1.60 mL, 30.0 mmol). Iisobutene was bubbled through the vigorously stirred solution until it was saturated. After 2 h, the reaction was completed and saturated aqueous $NaHCO_3$ was added to the mixture until gas formation ceased. The phases were then separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 80 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was evaporated. The crude material was distilled (64 – 67 °C/44 mbar) to give the title compound **183** as a colorless oil (44.7 g, 99%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.64 (t, 2H, *J* = 6.3 Hz), 3.48 (t, 2H, *J* = 5.8 Hz), 1.95 (tt, 2H, *J* = 6.3, 5.8 Hz), 1.18 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 80.4, 65.1, 41.2, 32.4, 28.1 ppm (3C); MS (EI) *m/z* (%): 135 (11), 115 (23), 93 (100), 57 (46), 48 (17); HRMS (EI): *m/z*: calcd. for $C_7H_{15}OCl$ [M^+]: 150.0811, found 150.0810.



***tert*-Butyl Ester 184.** Magnesium pellets (1.94 g, 79.8 mmol) were activated with 1,2-dibromoethane (one drop) before a small amount of the solution of chloride **183** (100 mg, 0.67 mmol) in THF (1.0 mL) was added. After Grignard formation was initiated, the remaining substrate **183** (11.8 g, 78.7 mmol) was added as a solution in THF (39 mL) via dropping funnel to the refluxing mixture. After 2 h, the Grignard formation was completed and the mixture was allowed to cool to ambient temperature. In a separate flask a solution of $ZnCl_2$ in THF (2.0 mL, 1.0 M) was prepared at 0 °C before triflate **181**[81-82] (11.2 g, 40.1 mmol) was added, followed by the freshly prepared solution of the Grignard reagent (40 mL, 1.9 M). After stirring for 2 h at 0 °C, the triflate was consumed and the reaction was quenched with saturated aqueous NH_4Cl (25 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL), the combined organic layers were dried over $MgSO_4$ and the solvent was evaporated. The crude material was purified by flash

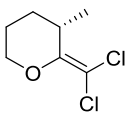


chromatography (SiO_2, pentane/EtOAc, 4/1) to yield the coupling product **184** as a colorless oil (6.47 g, 66%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.32 (tt, 2H, *J* = 5.7, 2.8 Hz), 2.35 – 2.27 (m, 1H), 1.66 – 1.49 (m, 2H), 1.54 – 1.40 (m, 2H), 1.43 (s, 9H), 1.17 (s, 9H), 1.10 ppm (d, 3H, *J* = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.4, 79.9, 72.6, 61.5, 40.4, 30.6, 28.5, 28.2 (3C), 27.7 (3C), 17.3 ppm; IR (film): $\tilde{\nu}$ = 2973, 1728, 1459, 1391, 1363, 1256, 1149, 1079, 849, 749 cm^{-1}; MS (EI) *m/z* (%): 171 (1), 131 (22), 115 (100), 103 (4), 97 (7), 69 (14), 57 (67), 56 (19), 55 (12), 41 (32); HRMS (ESI): *m/z*: calcd. for $C_{14}H_{28}O_3Na$ [*M*+Na$^+$]: 267.1928, found 267.1931.

δ-Lactone 174. A solution of *tert*-butyl ester **184** (4.89 g, 18.8 mmol) in CH_2Cl_2 (40 mL) was

treated with trifluoroacetic acid (8.0 mL, 100 mmol) at 0 °C. The mixture was allowed to warm to ambient temperature. After 16 h, the reaction was quenched by addition of saturated aqueous $NaHCO_3$. The mixture was extracted with CH_2Cl_2 (3 x 30 mL), the organic phases were dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography (SiO_2, pentane/Et_2O, 1/1) to yield δ-lactone **174** as a colorless oil (1.41 g, 66%, 90% ee). $[\alpha]_D^{20}$ = +59 (*c* = 1.07, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.24 – 4.14 (m, 2H), 2.02 – 1.94 (m, 1H), 1.78 (tt, 2H, *J* = 6.8, 5.9 Hz), 1.46 – 1.36 (m, 1H), 1.11 ppm (d, 3H, *J* = 6.9 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.2, 68.3, 34.3, 26.8, 21.8, 16.4 ppm; IR (film): $\tilde{\nu}$ = 2971, 2938, 2876, 1726, 1461, 1380, 1362, 1326, 1241, 1197, 1151, 1083, 1061, 1027, 1012, 943, 917, 730 cm^{-1}; MS (EI) *m/z* (%): 114 (30), 70 (21), 56 (43), 55 (100), 41 (37), 39 (19); HRMS (EI): *m/z*: calcd. for $C_6H_{10}O_2$ [*M*$^+$]: 114.0680, found 114.0681.

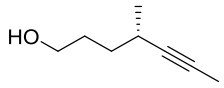
Dichloro Olefin 189. A solution of δ-lactone **174** (1.41 g, 12.4 mmol) and PPh_3 (12.9 g,



49.6 mmol) in THF (250 mL) was prepared. A solution of CCl_4 (29.2 mL, 301 mmol) in THF (50 mL) was added over 4 h to the refluxing mixture. Upon complete addition, the reaction mixture was stirred for 15 min and then allowed to cool to ambient temperature before H_2O (250 mL) was added. The aqueous phase was extracted with CH_2Cl_2 (3 x 150 mL), the organic layers were washed with saturated aqueous $NaHCO_3$ (150 mL), dried over $MgSO_4$ and concentrated to ca. 20 mL. Pentane (100 mL) was added to the residue under vigorous stirring to give a white precipitate that was removed by filtration. This procedure was repeated three times. Then, the solvent was evaporated and the crude material was purified by flash chromatography

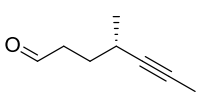
(SiO_2, pentane 100% → pentane/Et_2O, 49/1) to give the dichloro olefin **189** as a colorless oil (1.59 g, 71%). $[\alpha]_D^{20}$ = +125 (*c* = 0.96, $CHCl_3$); ^{1}H NMR (400 MHz, C_6D_6): δ = 3.75 (ddt, 1H, *J* = 10.9, 5.1, 1.9 Hz), 3.17 (ddd, 1H, *J* = 13.3, 10.9, 2.8 Hz), 2.80 (tt, 1H, *J* = 7.2, 5.1 Hz), 1.53 – 1.41 (m, 1H), 1,21 (tdd, 1H, *J* = 13.3, 5.4, 4.2 Hz), 1.08 – 1.02 (m, 1H), 0.92 (d, 3H, *J* = 7.2 Hz), 0.74 – 0.68 ppm (m, 1H); ^{13}C NMR (100 MHz, C_6D_6): δ = 154.4, 104.6, 70.3, 29.5, 28.2, 19.9, 17.3 ppm; IR (film): $\tilde{\nu}$ = 2939, 2871, 1731, 1623, 1375, 1274, 1249, 1178, 1134, 1072, 1010, 953, 920, 882 cm^{-1}; MS (EI) m/z(%): 184 (15), 182 (47), 180 (73), 165 (24), 145 (27), 139 (54), 110 (52), 70 (79), 55 (100), 27 (20); HRMS (EI): m/z: calcd. for $C_7H_{10}OCl_2$ [M^+]: 180.0109, found 180.0111.

Alkynol 190. A solution of dichloro olefin **189** (1.27 g, 6.99 mmol) in Et_2O (4 mL) and



$Cu(acac)_2$ (183 mg, 10 mol%) were subsequently added to a solution of methyllithium (13.1 mL, 21.0 mmol, 1.6 M) in Et_2O (60 mL). After stirring for 14 h, the reaction was complete and excess methyllithium was quenched by addition of H_2O (100 mL). The aqueous phase was extracted with Et_2O (3 x 150 mL), the organic layers were dried over $MgSO_4$ and the solvent was evaporated. The crude material was purified by flash chromatography (SiO_2, pentane/Et_2O, 1/1) to give the title compound as a colorless oil (829 mg, 92%, 90% ee). $[\alpha]_D^{20}$ = +37 (*c* = 1.05, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.10 (br s, 1H), 3.58 (t, 2H, *J* = 6.6 Hz), 2.37 – 2.29 (m, 1H), 1.72 (d, 3H, *J* = 2.4 Hz), 1.70 – 1.53 (m, 2H), 1.46 – 1.31 (m, 2H), 1.08 ppm (d, 3H, *J* = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 83.6, 75.9, 62.7, 35.5, 30.6, 25.8, 21.5, 3.4 ppm; IR (film): $\tilde{\nu}$ = 3340, 2922, 2870, 1452, 1376, 1339, 1055, 983, 896 cm^{-1}; MS (EI) *m/z* (%): 111 (9), 93 (11), 91 (16), 84 (11), 83 (14), 82 (87), 80 (12), 79 (23), 77 (23), 69 (17), 67 (100), 65 (26), 55 (15), 53 (12), 39 (14); HRMS (EI): *m/z*: calcd. for $C_8H_{14}O$ [M^+]: 126.1045, found 126.1045.

Aldehyde 68. Alcohol **190** (1.64 g, 13.0 mmol) was dissolved in MeCN (65 mL).



$[Cu(MeCN)_4]BF_4$ (204 mg, 5 mol%), bipyridine (101 mg, 5 mol%), TEMPO (101 mg, 5 mol%) and *N*-methyl imidazole (107 mg, 10 mol%) were added. The initial red color of the reaction solution had changed to dark green when the reaction was completed. The mixture was filtered through a pad of Celite and the solvent was evaporated. The residue was purified by flash chromatography (SiO_2, pentane/Et_2O, 9/1) to yield the title compound as a colorless oil (1.54 g, 96%, 90% ee). ^{1}H NMR (400 MHz,

$CDCl_3$): δ = 9.77 (s, 1H), 2.65 –2.50 (m, 2H), 2.44 – 2.41 (m, 1H), 1.81 – 1.73 (m, 1H), 1.76 (s, 3H), 1.63 (tdd, 1H, *J* = 14.3, 8.2, 6.2 Hz), 1.12 ppm (d, 3H, *J* = 7.0 Hz); ^{13}C NMR (100 MHz. $CDCl_3$): δ = 202.0, 82.1, 76.5, 41.6, 29.0, 25.2, 21.0, 3.0 ppm; IR (film): $\tilde{\nu}$ = 2971, 2922, 1723, 1454, 1376, 1335, 1259, 1021, 800 cm^{-1}; MS (EI) *m/z* (%): 96 (10), 82 (100), 81 (25), 80 (42), 79 (62), 77 (18), 67 (63), 65 (29), 55 (14), 53 (18), 41 (43), 39 (24); HRMS (ESI): *m/z*: calcd. for $C_8H_{13}O$ [*M*+H$^+$]: 125.0965, found 125.0966.

6.2.3. Synthesis of the Northwestern Fragment

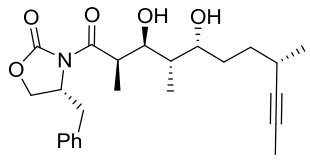
β-Hydroxyimide 409. A solution of (*n*-Bu)$_2$BOTf (29.4 mL, 29.4 mmol, 1.0 M in CH_2Cl_2) was added via syringe over a period of 10 min to a solution of compound (*ent*)-**86** (5.80 g, 24.9 mmol) in CH_2Cl_2 (47 mL) at −78 °C. Then Et_3N (4.49 mL, 32.4 mmol) was added dropwise over 15 min. The mixture was briefly allowed to warm to ambient temperature. After cooling to 0 °C, freshly distilled propanal (2.35 ml, 32.4 mmol) was added dropwise. After another 3.5 h, the reaction was quenched by addition of H_2O (28 mL), MeOH (74 mL) and H_2O_2 (28 mL, 30% wt). The mixture was stirred for 2.5 h and concentrated to a slurry, and the aqueous phase was extracted with EtOAc (3 x 90 mL). The organic layers were dried over $MgSO_4$ and concentrated. The crude material was purified by flash chromatography (SiO_2, pentane/EtOAc, 7/3) to afford the title compound as a colorless solid (6.66 g, 92%). $[\alpha]_D^{23}$ = −36.5 (*c* = 1.07, $CHCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28 – 7.19 (m, 3H), 7.14 – 7.12 (m, 2H), 4.64 (ddt, 1H, *J* = 9.4, 7.4, 3.3 Hz), 4.18 – 4.10 (m, 2H), 3.79 (ddd, 1H, *J* = 8.1, 5.1, 2.8 Hz), 3.72 (qd, 1H, *J* = 7.0, 2.7 Hz), 3.18 (dd, 1H, *J* = 13.4, 3.4 Hz), 2.79 (s, 1H), 2.72 (dd, 1H, *J* = 13.4, 9.4 Hz), 1.56 – 1.40 (m, 2H), 1.18 (d, 3H, *J* = 7.0 Hz), 0.91 ppm (t, 3H, *J* = 7.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.2, 155.7, 134.7, 129.1 (2C), 128.6 (2C), 127.1, 72.7, 65.9, 54.8, 41.3, 37.5, 26.4, 10.1, 9.9 ppm; IR (film): $\tilde{\nu}$ = 3524, 2975, 2937, 2880, 1755, 1697, 1478, 1456, 1373, 1346, 1326, 1264, 1208, 1185, 1115, 1098, 1069, 1055, 983, 969, 928, 764, 750, 706, 696 cm^{-1}; MS (EI) *m/z* (%): 291 (42), 273 (17), 245 (12), 244 (74), 233 (38), 178 (63), 158 (15), 142 (13), 134 (36), 133 (23), 118 (16), 117 (68), 116 (33), 115 (70), 97 (33), 96 (11), 92 (27), 91 (57), 86 (100), 85 (11), 69 (27), 65 (14), 59 (23), 57 (38), 56 (17), 45 (14), 42 (14), 41 (13), 31 (16), 29 (16); HRMS (ESI): *m/z*: calcd. for $C_{16}H_{21}NO_4Na$ [*M*+Na$^+$]: 314.1362, found 314.1363. The analytical and spectroscopic data are in agreement with those reported in the literature.[56a, 154]

β-Ketoimide 48. β-Hydroxyimide **409** (5.49 g, 18.8 mmol) was dissolved in CH_2Cl_2/DMSO (108 mL, 1:1) and the solution was cooled to −15 °C. Et_3N (8.03 mL, 57.1 mmol) was added in one portion, then a solution of SO_3·py (9.09 g, 57.1 mmol) in DMSO (81 mL) was slowly added via a dropping funnel. The reaction mixture was stirred for 3 h. Aqueous $KHSO_4$ (250 mL, 1.0 M) was added and the aqueous phase was extracted with Et_2O (3 x 200 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (40 mL) and brine (30 mL), dried over $MgSO_4$ and concentrated. The crude material was purified by flash chromatography (SiO_2, pentane/MTBE, 1/1) to afford the title compound **48** as a crystalline colorless solid (4.55 g, 83%). $[\alpha]_D^{23}$ = −129 (*c* = 1.38, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35 – 7.27 (m, 3H), 7.20 – 7.16 (m, 2H), 4.73 (ddt, 1H, *J* = 9.5, 7.8, 3.2 Hz), 4.60 (q, 1H, *J* = 7.3 Hz), 4.26 – 4.13 (m, 2H), 3.30 (dd, 1H, *J* = 13.4, 3.6 Hz), 2.77 (dd, 1H, *J* = 13.4, 9.5 Hz), 2.64 (dq, 2H, *J* = 11.0, 7.3 Hz), 1.43 (d, 3H, *J* = 7.3 Hz), 1.06 ppm (t, 3H, *J* = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 208.0, 170.1, 153.8, 135.1, 129.3 (2C), 128.9 (2C), 127.3, 66.4, 55.2, 52.6, 37.9, 34.0, 12.8, 7.5 ppm; IR (film): $\tilde{\nu}$ = 2981, 1766, 1713, 1696, 1451, 1386, 1352, 1337, 1280, 1247, 1223, 1215, 1179, 1120, 1070, 1049, 994, 958, 908, 763, 750, 705, 686 cm^{-1}; MS (EI) *m/z* (%): 289 (20), 260 (32), 233 (20), 178 (12), 142 (29), 134 (21), 133 (18), 117 (59), 116 (21), 113 (51), 91 (28), 57 (100), 56 (15), 29 (22); HRMS (ESI): *m/z*: calcd. for $C_{16}H_{19}NO_4Na$ [*M*+Na$^+$]: 312.1205, found 312.1206. The analytical and spectroscopic data are in agreement with those reported in the literature.[155]

Aldol 193. $Sn(OTf)_2$ (4.36 g, 10.5 mmol) was dispersed in CH_2Cl_2 (20 mL). The mixture was cooled to −20 °C. Upon addition of Et_3N (1.46 mL, 10.5 mmol) the colorless suspension turned pale yellow. Then a solution of β-ketoimide **48** (2.86 g, 9.89 mmol) in CH_2Cl_2 (10 mL) was added dropwise and the resulting mixture was stirred for 1 h at −20 °C before it was cooled to −78 °C and a solution of aldehyde **68** (766 mg, 6.18 mmol) in CH_2Cl_2 (10 mL) was added dropwise. Upon completion of the reaction, the mixture was diluted with CH_2Cl_2 (100 mL) and poured into a cooled (0 °C) aqueous solution of $NaHSO_4$ (150 mL, 1.0 M). The resulting mixture was vigorously stirred for 20 min. The aqueous phase was extracted with CH_2Cl_2 (3 x 100 mL), the combined organic phases were washed with saturated aqueous $NaHCO_3$ (40 mL), dried over $MgSO_4$ and concentrated. The crude material was purified by flash

chromatography (SiO_2, pentane/MTBE, 1/1) to afford the title compound as a colorless sticky oil (1.46 g, 57%).[156] $[\alpha]_D^{23}$ = −48.0 (*c* = 1.00, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35 – 7.32 (m, 2H), 7.30 – 7.28 (m, 1H), 7.21 – 7.19 (m, 2H), 4.87 (q, 1H, *J* = 7.3 Hz), 4.76 (ddt, 1H, *J* = 9.7, 8.0, 3.1 Hz), 4.27 (t, 1H, *J* = 8.0 Hz), 4.19 (dd, 1H, *J* = 9.1, 2.9 Hz), 3.94 (ddd, 1H, *J* = 9.0, 4.1, 2.7 Hz), 3.31 (dd, 1H, *J* = 13.4, 3.4 Hz), 2.83 – 2.76 (m, 2H), 2.49 (br, 1H), 2.44 – 2.39 (m, 1H), 1.78 (d, 3H, *J* = 2.3 Hz), 1.72 – 1.66 (m, 1H), 1.60 – 1.52 (m, 1H), 1.49 (d, 3H, *J* = 7.3 Hz), 1.47 – 1.40 (m, 2H), 1.25 (d, 3H, *J* = 7.2 Hz), 1.14 ppm (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 212.1, 170.3, 153.6, 135.0, 129.4 (2C), 129.0 (2C), 127.4, 83.3, 76.0, 70.9, 66.5, 55.3, 51.9, 48.4, 37.9, 33.4, 31.6, 25.6, 21.4, 12.9, 10.0, 3.5 ppm; IR (film): $\tilde{\nu}$ = 2970, 2940, 1775, 1711, 1690, 1454, 1357, 1289, 1212, 1115, 1077, 1049, 998, 923, 761, 742, 702 cm^{-1}; MS (EI) *m/z* (%): 344 (13), 289 (34), 260 (53), 233 (46), 178 (56), 177 (11), 167 (25), 142 (12), 135 (12), 134 (34), 133 (23), 125 (16), 123 (15), 118 (10), 117 (62), 116 (17), 113 (17), 112 (100), 107 (11), 93 (11), 92 (29), 91 (45), 86 (24), 83 (26), 82 (15), 80 (16), 79 (13), 67 (18), 65 (10), 56 (24), 55 (32); HRMS (ESI): *m/z*: calcd. for $C_{24}H_{31}NO_5Na$ [*M*+Na^+]: 436.2098, found 436.2094. The analytical and spectroscopic data are in agreement with those reported in the literature.[41]

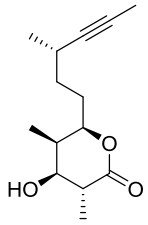
1,3-Diol 410. A solution of compound **193** (1.46 g, 3.53 mmol) in MeCN (44 mL) was added



to a solution of $Me_4NBH(OAc)_3$ (4.64 g, 17.7 mmol) in MeCN (70 mL) and AcOH (39 mL) via a dropping funnel at −50 °C. The mixture was allowed to warm to −10 °C. After stirring for 1 h, the reaction mixture was poured into a mixture of saturated aqueous Rochelle salt (350 mL) and CH_2Cl_2 (350 mL) (1:1) at 0 °C. Under vigorous stirring, saturated aqueous $NaHCO_3$ followed by solid $NaHCO_3$ were added until gas evolution ceased. The aqueous phase was extracted with CH_2Cl_2 (4 x 200 mL), the last batch was stirred with the aqueous phase for 5 min. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (SiO_2, pentane/EtOAc, 1/1) to afford the title compound as a colorless foam (1.16 g, 80%). $[\alpha]_D^{23}$ = −5.0 (*c* = 0.93, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36 – 7.28 (m, 3H), 7.21 – 7.19 (m, 2H), 4.71 (ddt, 1H, *J* = 9.4, 7.6, 3.2 Hz), 4.27 – 4.19 (m, 2H), 4.00 (dd, 1H, *J* = 9.1, 2.5 Hz), 3.90 (qd, 1H, *J* = 7.0, 2.5 Hz), 3.82 (dt, 1H, *J* = 9.7, 2.8 Hz), 3.65 (br, 1H), 3.25 (dd, 1H, *J* = 13.4, 3.4 Hz), 2.80 (dd, 1H, *J* = 13.4, 9.4 Hz), 2.47 – 2.35 (m, 1H), 1.87 (dqd, 1H, *J* = 9.4, 7.1, 2.5 Hz), 1.78 (d, 3H, *J* = 2.3 Hz), 1.70 –

1.42 (m, 5H), 1.28 (d, 3H, *J* = 7.0 Hz), 1.14 (d, 3H, *J* = 7.0 Hz), 0.87 ppm (d, 3H, *J* = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.7, 152.5, 134.6, 129.1 (2C), 128.6 (2C), 127.1, 83.3, 75.6, 73.4, 73.2, 65.9, 54.7, 39.2, 38.9, 37.5, 33.6, 30.2, 25.4, 21.1, 11.4, 9.8, 3.2 ppm; IR (film): $\tilde{\nu}$ = 2970, 2919, 1779, 1697, 1455, 1387, 1210, 1106, 1045, 1015, 972, 762, 702 cm^{-1}; MS (pos. ESI) *m*/*z* (%): 438 (*M*+Na$^+$, 100); HRMS (ESI): *m/z*: calcd. for $C_{24}H_{33}NO_5Na$ [*M*+Na$^+$]: 438.2254, found 438.2251. The analytical and spectroscopic data are in agreement with those reported in the literature.[41]

δ-Lactone 194. Diol **410** (878 mg, 2.13 mmol) was dissolved in THF/H_2O (21 mL, 3:1) and the



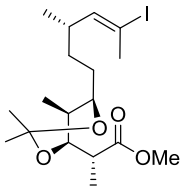
solution was cooled to 0 °C. The mixture was treated with H_2O_2 (0.85 mL, 30% wt) and LiOH (143 mg, 3.41 mmol). The resulting mixture was stirred at ambient temperature for 2 h until TLC control indicated full conversion of the diol **410**. The mixture was acidified with aqueous HCl (2.0 mL, 1.0 M) and stirred for 5 min before the aqueous phase was extracted with Et_2O (3 x 60 mL). The combined organic phases were dried over $MgSO_4$ and concentrated. The crude material was purified by flash chromatography (SiO_2, pentane/EtOAc, 7/3 → 1/1) to afford δ-lactone **194** as a colorless oil (512 mg, 99%). $[\alpha]_D^{23}$ = +95.2 (*c* = 0.75, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.80 (ddd, 1H, *J* = 8.7, 5.0, 2.4 Hz), 3.36 (dd, 1H, *J* = 10.4, 4.3 Hz), 2.47 – 2.35 (m, 2H), 2.16 (br, 1H), 1.98 (dddd, 1H, *J* = 13.1, 10.2, 8.6, 4.4 Hz), 1.72 – 1.58 (m, 2H), 1.68 (d, 3H, *J* = 2.4 Hz), 1.52 – 1.33 (m, 2H), 1.47 (d, 3H, *J* = 7.1 Hz), 1.22 (d, 3H, *J* = 6.9 Hz), 0.81 ppm (d, 3H, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.3, 83.6, 79.4, 76.8, 74.0, 40.4, 37.8, 33.4, 30.6, 26.3, 21.9, 14.7, 4.7, 3.6 ppm; IR (film): $\tilde{\nu}$ = 2941, 1766, 1713, 1696, 1475, 1464, 1451, 1386, 1353, 1337, 1280, 1247, 1223, 1214, 1179, 1120, 1085, 1070, 1049, 1032, 994, 973, 958, 908, 857, 825, 763, 750, 705, 686 cm^{-1}; MS (EI) *m/z* (%): 152 (11), 151 (45), 147 (11), 137 (10), 136 (17), 135 (23), 133 (11), 131 (12), 130 (12), 125 (50), 124 (17), 123 (35), 122 (12), 121 (40), 119 (20), 113 (49), 112 (16), 111 (10), 109 (56), 108 (31), 107 (81), 106 (12), 105 (34), 103 (15), 98 (42), 97 (21), 96 (32), 95 (48), 94 (17), 93 (74), 91 (53), 87 (16), 86 (12), 85 (77), 83 (22), 82 (81), 81 (49), 80 (93), 79 (90), 77 (31), 69 (43), 68 (26), 67 (100), 66 (15), 65 (28), 59 (13), 58 (35), 57 (69), 56 (31), 55 (72), 53 (27), 44 (19), 43 (44), 41 (67), 39 (27), 29 (21); HRMS (ESI): *m/z*: calcd. for $C_{14}H_{22}NO_3Na$ [*M*+Na$^+$]: 261.1459, found 261.1461. The analytical and spectroscopic data are in agreement with those reported in the literature.[41]

Methyl Ester 166. Camphorsulfonic acid (49 mg, 10 mol%) was added to a solution of δ-lactone **194** (512 mg, 2.11 mmol) in 2,2-dimethoxypropane (26 mL) and the reaction mixture was stirred at ambient temperature overnight. The mixture was diluted with Et_2O (50 mL), treated with saturated aqueous $NaHCO_3$ and the aqueous phase was extracted with Et_2O (3 x 50 mL). The combined organic phases were washed with brine (40 mL), dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (SiO_2, pentane/Et_2O, 7/3) to afford methyl ester **166** as a colorless oil (589 mg, 90%).[44a, 147] $[\alpha]_D^{20}$ = −1.86 (*c* = 0.59, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.76 (dt, 1H, *J* = 9.4, 4.4 Hz), 3.69 (s, 3H), 3.63 (dd, 1H, *J* = 7.7, 5.0 Hz), 2.60 – 2.54 (m, 1H), 2.43 – 2.37 (m, 1H), 1.87 – 1.82 (m, 1H), 1.79 (d, 3H, *J* = 2.3 Hz), 1.62 – 1.49 (m, 2H), 1.44 – 1.35 (m, 2H), 1.31 (s, 3H), 1.29 (s, 3H), 1.20 (d, 3H, *J* = 7.0 Hz), 1.13 (d, 3H, *J* = 6.9 Hz), 0.84 ppm (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.6, 100.2, 83.2, 75.4, 75.0, 68.7, 51.3, 42.6, 36.5, 33.0, 27.8, 25.3, 24.6, 23.3, 20.9, 11.7, 11.1, 3.2 ppm; IR (film): $\tilde{\nu}$ = 2983, 2937, 2877, 1738, 1456, 1434, 1379, 1224, 1198, 1166, 1126, 1090, 1018, 985, 954, 876, 855, 838 cm^{-1}; MS (pos. ESI) *m/z* (%): 333 (*M*+Na^+, 100); HRMS (ESI): *m/z*: calcd. for $C_{18}H_{30}NO_4Na$ [*M*+Na^+]: 333.2037, found 333.2036.

Alkenyl Silane 411. A solution of freshly prepared $LiSiMe_2Ph$[91] (6.70 mL, 2.01 mmol) in THF (5.1 mL) was added to CuCN (180 mg, 2.01 mmol) at 0 °C. After 30 min of stirring, the mixture was cooled to −78 °C and a solution of alkyne **166** (406 mg, 1.34 mmol) in THF (1.0 mL) was added dropwise. After 30 min, the reaction mixture was allowed to warm to 0 °C and saturated aqueous NH_4Cl (20 mL) was added. The aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. The crude material was purified by flash chromatography (SiO_2, pentane 100% → pentane/EtOAc 30/1) to afford the title compound as a colorless oil (557 mg, 93%). $[\alpha]_D^{23}$ = −18.0 (*c* = 0.52, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50 – 7.47 (m, 2H), 7.34 – 7.32 (m, 3H), 5.58 (d, 1H, *J* = 9.4 Hz), 3.74 – 3.69 (m, 1H), 3.69 (s, 3H), 3.62 (dd, 1H, *J* = 7.8, 5.0 Hz), 2.63 – 2.53 (m, 2H), 1.84 – 1.75 (m, 1H), 1.64 (d, 3H, *J* = 1.7 Hz), 1.47 – 1.34 (m, 2H), 1.31 (s, 3H), 1.30 (s, 3H), 1.28 – 1.25 (m, 2H), 1.19 (d, 3H, *J* = 6.9 Hz), 0.95 (d, 3H, *J* = 6.6 Hz), 0.81 (d, 3H, *J* = 6.8 Hz), 0.32 (s, 3H), 0.31 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.1, 147.8, 139.1, 134.1 (2C), 132.2, 128.9, 127.8 (2C), 100.7, 75.5, 69.4, 51.8, 43.1, 36.9, 33.3, 32.5, 28.5, 25.2, 23.8, 20.8,

15.1, 12.1, 11.6, −3.1, −3.3 ppm; IR (film): $\tilde{\nu}$ = 2986, 2953, 1739, 1618, 1456, 1428, 1379, 1320, 1290, 1247, 1224, 1200, 1173, 1200, 1173, 1109, 1055, 1020, 999, 985, 968, 956, 926, 880, 831, 811, 772, 746, 729, 699 cm^{-1}; MS (EI) *m/z* (%): 245 (14), 137 (23), 136 (14), 135 (100), 128 (19), 127 (13), 121 (13), 75 (11), 73 (15); HRMS (ESI): *m/z*: calcd. for $C_{26}H_{42}O_4SiNa$ [*M*+Na^+]: 469.2748, found 469.2745.

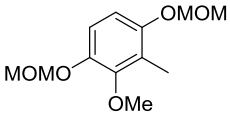
Alkenyl Iodide 164. A solution of alkenyl silane **411** (472 mg, 1.06 mmol) in HFIP[157] (11 mL)



was treated at 0 °C with 2,6-lutidine (0.50 mL, 4.3 mmol) and NIS (358 mg, 1.59 mmol) and the resulting mixture was stirred for 30 min at 0 °C. Then, saturated aqueous $Na_2S_2O_5$ (30 mL) was added to quench the reaction. The aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic phases were dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (SiO_2, pentane100% → pentane/EtOAc, 20/1) to afford alkenyl iodide **164** as a colorless oil (458 mg, 97%). $[\alpha]_D^{23}$ = +11.5 (*c* = 1.08, $CHCl_3$), ^{1}H NMR (400 MHz, C_6D_6): δ = 5.97 (d, 1H, *J* = 10.0 Hz), 3.80 (dd, 1H, *J* = 7.7, 4.8 Hz), 3.67 (dt, 1H, *J* = 9.1, 4.2 Hz), 3.38 (s, 3H), 2.49 (qd, 1H, *J* = 6.9, 4.4 Hz), 2.20 – 2.15 (m, 1H), 2.14 (s, 3H), 1.75 – 1.66 (m, 1H), 1.45 – 1.32 (m, 2H), 1.34 (s, 3H), 1.29 (d, 3H, *J* = 6.7 Hz), 1.29 (s, 3H), 1.13 – 1.00 (m, 2H), 0.75 (d, 3H, *J* = 6.8 Hz), 0.75 ppm (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, C_6D_6): δ = 174.2, 147.4, 100.7, 92.9, 75.8, 69.3, 51.3, 43.4, 37.7, 35.8, 33.4, 28.6, 27.8, 25.3, 23.9, 20.3, 12.3, 11.8 ppm; IR (film): $\tilde{\nu}$ = 2984, 2946, 1737, 1635, 1456, 1434, 1378, 1358, 1325, 1290, 1224, 1198, 1169, 1135, 1090, 1035, 1019, 986, 955, 878, 858, 839, 808, 765, 699 cm^{-1}; MS (EI) *m/z* (%): 380 (31), 293 (14), 253 (43), 235 (17), 208 (31), 195 (51), 183 (15), 175 (13), 147 (16), 137 (28), 129 (31), 128 (100), 125 (69), 113 (34), 107 (21), 97 (39), 96 (11), 95 (37), 83 (23), 82 (11), 81 (49), 79 (11), 69 (80), 68 (26), 67 (40), 59 (34), 55 (42), 53 (12), 43 (46), 41 (43), 29 (12); HRMS (ESI): *m/z*: calcd. for $C_{18}H_{31}O_4INa$ [*M*+Na^+]: 461.1160, found 461.1160.

6.2.4. Strategies Towards the Aromatic Core

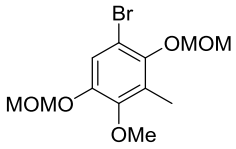
MOM-Ether 412. A solution of 2-methoxy-3-methylbenzene-1,4-diol (**200**) (1.01 g,



6.56 mmol) in DMF (3.4 mL) was added dropwise to a suspension of NaH (441 mg, 18.3 mmol) in DMF (2.7 mL) at 0 °C. The mixture was allowed to warm to ambient temperature over 1 h. After cooling to 0 °C, a solution of (chloromethyl)methyl ether (1.39 mL, 18.3 mmol) in DMF (1.4 mL) was added

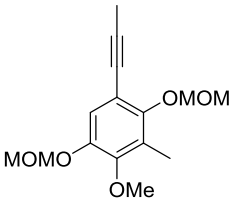
dropwise. After warming to rt, the mixture was stirred for 14 h. For work-up, aqueous NH_3 was added and the aqueous phase was extracted with CH_2Cl_2 (3 x 15 mL). The extracts were combined, washed with water (10 mL) and brine (10 mL), dried over Na_2SO_4, and concentrated. The crude material was purified by flash chromatography (SiO_2, pentane/EtOAc, 6/3) to yield the title compound **412** as a colorless oil (1.51 g, 95%). ^{1}H NMR (400 MHz, CD_3OD): δ = 6.89 (d, 1H, *J* = 9.0 Hz), 6.76 (d, 1H, *J* = 9.0 Hz), 5.13 (s, 2H), 5.12 (s, 2H), 3.78 (s, 3H), 3.48 (s, 3H), 3.45 (s, 3H), 2.14 ppm (s, 3H); ^{13}C NMR (100 MHz, CD_3OD): δ = 152.5, 150.4, 146.5, 123.0, 116.0, 111.1, 97.1, 96.3, 60.8, 56.4, 56.2, 9.3 ppm; IR (film): $\tilde{\nu}$ = 2934, 2900, 2825, 1594, 1484, 1402, 1272, 1245, 1224, 1206, 1150, 1101, 1089, 1062, 1040, 1009, 985, 940, 919, 802, 766, 714 cm^{-1}; MS (EI) *m/z* (%): 242 (29), 197 (11), 45 (100); HRMS (ESI): *m/z*: calcd. for $C_{12}H_{18}O_5Na$ [*M*+Na^+]: 265.1048, found 265.1046.

Aryl Bromide 201. A solution of compound **412** (1.51 g, 6.24 mmol) in MeCN (60 mL) was



cooled to −10 °C and treated with NBS (1.14 g, 6.43 mmol). The mixture was then warmed to 0 °C and stirring was continued for 4 h. The solvent was removed and the residue was purified by flash chromatography (SiO_2, pentane/MTBE, 8/2) to give aryl bromide **201** as a pale yellow oil (1.37 g, 68%). ^{1}H NMR (400 MHz, CD_3OD): δ = 7.22 (s, 1H), 5.16 (s, 2H), 5.00 (s, 2H), 3.80 (s, 3H), 3.60 (s, 3H), 3.45 (s, 3H), 2.25 ppm (s, 3H); ^{13}C NMR (100 MHz, CD_3OD): δ = 149.7, 149.5, 148.8, 119.4, 116.0, 111.2, 100.9, 97.7, 60.8, 58.2, 56.6, 11.0 ppm; IR (film): $\tilde{\nu}$ = 3373, 2942, 2829, 1651, 1588, 1473, 1376, 1287, 1233, 1205, 1151, 1081, 1036, 992, 954, 923, 840, 791, 778, 752, 724, 692, 666 cm^{-1}; GC-MS: t_R (70_20) = 10.1 min; MS (EI) *m/z* (%): 322 (7), 290 (1), 209 (2), 195 (5), 45 (100).

Alkyne 202. A suspension of sodium propyne (310 mg, 0.966 mmol) in THF (10 mL) was



prepared. Trimethylborate (568 μL, 5.00 mmol) was slowly added and the resulting solution was stirred for 30 min before $PdCl_2(dppf)\cdot CH_2Cl_2$ (91 mg, 10 mol%) and aryl bromide **201** (400 mg, 1.25 mmoL) were added. After refluxing for 12 h, the reaction mixture was cooled to ambient temperature and H_2O (10 mL) was added. The aqueous phase was extracted with MTBE (3 x 50 mL), the organic phases were dried over Na_2SO_4 and evaporated. The residue was purified by flash chromatography (SiO_2, pentane/MTBE, 8/2) to afford the title

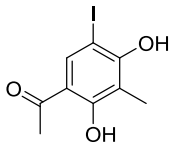
compound **202** as a colorless oil (270 mg, 99%). ^{1}H NMR (400 MHz, CD_3OD): δ = 6.97 (s, 1H), 5.14 (s, 2H), 5.10 (s, 2H), 3.79 (s, 3H), 3.57 (s, 3H), 3.48 (s, 3H), 2.18 (s, 3H), 2.04 ppm (s, 3H); ^{13}C NMR (100 MHz, CD_3OD): δ = 153.4, 150.1, 147.6, 127.2, 119.5, 114.2, 100.4, 96.6, 89.9, 79.2, 60.9, 57.9, 56.5, 10.3, 4.0 ppm; MS (EI) *m/z* (%): 280 (13), 250 (6), 235 (100), 205 (32), 175 (10), 138 (5), 83 (5); HRMS (ESI): *m/z*: calcd. for $C_{15}H_{20}O_5Na$ [*M*+Na^+]: 303.1206, found 303.1203.

Ketone 204. 2-Methylresorcinol (**203**) (5.00 g, 40.3 mmol) was added dropwise to $BF_3{\cdot}Et_2O$ (12.3 mL, 96.7 mmol). The mixture was stirred at 70 °C until a clear red solution was obtained. After cooling to ambient temperature, acetic anhydride (4.16 mL, 44.3 mmol) was added over 30 min under occasional cooling of the reaction vessel (exothermic reaction!). After complete addition, the mixture was heated to 80 °C. After 6 h, the orange suspension was allowed to cool to ambient temperature. Next, ice water was slowly added. The aqueous phase was extracted with Et_2O (3 x 100 mL) and the extracts were concentrated. The crude material was recrystallized from boiling methanol/H_2O (1:1, 250 mL) to yield the desired compound **204** as beige needles (5.59 g, 84%). ^{1}H NMR (400 MHz, CD_3OD): δ = 12.93 (s, 1H), 8.33 (s, 1H), 7.58 (d, 1H, *J* = 8.9 Hz), 6.40 (d, 1H, *J* = 8.9 Hz), 2.53 (s, 3H), 2.05 ppm (s, 3H); ^{13}C NMR (100 MHz, CD_3OD): δ = 204.4, 164.0, 163.9, 131.1, 114.0, 112.2, 107.9, 26.1, 7.5 ppm; IR (film): $\tilde{\nu}$ = 3160, 2924, 1613, 1591, 1493, 1429, 1374, 1304, 1271, 1177, 1130, 1090, 1014, 994, 931, 866, 805, 766, 750, 721 cm^{-1}; MS (EI) *m/z* (%): 166 (37), 152 (9), 151 (100), 95 (5), 77 (4); HRMS (ESIneg): *m/z*: calcd. for $C_9H_9O_3$ [*M*−H^+]: 165.0557, found 165.0557.

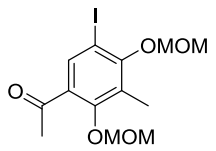
MOM-Ether 205. A solution of compound **204** (5.00 g, 30.1 mmol) in DMF (43 mL) was treated with NaH (2.89 g, 120.5 mmol, 60%) in small portions at 0 °C. The ice bath was removed and the mixture was allowed to stir for 30 min at ambient temperature before it was cooled to 0 °C and (chloromethyl)methyl ether (5.72 mL, 75.3 mmol) was added. The resulting yellow suspension was stirred for 14 h at rt. For work-up, H_2O (15 mL) was added and the aqueous phase was extracted with EtOAc (2 x 150 mL) and CH_2Cl_2 (2 x 150 mL), the organic phases were dried over $MgSO_4$ and concentrated. The crude material was purified by flash chromatography (SiO_2, hexanes/EtOAc, 3/1) to give the title compound **205** as an orange oil

(4.95 g, 65%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48 (d, 1H, *J* = 8.5 Hz), 6.89 (d, 1H, *J* = 8.5 Hz), 5.23 (s, 2H), 4.96 (s, 2H), 3.52 (s, 3H), 3.48 (s, 3H), 2.57 (s, 3H), 2.21 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.5, 159.3, 156.1, 128.5, 127.6, 121.7, 109.4, 101.1, 94.4, 58.0, 56.4, 30.2, 9.8 ppm; GC-MS: t_R (70_20) = 9.7 min; MS (EI) m/z (%): 254 (92), 239 (14), 223 (43), 211 (35), 192 (77), 180 (100), 163 (74), 149 (36), 136 (19).

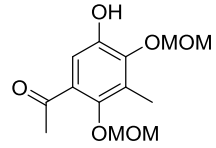
Aryl Iodide 208. A solution of ketone **204** (3.00 g, 18.1 mmol) in acetic acid (30 mL) was treated with NIS (4.45 g, 19.9 mmol) and sulfuric acid (0.30 mL). After 30 min the mixture was filtered through a pad of SiO_2 which was washed with hexanes/EtOAc (2 x 50 mL, 4:1). The filtrate was evaporated to afford the title compound **208** as a brown crystalline solid (4.99 g, 93%). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.96 (s, 1H), 10.25 (br s, 1H), 8.10 (s, 1H), 2.56 (s, 3H), 2.08 ppm (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 202.9, 161.8, 160.4, 138.6, 115.0, 111.6, 75.3, 26.4, 9.0 ppm; MS (EI) *m/z* (%): 292 (77), 278 (9), 277 (100), 221 (4), 150 (7); HRMS (ESIneg): *m/z*: calcd. for $C_9H_8O_3I$ [$M-H^+$]: 290.9523, found 290.9524.



Aryl Iodide 209. 1,8-Diazabicyclo[5.4.0]undec-7-en (1.28 mL, 8.56 mmol) was added to a solution of compound **208** (1.00 g, 3.42 mmol) in acetone (22 mL). (Chloromethyl)methyl ether (0.65 mL, 8.56 mmol) was then added dropwise and the reaction solution was stirred at reflux temperature for 1 h. For work-up, the slurry was filtered through a pad of Celite and the filtrate was evaporated. The residue was purified by flash chromatography (SiO_2, hexanes/EtOAc, 4/1) to yield compound **209** as a pale yellow oil (778 mg, 60%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.04 (s, 1H), 5.04 (s, 2H), 4.88 (s, 2H), 3.62 (s, 3H), 3.48 (s, 3H), 2.54 (s, 3H), 2.20 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.2, 147.9, 147.6, 145.3, 130.8, 126.4, 114.6, 101.1, 99.3, 57.8, 57.5, 30.3, 10.7 ppm; MS (EI) *m/z* (%): 380 (7), 348 (2), 318 (1), 304 (13), 45 (100); HRMS (ESI): *m/z*: calcd. for $C_{13}H_{17}O_5INa$ [$M+Na^+$]: 403.0013, found 403.0013.

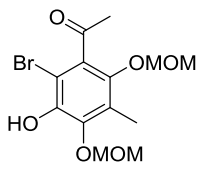


Phenol 210. Aryl iodide **209** (150 mg, 0.396 mmol), KOH (446 mg, 7.92 mmol) and *t*-BuXPhos (33 mg, 20 mol%) were added to a solution of 1,4-dioxane (2.93 mL) and H_2O (0.97 mL) and the mixture was degassed for 5 min by bubbling a stream of argon through. $Pd(dba)_2$ (23 mg, 10 mol%) was



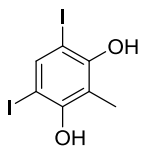
introduced and the reaction mixture was stirred for 6 h at reflux temperature. For work-up, the dark brown mixture was acidified by dropwise addition of aqueous HCl (1.0 M), the aqueous phase was extracted with EtOAc (3 x 50 mL), the organic phases were dried over $MgSO_4$ and evaporated. The crude material was purified by flash chromatography (SiO_2, pentane/EtOAc, 8/3) to give phenol **210** as a yellow oil (63 mg, 60%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34 (br s, 1H), 7.04 (s, 1H), 5.04 (s, 2H), 4.88 (s, 2H), 3.62 (s, 3H), 3.48 (s, 3H), 2.54 (s, 3H), 2.20 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.2, 147.9, 147.6, 145.3, 130.8, 126.4, 114.6, 101.1, 99.3, 57.8, 57.5, 30.3, 10.7 ppm; IR (film): $\tilde{\nu}$ = 3319, 2933, 1676, 1589, 1428, 1395, 1357, 1336, 1265, 1216, 1199, 1155, 1041, 955, 917, 809, 762, 699 cm^{-1}; GC-MS: t_R (70_20) = 10.5 min; MS (EI) *m/z* (%): 270 (9), 194 (12), 179 (4), 164 (4), 45 (100); HRMS (ESIpos): *m/z*: calcd. for $C_{13}H_{18}O_6Na$ [*M*+Na$^+$]: 293.0996, found 293.0996.

Aryl Bromide 211. A solution of *t*-BuNH_2 (7.8 μL, 74 μmol) and bromine (1.9 μL, 37 μmol) in



toluene (0.2 mL) was cooled to −100 °C. Phenol **210** (10 mg, 37 μmol) was dissolved in toluene (0.2 mL) and the solution was also cooled to −100 °C before the basic bromine solution was slowly introduced. After 30 min, the mixture was diluted with CH_2Cl_2 (1 mL) and H_2O (1 mL). Aqueous HCl (1.0 M) was added dropwise until the mixture was acidic. The aqueous phase was extracted with CH_2Cl_2 (3 x 8 mL), the combined organic phases were washed with aqueous $Na_2S_2O_3$ solution, dried over $MgSO_4$ and evaporated. The crude material was purified by flash chromatography (SiO_2, pentane 100% → pentane/EtOAc, 7/3) to afford aryl bromide **211** as a colorless oil (2.1 mg, 16%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.91 (br, 1H), 5.17 (s, 2H), 4.91 (s, 2H), 3.52 (s, 3H), 3.50 (s, 3H), 2.55 (s, 3H), 2.02 ppm (s, 3H); GC-MS: t_R (70_20) = 10.5 min; MS (EI) *m/z* (%): 349 (1), 313 (12), 285 (23), 242 (100), 207 (14), 177 (14).

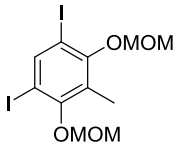
Diiodide 212. A solution of 2-methylbenzene-1,3-diol (**203**) (400 mg, 3.23 mmol) in acetic



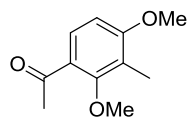
acid (5.6 mL) was treated with NIS (1.52 g, 6.77 mmol) and sulfuric acid (0.11 mL, 2.07 mmol). After 30 min, the reaction mixture was filtered through a pad of Celite which was rinsed with hexanes/EtOAc (20 mL, 10:1). The solvent was evaporated and the residue was purified by flash chromatography (SiO_2, hexanes/EtOAc, 10/1) to give diiodide **212** as a pale yellow solid (1.17 g, 96%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72 (s, 1H), 5.27 (s, 2H), 2.27 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$):

δ = 154.3, 140.9 (2C), 112.0, 75.9 (2C), 11.1 ppm; IR (film): $\tilde{\nu}$ = 3495, 3468, 3425, 2923, 2854, 1704, 1569, 1438, 1420, 1325, 1312, 1269, 1235, 1207, 1132, 1054, 855, 788, 716 cm^{-1}; MS (EI) *m/z* (%): 376 (100), 249 (10), 221 (5), 122 (12), 94 (11), 66 (12), 65 (14), 39 (17); HRMS (EI): *m/z*: calcd. for $C_7H_6O_2I_2$ [M^+]: 375.8454, found 375.8457.

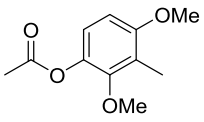
Diiodide 213. A solution of compound **212** (1.23 g, 3.00 mmol) in DMF (4.3 mL) was cooled to 0 °C before NaH (264 mg, 6.59 mmol, 60%) was added in small portions. The mixture was stirred for 20 min at ambient temperature before it was cooled to 0 °C and (chloromethyl)methyl ether (523 μL, 6.89 mmol) was introduced dropwise. The reaction mixture was warmed to ambient temperature and stirred for 20 min. The reaction was quenched with H_2O (2 mL) and the aqueous phase was extracted with EtOAc (3 x 20 mL), the organic phases were washed with brine (10 mL), dried over $MgSO_4$ and evaporated. The crude material was purified by flash chromatography (SiO_2, pentane/EtOAc, 4/1) to yield compound **213** as a colorless oil (712 mg, 51%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.10 (s, 1H), 5.17 (s, 2H), 5.03 (s, 2H), 3.67 (s, 3H), 3.46 (s, 3H), 2.25 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.6 (2C), 144.7, 128.8, 100.2 (2C), 88.1 (2C), 58.3 (2C), 10.8 ppm; IR (film): $\tilde{\nu}$ = 2934, 2902, 2826, 1713, 1574, 1461, 1423, 1387, 1257, 1228, 1202, 1185, 1153, 1102, 1077, 1047, 992, 955, 921, 880, 833, 798, 745 cm^{-1}; MS (EI) *m/z* (%): 464 (18), 418 (2), 388 (3), 358 (1), 337 (9), 45 (100); HRMS (ESIpos): *m/z*: calcd. for $C_{11}H_{14}O_4I_2Na$ [*M*+Na^+]: 486.8875, found 486.8874.



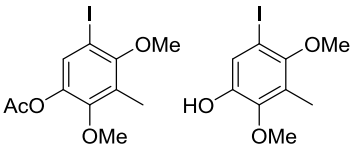
Ketone 228. Compound **204** (5.00 g, 30.1 mmol) was dissolved in acetone (60 mL) and dimethyl sulfate (6.20 mL, 75.2 mmol) and K_2CO_3 (12.5 g, 90.3 mmol) were added to the solution. The mixture was stirred for 17 h at rt. For work-up, the mixture was filtered through a pad of Celite to remove K_2CO_3, then aqueous NH_3 (10 mL, 24%) was added to remove excess dimethyl sulfate. The aqueous phase was extracted with MTBE (3 x 60 mL), the combined organic phases were washed with H_2O (20 mL), HCl (20 mL, 1.0 M) and brine (20 mL), dried over $MgSO_4$ and evaporated. The crude material was purified by flash chromatography (SiO_2, pentane/EtOAc, 9/1) to yield the desired compound **228** as a pale yellow oil (5.44 g, 93%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60 (d, 1H, *J* = 8.2 Hz), 6.67 (d, 1H, *J* = 8.2 Hz), 3.86 (s, 3H), 3.74 (s, 3H), 2.60 (s, 3H), 2.16 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.5, 161.8, 129.4, 128.6, 125.3, 105.5, 101.4, 61.5,



55.4, 29.9, 8.5 ppm; GC-MS: t_R (70_20) = 8.1 min; MS (EI) m/z (%): 194 (13), 179 (100), 136 (11), 91 (9).

Acetate 413. 

A solution of ketone **228** (5.00 g, 25.8 mmol) and *p*-toluenesulfonic acid (250 mg, 6 mol%) in CH_2Cl_2 (12 mL) was treated with a solution of *m*-CPBA (12.7 g, 51.5 mmol) in CH_2Cl_2 (12 mL). The mixture was allowed to warm to ambient temperature and was stirred for 14 h. Saturated aqueous $NaHCO_3$ was then added and the aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL), the organic phases were evaporated and the resulting residue was again washed with saturated aqueous $NaHCO_3$ to remove benzoic acid. After the solvent was removed, the residue was diluted with Et_2O (10 mL) and the mixture passed through a pad of $MgSO_4$. The filtrate was concentrated and the crude material was purified by flash chromatography (SiO_2, hexanes/EtOAc, 4/1) to yield the title compound **413** as an orange oil (3.76 g, 70%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.85 (d, 1H, *J* = 8.9 Hz), 6.58 (d, 1H, *J* = 8.9 Hz), 3.79 (s, 3H), 3.74 (s, 3H), 2.31 (s, 3H), 2.15 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.4, 156.0, 137.2, 133.3, 129.8, 119.3, 105.2, 60.4, 55.4, 20.4, 8.8 ppm; IR (film): $\tilde{\nu}$ = 2942, 2839, 1760, 1713, 1630, 1597, 1483, 1418, 1367, 1302, 1275, 1244, 1222, 1197, 1158, 1105, 1022, 1003, 980, 918, 885, 802, 771, 741, 718, 696 cm^{-1}; MS (EI) *m/z* (%): 210 (15), 169 (10), 168 (100), 158 (11), 156 (33), 153 (42), 141 (15), 139 (48), 125 (10), 111 (15); HRMS (ESI): *m/z*: calcd. for $C_{11}H_{14}O_4Na$ [*M*+Na^+]: 233.0784, found 233.0784.

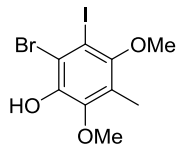
Aryl Iodide 229 and Phenol 414. 

229 **414**
NIS (6.10 g, 27.1 mmol) and sulfuric acid (0.63 mL, 11.8 mmol) were added to a solution of compound **413** (4.74 g, 22.6 mmol) in acetic acid (45 mL). After stirring for 30 min, the suspension was filtered through a pad of Celite. H_2O (25 mL) was added, the aqueous phase was extracted with MTBE (3 x 80 mL) and the organic phases were washed with aqueous $Na_2S_2O_3$ solution (20 mL), dried over Na_2SO_4 and concentrated. The yellow oil was subjected to the next step without further purification.

A solution of acetate **229** (6.84 g, 20.3 mmol) in MeOH (23 mL) was treated with a solution of KOH (2.27 g, 40.6 mmol) in MeOH/H_2O (6 mL, 10:1) and the resulting mixture was stirred for 2 h. For work-up, H_2O (60 mL) and aqueous HCl (35 mL, 2.0 M) were added. The aqueous

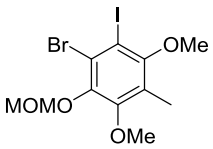
phase was extracted with MTBE (3 x 100 mL), the organic phases were washed with brine (50 mL), dried over $MgSO_4$ and evaporated. The residue was purified by flash chromatography (SiO_2, hexanes/EtOAc, 4/1) to afford the product **414** as a pale orange oil (6.17 g, 87%, over 2 steps). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.24 (s, 1H), 5.50 (br s, 1H), 3.77 (s, 3H), 3.72 (s, 3H), 2.28 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.5, 145.9, 145.8, 124.8, 121.8, 84.9, 60.5, 60.2, 10.4 ppm; IR (film): $\tilde{\nu}$ = 3375, 2937, 2834, 1704, 1580, 1471, 1451, 1403, 1359, 1336, 1279, 1229, 1193, 1163, 1030, 990, 881, 847, 774, 718, 701, 675, 629, 530, 510 cm^{-1}; MS (EI) *m/z* (%): 294 (100), 279 (52), 251 (9); HRMS (ESI): *m/z*: calcd. for $C_9H_{10}O_3I$ [M−H$^+$]: 292.9681, found 292.9680.

Aryl Bromide 230. Compound **414** (1.00 g, 3.40 mmol) was dissolved in MeCN (34 mL) and



the solution was cooled to −40 °C before NBS (680 mg, 3.82 mmol) was added portionwise. After 2 h, the solvent was removed and the residue was purified by flash chromatography (SiO_2, toluene/EtOAc, 9/1) to afford the desired aryl bromide **230** as a sticky yellow oil (790 mg, 62%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.87 (s, 1H), 3.80 (s, 3H), 3.70 (s, 3H), 2.24 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.5, 146.3, 143.6, 124.6, 113.7, 93.6, 60.4, 60.2, 10.5 ppm; IR (film): $\tilde{\nu}$ = 3408, 2939, 2836, 1567, 1450, 1403, 1275, 1225, 1193, 1178, 1090, 1039, 986, 897, 843, 801, 775, 759, 733, 675 cm^{-1}; GC-MS: t_R (70_20) = 10.6 min; MS (EI) *m/z* (%): 375 (17), 374 (98), 373 (19), 372 (100), 359 (48), 357 (47), 293 (10), 232 (13), 230 (11), 197 (22), 99 (36), 83 (13), 56 (29), 53 (11); HRMS (ESIneg): *m/z*: calcd. for $C_9H_9O_3BrI$ [M−H$^+$]: 370.8787, found 370.8785.

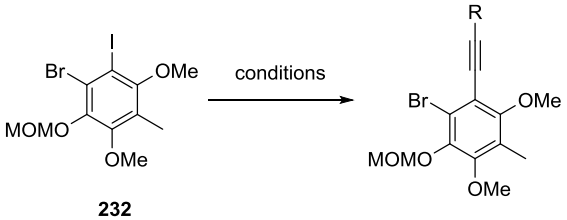
MOM-Ether 232. NaH (11 mg, 0.45 mmol) was added portionwise to a solution of phenol



230 (188 mg, 0.412 mmol) in THF (1.5 mL). After stirring for 30 min, the reaction mixture was cooled to 0 °C and (chloromethyl)methyl ether (34 mL, 0.45 mmol) was introduced. The mixture was allowed to warm to rt and was stirred for 14 h. The reaction was quenched by addition of H_2O (2 mL), the aqueous phase was extracted with MTBE (3 x 10 mL), the organic phases were washed with brine (4 mL), dried over $MgSO_4$ and evaporated. The crude material was purified by flash chromatography (SiO_2, pentane/EtOAc, 4/1) to yield the MOM-ether **232** as a colorless oil (147 mg, 84%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.12 (s, 2H), 3.80 (s, 3H), 3.72 (s, 3H), 3.65 (s, 3H), 2.23 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.8, 152.7, 144.5, 125.5, 122.3, 98.8,

95.3, 60.1, 60.0, 57.9, 10.5 ppm; IR (film): $\tilde{\nu}$ = 2933, 2852, 1447, 1412, 1390, 1374, 1286, 1229, 1206, 1159, 1103, 1025, 1025, 995, 927, 899, 814, 794, 773 cm^{-1}; MS (EI) *m/z* (%): 418 (13), 416 (13), 373 (9), 371 (9), 338 (13), 337 (100), 210 (8); HRMS (ESIpos): *m/z*: calcd. for $C_{11}H_{14}O_4BrINa$ [*M*+Na^+]: 438.9013, found 438.9013.

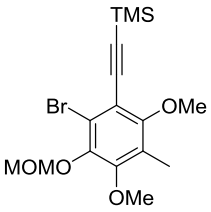
Table 7: Representative conditions for the alkynylation of **232** by cross-coupling.



232

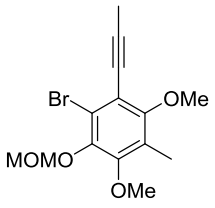
entry	catalyst	conditions	yield
1	10 mol% $PdCl_2(dppf)$	$B(OMe)_3$, THF, 1.5 equiv $NaCCCH_3$, 7 h, 70 °C	-
2	100 mol% $PdCl_2(PPh_3)_2$	Et_3N, CuI, THF, 6.0 equiv HCCTMS, 14 h, rt	95%
3	20 mol% $PdCl_2(PPh_3)_2$	Et_3N, CuI, THF, 6.0 equiv HCCTMS, 24 h, 70 °C	62%
4	20 mol% $PdCl_2(PPh_3)_2$	Et_3N, CuI, THF, 6.0 equiv 1-hexyne, 16 h, 65 °C	-
5	20 mol% $PdCl_2(P(o\text{-tol})_3)_2$	Et_3N, CuI, THF, 6.0 equiv 1-hexyne, 16 h, 65 °C	-
6	100 mol% $PdCl_2(PPh_3)_2$	Et_3N, CuI, THF, 20.0 equiv propyne 2 d, rt	5%

TMS-Acetylene 233. $PdCl_2(PPh_3)_2$ (17 mg, 24 μmol), CuI (14 mg, 72 μmol) and Et_3N (46 μL, 0.33 mmol) were added to a solution of aryl iodide **232** (10 mg, 24 μmol) in THF (0.25 mL). After 10 min, trimethylsilylacetylene (10 μL, 72 μmol) was slowly added to give a brown solution. After stirring for 24 h at 70 °C, the mixture was filtered through a pad of Celite and the filtrate was evaporated. The crude material was purified by flash chromatography (SiO_2, pentane/EtOAc, 15/1) to afford the title compound **233** as a colorless oil (5.0 mg, 62%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.11 (s, 2H), 3.86 (s, 3H), 3.80 (s, 3H), 3.66 (s, 3H), 2.14 (s, 3H), 0.23 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.8, 153.1, 144.4, 125.6, 118.8, 116.0, 107.7, 103.4, 99.3, 99.1, 60.6, 58.2, 9.49, 1.01 ppm (3C); IR (film): $\tilde{\nu}$ = 2958, 2931, 2156, 1733, 1573, 1455, 1400, 1385, 1249, 1210, 1161, 1125, 1094, 1041, 999, 932, 843, 797, 760, 700 cm^{-1}; MS (EI) *m/z* (%): 388 (18), 386 (18), 343 (13), 341 (12), 308 (21), 307 (80), 284 (16), 279 (14), 219 (13), 73



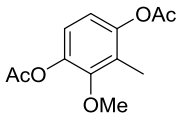
(49), 45 (100); HRMS (ESI): *m/z*: calcd. for $C_{16}H_{23}O_4BrSiNa$ [*M*+Na^+]: 409.0442, found 409.0441.

Alkyne 163. Trimethylborate (34 μL, 0.30 mmol) was added to a suspension of propynyl sodium (19 mg, 0.30 mmol) in THF (0.5 mL) and the mixture was stirred until a clear solution was obtained. *t*-BuXPhos (20 mg, 40 mol%), $PdCl_2(PPh_3)_2$ (17 mg, 20 mol%) and iodide **232** (50 mg, 0.12 mmol) were added and the orange solution was stirred at reflux temperature. After 3 h, the dark brown mixture was filtered through a pad of Celite and the filtrate was concentrated. The residue was purified by flash chromatography (SiO_2, toluene/EtOAc, 19/1) to yield the title compound **163** as a colorless oil (33 mg, 83%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.12 (s, 2H), 3.83 (s, 3H), 3.80 (s, 3H), 3.66 (s, 3H), 2.16 (s, 3H), 2.14 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.8, 151.9, 143.9, 125.1, 117.8, 98.7, 95.2, 88.7, 74.3, 60.3, 60.1, 55.8, 9.1, 4.3 ppm; MS (EI) *m/z* (%): 330 (18), 328 (18), 285 (17), 283 (17), 257 (13), 255 (15), 249 (100), 219 (15), 161 (17), 45 (50); HRMS (ESI): *m/z*: calcd. for $C_{14}H_{17}O_4BrNa$ [*M*+Na^+]: 351.0202, found 351.0203.



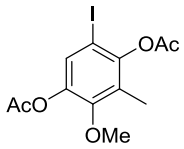
6.2.5. Synthesis of the Aromatic Core – Final Route

Diacetate 415. Diol **200** (2.50 g, 16.2 mmol) was dissolved in THF (125 mL) and the solution was cooled to −78 °C before Et_3N (11.2 mL, 81.1 mmol) was added in one portion. Acetyl chloride (2.36 mL, 33.3 mmol) was added dropwise. After complete addition, the mixture was allowed to slowly warm to 0 °C over 1 h. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ (100 mL) and H_2O (50 mL) and the aqueous phase was extracted with MTBE (3 x 200 mL). The organic phases were dried over $MgSO_4$ and concentrated. The crude material was purified by flash chromatography (SiO_2, pentane/EtOAc, 7/3) to afford diacetate **415** as a pale yellow oil (3.47 g, 90%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.90 (d, 1H, *J* = 8.7 Hz), 6.79 (d, 1H, *J* = 8.7 Hz), 3.74 (s, 3H), 2.28 (s, 3H), 2.26 (s, 3H), 2.09 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.6, 168.6, 150.3, 147.2, 141.2, 125.2, 120.1, 117.2, 60.4, 20.3, 20.3, 9.5 ppm; IR (film): $\tilde{\nu}$ = 1757, 1613, 1583, 1477, 1420, 1370, 1276, 1237, 1210, 1180, 1145, 1073, 1027, 1008, 980, 916, 897, 829, 797, 739, 657 cm^{-1}; MS (EI) *m/z* (%): 196 (15), 154 (100), 139 (22), 43 (19); HRMS



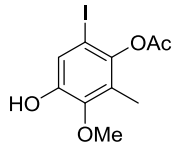
(ESI): *m/z*: calcd. for $C_{12}H_{14}O_5Na$ [*M*+Na^+]: 261.0737, found 261.0733. The analytical and spectroscopic data are in agreement with those reported in the literature.[46a]

Aryl Iodide 255. Diacetate **415** (2.74 g, 7.53 mmol) was dissolved in acetic acid (23 mL) and



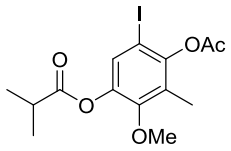
the solution was treated with H_2SO_4 (0.32 mL, 50 mol%) before NIS (2.88 g, 12.8 mmol) was added in one portion. The orange solution was stirred for 3 h and was then diluted with H_2O (50 mL). The aqueous phase was extracted with EtOAc (3 x 70 mL) and the organic phases were concentrated. The crude material was purified by flash chromatography (SiO_2, pentane/EtOAc, 4/1) to afford the title compound as a yellow solid (2.73 g, 99%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39 (s, 1H), 3.75 (s, 3H), 2.37 (s, 3H), 2.31 (s, 3H), 2.13 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.3, 167.5, 150.6, 148.1, 141.7, 129.6, 126.7, 83.2, 60.6, 20.6, 20.3, 10.7 ppm; IR (film): $\tilde{\nu}$ = 2941, 1763, 1468, 1423, 1408, 1367, 1285, 1228, 1166, 1086, 1031, 1007, 992, 919, 894, 872, 800, 681 cm^{-1}; MS (EI) *m/z* (%): 364 (14), 322 (23), 280 (100), 265 (20), 43 (26); HRMS (ESI): *m/z*: calcd. for $C_{12}H_{13}O_5Na$ [*M*+Na^+]: 386.9689, found 386.9700. The analytical and spectroscopic data are in agreement with those reported in the literature.[46a]

Phenol 254. Compound **255** (1.00 g, 2.75 mmol) was dissolved in MeOH (40 mL) and the



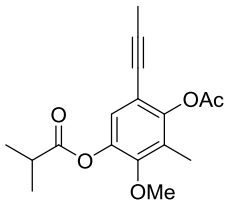
solution was cooled to 0 °C before a solution of K_2CO_3 (1.52 g, 11.0 mmol) in H_2O (5 mL) was added under stirring. The reaction was quenched after 3 h by addition of saturated aqueous NH_4Cl (25 mL) and the aqueous phase was extracted with EtOAc (3 x 100 mL). The organic phases were dried over Na_2SO_4 and concentrated to afford the title compound as a yellow oil (859 mg, 97%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27 (s, 1H), 5.56 (s, 1H), 3.77 (s, 3H), 2.36 (s, 3H), 2.14 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.7, 147.7, 146.1, 143.6, 125.4, 122.4, 84.8, 61.2, 21.1, 11.2 ppm; IR (film): $\tilde{\nu}$ = 1753, 1712, 1581, 1472, 1423, 1368, 1336, 1284, 1180, 1079, 1030, 1008, 989, 917, 873, 847, 794, 757, 727, 707, 668 cm^{-1}; MS (EI) *m/z* (%): 322 (15), 280 (100), 265 (40); HRMS (ESI): *m/z*: calcd. for $C_{10}H_{11}O_4INa$ [*M*+Na^+]: 344.9597, found 344.9594.

Propionate 416 and Alkyne 257. A solution of isobutyric acid (135 µL, 1.46 mmol), phenol **254** (376 mg, 1.17 mmol) and DMAP (14 mg, 10 mol%) in CH_2Cl_2 (2.3 mL) was cooled to 0 °C and treated with DCC (241 mg, 1.17 mmol). After 30 min, the slurry was filtered through a



416

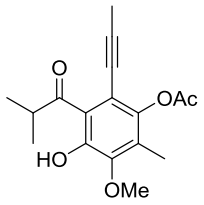
pad of SiO_2 and the filtrate was evaporated. The crude material was purified by flash chromatography (SiO_2, pentane/EtOAc, 4/1) to afford compound **416** (312 mg, 79%) as a colorless oil that was subjected to the next step without characterization.



257

A solution of propynyl sodium (67 mg, 1.1 mmol) in degassed THF (9.0 mL) was treated with trimethylborate (123 μL, 1.08 mmol) and the resulting solution was stirred for 10 min before *t*-BuXPhos (92 mg, 40 mol%), $PdCl_2(PPh_3)_2$ (78 mg, 20 mol%) and aryl iodide **416** (212 mg, 0.541 mmol) were successively added. The orange reaction mixture was stirred at reflux temperature for 1.5 h. For work-up, the mixture was filtered through a pad of Celite and the filtrate was concentrated. The residue was purified by flash chromatography (SiO_2, pentane/EtOAc, 8/1) to give the title compound **257** as a yellow oil (140 mg, 85%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.99 (s, 1H), 3.74 (s, 3H), 2.82 (hept, 1H, *J* = 7.0 Hz), 2.34 (s, 3H), 2.09 (s, 3H), 2.02 (s, 3H), 1.32 ppm (d, 6H, *J* = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.5, 168.1, 150.0, 148.3, 141.0, 125.6, 123.7, 113.6, 90.0, 73.8, 60.7, 33.7, 20.2, 18.6 (2x), 9.7, 4.0 ppm; IR (film): $\tilde{\nu}$ = 2975, 2936, 1759, 1480, 1427, 1368, 1339, 1247, 1207, 1177, 1107, 1089, 1072, 1048, 1008, 995, 909, 880, 816, 747, 691 cm^{-1}; MS (EI) *m/z* (%): 304 (16), 234 (13), 193 (12), 192 (100), 177 (13), 43 (18); HRMS (ESI): *m/z*: calcd. for $C_{17}H_{20}O_5Na$ [*M*+Na^+]: 327.1204, found 327.1203.

Ketone 258. In a quartz tube (30 cm x 1.2 cm), a solution of diester **257** (25 mg, 82 μmol) in ethanol (15 mL) was degassed by bubbling argon through it via canula for 30 min. The quartz tube was then sealed and positioned next to a quartz photo reactor (double-walled vessel with water cooling). A Hanovia 450 W medium pressure mercury gas lamp was put inside the quartz apparatus. The inner void containing the lamp was filled with argon and sealed with a plug of cotton to avoid ozone formation. The stirred solution was irradiated for 2 h causing a color change from colorless to pale orange. The solvent was removed and the crude material was purified by flash chromatography (SiO_2, pentane/EtOAc, 8/2) to yield the desired compound as a yellow oil (19 mg, 73%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.38 (s, 1H), 4.32 (sept, 1H, *J* = 6.9 Hz), 3.88 (s, 3H), 2.34 (s, 3H), 2.12 (s, 3H), 2.11 (s, 3H), 1.21 ppm (d, 6H, *J* = 6.9 Hz);

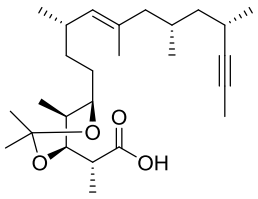


^{13}C NMR (100 MHz, $CDCl_3$): δ = 212.6, 169.1, 154.3, 147.4, 144.8, 131.8, 119.3, 112.3, 97.2, 74.6, 60.6, 38.3, 20.7, 19.6 (2C), 10.6, 4.9 ppm; MS (EI) *m/z* (%): 304 (64), 289 (13), 286 (14), 262 (40), 261 (26), 248 (12), 247 (70), 244 (26), 234 (14), 229 (24), 220 (14), 219 (100), 204 (14), 192 (43), 177 (12), 91 (13), 83 (10); HRMS (ESI): *m/z*: calcd. for $C_{17}H_{20}O_5Na$ [*M*+Na^+]: 327.1206, found 327.1203.

Methyl Ester 244. *tert*-Butyllithium (2.64 mL, 4.48 mmol, 1.70 M in pentane) was added to a solution of alkyl iodide **165** (560 mg, 2.24 mmol) in Et_2O (6.6 mL) at −78 °C. After stirring for 5 min, a solution of 9-MeO-9-BBN (5.39 mL, 5.39 mmol, 1.0 M in THF) and THF (0.5 mL) was added. After another 10 min, the mixture was allowed to warm to ambient temperature over 1 h. Then, a mixture of aqueous K_3PO_4 (0.87 mL, 2.61 mmol, 3.0 M), alkenyl iodide **164** (394 mg, 0.897 mmol) and $PdCl_2(dppf)\cdot CH_2Cl_2$ (64 mg, 10 mol%) in DMF (9.0 mL) was added and stirring was continued for 1 h. The reaction was quenched by addition of saturated aqueous NH_4Cl and the aqueous phase was extracted with MTBE (3 x 50 mL). The combined organic phases were washed with brine (30 mL), dried over $MgSO_4$ and concentrated. The crude material was purified by flash chromatography (SiO_2, pentane 100% → pentane/EtOAc, 30/1) to afford the title compound as a colorless oil (388 mg, quant.). $[\alpha]_D^{20}$ = +0.94 (*c* = 1.00, CH_2Cl_2), ^{1}H NMR (600 MHz, C_6D_6): δ = 5.00 (d, 1H, *J* = 9.4 Hz), 3.84 (dd, 1H, *J* = 7.3, 4.8 Hz), 3.80 (dt, 1H, *J* = 9.6, 4.4 Hz), 3.38 (s, 3H), 2.55 – 2.49 (m, 2H), 2.44 – 2.37 (m, 1H); 2.14 (dd, 1H, *J* = 13.0, 5.3 Hz), 1.99 – 1.93 (m, 1H), 1.81 – 1.76 (m, 1H), 1.67 (dd, 1H, *J* = 13.0, 9.0 Hz), 1.64 (d, 3H, *J* = 1.4 Hz), 1.63 – 1.57 (m, 1H), 1.59 (d, 3H, *J* = 2.4 Hz), 1.50 – 1.42 (m, 2H), 1.36 (s, 3H), 1.34 (s, 3H), 1.33 – 1.27 (m, 2H), 1.31 (d, 3H, *J* = 7.0 Hz), 1.24 – 1.18 (m, 1H), 1.16 (d, 3H, *J* = 6.8 Hz), 1.02 (d, 3H, *J* = 6.6 Hz), 0.90 (d, 3H, *J* = 6.6 Hz), 0.84 ppm (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (150 MHz, C_6D_6): δ = 174.2, 133.3, 132.8, 100.7, 84.2, 75.8, 75.7, 69.5, 51.1, 47.5, 45.3, 43.3, 37.3, 34.5, 32.8, 29.1, 29.1, 25.2, 24.2, 23.8, 21.9, 21.7, 20.2, 16.2, 12.3, 11.7, 3.4 ppm; IR (film): $\tilde{\nu}$ = 2952, 2920, 1740, 1455, 1435, 1379, 1328, 1291, 1225, 1196, 1167, 1087, 1056, 1020, 955, 877, 837, 809, 756 cm^{-1}; MS (EI) *m/z* (%): 434 (17), 376 (28), 289 (31), 249 (16), 248 (57), 233 (24), 219 (10), 206 (20), 205 (97), 191 (21), 189 (44), 183 (27), 177 (15), 164 (15), 163 (37), 159 (36), 150 (18), 149 (44), 147 (28), 135 (34), 134 (16), 133 (24), 129 (17), 128 (34), 127 (58), 126 (77), 125 (12), 124 (15), 123 (57), 122 (27), 121 (100), 120 (14), 119 (35), 113 (13), 107 (48), 105 (16), 97 (11), 95 (32), 93 (19),

83 (11), 69 (70), 59 (25), 55 (22), 43 (32); HRMS (ESI): *m/z*: calcd. for $C_{27}H_{46}NO_4Na$ [*M*+Na^+]: 457.3294, found 457.3297.

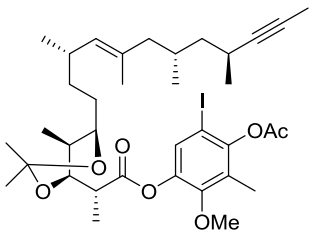
Carboxylic Acid 253. Methyl ester **244** (356 mg, 0.81 mmol) was dissolved in



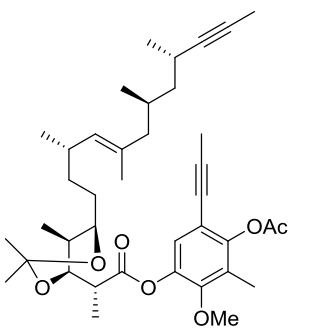
THF/MeOH/H_2O (10 mL, 2:2:1). After addition of LiOH (195 mg, 8.10 mmol), the solution was stirred for 16 h. CH_2Cl_2 (15 mL) was then added and the biphasic system was slightly acidified by dropwise addition of aqueous HCl (1.0 M). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. The residue was dried by azeotropic distillation with toluene (3 x 5 mL) to afford acid **253** as a colorless sticky oil (307 mg, 90%). $[\alpha]_D^{23}$ = −0.20 (*c* = 1.00, CH_2Cl_2), ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.0 (br, 1H), 4.86 (d, 1H, *J* = 8.3 Hz), 3.74 – 3.65 (m, 2H), 2.60 (dq, 1H, *J* = 7.0, 3.7 Hz), 2.48 – 2.42 (m, 1H), 2.38 – 2.31 (m, 1H), 2.05 (dd, 1H, = 12.8, 5.0 Hz), 1.83 – 1.72 (m, 2H), 1.78 (d, 3H, *J* = 2.4 Hz), 1.68 – 1.60 (m, 1H), 1.56 (d, 3H, *J* = 1.3 Hz), 1.48 – 1.39 (m, 1H), 1.32 (s, 3H), 1.31 (s, 3H), 1.30 – 1.22 (m, 5H), 1.20 (d, 3H, *J* = 7.0 Hz), 1.09 (d, 3H, *J* = 6.8 Hz), 0.92 (d, 3H, *J* = 6.6 Hz), 0.84 (d, 3H, *J* = 6.6 Hz), 0.80 ppm (d, 3H, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 179.1, 132.3, 132.2, 100.5, 83.8, 74.9, 74.8, 69.1, 47.0, 44.5, 42.4, 36.2, 33.4, 31.9, 28.3, 28.0, 24.6, 23.4, 23.3, 21.0, 21.0, 19.5, 15.7, 11.8, 10.6, 3.1 ppm; IR (film): $\tilde{\nu}$ = 2953, 2919, 1708, 1455, 1379, 1225, 1166, 1087, 1019, 968, 928, 909, 877 cm^{-1}; MS (EI) *m/z* (%): 362 (11), 289 (26), 248 (19), 233 (12), 227 (11), 220 (13), 205 (17), 203 (10), 191 (16), 177 (12), 175 (12), 169 (23), 164 (15), 163 (24), 161 (18), 151 (30), 150 (21), 149 (40), 147 (29), 137 (16), 136 (10), 135 (34), 134 (11), 133 (32), 127 (39), 126 (100), 125 (16), 124 (13), 123 (51), 122 (27), 121 (62), 120 (12), 119 (28), 114 (22), 111 (11), 110 (12), 109 (66), 108 (21), 107 (60), 105 (12), 97 (18), 96 (14), 95 (46), 93 (26), 91 (12), 85 (15), 83 (24), 82 (26), 81 (37), 79 (15), 69 (88), 68 (13), 67 (66), 59 (63), 57 (15), 55 (48), 43 (49), 41 (48); HRMS (ESI): *m/z*: calcd. for $C_{26}H_{44}NO_4Na$ [*M*+Na^+]: 443.3137, found 43.3132.

6.2.6. Assembly of the Fragements

Aryl Iodide 256. A solution of acid **253** (219 mg, 0.500 mmol), phenol **254** (178 mg, 0.550 mmol) and DMAP (21 mg, 33 mol%) in CH_2Cl_2 (1.0 mL) was prepared. EDCI·HCl (102 mg, 0.500 mmol) was added at 0 °C and the mixture was allowed to warm to ambient temperature and was stirred overnight. The mixture was filtered through a pad of cotton and SiO_2, the solvent was removed and the crude material was purified by flash chromatography (SiO_2, pentane 100% → pentane/EtOAc, 10/1) to afford the title compound as a colorless oil (279 mg, 77%). $[\alpha]_D^{20}$ = −6.4 (*c* = 0.50, CH_2Cl_2), ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34 (s, 1H), 4.88 (d, 1H, *J* = 9.3 Hz), 3.82 – 3.75 (m, 2H), 3.74 (s, 3H), 2.83 (qd, 1H, *J* = 7.0, 4.1 Hz), 2.48 – 2.40 (m, 1H), 2.38 – 2.32 (m, 1H), 2.36 (s, 3H), 2.13 (s, 3H), 2.06 (dd, 1H, *J* = 13.0, 5.1 Hz), 1.94 – 1.87 (m, 1H), 1.83 – 1.74 (m, 1H), 1.78 (d, 3H, *J* = 2.2 Hz), 1.67 – 1.61 (m, 1H), 1.57 (d, 3H, *J* = 1.1 Hz), 1.49 – 1.40 (m, 1H), 1.35 (s, 3H), 1.33 (s, 3H), 1.33 (s, 3H), 1.31 – 1.23 (m, 5H), 1.09 (d, 3H, *J* = 6.8 Hz), 0.93 (d, 3H, *J* = 6.6 Hz), 0.90 (s, 3H, *J* = 6.8 Hz), 0.81 ppm (d, 3H, *J* = 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.5, 168.0, 151.2, 148.4, 142.3, 132.8, 132.6, 130.0, 127.1, 100.7, 84.3, 83.6, 75.4, 75.3, 69.4, 61.1, 47.4, 45.0, 43.0, 36.6, 33.9, 32.4, 28.8, 28.6, 25.2, 24.0, 23.7, 21.5, 21.5, 21.0, 20.0, 16.2, 12.3, 11.3, 11.2, 3.6 ppm; IR (film): $\tilde{\nu}$ = 2952, 2920, 1768, 1468, 1426, 1370, 1328, 1286, 1224, 1182, 1086, 1019, 968, 916, 873, 800, 753, 666 cm^{-1}; MS (EI) *m/z* (%): 418 (22), 403 (11), 345 (26), 322 (59), 280 (100), 195 (18), 191 (19), 189 (10), 163 (11), 151 (31), 147 (10), 137 (12), 135 (29), 123 (32), 121 (35), 109 (49), 107 (32), 97 (10), 96 (40), 95 (32), 93 (12), 83 (23), 81 (20), 69 (60), 67 (28), 55 (20), 43 (36), 41 (16); HRMS (ESI): *m/z*: calcd. for $C_{36}H_{53}O_7INa$ [*M*+Na^+]: 747.2729, found 747.2728.

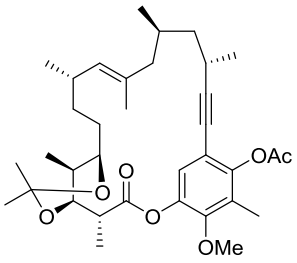


Diyne 252. Trimethylborate (110 μL, 0.969 mmol) was added to a slurry of sodium propyne (60 mg, 0.97 mmol) in THF (6.4 mL). The mixture was stirred for 10 min until a clear solution had formed. *t*-BuXPhos (33 mg, 20 mol%), $PdCl_2(PPh_3)_2$ (27 mg, 10 mol%) and iodide **256** (279 mg, 0.386 mmol) were added and the reaction mixture was stirred at reflux temperature for 2 h. The resulting black mixture was filtered through a pad of Celite and the filtrate was concentrated. The brown residue was subjected to flash chromatography (SiO_2, pentane/EtOAc, 1/0 → 10/1) to



afford diyne **252** as a colorless oil (192 mg, 78%). $[\alpha]_D^{20}$ = −5.1 (*c* = 0.57, $CHCl_3$), ^{1}H NMR (600 MHz, $CDCl_3$): δ = 6.96 (s, 1H), 4.88 (d, 1H, *J* = 9.5 Hz), 3.80 (dd, 1H, *J* = 7.5, 4.4 Hz), 3.76 (dt, 1H, *J* = 8.5, 4.6 Hz), 3.75 (s, 3H), 2.83 (dq, 1H, *J* = 7.1, 4.4 Hz), 2.46 – 2.43 (m, 1H), 2.39 – 2.34 (m, 1H), 2.34 (s, 3H), 2.09 (s, 3H), 2.06 (dd, 1H, *J* = 13.0, 5.3 Hz), 2.02 (s, 3H), 1.91 (ddq, 1H, *J* = 7.4, 6.8, 4.6 Hz), 1.81 – 1.76 (m, 1H), 1.79 (d, 3H, *J* = 2.3 Hz), 1.64 (ddd, 1H, *J* = 13.0, 8.9, 0.7 Hz), 1.58 (d, 3H, *J* = 1.1 Hz), 1.49 – 1.43 (m, 1H), 1.36 (s, 3H), 1.35 (d, 3H, *J* = 7.0 Hz), 1.33 (s, 3H), 1.32 – 1.25 (m, 5H), 1.10 (d, 3H, *J* = 6.8 Hz), 0.93 (d, 3H, *J* = 6.6 Hz), 0.90 (d, 3H, *J* = 6.8 Hz), 0.82 ppm (d, 3H, *J* = 6.6 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 172.6, 168.6, 150.5, 148.8, 141.4, 132.9, 132.7, 126.2, 124.2, 114.1, 100.8, 90.4, 84.8, 75.4, 75.4, 74.3, 69.5, 61.2, 47.5, 45.0, 43.2, 36.8, 34.0, 32.5, 28.8, 28.7, 25.3, 24.1, 23.8, 21.5, 21.5, 20.7, 20.0, 16.2, 12.4, 11.5, 10.2, 4.6, 3.6 ppm; IR (film): $\tilde{\nu}$ = 2919, 2280, 1768, 1481, 1455, 1379, 1341, 1330, 1247, 1225, 1207, 1186, 1108, 1074, 1022, 966, 912, 879, 812, 739, 703 cm^{-1}; MS (EI) *m/z* (%): 330 (19), 235 (12), 234 (70), 193 (14), 192 (100), 151 (13), 149 (12), 135 (14), 123 (14), 121 (17), 109 (24), 107 (16), 95 (16), 83 (11), 69 (28), 67 (15), 55 (11), 43 (13); HRMS (ESI): *m/z*: calcd. for $C_{39}H_{56}O_7Na$ [M^++Na]: 659.3924, found 659.3918.

Cycloalkyne 267. 5 Å molecular sieves (370 mg, 2 mg/μmol) were dispersed in freshly distilled toluene (93 mL). Diyne **252** (120 mg, 0.185 mmol) was azeotropically dried with toluene (3 x 3 mL) and was added as a solution in freshly distilled toluene (1 mL). The mixture was stirred for 30 min before a solution of complex **C4** was added (9.4 mg, 5.0 mol%, in 250 μL toluene). The resulting pale orange mixture was stirred for 1 h. For work-up, the mixture was filtered through a pad of silica which was rinsed with EtOAc. The crude material was purified by flash chromatography (SiO_2, pentane/EtOAc, 20/1) to afford the title compound as a colorless sticky oil (102 mg, 95%). For characterization purposes, trace impurities of the silanol ligand were removed by HPLC (150 mm, Kromasil, Ø 30 mm, MeOH/H_2O = 90:10, 35 mL/min, 308 K, 6.3 MPa). The impurity could also be removed by flash chromatography after the next transformation. $[\alpha]_D^{23}$ = +2.3 (*c* = 0.57, $CHCl_3$), ^{1}H NMR (600 MHz, $CDCl_3$): δ = 6.86 (s, 1H), 4.93 (d, 1H, *J* = 9.0 Hz), 3.91 (td, 1H, *J* = 7.1, 3.6 Hz), 3.76 (s, 3H), 3.51 (dd, 1H, *J* = 7.9, 5.3 Hz), 3.07 (dq, 1H, *J* = 7.9, 7.0 Hz), 2.85 – 2.79 (m, 1H), 2.48 – 2.43 (m, 1H), 2.34 (s, 3H), 2.13 – 2.10 (m, 1H), 2.10 (s, 3H), 1.99 – 1.94 (m, 1H), 1.92 (ddq, 1H, *J* = 6.8, 5.3, 3.5 Hz), 1.66 (d, 3H, *J* = 0.8 Hz), 1.52 (dd, 1H,



J = 14.0, 9.8 Hz), 1.47 – 1.42 (m, 2H), 1.41 – 1.39 (m, 1H), 1.39 (s, 6H), 1.38 (d, 3H, *J* = 7.0 Hz), 1.34 – 1.24 (m, 3H), 1.22 (d, 3H, *J* = 6.8 Hz), 0.96 (d, 3H, *J* = 6.7 Hz), 0.95 (d, 3H, *J* = 6.8 Hz), 0.92 ppm (d, 3H, *J* = 6.6 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 172.5, 168.5, 150.7, 148.2, 141.0, 133.3, 131.1, 126.3, 124.7, 114.3, 100.5, 99.2, 78.2, 76.3, 68.7, 61.1, 44.6, 44.5, 44.4, 35.5, 32.5, 31.6, 30.1, 27.1, 25.9, 25.3, 24.7, 21.5, 21.2, 20.7, 20.4, 18.3, 15.1, 13.0, 10.2 ppm; IR (film): $\tilde{\nu}$ = 2930, 1767, 1589, 1482, 1456, 1428, 1371, 1318, 1247, 1224, 1207, 1186, 1116, 1065, 997, 934, 851, 740, 709, 699 cm^{-1}; MS (ESIpos) *m/z* (%): 605 (*M*+Na^+, 100); HRMS (ESI): *m/z*: calcd. for $C_{35}H_{50}O_7Na$ [*M*+Na^+]: 605.3453, found 605.3449.

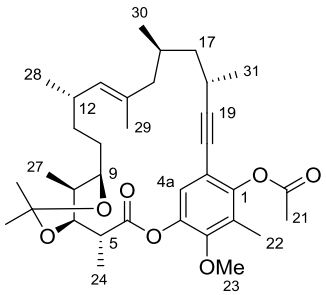
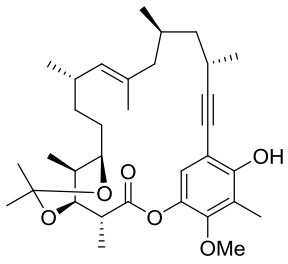


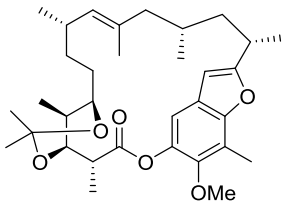
Table 8: ^{1}H and ^{13}C NMR data of cycloalkyne **267**; numbering scheme as shown in the insert.

^{1}H NMR (600 MHz, $CDCl_3$)						^{13}C NMR (150 MHz, $CDCl_3$)	
No.	δ (ppm)	Integral	Splitting	COSY	*J* (Hz)	δ (ppm)	HMBC
1	-	-	-	-	-	148.2	4a, 21, 22
2	-	-	-	-	-	126.3	22
3	-	-	-	-	-	150.7	4a, 22, 23
4	-	-	-	-	-	141.0	4a, 22
5	--	-	-	-	-	172.5	6, 7, 24
6	3.07	1H	dq	7, 24	7.9, 7.0	44.6	7, 8, 24
7	3.51	1H	dd	8, 24	7.9, 5.3	78.2	6, 8, 24, 27
8	1.92	1H	ddq	7, 9, 27	6.8, 5.3, 3.5	35.5	6, 7, 10, 27
9	3.91	1H	td	8, 10a, 10b	7.1, 3.6	68.7	7, 10, 11, 27
10	1.47 – 1.39	2H	m	9, 11a, 11b	-	27.1	9, 11, 12
11	1.34 – 1.24	2H	m	10, 11b, 12	-	32.5	9, 10, 12, 13, 28, 29
12	2.48 – 2.43	1H	m	11, 13, 28	-	31.6	10, 11, 13, 28, 29
13	4.93	1H	d	12, 15a, 29	9.0	131.1	12, 14, 15, 29
14	-	-	-	-	-	133.3	12, 15, 29
15a	2.13 – 2.10	1H	m	13, 15b, 16	-	44.4	13, 17, 29, 30
15b	1.52	1H	dd	15a, 16	14.0, 9.8	44.4	
16	1.99 – 1.94	1H	m	15a, 15b, 17a, 17b, 30	-	30.1	15, 17, 18, 30
17a	1.41 – 1.39	1H	m	16, 17b, 18	-	44.5	15, 18, 30, 31
17b	1.34 – 1.24	1H	m	16, 17a, 18	-		
18	2.85 – 2.79	1H	m	17a, 17b, 31	-	24.7	17, 31
19	-	-	-	-	-	99.2	17, 18, 31
20	-	-	-	-	-	76.3	4a, 17, 18, 22
21	2.34	3H	s	-	-	20.7	-
22	2.10	3H	s	4a	-	10.2	-
23	3.76	3H	s	-	-	61.1	-
24	1.38	3H	d	6	7.0	15.1	6, 7
25	-	-	-	-	-	100.5	7, 9, 26a, 26b
26a	1.39	6H	s	-	-	25.9	26b
26b				-	-	25.3	26a
27	0.95	3H	d	8	6.8	13.0	7, 8, 9
28	0.96	3H	d	12	6.7	20.4	11, 12, 13, 29
29	1.66	3H	d	13	0.8	18.3	13, 15
30	0.92	3H	d	16	6.6	21.2	15, 17
31	1.22	3H	d	18	6.8	21.5	17, 18

Phenol 268. Macrocycle **267** (100 mg, 0.172 mmol) was dissolved in MeOH (8.6 mL) and the solution was cooled to 0 °C before a solution of K_2CO_3 (47 mg, 0.34 mmol) in H_2O (0.2 mL) was added. The resulting mixture was stirred for 1.5 h at 0 °C. After completion of the reaction, the mixture was filtered through a small pad of silica which was washed with EtOAc. The solvent was removed and the crude material was purified by flash chromatography (SiO_2, petane 100% → pentane/EtOAc, 10/1) to afford the title compound as a colorless sticky oil (73 mg, 86%). $[\alpha]_D^{20}$ = −31.8 (*c* = 1.71, $CHCl_3$), ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.73 (s, 1H), 5.69 (s, 1H), 4.95 (d, 1H, *J* = 9.0 Hz), 3.90 (td, 1H, *J* = 7.4, 3.5 Hz), 3.75 (s, 3H), 3.53 (dd, 1H, *J* = 7.7, 5.1 Hz), 3.07 (dq, 1H, *J* = 7.1, 6.9 Hz), 2.92 – 2.84 (m, 1H), 2.48 – 2.40 (m, 1H), 2.18 (s, 3H), 2.18 – 2.15 (m, 1H), 2.01 – 1.97 (m, 1H), 1.95 – 1.90 (m, 1H), 1.66 (d, 3H, *J* = 1.3 Hz), 1.52 – 1.41 (m, 4H), 1.39 (s, 6H), 1.37 (d, 3H, *J* = 7.1 Hz), 1.34 – 1.28 (m, 2H), 1.26 (d, 3H, *J* = 6.9 Hz), 1.24 – 1.20 (m, 1H), 0.97 – 0.93 ppm (m, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.1, 153.2, 151.4, 136.6, 133.1, 131.0, 122.8, 118.9, 105.5, 101.9, 100.4, 78.3, 75.3, 68.7, 61.0, 44.4 (2C), 44.1, 34.9, 32.5, 31.7, 30.0, 27.3, 26.0, 25.5, 24.8, 21.7, 21.2, 20.4, 18.5, 15.0, 13.0, 9.5 ppm; IR (film): $\tilde{\nu}$ = 2931, 1756, 1713, 1483, 1454, 1423, 1377, 1317, 1251, 1220, 1159, 1111, 1095, 1023, 998, 881, 861, 798, 755, 663 cm^{-1}; MS (pos. ESI) *m/z* (%): 563 (*M*+Na$^+$, 100); HRMS (ESI): *m/z*: calcd. for $C_{33}H_{48}O_6Na$ [*M*+Na$^+$]: 563.3346, found 563.3343.



Benzofuran 61. A solution of [JohnphosAu]OTs (**C9**) (8.7 mg, 10 mol%) in CH_2Cl_2 (1.3 mL) was added to a freshly prepared solution of phenol **268** (70 mg, 0.13 mmol) in CH_2Cl_2 (1.0 mL). The resulting mixture was stirred at ambient temperature for 14 h. The mixture was filtered through a pad of SiO_2. Evaporation of the filtrate and purification of the residue by flash chromatography (SiO_2, pentane 100% → pentane/EtOAc, 9/1) afforded benzofuran **61** as a pale yellow oil (63 mg, 79%) that was further subjected to HPLC purification to remove trace impurities of the phosphine ligand. $[\alpha]_D^{20}$ = −27.1 (*c* = 0.35, CH_2Cl_2), ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.04 (s, 1H), 6.20 (s, 1H), 4.42 (d, 1H, *J* = 9.1 Hz), 3.80 (s, 3H), 3.77 (ddd, 1H, *J* = 9.4, 5.4, 3.4 Hz), 3.58 (dd, 1H, *J* = 9.9, 9.9 Hz), 3.14 – 3.10 (m, 1H), 3.05 (dq, 1H, *J* = 7.1, 4.5 Hz), 2.45 (s, 3H), 2.25 – 2.20 (m, 1H), 1.98 (d, 1H, *J* = 15.6 Hz), 1.91 (ddq, 1H, *J* = 6.9, 5.4, 3.4 Hz), 1.61 – 1.55 (m, 1H), 1.51 (s, 3H), 1.49 – 1.45 (m, 1H), 1.44 (s,



3H), 1.43 – 1.41 (m, 1H), 1.41 (s, 3H), 1.38 (d, 3H, *J* = 6.9 Hz), 1.35 – 1.33 (m, 1H), 1.33 (d, 3H, *J* = 7.1 Hz), 1.31 – 1.25 (m, 2H), 1.00 – 0.94 (m, 1H), 0.91 – 0.84 (m, 1H), 0.89 (d, 3H, *J* = 6.9 Hz), 0.82 (d, 3H, *J* = 6.4 Hz), 0.79 ppm (d, 3H, *J* = 6.7 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 172.8, 163.0, 151.6, 146.8, 140.4, 131.5, 129.4, 123.7, 115.7, 110.1, 102.9, 100.8, 78.4, 69.7, 61.7, 44.1, 42.8, 42.5, 33.8, 33.7, 32.3, 31.6, 28.3, 28.1, 26.9, 24.5, 21.6, 20.2, 19.2, 19.1, 14.4, 13.1, 9.4 ppm; IR (film): $\tilde{\nu}$ = 2930, 2872, 1758, 1604, 1456, 1417, 1377, 1324, 1226, 1194, 1108, 1024, 1002, 931, 861 cm^{-1}; MS (pos. ESI) *m/z* (%): 563 (*M*+Na$^+$, 100); HRMS (ESI): *m/z*: calcd. for $C_{33}H_{48}O_6Na$ [*M*+Na$^+$]: 563.3346, found 563.3343. The analytical and spectroscopic data are in agreement with those reported in the literature.[44a]

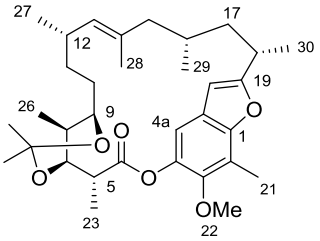
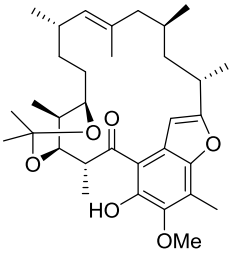


Table 9: ^{1}H and ^{13}C NMR data of benzofuran **61**; numbering scheme as shown in the insert.

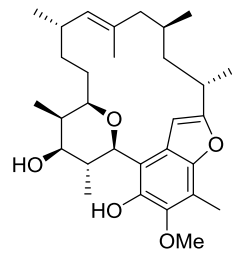
^{1}H NMR (600 MHz, $CDCl_3$)						^{13}C NMR (150 MHz, $CDCl_3$)	
No.	δ (ppm)	Integral	Splitting	COSY	*J* (Hz)	δ (ppm)	HMBC
1	-	-	-	-	-	151.6	4a, 20, 21
2	-	-	-	-	-	115.7	4a, 21
3	-	-	-	-	-	146.8	4a, 21, 22
4	-	-	-	-	-	140.4	4a
5	-	-	-	-	-	172.8	5, 6, 23
6	3.05	1H	dq	7, 23	7,1, 4.5	44.1	7, 8, 23
7	3.58	1H	dd	5, 8	9.9, 9.9	78.4	6, 8, 9, 23, 26
8	1.91	1H	ddq	7, 9, 26	6.9, 5.4, 3.4	33.7	6, 7, 9, 10, 26
9	3.77	1H	ddd	8, 10a, 10b	9.4, 5.4, 3.4	69.7	7, 10, 11, 26
10a	1.43 – 1-41	1H	m	9, 10b, 11a, 11b	-	28.1	9, 11, 12
10b	1.31 – 1.25	1H	m	9, 10a, 11a, 11b	-		
11a	1.00 – 0.94	1H	m	10a, 10b, 11b, 12	-	33.8	9, 10, 12, 13, 27
11b	0.91 – 0.84	1H	m	10a, 10b, 11a, 12	-		
12	2.25 – 2.20	1H	m	11a, 11b, 13, 27	-	32.3	10, 11, 13, 27, 28
13	4.42	1H	d	12, 15a, 28	9.1	129.4	11, 12, 15, 27, 28
14	-	-	-	-	-	131.5	12, 15, 28
15a	1.98	1H	d	13, 15b, 16, 28	15.6	42.5	13, 17, 28, 29
15b	1.35 – 1.33	1H	m	15a, 16	-		
16	1.31 – 1.27	1H	m	15a, 15b, 17a, 17b, 29	-	28.3	15, 17, 18, 29
17a	1.61 – 1.55	1H	m	16, 17b, 18	-	42.8	15, 18, 29, 30
17b	1.49 – 1.45	1H	m	16, 17a, 18	-		
18	3.14 – 3.10	1H	m	17a, 17b, 30	-	31.6	17, 20, 30
19	-	-	-	-	-	163.0	4a, 17, 18, 20, 30
20	6.20	1H	s	-	-	102.9	4a, 18
21	2.45	3H	s	4a	-	9.4	20
22	3.80	3H	s	-	-	61.7	21
23	1.33	3H	d	6	7.1	14.4	6, 7
24	-	-	-	-	-	100.8	7, 9, 25a, 25b
25a	1.44	3H	s	-	-	26.9	25b
25b	1.41	3H	s	-	-	24.5	25a
26	0.89	3H	d	8	6.9	13.1	7, 8, 9
27	0.79	3H	d	12	6.7	20.2	11, 12, 13
28	1.51	3H	s	13, 15a	-	19.1	13, 15
29	0.82	3H	d	16	6.4	21.6	15, 17
30	1.39	3H	d	18	6.9	19.2	18, 20

Photo-Fries Product 62. In a quartz tube (30 cm x 1.2 cm) a solution of benzofuran **61**



(37 mg, 68 μmol) in cyclohexane (15 mL) was degassed by bubbling argon through it via canula for 30 min. The quartz tube was sealed and positioned next to a quartz photo reactor (double-walled vessel with water cooling at high flow). A Heraeus 125 W high pressure mercury gas lamp was put inside the quartz apparatus. The inner void containing the lamp was filled with argon and sealed with a plug of cotton to avoid ozone formation. Under stirring, the pale yellow solution was irradiated for 3-5 h. The solvent was removed and the residue was purified by flash chromatography (SiO_2, pentane/EtOAc, 9/1) to afford ketone **62** as a bright yellow oil (31 mg, 85%). $[\alpha]_D^{23}$ = −50.4 (*c* = 0.30, CH_2Cl_2), ^{1}H NMR (500 MHz, $CDCl_3$): δ = 13.74 (s, 1H), 6.77 (s, 1H), 4.67 (d, 1H, *J* = 9.4 Hz), 3.90 (s, 3H), 3.89 – 3.82 (m, 2H), 3.60 (dd, 1H, *J* = 8.7, 6.7 Hz), 3.12 – 3.05 (m, 1H), 2.52 – 2.46 (m, 1H), 2.50 (s, 3H), 2.30 (d, 1H, *J* = 14.5 Hz), 1.84 – 1.78 (m, 1H), 1.70 (d, 3H, *J* = 1.3 Hz), 1.60 (td, 1H, *J* = 6.9, 4.2 Hz), 1.49 (dd, 1H, *J* = 5.0, 0.4 Hz), 1.47 – 1.44 (m, 2H), 1.43 – 1.30 (m, 1H), 1.39 – 1.18 (m, 2H), 1.37 (s, 3H), 1.36 (d, 3H, *J* = 6.0 Hz), 1.35 (s, 3H), 1.34 (d, 3H, *J* = 6.3 Hz), 1.18 – 1.10 (m, 1H), 0.83 (d, 3H, *J* = 6.7 Hz), 0.82 (d, 3H, *J* = 6.2 Hz), 0.71 ppm (d, 3H, *J* = 6.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 208.1, 163.7, 156.3, 147.2, 143.5, 132.5, 129.2, 125.2, 121.9, 110.6, 103.8, 100.3, 78.2, 68.4, 60.6, 47.2, 43.8, 43.6, 37.0, 32.1, 31.7, 31.2, 30.2, 26.9, 25.9, 24.4, 21.5, 20.9, 20.0, 19.5, 15.7, 12.5, 10.0 ppm; IR (film): $\tilde{\nu}$ = 2928, 1612, 1454, 1401, 1378, 1311, 1263, 1226, 1162, 1084, 1014, 991, 939, 809, 722 cm^{-1}; MS (pos. ESI) *m/z* (%): 563 (*M*+Na$^+$, 100); HRMS (ESI): *m/z*: calcd. for $C_{33}H_{48}O_6Na$ [*M*+Na$^+$]: 563.3347, found 563.3343. The analytical and spectroscopic data are in agreement with those reported in the literature.[44a]

Tetrahydropyran 63. $NaBH_4$ (4.9 mg, 0.13 mmol) was added to a solution of ketone **62**



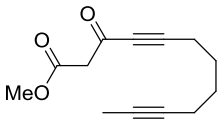
(17 mg, 32 μmol) in MeOH (0.64 mL) which caused an immediate color change from yellow to colorless. After 10 min, the reaction was quenched by the dropwise addition of aqueous HCl (0.33 mL, 0.5 M) and the mixture was stirred for 5 min before it was diluted and the aqueous phase was extracted with CH_2Cl_2 (3 x 120 mL). The combined organic phases were dried over $MgSO_4$ and concentrated. The crude material was applied in the next step without further purification.

The residue was dissolved in MeOH (0.2 mL) and the solution was treated with four drops of HCl (2.0 M). The mixture was stirred at ambient temperature overnight before it was diluted with H_2O (5 mL) and the aqueous phase was extracted with EtOAc (3 x 15 mL). The organic phases were dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (SiO_2, pentane/EtOAc, 3/2) to afford tetrahydropyran **63** as a colorless oil (14 mg, 89%). $[\alpha]_D^{23}$ = +16.3 (*c* = 0.17, $CHCl_3$), ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.55 (s, 1H), 5.53 (s, 1H), 4.60 (d, 1H, *J* = 9.8 Hz), 4.54 (d, 1H, *J* = 10.1 Hz), 3.83 (s, 3H), 3.66 – 3.62 (m, 1H), 3.44 (ddd, 1H, *J* = 11.3, 2.3, 1.5 Hz), 3.11 – 3.03 (m, 1H), 2.46 – 2.43 (m, 1H), 2.45 (s, 3H), 2.25 – 2.19 (m, 1H), 1.93 – 1.88 (m, 1H), 1.84 – 1.76 (m, 1H), 1.62 (s, 3H), 1.61 – 1.56 (m, 1H), 1.51 (d, 1H, *J* = 5.3 Hz), 1.48 – 1.41 (m, 2H), 1.38 (d, 3H, *J* = 6.9 Hz), 1.33 – 1.18 (m, 5H), 1.03 (d, 3H, *J* = 6.8 Hz), 0.90 (d, 3H, *J* = 6.6 Hz), 0.81 (d, 3H, *J* = 6.6 Hz), 0.76 ppm (d, 3H, *J* = 6.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.7, 148.2, 141.7, 141.5, 131.5, 129.0, 122.2, 115.7, 112.5, 104.8, 77.8, 77.4, 77.3, 61.4, 43.8, 41.8, 39.6, 38.7, 33.7, 32.5, 31.5, 31.2, 27.5, 21.8, 21.0, 19.6, 18.7, 12.8, 9.4, 6.6 ppm; IR (film): $\tilde{\nu}$ = 2925, 1454, 1404, 1383, 1324, 1216, 1106, 1055, 998, 974, 922, 852, 808 cm^{-1}; MS (EI) *m/z* (%): 485 (32), 484 (100), 466 (18), 456 (17), 245 (29); HRMS (ESI): *m/z*: calcd. for $C_{30}H_{44}O_5Na$ [*M*+Na$^+$]: 507.3082, found 507.3081. The analytical and spectroscopic data are in agreement with those reported in the literature.[44a]

6.3. Synthesis of a 4-Pyrone Natural Product

6.3.1. Preparation of Model Compounds

Methyl Ester 357. A solution of β-ketoacid **354** (1.10 g, 5.32 mmol) in CH_2Cl_2 (31 mL) was cooled to 0 °C before methanol (0.58 mL) and (trimethylsilyl)-diazomethane (2.29 mL, 14.4 mmol) were added. After stirring for 4 h, the reaction was quenched by addition of concentrated acetic acid (5 mL). H_2O (10 mL) was then added and the mixture was stirred for 10 min before the aqueous phase was extracted with EtOAc (3 x 50 mL). The combined organic phases were washed with H_2O (20 mL) and brine (20 mL), dried over Na_2SO_4 and concentrated. The crude material was purified by flash chromatography (SiO_2, pentane/EtOAc, 9/1) to give β-ketoester **357** as a pale yellow oil (890 mg, 40-70%). ^{1}H NMR (400 MHz, $CDCl_3$, mixture of keto/enol tautomers): δ = 11.77 (s, 0.18H), 5.25 (s, 0.18H), 3.72 (s, 2.20H), 3.70 (s, 0.62H), 3.54 (s, 1.64H), 2.37 (t, 2H, *J* = 7.0 Hz), 2.15 – 2.09 (m, 2H), 1.73 (t, 3H, *J* = 2.6 Hz), 1.69 – 1.62 (m, 2H), 1.57 – 1.50 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, mixture of keto (k)/enol (e)



tautomers): δ = 178.7 (k), 172.6 (e), 166.6 (k), 155.8 (e), 96.6 (k), 95.9 (e), 80.5 (k), 78.5 (e), 78.3 (k), 76.2 (k), 76.0 (e), 75.7 (e), 52.5 (k), 51.5 (e), 51.2 (k), 28.1 (e), 28.0 (k), 27.0 (e), 26.6 (k), 18.9 (e), 18.7 (k), 18.2 (e), 18.2 (k), 3.5 ppm (k/e); IR (film): $\tilde{\nu}$ = 2950, 2922, 2863, 2213, 1744, 1676, 1611, 1439, 1325, 1249, 1170, 1142, 1015, 806, 757, 689, 558 cm^{-1}; MS (EI) *m/z* (%): 220 (3), 219 (13), 205 (10), 177 (54), 162 (12), 161 (31), 160 (9), 147 (13), 146 (40), 145 (14), 131 (13), 119 (39), 118 (24), 117 (61), 115 (21), 105 (22), 104 (16), 103 (19), 101 (15), 93 (12), 92 (13), 91 (100), 79 (50), 77 (44), 69 (22), 67 (17), 66 (32), 65 (27), 59 (30), 57 (11), 55 (16), 53 (56), 51 (33), 43 (31), 39 (51), 31 (17); HRMS (ESI): *m/z*: calcd. for $C_{13}H_{16}O_3BrNa$ [*M*+Na^+]: 321.0096, found 321.0097.

α-Bromo-β-ketoester 358. Compound **357** (79 mg, 0.36 mmol) was dissolved in acetone (2.4 mL) and the solution was cooled to 0 °C. NBS (70 mg, 0.39 mmol) was added in one portion and the mixture was allowed to warm to ambient temperature. After 3 h, the reaction was filtered through a pad of Celite and the filtrate was evaporated. The residue was purified by flash chromatography (SiO_2, hexanes/toluene, 1/1) to yield the monobrominated compound **358** (28 mg, 26%) along with the dibrominated **359** (29 mg, 21%) and recovered starting material **357** (25 mg, 31%). ^{1}H NMR (400 MHz, $CDCl_3$, mixture of keto/enol tautomers): δ = 12.23 (s, 0.21H), 4.90 (s, 0.79H), 3.86 (s, 0.63H), 3.85 (s, 2.37H), 2.47 (t, 2H, *J* = 7.0 Hz), 2.19 – 2.15 (m, 2H), 1.77 (t, 3H, *J* = 2.6 Hz), 1.75 – 1.68 (m, 2H), 1.63 – 1.56 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, mixture of keto (k)/enol (e) tautomers): δ = 173.8 (k), 169.1 (e), 164.1 (k), 154.2 (e), 102.5 (e), 99.6 (k), 77.7 (e), 77.4 (k), 77.2 (k), 75.5 (k), 75.3 (e), 74.9 (e), 53.2 (k), 52.5 (e), 50.4 (e), 49.4 (k), 27.2 (e), 27.1 (k), 26.0 (e), 25.7 (k), 18.5 (e), 18.1 (k), 17.4 (e), 17.4 (k), 2.7 ppm (k/e); IR (film): $\tilde{\nu}$ = 2952, 2922, 2212, 1745, 1677, 1580, 1438, 1261, 1142, 1016, 798, 545 cm^{-1}; MS (EI) *m/z* (%): 299 (2), 297 (2), 284 (3), 282 (3), 220 (8), 219 (49), 204 (34), 187 (34), 160 (9), 159 (28), 147 (20), 131 (18), 119 (65), 118 (10), 117 (29), 115 (17), 105 (12), 104 (14), 103 (15), 93 (12), 91 (100), 79 (32), 77 (28), 69 (13), 66 (15), 65 (15), 53 (32); HRMS (ESI): *m/z*: calcd. for $C_{13}H_{15}O_3Na$ [*M*+Na^+]: 243.0993, found 243.0992.

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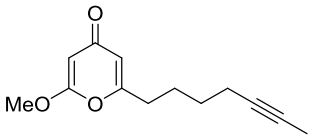
^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.92 (s, 3H), 2.51 (t, 2H, *J* = 6.9 Hz), 2.20 – 2.14 (m, 2H), 1.77 (t, 3H, *J* = 2.5 Hz), 1.76 – 1.70 (m, 2H), 1.64 – 1.57 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.9, 162.9, 101.6, 77.4, 75.5, 74.5, 58.4, 54.5, 27.1, 25.6, 18.2, 17.4, 2.7 ppm; MS (EI) *m/z* (%): 299 (13), 297 (12), 284 (28),

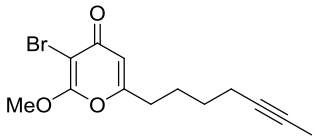
282 (30), 267 (8), 265 (7), 147 (19), 129 (11), 119 (66), 117 (22), 115 (14), 104 (12), 103 (14), 93 (10), 92 (8), 91 (100), 79 (34), 77 (31), 66 (13), 65 (15), 53 (26); HRMS (ESI): *m/z*: calcd. for $C_{13}H_{14}O_3Br_2Na$ [*M*+Na^+]: 398.9202, found 398.9202.

2-Methyl-4-pyrone 363. β-Ketoester **357** (100 mg, 0.45 mmol) was dissolved in acetic acid (2.2 mL) and [SPhosAu]NTf_2 (40 mg, 10 mol%) was added to the solution. The mixture was stirred for 18 h before the solvent was removed. and the crude material was purified by flash chromatography (SiO_2, CH_2Cl_2/Et_2O, 2/1) to yield the 4-pyrone **363** as a colorless solid (89 mg, 89%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.00 (d, 1H, *J* = 1.9 Hz), 5.46 (d, 1H, *J* = 1.9 Hz), 3.86 (s, 3H), 2.51 – 2.47 (m, 2H), 2.19 – 2.15 (m, 2H), 1.77 (t, 3H, *J* = 2.5 Hz), 1.76 – 1.70 (m, 2H), 1.58 – 1.48 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 179.0, 163.3, 159.7, 111.8, 89.9, 79.9, 76.0, 56.2, 33.4, 30.1, 23.4, 19.0, 3.9 ppm; MS (pos. ESI) *m/z* (%): 220 (8), 205 (11), 188 (2), 181 (16), 153 (25), 125 (100), 95 (21), 80 (11), 53 (44), 48 (67), 37 (11).



Exemplary Procedure for the Electrophilic Bromination of a model 4-Pyrone Substrate

3-Bromo-4-pyrone 364. A solution of 4-pyrone **363** (10 mg, 45 μmol) in THF (0.5 mL) was treated with NBS (8.0 mg, 45 μmol) in one portion. The mixture was stirred until the starting material was completely consumed (15 min). The mixture was filtered through a pad of Celite, the solvent was removed and the residue was purified by flash chromatography (SiO_2, CH_2Cl_2/Et_2O, 5/1) to give the title compound as a pale yellow solid (9.4 mg, 71%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.14 (s, 1H), 4.08 (s, 3H), 2.56 – 2.52 (m, 2H), 2.20 – 2.14 (m, 2H), 1.79 – 1.72 (m, 2H), 1.75 (t, 3H, *J* = 2.5 Hz), 1.56 – 1.49 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.5, 163.0, 162.7, 111.4, 90.3, 78.2, 76.5, 56.8, 32.1, 28.0, 25.5, 18.4, 3.5 ppm; IR (film): $\tilde{\nu}$ = 2940, 1775, 1706, 1656, 1562, 1460, 1430, 1335, 1291, 1175, 1097, 1014, 974, 922, 849, 816, 737, 631, 572 cm^{-1}; MS (pos. ESI) *m/z* (%): 282 (1), 266 (15), 219 (8), 217 (9), 204 (25), 202 (19), 149 (100), 67 (25), 53 (27), 37 (19); HRMS (ESIpos): *m/z*: calcd. for $C_{13}H_{15}O_3BrNa$ [*M*+H^+]: 321.0097, found: 321.0096.



6.3.2. Synthesis of the β-Ketoester Fragment

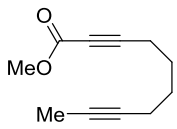
Silyl Ether 378. A LiHMDS solution was prepared by dropwise addition of a hexane solution of *n*-BuLi (60.8 mL, 97.2 mmol, 1.60 M), to a solution of HMDS (20.3 mL, 97.2 mmol) in THF (50 mL) at –78 °C. Then, the mixture was allowed to warm to 0 °C over 0.5 h. The resulting LiHMDS solution was cooled to –78 °C and was transferred by cannula to a solution of 1,7-octadiyne (**377**) (12.9 mL, 97.2 mmol) in THF (135 mL) at –78 °C. After stirring for 0.5 h, chlorotrimethylsilane (12.3 mL, 97.2 mmol) was added dropwise. The reaction mixture was stirred for 10 min and was then allowed to warm to ambient temperature. After stirring for additional 2 h, the reaction was quenched with water (200 mL). The aqueous phase was extracted with pentane (3 x 100 mL) and the extracts were combined, washed with aqueous HCl (200 mL, 1.0 M), water (200 mL) and brine (100 mL), dried over $MgSO_4$, and concentrated. The crude material was distilled with a Vigreux column (bp 75 – 78.5 °C, 7 mbar) to give silyl ether **378** (9.10 g, 52%) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.28 – 2.18 (m, 4H), 1.94 (t, 1H, *J* = 2.7 Hz), 1.67 – 1.59 (m, 4H), 0.14 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 107.0, 84.9, 84.3, 68.6, 27.7, 27.6, 19.5, 18.1, 0.3 ppm (3C); IR (film): $\tilde{\nu}$ = 3305, 2949, 2174, 1249, 837, 758, 697 cm^{-1}; MS (EI) *m/z* (%): 163 (47), 145 (16), 135 (72), 119 (10), 109 (20), 95 (14), 83 (33), 73 (93), 69 (12), 59 (100), 55 (12), 43 (25); HRMS (EI): *m/z*: calcd. for $C_{11}H_{19}Si$ [M^+]: 179.1256, found: 179.1254. The ^{1}H NMR data are identical to the previously reported.[137a]

The distillation residue was re-distilled using a Kugelrohr apparatus (100 – 120 °C/0.09 mbar) to give the disilylated product **379** as a colorless oil (4.07 g, 17%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.28 – 2.18 (m, 4H), 1.65 – 1.56 (m, 4H), 0.13 ppm (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 107.1 (2C), 84.8 (2C), 27.8 (2C), 19.5 (2C), 0.3 ppm (6C); IR (film): $\tilde{\nu}$ = 2957, 2174, 1248, 835, 757, 697 cm^{-1}; MS (EI): *m/z* (%) 162 (29), 147 (13), 73 (100), 67 (4), 59 (21); HRMS (EI): *m/z*: calcd. for $C_{14}H_{26}Si_2$ [M^+]: 250.1573, found: 250.1571. The ^{1}H and ^{13}C NMR data are identical to the reported previously.[137b]

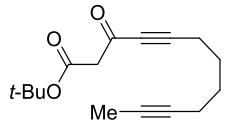
Diyne 380. A solution of *n*-butyllithium (39.9 mL, 63.9 mmol, 1.60 M in hexane) was added dropwise to a solution of **378** (7.60 g, 42.6 mmol,) in THF (200 mL) at –78 °C. After 1 h, iodomethane (5.30 mL, 85.2 mmol) was added dropwise. The reaction mixture was then allowed to warm to ambient temperature and was stirred for additional 2 h before it was cooled to 0 °C. The reaction was quenched with water (30 mL),

the aqueous phase was extracted with pentane (3 x 100 mL) and the extracts were combined, washed successively with water (30 mL) and brine (30 mL), dried over Na_2SO_4, and concentrated. The crude material was purified by distillation (119 – 125 °C/20 mbar) to give the desired product **380** as a colorless oil (7.42 g, 91%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.22 (t, 2H, *J* = 6.9 Hz), 2.17 – 2.10 (m, 2H), 1.76 (t, 3H, *J* = 2.5 Hz), 1.65 – 1.51 (m, 4H), 0.13 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 107.3, 84.7, 78.9, 75.8, 28.3, 27.9, 19.6, 18.4, 3.6, 0.3 ppm (3C); IR (film): $\tilde{\nu}$ = 2946, 2174, 1248, 837, 758, 697 cm^{-1}; MS (EI) *m/z* (%): 177 (18), 149 (21), 135 (11), 118 (17), 97 (16), 83 (13), 73 (100), 67 (6), 59 (40), 43 (10); HRMS (CI): *m/z*: calcd. for $C_{12}H_{21}Si$ [*M*+H$^+$]: 193.1413, found: 193.1411. The NMR data are identical to the previously reported.[138]

Methyl Ester 376. A solution of MeLi (23.7 mL, 37.9 mmol, 1.60 M in Et_2O) was added to a solution of **380** (3.65 g, 19.0 mmol) in THF (73 mL) at –78 °C. After stirring for 10 min, the reaction mixture was allowed to warm to 0 °C, was stirred for additional 6 h. The mixture was cooled to –78 °C before methyl chloroformate (3.70 mL, 47.9 mmol) was added dropwise. After 0.5 h, the reaction mixture was allowed to warm to 0 °C, and the reaction was quenched with saturated aqueous $NaHCO_3$ (50 mL). The aqueous phase was extracted with MTBE (3 x 150 mL) and the extracts were combined, washed with water (50 mL) and brine (50 mL), dried over Na_2SO_4, and concentrated. The residue was purified by flash chromatography (SiO_2, hexanes/EtOAc, 20/1) to give **376** as a colorless oil (2.90 g, 86%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.73 (s, 3H), 2.34 (t, 2H, *J* = 7.0 Hz), 2.18 – 2.10 (m, 2H), 1.75 (t, 3H, *J* = 2.4 Hz), 1.72 – 1.62 (m, 2H), 1.62 – 1.52 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.3, 89.5, 78.4, 76.2, 73.1, 52.6, 28.0, 26.7, 18.3, 18.3, 3.5 ppm; IR (film): $\tilde{\nu}$ = 2951, 2235, 1712, 1434, 1248, 1076, 751 cm^{-1}; MS (EI) *m/z* (%): 177 (15), 163 (14), 149 (15), 135 (22), 131 (6), 119 (53), 117 (54), 105 (23), 91 (100), 79 (59), 66 (31), 59 (13), 53 (57), 41 (48), 27 (33); HRMS (CI): *m/z*: calcd. for $C_{11}H_{15}O_2$ [*M+H*$^+$]: 179.1072, found: 179.1074. The analytical data are identical to the previously reported.[138]



β-Ketoester 354. A LDA solution was freshly prepared by dropwise addition of *n*-butyllithium (6.57 mL, 10.5 mmol, 1.60 M) to a stirred solution of diisopropylamine (1.48 mL, 10.5 mmol) in THF (15 mL) at –78 °C, followed by warming to 0 °C over 5 min. The

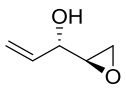


obtained LDA solution was cooled to –78 °C and *t*-butyl acetate (1.41 mL, 10.5 mmol) was added neat. After stirring for 0.5 h, a solution of **376** (950 mg, 5.33 mmol) in THF (15 mL) was added dropwise. The reaction mixture was stirred for 2 h at –78 °C and was then poured into saturated aqueous NH_4Cl (5.0 mL). The aqueous phase was extracted with MTBE (3 x 50 mL) and the extracts were combined, washed with water (15 mL) and brine (15 mL), dried over Na_2SO_4, and concentrated. The residue was purified by flash chromatography (SiO_2, hexanes/EtOAc, 20/1) to give **354** as a yellow oil (166 mg, 87%). ^{1}H NMR (400 MHz, $CDCl_3$, mixture of keto/enol tautomers): δ = 12.01 (s, 0.18H), 5.20 (s, 0.18), 3.45 (s, 1.38), 2.43 – 2.35 (m, 2H), 2.20 – 2.11 (m, 2H), 1.77 (br s, 3H), 1.74 – 1.64 (m, 2H), 1.64 – 1.53 (m, 2H), 1.47 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 179.6, 165.5, 98.0, 95.9, 82.3, 78.4, 76.3, 52.9, 28.4, 28.1 (3C), 26.8, 18.8, 18.3, 3.6 ppm; IR (film): $\tilde{\nu}$ = 2933, 2213, 1732, 1677, 1610, 1393, 1368, 1323, 1254, 1135, 956, 837, 732 cm^{-1}; MS (EI) *m/z* (%): 205 (13), 189 (14), 177 (37), 161 (15), 146 (32), 119 (21), 91 (25), 57 (100), 53 (11), 41 (28), 29 (11); HRMS (ESI): *m/z*: calcd. for $C_{16}H_{22}NaO_3$ [*M*+Na$^+$]: 285.1461, found: 285.1461.

β-Ketoacid 370. TFA (5.0 mL) was added to a solution of **354** (1.00 g, 3.81 mmol) in CH_2Cl_2 (5.0 mL). After stirring for 0.5 h, the reaction mixture was concentrated and the obtained brown oil was purified by flash chromatography (SiO_2, hexanes/EtOAc, 5/1 → EtOAc 100%) to give **370** as a purple/brown solid (777 mg, 99%). This compound was highly sensitive and could only be stored for a few days in a freezer. It was therefore submitted to the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$, mixture of keto/enol tautomers): δ = 11.56 (br s, 0.33H), 5.32 (s, 0.33H), 3.63 (s, 1.28H), 2.42 (t, 2H, *J* = 6.9 Hz), 2.20 – 2.11 (m, 2H), 1.76 (t, 3H, *J* = 2.5 Hz), 1.74 – 1.63 (m, 2H), 1.63 – 1.52 ppm (m, 2H); IR (film): $\tilde{\nu}$ = 2936, 2214, 1650, 1574, 1455, 1252, 1183, 1040, 965, 901, 804, 721, 689 cm^{-1}; MS (EI) *m/z* (%): 161 (18), 147 (50), 119 (51), 105 (17), 91 (66), 77 (26), 65 (16), 53 (35), 43 (100), 27 (23); HRMS (ESIneg): *m/z*: calcd. for $C_{12}H_{13}O_3$ [*M*−H$^+$]: 205.0870, found: 205.0872.

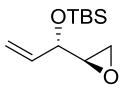
6.3.3. Synthesis of the Epoxide

Epoxide 387. A mixture of powdered MS 4 Å (2.00 g) and CH_2Cl_2 (60 mL) was cooled to –



35 °C before titanium tetraisopropoxide (1.76 mL, 10 mol%) and (+)-diisopropyl (L)-tartrate (1.62 mL, 7.73 mmol) were added successively. After stirring for 3 h at –35 °C, 1,4-pentadien-3-ol (**384**) (5.78 mL, 59.4 mmol) was added dropwise followed by cumene hydroperoxide (17.6 mL, 119 mmol). The reaction mixture was stirred for 38 h at –35 °C. The reaction was quenched by addition of saturated aqueous Na_2SO_4 (5.0 mL) and the mixture was diluted with MTBE (50 mL). After stirring for 3 h at ambient temperature, the resulting slurry was filtered through a pad of Celite and the yellow filtrate was concentrated. Excess cumene alcohol and cumene hydroperoxide were removed by flash chromatography (SiO_2, hexanes/MTBE, 5/1) to give the desired epoxide **387** as a colorless oil (4.87 g, 82%). $[\alpha]_D^{23}$ = +68.8 (*c* = 0.73, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.83 (ddd, 1H, *J* = 17.2, 10.5, 6.2 Hz), 5.38 (dt, 1H, *J* = 17.2, 1.3 Hz), 5.25 (dt, 1H, *J* = 10.5, 1.3 Hz), 4.34 – 4.28 (m, 1H), 3.08 (dt, 1H, *J* = 4.0, 3.0 Hz), 2.79 (dd, 1H, *J* = 5.0, 3.0 Hz), 2.74 (dd, 1H, *J* = 5.0, 4.0 Hz), 2.23 ppm (d, 1H, *J* = 3.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.6, 117.7, 70.3, 54.0, 43.6 ppm; IR (film): $\tilde{\nu}$ = 3417, 2997, 1427, 1251, 1024, 972, 930, 885, 832, 793, 756 cm^{-1}; MS (EI) *m/z* (%): 69 (22), 57 (100), 55 (24), 43 (29), 31 (18), 29 (55), 27 (29); HRMS (CI): *m/z*: calcd. for $C_5H_9O_2$ [*M*+H$^+$]: 101.0603, found: 101.0602. The spectral data are identical to the previously reported.[158]

TBS-Ether 417. TBSCl (6.96 g, 46.2 mmol) was added to a solution of **387** (4.20 g, 42.0 mmol)



and imidazole (6.00 g, 88.2 mmol) in DMF (42 mL) at 0 °C. After stirring for 1 h at 0 °C, the reaction mixture was diluted with MTBE (300 mL) and the organic phase was washed with water (4 x 100 mL) and brine (100 mL), dried over Na_2SO_4, and concentrated. The residue was purified by flash chromatography (SiO_2, hexanes/MTBE, 10/1) to give **417** as a colorless oil (8.09 g, 90%). $[\alpha]_D^{23}$ = +1.90 (*c* = 0.73, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.88 (ddd, 1H, *J* = 17.2, 10.4, 5.5 Hz), 5.32 (dt, 1H, *J* = 17.2, 1.5 Hz), 5.18 (dt, 1H, *J* = 10.4, 1.5 Hz), 4.12 (ddt, 1H, *J* = 5.5, 4.0, 1.5 Hz), 2.94 (td, 1H, *J* = 3.9, 3.1 Hz), 2.70 – 2.69 (m, 2H), 0.89 (s, 9H), 0.06 (s, 3H), 0.05 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.6, 116.0, 72.6, 54.6, 44.4, 25.9 (3C), 18.4, −4.6, −4.7 ppm; IR (film): $\tilde{\nu}$ = 2956, 2930, 2857, 1472, 1250, 1119, 1079, 1033, 1000, 926, 834, 774, 673 cm^{-1}; MS (EI) *m/z* (%): 171 (11), 157

(18), 127 (100), 101 (32), 75 (71), 59 (23), 45 (13); HRMS (ESI): *m/z*: calcd. for $C_{11}H_{22}NaO_2Si$ [*M*+Na^+]: 237.1281, found: 237.1283.

Epoxide 383. A mixture of **417** (8.00 g, 37.3 mmol), palladium on charcoal (10% Pd basis, 400 mg) and EtOAc (80 mL) was vigorously stirred under hydrogen atmosphere for 2 h. The mixture was filtered through a pad of Celite and the resulting filtrate was concentrated. The residue was distilled using a Kugelrohr apparatus (90 – 105 °C/9 mbar) to give **383** as a colorless oil (7.65 g, 95%). $[\alpha]_D^{23}$ = +13.0 (*c* = 0.730, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.51 (dt, 1H, *J* = 6.6 Hz), 2.86 (ddd, 1H, *J* = 4.6, 3.9, 2.6 Hz), 2.69 (dd, 1H, *J* = 5.5, 3.9 Hz), 2.65 (dd, 1H, *J* = 5.0, 2.6 Hz), 1.71 – 1.49 (m, 2H), 0.96 (t, 3H, *J* = 7.5 Hz), 0.88 (s, 9H), 0.043 (s, 3H), 0.041 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 72.5, 54.6, 44.9, 28.3, 26.0 (3C), 18.3, 9.4, −4.3, −4.7 ppm; IR (film): $\tilde{\nu}$ = 2957, 2930, 2857, 1463, 1251, 1110, 1074, 1017, 994, 833, 773 cm^{-1}; MS (EI) *m/z* (%): 173 (4), 159 (29), 129 (44), 117 (33), 101 (48), 89 (11), 75 (100), 59 (22); HRMS (ESI): *m/z*: calcd. for $C_{11}H_{24}NaO_2Si$ [*M*+Na^+]: 239.1438, found: 239.1438. The spectral data are identical to the previously reported.[159]

6.3.4. Synthesis of the Skipped Diene/Yne Fragment

Alkyne 418. 3-Butyn-1-ol (**386**) (25.0 g, 357 mmol) was added dropwise to a solution of *p*-TsOH·H_2O (67.8 mg, 10 mol%) in ethyl vinyl ether (68 mL) at 0 °C. After stirring for 5 h at 0 °C, the reaction was quenched by addition of saturated aqueous Na_2CO_3 (7.1 mL) and excess Na_2CO_3. The suspension was filtered through a frit and the filtrate was concentrated. The residue was distilled through a Vigreux column (68 – 73 °C/42 mbar) to give the ethoxyethyl ether **418** as a colorless oil (45.6 g, 90%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.74 (q, 1H, *J* = 5.4 Hz), 3.72 – 3.62 (m, 2H), 3.62 – 3.44 (m, 2H), 2.45 (dt, 2H, *J* = 6.9, 2.5 Hz), 1.97 (t, 1H, *J* = 2.5 Hz), 1.31 (d, 3H, *J* = 5.4 Hz), 1.20 ppm (t, 3H, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 99.7, 81.6, 69.3, 63.0, 61.1, 20.2, 19.9, 15.4 ppm; MS (EI) *m/z* (%): 127 (14), 97 (11), 73 (90), 67 (60), 53 (57), 43 (100), 40 (22), 29 (36); HRMS (CI): *m/z*: calcd. for $C_8H_{15}O_2$ [*M*+H^+]: 143.1072, found: 143.1071. The analytical data are identical to the previously reported.[160]

Skipped Diyne 385. 4-(1-Ethoxyethoxy)but-1-yne (**418**) (20.0 mL, 129 mmol) was added dropwise to a solution of EtMgBr (47 mL, 140 mmol, 3.0 M) in THF (160 mL) at 45 °C. After stirring for 0.5 h at 45 °C, copper(I) chloride (641 mg, 5 mol%) was added and the temperature was raised to and kept at 50 °C for 0.5 h. A solution of propargyl bromide (16.6 mL, 149 mmol, 80% in toluene) was added dropwise and the temperature was increased to 60 °C. After 1.5 h, the reaction mixture was cooled to 0 °C and poured into a solution of KCN (2.59 g) and NH_4Cl (19.7 g) in water (130 mL). The aqueous phase was extracted with MTBE (3 x 250 mL) and the extracts were combined, washed with water (100 mL) and brine (100 mL), dried over Na_2SO_4, and concentrated. The crude material was purified by distillation using a Vigreux column (30 – 41 °C/5 mbar) to give the desired product **385** as a pale yellow oil (19.1 g, 82%). The skipped diyne is very sensitive and must be stored under argon in the freezer. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.69 (q, 1H, *J* = 5.4 Hz), 3.68 – 3.57 (m, 2H), 3.55 – 3.41 (m, 2H), 3.11 (q, 2H, *J* = 2.5 Hz), 2.40 (tt, 2H, *J* = 7.0, 2.5 Hz), 2.02 (t, 1H, *J* = 2.5 Hz), 1.27 (d, 3H, *J* = 5.4 Hz), 1.16 ppm (t, 3H, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 99.6, 78.6, 78.1, 74.3, 68.6, 63.1, 61.0, 20.4, 19.8, 15.3, 9.6 ppm; MS (EI) *m/z* (%): 105 (12), 91 (38), 79 (18), 72 (81), 65 (33), 51 (11), 43 (100), 39 (14), 29 (26); HRMS (CI): *m/z*: calcd. for $C_{11}H_{17}O_2$ [*M*+H^+]: 181.1229, found: 181.1227.

Alcohol *anti*-382. A hexane solution of *n*-butyllithium (65.0 mL, 104 mmol, 1.60 M) was added dropwise to a solution of the skipped diyne **385** (18.7 g, 104 mmol) in Et_2O (120 mL) at –78 °C. After stirring for 0.5 h, $BF_3{\cdot}OEt_2$ (12.8 mL, 104 mmol) was added dropwise and the mixture was stirred for 5 min at –78 °C. A solution of the epoxide **383** (7.50 g, 34.7 mmol) in Et_2O (4.0 mL) was added. After stirring for 0.5 h at –78 °C, the mixture was poured into saturated aqueous $NaHCO_3$ (120 mL). The aqueous phase was extracted with MTBE (3 x 250 mL) and the extracts were combined, washed with water (50 mL) and brine (50 mL), dried over Na_2SO_4 and concentrated. The crude material was purified by flash chromatography (SiO_2, hexanes/EtOAc, 20/1 containing 1% Et_3N) to give *anti*-**382** as a pale yellow oil (8.12 g, 59%) that was submitted to the semihydrogenation without delay. $[\alpha]_D^{23}$ = +14.2 (*c* = 1.71, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.71 (q, 1H, *J* = 5.3 Hz), 3.71 – 3.59 (m, 4H), 3.57 – 3.42 (m, 2H), 3.12 (br s, 2H), 2.47 – 2.35 (m, 4H), 2.16 (br s, 1H), 1.63 – 1.40 (m, 2H), 1.30 (d, 3H, *J* = 5.3 Hz), 1.19 (t, 3H, *J* = 7.1 Hz), 0.90 (t, 3H, *J* = 7.5 Hz), 0.88 (s, 9H), 0.07 (s, 3H), 0.07 ppm

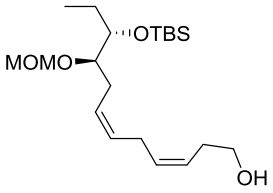
(s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 99.6, 77.5, 77.0, 76.7, 75.4, 75.2, 72.2, 63.3, 61.0, 26.0 (3C), 24.7, 22.8, 20.5, 19.9, 18.2, 15.4, 10.0, 9.4, −4.3, −4.4 ppm; IR (film): $\tilde{\nu}$ = 3491, 2930, 2858, 1463, 1380, 1253, 1132, 1086, 1055, 1003, 939, 834, 774, 668 cm^{-1}; MS (EI) *m/z* (%): 293 (12), 173 (51), 145 (13), 73 (100), 45 (21); HRMS (ESI): *m/z*: calcd. for $C_{22}H_{40}NaO_4Si$ [*M*+Na$^+$]: 419.2588, found: 419.2586.

Skipped Diene *anti*-388. Quinoline (14.1 mL, 119 mmol,) and palladium (3.04 g, 5% on $CaCO_3$, unpoisoned, reduced) were added to a solution of diyne *anti*-**382** (6.30 g, 15.9 mmol) in CH_2Cl_2 (46 mL). The heterogenous mixture was saturated with hydrogen using a balloon and stirred under hydrogen atmosphere for 2.5 h. The suspension was filtered through a pad of Celite and the filtrate was concentrated. The residue was purified by flash chromatography (SiO_2, hexanes/EtOAc, 20/1 containing 1% Et_3N) to give *anti*-**388** as a pale yellow oil (5.42 g, 87%). $[\alpha]_D^{23}$ = +5.2 (*c* = 1.22, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.55 – 5.37 (m, 4H), 4.69 (q, 1H, *J* = 5.3 Hz), 3.69 – 3.53 (m, 4H), 3.53 – 3.38 (m, 2H), 2.83 (t, 2H, *J* = 5.5 Hz), 2.38 – 2.31 (m, 2H), 2.29 – 2.16 (m, 2H), 2.08 (d, 1H, *J* = 3.3 Hz), 1.61 – 1.41 (m, 2H), 1.30 (d, 3H, *J* = 5.3 Hz), 1.20 (t, 3H, *J* = 7.1 Hz), 0.91 (t, 3H, *J* = 7.1 Hz), 0.91 (s, 9H), 0.08 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 130.6, 129.7, 126.5, 126.2, 99.6, 76.2, 74.0, 64.7, 60.9, 30.1, 28.3, 26.1, 26.0 (3C), 24.2, 20.0, 18.2, 15.5, 10.1, −4.3, −4.3 ppm; IR (film): $\tilde{\nu}$ = 3500, 2930, 2858, 1463, 1379, 1253, 1132, 1084, 1059, 1004, 940, 834, 774, 731 cm^{-1}; MS (EI) *m/z* (%): 355 (1), 336 (1), 297 (6), 271 (1), 253 (6), 173 (36), 145 (17), 107 (10), 73 (100), 45 (22); HRMS (ESI): *m/z*: calcd. for $C_{22}H_{44}NaO_4Si$ [*M*+Na$^+$]: 423.2901, found: 423.2903.

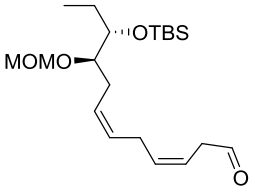
MOM-Ether *anti*-419. To a solution of alcohol *anti*-**388** (4.90 g, 12.2 mmol) in CH_2Cl_2 (180 mL) were added successively (*i*-Pr)$_2$NEt (32.0 mL, 183 mmol), (chloromethyl)methyl ether (8.36 mL, 110 mmol) and sodium iodide (6.60 g, 44.0 mmol). The mixture was stirred at 35 °C for 14 h. After cooling to ambient temperature, aqueous NH_3 was added and the aqueous phase was extracted with CH_2Cl_2 (3 x 200 mL). The extracts were combined, washed successively with water (50 mL) and brine (50 mL), dried over Na_2SO_4, and concentrated. The residue was purified by flash chromatography (SiO_2, hexanes/EtOAc, 30/1 containing 1% Et_3N) to give *anti*-**419** as a colorless oil (4.88 g, 90%). $[\alpha]_D^{23}$ = +14.2

(*c* = 1.28, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.52 – 5.37 (m, 4H), 4.72 (d, 1H, *J* = 6.7 Hz), 4.69 (q, 1H, *J* = 5.3 Hz), 4.62 (d, 1H, *J* = 6.7 Hz), 3.70 – 3.53 (m, 4H), 3.53 – 3.37 (m, 2H), 3.36 (s, 3H), 2.82 (t, 2H, *J* = 5.7 Hz), 2.39 – 2.22 (m, 4H), 1.60 – 1.41 (m, 2H), 1.30 (d, 3H, *J* = 5.3 Hz), 1.20 (t, 3H, *J* = 7.1 Hz), 0.92 (t, 3H, *J* = 7.4 Hz), 0.90 (s, 9H), 0.06 (s, 3H), 0.05 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 129.9, 129.6, 126.9, 126.3, 99.6, 96.0, 80.0, 75.6, 64.7, 60.9, 55.8, 28.8, 28.2, 26.1 (3C), 26.0, 25.7, 20.0, 18.3, 15.5, 10.4, −4.1, −4.5 ppm; IR (film): $\tilde{\nu}$ = 2930, 2885, 1463, 1378, 1252, 1134, 1099, 1035, 918, 834, 773 cm^{-1}; MS (EI) *m/z* (%): 209 (1), 173 (42), 145 (26), 89 (13), 73 (100), 59 (4), 45 (34); HRMS (ESI): *m/z*: calcd. for $C_{24}H_{48}NaO_5Si$ [*M*+Na^+]: 467.3163, found: 467.3162.

Alcohol *anti*-381. Pyridinium *p*-toluenesulfonate (2.71 g, 10.8 mmol) was added to a solution of *anti*-**419** (4.80 g, 10.8 mmol) in MeOH (410 mL). The reaction mixture was stirred for 2 h at 30 °C. Saturated aqueous $NaHCO_3$ was added, the mixture was concentrated to remove MeOH, and the residue was extracted with EtOAc (3 x 250 mL). The extracts were combined, washed with water (50 mL) and brine (50 mL), dried over Na_2SO_4, and concentrated. The crude material was purified by flash chromatography (SiO_2, hexanes/EtOAc, 5/1) to give *anti*-**381** as a colorless oil (3.62 g, 90%). $[\alpha]_D^{23}$ = +15.2 (*c* = 1.17, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.59 – 5.36 (m, 4H), 4.72 (d, 1H, *J* = 6.7 Hz), 4.62 (d, 1H, *J* = 6.7 Hz), 3.68 – 3.53 (m, 4H), 3.37 (s, 3H), 2.84 (t, 2H, *J* = 6.5 Hz), 2.39 – 2.22 (m, 4H), 1.62 – 1.41 (m, 3H), 0.92 (t, 3H, *J* = 7.5 Hz), 0.90 (s, 9H), 0.07 (s, 3H), 0.05 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 131.1, 129.5, 127.0, 125.8, 96.0, 80.0, 75.6, 62.4, 55.8, 31.1, 28.8, 26.1 (3C), 26.1, 25.7, 18.3, 10.4, −4.1, −4.5 ppm; IR (film): $\tilde{\nu}$ = 3359, 2929, 2857, 1463, 1252, 1142, 1101, 1035, 917, 833, 773 cm^{-1}; MS (EI) *m/z* (%): 283 (17), 173 (100), 145 (84), 115 (22), 89 (47), 73 (67), 59 (14), 45 (71); HRMS (ESI): *m/z*: calcd. for $C_{20}H_{40}NaO_4Si$ [*M*+Na^+]: 395.2588, found: 395.2588.

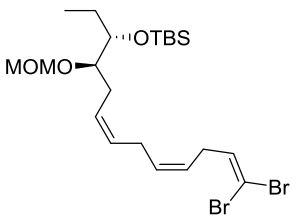


Aldehyde *anti*-420. Dess-Martin periodinane (6.01 g, 14.2 mmol) was added to a solution of alcohol *anti*-**381** (3.30 g, 8.86 mmol) in CH_2Cl_2 (200 mL) at 0 °C. After stirring for 10 min at 0 °C, the mixture was allowed to warm to ambient temperature and was stirred for additional 2 h. As a part of the alcohol remained, more Dess-Martin reagent (6.01 g, 14.2 mmol)



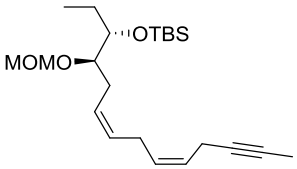
was added to the mixture and stirring was continued for 2 h. A mixture of saturated aqueous $NaHCO_3$ (18.3 mL) and saturated aqueous Na_2SO_3 (18.3 mL) was added and the resulting heterogeneous mixture was stirred vigorously for 15 min. The aqueous phase was extracted with CH_2Cl_2 (3 x 150 mL) and the extracts were combined, washed with saturated aqueous NH_4Cl (50 mL) and brine (50 mL), dried over Na_2SO_4, and concentrated to give aldehyde *anti*-**420** which was used in the next step without further purification. $[\alpha]_D^{23}$ = +13.3 (*c* = 1.02, $CHCl_3$); ^{1}H NMR (400 MHz, C_6D_6): δ = 9.24 (s, 1H), 5.62 – 5.48 (m, 2H), 5.48 – 5.31 (m, 2H), 4.69 (d, 1H, *J* = 6.7 Hz), 4.54 (d, 1H, *J* = 6.7 Hz), 3.71 – 3.60 (m, 2H), 3.23 (s, 3H), 2.70 (m, 3H,), 2.53 – 2.40 (m, 1H), 2.36 – 2.24 (m, 1H), 1.69 – 1.57 (m, 1H), 1.48 – 1.27 (m, 2H), 1.02 (s, 9H), 0.93 (t, 3H, *J* = 7.4 Hz), 0.16 (s, 3H), 0.09 ppm (s, 3H); ^{13}C NMR (100 MHz, C_6D_6): δ = 197.4, 132.6, 128.8, 127.9, 119.5, 96.0, 79.8, 76.1, 55.5, 42.5, 28.7, 26.5, 26.4, 26.2 (3C), 18.5, 10.6, −4.0, −4.4 ppm; IR (film): $\tilde{\nu}$ = 2929, 2856, 1727, 1463, 1252, 1142, 1100, 1034, 916, 834, 773 cm^{-1}; MS (EI) *m/z* (%): 173 (66), 145 (38), 117 (30), 89 (48), 73 (77), 59 (17), 45 (100); HRMS (ESI): *m/z*: calcd. for $C_{20}H_{38}NaO_4Si$ [*M*+Na^+]: 393.2432, found: 393.2429.

Dibromide *anti*-421. CBr_4 (5.88 g, 17.7 mmol) was added to a solution of PPh_3 (9.30 g, 35.4 mmol) in CH_2Cl_2 (120 mL) at 0 °C. After stirring for 0.5 h at 0 °C, the mixture was cooled to –78 °C before a solution of aldehyde *anti*-**420** in CH_2Cl_2 (35 mL) was added dropwise. After stirring for 0.5 h at –78 °C, hexane (100 mL) was added to the vigorously stirred mixture. The suspension was filtered through a pad of Celite which was washed with an cold (0 °C) mixture of hexanes/MTBE (100 mL, 4:1) and the filtrate was concentrated. The residue was dissolved in a mixture of hexane/MTBE (50 mL, 4:1), the resulting suspension was filtered through a pad of Celite, and the filtrate was concentrated again. The residue was purified by flash chromatography (SiO_2, hexanes/toluene, 10/1 → hexanes/EtOAc, 30/1) to give *anti*-**421** as a colorless oil (3.95 g, 85% over 2 steps). $[\alpha]_D^{23}$ = +11.8 (*c* = 1.11, $CHCl_3$); ^{1}H NMR (400 MHz, C_6D_6): δ = 6.07 (t, 1H, *J* = 7.3 Hz), 5.60 (dtt, 1H, *J* = 10.7, 7.4, 1.7 Hz), 5.43 (dtt, 1H, *J* = 10.5, 8.7, 1.6 Hz), 5.39 (dtt, 1H, *J* = 10.6, 8.8, 1.5 Hz), 5.13 (dtt, 1H, *J* = 10.5, 7.3, 1.6 Hz), 4.70 (d, 1H, *J* = 6.7 Hz), 4.56 (d, 1H, *J* = 6.7 Hz), 3.71 – 3.62 (m, 2H), 2.79 (m, 2H), 2.64 (tt, 2H, *J* = 7.3, 0.7 Hz), 2.54 – 2.43 (m, 1H), 2.38 – 2.29 (m, 1H), 1.70 – 1.58 (m, 1H), 1.48 – 1.37 (m, 1H), 1.02 (s, 9H), 0.94 (t, 3H, *J* = 7.5 Hz), 0.17 (s, 3H), 0.10 ppm (s, 3H); ^{13}C NMR (100 MHz, C_6D_6): δ = 137.0, 130.5, 129.1, 127.9, 124.4, 96.0, 89.8, 79.9,

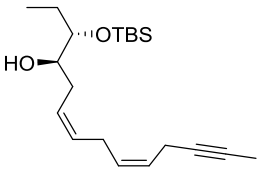


76.1, 55.5, 31.6, 28.9, 28.8, 26.5, 26.3 (3C), 18.5, 10.6, −3.9, −4.4 ppm; IR (film): $\tilde{\nu}$ = 2929, 2856, 1462, 1251, 1142, 1100, 1035, 917, 833, 773 cm^{-1}; MS (EI) *m/z* (%): 437 (22), 407 (1), 173 (100), 145 (73), 119 (28), 89 (50), 73 (59), 45 (74); HRMS (ESI): *m/z*: calcd. for $C_{21}H_{38}Br_2NaO_3Si$ [*M*+Na^+]: 547.0849, found: 547.0850.

Alkyne *anti*-389. A hexane solution of *n*-butyllithium (7.84 mL, 12.5 mmol, 1.60 M) was added dropwise to a solution of dibromide *anti*-**421** (3.30 g, 6.27 mmol) in THF (188 mL) at –78 °C. After stirring for 0.5 h at –78 °C, MeOTf (3.55 mL, 31.3 mmol) was added dropwise and the mixture was stirred for an additional 0.5 h at –78 °C. A mixture of THF and phosphate buffer (100 mL, pH 7, 1:1) was then carefully added carefully via the cold walls of the flask at –78 °C. The frozen mixture was shaken in the cooling bath to ensure good mixing with the organic phases. The mixture was then allowed to warm to ambient temperature and the aqueous phase was extracted with MTBE (3 x 100 mL). The extracts were washed with saturated aqueous $NaHCO_3$ (30 mL), water (30 mL) and brine (30 mL). The organic phase was dried over Na_2SO_4 and concentrated. The crude material was purified by flash chromatography (SiO_2, hexanes/toluene, 7/3 → toluene 100%) to give *anti*-**389** as a colorless oil (2.02 g, 79%). $[\alpha]_D^{23}$ = +14.9 (*c* = 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.54 – 5.37 (m, 4H), 4.72 (d, 1H, *J* = 6.7 Hz), 4.62 (d, 1H, *J* = 6.7 Hz), 3.63 (ddd, 1H, *J* = 7.3, 4.4, 2.9 Hz), 3.57 (ddd, 1H, *J* = 7.3, 5.3, 2.9 Hz), 3.36 (s, 3H), 2.93 – 2.88 (m, 2H), 2.83 – 2.79 (m, 2H), 2.37 – 2.22 (m, 2H), 1.78 (t, 3H, *J* = 2.6 Hz), 1.62 – 1.41 (m, 2H), 0.92 (t, 3H, *J* = 7.5 Hz), 0.90 (s, 9H), 0.07 (s, 3H), 0.05 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 129.3, 129.1, 127.3, 125.5, 96.0, 79.9, 77.4, 75.6, 75.6, 55.8, 28.9, 28.7, 26.1 (3C), 25.8, 18.3, 17.3, 10.4, 3.6, −4.1, −4.5 ppm; IR (film): $\tilde{\nu}$ = 2928, 2857, 1463, 1252, 1142, 1100, 1034, 917, 833, 773 cm^{-1}; MS (EI) *m/z* (%): 291 (18), 173 (99), 145 (100), 133 (24), 117 (29), 89 (60), 73 (84), 59 (19), 45 (79); HRMS (ESI): *m/z*: calcd. for $C_{22}H_{40}NaO_3Si$ [*M*+Na^+]: 403.2639, found: 403.2636.



Alcohol *anti*-393. A solution of MOM-ether *anti*-**389** (1.28 g, 3.35 mmol) in CH_2Cl_2 (367 mL) was cooled to −78 °C before a freshly prepared solution of Me_2BBr[149b] (5.7 mL, 5.7 mmol, 1.0 M in CH_2Cl_2) was slowly added via the cold walls of the flask. The colorless mixture was stirred for 40 min at −78 °C. After completion of the reaction, the cold solution was



transferred by canula into a vigorously stirred mixture of THF/H_2O/$NaHCO_3$ (300 mL, 1:1:1). The resulting suspension was stirred for 15 min before the aqueous phase was extracted with CH_2Cl_2 (3 x 100 mL), the organic phases were dried over Na_2SO_4 and concentrated. The crude material was purified by flash chromatography (SiO_2, pentane/EtOAc, 50/1 → 30/1) to afford alcohol *anti*-**393** as a colorless oil (970 mg, 86%). For characterization purposes an aliquot of the obtained material were purified by HPLC (UFLC SHIMADZU; Kromasil 100-5C18, 150 x 30 mm; 35 °C, 74 bar, 35 mL/min, methanol/H_2O = 85/15). $[\alpha]_D^{20}$ = +2.5 (*c* = 0.50, $CHCl_3$), ^{1}H NMR (600 MHz, C_6D_6): δ = 5.56 (dtt, 1H, *J* = 10.4, 7.0, 1.7 Hz), 5.50 (dtt, 1H, *J* = 10.7, 7.0, 1.4 Hz), 5.49 (dtt, 1H, *J* = 10.7, 6.9, 1.3 Hz), 5.41 (dtt, 1H, *J* = 10.5, 7.3, 1.7 Hz), 3.58 (dt, 1H, *J* = 8.5, 4.3 Hz), 3.54 (dt, 1H, *J* = 7.3, 4.2 Hz), 2.91 (ddqt, 2H, *J* = 7.0, 2.6, 1.9, 0.8 Hz), 2.79 (m, 2H), 2.34 – 2.23 (m, 2H), 1.77 (br s, 1H), 1.64 (dq, 1H, *J* = 13.9, 7.4 Hz), 1.55 (t, 3H, *J* = 2.6 Hz), 1.40 (ddq, 1H, *J* = 14.0, 7.4, 4.3 Hz), 0.96 (s, 9H), 0.91 (t, 3H, *J* = 7.5 Hz), 0.07 (s, 3H), 0.06 ppm (s, 3H); ^{13}C NMR (150 MHz, C_6D_6): δ = 130.2, 129.2, 127.0, 126.1, 77.6, 76.8, 75.7, 73.9, 30.6, 26.1 (3C), 26.0, 25.1, 18.4, 17.7, 10.1, 3.4, −4.2, −4.3 ppm; IR (film): $\tilde{\nu}$ = 2956, 2928, 2857, 1463, 1388, 1361, 1253, 1080, 1005, 939, 909, 834, 792, 774, 730, 671 cm^{-1}; MS (ESIpos) *m/z* (%): 359 (*M*+Na^+, 100); HRMS (ESI): *m/z*: calcd. for $C_{20}H_{36}O_2SiNa$ [*M*+Na^+]: 359.2377, found 359.2377.

6.3.5. Revised Synthesis of the Skipped Diene/Yne Fragment

Alkyne 422. Propargyl alcohol (**397**) (30.0 mL, 515 mmol) was added dropwise to a solution of *p*-TsOH·H_2O (98.0 mg, 0.1 mol%) in ethyl vinyl ether (74.0 mL) at 0 °C. After stirring for 5 h at 0 °C, the reaction was quenched with saturated aqueous Na_2CO_3 (10 mL) and excess of solid Na_2CO_3 was added to the resulting mixture. The suspension was filtered through a frit and the filtrate was concentrated. The crude product was distilled through a Vigreux column (58 – 64 °C/50 mbar) to give the ethoxyethyl ether **422** as a colorless oil (55.6 g, 84%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.85 (q, 1H, *J* = 5.4 Hz), 4.20 (d, 2H, *J* = 2.4 Hz), 3.65 (dq, 7.1, *J* = 9.4, 7.1 Hz), 3.51 (dq, 1H, *J* = 9.4, 7.1 Hz), 2.39 (t, 1H, *J* = 2.4 Hz), 1.33 (d, 3H, *J* = 5.4 Hz), 1.20 ppm (t, 3H, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 98.8, 80.2, 73.9, 60.9, 52.6, 19.8, 15.4 ppm; IR (film): $\tilde{\nu}$ = 2979, 2933, 2900, 1445, 1385, 1339, 1267, 1128, 1084, 1052, 1036, 991, 946, 927, 852, 823, 659, 631, 500 cm^{-1}; MS (EI): *m/z* (%) 113 (87), 85 (29), 83 (95), 73 (100), 57 (31), 55 (33), 45 (99), 43 (94),39 (95), 29 (61);

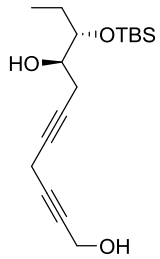
HRMS (CI): *m/z*: calcd. for $C_7H_{13}O_2$ [*M*+H^+]: 129.0916, found: 129.0915. The ^1H and ^{13}C NMR data are identical to the previously reported.[161]

Skipped Diyne 396. A solution of EtMgBr (39.6 mL, 119 mmol, 3.0 M in Et_2O) was diluted with THF (120 mL) and warmed to 45 °C. 3-(1-Ethoxyethoxy)prop-1-yne (**422**) (15.0 mL, 110 mmol) was added dropwise to the mixture at 45 °C. After stirring for 0.5 h at 45 °C, copper(I) chloride (546 mg, 5.00 mol%) was added and the temperature raised to and kept at 50 °C for 0.5 h. A solution of propargyl bromide (14.1 mL, 127 mmol, 80% in toluene) was added dropwise and the temperature was increased to 60 °C. After 1.5 h, the reaction mixture was cooled to ambient temperature and then poured into a solution of KCN (1.94 g) and NH_4Cl (14.8 g) in water (97.8 mL). The aqueous phase was extracted with MTBE (3 x 150 mL) and the extracts were combined, washed successively with water (50 mL) and brine (50 mL), dried over Na_2SO_4 and concentrated. The crude product was purified by distillation (53 – 55 °C/0.07 mbar) to give the desired product **396** as a pale yellow oil (12.4 g, 68%) which was very sensitive to air and must be stored under argon in a freezer. ^1H NMR (400 MHz, $CDCl_3$): δ = 4.82 (q, 1H, *J* = 5.4 Hz), 4.18 (dt, 2H, *J* = 2.2, 1.1 Hz), 3.64 (dq, 1H, *J* = 9.4, 7.1 Hz), 3.50 (dq, 1H, *J* = 9.4, 7.1 Hz), 3.21 – 3.18 (m, 2H), 2.05 (t, 1H, *J* = 2.8 Hz), 1.31 (d, 3H, *J* = 5.4 Hz), 1.19 ppm (t, 3H, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 98.7, 79.2, 77.9, 77.2, 69.1, 60.8, 53.1, 19.8, 15.4, 9.8 ppm; IR (film): $\tilde{\nu}$ = 3295, 2979, 2900, 1445, 1385, 1338, 1311, 1124, 1083, 1053, 1028, 979, 945, 927, 854 cm^{-1}; MS (EI) *m/z* (%): 151 (20), 121 (25), 93 (10), 77 (100), 73 (53), 65 (7), 51 (39), 45 (57); HRMS (CI): *m/z*: calcd. for $C_{10}H_{15}O_2$ [*M*+H^+]: 167.1072, found: 167.1073.

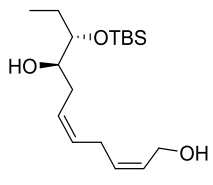
Alcohol *anti*-395. A hexane solution of *n*-butyllithium (2.60 mL, 4.16 mmol, 1.5 M) was added dropwise to a solution of the skipped diyne **396** (691 mg, 4.16 mmol) in THF (40 mL) at –78 °C. After stirring for 0.5 h, $BF_3{\cdot}OEt_2$ (513 µL, 4.16 mmol) was added dropwise and the mixture was stirred for 5 min at –78 °C. A solution of epoxide **383** (300 mg, 1.39 mmol) in THF (4.0 mL) was added to the reaction mixture which was stirred for 0.5 h at –78 °C and subsequently poured into saturated aqueous $NaHCO_3$ (40 mL). The aqueous phase was extracted with MTBE (3 x 50 mL) and the extracts were combined, washed with water (20 mL) and brine (20 mL), dried over Na_2SO_4, and concentrated. The crude product was purified by flash

chromatography (SiO_2, hexane/EtOAc, 10/1 containing 1% Et_3N) to give *anti*-**395** as a yellow oil (381 mg, 72%). $[\alpha]_D^{23}$ = +16.4 (*c* = 1.55, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.82 (q, 1H, *J* = 5.3 Hz), 4.18 (q, 2H, *J* = 2.2 Hz), 3.73 – 3.59 (m, 3H), 3.50 (dq, 1H, *J* = 9.4, 7.1 Hz), 3.19 (tt, 2H, *J* = 2.2, 2.2 Hz), 2.40 – 2.35 (m, 2H), 2.17 (br s, 1H), 1.63 – 1.40 (m, 2H), 1.32 (d, 3H, *J* = 5.3 Hz), 1.19 (t, 3H, *J* = 7.1 Hz), 0.90 (t, 3H, *J* = 7.4 Hz), 0.89 (s, 9H), 0.07 (s, 3H), 0.07 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 98.7, 80.3, 76.6, 75.9, 75.2, 72.1, 60.7, 53.1, 46.3, 26.0 (3C), 24.7, 22.8, 19.8, 18.2, 15.4, 10.1, 9.4, −4.3, −4.4 ppm; IR (film): $\tilde{\nu}$ = 3481, 2930, 2858, 1463, 1384, 1253, 1128, 1084, 1055, 1030, 1004, 928, 834, 774, 668 cm^{-1}; MS (EI) *m/z* (%): 279 (13), 235 (21), 173 (61), 145 (24), 115 (9), 91 (7), 73 (100), 45 (26); HRMS (ESI): *m/z*: calcd. for $C_{21}H_{38}NaO_4Si$ [*M*+Na$^+$]: 405.2432, found: 405.2428.

Diol *anti*-423. PPTS (509 mg, 2.03 mmol) was added to a solution of *anti*-**395** (775 mg, 2.03 mmol) in MeOH (100 mL). The reaction mixture was stirred for 1 h, before saturated aqueous $NaHCO_3$ was added. The mixture was concentrated to remove MeOH, and the residue was extracted with EtOAc (3 x 50 mL). The extracts were combined, washed with water (40 mL) and brine (40 mL), dried over Na_2SO_4, and concentrated. The crude material was purified by flash chromatography (SiO_2, hexane/EtOAc, 2/1 containing 1% Et_3N) to give *anti*-**423** as a yellow oil (615 mg, 98%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.25 (t, 2H, *J* = 2.2 Hz), 3.74 – 3.64 (m, 2H), 3.20 (tt, 2H, *J* = 2.3, 2.3 Hz), 2.41 – 2.36 (m, 2H), 1.64 – 1.39 (m, 2H), 0.91 (t, 3H, *J* = 7.5 Hz), 0.89 (s, 9H), 0.08 (s, 3H), 0.08 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 80.5, 78.7, 77.6, 75.8, 75.2, 72.2, 51.4, 26.0 (3C), 24.6, 22.8, 18.2, 10.1, 9.5, −4.3, −4.4 ppm; IR (film): $\tilde{\nu}$ = 3361, 2929, 2857, 1463, 1252, 1068, 1003, 834, 773, 668 cm^{-1}; MS (EI) *m/z* (%): 235 (21), 187 (11), 174 (14), 173 (100), 145 (53), 133 (14), 117 (19), 115 (27), 105 (13), 91 (16), 77 (12), 75 (98), 73 (82), 57 (23); HRMS (ESI): *m/z*: calcd. for $C_{17}H_{30}O_3SiNa$ [*M*+Na$^+$]: 333.1854, found: 333.1856.

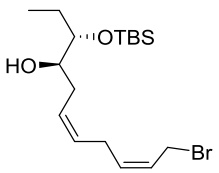


Skipped Diene *anti*-424. An solution of $NaBH_4$ (495 μL, 25 mol%, 1.0 M IN EtOH) was added to a solution of $Ni(OAc)_2 \cdot 4H_2O$ (138 mg, 25 mol%) in EtOH (0.7 mL). After the evolution of hydrogen had ceased, the resulting black suspension was cooled to –78 °C and the flask was filled with hydrogen gas. EDA (106 μL, 1.58 mmol) and a solution of the skipped diyne *anti*-**423** (615 mg,

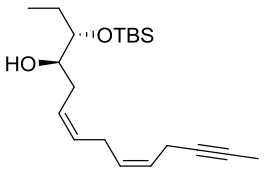


1.98 mmol) in EtOH (0.5 mL) were added and the mixture was allowed to reach ambient temperature. After stirring for 7 h, the mixture was diluted with EtOAc. The resulting suspension was filtered through a pad of Celite and the filtrate was concentrated. The crude product was purified by flash chromatography (SiO_2, hexane/EtOAc, 3/1 containing 1% Et_3N) to give *anti*-**424** as a pale yellow oil (489 mg, 79%). $[\alpha]_D^{23}$ = +2.2 (*c* = 1.80, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.70 – 5.60 (m, 1H), 5.59 – 5.43 (m, 3H), 4.27 – 4.21 (m, 1H), 4.17 – 4.08 (m, 1H), 3.65 – 3.54 (m, 2H), 2.99 – 2.92 (m, 1H), 2.84 – 2.74 (m, 1H), 2.32 – 2.16 (m, 2H), 2.05 (br s, 2H), 1.64 – 1.40 (m, 2H), 0.90 (t, 3H, *J* = 7.4 Hz), 0.90 (s, 9H), 0.07 (s, 3H), 0.07 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 130.7, 130.2, 128.8, 126.6, 76.1, 73.8, 58.4, 30.3, 26.1, 26.0 (3C), 24.3, 18.2, 9.9, −4.2, −4.3 ppm; IR (film): $\tilde{\nu}$ = 3361, 2929, 2857, 1463, 1253, 1082, 1004, 834, 773, 755, 666 cm^{-1}; MS (EI) *m/z* (%): 239 (12), 187 (21), 173 (80), 145 (60), 133 (43), 115 (17), 93 (50), 75 (100), 67 (13), 57 (20), 41 (13); HRMS (ESI): *m/z*: calcd. for $C_{17}H_{34}NaO_3Si$ [*M*+Na^+]: 337.2169, found: 337.2166.

Allyl Bromide *anti*-398. A solution of PPh_3 (84.3 mg, 0.322 mmol) in CH_2Cl_2 (1.5 mL) was added to a solution of *anti*-**424** (77.8 mg, 0.247 mmol) and CBr_4 (107 mg, 0.322 mmol) in CH_2Cl_2 (3.5 mL) at 0 °C. After stirring for 0.5 h at 0 °C, the reaction was quenched by addition of saturated aqueous NH_4Cl and the aqueous phase was extracted with MTBE (3 x 30 mL). The extracts were combined, washed with water (15 mL) and brine (15 mL), dried over Na_2SO_4, and concentrated, and the crude product was purified by flash chromatography (SiO_2, hexane/EtOAc, 20/1) to give *anti*-**398** as a colorless oil (85.3 mg, 91%). $[\alpha]_D^{23}$ = −3.4 (*c* = 1.05, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.76 (dtt, 1H, *J* = 10.4, 8.4, 1.7 Hz), 5.61 – 5.47 (m, 3H), 4.01 (dd, 2H, *J* = 8.3, 1.0 Hz), 3.66 – 3.57 (m, 2H), 2.92 (t, 2H, *J* = 6.6 Hz), 2.31 – 2.14 (m, 2H), 2.06 (br s, 1H), 1.64 – 1.40 (m, 2H), 0.92 (t, 3H, *J* = 7.5 Hz), 0.91 (s, 9H), 0.09 (s, 3H), 0.08 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 133.7, 128.9, 127.4, 125.8, 76.3, 73.9, 30.1, 27.0, 26.0 (3C), 25.6, 24.1, 18.3, 10.1, −4.2, −4.3 ppm; IR (film): $\tilde{\nu}$ = 3567, 2930, 2857, 1463, 1253, 1077, 1004, 834, 774, 754, 668 cm^{-1}; HRMS (ESI): *m/z*: calcd. for $C_{17}H_{33}BrNaO_2Si$ [*M*+Na^+]: 399.1326, found: 399.1329.

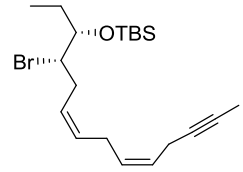


Alcohol *anti*-393. 1-Propynylmagnesium bromide (2.38 mL, 1.19 mmol, 0.5 M in THF) was



added to a suspension of CuI (38 mg, 50 mol%) in THF (10 mL) at −15 °C. The mixture was stirred for 0.5 h at −15 °C, before a solution of bromide *anti*-**398** (150 mg, 0.397 mmol) in THF (4.0 mL) was added dropwise. After stirring for 5 h at −10 °C, the reaction was quenched with saturated aqueous NH_4Cl and the mixture was warmed to ambient temperature before it was extracted with MTBE (3 x 15 mL). The extracts were combined, washed successively with water (5 mL) and brine (5 mL), dried over Na_2SO_4, and concentrated. The residue was purified by flash chromatography (SiO_2, hexane/EtOAc, 30/1) to give *anti*-**393** as colorless oil (108 mg, 81%). For characterization purposes an aliquot was purified by HPLC (UFLC SHIMADZU; Kromasil 100-5C18, 150 x 30 mm; 35 °C, 74 bar, 35 mL/min, methanol/H_2O = 85/15). $[\alpha]_D^{20}$ = +2.5 (*c* = 0.50, $CHCl_3$), ^{1}H NMR (600 MHz, C_6D_6): δ = 5.56 (dtt, 1H, *J* = 10.4, 7.0, 1.7 Hz), 5.50 (dtt, 1H, *J* = 10.7, 7.0, 1.4 Hz), 5.49 (dtt, 1H, *J* = 10.7, 6.9, 1.3 Hz), 5.41 (dtt, 1H, *J* = 10.5, 7.3, 1.7 Hz), 3.58 (dt, 1H, *J* = 8.5, 4.3 Hz), 3.54 (dt, 1H, *J* = 7.3, 4.2 Hz), 2.91 (ddqt, 2H, *J* = 7.0, 2.6, 1.9, 0.8 Hz), 2.79 (m, 2H), 2.34 – 2.23 (m, 2H), 1.77 (br s, 1H), 1.64 (dq, 1H, *J* = 13.9, 7.4 Hz), 1.55 (t, 3H, *J* = 2.6 Hz), 1.40 (ddq, 1H, *J* = 14.0, 7.4, 4.3 Hz), 0.96 (s, 9H), 0.91 (t, 3H, *J* = 7.5 Hz), 0.07 (s, 3H), 0.06 ppm (s, 3H); ^{13}C NMR (150 MHz, C_6D_6): δ = 130.2, 129.2, 127.0, 126.1, 77.6, 76.8, 75.7, 73.9, 30.6, 26.1 (3C), 26.0, 25.1, 18.4, 17.7, 10.1, 3.4, −4.2, −4.3 ppm; IR (film): $\tilde{\nu}$ = 2956, 2928, 2857, 1463, 1388, 1361, 1253, 1080, 1005, 939, 909, 834, 792, 774, 730, 671 cm^{-1}; MS (ESIpos) *m/z* (%): 359 (*M*+Na$^+$, 100); HRMS (ESI): *m/z*: calcd. for $C_{20}H_{36}O_2SiNa$ [*M*+Na$^+$]: 359.2377, found 359.2377.

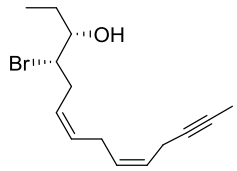
Bromide *syn*-399. PPh_3 (1.96 g, 7.49 mmol) was added to a solution of alcohol *anti*-**393**



(630 mg, 1.87 mmol) in toluene (62 mL) at 0 °C and the resulting mixture was stirred for 10 min before CBr_4 (2.48 g, 7.49 mmol) was introduced. After stirring for another 10 min, the flask was placed into a pre-heated oilbath at 65 °C and stirring was continued for 1 h. After cooling to room temperature, the pale yellow suspension was filtered through a pad of Celite which was carefully rinsed with pentane/EtOAc (20:1). The combined filtrates were concentrated and purified by flash chromatography (SiO_2, pentane/EtOAc, 200/1) to yield the bromide *syn*-**399** as a pale yellow oil (445 mg, 60%). The material was very unstable and must be stored under argon in a freezer. For characterization purposes an aliquot was

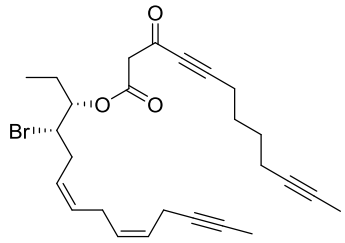
purified by HPLC (UFLC SHIMADZU; Kromasil 100-5C18, 150 x 30 mm; 25 °C, 61 bar, 35 mL/min, 210 nm, methanol/H_2O = 95/5). $[\alpha]_D^{20}$ = −16.2 (*c* = 1.01, $CHCl_3$); ^{1}H NMR (600 MHz, C_6D_6): δ = 5.56 (ddt, 1H, *J* = 10.4, 7.0, 1.7 Hz), 5.53 (dddt, 1H, *J* = 10.7, 7.6, 6.2, 1.4 Hz), 5.47 (ddt, 1H, *J* = 10.7, 7.0, 1.4 Hz), 5.39 (ddt, 1H, *J* = 10.5, 7.2, 1.7 Hz), 3.93 (dt, 1H, *J* = 10.1, 3.5 Hz), 3.63 (ddd, 1H, *J* = 7.7, 4.6, 3.3 Hz), 2.90 (ddqt, 2H, *J* = 7.0, 2.6, 1.9, 0.7 Hz), 2.78 (dq, 1H, *J* = 16.0, 7.1 Hz), 2.75 (dq, 1H, *J* = 16.0, 7.1 Hz); 2.69 (dddd, 1H, *J* = 15.5, 6.4, 3.6, 1.6 Hz), 2.61 (dddd, 1H, *J* = 15.2, 9.9, 7.5, 1.2 Hz), 1.89 (ddq, 1H, *J* = 13.6, 7.5, 4.6 Hz), 1.54 (t, 3H, *J* = 2.6 Hz), 1.44 (dq, 1H, *J* = 13.7, 7.5 Hz), 0.95 (s, 9H), 0.81 (t, 3H, *J* = 7.4 Hz), 0.00 (s, 3H), −0.01 ppm (s, 3H); ^{13}C NMR (150 MHz, C_6D_6): δ = 130.1, 128.9, 127.5, 126.3, 77.5, 76.7, 75.8, 59.4, 31.7, 26.3, 26.1, 26.0 (3C), 18.3, 17.7, 10.5, 3.4, −4.2, −4.3 ppm; IR (film): $\tilde{\nu}$ = 2956, 2929, 2857, 1462, 1382, 1361, 1254, 1094, 1048, 1005, 834, 794, 774, 726, 671 cm^{-1}; MS (pos. ESI) *m/z* (%): 421 (*M*+Na^+, 100); HRMS (ESI): *m/z*: calcd. for $C_{20}H_{35}OBrSiNa$ [*M*+Na^+]: 421.1536, found 421.1533.

Alcohol *syn*-372. In a Teflon vial, a solution of *syn*-**399** (432 mg, 1.08 mmol) in THF (18 mL) was carefully treated with HF·pyridine (3.41 mL, 37.8 mmol, 70% HF) at 0 °C. The resulting mixture was stirred for 5 h at 0 °C before it was diluted with EtOAc (10 mL) and H_2O (5 mL). A saturated aqueous solution of $NaHCO_3$ was added until the evolution of gas ceased. The mixture was extracted with EtOAc (3 x 30 mL), the combined organic phases were washed with brine (10 mL), dried over Na_2SO_4 and concentrated. The crude material was purified by flash chromatography (SiO_2, pentane/EtOAc, 15/1) to yield the free alcohol *syn*-**372** as a colorless oil (371 mg, 83%). The material was very unstable and should be immediately used in the next step. For characterization purposes an aliquot was purified by HPLC (UFLC SHIMADZU; Kromasil 100-5C18, 150 x 30 mm; 35 °C, 70 bar, 35 mL/min, 210 nm, methanol/H_2O = 75/25). $[\alpha]_D^{20}$ = −18.6 (*c* = 0.56, $CHCl_3$); ^{1}H NMR (600 MHz, C_6D_6): δ = 5.53 (dtt, 1H, *J* = 10.5, 7.0, 1.7 Hz), 5.42 (dtt, 1H, *J* = 10.7, 7.3, 1.6 Hz), 5.34 (dtt, 1H *J* = 10.4, 7.3, 1.7 Hz), 5.30 (dtt, 1H, *J* = 10.7, 7.3, 1.7 Hz), 3.73 (ddd, 1H, *J* = 7.9, 6.3, 2.9 Hz), 3.10 (m, 1H), 2.88 (ddqt, 2H, *J* = 7.0, 2.6, 1.8, 0.8 Hz), 2.70 (m, 2H), 2.60 (dddt, 1H, *J* = 15.0, 7.3, 6.3, 1.5 Hz), 2.56 (dddt, 1H, *J* = 15.0, 7.9, 7.2, 1.5 Hz), 1.55 (t, 3H, *J* = 2.6 Hz), 1.38 (dq, 1H, *J* = 13.7, 7.4 Hz), 1.35 – 1.33 (m, 1H), 1.30 (ddq, 1H, *J* = 13.7, 7.4, 4.7 Hz), 0.79 ppm (t, 3H, *J* = 7.4 Hz); ^{13}C NMR (150 MHz, C_6D_6): δ = 130.6, 128.8, 126.8, 126.2, 77.6, 75.8, 74.2, 63.3,

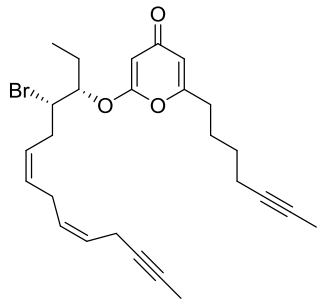


34.0, 29.1, 26.0, 17.7, 10.2, 3.4 ppm; IR (film): $\tilde{\nu}$ = 3436, 3020, 2964, 2920, 1710, 1424, 1375, 1222, 1112, 1059, 969, 792, 681, 535, 482 cm^{-1}; MS (EI) *m/z* (%): 187 (11), 147 (17), 145 (23), 133 (24), 132 (10), 131 (42), 129 (10), 121 (18), 119 (34), 118 (15), 117 (40), 115 (11), 107 (14), 106 (12), 105 (86), 93 (29), 92 (24), 91 (100), 85 (40), 81 (16), 79 (55), 78 (13), 77 (40), 69 (19), 67 (24), 65 (14), 59 (32), 57 (85), 55 (22), 53 (20), 43 (12), 41 (39), 39 (17), 29 (20); HRMS (ESI): *m/z*: calcd. for $C_{14}H_{21}OBrNa$ [*M*+Na^+]: 307.0667, found 307.0668.

β-Ketoester *syn*-374. A solution of acid **370** (298 mg, 1.45 mmol) in CH_2Cl_2 (16 mL) was added to a solution of alcohol *syn*-**372** (165 mg, 0.58 mmol) in CH_2Cl_2 (16 mL) at 0 °C. DCC (298 mg, 1.45 mmol) was introduced to the mixture followed by DMAP (21 mg, 30 mol%). The mixture was stirred for 0.5 h before it was diluted with MTBE (20 mL). The resulting suspension was filtered through a pad of Celite and the filtrate was concentrated. The residue was dissolved in a mixture of hexanes/MTBE (10 mL, 2:1) and the resulting suspension was filtered again through a pad of Celite. After evaporation of the filtrate, the crude product was purified by flash chromatography (SiO_2, hexanes/EtOAc, 10/1 → 5/1) to give the highly unstable title compound *syn*-**374** as a yellow oil (208 mg, 76%), which was directly used in the next step without further purification. $[\alpha]_D^{20}$ = −13.2 (*c* = 0.55, $CHCl_3$). MS (ESIpos) *m/z* (%): 495 (*M*+Na^+, 100); HRMS (ESI): *m/z*: calcd. for $C_{26}H_{33}O_3BrNa$ [*M*+Na^+]: 495.1507, found 495.1505.

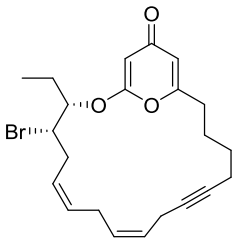


4-Pyrone *syn*-402. [SPhosAu]NTf_2 (**C12**) (6.2 mg, 3 mol%) was added to a solution of β-ketoester *syn*-**374** (110 mg, 0.23 mmol) in MeCN/AcOH (7.7 mL, 5:1). The reaction mixture was stirred for 38 h at ambient temperature befiore it was concentrated. The crude product was purified by flash chromatography (SiO_2, hexanes/EtOAc, 1/1 → EtOAc 100%) to give *syn*-**402** as a colorless oil (105 mg, 97%). For characterization purposes an aliquot was purified by HPLC (UFLC SHIMADZU; Kromasil 100-5C18, 150 x 30 mm; 25 °C, 75 bar, 35 mL/min, 244 nm, methanol/H_2O = 85/15). $[\alpha]_D^{20}$ = −41.9 (*c* = 0.44, $CHCl_3$); ^{1}H NMR (600 MHz, C_6D_6): δ = 5.95 (dt, 1H, *J* = 1.8, 0.7 Hz), 5.63 (d, 1H, *J* = 1.9 Hz), 5.52 (dtt, 1H, *J* = 10.5, 7.0, 1.7 Hz), 5.41 (dtt, 1H, *J* = 10.7, 7.4, 1.6 Hz), 5.28 (dtt, 1H, *J* = 10.5, 7.3, 1.8 Hz), 5.22 (dtt, 1H, *J* = 10.7, 7.1,



1.7 Hz), 4.01 (ddd, 1H, *J* = 7.2, 5.8, 3.5 Hz), 3.75 (ddd, 1H, *J* = 8.2, 5.9, 3.5 Hz), 2.84 (ddqt, 2H, *J* = 7.0, 1.8, 2.6, 0.8 Hz), 2.64 (dt, 1H, *J* = 15.8, 7.4 Hz), 2.60 (dt, 1H, *J* = 15.8, 7.3 Hz), 2.52 – 2.47 (m, 2H), 1.91 (tq, 2H, *J* = 7.0, 2.6 Hz), 1.85 (dd, 2H, *J* = 7.4, 0.7 Hz), 1.61 (ddq, 1H, *J* = 14.2, 5.8, 7.5 Hz), 1.56 (t, 3H, *J* = 2.5 Hz), 1.55 (t, 3H, *J* = 2.6 Hz), 1.52 (dq, 1H, *J* = 14.2, 7.3 Hz), 1.38 – 1.32 (m, 2H), 1.21 – 1.16 (m, 2H), 0.81 ppm (t, 3H, *J* = 7.5 Hz); ^{13}C NMR (150 MHz, C_6D_6): δ = 180.9, 166.8, 164.8, 131.2, 128.4, 126.4, 125.8, 112.8, 92.0, 82.5, 78.7, 77.4, 76.2, 75.9, 54.3, 32.8, 32.3, 28.4, 25.9, 25.8, 24.7, 18.7, 17.6, 9.4, 3.4, 3.4 ppm; IR (film): $\tilde{\nu}$ = 2919, 1659, 1577, 1404, 1240, 1157, 928, 858, 679 cm^{-1}; MS (EI) *m/z* (%): 393 (23), 208 (13), 207 (100), 187 (32), 165 (25), 159 (16), 147 (16), 146 (12), 145 (47), 143 (12), 135 (11), 132 (16), 131 (60), 129 (13), 123 (11), 119 (24), 118 (11), 117 (40), 111 (24), 109 (11), 107 (18), 106 (10), 105 (57), 95 (31), 93 (36), 92 (13), 91 (64), 81 (45), 80 (12), 79 (51), 77 (20), 69 (20), 55 (29), 53 (11), 43 (13), 41 (24); HRMS (ESI): *m/z*: calcd. for $C_{26}H_{33}O_3BrNa$ [*M*+Na$^+$]: 495.1507, found 495.1505.

Cycloalkyne *syn*-373. A solution of *syn*-**402** (30.0 mg, 63.0 μmol) in toluene (60 mL) was



stirred with activated MS 5 Å (powder, 440 mg) for 0.5 h before a solution of the molybdenum alkylidyne complex **C4** (3.3 mg, 5 mol%, in 50 μL toluene) was added to the mixture. After stirring for 2 h at rt, the reaction mixture was filtered through a pad of Celite which was thoroughly rinsed with acetone. The filtrate was concentrated and the residue was purified by flash chromatography (SiO_2, EtOAc 100% → EtOAc/acetone, 1/1) to give *syn*-**373** as a colorless oil (21.7 mg, 52.0 μmol, 82%). For characterization purposes an aliquot was purified by HPLC (UFLC SHIMADZU; Kromasil 100-5C18, 150 x 20 mm; 35 °C, 55 bar, 25 mL/min, 240 nm, acetonitrile/H_2O = 60/40). $[\alpha]_D^{20}$ = −42.1 (*c* = 1.05, $CHCl_3$), ^{1}H NMR (600 MHz, C_6D_6): δ = 5.87 (d, 1H, *J* = 1.8 Hz), 5.51 (d, 1H, *J* = 1.8 Hz), 5.48 – 5.45 (m, 1H), 5.46 – 5.42 (m, 1H), 5.33 (dtt, 1H, *J* = 10.3, 6.9, 1.3 Hz), 5.20 (dtt, 1H, *J* = 10.7, 7.3, 1.7 Hz), 3.75 (td, 1H, *J* = 6.8, 2.6 Hz), 3.63 (ddd, 1H, *J* = 9.5, 4.9, 2.6 Hz), 2.83 (dddt, 1H, *J* = 17.4, 8.0, 1.4, 2.1 Hz), 2.79 (dt, 1H, *J* = 16.3, 7.4 Hz), 2.73 (dt, 1H, *J* = 16.3, 6.9 Hz), 2.68 – 2.64 (m, 1H), 2.54 (dddt, 1H, *J* = 15.1, 9.5, 7.2, 1.6 Hz), 2.44 (dddt, 1H, *J* = 15.1, 7.3, 4.9, 1.6 Hz), 1.93 – 1.87 (m, 3H), 1.67 (dt, 1H, *J* = 14.2, 7.8 Hz), 1.65 – 1.55 (m, 2H), 1.44 – 1.37 (m, 2H), 1.09 – 0.99 (m, 2H), 0.55 ppm (t, 3H, *J* = 7.5 Hz); ^{13}C NMR (150 MHz, C_6D_6): δ = 180.3, 166.7, 164.5, 131.0, 129.9, 126.0, 125.2, 113.1, 91.5, 82.1, 79.3, 79.2, 54.4, 33.1, 32.6, 27.6,

26.2, 26.0, 24.9, 18.6, 17.3, 9.5 ppm; MS (pos. ESI) *m/z* (%): 441 (*M*+Na^+, 100); HRMS (ESI): *m/z*: calcd. for $C_{22}H_{27}O_3BrNa$ [*M*+Na^+]: 441.1037, found 441.1036.

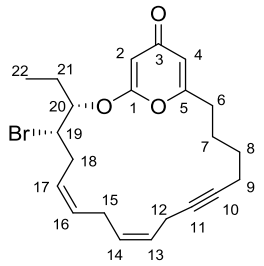


Table 10: ^{1}H and ^{13}C NMR data of macrocycle *syn*-**373**; numbering scheme as shown in the insert.

^{1}H NMR (600 MHz, C_6D_6)						^{13}C NMR (150 MHz, C_6D_6)	
No.	δ (ppm)	Integral	Splitting	COSY	*J* (Hz)	δ (ppm)	HMBC
1	-	-	-	-	-	166.7	2, 20
2	5.51	1H	d	4	1.8	91.5	4
3	-	-	-	-	-	180.3	2, 4
4	5.87	1H	d	2	1.8	113.1	2, 6a, 6b
5	-	-	-	-	-	164.5	4, 6a, 6b
6a	1.93 – 1.87	1H	m	6b, 7	-	32.6	4, 7, 8
6b	1.67	1H	dt	6a, 7	14.2, 7.8		
7	1.44 – 1.37	2H	m	6a, 6b, 8	-	26.2	6a, 6b, 8, 9
8	1.09 – 0.99	2H	m	7, 9	-	27.6	6a, 6b, 7, 9
9	1.90 – 1.87	2H	m	8, 12a, 12b	-	18.6	7, 8
10	-	-	-	-	-	79.3	8, 9
11	-	-	-	-	-	79.2	12a, 12b, 13, 14
12a	2.83	1H	dddt	9, 12b, 13	17.4, 8.0, 1.4, 2.1	17.3	9, 13, 14
12b	2.68 – 2.64	1H	m	9, 12a, 13	-		
13	5.48 – 5.45	1H	m	12a, 12b, 14	-	125.2	9, 12a, 12b, 14, 15a, 15b
14	5.33	1H	dtt	13, 15a, 15b	10.3, 6.9, 1.3	129.9	12a, 12b, 13, 15a, 15b
15a	2.79	1H	dt	14, 15b, 16	16.3, 7.4	26.0	13, 14, 16, 17
15b	2.73	1H	dt	14, 15a, 16	16.3, 6.9		
16	5.46 – 5.42	1H	m	15a, 15b, 17	-	131.0	14, 15a, 15b, 17, 18a, 18b
17	5.20	1H	dtt	15a, 15b, 16, 18a, 18b	10.7, 7.3, 1.7	126.0	15a, 15b, 16, 18a, 18b, 19
18a	2.54	1H	dddt	17, 19	15.1, 9.5, 7.2, 1.6	33.1	16, 17, 19, 20
18b	2.44	1H	dddt	17, 19	15.1, 7.3, 4.9, 1.6		
19	3.63	1H	ddd	18a, 18b, 20	9.5, 4.9, 2.6	54.4	17, 18a, 18b, 20, 21
20	3.75	1H	td	19, 21	6.8, 2.6	82.1	18a, 18b, 19, 21, 22
21	1.65 – 1.55	2H	m	20, 22	-	24.9	19, 20, 22
22	0.55	3H	t	21	7.5	9.5	20, 21

***syn*-11.** NBS (4.2 mg, 2.4 μmol) was added in solid form to a solution of *syn*-**373** (11 mg, 2.6 μmol) in THF (1.1 mL) at 0 °C. The pale yellow solution was immediately allowed to warm to ambient temperature. The reaction was closely monitored by TLC (pentane/EtOAc, 1/1). After complete consumption of the starting material, the mixture was diluted with pentane and filtered through a pad of Celite, which was carefully rinsed with pentane/EtOAc (1:1). The combined filtrates were concentrated and the residue was purified by flash chromatography (SiO_2, pentane/EtOAc, 1/1 → EtOAc 100%) to give *syn*-**11** as a colorless solid (5.3 mg, 40%). Crystals suitable for X-ray diffraction were grown from MeCN. For characterization purposes an aliquot was purified by HPLC (UFLC SHIMADZU; Kromasil 100-5C18, 150 x 20 mm; 35 °C, 50 bar, 20 mL/min, 264 nm, MeCN/H_2O = 60/40). M.p. 105 – 108 °C; $[\alpha]_D^{20}$ = −13.8 (*c* = 0.25, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 6.13 (s, 1H), 5.67 (dddt, 1H, *J* = 10.7, 7.6, 7.1, 1.4 Hz), 5.55 (dtt, 1H, *J* = 10.7, 7.1, 1.6 Hz), 5.51 – 5.45 (m, 2H), 4.80 (ddd, 1H, *J* = 7.4, 5.4, 4.6 Hz), 4.14 (ddd, 1H, *J* = 8.3, 5.5, 4.6 Hz), 2.91 – 2.88 (m, 2H), 2.90 – 2.78 (m, 2H), 2.73 (dddd, 1H, *J* = 15.1, 7.2, 5.4, 1.5 Hz), 2.72 (dddd, 1H, *J* = 15.2, 8.3, 7.0, 1.5 Hz), 2.56 (ddd, 1H, *J* = 14.7, 8.5, 6.4 Hz), 2.53 (ddd, 1H, *J* = 14.6, 8.4, 6.9 Hz), 2.26 – 2.24 (m, 2H), 1.96 (ddq, 1H, *J* = 14.3, 5.4, 7.5 Hz), 1.92 (dq, 1H, *J* = 14.3, 7.3 Hz), 1.83 (dtt, 1H, *J* = 13.9, 8.5, 6.8 Hz), 1.79 (dtt, 1H, *J* = 13.7, 8.5, 6.8 Hz), 1.57 – 1.52 (m, 2H), 1.03 ppm (t, 3H, *J* = 7.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 175.8, 163.1, 162.0, 130.8, 129.4, 125.9, 125.0, 111.8, 92.2, 84.6, 79.2, 79.0, 55.1, 33.6, 32.7, 27.8, 26.5, 26.4, 26.1, 18.6, 17.4, 9.7 ppm; IR (film): $\tilde{\nu}$ = 2926, 1659, 1573, 1459, 1379, 1324, 1262, 1157, 1091, 1013, 975, 918 cm^{-1}; MS (EI) *m/z* (%): 506 (32), 505 (82), 420 (13), 419 (25), 417 (26), 338 (12), 337 (17), 235 (19), 219 (29), 217 (28), 206 (21), 199 (20), 197 (20), 195 (21), 185 (38), 181 (23), 173 (25), 171 (59), 169 (34), 159 (25), 157 (44), 145 (44), 143 (58), 141 (27), 133 (33), 131 (62), 129 (87), 119 (32), 117 (81), 115 (29), 105 (57), 97 (22), 95 (33), 93 (38), 91 (100), 81 (42), 80 (14), 79 (58), 69 (25), 67 (50), 55 (40); HRMS (ESI): *m/z*: calcd. for $C_{22}H_{26}O_3Br_2Na$ [*M*+Na^+]: 519.0138, found 519.0141.

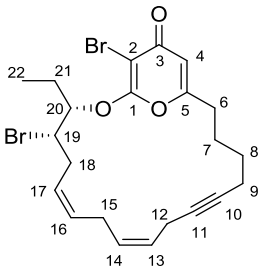
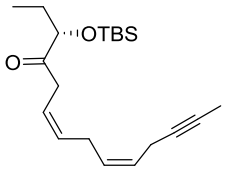


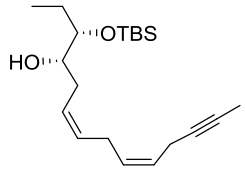
Table 11: ^{1}H and ^{13}C NMR data of synthetic 4-pyrone *syn*-**11**; numbering scheme as shown in the insert.

	^{1}H NMR (600 MHz, $CDCl_3$)					^{13}C NMR (150 MHz, $CDCl_3$)	
No.	δ (ppm)	Integral	Splitting	COSY	*J* (Hz)	δ (ppm)	HMBC
1	-	-	-	-	-	162.0	20
2	-	-	-	-	-	92.2	4
3	-	-	-	-	-	175.8	4
4	6.13	1H	s	-	-	111.8	6a, 6b
5	-	-	-	-	-	163.1	4, 6a, 6b, 7a, 7b
6a	2.56	1H	ddd	6b, 7a, 7b	14.7, 8.5, 6.4	32.7	4, 7a, 7b, 8
6b	2.53	1H	ddd	6a, 7a, 7b	14.6, 8.4, 6.9		
7a	1.83	1H	dtt	6a, 6b, 7b, 8	13.9, 8.5, 6.8	26.4	4, 6a, 6b, 8, 9
7b	1.79	1H	dtt	6a, 6b, 7a, 8	13.7, 8.5, 6.8		
8	1.57 – 1.52	2H	m	7a, 7b, 9	-	27.8	6a, 6b, 7a, 7b, 9
9	2.26 – 2.24	2H	m	8, 12	-	18.6	7a, 7b, 8
10	-	-	-	-	-	79.2	8, 9, 12
11	-	-	-	-	-	79.0	9, 12, 13
12	2.91 – 2.88	2H	m	9, 13	-	17.4	13, 14
13	5.51 – 5.45	1H	m	12	-	125.0	12, 15
14	5.51 – 5.45	1H	m	15	-	129.4	12, 15, 16
15	2.90 – 2.78	2H	m	14, 16, 17	-	26.1	13, 14, 16, 17
16	5.67	1H	dddt	15, 17, 18a, 18b	10.7, 7.6, 7.1, 1.4	130.8	14, 15, 17, 18a, 18b
17	5.55	1H	dtt	15, 16, 18a, 18b	10.7, 7.1, 1.6	125.9	15, 16, 18a, 18b, 19
18a	2.73	1H	dddd	16, 17, 18b, 19	15.1, 7.2, 5.4, 1.5	33.6	16, 17, 19, 20
18b	2.72	1H	dddd	16, 17, 18a, 19	15.2, 8.3, 7.0, 1.5		
19	4.14	1H	ddd	18a, 18b, 20	8.3, 5.5, 4.6	55.1	17, 18a, 18b, 21a, 21b
20	4.90	1H	ddd	19, 21a, 21b	7.4, 5.4, 4.6	84.6	18a, 18b, 19, 21a, 21b, 22
21a	1.96	1H	ddq	20, 22	14.3, 5.4, 7.5	26.5	19, 20, 22
21b	1.92	1H	dq	20, 22	14.3, 7.3		
22	1.03	3H	t	21a, 21b	7.4	9.7	20, 21a, 21b

Ketone 425. A solution of the Dess-Martin reagent (265 mg, 0.624 mmol) in CH_2Cl_2 (0.5 mL) was added to a solution of *anti*-**393** (140 mg, 0.416 mmol) in dry CH_2Cl_2 (8.7 mL) to 0 °C. The mixture was stirred for 10 min at 0 °C and for 2 h at ambient temperature before the reaction was quenched with a mixture of saturated aqueous $NaHCO_3$ and saturated aqueous Na_2SO_3 (2 mL, 1:1). The resulting slurry was vigorously stirred for 5 min before the aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed under reduced pressure. Ketone **425** was immediately used in the next step without further purification (138 mg, 99%).

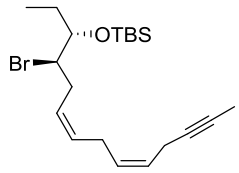


Alcohol *syn*-393. (*S*)-(−)- 1-Methyl-3,3-diphenyl-tetrahydropyrrolo(1,2-*c*)(1,3,2)oxazaborole[142a] (**403**) ((*S*)-CBS-reagent, 343 mg, 1.24 mmol) in toluene (1.8 mL) was treated with a solution of ketone **425** (138 mg, 0.413 mmol) in toluene (8.0 mL). After cooling to −78 °C, a solution of catecholborane (149 mg, 1.24 mmol) in toluene (3.0 mL) was added via syringe pump over the course of 5 h. Once the addition was complete, the mixture was stirred for 12 h at −78 °C. The reaction was quenched with MeOH (2.0 mL) at this temperature and the resulting slurry stirred at ambient temperature for 1 h. The mixture was washed twice with NaOH (3.0 mL, 0.2 M) and the combined aqueous phases were extracted with EtOAc (3 x 30 mL). The combined organic phases were washed with brine (20 mL), dried over Na_2SO_4 and concentrated. The crude material was purified by flash chromatography (SiO_2, pentane/EtOAc, 50/1 → 30/1) to yield alcohol *syn*-**393** as a colorless oil (112 mg, 81%). For characterization purposes an aliquot was purified by HPLC (UFLC SHIMADZU; Kromasil 100-5C18, 150 x 30 mm; 35 °C, 70 bar, 35 mL/min, 210 nm, MeOH/H_2O = 85/15). $[\alpha]_D^{20}$ = −2.4 (*c* = 0.40, $CHCl_3$). ^{1}H NMR (600 MHz, C_6D_6): δ = 5.61 (dtt, 1H, *J* = 10.8, 7.3, 1.6 Hz), 5.57 (dtt, 1H, *J* = 10.5, 7.0, 1.8 Hz), 5.50 (dtt, 1H, *J* = 10.8, 7.3, 1.6 Hz), 5.43 (dtt, 1H, *J* = 10.5, 7.2, 1.7 Hz), 3.54 (dt, 1H, *J* = 8.5, 4.1 Hz), 3.45 (dt, 1H, *J* = 5.8, 4.1 Hz), 2.92 (ddqt, 2H, *J* = 6.2, 2.6, 1.8, 0.8 Hz), 2.89 – 2.77 (m, 2H), 2.31 – 2.27 (m, 1H), 2.25 – 2.20 (m, 1H), 1.97 (br s, 1H), 1.67 (dq, 1H, *J* = 7.7, 6.0 Hz), 1.55 (t, 3H, *J* = 2.6 Hz), 1.44 – 1.37 (m, 1H), 0.94 (s, 9H), 0.86 (t, 3H, *J* = 7.5 Hz), 0.04 (s, 3H), 0.03 ppm (s, 3H); ^{13}C NMR (150 MHz, C_6D_6): δ = 129.6, 129.2, 127.2, 126.1, 77.6, 76.5, 75.7, 72.8, 32.0, 26.6, 26.1, 26.1 (3C), 18.4, 17.7, 9.8, 3.4, −4.1, −4.4 ppm; IR (film): $\tilde{\nu}$ = 2955, 2929, 2884, 2857, 1463, 1389, 1361, 1254, 1056, 1005, 939, 834, 774,

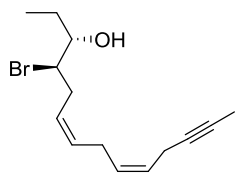


676 cm^{-1}; MS (EI) *m/z* (%): 336 (1), 279 (8), 203 (25), 187 (44), 174 (14), 173 (91), 145 (32), 134 (11), 133 (100), 131 (23), 119 (13), 117 (28), 115 (36), 93 (12), 91 (13), 75 (70), 73 (60); HRMS (ESI): *m/z*: calcd. for $C_{20}H_{36}OSiNa$ [*M*+Na^+]: 359.2377, found 359.2377.

Bromide *anti*-399. PPh_3 (341 mg, 1.30 mmol) was added to a solution of alcohol *syn*-**393** (97 mg, 0.288 mmol) in toluene (11 mL) at 0 °C and the resulting mixture was stirred for 10 min before CBr_4 (431 mg, 1.30 mmol) was introduced. After stirring for 10 min, the flask was placed into a pre-heated oilbath at 65 °C and the mixture stirred at this temperature for 1 h. After cooling to rt, the pale yellow suspension was filtered through a pad of Celite, which was carefully rinsed with pentane/EtOAc (15 mL, 20:1). The combined filtrates were concentrated and the residue was purified by flash chromatography (SiO_2, pentane/EtOAc, 200/1) to yield the bromide *anti*-**399** as a pale yellow oil (64 mg, 55%). The material was very unstable and must be stored under argon in a freezer. For characterization purposes an aliquot was purified by HPLC (UFLC SHIMADZU; Kromasil 100-5C18, 150 x 20 mm; 35 °C, 53 bar, 20 mL/min, 210 nm, MeOH/H_2O = 95/5). $[\alpha]_D^{20}$ = +9.0 (*c* = 0.30, $CHCl_3$). ^{1}H NMR (600 MHz, C_6D_6): δ = 5.56 (dtt, 1H, *J* = 10.5, 7.1, 1.7 Hz), 5.51 (dtt, 1H, *J* = 10.7, 6.7, 1.6 Hz), 5.46 (dtt, 1H, *J* = 10.7, 7.0, 1.3 Hz), 5.39 (dtt, 1H, *J* = 10.5, 7.3, 1.7 Hz), 3.95 (ddd, 1H, *J* = 9.5, 4.7, 4.3 Hz), 3.72 (dt, 1H, *J* = 5.2, 4.7 Hz), 2.90 (ddqt, 2H, *J* = 7.0, 1.8, 2.6, 0.8 Hz), 2.76 – 2.73 (m, 2H), 2.68 (dddd, 1H, *J* = 15.3, 6.8, 4.2, 1.3 Hz), 2.56 (dddd, 1H, *J* = 15.5, 9.5, 6.8, 1.2 Hz), 1.80 (ddq, 1H, *J* = 14.0, 6.2, 7.4 Hz), 1.54 (t, 3H, *J* = 2.6 Hz), 1.43 (ddq, 1H, *J* = 14.0, 4.6, 7.4 Hz), 0.99 (s, 9H), 0.82 (t, 3H, *J* = 7.5 Hz), 0.10 (s, 3H), 0.03 ppm (s, 3H); ^{13}C NMR (150 MHz, C_6D_6): δ = 130.0, 128.9, 127.4, 126.3, 77.5, 76.7, 75.8, 59.5, 32.3, 27.5, 26.1 (3C), 26.0, 18.4, 17.7, 9.1, 3.4, −4.2, −4.3 ppm; IR (film): $\tilde{\nu}$ = 2959, 2928, 2856, 1462, 1258, 1091, 1014, 836, 794, 777, 674 cm^{-1}; MS (EI) *m/z* (%): 319 (11), 197 (70), 195 (71), 187 (24), 173 (39), 159 (38), 145 (41), 139 (38), 137 (37), 135 (2), 133 (56), 131 (59), 119 (21), 117 (38), 115 (43), 107 (12), 93 (30), 91 (71), 79 (36), 75 (68), 73 (100), 67 (26), 55 (28); HRMS (ESI): *m/z*: calcd. for $C_{20}H_{35}OBrSiNa$ [$^+$+Na^+]: 421.1535, found 421.1533.

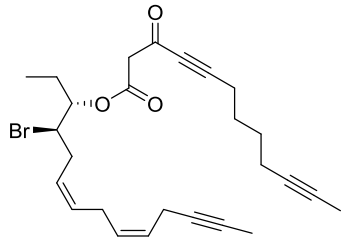


Alcohol *anti*-372. HF·pyridine (0.20 mL, 2.22 mmol, 70% HF) was added dropwise to a solution of bromide *anti*-**399** (47 mg, 0.12 mmol) in THF (1.0 mL) at 0 °C. The reaction mixture was then allowed to warm to ambient temperature and was stirred for 4 h before it



was cooled to 0 °C and diluted with EtOAc (10 mL) and H_2O (5 mL). Saturated aqueous $NaHCO_3$ was added until the evolution of gas ceased. The mixture was extracted with EtOAc (3 x 20 mL), the organic phases were washed with brine (20 mL), dried over Na_2SO_4 and concentrated. The crude material was purified by flash chromatography (SiO_2, pentane/EtOAc, 15/1) to yield alcohol *anti*-**372** as a colorless oil (18.5 mg, 55%). $[\alpha]_D^{20}$ = +19.2 (*c* = 0.10, $CHCl_3$). ^{1}H NMR (600 MHz, C_6D_6): δ = 5.55 (dtt, 1H, *J* = 10.5, 7.0, 1.7 Hz), 5.45 – 5.39 (m, 2H), 5.35 (dtt, 1H, *J* = 10.5, 7.3, 1.8 Hz), 3.79 (dt, 1H, *J* = 9.4, 4.3 Hz), 3.35 (dt, 1H, *J* = 8.7, 4.3 Hz), 2.88 – 2.85 (m, 2H), 2.69 – 2.66 (m, 2H), 2.56 – 2.51 (m, 1H), 2.46 – 2.42 (m, 1H), 1.54 (t, 3H, *J* = 2.7 Hz), 1.41 – 1.40 (m, 1H), 1.38 – 1.35 (m, 2H), 0.82 ppm (t, 3H, *J* = 7.5 Hz); ^{13}C NMR (150 MHz, C_6D_6): δ = 130.1, 128.9, 127.1, 126.2, 77.5, 75.9, 75.8, 62.5, 31.6, 27.0, 26.0, 17.7, 10.4, 3.4 ppm; IR (film): $\tilde{\nu}$ = 2963, 2923, 2359, 1738, 1670, 1456, 1259, 1013, 705, 681, 561, 432 cm^{-1}; MS (EI) *m/z* (%): 187 (11), 147 (17), 145 (23), 133 (24), 132 (10), 131 (42), 121 (18), 119 (34), 118 (15), 117 (40), 115 (11), 107 (14), 106 (12), 105 (86), 93 (29), 91 (100), 85 (40), 81 (16), 79 (55), 77 (40), 59 (32), 57 (85), 41 (39); HRMS (ESI): *m/z*: calcd. for $C_{14}H_{21}OBrNa$ [*M*+Na$^+$]: 307.0669, found 307.0668.

β-Ketoester *anti*-374. A solution of acid **370** (16 mg, 77 μmol) in CH_2Cl_2 (0.6 mL) was added



to a solution of alcohol *anti*-**372** (10 mg, 35 μmol) in CH_2Cl_2 (1.0 mL) at 0 °C. DCC (16 mg, 77 μmol) was then introduced at this temperature, followed after 5 min by DMAP (1.3 mg, 30 mol%). The mixture was stirred for 15 min at 0 °C before it was diluted with MTBE (3 mL). The resulting suspension was filtered through a pad of Celite and the filtrate was concentrated. The residue was dissolved in a mixture of hexanes/MTBE (1 mL, 2:1) and the suspension was filtered through a pad of Celite. Evaporation of the filtrate followed by purification of the crude product by flash chromatography (SiO_2, hexanes/EtOAc, 15/1 → 13/1) gave the highly unstable title compound as a yellow oil (13 mg, 78%, mixture of keto/enol tautomers) which was used directly in the next step without characterization.

4-Pyrone *anti*-402. [SPhosAu]NTf_2 (**C12**) (0.4 mg, 3 mol%) was added to a solution of the β-ketoester *anti*-**374** (10 mg, 21 μmol) in MeCN/AcOH (1.5 mL, 5:1). The reaction mixture was stirred for 38 h at ambient temperature before all volatile materials were evaporated. Purification of the crude product by flash chromatography (SiO_2, hexanes/ EtOAc, 1/1 → EtOAc 100%) gave *anti*-**402** as a colorless oil (8.4 mg, 84%). For characterization purposes an aliquot was purified by HPLC (UFLC SHIMADZU; Kromasil 100-5C18, 150 x 20 mm; 35 °C, 55 bar, 20 mL/min, 228 nm, MeCN/H_2O = 60/40). $[\alpha]_D^{20}$ = +13.6 (*c* = 0.09, $CHCl_3$). ^{1}H NMR (600 MHz, C_6D_6): δ = 5.92 (d, 1H, *J* = 1.8 Hz), 5.59 (d, 1H, *J* = 1.8 Hz), 5.55 (dtt, 1H, *J* = 10.5, 6.9, 1.7 Hz), 5.42 (dtt, 1H, *J* = 10.7, 7.3, 1.4 Hz), 5.31 (dtt, 1H, *J* = 10.5, 7.3, 1.7 Hz), 5.27 (dtt, 1H, *J* = 10.7, 7.2, 1.8 Hz), 4.09 (ddd, 1H, *J* = 9.1, 5.2, 3.6 Hz), 3.85 (dt, 1H, *J* = 8.5, 5.2 Hz), 2.86 (ddqt, 1H, *J* = 7.0, 1.6, 2.5, 0.7 Hz), 2.64 – 2.59 (m, 2H), 2.48 – 2.37 (m, 2H), 1.92 (tq, 2H, *J* = 7.2, 2.6 Hz), 1.84 – 1.81 (m, 2H), 1.58 – 1.56 (m, 2H), 1.57 (t, 3H, *J* = 2.5 Hz), 1.56 (t, 3H, *J* = 2.7 Hz), 1.35 – 1.31 (m, 2H), 1.20 – 1.16 (m, 2H), 0.68 ppm (t, 3H, *J* = 7.4 Hz); ^{13}C NMR (150 MHz, C_6D_6): δ = 180.4, 166.4, 164.4, 131.2, 128.5, 126.4, 125.7, 112.9, 92.1, 82.7, 78.7, 77.3, 76.2, 76.0, 53.9, 32.3, 32.2, 28.4, 26.0, 25.8, 24.5, 18.7, 17.7, 9.1, 3.4, 3.4 ppm; IR (film): $\tilde{\nu}$ = 3359, 2920, 2851, 1661, 1632, 1578, 1411, 1247, 1086, 859, 800, 700 cm^{-1}; MS (ESIpos) *m/z* (%): 495 (*M*+Na^+, 100); HRMS (ESI): *m/z*: calcd. for $C_{26}H_{33}O_3BrNa$ [*M*+Na^+]: 495.1506, found 495.1505.

Cycloalkyne *anti*-373. Activated MS 5 Å (powder, 70 mg) was added to a solution of *anti*-**402** (6.0 mg, 13 μmol) in toluene (7.0 mL) and the resulting suspension was stirred for 0.5 h before a solution of the molybdenum alkylidyne complex **C4** (0.7 mg, 5 mol%, in 50 μL toluene) was introduced. After stirring for 2 h, the mixture was filtered through a pad of Celite, which was rinsed with EtOAc and the combined filtrates were concentrated. The crude product was purified by flash chromatography (SiO_2, EtOAc 100% → EtOAc/acetone, 1/1) to remove traces of the silanol ligands. The material was further purified by HPLC (UFLC SHIMADZU; Kromasil 100-5C18, 150 x 20 mm; 35 °C, 55 bar, 20 mL/min, 240 nm, MeCN/H_2O = 60/40) to yield *anti*-**373** as a colorless oil (4.4 mg, 80%). $[\alpha]_D^{20}$ = −7.5 (*c* = , $CHCl_3$). ^{1}H NMR (600 MHz, C_6D_6): δ = 5.88 (d, 1H, *J* = 1.8 Hz), 5.55 (d, 1H, *J* = 1.8 Hz), 5.48 (dtt, 1H, *J* = 10.3, 7.3, 1.7 Hz), 5.46 (dtt, 1H, *J* = 10.6, 7.1, 1.5 Hz), 5.37 (dtt,

1H, *J* = 10.6, 7.6, 1.7 Hz), 5.35 (dtt, 1H, *J* = 10.3, 7.1, 1.4 Hz), 4.14 (td, 1H, *J* = 6.7, 4.0 Hz), 3.70 (ddd, 1H, *J* = 10.8, 5.0, 4.0 Hz), 2.79 – 2.76 (m, 4H), 2.58 – 2.53 (m, 1H), 2.50 – 2.45 (m, 1H), 1.93 (tt, 2H, *J* = 6.5, 2.3 Hz), 1.83 (ddd, 1H, *J* = 14.7, 9.2, 5.7 Hz), 1.74 – 1.69 (m, 1H), 1.61 – 1.54 (m, 1H), 1.49 – 1.43 (m, 2H), 1.39 – 1.34 (m, 1H), 1.07 – 1.01 (m, 2H), 0.63 ppm (t, 3H, *J* = 7.8 Hz); ^{13}C NMR (150 MHz, C_6D_6): δ = 180.3, 166.4, 164.2, 131.0, 129.9, 125.8, 125.3, 113.2, 92.2, 83.0, 79.3, 79.2, 53.6, 32.6, 31.9, 27.7, 26.2, 26.0, 24.6, 18.6, 17.3, 8.5 ppm; IR (film): $\tilde{\nu}$ = 2922, 2852, 1663, 1630, 1584, 1399, 1241, 1158, 928 cm^{-1}; MS (ESIpos) *m/z* (%): 443 (*M*+Na$^+$, 100); HRMS (ESI): *m/z*: calcd. for $C_{22}H_{27}O_3BrNa$ [*M*+Na$^+$]: 441.1037, found 441.1036.

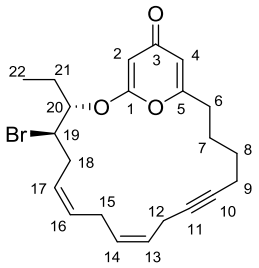
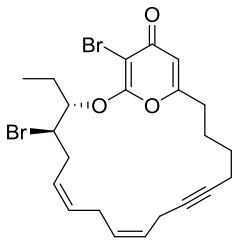


Table 12: ^{1}H and ^{13}C NMR data of macrocycle *anti*-**373**; numbering scheme as shown in the insert.

^{1}H NMR (600 MHz, C_6D_6)						^{13}C NMR (150 MHz, C_6D_6)	
No.	δ (ppm)	Integral	Splitting	COSY	*J* (Hz)	δ (ppm)	HMBC
1	-	-	-	-	-	166.4	2, 20
2	5.55	1H	d	4	1.8	92.2	4
3	-	-	-	-	-	180.3	2, 4
4	5.88	1H	d	2	1.8	113.2	2, 6a, 6b
5	-	-	-	-	-	164.2	4, 6a, 6b
6a	1.83	1H	ddd	6b, 7	14.7, 9.2, 5.7	31.9	4, 7, 8
6b	1.74 – 1.69	1H	m	6a, 7	-		
7a	1.49 – 1.43	1H	m	6a, 6b, 8	-	26.2	6a, 6b, 8, 9
7b	1.39 – 1-43	1H	m				
8	1.07 – 1.01	2H	m	7, 9	-	27.7	6a, 6b, 7, 9
9	1.93	2H	tt	8, 12a, 12b	6.5, 2.3	18.6	7, 8
10	-	-	-	-	-	79.3	8, 9
11	-	-	-	-	-	79.2	12a, 12b, 13, 14
12	2.79 – 2.76	2H	m	9, 12b, 13	-	17.3	9, 13, 14
13	5.48	1H	dtt	12a, 12b, 14	10.3, 7.3, 1.7	125.3	9, 12a, 12b, 14, 15a, 15b
14	5.35	1H	dtt	13, 15a, 15b	10.3, 7.1, 1.4	129.9	12a, 12b, 13, 15a, 15b
15	2.79 – 2.76	2H	m	14, 15b, 16	-	26.0	13, 14, 16, 17
16	5.37	1H	dtt	15a, 15b, 17	10.6, 7.6, 1.7	131.0	14, 15a, 15b, 17, 18a, 18b
17	5.46	1H	dtt	15a, 15b, 16, 18a, 18b	10.6, 7.1, 1.5	125.8	15a, 15b, 16, 18a, 18b, 19
18a	2.58 – 2.53	1H	m	17, 19	-	32.6	16, 17, 19, 20
18b	2.50 – 2.45	1H	m	17, 19	-		
19	3.70	1H	ddd	18a, 18b, 20	10.8, 5.0, 4.0	53.6	17, 18a, 18b, 20, 21
20	4.14	1H	td	19, 21	6.7, 4.0	83.0	18a, 18b, 19, 21, 22
21a	1.61 – 1.54	1H	m	20, 22	-	24.6	19, 20, 22
21b	1.49 – 1.43	1H	m	20, 22	-		
22	0.63	3H	t	21	7.8	8.5	20, 21

***anti*-11.** NBS (1.3 mg, 7.3 μmol) was added in one portion to a solution of cycloalkyne *anti*-



373 (3.4 mg, 8.1 μmol) in THF at 0 °C. The solution was allowed to warm to ambient temperature and the reaction was closely monitored by TLC (pentane/EtOAc, 1/1). After complete consumption of the starting material, the reaction mixture was diluted with pentane (1 mL) and filtered through a pad of Celite which was carefully rinsed with pentane/EtOAc (2 mL, 1:1). The combined filtrates were concentrated and the residue was purified by flash chromatography (SiO_2, pentane/EtOAc, 1/1 → EtOAc 100%) to give *anti*-**11** as a crystalline colorless solid (1.6 mg, 40%). $[\alpha]_D^{20}$ = +18.0 (*c* = 0.10, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 6.13 (s, 1H), 5.68 (dtt, 1H, *J* = 10.7, 7.4, 1.6 Hz), 5.54 – 5.48 (m, 2H), 5.45 (dddt, 1H, *J* = 10.7, 8.0, 6.2, 1.7 Hz), 4.86 (td, 1H, *J* = 7.1, 3.6 Hz), 4.15 (ddd, 1H, *J* = 9.1, 7.1, 4.8 Hz), 2.95 (ddt, 1H, *J* = 17.1, 6.5, 2.3 Hz), 2.91 – 2.87 (m, 2H), 2.83 (ddt, 1H, *J* = 17.1, 5.9, 2.5 Hz), 2.77 (ddddt, 1H, *J* = 15.2, 6.1, 4.9, 1.8, 0.9 Hz), 2.66 (dddd, 1H, *J* = 15.2, 9.1, 8.0, 1.4 Hz), 2.59 (ddd, 1H, *J* = 14.6, 9.3, 6.1 Hz), 2.51 (ddd, 1H, *J* = 14.7, 9.3, 6.3 Hz), 2.27 – 2.24 (m, 2H), 2.06 (dq, 1H, *J* = 14.9, 7.4 Hz), 2.05 (ddq, 1H, *J* = 14.8, 3.7, 7.4 Hz), 1.86 – 1.75 (m, 2H), 1.58 – 1.55 (m, 2H), 1.07 ppm (t, 3H, *J* = 7.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 175.6, 163.3, 161.7, 131.1, 129.9, 125.6, 125.0, 111.7, 92.3, 84.6, 79.2, 79.1, 53.8, 33.4, 33.0, 28.0, 26.6, 26.1, 25.6, 18.6, 17.1, 9.3 ppm; IR (film): $\tilde{\nu}$ = 2921, 2851, 1659, 1633, 1575, 1468, 1376, 1261, 1090, 800 cm^{-1}; MS (pos. ESI) *m/z* (%): 521 (*M*+Na^+, 100); HRMS (ESI): *m/z*: calcd. for $C_{22}H_{26}O_3Br_2Na$ [*M*+Na^+]: 519.0140, found 519.0141.

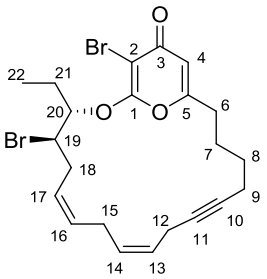


Table 13: ^{1}H and ^{13}C NMR data of synthetic 4-pyrone *anti*-**11**; numbering scheme as shown in the insert.

^{1}H NMR (600 MHz, $CDCl_3$)						^{13}C NMR (150 MHz, $CDCl_3$)	
No.	δ (ppm)	Integral	Splitting	COSY	*J* (Hz)	δ (ppm)	HMBC
1	-	-	-	-	-	161.7	20
2	-	-	-	-	-	92.3	4
3	-	-	-	-	-	175.6	4
4	6.13	1H	s	-	-	111.7	6a, 6b
5	-	-	-	-	-	163.3	4, 6a, 6b, 7
6a	2.59	1H	ddd	6b, 7	14.6, 9.3, 6.1	33.0	4, 7, 8
6b	2.51	1H	ddd	6a, 7	14.7, 9.3, 6.3		
7	1.86 – 1.75	2H	m	6a, 6b, 8	-	26.6	6a, 6b, 8, 9
8	1.58 – 1.55	2H	m	7, 9	-	28.0	6a, 6b, 7, 9
9	2.27 – 2.24	2H	m	8, 12	-	18.6	7, 8
10	-	-	-	-	-	79.2	8, 9, 12
11	-	-	-	-	-	79.1	9, 12
12a	2.95	1H	ddt	9, 12b, 13	17.1, 6.5, 2.3	17.1	13, 14
12b	2.83	1H	ddt	9, 12a, 13	17.1, 5.9, 2.5		
13	5.54 – 5.48	1H	m	12a, 12b	-	125.0	12a, 12b, 15
14	5.54 – 5.48	1H	m	15	-	129.9	13, 15
15	2.91 – 2.87	2H	m	14, 16	-	26.1	13, 14, 17
16	5.68	1H	dtt	15, 17	10.7, 7.4, 1.6	131.1	13, 15, 18a, 18b
17	5.45	1H	dddt	16, 18a, 18b	10.7, 8.0, 6.2, 1.7	125.6	15, 18a, 18b, 19
18a	2.77	1H	ddddt	17, 18b, 19	15.2, 6.1, 4.9, 1.8, 0.9	33.4	16, 17, 20
18b	2.66	1H	dddd	17, 18a, 19	15.2, 9.1, 8.0, 1.4		
19	4.15	1H	ddd	18a, 18b, 20	9.1, 7.1, 4.8	55.8	18a, 18b, 21a, 21b
20	4.86	1H	td	19, 21a, 21b	7.1, 3.6	84.6	18a, 18b, 19, 21a, 21b, 22
21a	2.06	1H	dq	20, 22	14.9, 7.4	25.6	19, 20, 22
21b	2.05	1H	ddq	20, 22	14.8, 3.7, 7.4		
22	1.05	3H	t	21a, 21b	7.4	9.3	20, 21a, 21b

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8. Appendix

8.1. List of Abbreviations

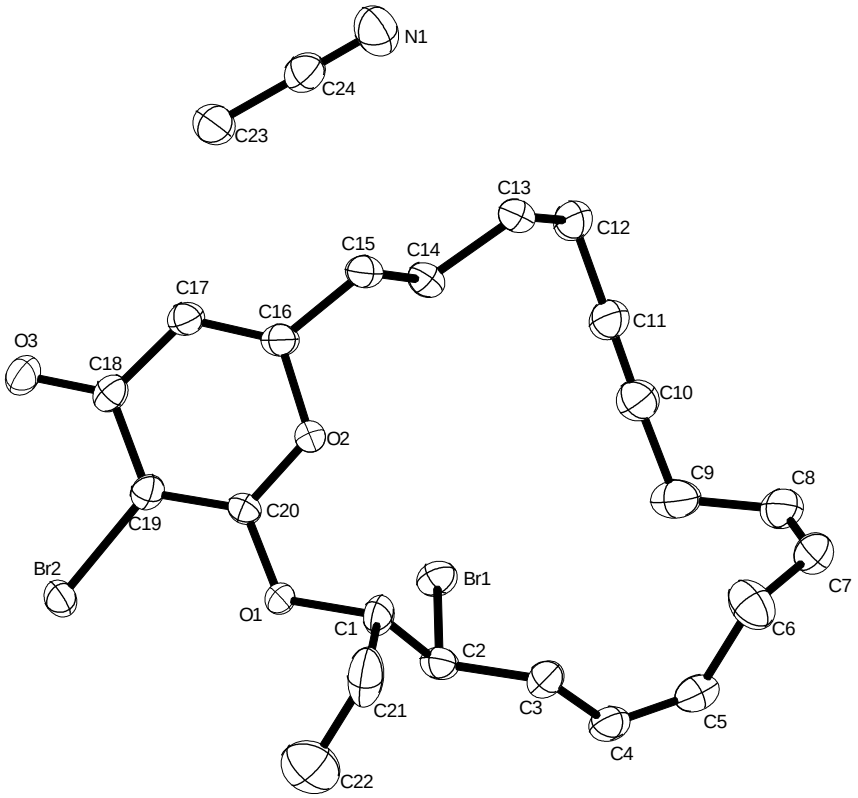
Ac	Acetyl
acac	Acetyl acetonate
Ar	Aromatic group
BBN	Borabicyclo[3.3.1.]nonane
Bn	Benzyl
br	Broad
Bu	Butyl
Bz	Benzoyl
calc.	Calculated
cat.	Catalytic
CBS	Corey-Bakshi-Shibata
CI	Chemical ionization
CoA	Coenzyme A
COSY	Correlation spectroscopy
Cp	Cyclopentadienyl
CP	Core particle
m-CPBA	*meta*-Chloroperoxybenzoic acid
CSA	Camphersulfonic acid
Cy	Cyclohexyl
Δ	Reflux temperature
d	Doublet
dba	Dibenzylideneacetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	*N,N´*-Dicyclohexylcarbodiimide
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEPT	Distorsionless enhancement by polarization transfer
DIBAl-H	Diisobutylaluminum hydride
DIPT	Diisopropyl tartrate
DMAP	4-(Dimethylamino)-pyridine
DMF	*N,N*-Dimethylformamide

DMP	Dess-Martin periodinane
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
DMSO	Dimethyl sulfoxide
dppf	1,1´-Bis(diphenylphosphino)ferrocene
dr	*Diastereomeric ratio*
EDCI	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
ee	*Enantiomeric excess*
EE	Ethoxyethyl ether
EI	Electron ionization
ent	Enantiomer
ESI	Electronspray ionization
Et	Ethyl
equiv	Equivalents
GC	Gas chromatography
HFIP	1,1,1,3,3,3-Hexafluoro-2-propanol
HMBC	Heteronuclear multiple quantum coherence
HMDS	Bis(trimethylsilyl)amine
HMTA	Hexamethylenetetramine
HPLC	High pressure liquid chromatography
HRMS	High resolution mass spectroscopy
HSQC	Heteronuclear single quantum coherence
HWE	Horner-Wadsworth-Emmons
i	Iso
IBX	2-Iodoxybenzoic acid
IC_{50}	Half maximal inhibitory concentration
Imid.	Imidazole
Ipc	Isopinocampheyl
IR	Infrared spectroscopy
LDA	Lithium diisopropylamide
m	Multiplet
Mc	Chloromethyl sulfonyl
Me	Methyl

MOM	Methoxymethyl
Mp.	Melting point
Ms	Methylsulfonyl
MS	Mass spetrometry
MS	Molecular sieves
MTBE	Methyl *tert*-butyl ether
MTPA	α-Methoxy-α-trifluoromethylphenylacetic acid
n	Normal
NACM	Nitrile alkyne cross-metathesis
NBS	*N*-Bromosuccinimide
NIS	*N*-Iodosuccinimide
NMI	1-Methylimidazole
NMO	*N*-Methylmorpholine-*N*-oxide
NMR	Nuclear magnetic resonance
NOE	Nuclear Overhauser effect
p	Para
PCC	Pyridinium chlorochromate
Ph	Phenyl
Piv	Pivaloyl
PKS	Polyketide Synthase
PLA_2	Phospholipase A_2
ppm	Parts per million
PPTS	Pyridinium-*para*-toluenesulfonate
Pr	Propyl
q	Quartet
quant.	Quantitative
R	Organic substituent
rac	Racemic
RCAM	Ring-closing alkyne metathesis
RCM	Ring-closing olefin metathesis
rt	Ambient temperature
s	Singlet

SAM	*S*-Adenosyl methionine
SEM	[2-(Trimethylsilyl)ethoxy]methyl acetal
sext	Sextet
Sp.	Species
S_N1	First order nucleophilic substitution
S_N2	Second order nucleophilic substitution
t	Tertiary
t	Triplet
TBAF	Tetra-*n*-butylammoniumfluoride
TBAI	Tetra-*n*-butylammoniumiodide
TBHP	*tert*-Butylhydroperoxide
TBS	*tert*-Butyldimethylsilyl
TEMPO	(2,2,6,6)-Tetramethylpiperidinyloxyl
TES	Triethylsilyl
tert	Tertiary
Tf	Triflate
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMEDA	Tetramethylethylenediamine
TMS	Trimethylsilyl
Ts	Tosyl

8.2. Crystallographic Data of 4-Pyrone *syn*-11



Identification code	9017sadabs	
Empirical formula	$C_{24}\ H_{29}\ Br_2\ N\ O_3$	
Color	colourless	
Formula weight	539.30 $g \cdot mol^{-1}$	
Temperature	100 K	
Wavelength	1.54178 Å	
Crystal system	ORTHORHOMBIC	
Space group	p 21 21 21, (no. 19)	
Unit cell dimensions	a = 4.7865(4) Å	α= 90°
	b = 20.3783(16) Å	β= 90°
	c = 24.3411(19) Å	γ = 90°
Volume	2374.2(3) $Å^3$	
Z	4	
Density (calculated)	1.509 $Mg \cdot m^{-3}$	
Absorption coefficient	4.525 mm^{-1}	
F(000)	1096 e	
Crystal size	0.25 x 0.07 x 0.05 mm^3	
θ range for data collection	2.828 to 67.738°	
Index ranges	$-5 \leq h \leq 5$, $-24 \leq k \leq 24$, $-28 \leq l \leq 29$	

Reflections collected	63947	
Independent reflections	4285 [R_{int} = 0.0665]	
Reflections with I>2σ(I)	4199	
Completeness to θ = 67.679°	99.8 %	
Absorption correction	Gaussian	
Max. and min. transmission	0.84498 and 0.24515	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4285 / 0 / 273	
Goodness-of-fit on F^2	1.064	
Final R indices [I>2σ(I)]	R_1 = 0.0331	wR^2 = 0.0877
R indices (all data)	R_1 = 0.0339	wR^2 = 0.0885
Absolute structure parameter	-0.009(7)	
Extinction coefficient	0	
Largest diff. peak and hole	1.044 and -0.872 e·$Å^{-3}$	

8.3. Comparison of NMR Data of the Natural 4-Pyrone and Synthetic *syn*- and *anti*-11

Table 14: Comparison of ^{1}H and ^{13}C NMR data of natural **11** and synthetic 4-pyrone *syn*-**11**; numbering scheme as shown in the insert above.

# (lit.)	# (reassigned)[1]	natural 11 ($CDCl_3$)[1,2]		synthetic *syn*-11 ($CDCl_3$)[3]		Δ (δ(*syn*-11)-δ(lit.))		*syn*-11 (C_6D_6)[4]	Δ (δ(*syn*-11)-δ(lit.))
		^{1}H	^{13}C	^{1}H	^{13}C	Δ ^{1}H	Δ ^{13}C	^{1}H	Δ ^{1}H
5	1	–	161,6	–	162,0	–	0,4	–	–
2	2	–	91,8	–	92,2	–	0,4	–	–
3	3	–	175,4	–	175,8	–	0,4	–	–
4	4	6,10	111,2	6,13	111,8	0,03	0,6	5,80	-0,30
1	5	–	162,9	–	163,1	–	0,2	–	–
18	6	2,58	32,3	2,56 2,53	32,7	-0,02 -0,05	0,4	1,68	-0,90
7	7	1,88	26,1	1,83 1,79	26,4	-0,05 -0,09	0,3	1,29	-0,59
8	8	1,60	27,5	1,55	27,8	-0,05	0,3	1,00	-0,60
12	9	2,22	18,2	2,25	18,6	0,03	0,4	1,91	-0,31
10	10	–	78,8	–	79,2	–	0,4	–	–
11	11	–	78,5	–	79,0	–	0,5	–	–
21	12	2,88	17,0	2,90	17,4	0,02	0,4	2,71	-0,17
14	13	5,40	124,6	5,47	125,0	0,07	0,4	5,31	-0,09
17	14	5,40	128,9	5,47	129,4	0,07	0,5	5,39	-0,01
15	15	2,88	25,7	2,85	26,1	-0,03	0,4	2,61	-0,27
13	16	5,40	130,3	5,67	130,8	0,27	0,5	5,47	0,07
16	17	5,40	125,5	5,55	125,9	0,15	0,4	5,47	0,07
6	18	2,72	33,2	2,73 2,72	33,6	0,01 0,00	0,4	2,48	-0,24
19	19	4,14	54,9	4,14	55,1	0,00	0,2	3,81	-0,33
20	20	4,90	84,2	4,80	84,6	-0,10	0,4	4,47	-0,43
12	21	1,92	26,1	1,96 1,92	26,5	0,04 0,00	0,4	1,53	-0,39
22	22	1,00	9,3	1,03	9,7	0,03	0,4	0,69	-0,31

[1] 1H and ^{13}C NMR shifts were reassigned according to 2D experiments.
[2] Source of data: R. Kazlauskas, P. T. Murphy, R. J. Wells, A. J. Blackman, *Aust. J. Chem.* **1982**, *35*, 113.
[3] Experiments were run on a 600 MHz/150 MHz NMR machine accordingly, 298 K.
[4] For comparison a ^{1}H NMR spectrum of *syn*-**11** was measured in C_6D_6.

Table 15: Comparison of ^{1}H and ^{13}C NMR data of natural **11** and synthetic 4-pyrone *anti*-**11**; numbering scheme as shown in the insert above.

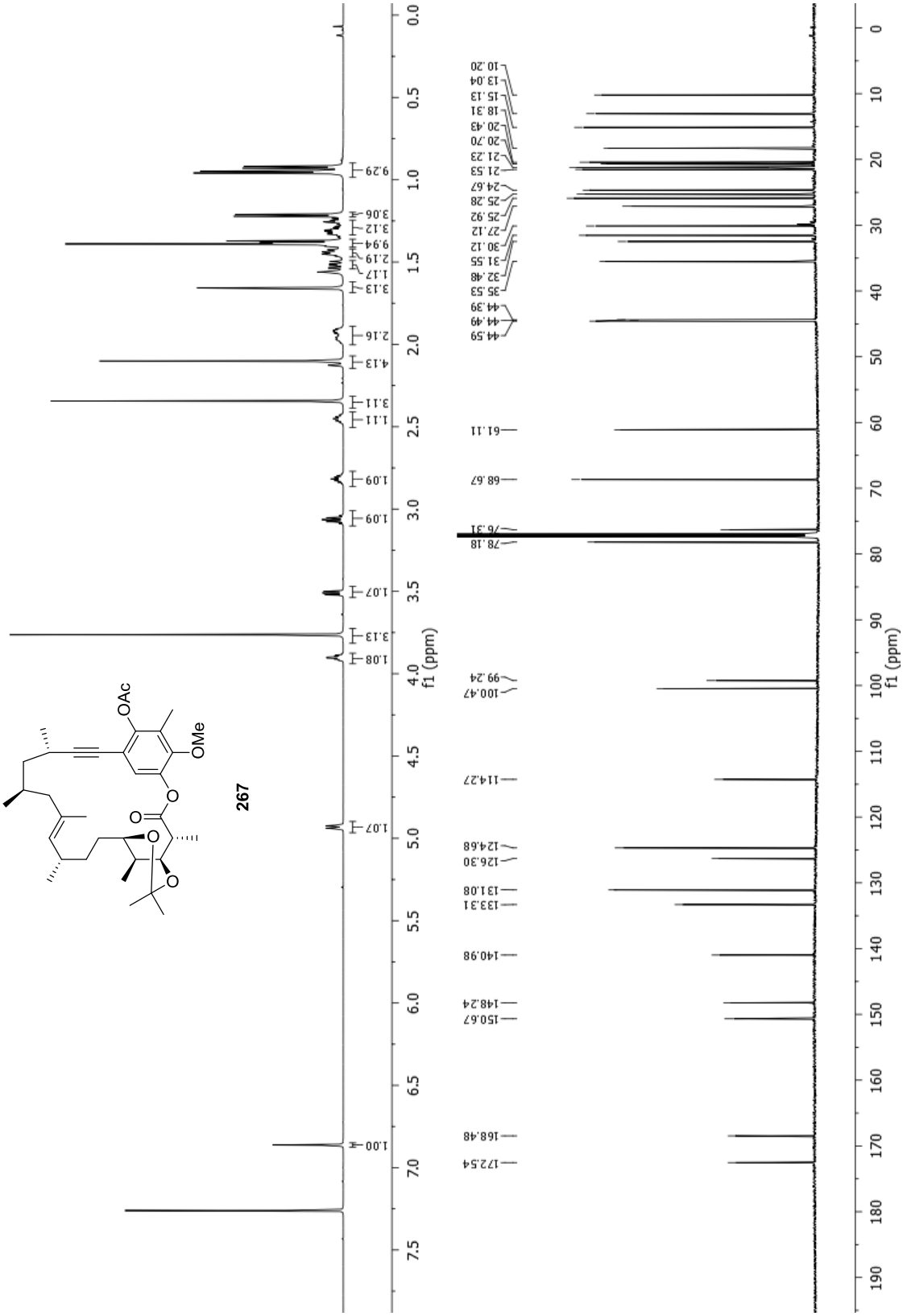
# (lit.)	# (reassigned)*	natural 11 ($CDCl_3$)*		synthetic *anti*- 11 ($CDCl_3$)		Δ (δ(*anti*-11)-δ(lit.))	
		^{1}H	^{13}C	^{1}H	^{13}C	Δ ^{1}H	Δ ^{13}C
5	1	–	161,6	–	161,7	–	0,1
2	2	–	91,8	–	92,3	–	0,5
3	3	–	175,4	–	175,6	–	0,2
4	4	6,10	111,2	6,13	111,7	0,03	0,5
1	5	–	162,9	–	163,3	–	0,4
18	6	2,58	32,3	2,59 2,51	33,0	0,01 -0,07	0,7
7	7	1,88	26,1	1,82 1,79	26,6	-0,06 -0,09	0,5
8	8	1,60	27,5	1,56	28,0	-0,04	0,5
12	9	2,22	18,2	2,26	18,6	0,04	0,4
10	10	–	78,8	–	79,2	–	0,4
11	11	–	78,5	–	79,1	–	0,6
21	12	2,88	17,0	2,95	17,1	0,07	0,1
14	13	5,40	124,6	5,51	125,0	0,11	0,4
17	14	5,40	128,9	5,51	129,9	0,11	1,0
15	15	2,88	25,7	2,89	26,1	0,01	0,4
13	16	5,40	130,3	5,68	131,1	0,28	0,8
16	17	5,40	125,5	5,45	125,6	0,05	0,1
6	18	2,72	33,2	2,77 2,66	33,4	0,05 -0,06	0,2
19	19	4,14	54,9	4,15	55,8	0,01	0,9
20	20	4,90	84,2	4,86	84,6	-0,04	0,4
12	21	1,92	26,1	2,06 2,05	25,6	0,14 0,13	-0,5
22	22	1,00	9,3	1,05	9,7	0,05	0,4

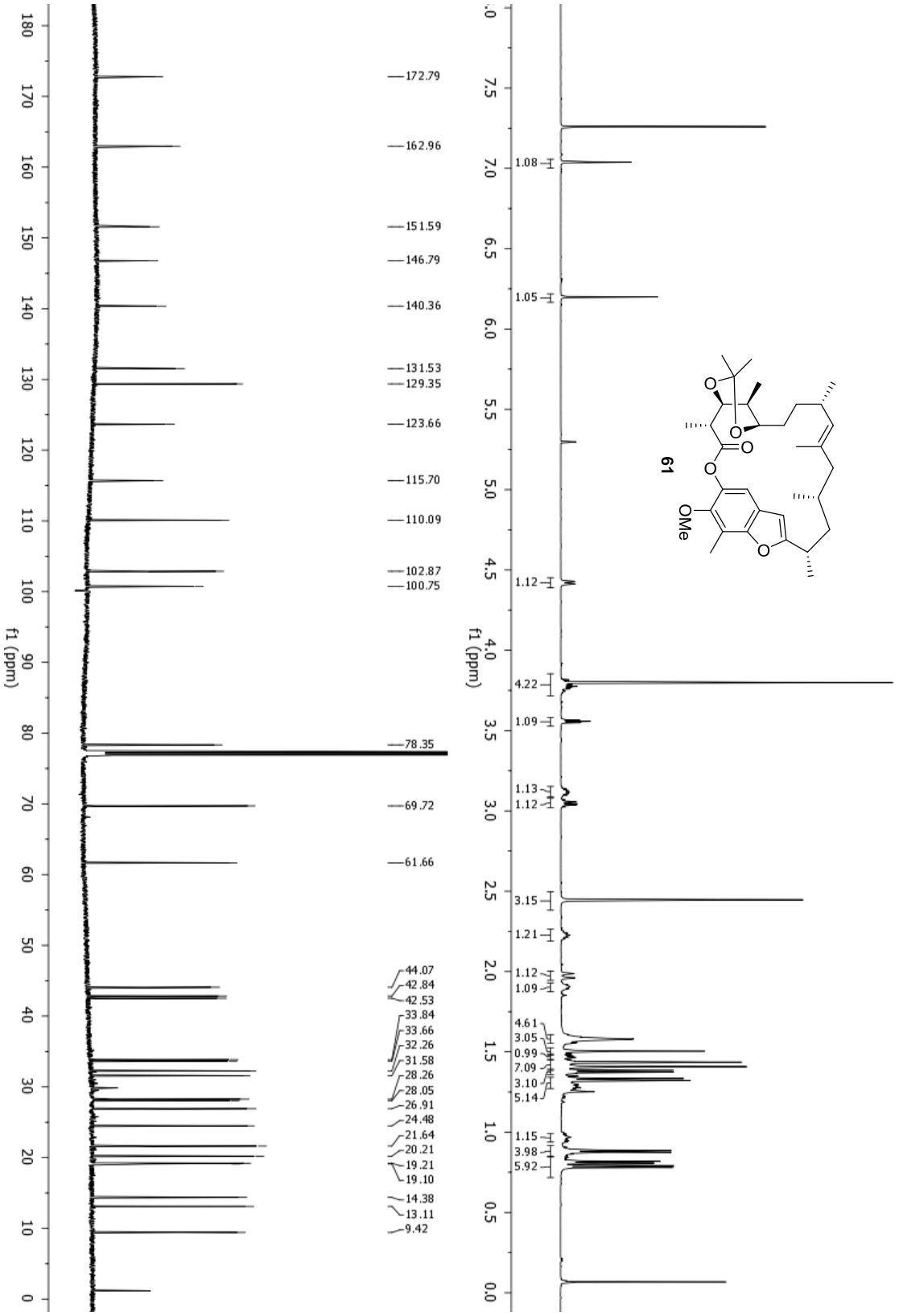
[1)] 1H and ^{13}C NMR shifts were reassigned according to 2D experiments.

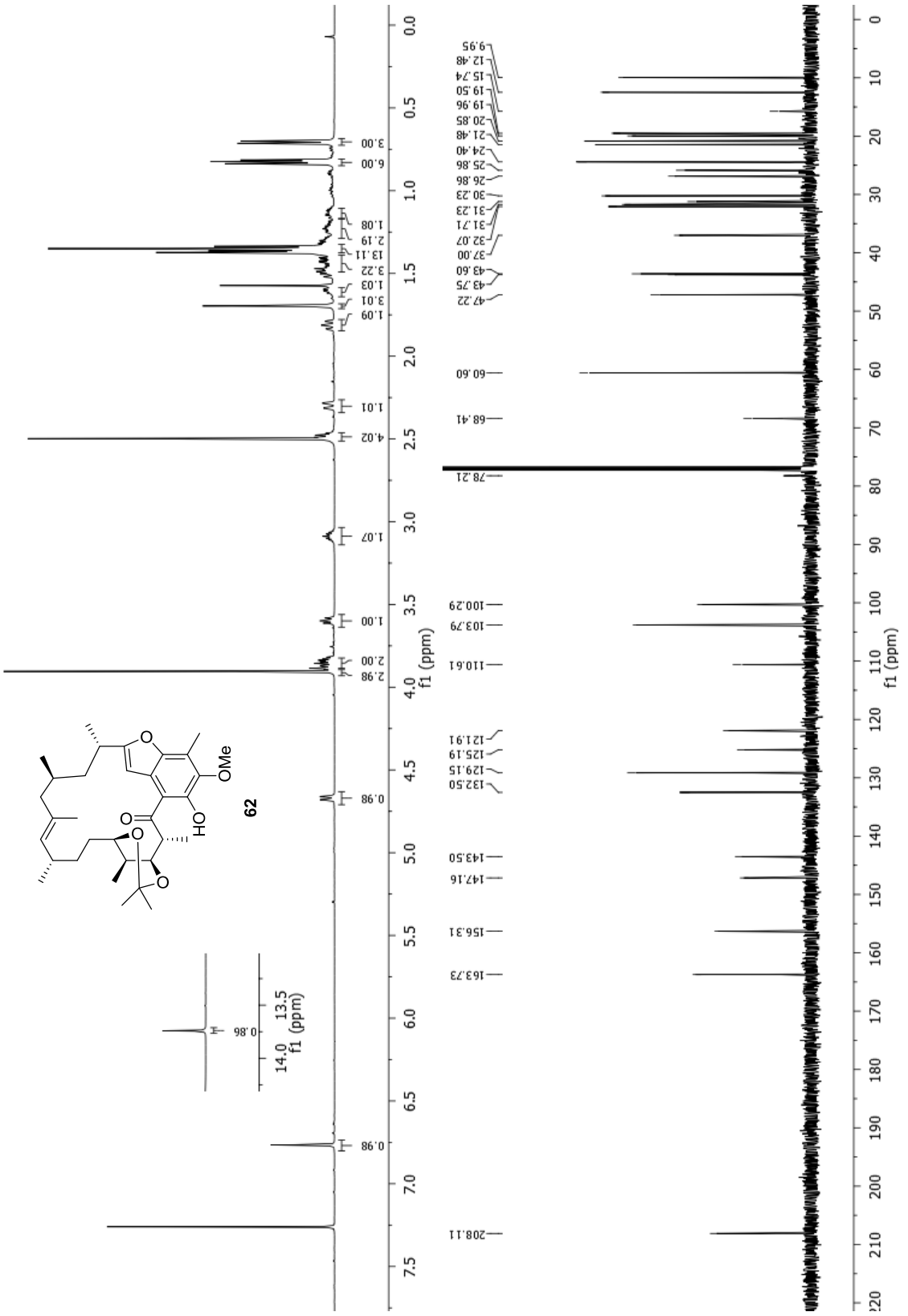
[2)] Source of data: R. Kazlauskas, P. T. Murphy, R. J. Wells, A. J. Blackman, *Aust. J. Chem.* **1982**, *35*, 113.

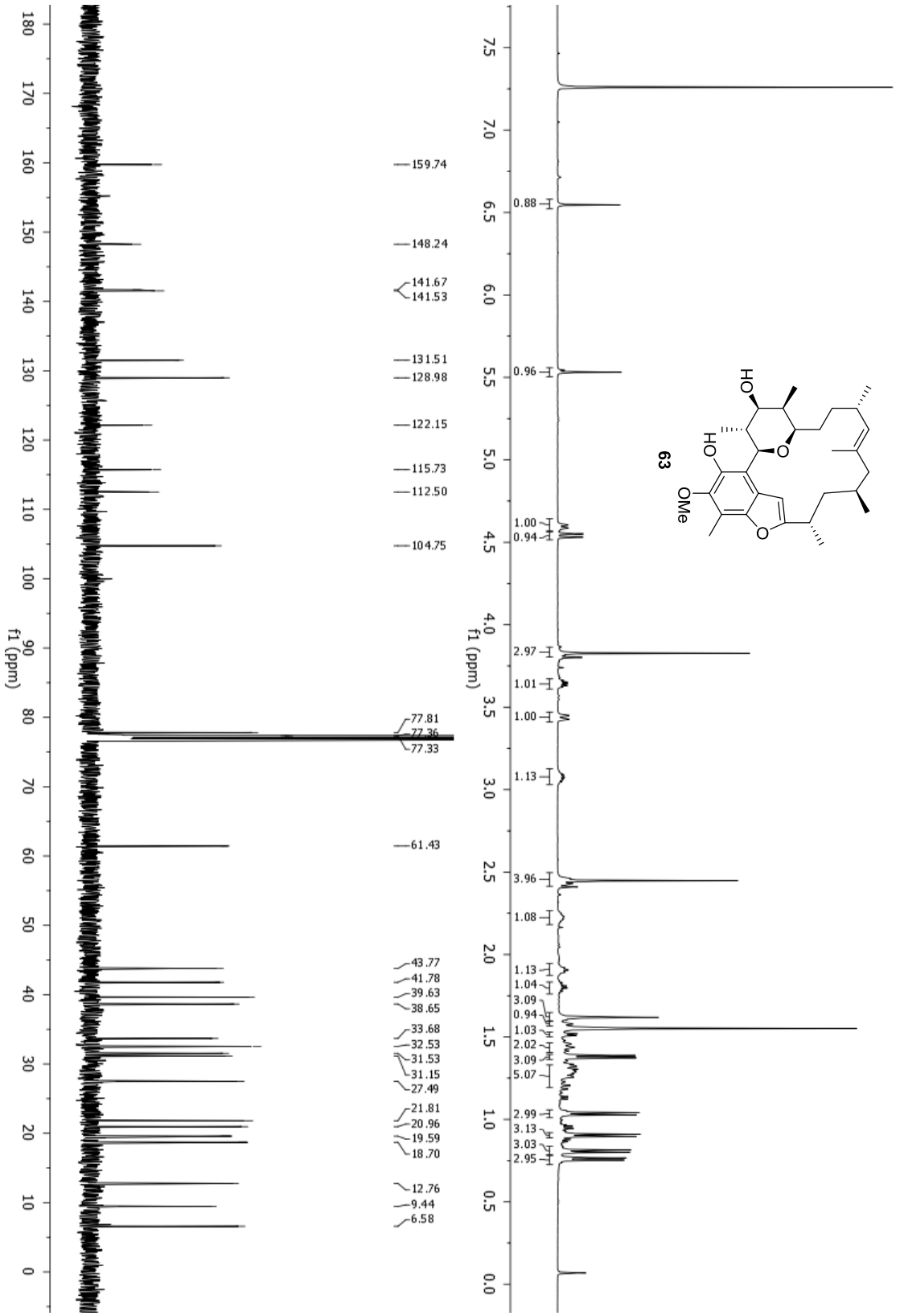
[3)] Experiments were run on a 600 MHz NMR machine, 298 K.

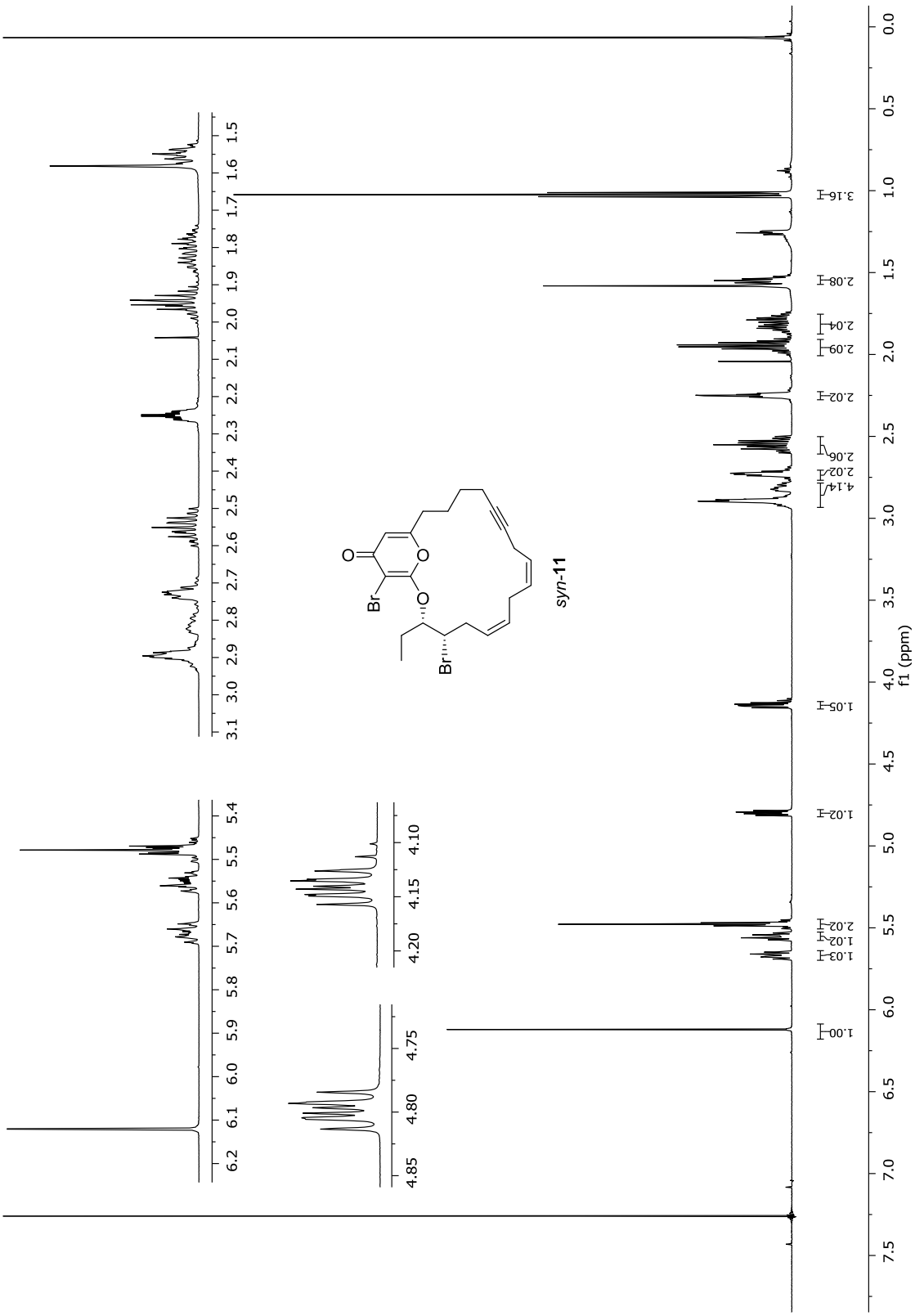
8.4. NMR Spectra of 267, 61, 62, 63, *syn*-11 and *anti*-11

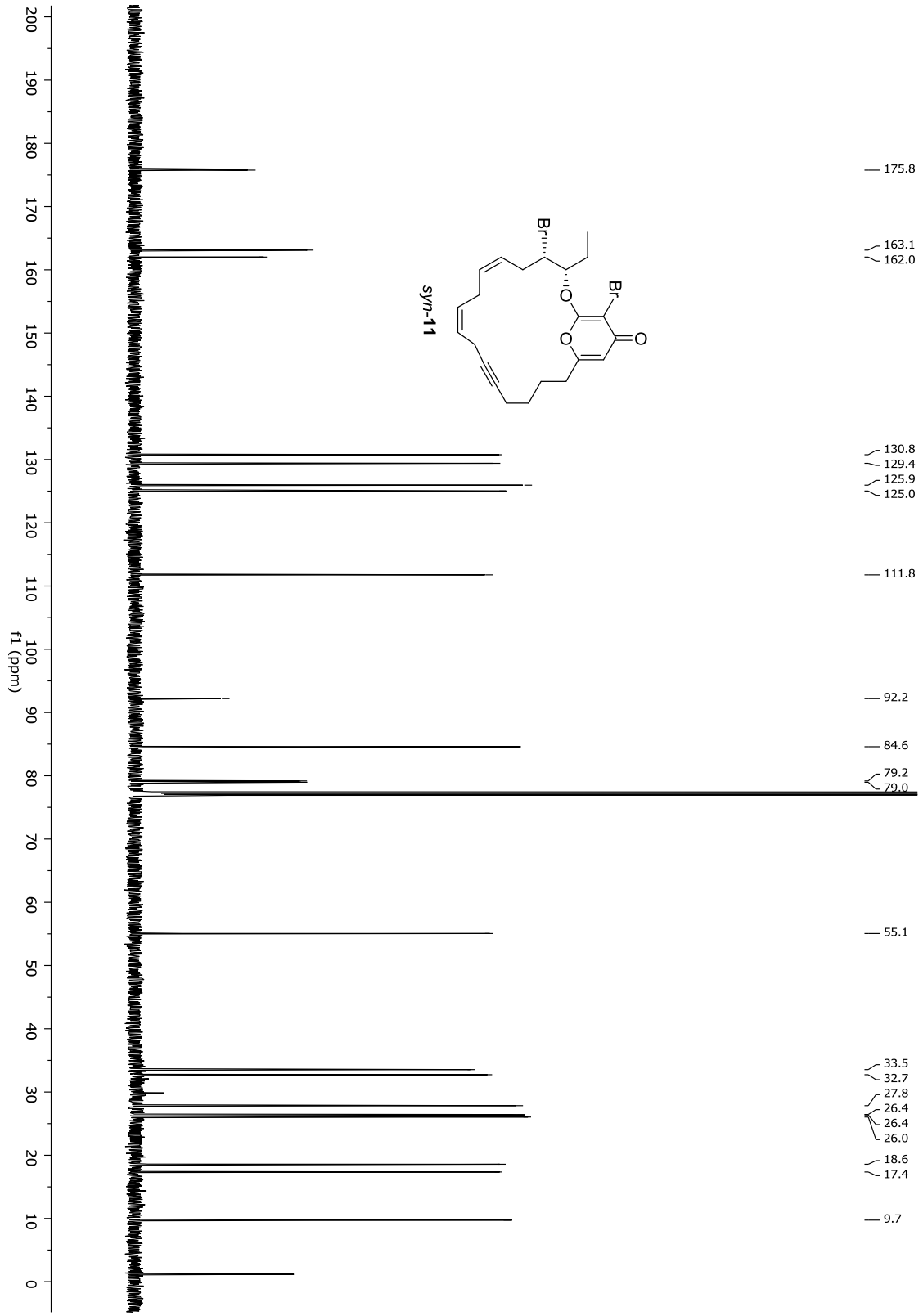


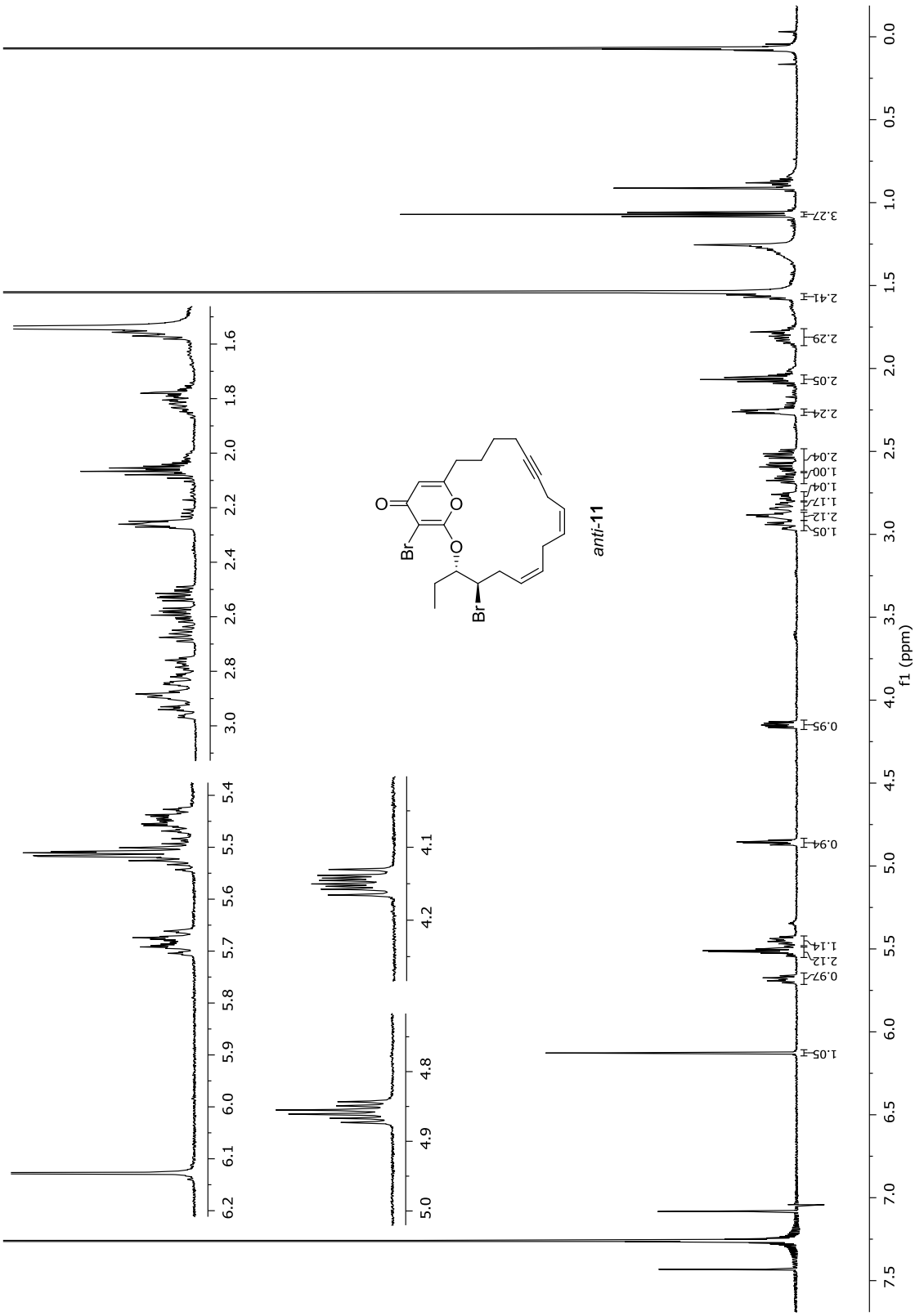

172.79
162.96
151.59
146.79
140.36
131.53
129.35
123.66
115.70
110.09
102.87
100.75
78.35
69.72
61.66
44.07
42.84
42.53
33.84
33.66
32.26
31.58
28.26
28.05
26.91
24.48
21.64
20.21
19.21
19.10
14.38
13.11
9.42
f1 (ppm)
1.08
1.05
1.12
4.22
1.09
1.13
1.12
3.15
1.21
1.12
1.09
4.61
3.05
0.99
7.09
3.10
5.14
1.15
3.98
5.92
f1 (ppm)
61
OMe

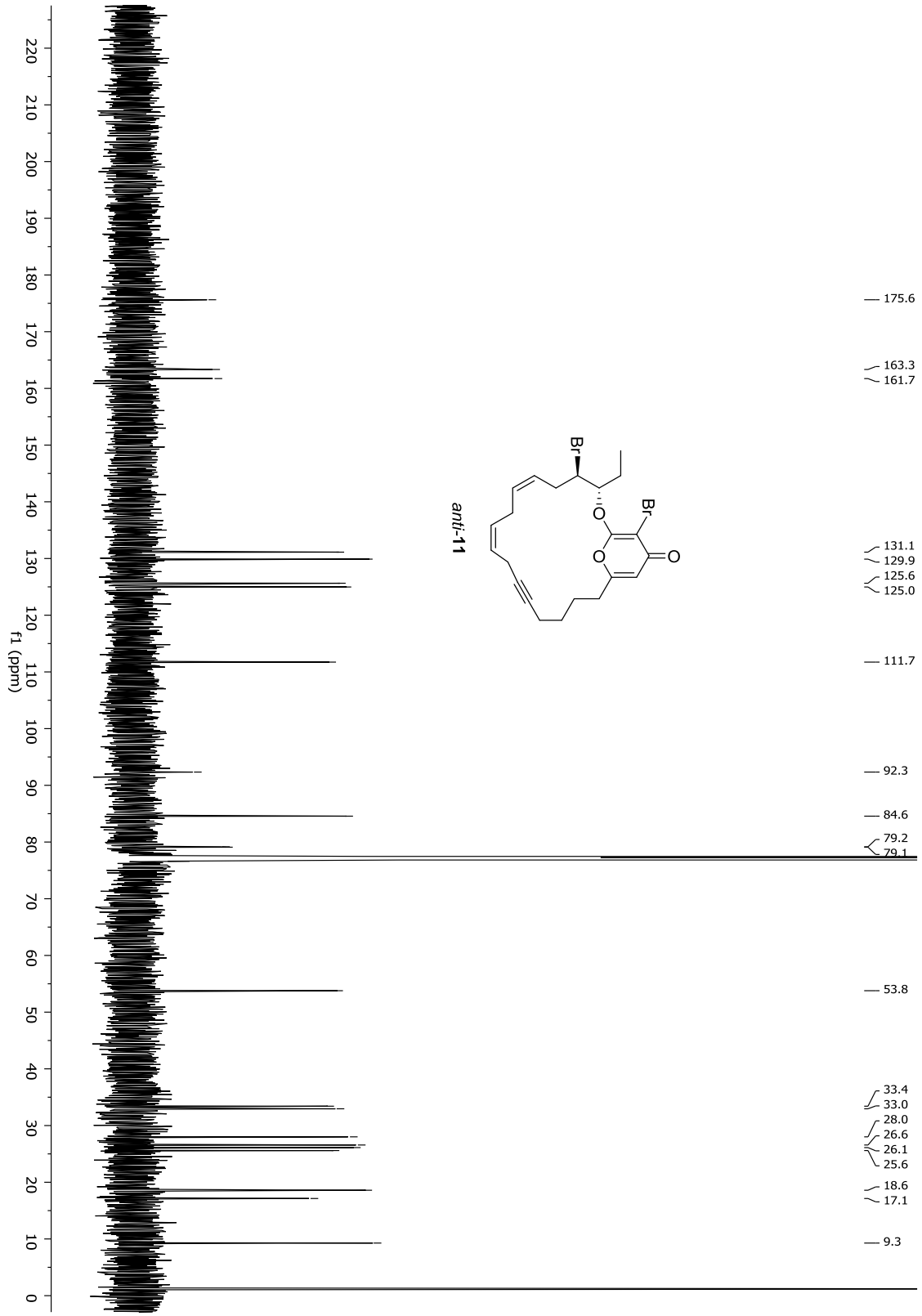

OMe
HO
O
O
O
O
62
f1 (ppm)
f1 (ppm)
f1 (ppm)


f1 (ppm)
159.74
148.24
141.67
141.53
131.51
128.98
122.15
115.73
112.50
104.75
77.81
77.36
77.33
61.43
43.77
41.78
39.63
38.65
33.68
32.53
31.53
31.15
27.49
21.81
20.96
19.59
18.70
12.76
9.44
6.58
0.88
0.96
1.00
0.94
2.97
1.01
1.00
1.13
3.96
1.08
1.13
1.04
3.09
0.94
1.03
2.02
3.09
5.07
2.99
3.13
3.03
2.95
HO
HO
O
OMe
O
63


Br
O
O
O
Br
syn-11
f1 (ppm)


f1 (ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
175.8
163.1
162.0
130.8
129.4
125.9
125.0
111.8
92.2
84.6
79.2
79.0
55.1
33.5
32.7
27.8
26.4
26.4
26.0
18.6
17.4
9.7
Br
Br
O
O
O
syn-11


anti-11
f1 (ppm)


f1 (ppm)
anti-11
Br
Br
O
O
O
175.6
163.3
161.7
131.1
129.9
125.6
125.0
111.7
92.3
84.6
79.2
79.1
53.8
33.4
33.0
28.0
26.6
26.1
25.6
18.6
17.1
9.3