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DISSERTATION

Titel der Dissertation

„Syntheses of Furanocembranoid Macrocycles

with Emphasis on the Total Synthesis of Providencin“

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Für meine Eltern Hermine und Helmut

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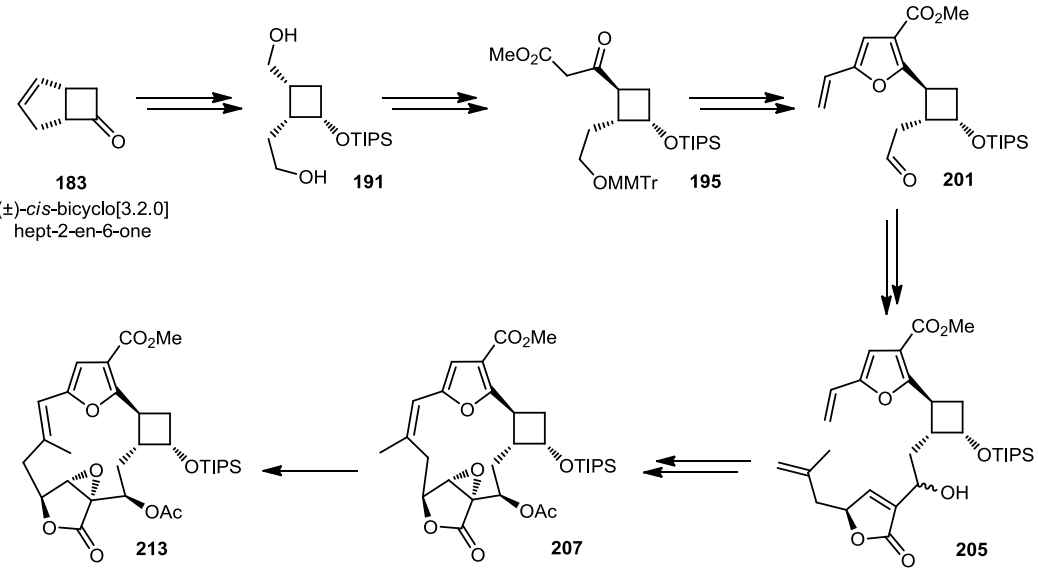
Graphical Abstract

Cyclobutane series – *Wipf* cyclization:



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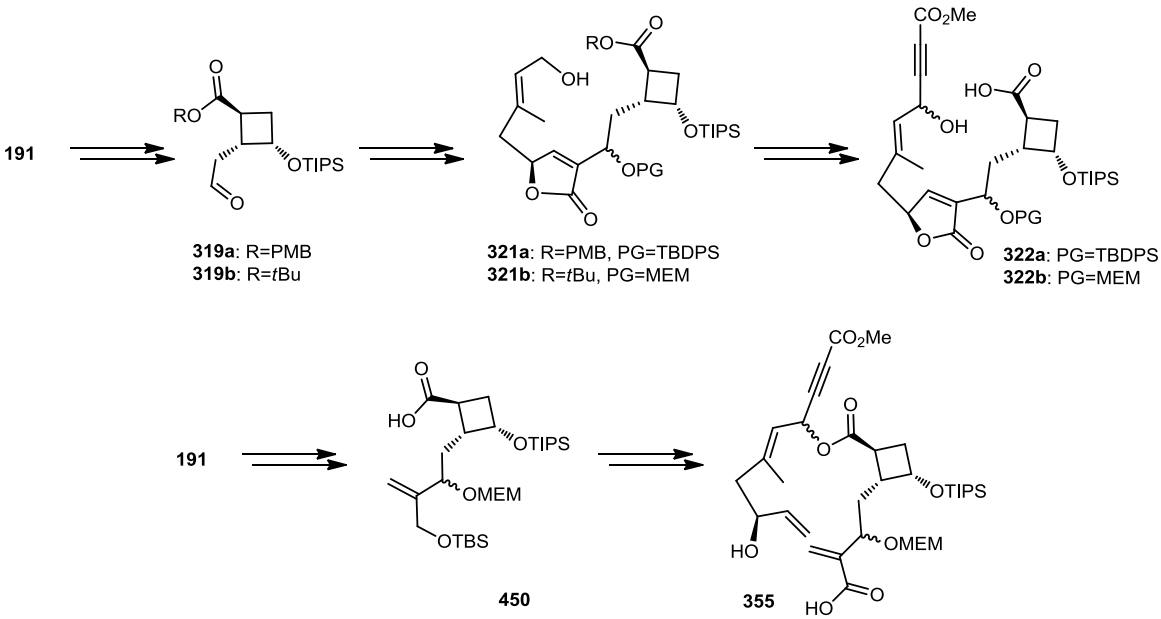
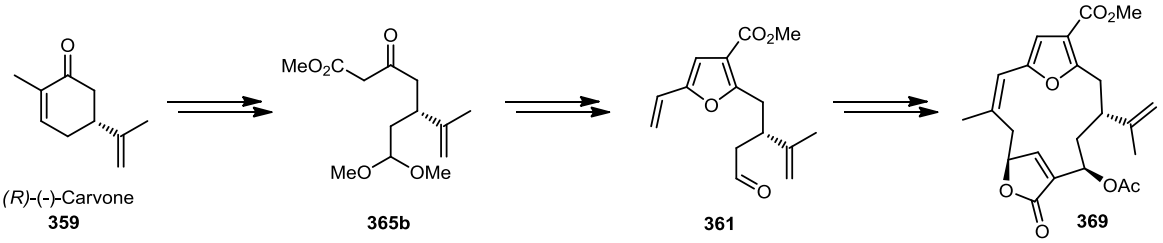


Isopropenyl series – *Wipf* cyclization:



Abstract

The class of furanocembranoid diterpenes is a huge, still growing family of marine natural products.[1] [2] Their interesting biological activities and complex molecular architectures, accompanied by their limited availability make them challenging synthetic targets. The vast majority of the family's constituents can be divided in three different classes, depending on their rearranged carbon-skeletons: pseudopteranes, gersolanes and furanocembranoids. Among each other, they mainly differ in their degrees of oxygenation and oxygenation patterns.

A well known member of the latter family is Providencin (**1**). It was first isolated and subsequently structure elucidated in 2003 by Rodriguez *et al.*.[3] The cyclic diterpene has some very interesting structural features. Its highly oxygenated hexacyclic structure is based on a previously undescribed bicyclo[12.2.0]hexadecane ring system. It bears nine stereogenic centers and its cyclobutanol subunit is four-fold substituted. Due to the highly strained ring system, the butenolide moiety is in a perpendicular orientation to the furan moiety, which makes the total synthesis of this molecule considerably difficult. To this day, no total synthesis has been published.

Herein several approaches with decreasing the molecule's ring strain are reported. The stepwise opening of rigid motifs should facilitate the crucial step of the macrocyclization. Four different, well established macrocyclization techniques were tested in two different synthetic series (cyclobutane- and isopropenyl-series): Ring closing metathesis,[4] *Horner-Wadsworth-Emmons* conditions,[5] macrolactonization,[6] and (transition) metal mediated carbon-carbon-bond forming reactions.[7] [8] The fragments of each approach were synthesized in a stereoselective and convergent manner.

The cyclobutane series exhibits this structural motif already in the starting material (±-*cis*-bicyclo[3.2.0]hept-2-en-6-one; **180**), whereas in the isopropenyl series (*R*)-(-)-Carvone (**359**) was used. The latter one is a chiral pool starting material and therefore, allows the total synthesis of diterpenes starting with a cyclic monoterpene.

The metathesis approaches in the cyclobutane, as well as in the isopropenyl series gave the most promising results and yielded highly advanced intermediates in the synthesis of Providencin (**1**). Since Providencin (**1**) is the only depicted member of the cembranoid family bearing a cyclobutane moiety in this position, the cyclobutane series is perfect for the synthesis of (**1**). In contrast, the isopropenyl series offers a flexible approach to the carbon-skeleton of numerous members of this family. Overall, most promising key intermediate **213** was synthesized in a 21-linear-steps sequence and provided access to a possible total synthesis of Providencin (**1**). Furthermore, the 14-step-synthesis of key intermediate **369** disclosed the biomimetic synthesis of Providencin (**1**) *en route* with numerous other natural products, such as Iopholide (**57**), Iophodiol A/B and Bipinnatin E (**58**).

Zusammenfassung

Furanocembranoide Diterpene sind eine riesige, stets wachsende Klasse mariner Naturstoffe.[1] [2] Sowohl ihre interessanten biologischen Eigenschaften und ihre komplexen molekularen Architekturen, als auch ihre begrenzte Verfügbarkeit, machen sie zu herausfordernden synthetischen Zielen. Die Mehrheit der Vertreter dieser Klasse lässt sich in drei Hauptgruppen unterteilen, die sich im Wesentlichen durch ihre umgelagerten Kohlenstoffgerüste unterscheiden: Pseudopterane, Gersolane und Furanocembranoide. Innerhalb dieser drei Klassen unterscheiden sich deren Vertreter hauptsächlich durch ihren Oxidationsgrad und ihr Oxidationsmuster.

Providencin (**1**) ist ein bekannter Vertreter der Furanocembranoide. Es wurde im Jahr 2003 von Rodriguez *et al*. isoliert und charakterisiert und besitzt einige seltene Strukturmotive, wie sein, bisher literatur-unbekanntes, hoch oxigeniertes Bicyclo[12.2.0]hexadecan-Skelett.[3] Des Weiteren besitzt Providencin (**1**) neun stereogene Zentren und eine vierfach substituierte Cyclobutan-Einheit. Wegen der hohen Ringspannung, die das Molekül aufweist, weichen Furan und Butenolid Untereinheit in eine zueinander orthogonale Position aus, welche die Totalsynthese von Providencin (**1**) erschweren. Bis heute ist keine Totalsynthese literaturbekannt.

Im Folgenden werden mehrere Zugänge präsentiert, welche die Ringspannung des Moleküls sukzessive herabsetzen. Die schrittweise Öffnung rigider Strukturmotive ermöglicht eine höhere Flexibilität und deshalb eine Erleichterung der schwierigen Makrozyklisierung. Dazu werden vier gut etablierte Makrozyklisierungsmethoden in zwei Syntheseserien (Cyclobutan- und Isopropenyl-Serie) verwendet: Ringschlussmetathese,[4] *Horner-Wadsworth-Emmons* Bedingungen,[5] Makro-laktonisierung und (Übergangs-)metall vermittelte Kohlenstoff-Kohlenstoff-Bindungs-knüpfung.[6] [7] [8] Die Fragmente der einzelnen Ansätze wurden stereoselektiv synthetisiert.

Ausgangsmaterial für die Cyclobutan-Serie war (±)-*cis*-Bicyclo[3.2.0]hept-2-en-6-on (**180**), welches den gewünschten viergliedrigen Ring bereits besitzt. Für die Isopropenyl-Serie wurde (*R*)-(-)-Carvon (**359**) als optimales Startmaterial gewählt.

Sowohl in der Cyclobutan-, als auch in der Isopropenyl-Serie erwies sich der Metathese Zugang als zielführend. Dadurch konnten hoch funktionalisierte, weit fortgeschrittene Zwischenstufen synthetisiert werden, wie zum Beispiel Verbindung **213** in einer 21-Stufen Sequenz oder Verbindung **369** in einer 14-Stufen Sequenz. Da Providencin (**1**) unter den furanocembranoiden Diterpenen der einzige Vertreter ist, der eine Cyclobutan-Untereinheit an dieser Position aufweist, ermöglicht die Cyclobutan-Serie lediglich die maßgeschneiderte Synthese von (**1**). Der Isopropenyl-Ansatz ermöglicht jedoch die Synthese zahlreicher weiterer Vertreter dieser Naturstoffklasse, wie zum Beispiel Iopholide (**57**), Iophodiol A/B und Bipinnatin E (**58**).

Publications, Oral Presentations and Posters Resulting from this Ph.D. Thesis

Publications:

"Synthetic efforts towards the synthesis of the complex diterpene providencin" (*Synlett*, **2009**, 9, 1357-1366.)

Oral Presentations:

Invited lecture at "Organic Chemistry Symposium" in Vienna. Title: "Towards the Total Synthesis of Providencin"

Invited lecture at the "Doktorandenworkshop – Naturstoffchemie" entitled "Probleme mit der Vorsehung: Auf dem Weg zu Providencin" in Bayreuth, Germany (May 2009).

Poster Presentations:

Poster presentation at BOSS XI-Congress in Genth, Belgium entitled "Towards the Total Synthesis of Providencin" (July 2008)

Poster presentation at IASOC in Ischia, Italy entitled "Towards the Total Synthesis of Providencin" (September 2008)

Poster presentation at „Organic Chemistry Symposium" in Paris, France 2009 entitled "Towards the Total Synthesis of Providencin" (February 2009)

Poster presentation at Synthesefest Munich, Germany entitled "Towards the Total Synthesis of Providencin" (March 2009)

Poster presentation at 10th Tetrahedron Symposium in Paris, France 2009 entitled "Towards the Total Synthesis of Providencin" (June 2009)

Participant at the Bayer PhD workshop 2010, Cologne, including poster presentation entitled "Towards the Total Synthesis of Providencin" (July 2010)

Poster presentation at ICOS-18 in Bergen, Norway 2010 entitled "Towards the Total Synthesis of Providencin" (September 2010)

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1 Introduction

1.1 Background

Natural products play an important role in the discovery of new drugs, but in many cases they can only be isolated from nature in very small quantities. If preliminary standardized screenings against various harmful cell-lines (cancer, malaria, HIV,...) show satisfying cytotoxic activity (IC_{50}-values), these natural products have to be synthesized in larger quantities. Therefore, the stereoselective total synthesis of complex natural products is a major challenge in organic chemistry. Its great advantage is that specific modifications in the NP's carbon/heteroatom skeleton can be done with ease, thus increasing the molecules' activity.[9]

Terpenes are an important class of natural products with a large structural diversity (Figure 1). Until now more than 30.000 different representatives of this class are known.[10] By reason of their high oxygenation degrees and their numerous stereogenic centers they are interesting and challenging synthetic targets for organic chemists.

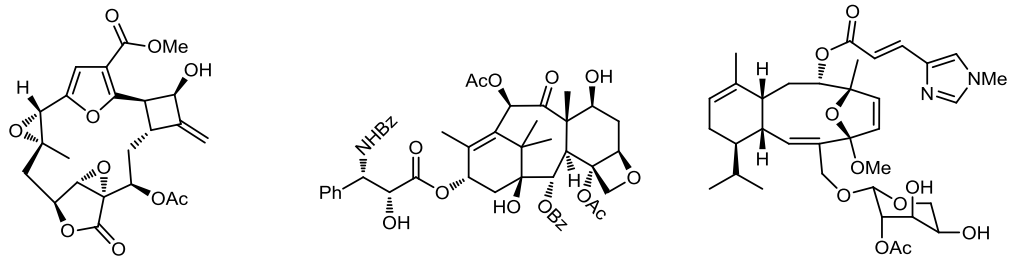


Figure 1: Different types of complex terpene structures: Providencin (1), a marine diterpene; Paclitaxel (A), one of the most important *anti* cancer drugs; Eleutherobin (B), a potent *anti* cancer drug.

1.2 Biosynthesis of terpenes

Terpenes can be divided – according to their number of carbon atoms – in hemi-, mono-, sesqui-, di-, sester-, tri- and tetraterpenes, with a C5, C10, C15, C20, C25, C30 and C40-carbon skeleton, respectively. All terpenes possess a common denominator: they are built up by head-to-tail or tail-to-tail linkage of C5-isoprenyl-units, where the isopropyl part of 2-methylbutane (isoprene) is defined as the head and the ethyl residue as the tail. This rule is called the isoprene rule and was found by *Ruzicka* and *Wallach* in 1959.[11] The resulting C-C-double bonds always have a *trans* configuration.

In nature, two different biogenetic pathways are known to synthesize terpenes: On the one hand the acetate-mevalonate pathway (Figure 2) and on the other hand the activated acetaldehyde-glyceraldehyde-3-phosphate pathway (Rhomer-pathway, non-mevalonate-pathway, Figure 3).[12] [13] Both of them result in the same C5-intermediates isopentenyl-pyrophosphate (**7**, IPP) and dimethyl-allyl-pyrophophate (**8**, DMAPP).

1.2.1 Acetate-Mevalonate-Pathway (MVA-pathway)

In this case, acetyl-coenzyme A (Ac-CoA, **2**) is the biogenetic precursor of terpenes. Two equivalents of Ac-CoA (**2**) are coupled to acetoacetyl-CoA (**3**), similar to the *Claisen* condensation.[14] Following the pattern of an aldol reaction, acetoacetyl-CoA (**3**) reacts with another equivalent of Ac-CoA (**2**) as a nucleophile. The resulting hydroxy-methyl-glutaryl-CoA (HMG-CoA, **4**) is enzymatically reduced (HMG-CoA-reductase) to (*R*)-mevalonic acid (MVA, **5**). Mevalonic acid **5** is then converted to the corresponding pyrophosphate **6** by an ATP-dependent kinase. This intermediate is subsequently decarboxylized and dehydrated to IPP (**7**), which can be isomerized by an Mg^{2+}-dependent isomerase to DMAPP (**8**) (Figure 2).

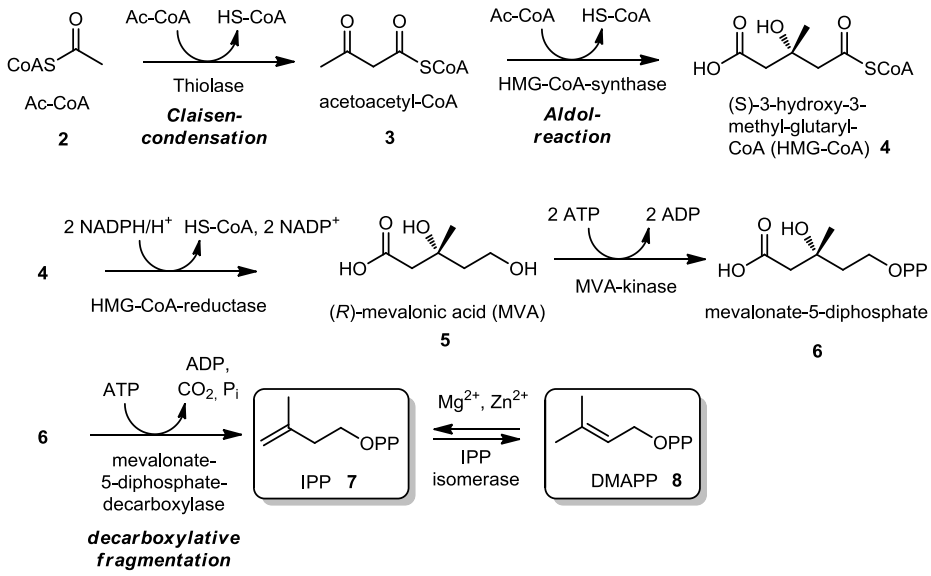


Figure 2: Scheme of the biogenesis of IPP (7) and DMAPP (8) *via* the mevalonate pathway.

1.2.2 The Rhomer Pathway (MEP-pathway)[13]

Following the non-mevalonate pathway, pyruvate (**9**) and glyceraldehyde (**11a**) are the biogenetic precursors of IPP (**7**) and DMAPP (**8**). In the first step, pyruvate (**9**) is attacked by the vitamin B1 derivate thiamine pyrophosphate (TPP, **19**), forming a reversible adduct **10**. After irreversible decarboxylation an *Umpolung*-reaction takes place and the former electrophilic ketone becomes nucleophilic (**11**), attacking glyceraldehyde-3-phosphate on C1 to yield **12**. After regeneration of TPP (**19**) by a retro aldol reaction, compound **13** (1-deoxyxylulose-5-phosphate, DXP) is generated. An acyloin rearrangement of **13** results in the formation of 2C-methyl-D-erythritol-4-phosphate (MEP, **14**). Repeated phosphorylation yields MEcPP (**16**), a cyclic diphosphate, which is then reduced *via* a yet unknown mechanism to IPP (**7**) and DMAPP (**8**) (Figure 3).

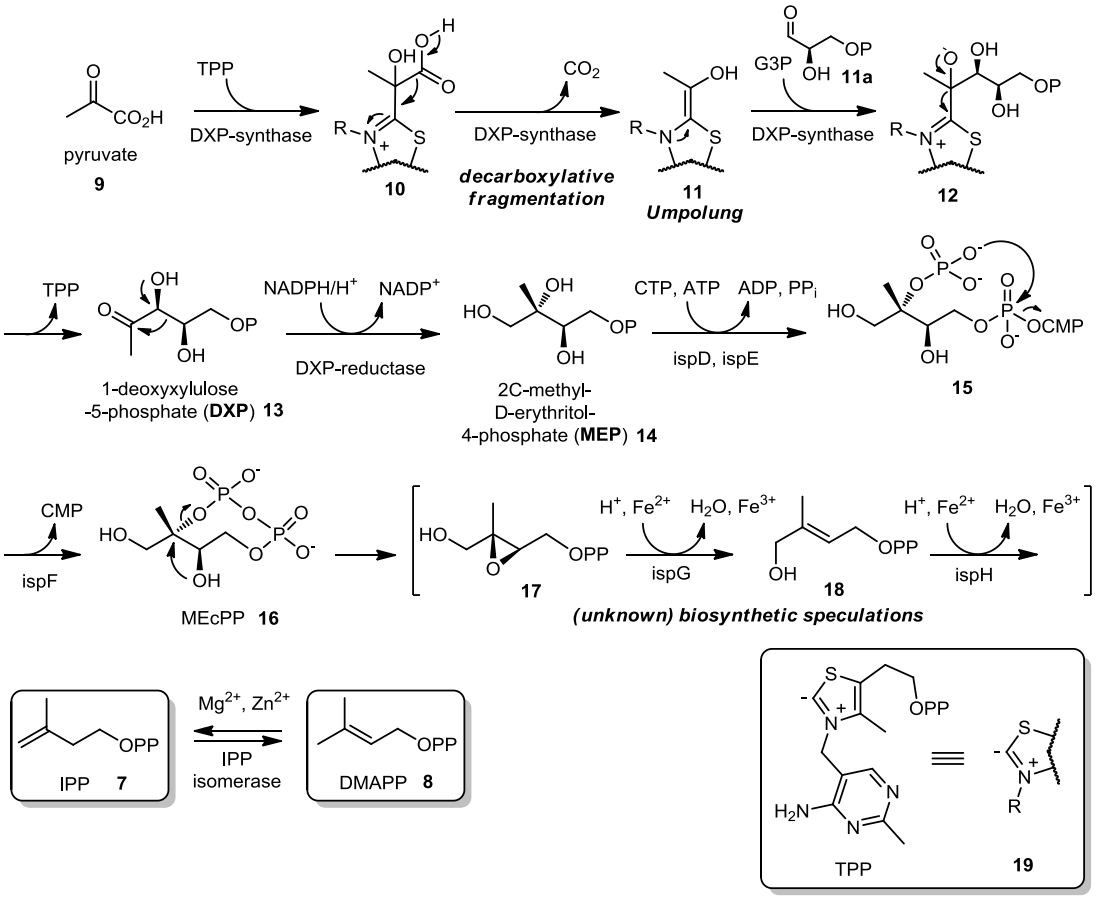


Figure 3: Scheme of the biogenesis of IPP and DMAPP *via* the non-mevalonate pathway.

The electrophilic allylic CH_2-group of DMAPP (**8**) and the nucleophilic methylene group of IPP (**7**) are connected by a head-to-tail linkage to the monoterpenoid geranyl phosphate (**20**, C10) by an *Alder-Ene*-like reaction.[15] Using the same mechanism again nature elongates geranyl phosphate (**20**) once more to farnesylphosphate (**21**, C15).

After another elongation using the same pathway, the C20-skeleton of geranyl-geranyldiphosphate (**22**, GGPP, C20) is finished. This intermediate is the basis for the synthesis of all diterpenes, such as Providencin (**1**) and Sarcofuranocembranolide A (**75**).Further chain elongation of geranyl-geranylphosphate (**22**) leads to the formation of sester-terpenes (**23**, C25). Tail-to-tail dimerization of two farnesyl subunits furnishes the squalene skeleton (**25**, C30), which is the starting material for the cationic cyclization to the steroid skeleton. Further, enzyme-based oxidations provide the large variety of different steroid based hormones, needed in living organisms. Repeated addition of further isoprene units to **23** lead to the formation of polyterpenes (**24**) and finally to gutta-percha, a natural polymer (Figure 4).[10]

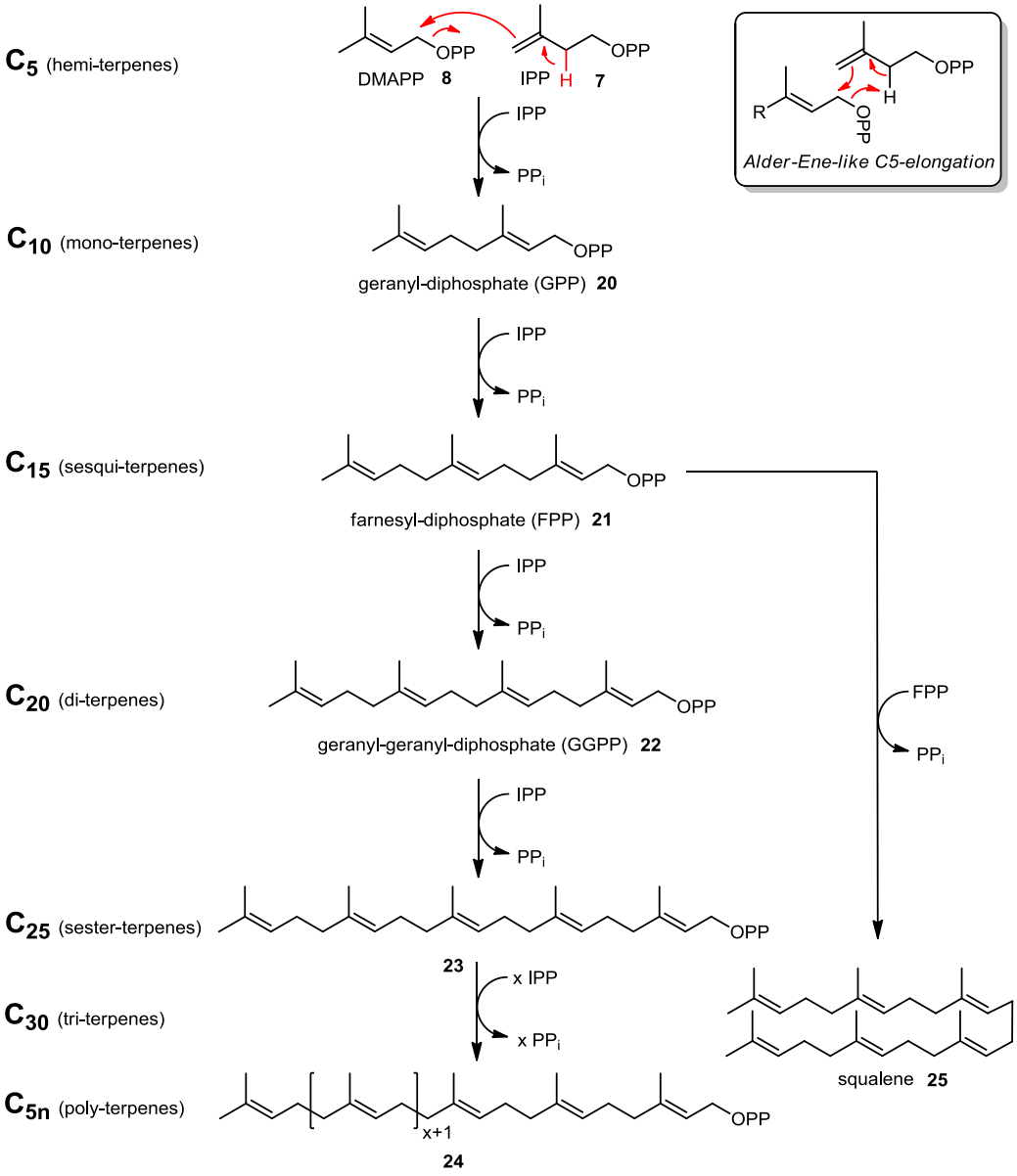


Figure 4: Biosynthesis of the carbon-skeleton of diterpenes.

1.3 Structure, Isolation and Biological Activity

In 1962, Dauben *et al.* re-characterized a hydrocarbon, which they called ***cembrene***.[16] Actually it was first isolated in 1951 by *Haagen-Smit*, *Wang* and *Mirov*.[17] The compound showed a molecular mass of 272 g/mol, which upon catalytic hydrogenation yielded a different product with a molecular mass of 280 g/mol, indicating the presence of four double bonds. Further analysis with NMR, IR and UV-VIS spectroscopy showed the presence of a conjugated diene system and five vinylic protons. Furthermore the double bonds seemed to be *trans* configured. Nevertheless the authors concluded that, "*Although no information is available with regard to the stereochemistry of the trisubstituted double bonds, from a study of models the structure written containing one cis bond appears to be more favored than an all trans structure*".[16] Furthermore, conducting oxidative degradation experiments they only found bi-functional products, concluding that the structure had to have a 14-membered macrocycle (**32a**) (Figure 5).

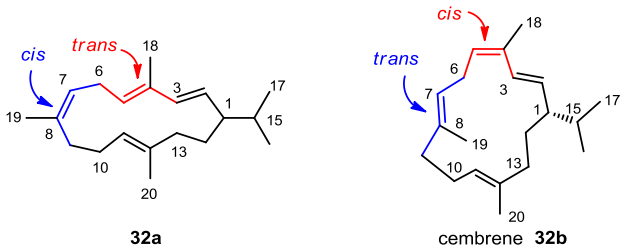


Figure 5: Originally proposed structure of cembrene (32a) and correct structure of cembrene (32b).

In 1960 Drew *et al*. showed a revised structure by crystallographic analysis.[18] Instead of an originally proposed $\Delta^{7,8}$ *cis*-double bond the authors could show that cembrene exhibits a $\Delta^{4,5}$ *cis* configured double bond (**32b**) (Figure 5). This was the cornerstone of the *cembrene-skeleton* with its characteristic $\Delta^{2,3}$- $\Delta^{4,5}$- $\Delta^{7,8}$- $\Delta^{11,12}$ double bond positions (Figure 6).

In 1966, Moore *et al*. reported a termite trail pheromone.[19] The very same diterpene was re-isolated in 1972 by *A. J. Birch* and coworkers and was given the name ***neocembrene-A*** (**30**, cembrene-A).[20] It features a slightly rearranged carbon skeleton in terms of the double bond positions and geometry. According to its double bond positions ($\Delta^{3,4}$- $\Delta^{7,8}$- $\Delta^{11,12}$- $\Delta^{15,16}$), the carbon skeleton of neocembrene-A is name giving for the neocembrene-skeleton (**26**) (Figure 6).

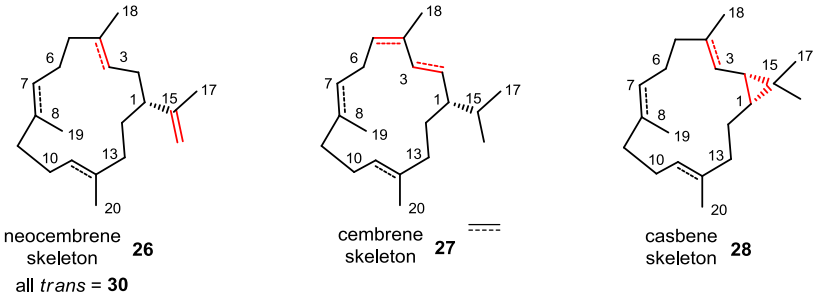


Figure 6: Skeletons of different 14-membered macrocyclic diterpenes. Dashed lines stand for mutable double bond geometry. The all *trans* configuration is most likely.

A very recent publication of Keasling *et al.* revealed the gene of the neocembrene synthase in *Euphorbiaceae* plants.[21] In contrast to the well known casbene synthase (EC 4.2.3.8), which is responsible for the formation of the dimethylcyclopropane subunit of casbenes (**28**), this enzyme catalyzes the selective formation of the isopropenyl group present in the neo-cembrene family (**26**).

Furanocembranoids, pseudopteranes and gersolanes represent a huge family of diterpenoids, which have been isolated exclusively from marine sources. All possess a (slightly rearranged) neo-cembrene or a casbene skeleton. Due to their attractive molecular architectures combined with considerable bioactivities, they have gained the interest of both, natural product chemists and synthetic chemists.

The vast majority of furanocembranoids, pseudopteranes and gersolanes have been isolated from gorgonian corals, which are also known as sea whips or sea fans. They can be found in the oceans all over the world, especially in the tropics and subtropics. The *habitus* of these corals is usually erect and flattened or whiplike and bushy. A colony of these polyps can be several feet in height and brightly colored, often purple, red or yellow.

Further information concerning the phylogeny of gorgonian octocorals is depicted in Figure 7.

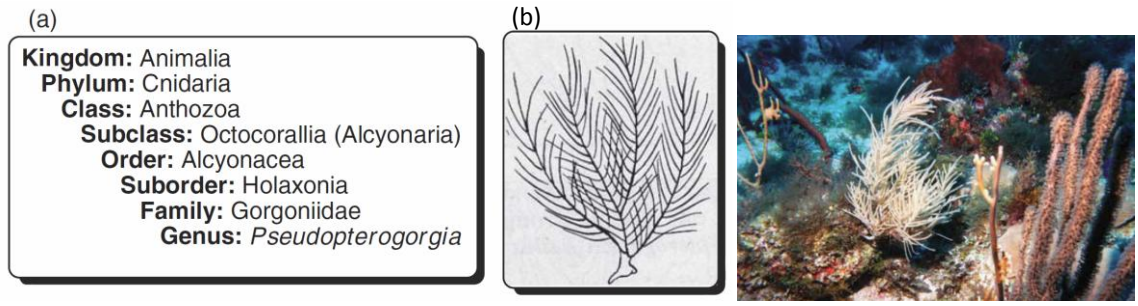


Figure 7: (a) phylogeny of gorgonian octocorals; (b) Phenotype of *pseudopterogorgia kallos*.[22]

Little is known about the complete biosynthesis of this class of molecules, especially about the enzymes responsible for the oxidation reactions. Some speculations assume that the cytochrome P450 complex is involved in these oxidative transformations. But, it is clearly shown that the biosynthesis of these molecules starts with geranyl-geranyldiphosphate (**22**, GGPP), which is derived from DMAPP (**8**) and IPP (**7**) as shown above (Figure 4).[1]

1.3.1 Cationic GGPP cyclizations

The numbering of the carbon atoms in the following descriptions of the different types of cationic cyclizations depends on the particularly formed carbon skeletons and therefore, differs for each substance class.[10] In general, type A cyclizations form a macrocyclic carbon skeleton, whereas type B cyclizations form numerous smaller cycles. Type A – type B cyclizations form in the first step a macrocyclic core, which is then constricted to multiple smaller rings. Type B – type A cyclizations, respectively, generate in the first step several smaller carbo cycles and adjacently form an additional carbo cycle.

Type A Cyclizations:[12]

After generation of a stabilized cation at C15 and subsequent formation of a carbon-carbon single bond between C1 and C2 the 14-membered macrocycle of furanocembranoids is finished by a type-A cyclization (**29**). Onto abstraction of a proton on C16 a new carbon-carbon double is formed and the positive charge on C15 is equalized, finishing the biosynthesis of the simplest member of the neo-cembrene family: cembrene-A (**30**). The 14-membered macrocycle is called neo-cembrene skeleton and it is the base for the biosynthetical formation of furanocembranoids.

As depicted in Figure 8 different reaction pathways can be figured out, leading to different carbon skeletons. A [1,3]-hydride shift (**31**) and subsequent proton abstraction would lead to the cembrene skeleton (**32b**), mentioned above. In contrast, β-proton abstraction would lead to the formation of a cyclopropane ring – boosted by the *Thorpe-Ingold* effect – and therefore to the formation of the casbene skeleton (**33**) (Figure 8).[23]

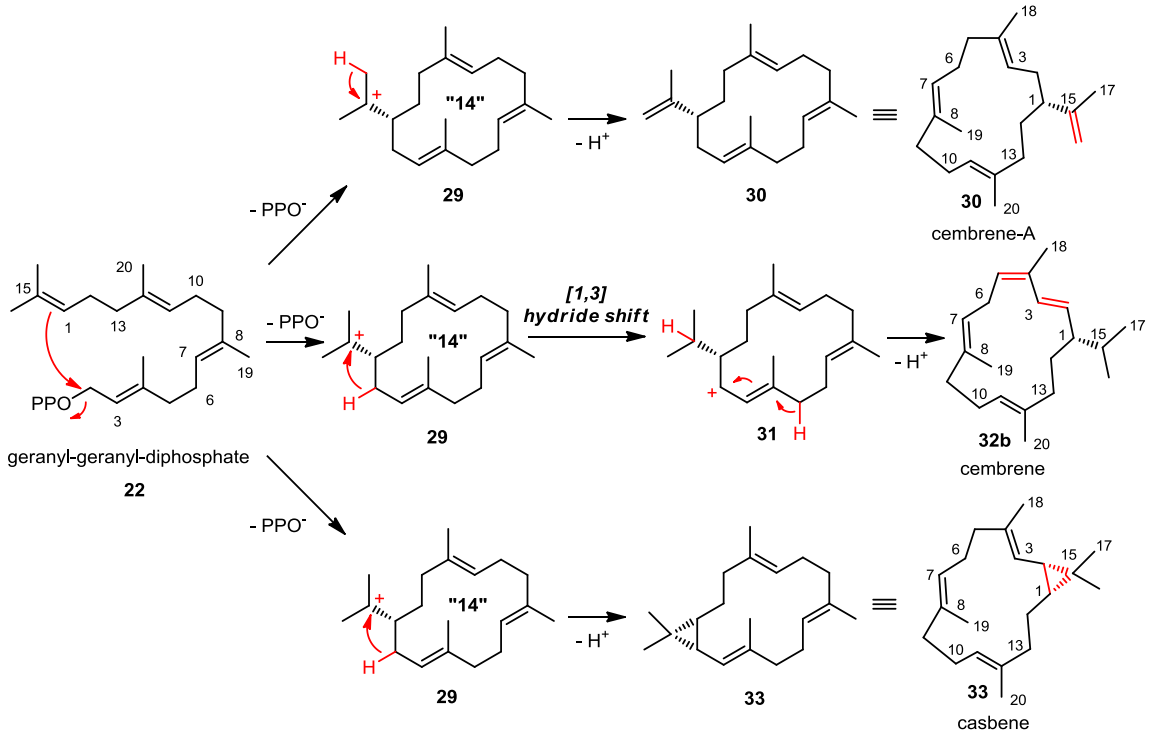


Figure 8: Biosynthetic cationic type A cyclizations of GGPP (cembrene-A features a neocembrene skeleton).

Type A – Type B Cyclizations:[12]

The formation of two different carbon-skeletons is described by this type of cyclization reaction: the taxane-skeleton (**39**) and the fusicoccane-skeleton (**36**). The formation of the fusicoccane-skeleton (**36**) starts with formation of a stabilized carbo cation on C1, which immediately cyclizes to C14. The formed 4,14-cyclocembrene-skeleton (**35**) is the basis for numerous natural products. Further proton promoted cyclization of C10 to C6 forms the fusicoccane-core (**36**), which consists of a 5-8-5-membered, tricyclic ring system. The formation of the taxane-skeleton (**39**) is induced by the generation of a stabilized carbo cation on C4. Two bond forming reactions between $\Delta^{5,15}$ and $\Delta^{1,14}$ result in the formation of the verticillane-skeleton (**38**), which can be further cyclized to the taxane-skeleton (**39**) by the generation of a $\Delta^{8,13}$-single bond (Figure 9). This carbon skeleton is the basis of one of the most potent *anti* cancer drug Paclitaxel (**A**, Figure 1).

Type B – Type A Cyclizations:[12]

The formation of the $\Delta^{4,5}$- and $\Delta^{9,10}$-single bonds to intermediates **40**, **43** and **46** (depending on the transition state) are the initial steps in these types of cyclizations. The formed substituted decaline core can now undergo various rearrangements. Double *Wagner-Meerwein* rearrangement (C3 to C5 and C20 to C9) and double [1,2]-hydride shift (C5-H to C10-H and C9-H to C8-H) provide bicyclic intermediate **41**.[24] Compound **41** has a new nomenclature according to Figure 9. S_N2' attack of C11 to C12 furnishes the eight-membered cycle of the pleuromutilin-core (**42**), which is completed by a [1,5]-hydride shift (C14-H to C10-H). The formation of the primarane-skeleton (**44**) is carried out starting from **43**, by a S_N2' attack of C17 to C13 furnishing **44**. Once again, compound **44** has a new nomenclature. Attack of C16 to C8, *Wagner-Meerwein* rearrangement (C12 to C15) and a final [1,2]-hydride shift (C17-H to C13-H) complete the biosynthesis of the kaurane-skeleton (**45**),[24] which is again the starting material for the rearrangement to the giberellane-skeleton (Figure 9).

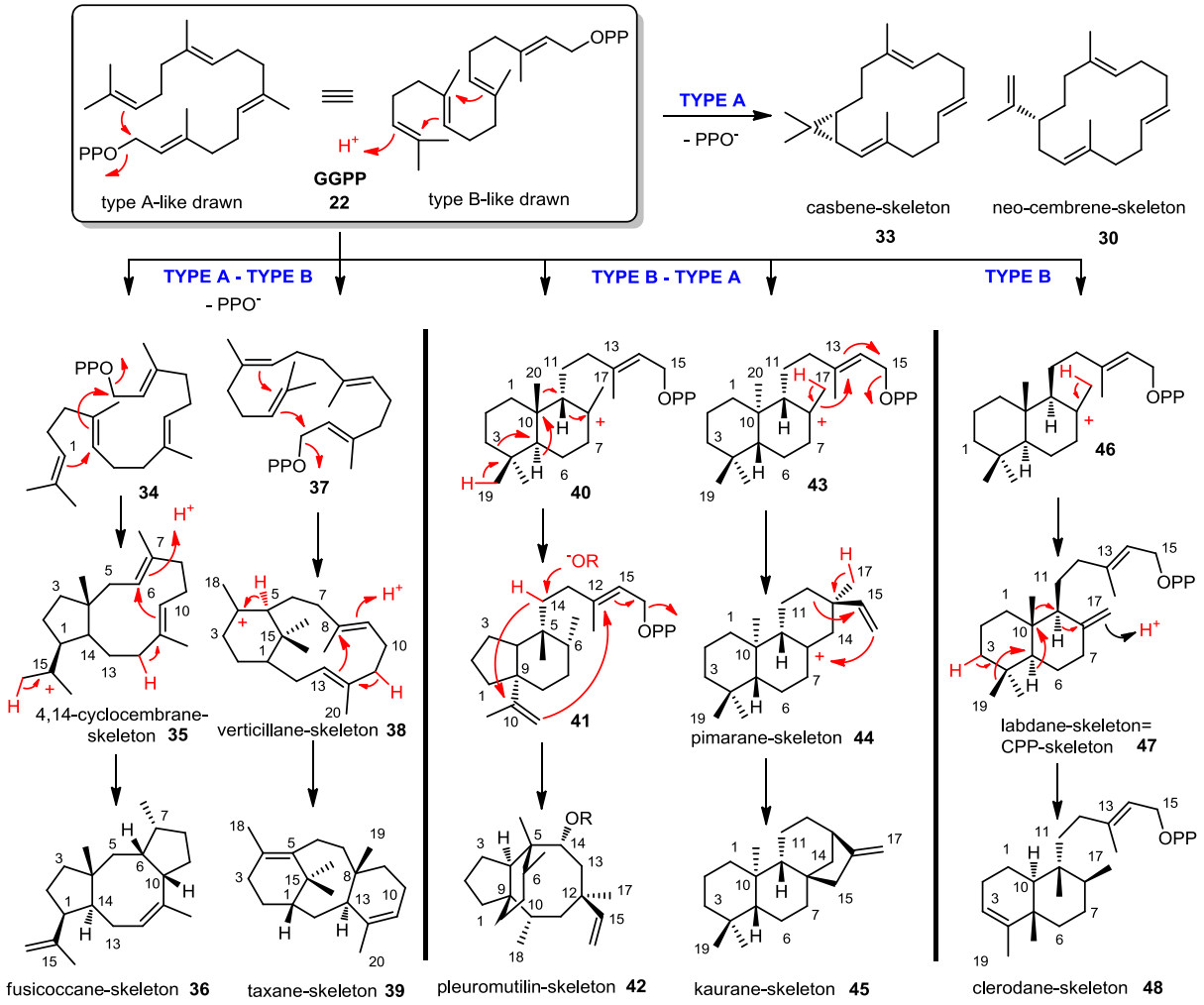


Figure 9: Different types of cationic GGPP-cyclizations, affording different carbon-skeletons.

Type B Cyclizations:[12]

Classic type B cyclizations are in fact the initial step of the type B – type A cyclization. The formation of the $\Delta^{4,5}$- and $\Delta^{9,10}$-single bonds result in the formation of intermediate **46**. Proton abstraction on C17 leads to the formation of **47**, the labdane-skeleton. This carbon skeleton can undergo double *Wagner-Meerwein* rearrangement (C19 to C5 and C20 to C9) and double [1,2]-hydride shift (C5-H to C10-H and C9-H to C8-H) to the clerodane-skeleton (**48**) upon proton abstraction on C3 (Figure 9).[24]

1.3.2 Furanocembranoids

The first family of marine derived diterpenes discussed in this thesis is the family of furanocembranoids. Furanocembranoids possess a 14-membered carbon-macrocycle (**30**), accompanied by a furan (C3-C6) and a butenolide (C10-C12; C20) moiety, hence they are referred as "furanocembranolides" in older literature. Furthermore, furanocembranoids very often show similar substitution patterns among themselves and their congeners (Figure 10, Figure 11):

- C2 often is hydroxylated
- C18 can attain all possible oxidation states
- The $\Delta^{7,8}$ double bond often undergoes oxidation and subsequent transformation
- The $\Delta^{11,12}$ double bond of the butenolide often undergoes epoxidation
- C13 is often oxidized, usually bearing an acetoxy group

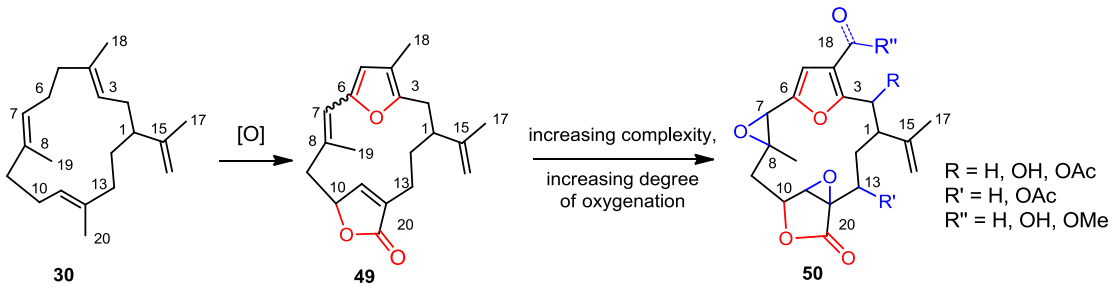


Figure 10: Common structural motives in furanocembranoids, including oxygenation pattern.

In terms of their established configurations, furanocembranoids are typically (*R*)-configured at C1. The double bond at $\Delta^{7,8}$ can be both (*E*)- or (*Z*)-configured. Interestingly, the corresponding epoxides appear to stem only from the (*E*)-configured alkenes, which could be an indication of the inherent instability of the other epoxides in the presence of the furan ring. (*Z*)-configured epoxides undergo rearrangements and epoxide-opening reactions to yield a tertiary alcohol at C8 (Figure 11).[1]

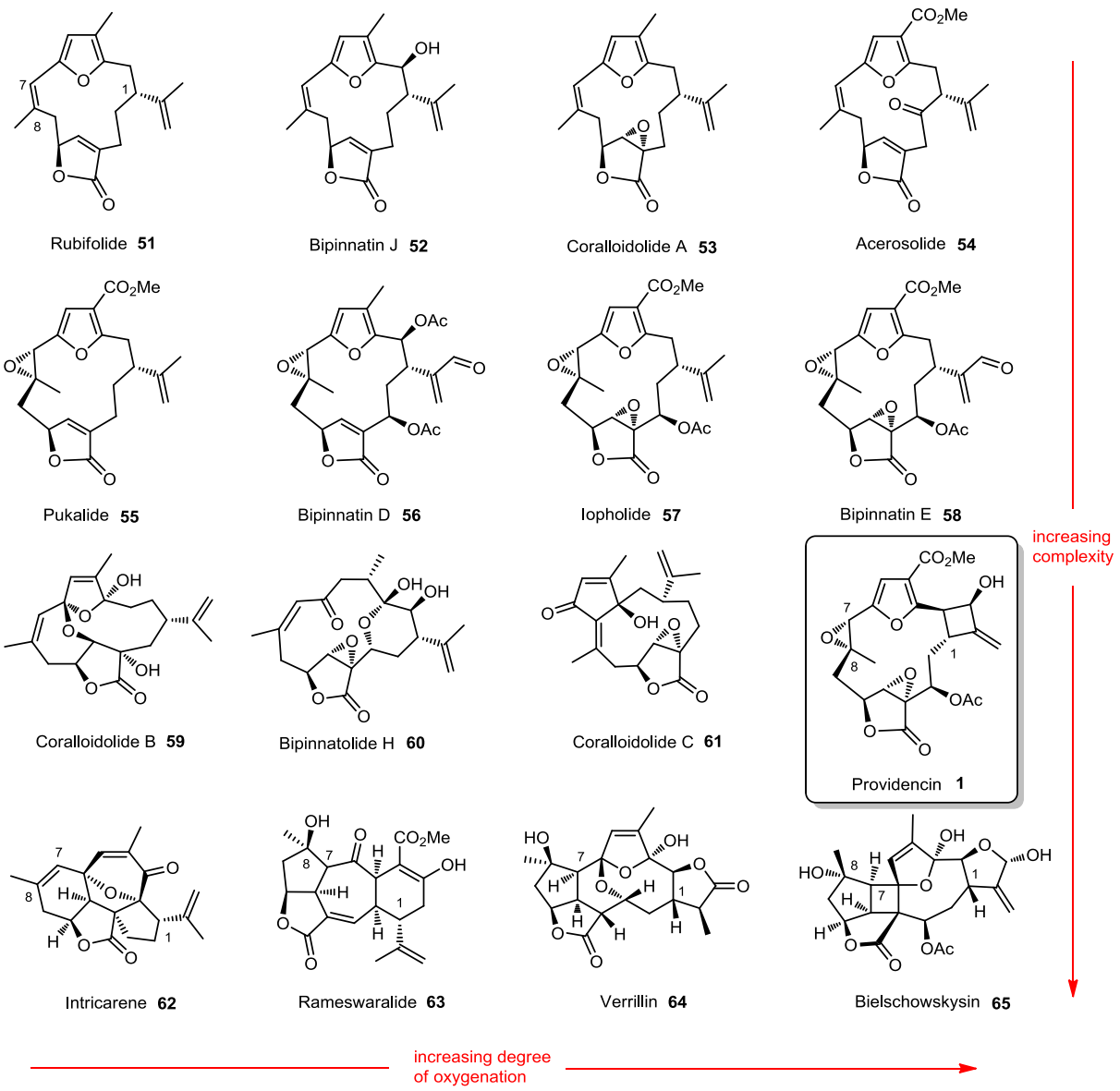


Figure 11: Representative members of the (furano)cembranoid family.

1.3.2.1 *Providencin*

Providencin (**1**) is a naturally occurring cytotoxin isolated from the Caribbean gorgonian octocoral *Pseudopterogorgia kallos* (Bielschowsky, 1918) by *Rodriguez* and coworkers.[3] The sea plume was collected near Providencia Island (Old Providence) located in the southwestern Caribbean Sea, among the oceanic islands, atolls and banks of the San Andrés and Providencia Archipelago, off the Nicaraguan shelf.

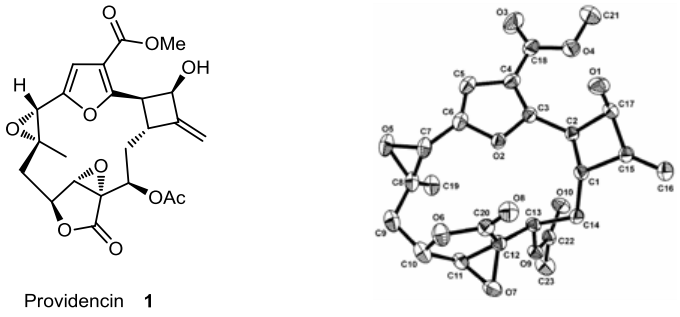


Figure 12: ORTEP diagram of Providencin with 30% probability of ellipsoids.

1.07kg of sun dried animal specimens were frozen, cut in small pieces and extracted with a 1:1 mixture of CH_2Cl_2 and methanol to result 166 g of crude extract. This was portioned between hexanes, $CHCl_3$ and EtOAc. The chloroform soluble material was purified by repeated silica gel and size exclusion chromatography to yield 20 mg (0.0019% w/w dry weight) of pure Providencin. Structure elucidation was performed by ^{1}H NMR, ^{13}C NMR, DEPT, ^{1}H-^{1}H-COSY, HMQC, HMBC, two dimensional NOESY, HREIMS, IR and single-crystal X-ray analysis (Figure 12). Providencin was isolated as an amorphous colorless solid with an optical rotation of $[\alpha]^{20}_{D}$=+7.9° (c = 1.2, $CHCl_3$). Its highly oxygenated hexacyclic structure is based on a previously undescribed bicyclo[12.2.0] hexadecane ring system.[3]

Providencin (**1**) shows modest in vitro cytotoxic activity against MCF-7 (breast cancer), NCI-H460 (nonsmall lung cancer) and SF-268 (CNS cancer).

Biosynthetically, Providencin seems to stem from Bipinnatin E (**58**, Figure 13). *Via* a Norrish type II reaction a proton in α-position to the furan moiety is abstracted and a stabilized benzylic radical is generated. After formation of an alkoxy radical both radicals recombine to the cyclobutanol ring, generating the final structure of Providencin (**1**).[1]

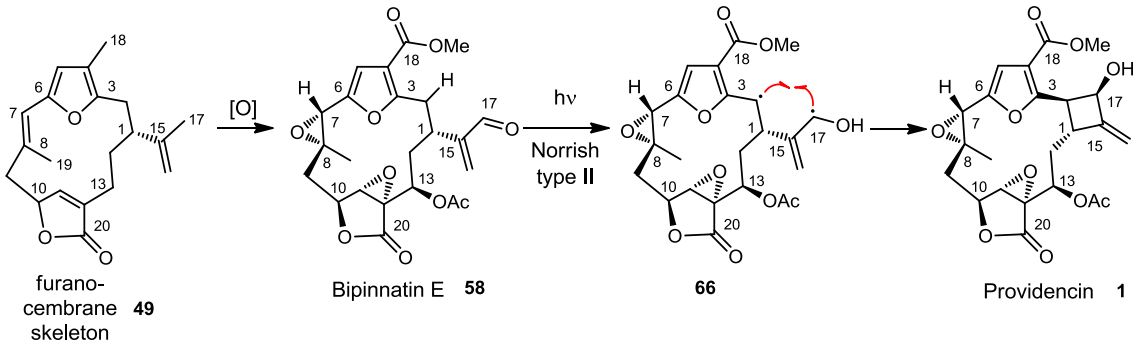
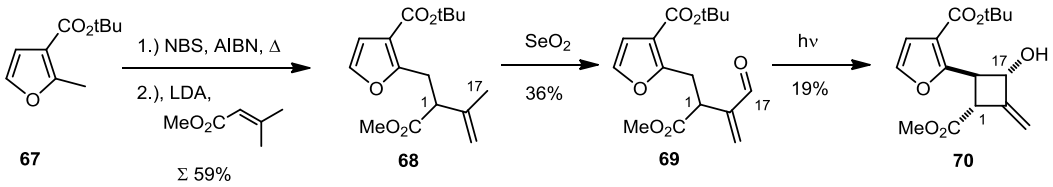


Figure 13: Speculative biosynthesis of Providencin.

This biosynthetic proposal is corroborated by the findings of Pattenden *et al.*, who published in 2006 the synthesis of a model system of the eastern part of Providencin (**1**). Starting from intermediate **68** bearing an isopropenyl group at C1, they were successful in oxidizing the allylic position on C17 (**69**), using SeO_2. Thus, they were able to install a structural motif, similar to that of Bipinnatin E (**58**). After irradiation with a 400W medium pressure Hg-lamp, they could isolate the desired cyclobutanol model system (**70**) in modest yield. Therefore, the group was able to show an experimental proof for the proposed biosynthetic pathway (Scheme 1).[25]



Scheme 1: Experimental corroboration of the proposed biosynthetic pathway of Providencin (1), by Pattenden *et al.*

Structurally, Providencin (**1**) shows some really challenging motifs. Due to the high ring strain the butenolide moiety is in a perpendicular position to the furan. The four-fold substituted cyclobutane ring, nine stereogenic centers and the high oxygenation degree make it a demanding target.

1.3.2.2 Sarcofuranocembranolide A

Sarcofuranocembranolide A (**75**) is a furanocembranoid with a rearranged unique 8,19-bisnorfuranocembrenolide carbon skeleton featuring a 13-membered macrocycle. It was isolated by Namikoshi *et al.* by the methanolic extraction of wet *Sarcophyton* sp. (Manado, North Sulawesi, Indonesia) together with 6 other cembrane-type natural products.[26] The crude extract was concentrated and purified by SiO_2, Sephadex LH-20 and Hypersil ODS column chromatographies followed by HPLC to yield 3.6 mg of pure Sarcofuranocembranolide A (**75**). Structure elucidation was performed by ^{1}H NMR, ^{13}C NMR, 2D NMR, HRFABMS and IR. An X-ray analysis is not available.

A structural specialty of Sarcofuranocembranolide A (**75**) is the contracted 13-membered carbon-macrocycle. The authors propose two different mechanisms for the ring contraction: an acyloin like and a *semi* pinacol like. Following the acyloin like pathway, the double bond first is dihydroxylated, followed by the oxidation of the secondary alcohol to the corresponding ketone (**71**). After an acyloin like rearrangement to intermediate **72** and deacetylation the carbon skeleton of Sarcofuranocembranolide A (**75**) is completed.[27] Following the semipinacol like pathway, the initiating step is an allylic oxidation at C9, followed by a dihydroxylation at C7 and C8. Now triol **73** undergoes a semipinacol like rearrangement furnishing intermediate **74**.[28] Deacetylation furnishes the carbon-skeleton of Sarcofuranocembranolide A (**75**) (Figure 14).

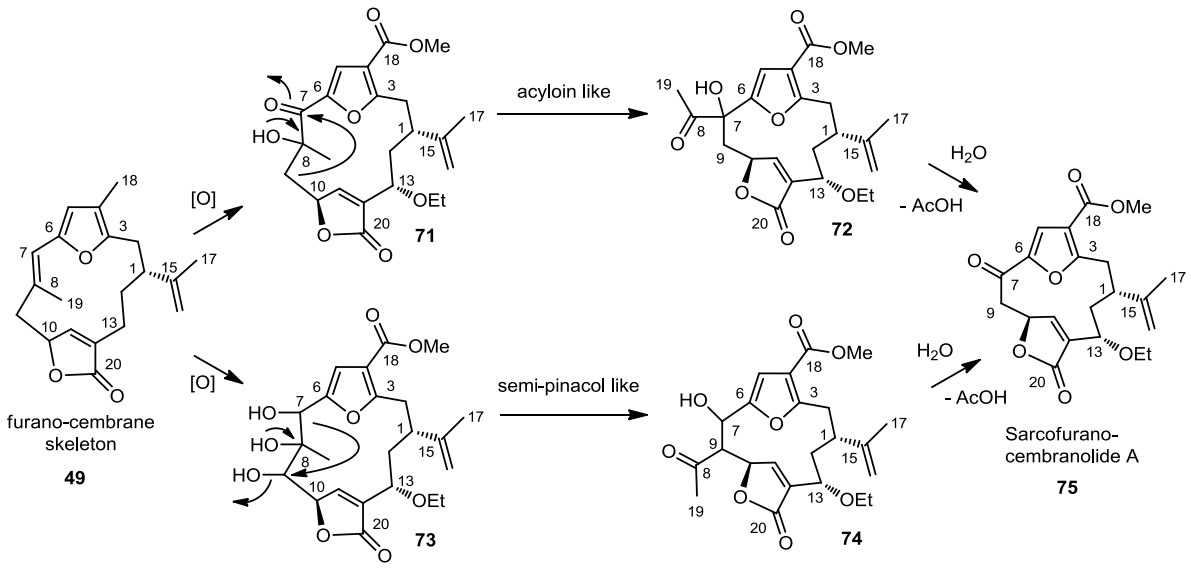


Figure 14: Speculative biosynthetic rearrangements to form 13-membered macrocycle of Sarcofuranocembranolide A.

1.3.3 Pseudopteranes

Pseudopteranes exhibit a slightly rearranged carbon-skeleton compared to the furanocembranoids. The 14-membered macrocycle is ring contracted to a 12-membered macrocycle accompanied by the formation of a second isopropenyl moiety (**76**).[1]

Rodriguez *et al.* showed that upon irradiation the furanocembrane skeleton of Bipinnatin J (**52**) rearranged to the pseudopterane skeleton of Kallolide A (**77**) *via* a photochemically allowed suprafacial [σ2s + π2s] 1,3-allyl shift. Thermally, this process is also Woodward-Hoffmann allowed, but would proceed under inversion of configuration. Upon irradiation, the $\Delta^{9,10}$-σ-bond of **52** migrates suprafacially to C7 with concomitant reorganization of the π-system. The configuration at C10 remains unchanged during the migration of the butenolide moiety (Figure 15).[29]

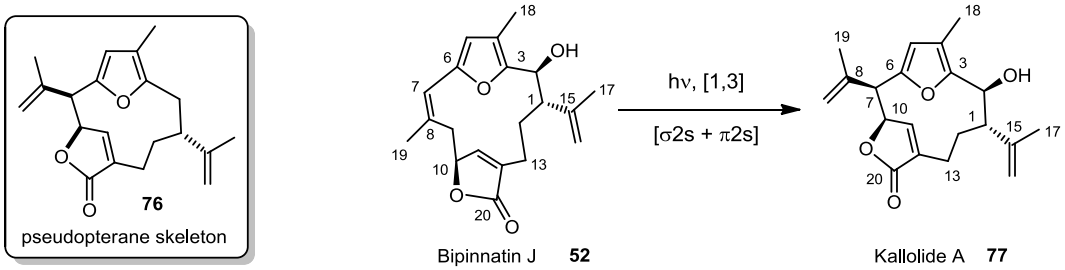


Figure 15: [1,3]-pericyclic rearrangement from furanocembranoid Bipinnatin J to pseudopteranes Kallolide A.

What remains to be investigated is whether these results represent a special case or reflect the general biosynthesis of pseudopteranes. Like in every living organism it is possible that these arrangements are, at least in some cases, enzyme mediated or occur in presence of a special binding protein.

1.3.4 Gersolanes

Gersolanes possess a ring contracted 13-membered macrocyclic carbon skeleton. But unlike in the pseudopterane family, the ring contraction leads to the formation of an addition cyclopropane ring (**78**).[1]

As in the case above, *Rodriguez* and coworkers published the experimental proof of the photochemically allowed cembrane – gersolane skeletal isomerization. The authors postulate an antarafacial [σ2a + π2a] [1,2]-group transfer. Upon irradiation, the $\Delta^{9,10}$-σ-bond of **52** migrates antarafacially to C7 and C8 with retention of configuration at C10 (**79**). Curiously, they observed an inversion of configuration at C2 selectively, which indicates the ease of formation of a "benzylic" carbo-cation in this position. Interestingly, they furthermore found traces of the oxidized furan product **81**, which is due to the formation of $^1O_2$ under these photochemical conditions (Figure 16).[29] It remains to be investigated, if this photo rearrangement is the general biosynthetic pathway.

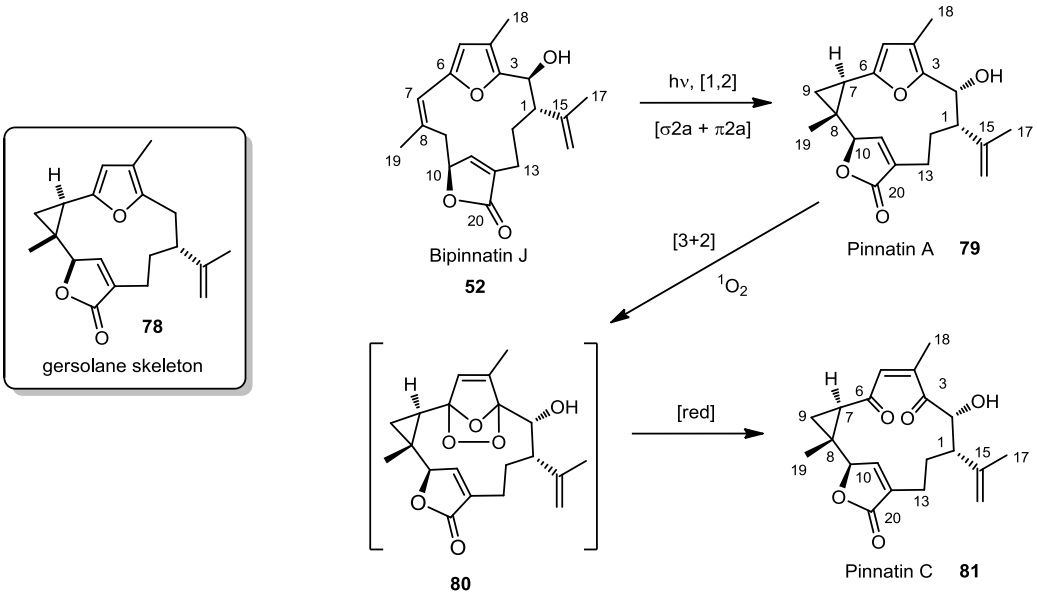


Figure 16: [1,2]-pericyclic rearrangement from furanocembranoid Bipinnatin J to gersolanes Pinnatin A & C.

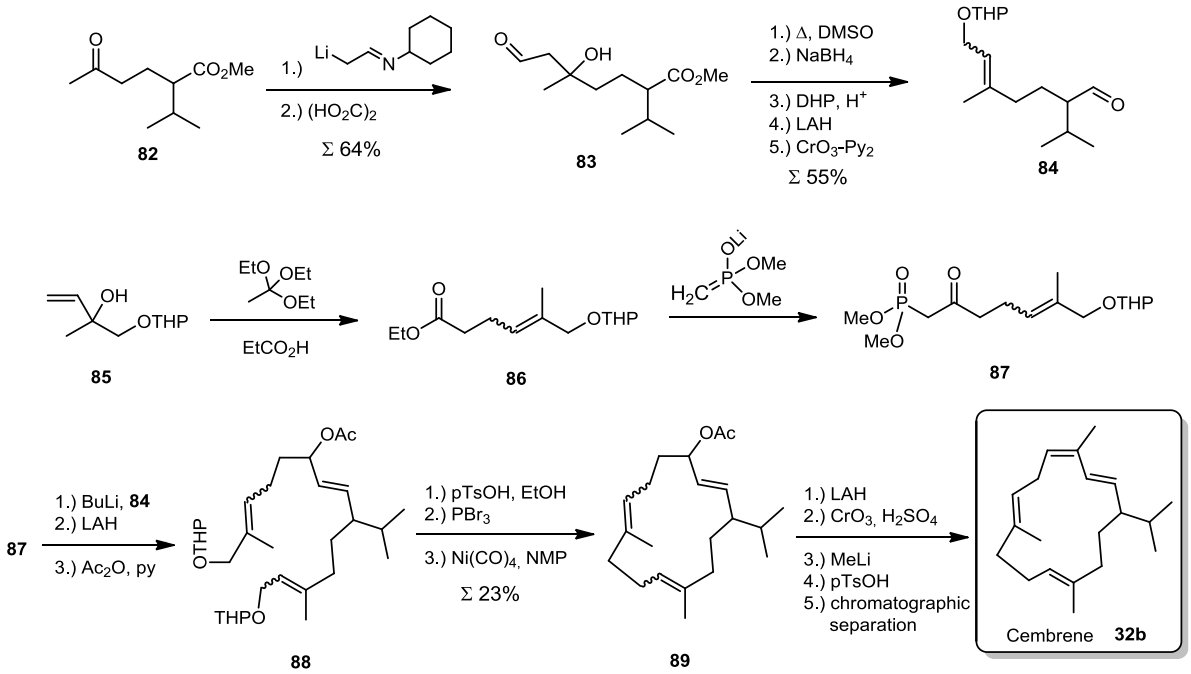
1.4 Selected Syntheses of Marine Diterpenes

The following syntheses of diterpenoids were particularly selected with regard to their structural relationship to Providencin (**1**) and Sarcofuranocembranolide A (**75**). The aim was to present an overview of syntheses using modern synthetic chemistry methods for the construction of a diterpenoid carbon framework.

Since Providencin (**1**) as well as Sarcofuranocembranolide A (**75**) exhibit an unique structure (cyclobutane and 13-membered macrocycle, respectively) only structurally related compounds can be presented. Due to the high ring strain in (*E*)-configured cembranes, most of the shown examples possess a (*Z*)-double bond geometry.

1.4.1 Dauben's Synthesis of Cembrene[30]

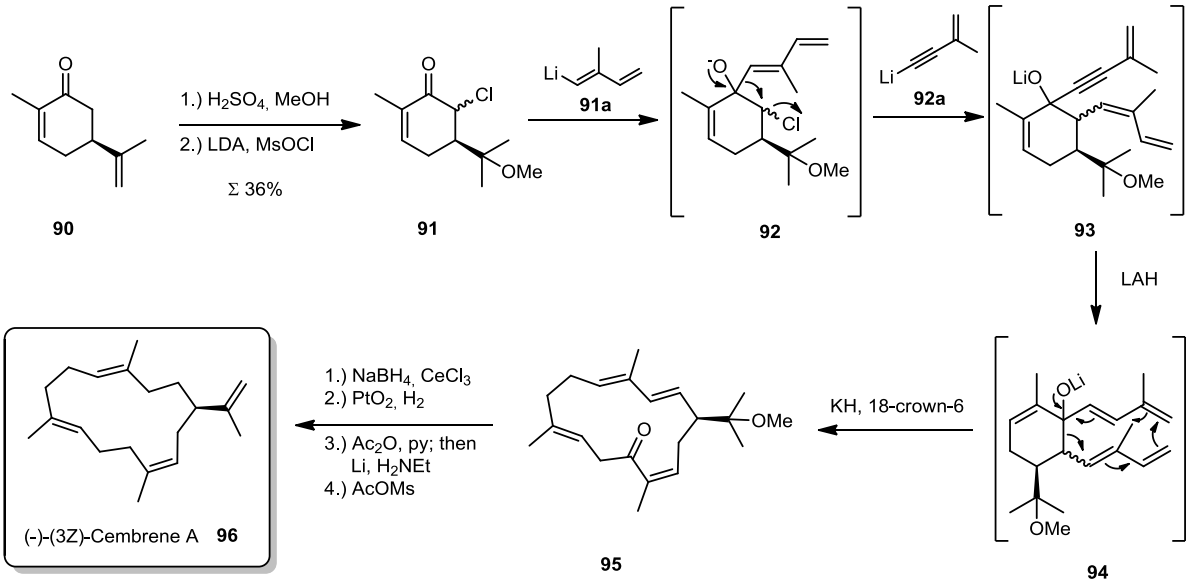
Dauben's approach was based on the findings of *Mirov* and *Roberts/Rowland* who showed that isocembrol upon treatment with mild acids stereospecifically yielded cembrene (**32b**).[31] This methodology was used in the last step for the introduction of the unstable diene system of cembrene (**32b**). Starting with **82**, the authors planned a nucleophilic addition – deprotection sequence yielding **83**. A reduction – protection – reduction sequence finally led to **84**, representing one of the two fragments of the convergent synthesis. The other fragment was synthesized starting from acetol THP ether by addition of vinyl lithium to yield **85**. Treatment of Intermediate **85** with ethyl orthoacetate under acidic conditions gave the *Claisen* rearranged product **86**.[32] After introduction of the β-keto phosphonate both fragments (**87** and **84**) were coupled by a HWE reaction giving >95% the *trans* isomer.[33] Reduction of the enone and acetylation yielded allylacetate **88**. Now the stage was set for double THP deprotection, introduction of the allyl bromides and $Ni(CO)_4$ mediated macrocyclization, yielding **89**. Reductive removal of the acetate, oxidation, methyl addition and acidic alcohol elimination yielded cembrene (**32b**) (Scheme 2).



Scheme 2: First total synthesis of the 14-membered macrocyclic core of cembrenes.

1.4.2 Wender's Synthesis of (-)-(*3Z*)-Cembrene A[34]

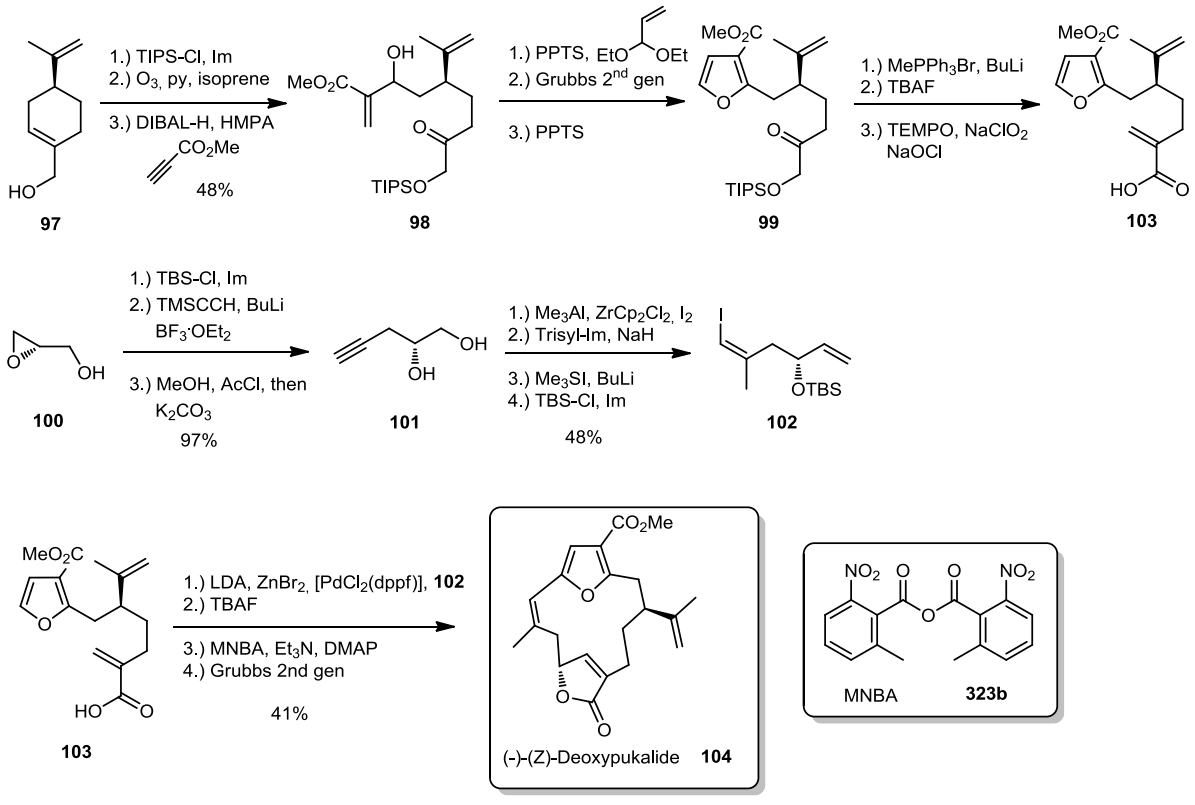
In 1985 *Wender* and *Holt* published a very short and atom economic approach to (*3Z*)-Cembrene A. Starting from (+)-Carvon (**90**) and by the addition of two isoprene units the authors were able to synthesize the target in only eight steps. In the first step methanol was added to the isopropenyl group under acidic conditions, affording the *Markownikoff* product.[35] Deprotonation with LDA and quenching with TfOCl afforded chloroketones **91**. Now the authors planned a tandem 1,2-addition – *semi* pinacol sequence,[28] which worked perfectly. First the 1,2 attack of 1-lithio-2-methyl-1,3-butadiene (**91a**) to the carbonyl moiety (**92**), followed by addition of lithium isopropenyl acetylide (**92a**). Upon warming up the molecule smoothly underwent *semi* pinacol rearrangement and addition of the alkynylide to the transiently liberated carbonyl (**93**).[28] Subsequent addition of LAH to the reaction mixture gave intermediate **94**, which was treated with 18-crown-6 and KH to induce an anion accelerated [5,5]-sigmatropic rearrangement to compound **95**. Now the ketone was reduced under *Luche* conditions and the excessive 1,2 disubstituted double bond was reduced using *Adam*'s catalyst.[36] [37] After acetylation the hydroxyl group was removed using *Birch* conditions.[38] Treatment with AcOMs yielded (-)-(*3Z*)-Cembrene A (**96**) in a very elegant way (Scheme 3).



Scheme 3: Pericyclic formation of the 14-membered macrocycle 95.

1.4.3 Donohoe's Synthesis of (-)-(*Z*)-Deoxypukalide[39]

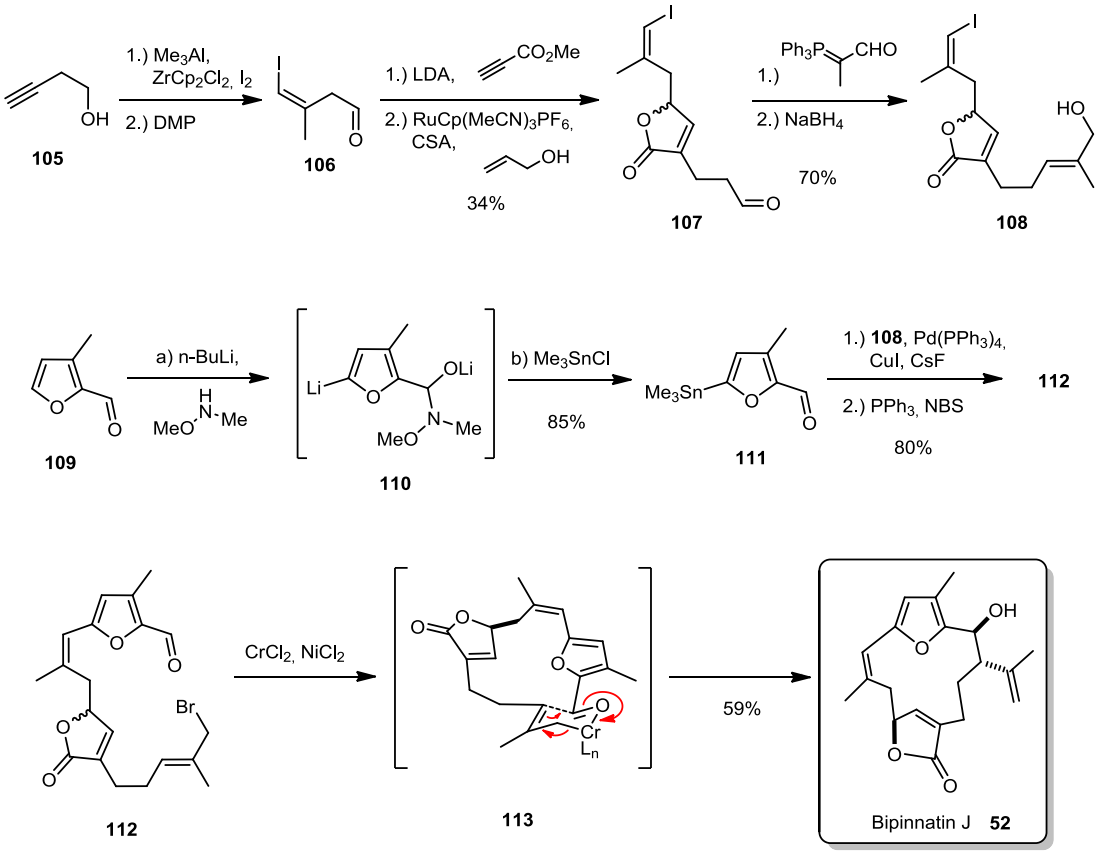
Donohoe *et al.* synthesized a terpene starting from a terpene. The elegant synthesis used perillyl alcohol (**97**) as starting material, which was converted to its TIPS ether and then carefully ozonolyzed at the more electron rich double bond. The resulting aldehyde was treated with the vinyl alane of methylpropionate to give *Morita-Baylis-Hillman* adduct **98** in 48% overall yield.[40] Treatment of **98** with acrolein dimethyl acetal in presence of PPTS gave a diene which was subjected to an olefin metathesis reaction using Grubbs 2nd generation catalyst (**GH2**) to provide furan **99** after treatment with PPTS. Olefination with methyl-*Wittig*-ylid, cleavage of the TIPS-ether and subsequent TEMPO oxidation of the resulting primary alcohol to the corresponding carboxylic acid gave intermediate **103** in 90% yield. Furthermore, (*S*)-glycidol (**100**) was converted into its TBS-ether and the epoxide was opened with deprotonated TMS-acetylene. After deprotection to **101** and carbo alumination at elevated temperature the resulting (*Z*)-vinyl iodide was obtained. This intermediate was treated with trisyl imidazole (*Hicks-Fraser-Reid* reaction) to give the epoxide which was then converted to the corresponding allyl alcohol by a protocol developed by *Alcaraz*.[41] [42] The resulting allylic alcohol was finally re-protected providing **102** in an excellent overall yield. After *Negishi* coupling of fragment **102** and **103**, the silyl group was cleaved.[43] The secondary alcohol was used for a macro lactonization according to *Shiina* and the butenolide moiety was closed by a metathesis reaction (Scheme 4).[44] [45]



Scheme 4: Donohoe's macrolactonization strategy.

1.4.4 Trauner's Synthesis of Bipinnatin J[46]

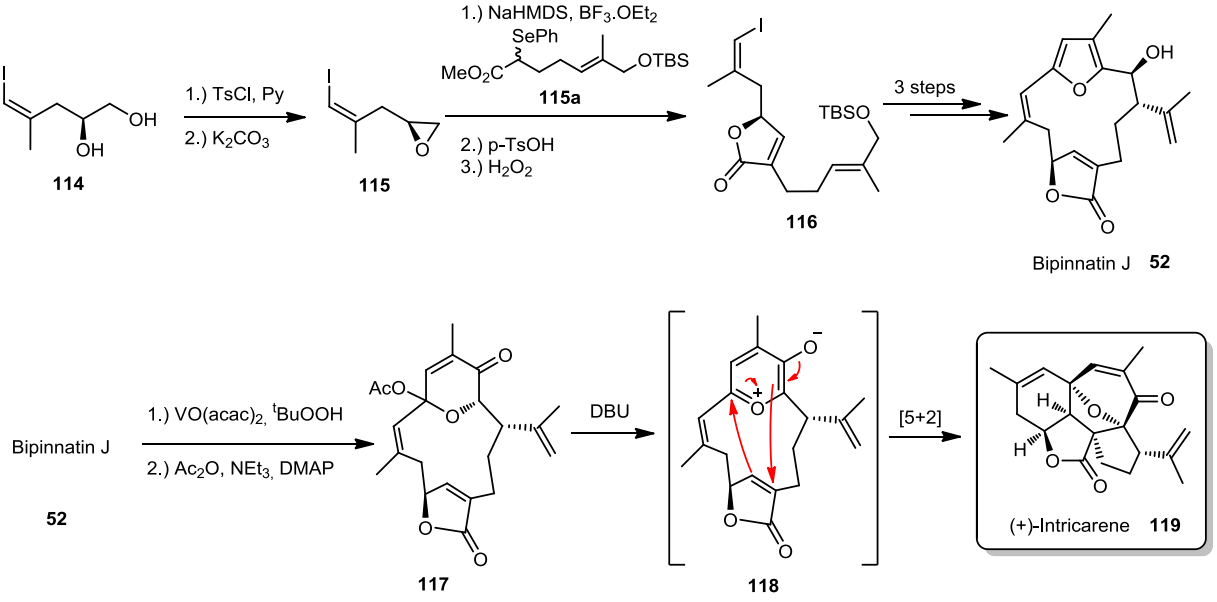
In 2005 Trauner *et al.* published a protecting group free total synthesis of racemic Bipinnatin J (**52**). Starting from 3-butyn-1-ol (**105**) the authors performed a carbo-alumination reaction followed by an oxidation with Dess-Martin-Periodinane (DMP). To the resulting aldehyde **106** methyl propiolate was added to afford a propargylic alcohol, which was subsequently converted with allyl alcohol by a Ru-catalyzed *Trost* enyne reaction to aldehyde **107** in 52% yield.[47] Now the stage was set for chain elongation by a *Wittig* olefination.[48] The resulting aldehyde was immediately reduced with $NaBH_4$ to afford allylic alcohol **108**, which represents the southern fragment of the convergent synthesis. The northern fragment was synthesized from 3-methyl-furfural (**109**). In a single step the authors were able to lithiate position 5 (**110**) and subsequently transform this species to the corresponding stannyl furfural **111** in 85% yield by the addition of Me_3SnCl. Both fragments were combined by a *Stille* cross coupling reaction in 92% yield.[49] After transforming the primary allylic alcohol in its bromide **112** by a modified *Appel* reaction using NBS and PPh_3,[50] the stage was set for the final key step of the synthesis: the transformation of **112** by a *Nozaki-Hiyama-Kishi* reaction to Bipinnatin J (**52**) in 59% yield.[51] Remarkably, almost only a single diastereoisomer (*d.r.* > 9:1) was formed, which was explained by the rigidity of **113** and the defined six-membered transition state of the reaction (Scheme 5).



Scheme 5: Trauner's protecting group free synthesis of Bipinnatin J (52).

1.4.5 Pattenden Synthesis of (+)-Intricarene[52]

In 2006 *Pattenden* presented a stereoselective synthesis of Intricarene (**119**). In fact this total synthesis made use of the actuality that Bipinnatin J (**52**) could be transformed in a biomimetically manner into Intricarene, so two total syntheses actually were presented. As the starting material compound **114** was used. Donhoe *et al*. made use of its enantiomer two years later for the synthesis of Deoxypukalide (**104**).[39] Compound **114** was transformed into the corresponding epoxide **115**, which was attacked by the sodium-enolate of **115a** in a non stereo specific way. After closure of the lactone and elimination of the selenium-species a *Stille* coupling with 3-methyl-furfurylstannane (**111**) was performed.[49] Hydroxy-bromide exchange and subsequent NHK ring closure completed the synthesis of Bipinnatin J (**52**).[51] An *Achmatowicz*-type reaction and acetylation afforded intermediate **117**, which formed upon treatment with base 1,3-dipol **118**.[53] This underwent a [5+2] cycloaddition to Intricarene (**119**) in overall 10% yield (Scheme 6).

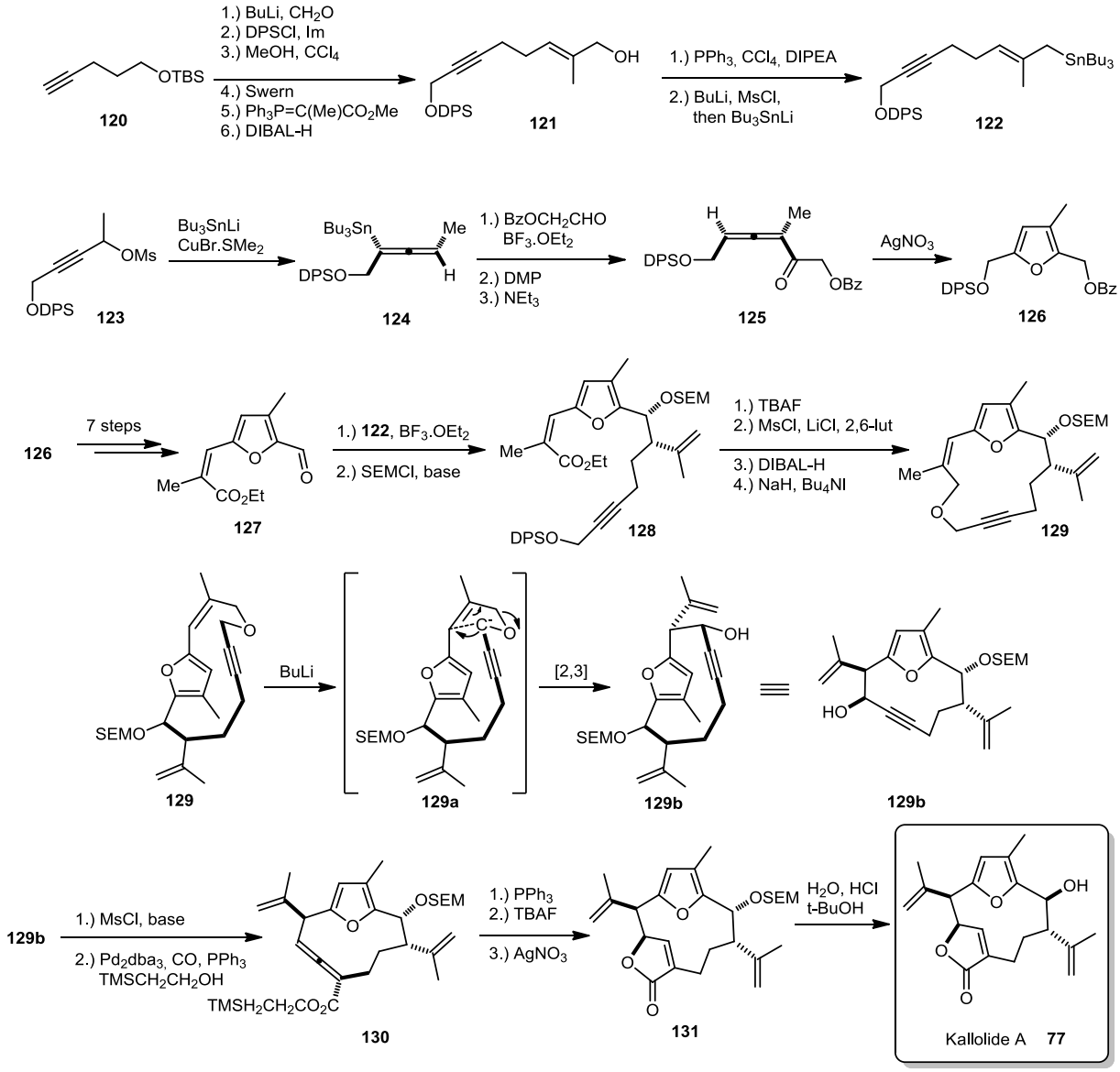


Scheme 6: Pattenden's [5+2] cycloaddition approach to Intricarene 119.

1.4.6 Marshall's Synthesis of Kallolide A[54]

This landmark synthesis was published in 1998. It started with TBS-protected pent-4-yne-1-ol (**120**), which was C_1 chain elongated at C5. The resulting primary alcohol was protected and the TBS group was cleaved. After an oxidation, (*E*)-selective *Wittig* olefination, reduction sequence allylic alcohol **121** was obtained,[48] which was transformed first into its chloride by an *Appel* reaction and then to the corresponding allylstannane by lithiation and adjacent transmetalation.[50] Intermediate **122** represented the southern fragment of the convergent synthesis. The northern fragment was synthesized starting from **123**.

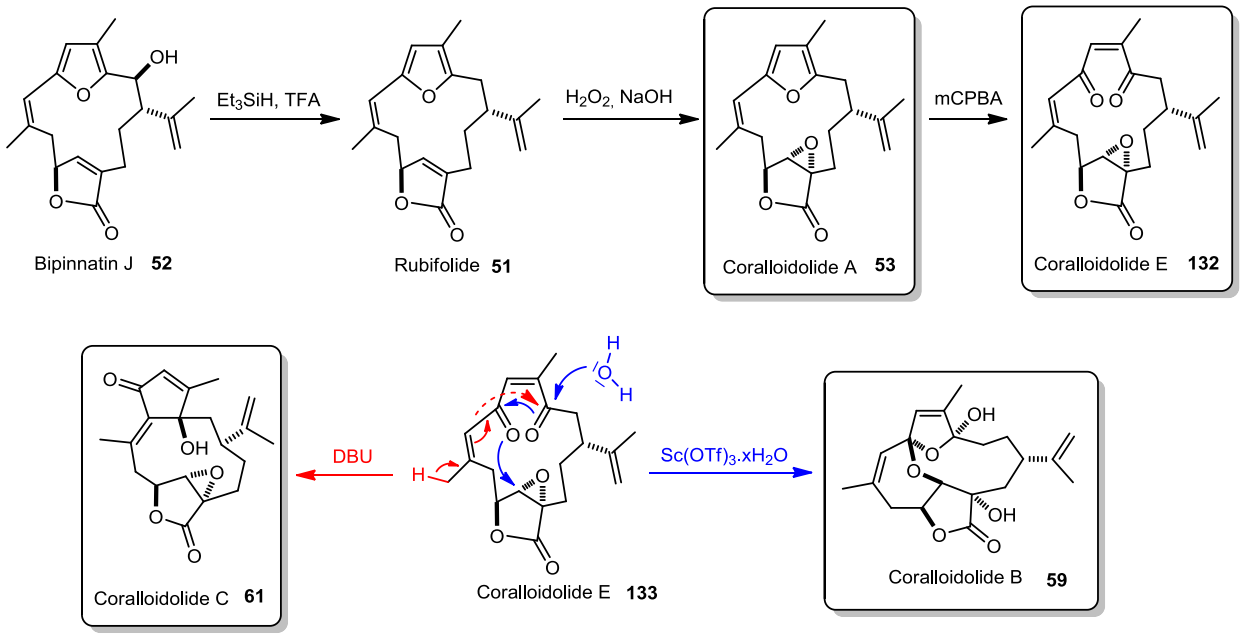
Conversion with Me_3SnLi gave allene **124**, which was reacted with benzoyl protected glycolaldehyde. After oxidation and basic allene formation (**125**), aromatization was performed under $AgNO_3$ catalysis. Seven steps were needed to transform **126** into **127**. $BF_3{\cdot}OEt_2$ mediated fragment coupling furnished the *syn* S_N2' product, which was converted to **128**. A *Finkelstein* reaction,[55] subsequent reduction of the ester and a *Williamson*'s macro-etherification were conducted.[56] Intermediate **129** was treated with n-BuLi and smoothly underwent a [2,3]-*Wittig* rearrangement. The resulting propargylic alcohol was mesylated. Pd_2dba_3 mediated CO insertion in the presence of $TMSCH_2CH_2OH$ gave the allenic ester, which had to be *cis*/*trans* isomerized with PPh_3. TBAF mediated silyl deprotection followed by an oxidative butenolide formation afforded intermediate **131**, which only had to be isomerized at the C2 position. This was performed *via* a S_N1 mechanism, according to findings of Abramson *et al.* (Scheme 7).[57]



Scheme 7: Marshall's synthesis of Kallolide A using extensive allene chemistry.

1.4.7 Trauner's Syntheses of Coralloidolides A, B, C and E[58]

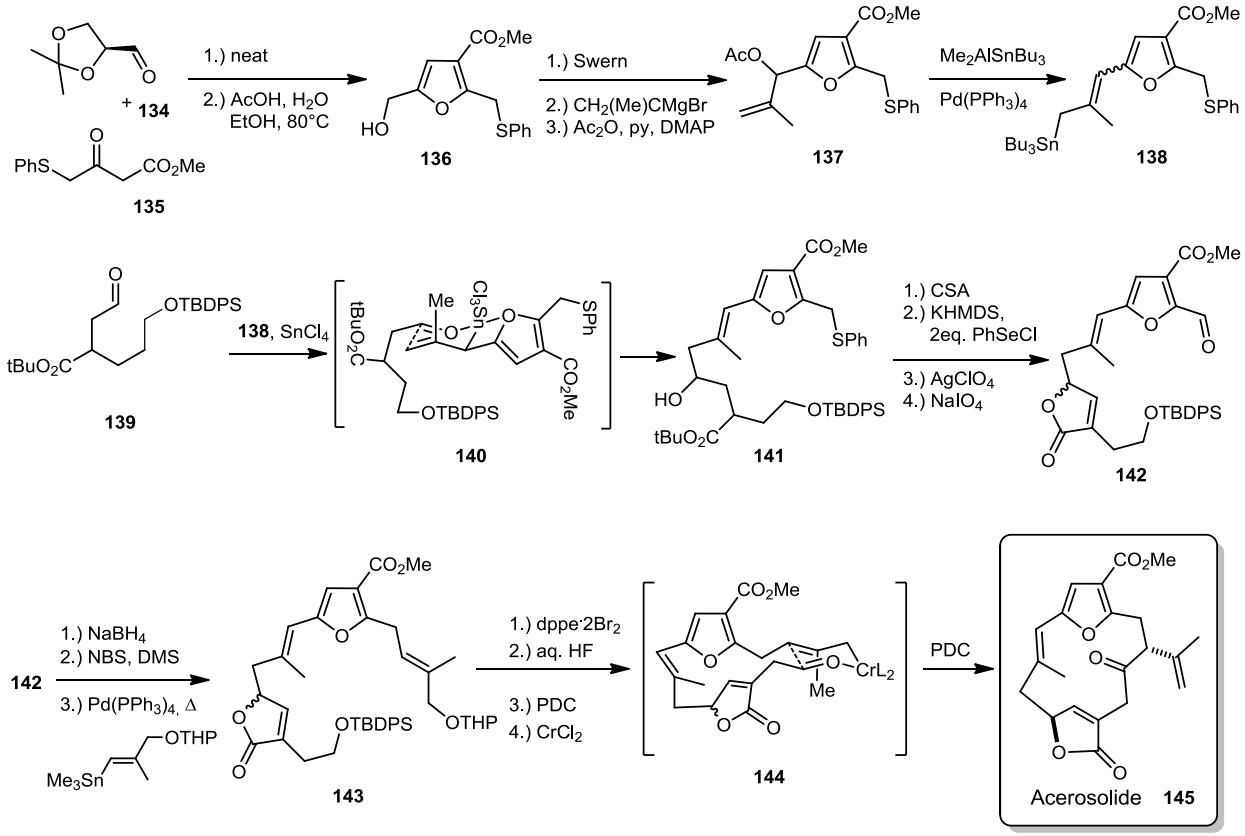
In 2010 Trauner *et al.* published biomimetic skeleton rearrangements of Bipinnatin J furnishing the Coralloidolide series. Interestingly, the Coralloidolides were the first furanocembranoids found in a Mediterranean organism, in contrast to most other members of the family, which are of Caribbean origin. Bipinnatin J (**52**) was reduced with Et_3SiH and CF_3CO_2H to Rubifolide (**51**). *Scheffer-Weitz* conditions led to Coralloidolide A (**53**).[59] Subsequent oxidation with *m*CPBA gave Coralloidolide E (**132**). Under Lewis acidic conditions Coralloidolide E (**132**) rearranged to Coralloidolide B (**59**), whereas under basic aldol conditions it gave Coralloidolide C (**61**). The authors report that both transformations were challenging. Therefore a careful screening of reagents was necessary to provide selective conversions (Scheme 8).



Scheme 8: Trauner's biomimetic transformations in the Coralloidolide-series.

1.4.8 Paquette's Synthesis of Acerosolide[60]

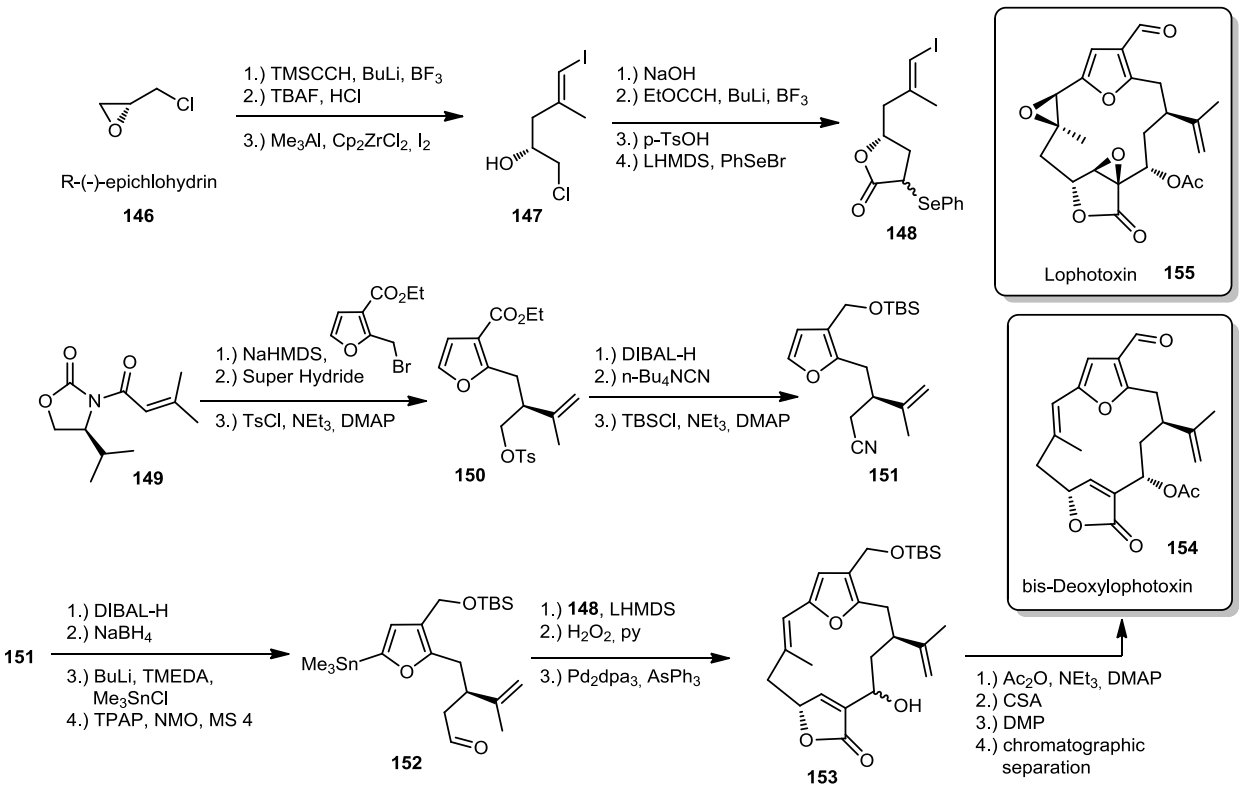
In 1993 Paquette *et al*. published the first total synthesis of a 14-membered furanocembranoide. Starting from acetonide protected glyceraldehydes (**134**) the authors were able to synthesize furan **136** in a very short and concise sequence. After *Swern* oxidation,[61] isopropenyl-Grignard addition and acetylation (**137**), a Pd-mediated *Tsuji-Trost* reaction afforded allyl stannane **138** in an inconsequential mixture of double bond isomers.[62] This intermediate was reacted with aldehyde **139** to give compound **141** as a single double bond isomer *via* chair like transition state **140**. Now the stage was set for the acidic closure of the butyrolactone. After introduction of two phenyl-selenium groups, one in α-position of the furan, the other in α-position of the lactone, the mixed acetal next to the furan was oxidatively deprotected using $AgClO_4$. Now, the second selenium group was oxidatively eliminated with $NaIO_4$ to yield compound **142**. Intermediate **142** was reduced and brominated. After a Pd-mediated *Stille* cross coupling **143** was obtained in satisfying yield.[49] Deprotection-bromination and deprotection followed by oxidation gave the macrocyclization precursor, which was cyclized under NHK conditions *via* transition state **144**.[51] A final oxidation step completed the synthesis of Acerosolide (**145**) (Scheme 9).



Scheme 9: Paquett's synthesis of Acerosolide.

1.4.9 Pattenden's Synthesis of Bis-Deoxylophotoxin[63]

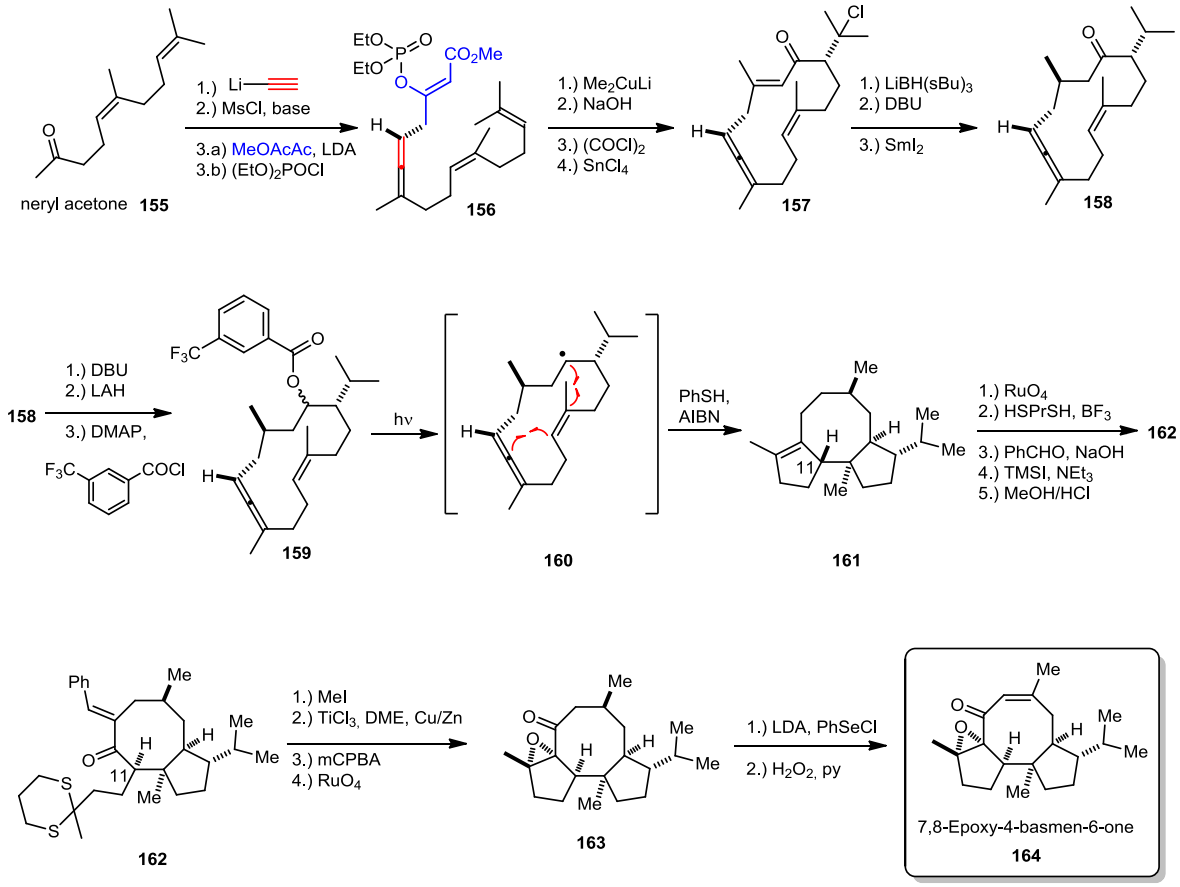
Pattenden's approach started with (*R*)-(-)-epichlorhydrin (**146**). TMS-acetylene selectively opened the epoxide. The formation of a *Schlosser-Fouquet* product was not observed.[64] Carboalumination provided (*E*)-vinyl iodide **147**. Construction of the butyrolactone and introduction of the phenyl selenyl ether furnished selenolactone **148**. The eastern fragment was synthesized enantioselectively using diastereoselective *Evans*' auxiliary induction.[65] Therefore, **149** was alkylated with 2-bromomethyl-3-furoate in satisfying yield. After reductive cleavage of the auxiliary and tosylation of the resulting alcohol (**150**), the ethylester was reduced with DIBAL-H to the corresponding alcohol. Now the stage was set for C1-elongation with n-Bu_4NCN, protection of the furanoic primary alcohol to yield **151**. A two step reduction protocol of the cyanide to the corresponding alcohol, treatment with n-BuLi and Me_3SnCl and subsequent oxidation finished the eastern fragment **152**. Both fragments were coupled in an aldol reaction and the phenylselenium ether was oxidatively eliminated. An intramolecular *Stille* reaction under the conditions described by Farina *et al.* (addition of $AsPh_3$) led to the desired macrocycle **153**,[66] that was further acetyleated, deprotected and oxidized to bis-Deoxylophotoxin (**154**) (Scheme 10).



Scheme 10: Pattenden's auxiliary based synthesis of bis-Deoxylophotoxin.

1.4.10 Myer's Synthesis of (±)-7,8-Epoxy-4-basmen-6-one[67]

Starting with commercially available neryl acetone (**155**) the authors presented the total synthesis of racemic **164** in 1993, isolated from tobacco. After the addition of lithium acetylide to **155**, the resulting propargylic alcohol was mesylated and treated with the dianion of methyl acetoacetate. Diethyl chloro phosphate was added, resulting in vinyl phosphate **156**. Conjugate methyl addition, saponification, conversion into the acid chloride and macrocyclization by conditions developed by Kato *et al*. finally yielded **157**.[68] Conjugate reduction, treatment with DBU and subsequent reduction using methanolic SmI_2 led to **158**. After epimerization with DBU and reduction of the ketone, the resulting secondary alcohol was acylated with m-(trifluoromethyl)benzoyl chloride. Irradiation of intermediate **159** and subsequent isomerization of the resulting double bonds led to **161**, *via* a *5-exo-trig* pathway. The stereochemistry at C11 was inverted. Therefore, the authors had to oxidatively cleave the double bond, selectively protect the methyl ketone as its dithioacetale, perform a *Knoevenagel* condensation with benzaldehyde and,[69] finally, perform the epimerization at C11 *via* the silylenolether **162**. A deprotection, *McMurry* coupling,[70] epoxidation, glycol-cleavage sequence was necessary furnishing intermediate **163**. Installation of a final double bond yielded the desired 7,8-Epoxy-4-basmen-6-one (**164**) (Scheme 11).



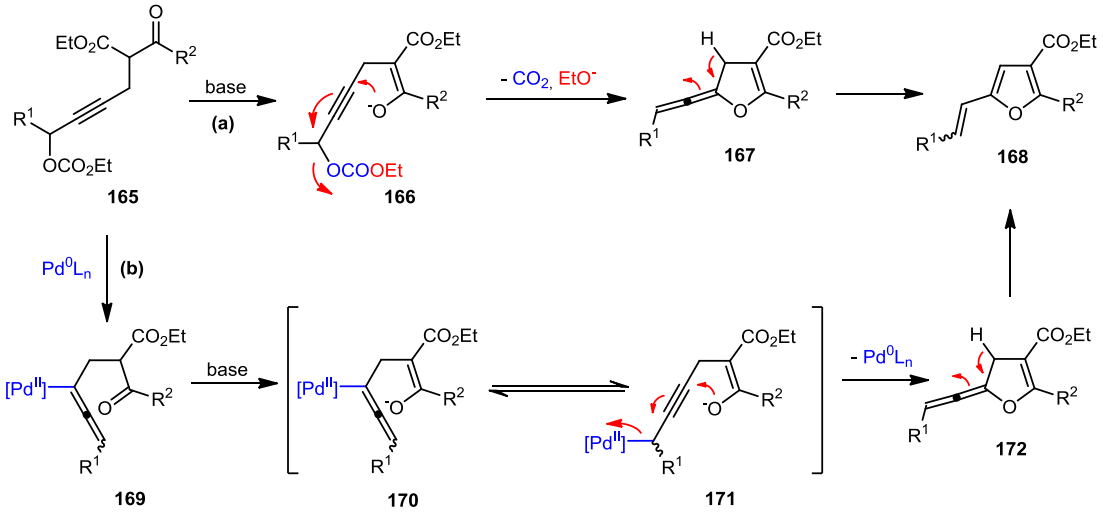
Scheme 11: Myer's radical transannular cyclization of a modified neocembrene skeleton.

1.5 Mechanisms of the Key Furan Cyclizations

In the following, a short overview and substrate scope of the used key furan cyclization is presented. The generation of a furan moiety is always accompanied with the generation of rigidity, but also the generation of aromatization energy. By a detailed discussion of the pertinent mechanism, a deeper understanding of the reactions' success or failure is obtained.

The Wipf Cyclization:[71]

This protocol is based on the fact, that alkynyl ketone enolates undergo a thermal S_N2' O-alkylation to provide the desired vinyl furans. Starting materials **165** are easily obtained by the alkylation of β-keto esters with the corresponding propargylic iodides. The initial step is the basic enolization of the carbonyl to **166**. The newly formed enolate **166** attacks the propargylic carbonate *via* a S_N2'-mechanism, forming fulvenoid structure **167**. During this process CO_2 and ethanol is liberated, which is an enormous entropic advantage. Furthermore, **167** smoothly forms the heteroaromatic compound **168**, due to liberation of the aromatization energy. An alternative mechanism takes place, if a Pd-catalyst is used. Starting with a *Tsuji-Trost* like formation of a Pd-allene species **169**,[62] followed by a nucleophilic attack of the enolate of β-keto ester (**170**), intermediate **172** is formed. This can tautomerize to furan **168** (Scheme 12).

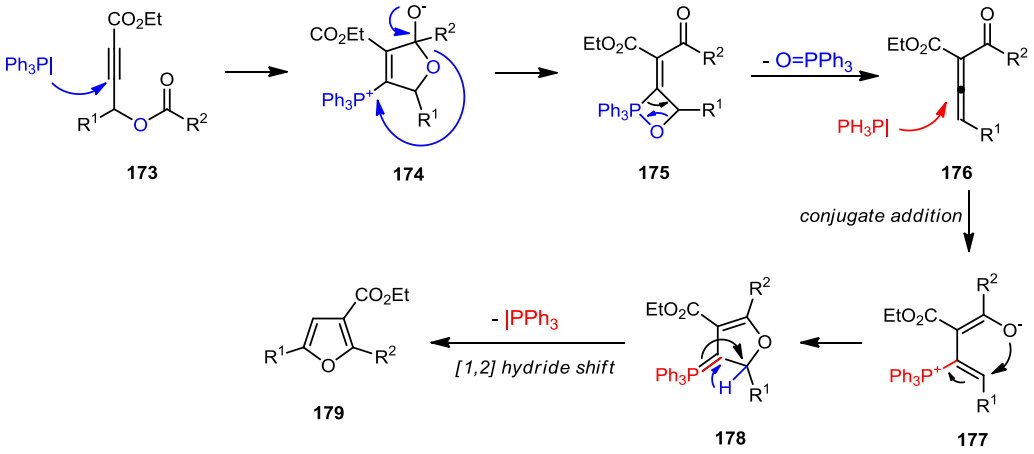


Scheme 12: Mechanism of the Wipf furan cyclization, (a) base mediated; (b) Pd-mediated.

As long as the substrates are base stable, or do not possess any functional groups, able to perform oxidative addition reactions (Pd-catalyst), this is a very versatile and useful method for the construction of vinyl furan moieties. Although this method facilitates the construction of 2,3,5-trisubstituted vinyl furans, it has a major disadvantage: the outcome of the geometry of the benzylic double bond cannot be controlled externally and is just substrate controlled.

The Krische Cyclization:[72]

The *Krische* protocol is based on the postulate that γ-acyloxy butynoates **173** react with stoichometric amounts of triphenylphosphine to allenic esters **176**, which, upon treatment with catalytic amounts of triphenylphosphine (or transition metal catalysts) react further to the substituted furans **179**. The starting material **173** is easily obtained by nucleophilic addition of propiolates to aldehydes, followed by an esterification with the desired carboxylic acid. The reaction starts with a conjugate addition of triphenylphosphine to the propiolate subunit. The newly formed nucleophile attacks the carbonyl moiety of the ester functionality and forms intermediate **174**. Compound **174** rearranges intermediately to betaine structure **175**, which upon elimination of triphenylphosphineoxid, releases allenic ester **176**. Conjugate addition of a catalytic amount of triphenylphosphine leads to intermediate **177**, which can cyclize to phosporylide **178**. After a [1,2]-hydride shift, elimination of triphenylphosphine and aromatization to a 2,3,5-trisubstituted furan (**179**) the sequence is finished (Figure 17). Furan cyclization proceeds most efficiently for substrates that embody electron deficient γ-acyloxy moieties, but work as well for other substrates.



product	**179a**	**179b**	**179c**	**179d**
yield	72%	81%	91%	77%
product	**179e**	**179f**	**179g**	**179h**
yield	83%	86%	83%	71%

Figure 17: Mechanism of the *Krische* cyclization and selected examples.

2 Results and Discussion

Providencin

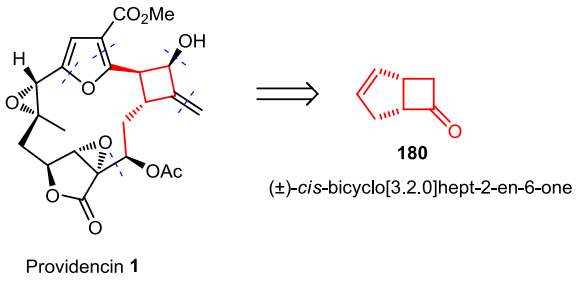
Providencin (**1**) drew our attention due to its complex molecular architecture and the ambition of accomplishing the first total synthesis of this amazing diterpene. From an organic chemist's point of view, the challenging hexacyclic structure of Providencin (**1**) and its very high degree of oxygenation (carbon/oxygen ratio = 2.3/1) make it an interesting synthetic target. Furthermore, possible medicinal applications require a larger amount of **1**, than the 20 mg batch isolated from the Caribbean gorgonian octocoral *Pseudopterogorgia kallos*.[3]

The main challenge of the synthesis of this molecule was the closure of the highly strained 13-membered macrocycle. Due to the high steric rigidness of the carbon skeleton (furan moiety in close proximity to the cyclobutane, butenolide moiety and "benzylic" epoxide) and the known high Prelog strain of 13-membered macrocycles,[73] macrocyclization techniques with a large entropic or enthalpic driving force were needed.[4, 6, 74] Therefore, either the metathesis reaction or the HWE reaction was chosen as the main strategy for macrocyclization.[5]

Another synthetic challenge was the regioselective installation of the 2,3,5-trisubstituted furan moiety. Many synthetic methodologies are known for the synthesis of furans,[75] but most of them either often require harsh reaction conditions, which are not suitable for highly functionalized molecules, or, build up the furan core from a linear, 1,4-dioxosubstituted alkyl chain. The second reason makes a convergent synthesis nearly impossible, thus, the methods presented by Wipf *et al.* and Krische *et al.* attracted our interest.[71-72]

2.1 Cyclobutane Series (*c*Bu)

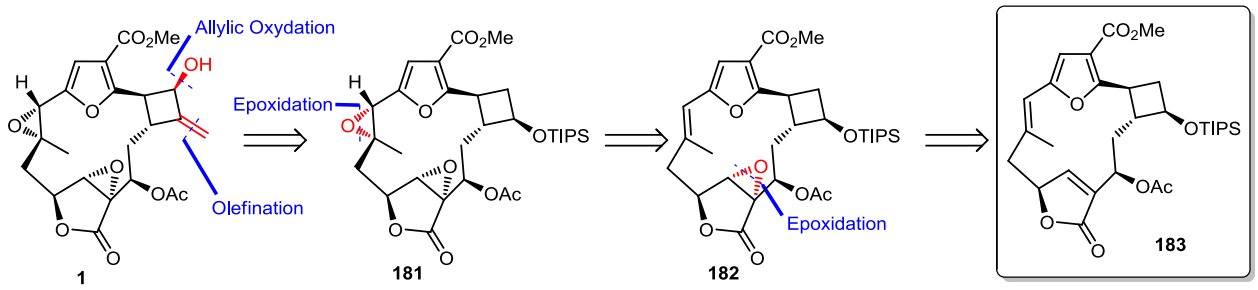
The idea of the cyclobutane series was the early introduction of the cyclobutane moiety into the molecule, since thermal or photochemical methods for the installation of a cyclobutane moiety often prove to be too harsh for highly functionalized molecules. Therefore, a starting material, already containing the desired moiety was chosen: (±)-*cis*-bicyclo[3.2.0]hept-2-en-6-one (**180**) (Scheme 13).



Scheme 13: Starting material of the *cBu*-series.

2.1.1 General Retrosynthetic Analysis

The first scissions of the retrosynthetic analysis were identical for all approaches of the *c*Bu-series. Starting with the removal of the allylic alcohol and the *exo*-methylene group on the cyclobutane moiety, leading to intermediate **181**, molecule degradation was continued by the reductive removal of the epoxides, which finally led to key intermediate **183**. The further systematic degradation of intermediate **183** differed mainly in the construction of the furan moiety and is described below (Scheme 14).



Scheme 14: Retrosynthetic simplification of Providencin (1) to key intermediate 183.

2.1.2 *Wipf*'s Furan Cyclization Approaches

All these approaches shared the palladium or base mediated furan closure developed by *Wipf* and coworkers,[71] where β-keto ester **195** was alkylated by different propargylic iodides. This method provided a very convergent approach, since complexity could be introduced through a simple alkylation reaction.

2.1.2.1 Ring Closing Metathesis Attempts

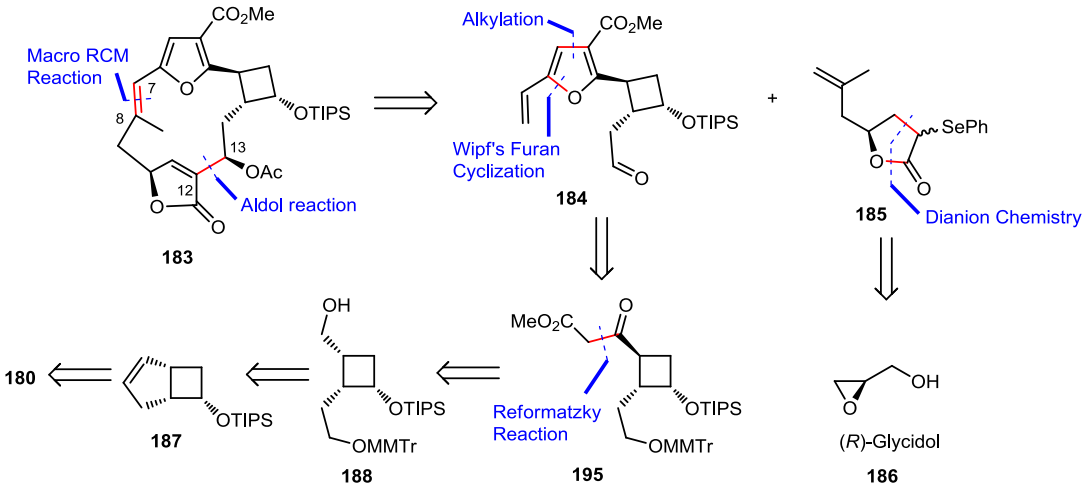
The intramolecular metathesis reaction provides many advantages, like an exothermic reaction profile, an increase of entropy and a high functional group tolerance. These convincing characteristics make it a promising choice for the macrocyclization reaction. Nevertheless, there are limitations, like hardly any possibilities for controlling the geometry of the formed double bond.

2.1.2.1.1 $\Delta^{7,8}$ Metathesis Approach

This approach is the most convergent one and has many advantages: The furan moiety, the butenolide moiety, as well as the cyclobutane moiety are already in place and only minor modifications have to be done after closing the strained macrocycle.

Retrosynthetic Analysis:

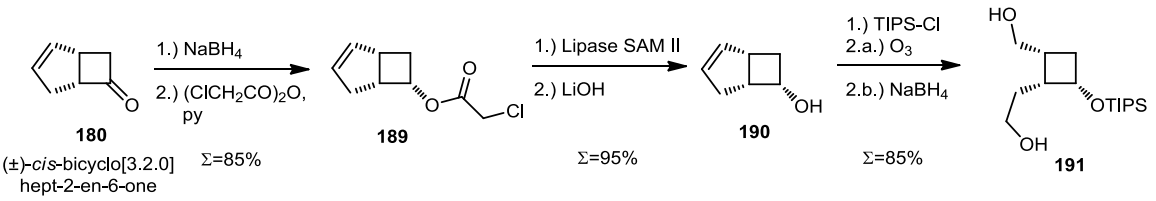
The simplification of key intermediate **183** started with the opening of the 14-membered carbo macrocycle at $\Delta^{7,8}$, followed by the cleavage of the $\Delta^{12,13}$ single bond, resulting in two equally large fragments **184** and **185**. Compound **184** could be further simplified to β-keto ester **195**, which could be derived from racemic (±)-*cis*-bicyclo[3.2.0]hept-2-en-6-one (**180**). The other fragment **185** could be simplified to (*R*)-glycidol (**186**), which is a cheap, chiral, and readily available starting material (Scheme 15).



Scheme 15: Retrosynthetic analysis of key intermediate 183 to commercially available starting materials.

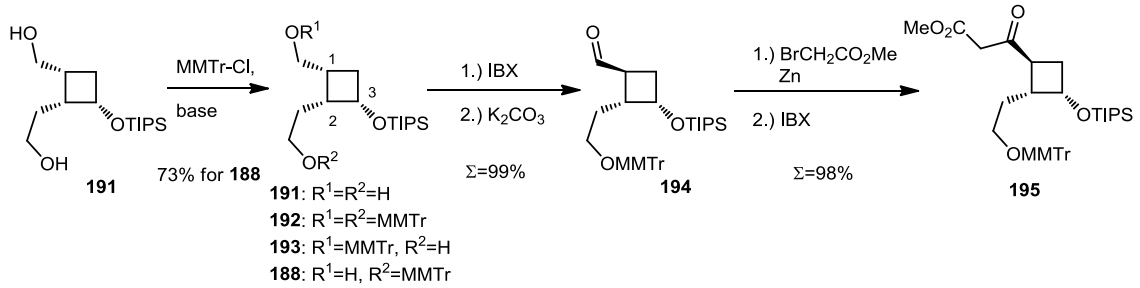
Synthesis:

The synthesis started with racemic (±)-*cis*-bicyclo[3.2.0]hept-2-en-6-one (**180**), that was reduced with $NaBH_4$ at low temperature using the open-book-effect to achieve a *d.r.* of >95:5. The resulting secondary alcohol was acetylated with chloro acetic acid anhydride yielding intermediate **189**, which was subjected to enzymatic chiral resolution using Lipase SAM II. The desired (*1S,5R,6S*)-isomer stayed untouched and was saponified using aqueous LiOH. Esterification of an analytical sample with (*S*)-*Mosher*'s chloride and analysis by ^{19}F-NMR showed an *e.e.* of 98%.[76] Primary alcohol **190** was protected as its TIPS-ether **187** and subjected to ozonolysis followed by reductive work up with $NaBH_4$. This completed the synthesis of key intermediate **191** (Scheme 16).



Scheme 16: Diastereoselective synthesis of intermediate 191.

The less hindered primary alcohol of diol **191** is converted to its MMTr-ether. Since both hydroxy moieties only have minor steric differences, this reaction proved to be troublesome in terms of regioselectivity. Figure 18 shows the used conditions and its results. Thereby, -42 °C proved to be the optimal temperature. Lower temperatures only resulted in dramatically longer reaction times, and higher temperatures resulted in worse regioselectivity. The correctness of the regiochemistry was approved by NOESY and HMBC experiments. Double-MMTr protected diol (**192**) was deprotected with CSA, thus recovering diol **191** (Figure 18).

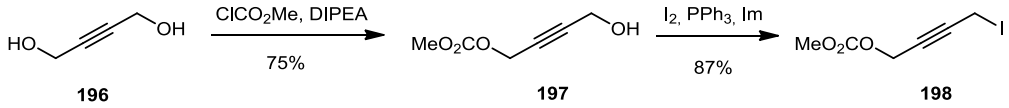


base	NEt_3	NEt_3	NEt_3	NEt_3	py	py	py	py
temperature	r.t.	0 °C	-42 °C	-78 °C	r.t.	0 °C	-42 °C	-78 °C
equivalents 193	1.0	1.0	1.0	1.0	1.0	1.0	***1.0***	1.0
equivalents 188	1.0	1.6	3.7	3.8	1.0	1.7	***4.1***	4.2

Figure 18: Selectivities for the mono-MMTr-protection of 188 and synthesis of key intermediate 195.

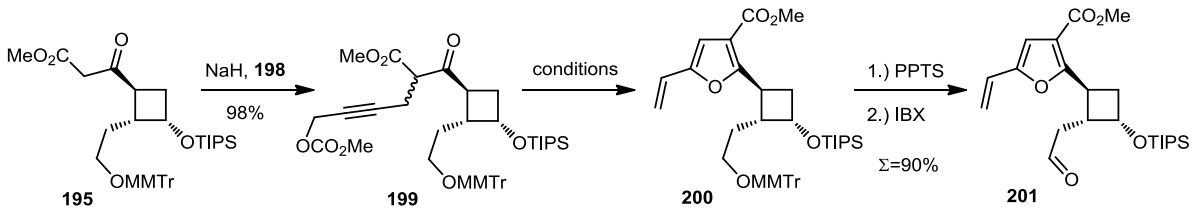
With **188** in hands, the stage was set for the oxidation of primary alcohol **188** to the corresponding aldehyde,[77] using IBX as oxidizing agent.[78] Epimerization at C1 with K_2CO_3 (**194**) and C_2-elongation was performed by a *Reformatzky* reaction and an aldol reaction,[79] but the latter gave worse yields (quantitative *vs.* 83%). The resulting secondary alcohol moiety was again oxidized with IBX,[78] giving key intermediate, *β*-keto ester **195** in very high yield (Figure 18).

The short synthesis of the side chain **188** was accomplished in two steps. But-2-yne-diol (**196**) was converted to its mono-methyl carbonate **197**, using methyl chloroformate, followed by an iodination of the remaining primary propargylic alcohol under modified *Appel* conditions (Scheme 17).[50]



Scheme 17: Synthesis of the side chain.

Deprotonation of β-keto ester **195** with NaH and subsequent alkylation with **198** furnished the furan cyclization precursor **199**. Unfortunately, the standard *Wipf* cyclization emerged difficultly and the yields never exceeded 45%. After some optimization, the yield could be improved to 78%, 95% based on recovered starting material, respectively (Figure 19). Finally, rather simple base catalysis (K_2CO_3) yielded vinylfuran **200** in acceptable yields. At this stage, the MMTr-group was cleaved and the resulting primary alcohol was oxidized with IBX to the corresponding aldehyde **201**. This sequence made the northern fragment **201** accessible in a very concise manner (Figure 19).

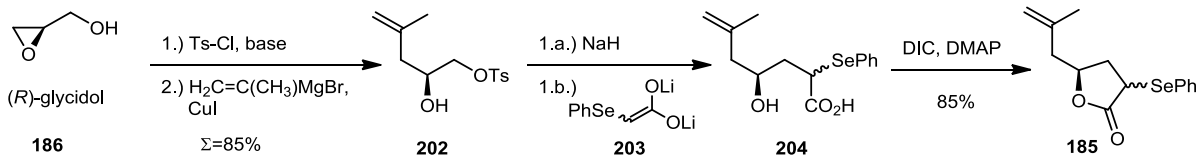


reagent	$Pd(OAc)_2$ K_2CO_3 THF	$Pd(OAc)_2$ K_2CO_3 CH_3CN, H_2O	$Pd(OAc)_2$ K_2CO_3 dioxane, µW	$Pd(OAc)_2$ K_2CO_3 THF, µW	$Hg(OAc)_2$ benzene	$Hg(OTf)_2$ benzene
yield	42%	34%	35%	37%	up to 40%	Up to 40%
reagent	AgOTf benzene	$AgIO_4$ acetone	$Ag(O_2CCF_3)_2$ $CaCO_3$	$AgNO_3$ $CaCO_3$ acetone	K_2CO_3 DMF, µW	**K_2CO_3** **DMF**
yield	31%	decomp.	14%	27%	65%	**78%**

Figure 19: Optimization of the furan cyclization and completion of the northern fragment 201.

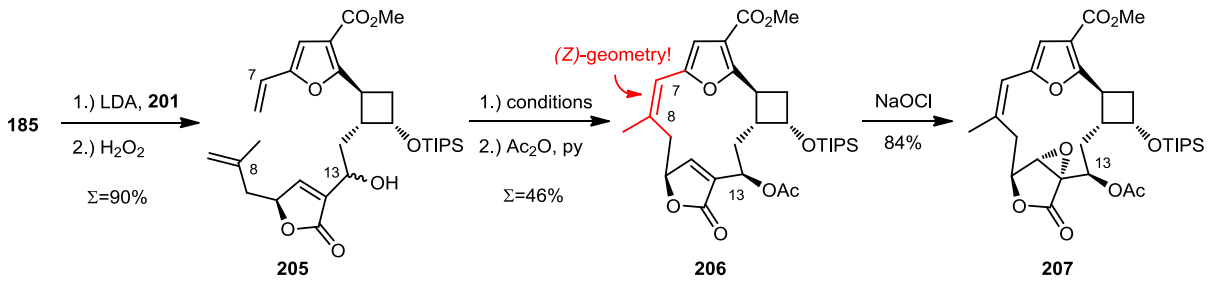
The synthesis of the southern fragment started with the tosylation of (*R*)-glycidol (**186**). The resulting (*S*)-configured tosylate was further converted by a Cu(I)-mediated epoxide opening reaction into secondary homoallylic alcohol **202**. The formation of the enantiomeric *Schlosser-Fouquet* product was not observed,[64] probably due to the fact that vinyl cuprates are soft nucleophiles, which preferentially attack soft electrophiles, according to the HSAB concept.

Secondary alcohol **202** was transformed to its corresponding epoxide, which subsequently was opened by the *in situ* generated dianion of phenyl selenyl acetic acid (**203**), yielding *seco* acid **204**. Highly diluted *Steglich* esterification using diisopropylcarbodiimide (DIC) yielded the southern fragment **185** (selenolactone) in high yields as an inconsequential mixture of diastereo isomers (*d.r.* = 1.5:1) (Scheme 18).[80]



Scheme 18: Synthesis of the southern fragment 185.

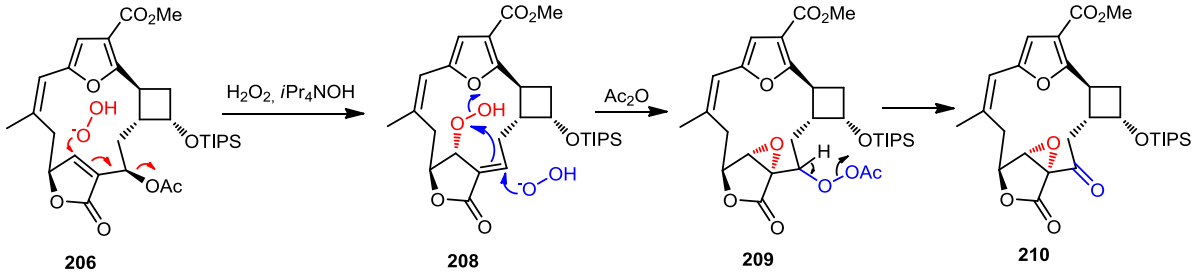
With both fragments in hand, the stage was set for fragment combination. This was accomplished by an aldol reaction, using LDA as the non-nucleophilic base. Subsequent oxidative selenoether elimination furnished butenolide **205**, which was the direct metathesis macrocyclization precursor. After some unsuccessful attempts, RCM using *Grubbs*' 2nd generation catalyst afforded the desired macrocycle in acceptable yields. Unfortunately, the geometry of the formed $\Delta^{7,8}$ double bond was (*Z*)-configured. Among other catalysts, only the *Grubbs-Hoveyda* 2nd generation catalyst showed conversion, but in lower yields. The C13-diastereoisomer could easily be separated by silica gel column chromatography at that stage. Acylation with acetic anhydride gave allylic acetate **206** in quantitative yield (Figure 20).



catalyst	G1	G2	GH2	G1	G2	GH2
solvent (Δ)	CH_2Cl_2	CH_2Cl_2	CH_2Cl_2	benzene	**benzene**	benzene
result	s.m. (**205**)	s.m. (**205**)	s.m. (**205**)	s.m. (**205**)	**46%**	39%

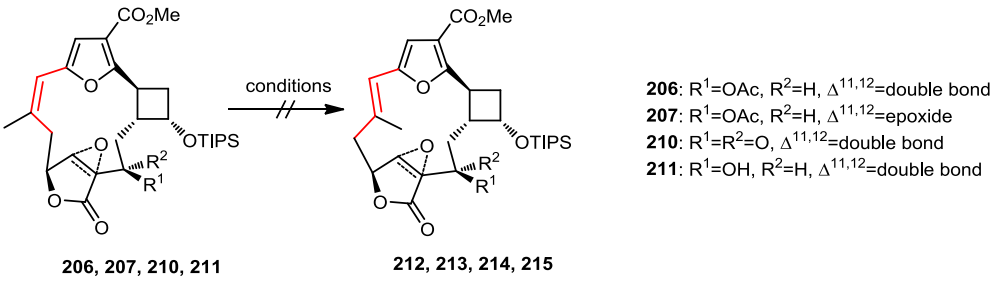
Figure 20: Macrocyclization of 205 and further conversion to 207.

The next step in the ongoing synthesis of Providencin (**1**) was the installation of the epoxide at the electron poor double bond of the butenolide. Surprisingly, classical *Scheffer-Weitz* conditions with ensuing acetylation gave unexpected epoxy-ketone **210** (Scheme 19). But NaOCl as oxidizing agent smoothly provided the desired epoxide **207** as single diastereoisomer (Figure 20).[81]



Scheme 19: Unexpected ketone formation during epoxidation.

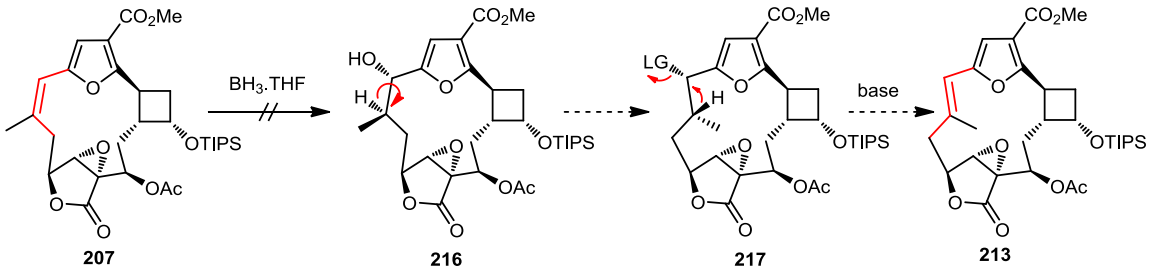
Although the macrocycle was closed, the double bond geometry and so the geometry of the in future installed benzylic epoxide was inverted. Therefore, many attempts for double bond inversion were performed. Methods using radical mechanisms are summarized in Figure 21.



reagent	I_2	I_2, hν (vis)	Ph_2Se_2	I_2	I_2, hν (vis)	Ph_2Se_2
solvent (Δ)	CH_2Cl_2	CH_2Cl_2	THF	CH_2Cl_2	CH_2Cl_2	THF
s.m.	**206**	**206**	**206**	**207**	**207**	**207**
result	s.m. (**212**)	s.m. (**212**)	s.m. (**212**)	s.m. (**213**)	s.m. (**213**)	s.m. (**213**)
reagent	I_2	I_2, hν (vis)	Ph_2Se_2	I_2	I_2, hν (vis)	Ph_2Se_2
solvent (Δ)	CH_2Cl_2	CH_2Cl_2	THF	CH_2Cl_2	CH_2Cl_2	THF
s.m.	**210**	**210**	**210**	**211**	**211**	**211**
result	s.m. (**214**)	s.m. (**214**)	s.m. (**214**)	s.m. (**215**)	s.m. (**215**)	s.m. (**215**)

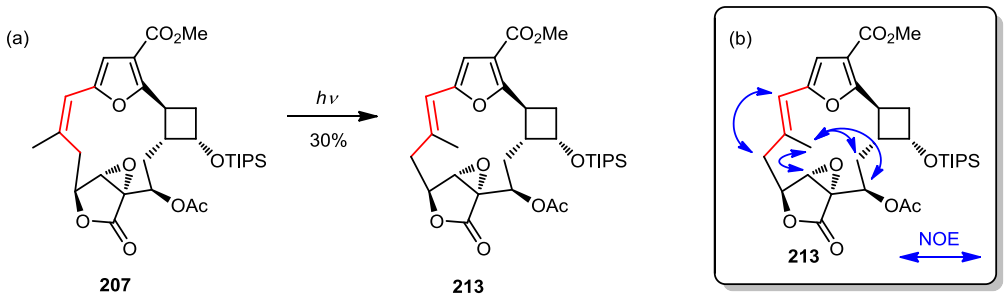
Figure 21: Unsuccessful radical double bond isomerization conditions.

Unfortunately, these radical conditions proved to be ineffective. To overcome these problems, a different strategy was applied, starting with a hydroboration of the undesired (*Z*)-olefin **207**. The general idea was a *syn* addition and an *anti* elimination following an E_2-mechanism. This should invert the double bond geometry, but all attempts to yield the desired borated product **216** failed under standard conditions (Scheme 20).



Scheme 20: Attempted double bond inversion by hydroboration/elimination sequence.

Apart from these attempts for double bond geometry inversion, many other different strategies were tested by *Gaich*,[82] like a bromohydrin strategy, a Corey-Winter strategy,[83] and many others. Unfortunately, these experiments did not deliver the desired (*E*)-double bond either.



Scheme 21: (a) Successful double bond inversion by irradiation of 207; (b) Spectroscopic evidence for (*E*)-double bond geometry.

(Photo)isomerization of carbon-carbon double bonds is a well known synthetic tool,[84] but due to the disappointing results of the initial isomerization experiments this approach was abandoned for a while. But life is a double edged sword. In 2010 *Pattenden* and coworkers published a UV-light mediated double bond isomerization on a member of the furanocembranoid family (*Z*-(+)-Deoxypukalide).[85] Inspired by their promising results, the advanced intermediate **207** was irradiated with a 100W UV-bulb. To our delight, we observed a smooth conversion to the highly strained (*E*)-macrocycle **213**, which showed a rotational barrier and therefore coexisted as a mixture of multiple atropisomers. Figure 22 shows the evolution of a clean NMR-spectrum at elevated temperatures. Careful 2D-NMR experiments (COSY, HSQC, HMBC, NOESY) clearly showed successful isomerization of the $\Delta^{7,8}$ double bond (Scheme 21).

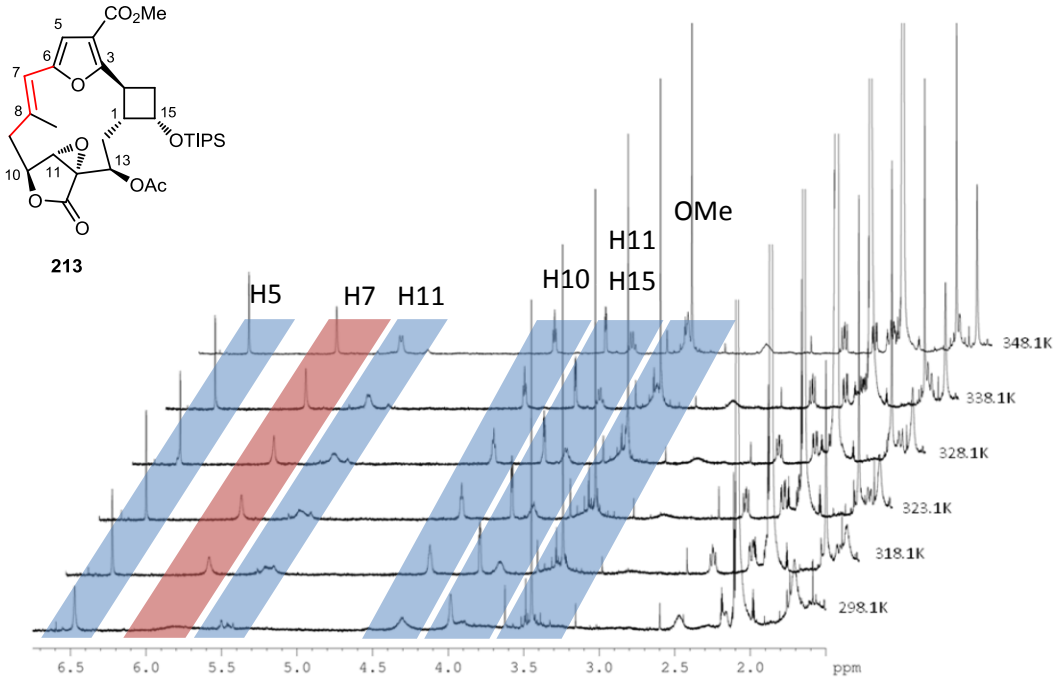


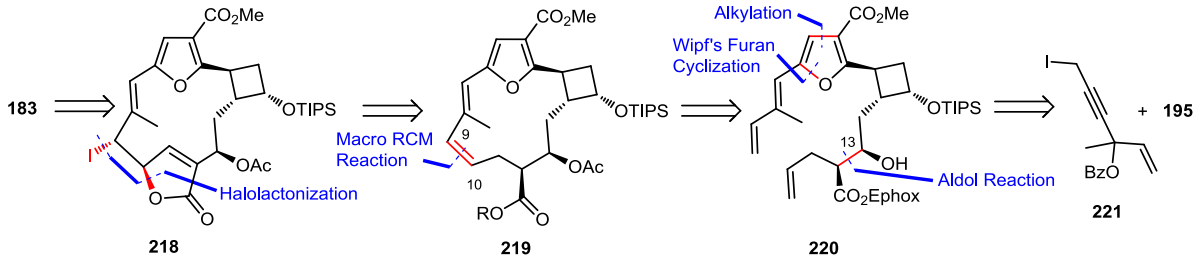
Figure 22: Temperature dependence of the NMR-spectra of atropisomers 213.

2.1.2.1.2 $\Delta^{9,10}$ Metathesis Approach

This approach shares some ideas with the first one, but has some major advantages. The stereoselective introduction of the secondary Δ^{13}-alcohol using auxiliary based chemistry and the independency of the outcome of the $\Delta^{9,10}$ double bond geometry after macrocyclization by metathesis. Nevertheless, many compromises have to be taken, like the removal of the allylic halogen after halolactonization and the late stage introduction of the butenolide $\Delta^{11,12}$ double bond.

Retrosynthetic Analysis:

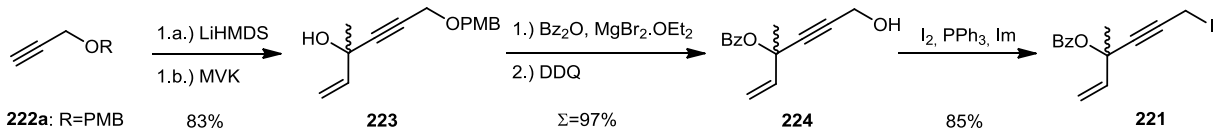
The first retrosynthetic simplification of key intermediate **183** was the opening of the southern butenolide, resulting in the free carboxylic acid **219**. The next step was the opening of the 14-membered macrocycle between $\Delta^{9,10}$ yielding triene **220**. Scission of the $\Delta^{12,13}$ single bond and opening of the furan gave an alkylated β-keto ester, which could be further simplified to **195** and **221** (Scheme 22).



Scheme 22: Retrosynthetic analysis of the $\Delta^{9,10}$ metathesis approach.

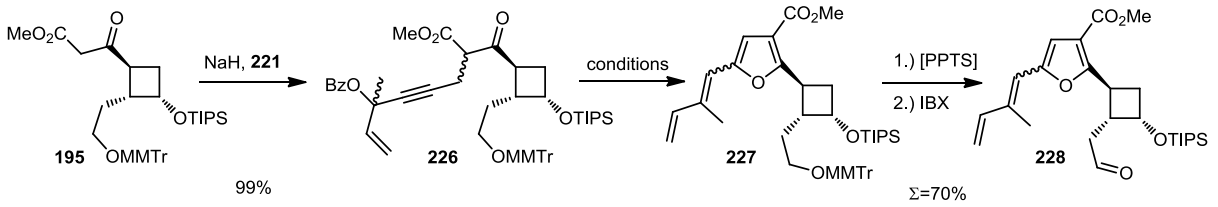
Synthesis:

Deprotonated literature known PMB-protected propargylic alcohol **222a** was added to the carbonyl moiety of methyl-vinyl-ketone (MVK).[86] The formation of a 1,4-addition product was not observed. The resulting tertiary alcohol **223** was transformed to its corresponding benzoate, using the protocol developed by *Vedejs* et al.[87] Oxidative cleavage of the primary PMB-ether yielded **224** and subsequent transformation to the propargylic iodide using *Appel* conditions gave alkylation fragment **221** in high overall yield (Scheme 23).[50]



Scheme 23: Synthesis of the alkylation side chain 221.

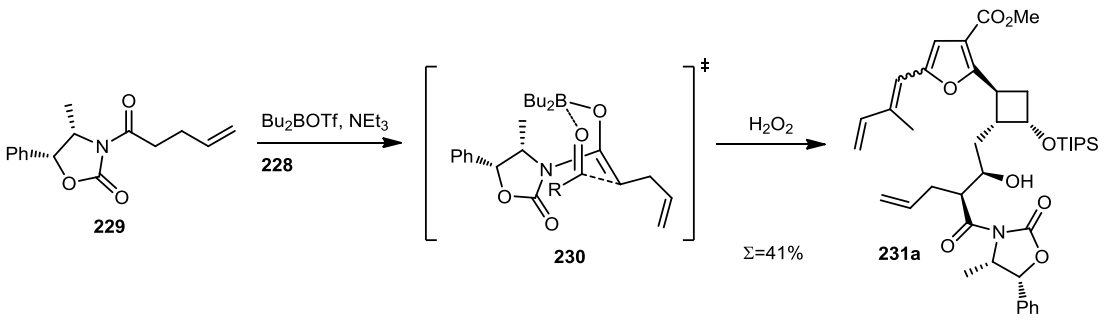
In analogy to the $\Delta^{7,8}$ metathesis approach, β-keto ester **195** was deprotonated with NaH and alkylated with propargylic iodide **221** giving intermediate **226**. Furan cyclization of **226** proofed to be troublesome. Under standard, as well as slightly modified *Wipf* conditions yields never exceeded 15% of a mixture of double bond isomers (*E/Z* = 4/1).[71] A possible reason could be the formation of a completely conjugated diene system, which is predisposed for Pd-coordination, activation and further (unselective) transformation. But with **227** in hands, the stage was set for the acid catalyzed liberation of the primary alcohol and subsequent oxidation to the corresponding aldehyde **228** using IBX as oxidizing agent (Figure 23).



reagent	$Pd(OAc)_2$, dppf, K_2CO_3	$Pd(OAc)_2$, dppf, K_2CO_3	K_2CO_3
solvent	CH_3CN	THF	DMF
result	decomposition	decomposition	15% yield (*E/Z* = 4/1)

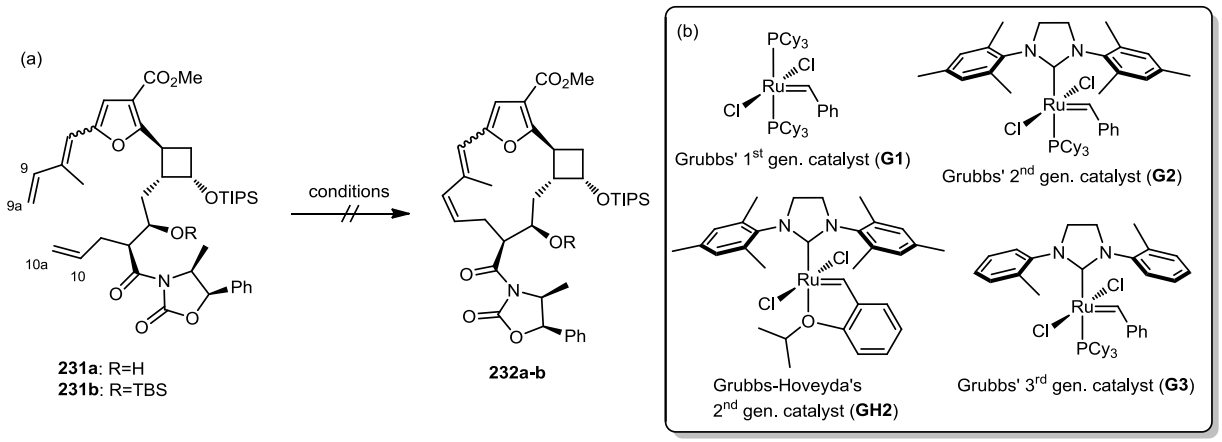
Figure 23: Furan cyclization and completion of the northern fragment 228.

In this approach, secondary alcohol **231a** should be generated stereoselectively using Evans' aldol methodology. Therefore, (*4S,5R*)-4-methyl-5-phenyloxazolidin-2-one was acylated with pent-4-enoic acid in a Steglich esterification using DIC.[80] Using Bu_2BOTf two possible *syn* aldol adducts can be generated,[65] but using the chiral induction of the EPHOX-auxiliary additional, aldol product **231a** could be generated *via* transition state **230** as a single diastereomer (Scheme 24).



Scheme 24: Transition state of the boron aldol and therewith generated stereochemistry.

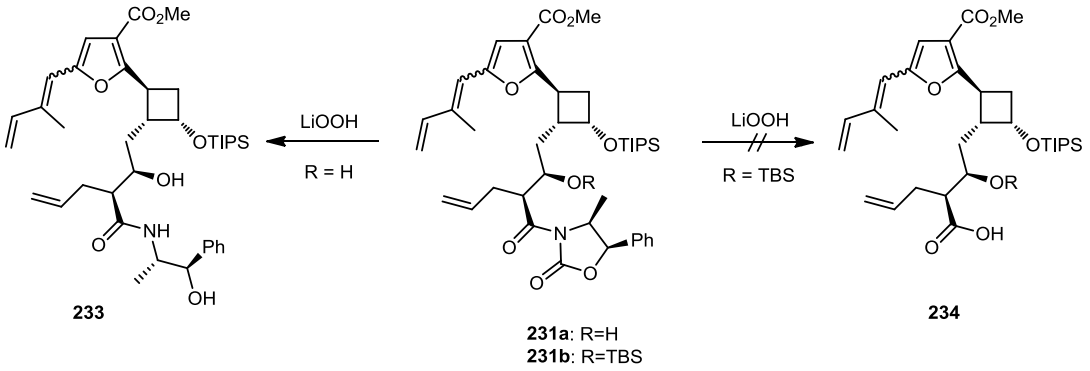
With the bulky auxiliary still in place, **231a, b** was subjected to a ring closing metathesis reaction using different ruthenium based catalysts and substitution patterns on C13-OH (Figure 24). Unfortunately none of the applied conditions led to the desired macrocycles **232a, b**, instead a homodimerization at the $\Delta^{10,10a}$-double bond took place, most likely due to a precoordinating effect of the heteroatoms of the auxiliary towards the metathesis catalysts.



catalyst	G1	G1	G2	G2	G3	G3
solvent (Δ)	CH_2Cl_2	benzene	CH_2Cl_2	benzene	CH_2Cl_2	benzene
s.m.	**231a**	**231a**	**231a**	**231a**	**231a**	**231a**
result	s.m.	s.m.	s.m.	homodimer	s.m.	homodimer
catalyst	G2	G2	G3	G3	GH2	GH2
solvent (Δ)	CH_2Cl_2	benzene	CH_2Cl_2	benzene	CH_2Cl_2	benzene
s.m.	**231b**	**231b**	**231b**	**231b**	**231b**	**231b**
result	s.m.	homodimer	s.m.	homodimer	s.m.	homodimer

Figure 24: (a) Unsuccessful attempts for the macrocyclization; (b) Structures of used metathesis catalysts.

Since the macrocyclization attempts of **231a** and **231b** only led to homodimerization, hydrolytic cleavage of the auxiliary was carried out prior to further RCM attempts. Therefore, standard conditions using the nucleophilicity enhancing α-effect of lithium-hydroperoxide were applied.[88] With the free alcohol moiety of **231a**, the ring opened product **233** was obtained, whereas with the TBS-protected alcohol **231b** no reaction to compound **234** was observed (Scheme 25). Any attempts to remove the auxiliary by the addition of thiolates failed.[89] Methanolysis did not lead to the formation of the desired product either.[90]



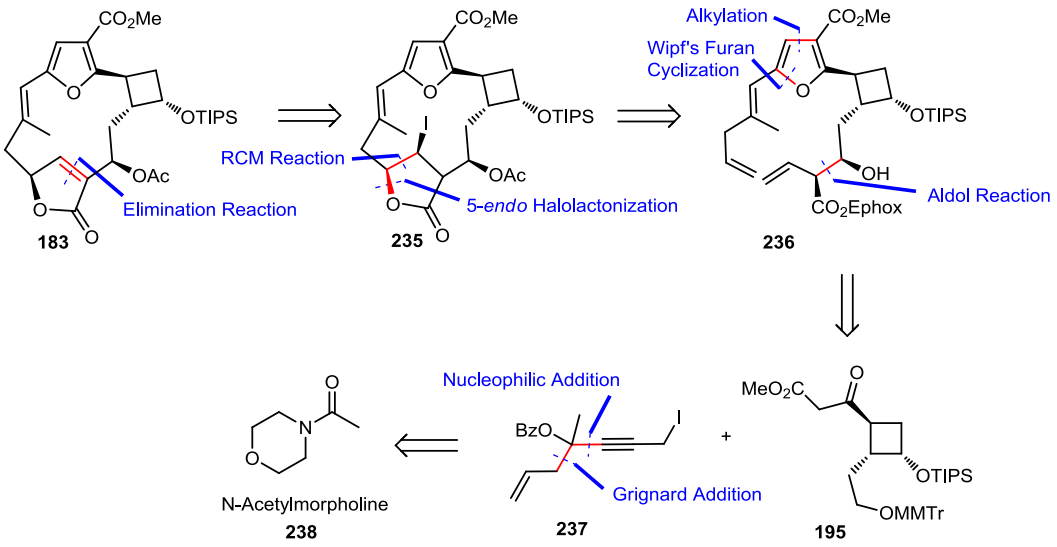
Scheme 25: Hydrolytic auxiliary cleavage attempts of 231a, b.

2.1.2.1.3 $\Delta^{10,11}$ Metathesis Approach

Similar to the second approach, this approach benefits from the stereoselective introduction of the secondary C13 alcohol by an Evans-type auxiliary methodology and the independency of the $\Delta^{10,11}$ double bond geometry, generated by metathesis-macrocyclization. Furthermore, the γ-lactone is closed by a 5-*endo* halolactonization, generating a secondary alkylhalide, which can be subsequently eliminated to the corresponding butenolide double bond by sterically demanding pyridine bases.[91] [92] Besides, the troublesome diene, generated by *Wipf*'s furan cyclization strategy and the allyl halide, generated by halolactonization in the former approach (**218**), are avoided.

Retrosynthetic Analysis:

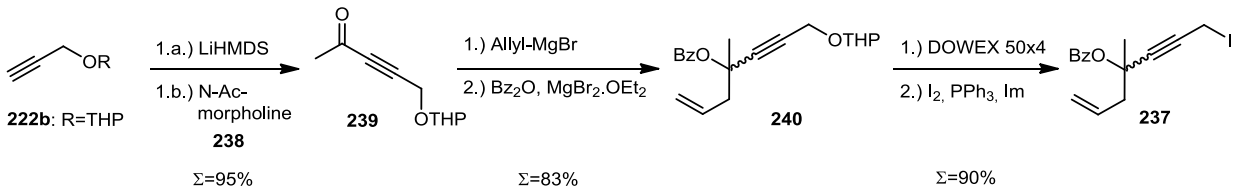
The first retrosynthetic step was the *anti-Markovnikoff* addition of hydrogen iodide to key intermediate **183**. After *retro*-halolactonization, the next step was the scission of key intermediate **235** at the $\Delta^{10,11}$ carbon-carbon bond. Further simplification was achieved by the opening of the 14-membered macrocycle at $\Delta^{10,11}$ yielding triene **236**. Scission of the $\Delta^{12,13}$ bond and opening of the furan gave alkylated β-keto ester, which could be further simplified to **195** and **237**. Compound **237** again, could be derived from *N*-acetylmorpholine (**238**) (Scheme 26).



Scheme 26: Retrosynthetic analysis of the $\Delta^{10,11}$ metathesis approach.

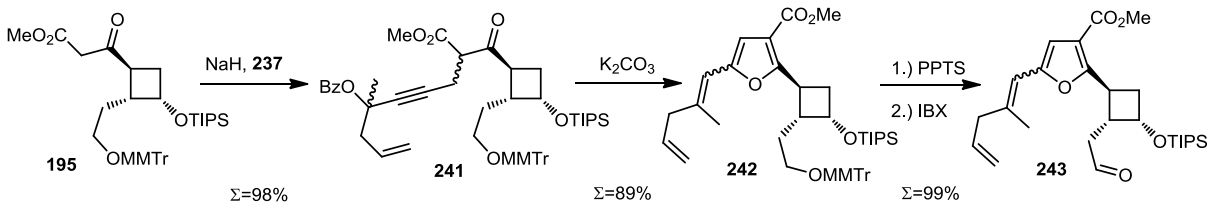
Synthesis:

THP-protected propargylic alcohol **222b** was deprotonated with LiHMDS and added to *N*-acetylmorpholine (**238**). The formed hemiaminal gave methylketone **239** upon aqueous workup. The hard nucleophile allyl magnesium bromide was added to the carbonyl moiety of **239** and the resulting tertiary alcohol was benzoylated using the protocol developed by *Vedej*.[87] The resulting tertiary benzoate **240** was treated with DOWEX 50x4 to liberate the primary propargylic alcohol, which was subsequently transformed to the corresponding propargylic iodide **237** by modified *Appel* conditions (Scheme 27).[50]



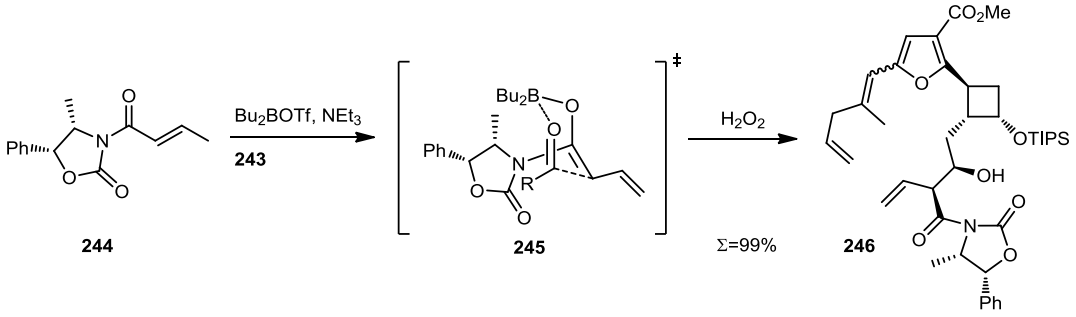
Scheme 27: 5-step synthesis of the side chain fragment.

Readily available β-keto ester **195** was deprotonated with NaH and subsequently alkylated with **237**. The resulting compound **241** was cyclized under basic conditions to vinylfuran **242**,[71] which was again deprotected with PPTS and oxidized using IBX as oxidizing agent to provide northern fragment **243** in very good overall yield (Scheme 28).



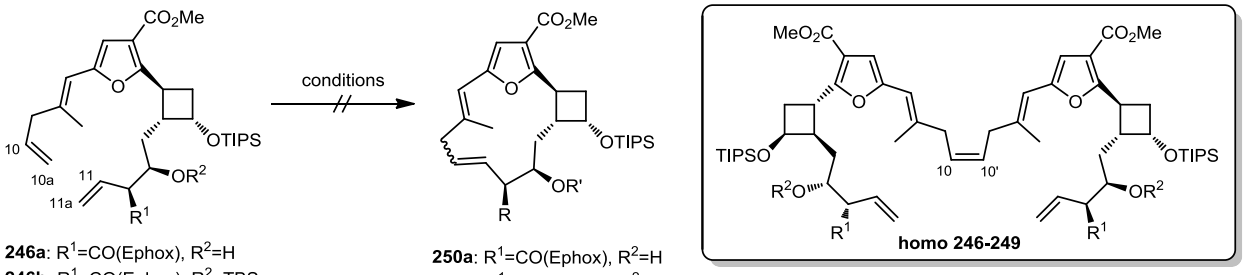
Scheme 28: Alkylation, furan closure and completion of the northern fragment.

Like in the former approach, the secondary alcohol should be generated stereoselectively using Evans' aldol chemistry. Therefore, (*4S,5R*)-4-methyl-5-phenyloxazolidin-2-one was acylated with crotonic acid chloride, according to literature.[93] γ-Deprotonation with NEt_3 and Bu_2BOTf provided the (*Z*)-enolate, which reacted, due to the chiral auxiliary in α-position over transition state **245** in a highly diastereoselective way to *syn* aldol product **246** (Scheme 29).



Scheme 29: Transition state of the boron aldol and therewith generated stereochemistry.

With the macrocyclization precursor **246** in hands, the stage was set for the synthesis' key step: the RCM reaction. First tries with the auxiliary still in place only led to the C10-C10 homodimerized product, even when using different substitution patterns at C13-OH (**246a, b**). The change to fluorinated solvents, which should increase the power of the used catalysts, had no effect on the formed products.[94] Reductive or hydrolytic cleavage of the auxiliary and subsequent metathesis once again led to the dimerized products,[88] probably again due to an effect of precoordination of the metathesis catalyst by the alcohol moieties in **247** and **249**. Therefore, both alcohols were protected as their silyl ethers to prevent this phenomenon and the resulting precursor **248** was subjected to a ring closing reaction. But in these cases as well, only the C10-C10 homodimers (**homo 246-249**) could be detected (Figure 25).



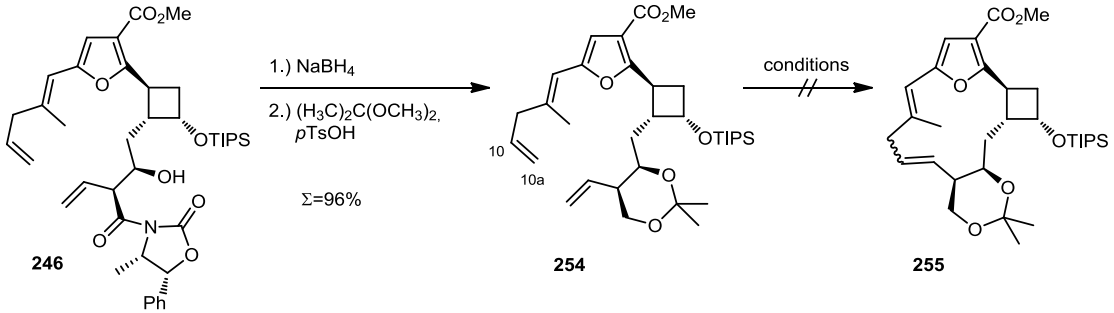
246a: R^1=CO(Ephox), R^2=H
246b: R^1=CO(Ephox), R^2=TBS
247: R^1=CH_2OH, R^2=TBS
248: R^1=CH_2OTMS, R^2=TES
249: R^1=CO_2H, R^2=TBS

250a: R^1=CO(Ephox), R^2=H
250b: R^1=CO(Ephox), R^2=TBS
251: R^1=CH_2OH, R^2=TBS
252: R^1=CH_2OTMS, R^2=TES
253: R^1=CO_2H, R^2=TBS

catalyst (solvent)	**G2** (C_6H_6)	**G2** (C_6H_6)	**G2** (C_6H_6)	**GH2** (C_6H_6)	**G2** (C_6F_6)
s.m.	**246a**	**246b**	**247**	**247**	**247**
result	homodimer	homodimer	homodimer	homodimer	homodimer
catalyst (solvent)	**G2** (C_6H_6)	**GH2** (C_6H_6)	**G2** (C_7H_8)	**G2** (C_6F_6)	**G2** (C_6H_6)
s.m.	**248**	**248**	**248**	**248**	**249**
result	homodimer	homodimer	homodimer	homodimer	homodimer

Figure 25: $\Delta^{10,11}$ Metathesis experiments and their outcome.

During the macrocyclization attempts shown in Figure 25, it could be observed, that the molecule avoided macrocyclization and rather underwent homodimerization. Therefore, the introduction of a rigid ring system, to make the unreactive olefin more accessible towards the metathesis reaction was plausible. Thus, an acetonide was installed and tricycle **254** was subjected to RCM reaction. Unfortunately, this idea proved to be unsuccessful as well and only the C10-C10-homodimer was formed (Figure 26).



catalyst (solvent)	**G2** (benzene)	**GH2** (benzene)	**G3** (benzene)
result	homodimer	homodimer	homodimer

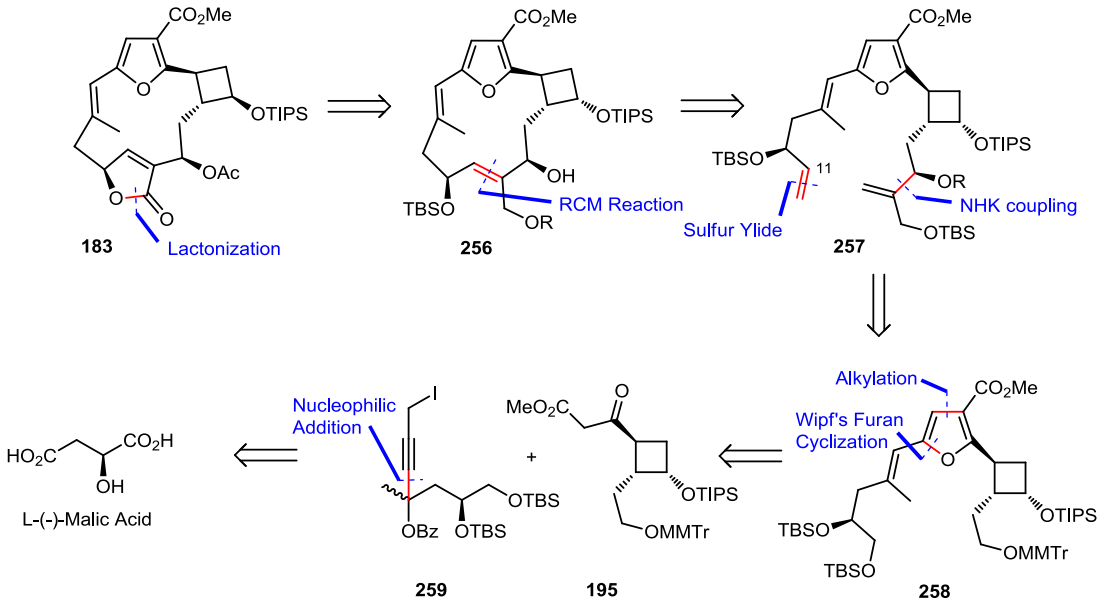
Figure 26: Generation of another $\Delta^{10,11}$ metathesis precursor and cyclization attempts.

2.1.2.1.4 $\Delta^{11,12}$ Metathesis Approach

This approach should make use of the $\Delta^{11,12}$-double bond generated by olefin metathesis to build up the butenolide structure. But it is noteworthy to mention, that, unlike in the auxiliary based approaches, the outcome of the double bond geometry is essential. An (*E*)-geometry is needed, to build up the butenolide successfully. Another advantage is the fixed (*E*)-geometry of the $\Delta^{7,8}$-double bond, that is generated by the *Wipf* method.[71]

Retrosynthetic Analysis:

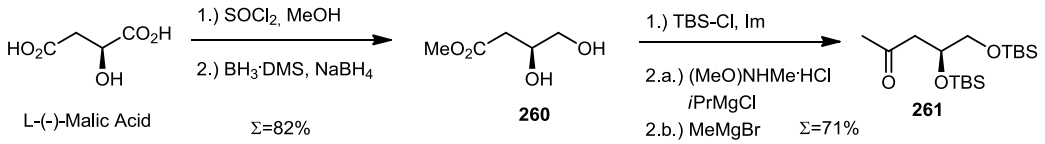
The first retrosynthetic simplification of this approach was the opening of the butenolide lactone, leading to intermediate **256**. The ester was reduced to its corresponding allylic alcohol and the macrocycle was opened giving triene **257**, which was further simplified by the removal of the mono substituted double bond at C11. Finally, the scission of the $\Delta^{12,13}$-carbon bond led to the removal of allyl alcohol in the south-east and to intermediate **258**. The furan moiety was opened and the β-keto ester dealkylated to **195**. The propargylic moiety of the side chain was removed, leading to a methyl ketone, which was derived from L-(-)-malic acid (Scheme 30).



Scheme 30: Retrosynthetic analysis of the $\Delta^{11,12}$ metathesis approach.

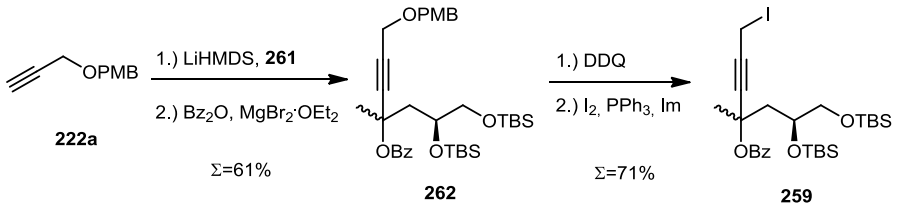
Synthesis:

L-(-)-Malic acid was converted to its dimethyl ester, which was chemoselectively reduced to the corresponding diol **260**.[95] [96] Both alcohol moieties in **260** were protected as their TBS-ethers and subsequently converted to the *Weinreb* amide derivative,[97] which was further transformed to methyl ketone **261** by the addition of methyl magnesium bromide (Scheme 31).



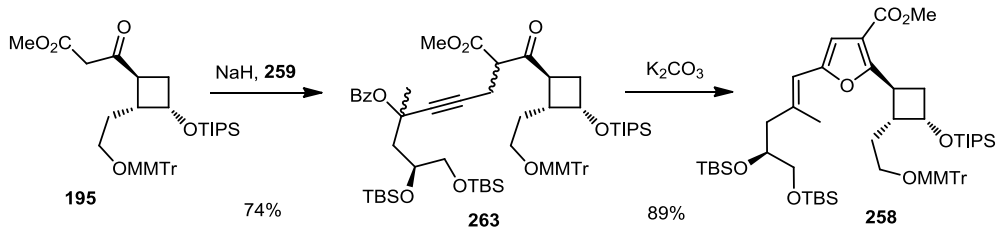
Scheme 31: Stereoselective synthesis of methyl ketone 261.

Deprotonated **222a** was subsequently added to methyl ketone **261**. The formed tertiary alcohol was obtained in a diastereo enriched way (*d.r.* = 4:1). Due to the loss of this stereo center during the following furan closure, the mixture was used and therefore converted to the corresponding benzoates **262** using the *Vedejs* protocol.[87] After oxidative cleavage of the PMB protecting group using DDQ, the primary alcohol was transformed into the corresponding propargylic iodide **259** by an *Appel*-reaction (Scheme 32).[50]



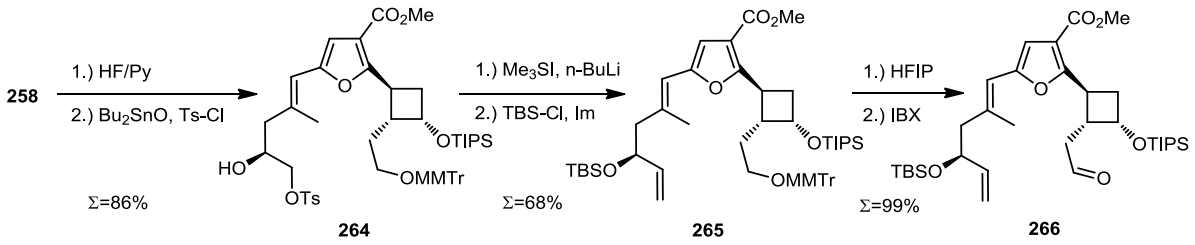
Scheme 32: Completion of the side chain 259.

After deprotonation with NaH, well established β-keto ester **195** was alkylated with propargylic iodide **259**. The resulting product **263** was then cyclized to vinyl furan **258** (*E/Z* = 4/1) using the methodology of *Wipf*.[71] Unfortunately, to the best of our knowledge, there is no possibility of controlling the double bond geometry by external methods, like ligand design. Only substrate dependent sterical parameters have an influence on the (*E/Z*)-ratio (Scheme 33).



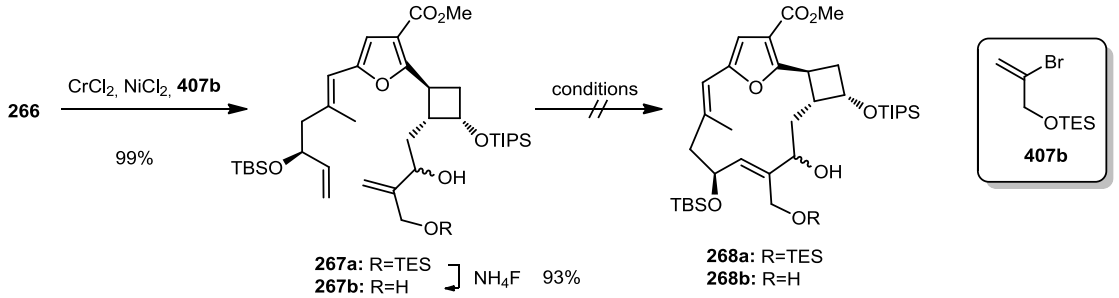
Scheme 33: Alkylation of 195 and furan closure by *Wipf*'s method.[71]

Furthermore, both TBS-protecting groups were cleaved by pyridine buffered hydrogen fluoride and the resulting primary alcohol was tosylated chemoselectively by the method developed by *Martinelli* and coworkers.[98] The resulting mono-tosylate **264** was transformed to allylic alcohol **265** by a slightly modified procedure of *Alcaraz*.[42] In this one pot reaction the epoxide was first closed and then re-opened by a sulfur ylide. Aldehyde **266** was generated by cleavage of the MMTr-group by solvolysis in HFIP and subsequent oxidation with IBX (Scheme 34).



Scheme 34: Installation of vinyl alcohol 265 and synthesis of aldehyde 266.

Further chain elongation was performed by a Cr(II)/Ni(II) NHK-coupling of **266** and **407b** in a diastereo enriched manner (*d.r.* = 2:1).[8, 51] The resulting compound **267a** was subsequently subjected to ring closing metathesis either with a free primary alcohol moiety (**267b**) or a TES-protected one (**267a**) (Figure 27). Unfortunately, none of the conditions applied led to the formation of the desired macrocycle **268a, b**.



catalyst (solvent)	**G2** (C_6H_6)	**GH2** (C_6H_6)	**G3** (C_6H_6)	**G2** (C_6H_6)	**GH2** (C_6H_6)	**G3** (C_6H_6)
s.m.	**267a**	**267a**	**267a**	**267b**	**267b**	**267b**
result	s.m.	s.m.	s.m.	s.m.	s.m.	s.m.

Figure 27: $\Delta^{11,12}$ Macrocyclization attempts of different precursors.

2.1.2.2 *Horner Wadsworth Emmons Macrocyclization Attempts*

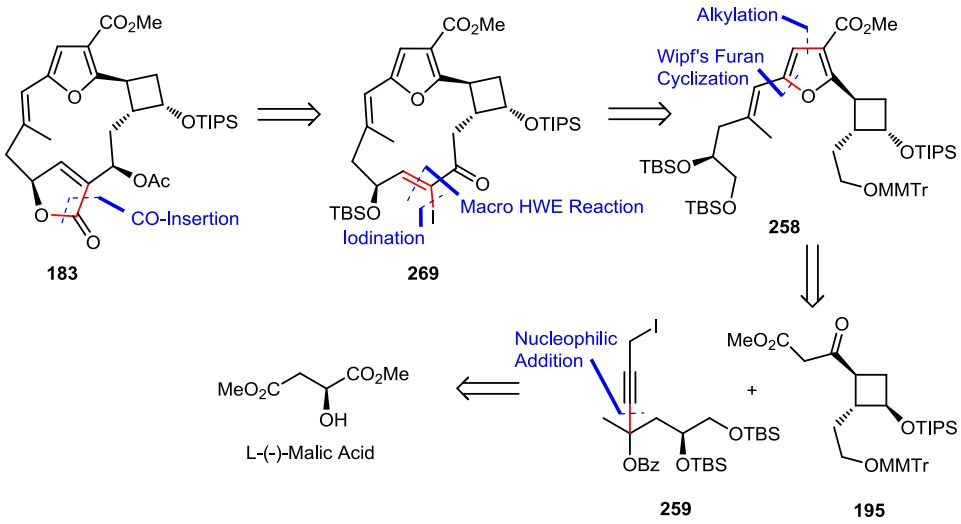
Since the massive strain of the 13-membered macrocycle so far prevented the formation of the sterically more demanding (*E*)-double bond in any position, a macrocyclization strategy is chosen, that can influence the outcome of the double bond geometry. Compared to the ring closing metathesis, where the geometry of the formed double bond is one of the last unsolved problems,[99] the HWE reaction is capable of controlling the outcome of the double bond geometry, by choosing the appropriate stereo-electronical substituents on the phosphonate moiety.[5, 100]

2.1.2.2.1 $\Delta^{11,12}$ *Horner Wadsworth Emmons* Approach (*c*Bu)

This approach releases strain by the removal of the butenolide moiety and thus, generating more degrees of freedom by ring opening. Due to these benefits the closure of the desired macrocycle should be facilitated. Installation of the butenolide moiety should be performed at a later synthetic stage.

Retrosynthetic Analysis:

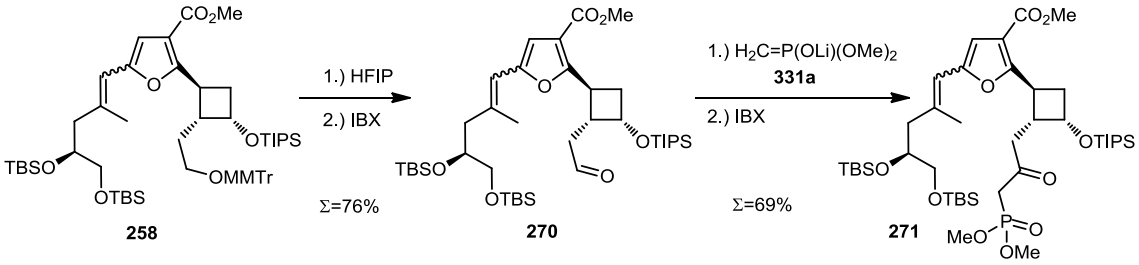
The first retrosynthetic scission was the opening of the ester of the butenolide moiety. Removal of the former ester-carbonyl and substitution with a vinyl halide led to intermediate **269**. Further ring opening, removal of dimethyl methylphosphonate and sequential reduction of the carbonyls to the corresponding alcohols led to known intermediate **258** (Scheme 35).



Scheme 35: Retrosynthetic analysis of the $\Delta^{11,12}$ HWE approach.

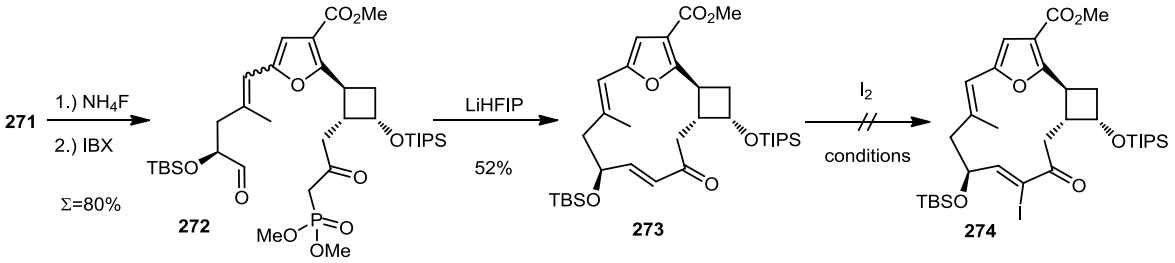
Synthesis:

Parts of the synthesis, like the preparation of **258** were already described in the $\Delta^{11,12}$-metathesis approach, within this approach, compound **258** was converted to aldehyde **270** by the selective cleavage of a MMTr-ether by solvolysis in hexafluoroisopropanol and subsequent oxidation of the resulting alcohol moiety to the corresponding aldehyde **270**. Both TBS-silyl ethers are stable under these mild conditions. Dimethyl methylphosphonate was converted to its Li-enolate (**331a**) using n-butyllithium as base and subsequently added to aldehyde **270**.[101] The resulting secondary alcohol was directly transformed to β-keto phosphonate **271** by oxidation with IBX (Scheme 36).



Scheme 36: Installation of the β-keto phosphonate 271.

Chemoselective cleavage of the primary TBS-ether and subsequent oxidation to the corresponding aldehyde led to macrocyclization precursor **272**, which smoothly underwent macrocyclization using lithium hexafluoroisopropanolate as base. The formation of the $\Delta^{7,8}$ (*Z*)-configured double bond isomer proceeded much faster than the formation of the (*E*)-configured double bond isomer (**273**), most probably caused by the high ring strain in the 13-membered macrocycle. The stage was set for the α-halogenation of the enone system (**274**). Unfortunately, all of the conditions applied led either to decomposition of the molecule or to recovered starting material (Figure 28).



conditions	py, CCl_4[102]	NEt_3, CH_2Cl_2	DMAP, THF[103]
result	s.m.	s.m.	decomposition

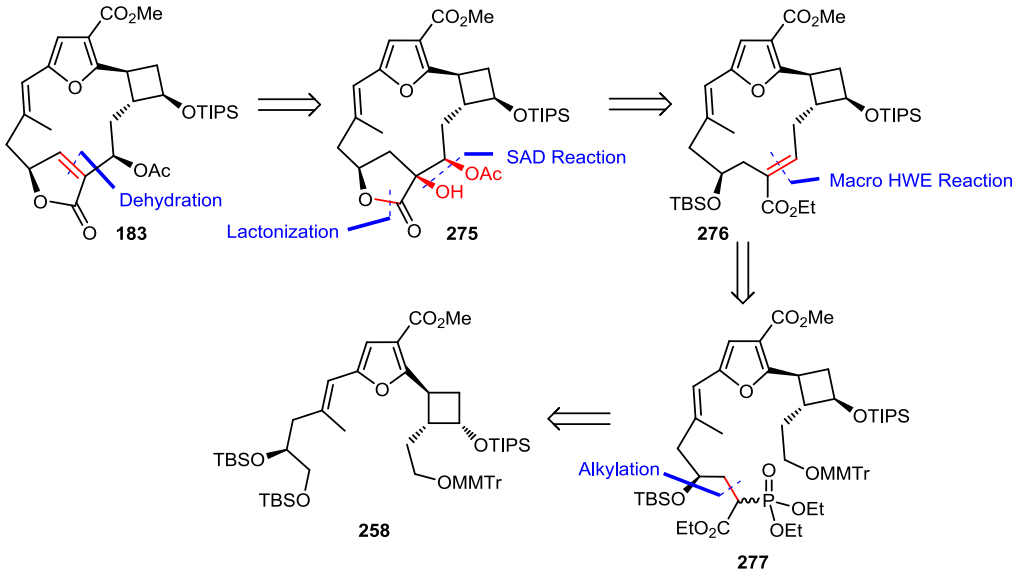
Figure 28: Closure of macrocycle 273 and α-halogenation attempts.

2.1.2.2.2 $\Delta^{12,13}$ Horner Wadsworth Emmons Approach

Since the $\Delta^{11,12}$-HWE approach smoothly gave macrocycle **273**, but made further C12-functionalization impossible, a slightly modified approach was designed. Here, the same macrocyclization strategy should be used, but the butenolide carbonyl group should already be in place. *Sharpless* asymmetric dihydroxylation (SAD) should introduce the desired secondary C13-hydroxy group in a diastereoselective way and subsequent dehydratation should generate the butenolide double bond.

Retrosynthetic Analysis:

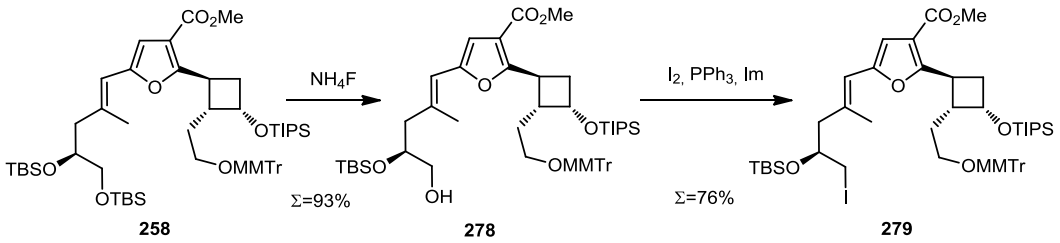
Markovnikov type addition of water to the butenolide double bond in **183** led to intermediate **275**, which was further simplified by the removal of the acetyl group and the vicinal diol. Opening of the butenolide led to intermediate **276**, which after opening of the macrocycle, was further deduced to intermediate **277**. Degradation of the β-keto phosphonate moiety led once again to well established key intermediate **258** (Scheme 37).



Scheme 37: Retrosynthetic analysis of the $\Delta^{12,13}$-HWE approach.

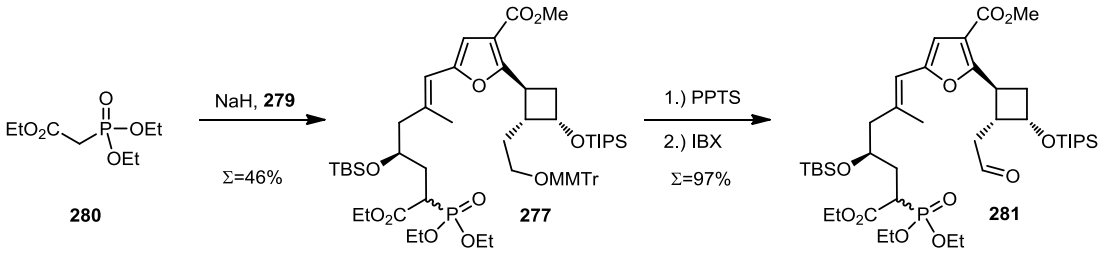
Synthesis:

TBS-ether **258** was chemoselectively cleaved by the use of NH_4F. The resulting primary alcohol moiety in **278** was subsequently converted to the corresponding iodide **279** under *Appel* conditions (Scheme 38).[50]



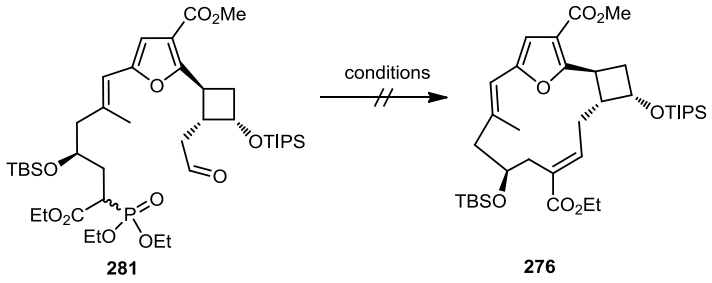
Scheme 38: Chemoselective deprotection and iodination of 258.

Commercially available triethyl phosphonoacetate (**280**) was deprotonated with NaH and alkylated with primary iodide **279** in high yields. The resulting β-keto phosphonate **277** was treated with the standard deprotection/oxidation reagents PPTS and IBX to afford macrocyclization precursor **281** (Scheme 39).



Scheme 39: Installation of the β-keto phosphonate and synthesis of the macrocyclization precursor.

Various macrocyclization conditions were carried out, but unfortunately, none of them were successful. Starting from gentle (modified) *Masamune-Roush* conditions,[104] covering previously applied lithium hexafluoroisopropanolate and NaH, up to K_2CO_3 in boiling toluene: None of them led to the formation of the desired macrocycle **276** (Figure 29).



base, additive	DBU, LiCl	DIPEA, LiCl	BuLi, HFIP	NaH	$Ba(OH)_2 \cdot 8H_2O$	K_2CO_3
solvent	CH_3CN	CH_2Cl_2	THF	THF	THF	toluene
result	s.m.	s.m.	s.m.	s.m.	s.m.	s.m.

Figure 29: Applied macro-olefination conditions.

2.1.2.3 *Miscellaneous Macrocyclization Attempts*

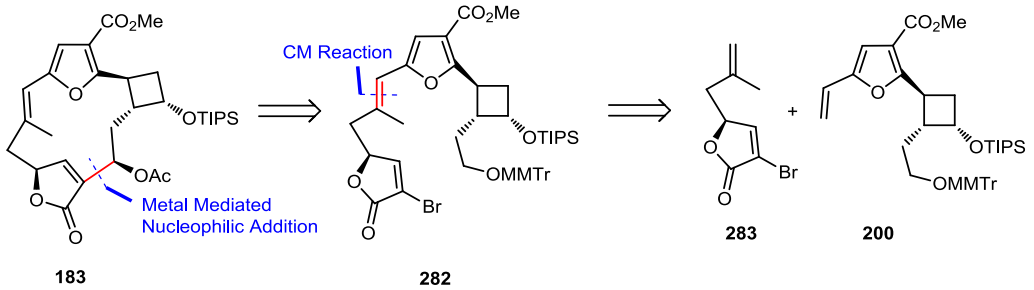
These approaches do not have a unique macrocyclization strategy in common, but the general idea in these approaches is the use of relatively large (transition) metals to precoordinate the two endings of the particular macrocyclization precursor followed by a nucleophilic addition to a carbonyl center.

2.1.2.3.1 Furan-Butenolide-$\Delta^{12,13}$ Approach

Encouraged by the power of SmI_2-mediated reactions and the easy accessibility of the starting materials,[7] this approach was started. The advantages are the well established route for the synthesis of the northern fragment and the rather short and straight synthesis of the southern fragment. Furthermore, the cross metathesis reaction, used for the fragment combination, offers a simple variation of the participating building blocks and thus, an easy variation of functional groups.

Retrosynthetic Analysis:

The first retrosynthetic scission of **183** in this approach was the removal of the acetate group and the subsequent opening of the macrocyclic carbon skeleton. Compound **282** was further simplified by the degradation of the $\Delta^{7,8}$-double bond yielding the two building blocks **283** and **200** (Scheme 40).

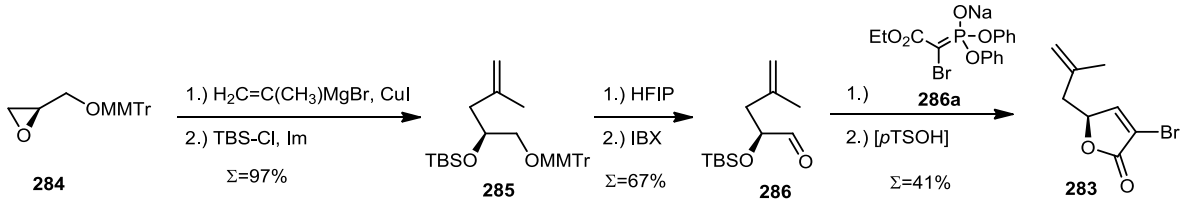


Scheme 40: Retrosynthetic analysis of the furan-butenolide $\Delta^{12,13}$ approach.

Synthesis:

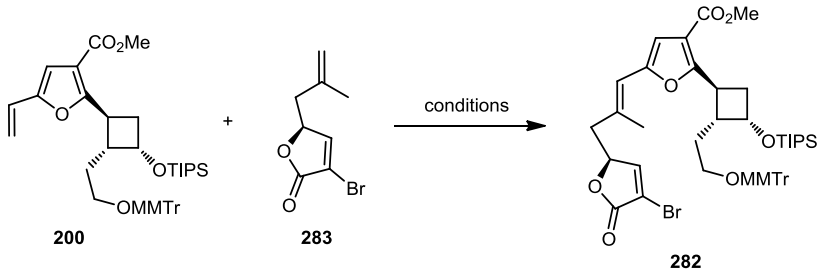
This approach started with literature known MMTr-protected (*R*)-glycidol **284**. Commercially available hard nucleophile isopropenyl magnesium bromide was transformed into its corresponding cuprate by the addition of Cu(I). With this *in situ* generated species, glycidol **284** was selectively opened and the resulting secondary alcohol protected as its TBS-ether to yield **285**. Chemoselective solvolysis of the MMTr-ether with HFIP generated the free primary alcohol moiety, which was subsequently transformed to the corresponding aldehyde **286** by an IBX oxidation.

α-Bromo-phosphonate (*Ando*'s variant,[105] **286a**) was deprotonated with NaH and aldehyde **286** was added. The resulting α-bromo enone was subsequently deprotected and cyclized under acid catalysis. Using this sequence, butenolide **283** was obtained in a high overall yield (Scheme 41).



Scheme 41: Short 6-step synthesis of intermediate 283.

Finally, the stage was set for the fragment combination by a cross metathesis reaction. It is well known, that every cross metathesis needs its own special conditions and that a general receipt for the selective generation of a cross metathesis product does not exist.[106] Thus, many different parameters were varied. When **G2** or **GH2** in refluxing benzene was used **282** could be isolated. When refluxing toluene was used, the yields were even better, but it had to be put up, that the amount of 1,1-disubstituted olefin **283** had to be raised. However, the yields never exceeded 21% (Figure 30).

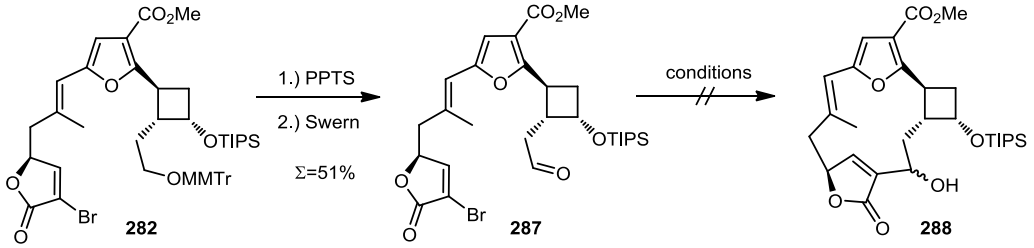


catalyst	G2	G2	G2	GH2	GH2	GH2
solvent (Δ)	CH_2Cl_2	benzene	toluene	CH_2Cl_2	benzene	toluene
200 / 283	1 / 3	1 / 3	1 / 4	1 / 3	1 / 3	1 / 4
result	s.m.	12%	21%	s.m.	15%	21%

Figure 30: Applied cross metathesis conditions; synthesis of 282.

The product **282** of the cross metathesis was deprotected under acidic conditions with pyridine buffered *p*TsOH. The resulting primary alcohol was oxidized under *Swern* conditions,[61] yielding macrocyclization precursor **287** in modest yield. SmI_2 mediated nucleophilic attack to the freshly generated aldehyde did not show any conversion,[107] [108] whereas the supplementary addition of HMPA led to the formation of a complex product mixture.[109] HPLC analysis identified six different products, but all of them only in trace amounts.

Standard NHK-coupling conditions did not form the desired macrocycle **288** either and heating the reaction to 75 °C only led to decomposition of the starting material **287** (Figure 31).[8, 51]



reagent	SmI_2	SmI_2 / HMPA	$CrCl_2$ / $NiCl_2$	$CrCl_2$ / $NiCl_2$
solvent (temp.)	THF (-78 °C)	THF (-78 °C)	DMF (r.t.)	DMF (75 °C)
result	s.m. (**287**)	decomposition	s.m. (**287**)	decomposition

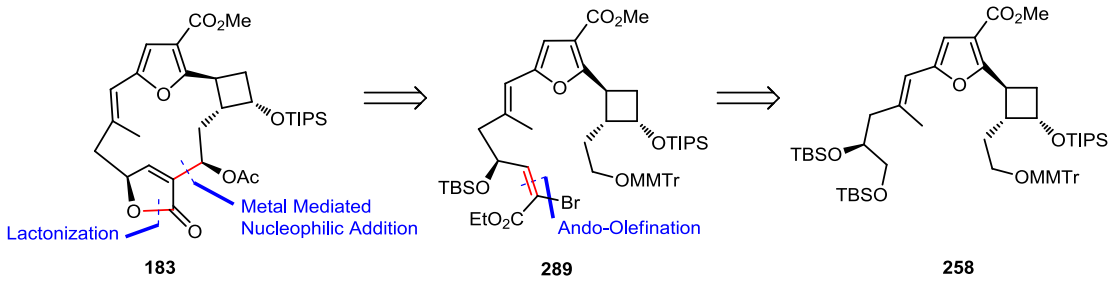
Figure 31: Synthesis of precursor 287 and attempted macrocyclization.

2.1.2.3.2 Furan-$\Delta^{12,13}$ Approach

The leading thought of this approach is the release of ring strain of the 13-membered macrocycle, by the selective opening of the butenolide moiety and thus, generating more degrees of freedom, which should ease the closure of the macrocycle. Advantages are the correct geometry of the $\Delta^{7,8}$ double bond and the closed furan moiety already in place.

Retrosynthetic Analysis:

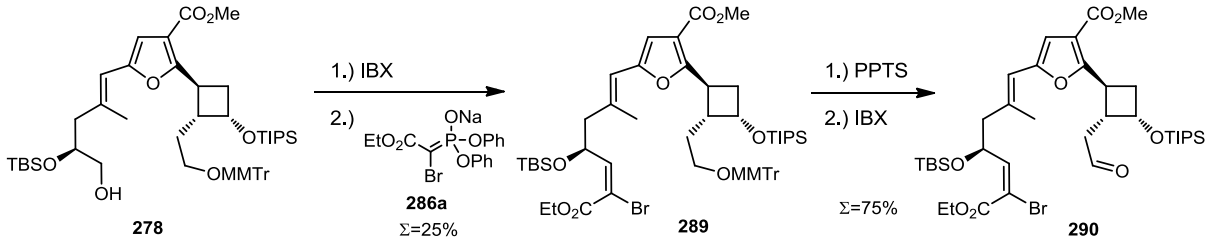
The retrosynthetic degradation started with the opening of the butenolide moiety of **183** and continues with the oxidative cleavage of the $\Delta^{11,12}$-double bond of **289**. Further reduction of the resulting aldehyde to the corresponding primary alcohol led to well established key intermediate **258** (Scheme 42).



Scheme 42: Retrosynthetic analysis of the furan $\Delta^{12,13}$ approach.

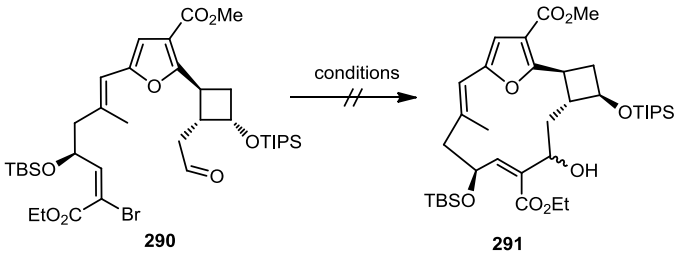
Synthesis:

Well established primary alcohol **278** was oxidized with IBX to the corresponding aldehyde, that was subsequently (*E*)-selectively olefinated by the use of the α-brominated derivative of *Ando*'s phosphonate **286a**.[105] [110] The resulting α-bromo enone **289** was subjected to acidic MMTr-ether cleavage conditions and the resultant primary alcohol was oxidized to aldehyde **290**, using IBX as the oxidizing reagent (Scheme 43).



Scheme 43: (*E*)-selective *Ando*'s olefination and synthesis of macrocyclization precursor 290.[110]

Aldehyde **290** constituted the macrocyclization precursor, which should lead to macrocyclic compound **291** under (transition) metal catalysis. Unfortunately, the idea of releasing strain was not fruitful, because none of the applied conditions, whether SmI_2 nor Cr(II)/Ni(II) led to the formation of the desired macrocycle **291** and thus, one step closer to Providencin (**1**) (Figure 32).[107]



reagent	SmI_2	SmI_2 / HMPA	$CrCl_2$ / $NiCl_2$
solvent	THF (-78 °C)	THF (-78 °C)	DMF (r.t.)
result	decomposition	decomposition	s.m.

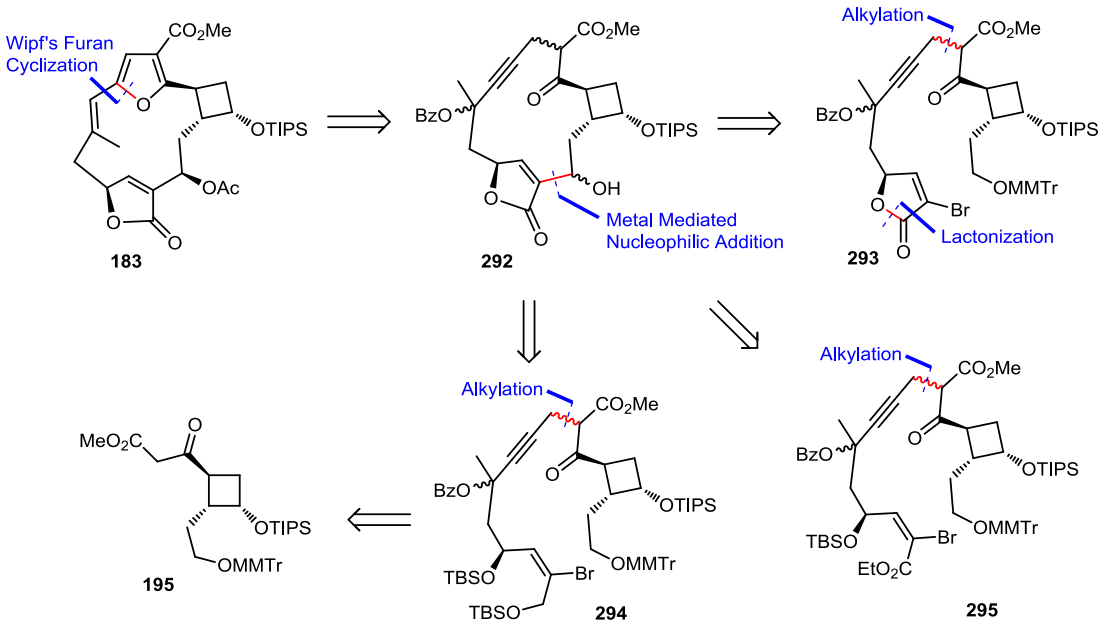
Figure 32: Attempted macrocyclization conditions.

2.1.2.3.3 $\Delta^{12,13}$ Approach

Unfortunately, the idea of releasing strain by opening of the butenolide moiety was not fruitful and did not lead to the formation of the desired macrocycle **291**. Therefore, another rigid element of the 13-membered macrocycle is opened: the furan moiety. Aromaticity means planarity and this automatically leads to rigidity. By opening of the furan moiety much strain is released and thus the closure of the carbon macrocycle should be simplified. Late stage furan closure by the *Wipf* methodology should be both,[71] enthalpically and entropically favored and therefore, should work with ease.

Retrosynthetic Analysis:

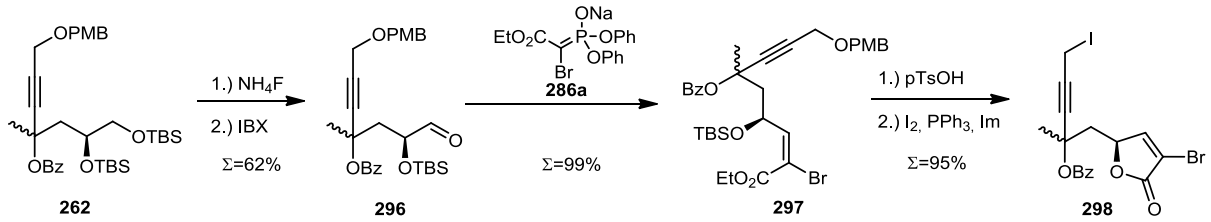
The first step in the retrosynthetic analysis was the scission of the C6-O bond to open the furan moiety, leading to intermediate **292**. Subsequent opening of the macrocycle gave intermediate **293**. This was further simplified by lactone hydrolysis which led to intermediate **295**. In **295** another rigid ring system was opened and thus, flexibility should be enhanced. Furthermore, α-bromo acrylic ester could be reduced to allylic silyl ether **294**, which should boost the electron density in the vinyl bromide and therefore, should ease the oxidative addition of the (transition) metal, which should alle*via*te the macrocyclization. Intermediates **293**-**295** were built up by alkylation of **195** with the corresponding propargylic iodides (**298**, **300**, **304**) (Scheme 44).



Scheme 44: Retrosynthetic analysis of the $\Delta^{12,13}$ approach.

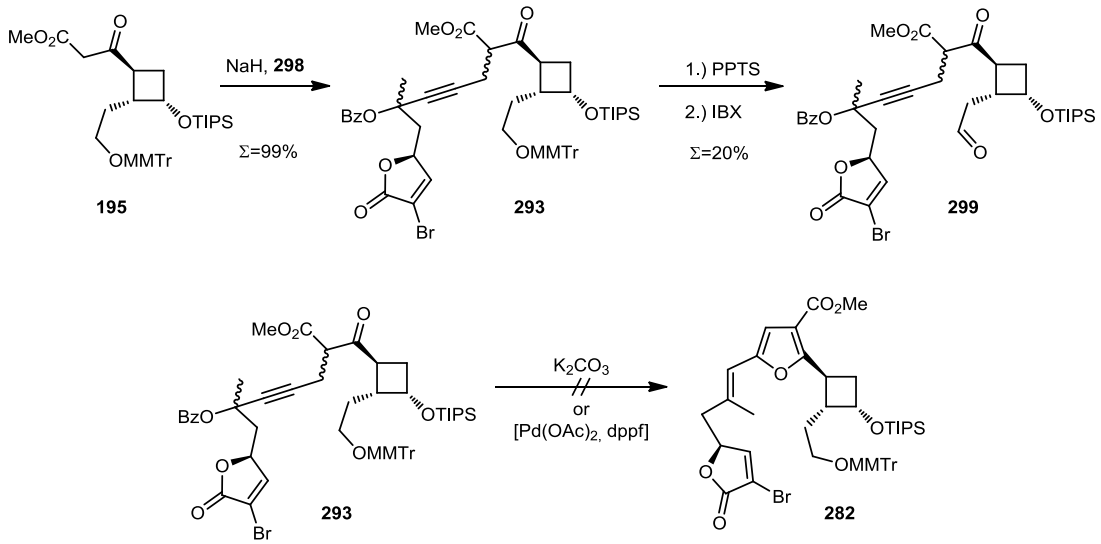
Synthesis:

Bis TBS-ether **262** was chemoselectively converted to the corresponding free alcohol by the weak fluoride donor ammoniumfluoride. The resulting primary alcohol was gently oxidized by the use of IBX to aldehyde **296**. (*E*)-selective olefination with α-brominated *Ando*'s phosphonate (**286a**) yielded compound **297**,[105] [110] which was treated with *p*TsOH. Under these conditions, three reactions took place in a row: First, cleavage of the TBS-ether, second, closure of the butenolide moiety and third, cleavage of the PMB-ether. Treatment of the resulting primary alcohol under modified *Appel* conditions led to propargylic iodide **298** (Scheme 45).[50]



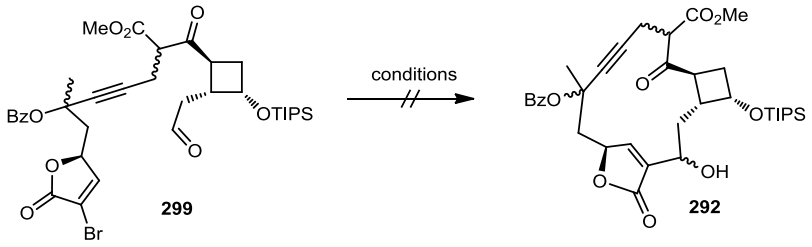
Scheme 45: Short 5-step synthesis of side chain 298.

Described β-keto ester **195** was enolized with NaH and alkylated with **298**. The resulting alkylated species **293** was transformed to **299** by a two step procedure, known from previous approaches. Finally **299** represented the finished macrocyclization precursor. Interestingly, *Wipf*'s furan cyclization methodology of precursor **293** to furan **282** was not applicable and only led to complete degradation.[71] This made the synthesis of **282** by this short and convergent route impossible (Scheme 46). Nevertheless, furan **282** could be obtained by CM, described in chapter ***2.1.2.3.1.***



Scheme 46: Synthesis of macrocyclization precursor 299; Attempted furan closure by *Wipf*'s conditions.[71]

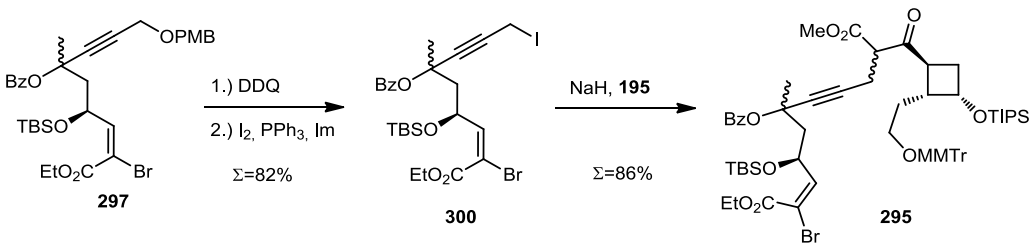
Within this approach, macrocyclization precursor **299** was used for further synthesis. The stage was set for one of the key steps and vinyl bromide **299** was treated with various (transition) metals to form macrocycle **292**. But whether SmI_2, nor Cr(II)/Ni(II) mediated the desired transformation to macrocycle **292**.[7] On the one hand side, the reason could be the remaining strain caused by the butenolide and the cyclobutane, on the other hand, it could be due to the electron deficiency of the vinyl bromide, anticipating in the oxidative insertion of the transition metal (Figure 33).



reagent	SmI_2	SmI_2 / HMPA	$CrCl_2$ / $NiCl_2$
solvent	THF (-78 °C)	THF (-78 °C)	DMF (r.t.)
result	decomposition	decomposition	s.m. (**300**)

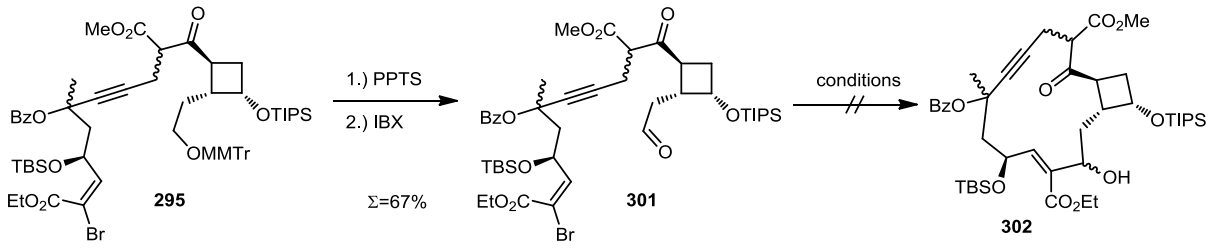
Figure 33: Attempted (transitions) metal mediated macrocyclization.

Thus, the concept was reinvestigated and it was decided to open two rigid rings, to ease the macrocyclization: the furan moiety and the butenolide moiety. Therefore, another alkylation substrate had to be synthesized. In fact, only the butenolide cyclization step had to be spared out and the PMB-ether **297** could directly be oxidatively cleaved and further be transformed to the corresponding propargylic iodide **300**. Again, β-keto ester **195** was deprotonated with NaH and subsequently alkylated with **300**, furnishing compound **295** (Scheme 47).



Scheme 47: Alkylation of 195 with 300.

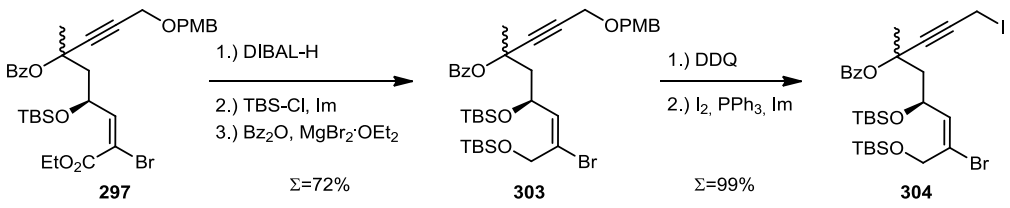
As for the other approaches, a two step deprotection/oxidation sequence led to the macrocyclization precursor **301**. The ring strain is reduced to a minimum and so expectations were high. But, much to our regret, none of the applied conditions led to the formation of the desired macrocyclic compound **302**. If this approach should work, the enhancement of the electron density in the vinyl bromide should be conducive (Figure 34).



reagent	SmI_2	SmI_2 / HMPA	$CrCl_2$ / $NiCl_2$
solvent	THF (-78 °C)	THF (-78 °C)	DMF (r.t.)
result	decomposition	decomposition	s.m.

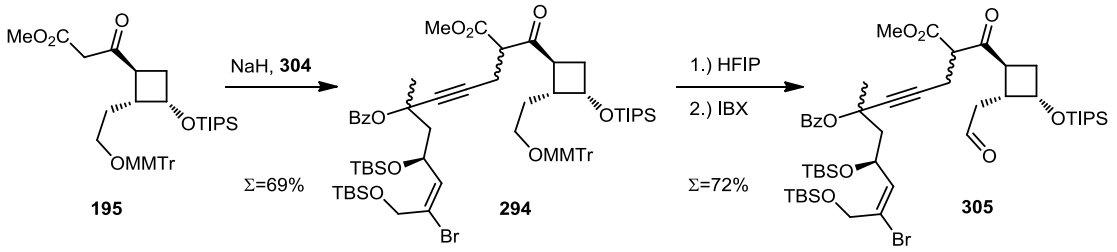
Figure 34: Synthesis of macrocyclization precursor 301 and attempted macrocyclization.

Thus, an alkylation fragment had been synthesized, where the ester was replaced by a protected allylic alcohol. Therefore, intermediate **297** was reduced with DIBAL-H. As the tertiary benzoylic ester was not stable under these conditions and was reduced as well, it had to be reinstalled. For this reason, the resulting primary alcohol was converted to its TBS-ether and afterwards *Vedejs*' protocol was applied to re-install the tertiary benzoate **303**.[87] Subsequent appliance of the well established deprotection/iodination sequence led to alkylation fragment **304** (Scheme 48).



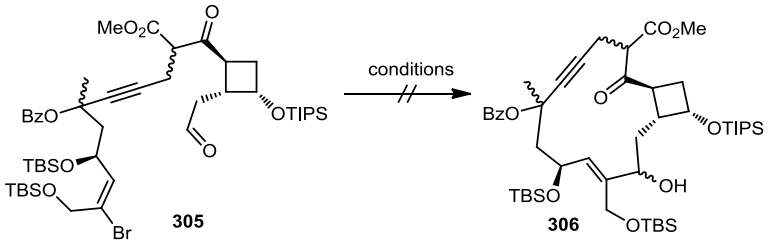
Scheme 48: 5-step synthesis of side chain 304.

Application of the known three step sequence to intermediate **195** – alkylation, deprotection and oxidation – resulted in the formation of the desired macrocyclization precursor **305** (Scheme 49).



Scheme 49: Alkylation of 195 and completion of macrocyclization precursor 305.

Compound **305** was subjected to many different cyclization conditions, but to our disappointment, none of them led to the formation of the desired macrocycle **306**. Unfortunately, two different extremes could be observed: either no reaction occurred or due to too many functional groups decomposition was observed (Figure 35).



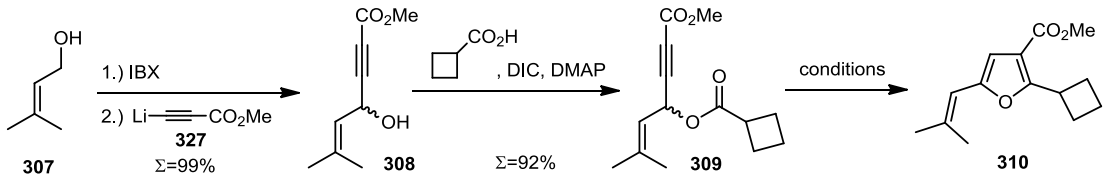
reagent	SmI_2	SmI_2 / HMPA	$CrCl_2$ / $NiCl_2$	$CrCl_2$ / $NiCl_2$	$CrCl_2$ / $NiCl_2$
solvent	THF (-78 °C)	THF (-78 °C)	DMF (r.t.)	DMF (40 °C)	DMF (75 °C)
result	decomposition	decomposition	s.m. (**305**)	s.m. (**305**)	decomposition

Figure 35: Attempted cyclization of 14-membered carbacycle 306.

2.1.3 Krische's Furan Cyclization Approaches

The common key intermediate of these approaches is the phosphine mediated furan closure developed by *Krische* and coworkers,[72] where a carboxy methyl substituted propargylic ester is transformed to a 2,3,5-trisubstituted furan moiety. The big advantage of this method is the preparation of the corresponding starting materials. Forming an ester bond is by far easier, than forming a carbon-carbon bond, thus the crucial step of macrocyclization can be accomplished by rather simple, well established macrolactonization techniques.[6] *Krische* describes a large number of different substrates,[72] which smoothly undergo furan cyclization. Since the shown examples are rather simple and do not have many functional groups, a model substance is synthesized.

Starting from 3,3-dimethyl allyl alcohol (**307**), oxidation and nucleophilic addition of **327** gave propargylic alcohol **308**. A *Steglich* esterification with cyclobutane carboxylic acid yielded cyclization precursor **309** in high yields,[80] which was subsequently subjected to *Krische*'s conditions (Figure 19).[72] Unfortunately, the suggested conditions did not lead to the formation of the desired heterocycle **310**, maybe due to the high steric demand of the phosphine substituents and leading to a decreased nucleophilicity. Therefore, these phosphines (PPh_3, $P(o\text{-}Tol)_3$) were replaced by more nucleophilic alkyl phosphines ($P(n\text{-}Bu)_3$, $P(n\text{-}Oct)_3$). To our delight precursor **309** underwent furan cyclization to **310** in good yields under these modified *Krische* conditions (Figure 36).



phosphine	PPh_3	PPh_3	$P(o\text{-}Tol)_3$	$P(o\text{-}Tol)_3$
solvent (°C)	EtOAc (110 °C)	EtOAc (μW, 110 °C)	C_6H_6 (r.t.)	C_6H_6 (110 °C)
result	s.m. (**309**)	s.m. (**309**)	s.m. (**309**)	s.m. (**309**)
phosphine	$P(n\text{-}Bu)_3$	$P(n\text{-}Bu)_3$	$P(n\text{-}Oct)_3$	$P(t\text{-}Bu)_3$
solvent (°C)	EtOAc (110 °C)	C_6H_6 (110 °C)	EtOAc (110 °C)	EtOAc (110 °C)
result	62%	60%	45%	s.m. (**309**)

Figure 36: Synthesis and cyclization of the of the *Krische* method model substrate 310.[72] All reactions were performed in a sealed tube.

2.1.3.1 *Macrolactonization Attempts*

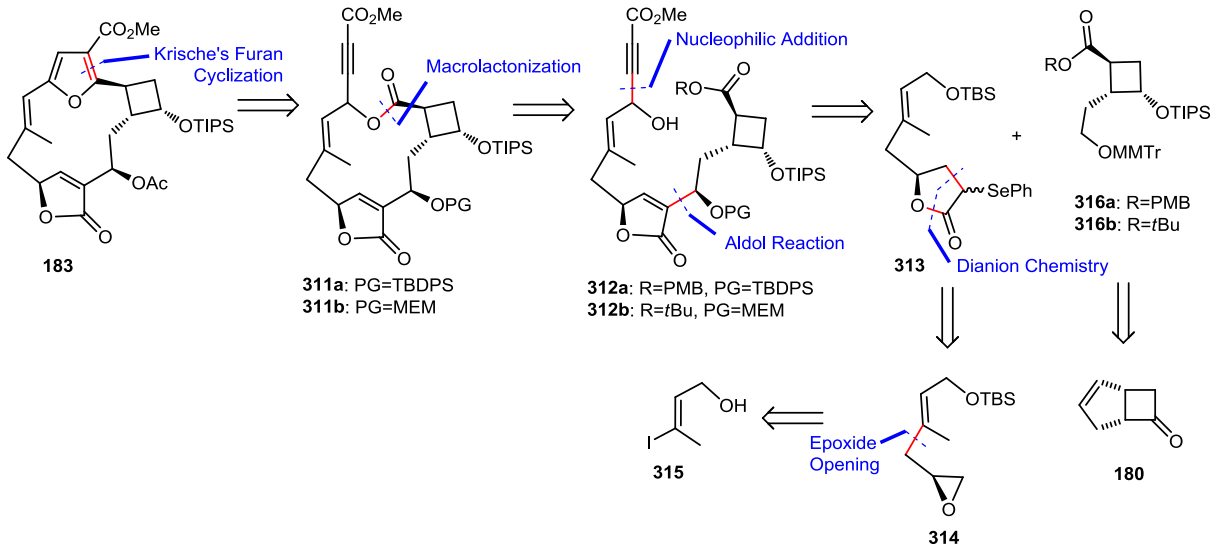
Macrolactonization is a well established synthetic technique in the total synthesis of natural products. Many different carboxyl activating reagents are published, thus, offering a large variation of possible condition. Using *Krische's* method, Providencin precursor **183** can be simplified to a molecule containing two lactones, both suitable for macrolactonization. Although, the *Krische* furan closure strategy offers the formation of a macrolactone,[72] it does not solve the problem of high ring strain of the Providencin (**1**) core.

2.1.3.1.1 Northern Lactone-Butenolide Approach

Having many structural motifs already installed, means more rigidity in the molecule. But, functionalization after ring closure implies working on a more complex molecule, which increases the danger of side reactions. Thus, a powerful macrolactonization reagent can probably overcome the ring strain and saves post functionalization. This approach makes use of the early installation of the cyclobutane, the $\Delta^{7,8}$ (*E*)-double bond and the butenolide moiety and closes the macrocycle and the furan moiety in one of the last steps.

Retrosynthetic Analysis:

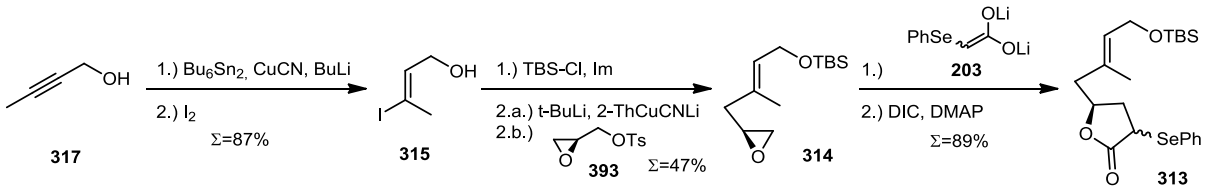
Opening of the furan in **183** led to macrolactones **311a, b**. After ester hydrolysis, *seco* compounds **312a, b** were obtained, that were further simplified by the removal of the propargylic ester. The scission of the $\Delta^{12,13}$ bond divided the compounds in two equally large fragments **313** and **316a, b**. Compound **313** was further simplified by the degradation of selenolactone **313** to epoxide **314**, which could be obtained from vinyl iodide **315** and tosylated (*R*)-glycidol (**393**). Esters **316a, b** were reduced to alcohol **188**, which could be derived from bicycloketone **180** (Scheme 50).



Scheme 50: Retrosynthetic analysis of the northern lactone butenolide approach.

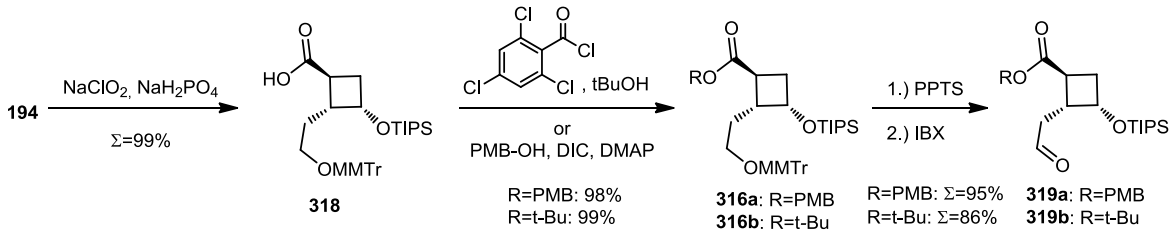
Synthesis:

But-2-yn-1-ol (**317**) was subjected to a hydrostannylation reaction yielding the corresponding stable vinyl stannane,[111] which was subsequently transformed to its vinyl iodide **315** by the addition of I_2. Installation of a primary TBS protecting group under standard conditions resulted in the formation of the precursor of a copper mediated addition-elimination cascade reaction. TBS-protected **315** was lithiated with t-BuLi and low order cuprate 2-thienyl(cyano)copper lithium was added.[112] The formed high order cuprate acts as a soft nucleophile and attacks tosylated (*R*)-glycidol **393** on the epoxide side. The formation of a *Schlosser-Fouquet* product was not observed.[64] The *in situ* formed alcoholate substituted the tosylate in a S_N^2 reaction and formed the epoxide **314**. Using the already in chapter ***2.1.2.1.1*** established dianion methodology of phenyl seleno acetic acid **203** and subsequent carbodiimin esterification formed desired selenolactone **313** in a short synthetic sequence (Scheme 51).[80]



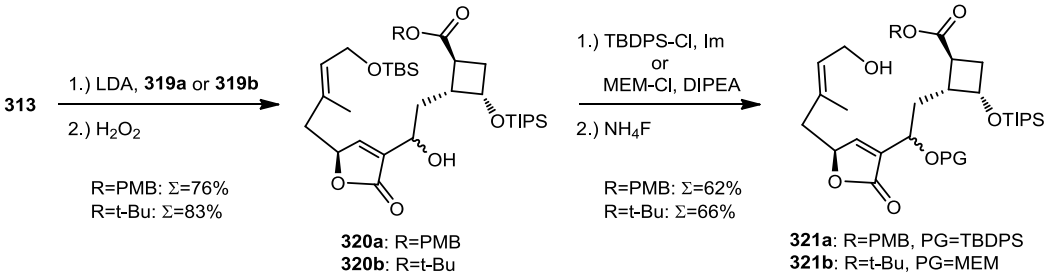
Scheme 51: Stereoselective synthesis of selenolactone 313.

Aldehyde **194** was oxidized to the corresponding carboxylic acid under *Pinnick* conditions. Two different esters were synthesized, a PMB-ester (**316a**) and a t-Bu-ester (**316b**). Both of them should be feasible to be deprotected orthogonally to the methyl ester of fragment **312a, b**. For the installation of the PMB-ester, *Steglich* conditions were applied, which unfortunately, did not work for the t-Bu series.[80] t-Butanol was sterically too demanding for this kind of reaction, therefore the *Yamaguchi* method was used.[113] In both cases esterification worked in high yields and delivered fragment **316a** and **316b**, respectively. A two step deprotection-oxidation sequence finally yielded the northern fragments **319a, b** (Scheme 52).



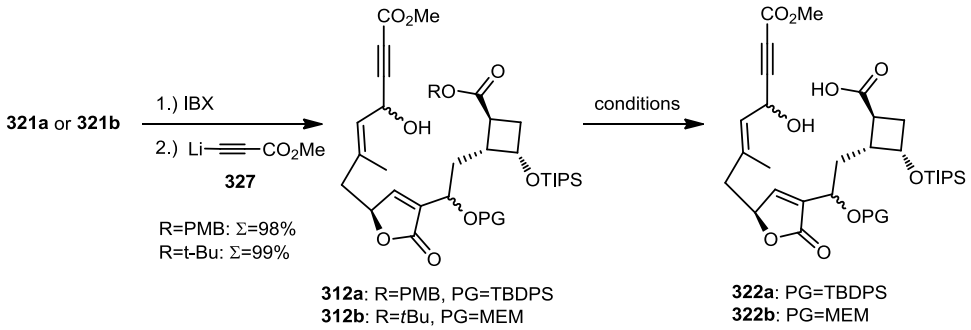
Scheme 52: Synthesis of the northern fragment 319a-b.

Fragment **313** was converted to its Li-enolate, using LDA and added to aldehydes **319a, b**, respectively. The resulting mixtures of diastereo isomers (*d.r.* = 3:1) were treated under oxidative conditions. Subsequent elimination of the seleno phenyl ether generated the butenolide double bond. The newly formed secondary alcohols **320a, b** were converted into the corresponding TBDPS-ether in the PMB-series and to the MEM-ether in the t-Bu-series. Chemoselective deprotection of the primary allylic alcohol with NH_4F yielded intermediates **321a, b** (Scheme 53).



Scheme 53: Fragment combination and installation of different protecting groups.

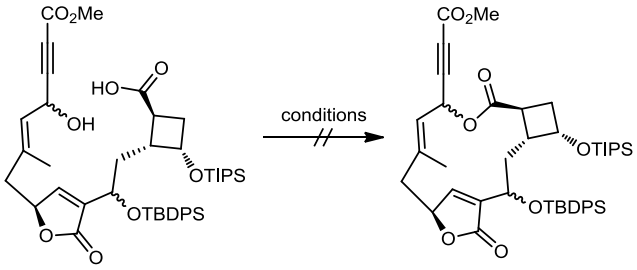
Primary alcohols **321a, b** were oxidized with IBX and lithiated methyl propiolate (**327**) was added. Now, the stage was set to liberate the carboxylic acids **322a, b**. Many different conditions were applied, but only one provided the desired *seco* compound **322a**. All others led, due to harsh reaction conditions, to decomposition of precursors **312a, b** (Figure 37).



reagent	Δ	TFA	Δ	SiO_2
solvent	neat	CH_2Cl_2	quinoline	toluene
s.m.	**312b**	**312b**	**312b**	**312b**
result	decomposition	decomposition	decomposition	s.m.
reagent	DDQ	CAN	TFA	TFA/Et_3SiH
solvent	CH_2Cl_2/buffer	CH_3CN/H_2O	CH_2Cl_2	CH_2Cl_2
s.m.	**312a**	**312a**	**312a**	**312a**
result	decomposition	decomposition	88% yield	87% yield

Figure 37: Different deprotection conditions for PMB- and t-Bu-esters.

Seco compound **322a** was subjected to a variety of different macrolactonization conditions. Unfortunately, none of them led to the formation of the desired macrolactone **311a**. Whether the well established *Yamaguchi* conditions,[113] nor the method developed by Shiina *et al.*,[44] nor carbodiimine methods were successful (Figure 38).



322a **311a**

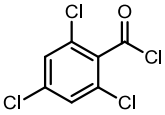
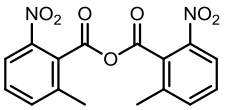
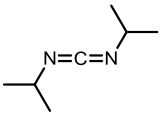
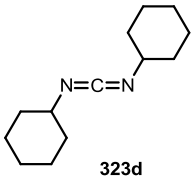
reagent	 **323a**	 **323b**	 **323c**	 **323d**
conditions	DMAP (*Yamaguchi*)[113]	DMAP (*Shiina*)[44]	DMAP (*Steglich*)[80]	DMAP·HCl (*Keck*)[114]
solvent	benzene	toluene	CH_2Cl_2	$CHCl_3$
result	decomposition	s.m.	s.m.	decomposition

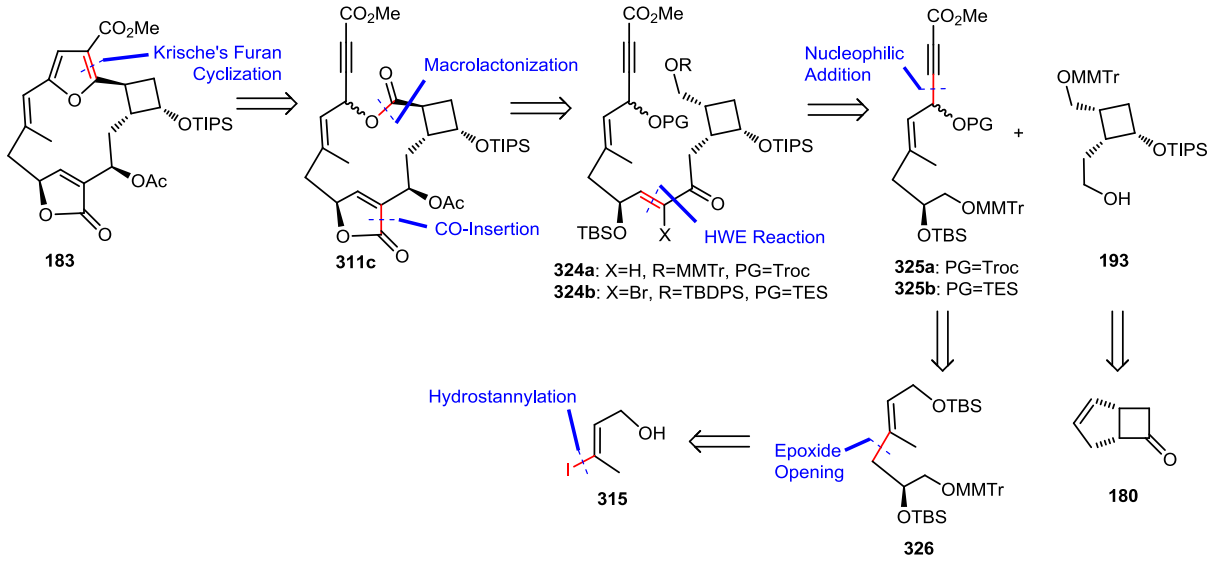
Figure 38: Macrolactonization attempts for precursor 322a.

2.1.3.1.2 Northern Lactone-*Horner Wadsworth Emmons* Approach

In the previous approach the structural motif of the butenolide was already installed. Within this approach, ring strain is reduced by the removal of the butenolide moiety. Combination of two fragments should be performed by a HWE reaction, generating a vinyl halide. This HWE reaction has to be (*Z*)-selective in case the halide is introduced by the phosphonate. This means, that the halide and the secondary alcohol moiety have to be on the same side of the double bond. If the halide is introduced in a later stage, the outcome of the double bond geometry is not important. Macrolactonization should be performed in the northern part of the molecule, with the cyclobutane in place. Furthermore, the (*E*)-geometry of the $\Delta^{7,8}$ double bond is already predefined.

Retrosynthetic Analysis:

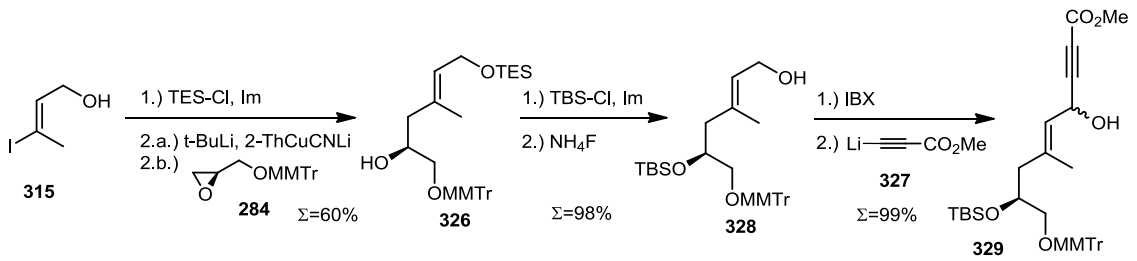
The furan moiety of crucial intermediate **183** was opened and macrolactone **311c** was received. Saponification of the lactone, reduction of the carboxylic acid and removal of the butenolide carbonyl yielded intermediates **324a, b**, that were further simplified by an oxidative cleavage of the $\Delta^{11,12}$ double bond resulting in the formation of **325a, b** and **193**, two building blocks similar in size. Scission of the $\Delta^{5,6}$ single bond in **325a-b** and removal of the southern C3-glycidol-subunit in **326** finally yielded building block **315** (Scheme 54).



Scheme 54: Retrosynthetic analysis of the northern lactone HWE approach.

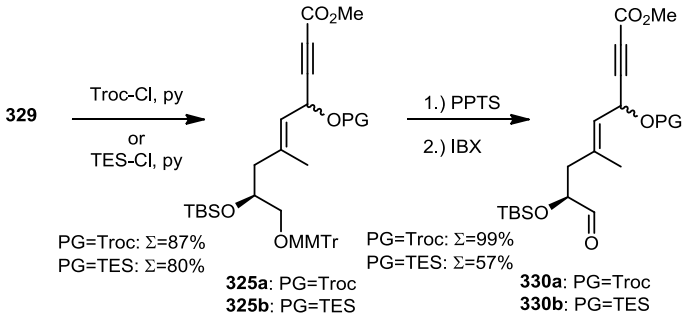
Synthesis:

Vinyl iodide **315** was converted to its TES-ether under standard conditions and lithiated by the addition of t-BuLi. The formation of the corresponding high order cuprate was carried out by the addition of 2-thienyl(cyano)copper lithium.[112] This soft nucleophile attacked MMTr-protected (*R*)-glycidol **284** on the epoxide side. The formed secondary alcohol **326** was converted to the corresponding TBS-ether and the primary silyl ether was chemoselectively cleaved with NH_4F. The resulting primary allylic alcohol **328** was oxidized using IBX as the oxidizing reagent and lithiated methyl propiolate (**327**) was subsequently added to finish the synthesis of **329** (Scheme 55).



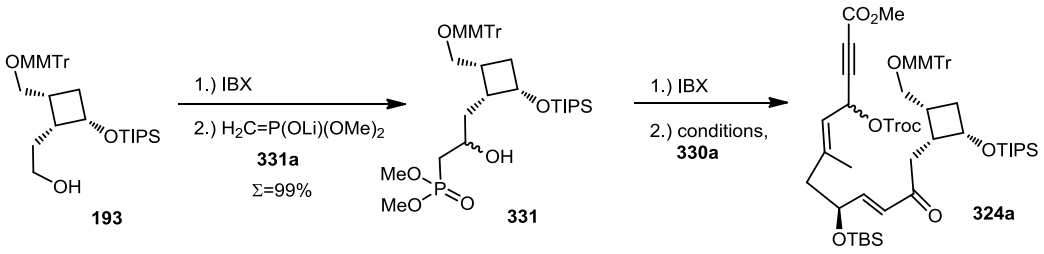
Scheme 55: 6-step synthesis of intermediate 329.

The secondary alcohol **329** was either converted to its Troc-carbonate **325a** or its TES-ether **325b**. A final deprotection-oxidation sequence yields the western fragments **330a-b** (Scheme 56).



Scheme 56: Installation of different protecting groups and completion of the fragment synthesis.

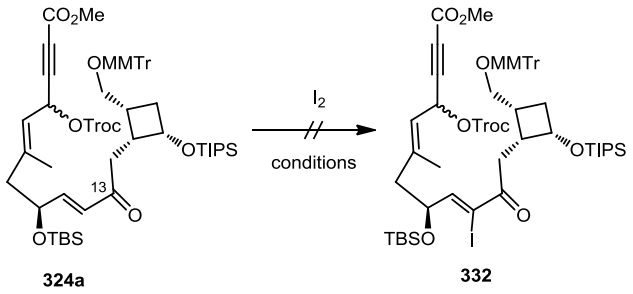
Mono-MMTr-ether **193** was oxidized with IBX and lithiated dimethyl-methyl phosphonate (**331a**) was added. The resulting β-hydroxy phosphonate **331** was oxidized to the corresponding β-keto phosphonate, which was subjected to HWE-olefination under various conditions. Every base used resulted in the formation of the desired (*E*)-configured double bond **324a**, but using LiHMDS as the base gave the best results (Figure 39).



base	K_2CO_3, 18-crown-6	KHMDS	LiHMDS
solvent (temp.)	THF (-10 °C)	THF (-78 °C)	THF (-78 °C)
yield	34% (*E* only)	39% (*E* only)	55% (*E* only)

Figure 39: Installation of β-keto phosphonate and applied HWE conditions.

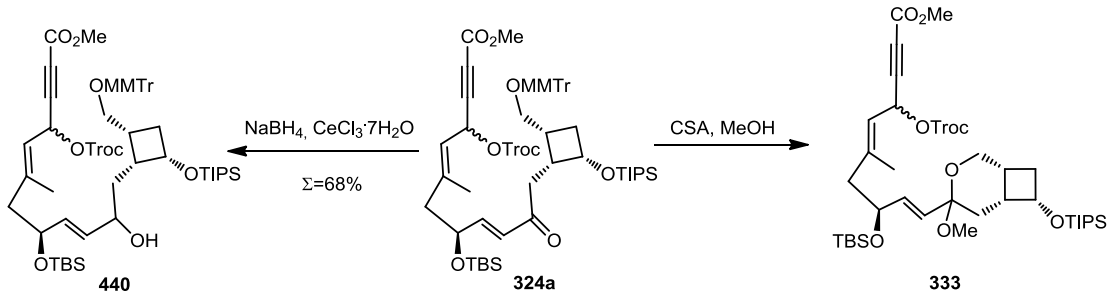
With the desired enone **324a** in hands, the stage was set for the introduction of the necessary halogen in α-position of the ketone. Literature provided a large variety of different methods for the introduction of α-halo enones,[115] [102] [103] but all of them starting with an unsubstituted *Michael*-system had one in common: the use of halogen and base. Unfortunately, all of the applied conditions were unsuccessful and did not form the desired α-halo enone **332** (Figure 40). Apart from that, *Luche* reduction of the C13 carbonyl of **324a** to provide the corresponding allylic alcohol **440** was successful,[36] but would only delay the problem of halide introduction to a later stage of the synthesis. Treatment of **324a** under acidic conditions for the attempted cleavage of the MMTr-ether led to the formation of cyclic acetal **333** (Scheme 57).



324a **332**

conditions	py, CCl_4[102]	NEt_3, CH_2Cl_2	DMAP, THF[103]
result	s.m. (**324a**)	s.m. (**324a**)	decomposition

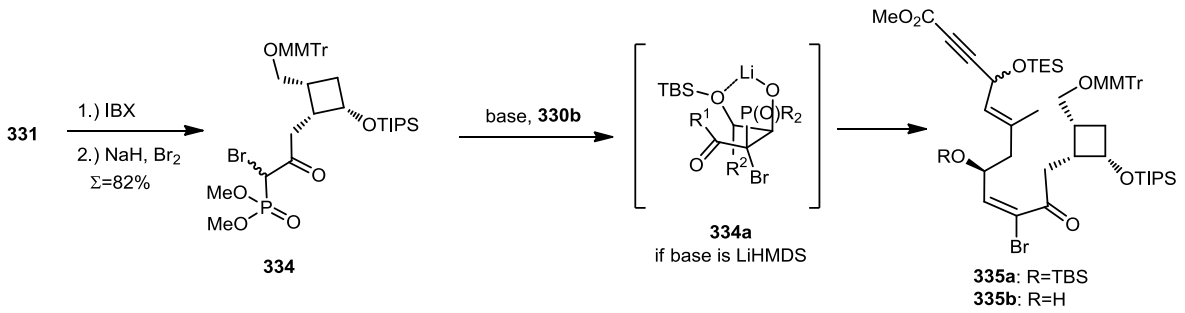
Figure 40: Attempted introduction of the α-iodine moiety.



440 **324a** **333**

Scheme 57: Undesired closure of a methyl acetal under acidic conditions.

Since the introduction of the halide at the $\Delta^{11,12}$ double bond was an unsolvable problem, the halide should be introduced at an earlier stage by a brominated β-keto phosphonate. Therefore, β-hydroxy phosphonate **331** was oxidized with IBX and deprotonated with NaH, followed by trapping of the enolate with bromine.[116] Substrate **334** was again enolized with different bases and subjected to HWE reaction conditions. Unfortunately, only the undesired (*E*)-isomers **335a, b** could be isolated, most probably due to the high steric demand of the bromine atom (Figure 41). The loss of the TBS-protecting group (**335b**) may be explained by Lewis acidic activation of the TBS-silyl ether *via* transition state **334a**.

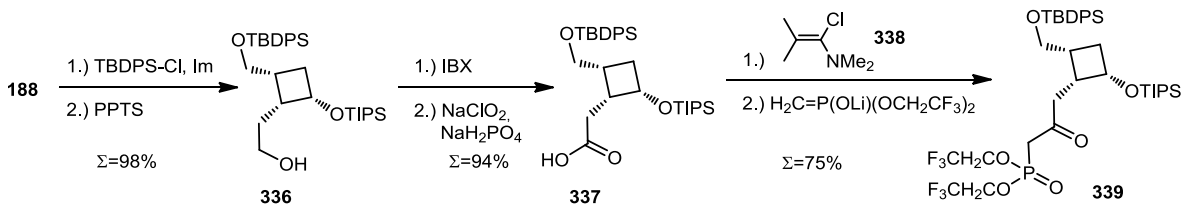


base	KOt-Bu, 18-crown-6	KOt-Bu	KHMDS	LiHMDS
solvent (temp.)	THF (-10 °C)	THF (0 °C)	THF (-78 °C)	THF (-78 °C)
R=	TBS (**335a**)	TBS (**335a**)	TBS (**335a**)	H (**335b**)
yield	27% (*E* only)	70% (*E* only)	35% (*E* only)	63% (*E* only)

Figure 41: Installation of an α-bromo-enone by HWE conditions.

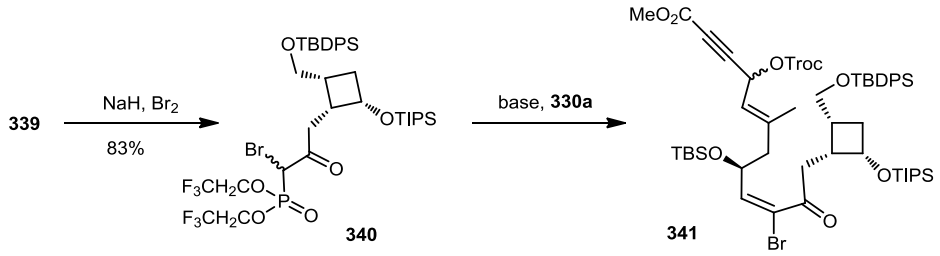
Due to the variation of the stereoelectronical properties of the phosphonate substituents, it should be possible to influence the outcome of the geometry of the formed double bond. In 1983 *Still* and *Gennari* reported on a (*Z*)-selective variation of the classical HWE reaction.[100] The two ethoxy substituents on the phosphorous atom were replaced by two trifluoroethoxy substituents and these electron withdrawing groups, together with a strong base formed exclusive (*Z*)-olefins. The synthesis of such substrates was a bit more complex, due to the high lability of di(trifluoroethyl) methyl enolates. Classical addition to an aldehyde and subsequent oxidation to the corresponding β-keto phosphonate was not practical.

Thus, mono-MMTr ether **188** was converted to its corresponding TBDPS-ether and the liberated primary alcohol **336** was oxidized stepwise to the corresponding carboxylic acid **337**. The carboxylic acid was transformed to its acid chloride using *Ghosez*' reagent (**338**) and lithium di(trifluoroethyl) methyl phosphonate was added to smoothly provide β-keto phosphonate **339** (Scheme 58).[117]



Scheme 58: Synthesis of the Still Gennari β-keto phosphonate.

Compound **339** was deprotonated with NaH, followed by trapping of the enolate with bromine. The brominated *Still-Gennari* phosphonate **340** was again enolized with different bases and subjected to HWE reaction (Figure 42). Once again and independently of the installed substituents on the phosphonate, only the undesired (*E*)-isomer **341** was formed, most probable due to the high steric demand of the bromine, which overruled the stereo electronical control of the phosphonate.

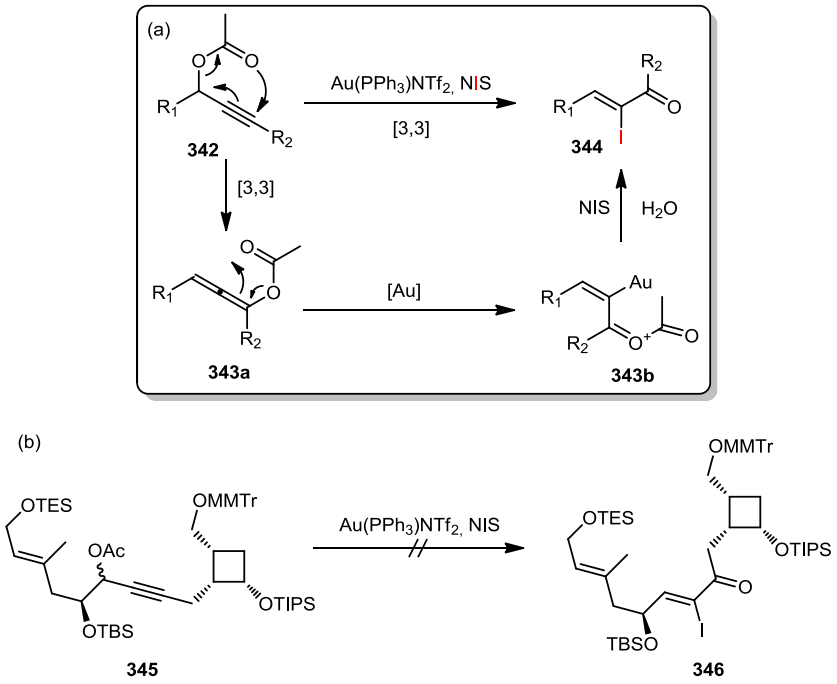


base	KOt-Bu	KHMDS	LiHMDS
solvent (temp.)	THF (-78 °C)	THF (-78 °C)	THF (-78 °C)
yield	26% (*E* only)	29% (*E* only)	46% (*E* only)

Figure 42: Applied conditions for the *Still Gennari* phosphonate.

Other (*Z*)-selective vinyl halide attempt:[118]

Since the introduction of a halide in α-position of the C13-carbonyl was not practicable by the methods used, a completely new structural motif was designed. Compound **345** should be converted to **346**, using a Au(I) mediated method developed by *Zhang*.[118] According to the authors, this methodology was highly *(Z)*-selective and proceeds *via* a [3,3]-sigmatropic shift of the acetyl-group (modified *Meyer-Schuster* rearrangement;[119] **342**, **343a**). The authors also presented several different examples, but with less functional groups. Nevertheless, these conditions were applied to precursor **345**, which was prepared by a four step sequence from established material **193**. To our disappointment, these conditions did not lead to the formation of the desired (*Z*)-vinyl iodide either **346** (Scheme 59).



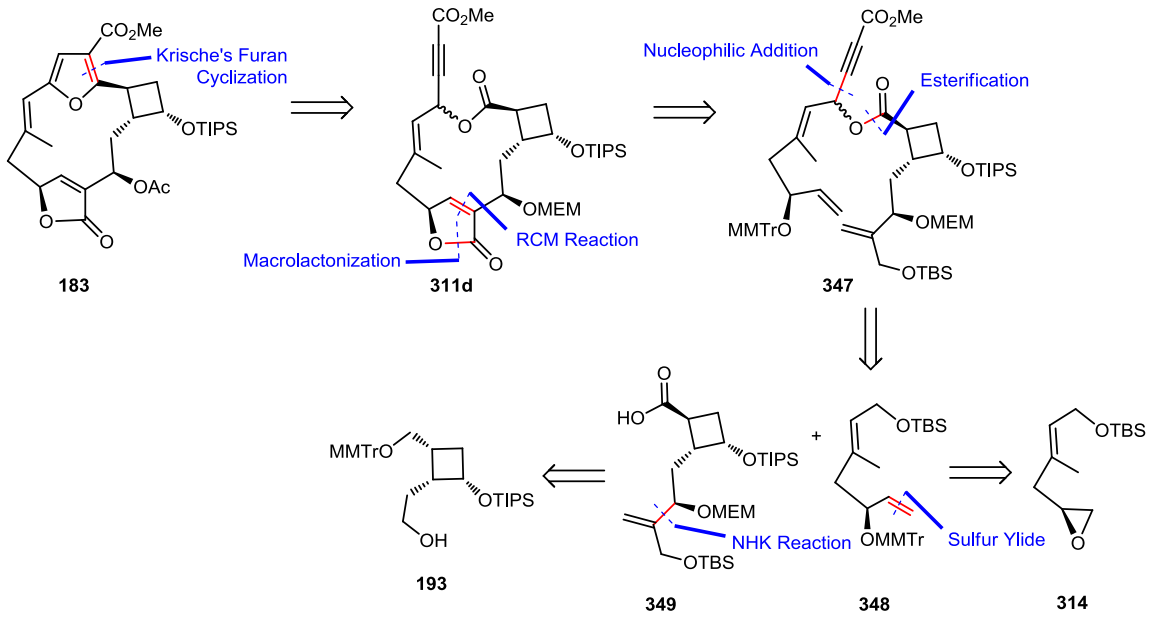
Scheme 59: (a) Au(I) mediated [3,3]-sigmatropic rearrangement and (b) Attempted (*Z*)-selective α-iodination.

2.1.3.1.3 Southern Lactone Approach

The other approaches using *Krische*'s method for furan cyclization seem to collapse due to high steric demand and rigidity of several functional groups (bromine, butenolide). Therefore, this approach uses the upper ester as linkage between two equally large fragments. The southern (butenolide) lactone is used as connection point for the macrocyclization.

Retrosynthetic Analysis:

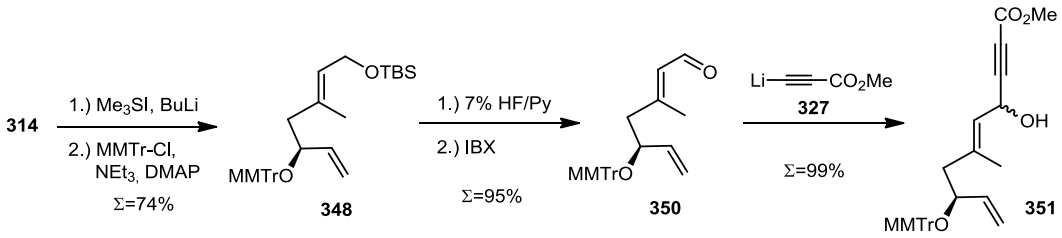
The furan moiety of crucial intermediate **183** was opened to macrolactone **311d**, followed by the opening of the $\Delta^{11,12}$ double bond of the butenolide by a formal cross metathesis with ethylene. Saponification of the macrolactone led to intermediate **347**. Another saponification of the northern lactone and after removal of methyl propiolate led to fragments **348** and **349**. Compound **348** could be further simplified to epoxide **314** and the eastern fragment could be degraded to well established mono-MMTr-ether **193** (Scheme 60).



Scheme 60: Retrosynthetic analysis of the southern lactone approach.

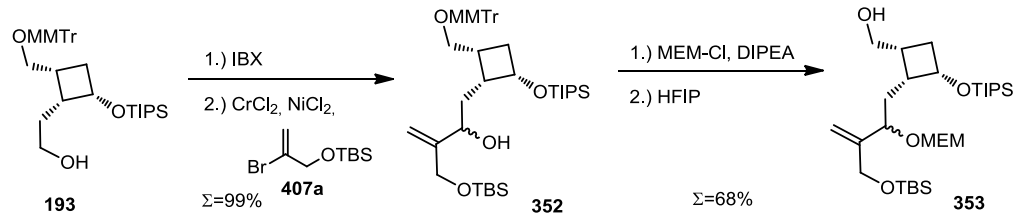
Synthesis:

Epoxide **314** was treated with trimethyl sulfur ylide, generated *in situ* by the treatment of trimethyl sulfur iodide with n-BuLi, and the resulting secondary allylic alcohol was converted to its MMTr-ether **348**. Cleavage of the remaining primary silyl ether with diluted hydrogen fluoride and subsequent oxidation with IBX yielded aldehyde **350**. Finally, addition of lithiated methyl propiolate (**327**) finished the synthesis of the western fragment **351** (Scheme 61).



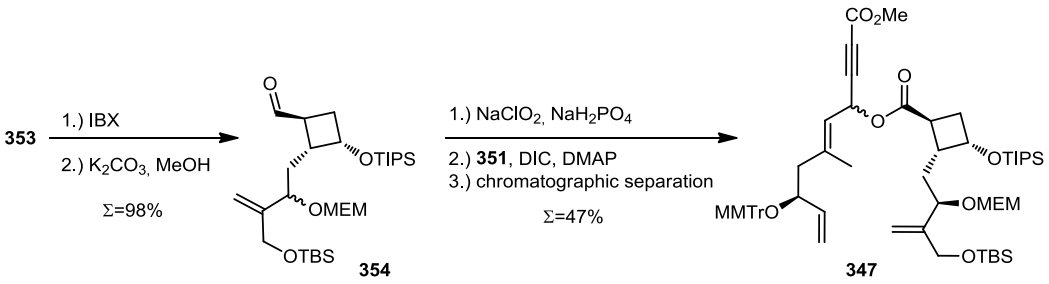
Scheme 61: 5-step synthesis of western fragment 351.

The eastern fragment of this approach was synthesized from well established alcohol **193**, which was oxidized to its corresponding aldehyde in the first step. Diastereo enriched (*d.r.* = 3.5:1) Cr(II)/Ni(II) catalyzed NHK reaction with **407a** yielded secondary alcohol **352**.[8, 51] This intermediate was converted to its MEM-ether under standard conditions and finally the primary MMTr-ether was cleaved chemoselectively by solvolysis in HFIP,[120] which completed the synthesis of compound **353** (Scheme 62).



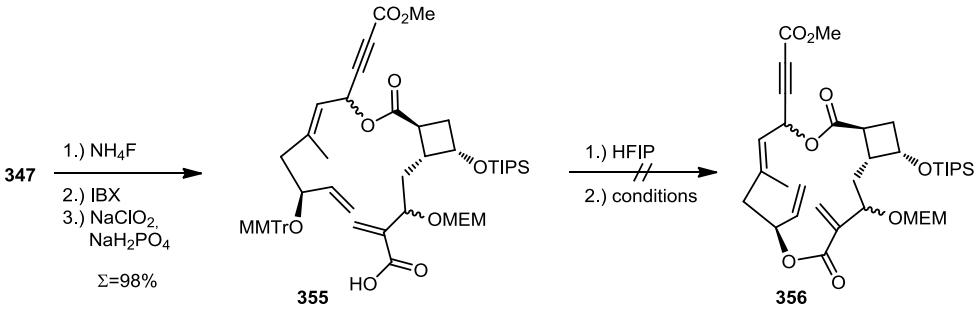
Scheme 62: Successful NHK-coupling and synthesis of 353.[51]

Oxidation of **353** using IBX as oxidizing agent and basic epimerization of the carbon center in α-position of the carbonyl resulted in the formation of aldehyde **354**, which was oxidized under *Pinnick* conditions to the corresponding carboxylic acid. Now, with both fragments in hand, the stage was set for fragment combination. Therefore, Steglich esterification conditions were used,[80] finally leading to advanced intermediate **347**. Even though, secondary MEM-protected alcohol was previously not introduced in a stereospecific way, it was possible to separate the diastereo isomers at this stage (Scheme 63).



Scheme 63: *Steglich* esterification of oxidized 354 (349) and 351.

Primary, allylic TBS-ether **347** was cleaved chemoselectively with NH_4F and the resulting primary alcohol was oxidized stepwise to the corresponding carboxylic acid **355**. Cleavage of the secondary MMTr-ether yielded the *seco* acid, which was the direct precursor for macrolactonization. Like in other macrolactonization approaches, many different reagents and conditions were applied, but, unfortunately, none of them led to the formation of the desired macrocycle **356** (Figure 43).



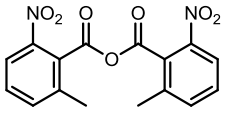
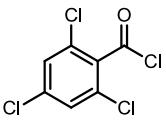
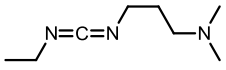
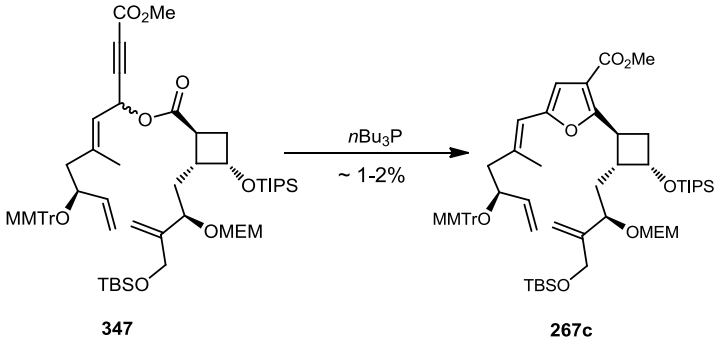
reagent	 **323b**	 **323a**	 **323e**
conditions	DMAP (Shiina)[44]	DMAP (Yamagucchi)[113]	DMAP·HCl (Keck)[114]
solvent	toluene	toluene	$CHCl_3$
result	s.m.	s.m.	decomposition

Figure 43: Installation of the *seco* acid and attempted macrolactonization conditions.

To proof the usability of the *Krische* method on highly functionalized molecules,[72] compound **347** was subjected to these conditions. To our disappointment, the reaction resulted in the formation of a complex mixture of products, probably due to the presence of four allylic ethers/esters, all of them capable to undergo a S_N2'-like reaction with good nucleophiles like alkyl phosphines. Nevertheless, trace amounts of the desired product **267c** could be isolated after intensive chromatographic separations (Scheme 64).



347 **267c**

Scheme 64: Application of *Krische* conditions to highly advanced intermediate 347.[72]

2.1.3.2 Ring Closing Metathesis Attempts

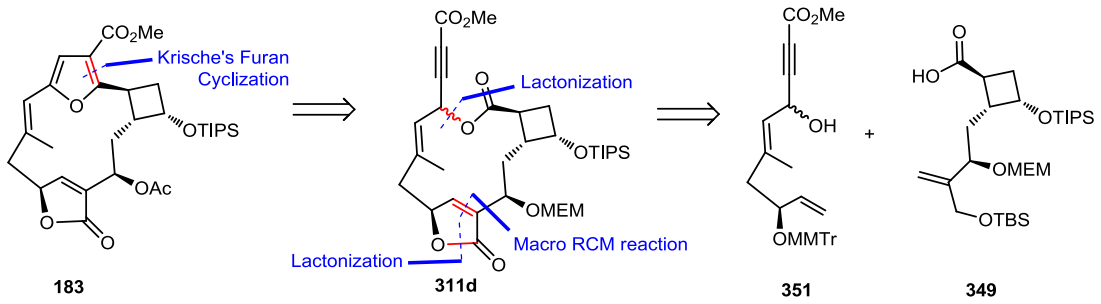
The RCM macrocyclization strategy in the *Krische* series has an exclusive advantage: The degrees of freedom of the non-closed furan moiety and the enthropically favored formation of ethylene during the macrocyclization reaction.

2.1.3.2.1 $\Delta^{11,12}$ Metathesis Approach

This approach is quite similar to the one described in chapter ***2.1.3.1.3*** and many related intermediates can be used. In fact, all degrees of freedom stay the same, only the macrocyclization strategy is different: A metathesis reaction, instead of a lactonization should be used.

Retrosynthetic Analysis:

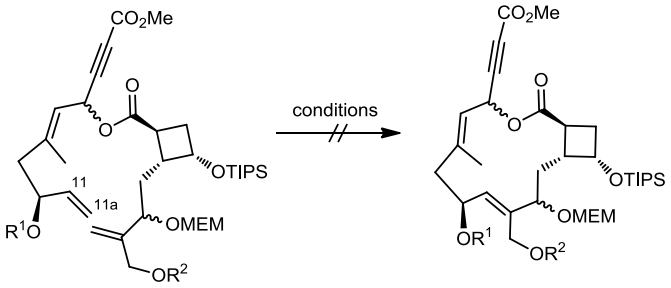
The furan moiety of crucial intermediate **183** was opened and macrolactone **311d** was received. Furthermore, the butenolide lactone was opened, followed by the cleavage of the double bond of the butenolide by a formal cross metathesis with ethylene. After saponification of the northern ester moiety, the two fragments **349** and **351** were obtained, both known from former approaches (Scheme 65).



Scheme 65: Retrosynthetic analysis of the $\Delta^{11,12}$ metathesis approach.

Synthesis:

Intermediates **357a-c** were subjected to a macro RCM reaction using different metathesis catalysts, different substitution patterns on various alcohols and different solvents (Figure 44). Unfortunately, in most cases only starting material was recovered, in the case of hexafluorobenzene (C_6F_6) was used as solvent,[94] the formation of a large variety of products could be observed and removal of both protecting groups R^1 and R^2 (R^1=R^2=H) resulted in the formation of a homodimer.



357a: R^1=MMTr, R^2=TBS
357b: R^1=H, R^2=TBS
357c: R^1=R^2=H

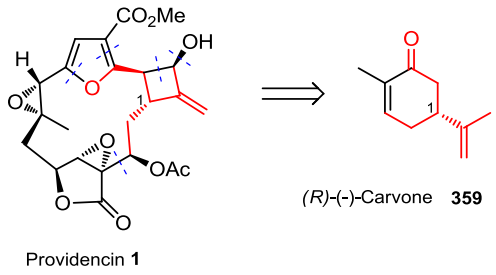
358a: R^1=MMTr, R^2=TBS
358b: R^1=H, R^2=TBS
358c: R^1=R^2=H

catalyst	G2	G2	G2	G2	G2
solvent (Δ)	CH_2Cl_2	C_6H_6	C_6F_6	C_6H_6	C_6H_6
s.m.	**357a**	**357a**	**357b**	**357b**	**357c**
result	s.m.	s.m.	decomposition	s.m.	homodimer

Figure 44: Attempted macrocyclization conditions for the synthesis of 358a-c.

2.2 Isopropenyl Series (*i*Pr)

Inspired by the biosynthesis proposed by *Pattenden* and *Trauner*,[25] [1] a biomimetic approach is designed. The main idea behind the *i*Pr-series is the late stage introduction of the cyclobutanol moiety and thus, increasing the degrees of freedom of the molecule. For this reason the macrocyclization should proceed much easier, or metathesis reaction results at least in the partial formation of the desired $\Delta^{7,8}$ (*E*)-double bond. The isopropenyl unit on C1 is a common structural motif in furanocembranoids. Therefore, a synthesis was planned using a monoterpene ((*R*)-(-)-Carvone, **359**) as starting material and converting it in a multistep sequence to the Providencin (**1**) (Scheme 66).



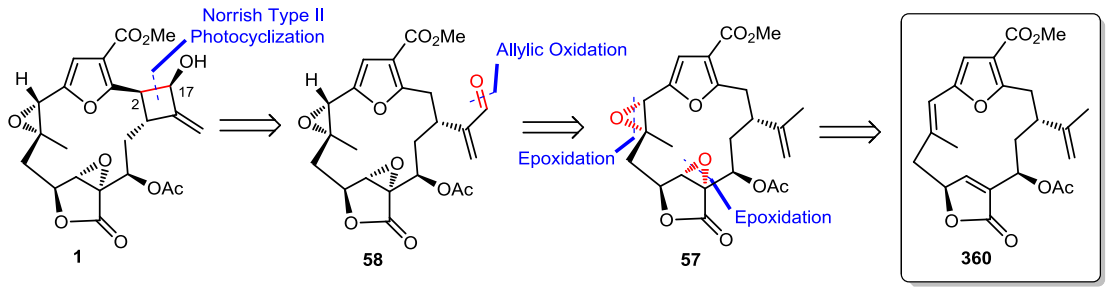
Scheme 66: Starting material of the *i*Pr-series.

2.2.1 *Wipf*'s Furan Cyclization Approaches

All these approaches share the palladium or base mediated furan closure developed by *Wipf* and coworkers.[71] Therein, β-keto ester **362** is alkylated by different propargylic iodides. This method offers a very convergent approach, since complexity can be introduced through a simple alkylation reaction.

Retrosynthetic Analysis:

The first scission in the simplification of Providencin (**1**) was between C2 and C17. The opening of the cyclobutanol moiety resulted in the generation of an α-substituted crotyl aldehyde **58** (Bipinnatin E), which was further simplified by reduction to compound **57** (Iopholide). Removal of both epoxides resulted in the formation of **360**, which is a key intermediate in the synthesis of Providencin (**1**) (Scheme 67).



Scheme 67: Retrosynthetic degradation to key intermediate 360.

2.2.1.1 Ring Closing Metathesis Attempts

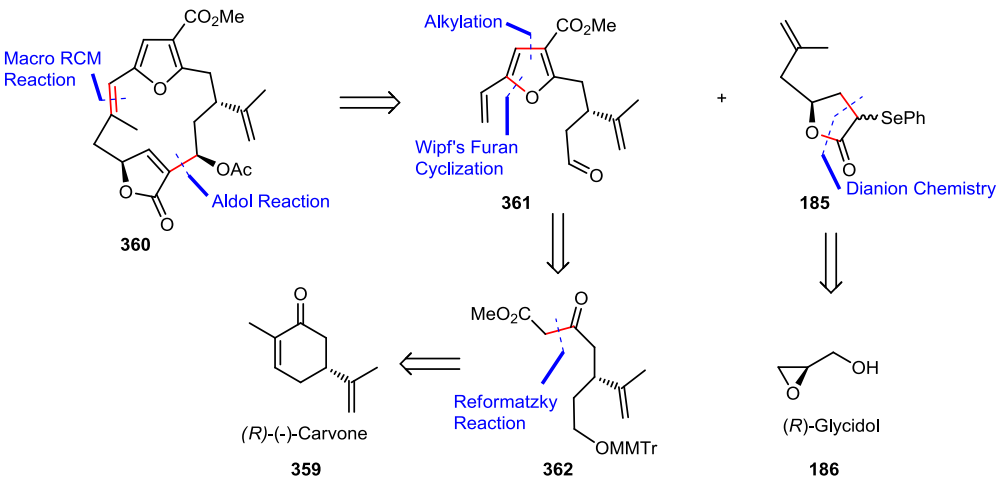
As the RCM reaction is a very powerful tool in organic synthesis it is widely used for the closure of (strained) macrocycles. Due to its high functional group tolerance, it is one of the most popular reactions and should be suitable for ring closure in this special case as well.

2.2.1.1.1 $\Delta^{7,8}$ Metathesis Approach

Although, macrocyclization by a RCM reaction in the *cBu*-series resulted in the exclusive formation of the (*Z*)-configured $\Delta^{7,8}$-double bond, the generation of more degrees of freedom and therefore minor ring strain (by cyclobutane opening) increases the possibility of an (*E*)-double bond formation.

Retrosynthetic Analysis:

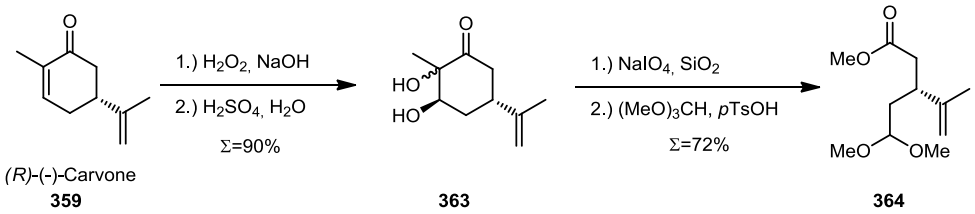
The first retrosynthetic simplification of intermediate **360** was the opening of the strained macrocycle and the cleavage of the $\Delta^{12,13}$-single bond, resulting in the northern and a southern fragments **361** and **185**. The latter one was already known from former approaches, the northern one could be further simplified by opening of the furan moiety and dealkylation to β-keto ester **362**, which was obtained by oxidative degradation of (*R*)-(-)-Carvone (**359**) (Scheme 68).



Scheme 68: Retrosynthetic analysis of the $\Delta^{7,8}$ metathesis approach.

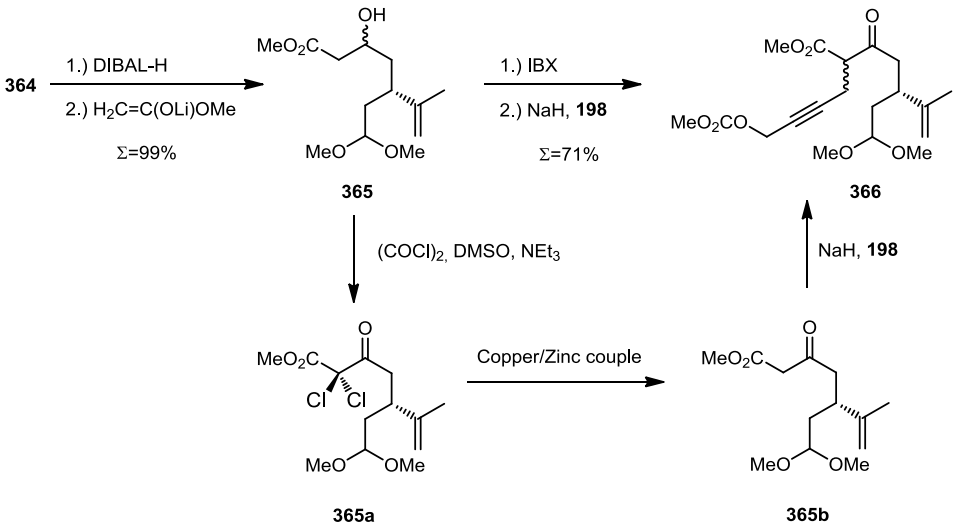
Synthesis:

Inspired by the work of Theodorakis *et al*.,[121] *Scheffer-Weitz* epoxidation of the electron poorer double bond of commercially available (*R*)-Carvone (**359**), followed by subsequent acidic epoxide opening resulted in the formation of diol **363**. Double *Malaprade* reaction,[122] elimination of acetic acid and subsequent one pot esterification and acetalization yielded key intermediate **364** (Scheme 69).



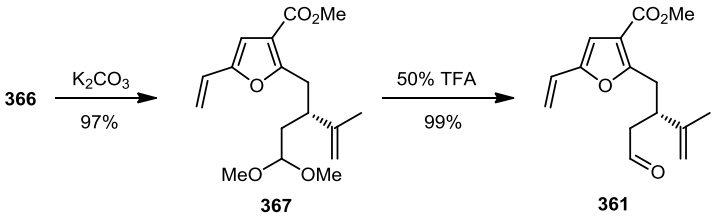
Scheme 69: 4-step synthesis of intermediate 364, starting from (*R*)-(-)-Carvone.

Careful reduction of ester **364** with sterically demanding DIBAL-H to the corresponding aldehyde and subsequent chain elongation by an aldol reaction formed secondary alcohol **365** as an inconsequential mixture of diastereo isomers. Oxidation to the corresponding β-keto ester using IBX as oxidizing agent and subsequent alkylation with well established propargylic iodide **198** yielded intermediate **366**. Conducting the oxidation reaction under *Swern* conditions,[61] the undesired α-chlorinated product **365a** was obtained, which could be reductively converted to **365b** with Copper/Zinc couple.[123] Subsequent alkylation with **198** furnished **366** (Scheme 70).



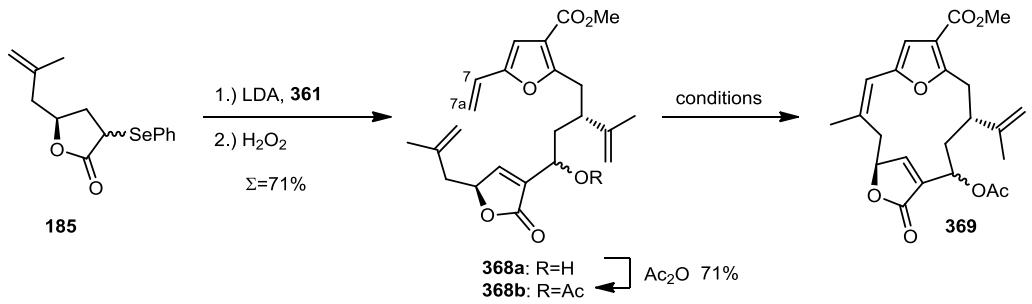
Scheme 70: 4-step synthesis of intermediate 366 and undesired α-chlorination (365a) using *Swern* conditions.[61]

Furan cyclization precursor **366** was treated with K_2CO_3 and smoothly underwent cyclization to furan **367**. Treatment of **367** with 50% aqueous TFA liberated the aldehyde and finished the synthesis of the northern fragment **361** (Scheme 71).



Scheme 71: Furan cyclization and completion of the northern fragment 361.

Selenolactone **185** was deprotonated with LDA and subsequently added to the northern fragment **361**. Oxidative elimination of the seleno phenyl ether to the corresponding butenolide yielded macrocyclization precursor **368a**. Unfortunately, any attempts to close the macrocycle with the free alcohol at C13 in place failed but the $\Delta^{7,7}$-homodimer was obtained. Acetylation of the free alcohol with acetic acid anhydride yielded **368b** and subsequent macrocyclization smoothly yielded macrocycle **369**. Careful 2D-NMR experiments revealed once again, that only the undesired (*Z*)-isomer was formed (Figure 45).



catalyst	G2	G2	G2	G2	GH2
solvent (Δ)	CH_2Cl_2	C_6H_6	CH_2Cl_2	C_6H_6	C_6H_6
s.m.	**368a**	**368a**	**368b**	**368b**	**368b**
result	homodimer	homodimer	s.m. (**368b**)	43% yield	38% yield

Figure 45: Fragment coupling and successful macrocyclization to 369.

2.2.1.2 Horner Wadsworth Emmons Macrocyclization Attempts

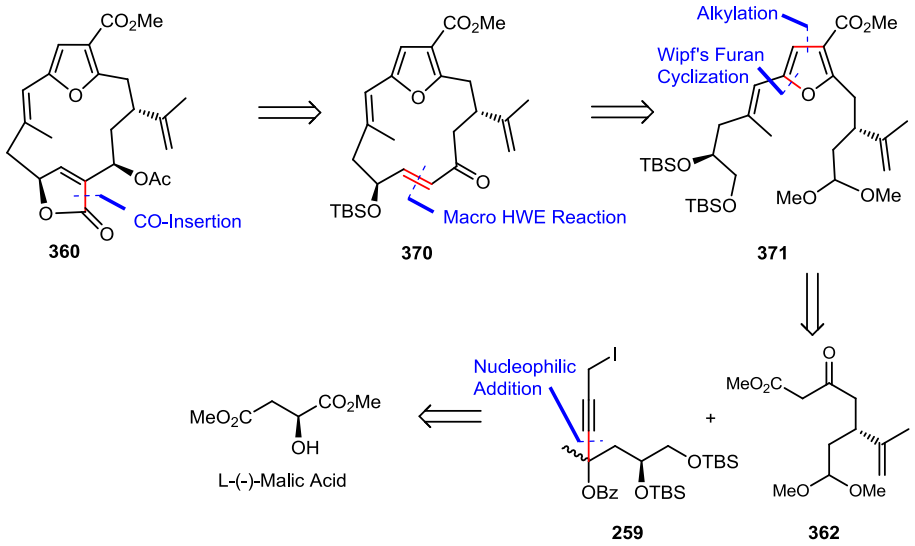
As the HWE reaction is a well established method for the formation of small, medium-sized and large rings, it should be used in this approach. The affinity of phosphor to oxygen, the enthropically auspicious formation of a phosphoric acid derivative and the possibility to influence the geometry of the formed double bond (unlike in the metathesis reaction) make it an excellent choice for macrocyclization.

2.2.1.2.1 $\Delta^{11,12}$ *Horner Wadsworth Emmons* Approach (*i*Pr)

This approach is designed as a proof of principle, to assure the usability of the conditions applied in the *c*Bu-series in the *i*Pr-series. Like in the *c*Bu-series, macrocyclization works smoothly and macrocycle **370** is formed in high overall yield.

Retrosynthetic Analysis:

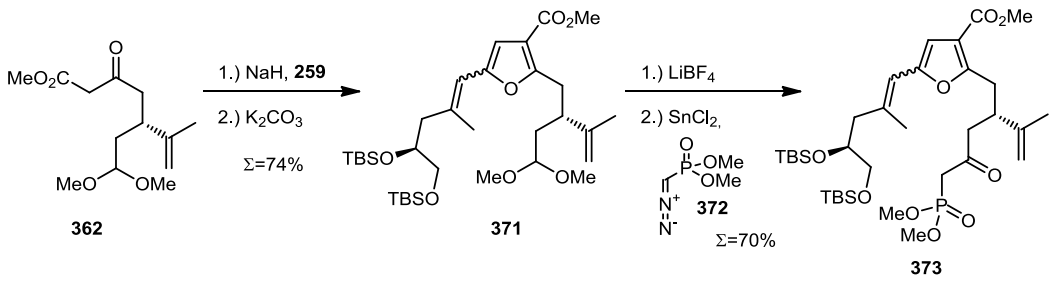
The first retrosynthetic scission was the removal of the butenolide carbonyl, leading to intermediate **370**. Oxidative ring opening at the $\Delta^{11,12}$ position to **371**, further opening of the furan moiety and de-alkylation led to well established fragments **362** and **259** (Scheme 72).



Scheme 72: Retrosynthetic analysis of the $\Delta^{11,12}$ HWE approach.

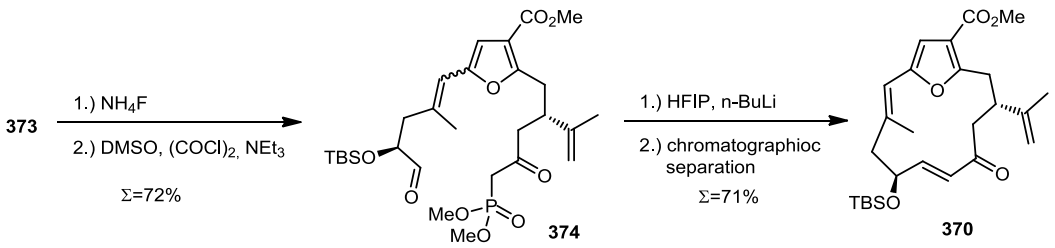
Synthesis:

β-Keto ester **362** was enolized by the addition of NaH and subsequently alkylated with propargylic iodide **259**. The resulting intermediate was treated with K_2CO_3 and smoothly underwent furan cyclization to product **371** according to the *Wipf*'s protocol.[71] Differentiation between the silyl-ethers and the dimethyl acetal proofed to be troublesome. But after some ineffective experiments, $LiBF_4$ in wet CH_3CN smoothly generated the free aldehyde,[124] which was subsequently converted to the β-keto phosphonate **373** using the *Gilbert-Seyferth*-reagent **372** in a tin mediated *Roskamp* reaction (Scheme 73).[125] [126]



Scheme 73: Furan closure and installation of the β-keto phosphonate 373 by a *Roskamp* reaction.

Chemoselective cleavage of the primary silyl-ether of **373** with NH_4F and subsequent oxidation under *Swern*-conditions to the corresponding aldehyde yielded macrocyclization precursor **374**.[61] Already in chapter ***2.1.2.2.1*** successfully applied macrocyclization conditions (LiHFIP) finally furnished the desired macrocycle **370** in acceptable yield (Scheme 74).



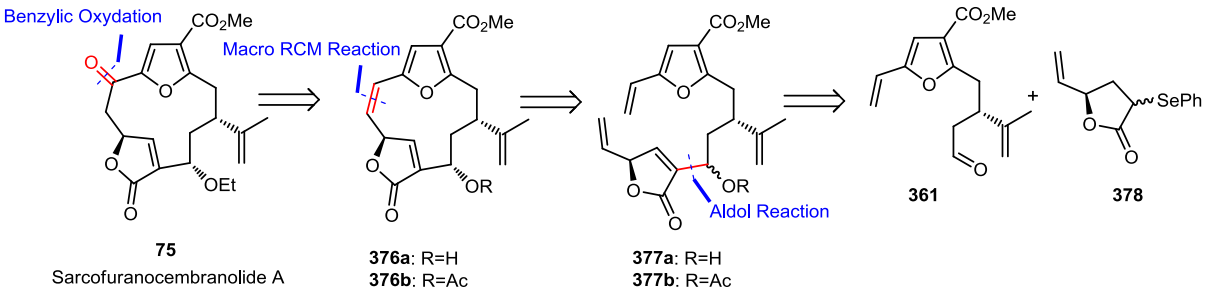
Scheme 74: Successful macrocyclization of 374 to 370 by a HWE reaction.

Sarcofuranocembranolide A

The aim to archive a total synthesis of Sarcofuranocembranolide A (**75**) resulted from the promising results of the synthesis of Providencin-precursors **206** and **369**. The geometry of the formed $\Delta^{7,8}$ double bond is not essential, due to its planned reduction to the corresponding alkane in a later stage. The syntheses of both, northern fragment **361** and southern fragment **378** are very similar to the ones of the Providencin (**1**) approaches.

Retrosynthetic Analysis:

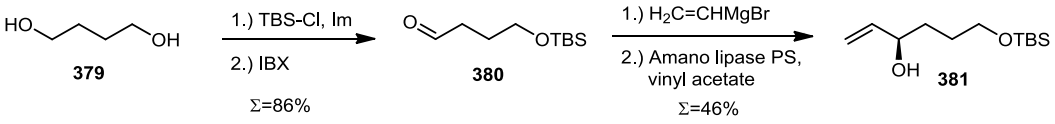
The first retrosynthetic scission was the removal of the benzylic ketone. FGA led to substructures **376a, b**, which was ring opened and thus, led to intermediate **377a, b**. Scission of the $\Delta^{11,12}$-bond led to the two main fragments of the synthesis **361** and **378** (Scheme 75).



Scheme 75: Retrosynthetic analysis of Sarcofuranocembranolide A (75).

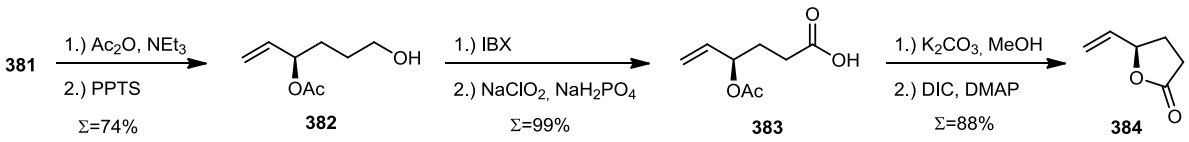
Synthesis:

The following sequence was performed according to Enders *et al.*.[127] Butan-1,4-diol (**379**) was converted to its mono TBS-ether and the remaining free alcohol was oxidized using IBX as the oxidizing agent. Addition of vinyl magnesium bromide to aldehyde **380** generated a racemic secondary allylic alcohol, which was deracemized by *Amano* lipase PS in the presence of vinyl acetate. The desired enantiomer was obtained as free alcohol **381** (Scheme 76).



Scheme 76: Synthesis and enzymatic resolution of 381.

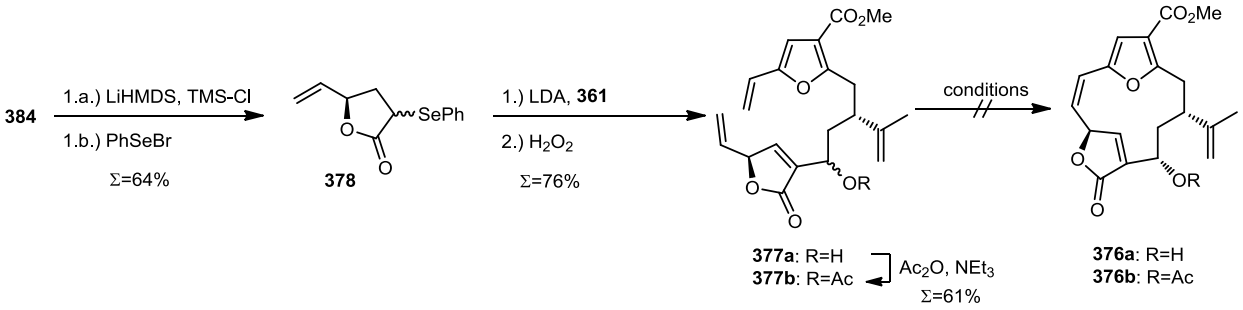
Optically active secondary allylic alcohol **381** was acetylated with acetic acid anhydride and the primary TBS-ether was cleaved with PPTS, which resulted in the formation of compound **382**. A two step oxidation procedure using IBX and the *Pinnick* protocol furnished acid **383**.[128] Basic hydrolysis of the acetate and carbodiimine mediated lactonization finally yielded lactone **384** (Scheme 77).



Scheme 77: Closure of the γ-butyrolactone 384.

Introduction of the phenyl seleno ether in **384** proofed to be troublesome. The formed mono selenated product **378** had an increased pK_a-value of the remaining α-proton, thus leading to a second enolization and selenation. Intercepting the formed lithium enolate with TMS-Cl and forming the TMS-enolether provided the mono selenated product **378** as single product after addition of phenyl selenyl bromide. Compound **378** was deprotonated with LDA and added to aldehyde **361**. Oxidative elimination of the seleno phenyl ether resulted in the formation of butenolide **377a**, which was subjected to ring closing metathesis. Unfortunately, none of the applied conditions led to the formation of the desired macrocycle **376a**.

Thus, secondary C12-alcohol was acetylated with acetic anhydride and once again subjected to ring closing metathesis. To our disappointment, these conditions also did not lead to the formation of desired macrocycle **376b**. In 2005 *Forman* and coworkers reported,[129] that the addition of (substituted) phenols could increase the activity of metathesis catalysts, but unfortunately this variation was not fruitful for this substrate **377b** (Figure 46).

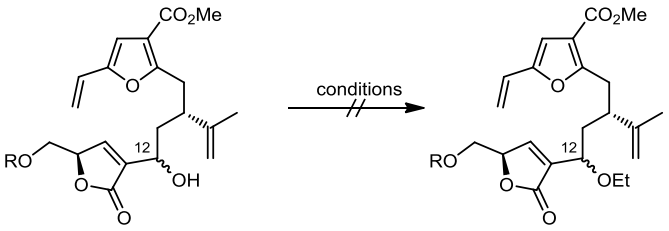


catalyst	**G1**	**G2**	**GH2**	**G2**
solvent	CH_2Cl_2	CH_2Cl_2	CH_2Cl_2	C_6H_6
s.m.	**377a**	**377a**	**377a**	**377a**
result	s.m.	s.m.	s.m.	s.m.
catalyst	**G1**	**G2**	**GH2**	**G2**
solvent	toluene	toluene	toluene	DCE
s.m.	**377a**	**377a**	**377a**	**377a**
result	s.m.	s.m.	s.m.	s.m.
catalyst	**G2**	**GH2**	**G1** (+ 4-MeO-Ph-OH)	**G2** (+ 4-MeO-Ph-OH)
solvent	toluene	toluene	toluene	toluene
s.m.	**377b**	**377b**	**377b**	**377b**
result	s.m.	s.m.	s.m.	s.m.

Figure 46: Fragment combination and attempted macrocyclization by RCM.

Etherification:

Model studies for the installation of the C12-ethyl ether were carried out on substrate **385a** and **385b**. None of the applied conditions led to the formation of the desired ethyl ether. In some cases only starting material could be recovered, in others the deprotonation of the C12-alcohol led to the formation of a complex product mixture (Figure 47).



reagent	Ag_2O	NaH, Et-I	NaH, Et-I	KO*t*Bu, Et-I	NaH, Et_2SO_4
solvent	EtI	THF	DMF	DMF	THF
s.m.	**385a**	**385a**	**385a**	**385a**	**385a**
result	s.m.	decomp.	decomp.	decomp.	decomp.
reagent	KOH, Et_2SO_4	BuLi, DMSO, EtI[130]	Et_3OBF_4,[131] proton sponge	NaH, EtI	KO*t*Bu, EtI
solvent	CH_3CN	THF	$CHCl_3$	DMF	DMF
s.m.	**385a**	**385a**	**385a**	**385b**	**385b**
result	s.m.	decomp.	s.m.	decomp.	decomp.
reagent	Ag_2O, EtI	KHMDS, EtI	BuLi, DMSO, EtI[130]	NaH, Et_2SO_4	Et_3OBF_4,[131] proton sponge
solvent	Et_2O	THF	THF	THF	$CHCl_3$
s.m.	**385b**	**385b**	**385b**	**385b**	**385b**
result	s.m.	decomp.	decomp.	decomp.	s.m.

Figure 47: Attempted installation of an ethyl ether at C12-OH.

3 Conclusion and Outlook

The aim of this Ph.D. research was the synthesis of highly strained furanocembranoid macrocycles. The 14-membered macrocyclic carbon skeleton is the common structural motif of this class of natural products and therefore, a fast and elegant synthesis of a suitable key intermediate could provide access to a large variety of different constituents of furanocembranoids. Providencin (**1**) is an extraordinary member of this family, since it exhibits an unique bicyclo[12.2.0]hexadecane ring system. The 13-membered carbo skeleton of Sarcofuranocembranolide A (**75**) is unique as well, due to its ring contracted, and even more strained carbon framework. Therefore, tailor-made macrocyclization precursors had to be prepared.

Two synthetic series, the isopropenyl-series (*i*Pr) and the cyclobutane-series (*c*Bu) were synthesized. Within these series two different methologies for the closure of the common furan moiety were established: the *Wipf* cyclization and the *Krische* cyclization.[71] [72] Due to the unique cyclobutane moiety, the *c*Bu series is only suitable for the construction of Providencin (**1**) precursors, while the *i*Pr-series is suitable for the synthesis of Iopholide (**57**), Bipinnatin E (**58**) and Providencin (**1**).

As necessary and practical possible, all intermediates were synthesized in a stereospecific way using modern synthetic methods. Within the *c*Bu-series, key intermediate **213** was synthesized in a 21-linear-steps sequence and provided access to a possible total synthesis of Providencin (**1**), while within the *i*Pr-series the 14-steps-synthesis of key intermediate **369** disclosed the biomimetic synthesis of Providencin (**1**) (Figure 48). Interestingly, metathesis reaction exclusively yielded the $\Delta^{7,8}$-(*Z*)-isomer of the desired macrocyclic compound **183**, most probably due to the high ring strain of the formed carbon skeleton. But subsequent photoisomerization produced the desired macrocycle **213**. Besides these synthetic achievements, only the *Horner-Wadsworth-Emmons* approaches were able to close the desired macrocycle, just to collapse later on due to other reasons. Every other approach preceded smoothly until macrocyclization. At this stage, these approaches turned out to be not suitable for the total synthesis of Providencin (**1**) or related compounds.

Although the successful closure of strained furanocembranoid macrocycles was a challenging goal to achieve, the successful total synthesis of Providencin, Bipinnatin E and/or Iopholide would extend the scope of the synthesized intermediates. As presented in Figure 48, only a few steps are missing. Starting from intermediate **213**, an epoxidation of the $\Delta^{7,8}$-double bond, followed by subsequent TIPS-ether cleavage and oxidation should lead to an intermediate, which only has to be olefinated and allylically oxidized to furnish Providencin (**1**).

On the other hand, intermediate **369**, is only three steps away from Iopholide (**57**), which could be converted to Bipinnatin E (**58**) by allylic oxidation and subsequently to Providencin (**1**) by a Norrish Type II photocyclization.

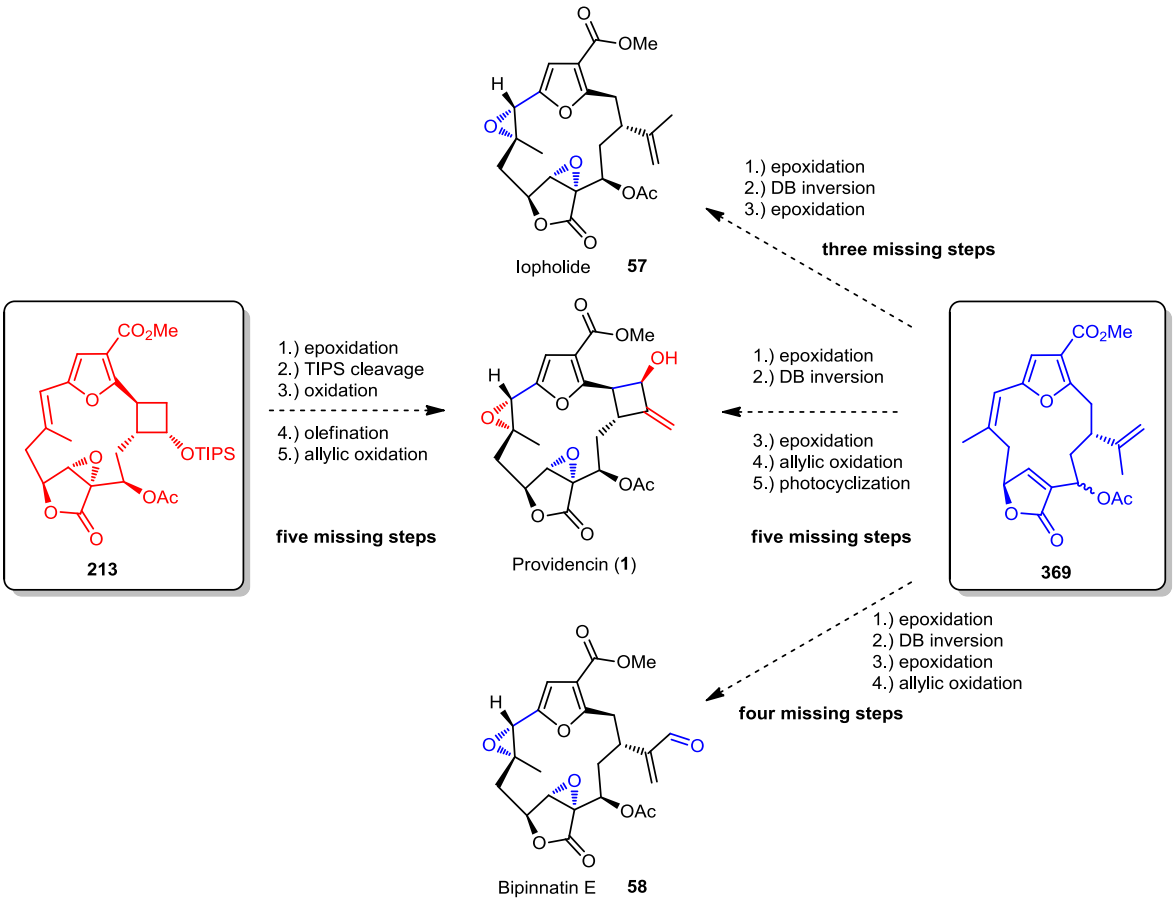


Figure 48: Missing steps from key intermediates 213 and 369 to Providencin (1), Iopholide (57) and Bipinnatin E (58), respectively.

Since Sarcofuranocembranolide A (**75**) is the only member of furanocembranoids, which exhibits a 13-membered, ring contracted macrocyclic carbon framework, intermediate **377a** is only suitable for the total synthesis of this molecule. This intermediate was synthesized in a 12-steps linear sequence, but macrocyclization using different metathesis catalysts was not successful, most probable due to the highly strained macrocycle in **376a** (Figure 49).

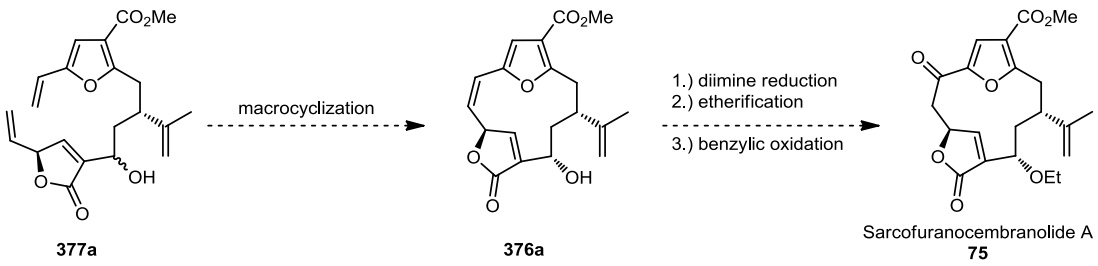


Figure 49: Missing steps to complete the total synthesis of Sarcofuranocembranolide A (75).

4 Experimental Section

4.1 General Methods

Solvents:

All solvents were distilled prior to use, except THF, which was purchased from *Sigma Aldrich* (99.9%, H_2O < 20ppm) or *Acros Organics* (99.85%, H_2O < 50 ppm) and used without further purification. Et_2O, benzene and toluene were dried with sodium. CH_2Cl_2 and $CHCl_3$ were passed through an Al_2O_3-$MgSO_4$ column or dried with P_2O_5. Acetone and hexane were dried using P_2O_5. DMF, DMSO, CH_3CN, NEt_3, *i*Pr_2NH, *i*Pr_2NEt, HMPA and 2,6-lutidine were dried with CaH_2. Pyridine was distilled from potassium hydroxide and methanol was refluxed over magnesium turnings for several hours and then distilled.

Synthetic Methods:

All reaction vessels were dried by repeated heating under vacuum (hot gun) followed by purging with dry argon. Oxygen- and moisture sensitive reactions were carried out under a slight argon overpressure (balloon) and in anhydrous solvents. Sensitive solutions and liquids were transferred *via* a double tipped needle or syringe through rubber septa. All reactions were stirred magnetically unless otherwise noted. Solvents for palladium catalyzed reactions and metathesis reactions were degassed by the "pump-freeze-thaw" method (at least four cycles).

Chemicals:

All commercially available reagents were used without further purification unless otherwise stated.

Chromatography:

Thin-layer chromatography (TLC)

All reactions were monitored using precoated *Merck* silica gel 60 F254 plates. UV active spots were detected at longwave UV (254nm) and shortwave UV (180 nm). For visualization, the following reagents were used: *Anisaldehyde* [anisaldehyde (6 g) in EtOH (250 mL) and conc. H_2SO_4 (25 mL)], *Ceric(IV)sulfate* [$Ce(SO_4)_2$ (0.1 g), phosphormolybdic acid (20 g) in H_2SO_4 (10%, 400 mL)] and *Potassium permanganate* [$KMnO_4$ (2.5 g) in 1N NaOH (500 mL)].

Column Chromatography

Preparative column chromatography was performed with silica gel 60 from *Merck* (0.040 - 0.063µm, 240 - 400 mesh), using as a rule of thumb 30-fold excess of silica gel based on the crude product weight. As a routine, conditioning of the column was performed by the "wet-packing" technique. Yields refer to chromatographically and spectroscopically pure compounds, unless otherwise stated.

Analytic and preparative HPLC

For the determination of diastereomeric ratios in analytic scale a *Jasco System* (PU-980 pump, UV-975 UV detector, RI-930 RI detector) with a Nucleosil 50 column (5µm, 4mm x 241mm) at ambient temperature was used. Preparative HPLC was performed on a *Dynamix System* (SD-1 pump, UV-1 UV-detector (λ = 254nm)) using a *Supersphere* 60 Si column (4µm, 25mm x 250mm, *Merck*) at ambient temperature.

Spectroscopy:

NMR-Spectroscopy

All NMR spectra were measured on a *Bruker Avance DRX-250*, a *Bruker Avance DRX-400*, a *Bruker AV400* or a *Bruker DRX-600* at 250.13MHz (62.89MHz), 400.13 MHz (100.61MHz) or 600.13MHz (150.90MHz), respectively. Chemical shifts are given in ppm and were referenced to the solvent residual peak(s). $CHCl_3$ (1H, δ = 7.26ppm; 13C, δ = 77.0ppm) or toluene (1H, δ = 7.09, 7.00, 6.98ppm; 13C, δ = 137.9, 129.2, 128.3, 125.5, 20.4ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, bs = broad singlet), coupling constant *J* in Hz, integration. Assignments of proton resonances were confirmed, when possible, by correlated spectroscopy.

Infrared-Spectroscopy

Infrared spectra were recorded as thin films on an ATR-unit on a *Perkin Elmer Spectrum 2000* FT-IR spectrometer or as thin films on a silicon plate on a *Perkin Elmer Spectrum 1600*-FT-IT.

Mass-Spectroscopy

Mass spectra were measured on a *Micro mass*, *trio 200 Fisions Instruments*. High-resolution mass spectra (HRMS) were performed on a *Finnigan MAT 8230* with a resolution of 10000.

Polarimetry:

Optical rotations were measured on a *P341 Perkin-Elmer* polarimeter in a 10cm cell at 20 °C with 589nm wavelength. The concentration *c* is given in g/100 mL.

Melting points:

Melting points (mp) were determined on a *Leica Galen III* apparatus and are uncorrected.

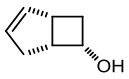
X-Ray Analysis:

Single crystal diffractions were collected on a *Bruker X8APEX II CCD* diffractometer. The structure was solved by direct methods and refined by full-matrix least-squares techniques. Non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms were placed at calculated positions and refined as riding atoms in the subsequent least squares model refinements. Structure solution and refinement was performed with the SHELX program (G.M. Sheldrick, *Program for crystal structure solution*, Universität Goettingen, 1997).

4.2 Providencin

4.2.1 $\Delta^{7,8}$ Metathesis Approach (*c*Bu)

(±)-*cis*-Bicyclo[3.2.0]hept-2-en-6-ol (**387**)

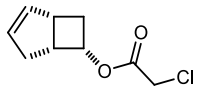


An adapted procedure of Fairlamb *et al*. was used.[132] $NaBH_4$ (3.5 g, 92.5 mmol, 0.5 eq.) was suspended in anhydrous MeOH (100 mL) and the solution was cooled to -78 °C. After the evolution of dihydrogen has ceased, a solution of (±)-*cis*-bicyclo[3.2.0]hept-2-en-6-one (20.0 g, 185.0 mmol, 1.0 eq.) in anhydrous MeOH (50ml) was added dropwise over a period of 15 minutes. The reaction mixture was stirred at -78 °C for one hour, before it was allowed to warm to r.t. The same amount of Et_2O (150 mL) and 50 mL of 2N HCl were added. The phases were separated and the organic phase was extracted three times with water. The combined aqueous phases were back-extracted three times with Et_2O/hexane (1/1). The combined organic phases were washed with brine and dried over $MgSO_4$. Careful evaporation (volatility of the product) gave 19.4 g (176.1 mmol, 95%) of **387** as slightly yellow liquid, which was of perfect purity for further conversion.

^{1}H-NMR (250MHz, $CDCl_3$): δ = 5.85 (bs, 2H); 4.42 (m, 1H); 3.16 (m, 1H); 3.02 (m, 1H); 2.76 (m, 1H); 2.69 (m, 1H); 2.40 (m, 1H); 1.68 (bs, 1H); 1.59 (ddd, *J* = 12.9, 4.5, 1.1Hz, 1H)

HRMS (ESI) (m/z): $[M+Na]^+$ calcd. for $C_7H_{10}ONa$: 133.0629; found: 133.0627

(±)-*cis*-bicyclo[3.2.0]hept-2-en-6-yl 2-chloroacetate (**189**)

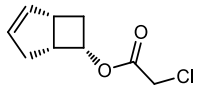


Racemic **387** (14 g, 127 mmol, 1.0 eq.) was dissolved in anhydrous CH_2Cl_2 (60 mL) and pyridine (15.4 mL, 191.0 mmol, 1.5 eq.) was added. The solution was cooled to 0 °C and a solution of chloro acetic acid anhydride (30.4 g, 178 mmol, 1.4 eq.) in anhydrous CH_2Cl_2 (60 mL) was added dropwise over a period of 30 minutes. After stirring the reaction mixture for one hour at 0 °C, MeOH was added and the solution was allowed to warm to r.t. CH_2Cl_2 was added and the mixture was washed several times with aqueous 1M HCl. After washing two times with water the organic phase was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography (hexane/EtOAc = 7/1) giving 21.1 g (113.1 mmol, 89%) of **189** as colorless oil.

^{1}H-NMR (250MHz, $CDCl_3$): δ = 5.82 (bs, 2H); 5.28 (dt, *J* = 8.1, 5.9Hz, 1H); 4.05 (s, 2H); 3.32 (m, 1H); 3.06 (m, 1H); 2.77 (m, 1H); 2.50 (m, 2H); 1.82 (m, 1H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_9H_{11}ClO_2$: 186.0448; found: 186.0443

(*1S,5R,6S*)-bicyclo[3.2.0]hept-2-en-6-yl 2-chloroacetate (**388**)



Racemic **189** (23.8 g, 127.5 mmol, 1.0 eq.) was dissolved in 200 mL of a 1:1 mixture of MTBE/pentane. 300 mL of a pH=7-buffer (50mM KH_2PO_4) were added and the biphasic system was vigorously stirred at r.t. 150 mg of Lipase SAM II were added to start the enzymatic resolution. The pH of the mixture was monitored and adjusted to 7 by a Merck Titrino 702SM using 0.5M NaOH. The reaction was stopped after a consumption of 130 mL of 0.5M NaOH by the addition of 2M HCl. The pH was adjusted to 4 and the phases were separated. The aqueous phase was extracted two times with Et_2O and the combined organic layers were dried using $MgSO_4$. Solvents were removed under reduced pressure and the residue was purified using silica gel chromatography (hexane/EtOAc = 7/1) giving optically pure **388** as colorless oil (11.4 g, 61.1 mmol, 96%).

^{1}H-NMR (250MHz, $CDCl_3$): δ = 5.82 (bs, 2H); 5.28 (dt, *J* = 8.1, 5.9Hz, 1H); 4.05 (s, 2H); 3.32 (m, 1H); 3.06 (m, 1H); 2.77 (m, 1H); 2.50 (m, 2H); 1.82 (m, 1H)

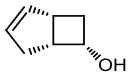
^{13}C-NMR (63MHz, $CDCl_3$): δ = 167.1; 134.6; 132.8; 70.1; 41.6; 41.4; 41.1; 37.0; 33.0

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_9H_{11}ClO_2$: 186.0448; found: 186.0451

IR (film): 2941; 1758; 1414; 1349; 1311; 1286; 1186; 1047; 1001cm^{-1}

$[\alpha]_D^{20}$: -19.6 (c=0.66; $CHCl_3$)

(*1S,5R,6S*)-bicyclo[3.2.0]hept-2-en-6-ol (**190**)

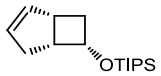


11.4 g of **388** (61.1 mmol, 1.0 eq.) were dissolved in 80 mL of MeOH. A solution of $LiOH.H_2O$ (7.7 g, 183.3 mmol, 3 eq.) in distilled water (40 mL) was slowly added at r.t. The reation mixture was allowed to stir at this temperature for 30 minutes. Et_2O was added and the pH of the aqueous phase was adjusted to 6-7. The phases were separated and the aqueous phase was extracted two more times with Et_2O. The combined organic extracts were dried over $MgSO_4$ and the solvent was carefully removed *in vacuo* (volatility of the product!), yielding alcohol **190** as colorless oil (6.7 g, 61.0 mmol, 99%).

^{1}H-NMR (250MHz, $CDCl_3$): δ = 5.85 (bs, 2H); 4.42 (m, 1H); 3.16 (m, 1H); 3.02 (m, 1H); 2.76 (m, 1H); 2.69 (m, 1H); 2.40 (m, 1H); 1.68 (bs, 1H); 1.59 (ddd, *J* = 12.9, 4.5, 1.1Hz, 1H)

HRMS (ESI) (m/z): $[M+Na]^+$ calcd. for $C_7H_{10}ONa$: 133.0629; found: 133.0632

((*1S,5R,6S*)-bicyclo[3.2.0]hept-2-en-6-yloxy)triisopropylsilane (**389**)

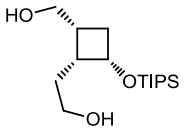


Secondary alcohol **190** (6.5 g, 59 mmol, 1.0 eq.) was dissolved in anhydrous DMF (60 mL) and imidazole (9.6 g, 141.1 mmol, 2 eq.) was added in one portion. Under Ar-atmosphere, the mixture was cooled to 0 °C and a solution of triisopropyl chloride (TIPS-Cl, 13.6 g, 70.6 mmol, 1.2 eq.) in anhydrous DMF (20 mL) was slowly added at 0 °C. The reaction mixture was allowed to warm to r.t. overnight. 100 mL of hexane/Et_2O (1/1) and 100 mL of saturated aqueous NH_4Cl were added and the phases separated. The organic phase was extracted with water twice. The combined aqueous phases were back-extracted two times with a 1/1 mixture of hexane/Et_2O and the combined organic layers were dried over $MgSO_4$. Evaporation of the solvent yielded silylether **389** (13.4 g, 50.2 mmol, 85%) as colorless oil, which was purified by silica gel column chromatography (hexane/EtOAc = 50/1).

^{1}H-NMR (250MHz, $CDCl_3$): δ = 5.80 (m, 2H); 4.53 (ddd, *J* = 7.8, 6.4, 2.1Hz, 1H); 3.13 (m, 1H); 2.96 (m, 1H); 2.84 (m, 1H); 2.61 (m, 1H); 2.31 (m, 1H); 1.63 (m, 1H); 1.03 (bs, 21H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{16}H_{30}OSi$: 266.2066; found: 266.2054

2-((*1R,2R,4S*)-2-(hydroxymethyl)-4-((triisopropylsilyl)oxy)cyclobutyl)ethanol (**191**)



Bicycle **389** (12.0 g, 45 mmol, 1.0 eq.) was dissolved in a 4/1 mixture of CH_2Cl_2/MeOH (450 mL). The solution was cooled to -78 °C and ozone was bubbled through it until it turned blue. The ozone generator was turned off and dehumidified air was further bubbled through the solution until the blue color disappeared. MeOH (360 mL) and $NaBH_4$ (6.8 g, 180 mmol, 4 eq.) were added and the reaction mixture was allowed to warm to r.t., where it was stirred for another 3h. The pH of the solution was adjusted to 4-5 with 1M HCl. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 twice. The combined organic layers were dried with Na_2SO_4 and the solvent was removed *in vacuo*. The crude product was of sufficient purity for further conversion. Diol **191** was obtained as white semi-solid (13.6 g, 45 mmol, quant.).

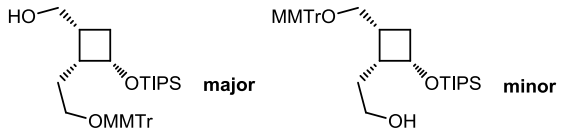
^{1}H-NMR (250MHz, $CDCl_3$): δ = 4.33 (m, 1H); 3.78 (m, 1H); 3.63 (m, 2H); 2.74 (m, 2H); 2.62 (m, 1H); 2.25 (m, 2H); 1.98 (m, 1H); 1.81 (m, 1H); 1.64 (m, 1H); 1.05 (bs, 21H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{16}H_{34}O_3Si$: 302.2277; found: 302.2282

$[\alpha]_D^{20}$: +45.6 (c=0.69; $CHCl_3$)

((*1R,2R,3S*)-2-(2-((4-methoxyphenyl)diphenylmethoxy)ethyl)-3-((triisopropylsilyl)oxy)cyclobutyl)methanol (**188**) and

2-((*1R,2R,4S*)-2-(((4-methoxyphenyl)diphenylmethoxy)methyl)-4-((triisopropylsilyl)oxy)cyclobutyl)ethanol (**193**)



Diol **191** (17.2 g, 56.9 mmol, 1.0 eq.) was dissolved in 500 mL anhydrous CH_2Cl_2 and DMAP (348 mg, 2.8 mmol, 0.05 eq.) and pyridine (3.67 mL, 45.5 mmol, 0.8 eq.) were added. The reaction mixture was cooled to -42 °C using an acetonitrile/dry ice cooling bath. A solution of MMTr-Cl (12.3 g, 40 mmol, 0.7 eq.) in 100 mL of anhydrous CH_2Cl_2 was added dropwise to the solution of the diol at low temperature. The reaction mixture was stirred for two hours at -42 °C and consecutively quenched by the addition of sat. aq. NH_4Cl solution. Under vigorous stirring the solution was allowed to warm to r.t. and the phases were separated. The aqueous phase was extracted twice with 100 mL CH_2Cl_2, respectively. The combined organic layers were dried with brine and $MgSO_4$. Solvents were removed under reduced pressure and the crude product was purified using silica gel chromatography (hexane/EtOAc = 10/1 - 7/1 - 5/1 - 4/1 - 3/1). The first eluted product was the di-MMTr-protected diol **192** (2.4 g, 2.9 mmol, 7%). The second eluted product was the wrong regio isomer **193** (3.3 g, 5.7 mmol, 14%). The desired alcohol **188** was isolated as slightly yellow oil (16.4 g, 29 mmol, 73%), but the remaining unprotected diol (starting material **191**) is still resting on the column.

Since the reaction produced a complex mixture of regio isomers, all had to be separated. As soon as the desired alcohol **188** was eluted, the di-MMTr-protected diol **192** was dissolved in CH_2Cl_2/MeOH (1/1, 30 mL) and PPTS (72 mg, 0.3 mmol, 0.1eq) was added. The reaction mixture was stirred at r.t. for 30 minutes. The solvents were removed under reduced pressure and the crude product was subjected to the same column chromatography described above. Now the elution was continued with pure EtOAc, first eluting MMTr-OH and then the diol **191**.

Major:

^{1}H-NMR (400MHz, $CDCl_3$): δ = 7.44 (m, 4H); 7.31 (m, 2H); 7.27 (m, 4H); 7.20 (m, 2H); 6.82 (m, 2H); 4.26 (ddd, *J* = 6.6, 6.6, 6.6Hz, 1H); 3.79 (s, 3H); 3.64 (m, 1H); 3.58 (m, 1H); 3.22 (m, 1H); 3.05 (m, 1H); 2.64 (m, 1H); 2.31 (m, 1H); 2.17 (m, 1H); 2.04 (m, 1H); 1.84 (bs, 1H); 1.80 (m, 1H); 1.69 (ddd, *J* = 11.1, 8.5, 6.6Hz, 1H); 0.97 (m, 21H)

^{13}C-NMR (100MHz, $CDCl_3$): δ = 158.4; 144.9; 136.3; 130.3; 128.5; 127.7; 126.7; 112.9; 86.3; 66.4; 63.4; 63.1; 55.2; 40.6; 34.3; 32.5; 24.1; 18.0; 17.9; 11.9

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{36}H_{50}O_4Si$: 574.3478; found: 574.3465

$[\alpha]_D^{20}$: +17.9 (c=1.10; $CHCl_3$)

Minor:

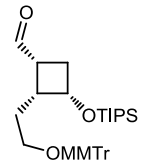
^{1}H-NMR (400MHz, $CDCl_3$): δ = 7.45 (m, 4H); 7.32 (m, 2H); 7.30 (m, 4H); 7.24 (m, 2H); 6.85 (m, 2H); 4.37 (ddd, *J* = 6.9, 6.9, 6.9Hz, 1H); 3.82 (s, 3H); 3.61 (m, 1H); 3.56 (m, 1H); 3.17 (dd, *J* = 9.2, 5.5Hz, 1H); 3.02 (dd, *J* = 9.2, 5.5Hz, 1H); 2.69 (m, 1H); 2.62 (bs, 1H); 2.35 (m, 1H); 2.33 (m, 1H); 1.85 (m, 1H); 1.71 (m, 1H); 1.52 (m, 1H); 1.07 (m, 21H)

^{13}C-NMR (100MHz, $CDCl_3$): δ = 158.5; 144.8; 135.9; 130.4; 128.4; 127.8; 126.9; 113.0; 86.1; 65.9; 63.8; 62.7; 55.2; 43.0; 35.4; 29.1; 35.4; 26.4; 18.0; 17.9; 12.1

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{36}H_{50}O_4Si$: 574.3478; found: 574.3460

$[\alpha]_D^{20}$: +19.8 (c=1.42; $CHCl_3$)

(*1R,2R,3S*)-2-(2-((4-methoxyphenyl)diphenylmethoxy)ethyl)-3-((triisopropylsilyl)oxy)cyclobutanecarbaldehyde (**390**)



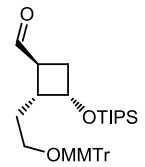
Mono-MMTr-protected triol **188** (8.6 g, 14.9 mmol, 1.0 eq.) was dissolved in anhydrous EtOAc (150 mL) and IBX (12.5 g, 44.6 mmol, 3 eq.) was added. The reaction mixture was refluxed until all starting material was consumed (approx. two hours). Now 150 mL of hexane were added and the suspension was filtered through a pad of celite 545 coarse. Removal of the solvents gave aldehyde **390** (8.6 g, 14.9 mmol, quant.) as colorless oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 9.66 (d, *J* = 2.3Hz, 1H); 7.41 (m, 4H); 7.27 (m, 6H); 7.21 (m, 2H); 6.81 (m, 2H); 4.36 (m, 1H); 3.79 (s, 3H); 3.08 (m, 3H); 2.78 (m, 1H); 2.41 (m, 1H); 2.23 (m, 1H); 2.10 (m, 1H); 1.75 (m, 1H); 0.97 (m, 21H)

^{13}C-NMR (100MHz, $CDCl_3$): δ = 202.9; 158.4; 144.8; 144.8; 136.1; 130.3; 128.4; 127.7; 126.7; 112.8; 86.1; 65.2; 62.9; 60.4; 55.2; 43.7; 41.6; 31.3; 24.8; 17.9; 17.9; 11.9

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{36}H_{48}O_4Si$: 572.3322; found: 574.3307

(*1S,2R,3S*)-2-(2-((4-methoxyphenyl)diphenylmethoxy)ethyl)-3-((triisopropylsilyl)oxy)cyclobutanecarbaldehyde (**194**)



7.6 g (13.3 mmol, 1.0 eq.) of aldehyde **390** were dissolved in as little anhydrous CH_2Cl_2 as possible. 150 mL of anhydrous MeOH and 18.5 g (133 mmol, 10 eq.) of finely ground K_2CO_3 were added. The reaction mixture was stirred for one hour and afterwards filtered through a pad of celite. Et_2O (100 mL) was added to the resulting solution. The pH of the solution was adjusted to 7 by the addition of 0.5M $KHSO_4$ solution and the phases were separated. The organic phase was extracted twice with water and the combined aqueous phases were back-extracted with Et_2O/hexane (1/1).

The combined organic layers were dried with $MgSO_4$ and the solvent was removed under reduced pressure giving 7.6 g (13.3 mmol, quant.) of inverted aldehyde **194** as colorless oil, which was of excellent purity.

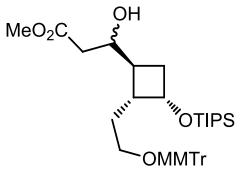
^{1}H-NMR (400MHz, $CDCl_3$): δ = 9.67 (d, *J* = 1.6Hz, 1H); 7.42 (m, 4H); 7.26 (m, 6H); 7.21 (m, 2H); 6.82 (m, 2H); 4.38 (m, 1H); 3.80 (s, 3H); 3.16 (m, 2H); 2.82 (m, 2H); 2.53 (m, 1H); 2.09 (m, 2H); 1.86 (m, 1H); 0.97 (m, 21H)

^{13}C-NMR (100MHz, $CDCl_3$): δ = 202.6; 158.4; 144.8; 136.0; 130.3; 128.4; 127.7; 126.7; 113.0; 86.2; 65.9; 61.8; 60.4; 55.2; 46.0; 41.2; 31.3; 28.5; 17.9; 17.9; 12.0

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{36}H_{48}O_4Si$: 572.3322; found: 574.3315

$[\alpha]_D^{20}$: +23.8 (c=0.61; $CHCl_3$)

Methyl-3-hydroxy-3-((*1S,2R,3S*)-2-(2-((4-methoxyphenyl)diphenylmethoxy)ethyl)-3-((triisopropylsilyl)oxy)cyclobutyl)propanoate (**391**)



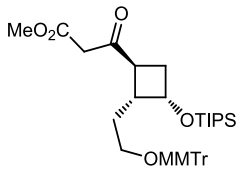
The reaction was carried out under Barbier conditions. Aldehyde **194** (7.6 g, 13.3 mmol, 1.0 eq.), bromo acetic acid methyl ester (1.59 mL, 17.3 mmol, 1.3 eq.) and zinc powder (1.4 g, 21.2 mmol, 1.6 eq.) were dissolved/suspended in anhydrous THF (60 mL). Local heating with a hot gun started the reaction, the solution turned green and started to reflux. After cessation of boiling the reaction mixture was heated at 40 °C for 30 minutes. The reaction mixture was quenched by the addition of saturated aqueous NH_4Cl. The phases were separated and the pH of the aqueous phases was set slightly acidic by the addition of 0.5M $KHSO_4$. The aqueous phase was extracted twice with Et_2O and the combined organic phases were dried with brine and $MgSO_4$. Removal of the solvent under reduced pressure and silica gel chromatography (hexane/EtOAc = 5/1 to 4/1; important to remove zink-impurities, which inhibit the following IBX oxidation!) yielded **391** (8.6 g, 13.3 mmol, quant.) as an inconsequential mixture of diastereo isomers.

^{1}H-NMR (250MHz, $CDCl_3$): δ = 7.43 (m, 4H); 7.27 (m, 8H); 6.81 (m, 2H); 4.40 (m, 1H); 3.89 (m, 1H); 3.79 (s, 3H); 3.68 (s, 3H); 3.09 (m, 2H); 2.72 (m, 1H); 2.31 (m, 2H); 2.05 (m, 3H); 1.79 (m, 3H); 1.00 (m, 21H)

^{13}C-NMR (100MHz, $CDCl_3$): δ = 173.5; 173.2; 158.4; 144.9; 136.1; 130.3; 128.4; 127.3; 126.6; 113.0; 86.4; 86.1; 70.9; 70.1; 66.2; 62.4; 61.9; 55.2; 51.7; 41.0; 40.7; 40.4; 40.2; 39.3; 33.4; 32.0; 29.1; 28.8; 18.0; 12.0

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{39}H_{54}O_6Si$: 646.3690; found: 646.3681

Methyl-3-((*1S,2R,3S*)-2-(2-((4-methoxyphenyl)diphenylmethoxy)ethyl)-3-((triisopropylsilyl)oxy)cyclobutyl)-3-oxopropanoate (**195**)



Secondary alcohol **391** (8.6 g, 13.3 mmol, 1.0 eq.) was dissolved in anhydrous EtOAc (130 mL) and IBX (11.2 g, 39.8 mmol, 3 eq.) was added. The suspension was heated to reflux for three hours. Now the suspension was cooled to r.t. and 130 mL hexane were added. The slurry was filtered through a pad of celite and the solvents were removed under reduced pressure. The crude product was purified by silica gel column chromatography (hexane/EtOAc = 5/1). β-keto ester **195** was obtained as a viscous slightly yellow oil (8.4 g, 13.0 mmol, 98%).

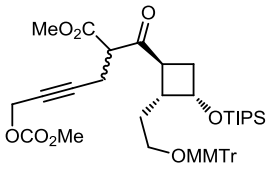
^{1}H-NMR (400MHz, $CDCl_3$): δ = 7.41 (m, 4H); 7.26 (m, 8H); 6.81 (m, 2H); 4.41 (m, 1H); 3.78 (s, 3H); 3.66 (s, 3H); 3.28 (m, 2H); 3.16 (m, 2H); 2.95 (ddd, *J* = 9.2, 4.5, 4.5Hz, 1H); 2.78 (m, 1H); 2.51 (dddd, *J* = 11.7, 4.3, 4.0, 3.3Hz, 1H); 2.11 (m, 2H); 1.83 (m, 1H); 1.00 (m, 21H)

^{13}C-NMR (100MHz, $CDCl_3$): δ = 203.9; 167.5; 158.5; 144.6; 136.0; 130.2; 128.4; 127.8; 126.8; 113.0; 86.3; 65.5; 62.0; 55.1; 52.2; 47.5; 45.6; 42.8; 33.0; 28.7; 17.8; 11.9

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{39}H_{52}O_6Si$: 644.3533; found: 644.3527

$[\alpha]_D^{20}$: +26.4 (c=0.60; $CHCl_3$)

Methyl-6-((ethoxycarbonyl)oxy)-2-((*1S,2R,3S*)-2-(2-((4-methoxyphenyl)diphenylmethoxy)ethyl)-3-((triisopropylsilyl)oxy)cyclobutanecarbonyl)hex-4-ynoate (**199**)



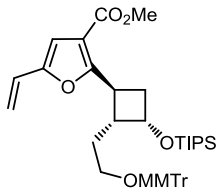
NaH (60% in mineral oil, 520 mg, 13.0 mmol, 1.0 eq.) was suspended in anhydrous THF (30 mL). The reaction mixture was cooled to 0 °C and a solution of β-keto ester **195** (8.4 g, 13.0 mmol, 1.0 eq.) in anhydrous THF (60 mL) was added. The reaction was stirred at 0 °C for 20 minutes and afterwards warmed to r.t. within 10 minutes. Then it was re-cooled to 0 °C and a solution of propargylic iodide **198** (3.3 g, 12.4 mmol, 0.95 eq.) in anhydrous THF (40 mL) was added uninterruptedly at 0 °C. The reaction mixture was stirred at this temperature for 20 minutes and then warmed to r.t. within 20 minutes before it was quenched with saturated aqueous NH_4Cl. Et_2O was added and the phases separated. The pH of the aqueous phase was adjusted to 6 with 0.5M $KHSO_4$ and it was extracted twice with Et_2O. The combined organic layers were dried with $MgSO_4$ and the solvent was removed under reduced pressure. Silica gel column chromatography (hexane/EtOAc = 7/1) yielded alkylated β-keto ester **199** as slightly yellow oil (9.5 g, 12.2 mmol, 98%).

^{1}H-NMR (600MHz, $CDCl_3$): δ = 7.42 (m, 4H); 7.28 (m, 6H); 7.21 (m, 2H); 6.82 (m, 2H); 4.61 (m, 1H); 4.56 (m, 1H); 4.40 (m, 1H); 3.79 (s, 3H); 3.77 (s, 3H); 3.58 (m, 4H); 3.16 (m, 2H); 3.07 (m, 1H); 2.86 (m, 1H); 2.66 (m, 2H); 2.49 (m, 1H); 2.15 (m, 2H); 1.81 (m, 1H); 0.99 (m, 21H)

^{13}C-NMR (150MHz, $CDCl_3$): δ = 205.1; 204.1; 168.4; 168.3; 158.5; 158.4; 144.8; 144.7; 144.6; 135.9; 130.3; 128.4; 128.3; 127.8; 127.7; 126.8; 126.7; 113.0; 86.2; 84.6; 75.5; 75.1; 65.4; 61.9; 61.8; 55.7; 55.5; 55.3; 55.1; 55.0; 52.6; 52.5; 45.8; 45.0; 42.4; 42.0; 33.3; 33.1; 28.9; 28.8; 18.1; 17.9; 17.8; 17.6; 11.9

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{39}H_{52}O_6Si$: 770.3850; found: 770.3843

Methyl-2-((*1S,2R,3S*)-2-(2-((4-methoxyphenyl)diphenylmethoxy)ethyl)-3-((triisopropylsilyl)oxy)cyclobutyl)-5-vinylfuran-3-carboxylate (**200**)



Alkylated β-keto ester **199** (9.5 g, 12.2 mmol, 1.0 eq.) was dissolved in anhydrous DMF (120 mL) under an Ar-atmosphere and finely ground anhydrous K_2CO_3 (11 g, 79.3 mmol, 6.5 eq.) was added. The reaction flask was sealed and the reaction mixture was heated to 90 °C (oil bath temperature 100 °C) for two hours. Stirring was stopped, the suspension was allowed to cool to r.t. and the suspended K_2CO_3 was allowed to settle down. The supernatant was decanted and remaining K_2CO_3 was washed four times with Et_2O (4x40 mL). The combined organic layers were quenched with 0.5M $KHSO_4$ and the pH was adjusted to 6. The phases were separated and the aqueous phase was washed 4 times with Et_2O/hexane (1/1). The combined organic layers were dried with $MgSO_4$ and the solvents were removed under reduced pressure. The crude product was purified by silica gel chromatography (hexane/EtOAc = 10/1) yielding pure vinyl furan **200** (6.8 g, 9.8 mmol, 80%).

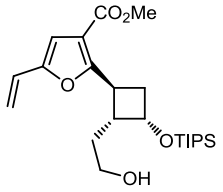
^{1}H-NMR (400MHz, $CDCl_3$): δ = 7.34 (m, 4H); 7.19 (m, 8H); 6.75 (d, *J* = 8.95Hz, 2H); 6.45 (s, 1H); 6.42 (dd, *J* = 17.5, 11.3Hz, 1H); 5.64 (dd, 17.5, 0.8Hz, 1H); 5.19 (dd, *J* = 11.3, 0.8Hz, 1H); 4.66 (m, 1H); 3.91 (m, 1H); 3.78 (s, 3H); 3.68 (s, 3H); 3.05 (m, 3H); 2.47 (m, 1H); 2.30 (m, 1H); 2.07 (m, 1H); 1.88 (m, 1H); 1.03 (m, 21H)

^{13}C-NMR (100MHz, $CDCl_3$): δ = 164.3; 158.5; 150.7; 144.9; 136.2; 130.3; 128.4; 127.6; 126.5; 124.5; 113.8; 112.9; 112.7; 108.8; 66.9; 61.5; 55.1; 51.1; 44.7; 36.4; 33.7; 29.1; 18.0; 12.1

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{43}H_{54}O_6Si$: 694.3690; found: 694.3692

$[\alpha]_D^{20}$: +16.4 (c=0.48; CH_2Cl_2)

Methyl-2-((*1S,2R,3S*)-2-(2-hydroxyethyl)-3-((triisopropylsilyl)oxy)cyclobutyl)-5-vinylfuran-3-carboxylate (**392**)



Vinyl furan **200** (6.8 g, 9.8 mmol, 1.0 eq.) was dissolved in 100 mL of a 4/1 mixture CH_2Cl_2/MeOH. PPTS (246 mg, 1.0 mmol, 0.1 eq.) was added and the reaction mixture was allowed to stir at r.t. until TLC analysis indicated full consumption of the starting material (approx. one hour). The reaction mixture was quenched with saturated aqueous $NaHCO_3$. The phases were separated and the aqueous layer was extracted two times with Et_2O. The combined organic layers were dried with $MgSO_4$ and the solvent was removed under reduced pressure. Purification by silica gel chromatography (hexane/EtOAc = 4/1) yielded free alcohol **392** as colorless viscous oil (3.9 g, 9.1 mmol, 93%).

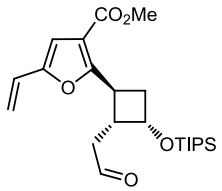
^{1}H-NMR (400MHz, $CDCl_3$): δ = 6.47 (s, 1H); 6.44 (dd, *J* = 17.5, 11.3Hz, 1H); 5.64 (dd, *J* = 17.5, 0.8Hz, 1H); 5.20 (dd, *J* = 11.3, 0.8Hz, 1H); 4.79 (m, 1H); 3.91 (m, 1H); 3.80 (s, 3H); 3.72 (m, 2H); 2.80 (m, 1H); 2.61 (m, 1H); 2.44 (m, 1H); 2.24 (t, *J* = 5.6Hz, 1H); 2.09 (m, 1H); 1.92 (m, 1H); 1.09 (m, 21H)

^{13}C-NMR (100MHz, $CDCl_3$): δ = 163.9; 151.0; 124.4; 112.9; 108.7; 66.7; 61.2; 51.4; 46.3; 35.9; 32.5; 31.8; 18.0; 17.9; 12.1

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{23}H_{38}O_5Si$: 422.2489; found: 422.2483

$[\alpha]_D^{20}$: +25.4 (c=0.50; $CHCl_3$)

Methyl-2-((*1S,2R,3S*)-2-(2-oxoethyl)-3-((triisopropylsilyl)oxy)cyclobutyl)-5-vinylfuran-3-carboxylate (**201**)



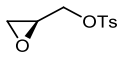
Primary alcohol **392** (3.9 g, 9.1 mmol, 1.0 eq.) was dissolved in anhydrous EtOAc (90 mL) and IBX (7.6 g, 27.3 mmol, 3 eq.) was added. The suspension was heated to reflux for three hours. Now the suspension was cooled to r.t. and 90 mL of hexane were added. The suspension was filtered through a pad of celite and the solvents were removed *in vacuo*. The crude product was purified by silica gel column chromatography (hexane/EtOAc = 5/1). Aldehyde **201** was obtained as viscous oil (3.7 g, 8.8 mmol, 97%).

^{1}H-NMR (400MHz, $CDCl_3$): δ = 9.79 (t, *J* = 1.5Hz, 1H); 6.48 (s, 1H); 6.44 (dd, *J* = 17.7, 11.3Hz, 1H); 5.66 (dd, 17.7, 0.8Hz, 1H); 5.22 (dd, *J* = 11.3, 0.8Hz, 1H); 4.77 (m, 1H); 4.02 (m, 1H); 3.80 (s, 3H); 3.21 (m, 1H); 2.97 (dd, *J* = 17.5, 1.5Hz, 1H); 2.66 (m, 2H); 2.37 (m, 1H); 1.07 (m, 21H)

^{13}C-NMR (100MHz, $CDCl_3$): δ = 201.8; 162.9; 157.4; 124.4; 113.1; 108.7; 66.6; 51.3; 43.1; 42.2; 35.8; 33.2; 17.9; 12.1

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{23}H_{36}O_5Si$: 420.2332; found: 420.2321

(*S*)-oxiran-2-ylmethyl 4-methylbenzenesulfonate (**393**)

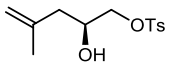


(*R*)-glycidol (**186**, 4.0 g, 54 mmol, 1.0 eq.) was dissolved in anhydrous CH_2Cl_2 (50 mL) and NEt_3 (15 mL, 108 mmol, 2 eq.) and DMAP (330 mg, 2.7 mmol, 0.05 eq.) were added. The solution was cooled to 0 °C and kept under an Ar-atmosphere. Tosyl-chloride (9.8 g, 51.0 mmol, 0.95 eq.) was dissolved in anhydrous CH_2Cl_2 (50 mL) and was added dropwise to the solution of glycidol. The reaction mixture was stirred for 90 minutes. The reaction was quenched by the addition of 0.5M $KHSO_4$. The phases were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried with brine and $MgSO_4$ and the solvent was removed under reduced pressure. Purification by silica gel column chromatography (hexane/EtOAc = 2/1) yielded tosylated glycidol **393** (11.6 g, 50.8 mmol, 94%).

^{1}H-NMR (400MHz, $CDCl_3$): δ = 7.81 (d, *J* = 8.3Hz, 2H); 7.36 (d, *J* = 8.3Hz, 2H); 4.25 (dd, *J* = 11.4, 3.6Hz, 1H); 3.96 (dd, *J* = 11.4, 6.1Hz, 1H); 3.19 (m, 1H); 2.81 (t, *J* = 4.5Hz, 1H); 2.59 (dd, *J* = 4.8, 2.5Hz, 1H); 2.45 (s, 3H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{10}H_{12}O_4S$: 228.0456; found: 228.0450

(*S*)-2-hydroxy-4-methylpent-4-en-1-yl 4-methylbenzenesulfonate (**202**)



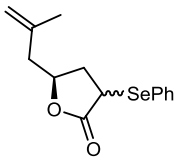
CuI (2.4 g, 12.8 mmol, 0.2 eq.) was suspended in a flame dried three neck round bottom flask in anhydrous THF (40 mL) and the suspension was cooled to -78 °C. 268 mL of a 0.5M solution of isopropenylmagnesium bromide (134 mmol, 2.1 eq.) in THF were added and the suspension turned into a yellow solution. The reaction mixture was allowed to stir for 45 minutes at -78 °C until 60 mL of a solution of tosylated glycidol **393** (14.6 g, 63.8 mmol, 1.0 eq.) in anhydrous THF was added dropwise. The reaction mixture was allowed to stir at -78 °C for 30 minutes. Then it was allowed to warm to -40 °C within two hours until it was quenched with NH_4Cl (no further warming, else the formed alcoholate eliminates the tosylate and forms the epoxide; volatile!). The biphasic mixture was allowed to warm to r.t. and Et_2O and 25% aqueous NH_3 were added. The phases were separated and the organic layer was repeatedly washed with a 3/1 mixture of NH_4Cl/NH_3. The combined aqueous extracts were back-extracted once with Et_2O and the combined organic layers were dried with $MgSO_4$. The solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography (hexane/EtOAc = 2/1) yielding tosylate **202** (15.5 g, 57 mmol, 90%).

^{1}H-NMR (400MHz, $CDCl_3$): δ = 7.81 (d, *J* = 8.3Hz, 2H); 7.36 (d, *J* = 8.3Hz, 2H); 4.86 (s, 1H), 4.76 (s, 1H); 4.00 (m, 3H); 2.46 (s, 3H); 2.18 (m, 2H); 2.06 (d, *J* = 3.8Hz, 1H); 1.73 (s, 3H)

^{13}C-NMR (100MHz, $CDCl_3$): δ = 145.0; 140.9; 132.8; 129.9; 129.3; 128.0; 114.2; 73.3; 70.4; 67.1; 44.6; 41.4; 22.5; 22.3; 21.6; 20.8

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{13}H_{18}O_4S$: 270.0926; found: 270.0919

(*5S*)-5-(2-methylallyl)-3-(phenylselanyl)dihydrofuran-2(3H)-one (**185**)



DIPA (25.2 mL, 180 mmol, 3.15 eq.) was mixed with anhydrous THF (130 mL) and the mixture was cooled to -10 °C when n-BuLi (2.5M in hexane; 68 mL, 171.0 mmol, 3 eq.) was added. The mixture was allowed to stir at -10 °C for 30 minutes. Consecutively, a solution of phenylselenyl acetic acid **397** (30.7 g, 143 mmol, 2.5 eq.) in anhydrous THF (100 mL) was added. The reaction mixture was stirred at -10 °C for 20 minutes , then the cooling bath was removed and the reaction mixture was allowed to stir at r.t for 90 minutes (formation of dianion, precipitating).

Meanwhile, NaH (60% in mineral oil, 2.3 g, 57 mmol, 1.0 eq.) was suspended in anhydrous THF (60 mL) at 0 °C. Tosylate **202** (15.5 g, 57 mmol, 1.0 eq.) dissolved in anhydrous THF (120 mL) and was added dropwise to the suspension of NaH at 0 °C. After 30 minutes the evolution of dihydrogen has ceased, the cooling bath was removed and stirring was continued for additional 30 minutes.

The suspension of the dianion was cooled to -78 °C and the suspension of the *in situ* generated epoxide was cannulated to the dianion. The reaction mixture was allowed to warm to r.t. slowly overnight. The reaction was quenched by the addition of NH_4Cl and water. Et_2O was added and the phases were separated. The aqueous phase was extracted twice with Et_2O and the combined organic layers were dried with $MgSO_4$. The solvent was removed under reduced pressure. The crude product was of sufficient purity for further conversion.

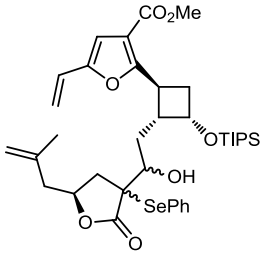
The crude product **204** (18.2 g) was dissolved in anhydrous CH_2Cl_2 (600 mL) and DMAP (696 mg, 5.7 mmol, 0.1 eq.) was added. The reaction was cooled to 0 °C and DIC (9.7 mL, 62.7 mmol, 1.1 eq.) was added. The reaction mixture was stirred at 0 °C for 90 minutes. The solvent was removed under reduced pressure and the crude product was purified using silica gel chromatography (hexane/EtOAc = 7/1). Selenolactone **185** was obtained as orange oil (14.3 g, 49 mmol, 85%) as an inconsequential mixture of diastereo isomers.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 7.69 (m, 2H); 7.35 (m, 1H); 7.34 (m, 2H); 4.84 (s, 1H); 4.73 (s, 1H); 4.42 (dddd, *J* = 7.0, 7.0, 6.8, 6.8Hz, 1H); 3.95 (dd, *J* = 6.5, 4.5Hz, 1H), 2.45 (dd, *J* = 14.3, 6.9Hz, 1H), 2.36 (m, 1H), 2.23 (dd, *J* = 14.3, 6.1Hz, 1H), 1.71 (s, 3H)

^{13}C-NMR (100MHz, $CDCl_3$): δ = 175.6; 140.1; 135.9; 129.9; 129.8; 129.2; 126.7; 113.9; 77.6; 43.2; 36.9; 36.5; 22.7

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{14}H_{16}O_2Se$: 296.0316; found: 296.0301

Methyl-2-((*1S,2R,3S*)-2-(2-hydroxy-2-((*5S*)-5-(2-methylallyl)-2-oxo-3-(phenylselanyl)tetrahydrofuran-3-yl)ethyl)-3-((triisopropylsilyl)oxy)cyclobutyl)-5-vinylfuran-3-carboxylate (**394**)



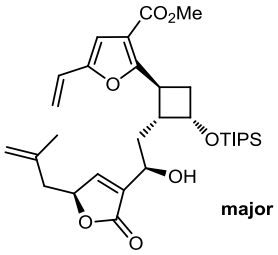
DIPA (1.6 mL, 11.4 mmol, 1.3 eq.) was dissolved in anhydrous THF (30 mL) and the mixture was cooled to -10 °C when n-BuLi (2.5M in hexane; 4.2 mL, 10.6 mmol, 1.2 eq.) was added. The mixture was allowed to stir at -10 °C for 30 min, before it was cooled to -78 °C. Then, a solution of selenolactone **185** (2.9 g, 9.7 mmol, 1.1 eq.) in anhydrous THF (20 mL) was added dropwise. Upon completion, the reaction mixture was allowed to stir for 30 minutes. A solution of aldehyde **201** (3.7 g, 8.8 mmol, 1.0 eq.) in anhydrous THF (30 mL) was added and the reaction mixture was stirred for one hour. The reaction was quenched by the addition of sat. aq. NH_4Cl. After addition of Et_2O, the phases were separated and the aqueous phase was neutralized by the addition of 0.5M $KHSO_4$. The aqueous layer was extracted twice with Et_2O and the combined organic phases were dried with $MgSO_4$. Purification by silica gel chromatography (hexane/EtOAc = 10/1) yielded diene **394** as colorless viscous oil (5.67 g, 7.9 mmol, 90%).

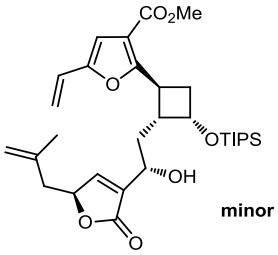
^{1}H-NMR (400MHz, $CDCl_3$): δ = 7.70 (m, 2H); 7.41 (m, 1H); 7.30 (m, 2H); 6.45 (s, 1H); 6.43 (dd, *J* = 17.3, 12.5Hz, 1H); 5.65 (d, *J* = 17.3Hz, 1H); 5.20 (d, *J* = 12.5Hz, 1H); 4.81 (bs, 1H); 4.76 (dddd, *J* = 9.0, 6.8, 6.8, 6.8Hz, 1H); 4.69 (bs, 1H); 4.16 (m, 1H); 3.91 (ddd, *J* = 9.1, 5.9, 5.8Hz, 1H); 3.86 (d, *J* = 10.7Hz, 1H); 3.79 (m, 1H); 3.75 (s, 3H); 3.03 (m, 1H); 2.83 (m, 1H); 2.61 (m, 1H); 2.44 (dd, *J* = 14.5, 7.0Hz, 1H), 2.35 (m, 1H), 2.22 (m, 2H), 2.20 (m, 1H); 2.18 (m, 1H); 1.65 (s, 3H); 1.11 (m, 21H)

^{13}C-NMR (100MHz, $CDCl_3$): δ = 164.7; 163.8; 151.3; 140.5; 138.8; 130.9; 129.6; 126.1; 124.8; 113.4; 114.1; 109.0; 76.3; 72.0; 67.5; 56.7; 45.5; 51.8; 43.6; 38.6; 36.1; 33.8; 32.3; 23.0; 18.4; 12.6

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{37}H_{52}O_7SeSi$: 716.2648; found: 716.2638

Methyl-2-((*1S,2R,3S*)-2-(2-hydroxy-2-((*S*)-5-(2-methylallyl)-2-oxo-2,5-dihydrofuran-3-yl)ethyl)-3-((triisopropylsilyl)oxy)cyclobutyl)-5-vinylfuran-3-carboxylate (**205**)





Diene **394** (5.67 g, 7.9 mmol, 1.0 eq.) was dissolved in CH_2Cl_2 (80 mL) and 20 mL of sat. aq. NH_4Cl were added. The biphasic mixture was cooled to 0 °C and 30% H_2O_2 (733 µL, 23.7 mmol, 3 eq.) was added. The reaction was stirred at 0 °C for one hour and then quenched by the addition of sat. aq. $Na_2S_2O_3$. Phases were separated and the organic phase was extracted 4 times with water. The organic layer was dried with $MgSO_4$ and the solvent was removed under reduced pressure. After silica gel chromatography (hexane/EtOAc = 2/1) butenolide **205** was obtained as colorless oil (4.4 g, 7.9 mmol, quant.) as an hardly separable mixture of diastereo isomers.

Major:

^{1}H-NMR (400MHz, $CDCl_3$): δ = 7.24 (t, *J* = 1.6Hz, 1H); 6.47 (s, 1H); 6.42 (dd, *J* = 17.4, 11.3Hz, 1H); 5.63 (d, *J* = 17.4Hz, 1H); 5.19 (d, *J* = 11.3Hz, 1H); 5.04 (tt, *J* = 6.9, 1.6Hz, 1H); 4.89 (bs, 1H); 4.83 (q, *J* = 6.9Hz, 1H); 4.79 (bs, 1H); 4.55 (d, *J* = 9.5Hz, 1H); 3.85 (m, 1H); 3.79 (s, 3H); 2.93 (m, 1H); 2.63 (m, 1H); 2.41 (m, 3H); 2.25 (ddd, *J* = 14.5, 7.1, 3.0Hz, 1H); 2.08 (m, 1H); 1.77 (s, 3H); 1.08 (m, 21H)

^{13}C-NMR (100MHz, $CDCl_3$): δ = 172.0; 164.3; 163.0; 150.8; 148.1; 139.6; 137.7; 124.3; 114.3; 114.1; 112.9; 108.7; 79.9; 66.7; 65.9; 51.5; 46.2; 41.3; 35.5; 35.3; 32.5; 29.6; 22.9; 17.9; 17.8; 17.8; 17.7; 12.4; 12.1; 11.9; 11.8

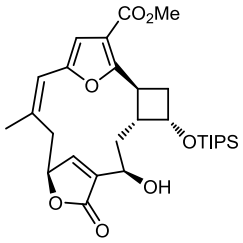
HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{31}H_{46}O_7Si$: 558.3013; found: 558.3010

Minor:

^{1}H-NMR (400MHz, $CDCl_3$): δ = 7.16 (t, *J* = 1.5Hz, 1H); 6.48 (s, 1H); 6.44 (dd, *J* = 17.5, 11.2Hz, 1H); 5.64 (d, *J* = 17.5Hz, 1H); 5.21 (d, *J* = 11.2Hz, 1H); 5.03 (tt, *J* = 6.9, 1.4Hz, 1H); 4.90 (bs, 1H); 4.81 (bs, 1H); 4.78 (q, *J* = 6.9Hz, 1H); 4.63 (m, 1H); 3.99 (m, 1H); 3.93 (d, *J* = 5.2Hz, 1H); 3.81 (s, 3H); 2.79 (m, 1H); 2.64 (m, 1H); 2.39 (m, 5H); 2. 06 (m, 1H); 1.78 (s, 3H); 1.08 (m, 21H)

^{13}C-NMR (100MHz, $CDCl_3$): δ = 172.0; 164.3; 163.2; 150.8; 148.5; 139.8; 136.7; 124.4; 114.2; 114.1; 113.0; 108.7; 80.0; 66.9; 66.1; 51.6; 45.5; 41.4; 35.7; 35.3; 34.1; 32.6; 22.9; 18.0; 17.8; 17.9; 12.1

(*1S,9S,11S,12R,14R,Z*)-methyl 14-hydroxy-3-methyl-16-oxo-11-((triisopropylsilyl)oxy)-17,19-dioxatetracyclo[13.2.1.15,8.09,12]nonadeca-3,5,7,15(18)-tetraene-7-carboxylate (**395**)



Benzene was degassed with 5 pump and freeze cycles. Both diastereo isomers of diene **205** (2.15 g, 3.85 mmol, 1.0 eq.) were dissolved in degassed benzene (2.4L; [1.6mM]) in a flame dried Schlenk flask and the reaction mixture was heated to reflux. Grubbs' second generation metathesis catalyst (653 mg, 0.77 mmol, 0.2 eq.) was dissolved in 20 mL degassed benzene and was added *via* a syringe over a period of 15h using a syringe pump. After the addition was completed the solvent was removed under reduced pressure. Purification by silica gel column chromatography yielded macrocycle **395** as colorless oil (946 mg, 1.78mmopl, 46%) and its diastereo isomer (620 mg, 1.17 mmol, 30%).

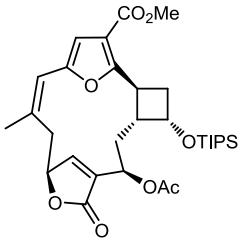
^{1}H-NMR (400MHz, $CDCl_3$): δ = 6.83 (s, 1H); 6.39 (s, 1H); 6.07 (s, 1H); 4.92 (m, 1H); 4.73 (m, 1H); 4.36 (dd, *J* = 5.9, 5.9Hz, 1H); 4.23 (ddd, *J* = 9.3, 9.3, 9.3Hz, 1H); 3.74 (s, 3H); 3.06 (dd, *J* = 11.7, 11.7Hz, 1H); 2.69 (dd, *J* = 11.7, 4.5Hz, 1H); 2.55 (m, 1H); 2.33 (m, 1H); 2.19 (m, 1H); 2.12 (m, 1H); 2.04 (m, 1H); 1.95 (s, 3H); 1.01 (m, 21H)

^{13}C-NMR (100MHz, $CDCl_3$): δ = 171.9; 164.4; 163.7; 152.5; 150.1; 143.4; 129.8; 117.5; 113.9; 111.8; 79.1; 69.4; 67.3; 51.8; 41.3; 40.8; 38.6; 38.4; 33.3; 26.6; 18.4; 18.2; 17.5

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{29}H_{42}O_7Si$: 530.2700; found: 530.2712

$[\alpha]_D^{20}$: +69.1 (c=0.42; CH_2Cl_2)

(*1S,9S,11S,12R,14R,Z*)-methyl 14-acetoxy-3-methyl-16-oxo-11-((triisopropylsilyl)oxy)-17,19-dioxatetracyclo[13.2.1.15,8.09,12]nonadeca-3,5,7,15(18)-tetraene-7-carboxylate (**206**)



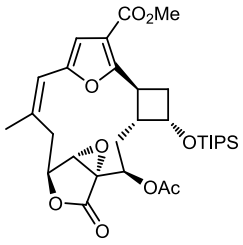
Macrocycle **395** (102 mg, 0.19 mmol, 1.0 eq.) was dissolved in anhydrous CH_2Cl_2 (3 mL) and DIPEA (37 µL, 0.21 mmol, 1.1eq) and DMAP (2.4 mg, 0.02 mmol, 0.1 eq.) were added. The reaction mixture was cooled to 0 °C and Ac_2O (18.9 µL, 0.2 mmol, 1.05 eq.) was added. The solution was allowed to stir at 0 °C for 45 minutes, then it was quenched by the addition of sat. aq. NH_4Cl. Phases were separated and the aqueous phase was extracted twice with CH_2Cl_2. The combined organic layers were dried with $MgSO_4$ and the solvent was removed under reduced pressure. Purification by silica gel chromatography yielded acetate **206** (109 mg, 0.19 mmol, quant.).

^{1}H-NMR (400MHz, $CDCl_3$): δ = 6.94 (d, *J* = 1.3Hz, 1H); 6.48 (s, 1H); 6.12 (s, 1H); 5.24 (dd, *J* = 12.0, 5.2Hz, 1H); 4.97 (ddd, *J* = 11.6, 4.6, 1.3Hz, 1H); 4.46 (t, *J* = 5.9Hz, 1H); 4.18 (q, *J* = 9.4Hz, 1H); 3.82 (s, 3H); 3.02 (dd, *J* = 11.9, 11.9Hz, 1H); 2.78 (dd, *J* = 11.9, 4.6Hz, 1H); 2.54 (m, 2H); 2.32 (dd, *J* = 11.4, 9.5Hz, 1H); 2.24 (dt, *J* = 12.5, 5.2Hz, 1H); 2.09 (m, 1H); 2.03 (s, 3H); 2.00 (s, 3H); 1.08 (m, 21H)

^{13}C-NMR (100MHz, $CDCl_3$): δ = 170.7; 170.6; 163.6; 162.2; 158.2; 149.8; 129.4; 128.4; 117.1; 113.9; 111.8; 78.0; 68.3; 67.0; 60.4; 51.5; 41.1; 40.5; 37.8; 36.4; 29.9; 26.1; 21.2; 18.0; 12.4; 12.1

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{31}H_{44}O_8Si$: 572.2805; found: 572.2793

(*Z*)-Pentacycle (**207**)



Acetate **206** (95 mg, 0.17 mmol, 1.0 eq.) was dissolved in anhydrous pyridine (2 mL) and the solution was cooled to -15 °C. Now 1.4 mL aqueous NaOCl (5% chlorine) were added dropwise and the reaction mixture was stirred for 5 minutes at -15 °C before it was quenched by the addition of a 1/1 mixture $Na_2S_2O_3$/NH_4Cl at low temperature. The aqueous phase was extracted three times with EtOAc and the combined organic layers were dried with $MgSO_4$. Solvents were removed under reduced pressure and purification by silica gel chromatography (hexane/EtOAc = 4/1) yielded (*Z*)-pentacycle **207** as colorless oil (84 mg, 0.14 mmol, 84%).

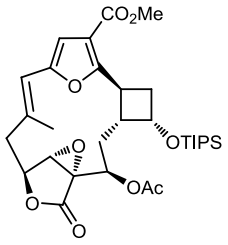
^{1}H-NMR (400MHz, $CDCl_3$): δ = 6.50 (s, 1H); 6.20 (d, *J* = 1.3Hz, 1H); 4.78 (dd, *J* = 12.4, 4.8Hz, 1H); 4.54 (dd, *J* = 12.4, 4.0Hz, 1H); 4.50 (m, 1H); 4.08 (q, *J* = 9.2Hz, 1H); 3.82 (s, 3H); 3.70 (s, 1H); 3.51 (dd, *J* = 12.6, 12.6Hz, 1H); 2.87 (m, 1H); 2.57 (m, 2H); 2.45 (m, 1H); 2.31 (dd, *J* = 13.6, 4.8Hz, 1H); 2.23 (m, 1H); 2.11 (s, 3H); 2.00 (d, *J* = 1.3Hz, 3H); 1.07 (m, 21H)

^{13}C-NMR (100MHz, $CDCl_3$): δ = 170.0; 168.3; 163.4; 161.8; 149.5; 129.2; 117.6; 113.9; 111.3; 75.8; 67.8; 67.5; 65.3; 58.1; 51.6; 39.6; 38.0; 36.6; 36.0; 30.3; 29.7; 29.3; 25.5; 22.7; 21.0; 18.0; 17.9; 12.0

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{31}H_{44}O_8Si$: 588.2755; found: 588.2751

$[\alpha]_D^{20}$: +96.2 (c=0.90; $CHCl_3$)

(*E*)-Pentacycle (**213**)

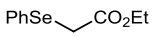


(*Z*)-pentacycle **207** (10 mg, 17 µmol, 1.0 eq.) was dissolved in anhydrous, degassed CH_3CN (2 mL) in a pyrex tube. The reaction mixture was irradiated with a 100W Hoenle Fe bulb for 30 minutes. Longer reaction times led to the formation of undesired side products. The solvent was removed under reduced pressure. Purification by silica gel chromatography (hexane/EtOAc = 4/1) yielded (*E*)-pentacycle **213** (3 mg, 5.1 µmol, 30%) as mixture of atropisomers.

^{1}H-NMR (600MHz, toluene-d_8, 348.1K): δ = 6.42 (d, *J* = 1.3Hz, 1H); 5.84 (s, 1H); 5.41 (d, *J* = 10.3Hz, 1H); 4.40 (dd, *J* = 5.4, 5.4Hz, 1H); 4.06 (dd, *J* = 4.0, 2.5Hz, 1H); 3.88 (q, *J* = 9.2Hz, 1H); 3.52 (m, 2H); 3.49 (s, 3H); 2.99 (m, 1H); 2.48 (dd, *J* = 12.3, 8.6Hz, 1H); 2.28 (dd, *J* = 13.9, 3.9Hz, 1H); 2.16 (m, 3H); 1.73 (s, 3H); 1.60 (s, 3H); 1.08 (m, 21H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{31}H_{44}O_8Si$: 588.2755; found: 588.2748

Ethyl 2-(phenylselanyl)acetate (**396**)

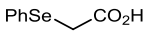


A procedure of *Arrica* and *Wirth* was used.[133] Diphenyldiselenide (10.0 g, 32 mmol, 1.0 eq.) was suspended in anhydrous EtOH (70 mL) and the mixture was cooled to 0 °C. Portionwise addition of $NaBH_4$ (3.64 g, 96 mmol, 3 eq.) yielded the selenate which was accompanied by decolorization. The reaction mixture was stirred for 10 minutes at 0 °C. A solution of chloro acetic acid ethyl ester (8.4 mL, 80.1 mmol, 2.5 eq.) in anhydrous EtOH (30 mL) was added dropwise. The reaction mixture was allowed to stir for one hour until it was quenched by the addition of sat. aq. NH_4Cl. After the addition of Et_2O, the phases were separated and the aqueous phase was extracted twice with Et_2O. The combined organic layers were dried with $MgSO_4$ and the solvents were removed under reduced pressure. The excess of ethyl-chloro-acetate was removed in high vacuum yielding **396** (15.6 g, 64 mmol, quant.) as colorless liquid.

^{1}H-NMR (250MHz, $CDCl_3$): δ = 7.59 (m, 2H); 7.29 (m, 3H); 4.13 (q, *J* = 7.1Hz, 2H); 3.51 (s, 2H); 1.2 (t, *J* = 7.1Hz, 3H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{10}H_{12}O_2Se$: 244.0003; found: 243.9995

2-(phenylselanyl)acetic acid (**397**)

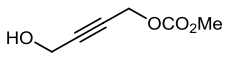


A procedure of *Arrica* and *Wirth* was used.[133] 15.6 g (64 mmol, 1.0 eq.) of ester **396** were dissolved in EtOH (100 mL) and the solution was cooled to 0 °C. After the addition of 100 mL 30% KOH the reaction mixture was allowed to stir for 1h. Acidification (pH = 1-2) with concentrated HCl and extraction with Et_2O, drying with $MgSO_4$ and removal of the solvents under reduced pressure yielded pure 2-(phenylselanyl)acetic acid **397** (13.7 g, 64 mmol, quant.) as white (seldom slightly colored) crystals.

^{1}H-NMR (250MHz, $CDCl_3$): δ = 10.50 (bs, 1H); 7.60 (m, 2H); 7.31 (m, 3H); 3.52 (s, 2H)

HRMS (ESI) (m/z): $[M+Na]^+$ calcd. for $C_8H_8O_2SeNa$: 238.9587; found: 238.99578

Ethyl-(4-hydroxybut-2-yn-1-yl) carbonate (**197**)

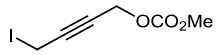


But-2-yne-1,4-diol (**196**, 15 g, 174 mmol, 3 eq.) was dissolved in anhydrous CH_2Cl_2 (350 mL) and the solution was cooled to 0 °C. DIPEA (33.5 mL, 191.7 mmol, 3.3 eq.) and DMAP (708 mg, 5.8 mmol, 0.1 eq.) were added to the solution before methyl chloro formate (4.49 mL, 58.1 mmol, 1.0 eq.) was added dropwise *via* a syringe. The reaction mixture was stirred at 0 °C for two hours before it was allowed to warm to r.t. overnight. The solution was concentrated to ¼ of its original volume and Et_2O and $NaHCO_3$ were added. The phases were separated and the organic phase was washed three times with sat. aq. $NaHCO_3$ before it was dried with brine and $MgSO_4$. The solvent was removed under reduced pressure. Purification by silica gel chromatography (hexane/EtOAc = 1/1) yielded propargylic carbonate **197** as colorless liquid (7.3 g, 50.7 mmol, 87%).

^{1}H-NMR (250MHz, $CDCl_3$): δ = 4.77 (bs, 2H); 4.30 (d, *J* = 6.3Hz, 2H); 3.81 (s, 3H); 1.89 (t, *J* = 6.3Hz, 1H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_6H_8O_4$: 144.0423; found: 144.0420

Ethyl-(4-iodobut-2-yn-1-yl) carbonate (**198**)



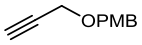
Imidazole (10.5 g, 153.6 mmol, 3 eq.), PPh_3 (26.9 g, 102.4 mmol, 2 eq.) and iodine (26.0 g, 102.4 mmol, 2 eq.) were added to 220 mL anhydrous CH_2Cl_2 and cooled to 0 °C. The suspension was stirred at 0 °C for 20 minutes while it turned yellow. To this suspension a solution of propargylic carbonate **197** (7.37 g, 51.2 mmol, 1.0 eq.) in anhydrous CH_2Cl_2 (30 mL) was rapidly added. The reaction mixture was stirred for one hour. Then it was quenched by the addition of 220 mL hexane. The precipitating triphenylphosphineoxide was filtered through a pad of celite and a solution of sat. aq. $Na_2S_2O_3$ and $NaHCO_3$ was added to the filtrate. The phases were separated and the organic phase was washed with $Na_2S_2O_3$, $NaHCO_3$ and brine before it was dried with $MgSO_4$. After removal of the solvent under reduced pressure, purification by silica gel chromatography yielded propargylic iodide **198** (10.3 g, 38.4 mmol, 75%) as slightly yellow liquid.

^{1}H-NMR (250MHz, $CDCl_3$): δ = 4.75 (bs, 2H); 3.81 (s, 3H); 3.70 (bs, 2H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_6H_7IO_3$: 253.9440; found: 253.9435

4.2.2 $\Delta^{9,10}$ Metathesis Approach (*c*Bu)

PMB-propargyl ether (**222a**)



A suspension of NaH (60% in mineral oil, 5.29 g, 132.2 mmol, 1.1 eq.) in anhydrous DMF (75 mL) was cooled to 0 °C and a solution of anisyl alcohol (16.6 g, 120 mmol, 1.0 eq.) in anhydrous DMF (20 mL) was added dropwise. Upon completion of the addition the reaction mixture was stirred for 2.5 hours. A solution of propargylic bromide (10 mL, 132.2 mmol, 1.1 eq.) in anhydrous DMF (20 mL) was added dropwise and the solution was allowed to warm to r.t. overnight. By the addition of 0.5M $KHSO_4$ the pH of the solution was adjusted to neutral and the slurry was extract three times with Et_2O/hexane (1/1). The combined organic layers were dried with $MgSO_4$ and the solvent was removed under reduced pressure. The excess of propargylic bromide was removed in high vacuum. PMB ether **222a** (20.7 g, 117.5 mmol, 98%) was obtained as slightly orange liquid.

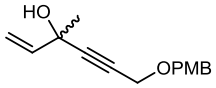
^{1}H-NMR (400MHz, $CDCl_3$): δ = 7.29 (d, *J* = 8.6Hz, 2H); 6.88 (d, *J* = 8.6Hz, 2H); 4.54 (s, 2H); 4.14 (d, *J* = 2.4Hz, 2H); 3.80 (s, 3H); 2.47 (t, *J* = 2.4Hz, 1H)

^{13}C-NMR (100MHz, $CDCl_3$): δ = 159.5; 129.9; 129.3; 113.9; 79.8; 74.6; 71.2; 56.7; 55.3

IR (film): 3288; 3001; 2937; 2907; 2837; 1612; 1585; 1513; 1464; 1442; 1386; 1352; 1302; 1250; 1175; 1079; 1034; 820; 637cm^{-1}

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{11}H_{12}O_2$: 176.0837; found: 176.0833

6-((4-methoxybenzyl)oxy)-3-methylhex-1-en-4-yn-3-ol (**223**)



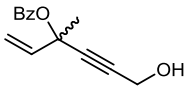
PMB ether **222a** (9.7 g, 55 mmol, 1.0 eq.) was dissolved in anhydrous THF (150 mL) and the solution was cooled to -78 °C. After dropwise addition of LiHMDS (1M, 60 mL, 60 mmol, 1.1 eq.) the reaction mixture was allowed to stir for one hour. A solution of methyl vinyl ketone (MVK; 4.24 g, 60 mmol, 1.1eq) in anhydrous THF (40 mL) was added dropwise. The reaction mixture was allowed to stir at -78 °C for two hours until it was quenched by the addition of sat. aq. NH_4Cl. After the addition of Et_2O the phases were separated and the pH of the aqueous phase was adjusted to 5.

The aqueous phase was extracted twice with Et_2O and the combined organic layers were dried with $MgSO_4$. Removal of the solvent under reduced pressure and purification by silica gel chromatography (hexane/EtOAc = 4/1) yielded allyl alcohol **223** (11.2 g, 45.7 mmol, 83%) as colorless oil.

^{1}H-NMR (250MHz, $CDCl_3$): δ = 7.28 (d, *J* = 8.6Hz, 2H); 6.88 (d, *J* = 8.6Hz, 2H); 5.99 (dd, *J* = 17.1, 10.2Hz, 1H); 5.51 (d, *J* = 17.1Hz, 1H); 5.14 (d, *J* = 10.2Hz, 1H); 4.53 (s, 2H); 4.20 (s, 2H); 3.81 (s, 3H); 2.06 (bs, 1H); 1.58 (s, 3H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{15}H_{18}O_3$: 246.1256; found: 246.1243

6-hydroxy-3-methylhex-1-en-4-yn-3-yl benzoate (**224**)



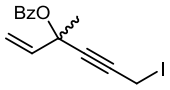
Allyl alcohol **223** (11.2 g, 45.7 mmol, 1.0 eq.) was dissolved in anhydrous THF (100 mL) and NEt_3 (19.3 mL, 137.1 mmol, 3 eq.) and benzoic acid anhydride (20.7 g, 91.4 mmol, 2 eq.) were added at r.t. The reaction mixture was cooled to 0 °C and $MgBr_2 \cdot OEt_2$ (23.6 g, 91.4 mmol, 2 eq.) was added portionwise. The solution was allowed to warm to r.t. within 30 minutes. Water and Et_2O were added and the phases were separated. The organic phase was washed with water and the combined aqueous phases were back-extracted with Et_2O. The combined organic layers were dried with $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was used without further purification.

To a solution of crude tertiary benzoate (10.7 g, 30.5 mmol, 1.0 eq.) in CH_2Cl_2 (600 mL) were added 100 mL of a pH=7-buffer (50mM KH_2PO_4). The vigorously stirred suspension was cooled to 0 °C and DDQ (10.4 g, 45.7 mmol, 1.5 eq.) was added portionwise. The suspension was allowed to stir overnight while it warmed to r.t. After addition of sat. aq. $NaHCO_3$, the phases were separated and the organic phase was washed 6 times with H_2O. The organic phase was dried with brine and $MgSO_4$, and removal of the solvent *in vacuo* gave crude propargylic alcohol. Purification by silica gel chromatography gave alcohol **224** in quantitative yield (7 g, 30.5 mmol, quant.).

^{1}H-NMR (250MHz, $CDCl_3$): δ = 8.00 (m, 2H); 7.54 (m, 1H); 7.41 (m, 2H); 6.08 (dd, *J* = 17.1, 10.2Hz, 1H); 5.63 (d, *J* = 17.1Hz, 1H); 5.27 (d, *J* = 10.2Hz, 1H); 4.36 (s, 2H); 2.96 (bs, 1H); 1.83 (s, 3H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{14}H_{14}O_3$: 230.0943; found: 230.0941

6-iodo-3-methylhex-1-en-4-yn-3-yl benzoate (**221**)

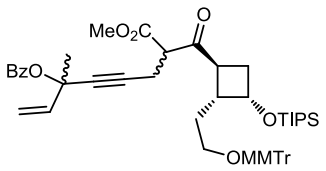


Imidazole (1.95 g, 28.7 mmol, 1.1 eq.), PPh_3 (7.5 g, 28.7 mmol, 1.1 eq.) and iodine (7.0 g, 27.4 mmol, 1.05 eq.) were added to 35 mL anhydrous CH_2Cl_2 and cooled to 0 °C. The suspension was stirred at 0 °C for 20 min, while it turned yellow. To this suspension a solution of propargylic benzoate **224** (6.0 g, 26.1 mmol, 1.0 eq.) in anhydrous CH_2Cl_2 (15 mL) was rapidly added. The reaction mixture was stirred for one hour. Then it was quenched by the addition of 60 mL hexane. The precipitating triphenylphosphineoxide was filter through a pad of celite and a solution of sat. aq. $Na_2S_2O_3$ and $NaHCO_3$ was added to the filtrate. The phases were separated and the organic phase was washed with $Na_2S_2O_3$, $NaHCO_3$ and brine before it was dried with $MgSO_4$. After removal of the solvent under reduced pressure, purification by silica gel chromatography (hexane/EtOAc = 4/1) yielded propargylic iodide **221** (7.5 g, 22.1 mmol, 85%) as slightly yellow liquid.

^{1}H-NMR (250MHz, $CDCl_3$): δ = 8.02 (m, 2H); 7.55 (m, 1H); 7.42 (m, 2H); 6.11 (dd, *J* = 17.1, 10.4Hz, 1H); 5.65 (d, *J* = 17.1Hz, 1H); 5.30 (d, *J* = 10.4Hz, 1H); 3.77 (s, 2H); 1.82 (s, 3H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{14}H_{13}IO_2$: 339.9960; found: 339.9948

8-methoxy-7-((*1S,2R,3S*)-2-(2-((4-methoxyphenyl)diphenylmethoxy)ethyl)-3-((triisopropylsilyl)oxy)cyclobutanecarbonyl)-3-methyl-8-oxooct-1-en-4-yn-3-yl benzoate (**226**)



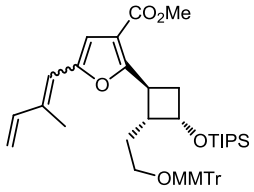
NaH (60% in mineral oil, 124 mg, 3.1 mmol, 1.0 eq.) was suspended in anhydrous THF (10 mL). The reaction mixture was cooled to 0 °C and a solution of β-keto ester **195** (2.0 g, 3.1 mmol, 1.0 eq.) in anhydrous THF (10 mL) was added. The reaction was stirred at 0 °C for 20 minutes and then warmed to r.t. within 10 minutes. Then it was re-cooled to 0 °C and a solution of propargylic iodide **221** (844 mg, 2.48 mmol, 0.8 eq.) was added uninterruptedly at 0 °C. The reaction mixture was stirred at this temperature for 20 minutes and then warmed to r.t. within 20 minutes before it was quenched with saturated aqueous NH_4Cl. Et_2O was added and the phases separated.

The pH of the aqueous phase was adjusted to 6 with 0.5M $KHSO_4$ and it was extracted twice with Et_2O. The combined organic layers were dried with $MgSO_4$ and the solvent was removed under reduced pressure. Silica gel column chromatography (hexane/EtOAc = 5/1) yielded alkylated β-keto ester **226** as slightly yellow oil (1.8 g, 2.1 mmol, 99%).

^{1}H-NMR (250MHz, $CDCl_3$): δ = 7.98 (m, 2H); 7.53 (m, 1H); 7.40 (m, 6H); 7.23 (m, 8H); 6.80 (2H); 6.04 (m, 1H); 5.54 (m, 1H); 5.21 (m, 1H); 4.40 (m, 1H); 3.78 (s, 3H); 3.57 (m, 4H); 3.13 (m, 2H); 2.74 (m, 4H); 2.47 (m, 1H); 2.11 (m, 2H); 1.75 (s, 3H); 1.24 (m, 1H); 0.97 (m, 21H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{53}H_{64}O_8Si$: 856.4370; found: 856.4364

Methyl-2-((*1S,2R,3S*)-2-(2-((4-methoxyphenyl)diphenylmethoxy)ethyl)-3-((triisopropylsilyl)oxy)cyclobutyl)-5-(2-methylbuta-1,3-dien-1-yl)furan-3-carboxylate (**227**)



$Pd(OAc)_2$ (2.6 mg, 11.7 µmol, 0.05 eq.) and dppf (7.8 mg, 14.0 µmol, 0.06 eq.) were premixed in anhydrous THF (2 mL) at r.t. in a flame dried Schlenk-tube under Ar-atmosphere for 1h. The color of the reaction mixture turned from yellow to a deep red. After this period of time a solution of **226** (200 mg, 0.23 mmol, 1.0 eq.) in anhydrous THF (3 mL) was added together with finely ground K_2CO_3 (211 mg, 1.52 mmol, 6.5 eq.). The reaction mixture was heated to reflux for four hours. It was quenched by the addition of 0.5M $KHSO_4$ solution and the pH was adjusted to 7. The aqueous phase was extracted three times with Et_2O. The combined organic layers were dried with $MgSO_4$ and removal of the solvent under reduced pressure yielded crude furan **227** (*E/Z* = 3/2). The crude product was dissolved in THF (5 mL) and Ph_2Se_2 (22 mg, 69 µmol; 0.3 eq.) was added. The reaction mixture was heated to reflux overnight. The solvent was removed under reduced pressure and purification by silica gel chromatography (hexane/EtOAc = 10/1 to 5/1) yielded pure furan **227** (26 mg, 0.35 mmol, 15%) as an inseparable mixture of its double bond isomers (*E/Z* = 4/1).

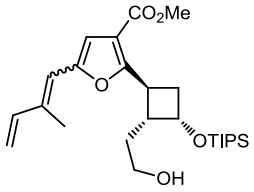
Major & minor:

^{1}H-NMR (400MHz, $CDCl_3$): δ = 7.34 (m, 4H); 7.20 (m, 8H); 6.75 (d, *J* = 8.8Hz, 2H); **6.54**, 6.46 (s, 1H); 6.48 (dd, *J* = 17.2, 11.0Hz, 1H); **6.18**, 6.05 (s, 1H); 5.40, **5.34** (d, *J* = 17.2, 1H); 5.26, **5.15** (d, *J* = 11.0Hz, 1H); 4.68 (m, 1H); 3.92 (m, 1H); 3.78, **3.77** (s, 3H); **3.70**, 3.69 (s, 3H); 3.05 (m, 3H); 2.47 (m, 1H); 2.34 (m, 1H); **2.12**, 2.00 (s, 3H); 2.07 (m, 1H); 1.90 (m, 1H); 1.04 (m, 21H)

^{13}C-NMR (100MHz, $CDCl_3$): δ = 164.0; 163.7; 163.6; 158.3; 150.9; 150.7; 145.0; 144.9; 141.0; 136.2; 134.9; 134.7; 133.6; 130.2; 129.5; 128.4; 127.7; 127.6; 126.7; 126.6; 126.5; 118.7; 116.6; 116.4; 114.0; 113.7; 113.5; 112.9; 112.8; 110.9; 110.6; 85.9; 66.8; 61.5; 55.1; 51.2; 51.1; 44.7; 44.5; 36.4; 33.5; 33.4; 29.2; 29.1; 20.3; 18.0; 14.2; 13.4; 12.1; 12.0; 11.9

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{46}H_{58}O_6Si$: 734.4003; found: 743.3995

Methyl-2-((*1S,2R,3S*)-2-(2-hydroxyethyl)-3-((triisopropylsilyl)oxy)cyclobutyl)-5-(2-methylbuta-1,3-dien-1-yl)furan-3-carboxylate (**398**)

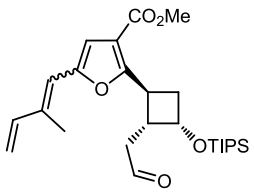


Diene **227** (440 mg, 0.60 mmol, 1.0 eq.) was dissolved in 6 mL of a 4/1 mixture CH_2Cl_2/MeOH. PPTS (15 mg, 0.06 mmol, 0.1 eq.) was added and the reaction mixture was allowed to stir at r.t. until TLC analysis indicated full consumption of the starting material (approx. one hour). The reaction mixture was quenched with saturated aqueous $NaHCO_3$. The phases were separated and the aqueous layer was extracted two times with Et_2O. The combined organic layers were dried with $MgSO_4$ and the solvent was removed under reduced pressure. Purification by silica gel chromatography (hexane/EtOAc = 4/1) yielded free alcohol **398** as colorless viscous oil (260 mg, 0.60 mmol, quant.).

^{1}H-NMR (250MHz, $CDCl_3$): δ = 6.55 (s, 1H); 6.48 (dd, *J* = 17.1, 10.6Hz, 1H); 6.18 (s, 1H); 5.34, (d, *J* = 17.1Hz, 1H); 5.15 (d, *J* = 10.6Hz, 1H); 4.78 (m, 1H); 3.92 (m, 1H); 3.81, (s, 3H); 3.73 (m, 2H); 2.80 (m, 1H); 2.60 (m, 1H); 2.47 (m, 1H); 2.23 (m, 1H); 2.13 (s, 3H); 2.07 (m, 1H); 1.90 (m, 1H); 1.08 (m, 21H)

HRMS (ESI) (m/z): $[M+Na]^+$ calcd. for $C_{26}H_{42}O_5SiNa$: 485.2699; found: 485.2687

Methyl-5-(2-methylbuta-1,3-dien-1-yl)-2-((*1S,2R,3S*)-2-(2-oxoethyl)-3-((triisopropylsilyl)oxy)cyclobutyl)furan-3-carboxylate (**228**)



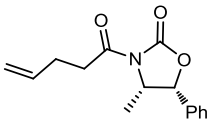
Primary alcohol **398** (10 mg, 21.6 µmol, 1.0 eq.) was dissolved in anhydrous EtOAc (2 mL) and IBX (18 mg, 64.8 µmol, 3 eq.) was added. The suspension was heated to reflux for three hours. Now the suspension was cooled to r.t. and 2 mL of hexane were added. The suspension was filtered through a pad of celite and the solvents were removed *in vacuo*. The crude product was purified by silica gel column chromatography (hexane/EtOAc = 5/1). Aldehyde **228** was obtained as viscous oil (7 mg, 15.2 µmol, 70%).

^{1}H-NMR (400MHz, $CDCl_3$): δ = 9.80 (t, *J* = 1.5Hz, 1H); 6.56 (s, 1H); 6.48 (dd, *J* = 17.5, 10.6Hz, 1H); 6.20 (s, 1H); 5.35, (d, *J* = 17.1Hz, 1H); 5.15 (d, *J* = 10.6Hz, 1H); 4.78 (m, 1H); 4.00 (m, 1H); 3.81 (m, 1H); 3.80, (s, 3H); 3.21 (m, 1H); 2.98 (ddd, *J* = 17.4, 8.1, 1.6Hz, 1H); 2.66 (m, 2H); 2.40 (m, 1H); 2.13 (s, 3H); 1.06 (m, 21H)

^{13}C-NMR (100MHz, $CDCl_3$): δ = 201.8; 162.3; 151.3; 149.4; 140.9; 135.2; 134.8; 118.5; 116.4; 113.8; 110.7; 66.5; 66.4; 51.4; 43.1; 42.2; 35.8; 32.9; 20.4; 17.9; 13.4; 12.0

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{26}H_{40}O_5Si$: 460.2645; found: 460.2641

(*4S,5R*)-4-methyl-3-(pent-4-enoyl)-5-phenyloxazolidin-2-one (**229**)



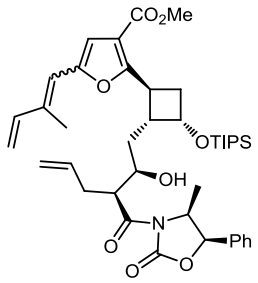
4-Pentenoic acid (1.0 g, 10 mmol, 1.0 eq.), (4S,5R)-4-methyl-5-phenyloxazolidin-2-one (1.77 g, 10 mmol, 1.0 eq.) and DMAP (122 mg, 1.0 mmol, 0.1 eq.) were dissolved in anhydrous CH_2Cl_2 (50 mL) in an Ar-atmosphere. DIC (1.7 mL, 11.0 mmol, 1.1 eq.) was added to the reaction mixture and the solution was allowed to stir at r.t. overnight. The solvent was removed under reduced pressure and the crude reaction mixture was purified by silica gel chromatography (hexane/EtOAc = 4/1) yielding pure **229** (2.07 g, 8 mmol, 80%) as white crystals.

^{1}H-NMR (250MHz, $CDCl_3$): δ = 7.37 (m, 5H); 5.88 (m, 1H); 5.66 (d, *J* = 7.3Hz, 1H); 5.09 (dd, *J* = 17.2, 1.5Hz, 1H); 5.02 (d, *J* = 10.4Hz, 1H); 4.76 (m, 1H); 3.07 (m, 2H); 2.44 (m, 2H); 0.89 (d, *J* = 6.7Hz, 3H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{15}H_{17}NO_3$: 259.1208; found: 259.1200

mp 70 – 71 °C

Methyl-2-((*1S,2R,3S*)-2-((*2R,3S*)-2-hydroxy-3-((*4S,5R*)-4-methyl-2-oxo-5-phenyloxazolidine-3-carbonyl)hex-5-en-1-yl)-3-((triisopropylsilyl)oxy)cyclobutyl)-5-(2-methylbuta-1,3-dien-1-yl)furan-3-carboxylate (**231**)



Di-*n*butyl boron trifluormethanesulfonate (1.0M in CH_2Cl_2, 1 mL, 2.2 eq.) and NEt_3 (158 µL, 1.13 mmol, 2.5 eq.) were added to a well stirred solution of **229** (235 mg, 0.91 mmol, 2 eq.) in anhydrous CH_2Cl_2 (8 mL) at 0 °C within 10 minutes. After complete addition, the reaction mixture was stirred for another 10 minutes at 0 °C and finally cooled to -78 °C. A solution of **228** (209 mg, 0.45 mmol, 1.0 eq.) in anhydrous CH_2Cl_2 (7 mL) was added dropwise and the reaction was allowed to stir at -78 °C for two hours and an additional hour at 0 °C. The reaction mixture was quenched by the addition of 2 mL of a pH=7-buffer (50mM KH_2PO_4) and 2 mL of MeOH at 0 °C. Further, 0.5 mL of H_2O_2 (30%) were added and the reaction was allowed to stir for 90 minutes at 0 °C. The organic layer was separated and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic layers were dried with brine and $MgSO_4$ and the solvents were removed under reduced pressure. Purification by silica gel chromatography (hexane/EtOAc = 2/1) yielded pure *syn*-aldol poduct **231** (133 mg, 0.18 mmol, 41%) as a colorless oil.

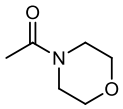
^{1}H-NMR (400MHz, $CDCl_3$): δ = 7.39 (m, 3H); 7.28 (m, 2H); 6.54 (s, 1H); 6.47 (dd, *J* = 17.3, 10.8Hz, 1H); 6.19 (s, 1H); 5.86 (m, 1H); 5.57 (d, *J* = 7.2Hz, 1H); 5.33 (m, 1H); 5.32 (d, *J* = 17.3Hz, 1H); 5.13 (d, *J* = 10.8Hz, 1H); 5.03 (dd, *J* = 17.1, 1.7Hz, 1H); 4.95 (d, *J* = 10.3Hz, 1H); 4.76 (m, 2H); 4.13 (m, 1H); 4.03 (m, 2H); 3.81 (s, 3H); 3.41 (m, 1H); 2.87 (m, 1H); 2.57 (m, 2H); 2.45 (m, 1H); 2.11 (s, 3H); 2.06 (m, 1H); 1.88 (m, 1H); 1.09 (m, 21H); 0.83 (d, *J* = 6.6Hz, 3H)

^{13}C-NMR (100MHz, $CDCl_3$): δ = 175.3; 164.5; 163.3; 152.6; 151.1; 141.0; 135.5; 135.0; 133.3; 128.7; 125.6; 118.5; 116.9; 114.1; 113.6; 110.7; 78.6; 70.9; 66.9; 55.0; 51.5; 47.4; 45.9; 45.8; 35.6; 33.2; 32.9; 32.4; 18.0; 14.5; 13.4; 12.1

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{41}H_{57}NO_8Si$: 719.3853; found: 719.3848

4.2.3 $\Delta^{10,11}$ Metathesis Approach (*c*Bu)

N-Acetylmorpholine (**238**)

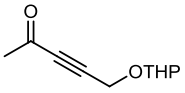


An adapted procedure of *Yadav* and *Babu* was used.[134] Acetic anhydride (5.19 mL, 55 mmol, 1.1 eq.) and morpholine (4.36 mL, 50 mmol, 1.0 eq.) were mixed and cooled to 0 °C. Al_2O_3 (7.65 g, 75 mmol, 1.5 eq.) was added (caution: extremely exothermic!) and the suspension was stirred for 20 minutes. CH_2Cl_2 was added and the suspension was filtered through a pad of celite. Sat. aq. $NaHCO_3$ was added and the phases were separated. The organic phase was extracted twice with $NaHCO_3$ and afterwards dried with brine and $MgSO_4$. Removal of the solvent under reduced pressure yielded pure *N*-acetylmorpholine **238** (6.46 g, 50 mmol, quant.) as colorless liquid.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 3.62 (m, 4H); 3.56 (m, 2H); 3.41 (m, 2H); 2.04 (s, 3H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_6H_{11}NO_2$: 129.0790; found: 129.0782

5-((tetrahydro-2H-pyran-2-yl)oxy)pent-3-yn-2-one (**239**)

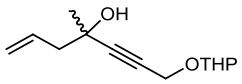


THP-protected propargylic alcohol (27.45 g, 196 mmol, 3 eq.) was dissolved in anhydrous THF (50 mL) and the solution was cooled to -78 °C. n-BuLi (2.5M in hexane; 78.3 mL, 196 mmol, 3 eq.) was added and the reaction mixture was allowed to stir at -78 °C for 30 minutes. A solution of *N*-acetylmorpholine **238** (8.43 g, 65 mmol, 1.0 eq.) in anhydrous THF (20 mL) was added and the reaction mixture was allowed to stir for four hours (-78 °C to -40 °C). The reaction mixture was quenched by the addition of sat. aq. NH_4Cl and Et_2O. The phases were separated and the pH of the aqueous phase was adjusted to neutral. The aqueous layer was extracted twice with Et_2O and the combined organic layers were dried with brine and $MgSO_4$. The solvent was removed under reduced pressure. Silica gel chromatography (hexane/EtOAc = 5/1) yielded pure yne-one **239** (11.3 g, 62 mmol, 95%) as colorless liquid.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 4.80 (t, *J* = 3.2Hz, 1H); 4.41 (d, *J* = 1.8Hz, 2H); 3.82 (m, 1H); 3.55 (m, 1H); 2.35 (s, 3H); 1.77 (m, 2H); 1.59 (m, 4H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{10}H_{14}O_3$: 182.0943; found: 182.0932

4-methyl-7-((tetrahydro-2H-pyran-2-yl)oxy)hept-1-en-5-yn-4-ol (**399**)



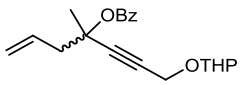
Ynone **239** (11.3 g, 62 mmol, 1.0 eq.) was dissolved in anhydrous THF (120 mL) and the solution was cooled to -78 °C. Allyl-MgBr (1M in THF, 81 mL, 81.0 mmol, 1.3 eq.) was slowly added and the reaction mixture was allowed to stir for two hours warming to -40 °C. The reaction was quenched by the addition of sat. aq. NH_4Cl and Et_2O was added. The phases were separated and the pH of the aqueous phase was adjusted to neutral. The aqueous layer was extracted twice with Et_2O and the combined organic layers were dried with brine and $MgSO_4$. The solvent was removed under reduced pressure. Silica gel chromatography (hexane/EtOAc = 5/1) yielded pure tertiary alcohol **399** (11.5 g, 51.5 mmol, 83%) as colorless liquid.

^{1}H-NMR (400MHz, CD_3OD): δ = 5.92 (m, 1H); 5.13 (m, 1H); 5.09 (bs, 1H); 4.82 (m, 2H); 4.27 (d, *J* = 1.5Hz, 2H); 3.84 (m, 1H); 3.51 (m, 1H); 2.40 (m, 2H); 1.77 (m, 2H); 1.55 (m, 4H); 1.41 (s, 3H)

^{13}C-NMR (100MHz, CD_3OD): δ = 134.7; 118.4; 116.6; 97.7; 90.6; 79.7; 67.7; 62.9; 54.8; 31.2; 29.2; 26.3; 20.0

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{13}H_{20}O_3$: 224.1412; found: 224.1401

4-methyl-7-((tetrahydro-2H-pyran-2-yl)oxy)hept-1-en-5-yn-4-yl benzoate (**240**)



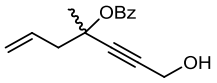
Tertiary alcohol **399** (3 g, 13.4 mmol, 1.0 eq.) was dissolved in anhydrous THF (100 mL) and NEt_3 (5.6 mL, 40.1 mmol, 3 eq.) and benzoic acid anhydride (6.1 g, 26.8 mmol, 2 eq.) were added at r.t. The reaction mixture was cooled to 0 °C and $MgBr_2 \cdot OEt_2$ (6.9 g, 26.8 mmol, 2 eq.) was added portionwise. The solution was allowed to warm to r.t. within 30 minutes. Water and Et_2O were added and the phases were separated.

The organic phase was washed with water and the combined aqueous phases were back-extracted with Et_2O. The combined organic layers were dried with $MgSO_4$ and the solvent was removed under reduced pressure. Purification by silica gel chromatography (hexane/EtOAc = 5/1) yielded tertiary benzoate **240** (4.4 g, 13.4 mmol, quant.) as colorless oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 7.98 (m, 2H); 7.50 (m, 1H); 7.39 (m, 2H); 5.92 (m, 1H); 5.16 (m, 2H); 4.83 (bs, 1H); 4.30 (s, 2H); 3.81 (m, 1H); 3.73 (m, 1H); 3.48 (m, 1H); 2.79 (m, 2H); 1.76 (s, 3H); 1.73 (m, 2H); 1.54 (m, 4H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{20}H_{24}O_4$: 328.1675; found: 328.1662

7-hydroxy-4-methylhept-1-en-5-yn-4-yl benzoate (**400**)

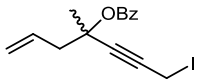


Tertiary benzoate **240** (5.9 g, 18 mmol, 1.0 eq.) was dissolved in MeOH (100 mL) and DOWEX 50x4 (approx. 2.5 g) was added. The reaction mixture was stirred at r.t. for two hours and then filtered through a pad of celite 545 coarse. The solvents were removed *in vacuo* and the crude product was subjected to silica gel column chromatography (hexane/EtOAc = 4/1). Free propargylic alcohol **400** (4.4 g, 18 mmol, quant.) was obtained as colorless oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 8.00 (m, 2H); 7.54 (m, 1H); 7.42 (m, 2H); 5.95 (m, 1H); 5.20 (m, 2H); 4.33 (s, 2H); 2.81 (m, 2H); 1.78 (s, 3H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{15}H_{16}O_3$: 244.1099; found: 244.1084

7-iodo-4-methylhept-1-en-5-yn-4-yl benzoate (**237**)



Imidazole (1.74 g, 25.5 mmol, 3 eq.), PPh_3 (4.46 g, 17 mmol, 2 eq.) and iodine (4.32 g, 17 mmol, 2 eq.) were added to 60 mL anhydrous CH_2Cl_2 and cooled to 0 °C. The suspension was stirred at 0 °C for 20 minutes while it turned yellow. To this suspension a solution of propargylic benzoate **400** (2.01 g, 8.5 mmol, 1.0 eq.) in anhydrous CH_2Cl_2 (20 mL) was rapidly added. The reaction mixture was stirred for one hour. Then it was quenched by the addition of 80 mL hexane.

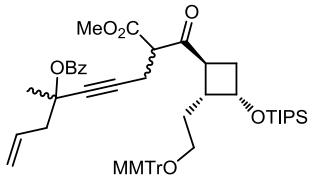
The precipitating triphenylphosphineoxide was filter through a pad of celite and a sat. aq. solution of $Na_2S_2O_3$ and $NaHCO_3$ was added to the filtrate. The phases were separated and the organic phase was washed with $Na_2S_2O_3$, $NaHCO_3$ and brine before it was dried with $MgSO_4$. After removal of the solvent under reduced pressure, purification by silica gel chromatography (hexane/EtOAc = 7/1) yielded propargylic iodide **237** (2.71 g, 7.7 mmol, 90%) as slightly yellow liquid.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 8.00 (m, 2H); 7.55 (m, 1H); 7.43 (m, 2H); 5.95 (m, 1H); 5.22 (m, 2H); 3.75 (s, 2H); 2.81 (m, 2H); 1.76 (s, 3H)

^{13}C-NMR (100MHz, $CDCl_3$): δ = 164.6; 136.3; 132.9; 132.0; 130.8; 129.8; 129.6; 128.3; 119.4; 85.1; 82.7; 74.6; 45.8; 26.0; -18.9

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{15}H_{15}IO_2$: 354.0117; found: 354.0105

9-methoxy-8-((*1S,2R,3S*)-2-(2-((4-methoxyphenyl)diphenylmethoxy)ethyl)-3-((triisopropylsilyl)oxy)cyclobutanecarbonyl)-4-methyl-9-oxonon-1-en-5-yn-4-yl benzoate (**241**)



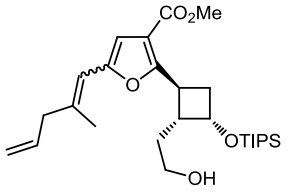
NaH (60% in mineral oil, 62 mg, 1.55 mmol, 1.0 eq.) was suspended in anhydrous THF (5 mL). The reaction mixture was cooled to 0 °C and a solution of β-keto ester **195** (1 g, 1.55 mmol, 1.0 eq.) in anhydrous THF (5 mL) was added. The reaction was stirred at 0 °C for 20 minutes and then warmed to r.t. within 10 minutes. Then it was re-cooled to 0 °C and a solution of propargylic iodide **237** (549 mg, 1.55 mmol, 1.0 eq.) was added uninterruptedly at 0 °C. The reaction mixture was stirred at this temperature for 20 minutes and then warmed to r.t. within 20 minutes before it was quenched with saturated aqueous NH_4Cl. Et_2O was added and the phases separated. The pH of the aqueous phase was adjusted to 6 with 0.5M $KHSO_4$ and it was extracted twice with Et_2O. The combined organic layers were dried with $MgSO_4$ and the solvent was removed under reduced pressure. Silica gel column chromatography (hexane/EtOAc = 7/1) yielded alkylated β-keto ester **241** as slightly yellow oil (1.32 g, 1.52 mmol, 98%).

^{1}H-NMR (400MHz, $CDCl_3$): δ = 7.96 (m, 2H); 7.52 (m, 1H); 7.40 (m, 6H); 7.28 (m, 6H); 7.19 (m, 2H); 6.81 (m, 2H); 5.88 (m, 1H); 5.16 (m, 2H); 4.40 (m, 1H); 3.78, 3.66 (m, 6H); 3.62 (d, *J* = 2.3Hz, 1H); 3.54 (d, *J* = 2.3Hz, 1H); 3.13 (m, 3H); 2.72 (m, 3H); 2.47 (m, 1H); 2.11 (m, 2H); 1.80 (m, 1H); 1.73 (m, 1H); 1.69 (m, 3H); 0.98 (m, 21H)

^{13}C-NMR (100MHz, $CDCl_3$): δ = 205.6; 168.7; 164.5; 158.4; 144.8; 136.0; 132.7; 132.4; 130.3; 129.5; 128.4; 128.2; 127.8; 127.7; 126.7; 119.0; 116.1; 113.2; 113.0; 86.2; 82.1; 74.7; 65.8; 65.5; 65.3; 61.8; 55.1; 52.4; 47.5; 46.0; 45.6; 44.9; 42.8; 42.2; 33.7; 33.0; 28.9; 26.4; 17.9; 12.0

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{54}H_{66}O_8Si$: 870.4527; found: 870.4513

Methyl-2-((*1S,2R,3S*)-2-(2-hydroxyethyl)-3-((triisopropylsilyl)oxy)cyclobutyl)-5-(2-methylpenta-1,4-dien-1-yl)furan-3-carboxylate (**401**)



Alkylated β-keto ester **241** (1.2 g, 1.38 mmol, 1.0 eq.) was dissolved in anhydrous DMF (28 mL) under an Ar-atmosphere and finely ground anhydrous K_2CO_3 (1.24 g, 8.95 mmol, 6.5 eq.) was added. The reaction flask was sealed and the reaction mixture was heated to 90 °C (oil bath temperature 100 °C) for two hours. The suspension was allowed to cool to r.t. and the suspended K_2CO_3 was allowed to settle down. The supernatant was decanted and remaining K_2CO_3 was washed four times with Et_2O (4x40 mL). The combined organic layers were quenched with 0.5M $KHSO_4$ and the pH was adjusted to 6. The phases were separated and the aqueous phase was washed 4 times with Et_2O/hexane (1/1). The combined organic layers were dried with $MgSO_4$ and the solvents were removed under reduced pressure. The crude product was purified by silica gel chromatography (hexane/EtOAc = 10/1 to 7/1) yielding pure vinyl furan **401a** (920 mg, 1.23 mmol, 89%) as an inseparable mixture of double bond isomers (*E/Z* = 2/1).

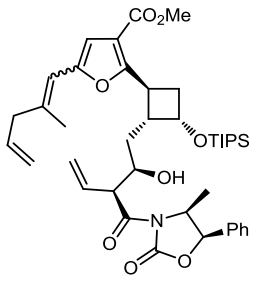
Vinyl furan **401a** (920 mg, 1.23 mmol, 1.0 eq.) was dissolved in 15 mL of a 4/1 mixture CH_2Cl_2/MeOH. PPTS (31 mg, 0.12 mmol, 0.1 eq.) was added and the reaction mixture was allowed to stir at r.t. until TLC analysis indicated full consumption of the starting material (approx. two hours). The reaction mixture was quenched with saturated aqueous $NaHCO_3$. The phases were separated and the aqueous layer was extracted two times with Et_2O. The combined organic layers were dried with $MgSO_4$ and the solvent was removed under reduced pressure. Purification by silica gel chromatography (hexane/EtOAc = 4/1) yielded free alcohol **401** as colorless viscous oil (580 mg, 1.22 mmol, 99%).

(*E*)-isomer:

^{1}H-NMR (400MHz, $CDCl_3$): δ = 6.40 (s, 1H); 6.02 (s, 1H); 5.86 (m, 1H); 5.14 (m, 1H); 5.08 (m, 1H); 4.73 (m, 1H); 3.90 (m, 1H); 3.80 (m, 3H); 3.71 (m, 2H); 2.90 (d, *J* = 6.7Hz, 1H); 2.77 (m, 2H); 2.58 (m, 1H); 2.42 (m, 1H); 2.04 (s, 3H); 1.93 (m, 1H); 1.88 (m, 1H); 1.71 (m, 1H); 1.07 (m, 21H)

HRMS (ESI) (m/z): $[M+Na]^+$ calcd. for $C_{27}H_{44}O_5SiNa$: 499.2856; found: 499.2841

Methyl-2-((*1S,2R,3S*)-2-((*2R,3S*)-2-hydroxy-3-((*4S,5R*)-4-methyl-2-oxo-5-phenyloxazolidine-3-carbonyl)pent-4-en-1-yl)-3-((triisopropylsilyl)oxy)cyclobutyl)-5-(2-methylpenta-1,4-dien-1-yl)furan-3-carboxylate (**246a**)



Primary alcohol **401** (580 mg, 1.22 mmol, 1.0 eq.) was dissolved in anhydrous EtOAc (12 mL) and IBX (1.02 g, 3.66 mmol, 3 eq.) was added. The suspension was heated to reflux for three hours. The suspension was cooled to r.t. and 12 mL of hexane were added. The suspension was filtered through a pad of celite and the solvents were removed under reduced pressure. The crude product was purified by silica gel column chromatography (hexane/EtOAc = 5/1). The aldehyde was obtained as viscous oil (580 mg, 1.22 mmol, quant.).

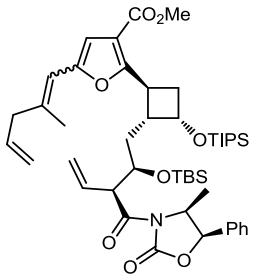
(*4S,5R*)-3-((*E*)-but-2-enoyl)-4-methyl-5-phenyloxazolidin-2-one (**244**, 114 mg, 0.46 mmol, 1.0 eq.) was dissolved in anhydrous CH_2Cl_2 (2 mL) and the solution was cooled to -78 °C. 460 µL of a 1M solution Bu_2BOTf (in CH_2Cl_2, 460 µL, 0.46 mmol, 1.0 eq.) were added dropwise. The reaction mixture was stirred for 30 minutes, then NEt_3 (81 µL, 0.58 mmol, 1.25 eq.) was added. The reaction mixture was stirred for 20 minutes then it was allowed to warm to 0 °C and stirring was continued for 90 minutes. The solution was re-cooled to -78 °C and a solution of the previously prepared aldehyde (220 mg, 0.46 mmol, 1.0 eq.) in anhydrous CH_2Cl_2 (2 mL) was added dropwise. The reaction mixture was stirred at -78 °C for two hours and at -25 °C overnight, before it was quenched with pH=7-buffer (50mM KH_2PO_4). 600 µL of a 2/1 mixture MeOH/H_2O_2 (30% aqueous solution) were added and the reaction mixture was stirred for 10 minutes at r.t. Additional CH_2Cl_2 was added and the phases were separated. The organic layer was extracted two times with water and brine. The solvent was removed *in vacuo* and purification by silica gel chromatography (hexane/EtOAc = 5/1 to 4/1) yielded pure aldol product **246a** (331 mg, 0.46 mmol, quant.) as colorless oil.

(*E*)-isomer:

^{1}H-NMR (400MHz, $CDCl_3$): δ = 7.39 (m, 3H); 7.27 (m, 2H); 6.39 (s, 1H); 6.02 (s, 1H); 6.01 (dd, *J* = 20.5, 8.6Hz, 1H); 5.83 (m, 1H); 5.61 (d, *J* = 7.2Hz, 1H); 5.31 (d, *J* = 15.9Hz, 2H); 5.09 (m, 2H); 5.08 (m, 1H); 4.74 (m, 2H); 4.46 (m, 1H); 4.17 (m, 1H); 3.99 (m, 1H); 3.79 (s, 3H); 3.49 (d, *J* = 2.8Hz, 1H); 3.15 (m, 1H); 2.87 (d, *J* = 6.7Hz, 1H); 2.57 (m, 1H); 2.40 (m, 1H); 2.04 (s, 3H); 1.86 (m, 2H); 1.07 (m, 21H); 0.85 (d, *J* = 6.6Hz, 3H)

HRMS (ESI) (m/z): $[M+Na]^+$ calcd. for $C_{41}H_{57}NO_8SiNa$: 742.3751; found: 742.3742

Methyl-2-((*1S,2R,3S*)-2-((*2R,3S*)-2-((tert-butyldimethylsilyl)oxy)-3-((*4S,5R*)-4-methyl-2-oxo-5-phenyloxazolidine-3-carbonyl)pent-4-en-1-yl)-3-((triisopropylsilyl)oxy)cyclobutyl)-5-(2-methylpenta-1,4-dien-1-yl)furan-3-carboxylate (**246b**)

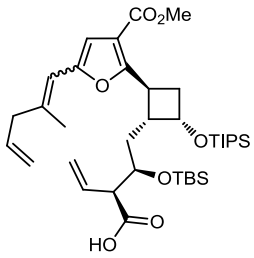


Secondary alcohol **246a** (70 mg, 0.1 mmol, 1.0 eq.) was dissolved in anhydrous CH_2Cl_2 (1 mL) and the reaction mixture was cooled to 0 °C. After the addition of 2,6-lutidine (47.1 µL, 0.4 mmol, 4 eq.) the solution was incubated at 0 °C for 5 minutes before TBS-OTf (46.5 µL, 0.2 mmol, 2 eq.) was added dropwise. The reaction mixture was stirred at 0 °C for 30 minutes and then quenched by the addition of sat. aq. $NaHCO_3$. The phases were separated and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were washed with NH_4Cl and brine. Drying with $MgSO_4$, concentration *in vacuo* and purification by silica gel chromatography (hexane/EtOAc = 5/1) yielded pure **246b** (85 mg, 0.1 mmol, quant.) as colorless oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 7.39 (m, 3H); 7.28 (m, 2H); 6.43 (s, 1H); 6.04 (m, 2H); 5.85 (m, 1H); 5.56 (d, *J* = 6.8Hz, 1H); 5.19 (d, *J* = 10.5Hz, 1H); 5.09 (m, 2H); 4.82 (m, 1H); 4.60 (m, 1H); 4.39 (m, 1H); 4.22 (m, 1H); 3.94 (m, 1H); 3.71 (s, 3H); 2.89 (d, *J* = 6.6Hz, 1H); 2.80 (m, 1H); 2.47 (m, 2H); 2.13 (m, 1H); 2.02 (s, 3H); 1.84 (m, 2H); 1.71 (m, 1H); 1.07 (m, 21H); 0.91 (s, 9H); 0.83 (d, *J* = 6.5Hz, 3H); 0.16 (s, 3H); 0.12 (s, 3H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{47}H_{71}NO_8Si_2$: 833.4718; found: 833.4715

(*S*)-2-((*R*)-1-((tert-butyldimethylsilyl)oxy)-2-((*1R,2S,4S*)-2-(3-(methoxycarbonyl)-5-(2-methylpenta-1,4-dien-1-yl)furan-2-yl)-4-((triisopropylsilyl)oxy)cyclobutyl)ethyl)but-3-enoic acid (**249**)

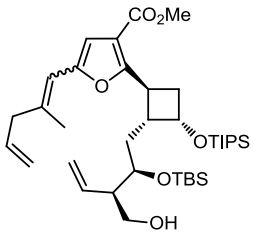


Compound **246b** (60 mg, 72 µmol, 1.0 eq.) was dissolved in THF (1 mL) and the solution was cooled to 0 °C. A mixture of $LiOH.H_2O$ (3.9 mg, 92.8 mmol, 1.3 mmol) and 30% H_2O_2 (19 µL, 180 µmol, 2.5 eq.) in water (300 µL) was added dropwise at low temperature. The reaction was allowed to stir at 0 °C overnight, before it was quenched by the addition of sat. aq. $Na_2S_2O_3$ and Et_2O. The phases were separated and the organic layer was washed twice with water before it was dried with brine and $MgSO_4$. The solvent was removed *in vacuo* and purification by silica gel chromatography (hexane/EtOAc = 3/1) yielded pure carboxylic acid **249** (17 mg, 25 µmol, 35%) as colorless semisolid.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 9.71 (bs, 1H); 6.41 (s, 1H); 6.00 (m, 2H); 5.85 (m, 1H); 5.21 (d, *J* = 10.3Hz, 1H); 5.13 (d, *J* = 5.5Hz, 1H); 5.03 (m, 2H); 4.64 (m, 1H); 4.31 (m, 2H); 4.00 (m, 1H); 3.81 (s, 3H); 2.90 (d, *J* = 6.7Hz, 1H); 2.83 (m, 1H); 2.65 (m, 1H); 2.56 (m, 1H); 2.33 (m, 1H); 1.99 (s, 3H); 1.88 (m, 1H); 1.74 (m, 1H); 1.05 (bs, 21H); 0.86 (s, 9H); 0.13 (s, 3H); 0.08 (s, 3H)

HRMS (ESI) (m/z): $[M+Na]^+$ calcd. for $C_{37}H_{62}O_7Si_2Na$: 697.3932; found: 697.3921

Methyl-2-((*1S,2R,3S*)-2-((*2R,3R*)-2-((tert-butyldimethylsilyl)oxy)-3-(hydroxymethyl)pent-4-en-1-yl)-3-((triisopropylsilyl)oxy)cyclobutyl)-5-(2-methylpenta-1,4-dien-1-yl)furan-3-carboxylate (**247**)

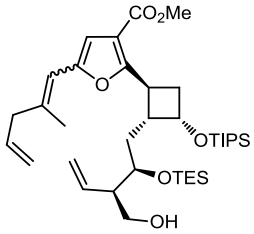


$NaBH_4$ (15.7 mg, 0.42 mmol, 6 eq.) was suspended in a 5/1 (1.5 mL) mixture of THF/water and the suspension was cooled to 0 °C. A solution of compound **246b** (57.7 mg, 69.2 µmol, 1.0 eq.) in anhydrous THF (1ml) was added dropwise. The reaction mixture was allowed to stir for 3 days until it was quenched by the addition sat. aq. NH_4Cl and Et_2O. The layers were separated and the aqueous layer was acidified to pH=4. The two phases were recombined and mixed vigorously. The phases were separated and the organic phase was washed twice with water, before it was dried with brine and $MgSO_4$. The solvent was removed under reduced pressure and silica gel chromatography (hexane/EtOAc = 15/1 to 10/1) yielded pure primary alcohol **247** (32 mg, 48.5 µmol, 70%) as colorless viscous oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 6.41 (s, 1H); 6.03 (m, 2H); 5.85 (m, 1H); 5.75 (m, 1H); 5.12 (m, 2H); 5.01 (d, *J* = 17.5Hz, 1H); 4.65 (m, 1H); 4.00 (m, 1H); 3.81 (s, 3H); 3.49 (m, 2H); 2.91 (d, *J* = 6.6Hz, 1H); 2.64 (m, 1H); 2.53 (m, 1H); 2.33 (m, 1H); 2.00 (s, 3H); 1.80 (m, 4H); 1.32 (m, 2H); 1.05 (bs, 21H); 0.88 (s, 9H); 0.13 (s, 3H); 0.10 (s, 3H)

HRMS (ESI) (m/z): $[M+Na]^+$ calcd. for $C_{37}H_{64}O_6Si_2Na$: 683.4139; found: 683.4127

Methyl-2-((*1S,2R,3S*)-2-((*2R,3R*)-3-(hydroxymethyl)-2-((triethylsilyl)oxy)pent-4-en-1-yl)-3-((triisopropylsilyl)oxy)cyclobutyl)-5-(2-methylpenta-1,4-dien-1-yl)furan-3-carboxylate (**402**)



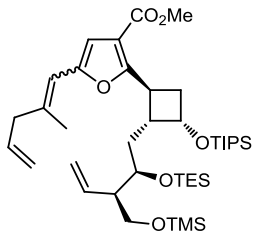
Alcohol **246a** (1.73 g, 2.4 mmol, 1.0 eq.) was dissolved in anhydrous CH_2Cl_2 (15 mL) and the reaction mixture was cooled to 0 °C. After the addition of 2,6-lutidine (1.03 g, 79.6 mmol, 4 eq.) the solution was incubated at 0 °C for 5 minutes before TES-OTf (1.27 g, 4.8 mmol, 2 eq.) was added dropwise. The reaction mixture was stirred at 0 °C for 30 minutes and then quenched by the addition of sat. aq. $NaHCO_3$. The phases were separated and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were washed with NH_4Cl and brine. Drying with $MgSO_4$, concentration *in vacuo* and purification by silica gel chromatography (hexane/EtOAc = 10/1) yielded the TES-ether (2.03 g, 2.4 mmol, quant.) as colorless oil.

The following reaction was performed according to an adapted protocol of Maier *et al*.[135] $NaBH_4$ (81.6 mg, 2.16 mmol, 6 eq.) was suspended in a 5/1 (6 mL) mixture of THF/water and the suspension was cooled to 0 °C. A solution of the previously prepared TES-ether (300 mg, 0.36 mmol, 1.0 eq.) in anhydrous THF (5ml) was added dropwise. The reaction mixture was allowed to stir for 3 days until it was quenched by the addition sat. aq. NH_4Cl and Et_2O. The layers were separated and the aqueous layer was acidified to pH=4. The two phases were recombined and mixed vigorously. The phases were separated and the organic phase was washed twice with water, before it was dried with brine and $MgSO_4$. The solvent was removed under reduced pressure and silica gel chromatography (hexane/EtOAc = 15/1 to 10/1) yielded pure primary alcohol **402** (154 mg, 0.23 mmol, 65%) as colorless viscous oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 6.40 (s, 1H); 6.03 (s, 1H); 5.81 (m, 2H); 5.75 (m, 1H); 5.12 (m, 3H); 5.02 (d, *J* = 17.4Hz, 1H); 4.66 (m, 1H); 4.01 (m, 2H); 3.80 (s, 3H); 3.55 (m, 1H); 3.50 (m, 1H); 3.17 (m, 1H); 2.90 (d, *J* = 6.7Hz, 1H); 2.66 (m, 1H); 2.52 (m, 1H); 2.34 (m, 1H); 2.00 (s, 3H); 1.98 (m, 2H); 1.86 (m, 1H); 1.06 (bs, 21H); 0.97 (t, *J* = 7.9Hz, 9H); 0.63 (q, *J* = 7.9Hz, 6H)

HRMS (ESI) (m/z): $[M+Na]^+$ calcd. for $C_{37}H_{64}O_6Si_2Na$: 683.4139; found: 683.4132

Methyl-5-(2-methylpenta-1,4-dien-1-yl)-2-((*1S,2R,3S*)-2-((*2R,3R*)-2-((triethylsilyl)oxy)-3-(((trimethylsilyl)oxy)methyl)pent-4-en-1-yl)-3-((triisopropylsilyl)oxy)cyclobutyl)furan-3-carboxylate (**248**)



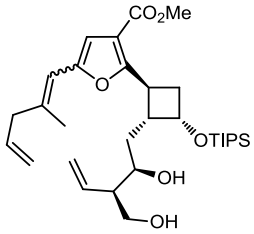
Primary alcohol **402** (100 mg, 0.15 mmol, 1.0 eq.) was dissolved in anhydrous DMF (2 mL) and imidazole (62 mg, 0.91 mmol, 6 eq.) was added in one portion. Under an Ar-atmosphere, the mixture was cooled to 0 °C and a solution of trimethylsilyl-chloride (TMS-Cl, 58 µL, 0.45 mmol, 3 eq.) in anhydrous DMF (200 µL) was slowly added at 0 °C. The reaction mixture was allowed to warm to r.t. overnight. 3 mL of hexane/Et_2O (1/1) and 100 mL of saturated aqueous NH_4Cl were added and the phases separated. The organic phase was extracted with water twice. The combined aqueous phases were twice back-extracted with a 1/1 mixture of hexane/Et_2O and the combined organic layers were dried over $MgSO_4$. Evaporation of the solvent and short filtration (product is of moderate stability on silica gel!) through a pad of silica gel yielded tri-silylether **248** (105 mg, 0.14 mmol, 95%) as colorless oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 6.40 (s, 1H); 6.03 (s, 1H); 5.85 (m, 1H); 5.72 (m, 1H); 5.07 (m, 4H); 4.64 (m, 1H); 4.02 (m, 1H); 3.89 (m, 1H); 3.80 (s, 3H); 3.50 (m, 1H); 3.41 (m, 1H); 3.17 (d, *J* = 6.6Hz, 1H); 2.90 (d, *J* = 6.6Hz, 1H); 2.73 (m, 1H); 2.43 (m, 1H); 2.32 (m, 1H); 2.01 (m, 1H); 2.00 (s, 3H); 1.86 (m, 1H); 1.77 (m, 1H); 1.06 (bs, 21H); 0.95 (t, *J* = 8.0Hz, 9H); 0.60 (q, *J* = 8.0Hz, 6H); -0.01 (s, 9H)

^{13}C-NMR (100MHz, $CDCl_3$): δ = 164.2; 162.3; 151.3; 150.9; 149.4; 137.3; 135.8; 135.7; 135.0; 120.5; 117.6; 116.8; 116.0; 114.5; 114.2; 108.5; 69.1; 67.0; 63.4; 51.1; 51.0; 44.9; 43.5; 38.3; 36.6; 34.2; 33.4; 29.7; 24.4; 18.7; 18.0; 12.1; 7.0; 5.2; 0.2; -0.6

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{40}H_{72}O_6Si_3$: 732.4637; found: 732.4631

Methyl-2-((*1S,2R,3S*)-2-((*2R,3R*)-2-hydroxy-3-(hydroxymethyl)pent-4-en-1-yl)-3-((triisopropylsilyl)oxy)cyclobutyl)-5-(2-methylpenta-1,4-dien-1-yl)furan-3-carboxylate (**403**)

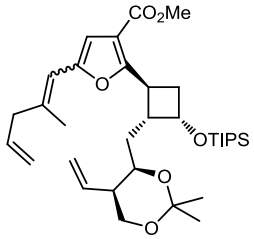


Primary alcohol **402** (115 mg, 0.17 mmol, 1.0 eq.) was dissolved in a 1/10 mixture of anhydrous CH_2Cl_2/MeOH (Σ=2 mL). Camphor sulphonic acid (CSA, 2 mg, 8.7 µmol, 0.05 eq.) was added and the reaction was allowed to stir overnight. The reaction was quenched by the addition of sat. aq. $NaHCO_3$ and the phases were separated. The aqueous layer was extracted twice with CH_2Cl_2 and the combined organic layers were dried with brine and Na_2SO_4. Removal of the solvent under reduced pressure and purification by silica gel chromatography (hexane/EtOAc = 2/1) yielded pure diol **403** (95 mg, 0.17 mmol, quant.) as colorless oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 6.40 (s, 1H); 6.02 (s, 1H); 5.88 (m, 2H); 5.15 (m, 4H); 4.72 (m, 1H); 4.00 (m, 2H); 3.80 (s, 3H); 3.75 (m, 2H); 3.25 (bs, 1H); 3.17 (d, *J* = 6.8Hz, 1H); 2.90 (d, *J* = 6.8Hz, 1H); 2.76 (m, 1H); 2.62 (m, 1H); 2.43 (m, 1H); 2.25 (m, 1H); 2.00 (s, 3H); 1.88 (m, 2H); 1.60 (bs, 1H); 1.06 (bs, 21H)

HRMS (ESI) (m/z): $[M+Na]^+$ calcd. for $C_{31}H_{50}O_6SiNa$: 569.3274; found: 569.3268

Methyl-2-((*1S,2R,3S*)-2-(((*4R,5R*)-2,2-dimethyl-5-vinyl-1,3-dioxan-4-yl)methyl)-3-((triisopropylsilyl)oxy)cyclobutyl)-5-(2-methylpenta-1,4-dien-1-yl)furan-3-carboxylate (**254**)



Diol **403** (95 mg, 0.17 mmol, 1.0 eq.) was dissolved in anhydrous dimethoxyethane (2 mL), dimethoxypropane (43 µL, 0.35 mmol, 2 eq.) and CSA (4 mg, 0.02 mmol, 0.1 eq.) were added. The reaction mixture was stirred at r.t. for one hour. The reaction was quenched by the addition of sat. aq. $NaHCO_3$ and the phases were separated.

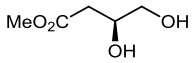
The organic layer was washed with water and dried with brine and $MgSO_4$. The solvents were removed under reduced pressure and the crude product was purified by silica gel chromatography (hexane/EtOAc = 7/1) yielding pure acetal **254** (9.6 mg, 16.3 mmol, 96%) as colorless oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 6.41 (s, 1H); 6.20 (ddd, *J* = 17.4, 9.9, 9.9Hz, 1H); 6.03 (s, 1H); 5.86 (m, 1H); 5.13 (m, 1H); 5.10 (m, 1H); 5.06 (d, *J* = 1.8Hz, 1H); 5.01 (d, *J* = 1.8Hz, 1H); 4.68 (m, 1H); 4.09 (m, 1H); 4.02 (m, 1H); 3.97 (m, 1H); 3.80 (s, 3H); 3.62 (dd, *J* = 11.2, 1.8Hz, 1H); 3.18 (d, *J* = 6.6Hz, 1H); 2.90 (d, *J* = 6.6Hz, 1H); 2.77 (m, 1H); 2.47 (m, 2H); 2.36 (m, 1H); 2.23 (m, 1H); 2.00 (s, 3H); 1.74 (m, 1H); 1.38 (s, 3H); 1.34 (s, 3H); 1.06 (bs, 21H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{34}H_{54}O_6Si$: 586.3690; found: 586.3687

4.2.4 $\Delta^{11,12}$ Metathesis Approach (*c*Bu)

(*S*)-ethyl 3,4-dihydroxybutanoate (**260**)

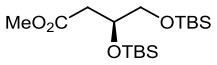


(-)-Malic acid dimethyl ester (8.5 g, 52.5 mmol, 1.0 eq.) was dissolved in anhydrous THF (120 mL) and the solution was cooled to 0 °C. BH_3·DMS (4.38 g, 54.2 mmol, 1.03 eq.) was added dropwise and the reaction mixture was allowed to stir for one hour before $NaBH_4$ (100 mg, 2.6 mmol, 0.05 eq.) was added. The reaction mixture was allowed to warm to r.t. and stirring was continued for one hour. MeOH (50 mL) and *p*TsOH (500 mg, 2.6 mmol, 0.05 eq.) were added and solvents were removed *in vacuo*. The crude mixture was again dissolved in MeOH (100 mL) and the solvent was removed under reduced pressure. The crude reaction mixture was dissolved in Et_2O and sat. aq. $NaHCO_3$ was added. The phases were separated and the organic phase was dried with brine and Na_2SO_4. The solvents were removed *in vacuo* yielding pure diol **260** (5.79 g, 43.2 mmol, 82%) as colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.14 (m, 1H); 3.73 (s, 3H); 3.69 (m, 1H); 3.53 (dd, *J* = 11.4, 6.1Hz, 1H); 2.55 (m, 2H)

HRMS (ESI) (m/z): $[M+Na]^+$ calcd. for $C_5H_{10}O_4Na$: 157.0477; found: 157.0472

(*S*)-ethyl 3,4-bis((tert-butyldimethylsilyl)oxy)butanoate (**404**)

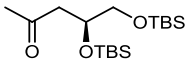


Diol **260** (5.11 g, 38.1 mmol, 1 eq.) was dissolved in anhydrous DMF (75 mL). Imidazole (11.68 g, 171.6 mmol, 4.5 eq.) was added to the solution and it was cooled to 0 °C. A solution of TBS-Cl (12.65 g, 83.9 mmol, 2.2 eq.) in anhydrous DMF (20 mL) was added. The reaction mixture was allowed to stir at 0 °C for one hour, and then it was quenched by the addition of sat. aq. NH_4Cl. Et_2O and hexane were added and the phases were separated. The organic layer was washed with NH_4Cl before it was dried with brine and $MgSO_4$. Purification by silica gel chromatography (hexane/EtOAc = 10/1) yielded pure bis-silylether **404** (13.1 g, 36.4 mmol, 95%) as colorless liquid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.14 (m, 1H); 3.66 (s, 3H); 3.59 (dd, *J* = 10.0, 5.1Hz, 1H); 3.53 (dd, *J* = 10.0, 7.2Hz, 1H); 2.64 (dd, *J* = 15.0, 4.4Hz, 1H); 2.37 (dd, *J* = 15.0, 8.0Hz, 1H); 0.89 (s, 9H); 0.85 (s, 9H); 0.05 (bs, 12H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{17}H_{38}O_4Si_2$: 362.2309; found: 362.2301

(*S*)-4,5-bis((tert-butyldimethylsilyl)oxy)pentan-2-one (**261**)



Bis silyl ether **404** (13.1 g, 36.4 mmol, 1 eq.) and *Weinreb* amine hydrochloride (5.32 g, 54.6 mmol, 1.5 eq.) were dissolved in anhydrous THF (75 mL) and the solution was cooled to -20 °C. *i*PrMgBr (2M in Et_2O; 54.6 mL, 109.1 mmol, 3 eq.) was added dropwise and the solution was allowed to warm to 0 °C where it was stirred for 30 minutes. The reaction was quenched by the addition of sat. aq. NH_4Cl and Et_2O was added. The phases were separated and the pH of the aqueous phase was adjusted to 5. The layers were recombined and the organic layer was washed twice with 0.1M HCl. The organic phase was dried with brine and $MgSO_4$ and the solvent was removed under reduced pressure yielding pure *Weinreb* amide **404a** (14.26 g, 36.4 mmol, quant.) as colorless oil.

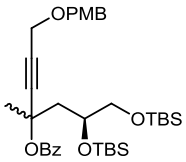
Weinreb amide **404a** (14.26 g, 36.4 mmol, 1.0 eq.) was dissolved in anhydrous THF (150 mL) and the solution was cooled to -78 °C. A solution of MeMgCl (3M in Et_2O; 14.6 mL, 43.7 mmol, 1.2 eq.) was added dropwise and the reaction mixture was allowed to warm to -20 °C within two hours. The reaction was quenched by the addition of sat. aq. NH_4Cl. Et_2O was added and the phases were separated.

The organic layer was washed with NH_4Cl before it was dried with brine and $MgSO_4$. Purification by silica gel chromatography (hexane/EtOAc = 10/1) yielded pure methyl ketone **261** (9.4 g, 27.1 mmol, 75%) as colorless liquid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.16 (m, 1H); 3.57 (dd, *J* = 10.0, 5.0Hz, 1H); 3.39 (dd, *J* = 10.0, 6.8Hz, 1H); 2.66 (dd, *J* = 15.3, 4.8Hz, 1H); 2.37 (dd, *J* = 15.3, 7.3Hz, 1H); 2.16 (s, 3H); 0.88 (s, 9H); 0.86 (s, 9H); 0.05 (m, 12H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{17}H_{38}O_3Si_2$: 346.2359; found: 346.2348

(*6S*)-6,7-bis((tert-butyldimethylsilyl)oxy)-1-((4-methoxybenzyl)oxy)-4-methylhept-2-yn-4-yl benzoate (**262**)



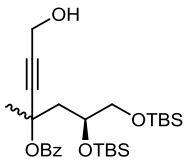
DIPA (4.4 mL, 31.2 mmol, 1.15 eq.) was dissolved in anhydrous THF (50 mL) and the mixture was cooled to -10 °C when n-BuLi (2.5M in hexane; 11.9 mL, 29.8 mmol, 1.1 eq.) was added. The mixture was allowed to stir at -10 °C for 30 min, before it was cooled to -78 °C. Then, a solution of propargylic ether **222a** (5 g, 28.5 mmol, 1.05 eq.) in anhydrous THF (20 mL) was added dropwise. Upon completion, the reaction mixture was allowed to stir for 30 minutes. A solution of methyl ketone **261** (9.4 g, 27.1 mmol, 1.0 eq.) in anhydrous THF (30 mL) was added and the reaction mixture was stirred for one hour. The reaction was quenched by the addition of sat. aq. NH_4Cl. After addition of Et_2O, phases were separated and the aqueous phase was neutralized by the addition of 0.5M $KHSO_4$. The aqueous layer was extracted twice with Et_2O and the combined organic phases were dried with $MgSO_4$. Purification by silica gel chromatography (hexane/EtOAc = 7/1) yielded tertiary alcohol as colorless viscous oil (10.3 g, 19.7 mmol, 73%) as an inconsequential mixture of diastereoisomers.

Tertiary alcohol (10.3 g, 19.7 mmol, 1.0 eq.) was dissolved in anhydrous THF (100 mL), NEt_3 (8.24 mL, 59.1 mmol, 3 eq.) and benzoic acid anhydride (8.91 g, 39.4 mmol, 2 eq.) were added at r.t. The reaction mixture was cooled to 0 °C and $MgBr_2 \cdot OEt_2$ (10.17 g, 39.4 mmol, 2 eq.) was added portionwise. The solution was allowed to warm to r.t. within 30 minutes. Water and Et_2O were added and the phases were separated. The organic phase was washed with water and the combined aqueous phases were back-extracted with Et_2O. The combined organic layers were dried with $MgSO_4$ and the solvent was removed under reduced pressure. Purification by silica gel chromatography (hexane/EtOAc = 7/1) yielded tertiary benzoate **262** (10.4 g, 16.6 mmol, 84%) as colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.02 (m, 2H); 7.55 (m, 1H); 7.42 (m, 2H); 7.29 (d, *J* = 8.5Hz, 2H); 6.85 (d, *J* = 8.5Hz, 2H); 4.55 (s, 2H); 4.19 (s, 2H); 3.79 (s, 3H); 3.66 (m, 1H); 3.60 (m, 1H); 2.50 (m, 1H); 2.02 (m, 2H); 1.90 (s, 3H); 0.88 (bs, 18H); 0.09 (s, 6H); 0.03 (s, 6H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{35}H_{54}O_6Si_2$: 626.3459; found: 626.3448

(*6S*)-6,7-bis((tert-butyldimethylsilyl)oxy)-1-hydroxy-4-methylhept-2-yn-4-yl benzoate (**405**)



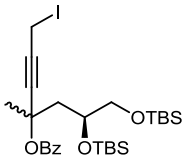
To a solution of benzoate **262** (10.4 g, 16.6 mmol, 1.0 eq.) in CH_2Cl_2 (150 mL) were added 15 mL of a pH=7-buffer (50mM KH_2PO_4). The vigorously stirred suspension was cooled to 0 °C and DDQ (5.65 g, 24.9 mmol, 1.5 eq.) was added portionwise. The suspension was allowed to stir overnight while it warmed to r.t. After addition of sat. aq. $NaHCO_3$, the phases were separated and the organic phase was washed 6 times with H_2O. The organic phase was dired with brine and $MgSO_4$, and removal of the solvent *in vacuo* gave crude propargylic alcohol. Purification by silica gel chromatography (hexane/EtOAc = 5/1) gave alcohol **405** in quantitative yield (8.41 g, 16.6 mmol, quant.)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.00 (m, 2H); 7.54 (m, 1H); 7.42 (m, 2H); 4.32 (s, 2H); 4.15 (dddd, *J* = 10.8, 10.8, 5.4, 5.4Hz, 1H); 3.65 (m, 2H); 2.49 (dd, *J* = 14.9, 5.8Hz, 1H); 2.13 (bs, 1H); 1.98 (dd, *J* = 14.1, 5.6 Hz, 1H); 1.87 (s, 3H); 0.89 (s, 18H); 0.09 (s, 6H); 0.04 (s, 6H)

^{13}C-NMR (100MHz, $CDCl_3$): δ = 164.7; 132.8; 130.9; 129.6; 128.3; 85.5; 84.7; 74.9; 71.2; 67.7; 51.1; 45.5; 27.9; 26.00; 25.9; 18.4; 18.1; -4.0; -4.5; -5.2

HRMS (ESI) (m/z): $[M+Na]^+$ calcd. for $C_{27}H_{46}O_5Si_2Na$: 529.2781; found: 529.2772

(*6S*)-6,7-bis((tert-butyldimethylsilyl)oxy)-1-iodo-4-methylhept-2-yn-4-yl benzoate (**259**)



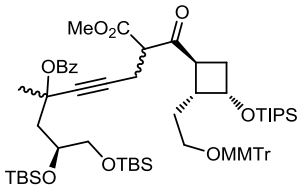
Imidazole (1.2 g, 17.8 mmol, 3 eq.), PPh_3 (3.1 g, 11.8 mmol, 2 eq.) and iodine (3.0 g, 11.8 mmol, 2 eq.) were added to 35 mL anhydrous CH_2Cl_2 and cooled to 0 °C. The suspension was stirred at 0 °C for 20 minutes while it turned yellow. To this suspension a solution of propargylic alcohol **405** (3.0 g, 5.9 mmol, 1.0 eq.) in anhydrous CH_2Cl_2 (25 mL) was rapidly added. The reaction mixture was stirred for one hour. Then it was quenched by the addition of 60 mL hexane. The precipitating triphenylphosphineoxide was filtered through a pad of celite and a sat. aq. solution of $Na_2S_2O_3$ and $NaHCO_3$ was added to the filtrate. The phases were separated and the organic phase was washed with $Na_2S_2O_3$, $NaHCO_3$ and brine before it was dried with $MgSO_4$. After removal of the solvent under reduced pressure, purification by silica gel chromatography (hexane/EtOAc = 7/1) yielded propargylic iodide **259** (2.58 g, 4.18 mmol, 71%) as slightly yellow liquid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.01 (m, 2H); 7.53 (m, 1H); 7.41 (m, 2H); 4.15 (m, 1H); 3.74 (s, 2H); 3.64 (m, 2H); 2.50 (dd, *J* = 14.3, 5.9Hz, 1H); 1.97 (dd, *J* = 14.3Hz, 5.9Hz, 1H); 1.84 (s, 3H); 0.89 (m, 18H); 0.13 (m, 6H); 0.05 (s, 6H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 164.5; 132.9; 131.0; 129.7; 128.4; 84.8; 83.2; 74.8; 71.0; 67.5; 45.7; 27.7; 26.0; 18.4; 18.0; -3.9; -4.4; -5.2

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{27}H_{45}IO_4Si_2$: 616.1901; found: 616.1894

(*2S*)-1,2-bis((tert-butyldimethylsilyl)oxy)-9-methoxy-8-((*1S,2R,3S*)-2-(2-((4-methoxyphenyl)diphenylmethoxy)ethyl)-3-((triisopropylsilyl)oxy)cyclobutanecarbonyl)-4-methyl-9-oxonon-5-yn-4-yl benzoate (**263**)



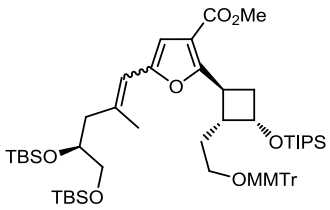
NaH (60% in mineral oil, 168 mg, 4.18 mmol, 1.0 eq.) was suspended in anhydrous THF (22 mL). The reaction mixture was cooled to 0 °C and a solution of β-keto ester **195** (2.7 g, 4.18 mmol, 1.0 eq.) in anhydrous THF (10 mL) was added. The reaction was stirred at 0 °C for 20 minutes and then warmed to r.t. within 10 minutes. Then it was re-cooled to 0 °C and a solution of propargylic iodide **259** (2.58 g, 4.18 mmol, 1.0 eq.) was added uninterruptedly at 0 °C. The reaction mixture was stirred at this temperature for 20 minutes and then warmed to r.t. within 20 minutes before it was quenched with saturated aqueous NH_4Cl. Et_2O was added and the phases separated. The pH of the aqueous phase was adjusted to 6 with 0.5M $KHSO_4$ and it was extracted twice with Et_2O. The combined organic layers were dried with $MgSO_4$ and the solvent was removed under reduced pressure. Silica gel column chromatography (hexane/EtOAc = 10/1 to 7/1) yielded alkylated β-keto ester **263** as slightly yellow oil (3.5 g, 3.1 mmol, 74%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.97 (m, 2H); 7.51 (m, 1H); 7.39 (m, 6H); 7.28 (m, 8H); 7.19 (m, 2H); 6.81 (m, 2H); 4.40 (m, 1H); 4.02 (m, 1H); 3.78 (m, 3H); 3.57 (m, 6H); 3.13 (m, 2H); 2.85 (m, 2H); 2.62 (m, 1H); 2.42 (m, 2H); 2.11 (m, 1H); 1.94 (m, 2H); 1.80 (m, 3H); 0.96 (m, 18H); 0.88 (m, 21H); 0.05 (m, 12H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 168.5; 158.3; 144.8; 135.8; 132.7; 130.6; 129.4; 128.4; 128.2; 127.7; 126.7; 112.9; 71.1; 67.7; 65.5; 61.6; 55.1; 52.4; 46.1; 45.4; 44.8; 42.2; 33.9; 33.0; 29.1; 28.9; 28.1; 25.9; 18.4; 18.0; 11.9; -4.0; -5.3

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{66}H_{96}O_{10}Si_3$: 1132.6311; found: 1132.6303

Methyl-5-((*S*)-4,5-bis((tert-butyldimethylsilyl)oxy)-2-methylpent-1-en-1-yl)-2-((*1S,2R,3S*)-2-(2-((4-methoxyphenyl)diphenylmethoxy)ethyl)-3-((triisopropylsilyl)oxy)cyclobutyl)furan-3-carboxylate (**258**)



Alkylated β-keto ester **263** (3.5 g, 3.1 mmol, 1.0 eq.) was dissolved in anhydrous DMF (30 mL) under an Ar-atmosphere and finely ground anhydrous K_2CO_3 (2.77 g, 20.1 mmol, 6.5 eq.) was added. The reaction flask was sealed and the reaction mixture was heated to 90 °C (oil bath temperature 100 °C) for two hours. The suspension was allowed to cool to r.t. and the suspended K_2CO_3 was allowed to settle down. The supernatant was decanted and remaining K_2CO_3 was washed four times with Et_2O (4x40 mL). The combined organic layers were quenched with 0.5M $KHSO_4$ and the pH was adjusted to 6. The phases were separated and the aqueous phase was washed 4 times with Et_2O/hexane (1/1). The combined organic layers were dried with $MgSO_4$ and the solvents were removed under reduced pressure. The crude product was purified by silica gel chromatography (hexane/EtOAc = 10/1) yielding pure vinyl furan **258** (2.8 g, 2.8 mmol, 89%) as a mixture of double bond isomers (*E/Z* = 4/1).

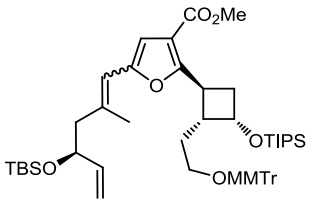
(*E*)-isomer:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.36 (m, 4H); 7.20 (m, 8H); 6.75 (m, 2H); 6.37 (s, 1H); 6.03 (s, 1H); 4.68 (dd, *J* = 12.6, 6.1Hz, 1H); 3.82 (m, 2H); 3.77 (s, 3H); 3.67 (s, 3H); 3.56 (dd, *J* = 9.8, 5.1Hz, 1H); 3.42 (dd, *J* = 9.8, 6.8Hz, 1H); 3.08 (dd, *J* = 13.0, 6.2Hz, 2H); 2.92 (m, 1H); 2.44 (m, 2H); 2.32 (m, 1H); 2.17 (dd, *J* = 13.1, 7.6Hz, 1H); 2.10 (m, 1H); 1.99 (s, 3H); 1.89 (m, 1H); 1.01 (s, 21H); 0.90 (s, 9H); 0.84 (s, 9H); 0.05 (s, 6H); 0.02 (s, 3H); -0.04 (s, 3H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 164.3; 162.5; 158.4; 151.1; 144.9; 136.1; 130.2; 128.4; 127.6; 126.6; 116.4; 113.5; 112.8; 108.1; 72.1; 67.2; 66.5; 61.7; 55.1; 45.9; 44.9; 36.3; 32.9; 29.2; 26.0; 19.6; 18.3; 17.9; -4.5; -4.8

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{59}H_{90}O_8Si_3$: 1010.5943; found: 1010.5940

Methyl-5-((*S,E*)-4-((tert-butyldimethylsilyl)oxy)-2-methylhexa-1,5-dien-1-yl)-2-((*1S,2R,3S*)-2-(2-((4-methoxyphenyl)diphenylmethoxy)ethyl)-3-((triisopropylsilyl)oxy)cyclobutyl)furan-3-carboxylate (**265**)



Bis TBS-ether **258** (1.0 g, 1.0 mmol, 1.0 eq.) was dissolved in anhydrous THF (3 mL) and the reaction mixture was cooled to 0 °C. 7%HF in pyridine (2.6 mL, 10.0 mmol, 10 eq.) was added dropwise and the reaction mixture was allowed to stir until TLC indicated complete consumption of the starting material (approx. 30 minutes). The reaction was quenched by the careful addition of sat. aq. $NaHCO_3$. The phases were separated and the organic layer was extracted twice with $NaHCO_3$. The combined organic layers were back-extracted twice with CH_2Cl_2 and the combined organic layers were dried with brine and $MgSO_4$. After removal of the solvent under reduced pressure silica gel chromatography (hexane/EtOAc = 1/1) yielded pure diol (712 mg, 0.91 mmol, 91%) as colorless oil.

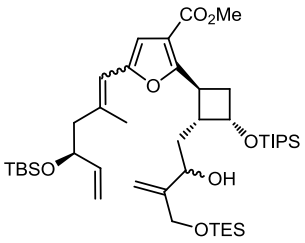
The previously prepared diol (705 mg, 0.9mol, 1.0 eq.) was dissolved in anhydrous CH_2Cl_2 (10 mL). NEt_3 (253 µL, 1.8 mmol, 2 eq.), DMAP (5.5 mg, 0.05 mmol, 0.05 eq.) and dibutyl tin oxide (247 mg, 1.0 mmol, 1.1 eq.) were added. The solution was cooled to 0 °C and kept under an Ar-atmosphere. After a period of 30 minutes, tosyl-chloride (163 mg, 0.86 mmol, 0.95 eq.) was dissolved in anhydrous CH_2Cl_2 (10 mL) and was added dropwise to the reaction mixture. The suspension was stirred for 90 minutes, before it was quenched by the addition of 0.5M $KHSO_4$. The phases were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried with brine and $MgSO_4$ and the solvent was removed under reduced pressure. Purification by silica gel column chromatography (hexane/EtOAc = 3/1 to 2/1) yielded mono tosylate **264** (793 mg, 0.85 mmol, 94%).

Trimethylsulfonium iodide (510 mg, 2.5 mmol, 3 eq.) was suspended in anhydrous THF (5 mL) and the suspension was cooled to -20 °C. n-BuLi (2.5M in hexane; 0.97 mL, 2.41 mmol, 2.9 eq.) was added dropwise and the reaction mixture was allowed to stir for 30 minutes. A solution of the previously prepared mono tosylate (780 mg, 0.83 mmol, 1.0 eq.) in anhydrous THF (5 mL) was slowly added and the mixture turned milky. The reaction mixture was stirred at -20 °C for two hours, then it was allowed to warm to r.t. within one hour and finally it was stirred at r.t. for another two hours before it was quenched with water at 0 °C. Et_2O was added and the phases were separated. The pH of the aqueous phase was carefully neutralized with 0.5M $KHSO_4$ and it was extracted two more times with Et_2O. The combined organic layers were dried with brine and $MgSO_4$ and the solvent was removed under reduced pressure. Silica gel chromatography (hexane/EtOAc = 5/1 to 4/1) yielded pure secondary allylic alcohol (457 mg, 0.59 mmol, 69%) as colorless oil.

Previously prepared allylic alcohol (450 mg, 0.58 mmol, 1.0 eq.) was dissolved in anhydrous DMF (4 mL) and imidazole (98.3 mg, 1.44 mmol, 2.5 eq.) was added. The reaction mixture was cooled to 0 °C and TBS-Cl (96 mg, 0.64 mmol, 1.1 eq.) was added. The solution was allowed to stir at 0 °C for one hour, before it was quenched by the addition of sat. aq. NH_4Cl. Et_2O and hexane were added and the phases were separated. The organic layer was washed with NH_4Cl and afterwards dried with brine and $MgSO_4$. The solvents were removed under reduced pressure. The resulting crude product was purified by silica gel chromatography (hexane/EtOAc = 7/1 to 5/1) and TBS-ether **264** was obtained as colorless viscous oil (508 mg, 0.57 mmol, 98%).

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{54}H_{76}O_7Si_2$: 892.5130; found: 892.5124

Methyl-5-((S,E)-4-((tert-butyldimethylsilyl)oxy)-2-methylhexa-1,5-dien-1-yl)-2-((1S,2R,3S)-2-((R)-2-hydroxy-3-(((triethylsilyl)oxy)methyl)but-3-en-1-yl)-3-((triisopropylsilyl)oxy)cyclobutyl)furan-3-carboxylate (**267a**)



Allylic TBS-ether **264** (500 mg, 0.56 mmol, 1.0 eq.) was dissolved in 5.6 mL of a 10/1 mixture CH_2Cl_2/MeOH. PPTS (28.1 mg, 0.11 mmol, 0.2 eq.) was added and the reaction mixture was allowed to stir at r.t. until TLC analysis indicated full consumption of the starting material (approx. three hours). The reaction mixture was quenched with saturated aqueous $NaHCO_3$. The phases were separated and the aqueous layer was extracted two times with Et_2O. The combined organic layers were dried with $MgSO_4$ and the solvent was removed under reduced pressure. Purification by silica gel chromatography (hexane/EtOAc = 5/1 to 3/1) yielded the free alcohol as colorless viscous oil (344 mg, 0.55 mmol, 99%).

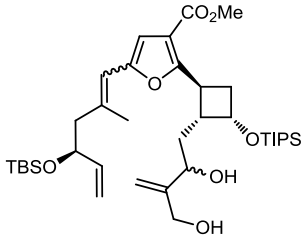
Previously prepared primary alcohol (340 mg, 0.55 mmol, 1.0 eq.) was dissolved in anhydrous EtOAc (6 mL) and IBX (463 mg, 1.6 mmol, 3 eq.) was added. The suspension was heated to reflux for three hours. Now the suspension was cooled to r.t. and 6 mL of hexane were added. The suspension was filtered through a pad of celite and the solvents were removed under reduced pressure. The crude product was used without further purification.

Anhydrous $NiCl_2$ (142 mg, 1.1 mmol, 2 eq.) and anhydrous $CrCl_2$ (336 mg, 2.74 mmol, 5 eq.) were suspended in anhydrous, degassed DMF (5 pump & freeze cycles, 3 mL) in a flame dried Schlenk tube, giving a dark green solution. The solution was cooled to 0 °C and solutions of aldehyde (340 mg, 0.55 mmol, 1.0 eq.) in anhydrous, degassed DMF (5 pump & freeze cycles, 3 mL) and vinylbromide **407b** (275 mg, 1.1 mmol, 2 eq.) in anhydrous, degassed DMF (5 pump & freeze cycles, 3 mL) were added dropwise isochronally. The reaction mixture was allowed to warm to r.t. overnight. NH_4Cl and EtOAc were added and the phases were separated. The organic layer was washed with water twice and dried with brine and $MgSO_4$. The solvent was removed *in vacuo* and purification by silica gel chromatography (hexane/EtOAc = 5/1) yielded pure NHK-product **267a** (433 mg, 0.55 mmol, quant.) as colorless oil (*d.r.* = 2.3/1).

^{1}H-NMR (400MHz, $CDCl_3$): δ = 6.37 (s, 1H); 6.00 (s, 1H); 5.84 (ddd, *J* = 17.1, 10.5, 5.9Hz, 1H); 5.18 (d, *J* = 17.1Hz, 1H); 5.05 (m, 2H); 4.92 (s, 1H); 4.75 (dd, *J* = 12.9, 6.1Hz, 1H); 4.27 (m, 3H); 4.14 (m, 1H); 4.00 (m, 1H); 3.80 (s, 3H); 3.10 (d, *J* = 5.2Hz, 1H); 2.76 (m, 1H); 2.53 (m, 1H); 2.34 (m, 3H); 2.15 (m, 1H); 2.01 (s, 3H); 1.97 (m, 1H); 1.07 (s, 21H); 0.94 (t, *J* = 7.8Hz, 9H); 0.87 (s, 9H); 0.60 (q, *J* = 7.8Hz, 6H); 0.02 (s, 3H); 0.01 (s, 3H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{43}H_{78}O_7Si_3$: 790.5055; found: 790.5048

Methyl-5-((*S,E*)-4-((tert-butyldimethylsilyl)oxy)-2-methylhexa-1,5-dien-1-yl)-2-((*1S,2R,3S*)-2-((*R*)-2-hydroxy-3-(hydroxymethyl)but-3-en-1-yl)-3-((triisopropylsilyl)oxy)cyclobutyl)furan-3-carboxylate (**267b**)



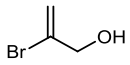
Primary TES-ether **267a** (150 mg, 0.19 mmol, 1.0 eq.) was dissolved in anhydrous MeOH (4 mL) and finely ground NH_4F (351 mg, 9.5 mmol, 50 eq.) was added. The reaction mixture was stirred at r.t. for 2 days. Water and Et_2O were added and the phases were separated. The organic layer was washed two times with water and dried with brine and $MgSO_4$. Silica gel chromatography (hexane/EtOAc = 2/1 to 0/1) yielded diol **267b** (119 mg, 0.18 mmol, 93%) as colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.37 (s, 1H); 6.01 (s, 1H); 5.84 (ddd, *J* = 17.1, 10.5, 5.9Hz, 1H); 5.19 (d, *J* = 17.1Hz, 1H); 5.05 (m, 2H); 4.98 (s, 1H); 4.75 (dd, *J* = 12.9, 6.1Hz, 1H); 4.41 (m, 1H); 4.27 (m, 2H); 3.98 (m, 1H); 4.00 (m, 1H); 3.81 (s, 3H); 3.30 (m, 1H); 2.76 (m, 1H); 2.61 (m, 1H); 2.45 (m, 1H); 2.32 (m, 3H); 2.18 (m, 1H); 2.02 (s, 3H); 1.08 (s, 21H); 0.88 (s, 9H); 0.02 (s, 3H); 0.01 (s, 3H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 162.5; 151.3; 150.1; 141.3; 135.8; 116.2; 113.8; 111.9; 108.2; 74.5; 72.8; 72.5; 66.8; 64.3; 51.5; 49.8; 45.7; 35.6; 35.0; 32.5; 27.5; 25.8; 19.6; 18.0; 17.9; 12.2; -4.5; -5.0

HRMS (ESI) (m/z): $[M+Na]^+$ calcd. for $C_{37}H_{64}O_7Si_2Na$: 699.4088; found: 699.4082

2-bromoprop-2-en-1-ol (**406**)



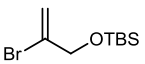
Anhydrous HBr was prepared according the procedure of *Duncan* using tetraline (10.6 mL, 77.4 mmol, 1.0 eq.) and bromine (16 mL, 309.6 mmol, 4 eq.).[136] NEt_4Br (26.0 g, 123.8 mmol, 1.6 eq.) was suspended in anhydrous CH_2Cl_2 (80 mL) and the solution was cooled to 0 °C when anhydrous HBr was bubbled through the suspension. The reaction mixture turned yellow and stirring was continued for 20 minutes at 0 °C and for 10 minutes at r.t. A solution of propargyl alcohol (4.16 mL, 77.4 mmol, 1.0 eq.) in anhydrous CH_2Cl_2 (10 mL) was added slowly. The solution was stirred at r.t for one hour and then heated to reflux for two hours.

The reaction mixture was allowed to cool to r.t. and water was added. The phases were separated and the organic phase was washed twice with water. The organic layer was dried with $MgSO_4$ and the solvent was removed *in vacuo*. Purification by distillation yielded pure vinyl bromide **406** (9 g, 65.8 mmol, 85%) as colorless liquid.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 5.93 (m, 1H); 5.58 (m, 1H); 4.23 (t, *J* = 1.1Hz, 2H); 2.42 (bs, 1H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for C_3H_5BrO: 135.9524; found: 135.9518

((2-bromoallyl)oxy)(tert-butyl)dimethylsilane (**407a**)

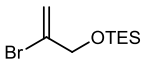


Vinyl bromide **406** (5 g, 36.5 mmol, 1.0 eq.) was dissolved in anhydrous DMF (100 mL) and imidazole (4.97 g, 73 mmol, 2 eq.) was added in one portion. Under Ar-atmosphere, the mixture was cooled to 0 °C and a solution of TBS-Cl (6.6 g, 43.8 mmol, 1.2 eq.) in anhydrous DMF (15 mL) was slowly added at 0 °C. The reaction mixture was allowed to warm to r.t. and stirring was continued for two hours. 100 mL of hexane/Et_2O (1/1) and 100 mL of saturated aqueous NH_4Cl were added and the phases were separated. The organic phase was extracted with water twice. The combined aqueous phases were twice back-extracted with a 1/1 mixture of hexane/Et_2O and the combined organic layers were dried over $MgSO_4$. Evaporation of the solvent yielded silylether **407a** (8.62 g, 34.3 mmol, 94%) as colorless oil, which was purified by silica gel column chromatography (hexane).

^{1}H-NMR (400MHz, $CDCl_3$): δ = 5.95 (d, *J* = 1.8Hz, 1H); 5.58 (d, *J* = 1.8Hz, 1H); 4.21 (t, *J* = 1.6Hz, 2H); 0.92 (s, 9H); 0.10 (s, 6H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_9H_{19}BrOSi$: 250.0389; found: 250.0382

((2-bromoallyl)oxy)triethylsilane (**407b**)



Vinyl bromide **406** (5 g, 36.5 mmol, 1.0 eq.) was dissolved in anhydrous DMF (100 mL) and imidazole (4.97 g, 73 mmol, 2 eq.) was added in one portion. Under Ar-atmosphere, the mixture was cooled to 0 °C and a solution of TES-Cl (6.6 g, 43.8 mmol, 1.2 eq.) in anhydrous DMF (15 mL) was slowly added at 0 °C.

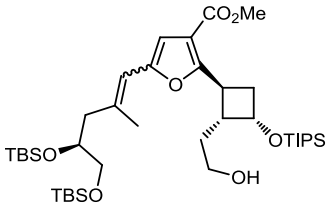
The reaction mixture was allowed to warm to r.t. and stirring was continued for two hours. 100 mL of hexane/Et_2O (1/1) and 100 mL of saturated aqueous NH_4Cl were added and the phases were separated. The organic phase was extracted with water twice. The combined aqueous phases were twice back-extracted with a 1/1 mixture of hexane/Et_2O and the combined organic layers were dried over $MgSO_4$. Evaporation of the solvent yielded silylether **407b** (8.34 g, 33.2 mmol, 91%) as colorless oil, which was purified by silica gel column chromatography (hexane).

^{1}H-NMR (400MHz, $CDCl_3$): δ = 5.98 (q, *J* = 1.8Hz, 1H); 5.53 (q, *J* = 1.6Hz, 1H); 4.21 (dd, *J* = 1.7, 1.7Hz, 2H); 0.98 (t, *J* = 8.0Hz, 9H); 0.64 (q, *J* = 8.0Hz, 6H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_9H_{19}BrOSi$: 250.0389; found: 250.0384

4.2.5 $\Delta^{11,12}$ Horner Wadsworth Emmons Approach (*c*Bu)

Methyl-5-((*S*)-4,5-bis((tert-butyldimethylsilyl)oxy)-2-methylpent-1-en-1-yl)-2-((*1S,2R,3S*)-2-(2-hydroxyethyl)-3-((triisopropylsilyl)oxy)cyclobutyl)furan-3-carboxylate (**408**)



Vinylfuran **258** (2.8 g, 2.8 mmol, 1.0 eq.) was dissolved in anhydrous CH_2Cl_2 (5 mL) and hexafluoroisopropanol (HFIP, 5 mL) was added. The solution was allowed to stir at r.t. for 15 minutes during which time it turned yellow. Anhydrous MeOH was added until the color disappeared and the solution was allowed to stir at r.t. for 3 days. Solvents were removed *in vacuo* and purification by silica gel chromatography (hexane/EtOAc = 5/1) yielded pure primary alcohol **408** (1.73 g, 2.3 mmol, 84%) as colorless viscous oil.

(*Z*)-isomer:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.53 (s, 1H); 6.05 (s, 1H); 4.68 (dd, *J* = 12.6, 6.3Hz, 1H); 3.92 (m, 1H); 3.78 (s, 3H); 3.69 (m, 2H); 3.59 (dd, *J* = 10.0, 5.2Hz, 1H); 3.44 (dd, *J* = 9.8, 6.6Hz, 1H); 2.78 (m, 1H); 2.60 (m, 3H); 2.37 (m, 1H); 2.24 (m, 1H); 2.05 (m, 1H); 1.92 (s, 3H); 1.86 (m, 1H); 1.07 (s, 21H); 0.89 (s, 9H); 0.81 (s, 9H); 0.05 (s, 6H); 0.03 (s, 3H); -0.03 (s, 3H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 164.7; 162.1; 137.6; 116.1; 113.3; 108.2; 71.8; 68.0; 67.0; 61.2; 51.2; 45.9; 38.8; 35.7; 32.9; 31.8; 26.0; 18.1; 12.3; -4.4; -4.8; -5.3

HRMS (ESI) (m/z): $[M+Na]^+$ calcd. for $C_{39}H_{74}O_7Si_3Na$: 761.4640; found: 761.4632

$[\alpha]_D^{20}$: +23.4 (c=0.19; $CHCl_3$)

(*E*)-isomer:

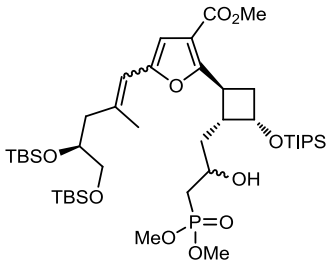
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.36 (s, 1H); 6.03 (s, 1H); 4.76 (q, *J* = 6.9Hz, 1H); 3.88 (m, 1H); 3.81 (m, 1H); 3.79 (s, 3H); 3.72 (m, 2H); 3.56 (dd, *J* = 9.9, 5.3Hz, 1H); 3.42 (dd, *J* = 9.9, 6.9Hz, 1H); 2.75 (m, 1H); 2.59 (m, 1H); 2.45 (m, 2H); 2.18 (dd, *J* = 13.2, 7.7Hz, 1H); 2.07 (m, 1H); 2.02 (s, 3H); 1.92 (m, 2H); 1.06 (s, 21H); 0.90 (s, 9H); 0.85 (s, 9H); 0.05 (s, 6H); 0.03 (s, 3H); -0.02 (s, 3H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 164.7; 162.5; 151.4; 140.9; 136.3; 116.2; 113.4; 112.7; 108.0; 71.9; 67.1; 66.6; 61.1; 51.3; 46.4; 45.8; 35.7; 32.0; 31.8; 25.9; 25.8; 19.5; 18.0; 17.9; 12.0; -4.5; -4.9; -5.3; -5.4

HRMS (ESI) (m/z): $[M+Na]^+$ calcd. for $C_{39}H_{74}O_7Si_3Na$: 761.4640; found: 761.4629

$[\alpha]_D^{20}$: -10.1 (c=0.35; $CHCl_3$)

Methyl-5-((*S*)-4,5-bis((tert-butyldimethylsilyl)oxy)-2-methylpent-1-en-1-yl)-2-((*1S,2R,3S*)-2-(3-(dimethoxyphosphoryl)-2-hydroxypropyl)-3-((triisopropylsilyl)oxy)cyclobutyl)furan-3-carboxylate (**409**)



Primary alcohol **408** (1.73 g, 2.3 mmol, 1.0 eq.) was dissolved in anhydrous EtOAc (25 mL) and IBX (1.93 g, 6.9 mmol, 3 eq.) was added. The suspension was heated to reflux for three hours. Now the suspension was cooled to r.t. and 25 mL of hexane were added. The suspension was filtered through a pad of celite and the solvents were removed *in vacuo*. The crude product was purified by silica gel column chromatography (hexane/EtOAc = 7/1). The aldehyde was obtained as viscous oil (1.55 g, 2.1 mmol, 90%).

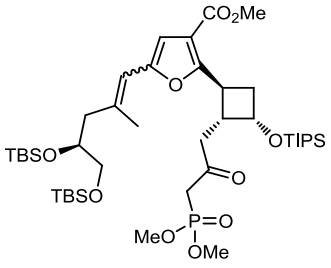
Dimethyl methylphosphonate (251 µL, 1.1 mmol, 1.0 eq.) was dissolved in anhydrous THF (10 mL) and the solution was cooled to -78 °C before n-BuLi (1.6M in hexane; 1.51 mL, 2.4 mmol, 1.15 eq.) was added dropwise. The reaction mixture was stirred for 30 minutes, and then a solution of the previously prepared aldehyde (1.55 g, 2.1 mmol, 1.0 eq.) in anhydrous THF (15 mL) was added dropwise. Stirring was continued for one hour. The reaction mixture was quenched by the addition of sat. aq. NH_4Cl. After the addition of Et_2O, the phases were separated and the neutralized aqueous layer was extracted twice with Et_2O. The combined organic layers were dried with $MgSO_4$ and the solvent was removed *in vacuo*. Purification by silica gel chromatography (hexane/EtOAc = 2/1) resulted β-hydroxy phosphonate **409** (1.5 g, 1.75 mmol, 83%) as colorless oil.

(*E*)-isomer:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.36 (s, 1H); 6.03 (s, 1H); 4.76 (m, 1H); 4.11 (m, 1H); 3.94 (m, 1H); 3.80 (s, 3H); 3.69 (m, 7H); 3.57 (m, 2H); 3.44 (m, 2H); 2.86 (m, 1H); 2.54 (m, 3H); 2.37 (m, 1H); 2.18 (dd, *J* = 13.3, 7.5Hz, 1H); 2.01 (s, 3H); 1.89 (m, 2H); 1.07 (bs, 21H); 0.91 (s, 9H); 0.86 (s, 9H); 0.06 (s, 6H); 0.04 (s, 3H); -0.01 (s, 3H)

HRMS (ESI) (m/z): $[M+Na]^+$ calcd. for $C_{42}H_{81}O_{10}PSi_3Na$: 883.4773; found: 883.4762

Methyl-5-((*S*)-4,5-bis((tert-butyldimethylsilyl)oxy)-2-methylpent-1-en-1-yl)-2-((*1S,2R,3S*)-2-(3-(dimethoxyphosphoryl)-2-oxopropyl)-3-((triisopropylsilyl)oxy)cyclobutyl)furan-3-carboxylate (**271**)



β-hydroxy phosphonate **409** (1.5 g, 1.75 mmol, 1.0 eq.) was dissolved in anhydrous EtOAc (20 mL) and IBX (1.47 g, 5.25 mmol, 3 eq.) was added. The suspension was heated to reflux for four hours. Now the suspension was cooled to r.t. and 20 mL of hexane were added. The suspension was filtered through a pad of celite and the solvents were removed under reduced pressure. The crude product was purified by silica gel column chromatography (hexane/EtOAc = 2/1). β-keto phosphonate **271** was obtained as viscous oil (1.25 g, 1.45 mmol, 83%).

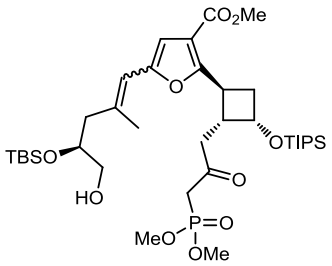
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.39 (s, 1H); 6.07 (s, 1H); 4.47 (dd, *J* = 14.9, 7.4Hz, 1H); 3.90 (m, 1H); 3.80 (s, 3H); 3.69 (d, *J* = 5.6Hz, 3H); 3.68 (d, *J* = 6.0Hz, 3H); 3.56 (dd, *J* = 10.0, 5.2Hz, 1H); 3.52 (m, 1H); 3.42 (dd, *J* = 9.8, 6.8Hz, 1H); 2.91 (m, 3H); 2.58 (m, 2H); 2.50 (m, 3H); 2.19 (dd, *J* = 13.6, 7.5Hz, 1H); 2.01 (s, 3H); 1.04 (s, 21H); 0.91 (s, 9H); 0.86 (s, 9H); 0.06 (s, 3H); 0.05 (s, 3H); 0.04 (s, 3H); 0.00 (s, 3H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 200.6; 164.2; 158.4; 152.1; 137.1; 116.2; 115.4; 108.2; 71.8; 67.1; 64.4; 52.7; 51.4; 45.8; 44.1; 41.7; 41.0; 39.3; 34.9; 27.1; 25.9; 19.7; 18.0; 12.1; -4.2; -4.8; -5.3

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{42}H_{79}O_{10}PSi_3$: 858.4719; found: 858.4708

$[\alpha]_D^{20}$: -43.3 (c=0.51; $CHCl_3$)

Methyl-5-((*S*)-4-((tert-butyldimethylsilyl)oxy)-5-hydroxy-2-methylpent-1-en-1-yl)-2-((*1S,2R,3S*)-2-(3-(dimethoxyphosphoryl)-2-oxopropyl)-3-((triisopropylsilyl)oxy)cyclobutyl)furan-3-carboxylate (**410**)

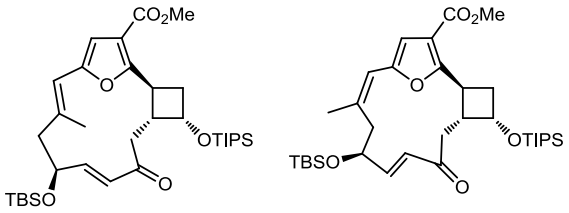


β-keto phosphonate **271** (320 mg, 0.37 mmol, 1.0 eq.) was dissolved in anhydrous MeOH (4 mL) and finely ground NH_4F (690 mg, 18.62 mmol, 50 eq.) was added. The reaction mixture was stirred at r.t. for 2 days. Water and Et_2O were added and the phases were separated. The organic layer was washed two times with water and dried with brine and $MgSO_4$. Silica gel chromatography (2/1 to 1/1) yielded primary alcohol **410** (248 mg, 0.33 mmol, 90%) as colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.39 (s, 1H); 6.04 (s, 1H); 4.71 (m, 1H); 3.98 (m, 2H); 3.77 (m, 7H); 3.64 (m, 2H); 3.59 (m, 1H); 3.10 (m, 3H); 2.86 (m, 1H); 2.68 (m, 1H); 2.54 (m, 2H); 2.33 (m, 3H); 2.02 (s, 3H); 1.89 (m, 1H); 1.05 (s, 21H); 0.90 (s, 9H); 0.10 (s, 3H); 0.06 (s, 3H)

HRMS (ESI) (m/z): $[M+Na]^+$ calcd. for $C_{36}H_{65}O_{10}PSi_2Na$: 767.3752; found: 767.3748

(*2S,4S,5R,8E,10S*)-methyl 10-((tert-butyldimethylsilyl)oxy)-12-methyl-7-oxo-4-((triisopropylsilyl)oxy)-17-oxatricyclo[12.2.1^{2,5}]heptadeca-1(16),8,12,14-tetraene-16-carboxylate (**273**)



Primary alcohol **410** (175 mg, 0.23 mmol, 1.0 eq.) was dissolved in anhydrous EtOAc (3 mL) and IBX (131 mg, 0.47 mmol, 2 eq.) was added. The suspension was heated to reflux for three hours. Now the suspension was cooled to r.t. and hexane (3 mL) was added. The suspension was filtered through a pad of celite and the solvents were removed under reduced pressure. The crude product was used without further purification.

HFIP (5 mL) was mixed with anhydrous THF (70 mL) and the solution was cooled to 0 °C. n-BuLi (2.5M in hexane; 161 µL, 0.4 mmol, 3 eq.) was added dropwise and the reaction mixture was incubated for one hour at 0 °C. A solution of the *seco* aldehyde (100 mg, 0.13 mmol, 1.0 eq.) in anhydrous THF (20 mL) was added using a syringe pump over a period of time of 16 hours. The reaction mixture was quenched by the addition of sat. aq. NH_4Cl and Et_2O was added. The phases were separated and the organic layer was dried with brine and $MgSO_4$. Removal of the solvents under reduced pressure and purification by silica gel chromatography (hexane/EtOAc = 7/1 to 4/1) yielded pure (*E*)-macrocycle **273** (42 mg, 0.07 mmol, 52%) as colorless semi-solid.

(*Z*)-isomer:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.61 (dd, *J* = 15.7, 3.7Hz, 1H); 6.53 (dd, *J* = 15.7, 3.7Hz, 1H); 6.36 (s, 1H); 5.94 (s, 1H); 4.56 (dd, *J* = 5.6, 5.6Hz, 1H); 4.41 (m, 1H); 4.07 (ddd, *J* = 9.6, 9.6, 9.6Hz, 1H); 3.77 (s, 3H); 3.28 (ddt, *J* = 10.4, 5.9, 4.6Hz, 1H); 3.15 (dd, *J* = 12.0, 9.8Hz, 1H); 2.74 (dd, *J* = 12.2, 4.5Hz, 1H); 2.69 (dd, *J* = 12.2, 10.6Hz, 1H); 2.39 (m, 1H); 2.35 (m, 1H); 2.20 (ddd, *J* = 11.9, 10.1, 5.5Hz, 1H); 1.96 (s, 3H); 1.09 (m, 21H); 0.94 (s, 9H); 0.10 (s, 3H); -0.12 (s, 3H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 202.3; 163.8; 162.0; 150.2; 149.1; 131.8; 126.8; 115.9; 113.9; 111.3; 70.2; 69.0; 51.3; 45.4; 43.3; 42.5; 37.8; 37.2; 26.1; 25.9; 18.4; 18.0; 12.1; -4.7; -5.0

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{34}H_{56}O_6Si_2$: 616.3615; found: 616.3612

(*E*)-isomer:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.53 (dd, *J* = 15.3, 5.5Hz, 1H); 6.35 (s, 1H); 6.10 (dd, *J* = 15.3, 1.5Hz, 1H); 5.92 (s, 1H); 4.53 (dd, *J* = 5.5, 5.5Hz, 1H); 4.33 (m, 1H); 4.03 (ddd, *J* = 8.4, 8.4, 8.4Hz, 1H); 3.71 (s, 3H); 3.24 (m, 1H); 2.94 (dd, *J* = 17.9, 8.2Hz, 1H); 2.51 (dd, *J* = 17.9, 5.8Hz, 1H); 2.46 (dd, *J* = 12.8, 5.3Hz, 1H); 2.29 (m, 1H); 2.23 (dd, *J* = 12.8, 9.5Hz, 1H); 2.13 (m, 1H); 1.82 (s, 3H); 0.96 (m, 21H); 0.84 (s, 9H); 0.00 (s, 3H); -0.02 (s, 3H)

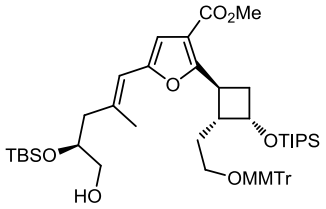
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 198.7; 164.4; 161.2; 150.8; 146.3; 133.7; 127.8; 117.3; 113.4; 108.3; 70.5; 67.7; 51.3; 50.2; 41.0; 40.1; 36.9; 34.4; 25.8; 19.1; 18.2; 18.0; 12.1; -4.7; -4.9

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{34}H_{56}O_6Si_2$: 616.3615; found: 616.3613

$[\alpha]_D^{20}$: -76.4 (c=0.16; $CHCl_3$)

4.2.6 $\Delta^{12,13}$ Horner Wadsworth Emmons Approach (*c*Bu)

Methyl-5-((*S*)-4-((tert-butyldimethylsilyl)oxy)-5-hydroxy-2-methylpent-1-en-1-yl)-2-((*1S,2R,3S*)-2-(2-((4-methoxyphenyl)diphenylmethoxy)ethyl)-3-((triisopropylsilyl)oxy)cyclobutyl)furan-3-carboxylate (**278**)

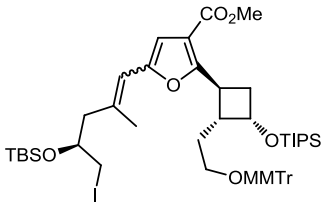


Compound **285** (286 mg, 0.32 mmol, 1.0 eq.) was dissolved in a 6/1 mixture of anhydrous CH_2Cl_2 (0.5 mL) and MeOH (3 mL) and finely ground NH_4F (590 mg, 15.9 mmol, 50 eq.) was added. The reaction mixture was stirred at r.t. for 2 days. Water and Et_2O were added and the phases were separated. The organic layer was washed two times with water and dried with brine and $MgSO_4$. Silica gel chromatography (4/1 to 3/1) yielded pure primary alcohol **278** (266 mg, 0.3 mmol, 93%) as colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.41 (m, 1H); 7.33 (m, 3H); 7.21 (m, 8H); 6.76 (d, *J* = 8.7Hz, 2H); 6.48 (s, 1H); 6.04 (s, 1H); 4.57 (m, 1H); 4.02 (m, 1H); 3.94 (m, 1H); 3.78 (s, 3H); 3.69 (s, 3H); 3.56 (m, 1H); 3.48 (m, 1H); 3.02 (m, 2H); 2.81 (m, 1H); 2.71 (dd, *J* = 13.4, 7.3Hz, 1H); 2.55 (dd, *J* = 13.4, 5.9Hz, 1H); 2.47 (m, 2H); 2.25 (m, 1H); 2.06 (m, 1H); 1.93 (s, 3H); 1.81 (m, 1H); 1.02 (s, 21H); 0.86 (s, 9H); 0.06 (s, 3H); 0.03 (s, 3H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{53}H_{76}O_8Si_2Na$: 919.4976; found: 919.4971

Methyl-5-((*S*)-4-((tert-butyldimethylsilyl)oxy)-5-iodo-2-methylpent-1-en-1-yl)-2-((*1S,2R,3S*)-2-(2-((4-methoxyphenyl)diphenylmethoxy)ethyl)-3-((triisopropylsilyl)oxy)cyclobutyl)furan-3-carboxylate (**279**)



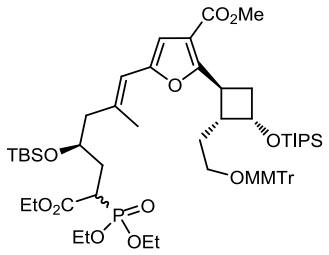
Imidazole (146 mg, 2.15 mmol, 3 eq.), PPh_3 (376 mg, 1.43 mmol, 2 eq.) and iodine (363 mg, 1.43 mmol, 2 eq.) were added to 4 mL anhydrous CH_2Cl_2 and cooled to 0 °C. The suspension was stirred at 0 °C for 20 minutes while it turned yellow. To this suspension a solution of primary alcohol **278** (530 mg, 0.72 mmol, 1.0 eq.) in anhydrous CH_2Cl_2 (3 mL) was added rapidly. The reaction mixture was stirred for one hour. Then it was quenched by the addition of 60 mL hexane. The precipitating triphenylphosphineoxide was filtered through a pad of celite and a sat. aq. solution of $Na_2S_2O_3$ and $NaHCO_3$ was added to the filtrate. The phases were separated and the organic phase was washed with $Na_2S_2O_3$, $NaHCO_3$ and brine before it was dried with $MgSO_4$. After removal of the solvent under reduced pressure, purification by silica gel chromatography (hexane/EtOAc = 20/1) yielded iodide **279** (550 mg, 0.55 mmol, 76%) as slightly yellow liquid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.34 (m, 4H); 7.20 (m, 8H); 6.75 (d, *J* = 9.0Hz, 2H); 6.40 (s, 1H); 6.07 (s, 1H); 4.66 (ddd, *J* = 12.2, 6.5, 6.5Hz, 1H); 3.86 (m, 1H); 3.77 (s, 3H); 3.71 (m, 1H); 3.68 (s, 3H); 3.21 (m, 2H); 3.08 (m, 2H); 2.96 (m, 2H); 2.47 (m, 2H); 2.35 (m, 2H); 2.10 (m, 1H); 2.01 (s, 3H); 1.88 (m, 1H); 1.76 (m, 1H); 1.02 (s, 21H); 0.88 (s, 9H); 0.08 (s, 3H); 0.00 (s, 3H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 162.8; 158.5; 150.9; 145.1; 134.6; 130.3; 128.4; 127.6; 126.6; 116.9; 112.8; 95.6; 70.2; 66.7; 61.5; 55.1; 51.1; 48.2; 44.6; 36.3; 33.2; 29.2; 25.8; 18.0; 13.7; 12.1; -4.4

HRMS (ESI) (m/z): $[M+Na]^+$ calcd. for $C_{53}H_{75}IO_7Si_2Na$: 1029.3994; found: 1029.3989

Methyl-5-((*4S*)-4-((tert-butyldimethylsilyl)oxy)-6-(dimethoxyphosphoryl)-7-ethoxy-2-methyl-7-oxohept-1-en-1-yl)-2-((*1S,2R,3S*)-2-(2-((4-methoxyphenyl)diphenylmethoxy)ethyl)-3-((triisopropylsilyl)oxy)cyclobutyl)furan-3-carboxylate (**277**)



NaH (60% in mineral oil; 26 mg, 0.66 mmol, 3 eq.) was suspended in anhydrous DMSO (700 µL) and the reaction mixture was cooled to 0 °C. Triethylphosphonoacetate (130 µL, 0.66 mmol, 3 eq.) was added dropwise and the solution was allowed to stir for 30 minutes at 0 °C. A solution of iodide **279** (220 mg, 0.22 mmol, 1.0 eq.) in anhydrous DMSO (1 mL) was added dropwise and the reaction mixture was allowed to warm to r.t. within one hour. Stirring was continued at r.t. for another hour before the reaction was quenched by the addition of sat. aq. NH_4Cl. Et_2O was added and the phases were separated. The organic phase was washed twice with water and the combined aqueous layers were back-extracted once with Et_2O. The combined organic layers were dried with brine and $MgSO_4$. Purification by silica gel chromatography yielded pure phosphonate **277** (110 mg, 0.1 mmol, 46%) as colorless oil. Furthermore, starting material **279** (75 mg, 74 µmol, 79% borsm.) was recovered.

Major:

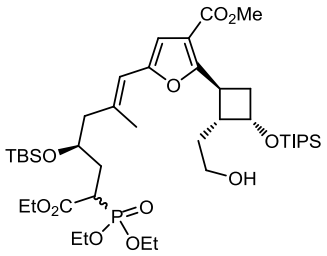
^{1}**H-NMR** (400 MHz, $CDCl_3$): δ = 7.34 (m, 4H); 7.20 (m, 8H); 6.75 (d, *J* = 8.7Hz, 2H); 6.38 (s, 1H); 6.01 (s, 1H); 4.66 (m, 1H); 4.22 (m, 2H); 4.11 (m, 5H); 3.86 (m, 1H); 3.77 (s, 3H); 3.68 (s, 3H); 3.25 (ddd, *J* = 12.4, 11.7, 1.8Hz, 1H); 3.07 (m, 2H); 2.93 (m, 1H); 2.44 (m, 1H); 2.33 (m, 1H); 2.23 (m, 2H); 2.09 (m, 2H); 1.98 (s, 3H); 1.81 (m, 2H); 1.29 (m, 9H); 1.02 (s, 21H); 0.88 (s, 9H); 0.04 (s, 3H); 0.02 (s, 3H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{61}H_{91}O_{12}PSi_2$: 1102.5787; found: 1102.5783

Minor:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.34 (m, 4H); 7.20 (m, 8H); 6.75 (d, *J* = 8.7Hz, 2H); 6.37 (s, 1H); 6.00 (s, 1H); 4.66 (m, 1H); 4.22 (m, 2H); 4.11 (m, 5H); 3.86 (m, 1H); 3.77 (s, 3H); 3.67 (s, 3H); 3.16 (ddd, *J* = 9.8, 9.8, 3.7Hz, 1H); 3.07 (m, 2H); 2.93 (m, 1H); 2.44 (m, 1H); 2.33 (m, 1H); 2.23 (m, 2H); 2.09 (m, 2H); 1.97 (s, 3H); 1.81 (m, 2H); 1.29 (m, 9H); 1.02 (s, 21H); 0.85 (s, 9H); 0.06 (s, 3H); -0.05 (s, 3H)

Methyl-5-((*4S*)-4-((tert-butyldimethylsilyl)oxy)-6-(dimethoxyphosphoryl)-7-ethoxy-2-methyl-7-oxohept-1-en-1-yl)-2-((*1S,2R,3S*)-2-(2-hydroxyethyl)-3-((triisopropylsilyl)oxy)cyclobutyl)furan-3-carboxylate (**411**)



Phosphonate **277** (200 mg, 0.18 mmol, 1.0 eq.) was dissolved in 2.2 mL of a 10/1 mixture CH_2Cl_2/MeOH. PPTS (7 mg, 36 µmol, 0.2 eq.) was added and the reaction mixture was allowed to stir at r.t. until TLC analysis indicated full consumption of the starting material (approx. three hours). The reaction mixture was quenched with saturated aqueous $NaHCO_3$. The phases were separated and the aqueous layer was extracted two times with Et_2O. The combined organic layers were dried with $MgSO_4$ and the solvent was removed under reduced pressure. Purification by silica gel chromatography (hexane/EtOAc = 3/1 to 0/1) yielded free alcohol **411** as colorless viscous oil (150 mg, 0.18 mmol, quant.).

Major:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.40 (s, 1H); 6.02 (s, 1H); 4.74 (ddd, *J* = 13.5, 6.6, 6.6Hz, 1H); 4.25 (m, 2H); 4.12 (m, 5H); 3.91 (m, 1H); 3.80 (s, 3H); 3.72 (m, 2H); 3.24 (ddd, *J* = 12.5, 11.5, 2.4Hz, 1H); 2.77 (m, 1H); 2.57 (m, 1H); 2.43 (m, 2H); 2.21 (m, 2H); 2.06 (m, 2H); 2.00 (s, 3H); 1.92 (m, 1H); 1.81 (m, 1H); 1.29 (m, 9H); 1.07 (s, 21H); 0.88 (s, 9H); 0.04 (s, 6H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 169.0; 164.6; 162.7; 151.1; 135.4; 116.3; 113.5; 108.5; 89.6; 69.1; 68.7; 66.7; 62.6; 61.3; 61.1; 51.4; 49.4; 48.1; 46.1; 42.3; 41.0; 35.7; 33.7; 32.4; 31.8; 25.8; 19.2; 18.0; 16.314.1; 12.1; -4.1; -4.9

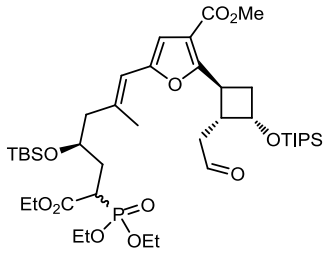
HRMS (ESI) (m/z): $[M+Na]^+$ calcd. for $C_{41}H_{75}O_{11}PSi_2Na$: 853.4483; found: 853.4476

Minor:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.38 (s, 1H); 6.00 (s, 1H); 4.74 (ddd, *J* = 13.5, 6.6, 6.6Hz, 1H); 4.25 (m, 2H); 4.12 (m, 5H); 3.91 (m, 1H); 3.80 (s, 3H); 3.72 (m, 2H); 3.12 (ddd, *J* = 13.7, 9.8, 4.0Hz, 1H); 2.77 (m, 1H); 2.57 (m, 1H); 2.43 (m, 2H); 2.21 (m, 2H); 2.06 (m, 2H); 1.99 (s, 3H); 1.92 (m, 1H); 1.81 (m, 1H); 1.29 (m, 9H); 1.07 (s, 21H); 0.86 (s, 9H); 0.07 (s, 3H); -0.02 (s, 3H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 169.5; 164.6; 162.7; 151.0; 135.1; 116.4; 113.5; 108.7; 89.6; 69.0; 68.8; 66.7; 62.8; 61.5; 51.4; 49.4; 48.1; 46.2; 42.5; 41.2; 35.7; 34.2; 32.2; 31.8; 25.8; 19.3; 17.9; 16.3; 14.1; 12.1; -4.6; -4.7

Methyl-5-((*4S*)-4-((tert-butyldimethylsilyl)oxy)-6-(dimethoxyphosphoryl)-7-ethoxy-2-methyl-7-oxohept-1-en-1-yl)-2-((*1S,2R,3S*)-2-(2-oxoethyl)-3-((triisopropylsilyl)oxy)cyclobutyl)furan-3-carboxylate (**281**)



Primary alcohol **411** (150 mg, 0.18 mmol, 1.0 eq.) was dissolved in anhydrous DMSO (2 mL) and IBX (101 mg, 0.36 mmol, 2 eq.) was added. The reaction mixtures was stirred at r.t. for 90 minutes or until all starting material was consumed. Now 2 mL of hexane and 2 mL of EtOAc were added and the suspension was filtered through a pad of celite 545 coarse. The filtrate was transferred to a separatory funnel and water was added. The phases were separated and the organic phase was washed twice with fresh water. The combined aqueous layers were back-extracted twice with EtOAc. The combined organic layers were dried with brine and $MgSO_4$ and the solvents were removed *in vacuo*. Purification by silica gel chromatography yielded aldehyde **281** (145 mg, 0.17 mmol, 97%) as colorless oil.

Major:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.78 (s, 1H); 6.40 (s, 1H); 6.03 (s, 1H); 4.73 (ddd, *J* = 11.8, 6.4, 6.4Hz, 1H); 4.21 (m, 3H); 3.98 (m, 2H); 3.78 (s, 3H); 3.24 (ddd, *J* = 12.3, 11.8, 2.0Hz, 1H); 3.15 (m, 1H); 2.95 (m, 1H); 2.63 (m, 2H); 2.39 (m, 2H); 2.23 (m, 2H); 2.16 (m, 1H); 2.04 (m, 1H); 1.99 (s, 3H); 1.81 (m, 2H); 1.29 (m, 9H); 1.04 (s, 21H); 0.87 (s, 9H); 0.03 (s, 6H)

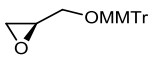
HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{41}H_{73}O_{11}PSi_2$: 828.4429; found: 828.4422

Minor:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.78 (s, 1H); 6.38 (s, 1H); 6.01 (s, 1H); 4.73 (ddd, *J* = 11.8, 6.4, 6.4Hz, 1H); 4.21 (m, 3H); 3.90 (m, 2H); 3.78 (s, 3H); 3.15 (m, 1H); 3.09 (ddd, *J* = 9.6, 9.6, 3.7Hz, 1H); 2.95 (m, 1H); 2.63 (m, 2H); 2.39 (m, 2H); 2.23 (m, 2H); 2.16 (m, 1H); 2.04 (m, 1H); 1.97 (s, 3H); 1.81 (m, 2H); 1.29 (m, 9H); 1.04 (s, 21H); 0.85 (s, 9H); 0.07 (s, 3H); 0.03 (s, 3H)

4.2.7 Furan-Butenolide-$\Delta^{12,13}$ Approach (*c*Bu)

(*S*)-2-(((4-methoxyphenyl)diphenylmethoxy)methyl)oxirane (**284**)

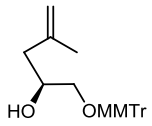


(*R*)-glycidol (**186**, 3.0 g, 40.5 mmol, 1.0 eq.) was dissolved in 200 mL anhydrous CH_2Cl_2, DMAP (247 mg, 2.0 mmol, 0.05 eq.) and pyridine (3.9 mL, 48.6 mmol, 1.2 eq.) were added. The reaction mixture was cooled to 0 °C. A solution of MMTr-Cl (13.76 g, 44.5 mmol, 1.1 eq.) in 100 mL of anhydrous CH_2Cl_2 was added dropwise at low temperature. The reaction mixture was stirred for two hours at 0 °C and then quenched by the addition of sat. aq. NH_4Cl solution and the phases were separated. The aqueous phase was extracted twice with 100 mL CH_2Cl_2. The combined organic layers were dried with brine and $MgSO_4$ and the solvent was removed under reduced pressure. Purification by silica gel chromatography (hexane/EtOAc = 10/1 to 7/1) yielded pure MMTr-glycidol **284** (13.6 g, 39.3 mmol, 97%) as slightly orange solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.46 (m, 3H); 7.31 (m, 7H); 7.20 (m, 2H); 6.84 (m, 2H); 3.80 (s, 3H); 3.32 (dd, *J* = 9.3, 2.0Hz, 1H); 3.14 (m, 2H); 2.77 (m, 1H); 2.62 (dd, *J* = 5.1, 2.3Hz, 1H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{23}H_{22}O_3$: 346.1569; found: 346.1562

(*S*)-1-((4-methoxyphenyl)diphenylmethoxy)-4-methylpent-4-en-2-ol (**412**)



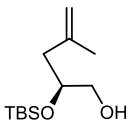
CuI (152 mg, 0.8 mmol, 0.2 eq.) was suspended in a flame dried three neck round bottom flask in anhydrous THF (3 mL) and the suspension was cooled to -78 °C. 16.7 mL of a 0.5M solution of isopropenylmagnesium bromide (8.4 mmol, 2.1 eq.) in anhydrous THF were added and the suspension turned to a yellow solution. The reaction mixture was allowed to stir for 45 minutes at -78 °C until 5 mL of a solution of MMTr-glycidol **284** (1.38 g, 3.98 mmol, 1.0 eq.) in anhydrous THF were added dropwise. The reaction mixture was allowed to stir at -78 °C for two hours until it was quenched with NH_4Cl. The biphasic mixture was allowed to warm to r.t. and Et_2O and 25% aqueous NH_3 were added. The phases were separated and the organic layer was repeatedly washed with a 3/1 mixture of NH_4Cl/NH_3. The combined aqueous extracts were back-extracted once with Et_2O and the combined organic layers were dried with $MgSO_4$. The solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography (hexane/EtOAc = 10/1 to 7/1) yielding compound **412** (1.5 g, 3.86 mmol, 97%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.45 (d, *J* = 7.8Hz, 4H); 7.33 (d, *J* = 8.9Hz, 2H); 7.26 (m, 4H); 7.18 (m, 2H); 6.81 (d, *J* = 8.9Hz, 2H); 4.77 (s, 1H); 4.71 (s, 1H); 3.91 (m, 1H); 3.72 (s, 3H); 3.14 (m, 2H); 2.34 (d, *J* = 3.0Hz, 1H); 2.16 (s, 1H); 2.15 (d, *J* = 2.2Hz, 1H); 1.69 (s, 3H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 158.5; 144.3; 142.1; 135.5; 130.2; 128.3; 127.7; 126.8; 113.0; 112.9; 86.3; 68.5; 67.4; 55.0; 42.1; 22.3

HRMS (ESI) (m/z): $[M+Na]^+$ calcd. for $C_{26}H_{28}O_3Na$: 411.1936; found: 411.1930

(*S*)-2-((tert-butyldimethylsilyl)oxy)-4-methylpent-4-en-1-ol (**413**)



Compound **412** (1.5 g, 3.86 mmol, 1.0 eq.) was dissolved in anhydrous DMF (15 mL) and imidazole (657 mg, 9.65 mmol, 2.5 eq.) was added. The reaction mixture was cooled to 0 °C and TBS-Cl (640 mg, 4.25 mmol, 1.1 eq.) was added.

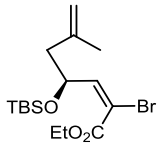
The solution was allowed to stir at 0 °C for one hour, before it was quenched by the addition of sat. aq. NH_4Cl. Et_2O and hexane were added and the phases were separated. The organic layer was washed with NH_4Cl and afterwards dried with brine and $MgSO_4$. The solvents were removed under reduced pressure. The resulting crude product was subsequently subjected to MMTr-deprotection.

The crude (1.94 g) product was dissolved in a 2/1 mixture of anhydrous CH_2Cl_2 (20 mL) and anhydrous MeOH (10 mL). The reaction mixture was cooled to 0 °C and CSA (90 mg, 0.39 mmol, 0.1 eq.) was added. The solution was allowed to stir for 30 minutes before it was quenched by the addition of sat. aq. $NaHCO_3$. The phases were separated and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were dried with brine and $MgSO_4$ and the solvent was removed *in vacuo*. Purification by silica gel chromatography (hexane/EtOAc = 10/1) yielded pure primary alcohol **413** (600 mg, 2.6 mmol, 67%) as colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.80 (s, 1H); 4.74 (s, 1H); 3.90 (m, 1H); 3.57 (m, 1H); 3.45 (m, 1H); 2.23 (d, *J* = 6.8Hz, 2H); 1.75 (s, 3H); 0.90 (s, 9H); 0.10 (s, 3H); 0.09 (s, 3H)

HRMS (ESI) (m/z): $[M+Na]^+$ calcd. for $C_{12}H_{26}O_2SiNa$: 253.1600; found: 253.1594

(*S,E*)-ethyl 2-bromo-4-((tert-butyldimethylsilyl)oxy)-6-methylhepta-2,6-dienoate (**414**)



Primary alcohol **413** (600 mg, 2.6 mmol, 1.0 eq.) was dissolved in anhydrous EtOAc (25 mL) and IBX (2.19 g, 7.8 mmol, 3 eq.) was added. The suspension was heated to reflux for three hours. Now the suspension was cooled to r.t. and 25 mL of hexane were added. The suspension was filtered through a pad of celite and the solvents were removed *in vacuo*. The crude product was of sufficient purity. In this way, the aldehyde was obtained as viscous oil (594 mg, 2.6 mmol, quant.).

A suspension of NaH (60% in mineral oil, 111 mg, 2.77 mmol, 1.0 eq.) in anhydrous THF (10 mL) was cooled to 0 °C and a solution of ethyl 2-bromo-2-(diphenoxyphosphoryl)acetate (1.15 g, 2.77 mmol, 1.0 eq.) in anhydrous THF (10 mL) was added dropwise. Upon completion of the addition the reaction mixture was stirred for 30 minutes.

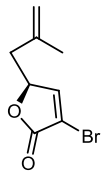
A solution of the previously prepared aldehyde (594 mg, 2.6 mmol, 0.94 eq.) in anhydrous THF (10 mL) was added dropwise and the solution was allowed to stir at 0 °C for 30 minutes (precipitation of a solid). The reaction was quenched by the addition of water. The phases were separated and the aqueous layer was extracted twice with Et_2O.

The combined organic layers were dried with brine and $MgSO_4$ and the solvents were removed under reduced pressure. Purification by silica gel chromatography yielded pure (*E*)-bromo-enone **414** (450 mg, 1.19 mmol, 46%) as colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.59 (d, *J* = 8.5Hz, 1H); 5.14 (ddd, *J* = 16.0; 4.9, 0.9Hz, 1H); 4.81 (m, 1H); 4.73 (m, 1H); 4.28 (dq, *J* = 7.1, 2.2Hz, 2H); 2.24 (m, 2H); 1.77 (s, 3H); 1.35 (t, *J* = 7.1Hz, 3H); 0.87 (s, 9H); 0.03 (s, 3H); 0.01 (s, 3H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{16}H_{29}BrO_3Si$: 376.1069; found: 376.1058

(*S*)-3-bromo-5-(2-methylallyl)furan-2(5H)-one (**283**)

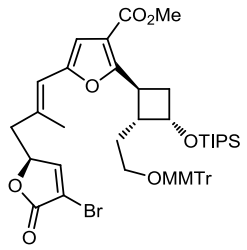


(*E*)-Bromo-enone **414** (450 mg, 1.19 mmol, 1.0 eq.) was dissolved in anhydrous MeOH (12 mL) and *p*TsOH (11.34 mg, 59.6 µmol, 0.05 eq.) was added. The reaction mixture was heated to reflux for two hours before it was allowed to cool to r.t. and sat. aq. $NaHCO_3$ and Et_2O was added. The phases were separated and the organic phase was dried with brine and $MgSO_4$. All solvents were removed *in vacuo* and purification by silica gel chromatography (hexane/EtOAc = 4/1) yielded pure bromo-butenolide **283** (227 mg, 1.05 mmol, 88%) as colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.53 (d, *J* = 1.8Hz, 1H); 5.10 (ddd, *J* = 7.0, 7.0, 1.8Hz, 1H); 4.96 (m, 1H); 4.84 (bs, 1H); 2.51 (m, 1H); 2.39 (m, 1H); 1.81 (s, 3H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_8H_9BrO_2$: 215.9786; found: 215.9779

Methyl-5-((*E*)-3-((*S*)-4-bromo-5-oxo-2,5-dihydrofuran-2-yl)-2-methylprop-1-en-1-yl)-2-((*1S,2R,3S*)-2-(2-((4-methoxyphenyl)diphenylmethoxy)ethyl)-3-((triisopropylsilyl)oxy)cyclobutyl)furan-3-carboxylate (**282**)



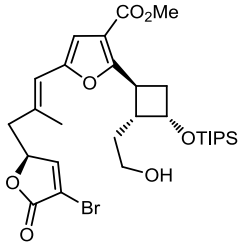
Bromo-butenolide **283** (67 mg, 0.31 mmol, 4 eq.) and vinylfuran **200** (52 mg, 75 µmol, 1.0 eq.) were dissolved in anhydrous, degassed (5 pump and freeze cycles) toluene (3 mL). The solution was heated to reflux overnight and a solution of Grubbs 2nd generation catalyst (17.5 mg, 20 µmol, 0.2 eq.) in anhydrous, degassed toluene (2 mL) was added slowly *via* a syringe pump within 10hours. After that period of time, the solvent was removed under reduced pressure. Purification by silica gel chromatography (hexane/EtOAc = 5/1 to 4/1) yielded pure compound **282** (14 mg, 16 µmol, 21%) as colorless semi-solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.53 (d, *J* = 1.8Hz, 1H); 7.34 (m, 4H); 7.20 (m, 8H); 6.75 (m, 2H); 6.47 (s, 1H); 6.08 (s, 1H); 5.11 (ddd, *J* = 6.9, 6.9, 1.8Hz, 1H); 4.64 (m, 1H); 3.90 (m, 1H); 3.77 (s, 3H); 3.70 (s, 3H); 3.05 (m, 3H); 2.63 (m, 1H); 2.48 (m, 2H); 2.31 (m, 1H); 2.07 (s, 3H); 1.89 (m, 2H); 1.02 (s, 21H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 164.0; 163.2; 158.3; 152.1; 150.0; 145.0; 144.9; 136.2; 130.9; 130.2; 128.4; 127.6; 126.6; 126.5; 117.8; 113.8; 112.8; 110.0; 85.9; 81.3; 66.8; 61.5; 55.1; 51.2; 44.4; 44.3; 36.3; 33.5; 29.2; 19.2; 18.0; 12.2; 12.1

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{49}H_{59}BrO_8Si$: 882.3163; found: 882.3158

Methyl-5-((*E*)-3-((*S*)-4-bromo-5-oxo-2,5-dihydrofuran-2-yl)-2-methylprop-1-en-1-yl)-2-((*1S,2R,3S*)-2-(2-hydroxyethyl)-3-((triisopropylsilyl)oxy)cyclobutyl)furan-3-carboxylate (**415**)



Compound **282** (14 mg, 15.8 µmol, 1.0 eq.) was dissolved in 1 mL of a 4/1 mixture CH_2Cl_2/MeOH. PPTS (0.4 mg, 1.6 µmol, 0.1 eq.) was added and the reaction mixture was allowed to stir at r.t. until TLC analysis indicated full consumption of the starting material (approx. one hour). The reaction mixture was quenched with saturated aqueous $NaHCO_3$. The phases were separated and the aqueous layer was extracted two times with CH_2Cl_2. The combined organic layers were dried with $MgSO_4$ and the solvent was removed under reduced pressure. Purification by silica gel chromatography (hexane/EtOAc = 2/1) yielded free alcohol **415** as colorless viscous oil (7.5 mg, 12.3 µmol, 78%).

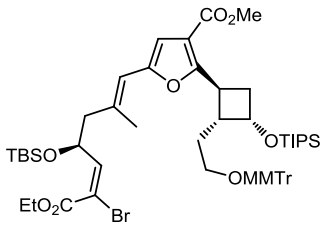
^{1}H-NMR (600 MHz, $CDCl_3$): δ = 7.55 (d, *J* = 1.7Hz, 1H); 6.48 (s, 1H); 6.11 (s, 1H); 5.15 (ddd, *J* = 6.7, 6.7, 1.8Hz, 1H); 4.75 (m, 1H); 3.93 (m, 1H); 3.81 (s, 3H); 3.72 (m, 2H); 2.79 (m, 1H); 2.60 (m, 2H); 2.44 (m, 1H); 2.23 (m, 2H); 2.10 (s, 3H); 1.91 (m, 2H); 1.07 (m, 21H)

^{13}C-NMR (150 MHz, $CDCl_3$): δ = 164.4; 163.4; 153.4; 152.0; 150.2; 131.1; 117.7; 113.7; 110.0; 105.2; 81.2; 66.6; 61.1; 55.1; 51.5; 46.2; 44.3; 35.7; 32.3; 31.7; 19.7; 19.2; 18.0; 17.9; 12.1

HRMS (ESI) (m/z): $[M+Na]^+$ calcd. for $C_{29}H_{43}BrO_7SiNa$: 633.1859; found: 633.1857

4.2.8 Furan-Δ^{12,13} Approach (*c*Bu)

Methyl-5-((*S,5E*)-6-bromo-4-((tert-butyldimethylsilyl)oxy)-7-ethoxy-2-methyl-7-oxohepta-1,5-dien-1-yl)-2-((*1S,2R,3S*)-2-(2-((4-methoxyphenyl)diphenylmethoxy)ethyl)-3-((triisopropylsilyl)oxy)cyclobutyl)furan-3-carboxylate (**289**)



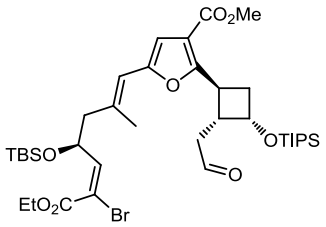
Primary alcohol **278** (266 mg, 0.3 mmol, 1.0 eq.) was dissolved in anhydrous EtOAc (3 mL) and IBX (249 mg, 0.89 mmol, 3 eq.) was added. The reaction mixtures was refluxed for two hours or until all starting material was consumed. Now 3 mL of hexane were added and the suspension was filtered through a pad of celite 545 coarse. Removal of the solvents gave the aldehyde (260 mg, 0.29 mmol, 98%) as colorless oil.

A suspension of NaH (60% in mineral oil, 260 mg, 0.32 mmol, 1.1 eq.) in anhydrous THF (1 mL) was cooled to 0 °C and a solution of ethyl 2-bromo-2-(diphenoxyphosphoryl)acetate (139 mg, 0.35 mmol, 1.2 eq.) in anhydrous THF (1 mL) was added dropwise. Upon completion of the addition the reaction mixture was stirred for 30 minutes. A solution of the previously prepared aldehyde (260 mg, 0.29 mmol, 1.0 eq.) in anhydrous THF (1 mL) was added dropwise and the solution was allowed to stir at 0 °C for 30 minutes (precipitation of a solid). The reaction was quenched by the addition of water. The phases were separated and the aqueous layer was extracted twice with Et_2O. The combined organic layers were dried with brine and $MgSO_4$ and the solvents were removed under reduced pressure. Purification by silica gel chromatography (hexane/EtOAc = 5/1) yielded pure (*E*)-bromo-enone **289** (80 mg, 76.6 µmol, 26%) as colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.42 (m, 1H); 7.34 (m, 3H); 7.21 (m, 8H); 6.76 (d, *J* = 8.7Hz, 2H); 6.67 (d, *J* = 8.5Hz, 1H); 6.50 (s, 1H); 6.06 (s, 1H); 5.27 (m, 1H); 4.60 (m, 1H); 4.26 (m, 2H); 3.94 (m, 1H); 3.78 (s, 3H); 3.69 (s, 3H); 3.04 (m, 2H); 2.75 (m, 1H); 2.49 (m, 2H); 2.31 (m, 2H); 2.09 (m, 1H); 1.95 (s, 3H); 1.90 (m, 1H); 1.32 (m, 3H); 1.03 (s, 21H); 0.79 (s, 9H); 0.00 (s, 3H); -0.04 (s, 3H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{57}H_{79}BrO_9Si_2$: 1042.4446; found: 1042.4438

Methyl-5-((*S,5E*)-6-bromo-4-((tert-butyldimethylsilyl)oxy)-7-ethoxy-2-methyl-7-oxohepta-1,5-dien-1-yl)-2-((*1S,2R,3S*)-2-(2-oxoethyl)-3-((triisopropylsilyl)oxy)cyclobutyl)furan-3-carboxylate (**290**)



Bromo-enone **289** (80 mg, 76.6 µmol, 1.0 eq.) was dissolved in 1 mL of a 4/1 mixture CH_2Cl_2/MeOH. PPTS (1.5 mg, 7.7 µmol, 0.1 eq.) was added and the reaction mixture was allowed to stir at r.t. until TLC analysis indicated full consumption of the starting material (approx. one day). The reaction mixture was quenched with saturated aqueous $NaHCO_3$. The phases were separated and the aqueous layer was extracted two times with CH_2Cl_2. The combined organic layers were dried with $MgSO_4$ and the solvent was removed under reduced pressure. Purification by silica gel chromatography (hexane/EtOAc = 4/1 to 3/1) yielded the free primary alcohol as colorless viscous oil (58 mg, 75.1 µmol, 98%).

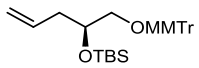
The previously prepared primary alcohol (58 mg, 75 µmol, 1.0 eq.) was dissolved in anhydrous EtOAc (2 mL) and IBX (42 mg, 0.15 mmol, 2 eq.) was added. The reaction mixtures was refluxed for two hours or until all starting material was consumed. Now 2 mL of hexane were added and the suspension was filtered through a pad of celite 545 coarse. Removal of the solvents and purification by silica gel chromatography (hexane/EtOAc = 5/1) gave aldehyde **290** (44 mg, 57.1 µmol, 76%.) as colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.78 (t, *J* = 1.5Hz, 1H); 6.67 (d, *J* = 8.6Hz, 1H); 6.54 (s, 1H); 6.08 (s, 1H); 5.27 (ddd, *J* = 8.4, 8.4, 4.5Hz, 1H); 4.69 (m, 1H); 4.27 (m, 2H); 4.03 (m, 1H); 3.79 (s, 3H); 3.19 (ddd, *J* = 7.1, 7.1, 7.1Hz, 1H); 2.97 (m, 2H); 2.66 (m, 2H); 2.34 (m, 2H); 1.95 (s, 3H); 1.33 (m, 3H); 1.05 (s, 21H); 0.80 (s, 9H); -0.01 (s, 3H); -0.04 (s, 3H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{57}H_{61}BrO_9Si_2$: 768.3088; found: 768.3074

4.2.9 $\Delta^{12,13}$ Approach (*c*Bu)

(*S*)-tert-butyl((1-((4-methoxyphenyl)diphenylmethoxy)pent-4-en-2-yl)oxy)dimethylsilane (**416**)



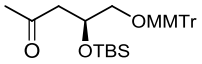
CuI (381 mg, 2 mmol, 0.2 eq.) was suspended in a flame dried three neck round bottom flask in anhydrous THF (30 mL) and the suspension was cooled to -78 °C. 21 mL of a 1M solution of vinylmagnesium bromide (21.0 mmol, 2.1 eq.) in anhydrous THF were added and the suspension turned to a yellow solution. The reaction mixture was allowed to stir for 45 minutes at -78 °C until 30 mL of a solution of MMTr-glycidol **284** (3.46 g, 10 mmol, 1.0 eq.) in anhydrous THF were added dropwise. The reaction mixture was allowed to stir at -78 °C for two hours until it was quenched with NH_4Cl. The biphasic mixture was allowed to warm to r.t. and Et_2O and 25% aqueous NH_3 were added. The phases were separated and the organic layer was repeatedly washed with a 3/1 mixture of NH_4Cl/NH_3. The combined aqueous extracts were back-extracted once with Et_2O and the combined organic layers were dried with $MgSO_4$. The solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography (hexane/EtOAc = 4/1) yielding the secondary homo allylic alcohol (3.74 g, 10 mmol, quant.).

The previously prepared secondary homo allylic alcohol (3.74 g, 10 mmol, 1.0 eq.) was dissolved in anhydrous DMF (15 mL) and imidazole (1.5 g, 22.0 mmol, 2.2 eq.) was added in one portion. Under Ar-atmosphere, the mixture was cooled to 0 °C and a solution of TBS-Cl (1.58 g, 10.5 mmol, 1.05 eq.) in anhydrous DMF (5 mL) was slowly added at 0 °C. The reaction mixture was allowed to warm to r.t. overnight. 50 mL of hexane/Et_2O (1/1) and 10 mL of saturated aqueous NH_4Cl were added and the phases separated. The organic phase was extracted with water twice. The combined aqueous phases were back-extracted twice with a 1/1 mixture of hexane/Et_2O and the combined organic layers were dried over $MgSO_4$. Evaporation of the solvent yielded silylether **416** (13.4 g, 50.2 mmol, 85%) as colorless oil, which was purified by silica gel column chromatography (hexane/EtOAc = 20/1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.46 (m, 4H); 7.34 (m, 2H); 7.28 (m, 4H); 7.21 (m, 2H); 6.82 (m, 2H); 5.74 (ddt, *J* = 7.2, 7.2, 7.1Hz, 1H); 5.01 (d, *J* = 17.2Hz, 1H); 4.96 (d, *J* = 10.3Hz, 1H); 3.80 (m, 1H); 3.79 (s, 3H); 3.03 (ddd, *J* = 17.6, 5.9, 5.2Hz, 2H); 2.44 (m, 1H); 2.25 (m, 1H); 0.86 (s, 9H); 0.03 (s, 3H); -0.01 (s, 3H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{31}H_{40}O_3Si$: 488.2747; found: 488.2741

(*S*)-4-((tert-butyldimethylsilyl)oxy)-5-((4-methoxyphenyl)diphenylmethoxy)pentan-2-one (**417**)

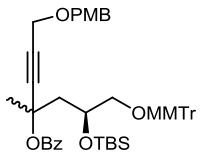


Olefin **146** (100 mg, 0.2 mmol, 1.0 eq.) was dissolved in DMF (1.5 mL) and THF (125 µL) and water (125 µL) were added. The final ratio of the three solvents was 6/1/1. Cu(I)Cl (8.1 mg, 0.08 mmol, 0.4 eq.) and $PdCl_2$ (7.26 mg, 0.02 mmol, 0.2 eq.) were added. Oxygen (O_2) was bubbled through the solution for three hours at r.t. Et_2O and sat. aq. $NaHCO_3$ were added and the phases were separated. The organic phase was washed once with water, before it was dried with brine and $MgSO_4$. The solvents were removed *in vacuo* and silica gel chromatography (hexane/EtOAc = 5/1) yielded pure methyl ketone **417** (100 mg, 0.2 mmol, 99%) as colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.43 (m, 4H); 7.29 (m, 6H); 7.22 (m, 2H); 6.83 (m, 2H); 4.28 (m, 1H); 3.80 (s, 3H); 3.10 (m, 1H); 2.97 (m, 1H); 2.77 (m, 1H); 2.61 (m, 1H); 2.13 (s, 3H); 0.81 (s, 9H); -0.01 (s, 3H); -0.07 (s, 3H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{31}H_{40}O_4Si$: 504.2696; found: 504.2691

(*6S*)-6-((tert-butyldimethylsilyl)oxy)-1-((4-methoxybenzyl)oxy)-7-((4-methoxyphenyl)diphenylmethoxy)-4-methylhept-2-yn-4-yl benzoate (**418**)



PMB ether **222a** (3.13 g, 17.8 mmol, 1.3 eq.) was dissolved in anhydrous THF (100 mL) and the solution was cooled to -78 °C. After dropwise addition of LiHMDS (1M, 16.4 mL, 16.4 mmol, 1.2 eq.) the reaction mixture was allowed to stir for one hour. A solution of methyl ketone **417** (6.9 g, 13.7 mmol, 1.0eq) in anhydrous THF (40 mL) was added dropwise. The reaction mixture was allowed to stir at -78 °C for two hours until it was quenched by the addition of sat. aq. NH_4Cl. After the addition of Et_2O the phases were separated and the pH of the aqueous phase adjusted to 5. The aqueous phase was extracted twice with Et_2O and the combined organic layers were dried with $MgSO_4$. Removal of the solvent under reduced pressure yielded the tertiary alcohol, which was used without further purification.

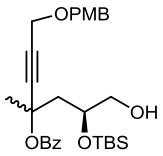
The previously prepared tertiary alcohol (136 mg, 0.2 mmol, 1.0 eq.) was dissolved in anhydrous THF (2 mL) and NEt_3 (84 µL, 0.6 mmol, 3 eq.) and benzoic acid anhydride (104 mg, 0.4 mmol, 2 eq.) were added at r.t. The reaction mixture was cooled to 0 °C and $MgBr_2 \cdot OEt_2$ (91 mg, 0.4 mmol, 2 eq.) was added. The solution was allowed to warm to r.t. within 30 minutes. Water and Et_2O were added and the phases were separated. The organic phase was washed with water and the combined aqueous phases were back-extracted with Et_2O. The combined organic layers were dried with $MgSO_4$ and the solvent was removed under reduced pressure. Purification by silica gel chromatography (hexane/EtOAc = 5/1) yielded tertiary benzoate **418** (157 mg, 0.2 mmol, quant.) as colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.01 (m, 2H); 7.55 (m, 1H); 7.45 (m, 4H); 7.40 (m, 2H); 7.26 (m, 10H); 6.84 (m, 2H); 6.78 (d, *J* = 8.9Hz, 2H); 4.54 (s, 2H); 4.26 (m, 1H); 4.12 (s, 2H); 3.78 (s, 3H); 3.77 (s, 3H); 3.19 (m, 1H); 3.16 (d, *J* = 5.8Hz, 1H); 2.64 (m, 1H); 2.25 (dd, *J* = 14.7, 6.6Hz, 1H); 1.83 (s, 3H); 0.83 (s, 9H); 0.01 (s, 3H); -0.06 (s, 3H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 164.5; 159.3; 158.4; 144.6; 135.9; 132.9; 131.0; 130.3; 129.9; 129.6; 129.2; 128.5; 128.2; 127.9; 127.8; 127.7; 127.1; 126.7; 113.8; 113.2; 113.0; 87.2; 86.3; 82.4; 81.7; 75.0; 74.4; 70.8; 69.7; 69.0; 67.8; 56.8; 55.2; 46.1; 28.0; 27.5; 25.9; 18.0; -4.2; -4.4

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{49}H_{56}O_7Si$: 784.3795; found: 784.3782

(*6S*)-6-((tert-butyldimethylsilyl)oxy)-7-hydroxy-1-((4-methoxybenzyl)oxy)-4-methylhept-2-yn-4-yl benzoate (**419**)



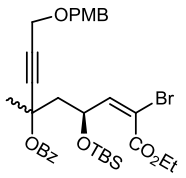
Tertiary benzoate **418** (157 mg, 0.2 mmol, 1.0 eq.) was dissolved in 2 mL of a 4/1 mixture CH_2Cl_2/MeOH. PPTS (10 mg, 40 µmol, 0.2 eq.) was added and the reaction mixture was allowed to stir at r.t. until TLC analysis indicated full consumption of the starting material (approx. one hour). The reaction mixture was quenched with saturated aqueous $NaHCO_3$. The phases were separated and the aqueous layer was extracted two times with Et_2O. The combined organic layers were dried with $MgSO_4$ and the solvent was removed under reduced pressure. Purification by silica gel chromatography (hexane/EtOAc = 4/1) yielded free alcohol **419** as colorless viscous oil (64 mg, 0.12 mmol, 62%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.01 (m, 2H); 7.56 (m, 1H); 7.44 (m, 2H); 7.28 (d, *J* = 8.8Hz, 2H); 6.85 (d, *J* = 8.8Hz, 2H); 4.54 (s, 2H); 4.18 (s, 2H); 4.17 (m, 1H); 3.79 (s, 3H and m, 1H); 3.68 (m, 1H); 2.43 (m, 1H); 2.31 (m, 1H); 1.89 (s, 3H); 1.62 (bs, 1H); 0.91 (s, 9H); 0.12 (s, 6H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 164.7; 159.4; 132.9; 130.8; 129.9; 129.8; 129.6; 129.4; 128.3; 113.8; 86.6; 82.3; 73.9; 71.1; 69.7; 66.6; 64.4; 56.9; 55.3; 45.2; 27.8; 25.8; 18.0; -4.4; -4.5

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{29}H_{40}O_6Si$: 512.2594; found: 512.2586

(*6S,E*)-8-bromo-6-((tert-butyldimethylsilyl)oxy)-9-ethoxy-1-((4-methoxybenzyl)oxy)-4-methyl-9-oxonon-7-en-2-yn-4-yl benzoate (**297**)



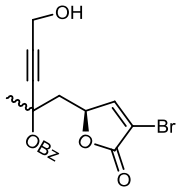
Oxalyl chloride (20 µL, 0.23 mmol, 2 eq.) was dissolved in anhydrous CH_2Cl_2 (1 mL) and the solution was cooled to -78 °C. A solution of anhydrous DMSO (33 µL, 0.47 mmol, 4 eq.) in anhydrous CH_2Cl_2 (200 µL) was added dropwise. The reaction mixture was allowed to stir at -78 °C for 45 minutes. A solution of alcohol **419** (60 mg, 0.12 mmol, 1.0 eq.) in anhydrous CH_2Cl_2 (1 mL) was added dropwise. The reaction mixture was allowed to stir for 90 minutes, before NEt_3 (98 µL, 0.7 mmol, 6 eq.) was added and the solution was allowed to warm to -20 °C within one hour. Sat. aq. NH_4Cl was added and the phases were separated. The aqueous layer was extracted twice with CH_2Cl_2 and the combined organic layers were dried with brine and $MgSO_4$. The solvent was removed under reduced pressure and the aldehyde (60 mg, 0.12 mmol, quant.) was used without further purification**.**

A suspension of NaH (60% in mineral oil, 7 mg, 0.18 mmol, 1.5 eq.) in anhydrous THF (500 µL) was cooled to 0 °C and a solution of ethyl 2-bromo-2-(diphenoxyphosphoryl)acetate (84 mg, 0.18 mmol, 1.5 eq.) in anhydrous THF (500 µL) was added dropwise. Upon completion of the addition the reaction mixture was stirred for 30 minutes. A solution of the previously prepared aldehyde (60 mg, 0.12 mmol, 1.0 eq.) in anhydrous THF (500 µL) was added dropwise and the solution was allowed to stir at 0 °C for 30 minutes (precipitation of a solid). The reaction was quenched by the addition of water. The phases were separated and the aqueous layer was extracted twice with Et_2O. The combined organic layers were dried with brine and $MgSO_4$ and the solvents were removed under reduced pressure. Purification by silica gel chromatography (hexane/EtOAc = 5/1) yielded pure (*E*)-bromo-enone **297** (79 mg, 0.12 mmol, quant.) as colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.02 (m, 2H); 7.55 (m, 1H); 7.43 (m, 2H); 7.29 (m, 2H); 6.85 (d, *J* = 8.6Hz, 2H); 6.65 (d, *J* = 8.8Hz, 1H); 5.51 (m, 1H); 4.56 (s, 2H); 4.21 (s, 2H); 4.18 (q, *J* = 7.2Hz, 2H); 3.79 (s, 3H); 2.38 (m, 2H); 1.92 (s, 3H); 1.25 (t, *J* = 7.2Hz, 3H); 0.86 (s, 9H); 0.06 (s, 3H); 0.02 (s, 3H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{33}H_{43}BrO_7Si$: 658.1961; found: 658.1954

1-((*S*)-4-bromo-5-oxo-2,5-dihydrofuran-2-yl)-5-hydroxy-2-methylpent-3-yn-2-yl benzoate (**420**)



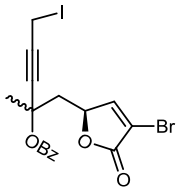
(*E*)-bromo-enone **297** (3.76 g, 5.7 mmol, 1.0 eq.) was dissolved in anhydrous MeOH (60 mL) and *p*TsOH (217 mg, 1.14mol, 0.2 eq.) was added. The reaction mixture was heated to reflux for four hours before it was allowed to cool to r.t. and sat. aq. $NaHCO_3$ and Et_2O was added. The phases were separated and the organic phase was dried with brine and $MgSO_4$. All solvents were removed *in vacuo* and purification by silica gel chromatography (hexane/EtOAc = 2/1) yielded pure bromo-butenolide **420** (2.05 g, 5.4mol, 95%) as colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.00 (m, 2H); 7.65 (d, *J* = 1.8Hz, 1H); 7.59 (m, 1H); 7.46 (m, 2H); 5.42 (dt, *J* = 7.4, 3.8Hz, 1H); 4.35 (s, 2H); 2.62 (dd, *J* = 14.3, 5.6Hz, 1H); 2.49 (m, 1H); 2.30 (dd, *J* = 14.3, 7.5Hz, 1H); 1.91 (s, 3H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 167.9; 164.6; 152.9; 133.4; 130.1; 129.7; 129.5; 128.6; 113.2; 86.5; 83.5; 79.9; 73.5; 50.9; 44.3; 27.6

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{17}H_{15}BrO_5$: 378.0103; found: 378.0097

1-((*S*)-4-bromo-5-oxo-2,5-dihydrofuran-2-yl)-5-iodo-2-methylpent-3-yn-2-yl benzoate (**298**)

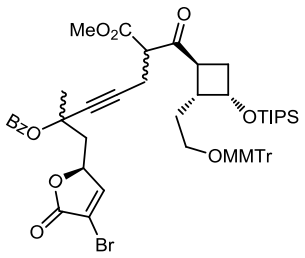


Imidazole (350 mg, 5.14 mmol, 3 eq.), PPh_3 (899 mg, 3.43 mmol, 2 eq.) and iodine (870 mg, 3.43 mmol, 2 eq.) were added to 15 mL anhydrous CH_2Cl_2 and cooled to 0 °C. The suspension was stirred at 0 °C for 20 minutes while it turned yellow. To this suspension a solution of propargylic alcohol **420** (650 mg, 1.71 mmol, 1.0 eq.) in anhydrous CH_2Cl_2 (5 mL) was added rapidly. The reaction mixture was stirred for one hour. Then it was quenched by the addition of hexane (20 mL). The precipitating triphenylphosphineoxide was filtered through a pad of celite and a sat. aq. solution of $Na_2S_2O_3$ and $NaHCO_3$ was added to the filtrate. The phases were separated and the organic phase was washed with $Na_2S_2O_3$, $NaHCO_3$ and brine before it was dried with $MgSO_4$. After removal of the solvent under reduced pressure, purification by silica gel chromatography yielded propargylic iodide **298** (836 g, 1.71 mmol, quant.) as slightly yellow liquid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.01 (m, 2H); 7.65 (d, *J* = 1.8Hz, 1H); 7.58 (m, 1H); 7.46 (m, 2H); 5.42 (dt, *J* = 7.4, 3.8Hz, 1H); 3.71 (s, 2H); 2.62 (dd, *J* = 14.3, 5.6Hz, 1H); 2.48 (m, 1H); 2.31 (dd, *J* = 14.2, 7.4Hz, 1H); 1.91 (s, 3H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{17}H_{14}BrIO_4$: 487.9120; found: 487.9115

1-((*S*)-4-bromo-5-oxo-2,5-dihydrofuran-2-yl)-7-methoxy-6-((*1S,2R,3S*)-2-(2-((4-methoxyphenyl)diphenylmethoxy)ethyl)-3-((triisopropylsilyl)oxy)cyclobutanecarbonyl)-2-methyl-7-oxohept-3-yn-2-yl benzoate (**293**)



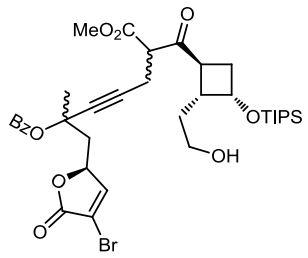
NaH (60% in mineral oil, 68 mg, 1.71 mmol, 1.0 eq.) was suspended in anhydrous THF (5 mL). The reaction mixture was cooled to 0 °C and a solution of β-keto ester **195** (1.1 g, 1.71 mmol, 1.0 eq.) in anhydrous THF (5 mL) was added.

The reaction was stirred at 0 °C for 20 minutes and then warmed to r.t. within 10 minutes. Then it was re-cooled to 0 °C and a solution of propargylic iodide **298** (836 mg, 1.71 mmol, 1.0 eq.) was added uninterruptedly at 0 °C. The reaction mixture was stirred at this temperature for 20 minutes and then warmed to r.t. within 20 minutes before it was quenched with saturated aqueous NH_4Cl. Et_2O was added and the phases separated. The pH of the aqueous phase was adjusted to 6 with 0.5M $KHSO_4$ and it was extracted twice with Et_2O. The combined organic layers were dried with $MgSO_4$ and the solvent was removed under reduced pressure. Silica gel column chromatography (hexane/EtOAc = 4/1) yielded alkylated β-keto ester **293** as slightly yellow oil (1.7 g, 1.7 mmol, 99%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.98 (m, 2H); 7.57 (m, 2H); 7.41 (m, 7H); 7.26 (m, 5H); 7.19 (m, 2H); 6.80 (m, 2H); 5.30 (m, 1H); 4.41 (m, 1H); 4.22 (m, 1H); 3.77 (s, 3H); 3.57 (m, 3H); 3.13 (m, 3H); 2.97 (m, 1H); 2.78 (m, 2H); 2.64 (m, 1H); 2.47 (m, 2H); 2.26 (m, 2H); 2.12 (m, 1H); 1.80 (m, 3H); 0.97 (m, 21H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{56}H_{65}BrO_{10}Si$: 1004.3530; found: 1004.3525

1-((*S*)-4-bromo-5-oxo-2,5-dihydrofuran-2-yl)-6-((*1S,2R,3S*)-2-(2-hydroxyethyl)-3-((triisopropylsilyl)oxy)cyclobutanecarbonyl)-7-methoxy-2-methyl-7-oxohept-3-yn-2-yl benzoate (**421**)

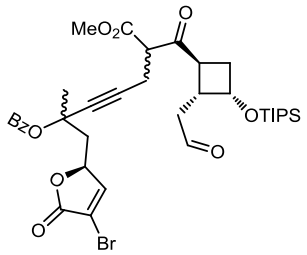


Alkylated β-keto ester **293** (1.7 g, 1.7 mmol, 1.0 eq.) was dissolved in a mixture of anhydrous CH_2Cl_2 (15 mL) and anhydrous MeOH (1.5 mL). The solution was cooled to 0 °C and CSA (42 mg, 0.17 mmol, 0.1 eq.) was added. The reaction mixture was allowed to stir for two hours before it was quenched by the addition of sat. aq. $NaHCO_3$. Phases were separated and the organic phase was dried with brine and $MgSO_4$. After removal of the solvent, purification by silica gel chromatography (hexane/EtOAc = 2/1) yielded pure primary alcohol **421** (600 mg, 0.82 mmol, 48%) as colorless viscous oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.03 (m, 1H); 7.94 (m, 1H); 7.66 (d, *J* = 1.8Hz, 1H); 7.59 (m, 1H); 7.46 (m, 2H); 5.38 (m, 1H); 4.45 (m, 1H); 3.85 (m, 1H); 3.71 (m, 3H); 3.68 (m, 2H); 3.25 (m, 1H); 2.80 (m, 3H); 2.53 (m, 1H); 2.45 (m, 1H); 2.38 (m, 1H); 2.28 (dd, *J* = 13.6, 7.5Hz, 1H); 2.14 (m, 1H); 1.96 (m, 1H); 1.85 (s, 3H); 1.80 (m, 1H); 1.03 (m, 21H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{36}H_{49}BrO_9Si$: 732.2329; found: 732.2322

1-((*S*)-4-bromo-5-oxo-2,5-dihydrofuran-2-yl)-7-methoxy-2-methyl-7-oxo-6-((*1S,2R,3S*)-2-(2-oxoethyl)-3-((triisopropylsilyl)oxy)cyclobutanecarbonyl)hept-3-yn-2-yl benzoate (**299**)



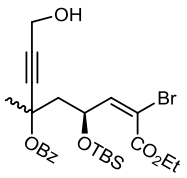
Primary alcohol **421** (100 mg, 0.14 mmol, 1.0 eq.) was dissolved in anhydrous EtOAc (2 mL) and IBX (76 mg, 0.27 mmol, 2 eq.) was added. The reaction mixtures was refluxed for two hours or until all starting material was consumed. Now 2 mL of hexane were added and the suspension was filtered through a pad of celite 545 coarse. Removal of the solvents and purification by silica gel chromatography (hexane/EtOAc = 3/1 to 2/1) gave aldehyde **299** (41 mg, 56 µmol, 41%) as colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.76 (m, 1H); 8.02 (m, 1H); 7.93 (m, 1H); 7.69 (d, *J* = 1.8Hz, 1H); 7.67 (m, 1H); 7.44 (m, 2H); 5.38 (m, 1H); 4.50 (m, 1H); 3.91 (m, 1H); 3.69 (s, 3H); 3.14 (m, 2H); 2.81 (m, 2H); 2.66 (m, 1H); 2.52 (m, 2H); 2.32 (m, 2H); 2.12 (m, 1H); 1.84 (m, 3H); 1.01 (s, 21H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 203.9; 201.4; 168.5; 164.5; 164.2; 153.3; 133.3; 130.3; 129.6; 129.5; 129.4; 128.5; 125.5; 112.8; 85.0; 84.8; 80.1; 79.6; 73.6; 73.1; 65.4; 56.3; 55.6; 52.7; 45.0; 44.6; 42.8; 39.1; 33.8; 30.3; 27.6; 22.2; 17.9; 12.0

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{36}H_{47}BrO_9Si$: 730.2173; found: 730.2168

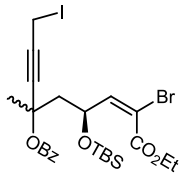
(*6S,E*)-8-bromo-6-((tert-butyldimethylsilyl)oxy)-9-ethoxy-1-hydroxy-4-methyl-9-oxonon-7-en-2-yn-4-yl benzoate (**422**)



To a solution of benzoate **297** (2.8 g, 4.2 mmol, 1.0 eq.) in CH_2Cl_2 (20 mL) were added 4 mL of a pH=7-buffer (50mM KH_2PO_4). The vigorously stirred suspension was cooled to 0 °C and DDQ (1.06 g, 4.7 mmol, 1.1 eq.) was added portionwise. The suspension was allowed to stir overnight while it warmed to r.t. After addition of sat. aq. $NaHCO_3$, the phases were separated and the organic phase was washed 6 times with H_2O. The organic phase was dried with brine and $MgSO_4$, and removal of the solvent *in vacuo* gave crude propargylic alcohol. Purification by silica gel chromatography (hexane/EtOAc = 3/1 to 2/1) gave alcohol **422** in quantitative yield (2.29 g, 4.2 mmol, quant.).

HRMS (ESI) (m/z): $[M+Na]^+$ calcd. for $C_{25}H_{35}BrO_6SiNa$: 561.1284; found: 561.1278

(*6S,E*)-8-bromo-6-((tert-butyldimethylsilyl)oxy)-9-ethoxy-1-iodo-4-methyl-9-oxonon-7-en-2-yn-4-yl benzoate (**300**)

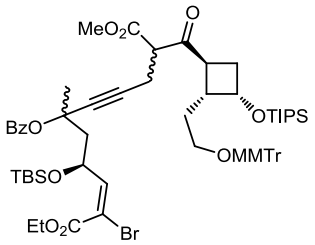


Imidazole (468 mg, 6.87 mmol, 3 eq.), PPh_3 (1.2 g, 4.58 mmol, 2 eq.) and iodine (1.16 g, 4.58 mmol, 2 eq.) were added to 30 mL anhydrous CH_2Cl_2 and cooled to 0 °C. The suspension was stirred at 0 °C for 20 minutes while it turned yellow. To this suspension a solution of propargylic benzoate **422** (2.29 g, 4.2 mmol, 1.0 eq.) in anhydrous CH_2Cl_2 (10 mL) was added rapidly. The reaction mixture was stirred for one hour. Then it was quenched by the addition of hexane (60 mL). The precipitating triphenylphosphineoxide was filtered through a pad of celite and a sat. aq. solution of $Na_2S_2O_3$ and $NaHCO_3$ was added to the filtrate. The phases were separated and the organic phase was washed with $Na_2S_2O_3$, $NaHCO_3$ and brine before it was dried with $MgSO_4$.

After removal of the solvent under reduced pressure, purification by silica gel chromatography (hexane/EtOAc = 4/1) yielded propargylic iodide **300** (2.45 g, 3.77 mmol, 82%) as slightly yellow liquid.

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{25}H_{34}BrIO_5Si$: 648.0404; found: 648.0400

(*4S,E*)-1-ethyl 11-methyl 6-(benzoyloxy)-2-bromo-4-((tert-butyldimethylsilyl)oxy)-10-((*1S,2R,3S*)-2-(2-((4-methoxyphenyl)diphenylmethoxy)ethyl)-3-((triisopropylsilyl)oxy)cyclobutanecarbonyl)-6-methylundec-2-en-7-ynedioate (**295**)

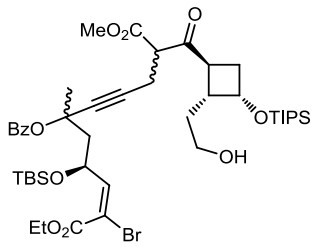


NaH (60% in mineral oil, 151 mg, 3.77 mmol, 1.0 eq.) was suspended in anhydrous THF (20 mL). The reaction mixture was cooled to 0 °C and a solution of β-keto ester **195** (2.43 g, 3.77 mmol, 1.0 eq.) in anhydrous THF (10 mL) was added. The reaction was stirred at 0 °C for 20 minutes and then warmed to r.t. within 10 minutes. Then it was re-cooled to 0 °C and a solution of propargylic iodide **300** (2.45 g, 3.77 mmol, 1.0 eq.) in anhydrous THF (10 mL) was added uninterruptedly at 0 °C. The reaction mixture was stirred at this temperature for 20 minutes and then warmed to r.t. within 20 minutes before it was quenched with saturated aqueous NH_4Cl. Et_2O was added and the phases separated. The pH of the aqueous phase was adjusted to 6 with 0.5M $KHSO_4$ and it was extracted twice with Et_2O. The combined organic layers were dried with $MgSO_4$ and the solvent was removed under reduced pressure. Silica gel column chromatography (hexane/EtOAc = 4/1) yielded alkylated β-keto ester **295** as slightly yellow oil (3.78 g, 3.24 mmol, 86%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.97 (m, 2H); 7.51 (m, 1H); 7.40 (m, 6H); 7.24 (m, 6H); 7.19 (m, 2H); 6.80 (m, 2H); 6.60 (m, 1H); 5.42 (m, 1H); 4.38 (m, 1H); 4.22 (m, 1H); 4.12 (m, 1H); 3.78 (s, 3H); 3.53 (m, 3H); 3.10 (m, 3H); 2.92 (m, 1H); 2.77 (m, 1H); 2.64 (m, 1H); 2.44 (m, 1H); 2.30 (m, 2H); 2.10 (m, 2H); 1.78 (m, 3H); 1.28 (m, 3H); 1.21 (m, 2H); 0.96 (s, 21H); 0.85 (s, 9H); 0.02 (m, 6H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{64}H_{85}BrO_{11}Si_2$: 1164.4814; found: 1164.4808

(*4S,E*)-1-ethyl 11-methyl 6-(benzoyloxy)-2-bromo-4-((tert-butyldimethylsilyl)oxy)-10-((*1S,2R,3S*)-2-(2-hydroxyethyl)-3-((triisopropylsilyl)oxy)cyclobutanecarbonyl)-6-methylundec-2-en-7-ynedioate (**423**)

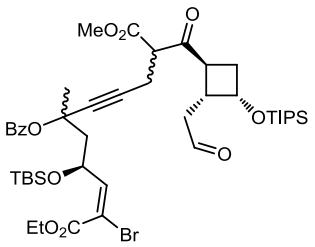


Alkylated β-keto ester **295** (250 mg, 0.21 mmol, 1.0 eq.) was dissolved in 10 mL of a 4/1 mixture CH_2Cl_2/MeOH. PPTS (2.7 mg, 0.01.0 mmol, 0.05 eq.) was added and the reaction mixture was allowed to stir at r.t. until TLC analysis indicated full consumption of the starting material (approx. three days). The reaction mixture was quenched with saturated aqueous $NaHCO_3$. The phases were separated and the aqueous layer was extracted two times with CH_2Cl_2. The combined organic layers were dried with $MgSO_4$ and the solvent was removed under reduced pressure. Purification by silica gel chromatography (hexane/EtOAc = 5/1 to 2/1) yielded free primary alcohol **423** as colorless viscous oil (100 mg, 0.14 mmol, 67%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.98 (m, 2H); 7.53 (m, 1H); 7.41 (m, 2H); 6.60 (m, 1H); 5.45 (m, 1H); 4.44 (m, 1H); 4.22 (m, 1H); 4.11 (m, 1H); 3.90 (m, 1H); 3.72 (m, 2H); 3.69 (m, 3H); 3.27 (m, 1H); 2.88 (m, 2H); 2.76 (m, 2H); 2.56 (m, 2H); 2.29 (m, 2H); 2.13 (m, 1H); 1.96 (m, 1H); 1.81 (s, 3H); 1.25 (m, 3H); 1.02 (s, 21H); 0.85 (s, 9H); 0.03 (m, 6H)

HRMS (ESI) (m/z): $[M+Na]^+$ calcd. for $C_{44}H_{69}BrO_{10}Si_2Na$: 915.3510; found: 915.3502

(*4S,E*)-1-ethyl 11-methyl 6-(benzoyloxy)-2-bromo-4-((tert-butyldimethylsilyl)oxy)-6-methyl-10-((*1S,2R,3S*)-2-(2-oxoethyl)-3-((triisopropylsilyl)oxy)cyclobutanecarbonyl)undec-2-en-7-ynedioate (**301**)



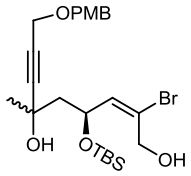
Primary alcohol **423** (100 mg, 0.14 mmol, 1.0 eq.) was dissolved in anhydrous EtOAc (2 mL) and IBX (96 mg, 0.34 mmol, 2.5 eq.) was added. The reaction mixtures was refluxed for two hours or until all starting material was consumed. Now 2 mL of hexane were added and the suspension was filtered through a pad of celite 545 coarse. Removal of the solvents gave aldehyde **301** (100 mg, 0.14 mmol, quant.) as colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.98 (m, 2H); 7.53 (m, 1H); 7.41 (m, 2H); 6.60 (m, 1H); 5.45 (m, 1H); 4.44 (m, 1H); 4.22 (m, 1H); 4.11 (m, 1H); 3.90 (m, 1H); 3.72 (m, 2H); 3.69 (m, 3H); 3.27 (m, 1H); 2.88 (m, 2H); 2.76 (m, 2H); 2.56 (m, 2H); 2.29 (m, 2H); 2.13 (m, 1H); 1.96 (m, 1H); 1.81 (s, 3H); 1.25 (m, 3H); 1.02 (s, 21H); 0.85 (s, 9H); 0.03 (m, 6H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 204.1; 201.4; 168.6; 164.4; 162.3; 149.9; 132.8; 130.9; 129.7; 129.6; 128.2; 125.5; 111.2; 82.9; 82.6; 81.9; 74.4; 73.8; 67.9; 67.1; 65.3; 62.4; 56.2; 55.8; 52.6; 47.7; 47.6; 45.2; 44.9; 42.8; 39.0; 38.8; 33.7; 33.5; 30.3; 29.7; 27.9; 25.7; 18.0; 17.9; 14.0; 11.9; -4.5; -4.8

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{44}H_{67}BrO_{10}Si_2$: 890.3456; found: 890.3447

(*6S,E*)-2-bromo-4-((tert-butyldimethylsilyl)oxy)-9-((4-methoxybenzyl)oxy)-6-methylnon-2-en-7-yne-1,6-diol (**424**)



Tertiary benzoate **297** (530 mg, 0.9 mmol, 1.0 eq.) was dissolved in anhydrous CH_2Cl_2 (8 mL) and the solution was cooled to -78 °C. A solution of DIBAL-H (1.5M in toluene; 2.35 mL, 3.52 mmol, 4.4 eq.) was added dropwise and the reaction mixture was allowed to stir at -78°c for two hours.

The reaction was quenched by the addition of sat. aq. K/Na-tartrate and it was allowed to warm to r.t. under vigorous stirring. The phases were separated and the aqueous phase was extracted twice with CH_2Cl_2. The combined organic layers were dried with brine and $MgSO_4$ and the solvent was removed under reduced pressure. Purification by silica gel chromatography (hexane/EtOAc = 3/1) yielded pure primary allylic alcohol **424** (480 mg, 0.78 mmol, 97%) as colorless oil.

Major:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.28 (d, *J* = 8.8Hz, 2H); 6.89 (d, *J* = 8.8Hz, 2H); 6.18 (d, *J* = 9.1Hz, 1H); 4.93 (m, 1H); 4.70 (d, *J* = 5.6Hz, 2H); 4.52 (s, 2H); 4.27 (m, 1H); 4.18 (s, 2H); 3.81 (s, 3H); 2.01 (m, 2H); 1.67 (m, 1H); 1.54 (s, 3H); 0.88 (s, 9H); 0.10 (s, 3H); 0.08 (s, 3H)

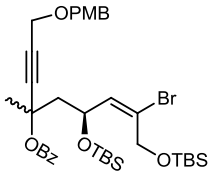
HRMS (ESI) (m/z): $[M+Na]^+$ calcd. for $C_{24}H_{37}BrO_5SiNa$: 535.1491; found: 535.1482

Minor:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.28 (d, *J* = 8.8Hz, 2H); 6.89 (d, *J* = 8.8Hz, 2H); 6.02 (d, *J* = 9.1Hz, 1H); 5.19 (m, 1H); 4.70 (d, *J* = 5.6Hz, 2H); 4.52 (s, 2H); 4.27 (m, 1H); 4.19 (d, *J* = 1.3Hz, 2H); 3.81 (s, 3H); 2.01 (m, 2H); 1.67 (m, 1H); 1.49 (s, 3H); 0.90 (s, 9H); 0.17 (s, 3H); 0.11 (s, 3H)

HRMS (ESI) (m/z): $[M+Na]^+$ calcd. for $C_{24}H_{37}BrO_5SiNa$: 535.1491; found: 535.1485

(*6S,E*)-8-bromo-6,9-bis((tert-butyldimethylsilyl)oxy)-1-((4-methoxybenzyl)oxy)-4-methylnon-7-en-2-yn-4-yl benzoate (**303**)



Primary alcohol **424** (480 mg, 0.78 mmol, 1.0 eq.) was dissolved in anhydrous DMF (5 mL) and imidazole (132 mg, 1.94 mmol, 2.5 eq.) was added in one portion. Under Ar-atmosphere, the mixture was cooled to 0 °C and a solution ofs TBS-Cl (129 mg, 0.85 mmol, 1.1 eq.) in anhydrous DMF (3 mL) was slowly added at 0 °C. The reaction mixture was allowed to warm to r.t. and stirring was continued for two hours. 10 mL of hexane/Et_2O (1/1) and 10 mL of saturated aqueous NH_4Cl were added and the phases separated. The organic phase was extracted with water twice.

The combined aqueous phases were twice back-extracted with a 1/1 mixture of hexane/Et_2O and the combined organic layers were dried over $MgSO_4$. Evaporation of the solvent yielded the desired silylether (557 mg, 0.76 mmol, 89%) as colorless oil.

The previously prepared tertiary alcohol (780 mg, 1.06 mmol, 1.0 eq.) was dissolved in anhydrous THF (10 mL) and NEt_3 (446 µL, 3.2 mmol, 3 eq.) and benzoic acid anhydride (482 mg, 2.13 mmol, 2 eq.) were added at r.t. The reaction mixture was cooled to 0 °C and $MgBr_2 \cdot OEt_2$ (551 mg, 2.13 mmol, 2 eq.) was added portionwise. The solution was allowed to warm to r.t. within 30 minutes. Water and Et_2O were added and the phases were separated. The organic phase was washed with water and the combined aqueous phases were back-extracted with Et_2O. The combined organic layers were dried with $MgSO_4$ and the solvent was removed under reduced pressure. Purification by silica gel chromatography (hexane/EtOAc = 5/1) yielded tertiary benzoate **303** (645 mg, 0.88 mmol, 83%) as colorless oil.

Major:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.02 (m, 2H); 7.56 (m, 1H); 7.44 (m, 2H); 7.28 (d, *J* = 8.7Hz, 2H); 6.85 (d, *J* = 8.7Hz, 2H); 6.05 (d, *J* = 9.1Hz, 1H); 4.93 (ddd, *J* = 9.1, 6.2, 6.2Hz, 1H); 4.55 (s, 2H); 4.19 (s, 2H); 4.04 (m, 2H); 3.80 (s, 3H); 2.38 (m, 2H); 1.89 (s, 3H); 0.88 (s, 9H); 0.85 (s, 9H); 0.09 (s, 3H); 0.07 (s, 3H); 0.02 (s, 3H); 0.00 (s, 3H)

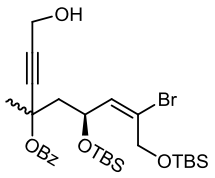
HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{37}H_{55}BrO_6Si_2$: 730.2721; found: 730.2711

Minor:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.02 (m, 2H); 7.56 (m, 1H); 7.44 (m, 2H); 7.28 (d, *J* = 8.7Hz, 2H); 6.85 (d, *J* = 8.7Hz, 2H); 6.00 (d, *J* = 9.2Hz, 1H); 4.80 (m, 1H); 4.54 (s, 2H); 4.19 (s, 2H); 4.04 (m, 2H); 3.80 (s, 3H); 2.23 (m, 2H); 1.88 (s, 3H); 0.86 (s, 9H); 0.83 (s, 9H); 0.10 (s, 3H); 0.04 (s, 3H); 0.03 (s, 3H); -0.04 (s, 3H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{37}H_{55}BrO_6Si_2$: 730.2721; found: 730.2713

(*6S,E*)-8-bromo-6,9-bis((tert-butyldimethylsilyl)oxy)-1-hydroxy-4-methylnon-7-en-2-yn-4-yl benzoate (**425**)



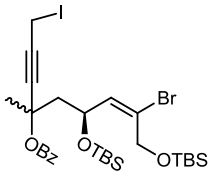
To a solution of benzoate **303** (640 mg, 0.87 mmol, 1.0 eq.) in CH_2Cl_2 (4 mL) were added 2 mL of a pH=7-buffer (50mM KH_2PO_4). The vigorously stirred suspension was cooled to 0 °C and DDQ (298 mg, 1.31 mmol, 1.5 eq.) was added portionwise. The suspension was allowed to stir for 2 days while it warmed to r.t. After addition of sat. aq. $NaHCO_3$, the phases were separated and the organic phase was washed 6 times with H_2O. The organic phase was dried with brine and $MgSO_4$, and removal of the solvent *in vacuo* gave crude propargylic alcohol. Purification by silica gel chromatography (hexane/EtOAc = 3/1) gave alcohol **425** in quantitative yield (530 mg, 0.87 mmol, quant.).

Major:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.01 (m, 2H); 7.55 (m, 1H); 7.42 (m, 2H); 6.05 (d, *J* = 9.0Hz, 1H); 4.92 (m, 1H); 4.19 (bs, 2H); 4.04 (m, 2H); 2.38 (m, 2H); 1.89 (s, 3H); 0.88 (s, 9H); 0.85 (s, 9H); 0.09 (s, 3H); 0.07 (s, 3H); 0.02 (s, 3H); 0.00 (s, 3H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{29}H_{47}BrO_5Si_2Na$: 633.2043; found: 633.2037

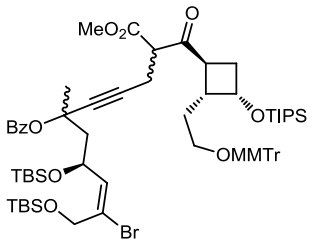
(*6S,E*)-8-bromo-6,9-bis((tert-butyldimethylsilyl)oxy)-1-iodo-4-methylnon-7-en-2-yn-4-yl benzoate (**304**)



Imidazole (179 mg, 2.62 mmol, 3 eq.), PPh_3 (459 mg, 1.75 mmol, 2 eq.) and iodine (444 mg, 1.75 mmol, 2 eq.) were added to 6 mL anhydrous CH_2Cl_2 and cooled to 0 °C. The suspension was stirred at 0 °C for 20 minutes while it turned yellow. To this suspension a solution of propargylic benzoate **425** (530 mg, 0.87 mmol, 1.0 eq.) in anhydrous CH_2Cl_2 (3 mL) was added rapidly. The reaction mixture was stirred for one hour. Then it was quenched by the addition of 60 mL hexane. The precipitating triphenylphosphineoxide was filtered through a pad of celite and a sat. aq. solution of $Na_2S_2O_3$ and $NaHCO_3$ was added to the filtrate. The phases were separated and the organic phase was washed with $Na_2S_2O_3$, $NaHCO_3$ and brine before it was dried with $MgSO_4$. After removal of the solvent under reduced pressure, purification by silica gel chromatography (hexane/EtOAc = 5/1) yielded propargylic iodide **304** (628 mg, 0.87 mmol, quant.) as slightly yellow liquid.

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{29}H_{46}BrIO_4Si_2$: 720.1163; found: 720.1158

(*4S,E*)-2-bromo-1,4-bis((tert-butyldimethylsilyl)oxy)-11-methoxy-10-((*1S,2R,3S*)-2-(2-((4-methoxyphenyl)diphenylmethoxy)ethyl)-3-((triisopropylsilyl)oxy)cyclobutanecarbonyl)-6-methyl-11-oxoundec-2-en-7-yn-6-yl benzoate (**294**)



NaH (60% in mineral oil, 34.8 mg, 0.87 mmol, 1.0 eq.) was suspended in anhydrous THF (3 mL). The reaction mixture was cooled to 0 °C and a solution of β-keto ester **195** (561 mg, 0.87 mmol, 1.0 eq.) in anhydrous THF (3 mL) was added. The reaction was stirred at 0 °C for 20 minutes and then warmed to r.t. within 10 minutes.

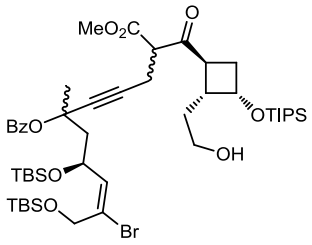
Then it was re-cooled to 0 °C and a solution of propargylic iodide **304** (628 mg, 0.87 mmol, 1.0 eq.) was added uninterruptedly at 0 °C. The reaction mixture was stirred at this temperature for 20 minutes and then warmed to r.t. within 20 minutes before it was quenched with saturated aqueous NH_4Cl. Et_2O was added and the phases separated. The pH of the aqueous phase was adjusted to 6 with 0.5M $KHSO_4$ and it was extracted twice with Et_2O. The combined organic layers were dried with $MgSO_4$ and the solvent was removed under reduced pressure. Silica gel column chromatography (hexane/EtOAc = 5/1 to 3/1) yielded alkylated β-keto ester **294** as slightly yellow oil (740 mg, 0.6 mmol, 69%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.96 (m, 2H); 7.52 (m, 1H); 7.40 (m, 6H); 7.26 (m, 6H); 7.19 (m, 2H); 6.80 (m, 2H); 6.00 (m, 1H); 4.83 (m, 1H); 4.53 (m, 1H); 4.39 (m, 1H); 4.03 (m, 1H); 3.78 (s, 3H); 3.54 (m, 4H); 3.13 (m, 3H); 2.81 (m, 2H); 2.65 (m, 1H); 2.44 (m, 1H); 2.27 (m, 1H); 2.13 (m, 3H); 1.75 (m, 4H); 0.97 (s, 21H); 0.88 (m, 18H); 0.05 (m, 12H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 204.1; 168.6; 164.3; 158.4; 144.8; 137.3; 136.0; 132.8; 130.8; 130.3; 129.6; 128.4; 128.3; 127.7; 126.7; 125.7; 113.0; 86.1; 82.7; 74.5; 67.4; 66.7; 65.5; 63.2; 61.7; 55.1; 52.4; 48.9; 46.0; 42.1; 33.8; 29.1; 27.9; 25.8; 17.9; 12.0; -4.2; -4.8

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{68}H_{97}BrO_{10}Si_3$: 1236.5573; found: 1236.5568

(*4S,E*)-2-bromo-1,4-bis((tert-butyldimethylsilyl)oxy)-10-((*1S,2R,3S*)-2-(2-hydroxyethyl)-3-((trisopropylsilyl)oxy)cyclobutanecarbonyl)-11-methoxy-6-methyl-11-oxoundec-2-en-7-yn-6-yl benzoate (**426**)



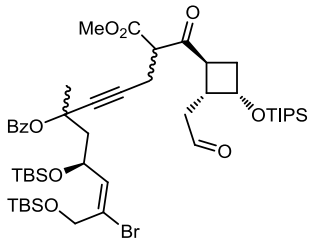
Vinyl bromide **294** (160 mg, 0.13 mmol, 1.0 eq.) was dissolved in 6.6 mL of a 10/1 mixture CH_2Cl_2/MeOH. PPTS (3.3 mg, 13 µmol, 0.1 eq.) was added and the reaction mixture was allowed to stir at r.t. until TLC analysis indicated full consumption of the starting material (approx. two hours). The reaction mixture was quenched with saturated aqueous $NaHCO_3$. The phases were separated and the aqueous layer was extracted two times with Et_2O. The combined organic layers were dried with $MgSO_4$ and the solvent was removed under reduced pressure. Purification by silica gel chromatography (hexane/EtOAc = 4/1) yielded free primary alcohol **426** as colorless viscous oil (90 mg, 93 µmol, 72%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.97 (m, 2H); 7.54 (m, 1H); 7.42 (m, 2H); 6.03 (m, 1H); 4.86 (m, 1H); 4.46 (m, 2H); 4.07 (m, 1H); 3.87 (m, 1H); 3.72 (m, 3H); 3.69 (m, 3H); 3.28 (m, 1H); 2.87 (m, 1H); 2.77 (m, 2H); 2.52 (m, 2H); 2.27 (m, 1H); 2.16 (m, 2H); 2.02 (m, 1H); 1.78 (m, 3H); 1.04 (m, 21H); 0.87 (m, 18H); 0.05 (m, 12H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 204.1; 168.5; 164.3; 137.6; 133.0; 129.7; 129.6; 128.4; 125.6; 115.9; 86.1; 82.6; 67.4; 66.0; 60.7; 55.7; 52.7; 49.3; 46.0; 42.4; 33.4; 31.3; 25.8; 17.9; 12.0; -4.2; -5.4

HRMS (ESI) (m/z): $[M+Na]^+$ calcd. for $C_{48}H_{81}BrO_9Si_3Na$: 987.4269; found: 987.4262

(*4S,E*)-2-bromo-1,4-bis((tert-butyldimethylsilyl)oxy)-11-methoxy-6-methyl-11-oxo-10-((*1S,2R,3S*)-2-(2-oxoethyl)-3-((triisopropylsilyl)oxy)cyclobutanecarbonyl)undec-2-en-7-yn-6-yl benzoate (**305**)



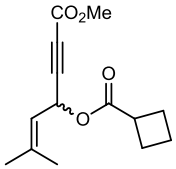
Primary alcohol **426** (80 mg, 83 µmol, 1.0 eq.) was dissolved in anhydrous DMSO (2 mL) and IBX (35 mg, 124 µmol, 1.5 eq.) was added. The reaction mixtures was stirred at r.t. for two hours or until all starting material was consumed. Now 2 mL of hexane and 2 mL of EtOAc were added and the suspension was filtered through a pad of celite 545 coarse. The filtrate was transferred to a separatory funnel and water was added. The phases were separated and the organic phase was washed twice with fresh water. The combined aqueous layers were back-extracted twice with EtOAc. The combined organic layers were dried with brine and $MgSO_4$ and the solvents were removed *in vacuo*. Aldehyde **305** (80 mg, 83 µmol, quant.) was obtained as colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.79 (m, 1H); 7.97 (m, 2H); 7.54 (m, 1H); 7.42 (m, 2H); 6.02 (dd, *J* = 9.1, 5.2Hz, 1H); 4.86 (m, 1H); 4.51 (m, 2H); 4.06 (m, 1H); 3.89 (m, 1H); 3.70 (m, 3H); 3.20 (m, 2H); 2.83 (m, 3H); 2.66 (m, 1H); 2.53 (m, 1H); 2.28 (m, 1H); 2.14 (m, 2H); 1.78 (m, 3H); 1.02 (s, 21H); 0.87 (m, 18H); 0.05 (m, 12H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{48}H_{79}BrO_9Si_3$: 962.4215; found: 962.4212

4.2.10 Northern Lactone-Butenolide Approach (*c*Bu)

7-methoxy-2-methyl-7-oxohept-2-en-5-yn-4-yl cyclobutanecarboxylate (**309**)



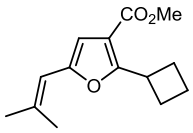
Methyl propiolate (1.9 mL, 22 mmol, 1.1 eq.) was dissolved in anhydrous THF (70 mL) and the reaction mixture was cooled to -78 °C. LiHMDS (1M in THF, 22 mL, 22 mmol, 1.1 eq.) was added dropwise and the solution was allowed to stir for 30 minutes. A solution of 3-methylbut-2-enal (1.68 g, 20 mmol, 1.0 eq.) in anhydrous THF (10 mL) was added dropwise. The reaction mixture was allowed to stir for 30 minutes until it was quenched by the addition of sat. aq. NH_4Cl. The phases were separated and the aqueous phase was carefully acidified and extracted twice with Et_2O. The combined organic phases were dried with $MgSO_4$ and the solvents were removed under reduced pressure. The resulting allylic alcohol **308** (3.44 g, 20 mmol, quant.) was of satisfying purity for further conversion.

Allylic alcohol **308** (3.44 g, 20 mmol, 1.0 eq.), cyclobutane carboxylic acid (2.08 mL, 22 mmol, 1.1 eq.) and DMAP (489 mg, 4 mmol, 0.2 eq.) were dissolved in anhydrous CH_2Cl_2 (80 mL) in an Ar-atmosphere. DIC (3.4 mL, 22 mmol, 1.1 eq.) was added to the reaction mixture and the solution was allowed to stir at r.t. overnight. The reaction mixture was quenched by the addition of sat. aq. $NaHCO_3$ and the phases were separated. The organic phase was extracted two more times with $NaHCO_3$ and the combined organic layers were dried with brine and $MgSO_4$. The solvent was removed under reduced pressure and the crude reaction mixture was purified by silica gel chromatography (hexane/EtOAc = 5/1) yielding pure ester **309** (4.6 g, 18.4 mmol, 92%) as colorless oil.

^{1}H-NMR (250 MHz, $CDCl_3$): δ = 6.13 (d, *J* = 8.9Hz, 1H); 5.30 (m, 1H); 3.77 (s, 3H); 3.15 (m, 1H); 2.24 (m, 4H); 1.96 (m, 2H); 1.77 (s, 3H); 1.76 (s, 3H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{14}H_{18}O_4$: 250.1205; found: 250.1194

Methyl-2-cyclobutyl-5-(2-methylprop-1-en-1-yl)furan-3-carboxylate (**310**)

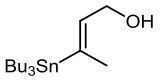


A solution of propargylic ester **309** (100 mg, 0.4 mmol, 1.0 eq.) in EtOAc (5 mL) was degassed with Ar for 3 minutes prior to use. Tri-*n*butyl phosphine (120 µL, 0.48 µL, 1.2 eq.) was added to the solution of substrate. The reaction vessel was sealed, heated to 110 °C, and allowed to stir for two hours. The reaction mixture was removed *in vacuo* onto silica gel and subjected to purification by flash chromatography (hexane/EtOAc = 1/0 – 50/1 – 20/1 – 10/1) to yield furan **310** (58 mg, 0.25 mmol, 62%).

^{1}H-NMR (250 MHz, $CDCl_3$): δ = 6.36 (s, 1H); 6.02 (bs, 1H); 4.21 (m, 1H); 3.79 (s, 3H); 2.32 (m, 6H); 2.00 (s, 3H); 1.91 (s, 3H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{14}H_{18}O_3$: 234.1256; found: 234.1250

(*E*)-3-(tributylstannyl)but-2-en-1-ol (**427**)



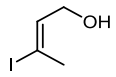
The preparation of 427 was performed according to Betzer *et al*.[111] Hexabutylditin (Bu_6Sn_2; 37.6 g, 65 mmol, 7.6 eq.) was dissolved in anhydrous THF (50 mL) and the solution was cooled to -78 °C before n-BuLi (2.5M in hexane; 26 mL, 65 mmol, 7.6 eq.) was added dropwise. The reaction mixture was allowed to stir at -40 °C for 30 and then transferred *via* a cannula to a -78 °C pre cooled suspension of dry CuCN (2.9 g, 32.4 mmol, 3.8 eq.) in anhydrous THF (50 mL). The suspension was stirred at -40 °C until it turned yellow (approx. 30 min). 21 mL of anhydrous MeOH were added and the reaction mixture was stirred at -10 °C for 30 minutes when it turned red. The reaction mixture was re-cooled to -78 °C and a solution of but-2-yn-1-ol (600 mg, 8.5 mmol, 1.0 eq.) in anhydrous THF (21 mL) was added dropwise. The solution was allowed to warm to -10 °C and stirred at this temperature overnight. 21 mL of anhydrous MeOH were added at -20 °C and the reaction mixture was stirred for another 15 minutes before 21 mL of H_2O were added.

After 15 minutes Et_2O was added and the phases were separated. The organic phase was extracted twice with NH_4Cl and the combined aqueous phases were back-extracted once with Et_2O. The combined organic layers were dried with brine and $MgSO_4$ and the solvent was removed under reduced pressure. Purification by silica gel chromatography (hexane/EtOAc = 7/1) yielded vinyl-stannane **427** (2.92 g, 8.1 mmol, 95%) as colorless liquid.

^{1}H-NMR (250 MHz, $CDCl_3$): δ = 5.75 (m, 1H); 4.26 (dd, *J* = 5.6, 5.6Hz, 2H); 1.89 (t, *J* = 22.1Hz, 3H); 1.48 (m, 6H); 1.31 (m, 8H); 0.89 (t, *J* = 7.1Hz, 14H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{16}H_{34}OSn$: 362.1632; found: 362.1621

(*E*)-3-iodobut-2-en-1-ol (**315**)

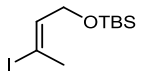


Iodine (786 mg, 2.77 mmol, 2 eq.) and Na_2CO_3 (294 mg, 2.77 mmol. 2 eq.) were suspended in anhydrous CH_2Cl_2 (6 mL) and cooled to 0 °C. A solution of vinyl-stannane **427** (2.92 g, 8.1 mmol, 1.0 eq.) in anhydrous CH_2Cl_2 (4 mL) was added dropwise over a period of 20 minutes. After stirring for one hour the reaction was quenched by the addition of sat. aq. $Na_2S_2O_3$ solution. The phases were separated and the aqueous layer was extracted three times with Et_2O. The combined organic layers were dried with $MgSO_4$ and the solvent was removed *in vacuo*. Silica gel chromatography (hexane/EtOAc = 1/0 to 4/1) yielded pure vinyliodide **315** (250 mg, 1.27 mmol, 92%) as colorless oil.

^{1}H-NMR (250 MHz, $CDCl_3$): δ = 6.40 (m, 1H); 4.09 (d, *J* = 6.2, 6.2Hz, 2H); 2.45 (s, 3H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for C_4H_7IO: 197.9542; found: 197.9537

(*E*)-tert-butyl((3-iodobut-2-en-1-yl)oxy)dimethylsilane (**428**)

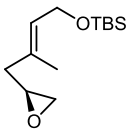


Vinyl iodide **315** (2.5 g, 12.6 mmol, 1.0 eq.) was dissolved in anhydrous CH_2Cl_2 (100 mL). Pyridine (5.11 mL, 63 mmol, 5 eq.) and DMAP (154 mg, 1.3 mmol, 0.1 eq.) were added to the solution and it was cooled to 0 °C. A solution of TBS-Cl (2.28 g, 15.1 mmol, 1.2 eq.) in anhydrous CH_2Cl_2 (20 mL) was added. The reaction mixture was allowed to stir at 0 °C for one hour, and then it was quenched by the addition of sat. aq. NH_4Cl. The phases were separated and the organic layer was washed with NH_4Cl. The organic layer was dried with brine and $MgSO_4$. Purification by silica gel chromatography (hexane/EtOAc = 10/1) yielded pure silyl ether **428** (3.7 g, 11.8 mmol, 94%) as colorless liquid.

^{1}H-NMR (250MHz, $CDCl_3$): δ = 6.30 (t, *J* = 6.5Hz, 1H); 4.12 (d, *J* = 6.5Hz, 1H); 2.41 (s, 3H); 0.89 (s, 9H); 0.07 (s, 6H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{10}H_{21}IOSi$: 312.0406; found: 312.0394

(*S,E*)-tert-butyldimethyl((3-methyl-4-(oxiran-2-yl)but-2-en-1-yl)oxy)silane (**314**)



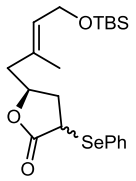
TBS-protected vinyl iodide **428** (312 mg, 1.0 mmol, 1.0 eq.) was dissolved in anhydrous Et_2O (5 mL) and the solution was cooled to -78 °C. t-BuLi (1.6M in pentane; 1.3 mL, 2.1 mmol, 2.1 eq.) was added dropwise. After completion of the addition stirring was continued for 30 minutes. Freshly prepared 2-thienyl-Cu(CN)Li (0.5M in THF; 2 mL, 1.0 mmol, 1.0 eq.) was added *via* cannula to the reaction mixture.[112] The solution turned yellow and stirring was continued for one hour at -78 °C. A solution of tosylated (*R*)-glycidol **393** (274 mg, 1.2 mmol, 1.2 eq.) in 3 mL anhydrous Et_2O was added dropwise. Stirring was continued at -78 °C for two hours and then at r.t. for one hour (the solution turned dark). The reaction mixture was quenched by the addition of a 3/1 mixture of sat. aq. NH_4Cl/25% aq. NH_4OH. The phases were separated and the organic layer was extracted twice with NH_4Cl before it was dried with brine and $MgSO_4$. Removal of the solvent under reduced pressure and purification by silica gel chromatography (hexane/EtOAc = 10/1) yielded pure epoxide **314** (120 mg, 0.5 mmol, 50%) as colorless oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 5.44 (ddd, *J* = 6.3, 6.3, 1.3Hz, 1H); 4.22 (dd, *J* = 6.3, 1.0Hz, 2H); 3.00 (m, 1H); 2.77 (m, 1H); 2.49 (dd, *J* = 2.3, 2.3Hz, 1H); 2.22 (m, 1H); 1.71 (s, 3H); 0.91 (s, 9H); 0.08 (s, 6H)

^{13}C-NMR (100MHz, $CDCl_3$): δ = 133.1; 126.9; 60.1; 51.2; 46.8; 42.4; 26.0; 18.4; 17.0; -5.1

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{13}H_{26}O_2Si$: 242.1702; found: 242.1698

(*5S*)-5-((*E*)-4-((tert-butyldimethylsilyl)oxy)-2-methylbut-2-en-1-yl)-3-(phenylselanyl)dihydrofuran-2(3H)-one (**313**)



DIPA (220 µL, 1.58 mmol, 3.15 eq.) was mixed with anhydrous THF (5 mL) and the mixture was cooled to -10 °C when n-BuLi (2.5M in hexane; 600 µL, 1.5 mmol, 3 eq.) was added. The mixture was allowed to stir at -10 °C for 30 minutes. Then, a solution of phenylselanyl acetic acid (**397**, 269 mg, 1.25 mmol, 2.5 eq.) in anhydrous THF (5 mL) was added. The reaction mixture was stirred at -10 °C for 20 min, then the cooling bath was removed and it was allowed to stir at r.t for 90 minutes (formation of dianion, precipitating). The suspension of the dianion was cooled to -78 °C and a solution of epoxide **314** (120 mg, 0.5 mmol, 1.0 eq.) was added dropwise to the dianion. The reaction mixture was allowed to warm to r.t. slowly overnight. The reaction was quenched by the addition of NH_4Cl and water. Et_2O was added and the phases were separated. The aqueous phase was extracted twice with Et_2O and the combined organic layers were dried with $MgSO_4$. The solvent was removed under reduced pressure. The crude product was of sufficient purity for further conversion.

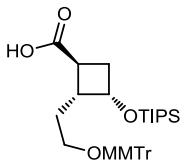
The crude product was dissolved in anhydrous CH_2Cl_2 (50 mL) and DMAP (6.1 mg, 0.05 mmol, 0.1 eq.) was added. The reaction was cooled to 0 °C and DIC (85.2 µL, 0.55 mmol, 1.1 eq.) was added. The reaction mixture was stirred at 0 °C for 90 minutes. The solvent was removed under reduced pressure und the crude product was purified using silica gel chromatography (hexane/EtOAc = 7/1). Selenolactone **313** was obtained as orange oil (195 mg, 0.45 mmol, 89%) as an inconsequential mixture of diastereo isomers.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 7.66 (m, 2H); 7.34 (m, 3H); 5.30 (dd, *J* = 6.2, 1.1Hz, 1H); 4.52 (m, 1H); 4.15 (d, *J* = 6.1Hz, 2H); 4.00 (dd, *J* = 9.6, 9.6Hz, 1H); 2.70 (m, 1H); 2.33 (m, 1H); 2.09 (m, 1H); 1.97 (m, 1H); 1.60 (s, 3H); 0.90 (s, 9H); 0.06 (s, 6H)

^{13}C-NMR (100MHz, $CDCl_3$): δ = 175.6; 135.7; 131.2; 129.4; 128.9; 128.7; 127.0; 77.6; 59.9; 45.1; 37.3; 36.9; 35.5; 26.0; 18.4; 16.8; -5.1

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{21}H_{32}O_3SeSi$: 440.1286; found: 440.1272

(*1S,2R,3S*)-2-(2-((4-methoxyphenyl)diphenylmethoxy)ethyl)-3-((triisopropylsilyl)oxy)cyclobutanecarboxylic acid (**318**)

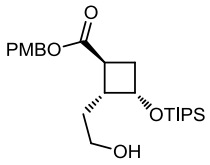


Aldehyde **194** (2 g, 3.5 mmol, 1.0 eq.) was dissolved in t-BuOH (22 mL) and 3.5 mL of 2-methyl-but-2-ene was added. The reaction mixture was cooled to 0 °C and an aqueous solution (13 mL) of $NaClO_2$ (4.74 g, 52.4 mmol, 15 eq.) and $NaH_2PO_4.H_2O$ (4.74 g, 34.4 mmol, 9.8 eq.) was added at once. The reaction mixture was stirred at 0 °C for one hour and Et_2O and water were added. The phases were separated and the organic layer was washed twice with water before it was dried with $MgSO_4$. Removal of the solvent under reduced pressure yielded pure carboxylic acid **318** (2 g, 3.5 mmol, quant.) as colorless oil.

^{1}H-NMR (250MHz, $CDCl_3$): δ = 7.44 (m, 4H); 7.27 (m, 8H); 6.84 (d, *J* = 8.8Hz, 2H); 5.25 (bs, 1H); 4.54 (m, 1H); 3.80 (s, 3H); 3.78 (m, 1H); 2.97 (m, 1H); 2.82 (m, 1H); 2.59 (m, 1H); 2.20 (m, 1H); 1.92 (m, 2H); 1.29 (m, 1H); 1.05 (s, 21H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{36}H_{48}O_5Si$: 588.3271; found: 588.3264

(*1S,2R,3S*)-4-methoxybenzyl 2-(2-hydroxyethyl)-3-((triisopropylsilyl)oxy)cyclobutanecarboxylate (**429a**)



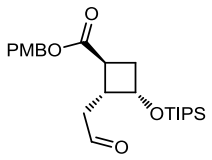
Carboxylic acid **318** (225 mg, 0.38 mmol, 1.0 eq.) and PMB-OH (106 mg, 0.76 mmol, 2 eq.) were dissolved in anhydrous CH_2Cl_2 (600 mL) and DMAP (4.6 mg, 38 µmol, 0.1 eq.) was added. The reaction was cooled to 0 °C and DIC (89 µL, 0.57 mmol, 1.5 eq.) was added. The reaction mixture was stirred at 0 °C for 90 minutes. The solvent was removed under reduced pressure und the crude product was purified using silica gel chromatography (hexane/EtOAc = 7/1). The PMB-ester was obtained as slightly yellow oil (264 mg, 0.37 mmol, 98%).

The previously prepared PMB-ester (264 mg, 0.37 mmol, 1.0 eq.) was dissolved in 5 mL of a 4/1 mixture CH_2Cl_2/MeOH. PPTS (9.3 mg, 37 µmol, 0.1 eq.) was added and the reaction mixture was allowed to stir at r.t. until TLC analysis indicated full consumption of the starting material (approx. one hour). The reaction mixture was quenched with saturated aqueous $NaHCO_3$. The phases were separated and the aqueous layer was extracted two times with Et_2O. The combined organic layers were dried with $MgSO_4$ and the solvent was removed under reduced pressure. Purification by silica gel chromatography (hexane/EtOAc = 4/1) yielded free alcohol **429a** as colorless viscous oil (153 mg, 0.35 mmol, 95%).

^{1}H-NMR (250MHz, $CDCl_3$): δ = 7.28 (d, *J* = 8.5Hz, 2H); 6.89 (d, *J* = 8.5Hz, 2H); 5.06 (s, 2H); 4.54 (m, 1H); 3.81 (s, 3H); 3.67 (m, 2H); 2.91 (m, 1H); 2.79 (m, 1H); 2.48 (m, 1H); 2.18 (m, 1H); 1.87 (m, 3H); 1.03 (s, 21H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{24}H_{40}O_5Si$: 436.2645; found: 436.2629

(*1S,2R,3S*)-4-methoxybenzyl 2-(2-oxoethyl)-3-((triisopropylsilyl)oxy)cyclobutanecarboxylate (**319a**)

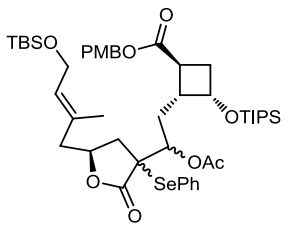


Primary alcohol **429a** (153 mg, 0.35 mmol, 1.0 eq.) was dissolved in anhydrous EtOAc (4 mL) and IBX (196 mg, 0.70 mmol, 2 eq.) was added. The reaction mixtures was refluxed for two hours or until all starting material was consumed. Now hexane (4 mL) was added and the suspension was filtered through a pad of celite 545 coarse. Removal of the solvents gave aldehyde **319a** (g, 0.35 mmol, quant.) as colorless oil.

^{1}H-NMR (250MHz, $CDCl_3$): δ = 9.80 (t, *J* = 1.8Hz, 1H); 7.28 (d, *J* = 8.5Hz, 2H); 6.89 (d, *J* = 8.5Hz, 2H); 5.06 (s, 2H); 4.54 (m, 1H); 3.81 (s, 3H); 2.89 (m, 1H); 2.59 (m, 1H); 2.50 (m, 1H); 2.32 (m, 2H); 2.25 (m, 1H); 1.04 (s, 21H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{24}H_{38}O_5Si$: 434.2489; found: 434.2489

(*1S,2R,3S*)-4-methoxybenzyl 2-(2-acetoxy-2-((5S)-5-((*E*)-4-((tert-butyldimethylsilyl)oxy)-2-methylbut-2-en-1-yl)-2-oxo-3-(phenylselanyl)tetrahydrofuran-3-yl)ethyl)-3-((triisopropylsilyl)oxy)cyclobutanecarboxylate (**430**)



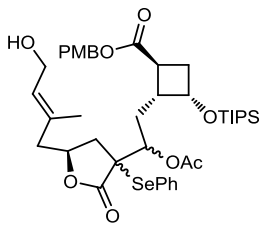
DIPA (21.7 µL, 0.16 mmol, 1.3 eq.) was dissolved in anhydrous THF (1 mL) and the mixture was cooled to -10 °C when n-BuLi (1.6M in hexane; 90 µL, 0.14 mmol, 1.2 eq.) was added. The mixture was allowed to stir at -10 °C for 30 min, before it was cooled to -78 °C. Then, a solution of selenolactone **313** (106 mg, 0.24 mmol, 2 eq.) in anhydrous THF (1 mL) was added dropwise. Upon completion, the reaction mixture was allowed to stir for 30 minutes. A solution of aldehyde **319a** (52.2 mg, 0.12 mmol, 1.0 eq.) in anhydrous THF (1 mL) was added and the reaction mixture was stirred for one hour. The reaction was quenched by the addition of sat. aq. NH_4Cl. After addition of Et_2O, phases were separated and the aqueous phase was neutralized by the addition of 0.5M $KHSO_4$. The aqueous layer was extracted twice with Et_2O and the combined organic phases were dried with $MgSO_4$. Purification by silica gel chromatography (hexane/EtOAc = 5/1) yielded the aldol product as colorless viscous oil (81.8 mg, 94 µmol, 78%).

The aldol product (81 mg, 94 µmol, 1.0 eq.) was dissolved in anhydrous CH_2Cl_2 (2 mL) and DIPEA (15 µL, 0.1 mmol, 1.1eq) and DMAP (1.1 mg, 9,4 µmol, 0.1 eq.) were added. The reaction mixture was cooled to 0 °C and Ac_2O (9.3 µL, 99 µmol, 1.05 eq.) was added. The solution was allowed to stir at 0 °C for 45 min, and then it was quenched by the addition of sat. aq. NH_4Cl. Phases were separated and the aqueous phase was extracted twice with CH_2Cl_2. The combined organic layers were dried with $MgSO_4$ and the solvent was removed under reduced pressure. Purification by silica gel chromatography yielded acetate **430** (83 mg, 91 µmol, 96%).

^{1}H-NMR (250MHz, $CDCl_3$): δ = 7.71 (m, 2H); 7.29 (m, 4H); 6.88 (d, *J* = 8.6Hz, 2H); 5.31 (m, 2H); 5.01 (m, 2H); 4.55 (m, 1H); 4.18 (d, *J* = 6.2Hz, 2H); 3.81 (s, 3H); 2.79 (m, 1H); 2.58 (m, 2H); 2.41 (m, 3H); 2.18 (m, 3H); 1.94 (m, 2H); 1.90 (s, 3H); 1.67 (m, 1H); 1.62 (s, 3H); 1.05 (s, 21H); 0.91 (s, 9H); 0.08 (s, 6H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{47}H_{72}O_9SeSi_2$: 916.3880; found: 916.3869

(*1S,2R,3S*)-4-methoxybenzyl 2-(2-acetoxy-2-((*5S*)-5-((*E*)-4-hydroxy-2-methylbut-2-en-1-yl)-2-oxo-3-(phenylselanyl)tetrahydrofuran-3-yl)ethyl)-3-((triisopropylsilyl)oxy)cyclobutanecarboxylate (**431**)

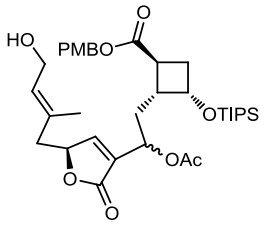


Compound **430** (83 mg, 90 µmol, 1.0 eq.) was dissolved in anhydrous THF (1 mL) and the reaction mixture was cooled to 0 °C. 7% HF in pyridine (53 µL, 0.18 mmol, 2 eq.) was added dropwise and the reaction mixture was allowed to stir for 15 minutes. The reaction was quenched by the careful addition of sat. aq. $NaHCO_3$. The phases were separated and the organic layer was extracted twice with $NaHCO_3$. The combined organic layers were back-extracted twice with CH_2Cl_2 and the combined organic layers were dried with brine and $MgSO_4$. After removal of the solvent under reduced pressure silica gel chromatography (hexane/EtOAc = 4/1) yielded pure allylic alcohol **431** (55 mg, 68 µmol, 76%) as colorless oil.

^{1}H-NMR (250MHz, $CDCl_3$): δ = 7.67 (m, 2H); 7.34 (m, 4H); 6.88 (d, *J* = 8.6Hz, 2H); 5.34 (m, 1H); 5.25 (m, 1H); 5.03 (m, 2H); 4.57 (m, 1H); 4.36 (m, 1H); 4.14 (m, 2H); 3.81 (s, 3H); 2.78 (m, 1H); 2.59 (m, 2H); 2.41 (m, 3H); 2.18 (m, 3H); 2.00 (m, 2H); 1.94 (s, 3H); 1.67 (m, 1H); 1.68, 1.57 (s, 3H); 1.04 (m, 21H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{41}H_{58}O_9SeSi$: 802.3015; found: 802.3002

(*1S,2R,3S*)-4-methoxybenzyl 2-(2-acetoxy-2-((*S*)-5-((*E*)-4-hydroxy-2-methylbut-2-en-1-yl)-2-oxo-2,5-dihydrofuran-3-yl)ethyl)-3-((triisopropylsilyl)oxy)cyclobutanecarboxylate (**432**)



Compound **431** (50 mg, 62 µmol, 1.0 eq.) was dissolved in CH_2Cl_2 (2 mL) and sat. aq. NH_4Cl (500 µL) was added. The biphasic mixture was cooled to 0 °C and 30% H_2O_2 (19.2 µL, 0.19 mmol, 3 eq.) was added. The reaction was stirred at 0 °C for one hour and then quenched by the addition of sat. aq. $Na_2S_2O_3$. Phases were separated and the organic phase was extracted 4 times with water. The organic layer was dried with $MgSO_4$ and the solvent was removed under reduced pressure. After silica gel chromatography (hexane/EtOAc = 2/1 to 1/1) butenolide **432** was obtained as colorless oil (40 mg, 62 µmol, quant.) as an inseparable mixture of diastereo isomers.

Major:

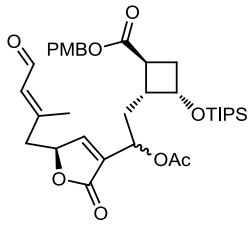
^{1}H-NMR (250MHz, $CDCl_3$): δ = 7.28 (d, *J* = 8.0Hz, 2H); 6.98 (s, 1H); 6.88 (d, *J* = 8.0Hz, 2H); 5.56 (m, 2H); 5.02 (m, 2H); 4.55 (m, 1H); 4.14 (m, 2H); 3.80 (s, 3H); 2.79 (m, 2H); 2.28 (m, 6H); 2.00 (s, 3H); 1.85 (m, 1H); 1.67 (s, 3H); 1.02 (s, 21H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{35}H_{52}O_9Si$: 644.3381; found: 644.3372

Minor:

^{1}H-NMR (250MHz, $CDCl_3$): δ = 7.28 (d, *J* = 8.0Hz, 2H); 7.11 (s, 1H); 6.88 (d, *J* = 8.0Hz, 2H); 5.42 (m, 2H); 4.93 (m, 2H); 4.55 (m, 1H); 4.14 (m, 2H); 3.80 (s, 3H); 2.79 (m, 2H); 2.28 (m, 6H); 1.98 (s, 3H); 1.85 (m, 1H); 1.70 (s, 3H); 1.02 (s, 21H)

(*1S,2R,3S*)-4-methoxybenzyl 2-(2-acetoxy-2-((*S*)-5-((*E*)-2-methyl-4-oxobut-2-en-1-yl)-2-oxo-2,5-dihydrofuran-3-yl)ethyl)-3-((triisopropylsilyl)oxy)cyclobutanecarboxylate (**433**)



Allylic alcohol **432** (40 mg, 62 µmol, 1.0 eq.) was dissolved in anhydrous EtOAc (2 mL) and IBX (52 mg, 0.19 mmol, 3 eq.) was added. The reaction mixtures was refluxed for two hours or until all starting material was consumed. Now hexane (2 mL) was added and the suspension was filtered through a pad of celite 545 coarse. Removal of the solvents gave aldehyde **433** (40 mg, 62 µmol, quant.) as colorless oil.

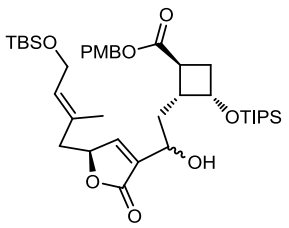
Major & minor:

^{1}H-NMR (400MHz, $CDCl_3$): δ = 10.0, **9.98** (d, *J* = 7.6Hz, 1H); 7.30 (d, *J* = 8.0Hz, 2H); 7.08, **7.01** (s, 1H); 6.90 (d, *J* = 8.0Hz, 2H); 5.95, **5.88** (d, *J* = 7.8Hz, 1H); 5.60 (m, 1H); 4.99 (m, 1H); 4.56 (m, 1H); 3.80 (s, 3H); 2.92, **2.78** (m, 1H); 2.69 (m, 1H); 2.46 (m, 3H); 2.31 (m, 1H); 2.23, **2.19** (s, 3H); 2.09 (m, 1H); 1.99 (s, 3H); 1.67 (m, 3H); 1.02 (s, 21H)

^{13}C-NMR (100MHz, $CDCl_3$): δ = 190.5; 175.1; 170.0; 169.8; 169.7; 159.7; 156.1; 156.0; 149.1; 148.8; 134.2; 133.8; 130.1; 129.9; 129.8; 128.1; 114.0; 113.9; 78.7; 68.0; 67.3; 66.6; 66.4; 66.2; 55.3; 43.6; 42.1; 41.1; 39.3; 39.1; 34.6; 34.5; 31.1; 30.9; 29.7; 24.7; 20.8; 20.7; 18.1; 17.9; 12.0

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{35}H_{50}O_9Si$: 642.3224; found: 642.3213

(*1S,2R,3S*)-4-methoxybenzyl 2-(2-((*S*)-5-((*E*)-4-((tert-butyldimethylsilyl)oxy)-2-methylbut-2-en-1-yl)-2-oxo-2,5-dihydrofuran-3-yl)-2-hydroxyethyl)-3-((triisopropylsilyl)oxy)cyclobutanecarboxylate (**320a**)



DIPA (0.21 mL, 1.60 mmol, 1.3 eq.) was dissolved in anhydrous THF (10 mL) and the mixture was cooled to -10 °C when n-BuLi (1.6M in hexane; 0.90 mL, 1.40 mmol, 1.2 eq.) was added. The mixture was allowed to stir at -10 °C for 30 min, before it was cooled to -78 °C. Then, a solution of selenolactone **313** (1.06 g, 2.40 mmol, 2 eq.) in anhydrous THF (10 mL) was added dropwise. Upon completion, the reaction mixture was allowed to stir for 30 minutes. A solution of aldehyde **319a** (522 mg, 1.2 mmol, 1.0 eq.) in anhydrous THF (10 mL) was added and the reaction mixture was stirred for one hour. The reaction was quenched by the addition of sat. aq. NH_4Cl. After addition of Et_2O, phases were separated and the aqueous phase was neutralized by the addition of 0.5M $KHSO_4$. The aqueous layer was extracted twice with Et_2O and the combined organic phases were dried with $MgSO_4$. The solvent was removed under reduced pressure to yield seleno ether as slightly orange oil (860 mg, 0.98 mmol, 82%).

Previously prepared seleno ether (500 mg, 0.57 mmol, 1.0 eq.) was dissolved in CH_2Cl_2 (6 mL) and sat. aq. NH_4Cl (1 mL) was added. The biphasic mixture was cooled to 0 °C and 30% H_2O_2 (177 µL, 1.72 mmol, 3 eq.) was added. The reaction was stirred at 0 °C for one hour and then quenched by the addition of sat. aq. $Na_2S_2O_3$. Phases were separated and the organic phase was extracted 4 times with water. The organic layer was dried with $MgSO_4$ and the solvent was removed under reduced pressure. After silica gel chromatography (hexane/EtOAc = 2/1) butenolide **320a** was obtained as colorless oil (402 mg, 0.56 mmol, 98%) as a separable mixture of diastereo isomers.

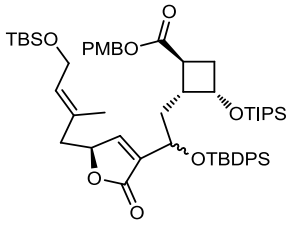
Major:

^{1}H-NMR (400MHz, $CDCl_3$): δ = 7.29 (d, *J* = 8.5Hz, 2H); 7.24 (s, 1H); 6.89 (d, *J* = 8.5Hz, 2H); 5.43 (t, *J* = 6.2Hz, 1H); 5.06 (s, 2H); 5.92 (m, 1H); 4.59 (m, 1H); 4.46 (m, 1H); 4.20 (d, *J* = 6.2Hz, 2H); 3.87 (m, 1H); 3.81 (s, 3H); 2.90 (m, 2H); 2.50 (m, 1H); 2.36 (m, 2H); 2.21 (m, 2H); 1.92 (m, 1H); 1.70 (s, 3H); 1.05 (s, 21H); 0.90 (s, 9H); 0.07 (s, 6H)

^{13}C-NMR (100MHz, $CDCl_3$): δ = 175.6; 172.0; 159.7; 148.3; 137.4; 130.9; 130.1; 130.0; 129.1; 127.9; 114.0; 80.3; 66.8; 66.5; 65.9; 65.7; 60.4; 60.0; 55.3; 43.3; 43.2; 39.2; 38.9; 35.1; 34.2; 26.0; 18.4; 17.9; 17.8; 17.0; 14.2; 12.1; -5.1

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{39}H_{64}O_8Si_2$: 716.4140; found: 716.4134

(*1S,2R,3S*)-4-methoxybenzyl 2-(2-((*S*)-5-((*E*)-4-((tert-butyldimethylsilyl)oxy)-2-methylbut-2-en-1-yl)-2-oxo-2,5-dihydrofuran-3-yl)-2-(tert-butyldiphenylsilyl)ethyl)-3-((triisopropylsilyl)oxy)cyclobutanecarboxylate (**433a**)

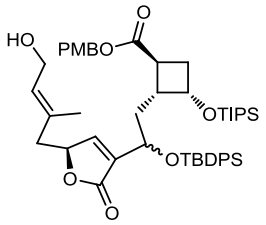


Secondary allylic alcohol **320a** (125 mg, 0.17 mmol, 1.0 eq.) was dissolved in anhydrous DMF (2 mL) and imidazole (35.5 mg, 0.52 mmol, 3 eq.) was added in one portion. Under Ar-atmosphere, the mixture was cooled to 0 °C and TBDPS-Cl (54.2 µL, 0.21 mmol, 1.2 eq.) was slowly added at 0 °C. The reaction mixture was allowed to warm to r.t. overnight and stirring was continued for 2 days. 4 mL of hexane/Et_2O (1/1) and 4 mL of saturated aqueous NH_4Cl were added and the phases were separated. The organic phase was extracted with water twice. The combined aqueous phases were twice back-extracted with a 1/1 mixture of hexane/Et_2O and the combined organic layers were dried over $MgSO_4$. Evaporation of the solvent yielded silylether **433a** (155 mg, 0.16 mmol, 93%) as colorless oil, which was purified by silica gel column chromatography (hexane/EtOAc = 5/1).

^{1}H-NMR (400MHz, $CDCl_3$): δ = 7.58 (m, 4H); 7.38 (m, 6H); 7.32 (d, *J* = 8.5Hz, 2H); 7.25 (s, 1H); 6.87 (d, *J* = 8.5Hz, 2H); 5.35 (t, *J* = 6.2Hz, 1H); 5.00 (m, 2H); 4.77 (m, 1H); 4.57 (m, 1H); 4.48 (m, 1H); 4.18 (d, *J* = 6.2Hz, 2H); 3.81 (s, 3H); 2.95 (m, 1H); 2.78 (m, 1H); 2.38 (m, 1H); 2.33 (m, 1H); 2.26 (m, 1H); 2.17 (m, 1H); 2.04 (m, 2H); 1.63 (s, 3H); 1.06 (s, 9H); 1.00 (s, 21H); 0.91 (s, 9H); 0.08 (s, 6H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{55}H_{82}O_8Si_3$: 954.5317; found: 954.5302

(*1S,2R,3S*)-4-methoxybenzyl 2-(2-(tert-butyldiphenylsilyl)-2-((*S*)-5-((*E*)-4-hydroxy-2-methylbut-2-en-1-yl)-2-oxo-2,5-dihydrofuran-3-yl)ethyl)-3-((triisopropylsilyl)oxy)cyclobutanecarboxylate (**321a**)

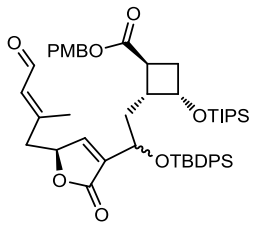


Compound **433a** (180 mg, 0.19 mmol, 1.0 eq.) was dissolved in anhydrous THF (3 mL) and the reaction mixture was cooled to 0 °C. 7%HF in pyridine (96 µL, 0.37 mmol, 2 eq.) was added dropwise and the reaction mixture was allowed to stir for 15 minutes. The reaction was quenched by the careful addition of sat. aq. $NaHCO_3$. The phases were separated and the organic layer was extracted twice with $NaHCO_3$. The combined organic layers were back-extracted twice with CH_2Cl_2 and the combined organic layers were dried with brine and $MgSO_4$. After removal of the solvent under reduced pressure silica gel chromatography (hexane/EtOAc = 4/1) yielded pure allylic alcohol **321a** (106 mg, 0.13 mmol, 67%) as colorless oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 7.58 (m, 4H); 7.38 (m, 6H); 7.25 (d, *J* = 8.5Hz, 2H); 6.94 (m, 1H); 6.87 (d, *J* = 8.5Hz, 2H); 5.41 (m, 1H); 5.03 (m, 2H); 4.83 (m, 1H); 4.62 (m, 1H); 4.52 (m, 2H); 4.16 (m, 2H); 3.80 (s, 3H); 3.04 (m, 1H); 2.76 (m, 1H); 2.35 (m, 1H); 2.15 (m, 2H); 2.05 (m, 1H); 1.89 (m, 2H); 1.66 (s, 3H); 1.05 (s, 9H); 0.99 (s, 21H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{49}H_{68}O_8Si_2$: 840.4453; found: 840.4447

(*1S,2R,3S*)-4-methoxybenzyl 2-(2-(tert-butyldiphenylsilyl)-2-((*S*)-5-((*E*)-2-methyl-4-oxobut-2-en-1-yl)-2-oxo-2,5-dihydrofuran-3-yl)ethyl)-3-((triisopropylsilyl)oxy)cyclobutanecarboxylate (**434a**)



Primary alcohol **321a** (66 mg, 78 µmol, 1.0 eq.) was dissolved in anhydrous EtOAc (2 mL) and IBX (65.9 mg, 0.24 mmol, 3 eq.) was added. The suspension was heated to reflux for three hours. The suspension was cooled to r.t. and hexane (2 mL) was added. The suspension was filtered through a pad of celite and the solvents were removed under reduced pressure. The crude product was purified by silica gel column chromatography (hexane/EtOAc = 5/1). Aldehyde **434a** was obtained as viscous oil (66 mg, 78 µmol, quant.).

Major:

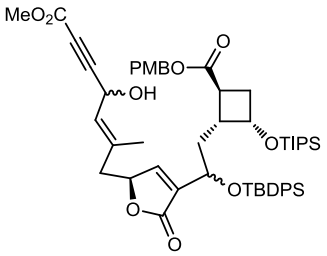
^{1}H-NMR (400MHz, $CDCl_3$): δ = 9.97 (d, *J* = 7.5Hz, 1H); 7.58 (m, 4H); 7.38 (m, 6H); 7.24 (d, *J* = 8.5Hz, 2H); 6.87 (d, *J* = 8.5Hz, 2H); 6.84 (m, 1H); 5.86 (dd, *J* = 7.8, 1.0Hz, 1H); 5.03 (m, 2H); 4.78 (m, 1H); 4.53 (m, 2H); 3.80 (s, 3H); 2.99 (m, 1H); 2.72 (m, 1H); 2.40 (m, 1H); 2.29 (m, 2H); 2.15 (d, *J* = 1.3Hz, 3H); 2.03 (m, 3H); 1.06 (s, 9H); 0.99 (s, 21H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{49}H_{66}O_8Si_2$: 838.4296; found: 838.4287

Minor:

^{1}H-NMR (400MHz, $CDCl_3$): δ = 9.96 (d, *J* = 7.5Hz, 1H); 7.58 (m, 4H); 7.38 (m, 6H); 7.24 (d, *J* = 8.5Hz, 2H); 6.87 (d, *J* = 8.5Hz, 2H); 6.84 (m, 1H); 5.80 (dd, *J* = 7.8, 1.0Hz, 1H); 5.03 (m, 2H); 4.68 (m, 1H); 4.53 (m, 2H); 3.79 (s, 3H); 2.99 (m, 1H); 2.81 (m, 1H); 2.40 (m, 1H); 2.29 (m, 2H); 2.13 (d, *J* = 1.3Hz, 3H); 2.03 (m, 3H); 1.06 (s, 9H); 0.99 (s, 21H)

(*1S,2R,3S*)-4-methoxybenzyl 2-(2-((tert-butyldiphenylsilyl)oxy)-2-((*5S*)-5-((*E*)-4-hydroxy-7-methoxy-2-methyl-7-oxohept-2-en-5-yn-1-yl)-2-oxo-2,5-dihydrofuran-3-yl)ethyl)-3-((triisopropylsilyl)oxy)cyclobutanecarboxylate (**312a**)



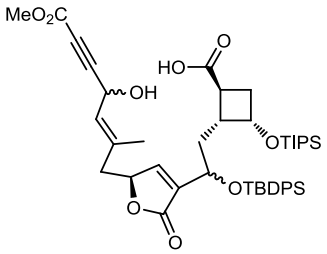
Methyl propiolate (7.2 µL, 80 µmol, 1.5 eq.) was dissolved in anhydrous THF (300 µL) and the reaction mixture was cooled to -78 °C. LiHMDS (1M in THF, 80 µL, 80 µmol, 1.5 eq.) was added dropwise and the solution was allowed to stir for 30 minutes. A solution of aldehyde **434a** (45 mg, 54 µmol, 1.0 eq.) in anhydrous THF (1 mL) was added dropwise. The reaction mixture was allowed to stir for 30 minutes until it was quenched by the addition of sat. aq. NH_4Cl. The phases were separated and the aqueous phases was carefully acidified and extracted twice with Et_2O. The combined organic phases were dried with $MgSO_4$ and the solvents were removed under reduced pressure. The resulting allylic alcohol **312a** (48 mg, 52 µmol, 98%) was of satisfying purity for further conversion.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 7.57 (m, 4H); 7.36 (m, 6H); 7.25 (m, 2H); 7.05 (s, 1H); 6.87 (m, 2H); 5.41 (m, 1H); 5.13 (m, 2H); 4.94 (m, 2H); 4.54 (m, 2H); 3.81 (s, 3H); 3.77 (m, 3H); 3.10 (m, 1H); 2.75 (m, 1H); 2.35 (m, 2H); 2.18 (m, 1H); 2.03 (m, 2H); 1.77, 1.70 (s, 3H); 1.63 (m, 1H); 1.06 (s, 9H); 0.99 (s, 21H)

^{13}C-NMR (100MHz, $CDCl_3$): δ = 176.4; 170.8; 159.6; 150.7; 150.2; 149.4; 137.0; 136.3; 136.1; 135.9; 135.8; 135.7; 133.5; 133.1; 132.8; 130.0; 129.9; 129.8; 128.6; 128.0; 127.7; 127.0; 126.9; 114.0; 87.3; 87.0; 79.7; 79.5; 79.0; 75.7; 68.4; 68.3; 66.5; 66.4; 66.3; 66.2; 58.7; 58.6; 58.5; 55.3; 52.7; 43.7; 42.4; 42.2; 41.0; 40.0; 39.3; 38.9; 38.6; 38.4; 35.6; 35.5; 34.7; 34.1; 32.9; 32.7; 29.7; 19.0; 17.9; 17.4; 17.1; 16.9; 11.9

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{53}H_{70}O_{10}Si_2$: 922.4508; found: 922.4492

(*1S,2R,3S*)-2-(2-((tert-butyldiphenylsilyl)oxy)-2-((*5S*)-5-((*E*)-4-hydroxy-7-methoxy-2-methyl-7-oxohept-2-en-5-yn-1-yl)-2-oxo-2,5-dihydrofuran-3-yl)ethyl)-3-((triisopropylsilyl)oxy)cyclobutanecarboxylic acid (**322a**)



Propargylic alcohol **312a** (8 mg, 8.7 µmol, 1.0 eq.) was dissolved in anhydrous CH_2Cl_2 (100 µL) and the solution was cooled to 0 °C. TFA (10 µL, 0.13 mmol, 15 eq.) was added dropwise and the reaction mixture was allowed to stir at 0 °C for 5 hours. The reaction was quenched by the addition of sat. aq. $NaHCO_3$ and the phases were separated. The organic layer was washed two times with $NaHCO_3$ and afterwards dried with $MgSO_4$. The solvent was removed under reduced pressure. Purification by silica gel chromatography yielded *seco* acid **322a** (6 mg, 7.6 µmol, 88%) as colorless semi-solid.

Major:

^{1}H-NMR (600MHz, $CDCl_3$): δ = 7.63 (m, 2H); 7.58 (m, 2H); 7.44 (m, 1H); 7.39 (m, 3H); 7.32 (m, 2H); 7.20 (t, *J* = 1.5Hz, 1H); 5.47 (d, *J* = 8.5Hz, 1H); 5.20 (d, *J* = 8.7Hz, 1H); 4.95 (m, 1H); 4.68 (m, 1H); 4.54 (m, 1H); 3.79 (s, 3H); 3.31 (m, 1H); 2.61 (m, 1H); 2.51 (m, 1H); 2.43 (m, 1H); 2.24 (m, 2H); 2.12 (m, 2H); 1.97 (m, 2H); 1.79 (d, *J* = 1.1Hz, 3H); 1.10 (s, 9H); 0.99 (m, 21H)

^{13}C-NMR (150MHz, $CDCl_3$): δ = 179.6; 170.4; 160.0; 151.1; 135.8; 135.5; 130.1; 127.8; 127.7; 126.8; 109.7; 90.1; 86.5; 79.5; 78.9; 75.8; 68.8; 66.6; 58.6; 53.0; 41.5; 38.5; 34.4; 27.0; 19.1; 17.9; 11.9

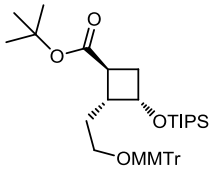
HRMS (ESI) (m/z): $[M+Na]^+$ calcd. for $C_{45}H_{62}O_9Si_2Na$: 825.3830; found: 825.3817

Minor:

^{1}H-NMR (600MHz, $CDCl_3$): δ = 7.63 (m, 2H); 7.58 (m, 2H); 7.44 (m, 1H); 7.39 (m, 3H); 7.32 (m, 2H); 7.10 (t, *J* = 1.5Hz, 1H); 5.47 (d, *J* = 8.5Hz, 1H); 5.16 (d, *J* = 8.0Hz, 1H); 4.90 (m, 1H); 4.64 (m, 1H); 4.54 (m, 1H); 3.79 (s, 3H); 3.18 (m, 1H); 2.68 (m, 1H); 2.61 (m, 1H); 2.51 (m, 1H); 2.24 (m, 2H); 2.12 (m, 2H); 1.97 (m, 2H);); 1.74 (d, *J* = 1.5Hz, 3H); 1.10 (s, 9H); 0.99 (m, 21H)

^{13}C-NMR (150MHz, $CDCl_3$): δ = 179.6; 170.4; 160.0; 151.1; 135.8; 135.5; 130.0; 127.8; 127.7; 126.8; 109.7; 90.1; 86.5; 79.5; 78.9; 75.8; 68.8; 66.5; 58.6; 52.9; 41.1; 38.5; 34.4; 27.0; 19.1; 17.9; 11.9

(*1S,2R,3S*)-tert-butyl 2-(2-((4-methoxyphenyl)diphenylmethoxy)ethyl)-3-((triisopropylsilyl)oxy)cyclobutanecarboxylate (**316b**)

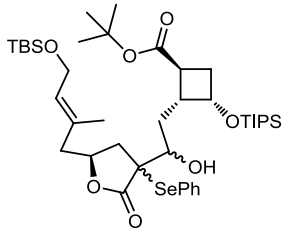


Carboxylic acid **318** (500 mg, 0.85 mmol, 1.0 eq.) was dissolved in anhydrous benzene (4 mL). NEt_3 (131 µL, 0.94 mmol, 1.1 eq.) and DMAP (208 mg, 1.7 mmol, 2 eq.) were added to the solution. Now, 2,4,6-trichlorbenzoyl chloride (133 µL, 0.85 mmol, 1.0 eq.) was added and the reaction mixture was allowed to stir for one hour. A solution of anhydrous t-BuOH (162 µL, 1.7 mmol, 2 eq.) in anhydrous CH_2Cl_2 (4 mL) was added dropwise. After completion of the addition stirring was continued for two hours. The reaction was quenched by the addition of sat. aq. NH_4Cl. Phases were separated and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were dried with $MgSO_4$ and the solvent was removed *in vacuo*. Purification by silica gel chromatography yielded pure t-butyl ester **316b** (548 mg, 0.85 mmol, quant.) as colorless oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 7.43 (m, 4H); 7.28 (m, 6H); 7.21 (m, 2H); 6.81 (m, 2H); 4.50 (m, 1H); 3.79 (s, 3H); 3.11 (m, 2H); 2.65 (m, 2H); 2.40 (m, 1H); 2.10 (m, 2H); 1.79 (m, 1H); 1.38 (s, 9H); 0.98 (s, 21H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{40}H_{56}O_5Si$: 644.3897; found: 644.3879

(*1S,2R,3S*)-tert-butyl 2-(2-((*5S*)-5-((*E*)-4-((tert-butyldimethylsilyl)oxy)-2-methylbut-2-en-1-yl)-2-oxo-3-(phenylselanyl)tetrahydrofuran-3-yl)-2-hydroxyethyl)-3-((triisopropylsilyl)oxy)cyclobutanecarboxylate (**435b**)

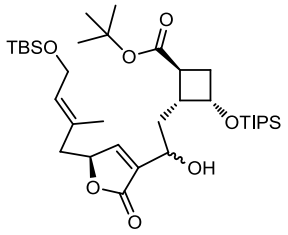


tert-Butyl ester **316b** (548 mg, 0.85 mmol, 1.0 eq.) was dissolved in 10 mL of a 4/1 mixture CH_2Cl_2/MeOH. PPTS (22 mg, 85 µmol, 0.1 eq.) was added and the reaction mixture was allowed to stir at r.t. until TLC analysis indicated full consumption of the starting material (approx. 1.5h). The reaction mixture was quenched with saturated aqueous $NaHCO_3$. The phases were separated and the aqueous layer was extracted two times with CH_2Cl_2. The combined organic layers were dried with $MgSO_4$ and the solvent was removed under reduced pressure. Purification by silica gel chromatography (hexane/EtOAc = 5/1) yielded the free primary alcohol as colorless viscous oil (272 mg, 0.73 mmol, 86%). The previously prepared primary alcohol (320 mg, 0.86 mmol, 1.0 eq.) was dissolved in anhydrous EtOAc (9 mL) and IBX (722 mg, 2.58 mmol, 3 eq.) was added. The suspension was heated to reflux for three hours. Now the suspension was cooled to r.t. and 9 mL of hexane were added. The suspension was filtered through a pad of celite and the solvents were removed under reduced pressure. The crude product (318 mg, 0.86 mmol, quant.) was used without further purification.

DIPA (146 µL, 1.03 mmol, 1.2 eq.) was dissolved in anhydrous THF (3 mL) and the mixture was cooled to -10 °C when n-BuLi (1.6M in hexane; 591 µL, 0.95 mmol, 1.1 eq.) was added. The mixture was allowed to stir at -10 °C for 30 min, before it was cooled to -78 °C. Then, a solution of selenolactone **313** (399 mg, 0.91 mmol, 1.05 eq.) in anhydrous THF (4 mL) was added dropwise. Upon completion, the reaction mixture was allowed to stir for 30 minutes. A solution of the previously prepared aldehyde (320 mg, 0.86 mmol, 1.0 eq.) in anhydrous THF (3 mL) was added and the reaction mixture was stirred for one hour. The reaction was quenched by the addition of sat. aq. NH_4Cl. After addition of Et_2O, phases were separated and the aqueous phase was neutralized by the addition of 0.5M $KHSO_4$. The aqueous layer was extracted twice with Et_2O and the combined organic phases were dried with $MgSO_4$. Purification by silica gel chromatography (hexane/EtOAc = 5/1) yielded **435b** as colorless viscous oil (697 mg, 0.86 mmol, quant.).

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{41}H_{70}O_7SeSi_2$: 810.3825; found: 810.3814

(*1S,2R,3S*)-tert-butyl 2-(2-((*S*)-5-((*E*)-4-((tert-butyldimethylsilyl)oxy)-2-methylbut-2-en-1-yl)-2-oxo-2,5-dihydrofuran-3-yl)-2-hydroxyethyl)-3-((triisopropylsilyl)oxy)cyclobutanecarboxylate (**320b**)



tert-Butyl ester **435b** (360 mg, 0.44 mmol, 1.0 eq.) was dissolved in CH_2Cl_2 (25 mL) and sat. aq. NH_4Cl (4 mL) was added. The biphasic mixture was cooled to 0 °C and 30% H_2O_2 (137 µL, 1.33 mmol, 3 eq.) was added. The reaction was stirred at 0 °C for one hour and then quenched by the addition of sat. aq. $Na_2S_2O_3$. The phases were separated and the organic phase was extracted 4 times with water. The organic layer was dried with $MgSO_4$ and the solvent was removed under reduced pressure. After silica gel chromatography (hexane/EtOAc = 4/1) butenolide **320b** was obtained as colorless oil (242 mg, 0.37 mmol, 83%) as a separable mixture of diastereo isomers.

Major:

^{1}H-NMR (400MHz, $CDCl_3$): δ = 7.27 (t, *J* = 1.5Hz, 1H); 5.45 (t, *J* = 6.0Hz, 1H); 5.04 (t, *J* = 6.3Hz, 1H); 4.61 (m, 1H); 4.55 (m, 1H); 4.25 (m, 1H); 4.10 (d, *J* = 6.0Hz, 2H); 2.88 (m, 1H); 2.73 (m, 1H); 2.38 (m, 4H); 2.20 (m, 1H); 1.92 (m, 1H); 1.72 (s, 3H); 1.45 (s, 9H); 1.05 (s, 21H); 0.90 (s, 9H); 0.07 (s, 6H)

^{13}C-NMR (100MHz, $CDCl_3$): δ = 175.3; 172.0; 156.0; 148.6; 136.9; 131.1; 128.9; 127.8; 80.9; 80.4; 67.1; 66.1; 65.8; 60.0; 43.2; 42.9; 40.3; 34.4; 34.3; 28.0; 26.0; 18.4; 17.9; 17.0; 12.1; -5.1

HRMS (ESI) (m/z): $[M+Na]^+$ calcd. for $C_{35}H_{64}O_7Si_2Na$: 675.4088; found: 675.4082

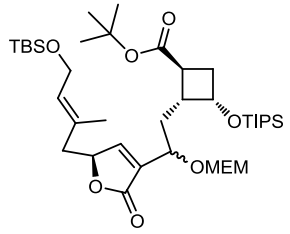
Minor:

^{1}H-NMR (400MHz, $CDCl_3$): δ = 7.29 (t, *J* = 1.5Hz, 1H); 5.44 (t, *J* = 6.1Hz, 1H); 5.13 (t, *J* = 6.9Hz, 1H); 4.59 (m, 1H); 4.48 (m, 1H); 4.20 (d, *J* = 6.1Hz, 2H); 4.18 (m, 1H); 2.79 (m, 1H); 2.41 (m, 3H); 2.21 (m, 1H); 1.89 (m, 1H); 1.71 (s, 3H); 1.57 (m, 1H); 1.45 (s, 9H); 1.05 (s, 21H); 0.90 (s, 9H); 0.07 (s, 6H)

^{13}C-NMR (100MHz, $CDCl_3$): δ = 175.3; 172.0; 156.0; 148.3; 137.6; 130.9; 130.7; 129.3; 129.1; 121.7; 82.1; 80.9; 80.3; 66.8; 65.8; 60.0; 43.3; 43.1; 40.3; 35.2; 34.3; 28.0; 26.0; 18.4; 17.9; 17.0; 12.1; -5.1

HRMS (ESI) (m/z): $[M+Na]^+$ calcd. for $C_{35}H_{64}O_7Si_2Na$: 675.4088; found: 675.4079

(*1S,2R,3S*)-tert-butyl 2-(2-((*S*)-5-((*E*)-4-((tert-butyldimethylsilyl)oxy)-2-methylbut-2-en-1-yl)-2-oxo-2,5-dihydrofuran-3-yl)-2-((2-methoxyethoxy)methoxy)ethyl)-3-((triisopropylsilyl)oxy)cyclobutanecarboxylate (**433b**)



Secondary allylic alcohol **320b** (400 mg, 0.61 mmol, 1.0 eq.) was dissolved in anhydrous CH_2Cl_2 (6 mL) and the solution was cooled to 0 °C. DIPEA (1.6 mL, 9.2 mmol, 15 eq.) was added and the reaction mixture was stirred for 15 minutes. A solution of MEM-Cl (700 µL, 6.1 mmol, 10 eq.) in anhydrous CH_2Cl_2 (2 mL) was added dropwise. The reaction mixture was allowed to warm to r.t. overnight, then it was quenched with sat. aq. NH_4Cl and the phases were separated. The aqueous phase was extracted twice with CH_2Cl_2 and the combined organic layers were dried with $MgSO_4$. The solvent was removed under reduced pressure. Purification by silica gel chromatography (hexane/EtOAc = 4/1) yielded pure compound **433b** (300 mg, 0.41 mmol, 66%) as colorless oil.

Major:

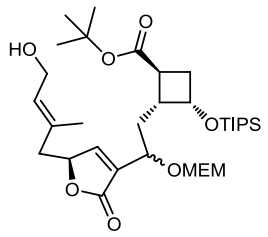
^{1}H-NMR (400MHz, $CDCl_3$): δ = 7.22 (m, 1H); 5.44 (m, 1H); 5.02 (m, 1H); 4.72 (s, 2H); 4.55 (m, 2H); 4.20 (m, 2H); 3.56 (m, 1H); 3.67 (m, 2H); 3.50 (m, 2H); 3.37 (s, 3H); 2.70 (m, 2H); 2.38 (m, 3H); 2.19 (m, 2H); 2.02 (m, 1H); 1.71 (s, 3H); 1.43 (s, 9H); 1.03 (s, 21H); 0.90 (s, 9H); 0.07 (s, 6H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{39}H_{72}O_9Si_2$: 740.4715; found: 740.4703

Minor:

^{1}H-NMR (400MHz, $CDCl_3$): δ = 7.22 (m, 1H); 5.44 (m, 1H); 5.02 (m, 1H); 4.72 (s, 2H); 4.55 (m, 2H); 4.20 (m, 2H); 3.73 (m, 1H); 3.67 (m, 2H); 3.50 (m, 2H); 3.35 (s, 3H); 2.70 (m, 2H); 2.38 (m, 3H); 2.19 (m, 2H); 2.02 (m, 1H); 1.71 (s, 3H); 1.44 (s, 9H); 1.03 (s, 21H); 0.90 (s, 9H); 0.07 (s, 6H)

(*1S,2R,3S*)-tert-butyl-2-(2-((*S*)-5-((*E*)-4-hydroxy-2-methylbut-2-en-1-yl)-2-oxo-2,5-dihydrofuran-3-yl)-2-((2-methoxyethoxy)methoxy)ethyl)-3-((triisopropylsilyl)oxy)cyclobutanecarboxylate (**321b**)



Compound **433b** (300 mg, 0.41 mmol, 1.0 eq.) was dissolved in anhydrous THF (5 mL) and the reaction mixture was cooled to 0 °C. 7%HF in pyridine (1.6 mL, 6.15 mmol, 15 eq.) was added dropwise and the reaction mixture was allowed to stir overnight. The reaction was quenched by the careful addition of sat. aq. $NaHCO_3$. The phases were separated and the organic layer was extracted twice with $NaHCO_3$. The combined organic layers were back-extracted twice with CH_2Cl_2 and the combined organic layers were dried with brine and $MgSO_4$. After removal of the solvent under reduced pressure silica gel chromatography (hexane/EtOAc = 1/1) yielded pure allylic alcohol **321b** (255 mg, 0.41 mmol, quant.) as slightly yellow oil.

Major:

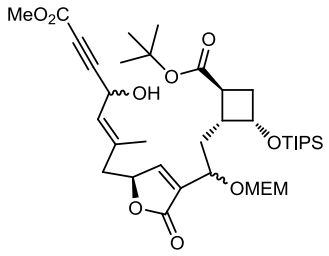
^{1}H-NMR (400MHz, $CDCl_3$): δ = 7.22 (t, *J* = 1.1Hz, 1H); 5.51 (t, *J* = 6.6Hz, 1H); 5.07 (m, 1H); 4.71 (m, 2H); 4.55 (m, 2H); 4.16 (d, *J* = 6.6Hz, 2H); 3.67 (m, 2H); 3.51 (m, 2H); 3.36 (s, 3H); 2.70 (m, 2H); 2.41 (m, 3H); 2.20 (m, 3H); 1.74 (s, 3H); 1.44 (s, 9H); 1.03 (s, 21H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{33}H_{58}O_9SiNa$: 649.3748; found: 649.3735

Minor:

^{1}H-NMR (400MHz, $CDCl_3$): δ = 7.27 (t, *J* = 1.1Hz, 1H); 5.56 (t, *J* = 6.6Hz, 1H); 5.07 (m, 1H); 4.71 (m, 2H); 4.55 (m, 2H); 4.18 (d, *J* = 6.6Hz, 2H); 3.67 (m, 2H); 3.51 (m, 2H); 3.37 (s, 3H); 2.70 (m, 2H); 2.41 (m, 3H); 2.00 (m, 3H); 1.74 (s, 3H); 1.43 (s, 9H); 1.03 (s, 21H)

(*1S,2R,3S*)-tert-butyl 2-(2-((*5S*)-5-((*E*)-4-hydroxy-7-methoxy-2-methyl-7-oxohept-2-en-5-yn-1-yl)-2-oxo-2,5-dihydrofuran-3-yl)-2-((2-methoxyethoxy)methoxy)ethyl)-3-((triisopropylsilyl)oxy)cyclobutanecarboxylate (**312b**)



Allylic alcohol **321b** (150 mg, 0.24 mmol, 1.0 eq.) was dissolved in anhydrous EtOAc (3 mL) and IBX (200 mg, 0.72 mmol, 3 eq.) was added. The reaction mixtures was refluxed for two hours or until all starting material was consumed. Hexane (3 mL) was added and the suspension was filtered through a pad of celite 545 coarse. Removal of the solvents gave crude aldehyde (150 mg, 0.24 mmol, quant.) as colorless oil.

Methyl propiolate (23.5 µL, 0.26 mmol, 1.1 eq.) was dissolved in anhydrous THF (2 mL) and the reaction mixture was cooled to -78 °C. LiHMDS (1M in THF, 0.26 mL, 0.26 mmol, 1.1 eq.) was added dropwise and the solution was allowed to stir for 30 minutes. A solution of the previously prepared aldehyde (150 mg, 0.24 mmol, 1.0 eq.) in anhydrous THF (2 mL) was added dropwise. The reaction mixture was allowed to stir for 30 minutes until it was quenched by the addition of sat. aq. NH_4Cl. The phases were separated and the aqueous phases was carefully acidified and extracted twice with Et_2O. The combined organic phases were dried with $MgSO_4$ and the solvents were removed under reduced pressure. The resulting allylic alcohol **312b** (168 mg, 0.24 mmol, 99%) was of satisfying purity for further conversion.

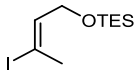
Major & minor:

^{1}H-NMR (400MHz, $CDCl_3$): δ = 7.20 (m, 1H); 5.45 (m, 1H); 5.17 (d, *J* = 8.0Hz, 1H); 5.03 (m, 1H); 4.72 (s, 2H); 4.56 (m, 2H); 3.77 (s, 3H); 3.67 (m, 2H); 3.51 (m, 2H); 3.37 (s, 3H); 2.72 (m, 1H); 2.62 (m, 1H); 2.35 (m, 3H); 2.21 (m, 2H); 2.02 (m, 2H); 1.80 (s, 3H); 1.43 (s, 9H); 1.03 (m, 21H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{37}H_{60}O_{11}SiNa$: 731.3803; found: 731.3794

4.2.11 Northern Lactone-Horner Wadsworth Emmons Approach (*c*Bu)

(*E*)-triethyl((3-iodobut-2-en-1-yl)oxy)silane (**436**)

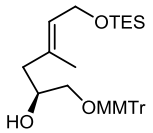


Vinyl iodide **315** (2.4 g, 12.2 mmol, 1.0 eq.) was dissolved in anhydrous CH_2Cl_2 (100 mL). Pyridine (4.95 mL, 61.0 mmol, 5 eq.) and DMAP (147 mg, 1.2 mmol, 0.1 eq.) were added to the solution and it was cooled to 0 °C. A solution of TES-Cl (5.12 mL, 30.5 mmol, 2.5 eq.) in anhydrous CH_2Cl_2 (20 mL) was added. The reaction mixture was allowed to stir at 0 °C for one hour, and then it was quenched by the addition of sat. aq. NH_4Cl. The phases were separated and the organic layer was washed with NH_4Cl. The organic layer was dried with brine and $MgSO_4$. Purification by silica gel chromatography (hexane/EtOAc = 10/1) yielded pure silyl ether **436** (3.35 g, 10.7 mmol, 88%) as colorless liquid.

^{1}H-NMR (250 MHz, $CDCl_3$): δ = 6.32 (t, *J* = 6.6Hz, 1H); 4.11 (d, *J* = 6.6Hz, 2H); 2.42 (s, 3H); 0.96 (t, *J* = 8.0Hz, 9H); 0.61 (q, *J* = 8.0Hz, 6H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{10}H_{21}IOSi$: 312.0406; found: 312.0397

(*S,E*)-1-((4-methoxyphenyl)diphenylmethoxy)-4-methyl-6-((triethylsilyl)oxy)hex-4-en-2-ol (**326**)



TES-protected vinyl iodide **436** (4.73 g, 15.15 mmol, 1.0 eq.) was dissolved in anhydrous Et_2O (100 mL) and the solution was cooled to -78 °C. t-BuLi (1.67M in pentane; 19 mL, 31.8 mmol, 2.1 eq.) was added dropwise. After completion of the addition stirring was continued for 30 minutes. Freshly prepared 2-thienyl-Cu(CN)Li (0.5M in THF; 36.4 mL, 18.18 mmol, 1.2 eq.) was added *via* cannula to the reaction mixture.[112] The solution turned yellow and stirring was continued for one hour at -78 °C. A solution of MMTr-protected (*R*)-glycidol **284** (6.3 g, 18.2 mmol, 1.2 eq.) in 20 mL anhydrous Et_2O was added dropwise. Stirring was continued at -78 °C for two hours and then at r.t. for one hour (the solution turned dark). The reaction mixture was quenched by the addition of a 3/1 mixture of sat. aq. NH_4Cl/25% aq. NH_4OH.

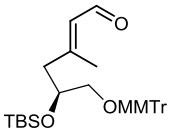
The phases were separated and the organic layer was extracted twice with NH_4Cl before it was dried with brine and $MgSO_4$. Removal of the solvent under reduced pressure and purification by silica gel chromatography (hexane/EtOAc = 10/1 to 5/1) yielded pure secondary alcohol **326** (5.5 g, 10.3 mmol, 68%) as slightly yellow, viscous oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 7.44 (d, *J* = 7.5Hz, 4H); 7.30 (m, 6H); 7.23 (m, 2H); 6.84 (d, *J* = 8.8Hz, 2H); 5.37 (dt, *J* = 6.3, 1.2Hz, 1H); 4.15 (d, *J* = 6.3Hz, 2H); 3.89 (m, 1H); 3.80 (s, 3H); 3.12 (m, 2H); 2.17 (m, 2H); 1.62 (s, 3H); 0.95 (t, *J* = 7.9Hz, 9H); 0.60 (q, *J* = 7.9Hz, 6H)

^{13}C-NMR (100MHz, $CDCl_3$): δ = 158.6; 144.4; 135.6; 133.6; 130.3; 129.2; 128.4; 127.9; 127.8; 127.5; 127.2; 126.9; 113.2; 86.4; 68.8; 67.4; 59.5; 55.2; 43.9; 16.4; 6.8; 4.5

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{33}H_{44}O_4Si$: 532.3009; found: 532.3000

(*S,E*)-5-((tert-butyldimethylsilyl)oxy)-6-((4-methoxyphenyl)diphenylmethoxy)-3-methylhex-2-enal (**437**)



Secondary alcohol **326** (1 g, 1.88 mmol, 1.0 eq.) was dissolved in anhydrous CH_2Cl_2 (20 mL) and 2,6-lutidine (1.1 mL, 9.4 mmol, 5 eq.) was added. The reaction mixture was cooled to 0 °C and TBS-OTf (603 µL, 2.6 mmol, 1.4 eq.) was added dropwise. The solution was allowed to stir for one hour. It was quenched by the addition of sat. aq. $NaHCO_3$ and the phases were separated. The aqueous phase was extracted twice with CH_2Cl_2 and the combined organic phases were washed with brine and dried with $MgSO_4$. After removal of the solvent under reduced pressure, purification by silica gel chromatography yielded pure tri-ether (1.21 g, 1.88 mmol, quant.) as slightly yellow viscous oil.

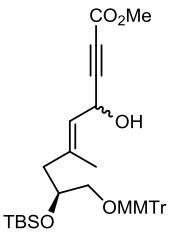
The previously prepared tri-ether (1.2 g, 1.86 mmol, 1.0 eq.) was dissolved in anhydrous THF (20 mL) and the reaction mixture was cooled to 0 °C. 7% HF in pyridine (1.08 mL, 3.7 mmol, 2 eq.) was added dropwise and the reaction mixture was allowed to stir for 15 minutes. The reaction was quenched by the careful addition of sat. aq. $NaHCO_3$. The phases were separated and the organic layer was extracted twice with $NaHCO_3$. The combined organic layers were back-extracted twice with CH_2Cl_2 and the combined organic layers were dried with brine and $MgSO_4$. After removal of the solvent under reduced pressure silica gel chromatography (hexane/EtOAc = 4/1) yielded the pure allylic alcohol (971 mg, 1.82 mmol, 98%) as slightly yellow oil.

The previously prepared primary alcohol (971 mg, 1.82 mmol, 1.0 eq.) was dissolved in anhydrous EtOAc (20 mL) and IBX (1.53 g, 5.47 mmol, 3 eq.) was added. The suspension was heated to reflux for three hours. Now the suspension was cooled to r.t. and 20 mL of hexane were added. The suspension was filtered through a pad of celite and the solvents were removed under reduced pressure. The crude product was purified by silica gel column chromatography (hexane/EtOAc = 5/1). Aldehyde **437** was obtained as viscous oil (966 mg, 1.82 mmol, quant.).

^{1}H-NMR (250MHz, $CDCl_3$): δ = 9.92 (d, *J* = 8.0Hz, 1H); 7.44 (d, *J* = 7.5Hz, 4H); 7.30 (m, 6H); 7.23 (m, 2H); 6.83 (d, *J* = 8.8Hz, 2H); 5.86 (d, *J* = 8.0Hz, 1H); 3.92 (m, 1H); 3.80 (s, 3H); 3.11 (m, 1H); 2.98 (m, 1H); 2.63 (m, 1H); 2.35 (m, 1H); 2.14 (s, 3H); 0.82 (s, 9H); -0.04 (s, 3H); -0.08 (s, 3H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{33}H_{42}O_4Si$: 530.2852; found: 530.2843

(*8S,E*)-methyl-8-((tert-butyldimethylsilyl)oxy)-4-hydroxy-9-((4-methoxyphenyl)diphenylmethoxy)-6-methylnon-5-en-2-ynoate (**329**)



Methyl propiolate (161 µL, 1.81 mmol, 1.5 eq.) was dissolved in anhydrous THF (7 mL) and the reaction mixture was cooled to -78 °C. LiHMDS (1M in THF, 1.87 mL, 1.87 mmol, 1.55 eq.) was added dropwise and the solution was allowed to stir for 30 minutes. A solution of aldehyde **437** (640 mg, 1.21 mmol, 1.0 eq.) in anhydrous THF (3 mL) was added dropwise. The reaction mixture was allowed to stir for 30 minutes until it was quenched by the addition of sat. aq. NH_4Cl. The phases were separated and the aqueous phase was carefully acidified and extracted twice with Et_2O. The combined organic phases were dried with $MgSO_4$ and the solvents were removed under reduced pressure. The resulting allylic alcohol **329** (744 mg, 1.2 mmol, 99%) was purified by silica gel chromatography (hexane/EtOAc = 4/1), whereupon two inseparable, inconsequential diastereoisomers (*d.r.* = 2/1) were obtained.

Major:

^{1}H-NMR (400MHz, $CDCl_3$): δ = 7.45 (m, 4H); 7.30 (m, 6H); 7.22 (m, 2H); 6.83 (d, *J* = 9.0Hz, 2H); 5.30 (dt, *J* = 8.4, 0.9Hz, 1H); 5.07 (m, 1H); 3.88 (m, 1H); 3.80 (s, 3H); 3.78 (s, 3H); 3.07 (m, 1H); 2.98 (m, 1H); 2.45 (m, 1H); 2.18 (m, 1H); 1.70 (m, 3H); 0.84 (s, 9H); 0.00 (s, 3H); -0.05 (s, 3H)

^{13}C-NMR (100MHz, $CDCl_3$): δ = 158.5; 153.8; 144.5; 139.8; 135.9; 132.6; 130.3; 128.5; 128.4; 128.3; 128.0; 127.7; 127.1; 126.8; 124.9; 113.3; 113.1; 87.3; 87.2; 86.3; 70.5; 70.2; 70.1; 66.8; 58.8; 55.2; 52.7; 45.0; 44.5; 25.8; 25.1; 18.0; 17.8; 17.4; -4.5; -4.8

HRMS (ESI) (m/z): $[M+Na]^+$ calcd. for $C_{37}H_{46}O_6SiNa$: 637.2961; found: 637.2947

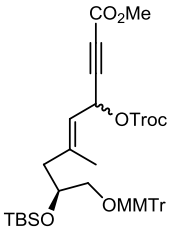
Minor:

^{1}H-NMR (400MHz, $CDCl_3$): δ = 7.45 (m, 4H); 7.30 (m, 6H); 7.22 (m, 2H); 6.83 (d, *J* = 9.0Hz, 2H); 5.30 (dt, *J* = 8.4, 0.9Hz, 1H); 5.07 (m, 1H); 3.88 (m, 1H); 3.80 (s, 3H); 3.77 (s, 3H); 3.07 (m, 1H); 2.98 (m, 1H); 2.45 (m, 1H); 2.18 (m, 1H); 1.70 (m, 3H); 0.85 (s, 9H); 0.00 (s, 3H); -0.04 (s, 3H)

^{13}C-NMR (100MHz, $CDCl_3$): δ = 158.5; 153.8; 144.6; 139.7; 135.9; 132.6; 130.4; 128.5; 128.4; 128.3; 128.0; 127.7; 127.1; 126.8; 125.0; 113.3; 113.1; 87.3; 87.2; 86.3; 70.5; 70.2; 70.1; 67.0; 58.7; 55.2; 52.7; 45.0; 44.5; 25.8; 25.1; 18.0; 17.8; 17.4; -4.5; -4.8

HRMS (ESI) (m/z): $[M+Na]^+$ calcd. for $C_{37}H_{46}O_6SiNa$: 637.2961; found: 637.2949

(*8S,E*)-methyl-8-((tert-butyldimethylsilyl)oxy)-9-((4-methoxyphenyl)diphenylmethoxy)-6-methyl-4-(((2,2,2-trichloroethoxy)carbonyl)oxy)non-5-en-2-ynoate (**325a**)



Allylic alcohol **329** (369 mg, 0.6 mmol, 1.0 eq.) was dissolved in anhydrous CH_2Cl_2 (6 mL), pyridine (145 µL, 1.8 mmol, 3 eq.) and DMAP (7.3 mg, 60 µmol, 0.1 eq.) were added. The reaction mixture was cooled to 0 °C and Troc-Cl (127 mg, 0.6 mmol, 1.0 eq.) was added dropwise. The solution was allowed to stir for one hour. It was quenched by the addition of sat. aq. $NaHCO_3$ and the phases were separated. The aqueous phase was extracted twice with CH_2Cl_2 and the combined organic phases were washed with brine and dried with $MgSO_4$.

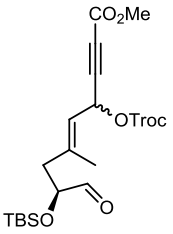
After removal of the solvent under reduced pressure, purification by silica gel chromatography (hexane/EtOAc = 5/1) yielded pure compound **325a** (412 mg, 0.52 mmol, 87%) as slightly yellow viscous oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 7.44 (d, *J* = 8.0Hz, 4H); 7.30 (m, 6H); 7.21 (m, 2H); 6.83 (d, *J* = 8.9Hz, 2H); 6.01 (d, *J* = 9.0Hz, 1H); 5.38 (d, *J* = 9.0Hz, 1H); 4.76 (m, 2H); 3.83 (m, 1H); 3.79 (s, 3H); 3.77 (s, 3H); 3.09 (m, 1H); 2.97 (m, 1H); 2.51 (m, 1H); 2.19 (m, 1H); 1.78 (m, 3H); 0.81 (s, 9H); -0.05 (m, 3H); -0.10 (s, 3H)

^{13}C-NMR (100MHz, $CDCl_3$): δ = 158.5; 153.3; 153.0; 144.5; 143.4; 143.3; 135.9; 130.3; 128.4; 127.8; 126.8; 119.8; 113.1; 86.4; 82.3; 82.2; 77.5; 77.0; 70.3; 70.2; 67.2; 65.8; 65.1; 65.0; 55.2; 52.8; 45.1; 45.0; 25.8; 17.9; 17.8; 15.3; -4.5; -5.0

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{40}H_{47}Cl_3O_8Si$: 788.2106; found: 788.2105

(*8S,E*)-methyl-8-((tert-butyldimethylsilyl)oxy)-6-methyl-9-oxo-4-(((2,2,2-trichloroethoxy)carbonyl)oxy)non-5-en-2-ynoate (**330a**)



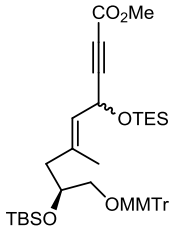
Compound **325a** (490 mg, 0.62 mmol, 1.0 eq.) was dissolved in 10 mL of a 4/1 mixture CH_2Cl_2/MeOH. PPTS (15.6 mg, 62 µmol, 0.1 eq.) was added and the reaction mixture was allowed to stir at r.t. until TLC analysis indicated full consumption of the starting material (approx. two hours). The reaction mixture was quenched with saturated aqueous $NaHCO_3$. The phases were separated and the aqueous layer was extracted two times with Et_2O. The combined organic layers were dried with $MgSO_4$ and the solvent was removed under reduced pressure. Purification by silica gel chromatography (hexane/EtOAc = 4/1) yielded the free primary alcohol as colorless viscous oil (317 mg, 0.61 mmol, 99%).

The previously prepared primary alcohol (317 mg, 0.61 mmol, 1.0 eq.) was dissolved in anhydrous EtOAc (6 mL) and IBX (512 mg, 1.83 mmol, 3 eq.) was added. The suspension was heated to reflux for three hours. Now the suspension was cooled to r.t. and 6 mL of hexane were added. The suspension was filtered through a pad of celite and the solvents were removed *in vacuo*. The crude product was purified by silica gel column chromatography (hexane/EtOAc = 5/1). Aldehyde **330a** was obtained as viscous oil (315 mg, 0.61 mmol, quant.).

^{1}H-NMR (250MHz, $CDCl_3$): δ = 9.61 (d, *J* = 1.2Hz, 1H); 6.04 (d, *J* = 8.9Hz, 1H); 5.48 (d, *J* = 8.9Hz, 1H); 4.76 (m, 2H); 4.09 (m, 1H); 3.78 (s, 3H); 2.36 (m, 2H); 1.82 (s, 3H); 0.90 (s, 9H); 0.06 (s, 3H); 0.03 (s, 3H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{20}H_{29}Cl_3O_7Si$: 514.0748; found: 514.0738

(*8S,E*)-methyl-8-((tert-butyldimethylsilyl)oxy)-9-((4-methoxyphenyl)diphenylmethoxy)-6-methyl-4-((triethylsilyl)oxy)non-5-en-2-ynoate (**325b**)

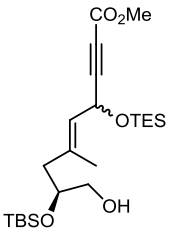


Allylic alcohol **329** (120 mg, 0.2 mmol, 1.0 eq.) was dissolved in anhydrous CH_2Cl_2 (5 mL). Pyridine (50 µL, 0.59 mmol, 3 eq.) and DMAP (1.2 mg, 10 µmol, 0.05 eq.) were added to the solution and it was cooled to 0 °C. A solution of TES-Cl (66 µL, 0.39 mmol, 2 eq.) in anhydrous CH_2Cl_2 (1 mL) was added. The reaction mixture was allowed to stir at 0 °C for one hour, and then it was quenched by the addition of sat. aq. NH_4Cl. The phases were separated and the organic layer was washed with NH_4Cl. The organic layer was dried with brine and $MgSO_4$. Purification by silica gel chromatography (hexane/EtOAc = 10/1) yielded pure silyl ether **325b** (116 mg, 0.16 mmol, 80%) as colorless liquid.

^{1}H-NMR (250MHz, $CDCl_3$): δ = 7.43 (m, 4H); 7.24 (m, 8H); 6.81 (m, 2H); 5.33 (m, 1H); 5.11 (m, 1H); 3.84 (m, 1H); 3.76 (s, 3H); 3.73 (s, 3H); 3.48 (m, 1H); 3.00 (m, 1H); 2.14 (m, 2H); 1.69 (m, 3H); 0.95 (m, 12H); 0.81 (m, 6H); 0.63 (m, 6H); 0.08 (s, 3H); -0.06 (m, 3H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{43}H_{60}O_6Si_2$: 728.3928; found: 728.3914

(*8S,E*)-methyl-8-((tert-butyldimethylsilyl)oxy)-9-hydroxy-6-methyl-4-((triethylsilyl)oxy)non-5-en-2-ynoate (**438**)

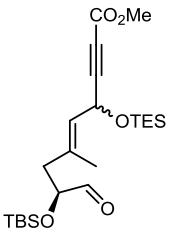


Bis-silylether **325b** (116 mg, 0.16 mmol, 1.0 eq.) was dissolved in anhydrous CH_2Cl_2 (2 mL) and hexafluoroisopropanol (HFIP, 2 mL) was added. The solution was allowed to stir at r.t. for 15 minutes during which time it turned yellow. Anhydrous MeOH was added until the color disappeared and the solution was allowed to stir at r.t. for 2 days. Solvents were removed *in vacuo* and purification by silica gel chromatography (hexane/EtOAc = 5/1) yielded pure primary alcohol **438** (50 mg, 0.11 mmol, 68%) as colorless viscous oil.

^{1}H-NMR (250MHz, $CDCl_3$): δ = 5.37 (d, *J* = 8.1Hz, 1H); 5.14 (d, *J* = 8.1Hz, 1H); 3.87 (m, 1H); 3.76 (s, 3H); 3.53 (m, 1H); 3.43 (m, 1H); 2.22 (d, *J* = 6.6Hz, 2H); 1.85 (t, *J* = 6.3Hz, 1H); 1.72 (s, 3H); 0.95 (t, *J* = 7.7Hz, 9H); 0.89 (s, 9H); 0.64 (q, *J* = 7.7Hz, 6H); 0.08 (s, 6H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{23}H_{44}O_5Si_2$: 456.2727; found: 456.2721

(*8S,E*)-methyl-8-((tert-butyldimethylsilyl)oxy)-6-methyl-9-oxo-4-((triethylsilyl)oxy)non-5-en-2-ynoate (**330b**)



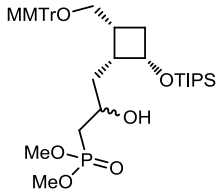
Oxalyl chloride (8.9 µL, 105 µmol, 2 eq.) was dissolved in anhydrous CH_2Cl_2 (1 mL) and the solution was cooled to -78 °C. A solution of anhydrous DMSO (14.9 µL, 0.21 mmol, 4 eq.) in anhydrous CH_2Cl_2 (200 µL) was added dropwise. The reaction mixture was allowed to stir at -78 °C for 45 minutes. A solution of alcohol **438** (24 mg, 53 µmol, 1.0 eq.) in anhydrous CH_2Cl_2 (1 mL) was added dropwise.

The reaction mixture was allowed to stir for 90 minutes, before NEt_3 (43.9 µL, 0.32 mmol, 6 eq.) was added and the solution was allowed to warm to -20 °C within one hour. Sat. aq. NH_4Cl was added and the phases were separated. The aqueous layer was extracted twice with CH_2Cl_2 and the combined organic layers were dried with brine and $MgSO_4$. The solvent was removed under reduced pressure and silica gel chromatography (hexane/EtOAc = 7/1) yielded pure aldehyde **330b** (20 mg, 44 µmol, 84%) as colorless oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 9.61 (d, *J* = 1.6Hz, 1H); 5.41 (d, *J* = 8.1Hz, 1H); 5.14 (d, *J* = 8.1Hz, 1H); 4.08 (m, 1H); 3.76 (s, 3H); 2.32 (m, 2H); 1.73 (s, 3H); 0.96 (t, *J* = 7.7Hz, 9H); 0.90 (s, 9H); 0.65 (q, *J* = 7.7Hz, 6H); 0.06 (s, 6H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{23}H_{42}O_5Si_2$: 454.2571; found: 454.2562

Dimethyl-(2-hydroxy-3-((*1R,2R,4S*)-2-(((4-methoxyphenyl)diphenylmethoxy)methyl)-4-((triisopropylsilyl)oxy)cyclobutyl)propyl)phosphonate (**331**)



Primary alcohol **193** (1.0 g, 1.74 mmol, 1.0 eq.) was dissolved in anhydrous EtOAc (20 mL) and IBX (975 mg, 3.5 mmol, 2 eq.) was added. The suspension was heated to reflux for four hours. Now the suspension was cooled to r.t. and 20 mL of hexane were added. The suspension was filtered through a pad of celite and the solvents were removed *in vacuo*. The crude product (997 mg, 1.74 mmol, quant.) was used without further purification.

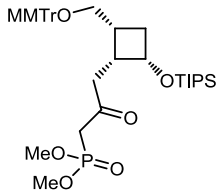
An adapted procedure of *Genov* and *Tebby* was used.[101] Dimethyl methylphosphonate (216 mg, 1.74 mmol, 1.0 eq.) was dissolved in anhydrous THF (12 mL) and the solution was cooled to -78 °C before n-BuLi (2.5M in hexane; 730 µL, 1.83 mmol, 1.05 eq.) was added dropwise. The reaction mixture was stirred for 30 minutes, then a solution of the previously prepared aldehyde (997 mg, 1.74 mmol, 1.0 eq.) in anhydrous THF (5 mL) was added dropwise. Stirring was continued for one hour. The reaction mixture was quenched by the addition of sat. aq. NH_4Cl. After the addition of Et_2O, the phases were separated and the neutralized aqueous layer was extracted twice with Et_2O. The combined organic layers were dried with $MgSO_4$ and the solvent was removed *in vacuo*.

The resulting β-hydroxy phosphonate **331** (1.2 g, 1.74 mmol, quant.) was of sufficient purity for further conversion.

^{1}H-NMR (250MHz, $CDCl_3$): δ = 7.42 (m, 4H); 7.27 (m, 8H); 6.82 (d, *J* = 8.8Hz, 2H); 4.35 (d, *J* = 7.0Hz, 1H); 4.02 (m, 1H); 3.79 (s, 3H); 3.64 (m, 6H); 3.03 (m, 2H); 2.79 (m, 1H); 2.32 (m, 2H); 1.62 (m, 3H); 1.43 (m, 1H); 1.26 (m, 1H); 1.02 (bs, 21H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{39}H_{57}O_7PSi$: 696.3611; found: 696.3604

Dimethyl-(3-((*1R,2R,4S*)-2-(((4-methoxyphenyl)diphenylmethoxy)methyl)-4-((triisopropylsilyl)oxy)cyclobutyl)-2-oxopropyl)phosphonate (**439**)



β-hydroxy phosphonate **331** (1.2 g, 1.74 mmol, 1.0 eq.) was dissolved in anhydrous EtOAc (20 mL) and IBX (1.46 g, 5.22 mmol, 3 eq.) was added. The suspension was heated to reflux for four hours. Now the suspension was cooled to r.t. and 20 mL of hexane were added. The suspension was filtered through a pad of celite and the solvents were removed *in vacuo*. The crude product was purified by silica gel column chromatography (hexane/EtOAc = 1/1). β-keto phosphonate **439** was obtained as viscous oil (1.1 g, 1.58 mmol, 91%).

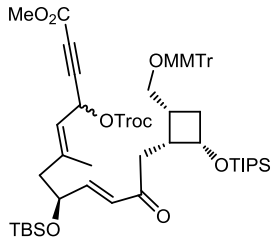
^{1}H-NMR (400MHz, $CDCl_3$): δ = 7.40 (m, 4H); 7.27 (m, 6H); 7.21 (m, 2H); 6.82 (d, *J* = 9.0Hz, 2H); 4.34 (m, 1H); 3.79 (s, 3H); 3.70 (d, J_{PH}=11.3Hz, 3H); 3.65 (d, J_{PH}=11.3Hz, 3H); 3.17 (m, 1H); 3.01 (m, 1H); 2.93 (m, 2H); 2.75 (m, 1H); 2.59 (m, 1H); 2.37 (m, 2H); 1.65 (m, 1H); 0.98 (s, 21H)

^{13}C-NMR (100MHz, $CDCl_3$): δ = 201.2; 158.5; 144.8; 144.6; 135.8; 130.3; 128.4; 128.3; 127.7; 126.8; 113.0; 86.1; 65.8; 65.6; 64.1; 55.2; 52.8; 52.7; 42.2; 40.9; 39.1; 38.5; 35.0; 29.6; 17.9; 17.8; 12.0

^{31}P-NMR (162MHz, $CDCl_3$): δ = 24.59

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{39}H_{55}O_7Si$: 694.3455; found: 694.3442

(*E*)-Enone (**324a**)



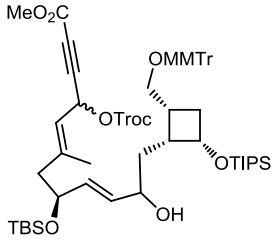
β-keto phosphonate **439** (296 mg, 0.43 mmol, 1.1 eq.) was dissolved in anhydrous THF (2 mL) and the reaction mixture was cooled to -78 °C. LiHMDS (1M in THF; 470 µL, 0.47 mmol, 1.2 eq.) was added dropwise and the reaction mixture was stirred at -78 °C for one hour until a solution of aldehyde **330a** (200 mg, 0.39 mmol, 1.0 eq.) in anhydrous THF (2 mL) was added dropwise. The solution was stirred 30 minutes at -78 °C, then it was allowed to warm to -10 °C with a rate of approx. 1 °C/minute. The reaction was quenched by the addition of sat. aq. NH_4Cl and Et_2O was added. The phases were separated and the aqueous layer was extracted twice with Et_2O. The combined organic layers were dried with $MgSO_4$ and the solvent was removed under reduced pressure. Purification by silica gel chromatography (hexane/EtOAc = 5/1) yielded pure enone **324a** (230 mg, 0.21 mmol, 55%) as colorless oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 7.41 (m, 4H); 7.27 (m, 6H); 7.21 (m, 2H); 6.82 (d, *J* = 8.9Hz, 2H); 6.55 (dd, *J* = 15.4, 5.4Hz, 1H); 6.12 (d, *J* = 15.4Hz, 1H); 6.04 (d, *J* = 8.9Hz, 1H); 5.42 (d, *J* = 8.9Hz, 1H); 4.77 (m, 2H); 4.34 (m, 2H); 3.79 (s, 3H); 3.78 (s, 3H); 3.23 (m, 1H); 3.04 (m, 2H); 2.86 (m, 1H); 2.39 (m, 3H); 2.14 (m, 2H); 1.81, 1.80 (s, 3H); 1.68 (m, 1H); 0.96 (s, 21H); 0.86 (m, 9H); -0.01, -0.07 (m, 6H)

^{13}C-NMR (100MHz, $CDCl_3$): δ = 199.2; 158.4; 146.4; 144.8; 144.7; 142.0; 141.9; 136.1; 130.2; 128.8; 128.7; 128.4; 128.3; 127.7; 126.7; 120.8; 113.0; 86.0; 82.0; 81.9; 77.1; 70.5; 70.4; 65.9; 64.9; 64.2; 60.4; 55.1; 52.9; 52.8; 47.2; 38.6; 34.9; 29.8; 25.8; 25.7; 21.0; 17.9; 17.7; 14.2; 12.0; -4.5; -5.0

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{57}H_{77}Cl_3O_{10}Si_2$: 1082.4121; found: 1082.4115

(*5E,8S,9E*)-methyl 8-((tert-butyldimethylsilyl)oxy)-11-hydroxy-12-((*1R,2R,4S*)-2-(((4-methoxyphenyl)diphenylmethoxy)methyl)-4-((triisopropylsilyl)oxy)cyclobutyl)-6-methyl-4-(((2,2,2-trichloroethoxy)carbonyl)oxy)dodeca-5,9-dien-2-ynoate (**440**)

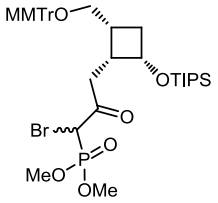


Enone **324a** (123 mg, 0.11 mmol, 1.0 eq.) was dissolved in anhydrous MeOH (2 mL) and $CeCl_3.7H_2O$ (127 mg, 0.24 mmol, 3 eq.) was added. The reaction mixture was cooled to -78 °C and $NaBH_4$ (10.7 mg, 0.28 mmol, 2.5 eq.) was added portionwise in an Ar-stream. The reaction was allowed to stir for one hour and then quenched by the addition of sat. aq. NH_4Cl. Et_2O was added and the phases were separated. The aqueous phase was carefully acidified to pH 5-6. The layers were recombined and mixed vigorously. Separation, pH adjusting and mixing cycle was repeated 3 times, then the separated organic layer was dried with $MgSO_4$ and the solvent was removed under reduced pressure giving pure allylic alcohol **440** (81 mg, 75 µmol, 68%) as colorless viscous oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 7.40 (m, 4H); 7.25 (m, 8H); 6.80 (d, *J* = 8.9Hz, 2H); 6.03 (d, *J* = 8.9Hz, 1H); 5.51 (m, 2H); 5.41 (d, *J* = 8.9Hz, 1H); 4.75 (m, 2H); 4.35 (m, 1H); 4.16 (m, 1H); 4.00 (m, 1H); 3.77 (s, 3H); 3.75 (s, 3H); 3.57 (m, 1H); 3.09 (m, 1H); 2.97 (m, 1H); 2.75 (m, 1H); 2.31 (m, 2H); 2.15 (m, 2H); 1.79 (s, 3H); 1.67 (m, 2H); 1.02 (m, 21H); 0.83 (m, 9H); -0.03 (m, 6H)

HRMS (ESI) (m/z): $[M+Na]^+$ calcd. for $C_{57}H_{79}Cl_3O_{10}Si_2Na$: 1107.4175; found: 1107.4164

Dimethyl-(1-bromo-3-((*1R,2R,4S*)-2-(((4-methoxyphenyl)diphenylmethoxy)methyl)-4-((triisopropylsilyl)oxy)cyclobutyl)-2-oxopropyl)phosphonate (**334**)



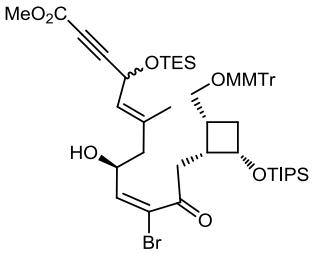
To a suspension of NaH (60% in mineral oil; 17.3 mg, 0.43 mmol, 1.0 eq.) in anhydrous THF (2 mL) was added a solution of β-keto phosphonate **439** (300 mg, 0.43 mmol, 1.0 eq.) in anhydrous THF (2 mL) dropwise at 0 °C.

The reaction mixture was stirred for 30 minutes at 0 °C and 15 minutes at r.t. After re-cooling to 0 °C bromine (15.5 µL, 0.3 mmol, 0.7 eq.) was added and the solution was allowed to stir for two hours at 0 °C. After quenching with aq. sat. $Na_2S_2O_3$ and addition of Et_2O, the phases were separated and the aqueous layer was extracted twice with Et_2O. The combined organic layers were dried with $MgSO_4$ and the solvent was removed *in vacuo*. Purification by silica gel chromatography yielded pure mono brominated β-keto phosphonate **334** (190 mg, 0.25 mmol, 82%) as colorless oil and β-keto phosphonate **439** (123 mg, 0.18 mmol, 98%borsm) with the same appearance.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 7.40 (m, 4H); 7.25 (m, 8H); 6.80 (d, *J* = 8.9Hz, 2H); 4.35 (m, 2H); 4.16 (m, 1H); 3.78 (s, 3H); 3.74 (m, 6H); 3.11 (m, 2H); 3.04 (m, 1H); 2.91 (m, 1H); 2.38 (m, 1H); 1.66 (m, 2H); 0.99 (m, 21H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{39}H_{54}BrO_7PSi$: 772.2560; found: 772.2554

(*E*)-α-bromo-enone (**335b**)



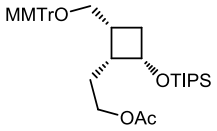
A flame dried Schlenk tube was charged with anhydrous THF (500 µL) and LiHMDS (1M in THF, 46 µL, 46 µmol, 1.05 eq.) was added. The solution was cooled to 0 °C. A solution of brominated β-keto phosphonate **334** (38 mg, 48 µmol, 1.1 eq.) in anhydrous THF (500 µL) was added dropwise and the reaction mixture was allowed to stir for 30 minutes. A solution of aldehyde **330b** (20 mg, 44 µmol, 1.0 eq.) in anhydrous THF (500 µL) was added dropwise. The solution was stirred 30 minutes at 0 °C and then was allowed to warm to r.t. overnight. The reaction was quenched by the addition of sat. aq. NH_4Cl and Et_2O was added. The phases were separated and the aqueous layer was extracted twice with Et_2O. The combined organic layers were dried with $MgSO_4$ and the solvent was removed *in vacuo*. Purification by silica gel chromatography (hexane/EtOAc = 5/1) yielded pure (*E*)-enone **335b** (36 mg, 31 µmol, 70%) as colorless oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 7.41 (m, 4H); 7.27 (m, 6H); 7.21 (m, 2H); 6.90 (d, *J* = 6.8Hz, 1H); 6.84 (d, *J* = 8.9Hz, 2H); 5.49 (d, *J* = 7.7Hz, 1H); 5.20 (d, *J* = 8.1Hz, 1H); 4.67 (m, 1H); 4.37 (q, *J* = 6.9Hz, 1H); 3.80 (s, 3H); 3.77 (s, 3H); 3.27 (m, 1H); 3.03 (m, 2H); 2.61 (m, 1H); 2.37 (m, 3H); 2.13 (m, 1H); 1.97 (m ,1H); 1.80 (s, 3H); 1.69 (m, 1H); 1.04 (m, 9H); 0.96 (s, 21H); 0.67 (m, 6H)

^{13}C-NMR (100MHz, $CDCl_3$): δ = 192.2; 158.4; 144.9; 144.7; 144.5; 135.8; 135.0; 134.8; 130.5; 130.3; 129.2; 128.3; 128.2; 127.9; 127.8; 127.2; 126.8; 126.7; 113.2; 113.1; 113.0; 87.3; 86.0; 75.5; 70.2; 70.0; 65.6; 63.7; 59.2; 55.3; 52.7; 44.6; 44.5; 39.1; 34.6; 32.7; 29.7; 29.5; 17.9; 17.8; 16.6; 12.2; 12.0; 6.7; 4.8

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{54}H_{75}BrO_8Si_2$: 986.4184; found: 986.4167

2-((1R,2R,4S)-2-(((4-methoxyphenyl)diphenylmethoxy)methyl)-4-((triisopropylsilyl)oxy)cyclobutyl)ethyl acetate (**441**)

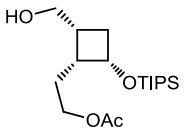


Mono MMTr-ether **193** (1 g, 1.75 mmol, 1.0 eq.) was dissolved in anhydrous CH_2Cl_2 (20 mL), NEt_3 (728 µL, 5.24 mmol, 3 eq.), and DMAP (11 mg, 87.5 µmol, 0.05 eq.) were added and the reaction mixture was cooled to 0 °C before AcCl (186 µL, 2.62 mmol, 1.5 eq.) was added dropwise. The solution was allowed to stir at 0 °C for 30 minutes before it was quenched by the addition of sat. aq. NH_4Cl. Phases were separated and the organic layer was dried with $MgSO_4$. The solvent was removed under reduced pressure yielding **441** (1 g, 1.6 mmol, 93%) of satisfying purity as slightly yellow oil.

^{1}H-NMR (250MHz, $CDCl_3$): δ = 7.42 (m, 4H); 7.25 (m, 8H); 6.82 (d, *J* = 8.9Hz, 2H); 4.31 (m, 1H); 4.04 (m, 2H); 3.80 (s, 3H); 3.11 (m, 1H); 2.99 (m, 1H); 2.72 (m, 1H); 2.59 (m, 1H); 2.31 (m, 2H); 1.99 (s, 3H); 1.61 (m ,2H); 1.00 (s, 21H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{38}H_{52}O_5Si$: 616.3584; found: 616.3568

2-((1R,2R,4S)-2-(hydroxymethyl)-4-((triisopropylsilyl)oxy)cyclobutyl)ethyl acetate (**442**)

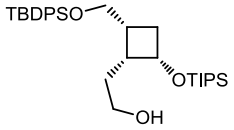


Crude **441** (1 g, 1.6 mmol, 1.0 eq.) was dissolved in anhydrous CH_2Cl_2 (20 mL) and cooled to 0 °C. A solution of CSA (18.6 mg, 0.08 mmol, 0.05 eq.) in anhydrous MeOH (2 mL) was added dropwise and the reaction mixture was allowed to stir for one hour at 0 °C. The reaction was quenched by the addition of aq. sat. $NaHCO_3$. The phases were separated and the aqueous phase was extracted twice with CH_2Cl_2. The combined organic layers were dried with $MgSO_4$ and the solvent was removed *in vacuo*. Purification by silica gel chromatography (hexane/EtOAc = 4/1) yielded pure primary alcohol **442** (453 mg, 1.3 mmol, 81%) as colorless oil.

^{1}H-NMR (250MHz, $CDCl_3$): δ = 4.33 (m, 1H); 4.13 (m, 2H); 3.67 (m, 2H); 2.58 (m, 1H); 2.32 (m, 1H); 2.19 (m, 1H); 2.04 (s, 3H); 2.00 (m, 2H); 1.77 (m ,2H); 1.04 (s, 21H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{18}H_{36}O_4Si$: 344.2383; found: 344.2374

2-((1R,2R,4S)-2-(((tert-butyldiphenylsilyl)oxy)methyl)-4-((triisopropylsilyl)oxy)cyclobutyl)ethanol (**336**)



Primary alcohol **442** (453 mg, 1.3 mmol, 1.0 eq.) was dissolved in anhydrous CH_2Cl_2 (10 mL). Pyridine (430 µL, 5.22 mmol, 4 eq.) and DMAP (16 mg, 0.13 mmol, 0.1 eq.) were added to the solution and it was cooled to 0 °C. A solution of TBDPS-Cl (718 mg, 2.61 mmol, 2 eq.) in anhydrous CH_2Cl_2 (3 mL) was added. The reaction mixture was allowed to stir at 0 °C for two hours, and then it was quenched by the addition of sat. aq. NH_4Cl. The phases were separated and the organic layer was washed with NH_4Cl. The organic layer was dried with brine and $MgSO_4$. Purification by silica gel chromatography (hexane/EtOAc = 10/1) yielded the pure silyl ether (758 mg, 1.3 mmol, quant.) as colorless liquid.

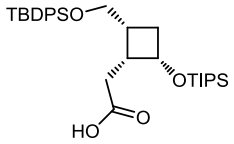
758 mg (1.3 mmol, 1.0 eq.) of the previously prepared silyl ether were dissolved in as little anhydrous CH_2Cl_2 as possible. 13 mL of anhydrous MeOH and 1.82 g (13.1 mmol, 10 eq.) of finely ground K_2CO_3 were added. The reaxtion mixture was stirred for one hour and then filtered through a pad of celite. Et_2O (100 mL) was added to the resulting solution.

The pH of the solution was adjusted to 7 by the addition of 0.5M $KHSO_4$ solution and the phases were separated. The organic phase was extracted twice with water and the combined aqueous phases were back-extracted with Et_2O/hexane (1/1). The combined organic layers were dried with $MgSO_4$ and the solvent was removed under reduced pressure. Purification by silica gel chromatography (hexane/EtOAc = 5/1) yielded 600 mg (1.11 mmol, 84%) of primary alcohol **336** as colorless oil.

^{1}H-NMR (250MHz, $CDCl_3$): δ = 7.65 (m, 4H); 7.41 (m, 6H); 4.31 (m, 1H); 3.70 (m, 4H); 2.76 (m, 1H); 2.66 (m, 1H); 2.17 (m, 2H); 1.97 (m, 1H); 1.80 (m, 1H); 1.66 (m, 1H); 1.04 (m, 30H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{32}H_{52}O_3Si_2$: 540.3455; found: 540.3442

2-((1R,2R,4S)-2-(((tert-butyldiphenylsilyl)oxy)methyl)-4-((triisopropylsilyl)oxy)cyclobutyl)acetic acid (**337**)



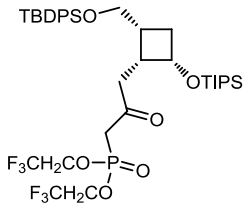
Mono-TBDPS-protected triol **336** (600 mg, 1.11 mmol, 1.0 eq.) was dissolved in anhydrous EtOAc (11 mL) and IBX (931 mg, 3.33 mmol, 3 eq.) was added. The reaction mixtures was refluxed for two hours or until all starting material was consumed. Now hexane (11 mL) was added and the suspension was filtered through a pad of celite 545 coarse. Removal of the solvents gave the aldehyde (560 mg, 1.04 mmol, 94%) as colorless oil, which was used without further purification.

The previously prepared aldehyde (560 mg, 1.04 mmol, 1.0 eq.) was dissolved in t-BuOH (5 mL) and 1 mL of 2-methyl-but-2-ene was added. The reaction mixture was cooled to 0 °C and an aqueous solution (3 mL) of $NaClO_2$ (1.4 g, 15.59 mmol, 15 eq.) and $NaH_2PO_4.H_2O$ (1.4 g, 10.1 mmol, 9.8 eq.) was added at once. The reaction mixture was stirred at 0 °C for one hour and Et_2O and water were added. The phases were separated and the organic layer was washed twice with water before it was dried with $MgSO_4$. Removal of the solvent under reduced pressure yielded pure carboxylic acid **337** (577 mg, 1.04 mmol, quant.) as colorless oil.

^{1}H-NMR (250MHz, $CDCl_3$): δ = 7.65 (m, 4H); 7.41 (m, 6H); 5.67 (bs, 1H); 4.39 (m, 1H); 3.65 (m, 2H); 3.05 (1H); 2.76 (m, 1H); 2.63 (m, 1H); 2.22 (m, 2H); 1.77 (m, 1H); 1.03 (m, 30H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{32}H_{50}O_4Si_2$: 554.3248; found: 554.3232

Bis(2,2,2-trifluoroethyl) (3-((1R,2R,4S)-2-(((tert-butyldiphenylsilyl)oxy)methyl)-4-((triisopropylsilyl)oxy)cyclobutyl)-2-oxopropyl)phosphonate (**339**)



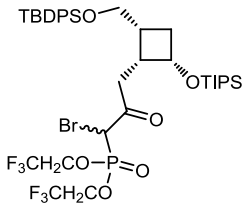
Carboxylic acid **337** (56 mg, 0.1 mmol, 1.0 eq.) was dissolved in anhydrous CH_2Cl_2 (1 mL) and the solution was cooled to 0 °C. Ghosez's reagent (1-Chloro-*N*,*N*,2-trimethyl-1-propenylamine; 134 mg, 1.0 mmol, 10 eq.) was added and the reaction mixture was stirred a 0 °C for four hours. After that period of time the solvent was removed *in vacuo* and the crude acid chloride was used without further purification.

Bis(2,2,2-trifluoroethyl) methylphosphonate (39 mg, 0.15 mmol, 1.5 eq.) was dissolved in anhydrous THF (1 mL) and the solution was cooled to -110 °C.[137] LiHMDS (1M in THF; 140 µL, 0.14 mmol, 1.4 eq.) was added dropwise and the temperature was controlled carefully. The reaction mixture was allowed to stir at -110 °C for 10 min, then it was cooled to -150 °C, where the solvent (THF) got solid. A solution of the previously prepared acid chloride (57 mg, 0.1 mmol, 1.0 eq.) in anhydrous THF (1 mL) was added dropwise to the solid THF. After the addition, the reaction mixture was allowed to warm to -110 °C again where it was stirred for 30 minutes. Afterwards it was again allowed to warm to -95 °C, where it was quenched by the addition of sat. aq. NH_4Cl and Et_2O. The phases were separated and the aqueous phase was extracted twice with Et_2O. The combined organic layers were dried with $MgSO_4$ and the solvent was removed *in vacuo*. Purification by silica gel chromatography (hexane/EtOAc = 5/1) yielded pure β-keto phosphonate **339** (59 mg, 0.08 mmol, 75%) as colorless oil.

^{1}H-NMR (250MHz, $CDCl_3$): δ = 7.63(m, 4H); 7.41 (m, 6H); 4.40 (m, 5H); 3.62 (d, *J* = 5.7Hz, 2H); 3.26 (s, 1H); 3.18 (s, 1H); 3.12 (m, 1H); 2.91 (m, 1H); 2.68 (m, 1H); 2.21 (m, 2H); 1.71 (m, 1H); 1.05 (s, 9H); 1.01 (s, 21H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{37}H_{55}F_6O_6PSi_2$: 796.3179; found: 796.3165

Bis(2,2,2-trifluoroethyl) (1-bromo-3-((1R,2R,4S)-2-(((tert-butyldiphenylsilyl)oxy)methyl)-4-((triisopropylsilyl)oxy)cyclobutyl)-2-oxopropyl)phosphonate (**340**)

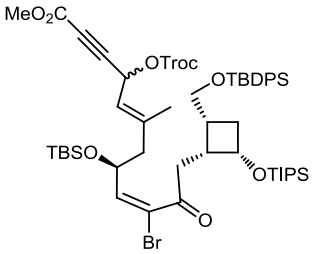


The following procedure was adapted from *Tago* and *Kogen*.[138] To a suspension of NaH (60% in mineral oil; 2.7 mg, 69 µmol, 1.0 eq.) in anhydrous THF (500 µL) was added a solution of β-keto phosphonate **339** (55 mg, 69 µmol, 1.0 eq.) in anhydrous THF (500 µL) dropwise at 0 °C. The reaction mixture was stirred for 30 minutes at 0 °C and 15 minutes at r.t. After re-cooling to 0 °C bromine (2.5 µL, 48 µmol, 0.7 eq.) was added and the solution was allowed to stir for two hours at 0 °C. After quenching with aq. sat. $Na_2S_2O_3$ and addition of Et_2O the phases were separated and the aqueous layers was extracted twice with Et_2O. The combined organic layers were dried with $MgSO_4$ and the solvent was removed *in vacuo*. Purification by silica gel chromatography (hexane/EtOAc = 5/1) yielded pure mono brominated β-keto phosphonate **340** (50 mg, 57 µmol, 83%) as colorless oil.

^{1}H-NMR (250MHz, $CDCl_3$): δ = 7.63(m, 4H); 7.41 (m, 6H); 4.47 (m, 5H); 3.62 (m, 2H); 3.10 (m, 3H); 2.24 (m, 2H); 1.72 (m, 2H); 1.04 (s, 9H); 1.01 (s, 21H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{37}H_{54}BrF_6O_6PSi_2$: 854.2284; found: 854.2271

(*E*)-α-bromo-enone (**341**)



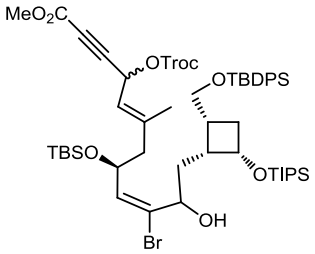
A flame dried Schlenk tube was charged with anhydrous THF (500 µL) and KO*t*Bu (3.4 mg, 30.4 µmol, 0.95 eq.) and 18-crown-6 (9.3 mg, 35.2 µmol, 1.1 eq.) were added. The solution was cooled to -78 °C. A solution of brominated β-keto phosphonate **340** (28 mg, 32 µmol, 1.0 eq.) in anhydrous THF (500 µL) was added dropwise and the reaction mixture was allowed to stir for 30 minutes. A solution of aldehyde **330a** (14.8 mg, 28.8 µmol, 1.0 eq.) in anhydrous THF (500 µL) was added dropwise. The solution was stirred for 30 minutes at -78 °C and then was allowed to warm to r.t. overnight. The reaction was quenched by the addition of sat. aq. NH_4Cl and Et_2O was added. The phases were separated and the aqueous layer was extracted twice with Et_2O. The combined organic layers were dried with $MgSO_4$ and the solvent was removed under reduced pressure. Purification by silica gel chromatography (hexane/EtOAc = 5/1) yielded pure (*E*)-enone **341** (20 mg, 17.6 µmol, 61%) as colorless oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 7.65 (m, 4H); 7.39 (m, 6H); 6.45 (d, *J* = 7.6Hz, 1H); 6.07 (d, *J* = 9.0Hz, 1H); 5.46 (d, *J* = 9.0Hz, 1H); 4.97 (dt, *J* = 8.2, 2.7Hz, 1H); 4.78, 4.76 (s, 2H); 4.38 (m, 2H); 3.78 (s, 3H); 3.67 (m, 2H); 3.14 (m, 1H); 2.79 (dd, *J* = 19.5, 3.9Hz, 1H); 2.25 (m, 3H); 1.88 (s, 3H); 1.46 (m, 1H); 1.29 (m, 2H); 1.03 (s, 9H); 0.99 (s, 21H); 0.82 (s, 9H); -0.10 (m, 6H)

^{13}C-NMR (100MHz, $CDCl_3$): δ = 196.8; 153.0; 150.5; 142.5; 142.3; 135.6; 133.8; 133.7; 129.6; 127.7; 127.6; 120.5; 117.9; 82.4; 82.2; 77.5; 77.1; 69.8; 69.7; 65.2; 65.1; 65.0; 64.7; 52.9; 52.8; 52.7; 45.9; 45.8; 38.7; 36.0; 34.6; 31.1; 26.9; 25.8; 25.7; 19.2; 18.0; 17.9; 17.4; 13.7; 12.0; -4.8; -5.1

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{53}H_{78}BrCl_3O_9Si_3$: 1126.3203; found: 1126.3194

(*E*)-α-bromo-allylic alcohol (**443**)



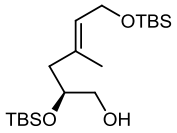
Enone **341** (17 mg, 15µmmol, 1.0 eq.) was dissolved in anhydrous MeOH (1 mL) and $CeCl_3.7H_2O$ (17 mg, 45 µmol, 3 eq.) was added. The reaction mixture was cooled to -78 °C and $NaBH_4$ (3.5 mg, 90 µmol, 6 eq.) was added portionwise in an Ar-stream. The reaction was allowed to stir for one hour and then quenched by the addition of sat. aq. NH_4Cl. Et_2O was added and the phases were separated. The aqueous phase was carefully acidified to pH 5-6. The layers were recombined and vigorously mixed. Separation, pH adjusting and mixing cycle was repeated 3 times, then the separated organic layer was dried with $MgSO_4$ and the solvent was removed under reduced pressure. Silica gel chromatography (hexane/EtOAc = 10/1) yielded pure allylic alcohol **443** (13.5 mg, 12 µmol, 79%) as colorless viscous oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 7.67 (m, 4H); 7.39 (m, 6H); 6.04 (d, *J* = 9.0Hz, 1H); 5.90 (d, *J* = 8.8Hz, 1H); 5.41 (t, *J* = 9.0Hz, 1H); 4.77 (s, 2H); 4.68 (m, 2H); 4.40 (m, 1H); 4.30 (m, 1H); 3.78 (s, 3H); 3.70 (m, 1H); 3.60 (m, 1H); 2.79 (m, 1H); 2.35 (m, 1H); 2.18 (m, 4H); 1.85 (m, 1H); 1.80, 1.78 (s, 3H); 1.46 (m, 1H); 1.09 (m, 9H); 1.03 (m, 21H); 0.85 (m, 9H); 0.00 (m, 6H)

^{13}C-NMR (100MHz, $CDCl_3$): δ = 152.9; 142.1; 136.4; 135.6; 130.5; 129.8; 129.6; 127.7; 127.6; 120.5; 97.5; 82.3; 77.1; 71.5; 71.4; 68.5; 68.4; 66.0; 65.0; 64.3; 63.9; 52.8; 43.2; 40.9; 35.0; 34.2; 32.3; 30.6; 29.7; 29.3; 26.9; 26.8; 25.7; 19.2; 19.1; 18.0; 17.9; 12.3; 12.0

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{53}H_{80}BrCl_3O_9Si_3$: 1128.3359; found: 1128.3347

(*S,E*)-2,6-bis((tert-butyldimethylsilyl)oxy)-4-methylhex-4-en-1-ol (**444**)



TBS-protected vinyl iodide **428** (2.81 g, 9.0 mmol, 1.0 eq.) was dissolved in anhydrous Et_2O (90 mL) and the solution was cooled to -78 °C. t-BuLi (1.6M in pentane; 11.8 mL, 18.9 mmol, 2.1 eq.) was added dropwise. After completion of the addition stirring was continued for 30 minutes. Freshly prepared 2-thienyl-Cu(CN)Li (0.5M in THF; 18.0 mL, 9.0 mmol, 1.0 eq.) was added *via* cannula to the reaction mixture.[112] The solution turned yellow and stirring was continued for one hour at -78 °C. A solution of MMTr-protected (*R*)-glycidol **284** (3.7 g, 10.8 mmol, 1.2 eq.) in 10 mL anhydrous Et_2O was added dropwise. Stirring was continued at -78 °C for two hours and then at r.t. for one hour (the solution turned dark). The reaction mixture was quenched by the addition of a 3/1 mixture of sat. aq. NH_4Cl/25% aq. NH_4OH. The phases were separated and the organic layer was extracted twice with NH_4Cl before it was dried with brine and $MgSO_4$. Removal of the solvent under reduced pressure and purification by silica gel chromatography (hexane/EtOAc = 10/1 to 5/1) yielded the pure secondary alcohol (3.8 g, 7.1 mmol, 79%) as slightly yellow, viscous oil.

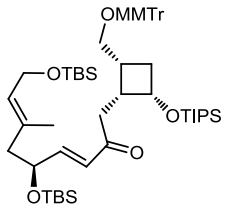
The previously prepared secondary alcohol (300 mg, 0.56 mmol, 1.0 eq.) was dissolved in anhydrous CH_2Cl_2 (6 mL) and 2,6-lutidine (211 mg, 1.97 mmol, 3.5 eq.) was added. The reaction mixture was cooled to 0 °C and TBS-OTf (168 µL, 0.73 mmol, 1.3 eq.) was added dropwise. The solution was allowed to stir for one hour. It was quenched by the addition of sat. aq. $NaHCO_3$ and the phases were separated. The aqueous phase was extracted twice with CH_2Cl_2 and the combined organic phases were washed with brine and dried with $MgSO_4$.After removal of the solvent under reduced pressure, purification by silica gel chromatography yielded the pure bis-ether (353 mg, 0.55 mmol, 97%) as slightly yellow viscous oil.

The previously prepared bis-ether (353 mg, 0.55 mmol, 1.0 eq.) was dissolved in 5 mL of a 4/1 mixture CH_2Cl_2/MeOH. PPTS (13.8 mg, 55 µmol, 0.1 eq.) was added and the reaction mixture was allowed to stir at r.t. until TLC analysis indicated full consumption of the starting material (approx. two hours). The reaction mixture was quenched with saturated aqueous $NaHCO_3$. The phases were separated and the aqueous layer was extracted two times with Et_2O. The combined organic layers were dried with $MgSO_4$ and the solvent was removed under reduced pressure. Purification by silica gel chromatography (hexane/EtOAc = 4/1) yielded free primary alcohol **444** as colorless viscous oil (131 mg, 0.35 mmol, 64%).

^{1}H-NMR (250MHz, $CDCl_3$): δ = 5.34 (t, *J* = 6.3Hz, 1H); 4.17 (m, 2H); 3.76 (m, 1H); 3.45 (m ,2H); 2.27 (m, 1H); 2.04 (m ,1H); 1.64 (s, 3H); 0.89 (s, 9H); 0.86 (s, 9H); 0.06 (s, 6H); 0.04 (s, 6H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{19}H_{42}O_3Si_2$: 374.2672; found: 374.2661

(*S,3E,7E*)-5,9-bis((tert-butyldimethylsilyl)oxy)-1-((*1R,2R,4S*)-2-(((4-methoxyphenyl)diphenylmethoxy)methyl)-4-((triisopropylsilyl)oxy)cyclobutyl)-7-methylnona-3,7-dien-2-one (**445**)



Primary alcohol **444** (131 mg, 0.35 mmol, 1.0 eq.) was dissolved in anhydrous EtOAc (4 mL) and IBX (197 mg, 0.70 mmol, 2 eq.) was added. The suspension was heated to reflux for three hours. Now the suspension was cooled to r.t. and 4 mL of hexane were added. The suspension was filtered through a pad of celite and the solvents were removed under reduced pressure. The crude product was of satisfying purity for further conversion. The aldehyde was obtained as viscous oil (131 mg, 0.35 mmol, quant.).

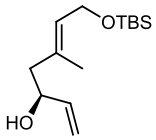
β-keto phosphonate **439** (60 mg, 86 µmol, 1.0 eq.) was dissolved in anhydrous THF (500 µL) and the reaction mixture was cooled to -78 °C. LiHMDS (1M in THF; 90 µL, 90 µmol, 1.05 eq.) was added dropwise and the reaction mixture was stirred at -78 °C for one hour until a solution of the previously prepared aldehyde (32 mg, 86 µmol, 1.0 eq.) in anhydrous THF (500 µL) was added dropwise. The solution was stirred for 30 minutes at -78 °C, then it was allowed to warm to -10 °C with a rate of approx. 1 °C/minute. The reaction was quenched by the addition of sat. aq. NH_4Cl and Et_2O was added. The phases were separated and the aqueous layer was extracted twice with Et_2O. The combined organic layers were dried with $MgSO_4$ and the solvent was removed under reduced pressure. Purification by silica gel chromatography (hexane/EtOAc = 5/1) yielded pure enone **445** (46 mg, 49 µmol, 57%) as colorless oil.

^{1}H-NMR (250MHz, $CDCl_3$): δ = 7.40 (m, 4H); 7.23 (m, 8H); 6.80 (d, *J* = 8.8Hz, 2H); 6.59 (dd, *J* = 15.8, 4.9Hz, 1H); 6.1 (dd, *J* = 15.8, 1.0Hz, 1H); 5.37 (m, 1H); 4.33 (m, 2H); 4.15 (d, *J* = 5.7Hz, 2H); 4.07 (m, 1H); 3.78 (s, 3H); 3.21 (m, 1H); 3.02 (m, 2H); 2.86 (m, 1H); 2.38 (m, 4H); 2.10 (m, 2H); 1.61 (s, 3H); 1.60 (m, 2H); 0.94 (s, 18H); 0.89 (s, 21H); 0.00 (m, 12H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{56}H_{88}O_6Si_3$: 940.5889; found: 940.5876

4.2.12 Southern Lactone Approach (*c*Bu)

(*S,E*)-7-((tert-butyldimethylsilyl)oxy)-5-methylhepta-1,5-dien-3-ol (**446**)



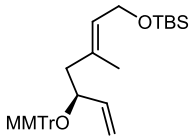
Trimethylsulfonium iodide (631 mg, 3.1 mmol, 3 eq.) was suspended in anhydrous THF (3 mL) and the suspension was cooled to -20 °C. n-BuLi (2.5M in hexane; 1.2 mL, 2.99 mmol, 2.9 eq.) was added dropwise and the reaction mixture was allowed to stir for 30 minutes. A solution of epoxide **314** (250 mg, 1.03 mmol, 1.0 eq.) in anhydrous THF (2 mL) was slowly added and the mixture turned milky. The reaction mixture was stirred at -20 °C for two hours, then it was allowed to warm to r.t. within one hour and finally it was stirred at r.t. for another two hours before it was quenched with water at 0 °C. Et_2O was added and the phases were separated. The pH of the aqueous phase was carefully neutralized with 0.5M $KHSO_4$ and it was extracted two more times with Et_2O. The combined organic layers were dried with brine and $MgSO_4$ and the solvent was removed under reduced pressure. Silica gel chromatography (hexane/EtOAc = 7/1 to 5/1) yielded pure secondary allylic alcohol **446** (195 mg, 0.76 mmol, 74%) as colorless oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 5.87 (ddd, *J* = 17.2, 10.6, 5.8Hz, 1H); 5.44 (dt, *J* = 6.2, 1.0Hz, 1H); 5.27 (dt, *J* = 17.2, 1.3Hz, 1H); 5.11 (dt, *J* = 10.6, 1.3Hz, 1H); 4.24 (m, 1H); 4.21 (d, *J* = 6.2Hz, 2H); 2.22 (m, 2H); 1.68 (s, 3H); 0.90 (s, 9H); 0.07 (s, 6H)

^{13}C-NMR (100MHz, $CDCl_3$): δ = 140.5; 133.1; 128.7; 114.6; 70.2; 60.0; 47.6; 26.0; 18.4; 16.5; -5.1

HRMS (ESI) (m/z): $[M+Na]^+$ calcd. for $C_{14}H_{28}O_2SiNa$: 279.1756; found: 279.1748

(*S,E*)-tert-butyl((5-((4-methoxyphenyl)diphenylmethoxy)-3-methylhepta-2,6-dien-1-yl)oxy)dimethylsilane (**348**)

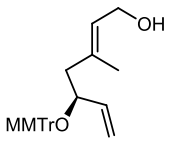


Allylic alcohol **446** (410 mg, 1.6 mmol, 1.0 eq.) was dissolved in 10 mL anhydrous CH_2Cl_2 and DMAP (20 mg, 0.16 mmol, 0.1 eq.) and pyridine (206 µL, 2.6 mmol, 1.6 eq.) were added. The reaction mixture was cooled to 0 °C. A solution of MMTr-Cl (741 mg, 2.4 mmol, 1.5 eq.) in anhydrous CH_2Cl_2 (3 mL) was added dropwise to the solution. The reaction mixture was allowed to warm to r.t. within two hours. Then it was quenched by the addition of sat. aq. NH_4Cl solution. Phases were separated and the aqueous phase was extracted twice with 100 mL CH_2Cl_2, respectively. The combined organic layers were dried with brine and $MgSO_4$. Solvents were removed under reduced pressure and the crude product was purified using silica gel chromatography (hexane/EtOAc = 7/1) yielding pure compound **348** (835 mg, 1.6 mmol, quant.) as slightly orange oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 7.52 (m, 4H); 7.39 (d, *J* = 8.9Hz, 2H); 7.23 (m, 6H); 6.80 (d, *J* = 8.9Hz, 2H); 5.65 (m, 1H); 5.18 (dt, *J* = 6.4, 1.1Hz, 1H); 4.79 (m, 2H); 4.09 (d, *J* = 6.2Hz, 2H); 4.01 (m, 1H); 3.79 (s, 3H); 1.85 (m, 2H); 1.36 (s, 3H); 0.88 (s, 9H); 0.03 (s, 6H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{34}H_{44}O_3Si$: 528.3060; found: 528.3051

(*S,E*)-5-((4-methoxyphenyl)diphenylmethoxy)-3-methylhepta-2,6-dien-1-ol (**447**)

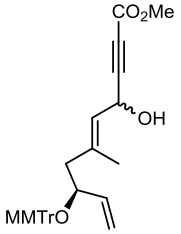


Compound **348** (850 mg, 1.6 mmol, 1.0 eq.) was dissolved in anhydrous THF (15 mL) and the reaction mixture was cooled to 0 °C. 7%HF in pyridine (4.2 mL, 16 mmol, 10 eq.) was added dropwise and the reaction mixture was allowed to stir overnight. The reaction was quenched by the careful addition of sat. aq. $NaHCO_3$. The phases were separated and the organic layer was extracted twice with $NaHCO_3$. The combined organic layers were back-extracted twice with CH_2Cl_2 and the combined organic layers were dried with brine and $MgSO_4$. After removal of the solvent under reduced pressure silica gel chromatography (hexane/EtOAc = 4/1) yielded pure allylic alcohol **447** (656 mg, 1.57 mmol, 98%) as slightly yellow oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 7.52 (m, 4H); 7.39 (d, *J* = 8.9Hz, 2H); 7.23 (m, 6H); 6.80 (d, *J* = 8.9Hz, 2H); 5.66 (m, 1H); 5.29 (t, *J* = 6.9Hz, 1H); 4.80 (m, 2H); 4.04 (m, 3H); 3.79 (s, 3H); 1.87 (m, 2H); 1.42 (s, 3H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{28}H_{30}O_3$: 414.2195; found: 414.2183

(*8S,E*)-methyl 4-hydroxy-8-((4-methoxyphenyl)diphenylmethoxy)-6-methyldeca-5,9-dien-2-ynoate (**351**)



Allylic alcohol **447** (600 mg, 1.45 mmol, 1.0 eq.) was dissolved in anhydrous EtOAc (15 mL) and IBX (1.22 g, 4.35 mmol, 3 eq.) was added. The reaction mixtures was refluxed for two hours or until all starting material was consumed. Hexane (15 mL) was added and the suspension was filtered through a pad of celite 545 coarse. Removal of the solvents gave the corresponding aldehyde (578 mg, 1.4 mmol, 97%) as colorless oil.

Methyl propiolate (194 µL, 2.18 mmol, 1.5 eq.) was dissolved in anhydrous THF (10 mL) and the reaction mixture was cooled to -78 °C. LiHMDS (1M in THF, 2.33 mL, 2.33 mmol, 1.6 eq.) was added dropwise and the solution was allowed to stir for 30 minutes. A solution of the previously prepared aldehyde (578 mg, 1.4 mmol, 1.0 eq.) in anhydrous THF (10 mL) was added dropwise. The reaction mixture was allowed to stir for 30 minutes until it was quenched by the addition of sat. aq. NH_4Cl. The phases were separated and the aqueous phase was carefully acidified and extracted twice with Et_2O. The combined organic phases were dried with $MgSO_4$ and the solvents were removed under reduced pressure. The resulting allylic alcohol **351** (695 mg, 1.4 mmol, quant.) was obtained as an inconsequential diastereomeric mixture (*d.r.* = 1.37/1) and was of satisfying purity for further conversion.

Major:

^{1}H-NMR (400MHz, $CDCl_3$): δ = 7.51 (m, 4H); 7.39 (d, *J* = 8.9Hz, 2H); 7.27 (m, 4H); 7.21 (d, *J* = 6.9Hz, 2H); 6.81 (d, *J* = 8.9Hz, 2H); 5.67 (m, 1H); 5.18 (m, 1H); 5.05 (m, 1H); 4.83 (m, 2H); 4.03 (m, 1H); 3.79 (s, 3H); 3.75 (s, 3H); 1.87 (m, 2H); 1.43 (s, 3H)

^{13}C-NMR (100MHz, $CDCl_3$): δ = 158.6; 153.9; 145.4; 139.1; 136.6; 136.0; 130.8; 128.9; 128.8; 127.6; 127.5; 126.8; 126.4; 114.1; 112.9; 87.8; 87.2; 75.3; 74.0; 59.2; 55.2; 52.6; 46.0; 17.3

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{32}H_{32}O_5Na$: 519.2147; found: 519.2132

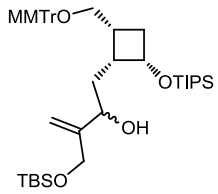
Minor:

^{1}H-NMR (400MHz, $CDCl_3$): δ = 7.51 (m, 4H); 7.39 (d, *J* = 8.9Hz, 2H); 7.27 (m, 4H); 7.21 (d, *J* = 6.9Hz, 2H); 6.81 (d, *J* = 8.9Hz, 2H); 5.67 (m, 1H); 5.18 (m, 1H); 5.05 (m, 1H); 4.83 (m, 2H); 4.03 (m, 1H); 3.79 (s, 3H); 3.73 (s, 3H); 1.77 (m, 2H); 1.43 (s, 3H)

^{13}C-NMR (100MHz, $CDCl_3$): δ = 158.6; 153.9; 145.5; 139.5; 136.6; 136.2; 130.8; 128.9; 128.8; 127.6; 127.5; 126.8; 126.3; 114.1; 112.9; 87.8; 87.1; 75.3; 74.0; 59.2; 55.2; 52.6; 46.2; 17.1

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{32}H_{32}O_5Na$: 519.2147; found: 519.2139

3-(((tert-butyldimethylsilyl)oxy)methyl)-1-((*1R,2R,4S*)-2-(((4-methoxyphenyl)diphenylmethoxy)methyl)-4-((triisopropylsilyl)oxy)cyclobutyl)but-3-en-2-ol (**352**)



Primary alcohol **193** (1.0 g, 1.74 mmol, 1.0 eq.) was dissolved in anhydrous EtOAc (20 mL) and IBX (975 mg, 3.5 mmol, 2 eq.) was added. The suspension was heated to reflux for four hours. Now the suspension was cooled to r.t. and 20 mL of hexane were added. The suspension was filtered through a pad of celite and the solvents were removed under reduced pressure. The crude product (997 mg, 1.74 mmol, quant.) was used without further purification.

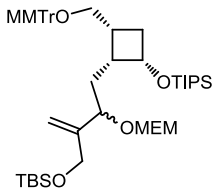
Anhydrous $NiCl_2$ (312 mg, 2.4 mmol, 2 eq.) and anhydrous $CrCl_2$ (737 mg, 6 mmol, 5 eq.) were suspended in anhydrous, degassed DMF (5 pump & freeze cycles, 3 mL) in a flame dried Schlenk tube, giving a dark green solution. The solution was cooled to 0 °C and solutions of the previously prepared aldehyde (690 mg, 1.2 mmol, 1.0 eq.) in anhydrous, degassed DMF (5 pump & freeze cycles, 3 mL) and vinylbromide **407a** (605 mg, 2.4 mmol, 2 eq.) in anhydrous, degassed DMF (5 pump & freeze cycles, 3 mL) were added dropwise isochronally. The reaction mixture was allowed to warm to r.t. overnight. NH_4Cl and EtOAc were added and the phases were separated. The organic layer was washed with water twice and dried with brine and $MgSO_4$. The solvent was removed *in vacuo* and purification by silica gel chromatography (hexane/EtOAc = 7/1) yielded pure NHK-product **352** (934 mg, 1.2 mmol, quant.) as colorless oil (*d.r.* = 1.34/1).

^{1}H-NMR (400MHz, $CDCl_3$): δ = 7.42 (m, 4H); 7.28 (m, 6H); 7.21 (m, 2H); 6.82 (m, 2H); 5.02 (m, 2H); 4.35 (m, 1H); 4.13 (m, 3H); 3.79 (s, 3H); 3.13 (m, 1H); 2.97 (m, 1H); 2.76 (m, 1H); 2.32 (m, 2H); 1.87 (m, 1H); 1.62 (m, 2H); 1.04 (m, 21H); 0.88 (d, *J* = 2.28Hz, 9H); 0.01 (m, 6H)

^{13}C-NMR (100MHz, $CDCl_3$): δ = 158.5; 151.0; 150.4; 144.8; 144.6; 144.5; 135.9; 130.2; 128.4; 128.3; 127.7; 126.8; 113.0; 109.4; 108.9; 86.0; 73.5; 71.5; 66.2; 66.1; 64.1; 64.0; 63.9; 63.3; 55.2; 42.8; 40.0; 35.6; 35.3; 30.1; 30.0; 29.0; 28.6; 25.9; 18.0; 17.9; 12.1; -5.4

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{45}H_{68}O_5Si_2$: 744.4605; found: 744.4594

8-(((*1R,2R,4S*)-2-(((4-methoxyphenyl)diphenylmethoxy)methyl)-4-((triisopropylsilyl)oxy)cyclobutyl)methyl)-12,12,13,13-tetramethyl-9-methylene-2,5,7,11-tetraoxa-12-silatetradecane (**448**)

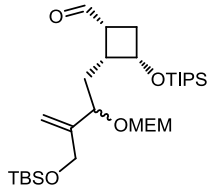


Secondary allylic alcohol **352** (930 mg, 1.2 mmol, 1.0 eq.) was dissolved in anhydrous CH_2Cl_2 (13 mL) and the solution was cooled to 0 °C. DIPEA (2.2 mL, 12.5 mmol, 10 eq.) was added and the reaction mixture was stirred for 15 minutes. MEM-Cl (712 µL, 6.24 mmol, 5 eq.) was added dropwise. The reaction mixture was allowed to warm to r.t. overnight, and then it was quenched with sat. aq. NH_4Cl and the phases were separated. The aqueous phase was extracted twice with CH_2Cl_2 and the combined organic layers were dried with $MgSO_4$. The solvent was removed under reduced pressure. Purification by silica gel chromatography (hexane/EtOAc = 7/1) yielded pure compound **448** (811 mg, 0.97 mmol, 78%) as colorless oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 7.41 (m, 4H); 7.28 (m, 6H); 7.21 (m, 2H); 6.81 (m, 2H); 5.02 (m, 2H); 4.77 (s, 1H); 4.73 (s, 1H); 4.35 (m, 1H); 4.13 (m, 3H); 3.79 (s, 3H); 3.72 (m, 2H); 3.57 (m, 2H); 3.40 (s, 3H); 3.13 (m, 1H); 2.97 (m, 1H); 2.76 (m, 1H); 2.32 (m, 2H); 1.87 (m, 1H); 1.58 (m, 2H); 1.03 (m, 21H); 0.88 (m, 9H); 0.01 (m, 6H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{49}H_{76}O_7Si_2$: 832.5130; found: 832.5122

(*1R,2R,3S*)-2-(3-(((tert-butyldimethylsilyl)oxy)methyl)-2-((2-methoxyethoxy)methoxy)but-3-en-1-yl)-3-((triisopropylsilyl)oxy)cyclobutanecarbaldehyde (**449**)



Bis allylic alcohol **448** (680 mg, 0.82 mmol, 1.0 eq.) was dissolved in anhydrous CH_2Cl_2 (3 mL) and hexafluoroisopropanol (HFIP, 3 mL) was added. The solution was allowed to stir at r.t. for 15 minutes during which time it turned yellow. Anhydrous MeOH was added until the color disappeared and the solution was allowed to stir at r.t. for 2 days. Solvents were removed under reduced pressure and purification by silica gel chromatography (hexane/EtOAc = 4/1) yielded the pure primary alcohol (400 mg, 0.71 mmol, 87%) as colorless viscous oil.

The previously prepared primary alcohol (400 mg, 0.71 mmol, 1.0 eq.) was dissolved in anhydrous EtOAc (7 mL) and IBX (500 g, 1.78 mmol, 2.5 eq.) was added. The reaction mixtures was refluxed for two hours or until all starting material was consumed. Now hexane (7 mL) was added and the suspension was filtered through a pad of celite 545 coarse. Removal of the solvents gave aldehyde **449** (400 mg, 0.71 mmol, quant.) as colorless oil.

Major:

^{1}H-NMR (400MHz, $CDCl_3$): δ = 9.88 (d, *J* = 2.5Hz, 1H); 5.25 (q, *J* = 2.0Hz, 1H); 5.05 (m, 1H); 4.66 (m, 1H); 4.55 (m, 1H); 4.41 (m, 1H); 4.09 (m, 3H); 3.76 (m, 1H); 3.55 (m, 3H); 3.38 (s, 3H); 3.13 (m, 1H); 2.84 (m, 1H); 2.40 (m, 1H); 2.26 (m, 1H); 1.95 (m, 1H); 1.80 (m, 1H); 1.04 (s, 21H); 0.90 (s, 9H); 0.05 (s, 6H)

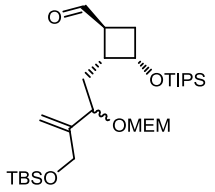
HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{29}H_{58}O_6Si_2$: 558.3772; found: 558.3764

Minor:

^{1}H-NMR (400MHz, $CDCl_3$): δ = 9.80 (d, *J* = 2.8Hz, 1H); 5.28 (q, *J* = 2.0Hz, 1H); 5.05 (m, 1H); 4.66 (m, 1H); 4.55 (m, 1H); 4.41 (m, 1H); 4.09 (m, 3H); 3.76 (m, 1H); 3.55 (m, 3H); 3.39 (s, 3H); 2.95 (m, 1H); 2.84 (m, 1H); 2.40 (m, 1H); 2.26 (m, 1H); 1.95 (m, 1H); 1.80 (m, 1H); 1.04 (s, 21H); 0.90 (s, 9H); 0.05 (s, 6H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{29}H_{58}O_6Si_2$: 558.3772; found: 558.3762

(*1S,2R,3S*)-2-(3-(((tert-butyldimethylsilyl)oxy)methyl)-2-((2-methoxyethoxy)methoxy)but-3-en-1-yl)-3-((triisopropylsilyl)oxy)cyclobutanecarbaldehyde (**354**)



400 mg (0.71 mmol, 1.0 eq.) of aldehyde **449** were dissolved in as little anhydrous CH_2Cl_2 as possible. Anhydrous MeOH (7 mL) and finely ground K_2CO_3 (1.0 g, 7.1 mmol, 10 eq.) were added. The reaction mixture was stirred for one hour and then filtered through a pad of celite. Et_2O (10 mL) was added to the resulting solution. The pH of the solution was adjusted to neutral by the addition of 0.5M $KHSO_4$ solution and the phases were separated. The organic phase was extracted twice with water and the combined aqueous phases were back-extracted with Et_2O/hexane (1/1). The combined organic layers were dried with $MgSO_4$ and the solvent was removed *in vacuo* giving 400 mg (0.71 mmol, quant.) of inverted aldehyde **354** as colorless oil, which was of excellent purity.

Major:

^{1}H-NMR (400MHz, $CDCl_3$): δ = 9.80 (d, *J* = 1.8Hz, 1H); 5.26 (q, *J* = 1.9Hz, 1H); 5.09 (d, *J* = 1.1Hz, 1H); 4.70 (m, 1H); 4.59 (m, 1H); 4.40 (m, 1H); 4.15 (m, 3H); 3.75 (m, 1H); 3.55 (m, 3H); 3.38 (s, 3H); 2.92 (m, 1H); 2.86 (m, 1H); 2.54 (m, 1H); 2.14 (m, 1H); 2.02 (m, 1H); 1.86 (m, 1H); 1.03 (s, 21H); 0.91 (s, 9H); 0.06 (m, 6H)

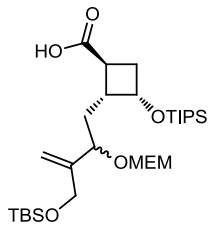
HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{29}H_{58}O_6Si_2$: 558.3772; found: 558.3763

Minor:

^{1}H-NMR (400MHz, $CDCl_3$): δ = 9.77 (d, *J* = 2.1Hz, 1H); 5.29 (q, *J* = 2.0Hz, 1H); 5.05 (d, *J* = 1.5Hz, 1H); 4.70 (m, 1H); 4.59 (m, 1H); 4.40 (m, 1H); 4.15 (m, 3H); 3.75 (m, 1H); 3.55 (m, 3H); 3.38 (s, 3H); 2.92 (m, 1H); 2.82 (m, 1H); 2.54 (m, 1H); 2.14 (m, 1H); 2.02 (m, 1H); 1.86 (m, 1H); 1.03 (s, 21H); 0.91 (s, 9H); 0.0m (m, 6H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{29}H_{58}O_6Si_2$: 558.3772; found: 558.3766

(*1S,2R,3S*)-2-(3-(((tert-butyldimethylsilyl)oxy)methyl)-2-((2-methoxyethoxy)methoxy)but-3-en-1-yl)-3-((triisopropylsilyl)oxy)cyclobutanecarboxylic acid (**450**)



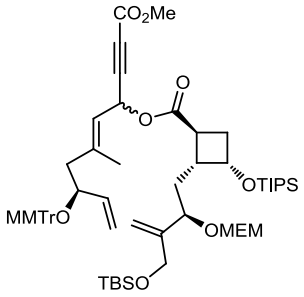
Aldehyde **354** (400 mg, 0.71 mmol, 1.0 eq.) was dissolved in t-BuOH (5 mL) and 2-methyl-but-2-ene (1 mL) was added. The reaction mixture was cooled to 0 °C and an aqueous solution (3 mL) of $NaClO_2$ (971 mg, 10.7 mmol, 15 eq.) and $NaH_2PO_4.H_2O$ (971 mg, 7.04 mmol, 9.8 eq.) was added at once. The reaction mixture was stirred at 0 °C for one hour and Et_2O and water were added. The phases were separated and the organic layer was washed twice with water before it was dried with $MgSO_4$. Removal of the solvent under reduced pressure and silica gel chromatography (EtOAc) yielded pure carboxylic acid **450** (411 mg, 0.71 mmol, quant.) as colorless oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 5.28 (m, 1H); 5.09 (d, *J* = 15.5Hz, 1H); 4.71 (t, *J* = 6.4Hz, 1H); 4.60 (m, 1H); 4.53 (m, 1H); 4.35 (m, 1H); 4.19 (m, 1H); 4.15 (m, 2H); 3.79 (m, 1H); 3.55 (m, 3H); 3.41, 3.38 (s, 3H); 2.91 (m, 1H); 2.56 (m, 1H); 2.22, 2.10 (m, 1H); 1.99 (m, 1H); 1.88 (m, 1H); 1.03 (s, 21H); 0.91 (s, 9H); 0.06 (m, 6H)

^{13}C-NMR (100MHz, $CDCl_3$): δ = 178.6; 147.4; 111.9; 93.1; 77.3; 75.3; 72.0; 67.4; 67.1; 66.4; 62.3; 61.7; 59.0; 42.8; 39.6; 34.2; 33.2; 25.9; 18.4; 18.0; 12.0; -5.5

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{29}H_{58}O_7Si_2$: 574.3721; found: 574.3714

(*1S,2R,3S*)-(*8S,E*)-1-methoxy-8-((4-methoxyphenyl)diphenylmethoxy)-6-methyl-1-oxodeca-5,9-dien-2-yn-4-yl 2-(3-(((tert-butyldimethylsilyl)oxy)methyl)-2-((2-methoxyethoxy)methoxy)but-3-en-1-yl)-3-((triisopropylsilyl)oxy)cyclobutanecarboxylate (**347**)



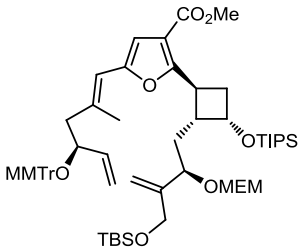
Carboxylic acid **450** (116 mg, 0.2 mmol, 1.0 eq.) and propargylic alcohol **351** (100 mg, 0.2 mmol, 1.0 eq.) were dissolved in anhydrous CH_2Cl_2 (2 mL) and DMAP (2.5 mg, 0.02 mmol, 0.1 eq.) was added. The reaction was cooled to 0 °C and DIC (34 µL, 0.22 mmol, 1.1 eq.) was added. The reaction mixture was stirred at 0 °C for 90 minutes. The solvent was removed under reduced pressure und the crude product was purified using silica gel chromatography (hexane/EtOAc = 7/1). Ester **347** was obtained as slightly yellow oil (100 mg, 0.09 mmol, 47%) as an inseparable mixture of diastereo isomers.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 7.29 (m, 10H); 7.17 (m, 2H); 6.84 (m, 2H); 6.12 (m, 1H); 5.85 (m, 1H); 5.41 (m, 1H); 5.27 (m, 2H); 5.11 (m, 2H); 4.69 (m, 1H); 4.59 (m, 2H); 4.26 (m, 1H); 4.15 (m, 3H); 3.80 (s, 3H); 2.77 (s, 3H); 3.70 (m, 1H); 3.61 (m, 1H); 3.52 (m, 2H); 3.38 (m, 3H); 2.85 (m, 1H); 2.71 (m, 1H); 2.45 (m, 1H); 2.24 (m, 3H); 2.00 (m, 1H); 1.82 (s, 3H); 1.78 (m, 1H); 1.04 (s, 21H); 0.92 (m, 9H); 0.06 (m, 6H)

^{13}C-NMR (100MHz, $CDCl_3$): δ = 174.3; 159.0; 153.2; 147.3; 147.5; 140.6; 139.1; 129.6; 128.3; 128.2; 127.5; 122.2; 115.5; 113.7; 111.9; 93.4; 84.0; 81.9; 76.8; 76.3; 72.2; 70.6; 67.6; 66.4; 62.6; 60.6; 59.4; 55.7; 53.2; 47.4; 42.8; 39.3; 34.8; 33.6; 26.5; 18.7; 18.4; 12.5; -5.0

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{61}H_{88}O_{11}Si_2$: 1052.5865; found: 1052.5853

Methyl-2-((*1S,2R,3S*)-2-(3-(((tert-butyldimethylsilyl)oxy)methyl)-2-((2-methoxyethoxy)methoxy)but-3-en-1-yl)-3-((triisopropylsilyl)oxy)cyclobutyl)-5-((*S,E*)-4-((4-methoxyphenyl)diphenylmethoxy)-2-methylhexa-1,5-dien-1-yl)furan-3-carboxylate (**267c**)



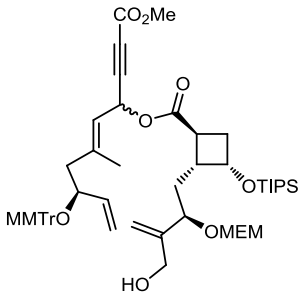
A solution of propargylic ester **347** (10 mg, 9.5 µmol, 1.0 eq.) in benzene (100 µL) was degassed with Ar for 3 minutes prior to use. Tri-*n*butyl phosphine (2.8 µL, 11.4 µmol, 1.2 eq.) was added to the solution of the substrate. The reaction vessel was sealed, heated to 110 °C, and allowed to stir for two hours. The reaction mixture was removed *in vacuo* onto silica gel and subjected to purification by flash chromatography (hexane/EtOAc = 7/1 to 5/1) to yield furan **267c** (1.5 mg, 1.5 µmol, 15%).

^{1}H-NMR (400MHz, $CDCl_3$): δ = 7.30 (m, 10H); 7.17 (m, 2H); 6.84 (m, 2H); 6.43 (s, 1H); 6.09 (s, 1H); 5.92 (m, 1H); 5.25 (m, 1H); 5.14 (m, 1H); 4.70 (m, 1H); 4.63 (m, 2H); 4.58 (m, 1H); 4.32 (m, 1H); 4.16 (m, 2H); 3.82 (s, 3H); 3.80 (s, 3H); 3.60 (m, 2H); 3.53 (m, 2H); 3.34 (m, 3H); 2.80 (m, 2H); 2.55 (m, 2H); 2.10 (m, 2H); 2.06 (m, 3H); 1.04 (m, 21H); 0.90 (s, 9H); 0.06 (s, 6H)

^{13}C-NMR (100MHz, $CDCl_3$): δ = 164.2; 162.1; 158.5; 151.3; 147.4; 147.3; 139.4; 135.0; 129.2; 128.1; 116.2; 114.0; 113.2; 111.8; 108.9; 92.7; 91.5; 76.8; 71.8; 66.5; 62.1; 58.9; 55.3; 51.4; 48.8; 33.6; 25.9; 18.5; 17.9; 12.1; -5.1

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{61}H_{88}O_{10}Si_2$: 1036.5916; found: 1036.5904

(*1S,2R,3S*)-(*8S,E*)-1-methoxy-8-((4-methoxyphenyl)diphenylmethoxy)-6-methyl-1-oxodeca-5,9-dien-2-yn-4-yl 2-(3-(hydroxymethyl)-2-((2-methoxyethoxy)methoxy)but-3-en-1-yl)-3-((triisopropylsilyl)oxy)cyclobutanecarboxylate (**451**)

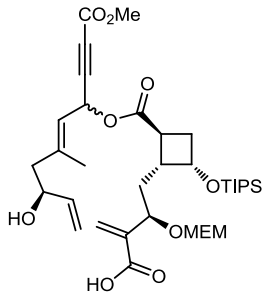


Ester **347** (50 mg, 47.5 µmol, 1.0 eq.) was dissolved in a 6/1 mixture of anhydrous CH_2Cl_2 (0.5 mL) and MeOH (3 mL) and finely ground NH_4F (70.3 mg, 1.9 mmol, 40 eq.) was added. The reaction mixture was stirred at r.t. for 2 days. Water and Et_2O were added and the phases were separated. The organic layer was washed two times with water and dried with brine and $MgSO_4$. Silica gel chromatography (2/1 to 1/1) yielded pure allylic alcohol **451** (40 mg, 43 µmol, 90%) as colorless oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 7.28 (m, 10H); 7.15 (m, 2H); 6.83 (m, 2H); 6.12 (m, 1H); 5.84 (m, 1H); 5.40 (m, 1H); 5.26 (m, 2H); 5.11 (m, 2H); 4.68 (m, 1H); 4.60 (m, 2H); 4.25 (m, 1H); 4.14 (m, 3H); 3.80 (s, 3H); 2.77 (s, 3H); 3.70 (m, 1H); 3.61 (m, 1H); 3.53 (m, 2H); 3.37 (m, 3H); 2.85 (m, 1H); 2.70 (m, 1H); 2.45 (m, 1H); 2.23 (m, 3H); 1.99 (m, 1H); 1.82 (s, 3H); 1.77 (m, 1H); 1.04 (s, 21H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{55}H_{74}O_{11}Si$: 938.5000; found: 938.4985

4-((*1R,2S,4S*)-2-((((*8S,E*)-8-hydroxy-1-methoxy-6-methyl-1-oxodeca-5,9-dien-2-yn-4-yl)oxy)carbonyl)-4-((triisopropylsilyl)oxy)cyclobutyl)-3-((2-methoxyethoxy)methoxy)-2-methylenebutanoic acid (**452**)



Allylic alcohol **451** (40 mg, 43 µmol, 1.0 eq.) was dissolved in anhydrous CH_2Cl_2 (3 mL) and MnO_2 (55.5 mg, 0.64 mmol, 15 eq.) was added in one portion. The reaction mixture was allowed to stir until TLC indicated full consumption of the starting material (approx. three days). The suspension was filtered through a pad of celite 545 coarse and the solvent was removed under reduced pressure, giving the pure corresponding aldehyde (40 mg, 43 µmol, quant.) as colorless oil.

The previously prepared aldehyde (40 mg, 43 µmol, 1.0 eq.) was dissolved in t-BuOH (250 µL) and 2-methyl-but-2-ene (50 µL) was added. The reaction mixture was cooled to 0 °C and an aqueous solution (150 µL) of $NaClO_2$ (57.9 mg, 0.64 mmol, 15 eq.) and $NaH_2PO_4.H_2O$ (57.9 mg, 0.42 mmol, 9.8 eq.) was added at once. The reaction mixture was stirred at 0 °C for one hour and Et_2O and water were added. The phases were separated and the organic layer was washed twice with water before it was dried with $MgSO_4$. Removal of the solvent under reduced pressure and silica gel chromatography (EtOAc) yielded the pure carboxylic acid (36 mg, 39 µmol, 90%) as colorless oil.

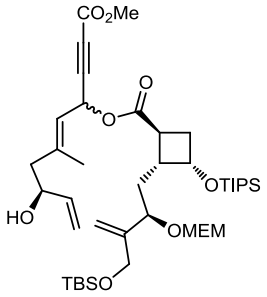
The previously prepared ester (30 mg, 32 µmol, 1.0 eq.) was dissolved in anhydrous CH_2Cl_2 (500 µL) and hexafluoroisopropanol (HFIP, 500 µL) was added. The solution was allowed to stir at r.t. for 15 minutes during which time it turned yellow. Anhydrous MeOH was added until the color disappeared and the solution was allowed to stir at r.t. for 2 days. Solvents were removed under reduced pressure and purification by silica gel chromatography (hexane/EtOAc = 1/1) yielded pure *seco* compound **452** (20 mg, 28 µmol, 93%) as colorless viscous oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 6.38 (m, 1H); 6.12 (m, 1H); 5.86 (m, 2H); 5.42 (m, 1H); 5.28 (m, 1H); 5.14 (m, 1H); 4.69 (m, 2H); 4.62 (m, 1H); 4.54 (m, 1H); 4.47 (m, 1H); 4.33 (m, 1H); 3.78 (m, 3H); 3.66 (m, 2H); 3.53 (m, 2H); 3.37 (m, 3H); 2.84 (m, 1H); 2.69 (m, 1H); 2.44 (m, 1H), 2.31 (m, 2H); 2.10 (m, 3H); 1.85 (m, 4H); 1.03 (m, 21H)

HRMS (ESI) (m/z): $[M+Na]^+$ calcd. for $C_{35}H_{56}O_{11}SiNa$: 703.3490; found: 703.3478

4.2.13 $\Delta^{11,12}$ Metathesis Approach (*c*Bu)

(*1S,2R,3S*)-(*8S,E*)-8-hydroxy-1-methoxy-6-methyl-1-oxodeca-5,9-dien-2-yn-4-yl 2-(3-(((tert-butyldimethylsilyl)oxy)methyl)-2-((2-methoxyethoxy)methoxy)but-3-en-1-yl)-3-((triisopropylsilyl)oxy)cyclobutanecarboxylate (**357b**)



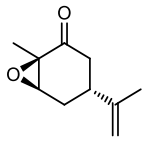
Ester **267c** (30 mg, 28.5 µmol, 1.0 eq.) was dissolved in anhydrous CH_2Cl_2 (500 µL) and hexafluoroisopropanol (HFIP, 500 µL) was added. The solution was allowed to stir at r.t. for 15 minutes during which time it turned yellow. Anhydrous MeOH was added until the color disappeared and the solution was allowed to stir at r.t. for 2 days. Solvents were removed under reduced pressure and purification by silica gel chromatography (hexane/EtOAc = 2/1) yielded pure primary alcohol **357b** (20 mg, 26 µmol, 95%) as colorless viscous oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 6.10 (m, 1H); 5.86 (m, 1H); 5.41 (m, 1H); 5.26 (m, 2H); 5.12 (m, 2H); 4.69 (m, 1H); 4.60 (m, 2H); 4.24 (m, 1H); 4.14 (m, 3H); 2.76 (s, 3H); 3.69 (m, 1H); 3.60 (m, 1H); 3.52 (m, 2H); 3.37 (m, 3H); 2.84 (m, 1H); 2.72 (m, 1H); 2.43 (m, 1H); 2.24 (m, 3H); 2.00 (m, 1H); 1.81 (s, 3H); 1.78 (m, 1H); 1.04 (s, 21H); 0.91 (m, 9H); 0.06 (m, 6H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{41}H_{72}O_{10}Si_2$: 780.4664; found: 780.4653

4.2.14 $\Delta^{7,8}$ Metathesis Approach (*i*Pr)

(*1R,4R,6R*)-1-methyl-4-(prop-1-en-2-yl)-7-oxabicyclo[4.1]heptan-2-one (Carvone oxide, **453**)

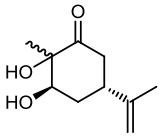


(*R*)-(-)-Carvone (**359**, 20 g, 133 mmol, 1.0 eq.) was dissolved in anhydrous MeOH (300 mL) and the solution was cooled to -20 °C. 10 mL of a 4M solution of NaOH (40 mmol, 0.3 eq.) and 18 mL of a 30% (w/w) solution of H_2O_2 (175 mmol, 1.31 eq.) were added dropwise. The solution was allowed to warm to 0 °C within four hours. The reaction mixture was quenched by the addition of 10 mL 4M HCl and sat. aq. $Na_2S_2O_3$. Et_2O and water were added and the phases were separated. The aqueous layer was extracted twice with Et_2O and the combined organic layers were dried with brine and $MgSO_4$. The solvent was removed under reduced pressure yielding pure carvone-oxide **453** (22.1 g, 133 mmol, quant.) as colorless liquid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.79 (m, 1H); 4.72 (d, *J* = 0.7Hz, 1H); 3.44 (dd, *J* = 3.0, 1.1Hz, 1H); 2.72 (m, 1H); 2.59 (ddd, *J* = 12.8, 7.8, 1.4Hz, 1H); 2.37 (ddd, *J* = 14.8, 3.0, 1.2Hz, 1H); 2.02 (dd, *J* = 17.7, 11.7Hz, 1H); 1.90 (ddd, *J* = 14.8, 11.1; 1.1Hz, 1H); 1.71 (s, 3H); 1.41 (s, 3H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{10}H_{14}O_2$: 166.0994; found: 166.0989

(*3R,5R*)-2,3-dihydroxy-2-methyl-5-(prop-1-en-2-yl)cyclohexanone (**363**)



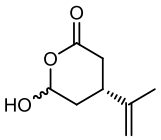
Carvone-oxide **453** (22.1 g, 133 mmol, 1.0 eq.) was dissolved in THF (600 mL) and a solution of H_2SO_4 (98%; 652 mg, 6.65 mmol, 0.05 eq.) in water (60 mL) was added. The reaction mixture was heated to reflux until TLC indicated complete consumption of the starting material (approx. two days). Water, hexane and Et_2O were added and the layers were separated. The aqueous layer was extracted twice with Et_2O and the combined organic layers were washed twice with brine and dried with $MgSO_4$. The solvent was removed under reduced pressure, yielding pure carvone-diol **363** (22 g, 119 mmol, 90%) as colorless liquid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.82 (m, 1H); 4.77 (d, *J* = 0.7Hz, 1H); 4.26 (bs, 1H); 4.05 (dd, *J* = 2.8, 2.8Hz, 1H); 3.00 (bs, 1H); 2.90 (m, 1H); 2.52 (m, 1H); 2.16 (m, 1H); 1.88 (m, 1H); 1.76 (s, 3H); 1.40 (s, 3H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 212.8; 146.5; 110.3; 78.2; 75.8; 41.6; 40.0; 33.0; 23.4; 20.6

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{10}H_{16}O_3Na$: 207.0997; found: 207.0986

(*4R*)-6-hydroxy-4-(prop-1-en-2-yl)tetrahydro-2H-pyran-2-one (**454**)

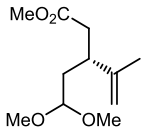


An adapted procedure of Rueping *et al.* was used.[139] A solution of carvone-diol **363** (22 g, 119 mmol, 1.0 eq.) in CH_2Cl_2 (200 mL) was added dropwise to a mechanically stirred slurry of 800 mL CH_2Cl_2, 100 mL water, 76 g SiO_2 and $NaIO_4$ (76.6 g, 0.36mol, 3 eq.) at 0 °C. The reaction mixture was allowed to warm to r.t. overnight (TLC completeness). The reaction mixture was filtered over a plug of celite coarse 545 and the residue was washed with CH_2Cl_2. The phases were separated and the organic phase was dried with brine and Na_2SO_4. The solvent was removed under reduced pressure and silica gel chromatography (CH_2Cl_2/MeOH = 30/1) yielded pure acylale **454** (14.4 g, 92.2 mmol, 78%) as colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.61 (bs, 1H); 4.84 (s, 1H); 4.82 (s, 1H); 3.12 (m, 1H); 2.54 (d, *J* = 7.2Hz, 2H); 2.47 (m, 2H); 1.73 (s, 3H)

HRMS (ESI) (m/z): $[M+Na]^+$ calcd. for $C_8H_{12}O_3Na$: 179.0684; found: 179.0679

(*R*)-methyl 3-(2,2-dimethoxyethyl)-4-methylpent-4-enoate (**364**)

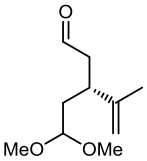


Acylale **454** (14.4 g, 92.2 mmol, 1.0 eq.) was dissolved in anhydrous MeOH (500 mL) and trimethyl ortho formate (50.4 mL, 461.0 mmol, 5 eq.) was added. *p*TsOH (877 mg, 4.6 mmol, 0.05 eq.) was added and the reaction was stirred at r.t. for four hours before it was quenched by the addition of sat. aq. $NaHCO_3$. The phases were separated and the organic phase was dried with brine and $MgSO_4$. The solvents were removed under reduced pressure and purification by silica gel chromatography (hexane/EtOAc = 3/1) yielded pure methyl ester **364** (18.4 g, 85 mmol, 92%) as colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.78 (s, 2H); 4.31 (dd, *J* = 7.3, 4.3Hz, 1H); 3.63 (s, 3H); 3.29 (s, 3H); 3.27 (s, 3H); 2.72 (m, 1H); 2.39 (s, 1H); 2.37 (d, *J* = 1.3Hz, 1H); 1.68 (s, 3H); 1.67 (m, 2H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{11}H_{20}O_4$: 216.1362; found: 216.1358

(*S*)-3-(2,2-dimethoxyethyl)-4-methylpent-4-enal (**455**)

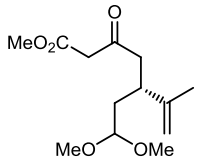


Methyl ester **364** (7.5 g, 34.7 mmol, 1.0 eq.) was dissolved in anhydrous CH_2Cl_2 (300 mL) and the solution was cooled to -78 °C. A solution of DIBAL-H (1.5M in toluene; 25.4 mL, 38.1 mmol, 1.1 eq.) was added dropwise (!) and the reaction mixture was allowed to stir at -78°c for two hours. The reaction was quenched by the addition of sat. aq. K/Na-tartrate and it was allowed to warm to r.t. under vigorous stirring. The phases were separated and the aqueous phase was extracted twice with CH_2Cl_2. The combined organic layers were dried with brine and $MgSO_4$ and the solvent was removed under reduced pressure, yielding pure aldehyde **455** (6.46 g, 34.7 mmol, quant.) as colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.66 (t, *J* = 2.3Hz, 1H); 4.83 (s, 2H); 4.33 (dd, *J* = 5.7, 5.7Hz, 1H); 3.32 (s, 3H); 3.29 (s, 3H); 2.85 (m, 1H); 2.47 (m, 1H); 2.45 (m, 1H); 1.70 (m, 2H); 1.69 (s, 3H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{10}H_{18}O_3$: 186.1256; found: 186.1252

(*R*)-methyl 5-(2,2-dimethoxyethyl)-6-methyl-3-oxohept-6-enoate (**362**)



DIPA (7.4 mL, 52.1 mmol, 1.5 eq.) was dissolved in anhydrous THF (150 mL) and the mixture was cooled to -10 °C when n-BuLi (2.5M in hexane; 19.5 mL, 48.6 mmol, 1.4 eq.) was added. The mixture was allowed to stir at -10 °C for 30 min, before it was cooled to -78 °C. Then, a solution of methyl acetate (3.6 mL, 45.1 mmol, 1.3 eq.) in anhydrous THF (50 mL) was added dropwise. Upon completion, the reaction mixture was allowed to stir for 30 minutes. A solution of aldehyde **455** (6.46 g, 34.7 mmol, 1.0 eq.) in anhydrous THF (50 mL) was added and the reaction mixture was stirred for one hour. The reaction was quenched by the addition of sat. aq. NH_4Cl. After addition of Et_2O, phases were separated and the aqueous phase was neutralized by the addition of 0.5M $KHSO_4$. The aqueous layer was extracted twice with Et_2O and the combined organic phases were dried with $MgSO_4$. Removal of the solvent yielded the corresponding β-hydroxy ester as colorless oil (9.0 g, 34.6 mmol, quant.).

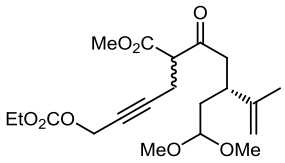
The previously prepared β-hydroxy ester (5.37 g, 20.6 mmol, 1.0 eq.) was dissolved in anhydrous EtOAc (200 mL) and IBX (17.3 g, 61.9 mmol, 3 eq.) was added. The reaction mixtures was refluxed for two hours or until all starting material was consumed. Now 200 mL of hexane were added and the suspension was filtered through a pad of celite 545 coarse. Removal of the solvents and purification by silica gel chromatography (hexane/EtOAc = 4/1) gave aldehyde **362** (3.76 g, 14.6 mmol, 71%) as colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.80 (s, 1H); 4.79 (s, 1H); 4.31 (dd, *J* = 7.3, 4.0Hz, 1H); 3.73 (s, 3H); 3.43 (d, *J* = 2.3Hz, 2H); 3.30 (s, 3H); 3.28 (s, 3H); 2.80 (m, 1H); 2.63 (s, 1H); 2.62 (d, *J* = 1.7Hz, 1H); 1.69 (s, 3H); 1.67 (m, 2H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{13}H_{22}O_5$: 258.1467; found: 258.1463

$[\alpha]_D^{20}$: -1.1 (c=1.55; $CHCl_3$)

(*5R*)-methyl 5-(2,2-dimethoxyethyl)-2-(4-((ethoxycarbonyl)oxy)but-2-yn-1-yl)-6-methyl-3-oxohept-6-enoate (**366**)

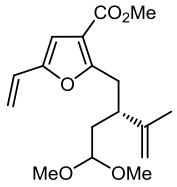


NaH (60% in mineral oil, 582 mg, 14.6 mmol, 1.0 eq.) was suspended in anhydrous THF (80 mL). The reaction mixture was cooled to 0 °C and a solution of β-keto ester **362** (3.76 g, 14.6 mmol, 1.0 eq.) in anhydrous THF (30 mL) was added. The reaction was stirred at 0 °C for 20 minutes and then warmed to r.t. within 10 minutes. Then it was re-cooled to 0 °C and a solution of propargylic iodide **198** (3.9 g, 14.6 mmol, 1.0 eq.) was added uninterruptedly at 0 °C. The reaction mixture was stirred at this temperature for 20 minutes and then warmed to r.t. within 20 minutes before it was quenched with saturated aqueous NH_4Cl. Et_2O was added and the phases separated. The pH of the aqueous phase was adjusted to 6 with 0.5M $KHSO_4$ and it was extracted twice with Et_2O. The combined organic layers were dried with $MgSO_4$ and the solvent was removed under reduced pressure. Silica gel column chromatography (hexane/EtOAc = 3/1 to 1/1) yielded alkylated β-keto ester **366** as colorless oil (5.25 g, 13.2 mmol, 90%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.78 (m, 2H); 4.65 (m, 2H); 4.30 (m, 1H); 4.21 (m, 2H); 3.73 (m, 3H); 3.68 (m, 1H); 3.30 (m, 3H); 3.28 (m, 3H); 2.96 (m, 1H); 2.82 (m, 1H); 2.74 (m, 2H); 2.68 (m, 1H); 1.68 (m, 4H); 1.56 (m, 1H); 1.31 (dt, *J* = 7.1, 1.8Hz, 3H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{20}H_{30}O_8$: 398.1941; found: 398.1935

(*S*)-methyl 2-(2-(2,2-dimethoxyethyl)-3-methylbut-3-en-1-yl)-5-vinylfuran-3-carboxylate (**367**)



Alkylated β-keto ester **366** (600 mg, 1.51 mmol, 1.0 eq.) was dissolved in anhydrous DMF (15 mL) under an Ar-atmosphere and finely ground anhydrous K_2CO_3 (1.36 g, 9.8 mmol, 6.5 eq.) was added. The reaction flask was sealed and the reaction mixture was heated to 90 °C (oil bath temperature 100 °C) for two hours.

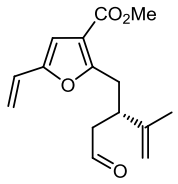
The suspension was allowed to cool to r.t. and the suspended K_2CO_3 was allowed to settle down. The supernatant was decanted and remaining K_2CO_3 was washed four times with Et_2O (4x20 mL). The combined organic layers were quenched with 0.5M $KHSO_4$ and the pH was adjusted to 6. The phases were separated and the aqueous phase was washed 4 times with Et_2O/hexane (1/1). The combined organic layers were dried with $MgSO_4$ and the solvents were removed under reduced pressure. The crude product was purified by silica gel chromatography (hexane/EtOAc = 2/1) yielding pure vinylfuran **367** (452 mg, 1.47 mmol, 97%) as colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.45 (s, 1H); 6.40 (dd, *J* = 17.5, 11.3Hz, 1H); 5.63 (dd, *J* = 17.5, 1.0Hz, 1H); 5.17 (dd, *J* = 11.3, 1.0Hz, 1H); 4.73 (s, 1H); 4.71 (s, 1H); 4.31 (dd, *J* = 6.8, 4.8Hz, 1H); 3.80 (s, 3H); 3.29 (s, 3H); 3.25 (s, 3H); 3.08 (m, 2H); 2.75 (m, 1H); 1.74 (m, 2H); 1.70 (s, 3H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 164.1; 160.7; 151.2; 145.9; 124.3; 115.3; 113.0; 112.5; 108.2; 102.9; 53.0; 52.4; 51.3; 42.4; 35.4; 32.1; 18.5

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{17}H_{24}O_5$: 308.1624; found: 308.1620

(*S*)-methyl 2-(3-methyl-2-(2-oxoethyl)but-3-en-1-yl)-5-vinylfuran-3-carboxylate (**361**)

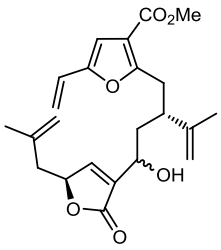


Vinyl furan **367** (4.0 g, 13 mmol, 1.0 eq.) was dissolved in $CHCl_3$ (65 mL) and the solution was cooled to 0 °C. 50% aqueous TFA (32 mL) was added and the solution was allowed to stir for three hours before it was quenched by the addition of sat. aq. $NaHCO_3$. Phases were separated and the organic layer was washed with brine and dried with $MgSO_4$. Removal of the solvent under reduced pressure yielded pure aldehyde **361** (3.4 g, 13 mmol, quant.) as colorless viscous oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.64 (dd, *J* = 2.5, 0.5Hz, 1H); 6.47 (s, 1H); 6.42 (dd, *J* = 17.5, 11.3Hz, 1H); 5.65 (dd, *J* = 17.5, 1.0Hz, 1H); 5.21 (dd, *J* = 11.3, 1.0Hz, 1H); 4.80 (s, 1H); 4.76 (s, 1H); 3.82 (s, 3H); 3.16 (m, 2H); 3.11 (m, 1H); 2.53 (m, 2H); 1.76 (s, 3H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{15}H_{18}O_4$: 262.1205; found: 262.1194

Methyl-2-((*2R*)-2-(2-hydroxy-2-((*S*)-5-(2-methylallyl)-2-oxo-2,5-dihydrofuran-3-yl)ethyl)-3-methylbut-3-en-1-yl)-5-vinylfuran-3-carboxylate (**368a**)



DIPA (181 µL, 1.28 mmol, 1.2 eq.) was dissolved in anhydrous THF (3 mL) and the mixture was cooled to -10 °C when n-BuLi (2.5M in hexane; 491 µL, 1.23 mmol, 1.15 eq.) was added. The mixture was allowed to stir at -10 °C for 30 min, before it was cooled to -78 °C. Then, a solution of selenolactone **185** (347 mg, 1.17 mmol, 1.1 eq.) in anhydrous THF (3 mL) was added dropwise. Upon completion, the reaction mixture was allowed to stir for 30 minutes. A solution of aldehyde **361** (280 mg, 1.07 mmol, 1.0 eq.) in anhydrous THF (3 mL) was added and the reaction mixture was stirred for one hour. The reaction was quenched by the addition of sat. aq. NH_4Cl. After addition of Et_2O, phases were separated and the aqueous phase was neutralized by the addition of 0.5M $KHSO_4$.

The aqueous layer was extracted twice with Et_2O and the combined organic phases were dried with $MgSO_4$. Evaporation of the solvent under reduced pressure yielded the desired triene as colorless viscous oil (590 mg, 1.06 mmol, 99%).

The previously prepared triene (590 mg, 1.07 mmol, 1.0 eq.) was dissolved in CH_2Cl_2 (50 mL) and 10 mL of sat. aq. NH_4Cl were added. The biphasic mixture was cooled to 0 °C and 30% H_2O_2 (330 µL, 3.2 mmol, 3 eq.) was added. The reaction was stirred at 0 °C for one hour and then quenched by the addition of sat. aq. $Na_2S_2O_3$. Phases were separated and the organic phase was extracted 4 times with water. The organic layer was dried with $MgSO_4$ and the solvent was removed under reduced pressure. After silica gel chromatography (hexane/EtOAc = 2/1) butenolide **368a** was obtained as colorless oil (307 mg, 0.77 mmol, 72%) as a mixture of diastereo isomers (2/1).

Major:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.23 (dd, *J* = 1.4, 1.4Hz, 1H); 6.44 (s, 1H); 6.40 (dd, *J* = 17.6, 11.3Hz, 1H); 5.62 (d, *J* = 17.6Hz, 1H); 5.17 (d, *J* = 11.3Hz, 1H); 5.07 (m, 1H); 4.91 (s, 1H); 4.82 (s, 1H); 4.78 (s, 1H); 4.76 (s, 1H); 4.44 (d, *J* = 9.8Hz, 1H); 3.80 (s, 3H); 3.15 (m, 1H); 3.05 (m, 1H); 2.97 (m, 1H); 2.57 (bs, 1H); 2.44 (m, 1H); 2.33 (m, 1H); 1.99 (m, 1H); 1.79 (s, 3H); 1.74 (s, 3H); 1.64 (m, 1H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 172.1; 164.2; 160.6; 151.2; 147.9; 145.5; 139.6; 137.0; 124.3; 115.2; 114.3; 113.5; 113.1; 108.1; 80.1; 65.2; 51.3; 43.0; 41.3; 38.0; 32.2; 22.9; 17.9

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{23}H_{28}O_6Na$: 423.1784; found: 423.1778

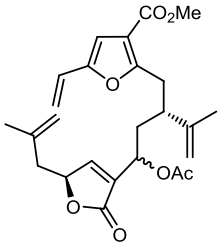
Minor:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.25 (dd, *J* = 1.4, 1.4Hz, 1H); 6.45 (s, 1H); 6.40 (dd, *J* = 17.6, 11.3Hz, 1H); 5.62 (d, *J* = 17.6Hz, 1H); 5.19 (d, *J* = 11.3Hz, 1H); 5.08 (m, 1H); 4.92 (s, 1H); 4.83 (s, 1H); 4.73 (s, 1H); 4.68 (s, 1H); 4.59 (bs, 1H); 3.81 (s, 3H); 3.29 (d, *J* = 3.7Hz, 1H); 3.21 (dd, *J* = 14.4, 5.5Hz, 1H); 3.03 (dd, *J* = 14.4, 9.4Hz, 1H); 2.77 (m, 1H); 2.44 (m, 1H); 2.35 (m, 1H); 2.00 (m, 1H); 1.80 (s, 3H); 1.79 (m, 1H); 1.74 (s, 3H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 172.2; 164.5; 161.2; 151.2; 148.4; 146.6; 139.6; 136.3; 124.3; 114.8; 114.4; 113.2; 112.7; 108.0; 80.2; 65.6; 51.5; 43.6; 41.3; 38.8; 31.1; 23.0; 18.6

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{23}H_{28}O_6Na$: 423.1784; found: 423.1775

Methyl-2-((2R)-2-(2-acetoxy-2-((*S*)-5-(2-methylallyl)-2-oxo-2,5-dihydrofuran-3-yl)ethyl)-3-methylbut-3-en-1-yl)-5-vinylfuran-3-carboxylate (**368b**)

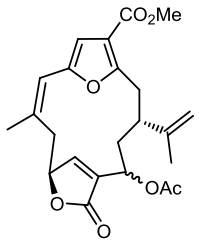


Butenolide **368a** (54 mg, 0.14 mmol, 1.0 eq.) was dissolved in anhydrous CH_2Cl_2 (2 mL) and pyridine (33 µL, 0.41 mmol, 3eq) and DMAP (1.7 mg, 14 µmol, 0.1 eq.) were added. The reaction mixture was cooled to 0 °C and Ac_2O (26 µL, 0.27 mmol, 2 eq.) was added. The solution was allowed to stir at 0 °C for 45 min, then it was quenched by the addition of sat. aq. NH_4Cl. Phases were separated and the aqueous phase was extracted twice with CH_2Cl_2. The combined organic layers were dried with $MgSO_4$ and the solvent was removed under reduced pressure. Purification by silica gel chromatography (hexane/EtOAc = 2/1) yielded acetate **368b** (44 mg, 0.1 mmol, 71%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.11 (dd, *J* = 1.4, 1.4Hz, 1H); 6.46 (s, 1H); 6.40 (dd, *J* = 17.5, 11.3Hz, 1H); 5.63 (d, *J* = 17.5Hz, 1H); 5.45 (m, 1H); 5.19 (d, *J* = 11.3Hz, 1H); 5.04 (m, 1H); 4.91 (s, 1H); 4.79 (m, 2H); 4.67 (s, 1H); 3.81 (s, 3H); 3.10 (m, 2H); 2.77 (m, 1H); 2.42 (m, 1H); 2.32 (m, 1H); 2.08 (m, 1H); 2.07 (s, 3H); 1.84 (m, 1H); 1.77 (s, 3H); 1.74 (s, 3H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{25}H_{30}O_7$: 442.1992; found: 442.1989

(*5S,11R,Z*)-methyl 9-acetoxy-3-methyl-7-oxo-11-(prop-1-en-2-yl)-6,16-dioxatricyclo[11.2.1.15,8]heptadeca-1(15),2,8(17),13-tetraene-14-carboxylate (**369**)



Benzene was degassed with 5 pump and freeze cycles. Both diastereo isomers of acetate **368b** (30 mg, 68 µmol, 1.0 eq.) were dissolved in degassed benzene (34 mL; [2.0mM]) in a flame dried Schlenk flask and the reaction mixture was heated to reflux. Grubbs' second generation metathesis catalyst (11.5 mg, 14 µmol, 0.2 eq.) was dissolved in 2 mL degassed benzene and was added *via* a syringe over a period of 15h using a syringe pump. After the addition was completed the solvent was removed under reduced pressure. Purification by silica gel column chromatography yielded macrocycle **369** as colorless oil (12 mg, 29 µmol, 43%).

Major:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.99 (s, 1H); 6.44 (s, 1H); 6.14 (s, 1H); 5.51 (dd, *J* = 7.5, 3.0Hz, 1H); 5.00 (dd, *J* = 11.7, 5.0Hz, 1H); 4.83 (s, 1H); 4.81 (s, 1H); 3.83 (s, 3H); 3.42 (dd, *J* = 16.7, 9.7Hz, 1H); 3.01 (dd, *J* = 11.8, 11.8Hz, 1H); 2.89 (dd, *J* = 16.7, 3.8Hz, 1H); 2.78 (dd, *J* = 12.0, 4.8Hz, 1H); 2.46 (m, 2H); 2.05 (s, 3H); 2.01 (s, 3H); 1.80 (s, 3H); 1.67 (m, 1H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 170.9; 170.1; 163.9; 160.0; 155.0; 150.2; 147.8; 131.1; 129.2; 117.1; 115.6; 111.0; 110.6; 78.0; 68.2; 51.5; 41.0; 40.3; 36.9; 32.4; 25.8; 20.9; 20.4

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{23}H_{26}O_7$: 414.1679; found: 414.1673

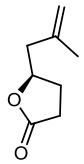
Minor:

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 7.21 (s, 1H); 6.46 (s, 1H); 6.13 (s, 1H); 5.38 (dd, *J* = 12.1, 4.2Hz, 1H); 5.08 (ddd, *J* = 12.0, 4.9, 1.6Hz, 1H); 4.98 (s, 1H); 4.96 (s, 1H); 3.83 (s, 3H); 3.53 (dd, *J* = 16.5, 12.9Hz, 1H); 3.12 (dd, *J* = 11.8, 11.8Hz, 1H); 2.81 (dd, *J* = 12.2, 4.9Hz, 1H); 2.69 (dd, *J* = 16.6, 3.8Hz, 1H); 2.32 (m, 1H); 2.13 (m, 1H); 2.02 (s, 3H); 1.95 (s, 3H); 1.80 (s, 3H); 1.26 (m, 1H)

^{13}C-NMR (150 MHz, $CDCl_3$): δ = 169.5; 169.4; 163.9; 153.9; 150.6; 129.9; 121.6; 116.9; 116.3; 113.8; 111.0; 78.7; 65.2; 51.6; 41.0; 39.7; 37.4; 32.2; 25.7; 20.9; 19.2

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{23}H_{26}O_7$: 414.1679; found: 414.1671

(*R*)-5-(2-methylallyl)dihydrofuran-2(3H)-one (**456**)



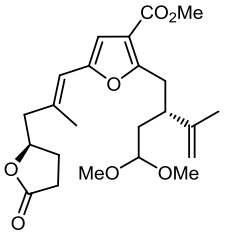
A mixture of sodium (1.31 g, 57.1 mmol, 8 eq.) and anhydrous EtOH (50 mL) was stirred at 0 °C until the evolution of dihydrogen has ceased. A solution of diethylmalonate (5.42 mL, 35.7 mmol, 5 eq.) in anhydrous EtOH (10 mL) was added and the reaction mixture was allowed to stir at 0 °C for 30 minutes. In the meantime a solution of tosylate **202** (1.93 g, 7.14 mmol, 1.0 eq.) in anhydrous THF (35 mL) was treated with NaH (60% suspension in mineral oil, 285 mg, 7.14 mmol, 1.0 eq.) at 0 °C for 30 minutes. After this period of time the suspension with the *in situ* generated epoxide was cannulated slowly to the solution of the sodium malonate. The reaction mixture was allowed to stir for four hours (TLC completeness) before it was quenched by the addition of 1M HCl. Et_2O was added and the phases were separated. The pH of the aqueous phase was adjusted to slightly acidic and the aqueous phase was extracted twice with Et_2O. The combined organic layers were dried with brine and $MgSO_4$ and the solvents were removed under reduced pressure. The desired lactone was obtained as colorless oil (700 mg, 3.3 mmol, 46%) and the crude product was of satisfying purity for further conversion.

The previously prepared lactone (700 mg, 3.3 mmol, 1.0 eq.) was dissolved in DMSO (6 mL), then LiCl (280 mg, 6.6 mmol, 2 eq.) and water (60 µL, 3.3 mmol, 1.0 eq.) were added. The reaction mixture was sealed and heated to 150 °C for two hours (*Krapcho* protocol).[140] Et_2O, hexane and sat. aq. NH_4Cl were added and the phases were separated. The organic phases was dried with brine and $MgSO_4$ and the solvent was removed *in vacuo*. Silica gel chromatography (hexane/EtOAC = 3/1 to 2/1) yielded pure lactone **456** (365 mg, 2.6 mmol, 79%) as colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.87 (s, 1H); 4.79 (s, 1H); 4.65 (m, 1H); 2.52 (m, 3H); 2.31 (m, 2H); 1.91 (m, 1H); 1.78 (s, 3H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_8H_{12}O_2$: 140.0837; found: 140.0834

Methyl-2-((*S*)-2-(2,2-dimethoxyethyl)-3-methylbut-3-en-1-yl)-5-((*E*)-2-methyl-3-((*R*)-5-oxotetrahydrofuran-2-yl)prop-1-en-1-yl)furan-3-carboxylate (**457**)

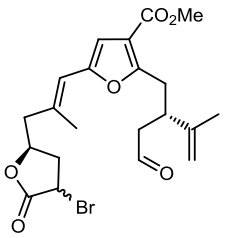


Lactone **456** (240 mg, 1.71 mmol, 2 eq.) and vinylfuran **367** (264 mg, 0.86 mmol, 1.0 eq.) were dissolved in anhydrous, degassed (5 pump and freeze cycles) benzene (160 mL). The solution was heated to reflux overnight and a solution of Grubbs-Hoveyda 2nd generation catalyst (108 mg, 0.17 mmol, 0.2 eq.) in anhydrous, degassed benzene (10 mL) was added slowly *via* a syringe pump within 10 hours. After that period of time, the solvent was removed under reduced pressure. Purification by silica gel chromatography (hexane/EtOAc = 5/1 to 1/1) yielded pure compound **457** (104 mg, 0.25 mmol, 29%) as colorless semi-solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.43 (s, 1H); 6.06 (s, 1H); 4.72 (s, 1H); 4.71 (s, 1H); 4.68 (m, 1H); 4.30 (dd, *J* = 5.8, 5.8Hz, 1H); 3.81 (s, 3H); 3.28 (s, 3H); 3.26 (s, 3H); 3.06 (m, 2H); 2.74 (m, 1H); 2.62 (m, 1H); 2.54 (m, 2H); 2.42 (m, 1H); 2.33 (m, 1H); 2.02 (s, 3H); 1.92 (m, 1H); 1.70 (s, 3H); 1.69 (m, 2H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{23}H_{32}O_7$: 420.2148; found: 420.2145

Methyl-5-((*E*)-3-((*2S*)-4-bromo-5-oxotetrahydrofuran-2-yl)-2-methylprop-1-en-1-yl)-2-((*S*)-3-methyl-2-(2-oxoethyl)but-3-en-1-yl)furan-3-carboxylate (**459**)



Compound **457** (47 mg, 0.11 mmol, 1.0 eq.) was dissolved in anhydrous THF (2 mL) and the solution was cooled to 0 °C. Bu_4NBr_3 (81 mg, 0.17 mmol, 1.5 eq.) was added portionwise and the reaction mixture was allowed to warm to r.t. within one hour. Stirring was continued for another two hours before the reaction was quenched by the addition of sat. aq. $Na_2S_2O_3$ solution. Et_2O was added and the phases were separated.

The organic layer was dried with brine and $MgSO_4$ and the solvents were removed under reduced pressure. The desired bromo-lactone **458** (49 mg, 98 µmol, 88%) was obtained as slightly yellow oil.

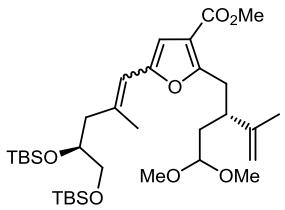
The previously prepared bromo-lactone **458** (49 mg, 98 µmol, 1.0 eq.) was dissolved in $CHCl_3$ (3 mL) and the solution was cooled to 0 °C. 50% aqueous TFA (1.5 mL) were added and the solution was allowed to stir for three hours before it was quenched by the addition of sat. aq. $NaHCO_3$. Phases were separated and the organic layer was washed with brine and dried with $MgSO_4$. Removal of the solvent under reduced pressure yielded pure aldehyde **459** (44 mg, 97 µmol, 99%) as colorless viscous oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.62 (m, 1H); 6.44 (s, 1H); 6.08 (s, 1H); 4.79 (s, 1H); 4.76 (s, 1H); 4.69 (m, 1H); 4.64 (m, 1H); 3.83 (s, 3H); 3.44 (m, 2H); 3.19 (m, 2H); 2.55 (m, 3H); 2.32 (m, 2H); 2.03 (s, 3H); 1.76 (s, 3H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{21}H_{25}BrO_6$: 452.0835; found: 452.0831

4.2.15 $\Delta^{11,12}$ Horner Wadsworth Emmons Approach (*i*Pr)

Methyl-5-((*S*)-4,5-bis((tert-butyldimethylsilyl)oxy)-2-methylpent-1-en-1-yl)-2-((*S*)-2-(2,2-dimethoxyethyl)-3-methylbut-3-en-1-yl)furan-3-carboxylate (**371**)



NaH (60% in mineral oil, 447 mg, 11.2 mmol, 1.0 eq.) was suspended in anhydrous THF (60 mL). The reaction mixture was cooled to 0 °C and a solution of β-keto ester **362** (4.8 g, 11.2 mmol, 1.0 eq.) in anhydrous THF (30 mL) was added. The reaction was stirred at 0 °C for 20 minutes and then warmed to r.t. within 10 minutes. Then it was re-cooled to 0 °C and a solution of propargylic iodide **259** (6.89 g, 11.2 mmol, 1.0 eq.) was added uninterruptedly at 0 °C. The reaction mixture was stirred at this temperature for 20 minutes and then warmed to r.t. within 20 minutes before it was quenched with saturated aqueous NH_4Cl. Et_2O was added and the phases separated.

The pH of the aqueous phase was adjusted to 6 with 0.5M $KHSO_4$ and it was extracted twice with Et_2O. The combined organic layers were dried with $MgSO_4$ and the solvent was removed under reduced pressure. The desired alkylated β-keto ester (6.9 g, 9.2 mmol, 83%) was obtained as slightly yellow oil.

Previously prepared alkylated β-keto ester (6.8 g, 9.1 mmol, 1.0 eq.) was dissolved in anhydrous DMF (100 mL) under an Ar-atmosphere and finely ground anhydrous K_2CO_3 (8.22 g, 59.2 mmol, 6.5 eq.) was added. The reaction flask was sealed and the reaction mixture was heated to 90 °C (oil bath temperature 100 °C) for two hours. Stirring was stopped, the suspension was allowed to cool to r.t. and the suspended K_2CO_3 was allowed to settle down. The supernatant was decanted and remaining K_2CO_3 was washed four times with Et_2O (4x40 mL). The combined organic layers were quenched with 0.5M $KHSO_4$ and the pH was adjusted to 6. The phases were separated and the aqueous phase was washed 4 times with Et_2O/hexane (1/1). The combined organic layers were dried with $MgSO_4$ and the solvents were removed under reduced pressure. The crude product was purified by silica gel chromatography (hexane/EtOAc = 7/1 to 5/1) yielding vinylfuran **371** (5.05 g, 8.1 mmol, 89%) as mixture of double bond isomers (*E/Z* = 2/1).

(*E*)-isomer:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.36 (s, 1H); 6.01 (s, 1H); 4.70 (s, 1H); 4.69 (s, 1H); 4.31 (m, 1H); 3.81 (s, 3H); 3.79 (m, 1H); 3.55 (dd, *J* = 9.9, 5.2Hz, 1H); 3.40 (dd, *J* = 9.9, 6.7Hz, 1H); 3.28 (s, 3H); 3.25 (s, 3H); 3.06 (m, 2H); 2.74 (m, 1H); 2.45 (m, 1H); 2.15 (dd, *J* = 13.3, 7.8Hz, 1H); 1.97 (s, 3H); 1.71 (m, 2H); 1.69 (s, 3H); 0.90 (s, 9H); 0.85 (s, 9H); 0.05 (s, 6H); -0.02 (s, 6H);

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 164.5; 159.2; 151.7; 151.2; 146.0; 137.7; 136.4; 116.2; 115.9; 115.0; 112.4; 107.6; 102.9; 71.9; 68.8; 67.1; 53.0; 52.3; 51.2; 45.9; 42.4; 38.7; 35.4; 32.1; 25.8; 19.4; 18.5; 18.0; -4.5; -5.4

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{33}H_{60}O_7Si_2$: 624.3878; found: 624.3871

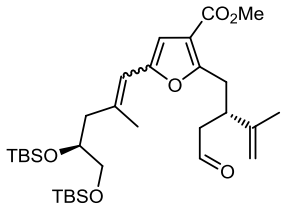
(*Z*)-isomer:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.54 (s, 1H); 6.04 (s, 1H); 4.70 (s, 1H); 4.69 (s, 1H); 4.31 (m, 1H); 3.94 (m, 1H); 3.79 (s, 3H); 3.60 (dd, *J* = 9.9, 5.2Hz, 1H); 3.45 (dd, *J* = 9.9, 6.7Hz, 1H); 3.28 (s, 3H); 3.24 (s, 3H); 3.06 (m, 2H); 2.74 (m, 1H); 2.57 (m, 1H); 2.52 (m, 1H); 1.91 (s, 3H); 1.71 (m, 2H); 1.69 (s, 3H); 0.89 (s, 9H); 0.83 (s, 9H); 0.05 (s, 6H); 0.03 (s, 3H); 0.02 (s, 3H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 164.5; 159.1; 151.7; 151.2; 146.1; 137.7; 136.4; 116.2; 115.9; 114.9; 112.3; 107.7; 102.9; 71.8; 68.0; 67.1; 52.9; 52.2; 51.1; 45.9; 42.4; 38.7; 35.3; 32.1; 25.9; 19.4; 18.5; 18.1; -4.8; -5.4

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{33}H_{60}O_7Si_2$: 624.3878; found: 624.3869

Methyl-5-((*S*)-4,5-bis((tert-butyldimethylsilyl)oxy)-2-methylpent-1-en-1-yl)-2-((*S*)-3-methyl-2-(2-oxoethyl)but-3-en-1-yl)furan-3-carboxylate (**460**)



$LiBF_4$ (197 mg, 2.1 mmol, 1.1 eq.) was dissolved in a mixture of CH_3CN/H_2O (20 mL/0.4 mL) and the reaction mixture was cooled to 0 °C. A solution of dimethyl acetal **371** (1.19 g, 1.9 mmol, 1.0 eq.) in 6 mL CH_3CN was added dropwise. The solution was stirred at 0 °C for two hours before it was quenched by the addition of water and Et_2O. Phases were separated and the organic layer was washed twice with water. After drying with brine and $MgSO_4$ the solvent was removed *in vacuo*. Purification by silica gel chromatography (hexane/EtOAc = 5/1) yielded aldehyde **460** (880 mg, 1.52 mmol, 80%) as colorless oil and a mixture of double bond isomers (2/1).

(*E*)-isomer:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.62 (dd, *J* = 2.5, 0.8Hz, 1H); 6.38 (s, 1H); 6.02 (s, 1H); 4.77 (s, 1H); 4.74 (s, 1H); 3.82 (s, 3H); 3.81 (m, 1H); 3.55 (dd, *J* = 9.9, 5.2Hz, 1H); 3.40 (dd, *J* = 9.9, 6.7Hz, 1H); 3.12 (m, 3H); 2.55 (m, 2H); 2.46 (m, 2H); 1.97 (s, 3H); 1.75 (s, 3H); 0.90 (s, 9H); 0.85 (s, 9H); 0.05 (s, 6H); -0.02 (s, 6H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 201.5; 164.4; 158.1; 152.1; 151.6; 145.3; 138.2; 137.0; 129.8; 116.2; 116.0; 115.7; 113.8; 112.5; 107.6; 102.9; 71.8; 68.0; 67.1; 51.3; 46.4; 45.9; 40.7; 38.7; 31.7; 25.8; 19.4; 18.3; 18.0; -4.5; -4.8

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{31}H_{54}O_6Si_2$: 578.3459; found: 578.3451

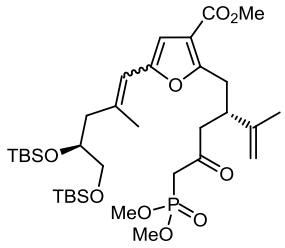
(*Z*)-isomer:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.60 (dd, *J* = 2.5, 0.8Hz, 1H); 6.55 (s, 1H); 6.04 (s, 1H); 4.78 (s, 1H); 4.76 (s, 1H); 3.94 (m, 1H); 3.80 (s, 3H); 3.61 (dd, *J* = 9.9, 5.2Hz, 1H); 3.45 (dd, *J* = 9.9, 6.7Hz, 1H); 3.12 (m, 3H); 2.55 (m, 2H); 2.45 (m, 2H); 1.92 (s, 3H); 1.75 (s, 3H); 0.89 (s, 9H); 0.83 (s, 9H); 0.05 (s, 6H); 0.03 (s, 3H); 0.02 (s, 3H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 201.5; 164.4; 158.1; 152.1; 151.6; 145.4; 138.2; 137.0; 129.6; 116.2; 116.0; 115.7; 113.8; 112.5; 107.7; 102.9; 71.8; 68.0; 67.1; 51.2; 46.4; 45.9; 40.7; 38.7; 31.7; 25.7; 19.4; 18.3; 18.0; -4.8; -5.3

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{31}H_{54}O_6Si_2$: 578.3459; found: 578.3453

Methyl-5-((*S*)-4,5-bis((tert-butyldimethylsilyl)oxy)-2-methylpent-1-en-1-yl)-2-((*S*)-5-(dimethoxyphosphoryl)-4-oxo-2-(prop-1-en-2-yl)pentyl)furan-3-carboxylate (**373**)



Aldehyde **460** (880 mg, 1.52 mmol, 1.0 eq.) and dimethyl (diazomethyl)phosphonate (684 mg, 4.56 mmol, 3 eq.) were dissolved in anhydrous CH_2Cl_2 (15 mL). Anhydrous $SnCl_2$ (432 mg, 2.28 mmol, 1.5 eq.) was added in one portion. The reaction mixture was stirred overnight at r.t. before it was quenched by the addition of sat. aq. NH_4Cl. The phases were separated and the neutralized aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were dried with $MgSO_4$ and the solvent was removed *in vacuo*. Purification by silica gel chromatography (hexane/EtOAc = 2/1 to 1/1) resulted β-keto phosphonate **373** (677 mg, 1.32 mmol, 87%) as colorless oil.

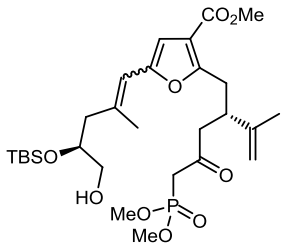
(*E*)-isomer:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.36 (s, 1H); 6.02 (s, 1H); 4.71 (s, 1H); 4.70 (s, 1H); 3.82 (s, 3H); 3.77 (s, 3H); 3.74 (s, 3H); 3.55 (dd, *J* = 9.9, 5.2Hz, 1H); 3.40 (dd, *J* = 9.9, 6.7Hz, 1H); 3.12 (m, 3H); 3.03 (m, 2H); 2.82 (m, 1H); 2.68 (m, 1H); 2.46 (dd, *J* = 13.3, 3.9Hz, 1H); 2.16 (dd, *J* = 13.3, 7.7Hz, 1H); 1.97 (s, 3H); 1.73 (s, 3H); 0.90 (s, 9H); 0.85 (s, 9H); 0.05 (s, 6H); -0.02 (s, 6H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 177.7; 164.4; 158.4; 152.0; 145.7; 136.8; 116.1; 112.1; 107.6; 71.9; 67.1; 53.0; 51.3; 47.4; 45.9; 42.0; 41.2; 40.7; 31.6; 26.0; 19.7; 19.4; -4.5; -5.3

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{34}H_{61}O_9PSi_2$: 700.3592; found: 700.3586

Methyl-5-((*S*)-4-((tert-butyldimethylsilyl)oxy)-5-hydroxy-2-methylpent-1-en-1-yl)-2-((*S*)-5-(dimethoxyphosphoryl)-4-oxo-2-(prop-1-en-2-yl)pentyl)furan-3-carboxylate (**461**)



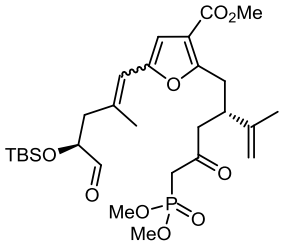
β-keto phosphonate **373** (67 mg, 0.1 mmol, 1.0 eq.) was dissolved in anhydrous MeOH (3 mL) and finely ground NH_4F (177 mg, 4.78 mmol, 50 eq.) was added. The reaction mixture was stirred at r.t. for 2 days. Water and Et_2O were added and the phases were separated. The organic layer was washed two times with water and dried with brine and $MgSO_4$. Silica gel chromatography (hexane/EtOAc = 1/1) yielded primary alcohol **461** (42 mg, 72 µmol, 72%) as colorless oil.

(*E*)-isomer:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.39 (s, 1H); 6.02 (s, 1H); 4.72 (s, 1H); 4.70 (s, 1H); 3.92 (m, 1H); 3.82 (s, 3H); 3.77 (s, 3H); 3.74 (s, 3H); 3.57 (m, 1H); 3.12 (m, 2H); 3.03 (m, 1H); 2.84 (m, 2H); 2.68 (m, 1H); 2.64 (m, 1H); 2.52 (m, 1H); 2.34 (d, *J* = 6.5Hz, 1H); 2.26 (m, 1H); 1.97 (s, 3H); 1.72 (s, 3H); 0.89 (s, 9H); 0.08 (s, 3H); 0.04 (s, 3H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{28}H_{47}O_9PSi$: 586.2727; found: 586.2724

Methyl-5-((*S*)-4-((tert-butyldimethylsilyl)oxy)-2-methyl-5-oxopent-1-en-1-yl)-2-((*S*)-5-(dimethoxyphosphoryl)-4-oxo-2-(prop-1-en-2-yl)pentyl)furan-3-carboxylate (**374**)



Primary alcohol **461** (42 mg, 72 µmol, 1.0 eq.) was dissolved in anhydrous DMSO (1.5 mL) and IBX (40 mg, 0.14 mmol, 2 eq.) was added. The reaction mixture was stirred at r.t. for two hours or until all starting material was consumed. 2 mL of hexane and 2 mL of EtOAc were added and the suspension was filtered through a pad of celite 545 coarse. The filtrate was transferred to a separatory funnel and water was added.

The phases were separated and the organic phase was washed twice with fresh water. The combined aqueous layers were back-extracted twice with EtOAc. The combined organic layers were dried with brine and $MgSO_4$ and the solvents were removed *in vacuo*. Aldehyde **374** (42 mg, 72 µmol, quant.) was obtained as colorless oil.

(*E*)-isomer:

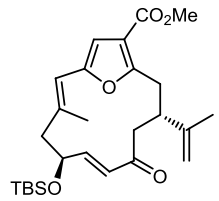
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.63 (d, *J* = 1.5Hz, 1H); 6.40 (s, 1H); 6.04 (s, 1H); 4.71 (s, 1H); 4.70 (s, 1H); 4.10 (ddd, *J* = 4.3, 4.1, 1.7Hz, 1H); 3.95 (m, 6H); 3.81 (s, 3H); 3.19 (m, 3H); 3.05 (m, 2H); 2.78 (m, 1H); 2.64 (m, 1H); 2.48 (dd, *J* = 13.6, 3.9Hz, 1H); 2.16 (dd, *J* = 13.6, 8.3Hz, 1H); 1.99 (s, 3H); 1.73 (s, 3H); 0.88 (s, 9H); -0.01 (s, 6H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 203.6; 194.1; 164.2; 158.5; 151.4; 145.1; 135.0; 133.8; 117.3; 116.4; 115.5; 112.5; 108.5; 76.9; 76.4; 56.2; 51.3; 43.9; 41.0; 40.2; 36.6; 31.4; 25.7; 19.8; 19.1; 18.1; -4.8; -5.1

^{31}P-NMR (162MHz, $CDCl_3$): δ = 11.8

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{28}H_{45}O_9PSi$: 584.2570; found: 584.2564

(*2E,5S,6E,10S*)-methyl 5-((tert-butyldimethylsilyl)oxy)-3-methyl-8-oxo-10-(prop-1-en-2-yl)-15-oxabicyclo[10.2.1]pentadeca-1(14),2,6,12-tetraene-13-carboxylate (**370**)



HFIP (100 µL) was mixed with anhydrous THF (15 mL) and the solution was cooled to 0 °C. n-BuLi (2.2M in cyclohexane; 78 µL, 171 µmol, 5 eq.) was added dropwise and the reaction mixture was incubated for one hour at 0 °C. A solution of *seco* aldehyde **374** (20 mg, 0.34 µmol, 1.0 eq.) in anhydrous THF (5 mL) was added using a syringe pump over a period of time of 16 hours. The reaction mixture was quenched by the addition of sat. aq. NH_4Cl and Et_2O was added. The phases were separated and the organic layer was dried with brine and $MgSO_4$. Removal of the solvents under reduced pressure and purification by silica gel chromatography (hexane/EtOAc = 7/1 to 4/1) yielded pure (*E*)-macrocycle **370** (11 mg, 24 µmol, 71%) as colorless semi-solid.

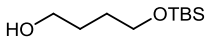
^{1}H-NMR (600 MHz, $CDCl_3$): δ = 6.80 (dd, *J* = 15.9, 3.0Hz, 1H); 6.39 (s, 1H); 6.25 (15.9, 1.9Hz, 1H); 6.05 (s, 1H); 4.83 (s, 1H); 4.77 (s, 1H); 4.45 (m, 1H); 3.79 (s, 3H); 3.38 (dd, *J* = 15.1, 8.3Hz, 1H); 3.12 (m, 1H); 3.07 (dd, *J* = 11.0, 1.5Hz, 1H); 2.89 (dd, *J* = 12.9, 9.0Hz, 1H); 2.75 (dd, *J* = 15.1, 3.8Hz, 1H); 2.30 (m, 2H); 2.17 (m, 1H); 2.00 (s, 3H); 1.81 (s, 3H); 0.94 (s, 9H); 0.13 (s, 3H); 0.11 (s, 3H)

^{13}C-NMR (150 MHz, $CDCl_3$): δ = 202.5; 164.1; 158.6; 151.3; 146.6; 134.3; 126.2; 120.2; 116.6; 116.3; 111.1; 109.9; 69.8; 65.9; 51.4; 44.7; 44.4; 41.3; 38.4; 29.7; 25.9; 25.6; 21.2; 15.3; -4.8; -4.9

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{26}H_{38}O_5Si$: 458.2489; found: 458.2486

4.3 Sarcofuranocembranolide A

4-((tert-butyldimethylsilyl)oxy)butan-1-ol (**462**)

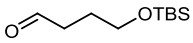


1,4-butandiol (**379**, 23.9 g, 265 mmol, 4 eq.) was dissolved in anhydrous DMF (200 mL) and imidazole (9.0 g, 132 mmol, 2 eq.) was added in one portion. Under Ar-atmosphere, the mixture was cooled to 0 °C and a solution of TBS-Cl (10.0 g, 66 mmol, 1.0 eq.) in anhydrous DMF (50 mL) was added slowly at 0 °C. The reaction mixture was allowed to warm to r.t. overnight. 100 mL of hexane/Et_2O (1/1) and 200 mL of saturated aqueous NH_4Cl were added and the phases separated. The organic phase was extracted with water twice. The combined aqueous phases were back-extracted twice with a 1/1 mixture of hexane/Et_2O and the combined organic layers were dried over $MgSO_4$. Evaporation of the solvent yielded mono silylether **462** (11.6 g, 57 mmol, 86%) as colorless oil, which was purified by silica gel column chromatography (hexane/EtOAc = 4/1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.67(t, *J* = 5.6Hz, 2H); 3.65 (t, *J* = 5.8Hz, 2H); 2.19 (bs, 1H); 1.65 (m, 4H); 0.90 (s, 9H); 0.07 (s, 6H)

HRMS (ESI) (m/z): $[M+Na]^+$ calcd. for $C_{10}H_{24}O_2SiNa$: 227.1443; found: 227.1439

4-((tert-butyldimethylsilyl)oxy)butanal (**380**)

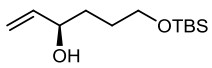


Mono silyl-ether **462** (11.6 g, 57 mmol, 1.0 eq.) was dissolved in anhydrous EtOAc (250 mL) and IBX (32 g, 144 mmol, 2 eq.) was added. The reaction mixtures was refluxed for two hours or until all starting material was consumed. Hexane (250 mL) was added and the suspension was filtered through a pad of celite 545 coarse. Removal of the solvents gave aldehyde **380** (11.5 g, 57 mmol, quant.) as colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.79 (t, *J* = 1.8Hz, 1H); 3.65 (t, *J* = 6.0Hz, 2H); 2.50 (dt, *J* = 7.0, 1.8Hz, 2H); 1.86 (m, 2H); 0.88 (s, 9H); 0.04 (s, 6H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{10}H_{22}O_2Si$: 202.1389; found: 202.1383

(*R*)-6-((tert-butyldimethylsilyl)oxy)hex-1-en-3-ol (**381**)



Adehyde **380** (15 g, 74 mmol, 1.0 eq.) was dissolved in anhydrous THF (600 mL) and the solution was cooled to -78 °C. Vinyl-MgBr (1M in THF, 89 mL, 89 mmol, 1.2 eq.) was added slowly and the reaction mixture was allowed to stir for two hours warming to -40 °C. The reaction was quenched by the addition of sat. aq. NH_4Cl and Et_2O was added. The phases were separated and the pH of the aqueous phase was adjusted to neutral. The aqueous layer was extracted twice with Et_2O and the combined organic layers were dried with brine and $MgSO_4$. The solvent was removed under reduced pressure yielding the desired racemic secondary alcohol (17 g, 74 mmol, quant.) as colorless liquid.

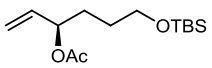
The racemate (17 g, 74 mmol, 1.0 eq.) was dissolved in DIPE (750 mL) and vinyl acetate (15.7 mL, 170 mmol, 2.3 eq.) and Amano lipase PS (19.24 g, [260 mg/mmol]) were added. The reaction mixture was vigorously stirred at 35 °C until NMR measurements indicated a conversion of 52% (approx. two days). The suspension was filtered through a pad of celite coarse 545 and the filtrate was dried with $MgSO_4$. Removal of the solvent under reduced pressure and silica gel chromatography (hexane/EtOAc = 4/1) yielded enantiomerically pure (*R*)-alcohol **381** (7.8 g, 33.9 mmol, 46%) as colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.86 (ddd, *J* = 17.2, 10.3, 5.9Hz, 1H); 5.21 (dt, *J* = 17.2, 1.6Hz, 1H); 5.07 (ddd, *J* = 10.3, 1.7, 1.2Hz, 1H); 4.12 (dd, *J* = 5.8, 11.0Hz, 1H); 3.63 (t, *J* = 5.8Hz, 2H); 2.77 (bs, 1H); 1.62 (m, 4H); 0.88 (s, 9H); 0.04 (s, 6H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 141.2; 114.1; 72.6; 63.4; 34.2; 28.6; 25.8; 18.2; -4.5

HRMS (ESI) (m/z): $[M+Na]^+$ calcd. for $C_{12}H_{26}O_2SiNa$: 263.1600; found: 263.1594

(*R*)-6-((tert-butyldimethylsilyl)oxy)hex-1-en-3-yl acetate (**463**)

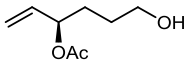


Secondary alcohol **381** (5 g, 21.7 mmol, 1.0 eq.) was dissolved in anhydrous CH_2Cl_2 (100 mL) and NEt_3 (6.1 mL, 43.4 mmol, 2eq) and DMAP (133 mg, 1.1 mmol, 0.05 eq.) were added. The reaction mixture was cooled to 0 °C and Ac_2O (2.46 mL, 26 mmol, 1.2 eq.) was added. The solution was allowed to stir at 0 °C for 45 min, and then it was quenched by the addition of sat. aq. NH_4Cl. Phases were separated and the aqueous phase was extracted twice with CH_2Cl_2. The combined organic layers were dried with $MgSO_4$ and the solvent was removed under reduced pressure. Purification by silica gel chromatography (hexane/EtOAc = 7/1) yielded acetate **463** (5.3 g, 19.5 mmol, 90%) as colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.78 (m, 1H); 5.20 (m, 3H); 3.61 (t, *J* = 6.1Hz, 2H); 2.04 (s, 3H); 1.59 (m, 4H); 0.89 (s, 9H); 0.04 (s, 6H)

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{14}H_{28}O_3Si$: 272.1808; found: 272.1802

(*R*)-6-hydroxyhex-1-en-3-yl acetate (**382**)

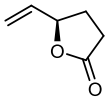


Primary silyl ether **463** (5.3 g, 19.5mol, 1.0 eq.) was dissolved in anhydrous CH_2Cl_2 (100 mL) and 490 mg PPTS (1.95 mmol, 0.1 eq.) in 10 mL anhydrous MeOH was added dropwise. The reaction mixture was stirred for two hours at r.t. The reaction was quenched by the addition of sat. aq. $NaHCO_3$. The phases were separated and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were dried with $MgSO_4$. After removal of the solvent the crude product was purified by silica gel chromatography (hexane/EtOAc = 3/1), giving pure primary alcohol **382** (2.5 g, 16 mmol, 82%) as colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.78 (m, 1H); 5.27 (m, 1H); 5.25 (dd, *J* = 17.4, 1.3Hz, 1H); 5.18 (dd; *J* = 10.5, 1.3Hz, 1H); 3.66 (t, *J* = 6.3Hz, 2H); 2.06 (s, 3H); 1.71 (m, 2H); 1.60 (m, 2H); 1.44 (bs, 1H)

HRMS (ESI) (m/z): $[M+Na]^+$ calcd. for $C_8H_{14}O_3Na$: 181.0841; found: 181.0835

(*R*)-5-vinyldihydrofuran-2(3H)-one (**384**)



Primary alcohol **382** (1.8 g, 11.4 mmol, 1.0 eq.) was dissolved in anhydrous EtOAc (100 mL) and IBX (6.4 g, 22.8 mmol, 2 eq.) was added. The reaction mixtures was refluxed for two hours or until all starting material was consumed. Hexane (100 mL) was added and the suspension was filtered through a pad of celite 545 coarse. Removal of the solvents gave the desired aldehyde (1.8 g, 11.4 mmol, quant.) as colorless oil.

The previously prepared aldehyde (1.8 g, 11.4 mmol, 1.0 eq.) was dissolved in t-BuOH (75 mL) and 2-methyl-but-2-ene (scavenger; 12 mL) were added. The reaction mixture was cooled to 0 °C and an aqueous solution (45 mL) of $NaClO_2$ (15.5 g, 171.0 mmol, 15 eq.) and $NaH_2PO_4.H_2O$ (15.5 g, 112.0 mmol, 9.8 eq.) was added at once. The reaction mixture was stirred at 0 °C for one hour and Et_2O and water were added. The phases were separated and the organic layer was washed twice with water before it was dried with $MgSO_4$. Removal of the solvent under reduced pressure yielded pure carboxylic acid (2.1 g, 11.3 mmol, 99%) as colorless oil, which was subsequently subjected to the next reaction.

1.8 g (9.7 mmol, 1.0 eq.) of the previously prepared carboxylic acid were dissolved in as little anhydrous CH_2Cl_2 as possible. 10 mL of anhydrous MeOH and 2.7 g (19.3 mmol, 2 eq.) of finely ground K_2CO_3 were added. The reaction mixture was stirred for one hour and then acidified by the addition of 1M HCl. CH_2Cl_2 was added and the phases were separated. The aqueous phase was extracted twice with CH_2Cl_2 and the combined organic layers were dried with Na_2SO_4. The solvent was removed *in vacuo* yielding 1.36 g (9 mmol, 93%) of the desired *seco*-acid as colorless oil.

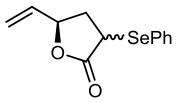
The previously prepared *seco*-acid (1.3 g, 9 mmol, 1.0 eq.) was dissolved in anhydrous CH_2Cl_2 (20 mL) and DMAP (110 mg, 0.9 mmol, 0.1 eq.) was added. The reaction was cooled to 0 °C and DIC (1.8 mL, 11.7 mmol, 1.3 eq.) was added. The reaction mixture was stirred at 0 °C for 90 minutes. The solvent was removed under reduced pressure und the crude product was purified using silica gel chromatography (hexane/EtOAc = 2/1 to 1/1). Vinyl lactone **384** was obtained as colorless oil (1.08 g, 8.55 mmol, 95%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.88 (m, 1H); 5.36 (dd, *J* = 17.2, 1.0Hz, 1H); 5.26 (dd; *J* = 10.6, 1.0Hz, 1H); 4.94 (m, 1H); 2.54 (m, 2H); 2.41 (m, 1H); 2.01 (m, 1H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 176.8; 135.5; 117.4; 80.4; 28.3; 28.2

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_6H_8O_2$: 112.0524; found: 112.0520

(*5R*)-3-(phenylselanyl)-5-vinyldihydrofuran-2(3H)-one (**378**)



An adopted procedure of Pattenden *et al*. was used.[141] Vinyl lactone **384** (1 g, 8.9 mmol, 1.0 eq.) was dissolved in anhydrous THF (80 mL) and the solution was cooled to -78 °C. LiHMDS (1M in THF; 10.7 mL, 10.7 mmol, 1.2 eq.) was added dropwise and the reaction mixture was allowed to stir for 30 minutes. TMS-Cl (1.42 mL, 11.1 mmol, 1.25 eq.) was added dropwise and the reaction mixture was again allowed to stir for 30 minutes. A solution of PhSeBr (2.63 g, 11.1 mmol, 1.25 eq.) in anhydrous THF (15 mL) was added drop wise and the solution was allowed to stir for another 30 minutes, before it was quenched by the addition of sat. aq. NH_4Cl. The phases were separated and the pH of the aqueous layer was adjusted to 6 by the careful addition of aq. 0.5M $KHSO_4$ solution. The aqueous phase was extracted twice with Et_2O and the combined organic layers were dried with brine and $MgSO_4$. The solvent was removed under reduced pressure and silica gel chromatography (hexane/EtOAc = 3/1 to 2/1) yielded pure selenolactone **378** (1.52 g, 5.7 mmol, 64%) as an inconsequential mixture of diastereo isomers.

Major:

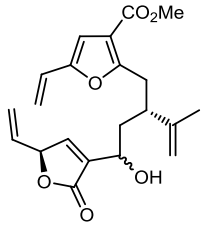
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.69 (m, 2H); 7.36 (m, 3H); 5.82 (m, 1H); 5.33 (dd, *J* = 17.2, 1.0Hz, 1H); 5.25 (dd; *J* = 10.6, 1.0Hz, 1H); 4.77 (m, 1H); 3.97 (dd, *J* = 6.8, 4.8Hz, 1H); 2.43 (m, 2H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 175.3; 135.9; 134.9; 129.5; 129.2; 118.2; 79.2; 36.8; 36.6; 29.7

^{77}Se-NMR (76 MHz, $CDCl_3$): δ = 622.9

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{12}H_{12}O_2Se$: 268.0003; found: 267.9994

Methyl-2-((*2R*)-2-(2-hydroxy-2-((*S*)-2-oxo-5-vinyl-2,5-dihydrofuran-3-yl)ethyl)-3-methylbut-3-en-1-yl)-5-vinylfuran-3-carboxylate (**377a**)



DIPA (1.02 mL, 7.3 mmol, 1.3 eq.) was dissolved in anhydrous THF (30 mL) and the mixture was cooled to -10 °C when n-BuLi (1.6M in hexane; 4.2 mL, 6.7 mmol, 1.2 eq.) was added. The mixture was allowed to stir at -10 °C for 30 min, before it was cooled to -78 °C. Then, a solution of selenolactone **378** (1.5 g, 5.6 mmol, 1.0 eq.) in anhydrous THF (10 mL) was added dropwise. Upon completion, the reaction mixture was allowed to stir for 30 minutes. A solution of aldehyde **361** (1.55 g, 5.9 mmol, 1.05 eq.) in anhydrous THF (10 mL) was added and the reaction mixture was stirred for one hour. The reaction was quenched by the addition of sat. aq. NH_4Cl. After addition of Et_2O, phases were separated and the aqueous phase was neutralized by the addition of 0.5M $KHSO_4$. The aqueous layer was extracted twice with Et_2O and the combined organic phases were dried with $MgSO_4$. Removal of the solvent under reduced pressure yielded the desired triene as colorless viscous oil (2.9 g, 5.5mol, 98%).

The previously prepared triene (2.9 g, 5.5 mmol, 1.0 eq.) was dissolved in CH_2Cl_2 (55 mL) and 20 mL of sat. aq. NH_4Cl were added. The biphasic mixture was cooled to 0 °C and 30% H_2O_2 (2 mL, 16.4 mmol, 3 eq.) was added. The reaction was stirred at 0 °C for one hour and then quenched by the addition of sat. aq. $Na_2S_2O_3$. Phases were separated and the organic phase was extracted 4 times with water. The organic layer was dried with $MgSO_4$ and the solvent was removed under reduced pressure. After silica gel chromatography (hexane/EtOAc = 3/1 to 2/1) butenolide **377a** was obtained as colorless oil (1.59 g, 4.3 mmol, 78%) as an inseparable mixture of diastereo isomers.

Major:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.16 (t, *J* = 1.6Hz, 1H); 6.46 (s, 1H); 6.41 (dd, *J* = 17.5, 11.3Hz, 1H); 5.69 (m, 1H); 5.63 (d, *J* = 17.5Hz, 1H); 5.46 (d, *J* = 17.0Hz, 1H); 5.34 (m, 2H); 5.18 (d, *J* = 11.3Hz, 1H); 4.80 (s, 1H); 4.78 (s, 1H); 4.46 (m, 1H); 3.81 (s, 3H); 3.11 (m, 2H); 2.98 (m, 1H); 2.47 (d, *J* = 5.6Hz, 1H); 2.01 (m, 1H); 1.76 (s, 3H); 1.66 (m, 1H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 172.0; 164.2; 160.6; 151.3; 146.7; 145.5; 136.9; 131.8; 124.4; 119.8; 115.2; 113.6; 113.1; 108.2; 82.0; 65.3; 51.4; 43.1; 37.9; 32.2; 18.0

HRMS (ESI) (m/z): $[M+Na]^+$ calcd. for $C_{21}H_{24}O_6Na$: 395.1471; found: 395.1466

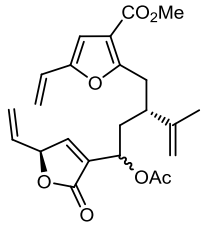
Minor:

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 7.19 (t, *J* = 1.5Hz, 1H); 6.45 (s, 1H); 6.40 (dd, *J* = 17.5, 11.3Hz, 1H); 5.70 (m, 1H); 5.63 (d, *J* = 17.5Hz, 1H); 5.47 (d, *J* = 17.1Hz, 1H); 5.35 (s, 1H); 5.34 (s, 1H); 5.19 (d, *J* = 11.3Hz, 1H); 4.73 (s, 1H); 4.68 (s, 1H); 4.62 (m, 1H); 3.81 (s, 3H); 3.30 (d, *J* = 5.3Hz, 1H); 3.22 (dd, *J* = 14.4, 5.5Hz, 1H); 3.02 (dd, *J* = 14.4, 9.5Hz, 1H); 2.78 (m, 1H); 2.00 (m, 1H); 1.79 (m, 1H); 1.74 (s, 3H)

^{13}C-NMR (150 MHz, $CDCl_3$): δ = 172.1; 164.3; 160.6; 151.2; 147.2; 146.6; 136.8; 131.8; 124.3; 119.8; 115.2; 113.2; 112.8; 108.0; 82.0; 65.6; 51.5; 43.6; 38.7; 31.0; 18.6

HRMS (ESI) (m/z): $[M+Na]^+$ calcd. for $C_{21}H_{24}O_6Na$: 395.1471; found: 395.1464

Methyl-2-((*2R*)-2-(2-acetoxy-2-((*S*)-2-oxo-5-vinyl-2,5-dihydrofuran-3-yl)ethyl)-3-methylbut-3-en-1-yl)-5-vinylfuran-3-carboxylate (**377b**)



Secondary allylic alcohol **377a** (100 mg, 0.27 mmol, 1.0 eq.) was dissolved in anhydrous CH_2Cl_2 (3 mL) and pyridine (26 µL, 0.32 mmol, 1.2eq) and DMAP (3.3 mg, 27 µmol, 0.1 eq.) were added. The reaction mixture was cooled to 0 °C and Ac_2O (30.5 µL, 0.32 mmol, 1.2 eq.) was added. The solution was allowed to stir at 0 °C for 45 min, then it was quenched by the addition of sat. aq. NH_4Cl. Phases were separated and the aqueous phase was extracted twice with CH_2Cl_2. The combined organic layers were dried with $MgSO_4$ and the solvent was removed under reduced pressure. Purification by silica gel chromatography (hexane/EtOAc = 4/1 to 3/1) yielded acetate **377b** (68 mg, 0.16 mmol, 61%).

Major:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.03 (bs, 1H); 6.46 (s, 1H); 6.40 (m, 1H); 5.64 (m, 2H); 5.45 (m, 2H); 5.33 (m, 2H); 5.19 (d, *J* = 11.4Hz, 1H); 4.78 (s, 1H); 4.67(s, 1H); 3.81 (s, 3H); 3.10 (m, 2H); 2.77 (m, 1H); 2.11 (m, 1H); 2.08 (s, 3H); 1.81 (m, 1H); 1.74 (s, 3H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 170.6; 169.7; 164.1; 160.3; 151.3; 149.1; 147.8; 144.6; 133.7; 131.7; 124.4; 120.4; 113.8; 113.1; 108.2; 81.7; 67.4; 51.3; 42.9; 35.2; 32.1; 20.8; 17.9

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{23}H_{26}O_7$: 414.1679; found: 414.1674

Minor:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.13 (bs, 1H); 6.45 (s, 1H); 6.39 (m, 1H); 5.64 (m, 2H); 5.45 (m, 2H); 5.33 (m, 2H); 5.18 (d, *J* = 11.4Hz, 1H); 4.69 (s, 1H); 4.61 (s, 1H); 3.80 (s, 3H); 3.07 (m, 2H); 2.68 (m, 1H); 2.11 (m, 1H); 2.04 (s, 3H); 1.81 (m, 1H); 1.72 (s, 3H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 170.6; 169.7; 164.1; 160.3; 151.3; 149.1; 147.8; 144.6; 132.8; 131.5; 124.3; 120.0; 113.8; 112.9; 108.2; 81.6; 67.4; 51.3; 43.4; 34.9; 32.0; 20.9; 18.2

HRMS (ESI) (m/z): $[M]^+$ calcd. for $C_{23}H_{26}O_7$: 414.1679; found: 414.1673

5 Appendices

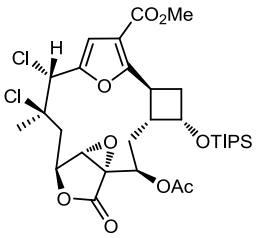
5.1 List of Abbreviations

Ac	acetyl
AIBN	2,2'-azobisisobutyronitrile
aq.	aqueous
Bn	benzyl
Bu	butyl
c	concentration
*c*Bu	cyclobutane/cyclobutyl
CM	cross metathesis
COSY	correlated spectroscopy
CSA	camphorsulfonic acidd
dba	dibenzylideneacetone
dppf	1,1'-bis(diphenylphosphino) ferrocene
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	N,N'-dicyclohexylcarbo-diimide
CH_2Cl_2	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL-H	diisobutylaluminium hydride
DIC	N,N'-diisopropylcarbodiimide
DIPEA	N,N-diisopropylethylamine
DMAP	4-(dimethylamino)pyridine
DMAPP	dimethyl-allyl-pyrophophate
DMF	N,N-dimethylformamide
DMP	Dess-Martin periodinane
DMS	dimethylsulfide
DMSO	dimethylsulfoxide
EDC	N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide
eq.	equivalent
et al.	latin: "et alii", meaning "and others"
etc.	latin: "et cetera", meaning "and so on"
HMPA	hexamethylphosphoramide
HSQC	heteronuclear single quantum coherence
HRMS	high resolution mass spectroscopy
HSQC	heteronuclear single quantum coherence
HPLC	high pressure/performance liquid chromatography
HWE	Horner-Wadsworth-Emmons
Hz	Hertz
IBX	o-iodoxybenzoic acid
IC_{50}	half maximal inhibitory concentration
IPP	isopentenyl-pyrophosphate

*i*Pr	2-propenyl
J	coupling constant
KHMDS	potassium hexamethyldisilazide
KOt-Bu	potassium tert-butoxide
LDA	lithium diisopropylamide
LG	leaving group
LiHMDS	lithium hexamethyldisilazide
mCPBA	*meta*-chloroperbenzoic acid
MEM	(2-methoxyethoxy)methyl
Ms	methansulfonyl
MS	mass spectroscopy
MVK	methyl vinyl ketone
NaHMDS	sodium hexamethyldisilazide
NBS	N-bromosuccinimide
NEt_3	triethylamine
NHK	Nozaki-Hiyama-Kishi
NIS	N-iodosuccinimide
NMR	nuclear magnetic resonance
NOE	nuclear *Overhauser* effect
NOESY	nuclear Overhauser effect spectroscopy
PG	protecting group
Ph	phenyl
PMB	*para*-methoxybenzyl
ppm	parts per million
Py	pyridine
R(1,2…n)	any substituent (if not otherwise stated)
RCM	ring closing metathesis
Rf	ratio of fronts (TLC)
r.t.	room temperature
sat.	saturated
SEM	(trimethylsilyl)ethoxymethyl
TBAF	tetra-n-butylammonium fluoride
TBAI	tetra-n-butylammonium iodide
TBDPS	tert-butyldiphenylsilyl
TBS	tert-butyldimethylsilyl
TEA	triethylamine
TES	triethylsilyl
TFA	trifluoroacetic acid
THF	tetrahydrofurane
THP	tetrahydropyran
Tf	trifluoromethanesulfonate
TLC	thin layer chromatography
TMS	trimethylsilyl
Troc	2,2,2-trichloroethyl carbonate
*p*TsOH	para-toluene-4-sulfonic acid

5.2 Single-Crystal Diffraction Data

Chlorinated (*Z*)-Pentacycle (**207a**)



207a

Empirical formula: $C_{31}H_{44}O_9Cl_2Si$
Formula weight (g/mol): 659.67
Space group: $P2_12_12_1$
Cell symmetry: orthorhombic
Temperature (K): 100
a (Å): 12.6266
b (Å): 12.6455
c (Å): 20.9213
V (Å^3): 3340.50
Z: 4
hkl (min/max): -13 ≤ h ≤ 15, -15 ≤ k ≤ 14, -25 ≤ l ≤ 25

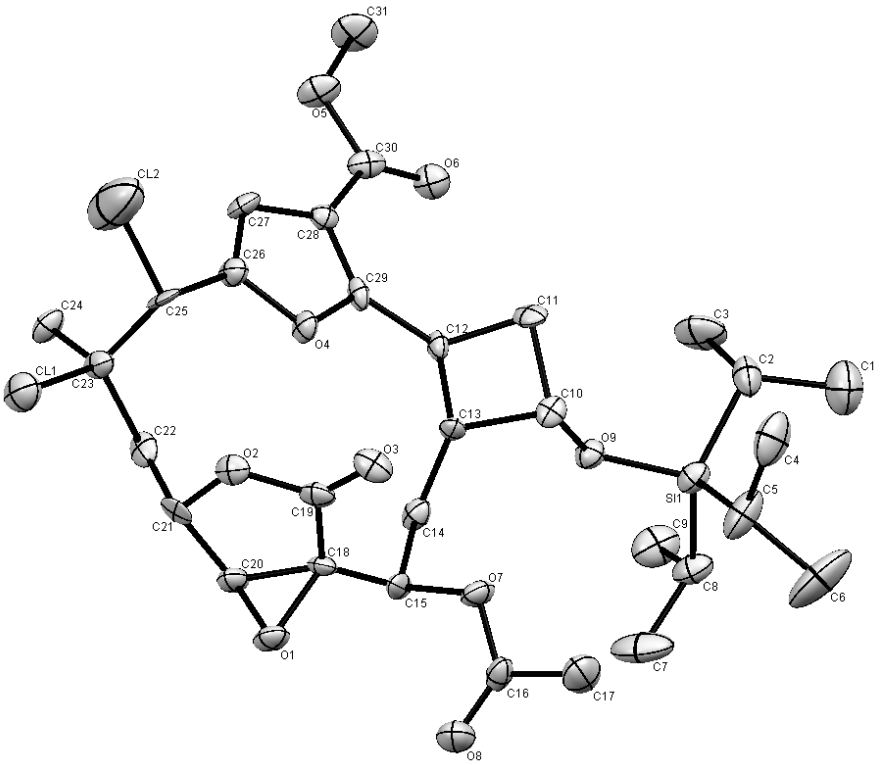
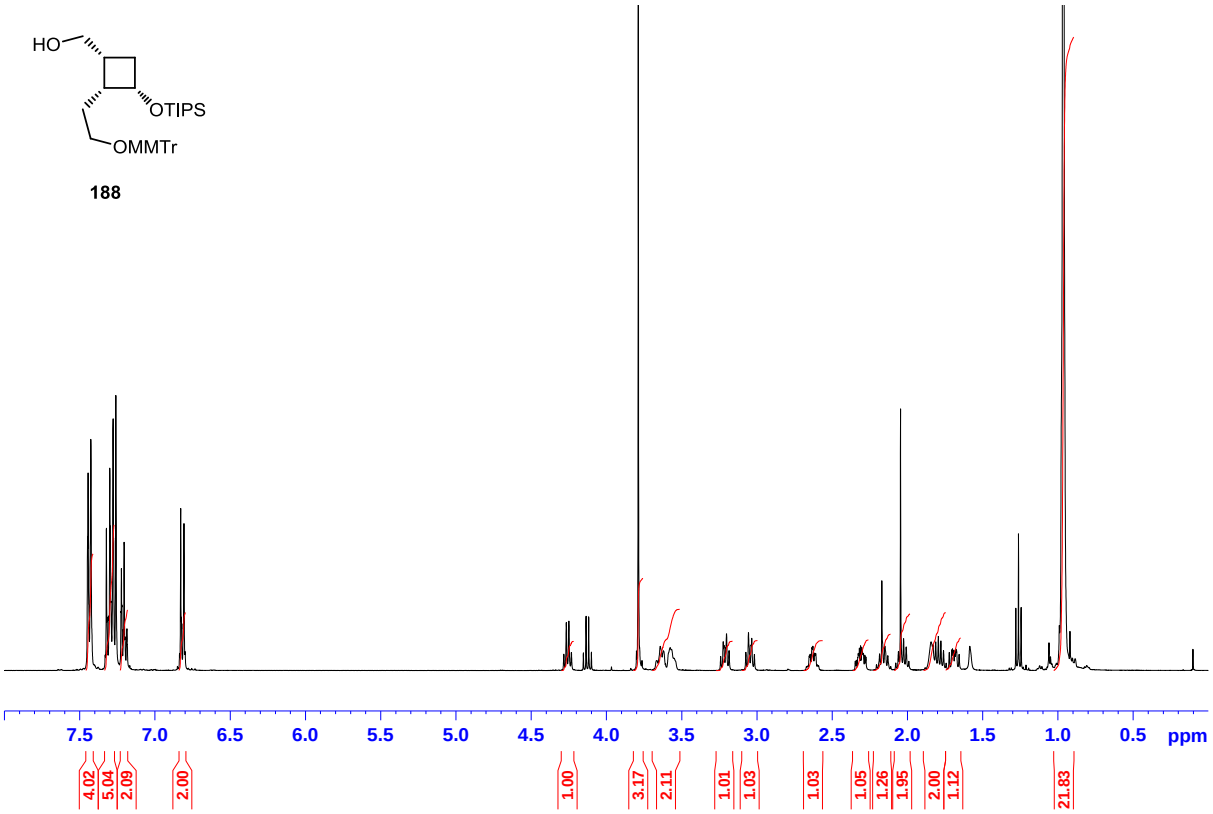
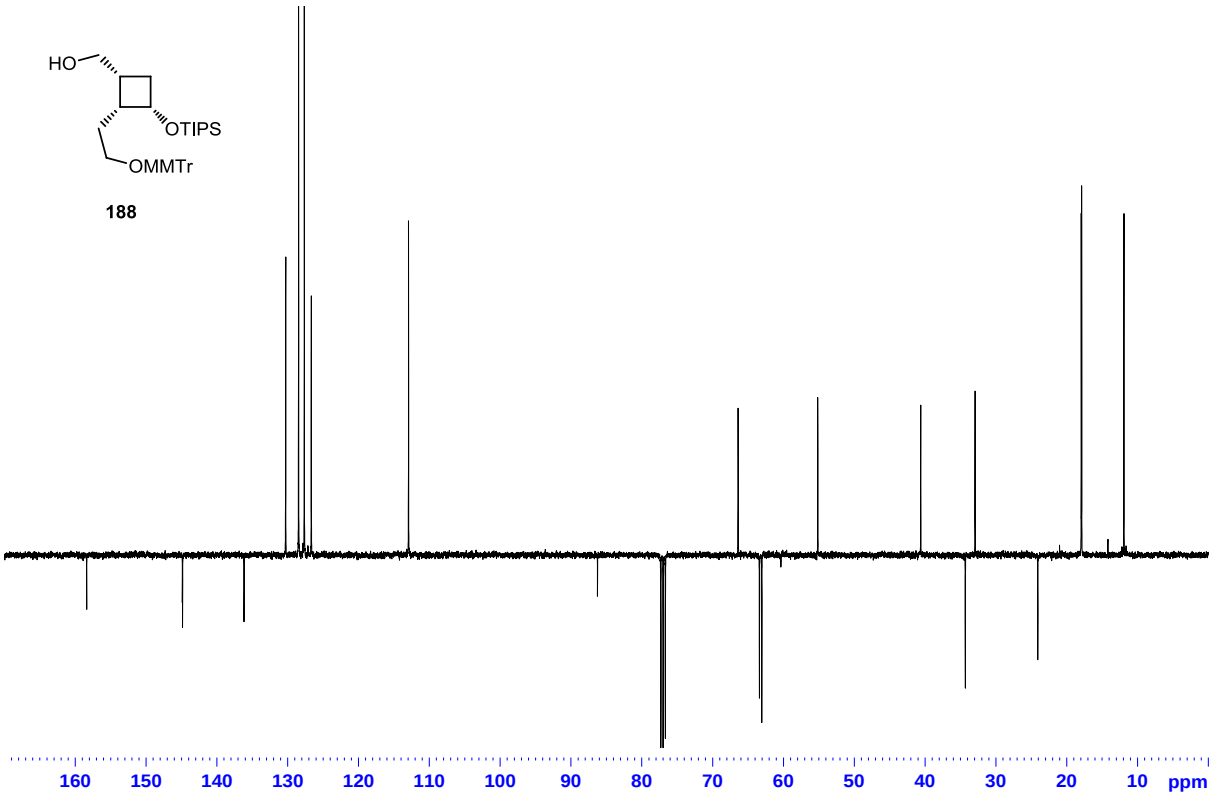


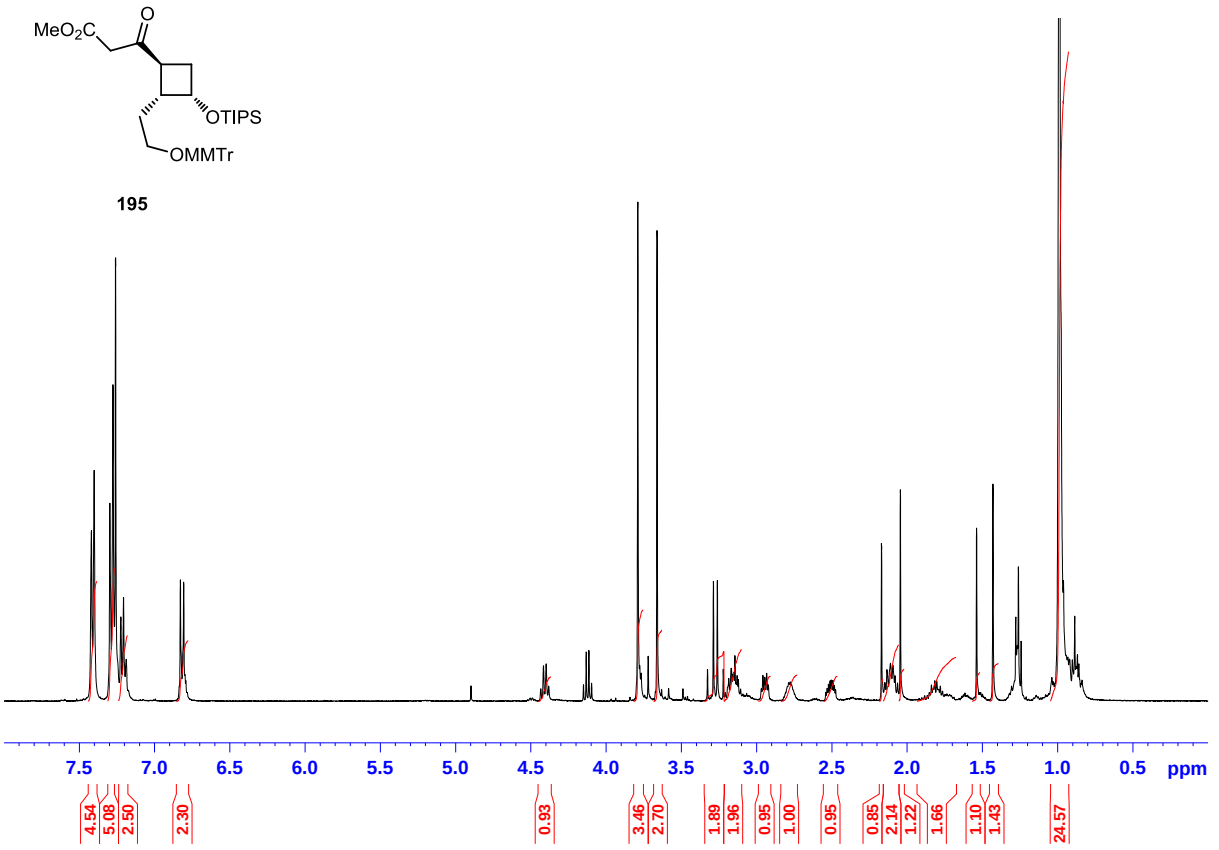
Figure 50: ORTEP diagram of 207a with 50% ellipsoid probability

5.3 Selected NMR-Spectra

5.3.1 $\Delta^{7,8}$ Metathesis Approach (*c*Bu)



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3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
4.54
5.08
2.50
2.30
0.93
3.46
2.70
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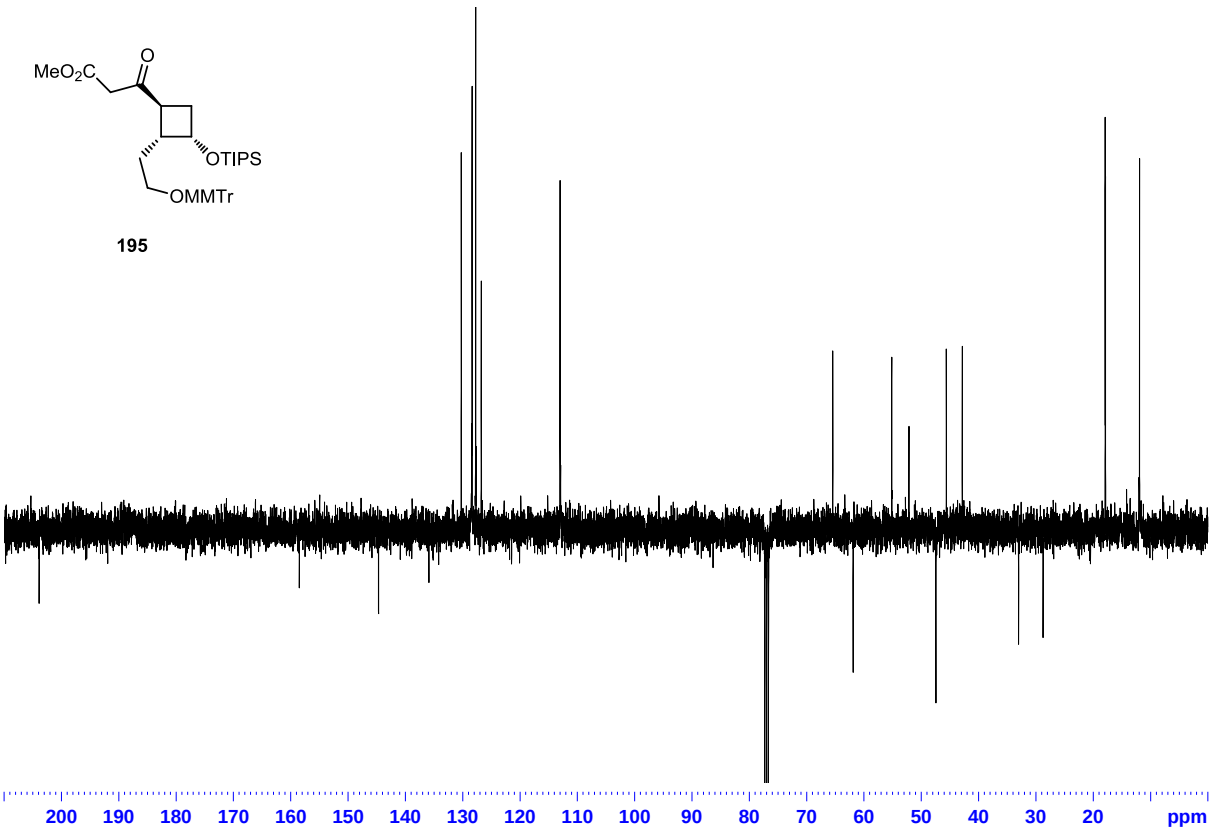
1.00
0.95
0.85
2.14
1.22
1.66
1.10
1.43
24.57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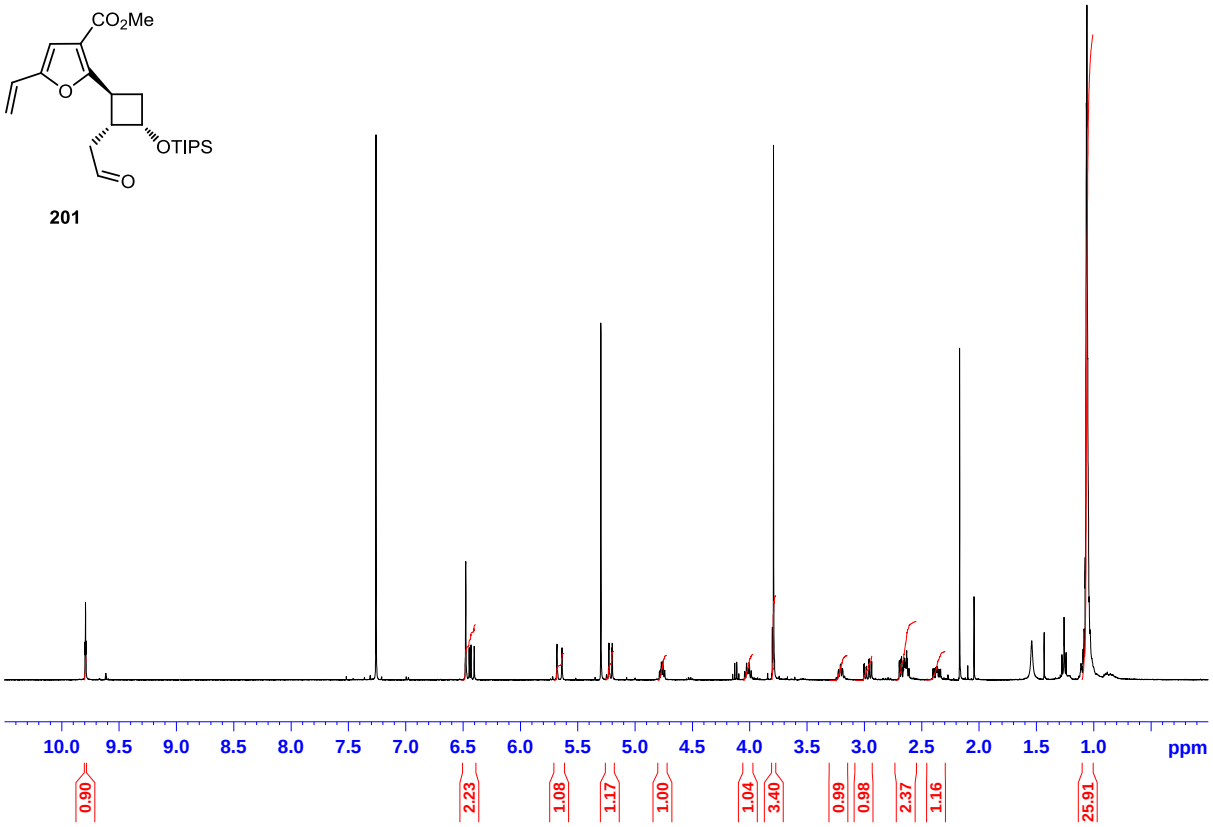
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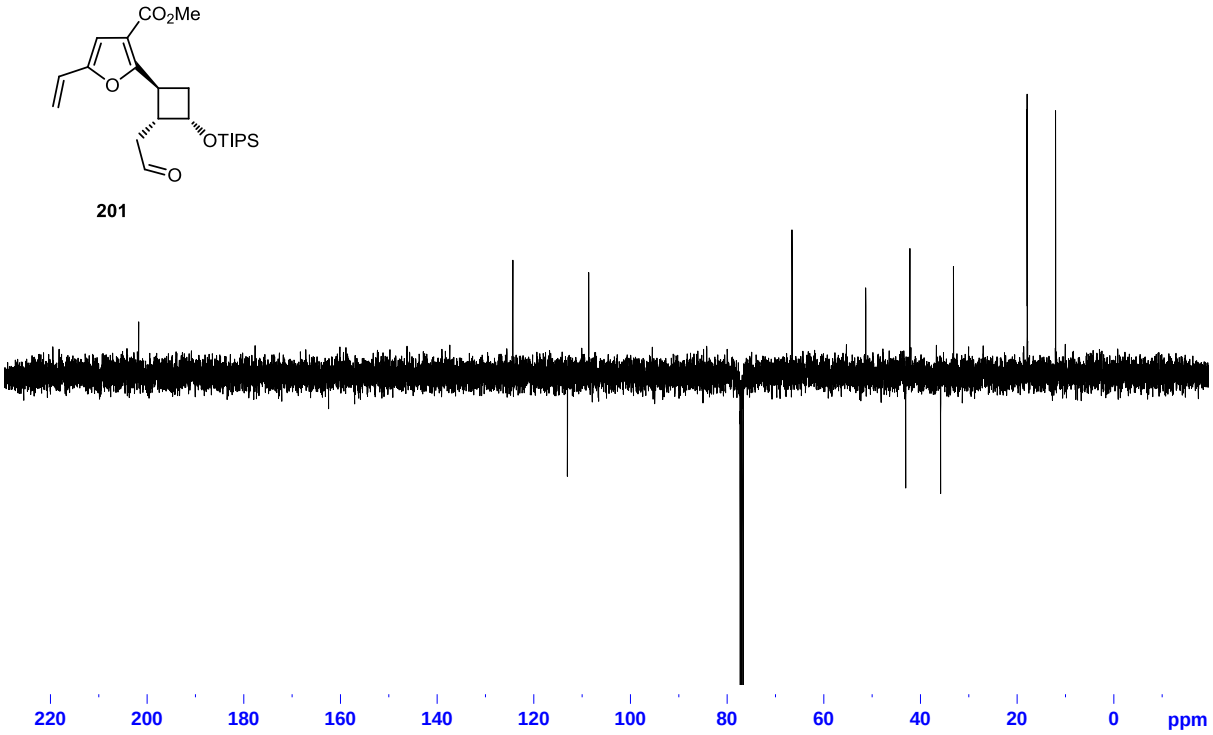
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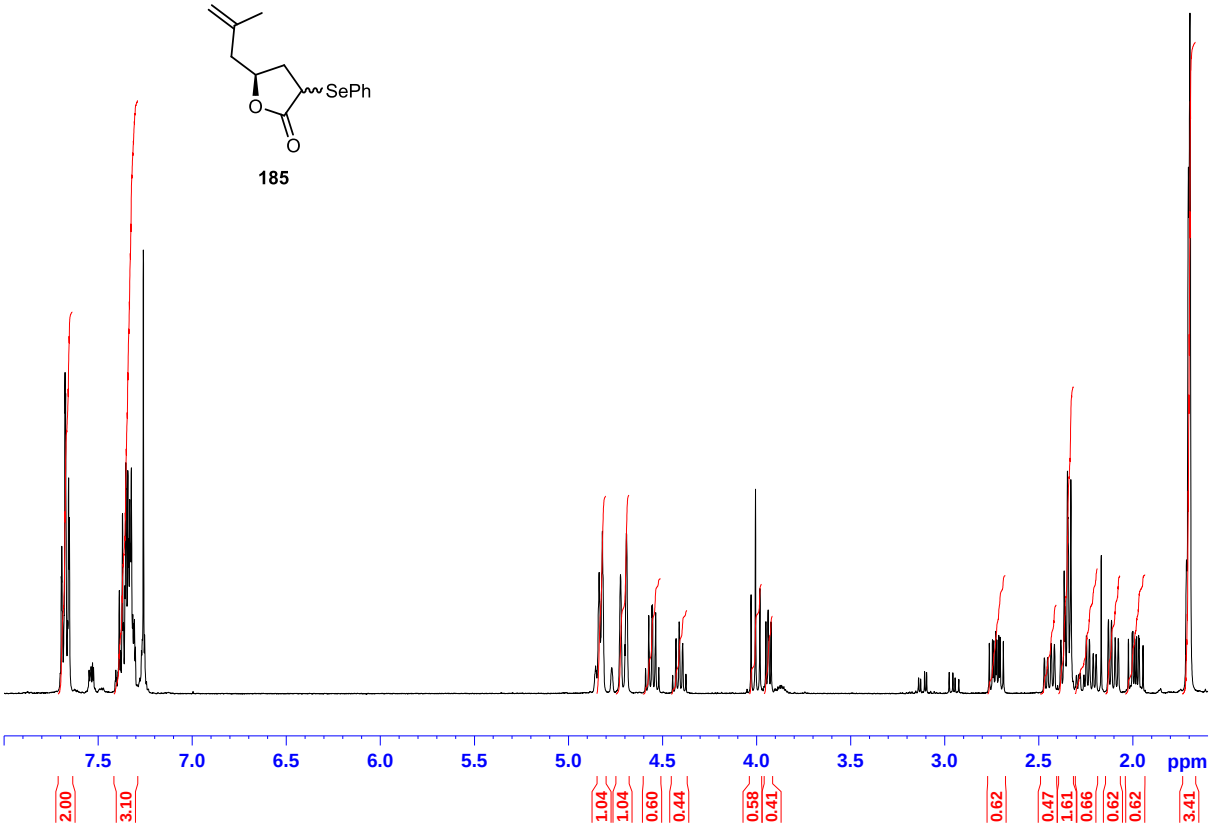
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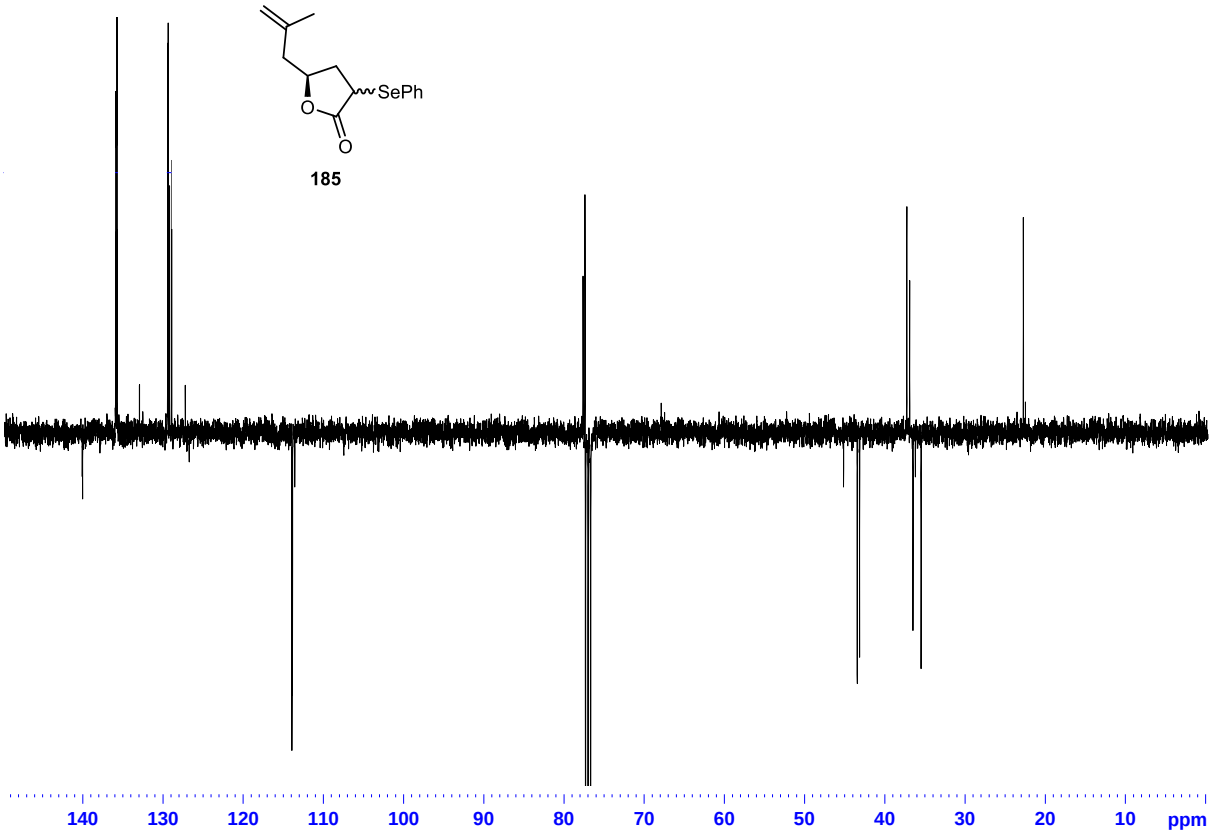
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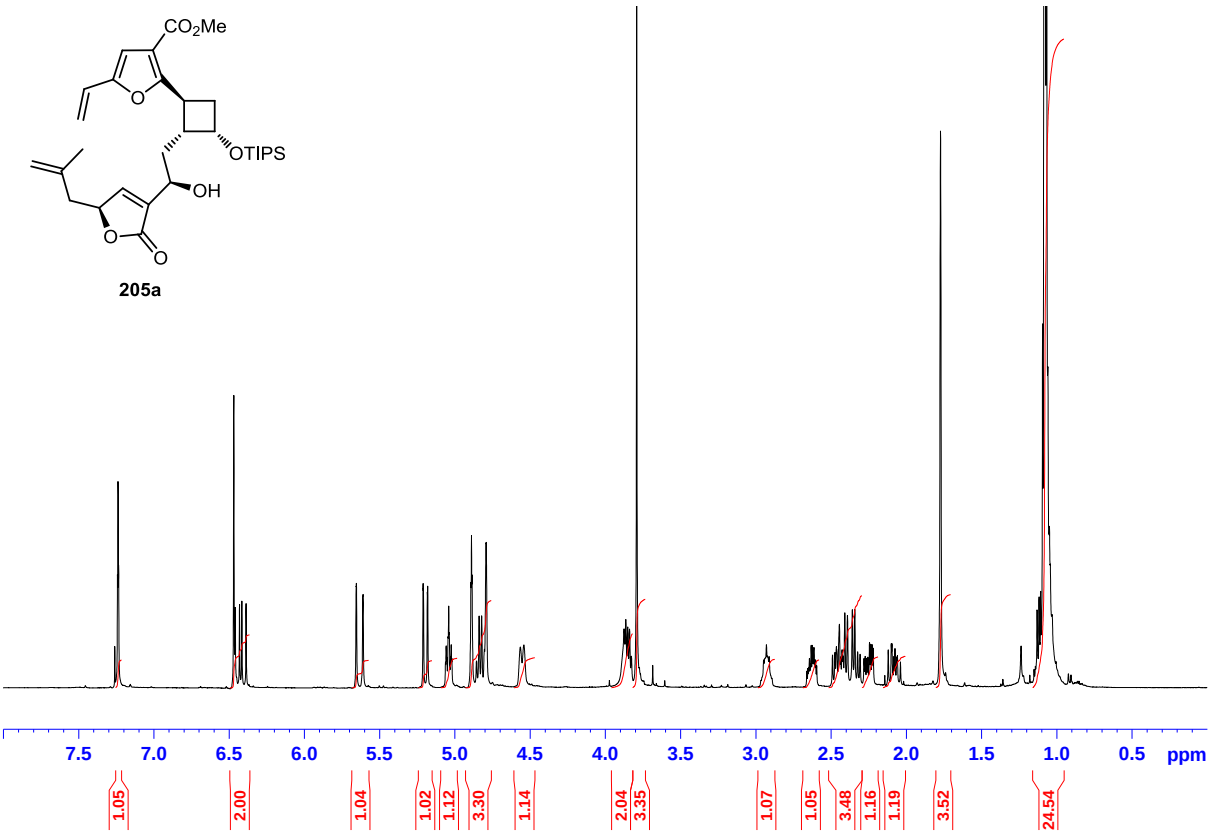
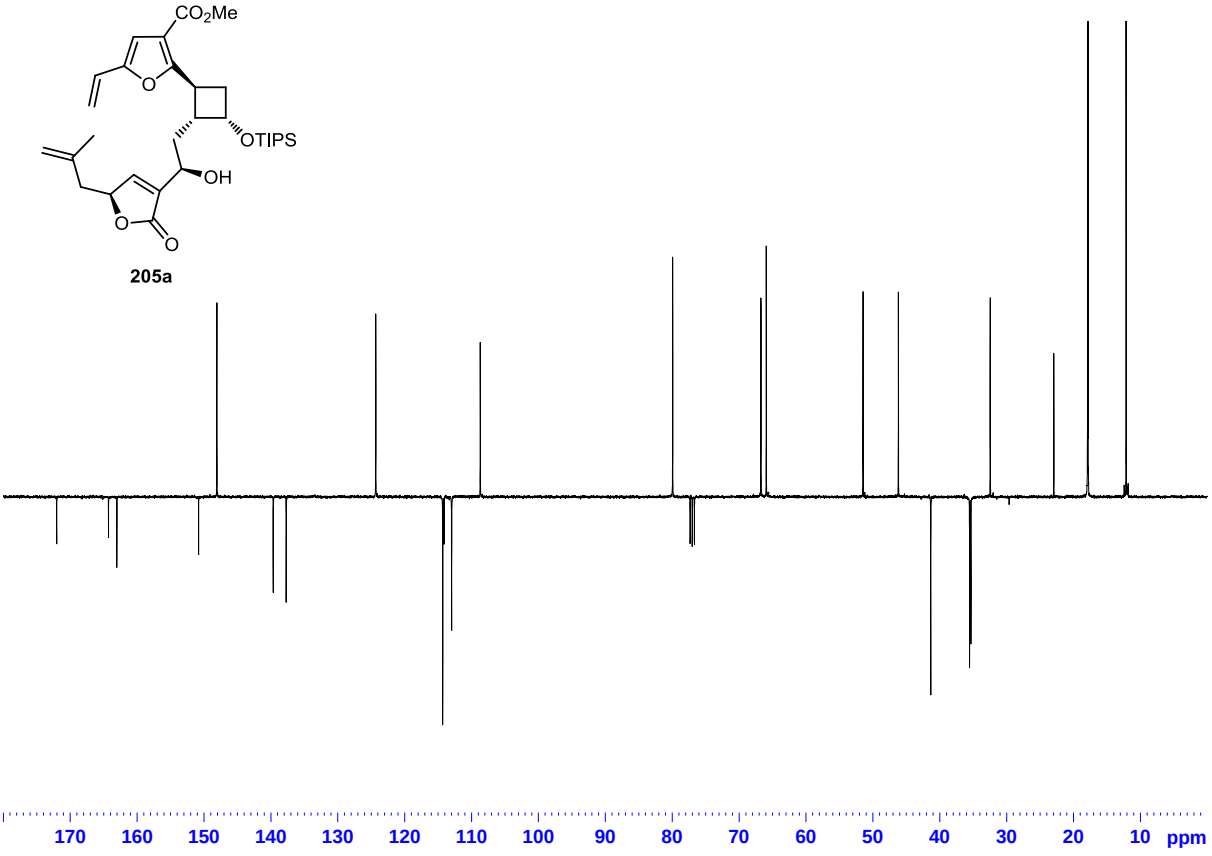
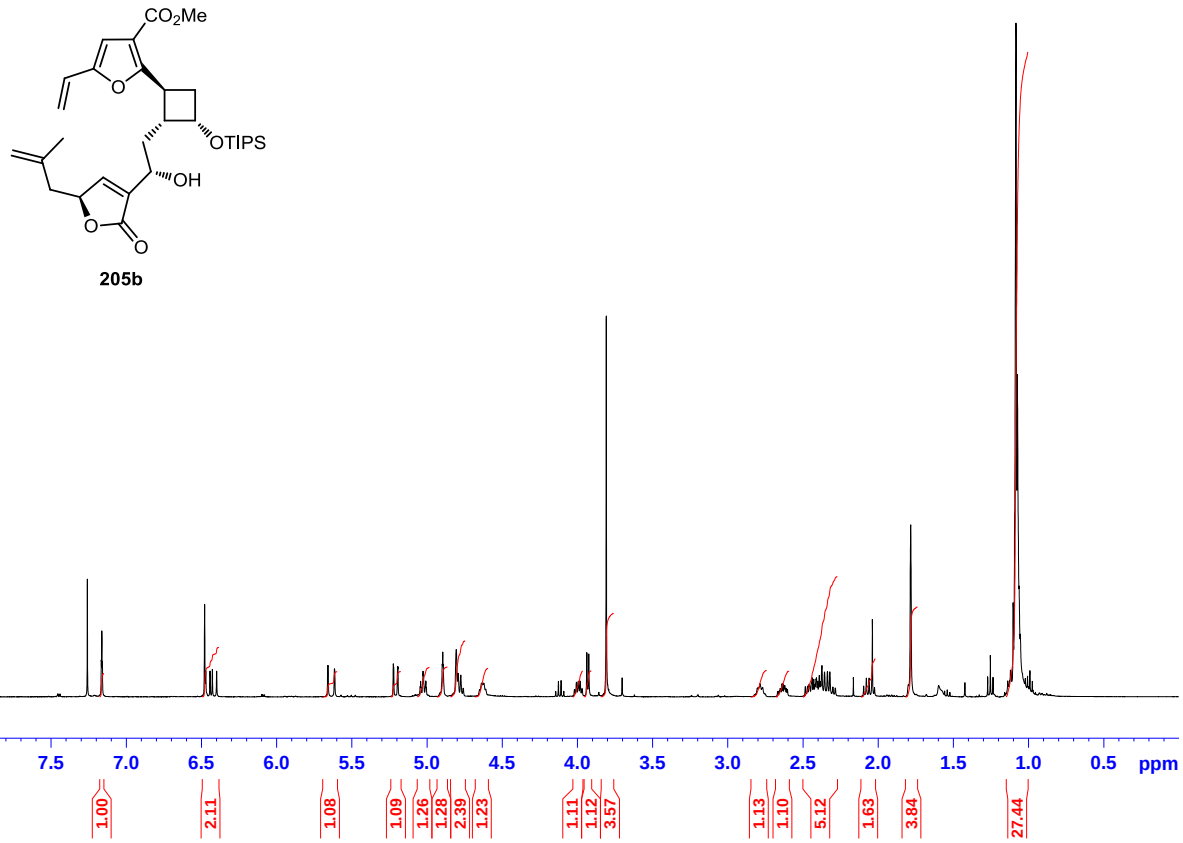
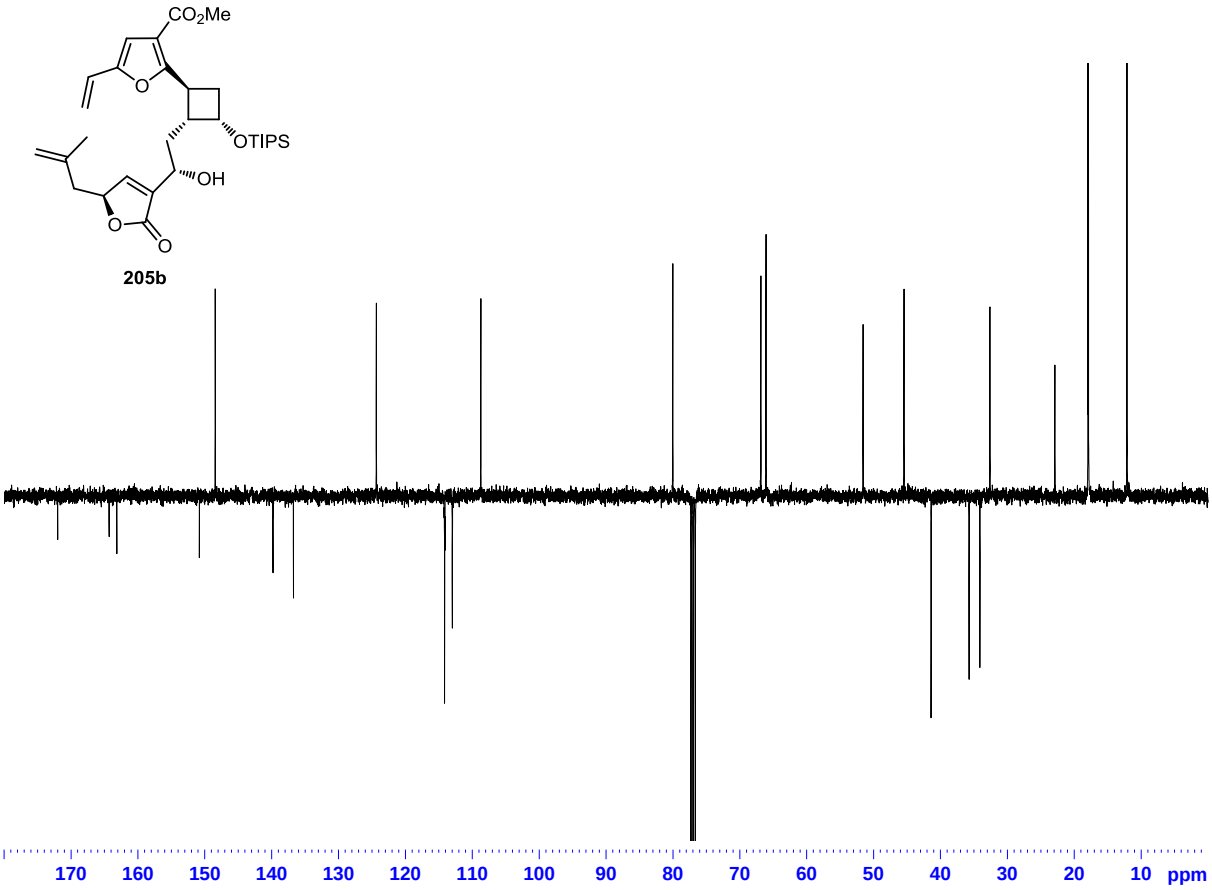
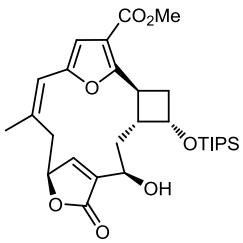
10
ppm


CO2Me
OTIPS
OH
O
O
O
205a
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.05
2.00
1.04
1.02
1.12
3.30
1.14
2.04
3.35
1.07
1.05
3.48
1.16
1.19
3.52
24.54


CO2Me
OTIPS
OH
O
O
205a
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

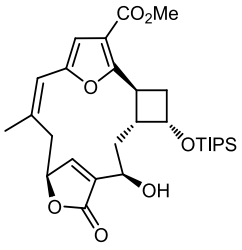

CO2Me
OTIPS
OH
205b
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.00
2.11
1.08
1.09
1.26
1.28
2.39
1.23
1.11
1.12
3.57
1.13
1.10
5.12
1.63
3.84
27.44


CO2Me
OTIPS
OH
205b
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


CO2Me
O
OTIPS
OH
O
O

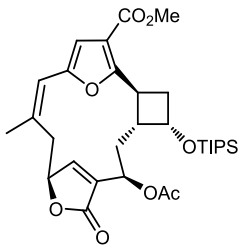
395

7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
0.99
1.00
1.01
1.14
0.95
1.11
1.01
3.18
0.82
1.02
1.18
1.37
3.03
1.41
2.78
3.02
32.56

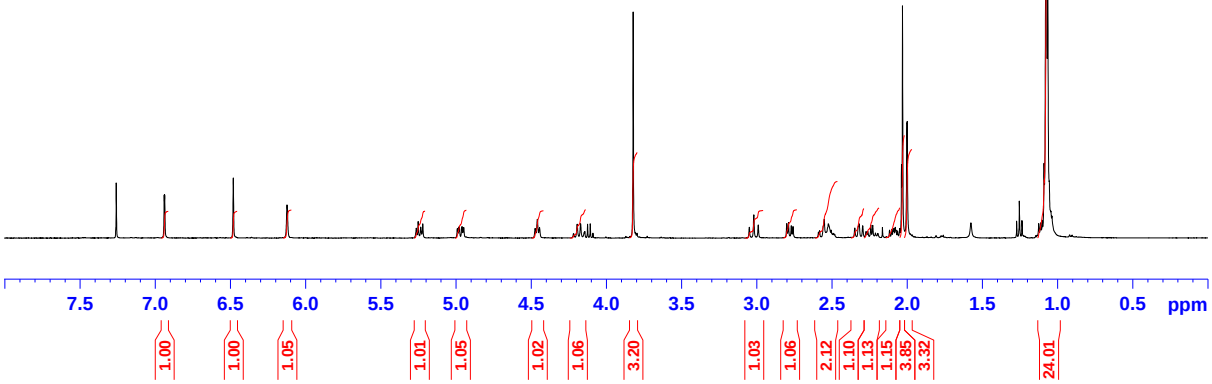

CO2Me
O
OTIPS
OH
O
O

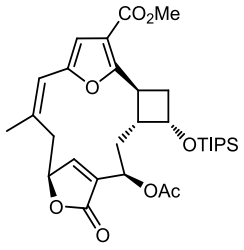
395

170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


CO2Me
O
OTIPS
OAc
O
O

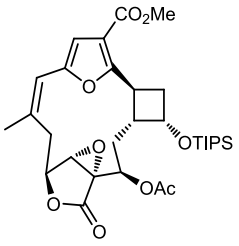
206


7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.00
1.00
1.05
1.01
1.05
1.02
1.06
3.20
1.03
1.06
2.12
1.10
1.13
1.15
3.85
3.32
24.01

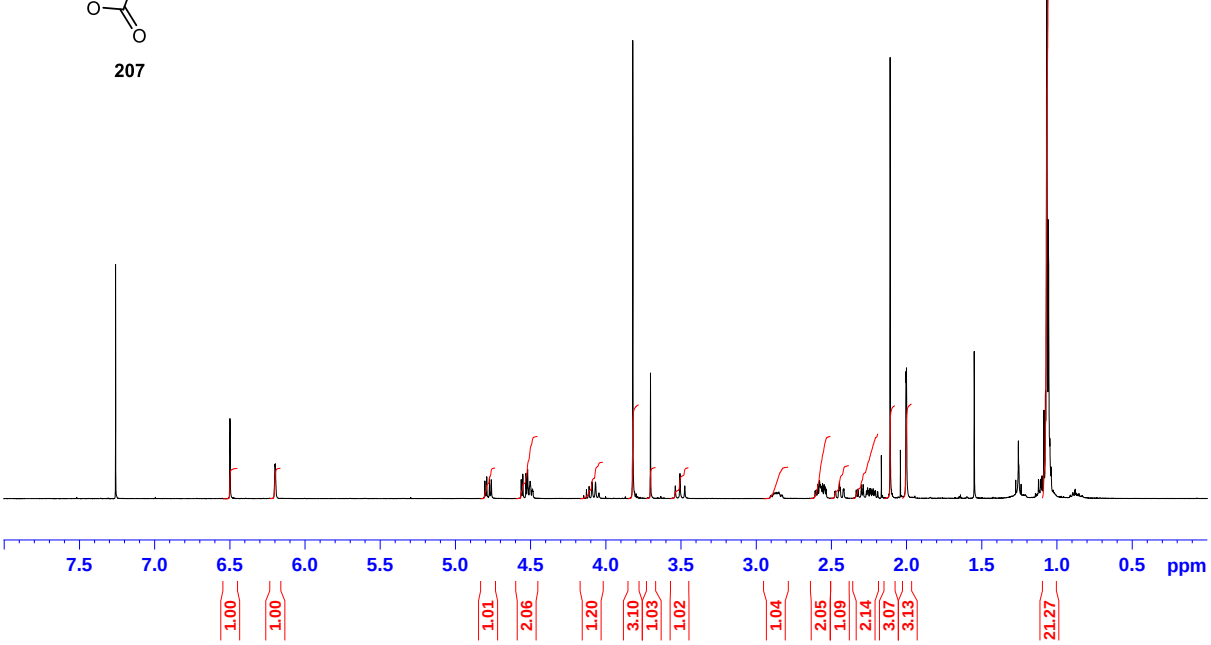

CO2Me
O
OTIPS
OAc
O
O

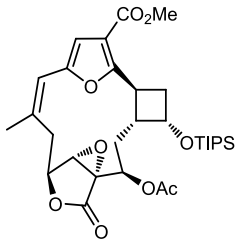
206

170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


CO2Me
OTIPS
OAc

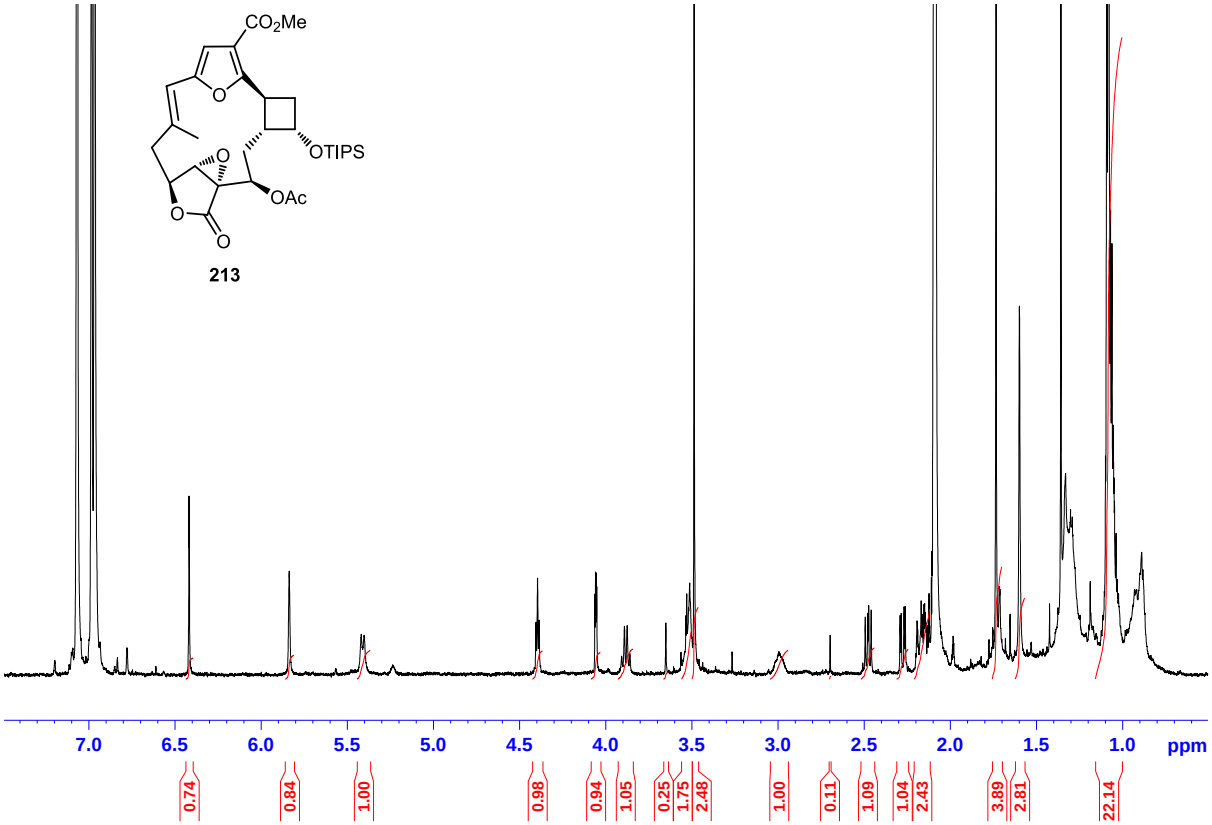
207

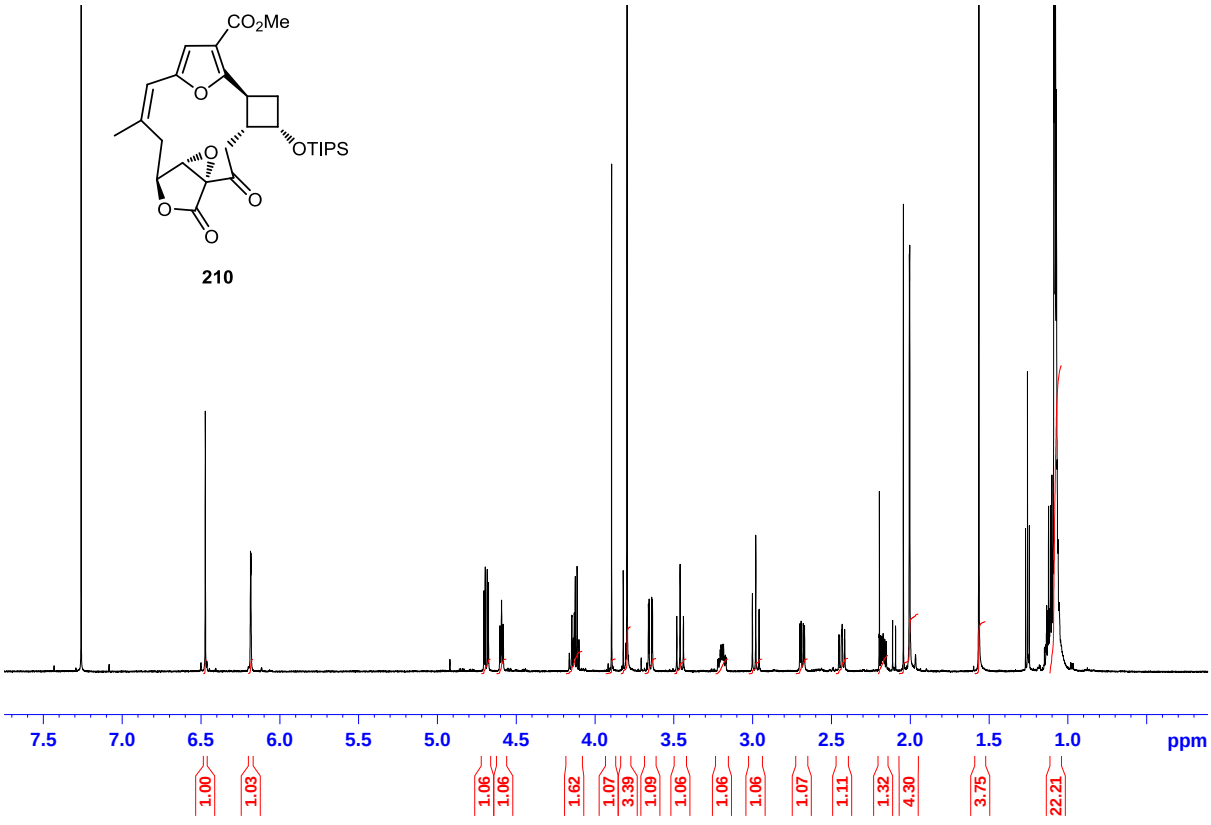

7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.00
1.00
1.01
2.06
1.20
3.10
1.03
1.02
1.04
2.05
1.09
2.14
3.07
3.13
21.27

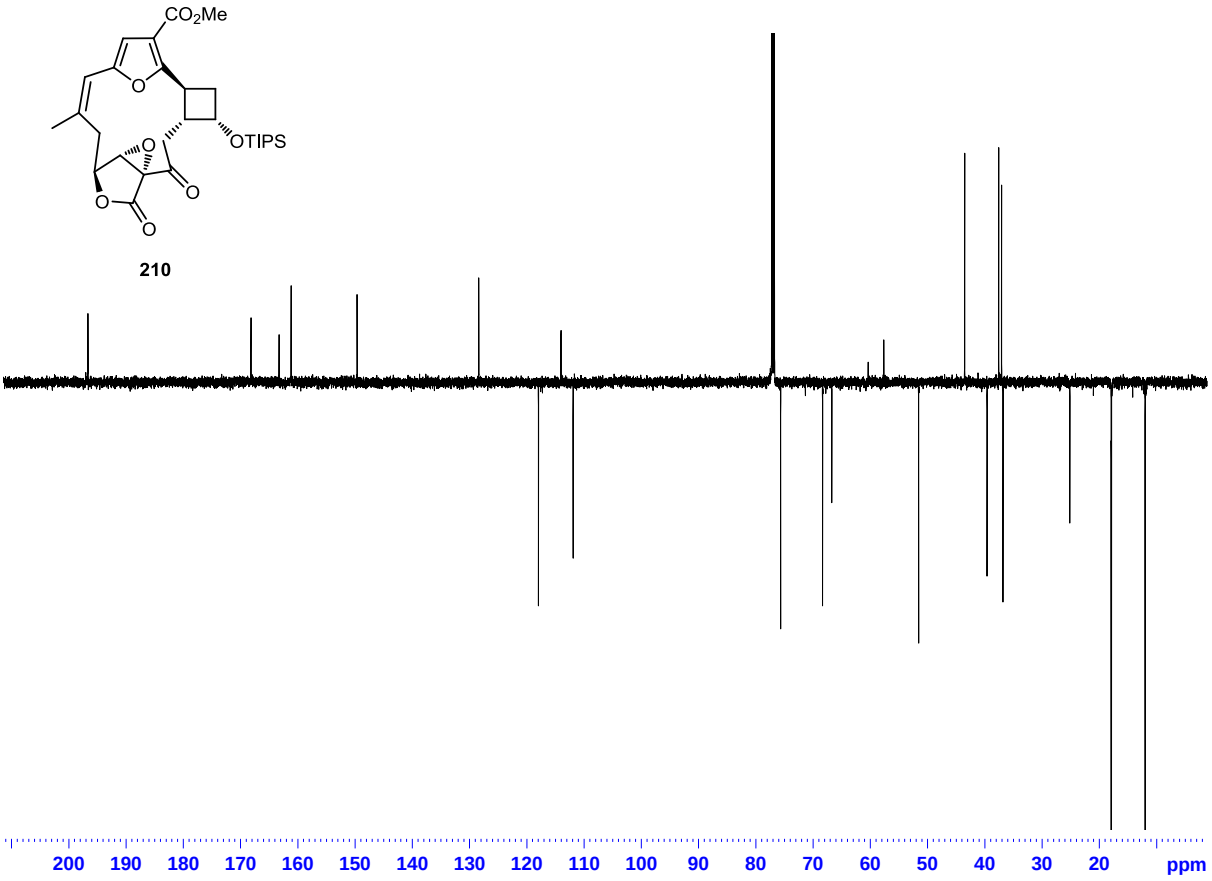

CO2Me
OTIPS
OAc

207

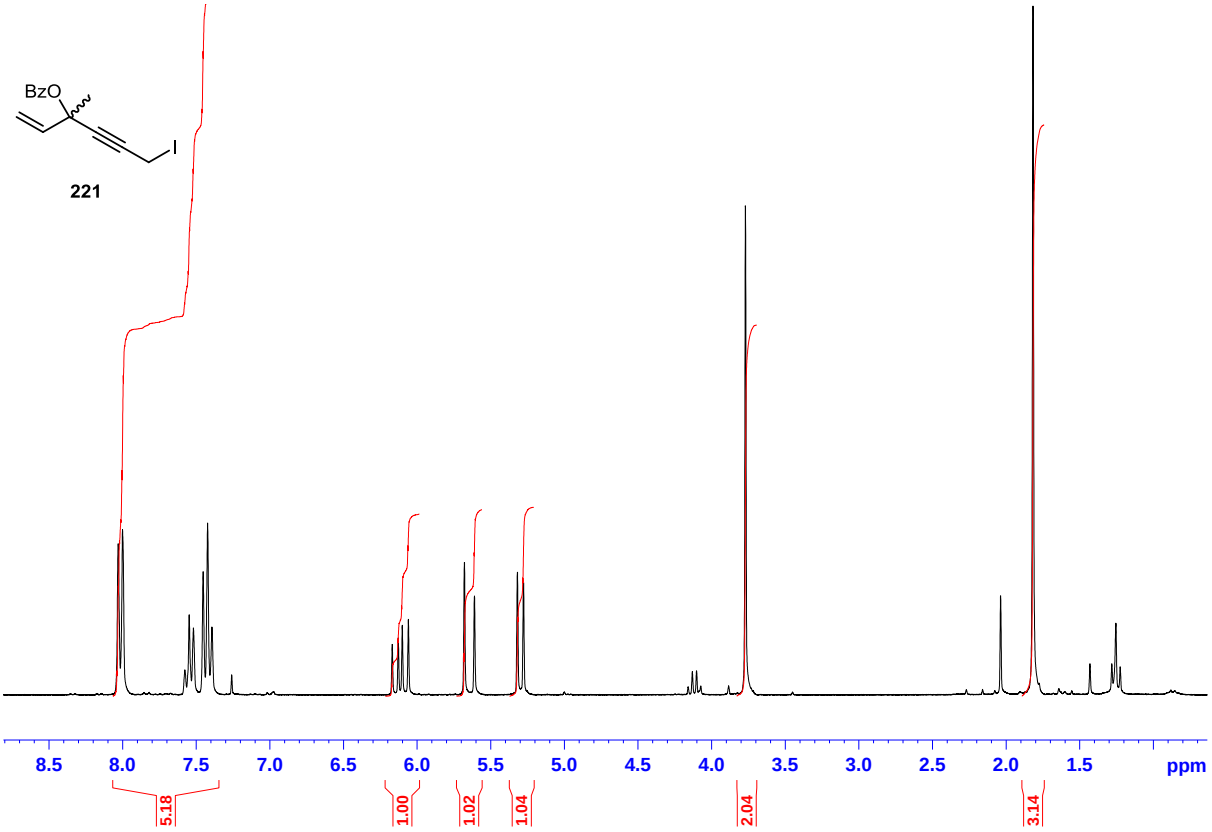
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

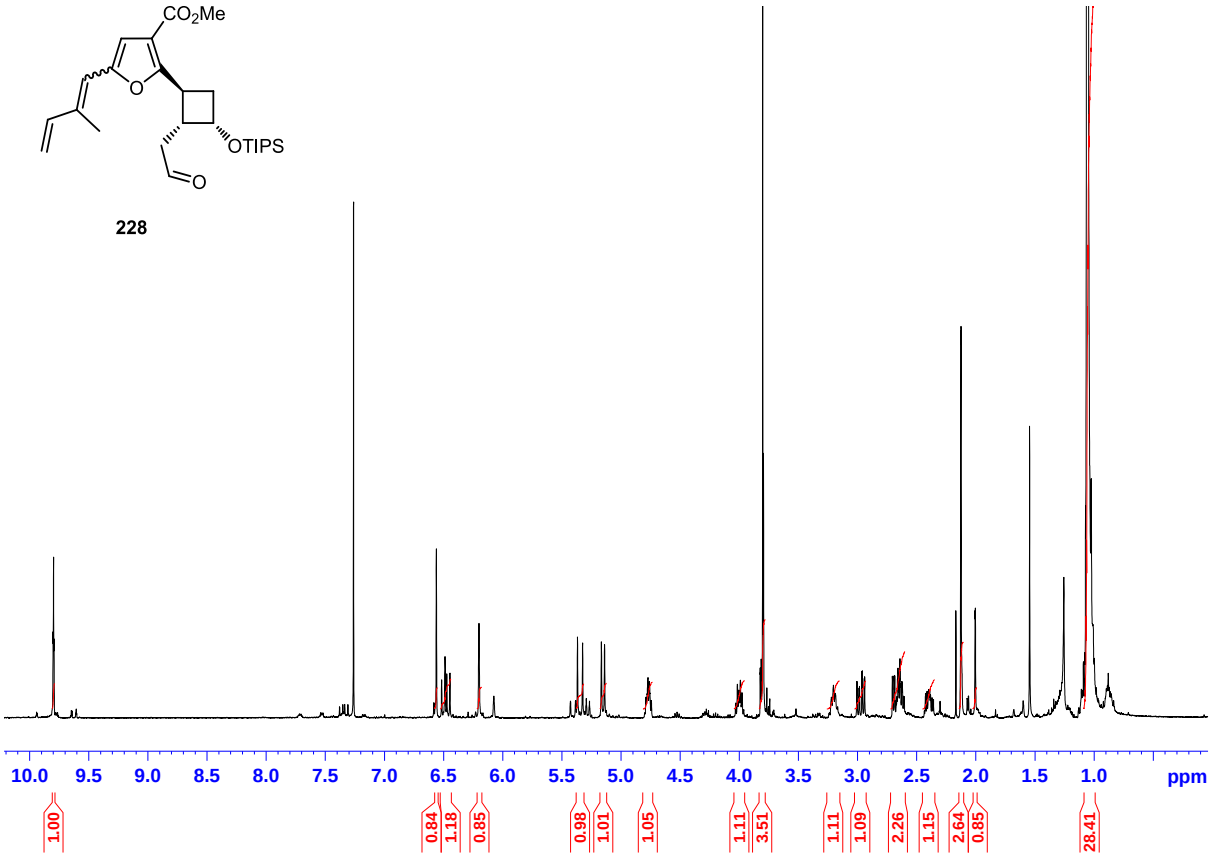

CO2Me
OTIPS
OAc
O
O
O
O
O
213
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
0.74
0.84
1.00
0.98
0.94
1.05
0.25
1.75
2.48
1.00
0.11
1.09
1.04
2.43
3.89
2.81
22.14

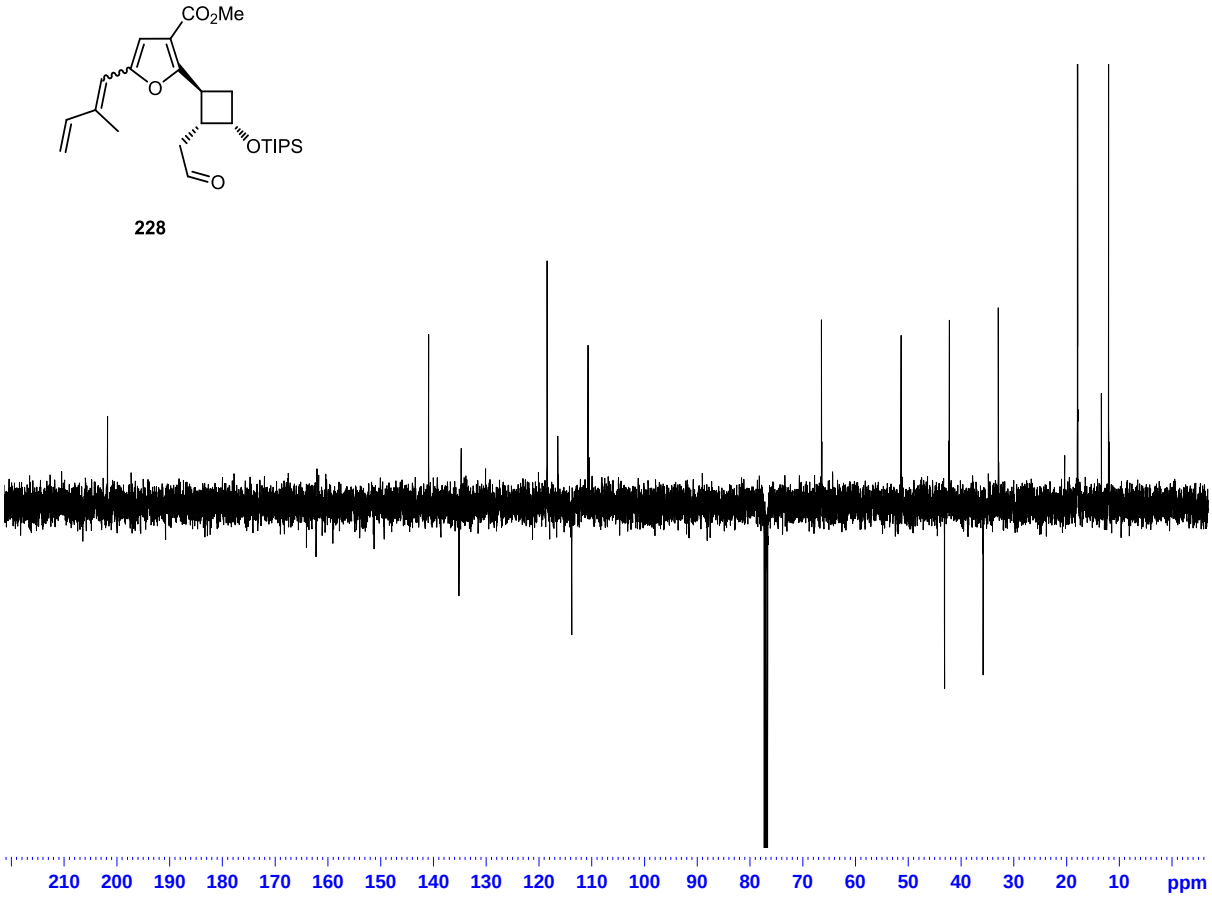

CO2Me
OTIPS
O
O
O
O
O
210
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
1.00
1.03
1.06
1.06
1.62
1.07
3.39
1.09
1.06
1.06
1.06
1.07
1.11
1.32
4.30
3.75
22.21

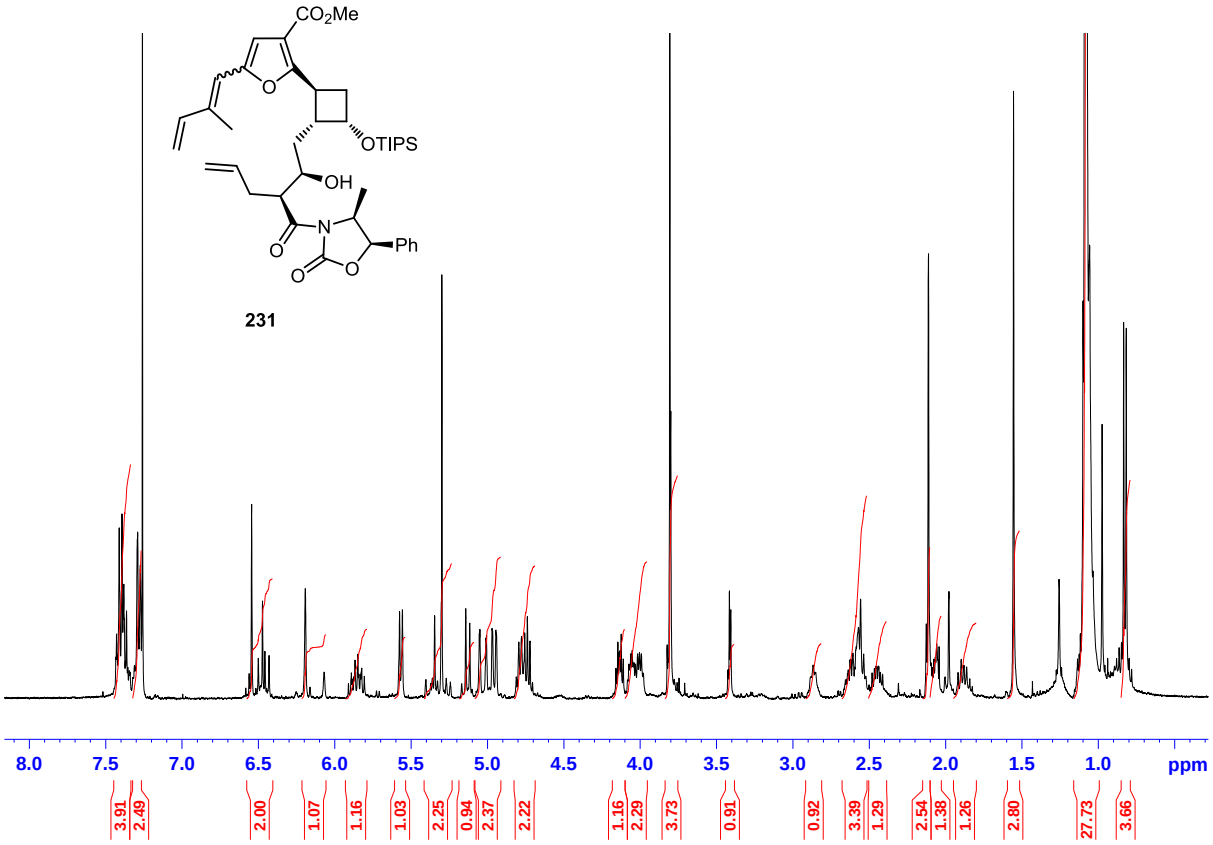


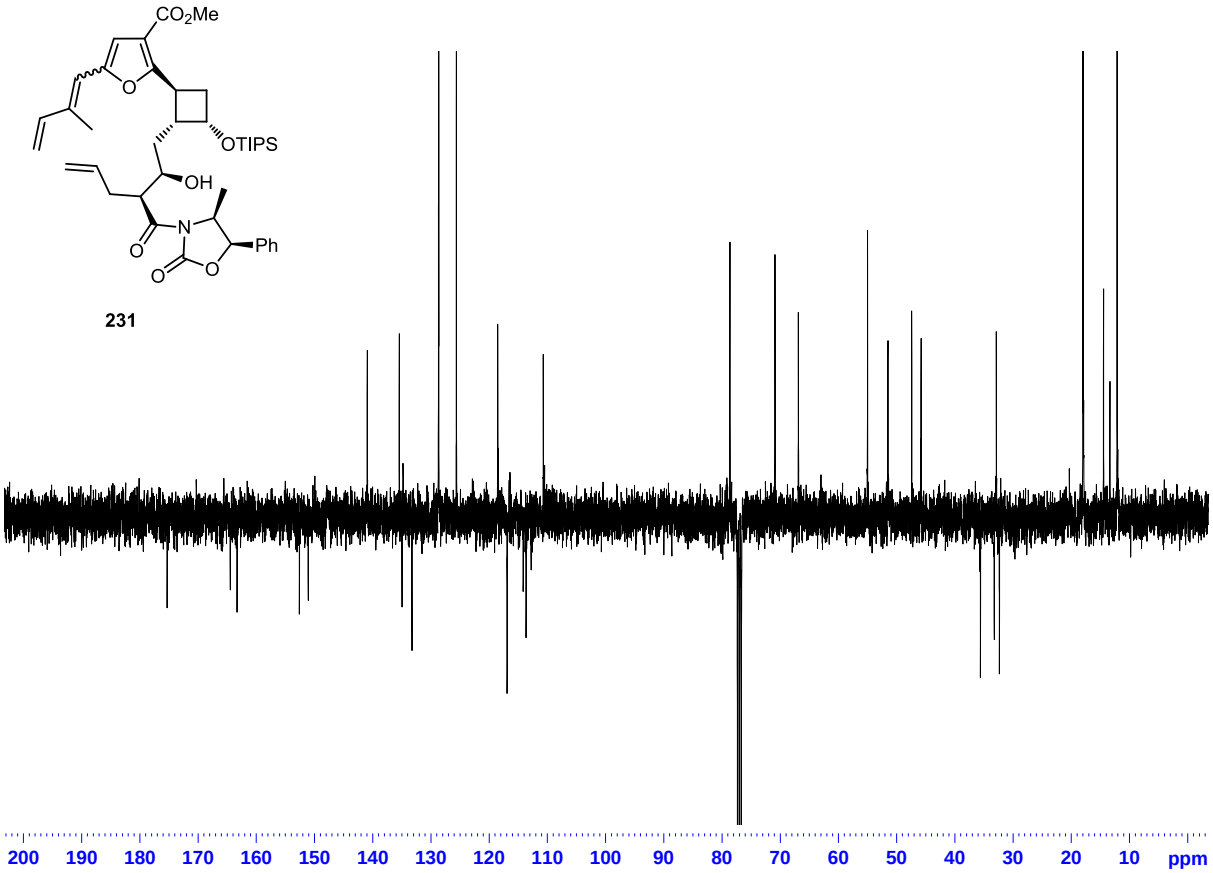
5.3.2 $\Delta^{9,10}$ Metathesis Approach (*c*Bu)



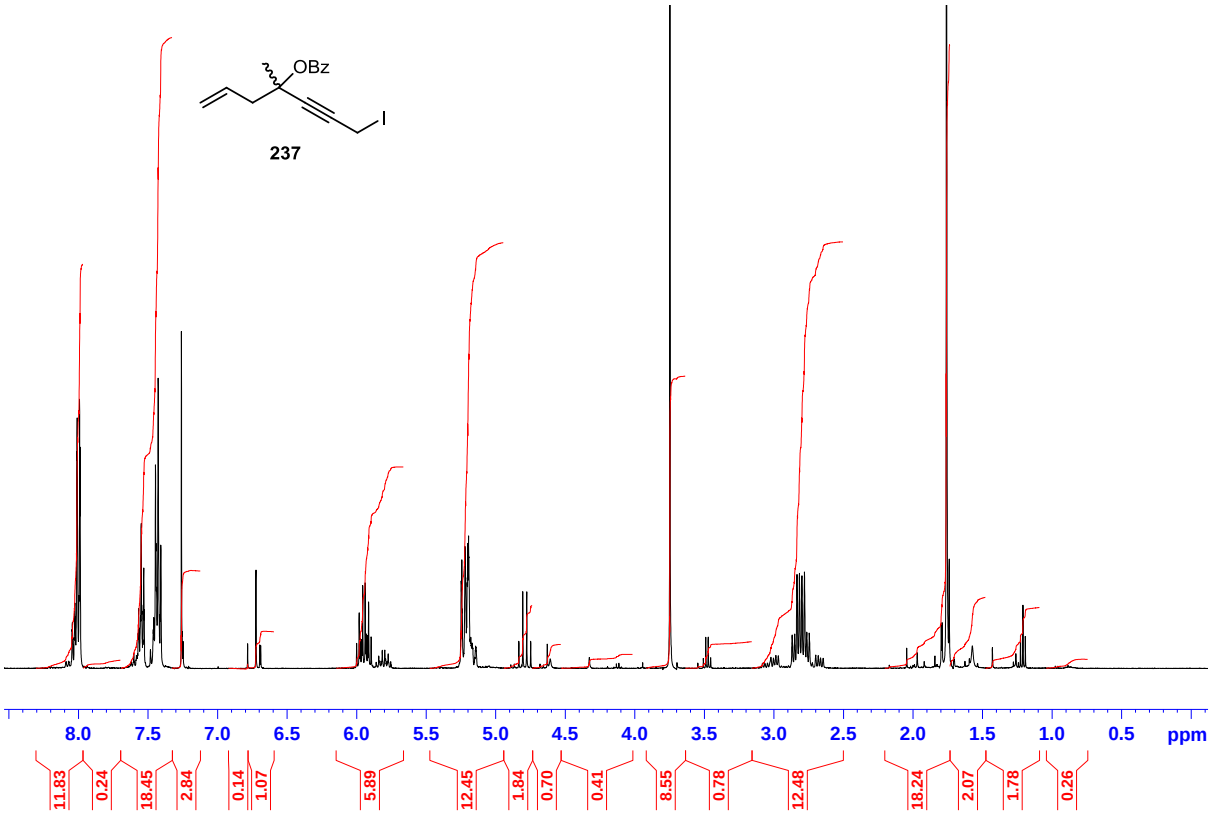

CO2Me
O
OTIPS
O
228
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
0.84
1.18
0.85
0.98
1.01
1.05
1.11
3.51
1.11
1.09
2.26
1.15
2.64
0.85
28.41

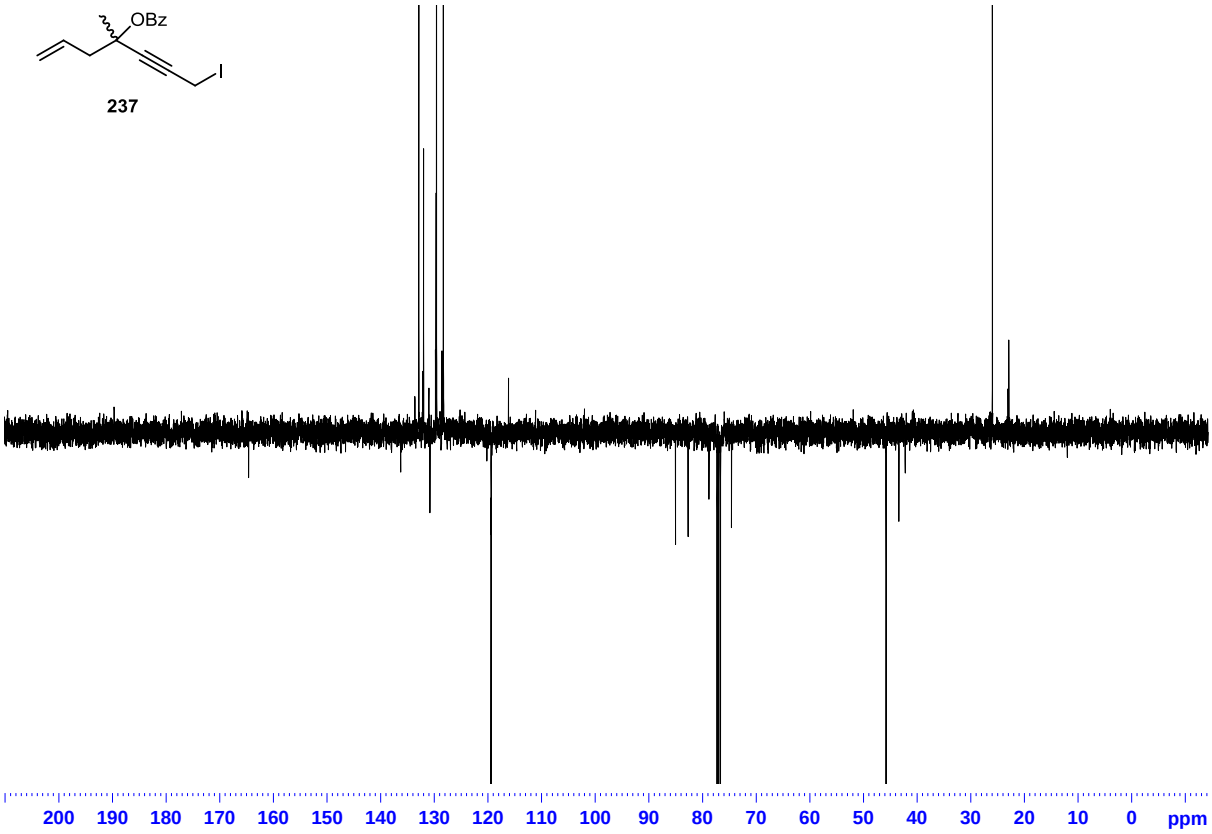

CO2Me
O
OTIPS
O
228
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

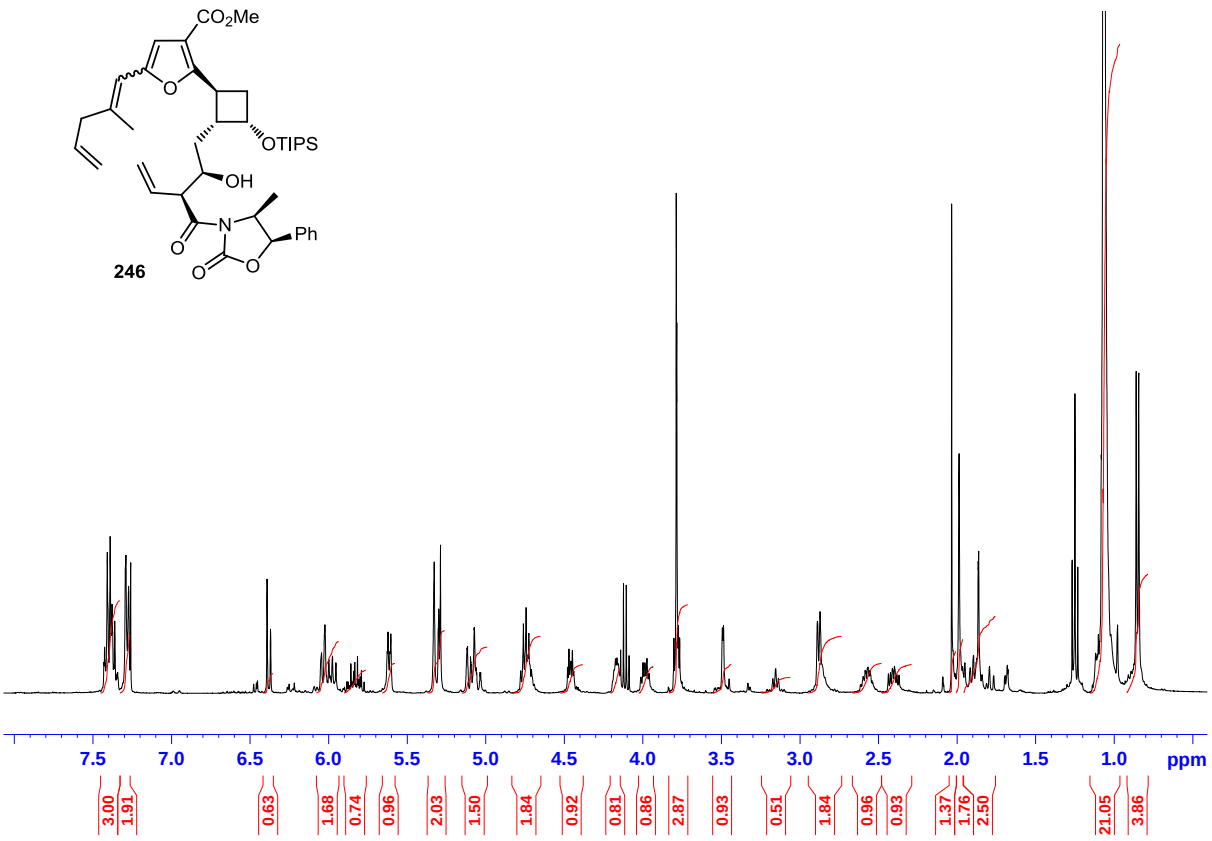

CO2Me
OTIPS
OH
N
O
Ph
231
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
3.91
2.49
2.00
1.07
1.16
1.03
2.25
0.94
2.37
2.22
1.16
2.29
3.73
0.91
0.92
3.39
1.29
2.54
1.38
1.26
2.80
27.73
3.66

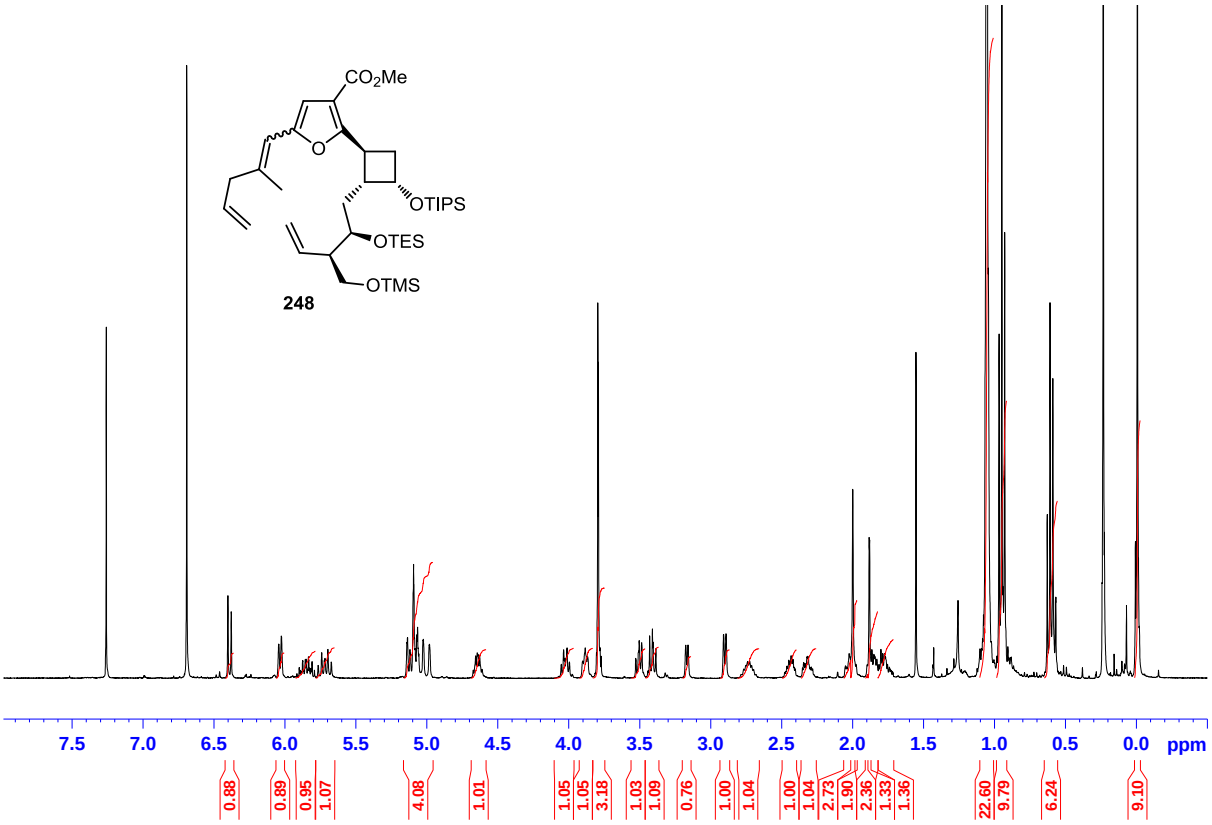

CO2Me
OTIPS
OH
N
O
Ph
231
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

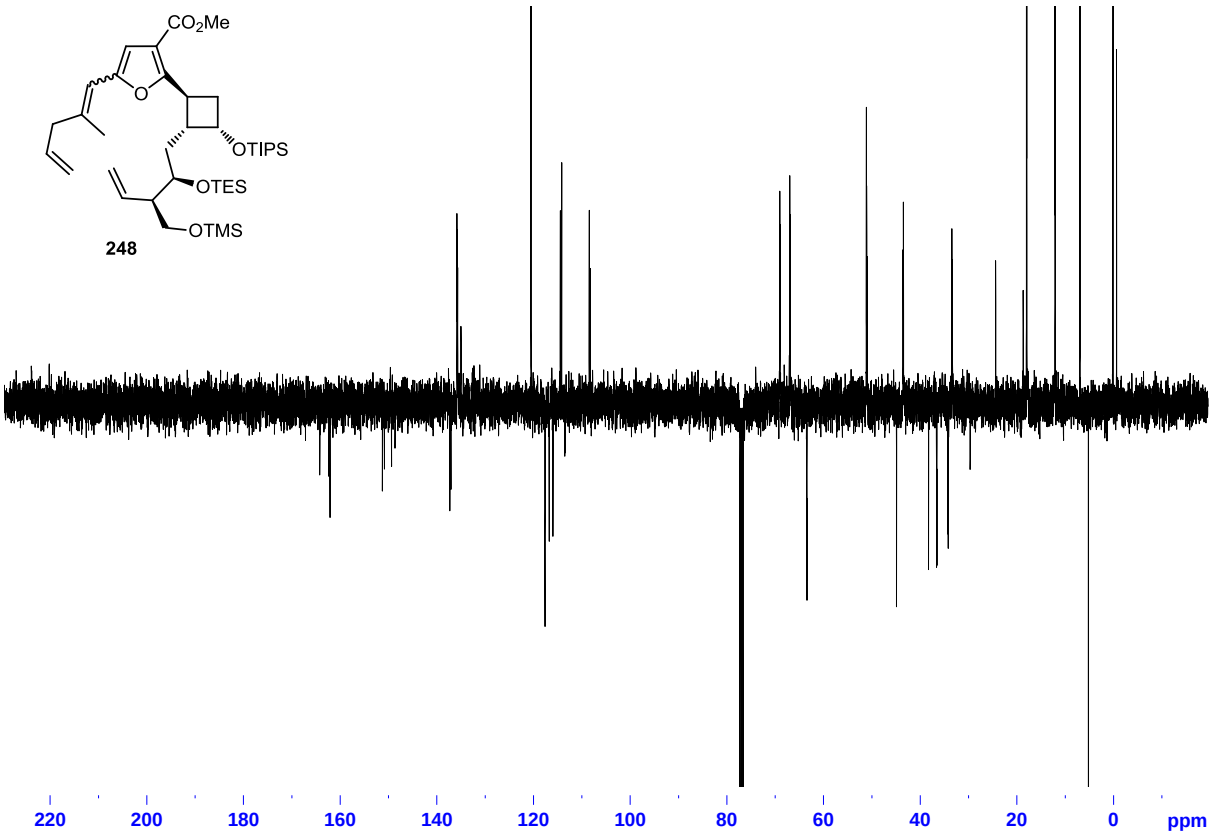
5.3.3 $\Delta^{10,11}$ Metathesis Approach (*c*Bu)

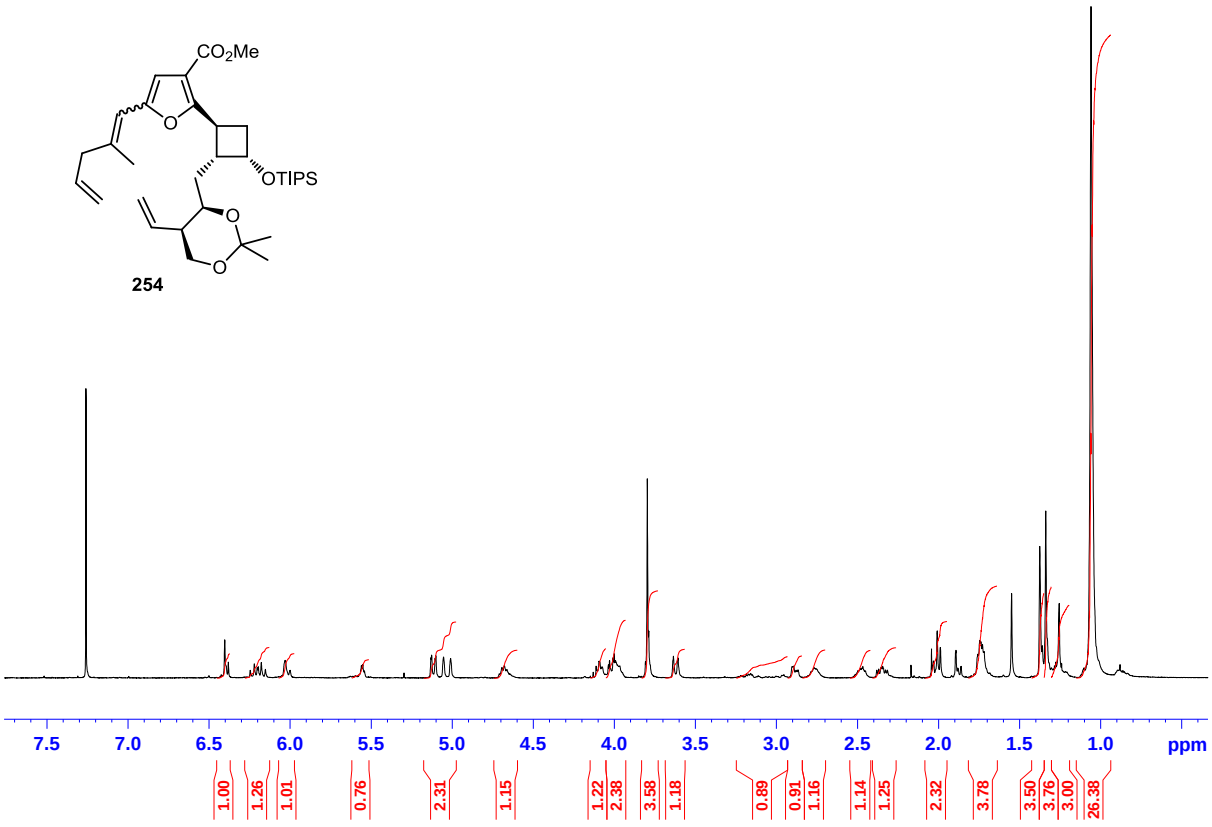


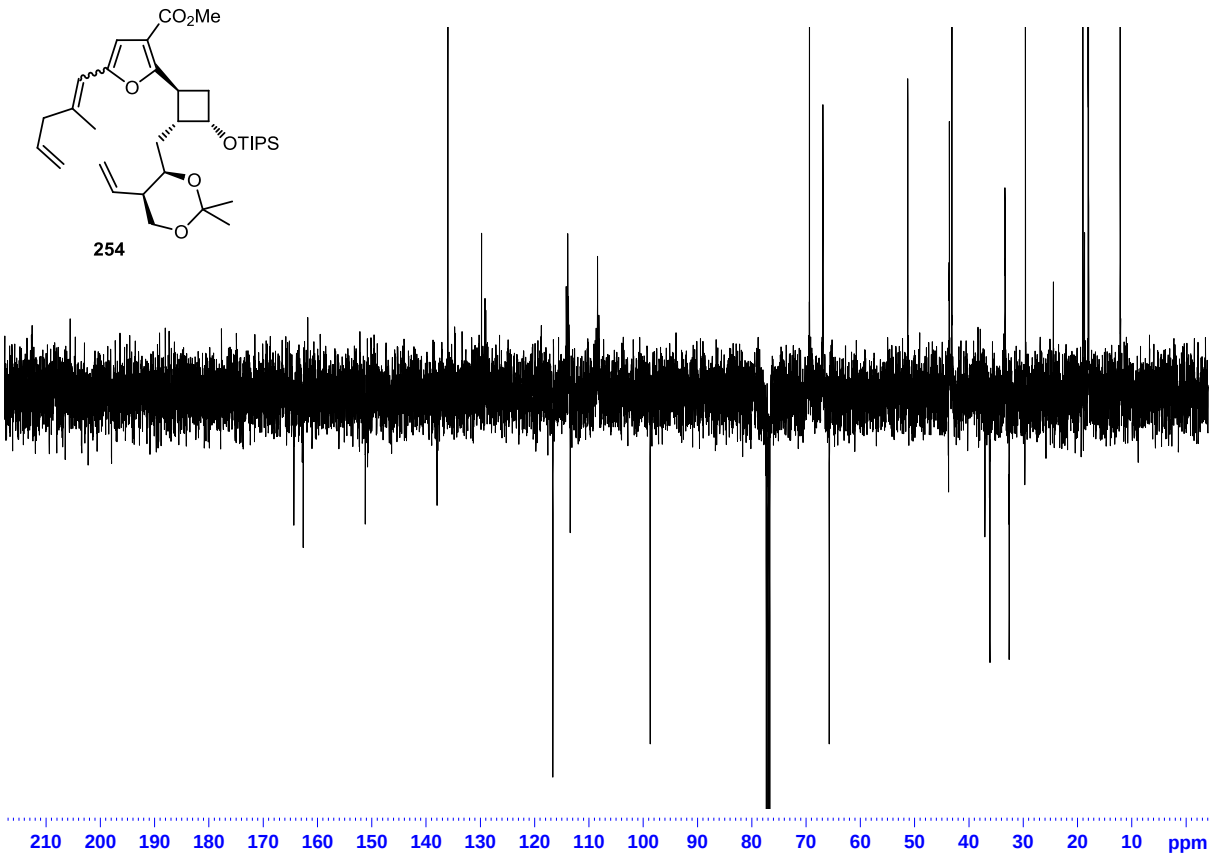



CO2Me
OTIPS
OH
N
Ph
O
O
O
246
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
3.00
1.91
0.63
1.68
0.74
0.96
2.03
1.50
1.84
0.92
0.81
0.86
2.87
0.93
0.51
1.84
0.96
0.93
1.37
1.76
2.50
21.05
3.86

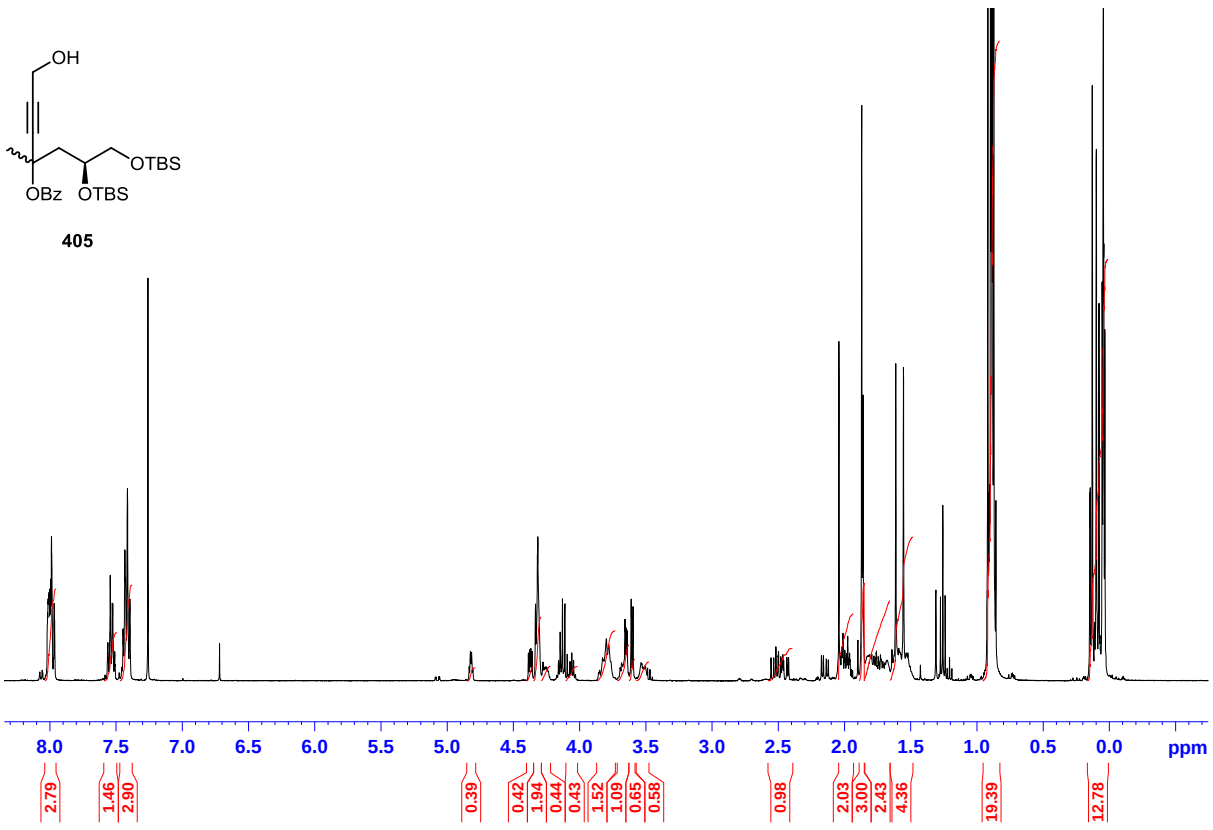

CO2Me
OTIPS
OTES
OTMS
O
248
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
0.88
0.89
0.95
1.07
4.08
1.01
1.05
1.05
3.18
1.03
1.09
0.76
1.00
1.04
1.00
1.04
2.73
1.90
2.36
1.33
1.36
22.60
9.79
6.24
9.10

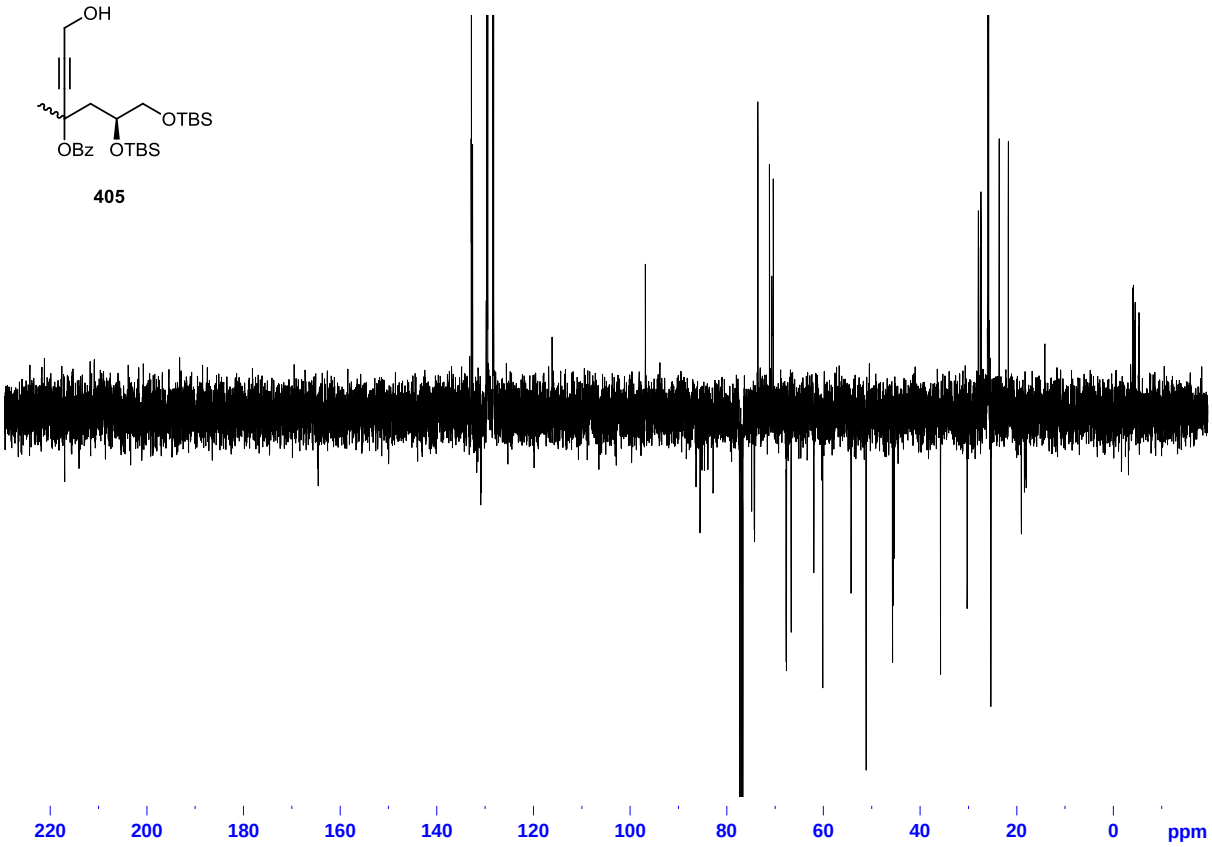

CO2Me
O
OTIPS
OTES
OTMS
248
220
200
180
160
140
120
100
80
60
40
20
0
ppm

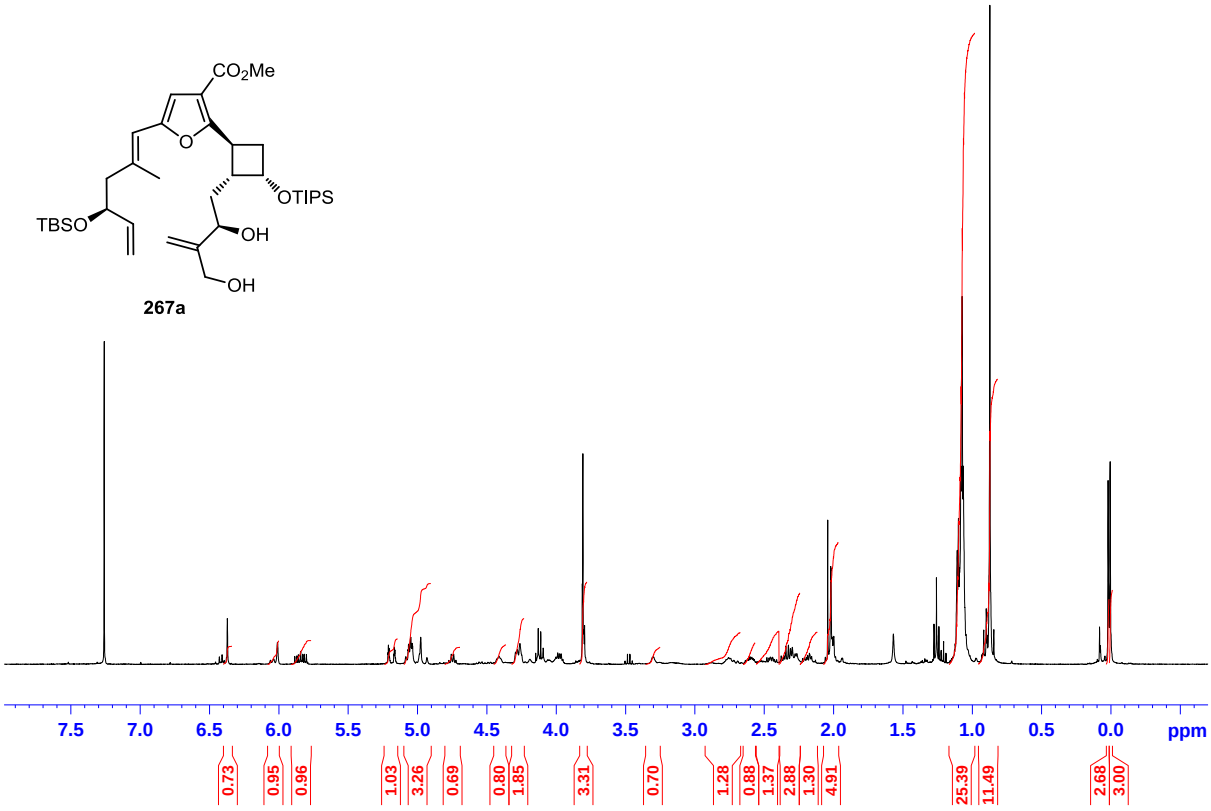

CO2Me
O
OTIPS
O
O
254
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
1.00
1.26
1.01
0.76
2.31
1.15
1.22
2.38
3.58
1.18
0.89
0.91
1.16
1.14
1.25
2.32
3.78
3.50
3.76
3.00
26.38

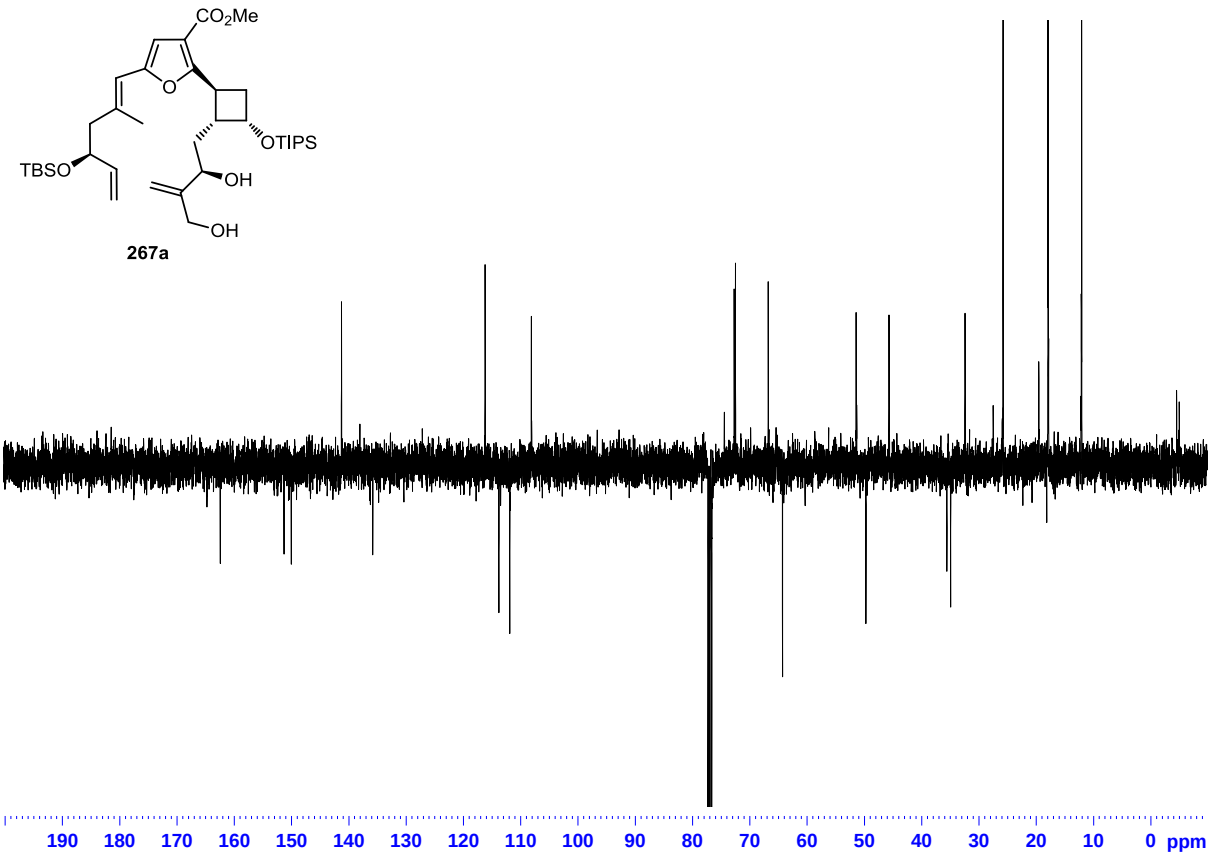


5.3.4 $\Delta^{11,12}$ Metathesis Approach (*c*Bu)

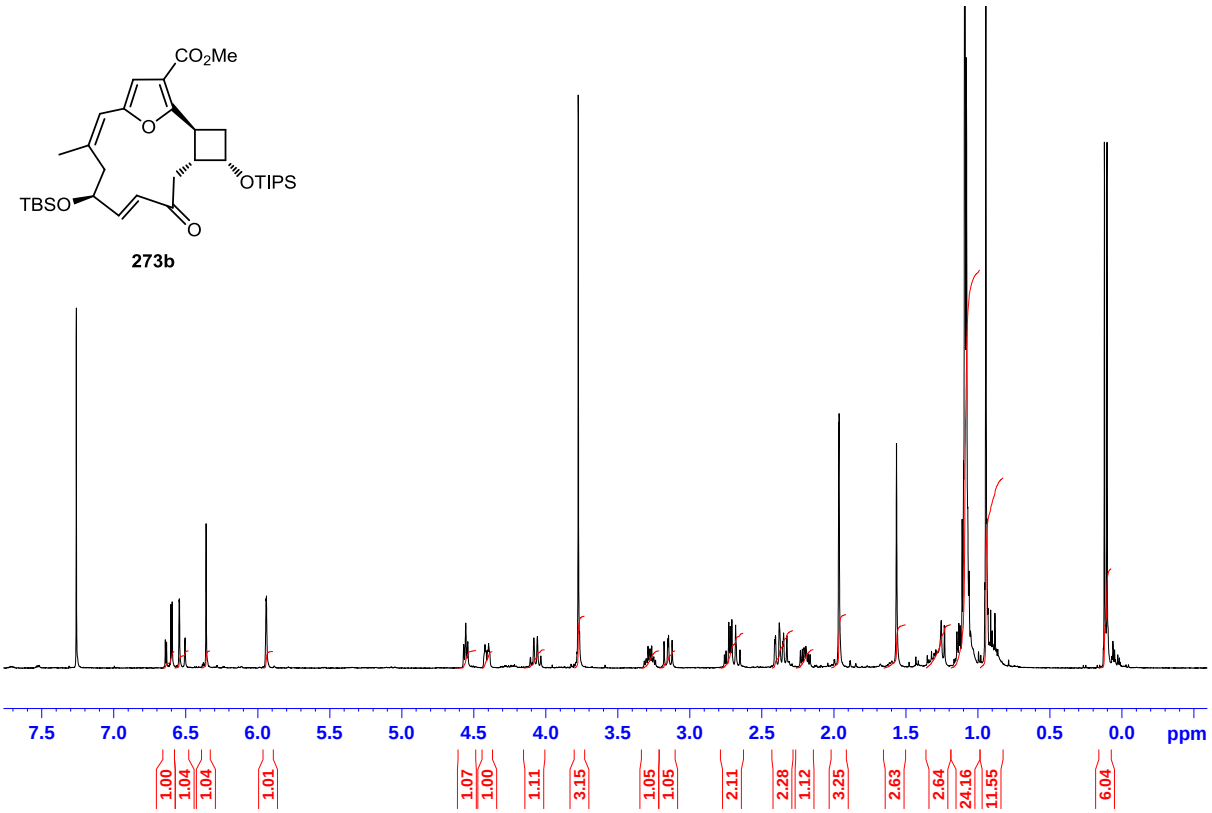


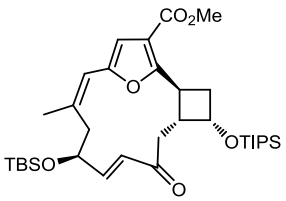

OH
OTBS
OBz
OTBS
405
220
200
180
160
140
120
100
80
60
40
20
0
ppm


CO2Me
O
OTIPS
TBSO
OH
OH
267a
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
0.73
0.95
0.96
1.03
3.26
0.69
0.80
1.85
3.31
0.70
1.28
0.88
1.37
2.88
1.30
4.91
25.39
11.49
2.68
3.00



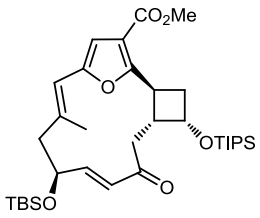
5.3.5 $\Delta^{11,12}$ Horner Wadsworth Emmons Approach (*c*Bu)




CO2Me
O
OTIPS
TBSO
O

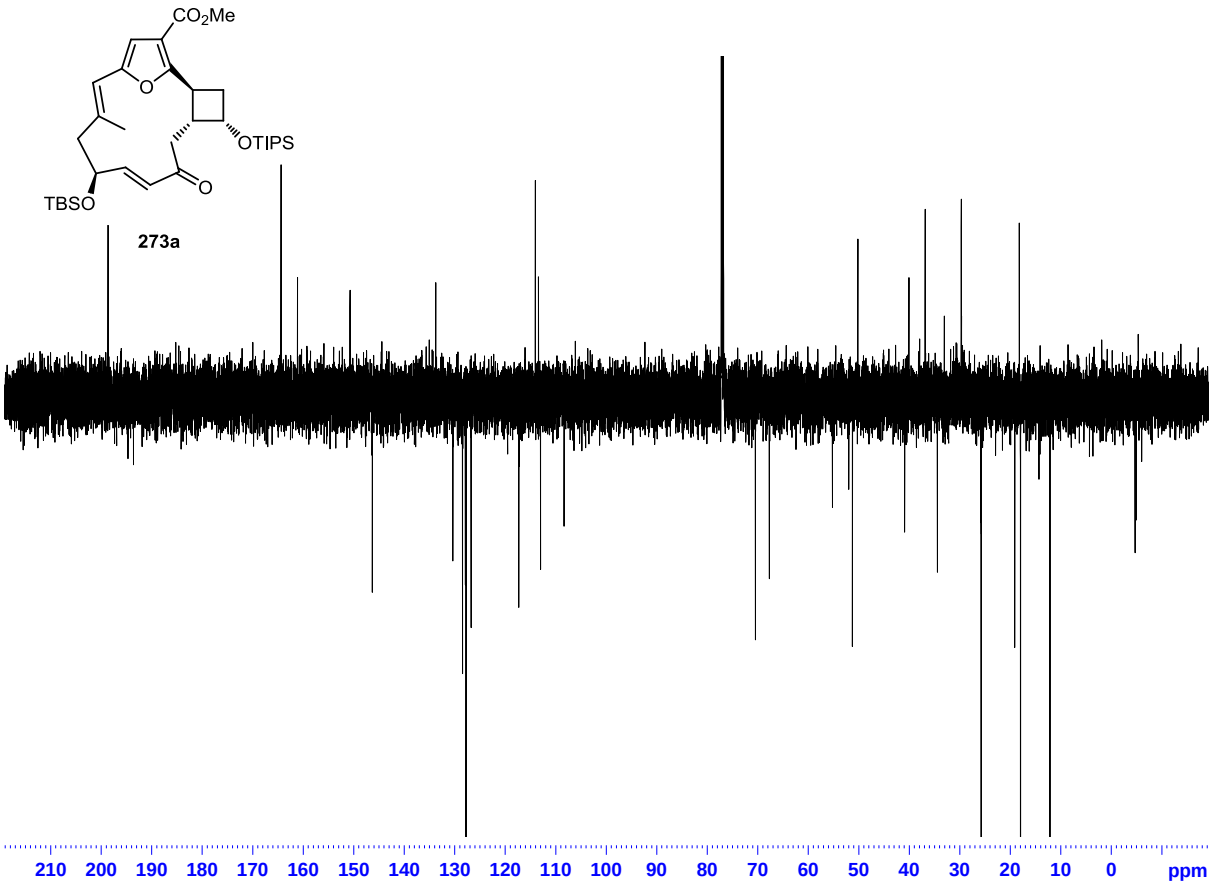
273b

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

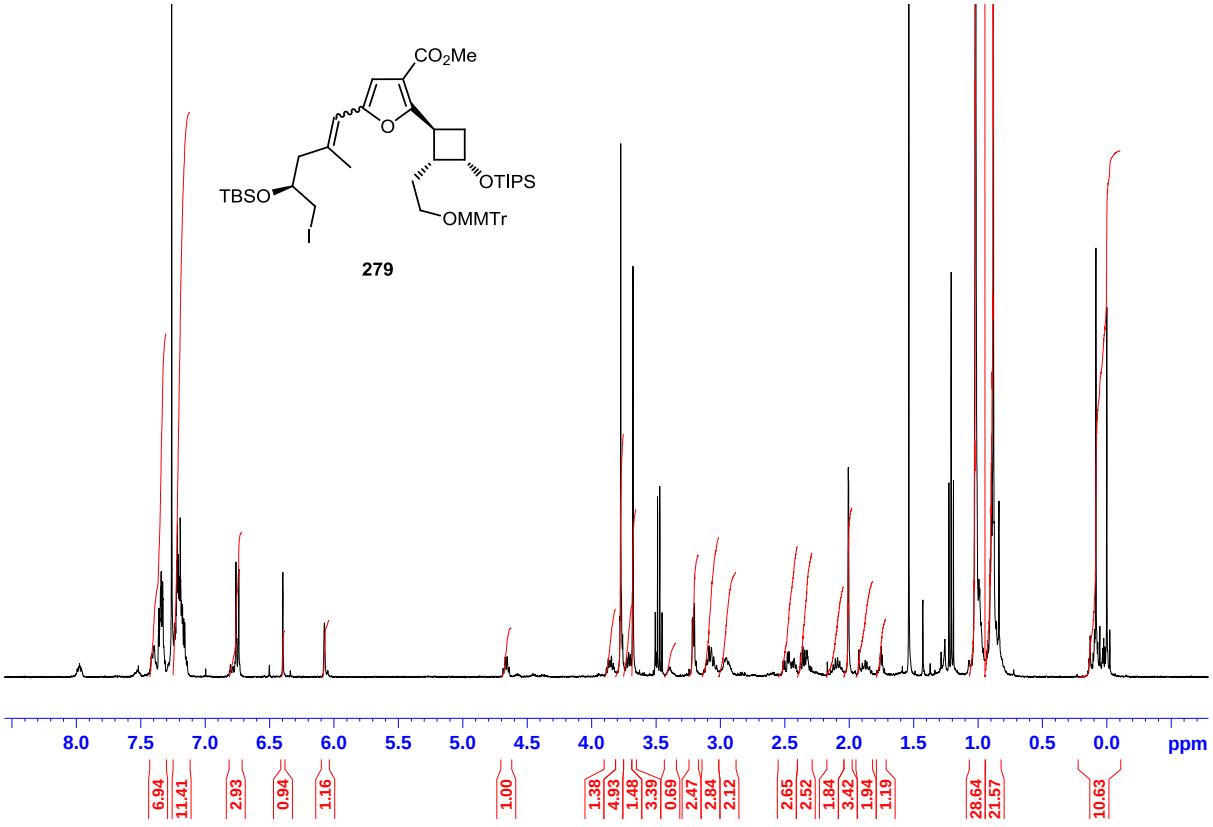

CO2Me
O
OTIPS
TBSO
O

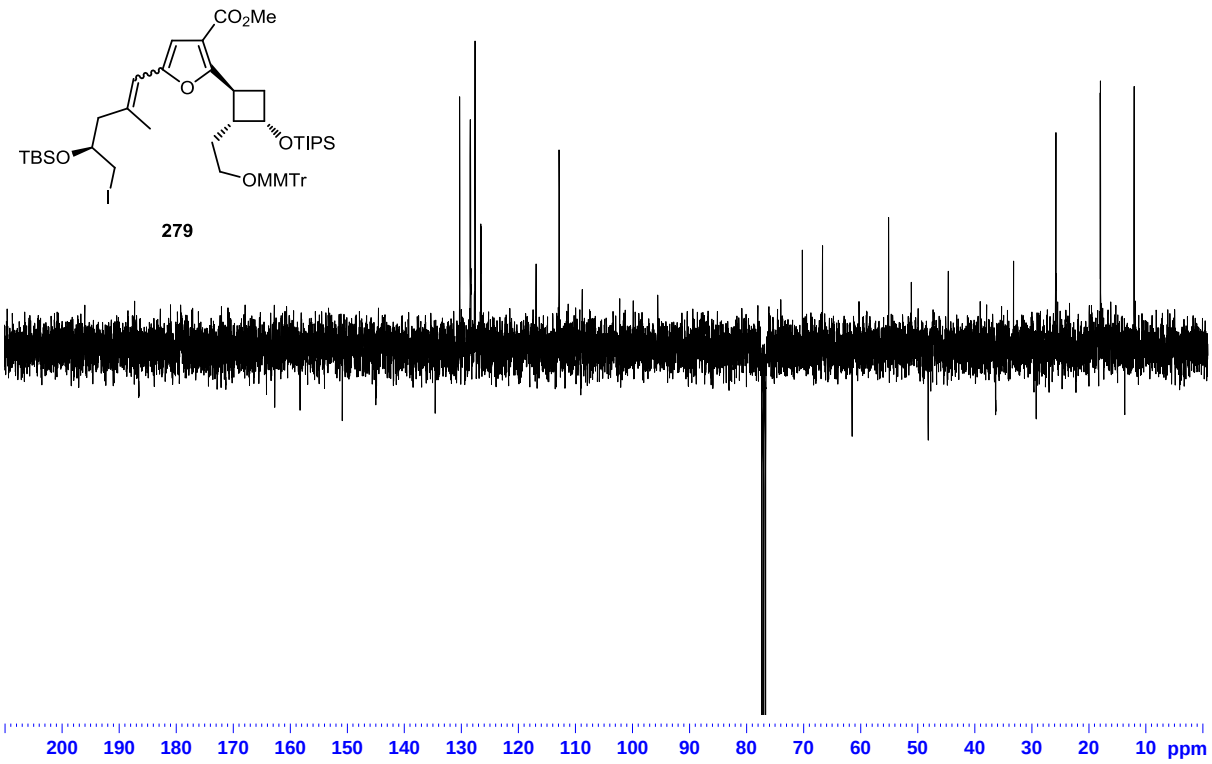
273a

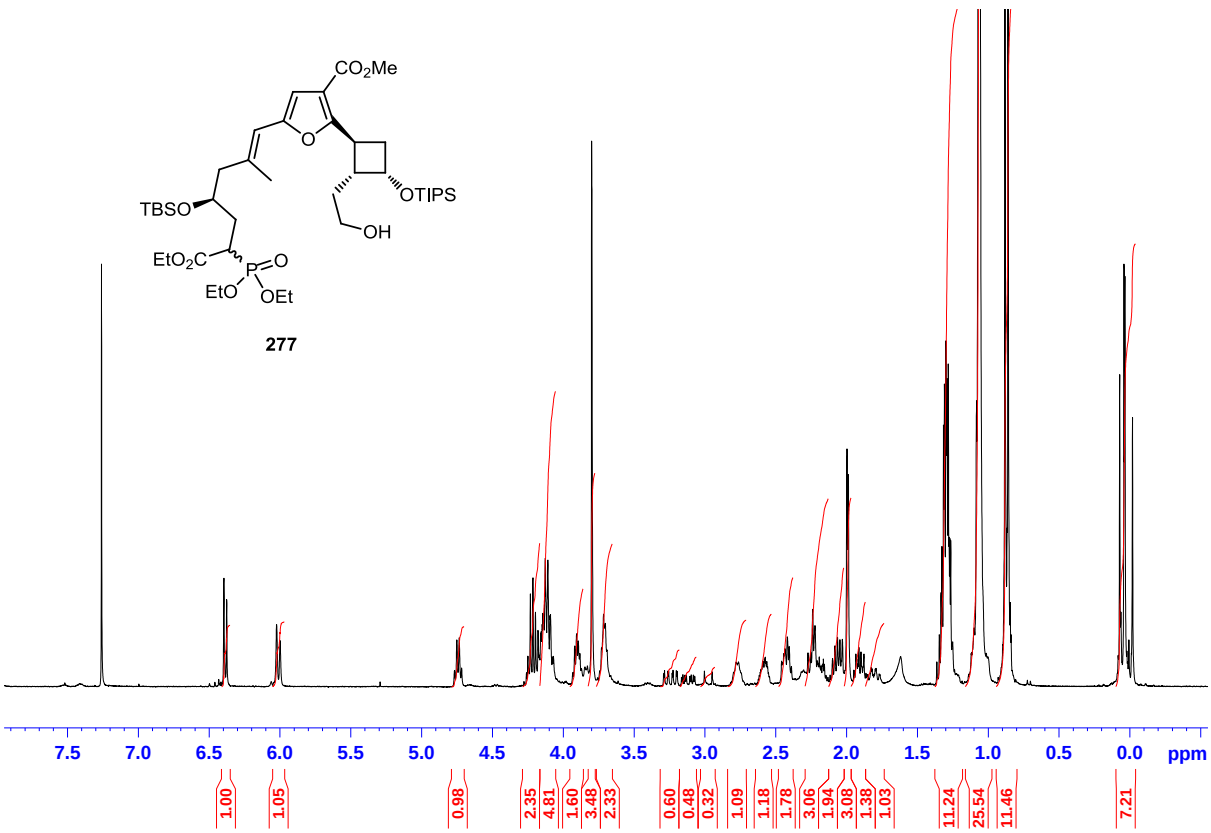
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
1.00
0.94
1.18
1.01
1.22
1.12
1.33
3.20
1.27
1.13
1.13
1.14
1.19
1.40
1.18
2.71
20.08
12.45
5.82

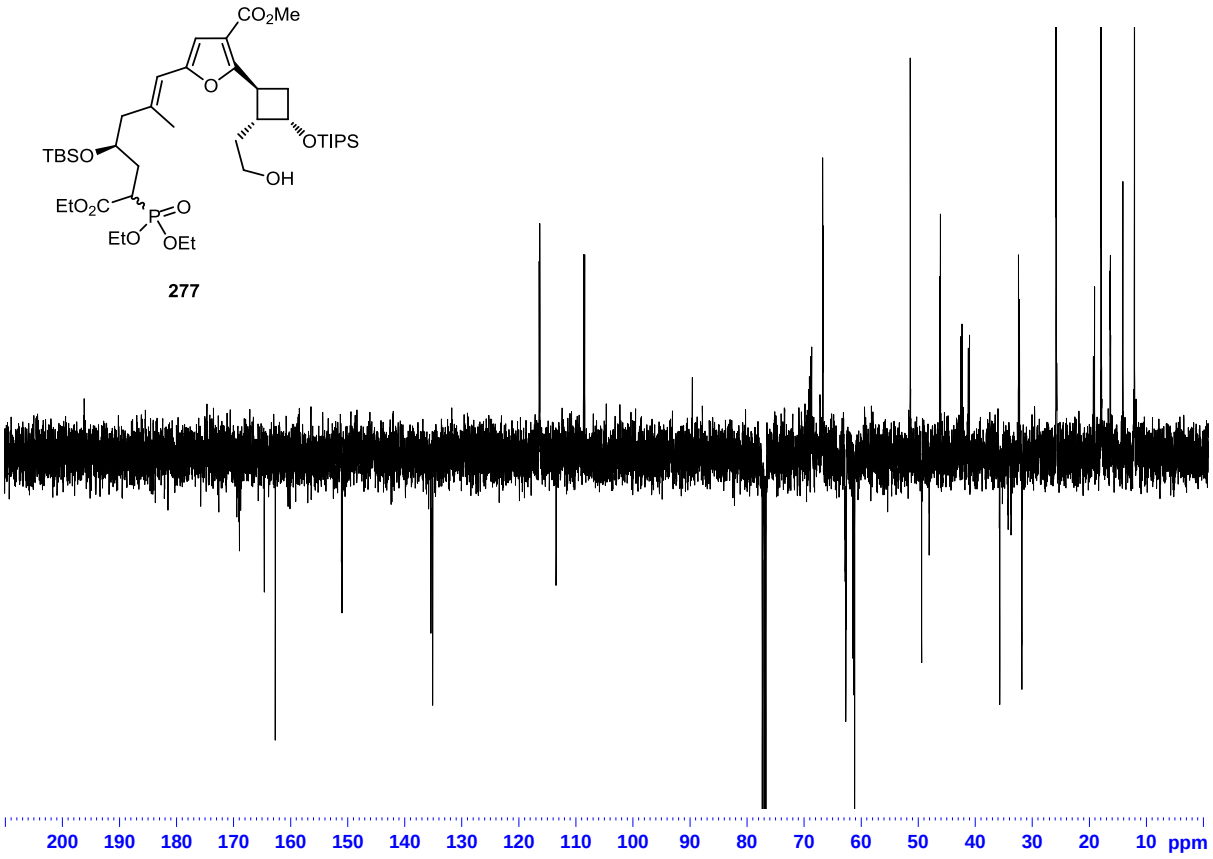


5.3.6 $\Delta^{12,13}$ Horner Wadsworth Emmons Approach (*c*Bu)

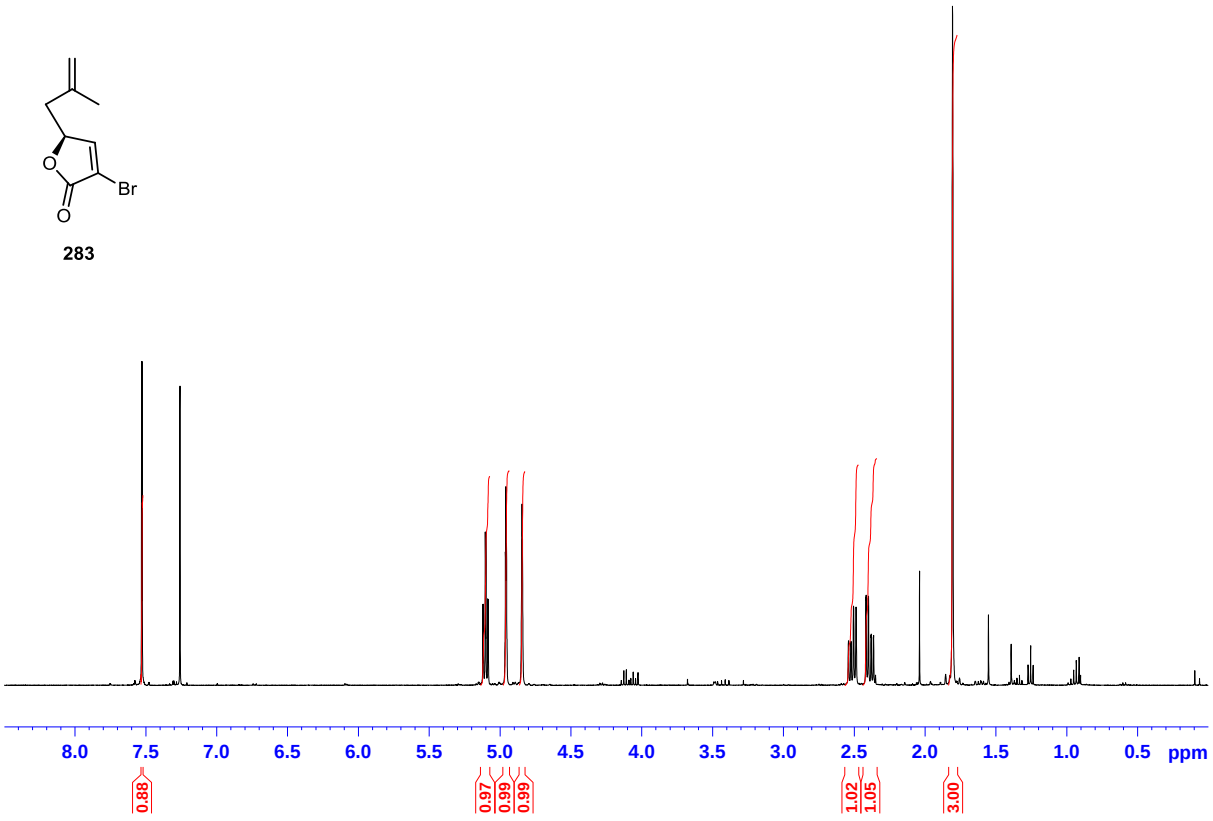


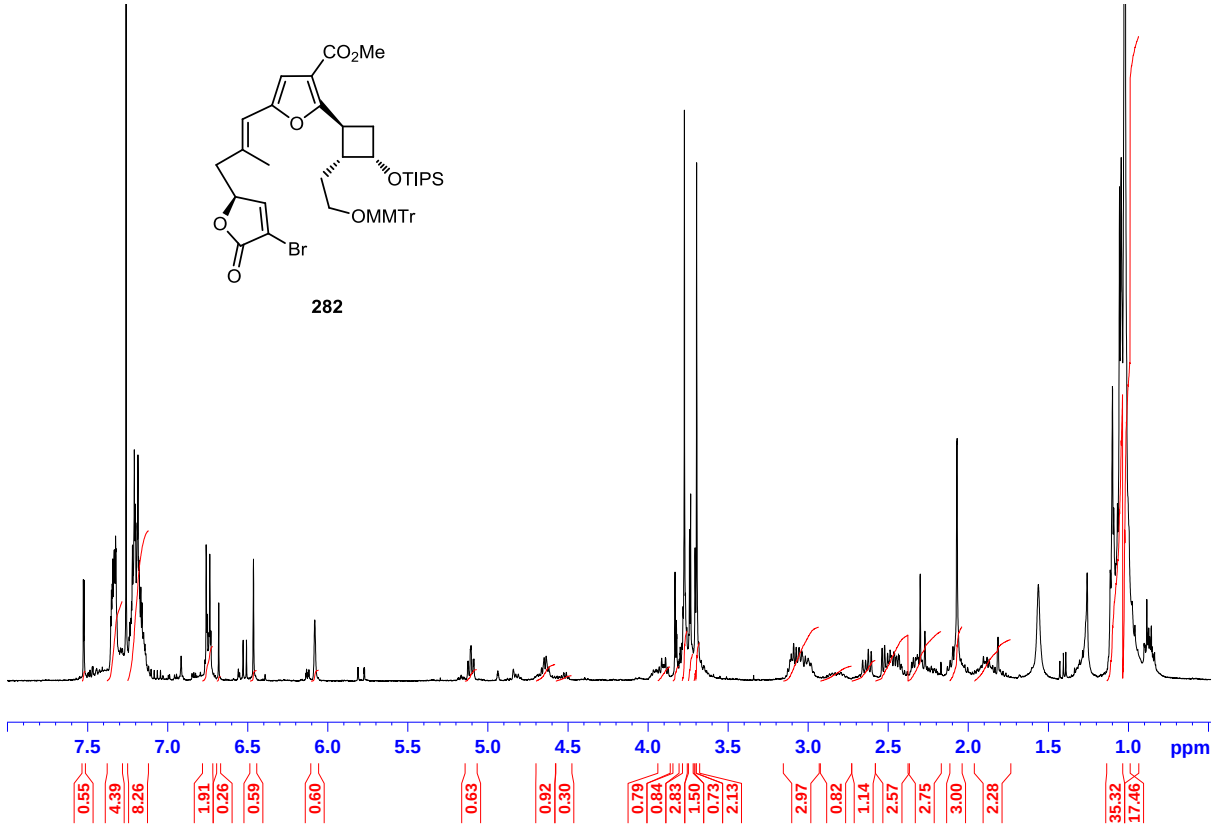

CO2Me
O
TBSO
OTIPS
OMMTr
I
279
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

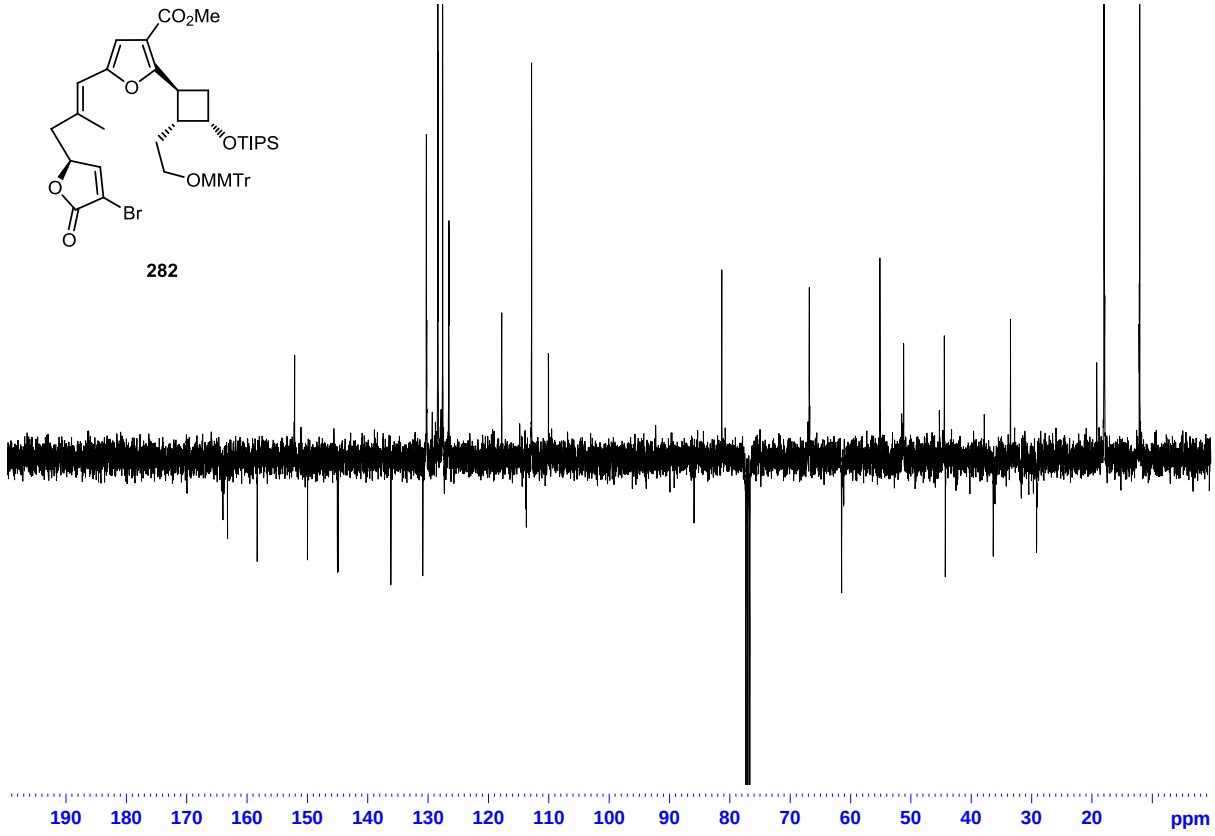

CO2Me
O
TBSO
OTIPS
OH
EtO2C
P
O
EtO
OEt
277
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
1.00 1.05 0.98 2.35 4.81 1.60 3.48 2.33 0.60 0.48 0.32 1.09 1.18 1.78 3.06 1.94 3.08 1.38 1.03 11.24 25.54 11.46 7.21

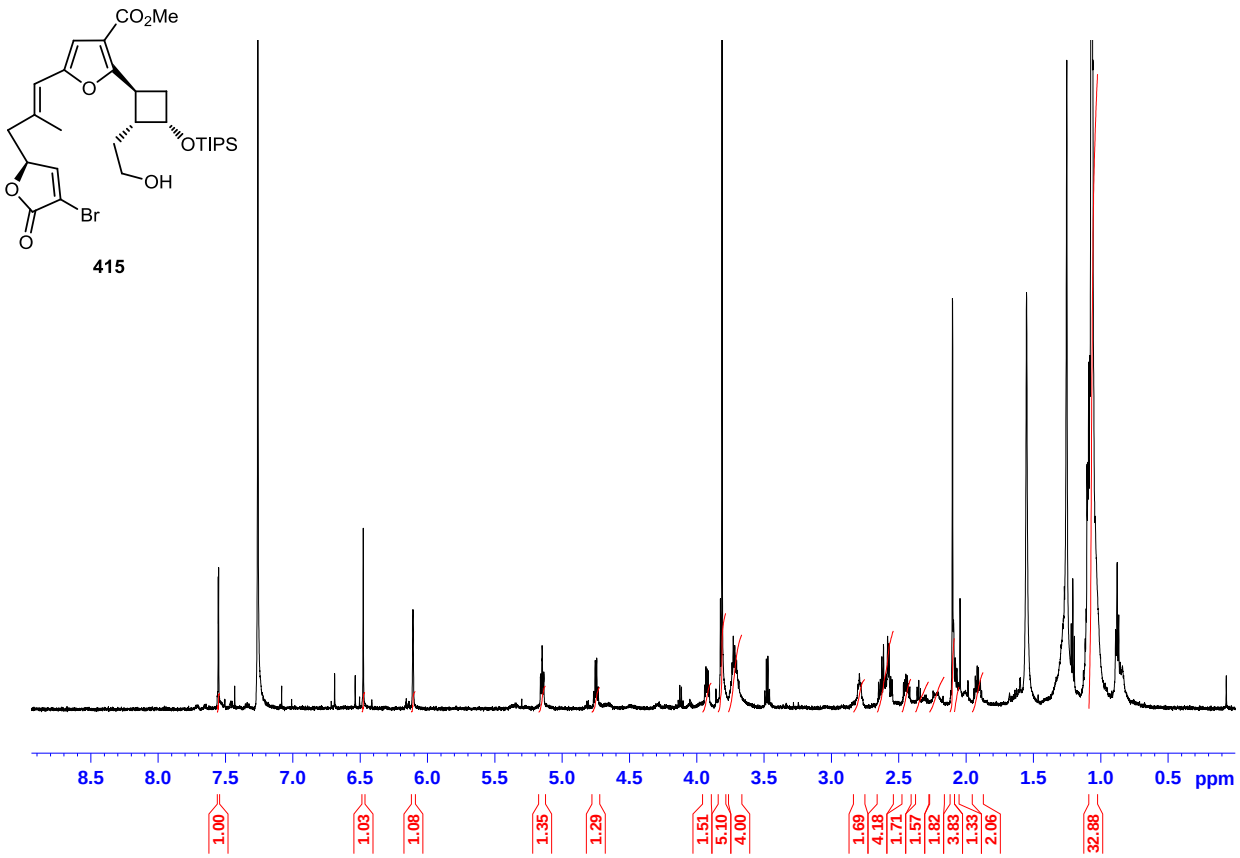


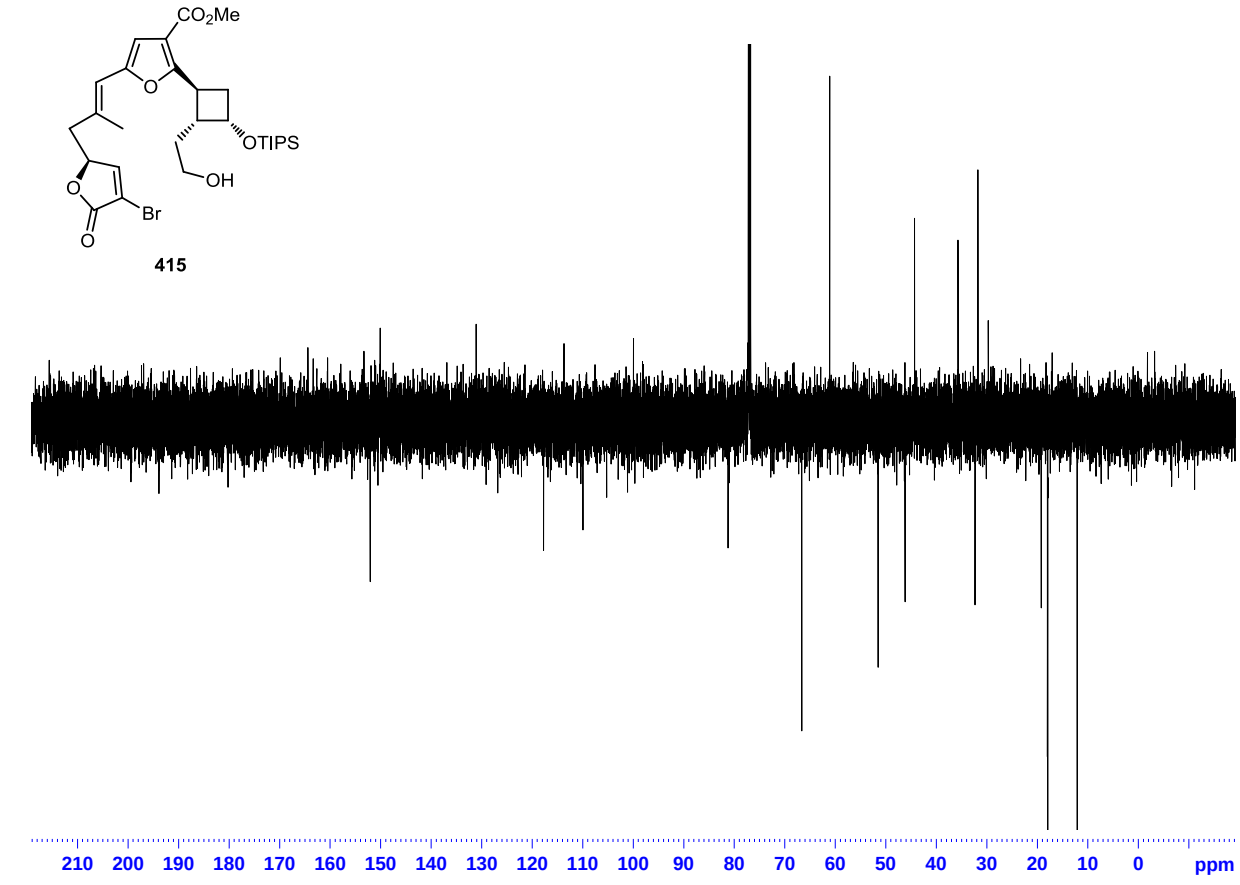
5.3.7 Furan-Butenolide-$\Delta^{12,13}$ Approach (*c*Bu)



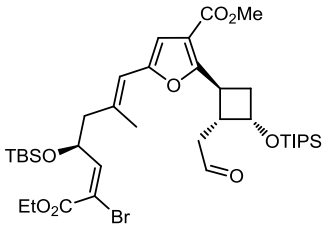

CO2Me
OTIPS
OMMTr
Br
O
O
O
282
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
0.55
4.39
8.26
1.91
0.26
0.59
0.60
0.63
0.92
0.30
0.79
0.84
2.83
1.50
0.73
2.13
2.97
0.82
1.14
2.57
2.75
3.00
2.28
35.32
17.46


CO2Me
OTIPS
OMMTr
Br
O
O
O
282
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm


CO2Me
O
OTIPS
OH
O
Br
O
415
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.00 1.03 1.08 1.35 1.29 1.51 5.10 4.00 1.69 4.18 1.71 1.57 1.82 3.83 1.33 2.06 32.88

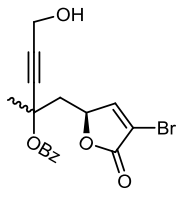

CO2Me
O
OTIPS
OH
O
Br
O
415
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

5.3.8 Furan-Δ[12,13] Approach (*c*Bu)

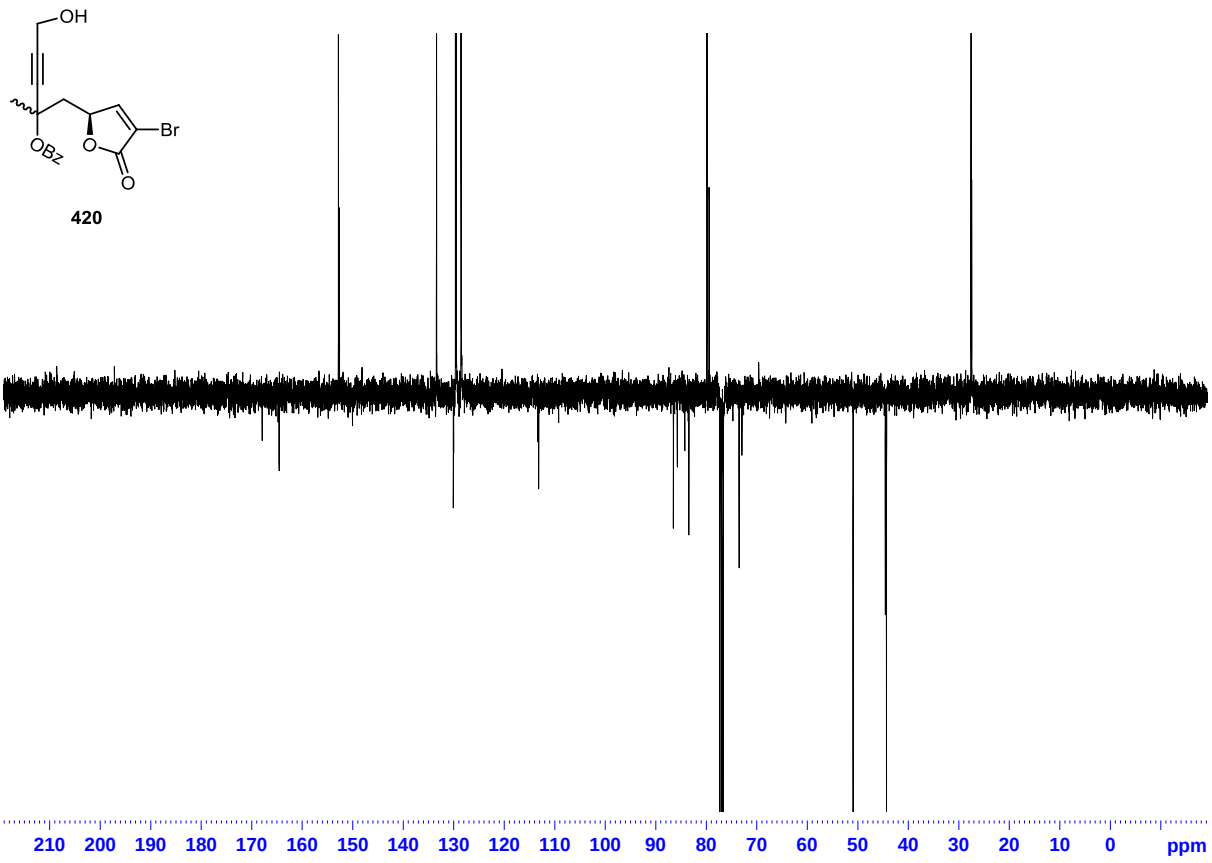


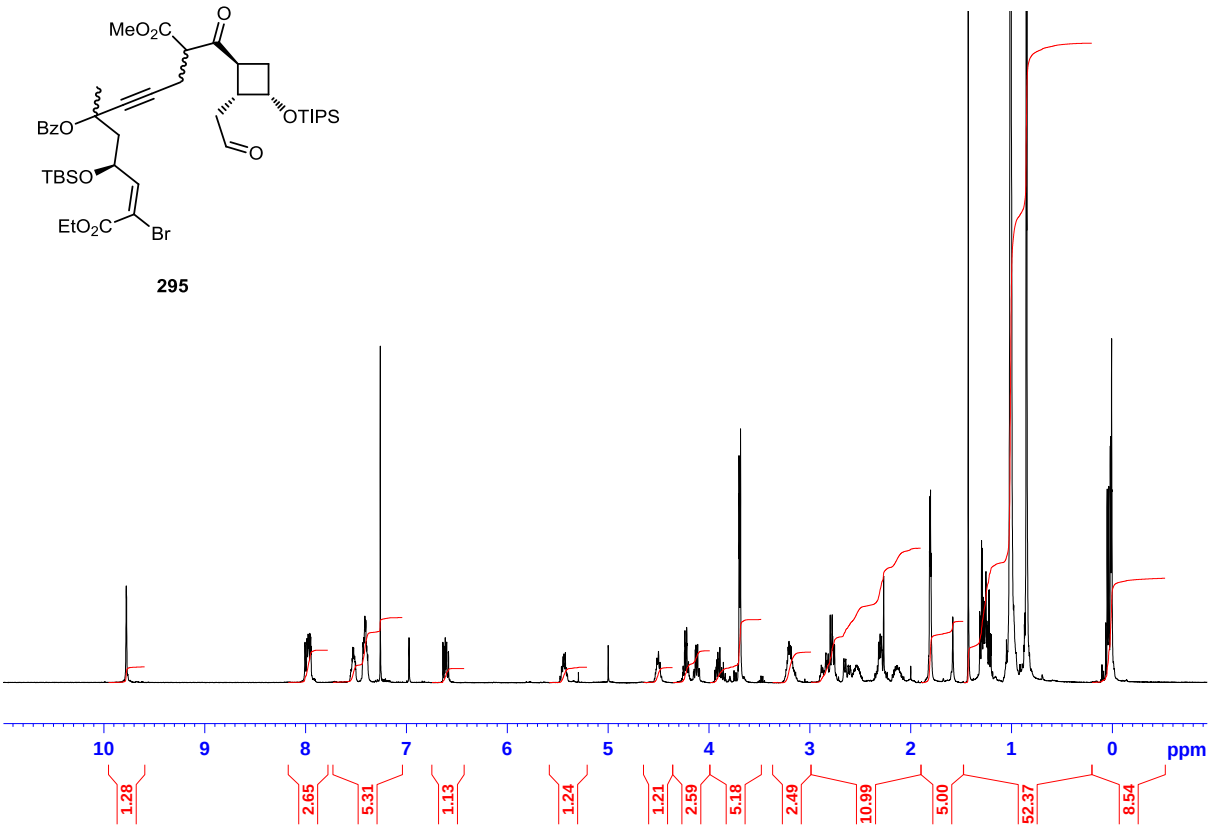
290

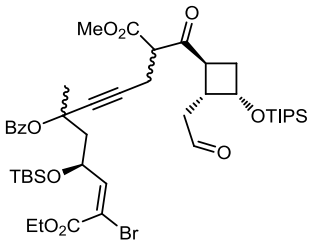
5.3.9 Δ[12,13] Approach (*c*Bu)



420

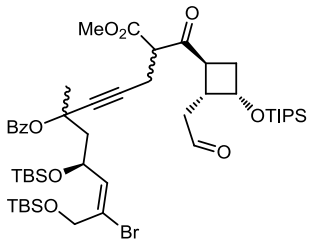

OH
OBz
O
Br
O
420
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


MeO2C
O
OTIPS
BzO
TBSO
O
EtO2C
Br
295
10 9 8 7 6 5 4 3 2 1 0 ppm
1.28
2.65
5.31
1.13
1.24
1.21
2.59
5.18
2.49
10.99
5.00
52.37
8.54


MeO2C
O
BzO
OTIPS
TBSO
O
EtO2C
Br

295

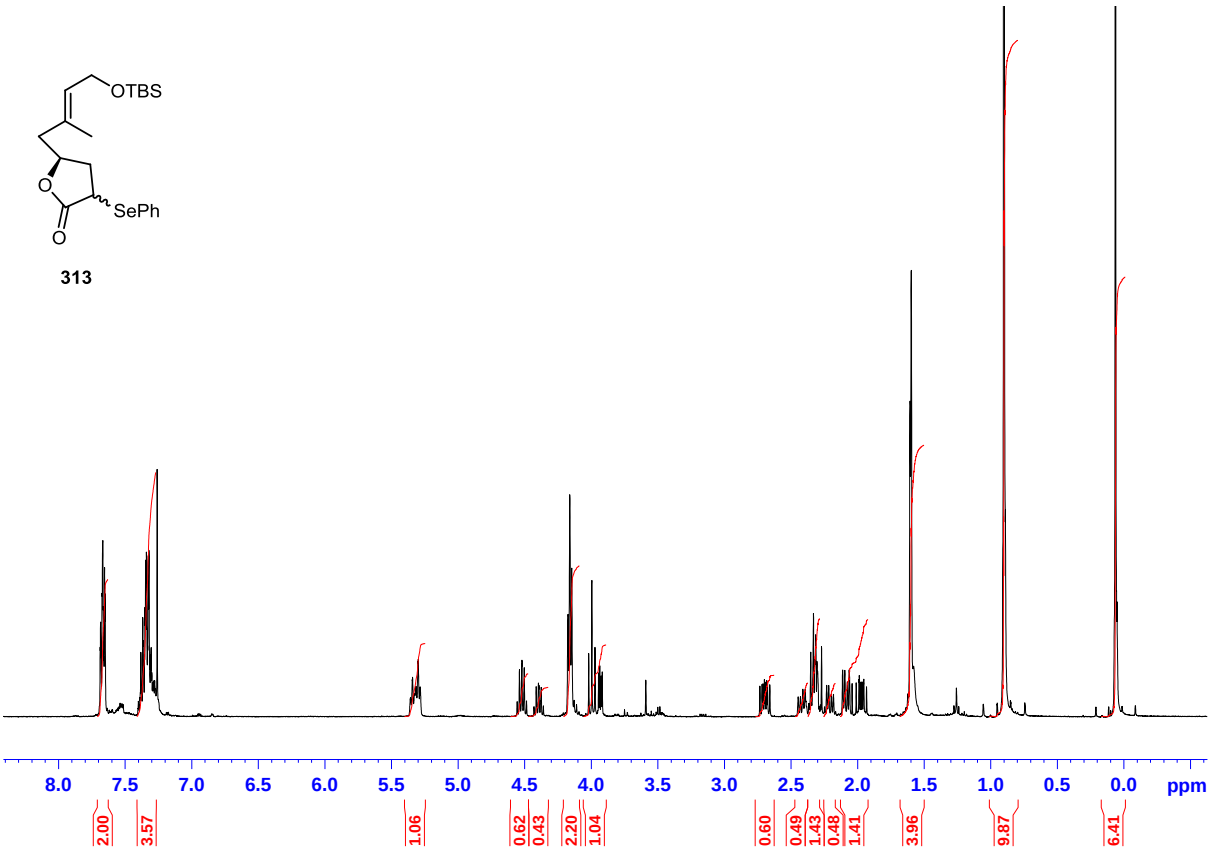
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

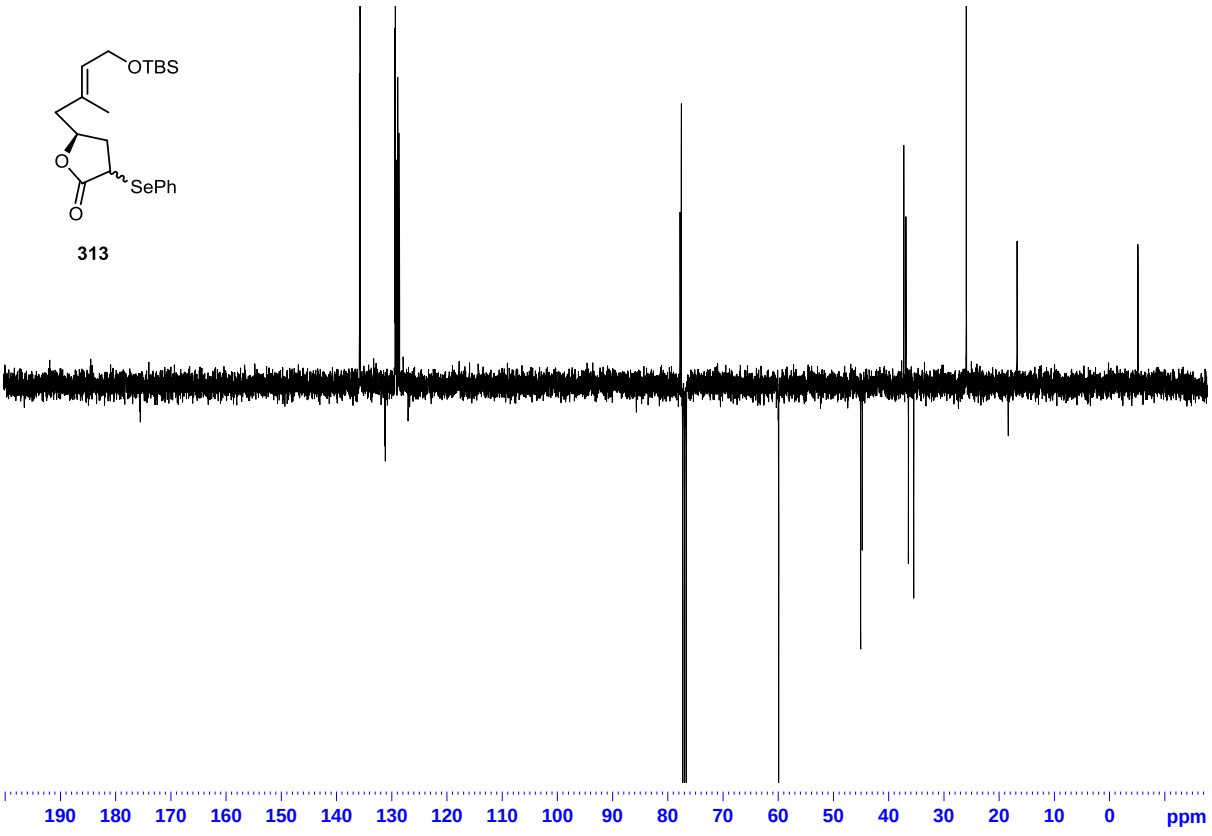

MeO2C
O
BzO
OTIPS
TBSO
TBSO
Br

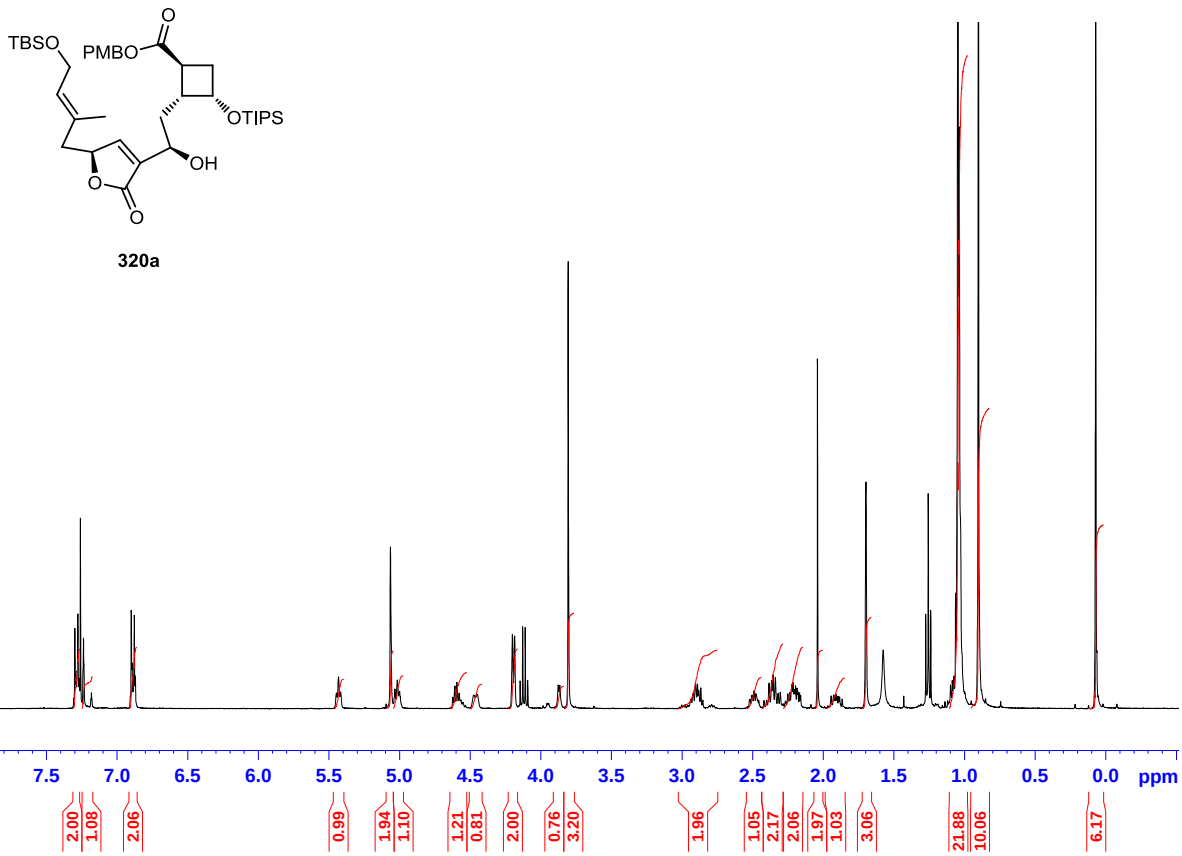
305

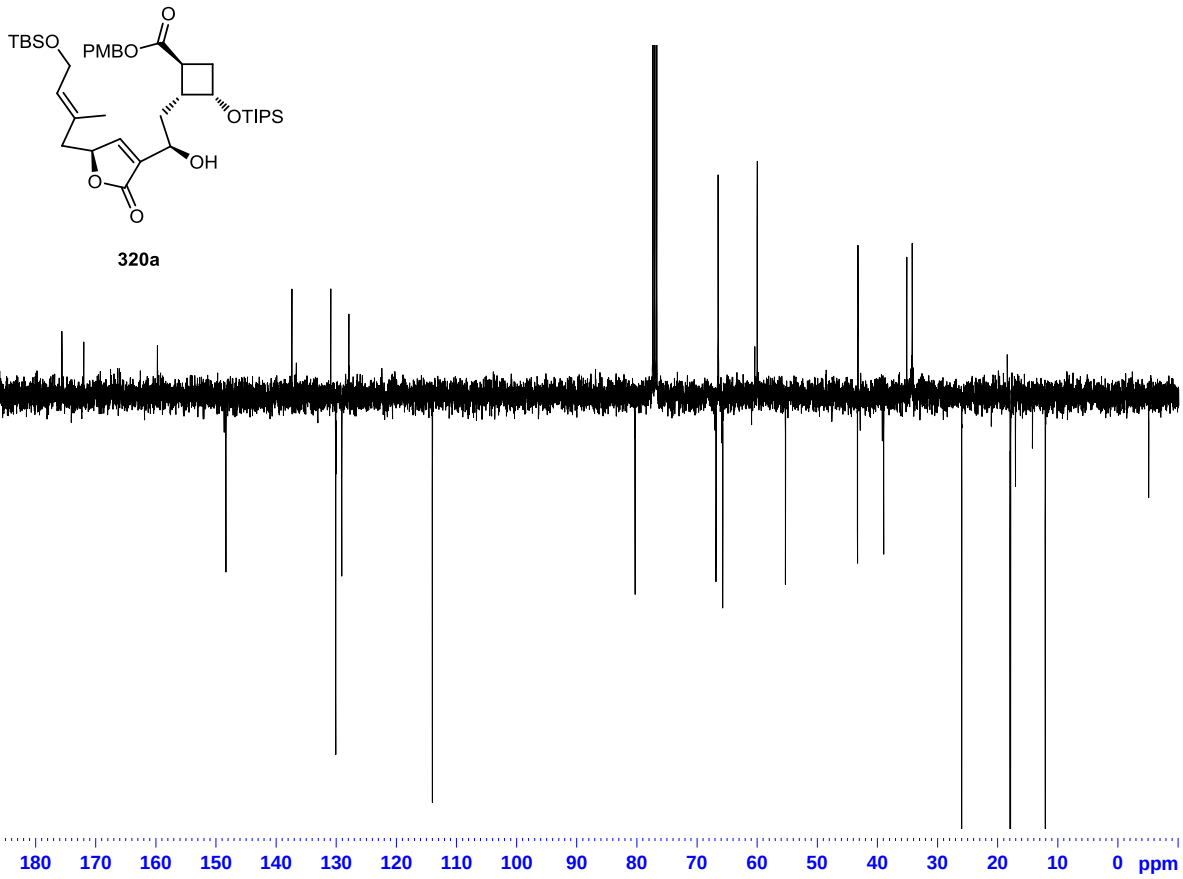
10 9 8 7 6 5 4 3 2 1 0 ppm
0.99
2.00
0.99
2.05
0.88
0.56
0.30
1.60
1.15
0.98
3.22
1.97
2.97
2.10
1.30
1.86
3.01
22.74
20.75
12.83

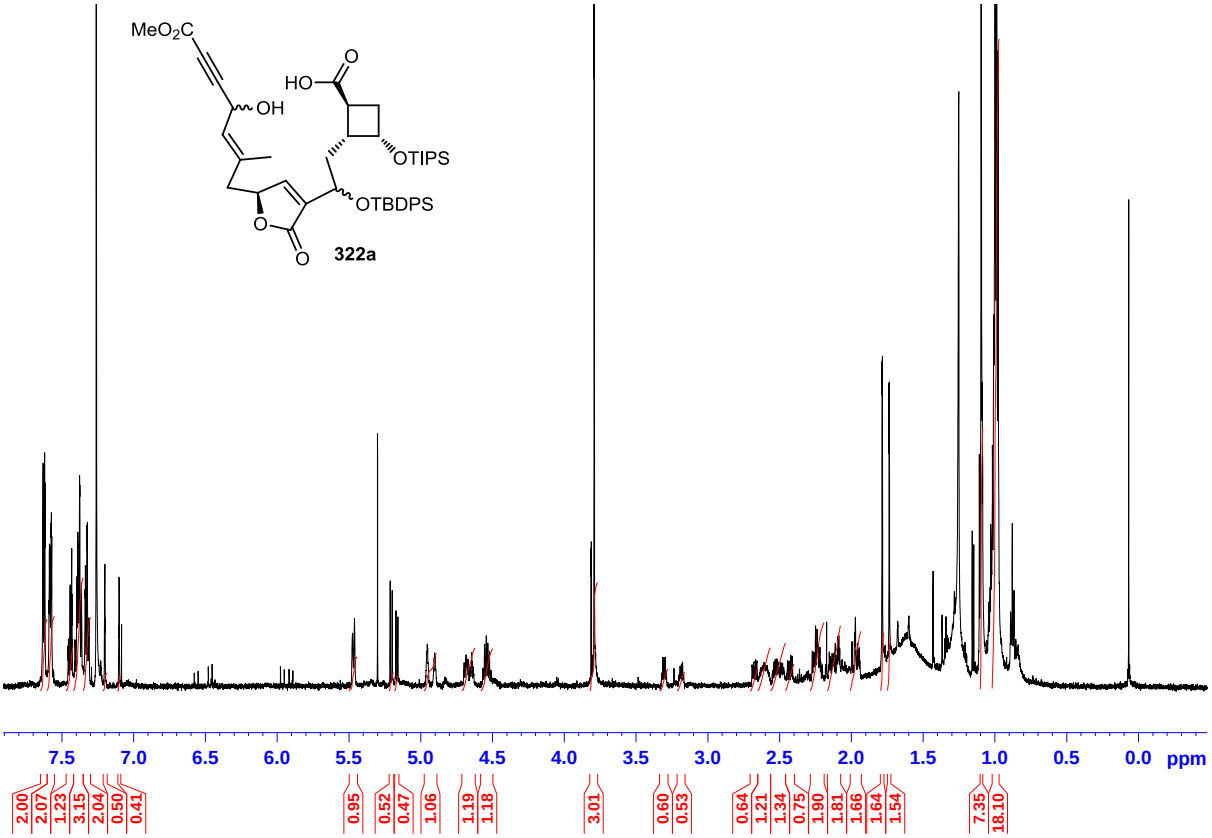
5.3.10 Northern Lactone-Butenolide Approach (*c*Bu)

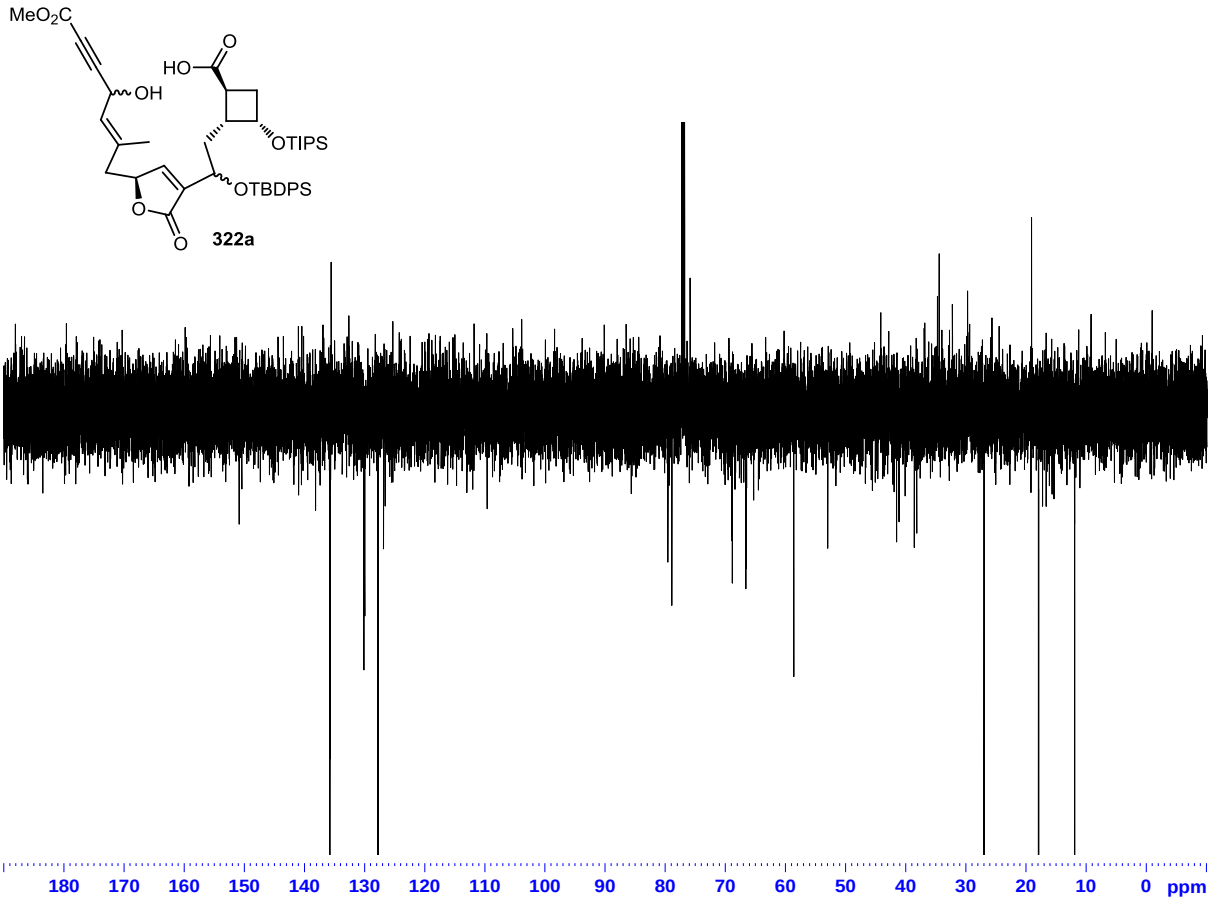




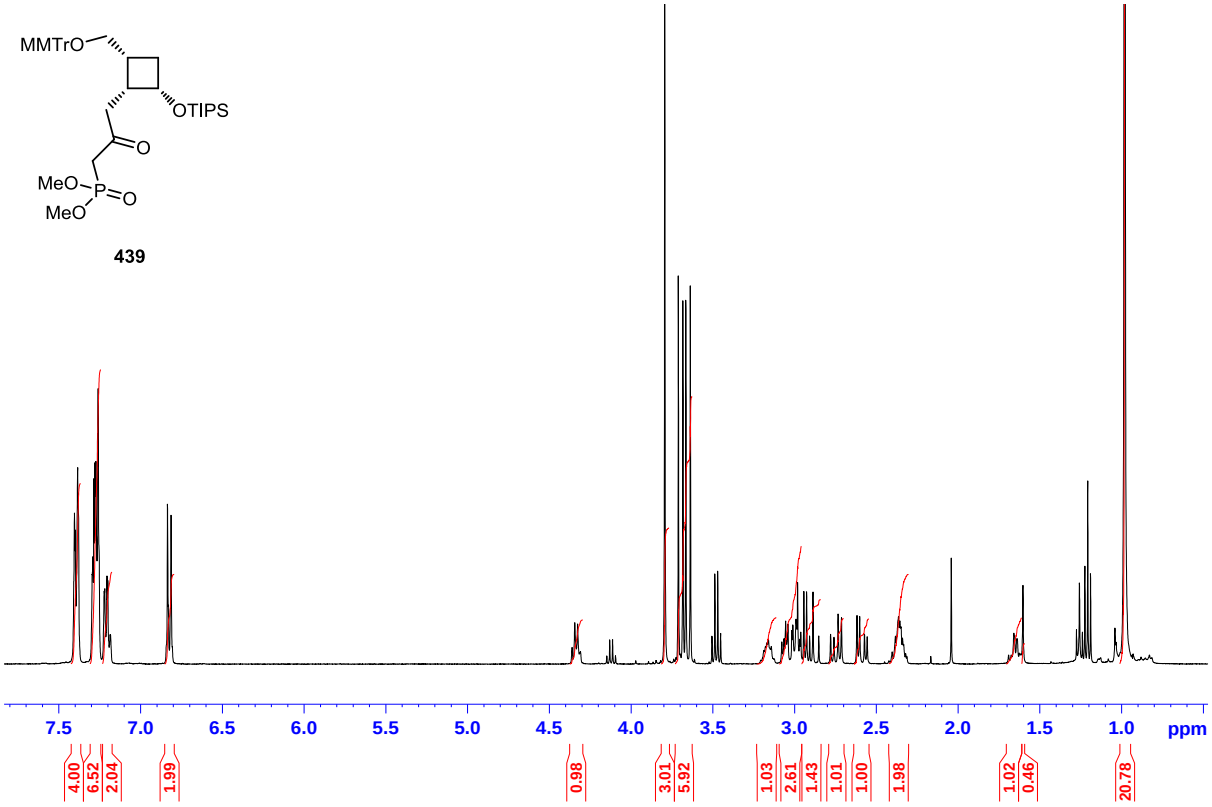

TBSO
PMBO
O
OTIPS
OH
O
O
320a
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
2.00
1.08
2.06
0.99
1.94
1.10
1.21
0.81
2.00
0.76
3.20
1.96
1.05
2.17
2.06
1.97
1.03
3.06
21.88
10.06
6.17

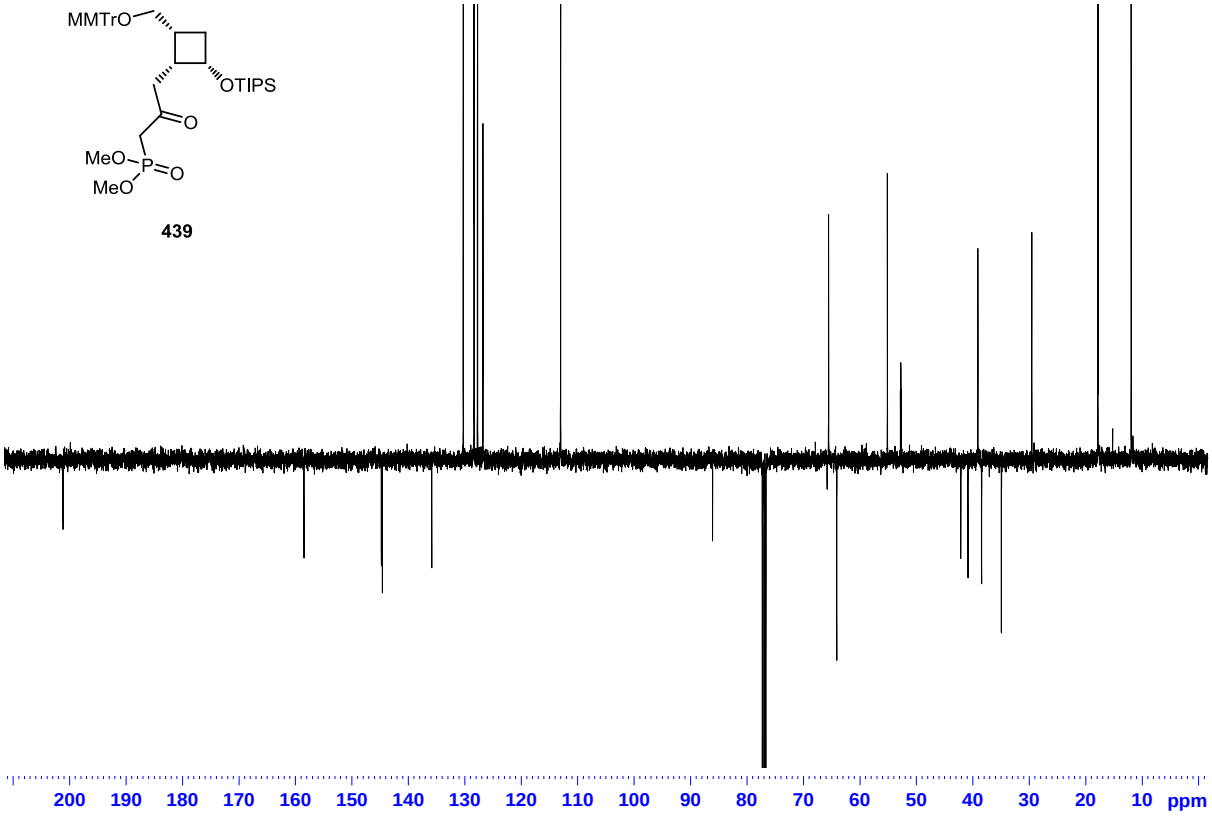

TBSO
PMBO
O
OTIPS
OH
O
O
320a
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

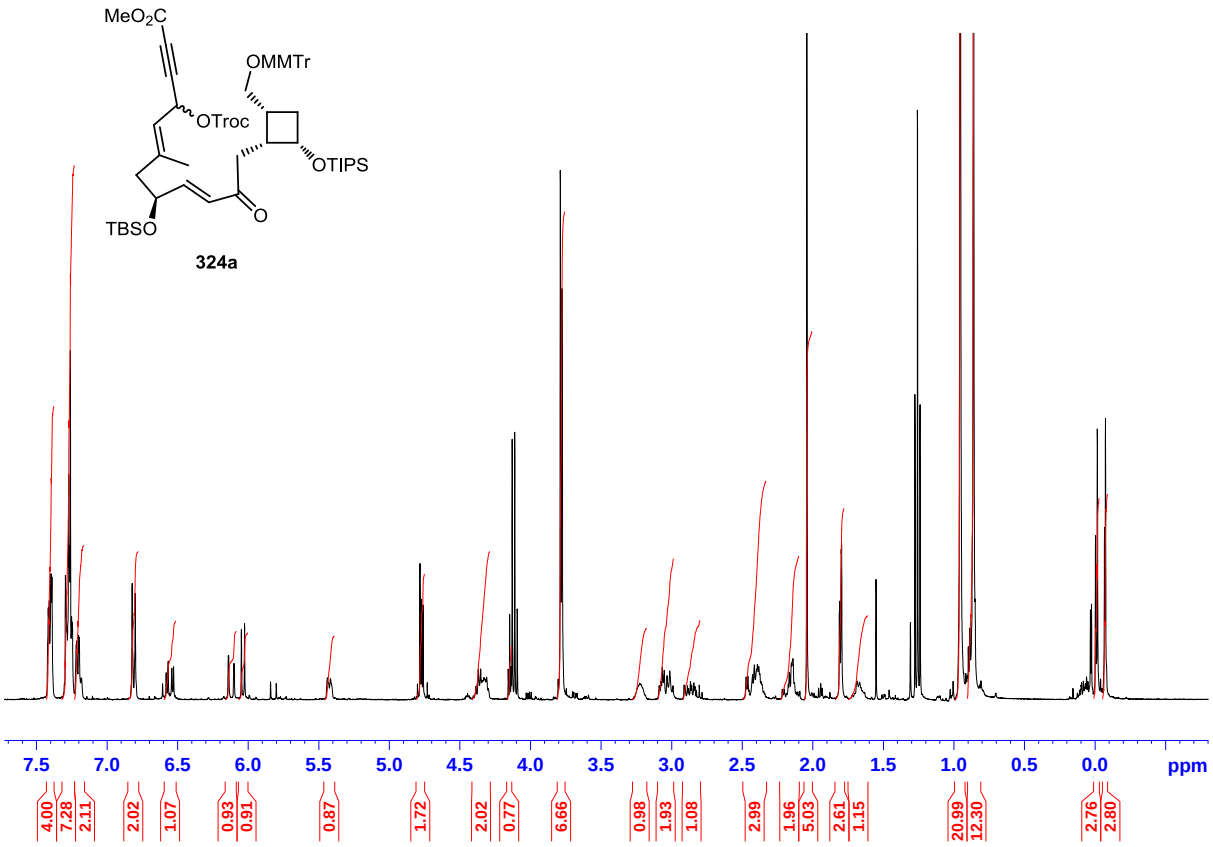

MeO2C
HO
O
OH
OTIPS
OTBDPS
O
O
322a
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
2.00 2.07 1.23 3.15 2.04 0.50 0.41 0.95 0.52 0.47 1.06 1.19 1.18 3.01 0.60 0.53 0.64 1.21 1.34 0.75 1.90 1.81 1.66 1.64 1.54 7.35 18.10


MeO2C
HO
O
OH
OTIPS
OTBDPS
O
O
322a
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

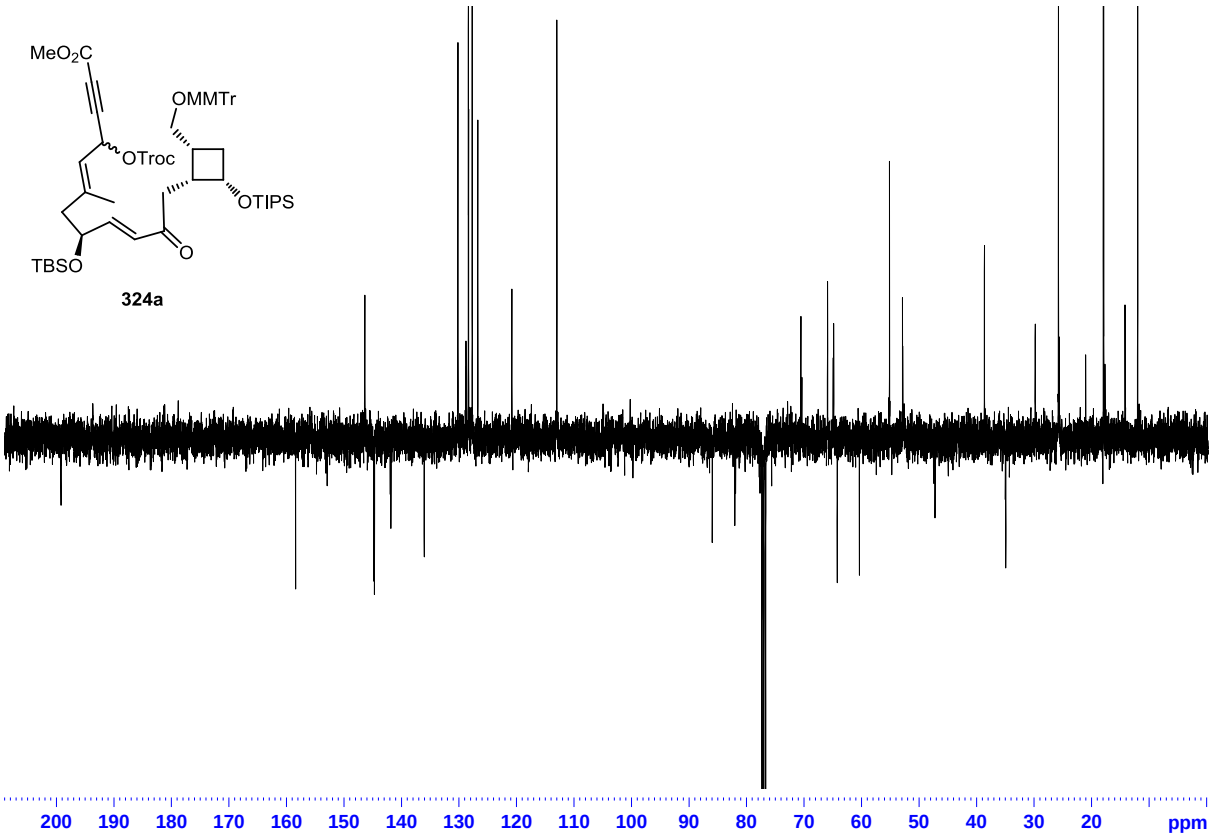
5.3.11 Northern Lactone-Horner Wadsworth Emmons Approach (*c*Bu)



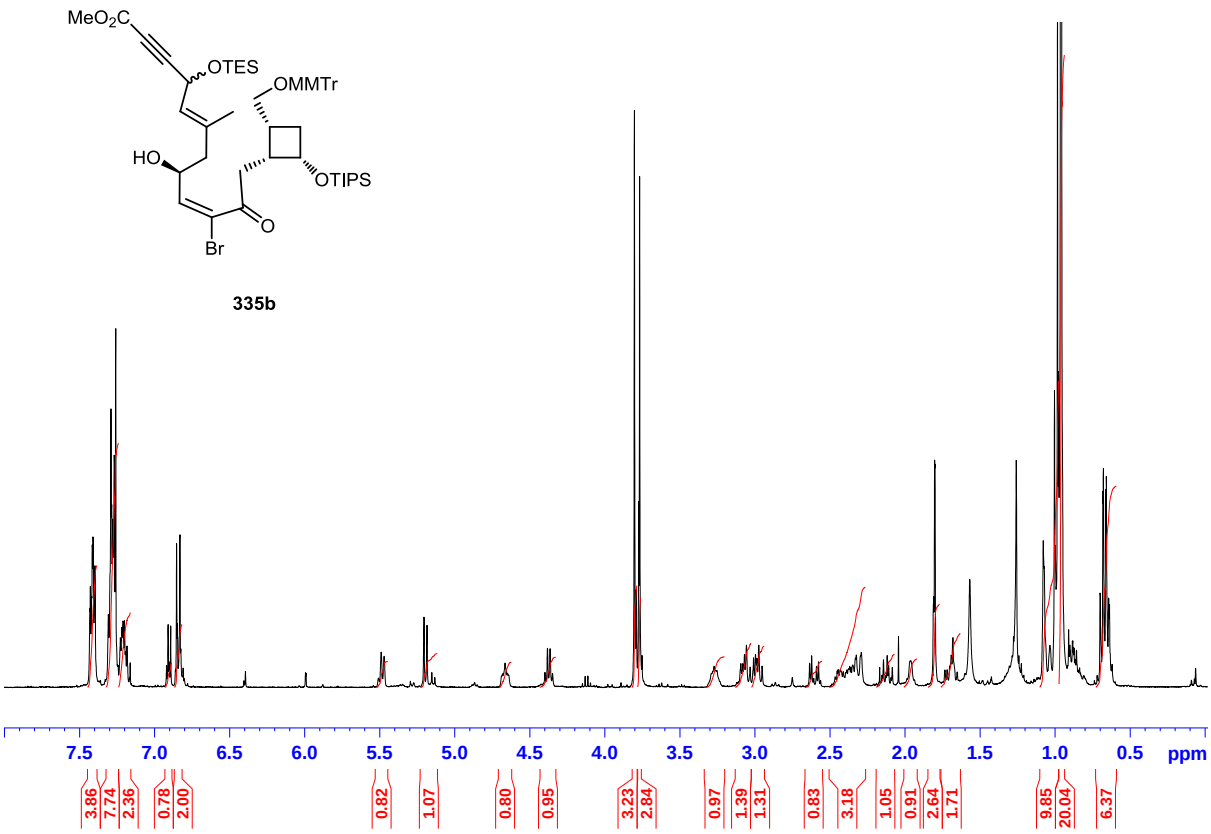


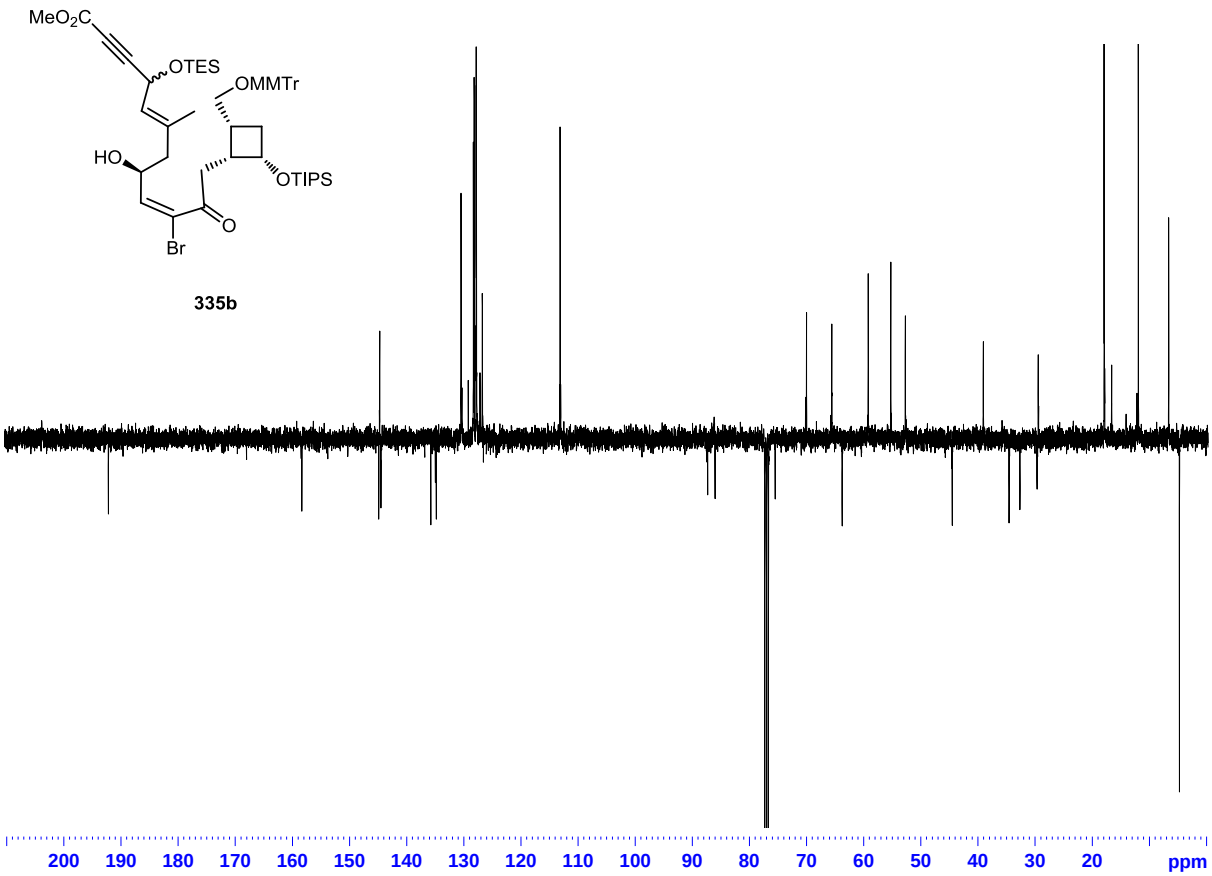

MeO2C
OMMTr
OTroc
OTIPS
TBSO
O
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
4.00
7.28
2.11
2.02
1.07
0.93
0.91
0.87
1.72
2.02
0.77
6.66
0.98
1.93
1.08
2.99
1.96
5.03
2.61
1.15
20.99
12.30
2.76
2.80

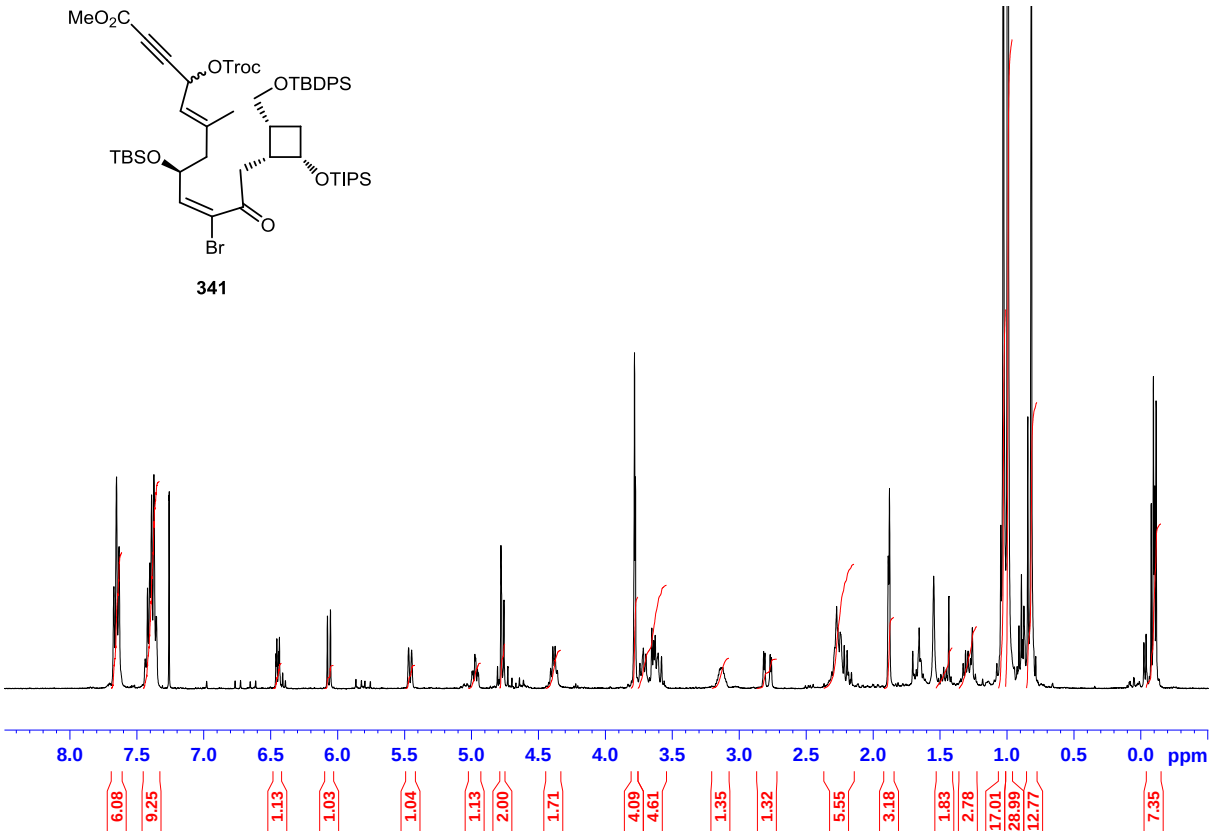
324a

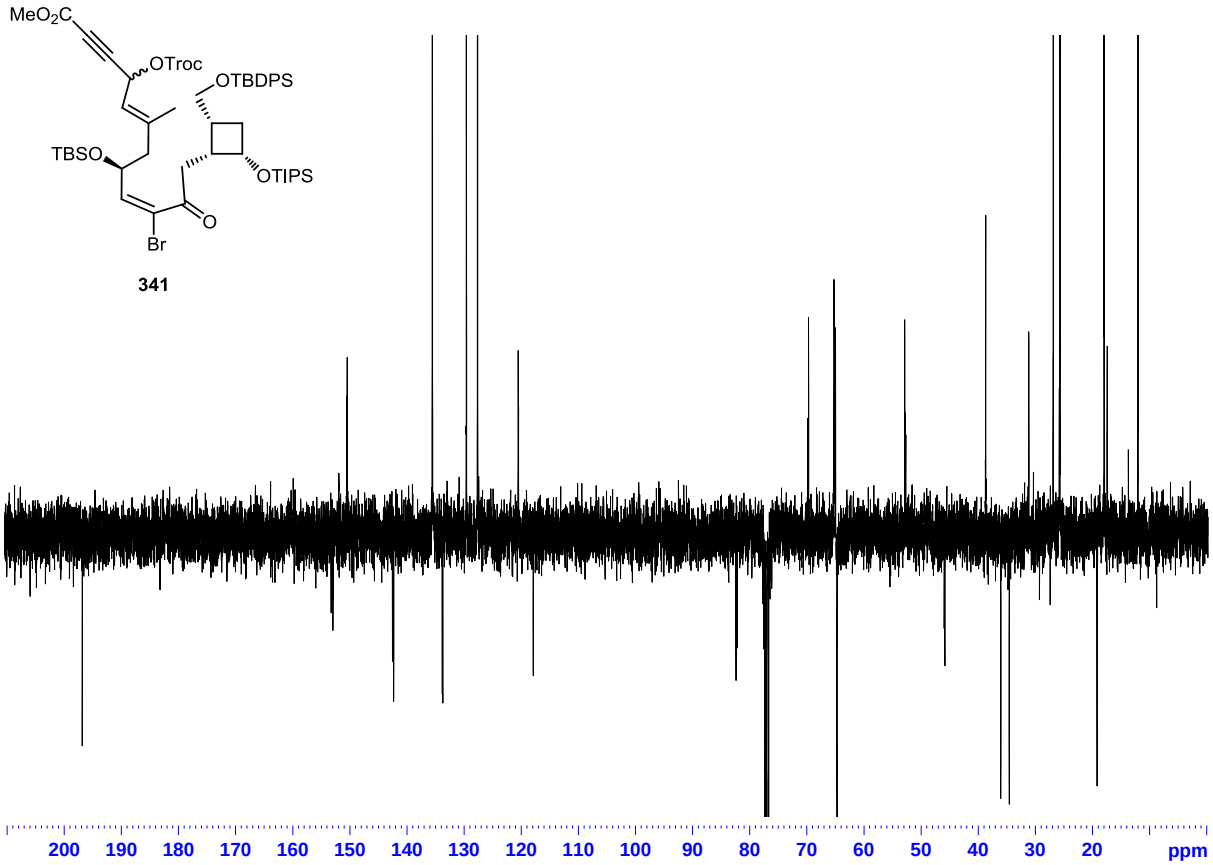

MeO2C
OMMTr
OTroc
OTIPS
TBSO
O
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

324a

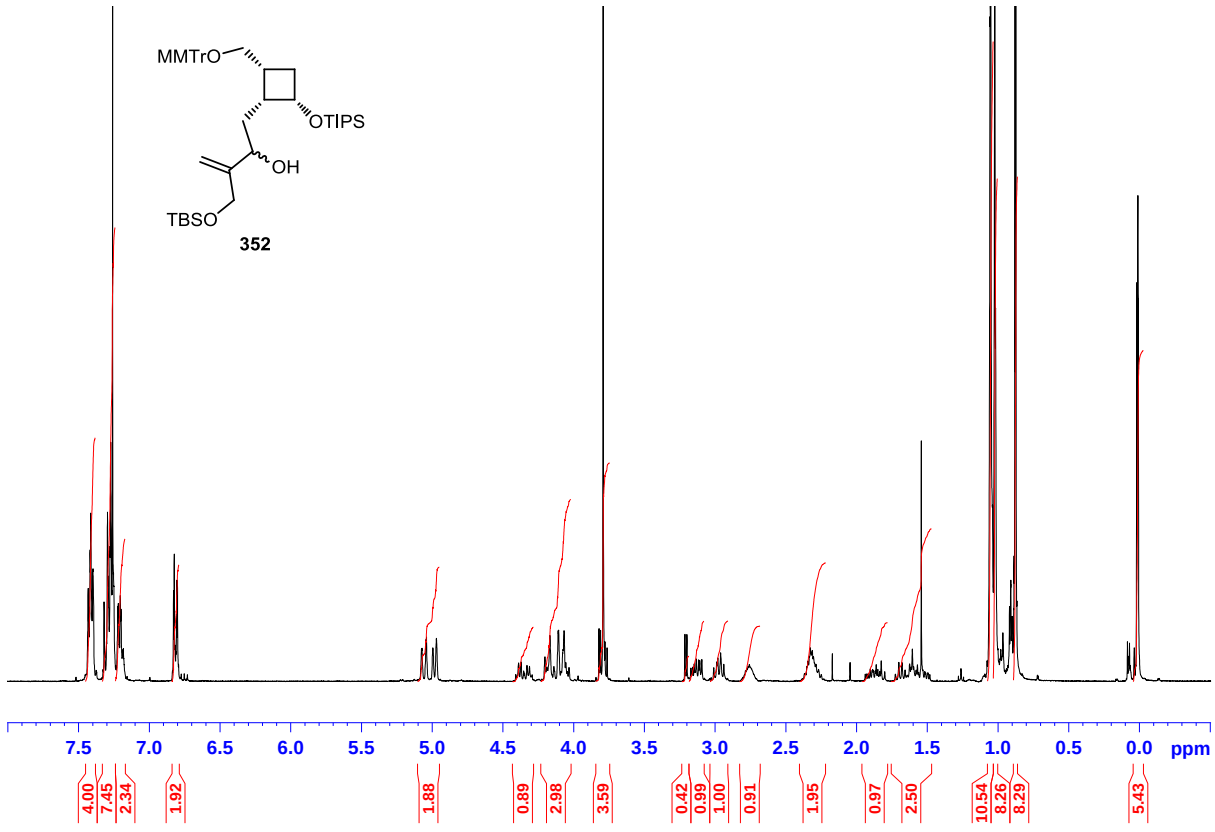

MeO2C
OTES
OMMTr
HO
OTIPS
O
Br
335b
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
3.86
7.74
2.36
0.78
2.00
0.82
1.07
0.80
0.95
3.23
2.84
0.97
1.39
1.31
0.83
3.18
1.05
0.91
2.64
1.71
9.85
20.04
6.37

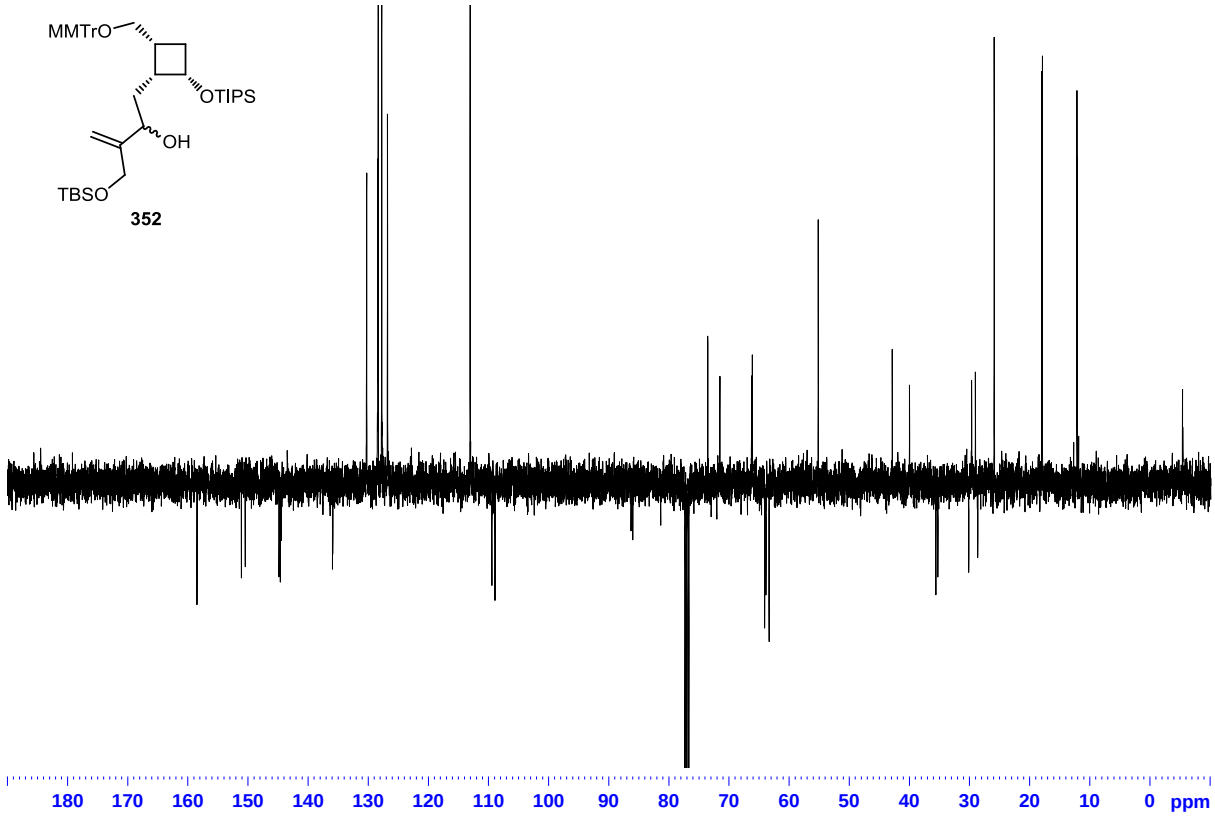

MeO2C
OTES
OMMTr
HO
OTIPS
O
Br
335b
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

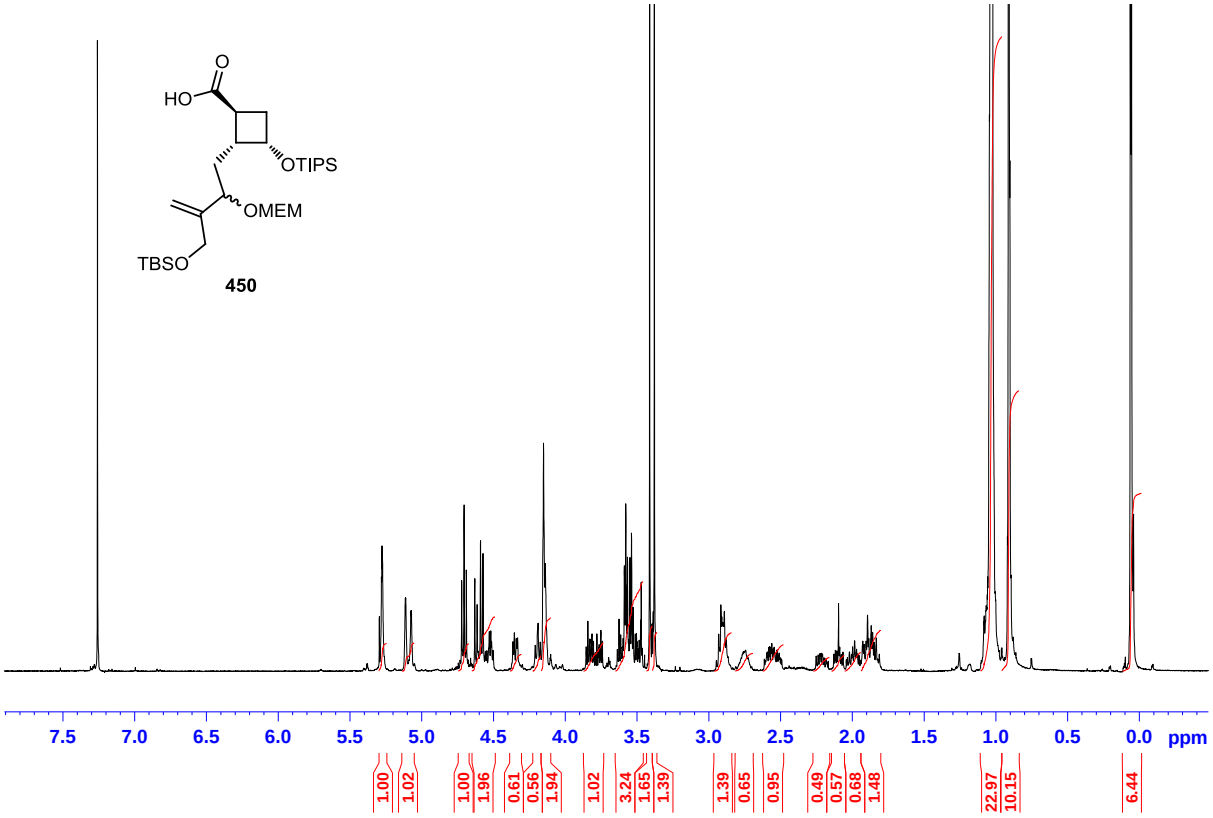

MeO2C
OTroc
OTBDPS
TBSO
OTIPS
O
Br
341
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
6.08 9.25 1.13 1.03 1.04 1.13 2.00 1.71 4.09 4.61 1.35 1.32 5.55 3.18 1.83 2.78 17.01 28.99 12.77 7.35

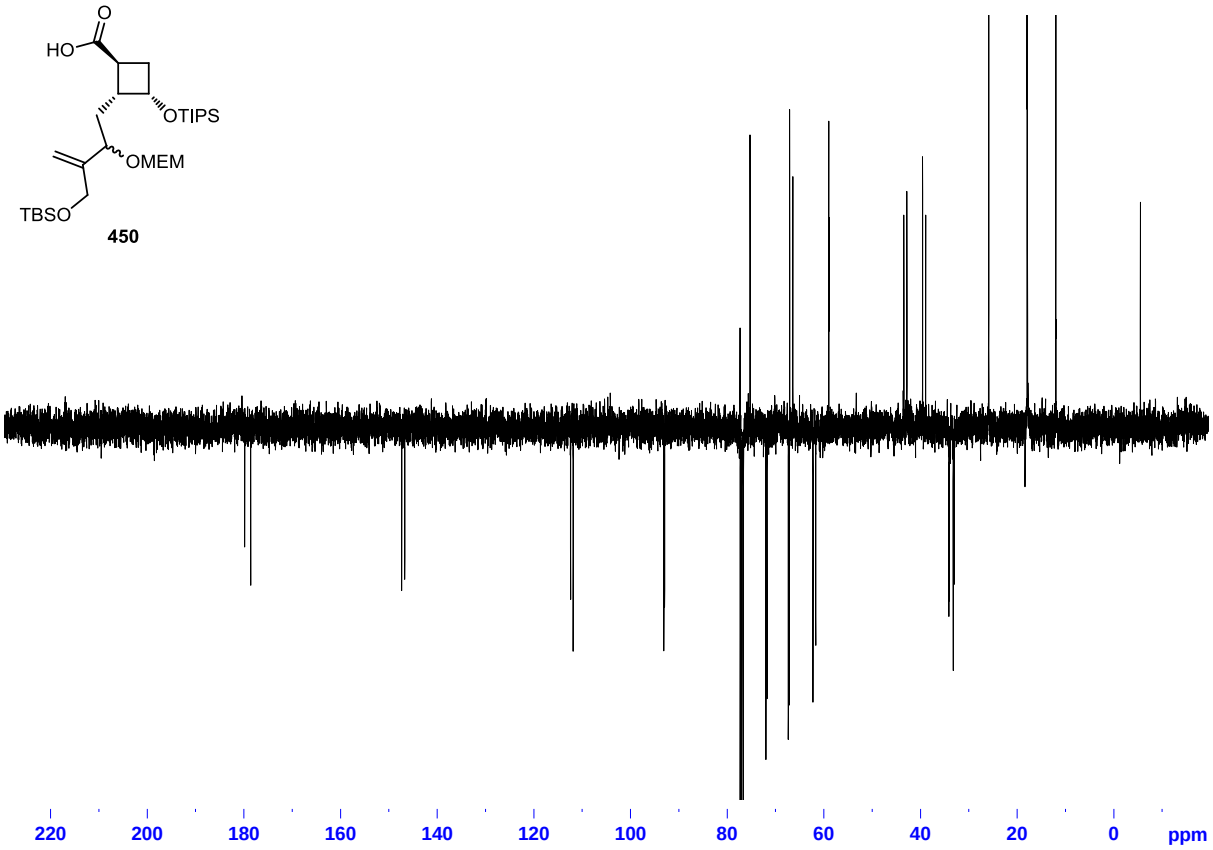

MeO2C
OTroc
OTBDPS
TBSO
OTIPS
O
Br
341
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

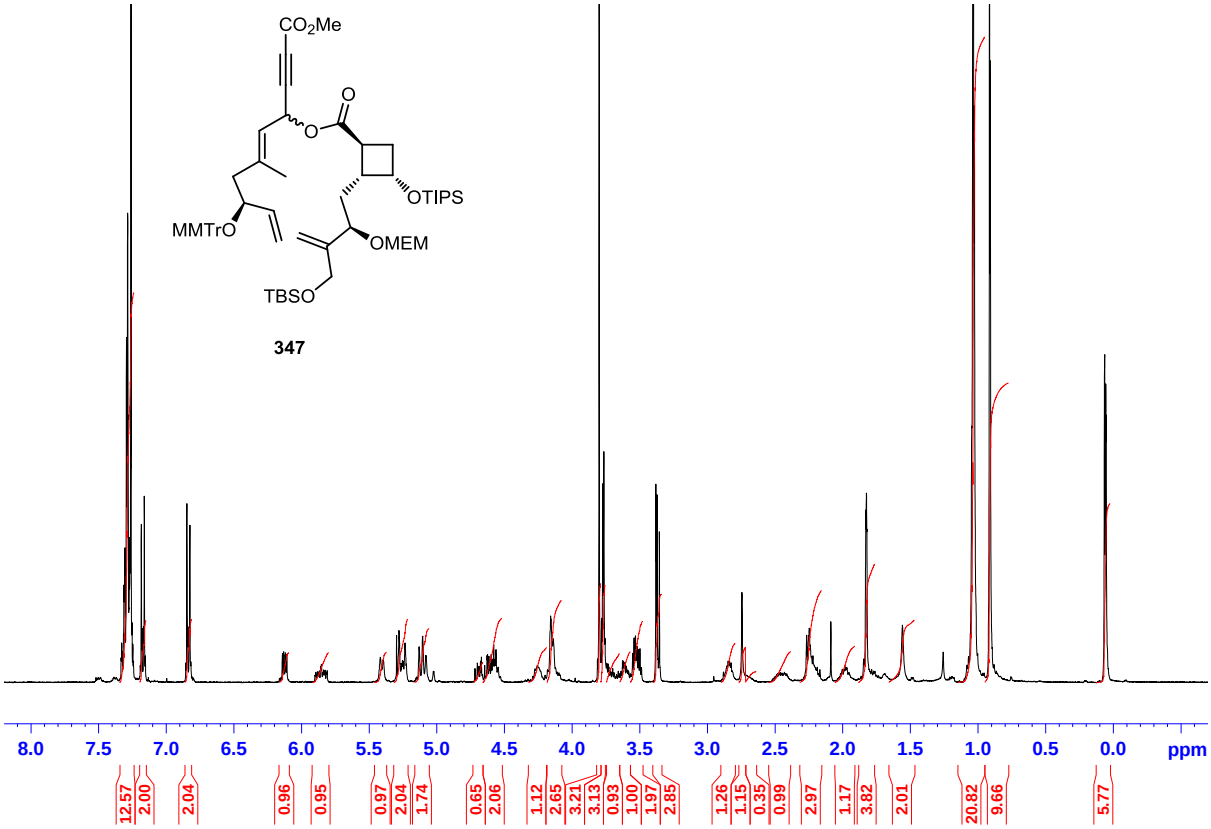
5.3.12 Southern Lactone Approach (*c*Bu)

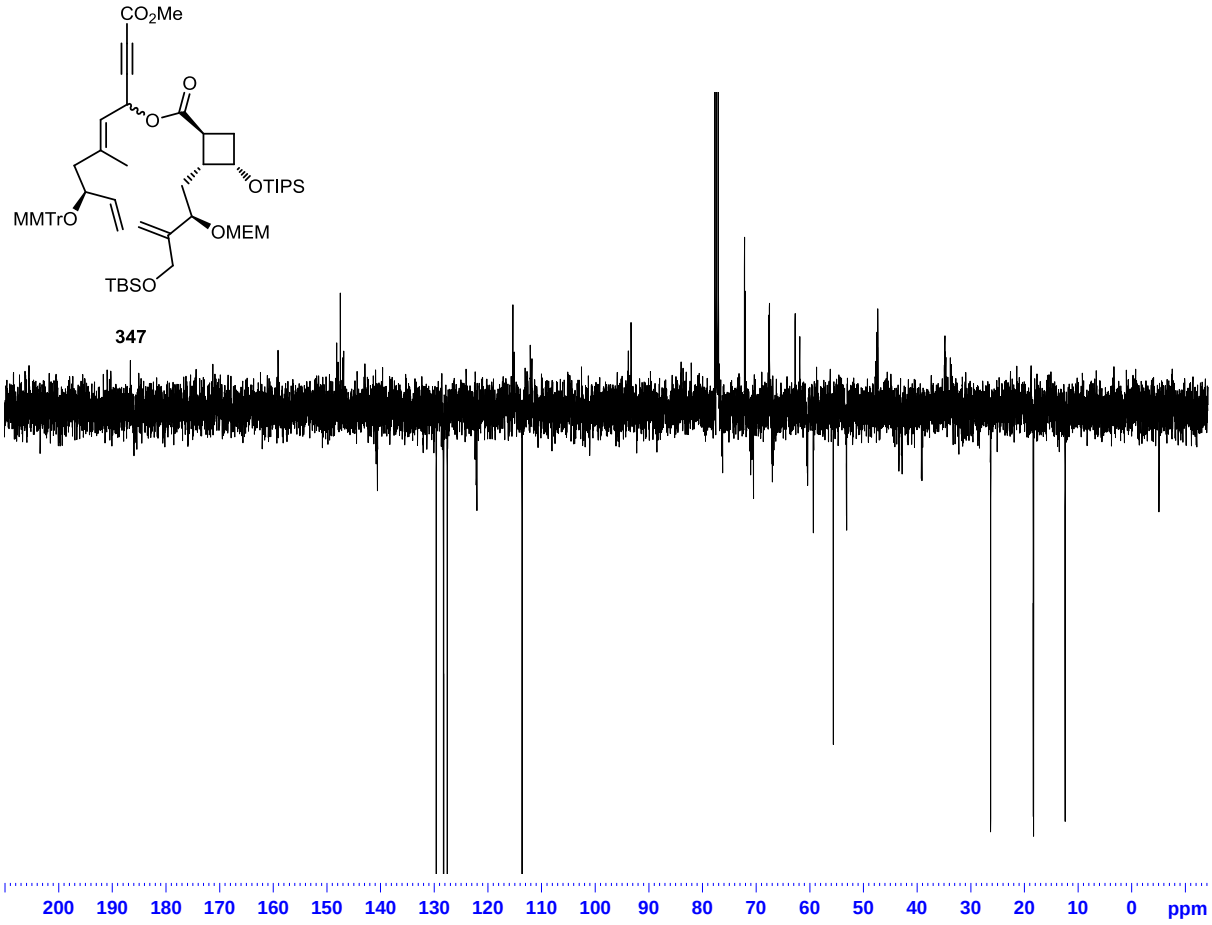




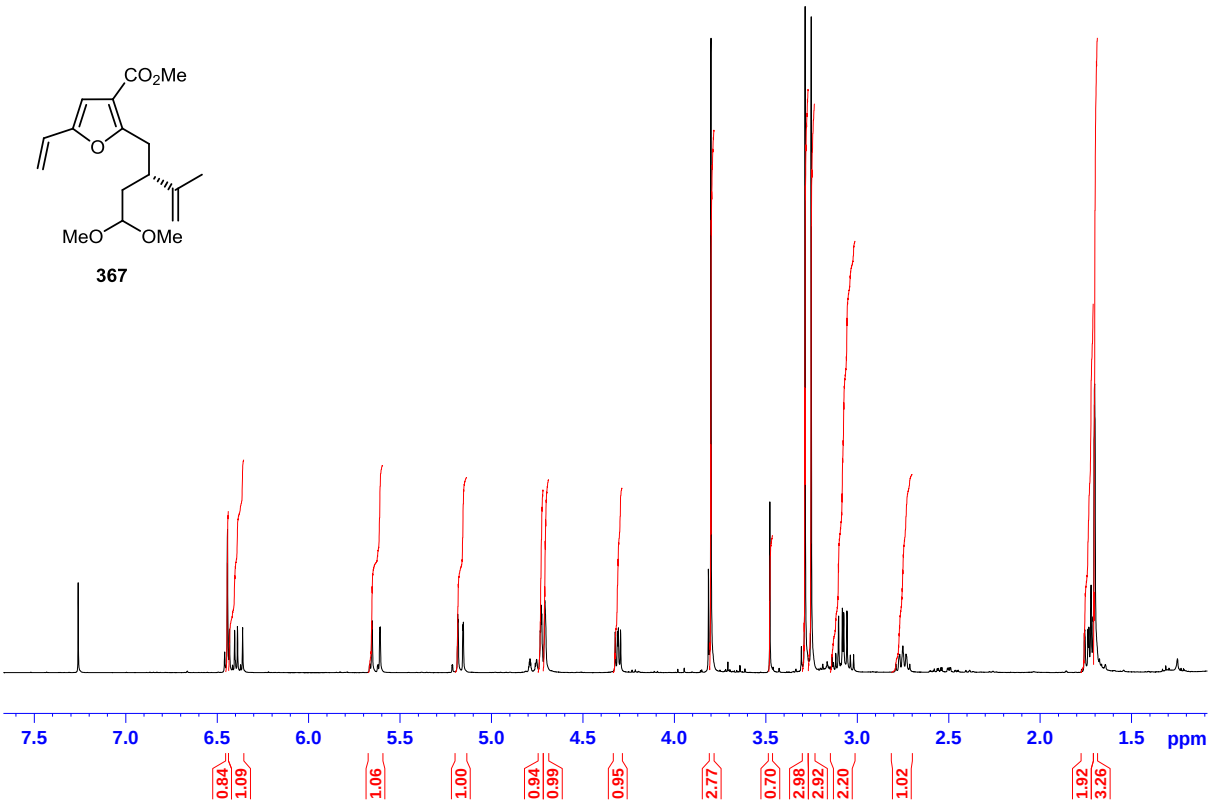

HO
O
OTIPS
OMEM
TBSO
450
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
1.00
1.02
1.00
1.96
0.61
0.56
1.94
1.02
3.24
1.65
1.39
1.39
0.65
0.95
0.49
0.57
0.68
1.48
22.97
10.15
6.44

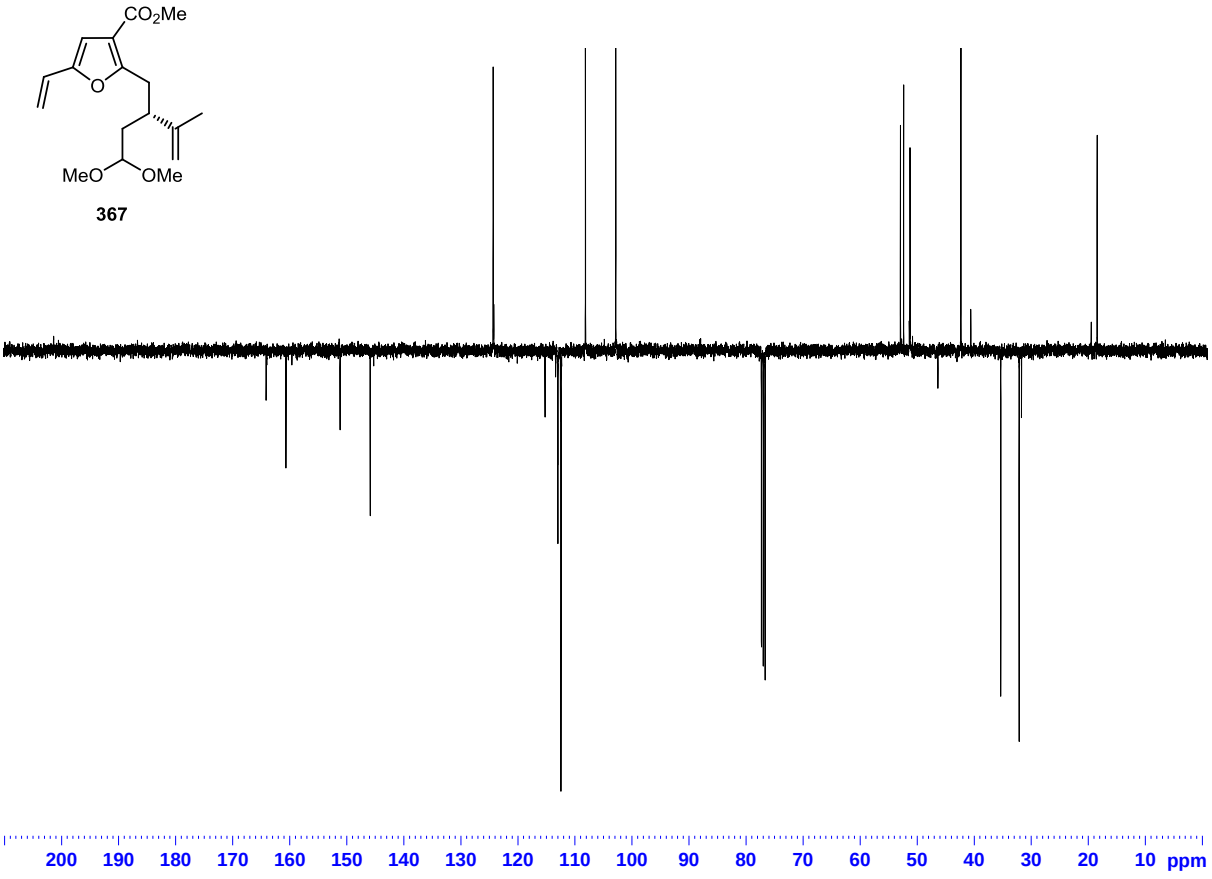

HO
O
OTIPS
OMEM
TBSO
450
220
200
180
160
140
120
100
80
60
40
20
0
ppm

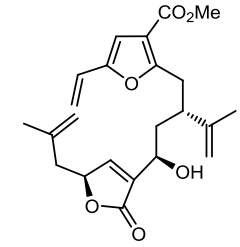

CO2Me
O
O
OTIPS
MMTrO
OMEM
TBSO
347
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
12.57
2.00
2.04
0.96
0.95
0.97
2.04
1.74
0.65
2.06
1.12
2.65
3.21
3.13
0.93
1.00
1.97
2.85
1.26
1.15
0.35
0.99
2.97
1.17
3.82
2.01
20.82
9.66
5.77


CO2Me
O
O
OTIPS
MMTrO
OMEM
TBSO
347
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

5.3.13 $\Delta^{7,8}$ Metathesis Approach (*i*Pr)

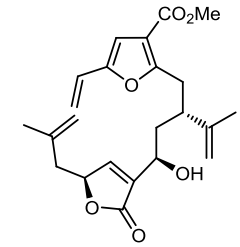





CO2Me
O
OH
O
O

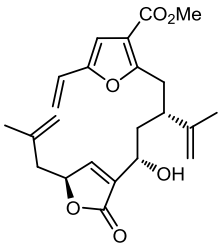
(*R*)-368a

7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.09
2.00
1.02
1.00
1.31
2.80
2.35
1.22
3.63
0.93
1.34
1.18
1.17
2.85
1.29
9.06
1.34


CO2Me
O
OH
O
O

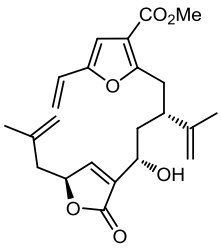
(*R*)-368a

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


CO2Me
O
OH
O
O

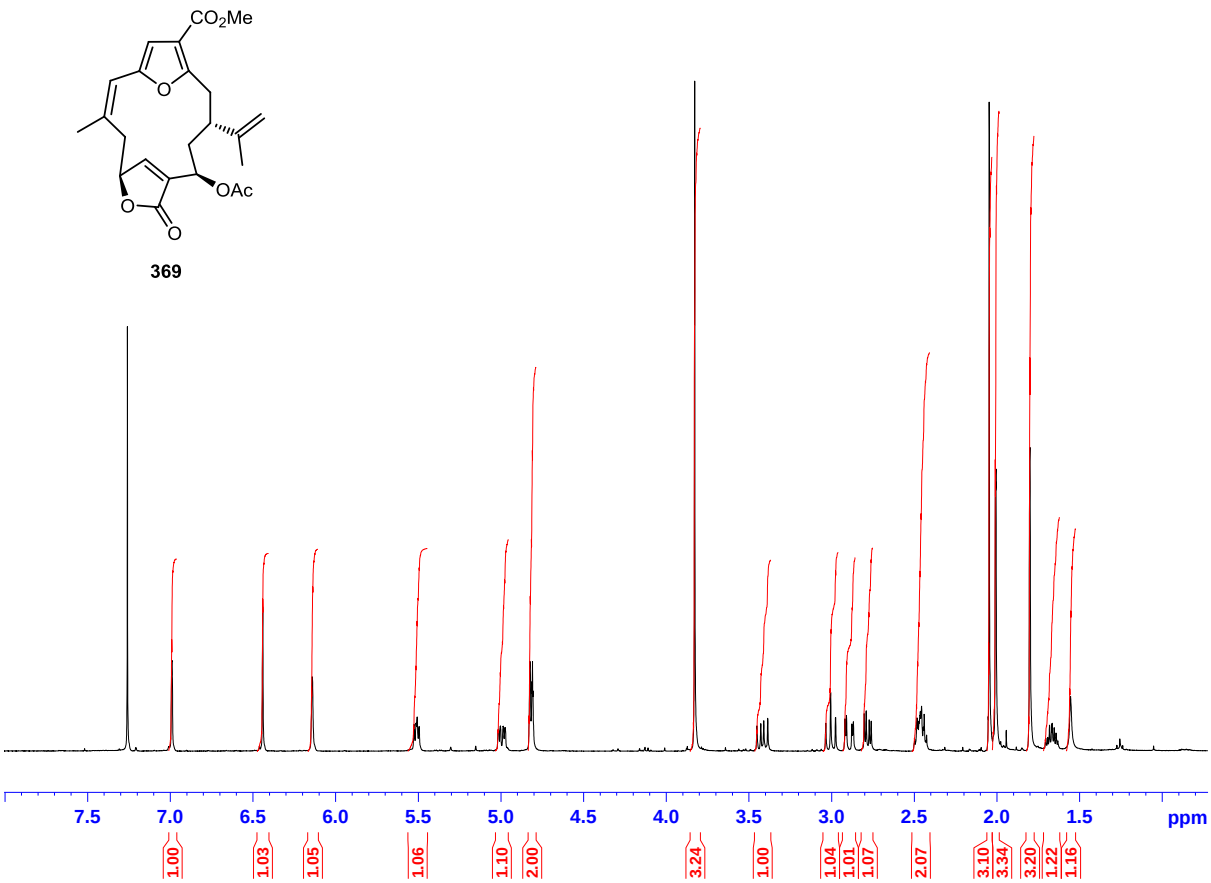
(*S*)-368a

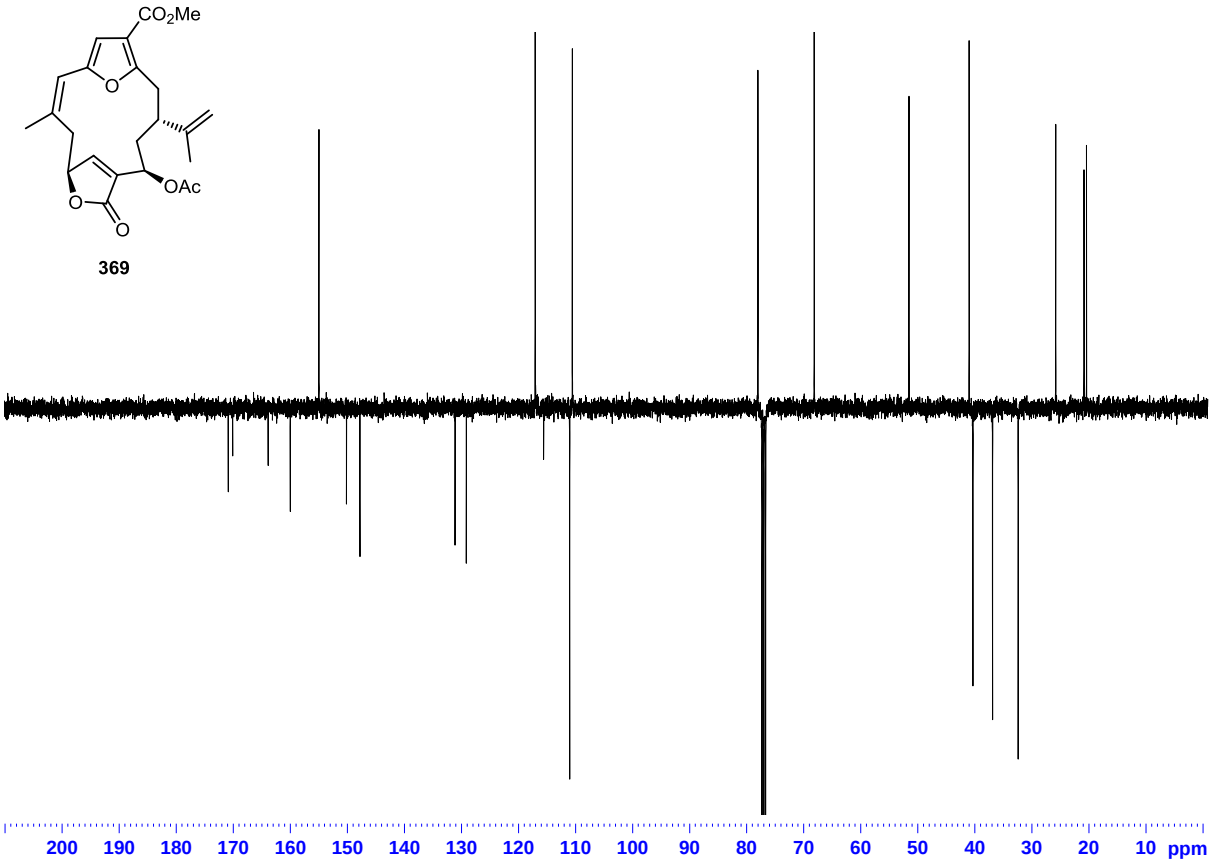
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.00
0.85
1.08
1.00
1.03
1.09
1.14
1.13
1.03
1.10
1.04
3.34
2.17
1.12
0.94
2.47
1.16
3.44
3.39
1.31


CO2Me
O
OH
O
O

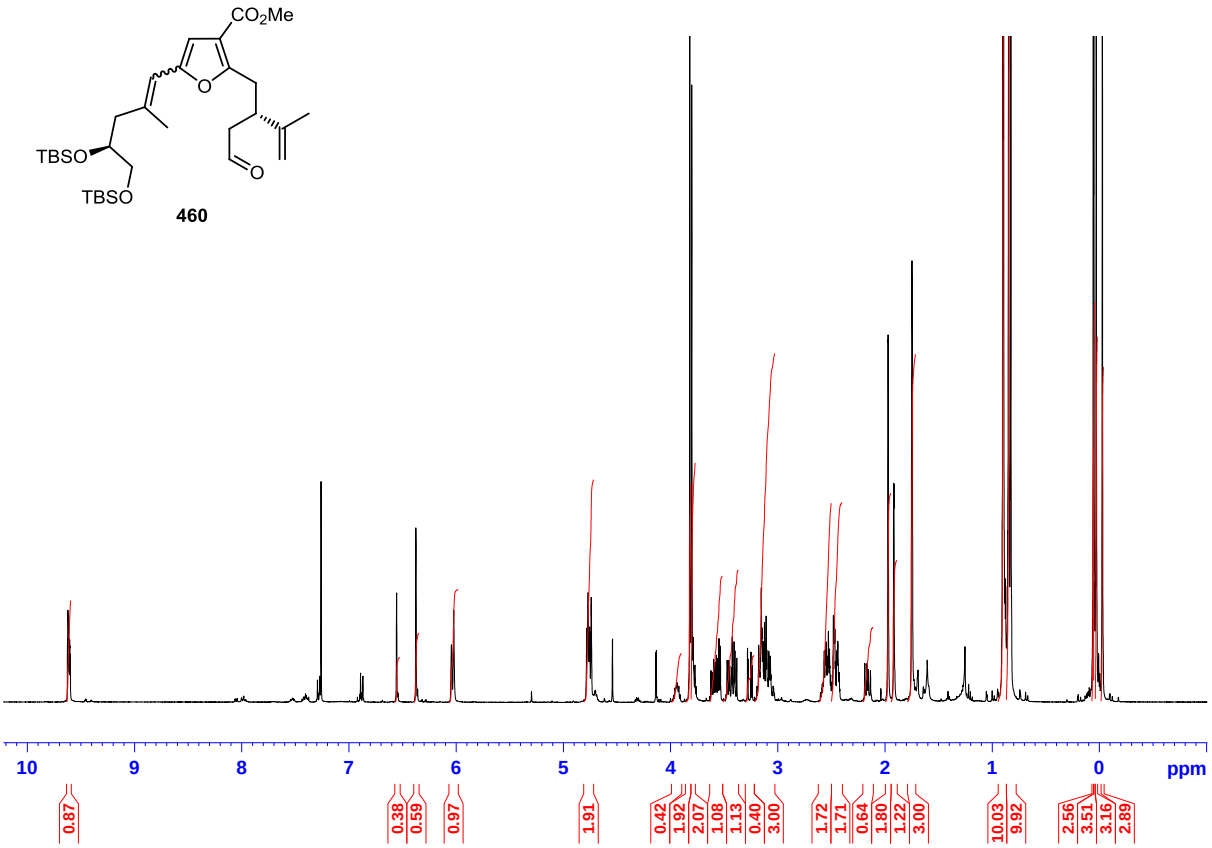
(*S*)-368a

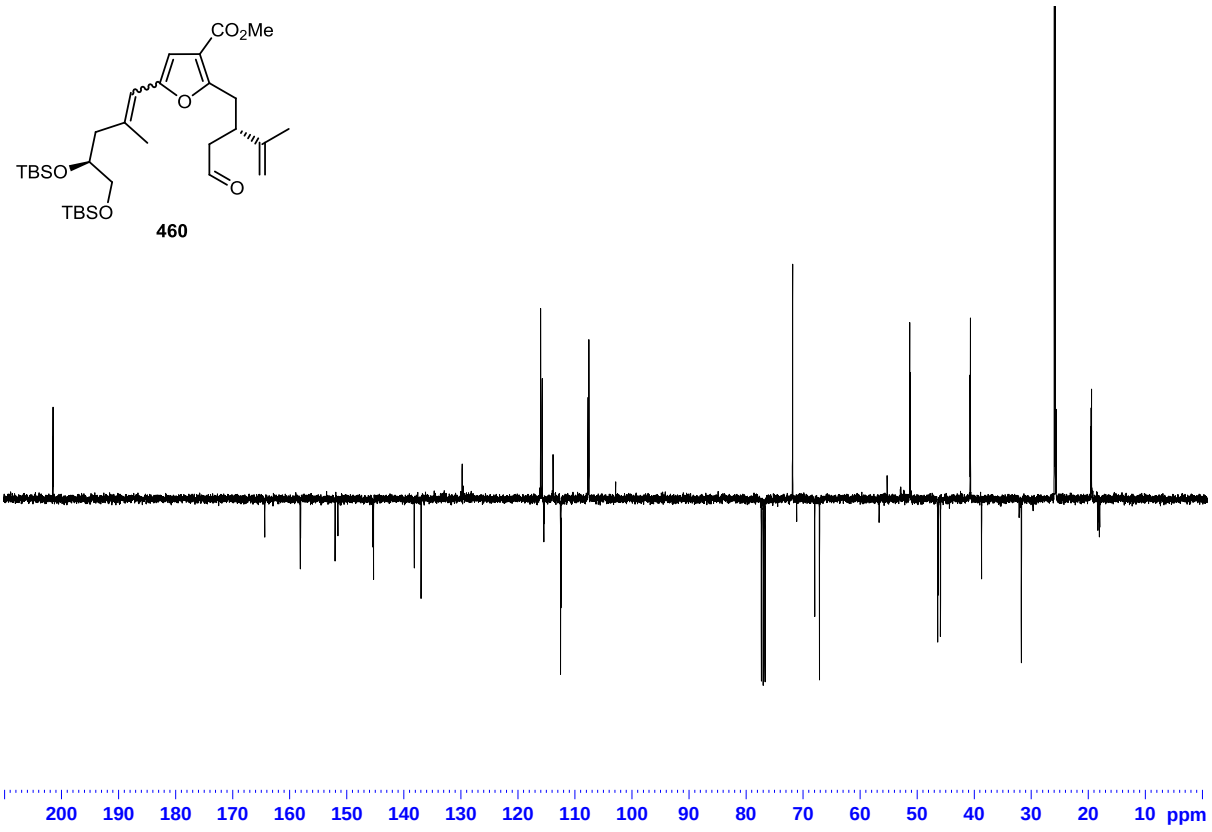
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

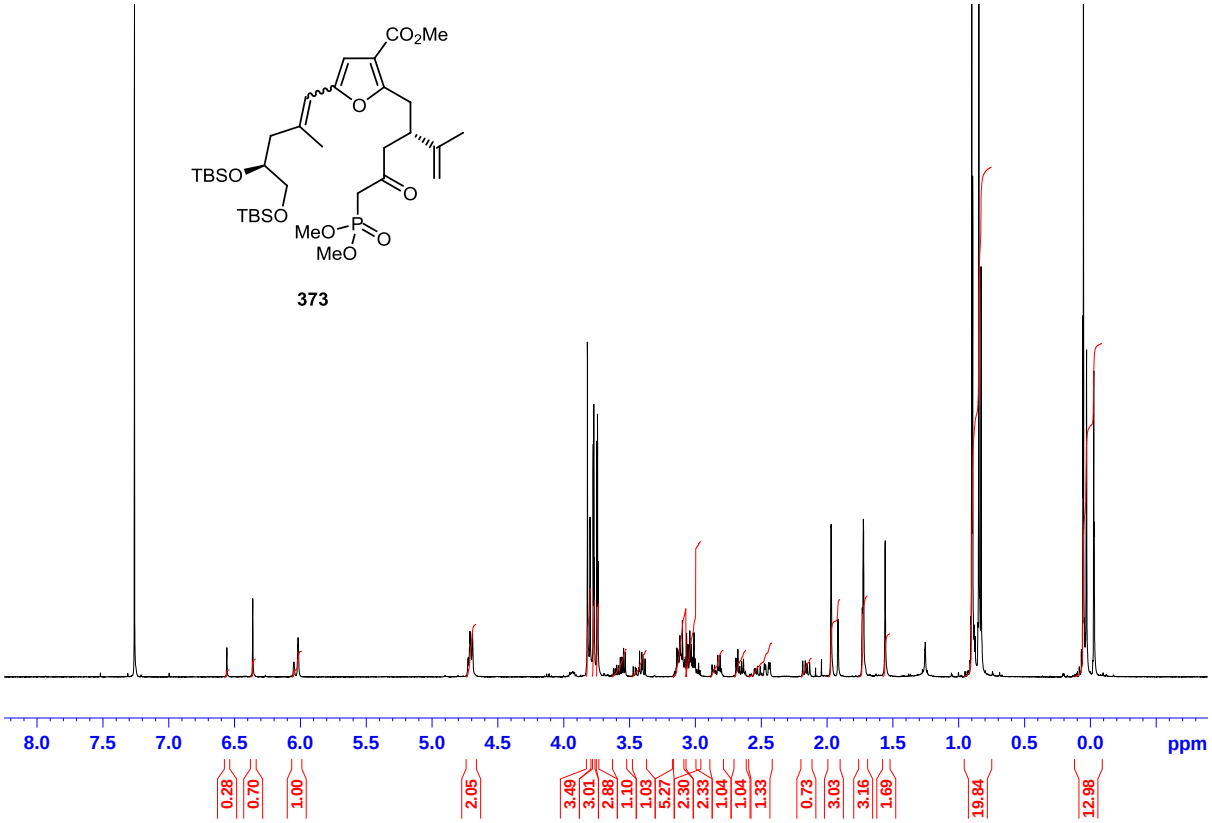

CO2Me
O
OAc
O
O
369
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm
1.00
1.03
1.05
1.06
1.10
2.00
3.24
1.00
1.04
1.01
1.07
2.07
3.10
3.34
3.20
1.22
1.16

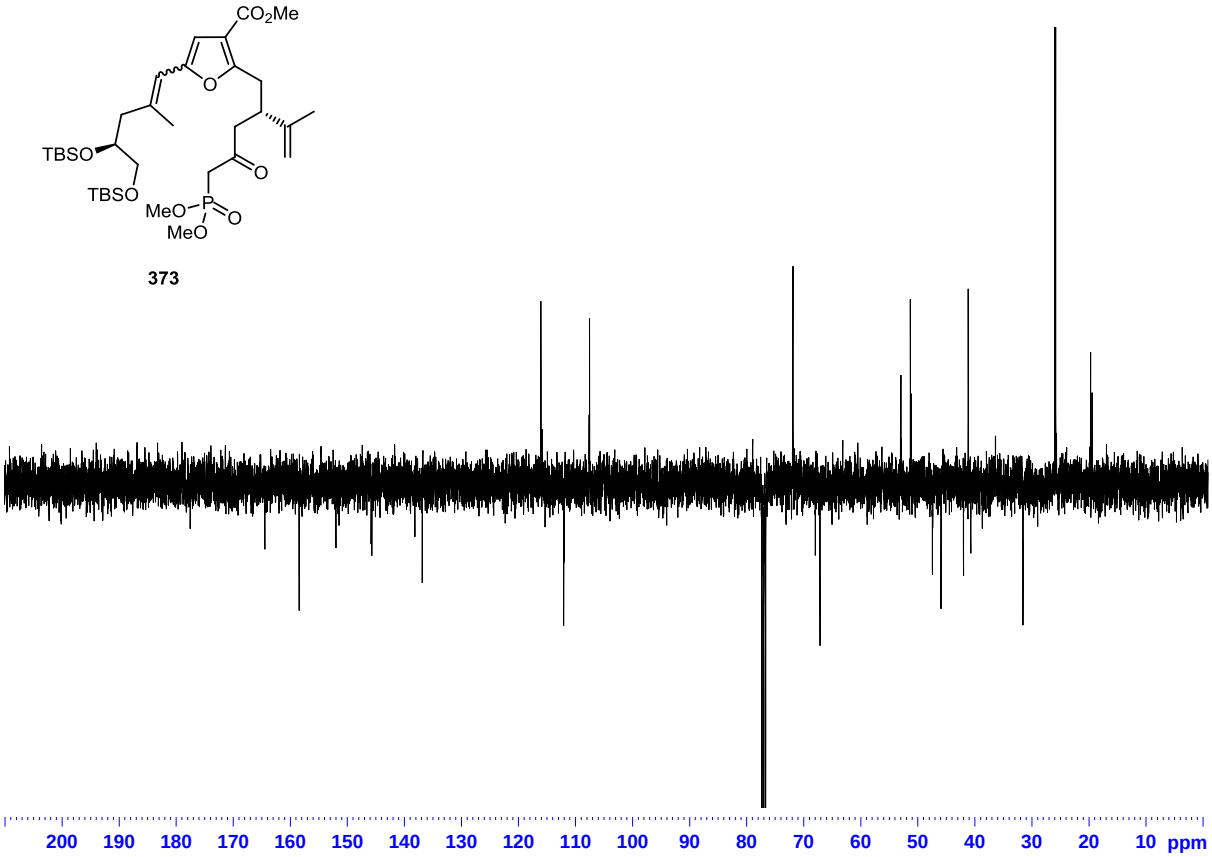

CO2Me
O
OAc
O
O
369
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

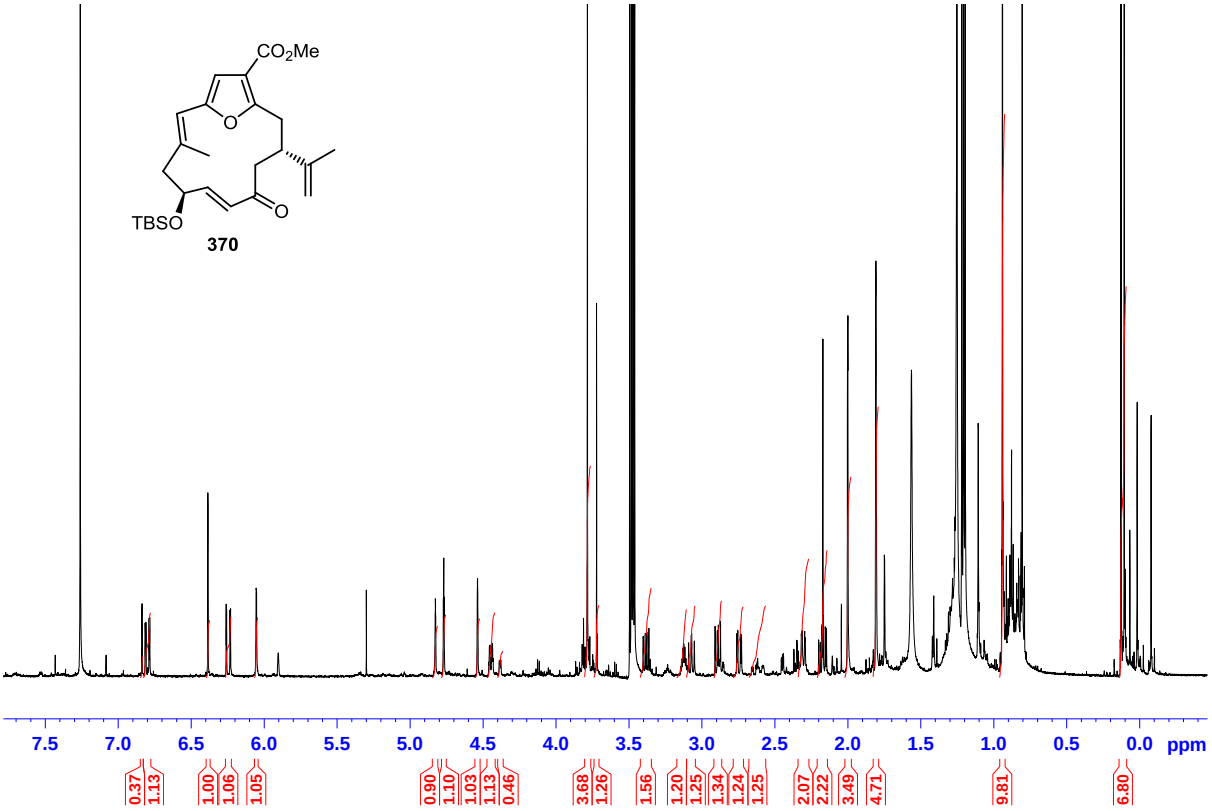
5.3.14 $\Delta^{11,12}$ Horner Wadsworth Emmons Approach (*i*Pr)

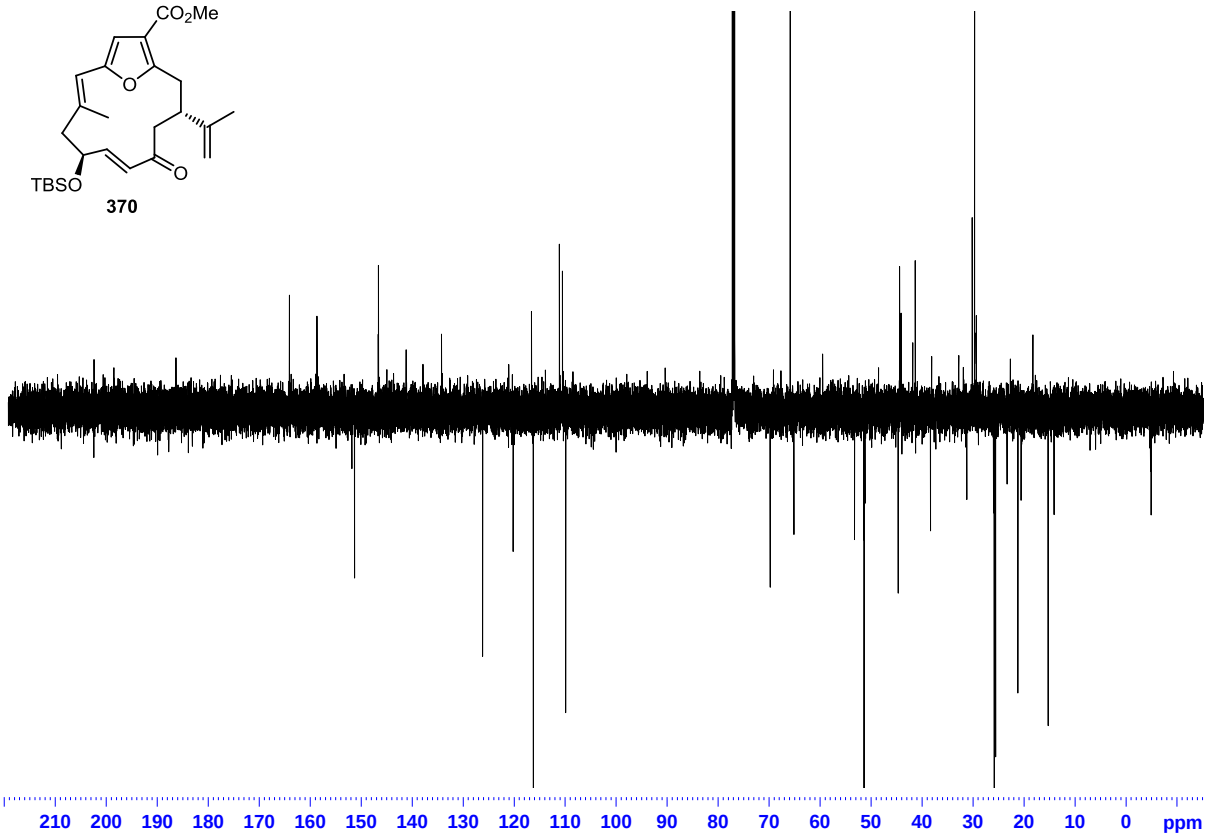




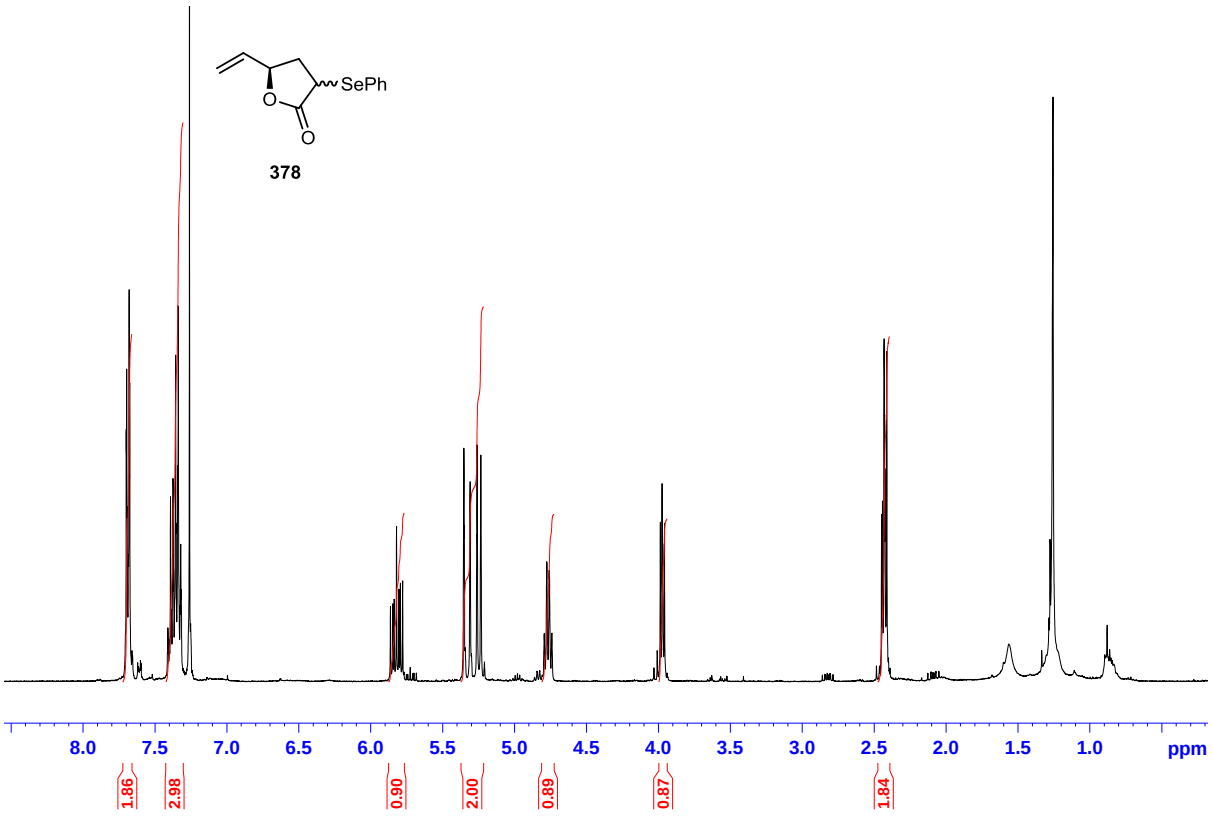

CO2Me
O
TBSO
TBSO
O
MeO
P
O
MeO
373
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
0.28
0.70
1.00
2.05
3.49
3.01
2.88
1.10
1.03
5.27
2.30
2.33
1.04
1.04
1.33
0.73
3.03
3.16
1.69
19.84
12.98

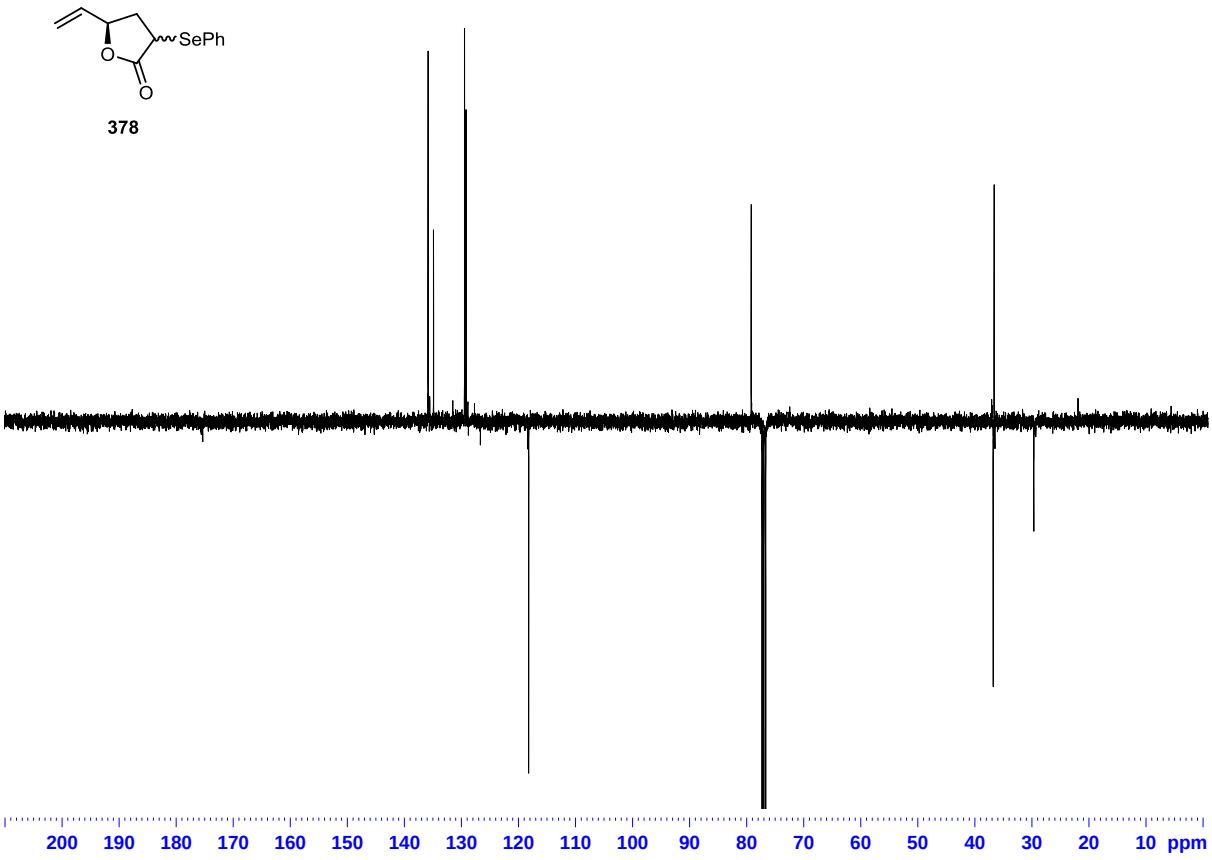

CO2Me
O
TBSO
TBSO
O
MeO
P
O
MeO
373
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

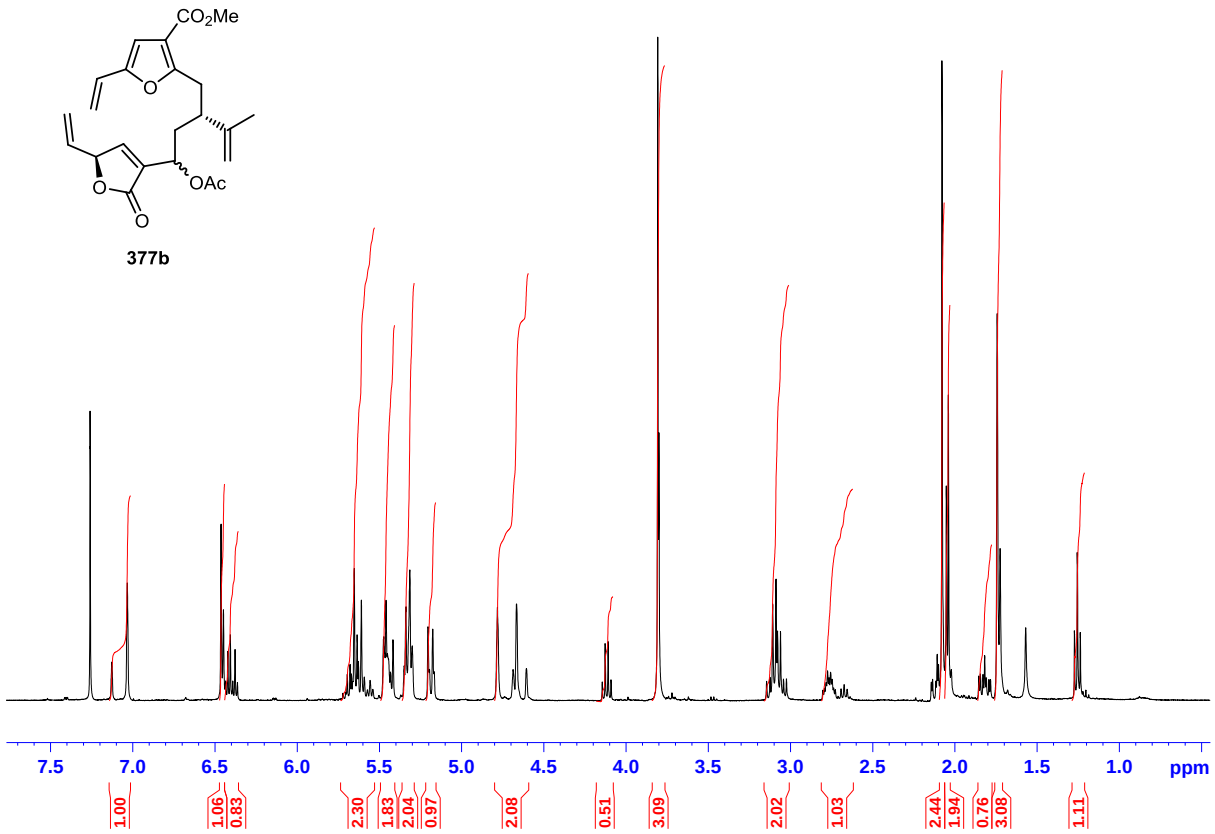

CO2Me
O
TBSO
O
370
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
0.37 1.13 1.00 1.06 1.05 0.90 1.10 1.03 1.13 0.46 3.68 1.26 1.56 1.20 1.25 1.34 1.24 1.25 2.07 2.22 3.49 4.71 9.81 6.80

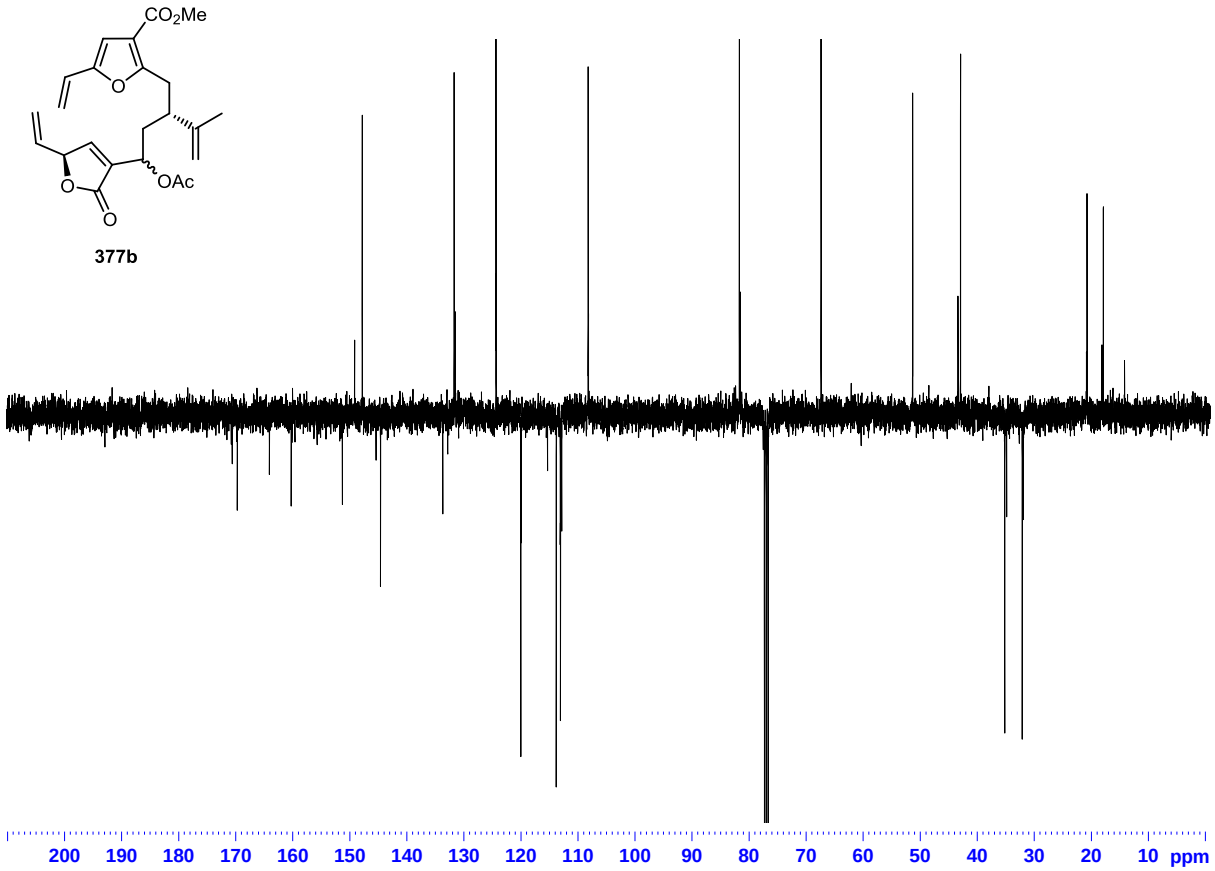

CO2Me
O
TBSO
O
370
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

5.3.15 Sarcofuranocembranolide A






CO2Me
O
OAc
O
O
377b
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
1.00
1.06
0.83
2.30
1.83
2.04
0.97
2.08
0.51
3.09
2.02
1.03
2.44
1.94
0.76
3.08
1.11


CO2Me
O
OAc
O
O
377b
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

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7 Curriculum Vitae

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Personal data

Date of birth	25th May 1981
Place of birth	Vienna
Nationality	Austria
Marital status	single
Military service	fulfilled (October 1999 – May 2000)

Education

Since March 2007	PhD student in the research group of Prof. Mulzer
Oct. 2000 – Nov. 2006	Vienna University of Technology, Study of Technical Chemistry Focal point: Organic synthesis Diploma Thesis: „Surface Modification of Superparamagnetic Ironoxide Nanoparticles“
Sept. 1991 – June 1999	High school Neulandschule, natural science sector

Practical training

July 2004 – February 2007	Medical University of Vienna, Internal Medicine I, scientific staff in the research group of Prof. I. Pabinger
Sept. 2002	Industrial internship at OMV AG Schwechat, Division: Research Development Application
August 2001	Industrial internship at OMV AG Schwechat, Division: Quality assurance lubricant
August 2000	Industrial internship at OMV AG Schwechat, Division: Materials administration

Other activities

Sept. 2004 – June 2005	Practical training at „Ich bin O.K.!"-club, supervision of children and teenagers with Down-syndrome.

Special skills

Languages

German	native
English	fluent
French	basic

IT-skills

Mac OSX, Windows, MS-Office, CorelDraw, as well as numerous chemistry orientated programs

Advanced Hardwareskills

Chemical Analysis (NMR, IR, TGA, UV-VIS, DLS, …)

Driving license, category A and B

Publications und presentations

2006 Oral presentation at GTH Congress in Basel, Topic: „Adaption of a kinetic assay for routine laboratory use“

2006 Posterpresentation at 232nd ACS Meeting in San Francisco (“Magnetic Nanoparticles with supramolecular recognition sites“)

2006 Posterpresentation at 8th Austrian Polymer Meeting in Linz

2006 Posterpresentation at 2nd STIPOMAT Workshop in Seggau/Graz

2007 ”Surface modified superparamagnetic ironoxide nanoparticles“ (*Chemical Monthly*, 2007, 138, 4, 315-320)

2007 “Telechelic Poly-N-isopropylacrylamides via NMP and click chemistry: livingness and grafting from methologies” (Macromolecules, 2007, 40, 9, 3097-3107)

2007 Oral presentation at “Organic Chemistry Symposium“ in Vienna. Title: ”Towards the Total Synthesis of Providencin“

2008 “Superparamagnetic iron oxide nanoparticles via ligand exchangreactions: organic 1,2-diols as versatile building blocks for surface engineering” (Journal of Nanomaterials, Volume 2008, Article ID 383020, 10 pages)

2008 Posterpresentation at BOSS XI-Congress in Genth, Belgium. Title: „Towards the Total Synthesis of Providencin“

2008 Posterpresentation at IASOC 2008 in Iscia, Italy. Title: ”Towards the Total Synthesis of Providencin“

2009 Posterpresentation at Synthesefest Munich, Germany. Title: ”Towards the Total Synthesis of Providencin“

2009 Posterpresentation at „Organic Chemistry Symposium“ in Paris, France. Title: ”Towards the Total Synthesis of Providencin“

2009 Invited lecture at the “Doktorandenworkshop – Naturstoffchemie” entitled "Probleme mit der Vorsehung: Auf dem Weg zu Providencin" in Bayreuth, Germany (May 2009).

2009 Posterpresentation at 10th Tetrahedron Symposium in Paris, France. Title: ”Towards the Total Synthesis of Providencin“

2009 “Synthetic efforts towards the synthesis of the complex diterpene providencin” (*Synlett*, 9, 1357-1366.)

2010 Participant at the Bayer PhD workshop, Cologne, including posterpresentation; Title: ”Towards the Total Synthesis of Providencin“

2010 Posterpresentation at ICOS-18 in Bergen, Norway. Title: ”Towards the Total Synthesis of Providencin“

2010 “Synthesis of the Lycopodium Alkaloid (+)-Lycoflexine” (*Journal of the American Chemical Society*, 2010, 132, 41, 14338-14339)

2011 “Circulating procoagulant microparticles in cancer patients” (Ann Hematol. 2011, 90, 4, 447-453