Total Synthesis of the Proposed Structure of the Macrolide Queenslandon and Towards the Total Synthesis of Natural Products Leiodermatolide and (−)-Englerin A

DISSERTATION

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der Eberhard-Karls-Universität Tübingen
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Doktors der Naturwissenschaften
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vorgelegt von
Vaidotas Navickas
aus Alytus, Litauen

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Dekan: Prof. Dr. W. Rosenstiel
1. Berichterstatter: Prof. Dr. M. E. Maier
2. Berichterstatter: Prof. Dr. Th. Ziegler
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I am indebted to say a few words about my supervisor Prof. Dr. Martin E. Maier. During my stay in Tübingen, I felt enormous freedom in setting my own ideas in the research where those were accompanied by kind support, numerous advices and excellent guidance. I thank him also for being a great inspirator as he always tried to present and share new ideas and literature examples with the group members.

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Especially I would like to thank Dmitry Ushakov for being a great team mate. His valuable discussions on our research work and his help in solving many synthetic puzzles were irreplaceable.

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Finally, I am thankful to the love and support that my parents and family gave to me.
my Family
Publications:


Poster presentations:


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Abbreviations

abs. absolute
Ac Acetyl
AIBN Azobisisobutyronitrile
aq. aqueous
ar. (arom.) aromatic
Bn Benzyl
br broad (NMR)
b.p. Boiling point
Bu Butyl
Bz Benzoyl
c Concentration
COSY Correlation Spectroscopy
Cp Cyclopentadienyl
CSA Camphor sulfonic acid
Cy cyclohexyl
δ Chemical shift in ppm (NMR)
d Doublet (NMR)
DBU 1,8-Diazabicyclo[5.4.0]undec-7-en
DCC N,N'-Dicyclohexylcarbodiimide
DCM Dichloromethane
DEAD Diethyl azodicarboxylate
DDQ 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIBALH Diisobutylaluminium hydride
DMAP 4-Dimethylaminopyridine
DMF N,N-Dimethylformamide
DMP Dess-Martin periodinane
DMSO Dimethylsulfoxide
dr Diastereomeric ratio
E trans
ee Enantiomeric excess
EI Electron impact
Eq. equation
ESI Electrospray ionization
Et Ethyl
Et₂O Diethyl ether
EtOAc Ethyl acetate
Abbreviations

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Introduction and the Goal of Research

Natural product synthesis serves as an inspiration for invention in organic chemistry for many years. Selection of a specific molecule for the synthesis is dependant on many issues: impressive biological activity, mode of action, structural assignment, an idea to test scope and limitation of newly developed methods and etc. Historically, students and individuals entering in this field are prone to concentrate on the synthetic approaches that share two main features: the so-called stop-and-go approach,\(^1\) and the implementation of orthogonal protecting-group strategies.\(^2,3\) However, recent decades clearly set guidelines for organic synthesis indicating, for example, an urgent need for new chemoselective methods and more efficient catalyst that would allow scalable and more efficient processes in industrial area. To support this, in 2007 R. H. Grubbs (2005 Nobel laureate in chemistry) stated, that “the major challenges are the construction of the molecules without using protecting group chemistry and the ability to put molecules together in fast and efficient ways”\(^4\). In recent years several new (or reintroduced) concepts for improving the synthesis towards natural and non-natural molecules have been brought forward. Terms like atom,\(^5\) step,\(^6\) redox\(^7\) economies and protecting group-free (PGF) synthesis\(^8\) could be found titled in many research publications indicating the impact of those on a current art and state of natural products synthesis. One should say those concepts became a “fashion line”, as several outstanding syntheses were realized with those guidelines setting very high standards in organic synthesis.\(^9\)

References mentioned above and willingness to follow those concepts of synthesis economies were part of an inspiration for preparing this thesis, where the purpose was to address synthetic challenges posed by three natural products. The chapter associated with the synthesis of the molecule queenslandon has a historical background. The study toward the synthesis was a long marathon where several graduate students and a postdoc tried to tackle the molecule unsuccessfully. Thus, an individual intention finally to complete the synthesis and to be the first one was a driving force. As it turned out, the synthesis presented for queenslandon revealed that the originally published structure requires revision. The work on leiodermatolide presented in the second part will be important for the determination of the stereochemistry of the macrolide, as the absolute and relative stereochemistry is not known for sure. In addition to that, a wish to develop a new strategy for the construction of the stereotetrad in this molecule and to test scope and limitations of several know methods were the purpose to choose the project. Terms of synthetic economies were the inspiration for the last part of the thesis. To exclude the extensive protecting group usage and to follow the redox economy concept were major reasons to select terpene englerin A as a study object.
Chapter I

Total Synthesis of the Proposed Structure of the Macrolide Queenslandon
Introduction

Natural polyketides cover an enormous structural space, even though simple building blocks like acetate and propionate are being used. Among the polyketides resorcylic acid lactones (RALs) represent a unique family of privileged structures. These 14-membered lactones are mycotoxins and are produced by fungal strains. The modes of action of RALs are also impressive and diverse. These were nicely described and summarized in many publications and theses inclusive our group. Furthermore, the discovery, that radicicol (10) is a potent and selective Hsp90 inhibitor renewed the interest in the RALs (Figure 1). Several RALs, which are characterized by a cis-enone in the macrocyclic ring, like LL-Z1640-2 (5) or radicicol A (4) are potent kinase inhibitors.

Figure 1. Structures of resorcylic acid lactones (RALs) bearing highly oxidized benzoic acid motif.

Among the RALs, macrolides like 6-9 are unique since they feature a highly oxidized benzoic acid motif. Furthermore, they are closely related to radicicol A (4) in structure. For example, hamigeromycin A (6) possesses completely the same structure like radicicol A, except for the lack of an enone double bond. According to recent work of Altmann et al., these structural similarities imply that the compound could be selective for kinases as well.

Among the mentioned RALs, queenslandon (1) is unique since it features a dihydroxyacetone subunit. It was isolated from the strain Chrysosporium queenslandadicum IFM51121. According to the original report queenslandon showed activity against several fungal strains but no bacteria. In order to further delineate its biological properties a synthetic route to queenslandon seemed highly desirable.
A strategy towards the core structure 15 of macrolide queenslandon was already described (Scheme 1). However, the approach turned out to be not flexible enough and failed to deliver the proposed structure of queenslandon itself. Thus, the aim of the synthesis is not even to design an efficient synthesis that would deliver the natural product, but also to confirm the relative stereochemistry of the molecule.

Scheme 1. Key reaction in the synthesis towards the core structure 15 of queenslandon.
**Retrosynthetic Consideration**

The major retrosynthetic cuts for the proposed structure of queenslandon (1) are metathesis (ring-closing\(^{19}\) or cross metathesis\(^{20}\)) and Mitsunobu reaction\(^ {21}\) (Scheme 2), these are the most obvious and widely used transformations in the synthesis of resorcylic acid lactones. Because of steric hindrance around the carboxylic function in hydroxy acids of RAL’s classical macrolactonization strategies frequently fail to give high yield of the macrolactone. Thus, advanced building block 16, carrying all the stereochemical information of 1, could come from D-ribose, which is relatively cheap and commercially available. The synthesis of styrene 17 could be easily achieved from the corresponding, literature known hydroxyphthalide (see results and discussion).

![Scheme 2. Retrosynthetic analysis of queenslandon (1).](image)

A more detailed disconnection of 16 is shown in Scheme 3. Here the allyl group in the aliphatic part could be formed from a pivaloyl protected alcohol function. Thus, the chain could be elongated via Mitsunobu reaction to give nitrile 18. This would be reduced to an aldehyde followed by Wittig olefination. A cross-metathesis between D-ribose derivative 19 and silyl protected 1-pentenol 20 would be perfect and allow for fast access to building block 16.

![Scheme 3. Retrosynthetic analysis of queenslandon’s aliphatic part 16.](image)
Results and Discussion

We started the synthesis by converting D-(+)-ribose into diol 21 via acetonide formation and Wittig olefination (Scheme 4).22 A subsequent pivaloylation followed by hydrolysis of the acetal, mediated by CuCl$_2$·2H$_2$O, led to triol 22 in 63% yield over two steps. A transacetalization on benzaldehyde dimethylacetal produced functionalized 1,3-dioxane thereby exposing the central hydroxyl function. This was then protected as PMB ether to give differently protected 19. Yield in this step was 57% due to side products which are alcohol 23 and bis-PMB ether 24. Other methods to improve the yield, like PMB imidate, cat. TfOH, Et$_2$O, gave exclusively triol 22.


As next, a cross-metathesis reaction between alkene 19 and pent-4-en-2-ol derivative 20 (1 equiv.) using Grubbs 2nd generation catalyst (5 mol%) at 80 °C in toluene provided the corresponding alkene in an excellent yield (Scheme 5). A subsequent catalytic hydrogenation of the double bond furnished the differently protected dioxane 25. The next steps were calling for deprotection of the pivalic ester, chain extension via Mitsunobu reaction to a nitrile followed by reduction to an aldehyde and olefination. Thus, 6.0 equiv. of DIBAL-H easily reduced ester 25 at −80 °C delivering an alcohol which was then subjected to a Mitsunobu reaction with acetone cyanohydrine to produce nitrile 18 in 72% yield over two steps. Subsequent DIBAL-H reduction gave the corresponding aldehyde which successfully underwent Wittig olefination with PPh$_3$MeBr resulting in alkene 16. This two steps protocol was achieved in 96% and 75% yields respectively. Deprotection of the TBS group proceeded cleanly (quantitative yield) by treatment of silyl ether 16 with a 33% solution of HF-pyridine complex in THF at −15 °C.
Results and Discussion

Scheme 5. Synthesis of alcohol 26 featuring cross-metathesis reaction.

As it was mentioned before, the aromatic part was prepared via Wittig olefination on literature known hydroxyphthalide 28 (Scheme 6). The starting material for olefination was synthesized from commercially available 2,4,5-trimethoxybenzoic acid (27) utilizing literature procedures. Thus, amide formation was followed by directed metalation, formylation and hydrolysis phtalide.


The aromatic acid 17 and alcohol 26 were combined via Mitsunobu esterification to provide benzoic ester 29 in excellent yield (Scheme 7). The ester 29 served as a precursor for various substrates 30-34 that were intended for RCM. The preparation of RCM precursors is summarized in Scheme 7. Thus, DDQ mediated deprotection of the PMB group, followed by Dess-Martin periodinane oxidation delivered ketone 30. This was then further modified via deprotection of the benzylidene acetal and protection of the two hydroxyl functions as TBS ether. We were also able to prepare metathesis precursors bearing a PMB group in the central position of the triol part (compounds 33-34).
Results and Discussion

Unfortunately, none of the substrates 29-34 could be cyclized with the Grubbs 2\textsuperscript{nd} generation catalyst (5 mol\%, PhCH\textsubscript{3}, 80 °C, 0.002-0.004 M). In case of Grubbs 1\textsuperscript{st} generation carbene no desired product could be obtained as well (Scheme 8).

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Scheme 8. Metathesis study on various substrates (29-34).

The fact that the nor-methoxy substrate 35 gave macro lactone 36 (26\%) in the presence of Grubbs 2\textsuperscript{nd} catalyst (5 mol\%, PhCH\textsubscript{3}, 80 °C, 0.002-0.004 M) points presumably to formation of a chelate of ruthenium carbene intermediate with the Lewis basic 4-methoxy ether unit (Scheme 9).

Scheme 7. Preparation of different RCM precursors.
Scheme 9. Cyclization of alkene 35 and proposed chelation of ruthenium carbine that inhibits the cyclization.

With these results, we turned to a strategy pioneered by Winssinger et al. for the synthesis of other resorcylic acid lactones. This is characterized by alkylation of a 2-(phenylselenylmethyl)benzoate 37 with an alkyl iodide 38 followed by elimination of the derived phenylselenoxide (Scheme 10).

Scheme 10. Establishing $E$-double bond geometry via selenium chemistry.

Accordingly, aldehyde 41 was reduced with NaBH$_4$ to give the corresponding alcohol, which was converted to alkyl iodide 42 by treating it with iodine and PPh$_3$ in dichloromethane (Scheme 11). Then alkyl iodide 42 was combined with seleno ether 31. Thus, selenide 47 was treated with LDA at $-80^\circ$C in THF/HMPA (10:1) and the resulting lithium anion was quenched with iodide 42. After work up crude selenoether was oxidized leading after elimination to $E$-alkene 43 in 75% yield. The coupling constant between the double bond protons is 16.3 Hz that clearly indicates $E$ configuration. Simultaneous cleavage of the trimethylsilylethanyl (TMSE) ester and the TBS ether furnished hydroxyl acid 44. A smooth cyclization of acid 44 took place under Mitsunobu conditions delivering macrocycle 45 in 77% yield.
Selective removal of the PMB protecting group was followed by oxidation to give ketone 46. Finally, the benzylideneacetal was cleaved by acid-catalyzed transacetalization. Treatment of the crude dihydroxy ketone with BCl₃ (4.0 equiv) at −50 °C, gave rise to the proposed structure of queenslandon (1). The chemoselective ether cleavage next to a carboxylic group is well known. However, this is also evident from the NOESY spectrum (see experimental section, p. 115) where the phenolic OH (3-OH) showed correlations to 17-H and 17-CH₃. In addition, the HMBC spectrum (see experimental section, p. 116) displays the expected correlations (5-OCH₃/C-5 and 6-OCH₃/C-6).

The ¹H-NMR signatures of 1 matched nicely the ones published for the simple model compound 15. In particular, a NOESY cross peak between 11-H (4.60−4.67) and 13-H (4.36−4.41) suggests the cis-orientation at these methine carbons. However, with regard to the published data for queenslandon some distinct discrepancies were observed (Figure 2). For example, there are big differences (δ ppm>3) for C12, C9, and C11 (δ ppm = 6.4). Thus, one might conclude that something is wrong with
Results and Discussion

C11 since both C9 and C12 are in vicinity to C11. Further support for this hypothesis comes from a comparison of the queenslandon structure 1 with the related compounds 5 and 8. The measured optical rotations for 1 are \([\alpha]^{20}_D = -41.0\) (c 0.5, CH₂Cl₂), \([\alpha]^{20}_D = -51.0\) (c 0.1, CH₃OH) and they differ from those reported in original paper. The literature value for the isolated queenslandon amounts to \([\alpha]^{20}_D = +24.4\) (c 0.028, CH₃OH).\(^{17}\) Macrolactone 1 showed moderate cytostatic activity with an IC₅₀ of 33 \(\mu\)g mL\(^{-1}\) (84 \(\mu\)M) against the mouse fibroblast cell line L929.

![Diagram of structure 1](image)

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**Figure 2.** Listing of \(^{13}\)C shifts of natural queenslandon and macrolactone 1.
Conclusion

In summary, the synthesis of the proposed structure of the macrolide queenslandon (1) was accomplished. The structural challenges of this molecule were a highly substituted electron-rich benzoic acid part and an aliphatic region featuring a dihydroxy ketone subunit. The aliphatic part was synthesized from D-(+)-ribose featuring hydroxyl function differentiation in triol 22 via benzylidene acetal formation and cross metathesis to extend the chain (Scheme 12).

Scheme 12. Synthesis of the aliphatic part for RCM (alkene 26) and alkylation (alkyliodide 42).

A ring-closing metathesis was studied on various substrates synthesized from alkene 26 and styrene 17 (Scheme 13).

Scheme 13. A ring-closing metathesis study on various substrates.
It turned out that none of the RCM precursors underwent ring closure. On the other hand, 6-nor-methoxy macrolactone 36 was obtained in a moderate yield, indicating the influence of the 6-OMe group into a chelate with the ruthenium complex.

Finally, an iodide 42 was used to alkylate the trimethylsilyl ethyl 2-methyl benzoate derivative 37. This led after elimination of phenylselanol to seco acid 43. The next six steps provided macrolactone 1, which spectral data did not correspond to queenslandon (Scheme 14). Since the biggest differences are observed for the chemical shifts around C11 it is likely that the configuration of C11 should be inverted. Thus, it is clear that the structure requires revision.

Scheme 14. An alkylation protocol leading to the proposed structure of macrolide queenslandon (1).
Chapter II

Approach Towards the Total Synthesis of the Macrolide Leiodermatolide
Introduction

Leiodermatolide (48) is a potent antimitotic agent, recently isolated by the group of Amy Wright from the sponge *Leiodermatium*, which belongs to the order Lithistida ([Figure 3](#)). It exhibits a nanomolar level cytotoxicity against a variety of human tumor cell lines (see [Figure 3](#)) while showing reduced toxicity to normal cell lines. Furthermore, it does not directly bind to tubulin. Leiodermatolide does not show much similarity to other cytotoxic polyketides, however it shares the carbamate function with palmerolide (49) and discodermolide (50). This novel polyketide features a 16-membered macrolide, with a 6-membered lactone ring on the side chain and has nine stereocenters together with a Z,Z and an E,E - diene system. Although, a report of Wright et. al. was based just on a flat structure of this macrolide, more recently additional data with stereochemical information appeared on the web.  

![Proposed structure of leiodermatolide (48) and structures of related compounds.](image)

**Figure 3.** Proposed structure of leiodermatolide (48) and structures of related compounds.

Taking into account the remarkably potent antiproliferative activity and structural features which are calling for proof, leiodermatolide (48) deserves an attention for total synthesis.
Retrosynthetic Consideration

As outlined in the retrosynthetic plan in Scheme 15, we decided to remove part of the side chain by cutting the C18-C19 trans double bond (Julia-Kocienski olefination). For macrolactone formation lactonization reactions (Yamaguchi/Mitsunobu) were considered. Alternatively, other C-C bond forming reactions like ring-closing metathesis might be options. The internal Z,Z-diene would come from an enyne precursor. This way, a Sonogashira cross-coupling followed by Z selective reduction is obvious. This leads to two building blocks 53 and 54, both having roughly equal size.

Scheme 15. Retrosynthetic analysis of leiodermatolide (48).

For the alkyne 53 we were optimistic about a Marshall-Tamaru reaction on a chiral aldehyde, where the E-double bond geometry would come from a carbometalation/Suzuki coupling sequence. The anti-stereochemistry at C14/C15 in 54 could be secured by applying the same Marshall-Tamaru reaction as well.
Results and Discussion

A side chain (sulfone 52) was synthesized by a graduate student Christian Rink (Scheme 16). Here he started the synthesis from known methyl (3S)-3-hydroxypentanolate 55, which was alkylated with MeI (Fräher-Seebach protocol 43) and the free hydroxyl function protected as TBS ether to provide silyl ether 56. This was then converted to Weinreb amide followed by Grignard reaction to give enone 57. Subsequent Michael addition of benzyl alcohol induced by 1,1,3,3-tetramethylguanidine 44 resulted in ketone 58 in 76% yield. In the next two steps, which were TBS deprotection and esterification, a Reformatsky precursor 59 was obtained. A smooth intramolecular Reformatsky reaction 45 took place when ester 59 was introduced to a SmI₂ solution at −78 °C giving alcohol 60 as a single isomer. However, the isomer formed in this step was wrong in regard to the proposed stereochemistry. The synthesis was continued towards the sulfone 52. Thus, protection of the tertiary hydroxyl function as TMS ether and debenzylilation with H₂/Pd delivered alcohol 61 in 77% yield over two steps. Triazole 62 moiety was installed via Mitsunobu reaction and the sulphur atom was oxidized with H₂O₂ to deliver sulfone 61a in 97% yield.

\[
\text{MeO}_2\text{C}-\text{CH}_2-\text{OH} \xrightarrow{\text{i}} \text{MeO}_2\text{C}-\text{CH}_2-\text{OTBS} \xrightarrow{\text{ii}} \text{MeO}_2\text{C}-\text{CH}_2-\text{OTBS} \xrightarrow{\text{iii}} \text{MeO}_2\text{C}-\text{CH}_2-\text{OTBS} \xrightarrow{\text{iv}} \text{MeO}_2\text{C}-\text{CH}_2-\text{OTBS} \xrightarrow{\text{v}} \text{MeO}_2\text{C}-\text{CH}_2-\text{OTBS} \xrightarrow{\text{vi}} \text{MeO}_2\text{C}-\text{CH}_2-\text{OTBS} \xrightarrow{\text{vii}} \text{MeO}_2\text{C}-\text{CH}_2-\text{OTBS}
\]

Conditions: i. a) LDA, MeI, HMPA, THF, −78 °C, (70%, dr = 85:15); b) TBSCI, DMAP, imid., DMF (93%). ii. a) MeONH-MeHCl, iPrMgCl, THF (88%); b) vinyIMgCl, THF, −10 °C to 0 °C (90%). iii. BrOH, TMG (76%). iv. a) HCl, MeOH (88%); b) BrCH₂COCl, Py, DMAP, CH₂Cl₂ (100%). v. Na, CH₃S, THF, −78 °C (88%); vi. a) TMSCl, imid., CH₂Cl₂ (96%); b) H₂, Pd/C, THF (90%). vii. a) 62, PPh₃, DEAD, THF (92%); b) (NH₄)₂Mo₇O₂⁴, H₂O₂, EtOH (97%).


For the synthesis of alkyne 53 we thought about Suzuki coupling 47 on E-iodoalkene 63 and Bestmann-Ohira alkynylation 48 (Scheme 17). For the synthesis of E-vinylidene 63 a zirconium mediated selective carboalumination/halogenation 49 seemed to be obvious and a Marshall-Tamaru reaction on chiral aldehyde 64 should secure an anti-Me/OH relationship.
As a starting material we selected aldehyde 64, which was obtained via L-Proline catalyzed cross-aldol reaction of α-silyloxyacetaldehyde using a known literature procedure (Scheme 18). With this aldehyde in hand we tested the Marshall-Tamaru conditions hoping for separable diastereomeric diols. To our surprise, when (R)-mesylate 67 (2.0 equiv.) was subjected into the reaction mixture containing Pd(OAc)₂ (0.05 equiv.), PPh₃ (0.05 equiv.) and aldehyde 64 followed by slow addition of diethyl zinc (3.0 equiv.) and stirring for 48 hours, diol 65 was isolated as a single isomer in 61% yield after chromatographic purification (Scheme 18). This reaction outcome can be understood based on Felkin-Anh-like transition state A which is akin to attack of an E-enolate to an α-substituted aldehyde (Scheme 18). Due to an angle of 120 ° between the C=O- and the OH-dipole this transition state also minimizes dipole interactions. We also assume that the major anti diastereomer 64 reacts faster than the corresponding syn isomer. Subsequent diol protection as acetal 65a

**Scheme 17.** Retrosynthetic scheme for ester 53.

**Scheme 18.** Synthesis of carbometalation precursor 66 and attempts to secure E-vinyliodide 63.
Additionally proved the 1,3-anti relationship. In particular, the two methyl groups of the acetal appear at similar chemical shifts in the $^{13}$C NMR spectrum (23.7 and 24.9 ppm, respectively).

After the TMS group was removed with K$_2$CO$_3$ in MeOH, a carboalumination procedure was evaluated. However, no desired product could be obtained employing known procedures (AlMe$_3$, [Cp$_2$ZrCl$_2$], I$_2$, solvent). In the case of water-accelerated carboalumination, just acetal deprotection could be observed. Thus, other strategies like olefination to prepare E-vinyl iodide 63 were considered (Scheme 19). Thus, an olefination precursor 68 was prepared form alkyne 66 via Kutscheroff hydration in 76% yield. Then, Takai olefination conditions were tested to prepare 63. However no reaction was observed. An olefination with ethyl ester 69 was also taken into account. Again, reaction with Wittig salt 69 failed to provide the desired product. The same observation was made in the case of Julia-Kocienski olefination.

With disappointing results mentioned above, we came to the idea to establish the E-double bond via Claisen or Ireland-Claisen rearrangements. Thus, vinyl magnesium bromide addition to ketone 68 at $-78 \, ^\circ\text{C}$ led to a smooth formation of a single isomer and in 65% yield (Scheme 20). This is probably isomer 71, who’s formation could be probably explained by chelation control (six-membered chelate complex). In addition, literature examples also support this outcome. This was then heated with 1,1,1-trimethoxyethane in the presence of catalytic amounts of propionic acid. However, even at a temperature of 110 °C the desired rearrangement did not take place. Temperature increase led to
decomposition of starting material. In the case of the Ireland-Claisen rearrangement we faced the problem at the acylation step, as all attempts to acylate the OH function failed.

\[
\begin{align*}
\text{Conditions: } & i. \text{ vinyMgBr, THF, –78 °C (65%);} \quad ii. 1,1,1\text{-trimethoxyethane, cat. 1-propionic acid, xylene, heat.}
\end{align*}
\]

**Scheme 20.** An attempt to secure the \(E\)-double bond via Claisen or Ireland-Claisen rearrangement.

After unsuccessful efforts to establish the \(E\)-substituted double bond in vinyl iodide 63 or ester 53 we decided to modify the retrosynthetic scheme namely to concentrate on ring-closing metathesis that would possibly create the desired double bond configuration at a later stage (**Scheme 21**).

**Scheme 21.** A modified retrosynthetic scheme for leiodermatolide core 51.

Thus, Sonogashira coupling partner alkyne 75 would come from a ketone via olefination and the carboxyl function on 15-OH would be installed via esterification with 1-pentenoic acid.
The synthesis of alkyne 75 we started with Tebbe olefination on ketone 68, followed by silyl deprotecting with TBAF. The resulting alcohol 77 was then treated with Dess-Martin periodinane followed by reaction with Bestman’s reagent to give corresponding alkyne 75 in 40% yield over two steps (Scheme 22).

**Scheme 22.** Transforming ketone 68 into Sonogashira coupling precursor 75.

With alkyne 75 in hand, we now concentrated on the construction of Z-vinyl iodide 54 (Scheme 23).

**Scheme 23.** Synthesis of Z-vinyl iodide 54.
As it was mentioned before vinyl iodide 54 could be accessed via Marshall-Tamaru reaction on an appropriate aldehyde. Thus, as a starting aldehyde we chose aldehyde 78, which easily underwent allenyl zincate addition to give alcohol 79 as a single isomer. The enantiomeric ratio of this was determined by Mosher analysis to be 97:3 (Figure 4). Subsequent alcohol protection with TBSOTf in presence of 2,6-lutidine furnished the corresponding silyl ether 80 in 70% yield.

Further functionalization of the triple bond called for terminal iodination and Z-selective reduction. Thus, treatment of trimethylsilyl alkyne 80 with N-iodosuccinimide in the presence of silver nitrate resulted in almost quantitative conversion to iodoalkyne 81, which was directly subjected to Z-specific diimide reduction. Thus, slow addition (6 h) of acetic acid to a solution of the iodoalkyne, potassium azodicarboxylate and pyridine gave Z-iodoalkene 54 in 77% yield over two steps.

Both building blocks 54 and 75 were then combined in a Sonogashira coupling reaction. Here, optimal conditions found to be Pd(PPh₃)₄ (5 mol%), Cul (50 mol%) and diethylamine as a solvent and base. These conditions led to complete conversion to enyne 83 in 68% yield (Scheme 24). The Z-selective reduction of the triple bond turned out to be challenging, as many of known literature methods (P2-Ni reduction; NbCl₅, Zn, HMPA, THF; Rieke Zn, THF, MeOH, H₂O) failed to provide desired diene 84, resulting mainly in a complex mixture of overreduction products (detected by HPLC). However, carefully optimized Lindlar reduction conditions allowed us to isolate diene 84 in 59% yield after chromatographic purification (Scheme 24).

The $^1$H NMR data nicely indicate a cis-relationship of the 11-H and 12-H protons, where coupling constant is 11.4 Hz (Figure 5).

Figure 5. Fragment of the $^1$H NMR spectrum of Z,Z-diene 84.
The TBS protecting group in 84 was removed with TBAF and simple Yamaguchi esterification with 1-pentenoic acid secured RCM precursor 85 in 63% yield over two steps (Scheme 25). A ring-closing metathesis on substrate 85 represents a big challenge as it contains five double bond where each those could participate in the metathesis reaction. For the RCM study we chose three readily available ruthenium catalysts – Grubbs 2nd, Hoveyda-Grubbs 2nd, and Grubbs 1st (Scheme 25). All of these catalysts were tested in CH₂Cl₂, PhCH₃ and PhH solvents at a substrate concentration of 1 mM. Stirring the RCM precursor 85 at room temperature in toluene or benzene gave no cyclized lactone. Just starting material was recovered in all cases. However, when the RCM reaction on ester 85 was tried in CH₂Cl₂ containing Grubbs 2nd generation catalyst a complex mixture of products formed. According to HPLC data, no molecular peak of the desired product could be detected. The increase in temperature (starting from 80 °C) resulted in decomposition of starting material with all three catalysts.

Scheme 25. Preparation of RCM precursor 85 and attempts to prepare macrocycle 51.

Next RCM precursor 87 with a triple bond was prepared following essentially the same procedures as for 85 (Scheme 26).
Again, running experiments with RCM catalyst mentioned in Scheme 25 no desired product was obtained, but in all cases starting material was isolated. Probably, due to the linear triple bond the molecule itself cannot undergo ring-closing for steric reasons.

With these unsuccessful results toward the preparation of leiodermatolide core 51, we decided to cancel the study of this route. On the other hand, there is still a playground to continue the study on ring-closing metathesis while screening other catalysts like Schrock’s molybdenum based catalyst or Grela’s ruthenium catalyst which are known to be one of most active metathesis carbenes in the literature (Scheme 27).


Scheme 27. Highly active ruthenium and molybdenum RCM catalysts.
Conclusion

In summary, a ring-closing metathesis approach towards the macrolactone of leiodermatolide (51) was studied. The key fragments – alkyne 75 and Z-iodoalkene 54 were prepared featuring a Marshall-Tamaru reaction (Scheme 28). An efficient protocol for preparation of the stereotetrad was developed starting from aldehyde 64, which was obtained via organocatalysis. This was then converted to diol 65 setting four stereocenters selectively and representing one of the shortest procedures to set this type of stereochemistry. Further four steps converted the triple bond into a propenyl moiety in 60% overall yield. Redox operations and Bestmann-Ohira alkynylation starting from silyl ethers 76 secured us to prepare alkyne 75 in overall 20% yield over 7 steps.


The same Marshall-Tamaru reaction served as a perfect synthetic tool for the synthesis of Z-iodoalkene 54. A rapid construction of two stereocenters followed by protection, terminal iodination and Z-selective reduction delivered PMB ether 54 in 44% yield over four steps starting from literature known aldehyde 78 (Scheme 29).
Scheme 29. Summary of the synthesis of Z-iodoalkene 54.

The Sonogashira coupling of the fragment mentioned above led to an enyne, which was then selectively hydrogenated under Lindlar conditions to give the conjugated Z,Z-double system in compound 84 (Scheme 30).

Scheme 30. Synthesis of RCM precursor 85.

The following two steps delivered ester 85, which unfortunately has failed to participate in a ring-closing metathesis reaction to secure leidematolide core 51.
Chapter III

Approach Towards the Total Synthesis of Terpene (−)-Englerin A*

* This work was done together with graduate student Dmitry B. Ushakov.


Introduction

The guaiane (–)-englerin A (88) is a sesquiterpene recently isolated from the plant *Phyllanthus engleri* by the group of Beutler et al. Englerin A (88) is an attractive synthetic target not only for his molecular architecture but also for its high selectivity and potency against various cell lines typical for renal cancer (Figure 6).

Figure 6. Structure of (–)-englerins A-B (88-90) and inhibition data of (–)-englerin A (88) on various renal cell lines.

The compound features an oxygen bridge in the seven-membered ring and seven contiguous stereocenters, including two quarternary centers. Most likely, this motif originates from a more common bicyclic sesquiterpene core. For this and for an option to find a more simple and readily available natural building block for a possible semisynthetic approach, one should take a glance on the likely biosynthetic pathway of (–)-englerin A (88) (Scheme 31). As it can be seen, a decalin structure, namely germacratriene (93) in nature is arising from farnesyl pyrophosphate (91) via a cationic cyclization. Macrocycle 93 is protonated and a subsequent 1,2-hydride shift delivers carbocation 95, which then through Wagner-Meerwein shift is converted to guaiene (98) which undergoes double bond migration processes to give 99. Further steps to englerin A core involve oxidation processes. In addition, this is a typical feature in terpene biosynthesis. First, the carbocyclic core is constructed followed by redox reactions to set the oxygen functionalities.
Taking into advance promising anticancer activity and its scarcity from natural sources, englerin A deserves attention as a synthetic target. Furthermore, the structure serves as an inspiration to invent new approaches and strategies towards bridged guainolides also\textsuperscript{79}.

\textbf{Scheme 31.} Possible key intermediates in the biosynthesis of (–)-enlgerin A.
Overview of Previous Syntheses

Less than one year after Beutler and co-workers reported the isolation of (–)-englerin (88), Christmann and co-workers completed the total synthesis of the (+)-enantiomer (107), thereby establishing the previously unknown absolute configuration of the natural product. The key features of this synthesis can be seen in Scheme 32. Here cis, trans-nepetalactone (102) served as a starting material, which could be easily obtained by distillation of commercially available catnip oil. Nepetalactone 102 was converted to aldehyde 103 in two steps which involved epoxidation and oxidative rearrangement. Diol 104 was synthesized in seven steps utilizing a diastereoselective Barbier reaction, epimerization and ring-closing metathesis as a key reactions. Then, selective protection of the secondary alcohol function as glycolate ester, epoxidation and transannular epoxide opening secured the core structure of (+)-englerin A and two further steps provided (+) enantiomer 107 itself.

Soon thereafter, two conceptually similar syntheses of (–)-englerin A (88) appeared from research groups of Ma and Echavarren. Here both strategies rely on a gold(I)-catalysed formal domino reaction on a linear ketoenyne precursor for the generation of englerin’s tricyclic core (Scheme 31). The two syntheses differ in their choice of the cyclization precursor and the gold(I) catalyst. The group of Echavarren chose geraniol as a starting material and in eight steps converted this to ketoenyne precursor (R = OTES) using Sharpless asymmetric epoxidation and a Mukayama aldol to generate two stereocenters. Ma’s cyclization precursor (R = H) was obtained in five steps from (R)-(+)citronellal featuring a boron-aldol reaction. Both groups then utilized an intramolecular [2+2+2] ketoenyne cycloaddition. Here in the first step, a 5-exo-dig cyclization takes place leading to cyclopropyl gold carbene 113 which reacts with carbonyl oxygen releasing the strain on the cyclopropane ring and
producing oxonium ion 114. Then, a Prins-cyclization takes place followed by proto-demetalation to give englerin’s A tricyclic skeleton. Both syntheses relied on functionalization of 115 featuring allylic oxidation and selective reduction of the double bond to establish a trans-fused ring orientation. While the core system 115 could be reached very fast, the subsequent functional group manipulations required a number of steps.

Scheme 33. A Comparative scheme for the synthesis of (−)-englerin A by Ma and Echavarren.

A [5+2] cycloaddition tactic was used in the total synthesis of (−)-englerin A by the Nicolaou/Chen group (Scheme 34). The synthesis they started from propargylic alcohol 116 which was converted to furan 117 featuring a gold(I)-catalyzed ring closure. An oxidopyrilium species 118, obtained in four steps via Achmatowitcz rearrangement, in the presence of chiral Oppolzer’s sulfonamide acrylate derivative 120 participated in a [5+2] cycloaddition reaction delivering oxabicyclic enone 119. As next, the group took a part in a rather long (16 steps) functionalization marathon featuring an intramolecular aldol reaction to form the cyclopentane ring and a Baeyer-Villiger oxidation to convert the methyl ketone moiety to an alcohol function. One should mention that together with the total synthesis first steps towards structure-activity relationship (SAR) of (−)-englerin A were made indicating the importance of the glycolic acid moiety.
Overview of Previous Syntheses

Scheme 34. Retrosynthetic disconnection of (−)-englerin A (88) by the Nicolaou/Chen group.

The group of Theodorakis achieved an enantioselective formal synthesis of (−)-englerin A (88) via a Rh-catalyzed [4+3] cycloaddition reaction. The key oxa-tricyclic compound 123 was obtained via the Davies Rh-catalyzed ring formation from readily available staring materials, namely substituted furan 121 and chiral diazo ester 122 (Scheme 35).

Scheme 35. A formal total synthesis of (−)-englerin A (88) by Theodorakis et al.

In the next step a Lewis acid incuced rearrangement of a β-hydroxyl enol ether took place securing ketone 124. Subsequent Rubottom oxidation and Stetter reaction delivered diketone 125. The next
steps involved elaboration of the enone system to the five-membered ring. Thus, an intramolecular aldol condensation and NaBH₄ reduction furnished the tricyclic englerin A skeleton. A selective hydroboration delivered the hydroxyl function at C9, while the Burgess protocol removed hydroxyl from the cyclopentene ring. Then reduction of the less substituted double bond and silyl deprotection gave rise to diol 128, which was described by Ma.

A conceptually very similar work recently appeared in Tetrahedron Letters from the group of Sun and Lin, where they utilized a cation-triggered asymmetric organocatalytic [4+3] cycloaddition reaction (Scheme 36).⁹⁷ According to work reported from Harmata et al. a [4+3] cycloaddition could be catalyzed by MacMillan’s catalyst (cat. A) giving a functionalized 8-oxa-bicyclo[3.2.1]octane structure.⁹⁸ Thus, starting from readily available starting materials – disubstituted furan 121 and dienal 129, a mixture of regioisomers 130 and 131 could be obtained (63%, 2.4:1, 130:131). In this case, the major isomer turned out to be the non-required one. Further steps they performed on a mixture of those. These included Grignard addition, acylation and catalytic deoxygenation. The five membered ring was constructed via intramolecular Heck reaction on triflate 133. In the second approach the group prepared the higher functionalized (+)-englerin’s A core structure 136 via Grignard addition on aldehyde 130 followed by intramolecular aldol condensation.

Scheme 36. Asymmetric organocatalytic [4+3] cycloaddition approach to the (−)-englerin A core.
**1st Generation Retrosynthetic Consideration**

Our retrosynthetic analysis of (–)-englerin A was based on a bimolecular carbonyl ylide-alkyne cycloaddition reaction (Scheme 37).99,100

![Scheme 37. Retrosynthetic analysis for englerin A (88).](image)

The advantage of this strategy is the simultaneous formation of the oxygen bridge in the course of the cycloaddition. Thus, carbonyl ylide 139 would react with propiolate 140 giving a bicyclic addition product (dipolarophile should approach the carbonyl ylide 139 opposite to the C4 methyl group). The intermediate carbonyl ylide should be available by rhodium(II)-catalyzed decomposition of diazoketoester 141. The latter can be traced back to (R)-(–)-carvone. Further functional group manipulation towards 88 would involve Curtius rearrangement of acrylazide 138, hydrolysis of the resulting vinyl isocyanate to give a ketone, which then would be reduced. The isopropyl group in 137 would come from an ester function, via a MeMgl addition/deoxygenation pathway.
Results and Discussion

We started the synthesis from commercially available and cheap (R)-(–)-carvone. Following known procedures, this terpene was easily transformed into alcohol 143 featuring enone epoxidation, regioselective epoxide opening and Favorskii rearrangement (Scheme 38).\(^{101,102}\) This five step synthetic protocol allowed us to prepare multigram quantities of alcohol 143. The hydroxyl group was then removed utilizing the Barton–McCombie\(^ {103}\) protocol on the corresponding xanthogenate giving ester 144 in 67% yield over two steps (Scheme 38).

![Scheme 38. Transforming (R)-(–)-carvone into ester 144.](image)

**Conditions:**

i. a) \(\text{H}_2\text{O}_2, \text{MeOH}, \text{NaOH}\); b) TFA, LiCl, THF; c) PPTPS, DHP, CH\(_2\)Cl\(_2\) (82%, 3 steps).

ii. a) \(\text{NaOMe}, \text{MeOH}, \text{Et}_2\text{O}\); b) PPTPS, MeOH, 50 °C (94%, 2 steps).

iii. a) \(\text{NaH}, \text{CS}_2, \text{MeI, THF}\); b) \(\text{Bu}_3\text{SnH, AlBN, PhMe, reflux (67%, 2 steps)}\).

As next, epimerization at C-5 was considered. However, all attempts to invert the configuration on ester 144, under basic conditions, gave inferior results. Thus, the ester function was successfully transformed into a corresponding aldehyde utilizing a two step protocol, namely Li\(\text{AlH}_4\) reduction and Parikh–Doering oxidation.\(^ {104}\) We found that this two step procedure was more reliable to perform on a large scale (25 g, 87%), as DIBAL-H reduction gave just the corresponding alcohol which was then oxidized with Dess-Martin periodinane\(^ {105}\) (5.0 g, 49% over two steps). Base-induced epimerization of aldehyde 145 was achieved with DBU in refluxing toluene (see Scheme 39) leading to trans orientation of the aldehyde group with respect to the larger isopropenyl group (\(\text{trans/cis} = 2:1\)). Subsequent ozonolysis of aldehyde 146 and reaction with ethyl diazoacetate, catalyzed by tin (II) chloride,\(^ {106}\) provided β-ketoester 147 as a single isomer in 66% yield over two steps. One should mention that the other diastereomer was not detected.
Finally, a diazotransfer reaction with sulfonyl azide\textsuperscript{107} furnished diazoketone 141 in 71\% yield. This thirteen step sequence allowed us to prepare gram quantities of $\beta$-ketoester 141 starting from (R)-(−)-carvone.

Bearing in hand diazoketone 141, we now were ready to test the proposed (see retrosynthesis) intramolecular carbonyl ylide formation promoted by Rh(II) and its subsequent cycloaddition. Here we decided to use allylpropionate (149) as a dipolarophile due to ease of further functionalization (Scheme 40). After careful experimentation, we found that heating of a mixture containing allylester 149, 1 mol \% of Rh\textsubscript{2}(OAc), and diazo compound 141 in toluene (100 °C) for 15 min led to the formation of cycloaddition product 150 as a single isomer. Lower temperatures and longer times gave inferior results (see Scheme 40).
When ethyl acrylate was used as a dipolarophile a mixture of diastereomers 152 was isolated in 16% yield. In the case of methyl vinyl ketone no desired product was detected. The cycloadduct 150 turned out to be sensitive to epimerization, for example, upon silica gel chromatography, leading exclusively to the corresponding cis-isomer. Therefore, crude ketodiester 150 was selectively reduced with NaBH₄ and the resulting alcohol converted to TES-ether 151 in 59% over three steps (starting from 141). At this stage we were not able to unambiguously determine the stereochemistry of the newly formed centers (orientation of oxygen bridge). This was clarified at a later stage (vide infra).

Further functionalization of the seven-membered ring called for degradation of the acrylate to a keto function. This was achieved via a classical Curtius rearrangement/hydrolysis sequence (Scheme 41). It was found that the allyl ester could be easily cleaved using 10 mol% of Wilkinson’s catalyst in an ethanol/water mixture (10:1) at 100 °C in 84% yield. In contrast, palladium-based methods failed to provide carboxylic acid 153. Now, acid 153 was converted to azide 154 in the presence of trichloroacetonitrile and PPh₃. Upon heating, azide 154 rearranged to the vinyl isocyanate which under acidic conditions was selectively hydrolyzed to ketone 155. It should be noted that under these conditions (HCl (5%), THF, rt) no deprotection of the TES group was observed. Subsequent reduction with NaBH₄ provided alcohol 156 as a single isomer. At this stage, key NOESY cross peaks between 1-H/8-H, 4-H/5-H, and 5-H/6-H (guanolid e numbering) suggested a structure of 156 where the oxygen bridge is on the opposite site with respect to the C4 methyl group (Scheme 41).
Nevertheless, we continued with further functional group manipulation that would allow for either a chemical correlation with a known compound or an X-ray structure. Thus, alcohol 156 was converted into bis silyl-ether 157 which called for ester conversion of the ester function to isopropyl group (Scheme 42). Accordingly, addition of freshly prepared MeMgI (6.0 equiv) to ester 157 at 0 °C gave tertiary alcohol 158 in quantitative yield. As next, we thought to apply the same radical deoxygenation conditions applied earlier. However, neither xanthogenate nor trifluoro acetate, did undergo deoxygenation. On the other hand, Burgess reagent\textsuperscript{111} (MeO\textsubscript{2}CN\textsuperscript{−}SO\textsubscript{2}N\textsuperscript{+}Et\textsubscript{3}) did the job providing alkene 159 which led to silyl ether 161 via catalytic hydrogenation (51% over 2 steps). TES deprotection on alkene 159 was achieved with TBAF to give alkenediol 160 in 65% yield.

**Scheme 41.** Transformation of cycloadduct 151 into TES-ether 157.

**Scheme 42.** Synthesis of diol 160.
Crystallization of 160 from a hexane/diethyl ether mixture provided crystals suitable for X-ray analysis (Figure 7) indicating the configuration of the stereocenters and conformation of the structure. The X-ray structure structure additionally proved the facial selectivity in the cycloaddition step which corroborated the NOESY data of ester 156.

Figure 7. X-ray structure of diol 160.

With these results in hand we took an effort to design a second generation approach for (−)-englerin A.
2nd Generation Retrosynthetic Consideration

The 2nd generation retrosynthetic analysis was based on a transannular cyclization of guaianolide 162, which could be induced by acid or by activating the double via a bromonium or mercurinium ion (Scheme 43).

![Scheme 43. 2nd generation retrosynthetic analysis of (-)-englerin A (88).](image)

Thus, alkene 162 could be generated from enone 163 via reduction of the double bond and isopropenyl installation via aldol condensation with acetone. For diol 163 we considered allylic oxidation of the corresponding enone, which may arise from keto epoxide 165 by intramolecular epoxide opening. Thus, an Oxy-Cope rearrangement would be possible for the synthesis of the decalin carbon framework. As it can be seen in Scheme 43, (-)-isopulegol was found to be a perfect precursor for 88 as it is a readily available starting material providing stereochemical information for C4 in (-)-englerin A.
Results and Discussion

The synthesis started with known literature procedures to prepare (−)-isopulegone. Thus, smooth PCC oxidation of (−)-isopulegol, followed by vinyl magnesium bromide addition gave multigram quantities of vinyl alcohol 166 in 92% yield (Scheme 44).

Scheme 44. Synthesis of hydroxy ketone 164 via anionic Oxy-Cope rearrangement and transannular epoxide opening.

Here is worth to mention that in the case of freshly, self made vinyl magnesium bromide the reaction proceeds very clean and the desired product could be distilled at low pressure. However, when commercially available vinyl magnesium bromide was used many side products were observed. Next, an anionic Oxy-Cope rearrangement was studied. Following classical conditions (KH, 18-crown-6 ether, THF) ketone 167 could be isolated in 71% yield. Although, this procedure allows for a rapid formation of the ten-membered ring, a crown ether issue should be considered as for 1 g of starting material we needed 3.3 g (3.0 equiv.) of 18-crown-6 ether! After careful experimentation we found that running the reaction without the crown ether mentioned above, just extension of reaction time (2 h vs. 12 h) led to the desired product as well. No loss in the yield could be detected. Simple mCPBA mediated epoxidation secured epoxide 165, whose structure was confirmed by X-ray analysis (Figure 8).
A regioselective enolate formation on ketoepoxide 165 in order to prepare the 5,7-fused ring system was found to be quite challenging. First attempts to override this problem gave interesting results. When freshly prepared LDA solution was added dropwise to a solution of ketone 165 at −78 °C a mixture of regioisomers 164 and 164a was obtained. Temperature change allowed us to increase the amount of the desired isomer. Furthermore, when NaH was added to a solution of 165 and the resulting suspension was immersed to a preheated (60 °C) oil bath for 5 min just the desired isomer 164 was formed in 90% yield. It can be assumed that the small hydride selectively deprotonates 5-H which is perfectly orthogonal to the keto group.

As can be seen in Scheme 45, the hydroxyl ketone 164 exists in equilibrium with cyclic hemiacetal 168. We found that for further functionalization of the seven-membered ring it was necessary to trap the compound as a ketone. We assumed that protection of hydroxy function by deprotonating the OH function with base would shift the equilibrium towards acetal 168. Thus, esterification in the presence of catalytic amount of acid (or Lewis acid) would be optimal. A selective C4-OH protection as a pivalic ester allowed us to separate ketone 170 in 60% yield from oxygen bridged pivalic ester 169. Furthermore, acetal 169 could be easily recycled via K$_2$CO$_3$ deprotection in methanol. An interesting result was
obtained, when ketone 170 was treated with phenyltrimethylammonium tribromide \((\text{C}_6\text{H}_5\text{N}^+(\text{CH}_3)_3\text{Br}_3^-)\)^117 in THF. As an X-ray structure shows (Figure 9) a bromide atom was introduced at the more substituted position of the keto function. This has additionally proven formation of the 5,7-fused ring system in the transannular epoxide opening.

![Figure 9. X-ray structure of bromo-170.](image)

With ketone 170 in hand, we tested various conditions in order to prepare enone 171. After careful experimentation we found that the kinetic enolate of 170 could be easily trapped as silyl ether at \(-40 °C\) and in subsequent Pd(OAc)\(_2\) mediated Saegusa-Ito oxidation converted to enone 171. Other methods, like phenylselenyl ether formation and subsequent elimination via selenoxide gave an unexpected product, enone 176 (Scheme 46).

![Scheme 46. Mechanistic rationale for the formation of lactone 176.](image)
It was observed that upon treating ketone 170 with LDA in absolute THF at −20 °C and then warming the reaction mixture to −5 °C in an ice/salt bath, a pivaloyl migration (Claisen condensation) occurred, followed by retro-Claisen condensation. The enolate 174 was quenched with PhSeCl to give selenide 175, which after oxidation with hydrogen peroxide resulted in enone 176. The structure of this was proven by X-ray crystallography (Figure 10).

![Figure 10. X-ray structure of rearrangement product 176.](image)

Further functionalization of the seven-membered ring was calling for allylic oxidation or allylic halogenation and subsequent S_N_2 reaction with acetate (Scheme 47).

![Scheme 47. Attempts on allylic substitution.](image)

However, allylic oxidation (methods like SeO_2; SeO_2, TBHP; SeO_2, AcOH (glac.)) on enone 171 has failed to work. Neither of the applied methods gave desired diol 177b and just starting material could be recovered. In the case of allylic bromination (NBS, AIBN, CCl_4) no desired allyl bromide could be isolated as well. Thus, considering these results, a new functionalization strategy which was based on oxygen
bridge formation in the first steps and then OH function installation via CH selective oxidation was started (Scheme 48)*.

![Scheme 48](image)

**Scheme 48.** Modified strategy for functionalization of the seven-membered ring.

According to the proposed functionalization strategy, disubstituted alkene 181 could arise from pivalic ester 170. Further modification would involve deprotection of the pivalic ester and reduction of a ketone function to prevent acetal formation. Then, by activating the double bond a transannular cyclization should take place. For the hydroxyl installation we were optimistic about Ch. White catalyst (Figure 11), which is known to oxidize the 4th CH bond from a keto or ester function.118,119

![Figure 11](image)

**Figure 11.** Structure of White catalyst B.

* Independent work of graduate student Dmitry B. Ushakov.
Conclusion

In summary, two different approaches towards the natural product (−)-englerin A have been studied. The first of them, was based on a 1,3-dipolar cycloaddition of a chiral carbonyl ylide (Scheme 49). Here (R)-(−)-carvone served as a perfect starting material delivering the stereochemical information at C4. Thus, in thirteen steps and 19% overall yield diazoketo ester 141 was obtained.

Scheme 49. Transforming (R)-(−)-carvone into diazoketo ester 141.

Further studies on the cycloaddition strategy revealed that the wrong isomer was formed in cycloaddition step. However, the studies on the functionalization of the seven membered ring was explored (Scheme 50).

Scheme 50. Rhodium (II) catalyzed 1,3-dipolar cycloaddition strategy to form an oxygen bridge in guaianolides.
Starting from di-ester 151, the TES ether 157 was synthesized in five steps featuring Curtius rearrangement, vinyl isocyanate hydrolysis and reduction of the keto function.

A second generation approach to (−)-englerin A was based on transannular epoxide opening in decalin structure 165 to form the 5,7-fused ring system. Thus, readily available (−)-isopulegol was transformed to 167 via anionic oxy-Cope rearrangement. Further two steps, which involved selective epoxidation and transannular epoxide opening, resulted in hydroxyketone 164 in 75% yield over two steps (Scheme 51).

\[
\text{(-)-Isopulegol} \xrightarrow{2\text{ steps, } 92\%} \text{166} \xrightarrow{\text{anionic Oxy-Cope rearrangement}} \text{167} \xrightarrow{83\%} \text{164}
\]

**Scheme 51.** Synthesis of hydroxyketone 164.

Next, functionalization of the seven membered ring was studied (Scheme 52). Firstly, the free hydroxyl function was protected as pivalic ester and the Saegusa-Ito oxidation protocol delivered enone 171. However, further attempts to substitute the allylic position failed.

\[
\text{164} \xrightarrow{\text{Protection/ enone formation}} \text{171} \xrightarrow{\times} \text{177a: } X = \text{Br} \quad \text{177b: } X = \text{OH}
\]

**Scheme 52.** Synthesis of the deoxy-(−)-englerin A core and attempts on its allylic substitution.
Experimental Section

General Remarks

Chemicals and working techniques

The chemicals were purchased from the firms Acros, Aldrich, Fluka, Lancaster, Avocado and Merck. All reagents were obtained from commercial suppliers, and were used without further purification unless otherwise stated. All solvents were distilled and/or dried prior to use by standard methodology except for those, which were reagent grades. The applied petroleum ether fraction had a boiling point of 40–60 °C. Anhydrous solvents were obtained as follows: THF, diethyl ether and toluene by distillation from sodium and benzophenone; dichloromethane and chloroform by distillation from calcium hydride; acetone by distillation from phosphorous pentoxide. Absolute triethylamine, pyridine and diisopropylethylamine were distilled over calcium hydride prior to use. Unless and otherwise mentioned, all the reactions were carried out under a nitrogen atmosphere and the reaction flasks were pre-dried by heat gun under high vacuum. All the chemicals, which were air or water sensitive, were stored under inert atmosphere. Compounds that are not described in the experimental part were synthesized according to the literature.

NMR-spectroscopy

All the spectra were measured on a Bruker Advance 400 spectrometer, which operated at 400 MHz for $^1$H and 100 MHz for $^{13}$C nuclei, respectively. $^1$H (400 MHz) and $^{13}$C NMR (100 MHz): spectra were recorded at 295 K either in CDCl$_3$ or [D$_6$]DMSO; chemical shifts are calibrated to the residual proton and carbon resonance of the solvent: CDCl$_3$ ($\delta$H = 7.25 ppm, $\delta$C = 77.0 ppm), [D$_6$]DMSO ($\delta$H = 2.49 ppm, $\delta$C = 39.5 ppm). Data are reported as follows: chemical shift (multiplicity: s = singlet, d = doublet, t = triplet, ddd = doublet of doublet of doublet, dt = doublet of triplet, td = triplet of doublet, m = multiplet, br = broadened, app. d = looks like doublet, J = coupling constant (Hz), integration, peak assignment.

Mass Spectrometry

Mass spectra were recorded on a Finnigan Triple-Stage-Quadrupol Spectrometer (TSQ-70) from Finnigan-Mat. High-resolution mass spectra were measured on a modified AMD Intectra MAT 711 A from the same company. The used mass spectrometric ionization methods were electron-impact (EI), fast-atom bombardment (FAB) or field desorption (FD). FT-ICR-mass spectrometry and HR-FT-ICR mass spectra were measured on an APEX 2 spectrometer from Bruker Daltonic with electrospray
ionization method (ESI). Some of the mass spectra were also measured on an Agilent 1100 series LC-MSD. Analytical HPLC-MS: HP 1100 Series connected with an ESI MS detector Agilent G1946C, positive mode with fragmentor voltage of 40 eV, column: Nucleosil 100–5, C-18 HD, 5 mm, 70 × 3 mm Macherey Nagel, eluent: NaCl solution (5 mM)/acetonitrile, gradient: 0/10/15/17/20 min with 20/80/80/99/99% acetonitrile, flow: 0.6 mL min⁻¹. High resolution mass (HRMS) are reported as follows: (ESI): calcd mass for the related compound followed by found mass.

**Polarimetry**

Optical rotations were measured on a JASCO Polarimeter P-1020. They are reported as follows: [α]°ₜemperature (concentration, solvent). The unit of c is g/100 mL. Anhydrous CH₂Cl₂ or MeOH was used as a solvent. For the measurement the sodium D line = 589 nm was used.

**Chromatographic Methods**

Flash column chromatography was performed using flash silica gel (40-63 µm, 230-400 mesh ASTM) from Macherey-Nagel.

Gas chromatography was performed on a CHROMPACK CP 9000 using a flame ionization detector, and carrier gas H₂. Chiral gas chromatographic analyses were carried out on a 13.5 m × 0.25 mm column filled with deactivated fused silica with 30% 6-TBDMS-2,3-diacyetyl-β-cyclodextrin in PS 086 (df = 0.13 µm) and carrier gas H₂ at 50 kPa and 30 °C.

For GC-MS coupled chromatography, a GC-system series 6890 with an injector series 7683 and MS-detector series 5973 from Hewlett Packard was used, with EI method, and carrier gas He. Analytical HPLC was performed on a Hewlett Packard HP 1100 system.

Analytical thin layer chromatography (TLC) was performed on precoated silica gel 60 F₂₅₄ plates (Merck) or Polygram Sil G/UV₂₅₄ (Macherey Nagel). The compounds were visualized by UV₂₅₄ light and the chromatography plates were developed with an aqueous solution of molybdophosphorous acid or an aqueous solution of potassium permanganate (heating with the hot gun). For preparation of the molybdate solution 20 g ammonium molybdate [(NH₄)₆Mo₇O₂₄•4H₂O] and 0.4 g Ce(SO₄)₂•4H₂O were dissolved in 400 mL of 10% H₂SO₄. The potassium permanganate solution was prepared from 2.5 g KMnO₄ and 12.5 g Na₂CO₃ in 250 mL H₂O.

**Experimental procedures**

All the experimental procedures are arranged in the ascending order as they appeared on the synthetic schemes.
I. Total Synthesis of the Proposed Structure of the Macrolide Queenslandon

(R)-2-((4R,5S)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)-2-hydroxyethyl pivalate (21a). To an ice-cooled solution of diol $^1$ 21 (16.65 g, 88.6 mmol) and DMAP (1.07 g, 8.8 mmol) in a CH$_2$Cl$_2$/pyridine mixture (120 mL, 5:1) was added PivCl (11.0 mL, 106.3 mmol) in a dropwise fashion. After the addition, the reaction mixture was allowed to warm to room temperature. Stirring was continued for 2 h before the reaction mixture was washed with 1N HCl (5 × 100 mL) and saturated NaCl (100 mL) solution. The organic layer was dried over MgSO$_4$, filtered, and concentrated in vacuo. The crude pivaloate 21a (22.8 g, 95%) was pure enough to be introduced to the next step without additional purification. R$_f$ = 0.25 (petroleum ether/EtOAc, 5:1); $\alpha$$_{20}^D$ = +9.7 (c 2.2, CH$_2$Cl$_2$); $^1$H NMR (400 MHz, CDCl$_3$): δ [ppm] = 1.21 (s, 9H, C(CH$_3$)$_3$), 1.34 (s, 3H, 2'-CH$_3$), 1.46 (s, 3H, 2'-CH$_3$), 3.84 (ddd, $J$ = 8.8, 6.4, 2.4 Hz, 1H, 2-H), 4.06 (dd, $J$ = 8.9, 6.4 Hz, 1H, 1-H), 4.15 (dd, $J$ = 11.7, 6.4 Hz, 1H, 1-H), 4.36 (dd, $J$ = 11.7, 2.3 Hz, 1H, 4'-H), 4.69 (app t, $J$ = 6.6, 6.6 Hz, 1H, 5'-H), 5.30 (app d, $J$ = 10.4 Hz, 1H, CH$_2$ vinyl), 5.44 (app d, $J$ = 10.4 Hz, 1H, CH$_2$ vinyl), 5.98 (ddd, $J$ = 17.1, 10.4, 6.9 Hz, 1H, CH vinyl); $^{13}$C NMR (150 MHz, CDCl$_3$): δ [ppm] = 25.3 (C(CH$_3$)$_3$), 27.2 (2'-CH$_3$), 27.7 (2'-CH$_3$), 38.9 (C(CH$_3$)$_3$), 66.6 (C-1), 68.8 (C-4'), 77.5 (C-2), 78.5 (C-5'), 109.0 (C-2'), 118.3 (CH$_2$ vinyl), 133.7 (CH vinyl), 179.1 (C=O); HRMS (ESI): [M+Na]$^+$ calcd for C$_{14}$H$_{24}$O$_5$Na 295.15159, found 295.15162.

(2R,3S,4S)-2,3,4-Trihydroxyhex-5-enyl pivalate (22). To an ice-cooled solution of acetonide 21a (10.56 g, 38.8 mmol) in acetonitrile (100 mL) was added CuCl$_2$·2H$_2$O (46.0 g, 271.6 mmol) portionwise within 1 h and then the reaction mixture was allowed to warm to room temperature. After being stirred for 12 h at room temperature, inorganic solids were filtered off, and the filter cake washed with acetonitrile (100 mL). The combined filtrates were washed with saturated NH$_4$Cl (3 × 100 mL), dried over Na$_2$SO$_4$, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (petroleum ether/EtOAc, 5:1) to give triol 22 (6.59 g, 73%) as a white amorphous solid. R$_f$ = 0.26 (petroleum ether/ EtOAc, 1:1); $\alpha$$_{20}^D$ = −6.7 (c 1.0, CH$_2$Cl$_2$); $^1$H NMR (400 MHz, CDCl$_3$):

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δ[ppm] = 1.22 (s, 9H, C(CH\textsubscript{3})\textsubscript{3}), 2.54 (br s, 3H, 3 × OH), 3.55 (dd, J = 7.9, 5.3 Hz, 1H, 3-H), 3.84 (ddd, J = 7.6, 4.3, 4.0 Hz, 1H, 2-H), 4.32–4.35 (m, 3H, 1-H, and 4-H), 5.32 (app d, J = 10.6 Hz, 1H, 6-H), 5.41 (app d, J = 17.2 Hz, 1H, 6-H), 5.99 (ddd, J = 17.2, 10.5, 6.7 Hz, 1H, 5-H); \textsuperscript{13}C NMR (150 MHz, CDCl\textsubscript{3}): δ[ppm] = 27.2 (C(CH\textsubscript{3})\textsubscript{3}), 39.0 (C(CH\textsubscript{3})\textsubscript{3}), 66.3 (C-1), 72.4 (C-2), 72.8 (C-3), 74.7 (C-4), 118.3 (C-6), 136.3 (C-5), 179.8 (C=O); HRMS (ESI): [M+Na]\textsuperscript{+} calcd for C\textsubscript{11}H\textsubscript{20}O\textsubscript{5}Na 255.12029, found 255.12023.

((4\textsuperscript{R},5\textsuperscript{S},6\textsuperscript{S})-5-Hydroxy-2-phenyl-6-vinyl-1,3-dioxan-4-yl)methyl pivalate (22a). To a solution of triol 22 (6.59 g, 28.0 mmol) in abs. CH\textsubscript{2}Cl\textsubscript{2} (80 mL) was added CSA (1.29 g, 5.6 mmol) followed by the dropwise addition of benzaldehydedimethylacetal (5.1 mL, 33.6 mmol) at room temperature. After being stirred for 1 h, the reaction mixture was washed with saturated NaHCO\textsubscript{3} (100 mL) and NaCl (100 mL) solutions, dried over MgSO\textsubscript{4}, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (petroleum ether/EtOAc, 5:1) to give hydroxydioxane 22a (8.3 g, 91%) as a colorless oil. R\textsubscript{f} = 0.17 (petroleum ether/EtOAc, 5:1); [α]\textsubscript{20}D = −31.3 (c 0.9, CH\textsubscript{2}Cl\textsubscript{2}); \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): δ[ppm] = 1.23 (s, 9H, C(CH\textsubscript{3})\textsubscript{3}), 3.30 (app t, J = 9.2, 9.2 Hz, 1H, 5-H), 3.84 (ddd, J = 9.3, 4.1, 2.8 Hz, 1H, 4-H), 4.07–4.11 (m, 1H, 6-H), 4.35 (dd, J = 12.1, 2.5 Hz, 1H, CH\textsubscript{2}), 4.56 (dd, J = 12.3, 4.6 Hz, 1H, CH\textsubscript{2}), 5.32 (app d, J = 10.6, 1H, CH\textsubscript{2} vinyl), 5.48 (app d, J = 17.2 Hz, 1H, CH\textsubscript{2} vinyl), 5.63 (s, 1H, CPh), 6.00 (ddd, J = 17.3, 10.4, 6.4, 1H, CH vinyl), 7.34–7.37 (m, 3H, m\textsubscript{CH}, p\textsubscript{CH} ar Ph), 7.48–7.50 (m, 2H, o\textsubscript{CH} ar Ph); \textsuperscript{13}C NMR (150 MHz, CDCl\textsubscript{3}): δ[ppm] = 27.2 (C(CH\textsubscript{3})\textsubscript{3}), 39.0 (C(CH\textsubscript{3})\textsubscript{3}), 63.5 (PivOCH\textsubscript{2}), 66.2 (C-5), 79.4 (C-4), 81.8 (C-6), 100.6 (C-2), 118.9 (CH vinyl), 126.2 (p\textsubscript{CH} ar Ph), 128.2 (o\textsubscript{CH} ar Ph), 129.0 (m\textsubscript{CH} ar Ph), 134.5 (2-CPh), 137.4 (CH\textsubscript{2} vinyl), 179.5 (C=O); HRMS (ESI): [M+Na]\textsuperscript{+} calcd for C\textsubscript{18}H\textsubscript{24}O\textsubscript{5}Na 343.15159, found 343.15164.

((2\textsuperscript{S},4\textsuperscript{R},5\textsuperscript{S},6\textsuperscript{S})-5-(4-Methoxybenzyloxy)-2-phenyl-6-vinyl-1,3-dioxan-4-yl)methyl pivalate (19). To a cooled (−5 °C) suspension of NaH (0.54 g, 13.4 mmol, 60% in mineral oil) in anhydrous DMF (40 mL) was added dropwise a solution of alcohol 22a (1.23 g, 3.8 mmol) in DMF (5 mL) at the same temperature. After complete addition, the reaction mixture was stirred for 1 h at −5 °C before a solution
of freshly prepared PMBBr\(^2\) (1.28 g, 6.4 mmol) in DMF (5 mL) was added. After being stirred for additional 2 h at −5 °C, the reaction was quenched with saturated NH\(_4\)Cl (10 mL) and the product was extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with water, saturated NaCl solution, dried over MgSO\(_4\), filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (petroleum ether/EtOAc, 10:1) to give PMB ether \(19\) (0.97 g, 57%) as a colorless oil. \(R_f = 0.26\) (petroleum ether/EtOAc, 10:1); \([\alpha]^{20}_D = +5.5\) (c 0.8, CH\(_2\)Cl\(_2\)); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 1.26\) (s, 9H, C(CH\(_3\)_3)), 3.40 (app t, \(J = 9.4, 9.4\) Hz, 1H, 5-H), 3.83 (s, 3H, OCH\(_3\)), 3.92 (ddd, \(J = 9.4, 4.6, 2.2\) Hz, 1H, 4-H), 4.21 (dd, \(J = 9.1, 6.6\) Hz, 1H, 6-H), 4.34 (dd, \(J = 12.0, 4.7\) Hz, 1H, CH\(_2\)PMP), 4.41–4.49 (m, 2H, CH\(_2\)PMP, PivOCH\(_3\)), 4.63 (app d, \(J = 10.1\) Hz, 1H, PivOCH\(_2\)), 5.39 (app d, \(J = 10.4\) Hz, 1H, CH\(_2\) vinyl), 5.58 (d, \(J = 10.4\) Hz, 1H, CH\(_2\) vinyl), 5.63 (s, 1H, 2-H), 6.09 (ddd, \(J = 17.3, 10.7, 6.6\) Hz, 1H, CH ar PMB), 6.90–6.92 (m, 2H, mCH ar PMB), 7.25–7.29 (m, 2H, \(m\) CH ar PMB), 7.35–7.39 (m, 3H, \(m\) CH ar Ph), \(13\)C NMR (150 MHz, CDCl\(_3\)): \(\delta = 27.2\) (C(CH\(_3\)_3)), 38.9 (C(CH\(_3\)_3)), 55.3 (OCH\(_3\)), 62.9 (CH\(_2\)PMP), 73.8 (C-5), 74.4 (PivOCH\(_2\)), 78.4 (C-4), 81.6 (C-6), 100.3 (C-2), 114.0 (oCH ar PMB), 118.8 (CH\(_2\) vinyl), 126.2 (oCH ar Ph), 128.2 (mCH ar Ph), 128.9 (pCH ar Ph), 129.4 (CH\(_2\)CH ar PMB), 129.8 (mCH ar PMB), 135.1 (CH vinyl), 137.5 (CCH ar Ph), 159.6 (COCH\(_3\) ar PMB), 178.2 (C=O); HRMS (ESI): [M+Na]\(^+\) calcd for C\(_{26}\)H\(_{32}\)O\(_6\)Na 463.20911, found 463.20878.

\((2S,4R,5S,6S)-6-(\text{R})-4-(\text{tert}-\text{Butyldimethylsilyloxy})\text{pentyl})-5-(4\text{-methoxybenzyloxy})-2\text{-phenyl-1,3-dioxan-4-yl})\text{methyl pivalate (25). Cross-metathesis: Alkene \(19\) (1.76 g, 4.0 mmol) was dissolved in degassed toluene (17.6 mL) and then alkene\(^3\) \(20\) (0.8 g, 4.0 mmol) was added. The reaction mixture was slightly warmed (to around 40–50 °C) and then Grubbs second generation catalyst (170 mg, 5 mol %) was added. The temperature was brought to 80 °C and maintained for 2 h. After that, air was bubbled through the reaction (for approx. 5 min) and the solvent was evaporated in vacuo. The crude product was purified by flash chromatography (petroleum ether/EtOAc, 10:1) to give metathesis product (1.80 g, 74%) as a colorless oil. \(R_f = 0.34\) (petroleum ether/EtOAc, 5:1); \([\alpha]^{20}_D = -9.8\) (c 0.4, 2Khartulyari, A. S.; Kapur, M.; Maier, M. Org. Lett. 2006, 8, 5833.  
Experimental Section

CH₂Cl₂); HRMS (ESI): [M+Na]⁺ calcd for C₃₅H₅₂O₇SiNa 635.35310, found 635.34213. Hydrogenation: Metathesis product, obtained above (1.64 g, 2.67 mmol) was dissolved in abs. EtOAc (5 mL), Pd/C (10% wt) was added and a balloon, filled with hydrogen, was attached through a rubber septum. The reaction mixture was stirred for 5 h at room temperature and then the palladium catalyst was filtered off through a pad of Celite®, which was washed with EtOAc (2 × 10 mL). The filtrate was concentrated in vacuo and the residue purified by flash chromatography (petroleum ether/ EtOAc, 10:1) to give protected polyol 25 (1.60 g, 98%) as colorless oil. Rf = 0.34 (petroleum ether/EtOAc, 5:1); [α]₂⁰°D = −0.1 (c 4.4, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃): δ[ppm] = 0.04 (s, 3H, Si(CH₃)₂), 0.05 (s, 3H, Si(CH₃)₂), 0.88 (s, 9H, SiC(CH₃)₃), 1.13 (d, J = 6.1 Hz, 3H, 4'-CH₃), 1.25 (s, 9H, C(CH₃)₃), 1.39–1.62 (m, 4H, 2 × CH₂), 1.85–1.90 (m, 2H, CH₂), 3.32 (app t, J = 9.1, 9.1 Hz, 1H, 5-H), 3.66 (app td, J = 8.7, 8.7, 2.4 Hz, 1H, 6-H), 3.77–3.80 (m, 4H, OCH₃, 4'-H), 3.86 (ddd, J = 9.4, 4.6, 2.0 Hz, 1H, 1-H), 4.30 (dd, J = 12.1, 4.7 Hz, 1H, PivOCH₂), 4.50–4.57 (m, 3H, PivOCH₂, CH₂PMP), 5.54 (s, 1H, 2-H), 6.88–6.91 (m, 2H, mCH ar PMB), 7.25–7.27 (m, 2H, oCH ar PMB), 7.33–7.36 (m, 3H, mCH, pCH ar Ph), 7.46–7.48 (m, 2H, oCH ar Ph); ¹³C NMR (150 MHz, CDCl₃): δ[ppm] = −4.7, −4.4 (Si(CH₃)₂), 18.1 (SiC(CH₃)₃), 21.3 (CH₂), 23.8 (C-5'), 25.9 (SiC(CH₃)₃), 27.2 (C(CH₃)₃), 32.1 (CH₂), 38.9 (C(CH₃)₃), 39.6 (CH₂), 55.3 (OCH₃), 63.0 (CH₂PMP), 68.5 (C-4'), 74.1 (C-5), 74.7 (PivOCH₂), 78.5 (C-4), 80.4 (C-6), 100.2 (C-2), 114.0 (oCH ar PMB), 126.0 (oCH ar Ph), 128.1 (mCH ar Ph), 128.6 (pCH ar Ph), 129.5 (CHCH₂ ar PMB), 129.7 (mCH ar PMB), 137.8 (CCH ar Ph), 159.6 (COCH₃), 178.2 (C=O); HRMS (ESI): [M+Na]⁺ calcd for C₃₅H₅₄O₇SiNa 637.35310, found 637.35287.

((2S,4R,5S,6S)-6-((R)-4-(tert-Butyldimethylsilyloxy)pentyl)-5-(4-methoxybenzyloxy)-2-phenyl-1,3-dioxan-4-yl)methanol (25a). A solution of pivaloate 25 (1.18 g, 1.92 mmol) in abs. CH₂Cl₂ (15 mL) was cooled to −80 °C and then DIBAL-H (11.52 mL,11.5 mmol, 1 M in hexane) was added over 1 h at the same temperature. The reaction mixture was stirred for an additional 1 h before saturated NH₄Cl (5 mL) was added dropwise and the reaction mixture was allowed to warm to room temperature. The layers were separated and the aqueous layer extracted with CH₂Cl₂ (2 × 10 mL). The combined organic extracts were washed with saturated NaCl solution (20 mL), dried over MgSO₄, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 5:1) to give alcohol 25a (0.82 g, 81%) as a colorless oil. Rf = 0.17 (petroleum ether/EtOAc, 5:1); [α]₂⁰°D = −22.4 (c 1.4, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃): δ[ppm] = 0.04 (s, 6H, Si(CH₃)₂), 0.87 (s, 9H,
Si(CH₃)₃, 1.12 (d, J = 6.1 Hz, 3H, 4′-CH₃), 1.36–1.60 (m, 4H, 2 × CH₂), 1.82–1.88 (m, 2H, CH₂), 1.95 (br s, 1H, OH), 3.38 (app t, J = 9.2 Hz, 1H, 5-H), 3.62–3.66 (m, 1H, 6-H), 3.70–3.73 (ddd, J = 9.2, 4.1, 2.5 Hz, 1H, 4-H), 3.77–3.80 (m, 4H, OCH₃), 3.93–3.96 (m, 1H, HOCH₂), 4.58 (s, CH₂PMP), 5.56 (s, 1H, 2-H), 6.88–6.90 (m, 2H, mCH ar PMB), 7.25–7.28 (m, 2H, oCH ar PMB), 7.34–7.38 (m, 3H, mCH, pCH ar Ph), 7.47–7.49 (m, 2H, oCH ar Ph); ¹³C NMR (150 MHz, CDCl₃): δ[ppm] = −4.7, −4.4 (Si(CH₃)₃), 18.1 (SiC(CH₃)₃), 21.3 (CH₂), 23.8 (C-5′), 25.9 (SiC(CH₃)₃), 32.0, 39.7 (CH₂), 55.3 (OCH₃), 62.2 (CH₂PMP), 68.5 (C-4′), 73.3 (C-5), 74.7 (PivOCH₂), 80.4 (C-4), 80.7 (C-6), 100.3 (C-2), 114.0 (oCH ar PMB), 126.1 (oCH ar Ph), 128.2 (mCH ar Ph), 128.8 (pCH ar Ph), 129.8 (mCH ar PMB), 137.8 (CCH ar Ph), 159.5 (COCH₃); HRMS (ESI): [M+Na]⁺ calcd for C₃₀H₃₅O₃SiNa 553.29559, found 553.29557.

2-((2S,4R,5S,6S)-6-((R)-4-(tert-Butyldimethylsilyloxy)pentyl)-5-(4-methoxybenzyloxy)-2-phenyl-1,3-dioxan-4-yl)acetonitrile (18). To a stirred solution of alcohol 25a (0.54 g, 1.0 mmol) in abs. diethyl ether (3.4 mL) was added PPh₃ (0.59 g, 2.2 mmol) at −5 °C. The mixture was stirred at the same temperature for 15 min before DEAD (0.98 mL, 2.2 mmol) was added dropwise. The reaction mixture became like a white paste. After 20 min acetone cyanohydrine (0.21 mL, 2.2 mmol) was added dropwise and the solids dissolved. The mixture was stirred at −5 °C for 6 h and for additional 12 h at room temperature. After that, the solvent was evaporated and the residue purified by flash chromatography (petroleum ether/EtOAc, 10:1) to give nitrile 18 (0.487 g, 89%) as a colorless oil. Rᵣ = 0.42 (petroleum ether/EtOAC, 5:1); [α]D° = −1.0 (c 1.4, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃): δ[ppm] = 0.03 (s, 3H, Si(CH₃)₂), 0.04 (s, 3H, Si(CH₃)₂), 0.87 (s, 9H, SiC(CH₃)₃), 1.12 (app d, J = 6.1 Hz, 3H, 4′-CH₃), 1.37–1.65 (m, 4H, 2 × CH₂), 1.86–1.88 (m, 2H, CH₂), 2.58 (dd, J = 17.0, 6.4, 1H, NCCH₂), 2.72 (dd, J = 17.1, 6.4 Hz, 1H, NCCH₂) 3.23 (app t, J = 9.2 Hz, 5-H), 3.63–3.68 (m, 1H, 6-H), 3.76–3.85 (m, 5H, OCH₃, 4-H, 4″-H), 4.52 (d, J = 10.9 Hz, 1H, CH₂PMP), 4.68 (d, J = 10.9 Hz, 1H, CH₂PMP), 5.54 (s, 1H, 2-H), 6.89–6.92 (m, 2H, mCH ar PMB), 7.25–7.27 (m, 2H, oCH ar PMB), 7.34–7.35 (m, 3H, mCH, pCH ar Ph), 7.47–7.49 (m, 2H, oCH ar Ph); ¹³C NMR (150 MHz, CDCl₃): δ[ppm] = −4.7, −4.4 (Si(CH₃)₃), 18.1 (SiC(CH₃)₃), 21.3 (NCCH₂), 21.4 (CH₂), 23.8 (C-5′), 25.9 (SiC(CH₃)₃), 32.1, 39.6 (CH₂), 55.3 (OCH₃), 68.4 (C-4′), 75.0 (CH₂PMP), 75.6 (C-6), 76.8 (C-4), 80.6 (C-5), 100.4 (C-2), 114.0 (oCH ar PMB), 116.9 (NC), 126.1 (oCH ar Ph), 128.2 (mCH ar Ph), 128.9 (pCH ar Ph), 129.2 (mCH ar PMB), 129.9 (mCH ar PMB), 137.1 (CCH ar Ph), 159.8 (COCH₃); HRMS (ESI): [M+Na]⁺ calcd for C₃₁H₄₃NO₅SiNa 562.29592, found 562.29624.
2-((2S,4R,5S,6S)-4-Allyl-6-(2-tert-butyldimethylsilyloxypentyl)-5-(4-methoxybenzyloxy)-2-phenyl-1,3-dioxan-4-yl)acetaldehyde (41). A solution of nitrile 18 (0.49 g, 0.90 mmol) in abs. CH₂Cl₂ (10 mL) was cooled to −80 °C followed by slow addition of DIBAL-H (5.4 mL, 1 M in hexane, 5.4 mmol). After being stirred for 1 h at −80 °C, saturated NH₄Cl solution was added and the mixture allowed to warm to room temperature. The organic layer was separated and the aqueous phase extracted with CH₂Cl₂ (2 × 10 mL). The combined organic layers were dried over MgSO₄, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 10:1) to give aldehyde 41 (469 mg, 96%) as a colorless oil. Rᶠ = 0.42 (petroleum ether/EtOAc, 5:1); [α]²⁰_D = −7.8 (c 1.7, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃): δ[ppm] = 0.06 (s, 6H, Si(CH₃)₂), 0.90 (s, 9H, SiC(CH₃)₃), 1.16 (d, J = 6.1 Hz, 3H, 4''-CH₃), 1.41–1.65 (m, 4H, 2 × CH₂), 1.87–1.91 (m, 2H, CH₂), 2.69 (ddd, J = 16.0, 7.6, 2.5 Hz, 1H, 2-H), 2.80 (ddd, J = 16.0, 4.5, 2.2 Hz, 1H, 1'-H), 3.14 (app t, J = 9.2, 9.2 Hz, 1H, 5'-H), 3.61 (m, 1H, 6'-H), 3.80–3.84 (m, 4H, OCH₃, 4''-H), 4.20 (m, 1H, 4'-H), 4.50 (d, J = 10.7 Hz, 1H, CH₂PMP), 4.61 (d, J = 10.7 Hz, 1H, CH₂PMP), 5.59 (s,1H, 2'-H), 6.90–6.92 (m, 2H, m'CH ar PMB), 7.25–7.27 (m, 2H, m'CH ar Ph), 7.34–7.36 (m, 3H, m'CH, p'CH ar PMB), 7.46–7.48 (m, 2H, o'CH ar Ph), 9.82 (app t, J = 2.3 Hz, 2.3 Hz, 1H, 1'-H); ¹³C NMR (150 MHz, CDCl₃): δ[ppm] = −4.7, −4.4 (Si(CH₃)₂), 18.1 (SiC(CH₃)₃), 21.3 (CH₂), 23.8 (4''-CH₃), 25.9 (SiC(CH₃)₃), 32.1 (CH₂), 39.6 (CH₂), 46.3 (C-2), 55.3 (OCH₃), 68.5 (C-4''), 74.7 (CH₂PMP), 75.9 (C-6'), 77.4 (C-5'), 80.8 (C-4'), 100.3 (C-2'), 114.0 (oCH ar PMB), 126.0 (oCH ar Ph), 128.1 (pCH ar Ph), 128.8 (mCH ar Ph), 129.3 (mCH ar PMB), 129.8 (mCH ar PMB), 137.5 (2'-CPh), 159.7 (COCH₃), 200.2 (C-1); HRMS (ESI): [M+Na]^+ calc'd for C₃₂H₅₀O₇SiNa 597.32180, found 597.32221.

(2S,4R,5S,6S)-4-Allyl-6-((R)-2-tert-butyldimethylsilyloxypentyl)-5-(4-methoxybenzyloxy)-2-phenyl-1,3-dioxane (16). To an ice-cooled suspension of PPh₃MeBr (0.36 g, 1.00 mmol) in THF (3
mL) was added KOtBu (0.11 g, 1.00 mmol) in two portions. The resulting yellow mixture was stirred for 15 min at the same temperature and then 0.5 h at room temperature. Then the suspension was recooled (ice/salt bath) before a solution of aldehyde 41 (0.18 g, 0.30 mmol) in THF (1 mL) was added dropwise. The mixture was allowed to warm slowly to room temperature (ca. 2 h). After that, water (2 mL) was added, the organic layer was separated and the aqueous phase extracted with Et₂O (2 × 5 mL). The combined organic layers were washed with saturated NaCl solution, dried over MgSO₄, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 20:1) to give alkene 16 (135 mg, 75%) as a colorless oil. Rₙ = 0.65 (petroleum ether/EtOAc, 5:1); [α]₂₀⁰_D = −14.3 (c 0.4, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃): δ[ppm] = 0.04 (s, 6H, Si(CH₃)₂), 0.88 (s, 9H, SiC(CH₃)₃), 1.13 (d, J = 6.1 Hz, 3H, 2'-CH₃), 1.35–1.41 (m, 1H, CH₂), 1.49–1.59 (m, 4H, CH₂), 1.83–1.86 (m, 1H, CH₂), 2.39–2.49 (m, 1H, CH₂), 2.65–2.69 (m, 1H, CH₂), 3.10 (m, 1H, 5-H), 3.55–3.81 (m, 6H, OCH₃, 4-H, 6-H, 2'-H), 4.58 (dd, J = 15.8, 10.7 Hz, 2H, CH₂PMP), 5.11–5.19 (m, 2H, CH₂=CH), 5.51 (s, 1H, 2-H), 5.96–6.06 (dddd, J = 17.0, 10.1, 6.9, 6.9 Hz, 1H, CH₂=CH₂), 6.89–6.91 (m, 2H, mCH ar PMB), 7.25–7.28 (m, 2H, oCH ar PMB), 7.31–7.36 (m, 3H, mCH, pCH ar Ph), 7.48–7.49 (m, 2H, oCH ar Ph); ¹³C NMR (150 MHz, CDCl₃): δ[ppm] = –4.7, –4.4 (Si(CH₃)₂), 18.1 (SiC(CH₃)₃), 21.4 (CH₂), 23.8 (2'-CH₃), 25.9 (SiC(CH₃)₃), 32.2 (CH₂), 36.4 (CH₂ allyl), 39.7 (CH₂), 55.3 (OCH₃), 68.6 (C-2'), 74.9 (CH₂PMP), 77.8 (C-4), 80.0 (C-6), 80.4 (C-5), 100.0 (C-2), 113.9 (oCH ar PMB), 117.1 (CH₂=CH), 126.0 (oCH ar Ph), 128.0 (pCH ar Ph), 128.5 (mCH ar Ph), 129.6 (mCH ar PMB), 129.9 (CH₂CH ar PMB), 134.6 (CH₂=CH), 138.2 (2-CPh), 159.5 (COCH₃); HRMS (ESI): [M+Na]⁺ calcd for C₃₂H₄₈O₅SiNa 563.31632, found 563.33628.

(R)-5-((2S,4S,5S,6R)-6-Allyl-5-(4-methoxybenzyl oxy)-2-phenyl-1,3-dioxan-4-yl)pentan-2-ol (26). A plastic test tube was charged with silyl ether 16 (0.11 g, 0.20 mmol) and abs. THF (15 mL). The solution was cooled to –30 °C and then HF-pyridine complex (1.8 mL, 70% HF) was added dropwise. The reaction mixture was allowed to warm to –15 °C and stirred overnight at this temperature. Then the mixture was partitioned between an ice-cooled mixture of EtOAc (10 mL) and saturated NaHCO₃ solution (20 mL). The organic layer was separated and aqueous phase extracted with EtOAc (2 × 10 mL). The combined organic layers were dried over MgSO₄, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 1:1) to give alcohol 26 (87 mg, quant.) as a colorless oil. Rₙ = 0.43 (petroleum ether/EtOAc, 1:5); [α]₂₀⁰_D = −22.1 (c 4.0, CH₂Cl₂); ¹H
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NMR (400 MHz, CDCl₃): δ[ppm] = 1.18 (d, J = 6.1 Hz, 3H, 2-CH₃), 1.40–1.63 (m, 6H, 3 × CH₂), 1.85–1.89 (m, 1H, CH₂), 2.40–2.47 (m, 1H, CH₂), 2.65–2.69 (m, 1H, OH), 3.11 (app t, J = 9.2, 9.2 Hz, 1H, 5’-H), 3.61–3.81 (m, 6H, OCH₃, 6’-H, 2-H, 4’-H), 4.58 (dd, J = 20.8, 10.4 Hz, 2H, CH₂PMP), 5.11–5.19 (m, 2H, CH₂=CH), 5.51 (s, 1H, 2’-H), 5.96–6.06 (dddd, J = 17.0, 10.1, 6.9, 6.9 Hz, 1H, CH₂=CH), 6.89–6.91 (m, 2H, mCH ar Ph), 7.25–7.28 (m, 2H, oCH ar Ph), 7.33–7.36 (m, 3H, mCH, pCH ar Ph), 7.48–7.49 (m, 2H, oCH ar Ph); ¹³C NMR (150 MHz, CDCl₃): δ[ppm] = 21.4 (CH₂), 23.5 (C-1), 31.9 (CH₂), 36.3 (CH₂), 39.2 (CH₂), 55.3 (OCH₃), 67.9 (C-2), 74.6 (CH₂PMP), 77.4 (C-6’), 80.0 (C-4’), 80.4 (C-5’), 100.1 (C-2’), 113.9 (oCH ar PMB), 117.2 (CH₂=CH), 126.0 (oCH ar Ph), 128.1 (pCH ar Ph), 128.6 (mCH ar Ph), 129.6 (mCH ar PMB), 134.4 (CH₂=CH), 138.1 (2’-CPh), 159.5 (COCH₃); HRMS (ESI): [M+Na]⁺ calcd for C₂₆H₃₄O₅Na 449.22985, found 449.22978.

3,4,6-Trimethoxy-2-vinylbenzoic acid (17). KOtBu (0.41 g, 3.34 mmol) was added in one portion to a stirred suspension of PPh₃MeBr (1.22 g, 3.34 mmol) in abs. THF (12 mL) at 0 °C. After 0.5 h hydroxyphthalide⁴ 26 (0.10 g, 0.42 mmol) was added in one portion and the mixture was allowed to warm to room temperature. After 2 h, water (2 mL) was added followed by addition of 1N HCl until the pH of the reaction mixture was approx. 2. The organic layers were separated and the aqueous phase extracted with EtOAc (2 × 10 mL). The combined organic extracts were washed with saturated NaCl solution (20 mL), dried over MgSO₄, filtered and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 1:4) to give styrene 17 (76 mg, 76%) as a white crystalline solid. Rf = 0.56 (petroleum ether/EtOAc, 1:4); ¹H NMR (400 MHz, CDCl₃): δ[ppm] = 3.70 (s, 3H, OCH₃), 3.87 (s, 3H, OCH₃), 3.90 (s, 3H, OCH₃), 5.49 (dd, J = 11.7, 1.3 Hz, 1H, CH₂ vinyl), 7.75 (dd, J = 17.8, 1.3 Hz, 1H, CH₂ vinyl), 6.46 (s, 1H, 5-H), 6.84 (dd, J = 17.8, 11.5 Hz, 1H, CH vinyl); ¹³C NMR (150 MHz, CDCl₃): δ[ppm] = 56.0, 56.7, 60.4 (OCH₃), 96.3 (C-5), 113.7 (CH₂ vinyl), 120.4, 130.4 (C aryl), 132.0 (CH vinyl), 141.0, 153.6, 154.8 (C aryl), 171.1 (C=O); HRMS (ESI): [M+Na]⁺ calcd for C₁₂H₁₄O₅Na 261.07390, found 261.07378.

(S)-5-((2S,4S,5S,6R)-6-Allyl-5-(4-methoxybenzyloxy)-2-phenyl-1,3-dioxan-4-yl)pentan-2-yl 3,4,6-trimethoxy-2-vinylbenzoate (29). DEAD (0.064 mL, 0.14 mmol) was added to a solution of styrene 17 (33.6 mg, 0.14 mmol) and alcohol 26 (40.0 mg, 0.09 mmol) in a toluene/EtO mixture (1.5 mL, 2:1) at 0 °C. Then the reaction was allowed to warm to room temperature and stirred for 2 h. Thereafter, the solvents were evaporated and the residue purified by flash chromatography (petroleum ether/EtOAc, 4:1) to give benzoic ester 29 (57.7 mg, 95%) as a white amorphous solid. Rf = 0.61 (petroleum ether/EtOAc, 1:1); [a]D20 = −6.0 (c 2.9, CH2Cl2); 1H NMR (400 MHz, CDCl3): δ[ppm] = 1.29 (d, J = 6.1 Hz, 3H, 2'-CH3), 1.44–1.80 (m, 4H, 2 × CH2), 1.87–1.90 (m, 2H, CH2), 2.38–2.45 (m, 1H, CH2), 2.63–2.67 (m, 1H, CH2), 3.08 (app t, J = 9.2, 9.2 Hz, 1H, 5''-H), 3.59–3.71 (m, 8H, 2 × OCH3, 6''-H, 4''-H), 3.77 (s, 3H, OCH3), 3.84 (s, 3H, OCH3), 4.55 (dd, J = 18.3, 10.7 Hz, CH2PMP), 5.09–5.17 (m, 3H, CH2=CH allyl, 2'-H), 5.39 (m, 1H, CH2=CH vinyl), 5.48 (s, 1H, CHPH), 5.70 (d, J = 17.8 Hz, 1H, CH2=CH vinyl), 5.94–6.04 (m, 1H, H2=C=CH allyl), 6.37 (s, 1H, 5-H), 6.72 (dd, J = 17.8, 11.4 Hz, 1H, CH=CH2 vinyl), 6.85–6.87 (m, 2H, mCH ar PMP), 7.23–7.25 (m, 2H, oCH ar PMP), 7.30–7.32 (m, 3H, mCH, pCH ar Ph), 7.45–7.46 (m, 2H, oCH ar Ph); 13C NMR (150 MHz, CDCl3): δ[ppm] = 19.9 (CH2), 21.2 (C-1'), 31.9 (CH2), 35.9 (CH2), 36.3 (CH2), 55.2 (CH3 of PMB), 56.0 (OCH3), 56.3 (OCH3), 60.4 (OCH3), 71.9 (C-2'), 74.6 (CH2PMP), 77.4 (C-6'''), 80.0 (C-4'''), 80.5 (C-5'''), 96.6 (C-5), 100.1 (C-2'''), 113.9 (oCH ar PMB), 116.1 (C aryl), 117.2 (CH2=CH vinyl), 120.4 (C aryl), 126.1 (oCH ar Ph), 128.0 (mCH ar Ph), 128.5 (pCH ar Ph), 129.6 (mCH ar PMB), 129.8 (CH2CH ar PMB), 130.2 (CH2=CH allyl), 130.4 (CH2=CH allyl), 134.5 (CH2=CH vinyl), 138.1 (2''-CPh), 140.7 (C aryl), 153.0 (C aryl), 153.8 (C aryl), 159.5 (COCH3 ar PMB), 167.4 (C=O); HRMS (ESI): [M+Na]+ calcd for C38H49O9Na 669.30340, found 669.30375.

(2S,6S,8R)-6,8-Dihydroxy-7-oxoundec-10-en-2-yl 3,4,6-trimethoxy-2-vinylbenzoate (31). a) PMB deprotection: To a cooled (0 °C) solution of benzoic ester 29 (57.0 mg, 0.09 mmol) in a mixture of...
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CH₂Cl₂/pH 7 phosphate buffer (2.4 mL, 5:1) was added DDQ (123 mg, 0.54 mmol) in one portion. After being stirred for 3 h at room temperature, the reaction mixture was recooled to 0 °C and saturated NaHCO₃ solution (2 mL) was added dropwise. The organic layer was separated and the aqueous phase extracted with CH₂Cl₂ (2 × 10 mL). The combined organic extracts were washed with saturated NaHCO₃ (5 mL) and NaCl (20 mL) solutions, dried over MgSO₄, filtered, and concentrated in vacuo to give the crude deprotection product (49.5 mg) which was directly introduced to the oxidation step. Rᵣ = 0.55 (petroleum ether/EtOAc, 1:1). Oxidation: A stirred solution of the deprotection product obtained above (49.5 mg, 0.09 mmol) in abs. CH₂Cl₂ (1 mL) was cooled in an ice/salt bath and then a solution of Dess–Martin periodinane (0.40 mL, 0.19 mmol, 15% wt in CH₂Cl₂) was added. The cooling bath was removed and after being stirred for 2 h at room temperature the reaction mixture was concentrated and the residue purified by flash chromatography (petroleum ether/EtOAc, 5:1) to give ketone 30 (47.9 mg, 97%) as a colorless oil which was directly introduced to the next step (acetal cleavage). Rᵣ = 0.58 (petroleum ether/EtOAc, 1:1); [α]²⁰D = +4.1 (c 1.2, CH₂Cl₂); HRMS (ESI): [M+Na]⁺ calcd for C₃₀H₃₆O₈Na 547.23024, found 547.23021. Acetal cleavage: To a solution of ketone 30 obtained above (47.9 mg, 0.09 mmol) in MeOH (1 mL) was added a mixture of conc. HCl/MeOH (1.05 mL, 20:1) dropwise. After 1.5 h dry K₂CO₃ was added until pH = 7 was reached. Then the solids were filtered off, washed with MeOH (5 mL) and the filtrate was then concentrated. The residue was purified by flash chromatography (petroleum ether/EtOAc, 1:1) to give dihydroxy ketone 31 (38.4 mg, 60% over 3 steps) as a colorless oil. Rᵣ = 0.24 (petroleum ether/EtOAc, 1:1); [α]²⁰D = +26.5 (c 0.8, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃): δ[ppm] = 1.29 (d, J = 6.1 Hz, 3H, 2'-CH₃), 1.50–1.70 (m, 4H, 2 × CH₂), 1.78–1.84 (m, 1H, CH₂), 1.96–1.98 (m, 1H, CH₂), 2.32 (ddd, J = 14.5, 7.6, 7.4 Hz, 1H, 9'-H), 2.63–2.69 (m, 1H, 9'-H), 3.68 (s, 6H, 2 × OCH₃), 3.86 (s, 3H, OCH₃), 4.44 (dd, J = 7.5, 4.2 Hz, 1H, 6'-H), 4.49 (dd, J = 7.0, 4.3 Hz, 1H, 8'-H), 5.11–5.20 (m, 3H, 11'-H, 2'-H), 5.43 (dd, J = 11.7, 1.5 Hz, 1H, CH₂ vinyl), 5.70 (dd, J = 17.8, 1.5 Hz, 1H, CH₂ vinyl), 5.72–5.76 (m, 1H, 10'-H), 6.44 (s, 1H, 5'-H), 6.70–6.77 (m, 1H, CH vinyl); ¹³C NMR (150 MHz, CDCl₃): δ[ppm] = 19.9 (C-1'), 20.9, 33.3, 35.5 (CH₂), 38.1 (C-5'), 56.1, 56.5, 60.5 (OCH₃), 71.5 (C-2'), 73.8 (C-8'), 74.7 (C-6'), 96.7 (C-5), 115.9 (CH₂ vinyl), 119.5 (C-11'), 120.5 (C aryl), 130.3 (C-10'), 130.5 (C aryl), 132.7 (CH vinyl), 140.8, 153.0, 154.0 (C aryl), 167.6 (C=O), 213.5 (C-9'); HRMS (ESI): [M+Na]⁺ calcd for C₂₃H₃₂O₈Na 459.19894, found 459.19900.

(2S,6S,8R)-6,8-Bis(tert-butyldimethylsilyloxy)-7-oxoundec-10-en-2-yl 3,4,6-trimethoxy-2-vinylbenzoate (32). A solution of dihydroxy ketone 31 (3.0 mg, 0.007 mmol) in CH₂Cl₂ (0.5 mL) was cooled to −40 °C. Then 2,6-lutidine (0.004 mL, 0.035 mmol) was added followed by addition of TBSOTf
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(0.0064 mL, 0.028 mmol). The temperature was raised to 0 °C and the mixture stirred overnight at 0 °C. After that, the reaction mixture was diluted with water (10 mL) and extracted with CH₂Cl₂ (2 × 5 mL). The combined organic extracts were washed with 1N HCl (10 mL), saturated NaHCO₃ and NaCl solutions, dried over MgSO₄, filtered and concentrated under reduced pressure. The crude ketone 32 (3.9 mg, 86%) was directly introduced into the subsequent RCM reaction. Rₚ = 0.69 (petroleum ether/EtOAc, 1:1).

(2S,6S,7S,8R)-6,8-Dihydroxy-7-(4-methoxybenzyloxy)undec-10-en-2-yl 3,4,6-trimethoxy-2-vinylbenzoate (33). To a solution of benzoic ester 29 (57.7 mg, 0.09 mmol) in MeOH (2 mL) was added a mixture of conc. HCl/MeOH (1.05 mL, 20:1) dropwise. After being stirred overnight, dry K₂CO₃ was added until pH = 7 was reached. Then the solids were filtered off, washed with MeOH (10 mL), and the filtrate concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 1:1) to give diol 33 (33.4 mg, 67%) as a colorless oil. Rₚ = 0.21 (petroleum ether/EtOAc, 1:1); [α]²⁰D = −8.3 (c 1.2, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃): δ[ppm] = 1.29 (d, J = 6.1 Hz, 3H, 2'-CH₃), 1.40–1.70 (m, 6H, 3 × CH₂), 1.98 (br.s, 2H, OH), 2.21–2.29 (m, 1H, 9'-H), 2.55–2.58 (m, 1H, 9'-H), 3.28 (app t, J = 5.8, 5.8 Hz, 1H, 7'-H), 3.69 (s, 3H, OCH₃), 3.79 (s, 6H, 2 × OCH₃), 3.81–3.85 (m, 2H, 6'-H, 8'-H), 3.87 (s, 3H, OCH₃), 4.56 (s, 2H, CH₂PMP), 5.14–5.18 (m, 3H, CH₂11'-H, 2'-H), 5.42 (app d, J = 17.8 Hz, 1H, CH₂ vinyl), 5.71 (app d, J = 17.8 Hz, 1H, CH₂ vinyl), 5.79–5.91 (m, 1H, 10'-H), 6.43 (s, 1H, 5-H), 6.74 (dd, J = 17.8, 11.7 Hz, CH vinyl), 6.86–6.88 (m, 2H, mCH ar PMP), 7.23–7.25 (m, 2H, oCH ar PMP); ¹³C NMR (150 MHz, CDCl₃): δ[ppm] = 19.8 (C-1'), 21.6, 32.6, 35.8 (CH₂), 38.3 (C-5'), 55.3, 56.1, 56.5, 60.4 (OCH₃), 71.7 (C-2'), 71.9 (C-7'), 72.9 (C-6'), 73.7 (C-8'), 83.8 (CH₂PMP), 96.7 (C-5), 113.9 (oCH ar PMB), 116.2 (C aryl), 118.5 (CH₂ vinyl), 120.5 (C aryl), 129.5 (mCH ar PMB), 130.2 (CH₂CH ar PMB), 130.3 (C-11'), 130.5 (C-10'), 134.8 (CH vinyl), 140.8, 153.0, 153.9 (C aryl), 159.4 (COCH₃ ar PMB), 167.5 (C=O); HRMS (ESI): [M+Na]⁺ calcd for C₃₁H₄₂O₉Na 581.27265, found 581.27260.
(2S,6S,7S,8R)-6,8-Bis(tert-butyldimethylsilyloxy)-7-(4-methoxybenzoyloxy)undec-10-en-2-yl 3,4,6-trimethoxy-2-vinylbenzoate (34). To a stirred and cooled (–50 °C) solution of diol 33 (9.6 mg, 0.017 mmol) in CH₂Cl₂ (2 mL), 2,6-lutidine (0.01 mL, 0.086 mmol) was added followed by addition of TBSOTf (0.016 mL, 0.071 mmol). After complete addition, the temperature was raised to 0 °C (approx. within 1 h) and the mixture was stirred overnight. Then water (1 mL) was added and the organic layer was separated. The aqueous phase was extracted with CH₂Cl₂ (2 × 5 mL) and the combined organic extracts were washed with 1N HCl (10 mL), saturated NaHCO₃ and NaCl solutions, dried over MgSO₄, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (petroleum ether/EtOAc, 2:1) to give protected diol 34 (13.5 mg, quant.) as a colorless oil. Rf = 0.75 (petroleum ether/EtOAc, 1:1); [α]₂₀°D = –5.0 (c 0.9, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃): δ[ppm] = 0.01, 0.04, 0.05, 0.06 (4 s, 3H each, Si(CH₃)₂), 0.85–0.89 (m, 18H, 2 × SiC(CH₃)₃), 1.05–1.70 (m, 8H, 3 × CH₂, 2'-CH₃), 2.26–2.29 (m, 1H, 9'-H), 2.42–2.47 (m, 1H, 9'-H), 3.47–3.48 (m, 1H, 7'-H), 3.68 (s, 3H, OCH₃), 3.78 (s, 2 × OCH₃), 3.83–3.86 (m, 5H, 6'-H, 8'H, OCH₃), 4.58–4.70 (dd, J = 17.8, 10.7 Hz, 2H, CH₂PMP), 5.04–5.07 (m, 3H, 12'-H, 2'-H), 5.42 (app d, J = 11.7 Hz, 1H, CH₂ vinyl), 5.71 (app d, J = 17.8 Hz, 1H, CH₂ vinyl), 5.86–5.92 (m, 1H, 10'-H), 6.42 (s, 1H, 5-H), 6.74 (m, 1H, CH vinyl), 6.82–6.84 (m, 2H, oCH ar PMB), 7.23–7.25 (m, 2H, oCH ar PMB); ¹³C NMR (150 MHz, CDCl₃): δ[ppm] = –4.5, –4.2, –4.3, –3.0 (Si(CH₃)₂), 18.0, 19.5 (C-1’), 21.0 (CH₂), 25.7, 25.9, 26.0, 27.0, 27.2, 29.7 (SiC(CH₃)₃), 32.0, 36.4 (CH₂), 37.1 (C-9’), 55.3, 56.1, 56.5, 60.4 (OCH₃), 72.1 (C-7’), 72.4 (C-2’), 72.6 (C-8’), 74.0 (C-6’), 84.5 (CH₂PMP), 96.7 (C-5), 113.7 (oCH ar PMB), 116.2 (C aryl), 117.0 (C-11’), 119.1 (CH₂ vinyl), 120.4 (C aryl), 129.4 (mCH ar PMB), 130.3 (CH₂CH ar PMB), 130.5 (C-11’), 131.3 (C-10’), 135.3 (CH vinyl), 140.8, 153.1, 153.9 (C aryl), 159.0 (COCH₃ ar PMB), 167.4 (C=O); HRMS (ESI): [M+Na]+ calcd for C₄₃H₇₀O₉Si₂Na 810.44561, found 810.44582.

(2S,6S,8R)-6,8-Dihydroxy-7-oxoundec-10-en-2-yl-2,4-dimethoxy-6-vinylbenzoate (35). Nor-methoxy substrate (2,4-dimethoxy-6-vinylbenzoic acid) was prepared in four steps (43% overall yield)
from 2,4-dimethoxy-6-vinylbenzoic acid$^5$ following essentially the same procedures as for dihydroxy ketone 35. Rf = 0.44 (petroleum ether/EtOAc, 1:1); [α]$^D_{20}$ = +35.4 (c 0.9, CH$_2$Cl$_2$); $^1$H NMR (400 MHz, CDCl$_3$): δ[ppm] = 1.33 (d, J = 6.1 Hz, 3H, 2'-CH$_3$), 1.56–1.59 (m, 4H, 2 × CH$_2$), 1.68–1.74 (m, 1H, CH$_2$), 1.97–1.99 (m, 1H, CH$_2$), 2.37–2.45 (m, 1H, 9'-H), 2.64–2.67 (m, 1H, 9'-H), 2.83 (br, 2H, OH), 3.79 (s, 3H, OCH$_3$), 3.82 (s, 3H, OCH$_3$), 4.41–4.44 (m, 1H, 6'-H), 4.49–4.50 (m, 1H, 8'-H), 5.16–5.19 (m, 3H, 11'-H, 2'-H), 5.32 (m, 1H, CH$_2$ vinyl), 5.70 (m, 1H, CH$_2$ vinyl), 5.75–5.80 (m, 1H, 10'-H), 6.39 (s, 1H, H aryl ), 6.63 (m, 1H, H aryl ), 6.72 (m, 1H, CH vinyl); $^{13}$C NMR (150 MHz, CDCl$_3$): δ[ppm] = 20.1 (C-1'), 21.0, 33.3, 35.5 (CH$_2$), 38.1 (C-9'), 55.4, 55.9 (OCH$_3$), 71.5 (C-2'), 73.8 (C-8'), 74.7 (C-6'), 98.3 (C aryl), 101.5 (C aryl), 116.5 (C-11''), 117.1 (C aryl), 119.5 (CH vinyl), 132.7 (C-10'), 133.7 (C aryl), 137.4 (CH$_2$ vinyl), 157.9, 161.4 (C aryl), 167.7 (C=O), 213.5 (C-7'); HRMS (ESI): [M+Na]$^+$ calcd for C$_{22}$H$_{30}$O$_7$Na 429.18893, found 429.18887.

Macrolactone (36). Dihydroxy ketone 35 was dissolved in degassed toluene (4.4 mL, 0.004 M) and then Grubbs $^{2}$nd catalyst (1.49 mg, 10 mol %) was added. The resulting mixture was heated for 1 h at 80 °C. After this time, the solvent was evaporated and the residue purified by flash chromatography (petroleum ether/EtOAc, 1:1) to give macrolactone 36 (1.7 mg, 26%) as a white amorphous paste. Rf = 0.46 (petroleum ether/EtOAc, 1:2); [α]$^D_{20}$ = –8.4 (c 0.12, CH$_2$Cl$_2$); $^1$H NMR (400 MHz, CDCl$_3$): δ[ppm] = 1.32 (d, J = 5.9 Hz, 3H, 17-CH$_3$), 1.47–1.83 (m, 4H, 2 × CH$_2$), 2.02–2.16 (m, 2H, CH$_2$), 2.58–2.65 (m, 1H, 11-H), 3.09–3.12 (m, 2H, 11-CH, 13-CH), 3.79–3.84 (m, 4H, 11-OH, OCH$_3$), 3.92 (s, 3H, OCH$_3$), 4.13–4.17 (m, 1H, 13-H), 4.58–4.60 (m, 1H, 11-H), 5.31–5.38 (m, 1H, 17-H), 5.84 (m, 1H, 9-H), 6.43–6.47 (m, 2H, 4-H, 6-H), 6.65 (m, 1H, 8-H); HRMS (ESI): [M+Na]$^+$ calcd for C$_{20}$H$_{20}$O$_7$Na 401.15762, found 401.15752.

2-((2S,4S,5S,6S)-6-((R)-4-(tert-Butyldimethylsilyloxy)pentyl)-5-(4-methoxybenzyloxy)-2-phenyl-1,3-dioxan-4-yl)ethanol (41a). A solution of aldehyde 41 (107 mg, 0.20 mmol) in a THF/MeOH mixture (3.3 mL, 10:1) was cooled in an ice/salt bath and NaBH₄ (17.1 mg, 0.24 mmol) was added in one portion. The reaction mixture was stirred in an ice bath for 1 h followed by the addition of saturated NH₄Cl solution (5 mL). The mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with saturated NaCl solution, dried over MgSO₄, filtered and concentrated in vacuo. The crude product was purified by flash chromatography (petroleum ether/EtOAc, 5:1) to give alcohol 41a (102 mg, 94%) as a colorless oil. Rᵣ = 0.77 (petroleum ether/EtOAc, 1:1); [α]₂⁰° = −2.3 (c 1.3, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃): δ[ppm] = 0.04 (s, 6H, Si(CH₃)₂), 0.87 (s, 9H, Si(CH₃)₃), 1.12 (d, J = 6.1 Hz, 3H, 4″-CH₃), 1.37–1.47 (m, 2H, CH₂), 1.58–1.73 (m, 2H, CH₂), 1.83–1.91 (m, 2H, CH₂), 2.13–2.18 (dddd, J = 14.4, 5.7, 5.7, 2.9 Hz, 2H, 2-H), 3.12 (app t, J = 9.0, 9.0 Hz, 1H, 5'-H), 3.64 (app td, J = 9.1, 9.1, 2.4 Hz, 1H, 6'-H), 3.77–3.88 (m, 7H, OCH₃, 4″-H, 1-H, 4'-H), 4.53–4.56 (m, 2H, CH₂PMP), 5.53 (s, 1H, 2'-H), 6.88–6.90 (m, 2H, mCH ar PMB), 7.24–7.26 (m, 2H, oCH ar PMB), 7.33–7.36 (m, 3H, mCH, pCH ar Ph), 7.44–7.46 (m, 2H, oCH ar Ph); ¹³C NMR (150 MHz, CDCl₃): δ[ppm] = −4.7, −4.3 (Si(CH₃)₂), 18.1 (Si(CH₃)₃), 21.5 (CH₂), 23.8 (4″-CH₃), 25.9 (Si(CH₃)₃), 32.2 (CH₂), 34.3 (C-2), 39.7 (CH₂), 55.3 (OCH₃), 60.7 (C-1), 68.5 (C-4″), 74.9 (CH₂PMP), 77.8 (C-6′), 80.2 (C-5′), 80.7 (C-4′), 100.2 (C-2′), 114.0 (oCH ar PMB), 125.9 (oCH ar Ph), 128.2 (pCH ar Ph), 128.7 (mCH ar Ph), 129.7 (mCH ar PMB), 137.8 (2′-CPh), 159.6 (COCH₃); HRMS (ESI): HRMS (ESI): [M+Na]⁺ calcd for C₃₁H₄₈O₆SiNa 567.31124, found 567.31077.

(2S,4S,5S,6R)-4-((R)-4-(tert-Butyldimethylsilyloxy)pentyl)-6-(2-iodoethyl)-5-(4-methoxybenzyloxy)-2-phenyl-1,3-dioxane (42). Iodine (407 mg, 1.60 mmol) was added to a cooled solution (ice bath) of PPh₃ (392 mg, 1.49 mmol) and imidazole (131 mg, 1.91 mmol) in abs. CH₂Cl₂ (3 mL). The resulting yellow suspension was stirred for 20 min at the same temperature before a solution of alcohol 41a (584
mg, 1.07 mmol) in abs. CH₂Cl₂ (1 mL) was added. The cooling bath was removed and the resulting yellowish suspension was stirred for additional 12 h at ambient temperature. After that, the CH₂Cl₂ was evaporated and the residue purified by flash chromatography (petroleum ether/EtOAc, 20:1) to give primary iodide 42 (655 mg, 93%) as a slightly yellow oil. R₂ = +19.2 (c 0.9, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃): δ[ppm] = 0.04 (s, 6H, Si(CH₃)₂), 0.88 (s, 9H, SiC(CH₃)₃), 1.13 (d, J = 6.1 Hz, 3H, 1''-CH₃), 1.37–1.47 (m, 4H, 2 × CH₂), 1.48–1.62 (m, 2H, CH₂), 1.67–1.76 (m, 1H, 1''''-H), 1.86–1.93 (m, 1H, 1''-H), 2.02 (ddddd, J = 14.2, 9.4, 7.6, 4.5 Hz, 1H, 2''''-H), 2.37 (ddddd, J = 14.3, 8.6, 8.6, 2.4 Hz, 1H, 2''-H), 3.07 (app t, J = 9.2 Hz, 1H, 5-H), 3.25–3.36 (m, 2H, 6-H, 4-H), 3.77–3.81 (m, 4H, OCH₃, 4'-H), 4.50–4.60 (m, 2H, CH₂PMP), 5.52 (s, 1H, 2-H), 6.89–6.91 (m, 2H, mCH ar PMB), 7.25–7.27 (m, 3H, mCH, pCH ar Ph), 7.46–7.48 (m, 2H, oCH ar Ph); ¹³C NMR (150 MHz, CDCl₃): δ[ppm] = −4.7, −4.3 (Si(CH₃)₂), 1.6 (C-2''), 18.1 (SiC(CH₃)₃), 21.5 (CH₂), 23.8 (C-1'), 25.9 (SiC(CH₃)₃), 32.2 (CH₂), 36.3 (C-1'') 39.7 (CH₂), 55.3 (OCH₃), 68.5 (C-4'), 74.8 (CH₂PMP), 77.6 (C-4), 80.0 (C-5), 80.6 (C-6), 100.0 (C-2), 114.0 (oCH ar PMB), 126.0 (oCH ar Ph), 128.1 (pCH ar Ph), 128.7 (mCH ar Ph), 129.6 (mCH ar PMB), 129.7 (CH₂CH ar PMB), 137.9 (2-CPh), 159.6 (COCH₃); HRMS (ESI): [M+Na]^+ calcd for C₃₁H₄₇IO₅SiNa 677.21297, found 677.21222.

2-(Trimethylsilyl)ethyl-2-((E)-3-((2S,4R,5S,6S)-6-((R)-4-(tert-butylidimethylsilyloxy)pentyl)-5-(4-methoxybenzyl oxy)-2-phenyl-1,3-dioxan-4-yl)prop-1-enyl)-3,4,6-trimethoxybenzoate (43).

**Alkylation:** To a solution of phenylbenzyl selenoether⁶ 47 (65.4 mg, 0.14 mmol) in a THF/HMPA mixture (3.3 mL, 10:1) was added dropwise a preformed solution of LDA (0.22 mmol) in THF (0.54 mL).

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at −80 °C whereby the reaction mixture turned red. After 20 min, a precooled (−40 °C) solution of alkyl iodide 42 (89.2 mg, 0.1 mmol) in abs. THF (0.5 mL) was added slowly and the resulting reaction mixture was stirred for 2 h at −80 °C before saturated NH₄Cl solution (5 mL) was added. The reaction mixture was allowed to warm to room temperature, then the layers were separated and the aqueous phase extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with saturated NaCl solution, dried over MgSO₄, filtered, and concentrated in vacuo to a volume of around 2 mL. This solution was filtered through a short pad of Celite® and the Celite® washed with EtOAc (2 × 10 mL). The combined organic washings were evaporated to give crude alkylation product (118.9 mg), which was directly introduced to the next step. Rₙ = 0.43 (petroleum ether/EtOAc, 3:1). Elimination: The crude alkylation product obtained above (119 mg, 0.1 mmol) was dissolved in abs. THF (2 mL) and H₂O₂ (0.026 mL, 0.25 mmol, 30%) was added at r.t. After being stirred for 2 h, the reaction was quenched with saturated Na₂S₂O₈ solution (2 mL), and the mixture extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with saturated NaCl solution, dried over MgSO₄, filtered, and evaporated. The crude product was purified by flash chromatography (petroleum ether/EtOAc, 8:1) to give styrene 43 (85.5 mg, 75% over 2 steps) as a colorless oil. Rₙ = 0.41 (petroleum ether/EtOAc, 3:1); [α]²⁰°D = +10.4 (c 0.5, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃): δ[ppm] = −0.04 (s, 9H, Si(CH₃)₃), 0.03 (s, 6H, Si(CH₃)₂), 0.87 (s, 9H, Si(CH₃)₃), 1.12 (d, J = 6.1 Hz, 3H, 4''''-CH₃), 1.40–1.88 (m, 8H, 2'-H), 2.53–2.63 (m, 1H, 3''-H), 2.78 (dd, J = 14.8, 7.6 Hz, 1H, 3'''-H), 3.14 (app t, J = 9.2 Hz, 1H, 5''''-H), 3.58–3.62 (m, 4H, OCH₃, 4''''-H), 3.71–3.80 (m, 8H, 2 × OCH₃, 4'''-H, 6'''-H), 3.87 (s, 3H, OCH₃), 4.20–4.35 (m, 2H, 1'-H), 4.56–4.65 (m, 2H, CH₂PMP), 5.49 (s, 1H, 2''''-H), 6.34–6.41 (m, 2H, 2'-H, 5-H), 6.55 (d, J = 16.3 Hz, 1H, 1'-H), 6.87–6.89 (m, 2H, mCH ar PMB), 7.25–7.32 (m, 5H, oCH ar Ph, pCH ar Ph), 7.47–7.49 (m, 2H, oCH ar Ph); ¹³C NMR (150 MHz, CDCl₃): δ[ppm] = −4.7, −4.4 (Si(CH₃)₂), −1.6 (TMS), 17.3 (SiC(CH₃)₃), 18.1 (C-2'), 21.6 (CH₂), 23.8 (4''''-CH₃), 25.9 (SiC(CH₃)₃), 32.8 (CH₂), 36.2 (C-3''), 39.7 (CH₂), 55.3, 56.1, 56.5, 60.4 (OCH₃), 63.5 (C-1'), 68.6 (C-4''''), 74.8 (CH₂PMP), 77.5 (C-6'''), 80.0 (C-5'''), 80.7 (C-4'''), 96.1 (C-5), 100.0 (C-2'''), 113.9 (oCH ar PMB), 116.1 (C aryl), 125.6 (oCH ar Ph), 126.1 (C-2''), 128.0 (pCH ar Ph), 128.4 (mCH ar Ph), 129.5 (mCH ar PMB), 130.0 (CH₂CH ar PMB), 130.5 (C aryl), 132.5 (C-1''), 138.3 (2-CPh), 140.7, 153.1, 153.8 (C aryl), 159.4 (COCH₃ ar PMB), 168.1 (C=O); HRMS (ESI): [M+Na]⁺ calcd for C₄₇H₇₀O₁₀Si₂Na 873.43997, found 873.43955.
**Experimental Section**

2-((E)-3-((2S,4R,5S,6S)-6-((R)-4-hydroxypentyl)-5-(4-methoxybenzyloxy)-2-phenyl-1,3-dioxan-4-yl)prop-1-enyl)-3,4,6-trimethoxybenzoic acid (44). To a cooled (ice bath) solution of ester 43 (85.5 mg, 0.1 mmol) in abs. THF (1.5 mL) was added TBAF (0.6 mL, 0.8 mmol, 1 M in THF) and the mixture was allowed to warm to room temperature. After being stirred overnight, saturated NH₄Cl solution (3 mL) was added to the mixture. The layers were separated and the aqueous phase extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over MgSO₄, filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography (petroleum ether/EtOAc, 1:2) to give hydroxy acid 44 (53.5 mg, 84%) as a white amorphous solid. Rᵣ = 0.68 (petroleum ether/EtOAc, 1:5); [α]²⁰D = +8.0 (c 0.2, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃): δ[ppm] = 1.13 (d, J = 6.1 Hz, 3H, 4‴-CH₃), 1.50–1.82 (m, 6H, 3 × CH₂), 2.63–2.64 (m, 1H, 3'-H), 2.78–2.82 (m, 1H, 3'-H), 3.23–3.27 (app t, J = 9.2, 9.2 Hz, 1H, 5‴-H), 3.62–3.65 (m, 4H, OCH₃, 4‴-H), 3.75–3.81 (m, 8H, 2 × OCH₃, 4″-H, 6″-H), 3.86 (s, 3H, OCH₃), 4.55–4.66 (m, 2H, CH₂PMP), 5.48 (s, 1H, 2″-H), 6.37–6.42 (m, 2H, 5-H, 2'-H), 6.61–6.65 (app d, J = 16.3 Hz, 1″-H), 6.85–6.87 (m, 2H, mCH ar PMB), 7.25–7.33 (m, 5H, mCH, pCH ar Ph, oCH ar PMB), 7.46–7.48 (m, 2H, oCH ar Ph), 8.58 (br s, 1H, CO₂H); ¹³C NMR (150 MHz, CDCl₃): δ[ppm] = 20.8 (CH₂), 23.2 (C-5‴″), 31.5 (CH₂), 35.8 (C-3‴), 38.8 (CH₂), 55.2, 56.0, 56.5, 60.4 (OCH₃), 68.1 (C-4‴″), 74.6 (CH₂PMP), 75.7 (C-6‴″), 79.8 (C-4‴″), 80.6 (C-5‴″), 96.0 (C-5), 100.5 (C-2‴″), 113.9 (oCH ar PMB), 126.2 (C-2‴), 128.1 (pCH ar Ph), 128.6 (mCH ar Ph), 129.5 (mCH ar PMB), 130.1 (CH₂CH ar PMB), 131.1 (C aryl), 132.4 (C-1‴), 138.0 (2″-CPh), 140.6, 153.2, 154.2 (C aryl), 159.3 (COCH₃ ar PMB), 176.8 (C=O); HRMS (ESI): [M+Na]⁺ calcd for C₃₆H₄₄O₁₀Na 659.28267, found 659.28274.

**Macrolactone 45.** To a solution of acid 44 (60.2 mg, 0.095 mmol) in abs. toluene (9.5 mL) was added PPh₃ (55.6 mg, 0.19 mmol) at 0 °C. After being stirred for 15 min at 0 °C, DEAD (0.097 mL, 0.19 mmol)
was added dropwise and the resulting mixture was allowed to warm to room temperature. After 12 h
the toluene was evaporated and the crude material purified by flash chromatography (petroleum ether/
EtOAc, 3:1) to give macrolactone 45 (45.3 mg, 77%) as a colorless oil. R<sub>f</sub> = 0.41 (petroleum ether/EtOAc, 1:1); [α]<sup>20</sup><sub>D</sub> = +52.4 (c 1.3, CH<sub>2</sub>Cl<sub>2</sub>); 1H NMR (400 MHz, CDCl<sub>3</sub>): δ[ppm] = 1.31 (d, J = 6.3 Hz, 3H, 17-CH<sub>3</sub>), 1.54–1.81 (m, 2H, CH<sub>2</sub>), 1.98–2.00 (m, 2H, CH<sub>2</sub>), 2.24–2.30 (m, 2H, CH<sub>2</sub>), 2.67–2.74 (m, 1H, 10-H), 2.80–2.84 (m, 1H, 10-H), 3.69 (s, 3H, OCH<sub>3</sub>), 3.78 (s, 3H, OCH<sub>3</sub>), 3.80–3.85 (m, 4H, OCH<sub>3</sub>, 12-H), 3.88–3.91 (m, 4H, OCH<sub>3</sub>, 13-H), 4.54–4.64 (m, 2H, CH<sub>2</sub>PMP), 5.35–5.39 (m, 1H, 17-H), 5.50 (s, 1H, CHPh), 6.46 (s, 1H, 4-H), 6.53–6.60 (m, 1H, 9-H), 6.66–6.70 (app d, J = 16.7 Hz, 1H, 8-H), 6.82–6.84 (m, 2H, mCH ar PMB), 7.21–7.41 (m, 5H, mCH, pCH ar Ph, oCH ar PMB), 7.64–7.66 (m, 2H, oCH ar Ph); 13C NMR (150 MHz, CDCl<sub>3</sub>): δ[ppm] = 17.9 (C-18), 18.9, 30.0, 34.1 (CH<sub>2</sub>), 36.4 (C-10), 55.2, 56.1, 56.5, 60.5 (OCH<sub>3</sub>), 70.1 (CH<sub>2</sub>PMP), 73.0 (C-17), 73.2 (C-13), 77.8 (C-11), 78.9 (C-12), 96.3 (C-4), 101.3 (CHPh), 113.9 (oCH ar PMB), 116.8 (C aryl), 126.8 (C-9), 127.0 (pCH ar Ph), 128.4 (mCH ar Ph), 129.1, 129.2 (mCH ar PMB), 130.3 (CH<sub>2</sub>CH ar PMB), 132.4 (C-8), 138.5 (CHCPh), 140.6, 153.0, 153.5 (C aryl), 159.3 (COC<sub>2</sub>H ar PMB), 167.9 (C=O); HRMS (ESI): [M+Na]<sup>+</sup> calcd for C<sub>36</sub>H<sub>42</sub>O<sub>9</sub>Na 657.24604, found 657.24650.

Alcohol 45a. Macrolactone 45 (12.7 mg, 0.021 mmol) was dissolved in abs. CH<sub>2</sub>Cl<sub>2</sub> (0.5 mL), then
water was added (0.25 mL) followed by DDQ (5.7 mg, 0.025 mmol). The resulting mixture was stirred
for 1 h at room temperature and then saturated NaHCO<sub>3</sub> solution was added. The layers were
separated and the aqueous layer extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 5 mL). The combined organic extracts
were washed with saturated NaHCO<sub>3</sub> and NaCl solutions (5 mL each), dried over MgSO<sub>4</sub>, and filtered.
The solvent was evaporated and the residue purified by flash chromatography (petroleum ether/EtOAc,
3:1) to give alcohol 45a (6.6 mg, 64%) as a white amorphous solid. R<sub>f</sub> = 0.28 (petroleum ether/EtOAc,
1:1); [α]<sup>20</sup><sub>D</sub> = +55.7 (c 0.6, CH<sub>2</sub>Cl<sub>2</sub>); 1H NMR (400 MHz, CDCl<sub>3</sub>): δ[ppm] = 1.30 (d, J = 6.4 Hz, 3H, 17-CH<sub>3</sub>), 1.50–1.75 (m, 4H, 2 × CH<sub>2</sub>), 2.08–2.22 (m, 2H, CH<sub>2</sub>), 2.64–2.77 (m, 2H, 9-H), 3.71 (s, 3H, OCH<sub>3</sub>), 3.74–3.72 (m, 5H, OCH<sub>3</sub>, 12-H, 13-H), 3.86–3.91 (m, 4H, OCH<sub>3</sub>, 11-H), 5.34–5.38 (m, 1H, 17-H), 5.46 (s, 1H, CHPh), 6.38–6.45 (m, 2H, 4-H, 9-H), 6.69 (d, J = 16.5 Hz, 1H, 8-H), 7.32–7.41 (m, 3H, mCH, pCH ar Ph), 7.65–7.67 (m, 2H, oCH ar Ph); 13C NMR (150 MHz, CDCl<sub>3</sub>): δ[ppm] = 17.2 (C-18), 19.0, 29.4, 34.5 (CH<sub>2</sub>), 35.1 (C-10), 56.1, 56.5, 60.7 (OCH<sub>3</sub>), 62.9 (C-17), 73.6 (C-13), 78.8 (C-11), 79.1 (C-12), 96.4 (C-4), 102.1 (CHPh), 116.8 (C aryl), 126.6 (C-9), 127.0 (pCH ar Ph), 129.1 (mCH ar Ph), 129.7 (pCH ar PMB), 132.0 (C-8), 138.2 (CHCPh), 140.4, 153.1, 153.3 (C aryl), 167.8 (C=O); HRMS (ESI): [M+Na]<sup>+</sup> calcd for C<sub>28</sub>H<sub>34</sub>O<sub>8</sub>Na 521.21459, found 521.21456.
**Ketone 46.** Dess–Martin periodinane (0.063 mL, 0.03 mmol, 15wt % in CH₂Cl₂) was added dropwise to a cooled (ice bath) solution of alcohol 45a (9.8 mg, 0.02 mmol) in abs. CH₂Cl₂ (1 mL). Then the reaction mixture was allowed to warm to room temperature and stirred for additional 2 h. After that, the resulting suspension was loaded directly on a flash column. Elution (petroleum ether/EtOAc, 1:1) gave ketone 46 (9.2 mg, 94%) as a white amorphous solid. Rᵣ = 0.34 (petroleum ether/EtOAc, 1:1); [α]²⁰ₒ = +25.4 (c 0.5, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃): δ[ppm] = 1.28 (d, J = 6.4 Hz, 3H, 17-CH₃), 1.41–1.64 (m, 4H, 2 × CH₂), 1.88–1.93 (m, 1H, CH₂), 2.10–2.14 (m, 1H, CH₂), 2.72–2.80 (m, 1H, 10-H), 3.09–3.15 (m, 1H, 10-H), 3.68 (s, 3H, OCH₃), 3.79 (s, 3H, OCH₃), 3.86 (s, 3H, OCH₃), 4.50–4.55 (m, 2H, 11-H, 13-H), 5.13–5.17 (m, 1H, 17-H), 5.94 (s, 1H, CHPh), 6.30 (app dt, J = 16.1, 7.0, 7.0 Hz, 1H, 9-H), 6.41 (s, 1H, 4-H), 6.47 (d, J = 16.3 Hz, 1H, 8-H), 7.35–7.44 (m, 3H, mCH, pCH ar Ph), 7.62–7.64 (m, 2H, oCH ar Ph); ¹³C NMR (150 MHz, CDCl₃): δ[ppm] = 19.9 (C-18), 20.4, 30.1, 36.4 (CH₂), 36.6 (C-10), 56.1, 56.5, 60.3 (OCH₃), 72.0 (C-17), 81.7 (C-13), 82.8 (C-11), 96.5 (C-4), 99.9 (CHPh), 116.2 (C aryl), 126.5 (C-9), 126.8 (oCH ar Ph), 128.5 (C aryl), 129.1 (mCH ar Ph), 129.3 (pCH ar Ph), 129.5 (C-8), 138.0 (CHCPh), 140.8, 152.7, 153.8 (C aryl), 167.4 (C=O ester), 207.5 (C=O ketone); HRMS (ESI): [M+Na]⁺ calcd for C₂₈H₃₂O₈Na 519.19894, found 519.19936.

**Dihydroxy ketone 1.** Acetal cleavage: Ketone 46 (15.5 mg, 0.03 mmol) was dissolved in MeOH (1 mL) and then a solution of MeOH/HCl conc. (1.05 mL, 20:1) was added dropwise at room temperature. After being stirred for 0.5 h, the solution was neutralized with saturated NaHCO₃ and the mixture extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with saturated NaCl solution, dried with MgSO₄, filtered, and concentrated in vacuo to provide the dihydroxy ketone (8.0 mg) as a yellow oil. The compound was directly introduced to the next step. OMe cleavage: To a solution of crude dihydroxy ketone obtained above (8.0 mg, 0.02 mmol) in abs. CH₂Cl₂ (1 mL) was added BCl₃ (0.08 mL, 0.08 mmol, 1 M sol in CH₂Cl₂) dropwise at −50 °C. After 20 min the reaction was quenched with saturated NaOAc (3 mL). The layers were separated and aqueous phase extracted with
CH$_2$Cl$_2$ (3 × 5 mL). The combined organic extracts were washed with saturated NaCl solution, dried over MgSO$_4$ and the solvent was evaporated. The residue was purified via flash chromatography (CH$_2$Cl$_2$/MeOH, 40:1) to give corresponding dihydroxy acetone 1 (5.2 mg, 43% over 2 steps) as a colorless crystalline solid. R$_f$ = 0.47 (petroleum ether/EtOAc, 1:5); [α]$^{20}_D$ = −41.0 (c 0.5, CH$_2$Cl$_2$), [α]$^{20}_D$ = −51.0 (c 0.1, CH$_3$OH); $^1$H NMR (400 MHz, CDCl$_3$): δ[ppm] = 1.18–1.33 (m, 2H, CH$_2$), 1.37 (d, J = 6.1 Hz, 3H, 17-CH$_3$), 1.45–1.75 (m, 3H, CH$_2$), 2.12–2.20 (m, 1H, CH$_2$), 2.70–2.76 (m, 1H, 9-H), 3.03–3.09 (m, 2H, 9-H, 13-OH), 3.44–3.49 (m, 1H, 11-OH), 3.58 (s, 3H, OCH$_3$), 3.86 (s, 3H, OCH$_3$), 4.36–4.41 (m, 1H, 13-H), 4.60–4.67 (m, 1H, 11-H), 5.00–5.06 (m, 1H, 17-H), 5.84 (dd, J = 15.3, 8.9, 3.3 Hz, 1H, 9-H), 6.40 (s, 1H, 4-H), 6.65 (app d, J = 15.3 Hz, 1H, 8-H), 11.56 (br s, 1H, OH aromatic); $^{13}$C NMR (150 MHz, CDCl$_3$): δ[ppm] = 20.5 (CH$_2$), 20.7 (17-CH$_3$), 32.5, 35.6 (CH$_2$), 37.0 (C-10), 55.9, 60.6 (OCH$_3$), 73.2 (C-17), 73.4 (C-11), 75.0 (C-13), 99.7 (C-4), 103.7 (Caryl), 126.6 (C-9), 127.3 (C-8), 133.5, 140.3, 158.7, 160.9 (Caryl), 170.7 (C=O ester), 213.0 (C=O ketone); HRMS (ESI): HRMS (ESI): [M+Na]$^+$ calcd for C$_{20}$H$_{30}$O$_8$Na 417.15199, found 417.15197.
II. Approach Towards the Total Synthesis of the Macrolide Leiodermatolide

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\begin{align*}
\text{(2R,3R,4S,5S)-1-(\text{tert-Butyldiphenylsilyloxy})-3,5\text{-dimethyl-7-(trimethylsilyl)hept-6-ynyl-2,4-diol}}
\end{align*}
\]

(65). A suspension of Pd(OAc)\(_2\) (0.181 g, 0.810 mmol, 10 mol\%) in abs. THF (50 mL) was cooled to –78 °C. Then finely powdered PPh\(_3\) (0.212 g, 0.810 mmol, 10 mol\%) was added under a slight flow of nitrogen. The resulting yellow solution was stirred for ca. 5 min. In separate flasks solutions of (R)-mesylate\(^7\) 67 (3.58 g, 1.62 mmol) and aldehyde\(^8\) 64 (2.90 g, 8.10 mmol) were prepared (both containing 2.0 mL of abs. THF). Then both were added dropwise to a solution of prepared catalyst at the same time. The resulting yellow solution was stirred for 20 min at –78 °C and then Et\(_2\)Zn (24.4 mL, 2.43 mmol, 1.0M in hexane) was introduced over 30 min. (syringe pump used). After complete addition, the reaction was allowed to warm to –10 °C (the cooling machine was switched off: in ca. 50 min reaction reached –10 °C) and stirred for ca. 2 d (TLC and HPLC monitoring). During this time the color changed to dark brown. Work up was done by dropwise addition of saturated NH\(_4\)Cl solution (ca. 200 mL) directly to the reaction mixture. Then the mixture was warmed to room temperature, the layers were separated, and the aqueous phase extracted with Et\(_2\)O (3 × 50 mL). The combined organic layers were washed with saturated NaCl solution (100 mL) and dried over Na\(_2\)SO\(_4\) containing norite decolorizing charcoal. After filtration and evaporation of solvents the residue was purified by flash chromatography (petroleum ether/EtOAc, 10:1) to give diol 65 (2.38 g, 61%, 73% based on anti isomer) as a colorless oil. R\(_f\) = 0.50 (petroleum ether/EtOAc, 5:1); \([\alpha]^{20}_{D} = -1.4\) (c 6.0, CH\(_2\)Cl\(_2\)); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta[ppm] = 0.17\) (s, 9H, TMS), 0.85 (d, J = 7.1 Hz, 3H, 3-CH\(_3\)), 1.08 (s, 9H, C(CH\(_3\))\(_3\)), 1.14 (d, J = 6.9 Hz, 3H, 5-CH\(_3\)), 1.88–1.91 (m, 1H, 3-H), 2.61–2.66 (m, 2H, 2 × OH), 3.05–3.07 (m, 1H, 5-H), 3.65–3.70 (m, 1H, 6-H), 3.76–3.81 (m, 3H, 2-H, CH\(_2\)), 7.38–7.46 (m, 6H, mCH, pCH ar Ph), 7.67–7.69 m, 4H, oCH ar Ph); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta[ppm] = 0.1\) (TMS), 9.2 (3-CH\(_3\)), 17.2 (5-CH\(_3\)), 19.2 (C(CH\(_3\))\(_3\)), 26.8 (C(CH\(_3\))\(_3\)), 32.0 (C-5), 35.8 (C-3), 65.9 (CH\(_2\)), 73.9 (C-4), 74.4 (C-2), 87.2

\(^7\) For preparation, see: Marshall, J. A.; Yanik, M. M.; Adams, N. D.; Ellis, K. C.; Chobanian, H. R. Org. Synth. 2005, 81, 157. The ee value of (R)-mesylate 67 was determined to be >99%.

\(^8\) Smith, A. B.; Tomioka, T.; Risatti, C. A.; Sperry, J. B.; Sfouggatakis, C. Org. Lett. 2008, 10, 4359. The aldehyde 64 was additionally purified by passing it through a short column of silica (petroleum ether/EtOAc, 9:1).
Experimental Section

(C≡CTMS), 108.5 (C≡CTMS), 127.7, 129.8, 133.1, 135.5 (C of SiPh₂); HRMS (ESI): [M+Na]+ calcd for C₈₂H₄₂O₃Si₂Na 505.25647, found 505.25627.

**((S)-3-((4S,5R,6R)-6-((tert-Butyldiphenylsilyloxy)methyl)-2,2,5-trimethyl-1,3-dioxan-4-yl)but-1-ynyl)trimethylsilane (65a).** To a solution of diol 65 (2.88 g, 5.97 mmol) in a mixture of abs. CH₂Cl₂ (8.0 mL) and 2,2-dimethoxypropane (3.0 mL) was added CSA (0.139 g, 0.60 mmol, 10 mol%) and the resulting solution stirred for 24 h at ambient temperature. After this time, the reaction mixture was diluted with CH₂Cl₂ (30 mL) and shaken with saturated NaHCO₃ solution (10 mL). The layer was extracted with CH₂Cl₂ (15 mL). The combined organic layers were washed with saturated NaCl solution (50 mL), dried over Na₂SO₄, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 40:1) to give acetonide 65a (2.32 g, 82%) as a colorless oil. 

Rf = 0.43 (petroleum ether/EtOAc, 20:1); [α]D = +25.8 (c 8.2, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃): δ [ppm] = 0.13 (s, 9H, TMS), 0.74 (d, J = 6.6 Hz, 3H, 5-CH₃), 1.05–1.06 (m, 12H, C(CH₃)₃, 3-CH₃), 1.37 (s, 6H, 2 × 2'-CH₃), 1.70 (app. ddq, J = 13.6, 11.2, 6.7 Hz, 1H, 5-H), 2.48 (app dq, J = 10.7, 6.7 Hz, 1H, 3-H), 3.37 (dd, J = 6.7, 3.9 Hz, 1H, 4-H), 3.58–3.66 (m, 2H, CH₂, 6-H), 3.71–3.76 (m, 1H, CH₂), 3.35–3.47 (m, 6H, mCH, pCH ar Ph), 7.68–7.70 (m, 4H, oCH ar Ph); ¹³C NMR (100 MHz, CDCl₃): δ [ppm] = 0.2 (TMS), 11.4 (5-CH₃), 16.5 (3-CH₃), 19.3 (C(CH₃)₃), 23.7 (2'-CH₃), 24.9 (2'-'CH₃), 26.8 (C(CH₃)₃), 28.1 (C-3), 34.1 (C-5), 56.9 (CH₂), 72.5 (C-6), 75.9 (C-4), 84.4 (C≡CTMS), 101.1 (C-2'), 109.5 (C≡CTMS), 127.6, 129.6 × 2, 133.6, 133.8, 135.7 (C of SiPh₂); HRMS (ESI): [M+Na]+ calcd for C₃₁H₄₆O₃Si₂Na 545.28777, found 545.288039.

**((4S,5R,6R)-4-((S)-But-3-yn-2-yl)-6-((tert-butyldiphenylsilyloxy)-2,2,5-trimethyl-1,3-dioxane (66).** A solution of acetonide 65a (0.082 g, 0.16 mmol) in dry MeOH (2.0 mL) and K₂CO₃ (0.044 g, 0.32 mmol) was stirred for 12 h at room temperature. Thereafter, the reaction mixture was poured into a separatory funnel containing saturated NH₄Cl (5 mL) solution and Et₂O (10 mL). The water layer was extracted with Et₂O (2 × 20 mL). The combined organic layers were dried over MgSO₄, filtered, and the solvent
Experimental Section

was evaporated to give alkyne 66 (0.069 g, 97%) as a colorless oil. The resulting compound was pure enough to be introduced to the next step. \( R_f = 0.40 \) (petroleum ether/EtOAc, 20:1); \( \left[ \alpha \right]^{20}_D = +19.8 \) (c 2.0, CH\(_2\)Cl\(_2\)); \( \text{\(^1\)H NMR (400 MHz, CDCl}_3\)}: \( \delta [\text{ppm}] = 0.76 \) (d, \( J = 6.8 \) Hz, 3H, 5-CH\(_3\)), 1.06 (s, 9H, C(CH\(_3\))\(_3\)), 1.09 (d, \( J = 6.8 \) Hz, 3H, 2'-CH\(_3\)), 1.38 (s, 6H, 2 × 2-CH\(_3\)), 1.73 (m, 1H, 5-H), 2.03 (d, \( J = 2.0 \) Hz, 1H, 4'-H), 2.50 (m, 1H, 2'-H), 3.38 (dd, \( J = 6.7,4.0 \) Hz, 1H, 4-H), 3.60–3.67 (m, 2H, 6-H, CH\(_2\)), 3.72–3.76 (m, 1H, CH\(_2\)), 7.35–7.44 (m, 6H, mCH, pCH ar Ph), 7.69–7.70 (m, 4H, oCH ar Ph); \( \text{\(^{13}\)C NMR (100 MHz, CDCl}_3\)}: \( \delta [\text{ppm}] = 11.5 \) (5-CH\(_3\)), 16.7 (2'-CH\(_3\)), 19.3 (C(CH\(_3\))\(_3\)), 23.7 (2-CH\(_3\)), 24.9 (2-CH\(_3\)), 26.8 (C(CH\(_3\))\(_3\)), 27.1 (C-5), 34.1 (C-2'), 65.9 (CH\(_2\)), 68.6 (C-3'), 72.3 (C-6), 75.8 (C-4), 86.8 (C-4'), 101.1 (C-2), 127.6, 129.6 × 2, 133.6, 133.7, 135.7 (C of SiPh\(_2\)); HRMS (ESI): \( [M+Na]^+ \) calcd for C\(_{28}\)H\(_{38}\)O\(_3\)SiNa 473.24824, found 473.24794.

![Image](image.png)

\((R)-3-(((4R,5R,6R)-6-((\text{tert-Butyldiphenylsilyloxy})methyl)-2,2,5-trimethyl-1,3-dioxan-4-yl)butan-2-one (68). To a solution of alkyne 66 (2.06 g, 4.60 mmol) in acetone (49 mL), PPTS (1.68 g, 6.90 mmol), Hg(OAc)\(_2\) (0.427 g, 1.38 mmol) and water (0.158 mL, 9.2 mmol) were added. The resulting clear solution was stirred for 18 h at ambient temperature. After this time the mixture was diluted with Et\(_2\)O (ca. 20 mL). White precipitates were removed by filtration through a short pad of silica gel and washed with Et\(_2\)O (2 × 20 mL). The filtrate was concentrated in vacuo, and residue was purified by flash chromatography (petroleum ether/EtOAc, 10:1) to give methyl ketone 68 (1.62 g, 76%) as a colorless oil. \( R_f = 0.30 \) (petroleum ether/EtOAc, 10:1); \( \left[ \alpha \right]^{20}_D = +2.6 \) (c 2.7, CH\(_2\)Cl\(_2\)); \( \text{\(^1\)H NMR (400 MHz, CDCl}_3\)}: \( \delta [\text{ppm}] = 0.77 \) (d, \( J = 6.9 \) Hz, 3H, 3-CH\(_3\)), 0.89 (d, \( J = 6.9 \) Hz, 3H, 5-CH\(_3\)), 1.05 (s, 9H, C(CH\(_3\))\(_3\)), 1.24 (s, 3H, 2'-CH\(_3\)), 1.28 (s, 3H, 2'-CH\(_3\)), 1.72 (app. td, \( J = 6.9,6.9,4.5 \) Hz, 1H, 5-H), 2.14 (s, 3H, 2-CH\(_3\)), 2.67 (app. dq, \( J = 10.9,6.9,6.9 \) Hz, 1H, 3-H), 3.37 (app. td \( J = 6.7,6.7,4.1 \) Hz, 1H, 6-H), 3.70 (m, 2H, CH\(_2\)OTBDPS), 3.83 (dd, \( J = 10.7,4.3 \) Hz, 1H, 4-H), 7.35–7.43 (m, 6H, mCH, pCH ar Ph), 7.68–7.69 (m, 4H, oCH ar Ph); \( \text{\(^{13}\)C NMR (100 MHz, CDCl}_3\)}: \( \delta [\text{ppm}] = 11.8 \) (5-CH\(_3\)), 12.3 (3-CH\(_3\)), 19.3 (C(CH\(_3\))\(_3\)), 23.6 (2'-CH\(_3\)), 24.9 (2'-CH\(_3\)), 26.8 (C(CH\(_3\))\(_3\)), 30.2 (2-CH\(_3\)), 33.4 (C-5), 46.6 (C-3), 65.9 (CH\(_2\)), 71.2 (C-6), 75.8 (C-4), 100.7 (C-2'), 127.6, 129.6 × 2, 133.6, 133.7, 135.7 (C of SiPh\(_2\)); HRMS (ESI): \( [M+Na]^+ \) calcd for C\(_{28}\)H\(_{40}\)O\(_4\)SiNa 491.25881, found 491.258623.
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(\(R\))-4-((4R,5R,6R)-6-((tert-Butyldiphenylsilyloxy)methyl)-2,2,5-trimethyl-1,3-dioxan-4-yl)-3-methylpent-1-en-3-ol (71). Ketone 68 (27.3 mg, 0.058 mmol) was dissolved in abs. THF (1.0 mL), cooled to \(-78^\circ\)C and then vinyl magnesium bromide (0.47 mL, 0.47 mmol, 1.0 M in THF) was added dropwise. The cooling bath was removed and the reaction mixture in ca. 30 min. reached room temperature. Saturated NH\(\text{4}\)Cl solution (0.5 mL) was introduced followed by dilution with Et\(\text{2}\)O (10 mL). The layers were separated and the aqueous phase extracted with Et\(\text{2}\)O (2 × 5 mL). After drying and evaporating the solvent, the residue was purified by flash chromatography (petroleum ether/EtOAc, 15:1) to give alcohol 71 (18.9 mg, 65%). \(R_f\) = 0.29 (petroleum ether/EtOAc, 10:1); \([\alpha]^{20}_{D} = +42.5\) (c 1.0, CH\(\text{2}\)Cl); \(^1\)H NMR (400 MHz, CDCl\(\text{3}\)): \(\delta\) [ppm] = 0.75 (d, \(J\) = 6.9 Hz, 3H, 1-H), 0.80 (d, \(J\) = 6.9 Hz, 3H, 5′-CH\(\text{3}\)), 1.04 (s, 9H, C(CH\(\text{3}\))\(\text{3}\)), 1.19 (s, 3H, 3-CH\(\text{3}\)), 1.33 (s, 6H, 2 ×2′-CH\(\text{3}\)), 1.71 (app. tq, \(J\) = 6.9, 3.4, 3.4, 3.4 Hz, 1H, 5′-H), 1.83 (app. dq, \(J\) = 10.8, 7.0, 7.0 Hz, 1H, 2-H), 3.40 (app. td, \(J\) = 6.6, 6.6, 3.8 Hz, 1H, 6′-H), 3.61–3.72 (m, 3H, CH\(\text{2}\)OTBDPS, 4′-H), 4.94 (s, 1H, OH), 5.13 (dd, \(J\) = 10.7, 1.8 Hz, 1H, 5-H), 5.36 (dd, \(J\) = 10.7, 1.8 Hz, 1H, 5-H), 5.97 (dd, \(J\) = 17.0, 10.7 Hz, 1H, 4-H), 7.34–7.43 (m, 6H, mCH, pCH ar Ph), 7.66–7.69 (m, 4H, oCH ar Ph); \(^{13}\)C NMR (100 MHz, CDCl\(\text{3}\)): \(\delta\) [ppm] = 12.0 (2-CH\(\text{3}\), 5′-CH\(\text{3}\)), 19.2 (C(CH\(\text{3}\))\(\text{3}\)), 23.9 (2′-CH\(\text{3}\)), 26.4 (2′-CH\(\text{3}\)), 26.8 (C(CH\(\text{3}\))\(\text{3}\)), 28.0 (3-CH\(\text{3}\)), 34.0 (C-5′), 42.2 (C-2), 65.9 (CH\(\text{2}\)OTBDPS), 73.2 (C-4′), 76.0 (C-6′), 76.2 (C-3), 101.1 (C-2′), 113.9 (C-5), 127.6, 127.7, 129.6, 129.7, 133.6, 133.7, 135.6, 135.7 (C of SiPh\(\text{2}\)), 140.7 (C-4). \([\text{M+Na}]^+\) calcd for C\(_{39}\)H\(_{44}\)O\(_4\)SiNa 519.29011, found 519.290362.

((4R,5R,6S)-2,2,5-Trimethyl-6-((S)-3-methylbut-3-en-2-yl)-1,3-dioxan-4-yl)methanol (77). Tebbe olefination: A solution of ketone 68 (0.577 g, 1.2 mmol) in abs. THF (4.0 mL) was cooled to \(-40^\circ\)C. Then a solution of Tebbe reagent\(^9\) (6.70 mL, 4.8 mmol, 1.0 M in PhCH\(\text{3}\)) was added dropwise. After complete addition (ca. 20 min), the cooling bath was removed and stirring continued for additional 1 h. The reaction mixture was diluted with Et\(\text{2}\)O (10 mL), and then 1\(\text{N}\) NaOH (ca. 2 mL) was added very

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slowly, followed by anhydrous Na$_2$SO$_4$ (for drying). The resulting suspension was transferred on a wet silica column (ca. 10 cm long) and eluted with a petroleum ether/EtOAc mixture (40:1) to give Tebbe olefination product (0.527 g, 92%, R$_f$ = 0.28, petroleum ether/EtOAc, 40:1), which was pure enough to be introduced to the next step. Deprotection: To cooled solution (ice/salt bath) of foregoing silyl ether in abs. THF (5 mL) was added TBAF·3H$_2$O was added in one portion followed by stirring for 12 h. Saturated NH$_4$Cl solution was added, layers were separated, and the aqueous phase extracted with EtOAc (3 × 5 mL). The combined organics layers were washed with saturated NaCl solution, dried over MgSO$_4$, filtered, and the filtrate concentrated in vacuo. The residue was purified via flash chromatography (petroleum ether/EtOAc, 5:1) to give alcohol 77 (0.30 g, 85%, 78% over 2 steps). R$_f$ = 0.24 (petroleum ether/EtOAc, 5:1); [$\alpha$]$^2_0$ = +16.3 (c 1.3, CH$_2$Cl$_2$); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$[ppm] = 0.89 (d, $J$ = 2.3 Hz, 3H, 2'-CH$_3$), 0.91 (d, $J$ = 2.3 Hz, 3H, 5-CH$_3$), 1.28 (s, 3H, 2-CH$_3$), 1.32 (s, 3H, 2-CH$_3$), 1.68 (s, 3H, 3'-CH$_3$), 1.76 (m, 1H, 2'-H), 2.17 (br. s, 1H, OH), 2.29 (m, 1H, 5-H), 3.38 (ddd, $J$ = 7.3, 7.3, 2.9 Hz, 1H, 4-H), 3.53–3.66 (m, 3H, CH$_2$, 6-H), 4.72 (d, $J$ = 9.1 Hz, 2H, 3'=CH$_2$); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$[ppm] = 11.8 (5-CH$_3$), 16.0 (C-1'), 19.3 (3'-CH$_3$), 23.9 (2-CH$_3$), 25.1 (2-CH$_3$), 33.5 (C-2'), 41.0 (C-5), 64.4 (CH$_2$), 71.3 (C-4), 75.8 (C-6), 100.9 (C-2), 110.6 (3'=CH$_2$), 148.1 (C-3'); HRMS (ESI): [M+Na]$^+$ calcd for C$_{13}$H$_{24}$O$_3$Na 251.32822, found 251.32856.

(4R,5R,6S)-4-Ethynyl-2,2,5-trimethyl-6-((S)-3-methylbut-3-en-2-yl)-1,3-dioxane (75). Oxidation: To a cooled solution (ice/salt bath) of alcohol 77 (0.290 g, 1.27 mmol) in abs. CH$_2$Cl$_2$ (2.0 mL) were added solid NaHCO$_3$ (0.640 g, 7.62 mmol) and Dess-Martin periodinane (0.638 g, 1.52 mmol) were added. After being stirred for 20 min, the cooling bath was removed and the mixture stirred for additional 2 h. After this time, resulting suspension was transferred to a baker, which already contained mixture of saturated solutions of Na$_2$S$_2$O$_3$ and NaHCO$_3$ (1:1, 5 mL). The mixture was stirred for 10 min and then extracted with CH$_2$Cl$_2$ (3 × 10 mL). The combined organic layers were washed with saturated NaCl solution, dried with Na$_2$SO$_4$, filtered, and evaporated to give corresponding aldehyde and white solids, which were removed by filtration through a cotton plug and washing with Et$_2$O (ca. 3 mL). R$_f$ = 0.57 (petroleum ether/EtOAc, 5:1). Alkynylation: To a solution of foregoing aldehyde in MeOH (5 mL) obtained above, was added diethyl-1-diazo-2-oxopropylphosphonate$^{10}$ (0.620 g, 2.54 mmol) and K$_2$CO$_3$ (0.701 g, 5.01 mmol). The resulting yellow solution was stirred for 6 h at room temperature. The

reaction mixture was diluted with Et<sub>2</sub>O (20 mL) and washed with an aqueous 5% NaHCO<sub>3</sub> solution. The layers were separated and the organic layer was washed with saturated NaCl solution and dried over Na<sub>2</sub>SO<sub>4</sub>. After filtration and evaporation of the solvent, the residue was purified via flash chromatography (petroleum ether/EtOAc, 80:1) to give alkyne 75 (0.113 g, 40% over 2 steps) as a colorless oil. R<sub>t</sub> = 0.52 (petroleum ether/EtOAc, 40:1); [α]<sup>20</sup><sub>D</sub> = +6.4 (c 1.1, CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ [ppm] = 0.93 (d, <sup>J</sup> = 7.1 Hz, 3H, 2'-CH<sub>3</sub>), 1.07 (d, <sup>J</sup> = 7.1 Hz, 3H, 5-CH<sub>3</sub>), 1.33 (s, 3H, 2-CH<sub>3</sub>), 1.53 (s, 3H, 2-CH<sub>3</sub>), 1.70 (s, 3H, 3'-CH<sub>3</sub>), 1.92 (app. qt, <sup>J</sup> = 6.9, 6.9, 6.9, 3.7, 3.5 Hz, 1H, 5-H), 2.29 (app. dq, <sup>J</sup> = 10.3, 7.0, 7.0 Hz, 1H, 2'-H), 2.50 (d, <sup>J</sup> = 2.5 Hz, 1H, C≡CH), 4.01 (dd, <sup>J</sup> = 10.4, 3.0 Hz, 1H, 6-H), 4.33 (dd, <sup>J</sup> = 3.9, 2.4 Hz, 1H, 4-H), 4.74 (d, <sup>J</sup> = 6.3 Hz, 2H, 3'-CH<sub>2</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ [ppm] = 11.3 (5-CH<sub>3</sub>), 15.6 (C-1'), 19.2 (C-4'), 23.2 (2-CH<sub>3</sub>), 28.2 (2-CH<sub>3</sub>), 36.5 (C-6), 41.8 (C-2'), 66.9 (C-4), 70.1 (C-5), 73.8 (C≡CH), 84.4 (C≡CH), 100.8 (C-2), 110.8 (3'=CH<sub>2</sub>), 147.9 (C-3'); HRMS (ESI): [M+Na]<sup>+</sup> calcd for C<sub>14</sub>H<sub>22</sub>O<sub>2</sub>Na 245.31308, found 245.31315.

(3S,4S,E)-7-(4-Methoxybenzyloxy)-3,5-dimethyl-1-(trimethylsilyl)hept-5-en-1-yn-4-ol (79). A suspension of Pd(OAc)<sub>2</sub> (0.072 g, 0.32 mmol, 5 mol%) in abs. THF (40 mL) was cooled to –78 °C. Then finely powdered PPh<sub>3</sub> (0.085 g, 0.32 mmol, 5 mol%) was added under a slight flow of nitrogen. The resulting yellow solution was stirred for ca. 5 min. In separate flasks solutions of (R)-mesylate 67 (2.13 g, 9.67 mmol) and aldehyde<sup>11</sup> 78 (1.42 g, 6.45 mmol) were prepared (both containing 1.5 mL of abs. THF). Then both were added dropwise to a solution of prepared catalyst at the same time. The yellow solution was stirred for 20 min at –78 °C before Et<sub>2</sub>Zn (19.4 mL, 19.3 mmol, 1.0 M in hexane) was introduced over 30 min using syringe pump. After complete addition, the reaction was allowed to warm to –5 °C (the cooling machine was switched off: within ca. 50 min reaction mixture reached –5 °C) and stirred for ca. 1 d (TLC and HPLC monitoring). During this time color changed to dark brown. For work-up saturated NH<sub>4</sub>Cl solution (ca. 100 mL) was added dropwise directly to the reaction mixture. After the mixture was warmed to room temperature, the layers were separated and the aqueous phase extracted with Et<sub>2</sub>O (3 × 30 mL). The combined organic layers were washed with saturated NaCl solution and dried over Na<sub>2</sub>SO<sub>4</sub> containing norite decolorizing charcoal. After filtration and evaporation of solvents, the residue was purified by flash chromatography (petroleum ether/EtOAc,

5:1) to give alcohol 79 (1.30 g, 58%) as a colorless oil. $R_f = 0.36$ (petroleum ether/EtOAc, 5:1); $[\alpha]_{D}^{20} = +10.6$ (c 3.4, CH$_2$Cl$_2$); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$[ppm] = 0.15 (s, 9H, TMS), 1.10 (d, $J = 7.1$ Hz, 3H, 3-CH$_3$), 1.61 (s, 3H, 5-CH$_3$), 2.67 (dq, $J = 7.2$, 7.0 Hz, 1H, 3-H), 3.79–3.80 (m, 4H, 4-H, OCH$_3$), 4.05 (d, $J = 6.4$ Hz, 2H, CH$_2$OPMB), 4.43 (s, 2H, CH$_2$PMP), 5.64 (dd, $J = 6.2$, 6.2 Hz, 1H, 6-H), 6.86 (d, $J = 8.7$ Hz, 2H, mCH ar Ph), 7.23 (d, $J = 8.7$ Hz, 2H, oCH ar Ph); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$[ppm] = –0.1 (TMS), 11.7 (5-CH$_3$), 17.5 (3-CH$_3$), 32.5 (C-3), 55.2 (OCH$_3$), 65.9 (C-7), 71.8 (CH$_2$PMP), 80.0 (C-4), 87.7 (C-1), 107.6 (C-2), 113.7 (oCH ar PMB), 125.6 (C-6), 129.3 (mCH ar PMB), 130.3 (C(2)H ar PMB), 137.8 (C-5), 159.2 (COCH$_3$); HRMS (ESI): [M+K]$^+$ calcd for C$_{20}$H$_{30}$O$_3$SiK 385.15958, found 385.18061.

(R)-((3S,4S,E)-7-(4-Methoxybenzoyloxy)-3,5-dimethyl-1-(trimethylsilyl)hept-5-en-1-yn-4-yl) 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (82). To a solution of alcohol 79 (50.0 mg, 0.14 mmol) in abs. CH$_2$Cl$_2$ (1 mL) were added (R)-Mosher acid (43.6 mg, 0.21 mmol), DCC (55.0 mg, 0.24 mmol) and DMAP (few crystals). After 1 h, the reaction mixture was concentrated and the residue was purified by flash chromatography (petroleum ether/EtOAc, 10:1) to yield Mosher ester 82 (61 mg, 70%) as a colorless oil. $R_f = 0.53$ (petroleum ether/EtOAc, 5:1); $[\alpha]_{D}^{20} = +57.1$ (c 5.1, CH$_2$Cl$_2$); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$[ppm] = 0.05 (s, 9H, TMS), 1.06 (d, $J = 7.1$ Hz, 3H, 3'-CH$_3$), 1.31 (s, 3H, 5'-CH$_3$), 2.73–2.82 (m, 1H, 3'-H), 3.62 (s, 3H, 2-OCH$_3$), 3.75 (s, 3H, OCH$_3$ ar PMB), 3.96 (d, $J = 6.4$ Hz, 2H, 7'-H), 4.35 (s, 2H, CH$_2$PMP), 5.26 (d, $J = 8.7$ Hz, 1H, 4'-H), 5.70 (t, $J = 6.0$ Hz, 1H, 6'-H), 6.82–6.84 (m, 2H, ar-H), 7.19–7.21 (m, 2H, ar-H), 7.25–7.32 (m, 5H, ar-H), 7.47–7.49 (m, 2H, ar-H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$[ppm] = –0.1 (TMS), 11.8 (5'-CH$_3$), 17.5 (3'-CH$_3$), 39.6 (C-3'), 55.2 (OCH$_3$), 56.0 (OCH$_3$), 65.4 (C-3'), 71.7 (CH$_2$PMP), 83.1 (C-2), 83.7 (C-1'), 84.4, 84.6 (C-2), 86.5 (C-4'), 107.4 (C-2'), 113.8 (C ary), 127.2 (C-6'), 128.2 (C ary), 128.3 (CF$_3$) 129.2, 129.4 (C=O ary), 130.1 (CF$_3$), 132.4, 133.4, 159.2 (C)=O ary), 165.4 (C=O ester).
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(3S,4S,E)-4-tert-Butyldimethylsilyloxy-7-(4-methoxybenzoyloxy)-3,5-dimethylhept-5-en-1-ynyl)trimethylsilane (80). Alcohol 79 (1.12 g, 3.23 mmol) was dissolved in abs. CH₂Cl₂ (15 mL) and cooled to −50 °C. 2,6-Lutidine (1.12 mL, 9.7 mmol) was added followed by TBSOTf (0.97 mL, 4.2 mmol). The cooling bath was removed and the mixture was allowed to stir overnight. Then it was diluted with water and extracted with CH₂Cl₂ (3 × 10 mL). The combined organic extracts were washed with 1N HCl solution, saturated solutions of NaHCO₃ (20 mL) and NaCl (20 mL), dried over MgSO₄, filtered, and concentrated at reduced pressure. Flash chromatography (petroleum ether/EtOAc, 20:1) of the residue gave silyl ether 80 (1.04 g, 70%) as a colorless oil. Rf = 0.51 (petroleum ether/EtOAc, 10:1); [α]20D = +9.9 (c 9.1, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃): δ[ppm] = 0.01 (s, 3H, Si(CH₃)₂tBu), 0.09 (s, 3H, Si(CH₃)₂tBu), 0.12 (s, 9H, TMS), 0.89 (s, 9H, tBu), 1.00 (d, J = 7.1 Hz, 3H, 3-CH₃), 1.56 (s, 3H, 5-CH₃), 2.57 (m, 1H, 3-H), 3.80 (s, 3H, OCH₃), 3.88 (d, J = 8.1 Hz, 1H, 4-H), 4.03 (d, J = 4.0 Hz, 2H, CH₂OPMB), 4.41 (s, 2H, CH₂PMP), 5.52 (dd, J = 6.1, 6.1 Hz, 1H, 6-H), 6.87 (d, J = 8.7 Hz, 2H, mCH ar Ph), 7.24 (d, J = 8.7 Hz, 2H, oCH ar Ph); ¹³C NMR (100 MHz, CDCl₃): δ[ppm] = −4.8 (Si(CH₃)₂tBu), −4.7 (Si(CH₃)₂tBu), 0.2 (TMS), 11.4 (5-CH₃), 17.7 (3-CH₃), 18.3 (C(CH₃)₃), 25.9 (C(CH₃)₃), 32.8 (C-3), 55.3 (OCH₃), 65.9 (C-7), 71.5 (CH₂OPMB), 81.6 (C-4), 84.8 (C-1), 110.4 (C-2), 113.8 (oCH ar PMB), 125.0 (C-6), 129.3 (mCH ar PMB), 130.5 (CCH₂ ar PMB), 139.2 (C-5), 159.1 (COCH₃); HRMS (ESI): [M+H]+ calcd for C₂₆H₄₅O₃Si₂ 461.29017, found 461.19662.

1-(((2E,4S,5S,6Z)-4-tert-Butyldimethylsilyloxy-7-iodo-3,5-dimethylhepta-2,6-dienyloxy)methyl)-4-methoxybenzene (54). To a solution of silyl acetylene 80 (0.627 g, 1.36 mmol) in dry DMF (2 mL) were added NIS (0.470 g, 1.92 mmol) and AgNO₃ (0.054 g, 0.32 mmol). The resulting solution was protected from light and stirred for 5 h at ambient temperature. Then the reaction mixture was diluted with EtOAc (20 mL), washed with water (2 × 10 mL), dried over NaSO₄, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 40:1) to give corresponding iodoalkyne (0.767 g, 94%) as slightly yellow oil. It was introduced directly to the next step. Z-selective reduction: To a solution of foregoing iodoalkyne (0.767 g, 1.49 mmol) in abs. MeOH (6.0 mL) were added pyridine (0.725 mL, 8.95 mmol) and KO₂CN=NCO₂K (1.49 g, 7.45 mmol) followed by the slow addition of acetic acid (0.5 mL, 8.95 mmol) over 6 h (syringe pump used). After this time,
the mixture was diluted with EtOAc (20 mL), washed with water (2 × 20 mL), saturated NaHCO₃ and saturated NaCl solutions. The organic layer was dried over Na₂SO₄, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 40:1) to give Z-iodoalkene 54 (0.629 g, 82%, 77% over 2 steps) as a slightly yellow oil. Rᵣ = 0.45 (petroleum ether/EtOAc, 20:1); [α]²⁰ₒ = −15.6 (c 2.3, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃): δ[ppm] = −0.01 (s, 3H, Si(CH₃)₂tBu), 0.04 (s, 3H, Si(CH₃)₂tBu), 0.90 (s, 9H, tBu), 0.94 (d, J = 6.9 Hz, 3H, 5-CH₃), 1.61 (s, 3H, 3-CH₃), 2.67–2.76 (m, 1H, 5-H), 3.80 (s, 3H, OCH₃), 3.91 (d, J = 5.1 Hz, 1H, 4-H), 4.06 (d, J = 6.4 Hz, 2H, CH₂OPMB), 4.42 (s, 2H, CH₂OPMP), 5.54 (dd, J = 6.4, 6.4 Hz, 1H, 2-H), 6.07 (dd, J = 8.9, 7.4 Hz, 1H, 6-H), 6.15 (d, J = 7.4 Hz, 1H, 7-H), 6.88 (d, J = 8.7, 2H, oCH ar Ph), 7.26 (d, J = 8.7, 2H, oCH ar Ph); ¹³C NMR (100 MHz, CDCl₃): δ[ppm] = −5.1 (Si(CH₃)₂tBu), −4.5 (Si(CH₃)₂tBu), 12.6 (5-CH₃), 16.6 (3-CH₃), 18.1 (C(CH₃)₃), 25.8 (C(CH₃)₃), 44.1 (C-5), 55.2 (OCH₃), 65.9 (C-1), 71.3 (CH₂PMP), 80.6 (C-7), 81.7 (C-4), 113.7 (oCH ar PMB), 123.5 (C-2), 129.2 (mCH ar PMB), 130.6 (C(CH₂ar PMB), 139.8 (CH₂OPMP), 143.7 (C-6), 159.1 (COCH₃); HRMS (ESI): [M+Na]⁺ calcd for C₂₃H₃₇IO₃SiNa 539.14489, found 539.145186.

(4R,5R,6S)-4-((3Z,5S,6S,7E)-6-tert-Butyldimethylsilyloxy-9-(4-methoxybenzyloxy)-5,7-dimethylnona-3,7-dien-1-ynyl)-2,2,5-trimethyl-6-((S)-3-methylbut-3-en-2-yl)-1,3-dioxane (83). To a Schlenk tube were added Z-iodoalkene 54 (16.3 mg, 0.032 mmol) and alkyne 75 (7.0 mg, 0.032 mol). Then freshly distilled Et₂NH (1 mL) was added followed by CuI (1.5 mg, 0.008 mmol, 25 mol%) and Pd(PPh₃)₄ (1.9 mg, 0.0016 mmol, 5 mol%). The resulting solution was allowed to stir for 2 h at r.t. After this time, the solvent was evaporated under nitrogen flow and Et₂O (3 mL) and sat. NH₄Cl (1 mL) were introduced. The layers were separated and the organic layer washed with saturated NaCl solution, dried over Na₂SO₄, filtered, and evaporated. The residue was purified by flash chromatography (petroleum ether/EtOAc, 30:1) to give enyne 83 (13.5 mg, 68%) as a slightly yellow oil. Rᵣ = 0.59 (petroleum ether/EtOAc, 10:1); [α]²⁰ₒ = +61.0 (c 0.4, MeOH); ¹H NMR (400 MHz, CDCl₃): δ[ppm] = −0.03 (Si(CH₃)₂tBu), 0.01 (Si(CH₃)₂tBu), 0.87 (s, 9H, tBu), 0.91 (d, J = 3.0 Hz, 3H, 2'-CH₃), 0.93 (d, J = 3.0 Hz, 3H, 5''-CH₃), 1.07 (d, J = 7.0 Hz, 3H, 5'-CH₃), 1.33 (s, 3H, 2'-CH₃), 1.55 (s, 3H, 2-CH₃), 1.57 (s, 3H, 7''-CH₃), 1.69 (s, 3H, 3'-CH₃), 1.85–1.88 (m, 1H, 5-H), 2.25–2.33 (m, 1H, 2'-H), 2.87–2.95 (m, 1H,
5''-H), 3.80 (s, 3H, OCH₃), 3.81–3.82 (m, 1H, 6''-H), 4.01–4.04 (m, 3H, 6-H, CH₂OPMB), 4.40 (s, 2H, CH₂PMP), 4.47–4.54 (m, 1H, 4-H), 4.74 (d, J = 5.6 Hz, 2H, 3''-CH₂), 5.47–5.43 (m, 2H, 3''-H, 8''-H), 5.83 (dd, J = 10.2 Hz, 1H, 4''-H), 6.87 (d, J = 8.7 Hz, 2H, mCH ar Ph), 7.24 (d, J = 8.7 Hz, 2H, oCH ar Ph); ¹³C NMR (100 MHz, CDCl₃): δ[ppm] = –5.0 (Si(CH₃)₂Bu), –4.5 (Si(CH₃)₂Bu), 11.3 (5-CH₃), 12.3 (C-4''), 15.6 (2''-CH₃), 17.6 (5''-CH₃), 18.2 (C(CH₃)₃), 19.2 (7''-CH₃), 23.4 (2-CH₃), 25.8 (C(CH₃)₃), 28.7 (2-CH₃), 36.4 (C-5), 39.8 (C-5''), 41.9 (C-2'), 55.3 (OCH₃), 65.9 (C-1), 67.9 (C-4), 70.2 (C-6), 71.3 (CH₂PMP), 81.4 (C-1''), 82.9 (C-6''), 93.0 (C-2''), 100.4 (C-2), 108.5 (C-3''), 110.5 (3'-CH₃), 113.8 (oCH ar PMB), 123.6 (C-8''), 129.3 (mCH ar PMB), 130.6 (CCH₂ ar PMB), 140.0 (C-7''), 147.0 (C-4''), 148.0 (C-3'), 159.1 (COCH₃); HRMS (ESI): [M+Na]⁺ calcd for C₉₇H₈₄O₃SiNa 633.92865, found 633.92893.

(4S,5S,6S)-4-((1Z,3Z,5S,6S,7E)-6-tert-Butyldimethylsilyloxy-9-(4-methoxybenzyl oxy)-5,7-dimethylinona-1,3,7-trienyl)-2,5-trimethyl-6-((S)-3-methylbut-3-en-2-yl)-1,3-dioxane (84). Enyne 83 (51.5 mg, 0.08 mmol) was dissolved in a mixture of abs. EtOAc and 1-hexene (1:1, 10 mL) and Lindlar cat.¹² (5 wt% Pd on CaCO₃, poisoned with lead, 25.8 mg, 50 wt%) and quinoline (25.8 mg, 0.20 mmol) were added. The flask was closed with a rubber septum and a balloon with hydrogen was attached. The system was filled with hydrogen and stirred for 36 h (HPLC monitoring). Then the solvents were evaporated and the residue purified by flash chromatography (petroleum ether/EtOAc, 30:1) to give Z,Z-diene 84 (30.6 mg, 59%) as a colorless oil. Rᵣ = 0.59 (petroleum ether/EtOAc, 10:1); [α]₂⁰°D = –12.6 (c 0.7, MeOH); ¹H NMR (400 MHz, CDCl₃): δ[ppm] = –0.04 (Si(CH₃)₂Bu), 0.01 (Si(CH₃)₂Bu), 0.84 (m, 12H, tBu, 5''-CH₃), 0.85 (d, J = 2.3 Hz, 5-CH₃), 0.87 (d, J = 6.8 Hz, 3H, 2''-CH₃), 1.31 (s, 3H, 2-CH₃), 1.37 (s, 3H, 2',CH₃), 1.58 (s, 3H, 7''-CH₃), 1.70 (s, 3H, 3',CH₃), 1.77 (app. ddq, J = 13.9, 11.6, 6.8 Hz, 1H, 5-H), 2.32 (app. dq, J = 10.7, 6.9 Hz, 1H, 2'-H), 2.79 (app. dq, J = 16.8, 14.0, 7.3 Hz, 1H, 5''-H), 3.69–3.75 (m, 2H, 6-H, 6''-H), 3.80 (s, 3H, OCH₃), 4.03 (d, J = 6.3 Hz, 2H, 9''-H), 4.23 (dd, J = 8.2, 8.2 Hz, 1H, 4'-H), 4.40 (s, 2H, CH₂PMP), 4.73 (d, J = 12.9 Hz, 2H, 3'-CH₂), 5.39–5.44 (m, 2H, 4''-H, 1''-H), 5.47–5.53 (m, 1H, 8''-H), 6.28 (dd, J = 11.4, 11.4 Hz, 1H, 3''-H), 6.43 (dd, J = 11.4, 11.4 Hz, 1H, 2''-H), 6.86 (d, J = 8.7 Hz, 2H, mCH ar Ph), 7.24 (d, J = 8.7 Hz, 2H, oCH ar Ph); ¹³C NMR (100 MHz, CDCl₃): δ[ppm] = –5.0 (Si(CH₃)₂Bu), –4.5 (Si(CH₃)₂Bu), 10.9 (5-CH₃), 11.9 (7''-CH₃), 16.1 (C-2''), 17.9 (5''-CH₃), 18.2 (C(CH₃)₃), 19.2 (C-4'), 24.3 (2-CH₃), 25.8 (2-CH₃), 25.9 (C(CH₃)₃), 36.7 (C-5''), 39.0 (C-5), 41.3 (C-2'), 55.3 (OCH₃), 65.9 (C-9''), 70.7 (C-4'), 71.0 (C-6), 71.4 (CH₂PMP), 82.2 (C-

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¹² Catalyst was ordered from Merck Schuchardt OHG company. Product number in catalog: 8.10489.0005
(2E,4S,5S,6Z,8Z)-1-(4-Methoxybenzyloxy)-3,5-dimethyl-9-((4S,5S,6S)-2,2,5-trimethyl-6-((S)-3-methylbut-3-en-2-yl)-1,3-dioxan-4-yl)nona-2,6,8-trien-4-ol (84a).

Silyl ether 84 (30.6 mg, 0.048 mmol) was dissolved in abs. THF (1 mL) and cooled in an ice/salt bath. Then TBAF·3H₂O was added in one portion and the resulting solution was allowed to stir for 12 h. The reaction mixture was diluted with EtOAc (10 mL) and saturated NH₄Cl solution (3 mL). The layers were separated and aqueous phase extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine, dried over MgSO₄, and evaporated. The residue was then purified by flash chromatography (petroleum ether/EtOAc, 5:1) to give alcohol 84a (16.9 mg, 68%) as a colorless oil, which was directly introduced to the next step. Rᵢ = 0.72 (petroleum ether/EtOAc, 1:1).

(2E,4S,5S,6Z,8Z)-1-(4-Methoxybenzyloxy)-3,5-dimethyl-9-((4S,5S,6S)-2,2,5-trimethyl-6-((S)-3-methylbut-3-en-2-yl)-1,3-dioxan-4-yl)nona-2,6,8-trien-4-yl pent-4-enoate (85). A round bottom flask was charged with alcohol 84a (6.0 mg, 0.012 mmol), abs. toluene (0.4 mL) and 4-pentenoic acid (1.5 µL, 0.015 mmol) followed by abs. Et₃N (5.1 µL, 0.036 mmol). Then 2,4,6-trichlorbenzoyl chloride (2.3 µL, 0.015 mmol) was added and the resulting solution stirred for 40 min. After this time, solution of DMAP (1.5 mg, 0.012 mmol) in abs. toluene (0.2 mL) was added and the resulting solution stirred for 30 min. White solids formed. Toluene was evaporated under a flow of nitrogen and the residue purified by flash chromatography (petroleum ether/EtOAc, 5:1) to give ester 85 (6.5 mg, 93%) as a colorless oil. Rᵢ = 0.69 (petroleum ether/EtOAc, 5:1); [α]²⁰D = +8.5 (c 1.4, MeOH); ¹H NMR (400 MHz, CDCl₃): δ[ppm] = 0.86 (d, J = 6.8 Hz, 3H, 5''-CH₃), 0.91 (d, J = 1.8, 3H, 2'''-CH₃), 0.92 (d, J = 1.6 Hz, 3H, 7'''-CH₃), 1.31 (s, 3H, 2''-CH₃), 1.36 (s, 3H, 2''-CH₃), 1.63 (s, 3H, 3'-CH₃), 1.70 (s, 3H, 3''-CH₃), 1.76 (m, 1H, 5''-H), 2.27–2.40 (m, 5H, 2'''-H, 2-H, 3-H), 2.95–3.04 (m, 1H, 5'-H), 3.71 (dd, J = 10.9, 4.6 Hz, 1H,
Experimental Section

(2E,4S,5S,6Z)-1-(4-Methoxybenzyl oxy)-3,5-dimethyl-9-((4R,5R,6S)-2,2,5-trimethyl-6-((S)-3-methylbut-3-en-2-yl)-1,3-dioxan-4-yl)nona-2,6-dien-8-yn-4-ol (86). To a cooled (ice/salt bath) solution of TBS ether 83 (10.0 mg, 0.016 mmol) in abs. THF (1.0 mL) was added solid TBAF·3H2O in one portion. Then the flask was removed from the cooling bath and allowed to stir overnight at room temperature. The reaction was diluted with Et2O (10 mL) and washed with saturated NH4Cl solution. The aqueous phase was additionally extracted with Et2O (3 × 5 mL) and the combined organic layers dried over Na2SO4. After filtration the solvent was evaporated, and the residue purified by flash chromatography (petroleum ether/EtOAc, 5:1) to give alcohol 86 (6.0 mg, 76%). Rf = 0.72 (petroleum ether/EtOAc, 1:1); [α]D20 = +71.0 (c 1.2, MeOH); 1H NMR (400 MHz, CDCl3): δ [ppm] = 0.92 (d, J = 6.8 Hz, 3H, 2''-CH3), 0.95 (d, J = 7.0 Hz, 3H, 5-CH3), 1.08 (d, J = 7.0 Hz, 3H, 5''-CH3), 1.33 (s, 3H, 2'-CH3), 1.54 (s, 3H, 2''-CH3), 1.63 (s, 3H, 3-CH3), 1.69 (s, 3H, 3''-CH3), 1.90 (app. d, J = 10.2, 6.8, 3.4 Hz, 1H, 5'-H), 2.29 (app. dd, J = 13.9, 10.5, 7.0 Hz, 1H, 2''-H), 2.96 (app. dd, J = 9.5, 7.2, 7.2 Hz, 1H, 5-H), 3.79–3.82 (m, 4H, OCH3, 4-H), 3.97–4.06 (m, 3H, CH2OPMB, 6'-H), 4.43 (m, 2H, CH2PMP), 4.50 (dd, J = 3.5, 2.0 Hz, 1H, 4'-H), 4.73–4.75 (m, 2H, 3''-CH2), 5.60–5.64 (m, 2H, 7-H, 2-H), 5.79–5.88 (m, 1H, 6-H), 6.85–6.89 (m, 2H, mCH ar Ph), 7.24–7.26 (m, 2H, oCH ar Ph); 13C NMR (100 MHz, CDCl3): δ [ppm] = 11.3 (5'-CH3), 11.8 (3-CH3), 15.6 (2''-CH3), 17.2 (5-CH3), 19.3 (3''-CH3), 23.4 (2'-CH3), 28.5 (2''-CH3), 36.5 (C-5'), 38.8 (C-5), 41.9 (C-2''), 55.3 (OCH3), 65.9 (CH2OPMB), 67.8 (C-4'), 70.3 (C-6'), 71.9 (CH2PMP), 81.1 (C-4), 82.2 (C-8), 94.1 (C-9), 100.5 (C-2'), 110.2 (C-2), 110.8 (3''-CH2), 113.8 (oCH ar PMB), 124.9 (C-7), 129.4 (mCH ar PMB), 130.4 (CCH2 ar PMB), 139.0 (C-3), 145.8 (C-6), 191.3 (C-1'H), 191.9 (C-1''').
147.9 (C-3''), 159.2 (COCH₃); HRMS (ESI): [M+Na]^+ calcd for C₃₁H₄₄O₅SiNa 519.30810, found 519.30844.

(2E,4S,5S,6Z)-1-(4-Methoxybenzyloxy)-3,5-dimethyl-9-((4R,5R,6S)-2,2,5-trimethyl-6-((S)-3-methylbut-3-en-2-yl)-1,3-dioxan-4-yl)nona-2,6-dien-8-yn-4-yl pent-4-enoate (87). A round bottom flask was charged with alcohol 86 (9.0 mg, 0.018 mmol), abs. toluene (0.6 mL) and 4-pentenoic acid (2.3 µL, 0.023 mmol) followed by abs. Et₃N (7.7 µL, 0.054 mmol). Then 2,4,6-trichlorobenzoyl chloride (3.5 µL, 0.029 mmol) was added and the resulting solution stirred for 40 min. After this time, solution of DMAP (2.3 mg, 0.018 mmol) in abs. toluene (0.4 mL) was added and the resulting solution stirred for 30 min. White solids formed. Toluene was evaporated under a flow of nitrogen and the residue purified by flash chromatography (petroleum ether/EtOAc, 5:1) to give ester 87 (10.0 mg, 95%) as a colorless oil. Rᵣ = 0.69 (petroleum ether/EtOAc, 5:1); [α]²⁰ₒ +75.0 (c 1.2, MeOH); ¹H NMR (400 MHz, CDCl₃): δ[ppm] = 0.92 (d, J = 7.1 Hz, 3H, 2'''-CH₃), 0.96 (d, J = 6.8 Hz, 3H, 5'-CH₃), 1.07 (d, J = 6.8 Hz, 3H, 5''-CH₃), 1.34 (s, 3H, 2''-CH₃), 1.54 (s, 3H, 2'-CH₃), 1.63 (s, 3H, 3'-CH₃), 1.69 (s, 3H, 3''-CH₃), 1.90 (app. qt, J = 6.7, 6.7, 6.7, 3.4, 3.4 Hz, 1H, 5''-H), 2.26–2.42 (m, 5H, 3-H, 2-H, 2'''-H), 3.08–3.17 (m, 1H, 5'-H), 3.79 (s, 3H, OCH₃), 3.97–4.05 (m, 3H, CH₂OPMB, 6''-H), 4.40 (s, 2H, CH₂PMP), 4.50 (dd, J = 3.4, 1.9 Hz, 1H, 4''-H), 4.73–4.77 (m, 2H, 3'''-CH₂), 4.96–5.09 (m, 3H, 4'-H, 5-H), 5.49–5.54 (m, 1H, 7'-H), 5.60 (app. t, J = 6.3, 6.3 Hz, 1H, 2'-H), 5.71–5.84 (m, 2H, 6'-H, 4-H), 5.85–5.87 (m, 2H, mCH ar Ph), 7.23–7.25 (m, 2H, oCH ar Ph); ¹³C NMR (100 MHz, CDCl₃): δ[ppm] = 11.3 (5''-CH₃), 12.8 (2'-CH₃), 15.6 (2''-CH₃), 17.0 (5'-CH₃), 19.3 (3''-CH₃), 23.4 (2''-CH₃), 28.5 (2''-CH₃), 28.8 (C-3), 33.7 (C-2'''), 36.6 (C-5'), 37.3 (C-5''), 41.9 (C-2), 55.3 (OCH₃), 65.7 (CH₂OPMB), 67.8 (C-4''), 70.3 (C-6''), 71.6 (CH₂PMP), 81.0 (C-4'), 82.2 (C-8'), 93.9 (C-9'), 100.4 (C-2''), 109.7 (C-2'), 110.8 (3''-CH₂), 113.8 (oCH ar PMB), 115.4 (C-5), 125.9 (C-7'), 129.4 (mCH ar PMB), 130.3 (CCH₂ ar PMB), 135.2 (C-3'), 136.7 (C-6'), 145.0 (C-4), 147.8 (C-3''), 159.2 (COCH₃), 172.0 (C=O). HRMS (ESI): [M+Na]^+ calcd for C₅₈H₇₀O₈Na 601.34996, found 601.349374.
**III. Approach Towards the Total Synthesis of Terpene (–)-Englerin A**

(1S,2R,5R)-Methyl 2-methyl-5-(prop-1-en-2-yl)cyclopentanecarboxylate (144). *Xanthate formation:* NaH (60% dispersion in oil, 22.0 g, 550 mmol) was added to a stirred solution of alcohol\(^{13}\) 143 (11.2 g, 57.0 mmol) and imidazole (ca. 300 mg) in THF (200 mL) at 0 °C. The cooling bath was removed. After 15 min the reaction was recooled to 0 °C and CS\(_2\) (38 mL, 612 mmol) was added dropwise. The mixture was allowed to warm to ambient temperature and after 1 h recooled to 0 °C before Mel (40 mL, 600 mmol) was added dropwise. After 3 h the reaction was quenched by careful addition of water (200 mL) at 0 °C. The mixture was extracted with CH\(_2\)Cl\(_2\) (3 × 100 mL). The combined organic layers were washed with water (2 × 200 mL), dried over MgSO\(_4\), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (5% ethyl acetate in petroleum ether) to give the titled xanthate (16.2 g, 98%) as a yellow oil which was directly introduced to the next step. \(R_f = 0.43\) (petroleum ether/EtOAc, 9:1).

*Reduction:* Tributylstannane (20.0 mL, 77.0 mmol) was added to a stirred solution of xanthate (16.2 g, 56.0 mmol) in dry toluene (200 mL) under N\(_2\). The mixture was stirred for 5 min, and then AIBN (ca. 100 mg) was added. The resulting mixture was heated under reflux for 1 h and then the reaction was allowed to cool to ambient temperature, washed with water (3 × 100 mL) and saturated NaCl solution (100 mL). The organic layer was dried over MgSO\(_4\), filtered, and concentrated in vacuo. The resulting colorless oil was distilled under reduced pressure (b.p. 90–95 °C, 25 mbar) to afford the title compound 144 (6.9 g, 67%, over 2 steps). \(R_f = 0.60\) (petroleum ether/EtOAc, 9:1); \([\alpha]^{20}_{D} = +19.8\) (c 1.00, Et\(_2\)O); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta [ppm] = 1.02\) (d, \(J = 6.9\) Hz, 3H, CH\(_3\)), 1.16 (ddddd, \(J = 12.5, 10.5, 8.7, 7.8\) Hz, 1H, 3-H), 1.71 (s, 3H, CH\(_3\)), 1.71–1.77 (m, 1H, 4-H), 1.83 (ddddd, \(J = 12.6, 10.2, 10.2, 7.6\) Hz, 1H, 4-H), 2.02 (ddddd, \(J = 12.5, 7.7, 7.7, 2.4\) Hz, 1H, 3-H), 2.41 (ddddd, \(J = 14.2, 14.2, 6.6, 6.6\) Hz, 1H, 2-H), 2.56 (dd, \(J = 8.9, 6.1\) Hz, 1H, 1-H), 2.76 (ddddd, \(J = 9.4, 9.4, 6.7\) Hz, 1H, 5-H), 3.55 (s, 3H, OCH\(_3\)), 4.67 (br s, 1H, CH\(_2\)) \(_2\)C(C\(_3\)), 4.72 (br s, 1H, CH\(_2\)) \(_2\)C(C\(_3\)); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta [ppm] = 21.2\) (CH\(_3\)), 22.6 (CH\(_2\)) \(_2\)C(C\(_3\)), 29.7 (C-4), 33.7 (C-3), 36.9 (C-2), 49.7 (C-5), 51.0 (OCH\(_3\)), 55.6 (C-1), 110.7 (CH\(_2\)) \(_2\)C(C\(_3\)), 145.5 (CH\(_2\)) \(_2\)C(C\(_3\)), 175.1 (CO\(_2\)CH\(_3\)); HRMS (ESI): [M+Na]\(^{+}\) calcd for C\(_{11}\)H\(_{18}\)O\(_2\)Na 205.11990, found 205.11972; The spectral data are identical to those previously reported.\(^{14}\)


(1S,2R,5R)-2-Methyl-5-(prop-1-en-2-yl)cyclopentane-carbaldehyde (145). Reduction: a solution of ester 144 (25.1 g, 0.14 mol) in diethyl ether (200 mL) was added dropwise to a suspension of lithium aluminium hydride (6.3 g, 0.17 mol) in diethyl ether (300 mL) at 0 °C. The mixture was stirred at room temperature for 2 d and then was quenched by careful addition of 15% NaOH (70 mL) and water (200 mL). Stirring was continued for 15 min, before MgSO₄ was added, the mixture stirred for additional 15 min, and filtered to remove salts. Evaporation of the solvent yielded crude alcohol (21.0 g), which was introduced to the next reaction without further purification. Rᶠ = 0.25 (petroleum ether/EtOAc, 9:1). To a stirred solution of the foregoing alcohol (21.0 g, 0.14 mol) in CH₂Cl₂ (700 mL) were added at room temperature Et₃N (230 mL, 1.66 mol) and a solution of SO₃×Py (125 g, 0.78 mol) in DMSO (400 mL). The reaction mixture was stirred for 1 h before it was quenched with water (300 mL) and extracted with ethyl acetate (3 × 200 mL). The combined organic layers were washed with water (200 mL), 1 N HCl (2 × 200 mL), water (2 × 200 mL), saturated NaCl solution (200 mL), dried over MgSO₄, filtered, and concentrated in vacuo. The residue was distilled at low pressure (b.p. 100–105 °C, 25 mbar) to give aldehyde 145 as a colorless oil (18.0 g, 87%, over 2 steps). Rᶠ = 0.65 (petroleum ether/EtOAc, 9:1); the spectral data are identical to those previously reported.¹⁵

(1R,2R,5R)-2-Methyl-5-(prop-1-en-2-yl)cyclopentane-carbaldehyde (146). DBU (0.2 mL) was added to a stirred solution of aldehyde 145 (17.0 g, 0.11 mol) in toluene (150 mL). The resulting mixture was stirred under reflux for 2 d. Then the solvent was carefully evaporated to afford a mixture of two stereoisomers 146/145 in a ratio of 2:1 (16.5 g, 97%) [as determined by ¹H NMR spectroscopy via integration of the aldehyde signals (145: 9.48 ppm, 146: 9.72 ppm). ¹H NMR (400 MHz, CDCl₃): δ[ppm] = 0.98 (d, J = 7.1 Hz, 3H, CH₃); 1.13–1.34 (m, 2H); 1.43–1.54 (m, 1H); 1.84–2.02 (m, 1H); 1.63 (s, 3H, CH₂C=CH₂); 2.41–2.49 (m, 1H, 2-H); 2.62 (ddd, J = 8.7, 8.7, 3.4 Hz, 1H, 1-H); 2.98 (ddd, J = 8.5,

8.5, 8.5 Hz, 1H, 5-H), 4.64 (br s, 1H, CH₂C=CH₂), 4.65 (br s, 1H, CH₂C=CH₂), 9.72 (d, J = 3.8 Hz, 1H, CH=O).

(1R,2R,5R)-2-Acetyl-5-methylcyclopentanecarbaldehyde (146a). Nitrogen was bubbled through the solution of aldehyde 146 (4.0 g, 27 mmol) in CH₂Cl₂ (40 ml) at −78 °C before ozone was bubbled until a deep blue color was observed. Nitrogen was again applied until no blue color remained. After the addition of PPh₃ (10.5 g, 40 mmol) the reaction mixture was stirred overnight at room temperature. Rᵣ (ketoaldehyde 146a) = 0.43 (petroleum ether/EtOAc, 4:1). This solution was used as such for the subsequent keto ester formation. An analytical sample was prepared after evaporation of the solvent followed by flash chromatography (petroleum ether/Et₂O, 9:1). [α]₂₀°D = +25.5 (c 0.85, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃): δ[ppm] = 1.03 (d, J = 7.1 Hz, 3H, CH₃), 1.32 (ddd, J = 15.4, 12.5, 7.6 Hz, 1H, 4-H), 1.65 (ddd, J = 16.1, 12.8, 8.0 Hz, 1H, 3-H), 1.88 (ddd, J = 12.6, 7.8, 6.4, 5.0 Hz, 1H, 4-H), 2.10 (ddd, J = 9.9, 7.5, 5.0, 2.5 Hz, 1H, 3-H), 2.17 (s, 3H, CH₃C=O), 2.56 (app dddq, J = 14.5, 14.5, 7.4, 7.1 Hz, 1H, 5-H), 3.25 (ddd, J = 8.4, 7.0, 1.1 Hz, 1H, 1-H), 3.48 (ddd, J = 9.5, 7.6, 7.5 Hz, 1H, 2-H), 9.81 (d, J = 0.8 Hz, 1H, CH=O); ¹³C NMR (100 MHz, CDCl₃): δ[ppm] = 16.4 (CHCH₃), 27.7 (C-3), 29.1 (CH₂C=O), 34.2 (C-4), 36.6 (C-5), 49.5 (C-2), 56.4 (C-1), 203.1 (CH=O), 209.0 (CH₂C=O); HRMS (ESI): [M+Na+MeOH]+ calcd for C₁₀H₁₈O₃Na 209.11429, found 209.11450.

Ethyl 3-((1'R,2'R,5'R)-2'-acetyl-5'-methylcyclopentyl)-3-oxopropanoate (147). Anhydrous tin (II) chloride¹⁶ (9.0 g, 47 mmol) was added, followed by dropwise addition of ethyl diazoacetate (8 mL, 73 mmol) to the foregoing solution of crude ketoaldehyde 146a in CH₂Cl₂ (the quenched ozonolysis solution). Stirring was continued for 2 h, and then the mixture was transferred to a separatory funnel,

¹⁶ SnCl₂·H₂O was dehydrated by slow addition to a vigorously stirred solution of acetic anhydride (120 g salt per 100 g anhydride). After 1 h, the anhydrous SnCl₂ was filtered, washed with anhydrous Et₂O to remove acetic acid and anhydride, and dried under vacuum. Armarego, W.L.F., Chai, C.L.L., Purification of laboratory chemicals, 2003, 5th edition, p 478.
containing saturated NaCl (100 mL) and diethyl ether (200 mL). After separation of the layers, the aqueous phase was extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with water (100 mL), saturated NaCl solution (100 mL), dried over MgSO₄, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/Et₂O, 4:1) to give β-keto ester 147 (2.5 g, 66%, over 2 steps) as a colorless oil. Rᵣ = 0.30 (petroleum ether/EtOAc, 4:1); [α]₂⁰⁻D = −11.7 (c 1.02, MeOH); ¹H NMR (400 MHz, CDCl₃): δ[ppm] = 0.83 (d, J = 7.3 Hz, 3H, CH₃), 1.24 (dd, J = 7.3, 7.3 Hz, 3H, OCH₂CH₃), 1.42–1.50 (m, 1H, 4'-H), 1.58–1.67 (m, 1H, 3'-H), 1.82–1.92 (m, 1H, 4'-H), 2.07–2.20 (m, 1H, 3'-H), 2.13 (s, 3H, CH₃C=O), 2.54 (app dddq, J = 13.7, 11.3, 7.0, 7.0 Hz, 1H, 5'-H), 3.40–3.48 (m, 2H, 1'-H, 2'-H), 3.47 (s, 2H, 2-H), 4.11–4.30 (m, 2H, OCH₂CH₃); ¹³C NMR (100 MHz, CDCl₃): δ[ppm] = 14.0 (OCH₂CH₃), 16.4 (CH₃C=O), 27.0 (C-3'), 29.3 (C-5'), 33.8 (C-4'), 37.0 (C-5'), 49.8 (C-3), 51.2 (C-1'), 57.0 (C-2'), 61.3 (OCH₂CH₃), 166.8 (C-1), 203.3 (C-3), 209.2 (CH₃C=O); HRMS (ESI): [M+Na]⁺ calcd for C₁₃H₂₀O₄Na 263.12538, found 263.12538.

Ethyl 3-((1'R,2'R,5'R)-2'-acetyl-5'-methylcyclopentyl)-2-diazo-3-oxopropanoate (147). Triethylamine (3.9 mL, 28.0 mmol) was added dropwise at 0 °C to a solution of β-keto ester 147 (3.4 g, 14 mmol) and p-acetamidobenzenesulfonyl azide¹⁷ (p-ABSA) (4.3 g, 18 mmol) in acetonitrile (60 mL). The mixture was stirred for 2 h and quenched with saturated NH₄Cl solution (30 mL). The layers were separated, and the aqueous layer was extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with water (100 mL) and saturated NaCl solution (100 mL), dried over MgSO₄, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 9:1) to give diazo compound 141 (2.7 g, 71%) as a yellow oil. Rᵣ = 0.70 (petroleum ether/EtOAc, 2:1); [α]₂⁰⁻D = −39.2 (c 1.76, MeOH); ¹H NMR (400 MHz, CDCl₃): δ[ppm] = 0.80 (d, J = 7.1 Hz, 3H, CH₃), 1.30 (dd, J = 7.2, 7.2 Hz, 3H, OCH₂CH₃), 1.39 (dddd, J = 12.8, 7.6, 7.4, 5.8 Hz, 1H, 4'-H), 1.63 (ddddd, J = 12.5, 8.9, 8.8, 8.2 Hz, 1H, 3'-H), 1.94 (ddddd, J = 12.4, 8.6, 8.8, 5.0 Hz, 1H, 4'-H), 2.07–2.13 (m, 1H, 3'-H), 2.12 (s, 3H, CH₃C=O), 2.61 (app dddq, J = 14.2, 14.2, 6.9, 6.8 Hz, 1H, 5'-H), 3.56 (ddd, J = 18.7, 9.4, 9.4 Hz, 1H, 2'-H), 4.07 (dd, J = 8.6 Hz, 1H, 1'-H), 4.23–4.31 (m, 2H, OCH₂CH₃); ¹³C NMR (100 MHz, CDCl₃): δ[ppm] = 14.2 (OCH₂CH₃), 16.8 (CH₃C=O), 27.4 (C-3'), 29.1 (CH₃C=O), 34.0 (C-4'), 36.2 (C-5'), 52.6 (C-2'), 53.1 (C-1'), 61.4 (OCH₂CH₃), 160.9 (C-1), 192.9 (C-3), 209.2 (CH₃C=O); HRMS (ESI): [M+Na]⁺ calcd for C₁₃H₂₆O₄N₂Na 289.11588, found 289.11592.

(1R,3aR,4R,7R,8aR)-5-Allyl 7-ethyl 1,4-dimethyl-8-oxo-1,2,3,3a,4,7,8,8a-octahydro-4,7-epoxyazulene-5,7-dicarboxylate (150). Rh$_2$(OAc)$_4$ (30 mg, 1 mol%) was added to a mixture of diazo compound 141 (1.0 g, 3.8 mmol) and allyl propiolate$^{18}$ 149 (2 mL) in toluene (50 mL) at room temperature. Then the closed Schlenck tube was transferred to a preheated oil bath (100 ºC) and kept with stirring at this temperature for 15 min. The mixture was allowed to cool to room temperature and filtered through a pad of Celite, using diethyl ether as a rinse. The filtrate was concentrated in vacuo to afford crude cycloadduct 150 (1.32 g) as a yellowish oil, which was used in the next step without further purification (epimerization at C-8a was detected while purifying by silica flash chromatography). $R_f = 0.50$ (petroleum ether/EtOAc, 4:1); [$\alpha$]$^20_D = +74.4$ (c 1.84, CH$_2$Cl$_2$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$[ppm] : 0.95 (d, $J$ = 6.9 Hz, 3H, CHC$_3$H$_3$), 1.31 (dd, $J$ = 7.1, 7.1 Hz, 3H, OCH$_2$CH$_3$), 1.69 (s, 3H, OCCH$_3$), 3.28 (dd, $J$ = 11.7, 6.4 Hz, 8a-H), 1.27–1.42 (m, 2H, OC$_2$H$_2$CH$_3$), 4.67 (dd, $J$ = 5.8, 5.8 Hz, 2H, OCH$_2$CH=CH$_2$), 5.26 (dd, $J$ = 10.4, 1.0 Hz, 1H, OCH$_2$CH=CH$_2$), 5.33 (dd, $J$ = 17.0, 1.3 Hz, 1H, OCH$_2$CH=CH$_2$), 5.92 (dddd, $J$ = 16.8, 10.9, 5.8, 5.5 Hz, 1H, OCH$_2$CH=CH$_2$), 6.93 (s, 1H, 6-H); further protons could not be assigned. $^{13}$C NMR (100 MHz, CDCl$_3$); $\delta$[ppm] = 14.1 (OCH$_2$CH$_3$), 17.7 (OCCH$_3$), 18.8 (CHCH$_3$), 27.0 (C-3), 29.0 (C-2), 29.8 (C-1), 47.1 (C-3a), 57.0 (C-8a), 62.5 (OCH$_2$CH$_3$), 65.6 (OCH$_2$CH=CH$_2$), 87.2 (C-4), 93.2 (C-7), 118.9 (OCH$_2$CH=CH$_2$), 131.4 (OCH$_2$CH=CH$_2$), 137.2 (C-6), 146.0 (C-5), 146.0 (CO$_2$ Allyl), 164.3 (CO$_2$ Et), 201.4 (C=O); HRMS (ESI): [M+Na]$^+$ calcd for C$_{19}$H$_{24}$O$_6$Na 371.14651, found 371.14627.

(1R,3aR,4R,7R,8S,8aR)-5-Allyl 7-ethyl 8-hydroxy-1,4-dimethyl-1,2,3,3a,4,7,8,8a-octahydro-4,7-epoxyazulene-5,7-dicarboxylate (150a). Cerium (III) chloride heptahydrate (3.5 g, 9.5 mmol) was added to the solution of crude ketone 150 (1.1 g, 3.2 mmol) in methanol (20 mL) and the mixture stirred for 30 min at room temperature, before it was cooled to $-78^\circ$C and sodium borohydride (240 mg, 6.4 mmol) was added in portions. Stirring was continued for 2 h at the same temperature. The reaction was quenched by slow addition of water, and most of methanol was removed in vacuo. Diethyl ether (100

mL) and water (100 mL) were added, the layers separated, and the aqueous layer was extracted with diethyl ether (4 × 50 mL). The combined organic layers were washed with saturated NaCl solution, dried over MgSO₄, filtered, and concentrated in vacuo to give crude alcohol 150a (1.1 g) as a yellowish oil, which was used in the next step without further purification. Rf = 0.20 (petroleum ether/EtOAc, 4:1); An analytical sample was obtained by flash chromatography (petroleum ether/EtOAc, 9:1). [α]D²⁰ = +17.0 (c 2.38, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃): δ[ppm] = 0.95 (d, J = 7.1 Hz, 3H, CH₂Cl₂), 0.98–1.03 (m, 1H, 2-H), 1.23–1.34 (m, 1H, 3-H), 1.31 (dd, J = 7.1, 7.1 Hz, 3H, OCH₂CH₂), 1.56 (s, 1H, OCH₂CH₃), 1.72–1.78 (m, 1H, 3-H), 1.87 (ddd, J = 12.1, 12.1, 6.5 Hz, 1H, 3a-H), 1.94–2.02 (m, 2H, 2-H, OH), 2.17 (ddd, J = 12.5, 7.4, 4.6 Hz, 1H, 8a-H), 2.25 (app ddq, J = 7.4, 7.4, 2.9 Hz, 1H, 1-H), 4.28 (2 app dq, J = 14.2, 7.1, 2H, OCH₂), 4.51 (dd, J = 4.7, 4.7 Hz, 1H, 9-H), 4.66 (dd, J = 13.3, 5.7 Hz, 2H, OCH₂CH=CH₂), 5.24 (dd, J = 10.4, 1.0 Hz, 1H, OCH₂CH=CH₂), 5.33 (dd, J = 17.0, 1.3 Hz, 1H, OCH₂CH=CH₂), 5.93 (dddd, J = 16.8, 10.9, 5.8, 5.5 Hz, 1H, OCH₂CH=CH₂), 7.02 (s, 1H, 6-H); ¹³C NMR (100 MHz, CDCl₃): δ[ppm] = 14.2 (OCH₂CH₃), 19.1 (OCCH₃), 20.1 (CHCH₃), 25.8 (C-3), 31.1 (C-2), 32.5 (C-1), 35.7 (C-3a), 47.8 (C-8a), 61.9 (OCH₂CH₃), 65.3 (OCH₂CH=CH₂), 73.5 (C-8), 87.2 (C-4), 88.4 (C-7), 118.5 (OCH₂CH=CH₂), 131.7 (OCH₂CH=CH₂), 141.9 (C-6), 144.6 (C-5), 162.6 (CO₂Allyl), 170.2 (CO₂Et); HRMS (ESI): [M+Na]⁺ calcd for C₁₉H₂₆O₈Na 373.16216, found 373.16217.

Experimental Section

(1R,3aR,4R,7R,8R,8aR)-5-Allyl 7-ethyl 1,4-dimethyl-8-((triethylsilyl)oxy)-1,2,3,3a,4,7,8,8a-octahydro-4,7-epoxyazulene-5,7-dicarboxylate (151). 2,6-Lutidine (0.2 mL, 1.7 mmol) was added dropwise to a solution of alcohol 150a (150 mg, 0.43 mmol) in CH₂Cl₂ (5 mL) at –78 °C. Then TES-triflate (0.2 mL, 0.8 mmol) was added at the same temperature. The mixture was allowed to warm to room temperature, filtered through a pad of silica gel, washed with 50% solution of ethyl acetate in petroleum ether, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 25:1) to give TES-ether 151 (118 mg, 59% over 3 steps) as a colorless oil. Rf = 0.53 (petroleum ether/EtOAc, 9:1); [α]D²⁰ = +28.2 (c 2.36, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃): δ[ppm] = 0.61 (ddd, J = 15.8, 7.6, 7.6 Hz, 6H, Si(CH₂CH₃)₃), 0.88 (d, J = 6.9 Hz, 3H, CHCH₃), 0.93 (dd, J = 7.9, 7.9 Hz, 9H, Si(CH₂CH₃)₃), 0.97–1.05 (m, 1H, 2-H), 1.24–1.33 (m, 1H, 3-H), 1.33 (dd, J = 7.4, 7.4 Hz, 3H, OCH₂CH₃), 1.54 (s, 3H, OCCH₃), 1.68–1.75 (m, 1H, 3-H), 1.87–1.96 (m, 2H, H-2, 3a-H), 2.07 (ddd, J = 12.5, 6.4, 4.3 Hz, 1H, 8a-H), 2.15–2.25 (m, 1H, 1-H), 4.28 (2 app dq, J = 10.9, 7.4 Hz, 2H, OCH₂CH₃), 4.60–4.75 (m, 3H, 8-H, OCH₂CH=CH₂), 5.24 (dd, J = 10.4, 0.8 Hz, 1H, OCH₂CH=CH₂), 5.33 (dd, J = 17.3, 1.3 Hz, 1H, OCH₂CH=CH₂), 6.98 (s, 1H, 6-H); ¹³C NMR (100 MHz, CDCl₃): δ[ppm] = 4.8 (Si(CH₂CH₃)₃), 6.8
Experimental Section

(Si(CH₂CH₃)₃), 14.2 (OCH₃CH₃), 19.4 (OCCH₃), 19.6 (CHCH₃), 24.8 (C-3), 31.1 (C-2), 32.9 (C-1), 35.2 (C-3a), 48.3 (C-8a), 61.9 (OCH₂CH₃), 65.0 (OCH₂CH=CH₂), 73.3 (C-8), 86.8 (C-4), 89.2 (C-7), 118.0 (OCH₂CH=CH₂), 132.0 (OCH₂CH=CH₂), 142.8 (C-6), 143.1 (C-5), 162.8 (CO₂Allyl), 170.1 (CO₂Et); HRMS (ESI): [M+Na]+ calcd for C₂₅H₄₀O₆SiNa 487.24864, found 487.24857.

(1R,3aR,4R,7R,8R,8aR)-7-(Ethoxycarbonyl)-1,4-dimethyl-8-((triethylsilyl)oxy)-1,2,3,3a,4,7,8,8a-octahydro-4,7-epoxyazulene-5-carboxylic acid (153). RhCl(PPh₃)₃ (10 mg) was added to a solution of allyl ester 151 (42 mg, 0.09 mmol) in a mixture of water/ethanol (2 mL, 1:10). Then the closed flask was transferred to a preheated (100 °C) oil bath. The mixture was stirred for 1 h at this temperature, cooled, and then the solvents were removed in vacuo. The residue was purified by flash chromatography (petroleum ether/Et₂O/AcOH (glac.), 4:1:0.01) to give carboxylic acid 153 (32 mg, 84%) as a colorless oil. Rᵣ = 0.2 (petroleum ether/Et₂O/AcOH (glac.), 4:1:0.01); [α]₂⁰ = +50.6 (c 3.48, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃): δ[ppm] = 0.62 (ddd, J = 15.9, 7.8, 7.8 Hz, 6H, Si(CH₂CH₃)₃), 0.90 (d, J = 7.1 Hz, 3H, CHCH₃), 0.94 (ddd, J = 8.1, 8.1 Hz, 9H, Si(CH₂CH₃)₃), 0.99–1.07 (m, 1H, 2-H), 1.26–1.37 (m, 1H, 3-H), 1.33 (dd, J = 7.1, 7.1 Hz, 3H, OCH₂CH₃), 1.55 (s, 3H, OCH₃), 1.68–1.76 (m, 1H, 3-H), 1.88–1.96 (m, 2H, 3a-H, 2-H), 2.09 (ddd, J = 12.4, 6.4, 4.4 Hz, 1H, 8a-H), 2.17–2.26 (m, 1H, 1-H), 4.29 (2 app dq, J = 10.9, 7.4 Hz, 2H, OCH₂CH₃), 4.67 (d, J = 4.3 Hz, 1H, 8-H), 7.14 (s, 1H, 6-H); ¹³C NMR (100 MHz, CDCl₃): δ[ppm] = 4.8 (Si(CH₂CH₃)₃), 6.9 (Si(CH₂CH₃)₃), 14.1 (OCH₂CH₃), 19.4 (OCH₃), 19.6 (CHCH₃), 24.8 (C-3), 31.0 (C-2), 32.9 (C-1), 35.2 (C-3a), 48.4 (C-8a), 61.9 (OCH₂CH₃), 73.4 (C-8), 86.7 (C-4), 89.2 (C-7), 142.8 (C-5), 145.7 (C-6), 168.2 (CO₂Et), 169.9 (CO₂H); HRMS (ESI): [M+Na]+ calcd for C₂₂H₃₆O₆SiNa 447.21734, found 447.21730.

(1R,3aR,4R,7R,8R,8aR)-Ethyl 5-(azidocarbonyl)-1,4-dimethyl-8-((triethylsilyl)oxy)-1,2,3,3a,4,7,8,8a-octahydro-4,7-epoxyazulene-7-carboxylate (154). Trichloroacetonitrile (0.03 mL, 0.33 mmol) was added dropwise to a stirred solution of carboxylic acid 153 (70 mg, 0.16 mmol), sodium azide (16 mg, 0.25 mmol), PPh₃ (86 mg, 0.33 mmol) in acetone (2 mL) at room temperature. After 30 min the solvent was removed by a flow of nitrogen and the residue was purified by flash chromatography (petroleum ether/Et₂O/AcOH (glac.), 4:1:0.01) to give ester 154 (54 mg, 87%) as a colorless oil. Rᵣ = 0.2 (petroleum ether/Et₂O/AcOH (glac.), 4:1:0.01); [α]₂⁰ = +50.6 (c 3.48, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃): δ[ppm] = 0.62 (ddd, J = 15.9, 7.8, 7.8 Hz, 6H, Si(CH₂CH₃)₃), 0.90 (d, J = 7.1 Hz, 3H, CHCH₃), 0.94 (ddd, J = 8.1, 8.1 Hz, 9H, Si(CH₂CH₃)₃), 0.99–1.07 (m, 1H, 2-H), 1.26–1.37 (m, 1H, 3-H), 1.33 (dd, J = 7.1, 7.1 Hz, 3H, OCH₂CH₃), 1.55 (s, 3H, OCH₃), 1.68–1.76 (m, 1H, 3-H), 1.88–1.96 (m, 2H, 3a-H, 2-H), 2.09 (ddd, J = 12.4, 6.4, 4.4 Hz, 1H, 8a-H), 2.17–2.26 (m, 1H, 1-H), 4.29 (2 app dq, J = 10.9, 7.4 Hz, 2H, OCH₂CH₃), 4.67 (d, J = 4.3 Hz, 1H, 8-H), 7.14 (s, 1H, 6-H); ¹³C NMR (100 MHz, CDCl₃): δ[ppm] = 4.8 (Si(CH₂CH₃)₃), 6.9 (Si(CH₂CH₃)₃), 14.1 (OCH₂CH₃), 19.4 (OCH₃), 19.6 (CHCH₃), 24.8 (C-3), 31.0 (C-2), 32.9 (C-1), 35.2 (C-3a), 48.4 (C-8a), 61.9 (OCH₂CH₃), 73.4 (C-8), 86.7 (C-4), 89.2 (C-7), 142.8 (C-5), 145.7 (C-6), 168.2 (CO₂Et), 169.9 (CO₂H); HRMS (ESI): [M+Na]+ calcd for C₂₂H₃₆O₆SiNa 447.21734, found 447.21730.
Experimental Section

chromatography (petroleum ether/EtOAc, 25:1) to give azide 154 (66 mg, 90%) as a colorless oil. Rf = 0.37 (petroleum ether/EtOAc, 9:1); [α]20D° = +40.1 (c 1.63, MeOH); 1H NMR (400 MHz, CDCl3): δ[ppm] = 0.61 (ddd, J = 15.9, 7.8, 7.8 Hz, 6H, Si(CH2CH3)3), 0.88 (d, J = 7.1 Hz, 3H, CHCH3), 0.94 (dd, J = 8.1, 8.1 Hz, 9H, Si(CH2CH3)3), 0.97–1.05 (m, 1H, 2-H), 1.25–1.37 (m, 1H, 3-H), 1.32 (dd, J = 7.1, 7.1 Hz, 3H, OCH2CH3), 1.54 (s, 3H, OCCH3), 1.68–1.76 (m, 1H, 1-H), 1.81–1.95 (m, 2H, 3a-H, 2-H), 2.06 (ddd, J = 12.4, 6.4, 4.4 Hz, 1H, 8a-H), 2.15–2.25 (m, 1H, 1-H), 4.28 (2 app dq, J = 10.9, 7.4 Hz, 2H, OCH2CH3), 4.66 (d, J = 4.3 Hz, 1H, 6-H); 13C NMR (100 MHz, CDCl3): δ[ppm]: 4.8 (Si(CH2CH3)3), 6.8 (Si(CH2CH3)3), 14.1 (OCH2CH3), 19.2 (OCCH3), 19.5 (CHCH3), 24.7 (C-3), 31.0 (C-2), 32.9 (C-1), 35.2 (C-3a), 48.3 (C-8a), 62.0 (OCH2CH3), 73.4 (C-8), 86.9 (C-4), 89.2 (C-7), 144.4 (C-5), 145.8 (C-6), 168.4 (CO2Et), 169.7 (CON); HRMS (ESI): [M+Na]+ calcd for C22H38N3O5SiNa 472.22382, found 472.22384.

Azide 154 (66 mg, 0.15 mmol) was dissolved in toluene (2 mL) and stirred for 1 h at 100 °C. Then the solvent was removed in vacuo, the residue was dissolved in THF (2 mL) followed by the addition of 5% HCl (0.5 mL) and THF (0.5 mL). Stirring was continued for 15 min, then the reaction was quenched with triethylamine (0.5 mL) and the solvents were evaporated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 25:1) to give ketone 155 (48 mg, 83%) as a colorless oil. Rf = 0.53 (petroleum ether/EtOAc, 9:1); [α]20D° = +0.5 (c 0.98, CH2Cl2); 1H NMR (400 MHz, CDCl3): δ[ppm] = 0.60 (ddd, J = 16.8, 9.9, 8.4, 1.8 Hz, 6H, Si(CH2CH3)3), 0.92 (d, J = 9.4 Hz, 3H, CHCH3), 0.93 (dd, J = 8.1, 8.1 Hz, 9H, Si(CH2CH3)3), 1.13–1.21 (m, 1H, 2-H), 1.26 (s, 3H, OCCH3), 1.32 (dd, J = 7.1, 7.1 Hz, 3H, OCH2CH3), 1.40 (ddd, J = 10.9, 7.2, 1.3 Hz, 1H, 3-H), 1.60–1.68 (m, 1H, 3-H), 1.85 (dd, J = 13.2, 10.7, 7.4 Hz, 1H, 3a-H), 1.92–2.02 (m, 2H, 2-H, 8a-H), 2.22–2.31 (m, 1H, 1-H), 2.60 (d, J = 18.1 Hz, 1H, 6-H), 3.10 (d, J = 18.1 Hz, 1H, 6-H), 4.28 (2 app dq, J = 10.8, 7.1 Hz, 2H, OCH2CH3), 4.73 (d, J = 4.1 Hz, 1H, 8-H); 13C NMR (100 MHz, CDCl3): δ[ppm] = 4.8 (Si(CH2CH3)3), 6.9 (Si(CH2CH3)3), 14.1 (OCH2CH3), 16.5 (OCCH3), 19.2 (CHCH3), 24.0 (C-3), 32.4 (C-1), 32.6 (C-2), 36.4 (C-3a), 38.8 (C-6), 45.2 (C-8a), 62.0 (OCH2CH3), 71.2 (C-8), 83.0 (C-4), 84.2 (C-7), 171.4 (CO2Et), 214.6 (C=O); HRMS (ESI): [M+Na]+ calcd for C21H36O5SiNa 419.22424, found 419.22238.
(1R,3aR,4R,5R,7R,8R,8aR)-Ethyl 5-hydroxy-1,4-dimethyl-8-(triethylsilyl)oxy)deca-hydro-4,7-epoxyazulene-7-carboxylate (156). Sodium borohydride (21 mg, 0.55 mmol) was added in portions to a stirred solution of ketone 155 (150 mg, 0.38 mmol) in methanol/THF (6.6 mL, 1:10) at −10 °C. The mixture was allowed to warm to room temperature, and then quenched by careful addition of water. Most of the organic solvents were evaporated in vacuo, the residue was diluted with water (10 mL), and the mixture extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over MgSO$_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 4:1) to give alcohol 156 (150 mg, 85%) as a colorless oil. R$_f$ = 0.37 (petroleum ether/EtOAc, 4:1); [α]$_{20}^D$ = +5.8 (c 2.46, CH$_2$Cl$_2$); $^{1}$H NMR (400 MHz, DMSO): δ[ppm] = 0.48–0.55 (m, 6H, Si(CH$_2$CH$_3$)$_3$), 0.88 (dd, $J$ = 8.1, 8.1 Hz, 9H, Si(CH$_2$CH$_3$)$_3$), 0.96 (d, $J$ = 6.8 Hz, 3H, CHCH$_3$), 1.09 (s, 3H, OCCH$_3$), 1.10–1.35 (m, 2H, 2-H, 3-H), 1.21 (dd, $J$ = 7.1, 7.1 Hz, 3H, OCH$_2$CH$_3$), 1.47 (ddd, $J$ = 12.4, 8.3, 8.3, 4.3 Hz, 1H, 1-H, 3-H), 1.71 (ddd, $J$ = 13.8, 6.2, 6.1, 1H, 8a-H), 1.87–1.96 (m, 1H, 2-H), 2.14 (dd, $J$ = 13.3, 8.0 Hz, 1H, 6-H), 2.19–2.35 (m, 3H, 1-H, 3a-H, 6-H), 3.60 (ddd, $J$ = 8.6, 8.6, 4.3 Hz, 1H, 5-H), 4.10 (2 app dq, $J$ = 10.9, 7.1 Hz, 2H, OCH$_2$CH$_3$), 4.63 (d, $J$ = 6.1 Hz, 1H, 8-H), 5.20 (d, $J$ = 4.3 Hz, 1H, OH); $^{13}$C NMR (100 MHz, CDCl$_3$): δ[ppm] = 4.3 (SiCH$_2$CH$_3$), 6.7 (SiCH$_2$CH$_3$), 13.9 (OCH$_2$CH$_3$), 18.8 (CHCH$_3$), 19.9 (OCCH$_3$), 23.8 (C-3), 32.0 (C-1), 32.7 (C-3a), 32.8 (C-6), 33.6 (C-2), 44.2 (C-8a), 61.0 (OCH$_2$CH$_3$), 70.8 (C-8), 76.8 (C-5), 82.5 (C-4), 83.3 (C-7), 171.8 (CO$_2$Et); HRMS (ESI): [M+Na]$^+$ calcd for C$_{21}$H$_{38}$O$_5$SiNa 421.23807, found 421.23845.

(1R,3aR,4R,5R,7R,8R,8aR)-Ethyl 1,4-dimethyl-5,8-bis((triethylsilyl)oxy)decahydro-4,7-epoxyazulene-7-carboxylate (157). 2,6-Lutidine (0.13 mL, 1.15 mmol) was added dropwise to a solution of alcohol 156 (150 mg, 0.38 mmol) in CH$_2$Cl$_2$ (10 mL) at −78 °C. Then TES-triflate (0.13 mL, 0.58 mmol) was added at the same temperature. The mixture was allowed to warm to room temperature (ca 3 h), filtered through a pad of silica gel, the filter cake was washed with mixture of petroleum ether/EtOAc (1:1), and the filtrates concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 25:1) to afford TES-ether 157 (159 mg, 82% over 2 steps). R$_f$ = 0.55 (petroleum ether/EtOAc, 9:1); [α]$_{20}^D$ = +2.0 (c 6.00, CH$_2$Cl$_2$); $^{1}$H NMR (400 MHz, CDCl$_3$): δ[ppm]
2-((1R,3aR,4R,5R,7R,8R,8aR)-1,4-Dimethyl-5,8-bis((triethylsilyl)oxy)decahydro-4,7-epoxyazulen-7-yl)propan-2-ol (158). Freshly prepared methylmagnesium iodide (0.12 mL, 1 M solution in Et₂O, 0.12 mmol) was added dropwise to a stirred solution of ester 157 (10 mg, 0.019 mmol) in THF (1 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and quenched with saturated NH₄Cl (0.5 mL), diluted with water (2 mL) and extracted with diethyl ether (3 × 5 mL). The combined organic layers were washed with saturated NaCl solution (2 × 10 mL), dried over MgSO₄, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 25:1) to give tertiary alcohol 158 (9.7 mg, 100%) as a colorless oil. R₉ = 0.48 (petroleum ether/EtOAc, 9:1); [α]₂⁰_D = +3.4 (c 1.0, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃): δ [ppm] = 0.57 (ddd, J = 16.7, 8.6, 1.3 Hz, 6H, Si(CH₂CH₃)₃), 0.65 (ddd, J = 15.9, 7.9, 2.3 Hz, 6H, Si(CH₂CH₃)₃), 0.94 (dd, J = 7.8, 7.8 Hz, 9H, Si(CH₂CH₃)₃), 0.96 (dd, J = 8.1, 8.1 Hz, 9H, Si(CH₂CH₃)₃), 1.00 (d, J = 7.1 Hz, 3H, CHCH₃), 1.14 (s, 3H, OCCH₃), 1.16 (s, 3H, C(CH₃)₂), 1.18 (s, 3H, C(CH₃)₂), 1.22–1.28 (m, 1H, 2-H), 1.35 (ddddd, J = 12.2, 10.3, 10.3, 6.2 Hz, 1H, 3-H), 1.49–1.58 (m, 1H, 3-H), 1.69 (dd, J = 13.6, 6.4, 4.7 Hz, 1H, 8a-H), 1.88 (dddd, J = 12.1, 10.5, 7.1, 4.9 Hz, 1H, 2-H), 1.98 (dd, J = 13.0, 9.7 Hz, 1H, 6-H), 2.15–2.24 (m, 2H, 1-H, 6-H), 2.25 (ddd, J = 13.6, 10.0, 9.0 Hz, 1H, 3a-H), 3.66 (dd, J = 9.6, 6.6 Hz, 1H, 5-H), 4.45 (d, J = 4.6 Hz, 1H, 8-H); ¹³C NMR (100 MHz, CDCl₃): δ [ppm] = 4.9 (SiCH₂CH₃), 5.9 (SiCH₂CH₃), 6.8 (SiCH₂CH₃), 7.2 (SiCH₂CH₃), 18.6 (CHCH₃), 21.2 (OCCH₃), 24.0 (C-3), 24.8 (C(CH₃)₂), 24.8 (C(CH₃)₂), 32.6 (C-1), 32.7 (C-6), 33.1 (C-3a), 34.9 (C-2), 45.9 (C-8a), 71.0 (C-8), 73.3 (C(CH₃)₂), 79.6 (C-5), 81.4 (C-4), 89.1 (C-7); HRMS (ESI): [M+Na]⁺ calcd for C₂₇H₄₆O₇Si₂Na 535.32455, found 535.325022.
\(((1R,3aR,4R,5R,7S,8R,8aR)-1,4-Dimethyl-7-(prop-1-en-2-yl)decahydro-4,7-epoxyazulene-5,8-diyl)bis(oxy))bis(triethylsilane) \((159)\). Burgess reagent\(^{19}\) (10 mg, 0.040 mmol) was added to a stirred solution of alcohol \(158\) (5 mg, 0.010 mmol) in abs. toluene (1 mL) and the mixture was stirred at 110 °C for 5 min. Then the solvent was evaporated and the residue purified by flash chromatography (petroleum ether/EtOAc, 30:1) providing alkene \(159\) (3.4 mg, 71%) as a colorless oil. \(R_f = 0.31\) (petroleum ether/EtOAc, 33:1); \(\alpha\)\(^{20D} = +4.8\) (c 0.31, CH\(_2\)Cl\(_2\)); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) [ppm] = 0.50–0.60 (m, 12H, (Si(CH\(_2\)CH\(_3\))\(_3\))\(_2\)), 0.92 (dd, \(J = 7.8, 7.8\) Hz, 9H, Si(CH\(_2\)CH\(_3\))\(_3\)), 0.95 (dd, \(J = 8.1, 8.1\) Hz, 9H, Si(CH\(_2\)CH\(_3\))\(_3\)), 1.00 (d, \(J = 6.8\) Hz, 3H, CH\(_3\CH\(_3\))\(_3\)), 1.16 (s, 3H, OC\(_3\)H\(_3\)), 1.21–1.27 (m, 1H, 2-H), 1.30–1.39 (m, 1H, 3-H), 1.49–1.58 (m, 1H, 3-H), 1.73 (ddd, \(J = 14.0, 5.9, 5.8\) Hz, 1H, 8a-H), 1.77 (s, 3H, CH\(_2\)=CH\(_2\)), 1.84–1.93 (m, 1H, 2-H), 2.04 (dd, \(J = 13.0, 9.2\) Hz, 1H, 6-H), 2.19–2.24 (m, 1H, 1-H), 2.29 (dd, \(J = 13.1, 7.3\) Hz, 1H, 6-H), 2.49 (ddd, \(J = 14.0, 10.1, 8.7\) Hz, 1H, 3a-H), 3.68 (dd, \(J = 9.3, 7.3\) Hz, 1H, 5-H), 4.25 (d, \(J = 6.1\) Hz, 1H, 8-H), 4.88 (dd, \(J = 1.4, 1.4\) Hz, 1H, C=CH\(_2\)), 4.91 (br.s, 1H, C=CH\(_2\)); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) [ppm] = 5.0 (Si\(_3\)H\(_2\)CH\(_3\)), 5.4 (Si\(_3\)H\(_2\)CH\(_3\)), 6.8 (Si\(_3\)H\(_2\)CH\(_3\)), 7.0 (Si\(_3\)H\(_2\)CH\(_3\)), 18.4 (CH\(_3\)=CH\(_2\)), 18.6 (CH\(_2\)CH\(_3\)), 20.7 (OC\(_3\)H\(_3\)), 23.9 (C-3), 32.8 (C-3a), 32.9 (C-1), 34.0 (C-2), 35.0 (C-6), 45.7 (C-8a), 72.4 (C-8), 78.7 (C-5), 80.9 (C-4), 85.9 (C-7), 112.1 (CH\(_3\)=CH\(_2\)), 147.0 (CH\(_3\)=CH\(_2\)); HRMS (ESI): [M+Na]\(^+\) calcd for C\(_{27}\)H\(_{52}\)O\(_3\)Si\(_2\)Na 503.33472, found 503.33510.

\(((1R,3aR,4R,5R,7S,8R,8aR)-1,4-Dimethyl-7-(prop-2-yl)decahydro-4,7-epoxyazulene-5,8-diyl)bis(oxy))bis(triethylsilane) \((161)\). A 5 mL round-bottom flask was charged with alkene \(159\) (3.40 mg, 0.007 mmol) and a stirring bar. Absolute ethyl acetate (1 mL) and Pd/C 10% (4.00 mg) were added with stirring. The reaction was placed under H\(_2\) atmosphere and stirred for 2 h at room temperature. The reaction mixture was filtered through a pad of Celite\(^{19}\) and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 100:1) to afford the title

compound 161 (2.5 mg, 72%) as a colorless oil. \( R_f = 0.60 \) (petroleum ether/ EtOAc, 60:1); \([\alpha]_{D}^{20} = +2.7 \) (c 0.55, CH<sub>2</sub>Cl<sub>2</sub>); \(^1\)H NMR (400 MHz, CDCl<sub>3</sub>): \( \delta [\text{ppm}] = 0.52–0.64 \) (m, 12H, (Si(CH<sub>2</sub>CH<sub>3</sub>)<sub>3</sub>), 0.92–1.01 (m, 27H, (Si(CH<sub>2</sub>CH<sub>3</sub>)<sub>3</sub>, (CHCH<sub>3</sub>)<sub>2</sub>, 1.12 (s, 3H, OCCH<sub>3</sub>), 1.17–1.35 (m, 2H, 2-H, 3-H), 1.47–1.52 (m, 1H, 3-H), 1.60–1.74 (m, 3H, 8a-H, 6-H C(CH<sub>3</sub>)<sub>2</sub>), 1.85–1.94 (m, 1H, 2-H), 2.17–2.24 (m, 2H, 6-H, 1-H), 2.40 (ddd, \( J = 13.8, 10.4, 8.6 \) Hz, 1H, 3a-H), 3.52 (dd, \( J = 8.6, 8.6 \) Hz, 1H, 5-H), 4.36 (d, \( J = 6.1 \) Hz, 1H, 8-H); \(^{13}\)C NMR (100 MHz, CDCl<sub>3</sub>): \( \delta [\text{ppm}] = 5.0 \) (SiCH<sub>2</sub>CH<sub>3</sub>), 5.3 (SiCH<sub>2</sub>CH<sub>3</sub>), 6.8 (SiCH<sub>2</sub>CH<sub>3</sub>), 7.0 (SiCH<sub>2</sub>CH<sub>3</sub>), 16.6 (CH(CH<sub>3</sub>)<sub>2</sub>), 16.8 (CH(CH<sub>3</sub>)<sub>2</sub>), 18.9 (CHCH<sub>3</sub>), 20.4 (OCCH<sub>3</sub>), 24.0 (CH(CH<sub>3</sub>)<sub>2</sub>), 31.6 (C-3), 32.6 (C-3a), 33.6 (C-1), 34.1 (C-2), 34.7 (C-6), 46.0 (C-8a), 71.3 (C-8), 78.9 (C-5), 80.6 (C-4), 85.4 (C-7); HRMS (ESI): [M+Na]<sup>+</sup> calcd for C<sub>27</sub>H<sub>54</sub>O<sub>3</sub>SiNa 505.35037, found 505.35007.

(1R,3aR,4R,5R,7S,8R,8aR)-1,4-Dimethyl-7-(prop-1-en-2-yl)decahydro-4,7-epoxyazulene-5,8-diol (160). TBAF × 3H<sub>2</sub>O (38.5 mg, 0.120 mmol) was added in one portion to a stirred solution of silyl ether 159 (6.9 mg, 0.012 mmol) in anhydrous THF (1 mL) at 0 °C. Then the cooling bath was removed and the mixture stirred overnight at room temperature. The solvent was evaporated in vacuo and the residue purified by flash chromatography (petroleum ether/EtOAc, 2:1) to give alcohol 160 (2.0 mg, 6.5%) as white crystals. \( R_f = 0.32 \) (petroleum ether/EtOAc, 2:1); \([\alpha]_{D}^{20} = +2.5 \) (c 0.2, CH<sub>2</sub>Cl<sub>2</sub>); \(^1\)H NMR (400 MHz, CDCl<sub>3</sub>): \( \delta [\text{ppm}] = 1.08 \) (d, \( J = 7.3 \) Hz, 3H, CHCH<sub>3</sub>), 1.19–1.27 (m, 1H, 2-H), 1.27 (s, 3H, OCCH<sub>3</sub>), 1.36 (dddd, \( J = 11.6, 11.6, 9.1, 9.1 \) Hz, 1H, 3-H), 1.58–1.65 (m, 1H, 3-H), 1.75 (dd, \( J = 1.4, 0.9 \) Hz, 3H, CH<sub>2</sub>C=CH<sub>2</sub>), 1.86 (ddd, \( J = 13.6, 8.0, 4.2 \) Hz, 1H, 8a-H), 1.97 (dd, \( J = 13.4, 9.6 \) Hz, 1H, 6-H), 2.07–2.15 (m, 1H, 2-H), 2.24–2.37 (m, 3H, 1-H, 3a-H, 6-H), 3.91 (dd, \( J = 9.6, 4.8 \) Hz, 1H, 5-H), 4.17 (d, \( J = 4.3 \) Hz, 1H, 8-H), 4.70 (ddd, \( J = 3.2, 1.5, 1.4 \) Hz, 1H, CH<sub>2</sub>C=CH<sub>2</sub>), 4.93 (dd, \( J = 1.9, 0.9 \) Hz, 1H, CH<sub>2</sub>C=CH<sub>2</sub>); \(^{13}\)C NMR (100 MHz, CDCl<sub>3</sub>): \( \delta [\text{ppm}] = 18.5 \) (CH<sub>3</sub>C=CH<sub>2</sub>), 20.4 (CHCH<sub>3</sub>), 21.5 (OCCH<sub>3</sub>), 26.0 (C-3), 31.4 (C-3a), 33.8 (C-1), 34.4 (C-2), 38.4 (C-6), 44.8 (C-8a), 73.8 (C-8), 78.9 (C-5), 81.7 (C-4), 86.0 (C-7), 107.9 (CH<sub>3</sub>C=CH<sub>2</sub>), 148.4 (CH<sub>3</sub>C=CH<sub>2</sub>); HRMS (ESI): [M+Na]<sup>+</sup> calcd for C<sub>15</sub>H<sub>20</sub>O<sub>3</sub>Na 275.16177, found 275.16169.

![Diagram](image-url)
(1R,2S,5R)-5-Methyl-2-(prop-1-en-2-yl)-1-vinylcyclohexanol (166). Freshly prepared vinylmagnesium bromide\(^\text{20}\) (250 mL, 1.7 M solution in THF, 0.42 mol) was added dropwise to a stirred solution of (-)-isopulegone (47.0 g, 0.33 mol) in THF (300 mL) at –80 °C. The reaction mixture was allowed to warm to room temperature and quenched with saturated \(\text{NH}_4\text{Cl}\) (50 mL), diluted with water (200 mL), and extracted with diethyl ether (3 × 100 mL). The combined organic layers were washed with saturated NaCl solution (2 × 100 mL), dried over MgSO\(_4\), filtered, and concentrated in vacuo. The residue was distilled at low pressure (b.p. 45–50 °C, 6 × 10\(^{-3}\) mbar) to give alcohol 166 as a colorless oil (55.7 g, 92%). \(R_f = 0.69\) (petroleum ether/EtOAc, 9:1); \([\alpha]_{D}^{20} = +17.2\ (c 2.49, \text{MeOH}); \) \(^1\text{H NMR}\ (400\text{ MHz, CDCl}_3): \delta[ppm] = 0.86\) (d, \(J = 6.6\) Hz, 3H, 5-CH\(_3\)), 0.90–1.01 (m, 1H, 4-H), 1.10 (ddd, \(J = 14.0, 12.2, 2.0\) Hz, 1H, 6-H), 1.47 (ddd, \(J = 13.2, 6.4, 3.6\) Hz, 1H, 3-H), 1.61 (ddd, \(J = 13.7, 3.3, 2.3\) Hz, 1H, 6-H), 1.74 (s, 3H, 2'-CH\(_3\)), 1.76–1.83 (m, 3H, 3-H, 4-H, 5-H), 1.98 (dd, \(J = 13.0, 3.3\) Hz, 1H, 2-H), 4.73 (s, 1H, 1'-H), 4.87 (s, 1H, 1'-H), 4.96 (dd, \(J = 10.7, 1.3\) Hz, 1H, CH\(_2\) vinyl), 5.16 (dd, \(J = 17.2, 1.1\) Hz, 1H, CH\(_2\) vinyl), 5.86 (dd, \(J = 17.0, 10.7\) Hz, 1H, CH vinyl); \(^{13}\text{C NMR}\ (100\text{ MHz, CDCl}_3): \delta[ppm] = 22.2\) (5-CH\(_3\)), 25.7 (2'-CH\(_3\)), 27.4 (C-5, C-3), 34.8 (C-4), 46.5 (C-6), 52.0 (C-2), 73.2 (C-1), 110.6 (CH\(_2\) vinyl), 111.7 (C-1'), 146.2 (CH vinyl), 148.1 (C-2'); \(\text{HRMS (ESI): [M+Na]}^+\) calcd for C\(_{12}\)H\(_{20}\)ONa 203.14064, found 203.140504.

(9R,E)-5,9-Dimethylcyclodec-5-enone (167). A solution of alcohol 166 (3.0 g, 16.7 mmol) in abs. THF (20 mL) was added to a stirred suspension of KH (2.0 g, 50 mmol)\(^\text{21}\) in THF (40 mL). The resulting mixture was stirred under reflux for 12 h. Then the reaction mixture was quenched with ethanol (10 mL) at –78 °C, diluted with water (100 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with saturated NaCl solution (2 × 50 mL), dried over MgSO\(_4\), filtered, and concentrated in vacuo. The residue was distilled at low pressure (55–60 °C, 10\(^{-2}\) mbar) to give ketone 167 as a colorless oil (2.13 g, 71%). \(R_f = 0.59\) (petroleum ether/EtOAc, 9:1); \([\alpha]_{D}^{20} = +2.9\ (c 1.0,\)
MeOH); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$[ppm] = 0.92 (d, $J = 6.8$ Hz, 3H, 9-CH$_3$), 1.17–1.23 (m, 1H), 1.43 (s, 3H, 5-CH$_3$), 1.60–1.68 (m, 2H), 1.80–1.85 (m, 1H), 1.95–2.15 (m, 1H, 9-H), 2.20–2.35 (m, 2H), 2.57–2.63 (m, 1H), 5.12–5.14 (m, 6-H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$[ppm] = 15.9 (5-CH$_3$), 24.8 (9-CH$_3$), 25.8, 27.3 (CH$_2$), 28.8 (C-9), 37.3, 41.3, 43.1, 53.3 (CH$_2$), 126.4 (C-6), 138.0 (C-5), 208.7 (C=O); HRMS (ESI): [M+Na]$^+$ calcd for C$_{12}$H$_{20}$ONa 203.14064, found 203.140461.

$^{1}R,7R,10R$-1,7-Dimethyl-11-oxa-bicyclo[8.1.0]undecan-5-one (165). $m$CPBA (11.5 g, 47.0 mmol, 70–75%) was added to a stirred solution of ketone 167 (7.0 g, 39 mmol) in CH$_2$Cl$_2$ (400 mL) and stirred overnight at ambient temperature. The reaction mixture was quenched with saturated Na$_2$S$_2$O$_3$ solution (100 mL) and stirred for additional 1 hour. The organic layer was separated and washed with saturated NaHCO$_3$ solution (2 × 100 mL), water (100 mL), saturated NaCl solution (100 mL), dried over MgSO$_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 15:1) to give epoxide 165 (6.3 g, 83%) as a white crystals (m.p. 66–67.5 °C, from petroleum ether). $R_f$ = 0.24 (petroleum ether/EtOAc, 9:1); $[^{20}$D$]_D$ = –0.4 (c 1.29, MeOH); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$[ppm] = 0.84–0.92 (ddd, $J = 13.7, 13.7, 3.3$ Hz, 1H, 2-H), 0.96 (d, $J = 7.4$ Hz, 3H, 7-CH$_3$), 1.15 (s, 3H, 1-CH$_3$), 1.25–1.45 (m, 2H, 8-H, 9-H), 1.55–1.65 (m, 1H, 3-H), 1.79–1.85 (m, 2H, 8-H, 9-H), 2.10–2.20 (m, 2H, 2-H, 3-H), 2.24–2.43 (m, 4H, 4-H, 4-H, 6-H, 7-H), 2.56 (dd, $J = 17.5, 10.3$ Hz, 1H, 6-H), 2.63 (dd, $J = 7.5, 0.9$ Hz, 1H, 10-H), $^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$[ppm] = 16.1 (1-CH$_3$), 20.2 (C-3), 23.4 (7-CH$_3$), 26.4 (C-9), 28.8 (C-7), 35.9 (C-8), 40.5 (C-2), 43.2 (C-4), 52.3 (C-6), 61.5 (C-1), 63.2 (C-10), 210.3 (C=O); HRMS (ESI): [M+Na]$^+$ calcd for C$_{12}$H$_{20}$O$_2$Na 219.13555, found 219.135501.

$^{1}R,3aR,4R,8aS$-4-Hydroxy-1,4-dimethyl-octahydroazulen-4(2H)-one (164) and $^{1}R,3aR,4R,8S,8aS$-1,4-Dimethyldecahydro-4,8-epoxyazulen-8-ol (168). A solution of epoxide 165 (7.0 g, 35.7 mmol) in THF (50 mL) was added to the suspension of NaH$^{22}$ (6.0 g, 150.0 mmol, 60% dispersed in mineral oil) in THF (200 mL) and stirred under reflux for 1 h. Then the reaction mixture was cooled to −10 °C and quenched with saturated NH$_4$Cl solution (50 mL), diluted with water (100

$^{22}$ NaH was washed with abs. $n$-hexane (3 × 10 mL) before it was used.
mL), and extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with 1M HCl solution (50 mL), water (50 mL), saturated NaCl solution (50 mL), dried over MgSO$_4$, filtered, and concentrating in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 9:1) to give an inseparable mixture of ketone 164 and hemiketal 168, which were introduced in the next step without further purification (6.0 g, quant.). $R_f = 0.32$ (petroleum ether/EtOAc, 2:1).

(1$R$,3a$R$,4$R$,8a$S$)-1,4-Dimethyl-8-oxo-decahydroazulen-4-yl-pivalate (170). Pivalic anhydride (16 ml, 79.1 mmol) was added dropwise to a stirred solution of a mixture of 164 and 168 (4.3 g, 21.9 mmol) in dry acetonitrile (90 mL) at −10 °C, followed by addition of Sc(OTf)$_3$ (0.1 g, 0.2 mmol) solution in acetonitrile (1 mL) at the same temperature. The resulting mixture was stirred overnight at 0 °C, quenched with saturated NaHCO$_3$ solution (50 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic extracts were washed with saturated NaCl solution (50 mL), dried over MgSO$_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 25:1) to give pivalic ketone 170 (3.7 g, 61%) and protected hemiketal 169 (2.3 g, 37%) as colorless oils. Hemiketal 169: $R_f = 0.75$ (Petroleum ether/EtOAc, 4:1); $[\alpha]_{20}^{20} = +10.7$ (c 1.3, CH$_2$Cl$_2$); $^1$H NMR (400 MHz, CDCl$_3$): δ[ppm] = 0.99 (d, $J = 6.1$ Hz, 3H, 1-CH$_3$), 1.15 (s, 9H, (CH$_3$)$_3$), 1.26 (s, 3H, 4-CH$_3$), 1.40–1.68 (m, 6H, 5-H, 6-H, 2-H), 1.88–1.99 (m, 2H, 7-H), 2.14–2.22 (m, 2H, 3-H), 2.31–2.35 (ddd, $J = 11.9$, 11.7, 6.2 Hz, 1H, 1-H), 2.46 (dd, $J = 13.8$, 8.2 Hz, 3a-H), 2.79 (ddd, $J = 13.6$, 8.6, 8.6 Hz, 1H, 8a-H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ[ppm] = 17.9 (1-CH$_3$), 20.9 (CH$_2$), 25.0 (4-CH$_3$), 27.0 (CO(CH$_3$)$_3$), 27.9, 28.9, 31.8, 33.7, 38.5, 39.0 (CH$_2$), 41.1 (C-1), 54.5 (C-8a), 62.5 (C-3a), 82.1 (C-8), 110.0 (C-4), 185.0 (CO(CH$_3$)$_3$). Pivalic ketone 170: $R_f = 0.65$ (Petroleum ether/EtOAc, 4:1); $[\alpha]_{20}^{20} = +22.5$ (c 1.0, CH$_2$Cl$_2$); $^1$H NMR (400 MHz, CDCl$_3$): δ[ppm] = 1.05 (d, $J = 6.4$ Hz, 3H, 1-CH$_3$), 1.12 (s, 9H, (CH$_3$)$_3$), 1.20–1.25 (m, 1H, 2-H), 1.48 (s, 3H, 4-CH$_3$), 1.54–1.85 (m, 4H, 2 × 3-H, 5-H, 2 × 6-H), 1.96–2.12 (m, 2H, 1-H, 2-H), 2.31–2.43 (m, 3H, 5-H, 7-H, 8a-H), 2.61 (ddd, $J = 11.7$, 11.7, 3.3 Hz, 1H, 7-H), 2.95 (ddd, $J = 11.2$, 11.2, 7.1 Hz, 1H, 3a-H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ[ppm] = 19.9 (1-CH$_3$), 21.2 (CH$_2$), 26.2 (4-CH$_3$), 27.1 (CO(CH$_3$)$_3$), 29.4, 35.3, 35.4, 39.2 (CH$_2$), 39.6 (CO(CH$_3$)$_3$), 41.6 (C-1), 49.5 (C-3a), 61.4 (C-8a), 86.1 (C-4), 177.7 (C=O ester), 212.4 (C=O ketone).
Experimental Section

(1R,3aR,4R,8aS)-1,4-Dimethyl-8-oxo-1,2,3,3a,4,5,8,8a-octahydroazulen-4-yl pivalate (171). TBS enol ether formation. n-BuLi (0.43 mL, 2.5 M in THF) was added to a flask containing abs. THF (1.5 mL). The resulting solution was cooled to −20 °C and then DIPEA (0.17 mL, 1.18 mmol) was added. The resulting LDA solution was stirred at −20 °C for 1 h and recooled to −40 °C. A solution of ketone 170 (100 mg, 0.36 mmol) in abs. THF (1.0 mL) was introduced dropwise at −40 °C. The resulting solution was stirred at the same temperature for 2 h and then a solution of TBSCl (217 mg, 1.44 mmol) in abs. THF (1.0 mL) was added followed by HMPA (0.1 mL, 0.54 mmol). The reaction mixture was allowed to warm to room temperature. After being stirred overnight, water (10 mL) was added. The organic layer was separated and the water phase extracted with Et2O (3 × 20 mL). The combined organic layers were washed with saturated NaCl solution (2 × 20 mL), dried over MgSO4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc/Et3N, 40:1:0.12) to give TBS enol ether (131 mg, 93%) as a colorless oil. Rf = 0.37 (Petroleum ether/EtOAc, 33:1). The compound was directly introduced to the next step. Saegusa-Ito oxidation. To a solution of TBS enol ether obtained above in dry DMSO (3.0 mL) was added Pd(OAc)2 (11.2 mg, 0.05 mmol). The reaction mixture was placed under oxygen and stirred at 50 °C for 24 h. After this time, the reaction mixture was diluted with Et2O (10 mL) followed by water addition (5 mL). The layers were separated and the aqueous phase extracted with Et2O (3 × 10 mL). The combined organic extracts were washed with saturated NaCl solution (2 × 10 mL), dried over MgSO4, filtered, and concentrated in vacuo. The residue was purified via flash chromatography (petroleum ether/EtOAc, 9:1) to give enone 171 (76 mg, 83%) as a colorless oil. Rf = 0.42 (Petroleum ether/EtOAc, 9:1); [α]D20 = −21.3 (c 0.39, MeOH); 1H NMR (400 MHz, CDCl3): δ[ppm] = 0.97 (d, J = 5.8 Hz, 3H, 1-CH3), 1.06 (s, 9H, tBu), 1.15–1.24 (m, 2H, CH2), 1.46 (s, 3H, 4-CH3), 1.86–2.03 (m, 2H, 3a-H, CH2), 2.50 (dd, J = 10.6, 10.6 Hz, 1H, CH2), 2.61–2.67 (m, 1H, 5-H), 2.80–2.87 (m, 1H, 8a-H), 3.26–3.32 (m, 1H, 5-H), 5.90 (dd, J = 12.1, 2.9 Hz, 1H, 7-H), 6.10 (ddd, J = 12.1, 6.7, 2.7 Hz 1H, 6-H); 13C NMR (100 MHz, CDCl3): δ[ppm] = 18.2 (1-CH3), 25.0 (4-CH3), 27.0 (C(CH3)3), 28.5 (CH2), 34.8 (CH2), 36.9 (C-1), 39.4 (C(CH3)3), 40.8 (C-5), 50.6 (C-3a), 63.7 (C-8a), 85.0 (C-4), 130.9 (C-7), 137.0 (C-6), 177.9 (C=O ester), 204.2 (C=O ketone).
(3R,3aR,6R,6aS)-3-((E)-5,5-Dimethyl-4-oxohex-2-enyl)-3,6-dimethylhexahydro-1H-cyclopenta[c]furan-1-one (176). n-BuLi (0.20 mL, 2.5M in THF) was added to a flask containing abs. THF (1.0 mL). The resulting solution was cooled to −20 °C and then DIPEA (0.07 mL, 0.40 mmol) was added. The resulting LDA solution was stirred at −20 °C for 1 h. Then a solution of ketone 170 (30.0 mg, 0.11 mmol) in abs. THF (1.0 mL) was added at −20 °C. The resulting solution was warmed to −5 °C and stirred for 40 min. After this time, the reaction mixture was recooled to −78 °C and a solution of PhSeCl (57.4 mg, 0.33 mmol) in THF (0.5 mL) was added dropwise. The resulting yellow solution was allowed to stir overnight at −40 °C and then quenched with saturated NH₄Cl solution (5 mL). The layers were separated and aqueous phase extracted with EtOAc (3 × 10 mL). The combined organics were washed with saturated NaCl solution, dried over MgSO₄, filtered, and concentrated in vacuo. The residue was dissolved in THF (1 mL) and H₂O₂ (0.1 mL, 1.1 mmol, 30% in water) was added in one portion. The resulting solution was stirred overnight and then diluted with water (5 mL). The layers were separated and the aqueous phase extracted with EtOAc (3 × 10 mL). The combined organics were washed with saturated Na₂S₂O₈ solution (2 × 10 mL), saturated NaCl solution (20 mL), dried over MgSO₄, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 20:1) to give enone 176 (15 mg, 50%) as a colorless oil. Rᵣ = 0.42 (Petroleum ether/EtOAc, 9:1); [α]ᵣ²⁰ = +10.7 (c 1.5, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃): δ[ppm] = 1.13–1.14 (m, 12H, 5'-(CH₃)₃, 6-CH₃), 1.17–1.25 (m, 1H, 5-H), 1.35 (s, 3H, 3-CH₃), 1.52–1.57 (m, 1H, 5-H), 1.80–1.96 (m, 2H, 4-H), 2.33–2.40 (m, 1H, 6-H), 2.53–2.69 (m, 3H, 1'-H, 3a-H), 2.76 (dd, J = 8.6, 4.1 Hz, 1H, 6a-H), 6.60 (app d, J = 15.2 Hz, 1H, 3'-H), 6.83 (ddd, J = 15.2, 7.6, 7.6, 1H, 2'-H); ¹³C NMR (100 MHz, CDCl₃): δ[ppm] = 21.3 (6-CH₃), 26.0 (5-(CH₃)₃), 27.0 (3-CH₃), 27.6 (C-4), 35.4 (C-5), 37.7 (C-6), 40.0 (C-1'), 42.9 (C-5'), 49.8 (C-3a), 53.5 (C-6a), 84.7 (C-3), 128.2 (C-3'), 140.2 (C-2'), 179.3 (C=O ester), 203.7 (C=O ketone).
Selected NMR spectra for important compounds

Additional spectra are included in the supporting information of the published papers from this work and are available free of charge via Internet at http://www.sciencedirect.com/, http://pubs.acs.org and http://www.thieme-chemistry.com/products/journals/synlett.html
Appendix

PMBO
PivO
Ph

19

Chloroform-d

ppm
Appendix

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

OTBS
PMBO
PivO
Ph
25

Chloroform-d

25
NOESY spectrum of 1
HMBC spectrum of 1

4-H / C-5
8-H / C-6
5-OCH3 / C-5
4-H / C-6
6-OCH3 / C-6
Appendix

![NMR Spectrum](image)

**Chemical Shifts (ppm):**
- 1.0
- 1.5
- 2.0
- 2.5
- 3.0
- 3.5
- 4.0
- 4.5
- 5.0
- 5.5
- 6.0
- 6.5
- 7.0

** notable peaks:**
- CO₂Me
- 144

**Chemical Formula:** Chloroform-d
Appendix

Chloroform-d

[Chemical Structure Image]

141

ppm

141

14.2
16.8
27.4
29.1
34.0
36.1
52.6
53.1
61.4
160.9
192.9
209.2


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41 see also: Jägel, J.; Maier, M. E. Synlett 2006, 693-696.
46 For a review, see: Fürstner, A. Synthesis 1989, 571-590.
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