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Synthesis of the Acyclic Carbon Skeleton of Filipin III

Elodie BRUN, Véronique BELLOSTA and Janine COSSY*

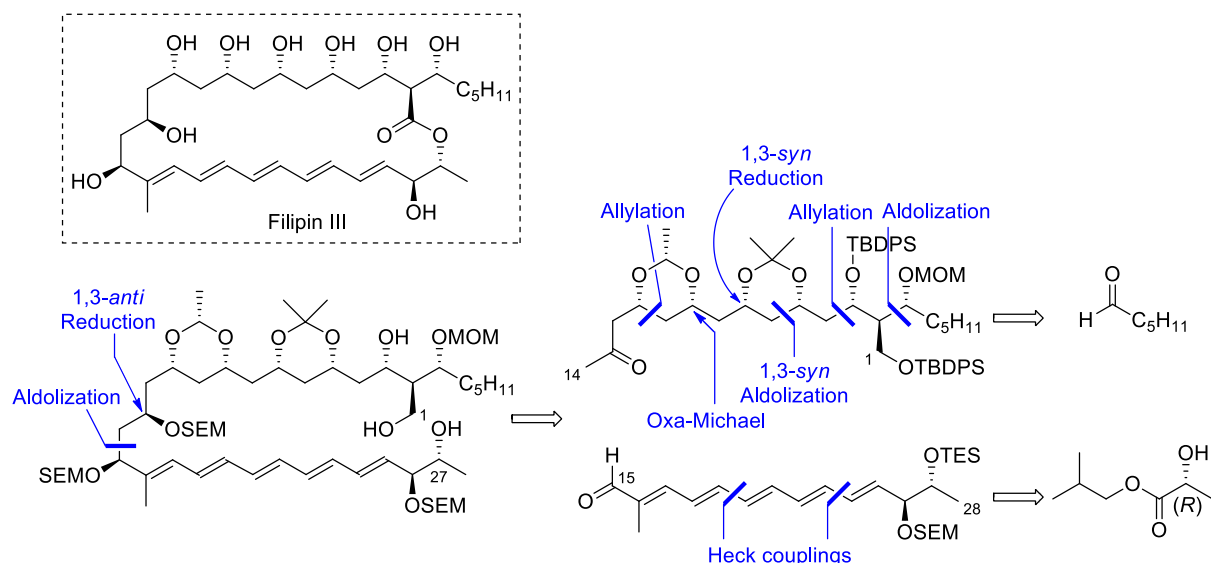
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Abstract

The synthesis of the carbon skeleton of filipin III, a polyenic macrolactone possessing 11 stereogenic centers, has been achieved using a convergent strategy with a longest linear sequence of 19 steps starting from hexanal. The construction of the polyene has been realized by using two successive Heck couplings as the key steps. The control of the stereogenic centers of the polyol fragment has been performed by utilizing an Evans aldolization, a 1,3-*syn* aldolization, enantio- and diastereoselective allylations, an hemiacetalization/oxa-Michael sequence and a 1,3-*syn* reduction. The polyol and polyenic fragments have been coupled using a 1,5-*anti* diastereoselective aldolization followed by a 1,3-*anti* reduction.

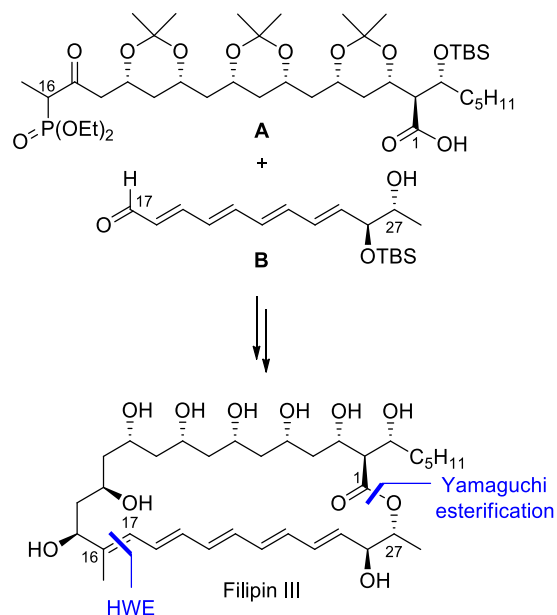


INTRODUCTION

Filipins were isolated from the cell culture filtrates of *Streptomyces filipensis* which were collected in the Philippine Islands.¹ A mixture of at least eight compounds was found in these filtrates and four fractions were separated: filipin I (4%), filipin II (25%), filipin III (53%) and filipin IV (18%).² The structure of the major compound, filipin III, was determined by degradation studies³ and its relative and absolute stereochemistry was determined by synthesis.⁴ Filipin III is a polyenic macrocycle which possesses antibiotic properties⁵ but this product is too toxic to have therapeutic applications. However, filipin III has been widely used as a histochemical stain for cholesterol to study its distribution and to quantify it in cell membranes.⁶ This strong interaction between cholesterol and filipin III has been used clinically in the study and the diagnosis of the Type C Niemann-Pick disease.⁷ Moreover, filipin III was shown to prevent the pathological accumulation of the membrane-bound prion protein, whose expression is a key event in the pathogenesis of transmissible spongiform encephalopathies.⁸

The synthesis of the C1-C15 polyol fragment of filipin III has been published by Kiyooka *et al.*⁹ and the synthesis of the C1-C10 fragment of the enantiomer of filipin III has been realized by Brückner and Walleser¹⁰ but it is worth noting that only one total synthesis of filipin III has been reported to date by Rychnovsky *et al.*¹¹ This synthesis is convergent and has been achieved from a polyol fragment **A** and a polyenic fragment **B** which have been coupled by using at first a Yamaguchi esterification and then an intramolecular Horner-Wadsworth-Emmons (HWE) reaction to construct the macrocycle (Scheme 1).

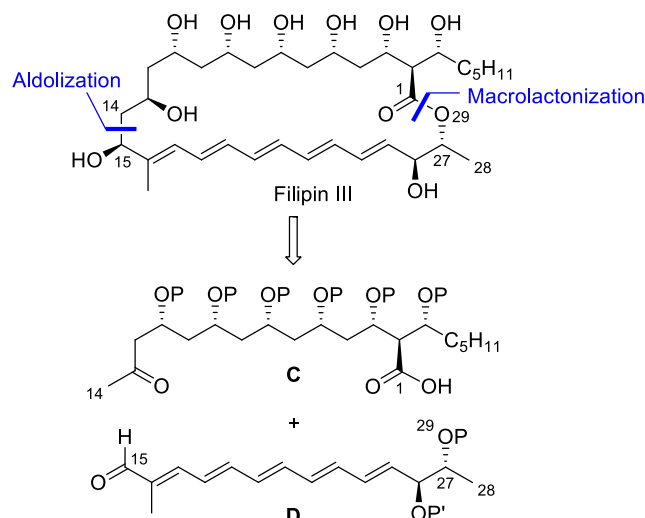
Scheme 1. Synthesis of filipin III by Rychnovsky *et al.*



In the context of our program concerning the synthesis of natural products¹² and the study of their biological mechanism of action, we became interested in the synthesis of filipin III, to access several analogues in order to modulate its biological activity. Here, we would like to report our efforts toward the synthesis of the carbon skeleton of filipin III.

From a retrosynthetic analysis, we planned to access filipin III from two fragments: a polyol fragment **C** and a polyenic fragment **D**. The assembly of the two fragments would be achieved by using a diastereoselective aldolization to form the C14-C15 bond and the final step would be a macrolactonization to form the C1-O29 bond (Scheme 2).

Scheme 2. Retrosynthesis



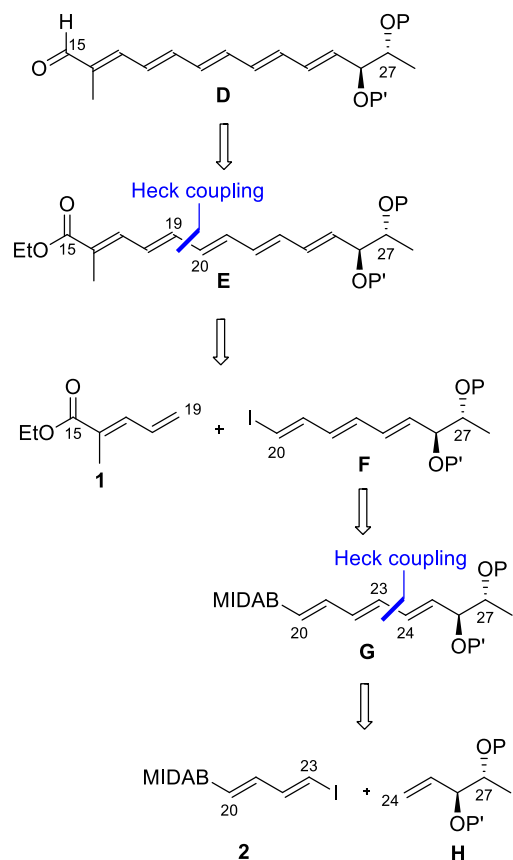
RESULTS AND DISCUSSION

Synthesis of the C15-C28 fragment (fragment D)

The C15-C28 fragment of filipin III is a conjugated pentaenic aldehyde possessing a 1,2-*anti*-diol unit. The aldehyde function would allow the formation of the C14-C15 bond by performing an aldol condensation.

Our retrosynthetic analysis of the polyenic fragment is based on a method developed by Burke and co-workers to synthesize polyenes using successive chemoselective palladium-catalyzed cross-couplings involving alkenyl boronic esters derived from *N*-methyliminodiacetic acid (MIDA),¹³ which was recently extended by our group to more complex polyenes and applied to the synthesis of the polyenic fragment of mirabaline.¹⁴ Based on this strategy, two Heck couplings were envisaged to build up the polyenic fragment, one to form the C19-C20 bond and the second one to form the C23-C24 bond (Scheme 3). By planning these two Heck couplings, the conjugated iodo-triene **F** and iodo-diene **2** have to be synthesized and then respectively coupled with the conjugated dienic ester **1** and the allylic 1,2-diol **H**.

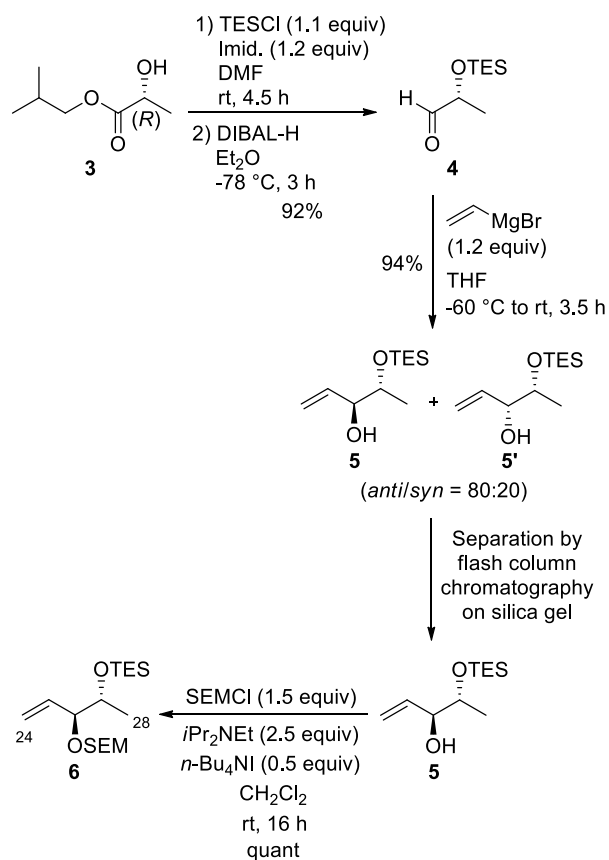
Scheme 3. Retrosynthesis of the C15-C28 fragment



The synthesis of the α,β -unsaturated 1,2-diol **H** was realized in four steps starting from the commercially available (*R*)-isobutyl lactate **3** (Scheme 4). After protection of the alcohol (TESCl, imidazole, DMF) and reduction of the ester (DIBAL-H, Et₂O, -78 °C), lactate **3** was transformed to aldehyde **4**¹⁵ (92%) which was then treated with vinylmagnesium bromide (THF, -60 °C to rt) to furnish a mixture of the two diastereomeric alcohols **5** and **5'** in 94% yield, in a ratio of 80:20 in favor of the *anti*-isomer **5** which corresponds to the expected Felkin-Anh adduct. These two diastereomers were separated by column chromatography on silica gel to afford the pure desired 1,2-*anti*-diol **5**. As planned in our retrosynthesis, a Yamaguchi macrolactonization is envisioned to access filipin III and a selective deprotection of the hydroxyl present at C27 is thus required.

Therefore, to protect the hydroxyl group present at C26, an orthogonal protecting group to the TES group, present at C27, had to be used and a SEM group was chosen to this end. After treatment of **5** with SEMCl (*i*Pr₂NEt, *n*-Bu₄NI, CH₂Cl₂, rt, 16 h), the protected diol **6** was isolated in quantitative yield (Scheme 4).

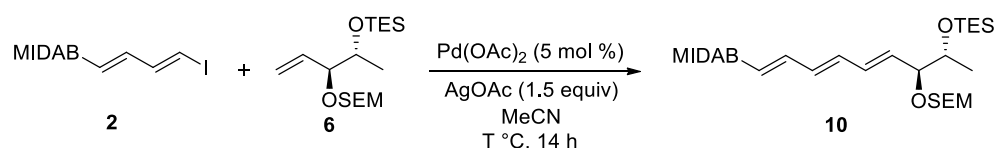
Scheme 4. Synthesis of the 1,2-diol **6**



The synthesis of the iodo-diene **2**¹⁴ was then achieved (Scheme 5). The synthesis started with the hydrostannylation followed by the iodo-destannylation of alkyne **7** to produce **8** (Bu₃SnH, AIBN then I₂, THF, -78 °C to rt, 72%) (Scheme 5). The obtained vinyl iodide **8** was then involved in a Heck coupling with vinyltrimethylsilane [Pd(OAc)₂, AgOAc, MeCN, 80 °C] leading to a mixture of the desired diene **9** and the branched diene **9'** in a ratio of 80:20 (72%) which, at this stage, could not be separated. However, after iodo-desilylation using NIS at 0 °C (MeCN, 6 h) and

purification by column chromatography on silica gel, the two iodo-isomers were separated, and the desired linear iodo-diene **2** was isolated in 80% yield (Scheme 5).¹⁶ With **2** and **6** in hand, the second Heck coupling was examined. When iodo-diene **2** was treated with 1.5 equiv of diol **6**, in the presence of Pd(OAc)₂ (5 mol %) and AgOAc (1.5 equiv) in MeCN for 14 h at 80 °C, using previously described conditions,¹⁴ only 15% of the desired coupling product **10** were obtained (Table 1, entry 1). A decrease of the temperature to 50 °C did not increase the yield in **10** (16%) (Table 1, entry 2). On the contrary, when the reaction was performed at 50 °C, using 5 equiv of 1,2-diol **6**, the yield in **10** was increased to 44% (Table 1, entry 3).¹⁷

Table 1. Optimization of the second Heck coupling



| entry | 6 | T (°C) | yield (%) ^a |
|-------|------------------|--------------|------------------------|
| 1 | 1.5 equiv | 80 °C | 15 |
| 2 | 1.5 equiv | 50 °C | 16 |
| 3 | 5.0 equiv | 50 °C | 44 |

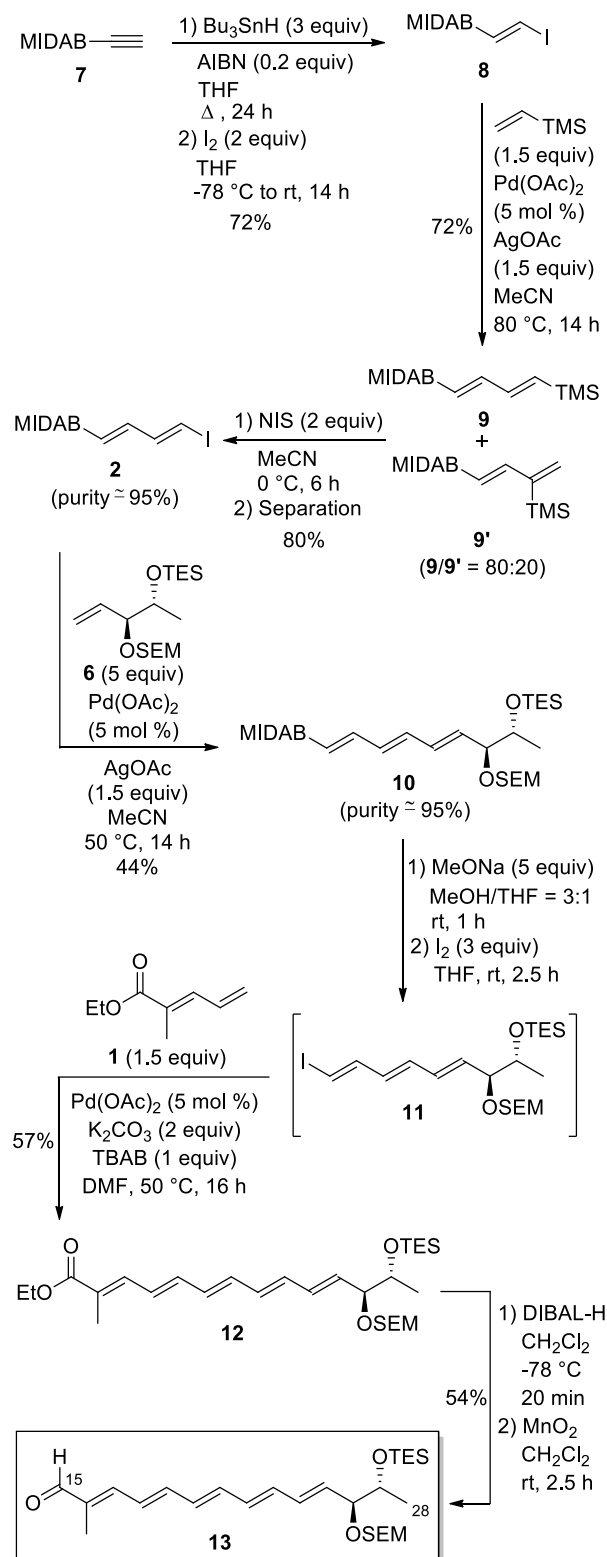
^a Isolated yield

To access pentadiene **E**, compound **10** has to be transformed into an iodo-triene of type **F**. Thus, the MIDA boronate **10** was hydrolyzed using sodium methylate (MeONa, MeOH/THF = 3:1, rt, 1 h) and the resulting boronic acid was involved in an iodo-deborylation (I₂, THF, rt, 2.5 h) to produce iodo-triene **11** which was not purified but directly involved in a Heck coupling with the dienic ester **1**¹⁸ utilizing Jeffery's conditions¹⁹ [Pd(OAc)₂, K₂CO₃, TBAB, DMF, 50 °C, 16 h] providing the desired conjugated pentaenic ester **12** in 57% yield over the three steps. After reduction of the ester (DIBAL-H, -78°C), the resulting alcohol was not purified but directly

oxidized by MnO₂ to produce the desired aldehyde **13** in 54% yield over the two steps (Scheme 5).

It is worth mentioning that aldehyde **13** is prone to degradation, so it has to be synthesized and used rapidly after its preparation. The pentaenic fragment **13** was thus synthesized in 10 steps from (*R*)-isobutyl lactate **3** with a global yield of 12% (Scheme 5).

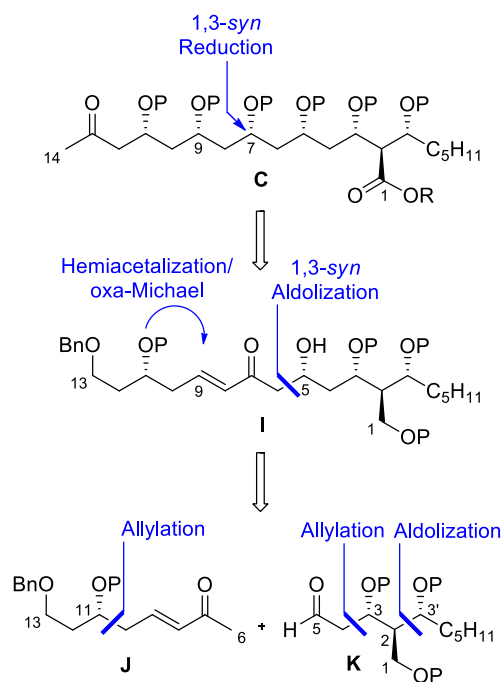
Scheme 5. Synthesis of the pentaenic aldehyde **13**



Synthesis of the C1-C14 fragment (fragment C)

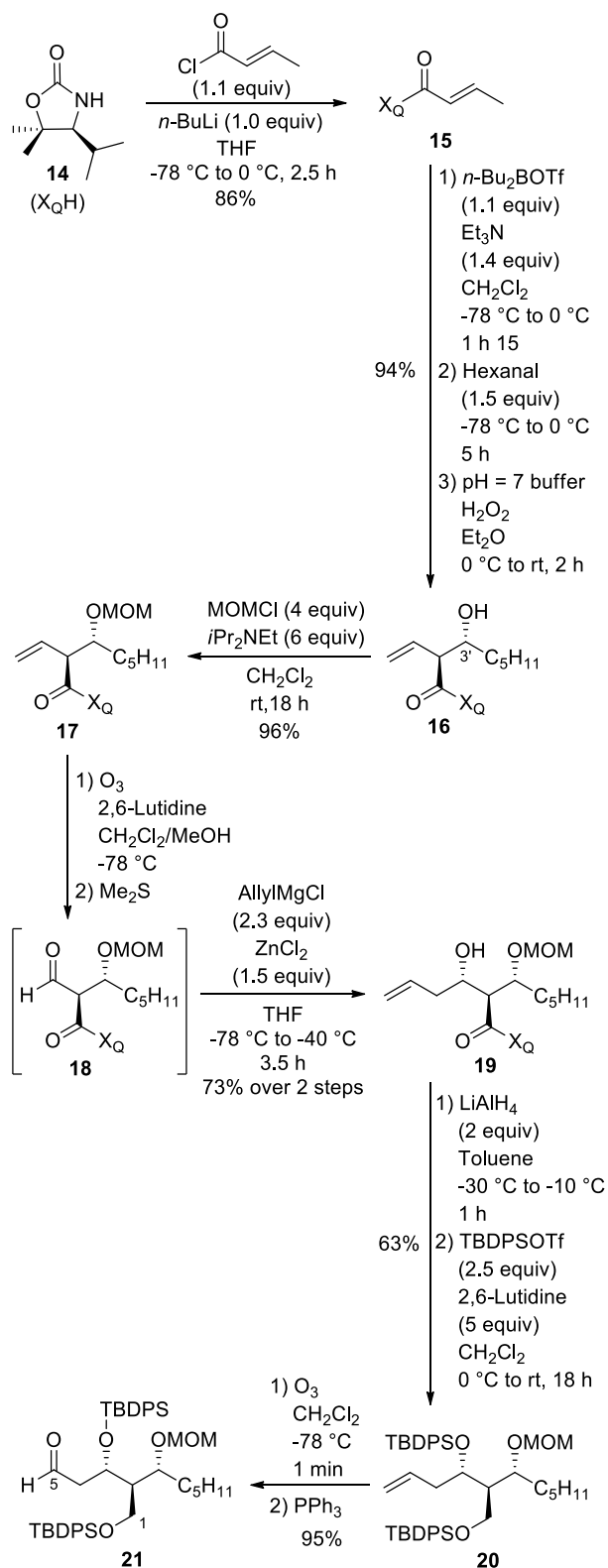
The synthesis of the polyol fragment **C** was envisaged from enone **I** which would be prepared from the α,β -unsaturated ketone **J** and the β -hydroxy aldehyde **K** (Scheme 6). The control of the stereogenic centers at C2 and C3' in **K** would be achieved by using an Evans aldol condensation. The C3 and C11 stereogenic centers in **K** and **J** would be introduced by using respectively a diastereoselective and an enantioselective allylation of the corresponding aldehydes. An aldol condensation between **J** and **K** would allow the control of the stereogenic center at C5 according to a 1,3-*syn* control. The stereogenic center at C9 would be introduced by using an hemiacetalization/oxa-Michael addition sequence applied to enone **I** and, finally, the control of the C7 stereogenic center would be achieved by a 1,3-*syn* diastereoselective reduction of the resulting β -hydroxy ketone (Scheme 6).

Scheme 6. Retrosynthesis of the C1-C14 fragment



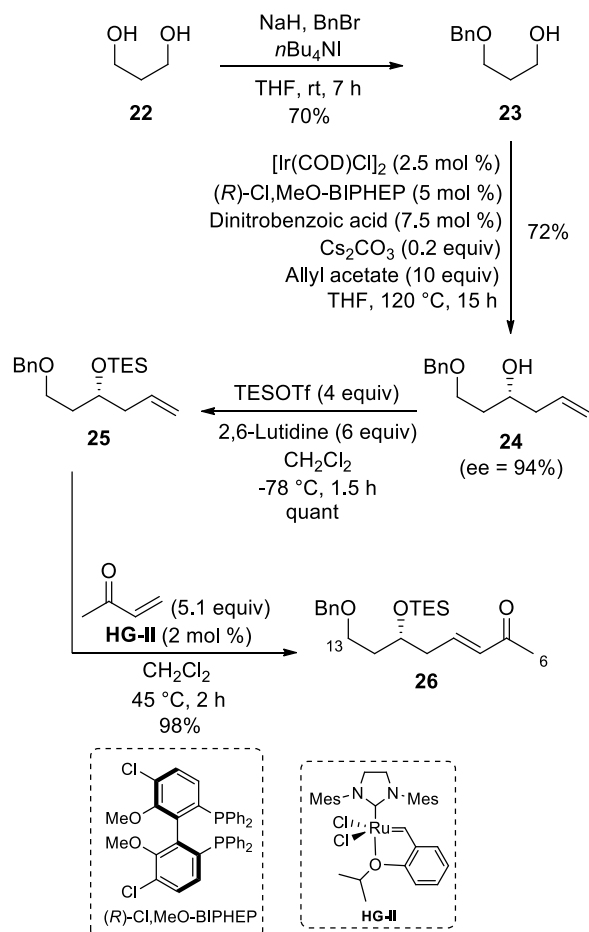
The synthesis of the C1-C5 fragment, compound **21**, started with the unsaturated oxazolidinone **15** prepared by acylation of the (*S*)-4-isopropyl-5,5-dimethyloxazolidin-2-one **14**.^{20,21,22} After treatment of **15** under Evans conditions [*n*-Bu₂BOTf (1.1 equiv), Et₃N (1.4 equiv), CH₂Cl₂, -78 °C],²³ the enol borinate was condensed with hexanal which, after oxidative treatment (H₂O₂, pH = 7 buffer), led to the aldol product **16** as a single detectable diastereomer (by ¹H NMR), in 94% yield. After protection of the hydroxyl group [MOMCl (4 equiv), *i*Pr₂NEt, CH₂Cl₂, rt, 18 h], the resulting MOM ether **17** was ozonolyzed and the obtained aldehyde **18** was directly treated with allylmagnesium chloride in the presence of ZnCl₂²⁴ to produce the homoallylic alcohol **19** as a single detectable diastereomer in 73% yield (from **17**).²⁵ The homoallylic alcohol **19** was then transformed in three steps into aldehyde **21**. After cleavage of the chiral auxiliary by LiAlH₄ (toluene, -30 °C to -10 °C),²⁶ the resulting diol was directly protected (TBDPSOTf, 2,6-lutidine, CH₂Cl₂) to furnish compound **20** (63% over the 2 steps) which, after ozonolysis, led to the desired aldehyde **21** (O₃, CH₂Cl₂, -78 °C then PPh₃, 95%). The C1-C5 fragment was thus obtained from hexanal in 7 steps for the longest linear sequence and with an overall yield of 39% (Scheme 7).

Scheme 7. Synthesis of the C1-C5 fragment



Methyl ketone **26**, which represents the C6-C13 fragment, was obtained in 4 steps from 1,3-propanediol **22**. The diol was first monobenzylated to produce **23**²⁷ and after a catalytic enantioselective allylation using the conditions developed by Krische *et al.*,²⁸ the homoallylic alcohol **24** was isolated in 72% yield with an enantiomeric excess of 94%.²⁹ After protection of the alcohol, the resulting silyl ether **25**³⁰ was involved in a cross-metathesis with methyl vinyl ketone [5.1 equiv, **HG-II** (2 mol %), CH₂Cl₂, 45 °C, 2 h] and the α,β-unsaturated ketone **26** was isolated in 98% yield (Scheme 8).

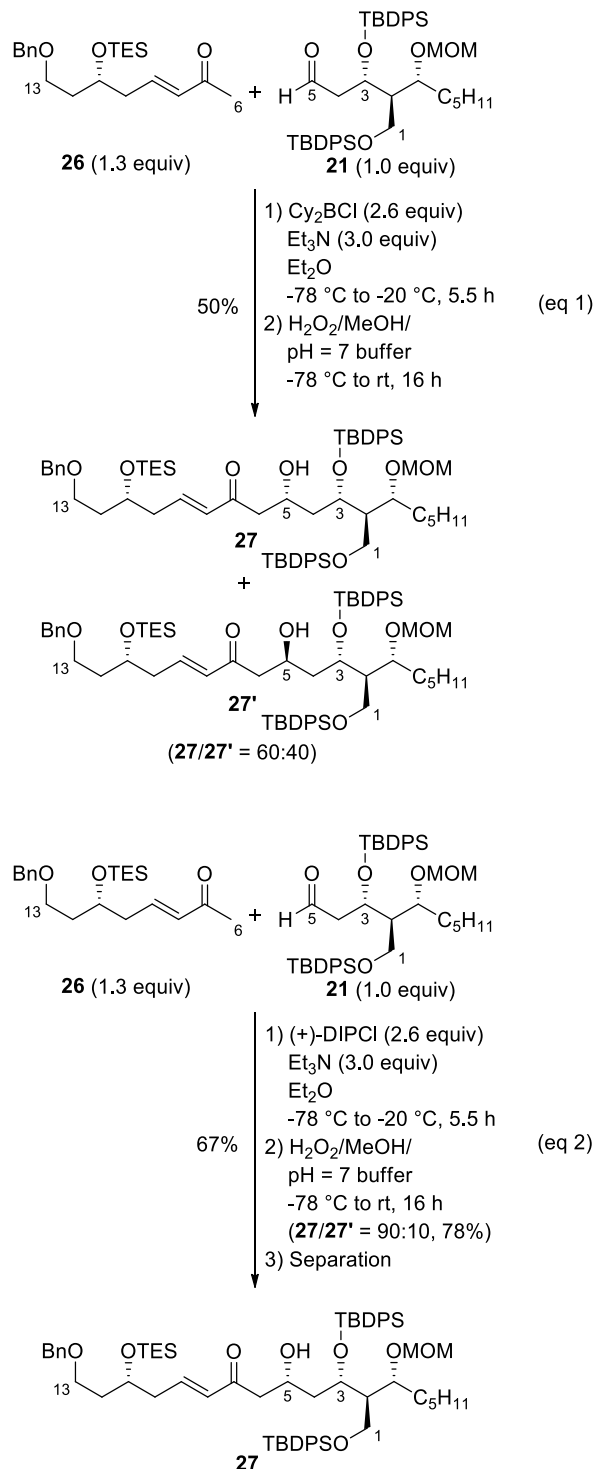
Scheme 8. Synthesis of the C6-C13 fragment



Having methyl ketone **26** and aldehyde **21** in hand, a diastereoselective aldol condensation has to be performed to access the C1-C13 fragment of filipin III. As the stereogenic center at C5 has to be introduced in a stereocontrolled manner, we took advantage of the preexisting hydroxyl group present at C3 in compound **21**, and the Paterson's conditions were chosen to control the diastereoselectivity.³¹

Different dialkyl borane reagents have been tried to favor the 1,3-*syn* control between the hydroxyl groups at C3 and C5 during the aldolization. When methyl ketone enol borinate was prepared using chlorodicyclohexylborane [(2.6 equiv) in the presence of Et₃N (3.0 equiv) in Et₂O at 0 °C] and condensed with aldehyde **21**, two diastereomers **27** and **27'** were obtained in 50% yield³² in a ratio of 60:40 in favor of the 1,3-*syn* product **27** (Scheme 9, eq 1).³¹ The diastereoselectivity in favor of **27** was improved when the methyl ketone enol borinate was prepared with (+)-chlorodiisopinocampheylborane [(+)-DIPCl],³³ using the same reaction conditions as previously, as the ratio of **27/27'** was improved to 90:10. After separation of the two diastereomers by flash column chromatography on silica gel, **27** was isolated with a yield of 67% (from aldehyde **21**) (Scheme 9, eq 2). We have to point out that the 1,3-*syn* stereoselectivity was latter verified on compound **29** (*vide infra*).

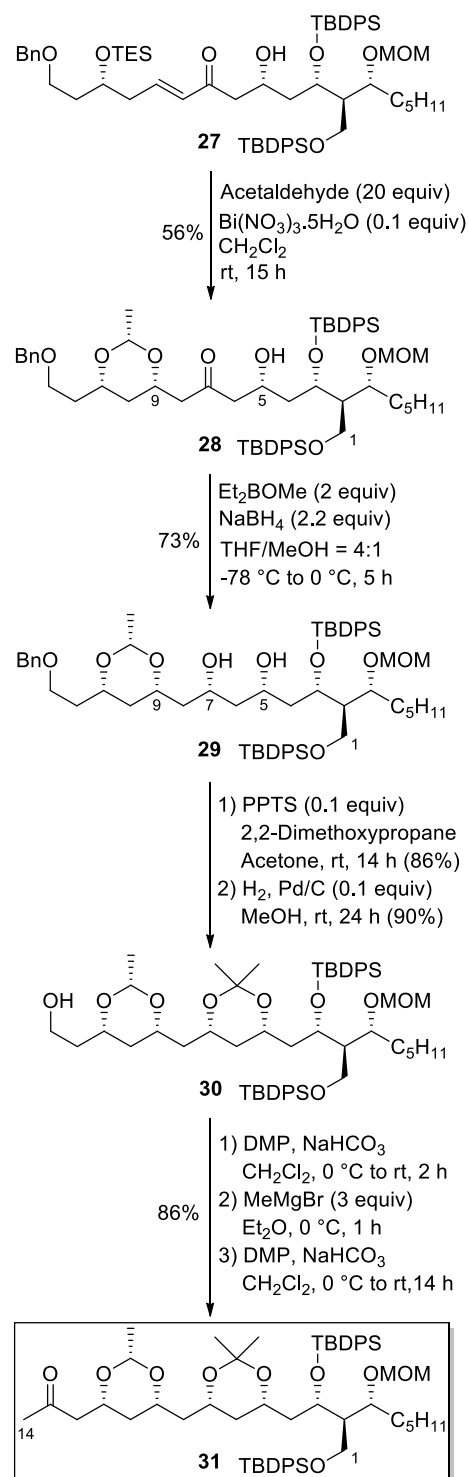
Scheme 9. Synthesis of the C1-C13 fragment



Two stereogenic centers remained to be controlled in fragment C1-C13. At first, the stereogenic center at C9 was introduced by using an hemiacetalization/1,4-addition sequence

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2
3 applied to the α,β -unsaturated ketone **27** in the presence of acetaldehyde, catalyzed by
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5 Bi(NO₃)₃·5H₂O (0.1 equiv) (CH₂Cl₂, rt, 15 h).³⁴ It was not necessary to cleave the triethylsilyl
6
7 group as, under these conditions, the acetal **28** was directly obtained in 56% yield as a single
8
9 detectable diastereomer. The last stereogenic center at C7 was controlled by realizing a 1,3-*syn*
10
11 diastereoselective reduction of the β -hydroxyketone **28** (Et₂BOMe, NaBH₄, MeOH/THF = 1:4,
12
13 –78 °C to 0 °C)³⁵ to afford the 1,3-*syn* diol **29** in 73% yield, again as a single detectable
14
15 diastereomer. The transformation of **29** to methyl ketone **31** was finally realized in 5 steps. After
16
17 protection of the diol (dimethoxypropane, PPTS, rt) and deprotection of the benzyl alcohol (Pd/C,
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19 H₂, MeOH, rt), compound **30** was isolated in 77% yield. After oxidation (DMP, NaHCO₃), addition
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21 of methylmagnesium bromide (Et₂O, 0 °C) and oxidation (DMP, NaHCO₃), the desired methyl
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23 ketone **31** was isolated in 86% yield over the 3 steps (Scheme 10).
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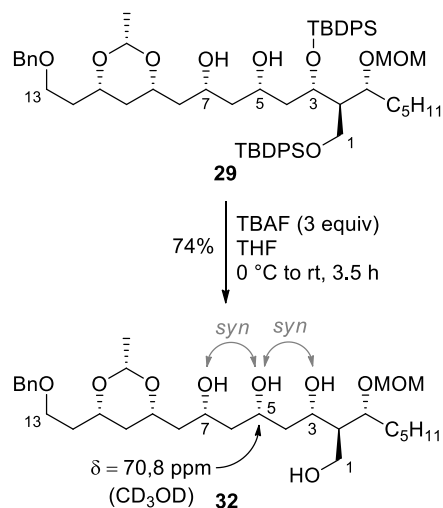
Scheme 10. Synthesis of the C1-C14 methyl ketone



It is worth noting that compound **29** was also transformed into the 1,3,5-deprotected triol **32** in order to confirm the relative stereochemistry between the hydroxyl groups present at C3, C5

and C7 using Kishi's ^{13}C NMR database.³⁶ Treatment of **29** with TBAF (THF, 0 °C) gave tetraol **32** in 74% yield and the analysis of its ^{13}C NMR spectrum in deuterated methanol showed a chemical shift at 70.8 ppm for C5, which is in accordance with a *syn/syn* relative stereochemistry between the hydroxyl groups at C3, C5 and C7 (Scheme 11).

Scheme 11. Determination of the relative stereochemistry of **29**



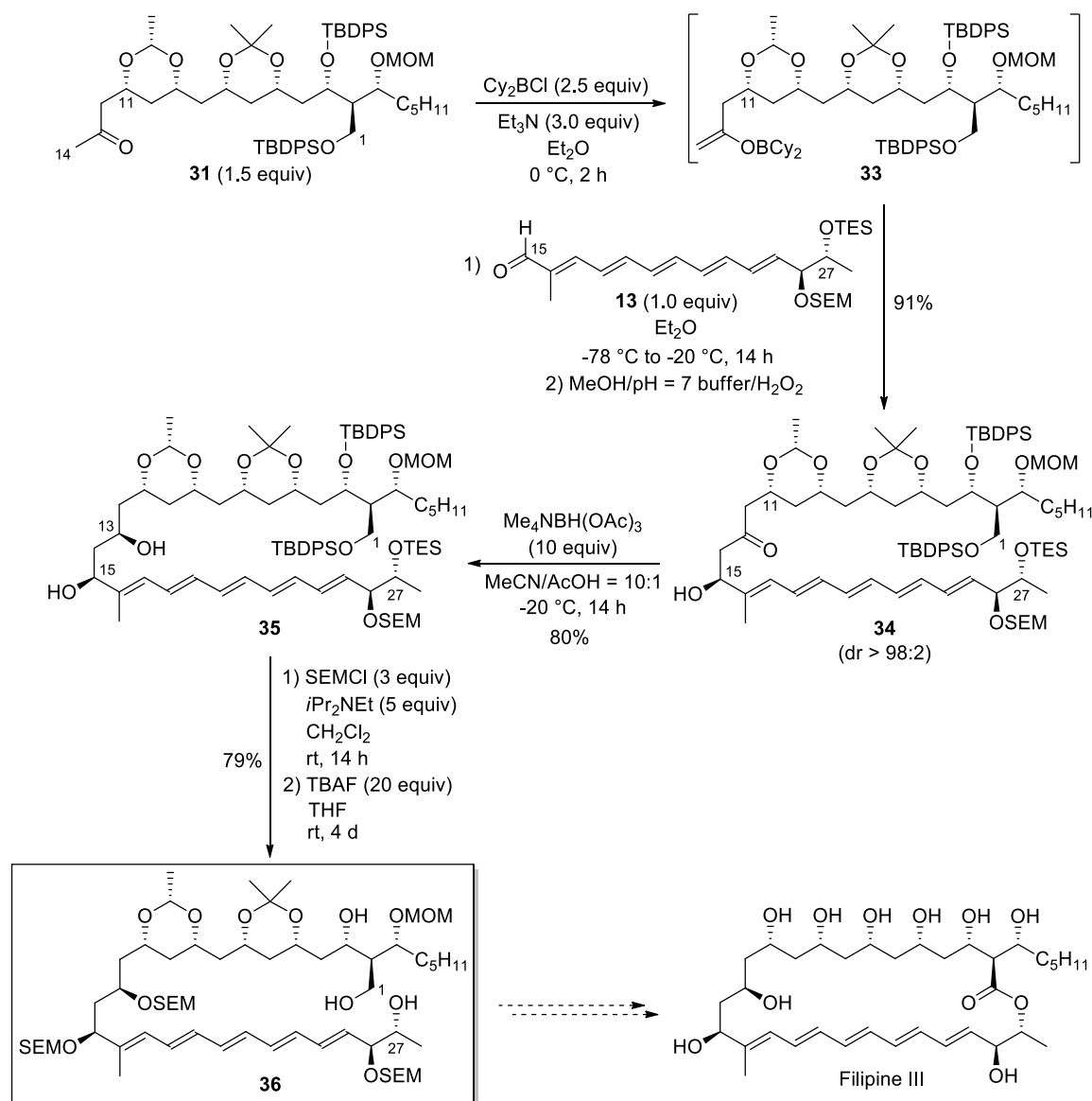
Synthesis of the carbon skeleton of filipin III

Having the C1-C14 and C15-C28 fragments in hand, a 1,5-*anti* diastereoselective aldol condensation had to be performed to access the carbon skeleton of filipin III and to introduce the stereogenic center at C15.

Methyl ketone **31** was thus involved in an aldol condensation with aldehyde **13** under the Paterson's conditions (Cy₂BCl, Et₃N, Et₂O, -78 °C to -20 °C, 14 h) to produce the β -hydroxyketone **34** in 91% yield as a single detectable diastereomer resulting from a 1,5-*anti* control from the acetal at C11.³⁷ The obtained β -hydroxyketone was stereoselectively reduced using Me₄NBH(OAc)₃ (10 equiv, MeCN/AcOH = 10:1, -20 °C, 14 h)³⁸ to produce the 1,3-*anti* diol

35 again as a single detectable diastereomer (80%). After a SEM-protection of the C13 and C15 hydroxyl groups (SEMCl, *i*Pr₂NEt, CH₂Cl₂, rt), followed by the cleavage of the silyl ethers (TBAF, THF, rt), we were able to isolate compound **36** (79%) which corresponds to the carbon skeleton of filipin III with all the stereogenic centers in place (Scheme 12).

Scheme 12. Construction of the carbon skeleton of filipin III



Unfortunately, if the primary alcohol at C1 was selectively oxidized to the corresponding aldehyde, using TEMPO in the presence of a catalytic amount of [bis(acetoxy)-iodo]benzene (BAIB),³⁹ it was not possible to oxidize this aldehyde to the corresponding acid which would have allowed the formation of the macrolactone. Even under the mild Pinnick-Lindgren oxidation conditions (NaClO₂, NaH₂PO₄, 2-methylbut-2-ene), which proved to be efficient in several syntheses of polyenic natural products,⁴⁰ the aldehyde was transformed to a complex mixture due to the degradation of the polyenic moiety under these oxidative conditions. In addition, the direct selective oxidation of the primary alcohol to the corresponding acid using Epp and Widlanski conditions [TEMPO, PhI(OAc)₂, MeCN/H₂O = 1:1],⁴¹ conditions which were also used in several total syntheses,⁴² led to the decomposition of compound **36**, and we were never able to obtain the desired carboxylic acid.

CONCLUSION

The strategy which has been envisioned to construct the macrocyclic core of filipin III, even if reported to be successful in the syntheses of several polyenic natural products,^{40,42} proved to be inefficient in our case, probably due to the instability of the polyenic moiety during the last steps. Due to our previous failures in the synthesis of wortmannilactone (concomitantly realized to the synthesis of filipin III),⁴³ we would like to stress on avoiding the use of an oxidation/macrolactonization sequence at the last crucial step to access polyenic macrolactones. One advice would be to favor a Horner-Wadsworth-Emmons reaction to construct one of the olefin of the polyene and to access the macrocycle, a strategy which was used by Rychnovsky *et al.* for the synthesis of filipin III¹¹ as well as in our final successful attempt to access

wortmannilactone.^{12b,43} A cross-coupling reaction would be another alternative to install the sensitive polyene moiety in one of the latest step of the synthesis.

EXPERIMENTAL SECTION

General experimental methods: All reactions were carried out under anhydrous conditions, using flame-dried glassware and under an argon atmosphere. CH₂Cl₂, Et₃N and *i*Pr₂NEt were distilled from CaH₂; Et₂O and THF were distilled from Na/benzophenone. Other reagents were obtained from commercial suppliers and used as received. TLC was performed on silica gel plates with UV and *p*-anisaldehyde or KMnO₄ stain visualization. Flash chromatography was performed on silica gel (230-400 mesh). Optical rotations were measured using a polarimeter with a 1 dm path length. Infrared (IR) spectra were recorded on an ATR plate, wave numbers are indicated in cm⁻¹. ¹H NMR spectra were recorded at 400 MHz in CDCl₃, acetone-d₆, C₆D₆, or CD₃OD and data are reported as follows: chemical shift in ppm from tetramethylsilane or residual solvent signals (CHCl₃: 7.26 ppm, acetone-d₅: 2.05 ppm, C₆D₅H: 7.16 ppm, MeOD-d₃: 3.31 ppm) as an internal standard, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintuplet, hept = heptuplet, m = multiplet or overlap of non equivalent resonances, br = broad), coupling constant in Hz, integration. ¹³C NMR spectra were recorded at 100 MHz in CDCl₃, acetone-d₆, C₆D₆, or CD₃OD and data are reported as follows: chemical shift in ppm from tetramethylsilane with the solvent as an internal indicator (CDCl₃: 77.16 ppm, acetone-d₆: 29.84 and 206.26 ppm, C₆D₆: 128.06 ppm, MeOD-d₄: 49.00 ppm). Mass spectra were realized with a gas chromatograph-mass spectrometer by electronic impact. High resolution mass spectra (HRMS) were performed with an orbitrap mass analyzer by electrospray ionization.

(E)-Ethyl 2-methylpenta-2,4-dienoate (1):¹⁸ To a solution of (carboethoxyethylidene)triphenylphosphorane (2 g, 5.5 mmol, 1.0 equiv) in dry CH₂Cl₂ (16 mL) was added acrolein (0.37 mL, 5.5 mmol, 1.0 equiv) dropwise. The mixture was stirred at rt for 1 h and then heated at 38 °C for 3.5 h. The solution was cooled to rt, concentrated under *vacuum* and then pentane was added (20 mL). The suspension was filtered over Celite® and the filtrate was concentrated under *vacuum*. Purification of the crude material by flash column chromatography on silica gel (pentane/Et₂O = 98:2) afforded the dienic ester **1** (517 mg, 3.69 mmol, 67%) as a colorless oil. The spectral data are in agreement with those reported in the literature.¹⁸ IR: ν 3091, 2982, 2933, 1705, 1633, 1596, 1446, 1421, 1392, 1367, 1341, 1244, 1195, 1176, 1100, 1034, 1008, 990, 928 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 7.17 (br d, J = 11.4 Hz, 1H), 6.66 (ddd, J = 16.8 Hz, J = 11.3 Hz, J = 10.1 Hz, 1H), 5.57 (br d, J = 16.8 Hz, 1H), 5.45 (br d, J = 10.0 Hz, 1H), 4.22 (q, J = 7.1 Hz, 2H), 1.96 (br d, J = 1.3 Hz, 3H), 1.31 (t, J = 7.1 Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz): δ 168.5, 138.4, 132.4, 128.3, 124.2, 60.8, 14.4, 12.8; MS (EI) m/z : 140 (M⁺, 25), 112 (36), 111 [(M-Et)⁺, 23], 97 (16), 96 (11), 95 [(M-EtO)⁺, 57], 69 (15), 67 (100), 66 (31), 65 (36), 56 (12), 55 (13).

[(1E,3E)-4-Iodobuta-1,3-dien-1-yl]boronic acid MIDA ester (2):¹⁴ To a solution of vinyl trimethylsilane **9** used as a 80:20 mixture with **9'** (500 mg, 1.78 mmol, 1.0 equiv) in anhydrous MeCN (17.8 mL) cooled to 0 °C was added NIS (800 mg, 3.56 mmol, 2.0 equiv). The mixture was stirred at 0 °C in the absence of light for 6 h, and then quenched by the addition of a saturated aqueous solution of Na₂S₂O₃ (20 mL). EtOAc (20 mL) was added, the layers were separated and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under *vacuum*. The crude material was purified by flash column chromatography on silica gel (Et₂O/acetone = 8:2 to 7:3) to afford the iododiene **2** (476

mg, 1.42 mmol, 80%) as a yellow viscous foam. The spectral data are in agreement with those reported in the literature.¹⁴ IR: ν 3007, 2958, 1753, 1698, 1616, 1458, 1336, 1285, 1247, 1154, 1119, 1083, 1023, 997, 954, 890, 872, 835 cm^{-1} ; ^1H NMR (acetone- d_6 , 400 MHz): δ 7.15 (ddd, $J = 14.4$, $J = 10.4$ and $J = 0.8$ Hz, 1H), 6.67 (br d, $J = 14.4$ Hz, 1H), 6.53 (dd, $J = 17.4$ and $J = 10.5$ Hz, 1H), 5.77 (d, $J = 17.4$ Hz, 1H), 4.23 ($d_{\text{AB syst}}$, $J = 16.8$ Hz, 2H), 4.05 ($d_{\text{AB syst}}$, $J = 16.8$ Hz, 2H), 3.02 (s, 3H); ^{13}C NMR (acetone- d_6 , 100 MHz): δ 169.0 (2C), 148.3, 142.5, 82.1, 62.2 (2C), 47.4, C-B not visible.⁴⁴

Synthesis of 4:

(*R*)-Isobutyl 2-(triethylsilyloxy)propanoate (3'):¹⁵ To a solution of (*R*)-isobutyl lactate **3** (7.1 g, 48.6 mmol, 1.0 equiv) in DMF (50 mL) were added imidazole (3.9 g, 57.3 mmol, 1.2 equiv) and TESCOI (8.5 mL, 50 mmol, 1.1 equiv). The mixture was stirred at rt for 4.5 h and then quenched by addition of H_2O (20 mL). Et_2O (50 mL) was added, the layers were separated and the aqueous layer was extracted with Et_2O (4×50 mL). The combined organic layers were washed with brine (2×10 mL), dried over MgSO_4 , filtered and concentrated under *vacuum*. The crude material was purified by flash column chromatography on silica gel (petroleum ether/ Et_2O = 95:5) to afford the silyl ether **3'** (12.62 g, 48.5 mmol, quant) as a colorless oil. The spectral data are in agreement with those reported in the literature.¹⁵ $[\alpha]_{\text{D}}^{20} + 25.3$ (c 0.04, CHCl_3); IR: ν 2956, 2877, 1756, 1459, 1141, 1002 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz): δ 4.32 (q, $J = 6.7$ Hz, 1H), 3.92 ($dd_{\text{AB syst}}$, $J = 10.6$ and $J = 6.8$ Hz, 1H), 3.87 ($dd_{\text{AB syst}}$, $J = 10.6$ and $J = 6.7$ Hz, 1H), 1.95 (hept, $J = 6.7$ Hz, 1H), 1.40 (d, $J = 6.7$ Hz, 3H), 0.98-0.90 (m, 15H), 0.62 (q, $J = 8.0$ Hz, 6H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 174.2, 70.8, 68.1, 27.8, 21.6, 19.09, 19.07, 6.7 (3C), 4.6 (3C); MS (EI) m/z : 231 [(M-Et) $^+$, 3], 203

[(M-*i*Bu)⁺, 11], 176 (14), 175 (100), 159 (40), 147 (22), 131 (TESO⁺, 21), 119 (28), 115 (TES⁺, 25), 103 (62), 87 (25), 75 (27), 59 (22), 58 (11), 57 (*i*Bu⁺, 27).

(*R*)-2-(Triethylsilyloxy)propanal (4):¹⁵ To a solution of previously synthesized ester **3'** (2.6 g, 10 mmol, 1.0 equiv) in dry Et₂O (40 mL), cooled to −78 °C, was added dropwise a solution of DIBAL-H (15 mL, 1M in hexanes, 15 mmol, 1.5 equiv) over a period of 20 min. The mixture was stirred for 3 h at −78 °C, then quenched by the addition of H₂O (20 mL), and warmed to rt. The gel formed was dissolved by the addition of an aqueous solution of HCl (10% in weight). The layers were separated and the aqueous layer was extracted with Et₂O (3 × 30 mL). The combined organic layers were washed with brine (20 mL), dried over MgSO₄, filtered and concentrated under *vacuum*. The crude material was purified by flash column chromatography on silica gel (petroleum ether/Et₂O = 95:5) to afford aldehyde **4** (1.74 g, 9.2 mmol, 92%) as a colorless oil. The spectral data are in agreement with those reported in the literature.¹⁵ [α]_D²⁰ + 10 (*c* 1.56, CHCl₃) {for *ent*-**4** [α]_D²⁰_{lit} − 11.5 (*c* 1.55, CHCl₃)}^{15b} IR: ν 2956, 2878, 1739, 1459, 1375, 1239, 1135, 1096, 1006 cm^{−1}; ¹H NMR (CDCl₃, 400 MHz): δ 9.62 (d, *J* = 1.4 Hz, 1H), 4.08 (qd, *J* = 6.8 and *J* = 1.4 Hz, 1H), 1.29 (d, *J* = 6.8 Hz, 3H), 0.97 (t, *J* = 7.9 Hz, 9H), 0.64 (q, *J* = 7.9 Hz, 6H); ¹³C NMR (CDCl₃, 100 MHz): δ 204.3, 73.5, 18.6, 6.7 (3C), 4.7 (3C); MS (EI) *m/z*: 159 [(M-CHO)⁺, 98], 131 (100), 115 (49), 103 (29), 87 (75), 75 (25), 59 (41).

(3*S*,4*R*)-4-(Triethylsilyloxy)pent-1-en-3-ol (5): To a solution of vinylmagnesium bromide (10.8 mL, 1M in THF, 10.8 mmol, 1.2 equiv) in dry THF (15 mL), cooled to −60 °C, was cannulated a solution of aldehyde **4** (1.7 g, 9.0 mmol, 1.0 equiv) in dry THF (10 mL). The mixture was stirred at −60 °C for 30 min, then warmed to rt and stirred for 3 h. The reaction mixture was quenched by the addition of a saturated aqueous solution of NH₄Cl (20 mL) and H₂O (20 mL). Et₂O (30 mL)

was added, the layers were separated and the aqueous layer was extracted with Et₂O (3 × 50 mL). The combined organic layers were washed with brine (20 mL), dried over MgSO₄, filtered and concentrated under *vacuum*. The crude material was purified by flash column chromatography on silica gel (petroleum ether/EtOAc = 98:2) to afford the alcohols **5** and **5'** as a mixture of diastereomers in a 80:20 ratio (1.84 g, 8.5 mmol, 94%) as a colorless oil. The spectral data are in agreement with those reported in the literature.^{15a} Separation of the two diastereomers by flash column chromatography on silica gel (CH₂Cl₂) afforded pure **5**. [α]_D²⁰ – 21.7 (*c* 1.02, CHCl₃); IR: ν 3462, 3080, 2956, 2912, 2878, 1459, 1416, 1379, 1239, 1130, 1093, 1005, 972, 933 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 5.82 (ddd, *J* = 17.3, *J* = 10.5 and *J* = 6.1 Hz, 1H), 5.30 (dt_{app}, *J* = 17.3 and *J* = 1.6 Hz, 1H), 5.19 (dt_{app}, *J* = 10.5 and *J* = 1.5 Hz, 1H), 4.05 (m, 1H), 3.86 (qd, *J* = 6.3 and *J* = 3.6 Hz, 1H), 2.36 (br d, *J* = 4.0 Hz, 1H, OH), 1.09 (d, *J* = 6.3 Hz, 3H), 0.97 (t, *J* = 7.9 Hz, 9H), 0.62 (q, *J* = 7.9 Hz, 6H); ¹³C NMR (CDCl₃, 100 MHz): δ 136.6, 116.5, 76.7, 71.1, 17.5, 6.9 (3C), 4.9 (3C); MS (EI) *m/z*: 198 [(M-H₂O)⁺, 1], 187 [(M-Et)⁺, 32], 159 (30), 131 (26), 115 (51), 103 (100), 87 (54), 75 (77), 59 (24).

(3*S*,4*R*)-4-(Triethylsilyloxy)-3-[(trimethylsilylethoxy)methoxy]pent-1-ene (6): To a solution of alcohol **5** (1.25 g, 5.77 mmol, 1.0 equiv) in dry CH₂Cl₂ (24 mL) were added *i*Pr₂NEt (2.4 mL, 14.5 mmol, 2.5 equiv), *n*-Bu₄NI (1.07 g, 2.9 mmol, 0.5 equiv) and SEMCl (1.53 mL, 8.64 mmol, 1.5 equiv). The mixture was stirred at rt for 16 h and then quenched by the addition of H₂O (30 mL). The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (3 × 45 mL). The combined organic layers were washed with brine, dried over MgSO₄, filtered and concentrated under *vacuum*. The crude material was purified by flash column chromatography on silica gel (petroleum ether/Et₂O = 99:1) to afford the acetal **6** (2.0 g, 5.77 mmol, quant) as a colorless oil. [α]_D²⁰ + 51.4 (*c* 1.04, CHCl₃); IR: ν 3079, 2955, 2878, 1684, 1459, 1416, 1377, 1249, 1107, 1031,

1010, 925, 860 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz): δ 5.73 (ddd, $J = 16.8$, $J = 11.1$ and $J = 7.5$ Hz, 1H), 5.26-5.19 (m, 2H), 4.69 ($d_{\text{AB syst}}$, $J = 6.8$ Hz, 1H), 4.64 ($d_{\text{AB syst}}$, $J = 6.8$ Hz, 1H), 3.87-3.78 (m, 2H), 3.74-3.50 (m, 2H), 1.15 (d, $J = 6.1$ Hz, 3H), 0.94 (t, $J = 7.9$ Hz, 9H), 0.98-0.88 (m, 2H), 0.58 (q, $J = 7.9$ Hz, 6H), 0.01 (s, 9H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 135.8, 118.7, 92.4, 81.7, 70.8, 65.2, 20.0, 18.2, 7.0 (3C), 5.1 (3C), -1.3 (3C); MS (EI) m/z : 309 (1), 287 (1), 273 [(M-TMS) $^+$, 1], 259 (10), 215 (8), 199 (20), 175 (10), 159 (67), 147 (10), 131 (40), 115 (63), 103 (32), 87 (35), 73 (100), 59 (17); HRMS (ESI): Calculated for $\text{C}_{17}\text{H}_{38}\text{O}_3\text{Si}_2\text{Na}$ [M + Na] $^+$: 369.2252, found: 369.2251.

(E)-(2-Iodovinyl)boronic acid MIDA ester (8):¹⁴ To a suspension of alkyne **7** (2.5 g, 13.8 mmol, 1.0 equiv) in dry THF (60 mL) were added AIBN (227 mg, 1.38 mmol, 0.1 equiv) and Bu_3SnH (5.6 mL, 20.8 mmol, 1.5 equiv). The mixture was heated at reflux for 16 h and then AIBN (227 mg, 1.38 mmol, 0.1 equiv) and Bu_3SnH (5.6 mL, 20.8 mmol, 1.5 equiv) were added again. After 8 h of reflux, the solution was cooled to -78 $^\circ\text{C}$ and a solution of I_2 (7.0 g, 27.6 mmol, 2.0 equiv) in dry THF (40 mL) was added dropwise over 1 h. The mixture was stirred at -78 $^\circ\text{C}$, progressively warmed to rt overnight, and then quenched by the addition of a saturated aqueous solution of $\text{Na}_2\text{S}_2\text{O}_3$ (40 mL). EtOAc (50 mL) was added, the layers were separated and the aqueous layer was extracted with EtOAc (2×50 mL). The combined organic layers were washed with brine, dried over MgSO_4 , filtered and concentrated under *vacuum*. The resulting solid was suspended in Et_2O , filtered, washed with additional Et_2O to give the vinyl iodide **8** (3.07 g, 9.9 mmol, 72%) as a white solid. The spectral data are in agreement with those reported in the literature.¹⁴ mp: 163-165 $^\circ\text{C}$ (lit.:¹⁴ 145 $^\circ\text{C}$); IR: ν 3005, 2961, 1745, 1708, 1569, 1451, 1336, 1283, 1184, 1154, 1104, 1077, 1022, 1005, 965, 952, 893 cm^{-1} ; ^1H NMR (acetone- d_6 , 400 MHz): δ 6.91 (d, $J = 15.6$ Hz, 1H), 6.82 (d, $J = 15.6$ Hz, 1H), 4.27 ($d_{\text{AB syst}}$, $J = 16.9$ Hz, 2H), 4.11 ($d_{\text{AB syst}}$, $J = 16.9$ Hz, 2H), 3.08 (s, 3H); ^{13}C NMR (acetone- d_6 , 100 MHz): δ 168.6 (2C), 90.2, 62.6 (2C), 47.6, C-B not visible.⁴⁴

[(1E,3E)-4-(Trimethylsilyl)buta-1,3-dien-1-yl]boronic acid MIDA ester (9):¹⁴ To a solution of vinyl iodide **8** (1.0 g, 3.24 mmol, 1.0 equiv) in anhydrous MeCN (22 mL) in a vial, were added AgOAc (810 mg, 4.85 mmol, 1.5 equiv), Pd(OAc)₂ (36 mg, 0.16 mmol, 0.05 equiv) and vinyltrimethylsilane (0.71 mL, 4.82 mmol, 1.5 equiv). The vial was sealed and the mixture was heated at 80 °C for 14 h. The mixture was then cooled to rt, transferred into a flask containing Celite® using acetone and concentrated under *vacuum* to give a grey powder. Purification of the crude material by flash column chromatography on silica gel (solid loading, Et₂O/acetone = 10:0 to 8:2) afforded the desired diene **9** as an unseparable mixture with the branched isomer **9'** in a 8:2 ratio (660 mg, 2.35 mmol, 72%) and as a beige solid. The spectral data are in agreement with those reported in the literature.¹⁴ mp: 205-207 °C (lit.:¹⁴ 210 °C); IR (mixture of isomers): ν 3016, 2956, 2899, 1753, 1624, 1572, 1462, 1333, 1294, 1246, 1175, 1155, 1118, 1083, 1000, 966, 952, 851 cm⁻¹; ¹H NMR (acetone-d₆, 400 MHz, major isomer): δ 6.66-6.52 (m, 2H), 5.92 (d, J = 17.9 Hz, 1H), 5.74 (d, J = 17.0 Hz, 1H), 4.22 (d_{AB} syst, J = 16.8 Hz, 2H), 4.04 (d_{AB} syst, J = 16.8 Hz, 2H), 3.01 (s, 3H), 0.08 (s, 9H); ¹³C NMR (acetone-d₆, 100 MHz, major isomer): δ 169.0 (2C), 147.3, 145.9, 135.1, 62.3 (2C), 47.4, -1.3 (3C), C-B not visible.⁴⁴

{(1E,3E,5E,7S,8R)-8-(Triethylsilyloxy)-7-[2-(trimethylsilyl)ethoxy]methoxy}nona-1,3,5-trien-1-yl}boronic acid MIDA ester (10): To a solution of vinyl iodide **2** (330 mg, 0.98 mmol, 1.0 equiv) in anhydrous MeCN (11.2 mL) in a vial, were added the protected allylic alcohol **6** (1.70 g, 4.9 mmol, 5.0 equiv), AgOAc (246 mg, 1.48 mmol, 1.5 equiv), and Pd(OAc)₂ (11 mg, 0.05 mmol, 0.05 equiv). The vial was sealed and the mixture was heated at 50 °C for 14 h. The mixture was then cooled to rt, diluted with acetone, transferred into a flask containing Celite® and concentrated under *vacuum* to give a grey powder. Purification of the crude material by flash

column chromatography on silica gel (solid loading, Et₂O/acetone = 10:0 to 8:2) afforded the desired triene **10** contaminated with traces of another unidentified isomer (95% purity, 238 mg, 0.43 mmol, 44%) as a yellow oil. $[\alpha]_D^{20} + 78.9$ (*c* 1.0, acetone); IR: ν 2956, 2879, 1769, 1623, 1586, 1461, 1379, 1340, 1299, 1250, 1196, 1110, 1028, 990, 959, 863, 838 cm⁻¹; ¹H NMR (acetone-d₆, 400 MHz): δ 6.62 (br dd, *J* = 17.3 and *J* = 9.4 Hz, 1H), 6.40-6.25 (m, 3H), 5.74 (m, 1H), 5.73 (d, *J* = 17.4 Hz, 1H), 4.64 (br s, 2H), 4.21 (d_{AB syst}, *J* = 16.9 Hz, 2H), 4.03 (dd_{AB syst}, *J* = 16.9 and *J* = 1.4 Hz, 2H), 3.94-3.87 (m, 2H), 3.73 (td, *J* = 9.5 and *J* = 7.4 Hz, 1H), 3.57 (td, *J* = 9.1 and *J* = 7.4 Hz, 1H), 2.99 (s, 3H), 1.13 (d, *J* = 6.0 Hz, 3H), 0.96 (t, *J* = 8.0 Hz, 9H), 0.98-0.89 (m, 2H), 0.61 (q, *J* = 8.0 Hz, 6H), 0.03 (s, 9H); ¹³C NMR (acetone-d₆, 100 MHz): δ 169.0 (2C), 143.2, 135.8, 134.6, 133.7, 132.8, 92.8, 81.4, 71.6, 65.4, 62.3 (2C), 47.3, 20.5, 18.5, 7.2 (3C), 5.5 (3C), -1.3 (3C), C-B not visible;⁴⁴ HRMS (ESI): Calculated for C₂₆H₄₈BNO₇Si₂Na [M + Na]⁺: 576.2955, found: 576.2952.

(2E,4E,6E,8E,10E,12S,13R)-Ethyl 2-methyl-13-(triethylsilyloxy)-12-[[2-(trimethylsilyl)ethoxy]-methoxy]tetradeca-2,4,6,8,10-pentaenoate (12): To a solution of triene **10** (160 mg, 0.29 mmol, 1.0 equiv) in a mixture of THF (2.1 mL) and MeOH (0.7 mL) was added MeONa (78 mg, 1.44 mmol, 5.0 equiv). The mixture was stirred at rt in the dark for 1 h and then a solution of I₂ (220 mg, 0.87 mmol, 3.0 equiv) in dry THF (2.1 mL) was added. The mixture was stirred at rt in the dark for 2.5 h and then a pH 7 buffer (5 mL) was added. The mixture was diluted with Et₂O (5 mL), the layers were separated and the organic layer was washed with a saturated aqueous solution of Na₂S₂O₃ (5 mL). The aqueous layer was then extracted with Et₂O (3 × 5 mL). The combined organic layers were washed with brine, dried over MgSO₄, filtered and concentrated under *vacuum* to afford the iodotriene **11**, which was not purified but directly involved in the next step.

To the unpurified iodotriene **11** were added K_2CO_3 (80 mg, 0.58 mmol, 2.0 equiv), $\text{Pd}(\text{OAc})_2$ (3.3 mg, 0.015 mmol, 0.05 equiv) and $n\text{-Bu}_4\text{Br}$ (93 mg, 0.29 mmol, 1.0 equiv). The mixture was degassed under *vacuum* and refilled with argon, three times. The ester **1** (61 mg, 0.435 mmol, 1.5 equiv) and DMF (3 mL) were then added and the mixture was stirred in the dark and heated at 50 °C for 16 h, and then cooled to rt. Et_2O (5 mL) was added followed by a saturated aqueous solution of NaCl (5 mL). The layers were separated and the aqueous layer was then extracted with Et_2O (3×5 mL). The combined organic layers were washed with H_2O , dried over MgSO_4 , filtered and concentrated under *vacuum*. Purification of the crude material by flash column chromatography on silica gel (pentane/ Et_2O = 95:5) afforded the pentaenic ester **12** (89 mg, 0.166 mmol, 57%) as a bright yellow oil. $[\alpha]_{\text{D}}^{20} + 112.6$ (c 1.0, CHCl_3); IR: ν 3022, 2954, 2877, 1702, 1620, 1577, 1458, 1415, 1367, 1241, 1219, 1162, 1140, 1101, 1028, 1003, 937, 920, 860, 836 cm^{-1} ; ^1H NMR (C_6D_6 , 400 MHz): δ 7.51 (dq, $J = 11.0$ and $J = 1.4$ Hz, 1H), 6.42-6.08 (m, 7H), 5.85 (dd, $J = 15.3$ and $J = 7.9$ Hz, 1H), 4.85 ($\text{d}_{\text{AB syst}}$, $J = 6.8$ Hz, 1H), 4.72 ($\text{d}_{\text{AB syst}}$, $J = 6.8$ Hz, 1H), 4.14 (br dd, $J = 7.9$ and $J = 4.8$ Hz, 1H), 4.10 (q, $J = 7.1$ Hz, 2H), 4.01 (qd, $J = 6.2$ and $J = 4.6$ Hz, 1H), 3.86 (m, 1H), 3.61 (m, 1H), 1.98 (d, $J = 1.3$ Hz, 3H), 1.30 (d, $J = 6.2$ Hz, 3H), 1.07 (t, $J = 8.0$ Hz, 9H), 1.08-0.98 (m, 2H), 1.03 (t, $J = 7.1$ Hz, 3H), 0.68 (q, $J = 8.2$ Hz, 6H), 0.03 (s, 9H); ^{13}C NMR (C_6D_6 , 100 MHz): δ 167.9, 139.5, 138.3, 136.3, 134.6, 134.4, 133.3, 132.9, 128.5 (2C), 127.7, 92.6, 81.2, 71.4, 65.3, 60.5, 20.7, 18.3, 14.4, 13.1, 7.2 (3C), 5.5 (3C), -1.3 (3C); HRMS (ESI): Calculated for $\text{C}_{29}\text{H}_{52}\text{O}_5\text{Si}_2\text{Na}$ $[\text{M} + \text{Na}]^+$: 559.3246, found: 559.3238.

(2E,4E,6E,8E,10E,12S,13R)-2-Methyl-13-(triethylsilyloxy)-12-[[2-(trimethylsilyl)ethoxy]

methoxy}tetradeca-2,4,6,8,10-pentaenal (13): To a solution of ester **12** (69 mg, 128 μmol , 1.0 equiv) in dry CH_2Cl_2 (2.4 mL) cooled to -78 °C was added DIBAL-H (0.39 mL, 1 M in toluene, 0.39 mmol, 3.0 equiv) dropwise. The mixture was stirred at -78 °C in the dark for 20 min, then

MeOH (1 mL) was added. The mixture was poured into a saturated aqueous solution of Rochelle's salt (20 mL) and stirred at rt in the dark for 2 h. The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (3 × 20 mL). The combined organic layers were washed with brine, dried over MgSO₄, filtered and concentrated under *vacuum* to afford the allylic alcohol, which was not purified but directly engaged in the next step.

To a solution of crude allylic alcohol in dry CH₂Cl₂ (4.5 mL) was added freshly prepared MnO₂ (110 mg, 1.27 mmol, 10 equiv). The mixture was stirred at rt in the dark for 2.5 h, and then filtered through a pad of Celite®. The filtrate was concentrated under *vacuum* and then purified by flash column chromatography on silica gel (petroleum ether/EtOAc = 95:5) to afford the pentaenic aldehyde **13** (34 mg, 69 μmol, 54%) as a bright yellow oil. $[\alpha]_D^{20} + 129.6$ (*c* 1.0, CH₃CN); IR: ν 2953, 2877, 1678, 1667, 1618, 1573, 1459, 1408, 1378, 1361, 1248, 1198, 1177, 1097, 1003, 937, 859, 835 cm⁻¹; ¹H NMR (C₆D₆, 400 MHz): δ 9.39 (s, 1H), 6.42-6.12 (m, 7H), 6.05 (dd, *J* = 14.2 and *J* = 10.1 Hz, 1H), 5.88 (dd, *J* = 15.1 and *J* = 7.9 Hz, 1H), 4.84 (d_{AB syst}, *J* = 6.8 Hz, 1H), 4.71 (d_{AB syst}, *J* = 6.8 Hz, 1H), 4.13 (dd, *J* = 7.7 and *J* = 4.6 Hz, 1H), 3.99 (qd, *J* = 6.2 and *J* = 4.7 Hz, 1H), 3.84 (m, 1H), 3.61 (m, 1H), 1.77 (br s, 3H), 1.29 (d, *J* = 6.2 Hz, 3H), 1.06 (t, *J* = 8.0 Hz, 9H), 0.99 (t_{app}, *J* = 8.0 Hz, 2H), 0.67 (q, *J* = 8.0 Hz, 6H), 0.02 (s, 9H); ¹³C NMR (C₆D₆, 100 MHz): δ 193.3, 147.2, 140.7, 137.9, 137.5, 135.2, 134.4, 133.7, 133.0, 132.9, 127.9, 92.7, 81.1, 71.4, 65.4, 20.7, 18.3, 9.7, 7.2 (3C), 5.5 (3C), -1.3 (3C); HRMS (ESI): Calculated for C₂₇H₄₈O₄Si₂Na [M + Na]⁺: 515.2983, found: 515.2981.

(E)-(S)-3-(But-2-enoyl)-4-isopropyl-5,5-dimethyloxazolidin-2-one (15):²¹ To a solution of oxazolidinone **14** (2.0 g, 12.7 mmol, 1.0 equiv) in dry THF (40 mL) cooled to -78 °C was added *n*-BuLi (5.08 mL, 2.5 M in hexanes, 12.7 mmol, 1.0 equiv). The mixture was stirred at -78 °C for

15 min and then crotonyl chloride (1.34 mL, 14.0 mmol, 1.1 equiv) was added dropwise. The mixture was stirred at -78°C for 1 h, then at 0°C for 1.5 h, and quenched by the addition of a saturated aqueous solution of NH_4Cl (40 mL). Et_2O (40 mL) was added and the layers were separated. The organic layer was washed with a saturated aqueous solution of NaHCO_3 and then with brine, dried over MgSO_4 , filtered and concentrated under *vacuum*. The crude material was purified by flash column chromatography on silica gel (petroleum ether/ EtOAc = 90:10) to afford the acyloxazolidonone **15** (2.46 g, 10.9 mmol, 86%) as a white solid. The spectral data are in agreement with those reported in the literature.²¹ mp: $66-68^{\circ}\text{C}$ (lit.:²¹ $69-70^{\circ}\text{C}$); $[\alpha]_{\text{D}}^{20} + 58.2$ (c 1.0, CHCl_3); $[\alpha]_{\text{D}}^{20}$ lit + 52 (c 1.0, CHCl_3);^{21c} IR: ν 2971, 2935, 2880, 1753, 1686, 1633, 1447, 1390, 1375, 1361, 1336, 1314, 1298, 1279, 1219, 1174, 1126, 1072, 1032, 974, 924, 832 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz): δ 7.32 (br d, $J = 15.3\text{ Hz}$, 1H), 7.15 (m, 1H), 4.22 (br d, $J = 3.4\text{ Hz}$, 1H), 2.16 (m, 1H), 1.96 (br d, $J = 6.8\text{ Hz}$, 3H), 1.52 (s, 3H), 1.39 (s, 3H), 1.04 (d, $J = 7.0\text{ Hz}$, 3H), 0.96 (d, $J = 6.8\text{ Hz}$, 3H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 165.8, 153.7, 146.7, 122.1, 82.9, 66.4, 29.8, 28.9, 21.6, 21.5, 18.6, 17.2; MS (EI) m/z : 225 (M^+ , 2), 210 [$(\text{M}-\text{Me})^+$, 2], 182 (9), 70 (7), 69 (100).

(S)-3-[(2S,3R)-3-Hydroxy-2-vinyloctanoyl]-4-isopropyl-5,5-dimethyloxazolidin-2-one (16):

To a solution of acyloxazolidinone **15** (2.04 g, 9.06 mmol, 1.0 equiv) in dry CH_2Cl_2 (36 mL) cooled to -78°C was added Bu_2BOTf (10 mL, 1 M in CH_2Cl_2 , 10 mmol, 1.1 equiv). The mixture was stirred at -78°C for 5 min and then Et_3N (1.76 mL, 12.66 mmol, 1.4 equiv) was added. After stirring for 1 h at -78°C , the temperature was raised up to 0°C for 15 min and finally cooled to -78°C . Hexanal (1.67 mL, 13.59 mmol, 1.5 equiv) was added and the mixture was stirred at -78°C , progressively warmed to 0°C over a period of 5 h and then quenched by addition of an aqueous solution of NH_4Cl (125 mL). A 1:1 mixture of petroleum ether and EtOAc (125 mL) was added

and the layers were separated. The organic layer was washed with brine and then concentrated under *vacuum*. The residue was dissolved in Et₂O (75 mL) and cooled to 0 °C. A pH 7 buffer solution (20 mL) and H₂O₂ (30% in weight, 20 mL) were added. The mixture was progressively warmed to rt and stirred for 2 h. H₂O (200 mL) was then added, followed by the addition of a 1:1 mixture of petroleum ether and EtOAc (200 mL). The layers were separated, the organic layer was washed with a saturated aqueous solution of NaHCO₃ and then with brine, dried over MgSO₄, filtered and concentrated under *vacuum*. The crude material was purified by flash column chromatography on silica gel (petroleum ether/EtOAc = 90:10) to afford the aldol **16** (2.76 g, 8.48 mmol, 94%) as a single diastereomer and as a colorless oil. $[\alpha]_D^{20} - 28.2$ (*c* 1.0, CHCl₃); IR: ν 3505, 2959, 2933, 2861, 1771, 1691, 1634, 1466, 1394, 1363, 1312, 1279, 1217, 1172, 1119, 1069, 996, 963, 929 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 5.99 (ddd, *J* = 17.2, *J* = 10.2 and *J* = 9.1 Hz, 1H), 5.47 (br d, *J* = 17.2 Hz, 1H), 5.38 (dd, *J* = 10.2 and *J* = 1.5 Hz, 1H), 4.64 (dd, *J* = 9.0 and *J* = 3.7 Hz, 1H), 4.21 (d, *J* = 3.1 Hz, 1H), 3.95 (m, 1H), 3.08 (br d, *J* = 1.7 Hz, 1H, OH), 2.13 (heptd, *J* = 6.9 Hz, *J* = 3.1 Hz, 1H), 1.52 (s, 3H), 1.54-1.40 (m, 2H), 1.41 (s, 3H), 1.38-1.24 (m, 6H), 0.99 (d, *J* = 7.0 Hz, 3H), 0.92 (d, *J* = 6.8 Hz, 3H), 0.88 (t, *J* = 6.8 Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz): δ 175.2, 153.2, 131.9, 121.7, 82.9, 71.7, 66.1, 52.2, 34.1, 31.9, 30.0, 28.9, 25.4, 22.7, 21.6, 21.4, 16.8, 14.2; MS (EI) *m/z*: 225 (2), 210 (1), 182 (4), 181 (3), 114 (33), 98 (6), 97 (9), 96 (10), 88 (9), 70 (37), 69 (100), 68 (28), 55 (20); HRMS (ESI): Calculated for C₁₈H₃₁NO₄Na [M + Na]⁺: 348.2145, found: 348.2143.

(S)-4-Isopropyl-3-[(2S,3R)-3-(methoxymethoxy)-2-vinyloctanoyl]-5,5-dimethyloxazolidin-2-one (17): To a solution of alcohol **16** (1.2 g, 3.69 mmol, 1.0 equiv) in dry CH₂Cl₂ (40 mL) were added *i*Pr₂NEt (3.7 mL, 22.3 mmol, 6.0 equiv) and MOMCl (1.1 mL, 14.9 mmol, 4.0 equiv) dropwise. The mixture was stirred at rt for 18 h and then quenched by the addition of H₂O (20 mL).

The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3×20 mL). The combined organic layers were dried over MgSO_4 , filtered and concentrated under *vacuum*. The crude material was purified by flash column chromatography on silica gel (petroleum ether/EtOAc = 90:10) to afford the protected alcohol **17** (1.31 g, 35.4 mmol, 96%) as a colorless oil. $[\alpha]_{\text{D}}^{20} + 53.6$ (*c* 1.01, CHCl_3); IR: ν 2932, 1771, 1695, 1637, 1466, 1394, 1362, 1312, 1278, 1217, 1170, 1118, 1096, 1068, 1035, 998, 964, 919, 859 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz): δ 6.02 (ddd, $J = 17.3$, $J = 10.1$ and $J = 9.0$ Hz, 1H), 5.33 (br d, $J = 17.3$ Hz, 1H), 5.27 (dd, $J = 10.1$ and $J = 1.5$ Hz, 1H), 4.83 (dd, $J = 8.9$ and $J = 5.8$ Hz, 1H), 4.65 ($\text{d}_{\text{AB syst}}$, $J = 7.1$ Hz, 1H), 4.57 ($\text{d}_{\text{AB syst}}$, $J = 7.1$ Hz, 1H), 4.15 (d, $J = 3.3$ Hz, 1H), 3.88 (m, 1H), 3.34 (s, 3H), 2.15 (heptd, $J = 6.9$ and $J = 3.2$ Hz, 1H), 1.58-1.50 (m, 2H), 1.51 (s, 3H), 1.42 (s, 3H), 1.36-1.21 (m, 6H), 1.01 (d, $J = 7.0$ Hz, 3H), 0.93 (d, $J = 6.9$ Hz, 3H), 0.87 (t, $J = 6.8$ Hz, 3H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 172.8, 153.5, 134.0, 119.7, 96.6, 82.8, 79.4, 66.7, 56.1, 51.6, 32.9, 32.0, 29.8, 28.6, 25.2, 22.7, 21.58, 21.53, 17.1, 14.2; MS (EI) m/z : 279 (17), 278 (78), 277 (7), 202 (18), 201 (100), 200 (25), 199 (44), 181 (15), 155 (15), 154 (98), 153 (9), 152 (16), 149 (6), 124 (6), 123 (8), 77 (8), 51 (14); HRMS (ESI): Calculated for $\text{C}_{20}\text{H}_{35}\text{NO}_5\text{Na}$ [$\text{M} + \text{Na}$] $^+$: 392.2407, found: 392.2409.

(S)-3-((2S,3R)-2-[(S)-1-Hydroxybut-3-en-1-yl]-3-(methoxymethoxy)octanoyl)-4-isopropyl-5,5-dimethyloxazolidin-2-one (19): To a solution of alkene **17** (1.06 g, 2.87 mmol, 1.0 equiv) in a mixture of dry CH_2Cl_2 (14 mL) and anhydrous MeOH (14 mL) were added 2,6-lutidine (0.17 mL, 1.46 mmol, 0.5 equiv) and a trace of Sudan III dye. Ozone was bubbled through the pink solution, cooled to -78 $^{\circ}\text{C}$, until the color of the dye faded. The reaction mixture was replaced under oxygen and then under argon atmosphere, Me_2S (2.1 mL, 28.4 mmol, 10 equiv) was added and the mixture was warmed to rt and stirred for 1.25 h. Petroleum ether (15 mL) and H_2O (15 mL) were added and the layers were separated. The organic layer was washed with a saturated aqueous

solution of CuSO₄, then with H₂O and then with brine, dried over MgSO₄, filtered and concentrated under *vacuum* to afford the aldehyde **18** which was not purified but directly engaged in the next step.

To a suspension of ZnCl₂ (586 mg, 4.30 mmol, 1.5 equiv) in dry THF (14 mL), cooled to 0 °C, was added allylmagnesium chloride (3.3 mL, 2M in THF, 6.6 mmol, 2.3 equiv). The mixture was stirred at 0 °C for 5 min, then at rt for 30 min, then cooled down to –78 °C and a solution of crude aldehyde **18** in dry THF (15 mL) was cannulated. The mixture was stirred at –78 °C, progressively warmed to –40 °C over 1 h and stirred at this temperature for 2.5 h. The reaction mixture was quenched by the addition of a saturated aqueous solution of NH₄Cl (30 mL), warmed to rt and diluted with EtOAc (30 mL) and H₂O (20 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine, dried over MgSO₄, filtered and concentrated under *vacuum*. The crude material was purified by flash column chromatography on silica gel (petroleum ether/EtOAc = 98:2 to 90:10) to afford the homoallylic alcohol **19** (870 mg, 2.10 mmol, 73%) as a single diastereomer and as a white solid. mp: 75-77 °C; $[\alpha]_D^{20} + 75.7$ (*c* 1.05, CHCl₃); IR: ν 3669, 3477, 2958, 2931, 1774, 1691, 1642, 1467, 1395, 1377, 1362, 1312, 1278, 1217, 1172, 1119, 1068, 1022, 968, 915, 859 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 5.90 (m, 1H), 5.20-5.14 (m, 2H), 4.68 (d_{AB} syst, *J* = 7.1 Hz, 1H), 4.50 (d_{AB} syst, *J* = 7.1 Hz, 1H), 4.49 (dd, *J* = 7.9 and *J* = 6.1 Hz, 1H), 4.15 (d, *J* = 3.1 Hz, 1H), 4.14-4.07 (m, 2H), 3.37 (s, 3H), 2.46 (d, *J* = 4.3 Hz, 1H, OH), 2.40 (m, 1H), 2.28 (m, 1H), 2.15 (heptd, *J* = 6.8 Hz, *J* = 3.1 Hz, 1H), 1.71 (m, 1H), 1.51 (s, 3H), 1.47-1.37 (m, 2H), 1.41 (s, 3H), 1.35-1.20 (m, 5H), 1.05 (d, *J* = 7.0 Hz, 3H), 0.97 (d, *J* = 6.8 Hz, 3H), 0.87 (t, *J* = 6.9 Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz): δ 172.9, 154.0, 134.4, 118.9, 96.2, 83.0, 77.5, 70.2, 67.2, 56.3, 50.5, 39.5, 32.0, 31.9, 29.8, 28.3, 25.5, 22.8, 21.8, 21.5, 17.2, 14.2; MS (EI) *m/z*: 281 (2), 238 (3), 210 (4), 199 (3), 158 (6), 126 (8), 125 (89),

124 (10), 114 (7), 97 (15), 81 (14), 68 (16), 55 (100); HRMS (ESI): Calculated for $C_{22}H_{39}NO_6Na$ $[M + Na]^+$: 436.2670, found: 436.2670.

(S)-3-((2R,3R)-3-Hydroxy-2-[(S)-1-hydroxybut-3-en-1-yl]octanoyl)-4-isopropyl-5,5-

dimethyloxazolidin-2-one (19'): To a solution of ether **19** (60 mg, 0.144 mmol, 1 equiv) in dry CH_2Cl_2 (6 mL) cooled to $-30\text{ }^{\circ}C$ was added TMSBr (75 μ L, 0.57 mmol, 4.0 equiv). The mixture was stirred at $-30\text{ }^{\circ}C$, progressively warmed to $-20\text{ }^{\circ}C$ and stirred for 1 h. A saturated aqueous solution of $NaHCO_3$ (5 mL) was added, the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under *vacuum*. Purification of the crude material by flash column chromatography on silica gel (petroleum ether/EtOAc = 80:20) afforded the corresponding diol **19'** (42 mg, 0.114 mmol, 79%) as a colorless oil. $[\alpha]_D^{20} + 36.3$ (c 1.1, $CHCl_3$); IR: ν 3447, 2958, 2933, 2873, 1770, 1688, 1643, 1466, 1394, 1363, 1314, 1278, 1217, 1174, 1121, 1072, 996, 964, 915, 860 cm^{-1} ; 1H NMR ($CDCl_3$, 400 MHz): δ 5.90 (m, 1H), 5.21-5.15 (m, 2H), 4.32 (t_{app} , $J = 7.4$ Hz, 1H), 4.21 (m, 1H), 4.20 (d, $J = 2.7$ Hz, 1H), 4.13 (m, 1H), 3.25 (br s, 1H, OH), 3.04 (br s, 1H, OH), 2.41 (m, 1H), 2.34 (m, 1H), 2.16 (heptd, $J = 7.1$ and $J = 2.7$ Hz, 1H), 1.53 (s, 3H), 1.50-1.42 (m, 2H), 1.40 (s, 3H), 1.38-1.20 (m, 6H), 1.04 (d, $J = 7.0$ Hz, 3H), 0.98 (d, $J = 6.9$ Hz, 3H), 0.87 (t, $J = 6.9$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.4, 154.0, 134.2, 119.0, 83.0, 73.3, 72.6, 66.9, 53.4, 39.8, 34.8, 31.8, 29.9, 28.8, 25.5, 22.7, 21.7, 21.5, 17.1, 14.1; MS (EI) m/z : 251 (1), 210 (16), 114 (16), 97 (18), 96 (10), 95 (100), 94 (16), 70 (11), 67 (56), 66 (20), 65 (11), 55 (18); HRMS (ESI): Calculated for $C_{20}H_{35}NO_5Na$ $[M + Na]^+$: 392.2407, found: 392.2408.

(S)-3-[(4S,5R,6R)-4-Allyl-2,2-dimethyl-6-pentyl-1,3-dioxane-5-carbonyl]-4-isopropyl-5,5-

dimethyloxazolidin-2-one (19''): To a solution of diol **19'** (32 mg, 0.087 mmol, 1 equiv) in a mixture of acetone (1 mL) and 2,2-dimethoxypropane (0.5 mL) was added PPTS (2.2 mg, 8.8 μ mol, 0.1 equiv). The mixture was stirred at rt for 4 h, and then quenched by addition of one drop of Et₃N. Evaporation of the solvents and purification of the crude material by flash column chromatography (petroleum ether/EtOAc = 95:5) afforded the acetonide **19''** (33 mg, 0.081 mmol, 93%) as a colorless oil. $[\alpha]_D^{20} + 27.6$ (*c* 1.0, CHCl₃); IR: ν 3077, 2933, 1774, 1685, 1643, 1465, 1429, 1392, 1362, 1310, 1276, 1217, 1201, 1170, 1120, 1068, 1019, 999, 963, 947, 912, 865 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 5.89 (m, 1H), 5.05 (br d, *J* = 17.1 Hz, 1H), 5.04 (br d, *J* = 11.2 Hz, 1H), 4.20 (d, *J* = 2.4 Hz, 1H), 4.15 (td_{app}, *J* = 9.0 and *J* = 2.4 Hz, 1H), 4.07-3.99 (m, 2H), 2.40 (m, 1H), 2.26-2.14 (m, 2H), 1.53 (s, 3H), 1.49 (s, 3H), 1.47 (m, 1H), 1.41 (s, 3H), 1.38 (s, 3H), 1.30-1.16 (m, 7H), 1.04 (d, *J* = 7.0 Hz, 3H), 0.99 (d, *J* = 6.9 Hz, 3H), 0.85 (t, *J* = 7.0 Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz): δ 173.3, 153.1, 134.5, 116.9, 98.8, 82.5, 72.3, 71.7, 66.7, 49.1, 38.7, 34.4, 31.8, 30.0, 29.9, 28.9, 24.8, 22.6, 21.8, 21.5, 19.7, 17.1, 14.2; MS (EI) *m/z*: 394 [(M-Me)⁺, 15], 334 (5), 310 (13), 290 (8), 252 (11), 251 (10), 210 (17), 158 (42), 125 (31), 114 (27), 98 (10), 97 (42), 96 (11), 95 (55), 94 (15), 88 (29), 83 (14), 82 (14), 81 (20), 79 (13), 71 (20), 70 (24), 69 (19), 68 (11), 67 (56), 66 (11), 59 (24), 58 (29), 57 (29), 56 (27), 55 (100), 54 (18), 53 (10); HRMS (ESI): Calculated for C₂₃H₃₉NO₅Na [M + Na]⁺: 432.2720, found: 432.2722.

(4S,5R,6R)-4-(tert-Butyldiphenylsilyloxy)-5-[(tert-butyldiphenylsilyloxy)methyl]-6-

(methoxymethoxy)undec-1-ene (20): To a solution of carbamate **19** (0.7 g, 1.69 mmol, 1.0 equiv) in toluene (30 mL) cooled to -30 °C was added LiAlH₄ (3.4 mL, 1M in THF, 3.4 mmol, 2.0 equiv). The mixture was stirred at -30 °C and progressively warmed to -10 °C. After 1 h, a saturated

aqueous solution of Rochelle's salt (30 mL) was added. The mixture was warmed to rt, Et₂O (30 mL) was added, and the mixture was stirred at rt for 3 h. The layers were separated and the aqueous layer was extracted with Et₂O (3 × 15 mL). The combined organic layers were washed with brine, dried over MgSO₄, filtered and concentrated under *vacuum* to afford the corresponding diol which was not purified but directly engaged in the next step.

To a solution of crude diol in dry CH₂Cl₂ (30 mL) cooled to 0 °C were added 2,6-lutidine (1.0 mL, 8.6 mmol, 5.0 equiv) and TBDPSOTf (1.67 g, 4.3 mmol, 2.5 equiv) dropwise. The mixture was warmed to rt, stirred for 18 h and then quenched by the addition of H₂O (15 mL). The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (3 × 15 mL). The combined organic layers were dried over MgSO₄, filtered and concentrated under *vacuum*. The crude material was purified by flash column chromatography on silica gel (petroleum ether/EtOAc = 99:1 to 98:2) to afford the silyl ether **20** (0.79 g, 1.07 mmol, 63%) as a viscous colorless oil.

[α]_D²⁰ + 43.5 (*c* 2.0, CHCl₃); IR: ν 3072, 2955, 2930, 2891, 2857, 1640, 1590, 1472, 1428, 1390, 1361, 1261, 1217, 1190, 1106, 1036, 999, 917, 822 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 7.73-7.66 (m, 4H), 7.64-7.60 (m, 4H), 7.43-7.30 (m, 12H), 5.45 (ddt, *J* = 17.2, *J* = 10.2 and *J* = 7.1 Hz, 1H), 4.81 (br d, *J* = 10.2 Hz, 1H), 4.73 (br d, *J* = 17.3 Hz, 1H), 4.38 (d_{AB syst}, *J* = 6.9 Hz, 1H), 4.29 (m, 1H), 4.27 (d_{AB syst}, *J* = 6.9 Hz, 1H), 4.02 (dd, *J* = 10.1 and *J* = 7.6 Hz, 1H), 3.89-3.83 (m, 2H), 3.23 (s, 3H), 2.35 (m, 1H), 2.14 (m, 1H), 1.85 (m, 1H), 1.73 (m, 1H), 1.37-1.12 (m, 7H), 1.05 (s, 9H), 1.01 (s, 9H), 0.85 (t, *J* = 7.0 Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz): δ 136.23 (2C), 136.18 (2C), 135.9 (2C), 135.8 (2C), 135.4, 134.6, 133.9 (2C), 133.7, 129.8, 129.7, 129.64, 129.58, 127.72 (2C), 127.70 (2C), 127.69 (2C), 127.5 (2C), 116.9, 95.3, 75.8, 71.4, 60.0, 55.7, 47.1, 39.3, 32.2, 32.1, 27.3 (3C), 27.1 (3C), 26.1, 22.9, 19.6, 19.3, 14.3; HRMS (ESI): Calculated for C₄₆H₆₄O₄Si₂Na [M + Na]⁺: 759.4235, found: 759.4237.

(3*S*,4*R*,5*R*)-3-(*tert*-Butyldiphenylsilyloxy)-4-[(*tert*-butyldiphenylsilyloxy)methyl]-5-

(methoxymethoxy)decanal (21): To a solution of alkene **20** (188 mg, 0.255 mmol, 1.0 equiv) in dry CH₂Cl₂ (11 mL) was added a trace of Sudan III dye. Ozone was bubbled through the pink solution cooled to –78 °C until the color of the dye faded. The reaction mixture was replaced under oxygen and then under argon atmosphere, PPh₃ (100 mg, 0.381 mmol, 1.5 equiv) was added and the mixture was progressively warmed to rt overnight. The reaction mixture was dried over MgSO₄, filtered and concentrated under *vacuum*. The crude material was purified by flash column chromatography on silica gel (petroleum ether/EtOAc = 95:5) to afford the aldehyde **21** (178 mg, 0.241 mmol, 95%) as a pink oil. $[\alpha]_D^{20} - 12.8$ (*c* 1.01, CHCl₃); IR: ν 3071, 3049, 2955, 2931, 2892, 2858, 2717, 1728, 1590, 1472, 1428, 1390, 1362, 1261, 1212, 1147, 1110, 1035, 920, 823 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 9.29 (dd, *J* = 2.6 and *J* = 1.9 Hz, 1H), 7.68-7.59 (m, 8H), 7.45-7.31 (m, 12H), 4.65 (m, 1H), 4.40 (d_{AB syst}, *J* = 6.8 Hz, 1H), 4.38 (d_{AB syst}, *J* = 6.8 Hz, 1H), 3.90 (br d, *J* = 5.5 Hz, 2H), 3.79 (td, *J* = 5.9 and *J* = 5.3 Hz, 1H), 3.13 (s, 3H), 2.69 (ddd_{AB syst}, *J* = 16.5, *J* = 4.2 and *J* = 1.8 Hz, 1H), 2.51 (ddd_{AB syst}, *J* = 16.5, *J* = 7.6 and *J* = 2.9 Hz, 1H), 2.01 (m, 1H), 1.34-1.27 (m, 2H), 1.22-1.15 (m, 2H), 1.12-1.02 (m, 4H), 1.06 (s, 9H), 1.00 (s, 9H), 0.84 (t, *J* = 7.1 Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz): δ 202.3, 136.19 (2C), 136.16 (2C), 135.9 (4C), 133.6, 133.5 (2C), 133.4, 130.0 (2C), 129.86, 129.84, 127.84 (2C), 127.83 (2C), 127.78 (4C), 96.4, 76.5, 67.2, 59.8, 55.8, 49.3, 48.8, 32.02, 31.98, 27.1 (6C), 25.2, 22.8, 19.4, 19.3, 14.2; HRMS (ESI): Calculated for C₄₅H₆₂O₅Si₂Na [M + Na]⁺: 761.4028, found: 761.4032.

3-(Benzyloxy)propan-1-ol (23):²⁷ To a suspension of sodium hydride (60% in oil, 1.6 g, 40 mmol, 1 equiv) in dry THF (80 mL) was added dropwise 1,3-propanediol **22** (2.9 mL, 40 mmol, 1 equiv).

The mixture was stirred at rt for 45 min. *n*-Bu₄NI was then added (7.4 g, 20 mmol, 0.5 equiv), and benzyl bromide (4.8 mL, 40 mmol, 1 equiv) was added dropwise. The reaction mixture was stirred for 7 h and quenched by the addition of H₂O (80 mL). The phases were separated and the aqueous layer was extracted three times with Et₂O (3 × 80 mL). The combined organic layers were washed with brine, dried over MgSO₄, filtered and concentrated under *vacuum*. The crude material was then purified by flash column chromatography on silica gel (petroleum ether/EtOAc = 8:2) to afford 3-(benzyloxy)propan-1-ol **23** (4.67 g, 28.1 mmol, 70%) as a yellow oil. The spectral data match those reported in the literature.²⁷ IR: ν 3375, 3030, 2943, 2863, 1496, 1454, 1365, 1205, 1073, 1026, 972, 910 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 7.38-7.26 (m, 5H), 4.53 (s, 2H), 3.79 (t, *J* = 5.7 Hz, 2H), 3.67 (t, *J* = 5.7 Hz, 2H), 2.27 (br s, 1H, OH), 1.87 (quint_{app}, *J* = 5.7 Hz, 2H); ¹³C NMR (CDCl₃, 100 MHz): δ 138.1, 128.5 (2C), 127.73, 127.69 (2C), 73.2, 69.1, 61.5, 32.2; MS (EI) *m/z*: 166 (M⁺, 2), 147 (3), 130 (1), 120 (3), 107 (BnO⁺, 97), 91 (Bn⁺, 100), 79 (29), 77 (Ph⁺, 13), 65 (19), 51 (7).

(*R*)-1-(Benzyloxy)hex-5-en-3-ol (24):²⁸ To a solution of alcohol **23** (396 mg, 2.39 mmol, 1 equiv) in dry THF (12 mL) in a vial were added [Ir(COD)Cl]₂ (41 mg, 0.06 mmol 2.5 mol%), (*R*)-BIPHEP (78 mg, 0.12 mmol, 5 mol%), Cs₂CO₃ (156 mg, 0.48 mmol, 0.2 equiv), 3,4-dinitrobenzoic acid (38 mg, 0.18 mmol, 7.5 mol%) and allyl acetate (2.58 mL, 23.9 mmol, 10 equiv). The vial was sealed and heated at 120 °C. After 15 h, the mixture was cooled to rt, transferred into a flask containing Celite® and concentrated under *vacuum*. The crude material was then purified by flash column chromatography on silica gel (petroleum ether/EtOAc = 9:1 to 85:15) to afford the alcohol **24** (354 mg, 1.72 mmol, 72%, ee = 94%) as a yellow oil. The spectral data are in agreement with those reported in the literature.²⁸ [α]_D²⁰ + 4.5 (*c* 1.01, CHCl₃); IR: ν 3421, 3067, 3031, 2918, 2861, 1641, 1496, 1454, 1419, 1364, 1309, 1205, 1077, 1027, 996, 913 cm⁻¹; ¹H NMR

(CDCl₃, 400 MHz): δ 7.37-7.26 (m, 5H), 5.83 (ddt, $J = 16.9$, $J = 10.3$ and $J = 7.1$ Hz, 1H), 5.14-5.07 (m, 2H), 4.53 (s, 2H), 3.88 (m, 1H), 3.72 (dt_{AB syst}, $J = 9.4$ and $J = 5.1$ Hz, 1H), 3.65 (m, 1H), 2.88 (br s, 1H, OH), 2.27-2.23 (m, 2H), 1.79-1.74 (m, 2H); ¹³C NMR (CDCl₃, 100 MHz): δ 138.0, 134.9, 128.5 (2C), 127.8, 127.7 (2C), 117.6, 73.3, 70.4, 69.0, 41.9, 35.9; MS (EI) m/z : 129 [(M-Ph)⁺, 1], 107 (BnO⁺, 26), 92 (11), 91 (Bn⁺, 100), 79 (19), 77 (Ph⁺, 15), 65 (16), 51 (11).

(R)-{[1-(Benzyloxy)hex-5-en-3-yl]oxy}triethylsilane (25):³⁰ To a solution of alcohol **24** (320 mg, 1.55 mmol, 1 equiv) in dry CH₂Cl₂ (15.5 mL) cooled to -78 °C were added 2,6-lutidine (1.08 mL, 9.27 mmol, 6 equiv) and TESOTf (1.4 mL, 6.14 mmol, 4 equiv). The reaction mixture was stirred at -78 °C for 1.5 h, H₂O (15 mL) was added and the mixture was warmed to rt. The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (3 × 20 mL). The combined organic layers were dried over MgSO₄, filtered and concentrated under *vacuum*. The crude material was then purified by flash column chromatography on silica gel (petroleum ether/EtOAc = 99:1) to afford the silylated alcohol **25** (496 mg, 1.55 mmol, quant) as a colorless oil. The spectral data match those reported in the literature.³⁰ [α]_D²⁰ - 16.2 (*c* 1.5, CHCl₃); IR: ν 3068, 3031, 2953, 2912, 2876, 1641, 1496, 1455, 1365, 1238, 1094, 1047, 1004, 911 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 7.37-7.33 (m, 4H), 7.29 (m, 1H), 5.83 (m, 1H), 5.08-5.02 (m, 2H), 4.52 (d_{AB syst}, $J = 11.9$ Hz, 1H), 4.47 (d_{AB syst}, $J = 11.9$ Hz, 1H), 3.93 (m, 1H), 3.60-3.51 (m, 2H), 2.30-2.19 (m, 2H), 1.82 (m, 1H), 1.71 (m, 1H), 0.96 (t, $J = 8.1$ Hz, 9H), 0.60 (q, $J = 8.1$ Hz, 6H); ¹³C NMR (CDCl₃, 100 MHz): δ 138.6, 134.9, 128.4 (2C), 127.7 (2C), 127.5, 117.1, 73.0, 69.0, 67.1, 42.4, 36.8, 6.9 (3C), 5.0 (3C); MS (EI) m/z : 291 [(M-Et)⁺, 1], 173 (10), 131 (TESO⁺, 3), 129 (3), 115 (TES⁺, 6), 91 (Bn⁺, 100).

(R,E)-8-(Benzyloxy)-6-(triethylsilyloxy)oct-3-en-2-one (26): To a solution of alkene **25** (334 mg, 1.04 mmol, 1 equiv) in dry CH₂Cl₂ (9 mL) were added methyl vinylketone (0.44 mL, 5.29 mmol,

5.1 equiv) and Hoveyda-Grubbs second generation catalyst (13 mg, 0.021 mmol, 0.02 equiv). The mixture was heated at reflux for 2 h, then cooled to rt and concentrated under *vacuum*. The crude material was then purified by flash column chromatography on silica gel (petroleum ether/EtOAc = 95:5 to 92:8) to afford the methyl ketone **26** (370 mg, 1.02 mmol, 98%) as a colorless oil. $[\alpha]_D^{20} - 11.5$ (*c* 1.02, CHCl₃); IR: ν 2953, 2912, 2876, 1699, 1676, 1629, 1455, 1416, 1360, 1252, 1203, 1173, 1095, 1045, 1005, 982 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 7.37-7.26 (m, 5H), 6.81 (dt, *J* = 16.0 and *J* = 7.4 Hz, 1H), 6.07 (dt, *J* = 16.0 and *J* = 1.2 Hz, 1H), 4.51 (d_{AB} syst, *J* = 11.8 Hz, 1H), 4.46 (d_{AB} syst, *J* = 11.8 Hz, 1H), 4.03 (m, 1H), 3.58-3.49 (m, 2H), 2.47-2.32 (m, 2H), 2.24 (s, 3H), 1.78-1.73 (m, 2H), 0.95 (t, *J* = 7.9 Hz, 9H), 0.60 (q, *J* = 8.0 Hz, 6H); ¹³C NMR (CDCl₃, 100 MHz): δ 198.5, 144.7, 138.3, 133.5, 128.4 (2C), 127.7 (2C), 127.6, 73.1, 68.4, 66.7, 40.8, 37.4, 26.7, 6.9 (3C), 5.0 (3C); MS (EI) *m/z*: 279 (1), 173 (7), 115 (TES⁺, 5), 107 (BnO⁺, 3), 103 (18), 91 (Bn⁺, 100), 75 (24); HRMS (ESI): Calculated for C₂₁H₃₄O₃SiNa [M + Na]⁺: 385.2169, found: 385.2175.

(5*R*,6*R*,7*S*,9*R*,15*R*,*E*)-15-[2-(Benzyloxy)ethyl]-7-(*tert*-butyldiphenylsilyloxy)-6-[(*tert*-butyldiphenylsilyloxy)methyl]-17,17-diethyl-9-hydroxy-5-pentyl-2,4,16-trioxa-17-

silanonadec-12-en-11-one (27): To a solution of (+)-DIPCl (103 mg, 0.32 mmol, 2.6 equiv) in dry Et₂O (1 mL) cooled to 0 °C were added Et₃N (50 μ L, 0.36 mmol, 3.0 equiv) and a solution of enone **26** (59 mg, 0.16 mmol, 1.3 equiv) in dry Et₂O (2 mL). The mixture was stirred at 0 °C for 2 h and then cooled to -78 °C. A solution of aldehyde **21** (90 mg, 0.122 mmol, 1.0 equiv) in dry Et₂O (1.8 mL) was cannulated and the mixture was progressively warmed to -20 °C and stirred at this temperature. After 5.5 h, the reaction was quenched by the addition of a mixture of MeOH/pH 7 buffer/35% aqueous H₂O₂ = 1:1:1 (5 mL) and the solution was progressively warmed up to rt overnight. The mixture was cooled to 0 °C and a saturated aqueous solution of Na₂S₂O₃ (5 mL)

was added dropwise over a period of 30 min. The layers were separated and the aqueous layer was extracted with Et₂O (3 × 10 mL). The combined organic layers were dried over MgSO₄, filtered and concentrated under *vacuum* to afford a mixture of diastereomers **27** and **27'** in a 90:10 ratio. The crude material was purified by flash column chromatography on silica gel (petroleum ether/EtOAc = 92:8 to 90:10) and the diastereomers were separated to afford **27** (90 mg, 0.082 mmol, 67%) as a colorless oil. $[\alpha]_D^{20} + 4.2$ (*c* 1.0, CHCl₃); IR: ν 3498, 3070, 2954, 2932, 2877, 2858, 1737, 1665, 1628, 1589, 1456, 1428, 1378, 1257, 1188, 1111, 1037, 916, 823 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 7.68-7.62 (m, 8H), 7.44-7.25 (m, 17H), 6.64 (dt, *J* = 15.8 and *J* = 7.3 Hz, 1H), 5.87 (d, *J* = 15.9 Hz, 1H), 4.51 (d_{AB syst}, *J* = 11.8 Hz, 1H), 4.46 (d_{AB syst}, *J* = 11.9 Hz, 1H), 4.42 (d_{AB syst}, *J* = 6.8 Hz, 1H), 4.34 (d_{AB syst}, *J* = 6.7 Hz, 1H), 4.24 (m, 1H), 4.05-3.93 (m, 3H), 3.88 (dd_{AB syst}, *J* = 9.9 and *J* = 6.2 Hz, 1H), 3.81 (m, 1H), 3.57-3.48 (m, 2H), 3.20 (s, 3H), 3.04 (br d, *J* = 2.2 Hz, 1H, OH), 2.42-2.25 (m, 2H), 2.19 (dd, *J* = 17.6 and *J* = 9.0 Hz, 1H), 2.06 (m, 1H), 1.92 (dd, *J* = 17.8 and *J* = 2.2 Hz, 1H), 1.82-1.60 (m, 4H), 1.53 (m, 1H), 1.37-1.10 (m, 7H), 1.06 (s, 9H), 1.02 (s, 9H), 0.94 (t, *J* = 7.9 Hz, 9H), 0.83 (t, *J* = 6.5 Hz, 3H), 0.58 (q, *J* = 7.8 Hz, 6H); ¹³C NMR (CDCl₃, 100 MHz): δ 200.2, 143.9, 138.5, 136.3 (2C), 136.2 (2C), 135.9 (2C), 135.8 (2C), 134.0, 133.9, 133.8 (2C), 132.6, 129.8 (3C), 129.7, 128.5 (2C), 127.84 (2C), 127.76 (7C), 127.65 (2C), 96.1, 76.5, 73.2, 69.2, 68.4, 66.7, 65.4, 60.1, 55.7, 48.5, 45.5, 41.0, 40.8, 37.3, 32.5, 32.0, 27.2 (3C), 27.1 (3C), 25.6, 22.8, 19.5, 19.4, 14.2, 7.0 (3C), 5.1 (3C); HRMS (ESI): Calculated for C₆₆H₉₆O₈Si₃Na [M + Na]⁺: 1123.6305, found: 1123.6300.

(4*R*,6*S*,7*R*,8*R*)-1-[(2*S*,4*S*,6*S*)-6-[2-(Benzyloxy)ethyl]-2-methyl-1,3-dioxan-4-yl]-6-(*tert*-butyldiphenylsilyloxy)-7-[(*tert*-butyldiphenylsilyloxy)methyl]-4-hydroxy-8-

(methoxymethoxy)tridecan-2-one (28): To a solution of silyl ether **27** (775 mg, 0.70 mmol, 1.0 equiv) in dry CH₂Cl₂ (35 mL) were added acetaldehyde (0.78 mL, 14 mmol, 20 equiv) and

Bi(NO₃)₃·5H₂O (35 mg, 0.072 mmol, 0.1 equiv). The mixture was stirred at rt for 15 h and then quenched by the addition of a saturated aqueous solution of NaHCO₃ (35 mL). The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (3 × 25 mL). The combined organic layers were dried over MgSO₄, filtered and concentrated under *vacuum*. The crude material was purified by column chromatography on silica gel (petroleum ether/EtOAc = 80:20) to afford the β-hydroxyketone **28** (407 mg, 0.39 mmol, 56%) as a yellow oil. [α]_D²⁰ + 3.3 (*c* 1.0, CHCl₃); IR: ν 3501, 3071, 2930, 2857, 1711, 1589, 1472, 1428, 1378, 1363, 1110, 1035, 918, 823 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 7.68-7.60 (m, 8H), 7.44-7.27 (m, 17H), 4.64 (q, *J* = 5.2 Hz, 1H), 4.53 (d_{AB} syst, *J* = 12.1 Hz, 1H), 4.48 (d_{AB} syst, *J* = 12.0 Hz, 1H), 4.42 (d_{AB} syst, *J* = 6.8 Hz, 1H), 4.36 (d_{AB} syst, *J* = 6.8 Hz, 1H), 4.23 (m, 1H), 4.01-3.85 (m, 4H), 3.83-3.75 (m, 2H), 3.64-3.52 (m, 2H), 3.20 (s, 3H), 2.85 (br d, *J* = 3.1 Hz, 1H, OH), 2.49 (dd, *J* = 16.2 and *J* = 7.2 Hz, 1H), 2.17 (dd, *J* = 16.2 and *J* = 5.3 Hz, 1H), 2.14 (dd, *J* = 18.0 and *J* = 9.2 Hz, 1H), 2.05 (m, 1H), 1.85-1.71 (m, 4H), 1.64 (m, 1H), 1.52 (m, 1H), 1.33-1.23 (m, 2H), 1.23 (d, *J* = 5.1 Hz, 3H), 1.18-1.10 (m, 7H), 1.06 (s, 9H), 1.02 (s, 9H), 0.83 (t, *J* = 6.7 Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz): δ 209.1, 138.6, 136.3 (2C), 136.2 (2C), 135.9 (2C), 135.8 (2C), 134.0, 133.8, 133.71, 133.68, 129.83, 129.78 (2C), 129.74, 128.5 (2C), 127.8 (9C), 127.7 (2C), 98.7, 96.1, 76.5, 73.2, 73.1, 72.1, 69.4, 66.1, 65.5, 60.0, 55.7, 49.6, 49.1, 48.6, 40.8, 36.8, 36.2, 32.4, 32.0, 27.2 (3C), 27.1 (3C), 25.4, 22.8, 21.1, 19.5, 19.4, 14.2; HRMS (ESI): Calculated for C₆₂H₈₆O₉Si₂Na [M + Na]⁺: 1053.5703, found: 1053.5695.

(2R,4S,6S,7R,8R)-1-[(2S,4R,6S)-6-[2-(Benzyloxy)ethyl]-2-methyl-1,3-dioxan-4-yl]-6-(tert-butyl)diphenylsilyloxy)-7-[(tert-butyl)diphenylsilyloxy)methyl]-8-

(methoxymethoxy)tridecane-2,4-diol (29): To a solution of β-hydroxyketone **28** (350 mg, 0.34 mmol, 1 equiv) in a mixture of dry THF (6 mL) and anhydrous MeOH (1.5 mL) cooled to -78 °C was added Et₂BOMe (0.68 mL, 1M in THF, 0.68 mmol, 2.0 equiv). The mixture was stirred at

–78 °C for 1 h. NaBH₄ (28 mg, 0.74 mmol, 2.2 equiv) was added and the mixture was progressively warmed up to 0 °C over a period of 5 h. Glacial acetic acid (2.3 mL) and EtOAc (10 mL) were then added and the solution was warmed to rt. A saturated aqueous solution of NaHCO₃ (5 mL) was added, the layers were separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine, dried over MgSO₄, filtered and concentrated under *vacuum*. The crude material was co-evaporated with MeOH, to realize the hydrolysis of the boronate, until no more boronate was visible by TLC. The residual mixture was then purified by flash column chromatography on silica gel (petroleum ether/EtOAc = 8:2 to 75:25) to afford the diol **29** (255 mg, 0.25 mmol, 73%) as a pale yellow oil. $[\alpha]_D^{20} + 4.6$ (*c* 0.9, CHCl₃); IR: ν 3484, 3071, 2931, 2857, 1472, 1428, 1379, 1363, 1341, 1310, 1263, 1145, 1105, 1036, 918, 822 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 7.70-7.61 (m, 8H), 7.44-7.26 (m, 17H), 4.69 (q, *J* = 5.1 Hz, 1H), 4.54 (d_{AB syst}, *J* = 12.2 Hz, 1H), 4.50 (d_{AB syst}, *J* = 12.1 Hz, 1H), 4.42 (d_{AB syst}, *J* = 6.8 Hz, 1H), 4.33 (d_{AB syst}, *J* = 6.8 Hz, 1H), 4.30 (m, 1H), 3.97 (dd_{AB syst}, *J* = 10.1 and *J* = 6.0 Hz, 1H), 3.89 (dd_{AB syst}, *J* = 9.8 and *J* = 5.9 Hz, 1H), 3.85-3.76 (m, 3H), 3.71 (m, 1H), 3.66-3.53 (m, 3H), 3.33 (br s, 1H, OH), 3.20 (s, 3H), 2.05 (m, 1H), 1.87-1.73 (m, 3H), 1.63 (m, 1H), 1.56-1.47 (m, 3H), 1.30 (m, 1H), 1.28 (d, *J* = 5.0 Hz, 3H), 1.21-1.11 (m, 9H), 1.06 (s, 9H), 1.02 (s, 9H), 0.88 (m, 1H), 0.83 (t, *J* = 6.7 Hz, 3H), one OH not visible; ¹³C NMR (CDCl₃, 100 MHz): δ 138.6, 136.28 (2C), 136.25 (2C), 135.91 (2C), 135.86 (2C), 134.2, 134.0, 133.70, 133.68, 129.8 (2C), 129.74, 129.68, 128.5 (2C), 127.80 (2C), 127.78 (4C), 127.76, 127.67 (2C), 127.66 (2C), 98.6, 96.0, 76.6, 76.2, 73.3, 73.1, 71.3, 70.1, 69.9, 66.1, 60.1, 55.7, 48.6, 43.0, 42.7, 41.9, 37.0, 36.2, 32.3, 32.0, 27.2 (3C), 27.1 (3C), 25.4, 22.8, 21.2, 19.5, 19.4, 14.2; HRMS (ESI): Calculated for C₆₂H₈₈O₉Si₂Na [M + Na]⁺: 1055.5859, found: 1055.5849.

Synthesis of 30:

(5*R*,6*R*,7*S*)-7-[[[(4*S*,6*S*)-6-[[[(2*S*,4*S*,6*S*)-6-[2-(Benzyloxy)ethyl]-2-methyl-1,3-dioxan-4-yl]methyl]-2,2-dimethyl-1,3-dioxan-4-yl]methyl]-6-[(*tert*-butyldiphenylsilyloxy)methyl]-10,10-dimethyl-5-pentyl-9,9-diphenyl-2,4,8-trioxa-9-silaundecane (30'): To a solution of diol **29** (253 mg, 0.245 mmol, 1 equiv) in a mixture of acetone (8.4 mL) and 2,2-dimethoxypropane (4.2 mL) was added PPTS (6 mg, 0.024 mmol, 0.1 equiv). The mixture was stirred at rt for 14 h and then quenched by the addition of a few drops of Et₃N. After evaporation of the solvents under *vacuum*, the crude material was purified by flash column chromatography on silica gel (petroleum ether/EtOAc = 9:1 to 88:12) to afford the corresponding acetonide **30'** (227 mg, 0.211 mmol, 86%) as a colorless oil. $[\alpha]_D^{20} + 4.4$ (*c* 1.3, CHCl₃); IR: ν 3071, 2992, 2931, 2858, 1590, 1472, 1428, 1379, 1363, 1263, 1201, 1125, 1036, 823 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 7.72-7.63 (m, 8H), 7.42-7.27 (m, 17H), 4.65 (q, *J* = 5.0 Hz, 1H), 4.55 (d_{AB syst}, *J* = 12.1 Hz, 1H), 4.51 (d_{AB syst}, *J* = 12.0 Hz, 1H), 4.43 (d_{AB syst}, *J* = 6.8 Hz, 1H), 4.36 (d_{AB syst}, *J* = 6.8 Hz, 1H), 4.19-4.11 (m, 2H), 3.89-3.73 (m, 3H), 3.71-3.49 (m, 4H), 3.27 (m, 1H), 3.20 (s, 3H), 2.10 (m, 1H), 1.92-1.78 (m, 2H), 1.63-1.52 (m, 4H), 1.49-1.43 (m, 2H), 1.29 (d, *J* = 5.0 Hz, 3H), 1.25-1.10 (m, 8H), 1.19 (s, 3H), 1.07 (s, 9H), 1.01 (s, 12H), 0.85 (t, *J* = 6.9 Hz, 3H), 0.62 (q, *J* = 11.9 Hz, 1H), 0.35 (br d, *J* = 12.4 Hz, 1H); ¹³C NMR (CDCl₃, 100 MHz): δ 138.6, 136.2 (2C), 136.1 (2C), 135.84 (2C), 135.81 (2C), 134.2, 133.9 (2C), 133.7, 129.9, 129.74 (2C), 129.69, 128.5 (2C), 127.82 (2C), 127.77 (8C), 127.7, 98.6, 98.1, 96.4, 76.9, 73.23, 73.21, 72.5, 67.3, 66.4, 66.3, 64.7, 60.0, 55.6, 49.7, 42.1, 41.7, 36.5, 36.4, 36.1, 32.7, 32.0, 30.1, 27.1 (3C), 27.0 (3C), 25.8, 22.8, 21.3, 19.6, 19.5, 19.4, 14.2; HRMS (ESI): Calculated for C₆₅H₉₂O₉Si₂Na [M + Na]⁺: 1095.6172, found: 1095.6164.

2-[(2*S*,4*S*,6*S*)-6-[[[(4*S*,6*S*)-6-[(2*S*,3*R*,4*R*)-2-(*tert*-Butyldiphenylsilyloxy)-3-[(*tert*-butyldiphenylsilyloxy)methyl]-4-(methoxymethoxy)nonyl]-2,2-dimethyl-1,3-dioxan-4-yl]methyl]-2-methyl-1,3-dioxan-4-yl]ethanol (30): To a solution of benzyl alcohol **30'** (225 mg,

0.210 mmol, 1 equiv) in anhydrous MeOH (15 mL) was added Pd/C (45 mg, 5% in weight, 0.021 mmol, 0.1 equiv). The mixture was degassed and stirred at rt for 24 h under 1 atm of H₂. The mixture was then replaced under argon, filtered through a pad of Celite® and concentrated under *vacuum*. The crude material was then purified by flash column chromatography on silica gel (petroleum ether/EtOAc = 7:3) to afford the alcohol **30** (185 mg, 0.188 mmol, 90%) as a colorless viscous oil. $[\alpha]_D^{20} + 7.4$ (*c* 1.0, CHCl₃); IR: ν 3484, 3071, 3049, 2993, 2932, 2858, 1590, 1472, 1428, 1379, 1341, 1263, 1201, 1134, 1110, 1037, 953, 851, 823 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 7.72-7.63 (m, 8H), 7.45-7.28 (m, 12H), 4.69 (q, *J* = 5.1 Hz, 1H), 4.43 (d_{AB syst}, *J* = 6.8 Hz, 1H), 4.36 (d_{AB syst}, *J* = 6.8 Hz, 1H), 4.19-4.12 (m, 2H), 3.89-3.81 (m, 5H), 3.69 (m, 1H), 3.54 (m, 1H), 3.30 (m, 1H), 3.21 (s, 3H), 2.36 (br s, 1H, OH), 2.11 (m, 1H), 1.89-1.74 (m, 2H), 1.64-1.56 (m, 4H), 1.50-1.41 (m, 2H), 1.31 (d, *J* = 5.0 Hz, 3H), 1.33-1.11 (m, 8H), 1.20 (s, 3H), 1.07 (s, 9H), 1.01 (s, 12H), 0.85 (t, *J* = 6.7 Hz, 3H), 0.63 (q_{app}, *J* = 11.9 Hz, 1H), 0.36 (br d, *J* = 12.8 Hz, 1H). ¹³C NMR (CDCl₃, 100 MHz): δ 136.22 (2C), 136.15 (2C), 135.84 (2C), 135.82 (2C), 134.3, 133.9 (2C), 133.7, 129.9, 129.74 (2C), 129.70, 127.8 (6C), 127.7 (2C), 98.6, 98.2, 96.4, 76.9, 76.0, 72.6, 67.4, 66.4, 64.7, 60.8, 60.0, 55.6, 49.7, 41.9, 41.7, 38.1, 36.2, 36.1, 32.7, 32.1, 30.1, 27.2 (3C), 27.1 (3C), 25.8, 22.8, 21.3, 19.63, 19.55, 19.4, 14.2; HRMS (ESI): Calculated for C₅₈H₈₆O₉Si₂Na [M + Na]⁺: 1005.5703, found: 1005.5693.

1-[(2*S*,4*S*,6*S*)-6-[[[(4*S*,6*S*)-6-{(2*S*,3*R*,4*R*)-2-(*tert*-Butyldiphenylsilyloxy)-3-[(*tert*-butyldiphenylsilyloxy)methyl]-4-(methoxymethoxy)nonyl]-2,2-dimethyl-1,3-dioxan-4-yl]methyl]-2-methyl-1,3-dioxan-4-yl]propan-2-one (31**):** To a solution of alcohol **30** (82 mg, 84 μ mol, 1.0 equiv) in dry CH₂Cl₂ (2.7 mL) was added NaHCO₃ (14 mg, 0.17 mmol, 2.0 equiv), the solution was cooled to 0 °C and DMP (106 mg, 0.25 mmol, 3.0 equiv) was added. The mixture was progressively warmed to rt and stirred for 2 h. A saturated aqueous solution of NaHCO₃ (2.5 mL)

was added, followed by the addition of Et₂O (5 mL). The layers were separated and the aqueous layer was extracted with Et₂O (3 × 5 mL). The combined organic layers were washed with H₂O, dried over MgSO₄, filtered and concentrated under *vacuum* to afford the aldehyde, which was not purified but directly engaged in the next step.

To a solution of the crude aldehyde in dry Et₂O (2.7 mL) at 0 °C was added MeMgBr (0.08 mL, 3 M in Et₂O, 0.24 mmol, 3.0 equiv). After 1 h, the reaction was quenched by the addition of a saturated aqueous solution of NH₄Cl (3 mL). The layers were separated and the aqueous layer was extracted with Et₂O (3 × 5 mL). The combined organic layers were washed with brine, dried over MgSO₄, filtered and concentrated under *vacuum* to afford the desired secondary alcohol as a mixture of diastereomers which were not purified but directly engaged in the next oxidation step.

To a solution of crude alcohol in dry CH₂Cl₂ (3.6 mL) was added NaHCO₃ (14 mg, 0.17 mmol, 2.0 equiv). The solution was cooled to 0 °C and DMP (106 mg, 0.25 mmol, 3.0 equiv) was added to the mixture, which was progressively warmed to rt. After 14 h, a saturated aqueous solution of NaHCO₃ (5 mL) was added, followed by the addition of Et₂O (10 mL). After 15 min, the layers were separated and the aqueous layer was extracted with Et₂O (3 × 5 mL). The combined organic layers were washed with H₂O, dried over MgSO₄, filtered and concentrated under *vacuum*. Purification of the crude material by flash column chromatography on silica gel (petroleum ether/EtOAc = 85:15) afforded the methylketone **31** (72 mg, 72 μmol, 86%) as a colorless viscous oil. $[\alpha]_D^{20} + 12.4$ (*c* 0.95, CHCl₃); IR: ν 3072, 2993, 2932, 2858, 1719, 1589, 1472, 1428, 1379, 1361, 1260, 1200, 1111, 1037, 944, 823 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 7.72-7.63 (m, 8H), 7.45-7.28 (m, 12H), 4.68 (q, *J* = 5.2 Hz, 1H), 4.43 (d_{AB syst}, *J* = 6.8 Hz, 1H), 4.36 (d_{AB syst}, *J* = 6.7 Hz, 1H), 4.19-4.13 (m, 2H), 4.07 (m, 1H), 3.87 (dd, *J* = 9.8 and *J* = 7.3 Hz, 1H), 3.83 (m, 1H), 3.69 (m, 1H), 3.54 (m, 1H), 3.30 (m, 1H), 3.20 (s, 3H), 2.80 (dd_{AB syst}, *J* = 16.0 and *J* = 7.3 Hz, 1H), 2.51 (dd_{AB syst}, *J* = 16.0 and *J* = 5.1 Hz, 1H), 2.22 (s, 3H), 2.10 (m, 1H), 1.64-1.44 (m, 6H), 1.28

(d, $J = 5.1$ Hz, 3H), 1.25-1.10 (m, 8H), 1.20 (s, 3H), 1.07 (s, 9H), 1.01 (s, 3H), 1.00 (s, 9H), 0.85 (t, $J = 6.8$ Hz, 3H), 0.62 (q_{app}, $J = 12.4$ Hz, 1H), 0.37 (br d, $J = 12.6$ Hz, 1H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 206.9, 136.2 (2C), 136.1 (2C), 135.84 (2C), 135.81 (2C), 134.3, 133.9 (2C), 133.7, 129.8, 129.74 (2C), 129.69, 127.8 (6C), 127.7 (2C), 98.7, 98.2, 96.4, 76.9, 72.4 (2C), 67.4, 66.4, 64.7, 60.0, 55.6, 49.7, 49.6, 42.0, 41.7, 36.1 (2C), 32.7, 32.1, 31.4, 30.1, 27.2 (3C), 27.1 (3C), 25.8, 22.8, 21.2, 19.62, 19.55, 19.4, 14.2; HRMS (ESI): Calculated for $\text{C}_{59}\text{H}_{86}\text{O}_9\text{Si}_2\text{Na}$ [$\text{M} + \text{Na}$] $^{+}$: 1017.5703, found: 1017.5692.

(2*S*,3*S*,5*S*,7*R*)-8-[(2*S*,4*R*,6*S*)-6-[2-(Benzyloxy)ethyl]-2-methyl-1,3-dioxan-4-yl]-2-[(*R*)-1-

(methoxymethoxy)hexyl]octane-1,3,5,7-tetraol (32**):** To a solution of silyl ether **29** (20 mg, 0.019 mmol, 1 equiv) in dry THF (2 mL) cooled to 0 °C was added TBAF (58 μL , 1M in THF, 0.058 mmol, 3.0 equiv). The mixture was stirred at rt for 3.5 h and then quenched by addition of H_2O (2 mL). After addition of EtOAc (5 mL), the layers were separated and the aqueous layer was extracted with EtOAc (4 \times 5 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 , filtered and concentrated under *vacuum*. The crude material was purified by flash column chromatography on silica gel ($\text{CH}_2\text{Cl}_2/\text{MeOH} = 98:2$) to afford the tetraol **32** (8 mg, 0.014 mmol, 74%) as a colorless oil. $[\alpha]_{\text{D}}^{20} - 13.1$ (c 0.4, CHCl_3); IR: ν 3420, 2925, 2857, 1454, 1378, 1340, 1143, 1099, 1035, 918, 848 cm^{-1} ; ^1H NMR (CD_3OD , 400 MHz): δ 7.36-7.25 (m, 5H), 4.71 (q, $J = 5.0$ Hz, 1H), 4.68 (d_{AB syst}, $J = 6.9$ Hz, 1H), 4.62 (d_{AB syst}, $J = 6.8$ Hz, 1H), 4.51 (d_{AB syst}, $J = 12.0$ Hz, 1H), 4.47 (d_{AB syst}, $J = 12.0$ Hz, 1H), 4.05-3.92 (m, 3H), 3.89-3.78 (m, 3H), 3.77-3.66 (m, 2H), 3.65-3.52 (m, 2H), 3.37 (s, 3H), 1.91-1.83 (m, 2H), 1.79-1.72 (m, 2H), 1.70 (m, 1H), 1.68-1.56 (m, 5H), 1.52-1.44 (m, 2H), 1.37-1.27 (m, 6H), 1.24 (d, $J = 5.3$ Hz, 3H), 1.20 (m, 1H), 0.92 (t, $J = 6.7$ Hz, 3H), four OH not visible; ^{13}C NMR (CD_3OD , 100 MHz): δ 139.8, 129.4 (2C), 128.9 (2C), 128.7, 99.7, 97.4, 78.6, 75.4, 74.7, 73.9, 71.1, 70.9, 68.3, 67.1, 60.1, 56.1, 50.6, 45.1, 44.3,

42.2, 38.0, 37.1, 33.1, 32.8, 26.8, 23.7, 21.4, 14.4; HRMS (ESI): Calculated for C₃₀H₅₂O₉Na [M + Na]⁺: 579.3504, found: 579.3493.

(4*S*,5*E*,7*E*,9*E*,11*E*,13*E*,15*S*,16*R*)-1-[[*(2R,4R,6S)*-6-[[*(4S,6S)*-6-{*(2S,3R,4R)*-2-(*tert*-Butyldiphenylsilyloxy)-3-[(*tert*-butyldiphenylsilyloxy)methyl]-4-(methoxymethoxy)nonyl]-2,2-dimethyl-1,3-dioxan-4-yl]methyl]-2-methyl-1,3-dioxan-4-yl]-4-hydroxy-5-methyl-16-(triethylsilyloxy)-15-[(2-(trimethylsilyl)ethoxy)methoxy]heptadeca-5,7,9,11,13-pentaen-2-one (34): To a solution of ketone **31** (67 mg, 0.067 mmol, 1.5 equiv) in dry Et₂O (3 mL) cooled to 0 °C were added Et₃N (19 µL, 0.137 mmol, 3.0 equiv) and chlorodicyclohexylborane (0.11 mL, 1M in hexanes, 0.11 mmol, 2.5 equiv). The mixture was stirred at 0 °C for 2 h and then cooled to -78 °C. A solution of aldehyde **13** (22 mg, 0.045 mmol, 1.0 equiv) in dry Et₂O (5 mL) was added to the boronate **33** and the mixture was progressively warmed to -20 °C and stirred at this temperature. After 14 h, the reaction was quenched by the addition of a mixture of MeOH/pH 7 buffer/35% aqueous H₂O₂ = 1:1:1 (6 mL) and the solution was progressively warmed to rt and stirred for 2 h. The mixture was cooled to 0 °C and a saturated aqueous solution of Na₂S₂O₃ (5 mL) was added dropwise over a period of 30 min. The layers were separated and the aqueous layer was extracted with Et₂O (3 × 10 mL). The combined organic layers were washed with brine, dried over MgSO₄, filtered and concentrated under *vacuum*. The crude material was purified by flash column chromatography on silica gel (petroleum ether/EtOAc = 85:15 to 75:25) to afford **34** (61 mg, 0.041 mmol, 91%) as a single diastereomer and as a yellow oil. [α]_D²⁰ + 40.4 (*c* 1.0, CH₃CN); IR: ν 3449, 3071, 2953, 2931, 2876, 2858, 1715, 1617, 1589, 1461, 1428, 1378, 1331, 1249, 1199, 1105, 1035, 1002, 949, 920, 859, 834 cm⁻¹; ¹H NMR (C₆D₆, 400 MHz): δ 7.89-7.80 (m, 8H), 7.32-7.22 (m, 12H), 6.48-6.36 (m, 2H), 6.30-6.16 (m, 6H), 5.81 (dd, *J* = 15.2 and *J* = 8.1 Hz, 1H), 4.86 (d_{AB} syst, *J* = 6.8 Hz, 1H), 4.72 (d_{AB} syst, *J* = 6.8 Hz, 1H), 4.60-4.50 (m, 3H), 4.56 (d_{AB} syst, *J* = 6.7 Hz, 1H),

4.43 (dd, $J = 9.8$ and $J = 6.0$ Hz, 1H), 4.39 (d_{AB syst}, $J = 6.8$ Hz, 1H), 4.23 (dd, $J = 9.7$ and $J = 6.4$ Hz, 1H), 4.14 (dd, $J = 7.8$ and $J = 4.6$ Hz, 1H), 4.12 (m, 1H), 4.04-3.97 (m, 2H), 3.92-3.82 (m, 2H), 3.76 (m, 1H), 3.70-3.57 (m, 2H), 3.12 (s, 3H), 2.75 (br s, 1H, OH), 2.56 (dd, $J = 15.8$ and $J = 7.4$ Hz, 1H), 2.49 (dd, $J = 16.5$ and $J = 9.5$ Hz, 1H), 2.42 (m, 1H), 2.32 (dd, $J = 16.5$ and $J = 2.8$ Hz, 1H), 2.19 (dd, $J = 15.8$ and $J = 5.0$ Hz, 1H), 2.09-1.96 (m, 2H), 1.94-1.79 (m, 2H), 1.64 (s, 3H), 1.64 (m, 1H), 1.51-1.40 (m, 3H), 1.47 (s, 3H), 1.33 (d, $J = 5.0$ Hz, 3H), 1.30 (d, $J = 6.2$ Hz, 3H), 1.26 (s, 3H), 1.25-1.15 (m, 6H), 1.22 (s, 9H), 1.18 (s, 9H), 1.06 (t, $J = 8.0$ Hz, 9H), 1.05-0.95 (m, 2H), 0.93 (m, 1H), 0.90 (t, $J = 7.2$ Hz, 3H), 0.67 (m, 1H), 0.67 (q, $J = 8.2$ Hz, 6H), 0.03 (s, 9H); ^{13}C NMR (C_6D_6 , 100 MHz): δ 207.9, 139.6, 136.6 (2C), 136.5 (2C), 136.22 (2C), 136.17 (2C), 135.0, 134.8, 134.3, 134.2 (3C), 133.8, 133.6, 133.2, 132.6, 131.6, 130.2, 130.0 (3C), 129.4, 128.16 (2C), 128.13 (2C), 128.11 (2C), 128.06 (2C), 125.7, 98.8, 98.4, 96.5, 92.5, 81.2, 76.8, 72.7, 72.60, 72.55, 71.5, 68.3, 66.7, 65.31, 65.28, 60.6, 55.5, 49.7, 49.65, 49.54, 42.7, 42.1, 36.8, 36.6, 33.0, 32.4, 30.5, 27.35 (3C), 27.32 (3C), 26.2, 23.1, 21.4, 20.7, 20.0, 19.8, 19.6, 18.3, 14.4, 13.1, 7.3 (3C), 5.5 (3C), -1.2 (3C); HRMS (ESI): Calculated for $\text{C}_{86}\text{H}_{134}\text{O}_{13}\text{Si}_4\text{Na}[\text{M} + \text{Na}]^+$: 1509.8794, found: 1509.8774.

(2*S*,4*S*,5*E*,7*E*,9*E*,11*E*,13*E*,15*S*,16*R*)-1-[(2*S*,4*S*,6*S*)-6-[(4*S*,6*S*)-6-[(2*S*,3*R*,4*R*)-2-(*tert*-Butyldiphenylsilyloxy)-3-[(*tert*-butyldiphenylsilyloxy)methyl]-4-(methoxymethoxy)nonyl]-2,2-dimethyl-1,3-dioxan-4-yl)methyl]-2-methyl-1,3-dioxan-4-yl]-5-methyl-16-(triethylsilyloxy)-15-[2-(trimethylsilyl)ethoxy]methoxy}heptadeca-5,7,9,11,13-pentaene-2,4-diol (35): To a solution of $\text{Me}_4\text{NBH}(\text{OAc})_3$ (80 mg, 0.305 mmol, 10 equiv) in anhydrous CH_3CN (0.9 mL) was added glacial acetic acid (0.9 mL) dropwise. The mixture was stirred until it became clear and then cooled to -20°C . A solution of β -hydroxyketone **34** (45 mg, 0.030 mmol, 1.0 equiv) in CH_3CN (8.1 mL) was cannulated and the resulting solution was stirred at -20°C for 14 h. The

reaction mixture was then poured into a 1:1 mixture of a saturated aqueous solution of Rochelle's salt and a saturated aqueous solution of NaHCO₃ cooled to 0 °C and stirred at rt for 3 h. EtOAc (10 mL) was added, the layers were separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with a saturated aqueous solution of NaHCO₃ (20 mL), then with brine (20 mL), dried over MgSO₄, filtered and concentrated under *vacuum*. The crude material was purified by flash column chromatography on silica gel (pentane/EtOAc = 75:25 to 7:3) to afford the diol **35** (36 mg, 0.024 mmol, 80%) as a yellow oil. $[\alpha]_D^{20} + 38.4$ (*c* 1.0, CH₃CN); IR: ν 3455, 3071, 2952, 2933, 2877, 2858, 1589, 1472, 1428, 1378, 1249, 1200, 1110, 1036, 1002, 947, 859, 834 cm⁻¹; ¹H NMR (C₆D₆, 400 MHz): δ 7.88-7.80 (m, 8H), 7.30-7.20 (m, 12H), 6.60-6.47 (m, 2H), 6.40 (br dd, *J* = 15.0 and *J* = 9.5 Hz, 1H), 6.34-6.26 (m, 2H), 6.26-6.16 (m, 3H), 5.80 (dd, *J* = 15.2 and *J* = 8.0 Hz, 1H), 4.87 (d_{AB syst}, *J* = 6.8 Hz, 1H), 4.72 (d_{AB syst}, *J* = 6.8 Hz, 1H), 4.60-4.48 (m, 3H), 4.45-4.37 (m, 3H), 4.25-4.06 (m, 4H), 4.00 (m, 1H), 3.92-3.82 (m, 2H), 3.72 (m, 1H), 3.65-3.57 (m, 2H), 3.45 (m, 1H), 3.11 (s, 3H), 2.42 (m, 1H), 2.08-1.97 (m, 2H), 1.91-1.77 (m, 3H), 1.76 (s, 3H), 1.76-1.60 (m, 3H), 1.47 (s, 3H), 1.43-1.15 (m, 16H), 1.23 (s, 9H), 1.18 (s, 12H), 1.07 (t, *J* = 8.0 Hz, 9H), 1.06-0.95 (m, 2H), 0.93-0.88 (m, 4H), 0.68 (q, *J* = 7.8 Hz, 6H), 0.65 (m, 1H), 0.03 (s, 9H), two OH not visible; ¹³C NMR (C₆D₆, 100 MHz): δ 141.8, 136.6 (2C), 136.5 (2C), 136.23 (2C), 136.17 (2C), 135.0, 134.8, 134.4, 134.3, 134.2 (2C), 134.0, 133.1, 132.8, 132.4, 131.3, 130.2, 130.0 (3C), 129.8, 128.15 (2C), 128.12 (2C), 128.08 (2C), 128.05 (2C), 125.0, 98.6, 98.4, 96.5, 92.5, 81.3, 77.2, 76.9, 74.1, 72.7, 71.5, 69.6, 68.3, 66.7, 65.27, 65.25, 60.6, 55.5, 49.7, 43.1, 42.6, 42.1 (2C), 36.8 (2C), 33.0, 32.4, 30.5, 27.35 (3C), 27.32 (3C), 26.1, 23.1, 21.3, 20.6, 20.0, 19.8, 19.6, 18.3, 14.4, 13.6, 7.2 (3C), 5.5 (3C), -1.2 (3C); HRMS (ESI): Calculated for C₈₆H₁₃₆O₁₃Si₄Na [M + Na]⁺: 1511.8950, found: 1511.8916.

Synthesis of 36:

**(8*S*,9*E*,11*E*,13*E*,15*E*,17*E*,19*S*,21*R*)-21-[[[(2*S*,4*S*,6*S*)-6-[[[(4*S*,6*S*)-6-[(2*S*,3*R*,4*R*)-2-(*tert*-
 Butyldiphenylsilyloxy)-3-[(*tert*-butyldiphenylsilyloxy)methyl]-4-(methoxymethoxy)nonyl]-
 2,2-dimethyl-1,3-dioxan-4-yl]methyl]-2-methyl-1,3-dioxan-4-yl]methyl]-2,2,18,27,27-
 pentamethyl-8-[(*R*)-1-(triethylsilyloxy)ethyl]-19-[[2-(trimethylsilyl)ethoxy]methoxy]-
 5,7,22,24-tetraoxa-2,27-disilaoctacos-9,11,13,15,17-pentaene (36')**: To a solution of diol **35**
 (36 mg, 0.024 mmol, 1.0 equiv) in dry CH₂Cl₂ (1 mL) were added *i*Pr₂NEt (24 μL, 0.145 mmol, 6
 equiv) and SEMCl (17 μL, 0.096 mmol, 4 equiv) dropwise. The mixture was stirred at rt for 14 h
 and then quenched by addition of H₂O (1 mL). The layers were separated and the aqueous layer
 was extracted with CH₂Cl₂ (3 × 5 mL). The combined organic layers were washed with brine, dried
 over MgSO₄, filtered and concentrated under *vacuum*. The crude material was purified by flash
 column chromatography on silica gel (pentane/EtOAc = 9:1) to afford the corresponding ether **36'**
 (39 mg, 0.022 mmol, 92%). [α]_D²⁰ + 13.3 (*c* 1.0, CH₃CN); IR: ν 3071, 2953, 2877, 1650, 1589,
 1463, 1428, 1378, 1249, 1200, 1105, 1034, 1005, 939, 920, 860, 836 cm⁻¹; ¹H NMR (C₆D₆, 400
 MHz): δ 7.89-7.80 (m, 8H), 7.33-7.22 (m, 12H), 6.49 (dd, *J* = 13.5 and *J* = 11.4 Hz, 1H), 6.39 (m,
 1H), 6.31 (br d, *J* = 11.4 Hz, 1H), 6.27-6.17 (m, 5H), 5.81 (dd, *J* = 15.2 and *J* = 8.0 Hz, 1H), 4.93
 (d_{AB} syst, *J* = 7.0 Hz, 1H), 4.89 (d_{AB} syst, *J* = 7.0 Hz, 1H), 4.86 (d_{AB} syst, *J* = 6.8 Hz, 1H), 4.77 (d_{AB}
 syst, *J* = 6.7 Hz, 1H), 4.73-4.68 (m, 2H), 4.64 (q, *J* = 5.1 Hz, 1H), 4.59-4.51 (m, 3H), 4.42 (dd, *J* =
 9.8 and *J* = 6.0 Hz, 1H), 4.39 (d, *J* = 6.8 Hz, 1H), 4.27-4.17 (m, 2H), 4.16-4.05 (m, 2H), 4.00 (m,
 1H), 3.94-3.56 (m, 10H), 3.12 (s, 3H), 2.42 (m, 1H), 2.28 (m, 1H), 2.13 (m, 1H), 2.06-1.90 (m,
 4H), 1.89-1.76 (m, 6H), 1.65 (m, 1H), 1.58 (m, 1H), 1.47 (s, 3H), 1.42 (d, *J* = 5.0 Hz, 3H), 1.37-
 1.15 (m, 7H), 1.30 (d, *J* = 6.2 Hz, 3H), 1.28 (s, 3H), 1.22 (s, 9H), 1.19 (s, 9H), 1.07 (t, *J* = 8.0 Hz,
 9H), 1.05-0.95 (m, 6H), 0.93-0.88 (m, 4H), 0.71 (m, 1H), 0.68 (q, *J* = 8.1 Hz, 6H), 0.05 (s, 9H),
 0.04 (s, 9H), 0.03 (s, 9H); ¹³C NMR (C₆D₆, 100 MHz): δ 138.8, 136.6 (2C), 136.5 (2C), 136.23
 (2C), 136.17 (2C), 135.0, 134.8, 134.26, 134.24, 134.19, 134.12, 133.8 (2C), 133.3, 132.7, 131.6,

130.14, 130.08, 130.0 (2C), 129.2, 128.4 (2C), 128.3, 128.2 (2C), 128.1 (2C), 128.0 (2C), 98.8, 98.4, 96.5, 95.2, 93.0, 92.5, 81.2, 79.0, 76.9, 73.4, 73.3, 72.8, 71.5, 68.3, 66.7, 65.8, 65.6, 65.4, 65.3, 60.6, 55.5, 49.6, 42.9, 42.6, 42.1, 40.8, 37.4, 36.9, 33.0, 32.4, 30.6, 27.4 (6C), 26.2, 23.1, 21.7, 20.7, 20.0, 19.8, 19.6, 18.43, 18.36, 18.3, 14.4, 12.5, 7.3 (3C), 5.5 (3C), -1.17 (3C), -1.18 (3C), -1.24 (3C); HRMS (ESI): Calculated for $C_{98}H_{164}O_{15}Si_6Na [M + Na]^+$: 1772.0578, found: 1772.0565.

(2S,3S)-4-[(4R,6S)-6-[(2S,4S,6S)-6-[(2R,4S,5E,7E,9E,11E,13E,15S,16R)-16-Hydroxy-5-methyl-2,4,15-tris[2-(trimethylsilyl)ethoxy]methoxy]heptadeca-5,7,9,11,13-pentaen-1-yl]-2-methyl-1,3-dioxan-4-yl]methyl]-2,2-dimethyl-1,3-dioxan-4-yl]-2-[(R)-1-(methoxymethoxy)hexyl]butane-1,3-diol (36): To a solution of silyl ether **36'** (38 mg, 0.022 mmol, 1 equiv) in dry THF (1.5 mL) was added TBAF (0.22 mL, 1M in THF, 0.22 mmol, 10 equiv). The mixture was stirred at rt for 2 days, then TBAF (0.22 mL, 1M in THF, 0.22 mmol, 10 equiv) was added and the mixture was stirred at rt for 2 days. The reaction was quenched by the addition of H₂O (2 mL). EtOAc (5 mL) was added, the layers were separated and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated under *vacuum*. The crude material was purified by flash column chromatography on silica gel (pentane/EtOAc = 5:5 to 4:6) to afford the triol **36** (22 mg, 0.019 mmol, 86%) as a yellow oil. $[\alpha]_D^{20} + 15.3$ (c 0.65, CH₃CN); IR: ν 3481, 2952, 2925, 1379, 1249, 1200, 1131, 1099, 1028, 938, 921, 860, 836 cm⁻¹; ¹H NMR (C₆D₆, 400 MHz): δ 6.46 (dd, $J = 14.3$ and $J = 11.3$ Hz, 1H), 6.37 (dd, $J = 15.1$ and $J = 9.8$ Hz, 1H), 6.30-6.13 (m, 6H), 5.68 (dd, $J = 15.0$ and $J = 7.9$ Hz, 1H), 4.87 (d_{AB syst}, $J = 7.0$ Hz, 1H), 4.81 (d_{AB syst}, $J = 7.0$ Hz, 1H), 4.76 (d_{AB syst}, $J = 5.2$ Hz, 1H), 4.75 (d_{AB syst}, $J = 5.2$ Hz, 1H), 4.67 (m, 1H), 4.67 (d_{AB syst}, $J = 6.0$ Hz, 1H), 4.61 (d_{AB syst}, $J = 6.4$ Hz, 1H), 4.59 (d_{AB syst}, $J = 6.2$ Hz, 1H), 4.54 (d_{AB syst}, $J = 6.7$ Hz, 1H),

4.48 (m, 1H), 4.17 (m, 1H), 4.13-3.84 (m, 11H), 3.81-3.75 (m, 2H), 3.72 (m, 1H), 3.61 (m, 1H), 3.50 (m, 1H), 3.22 (s, 3H), 2.85 (br s, 1H, OH), 2.42 (br s, 1H, OH), 2.27-2.16 (m, 2H), 2.15-2.00 (m, 5H), 1.82 (s, 3H), 1.89-1.65 (m, 4H), 1.60-1.50 (m, 2H), 1.44 (d, $J = 5.0$ Hz, 3H), 1.37 (s, 3H), 1.36-1.26 (m, 7H), 1.25 (s, 3H), 1.22 (d, $J = 6.4$ Hz, 3H), 1.17 (m, 1H), 1.05-0.95 (m, 6H), 0.92-0.88 (m, 3H), 0.04 (s, 9H), 0.02 (s, 9H), 0.00 (s, 9H), one OH not visible; ^{13}C NMR (C_6D_6 , 100 MHz): δ 138.5, 135.2, 134.2, 134.0, 133.8, 133.4, 132.7, 130.3, 129.1, 128.7, 98.9, 98.8, 96.7, 94.9, 92.9, 92.8, 81.8, 79.1, 78.7, 73.5, 72.8, 72.6, 71.9, 71.1, 70.0, 65.7, 65.6, 65.52, 65.46, 61.7, 55.7, 49.3, 42.8, 42.3, 41.3, 40.3, 37.5, 37.2, 32.4, 32.2, 30.4, 26.2, 23.1, 21.7, 19.9, 18.51, 18.45, 18.36, 18.3, 14.4, 12.1, -1.19 (3C), -1.23 (3C), -1.3 (3C); HRMS (ESI): Calculated for $\text{C}_{60}\text{H}_{114}\text{O}_{15}\text{Si}_3\text{Na}$ $[\text{M} + \text{Na}]^+$: 1181.7358, found: 1181.7338.

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SUPPORTING INFORMATION

Copies of ^1H and ^{13}C NMR spectra for all compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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