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Apoptolidinone A: Synthesis of the Apoptolidin A Aglycone

Julia Schuppan, Hermut Wehlan, Sonja Keiper, and Ulrich Koert*[a]

Abstract: An efficient stereocontrolled synthesis of apoptolidinone A, the aglycone of apoptolidin A is described. The synthetic strategy relies on a cross coupling between C11/C12 of a northern half (C1–C11) and a southern part (C12–C28) followed by a ring-size selective macrolactonization. Key steps for the introduction of the southern half stereocenters are a stereoselective aldol reaction, a substrate controlled dihydroxylation and a chelation-controlled Grignard/aldehyde addition. The conjugated triene of the northern half was built up successively by *E*-selective Wittig reactions. L-Malic acid was chosen as the chiral pool source for the C8/C9 stereocenters. The final cleavage of the silyl ethers and the conversion of the C21 methyl ketal into the hemiketal was achieved by HF·pyridine.

Keywords: apoptolidin · dihydroxylation · natural products · stereoselective synthesis · total synthesis

Introduction

Natural products that selectively induce apoptosis (programmed cell death) in tumor cells have a considerable potential for medicinal chemistry.[1] Among the numerous naturally occurring apoptosis inducers, apoptolidins hold a prominent position. Apoptolidin A (**1**) was isolated by Hayakawa et al. from *Nocardiopsis* sp. in 1997 (Figure 1).[2] It selectively induces apoptosis in rat glia cells transformed with the E1A oncogene ($IC_{50} = 11\ ng\,mL^{-1}$) but not in untransformed cell lines.[3] Apoptolidin A (**1**) is a 20-membered macrolactone with a side chain containing a cyclic six-membered hemiketal. 6-Deoxy-4-*O*-methyl-L-glucose is attached to O9 and a disaccharide consisting of L-olivomycose and D-oleandrose is linked to O27. The chemistry and biology of apoptolidin A (**1**) was investigated in main part by Khosla[4] and Wender[5] and its apoptotic activity was correlated with its inhibition of mitochondrial F_0-F_1-ATPase. Apoptolidin B (**2**) and apoptolidin C (**3**) differ from **1** by the lack of the C16 hydroxyl group and different substituents at C20.[6] The promising biological properties and the structural challenges of the apoptolidins evoked synthetic efforts, which culminated in the total syntheses of apoptolidin A (**1**) by Nicolaou's group[7] and our own synthesis.[8] The aglycone of apoptolidin A named apoptoldinone A (**4**) was synthesized besides a contribution from these laboratories[9] by Sulikowsky,[10] Crimmins[11] and by Nicolaou.[7] In addition, several valuable studies on apoptolidins have been published.[12] Here, and in the following contribution, we report in detail our synthetic route to the apoptolidins.[13]

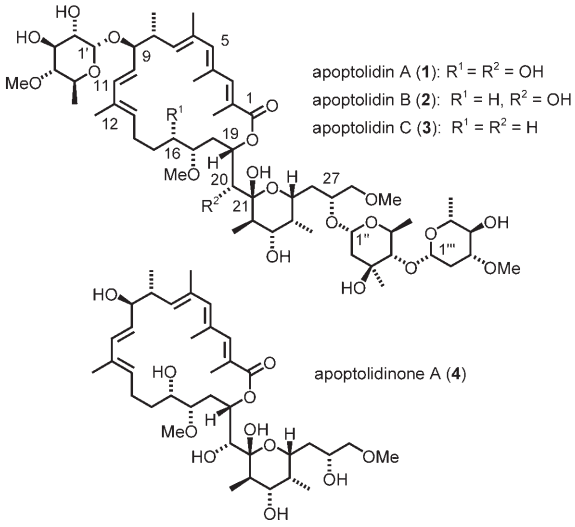


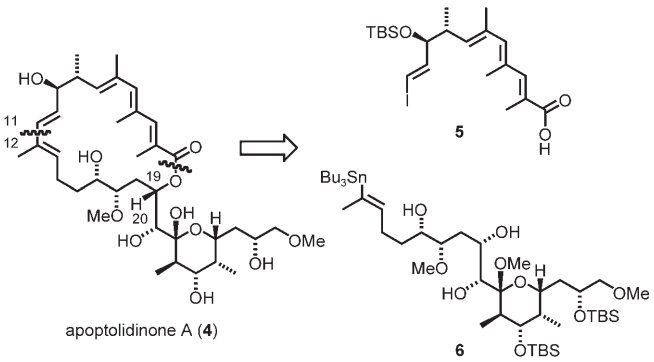
Figure 1. Structures of apoptolidin A (**1**), apoptolidin B (**2**), apoptolidin C (**3**) and apoptolidinone A (**4**).

Results and Discussion

Our synthetic plan was first focused on an efficient route to the aglycone. The retrosynthetic analysis of apoptolidinone

[a] Dr. J. Schuppan, Dr. H. Wehlan, Dr. S. Keiper, Prof. Dr. U. Koert
Fachbereich Chemie, Philipps-Universität Marburg
Hans-Meerwein-Strasse, 35032 Marburg (Germany)
Fax: (+49) 6421-282-5677
E-mail: koert@chemie.uni-marburg.de

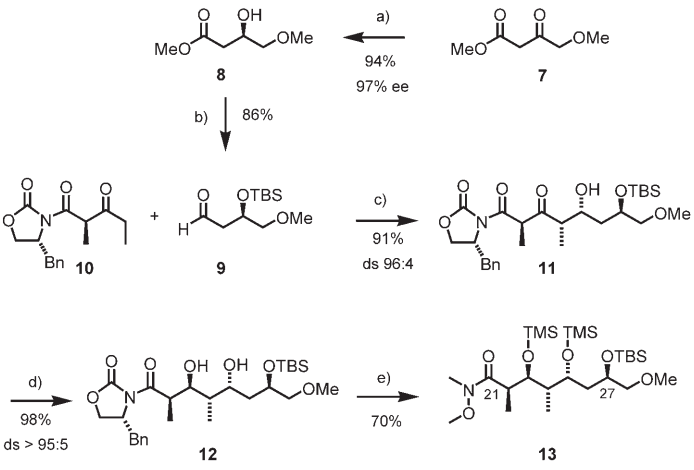
(**4**) led to two strategic disconnections (Scheme 1): a sp^2–sp^2 cross-coupling for the C11−C12 bond and a macrolactonization to close the 20-membered macrolide. From these considerations resulted a C1–C11 fragment **5** (northern half) and a C12–C28 fragment **6** (southern half). No protective group differentiation between the hydroxy groups at C16, C19 and C20 was chosen, because—based on molecular model considerations—we expected a ring-size selective macrolactonization.



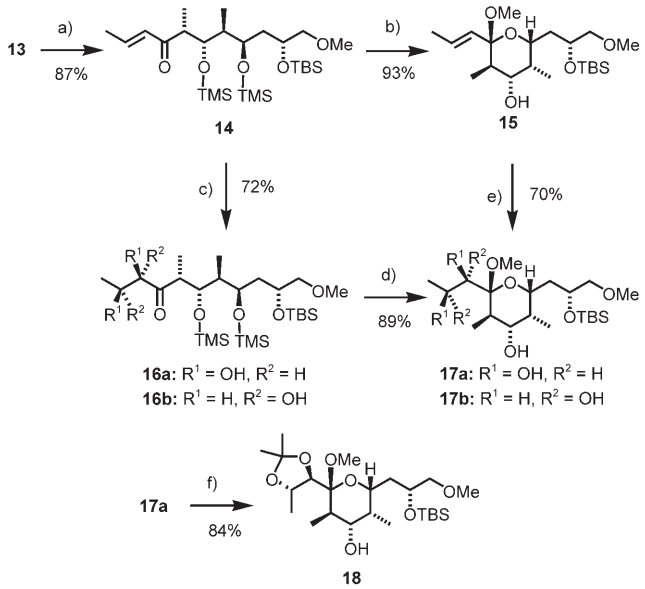
Scheme 1. Retrosynthetic analysis of apoptolidinone A (**4**).

The starting point of the synthesis of the southern half was β-ketoester **7** (Scheme 2). Asymmetric hydrogenation with Ru-(*S*)-BINAP[14] gave β-hydroxyester **8** with 97% *ee* (determined by HPLC). After TBS protection, the ester was reduced to aldehyde **9**. A stannous triflate-mediated *syn*-stereoselective Evans aldol reaction[15] of β-ketoimide **10**[16] with aldehyde **9** gave aldol product **11** in excellent yield with 96:4 diastereoselectivity. The relative configuration of **11** was proven by X-ray structure analysis.[12a] The *anti*-selective reduction of β-ketoimide **11** provided β-hydroxy imide **12** with a $>$ 95:5 diastereoselectivity.[17] The use of $NaBH(OAc)_3$ was superior to $Me_4NBH(OAc)_3$ with respect to yield and ease of workup in $>$ 20 mmol scale. Transamidation of **12** to the Weinreb amide[18] and subsequent TMS protection gave compound **13**. The free hydroxy group in **12** is a prerequisite for the successful transamidation due to the precomplexation of the aluminium reagent.[19]

The introduction of the C19–C20 diol was intended by a dihydroxylation of a corresponding (*E*)-alkene precursor. Exploratory studies towards a stereocontrolled dihydroxylation[20] of this alkene were conducted with an (*E*)-propenyl model system first (Scheme 3). For this purpose, Weinreb amide **13** was allowed to react with (*E*)-propenyl lithium to produce α,β-unsaturated ketone **14**. The latter could be converted smoothly into cyclic methyl ketal **15** by treatment with pyridinium *p*-toluene sulfonate (PPTS) in MeOH. The reagent controlled dihydroxylation of alkenone **14** with AD-mix α gave a 3:1 mixture of diols **16a** and **16b** favouring the desired diastereomer **16a**. The use of AD-mix β resulted in a 1:8 diastereoselectivity in unfavor of **16a**. The diastereomeric mixture of diols **16a**/**16b** was transformed into the cyclic methyl ketals **17a**/**17b**, which could be easily separated by chromatography. The modest selectivity for the reagent-controlled dihydroxylation of **14** led us to investigate the stereocontrolled dihydroxylation of alkene **15**. Compound **15** gave under substrate-controlled conditions ($[K_2OsO_2(OH)_4]$, NMO) a 2:1 mixture of **17a** and **17b**. Thus the stereocenters of the THP ring direct the dihydroxylation into the desired direction. Attempts to improve the stereoselectivity by use of AD-mix α or β were not successful. Diol **17a** was converted into acetonide **18**. An X-ray structure of **18**[12a] verified the stereochemical assignments of



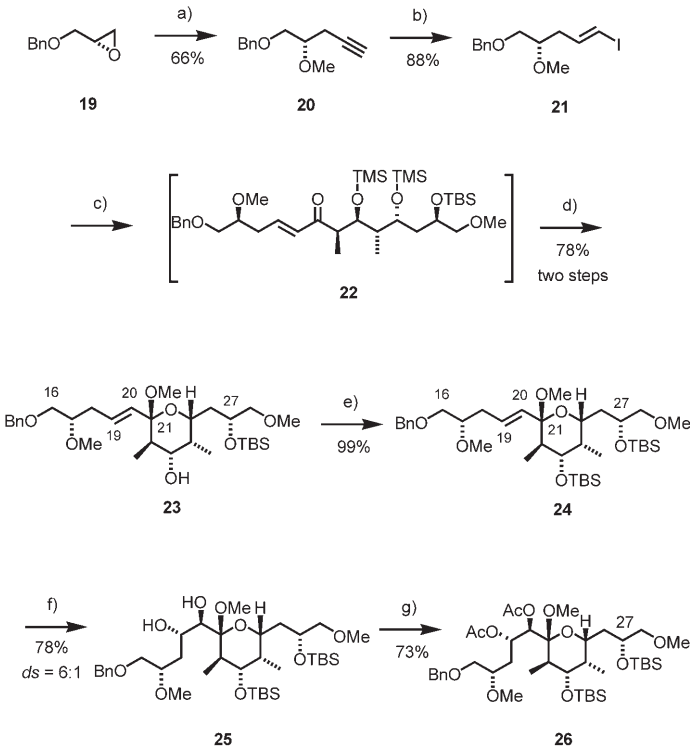
Scheme 2. a) $[RuCl_2(C_6H_6)]_2$, (*S*)-BINAP, H_2, MeOH, DMF, 95°C; b) i) TBSCl, imidazole, 28°C; ii) DIBAH, CH_2Cl_2, −78°C; c) $Sn(OTf)_2$, Et_3N, CH_2Cl_2, −78°C; d) $NaBH(OAc)_3$, HOAc, CH_3CN, −20 → 25°C; e) i) $AlMe_3$, Me(MeO)NH·HCl, CH_2Cl_2, −10°C; ii) TMSCl, imidazole, 0°C.



Scheme 3. a) (*E*)-1-bromo-1-propene, *t*BuLi, Et_2O, −78°C; b) PPTS, MeOH, CH_2Cl_2, 0°C; c) AD-mix α, *t*BuOH/H_2O, 0°C, **16a**/**16b** 3:1; d) PPTS, MeOH, CH_2Cl_2, 0°C; e) $[K_2OsO_2(OH)_4]$, NMO, THF/H_2O/*t*BuOH, 20°C; f) 2,2-dimethoxypropane, CSA, 0°C. PPTS = pyridinium *p*-toluenesulfonate, NMO = *N*-methylmorpholine-*N*-oxide, CSA = camphorsulfonic acid.

the dihydroxylation step and the earlier aldol reaction (**9** + **10** → **11**).

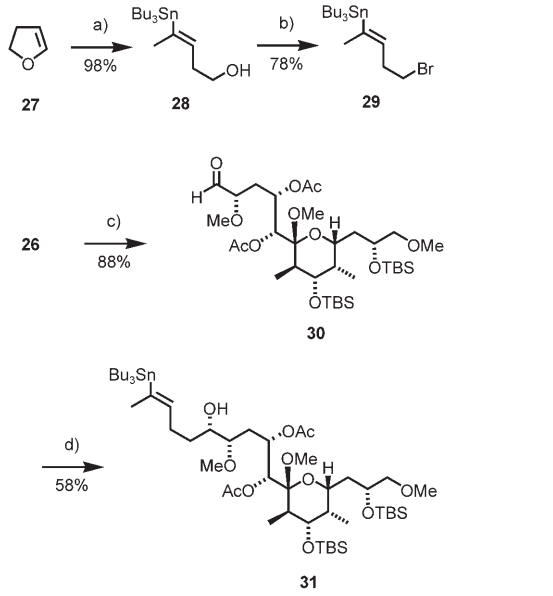
Having collected information about the dihydroxylation from the model system we turned back on the route towards apoptolidinone A (Scheme 4). Epoxide **19**[21] was opened at



Scheme 4. a) i) $LiCCSiMe_3$, $BF_3{\cdot}OEt_2$, THF, −78 °C; ii) LiHMDS, MeI, THF, 40 °C; iii) Bu_4NF, THF, 0 °C; b) $[Cp_2ZrCl_2]$, $LiEt_3BH$, NIS, THF, 20 °C; c) **21**, *t*BuLi, Et_2O, −78 °C, then **13**; d) PPTS, MeOH/CH_2Cl_2 1:1, 0 °C; e) TBS triflate, 2,6-lutidine, CH_2Cl_2; f) $[K_2OsO_2(OH)_4]$, NMO, THF/H_2O/*t*BuOH, 0 → 10 °C; g) Ac_2O, pyridine, DMAP, 40 °C. LiHMDS = lithium hexamethyldisilazide, NIS = *N*-iodosuccinimide, PPTS = pyridinium *p*-toluene sulfonate, DMAP = 4-*N*,*N*-dimethylaminopyridine.

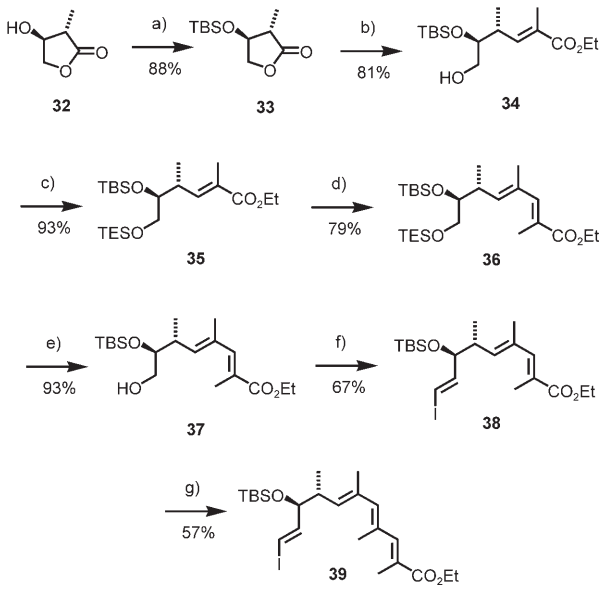
the terminal position with lithiated TMS acetylene.[22] A following methyl ether formation and TMS deprotection gave alkyne **20** in 66% overall yield. A hydrozirconation/iodolysis[23] provided (*E*)-alkenyl iodide **21**. Iodine–lithium exchange of **21** followed by acylation with Weinreb amide **13** and treatment of the resulting ketone **22** with PPTS in MeOH gave methyl ketal **23**. After TBS protection to **24** the substrate controlled dihydroxylation gave diol **25** with a 6:1 stereoselectivity, which was converted into diacetate **26**. The low reactivity of the double bond in **24** required a reaction time of several days at 0–10 °C. The undesired minor isomer of the dihydroxylation was separated chromatographically at the diacetate stage.

The last part of the synthesis of the southern half **31** required the introduction of the missing C12–C15 fragment (Scheme 5). The stereoselective synthesis of the trisubstituted alkenyl stannane started from dihydrofuran. Using the Ardisson/Pancrazi modification[24] of Kocienskis's procedure[25] the corresponding 5-lithio-2,3-dihydrofuran was converted into the cyclic α-alkoxyalkenylcuprate, which upon dyotropic rearrangement and subsequent methylation gave alcohol **28**. From **28**, bromide **29** was obtained. Aldehyde **30** was obtained from **26** by hydrogenolytic benzyl ether cleavage followed by Dess–Martin oxidation of the resulting alcohol. Bromide **29** could be converted into the corresponding Grignard reagent, which was allowed to react with aldehyde **30** to yield alcohol **31**. The stereoselectivity of this chelation-controlled[26] reaction was determined to be 96:4 by ^{1}H NMR. Noteworthy for the Grignard reaction is the compatibility of the stannyl group with the organomagnesium functionality.

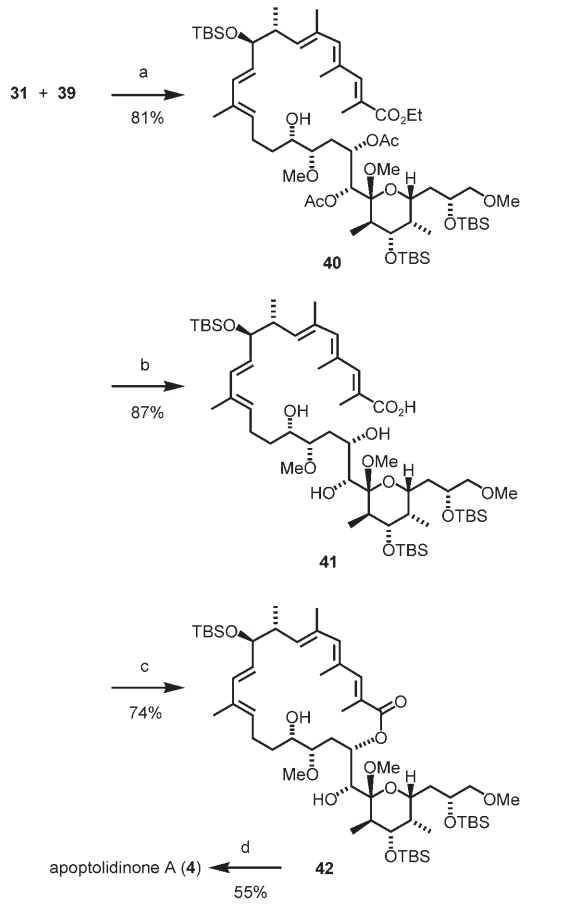


Scheme 5. a) Dihydrofuran, *t*BuLi, −60 °C; $[Bu_3Sn(Bu)CuCN]Li_2$, THF, MeI, −30 °C; b) i) MsCl, Et_3N, CH_2Cl_2, 0 °C; ii) LiBr, acetone, 50 °C; c) i) H_2, $Pd(OH)_2$/C, EtOAc, 20 °C, 1 h; ii) Dess–Martin periodinane, pyridine, CH_2Cl_2; d) **29**, Mg, 1,2-dibromoethane, Et_2O, 20 °C, then −78 °C addition of **30**.

The synthesis of the C1–C11 fragment (northern half) required the generation of the C8/C9 stereocenters and the assembly of a conjugated all-trisubstituted triene C2–C7 (Scheme 6). L-malic acid was chosen as the chiral pool source for the C8/C9 part from which β-hydroxy-γ-lactone **32** was prepared.[27] The hydroxy group in **32** was TBS protected to **33**. A linear, successive introduction of the three double bonds was chosen for the synthesis of the conjugated triene. Reduction of lactone **33** to the corresponding lactol followed by a Wittig reaction generated the C6/C7 double bond. The *E*-stereoisomer **34** which was formed with a 96:4 selectivity was obtained as a pure stereoisomer after chromatography. The primary alcohol in **34** was TES protected to **35**, which could be transformed smoothly via the corresponding aldehyde and a subsequent Wittig olefination into α,β,γ,δ-unsaturated ester **36**. Preliminary experiments with the introduction of the third conjugated double bond



Scheme 6. a) *t*BuMe$_2$SiOTf, 2,6-lutidine, CH_2Cl_2, 0 °C; b) i) DIBAH, CH_2Cl_2, −78 °C; ii) $Ph_3P{=}CCH_3CO_2Et$, toluene, 100 °C; c) Et_3SiCl, imidazole, CH_2Cl_2, 0 °C; d) i) DIBAH, toluene, −78 °C; ii) MnO_2, CH_2Cl_2, 40 °C; iii) $Ph_3P{=}CCH_3CO_2Et$, toluene, 100 °C; e) camphorsulfonic acid, MeOH/CH_2Cl_2, 0 °C; f) i) Dess–Martin periodinane, pyridine, CH_2Cl_2, 20 °C; ii) $CrCl_2$, CHI_3, cat. hydroquinone, THF, 1,4-dioxane, 20 °C; g) i) DIBAH, toluene, −78 °C; ii) MnO_2, CH_2Cl_2, 20 °C; iii) $Ph_3P{=}CCH_3CO_2Et$, toluene, 100 °C; DIBAH = diisobutylaluminium hydride.



Scheme 7. a) Cu^I-thiophene-2-carboxylate, *N*-methylpyrrolidinone, −10 °C; b) LiOH, THF/MeOH/H_2O, 40 °C; c) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, 25 °C, then DMAP, toluene, 80 °C; d) HF·pyridine, THF, 0 → 25 °C.

showed that the conjugated triene system is light-sensitive and can isomerize to a mixture of side products. For this reason, the introduction of the C2/C3 double bond was postponed to a later stage and the synthesis of the C10/C11 alkenyl iodide was addressed next. The primary TES ether in **36** could be cleaved chemoselectively with camphorsulfonic acid at 0 °C. The resulting alcohol **37** was Dess–Martin oxidized to the corresponding aldehyde, which could be converted into (*E*)-alkenyl iodide **38** following Takai's procedure.[28] Attempts to prepare an alkenyl stannane from **36** via Corey–Fuchs reaction[29] of the aldehyde and Pd-mediated hydrostannylation[30] of the resulting alkyne led to a 4:1 mixture of regioisomeric alkenyl stannanes. This lack of regioselectivity led us to reject the alkenyl stannane option for the northern half. The final step for the northern half introduced the C2/C3 double bond by another ester/aldehyde/Wittig sequence (**38** → **39**). This reaction and all following steps were performed in amber colored glassware with exclusion of bright daylight to prevent the triene photoisomerization. The photosensitivity was observed only for the acyclic intermediates **39**, **40**, and **41** but not for the ring-closed macrolides.

The final part of the synthesis focused on the coupling of the southern and the northern half as well as on the macrolactonization (Scheme 7). Several attempts for a Pd^0-mediated Stille coupling[31] between **31** and **39** were disappointing (yield < 30% at prolonged reaction times and 60 °C). In contrast, the use of 2 equiv of Cu^I-thiophene carboxylate[32] gave an 81% yield of the desired coupling product **40** under very mild conditions (−10 °C, 1 h). It is instructive to compare this cross-coupling step with the related reaction from Nicolaou's synthesis.[7] In Nicolaou's case the Pd coupling worked fine for the combination monosubstituted alkenylstannane/disubstituted alkenyl iodide. In our case a Cu^I coupling was required for the combination monosubstituted alkenyl iodide/disubstituted alkenylstannane.

The following hydrolysis of the ethyl ester and the two acetates in **40** with LiOH in THF/MeOH/H_2O required longer reaction times (28 h) and elevated temperatures (40 °C). Trihydroxy acid **41** was obtained in 87% yield. The macrolactonization of **41** according to the modified Yamaguchi procedure[33] produced 20-membered macrolide **42** in 74% yield. The ring-size selectivity of this step is remarkable. No 21-membered lactone could be identified. Treatment of **42** with HF·pyridine cleaved all silyl ethers and converted the C21 methyl ketal into the hemiketal. The target compound apoptolidinone A (**4**) was obtained in 55% yield.

The aglycone alone exhibited no antitumor activity (IC_{50} > 10 μM) against several cancer cell lines (A431, MeTu, Hecat).

This showed the necessity of the sugar residues for the bioactivity and motivated us to complete the total synthesis of apoptolidin A (**1**) itself. The results of these efforts are described in the following manuscript.[13]

Conclusion

The synthesis of apoptolidinone A (**4**) described here provides an efficient synthetic access to this molecular framework. It forms the basis for the attachment of the sugar residues at C9 and C27 and the total synthesis of apoptolidin A (**1**). Although the present route is efficient, it leads to a methyl ketal at C21. The conversion of this methyl ketal into the hemiketal in the presence of the acid labile O27 disaccharide will be a challenge for the total synthesis of the natural product itself.

Experimental Section

General methods: All reactions sensitive to air or moisture were conducted in flame-dried glassware under an atmosphere of dry Argon. THF and Et_2O were distilled from sodium/benzophenone. CH_2Cl_2, toluene, hexanes, pyridine, and Et_3N were distilled from CaH_2. All starting materials and reagents were used as received unless noted otherwise. Thin layer chromatography was performed on glass-supported Merck silica gel 60 F_{254} plates. Spots were visualized by UV light and by heat staining with 2% molybdophosphoric acid in ethanol. Column chromatography was performed on Merck silica gel 60 (63–200 μm). Melting points were measured with a Büchi Melting Point Apparatus and are not corrected. IR Spectra were measured with a Bruker FT-IR spectrometer. ^1H and ^{13}C NMR spectra were recorded with Bruker spectrometers ARX-200, AC-300, AV-300, AMX-400, DRX-400, DRX-500, DRX-600. $CDCl_3$ was used as normal solvent. TMS was used as internal standard. Optical rotations: Perkin–Elmer polarimeter 241, cuvette path length 10 cm; $CHCl_3$ for spectroscopy was filtered over basic aluminium oxide before use. Microanalysis: CHN rapid, Heraeus. HRMS: Finnigan LTQ FT (ESI). MTBE = *tert*-butyl methyl ether; PE = petrol ether (b.p. range 40–60 °C.

(3*R*)-3-Hydroxy-4-methoxybutyric acid methylester (8): $[RuCl_2(C_6H_6)]_2$ (126 mg, 0.25 mmol) and (*S*)-BINAP (255 mg, 0.41 mmol) were dissolved in DMF (5 mL) and stirred for 15 min at 115 °C. After cooling the catalyst solution was transferred into an autoclave. Freshly distilled 4-methoxyacetoacetic acid methylester (**7**) (9.97 g, 68.2 mmol) was dissolved in MeOH (30 mL), degassed and then transferred into the high pressure reaction vessel. The autoclave was filled with hydrogen (6 bar) and the solution was vigorously stirred for 42 h at 90 °C. After cooling the solvents were removed and the residue was purified by flash chromatography (450 silica gel, pentane/MTBE 1:2) to yield alcohol **8** (9.5 g, 64 mmol, 94%) as a light yellow oil. $R_f = 0.39$ (MTBE); HPLC: $t_R =$ 15.2 min (Chiracel-OD-H, 6% *i*PrOH in *n*-hexane, 1 mL min^{-1}, 23 °C); $[\alpha]_D^{23} = +25.4$ ($c = 1.00$, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): $\delta = 2.51$ (d, $J = 6.3$ Hz, 2H, 2-H_2), 2.93 (d, $J = 4.3$ Hz, 1H, OH), 3.29–3.47 (m, 2H, 4-H_2), 3.37 (s, 3H, OCH_3), 3.69 (s, 3H, CO_2CH_3), 4.11–4.27 (m, 1H, 3-H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 37.7$ (C-2), 51.0 (CO_2CH_3), 58.3 (OCH_3), 66.2 (C-3), 75.3 (C-4), 171.7 (C-1); IR (film): $\tilde{\nu} = 3446$ (br s), 2926 (s), 1736 (s), 1439 (s), 1004 (m), 967 cm^{-1} (m); elemental analysis calcd (%) for $C_6H_{12}O_4$ (148.16): C 48.64, H 8.16; found C 48.37, H 8.12.

(3*R*)-3-*tert*-Butyldimethylsilyloxy-4-methoxybutanal (9): *TBS protection:* Alcohol **8** (8.15 g, 55.0 mmol) was dissolved in DMF (80 mL) and cooled to 0 °C. Imidazole (8.60 g, 127 mmol) and TBSCl (21.6 g, 71.5 mmol, 50% in toluene) were added. The cooling bath was removed and the mixture was stirred 14 h at 2 °C. The mixture was added to MTBE (150 mL) and satd aq NH_4Cl (150 mL). The aqueous layer was extracted with MTBE (3 × 100 mL). The combined organic layers were washed with brine (150 mL), dried with Na_2SO_4, concentrated and the residue was purified by flash chromatography (400 g silica gel, pentane/MTBE 20:1 → 5:1) to yield corresponding silyl ether (13.4 g, 50.9 mmol, 93%) as a colorless oil. $R_f = 0.54$ (*n*-hexane/MTBE 5:1); $[\alpha]_D^{23} = +24.0$ ($c = 1.03$, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): $\delta = 0.03$, 0.05 (2s, 6H, $SiCH_3$), 0.83 (s, 9H, SiC-$(CH_3)_3$), 2.40 (dd, $J = 14.8$, 4.8 Hz, 1H, 2-H), 2.56 (dd, $J = 14.8$, 7.8 Hz, 1H, 2-H), 3.32 (s, 3H, OCH_3), 3.25 (dd, $J = 9.6$, 5.3 Hz, 1H, 4-H), 3.48 (dd, $J = 9.8$, 6.9 Hz, 1H, 4-H), 3.64 (s, 3H, CO_2CH_3), 4.17–4.29 (m, 1H, 3-H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = -5.3$, −4.7 (Si-CH_3), 17.9 (Si*C*-$(CH_3)_3$), 25.6 (SiC(CH_3)$_3$), 40.0 (C-2), 51.3 (CO_2CH_3), 58.9 (OCH_3), 68.4 (C-3), 76.5 (C-4), 171.8 (C-1); IR (film): $\tilde{\nu} = 2955$ (s), 2930 (s), 2858 (s), 1744 (s), 1463 (m), 1438 (m), 1254 (m), 1129 (m), 838 (m), 779 cm^{-1} (m); elemental analysis calcd (%) for $C_{12}H_{26}O_4Si$ (262.42): C 54.92, H 9.99; found C 54.66, H 9.86.

DIBAH reduction: The TBS-protected ester (9.90 g, 37.7 mmol) was dissolved in CH_2Cl_2 (250 mL) and cooled to −78 °C. DIBAH (45 mL, 45 mmol, 1.0 M in PE) was added via dropping funnel within 2 h, so that the internal temperature was lower than −74 °C. After complete addition the mixture was stirred for 1 h at −78 °C and the reaction was quenched by addition of MeOH (20 mL). The reaction mixture was added to a solution of Rochelles salt (1.0 M, 700 mL). After 3 h stirring the two layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried with $MgSO_4$, concentrated and the residue was purified by flash chromatography (260 g silica gel, pentane/MTBE 10:1) to yield aldehyde **9** (8.02 g, 34.5 mmol, 92%) as a colorless oil. $R_f = 0.40$ (*n*-hexane/MTBE 5:1); $[\alpha]_D^{23} = +9.7$ ($c = 1.10$, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): $\delta = 0.06$, 0.07 (2s, 6H, $SiCH_3$), 0.85 (s, 9H, SiC(CH_3)$_3$), 2.45–2.68 (m, 2H, 2-H_2), 3.28 (dd, $J = 10.0$, 6.3 Hz, 1H, 4-H), 3.33 (s, 3H, OCH_3), 3.39 (dd, $J = 9.5$, 5.3 Hz, 1H, 4-H), 4.23–4.37 (m, 1H, 3-H), 9.78 (t, $J = 2.4$ Hz, 1H, 1-H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = -5.3$, −4.8 ($SiCH_3$), 17.7 (Si*C*(CH_3)$_3$), 25.5 (SiC(*C*H_3)$_3$), 48.5 (C-2), 58.7 (OCH_3), 66.9 (C-3), 76.3 (C-4), 200.6 (C-1); IR (film): $\tilde{\nu} =$ 2930 (s), 2858 (s), 1733 (s), 1464 (s), 1362 (m), 1254 (s), 1122 (s), 1006 (m), 838 (s), 778 cm^{-1} (s).

(4*R*,2′*R*,4′*S*,5′*R*,7′*R*)-4-Benzyl-3-(7′-*tert*-butyldimethylsilyloxy-5′-hydroxy-8′-methoxy-2′,4′-dimethyl-1′,3′-dioxooctyl)-1,3-oxazolidin-2-one (11): Sn-$(OTf)_2$ (9.30 g, 22.3 mmol) was washed three times with dry Et_2O and the white solid was dried under high vacuum (30 min). The purified $Sn(OTf)_2$ was suspended in CH_2Cl_2 (60 mL) and cooled to −20 °C. NEt_3 (3.1 mL, 22 mmol) was added and the solution was stirred for 5 min at 20 °C. Oxazolidinone **10** (5.38 g, 18.6 mmol) in CH_2Cl_2 (23 mL) was added via dropping funnel to the yellow colored solution. After stirring for 45 min at −20 °C the mixture was cooled to −78 °C and aldehyde **9** (4.32 g, 18.6 mmol) in CH_2Cl_2 (23 mL) was added slowly (internal temperature < −75 °C). The mixture was stirred for 1 h at −78 °C and then added to 800 mL of an ice cooled 1:1 mixture of CH_2Cl_2 and aq $NaHSO_4$ (1 M). After 20 min stirring at 20 °C the two layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with satd aq $NaHCO_3$ (500 mL), dried with $MgSO_4$, concentrated and the residue was purified by flash chromatography (260 g silica gel, pentane/MTBE 3:2) to yield alcohol **11** (8.86 g, 17.0 mmol, 91%) as a colorless oil. $R_f = 0.50$ (*n*-hexane/MTBE 3:2); HPLC: $t_R = 15.9$ min (Superspher-Si60, 3% *i*PrOH in *n*-hexane, 1.0 mL min^{-1}, 39 °C); $[\alpha]_D^{23} = -29.5$ ($c = 1.10$, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.08$ (2s, 6H, $SiCH_3$), 0.88 (s, 9H, SiC(CH_3)$_3$), 1.21 (d, $J =$ 7.1 Hz, 3H, 4′-CH_3), 1.47 (d, $J = 7.3$ Hz, 3H, 2′-CH_3), 1.41–1.72 (m, 2H, 6′-H_2), 2.77 (dd, $J = 13.2$, 9.8 Hz, 1H, CHPh), 2.79–2.91 (m, 1H, 4′-H), 3.25–3.43 (m, 3H, CHPh, 8-H_2), 3.34 (s, 3H, OCH_3), 3.99–4.21 (m, 2H, 5′-H, 7′-H), 4.18 (dd, $J = 9.2$, 2.8 Hz, 1H, 5-H), 4.25 (dd, $J = 8.4$, 8.2 Hz, 1H, 5-H), 4.68–4.80 (m, 1H, 4-H), 4.89 (q, $J = 7.2$ Hz, 1H, 2′-H), 7.14–7.39 (m, 5H, Ph); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = -5.1$, −4.6 ($SiCH_3$), 11.3 (2′-CH_3), 12.8 (4′-CH_3), 18.0 (Si*C*(CH_3)$_3$), 25.8 (SiC(*C*H_3)$_3$), 37.8 (C-6′), 38.0 (*C*H_2Ph), 49.6 (C-4′), 52.1 (C-2′), 55.2 (C-4), 58.9 (OCH_3), 66.3 (C-5), 68.5 (C-5′), 69.4 (C-7′), 76.6 (C-8′), 127.3, 128.9, 129.3, 135.0 (Ph), 153.3 (C-2), 170.6 (C-1′), 210.9 (C-3′); IR (film): $\tilde{\nu} = 3534$ (br s), 2929 (s), 2857 (s), 1782 (s), 1715 (s), 1488 (s), 1361 (s), 1249 (s), 1124 (s), 1005 (s),

838 (s), 778 cm^{-1} (s); elemental analysis calcd (%) for $C_{27}H_{43}NO_7Si$ (521.72): C 62.16, H 8.31, N 2.68; found C 62.39, H 8.08, N 2.52.

(4*R*,2′*R*,3′*S*,4′*S*,5′*R*,7′*R*)-4-Benzyl-3-(7′-*tert*-butyldimethylsilyloxy-3′,5′-dihydroxy-8′-methoxy-2′,4′-dimethyl-1′-oxooctyl)-1,3-oxazolidin-2-one (12): $NaBH_4$ (7.98 g, 211 mmol) was added in portions at 10 °C within 45 min to glacial acetic acid (350 mL). The mixture was stirred for 1 h at 10 °C and ketone **11** (11.0 g, 21.1 mmol) in glacial acetic acid (70 mL) was added within 20 min. The reaction was warmed to 20 °C and stirred for 30 min. The solvent was removed and satd aq $NaHCO_3$ (600 mL) and CH_2Cl_2 (200 mL) were added carefully. After separation of the two layers the aqueous layer was extracted with CH_2Cl_2 (2×100 mL). The combined organic layers were dried with $MgSO_4$ and the solvent was removed in vacuo. The residue was taken up in MeOH (200 mL) and AcOH (5 mL) and the solvents were evaporated. The residue was azeotroped with MeOH (2×200 mL), toluene (2×100 mL) and the product was dried under high vacuum for 14 h to give diol **12** (10.9 g, 20.8 mmol, 98 %) as a colorless, viscous oil. R_f = 0.44 (*n*-hexane/MTBE 1:3); $[\alpha]_D^{21}$ = −7.9 (*c* = 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.07, 0.08 (2 s, 6 H, $SiCH_3$), 0.82–0.90 (m, 12 H, $SiC(CH_3)_3$, 4′-CH_3), 1.25 (d, *J* = 6.8 Hz, 3 H, 2′-CH_3), 1.51–1.63 (m, 1 H, 6′-H), 1.72–1.91 (m, 2 H, 6′-H, 4′-H), 2.75 (dd, *J* = 13.3, 9.6 Hz, 1 H, CHPh), 3.27 (dd, *J* = 13.4, 3.2 Hz, 1 H, CHPh), 3.33 (s, 3 H, OCH_3), 3.27–3.43 (m, 2 H, 8′-H_2), 3.83–4.25 (m, 6 H, 2′-H, 3′-H, 5′-H, 7′-H, 5-H_2), 4.62–4.73 (m, 1 H, 4-H), 7.12–7.37 (m, 5 H, Ph); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = −5.1, −4.6 ($SiCH_3$), 9.76 (2′-CH_3), 12.0 (4′-CH_3), 18.0 ($SiC(CH_3)_3$), 25.8 ($SiC(CH_3)_3$), 36.4 (C-6′), 37.7 (CH_2Ph), 39.4 (C-4′), 40.1 (C-2′), 55.3 (C-4), 59.0 (OCH_3), 66.1 (C-5), 69.9 (C-5′), 71.0 (C-7′), 73.7 (C-3′), 76.3 (C-8′), 127.4, 128.9, 129.4, 135.2 (Ph), 153.0 (C-2), 177.1 (C-1′); IR (film): $\tilde{\nu}$ = 3483 (br s), 2929 (s), 2858 (s), 1782 (s), 1697 (s), 1458 (s), 1389 (s), 1211 (s), 1112 (s), 910 (s), 734 cm^{-1} (s); elemental analysis calcd (%) for $C_{27}H_{45}NO_7Si$ (523.73): C 61.92, H 8.66, N 2.67; found C 61.69, H 8.26, N 2.42.

(2*R*,3*S*,4*S*,5*R*,7*R*)-7-*tert*-Butyldimethylsilyloxy-*N*,8-dimethoxy-*N*,2,4-trimethyl-3,5-di(trimethylsilyloxy)octamide (13): *Transamidation:* (MeO)-MeNH·HCl (14.3 g, 147 mmol) was dissolved in CH_2Cl_2 (220 mL) and cooled to −10 °C. $AlMe_3$ (74 mL, 147 mmol, 2 M in hexane) was added and the mixture was stirred at 20 °C for 1 h. The mixture was cooled to −10 °C and oxazolidinone **12** (10.9 g, 20.8 mmol) in CH_2Cl_2 (220 mL) was slowly added. After stirring for 4 h at −10 °C the mixture was added via cannula to a solution of Rochelles salt (1.5 L, 1.0 M) at 0 °C. After 12 h stirring the two layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3×140 mL). The combined organic layers were washed with brine (200 mL), dried with $MgSO_4$, concentrated and the residue was purified by flash chromatography (300 g silica gel, pentane/MTBE 1:1→2:3) to yield the corresponding amide (6.90 g, 16.9 mmol, 81 %) as a colorless oil. R_f = 0.29 (*n*-hexane/MTBE 1:4); $[\alpha]_D^{20}$ = +20.1 (*c* = 1.10, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.07, 0.08 (2 s, 6 H, $SiCH_3$), 0.82 (d, *J* = 6.8 Hz, 3 H, 4-CH_3), 0.87 (s, 9 H, $SiC(CH_3)_3$), 1.16 (d, *J* = 6.8 Hz, 3 H, 2-CH_3), 1.41–1.53 (m, 1 H, 6-H), 1.68–1.86 (m, 2 H, 6-H, 4-H), 2.95–3.07 (m, 1 H, 2-H), 3.17 (s, 3 H, N-CH_3), 3.33 (s, 3 H, OCH_3), 3.28–3.40 (m, 2 H, 8-H_2), 3.68 (s, 3 H, $NOCH_3$), 3.71 (br s, 1 H, OH), 3.79–3.87 (m, 1 H, 3-H), 3.98–4.15 (m, 2 H, 7-H, 5-H), 4.37 (s, 1 H, OH); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = −5.0, −4.5 ($SiCH_3$), 10.1 (2-CH_3), 12.0 (4-CH_3), 18.1 ($SiC(CH_3)_3$), 25.9 ($SiC(CH_3)_3$), 32.3 (br, *N*-CH_3), 40.1 (C-2), 40.5 (C-6), 41.8 (C-4), 58.9 (OCH_3), 60.8 (*N*-OCH_3), 69.5 (C-7), 69.8 (C-5), 74.9 (C-3), 76.8 (C-8), 176.7 (C-1); IR (film): $\tilde{\nu}$ = 3450 (br m), 2929 (s), 2856 (m), 1637 (s), 1462 (m), 1405 (s), 1107 (s), 987 (s), 837 (s), 777 cm^{-1} (s); HR-MS (EI): *m*/*z*: calcd for $C_{19}H_{41}NO_6SiH$: 408.2781; found 408.2784 $[M+H]^+$.

TMS protection: The diol (4.40 g, 10.8 mmol) was dissolved in CH_2Cl_2 (170 mL) and cooled to 0 °C. Imidazole (5.9 mg, 86 mmol) and TMSCl (8.2 mL, 65 mmol) were added. After 2 h stirring at 0 °C the mixture was quenched with phosphate buffer (120 mL, 1 M, pH 7). The aqueous layer was extracted with MTBE (3×100 mL). The combined organic layers were washed with brine (120 mL), dried with $MgSO_4$, concentrated and the residue was purified by flash chromatography (260 g silica gel, pentane/MTBE 3:2) to yield (bis)silyl ether **13** (5.1 g, 9.2 mmol, 86 %) as a colorless oil. R_f = 0.67 (*n*-hexane/MTBE 2:3); $[\alpha]_D^{23}$ = −18.6 (*c* = 1.00, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.04, 0.05, 0.08, 0.09 (4 s, 24 H, $Si(CH_3)_3$, $SiCH_3$), 0.83 (d, *J* = 7.0 Hz, 3 H, 4-CH_3), 0.86 (s, 9 H, $SiC(CH_3)_3$), 1.03 (d, *J* = 7.0 Hz, 3 H, 2-CH_3), 1.45–1.47 (m, 1 H, 6-H), 1.62–1.84 (m, 2 H, 6-H, 4-H), 2.91–3.08 (m, 1 H, 2-H), 3.15 (s, 3 H, N-CH_3), 3.21–3.37 (m, 2 H, 8-H_2), 3.32 (s, 3 H, OCH_3), 3.61–3.75 (m, 1 H, 7-H), 3.66 (s, 3 H, $NOCH_3$), 3.89–3.97 (m, 1 H, 5-H), 4.01 (dd, *J* = 7.5, 3.5 Hz, 1 H, 3-H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = −4.6, −4.3 ($SiCH_3$, TBS), 0.8, 1.2 ($SiCH_3$, TMS), 10.5, 10.6 (2-CH_3, 4-CH_3), 18.2 ($SiC(CH_3)_3$), 25.9 ($SiC(CH_3)_3$), 32.3 (*N*-CH_3), 38.8 (C-2), 40.5 (C-6), 41.7 (C-4), 58.9 (OCH_3), 60.8 (*N*-OCH_3), 69.5 (C-7), 69.8 (C-5), 74.9 (C-3), 79.8 (C-8), 176.7 (C-1); IR (film): $\tilde{\nu}$ = 2956 (s), 2897 (m), 1673 (s), 1462 (m), 1383 (m), 1251 (s), 1116 (s), 839 (s), 777(m), 752 cm^{-1} (m); HR-MS (EI): *m*/*z*: calcd for $C_{24}H_{54}NO_6Si_3$: 536.3259; found 536.3258 $[M-CH_3]^+$.

(*E*,5*R*,6*S*,7*S*,8*R*,10*R*)-10-*tert*-Butyldimethylsilyloxy-8-methoxy-5,7-dimethyl-6,8-di(trimethylsilyloxy)-undec-2-en-4-one (14): (*E*)-1-Bromo-1-propene (29 μL, 0.34 mmol) was added to *t*BuLi (0.42 mL, 1.48 M in pentane, 0.62 mmol) in Et_2O (25 mL) at −78 °C. The solution was stirred for 10 min at −78 °C and then for 10 min at −40 °C. After recooling to −78 °C, amide **13** (156 mg, 0.283 mmol) dissolved in Et_2O (2.5 mL) was added dropwise. The reaction mixture was stirred for 4 h at −78 °C, when satd aq $NaHSO_4$ (10 mL) and Et_2O (10 mL) were added. The aqueous layer was extracted with Et_2O (3×10 mL). The combined organic layers were washed with brine (2×5 mL) and dried with $MgSO_4$. Purification by flash chromatography (4 g silica gel, pentane/MTBE 3:2) gave alkenyl ketone **14** (131 mg, 0.246 mmol, 87 %) as a colorless oil. R_f = 0.67 (*n*-hexane/MTBE 5:1); $[\alpha]_D^{23}$ = −38.1 (*c* = 1.34, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.02, 0.04, 0.05, 0.08 (4 s, 24 H, Si-CH_3), 0.84 (d, *J* = 7.3 Hz, 3 H, 7-CH_3), 0.86 (s, 9 H, Si-$C(CH_3)_3$), 1.01 (d, *J* = 6.8 Hz, 3 H, 5-CH_3), 1.49–1.82 (m, 3 H, 7-H, 9-H_2), 1.86 (dd, *J* = 6.9, 1.6 Hz, 3 H, 1-H_3), 2.87 (dq, *J* = 6.8, 3.4 Hz, 1 H, 5-H), 3.23–3.33 (m, 2 H, 11-H_2), 3.31 (s, 3 H, 11-OCH_3), 3.64–3.72 (m, 1 H, 10-H), 3.93 (ddd, *J* = 8.1, 5.9, 2.1 Hz, 1 H, 8-H), 4.07 (dd, *J* = 7.3, 3.3 Hz, 1 H, 6-H), 6.18 (dq, *J* = 15.6, 1.6 Hz, 1 H, 3-H), 6.82 (dq, *J* = 15.6, 6.9 Hz, 1 H, 2-H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = −4.6, −4.3 (Si-CH_3,TBS), 0.9, 1.1 (Si-CH_3, TMS), 9.9, 10.9 (5-CH_3, 7-CH_3), 18.1 (C-1), 18.2 (Si-$C(CH_3)_3$), 25.9 (Si-$C(CH_3)_3$), 40.5 (C-9), 42.0 (C-7), 47.5 (C-5), 58.9 (11-OCH_3), 69.5 (C-10), 70.0 (C-8), 74.6 (C-6), 76.8 (C-11), 130.7 (C-3), 142.0 (C-2), 201.8 (C-4); IR (film): $\tilde{\nu}$ = 2956 (s), 2929 (s), 2857 (m), 1699 (m), 1675 (m), 1633 (m), 1463 (m), 1251 (s), 1116 (s), 839 (s), 776 (m), 751 cm^{-1} (m); HR-MS (EI): *m*/*z*: calcd for $C_{26}H_{56}O_5Si_3$: 517.3201; found 517.3201 $[M-CH_3]^+$.

(*E*,2*R*,3*R*,4*S*,5*R*,6*R*,2′*R*)-6-[2′-*tert*-Butyldimethylsilyloxy-3′-methoxypropyl]-4-hydroxy-2-methoxy-3,5-dimethyl-2-[1″-propenyl]-2,3,5,6-tetrahydro-4*H*-pyran (15): Enone **14** (75 mg, 0.14 mmol) was dissolved in CH_2Cl_2 (0.6 mL) and MeOH (0.5 mL) at 0 °C. PPTS (3.5 mg, 0.014 mmol) was added and the reaction mixture was stirred for 1.5 h at 0 °C. Satd aq $NaHCO_3$ (3 mL) and CH_2Cl_2 (3 mL) were added. The aqueous layer was extracted with CH_2Cl_2 (3×3 mL). The combined organic layers were washed with brine (10 mL) and dried with $MgSO_4$. Purification by flash chromatography (3 g silica gel, PE/MTBE 5:1) gave methyl ketal **15** (51 mg, 0.13 mmol, 93 %) as a colorless oil. R_f = 0.19 (*n*-hexane/MTBE 5:1); $[\alpha]_D^{23}$ = +41.8 (*c* = 0.98, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.03, 0.04 (2 s, 6 H, Si-CH_3), 0.85 (s, 9 H, Si-$C(CH_3)_3$), 0.86 (d, *J* = 6.6 Hz, 3 H, 5-CH_3), 0.98 (d, *J* = 6.8 Hz, 3 H, 3-CH_3), 1.43–1.58 (m, 2 H, 1′-H_2, 3-H), 1.69 (dd, *J* = 1.70, 6.6 Hz, 3 H, 3″-H), 1.71–1.84 (m, 2 H, 1′-H_2, 5-H), 3.06 (s, 3 H, 2-OCH_3), 3.22–3.38 (m, 2 H, 3′-H_2), 3.30 (s, 3 H, 3′-OCH_3), 3.75–3.96 (m, 3 H, 2′-H, 6-H, 4-H), 5.38 (dq, *J* = 15.5, 1.6 Hz, 1 H, 1″-H), 5.80 (dq, 1 H, *J* = 15.6, 6.6 Hz, 2″-H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = −4.7, −3.9 (Si-CH_3), 4.9 (5-CH_3), 11.2 (3-CH_3), 17.6 (C-3″), 18.2 (Si-$C(CH_3)_3$), 25.9 (Si-$C(CH_3)_3$), 38.5 (C-1′), 39.0 (C-5), 40.7 (C-3), 48.8 (2-OCH_3), 58.8 (3′-OCH_3), 67.9 (C-6), 70.0 (C-2′), 72.8 (C-4), 77.8 (C-3′), 101.0 (C-2), 128.3 (C-2″), 130.0 (C-1″); IR (film): $\tilde{\nu}$ = 3449 (br), 2929 (s), 2888 (s), 2857 (s), 1460 (s), 1386 (m), 1251 (m), 1110 (s), 1062 (s), 974 (m), 835 (m), 776 cm^{-1} (s); HR-MS (EI): *m*/*z*: calcd for $C_{21}H_{42}O_6Si$: 317.2617; found 371.2616 $[M-OCH_3]^+$.

(2*S*,3*R*,5*R*,6*S*,7*S*,8*R*,10*R*)-10-*tert*-Butyldimethylsilyloxy-2,3-dihydroxy-11-methoxy-5,7-dimethyl-6,8-di(trimethylsilyloxy)-undecan-4-one (16a) and (2*R*,3*S*,5*R*,6*S*,7*S*,8*R*,10*R*)-10-*tert*-butyldimethylsilyloxy-2,3-dihydroxy-11-methoxy-5,7-dimethyl-6,8-di(trimethylsilyloxy)-undecan-4-one (16b): AD-mix α (89 mg) was dissolved in *t*BuOH (0.2 mL) and H_2O (0.5 mL)

at 0 °C. After addition of enone **14** (34 mg, 0.064 mmol) dissolved in *t*BuOH (0.3 mL) the reaction mixture was stirred for 14 h at 0–7 °C. Na_2SO_3 (80 mg, 0.64 mmol), H_2O (3 mL) and CH_2Cl_2 (4 mL) were added. After stirring for 10 min the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3×5 mL). The combined organic layers were washed subsequently with NaOH (1 M, 10 mL) and brine (10 mL) and dried with $MgSO_4$. Purification by flash chromatography (1 g silica gel, *n*-hexane/AcOEt 3:1) gave a 3:1 mixture of diols **16a** and **16b** (26 mg, 0.046 mmol, 72 %) as a colorless oil. R_f = 0.50 (*n*-hexane/MTBE 1:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.04, 0.06, 0.07, 0.10 (4 s, Si-CH_3), 0.78–0.88 (m, 7-CH_3, Si-C(CH_3)$_3$), 1.06 (d, J = 6.8 Hz, 6 H, 5-CH_3), 1.12 (d, J = 7.2 Hz, 3 H, 5-CH_3), 1.31 (d, J = 6.4 Hz, 9 H, 1-H_3), 1.47–1.57 (m, 3 H, 7-H), 1.60–1.89 (m, 6 H, 9-H_2), 2.97 (dq, J = 7.2, 2.6 Hz, 1 H, 5-H), 3.06 (dq, J = 6.7, 2.4 Hz, 2 H, 5-H), 3.23–3.34 (m, 15 H, 11-H_2, 11-OCH_3), 3.64–3.74 (m, 3 H, 10-H), 3.81 (d, J = 4.9 Hz, 2 H, 2-OH), 3.84 (d, J = 5.1 Hz, 1 H, 2-OH), 3.93–4.01 (m, 6 H, 6-H, 8-H), 4.07–4.27 (m, 9 H, 3-H, 2-H, 3-OH); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = −4.6, −4.5, −4.3, −4.2 (Si-CH_3, TBS), 0.77, 0.82, 1.2, 1.3 (Si-CH_3, TMS), 8.8, 10.3, 10.8, 10.9 (5-CH_3, 7-CH_3), 18.21, 18.22 (Si-*C*(CH_3)$_3$), 20.4, 20.5 (C-1), 25.9 (Si-C(*C*H_3)$_3$), 40.3, 40.6 (C-9), 41.9, 42.2 (C-7), 44.6, 45.6 (C-5), 58.95, 58.98 (11-OCH_3), 67.8, 68.5 (C-2), 69.3, 69.5 (C-6), 69.7, 69.8 (C-8), 72.4, 74.7 (C-6), 76.8, 76.9 (C-11), 78.1, 78.3 (C-3), 212.1, 213.1 (C-4); IR (film): $\tilde{\nu}$ = 3456 (br), 2956 (s), 2930 (s), 2858 (m), 1711 (m), 1463 (m), 1385 (m), 1252 (s), 1116 (s), 1029 (m), 838 (s), 776 (m), 751 cm^{-1} (m); HR-MS (EI): m/z: calcd for $C_{25}H_{55}O_7Si_3$: calcd 551.3256; found 551.3264 $[M-CH_3]^+$.

Dihydroxylation of enone **14** (30 mg, 0.056 mmol) with AD-mix β (78 mg) afforded a 1:8 mixture of diols **16a** and **16b** (25 mg, 0.044 mmol, 78 %).

(2*R*,3*R*,4*S*,5*R*,6*R*,2′*R*,1″*R*,2″*S*)-6-[2′-*tert*-Butyldimethylsilyloxy-3′-methoxypropyl]-2-[1″,2″-dihydroxypropyl]-4-hydroxy-2-methoxy-3,5-dimethyl-2,3,5,6-tetrahydro-4*H*-pyran (17a) from ketone 16a: A mixture of dihydroxyketones **16a**/**16b** (89 mg, 0.16 mmol) was dissolved in MeOH (0.5 mL) and CH_2Cl_2 (0.5 mL) at 0 °C. PPTS (4 mg, 0.02 mmol) was added and the reaction mixture was stirred for 1 h. Satd aq $NaHCO_3$ (3 mL) was added. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3×5 mL). The combined organic layers were washed with brine (10 mL) and dried with $MgSO_4$. Purification by flash chromatography (5 g silica gel, PE/MTBE 1:2) gave dihydroxy methylketal **17a** (7 mg, 0.02 mmol, 12 %) as a colorless oil and diastereomeric methyl ketal **17b** (45 mg, 77 %) which contained inseparable quantities of its hemiketal. R_f = 0.13 (**17a**) and 0.31 (**17b**) (*n*-hexane/MTBE 1:3). **17a**: $[\alpha]_D^{23}$ = +40 (c = 0.06, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.03, 0.04 (2 s, 6 H, Si-CH_3), 0.84–0.88 (m, 12 H, 5-CH_3, Si-C(CH_3)$_3$), 1.06 (d, J = 6.6 Hz, 3 H, 3-CH_3), 1.25 (d, J = 6.6 Hz, 3 H, 3″-H_3), 1.50 (ddd, J = 14.4, 7.4, 3.9 Hz, 1 H, 1′-H_2), 1.73 (ddd, J = 14.4, 8.2, 4.2 Hz, 1 H, 1′-H_2), 1.79–1.86 (m, 1 H, 5-H), 2.08 (dq, J = 10.9, 6.6 Hz, 1 H, 3-H), 3.26 (s, 3 H, 2-OCH_3), 3.25–3.32 (m, 2 H, 3′-H_2), 3.31 (s, 3 H, 3′-OCH_3), 3.41–3.44 (m, 1 H, 1″-H), 3.76 (dd, J = 10.9, 4.7 Hz, 1 H, 4-H), 3.85–3.92 (m, 2 H, 6-H, 2′-H), 4.05 (dq, J = 6.4, 2.4 Hz, 1 H, 2″-H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = −4.7, −3.9 (Si-CH_3), 5.0 (5-CH_3), 11.4 (3-CH_3), 18.2 (Si-*C*(CH_3)$_3$), 21.0 (C-3″), 25.9 (Si-C(*C*H_3)$_3$), 35.9 (C-3), 38.5 (C-1′), 38.6 (C-5), 48.7 (2-OCH_3), 58.9 (3′-OCH_3), 66.6 (C-2″), 69.4, 69.6 (C-6, C-2′), 72.6 (C-4), 75.3 (C-1″), 77.2 (C-3′), 102.6 (C-2); IR (film): $\tilde{\nu}$ = 3443 (br), 2929 (s), 2891 (s), 2857 (s), 1460 (m), 1388 (m), 1252 (m), 1112 (s), 1015 (s), 836 (s), 777 cm^{-1} (s); HR-MS (EI): m/z: calcd for $C_{18}H_{37}O_5Si$: 361.2410; found 361.2413 $[M-C_3H_7O_2]^+$. **17b** containing impurities of its hemiketal: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.040, 0.044, 0.05 (3 s, Si-CH_3), 0.79–0.88 (m, 5-CH_3, Si-C(CH_3)$_3$), 0.94, 0.96 (2d, J = 5.5, 5.5 Hz, 6 H, 3-CH_3), 1.17, 1.19 (2d, J = 6.2, 6.4 Hz, 6 H, 3″-H_3), 1.29–1.52 (m, 2 H, 1′-H_2), 1.64–1.86 (m, 6 H, 3-H, 5-H, 1′-H_2), 2.71, 2.85 (2 d, J = 9.8, 8.9 Hz, 2 H, 1″-OH), 3.14–3.33 (m, 6 H, 1″-H, 3′-H_2), 3.26, 3.28 (2 s, 6 H, 3′-OCH_3), 3.37 (s, 3 H, 2-OCH_3), 3.47–3.53 (m, 2 H, 2″-OH), 3.67–3.92 (m, 6 H, 4-H, 4-OH, 2′-H), 3.94–4.16 (m, 4 H, 6-H, 2″-H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = −4.8, −4.7, −4.2, −4.0 (Si-CH_3), 5.0, 5.1 (5-CH_3), 11.3, 11.7 (3-CH_3), 18.0, 18.1 (Si-*C*(CH_3)$_3$), 19.6, 20.0 (C-3″), 25.8, 25.9 (Si-C(*C*H_3)$_3$), 35.5, 36.5 (C-3), 38.4, 38.7 (C-1′), 38.9, 39.5 (C-5), 51.6 (2-OCH_3), 59.0, 59.1 (3′-OCH_3), 64.9, 66.8 (C-2″), 67.6, 68.9, 69.5, 69.6 (C-6, C-2′), 72.36, 72.40 (C-4), 73.9, 76.2 (C-1″), 77.1, 77.3 (C-3′), 100.5, 101.8 (C-2).

(2*R*,3*R*,4*S*,5*R*,6*R*,2′*R*,1″*R*,2″*S*)-6-(2′-*tert*-Butyldimethylsilyloxy-3′-methoxypropyl)-2-(1″,2″-dihydroxypropyl)-4-hydroxy-2-methoxy-3,5-dimethyl-2,3,5,6-tetrahydro-4*H*-pyran (17a) by dihydroxylation of alkene 15: $[K_2OsO_2(OH)_4]$ (1 mg, 3 μmol) and NMO (26 mg, 0.12 mmol) was added to alkene **15** (26 mg, 0.065 mmol) dissolved in THF/H_2O/*t*BuOH (4:1:4, 3 mL). The reaction mixture was stirred for 8 d at 20 °C. Na_2SO_3 (180 mg), H_2O (3 mL) and MTBE (3 mL) were added. The layers were separated and the aqueous layer was extracted with MTBE (3×3 mL). The combined organic layers were washed with brine (10 mL) and dried with $MgSO_4$. Purification by chromatography (2.5 g silica gel, PE/MTBE 1:2) gave a 2:1 mixture of diols **17a**/**17b** (20 mg, 0.046 mmol, 70 %). Both isomers could be separated by a second chromatography (5 g silica gel, PE/MTBE 1:2) to yield **17a** (13 mg, 0.030 mmol, 46 %) and **17b** (6 mg, 0.014 mmol, 21 %). The analytical data for **17a** were identical with the data for the product obtained from **16a**.

(2*R*,3*R*,4*S*,5*R*,6*R*,2′*R*,4″*R*,5″*S*)-6-(2′-*tert*-Butyldimethylsilyloxy-3′-methoxypropyl)-4-hydroxy-2-methoxy-3,5-dimethyl-2-(2″,2″,5″-trimethyl-1″,3″-dioxolan-4″-yl)-2,3,5,6-tetrahydro-4*H*-pyran (18): Triol **17a** (10 mg, 0.023 mmol) was dissolved in 2,2-dimethoxypropane (0.5 mL) at 0 °C. CSA (1 mg, 4 μmol) was added and the reaction mixture was stirred for 30 min. Et_3N (0.2 mL) in toluene (3 mL) was added. After removal of the solvents in vacuo the residue was purified by chromatography (6 g silica gel, PE/MTBE 5:1 → 1:1) to afford acetonide **18** (9 mg, 0.019 mmol, 84 %) as a crystalline solid. Recrystallization from MeOH/H_2O gave crystals suitable for X-ray structure analysis.[12a] M.p. 86 °C; R_f = 0.80 (*n*-hexane/MTBE 1:3); $[\alpha]_D^{23}$ = +64 (c = 0.22, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.04 (s, 6 H, Si-CH_3), 0.82 (d, J = 7.0 Hz, 3 H, 5-CH_3), 0.86 (s, 9 H, Si-C(CH_3)$_3$), 1.20 (d, J = 6.6 Hz, 3 H, 3-CH_3), 1.31 (d, J = 5.8 Hz, 3 H, 5″-CH_3), 1.37 (s, 3 H, 2″-CH_3), 1.41 (s, 3 H, 2″-CH_3), 1.45 (ddd, J = 14.2, 7.4, 3.5 Hz, 1 H, 1′-H_2), 1.68 (ddd, J = 14.3, 8.3, 4.3 Hz, 1 H, 1′-H_2), 1.74–1.86 (m, 2 H, 3-H, 5-H), 3.22–3.35 (m, 2 H, 3′-H_2), 3.27 (s, 3 H, 2-OCH_3), 3.31 (s, 3 H, 3′-OCH_3), 3.47 (s, 1 H, 4-OH), 3.77 (d, J = 8.3 Hz, 1 H, 4″-H), 3.79 (dd, J = 10.2, 5.1 Hz, 1 H, 4-H), 3.94–4.00 (m, 2 H, 2′-H, 6-H), 4.05 (dq, J = 8.3, 5.9 Hz, 1 H, 5″-H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = −4.7, −3.9 (Si-CH_3), 5.0 (5-CH_3), 11.6 (3-CH_3), 18.2 (Si-*C*(CH_3)$_3$), 19.1 (5″-CH_3), 25.9 (Si-C(*C*H_3)$_3$), 26.9, 27.0 (2″-CH_3), 36.0 (C-3), 38.3 (C-1′), 38.6 (C-5), 47.8 (2-OCH_3), 58.8 (3′-OCH_3), 68.2, 69.8 (C-2′, C-6), 73.3 (C-4), 73.8 (C-5″), 77.6 (C-3′), 81.9 (C-4″), 100.0 (C-2), 108.0 (C-2″); IR (film): $\tilde{\nu}$ = 3460 (br), 2931 (s), 2893 (s), 1463 (m), 1380 (m), 1249 (s), 1086 (s), 1017 (s), 933 (m), 836 (s), 777 (s), 734 cm^{-1} (m); HR-MS (EI): m/z: calcd for $C_{23}H_{45}O_7Si$: 461.2935; found 461.2933 $[M-CH_3]^+$.

(2*S*)-1-*O*-Benzyl-2-methoxypent-4-in-1-ol (20): *Epoxide opening:* *n*BuLi (52 mL, 2.5 M in hexane, 130 mmol) was added at −40 °C over 15 min to a solution of (trimethylsilyl)acetylene (18.0 mL, 130 mmol) in THF (200 mL). After 10 min, the solution was cooled to −78 °C and (*R*)-benzylglycidol in THF (100 mL) was added dropwise. Then, $BF_3{\cdot}OEt_2$ (9.7 mL, 78 mmol) in THF (50 mL) was added dropwise. After 2 h at −78 °C, Et_3N (11 mL, 78 mmol) was added and the reaction mixture was stirred for 30 min at −78 °C. Then, it was transferred via a Teflon cannula into satd aq $NaHCO_3$ (250 mL) cooled to 0 °C. MTBE (250 mL) was added and the layers were separated. The aqueous layer was extracted with MTBE (3×50 mL). The combined organic layers were subsequently washed with $NaHSO_4$ (1 M, 100 mL), satd aq $NaHCO_3$ (50 mL), brine (150 mL) and dried with $MgSO_4$. After removal of the solvents in vacuo, the corresponding alcohol was obtained. A 50 mg sample of the alcohol was purified by chromatography (5 g silica gel, pentane/MTBE 3:1) for analytical purposes: R_f = 0.19 (*n*-hexane/MTBE 3:1); $[\alpha]_D^{23}$ = +16.9 (c = 1.34, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.02 (s, 9 H, TMS), 2.28–2.38 (m, 2 H, 3-H_2), 2.40 (m, 1 H, OH), 3.35 (dd, J = 9.9, 6.3 Hz, 1 H, 1-H), 3.47 (dd, J = 9.9, 3.5 Hz, 1 H, 1-H), 3.73–3.90 (m, 1 H, 2-H), 4.43 (s, 2 H, O*C*H_2Ph), 7.24–7.32 (m, 5 H, Ph); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 0.0 ($SiMe_3$), 24.9 (C-3), 68.8 (C-2), 72.7 (C-1), 73.4 (O*C*H_2Ph), 87.2 (C-4), 102.5 (C-5), 127.7, 127.8, 128.4 (CH, Ph), 137.8 (C_q, Ph); IR (film): $\tilde{\nu}$ = 3428 (bm), 3058 (m), 2956 (m), 2904 (s), 2858 (w), 2178 (w), 1454 (m), 1248 (s), 1111 (s), 847 (s), 767 (s), 705 cm^{-1} (m); HR-MS (EI): m/z: calcd for $C_{15}H_{22}O_2Si$: 262.1389; found 262.1392 $[M]^+$.

Methylation and subsequent TMS deprotection: A solution of LHMDS in THF was prepared by addition of *n*BuLi (80 mL, 2.5 M in hexane,

200 mmol) to hexamethyldisilazane (40 mL, 200 mmol) in THF (200 mL) at −20 °C. The solution was stirred for 45 min after the addition. The LHMDS solution was transferred via a Teflon cannula to a solution of the alcohol (18 g, 65 mmol) and methyl iodide (28 mL, 460 mmol) in THF (150 mL) cooled to 0 °C. After 30 min, the reaction mixture was stirred for 16 h at 40 °C. For workup it was added to an ice-cold NH_4Cl/NH_3 4:1 buffer solution (300 mL). After stirring for 1 h, the organic solvents were evaporated in vacuo. The remaining aqueous layer was extracted with MTBE (3×150 mL). The combined organic layers were washed with brine (150 mL) and dried with $MgSO_4$. After removal of the solvent the remaining TMS-methyl ether was dissolved in THF (150 mL) at 0 °C. Tetrabutylammonium fluoride (21 g, 66 mmol) dissolved in THF (100 mL) was added and the reaction mixture was stirred for 90 min. Work up was started by addition of satd aq NH_4Cl (200 mL). The organic solvents were removed in vacuo. The remaining aqueous layer was extracted with MTBE (3×150 mL). The combined organic layers were washed with brine (150 mL) and dried with $MgSO_4$. Purification by chromatography (500 g silica gel, pentane/MTBE 10:1 → 7:1) gave alkyne **20** (8.8 g, 66 %) as a light yellow liquid. R_f = 0.25 (*n*-hexane/MTBE 7:1); $[\alpha]_D^{23}$ = +13.1 (*c* = 1.12, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.88 (t, J = 2.7 Hz, 1H, 5-H), 2.31–2.49 (m, 2H, 3-H2), 3.35 (s, 3H, OCH_3), 3.40–3.49 (m, 1H, 2-H), 3.49–3.61 (m, 2H, 1-H2), 4.48 (s, 2H, OCH_2Ph), 7.14–7.25 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.9 (C-3), 57.7 (OCH_3), 69.5 (C-5), 70.6 (C-1), 73.5 (CH_2Ph), 78.4 (C-2), 80.6 (C-4), 127.60, 127.64, 128.3 (CH, Ph), 138.1 (C, Ph); IR (film): $\tilde{\nu}$ = 3293 (s), 3060 (m), 3030 (m), 2983 (m), 2913 (s), 2866 (s), 2831 (m), 2120 (w), 1454 (s), 1358 (m), 1202 (m), 1110 (s), 738 (s), 699 cm^{-1} (s); elemental analysis calcd (%) for $C_{13}H_{16}O_2$: C 76.44, H 7.90; found C 76.61, H 8.15.

(2*S*,4*E*)-1-*O*-Benzyl-2-methoxy-5-iodopent-4-en-1-ol (21): All operations were carried out with exclusion of sunlight in amber colored glassware. $LiEt_3BH$ (18.1 mL, 1 M in THF, 18.1 mmol) was added at 20 °C during 20 min to a solution of $[Cp_2ZrCl_2]$ (5.29 g, 18.1 mmol) in THF (150 mL). After 1 h, alkyne **20** (1.85 g, 9.05 mmol) in THF (40 mL) was added dropwise. At the end of the addition the colorless suspension had turned into a yellow solution. After 15 min NIS (4.48 g, 19.9 mmol) was added and the reaction mixture was stirred for additional 10 min. $NaHCO_3$ (60 mL) and $Na_2S_2O_3$ (1 M, 15 mL) was added. The THF was removed in vacuo and the remaining aqueous layer was extracted with pentane/MTBE 10:1 (3×100 mL). The combined organic layers were washed with brine (100 mL) and dried with $MgSO_4$. Purification by chromatography (100 g silica gel, pentane/MTBE 10:1) gave alkenyl iodide **21** (2.64 g, 7.94 mmol, 88 %) as a colorless liquid. R_f = 0.26 (*n*-hexane/MTBE 7:1); $[\alpha]_D^{23}$ = +2.3 (*c* = 1.20, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.22–2.42 (m, 2H, 3-H_2), 3.46–3.43 (m,1H, 2-H), 3.40 (s, 3H, OCH_3), 3.44–3.49 (m, 2H, 1-H_2), 4.54 (s, 2H, OCH_2Ph), 6.06 (d, *J* = 14.5 Hz, 1H, 5-H), 6.51 (dt, J = 14.6, 7.3 Hz, 1H, 5-H), 7.25–7.41 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 37.7 (C-3), 57.6 (OCH_3), 70.8 (C-1), 73.4 (CH_2Ph), 77.0 (C-5), 78.7 (C-2), 80.6 (C-4), 127.7, 128.4 (CH, Ph), 138.0 (C, Ph), 142.1 (C-4); IR (film): $\tilde{\nu}$ = 3058 (m), 3030 (m), 2975 (m), 2929 (s), 2900 (s), 2861 (s), 2829 (s), 1494 (m), 1453 (s), 1362 (m), 1190 (m), 1108 (s), 949 (s), 737 (s), 698 cm^{-1} (s); HR-MS (EI): *m*/*z*: calcd for $C_{13}H_{17}O_2I$: 332.0273; found 332.0271 $[M]^+$.

Tetrahydropyran methyl ketal 23: Iodide **21** (2.7 g, 8.2 mmol) was dissolved in Et_2O (300 mL) and cooled to −78 °C. *t*BuLi (8.9 mL, 1.7 M in pentane, 15 mmol) was added slowly. The mixture was stirred for 1.5 h at −78 °C and then amide **13** (2.0 g, 3.6 mmol) (azeotroped with toluene 3× 15 mL) in Et_2O (180 mL) was added within 1 h. After stirring for 3.5 h at −78 °C the reaction was quenched with *i*PrOH (7.5 mL) and the cooling bath was removed. $NaHCO_3$ (200 mL) was added and the two layers were separated. The aqueous layer was extracted with MTBE (3× 100 mL). The combined organic layers were washed with brine (140 mL), dried with $MgSO_4$ and concentrated. The residue was dissolved in MeOH/CH_2Cl_2 1:1 (60 mL) and PPTS (90 mg, 0.36 mmol) was added at 0 °C. After stirring for 30 min at 0 °C, $NaHCO_3$ (40 mL) was added and the aqueous layer was extracted with MTBE (3×50 mL). The combined organic layers were washed with brine (100 mL), dried with $MgSO_4$, concentrated and the residue was purified by flash chromatography (250 g silica gel, pentane/MTBE 3:1) to yield methyl ketal **23** (1.58 g, 2.80 mmol, 78 %, 2 steps) as a colorless oil. R_f = 0.35 (*n*-hexane/MTBE 1:1); $[\alpha]_D^{24}$ = +53.1 (*c* = 1.03, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.03, 0.04 (2s, 6H, $SiCH_3$), 0.83–0.90 (m, 12H, 5-CH_3, $SiC(CH_3)_3$), 0.95 (d, *J* = 6.8 Hz, 3H, 3-CH_3), 1.35 (d, *J* = 5.6 Hz, 1H, OH), 1.43–1.57 (m, 2H, 3-H, 1″-H), 1.68–1.87 (m, 2H, 5-H, 1″-H), 2.25–2.36 (m, 2H, 3′-H_2), 3.04 (s, 3H, 2-OCH_3), 3.25 (dd, *J* = 9.8, 6.1 Hz, 1H, 3″-H), 3.30 (s, 3H, OCH_3), 3.37–3.48 (m, 3H, 4′-H, 5′-H_2), 3.40 (s, 3H, OCH_3), 3.74–3.96 (m, 3H, 4-H, 6-H, 2″-H), 4.50 (d, *J* = 12.2 Hz, 1H, CHPh), 4.55 (d, *J* = 12.2, 1H, CHPh), 5.41 (bd, *J* = 15.6 Hz, 1H, 1′-H), 5.76 (ddd, *J* = 15.5, 7.3, 7.3 Hz, 1H, 2′-H), 7.22–7.36 (m, 5H, Ph); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = −4.8, 3.9 ($SiCH_3$), 4.9 (5-CH_3), 11.1 (3-CH_3), 18.2 (Si$C(CH_3)_3$), 25.9 (Si-C(CH_3)$_3$), 34.0 (C-3′), 38.4 (C-1″), 39.0 (C-5), 40.5 (C-3), 48.8 (2-OCH_3), 57.4, 58.7 (4′-OCH_3, 3″-OCH_3), 67.9 (C-6), 69.9 (C-2″), 71.5 (C-5′), 72.5 (C-4), 73.3 (CH_2Ph), 77.7 (C-3″), 79.7 (C-4′), 100.9 (C-2), 127.5, 127.6, 128.3, 138.2 (Ph), 128.9 (C-2′), 131.5 (C-1′); IR (film): $\tilde{\nu}$ = 3470 (br s), 2929 (s), 2891 (s), 1462 (m), 1362 (m), 1251 (m), 1108 (s), 985 (s), 833 (s), 735 cm^{-1} (m); HR-MS (EI): *m*/*z*: calcd for $C_{31}H_{54}O_7Si$: 566.3639; found 566.3645 $[M]^+$.

TBS-protected THP ketal 24: 2,6-Lutidine (0.36 mL, 3.1 mmol) and TBS triflate (0.66 mL, 2.9 mmol) were added at −78 °C to alcohol **23** (1.08 g, 1.91 mmol) dissolved in CH_2Cl_2 (70 mL). After stirring for 3 h, $NaHCO_3$ (50 mL) was added. The reaction mixture was warmed to 20 °C and the layers were separated. The aqueous layer was extracted with MTBE (3× 50 mL). The combined organic layers were washed with brine (150 mL) and dried with $MgSO_4$. Chromatography (20 g silica gel, PE/MTBE 10:1) yielded TBS ether **24** (1.29 g, 1.89 mmol, 99 %) as a colorless oil. R_f = 0.64 (*n*-hexane/MTBE 3:1); $[\alpha]_D^{24}$ = +57.4 (*c* = 1.01, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.04, 0.07, 0.08 (3s, 12H, Si-CH_3), 0.84–0.94 (m, 24H, 3-CH_3, 5-CH_3, Si-$C(CH_3)_3$), 1.42–1.61 (m, 2H, 3-H, 1″-H_2), 1.63–1.80 (m, 2H, 5-H, 1″-H_2), 2.28–2.34 (m, 2H, 3′-H_2), 3.06 (s, 3H, 2-OCH_3), 3.23–3.50 (m, 5H, 4′-H, 5′-H_2, 3″-H_2), 3.32, 3.42 (2s, 6H, 4′-OCH_3, 3″-OCH_3), 3.78 (dd, *J* = 10.5, 4.7 Hz, 1H, 4-H), 3.83–3.97 (m, 2H, 6-H, 2″-H), 4.49–4.60 (m, 2H, CH_2Ph), 5.44 (d, *J* = 15.6 Hz, 1H, 1′-H), 5.70–5.82 (m, 1H, 2′-H), 7.14–7.35 (m, 5H, Ph); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = −4.8, −4.7, −4.3, −3.8 (Si-CH_3), 5.1 (5-CH_3), 11.8 (3-CH_3), 18.1, 18.2 (Si-$C(CH_3)_3$), 25.8, 25.9 (Si-C(CH_3)$_3$), 34.0 (C-3′), 38.7 (C-1″), 40.0 (C-5), 40.7 (C-3), 48.8 (2-OCH_3), 57.4, 58.7 (4′-OCH_3, 3″-OCH_3), 67.9 (C-6), 70.2 (C-2″), 71.5 (C-5′), 73.34 (C-4), 73.35 (CH_2Ph), 77.8 (C-3″), 79.8 (C-4′), 101.2 (C-2), 127.57, 127.61, 128.2, 138.2 (Ph), 128.7 (C-2′), 131.9 (C-1′); IR (film): $\tilde{\nu}$ = 2929 (s), 2988 (s), 2857 (s), 1462 (m), 1360 (w), 1252 (m), 1107 (s), 1066 (s), 836 (s), 775 (s), 698 (w), 675 cm^{-1} (w); HR-MS (EI): *m*/*z*: calcd for $C_{37}H_{68}O_7Si_2$: 680.4504; found 680.4501 $[M]^+$.

Diol 25: $[K_2OsO_2(OH)_4]$ (27 mg, 0.074 mmol) and NMO (497 mg, 3.68 mmol) was added to alkene **24** (836 mg, 1.23 mmol) dissolved in *t*BuOH (12 mL)/H_2O (6 mL). The reaction mixture was stirred for 9 d at 0–10 °C. Na_2SO_3 (458 mg, 1.85 mmol), H_2O (15 mL) and MTBE (15 mL) were added. The layers were separated and the aqueous layer was extracted with MTBE (3×10 mL). The combined organic layers were washed with brine (30 mL) and dried with $MgSO_4$. Purification by chromatography (50 g silica gel, PE/MTBE 1:1) gave diol **25** (686 mg, 0.959 mmol, 78 %) with a 6:1 diastereomeric ratio. An analytical sample of diasteromeric pure diol **25** was obtained by a second chromatography. R_f = 0.64 (**25**), 0.30 (epimer) (*n*-hexane/MTBE 3:1); $[\alpha]_D^{24}$ = +48.0 (*c* = 1.04, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 6:1 mixture of **25** and its diastereomer (**ds**)): δ = −0.06, −0.03, −0.02 (3s, Si-CH_3), 0.76–0.83 (m, 3-CH_3 (**ds**), 5-CH_3, Si-$C(CH_3)_3$), 0.91 (d, *J* = 6.6 Hz, 18H, 3-CH_3 (**25**)), 1.33–1.46 (m, 7H, 1″-H_2), 1.55–1.77 (m, 28H, 5-H, 3′-H_2, 1″-H_2), 1.91–2.01 (m, 7H, 3-H), 2.67 (d, *J* = 5.8 Hz, 1H, 1′-OH (**ds**)), 3.15–3.25 (m, 21H, 2′-OH, 3″-H_2), 3.19 (s, 18H, 2-OCH_3 (**25**)), 3.22 (s, 18H, 3″-OCH_3 (**25**)), 3.24 (s, 3H, 2-OCH_3 (**ds**)), 3.32, 3.34 (2s, 6H, 4′-OCH_3 (**25**), 3″-OCH_3 (**ds**)), 3.36 (s, 18H, 4′-OCH_3 (**25**)), 3.39–3.50 (m, 21H, 1′-H, 5′-H_2), 3.57–3.69 (m, 15H, 4-H, 4′-H, 2′-H (**ds**)), 3.75–3.87 (m, 14H, 6-H, 2″-H), 3.96–4.06 (m, 6H, 2′-H (**25**)), 4.41–4.52 (m, 14H, CH_2Ph), 7.04–7.27 (m, 35H, Ph); ^{13}C NMR (75.5 MHz, $CDCl_3$): **25**: δ = −4.8, −4.7, −4.4, −3.9 (Si-CH_3), 5.3 (5-CH_3), 12.1 (3-CH_3), 18.1, 18.2 (Si-$C(CH_3)_3$), 25.8, 25.9 (Si-C(CH_3)$_3$), 35.9 (C-3), 37.2 (C-3′), 38.7 (C-1″), 39.7 (C-5), 48.4 (2-OCH_3), 57.9, 58.8 (4′-OCH_3, 3″-OCH_3), 67.3 (C-2′), 69.0, 69.9 (C-6, C-2″), 71.8 (C-5′), 73.3 (C-4), 73.4 (CH_2Ph), 74.7 (C-1′), 77.5 (C-3″), 77.6 (C-4′), 102.6 (C-2), 127.59, 127.61, 128.4, 138.1 (Ph); **ds**: δ = −4.9, −4.8, −4.4, −3.9 (Si-CH_3), 5.3 (5-CH_3), 11.6 (3-CH_3), 18.0, 18.1 (Si-$C(CH_3)_3$), 25.8, 25.9 (Si-C-

(CH_3)$_3$), 35.0 (C-3′), 36.8 (C-3), 38.8 (C-1″), 39.9 (C-5), 51.4 (2-OCH_3), 57.1, 58.8 (4′-OCH_3, 3″-OCH_3), 68.1, 69.3, 69.8 (C-6, C-2′, C-2″), 71.7 (C-5′), 72.7 (CH_2Ph), 73.2 (C-4), 75.1 (C-1′), 77.4 (C-3″), 77.9 (C-4′), 101.8 (C-2), 127.5, 127.6, 128.3, 138.1 (Ph); IR (film): $\tilde{\nu}$ = 3494 (br s), 2930 (s), 2888 (s), 2857 (s), 1463 (m), 1387 (w), 1361 (w), 1253 (m), 1106 (s), 1069 (s), 835 (s), 776 (m), 698 cm^{-1} (w); HR-MS (EI): *m*/*z*: calcd for $C_{36}H_{65}O_7Si_2$: 665.4269; found 665.4271 [$M-OCH_3-H_2O$]$^+$.

Diacetate 26: Acetic anhydride (3 mL) and DMAP (3 mg, 0.02 mmol) was added to diol **25** (436 mg, 0.610 mmol, 6:1 diastereomeric mixture) dissolved in pyridine (9 mL). The reaction mixture was stirred for 13 h at 40 °C. After cooling to 20 °C, pH 7 phosphate buffer (15 mL, 1 M) and MTBE (15 mL) were added. The layers were separated and the aqueous layer was extracted with MTBE (10 mL). The combined organic layers were subsequently washed with $NaHCO_3$ (30 mL) and brine (30 mL) and dried with $MgSO_4$. Chromatography (20 g silica gel, cyclohexane/AcOEt 10:1) gave diacetate **26** (356 mg, 0.445 mmol, 73 %) and the diastereomeric diacetate (49 mg, 0.061 mmol, 10 %). **26**: R_f = 0.60 (*n*-hexane/MTBE 1:1); $[\alpha]_D^{24}$ = +36.5 (*c* = 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = −0.01, 0.02, 0.03 (3 s, 12 H, Si-CH_3), 0.80–0.88 (m, 21 H, 5-CH_3, Si-C(CH_3)$_3$), 1.02 (d, *J* = 6.8 Hz, 3 H, 3-CH_3), 1.43 (ddd, *J* = 14.6, 7.9, 3.3 Hz, 1 H, 1″-H_2), 1.59–1.71 (m, 3 H, 5-H, 3′-H_2, 1″-H_2), 1.79 (dq, *J* = 10.1, 6.7 Hz, 1 H, 3-H), 1.91–2.02 (m, 1 H, 3′-H_2), 1.99, 2.06 (2 s, 6 H, OAc), 3.08 (s, 3 H, 2-OCH_3), 3.17–3.30 (m, 3 H, 4′-H, 3″-H_2), 3.27, 3.36 (2 s, 6 H, 4′-OCH_3, 3″-OCH_3), 3.41–3.45 (m, 2 H, 5′-H_2), 3.70 (dd, *J* = 10.2, 4.7 Hz, 1 H, 4-H), 3.82 (ddd, *J* = 7.7, 2.8, 2.8 Hz, 1 H, 6-H), 3.85–3.93 (m, 1 H, 2″-H), 4.46–4.56 (m, 2 H, CH_2Ph), 5.00 (d, *J* = 5.5 Hz, 1 H, 1′-H), 5.41 (ddd, *J* = 9.1, 3.6, 5.5 Hz, 1 H, 2′-H), 7.22–7.32 (m, 5 H, Ph); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = −4.9, −4.8, −4.3, −3.8 (Si-CH_3), 5.1 (5-CH_3), 11.2 (3-CH_3), 18.1, 18.2 (Si-*C*(CH_3)$_3$), 20.8, 20.9 (2 OAc), 25.8, 25.9 (Si-C-(CH_3)$_3$), 35.7 (C-3′), 36.5 (C-3), 38.5 (C-1″), 39.6 (C-5), 47.9 (2-OCH_3), 58.1, 58.7 (4′-OCH_3, 3″-OCH_3), 69.0, 69.2 (C-6, C-2′), 69.9 (C-2″), 72.1 (C-5′), 73.0, 73.1 (C-4, C-1′), 73.3 (*C*H_2Ph), 76.5 (C-4′), 77.6 (C-3″), 100.8 (C-2), 127.5, 128.3, 138.2 (Ph), 169.8, 170.0 (2 OAc); IR (film): $\tilde{\nu}$ = 2954 (s), 2930 (s), 2892 (s), 2857 (s), 1748 (s), 1463 (m), 1370 (m), 1249 (s), 1227 (s), 1104 (s), 1072 (s), 836 (m), 775 cm^{-1} (m); HR-MS (EI): *m*/*z*: calcd for $C_{40}H_{71}O_{10}Si_2$: 767.4586; found 767.4581 [$M-OCH_3$]$^+$. Diastereomeric diacetate: R_f = 0.41 (*n*-hexane/MTBE 1:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.00, 0.02, 0.03, 0.04 (4 s, 12 H, Si-CH_3), 0.81 (d, *J* = 7.0 Hz, 3 H, 5-CH_3), 0.85, 0.87 (2 s, 18 H, Si-C(CH_3)$_3$), 0.90 (d, *J* = 6.6 Hz, 3 H, 3-CH_3), 1.42–1.48 (m, 1 H, 1″-H_2), 1.57–1.88 (m, 5 H, 3-H, 5-H, 3′-H_2, 1″-H_2), 1.99, 2.06 (2 s, 6 H, OAc), 3.21–3.37 (m, 2 H, 3″-H_2), 3.27, 3.30, 3.33 (3 s, 9 H, 2-OCH_3, 4′-OCH_3, 3″-OCH_3), 3.40–3.47 (m, 3 H, 4′-H, 5′-H_2), 3.63 (dd, *J* = 10.4, 4.7 Hz, 1 H, 4-H), 3.73–3.79 (m, 1 H, 6-H), 3.85–3.94 (m, 1 H, 2″-H), 4.46–4.55 (m, 2 H, CH_2Ph), 5.19 (d, *J* = 5.1 Hz, 1 H, 1′-H), 5.40 (dt, *J* = 8.1, 5.1 Hz, 1 H, 2′-H), 7.22–7.32 (m, 5 H, Ph); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = −4.9, −4.7, −4.3, −3.8 (Si-CH_3), 5.0 (5-CH_3), 11.9 (3-CH_3), 18.1, 18.2 (Si-*C*(CH_3)$_3$), 21.0, 21.1 (2 OAc), 25.8, 25.9 (Si-C-(*C*H_3)$_3$), 33.9 (C-3′), 38.0 (C-3), 38.5 (C-1″), 39.5 (C-5), 49.7 (2-OCH_3), 57.1, 58.7 (4′-OCH_3, 3″-OCH_3), 69.3, 69.4 (C-6, C-2′), 70.1 (C-2″), 71.1 (C-5′), 73.2 (*C*H_2Ph), 73.8 (C-4), 74.6 (C-1′), 77.5 (C-4′), 77.6 (C-3″), 101.3 (C-2), 127.5, 127.6, 128.3, 138.2 (Ph), 169.9, 170.0 (2 OAc).

(*E*)-4-Tributylstannylpent-3-en-1-ol (28): *Preparation of the mixed cuprate [$Bu_3Sn(Bu)CuCN$]Li_2*: *n*BuLi (16 mL, 2.5 M in hexane, 40 mmol) was added slowly at −30 °C to a suspension of CuCN (1.8 g, 20 mmol) in Et_2O (40 mL)/THF (24 mL). The reaction mixture was stirred for 15 min at −10 °C. After cooling to −30 °C *n*Bu_3SnH (11 mL, 40 mmol) was added dropwise.

Metallation of dihydrofuran: *t*BuLi (14 mL, 1.7 M in pentane, 24 mmol) was added at −60 °C over 5 min to dihydrofuran (1.7 mL, 20 mmol) in THF (20 mL). The reaction mixture was stirred at 0 °C for 50 min.

Reaction of the lithiated dihydrofuran with the mixed cuprate: The solution of the lithiated dihydrofuran was cooled to −30 °C. To this was added via a transfer needle the solution of the mixed cuprate. The reaction mixture was stirred at 0 °C for 90 min. Next it was cooled to −30 °C and MeI (8.8 mL, 0.14 mol) was added dropwise. The mixture was then kept at 20 °C for 3 h. Satd aq NH_4Cl/satd aq NH_3 (150 mL, 4:1) was added for starting the work up. After 30 min, the deep blue mixture was extracted with MTBE (3 × 100 mL). The combined organic layers were washed with brine (100 mL) and dried with $MgSO_4$. Chromatography (350 g silica gel, PE/MTBE 5:1, 0.5 % Et_3N) gave alcohol **28** (4.62 g, 12.3 mmol, 62 %) as pure *E* isomer and a second fraction of **28** with a > 90:10 *E* selectivity (2.7 g, 7.2 mmol, 36 %). R_f = 0.28 (*n*-hexane/MTBE 3:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.81–0.91 (m, 15 H, Sn$CH_2C_2H_4CH_3$), 1.28 (tq, *J* = 7.3, 7.3 Hz, 6 H, $SnC_2H_4CH_2CH_3$), 1.40–1.52 (m, 6 H, $SnCH_2CH_2C_2H_5$), 1.76–1.94 (m, 3 H, 5-H_3), 2.40 (qd, *J* = 6.6, 0.8 Hz, 2 H, 2-H_2), 3.63 (dt, *J* = 6.0, 5.8 Hz, 2 H, 1-H_2), 5.33–5.66 (m, 1 H, 3-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 9.1 (dt, *J*(C,Sn) = 157, 165 Hz, Sn*C*$H_2C_3H_7$), 13.7 ($SnC_3H_6CH_3$), 19.3 (C5), 27.3, 29.1 ($SnCH_2C_2H_4CH_3$), 31.7 (C2), 62.2 (C1), 135.7 (C3), 142.4 (C4); IR (film): $\tilde{\nu}$ = 2956 (s), 2924 (s), 2871 (s), 2851 (s), 1458 (s), 1420 (m), 1264 (s), 1204, (s), 1072, (m), 960 (m), 870 cm^{-1} (m).

(*E*)-1-Bromo-4-tributylstannyl-pent-3-ene (29): Et_3N (1.6 mL, 11 mmol) and MsCl (0.80 mL, 10 mmol) were added at 0 °C successively to a solution of alcohol **28** (3.22 g, 8.58 mmol) in CH_2Cl_2. After 1 h at 0 °C, H_2O (50 mL) and MTBE (100 mL) were added. The aqueous layer was extracted with MTBE (3 × 50 mL). The combined organic layers were washed with brine (50 mL) and dried with Na_2SO_4. The solvents were removed in vacuo. Toluene (20 mL) was added and subsequently removed in vacuo. The mesylate thus obtained was dissolved in acetone (30 mL) at 20 °C. LiBr (2.6 g, 30 mmol) was added and the reaction mixture was stirred for 2.5 h at 50 °C. After cooling to 20 °C, H_2O (100 mL) was added. The aqueous layer was extracted with PE (3 × 100 mL). The combined organic layers were washed with brine (100 mL) and dried with $MgSO_4$. Chromatography (100 g silica gel, PE/1 % Et_3N) gave bromide **29** (2.9 g, 6.7 mmol, 78 %) as a colorless liquid. R_f = 0.66 (*n*-hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.74–0.97 (m, 15 H, Sn$CH_2C_2H_4CH_3$), 1.29 (tq, *J* = 7.3, 7.3 Hz, 6 H, $SnC_2H_4CH_2CH_3$), 1.40–1.53 (m, 6 H, $SnCH_2CH_2C_2H_5$), 1.74–1.92 (m, 3 H, 5-H_3), 2.67 (q, *J* = 7.2 Hz, 2 H, 2-H_2), 3.36 (t, *J* = 7.4 Hz, 2 H, 1-H_2), 5.32–5.63 (m, 1 H, 3-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 9.1 (dt, *J*(C,Sn) = 158, 165 Hz, Sn*C*$H_2C_3H_7$), 13.7 ($SnC_3H_6CH_3$), 19.3 (C5), 27.3, 29.1 ($SnCH_2C_2H_4CH_3$), 31.6, 32.5 (C1, C2), 136.2 (C3), 142.4 (C4); elemental analysis calcd (%) for $C_{17}H_{35}BrSn$ (438.06): C 46.61, H 8.05, Br 18.24; found C 46.71, H 8.05, Br 18.16.

Aldehyde 30: *Benzyl ether cleavage*: $Pd(OH)_2$/C (70 mg, 20 wt %) was added to benzyl ether **26** in AcOEt (30 mL). After hydrogenation (1 atm) at 20 °C for 1 h TLC control showed complete turnover. The solvent was evaporated. The residue was taken up in toluene (3 mL) and purified by chromatography (70 g silica gel, PE/MTBE 5:1) to give the corresponding alcohol (767 mg, 1.08 mmol, 98 %) as a colorless oil. R_f = 0.32 (*n*-hexane/MTBE 1:2); $[\alpha]_D^{24}$ = +44.4 (*c* = 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = −0.02, 0.01, 0.02 (3 s, 12 H, Si-CH_3), 0.78–0.86 (m, 21 H, 5-CH_3, Si-C(CH_3)$_3$), 1.01 (d, *J* = 6.6 Hz, 3 H, 3-CH_3), 1.41 (ddd, *J* = 14.4, 8.0, 3.1 Hz, 1 H, 1″-H_2), 1.51–1.86 (m, 5 H, 3-H, 5-H, 3′-H_2, 5′-OH, 1″-H_2), 1.98–2.11 (m, 1 H, 3′-H_2), 2.00, 2.06 (2 s, 6 H, OAc), 3.07 (s, 3 H, 2-OCH_3), 3.18–3.30 (m, 3 H, 4′-H, 3″-H_2), 3.30, 3.34 (2 s, 6 H, 4′-OCH_3, 3″-OCH_3), 3.37–3.47 (m, 1 H, 5′-H_2), 3.65–3.75 (m, 2 H, 4-H, 5′-H_2), 3.82 (ddd, *J* = 8.1, 2.6, 2.6 Hz, 1 H, 6-H), 3.85–3.93 (m, 1 H, 2″-H), 5.01 (d, *J* = 5.1 Hz, 1 H, 1′-H), 5.30 (ddd, *J* = 8.1, 4.9, 4.9 Hz, 1 H, 2′-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = −4.9, −4.7, −4.3, −3.7 (Si-CH_3), 5.1 (5-CH_3), 11.2 (3-CH_3), 18.1, 18.2 (Si-*C*(CH_3)$_3$), 20.8, 20.9 (2 OAc), 25.8, 25.9 (Si-C-(*C*H_3)$_3$), 34.6 (C-3′), 36.5 (C-3), 38.6 (C-1″), 39.6 (C-5), 47.9 (2-OCH_3), 57.5, 58.8 (4′-OCH_3, 3″-OCH_3), 63.4 (C-5′), 69.0, 69.1 (C-6, C-2′), 69.8 (C-2″), 72.5 (C-4), 73.0 (C-1′), 77.5 (C-3″), 77.9 (C-4′), 100.8 (C-2), 169.9, 170.1 (2 OAc); IR (film): $\tilde{\nu}$ = 3472 (br), 2953 (s), 2930 (s), 2891 (s), 2858 (s), 1746 (s), 1463 (m), 1373 (m), 1250 (s), 1228 (s), 1072 (s), 869 (m), 835 (m), 774 cm^{-1} (m); HR-MS (EI): *m*/*z*: calcd for $C_{33}H_{65}O_{10}Si_2$: 677.4116; found 677.4112 [$M-OCH_3$]$^+$.

Dess–Martin oxidation: Dess–Martin periodinane (245 mg, 577 μmol) was dissolved in CH_2Cl_2 (5 mL) and pyridine (93 μL, 1.2 mmol) was added at 20 °C. The alcohol (315 mg, 0.444 mmol) dissolved in CH_2Cl_2 (3 mL) was added and the reaction mixture was stirred for 45 min. $NaHCO_3$ (20 mL), water (3 mL), $Na_2S_2O_3$ (211 mg, 1.33 mmol), and MTBE (20 mL) were added and the mixture was stirred for 10 min. The aqueous layer was extracted with MTBE (3 × 10 mL). The combined organic layers were washed with brine (40 mL), dried with $MgSO_4$, concentrated and the residue was purified by chromatography (25 g silica gel, pentane/MTBE 1:1)

to yield the sensitive aldehyde **30** (289 mg, 0.409 mmol, 92%) as a colorless oil. R_f=0.36 (MTBE/*n*-hexane 1:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ= −0.02, 0.00, 0.01 (3s, 12H, Si-CH_3), 0.77–0.86 (m, 21H, 5′-CH_3, Si-C-$(CH_3)_3$), 1.00 (d, J=6.6 Hz, 3H, 3′-CH_3), 1.42 (ddd, J=14.3, 7.9, 3.4 Hz, 1H, 1″-H_2), 1.60–1.85 (m, 4H, 3-H_2, 3′-H, 5′-H, 1″-H_2), 1.94–2.05 (m, 1H, 3-H_2), 1.99, 2.04 (2s, 6H, OAc), 3.06 (s, 3H, 2′-OCH_3), 3.21–3.79 (m, 2H, 3″-H_2), 3.27, 3.37 (2s, 6H, 2-OCH_3, 3″-OCH_3), 3.35–3.45 (m, 1H, 2-H), 3.68 (dd, J=10.4, 4.7 Hz, 1H, 4′-H), 3.81 (ddd, J=7.8, 2.8, 2.7 Hz, 1H, 6′-H), 3.84–3.92 (m, 1H, 2″-H), 4.99 (d, J=5.7 Hz, 1H, 5-H), 5.39 (ddd, J= 9.4, 5.6, 3.0 Hz, 1H, 4-H), 9.57 (d, J=2.1 Hz, 1H, 1-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ= −4.9, −4.8, −4.4, −3.8 (Si-CH_3), 5.0 (5′-CH_3), 11.2 (3′-CH_3), 18.0, 18.2 (Si-*C*$(CH_3)_3$), 20.7, 20.8 (2 OAc), 25.8, 25.9 (Si-C-(*C*H_3)$_3$), 33.5 (C-3), 36.5 (C-3′), 38.4 (C-1″), 39.5 (C-5′), 47.9 (2′-OCH_3), 58.6, 58.7 (2-OCH_3, 3″-OCH_3), 68.1 (C-4), 69.2 (C-6′), 69.8 (C-2″), 72.8, 73.0 (C-4′, C-5), 77.4 (C-3″), 82.4 (C-2), 100.7 (C-2′), 169.7, 170.0 (2 OAc), 203.0 (C-1).

Alcohol 31: Bromide **29** (2.297 g, 5.244 mmol) and 1,2-dibromoethane (0.45 mL, 5.2 mmol) in Et_2O (5 mL) were added dropwise to magnesium turnings (254 mg, 10.5 mmol). The rate of bromide addition was adjusted so that a gentle boiling of the reaction mixture was maintained. Et_2O (5 mL) was added and the solution of the Grignard reagent was cooled to −78°C. Aldehyde **30** (618 mg, 0.874 mmol) dissolved in Et_2O (4 mL) was added dropwise. After stirring at −78°C for 3.5 h, the reaction was quenched by addition of *i*PrOH (4 mL). The reaction mixture was warmed to 20°C and then separated between $NaHCO_3$ (20 mL) and MTBE (20 mL). The aqueous layer was extracted with MTBE (3× 10 mL). The combined organic layers were washed with brine (40 mL) and dried with $MgSO_4$. Chromatography (100 g silica gel, PE/MTBE 5:1) gave alcohol **31** (542 mg, 0.508 mmol, 58%) as a colorless oil. R_f=0.52 (*n*-hexane/MTBE 1:1); $[\alpha]_D^{24}$=+27.6 (c=1.00, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ= −0.01, 0.01, 0.016, 0.020 (4s, 12H, Si-CH_3), 0.80–0.87 (m, 36H, Si-C$(CH_3)_3$, Sn-*n*Bu, 5′-CH_3), 1.02 (d, J=6.6 Hz, 3H, 3′-CH_3), 1.23–1.31 (m, 6H, Sn-*n*Bu), 1.38–1.50 (m, 7H, Sn-*n*Bu, 1″-H_2), 1.50–1.56 (m, 1H, 5-H_2), 1.61–1.72 (m, 3H, 5′-H, 8-H_2, 1″-H_2), 1.78–1.86 (m, 1H, 3′-H), 1.81 (s, 3H, 1-H_3), 1.99–2.06 (m, 1H, 8-H_2), 2.00, 2.05 (2s, 6H, OAc), 2.11 (d, J=5.8 Hz, 1H, 6-OH), 2.12–2.20 (m, 1H, 4-H_2), 2.25–2.32 (m, 1H, 4-H_2), 3.03–3.06 (m, 1H, 7-H), 3.08 (s, 3H, 2′-OCH_3), 3.23–3.27 (m, 2H, 3″-H_2), 3.28 (s, 3H, 3″-OCH_3), 3.39 (s, 3H, 7-OCH_3), 3.43–3.50 (m, 1H, 6-H), 3.69 (dd, J=10.0, 4.9 Hz, 1H, 4′-H), 3.80–3.84 (m, 1H, 6′-H), 3.86–3.91 (m, 1H, 2″-H), 5.01 (d, J=5.7 Hz, 1H, 10-H), 5.33 (ddd, J=8.8, 5.3, 3.7 Hz, 1H, 9-H), 5.47–5.51 (m, 1H, 3-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ= −4.9, −4.7, −4.3, −3.8 (Si-CH_3), 5.1 (C-5′), 9.0 (Sn-*n*Bu), 11.2 (C-3′), 13.7 (Sn-*n*Bu), 18.1, 18.2 (Si-*C*$(CH_3)_3$), 19.1 (C-1), 20.9 (2 OAc), 24.7 (C-4), 25.8, 25.9 (Si-C(*C*H_3)$_3$), 27.3, 29.1 (Sn-*n*Bu), 33.2 (C-5), 34.9 (C-8), 36.5 (C-3′), 38.6 (C-1″), 39.6 (C-5′), 47.9 (2′-OCH_3), 58.8 (3″-OCH_3), 59.5 (7-OCH_3), 69.1 (C-6′), 69.4 (C-9), 69.8 (C-2″), 72.9, 73.0, 73.1 (C-6, C-10, C-4′), 77.5 (C-3″), 80.4 (C-7), 100.8 (C-2′), 138.6 (C-2), 140.2 (C-3), 168.8, 170.2 (2 OAc); IR (film): $\tilde{\nu}$=3482 (br w), 2956 (s), 2929 (s), 2857 (s), 1748 (s), 1463 (m), 1373 (m), 1249 (s), 1228 (s), 1071 (s), 869 (m), 836 (m), 774 cm^{-1} (m); HR-MS (EI): m/z: calcd for $C_{47}H_{93}O_{11}Si_2Sn$: 1009.5278; found 1009.5280 $[M-C(CH_3)_3]^+$.

(2*S*,3*S*)-3-*tert*-Butyldimethylsilyloxy-2-methyl-γ-butanolide (33): Alcohol **32** (2.52 g, 21.7 mmol) was dissolved in CH_2Cl_2 (85 mL) and cooled to 0°C. 2,6-Lutidine (5.1 mL, 43 mmol) and TBSOTf (6.0 mL, 26 mmol) were added and the solution was stirred for 4 h at 0°C. The reaction was quenched by addition of $NaHCO_3$ (40 mL) and water (40 mL). The aqueous layer was extracted with CH_2Cl_2 (3×50 mL). The combined organic layers were washed with brine (60 mL), dried with Na_2SO_4, and the solvent was evaporated. The residue was purified by flash chromatography (180 g silica gel, pentane/MTBE 9:1) to yield silyl ether **33** (4.40 g, 19.1 mmol, 88%) as a colorless oil. R_f=0.47 (*n*-hexane/MTBE 5:1); $[\alpha]_D^{22}$= −2.1 (c=1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ=0.05, 0.06 (2s, 6H, $SiCH_3$), 0.86 (s, 9H, $SiC(CH_3)_3$), 1.23 (d, J=7.2 Hz, 3H, 2-CH_3), 2.47 (dq, J=7.3, 6.9 Hz, 1H, 2-H), 3.90 (ddd, J=8.9, 6.1, 0.3 Hz, 1H, 4-H), 4.07–4.19 (m, 1H, 3-H), 4.33 (dd, J=9.0, 6.2 Hz, 1H, 4-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ= −4.8 (2C, $SiCH_3$), 12.7 (2-CH_3), 17.9 (Si*C*$(CH_3)_3$), 25.6 (SiC(*C*H_3)$_3$), 43.3 (C-2), 72.4 (C-4), 74.7 (C-3), 177.7 (C-1); IR (film): $\tilde{\nu}$=2956 (m), 1784 (s), 1345 (s), 1129 (s), 1001 cm^{-1} (s); elemental analysis calcd (%) for $C_{11}H_{22}O_3Si$ (230.38): C 57.35, H 9.63; found C 57.48, H 9.44.

(2*E*,4*R*,5*S*)-Ethyl 5-*tert*-butyldimethylsilyloxy-6-hydroxy-2,4-dimethyl-hex-2-enoate (34): Lactone **33** (4.40 g, 19.1 mmol) was dissolved in CH_2Cl_2 (90 mL) at −78°C and DIBAH (29 mL, 1.0 M in PE, 29 mmol) was added dropwise. After stirring for 30 min at −78°C, the reaction was quenched by addition to a cooled (0°C) solution of Rochelles salt (150 mL, 1.0 M). After 1.5 h stirring the two layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3×40 mL). The combined organic layers were dried with $MgSO_4$ and concentrated. The crude lactol (4.40 g, 18.9 mmol, 99%) was used for the next step without purification. The lactol was azeotroped with toluene (3×10 mL) and dissolved in toluene (660 mL). $Ph_3PC(CH_3)CO_2Et$ (17.1 g, 47.3 mmol) was added and the mixture was heated under reflux for 20 h. The solvent was removed and the residue was purified by flash chromatography (450 g silica gel, pentane/MTBE 5:1) to give ester **34** (4.90 g, 15.5 mmol, 82%) as a colorless oil. R_f=0.52 (*n*-hexane/MTBE 1:1); $[\alpha]_D^{22}$=+25.8 (c=1.31, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ=0.057, 0.064 (2s, 6H, $SiCH_3$), 0.89 (s, 9H, $SiC(CH_3)_3$), 0.99 (d, J=6.8 Hz, 3H, 4-CH_3), 1.26 (t, J=7.1 Hz, 3H, $CO_2CH_2CH_3$), 1.78–1.90 (m, 1H, OH), 1.83 (d, J=1.5 Hz, 3H, 2-CH_3), 2.65–2.84 (m, 1H, 4-H), 3.37–3.59 (m, 3H, 5-H, 6-H_2), 4.15 (q, J=7.1 Hz, 2H, $CO_2CH_2CH_3$), 6.55 (dq, J=10.3, 1.3 Hz, 1H, 3-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ= −4.7, −4.3 ($SiCH_3$), 12.6 (2-CH_3), 14.3 (CH_3CH_2O), 15.8 (4-CH_3), 18.1 (Si*C*$(CH_3)_3$), 25.7 (SiC(*C*H_3)$_3$), 36.2 (C-4), 60.5 (OCH_2CH_3), 64.7 (C-6), 75.8 (C-5), 127.9 (C-2), 143.6 (C-3), 168.2 (C-1); IR (film): $\tilde{\nu}$=3490 (br s), 2957 (s), 2930 (s), 2885 (s), 2859 (s), 1712 (s), 1369 (s), 1254 (s), 1116 (s), 1049 cm^{-1} (s); elemental analysis calcd (%) for $C_{16}H_{32}O_4Si$ (316.51): C 60.72, H 10.19; found C 60.49, H 10.38.

(2*E*,4*R*,5*S*)-Ethyl 5-*tert*-butyldimethylsilyloxy-2,4-dimethyl-6-triethylsilyl-oxy-hex-2-enoate (35): Imidazole (2.1 g, 31 mmol) and TESCl (3.1 mL, 19 mmol) were added at 0°C to alcohol **34** (4.90 g, 15.5 mmol) in CH_2Cl_2 (90 mL). After stirring for 30 min at 0°C, the reaction was quenched with phosphate buffer solution (50 mL, 1.0 M, pH 7) and the aqueous layer was extracted with MTBE (3×70 mL). The combined organic layers were washed with brine (80 mL), dried with $MgSO_4$ and the solvents were evaporated. The crude product was purified by flash chromatography (500 g silica gel, pentane/MTBE 9:1) to give bis(silylether) **35** (6.20 g, 14.4 mmol, 93%) as a colorless oil. R_f=0.21 (*n*-hexane/CH_2Cl_2 5:1); $[\alpha]_D^{23}$=+0.21 (c=0.96, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ= −0.03, −0.02 (2s, 6H, $SiCH_3$), 0.58 (q, J=7.9 Hz, 6H, $SiCH_2CH_3$), 0.87 (s, 9H, $SiC(CH_3)_3$), 0.93 (t, J=7.9 Hz, 9H, $SiCH_2CH_3$), 0.96 (d, J=6.5 Hz, 3H, 4-CH_3), 1.26 (t, J=7.1 Hz, 3H, $CO_2CH_2CH_3$), 1.82 (d, J=1.5 Hz, 3H, 2-CH_3), 2.65–2.83 (m, 1H, 4-H), 3.42–3.49 (m, 2H, 6-H_2), 3.51–3.62 (m, 1H, 5-H), 4.05–4.25 (m, 2H, $CO_2CH_2CH_3$), 6.71 (dq, J=10.4, 1.2 Hz, 1H, 3-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ= −5.0, −4.2 ($SiCH_3$), 4.3 ($SiCH_2CH_3$), 6.7 ($SiCH_2CH_3$), 12.4 (2-CH_3), 13.2 (4-CH_3), 14.3 ($CO_2CH_2CH_3$), 18.2 (Si*C*$(CH_3)_3$), 25.9 (SiC(*C*H_3)$_3$), 35.4 (C-4), 60.3 ($CO_2CH_2CH_3$), 64.8 (C-6), 75.6 (C-5), 126.4 (C-2), 145.6 (C-3), 168.4 (C-1); IR (film): $\tilde{\nu}$=2957 (s), 2936 (s), 2878 (s), 1714 (s), 1463 (s), 1367 (s), 1254 (s), 1080 cm^{-1} (s); elemental analysis calcd (%) for $C_{22}H_{46}O_4Si_2$ (430.77): C 61.34, H 10.76; found C 61.33, H 10.87.

(2*E*,4*E*,6*R*,7*S*)-Ethyl 7-*tert*-butyldimethylsilyloxy-2,4,6-trimethyl-8-triethylsilyloxyocta-2,4-dienoate (36): *DIBAH reduction:* Ester **35** (6.20 g, 14.4 mmol) was dissolved in toluene (120 mL) at −78°C and DIBAH (32 mL, 1.0 M in PE, 32 mmol) was added dropwise. After stirring for 30 min at −78°C, the reaction was quenched by addition via cannula to a cooled (0°C) solution of Rochelles salt (450 mL, 1.0 M). After 2 h stirring the two layers were separated and the aqueous layer was extracted with MTBE (3×70 mL). The combined organic layers were washed with brine (80 mL), dried with Na_2SO_4 and concentrated. The crude allylic alcohol (5.50 g, 14.1 mmol, 98%) was used for the next step without purification. R_f=0.47 (*n*-hexane/MTBE 1:1); $[\alpha]_D^{23}$= −20.2 (c=0.96, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ=0.01, 0.03 (2s, 6H, $SiCH_3$), 0.57 (q, J=8.1 Hz, 6H, $SiCH_2CH_3$), 0.87 (s, 9H, $SiC(CH_3)_3$), 0.91 (d, J=6.8 Hz, 3H, 4-CH_3), 0.93 (t, J=7.6 Hz, 9H, $SiCH_2CH_3$), 1.20 (t, J=6.0 Hz, 1H, OH), 1.65 (d, J= 1.2 Hz, 3H, 2-CH_3), 2.54–2.68 (m, 1H, 4-H), 3.37–3.55 (m, 3H, 5-H, 6-H_2), 3.97 (d, J=5.1 Hz, 2H, 1-H_2), 5.33 (dq, J=9.6, 1.1 Hz, 1H, 3-H);

^{13}C NMR (75 MHz, $CDCl_3$): $\delta = -4.8$, -4.1 ($SiCH_3$), 4.4 ($SiCH_2CH_3$), 6.8 ($SiCH_2CH_3$), 13.8 (2-CH_3), 14.6 (4-CH_3), 18.2 ($SiC(CH_3)_3$), 25.9 ($SiC(CH_3)_3$), 34.4 (C-4), 65.1 (C-6), 69.1 (C-1), 76.8 (C-5), 130.4 (C-3), 144.7 (C-2); IR (film): $\tilde{\nu} = 3338$ (br s), 2957 (s), 2930 (s), 2878 (s), 2859 (s), 1462 (s), 1252 (s), 1126 cm^{-1} (s); elemental analysis calcd (%) for $C_{20}H_{44}O_3Si_2$ (388.73): C 61.79, H 11.41; found C 61.76, H 11.52.

MnO_2 oxidation: MnO_2 (27.5 g, 316 mmol) was added at 20 °C to the allylic alcohol (5.50 g, 14.1 mmol) dissolved in CH_2Cl_2 (220 mL). The reaction mixture was heated to 40 °C for 30 min. After cooling to 20 °C the mixture was filtered over a pad of Celite and the residue was washed with CH_2Cl_2 (200 mL). The solvent was removed and the aldehyde (5.40 g, 14.0 mmol, 99 %) thus obtained was used directly for the following Wittig reaction. $R_f = 0.78$ (*n*-hexane/MTBE 4:1); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 0.01$, 0.03 (2 s, 6 H, $SiCH_3$), 0.58 (q, $J = 8.0$ Hz, 6 H, $SiCH_2CH_3$), 0.87 (s, 9 H, $SiC(CH_3)_3$), 0.93 (t, $J = 7.6$ Hz, 9 H, $SiCH_2CH_3$), 1.03 (d, $J = 6.8$ Hz, 3 H, 4-CH_3), 1.74 (d, $J = 1.5$ Hz, 3 H, 2-CH_3), 2.86–3.06 (m, 1 H, 4-H), 3.44–3.53 (m, 2 H, 6-H_2), 3.56–3.68 (m, 1 H, 5-H), 6.45 (dq, $J = 10.2$, 1.2 Hz, 1 H, 3-H), 9.36 (s, 1 H, 1-H).

Wittig olefination: The crude aldehyde was azeotroped with toluene (3 × 20 mL) and dissolved in toluene (700 mL). $Ph_3PC(CH_3)CO_2Et$ (20.3 g, 56.0 mmol) was added and the mixture was heated under reflux for 14 h. The solvent was removed and the residue was purified by flash chromatography (550 g silica gel, pentane/CH_2Cl_2 2:1) to yield dienoate **36** (5.30 g, 11.3 mmol, 81 %) as a colorless oil. Starting from this step all reactions were carried out under exclusion of sun light (working with amber colored glassware in a shaded fume hood). $R_f = 0.44$ (*n*-hexane/CH_2Cl_2 1:1); $[\alpha]_D^{23} = +11.8$ ($c = 0.97$, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 0.01$, 0.03 (2 s, 6 H, $SiCH_3$), 0.57 (q, $J = 7.8$ Hz, 6 H, $SiCH_2CH_3$), 0.86 (s, 9 H, $SiC(CH_3)_3$), 0.88–1.00 (m, 12 H, 6-CH_3, $SiCH_2CH_3$), 1.28 (t, $J = 7.0$ Hz, 3 H, $CO_2CH_2CH_3$), 1.82 (d, $J = 1.3$ Hz, 3 H, 4-CH_3), 1.98 (d, $J = 1.5$ Hz, 3 H, 2-CH_3), 2.60–2.80 (m, 1 H, 6-H), 3.39–3.60 (m, 3 H, 7-H, 8-H_2), 4.18 (q, $J = 7.1$ Hz, 2 H, $CO_2CH_2CH_3$), 5.52 (d, $J = 9.8$ Hz, 1 H, 5-H), 7.09 (br s, 1 H, 3-H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = -4.8$, -4.0 ($SiCH_3$), 4.3 ($SiCH_2CH_3$), 6.8 ($SiCH_2CH_3$), 14.0 (2-CH_3), 14.3 ($CO_2CH_2CH_3$), 14.7 (6-CH_3), 16.5 (4-CH_3), 18.2 ($SiC(CH_3)_3$), 25.9 ($SiC(CH_3)_3$), 35.4 (C-6), 60.5 ($CO_2CH_2CH_3$), 65.2 (C-8), 76.6 (C-7), 125.3 (C-4), 131.1 (C-2), 139.9 (C-5), 143.1 (C-3), 169.2 (C-1); IR (film): $\tilde{\nu} =$ 2957 (s), 2931 (s), 2859 (s), 1710 (s), 1463 (s), 1367 (s), 1252 (s), 1112 cm^{-1} (s); elemental analysis calcd (%) for $C_{25}H_{50}O_4Si_2$ (470.83): C 63.77, H 10.70; found C 63.62, H 10.91.

(2*E*,4*E*,6*R*,7*S*)-Ethyl 7-*tert*-butyldimethylsilyloxy-8-hydroxy-2,4,6-trimethylocta-2,4-dienoate (37): TES ether **36** (5.30 g, 11.3 mmol) was dissolved in CH_2Cl_2 (60 mL) and MeOH (30 mL) and cooled to 0 °C. CSA (0.21 g, 0.91 mmol) was added in portions. The reaction was monitored by TLC (*n*-hexane/CH_2Cl_2 1:1). The reaction was quenched after 15 min by addition of phosphate buffer (50 mL, 1.0 M, pH 7) and MTBE (100 mL). The layers were separated and the aqueous layer was extracted with MTBE (3 × 50 mL). The combined organic layers were washed with brine (60 mL), dried with $MgSO_4$, concentrated and the resulting crude oil was purified by flash chromatography (550 g silica gel, pentane/MTBE 5:1) to obtain the corresponding alcohol **37** (3.80 g, 10.5 mmol, 93 %) as a colorless oil. $R_f = 0.45$ (*n*-hexane/MTBE 1:1); $[\alpha]_D^{23} = +0.39$ ($c = 1.04$, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 0.08$ (2 s, 6 H, $SiCH_3$), 0.90 (s, 9 H, $SiC(CH_3)_3$), 1.00 (d, $J = 6.8$ Hz, 3 H, 6-CH_3), 1.28 (t, $J = 7.1$ Hz, 3 H, $CO_2CH_2CH_3$), 1.85 (d, $J = 1.3$ Hz, 3 H, 4-CH_3), 1.97 (d, $J = 1.3$ Hz, 3 H, 2-CH_3), 2.65–2.85 (m, 1 H, 6-H), 3.39–3.60 (m, 3 H, 7-H, 8-H_2), 4.18 (q, $J =$ 7.2 Hz, 2 H, $CO_2CH_2CH_3$), 5.36 (d, $J = 10.0$ Hz, 1 H, 5-H), 7.07 (s, 1 H, 3-H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = -4.6$, -4.3 ($SiCH_3$), 14.0 (2-CH_3), 14.3 ($CO_2CH_2CH_3$), 16.6 (4-CH_3), 17.1 (6-CH_3), 18.1 ($SiC(CH_3)_3$), 25.9 ($SiC(CH_3)_3$), 36.0 (C-6), 60.6 ($CO_2CH_2CH_3$), 64.6 (C-8), 76.4 (C-7), 125.8 (C-4), 132.6 (C-2), 137.9 (C-5), 142.7 (C-3), 169.1 (C-1); IR (film): $\tilde{\nu} =$ 3495 (br s), 2957 (s), 2884 (s), 1708 (s), 1460 (s), 1368 (s), 1253 (s), 1047 (s), 1034 cm^{-1} (s); elemental analysis calcd (%) for $C_{19}H_{36}O_4Si$ (356.57): C 64.00, H 10.18; found C 63.72, H 10.16.

(2*E*,4*E*,8*E*,6*R*,7*S*)-Ethyl 7-*tert*-butylsilyloxy-9-iodo-2,4,6-trimethylnona-2,4,8-trienoate (38): *Dess–Martin oxidation:* Alcohol **37** (633 mg, 1.78 mmol) was dissolved in CH_2Cl_2 (10 mL) at 0 °C. Pyridine (0.35 mL, 4.4 mmol) and DMP (925 mg, 2.18 mmol) were added. The mixture was stirred for 1 h at 20 °C. The reaction was quenched by addition of $NaHCO_3$ (30 mL) and $Na_2S_2O_3$ (3.1 g, 13 mmol). After stirring for 30 min, the layers were separated and the aqueous layer was extracted with MTBE (3 × 40 mL). The combined organic layers were washed with brine (30 mL), dried with $MgSO_4$ and concentrated. The crude aldehyde (630 mg, 1.78 mmol) was used for the next step without purification.

Takai reaction: $CrCl_2$ (1.46 g, 11.9 mmol) was treated with a degassed mixture of 1,4-dioxane and THF (5 mL, 4:1). After 10 min a mixture of the crude aldehyde (630 mg, 1.78 mmol), CHI_3 (1.4 g, 3.6 mmol) and hydrochinone (5 mg, 0.05 mmol) in a mixture of 1,4-dioxane and THF (20 mL, 4:1) was added via cannula to the $CrCl_2$ suspension at 20 °C. After stirring for 16 h the reaction was quenched by addition of pentane/MTBE 3:1 (50 mL). The mixture was filtered over a pad of Celite and washed with pentane/MTBE (3:1, 200 mL). The organic layer was washed subsequently with aq 1.0 M $Na_2S_2O_3$ (50 mL) and brine (50 mL). After drying with $MgSO_4$ the solvents were evaporated and the crude product was purified by chromatography (100 g silica gel, pentane/CH_2Cl_2 4:1 → 2:1) to yield colorless iodide **38** (571 mg, 1.19 mmol, 67 %, 2 steps) as a single *E* isomer. $R_f = 0.34$ (*n*-hexane/CH_2Cl_2 1:1); $[\alpha]_D^{23} = +$ 25.8 ($c = 0.19$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = -0.04$, -0.05 (2 s, 6 H, $SiCH_3$), 0.88 (d, $J = 6.8$ Hz, 3 H, 6-CH_3),0.90 (s, 9 H, $SiC(CH_3)_3$), 1.01 (t, $J = 7.1$ Hz, 3 H, $CO_2CH_2CH_3$), 1.57 (d, $J = 1.3$ Hz, 3 H, 4-CH_3), 2.11 (d, $J = 1.3$ Hz, 3 H, 2-CH_3), 2.32–2.46 (m, 1 H, 6-H), 3.59 (dt, $J = 6.6$, 0.9 Hz, 1 H, 7-H), 4.07 (q, $J = 7.1$ Hz, 2 H, $CO_2CH_2CH_3$), 5.25 (d, $J = 10.0$ Hz, 1 H, 5-H), 6.00 (dd, $J = 14.4$, 1.0 Hz, 1 H, 9-H), 6.42 (dd, $J = 14.5$, 6.8 Hz, 1 H, 8-H), 7.38 (s, 1 H, 3-H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = -5.0$, -4.4 ($SiCH_3$), 14.1 (2-CH_3), 14.3 ($CO_2CH_2CH_3$), 16.3 (4-CH_3), 16.7 (6-CH_3), 18.2 ($SiC(CH_3)_3$), 25.8 ($SiC(CH_3)_3$), 39.7 (C-6), 60.6 ($CO_2CH_2CH_3$), 76.7 (C-9), 78.9 (C-7), 126.0 (C-4), 132.4 (C-2), 136.6 (C-5), 142.7 (C-3), 147.6 (C-8), 169.1 (C-1); IR (film): $\tilde{\nu} = 2957$ (s), 2930 (s), 2897 (s), 2858 (s), 1708 (s), 1460 (s), 1366 (s), 1252 (s), 1034 cm^{-1} (s); elemental analysis calcd (%) for $C_{20}H_{35}IO_3Si$ (478.48): C 50.20, H 7.37; found C 49.98, H 7.31; HR-MS (ESI): *m/z*: calcd for: 479.1478; found 479.1486 $[M+H]^+$.

Ethyl (2*E*,4*E*,6*E*,10*E*,8*R*,9*S*)-9-*tert*-Butyldimethylsilyloxy-11-iodo-2,4,6,8-tetramethylundecatetra-2,4,6,10-enoate (39): *DIBAH reduction:* Ester **38** (571 mg, 1.19 mmol) was dissolved in toluene (17 mL) at −78 °C and DIBAH (2.6 mL, 1.0 M in PE, 2.6 mmol) was added via syringe within 10 min. After stirring for 30 min at −78 °C, the reaction was quenched by addition via cannula to a cooled (0 °C) solution of Rochelles salt (50 mL, 1.0 M). After 1 h stirring the two layers were separated and the aqueous layer was extracted with MTBE (3 × 40 mL). The combined organic layers were washed with brine (30 mL), dried with $MgSO_4$, concentrated and the residue was purified by flash chromatography (60 g silica gel, pentane/MTBE 6:1 → 4:1) to give the corresponding alcohol (510 mg, 1.17 mmol, 98 %) as a colorless oil. $R_f = 0.44$ ($CHCl_3$/MeOH 100:1); $[\alpha]_D^{23} = -22.9$ ($c = 0.19$, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = -0.01$, 0.02 (2 s, 6 H, $SiCH_3$), 0.87 (s, 9 H, $SiC(CH_3)_3$), 0.96 (d, $J = 6.8$ Hz, 3 H, 6-CH_3), 1.71 (d, $J = 1.0$ Hz, 3 H, 4-CH_3), 1.77 (d, $J = 1.0$ Hz, 3 H, 2-CH_3), 2.41–2.61 (m, 1 H, 6-H), 3.84 (t, $J = 6.5$ Hz, 1 H, 7-H), 4.03 (br s, 2 H, 2-H_2), 5.06 (d, $J = 9.8$ Hz, 1 H, 5-H), 5.84 (s, 1 H, 3-H), 6.15 (dd, $J = 14.3$, 1.0 Hz, 1 H, 9-H), 6.51 (dd, $J = 14.4$, 6.4 Hz, 1 H, 8-H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = -4.9$, -4.4 ($SiCH_3$), 15.4 (2-CH_3), 16.7 (4-CH_3), 17.3 (6-CH_3), 18.2 ($SiC(CH_3)_3$), 25.8 ($SiC(CH_3)_3$), 39.6 (C-6), 69.3 (C-1), 76.3 (C-7), 79.2 (C-9), 129.3 (C-3), 131.7 (C-5), 133.1 (C-2), 134.7 (C-4), 148.0 (C-8); IR (film): $\tilde{\nu} = 3332$ (br s), 2957 (s), 2929 (s), 2858 (s), 1463 (s), 1361 (s), 1257 (s), 1165 (s), 1068 (s), 1006 cm^{-1} (s); HR-MS (ESI): *m/z*: calcd for $C_{18}H_{33}IO_2SiNa$: 459.1192; found 459.1198 $[M+Na]^+$.

MnO_2 oxidation: To the allylic alcohol (605 mg, 1.39 mmol) in CH_2Cl_2 (15 mL) was added MnO_2 (4.24 g, 48.8 mmol). After 2 h at 20 °C, the mixture was filtered over a pad of Celite and the residue was washed with CH_2Cl_2 (100 mL). The solvent was removed and the crude aldehyde was used directly for the following Wittig reaction. $R_f = 0.28$ (*n*-hexane/MTBE 1:1); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = -0.00$, 0.02 (2 s, 6 H, Si-CH_3), 0.87 (s, 9 H, Si-$C(CH_3)_3$), 1.01 (d, $J = 6.8$ Hz, 3 H, 6-CH_3), 1.92 (s, 3 H, 4-CH_3), 1.93 (s, 3 H, 2-CH_3), 2.55–2.71 (m, 1 H, 6-H), 3.93 (t, $J =$ 5.7 Hz, 1 H, 7-H), 5.61 (d, $J = 9.8$ Hz, 1 H, 5-H), 6.21 (dd, $J = 14.3$, 0.8 Hz, 1 H, 9-H), 6.50 (dd, $J = 14.5$, 6.2 Hz, 1 H, 8-H), 6.68 (s, 1 H, 3-H), 9.37 (s, 1 H, 1-H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = -5.0$, -4.4 (Si-CH_3), 10.8 (2-

CH_3), 15.9 (4-CH_3), 16.5 (6-CH_3), 18.2 (Si-$C(CH_3)_3$), 25.8 (Si-C(CH_3)$_3$), 39.7 (C-6), 76.9 (C-9), 78.6 (C-7), 133.1 (C-2), 141.3 (C-5), 147.2 (C-8), 154.6 (C-3), 196.1 (C-1).

Wittig olefination: The crude aldehyde was azeotroped with toluene (3× 10 mL) and dissolved in toluene (60 mL). $Ph_3PC(CH_3)CO_2Et$ (3.03 g, 8.32 mmol) was added and the mixture was heated under reflux for 26 h. The solvent was removed and the residue was purified by chromatography (25 g silica gel, PE/MTBE 30:1, 0.1% Et_3N) to yield tetraenoate **39** (418 mg, 0.806 mmol, 58%) as a colorless oil. R_f=0.41 (*n*-hexane/CH_2Cl_2 1:1); $[\alpha]_D^{23}$=+13.7 (*c*=0.49, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ= −0.01, 0.02 (2s, 6H, Si-CH_3), 0.87 (s, 9H, Si-C(CH_3)$_3$), 0.98 (d, *J*=6.8 Hz, 3H, 8-CH_3), 1.29 (t, *J*=7.0 Hz, 3H, $CO_2CH_2CH_3$), 1.74 (d, *J*=1.1 Hz, 3H, 6-CH_3), 1.96 (d, *J*=1.1 Hz, 3H, 4-CH_3), 2.01 (d, *J*=1.1 Hz, 3H, 2-CH_3), 2.48–2.61 (m, 1H, 8-H), 3.88 (t, *J*=5.8 Hz, 1H, 9-H), 4.19 (q, *J*= 7.2 Hz, 2H, $CO_2CH_2CH_3$), 5.17 (d, *J*=9.8 Hz, 1H, 7-H), 5.98 (s, 1H, 5-H), 6.17 (dd, *J*=14.5, 0.9 Hz, 1H, 11-H), 6.51 (dd, *J*=14.3, 6.4 Hz, 1H, 10-H), 7.13 (s, 1H, 3-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ= −5.0, −4.4 (Si-CH_3), 14.1 (2-CH_3), 14.3 ($CO_2CH_2CH_3$), 16.3 (8-CH_3), 17.2 (6-CH_3), 18.2 (Si-$C(CH_3)_3$), 18.4 (4-CH_3), 25.8 (Si-C(CH_3)$_3$), 39.6 (C-8), 60.6 ($CO_2CH_2CH_3$), 76.4 (C-9), 79.0 (C-11), 125.9 (C-2), 131.8 (C-6), 132.6 (C-4), 133.6 (C-7), 138.8 (C-5), 143.6 (C-3), 147.8 (C-10), 169.1 (C-1); IR (film): $\tilde{\nu}$=2957 (s), 2929 (s), 2857 (s), 1706 (s), 1463 (ms), 1366 (m), 1251 (s), 1112 (m), 1068 (m), 1033 (m), 949 (m), 836 (s), 776 cm^{-1} (s); HR-MS (EI): *m*/*z*: calcd for $C_{23}H_{40}IO_3Si$: 519.1791; found 519.1799 $[M+H]^+$.

Ethyl (2*E*,4*E*,6*E*,10*E*,12*E*,8*R*,9*R*,16*S*,17*S*,19*S*,20*R*,2′*R*,3′*R*,4′*S*,5′*R*,6′*R*,2″*R*)-19,20-Diacetoxy-9-*tert*-butyldimethylsilyloxy-[4′-*tert*-butyldimethylsilyloxy-6′-[[2″-*tert*-butyldimethylsilyloxy-3″-methoxypropyl]]-2′-methoxy-3′,5′-dimethyl-2′,3′,5′,6′-tetrahydro-4*H*-pyran-2′-yl]-16-hydroxy-17-methoxy-2,4,6,8,12-pentamethyl-2,4,6,10,12-eicosapentaenoate (40): Alkenyl stannane **31** (150 mg, 0.141 mmol) and alkenyl iodide **39** (89 mg, 0.17 mmol) were dissolved in degassed *N*-methyl pyrrolidone (5 mL). Cu^I-thiophene-2-carboxylate (66 mg, 0.36 mmol) was added at −10°C and the brown colored reaction mixture was stirred at −10°C for 90 min. MTBE (2 mL) was added and the mixture was filtered over neutral aluminium oxide (7 g). The aluminium oxide was washed with MTBE (20 mL). The combined filtrates were subsequently washed with water (5 mL) and brine (20 mL) and dried with $MgSO_4$. Chromatography (25 g silica gel, cyclohexane/AcOEt 5:1, 0.25% Et_3N) gave the coupling product **40** (133 mg, 0.114 mmol, 81%) as a colorless oil. R_f=0.66 (*n*-hexane/MTBE 1:2); $[\alpha]_D^{23}$=+64.7 (*c*=1.02, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.08, 0.10, 0.126, 0.129, 0.134, 0.161 (6s, 18H, Si-CH_3), 0.98, 1.01, 1.04 (3s, 27H, Si-C(CH_3)$_3$), 1.00–1.05 (m, 3H, OCH_2CH_3), 1.14 (d, *J*=6.7 Hz, 3H, 8-CH_3), 1.20 (d, *J*=7.0 Hz, 3H, 24-CH_3), 1.51 (d, *J*=6.6 Hz, 3H, 22-CH_3), 1.50–1.58 (m, 2H, 15-H_2), 1.63 (ddd, *J*=14.4, 8.1, 3.1 Hz, 1H, 26-H_2), 1.67 (d, *J*=1.0 Hz, 3H, 6-CH_3), 1.75 (s, 3H, 12-CH_3), 1.79, 1.80 (2s, 6H, OAc), 1.87–1.95 (m, 3H, 18-H_2, 24-H, 26-H_2), 1.92 (d, *J*=1.1 Hz, 3H, 4-CH_3), 2.14 (d, *J*=1.4 Hz, 3H, 2-CH_3), 2.20–2.27 (m, 1H, 14-H_2), 2.27–2.33 (m, 2H, 18-H_2, 22-H), 2.36–2.43 (m, 1H, 14-H_2), 2.65–2.72 (m, 1H, 8-H), 3.11–3.16 (m, 1H, 17-H), 3.12 (s, 3H, 28-OCH_3), 3.22–3.24 (m, 2H, 28-H_2), 3.30, 3.34 (2s, 6H, 17-OCH_3, 21-OCH_3), 3.48–3.53 (m, 1H, 16-H), 4.05–4.15 (m, 5H, 9-H, 23-H, 27-H, OCH_2CH_3), 4.18 (ddd, *J*=8.1, 2.7, 2.7 Hz, 1H, 25-H), 5.40 (d, *J*=9.9 Hz, 1H, 7-H), 5.47 (d, *J*=5.3 Hz, 1H, 20-H), 5.52–5.56 (m, 1H, 13-H), 5.66 (dd, *J*=15.7, 7.2 Hz, 1H, 10-H), 5.79–5.83 (m, 1H, 19-H), 6.03 (s, 1H, 5-H), 6.29 (d, *J*=15.7 Hz, 1H, 11-H), 7.48 (s, 1H, 3-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ= −4.7, −4.6, −4.5, −4.2, −3.7, −3.4 (Si-CH_3), 5.6 (24-CH_3), 11.9 (22-CH_3), 12.6 (12-CH_3), 14.39, 14.42 (2-CH_3, $CO_2CH_2CH_3$), 16.8 (8-CH_3), 17.3 (6-CH_3), 18.36 (Si-$C(CH_3)_3$), 18.42 (4-CH_3), 18.48, 18.53 (Si-C(CH_3)$_3$), 20.5, 20.6 (OAc), 25.4 (C-14), 26.1, 26.15, 26.23 (Si-C(CH_3)$_3$), 33.4 (C-15), 35.1 (C-18), 37.3 (C-22), 39.2 (C-26), 40.5 (C-24), 41.0 (C-8), 48.2 (21-OCH_3), 58.5 (28-OCH_3), 59.2 (17-OCH_3), 60.5 ($CO_2CH_2CH_3$), 69.6 (C-19, C-25), 70.4 (C-27), 72.5 (C-16), 73.3 (C-20), 73.8 (C-23), 78.0 (C-28), 78.5 (C-9), 81.1 (C-17), 101.5 (C-21), 126.4 (C-6), 127.9 (C-12), 129.0 (C-10), 132.0 (C-4), 132.6 (C-13), 133.7 (C-2), 135.2 (C-7), 135.8 (C-11), 139.3 (C-5), 143.8 (C-3), 168.5, 169.4, 169.8 (C-1, OAc); IR (film): $\tilde{\nu}$=2954 (s), 2930 (s), 2894 (s), 2858 (s), 1748 (s), 1706 (m), 1463 (m), 1371 (m), 1251 (s), 1109 (m), 1071 (m), 1030 (m), 835 (s), 775 cm^{-1} (m); HR-MS (FAB): *m*/*z*: calcd for $C_{62}H_{114}O_{14}Si_3$: 1166.7516; found 1166.7524 $[M]^+$.

(2*E*,4*E*,6*E*,10*E*,12*E*,8*R*,9*R*,16*S*,17*S*,19*S*,20*R*,2′*R*,3′*R*,4′*S*,5′*R*,6′*R*,2″*R*)-9-*tert*-Butyldimethylsilyloxy-[4′-*tert*-butyldimethylsilyloxy-6′-[[2″-*tert*-butyldimethylsilyloxy-3″-methoxypropyl]]-2′-methoxy-3′,5′-dimethyl-2′,3′,5′,6′-tetrahydro-4*H*-pyran-2′-yl]-10,19,20-trihydroxy-17-methoxy-2,4,6,8,12-pentamethyl-2,4,6,10,12-eicosapentaenoic acid (41): Ethyl ester **40** (112 mg, 0.096 mmol) and LiOH (24 mg, 0.58 mmol) were stirred in THF/MeOH/H_2O 2:1:1 (4 mL) for 28 h at 40°C. The reaction mixture was partitioned between water (10 mL) and AcOEt (10 mL). The aqueous layer was extracted with AcOEt (2×10 mL). The combined organic layers were washed with brine (20 mL) and dried with $MgSO_4$. Chromatography (10 g silica gel, CH_2Cl_2/MeOH 20:1) gave trihydroxy carboxylic acid **41** (88 mg, 0.083 mmol, 87%) as a colorless oil. R_f=0.30 (CH_2Cl_2/MeOH 20:1); $[\alpha]_D^{23}$=+81 (*c*=0.90, $CHCl_3$); ^{1}H NMR (600 MHz, C_6D_6): δ= −0.08, −0.05, −0.04, −0.02, −0.01 (5s, 18H, Si-CH_3), 0.80, 0.81, 0.82 (3s, 27H, Si-C(CH_3)$_3$), 0.78–0.83 (m, 3H, 24-CH_3), 0.92 (d, *J*=6.8 Hz, 3H, 8-CH_3), 0.96 (d, *J*=6.6 Hz, 3H, 22-CH_3), 1.30–1.41 (m, 2H, 15-H_2, 26-H_2), 1.43–1.52 (m, 1H, 15-H_2), 1.53–1.68 (m, 4H, 18-H_2, 24-H, 26-H_2), 1.66 (s, 6H, 6-CH_3, 12-CH_3), 1.86 (d, *J*=0.9 Hz, 3H, 4-CH_3), 1.89 (d, *J*= 1.1 Hz, 3H, 2-CH_3), 1.91–2.02 (m, 1H, 22-H), 2.06–2.30 (m, 2H, 14-H_2), 2.44–2.58 (m, 1H, 8-H), 3.17 (s, 3H, 21-OCH_3), 3.20–3.32 (m, 3H, 17-H, 28-H_2), 3.22, 3.36 (2s, 6H, 17-OCH_3, 28-OCH_3), 3.42 (d, *J*=2.8 Hz, 1H, 20-H), 3.48–3.56 (m, 1H, 16-H), 3.70 (dd, *J*=10.6, 4.7 Hz, 1H, 23-H), 3.78–3.89 (m, 3H, 19-H, 25-H, 27-H), 3.95 (dd, *J*=6.6, 6.6 Hz, 1H, 9-H), 5.17 (d, *J*=9.6 Hz, 1H, 7-H), 5.37 (dd, *J*=7.9, 7.4 Hz, 1H, 13-H), 5.44 (dd, *J*=15.6, 7.2 Hz, 1H, 10-H), 5.89 (s, 1H, 5-H), 6.07 (d, *J*=15.8 Hz, 1H, 11-H), 7.06 (s, 1H, 3-H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ= −4.54, −4.50, −4.4, −4.0, −3.6, −3.4 (Si-CH_3), 6.1 (C-24), 12.72, 12.74 (C-12, C-22), 14.4 (2-CH_3), 17.0 (8-CH_3), 17.6 (6-CH_3), 18.7 (4-CH_3), 19.0, 19.1, 19.2 (Si-$C(CH_3)_3$), 25.8 (C-14), 26.4, 26.5, 26.6 (Si-C(CH_3)$_3$), 33.2 (C-15), 37.3 (C-22), 37.7 (C-18), 39.9 (C-26), 41.3 (C-24), 41.7 (C-8), 48.2 (21-OCH_3), 59.2, 59.4 (17-OCH_3, 28-OCH_3), 68.3, 69.8, 71.5 (C-19, C-25, C-27), 72.8 (C-16), 75.1 (C-23), 75.6 (C-20), 78.9 (C-28), 79.4 (C-9), 82.5 (C-17), 103.2 (C-21), 129.6 (C-10), 132.88, 132.94, 134.6 (C-2, C-4, C-6), 133.2 (C-13), 136.0 (C-7), 136.8 (C-11), 140.1 (C-5), 145.1 (C-3), 172.6 (C-1); IR (film): $\tilde{\nu}$=3434 (s), 2953 (s), 2930 (s), 2892 (s), 2857 (s), 1681 (s), 1462 (s), 1362 (s), 1257 (s), 1069 (s), 835 (s), 776 cm^{-1} (s); HR-MS (FAB): *m*/*z*: calcd for $C_{56}H_{106}O_{12}Si_3Na$: 1077.6890; found 1077.6876 $[M+Na]^+$.

9,23,27-Tri-*O*-(*tert*-butyldimethylsilyl)-21-*O*-methylapoptolidinone A (42): Et_3N (0.12 mL, 0.83 mmol) was added at 20°C to trihydroxy carboxylic acid **41** (88 mg, 83 μmol) in THF (5 mL). After 5 min 2,4,6-trichlorobenzoic acid chloride (0.13 mL, 0.83 mmol) was added. The reaction mixture was stirred at 20°C for 18 h. It was diluted with toluene (25 mL), transferred into an addition funnel and added dropwise over 6 h to a solution of DMAP (102 mg, 0.834 mmol) in toluene (50 mL) at 80°C. After cooling to 20°C, phosphate buffer (70 mL, 1 M, pH 7) was added. The aqueous layer was extracted with MTBE (3×50 mL). The combined organic layers were washed with brine (100 mL) and dried with $MgSO_4$. Chromatography (30 g silica gel, PE/MTBE 4:1) gave macrolide **42** (64 mg, 62 mmol, 74%) as a colorless oil. R_f=0.57 (*n*-hexane/MTBE 1:1); $[\alpha]_D^{23}$=+46 (*c*=0.60, $CHCl_3$); ^{1}H NMR (600 MHz, C_6D_6): δ=0.07, 0.15, 0.16, 0.17, 0.18 (5s, 18H, Si-CH_3), 0.99, 1.02, 1.05 (3s, 27H, Si-C(CH_3)$_3$), 1.19 (d, *J*=6.7 Hz, 3H, 8-CH_3), 1.27 (d, *J*=6.9 Hz, 3H, 24-CH_3), 1.41–1.48 (m, 2H, 15-H_2), 1.50 (d, *J*=6.7 Hz, 3H, 22-CH_3), 1.55 (s, 3H, 12-CH_3), 1.62–1.66 (m, 1H, 26-H_2), 1.67 (d, *J*=1.0 Hz, 3H, 6-CH_3), 1.84 (s, 3H, 4-CH_3), 1.88–1.95 (m, 2H, 24-H, 26-H_2), 2.05–2.10 (m, 1H, 14-H_2), 2.14 (s, 3H, 2-CH_3), 2.16 (brs, 1H, 16-OH), 2.22–2.32 (m, 3H, 18-H_2, 22-H), 2.39–2.42 (m, 1H, 20-OH), 2.47–2.54 (m, 1H, 14-H_2), 2.55–2.61 (m, 1H, 8-H), 3.02–3.06 (m, 1H, 17-H), 3.06 (s, 3H, 28-OCH_3), 3.16–3.22 (m, 2H, 28-H_2), 3.28 (s, 3H, 21-OCH_3), 3.38 (s, 3H, 17-OCH_3), 3.48–3.53 (m, 1H, 16-H), 3.81 (dd, *J*=8.5, 8.3 Hz, 1H, 9-H), 3.89 (dd, *J*=4.9, 4.6 Hz, 1H, 20-H), 4.10–4.15 (m, 2H, 23-H, 27-H), 4.18–4.21 (m, 1H, 25-H), 5.05 (d, *J*=9.8 Hz, 1H, 7-H), 5.35 (dd, *J*=15.6, 8.6 Hz, 1H, 10-H), 5.53 (dd, *J*=10.0, 5.8 Hz, 1H, 13-H), 5.92–5.95 (m, 1H, 19-H), 5.95 (d, *J*=15.8 Hz, 1H, 11-H), 6.20 (s, 1H, 5H), 7.55 (s, 1H, 3-H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ= −4.7, −4.6, −4.5, −4.2, −3.5, −3.4 (Si-CH_3), 5.8 (24-CH_3), 11.8, 11.9 (12-CH_3, 22-CH_3), 14.2 (2-CH_3), 16.2 (6-CH_3), 17.4 (4-CH_3), 18.1 (8-CH_3), 18.3, 18.4, 18.6 (Si-$C(CH_3)_3$), 25.0 (C-14), 26.1, 26.2, 26.3 (Si-C(CH_3)$_3$), 34.9 (C-15), 37.1 (C-22), 38.3 (C-18), 39.2 (C-26),

40.6, 40.8 (C-8, C-24), 47.9 (21-OCH_3), 58.5 (28-OCH_3), 60.3 (17-OCH_3), 69.5 (C-25), 70.7, 73.5 (C-23, C-27), 72.0 (C-19), 74.2 (C-16), 75.9 (C-20), 78.0 (C-28), 81.3 (C-9), 82.3 (C-17), 102.1 (C-21), 124.1, 131.9, 132.1, 133.4 (C-2, C-4, C-6, C-12), 129.1 (C-10), 132.8 (C-13), 136.7 (C-11), 141.5 (C-7), 145.0 (C-5), 145.9 (C-3), 169.7 (C-1); IR (film): $\tilde{\nu}=3103$ (s), 2929 (s), 2856 (s), 1699 (m), 1401 (s), 1257 (m), 1074 (m), 835 (m), 776 (m), 741 cm^{-1} (s); HR-MS (FAB): m/z: calcd for $C_{56}H_{104}O_{11}Si_3$: 1036.6887; found 1036.6910 $[M]^+$.

Apoptolidinone A (4): Trisilyl ether **42** (11 mg, 11 μmol) was dissolved at 0 °C in THF (0.6 mL) in a polypropylene flask. HF·py (60 μL, 2.1 mmol) was added and the reaction mixture was stirred for 8 h at 0 °C. Further HF·py (60 μL, 2.1 mmol) was added and the reaction mixture was stirred at 20 °C for 15 h. After cooling to 0 °C, HF·py (80 μL, 2.8 mmol) was added and the reaction mixture was stirred for 9 h. $NaHCO_3$ (3 mL) and AcOEt (3 mL) were added. The aqueous layer was extracted with AcOEt (3×3 mL). The combined organic layers were washed with brine (8 mL) and dried with $MgSO_4$. Chromatography (2 g silica gel, CH_2Cl_2/MeOH 15:1) gave apoptolidinone A (**4**) (4 mg, 6 μmol, 55 %) as a colorless solid. $R_f=0.09$ (CH_2Cl_2/MeOH 15:1); $[\alpha]_D^{23}=+70$ ($c=0.3$, MeOH); ^1H NMR (600 MHz, CD_3OD): $\delta=0.88$ (d, $J=6.7$ Hz, 3H, 24-CH_3), 1.02 (d, $J=6.7$ Hz, 3H, 22-CH_3), 1.13 (d, $J=6.3$ Hz, 3H, 8-CH_3), 1.26–1.32 (m, 1H, 26-H_2), 1.37–1.44 (m, 1H, 15-H_2), 1.51–1.60 (m, 2H, 15-H_2, 26-H_2), 1.67 (s, 3H, 12-CH_3), 1.72–1.78 (m, 2H, 18-H_2, 24-H), 1.92 (s, 3H, 6-CH_3), 2.02–2.09 (m, 2H, 14-H_2, 22-H), 2.11 (s, 3H, 2-CH_3), 2.13–2.18 (m, 1H, 18-H_2), 2.19 (s, 3H, 4-CH_3), 2.41–2.52 (m, 2H, 8-H, 14-H_2), 2.73 (dd, $J=9.9$, 4.4 Hz, 1H, 17-H), 3.15–3.23 (m, 2H, 28-H_2), 3.30 (s, 3H, 28-OCH_3), 3.36 (s, 3H, 17-OCH_3), 3.42–3.45 (m, 1H, 16-H), 3.53–3.58 (m, 2H, 20-H, 27-H), 3.73–3.79 (m, 2H, 9-H, 23-H), 4.09 (ddd, $J=8.5$, 2.8, 2.5 Hz, 1H, 25-H), 5.22 (d, $J=10.2$ Hz, 1H, 7-H), 5.29–5.32 (m, 1H, 19-H), 5.33 (dd, $J=15.4$, 8.8 Hz, 1H, 10-H), 5.64 (dd, $J=9.3$, 6.9 Hz, 1H, 13-H), 6.10 (d, $J=15.7$ Hz, 1H, 11-H), 6.19 (s, 1H, 5-H), 7.37 (s, 1H, 3-H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta=5.3$ (24-CH_3), 12.1, 12.2 (12-CH_3, 22-CH_3), 14.0 (2-CH_3), 16.4 (6-CH_3), 17.7, 17.8 (4-CH_3, 8-CH_3), 24.5 (C-14), 36.4 (C-22), 36.6 (C-15), 38.4 (C-26), 38.6 (C-18), 40.8, 41.0 (C-8, C-24), 59.4 (28-OCH_3), 61.4 (17-OCH_3), 68.1 (C-27), 69.2 (C-25), 72.3 (C-19), 73.7 (C-23), 74.6 (C-16), 75.5 (C-20), 78.6 (C-28), 80.6 (C-9), 83.8 (C-17), 101.3 (C-21), 123.8, 133.0, 133.1, 134.9 (C-2, C-4, C-6, C-12), 129.6 (C-10), 132.6 (C-13), 137.7 (C-11), 143.6 (C-7), 147.3 (C-5), 149.1 (C-3), 172.6 (C-1); IR (film): $\tilde{\nu}=3414$ (s), 2927 (s), 1667 (s), 1458 (m), 1256 (s), 1092 (s), 1020 (s), 732 (s), 669 cm^{-1} (s); HR-MS (FAB): m/z: calcd for $C_{37}H_{60}O_{11}Na$: 703.4033; found 703.4029 $[M+Na]^+$.

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[1] P. T. Daniel, U. Koert, J. Schuppan, *Angew. Chem.* **2006**, *118*, 886–908; *Angew. Chem. Int. Ed.* **2006**, *45*, 872–893.
[2] J. W. Kim, H. Adachi, K. Shin-ya, Y. Hayakawa, H. Seto, *J. Antibiot.* **1997**, *50*, 628–630.
[3] Y. Hayakawa, J. W. Kim, H. Adachi, K. Shin-ya, K. Fujita, H. Seto, *J. Am. Chem. Soc.* **1998**, *120*, 3524–3525.
[4] a) A. R. Salomon, D. W. Voehringer, L. A. Herzenberg, C. Khosla, *Proc. Natl. Acad. Sci. USA* **2000**, *97*, 14766–14771; b) A. R. Salomon, D. W. Voehringer, L. A. Herzenberg, C. Khosla, *Chem. Biol.* **2001**, *8*, 71–80; c) A. R. Salomon, Y. Zhang, H. Seto, C. Khosla, *Org. Lett.* **2001**, *3*, 57–59.
[5] a) P. A. Wender, A. V. Gulledge, O. D. Jankowski, H. Seto, *Org. Lett.* **2002**, *4*, 3819–3822; b) P. A. Wender, O. D. Jankowski, E. A. Tabet, H. Seto, *Org. Lett.* **2003**, *5*, 487–490.
[6] P. A. Wender, M. Sukopp, K. Longcore, *Org. Lett.* **2005**, *7*, 3025–3028.
[7] a) K. C. Nicolaou, Y. Li, K. C. Fylaktakidou, H. J. Mitchell, H. X. Wei, B. Weyershausen, *Angew. Chem.* **2001**, *113*, 3968–3972; *Angew. Chem. Int. Ed.* **2001**, *40*, 3849–3854; b) K. C. Nicolaou, Y. Li, K. C. Fylaktakidou, H. J. Mitchell, K. Sugita, *Angew. Chem.* **2001**, *113*, 3972–3976; *Angew. Chem. Int. Ed.* **2001**, *40*, 3854–3857; c) K. C. Nicolaou, K. C. Fylaktakidou, H. Monenschein, Y. Li, B. Weyershausen, H. J. Mitchell, H. X. Wei, P. Guntupalli, D. Hepworth, K. Sugita, *J. Am. Chem. Soc.* **2003**, *125*, 15433–15442; d) K. C. Nicolaou, Y. Li, K. Sugita, H. Monenschein, P. Guntupalli, H. J. Mitchell, K. C. Fylaktakidou, D. Vourloumis, P. Giannakakou, A. O'Brate, *J. Am. Chem. Soc.* **2003**, *125*, 15443–15454.
[8] H. Wehlan, M. Dauber, M. T. Mujica Fernaud, J. Schuppan, M. E. Juarez Garcia, R. Mahrwald, U. Koert, *Angew. Chem.* **2004**, *116*, 4698–4702; *Angew. Chem. Int. Ed.* **2004**, *43*, 4597–4601.
[9] J. Schuppan, H. Wehlan, S. Keiper, U. Koert, *Angew. Chem.* **2001**, *113*, 2125–2128; *Angew. Chem. Int. Ed.* **2001**, *40*, 2063–2066.
[10] B. Wu, Q. Liu, G. A. Sulikowski, *Angew. Chem.* **2004**, *116*, 6841–6843; *Angew. Chem. Int. Ed.* **2004**, *43*, 6673–6675.
[11] M. T. Crimmins, H. S. Christie, K. Chaudhary, A. Long, *J. Am. Chem. Soc.* **2005**, *127*, 13810–13812.
[12] a) J. Schuppan, B. Ziemer, U. Koert, *Tetrahedron Lett.* **2000**, *41*, 621–624; b) K. C. Nicolaou, Y. Li, B. Weyershausen, H.-X. Wei, *Chem. Commun.* **2000**, 307–308; c) G. A. Sulikowski, W.-M. Lee, B. Jin, B. Wu, *Org. Lett.* **2000**, *2*, 1439–1442; d) K. Toshima, T. Arita, K. Kato, D. Tanaka, S. Matsumura, *Tetrahedron Lett.* **2001**, *42*, 8873–8876; e) Y. Chen, J. B. Evarts, E. Torres, P. L. Fuchs, *Org. Lett.* **2002**, *4*, 3571–3574; f) J. D. Pennington, H. J. Williams, A. R. Salomon, G. A. Sulikowski, *Org. Lett.* **2002**, *4*, 3823–3825; g) K. Abe, K. Kato, T. Arai, M. A. Rahim, I. Sultana, S. Matsumura, K. Toshima, *Tetrahedron Lett.* **2004**, *45*, 8849–8853; h) W. D. Paquette, R. E. Taylor, *Org. Lett.* **2004**, *6*, 103–106; i) M. T. Crimmins, A. Long, *Org. Lett.* **2005**, *7*, 4157–4160; j) B. Jin, Q. Liu, G. A. Sulikowski, *Tetrahedron*, **2005**, *61*, 401–408.
[13] H. Wehlan, M. Dauber, M. T. M. Fernaud, J. Schuppan, S. Keiper, R. Mahrwald, M.-E. J. Garcia, U. Koert, *Chem. Eur. J.* **2006**, *12*, 7378–7397.
[14] a) M. Kitamura, M. Tokunaga, T. Ohkuma, R. Noyori, *Org. Synth.* **1993**, *71*, 1–13; b) M. J. Burk, T. G. P. Harper, C. S. Kalberg, *J. Am. Chem. Soc.* **1995**, *117*, 4423–4424.
[15] a) D. A. Evans, J. S. Clark, R. Metternich, V. J. Novack, G. S. Sheppard, *J. Am. Chem. Soc.* **1990**, *112*, 866–868; b) D. A. Evans, A. S. Kim, R. Metternich, V. J. Novack, *J. Am. Chem. Soc.* **1998**, *120*, 5921–5942.
[16] D. A. Evans, H. P. Ng, J. S. Clark, D. L. Rieger, *Tetrahedron* **1992**, *48*, 2127–2142.
[17] a) D. A. Evans, K. T. Chapman, E. M. Carreira, *J. Am. Chem. Soc.* **1988**, *110*, 3560–3578; b) D. A. Evans, A. H. Hoveyda, *J. Am. Chem. Soc.* **1990**, *112*, 6447–6449.
[18] a) A. Basha, M. Liptom, S. M. Weinreb, *Tetrahedron Lett.* **1977**, 4171–4174; b) S. Nahm, S. M. Weinreb, *Tetrahedron Lett.* **1981**, *22*, 2815–3818.
[19] D. A. Evans, S. K. Bender, J. Morris, *J. Am. Chem. Soc.* **1988**, *110*, 2506–2526.
[20] H. Kolb, K. B. Sharpless in *Transition Metals for Organic Synthesis* (Eds.: M. Beller, C. Bolm), Wiley-VCH, Weinheim, 2nd ed., **2004**, pp. 275–298.
[21] B. Tse, *J. Am. Chem. Soc.* **1996**, *118*, 7094–7100.
[22] J. Mulzer, K. D. Graske, B. Kirste, *Liebigs Ann. Chem.* **1988**, 891–897.
[23] B. H. Lipshutz, R. Keil, E. L. Ellsworth, *Tetrahedron Lett.* **1990**, *31*, 7257–7260.
[24] V. Fargeas, P. LeMenez, I. Berque, J. Ardisson, A. Pancrazi, *Tetrahedron* **1996**, *52*, 6613–6634.
[25] P. Kocienski, C. Barber, *Pure Appl. Chem.* **1990**, *62*, 1933–1940.
[26] M. T. Reetz, *Angew. Chem.* **1984**, *96*, 542–555; *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 556–569.
[27] A. R. Chamberlin, M. Dezube, *Tetrahedron Lett.* **1982**, *23*, 3055–3058.
[28] K. Takai, K. Nitta, K. Utimoto, *J. Am. Chem. Soc.* **1986**, *108*, 7408–7410.
[29] E. J. Corey, P. L. Fuchs, *Tetrahedron Lett.* **1972**, 3769–3772.

[30] H. X. Zhang, F. Guibe, G. Balavoine, *J. Org. Chem.* **1990**, *55*, 1857–1867.
[31] a) J. K. Stille, *Angew. Chem.* **1986**, *98*, 504–519; *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 508–523; b) T. N. Mitchell, *Synthesis* **1992**, 803–815.
[32] G. D. Allred, L. S. Liebeskind, *J. Am. Chem. Soc.* **1996**, *118*, 2748–2749.
[33] M. Hikota, H. Tone, K. Horita, O. Yonemitsu, *J. Org. Chem.* **1990**, *55*, 7–9.

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