

Stereoselective Synthesis of the Monomeric Unit of SCH 351448

J. René Backes^[a] and Ulrich Koert^{*[a]}

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The monomeric unit of the macrodiolide SCH 351448 has been synthesized from three building blocks. Strategic disconnections were chosen between C21–C22 (Wittig) and C10–C11 (stereoselective aldol). The *cis* configuration of both

2,6-disubstituted tetrahydropyran rings was established by a stereoselective cationic reduction.

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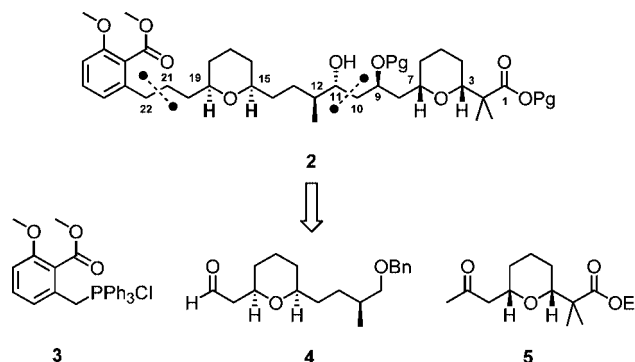
Introduction

The macrodiolide SCH 351448, which was isolated in 2000 from a *Micromonospora* sp.,^[1] received interest because of its ability to activate transcription of the low-den-

sity lipoprotein (LDL) receptor promoter (Figure 1, A). Its ionophoric properties are revealed by the X-ray-structure of the mono sodium salt (Figure 1, B). The bioactivity of SCH 351448 brought the compound into the synthetic focus resulting in the total syntheses of Lee,^[2] De Brabander,^[3] and Leighton.^[4] Here, we report our results on an efficient, stereoselective synthesis of the monomeric unit of SCH 351448.

Results and Discussion

The methyl ester **2**, which was chosen as a synthetic equivalent for the seco acid, could be assembled from three building blocks: the phosphonium salt **3**,^[5] the aldehyde **4**, and the ketone **5** (Scheme 1). First, a Wittig reaction between **3** and **4** was devised for the formation of the C21–C22 bond. Thereafter, a stereoselective aldol reaction could be used for the formation of the C10–C11 bond. Both building blocks **4** and **5** share a *cis*-2,6-disubstituted tetrahydropyran (THP) ring as the common motif.



Scheme 1. Retrosynthetic analysis of the monomeric unit **2**, Pg = protective group.

Starting point for the synthesis of the phosphonium salt **3** was *N,N*-dimethyl-3-methoxy benzylamine (**6**)

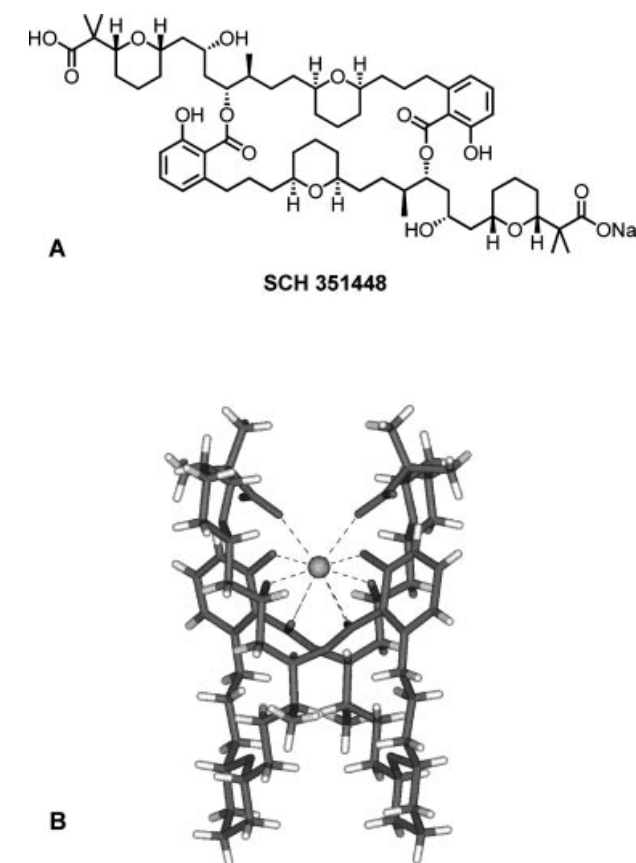
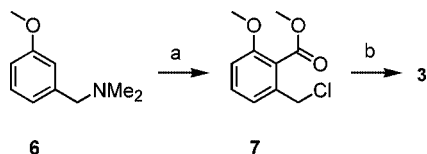


Figure 1. A SCH 351448; B X-ray structure of the mono sodium salt.

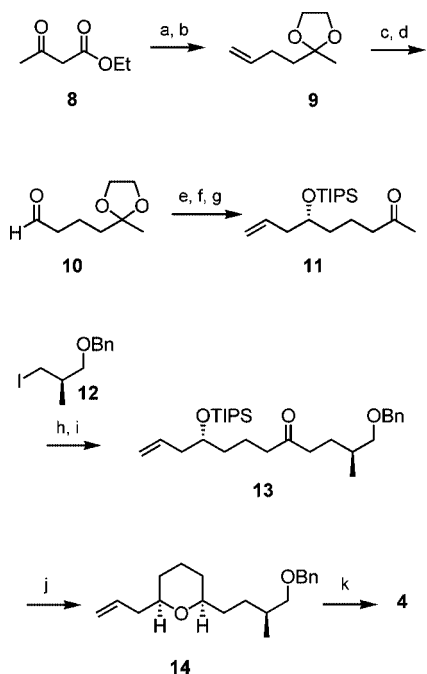
[a] Fachbereich Chemie, Philipps-Universität Marburg, Hans-Meerwein-Strasse, 35032 Marburg
E-mail: koert@chemie.uni-marburg.de

(Scheme 2). Lithiation of **6** and subsequent treatment with an excess of methyl chloroformate gave the benzylchloride **7**,^[5] which was converted into the phosphonium salt **3**.



Scheme 2. a) *n*BuLi, 5.5 equiv. ClCOOMe, CH₂Cl₂, –78 °C, 26%; b) PPh₃, MeCN, reflux, 94%.

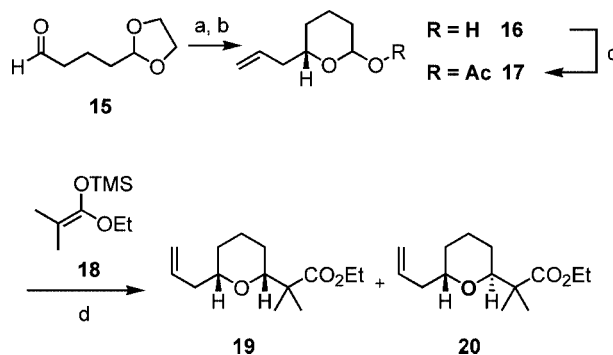
The aldehyde **4** was accessible from acetoacetic acid ester **8** (Scheme 3). Allylation of **8** followed by hydrolysis/decarboxylation and ketalization provided compound **9**.^[6] Hydroboration of the terminal alkene and a subsequent Swern oxidation led to the aldehyde **10**. Asymmetric Brown allylation^[7] of **10** gave the corresponding homoallylic alcohol. Mosher ester analysis exhibited a 88:12 enantioselectivity. After TIPS protection and deketalization the ketone **11** was obtained. The next task was the alkylation of **11** with the iodide **12**.^[8] Initial attempts for the direct alkylation of the ketone (LDA, LHMDs, KHMDS, addition of HMPT) were unsatisfying. Therefore, the way over the corresponding dimethyl hydrazone was chosen, which gave the desired product **13** in 88% overall yield. Treatment of **13** with Et₃SiH, BF₃·OEt₂ resulted in the cleavage of the TIPS ether followed by a *cis*-selective reduction of the hemiketal intermediate to yield the 2,6-disubstituted THP **14**. The relative



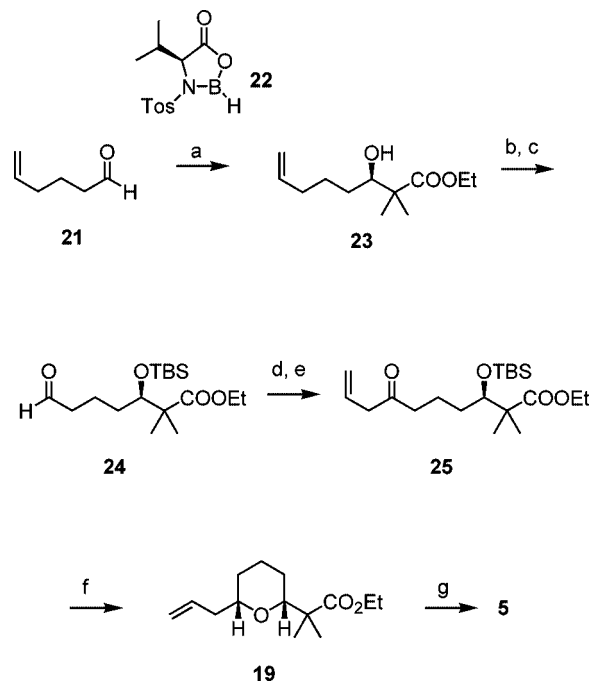
Scheme 3. a) i: NaOEt, AllBr; ii: NaOH, reflux; iii: HCl 56%; b) HO(CH₂)₂OH, *p*TosOH, THF, reflux, 68%; c) BH₃·THF, 0 °C, THF, H₂O₂/NaOH, 92%; d) (COCl)₂, DMSO, NEt₃, CH₂Cl₂, –78 °C, 90%; e) (–)-Ipc₂Ball, Et₂O, H₂O₂/NaOH, –78 °C, 92%; f) TIPSOTf, 2,6-lutidine, CH₂Cl₂, 98%; g) acetone, *p*TosOH, reflux, 87%; h) Me₂N-NH₂, TMSCl, 0 °C, 94%; i) LDA, HMPT, THF, **12**, –78 °C; Amberlyst 50, 20 °C, 94%; j) BF₃·OEt₂, HSiEt₃, MeCN, –35 °C, 93%; k) O₃, CH₂Cl₂, –78 °C, PPh₃, 86%.

configuration of **14** was assigned by NMR based on a H₂–H₆ NOE contact. Ozonolysis of the terminal double bond in **14** gave the aldehyde **4**.

The synthesis of the third building block **5** required the introduction of a geminal dimethyl group adjacent to the THP ring. Our first synthetic route towards **5** is summarized in Scheme 4. Allylation of the aldehyde **15**^[9] gave after acetal cleavage the lactol **16** and subsequently the acetate **17** (Scheme 4). The Lewis acid mediated addition of the TMS-ketene acetal **18**^[10] led to a mixture of the two diastereomers **19/20** (*cis/trans*), which could be separated by chromatography. With BF₃·OEt₂ and TMSOTf the undesired *trans* compound **20** was the main isomer obtained. The relative configurations of **19** and **20** were assigned by NMR based NOE contacts.



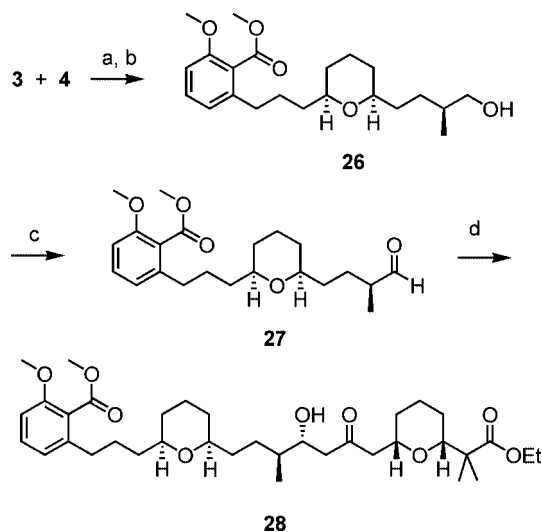
Scheme 4. a) (–)-Ipc₂Ball, Et₂O, –78 °C, then NaOH/H₂O₂, 94%; b) 2 *N* HCl/THF, 30 °C, 86%; c) KHMDS, Ac₂O, THF, –78 °C → 20 °C, 73%; d) **18**, BF₃·OEt₂, TMSOTf, CH₂Cl₂, Et₂O, THF, 30–89%.



Scheme 5. a) **18**, CH₂Cl₂, –78 °C, 75%; b) TBSOTf, 2,6-lutidine, CH₂Cl₂, 0 °C, 99%; c) O₃, CH₂Cl₂, –78 °C, PPh₃, 82%; d) AllBpinacol, THF, 0 °C, e) Dess–Martin periodinane, pyridine, CH₂Cl₂, 0 °C → 20 °C, 72%; f) HSiEt₃, BF₃·OEt₂, MeCN, –35 °C, 98%; g) PdCl₂, CuCl, O₂, DMF/H₂O, 20 °C, 89%.

The lack of stereoselectivity in the addition of the ketene acetal **18** to the acetate **17** led to development of an improved second synthetic route for compound **5** (Scheme 5). This time, the introduction of the first stereocenter was achieved by an asymmetric aldol reaction of the aldehyde **21**^[11] and the ketene acetal **18**. Using the oxazaborolidinone **22**^[12] as chiral promoter the product **23** was obtained in 75% yield. NMR-analysis of the corresponding Mosher ester showed an enantioselectivity of > 95:5. Compound **23** was converted via TBS-protection and subsequent ozonolysis into the aldehyde **24**. The latter was allowed to react with 2-allyl-4,4,5,5-tetramethyl-1,3-dioxane-2-borolane to yield the corresponding homoallylic alcohol which was oxidized following the Dess–Martin protocol to the ketone **25**. A *cis* selective cationic reduction of **25** with Et₃SiH and BF₃·OEt₂ gave the 2,6-disubstituted THP **19** in 98% yield as the exclusive stereoisomer. The Wacker oxidation of **19** led to the desired methyl ketone **5** in 89% yield.

Having all three building blocks at hand, we addressed their assembly into the target compound (Scheme 6). First, the Wittig reaction of the phosphonium salt **3** with the aldehyde **4** was used for the formation C21–C22 bond. The subsequent hydrogenation of the double bond and the simultaneous hydrogenolysis of the benzyl ether gave the alcohol **26** in 83% yield from **4**. A Dess–Martin oxidation of **26** produced the aldehyde **27**. The following boron mediated

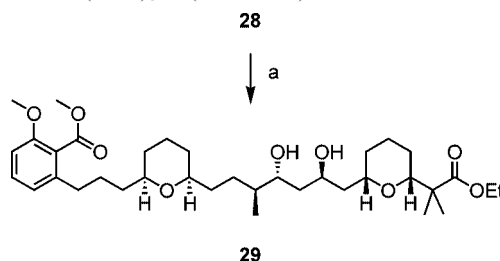


Scheme 6. a) LiHMDS, THF, –78 °C, 84%; b) H₂, Pd(OH)₂/C, MeOH, 99%; c) Dess–Martin periodinane, pyridine, CH₂Cl₂, 0 °C → 20 °C, 84%; d) **5**, NEt₃, Bu₂BOTf, then **27**, Et₂O, 55%.

stereoselective aldol reaction with the methyl ketone **5** proceeded with a 1,5-induction from the ketone and an *anti*-Felkin mode with respect to the aldehyde.^[13] Using Et₃N as a base only the stereoisomer **28** was obtained in 55% yield.

The stereochemical assignment of the *anti*-Felkin configuration in **28** was possible according to the NMR-analysis of Roush et al.^[14] Table 1 shows representative chemical shifts and coupling constants for γ -methyl- β -hydroxy ketones. The experimental data for **28** are $J(\text{H}_\alpha\text{H}_\beta) = 9.5$ Hz and $J(\text{H}_\alpha\text{H}_\beta) < 2.5$ Hz and thus indicate the *anti*-Felkin configuration.

The final step of the synthesis was the stereoselective reduction of the β -hydroxy ketone **28** to the *anti*-1,3-diol **29** using NMe₄B(OAc)₃H (Scheme 7).^[15]



Scheme 7. a) Me₄NB(OAc)₃H, AcOH, Me₂CO, 20 °C, 85%.

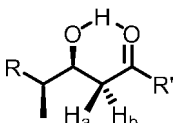
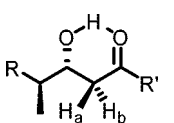
Conclusions

An efficient, stereoselective synthesis of the monomeric unit of the macrodiolide SCH 351448 has been achieved. A modular strategy was applied with three building blocks **3**, **4** and **5** and disconnections between C21–C22 (Wittig) and C10–C11 (stereoselective aldol). The *cis*-2,6-disubstituted tetrahydropyran rings were synthesized by a stereoselective cationic reduction. This work paves the way for a total synthesis of the natural product provided that a protective group differentiation between OH(C9) and OH(C11) will be possible. Derivatives of SCH 351448 with interesting effects on blood-cholesterol level should also be accessible.

Experimental Section

General: All reactions sensitive to air or moisture were conducted in flame-dried glassware under an atmosphere of dry Argon. THF and Et₂O were distilled from sodium benzophenone. CH₂Cl₂, toluene, hexanes, pyridine, and Et₃N were distilled from CaH₂. All starting materials and reagents were used as received unless noted

Table 1. J (H_a/H_b, H_β) in γ -methyl- β -hydroxy ketones from Roush et al.^[14]

					
<i>syn</i> -Felkin	H _a	H _b	<i>anti</i> -Felkin	H _a	H _b
δ [ppm]	2.64–2.88	2.20–2.52	δ [ppm]	2.58–2.84	2.16–2.65
J [Hz] with β -H	7.8–10.0	1.1–5.4	J [Hz] with β -H	1.5–2.8	9.2–12.5

otherwise. Thin layer chromatography was performed on glass-supported Merck silica gel 60 F₂₅₄ 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). The eluent for the preparative separations was chosen according to the TLC eluent. 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 ¹³C-NMR spectra were recorded with Bruker spectrometers ARX-200, AC-300, AV-300, AMX-400, DRX-400, DRX-500, DRX-600. CDCl₃ was used as normal solvent. TMS was used as internal standard. Optical rotations: Perkin-Elmer polarimeter 241, cuvette path length 10 cm, *T* = 22 °C. CHCl₃ for spectroscopy was filtered through basic aluminium oxide before use. Microanalysis: CHN rapid, Heraeus. HRMS: Finnigan LTQ FT (ESI). MTBE = *tert*-butyl methyl ether.

General Procedure 1 (GP1). Ozonolysis: At –78 °C ozone was bubbled through a solution of the olefin (5 g/100 mL) in CH₂Cl₂ until the colour change to blue was observed. After the removal of excess O₃ with O₂, 1 equiv. of solid PPh₃ was added and the reaction was warmed to 20 °C. The solvents were removed and the residue purified by chromatography on silica.

Methyl 2-Chloromethyl-6-methoxybenzoate (7): A solution of *N,N*-dimethyl-3-methoxybenzylamine (15.0 g, 90.8 mmol) at –10 °C was treated with *n*BuLi (49 mL, 2.5 M in hexane, 123 mmol) and stirred for 30 min. At –78 °C, methyl chloroformate (39 mL, 500 mmol) was added. The solution was kept at –78 °C for another 30 min and warmed to 20 °C overnight. Washing of the solution with water (2 × 200 mL), extraction of the aqueous layer with CH₂Cl₂ (2 × 150 mL), drying of the combined organic layers with MgSO₄ and fractional distillation afforded the methyl ester **7** (5.00 g, 23.3 mmol, 26%) as a colourless liquid; b.p. 108–115 °C (1013 mbar); *R*_f = 0.26 (17% MTBE in pentane). ¹H NMR (300 MHz): δ = 3.83 (s, 3 H, OMe), 3.95 (s, 3 H, COOMe), 4.59 (s, 2 H, Bn), 6.91 (d, *J* = 8.4 Hz, 1 H, H5), 7.02 (d, *J* = 7.8 Hz, 1 H, H3), 7.35 (dd, *J* = 8.4, 7.8 Hz, 1 H, H4) ppm. ¹³C NMR (75 MHz): δ = 43.3 (CBn), 52.4 (COMe), 56.1 (CCOOMe), 111.5 (C3), 121.7 (C5), 123.0 (C2), 131.0 (C4), 136.2 (C1), 156.8 (CCOMe), 167.4 (CCOOR) ppm. C₁₀H₁₁ClO₃ (214.65): calcd. C 55.96, H 5.17; found C 55.84, H 5.22.

Phosphonium Chloride 3: A solution of chloride **7** (2.00 g, 9.32 mmol) and triphenylphosphane (2.40 g, 9.32 mmol) in MeCN (15 mL) was refluxed for 72 h. After removal of the solvent the residue was triturated with Et₂O (20 mL) to yield the phosphonium salt **8** (4.20 g, 8.81 mmol, 94%) as a transparent solid. m.p. 211 °C CH₂Cl₂/*n*-hexane; ¹H NMR (500 MHz, ³¹P-decoupled): δ = 3.46 (s, 3 H, OMe), 3.68 (s, 3 H, COOMe), 5.30 (d, *J* = 14.4 Hz, 2 H, Bn), 6.84 (dd, *J* = 8.3, 2.1 Hz, 1 H, HAr), 6.89 (dd, *J* = 7.7, 2.4 Hz, 1 H, HAr), 7.16 (ddd, *J* = 8.3, 7.7, 0.6 Hz, 1 H, HAr), 7.24–7.56 (m, 12 H, PPh₃), 7.68–7.72 (m, 3 H, PPh₃) ppm. ¹³C NMR (125 MHz, ³¹P-decoupled): δ = 28.8, 52.1, 56.3, 112.2, 117.6 (3C), 123.1, 123.8, 128.4, 129.9 (6C), 132.0, 134.1 (6C), 134.9 (3C), 158.4, 167.1 ppm. ³¹P NMR (202 MHz): δ = 22.36 ppm.

2,2-Ethylendioxy-5-hexene (9):^[6] To a solution of acetoacetic acid ester **8** (117 mL, 0.92 mol) in ethanol (300 mL) sodium (17.3 g, 0.76 mol) was added and the resulting solution was cooled to 0 °C. Allylbromide (59 mL, 0.69 mol) was added over 30 min and the solution was stirred for 3 h at 20 °C and 4 h at 60 °C. The suspension was filtered and the solvent removed in vacuo. The residue was dissolved in NaOH (200 mL, 10% aq.) and heated to 60 °C for 3 h. After cooling to 20 °C, the solution was acidified to pH < 3. Extraction of the aqueous layer with Et₂O (3 × 100 mL), washing

of the combined organic layers with NaHCO₃ and brine (100 mL each), drying with MgSO₄ and fractional distillation yielded the corresponding hexenone (37.8 g, 385 mmol, 56%) as a colourless liquid, which was dissolved in toluene (200 mL) and treated with ethylene glycol (25 mL, 462 mmol) and *p*TosOH (1.33 g, 7.7 mmol) and refluxed at a Dean–Stark apparatus. The solution was washed with NaHCO₃ (100 mL) and H₂O (100 mL), dried with MgSO₄ and fractionally distilled to yield the ketal **9** (35.9 g, 253 mmol, 66%) as a colourless liquid. b.p. 75 °C (1013 mbar). ¹H NMR (300 MHz): δ = 1.29 (s, 3 H, HMe), 1.67–1.76 (m, 2 H, HCH₂), 2.09–2.14 (m, 2 H, HCH₂), 3.87–3.95 (m, 4 H, O-CH₂-CH₂-O), 4.91 (dd, *J* = 10.2, 1.5 Hz, 1 H, H₂C=C), 4.99 (dd, *J* = 17.1, 1.5 Hz, 1 H, H₂C=CHR), 5.81 (ddt, *J* = 17.1, 10.2, 6.6 Hz, 1 H, H₂C=CHR) ppm. ¹³C NMR (75 MHz): δ = 23.8, 28.3, 38.2, 64.6 (2C), 109.7, 114.1, 138.4 ppm.

Aldehyde 10. Hydroboration: Olefin **9** (10.0 g, 70.3 mmol) was dissolved in THF (100 mL) at 0 °C and BH₃·THF (23.4 mL, 1 M in THF, 23.4 mmol) was added dropwise. The solution was warmed to 20 °C and stirred for 3 h, whereafter it was cooled to 0 °C and treated with 30% H₂O₂/3 M NaOH (70 mL, 1:3). After vigorous stirring at 20 °C for 1 h the layers were separated and the aqueous layer was extracted with MTBE (5 × 50 mL). The combined organic layers were dried with MgSO₄ and the solvent was removed in vacuo. Purification by silica gel chromatography gave the corresponding alcohol (10.3 g, 64.3 mmol, 91%) as a colourless liquid; b.p. 96 °C (1013 mbar). ¹H NMR (200 MHz): δ = 1.31 (s, 3 H, HMe), 1.40–1.72 (m, 6 H, HAlk), 3.64 (t, *J* = 6.1 Hz, 2 H, CH₂-OH), 3.90–3.97 (m, 4 H, O-C₂H₄-O) (OH not detected) ppm. ¹³C NMR (50 MHz): δ = 20.2 (CMe), 23.7, 32.8, 38.8 (3 × CH₂), 62.8 (CH₂OH), 64.6 (2C, O-C₂H₄-O), 110.0 (C_q) ppm. HRMS (EI) calcd. 160.1094 [M⁺]; found 160.1089. **Swern Oxidation:** To oxalyl chloride (1.53 g, 12.0 mmol) in CH₂Cl₂ (150 mL) at –78 °C was added dropwise DMSO (1.88 g, 24.0 mmol) in CH₂Cl₂ (5 mL). The reaction mixture was stirred for 10 min before the alcohol (1.75 g, 10.9 mmol) in CH₂Cl₂ (5 mL) was added dropwise. After 5 min stirring at –78 °C, Et₃N (5.53 g, 55.0 mmol) was added. 5 min later the solution was warmed to 20 °C. It was poured into H₂O (100 mL). The aqueous layer was extracted with CH₂Cl₂ (3 × 75 mL) and the combined organic layers were washed with brine (100 mL) and dried with MgSO₄. The solvent was removed and the residue purified by chromatography to yield the aldehyde **10** (1.55 g, 9.80 mmol, 90%) as a colourless oil. *R*_f = 0.31 (50% MTBE in hexane); b.p. 68 °C (0.01 mbar). ¹H NMR (200 MHz): δ = 1.27 (s, 3 H, CH₃), 1.56–1.78 (m, 4 H, 2 × CH₂), 2.42 (td, *J* = 6.8, 1.4 Hz, 2 H, CH₂CHO), 3.85–3.96 (m, 4 H, O-C₂H₄-O), 9.71 (t, *J* = 1.4 Hz, 1 H, CHO) ppm. ¹³C NMR (50 MHz): δ = 16.5 (Me), 23.7, 38.2 (2 × CH₂), 43.7 (CH₂CHO), 64.5 (2C, O-C₂H₄-O), 109.5 (C_q), 202.3 (CHO) ppm.

Methyl Ketone 11. Brown Allylation: (–)-Bis(isopinocampheyl)-methoxyborane (4.67 g, 14.7 mmol) in Et₂O 70 mL was cooled to 0 °C and treated with allylmagnesium bromide (7.8 mL, 1.63 M in Et₂O, 12.7 mmol). After stirring for 45 min, the solution was cooled to –78 °C, the solids deposited and the supernatant was transferred through a cannula to aldehyde **10** (1.55 g, 9.77 mmol) in Et₂O (20 mL) at –78 °C. After 1.5 h the solution was warmed to 20 °C and poured into 30% H₂O₂/3 M NaOH (75 mL, 1:2). After 1 h at 20 °C and 3 h at 40 °C the aqueous layer was extracted with MTBE (3 × 50 mL), the combined organic layers were dried with MgSO₄ and the solvents removed in vacuo. Chromatographic purification delivered the homoallyl alcohol (1.80 g, 8.99 mmol, 92%) as a colourless oil. *R*_f = 0.17 (50% MTBE in hexane). ¹H NMR (500 MHz): δ = 1.32 (s, 3 H, CH₃), 1.42–1.71 (m, 7H, 3 × CH₂, OH), 2.15 (dt, *J* = 14.0, 7.9 Hz, 1 H, CH₂-CH=C), 2.30 (dddt, *J* =

14.0, 6.5, 4.3, 1.3 Hz, 1 H, $\text{CH}_2\text{-CH}=\text{C}$), 3.63–3.68 (m, 1 H, CHOH), 3.90–3.97 (m, 4 H, $\text{O-C}_2\text{H}_4\text{-O}$), 5.11–5.15 (m, 2 H, $\text{H}_2\text{C}=\text{CH-}$), 5.78–5.87 (m, 1 H, $\text{H}_2\text{C}=\text{CH-}$) ppm. ^{13}C NMR (125 MHz): δ = 20.2 (CMe), 23.7, 36.9, 39.0 ($\text{C}_3\times\text{CH}_2$), 41.9 ($\text{CCH}_2\text{-CH}=\text{C}$), 64.6 (2C, $\text{O-C}_2\text{H}_4\text{-O}$), 70.6 (CC-O), 110.0 (C_q), 118.1 ($\text{CH}_2=\text{C-}$), 134.8 ($\text{CH}_2=\text{C-}$) ppm. IR: $\tilde{\nu}$ = 3445 (br. s), 3075 (m), 2947 (s), 1641 (m), 1220 (s), 1142 (s), 1065 (br. s) cm^{-1} . $[\alpha]_{\text{D}} = +4.8$, c = 4.04. $\text{C}_{11}\text{H}_{20}\text{O}_3$ (200.27): calcd. C 65.97, H 10.07; found C 65.81, H 10.10. **TIPS-Protection:** TIPSOTf (9.4 mL, 67.4 mmol) was added dropwise to a solution of the alcohol (5.4 g, 27.0 mmol) and 2,6-lutidine (7.2 mL, 67.4 mmol) in CH_2Cl_2 (150 mL) at 0 °C. After stirring for 1 h at 20 °C, the reaction mixture was poured into NH_4Cl (100 mL). The aqueous layer was extracted with MTBE (3 $\times$ 75 mL), the combined organic layers were dried with MgSO_4 evaporated and purified by chromatography to yield the silyl ether ketal (9.40 g, 26.3 mmol, 98%) as a colourless oil. R_f = 0.40 (10% MTBE in hexane). ^1H NMR (300 MHz): δ = 1.06 (br. s, 21 H, TIPS), 1.31 (s, 3 H, CH_3), 1.38–1.54 (m, 4 H, $2\times\text{CH}_2$), 1.57–1.66 (m, 2 H), 2.20–2.35 (m, 2 H, $\text{CH}_2\text{CH}=\text{CH}_2$), 3.82–3.97 (m, 5 H, $\text{O-C}_2\text{H}_4\text{-O}$, R_2CHOR), 5.00–5.08 (m, 2 H, $\text{CH}_2=\text{CH-}$), 5.77 (ddt, J = 17.2, 10.2, 7.1 Hz, 1 H, $\text{CH}_2=\text{CH-}$) ppm. ^{13}C NMR (75 MHz): δ = 12.6 (3C, TIPS), 18.2 (6C, TIPS), 19.5 (Me), 23.7, 36.7, 39.4 ($3\times\text{CH}_2$), 41.3 ($\text{C-CH}=\text{C}$), 64.6 (2C, $\text{O-C}_2\text{H}_4\text{-O}$), 71.9 (CO), 110.1 (C_q), 116.7 ($\text{CH}=\text{CH}_2$), 135.1 ($\text{CH}=\text{CH}_2$) ppm. $[\alpha]_{\text{D}} = +5.25$, c = 2.42 (CHCl_3). HR-MS (ESI) $[\text{C}_{20}\text{H}_{40}\text{SiO}_3 + \text{Na}]^+$ calcd. 357.2819; found 357.2824. **Deketalization:** Silyl ether ketal (2.99 g, 8.37 mmol) and $p\text{TosOH}$ (117 mg) were dissolved in acetone/ H_2O (125 mL, 9:1), and refluxed until TLC control showed complete conversion. After washing with NaHCO_3 (50 mL), the aqueous layer was extracted with MTBE (3 $\times$ 50 mL), the combined organic layers were dried with MgSO_4 and after removal of solvents in vacuo chromatographic purification yielded the ketone **11** (2.27 g, 7.27 mmol, 87%) as a colourless oil. R_f = 0.36 (10% MTBE in hexane). ^1H NMR (400 MHz): δ = 1.06 (br. s, 21 H, TIPS), 1.39–1.54 (m, 2 H, H_4), 1.57–1.68 (m, 2 H, H_5), 2.12 (s, 3 H, H_1), 2.23–2.34 (m, 2 H, H_3), 2.37–2.46 (m, 2 H, H_7), 3.85–3.90 (m, 1 H, H_6), 5.01–5.08 (m, 2 H, H_9), 5.77 (ddt, J = 17.2, 10.2, 7.1 Hz, 1 H, H_8) ppm. ^{13}C NMR (100 MHz): δ = 12.6 (3C, TIPS), 18.2 (6C, TIPS), 19.1 (C_4), 29.7 (C_5), 35.8 (C_1), 41.2 (C_3), 44.0 (C_7), 71.9 (C_6), 116.9 (C_9), 134.8 (C_8), 208.9 ($\text{C}=\text{O}$) ppm. $\text{C}_{18}\text{H}_{36}\text{O}_2\text{Si}$ (312.56): calcd. C 69.17, H 11.61; found C 68.87, H 11.70.

(2S,9R)-1-Benzyloxy-2-methyl-9-triisopropylsiloxy-11-dodecen-5-one (13). Hydrazone Formation: To a solution of ketone **11** (2.48 g, 7.93 mmol) in N,N -dimethylhydrazine (20 mL) at 0 °C was added dropwise chlorotrimethylsilane (1.30 g, 11.9 mmol). The solution was kept at 0 °C for 30 min and not converted hydrazine was volatilised in an argon stream. The residue was dissolved in a small amount of solvent and filtered through a short pad of silica gel to give recovered starting material (213 mg) and hydrazone (2.43 g, 6.84 mmol, 94%). **Alkylation:** To freshly prepared LDA (5.70 mmol) in THF (20 mL) at –78 °C was added the hydrazone (2.04 g, 5.70 mmol) in THF (5 mL) over 5 min. The solution was kept at –78 °C for 45 min and treated successively with HMPT (2.04 g, 11.4 mmol) in THF (5 mL) and iodide **12** in THF (5 mL). The solution was kept at –78 °C for additional 15 min and then allowed to reach 20 °C during 3 h. The reaction mixture was poured into NH_4Cl (45 mL). The aqueous phase was extracted with MTBE (3 $\times$ 30 mL), the combined organic layers dried with MgSO_4 and the solvents removed in vacuo. **Hydrazone Cleavage:** The residue was dissolved in acetone (30 mL). Amberlyst 15 (1.00 g) was added and the suspension was vigorously stirred for 1 h. The filtrate was concentrated and purified by chromatography to give ketone **13** (2.68 g, 5.64 mmol, 94%) as a colourless oil. R_f

= 0.50 (10% MTBE in hexane). ^1H NMR (400 MHz): δ = 0.92 (d, J = 6.6 Hz, 3 H, CH_3), 1.06 (br. s, 21 H, TIPS), br. 1.38–1.53 (m, 3 H, $2\times\text{H}_8$, H_3), 1.57–1.65 (m, 2 H, H_7), 1.68–1.81 (m, 2 H, H_3 , H_2), 2.22–2.30 (m, 2 H, H_{10}), 2.32–2.48 (m, 4 H, H_6 , H_4), 3.25–3.33 (m, 2 H, H_{11}), 3.87 (quint, J = 5.4 Hz, 1 H, H_9), 4.49 (s, 2 H, OBn), 5.01–5.08 (m, 2 H, H_{12}), 5.82 (ddt, J = 17.2, 10.2, 7.1 Hz, 1 H, H_{11}), 7.25–7.37 (m, 5 H, Bn) ppm. ^{13}C NMR (100 MHz): δ = 12.6 (3C, TIPS), 17.0 (CH_3), 18.2 (6C, TIPS), 19.2 (C_7), 27.7 (C_3), 33.1 (C_2), 35.9 (C_8), 40.3 (C_4), 41.2 (C_{10}), 42.9 (C_6), 71.7 (C_9), 73.0 (Bn), 75.6 (C_1), 116.8 (C_{12}), 127.5 (C_{ar}H), 127.5 (2C, C_{ar}), 128.3 (2C, C_{ar}), 134.9 ($\text{C}_{ar,q}$), 139.0 (C_{11}), 211.1 ($\text{C}=\text{O}$) ppm. IR: $\tilde{\nu}$ = 3071 (w), 3030 (w), 2942 (s), 2866 (s), 1715 (s), 1641 (w), 1460 (s), 1103 (s), 1063 (s), 998 (m) cm^{-1} . $[\alpha]_{\text{D}} = +0.70$, c = 2.00 (CHCl_3). $\text{C}_{29}\text{H}_{50}\text{O}_3\text{Si}$ (474.79): calcd. C 70.36, H 10.61; found C 70.31, H 10.61.

(2R,6S,3'S)-2-Allyl-6-(4-benzyloxy-3-methylbutyl)tetrahydropyran (14) *cis*-THP Ether (14): Triethylsilane (2.57 g, 22.09 mmol) and dodecenone **13** (2.62 g, 5.52 mmol) were dissolved in MeCN (40 mL) at –35 °C. Boron trifluoride–diethyl ether (1.57 g, 11.05 mmol) was added. The solution was warmed to 25 °C and poured into water (40 mL). The aqueous layer was extracted with MTBE and (3 $\times$ 40 mL) and the combined organic layers were dried with MgSO_4 . Chromatographic purification gave the *cis* THP **14** (1.55 g, 5.12 mmol, 93%) as a colourless liquid. R_f = 0.63 (10% MTBE in hexane). ^1H NMR (500 MHz): δ = 0.94 (d, J = 6.9 Hz, 3 H, Me), 1.10–1.20 (m, 3 H, H_2' , H_3 , H_5), 1.42–1.51 (m, 3 H, $2\text{H}_1'$, H_4), 1.54–1.60 (m, 3 H, H_2' , H_3 , H_5), 1.74–1.84 (m, 2 H, H_3' , H_4), 2.14 (ddd, J = 14.0, 7.3, 6.4 Hz, 1 H, H_{all}), 2.28 (ddd, J = 14.0, 6.7, 6.6 Hz, 1 H, H_{all}), 3.19–3.25 (m, 1 H, H_6), 3.24 (dd, J = 9.1, 6.8 Hz, 1 H, H_4'), 3.30 (ddt, J = 11.0, 6.4, 1.8 Hz, 1 H, H_2), 3.35 (dd, J = 9.1, 5.8 Hz, 1 H, H_4'), 4.50 (s, 2 H, Bn), 5.01 (d, J = 10.1 Hz, 1 H, H_{all}), 5.06 (d, J = 17.2 Hz, 1 H, H_{all}), 5.85 (dddd, J = 17.2, 10.1, 7.3, 6.7 Hz, 1 H, H_{all}), 7.25–7.35 (m, 5 H, Bn) ppm. ^{13}C NMR (75 MHz): δ = 17.1 (CMe), 23.7 (C_4), 29.5, 31.2 ($\text{C}_3,5$), 31.5 (C_2'), 33.5 (C_3'), 33.9 (C_1'), 41.0 (C_{all}), 72.9 (Bn), 75.9 (C_4'), 77.4 (C_2), 78.3 (C_6), 116.2 (C_{all}), 127.4 (C_{ar}H), 127.5 (2 C_{ar}H), 128.3 (2 C_{ar}H), 135.4 (C_{all}), 138.9 ($\text{C}_{ar,q}$) ppm. IR: $\tilde{\nu}$ = 3069 (m), 3030 (m), 2934 (s), 2852 (s), 1641 (w), 1455 (m), 1368 (m), 1199 (m), 1087 (s), 911 (m), 736 (s), 697 (s) cm^{-1} . $\text{C}_{20}\text{H}_{30}\text{O}_2$ (302.45): calcd. C 79.42, H 10.00; found C 79.36, H 10.01. HR-MS (ESI) $[\text{C}_{20}\text{H}_{30}\text{O}_2 + \text{Na}]^+$ calcd. 325.2144; found 325.2142.

THP-Aldehyde 4. Ozonolysis: Following GP1 the alkene **14** (530 mg, 1.75 mmol) was converted into aldehyde **4** (458 mg, 1.50 mmol, 86%). R_f = 0.30 (10% MTBE in hexane). ^1H NMR (300 MHz): δ = 0.92 (d, J = 6.8 Hz, 3 H, Me) 1.05–1.32 (m, 3 H, H_2' , 3, 5), 1.38–1.63 (m, 6 H, $2\text{H}_1'$, 2', 3–5), 1.69–1.78 (m, 1 H, H_3'), 1.80–1.88 (m, 1 H, H_4), 2.43 (ddd, J = 16.2, 4.6, 2.2 Hz, 1 H, $\text{H}_{1''}$), 2.58 (ddd, J = 16.2, 8.2, 2.7 Hz, 1 H, $\text{H}_{1''}$), 3.22 (dd, J = 9.1, 6.8 Hz, 1 H, H_4'), 3.16–3.34 (m, 1 H, H_2), 3.32 (dd, J = 9.1, 6.0 Hz, 1 H, H_4'), 3.83 (dddd, J = 10.9, 8.2, 4.6, 2.0 Hz, 1 H, H_6), 4.49 (s, 2 H, Bn), 7.09–7.37 (m, 5 H, Ar), 9.79 (dd, J = 2.2, 2.7 Hz, 1 H, CHO) ppm. ^{13}C NMR (125 MHz): δ = 17.1 (Me), 23.5 (C_4), 29.5, 31.1, 31.5 (C_5), 33.4 (C_3'), 33.7, 50.0 ($\text{C}_{1''}$), 72.3 (Bn), 73.1 (C_2), 75.8 (C_2'), 78.5 (C_5), 127.4 (C_{ar}H), 127.5 (2 C_{ar}), 128.3 (2 C_{ar}), 138.8 ($\text{C}_{ar,q}$), 201.8 (CHO) ppm. IR: $\tilde{\nu}$ = 3063 (w), 3030 (w), 2934 (s), 2854 (s), 2724 (m), 1726 (s), 1456 (m), 1370 (m), 1200 (m), 1099 (s), 739 (m), 699 (m) cm^{-1} . $[\alpha]_{\text{D}} = +3.7$, c = 2.00 (CHCl_3). HR-MS (ESI) $[\text{C}_{19}\text{H}_{28}\text{O}_3 + \text{Na}]^+$ calcd. 327.1936; found 327.1934.

(6S)-6-Allyltetrahydropyran-2-ol 16. Allylation: To a solution of (+)-diisopinocampheylmethoxyborane (10.2 g, 31.2 mmol) at 0 °C in Et_2O (140 mL) was added a solution of allylmagnesium bromide (16.7 mL, c = 1.67 M in Et_2O , 27.5 mmol). After 45 min stirring at 0 °C the solution was cooled to –78 °C and aldehyde **15**^[10] (3.00 g,

20.8 mmol) in Et₂O (10 mL) was added dropwise. The reaction was kept at –78 °C for 1.5 h and quenched with a mixture of 30% H₂O₂/3N NaOH (150 mL, 1:2). Stirring for 30 min at 20 °C, extraction of the aqueous layer with Et₂O (3 × 75 mL), drying of the combined organic layers with MgSO₄ and subsequent column chromatography of the crude product delivered the homoallyl alcohol (3.65 g, 19.6 mmol, 94%) as a colourless oil. *R*_f = 0.15 (50% MTBE in hexane). ¹H NMR (200 MHz): δ = 1.43–1.75 (m, 6 H, H4–H6), 2.06–2.38 (m, 2 H, H8), 3.66 (br. s, 1 H, H7), 3.78–4.04 (m, 4 H, O–C₂H₄–O), 4.86 (t, *J* = 4.63 Hz, 1 H, H3), 5.08–5.19 (m, 2 H, H10), 5.82 (dddd, *J* = 17.6, 9.6, 7.9, 6.4 Hz, 1 H, H9) ppm. ¹³C NMR (50 MHz): δ = 20.0, 33.6, 36.4 (C4–C6), 41.8 (C8), 64.7 (C7), 70.4 (2C, O–C₂H₄–O), 104.4 (C3), 117.9 (C10), 134.8 (C9) ppm. [*a*]_D = +0.40, *c* = 1.00 (CHCl₃). HRMS (EI) calcd. 186.1250 [M⁺]; found 186.1209. **Lactol Formation:** The homoallyl alcohol (0.90 g, 4.83 mmol) was dissolved in THF/2 N HCl_{aq} (60 mL, 5:1) and stirred at 30 °C for 8 h. NaHCO₃ (30 mL) was added and the aqueous layer was extracted with MTBE (3 × 30 mL). Drying of the combined organic layers with MgSO₄ and subsequent column chromatography furnished the lactol **16** (590 mg, 41.5 mmol, 86%) as a colourless liquid. *R*_f = 0.40 (50% MTBE in hexane). ¹H NMR (200 MHz): δ = 1.10–2.00 (m, 6 H), 2.10–2.40 (m, 2 H), 3.39 (dtd, *J* = 11.3, 6.2, 1.8 Hz, 1 H, α-ds), 3.63 (br. s, 1 H, β-OH), 3.94 (dtd, *J* = 11.4, 6.3, 1.7 Hz, 1 H, β-ds), 4.35 (br. s, 1 H, α-OH), 4.65 (dd, *J* = 6.4, 4.7 Hz, 1 H, α-ds), 4.99–5.09 (m, 2 H), 5.19–5.30 (m, 1 H, β-ds), 5.67–5.90 (m, 1 H) ppm. ¹³C NMR (75 MHz): δ = 17.7 (β), 22.3 (α), 30.1 (β), 30.3 (α), 31.1 (β), 32.9 (α), 40.3 (α), 40.5 (β), 68.2 (β), 75.8 (α), 91.7 (β), 96.4 (α), 116.7 (β), 116.9 (α), 134.5 (α), 134.7 (β) ppm. IR: ν̄ = 3405 (br. s), 1031 (s), 980 (s), 914 (s) cm^{–1}. [*a*]_D = +24.4, *c* = 3.20 (CHCl₃).

(6*S*)-2-Acetoxy-6-allyltetrahydropyran (17): To the lactol **16** (380 mg, 2.70 mmol) in THF (10 mL) was added at –78 °C KHMDS (559 mg, 3.20 mmol) in THF (10 mL) and after 15 min Ac₂O (0.30 mL, 2.80 mmol). After stirring for 60 min at –78 °C the reaction was warmed to 20 °C and quenched with NH₄Cl (15 mL). The aqueous layer was extracted with Et₂O (3 × 15 mL) and the combined organic layers were dried with Na₂SO₄. Purification by silica gel chromatography yielded the acetate **17** (356 mg, 1.93 mmol, 73%) as a colourless liquid. *R*_f = 0.47 (50% MTBE in hexane). ¹H NMR (500 MHz): δ = 1.15–1.26 (m, 1 H), 1.40–1.61 (m, 3 H), 1.75–1.91 (m, 2 H), 2.08 (s, 3 H), 2.17–2.25 (m, 1 H), 2.33–2.40 (m, 1 H), 3.56 (dtd, *J* = 10.9, 6.7, 2.0 Hz, 1 H), 5.02 (d, *J* = 10.0 Hz, 1 H), 5.06 (d, *J* = 17.1 Hz, 1 H), 5.63 (dd, *J* = 9.5, 2.1 Hz, 1 H), 5.79 (dtd, *J* = 17.1, 10.0, 6.7 Hz, 1 H) ppm. ¹³C NMR (125 MHz): δ = 21.2, 21.5, 29.6, 29.8, 40.1, 76.5, 94.8, 117.0, 134.2, 169.3 ppm.

(2'*S*,6'*R*)-2-(6'-Allyl-2'-tetrahydropyranyl)-2-methylethylpropionate (19): A solution of the acetate **17** in the given solvent at –78 °C was subsequently treated with 2 equiv. of the ketene acetal **18** and 1 equiv. of Lewis acid (Table 2). The reaction was quenched with pH7 buffer and the aqueous layer extracted with Et₂O. Drying of the combined organic layers with MgSO₄ and chromatographic purification led to the *cis* THP **19** and the *trans* THP **20**.

(2'*R*,6'*S*)-2-(6'-Allyl-2'-tetrahydropyranyl)-2-methylethylpropionate (19): *R*_f = 0.64 (10% MTBE in hexane). ¹H NMR (500 MHz): δ = 1.10 (s, 3 H, H2a), 1.13 (dd, *J* = 11.2, 3.9 Hz, 1 H), 1.17 (s, 3 H,

H2b), 1.19–1.30 (m, 1 H), 1.24 (t, *J* = 7.1 Hz, 3 H, OEt), 1.42–1.56 (m, 3 H), 1.82–1.88 (m, 1 H), 2.11 (dt, *J* = 13.9, 6.7 Hz, 1 H, H8), 2.21 (dt, *J* = 13.9, 6.9 Hz, 1 H, H8), 3.31 (dddd, *J* = 11.0, 7.1, 5.4, 1.7 Hz, 1 H, H7), 3.50 (dd, *J* = 11.4, 1.9 Hz, 1 H, H3), 4.09 (dq, *J* = 10.8, 7.1 Hz, 1 H, OEt), 4.14 (dq, *J* = 10.8, 7.1 Hz, 1 H, OEt), 4.97 (dd, *J* = 10.2, 1.5 Hz, 1 H, H10), 5.01 (dd, *J* = 17.2, 1.5 Hz, 1 H, H10), 5.78 (dddd, *J* = 17.2, 10.2, 6.9, 6.7 Hz, 1 H, H9) ppm. ¹³C NMR (125 MHz): δ = 14.2 (OEt), 20.4 (C2a), 21.0 (C2b), 23.6, 25.1, 31.1 (C4–C6), 40.8 (C8), 46.5 (C2), 60.2 (OEt), 77.7 (C7), 82.2 (C3), 115.9 (C10), 135.5 (C9), 177.0 (C1) ppm. [*a*]_D = +5.4, *c* = 2.38 (CHCl₃). C₁₄H₂₄O₃ (240.34): calcd. C 69.96, H 10.07; found C 70.10, H 10.11.

(2'*S*,6'*S*)-2-(6'-Allyl-2'-tetrahydropyranyl)-2-methylethylpropionate (20): *R*_f = 0.62 (10% MTBE in hexane). ¹H NMR (300 MHz): δ = 1.09 (s, 3 H, H2a), 1.15 (s, 3 H, H2b), 1.25 (t, *J* = 7.1 Hz, 3 H, OEt), 1.29–1.38 (m, 1 H), 1.42–1.53 (m, 2 H), 1.61–1.69 (m, 3 H), 2.26 (dt, *J* = 14.2, 7.4 Hz, 1 H, H8), 2.55 (ddd, *J* = 14.2, 7.4, 6.5 Hz, 1 H, H8), 3.77 (dd, *J* = 11.4, 1.8 Hz, 1 H, H3), 3.93–3.99 (m, 1 H, H7), 4.09 (dq, *J* = 10.5, 7.1 Hz, 1 H, OEt), 4.14 (dq, *J* = 10.5, 7.1 Hz, 1 H, OEt), 5.01 (d, *J* = 10.3 Hz, 1 H, H10), 5.05 (d, *J* = 17.2 Hz, 1 H, H10), 5.76 (dddd, *J* = 17.2, 10.3, 7.4, 6.5 Hz, 1 H, H9) ppm. ¹³C NMR (50 MHz): δ = 14.6, 18.8, 20.5, 21.2, 25.8, 27.7, 34.4, 46.8, 60.9, 73.3, 76.8, 116.4, 135.9, 177.1 ppm.

Hydroxy Ester 23: A solution of *N*-Tos-L-valine (25.4 g, 93.7 mmol) in CH₂Cl₂ (250 mL) was treated with borane/THF solution (80 mL, 1 M in THF, 80 mmol). After 30 min at 0 °C and 30 min at 20 °C the solution was cooled to –78 °C. The aldehyde **21** (8.00 g, 81.5 mmol) and subsequently TMS-ketene acetal **18** (16.5 g, 89.7 mmol) were added dropwise. After 30 min pH7 buffer (75 mL) was added. The reaction mixture was vigorously stirred for 15 min and poured into a two-layer system of NaCl (150 mL) and MTBE (75 mL). The layers were separated and the aqueous layer was extracted with MTBE (3 × 100 mL). The combined organic layers were dried with MgSO₄. Chromatographic purification yielded the alcohol **23** (9.12 g, 42.6 mmol, 52%) and its TMS ether (5.33 g, 18.6 mmol, 23%) as colourless liquids. Acidic treatment converted the TMS ether into **23**.

Hydroxy Ester 23: *R*_f = 0.16 (17% MTBE in hexane). ¹H NMR (500 MHz): δ = 1.16 (s, 3 H, H2a), 1.19 (s, 3 H, H2b), 1.27 (t, *J* = 7.1 Hz, 3 H, OEt), 1.27–1.32 (m, 1 H), 1.39–1.50 (m, 2 H), 1.66–1.74 (m, 1 H), 2.02–2.15 (m, 2 H, H6), 2.44 (d, *J* = 7.0 Hz, 1 H, OH), 3.60 (dd, *J* = 10.5, 7.0, 1.7 Hz, 1 H, H3), 4.16 (q, *J* = 7.1 Hz, 2 H, OEt), 4.95 (bd, *J* = 10.3 Hz, 1 H, H8), 5.01 (dq, *J* = 17.1, 1.6 Hz, 1 H, H8), 5.81 (dtd, *J* = 17.1, 10.3, 6.7 Hz, 1 H, H7) ppm. ¹³C NMR (125 MHz): δ = 14.1 (OEt), 20.4 (C2a), 22.4 (C2b), 25.9, 31.1, 33.0 (C6), 47.0 (C2), 60.6 (OEt), 76.6 (C3), 114.6 (C7), 138.7 (C8), 177.7 (COOR) ppm. [*a*]₅₇₈ = +15.00, *c* = 3.06 (CHCl₃). C₁₂H₂₂O₃ (214.30): calcd. C 67.26, H 10.35; found C 67.07, H 10.44. **TMS Ether of 23:** *R*_f = 0.40 (5% MTBE in hexane). ¹H NMR (500 MHz): δ = 0.11 (s, 9 H, TMS), 1.07 (s, 3 H, H2a), 1.14 (s, 3 H, H2b), 1.25 (t, *J* = 7.13 Hz, 3 H, OEt), 1.28–1.40 (m, 3 H), 1.51–1.60 (m, 1 H), 1.97–2.12 (m, 2 H, H6), 3.88 (dd, *J* = 8.8, 2.3 Hz, 1 H, H3), 4.11 (dq, *J* = 11.0, 7.1 Hz, 1 H, OEt), 4.17 (dq, *J* = 11.0, 7.1 Hz, 1 H, OEt) 4.95 (d, *J* = 10.4 Hz, 1 H, H8), 5.00 (dq, *J* = 17.1, 1.6 Hz, 1 H, H8), 5.79 (dtd, *J* = 17.1, 10.4, 1.6 Hz, 1 H, H7) ppm. ¹³C NMR (125 MHz): δ = 0.7 (3C, TMS), 14.1

Table 2. Selected reaction conditions for the addition of **18** to **17**.

Scale	Solvent	Lewis acid	Time	Yield	<i>cis/trans</i>
47 mg (0.26 mmol)	CH ₂ Cl ₂	BF ₃ ·OEt ₂	8 h	48 mg, 78%	2:3
44 mg (0.24 mmol)	Et ₂ O	TMSOTf	24 h	38 mg, 66%	1:20

(OEt), 19.8 (C2a), 21.9 (C2b), 26.2, 32.4, 33.7 (C6), 48.0 (C2), 60.2 (OEt), 77.4 (C3), 114.5 (C7), 138.5 (C8), 177.1 (COOR) ppm. $[\alpha]_D^{25} = +9.2$, $c = 3.08$ (CHCl₃). C₁₅H₃₀O₃Si (286.48): calcd. C 62.89, H 10.55; found C 62.73, H 10.47.

Aldehyde 24. TBS Protection: The alcohol **23** (3.00 g, 14.0 mmol) was dissolved in THF (50 mL) at 0 °C. 2,6-Lutidine (3.8 mL, 35.0 mmol) and TBS-triflate (4.20 g, 16.8 mmol) were added dropwise subsequently. After 2 h stirring at 0 °C the reaction mixture was warmed to 20 °C and quenched with NH₄Cl (40 mL). The aqueous layer was extracted with MTBE (3 × 25 mL), the combined organic layers were dried with MgSO₄. Chromatographic purification gave the corresponding TBS ether (4.55 g, 13.9 mmol, 99%) as a colorless oil. $R_f = 0.63$ (10% MTBE in hexane). ¹H NMR (300 MHz): $\delta = 0.03$ (s, 3 H, TBS), 0.07 (s, 3 H, TBS), 0.87 (s, 9 H, TBS), 1.07 (s, 3 H, CH₃), 1.15 (s, 3 H, CH₃), 1.24 (t, $J = 7.0$ Hz, 3 H, OEt), 1.29–1.42 (m, 3 H), 1.47–1.63 (m, 1 H), 1.93–2.09 (m, 2 H, H6), 3.87 (t, $J = 5.3$ Hz, 1 H, H3), 4.07 (dq, $J = 11.1$, 7.0 Hz, 1 H, OEt), 4.12 (dq, $J = 11.1$, 7.0 Hz, 1 H, OEt), 4.91–5.02 (m, 2 H, H8), 5.77 (ddt, $J = 17.0$, 10.3, 6.7 Hz, 1 H, H7) ppm. ¹³C NMR (75 MHz): $\delta = -4.2$ (TBS), -3.7 (TBS), 14.1 (OEt), 18.3 (TBS), 19.7 (C2a), 22.5 (C2b), 26.0 (C3, TBS), 26.4, 33.6, 34.0 (C6), 48.3 (C2), 60.2 (OEt), 77.0 (C3), 114.5 (C8), 138.5 (C7), 177.2 (COOR) ppm. $[\alpha]_D^{25} = -1.30$, $c = 1.00$ (MTBE). C₁₈H₃₆O₃Si (328.56): calcd. C 65.80, H 11.04; found C 65.51, H 10.96. **Ozonolysis:** Following GP1 the alkene (2.00 g, 6.09 mmol) was converted into the aldehyde **24** (1.66 g, 5.01 mmol, 82%). ¹H NMR (300 MHz): $\delta = 0.03$ (s, 3 H, TBS), 0.07 (s, 3 H, TBS), 0.87 (s, 9 H, TBS), 1.06 (s, 3 H, CH₃), 1.14 (s, 3 H, CH₃), 1.23 (t, $J = 7.2$ Hz, 3 H, OEt), 1.34–1.42 (m, 2 H, H4), 1.47–1.62 (m, 1 H, H5), 1.71–1.85 (m, 1 H, H5), 2.40 (ddd, $J = 8.1$, 6.9, 1.2 Hz, 2 H, H6), 3.88 (t, $J = 5.3$ Hz, 1 H, H3), 4.07 (dq, $J = 11.2$, 7.0 Hz, 1 H, OEt), 4.11 (dq, $J = 11.2$, 7.0 Hz, 1 H, OEt), 9.73 (t, $J = 1.6$ Hz, 1 H, CHO) ppm. ¹³C NMR (75 MHz): $\delta = -4.2$ (TBS), -3.7 (TBS), 14.1 (OEt), 18.3 (TBS), 19.6, 19.7 (Me, C5), 22.6 (Me), 26.0 (C3, TBS), 33.6 (C4), 44.0 (C6), 48.2 (C2), 60.3 (OEt), 76.6 (C3), 177.0 (C1), 201.9 (CHO) ppm. $[\alpha]_D^{25} = -1.1$, $c = 2.14$ (CHCl₃).

Ketone 25. Allylation: To a solution of the aldehyde **24** (3.34 g, 10.1 mmol) in THF (50 mL) was added 2-allyl-4,4,5,5-tetramethyl-1,3-dioxane-2-borolane (1.88 g, 11.1 mmol) in THF (2 mL) at 0 °C. The reaction mixture was warmed to 20 °C and stirred for another 12 h. It was poured into NaHCO₃/H₂O (50 mL, 1:1) and stirred for 1 h. The aqueous layer was extracted with MTBE (3 × 40 mL) and the combined organic layers were dried with Na₂SO₄. Removal of the solvents and purification by chromatography led to the corresponding homoallylic alcohol 3.38 g (9.09 mmol, 90%). **Dess–Martin Oxidation:** To a solution of the homoallylic alcohol (2.70 g, 7.25 mmol) in CH₂Cl₂ (50 mL) at 20 °C was added pyridine (2.35 mL, 28.94 mmol) followed by Dess–Martin periodinane (6.15 g, 14.49 mmol). The clear solution was stirred for 12 h at 20 °C and poured into a solution of 2.5 g Na₂S₂O₃ in 30 mL satd. aq. NaHCO₃, which was vigorously stirred for another 1 h. The aqueous layer was extracted with MTBE (3 × 25 mL) and the combined organic layers were dried with Na₂SO₄. Purification by chromatography gave the ketone **25** (2.15 g, 5.80 mmol, 80%) as a colorless oil. $R_f = 0.20$ (17% MTBE in pentane). ¹H NMR (400 MHz): $\delta = 0.03$ (s, 3 H, TBS), 0.07 (s, 3 H, TBS), 0.87 (s, 9 H, TBS), 1.06 (s, 3 H, CH₃), 1.14 (s, 3 H, CH₃), 1.24 (t, $J = 7.1$ Hz, 3 H, OEt), 1.31–1.38 (m, 2 H, H4), 1.43–1.55 (m, 1 H, H5), 1.67–1.78 (m, 1 H, H5), 2.40 (t, $J = 7.3$ Hz, 2 H, H6), 3.14 (d, $J = 7.1$ Hz, 2 H, H8), 3.86 (dd, $J = 6.1$, 4.6 Hz, 1 H, H3), 4.07 (dq, $J = 10.4$, 7.3 Hz, 1 H, OEt), 4.11 (dq, $J = 10.4$, 7.3 Hz, 1 H, OEt), 5.12 (dd, $J = 17.1$, 1.0 Hz, 1 H, H10), 5.17 (dd, $J = 10.4$, 1.0 Hz, 1 H, H10) 5.90 (ddt, $J = 17.1$, 10.2, 7.1 Hz, 1 H, H9) ppm. ¹³C NMR

(100 MHz): $\delta = -4.2$ (TBS), -3.7 (TBS), 14.1 (OEt), 18.3 (OEt), 19.6 (Me), 21.2 (C5), 22.5 (Me), 26.0 (C3, TBS), 33.6 (C4), 42.4 (C6), 47.7 (C8), 48.2 (C2), 60.3 (OEt), 76.2 (C3), 118.7 (C10), 130.6 (C9), 177.1 (COOR), 208.1 (C8) ppm. C₂₀H₃₈O₄Si (370.60): calcd. C 64.82, H 10.34; found C 64.52, H 10.20.

cis THP Ester 19 (from 25): Triethylsilane (2.45 g, 21.05 mmol) and the ketone **25** (1.95 g, 5.26 mmol) were dissolved in MeCN (25 mL) at -35 °C. Boron trifluoride–diethyl ether (1.49 g, 10.52 mmol) was added. The solution was warmed to 20 °C and poured into water (25 mL). The aqueous layer was extracted with MTBE (3 × 25 mL) and the combined organic layers were dried with MgSO₄. Chromatographic purification gave the *cis* THP ester **19** (1.24 g, 5.15 mmol, 98%) which was identical with respect to its analytical data with the compound prepared from **17**.

Methyl Ketone 5: CuCl (62 mg, 624 μ mol) was suspended in DMF/H₂O (8 mL, 7:1), and the solvent was thoroughly saturated with argon gas. PdCl₂ (11 mg, 62.4 μ mol) was added. The suspension was saturated with oxygen until the colour changed back to green. The olefin **19** (150 mg, 624 μ mol) was added and the suspension was vigorously stirred under oxygen until the black colour changed back to green. The suspension was poured into NH₄Cl (20 mL) and extracted with MTBE (3 × 20 mL). The combined organic layers were dried with MgSO₄. Purification by chromatography gave the methyl ketone **5** (143 mg, 448 mmol, 89%) as a colorless oil. $R_f = 0.17$ (17% MTBE in hexane). ¹H NMR (400 MHz): $\delta = 1.08$ (s, 3 H, CH₃), 1.14 (s, 3 H, CH₃), 1.15–1.19 (m, 1 H, H6), 1.23 (t, $J = 7.2$ Hz, 3 H, OEt), 1.22–1.30 (m, 1 H, H4), 1.44–1.62 (m, 3 H, H4–6), 1.83–1.90 (m, 1 H, H5), 2.14 (s, 3 H, H10), 2.34 (dd, $J = 14.5$, 4.1 Hz, 1 H, H8), 2.58 (dd, $J = 14.5$, 8.8 Hz, 1 H, H8) 3.54 (dd, $J = 11.4$, 1.7 Hz, 1 H, H3), 3.75 (dddd, $J = 11.0$, 8.8, 4.1, 2.0 Hz, 1 H, H7), 4.02 (q, $J = 7.2$ Hz, 2 H, OEt) ppm. ¹³C NMR (100 MHz): $\delta = 14.1$ (OEt), 20.0 (Me), 21.2 (Me), 23.4 (C5), 24.7 (C6), 31.2 (C10), 31.4 (C4), 46.4 (C2), 50.1 (C8), 60.3 (OEt), 75.2 (C7), 82.3 (C3), 176.7 (COOR), 208.2 (C=O) ppm. $[\alpha]_D^{25} = +13.2$, $c = 3.70$ (CHCl₃). HR-MS (ESI): [C₁₄H₂₄O₄ + Na]⁺ calcd. 279.1567; found 279.1565. C₁₄H₂₄O₄ (256.34): calcd. C 65.60, H 9.44; found C 65.15, H 9.59.

(2S,6S,3'S)-2-(4-Hydroxy-3-methylbutyl)-6-[3-(3-methoxy-2-methoxycarbonylphenyl)propyl]tetrahydropyran (26). Wittig Reaction: Wittig salt **3** (3.69 g, 7.74 mmol) suspended in THF (150 mL) at 0 °C was treated with LiHMDS (7.8 mmol, 1 M in THF). After 30 min at 0 °C, the solution was cooled to -78 °C. The aldehyde **4** (1.57 g, 5.15 mmol) was added. After 30 min the reaction was warmed to 20 °C (overnight). The solvents were removed in vacuo and the residue chromatographically purified to deliver the olefin (2.02 g, 4.33 mmol, 84%) as a 1:1 mixture of the isomers, which could not be separated. $R_f = 0.28$ (17% MTBE in hexane). HR-MS (ESI) [C₂₉H₃₈O₅ + Na]⁺ calcd.: 489.2605 found: 489.2611. **Hydrogenation:** The olefin (1.52 g, 3.26 mmol) was dissolved in THF (50 mL) and treated with a catalytic amount of Pd(OH)₂/C (10%, wet). The suspension was vigorously stirred under H₂-Atmosphere for 2 h. The filtrate was concentrated and chromatographically purified to furnish alcohol **26** (1.22 g, 3.22 mmol, 99%) as a colorless oil. $R_f = 0.20$ (50% MTBE in pentane). ¹H NMR (400 MHz): $\delta = 0.91$ (d, $J = 6.7$ Hz, 3 H, Me), 1.09–1.19 (m, 3 H, H3, 6, 8), 1.31–1.67 (m, 10H, OH), 1.71–1.82 (m, 2 H, H2, 7), 2.49–2.61 (m, 2 H, H12), 3.16–3.25 (m, 2 H, H5,9), 3.43 (dd, $J = 10.7$, 6.7 Hz, 1 H, H1), 3.49 (dd, $J = 10.7$, 5.7 Hz, 1 H, H1), 3.81 (s, 3 H, OMe), 3.90 (s, 3 H, OMe), 6.75 (d, $J = 8.3$ Hz, 1 H, H16), 6.82 (d, $J = 7.6$ Hz, 1 H, H14), 7.26 (dd, $J = 8.3$, 7.6 Hz, 1 H, H15) ppm. ¹³C NMR (100 MHz): $\delta = 16.7$ (Me), 23.7 (C7), 27.2 (11), 29.1 (C4), 31.7 (C2, C6, C8), 33.4 (C12), 33.8 (C3), 35.8 (C2), 36.3 (C10), 52.2

(OMe), 55.9 (OMe), 68.2 (C1), 77.6, 78.3 (C5,9), 108.4 (C16), 121.5 (C14), 123.5 (C13), 130.2 (C15), 141.1 (C18), 156.3 (C17), 168.9 (C19) ppm. IR: $\tilde{\nu}$ = 3430 (br. s), 2934 (s), 2863 (s), 1733 (s), 1585 (s), 1469 (s), 1267 (s), 1076 (s), 755 (s) cm^{-1} . $[\alpha]_{\text{D}} = -5.50$, $c = 2.00$ (CHCl_3). HR-MS (ESI) $[\text{C}_{22}\text{H}_{34}\text{O}_5 + \text{Na}]^+$ calcd. 401.2298; found 401.2297.

Aldehyde 27: To a solution of alcohol **26** (238 mg, 0.63 mmol) in CH_2Cl_2 (10 mL) were added every 30 min 5 mL of a solution of pyridine (300 mg) and Dess–Martin periodinane (800 mg, 1.89 mmol) in CH_2Cl_2 (25 mL). After three amounts the clear solution was poured into a solution of 5 g $\text{Na}_2\text{S}_2\text{O}_3$ in 50 mL satd. aq. NaHCO_3 , which was vigorously stirred for another 30 min. The aqueous layer was extracted with CH_2Cl_2 (3×25 mL) and the combined organic layers were dried with MgSO_4 . Purification by chromatography gave the aldehyde **27** (200 mg, 0.53 mmol, 84%) as a colourless oil. $R_f = 0.44$ (50% MTBE in pentane). ^1H NMR (500 MHz): δ = 1.08 (d, $J = 6.9$ Hz, 3 H, Me), 1.12–1.20 (m, 2 H), 1.36–1.6 (m, 9 H, H3, 4, 6, 7, 8, 10, 11), 1.71–1.82 (m, 2 H, H11,7), 1.87–1.94 (m, 1 H, H3), 2.34 (ddq, $J = 6.7, 6.7, 6.7$ Hz, 1 H, H2), 2.53 (dt, $J = 13.6, 6.2$ Hz, 1 H, H12), 2.57 (dt, $J = 13.6, 6.2$ Hz, 1 H, H12), 3.18–3.25 (m, 2 H, H5,9), 3.81 (s, 3 H, OMe), 3.90 (s, 3 H, OMe), 6.75 (d, $J = 8.3$ Hz, 1 H, H14), 6.82 (d, $J = 7.8$ Hz, 1 H, H16), 7.26 (dd, $J = 8.3, 7.8$ Hz, 1 H, H15), 9.61 (d, $J = 1.6$ Hz, 1 H, CHO) ppm. ^{13}C NMR (125 MHz): δ = 13.2 (Me), 23.6 (C7), 26.5 (C3), 27.1 (C11), 31.6, 31.7 (C6, 8), 33.3 (C12), 33.7 (C10), 36.2 (C4), 46.1 (C2), 52.1 (OMe), 55.8 (OMe), 77.4, 77.5 (C5,9), 108.4 (C16), 121.4 (C14), 123.5 (C13), 130.2 (C15), 141.0 (C18), 156.2 (C17), 168.8 (C19), 205.2 (CHO) ppm. IR: $\tilde{\nu}$ = 2936 (s), 2981 (s), 1732 (s), 1585 (m), 1470 (m), 1268 (s), 1111 (s), 1075 (s), 755 (m) cm^{-1} . $[\alpha]_{\text{D}} = +11.4$, $c = 0.50$ (CHCl_3). $\text{C}_{22}\text{H}_{32}\text{O}_5$ (376.49): calcd. C 70.18, H 8.57; found C 69.74, H 8.43.

γ -Methyl- β -anti-hydroxy Ketone 28: Methyl ketone **5** (337 mg, 1.32 mmol) was dissolved in Et_2O at -78°C and treated with NET_3 (145 mg, 1.43 mmol). After 20 min dibutylboron triflate (1.38 mmol, 1 M in Et_2O) was added. After 10 min aldehyde **27** (450 mg, 1.20 mmol) was added. The reaction was kept at -78°C for 5 h, treated with $\text{MeOH}/\text{pH7 buffer}/\text{H}_2\text{O}_2$ (40 mL, 2:2:1) and warmed to 20°C . After vigorous stirring for 30 min the aqueous layer was extracted with MTBE (3×50 mL) and the combined organic layers were dried with MgSO_4 . Purification by chromatography gave the β -hydroxy ketone **28** (414 mg, 664 μmol , 55%) as a colourless oil. $R_f = 0.20$ (50% MTBE in pentane). ^1H NMR (500 MHz): δ = 0.89 (d, $J = 6.7$ Hz, 3 H, Me), 0.86–0.93 (m, 1 H), 1.07 (s, 3 H, Me), 1.12 (s, 3 H, Me), 1.10–1.20 (m, 3 H), 1.23 (t, $J = 7.1$ Hz, 3 H, OEt), 1.33–1.66 (m, 12 H), 1.68–1.88 (m, 5 H), 2.34 (dd, $J = 14.7, 7.1$ Hz, 1 H, H8), 2.49 (dd, $J = 16.9, 9.5$ Hz, 1 H, H10), 2.52–2.64 (m, 4 H, H8,10, H22), 3.11 (d, $J = 3.2$ Hz, 1 H, OH), 3.16–3.24 (m, 2 H, H15,19), 3.51 (dd, $J = 11.1, 1.1$ Hz, 1 H, H3), 3.75–3.79 (m, 1 H, H7), 3.80 (s, 3 H, H27a), 3.85–3.88 (m, 1 H, H11), 3.89 (s, 3 H, H29a), 4.09 (q, $J = 7.1$ Hz, 2 H, OEt), 6.74 (d, $J = 8.0$ Hz, 1 H, H24), 6.82 (d, $J = 8.0$ Hz, 1 H, H26), 7.25 (dd, $J = 8.0, 8.0$ Hz, 1 H, H25) ppm. ^{13}C NMR (125 MHz): δ = 14.1 (OEt), 15.1 (C12a), 20.4 (C2a), 21.0 (C2b), 23.4 (C5), 23.7 (C17), 24.8 (C4), 27.2 (C21), 28.0 (C14), 31.3 (C6), 31.6, 31.7 (C18, C16), 33.4 (C20), 34.0 (C13), 36.3 (C22), 38.1 (C12), 46.3 (C2), 47.3 (C10), 49.9 (C8), 52.1 (C29a), 55.8 (C27a), 60.3 (OEt), 71.1 (C11), 74.9 (C7), 77.6, 78.2 (C15, C19), 82.3 (C3), 108.4 (C26), 121.5 (C24), 123.6 (C23), 130.2 (C25), 141.1 (C28), 156.3 (C27), 168.8 (C29), 176.6 (C1), 211.3 (C9) ppm. IR: $\tilde{\nu}$ = 3464 (br. s), 2936 (s), 2864 (s), 1732 (s), 1585 (m), 1470 (s), 1269 (s), 1079 (s), 1047 (s), 756 (s) cm^{-1} . $[\alpha]_{\text{D}} = +8.2$, $c = 2.00$ (CHCl_3). HR-MS (ESI) $[\text{C}_{36}\text{H}_{56}\text{O}_9 + \text{Na}]^+$ calcd. 655.3817; found 655.3820.

Diol 29: Tetramethylammonium triacetoxymethylborohydride (1.62 g, 6.16 mmol) in acetone (20 mL) was treated with acetic acid (740 μL , 12.3 mmol) and stirred at 0°C for 30 min. To the clear solution hydroxy ketone **28** (390 mg, 616 μmol) in acetone (10 mL) was added via a cannula. After 4 h at 0°C the solution was warmed to 20°C and stirred for another 8 h. The reaction was poured into satd. aq. Na/K tartrate (30 mL) and vigorously stirred for 15 min. Satd. aq. NaHCO_3 (20 mL) was added, the aqueous layer was extracted with MTBE (5×40 mL), the combined organic layers dried with Na_2SO_4 and concentrated. Chromatographic purification gave 1,3-*anti*-diol **29** (334 mg, 526 μmol , 55%) as a colourless oil. $R_f = 0.10$ (50% MTBE in hexane); 0.25 (EtOAc). ^1H NMR (500 MHz): δ = 0.86 (d, $J = 6.7$ Hz, 3 H, H12a), 1.08–1.14 (m, 2 H), 1.12 (s, 3 H, H2a), 1.15 (s, 3 H, H2b), 1.24 (t, $J = 7.1$ Hz, 3 H, OEt), 1.20–1.33 (m, 3 H), 1.26–1.67 (m, 15 H), 1.69–1.80 (m, 4 H), 1.83–1.88 (m, 1 H), 2.52 (ddd, $J = 13.9, 9.0, 6.2$ Hz, 1 H, H22), 2.56 (ddd, $J = 13.9, 9.0, 6.3$ Hz, 1 H, H22), 3.16–3.24 (m, 2 H, H15,19), 3.28 (br. s, 1 H, OH), 3.57 (dd, $J = 11.3, 1.2$ Hz, 1 H, H3), 3.55–3.61 (m, 1 H, H7), 3.70–3.75 (m, 1 H, H9), 3.80 (s, 3 H, H29a), 3.86 (br. s, 1 H, OH), 3.89 (s, 3 H, H27a), 4.10 (dq, $J = 10.8, 7.1$ Hz, 1 H, OEt), 4.09–4.14 (m, 1 H, H11), 4.15 (dq, $J = 10.8, 7.1$ Hz, 1 H, OEt), 6.74 (d, $J = 8.3$ Hz, 1 H, H26), 6.82 (d, $J = 7.6$ Hz, 1 H, H24), 7.25 (dd, $J = 8.3, 7.6$ Hz, 1 H, H25) ppm. ^{13}C NMR (125 MHz): δ = 14.1 (OEt), 15.2 (C12a), 19.9 (C2a), 21.8 (C2b), 23.2 (C5), 23.7 (C17), 24.8 (C4), 27.1 (C21), 28.1 (C14), 31.5, 31.7 (C16, C18), 32.0 (C6), 33.4 (C20), 34.1 (C13), 36.3 (C22), 38.7 (C12), 38.9, 42.5 (C8, C10), 46.4 (C2), 52.1 (C29a), 55.9 (C27a), 60.7 (OEt), 70.4 (C11), 72.3 (C9), 77.6, 78.3 (C15, C19), 80.1 (C7), 83.0 (C3), 108.4 (C26), 121.5 (C24), 123.6 (C23), 130.2 (C25), 141.2 (C28), 156.2 (C27), 168.9 (C29), 176.7 (C1) ppm. $[\alpha]_{\text{D}} = -1.45$, $c = 2.75$ (CHCl_3). HR-MS (ESI) $[\text{C}_{36}\text{H}_{58}\text{O}_9 + \text{H}]^+$ calcd. 635.4154; found 635.4148.

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