Synthesis of a diastereoisomer of the C-15 ~ C-26 segment of amphidinolide L

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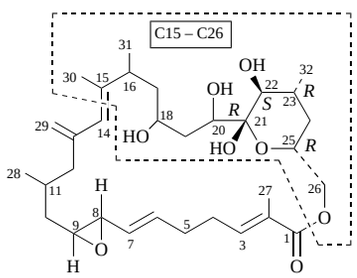
In order to determine the absolute stereochemistry of amphidinolide L 1, a cytotoxic macrolide from a marine dinoflagellate, (16*R*, 18*S*, 20*R*, 22*S*, 23*R*, and 25*R*)-2, one of the eight possible diastereoisomers of the C(15)–C(26) segment has been synthesized, thus providing an authentic sample for degradation studies of 1.

Marine dinoflagellates of the genus *Amphidinium* have proven to be a rich source of bioactive substances with a unique carbon framework.[1] Recently we have isolated a new cytotoxic 27-membered macrolide, amphidinolide L **1**, from a culture of the



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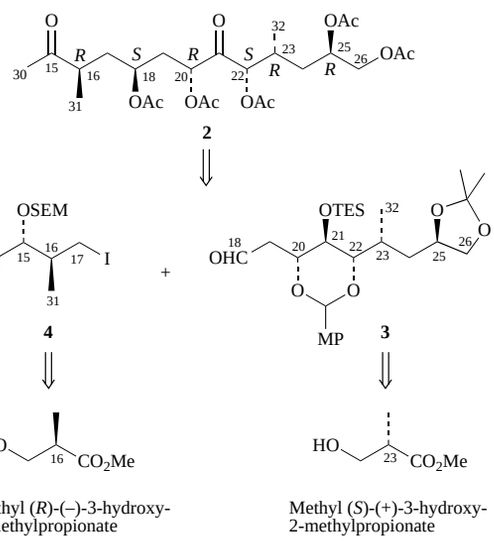
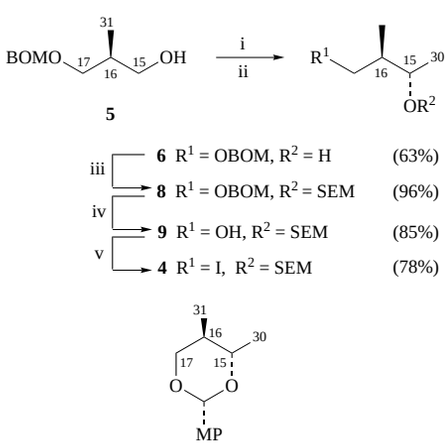
dinoflagellate *Amphidinium* sp. which was separated from the Okinawan marine flatworm *Amphiscolops breviviridis*.[2] The absolute stereochemistry of 4 (C-21, C-22, C-23, and C-25) out of the 10 chiral centres in **1** has been established by a combination of enantioselective synthesis of the two diastereoisomers of the C(21)–C(26) segment and NOE data for **1**.[2] However, the absolute configurations at C-8, C-9, C-11, C-16, C-18, and C-20 remained to be clarified. In order to determine the absolute configurations at C-16, C-18 and C-20 in **1**, we planned to synthesize eight of the possible diastereoisomers of the C(15)–C(26) segment, which was expected to be obtained by ozonolysis of amphidinolide L **1**. The synthetic route was based on a convergent strategy through cross-coupling between the aldehyde **3** and the iodide **4** (Scheme 1), which can be derived from commercially available methyl (*S*)-(+)- and (*R*)-(−)-3-hydroxy-2-methylpropionate, respectively. This paper describes the synthesis of (16*R*, 18*S*, 20*R*, 22*S*, 23*R*, 25*R*)-**2**, one of eight possible diastereoisomers for the C(15)–C(26) segment of **1**.

Results and discussion

The known alcohol[3] **5**, prepared from methyl (*R*)-(−)-3-hydroxy-2-methylpropionate in two steps, was subjected to Swern oxidation followed by treatment with Me_2CuLi in Et_2O to afford the alcohol **6** (63%) as a single diastereoisomer (Scheme 2). The relative stereochemistry of the hydroxy group in **6** was elucidated on the basis of the vicinal coupling constants† of the corresponding *p*-methoxybenzylidene acetal **7**. The alcohol **6** was treated with 2-(trimethylsilyl)ethoxymethyl chloride (SEMCl) to yield **8**, and then hydrogenated with Raney



Scheme 1 Retrosynthesis of the C(15)–C(26) segment **2** of amphidinolide L (**1**)

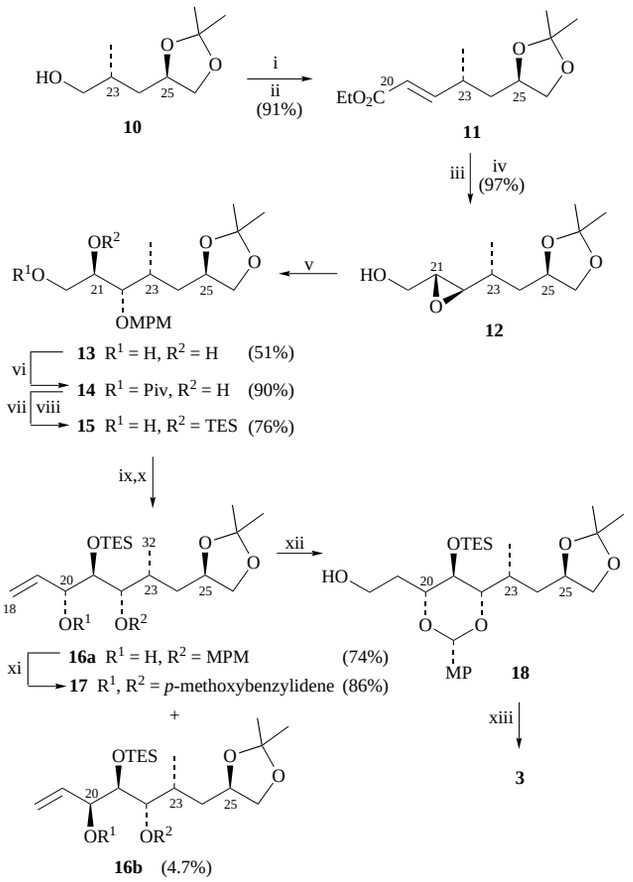


Scheme 2 *Reagents and conditions:* i, DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C, 45 min, then Et_3N, −50 °C; ii, CuI, MeLi, Et_2O, −78 °C; iii, SEMCl, Pr^i_2NEt, CH_2Cl_2, RT, 40 min; iv, Raney Ni, H_2, EtOH, 120 min; v, I_2, Ph_3P, imidazole, benzene, RT, 20 min

Ni under an H_2 atmosphere to give the SEM alcohol **9**. Iodination of **9** led to the (15*S*,16*S*)-iodide **4** in 40% yield for the 5 steps.

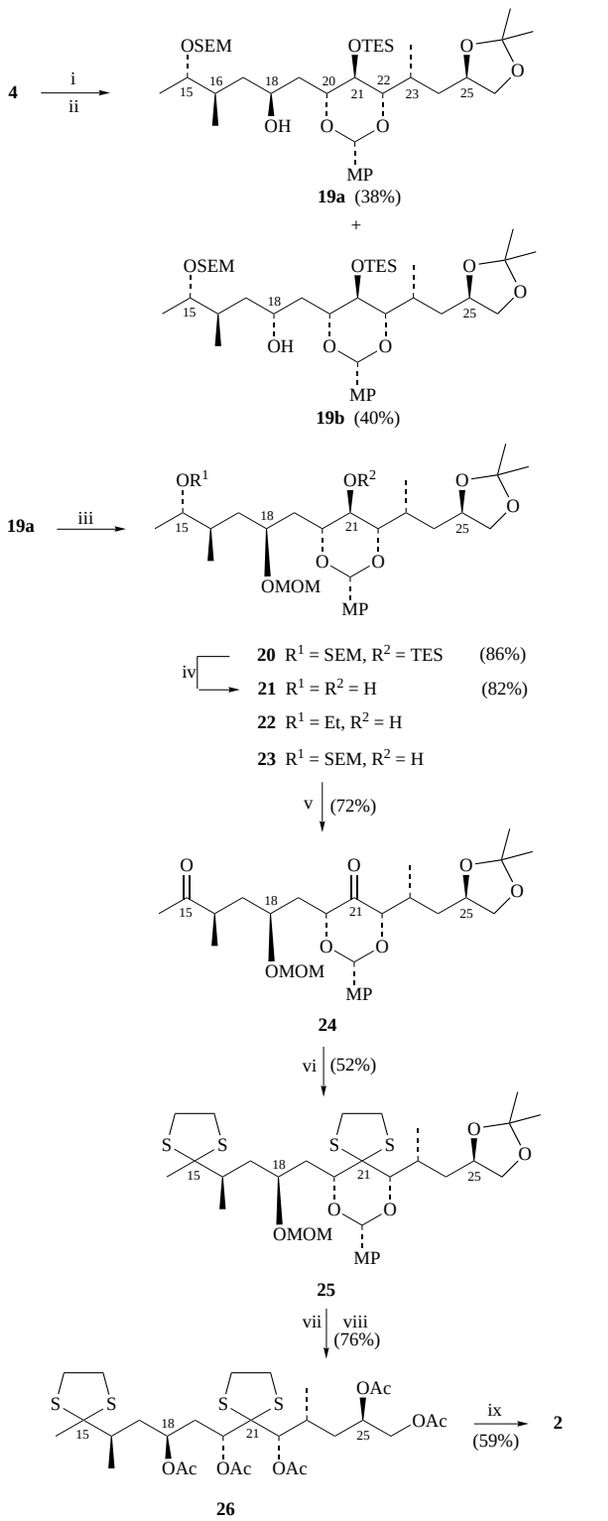
The (23*R*,25*R*)-alcohol **10**, prepared from methyl (*S*)-(+)-3-hydroxy-2-methylpropionate by a 9-step sequence,[2] was applied to Swern oxidation followed by Wittig reaction to afford the

† The proton–proton coupling constants for 15/16, 16/17α, and 16/17β were found to be 9.6, 11.3, and 4.7 Hz, respectively.



Scheme 3 *Reagents and conditions:* i, DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C, 45 min, then Et_3N, −50 °C; ii, Ph_3PCHCO_2Et, toluene, 50 °C, 12 h; iii, DIBAL, CH_2Cl_2, −78 °C, 30 min; iv, (−)-DET, $Ti(Pr^iO)_4$, Bu^tOOH, MS-4 Å, −20 °C, 19 h; v, MPMOH, $TI(OPr^i)_4$, toluene, 100 °C, 2 h; vi, PivCl, pyridine, RT, 2.5 h; vii, TESCl, imidazole, CH_2Cl_2, RT, 1 h; viii, DIBAL, CH_2Cl_2, −78 °C, 30 min; ix, DMSO, $(COCl)_2$, CH_2Cl_2, −78 C, 1 h, then Et_3N, −50 °C; x, vinylMgBr, THF, −78 °C, and then RT, 15 h; xi, DDQ, CH_2Cl_2, phosphate buffer, RT, 10 min; xii, 9-BBN, THF, RT, 9 h, and then NaOH, H_2O_2, RT, 15 h; xiii, DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C, 30 min, then Et_3N, −50 °C

ethyl ester **11** (Scheme 3). Reduction of **11** with DIBAL and then Sharpless epoxidation with (2*R*,3*R*)-(+)-diethyl tartrate gave the epoxy alcohol **12**, which was subjected to regio- and stereo-selective ring opening of the epoxide with titanium tetra(*p*-methoxybenzyl)alkoxide $[Ti(OMPM)_4]$[4] to yield a (12:1) mixture of the 1,2- **13** and 1,3-diol (51%). After a three-step conversion of the mixture, the desired 1,2-diol was obtained as the triethylsiloxy alcohol **15** (68%). Swern oxidation of **15** afforded the corresponding aldehyde, which was treated with vinylmagnesium bromide in THF to give the 20,21-*anti* **16a** and -*syn* isomers **16b** in 74 and 4.7% yield, respectively, for the two steps. The stereochemistry of the major 20,21-*anti*-alcohol **16a** was assigned on the basis of the NOESY data for the corresponding 4-methoxybenzylidene acetal **17**, which was obtained by treatment of **16a** with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) in THF/1 M phosphate buffer adjusted to pH 7 (9:1).[5] The stereoselectivity of the Grignard reaction of the aldehyde form of **15** can be explained by nucleophilic addition *via* a Felkin–Anh model.[6] Hydroboration of **17** with 9-borabicyclo[3.3.1]nonane (9-BBN) and then treatment with hydroperoxide under alkaline conditions gave the alcohol **18** (85%), which was oxidized to the corresponding aldehyde **3**. The cross-coupling reaction between **3** and **4** was performed by treatment of the latter with Bu^tLi (2 equiv.) in diethyl ether–pentane (2:3) at −78 °C,[7] followed by addition of **3** to afford the (18*S*)-**19a** and (18*R*)-isomers **19b** in 38 and 40% yield, respectively (Scheme 4). The absolute stereochemistry at C-18



Scheme 4 *Reagents and conditions:* i, Bu^tLi, Et_2O–pentane (2:3), −78 °C, 10 min and then RT, 1 h; ii, **3**, −78 °C, 10 min, and then RT, 11 h; iii, MOMCl, Pr^i_2NEt, CH_2Cl_2, RT, 17 h; 20 °C; iv, TBAF, MS-4 Å, DMPU, 80 °C, 15 h; v, TPAP, NMO, MS-4 Å, CH_2Cl_2, RT, 10 h; vi, $TMSSCH_2CH_2STMS$, ZnI_2, Et_2O, 0 °C, 10 h; vii, TsOH, THF, RT, 5 h; viii, Ac_2O, pyridine, RT, 17 h; ix, $Hg(ClO_4)_2$, $CaCO_3$, MeOH–$CHCl_3$ (1:1), RT, 10 min

of **19a** and **19b** was assigned on the basis of a modified Mosher method.[8,‡] The hydroxy group at C-18 of **19a** was protected to

‡ $\Delta\delta$ Values [$\Delta\delta$ (in Hz) = $\delta_S - \delta_R$] obtained for chemical shifts differences of (*S*)- and (*R*)-MTPA esters of **19b**: H-16, +13.4; H_2-17, +48.1 and +24.8; H-18, +18.0; H_2-19, −40.8 and −50.3; H-20, −37.8; H-21, −13.7; H-22, −13.2; H-23, −6.6; H_2-24, −0.7 and +4.6; H-25, +1.0; H_2-26, +1.1 and +4.0; H_3-30, +52.3; H_3-31, +42.3.

afford the MOM ether **20**. Both TES and SEM groups in **20** were removed by treatment with tetrabutylammonium fluoride (TBAF) in 1,3-dimethyl-3,4,5,6-tetrahydropyrimidin-2(1*H*)-one (DMPU)[9] to yield the diol **21** (82%), while deprotection using HMPA in place of DMPU gave unwanted ethyl ether **22** (11%), which may be generated through elimination of the TMS group, together with **21** (35%) and **23** (33%). The hydroxy groups in **21** were oxidized with tetrapropylammonium perruthenate (TPAP)[10] to give the diketone **24**. An attempt at deprotection of **24** under acidic conditions gave a complex mixture, which was probably generated by hydration of the carbonyl groups. Therefore, the diketone **24** was converted into the bisdithiolane **25** by treatment of **24** with ethylenedithiobis(trimethylsilane) and zinc iodide.[11] Deprotection with TsOH and then acetylation afforded the pentaacetate **26** in 76% yield for the two steps. Finally, deprotection of the dithiolanes in **26** with mercuric perchlorate [$Hg(ClO_4)_2$] and $CaCO_3$[12] furnished (16*R*,18*S*,20*R*,22*S*,23*R*,25*R*)-**2**, a diastereoisomer of the C(15)–C(26) segment of amphidinolide L **1** (59%). Synthesis of the remaining seven possible diastereoisomers of the segment according to the present strategy is currently in progress. We anticipate that ozonolysis will give one of the eight diastereoisomers although the experiment has yet to be carried out. Further large-scale cultivation of the algae is in progress to provide sufficient quantities of **1** for degradation experiments.

Experimental

The IR and UV spectra were recorded on a JASCO FT/IR-5300 and JASCO Ubest-35 spectrophotometer, respectively. Optical rotations were recorded on a JASCO DIP-360 polarimeter and $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. ^{1}H and ^{13}C NMR spectra were recorded on Bruker ARX-500 and JEOL EX-400 spectrometers, respectively; *J* values recorded in Hz. FAB mass spectra were obtained on a JEOL HX-110 spectrometer using glycerol as a matrix. EI mass spectra (EIMS) were recorded on a JEOL DX-303 spectrometer.

(2*R*,3*S*)-1-Benzyloxymethyloxy-2-methylbutan-3-ol 6

To a solution of oxalyl chloride (2.5 ml, 29 mmol) in CH_2Cl_2 (60 ml), DMSO (3.0 ml, 43 mmol) in CH_2Cl_2 (6 ml) was slowly added at −78 °C. The mixture was stirred for 10 min after which it was treated dropwise with a solution of (*S*)-(−)-3-benzyloxymethyloxy-2-methylpropan-1-ol[5] **5** (3.0 g, 14.3 mmol) in CH_2Cl_2 (30 ml). After being stirred at −78 °C for 45 min, the mixture was then treated with triethylamine (9.9 ml, 71 mmol) and allowed to warm to −50 °C. After addition of saturated aqueous NH_4Cl to the reaction mixture, it was extracted with Et_2O. The extract was washed with water and brine, dried ($MgSO_4$) and evaporated to afford a crude aldehyde, which was used in the following reaction without separation. CuI (5.15 g, 27.1 mmol) in Et_2O (15 ml) was treated with an Et_2O solution of 1.4 M MeLi (38.6 ml, 54.1 mmol) at −20 °C for 15 min after which the stirred reaction mixture was cooled to −78 °C and treated with the crude aldehyde (3.13 g) in Et_2O (20 ml). Stirring was continued for 12 h, after which the reaction mixture was partitioned between Et_2O and saturated aqueous NH_4Cl. The organic phase was separated, washed with water and brine, dried ($MgSO_4$) and evaporated *in vacuo*. The residue was purified by a silica gel column (hexane–EtOAc, 3:1) to afford compound **6** (1.75 g, 9.07 mmol, 63.4%) as a colourless oil, $[\alpha]_D^{25}$ −16 (*c* 1, $CDCl_3$); ν_{max}/cm^{-1} 3200, and 1600; δ_H($CDCl_3$) 0.90 (3H, d, *J* 7.0), 1.20 (3H, d, *J* 6.3), 1.77 (1H, m), 2.94 (1H, d, *J* 3.3), 3.57 (1H, dd, *J* 7.5 and 9.7), 3.71 (1H, dd, *J* 4.7 and 9.7), 4.62 (2H, s), 4.76 (2H, s), 4.75 (2H, s) and 7.3–7.4 (5H, m); *m*/*z* (EIMS) 210 (M^+); *m*/*z* (HREIMS) 210.1264 (M^+. Calc. for $C_{12}H_{18}O_3$: 210.1256).

(2*R*,3*S*)-1-Benzyloxymethyloxy-2-methyl-3-[2-(trimethylsilyl)-ethoxymethyloxy]butane 8

A solution of compound **6** (1.22 g, 5.42 mmol) in CH_2Cl_2 (10 ml) was treated with Pr^i_2NEt (3.8 ml, 22 mmol) and SEMCl (1.9 ml, 11 mmol) at room temperature for 40 min. After addition to it of 1 M aq. HCl, the reaction mixture was extracted with Et_2O. The extract was washed with saturated aqueous $NaHCO_3$, water, and brine, dried (Na_2SO_4) and evaporated to give a residue. This was purified by a silica gel column (hexane–EtOAc, 19:1) to afford compound **8** (1.85 g, 5.22 mmol, 96%) as a colourless oil; $[\alpha]_D^{25}$ −11 (*c* 1, $CDCl_3$); ν_{max}/cm^{-1} 2980, 2850 and 1600; δ_H($CDCl_3$) 0.02 (9H, s), 0.94 (3H, d, *J* 7.1), 0.95 (2H, t, *J* 8.6), 1.20 (3H, d, *J* 6.1), 1.71 (1H, m), 2.69 (1H, br d, *J* 5.9), 3.5–3.8 (5H, m), 4.67 (1H, d, *J* 7.0) and 4.75 (1H, d, *J* 7.0); *m*/*z* (EIMS) 344 (M^+); *m*/*z* (HREIMS) 344.2045 (M^+. Calc. for $C_{18}H_{32}O_4Si$: 344.2021).

(2*R*,3*S*)-2-Methyl-3-[2-(trimethylsilyl)ethoxymethoxy]-butan-1-ol 9

To a stirred solution of compound **8** (1.85 g, 5.22 mmol) in EtOH (2 ml) was added a suspension of 50% Raney Ni® in EtOH (5 ml). Stirring was continued for 120 h at room temperature under an H_2 atmosphere, after which the mixture was filtered through Celite to remove the catalyst and the filtrate was evaporated to give a residue. This was purified on a silica gel column (hexane–EtOAc, 4:1) to afford compound **9** (1.04 g, 4.43 mmol, 84.9%) as a colourless oil; $[\alpha]_D^{25}$ −8 (*c* 1, $CDCl_3$); ν_{max}/cm^{-1} 3400, 2980 and 1605; δ_H($CDCl_3$) 0.02 (9H, s), 0.94 (3H, d, *J* 7.1), 0.95 (2H, t, *J* 8.6), 1.20 (3H, d, *J* 6.1), 1.71 (1H, m), 2.69 (1H, br d, *J* 5.9), 3.5–3.8 (5H, m), 4.67 (1H, d, *J* 7.0) and 4.75 (1H, d, *J* 7.0); *m*/*z* (EIMS) 238 (M^+); *m*/*z* (HREIMS) 238.1586 (M^+. Calc. for $C_{11}H_{26}O_3Si$: 238.1603).

(2*S*,3*S*)-1-Iodo-2-methyl-3-[2-(trimethylsilyl)ethoxymethoxy]-butane 4

To a solution of compound **9** (948 mg, 4.00 mmol) in C_6H_6 (30 ml) was added Ph_3P (3.2 ml, 12 mmol), imidazole (817 mg, 12.0 mmol) and iodine (2.03 g, 8.00 mmol) at room temperature. After being stirred for 20 min, the mixture was filtered through Celite to remove insoluble materials, and the filtrate was evaporated to give a residue. This was purified by a silica gel column (hexane–$CHCl_3$, 9:1) to afford compound **4** (1.08 g, 3.12 mmol, 78.1%) as a colourless oil, $[\alpha]_D^{25}$ −23 (*c* 1, $CDCl_3$); ν_{max}/cm^{-1} 2980, 1600 and 1430; δ_H($CDCl_3$) 0.03 (3H, s), 0.93 (1H, d, *J* 7.7), 0.97 (1H, d, *J* 7.7), 0.99 (3H, d, *J* 6.9), 1.16 (3H, d, *J* 6.3), 1.55 (1H, m), 3.31 (2H, m), 3.55 (1H, m), 3.56 (1H, m), 3.64 (2H, m), 4.70 (1H, d, *J* 7.1), and 4.75 (1H, d, *J* 7.1); *m*/*z* (EIMS) 348 (M^+); *m*/*z* (HREIMS) 348.0570 (M^+. Calc. for $C_{11}H_{25}IO_2Si$: 348.0579).

Ethyl (2*E*,4*R*,6*R*)-6,7-isopropylidenedioxy-4-methylhept-2-enoate 11

To a solution of oxalyl chloride (1.5 ml, 17 mmol) in CH_2Cl_2 (30 ml), DMSO (1.8 ml, 26 mmol) in CH_2Cl_2 (2 ml) was slowly added at −78 °C, and the mixture was stirred for 10 min. It was then treated dropwise with a solution of (2*R*,4*R*)-4,5-isopropylidenedioxy-2-methylpentan-1-ol[2] **10**, (1.50 g, 8.60 mmol) in CH_2Cl_2 (10 ml). After being stirred at −78 °C for 45 min, the mixture was heated with Et_3N (6.0 ml, 43 mmol) and then allowed to warm to −50 °C. After addition to it of saturated aqueous NH_4Cl, the reaction mixture was extracted with Et_2O. The extract was washed with water and brine, dried ($MgSO_4$) and evaporated to afford a crude aldehyde (1.55 g), which was used in the following reaction without separation. To a stirred solution of the crude aldehyde in toluene (30 ml) was added triphenyl(ethoxycarbonylmethylene)phosphorane (4.50 g, 12.9 mmol) at room temperature, and stirring was continued at 50 °C for 12 h. After this the mixture was concentrated by solvent evaporation *in vacuo*, after which the residue was purified by a silica gel column (hexane–EtOAc, 19:1) to give compound **11** (1.90 g, 7.84 mmol, 91%) as a colourless oil; $[\alpha]_D^{25}$ +13 (*c* 1,

$CDCl_3$); ν_{max}/cm^{-1} 3000, 2950, 1725, 1660, 1465, 1385 and 1275; $\delta_H(CDCl_3)$ 1.09 (3H, d, *J* 6.7), 1.28 (3H, t, *J* 7.0), 1.33 (3H, s), 1.39 (3H, s), 1.47 (1H, ddd, *J* 5.7, 7.6 and 13.5), 1.80 (1H, m), 2.45 (1H, m), 3.49 (1H, t, *J* 7.1), 4.03 (1H, dd, *J* 5.9 and 7.1), 4.08 (1H, m), 4.12 (1H, d, *J* 7.1), 4.23 (1H, d, *J* 7.1), 5.78 (1H, dd, *J* 1.2 and 15.8) and 6.89 (1H, dd, *J* 7.8 and 15.8); *m/z* (FABMS, Pos.) 243 $(M + H)^+$; *m/z* (HRFABMS) 243.1612 [$(M + H)^+$. Calc. for $C_{13}H_{23}O_4$: 243.1596].

(2*R*,3*R*,4*R*,6*R*)-6,7-Isopropylidenedioxy-2,3-epoxy-4-methylheptan-1-ol 12

A solution of compound **11** (300 mg, 1.24 mmol) in CH_2Cl_2 (3 ml) was treated dropwise with a 0.93 M hexane solution of DIBAL (3.7 ml, 3.5 mmol), and the mixture was stirred at −78 °C for 30 min. After addition of MeOH (100 μl) to the mixture to decompose excess of reagent, it was allowed to warm to room temperature. Et_2O and saturated aqueous potassium sodium tartrate were added to the reaction mixture, which was then stirred vigorously for 1 h. After this, the mixture was extracted with EtOAc, and the organic phase was washed with water and brine, dried ($MgSO_4$) and evaporated *in vacuo* to afford a crude alcohol (242 mg). This was subjected to the following reaction. To a stirred suspension of 4 Å molecular sieves (200 mg) in CH_2Cl_2 (1.5 ml) containing diethyl (−)-tartrate (130 mg, 630 μmol) was first added titanium tetraisopropoxide (150 μl, 500 μmol) at −20 °C, and then, dropwise, a solution of the crude alcohol (242 mg) in CH_2Cl_2 (3 ml). After being stirred for 30 min the mixture was treated with a 3.5 M toluene solution of *tert*-butyl hydroperoxide (1.10 ml, 3.85 mmol) and stirring continued at −20 °C for 19 h. It was then poured into a cold and stirred solution of $FeSO_4 \cdot 7H_2O$ (700 mg) and tartaric acid (200 mg) in water (2 ml). The mixture was then filtered to remove insoluble materials, treated with 30% NaOH in brine and stirred at 0 °C for 1 h. After this the mixture was extracted with CH_2Cl_2 and the extract was washed with water and brine, dried ($MgSO_4$) and evaporated to give a residue which was purified on a silica gel column (hexane–EtOAc, 5:1) to afford compound **12** (260 mg, 1.20 mmol, 97%) as a colourless oil; $[\alpha]_D^{25}$ −9 (*c* 1, $CHCl_3$); ν_{max}/cm^{-1} 3470, 2995, 1655, 1380, 1260, 1220 and 1165; $\delta_H(CDCl_3)$ 0.99 (3H, d, *J* 6.7), 1.35 (3H, s), 1.40 (3H, s), 1.40–1.63 (2H, m), 1.76–1.90 (2H, m), 2.81 (1H, dd, *J* 2.3 and 7.2), 2.95 (1H, m), 3.50 (1H, t, *J* 7.6), 3.63 (1H, ddd, *J* 4.2, 7.2 and 12.5), 3.88 (1H, ddd, *J* 2.8, 5.4 and 12.5), 4.07 (1H, dd, *J* 5.9 and 7.9) and 4.26 (1H, m); *m/z* (FABMS, Pos.) 217 $(M + H)^+$, 154 and 136; *m/z* (HRFABMS) 217.1451 [$(M + H)^+$. Calc. for $C_{11}H_{21}O_4$: 217.1440].

(2*R*,3*S*,4*R*,6*R*)-6,7-Isopropylidenedioxy-3-(4-methoxybenzyloxy)-4-methylheptane-1,2-diol 13

A mixture of *p*-methoxybenzyl alcohol (7.9 ml, 64 mmol) and titanium tetraisopropoxide (3.1 ml, 11 mmol) was stirred at 90 °C for 30 min and then evaporated under reduced pressure. A solution of **12** (1.59 g, 7.35 mmol) in toluene (12 ml) was added to the residue, and stirring was continued at 100 °C for 2 h. After this, the mixture was concentrated by solvent evaporation, and then treated with EtOAc and 5% aq. H_2SO_4. It was then extracted with EtOAc. The extract was washed with saturated aqueous $NaHCO_3$, water and brine, dried ($MgSO_4$) and evaporated. The resulting residue was subjected to chromatography on a silica gel column (hexane–EtOAc, 3:1) to afford a mixture (12:1) of **13** (1.32 g, 3.72 mmol, 51%) and the corresponding 1,3-diol as a colourless oil; ν_{max}/cm^{-1} 3440, 2950, 1620, 1380, 1260 and 1220; $\delta_H(CDCl_3)$ 1.03 (3H, d, *J* 7.0), 1.35 (3H, s), 1.40 (3H, s), 1.42 (1H, ddd, *J* 3.9, 9.5 and 17.5), 1.75 (1H, ddd, *J* 4.5, 8.8 and 17.5), 2.11 (1H, m), 2.37 (1H, d, *J* 5.8), 3.44–3.51 (2H, m), 3.74 (2H, d, *J* 4.5), 4.06 (1H, dd, *J* 5.8 and 7.6), 4.12–4.22 (1H, m), 4.50 (1H, d, *J* 10.9), 4.60 (1H, d, *J* 10.9), 6.88 (2H, d, *J* 8.6) and 7.25 (2H, d, *J* 8.6); *m/z* (FABMS, Pos.) 355 $(M + H)^+$; *m/z* (HRFABMS) 355.2122 [$(M + H)^+$. Calc. for $C_{19}H_{31}O_6$: 355.2120].

(2*R*,3*S*,4*R*,6*R*)-6,7-Isopropylidenedioxy-3-(4-methoxybenzyloxy)-4-methyl-1-trimethylacetoxyheptan-2-ol 14

Compound **13** (1.30 g, 3.69 mmol) was treated with pyridine (25 ml) and pivaloyl chloride (500 μl, 4.03 mmol) at room temperature for 2.5 h. After concentration of the mixture by solvent evaporation, the residue was purified on a silica gel column (hexane–EtOAc, 9:1) to afford compound **14** (1.45 g, 3.42 mmol, 90%) as a colourless oil; $[\alpha]_D^{25}$ −9 (*c* 1, $CHCl_3$); ν_{max}/cm^{-1} 3400, 2940, 1605, 1360, 1295 and 1240; $\delta_H(CDCl_3)$ 1.01 (3H, d, *J* 6.7), 1.23 (9H, s), 1.35 (3H, s), 1.40 (3H, s), 1.48 (1H, ddd, *J* 4.0, 9.0 and 13.7), 1.78 (1H, ddd, *J* 5.0, 8.6 and 13.7), 2.15 (1H, m), 3.46 (1H, dd, *J* 3.2 and 7.2), 3.49 (1H, t, *J* 7.6), 3.80 (3H, s), 3.89 (1H, m), 3.90 (1H, m), 4.06 (1H, dd, *J* 5.8 and 7.8), 4.12–4.24 (2H, m), 4.37 (2H, dd, *J* 2.7 and 11.8), 4.49 (1H, d, *J* 10.7), 4.58 (1H, d, *J* 10.7), 6.87 (2H, d, *J* 8.6) and 7.25 (2H, d, *J* 8.6); *m/z* (FABMS, Pos.) 439 $(M + H)^+$; *m/z* (HRFABMS) 439.2710 [$(M + H)^+$. Calc. for $C_{24}H_{39}O_7$: 439.2695].

(2*R*,3*S*,4*R*,6*R*)-6,7-Isopropylidenedioxy-3-(4-methoxybenzyloxy)-4-methyl-2-triethylsilyloxyheptan-1-ol 15

To a stirred solution of the pivaloyl derivative **14** (1.08 g, 2.46 mmol) in CH_2Cl_2 (10 ml) were added TESCl (1.7 ml, 9.9 mmol) and imidazole (1.00 g, 14.7 mmol) at room temperature, and stirring was continued for 1 h. After dilution with water, the reaction mixture was extracted with CH_2Cl_2. The extract was washed with water and brine, dried ($MgSO_4$) and evaporated to afford a crude triethylsilylate. This was dissolved in CH_2Cl_2 (15 ml) and treated with a 0.93 M solution of DIBAL in hexane (10.5 ml, 9.85 mmol) at −78 °C. After being stirred for 30 min, the reaction mixture was treated with MeOH (10 ml) and allowed to warm to room temperature. After this, Et_2O and saturated aqueous potassium sodium tartrate were added to the reaction mixture which was then stirred vigorously; it was then extracted with Et_2O. The extract was washed with water and brine, dried ($MgSO_4$) and evaporated to give a residue. This was purified on a silica gel column (hexane–EtOAc, 17:3) to afford compound **15** (872 mg, 1.86 mmol, 76%) as a colourless oil; $[\alpha]_D$ −12 (*c* 1, $CHCl_3$); ν_{max}/cm^{-1} 3400, 2950, 1600, 1230 and 1060; $\delta_H(CDCl_3)$ 0.64 (6H, q, *J* 7.7), 0.98 (9H, t, *J* 7.7), 0.99 (3H, d, *J* 7.3), 1.34 (3H, s), 1.39 (3H, s), 1.45 (1H, ddd, *J* 4.7, 8.7 and 13.4), 1.75 (1H, ddd, *J* 5.4, 8.0 and 13.4), 2.05 (1H, br dd, *J* 3.7 and 8.2), 3.47 (2H, m), 3.63–3.77 (3H, m), 3.80 (3H, s), 4.05 (1H, dd, *J* 5.9 and 7.4), 4.15 (1H, m), 4.55 (1H, d, *J* 10.7), 4.65 (1H, d, *J* 10.7), 6.87 (2H, d, *J* 8.6) and 7.27 (2H, d, *J* 8.6); *m/z* (FABMS, Pos.) 469 $(M + H)^+$; *m/z* (HRFABMS) 473.2921 [$(M + H)^+$. Calc. for $C_{25}H_{45}O_6Si$: 473.2936].

Grignard reaction of aldehyde from 15 with vinylMgBr

DMSO (91 μl, 1.3 mmol) in CH_2Cl_2 (120 μl) was slowly added at −78 °C to a solution of oxalyl chloride (75 μl, 853 μmol) in CH_2Cl_2 (1.5 ml), and the mixture was stirred for 10 min. It was then treated dropwise with a solution of compound **15** (100 mg, 213 μmol) in CH_2Cl_2 (300 μl). After being stirred at −78 °C for 45 min, the reaction mixture was treated with Et_3N (300 μl, 2.1 mmol) and then allowed to warm to −50 °C. After addition of saturated aqueous NH_4Cl to it, the reaction mixture was extracted with Et_2O. The extract was washed with water and brine, dried ($MgSO_4$) and evaporated to afford a crude aldehyde (139 mg), which was used in the following reaction without separation. To a 1 M THF solution of vinylmagnesium bromide (640 μl, 640 μmol) in THF (500 μl) was added a solution of the crude aldehyde (139 mg) in THF (2 ml) at −78 °C. The reaction mixture was stirred for 15 h and then gradually allowed to warm to room temperature. After addition to it of saturated aqueous NH_4Cl, the reaction mixture was extracted with Et_2O. The extract was washed with water and brine, dried ($MgSO_4$) and evaporated. The residue was purified by chromatography on a silica gel column (hexane–EtOAc, 17:3) to afford (3*R*,4*R*,5*S*,6*R*,8*R*)-8,9-isopropylidenedioxy-6-methyl-5-

(4-methoxybenzyloxy)-4-triethylsilyloxynon-1-en-3-ol **16a** (78.4 mg, 158 μmol, 74%) and the 3*S*-isomer **16b** (5.0 mg, 10 μmol, 4.7%). Compound **16a** was a colourless oil; $[\alpha]_D^{25}$ −1.64 (*c* 3, $CHCl_3$); ν_{max}/cm^{-1} 3460, 2860, 1605, 1455, 1105 and 1005; $\delta_H(CDCl_3)$ 0.65 (6H, q, *J* 7.9), 0.98 (9H, t, *J* 7.9), 0.99 (3H, d, *J* 7.3), 1.34 (3H, s), 1.39 (3H, s), 1.45 (1H, ddd, *J* 4.6, 8.5 and 13.5), 1.75 (1H, ddd, *J* 5.5, 8.2 and 13.5), 2.13 (1H, m), 2.51 (1H, br s), 3.45 (1H, dd, *J* 2.5 and 6.3), 3.46 (1H, t, *J* 7.5), 3.79 (2H, m), 3.80 (3H, s), 4.05 (1H, dd, *J* 6.0 and 7.8), 4.14 (1H, m), 4.29 (1H, dd, *J* 4.7 and 6.0), 4.50 (1H, d, *J* 10.9), 4.59 (1H, d, *J* 10.8), 5.20 (1H, br d, *J* 10.5), 5.32 (1H, br d, *J* 17.3), 6.02 (1H, ddd, *J* 6.2, 10.5 and 17.0), 6.87 (2H, d, *J* 8.6) and 7.27 (2H, d, *J* 8.6); *m*/*z* (FABMS, Pos.) 499 $(M + H)^+$; *m*/*z* (HRFABMS) 499.3090 $[(M + H)^+$. Calc. for $C_{26}H_{47}O_6Si$: 499.3093].

Compound **16b** was a colourless oil; $[\alpha]_D^{25}$ −3.4 (*c* 1, $CHCl_3$); ν_{max}/cm^{-1} 3460, 2860, 1605, 1455, 1105, 1060 and 1005; $\delta_H(CDCl_3)$ 0.65 (6H, q, *J* 7.9), 0.98 (9H, t, *J* 7.9), 0.99 (3H, d, *J* 7.3), 1.34 (3H, s), 1.39 (3H, s), 1.51 (1H, ddd, *J* 4.6, 6.5 and 13.5), 1.59 (1H, ddd, *J* 5.5, 7.2 and 13.5), 2.22 (1H, m), 2.50 (1H, br s), 3.45 (1H, dd, *J* 2.5 and 6.3), 3.46 (1H, t, *J* 7.5), 3.79 (2H, m), 3.80 (3H, s), 4.07 (1H, t, *J* 3.2), 4.15 (1H, m), 4.20 (1H, dd, *J* 4.7 and 6.0), 4.50 (1H, d, *J* 10.9), 4.59 (1H, d, *J* 10.8), 5.20 (1H, br d, *J* 10.5), 5.32 (1H, br d, *J* 17.3), 6.02 (1H, ddd, *J* 6.2, 10.5 and 17.0), 6.87 (2H, d, *J* 8.6) and 7.27 (2H, d, *J* 8.6); *m*/*z* (FABMS, Pos.) 499 $(M + H)^+$; *m*/*z* (HRFABMS) 499.3098 $[(M + H)^+$. Calc. for $C_{26}H_{47}O_6Si$: 499.3093].

(3*R*,4*R*,5*S*,6*R*,8*R*)-8,9-Isopropylidenedioxy-6-methyl-3,5-(4-methoxybenzylidenedioxy)-4-triethylsilyloxynon-1-ene 17

To a stirred solution of compound **16a** (86.0 mg, 173 μmol) in CH_2Cl_2 (4 ml) and 1 M potassium phosphate buffer (pH 7.0; 0.22 ml) was added DDQ (78.9 mg, 348 μmol) and stirring was continued at room temperature for 10 min. After addition to it of saturated aqueous $NaHCO_3$, the reaction mixture was extracted with EtOAc. The extract was washed with water and brine, dried ($MgSO_4$) and evaporated to give a residue, which was purified on a silica gel column (hexane–EtOAc, 9:1) to afford compound **17** (73.6 mg, 149 μmol, 86%) as a colourless oil; $[\alpha]_D^{25}$ −10 (*c* 0.51, $CHCl_3$); ν_{max}/cm^{-1} 2945, 1610, 1455 and 1245; $\delta_H(CDCl_3)$ 0.63 (6H, q, *J* 7.8), 0.97 (9H, t, *J* 8.0), 1.00 (3H, d, *J* 6.9), 1.34 (3H, s), 1.39 (3H, s), 1.62 (1H, ddd, *J* 5.0, 8.5 and 13.5), 1.77 (1H, ddd, *J* 5.7, 8.2 and 13.5), 2.18 (1H, m), 3.40–3.60 (3H, m), 3.80 (3H, s), 3.98 (1H, t, *J* 7.5), 4.06 (1H, dd, *J* 6.2 and 7.7), 4.19 (1H, m), 5.29 (1H, d, *J* 10.5), 5.45 (1H, d, *J* 17.2), 5.53 (1H, s), 5.97 (1H, ddd, *J* 6.6, 10.5 and 17.1), 6.87 (2H, d, *J* 8.6) and 7.41 (2H, d, *J* 8.6); *m*/*z* (FABMS, Pos.) 497 $(M + H)^+$; *m*/*z* (HRFABMS) 497.2929 $[(M + H)^+$. Calc. for $C_{27}H_{47}O_6Si$: 497.2936].

(3*R*,4*R*,5*S*,6*R*,8*R*)-8,9-Isopropylidenedioxy-6-methyl-3,5-(4-methoxybenzylidenedioxy)-4-triethylsilyloxynonan-1-ol 18

To a stirred solution of compound **17** (42.0 mg, 85.2 μmol) in THF (800 μl) was added 0.5 M 9-BBN in THF (850 μl, 426 μmol), and stirring was continued at room temperature for 9 h. The reaction mixture was treated with 3 M aqueous NaOH (220 μl) and 30% H_2O_2 (220 μl), after which it was stirred at room temperature for 15 h. The reaction mixture was extracted with EtOAc, and the extract was washed with water and brine, dried ($MgSO_4$) and evaporated to give a residue. This was purified on a silica gel column (hexane–EtOAc, 9:1) to afford compound **18** (36.8 mg, 72.2 mmol, 85%) as a colourless oil; $[\alpha]_D^{25}$ −9.66 (*c* 1.48, $CHCl_3$); ν_{max}/cm^{-1} 3240, 2940, 1610, 1455 and 1380; $\delta_H(CDCl_3)$ 0.66 (6H, q, *J* 7.6), 0.99 (9H, t, *J* 6.5), 1.01 (3H, d, *J* 6.5), 1.34 (3H, s), 1.38 (3H, s), 1.45–1.90 (3H, m), 2.05–2.23 (2H, m), 3.30–3.56 (3H, m), 3.74 (1H, m), 3.80 (3H, s), 3.86 (1H, m), 4.05 (1H, dd, *J* 1.6 and 5.9), 4.17 (1H, m), 5.50 (1H, s), 6.87 (2H, d, *J* 8.7) and 7.36 (2H, d, *J* 8.7); *m*/*z* (FABMS, Pos.) 511 $(M + H)^+$; *m*/*z* (HRFABMS) 511.3119 $[(M + H)^+$. Calc. for $C_{27}H_{47}O_7Si$: 511.3091].

Coupling reaction between compounds 3 and 4

To a solution of oxalyl chloride (20 μl, 230 μmol) in CH_2Cl_2 (450 μl), DMSO (24 μl, 350 μmol) in CH_2Cl_2 (100 μl) was slowly added at −78 °C. The mixture was stirred for 10 min after which it was treated dropwise with a solution of compound **18** (57.3 mg, 112 μmol) in CH_2Cl_2 (200 μl). After being stirred at −78 °C for 45 min, the mixture was treated with Et_3N (80 μl, 580 μmol) and then allowed to warm to −50 °C. After addition to it of saturated aqueous NH_4Cl, the reaction mixture was extracted with Et_2O. The extract was washed with water and brine, dried ($MgSO_4$) and evaporated to afford the crude aldehyde **3** (57.2 mg), which was used in the following reaction without separation. To a stirred solution of **4** (84.7 mg, 253 μmol) in a mixture of Et_2O–pentane (2:3; 300 μl), was added a 1.7 M solution of Bu^{t}Li in pentane (300 μl, 510 μmol); stirring was continued at −78 °C for 10 min and then at room temperature for 1 h. After this a solution of the crude aldehyde (57.2 mg) in Et_2O (1.2 ml) was added at −78 °C to the reaction mixture which was then stirred at room temperature for 11 h. After addition to it of saturated aqueous NH_4Cl, the reaction mixture was extracted with Et_2O. The extract was washed with water and brine, dried ($MgSO_4$) and evaporated. The residue was chromatographed on a silica gel column (hexane–EtOAc, 9:1) to afford (2*S*,3*R*,5*S*,7*R*,8*R*,9*S*,10*R*,12*R*)-12,13-isopropylidenedioxy-3,10-dimethyl-7,9-(4-methoxybenzylidenedioxy)-8-triethylsilyloxy-2-[2-(trimethylsilyl)ethoxymethoxy]tridecan-5-ol **19a** (26.9 mg, 37.0 μmol, 38%) and the 5*R*-isomer **19b** (29.3 mg, 40.3 μmol, 40%) as a colourless oil. Compound **19a**: $[\alpha]_D^{25}$ +2.6 (*c* 0.56, $CDCl_3$); ν_{max}/cm^{-1} 3380, 2860, 1605, 1505, 1370 and 1240; $\delta_H(CDCl_3)$ 0.01 (9H, s), 0.56 (9H, q, *J* 7.9), 0.95 (3H, d, *J* 6.6), 0.96 (2H, m), 0.98 (6H, t, *J* 8.0), 1.00 (3H, d, *J* 6.7), 1.16 (3H, d, *J* 6.4), 1.16 (1H, m), 1.33 (3H, s), 1.37 (3H, s), 1.60 (1H, ddd, *J* 4.7, 8.7 and 13.6), 1.68 (1H, m), 1.71 (1H, m), 1.72 (1H, ddd, *J* 5.6, 8.6 and 13.6), 1.90 (1H, m), 2.00 (1H, br d, *J* 14.3), 2.15 (1H, m), 3.28 (1H, br s), 3.43 (1H, t, *J* 8.8), 3.50 (1H, t, *J* 7.4), 3.55 (1H, m), 3.61 (1H, m), 3.63 (1H, t, *J* 8.8), 3.79 (1H, m), 3.79 (3H, s), 3.98 (1H, m), 4.04 (1H, dd, *J* 6.1 and 7.9), 4.17 (1H, m), 4.67 (1H, d, *J* 7.0), 4.71 (1H, d, *J* 7.0), 5.52 (1H, s), 6.84 (2H, d, *J* 8.7), and 7.34 (2H, d, *J* 8.7); *m*/*z* (FABMS, Pos.) 735 $(M + H)^+$; *m*/*z* (HRFABMS) 735.4551 $[(M + H)^+$. Calc. for $C_{38}H_{71}O_9Si_2$: 735.4539].

Compound **19b** $[\alpha]_D^{25}$ −8.2 (*c* 0.19, $CDCl_3$); ν_{max}/cm^{-1} 3380, 2860, 1605, 1510, 1370 and 1240; $\delta_H(CDCl_3)$ 0.00 (9H, s), 0.65 (9H, q, *J* 7.9), 0.96 (2H, m), 0.97 (3H, d, *J* 7.0), 0.99 (6H, t, *J* 7.9), 1.01 (3H, d, *J* 6.8), 1.12 (3H, d, *J* 6.2), 1.34 (1H, s), 1.38 (3H, s), 1.48 (1H, m), 1.56 (1H, m), 1.62 (1H, ddd, *J* 4.7, 8.5 and 13.4), 1.69 (1H, ddd, *J* 2.3, 9.5 and 14.0), 1.76 (1H, ddd, *J* 5.6, 8.5 and 13.4), 1.83 (1H, m), 1.93 (1H, ddd, *J* 2.5, 8.4 and 14.0), 2.16 (1H, m), 2.76 (1H, br d, *J* 10.3), 3.46 (1H, t, *J* 8.8), 3.51 (1H, t, *J* 7.5), 3.53 (1H, m), 3.63 (2H, t, *J* 8.3), 3.64 (1H, m), 3.80 (3H, s), 3.84 (1H, m), 4.03 (1H, m), 4.06 (1H, dd, *J* 6.1 and 7.9), 4.19 (1H, m), 4.68 (1H, d, *J* 6.8), 4.73 (1H, d, *J* 6.8), 5.50 (1H, s), 6.85 (2H, d, *J* 8.7) and 7.37 (2H, d, *J* 8.7); *m*/*z* (FABMS, Pos.) 735 $(M + H)^+$; *m*/*z* (HRFABMS) 735.4526 $[(M + H)^+$. Calc. for $C_{38}H_{71}O_9Si_2$: 735.4539].

(2*S*,3*R*,5*S*,7*R*,8*R*,9*S*,10*R*,12*R*)-12,13-Isopropylidenedioxy-3,10-dimethyl-7,9-(4-methoxybenzylidenedioxy)-5-methoxymethoxy-8-triethylsilyloxy-2-[2-(trimethylsilyl)ethoxymethoxy]tridecane 20

A CH_2Cl_2 solution (30 μl) of compound **19a** (26.0 mg, 40.3 μmol) was treated with Pr$^i_2$NEt (120 μl, 700 μmol) and chloromethyl methyl ether (MOMCl, 20 μl, 260 μmol) at room temperature for 17 h. After addition of 1 M aqueous HCl, the reaction mixture was extracted with $CHCl_3$. The extract was washed with water and brine, dried ($MgSO_4$) and evaporated to afford a residue. This was purified on a silica gel column (hexane–EtOAc, 9:1) to afford compound **20** (25.8 mg, 34.7 μmol, 86%) as a colourless oil; $[\alpha]_D^{23}$ +12 (*c* 0.28, $CHCl_3$); ν_{max}/cm^{-1} 2955, 1620, 1520, 1380, 1250, 1115, 1035 and 835;

$\delta_H(CDCl_3)$ 0.01 (9H, s), 0.66 (6H, q, *J* 7.9), 0.91 (3H, d, *J* 6.7), 0.99 (9H, t, *J* 7.9), 1.00 (3H, d, *J* 6.7), 1.08 (3H, d, *J* 6.3), 1.35 (3H, s), 1.39 (3H, s), 1.44 (1H, ddd, *J* 5.0, 9.0 and 14.0), 1.5–1.7 (3H, m), 1.79 (1H, ddd, *J* 5.6, 8.3 and 13.8), 1.95 (1H, br dd, *J* 10.1 and 12.6), 2.17 (1H, m), 3.39 (3H, s), 3.39 (1H, dd, *J* 8.8 and 20.4), 3.52 (1H, br d, *J* 9.4), 3.53 (1H, d, *J* 7.4), 3.58 (1H, m), 3.63 (2H, m), 3.75 (1H, br t, *J* 9.0), 3.80 (3H, s), 3.94 (1H, m), 4.07 (1H, dd, *J* 5.9 and 7.8), 4.20 (1H, m), 4.64 (1H, d, *J* 6.7), 4.65 (1H, d, *J* 7.0), 4.70 (1H, d, *J* 7.0), 4.73 (1H, d, *J* 6.7), 5.47 (1H, s), 6.87 (2H, d, *J* 8.7) and 7.39 (1H, d, *J* 8.7); *m/z* (FABMS, Pos.) 779 $(M + H)^+$; *m/z* (HRFABMS) 779.4786 $[(M + H)^+$. Calc. for $C_{40}H_{75}O_{10}Si_2$: 779.4801].

(2*S*,3*R*,5*S*,7*R*,8*R*,9*S*,10*R*,12*R*)-3,10-Dimethyl-12,13-isopropylidenedioxy-7,9-(4-methoxybenzylidenedioxy)-5-methoxymethoxytridecane-2,8-diol 21

To a solution of the MOM derivative **20** (22 mg, 29.7 μmol) was added a 1 M THF solution (100 μl, 100 μmol) of TBAF after which the solvent was evaporated *in vacuo*. 1,3-Dimethyl-3,4,5,6-tetrahydropyrimidin-2(1*H*)-one (DMPU, 30 μl) and crushed 4 Å molecular sieves (10 mg) were added to the residue, and the reaction mixture was stirred at 80 °C for 15 h. After addition of Et_2O and water, the reaction mixture was extracted with Et_2O. The extract was washed with water, dried ($MgSO_4$) and evaporated *in vacuo*. The residue was chromatographed on a silica gel column (hexane–EtOAc, 95:5) to afford compound **21** (12.8 mg, 24.3 μmol, 82%) as a colourless oil; $[\alpha]_D^{25}$ +11 (*c* 0.90, $CHCl_3$); ν_{max}/cm^{-1} 3340, 2970, 2935, 1620, 1520, 1380, 1250, 1035 and 665; $\delta_H(CDCl_3)$ 0.90 (3H, d, *J* 6.3), 1.03 (3H, d, *J* 6.9), 1.13 (3H, d, *J* 6.3), 1.35 (3H, s), 1.40 (3H, s), 1.50–1.72 (5H, m), 1.75–1.85 (2H, m), 2.0–2.1 (2H, m), 2.25 (1H, m), 3.60 (1H, br d, *J* 4.8), 3.41 (3H, s), 3.50 (1H, d, *J* 9.2), 3.52 (1H, dd, *J* 2.2 and 9.2), 3.58 (1H, m), 3.71 (1H, dt, *J* 5.9 and 8.8), 3.80 (3H, s), 3.99 (1H, m), 4.06 (1H, dd, *J* 6.0 and 7.7), 4.22 (1H, m), 4.69 (1H, d, *J* 6.9), 4.75 (1H, d, *J* 6.8), 5.48 (1H, s), 6.87 (2H, d, *J* 8.7) and 7.38 (2H, d, *J* 8.7); *m/z* (FABMS, Pos.) 527 $(M + H)^+$; *m/z* (HRFABMS) 527.3201 $[(M + H)^+$. Calc. for $C_{28}H_{47}O_9$: 527.3219].

(3*R*,5*S*,7*R*,9*S*,10*R*,12*R*)-3,10-Dimethyl-12,13-isopropylidenedioxy-7,9-(4-methoxybenzylidenedioxy)-5-methoxymethoxytridecane-2,8-dione 24

To a solution of the diol derivative **21** (12.5 mg, 23.7 μmol) in CH_2Cl_2 (20 μl) were added 4 Å (molecular sieves 10 mg) and 4-methylmorpholine *N*-oxide (8.4 mg, 70 μmol). After the mixture had been stirred at room temperature for 10 min, tetrapropylammonium perruthenate (80 μg, 0.23 μmol) was added to it, and stirring was continued at room temperature for 3 h. After insoluble materials had been filtered off from the reaction mixture, it was evaporated *in vacuo*, and the residue was purified by chromatography on a silica gel column (hexane–EtOAc, 4:1) to afford compound **24** (8.9 mg, 17.1 μmol, 72%) as a colourless oil; $[\alpha]_D^{25}$ +10 (*c* 0.90, $CHCl_3$); ν_{max}/cm^{-1} 2950, 1705, 1610, 1510, 1380, 1245 and 1025; $\delta_H(CDCl_3)$ 0.99 (3H, d, *J* 6.8), 1.07 (3H, d, *J* 7.0), 1.34 (3H, s), 1.39 (3H, s), 1.49 (1H, m), 1.55 (1H, m), 1.75 (1H, ddd, *J* 3.5, 10.2 and 14.2), 1.81 (1H, ddd, *J* 6.3, 8.7 and 14.6), 2.01 (1H, dd, *J* 5.1 and 8.4), 2.05 (1H, m), 2.15 (3H, s), 2.23 (1H, ddd, *J* 3.9, 6.8 and 14.6), 2.51 (1H, m), 2.72 (1H, m), 3.35 (3H, s), 3.52 (1H, t, *J* 7.7), 3.82 (1H, m), 3.82 (3H, s), 4.05 (1H, dd, *J* 6.2 and 8.0), 4.17 (1H, m), 4.51 (1H, br s), 4.53 (1H, dd, *J* 2.6 and 3.8), 4.57 (1H, m), 4.66 (1H, d, *J* 6.8), 5.93 (1H, s), 6.91 (2H, d, *J* 8.8) and 7.44 (2H, d, *J* 6.9); *m/z* (FABMS, Pos.) $(M + H)^+$; *m/z* (HRFABMS) 523.2886 $[(M + H)^+$. Calc. for $C_{28}H_{43}O_9$; 523.2906].

(3*R*,5*S*,7*R*,9*S*,10*R*,12*R*)-2,8-Di(1,3-dithiolan-2-yl)-3,10-dimethyl-12,13-isopropylidenedioxy-7,9-(4-methoxybenzylidenedioxy)-5-methoxymethoxytridecane 25

To a solution of diketone **24** (8.5 mg, 16.3 μmol) and zinc iodide (0.1 mg, 0.3 μmol) in diethyl ether (50 μl) was added ethylenedithiobis(trimethylsilane) (15.5 mg, 65.2 μmol) at −20 °C, and the reaction mixture was stirred at 0 °C for 5 h. After addition to it of water, the mixture was extracted with diethyl ether, and the extract was purified on a silica gel column (hexane–EtOAc, 8:1) to afford compound **25** (5.7 mg, 8.5 μmol, 52%) as a colourless oil, together with recovered **24** (2.9 mg, 5.5 μmol, 34%).

Compound **25** $[\alpha]_D^{25}$ +13 (*c* 0.40, $CDCl_3$); ν_{max}/cm^{-1} 2970, 1620, 1520, 1380, 1250, 1035 and 655; $\delta_H(CDCl_3)$ 0.90 (3H, d, *J* 6.3), 1.03 (3H, d, *J* 6.9), 1.34 (3H, s), 1.35 (3H, s), 1.40 (3H, s), 1.40–1.90 (11H, m), 2.0–2.1 (2H, m), 2.35 (1H, m), 3.60 (1H, br d, *J* 4.8), 3.41 (3H, s), 3.53 (1H, d, *J* 9.2), 3.54 (1H, dd, *J* 2.2 and 9.2), 3.60 (1H, m), 3.71 (1H, dt, *J* 5.9 and 8.8), 3.80 (3H, s), 3.84 (1H, m), 4.02 (1H, dd, *J* 6.0 and 7.7), 4.12 (1H, m), 4.70 (1H, d, *J* 6.9), 4.75 (1H, d, *J* 6.8), 5.50 (1H, s), 6.87 (2H, d, *J* 8.7) and 7.38 (2H, d, *J* 8.7); *m/z* (FABMS Pos.) 675 $(M + H)^+$; *m/z* (HRFABMS) 675.2532 $[(M + H)^+$. Calc. for $C_{32}H_{51}O_7S_4$: 675.2517].

(3*R*,5*S*,7*R*,9*S*,10*R*,12*R*)-2,8-Di(1,3-dithiolan-2-yl)-3,10-dimethyl-5,7,9,12,13-pentaacetyloxytridecane 26

To a solution of the dithiolane **25** (6.2 mg, 9.1 μmol) in THF (50 μl) was added $TsOH \cdot H_2O$ (0.1 mg, 0.5 μmol) and stirring was continued at room temperature for 5 h. After addition to it of 0.1 M aqueous $NaHCO_3$, the reaction mixture was extracted with EtOAc, and the extract washed with water. It was then evaporated *in vacuo*, and the residue was treated with Ac_2O (50 μl) and pyridine (50 μl) at room temperature for 17 h. After evaporation of the solvent from the mixture, the residue was chromatographed on silica gel (hexane–EtOAc, 10:1) to afford compound **26** (4.7 mg, 6.9 mmol, 76%) as a colourless oil; $[\alpha]_D^{25}$ +8 (*c* 0.32, $CHCl_3$); ν_{max}/cm^{-1} 2970, 2935, 1720, 1620, 1520, 1380 and 1035; $\delta_H(CDCl_3)$ 0.90 (3H, d, *J* 6.3), 1.03 (3H, d, *J* 6.9), 1.34 (3H, d, *J* 6.3), 1.40–1.95 (11H, m), 2.04 (1H, m), 2.05 (3H, s), 2.08 (1H, m), 2.08 (3H, s), 2.10 (6H, s), 2.11 (3H, s), 2.32 (1H, m), 4.67 (1H, m), 4.87 (1H, m), 4.97 (1H, m), 5.01 (1H, dd, *J* 6.0 and 7.7), 5.33 (1H, m) and 5.68 (2H, m); *m/z* (FABMS, Pos.) 683 $(M + H)^+$; *m/z* (HRFABMS) 683.2025 $[(M + H)^+$. Calc. for $C_{29}H_{47}O_{10}S_4$: 683.2051].

(3*R*,5*S*,7*R*,9*S*,10*R*,12*R*)-3,10-Dimethyl-5,7,9,12,13-pentaacetyloxytridecane-2,8-dione 2

To a solution of **26** (2.0 mg, 2.9 μmol) in $CHCl_3$ (40 μl) were added $CaCO_3$ (0.6 mg, 6 μmol) and then a 1 M methanolic solution of $Hg(ClO_4)_2$ (6 μl, 6 μmol). The mixture was stirred at room temperature for 10 min, after which it was diluted with diethyl ether (500 μl), filtered and evaporated *in vacuo*. The residue was purified on a silica gel column (hexane–EtOAc, 4:1) to afford **2** (0.9 mg, 1.7 μmol, 59%) as colourless oil; $[\alpha]_D^{25}$ +12 (*c* 0.10, $CHCl_3$); ν_{max}/cm^{-1} 2970, 2950, 1740, 1720, 1620, 1520, 1250 and 1035; $\delta_H(CDCl_3)$ 0.90 (3H, d, *J* 6.3), 1.03 (3H, d, *J* 6.9), 1.34 (3H, d, *J* 6.3), 1.40–1.65 (4H, m), 1.80–1.95 (3H, m), 2.05 (3H, s), 2.08 (3H, s), 2.09 (1H, m), 2.10 (6H, s), 2.11 (3H, s), 2.13 (1H, m), 2.18 (3H, s), 2.24 (1H, m), 4.54 (1H, m), 4.69 (1H, m), 4.86 (1H, m), 5.06 (1H, dd, *J* 6.0 and 7.7), 5.23 (1H, m) and 5.64 (1H, m); *m/z* (FABMS, Pos.) 531 $(M + H)^+$; *m/z* (HRFABMS) 531.2409 $[(M + H)^+$. Calc. for $C_{44}H_{65}O_{12}$: 531.2441].

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