Convergent synthesis of the spiroketal core of the HIV-1 protease inhibitors the didemnaketals

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A stereocontrolled and efficient synthetic approach to the spiroketal compound **4a** and its C1″-epimer **4b**, the core of the HIV-protease inhibitor didemnaketals isolated from the ascidian *Didemnum* sp., is developed through a multi-step approach from natural L-(−)-menthone. This route involves the highly diastereoselective construction of four chiral carbon centers by intramolecular chiral induction.

Introduction

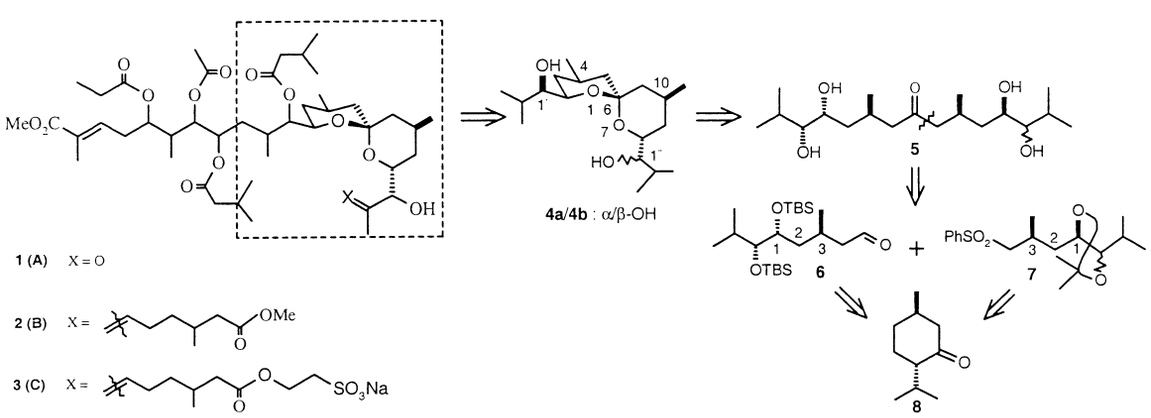
The didemnaketals, new complex, naturally occuring marine spiroketal compounds isolated from the ascidian *Didemnum* sp. by Faulkner and colleagues, have been found to inhibit HIV-1 protease, with IC_{50}-values of **1** and **2** being 2 μM and 10 μM, respectively.[1] In addition, their structural features, which include the presence of two branching methyl groups at two β-positions of the spiro center and a long side-chain bearing multi-acetoxy groups, are significant. However, their synthesis has not been reported previously, and it is important to perform studies toward their total synthesis. Our research interest in the chemistry of this class of compound is focused on the development of an efficient synthetic approach, in which the construction of the key spiroketals **4a/4b** is the challenging work. Since the original report did not determine the absolute stereochemistry of the naturally occurring didemnaketals, we selected a pair of epimers **4a/4b** as the target molecules with such configurations as shown in Scheme 1. In this paper we present a convergent stereocontrolled approach to the spiroketals **4a/4b**.

Results and discussion

In developing a synthetic strategy to access **4a/4b** (Scheme 1), the synthesis of the key open-chain δ,δ′-dihydroxy ketone intermediate **5** was envisaged,[2] which would be further disconnected into two similar pieces **6** and **7**, in terms of its structural symmetry. Both **6** and **7** contain the similar key '1-oxygen-3-methyl' moiety, which reminded us that the abundant and natural L-(−)-menthone **8** could be employed as a starting material due to the presence of a chiral methyl in **8**. So our synthesis work started from the construction of two intermediates **6** and **7**.

The construction of intermediate **6** from **8** is shown in Scheme 2. Thus, the known α,β-unsaturated ketone **9** was prepared from L-(−)-menthone using a literature procedure,[3] and then was subjected to stereoselective epoxidation with basic H_2O_2 to afford exclusively the epoxy ketone **10** in 71% yield.[4] After several attempts to ring open **10** with hydrazine, the key allylic alcohol intermediate **11** was prepared in reasonable yield (65%).[5] Direct ozonization of **11** without protecting the hydroxy group by carefully monitoring the reaction formed the keto-aldehyde product, which was obtained actually as an intramolecular hemiacetal **12** (2 isomers, *ca.* 1/1) in 85% yield. Subsequent reduction of the ketone carbonyl of **12** with $NaBH_4$ at low temperature gave the sole product **13** in 80% yield. Fortunately, the stereochemistry of the newly formed hydroxy group of **13** was determined to have the α-hydroxy configuration on the basis of the NOESY spectra for the acetonide of **14**. Thus, all of the chiral carbon centers required for the intermediate **6** were constructed. Trans-acetalization of the hemiacetal **13** with propane-1,3-dithiol, followed by protection of the two hydroxy groups with TBSCl (*tert*-butyldimethylsilyl chloride), and final deprotection of the aldehyde carbonyl, afforded the intermediate **6** (52% yield, three steps).

Preparation of the intermediate **7** is presented in Scheme 3, in which the initial reduction of the α,β-unsaturated ketone **9** with $NaBH_4$ furnished exclusively the allylic alcohol **16** in 90% yield. The stereochemistry of the newly formed hydroxy group of **16**



Scheme 1

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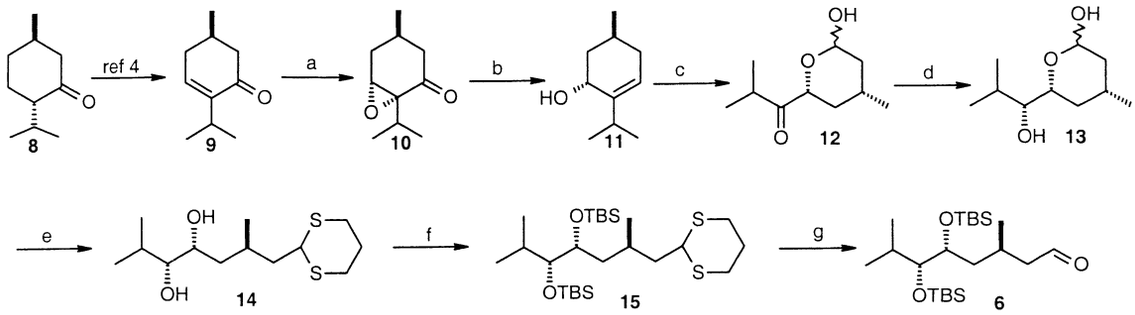
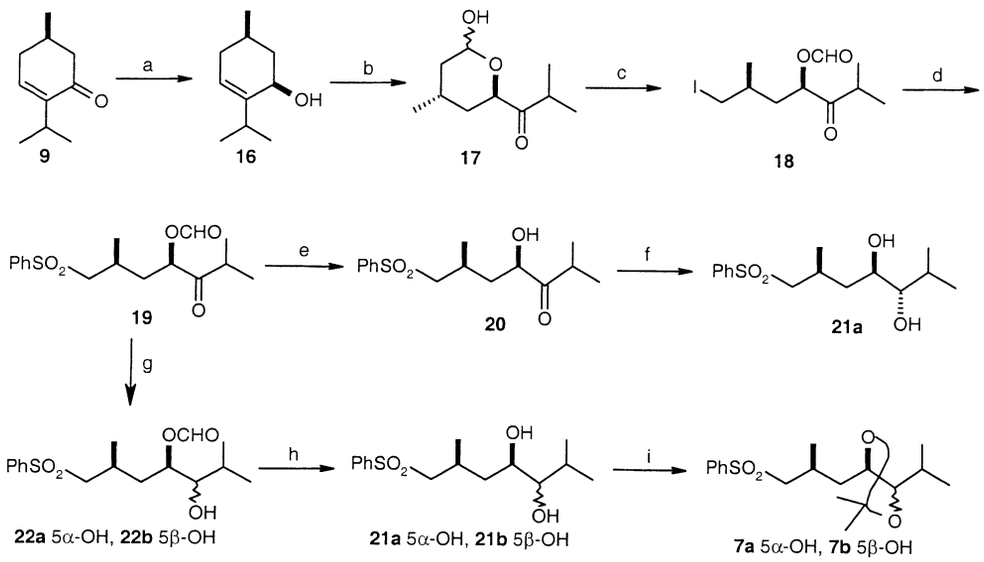


Scheme 2 *Reagents and conditions (yields)*: (a) H_2O_2, NaOH, MeOH, 25 °C (71%); (b) 85% $NH_2NH_2{\cdot}H_2O$, HOAc, 25 °C (65%); (c) O_3, CH_2Cl_2, −78 °C; then Me_2S (85%); (d) $NaBH_4$, MeOH, −78 °C (80%); (e) propane-1,3-dithiol, $BF_3{\cdot}OEt_2$, 0 °C (78%); (f) TBDMSCl, imidazole, DMF, 90 °C; (g) $CaCO_3$, $HgCl_2$, 80% MeCN–water (66%) (2 steps).



Scheme 3 *Reagents and conditions (yields)*: (a) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, 0 °C (90%); (b) O_3, CH_2Cl_2, −78 °C; then Me_2S (85%); (c) I_2, IBDA, *hv*, 25 °C (70%); (d) $PhSO_2Na$, DMF (90%); (e) K_2CO_3, MeOH, 25 °C (88%); (f) $Zn(BH_4)_2$, THF, 0 °C (93%); (g) $NaBH_4$, MeOH, −78 °C (90%); (h) K_2CO_3, MeOH, 25 °C; (i) acetone, PTSA (84%) (2 steps). IBDA = (Diacetoxyiodo)benzene.

was established to have the β-configuration from the literature.[6] Direct ozonization of **16** in the same way as **11** afforded the hemiacetal **17** (2 isomers, *ca.* 1/1) in 85% yield, which was subjected to decarboxylation–iodination with (diacetoxyiodo)-benzene (IBDA) to afford the iodide **18** (70%) bearing the C4-formyloxy group.[7] Sulphonation of **18** with $PhSO_2Na$ gave the sulfone **19** in 90% yield.[8] Deformylation of **19** with K_2CO_3–MeOH followed by a regular reduction with $NaBH_4$ gave the diol **21** as a mixture of two isomers (*ca.* 1/1), which could not be separated by column chromatography. The $Zn(BH_4)_2$ reduction of the ketone carbonyl of **20** following a literature procedure could furnish predominantly the product **21a** with the α-hydroxy configuration in 93% yield,[8] but its epimer **21b** with the β-hydroxy configuration has not been obtained due to that no direct procedure is available. Therefore, direct reduction of **19** afforded **22a** and **22b** in 90% yield, which could be separated by column chromatography. Deformylation of **22a** and **22b** separately with K_2CO_3–MeOH then furnished **21a** and **21b** in the same 88% yield, respectively. The stereochemistry of **21a** was further determined by the NOESY spectra of **7a**. Thus, the diastereoselective construction of two chiral carbon centers bearing hydroxy groups was achieved. Protection of the two hydroxy groups of **21a** and **21b** as an acetonide furnished the intermediates **7a** and **7b** in the same 95% yield, respectively.

The coupling of **6** and **7a** was performed as shown in Scheme 4. Deprotonation of the sulfone **7a** with *n*-BuLi, followed by the addition of aldehyde **6**, led to the β-hydroxy sulfone **23a** in 73% yield.[9] Oxidation of the hydroxy group of **23a** with PDC, followed by desulfonation with 6% sodium amalgam, gave the precursor **24a** (66%) for the spirocyclization,[10] which corresponded to the open-chain intermediate **5**. Thus, treatment of **24a** with a solution of 40% aq. hydrofluoric acid and acetonitrile led to full deprotection–spirocyclization to form the target spiroketal **4a** in 67% yield.[11] In the same way above, the epimer **4b** also has been synthesized from the diastereoisomerically pure **7b** (30% yield, three steps *via* intermediates **23b** and **24b**).

In conclusion, an efficient synthetic approach to the spiroketal core of the HIV-1 protease inhibitor didemnaketals is described. Further studies concerning the total synthesis and biological activity are ongoing.

Experimental

^1H NMR and ^{13}C NMR spectra were recorded for $CDCl_3$ solutions on a Bruker 200 MHz or a Bruker 400 MHz instrument with TMS as internal standard. *J*-Values are in Hz. MS data were measured with EI (70 eV) and HRMS data were measured with FAB or ESI techniques. Optical rotations were determined on Perkin-Elmer Model 341, and $[\alpha]_D$-values are given in units of 10^{-1} deg cm^2 g^{-1}. Compounds were purified by column chromatography on silica gel H, from the Qingdao Marine Chemical Factory, and elution with solvent mixtures of light petroleum (distillation range 60–90 °C) and ethyl acetate. Ether refers to diethyl ether.

(1*R*,4*R*,6*R*)-1-Isopropyl-4-methyl-7-oxa-bicyclo[4.1.0]heptan-2-one 10

To a stirred solution of **9** (1.86 g, 12.2 mmol) and 30% hydrogen peroxide (4.6 mL) in methanol (30 mL) was added 6 M NaOH

(1.0 mL) at room temperature. The mixture was stirred for 7 h after which the solvent was removed *in vacuo*. The residue was extracted with ether (3 × 30 mL) and the extracts were washed with brine, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was purified by column chromatography to give **10** (1.46 g, 71%), $[\alpha]_D^{25}$ +61 (*c* 1.0 in MeOH); δ_H(200 MHz) 3.46 (1H, br s, CH_2CHO), 2.75–1.65 (6H, m, CH_2CHCH_2 and $CHMe_2$), 1.10 (6H, d, *J* 6.8, $CHMe_2$), 0.90 (3H, d, *J* 6.5, $CHCH_3$); δ_C(50 MHz) 205.5 (C), 63.6 (C), 57.2 (CH), 46.0, 31.7, 25.6, 23.7, 21.0, 18.4, 16.0 (2 × CH, 2 × CH_2 and 3 × CH_3).

(1*R*,5*S*)-2-Isopropyl-5-methylcyclohex-2-enol 11

To a stirred solution of **10** (2.68 g, 16.0 mmol) and 85% hydrazine hydrate (18.0 mL) in methanol (40 mL) was added a portion of acetic acid at 0 °C. After stirring of the mixture for 8 h at room temperature, the solvent was removed *in vacuo*. The residue was extracted with ether (3 × 40 mL), and the extracts were washed successively with saturated aq. $NaHCO_3$ and brine, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was purified by column chromatography to give **11** (1.58 g, 65%), $[\alpha]_D^{25}$ +68 (*c* 0.57 in EtOH); δ_H(400 MHz) 5.53 (1H, m, CH_2CH=C), 4.11 (1H, br s, $CCHOHCH_2$), 2.42 (1H, m, $CHCMe_2$), 2.15–1.24 (5H, m, CH_2CHCH_2), 1.05 (3H, d, *J* 7.0, $CHMe^AMe^B$), 1.03 (3H, d, *J* 7.0, $CHMe^AMe^B$), 0.94 (3H, d, *J* 6.5, $CHCH_3$).

(4*R*,6*R*)-2-Hydroxy-4-methyl-6-(2′-methylpropionyl)tetrahydropyran 12

Into a cold (−78 °C) solution of compound **11** (1.0 g, 5.9 mmol) in CH_2Cl_2 (50 mL) was bubbled ozone. When the reaction was complete (TLC) the reaction mixture was treated with Me_2S (2 mL), stirred overnight, and evaporated *in vacuo*. The residue was purified by column chromatography to give **12** (1.0 g, 85%) as a mixture of two isomers in the ratio 1 : 1. δ_H(400 MHz) (2 isomers) 5.47 (1H, d, *J* 3.2, $OCHOH$), 4.79 (1H, dd, *J* 9.4 and 1.9, $OCHOH$), 4.60 (1H, dd, *J* 12.2 and 2.4, CH_2CHOCH), 4.04 (1H, dd, *J* 11.8 and 2.4, CH_2CHOCH), 3.12 (1H, m, $CHCMe_2$), 2.99 (1H, m, $CHCMe_2$), 2.25–0.90 (10H, m, 2 × CH_2CHCH_2), 1.08 (12H, d, *J* 6.8, 2 × $CHCMe_2$), 1.01 (3H, d, *J* 6.0, $CHCH_3$), 0.95 (3H, d, *J* 6.0, $CHCH_3$); δ_C(100 MHz) 213.8 (C), 213.0 (C), 96.4 (CH), 92.3 (CH), 79.6 (CH), 73.3 (CH), 41.0 (CH_2), 37.8 (CH_2), 37.4 (CH), 36.0 (CH), 35.8 (CH_2), 35.4 (CH_2), 30.0 (CH), 29.3 (CH), 23.8 (CH_3), 22.0 (CH_3), 21.6 (CH_3), 18.3 (CH_3), 18.2 (CH_3), 14.1 (CH_3); *m*/*z* (EI) 185 (M^+ − 1, 4%), 169 (30), 115 (64), 71 (100); HRMS (ESI) Found: $(M + Na)^+$, 209.1144. $C_{10}H_{18}O_3Na$ requires *M* + *Na*, 209.1148.

(4*R*,6*R*)-6-[(1*R*)-1-Hydroxy-2-methylpropyl)]-4-methyltetrahydropyran-2-ol 13

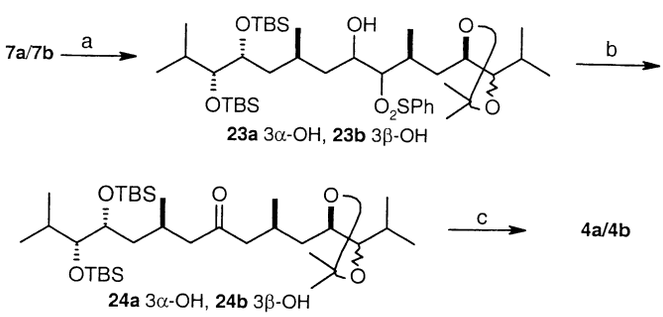
To a cooled (−78 °C), stirred solution of **12** (1.1 g, 5.90 mmol) in MeOH (30 mL) was added $NaBH_4$ (210 mg, 5.90 mmol). The mixture was stirred at −78 °C for 1.0 h, then the solvent was removed *in vacuo*. The obtained residue was diluted with ether (80 mL) and the extracts were washed successively with water (20 mL) and brine, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was purified by column chromatography to give **13** (0.89 g, 80%) as a mixture of two isomers in the ratio 1 : 1 as a colorless oil. δ_H(400 MHz) (2 isomers) 5.37 (1H, d, *J* 2.5, $OCHOH$), 4.77 (1H, dd, *J* 9.7 and 1.3, $OCHOH$), 4.07 (1H, dt, *J* 9.7 and 2.5, CH_2CHOCH), 3.54 (1H, ddd, *J* 11.5, 3.5 and 2.5, CH_2CHOCH), 3.38 (1H, dd, *J* 8.1 and 3.5, $CHCHOHCH$), 3.27 (1H, dd, *J* 8.1 and 3.5, $CHCHOHCH$), 1.90–1.07 (12H, m, 2 × CH_2CHCH_2 and 2 × $CHCMe_2$), 1.01 (6H, d, *J* 6.4, $CHCMe_2$), 1.00 (3H, d, *J* 6.4, $CHCH_3$), 0.95 (3H, d, *J* 6.6, $CHMe^AMe^B$), 0.88 (3H, d, *J* 6.6, $CHMe^AMe^B$), 0.86 (3H, d, *J* 6.6, $CHCH_3$); δ_C(100 MHz) 96.2 (CH), 92.2 (CH), 78.4 (CH), 78.1 (CH), 76.3 (CH), 69.7 (CH), 41.4, 38.4, 32.0, 31.4, 29.8, 29.3, 29.2, 28.7, 23.1, 22.3, 21.8, 19.0, 18.8, 18.7 (4 × CH, 4 × CH_2 and 6 × CH_3); *m*/*z* (2 isomers) (EI) 171 ($M^+ + 1 - H_2O$, 8%), 170 ($M^+ - H_2O$, 13), 115 (92), 71 (100); HRMS (ESI) Found: $(M + H)^+$, 211.1144. $C_{10}H_{21}O_3$ requires *M* + *H*, 209.1148.

2-[(2*R*,4*R*,5*R*)-4,5-Dihydroxy-2,6-dimethylheptyl]-1,3-dithiane 14

To a solution of **13** (800 mg, 4.26 mmol) in CH_2Cl_2 (15 mL) were added propane-1,3-dithiol (1.6 mL, 16.0 mmol) and $BF_3{\cdot}Et_2O$ (0.20 mL). Stirring was continued for 1.5 h at 0 °C. The mixture was diluted with CH_2Cl_2 and saturated aq. $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic layers were dried over Na_2SO_4 and evaporated *in vacuo*. The residue was purified by column chromatography to give **14** (0.88 g, 78%), $[\alpha]_D^{25}$ +23 (*c* 1.0 in $CHCl_3$); δ_H(400 MHz) 4.10 (1H, m, CH_2CHS_2), 3.98 (1H, m, $CH_2CHOHCH$), 3.66 (1H, dd, *J* 8.1 and 3.8, $CHCHOHCH$), 2.91–2.79 (4H, m, $SCH_2CH_2CH_2S$), 2.11–1.17 (8H, m, CH_2CHCH_2, $SCH_2CH_2CH_2S$ and $CHCMe_2$), 1.04 (3H, d, *J* 6.6, $CHMe^AMe^B$), 0.97 (3H, d, *J* 6.6, $CHMe^AMe^B$), 0.87 (3H, d, *J* 6.8, $CHCH_3$); δ_C(100 MHz) 83.9 (CH), 75.0 (CH), 45.1 (CH), 43.9 (CH_2), 35.9 (CH_2), 30.8 (CH_2), 30.6 (CH_2), 28.8 (CH), 27.3 (CH_2), 25.9 (CH), 20.4 (CH_3), 19.0 (CH_3), 18.7 (CH_3); *m*/*z* (EI) 278 (M^+, 6%), 246 (56), 131 (59), 105 (100); HRMS (FAB) Found: $(M + H)^+$, 279.1200. $C_{13}H_{27}O_2S_2$ requires *M* + *H*, 279.1212.

2-[(2*R*,4*R*,5*R*)-4,5-Isopropylidenedioxy-2,6-dimethylheptyl]-1,3-dithiane, the acetonide of 14

To a solution of **14** (55 mg, 0.21 mmol) in dry acetone (2 mL) was added a catalytic amount of PTSA. The mixture was stirred for 8 h at room temperature, and was then diluted with ether (30 mL) and washed successively with saturated aq. $NaHCO_3$ and brine, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was purified by column chromatography to give the acetonide of **14** (50 mg, 79%), $[\alpha]_D^{25}$ +69 (*c* 1.0 in



Scheme 4 *Reagents and conditions (yields)*: (a) *n*-BuLi, THF, −78 °C, 30 min; then **6**, −78 °C, 2.5 h (73%); (b) i) PDC, CH_2Cl_2; ii) Na(Hg), MeOH, 0 °C (66%); (c) 40% HF, MeCN, 25 °C (67%).

$CHCl_3$); δ_H(400 MHz) 4.05 (1H, ddd, *J* 11.6, 5.0 and 2.4, $CH_2CHOHCH$), 4.03 (1H, t, *J* 7.4, CH_2CHS_2), 3.59 (1H, dd, *J* 9.8 and 5.0, $CHCHOHCH$), 2.91–2.70 (4H, m, $SCH_2CH_2CH_2S$), 2.10–0.85 (8H, m, $CHMe_2$, CH_2CHCH_2 and $SCH_2CH_2CH_2S$), 1.38 (3H, s, CMe^AMe^B), 1.26 (3H, s, CMe^AMe^B), 0.97 (3H, d, *J* 6.5, $CHMe^AMe^B$), 0.89 (3H, d, *J* 6.5, $CHMe^AMe^B$), 0.78 (3H, d, *J* 6.6, $CHCH_3$); δ_C(100 MHz) 107.5 (C), 83.9 (CH), 74.9 (CH), 45.2 (CH), 43.9 (CH_2), 35.9 (CH_2), 30.4 (2 × CH_2), 28.7 (CH_3), 27.2 (CH), 26.2 (CH_3), 26.0 (CH_2), 25.9 (CH), 20.4 (CH_3), 19.0 (CH_3), 18.7 (CH_3); HRMS (FAB) Found: $(M + H)^+$, 319.1598. $C_{16}H_{31}O_2S_2$ requires *M* + *H*, 319.1602.

2-[(2*R*,4*R*,5*R*)-4,5-Bis(*tert*-butyldimethylsilyloxy)-2,6-dimethylheptyl]-1,3-dithiane 15

To a solution of diols **14** (840 mg, 3.02 mmol) in DMF (5 mL) were added imidazole (1.03 g, 15.2 mmol) and TBDMSCl (1.09 g, 7.2 mmol). The reaction mixture was stirred for 24 h at 90 °C, then diluted with ether (80 mL), washed successively with water (3 × 20 mL) and brine, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was purified by column chromatography to give **15** (1.26 g, 82%), $[\alpha]_D^{25}$ +12.0 (*c* 1.26 in $CHCl_3$); δ_H(400 MHz) 4.08 (1H, dd, *J* 6.8 and 8.1, CH_2CHS_2), 3.76 (1H, d, *J* 9.7, $CHOH$), 3.34 (1H, d, *J* 7.6, $CHOH$), 2.91–2.78 (4H, m, $SCH_2CH_2CH_2S$), 2.10–1.10 (8H, m, $CHMe_2$, CH_2CHCH_2 and $SCH_2CH_2CH_2S$), 0.91–0.86 (27H, m, 2 × CMe_3, $CHCH_3$ and $CHMe_2$), 0.12 (3H, s, $SiCH_3$), 0.07 (3H, s, $SiCH_3$), 0.06 (3H, s, $SiCH_3$), 0.04 (3H, s, $SiCH_3$); δ_C(100 MHz) 83.0 (CH), 72.7 (CH), 45.6 (CH), 43.7 (CH_2), 39.8 (CH_2), 31.8 (CH_2), 30.6 (CH), 30.5 (CH_2), 26.2 (6 × CH_3, CH_2), 25.8 (CH), 20.3 (CH_3), 19.3 (CH_3), 18.9 (CH_3), 18.5 (C), 18.1 (C), −3.4 (CH_3), −3.5 (CH_3), −4.6 (CH_3), −4.8 (CH_3); *m*/*z* (EI) 449 (M^+ − 57, 3%), 319 (20), 185 (50), 147 (59), 84 (100).

(3*R*,5*R*,6*R*)-5,6-Bis(*tert*-butyldimethylsilyloxy)-3,7-dimethyloctanal 6

A solution of the dithiane **15** (900 mg, 1.78 mmol) in 80% acetonitrile (25 mL) was added to an efficiently stirred solution of mercuric chloride (2.01 g, 7.48 mmol) and powdered calcium carbonate (748 mg, 7.48 mmol) in 80% acetonitrile (30 mL). The mixture was stirred and heated at reflux under nitrogen for 24 h, cooled, and filtered through Super Cel., and the filter cake was washed thoroughly with ether. The organic phase of the filtrate was washed successively with 5 M aq. NH_4OAc, water, and brine, dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. The residue was purified by column chromatography to give **6** (600 mg, 81%), $[\alpha]_D^{25}$ +22.0 (*c* 2.7 in $CHCl_3$); δ_H(400 MHz) 9.72 (1H, t, *J* 2.5, CH_2CHO), 3.80 (1H, dd, *J* 8.4 and 1.3, $CHOTBDMS$), 3.35 (1H, dd, *J* 6.6 and 1.1, $CHOTBDMS$), 2.31–1.23 (6H, m, $CHMe_2$, CH_2CHCH_2), 0.96–0.86 (27H, m, 2 × CMe_3, $CHCH_3$ and $CHMe_2$), 0.09 (3H, s, $SiCH_3$), 0.08 (3H, s, $SiCH_3$), 0.07 (3H, s, $SiCH_3$), 0.04 (3H, s, $SiCH_3$); δ_C(100 MHz) 202.6 (CH), 82.8 (CH), 72.8 (CH), 52.1 (CH_2), 39.9 (CH), 31.9 (CH_2), 28.9 (6 × CH_3), 24.4 (CH), 20.2 (CH_3), 19.2 (CH_3), 19.1 (CH_3), 18.4 (C), 18.2 (C), −3.4 (CH_3), −3.4 (CH_3), −4.7 (CH_3), −4.9 (CH_3); *m*/*z* (EI) 401 (M^+ − Me, 1%), 359 (M^+ − 57, 2), 303 (2), 259 (2), 187 (44), 84 (100); HRMS (ESI) Found: $(M + H)^+$, 417.3213. $C_{22}H_{49}O_3Si_2$ requires *M* + *H*, 417.3215.

(1*R*,5*R*)-Menth-4-en-3-ol 16

To an ice–water-bath-cooled mixture of (−)-menth-4-en-3-one **9** (10 g, 66 mmol) and cerous choride (24.5 g, 66 mmol) in MeOH (150 mL) was added $NaBH_4$ (2.5 g, 66 mol) and the mixture was stirred for 30 min, then the solvent was removed *in vacuo*, the obtained residue was diluted with ether and 5% aq. HCl, and the aqueous layer was extracted with ether. The combined organic layer was washed successively with saturated aq. $NaHCO_3$ and brine, and dried over Na_2SO_4. The solvent was removed *in vacuo* to give **16** (9.1 g, 90%), which was directly used in the next reaction. $[\alpha]_D^{25}$ −43.9 (*c* 2.5 in $CHCl_3$); δ_H(400 MHz) 5.40 (1H, m, $C{=}CHCH_2$), 4.29 (1H, t, *J* 6.7, CH_2CHOHC), 2.59–0.89 (6H, m, CH_2CHCH_2 and $CHMe_2$), 1.01 (3H, d, *J* 6.8, $CHMe^AMe^B$), 1.0 (3H, d, *J* 6.8, $CHMe^AMe^B$), 0.91 (3H, d, *J* 7.6, $CHCH_3$); δ_C(100 MHz) 145.9 (C), 120.3 (CH), 68.6 (CH), 42.3 (CH_2), 34.3 (CH_2), 28.2 (2 × CH), 22.6 (CH_3), 21.8 (CH_3), 20.8 (CH_3); *m*/*z* (EI) 154 (M^+, 4%), 139 (22), 111 (100), 43 (38).

(4*S*,6*R*)-2-Hydroxy-4-methyl-6-(2′-methylpropionyl)tetrahydropyran 17

Into a cold (−78 °C) solution of compound **16** (1.0 g, 5.9 mmol) in CH_2Cl_2 (50 mL) was bubbled ozone. When the reaction was complete (TLC) the reaction mixture was treated with Me_2S (2 mL), stirred overnight, and evaporated *in vacuo*. The residue was purified by column chromatography to give **17** (1.0 g, 85%) as a mixture of two isomers. δ_H(400 MHz) (2 isomers) 5.15 (2H, m, 2 × $OCHOH$), 4.66 (1H, t, *J* 5.2, CH_2CHOCH), 4.41 (1H, dd, *J* 7.0 and 4.9, CH_2CHOCH), 3.14 (1H, m, $CHMe_2$), 3.01 (1H, m, $CHMe_2$), 2.53–0.90 (10H, m, 2 × CH_2CHCH_2), 1.10–1.02 (18H, m, 2 × $CHCH_3$ and 2 × $CHMe_2$); δ_C(100 MHz) 215.4 (C), 215.3 (C), 93.0 (CH), 92.4 (CH), 75.4 (CH), 74.8 (CH), 40.9 (CH_2), 39.8 (CH_2), 35.9 (CH), 35.6 (CH), 32.5 (2 × CH_2), 25.1 (CH), 22.5 (CH), 21.4 (CH_3), 20.0 (CH_3), 18.8 (CH_3), 18.7 (CH_3), 18.2 (CH_3), 18.1 (CH_3); *m*/*z* (EI) 186 (M^+, 1%), 168 (1), 143 (1), 115 (28), 71 (100), 43 (38); HRMS (ESI) Found: $(M + Na)^+$, 209.1144. $C_{10}H_{18}O_3Na$ requires *M* + *Na*, 209.1148.

(1*R*)-1-[(2*S*)-3-Iodo-2-methylpropyl]-3-methyl-2-oxobutyl formate 18

To a mixture of lactol **17** (2.0 g, 9.6 mmol) in cyclohexane (50 mL) were added iodosylbenzene diacetate (IBDA) (5.56 g, 17.3 mmol) and iodine (2.92 g, 11.5 mmol). The reaction mixture was stirred under argon and irradiation with two 100 W tungsten-filament bulbs for 1.0 h, and then diluted with ether (100 mL), washed successively with aq. $Na_2S_2O_3$ and brine, and dried over Na_2SO_4. The solvent was removed *in vacuo* to give **18** (2.1 g, 70%), $[\alpha]_D^{25}$ −3.8 (*c* 1.75 in $CHCl_3$); δ_H(400 MHz) 8.11 (1H, s, OCHO), 5.27 (1H, dd, *J* 10.3 and 3.1, CH_2CHOC), 3.29 (2H, d, *J* 4.1, $CHCH_2I$), 2.9 (1H, m, $CHMe_2$), 1.83–1.50 (3H, m, ICH_2CHCH_2CHO), 1.21 (3H, d, *J* 7.1, $CHCH_3$), 1.12 (3H, d, *J* 6.6, $CHMe^AMe^B$), 1.02 (3H, d, *J* 6.6, $CHMe^AMe^B$); δ_C(100 MHz) 209.3 (C), 160.0 (CH), 74.4 (CH), 37.1 (CH), 36.4 (CH_2), 30.0 (CH), 21.4 (CH_3), 19.1 (CH_3), 17.8 (CH_3), 16.4 (CH_2); *m*/*z* (EI) 312 (M^+, 1%), 241 (6), 169 (17), 139 (25), 71 (100).

(2*S*,4*R*)-4-Formyloxy-2,6-dimethyl-5-oxoheptyl phenyl sulfone 19

To a solution of the above iodide **18** (1.60 g, 5.13 mmol) in DMF (6 mL) was added sodium benzenesulfinate (1.54 g, 9.23 mmol) and the solution was stirred for 12 h at 60 °C. The reaction mixture was poured into water (20 mL) and extracted with ether (3 × 30 mL). The ethereal layer was washed with brine (30 mL), dried over Na_2SO_4, and evaporated *in vacuo*. The residue was purified by column chromatography to give **19** (1.51 g, 90%), $[\alpha]_D^{25}$ −9.0 (*c* 0.9 in $CHCl_3$); δ_H(400 MHz) 8.01 (1H, s, OCHO), 7.91–7.60 (5H, m, ArH), 5.31 (1H, dd, *J* 9.8 and 3.1, $CH_2CHOCHO$), 3.20 (1H, dd, *J* 14.2 and 4.6, $CHCH^ACH^BS$), 3.01 (1H, dd, *J* 14.1 and 7.3, $CHCH^ACH^BS$), 2.83 (1H, m, $CHMe_2$), 2.31–1.70 (3H, m, CH_2CHCH_2CHO), 1.21 (3H, d, *J* 7.0, $CHMe^AMe^B$), 1.17 (3H, d, *J* 7.0, $CHMe^AMe^B$), 1.07 (3H, d, *J* 6.6, $CHCH_3$); δ_C(100 MHz) 209.4 (C), 159.8 (CH), 139.9 (C), 133.8 (CH), 129.4 (2 × CH), 127.7 (2 × CH), 74.7 (CH), 61.2 (CH_2), 36.9, 36.5, 26.2, 20.8, 19.0, 17.8 (2 × CH, CH_2 and 3 × CH_3); *m*/*z* (EI) 298 (M^+ + 1 − CHO, 8%), 255 (8), 227

(100), 143 (18), 71 (48); HRMS (ESI) Found: (M + Na)$^+$, 349.1080. $C_{16}H_{22}O_5SNa$ requires *M* + *Na*, 349.1080.

(2*S*,4*R*)-4-Hydroxy-2,6-dimethyl-5-oxoheptyl phenyl sulfone 20

Compound **19** (326 mg, 1.00 mmol) was dissolved in MeOH (4 mL), then the solution was added to a suspension of K_2CO_3 (220 mg, 1.60 mmol) in MeOH (4 mL) and stirred for 2 h at room temperature. The reaction mixture was diluted with EtOAc (80 mL) and washed with brine (3 × 20 mL), dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. The residue was purified by column chromatography to afford **21a** (262 mg, 88%), δ_H(400 MHz) 7.93 (2H, d, *J* 7.8, ArH), 7.67 (1H, t, *J* 7.8, ArH), 7.58 (2H, t, *J* 7.8, ArH), 4.37 (1H, dd, *J* 9.97 and 2.5, CH_2CHOHC), 3.35 (1H, dd, *J* 14.1 and 5.0, $CHCH^ACH^BS$), 3.10 (1H, dd, *J* 14.4 and 7.1, $CHCH^ACH^BS$), 2.84 (1H, m, $CHMe_2$), 2.46–1.43 (3H, m, CH_2CHCH_2CHOH), 1.21 (3H, d, *J* 6.7, $CHMe^AMe^B$), 1.13 (3H, d, *J* 6.6, $CHCH_3$), 1.10 (3H, d, *J* 6.7, $CHMe^AMe^B$); δ_C(100 MHz) 215.8 (C), 140.1 (C), 133.6 (CH), 129.3 (2 × CH), 127.8 (2 × CH), 73.3 (CH), 61.4 (CH_2), 39.3, 35.9, 26.7, 20.6, 19.4, 17.6 (2 × CH, CH_2 and 3 × CH_3); *m*/*z* (EI) 298 (M$^+$, 1%), 227 (100), 143 (22).

(2*S*,4*R*,5*S*)-4-Formyloxy-5-hydroxy-2,6-dimethylheptyl phenyl sulfone 22a and (2*S*,4*R*,5*R*)-4-formyloxy-5-hydroxy-2,6-dimethylheptyl phenyl sulfone 22b

To a cooled (−78 °C), stirred solution of **19** (1.51 g, 4.62 mmol) in MeOH (20 mL) was added $NaBH_4$ (176 mg, 4.62 mmol). The mixture was stirred for 1 h at −78 °C, then diluted with EtOAc (30 mL) and saturated aq. NH_4Cl. The aqueous layer was extracted with EtOAc (2 × 20 mL) and the combined organic layer was washed with H_2O and brine, dried over Na_2SO_4 and evaporated *in vacuo*. The residue was purified by column chromatography to give **22a** and **22b** (680 mg and 680 mg, 90%), which were directly used in the next step.

(2*S*,4*R*,5*S*)-4,5-Dihydroxy-2,6-dimethylheptyl phenyl sulfone 21a

Method A. To a solution of **20** (300 mg, 1.0 mmol) in dry THF (5 mL) was added $Zn(BH_4)_2$ in THF at 0 °C. The mixture was stirred for 1.0 h, and then diluted with ether (50 mL) and washed with brine, dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. The residue was purified by column chromatography to afford **21a** (280 mg, 93%), δ_H(400 MHz) 7.88 (2H, d, *J* 7.7, ArH), 7.63 (1H, t, *J* 7.4, ArH), 7.54 (2H, t, *J* 7.8, ArH), 3.70 (1H, dd, *J* 3.6 and 8.1, C*H*OH), 3.26 (2H, m, C*H*OH and $CHCH^ACH^BS$), 2.96 (1H, dd, *J* 14.3 and 6.9, $CHCH^ACH^BS$), 2.41 (1H, m, $CHMe_2$), 2.44–1.47 (3H, m, CH_2CHCH_2CHOH), 1.06 (3H, d, *J* 6.9, $CHCH_3$), 0.94 (3H, d, *J* 6.7, $CHMe^AMe^B$), 0.83 (3H, d, *J* 6.7, $CHMe^AMe^B$).

Method B. Compound **22a** (680 mg, 2.07 mmol) was dissolved in MeOH (6 mL) then the solution was added to a suspension of K_2CO_3 (450 mg, 3.25 mmol) in MeOH (4 mL) and stirred for 2 h at room temperature. The reaction mixture was diluted with EtOAc (100 mL) and washed with brine (3 × 20 mL), dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. The residue was purified by column chromatography to afford **21a** (546 mg, 88%), $[\alpha]_D^{25}$ +14.2 (*c* 0.70 in $CHCl_3$); δ_H(400 MHz) 7.90 (2H, d, *J* 7.7, ArH), 7.65 (1H, t, *J* 7.4, ArH), 7.56 (2H, t, *J* 7.8, ArH), 3.72 (1H, dd, *J* 3.6 and 8.1, C*H*OH), 3.28 (2H, m, C*H*OH and $CHCH^ACH^BS$), 2.98 (1H, dd, *J* 14.3 and 6.9, $CHCH^ACH^BS$), 2.43 (1H, m, $CHMe_2$), 2.44–1.49 (3H, m, CH_2CHCH_2CHOH), 1.08 (3H, d, *J* 6.9, $CHCH_3$), 0.96 (3H, d, *J* 6.7, $CHMe^AMe^B$), 0.85 (3H, d, *J* 6.7, $CHMe^AMe^B$); δ_C(100 MHz) 139.7 (C), 133.7 (CH), 129.3 (2 × CH), 127.8 (2 × CH), 79.9 (CH), 69.3 (CH), 61.6 (CH_2), 36.8, 29.7, 25.4, 21.4, 19.0, 18.4 (2 × CH, CH_2 and 3 × CH_3); *m*/*z* (EI) 283 (M$^+$ + 1 − H_2O, 1%), 267 (2), 239 (5), 227 (91), 143 (100), 85 (91), 77 (72); HRMS (ESI) Found: (M + H)$^+$, 301.1467. $C_{15}H_{23}O_4S$ requires *M* + *H*, 301.1468.

(2*S*,4*R*,5*R*)-4,5-Dihydroxy-2,6-dimethylheptyl phenyl sulfone 21b

Following the same procedure as for **21a**, compound **22b** (640 mg, 1.95 mmol) afforded **21b** (520 mg, 88%), $[\alpha]_D^{25}$ +6.1 (*c* 0.93 in $CHCl_3$); δ_H(400 MHz) 7.90 (2H, d, *J* 7.6, ArH), 7.64 (1H, t, *J* 7.7, ArH), 7.55 (2H, t, *J* 7.9, ArH), 3.66 (1H, m, $CH_2CHOHCH$), 3.27 (1H, dd, *J* 14.5 and 5.4, $CHCH^ACH^BS$), 3.06 (1H, t, *J* 5.3, $CHCHOHCH$), 3.00 (1H, dd, *J* 14.1 and 6.6, $CHCH^ACH^BS$), 2.35 (1H, m, $CHMe_2$), 1.73 (1H, m, $CHCH_3$), 1.57 (2H, m, CH_2CHCH_2CHOH), 1.09 (3H, d, *J* 6.7, $CHMe^AMe^B$), 0.93 (3H, d, *J* 6.9, $CHCH_3$), 0.90 (3H, d, *J* 6.7, $CHMe^AMe^B$); δ_C(100 MHz) 139.8 (C), 133.6 (CH), 129.3 (2 × CH), 127.7 (2 × CH), 78.8 (CH), 68.9 (CH), 61.7 (CH_2), 40.1, 29.9, 25.4, 21.0, 19.7, 16.9 (2 × CH, CH_2 and 3 × CH_3); *m*/*z* (EI) 282 (M$^+$ − H_2O, 1%), 267 (2), 257 (4), 239 (11), 227 (100), 143 (55); HRMS (ESI) Found: (M + H)$^+$, 301.1467. $C_{15}H_{23}O_4S$ requires *M* + *H*, 301.1468.

(2*S*,4*R*,5*S*)-4,5-Isopropylidenedioxy-2,6-dimethylheptyl phenyl sulfone 7a

To a solution of the above product **21a** (540 mg, 1.8 mmol) in dry acetone (5 mL) were added DMP (2,2-dimethoxypropane) (2 mL) and a catalytic amount of PTSA and the mixture was stirred at room temperature for 12 h. The reaction mixture was diluted with ether (80 mL) and washed successively with saturated aq. $NaHCO_3$ (20 mL) and brine (20 mL), dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. The residue was purified by column chromatography to afford **7a** (580 mg, 95%), $[\alpha]_D^{25}$ +42.2 (*c* 0.67 in $CHCl_3$); δ_H(400 MHz) 7.91 (2H, d, *J* 7.2, ArH), 7.62 (1H, t, *J* 7.3, ArH), 7.55 (2H, t, *J* 7.3, ArH), 4.05 (1H, m, $CH_2CHOHCH$), 3.62 (1H, dd, *J* 5.2 and 9.3, $CHCHOHCH$), 3.25 (1H, dd, *J* 4.5 and 14.3, $CHCH^ACH^BS$), 3.00 (1H, dd, *J* 7.9 and 14.1, $CHCH^ACH^BS$), 2.35 (1H, m, $CHMe_2$), 1.71 (1H, m, $CHCH_3$), 1.52 (2H, m, CH_2CHCH_2CHOH), 1.33 (3H, s, CMe^AMe^B), 1.26 (3H, s, CMe^AMe^B), 1.19 (3H, d, *J* 6.9, $CHCH_3$), 1.00 (3H, d, *J* 6.6, $CHMe^AMe^B$), 0.84 (3H, d, *J* 6.6, $CHMe^AMe^B$); δ_C(100 MHz) 140.2 (C), 133.4 (CH), 129.1 (2 × CH), 127.8 (2 × CH), 107.5 (C), 83.7 (CH), 74.9 (CH), 61.3 (CH_2), 35.7, 28.3, 27.3, 26.3, 25.9, 20.7, 20.1, 19.1 (2 × CH, CH_2 and 5 × CH_3); *m*/*z* (EI) 325 (M$^+$ − Me, 32%), 283 (35), 239 (51), 123 (100); HRMS (ESI) Found: (M + H)$^+$, 341.1782. $C_{18}H_{29}O_4S$ requires *M* + *H*, 341.1785.

(2*S*,4*R*,5*R*)-4,5-Isopropylidenedioxy-2,6-dimethylheptyl phenyl sulfone 7b

Following the same procedure as for **7a**, compound **21b** (520 mg, 1.73 mmol) afforded **7b** (509 mg, 87%), $[\alpha]_D^{25}$ +16.5 (*c* 0.70 in $CHCl_3$); δ_H(400 MHz) 7.91 (2H, d, *J* 7.6, ArH), 7.63 (1H, t, *J* 7.5, ArH), 7.55 (2H, t, *J* 7.7, ArH), 3.73 (1H, m, $CH_2CHOHCH$), 3.31 (2H, m, $CHCHOHCH$ and $CHCH^ACH^BS$), 3.00 (1H, dd, *J* 7.4 and 14.3, $CHCH^ACH^BS$), 2.31 (1H, m, $CHMe_2$), 1.71 (2H, m, CH_2CHCH_2CHOH), 1.53 (1H, m, $CHCH_3$), 1.30 (3H, s, CMe^AMe^B), 1.28 (3H, s, CMe^AMe^B), 1.16 (3H, d, *J* 6.8, $CHMe^AMe^B$), 0.94 (3H, d, *J* 6.8, $CHMe^AMe^B$), 0.90 (3H, d, *J* 6.9, $CHCH_3$); δ_C(100 MHz) 140.1 (C), 133.4 (CH), 129.2 (2 × CH), 127.8 (2 × CH), 107.9 (C), 86.0 (CH), 76.4 (CH), 61.8 (CH_2), 40.3, 30.5, 27.3, 27.0, 27.0, 20.3, 19.2, 18.2 (2 × CH, CH_2 and 5 × CH_3); *m*/*z* (EI) 325 (M$^+$ − Me, 45%), 283 (9), 239 (48), 149 (34), 123 (100); HRMS (ESI) Found: (M + H)$^+$, 341.1782. $C_{18}H_{29}O_4S$ requires *M* + *H*, 341.1785.

(3*R*,4*R*,6*R*,10*S*,12*R*,13*S*)-3,4-Bis(*tert*-butyldimethylsilyloxy)-12,13-isopropylidenedioxy-2,6,10,14-tetramethylpentadecan-8-one 24a

To a solution of sulfone **7a** (283 mg, 0.83 mmol) in THF (4 mL) at −78 °C under Ar was added dropwise 1.60 M *n*-butyllithium

(0.55 mL, 0.88 mmol) and the solution was stirred at the same temperature for 30 min. To the solution at −78 °C was added dropwise the aldehyde **6** (380 mg, 0.92 mmol) dissolved in THF (3 mL) and the mixture was stirred at the same temperature for 2.5 h. The reaction was quenched with saturated aq. NH_4Cl (2 mL) and the temperature was allowed to warm to ambient. The reaction mixture was poured into water (10 mL) and extracted with ether (3 × 20 mL). The ethereal layer was washed with brine (20 mL), dried with anhydrous Na_2SO_4, and evaporated *in vacuo*. The residue was purified by column chromatography to give coupling product **23a** (458 mg, 73%), which was directly used in the next reaction.

To a magnetically stirred solution of PDC (945 mg, 3.66 mmol) in CH_2Cl_2 (10 mL) was added a solution of **23a** (458 mg, 0.61 mmol) in CH_2Cl_2 (5 mL) at room temperature. The reaction mixture was stirred for 15 min, the solution was passed through a short column of Al_2O_3, and the solvent was evaporated *in vacuo*. The residue was purified by column chromatography to furnish the α-sulfonyl ketone (421 mg, 0.56 mmol), which was directly used in the next reaction.

To a stirred solution of above product (421 mg, 0.56 mmol) and anhydrous Na_2HPO_4 (319 mg, 2.24 mmol) in MeOH (10 mL) was added pulverized 6% sodium amalgam (1.0 g) at room temperature. The reaction mixture was vigorously stirred for 1 h until TLC showed complete conversion. The mixture was poured into saturated aq. NH_4Cl (10 mL) and extracted with ether (3 × 20 mL), the combined extracts were washed with brine, dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. The residue was purified by column chromatography to give **24a** (255 mg, 50% in overall yield in three steps), $[a]_D^{25}$ +27.0 (*c* 3.3 in $CHCl_3$); δ_H(400 MHz) 4.07 (1H, m, $CH_2CHOTBDMS$), 3.76 (1H, d, *J* 9.6, CHOC), 3.63 (1H, dd, *J* 5.0 and 9.1, CHCHOTBDMS), 3.32 (1H, d, *J* 6.6, CHOC), 2.52–0.85 (12H, m, 4 × CH and 4 × CH_2), 1.41 (3H, s, CMe^AMe^B), 1.31 (3H, s, CMe^AMe^B), 1.01 (3H, d, *J* 6.5, $CHCH_3$), 0.97 (3H, d, *J* 5.9, $CHCH_3$), 0.93–0.84 (30H, m, 2 × CMe_3 and 2 × $CHMe_2$), 0.09 (3H, s, $SiCH_3$), 0.08 (3H, s, $SiCH_3$), 0.07 (3H, s, $SiCH_3$), 0.03 (3H, s, $SiCH_3$); δ_C(100 MHz) 210.2 (C), 107.5 (C), 83.8 (CH), 82.9 (CH), 75.7 (CH), 72.9 (CH), 52.3 (CH_2), 49.0 (CH_2), 40.0 (CH_2), 36.0 (CH_2), 31.9, 28.5, 27.4, 26.3, 26.1 (6 × CH_3), 25.9, 25.6, 21.1, 20.3, 20.2, 19.4, 19.3, 19.2 (4 × CH and 8 × CH_3), 18.5 (C), 18.2 (C), −3.4 (CH_3), −3.5 (CH_3), −4.6 (CH_3), −4.9 (CH_3); HRMS (ESI) Found: M^+, 614.4762. $C_{34}H_{70}O_5Si_2$ requires *M*, 614.4754.

(3*R*,4*R*,6*R*,10*S*,12*R*,13*R*)-3,4-Bis(*tert*-butyldimethylsilyloxy)-12,13-isopropylidenedioxy-2,6,10,14-tetramethylpentadecan-8-one 24b

Following the same procedure as for **24a**, compound **7b** (390 mg, 0.52 mmol) gave **24b** (320 mg, 50% overall yield in three steps), $[a]_D^{25}$ +12.1 (*c* 3.0 in $CHCl_3$); δ_H(400 MHz) 3.78 (2H, m, $CH_2CHOTBDMS$ and CHOC), 3.38 (1H, t, *J* 6.7, CHCHOTBDMS), 3.33 (1H, d, *J* 6.7, CHOC), 2.53–0.87 (12H, m, 4 × CH and 4 × CH_2), 1.35 (6H, s, CMe_2), 0.97 (3H, d, *J* 6.6, $CHCH_3$), 0.94 (3H, d, *J* 6.9, $CHCH_3$), 0.93–0.84 (30H, m, 2 × CMe_3 and 2 × $CHMe_2$), 0.09 (3H, s, $SiCH_3$), 0.08 (3H, s, $SiCH_3$), 0.07 (3H, s, $SiCH_3$), 0.04 (3H, s, $SiCH_3$); δ_C(100 MHz) 210.0 (C), 107.9 (C), 86.3 (CH), 82.9 (CH), 77.1 (CH), 72.9 (CH), 52.3 (CH_2), 49.6 (CH_2), 41.0 (CH_2), 40.0 (CH_2), 31.9, 30.7, 27.4, 27.2, 27.1, 27.0 (6 × CH_3), 25.9, 25.6, 20.6, 20.3, 19.4, 19.3, 18.5 (C), 18.4 (C), 18.2 (4 × CH and 8 × CH_3), −3.3 (CH_3), −3.4 (CH_3), −4.6 (CH_3), −4.8 (CH_3); HRMS (FAB) Found: M^+, 614.4762. $C_{34}H_{70}O_5Si_2$ requires *M*, 614.4754.

(1*R*)-1-{(2*R*,4*R*,6*S*,8*R*,10*S*)-8-[(1*R*)-1-Hydroxy-2-methylpropyl)]-4,10-dimethyl-1,7-dioxaspiro[5.5]undecan-2-yl}-2-methylpropan-1-ol 4a

The substrate **24a** (255 mg, 0.42 mmol) was dissolved in acetonitrile containing 40% aq. HF (1 mL). TLC monitoring was carried out by spotting liquid directly onto a silica gel plate. When deprotection was complete, ether and water were added. The aqueous phase was extracted with ether (3 × 20 mL), and the combined extracts were washed successively with $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. The residue was purified by column chromatography to give **4a** (92 mg, 67%), $[a]_D^{25}$ −39.8 (*c* 2.15 in $CHCl_3$); δ_H(400 MHz) 3.82 (1H, ddd, *J* 3.3, 4.2 and 12.0, CH_2CHOC), 3.69 (1H, ddd, *J* 2.4, 4.2 and 11.6, CH_2CHOC), 3.28 (2H, m, 2 × CHCHOH), 2.15–0.85 (12H, m, 4 × CH and 4 × CH_2), 1.17 (3H, d, *J* 7.2, $CHCH_3$), 0.99 (3H, d, *J* 6.6, $CHCH_3$), 0.97 (3H, d, *J* 6.7, $CHMe^AMe^B$), 0.89 (3H, d, *J* 6.7, $CHMe^AMe^B$), 0.88 (3H, d, *J* 6.8, $CHMe^AMe^B$), 0.87 (3H, d, *J* 6.8, $CHMe^AMe^B$); δ_C(100 MHz) 98.5 (C), 78.9 (CH), 78.7 (CH), 70.6 (CH), 65.4 (CH), 44.4 (CH_2), 40.7 (CH_2), 31.9 (CH_2), 29.5 (CH_2), 29.1, 29.0, 24.6, 24.5, 22.2, 20.8, 19.0, 19.0, 18.6, 18.4 (4 × CH and 6 × CH_3); *m*/*z* (EI) 328 (M^+, 1%), 285 (1), 255 (65), 149 (34), 43 (100); HRMS (ESI) Found: $(M + H)^+$, 329.2682. $C_{19}H_{37}O_4$ requires *M* + *H*, 329.2686.

(1*R*)-1-{(2*R*,4*R*,6*S*,8*R*,10*S*)-8-[(1*S*)-1-Hydroxy-2-methylpropyl)]-4,10-dimethyl-1,7-dioxaspiro[5.5]undecan-2-yl}-2-methylpropan-1-ol 4b

Following the same procedure as for **4a**, compound **24b** (230 mg, 0.37 mmol) gave **4b** (82 mg, 67%), $[a]_D^{25}$ −28.5 (*c* 2.0 in $CHCl_3$); δ_H(400 MHz) 3.83 (1H, ddd, *J* 3.3, 5.1 and 11.6, CH_2CHOC), 3.74 (1H, dt, *J* 2.9 and 11.6, CH_2CHOC), 3.28 (1H, dd, *J* 3.6 and 8.2, CHCHOH), 3.74 (1H, t, *J* 4.9, CHCHOH), 2.15–0.85 (12H, m, 4 × CH and 4 × CH_2), 1.19 (3H, d, *J* 7.1, $CHCH_3$), 1.02 (3H, d, *J* 6.6, $CHMe^AMe^B$), 0.97 (3H, d, *J* 6.9, $CHCH_3$), 0.94 (3H, d, *J* 6.7, $CHMe^AMe^B$), 0.89 (3H, d, *J* 6.7, $CHMe^AMe^B$), 0.86 (3H, d, *J* 6.7, $CHMe^AMe^B$); δ_C(100 MHz) 98.2 (C), 78.8 (CH), 78.7 (CH), 70.7 (CH), 65.4 (CH), 44.4 (CH_2), 40.5 (CH_2), 32.9 (CH_2), 31.5 (CH_2), 29.8, 29.2, 24.8, 24.7, 22.2, 20.8, 20.1, 19.0, 18.9, 16.8 (4 × CH and 6 × CH_3); *m*/*z* (EI) 328 (M^+, 1%), 285 (3), 255 (66), 43 (100); HRMS (ESI) Found: $(M + H)^+$, 329.2682. $C_{19}H_{37}O_4$ requires *M* + *H*, 329.2686.

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