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A convergent synthesis of the spiroketal moiety of the HIV-1 protease inhibitors didemnaketals

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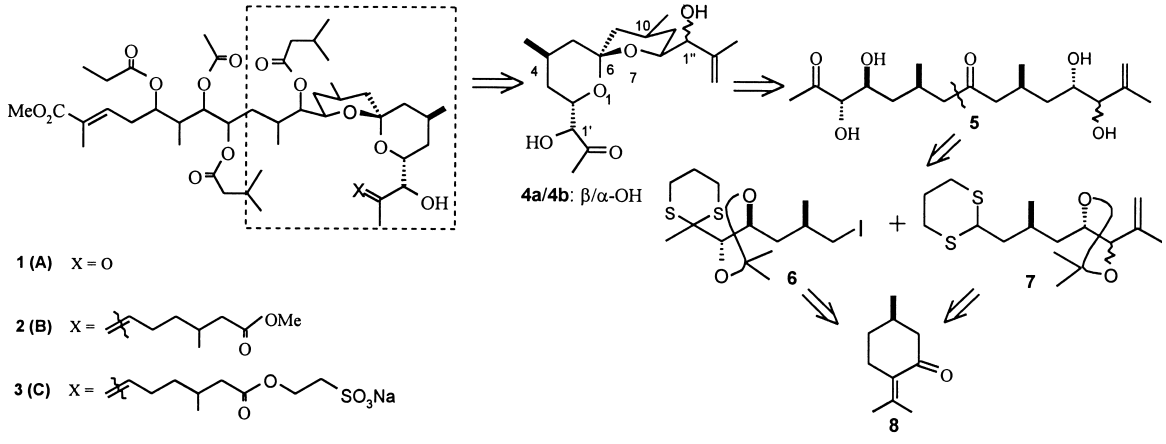
Abstract—The stereoselective synthesis of the spiroketal fragment **4a** and its C1″-epimer **4b** of the HIV-1 protease inhibitors didemnaketals has been carried out through multisteps from the natural (*R*)-(+)-pulegone, which involved the diastereoselective construction of four chiral carbon centers by intramolecular chiral induction.

1. Introduction

In 1991, Faulkner and colleagues reported that didemnaketals A (**1**) and B (**2**) (Scheme 1) were isolated from the ascidian *didemnum* sp. at Auluptagel Island, Palau, and found to inhibit HIV-1 protease with an IC_{50} of 2 and 10 μM, respectively.[1] Their later reinvestigation of the ascidian *didemnum* sp. revealed that the previously reported metabolites, didemnaketals A (**1**) and B (**2**), were artifacts formed as a result of prolonged storage of the ascidian in methanol. Fresh extracts gave a single terpenoid, didemnaketal C (**3**), which on methanolysis yielded didemnaketal B (**2**), and didemnaketal A (**1**) was presumably an autoxidation product of didemnaketal B (**2**). Interestingly, didemnaketal C (**3**) did not inhibit HIV-1 protease in a peptidolysis assay.[2] The structures of the didemnaketals were characterized by Faulkner and colleagues through extensive NMR studies and their absolute configurations were not known. Because the didemnaketals are potent, non-nitrogen containing HIV-1 protease inhibitors with novel structures and good initial activity and their synthesis has not been reported till now, it is significant to perform studies toward the total synthesis of this kind of compound. In connection with our study on this subject, a recent effort is focused on the development of an efficient synthetic approach to this kind of compound and their analogues for the purpose of further investigation of their biological activity. In our previous communication,[3] we have described an approach to **4a/4b** and herein we report a full account of the relevant details.

Due to the undetermined absolute stereochemistry of



Scheme 1.

Keywords: spiroketal moiety; HIV-1 protease; intramolecular chiral induction.
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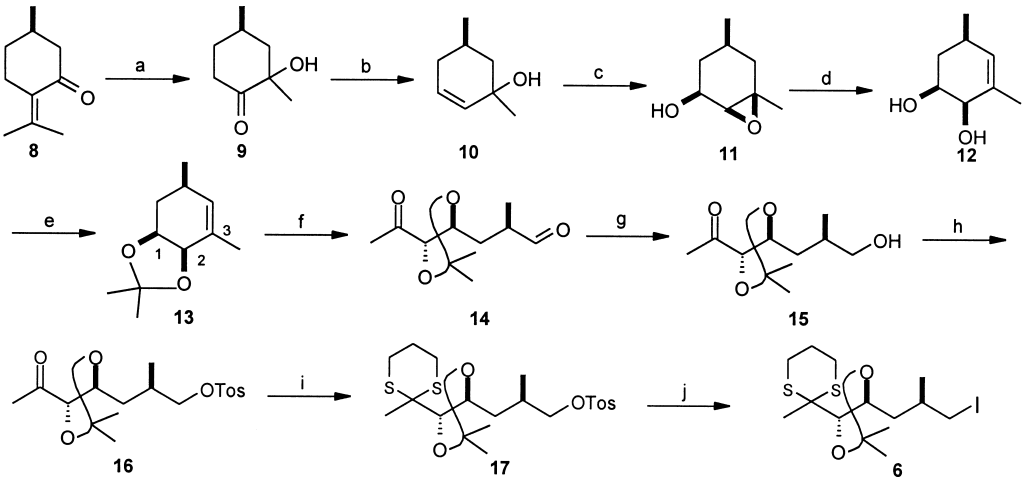


Scheme 2. PTS=*p*-toluene sulphonic acid, *Reagents and conditions*: (a) (i) CH_3Li, Et_2O; (ii) O_3, CH_2Cl_2, −78°C, 83% (2 steps); (b) (i) tos-$NHNH_2$, THF; (ii) *n*-BuLi, THF, 80% (2 steps); (c) (i) PCC, CH_2Cl_2; (ii) $NaBH_4$, MeOH; (iii) *m*-CPBA, CH_2Cl_2, 41% (3 steps); (d) $H_2N(CH)_2NHLi$, 40%; (e) acetone, PTS, 84%; (f) O_3, CH_2Cl_2, 78°C, 85%; (g) $NaBH_4$, EtOH–CH_2Cl_2 (3:7), 80%; (h) TosCl, Py, DMAP, 94%; (i) (i) $HS(CH_2)_3SH$, $BF_3{\cdot}OEt_2$; (ii) acetone, PTS, 78% (2 steps); (j) NaI, acetone, 64%.

didemnaketals, we designed and synthesized target molecules **4a/4b**, whose absolute stereochemistry was as indicated in Scheme 1. Spiroketals **4a/4b** were accessed from acyclic precursor **5** via an acid-catalyzed spiroketalization under thermodynamic control. Precursor **5** in turn would be obtained by coupling iodide **6** with dithiane **7**. Our strategy for **4a/4b** relied on whether the dithiane–iodide coupling reactions would proceed and this strategy held the promise of considerable flexibility in the coupling reaction. It was clear that the precursors **6** and **7** contained the similar key '1-oxygen-3-methyl' moiety, so the naturally abundant (*R*)-(+)-pulegone **8** was regarded to be the appropriate starting material.

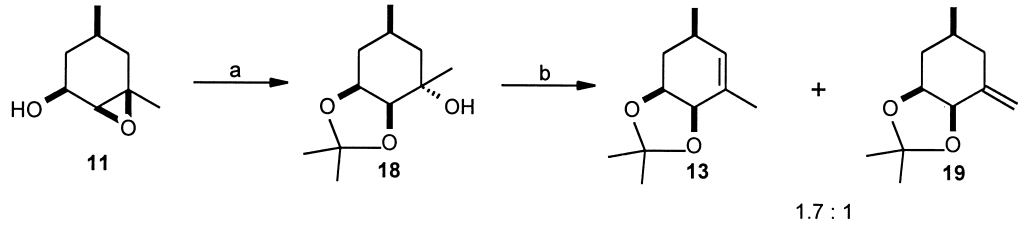
2. Results and discussions

2.1. Construction of iodide 6

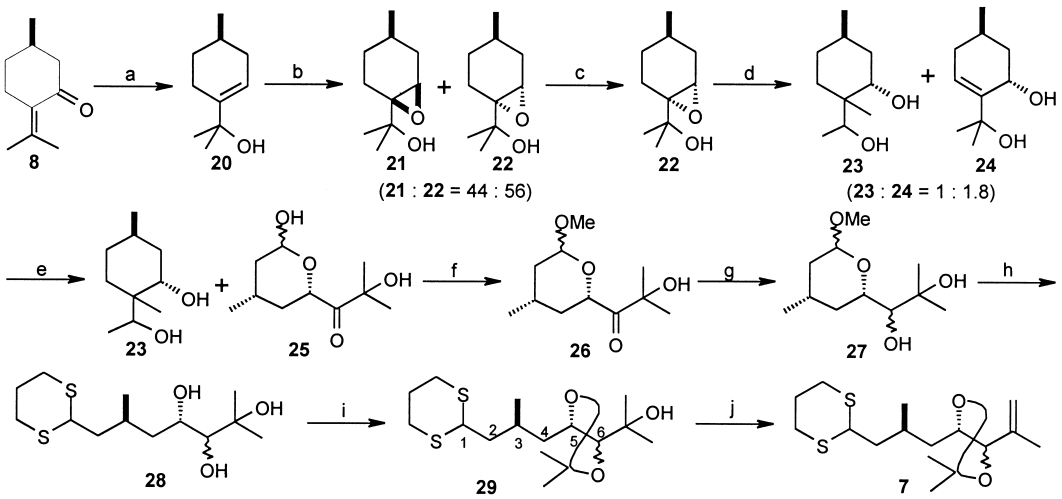
The preparation of the intermediate **6** is presented in Scheme 2. Methylation of the carbonyl of pulegone **8** with MeLi and then ozonization-cleavage of the C=C bond afforded the α-hydroxy ketone **9**, which was converted to the allylic alcohol **10** by hydrazonization with *p*-toluenesulfonyl hydrazine followed by treatment with *n*-BuLi.[4] The PCC oxidative rearrangement of the tertiary allylic alcohol **10**[5] followed by reduction of the formed ketone with $NaBH_4$ and then epoxidation with *m*-CPBA afforded the α-hydroxy epoxide **11** as a single product. At first, treatment of **11** with CF_3COOH followed by protection of the secondary hydroxy with acetone and then elimination of the tertiary hydroxy furnished a mixture of the *endo*- and *exo*-olefins **13** and **19** in a 1.7:1 ratio (by ^1H NMR) in low yield, which could not be separated at this stage (Scheme 3). Fortunately, compound **11** could undergo a base-mediated rearrangement to give the allylic alcohol **12** (40%). The literature had reported the rearrangement of simple epoxides;[6] here, we also had success with α-hydroxy epoxide, and the low yield possibly came from the influence of the neighboring hydroxy. Thus, we had succeeded in diastereoselective construction of two chiral carbon centers bearing hydroxy groups. Protection of alcohol **12** with acetone also furnished **13** on the basis of ^1H NMR. The stereochemistry of **12** was further determined by the only correlations between H-2 and H-1 and between H-2 and C5-methyl on the basis of NOESY spectra for **13**. Ozonization of the olefin **13** provided the open-chain ketone-aldehyde **14**. Selective reduction of aldehyde **14** with $NaBH_4$ followed by protection of the resulting alcohol furnished **16**.[7,8] Protection of the ketone carbonyl and subsequent iodination reaction led to iodide **6**.[8]

2.2. Construction of dithiane 7

The preparation of the second intermediate **7** is depicted in Scheme 4. Reduction of ketone **8** with $NaBH_4$ followed by a developed acid-promoted rearrangement of the allylic alcohol afforded **20**.[9] Epoxidation of the tertiary α-hydroxy olefin **20** with *t*-BuO_2H/$VO(acac)_2$ formed a mixture of **22** and its *syn*-epoxide isomer **21** (56:44), which were hard to separate on chromatography. As yet we have not been able



Scheme 3. *Reagents and conditions*: (a) (i) CF_3CO_2H, H_2O; (ii) acetone, *p*-toluene sulphonic acid, 71% (2 steps); (b) $SOCl_2$, Py, 60%.

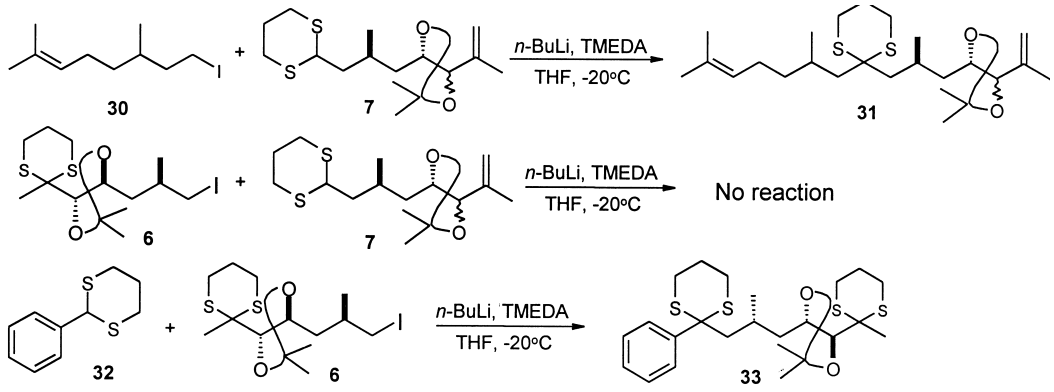


Scheme 4. *Reagents and conditions*: (a) (i) $NaBH_4$, MeOH; (ii) 30% AcOH; (b) *t*-BuO_2H, $VO(acac)_2$; (c) PCC, CH_2Cl_2, rt, 42% (4 steps); (d) Al(*i*-PrO)$_3$, *i*-PrOH; (e) O_3, CH_2Cl_2 −78°C; (f) DMP, acetone, PTS, 40% (3 steps); (g) $NaBH_4$, MeOH, 80% (h) $HS(CH_2)_3SH$, $BF_3{\cdot}Et_2O$, 77%; (i) acetone, PTS, 95%; (j) $SOCl_2$, Py, 60%.

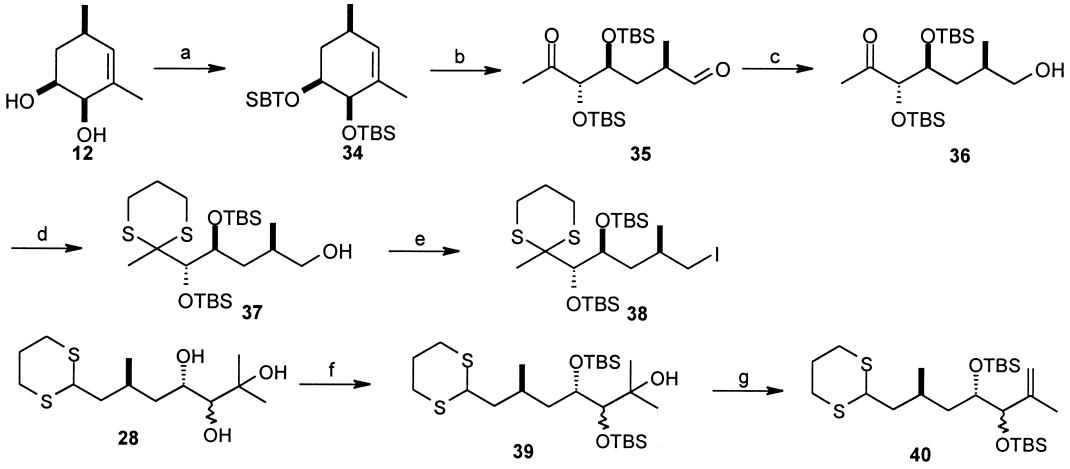
to obtain the single epoxide **22** even by Sharpless asymmetric epoxidation. Fortunately, however, we succeeded in the purification of **22** by a PCC oxidation method we developed.[10] The subsequent Lewis acid-mediated rearrangement of **22** afforded the allylic alcohol **24**, whose stereochemistry had been determined by 1D and 2D NMR, together with **23** as a byproduct.[11] Thus, we have succeeded in the diastereoselective construction of the hydroxy-bearing carbon center. The low yield of the allylic alcohol **24** came from the formation of a reductive rearrangement product **23**.[11] Because it was difficult to separate **23** and **24**, direct ozonization of the mixture afforded **23** and hemiacetal **25** (1:1) as a mixture which was difficult to separate. Treatment of **23** and **25** with DMP/acetone gave **26**, which was easily separated from the acetonide of **23**. Reduction of ketone carbonyl of **26** with $NaBH_4$ in situ gave a mixture of **27** as four isomers (5:5:1:1). We have not made any attempt to carry out the stereocontrolled reduction of the carbonyl for the reasons mentioned above. The major reduction product **27** would be of the β-hydroxy configuration on the basis of both the transition-state analysis and the strong correlations between H-5 and H-6 and between both H-5 and H-6 and the same acetonide methyl in the NOESY spectra for the major isomer of the acetonides of **29**. Finally, the transacetalization of **27** with 1,3-thiopropanol, followed by protection of the two secondary hydroxy groups with acetone and then elimination of the tertiary hydroxy gave the compound **7** with the terminal double bond for the later functionization.

2.3. Dithiane metalation

Dithiane **7** was then examined for its susceptibility to metalation (Scheme 5). The study was performed by treatment of **7** with *n*-BuLi and additive tetramethylethylenediamine (TMEDA), followed by addition of iodide **30** at −20°C,[12] and led to the coupling compound **31** in 85% yield. With the good result, we turned to couple iodide **6** with dithiane **7**. Unfortunately, the coupling reaction did not happen even though various bases and additives were explored. Then the reaction activity of iodide **6** was examined through coupling of **6** with dithiane **32**. It led to coupling dithiane **33** in 67% yield. Our results suggest that the steric hindrance may be the source of the difficulty. The steric hindrance could be decreased by protection of the alcohol moieties of **6** and **7** as TBS ethers, according to molecular mechanics calculations for a closely related model. So protection of alcohol **12** as the TBS ether (Scheme 6), then conversion by the regular route furnished **38**. Similarly, protection of alcohol **28** as the TBS ether (Scheme 6) followed by elimination of the



Scheme 5.

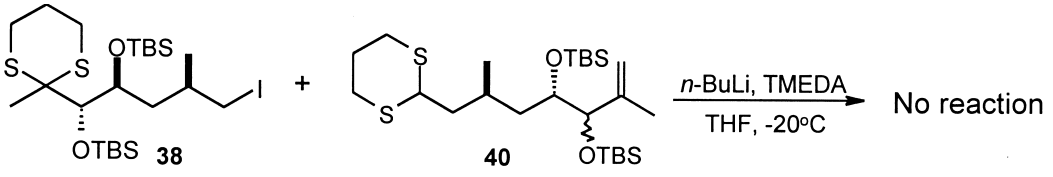


Scheme 6. *Reagents and conditions*: (a) TBSCl, imid.; (b) O_3, CH_2Cl_2 −78°C, 46% (2 steps); (c) $NaBH_4$, EtOH–CH_2Cl_2 (3:7), 80%; (d) $HS(CH_2)_3SH$, $BF_3{\cdot}OEt_2$, 82%; (e) I_2, Ph_3P, imid., 75%; (f) TBSCI, imid., 80°C, 40%; (g) $SOCl_2$, Py, 76%.

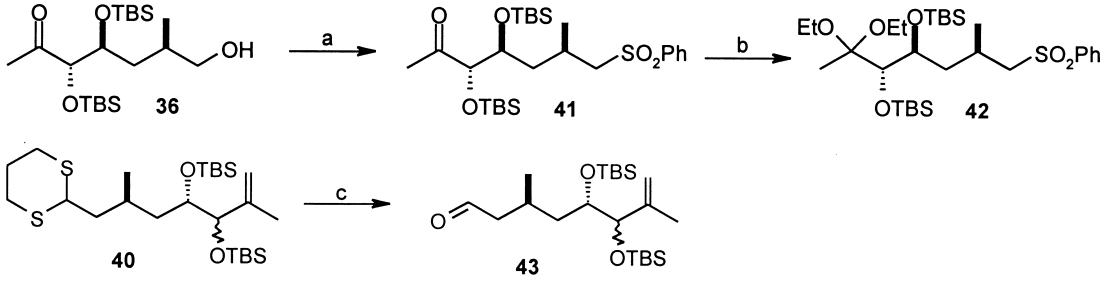
tertiary hydroxy afforded dithiane **40**. Unfortunately, the coupling of **40** with iodide **38** (*n*-butyllithium, TMEDA/THF) also did not occur (Scheme 7). So we had to change our strategy and design sulfone **42** and aldehyde **43** as valid precursors (Scheme 8).

Initial treatment of iodide **38** with $PhSO_2Na$ afforded no reaction.[13] Corey's iodination of alcohol **36** followed by substitution of iodide with $PhSO_2Na$ furnished **41**.[13,14] Protection of ketone **41** with 1,3-thiopropanol did not occur either. The steric hindrance may be the source of the difficulty. Fortunately, protection of ketone **41** with $HC(OEt)_3$ led to sulfone **42**. Removal of dithiane from **40** with $HgCl_2$ and $CaCO_3$ afforded aldehyde **43**.

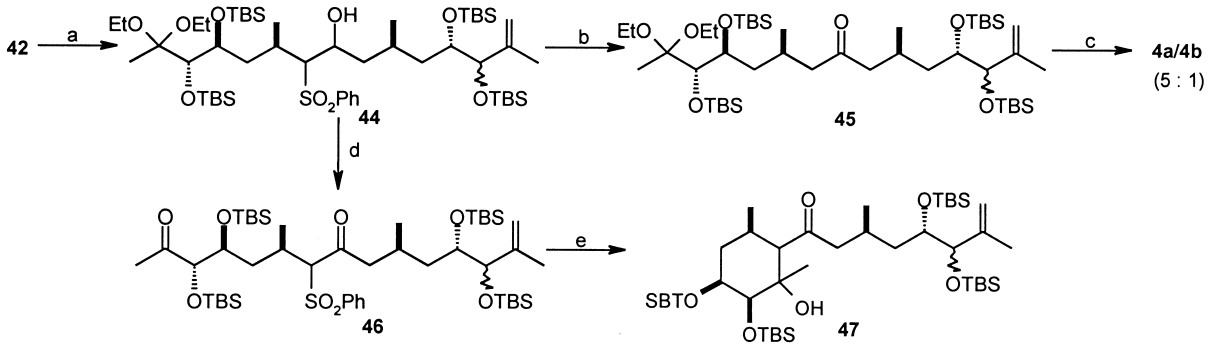
The coupling of **42** and **43** was carried out, as shown in Scheme 9. Metalation of **42** with *n*-BuLi in THF followed by addition of aldehyde **43** at −78°C led to alcohol **44**.[13] Swern oxidation of **44** provided diketone **46**, form which the sulfonyl group was removed with tri-*n*-butyltin hydride or 6% sodium amalgam to give undesired product **47**. So it was necessary that the protecting group of C2 ketone carbonyl of **46** could not be removed when it was oxidized. Fortunately, oxidation of the hydroxy group of **44** with PDC and then removal of the sulfonyl group with 6% sodium amalgam furnished ketone **45** as a mixture of two isomers (5:1) corresponding to the open-chain polyhydroxy intermediate **5**.[15] The subsequent full deprotection of the carbonyl and the hydroxy groups with a mixture of 40% aqueous hydrogen fluoride and acetonitrile led to the final spiroketals **4a/4b** as an oily mixture.[16] The isolated samples of **4a** and **4b** (10 mg and 2 mg) have been obtained by HPLC for structure determination by 1D and 2D NMR and mass spectroscopy. Thus, we have succeeded in the stereocontrolled synthesis of the key mother spiroketals of the HIV-1 protease inhibitive didemnaketals. Further total synthetic studies and bioactive investigations are ongoing.



Scheme 7.



Scheme 8. *Reagents and conditions*: (a) (i) I_2, Ph_3P, imid.; (ii) $PhSO_2Na$, DMF, 80% (2 steps); (b) $HC(OEt)_3$, EtOH, PTS, 64%; (c) $HgCl_2$, $CaCO_3$, 80% MeCN/H_2O, 84%.



Scheme 9. *Reagents and conditions*: (a) *n*-BuLi, THF, −78°C, 30 min, then **43**, −78°C, 2.5 h, 80%; (b) (i) PDC, CH_2Cl_2; (ii) Na(Hg), MeOH, 64% (2 steps); (c) 40% HF, MeCN, 60%; (d) $(COCl)_2$, DMSO, CH_2Cl_2, then Et_3N, 74%; (e) *n*-Bu_3SnH, AIBN, toluene, reflux, 73%; or Na(Hg), MeOH, 78%.

3. Experimental

3.1. General

^1H and ^{13}C NMR spectra were recorded on 80, 200 and 400 MHz instruments with TMS as internal standard. 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. The compounds were purified by column chromatography on silica gel H, from the Qingdao Marine Chemical Factory, eluting with the solvent mixture of light petroleum (bp 60–90°C) and ethyl acetate.

3.1.1. (4*R*)-2-Hydroxy-2,4-dimethyl-1-cyclohexanone (9). To a solution of 85% pulegone **8** (10 g, 55.9 mmol) in 40 mL of Et_2O at 0°C under Ar was added dropwise 112 mL (112 mmol) of methyllithium (1.0 M in Et_2O) and the solution was stirred for 2.5 h at room temperature. The reaction mixture was carefully poured into 100 mL of ice-water and extracted with ether (3×100 mL). The ethereal layer was washed with brine (3×40 mL), dried over anhydrous Na_2SO_4 and evaporated in vacuo. The residue was directly used in the next reaction.

Through a cold (−78°C) solution of the above product in 150 mL of CH_2Cl_2 ozone was bubbled. When the reaction was complete by TLC analysis, Me_2S (10 mL) was added and the reaction mixture was stirred for overnight. The solvent was evaporated in vacuo. The residue was purified by column chromatography (15% EtOAc/petroleum) to provide **9** (6.4 g, 80% overall yield in two steps) as a colorless oil. $[\alpha]_D^{25}=+77.2$ (*c* 1.0, $CHCl_3$); ^1H NMR (80 MHz, $CDCl_3$) δ: 2.74–1.08 (m, 7H), 1.39 (s, 3H), 0.95 (d, 3H, *J*=5.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 214.5, 75.6, 50.0, 36.8, 35.7, 29.7, 25.8, 21.1; EI-MS *m/z* (%): 142 (M^+, 9), 98 (54), 85 (99), 43 (100); FAB-HRMS: *m/z* calcd for $C_8H_{15}O_2$ (M+H) 143.1072; found 143.1031.

3.1.2. (5*R*)-1,5-Dimethyl-2-cyclohexen-1-ol (10). To a solution of ketone **9** (5.68 g, 40 mmol) in 120 mL of dry THF was added *p*-toluenesulfonylhydrazine (7.44 g, 40 mmol) and 1.0 mL concentrated hydrochloric acid. The reaction was stirred at room temperature for 1.5 h, then the solvent was removed in vacuo. The residue was directly used in the next reaction. To a solution of above hydrazone in 100 mL of dry THF was added dropwise 69 mL (120 mmol) of *n*-BuLi (1.74 M in 30–60°C petroleum) and the solution was stirred for 2.0 h at room temperature. The reaction was carefully quenched with 30 mL of saturated aqueous NH_4Cl at 0°C. The mixture was poured into water (50 mL) and extracted with ether (3×60 mL). The ethereal layer was washed with brine (3×40 mL), dried over anhydrous Na_2SO_4, and evaporated in vacuo. The residue was purified by column chromatography (10% EtOAc/petroleum) to provide **10** (4.0 g, 80% overall yield in two steps) as a colorless oil. $[\alpha]_D^{25}=-46.4$ (*c* 1.0, $CHCl_3$); ^1H NMR (80 MHz, $CDCl_3$) δ: 5.64–5.60 (m, 2H), 2.02–1.22 (m, 5H), 1.30 (s, 3H), 0.99 (d, 3H, *J*=5.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 134.3, 126.9, 70.8, 47.5, 33.8, 28.8, 28.3, 22.0; EI-MS *m/z* (%): 126 (M^+, 10), 111 (49), 93 (89), 77 (17), 55 (61), 43 (100).

3.1.3. (1*S*,2*S*,3*R*,5*R*)-2,3-Epoxy-3,5-dimethyl-1-cyclohexanol (11). To a magnetically stirred slurry of PCC (13.8 g, 64 mmol) in 120 mL of CH_2Cl_2 was added in one portion a solution of **10** (4.0 g, 32 mmol) in 40 mL of CH_2Cl_2 at room temperature. After the resulting dark red black mixture was stirred for 2.0 h at room temperature, the mixture was diluted with diethyl ether, filtered through Al_2O_3 and the filtrate was evaporated in vacuo. The residue was directly used in the next reaction.

To a solution of the above residue in 60 mL MeOH was added $NaBH_4$ (1.21 g, 32 mmol) at 0°C. The mixture was stirred at 0°C for 30 min, then the solvent was removed in vacuo. The obtained residue was poured into water (50 mL) and extracted with ether (3×50 mL). The combined organic layers were washed with brine (3×30 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was directly used in the next reaction.

To a solution of the above residue (2.8 g, 22 mmol) in 40 mL CH_2Cl_2 at 0°C was added 75% *m*-CPBA (5.1 g, 22 mmol) and the solution was stirred at 0°C for 1.5 h. The reaction mixture was poured into 40 mL of saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3×30 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4 and evaporated in vacuo. The residue was purified by column chromatography to give **11** (1.9 g, 41% overall yield in three steps) as a colorless oil. $[\alpha]_D^{25}=+14.4$ (*c* 1.60, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 3.97 (dd, 1H, *J*=10.7, 5.6 Hz), 3.11 (s, 1H), 1.75–1.06 (m, 5H),

1.34 (s, 3H), 0.88 (d, 3H, J=6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 69.0, 63.1, 61.5, 36.7, 35.6, 28.0, 24.1, 21.3; EI-MS m/z (%): 142 (M^+, <1), 124 (1), 98 (7), 84 (56), 71 (35), 43 (100); FAB-HRMS: m/z calcd for $C_8H_{15}O_2$ (M+H) 143.1072; found 143.1169.

3.1.4. (1*S*,2*R*,5*R*)-1,2-Dihydroxy-3,5-dimethyl-3-cyclohexene (12). Lithium metal (0.34 g, 48 mmol) was carefully added to 10 mL of absolute ethylenediamine in a flame-dried 25 mL three-necked flask. The mixture was brought to 110°C until the evolution of hydrogen was completed, a blue solution resulted. The epoxide **11** was added in one portion. The temperature was raised to 110°C and maintained for 5 h. After cooling to room temperature, the mixture was hydrolyzed by pouring into 75 mL of ice-water and was extracted with EtOAc (3×50 mL). The organic phase was washed with saturated NH_4Cl solution (50 mL) and brine (50 mL), dried over anhydrous Na_2SO_4 and evaporated in vacuo. The residue was purified by column chromatography to afford **12** (320 mg, 40%) as a colorless solid. $[\alpha]_D^{25}=-32.6$ (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.32 (s, 1H), 3.79 (d, 1H, J=4.0 Hz), 3.59 (dt, 1H, J=12.5, 3.9 Hz), 3.18 (brs, 2H), 2.13–1.17 (m, 3H), 1.74 (brs, 3H), 0.93 (d, 3H, J=7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 132.6, 132.3, 69.8, 69.7, 33.7, 30.9, 21.3, 21.0; EI-MS m/z (%): 142 (M^+, 5), 124 (11), 109 (16), 98 (100), 83 (38), 41 (38); ESI-HRMS: m/z calcd for $C_8H_{14}O_2Na$ (M+Na) 165.0891; found 165.0888.

3.1.5. (1*S*,2*R*,5*R*)-1,2-Isopropylidenedioxy-3,5-dimethyl-3-cyclohexene (13). To a solution of **12** (200 mg, 1.41 mmol) in 2 mL dry acetone was added a catalytic amount of PTS and was stirred at room temperature for 12 h. The reaction mixture was diluted with ether (50 mL) and washed with saturated aqueous $NaHCO_3$ solution (10 mL) and brine (20 mL), dried over anhydrous Na_2SO_4 and evaporated in vacuo. The residue was purified by column chromatography to give **13** (215 mg, 84%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.47 (s, 1H), 4.24 (d, 1H, J=6.05 Hz), 4.20–4.15 (m, 1H), 2.08–1.15 (m, 3H), 1.83 (brs, 3H), 1.48 (s, 3H), 1.39 (s, 3H), 1.04 (d, 3H, J=7.1 Hz); ESI-HRMS: m/z calcd for $C_{11}H_{19}O_2$ (M+H) 183.1830; found 183.1384.

3.1.6. (1*S*,2*S*,3*S*,5*R*)-1,2-Isopropylidenedioxy-3,5-dimethyl-3-cyclohexanol (18). To a solution of **11** (200 mg, 1.41 mmol) in 3 mL of 20% H_2O/dioxane was added 0.4 mL CF_3CO_2H and the solution was stirred at room temperature for overnight. The reaction mixture was evaporated in vacuo and the residue was directly used in the next step. To a solution of the above residue in 4 mL dry acetone was added a catalytic amount of PTS and the resulting mixture was stirred at room temperature for 12 h. The reaction mixture was diluted with ether (50 mL) and washed with saturated $NaHCO_3$ (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 **18** (200 mg, 71%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.25 (ddd, 1H, J=10.1, 6.6, 4.7 Hz), 3.75 (d, 1H, J=4.7 Hz), 1.83–1.01 (m, 5H), 1.48 (s, 3H), 1.34 (s, 3H), 1.33 (s, 3H), 0.91 (d, 3H, J=6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 108.3, 79.7, 74.3, 71.6, 42.8, 37.9, 28.6, 28.3, 26.5, 24.3, 21.8; EI-MS m/z (%): 200 (M^+, <1), 185 (11), 125 (13), 107 (27), 84 (41), 43 (100); FAB-HRMS: m/z calcd for $C_{11}H_{21}O_3$ (M+H) 201.1491; found 201.1531.

3.1.7. (1*S*,2*R*,5*R*)-1,2-Isopropylidenedioxy-3,5-dimethyl-3-cyclohexene (13). To a solution of **18** (200 mg, 1.0 mmol) in 2 mL dry pyridine was added 0.4 mL of thionyl chloride at 0°C and the reaction mixture was stirred at 0°C for 1 h. The mixture was quenched by pouring into 30 mL of ice-water and extracted with ether (3×20 mL). The ethereal layer was washed with diluted HCl, saturated $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4 and evaporated in vacuo. The residue was purified by column chromatography to give **13** (70 mg, 35%) and **19** (50 mg, 25%) as colorless oil. Compound **13**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.47 (s, 1H), 4.23 (d, 1H, J=6.0 Hz), 4.20–4.14 (m, 1H), 2.08–1.15 (m, 3H), 1.83 (brs, 3H), 1.48 (s, 3H), 1.38 (s, 3H), 1.04 (d, 3H, J=6.9 Hz). Compound **19**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.15 (s, 1H), 5.07 (s, 1H), 4.42 (d, 1H, J=5.1 Hz), 4.20–4.14 (m, 1H), 2.08–1.15 (m, 5H), 1.53 (s, 3H), 1.38 (s, 3H), 0.97 (d, 3H, J=6.5 Hz).

3.1.8. (2*R*,4*S*,5*S*)-4,5-Isopropylidenedioxy-2-methyl-6-oxy-heptylaldehyde (14). Through a cold (−78°C) solution of **13** (300 mg, 1.65 mmol) in 50 mL CH_2Cl_2 ozone was bubbled. When the reaction was completed (TLC), the reaction mixture was added Me_2S (2 mL), stirred overnight and evaporated in vacuo. The residue was purified by column chromatography to give **14** (300 mg, 80%) as a colorless oil. ^{1}H NMR (80 MHz, $CDCl_3$) δ: 9.65 (d, 1H, J=1.0 Hz), 4.52–4.42 (m, 2H), 2.25 (s, 3H), 2.64–0.96 (m, 3H), 1.59 (s, 3H), 1.36 (s, 3H), 1.17 (d, 3H, J=7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 209.3, 203.7, 110.1, 82.6, 75.3, 43.4, 31.2, 28.4, 27.0, 24.8, 13.8; EI-MS m/z (%): 215 (M^++1, 1), 199 (M^+−15, 1), 171 (8), 83 (37), 43 (100); FAB-HRMS: m/z calcd for $C_{11}H_{19}O_4$ (M+H) 215.1283; found 215.1338.

3.1.9. (2*R*,4*S*,5*S*)-4,5-Isopropylidenedioxy-1-hydroxy-2-methylheptan-6-one (15). $NaBH_4$ (440 mg) was dissolved in EtOH (33 mL) and CH_2Cl_2 (77 mL). The mixture was cooled to −78°C and keto-aldehyde **14** (580 mg, 2.7 mmol) was added. After stirring for 1 h acetaldehyde (distilled 5 mL) was added and the reaction mixture was allowed to warm to room temperature. The resulting solution was diluted with CH_2Cl_2, washed with diluted base, dried over Na_2SO_4 and evaporated in vacuo. The residue was purified by column chromatography to give **15** (470 mg, 80%) as a colorless oil. ^{1}H NMR (80 MHz, $CDCl_3$) δ: 4.67–4.32 (m, 2H), 3.52 (d, 2H, J=5.6 Hz); 2.24 (s, 3H), 2.12–1.13 (m, 3H), 1.63 (s, 3H), 1.41 (s, 3H), 0.98 (d, 3H, J=6.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 210.2, 109.9, 83.0, 75.8, 67.1, 33.4, 33.2, 28.5, 27.0, 24.9, 16.9; EI-MS m/z (%): 201 (M^+−15, 1), 173 (4), 115 (24), 85 (21), 59 (57), 43 (100); FAB-HRMS: m/z calcd for $C_{11}H_{21}O_4$ (M+H) 217.1440; found 217.1484.

3.1.10. (2*R*,4*S*,5*S*)-4,5-Isopropylidenedioxy-1-(*p*-toluenesulfonyl)oxy-2-methylheptan-6-one (16). The alcohol **15** (350 mg, 1.60 mmol) was dissolved in dry pyridine (3 mL), and *p*-toluenesulfonyl chloride (340 mg, 1.78 mmol) was added. After 24 h at room temperature, the reaction mixture was diluted with ether, washed with saturated potassium

bicarbonate, and purified by column chromatography to give **16** (563 mg, 94%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.79 (d, 2H, J=8.2 Hz); 7.36 (d, 2H, J=8.2 Hz); 4.30–4.20 (m, 2H), 3.91 (d, 2H, J=6.0 Hz); 2.46 (s, 3H), 2.18 (s, 3H), 2.04–1.18 (m, 3H), 1.55 (s, 3H), 1.32 (s, 3H), 0.95 (d, 3H, J=6.8 Hz).

3.1.11. (2*R*,4*S*,5*S*)-4,5-Isopropylidenedioxy-6,6-(1,3-dithiane)-1-(*p*-toluenesulfonyl)oxy-2-methylheptane (17). A mixture of **16** (300 mg, 0.81 mmol), 1,3-propanedithiol (0.3 mL, 3.0 mmol) and $BF_3{\cdot}Et_2O$ (0.025 mL) in dry CH_2Cl_2 (10 mL) was stirred for 1.5 h at 0°C. The mixture was diluted with CH_2Cl_2 and saturated $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (2×20 mL), dried over Na_2SO_4 and evaporated in vacuo. The residue was purified by column chromatography and was directly used in the next step.

To a solution of the above residue in 4 mL dry acetone was added a catalytic amount of PTS and the resulting mixture was stirred at room temperature for 12 h. The reaction mixture was diluted with ether (50 mL), washed with saturated $NaHCO_3$ (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 **17** (290 mg, 78% overall yield in two steps) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.79 (d, 2H, J=8.2 Hz); 7.34 (d, 2H, J=8.2 Hz); 4.39 (d, 1H, J=5.6 Hz), 4.17–4.09 (m, 1H), 4.00–3.94 (m, 2H), 3.05–2.95 (m, 2H), 2.88–2.80 (m, 2H), 2.45 (s, 3H), 2.15–1.67 (m, 5H), 1.66 (s, 3H), 1.47 (s, 3H), 1.34 (s, 3H), 1.00 (d, 3H, J=7.0 Hz); EI-MS m/z (%): 460 (M^+, <1), 385 (1), 327 (5), 133 (100), 91 (15).

3.1.12. (2*R*,4*S*,5*S*)-4,5-Isopropylidenedioxy-6,6-(1,3-dithiane)-1-iodide-2-methylheptane (6). The tosylate **17** (230 mg, 0.5 mmol) was dissolved in acetone (10 mL), and sodium iodide (300 mg, 2.0 mmol) was added, followed by heating under reflux. When the reaction was completed (TLC), the reaction mixture was concentrated; silica gel column chromatography of the residue afforded the iodide **6** (146 mg, 64%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.48 (d, 1H, J=5.6 Hz), 4.20 (dd, 1H, J=5.6, 14.0 Hz), 3.33 (d, 2H, J=4.2 Hz), 3.08–3.02 (m, 2H), 2.86–2.80 (m, 2H), 2.10–1.90 (m, 2H), 1.81–1.20 (m, 3H), 1.72 (s, 3H), 1.51 (s, 3H), 1.40 (s, 3H), 1.03 (d, 3H, J=6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 107.8, 82.8, 76.3, 48.4, 37.0, 30.8, 28.1, 26.8, 26.7, 25.9, 24.7 (2C), 22.0, 17.8; EI-MS m/z (%): 416 (M^+, <1), 341 (1), 225 (3), 133 (100); ESI-HRMS: m/z calcd for $C_{14}H_{26}S_2O_2I$ (M+H) 417.0418; found 417.0412.

3.1.13. (1*S*,2*R*,5*R*)-1,2-Di[(*tert*-butyldimethylsilyl)oxy]-3,5-dimethyl-3-cyclohexene (34). To a solution of diol **12** (284 mg, 2 mmol) in 5 mL DMF was added imidazole (680 mg, 10 mmol) and TBSCl (725 mg, 4.8 mmol). The reaction mixture was stirred for 12 h at room temperature, then diluted with ether (80 mL), washed successively with water (2×20 mL) and brine, dried over anhydrous Na_2SO_4 and evaporated in vacuo. The residue was directly used in the next reaction. $[\alpha]_D^{25}$=−17.8 (c 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ: 5.20 (brs, 1H), 3.76 (d, 1H, J=2.6 Hz), 3.63 (m, 1H), 2.13–0.9 (m, 3H), 1.72 (brs, 3H), 0.96 (d, 3H, J=7.0 Hz), 0.93 (s, 9H), 0.88 (s, 9H), 0.11 (s, 3H), 0.08 (s, 6H), 0.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 134.1, 129.9, 72.7, 72.4, 33.4, 31.8, 26.3 (3C), 26.0 (3C), 25.8, 21.7, 18.6, 18.4, −3.7, −4.2, −4.4, −4.6; EI-MS m/z (%): 355 (M^+−15, <1), 313 (M^+−57, 23), 212 (20), 147 (96), 107 (100); ESI-HRMS: m/z calcd for $C_{20}H_{42}Si_2O_2Na$ (M+Na) 393.2621; found 393.2616.

3.1.14. (2*R*,4*S*,5*S*)-4,5-Di[(*tert*-butyldimethylsilyl)oxy]-2-methyl-6-oxy-heptylaldehyde (35). To a cold (−78°C) solution of the above product in 50 mL CH_2Cl_2 ozone was bubbled. When the reaction was complete (TLC) the reaction mixture was treated with Me_2S (2 mL) and stirred overnight and evaporated in vacuo. The residue was purified by column chromatography to give **35** (370 mg, 46% overall yield for two steps) as a colorless oil. $[\alpha]_D^{25}$=−16.0 (c 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ: 9.60 (d, 1H, J=1.6 Hz), 3.99–3.92 (m, 2H), 2.20 (s, 3H), 2.52–0.85 (m, 3H), 1.10 (d, 3H, J=7.2 Hz), 0.95 (s, 9H), 0.91 (s, 9H), 0.13 (s, 3H), 0.11 (s, 3H), 0.10 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 211.0, 204.0, 81.9, 74.0, 42.6, 34.5, 27.7, 25.8 (6C), 18.3, 18.2, 14.3, −3.9, −4.7, −4.9, −5.0; EI-MS m/z (%): 345 (M^+−57, 1), 245 (29), 215 (49), 73 (100); ESI-HRMS: m/z calcd for $C_{20}H_{42}Si_2O_4Na$ (M+Na) 425.2519; found 425.2509.

3.1.15. (2*R*,4*S*,5*S*)-4,5-Di[(*tert*-butyldimethylsilyl)oxy]-1-hydroxy-2-methylheptan-6-one (36). $NaBH_4$ (440 mg) was dissolved in EtOH (33 mL) and CH_2Cl_2 (77 mL). The mixture was cooled to −78°C and keto-aldehyde **35** (1.1 g, 2.7 mmol) was added. After stirring for 1 h acetaldehyde (distilled 5 mL) was added and the reaction mixture was allowed to warm to room temperature. The resulting solution was diluted with CH_2Cl_2, washed with saturated $NaHCO_3$ solution, dried over Na_2SO_4 and evaporated in vacuo. The residue was purified by column chromatography to give **36** (870 mg, 80%) as a colorless oil. $[\alpha]_D^{25}$=+2.4 (c 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ: 4.02 (d, 1H, J=3.0 Hz), 3.97–3.91 (m, 1H), 3.42 (dd, 2H, J=2.0, 5.8 Hz), 2.19 (s, 3H), 1.73–0.80 (m, 3H), 0.94 (d, 3H, J=5.4 Hz), 0.94 (s, 9H), 0.87 (s, 9H), 0.10 (s, 3H), 0.08 (s, 3H), 0.06 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 212.0, 80.9, 74.7, 68.4, 37.9, 32.3, 27.9, 25.8 (6C), 18.2, 18.1, 17.5, −4.3, −4.7, −4.8, −5.0; EI-MS m/z (%): 347 (M^+−57, <1), 245 (7), 215 (9), 85 (100), 73 (92); ESI-HRMS: m/z calcd for $C_{20}H_{44}Si_2O_4Na$ (M+Na) 427.2676; found 427.2675.

3.1.16. (2*R*,4*S*,5*S*)-4,5-Di[(*tert*-butyldimethylsilyl)oxy]-6,6-(1,3-dithiane)-1-hydroxy-2-methylheptane (37). A mixture of **36** (404 mg, 1.0 mmol), 1,3-propanedithiol (0.4 mL, 4.0 mmol) and $BF_3{\cdot}Et_2O$ (0.05 mL) in dry CH_2Cl_2 (10 mL) was stirred for 1.5 h at 0°C. The mixture was diluted with CH_2Cl_2 and saturated $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (3×20 mL), dried over Na_2SO_4 and evaporated in vacuo. The residue was purified by column chromatography to give **37** (400 mg, 82%) as a colorless oil. $[\alpha]_D^{25}$=−15.6 (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.50 (d, 1H, J=5.4 Hz), 3.87 (s, 1H), 3.64 (dd, 1H, J=4.8, 11.0 Hz), 3.58 (dd, 1H, J=4.2, 11.3 Hz), 3.04–2.91 (m, 2H), 2.80–2.70 (m, 2H), 2.10–1.39 (m, 5H), 1.79 (s, 3H), 0.97 (d, 3H,

J=6.7 Hz), 0.94 (s, 9H), 0.91 (s, 9H), 0.20 (s, 3H), 0.17 (s, 3H), 0.14 (s, 3H), 0.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 84.2, 72.0, 66.8, 55.0, 37.6, 31.8, 26.4, 26.2 (3C), 26.1 (3C), 25.7 (3C), 18.9, 18.6, 18.2, −3.4 (2C), −4.6, −5.1; EI-MS m/z (%): 437 (M^+−57, 1), 305 (7), 229 (9), 133 (100), 73 (92); ESI-HRMS: m/z calcd for $C_{23}H_{51}O_3S_2Si_2$ (M+H) 495.2813; found 495.2822.

3.1.17. (2*R*,4*S*,5*S*)-4,5-Di[(*tert*-butyldimethylsilyl)oxy]-6,6-(1,3-dithiane)-1-iodide-2-methylheptane (38). To a cooled (0°C) solution of alcohol **37** (620 mg, 1.53 mmol), triphenylphosphine (523 mg, 2.0 mmol) and imidazole (146 mg, 2.15 mmol) in 15 mL toluene was added iodine (564 mg, 2.2 mmol) resulting in a pale yellow suspension. After being stirred for 1 h (TLC), the reaction mixture was diluted with ether and sequentially washed with saturated aqueous $Na_2S_2O_3$, $CuSO_4$ and water, dried over Na_2SO_4 and evaporated in vacuo. The residue was purified by column chromatography to give **38** (700 mg, 90%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.36 (d, 1H, J=5.7 Hz), 3.98 (s, 1H), 3.42 (dd, 1H, J=3.0, 9.6 Hz), 3.06 (dd, 1H, J=7.6, 9.6 Hz), 2.93–2.86 (m, 2H), 2.81–2.76 (m, 2H), 2.02–1.43 (m, 5H), 1.72 (s, 3H), 1.03 (d, 3H, J=6.6 Hz), 0.94 (s, 9H), 0.92 (s, 9H), 0.20 (s, 3H), 0.18 (s, 3H), 0.16 (s, 3H), 0.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 83.1, 71.4, 54.8, 39.9 (2C), 31.6, 26.2 (4C), 26.1 (3C), 25.2, 24.7, 22.9, 18.7, 18.2, 16.9, −2.9, −3.0, −4.9, −5.0; EI-MS m/z (%): 604 (M^+, <1), 547 (M^+−57, 1), 471 (3), 133 (100), 73 (96); ESI-HRMS: m/z calcd for $C_{23}H_{49}O_2$ Si_2S_2INa (M+Na) 627.1655; found 627.1649.

3.1.18. (2*R*,4*S*,5*S*)-4,5-Di[(*tert*-butyldimethylsilyl)oxy]-1-(phenylsulfonyl)-2-methylheptan-6-one (41). To a cooled (0°C) solution of alcohol **36** (620 mg, 1.53 mmol), triphenylphosphine (523 mg, 2.0 mmol) and imidazole (146 mg, 2.15 mmol) in 15 mL toluene was added iodine (564 mg, 2.2 mmol) resulting in a pale yellow suspension. After being stirred for 1 h (TLC), the reaction mixture was diluted with ether and sequentially washed with saturated aqueous $Na_2S_2O_3$, $CuSO_4$ and water, dried over Na_2SO_4 and evaporated in vacuo. The residue was purified by column chromatography and the product was directly used in the next reaction.

To a solution of the above iodide in 5 mL DMF was added sodium benzensulfinate (346 mg, 2.08 mmol) and the solution was stirred for 12 h. The reaction mixture was poured into 20 mL water 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 **41** (640 mg, 80% overall yield in two steps). $[\alpha]_D^{25}$=−2.3 (c 2.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.91–7.56 (m, 5H), 3.93–3.87 (m, 2H), 3.19 (dd, 1H, J=3.5, 14.0 Hz), 2.88 (dd, 1H, J=9.2, 14.0 Hz), 2.14 (s, 3H), 2.16–0.83 (m, 3H), 1.15 (d, 3H, J=6.7 Hz), 0.91 (s, 9H), 0.84 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H), 0.04 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 211.2, 140.3, 133.5, 129.3 (2C), 127.8 (2C), 81.2, 74.1, 62.7, 40.9, 27.7, 25.8 (6C), 25.6, 20.4, 18.1, 17.9, −4.2, −4.7, −4.8, −5.1; EI-MS m/z (%): 471 (M^+−57, 3), 427 (5), 341 (90), 245 (68), 73 (100); ESI-HRMS: m/z calcd for $C_{26}H_{48}O_5Si_2SNa$ (M+Na) 551.2659; found 551.2657.

3.1.19. (2*R*,4*S*,5*S*)-4,5-Di[(*tert*-butyldimethylsilyl)oxy]-6,6-diethyloxy-1-(phenylsulfonyl)-2-methylheptane (42). To a solution of **41** (170 mg, 0.322 mmol) in 5 mL EtOH was added 0.5 mL of triethyl orthoformate and catalytic PTS. The mixture was refluxed under nitrogen for 1.5 h and then diluted with 50 mL of ether. The ethereal layer was washed with a 1:1 mixture of 5% NaOH and brine, water and brine, dried over Na_2SO_4 and evaporated in vacuo. The residue was purified by column chromatography to give **42** (128 mg, 64%) as a colorless oil. $[\alpha]_D^{25}$=−15.8 (c 2.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.92–7.67 (m, 5H), 4.07 (d, 1H, J=7.8 Hz), 3.83 (brs, 1H), 3.50–3.38 (m, 4H), 3.17 (dd, 1H, J=3.3, 14.0 Hz), 3.06 (dd, 1H, J=9.6, 14.0 Hz), 2.05–1.49 (m, 3H), 1.18 (s, 3H), 1.13–1.06 (m, 9H), 0.89 (s, 18H), 0.15 (s, 3H), 0.12 (s, 3H), 0.08 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 142.1, 134.4, 130.3 (2C), 128.4 (2C), 102.8, 80.6, 72.5, 62.5, 57.3, 55.9, 41.2, 26.8, 26.5 (3C), 26.3 (3C), 21.8, 18.9, 18.6 (2C), 15.7, 15.5, −3.0, −3.4, −4.7, −4.8; EI-MS m/z (%): 556 (M^++1−57, 1), 499 (12), 341 (100), 117 (89), 73 (82); ESI-HRMS: m/z calcd for $C_{30}H_{58}O_6Si_2SNa$ (M+Na) 625.3390; found 625.3389.

3.1.20. 3-*p*-Menthen-8-ol (20). To a mixture of (+)-pulegone **8** (10 g, 66.0 mmol) and cerium trichloride (24.5 g, 66.0 mmol) in methanol in an ice-water bath was added $NaBH_4$ (2.5 g, 66.0 mol) and the mixture was stirred for 30 min, then the solvent was removed in vacuo. The obtained residue was diluted with ether and a 5% HCl solution the aqueous layer was extracted with ether. The combined organic layer was washed with saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4. The solvent was removed in vacuo and the residue was directly used in next reaction. ^{1}H NMR δ: 4.67 (dd, 1H, J=4.8, 4.2 Hz), 2.25–1.40 (m, 7H), 1.75 (s, 3H), 1.65 (s, 3H), 1.07 (d, 3H, J=6.7 Hz): ^{13}C NMR δ: 132.7, 126.6, 68.3, 39.5, 31.9, 26.7, 22.2, 21.6, 20.5, 19.8.

A mixture of the above product and 150 mL 30% AcOH was stirred for 1 h at 50–55°C. Then the mixture was cooled with ice-water bath. The solution was neutralized with solid $NaHCO_3$ and extracted with ether. The combined organic layer was washed with brine, dried over Na_2SO_4. The solvent was removed in vacuo to give the compound **20** as a colorless oil, which was directly used in the next reaction. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.64 (dd, 1H, J=5.4, 2.4 Hz), 2.12–1.20 (m, 7H), 1.25 (s, 3H), 1.24 (s, 3H), 0.88 (d, 3H, J=6.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 143.4, 118.4, 72.8, 33.6, 31.3, 28.8 (2C), 28.2, 24.4, 21.6; EI-MS m/z (%): 155 (M^++1, 1), 154 (5), 121 (14), 95 (10), 91 (17), 59 (22), 55 (10), 43 (100).

3.1.21. (1*R*,3*S*,4*R*)-3,4-Epoxy-*p*-menthen-8-ol (22). To a solution of the above compound **20** and a catalytic amount of vanadyl acetylacetonate in benzene (150 mL) was added dropwise *tert*-butyl hydroperoxide (20 mL) with stirring. After addition, stirring was continued for 2 h. The reaction system was washed with saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4 and purified by column chromatography to afford the mixture of two isomers of **21/22**, which was used directly in the next step.

To a magnetically stirred slurry of PCC (20.7 g, 96 mmol)

in 150 mL of CH_2Cl_2 was added in one portion a solution of **21/22** in 40 mL of CH_2Cl_2 at room temperature. After the resulting dark red black mixture was allowed to stir for 4.0 h at room temperature, the mixture was diluted with diethyl ether, filtered through Al_2O_3. The filtrate was evaporated in vacuo and the residue was purified by column chromatography to give **22** (5.0 g, 42% overall yield in four steps) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.34 (s, 1H), 2.16–1.22 (m, 7H), 1.18 (s, 2×3H), 0.82 (d, 3H, J=6.6 Hz): ^{13}C NMR (100 MHz, $CDCl_3$) δ: 69.9, 64.8, 56.3, 33.7, 30.0, 25.3, 25.2, 24.5, 24.2, 21.3; EI-MS m/z (%): 155 (M^+-15, 4), 112 (13), 97 (34), 70 (100), 59 (43), 55 (35), 43 (86); HRMS: m/z calcd for $C_9H_{15}O_2$ (M^+-CH_3) 155.1068; found 155.1055.

3.1.22. (1*R*,4*S*)-4-*p*-Menthen-3,8-diol (24). A mixture of epoxide **22** (2 g, 11.8 mmol), aluminium isopropoxide (4.0 g, 23.5 mmol) and 2-propanol (30 mL) was refluxed with stirring under Ar for 8 h, then the solvent was removed and the obtained gel residue was partitioned with ether and a 10% NaOH solution. The aqueous layer was extracted with ether. The combined organic layer was washed with water and brine, dried over Na_2SO_4 and purified by column chromatography to afford a mixture of **23/24**, which was directly used in the next step. Compound **24**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.73 (dd, 1H, J=5.4, 2.4 Hz), 4.45 (d, 1H, J=1.3 Hz), 2.19–1.45 (m, 5H), 1.38 (s, 3H), 1.32 (s, 3H), 0.93 (d, 3H, J=6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 142.9, 124.3, 73.7, 64.4, 39.6, 34.1, 30.1, 29.7, 22.6, 21.5; EI-MS m/z (%): 152 (M^+-15, 7), 137 (22), 109 (14), 95 (18), 43 (100); HRMS: m/z calcd for $C_{10}H_{18}O$ (M^+-H_2O) 152.1197; found 152.1177. Compound **23**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.79 (q, 1H, J=6.4 Hz), 3.66 (s, 1H), 0.96–1.83 (m, 7H), 1.08 (d, 3H, J=6.4 Hz), 0.85 (d, 3H, J=6.4 Hz), 0.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 76.7, 75.7, 39.4, 38.9, 29.6, 25.8, 23.8, 22.2, 19.6, 17.3; GS-MS m/z (%): 154 (M^+-18, 2), 139 (7), 110 (77), 95 (100), 81 (33); HRMS: m/z calcd for $C_{10}H_{15}O$ ($M^+-H_2O-CH_3$) 139.1119; found 139.1105.

3.1.23. (4*S*,6*S*)-2-Methyloxy-4-methyl-6(2′-hydroxy-2′-methylpropionyl)-tetrahydropyran (26). Through a cold (−78°C) solution of compound **23/24** (1.9 g) in 50 mL CH_2Cl_2 ozone was bubbled. When the reaction was complete (TLC) the reaction mixture was treated with 2 mL Me_2S and stirred overnight and evaporated in vacuo. The residue was purified by column chromatography to give **23/25** as a mixture of two isomers, which was directly used in the next step. Compound **25** (two diastereoisomers). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.43 (d, 1H, J=3.0 Hz), 4.88 (dd, 1H, J=11.8, 2.4 Hz), 4.78 (dd, 1H, J=9.6, 2.0 Hz), 4.34 (dd, 1H, J=11.8, 2.4 Hz), 2.14–1.14 (m, 10H), 1.39 (s, 3H), 1.37 (s, 3H), 1.36 (s, 3H), 1.32 (s, 3H), 0.97 (d, 3H, J=6.3 Hz); 0.93 (d, 3H, J=6.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 212.2, 210.8, 96.4, 92.0, 78.4, 77.6, 77.6, 71.8, 40.5, 37.9, 35.7, 35.2, 28.8, 26.7, 26.7, 26.2, 26.2, 23.2, 21.8, 21.4; EI-MS m/z (%): 169 (M^+-Me-H_2O, 1), 98 (46) 83 (31), 71 (59), 59 (100), 43 (54).

To a solution of the above product in 25 mL acetone was added 2 mL DMP and catalytic amount of PTS. The mixture was stirred overnight at room temperature and then diluted with ether and washed with saturated $NaHCO_3$ and brine, dried over Na_2SO_4 and evaporated in vacuo. The residue was purified by column chromatography to give **26** (two diastereoisomers) (650 mg, 40% overall yield in three steps) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.83 (d, 1H, J=3.3 Hz), 4.60 (dd, 1H, J=11.8, 2.5 Hz), 4.35 (dd, 1H, J=2.1, 9.6 Hz), 4.22 (dd, 1H, J=2.5, 11.9 Hz), 3.47 (s, 3H), 3.34 (s, 3H), 1.91–1.06 (m, 10H), 1.40 (s, 3H), 1.39 (s, 3H), 1.38 (s, 6H), 0.95 (d, 3H, J=6.5 Hz), 0.87 (d, 3H, J=6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 211.9, 210.8, 103.7, 99.2, 79.4, 77.4 (2C), 72.5, 56.5, 55.3, 39.0, 37.7, 36.3, 35.7, 28.8, 26.4, 26.3, 26.2, 26.1, 24.0, 21.9, 21.6; EI-MS m/z (%): 185 (M^+-31, 3), 129 (18), 85 (100), 43 (49); ESI-HRMS: m/z calcd for $C_{11}H_{20}O_4Na$ (M+Na): 239.1259; found 239.1253.

3.1.24. 2-[(2*S*,5*S*,6*R*)-4,5,6-Trihydroxy-2,6-dimethylheptyl]-1,3-dithiane (28). To a cooled (−78°C), stirred solution of **26** (400 mg, 1.85 mmol) in 8 mL MeOH was added $NaBH_4$ (70 mg, 1.85 mmol). The mixture was stirred for 1 h, then the solvent was removed. The obtained residue was diluted with EtOAc and 10 mL 5% HCl solution. The aqueous layer was extracted with EtOAc and the combined organic layer was washed with saturated $NaHCO_3$ and brine, dried over Na_2SO_4 and evaporated in vacuo. The residue was purified by column chromatography to give **27** (320 mg, 80%) as a mixture of four diastereoisomers, which was directly used in the next step.

A mixture of **27** (800 mg, 3.67 mmol), 1,3-propanedithiol (4 mL, 40.0 mmol) and $BF_3{\cdot}Et_2O$ (1.0 mL) in dry CH_2Cl_2 (10 mL) was stirred for 1.5 h at 0°C. The mixture was diluted with EtOAc and saturated $NaHCO_3$. The aqueous layer was extracted with EtOAc (3×20 mL), dried over Na_2SO_4 and evaporated in vacuo. The residue was purified by column chromatography to give **28** (830 mg, 77%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.12 (t, 1H, J=7.6 Hz), 4.06 (dd, 1H, J=4.1, 9.2 Hz), 3.07 (brs, 1H), 2.93–2.78 (m, 4H), 2.13–1.12 (m, 7H), 1.29 (s, 3H), 1.28 (s, 3H), 0.97 (d, 3H, J=6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 77.2, 74.2, 68.8, 45.3, 42.8, 41.2, 30.5, 30.3, 27.2, 26.3, 26.2, 26.0, 19.6; EI-MS m/z (%): 294 (M^+, 20), 276 (5), 258 (3), 159 (54), 119 (100), 84 (59), 59 (46); ESI-HRMS: m/z calcd for $C_{13}H_{26}O_3S_2Na$ (M+Na): 317.1221; found 317.1210.

3.1.25. 2-[(2*S*,5*S*,6*R*)-4,5-Isopropylidenedioxy-6-hydroxy-2,6-dimethylheptyl]-1,3-dithiane (29). To a solution of **28** (830 mg, 2.83 mmol) in 6 mL dry acetone was added a catalytic amount of PTS and the mixture was stirred at room temperature for 12 h. The reaction mixture was diluted with ether (80 mL) and washed with saturated $NaHCO_3$ (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 **29** (890 mg, 95% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.15–4.03 (m, 2H), 3.50 (d, 1H, J=7.8 Hz), 2.92–2.78 (m, 4H), 2.14–1.10 (m, 7H), 1.39 (s, 3H), 1.38 (s, 3H), 1.25 (s, 3H), 1.19 (s, 3H), 0.99 (d, 3H, J=6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 108.4, 87.3, 74.6, 69.9, 45.3, 43.3, 42.7, 30.5, 30.3, 27.8, 27.6, 27.5, 27.1, 26.0, 24.7, 18.9; EI-MS m/z (%): 334 (M^+, 4), 319 (6), 217 (23), 159 (37), 119 (91), 59 (100); FAB-HRMS: m/z calcd for $C_{16}H_{31}O_3S_2$ (M+H:) 335.1715; found 335.1695.

3.1.26. 2-[(2*S*,5*S*)-4,5-Isopropylidenedioxy-2,6-dimethylhept-6-enyl]-1,3-dithiane (7). To a solution of **29** (100 mg, 0.3 mmol) in 2 mL dry pyridine was added 0.4 mL of thionyl chloride at 0°C and the reaction mixture was stirred at 0°C for 1 h. The mixture was quenched by poured into 20 mL of ice-water and extracted with ether (3×20 mL). The ethereal layer was washed with diluted HCl, saturated $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4 and evaporated in vacuo. The residue was purified by column chromatography to give **7** (60 mg, 64%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.04 (s, 1H), 4.96 (s, 1H), 4.09 (dd, 1H, *J*=8.4 Hz), 3.98 (d, 1H, *J*=8.8, 5.9 Hz), 3.81 (dt, 1H, *J*=2.9, 8.8 Hz), 2.93–2.79 (m, 4H), 2.17–1.15 (m, 7H), 1.78 (s, 3H), 1.41 (s, 6H), 0.96 (d, 3H, *J*=6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 141.6, 114.5, 108.5, 85.5, 76.2, 45.3, 43.0, 39.5, 30.5, 30.3, 27.5 (2C), 26.8, 26.0, 19.2, 17.4; EI-MS *m*/*z* (%): 316 (M^+, 7), 301 (3), 159 (36), 112 (100); FAB-HRMS: *m*/*z* calcd for $C_{16}H_{29}O_2S_2$ (M+H) 317.1609; found 317.1590.

3.1.27. 2-[(2*S*,5*S*,6*R*)-4,5-Di[(*tert*-butyldimethylsilyl)oxy]-6-hydroxy-2,6-dimethylheptyl]-1,3-dithiane (39). To a solution of **28** (810 mg, 2.76 mmol) in 5 mL DMF was added imidazole (936 mg, 13.8 mmol) and TBSCl (1.0 g, 6.61 mmol). The reaction mixture was stirred for 24 h at 80°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 **39** (580 mg, 40%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.06 (dd, 1H, *J*=6.4, 8.7 Hz), 3.80–3.76 (m, 1H), 3.53 (d, 1H, *J*=6.0 Hz), 2.86–2.76 (m, 4H), 2.11–0.84 (m, 7H), 1.24 (s, 3H), 1.20 (s, 3H), 0.92 (s, 9H), 0.90 (s, 9H), 0.85 (d, 3H, *J*=6.5 Hz), 0.11 (s, 3H), 0.09 (s, 3H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 78.4, 74.4, 73.8, 45.3, 43.7, 39.0, 30.3, 30.2, 29.7, 28.6, 28.3, 25.8, 26.1 (3C), 25.9 (3C), 18.4, 18.0, 17.9, −3.5, −3.6, −4.7, −4.8; EI-MS *m*/*z* (%): 504 (M^+−18, <1), 465 (M^+−57, <1), 407 (2), 333 (7), 319 (66), 185 (100), 73 (80); ESI-HRMS: *m*/*z* calcd for $C_{25}H_{54}O_3Si_2S_2Na$ (M+Na) 545.2951; found 545.2933.

3.1.28. 2-[(2*S*,5*S*,6*R*)-4,5-Di[(*tert*-butyldimethylsilyl)oxy]-2,6-dimethylhept-6-enyl]-1,3-dithiane (40). To a solution of **39** (400 mg, 0.77 mmol) in 4 mL dry pyridine was added 1.0 mL of thionyl chloride at 0°C and the reaction mixture was stirred at 0°C for 1 h. The mixture was quenched by poured into 30 mL of ice-water and extracted with ether (3×20 mL). The ethereal layer was washed with dilute HCl, saturated $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4 and evaporated in vacuo. The residue was purified by column chromatography to give **40** (290 mg, 76%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.97 (s, 1H), 4.86 (s, 1H), 4.10–4.04 (m, 2H), 3.69–3.65 (m, 1H), 2.90–2.78 (m, 4H), 2.12–0.83 (m, 7H), 1.77 (s, 3H), 0.91–0.87 (m, 21H), 0.10 (s, 3H), 0.08 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 144.7, 111.8, 77.2, 73.6, 45.4, 43.7, 39.1, 30.4, 30.2, 26.1 (2C), 26.0 (3C), 25.9 (3C), 21.2, 19.1, 18.2, 18.0, −3.6, −4.8, −4.8, −5.0; EI-MS *m*/*z* (%): 504 (M^+, <1), 447 (M^+−57, 2), 319 (61), 185 (100), 73 (52); ESI-HRMS: *m*/*z* calcd for $C_{25}H_{53}O_2S_2Si_2$ (M+H) 505.3020; found 505.3012.

3.1.29. (3*S*,6*S*,7*R*)-5,6-Di[(*tert*-butyldimethylsilyl)oxy]-3,7-dimethyl-7-octenal (43). A solution of the dithiane **40** (420 mg, 0.83 mmol) in aqueous 4.4 mL 80% acetonitrile was added to an efficiently stirred solution of mercuric chloride (640 mg, 2.3 mmol) and powdered calcium carbonate (230 g, 2.3 mmol) in the same solvent mixture (15 mL). The mixture was stirred and heated at reflux under nitrogen for 24 h, cooled, and filtered through celite, the filter cake was washed thoroughly with ether. The organic phase of the filtrate was washed with water and brine, dried over anhydrous Na_2SO_4 and evaporated in vacuo. The residue was purified by column chromatography to give **43** (290 mg, 84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.72 (t, 1H, *J*=2.0 Hz), 4.98 (s, 1H), 4.87 (s, 1H), 4.06 (d, 1H, *J*=3.7 Hz), 3.74–3.68 (m, 1H), 2.35–1.21 (m, 5H), 1.76 (s, 3H), 0.94–0.89 (m, 21H), 0.12 (s, 3H), 0.09 (s, 3H), 0.05 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 202.9, 144.4, 111.9, 77.2, 73.6, 51.9, 38.9, 25.9 (3C), 25.8 (3C), 24.3, 21.3, 19.5, 18.1, 18.0, −3.5, −4.8, −4.9, −5.0; EI-MS *m*/*z* (%): 357 (M^+−57, 3), 229 (79), 185 (26), 73 (100); ESI-HRMS: *m*/*z* calcd for $C_{22}H_{46}O_3Si_2Na$ (M+Na) 437.2883; found 437.2883.

3.1.30. (3*R*,4*S*,6*R*,10*S*,12*S*,13*R*)-3,4,12,13-Tetra[(*tert*-butyldimethylsilyl)oxy]-2,2-diethyloxy-6,10,14-trimethyl-14-pentadecen-8-one (45). To a solution of sulfone **42** (215 mg, 0.36 mmol) in 2 mL of THF at −78°C under Ar was added dropwise 0.21 mL (0.37 mmol) of *n*-butyllithium (1.75 M in petroleum) and the solution was stirred at the same temperature for 30 min. To the solution at −78°C was added dropwise aldehyde **43** (186 mg, 0.37 mmol) dissolved in 3 mL of THF and the mixture was stirred at the same temperature for 2.5 h. The reaction was quenched with 2 mL of saturated aqueous NH_4Cl and the temperature was allowed to warm to room temperature. The reaction mixture was poured into water (10 mL) and extracted with ether (3×20 mL). The ethereal layer was washed with 20 mL of brine, dried over anhydrous Na_2SO_4 and evaporated in vacuo. The residue was purified by column chromatography to give adduct **44**, which was directly used in the next reaction.

To a magnetically stirred of PDC (445 mg, 1.7 mmol) in 10 mL of CH_2Cl_2 was added a solution of the above product (293 mg, 0.29 mmol) in 5 mL of CH_2Cl_2 at room temperature. The reaction mixture was stirred for 15 min at room temperature. 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 α-sulfonyl ketone (263 mg, 0.26 mmol), which was directly used in the next reaction.

To a stirred solution of the above sulfone (263 mg, 0.26 mmol) and anhydrous Na_2HPO_4 (148 mg, 1.04 mmol) in MeOH (5 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 NH_4Cl (10 mL) and extracted with ether (3×20 mL), washed with brine, dried over anhydrous Na_2SO_4 and evaporated in vacuo. The residue was purified by column chromatography to give **45** (159 mg, 50% overall yield in three steps). ^{1}H

NMR (400 MHz, $CDCl_3$) δ: 4.99 (s, 1H), 4.86 (s, 1H), 4.12 (brs, 1H), 4.07 (d, 1H, J=9.3 Hz), 3.87 (brs, 1H), 3.80–3.75 (m, 1H), 3.57–3.40 (m, 4H), 2.45–0.85 (m, 10H), 1.77 (s, 3H), 1.20 (s, 3H), 1.16 (t, 3H, J=7.2 Hz), 1.12 (t, 3H, J=7.0 Hz), 0.92–0.85 (m, 42H), 0.16–0.03 (m, 24H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 209.6, 145.6, 112.2, 102.7, 80.5, 78.0, 74.4, 72.6, 56.9, 55.7, 52.5, 49.7, 40.6, 39.7, 26.5 (3C), 26.4 (3C), 26.2 (3C), 26.3 (3C), 25.9, 22.1, 21.6, 19.8, 19.6, 19.0, 18.6 (4C), 15.8, 15.5, −3.1, −3.3, −4.5, −4.6, −4.7, −4.7, −4.8, −4.9; ESI-HRMS: *m/z* calcd for $C_{46}H_{98}O_7Si_4Na$ (M+Na) 897.6288; found 897.6302.

3.1.31. (2*R*,3*S*,5*R*,3′*S*,5′*S*,6′*R*)-6-[5′,6′-Di(*tert*-butyldimethylsilyl)oxy-3′,7′-dimethyl-7′-octenal]-2,3-di(*tert*-butyldimethylsilyl)oxy-1,5-dimethyl-cyclohexanol (47). To a solution of oxalyl chloride (0.200 mL, 2.30 mmol) in 3 mL of CH_2Cl_2 at −78°C under Ar was added dropwise 0.327 mL (4.60 mmol) of dimethyl sulfoxide dissolved in 2 mL of CH_2Cl_2 and the solution was stirred at the same temperature for 10 min. To the solution at −78°C was added dropwise the above coupling adduct **44** (320 mg, 0.32 mmol) dissolved in 3 mL of CH_2Cl_2 and the mixture was stirred at the same temperature for 1 h. To the solution at −78°C was added 0.88 mL (6.6 mmol) of triethylamine and then the mixture was vigorously stirred at 0°C for an additional 2.5 h. The reaction mixture was poured into 25 mL of water and extracted with ether (3×20 mL). The extracts were washed with 50 mL of brine, dried over anhydrous Na_2SO_4, and evaporated in vacuo. The residue was purified by column chromatography to give **46** (240 mg, 74%), which was directly used in the next reaction.

Method A. To a solution of the above product **46** (90 mg, 0.09 mmol) and 2,2′-azobisisobutyronitrile (18 mg, 0.11 mmol) in 5 mL of toluene at room temperature under Ar was added 0.05 mL (0.19 mmol) of tributyltin hydride and then the mixture was stirred at reflux for 5 h. An oil bath was removed and the reaction mixture was concentrated in vacuo. The residue was purified by column chromatography to give **47** (53 mg, 73%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.99 (s, 1H), 4.87 (s, 1H), 4.36–4.31 (m, 1H), 4.12 (brs, 1H), 3.80–3.72 (m, 1H), 3.48 (d, 1H, J=2.2 Hz), 2.66–0.85 (m, 9H), 1.77 (brs, 3H), 1.14 (s, 3H), 0.92–0.85 (m, 42H), 0.17–0.04 (m, 24H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 217.3, 145.7, 112.3, 79.9, 78.1, 74.5, 70.7, 59.7, 55.5, 39.9, 37.3, 30.9, 27.6, 26.7 (3C), 26.6 (3C), 26.5, 26.3 (3C), 26.2 (3C), 24.7, 21.5, 20.5, 20.1, 19.7, 19.1, 18.7, 18.6, −2.9, −3.3, −4.1, −4.4, −4.5 (2C), −4.6, −4.8; ESI-HRMS: *m/z* calcd for $C_{42}H_{88}O_6Si_4Na$ (M+Na) 823.5556; found 823.5573.

Method B. To a stirred solution of the above sulfone (90 mg, 0.09 mmol) and anhydrous Na_2HPO_4 (51 mg, 0.36 mmol) in MeOH (3 mL) was added pulverized 6% sodium amalgam (0.3 g) at room temperature. The reaction mixture was vigorously stirred for 1 h until TLC showed complete conversion. The mixture was poured into saturated NH_4Cl (10 mL) and extracted with ether (3×20 mL), washed with brine, dried with anhydrous Na_2SO_4 and evaporated in vacuo. The residue was purified by column chromatography to give **47** (60 mg, 79%).

3.1.32. (2*S*,4*R*,6*R*,8*S*,10*S*,1′*R*,1″*R*)-2-(Acetylhydroxymethyl)-4,10-dimethyl-8-(isopropenylhydroxymethyl)-1,7-dioxaspiro[5,5]-undecane (4a) and its C1″-epimer (4b). The substrate **45** (90 mg, 0.10 mmol) was dissolved in acetonitrile containg 1 mL of a 40% aqueous solution of HF. TLC monitoring was carried out by spotting an aliquot directly onto a silica gel plate and when deprotection was complete, ether and water was added. The aqueous phase was extracted with ether (3×20 mL), washed 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**+**4b** (20 mg, 60%).

HPLC gave **4a** (10 mg) and **4b** (2 mg). Compound **4a** (white solid): $[\alpha]_D^{25}$=96.7 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.01 (s, 1H), 4.96 (s, 1H), 4.17 (d, 1H, J=5.2 Hz), 3.91 (ddd, 1H, J=11.5, 5.4, 2.7 Hz), 3.86 (d, 1H, J=6.0 Hz), 3.56 (ddd, 1H, J=11.7, 6.0, 2.2 Hz), 2.59–0.88 (m, 10H), 2.31 (s, 3H), 1.75 (s, 3H), 1.15 (d, 3H, J=7.3 Hz), 0.87 (d, 3H, J=6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 209.1, 143.9, 113.4, 98.7, 79.3, 78.3, 71.1, 67.3, 44.0, 40.1, 35.3, 31.5, 27.9, 24.8, 24.4, 22.0, 20.9, 18.2; EI-MS *m/z* (%): 255 (M^+−71, 58), 237 (22), 177 (20), 149 (26), 113 (72), 43 (100). Compound **4b** (white solid): $[\alpha]_D^{25}$=+50 (*c* 0.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.05 (s, 1H), 4.94 (s, 1H), 4.14 (brs, 1H), 4.09 (d, 1H, J=3.9 Hz), 3.88 (ddd, 1H, J=11.6, 5.7, 2.8 Hz), 3.60 (ddd, 1H, J=12.0, 4.0, 2.4 Hz), 2.31–0.88 (m, 10H), 2.32 (s, 3H), 1.73 (s, 3H), 1.18 (d, 3H, J=7.3 Hz), 0.88 (d, 3H, J=6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 209.5, 143.3, 112.1, 98.8, 79.2, 76.8, 71.3, 67.6, 44.0, 40.1, 31.9, 29.7, 28.2, 24.7, 24.6, 22.1, 20.6, 19.3; EI-MS *m/z* (%): 255 (M^+−71, 100), 237 (32), 177 (27), 149 (38), 113 (56), 43 (86); ESI-HRMS: *m/z* calcd for $C_{18}H_{30}O_5Na$ (M+Na) 349.1990; found 349.1981.

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