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Synthetic studies of didemnaketal analogue — construction of the (+)- and (−)-5,6-dihydroxy-3,7-dimethyl-octanal intermediates

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Abstract

A synthetic procedure for construction of the (+)-(3*R*,5*R*,6*R*)-5,6-dihydroxy-3,7-dimethyl-octanal and (−)-(3*S*,5*S*,6*S*)-5,6-dihydroxy-3,7-dimethyl-octanal derivatives, the intermediates for synthesis of the HIV-active didemnaketal analogue, was developed via a series of reactions from the natural (−)-menthone.

1. Introduction

The naturally occuring didemnaketals A (**1**) and B (**2**) are two important leading components isolated from *Ascidian didemnum* sp. by D. J. Faulkner and co-workers,[1] which exhibited significant inhibition of HIV-1 protease. However, the further investigation regarding the synthesis and biological activity of these kinds of spiroketals has not been reported. Our research interest in this field is focused on their synthetic methodology and, as part of our recent research directed towards the total synthesis of the analogue **3**, we herein report an efficient procedure for the enantioselective synthesis of (+)- and (−)-5,6-dihydroxy-3,7-dimethyl-octanal intermediates **5** and **23**.

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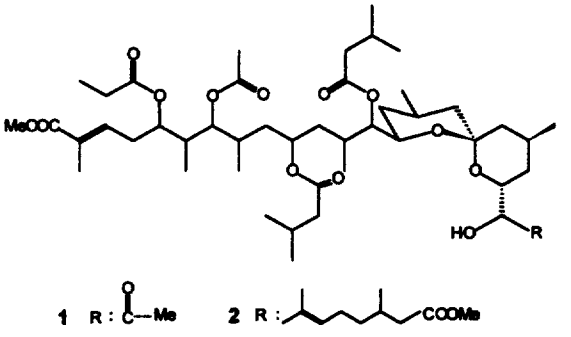
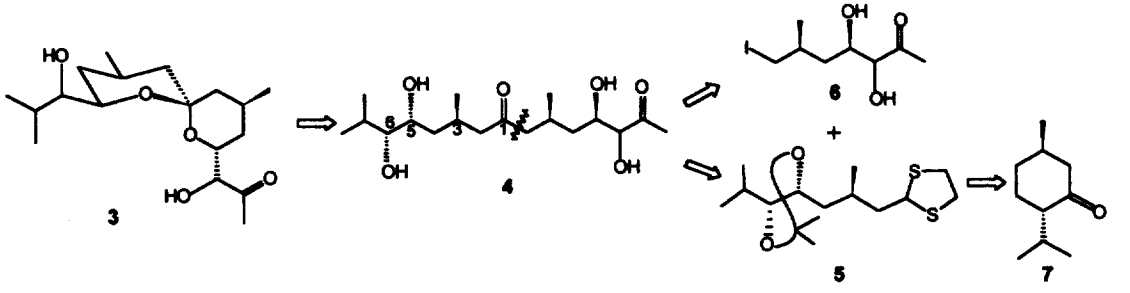


Didemnaketals A and B

2. Results and discussion

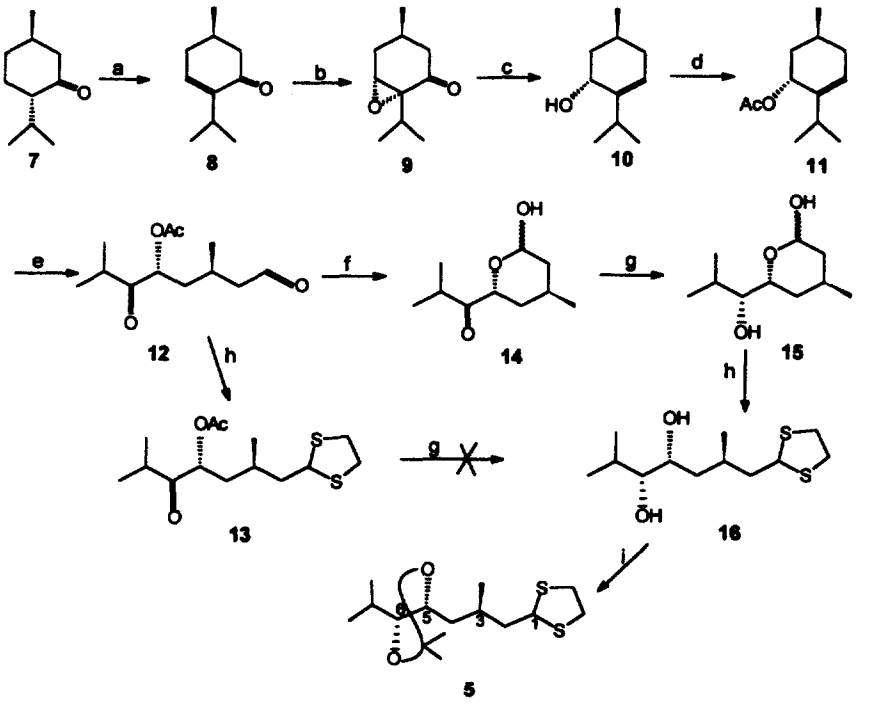
Based on the retrosynthetic consideration (Scheme 1), synthesis of the target compound **3** is attributed to that of the linear intermediate **4**, which can be constructed from two intermediates **5** and **6**. Furthermore, **5** can be synthesized from the (−)-menthone **7**, a versatile natural source bearing an *R*-methyl group.[2]



Scheme 1.

As shown in Scheme 2, (−)-menthone **7**, when brominated with NBS and successively dehydrobrominated with quinoline, formed the α,β-unsaturated menthone **8** in the yield of 68%,[3] which was epoxidized with H_2O_2:NaOH to provide the epoxy menthone **9** as the exclusive product.[4] Treatment of **9** with 85% $NH_2NH_2 \cdot H_2O$ gave **10** as the only product and no other isomer was separated or even detected by NMR spectroscopy.[5] Thus the second stereogenic center was conveniently constructed. Protection of **10** with acetic anhydride followed by ozonization gave the linear ketoaldedyde **12**.

Since the stereochemistry of the carbon in **3**, corresponding to C-6 in **4** remained to be determined, our initial effort was the construction of either the *R*- or *S*-configuration of C-6, which would be matched with the natural products. Thus, we first protected **12** with 1,2-ethandithiol and then attempted to reduce **13** directly with $NaBH_4$ or $LiAlH_4$. Unfortunately, a very complicated mixture (not identified) was formed in both cases. Thus, compound **12** was hydrolyzed with K_2CO_3/MeOH and spontaneously the self-protected hemi-acetal **14** was formed which, though a mixture of two isomers, underwent an effectively diastereoselective reduction when treated with $NaBH_4$ at low temperature to give compound **15** as a mixture of two isomers in high yield. In order to determine the absolute configuration of C-6, the aldehyde group of the hemi-acetal **15** was protected with 1,2-ethandithiol and the two hydroxyls with acetone to

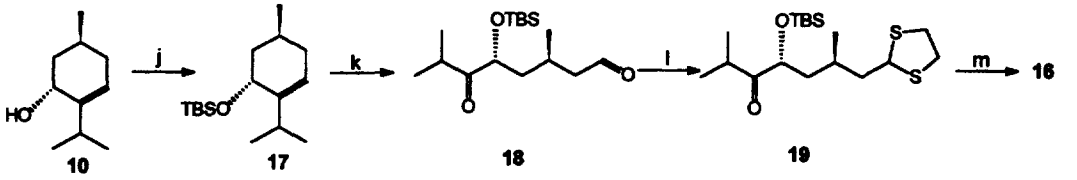


Reagents: a) NBS, quinoline, CCl_4 (68%); b) H_2O_2, NaOH, MeOH (71%); c) 85% $NH_2NH_2.H_2O$ (65%); d) Ac_2O, Py (96%); e) O_3, CH_2Cl_2, then Zn, HOAc (95%); f) K_2CO_3, MeOH (93%); g) $NaBH_4$, MeOH (98%); h) 1,2-ethandithiol, $BF_3.OEt_2$, CH_2Cl_2 (75%); i) Acetone, PTS (79%).

Scheme 2.

give the compound **5**. The NOESY technique demonstrated that the absolute configurations were 5*R* and 6*R*.

Alternatively, compound **5** could also be synthesized from a TBSCl (*tert*-butyldimethylsilyl chloride) protected derivative **17** of **10**. As shown in Scheme 3, **10** was protected with TBSCl and then ozonized to give **18**. Protection of **18** with 1,2-ethandithiol followed by reduction with Red-Al afforded the intermediate **16** in good yield and diastereoselectivity (de>98%).

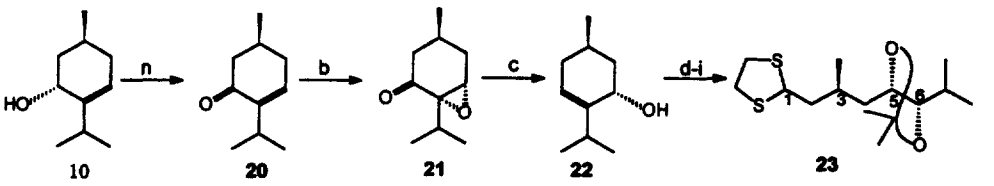


Reagents: j) TBSCl, imidazole, DMF (95%); k) O_3, CH_2Cl_2, then Zn, HOAc (92%); l) 1,2-ethandithiol, CH_2Cl_2 (78%); m) Red-Al, toluene (80%).

Scheme 3.

For the synthesis of the enantiomer of **3**, a method for the synthesis of the enantiomer of **5** has also been developed. This procedure simply included a three-step configurational conversion from **10** to **22** as shown in Scheme 4. Thus, oxidation of **10** with PCC followed by epoxidation and Wharton reaction gave the enantiomer **22** of **10**. Following the same procedures as (d)–(i) in Scheme 2, the synthesis of the

enantiomer **23** was carried out. The total synthesis of **3** is still continuing and will be reported in the near future.



Reagents: n) PCC, CH_2Cl_2(80%); b-i) Same as in scheme 2.

Scheme 4.

3. Experimental

3.1. General

The ^1H NMR, ^{13}C NMR and DEPT data were recorded in $CDCl_3$ solution with Brucker AM-80 or AM-400 MHz spectrometers. The chemical shifts are reported in ppm relative to TMS or $CDCl_3$. Optical rotations were determined on a JASCO J-20C polarimeter with a 0.2 dm tube. GC–MS, MS and HRMS data were measured with EI (70 eV) or FAB techniques. Column chromatographies were generally performed on silica gel (200–300 mesh) eluting with petroleum ether:EtOAc (30:1→10:2.5) and TLC inspections on silica gel F_{254} plates with petroleum ether:EtOAc (10:2.5) if not noted especially below.

3.2. (2R,3R,5R)-2-Isopropyl-5-methyl-2,3-epoxy-cyclohexan-1-one 9

To a stirred solution of **8** (1.86 g, 12.2 mmol, prepared by a literature procedure[3]) and 4.6 ml of 30% hydrogen peroxide in 30 ml methanol, was added 1 ml 6 N NaOH 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 washed with brine, dried over Na_2SO_4 and purified by column chromatography to give **9** as a colorless oil (1.46 g, 71%). $[\alpha]_D^{25}$=+61 (c 1.0, MeOH); ^1H NMR δ 3.46 (br, 1H), 2.75–1.65 (m, 6H), 1.10 (d, *J*=6.8 Hz, 6H), 0.90 (d, *J*=6.5 Hz, 3H). ^{13}C NMR δ 205.5, 63.6, 57.2, 46.0, 31.7, 25.6, 23.7, 21.0, 18.4, 16.0.

3.3. (1R,5R)-2-Isopropyl-5-methyl-2,3-ene-cyclohexan-1-ol 10

To the compound **9** (150 mg, 0.89 mmol) was added 85% hydrazine hydrate (500 mg, 10 mmol) at room temperature. After stirring for 10 min at room temperature, the mixture was heated slowly to reflux (120°C) and kept at reflux temperature until the epoxy ketone **9** was completely dissolved. After cooling, the reaction mixture was diluted with ether (50 ml) and then washed with water (3×10 ml) and brine (2×10 ml), dried over Na_2SO_4 and purified by column chromatography to give **10** as a yellowish oil (89 mg, 65%). $[\alpha]_D^{25}$=+68 (c 0.57, EtOH); ^1H NMR δ 5.53 (m, 1H), 4.11 (br s, 1H), 2.42 (heptet, *J*=7.0 Hz 1H), 2.15–1.24 (m, 7H), 1.05 (d, *J*=7.0 Hz, 1H), 1.03 (d, *J*=7.0 Hz, 3H), 0.94 (d, *J*=6.5 Hz, 3H).

3.4. (3R,5R)-2-Isopropyl-3-acetoxy-5-methyl-cyclohexene 11

To the compound **10** (950 mg, 6.2 mmol) were added acetic anhydride (3.46 g, 33.8 mmol) and 0.2 ml dry pyridine. The mixture was stirred for 20 h and then water (1 ml) was added. After stirring for 5 h, the system was neutralized with saturated $NaCHO_3$ solution (ca. 30 ml) and then extracted with ether (3×50 mL). The combined organic layer was washed with water (3×20 ml) and brine (3×20 ml), dried over Na_2SO_4 and purified by column chromatography to give the pure product **11** (1.16 g, 96%) as a yellowish oil. $[\alpha]_D^{25}$=+118 (c 0.02, $CHCl_3$); ^{1}H NMR δ 5.73 (br, 1H), 5.40 (br, 1H), 2.32–1.26 (m, 6H), 2.06 (s, 3H), 1.06 (d, *J*=6.7 Hz, 3H), 1.00 (d, *J*=6.7 Hz, 3H), 0.85 (d, *J*=6.0 Hz, 3H).

3.5. (3R,5R)-3,7-Dimethyl-5-acetoxy-6-oxo-octanal 12

Into a cold (−78°C) solution of compound **11** (2.5 g, 12.76 mmol) in 30 ml MeOH and 150 ml CH_2Cl_2 was bubbled ozone until the solution became light blue. The ozone addition was stopped, and the solution was stirred under argon at −78°C for 15 min and at 25°C for 30 min. Then zinc dust (15 g) and acetic acid (33 ml) were added to the solution, and the resulting mixture was stirred at 25°C for 30 min and filtered. The filtrate was neutralized with 5 N NaOH solution (100 ml), the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3×60 ml). The combined organic layer was washed with water (3×20 ml) and brine (3×20 ml), dried over Na_2SO_4 and purified by column chromatography to give **12** (2.76 g, 95%) as a colorless oil. $[\alpha]_D^{25}$=−6 (c 0.03, $CHCl_3$); ^{1}H NMR δ 9.76 (m, 1H), 5.20 (dd, *J*=10.7, 2.7 Hz, 1H), 2.80 (heptet, *J*=6.9 Hz, 1H), 2.40–1.70 (m, 5H), 2.15 (s, 3H), 1.16 (d, *J*=6.9 Hz, 3H), 1.07 (d, *J*=6.9 Hz, 3H), 1.00 (d, *J*=6.6 Hz, 3H); ^{13}C NMR δ 210.9, 201.4, 170.4, 75.4, 51.0, 36.8, 36.7, 24.8, 20.6, 19.0, 18.9, 17.8.

3.6. (4R,6R)-2-Hydroxy-4-methyl-6-(2′-methylpropionyl)-tetrahydropyran 14

Compound **12** (1.7 g, 7.46 mmol) was dissolved in MeOH (15 ml) and then the solution was added to a suspension of K_2CO_3 (3.4 g, 24.6 mmol) in MeOH (10 ml) and stirred for 2 h at room temperature. The suspension was filtered, and the filtrate was washed with MeOH (3×10 ml) and then concentrated in vacuo. The obtained residue was diluted with ether (100 ml), washed with saturated NH_4Cl solution (2×30 ml) and brine (2×30 ml), dried over Na_2SO_4 and purified by column chromatography to give the mixture of two isomers of **14** in the ratio of 3:2 (determined by NMR spectra) as a colorless oil (1.29 g, 93%). ^{1}H NMR (major) δ 5.47 (d, *J*=2.6 Hz, 1H), 4.60 (dd, *J*=12.0, 2.4 Hz, 1H), 3.12 (heptet, *J*=7.0 Hz, 1H), 1.95–1.23 (m, 5H), 1.08 (d, *J*=7.0 Hz, 6H), 0.95 (d, *J*=6.0 Hz, 3H); (minor) δ 4.79 (d, *J*=9.2 Hz, 1H), 4.04 (dd, *J*=12.0, 2.4 Hz, 1H), 2.99 (heptet, *J*=6.8 Hz, 1H), 1.95–1.23 (m, 5H), 1.08 (d, *J*=6.8 Hz, 6H), 1.01 (d, *J*=6.0 Hz, 3H); ^{13}C NMR δ 213.8, 213.0, 96.4, 92.3, 79.6, 73.3, 41.0, 37.8, 37.4, 36.0, 35.8, 35.4, 30.0, 29.3, 23.8, 22.0, 21.6, 18.3, 18.2, 14.1; EI-MS (two isomers) m/z (%) 185 (M^+−1, 4), 169 (30), 115 (64), 71 (100); FAB-HRMS: 169.1184, calcd for $C_{10}H_{16}O_2$+H: 169.1224.

3.7. (4R,6R,7R)-2-Hydroxy-4-methyl-6-(1′-hydroxy-2′-methylpropyl)-tetrahydropyran 15

To a cooled (−78°C), stirred solution of **14** (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 h, then the solvent was removed in vacuo. The obtained residue was diluted with ether (50 ml) and washed with H_2O (2×10 ml) and brine (2×10 ml), dried (Na_2SO_4) and purified by column chromatography to give the mixture of two isomers of **15** in the ratio of 1:1 as a colorless oil (1.08 g, 98%). ^{1}H NMR (two isomers) δ 5.37 (d, *J*=2.5 Hz, 1H),

4.77 (dd, J=9.7, 1.3 Hz, 1H), 4.07 (dt, J=9.7, 2.5 Hz, 1H), 3.54 (ddd, J=11.5, 3.5, 2.5 Hz, 1H), 3.38 (dd, J=8.1, 3.5 Hz, 1H), 3.27 (dd, J=8.1, 3.5 Hz, 1H), 1.90–1.07 (m, 12H), 1.01 (d, J=6.4 Hz, 6H), 1.00 (d, J=6.4 Hz, 3H), 0.95 (d, J=6.6 Hz, 3H), 0.86, 0.88 (2d, J=6.6 Hz, 6H); ^{13}C NMR δ 96.2, 92.2, 78.4, 78.1, 76.3, 69.7, 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; EI-MS (two isomers) m/z (%) 171 (M^+-17, 8), 170 (M^+-18, 13), 115 (92), 71 (100); FAB-HRMS: 171.1447, calcd for $C_{10}H_{18}O_2$+H: 171.1380.

3.8. (3R,5R,6R)-3,7-Dimethyl-5,6-dihydroxy-octanan-ethanedithiolketal **16**

To a solution of **15** (200 mg, 1.06 mmol) in 5 ml CH_2Cl_2 were added 0.08 ml $BF_3 \cdot OEt_2$ and 1,2-ethandithiol (0.11 ml, 1.31 mmol), and stirring was continued for 2 h at room temperature. After the addition of water (2 ml), the mixture was extracted with CH_2Cl_2 (3×20 ml). The combined organic layer was washed with brine (2×10 ml), dried over Na_2SO_4 and purified by column chromatography to give **16** (210 mg, 75%) as an amorphous solid. $[\alpha]_D^{25}$=+23 (c 0.01, $CHCl_3$); ^{1}H NMR δ 4.60 (t, J=7.1 Hz, 1H), 3.78 (br, 1H), 3.31 (dd, J=8.1, 3.8 Hz, 1H), 3.23 (m, 4H), 2.11 (br, 2H), 1.82–1.20 (m, 6H), 1.01 (d, J=6.6 Hz, 3H), 0.97 (d, J=6.6 Hz, 3H), 0.87 (d, J=6.8 Hz, 3H); ^{13}C NMR δ 80.2, 69.8, 51.6, 47.2, 38.3, 38.2, 36.6, 30.0, 29.5, 19.0, 18.7, 16.8; EI-MS m/z (%): 264 (M^+, 6), 246 (56), 131 (59), 105 (100); FAB-HRMS: 264.1200, calcd for $C_{12}H_{24}S_2O_2$: 264.1212.

3.9. (3R,5R,6R)-3,7-Dimethyl-5,6-acetonide-octanan-ethanedithiolketal **5**

To a solution of **16** (55 mg, 0.208 mmol) in 2 ml dry acetone was added a catalytic amount of PTS. The mixture was stood for 1 day at room temperature, and was then diluted with ether (20 ml) and washed with saturated $NaHCO_3$ solution (3×5 ml) and brine (2×5 ml), dried over Na_2SO_4 and purified by column chromatography to give **5** as a yellowish oil (50 mg, 79%). $[\alpha]_D^{25}$=+69 (c 0.01, $CHCl_3$); ^{1}H NMR δ 4.51 (t, J=7.4 Hz, 1H), 4.05 (ddd, J=11.6, 5.0, 2.4 Hz, 1H), 3.59 (dd, J=9.8, 5.0 Hz, 1H), 3.08–3.21 (m, 4H), 1.61–1.87 (br, 1H), 1.55–1.75 (m, 5H), 1.39 (s, 3H), 1.27 (s, 3H), 0.96 (d, J=6.6 Hz, 3H), 0.92 (d, J=6.6 Hz, 3H), 0.78 (d, J=6.6 Hz, 3H); ^{13}C NMR δ 18.7, 19.0, 20.4, 26.2, 28.8, 27.3, 29.2, 35.8, 38.3, 38.3, 47.5, 51.5, 74.9, 83.9, 107.5; EI-MS *m/z* (%) 304 (M^+, 15), 289 (43), 145 (64), 105 (100); FAB-HRMS: 305.1544, calcd for $C_{15}H_{28}O_2S_2$+H: 305.1602.

*3.10. (3R,5R)-2-Isopropyl-3-*t*-butylchlorodimethoxy-5-methyl-cyclohexene* **17**

To a solution of **10** (730 mg, 4.74 mmol) in 2 ml dry DMF were added imidazole (717 mg, 11.8 mmol) and *tert*-butyldimethylsilyl chloride (857 mg, 5.7 mmol). The mixture was stirred at room temperature for 2 h, then diluted with ether (100 ml), washed successively with water (2×20 ml) and brine (2×20 ml), dried over Na_2SO_4 and concentrated to give **17** (1.14 g, 95%) as a colorless oil. ^{1}H NMR δ 5.50 (br, 1H), 4.18 (br, 1H), 2.34–1.25 (m, 6H), 1.08 (d, J=6.0 Hz, 3H), 1.00 (d, J=6.6 Hz, 3H), 0.94 (d, J=6.0 Hz, 3H), 0.92 (s, 9H), 0.12 (s, 6H).

*3.11. (3R,5R)-3,7-Dimethyl-5-*t*-butylchlorodimethoxy-6-oxo-octanal* **18**

Following the same procedure as **12**, the compound **17** (1.34 g, 5.0 mmol) gave **18** (1.38 g, 92%) as a colorless oil. ^{1}H NMR δ 9.72 (t, J=1.8 Hz, 1H), 4.20 (dd, J=7.8, 5.2 Hz, 1H), 3.01 (m, 1H), 2.33–1.45 (m, 5H), 1.08 (d, J=6.9 Hz, 3H), 1.04 (d, J=6.9 Hz, 3H), 0.94 (d, J=6.9 Hz, 3H), 0.92 (s, 9H), 0.05 (s, 6H).

3.12. (3R,5R)-3,7-Dimethyl-5-t-butylchlorodimethoxy-6-oxo-octanan-ethanedithioketal 19

Following the same procedure as **16**, the compound **18** (100 mg, 0.33 mmol) gave **19** (98 mg, 75%) as a colorless oil. ^{1}H NMR δ 4.63 (t, *J*=7.3 Hz, 1H), 4.20 (dd, *J*=9.0, 3.7 Hz, 1H), 3.70 (m, 1H), 3.23 (m, 4H), 2.70–1.62 (m, 5H), 1.16 (d, *J*=6.8 Hz, 3H), 1.07 (d, *J*=6.8 Hz, 3H), 0.98 (d, *J*=6.5 Hz, 3H), 0.94 (s, 9H), 0.07 (s, 6H).

3.13. (3R,5R,6R)-3,7-Dimethyl-5,6-dihydroxy-octanan-ethanedithiolketal 16

To a solution of **19** (360 mg, 0.96 mmol) in toluene (10 ml) was added a solution of 10% vitride (Red-Al) in toluene (7.5 ml) at −78°C under Ar. The mixture was stirred for 3 h at the same temperature and then stirred overnight at room temperature. After the addition of water (2 ml) and 10% HCl solution (5 ml), the mixture was extracted with ether (3×20 ml). The organic layer was washed with 10% HCl solution (2×5 ml), saturated $NaCHO_3$ solution (2×5 ml) and brine (2×5 ml), succesively, dried over Na_2SO_4, and purified by column chromatography to afford **16** (200 mg, 80%) as an amorphous solid.

3.14. (S)-(+)-p-Menth-4-en-3-one 20

A solution of the alcohol **10** (2.10 g, 13.6 mmol) was added in one portion to the suspension of PCC (5.03 g, 27.2 mmol) in dry CH_2Cl_2 (80 ml), and stirring was continued for 7 h at room temperature. After addition of Florisil, the mixture was diluted with CH_2Cl_2 and filtered through Celite. Concentration of the filtrate followed by column chromatography gave **20** as a colorless oil. $[\alpha]_D^{25}$=+48 (c 0.02, $CHCl_3$). The spectra data of **20** were consistent with those of its enantiomer.

3.15. (3S,5S,6S)-3,7-Dimethyl-5,6-acetonide-octanan-ethanedithiolketal 23

The procedures for syntheses of **21** to **23** were the same as those of their enantiomers above, and the spectra data of all those compounds were consistent with those of their antipodals. The rotation of **23** was $[\alpha]_D^{25}$=−68 (c 0.01, $CHCl_3$).

Acknowledgements

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