Synthesis of Optically Active Bicyclo[3.3.0]octane Skeleton Using Transannular Reaction

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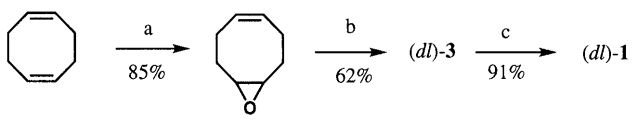
Optically active 5-cyclooctene-1,2-diol derivatives prepared by an enzymatic procedure have been converted into bicyclo[3.3.0]octane derivatives by transannular reaction with complete inversion of the stereogenic center linked to the leaving group. Formal synthesis of (+)-iridomyrmecin has been achieved starting from (*S,S*)-5-cyclooctene-1,2-diol by using this process.

Key words enantioselective hydrolysis; enzymatic procedure; 5-cyclooctene-1,2-diol; bicyclo[3.3.0]octane; iridomyrmecin; transannular reaction

The bicyclo[3.3.0]octane skeleton has been widely used as a synthetic intermediate of biologically active compounds such as carbacyclin,[1a] capnellanes[1b] and iridoids.[1c] Here, we wish to report the preparation of enantiomerically pure bicyclo[3.3.0]octane derivatives by transannular reaction starting from optically active 5-cyclooctene-1,2-diol prepared by an enzymatic procedure.

First, the preparation of optically active 5-cyclooctene-1,2-diol (**3**) was studied by using enzymatic enantioselective hydrolysis. According to our reported method,[2] *Pseudomonas fluorescens* lipase (PFL)[3] afforded satisfactory results in kinetic resolution of the corresponding diacetate (*dl*)-**1**, which was prepared from cycloocta-1,5-diene by a three-step sequence (epoxidation, ring opening of the epoxide and acetylation). That is to say, PFL-catalyzed hydrolysis of (*dl*)-**1** in a phosphate buffer (0.1 M, pH 7.0) afforded the monoacetate (1*R*,2*R*)-**2** of >99% enantiomeric excess (e.e.) in 34% yield and (*S,S*)-**1** (50% e.e., 54% yield). (Chart 2). Enantiomeric excess of the reaction products was determined by Mosher's method[4] using 270 MHz ^{1}H-NMR spectroscopy, and their absolute configuration was determined by comparison of the specific rotations with reported values[5] after conversion of (*S,S*)-**3** into the corresponding (*S,S*)-cyclooctane-1,2-diol by hydrogenation of the olefin.

The result that the absolute configuration of the hydrolyzed product **2** was 1*R*, 2*R* is in agreement with our previous results on PFL-catalyzed hydrolysis of 5- to 7-membered ring substrates.[2] To prepare both enantiomers of **3** in enantiomerically pure form, the recovered (*S,S*)-**1** of 50% e.e. was submitted to the same enzymatic reaction for **2** weeks, and (*S,S*)-**1** of >99% e.e. was obtained in 40% yield from (*dl*)-**1** (theoretical maximum 50% yield). The obtained (*R,R*)-**2** and (*S,S*)-**1** were converted into (*R,R*)-**3** and (*S,S*)-**3** of >99% e.e., respectively, by usual solvolysis.



Reagent: a) *m*-CPBA, $NaHCO_3$; b) aqueous H_2SO_4; c) Ac_2O, pyridine.

Chart 1

Next, the conversion of cyclooctene derivatives (**5**, **6**) into bicyclo[3.3.0]octanes by transannular reaction was studied. Compounds **5** and **6** were sequentially prepared from (*S,S*)-**3** (monoacetylation, protection of the hydroxyl group as a methoxyethoxymethyl (MEM) ether, solvolysis of the acetoxy group, and mesylation of the hydroxyl group) as shown in Chart 3.[6] The reaction of **6** under thermal conditions using Na_2CO_3 in aqueous tetrahydrofuran (THF) according to Whitesell and Matthews' procedure[1c] afforded bicyclic products **7** in 91% yield as a 1 : 1 diastereomeric mixture at the C-2 position and **8** in 7% yield. An attempt to find a more effective leaving group as a triflate gave a different result. The reaction of **5** with trifluoromethanesulfonic anhydride (Tf_2O) in the presence of pyridine in CH_2Cl_2 at −45 °C did not afford the corresponding triflate, but the bicyclic compound **8** in 70% yield as the sole product. Relative configuration of the C-5 and C-6 positions of **7** was determined after conversion into 2-*epi*-**14** as shown in Chart 5 (*vide infra*). Absolute stereochemistry of the C-1 and C-5 positions of **7** was confirmed after conversion into (*S,S*)-bicyclo[3.3.0]octane-2,6-dione (**11**) by a three-step sequence

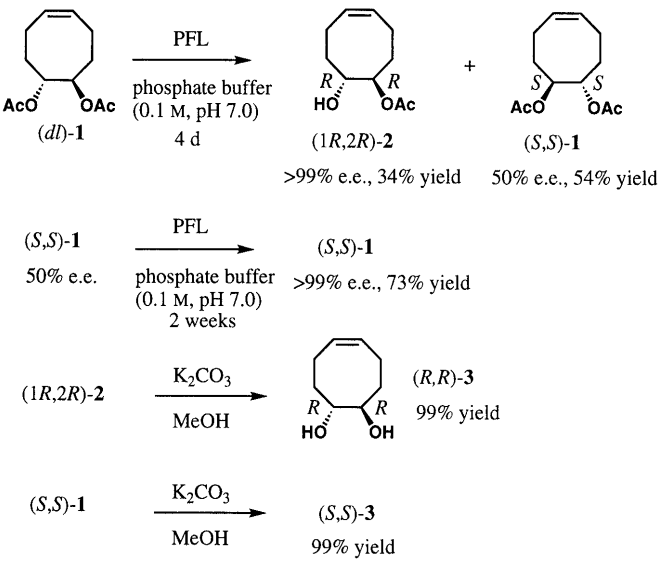


Chart 2. Preparation of Enantiomerically Pure Diol **3**

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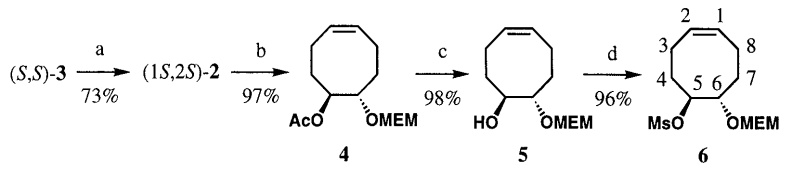
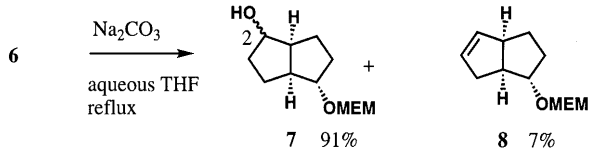


Reagent : a) Ac_2O, pyridine; b) MEMCl, iso-Pr_2NEt; c) K_2CO_3, MeOH; d) MsCl, pyridine



(a 1:1 mixture of diastereomers)

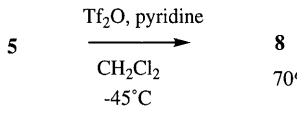


Chart 3

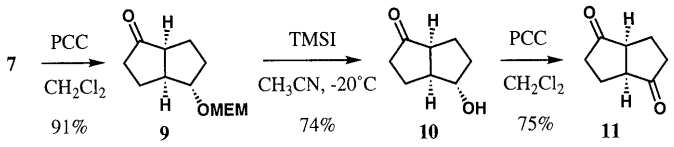
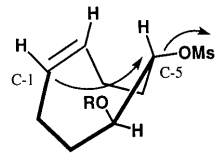


Chart 4

Attack from *re*-face of C-1



Elimination *via* S_N2 Process

Fig. 1

(pyridinium chlorochromate (PCC) oxidation into **9**, deprotection of the MEM ether, and PCC oxidation), as shown in Chart 4. Specific rotation of **11** showed $[\alpha]_D^{22}$ +407° (c=0.30, EtOH) (lit.[7] for (1*S*, 5*S*)-**11**: $[\alpha]_D$ +401° (c=2.00, EtOH)). The above result shows that transannular cyclization proceeded with complete inversion of the stereogenic center at the C-5 position of **6** and also with diastereoface (*re*-face) selectivity at C-1, and led us to consider the reaction pathway shown in Fig. 1. This is the first direct chemical evidence of the absolute stereochemistry of an S_N2-type transannular cyclization.

As a synthetic application of this reaction, we studied the formal synthesis of a component of the Argentinian ant *Iridomyrmex Humilis* defensive secretion, (+)-iridomyrmecin,[8] which is an iridoid monoterpene lactone bearing four chiral centers (Chart 5). Reaction of the ketone **9** with MeMgBr gave the alcohol **12** in 89% yield with complete diastereoselectivity by a convex-face approach of the reagent. The regioselective dehydration of **12** was achieved under thermodynamically controlled conditions using pyridinium *p*-toluenesulfonate (PPTS) to give **13** in 60% yield.[9] Deprotection of the MEM group of **13** by trimethylsilyl (TMS) iodide gave the corresponding alcohol **14** in 81% yield. The relative stereochemistry between C-1 and C-2 of **14** was confirmed by examination of the nuclear Overhauser effect spectroscopy (NOESY)-^{1}H–^{1}H-NMR spectra of **14** and 2-*epi*-**14**, which was obtained after epimerization of the hydroxyl group at the C-2 positon of **14** by PCC oxidation to a ketone and subsequent diastereoselective reduction of the ketone (convex-face approach of the reagent). The signal correlation between C1-H and C2-H was only observed in the case of 2-*epi*-**14** [δ 2.96 (1H, m, C1-H), 4.18 (1H, m, C2-H)]. Iodation of **14** with triphenylphosphine and iodine unexpectedly gave a 2 : 1 mixture of the desired **15a** and undesired **15b**, which suggests that the reaction did not completely proceed *via* an S_N2 process. The stereochemistry of **15a, b** was determined from the chemical shift values of C6-H in the ^{1}H-NMR spectrum. The proton signal at C6-H of **15b** was detected at higher field (3.98 ppm) than that of **15a** (4.26 ppm) owing to the shielding effect of the bicyclooctene skeleton. The inseparable mixture of **15a, b** was converted into a mixture of the target intermediate **17a** and its C-6 epimer **17b** *via* **16a, b** by a two-step sequence (methylation with $Me_2Cu(CN)Li_2$, and hydroboration with B_2H_6) in 25% yield from **15a, b**. The target molecule **17a** was obtained after purification by gel permeation chromatography (GPC). Spectroscopic data of **17a** were identical with those of our previous authentic sample.[10]

Experimental

IR spectra were measured on a JASCO A-202 spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were measured with a JNM-GX 270 spectrometer. MS were taken on a JEOL SX-102A spectrometer. Specific rotations were measured on a JASCO DIP-360 polarimeter. Diethyl ether and THF were dried and distilled from sodium-benzophenone ketyl under an Ar atmosphere prior to use. For column chromatography, silica gel (Merck, Kieselgel 60, 70—230 mesh) was used.

Enzymatic Hydrolysis of (*dl*)-1 PFL (1.0 g) was added to a stirred suspension of a diacetate **1** (2.6 g, 10 mmol) in phosphate buffer (0.1 M, pH 7.0, 200 ml) at 30 °C. The whole was stirred at the same temperature for the durations given in Chart 2, and extracted with EtOAc (100 ml × 3). The combined extracts were washed with brine, and dried over $MgSO_4$. After removal of the solvent, the residue was purified by silica gel column

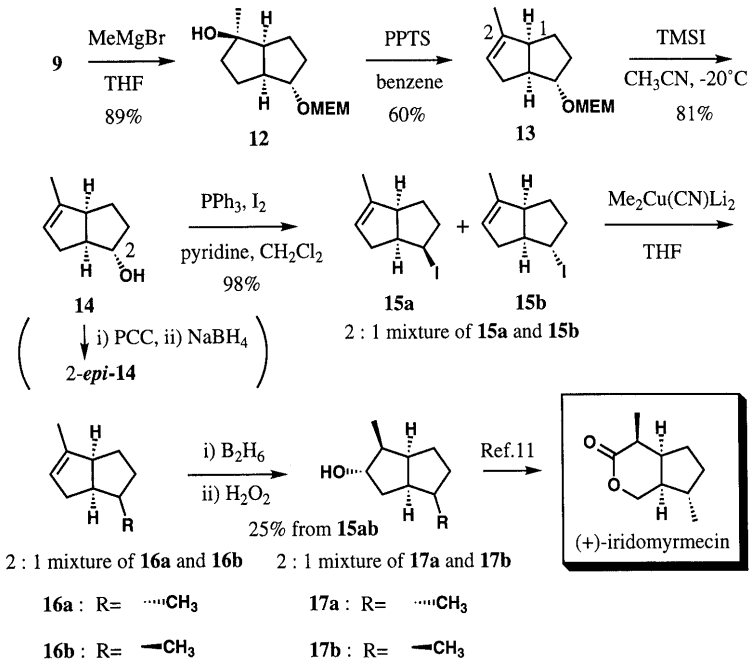


Chart 5. Formal Synthesis of Iridomyrmecin

chromatography to afford the monoacetate **2** (625 mg, 34%, >99% e.e.) and recovered diacetate **1** (1.4 g, 54%, 50% e.e.).

(1*R*,2*R*)-2-Acetoxy-5-cyclooctene-1-ol (**2**) (>99% e.e.): A colorless oil, $[\alpha]_D^{23}$ −2.5° (*c*=0.35, $CHCl_3$). IR (neat) cm^{-1}: 3450 (OH), 1720 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 5.72—5.56 (m, 2H, CH=CH), 4.96 (dt, *J*=3.6, 8.9 Hz, 1H, CHOAc), 3.90 (m, 1H), 2.09 (s, 3H, CH_3COO). HR-MS (FAB) *m/z*: 185.1182 (Calcd for $C_{10}H_{17}O_3$: 185.1178). EI-MS *m/z* (rel. int. %): 184 (M^+, 0.4), 142 (30), 80 (27), 67 (26), 43 (100).

MTPA Ester of **2**: The 270 MHz ^{1}H-NMR spectrum of the (+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA) ester derived from the monoacetate (±)-**2** showed the methoxy proton signal at δ: 3.52 (s, 1.5H) and 3.49 (s, 1.5H), while the corresponding signal from (−)-**2** was observed at δ 3.49 (s, 3H) only.

(*S*,*S*)-5,6-Diacetoxy-1-cyclooctene (**1**): A colorless oil, $[\alpha]_D^{23}$ −40.4° (*c*=1.00, $CHCl_3$) for 50% e.e., which was submitted to the same enzymatic procedure as described above. (5*S*,6*S*)-**1** (1.0 g, 73% from (5*S*,6*S*)-**1** of 50% e.e.) was recovered as a colorless oil, $[\alpha]_D^{23}$ −80.8° (*c*=3.7, $CHCl_3$) for >99% e.e. The enantiomeric excess was determined after conversion into the bis-MTPA ester of the corresponding diol **3**.

(*R*,*R*)-5-Cyclooctene-1,2-diol (3) A mixture of (*R*,*R*)-**2** (1.05 g, 4.65 mmol) and K_2CO_3 (32 mg, 0.23 mmol) in MeOH (10 ml) was stirred at 0 °C for 8 h. The mixture was neutralized with 5% aqueous HCl, then extracted with EtOAc, and the combined extracts were dried over $MgSO_4$. Removal of the solvent *in vacuo* gave an oily residue, which was purified by column chromatography on silica gel. The fraction eluted with 10% EtOAc in hexane afforded (*R*,*R*)-**3** (983 mg, 99%) as colorless crystals, $[\alpha]_D^{23}$ −18.2° (*c*=0.20, $CHCl_3$) for >99% e.e. IR (KBr) cm^{-1}: 3350 (OH), 2900, 1030. ^{1}H-NMR ($CDCl_3$) δ: 5.66—5.55 (m, 2H, CH=CH), 3.73—3.64 (m, 2H, CHOH), 2.66 (s, 2H, OH).

(*S*,*S*)-**3**: $[\alpha]_D^{23}$ +19.3° (*c*=2.2, $CHCl_3$) for >99% e.e. bis-MTPA Ester of **3**: The 270 MHz ^{1}H-NMR spectrum of the bis-(+)-MTPA ester derived from the diol (±)-**3** showed the methoxy proton signal at δ 3.46 (s, 3H) and 3.36 (s, 3H), while the corresponding signal from (*S*,*S*)-**3** was observed at δ 3.36 (s, 6H) only.

(*S*,*S*)-Cyclooctane-1,2-diol A suspension of 5% Pd–C (30 mg) and (*S*,*S*)-**3** (50 mg, 0.35 mmol) in MeOH (5 ml) was stirred under an H_2 atmosphere until reduction was completed. The catalyst was filtered off, and the solvent was removed *in vacuo* to give an oily residue, which was purified by column chromatography on silica gel. The fraction eluted with 10% EtOAc in hexane afforded (*S*,*S*)-cyclooctane-1,2-diol (46 mg, 90%), $[\alpha]_D^{23}$ +15.8° (*c*=1.5, EtOH). (lit.[5] for (*S*,*S*)-cyclooctane-1,2-diol: $[\alpha]_D^{22}$ +16.9° (*c*=1.33, EtOH)).

(1*S*,2*S*)-**2**: Ac_2O (0.8 ml, 8.87 mmol) was added to a stirred solution of (*S*,*S*)-**3** (1.05 g, 7.39 mmol) and pyridine (0.9 ml, 1.11 mmol) in CH_2Cl_2 10 ml) at 0 °C. After having been stirred for 4 h at room temperature, the mixture was neutralized with 5% aqueous $NaHCO_3$ and extracted with EtOAc, and the combined extracts were dried over $MgSO_4$. Removal of the solvent *in vacuo* gave an oily residue, which was purified by column chromatography on silica gel. The fraction eluted with 10% EtOAc in hexane afforded (1*S*,2*S*)-**2** (992.6 mg, 73%) as a colorless oil.

(5*S*,6*S*)-5-Acetoxy-6-(methoxyethoxymethoxy)-1-cyclooctene (4) MEM chloride (2.8 ml, 22.5 mmol) was added dropwise to a stirred solution of (1*S*,2*S*)-**2** (830 mg, 4.5 mmol) and *N*,*N*-diisopropylethylamine (5.8 g, 45 mmol) in CH_2Cl_2 (100 ml) at 0 °C. The solution was stirred for 6 h, diluted with brine, and extracted with EtOAc, and the combined extracts were dried over $MgSO_4$. Removal of the solvent *in vacuo* gave an oily residue, which was purified by column chromatography on silica gel. The fraction eluted with 20% EtOAc in hexane afforded **4** (1.19 g, 97%) as a colorless oil, $[\alpha]_D^{26}$ −62.6° (*c*=4.02, $CHCl_3$). IR (neat) cm^{-1}: 1735 (C=O), 1653, 1100. ^{1}H-NMR ($CDCl_3$) δ: 5.66—5.55 (m, 2H, CH=CH), 5.07 (td, *J*=3.9, 8.7 Hz, 1H, CHOAc), 4.72 (s, 2H, OCH_2O), 3.88 (td, *J*=3.9, 8.7 Hz, 1H, CHOMEM), 3.8—3.6 (m, 2H, OCH_2CH_2O), 3.6—3.5 (m, 2H, OCH_2CH_2O), 3.40 (s, 3H, OCH_3), 2.04 (s, 3H, CH_3COO). EI-MS *m/z* (rel. int. %): 272 (M^+, 0.1), 89 (73), 59 (100), 43 (61).

(1*S*,2*S*)-2-(Methoxyethoxymethoxy)-5-cyclooctene-1-ol (5) A mixture of **4** (1.19 g, 4.38 mmol) and K_2CO_3 (181 mg, 1.3 mmol) in MeOH (30 ml) was stirred at room temperature for 12 h. Removal of the solvent *in vacuo* gave an oily residue, which was purified by column chromatography on silica gel. The fraction eluted with 40% EtOAc in hexane afforded **5** (980 mg, 98%) as a colorless oil, $[\alpha]_D^{26}$ +26.4° (*c*=2.89, $CHCl_3$). IR (neat) cm^{-1}: 3480 (OH), 720. ^{1}H-NMR ($CDCl_3$) δ: 5.67—5.51 (m, 2H, CH=CH), 4.84—4.76 (m, 2H, OCH_2O), 3.75 (m, 1H, CHOH), 3.77—3.74 (m, 2H, OCH_2CH_2O), 3.67 (td, *J*=3.6, 8.6 Hz, 1H, CHOMEM), 3.58—3.55 (m, 2H, OCH_2CH_2O), 3.40 (s, 3H, OCH_3), 3.24 (s, 1H, OH). EI-MS *m/z* (rel. int. %): 230 (M^+, 1), 89 (90), 67 (38), 59 (100), 45 (85).

(5*S*,6*S*)-5-Methanesulfonyloxy-6-(methoxyethoxymethoxy)-1-cyclooctene (6) Methanesulfonyl chlroride (1.9 ml, 22.5 mmol) was added dropwise to a stirred solution of **5** (2.60 g, 10.7 mmol) in pyridine (6 ml) at 0 °C. After having been stirred for 30 min at room temperature, the mixture was poured onto ice, and the whole was extracted with EtOAc. The extracts were washed with brine, and dried over $MgSO_4$. Removal of the solvent *in vacuo* gave an oily residue, which was purified by column chromatography on silica gel. The fraction eluted with 30% EtOAc in hexane afforded **6** (3.19 g, 96%) as a colorless oil, $[\alpha]_D^{24}$ −35.1° (*c*=3.65, $CHCl_3$). IR (neat) cm^{-1}: 1350, 1170 (SO_3). ^{1}H-NMR ($CDCl_3$) δ: 5.66—5.54 (m, 2H, CH=CH), 4.80 (m, 1H, $CHOSO_2CH_3$), 4.78 (m, 2H, OCH_2O), 3.97 (td, *J*=3.6, 7.9 Hz, 1H, CHOMEM), 3.8—3.7 (m, 2H, OCH_2CH_2O), 3.7—3.5 (m, 2H, OCH_2CH_2O), 3.40 (s, 3H, OCH_3), 3.00 (s, 3H, OSO_2CH_3). ^{13}C-NMR ($CDCl_3$) δ: 128.9 (d), 128.0 (d), 95.4 (t), 86.0 (d), 78.1 (d), 71.8 (t), 67.3 (t), 59.1 (q), 38.2 (q), 30.9 (t), 29.5

(t), 23.3 (t), 23.1 (t). FD-MS *m/z* (rel. int. %): 308 (M^+, 100).

(1*S*,2*R*,5*S*,6*S*)- and (1*S*,2*S*,5*S*,6*S*)-6-(Methoxyethoxymethoxy)bicyclo[3.3.0]octan-2-ol (7) and (1*S*,5*S*,6*S*)-6-(Methoxyethoxymethoxy)bicyclo[3.3.0]oct-2-ene (8) A mixture of **6** (3.80 g, 1.23 mmol) and Na_2CO_3 (3.90 g, 3.69 mmol) in H_2O (30 ml) and THF (30 ml) was refluxed for 24 h. The whole was extracted with diethyl ether, and the combined extracts were washed with brine, and dried over $MgSO_4$. Removal of the solvent *in vacuo* gave an oily residue, which was purified by column chromatography on silica gel. The fraction eluted with 60% EtOAc in hexane afforded **7** (2.63 g, 91%) and **8** (183 mg, 7%).

7: A colorless oil, IR (neat) cm^{-1}: 3450 (OH). ^{1}H-NMR ($CDCl_3$) δ: 4.74 (m, 2H, OCH_2O), 4.19 (m, 1H, C<u>H</u>OMEM), 3.88 (m, 1H, C<u>H</u>OH), 3.70—3.68 (m, 2H, OC<u>H</u>$_2$CH$_2$O), 3.58—3.55 (m, 2H, OCH$_2$C<u>H</u>$_2$O), 3.40 (s, 3H, OCH_3), 2.59 (m, 1H, CH), 2.40 (m, 1H, CH). FAB-MS *m/z* 231 (M^++H).

8: A colorless oil, $[\alpha]_D^{22}$ +3.1° (*c*=0.47, $CHCl_3$). IR (neat) cm^{-1}: 2920, 1100, 1040. ^{1}H-NMR ($CDCl_3$) δ 5.56—5.49 (m, 2H, CH=CH), 4.75 (s, 2H, OCH_2O), 3.77—3.73 (br s, 1H, C<u>H</u>OMEM), 3.73—3.69 (m, 2H, OC<u>H</u>$_2$CH$_2$O), 3.56—3.55 (m, 2H, OCH$_2$C<u>H</u>$_2$O), 3.40 (s, 3H, OCH_3), 3.26 (m, 1H, CH), 2.13 (m, 1H, CH). ^{13}C-NMR ($CDCl_3$) δ: 134.4 (d), 128.6 (d), 93.9 (t), 85.6 (d), 71.8 (t), 66.8 (t), 59.0 (q), 49.1 (d), 46.6 (d), 38.3 (t), 30.3 (t), 29.0 (t). EI-MS *m/z* (rel. int. %): 212 (M^+, 1), 182 (49), 137 (74), 136 (68), 123 (39), 122 (55), 118 (100).

Reaction of (1*S*,2*S*)-5 with Tf_2O Tf_2O (0.8 ml, 4.76 mmol) was added dropwise to a stirred solution of **5** (859 mg, 3.74 mmol) in CH_2Cl_2 (2 ml) and pyridine (2 ml) at −45 °C under an Ar atmosphere. The reaction mixture was stirred for 10 h at −45 °C, diluted with brine, and extracted with EtOAc. The combined extracts were washed with brine, and dried over $MgSO_4$. Removal of the solvent *in vacuo* gave an oily residue, which was purified by column chromatography on silica gel. The fraction eluted with 60% EtOAc in hexane afforded **8** (554 mg, 70%).

(1*S*,5*S*,6*S*)-6-(Methoxyethoxymethoxy)bicyclo[3.3.0]octan-2-one (9) PCC (477 mg, 0.43 mmol) was added to a stirred solution of **7** (100 mg, 0.43 mmol) in CH_2Cl_2 (5 ml). After having been stirred for 6 h, the reaction mixture was diluted with diethyl ether, and a black solid was filtered off using a Florisil short column. Removal of the solvent *in vacuo* gave an oily residue, which was purified by column chromatography on silica gel. The fraction eluted with 50% EtOAc in hexane afforded **9** (90 mg, 91%) as a colorless oil, $[\alpha]_D^{22}$ +83.3° (*c*=1.70, $CHCl_3$). IR (neat) cm^{-1}: 1740 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 4.76 (m, 2H, OCH_2O), 3.98 (m, 1H, C<u>H</u>OMEM), 3.73—3.69 (m, 2H, OC<u>H</u>$_2$CH$_2$O), 3.59—3.55 (m, 2H, OCH$_2$C<u>H</u>$_2$O), 3.40 (s, 3H, OCH_3), 2.87—2.66 (m, 2H, CH). EI-MS *m/z* (rel. int. %): 228 (M^+, 3), 123 (16), 89 (100), 59 (92), 45 (15).

(1*S*,5*S*,6*S*)-6-Hydroxybicyclo[3.3.0]octan-2-one (10) TMSCl (0.13 ml, 1.0 mmol) was added dropwise to a stirred solution of NaI (156 mg, 1.0 mmol) in CH_3CN (2 ml) at −20 °C under an Ar atmosphere. A solution of **9** (109 mg, 0.48 mmol) in CH_3CN (2 ml) was added dropwise to the stirred solution at −20 °C. The reaction mixture was stirred for 1 h, diluted with 5% aqueous NH_4Cl, and extracted with $CHCl_3$. The combined extracts were washed with brine, and dried over Na_2SO_4. Removal of the solvent *in vacuo* gave an oily residue, which was purified by column chromatography on silica gel. The fraction eluted with 50% EtOAc in hexane afforded **10** (49 mg, 74%) as a colorless oil, $[\alpha]_D^{22}$ +167.6° (*c*=0.43, $CHCl_3$). IR (neat) cm^{-1}: 3400 (OH), 1720 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 4.10 (m, 1H, C<u>H</u>OH), 2.81—2.66 (m, 2H, CH). EI-MS *m/z* (rel. int. %): 140 (M^+, 29), 97 (21), 83 (100), 80 (25), 79 (21), 67 (30), 55 (25).

(1*S*,5*S*)-Bicyclo[3.3.0]octane-2,6-dione (11) Compound **11** was prepared from compound **10** in a similar manner to that described for the preparation of **9**.

11: A white foam, mp 44—46 °C. (lit. 45—46 °C). $[\alpha]_D^{22}$ +407° (*c*=0.30, EtOH). IR (KBr) cm^{-1}: 1738 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 2.93 (t, *J*=12.8 Hz, 2H, CH_2CO), 2.38 (dt, *J*=6.6, 17.4 Hz, 2H, CH). ^{13}C-NMR ($CDCl_3$) δ 220.0 (s), 49.2 (d), 37.5 (t), 23.0 (t). EI-MS *m/z* (rel. int. %): 138 (M^+, 70), 83 (100), 68 (34), 67 (34).

(1*S*,2*R*,5*S*,6*S*)-6-(Methoxyethoxymethoxy)-2-methylbicyclo[3.3.0]-oct-2-ol (12) MeMgBr (0.92 M solution in THF, 2.5 ml, 2.33 mmol) was added dropwise to a stirred solution of **9** (353 mg, 1.55 mmol) in THF (3 ml) at −78 °C under an Ar atmosphere. After having been stirred for 5 min at −78 °C, the reaction was quenched with 5% aqueous NH_4Cl. The mixture was extracted with diethyl ether, and the extracts were washed with brine, and dried over $MgSO_4$. Removal of the solvent *in vacuo* gave an oily residue, which was purified by column chromatography on silica gel. The fraction eluted with 30% diethyl ether in pentane afforded **12** (337 mg, 89%) as a colorless oil, $[\alpha]_D^{25}$ +31.5° (*c*=1.77, $CHCl_3$). IR (neat) cm^{-1}: 3350 (OH). ^{1}H-NMR ($CDCl_3$) δ: 4.73 (s, 2H, OCH_2O), 3.90 (td, *J*=3.6, 7.9 Hz, 1H, C<u>H</u>OMEM), 3.71—3.68 (m, 2H, OC<u>H</u>$_2$CH$_2$O), 3.58—3.55 (m, 2H, OCH$_2$C<u>H</u>$_2$O), 3.40 (s, 3H, OCH_3), 2.47 (m, 1H, CH), 2.30 (dt, *J*=4.4, 9.2 Hz, 1H, CH), 1.28 (s, 3H, CH_3). ^{13}C-NMR ($CDCl_3$) δ 94.7 (t), 85.2 (d), 79.8 (s), 71.8 (t), 66.7 (t), 59.0 (q), 52.0 (d), 49.7 (d), 40.9 (t), 32.8 (t), 28.4 (q), 28.3 (t), 23.5 (t). FD-MS *m/z* (rel. int. %): 245 (M^++H, 100), 227 (45).

(1*S*,5*S*,6*S*)-6-(Methoxyethoxymethoxy)-2-methylbicyclo[3.3.0]oct-2-ene (13) PPTS (6.5 mg, 0.03 mmol) was added to a solution of **12** (337 mg, 1.38 mmol) in benzene (30 ml), and the resulting mixture was refluxed with azeotropic removal of water for 5 h. After four additions of PPTS (6.5 mg × 4) at intervals of 5 h under the above conditions, the reaction mixture was diluted with brine, extracted with diethyl ether, and dried over $MgSO_4$. Removal of the solvent *in vacuo* gave an oily residue, which was purified by column chromatography on silica gel. The fraction eluted with 30% diethyl ether in pentane afforded **13** (188 mg, 60%) as a colorless oil, ^{1}H-NMR ($CDCl_3$) δ: 5.12 (t, *J*=1.7 Hz, 1H, =CH), 4.75 (s, 2H, OCH_2O), 3.84 (q, *J*=3.4 Hz, 1H, C<u>H</u>OMEM), 3.73—3.69 (m, 2H, OC<u>H</u>$_2$CH$_2$O), 3.59—3.55 (m, 2H, OCH$_2$C<u>H</u>$_2$O), 3.40 (s, 3H, OCH_3), 3.01 (t, *J*=7.9 Hz, 1H, C<u>H</u>CHOMEM).

(1*S*,2*S*,5*S*)-6-Methylbicyclo[3.3.0]oct-6-ene-2-ol (14) Compound **14** was prepared from **13** in a similar manner to that described for the preparation of **10**.

14: A colorless oil, $[\alpha]_D^{24}$ +9.41° (*c*=1.36, $CHCl_3$). IR (neat) cm^{-1}: 3350 (OH). ^{1}H-NMR ($CDCl_3$) δ: 5.13 (t, *J*=1.3 Hz, 1H, =CH), 3.95 (m, 1H, C<u>H</u>OH), 3.07 (m, 1H, C<u>H</u>CHOH), 2.58 (m, 1H, C<u>H</u>CCH$_3$), 2.56 (s, 1H, OH), 1.66 (s, 3H, CH_3). ^{13}C-NMR ($CDCl_3$) δ: 144.9 (s), 122.6 (d), 81.0 (d), 52.3 (d), 50.7 (d), 37.2 (t), 33.3 (t), 26.8 (t), 15.0 (q). EI-MS *m/z* (rel. int. %): 138 (M^+, 26), 83 (100), 81 (53), 80 (45), 79 (66).

(1*S*,5*S*,6*R*)- and (1*S*,5*S*,6*S*)-6-Iodo-2-methylbicyclo[3.3.0]oct-2-ene (15) (**15a**:**15b**=2:1) A mixture of I_2 (940 mg, 3.62 mmol) and Ph_3P (969 mg, 3.62 mmol) in benzene (5 ml) was stirred at room temperature for 20 min. A solution of **14** (100 mg, 0.72 mmol) in pyridine (2 ml) was added dropwise to the mixture, and the whole was refluxed for 6 h. After having been cooled to room temperature, the reaction mixture was diluted with aqueous $Na_2S_2O_3$, and extracted with diethyl ether. The extracts were washed with brine, and dried over $MgSO_4$. Removal of the solvent *in vacuo* gave an oily residue, which was purified by column chromatography on silica gel. The fraction eluted with hexane afforded **15** (180 mg, 98%) as a colorless oil, ^{1}H-NMR ($CDCl_3$) δ: 5.20, (m, 2/3 H, =CH of **15a**), 5.12 (m, 1/3 H, =CH of **15b**), 4.26 (td, *J*=1.3, 5.4 Hz, 2/3 H, CHI of **15a**), 3.98 (q, *J*=5.2 Hz, 1/3 H, CHI of **15b**), 3.15 (m, 1H, C<u>H</u>CHI), 2.88 (ddd, *J*=5.3, 5.6, 5.6 Hz, 1H, C<u>H</u>CHCH$_3$), 1.66—1.63 (m, 3H, CH_3). EI-MS *m/z* (rel. int. %): 248 (M^+, 0.1), 127 (46), 121 (100), 120 (52), 105 (53), 93 (77), 79 (54).

(1*S*,2*S*,3*S*,5*S*,6*S*)- and (1*S*,2*S*,3*S*,5*S*,6*R*)-2,6-Dimethylbicyclo[3.3.0]-octan-3-ol (17) A solution of MeLi (1.5 M solution in THF, 5.7 ml, 8.50 mmol) was added dropwise to a stirred solution of CuCN (381 mg, 4.25 mmol) in THF (8 ml) at −40 °C under an Ar atmosphere. The mixture was stirred for 5 min, then a solution of **15** (170 mg, 0.71 mmol) in THF (2 ml) was added dropwise to it, and the whole was stirred at −78 °C. Stirring was continued for 10 h, then the reaction mixture was diluted with brine, and extracted with diethyl ether. The extracts were washed with brine, and dried over $MgSO_4$. Removal of the solvent *in vacuo* gave an oily residue, which was dissolved in THF (1 ml). A solution of borane-methyl sulfide complex (2.0 M in THF, 0.65 ml, 1.3 mmol) was added to this solution at 0 °C. The whole was stirred for 20 min, then 30% aqueous KOH (1 ml, 5.3 mmol) and H_2O_2 (30% solution in water, 0.9 ml, 7.94 mmol) were added successively at 0 °C, and the mixture was stirred for 50 min at 0 °C. It was diluted with diethyl ether, washed with brine, and dried over Na_2SO_4. Removal of the solvent *in vacuo* gave an oily residue, which was purified by column chromatography on silica gel. The fraction eluted with hexane afforded a 2:1 diastereomixture of **17** (27 mg, 25% from **15**). An analytical sample of **17a** was obtained after further purification by gel permeation chromatography (GPC).

17a: A colorless oil, $[\alpha]_D^{24}$ +55.3° (*c*=0.72, $CHCl_3$). IR (neat) cm^{-1}: 3350 (OH). ^{1}H-NMR ($CDCl_3$) δ3.66 (m, 1H, HOC<u>H</u>), 2.47 (q, 1H, *J*=18.3, 9.2 Hz, CH_2CH_2CH), 2.27—1.25 (m, 10H), 1.00 (d, *J*=6.6 Hz, 3H, HOCHCHC<u>H</u>$_3$), 0.99 (d, *J*=6.6 Hz, 3 H, CH_2CHCH_3). ^{13}C-NMR ($CDCl_3$) δ: 77.5 (d), 46.6 (d), 45.3 (d), 44.3 (d), 43.9 (d), 40.0 (t), 35.6 (t), 28.0 (t), 19.5 (q), 12.6 (q). EI-MS *m/z* (rel. int. %): 154 (M^+-H_2O, 7), 121 (13), 102 (17), 95 (22), 94 (13), 81 (100).

The spectroscopic data were identical with those of an authentic sample.[10]

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References and Notes

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