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

Tamaki Horikawa, Yoshihiko Norimine, Masakazu Tanaka, Kiyoshi Sakai, and Hiroshi Suemune

Faculty of Pharmaceutical Sciences, Kyushu University, Higashi-ku, Fukuoka 812-82, Japan and Kyushu Women’s University, Kitakyushu 807, Japan. Received July 16, 1997; accepted August 29, 1997

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, capnellanes and iridoids. Here, we wish to report the preparation of enantioselectively 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, Pseudomonas fluorescens lipase (PFL) 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 monoacetoxy (1R,2R)-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 using 270 MHz 1H-NMR spectroscopy, and their absolute configuration was determined by comparison of the specific rotations with reported values 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 1R, 2R is in agreement with our previous results on PFL-catalyzed hydrolysis of 5- to 7-membered ring substrates. 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.

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 hydroxy group as a methoxymethyl (MEM) ether, solvolysis of the acetoxy group, and mesylation of the hydroxy group) as shown in Chart 3. The reaction of 6 under thermal conditions using Na2CO3 in aqueous tetrahydrofuran (THF) according to Whitesell and Matthews’ procedure 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 (Tf2O) in the presence of pyridine in CH2Cl2 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 1](attachment:chart1.png)

Reagent: a) m-CPBA, NaHCO3; b) aqueous H2SO4; c) Ac2O, pyridine.

![Chart 2](attachment:chart2.png)

Preparation of Enantiomerically Pure Diol 3

© 1998 Pharmaceutical Society of Japan
Reagent: a) Ac₂O, pyridine; b) MEMCl, iso-Pr₂NE; c) K₂CO₃, MeOH; d) MsCl, pyridine

![Chemical Reaction Diagram](image)

(a 1:1 mixture of diastereomers)

Chart 3

![Chart 4](image)

As a synthetic application of this reaction, we studied the formal synthesis of a component of the Argentinian ant *Iridomyrmex Humulis* defensive secretion, (+)-iridomyrmecin, which is an iridoid monoterpenic 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. 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) 1H–1H-NMR spectra of 14 and 2-epi-14, which was obtained after epimerization of the hydroxyl group at the C-2 position 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)]. Iodination 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 Sn2 process. The stereochemistry of 15a,b was determined from the chemical shift values of C6-H in the 1H-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 Me₂Cu(CN)Li₂, and hydroboration with B₂H₆) 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.

**Experimental**

1H- and 13C-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 (d)**-1 PFL (1.0g) was added to a stirred suspension of a diacetate 1 (2.6g, 10mmol) 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 MgSO₄. After removal of the solvent, the residue was purified by silica gel column...
Chart 5. Formal Synthesis of Iridomycinin

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

(1R,2R)-2-Acetoxy-5-cycloocten-1-ol (2) (>99% e.e.): A colorless oil, [α]D 25 = 2.9° (c=0.35, CHCl3), [LR] (neat) cm-1: 3450 (OH), 1720 (C=O). HR-MS (FAB m/z): 185.1182 [Calc'd for C10H13O2: 185.1187]. EI-MS m/z (rel. int. %): 184 (M+, 0.4), 142 (30), 80 (27), 67 (26), 43 (100).

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

(S,S)-5,6-Diacyloxy-1-cyclooctene (1): A colorless oil, [α]D 25 = 40.4° (c=1.00, CHCl3) for 50% e.e., which was submitted to the same enzymatic procedure as described above. (S,S)-5,6-1 (1.0 g, 73% from (S,S)-5,6-5,6% e.e.) was recovered as a colorless oil, [α]D 25 = 80.8° (c=3.7, CHCl3) for >99% e.e. The enantiomeric excess was determined after conversion into the bis-MTPA ester of the corresponding diol 3.

(1R,2R)-Cyclooctane-1,2-diol (3) A mixture of (1R,2R)-2 (1.05 g, 4.65 mmol) and K2CO3 (12 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 MgSO4.

Removal of the solvent in vacuo gave an oil residue, which was purified by column chromatography on silica gel. The fraction eluted with 10% EtOAc in hexane afforded (R,R)-2 (983 mg, 99%) as a colorless crystals, [α]D 25 = 18.2° (c=0.20, CHCl3) for >99% e.e. IR (KBr) cm-1: 3350 (OH), 2980, 1030. 1H-NMR (CDCl3) δ: 5.66-5.55 (m, 2H, CH=CH), 3.73-3.64 (m, 2H, CH2O), 2.66 (s, 2H, OH).

(S,S)-3: [α]D 25 = 19.3° (c=2.2, CHCl3) for >99% e.e. b/c MTPA Ester of 5: The 270 MHz 1H NMR spectrum of the bis-(+)MTPA ester derived from the diol 3 showed the methoxyl 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 3.26 (s, 6H) only.

(S,S)-5-Methanesulfonoyloxy-6-(methoxynemethoxy) 1-cyclooctane (6) Methanesulfonyl chloride (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 MgSO4. Removal of the solvent in vacuo gave an oil residue, which was purified by column chromatography on silica gel. The fraction eluted with 10% EtOAc in hexane afforded 6 (3.19 g, 96%) as a colorless oil, [α]D 25 = 35.1° (c=3.65, CHCl3), IR (neat) cm-1: 3130, 1570 (SO3). 1H-NMR (CDCl3) δ: 5.66-5.54 (m, 2H, CH=CH), 4.80 (m, 1H, CH2OSEt), 4.78 (m, 2H, CH2OCH2), 3.97 (td, J=3.6, 7.9 Hz, 1H, CH2D), 3.73 (m, 2H, OCH2CH2O), 3.37-3.55 (m, 2H, OCH2CH2, OCH2CH2O), 3.40 (s, 3H, OCH3), 3.24 (s, 3H, OCH3). EI-MS m/z (rel. int. %): 320 (M+, 1), 89 (20), 67 (38), 59 (100), 45 (85).

(5S,6S)-5-Methanesulfonoyloxy-6-(methoxynemethoxy) 1-cyclooctane (7) Methanesulfonyl chloride (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 MgSO4. Removal of the solvent in vacuo gave an oil residue, which was purified by column chromatography on silica gel. The fraction eluted with 10% EtOAc in hexane afforded 7 (3.19 g, 96%) as a colorless oil, [α]D 25 = 35.1° (c=3.65, CHCl3), IR (neat) cm-1: 3130, 1570 (SO3). 1H-NMR (CDCl3) δ: 5.66-5.54 (m, 2H, CH=CH), 4.80 (m, 1H, CH2OSEt), 4.78 (m, 2H, CH2OCH2), 3.97 (td, J=3.6, 7.9 Hz, 1H, CH2D), 3.73 (m, 2H, OCH2CH2O), 3.37-3.55 (m, 2H, OCH2CH2, OCH2CH2O), 3.40 (s, 3H, OCH3), 3.24 (s, 3H, OCH3). EI-MS m/z (rel. int. %): 320 (M+, 1), 89 (20), 67 (38), 59 (100), 45 (85).
(t), 23.3 (t), 23.1 (t). FD-MS m/z (rel. int. %) 308 (M+, 100).

(1S,2R,5S,6S)- and (1S,2S,5S,6R)-6-(Methoxyethoxymethoxy)butylcyclo[3.3.0]oct-2-ene (9) 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 azetropic removal of water for 5 h. After four additions of PPTS (6.5 mg x 4) at intervals of 5 h under the above conditions, the reaction mixture was diluted with water, washed with ethyl ether, and dried over MgSO4. Removal of the solvent in vacuo gave an oily residue, which was purified by column chromatography on silica gel. The fraction eluted with 30% ethyl ether in pentane afforded 12 (186 mg, 60%) as a colorless oil, 1H-NMR (CDCl3) δ 5.12 (t, J = 1.7 Hz, 1H), 4.75 (s, 2H, OCH2O), 3.84 (q, J = 3.4 Hz, 1H, CH2OCH2), 3.73-3.69 (m, 2H, CH2OCH2O), 3.59-3.55 (m, 2H, OCH2CH2O), 3.40 (s, 3H, OCH3), 2.59 (m, 1H, CH), 2.40 (m, 1H, CH). FAB-MS m/z: 231 (M+H+).

(1S,2S,5S,6R)-6-(Methoxyethoxyethoxy)methylcyclo[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 azetropic removal of water for 5 h. After four additions of PPTS (6.5 mg x 4) at intervals of 5 h under the above conditions, the reaction mixture was diluted with water, washed with ethyl ether, and dried over MgSO4. Removal of the solvent in vacuo gave an oily residue, which was purified by column chromatography on silica gel. The fraction eluted with 30% ethyl ether in pentane afforded 13 (186 mg, 60%) as a colorless oil, 1H-NMR (CDCl3) δ 5.12 (t, J = 1.7 Hz, 1H, =CH), 4.75 (s, 2H, OCH2O), 3.84 (q, J = 3.4 Hz, 1H, CH2OCH2), 3.73-3.69 (m, 2H, CH2OCH2O), 3.59-3.55 (m, 2H, OCH2CH2O), 3.40 (s, 3H, OCH3), 3.01 (t, J = 7.9 Hz, 1H, CH2OCH2).

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

14: A colorless oil, [α]D20 +9.4° (c = 1.36, CHCl3). IR (neat) cm⁻¹: 3350 (OH), 1255-1215 (C-O). 1H-NMR (CDCl3) δ: 5.13 (t, J = 1.1 Hz, 1H, =CH), 3.95 (m, 1H, CH2OCH2), 3.07 (m, 1H, CH2OCH2O), 2.58 (m, 1H, CH2CH2O), 2.56 (s, 1H, OH), 1.65 (s, 3H, CH3). 13C-NMR (CDCl3) δ: 144.9 (s), 122.6 (d), 81.0 (d), 52.3 (s), 50.7 (d), 37.2 (t), 33.7 (t), 16.8 (t). EI-MS m/z (rel. int. %): 138 (M+ 26), 83 (100), 81 (53), 80 (45), 79 (15), 73, 69, 57.

(1S,2S,5S,6R)- and (1S,2S,5S,6S)-6-Iodo-methylcyclo[3.3.0]oct-2-ene (15) 15a: 15b = 2: 1 A mixture of I₂ (940 mg, 3.62 mmol) and Ph²P (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 Na2SO₄ and extracted with ethyl ether. The extracts were washed with water, and dried over MgSO₄. 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, 1H-NMR (CDCl₃) δ: 5.20, 2.03 (m, 2H, CH = CH₃), 5.12 (m, 1.3 Hz, CH = CH₂), 3.53, 3.01 (m, 1H, CH₂ = CH), 2.50-3.00 (m, 2H, CH₂). MS m/z (rel. int. %): 284 (M+ 1), 128, 127, 126, 101, 94 (100), 93, 77, 59.

(1S,2S,5S,6R)- and (1S,2S,5S,6S)-2,6-Dimethylcyclo[3.3.0]oct-3-ene-1-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 the mixture, and the whole was stirred at -78 °C. Stirring was continued for 10 h, then the reaction mixture was diluted with water, and extracted with diethyl ether. The extracts were washed with water, and dried over MgSO₄. 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 17 (27 mg, 25% from 15). An analytical sample of 17a was obtained after further purification by gel permeation chromatography (GPC).

(1S,2S,5S,6S)- and (1S,2S,5S,6R)-6-(Methoxyethoxyethoxy)methylcyclo[3.3.0]oct-2-ene (20) MeBr₂ (0.92 mm 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 (20 ml) under an Ar atmosphere. After having been stirred for 5 min at -78 °C, the reaction was quenched with 5% aqueous HCl. The mixture was extracted with diethyl ether, and the extracts were washed with water, and dried over MgSO₄. 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, [α]D20 +31.5° (c = 1.77, CHCl₃). IR (neat) cm⁻¹: 3350 (OH). 1H-NMR (CDCl₃) δ: 4.73 (s, 2H, OCH₃), 3.50 (td, J = 3.6, 7.9 Hz, 1H, CH₂OCH₂), 3.71-3.68 (m, 2H, OCH₂CH₂O), 3.58-3.55 (m, 2H, OCH₂CH₂O), 3.40 (s, 3H, OCH₃), 2.47 (m, 1H, CH), 2.30 (dt, J = 4.4, 9.2 Hz, 1H, CH), 1.28 (s, 3H, CH₃). 13C-NMR (CDCl₃) δ: 59.47 (t), 85.2 (d), 79.8 (s), 71.8 (t), 66.7 (t), 59.9 (q), 52.0 (d), 49.7 (d), 49.0 (d), 32.8 (t), 28.4 (q), 28.3 (t), 23.5 (t). FD-MS m/z (rel. int. %): 245 (M+ H, 100), 227 (45).

(1S,2S,5S,6S)-6-Methylcyclo[3.3.0]oct-2-ene-6-ol (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 azetropic removal of water for 5 h. After four additions of PPTS (6.5 mg x 4) at intervals of 5 h under the above conditions, the reaction mixture was diluted with water, washed with ethyl ether, and dried over MgSO₄. 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 (186 mg, 60%) as a colorless oil, 1H-NMR (CDCl₃) δ: 5.12 (t, J = 1.7 Hz, 1H, =CH), 4.75 (s, 2H, OCH₂O), 3.84 (q, J = 3.4 Hz, 1H, CH₂OCH₂), 3.73-3.69 (m, 2H, CH₂OCH₂O), 3.59-3.55 (m, 2H, OCH₂CH₂O), 3.40 (s, 3H, OCH₃), 3.01 (t, J = 7.9 Hz, 1H, CH₂OCH₂).
The spectroscopic data were identical with those of an authentic sample.10

Acknowledgments The authors thank Amano Pharmaceutical Co., Ltd., for generously providing lipases, and Dr. Ryuichi Isobe, Mr. Yoshitsugu Tanaka, and Ms. Yasuko Soeda for the measurement of MS and NMR spectra.

References and Notes


3) PFL has been reclassified as P. cepacia lipase (PCL). However, we have used the former name for the sake of uniformity with previous results.


6) The monoprotection of the diol with MEMCI was directly attempted, but was not effective.


9) In the case of using SOCl2 in pyridine at 0°C, the dehydration of 12 proceeded to give the undesired isomer (C-5 olefin) as a major product (13 (C-6 olefin): undesired isomer = 3:7).