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Synthesis of Optically Active 9-Oxabicyclo[3.3.1]nona-2,6-diene as a Cycloocta-1,5-diene Equivalent and the Corresponding Tetrol

Akira Takahashi, Mariko Aso, Masakazu Tanaka and Hiroshi Suemune*

Graduate School of Pharmaceutical Sciences, Kyushu University, Fukuoka 812-8582, Japan

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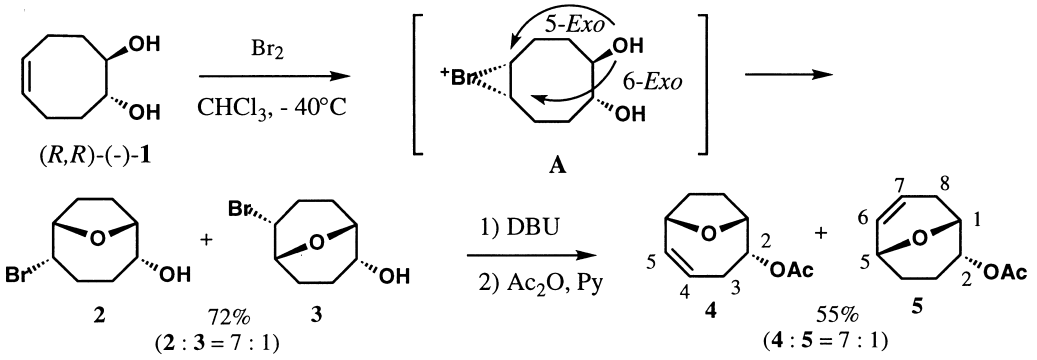
Abstract—Highly enantio- and diastereo-selective synthesis of C_2-symmetric 9-oxabicyclo[3.3.1]nona-2,6-diene and the corresponding C_2-symmetric 2,3,6,7-tetrol has been achieved starting from optically active 5-cyclooctene-1,2-diol prepared by an enzymatic procedure.

Recently, numerous optically active phosphines and amines have been used as a chiral ligand for developing catalytic asymmetric reactions with various metals such as palladium, rhodium and so on. In the procedure for preparation of these metal complexes, cycloocta-1,5-diene was commonly used as a bidentate olefinic ligand.[1] In this report, we wish to describe the synthesis of optically active 9-oxabicyclo[3.3.1]nona-2,6-diene[2] **15** as a chiral cycloocta-1,5-diene equivalent and the corresponding tetrol **26**. The final aim of this work is to develop an asymmetric reaction using a metal complex with these compounds as a chiral ligand.

The synthetic route to **15** was planned as follows: (i) diastereoselective addition of bromine to optically active cyclooctene derivatives; (ii) an ether bridge formation to construct the 9-oxabicyclo[3.3.1]nonane skeleton; (iii) introduction of double bonds at the C2- and C6-positions of **15**.

Both enantiomers of 5-cyclooctene-1,2-diol **1** as the starting material were prepared by an enzymatic procedure previously reported by us.[3] First, diastereoselective addition of bromine to (−)-**1** was studied. Reaction of (−)-**1** with bromine in $CHCl_3$ at −40°C unexpectedly afforded a mixture of bicyclic ether-bridged products[4] **2** and **3** (72% yield) in the ratio of 7 to 1. This mixture was submitted to dehydrobromination with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and subsequent acetylation to afford an inseparable mixture of **4** and **5** (55% yield) in the same ratio of 7 to 1. In the ^1H–^1H COSY spectrum of the major part of this mixture, the connections in the order of C2-H, C3-2H, C4-H and C5-H of **4** were observed, which suggests that the major product has a 9-oxabicyclo[4.2.1]non-2-ene skeleton (Scheme 1). The ether bond formation from (−)-**1** might proceed with complete diastereoselectivity via bromonium cation (**A**), and 5-exo ring closure is favored over 6-exo ring closure in terms of regioselectivity. Details for the determination of the stereochemistry of the initial products **2** and **3** are given below.

Next, addition of bromine to the acetonide **6**, prepared from



Scheme 1.

Keywords: chiral ligand; bidentate olefinic ligand; 5-cyclooctene-1,2-diol.
* Corresponding author. E-mail: suemune@lyra.phar.kyushu-u.ac.jp

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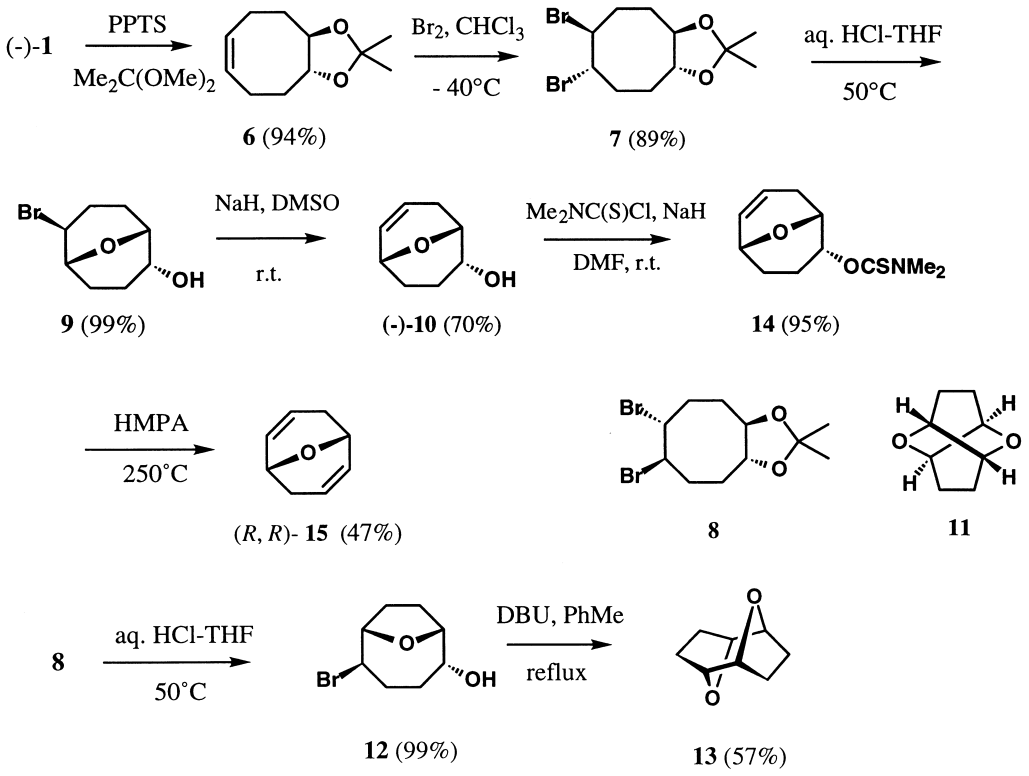
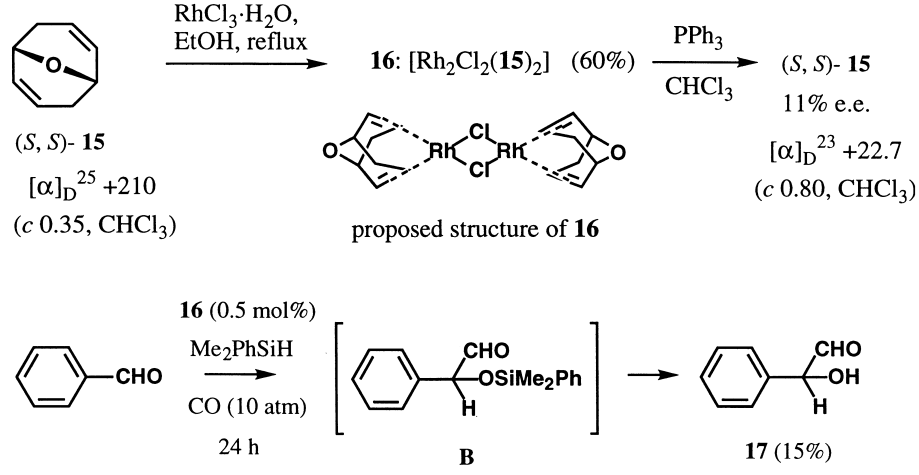
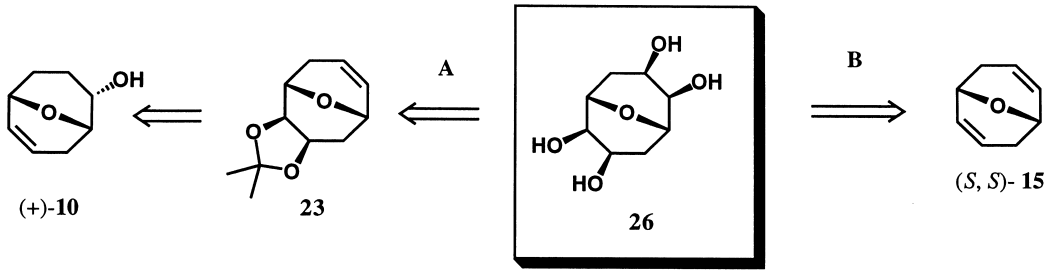


Scheme 2.



Scheme 3.



Scheme 4.

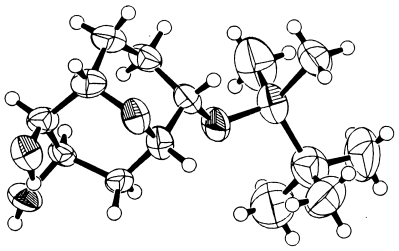
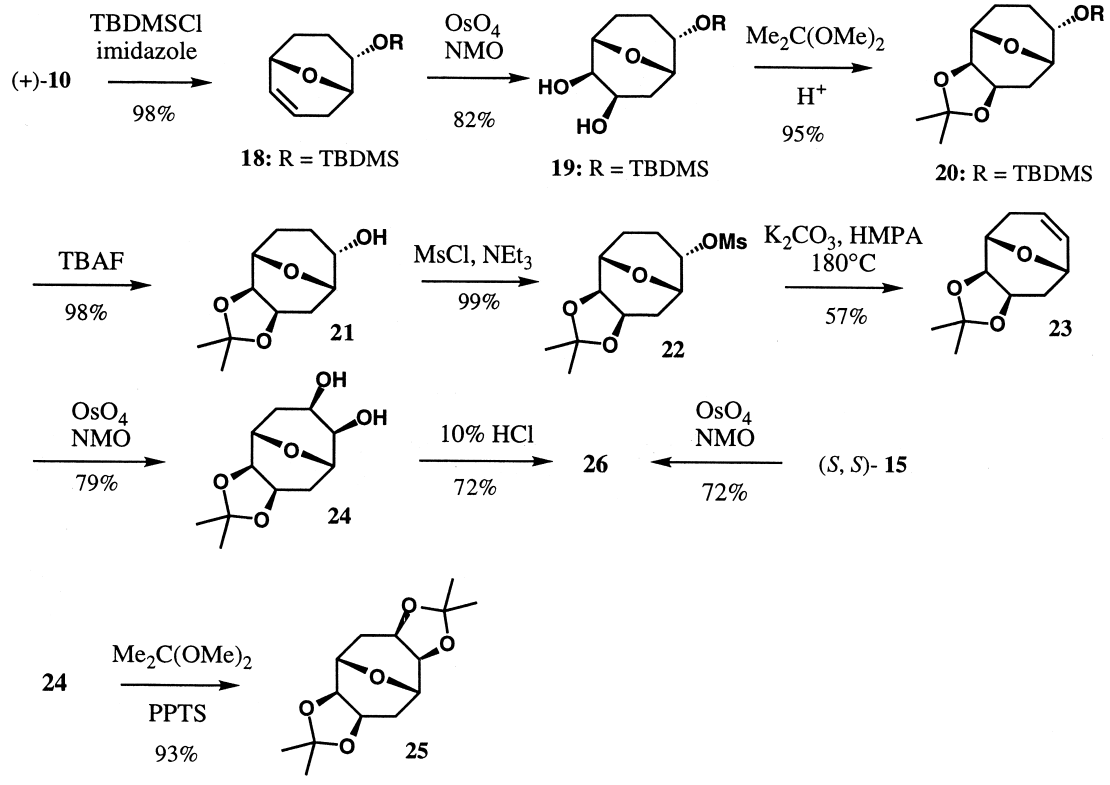


Figure 1. ORTEP-diagram of **19**.

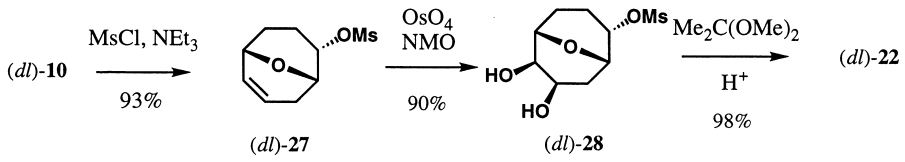
(−)-**1** in 94% yield in the usual manner, was examined. This reaction afforded two diastereomers of *trans*-addition products **7** (89%) and **8** (9%) with C_2-axis. The structure of these products was determined by the following chemical transformations. Acidic treatment of **7** gave **9** in 99% yield, whose ^{1}H NMR spectrum was not identical with that of **3**. Subsequent dehydrobromination of **9** under basic conditions afforded the desired **10** and the optically active D_2-symmetric 2,7-dioxatwistan **11** ($[\alpha]_D^{27}=-221$ (*c* 0.67, $CHCl_3$); lit.[5] $[\alpha]_D=-225$ (*c* 0.285, $CHCl_3$)). Among several reaction conditions employed, NaH in dimethylsulfoxide (DMSO) gave the best result in terms of the yield of **10** (70%). Furthermore, the yield of **11** was raised up to 35% in the case of using DBU in refluxing toluene. This process might be interesting as a novel procedure to prepare the optically active dioxatwistan **11**. After quantitative acetylation of **10** into **5**, the skeleton of **5** could be determined by its ^{1}H–^{1}H COSY spectrum, in which the connections in the order of C2-H, C1-H, C8-2H, C7-H, C6-H and C5-H were observed. On the other hand, similar acid treatment of **8** gave **12** in 99% yield, whose ^{1}H NMR spectrum was not identical with that of **2**, and subsequent basic treatment of **12** with DBU gave an achiral bis-ether **13** with σ-symmetry in 57% yield. For the reactions from **7** and **8**, ether bond formation might proceed via an intramolecular S_N2 process. Taking the results mentioned above into consideration, the structures of **2**–**5**, **7**–**10** and **12** were determined as depicted in Schemes 1 and 2.

Next, dehydroxylation of **10** was studied to synthesize the target molecule (*R*,*R*)-**15**. Compound **10** was converted into the corresponding *N*,*N*-dimethylthiocarbamate **14** (95%) in the usual manner. Elimination reaction of **14** under thermal conditions gave the desired (*R*,*R*)-**15** in reasonable yields (47% as isolated yield). In this reaction, not so many by-products were observed, but the volatility of **15** might cause the slightly decreased yield. ^{1}H and ^{13}C NMR spectra of the (*R*,*R*)-**15** showed its C_2-symmetric property; the ^{1}H NMR spectrum showed five kinds of protons and the ^{13}C NMR spectrum four kinds of carbons. Compound (*S*,*S*)-**15** was also synthesized starting from (*S*,*S*)-(+)-**1**.

As a preliminary study for the application of optically active **15**, synthesis of the complex with rhodium trichloride was performed. According to the method for preparation of RhCl(cycloocta-1,5-diene)$_2$, a mixture of $RhCl_3$ and (*S*,*S*)-**15** in EtOH was refluxed for 2 h. The resulting crude yellow precipitate **16** (60%) was collected. The high-resolution mass spectrum of **16** supported Rh_2Cl_2(**15**)$_2$ as a molecular mass, and its ^{1}H NMR spectrum suggested its structure as depicted in Scheme 3. To our regret, racemization of (*S*,*S*)-**15**, which might be caused through the shift of both double bonds, was observed during this complex formation; a ligand exchange of **16** with PPh_3 in $CHCl_3$ gave (*S*,*S*)-**15**



Scheme 5.



Scheme 6.

of 11% ee. In addition, a preliminary study of silylformylation[6] of benzaldehyde using **16** did not afford satisfactory results; this reaction afforded a hydroxy aldehyde **17**, which might be obtained via a desired product **B**, in only 15% yield. As a result, a further molecular design might be required to use **15**-type of compound as a chiral ligand.

Synthesis of C_2-symmetric 9-oxabicyclo[3.3.1]nonane-2,3,6,7-tetrol

Two synthetic plans of (1*S*,2*R*,3*R*,5*S*,6*R*,7*R*)-9-oxabicyclo[3.3.1]nonane-2,3,6,7-tetrol **26** were considered. One was a stepwise process starting from (+)-**10** via **23** (Path A), and the other was a direct one-step process from (*S*,*S*)-**15** (Path B) (Scheme 4).

At first, the hydroxy group of (+)-**10** was protected as *tert*-butyldimethylsilyl (TBDMS) ether **18** (98%) and subsequent OsO_4-catalyzed *cis*-dihydroxylation gave the *syn*-diol **19** (82%) with complete diastereoselectivity. The stereochemical structure of **19** was finally determined by X-ray analysis (Fig. 1). Protection of *cis*-diol functions of **19** as an acetonide **20** (95%) and further cleavage of TBDMS ether linkage gave **21** (98%).

Subsequent mesylation of **21** and elimination of mesylate gave the desired **23** (56% from **21**). The OsO_4-catalyzed *cis*-dihydroxylation of **23** afforded the desired *syn*,*syn*-**24** in 79% yield. The structure of **24** was confirmed by conversion into bisacetonide **25** of C_2-symmetry. Acidic treatment of **24** afforded the target molecule **26** in 72% yield and its spectroscopic analyses supported the structure (Scheme 5). The synthetic route from **10** to the mesylate **22** (Scheme 6) could be shortened by direct mesylation of **10** into **27** and subsequent similar transformation via **28**.[7]

The *syn*-selectivity of OsO_4-catalyzed *cis*-dihydroxylation[8] of **18**, **27** and **23** strongly encouraged us to undertake direct synthesis of **26** from (*S*,*S*)-**15** (Path B). In accordance with our expectation, OsO_4-catalyzed *cis*-dihydroxylation of (*S*,*S*)-**15** afforded **26** in 72% yield in a completely diastereoselective manner.

Experimental

Melting points were taken on a Yanagimoto melting point apparatus and are not corrected. ^{1}H NMR spectra were obtained on a JEOL GX-270 (270 MHz) or a JEOL JMN-GX-500 (500 MHz) spectrometer. ^{13}C NMR spectra were taken on a JEOL GX-270 (68 MHz) spectrometer. Mass spectra and high-resolution mass spectra were measured on a JEOL JMS-610H or a JEOL JMS-SX 102 spectrometer. IR spectra were taken on a JASCO IR A-100 infrared spectrophotometer. Specific rotations were measured on a JASCO DIP-360 digital polarometer. Column chromatography was carried out on silica gel 70–230 mesh (Merck, Kieselgel 60).

A mixture of (1*R*,2*R*,5*S*,6*S*)-5-bromo-9-oxabicyclo[4.2.1]-nonan-2-ol (2) and (1*R*,2*R*,5*R*,6*R*)-6-bromo-9-oxabicyclo-[3.3.1]nonan-2-ol (3). To a solution of (*R*,*R*)-(−)-**1** (462 mg, 3.25 mmol) in $CHCl_3$ (6 ml) was added dropwise a solution of Br_2 (0.2 ml, 3.9 mmol) in $CHCl_3$ (5 ml) at −40°C and the mixture was stirred for 1 h. The reaction mixture was allowed to warm to room temperature, and saturated aqueous sodium hydrogen sulfite was added to the reaction mixture. The mixture was extracted with $CHCl_3$. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, and dried over Na_2SO_4. After removal of solvent in vacuo, the residue was purified by silica gel column chromatography. Elution with hexane–AcOEt=2:1 to 1:1 gave **2** and **3** as an inseparable mixture (517 mg; 72%) in the ratio of 7 to 1; EIMS (*m*/*z*) 221 $[M+H]^+$, 223 $[M+H+2]^+$; **2**: ^{1}H NMR (δ, $CDCl_3$) 4.60–4.51 (m, 2H), 4.26–4.11 (m, 2H), 2.40–1.05 (m, 9H); ^{13}C NMR (δ, $CDCl_3$) 82.0 (d), 80.9 (d), 71.1 (d), 54.3 (d), 32.1 (t), 29.7 (t), 26.6 (t), 24.8 (t); **3**: ^{1}H NMR (δ, $CDCl_3$) 4.55 (m, 1H), 4.20–4.03 (m, 2H), 3.89 (m, 1H).

A mixture of (1*R*,2*R*,6*S*)-9-oxabicyclo[4.2.1]non-4-en-2-yl acetate (4) and (1*R*,2*R*,5*R*)-9-oxabicyclo[3.3.1]non-6-en-2-yl acetate (5). To a solution of a mixture of **2** and **3** (100 mg, 0.45 mmol) in toluene (2 ml) was added DBU (0.68 ml, 4.54 mmol) and the whole was refluxed for 30 h. After cooling, H_2O was added to the reaction mixture and the whole was extracted with Et_2O. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (2 ml), and $(CH_3CO)_2O$ (42 μl, 0.45 mmol), pyridine (36 μl, 0.45 mmol) and 4-dimethylaminopyridine (10 mg) were added. The mixture was stirred at room temperature for 16 h. After addition of H_2O, the whole was extracted with CH_2Cl_2. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, and dried over Na_2SO_4. After removal of solvent in vacuo, the residue was purified by silica gel column chromatography. Elution with hexane–AcOEt=5:1 gave **4** and **5** as an inseparable mixture (45 mg; 55%) in the ratio of 7 to 1; IR ($CHCl_3$) 2945, 1735 cm^{-1}; **4**; ^{1}H NMR (δ, $CDCl_3$) 5.94 (ddd, *J*=11.6, 5.6, 3.0 Hz, 1H), 5.48 (ddd, *J*=11.6, 6.9, 3.6 Hz, 1H), 5.03 (ddd, *J*=9.6, 5.6, 4.0 Hz, 1H), 4.59 (dd, *J*=7.6, 5.6 Hz, 1H), 4.50 (m, 1H), 2.67 (dt, *J*=16.8, 6.3 Hz, 1H), 2.25 (m, 1H), 2.05 (s, 3H), 2.16–1.95 (m, 3H), 1.83 (m, 1H). **5**; ^{1}H NMR (δ, $CDCl_3$) 5.98 (ddd, *J*=10.2, 4.0, 3.0 Hz, 1H), 5.73 (ddt, *J*=10.2, 4.6, 2.3 Hz, 1H), 5.00 (dt, *J*=11.6, 5.6 Hz, 1H), 4.25 (m, 1H), 4.19 (m, 1H), 2.44 (dm,

J=18.8 Hz, 1H), 2.13 (ddd, J=18.8, 4.3, 2.3 Hz, 1H), 2.52 (s, 3H), 2.00 (m, 1H), 1.85–1.74 (m, 2H), 1.59 (dm, J=13.2 Hz, 1H).

(1*R*,8*R*)-10,10-Dimethyl-9,11-dioxabicyclo[6.3.0]undec-4-ene (6). A mixture of (*R*,*R*)-(−)-(**1**) (3.25 g, 22.9 mmol), 2,2-dimethoxypropane (4.2 ml, 34.4 mmol) and catalytic amount of PPTS in acetone (30 ml) was stirred at room temperature for 5 h. After the addition of saturated aqueous $NaHCO_3$ (10 ml), the whole was concentrated in vacuo and the aqueous residue was extracted with ether. The ether extract was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography. Elution with hexane–AcOEt=10:1 gave **6** (3.90 g, 94%) as a colorless oil; $[\alpha]_D^{27}$=−98.9 (*c* 1.89, $CHCl_3$); IR (neat) 2940, 1050 cm^{-1}; ^1H NMR (δ, $CDCl_3$) 5.67–5.63 (m, 2H), 3.95–3.91 (m, 2H), 2.31–2.07 (m, 6H), 1.52–1.42 (m, 2H), 1.37 (s, 6H); MS (*m*/*z*) 182 [M^+]; HRMS calcd for $C_{11}H_{18}O_2$ [M^+] 182.1306, found 182.1311.

(1*R*,4*S*,5*S*,8*R*)-4,5-Dibromo-10,10-dimethyl-9,11-dioxabicyclo[6.3.0]undecane (7) and (1*R*,4*R*,5*R*,8*R*)-4,5-dibromo-10,10-dimethyl-9,11-dioxabicyclo[6.3.0]undecane (8). To a solution of **6** (814 mg, 4.47 mmol) in $CHCl_3$ (10 ml) was added dropwise a solution of Br_2 (345 ml, 6.70 mmol) in $CHCl_3$ (7 ml) at −40°C. Similar treatment to that described for **2** and **3** afforded crude products, which were purified by silica gel column chromatography. Elution with hexane–AcOEt=10:1 gave **7** (1.35 g; 89%) and **8** (137 mg, 9%). **7**: a colorless oil; $[\alpha]_D^{28}$=+24.7 (*c* 1.32, $CHCl_3$); IR (neat) 3000, 2940, 2860, 1440, 1380, 1220, 1050 cm^{-1}; ^1H NMR (δ, $CDCl_3$) 4.72 (bs, 2H), 3.64 (bs, 2H), 2.55 (bs, 2H), 2.18 (bs, 2H), 2.15 (bs, 4H), 1.38 (s, 6H); ^{13}C NMR (δ, $CDCl_3$) 105.9 (s), 82.6 (d), 57.0 (d), 29.1 (t), 27.4 (t), 27.0 (q); MS (*m*/*z*) 343 [M+H]$^+$; HRMS calcd for $C_8H_{19}O_2Br_2$ [M+H]$^+$ 342.9732, found 342.9745. **8**: colorless solid; mp 115–116°C (Et_2O); $[\alpha]_D^{29}$=−87.4 (*c* 0.97, $CHCl_3$); IR ($CHCl_3$) 3000, 2950, 2860, 1460, 1380, 1250, 1060 cm^{-1}; ^1H NMR (δ, $CDCl_3$) 4.34–4.32 (m, 2H), 3.90–3.88 (m, 2H), 2.44–2.35 (m, 4H), 2.14–2.09 (m, 2H), 1.69–1.63 (m, 2H), 1.39 (s, 6H); ^{13}C NMR (δ, $CDCl_3$) 107.9 (s), 78.1 (d), 60.1 (d), 31.3 (t), 31.2 (t), 26.9 (q); MS (*m*/*z*) 343 [M+H]$^+$; HRMS calcd for $C_8H_{19}O_2Br_2$ [M+H]$^+$ 342.9732, found 342.9738.

(1*R*,2*R*,5*R*,6*S*)-6-Bromo-9-oxabicyclo[3.3.1]nonan-2-ol (9). A mixture of **7** (1.32 g, 3.86 mmol) and 1N HCl (5 ml) in THF (5 ml) was heated at 50°C for 9 h. After cooling, the reaction mixture was neutralized with saturated aqueous $NaHCO_3$ and extracted with AcOEt. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography. Elution with hexane–AcOEt=1:1 gave **9** (852 mg, 99%) as a colorless oil; $[\alpha]_D^{28}$=−3.1 (*c* 0.95, $CHCl_3$); IR (neat) 3400, 2940, 1080, 1030 cm^{-1}; ^1H NMR (δ, $CDCl_3$) 4.33 (m, 1H), 4.13–4.05 (m, 2H), 3.93 (t, J=5.9 Hz, 1H), 2.50–2.17 (m, 2H), 2.14–1.96 (m, 4H), 1.89–1.68 (m, 3H); ^{13}C NMR (δ, $CDCl_3$) 71.9 (d), 69.9 (d), 68.1 (d), 52.9 (d), 29.0 (t), 27.5 (t), 27.4 (t), 18.0 (t); MS (*m*/*z*) 221 [M+H]$^+$; HRMS calcd for $C_8H_{14}O_2Br$ [M+H]$^+$ 221.0177, found 221.0189.

(1*R*,2*R*,5*R*)-9-Oxabicyclo[3.3.1]non-6-en-2-ol (10) and (1*R*,3*R*,6*R*,8*R*)-2,7-dioxatricyclo[4.4.0.0^{3,8}]decane ((−)-2,7-Dioxatwistan) (11). *With DBU in toluene:* To a solution of **9** (132 mg, 597 μmol) in toluene (14 ml) was added DBU (0.9 ml, 5.97 mmol) and the mixture was refluxed for 1 day. H_2O was added to the reaction mixture and the whole was extracted with Et_2O. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography. Elution with hexane–AcOEt=2:1 to 1:1 gave **10** (38 mg, 46%) and **11** (30 mg, 35%). **10**: a colorless oil; $[\alpha]_D^{28}$= −98.8 (*c* 0.63, $CHCl_3$); IR (neat) 3400, 2920, 1060, 1040, 1020 cm^{-1}; ^1H NMR (δ, $CDCl_3$) 5.97 (dt, J=9.9, 3.3 Hz, 1H), 5.72 (ddt, J=10.2, 4.6, 2.3 Hz, 1H), 4.23 (t, J=4.6 Hz, 1H), 4.09 (t, J=6.3 Hz, 1H), 3.97 (m, 1H), 2.45–2.18 (m, 2H), 2.00–1.55 (m, 5H); ^{13}C NMR (δ, $CDCl_3$) 127.6 (d), 126.4 (d), 70.4 (d), 69.2 (d), 66.0 (d), 28.8 (t), 24.0 (t), 22.2 (t); MS (*m*/*z*) 140 [M^+]; HRMS calcd for C8H12O2 [M]$^+$ 140.0837, found 140.0845. **11**: colorless solid; mp 110–112°C (Et_2O); $[\alpha]_D^{27}$=−221 (*c* 0.67, $CHCl_3$), lit.[5] $[\alpha]_D$= −225 (*c* 0.285, $CHCl_3$); IR ($CHCl_3$) 3020, 2980, 2880, 1460, 1320, 1090, 1020 cm^{-1}; ^1H NMR (δ, $CDCl_3$) 3.86 (d, J=4.0 Hz, 4H), 2.13–1.99 (m, 4H), 1.78–1.67 (m, 4H); ^{13}C NMR (δ, $CDCl_3$) 72.4 (d), 22.9 (t); MS (*m*/*z*) 140 [M^+].

With NaH in DMSO: To a solution of **9** (545 mg, 2.46 mmol) in dry DMSO (10 ml) was added NaH (400 mg, 9.84 mmol) under an Ar atmosphere and the mixture was stirred at room temperature for 3 h. After addition of saturated aqueous ammonium chloride solution, the whole was extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by silica gel column chromatography gave **10** (239 mg; 70%) and **11** (73 mg; 21%).

(1*R*,2*R*,5*R*,6*S*)-5-Bromo-9-oxabicyclo[4.2.1]nonan-2-ol (12). A mixture of **8** (95 mg, 279 mmol) and 1N HCl (3 ml) in THF (3 ml) was heated at 50°C for 7 h. The reaction mixture was neutralized with saturated aqueous $NaHCO_3$ and extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography. Elution with hexane–AcOEt=1:1 gave **12** (61 mg; 99%) as colorless solids; $[\alpha]_D^{28}$=+24.3 (*c* 1.15, $CHCl_3$); IR ($CHCl_3$) 3400, 2940, 1470, 1440, 1200, 1060, 1030 cm^{-1}; ^1H NMR (δ, $CDCl_3$) 4.79 (dd, J=9.2, 2.6 Hz, 1H), 4.46 (m, 1H), 4.13–4.03 (m, 2H), 2.33–1.83 (m, 6H), 1.76–1.35 (m, 3H); ^{13}C NMR (δ, $CDCl_3$) 85.1 (d), 81.4 (d), 71.9 (d), 58.3 (d), 32.4 (t), 30.8 (t), 30.7 (t), 23.1 (t); MS (*m*/*z*) 221 ([M+H]$^+$); HRMS calcd for $C_8H_{14}O_2Br$ [M+H]$^+$ 221.0177, found 221.0171.

***cis-transoid-cis*-9,10-Dioxatricyclo[4.2.1.1^{2,5}]decane (13)** To a solution of **12** (84.0 mg, 380 mmol) in dry toluene (10 ml) was added DBU (0.28 ml, 1.90 mmol) and the mixture was refluxed for 20 h. After dilution with H_2O, the whole was extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography. Elution with hexane–AcOEt=2:1 gave **13** (30 mg; 57%) as colorless solids; IR ($CHCl_3$) 2960, 2860, 1460, 1140, 1100 cm^{-1}; ^1H NMR (δ,

$CDCl_3$) 3.93–3.91 (m, 4H), 2.23–2.16 (m, 4H), 1.84–1.79 (m, 4H); MS (*m/z*) 140 [M^+]; HRMS calcd for $C_8H_{12}O_2$ [M^+] 140.0837, found 140.0842.

(1*R*,2*R*,5*R*)-9-Oxabicyclo[3.3.1]non-6-en-2-yl *N*,*N*-dimethylthiocarbamate (14). To a solution of (−)-**10** (267 mg, 1.91 mmol) in DMF (3 ml) were successively added NaH (92 mg, 2.3 mmol) and *N*,*N*-dimethylthiocarbamoyl chloride (354 mg, 2.86 mmol) under an Ar atmosphere, and the whole was stirred at room temperature for 5 h. After addition of H_2O, the mixture was extracted with ether and the organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography. Elution with hexane–AcOEt=3:1 gave **14** (411 mg; 95%) as a colorless oil; $[\alpha]_D^{24}=-94.8$ (*c* 2.0, $CHCl_3$); IR (neat) 2940, 1510, 1390, 1280, 1180, 1050 cm^{-1}; ^1H NMR (δ, $CDCl_3$) 5.99 (dt, *J*=10.2, 3.6 Hz, 1H), 5.75 (ddt, *J*=10.2, 4.3, 2.3 Hz, 1H), 5.61 (dt, *J*=11.5, 5.9 Hz, 1H), 4.34 (t, *J*=6.3 Hz, 1H), 4.27 (t, *J*=4.6 Hz, 1H), 3.36 (s, 3H), 3.11 (s, 3H), 2.49 (dddt, *J*=19.1, 7.6, 2.3, 2.0 Hz, 1H), 2.14–1.96 (m, 3H), 1.82 (m, 1H), 1.61 (m, 1H); MS (*m/z*) 228.1 [M+H^+].

(1*R*,5*R*)-9-Oxabicyclo[3.3.1]nona-2,6-diene (*R*,*R*)-(15). A solution of **14** (161 mg, 0.71 mmol) in HMPA (3 ml) was heated at 250°C for 4.5 h in a sealed tube. After dilution with H_2O, the whole was extracted with pentane. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography. Elution with pentane–ether=8:1 gave (*R*,*R*)-**15** (40 mg; 47%) as colorless solids; mp 34°C (pentane); $[\alpha]_D^{28}=-216$ (*c* 0.40, $CHCl_3$); IR ($CHCl_3$) 3000, 2930, 2840, 1410, 1380, 1320, 1270, 1180, 1050 cm^{-1}; ^1H NMR (δ, $CDCl_3$) 5.86–5.73 (m, 4H), 4.50–4.46 (m, 2H), 2.60–2.49 (m, 2H), 1.76 (dd, *J*=16.8, 4.3 Hz, 2H); ^{13}C NMR (δ, $CDCl_3$) 129.7 (d), 122.7 (d), 66.4 (d), 28.3 (t); MS (*m/z*) 122 [M^+]; HRMS calcd for $C_8H_{10}O$ [$M]^+$ 122.0731, found 122.0726. (*S*,*S*)-(**15**) ($[\alpha]_D^{28}=+210$ (*c* 0.35, $CHCl_3$)) was also synthesized starting from (*S*,*S*)-(+)-**1**.

Rhodium complex (16; $Rh_2Cl_2(15)_2$). To a solution of (*S*,*S*)-**15** (280 mg, 2.28 mmol) in EtOH (5 ml) was added $RhCl_3{\cdot}3H_2O$ (100 mg, 0.38 mmol) and the mixture was refluxed for 3 days. The resulting precipitate was collected by filtration to give crude **16** (60 mg; 60%) as brown powder; ^1H NMR (δ, $CDCl_3$) 4.91–4.86 (m, 2H), 4.12 (s, 4H), 2.64–2.61 (m, 2H), 2.39–2.36 (m, 2H); MS (*m/z*) 520 [M^+]; HRMS calcd for $C_{16}H_{20}O_2Cl_2Rh_2$ [$M]^+$ 519.8950, found 519.8928.

(1*S*,2*S*,5*S*)-2-*t*-Butyldimethylsilyloxy-9-oxabicyclo[3.3.1]non-6-ene (18). A mixture of (+)-**10** (1.13 g, 8.07 mmol), imidazole (824 mg, 12.1 mmol), and *t*-butyldimethylsilyl chloride (1.80 g, 12.1 mmol) in CH_2Cl_2 (10 ml) was stirred at room temperature for 6 h. After dilution with H_2O, the whole was extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography. Elution with hexane–AcOEt=50:1 gave **18** (2.00 g; 98%) as a colorless oil; $[\alpha]_D^{24}=+42.6$ (*c* 0.86, $CHCl_3$); IR (neat) 2930, 2850, 1470, 1250, 1100 cm^{-1}; ^1H NMR (δ, $CDCl_3$) 5.93 (dt, *J*=10.2, 3.6 Hz, 1H), 5.66 (ddt, *J*=10.2, 4.6, 2.3 Hz, 1H), 4.17 (t, *J*=4.6 Hz, 1H), 3.95–3.83 (m, 2H), 2.29–2.27 (m, 2H), 1.89 (m, 1H), 1.68–1.60 (m, 2H), 1.50 (m, 1H), 0.85 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H); MS (*m/z*) 254 [M^+]; HRMS calcd for $C_{14}H_{26}O_2Si$ [M^+] 254.1702, found 254.1708.

(1*S*,2*R*,3*R*,5*S*,6*S*)-6-*t*-Butyldimethylsilyloxy-9-oxabicyclo-[3.3.1]nonane-2,3-diol (19). To a mixed solution of **18** (50 mg, 197 μmol) in acetone (10 ml) and H_2O (5 ml) were successively added 50% aqueous *N*-methylmorpholine *N*-oxide solution (0.14 ml, 0.59 mmol) and 0.5% aqueous OsO_4 solution (0.2 ml, 3.94 μmol) at 0°C. The whole was stirred at room temperature for 12 h. Saturated aqueous sodium hydrogen sulfite solution and florisil were added and the resulting mixture was stirred for further 30 min and passed through a celite pad. The filtrate was concentrated in vacuo and the residue was extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography. Elution with hexane–AcOEt=1:1 gave **19** (47 mg; 82%) as colorless needles. mp 78–81°C (hexane); $[\alpha]_D^{23}=+15.3$ (*c* 0.55, $CHCl_3$); IR ($CHCl_3$) 3500, 3380, 2900, 2800, 1220, 1080 cm^{-1}; ^1H NMR (δ, $CDCl_3$) 4.12 (bs, 1H), 3.98 (dd, *J*=6.9, 2.0 Hz, 1H), 3.93 (m, 1H), 3.85 (t, *J*=5.6 Hz, 1H), 3.63 (bs, 1H), 2.53 (bs, D_2O exchangeable, 1H), 2.47 (bs, D_2O exchangeable, 1H), 2.27 (dd, *J*=13.9, 6.6 Hz, 2H), 2.00 (dt, *J*=13.9, 6.6 Hz, 1H), 1.90 (m, 1H), 1.77–1.64 (m, 2H), 1.44 (dd, *J*=13.5, 10.6, 5.9 Hz, 1H), 0.87 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (δ, $CDCl_3$) 72.3 (d), 72.1 (d), 71.3 (d), 67.9 (d), 64.8 (d), 28.7 (t), 28.5 (t), 25.7 (q), 24.4 (t), 17.9 (s), −4.6 (q), −4.9 (q); MS (*m/z*) 289 [M+$H]^+$; HRMS calcd for $C_{14}H_{29}O_4Si$ [M+$H]^+$ 289.1835, found 289.1817.

X-Ray structure determination of compound 19. Crystal data: $C_{14}H_{28}O_4Si$, *M*=288.46. Orthorhombic, *a*=7.131(2), *b*=36.972(3), *c*=6.409(2) Å, *V*=1689.7(5) $Å^3$ (from centering angles for 25 reflections ($40.6\leq 2\theta\leq 49.3°$, λ=1.54178 Å, *T*=296 K), space group $P2_12_12_1$ (No. 19), *Z*=4, *Dc*=1.134 g cm^{-3}, colorless needle 0.40×0.10×0.10 mm, μ(Cu-*K*α)=12.95 cm^{-1}. Data collection and processing: Rigaku AFC5R four-circle diffractometer, $\omega-2\theta$ scans with ω scan width $(1.05+0.30\tan\theta)°$, filtered Cu-*K*α X-radiation; 1526 reflections measured ($2\theta_{max}$=120°), giving 746 with $I\geq 3.00\sigma(I)$. No crystal decay was observed. Structure solution and refinement: the structure was solved by direct methods using SIR92[9] and expanded using Fourier techniques.[10] All non-hydrogen atoms were given anisotropic thermal parameters and hydrogen atoms included in calculated positions given isotropic thermal parameters. The final cycle of full-matrix least-squares refinement based on 746 reflections gave a conventional *R* factor of 0.059 (*Rw*=0.053). The largest peak and hole in the final difference Fourier map were 0.12 and −0.12 e $Å^{-3}$. All calculations were performed using the teXsan[11] crystallographic package of Molecular Structure Corporation.

(1*S*,2*S*,6*R*,8*S*,9*S*)-9-*t*-Butyldimethylsilyloxy-4,4-dimethyl-3,5,12-trioxatricyclo[6.3.1.$0^{2,6}$]dodecane (20). A mixture of **19** (213 mg, 0.74 mmol), 2,2-dimethoxypropane (0.14 ml, 1.11 mmol) and catalytic amount of *p*-toluenesulfonic acid in acetone (5 ml) was stirred at room temperature for 3 h. The reaction mixture was neutralized with saturated aqueous $NaHCO_3$ and the mixture was concentrated

in vacuo. The residue was extracted with ether. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography. Elution with hexane–AcOEt=10:1 gave **20** (231 mg; 95%) as a colorless oil; $[\alpha]_D^{26}$=+30.9 (*c* 1.60, $CHCl_3$); IR (neat) 2900, 2820, 1440, 1360, 1220, 1080 cm^{-1}; ^1H NMR (δ, $CDCl_3$) 4.46 (dt, *J*=8.6, 5.9 Hz, 1H), 4.19 (d, *J*=5.3 Hz, 1H), 4.14–3.87 (m, 3H), 2.27 (dd, *J*=13.9, 8.3 Hz, 1H), 2.17–1.63 (m, 4H), 1.56 (s, 3H), 1.35 (s, 3H), 1.25 (m, 1H), 0.86 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); MS (*m/z*) 329 $[M+H]^+$; HRMS calcd for $C_{17}H_{33}O_4Si$ $[M+H]^+$ 329.2148, found 329.2160.

(1*S*,2*S*,6*R*,8*S*,9*S*)-4,4-Dimethyl-3,5,12-trioxatricyclo-[6.3.1.0^{2,6}]dodecan-9-ol (21). To a solution of **20** (57 mg, 172 μmol) in THF (3 ml) was added 1.0 M TBAF in THF (345 μl, 345 μmol) and the whole was stirred at room temperature for 5 h. After removal of the solvent in vacuo, H_2O was added to the residue and the mixture was extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography. Elution with hexane–AcOEt=1:2 gave **21** (36 mg; 98%) as colorless needles; mp 115–116°C (Et_2O); $[\alpha]_D^{23}$=+46.5 (*c* 0.86, $CHCl_3$); IR ($CHCl_3$) 3600, 3450, 3000, 2950, 1380, 1100, 1050 cm^{-1}; ^1H NMR (δ, $CDCl_3$) 4.46 (dt, *J*=8.6, 5.9 Hz, 1H), 4.21 (d, *J*=5.6 Hz, 1H), 4.04–3.95 (m, 2H), 3.89 (t, *J*=5.9 Hz, 1H), 2.25 (dd, *J*=14.5, 8.3 Hz, 1H), 2.09–1.94 (m, 2H), 1.85 (ddd, *J*=14.5, 8.6, 7.3 Hz, 1H), 1.79–1.66 (m, 2H), 1.57 (s, 3H), 1.35 (s, 3H), 1.26 (m, 1H); ^{13}C NMR (δ, $CDCl_3$) 107.2 (s), 74.6 (d), 71.3 (d), 69.5 (d), 68.5 (d), 69.7 (d), 28.3 (q), 28.0 (t), 27.9 (t), 27.7 (t), 26.4 (q); MS (*m/z*) 215 $[M+H]^+$; Anal. calcd for $C_{11}H_{18}O_4$: C 61.65, H 8.47; found: C 61.62, H 8.44.

(1*S*,2*S*,6*R*,8*S*,9*S*)-9-Methanesulfonyloxy-4,4-dimethyl-3,5,12-trioxatricyclo[6.3.1.0^{2,6}]dodecane (22). To a mixture of **21** (1.22 g, 5.70 mmol) and NEt_3 (1.2 ml, 8.55 mmol) in dry CH_2Cl_2 (10 ml) was added methanesulfonyl chloride (0.66 ml, 8.55 mmol) and the mixture was stirred at room temperature for 20 h. The reaction was stopped by addition of H_2O and the mixture was extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography. Elution with hexane–AcOEt=1:1 gave **22** (1.65 g; 99%) as colorless needles; mp 153–155°C (Et_2O); $[\alpha]_D^{27}$=+31.6 (*c* 0.57, $CHCl_3$); IR ($CHCl_3$) 3000, 2950, 1360, 1170, 1050 cm^{-1}; ^1H NMR (δ, $CDCl_3$) 4.87 (dt, *J*=11.9, 5.9 Hz, 1H), 4.47 (dt, *J*=8.6, 5.9 Hz, 1H), 4.25 (d, *J*=5.6 Hz, 1H), 4.20 (t, *J*=5.9 Hz, 1H), 3.92 (d, *J*=5.9 Hz, 1H), 3.03 (s, 3H), 2.24–2.05 (m, 3H), 2.03–1.89 (m, 1H), 1.83–1.75 (m, 1H), 1.62–1.50 (m, 5H), 1.35 (s, 3H); ^{13}C NMR (δ, $CDCl_3$) 108.2 (s), 76.2 (d), 74.3 (d), 69.0 (d), 68.8 (d), 68.5 (d), 38.6 (q), 28.5 (t), 28.2 (q), 26.8 (t), 26.4 (q), 26.0 (t); MS (*m/z*) 293 $[M+H]^+$; HRMS calcd for $C_{12}H_{21}O_6S$ $[M+H]^+$ 293.1059, found 293.1051.

(1*S*,2*S*,6*R*,8*S*)-4,4-Dimethyl-3,5,12-trioxatricyclo-[6.3.1.0^{2,6}]dodec-9-ene (23). To a solution of K_2CO_3 (168 mg, 1.21 mmol) in HMPA (2 ml) was added a solution of **22** (236.2 mg. 809 μmol) in HMPA (4 ml) at 180°C under an Ar atmosphere. The mixture was stirred at 180°C for 1.5 h. Saturated aqueous ammonium chloride was added to the reaction mixture and the whole was extracted with ether. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography. Elution with hexane–AcOEt=5:1 gave **23** (91 mg; 57%) as colorless needles; mp 62–63°C (hexane); $[\alpha]_D^{24}$=+154 (*c* 0.83, $CHCl_3$); IR ($CHCl_3$) 3000, 2940, 1380, 1360, 1050 cm^{-1}; ^1H NMR (δ, $CDCl_3$) 5.84 (m, 1H), 5.72 (m, 1H), 4.53 (d, *J*=7.3 Hz, 1H), 4.32 (m, 1H), 4.29 (dt, *J*=8.6, 5.3 Hz, 1H), 3.92 (d, *J*=5.3 Hz, 1H), 2.73 (m, 1H), 1.88 (ddt, *J*=18.1, 5.0, 0.7 Hz, 1H), 1.85 (dd, *J*=8.6, 3.6 Hz, 1H), 1.56 (s, 3H), 1.37 (s, 3H); ^{13}C NMR (δ, $CDCl_3$) 128.6 (d), 123.9 (d), 107.8 (s), 76.7 (d), 69.9 (d), 68.8 (d), 66.9 (d), 31.6 (t), 28.4 (q), 28.2 (t), 26.5 (q); MS (*m/z*) 197 $[M+H]^+$; HRMS calcd for $C_{11}H_{17}O_3$ $[M+H]^+$ 197.1178, found 197.1155.

(1*S*,2*S*,6*R*,8*S*,9*R*,10*R*)-4,4-Dimethyl-3,5,12-trioxatricyclo-[6.3.1.0^{2,6}]dodecane-9,10-diol (24). By the similar procedure to that described for preparation of **19** from **18**, compound **23** (82 mg, 416 mmol) was converted to **24** (76 mg; 79%). Colorless solids; $[\alpha]_D^{24}$=+95.9 (*c* 0.56, $CHCl_3$); IR ($CHCl_3$) 3570, 3420, 3000, 2950, 1380, 1060 cm^{-1}; ^1H NMR (δ, $CDCl_3$) 4.38 (d, *J*=5.9 Hz, 1H), 4.28 (dt, *J*=8.6, 5.9 Hz, 1H), 4.17 (d, *J*=7.3 Hz, 1H), 3.98 (d, *J*=5.9 Hz, 1H), 3.72 (m, 1H), 2.34 (d, *J*=5.3 Hz, D_2O exchangeable, 1H), 2.31 (d, *J*=4.3 Hz, D_2O exchangeable, 1H), 2.12–1.81 (m, 4H), 1.55 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (δ, $CDCl_3$) 108.7 (s), 74.6 (d), 72.8 (d), 71.4 (d), 69.7 (d), 68.8 (d), 64.6 (d), 32.0 (t), 30.9 (t), 28.2 (q), 26.3 (q); MS (*m/z*) 231 $[M+H]^+$; HRMS calcd for $C_{11}H_{19}O_5$ $[M+H]^+$ 231.1232, found 231.1245.

(1*S*,2*S*,6*R*,8*S*,9*S*,13*R*)-4,4,11,11-Tetramethyl-3,5,10,12,15-pentaoxatetracyclo[6.6.1.0^{2,6}.0^{9,13}]pentadecane (25). By the similar procedure to that described for preparation of **20** from **19**, compound **24** (17 mg, 75 mmol) was converted to **25** (19 mg; 93%). Colorless solids; mp 190–192°C (Et_2O); $[\alpha]_D^{22}$=+88.7 (*c* 0.53, $CHCl_3$); IR ($CHCl_3$) 2980, 2940, 1380, 1360, 1060, 1040 cm^{-1}; ^1H NMR (δ, $CDCl_3$) 4.38–4.36 (m, 2H), 4.19–4.11 (m, 2H), 3.93 (d, *J*=5.3 Hz, 2H), 2.04 (ddd, *J*=13.9, 10.2, 5.9 Hz, 2H), 1.88 (ddd, *J*=13.9, 7.6, 2.0 Hz, 2H), 1.55 (s, 6H), 1.35 (s, 6H); ^{13}C NMR (δ, $CDCl_3$) 108.8 (s), 74.6 (d), 69.7 (d), 68.7 (d), 32.3 (t), 28.4 (q), 26.5 (q); MS (*m/z*) 271 $[M+H]^+$; Anal. calcd for $C_{14}H_{22}O_5$: C 62.19, H 8.21; found: C 62.13, H 8.25.

(1*S*,2*R*,3*R*,5*S*,6*R*,7*R*)-9-Oxabicyclo[3.3.1]nonane-2,3,6,7-tetraol (26). ***26** from **24**:* To a solution of **24** (17 mg, 72 μmol) in MeOH (2 ml) was added 10% HCl (0.5 ml) and the mixture was refluxed for 2 days. The solvent was evaporated in vacuo and the residue was purified by preparative TLC ($CHCl_3$–MeOH=7:3), which gave **26** (11.9 mg, 72%) as colorless solids; mp. 159–160°C (MeOH−H_2O); $[\alpha]_D^{22}$=+88.7 (*c* 0.53, H_2O); IR (KBr) 3400, 3270, 2930, 1460, 1370, 1220, 1190, 1040 cm^{-1}; ^1H NMR (δ, *d*-DMSO) 4.42 (d, *J*=6.6 Hz, 2H), 4.24 (d, *J*=4.3 Hz, 2H), 3.85 (d, *J*=6.9 Hz, 2H), 3.79–3.69 (m, 2H), 3.43–3.39 (m, 2H), 1.75 (ddd, *J*=13.5, 11.6, 6.9 Hz, 2H), 1.54 (dd, *J*=13.5, 6.6 Hz, 2H); ^{13}C NMR (δ, *d*-DMSO) 73.1 (d), 70.0 (d), 63.3 (d), 30.8 (t); MS (*m/z*) 191 $[M+H]^+$;

Anal. calcd for $C_8H_{14}O_5$: C 50.50, H 7.42; found: C 50.53, H 7.48.

***26** from (S,S)-**15**:* To a solution of (*S*,*S*)-**15** (164 mg, 1.34 mmol) in a mixture of acetone and H_2O (3:1; 4 ml) were added 50% aqueous *N*-methylmorpholine *N*-oxide solution (1.90 ml, 8.04 mmol), then 0.5% aqueous OsO_4 solution (2.0 ml, 0.04 mmol) and the mixture was stirred at room temperature for 30 h. The resulting precipitate was collected by filtration and recrystallized from MeOH−H_2O gave **26** (183 mg, 72%).

(1*RS*,2*RS*,5*RS*)-2-Methanesulfonyloxy-9-oxabicyclo-[3.3.1]non-6-ene (*dl*)-(27). To a solution of (*dl*)-**10** (5.06 g, 36.1 mmol) in CH_2Cl_2 (100 ml) were added NEt_3 (7 ml, 50.5 mmol) and methanesulfonyl chloride (3.9 ml, 50.5 mmol) and the whole was stirred at room temperature for 9 h. After addition of saturated aqueous ammonium chloride, the mixture was extracted with CH_2Cl_2 and the organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography. Elution with hexane–AcOEt=2:1 gave (*dl*)-**27** (7.32 g; 93%) as colorless solids; IR ($CHCl_3$) 3030, 2950, 1360, 1335, 1175, 1170 cm^{-1}; ^1H NMR (δ, $CDCl_3$) 5.99 (dt, *J*=10.2, 3.6 Hz, 1H), 5.73 (ddd, *J*=10.2, 4.3, 2.3 Hz, 1H), 4.88 (m, 1H), 4.32–4.24 (m, 2H), 3.03 (s, 3H), 2.50 (dm, *J*=19.1 Hz, 1H), 2.21 (ddd, *J*=19.1, 4.3, 2.0 Hz, 1H), 2.08–1.98 (m, 2H), 1.69–1.64 (m, 1H).

(1*RS*,2*SR*,3*SR*,5*RS*,6*RS*)-6-Methanesulfonyloxy-9-oxabicyclo[3.3.1]nonane-2,3-diol (*dl*)-(28). By the similar procedure to that described for preparation of **19** from **18**, compound (*dl*)-**27** (139 mg, 637 μmol) was converted to (*dl*)-**28** (144 mg; 90%). Colorless solids; ^1H NMR (δ, $CDCl_3$) 4.93 (m, 1H), 4.23–4.14 (m, 2H), 4.06 (m, 1H), 3.69 (bs, 1H), 3.05 (s, 3H), 2.50 (bs, 2H), 2.27–2.05 (m, 3H), 1.96–1.71 (m, 3H).

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