Enantioselective Approach to Polyhydroxylated Compounds Using Chiral Sulfoxides: Synthesis of Enantiomerically Pure *myo*-Inositol and Pyrrolidine Derivatives

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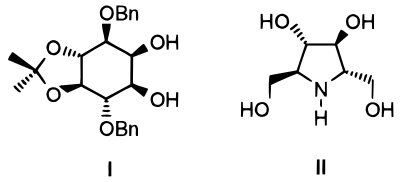
A short enantioselective synthesis of the biologically important *myo*-inositol derivative **I** and the pyrrolidine derivative **II** is described. The molecule **3**, a diketo disulfoxide readily made from tartaric acid, is the key intermediate. The sulfinyl group controlled completely the very high stereoselection observed.

The increasing evidence indicating that oligosaccharides play a pivotal role in important biological events such as cell−cell communication and cell-mediated processes has led to considerable interest in carbohydrates and their analogues.[1]

The necessity for new preparations of enantiomerically pure myo inositol derivatives such as **I**[2a] (Figure 1) arose from the discovery of the phophoinositide pathway,[3] a new signal transduction system. Moreover, it has recently been postulated that a family of uncharacterized inositol phosphoglycans (IPG) bears the partial structure of putative modulators involved in the cellular response to insulin[4,5] as the second messenger.

Compound **II**[2b] (Figure 1) belongs to the family of the so-called azasugars, which are among the most powerful glycosidase inhibitors and are potential chemotherapeutic agents for the treatment of diabetes, cancer, or viral replication, including the human immunodeficiency virus (HIV).[6]

myo-Inositol derivatives have already been prepared by multistep syntheses from different carbohydrates: D-glucurono-6,3-lactone,[7a] D-mannitol,[7b] and L-iditol.[7c] Only one synthesis started from a tartaric acid derivative and used a Sharpless epoxidation to create the two last chiral hydroxylic centers.[7d] The aza-sugar **II** was also synthesized from L-sorbose,[8a] D-glucose,[8b] and D-mannitol.[8c] There is no report of a total synthesis for this compound.



I II

Figure 1.

We report in this paper a short enantioselective synthesis of the two carbohydrate mimics **I** and **II**.

Our approach to cyclitols and azasugars is based on the use of chiral sulfoxides in an efficient enantioselective synthesis of the intermediate alditols **6** and **6′**[9] from D-(−)- and L-(+)-dimethyl 2,3-*O*-isopropylidenetartrate. Condensation of the anion of (−)-(*S*)-methyl *p*-tolyl sulfoxide **2** with the readily available D-(−)-tartrate **1** led to the *β*-diketo sulfoxide **3** in 76% yield (Scheme 1). DIBAL reduction of **3** yielded the C_2-symmetric dihydroxy sulfoxide **4** as a single isomer, as shown by ^{1}H NMR and ^{13}C NMR of the crude product. The absolute configuration of the newly created carbinols has been deduced from our previous results with related systems.[10] The large nonequivalence ($\Delta\nu$ = 64 Hz) of the two methylenic protons α to the sulfinyl group was always observed for

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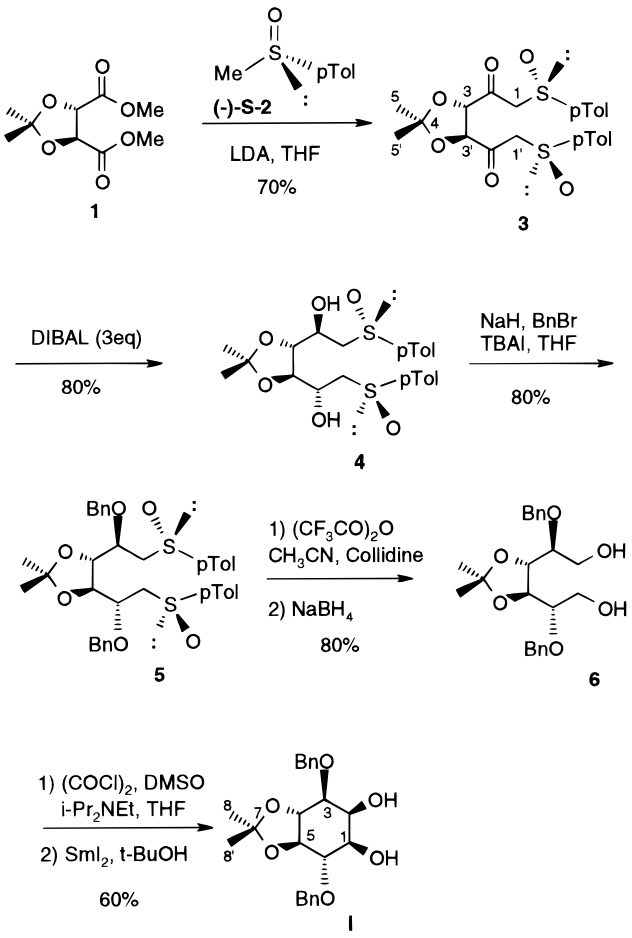
Scheme 1



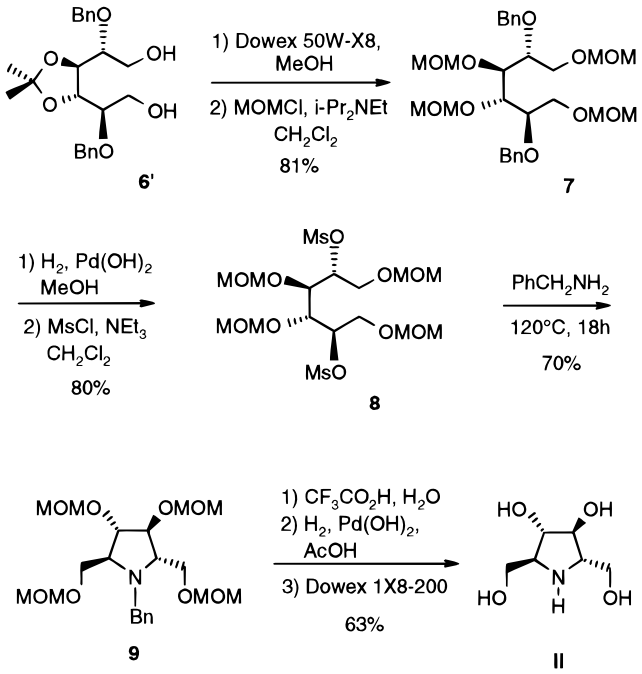
a (*SS*,2*R*) relative configuration. Bisprotection of the diol **4** was achieved with sodium hydride and benzyl bromide in DMF to give the compound **5** in 80% yield. One-pot Pummerer rearrangement[11] using trifluoroacetic anhydride at 0 °C and sodium borohydride reduction led to the optically pure L-iditol derivative **6** in 80% yield.

The same reaction sequence (Scheme 2) from L-(+)-diethyl 2,3-*O*-isopropylidenetartrate and (*R*)-(+)-methyl *p*-tolyl sulfoxide afforded the optically pure D-iditol derivative **6′**. Thus, both L and D isomers of iditol derivatives **6** and **6′** are obtained in 38% overall yield, in only three steps from a dimethyl tartrate derivative.

Finally, a one-pot reaction including Swern oxidation of the diol **6** to the dialdehyde followed by SmI_2-promoted pinacol coupling[12] led to the *cis*-diol **I**[13] in 60% yield (Scheme 1, 22% overall yield in five steps).

The pyrrolidinic compound **II** was obtained by cyclization with benzylamine of the mesylate **8**, which was

Scheme 2



prepared from **6′** in four steps (Scheme 2): acetonide hydrolysis with acidic resin, followed by complete protection of the resulting tetrol with methoxymethyl chloride affording the 2,5-di-*O*-benzyl-D-iditol derivative **7** in 65% overall yield. Debenzylation of **7** with Pearlman catalyst in methanol followed by dimesylation of the resulting diol gave **8** in 80% overall yield. Stereoselective cyclization to the azasugar **9** was carried out by heating the dimesylate **8** in benzylamine at 120 °C for 18 h. The displacement reaction occurred with complete inversion of configuration[8c] at C-2 and C-5 leading to 2,5-dideoxy-2,5-(*N*-benzylimino)-1,3,4,6-tetrakis-*O*-(methoxymethyl)-D-iditol **9** in 70% yield. Removal of MOM groups followed by debenzylation using Pearlman catalyst in acetic acid gave, after neutralization and purification by ion-exchange chromatography, 2(*S*),5(*S*)-bis(hydroxymethyl)-3(*S*),4(*S*)-dihydroxypyrrolidine **II** (63% yield), showing all the described characteristics[8a,b] of the known enantiomer of **II** and an opposite optical rotation $[\alpha]^{22}_D$ −54 (*c* 0.3, H_2O) [lit.[8a,b] $[\alpha]^{22}_D$ +53.8 (*c* 0.3, H_2O)].

In conclusion, these results provide an efficient and short enantioselective synthesis of L- and D-iditol derivatives **6** and **6′**. The same procedure can be easily applied to the preparation of all the stereoisomers of the alditols intermediates just by changing the absolute configuration of the starting sulfoxide and tartrate.

Experimental Section

(−)-[3(*S*),3′(*S*),S(*S*)]-1,1′-Di-*p*-tolylsulfinyl-3,3′-isopropylidenedioxy-2,2′-hexanedione (3). To a solution of 1.14 mL (4 equiv, 8.12 mmol) of diisopropylamine in 10 mL of THF was added 5.24 mL of BuLi, 1.55 M in hexane (8.12 mmol, 4 equiv) at −78 °C under argon. The solution was stirred for 30 min, 1.25 g (4 equiv, 8.12 mmol) of (−)-(*S*)-methyl *p*-tolyl sulfoxide **2** in 10 mL of THF was dropwise added, and immediately after the addition the temperature was raised to −40 °C. Stirring was continued for 30 min, and then the reaction mixture was cooled again to −78 °C and 500 mg (2.03 mmol, 1 equiv) of D-(−)-isopropylidenedimethyl tartrate **1** in 10 mL of THF was added. After 2 h at −78 °C, the reaction was quenched with saturated NH_4Cl and extracted several times with AcOEt. The

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(13) D-*myo*-Inositol derivative **I**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.3 (m, 10H, arom), 4.83 (AB system, 2H, J_{AB} = 23.8 Hz, $\Delta\nu$ = 47.8 Hz, CH_2Ph), 4.79 (AB system, 2H, J_{AB} = 11.9 Hz, $\Delta\nu$ = 32.5 Hz, CH_2Ph), 4.24 (br td, 1H, *J* = 3.5, 1.5 Hz, H-2), 4.06 (t, 1H, *J* = 10 Hz, H-4), 3.82 (dd, 1H, *J* = 8.5, 10 Hz, H-6), 3.61 (dd, 1H, *J* = 10 Hz, H-3), 3.58 (td, 1H, 8.5 Hz, *J* = 3.5 Hz, H-1), 3.39 (t, 1H, *J* = 10 Hz), 2.65 (d, 1H, *J* = 8.5 Hz, OH), 2.62 (d, 1H, *J* = 1.5 Hz, OH), 1.49 (s, 3H, CH_3), 1.47 (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.44, 137.97, 128.61, 128.51, 128.05, 127.83, 127.09 (arom), 112.02, 79.4, 78.25, 77.67, 76.52, 73.6, 73.06, 71.83, 27.15, 27.10. The coupling constants of the cyclic protons are identical to those of the known D-*myo*-inositol derivative[7b] in which the benzyl protecting group was replaced by a TBDPS group.

organic layer was washed with HCl 10% and brine and dried over $MgSO_4$. Filtration and evaporation gave a white solid, which was washed with Et_2O to give the desired product **3** in 70% yield: mp 126 °C; $[\alpha]_D = -303$ ($c = 2.0$, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 7.32−7.59 (AB system, 8H, $J_{AB} = 8.2$ Hz, $\Delta\nu = 41$ Hz), 4.61 (s, 2H, H-3), 4.08 (AB system, 4H, $J_{AB} = 13.75$ Hz, $\Delta\nu = 48$ Hz), 2.42 (s, 6H), 1.33 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 199.52, 142.59, 139.69, 130.29, 124.25, 113.39, 81.52, 64.88, 26.07, 21.58. Anal. Calcd for $C_{23}H_{26}O_6S_2$: C, 59.70; H, 5.60. Found: C, 59.72; H, 5.5.

(−)-[2(*S*),2′(*S*),3(*R*),3′(*R*),S(*S*)]-1,1′-Di-*p*-tolylsulfinyl-3,3′-isopropylidenedioxy-2,2′-hexanediol (4). To a solution of 0.25 g (0.54 mmol, 1 equiv) of the bisketo sulfoxide **3** in 9.5 mL of THF was dropwise added 1.62 mL (1.62 mmol, 3 equiv) of a 1 M solution of DIBAH at −78 °C. When all the starting material had disappeared according to TLC (hexane/EtOAc 2:8), the reaction mixture was quenched by addition of 0.85 mL of MeOH. After evaporation of the solvents, 13 mL of EtOAc and 13 mL of sodium tartrate were added. The mixture was stirred at room temperature for 30 min. The organic layer was washed with brine, dried over $MgSO_4$, filtrated, and concentrated. The resulting solid was washed with acetone to give **4** in 85% yield: mp 186 °C; $[\alpha]_D = -196$ ($c = 2.0$, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 7.28−7.53 (AB system, 8H, $J_{AB} = 9$ Hz), 5.12 (d, 2H, $J = 6$ Hz), 4.22−4.3 (X part of an ABX system, m, 2H), 4.15 (s, 2H), 2.89−3.23 (AB part of an ABX system, 4H, $J_{AB} = 12.5$ Hz, $J_{AX} = 10$ Hz, $J_{BX} = 2.5$ Hz, $\Delta\nu = 64$ Hz), 2.4 (s, 6H), 1.4 (s, 6H); ^{13}C NMR (50 MHZ, $CDCl_3$) δ 141.6, 140.00, 130.00, 124.00, 110.00, 63.46, 62.50, 63.46, 26.90, 21.50. Anal. Calcd for $C_{23}H_{30}O_6S_2$: C, 59.20; H, 6.48. Found: C, 58.91; H, 6.43.

(−)-[2(*S*),2′(*S*),3(*R*),3′(*R*),S(*S*)]-1,1′-Di-*p*-tolylsulfinyl-2,2′-dibenzyloxy-3,3′-isopropylidenedioxyhexane (5). To a solution of 50 mg of the di-β-hydroxy sulfoxide **4** (0.107 mmol, 1 equiv) in 5 mL of dry THF were slowly added under argon NaH (60 mg, 0.235 mmol, 2.2 equiv), tetrabutylammonium iodide (7.9 mg, 0.0214 mmol), and benzyl bromide (0.1 mL, 0.235 mmol) at 0 °C. The reaction mixture was stirred at room temperature until all the starting material had disappeared (TLC, hexane/EtOAc 2/8) and hydrolyzed at 0 °C with saturated NH_4Cl. After extraction with AcOEt (3 × 5 mL), the organic layer was washed with brine, dried over $MgSO_4$, and concentrated under vacuum. Flash column chromatography (hexane/EtOAc 4:6) of the crude product gave 80% yield of the product **5** as a yellow solid: mp 37−38 °C; $[\alpha]_D = -131$ ($c = 0.8$, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 7.39 (m, 18H), 4.74 (AB system, 4H, $J_{AB} = 11$ Hz, $\Delta\nu = 33.8$ Hz), 4.02−3.95 (m, 4H), 2.90 (d, 4H, $J = 6$ Hz), 2.4 (s, 6H), 1.34 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$), δ 141.58, 141.05, 137.55, 130.14, 128.58, 128.30, 128.10, 123.96, 109.33, 74.31, 78.62, 72.53, 61.14, 27.08, 21.48. Anal. Calcd for $C_{37}H_{42}O_6S_2$: C, 68.69; H, 6.54. Found: C, 68.88; H, 6.51.

(+)-[2(*S*),2′(*S*),3(*R*),3′(*R*)]-2,2′-Dibenzyloxy-3,3′-isopropylidenedioxy-1,1′-hexanediol (6). To a solution of the bis-sulfoxide **5** (200 mg, 0.31 mmol, 1 equiv) in 3 mL of acetonitrile at 0 °C were added successively *sym*-collidine (0.239 mL, 1.81 mmol, 5.85 equiv) and trifluoroacetic anhydride (0.423 mL, 3.01 mmol, 9.71 equiv). The reaction was stirred for 30 min and then hydrolyzed by addition of 1 mL of water; the pH was then adjusted to 7 by addition of K_2CO_3, and the temperature was raised to room temperature. After 30 min, the thioacetal intermediate was reduced by addition of 71.65 mg (1.86 mmol, 6 equiv) of $NaBH_4$, and stirring was continued for 40 min. The reaction was quenched with saturated NH_4Cl. The aqueous layer was extracted with AcOEt, and the combined organic layers were washed successively with 10 mL of 1 N HCl, 10 mL of saturated $NaHCO_3$, and finally with 20 mL of brine. After being dried over $MgSO_4$, the solution was concentrated under vacuum, and the crude product was purified by flash chromatography (silica gel, EtOAc/hexane 1:1) to give 80% of compound **6** as a white solid: mp 52 °C; $[\alpha]_D = +21$ ($c = 2.0$, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 7.3 (m, 10H), 4.64 (AB system, 4H, $J_{AB} = 12$ Hz, $\Delta\nu = 24$ Hz), 4.27 (dd, 2H, $J = 2$, 1 Hz), 3.76 (AB part of an ABX system, 4H, $J_{AB} = 13$ Hz, $J_{AX} = 4.3$ Hz, $J_{BX} = 4.8$ Hz, $\Delta\nu = 29$ Hz), 3.48 (X part of an ABX system, m, 2H), 2.38 (m, 2H), 1.43 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 138.07, 128.55, 128.10, 127.96, 109.54, 77.65, 77.16, 72.61, 61.93, 27.04. Anal. Calcd for $C_{27}H_{30}O_6$: C, 68;00. H, 7.50. Found: C, 67.56; H, 7.38.

3,6-Di-*O*-benzyl-4,5-*O*-isopropylidene-*myo*-inositol (I). To a solution of oxalyl chloride (50 mL, 0.57 mmol, 2.3 equiv) in dry THF (1.5 mL) was added dimethyl sulfoxide (84 mL, 1.19 mmol, 4.8 equiv) at −60 °C under argon. After 15 min, a solution of diol **6** (100 mg, 0.25 mmol, 1 equiv) in THF (2 mL) was added dropwise. After an additional 30 min, diisopropylamine (0.435 mL, 2.5 mmol, 10 equiv) was added and the reaction warmed to 0 °C during 2 h. The solution was diluted with THF (6.5 mL), cooled to −25 °C, and treated with a freshly prepared 0.1 M solution of SmI_2 (7.5 mL, 0.75 mmol) and *tert*-butyl alcohol (70 mL, 0.75 mmol). The reaction mixture was allowed to warm to room temperature during 3 h, stirred for another 12 h, and then hydrolyzed with saturated $NaHCO_3$. AcOEt (10 mL) was added, the reaction mixture was stirred vigorously for 30 min, the aqueous layer was extracted several times with AcOEt, and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under vaccuum. The crude product was purified by flash chromatography (silica gel, EtOAc/hexane 1:1) to give a 60% yield of the compound **I** as a white solid: mp 104−106 °C; $[\alpha]_D = -55$ ($c = 1.0$, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 7.3 (m, 10H), 4.83 (AB system, 2H, $J_{AB} = 23.8$ Hz, $\Delta\nu = 47.8$ Hz), 4.79 (AB system, 2H, $J_{AB} = 11.9$ Hz, $\Delta\nu = 32.5$ Hz), 4.24 (br td, 1H, $J = 3.5$, 1.5 Hz), 4.06 (t, 1H, $J = 10$ Hz), 3.82 (dd, 1H, $J = 8.5$, 10 Hz), 3.61 (dd, 1H, $J = 3$, 10 Hz), 3.58 (td, 1H, 8.5 Hz, $J = 3.5$ Hz), 3.39 (t, 1H, $J = 10$ Hz), 2.65 (d, 1H, $J = 8.5$ Hz), 2.62 (d, 1H, $J = 1.5$ Hz), 1.49 (s, 3H), 1.47 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$), δ 138.44, 137.97, 128.61 128.51, 128.05, 127.83, 127.09, 112.02, 79.4, 78.25, 77.67, 76.52, 73.6, 73.06, 71.83, 27.15, 27.10. Anal. Calcd for $C_{23}H_{28}O_6$: C, 68.90; H, 7.0.04. Found: C, 68.43; H, 6.95.

(−)-(2*R*,5*R*)-Dibenzyloxy-(3*S*,4*S*)-1,3,4,6-tetra(methoxymethyl) hexane (7). (a) (−)-[2(*R*),2′(*R*),3(*S*),3′(*S*)]-2,2′-Dibenzyloxy-3,3′-isopropylidenedioxy-1,1′-hexanediol (**6′**), enantiomer of **6**, was prepared by the same route from (+)-(*R*)-methyl *p*-tolyl sulfoxide and l-(+)-Isopropylidenedimethyl tartrate.

(b) To a solution of the acetonide **6′** (823 mg, 2.04 mmol) in 43 mL of methanol was added 930 mg of acidic resin (Dowex 50W-X8). The reaction mixture was stirred for 16 h under reflux, filtered, and concentrated under reduced pressure. The crude residue was purified either by crystallization from AcOEt−hexane or by flash chromatography (silica gel, AcOEt/hexane 5:1) to give (−)-2(*R*),5(*R*)-dibenzyloxy-3(*S*),4(*S*)-dihydroxy-1,6-hexanediol in 88% yield as a white solid: mp 83 °C; $[\alpha]_D = -18$ ($c = 1$, acetone); ^1H NMR (200 MHz, $CDCl_3$) δ 7,3 (s, 10 H), 4.59 (AB system, $J = 11.6$ Hz, 4 H), 3.97 (d, $J = 3.6$ Hz, 2 H), 3.78 (AB part of an ABX system, $J = 12.3$ Hz (AB), $J_{AX} = 3.6$, $J_{BX} = 3.7$ Hz, 4 H), 3.53 (X part of an of ABX system, $J = 3.6$, 3.7 Hz, 2 H), 3.15 (br s, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$), δ 137.7, 128.6, 128.02, 128.01, 79.2, 71.9, 70.2, 60.5; IR ($CHCl_3$) ν 3400, 1450 cm^{-1}. Anal. Calcd for $C_{20}H_{26}O_6$: C, 66.28; H, 7.23. Found: C, 65.98; H, 7.53.

(b) To a solution of the preceding diol (415 mg, 1.14 mmol) in 10 mL of anhydrous CH_2Cl_2 were added *N*,*N*-diisopropylethylamine (1.6 mL, 9.20 mmol) and chloromethyl methyl ether (1.7 mL, 22.92 mmol). After being stirred for 3 h at rt under argon, the reaction mixture was diluted with CH_2Cl_2, and saturated aqueous $NaHCO_3$ (250 mL) at 0 °C was added. After extraction with CH_2Cl_2, the combined organics were dried over $MgSO_4$, filtered and, concentrated in vacuo. The residue was purified by silica gel column chromatography (AcOEt/hexane 4:5) to afford a 92% yield of compound **7** as a colorless oil: $[\alpha]_D = -27.5$ ($c = 2$, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 7.30 (s, 10 H), 4.78 (AB, $J = 7$ Hz, 4 H), 4.62 (s, 4 H), 4.63 (AB, $J = 11.7$ Hz, 4 H), 3.94 (d, $J = 1.6$ Hz, 2 H), 3.75 (s, 6 H), 3.37 (s, 6 H), 3.35 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.6, 127.6, 127.3, 126.9, 97.98, 96.02, 77.7, 75.7, 72.2, 66.9, 55.6, 54.5; IR ($CHCl_3$) ν 2890, 1595, 1450, 1115, 1035 cm^{-1}.

(+)-(3S,4S)-1,3,4,6-Tetra(methoxymethyl)-2(*R*),5(*R*)-

dimethanesulfonylhexane (8). (a) A solution of compound **7** (550 mg, 1 mmol) in methanol (180 mL) was debenzylated with H_2 over 20% $Pd(OH)_2$ (0.39 mmol) at atmospheric pressure for 3 h. The mixture was filtered through Celite, and the solvent was evaporated in vacuo. The remaining residue was purified by silica gel chromatography with AcOEt as eluent, affording 85% of (−)-(3*S*,4*S*)-1,3,4,6-tetra(methoxymethyl)-2(*R*),5(*R*)-hexanediol as a colorless oil: $[\alpha]_D = -9.7$ (*c* = 0.65, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.72 (AB, *J* = 7.1 Hz, 4 H), 4.64 (s, 4 H), 4.14 (t, *J* = 6.3 Hz, 2 H), 3.84 (s, 2), 3.52 (d, *J* = 6.3 Hz, 4 H), 3.63 (s, 6H), 3.39 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 97.7, 96.4, 76.9, 68.8, 67.5, 55.84, 55.0; IR ($CHCl_3$), ν 3380 cm^{-1}; HRMS for $C_{14}H_{30}O_{10}H^+$ [M + H^+] calcd 359.1917, found 359.1930

(b) To a solution of the preceding diol (226 mg, 0.63 mmol) in 8 mL of anhydrous CH_2Cl_2 was added triethylamine (229 mL, 1.64 mmol). The solution was cooled to 0 °C, and methanesulfonyl chloride (107 mL, 1.39 mmol) was added dropwise. The mixture was allowed to stir at 0 °C for 30 min and then poured into 1 N HCl at 0 °C. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with saturated $NaHCO_3$ and brine. After drying ($MgSO_4$), the solution was concentrated in vacuo. The crude residue was purified by silica gel chromatography (AcOEt/hexane 2:1) to give the bismesylate **8** in 94% yield as a colorless oil: $[\alpha]_D = +5$ (*c* = 1.5, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.08 (m, 2 H), 4.75 (AB system, *J* = 6.45 Hz, 4 H), 4.64 (AB, *J* = 7 Hz, 4 H), 3.91 (AB system, *J* = 2.7 Hz, 4 H), 3.89 (s, 2 H), 3.42 (s, 6 H), 3.36 (s, 6 H), 3.10 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 98.8, 96.4, 80.8, 75.8, 66.6, 56.6, 55.5, 38.5; IR ($CHCl_3$) ν 2900, 1200, 980, 770 cm^{-1}; HRMS for $C_{16}H_{34}O_{14}S_2Na^+$ [M + Na^+] calcd 537.1288, found 537.1286.

(+)-*N*-Benzyl-3(*S*),4(*S*)-di(methoxymethyl)-2(*S*),5(*S*)-bis[(methoxymethyl)methyl]pyrrolidine (9). The dimesylated compound **8** (290 mg, 0.56 mmol) and benzylamine (12 mL, 110 mmol) were heated to 120 °C for 18 h. The excess of benzylamine was removed by distillation (bp 73 °C, 18 mmHg). The remaining residue was purified by silica gel chromatography (AcOEt/hexane 3:5) to afford 56% of the pyrrolidine **9** as a colorless oil: $[\alpha]_D = +33$ (*c* = 0.5, $CHCl_3$); ^{1}H NMR (200 MHz,$CDCl_3$) δ 7.29 (m, 5 H), 4.7 (AB, *J* = 6.5 Hz, 4 H), 4.58 (s, 4 H), 4.1 (d, *J* = 4.3 Hz, 2 H), 3.97 (AB, *J* = 14.5 Hz, 2 H), 3.65 (AB, *J* = 11 Hz, 4 H), 3.36 (s, 6 H), 3.32 (s, 6 H), 3.20 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.5, 128.2, 128.1, 126.7, 96.6, 95.7, 83.3, 66.4, 65.4, 55.4, 55.2, 51.6; HRMS calcd for $C_{21}H_{35}NO_8H^+$ [M + H^+] 430.2441, found 430.2433.

(−)-2(*S*),5(*S*)-Bis(hydroxymethyl)-3(*S*),4(*S*)-dihydroxypyrrolidine (II). (a) To remove the MOM protecting groups, the pyrrolidine **9** (119 mg, 0.27 mmol) was dissolved in trifluoroacetic acid (4 mL) and 0.1 mL of water was added. The reaction mixture was stirred for 7 h at rt, and then solvents were evaporated at reduced presure. The remaining residue was chromatographed (Dowex 1 × 8-200 ion-exchange resin and eluted with water); after evaporation of solvent in vacuo, the product was purified by flash chromatography (silica gel, AcOEt/methanol 12:1) to afford 70% of (+)-*N*-benzyl-2(*S*),5-(*S*)-bis(hydroxymethyl)-3(*S*),4(*S*)-dihydroxypyrrolidine as a colorless oil: $[\alpha]_D = +20$ (*c* = 0.35, CH_3OH); ^{1}H NMR (200 MHz,CD_3OD) δ 7.34 (m, 5 H), 4.02 (AB, *J* = 4.5 Hz, 2 H), 4.01 (dd, *J* = 8.6, 2.7 Hz, 2H), 3.69 (AB of ABX, *J* = 11.3, 3.2, 4.8 Hz, 4 H), 3.07 (m, 2H); ^{13}C NMR (75 MHz, CD_3OD) δ 141.3, 129.3, 127.8, 80.6, 71.1, 61.6, 52.6; HRMS for $C_{13}H_{19}NO_4H^+$ [M + H^+] calcd 254.1392, found 254.1387.

(b) A solution of the preceding *N*-benzylpyrrolidine (26 mg, 0.15 mmol) in acetic acid (15 mL) was debenzylated with H_2 over 20% $Pd(OH)_2$ (20 mg) at atmospheric pressure for 3 h. The mixture was filtered through Celite, and the solvent was evaporated in vacuo. The crude residue was purified by ion-exchange chromatography Dowex 1 × 8-200 and then eluted with methanol to give **II** in 90% yield as a colorless solid: $[\alpha]_D = -54.3$ (*c* = 0.3, H_2O) [lit.[8a,b] *ent*-**II** $[\alpha]_D = +53.8$ (*c* = 0.3, H_2O)]; ^{1}H NMR (200 MHz, D_2O) δ 3.78 (dt, 2 H), 3.6, 3.5 (2dd, 4 H), 3.08 (m, 2 H); ^{13}C NMR (75 MHz, D_2O) δ 79.5, 65.4, 63.4.

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