Improved Syntheses of Both Enantiomers of 1,2,5,6-Diepoxyhexane from (2*S*,5*S*)-1,2,5,6-Hexanetetrol

Nobuo Machinaga, Chihiro Kibayashi*

Tokyo College of Pharmacy, Horinouchi, Hachioji, Tokyo 192-03, Japan

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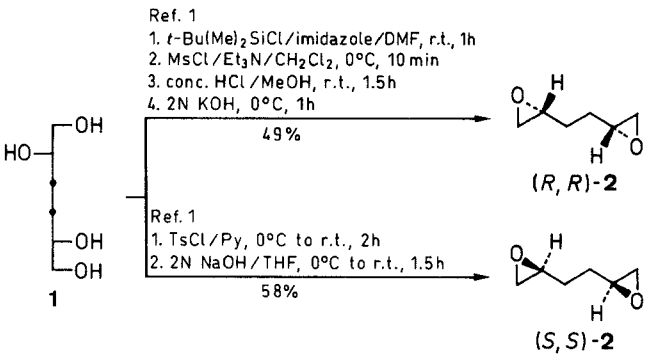
Several methods for the preparation of (2*R*,5*R*)- and (2*S*,5*S*)-1,2,5,6-diepoxyhexane (**2**) from 3,4-dideoxy-D-*threo*-hexitol [(2*S*,5*S*)-1,2,5,6-hexanetetrol (**1**)] as a single common chiral synthon are described. Among these methods, the methods via (2*S*,5*S*)-1,6-bis(pivaloyloxy)-2,5-hexanediol and (2*S*,5*S*)-2,5-bis(benzoyloxy)-1,6-dibromohexane, both derived from **1**, provide the best results in terms of the selectivity, yield, and optical purity for the preparation of (*R*,*R*)-**2** and (*S*,*S*)-**2**, respectively.

Very recently, we have shown that both the enantiomers of 1,2,5,6-diepoxyhexane, (*R*,*R*)-**2** and (*S*,*S*)-**2**, can be used as versatile C_2 symmetric chiral building blocks in the enantiodivergent synthesis of natural products.[1] Both the chiral diepoxides, (*R*,*R*)-**2** and (*S*,*S*)-**2** were prepared by using 3,4-dideoxy-D-*threo*-hexitol (**1**), available from D-mannitol, as a common chiral synthon according to the reaction sequence depicted in Scheme 1.[1] These methods are however somewhat limited by the moderate overall yield and a high cost of the reagent. Therefore, there still exists a need for improvements embodied in this issue.

We wish to report here more efficient, practical procedures for the preparation of optically pure both enantiomers of diepoxide **2** starting from the tetrol **1** as a single common chiral synthon.

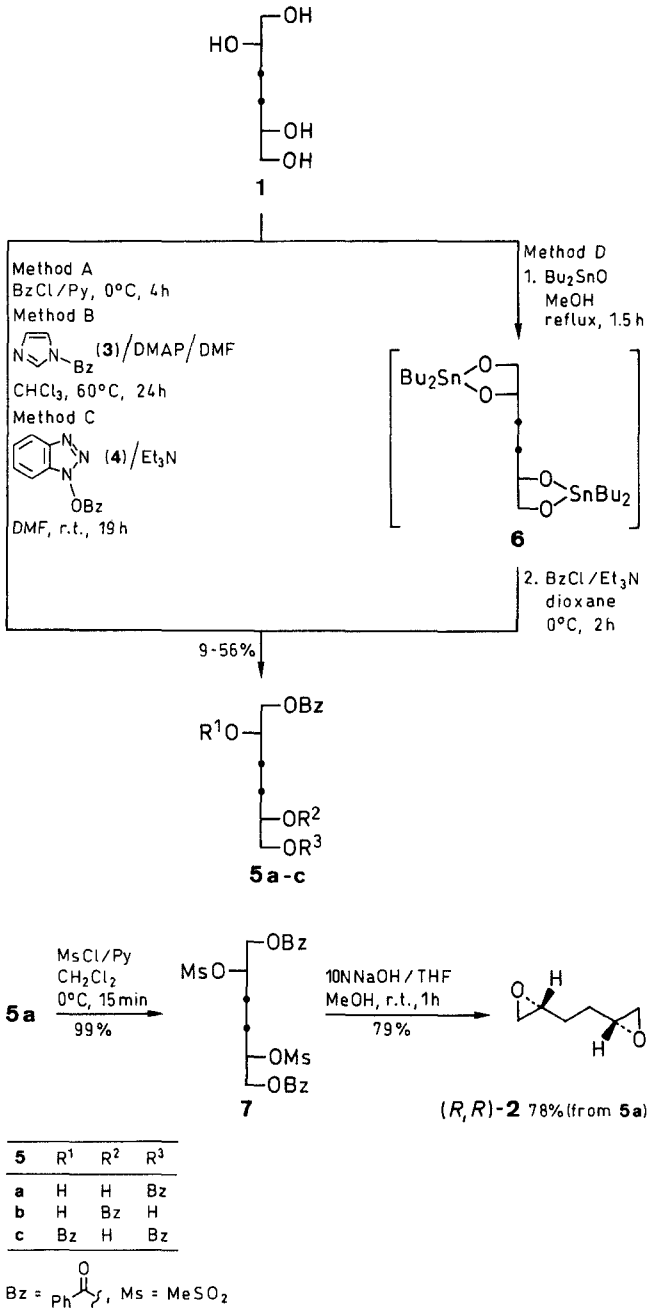
For the preparation of (*R*,*R*)-**2**, the previously reported four-step procedure (Scheme 1) employed the silyl group for the protection of the primary alcohols using expensive



Scheme 1

tert-butyldimethylsilyl chloride which hampers scaling up in the preparation of (*R*,*R*)-**2**. In an attempt to obviate this problem and to shorten the reaction sequence, our initial efforts addressed the regioselective benzoylation of the two primary hydroxy groups of **1** (Scheme 2). Our results on benzoylation of **1** are recorded in the Table. In all cases (Methods A–D), the desired 1,6-di-*O*-benzoyl product **5a** proved to be formed with unsatisfactory regioselectivity, accompanied by the formation of appreciable amounts of the undesired 1,5-di- and 1,2,6-tri-*O*-substituted products **5b** and **5c**. The 1,6-dibenzoate **5a** obtained was converted to the bismethanesulfonate **7**.

which was subsequently subjected to cyclization via hydrolysis and S_N2 displacement as a one-pot sequence under basic conditions (10 N sodium hydroxide), affording the diepoxide (*R,R*)-**2** as a single product in 78% yield from **5a**.



5	R^1	R^2	R^3
a	H	H	Bz
b	H	Bz	H
c	Bz	H	Bz

Bz = , Ms = $MeSO_2$

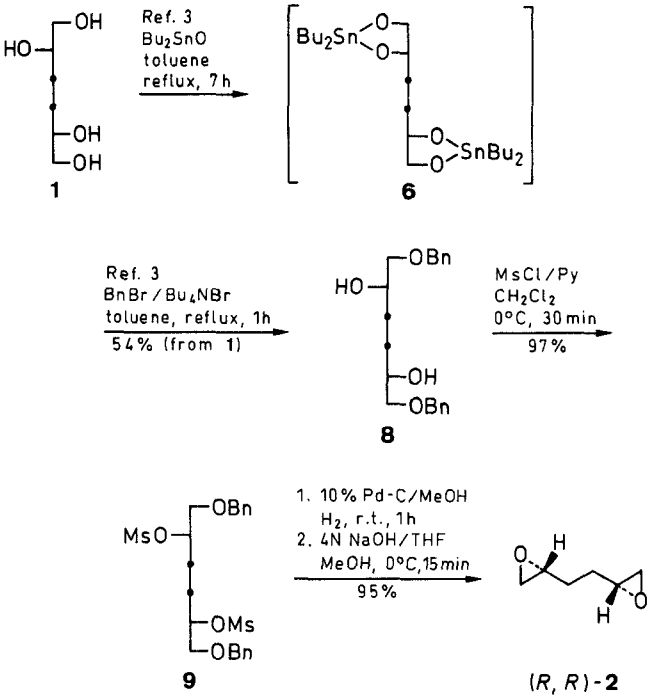
Scheme 2

Table. Benzoylation of (2*S*,5*S*)-Tetrol **1** to give 1,6-Dibenzoyl, 1,5-Dibenzoyl and 1,2,6-Tribenzoyl Derivatives **5a–c**

Method	Yield (%)[a]		
	5a	**5b**	**5c**
A	56	9	12
B	30		28
C	48		20
D	46	20	

[a] Yield of isolated product.

The intermediate organotin derivative **6** used in Method D[2] was utilized for an alternative preparation of (*R,R*)-**2**. Thus, **6**, prepared in situ by heating a solution of **1** and dibutyltin oxide in toluene, was regioselectively converted to the 1,6-dibenzyl ether **8** according to the reported procedure[3] in 54% overall yield from **1** (Scheme 3). The 2,5-*O*-bismethanesulfonate **9** derived from **8** was transformed into (*R,R*)-**2** in 95% yield by hydrogenolytic debenzylation (H_2, Pd-C) followed by basic treatment.

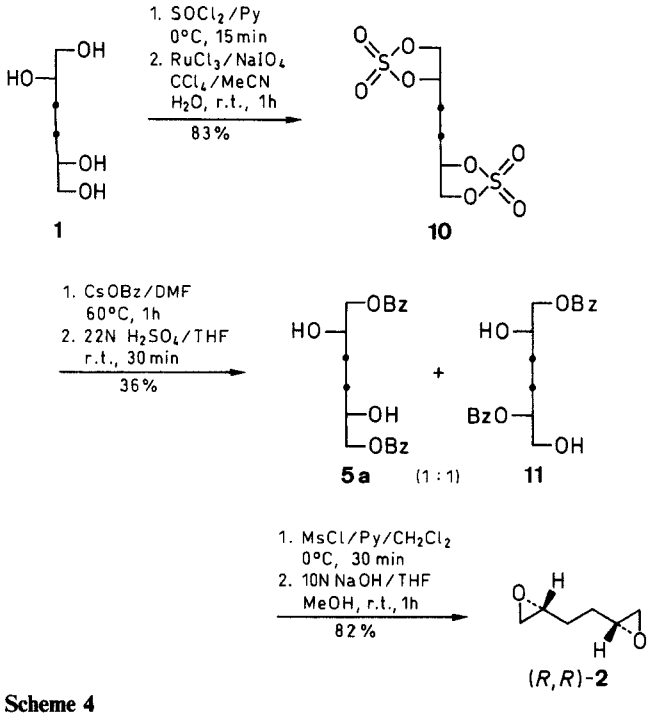


Scheme 3

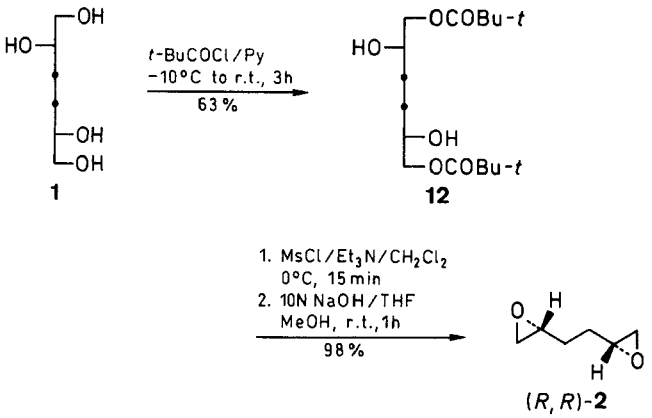
In an alternative procedure for regioselective benzoylation of **1**, we envisioned utilization of the bicyclic sulfate **10** which was available from **1** by treatment with thionyl chloride followed by a catalytic amount of ruthenium tetraoxide (prepared from ruthenium(III) chloride/sodium periodate) in 83% yield based on Sharpless' procedure (Scheme 4).[4] Treatment of **9** with cesium benzoate resulted in nucleophilic ring opening to afford the acyclic sulfate which was without isolation hydrolyzed by acid to give a 1:1 mixture (36% yield) of 1,6- and 1,5-di-*O*-benzoyl derivatives **5a** and **11**. Without separation, this mixture could be converted to (*R,R*)-**2** in 82% yield by two-step sequence involving mesylation and basic treatment.

Although methods developed here complement the one previously reported[1] it does not allow us to obtain (*R,R*)-**2** from **1** in satisfactory overall yield. The best result, however, was obtained when the pivaloyl group was used as a protecting group of the primary alcohol.

Accordingly, the selective protection was carried out by treatment of **1** with 2 equivalents of pivaloyl chloride in pyridine to give the 1,6-dipivalate **12** in 63% yield, which was very smoothly converted to (*R,R*)-**2** by mesylation/basic treatment sequence in almost quantitative yield (Scheme 5). The enantiomeric purity of synthetic (*R,R*)-**2** was determined to be > 99.5% ee.



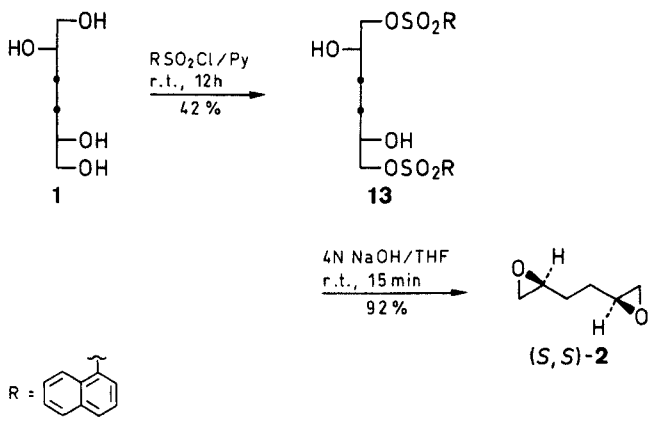
Scheme 4



Scheme 5

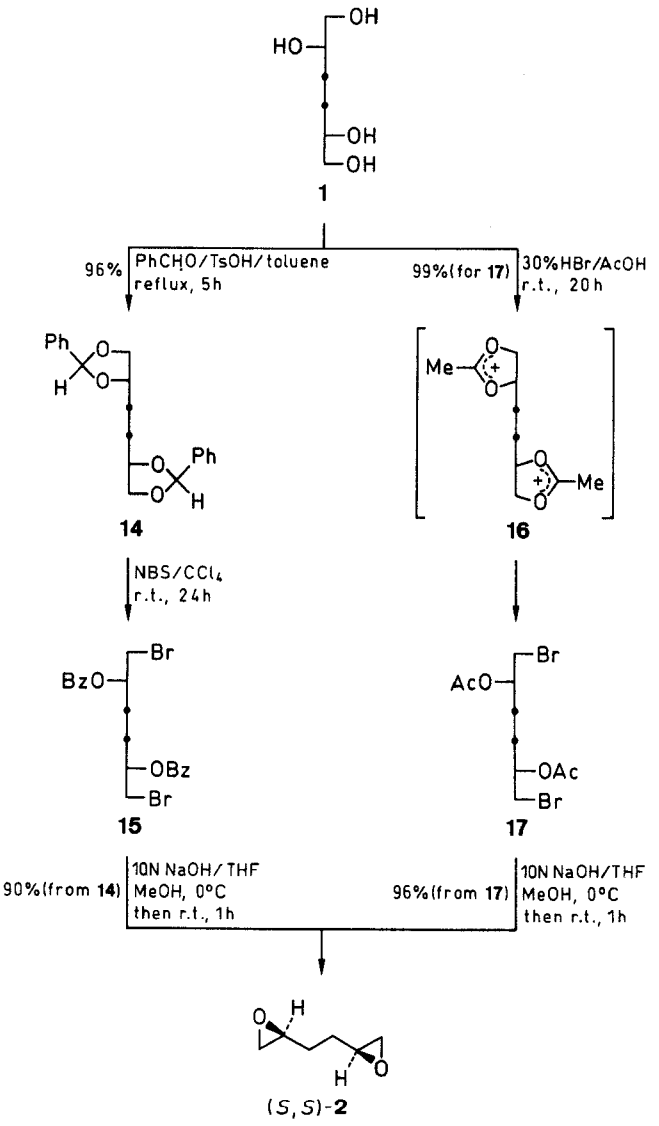
We next examined the preparation of th *S,S*-enantiomer of the diepoxide, (*S,S*)-**2**, from **1**. In our initial study in this regard, we considered using a more bulky sulfonylation reagent to improve the regioselectivity in tosylation employed in the previously reported epoxidation.[1] Thus, **1** was allowed to react with 1-naphthalenesulfonyl chloride in pyridine to provide the 1,6-di-*O*-sulfonyl product **13** in 42% yield (Scheme 6) along with an inseparable mixture of the products. Compound **13** was easily converted to (*S,S*)-**2** under basic conditions, however the overall yield from **1** (38%) was lower than that observed in the previously reported procedure via the 1,6-ditosylate (58%).[1]

Our next attempts to prepare (*S,S*)-**2** were aimed at the diastereoselective introduction of bromine at C-1 and C-6 for obtaining an efficient precursor for epoxidation. Thus, **1** was converted to the bisbenzylidene acetal **14** (with benzaldehyde/*p*-toluenesulfonic acid/toluene) in 96% yield (Scheme 7). Exposing **14** to 2.2 molar equiv of *N*-bromosuccinimide (NBS) in carbon tetrachloride led to regioselective ring opening (Hanessian–Hullar reac-



Scheme 6

tion),[5] furnishing the bisbenzoyloxy bromide **15** as a single product, which was then treated under basic conditions[6] to generate objective (*S,S*)-**2** with the enantiomeric purity of > 99.5% ee and in 90% yield from **14**. In another way, the more convenient direct approach to the primary 1,6-dibromide was successfully achieved by



Scheme 7

treatment of **1** with 30% hydrogen bromide in acetic acid at room temperature. The reaction proceeds via a biscyclic acetoxonium ion **16** which is opened regioselectively by bromide ion[7] to provide the 2,5-diacetoxy-1,6-dibromo derivative **17**.[8] Cyclization to form the diepoxide (*S,S*)-**2** was carried out under basic conditions in 95% overall yield from **1**. This method was easy to execute and provided an excellent overall yield, however the enantiomeric purity was slightly lowered to 97% ee.

In conclusion, among the methods described above, the methods via the di-*O*-pivaloyl intermediate **12** (Scheme 5) and via the bisbenzoyloxy bromide **15** (Scheme 7) provide the best results for the preparation of (*R,R*)-**2** and (*S,S*)-**2**, respectively. The advantages of these synthetic methods are high overall yields [62% and 87% from **1** for (*R,R*)-**2** and (*S,S*)-**2**, respectively] and optical purities (> 99.5% ee), low cost, and easy to conduct and, hence, render these routes superior to previously reported procedures.

Melting points were determined by using a Yanagimoto micro melting point apparatus and are uncorrected. Optical rotations were measured with a JASCO DIP-360 digital polarimeter in a 1-dm cell. IR spectra were determined on a Perkin-Elmer 1710 FTIR spectrophotometer. ^1H and ^{13}C NMR spectra were taken at 300 MHz on a Varian Gemini 300 spectrometer (unless otherwise stated) and at 90 MHz for ^1H NMR on a Varian EM 390 spectrometer with TMS as internal standard. Mass spectra were obtained with a Hitachi RMU-7L double-focusing mass spectrometer at 70 eV. Enantiomeric purity was determined by GC-mass spectral analyses, which were performed with a Delsi Nermag Auto Mass spectrometer operating at 70 eV, interfaced with a Hewlett Packard GC-HP 5890 Series II gas chromatograph, equiped with a 0.25 mm × 25 m Chrompack capillary column packed with WCOT fused silica gel (CP-cyclodextrin-B-236-M-19 is stationary phase). Analytical TLC was performed on Merck precoated silica gel 60 F254 plates. Merck silica gel 60 (230–400 mesh) was used for column chromatography.

(2,5*S*)-1,6-Bis(benzoyloxy)-2,5-hexanediol (5a):

Method A: To a stirred solution of **1** (1.00 g, 6.66 mmol) in pyridine (14 mL) was added a solution of BzCl (1.88 g, 13.4 mmol) in CH_2Cl_2 (5 mL) at 0 °C. After being stirred at 0 °C for 4 h, the mixture was poured into 10% aq HCl (100 mL) at 0 °C and extracted with $CHCl_3$ (3 × 100 mL). The organic phase was washed with H_2O (100 mL), sat. aq $NaHCO_3$ (100 mL), and H_2O (50 mL), and dried ($MgSO_4$). The solvent was evaporated and the residue was chromatographed on silica gel (eluent: $CHCl_3$/MeOH, 20:1). The first fraction afforded (2*S*,5*S*)-1,2,6-tris(benzoyloxy)-5-hexanol (**5c**) (371 mg) as a colorless oil. The second fraction afforded **5a** (1.33 g) as a white solid, which was recrystallized from $CHCl_3$/hexane to give an analytical sample as white needles. The third fraction afforded (2*S*,5*S*)-1,5-bis(benzoyloxy)-2,6-hexanediol (**5b**) (212 mg) as a colorless oil.

5a; yield: 1.33 g (56%); mp 110.5–111.5 °C; $[\alpha]_D^{27}$ + 2.5° (*c* = 2.69, $CHCl_3$).

$C_{20}H_{22}O_6$	calc.	C 67.03	H 6.19
(358.4)	found	66.99	6.21

IR (KBr): ν = 3532 (br, OH), 3058, 2977, 2946, 2916, 2852, 1703, 1601, 1584, 1451, 1397, 1284, 1191, 1178, 1133, 1112, 1095, 1060, 1029, 970, 941, 885, 711 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.64–1.89 [m, 4H, $(CH_2)_2$], 3.11 (d, 2H, *J* = 3.8 Hz, 2 OH), 4.05 (br s, 2H, H-2, H-5), 4.28 (dd, 2H, *J* = 11.4, 6.8 Hz, 2H of H-1, H-6), 4.39 (dd, 2H, *J* = 11.4, 3.6 Hz, 2H of H-1, H-6), 7.42–8.07 (m, 10 H_{arom}).

^{13}C NMR ($CDCl_3$): δ = 29.89, 69.05, 70.10, 128.42, 129.68, 129.84, 133.18, 166.75.

MS (EI): *m/z* (%) = 359 (0.2, M^+ + 1), 341 (0.4), 223 (0.8), 205 (34), 105 (100).

(2*S*,5*S*)-1,6-Bis(benzoyloxy)-2,5-bis(methylsulfonyloxy)hexane (7):

To a cooled (0 °C), stirred solution of **5a** (200 mg, 0.558 mmol) in pyridine (4 mL) was added a solution of $MeSO_2Cl$ (158 mg, 1.38 mmol) in CH_2Cl_2 (2 mL) and the mixture was stirred at 0 °C for 15 min. The mixture was poured into ice-cooled 10% aq HCl (100 mL) and extracted with $CHCl_3$/EtOAc (3 × 50 mL). The combined organic phases were washed with H_2O (50 mL), sat. aq $NaHCO_3$ (50 mL), and H_2O (50 mL). After drying ($MgSO_4$), the solvent was evaporated and the residue was passed through a short column of silica gel (eluent: $CHCl_3$/MeOH, 20:1) to remove unreacted $MeSO_2Cl$, affording **7** (283 mg, 99%) as colorless crystals. A sample was recrystallized from CH_2Cl_2/hexane to give white pillars; mp 108–109 °C; $[\alpha]_D^{28}$ + 14.3° (*c* = 1.13, $CHCl_3$).

$C_{22}H_{26}O_{10}S_2$	calc.	C 51.35	H 5.09
(514.6)	found	51.36	5.06

^1H NMR ($CDCl_3$): δ = 2.00 [m, 4H, $(CH_2)_2$], 3.03 (s, 6H, 2 CH_3), 4.42 (dd, 2H, *J* = 12.4, 6.6 Hz, 2H of H-1, H-6), 4.54 (dd, 2H, *J* = 12.4, 3.3 Hz, 2H of H-1, H-6), 5.10 (m, 2H, H-2, H-5), 7.40–8.06 (m, 10 H_{arom}).

5b; yield: 212 mg (9%); $[\alpha]_D^{29}$ − 15.8° (*c* = 0.46, $CHCl_3$).

IR (film): ν = 3450 (br, OH), 2960, 2956, 2940, 1718, 1452, 1316, 1278, 1118, 1071, 711, 669 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.64–2.06 [m, 4H, $(CH_2)_2$], 2.93 (br s, 1H, OH), 3.09 (br s, 1H, OH), 3.81 (br s, 2H, H-6), 4.04 (br s, 1H, H-2), 4.21–4.38 (m, 2H, H-1), 5.23 (sext, 1H, H-5), 7.36–8.05 (m, 10 H_{arom}).

MS (EI): *m/z* (%) = 359 (0.2, M^+ + 1), 341 (0.3), 237 (0.4), 223 0.6), 218 (1), 205 (25), 105 (100).

5c; yield: 371 mg (12%); $[\alpha]_D^{29}$ − 8.2° (*c* = 2.04, $CHCl_3$).

IR (film): ν = 3500 (br, OH), 2957, 1717, 1493, 1316, 1274, 1114, 710 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.71–1.80 (m, 2H, H-4), 1.93–2.18 (m, 2H, H-3), 2.62 (br s, 1H, OH), 4.08 (br s, 1H, H-5), 4.26 (dd, 1H, *J* = 11.4, 6.6 Hz, H-6), 4.37 (dd, 1H, *J* = 11.4, 3.7 Hz, H-6), 4.50 (dd, 1H, *J* = 11.9, 6.4 Hz, H-1), 4.58 (dd, 1H, *J* = 11.9, 3.7 Hz, H-1), 5.58 (m, 1H, H-2), 7.37–8.06 (m, 15 H_{arom}).

MS (EI): *m/z* (%) (no molecular ion) = 445 (0.2), 432 (0.4), 327 (3), 205 (53), 105 (100).

MS (CI, isobutane): *m/z* (%) = 463 (M^+ + 1, 0.5), 445 (5), 341 (42), 237 (3), 219 (16), 205 (20), 105 (100).

Method B: To a solution of **1** (150 mg, 1.00 mmol) and 4-dimethylaminopyridine (DMAP, 244 mg, 2.00 mmol) in DMF (3 mL) was added a solution of 1-benzoylimidazole in $CHCl_3$ (5 mL), prepared from imidazole (272 mg, 4.00 mmol) and BzCl (281 mg, 2.00 mmol),[9] and the mixture was stirred at 60 °C for 24 h. The mixture was then diluted with Et_2O (100 mL), washed with H_2O (50 mL), and dried ($MgSO_4$). Evaporation of the solvent and chromatography on silica gel (eluent: hexane/EtOAc, 1:1) gave **5a** and **5c** (see Table).

Method C: A solution of **1** (150 mg, 1.00 mmol), 1-(benzoyloxy)-benzotriazole (526 mg, 2.20 mmol), and Et_3N (223 mg, 2.20 mmol) in DMF (6 mL) was stirred at r.t. for 19 h. The mixture was worked up in the same manner as described in Method B to afford **5a** and **5c** (see Table).

Method D: To a solution of **1** (150 mg, 1.00 mmol) in MeOH (10 mL) was added Bu_2SnO (498 mg, 2.00 mmol) and the mixture was refluxed for 1.5 h. The mixture containing the in situ generated bisstanoxane **6** was condensed in vacuo and dioxane (10 mL) was added to the residual solid. The mixture was cooled to 0 °C and a solution of BzCl (309 mg, 2.20 mmol) and Et_3N (223 mg, 2.20 mmol) in dioxane (10 mL) was added. The resulting mixture was stirred at r.t. for 2 h and filtered. The filtrate was concentrated and the residue was chromatographed on silica gel (eluent: $CHCl_3$/MeOH, 20:1) to give **5a** and **5b**.

^{13}C NMR ($CDCl_3$): δ = 26.71, 38.54, 65.20, 78.39, 128.42, 129.15, 129.56, 133.31, 165.81.

MS (EI): m/z (%) = 419 (1, $M^+ - CH_4O_3S$), 379 (1), 322 (4), 296 (10), 217 (6), 200 (13), 179 (8), 174 (9), 105 (100).

(2*S*,5*S*)-1,6-Bis(benzyloxy)-2,5-hexanediol (8):
A mixture of **1** (100 mg, 0.67 mmol) and Bu_2SnO (417 mg, 1.68 mmol) in toluene (15 mL) was refluxed for 7 h. After cooling to r.t., BnBr (458 mg, 2.68 mmol) and Bu_4NBr (259 mg, 0.803 mmol) was added to the mixture containing the bisstanoxane **6** in situ formed and the resulting mixture was refluxed for 1 h. The mixture was cooled to r.t., poured into H_2O (30 mL), and filtered through a Celite pad. The filtrate was separated and the aqueous phase was extracted with Et_2O (3 × 30 mL). The combined organic phases were washed with H_2O (2 × 30 mL), dried ($MgSO_4$), and concentrated. The residual oil was purified by column chromatography on silica gel (hexane/EtOAc, 1:1) to give **8** as a colorless oil; yield: 120 mg (54%).

^1H NMR ($CDCl_3$): δ = 1.54 [m, 4H, $(CH_2)_2$], 3.20 (br s, 2H, 2OH), 3.29 (dd, 2H, J = 10.8, 7.2 Hz, 2H of H-1, H-6), 3.40 (dd, 2H, J = 10.8, 4.8 Hz, 2H of H-1, H-6), 3.76 (m, 2H, H-2, H-5), 4.49 (s, 4H, 2 $PhCH_2$), 7.28 (m, 10 H_{arom}).

^{13}C NMR ($CDCl_3$) ($CDCl_3$): δ = 29.49, 70.24, 73.20, 74.43, 127.65, 128.33, 137.91.

(2*S*,5*S*)-1,6-Bis(benzyloxy)-2,5-bis(methylsulfonyloxy)hexane (9):
To a stirred solution of **8** (289 mg, 0.875 mmol) in pyridine (5 mL) cooled to 0°C, was added a solution of $MeSO_2Cl$ (300 mg, 2.62 mmol) in CH_2Cl_2 (2 mL) and the mixture was stirred at 0°C for 30 min. The mixture was diluted in Et_2O (100 mL), washed with H_2O (50 mL), 10% aq HCl (50 mL), and H_2O (30 mL), and dried ($MgSO_4$). Evaporation of the solvent and purification by short column chromatography on silica gel (eluent: hexane/EtOAc, 2:1) afford **9** as a colorless oil; yield: 415 mg (97%).

^1H NMR ($CDCl_3$, 90 MHz): δ = 1.76 [t, 4H, J = 3.0 Hz, $(CH_2)_2$], 2.96 (s, 6H, 2 CH_3), 3.57 (d, 4H, J = 6.3 Hz, H-1, H-6), 4.51 (s, 4H, 2 $PhCH_2$), 4.90 (m, 2H, H-2, H-5), 7.38 (m, 10 H_{arom}).

^{13}C NMR ($CDCl_3$): δ = 26.35, 38.22, 71.53, 73.14, 80.98, 127.61, 127.65, 128.35, 136.98.

1,2-Bis[(4*S*)-2,2-dioxo-1,3,2-dioxathiolane-4-yl]ethane (10):
To a stirred solution of **1** (300 mg, 2.00 mmol) in pyridine (5 mL) cooled to 0°C, was added a solution of $SOCl_2$ (595 mg, 5.00 mmol) in CH_2Cl_2 (2 mL) and the mixture was stirred at 0°C for 15 min. The mixture was poured into an ice-cooled 10% aq HCl (50 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were washed with H_2O (50 mL) and dried ($MgSO_4$). The solvent was removed by evaporation to give a pale yellow oil, which was dissolved in a mixture of CCl_4/MeCN/H_2O (9 mL, 1:1:1). The resulting solution was cooled to 0°C and $NaIO_4$ (2.14 g, 10.0 mmol) and $RuCl_3 \cdot xH_2O$ (20 mg) were added. After being stirred at r.t. for 1 h, the mixture was diluted with EtOAc (100 mL) and washed with H_2O (100 mL) and sat. aq $NaHCO_3$ (100 mL). Drying ($MgSO_4$) followed by evaporation provided a white solid, which was recrystallized from EtOAc/hexane to give **10** as white needles; yield: 455 mg (83%); mp 111.5–113.5°C; $[\alpha]_D^{29}$ − 38.0° (c = 0.92, MeCN).

$C_6H_{10}O_8S_2$	calc.	C 26.28	H 3.68
(274.3)	found	26.52	3.66

^1H NMR ($CDCl_3$): δ = 2.00–2.22 [m, 4H, $(CH_2)_2$], 4.41 (dd, 2H, J = 8.9, 7.2 Hz, 2H of H-1, H-6), 4.80 (dd, 2H, J = 8.9, 6.2 Hz, 2H of H-1, H-6), 5.08 (m, 2H, H-2, H-5).

^{13}C NMR ($CDCl_3$): δ = 27.41, 71.93, 80.76.

(2*S*,5*S*)-1,6-Bis(pivaloyloxy)-2,5-hexanediol (12):
To a stirred solution of **1** (1.50 g, 10.0 mmol) in pyridine (40 mL) cooled to − 10°C, was added a solution of *t*-BuCOCl (2.41 g, 20.0 mmol) in CH_2Cl_2 (20 mL) and the mixture was stirred at r.t. for 3 h. The mixture was poured into an ice-cooled 10% aq HCl (200 mL) and extracted with Et_2O (3 × 100 mL). The ether solution was washed with H_2O (100 mL), sat. aq $NaHCO_3$ (100 mL), and H_2O (50 mL), and dried ($MgSO_4$). The solvent was evaported and the residue was chromatographed on silica gel (eluent: hexane/EtOAc, 2:1) to give a white solid, which was recrysallized from Et_2O/hexane to yield **12** as white needles; yield: 2.00 g (63%); mp 80.5–81.5°C; $[\alpha]_D^{29}$ − 1.0° (c = 1.57, $CHCl_3$).

$C_{16}H_{30}O_6$	calc.	C 60.36	H 9.50
(318.4)	found	60.49	9.47

IR (KBr): ν = 3261 (br, OH), 2972, 2877, 1720, 1483, 1285, 1168, 1126, 1082 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.19 [s, 18H, 2 $C(CH_3)_3$], 1.62 [m, 4H, $(CH_2)_2$], 3.18 (br s, 2H, 2OH), 3.84 (m, 2H, H-2, H-5), 3.98 (dd, 2H, J = 11.3, 6.4 Hz, 2H of H-1, H-6), 4.07 (dd, 2H, J = 11.3, 4.2 Hz, 2H of H-1, H-6).

^{13}C NMR ($CDCl_3$): δ = 27.09, 29.66, 38.76, 68.25, 69.77, 178.68.

MS (CI, isobutane): m/z (%) = 319 (2, $M^+ + 1$), 302 (18), 301 (100), 217 (25), 199 (40), 185 (73), 115 (22), 101 (31), 85 (77).

Nucleophilic Ring Opening of 10:
To a solution of **10** (200 mg, 0.729 mmol) in DMF (5 mL) was added CsOBz (570 mg, 2.19 mmol) and the mixture was stirred at 60°C for 1 h. DMF was removed in vacuo and THF (5 mL) was added to the residue. To this mixture was added 22 N (60%) H_2SO_4 (0.4 mL) and the mixture was stirred at r.t. for 30 min. After addition of H_2O (50 mL), the mixture was extracted with CH_2Cl_2 (3 × 50 mL) and the combined organic phases were washed with H_2O (50 mL), sat. aq $NaHCO_3$ (50 mL), and H_2O (50 mL), and dried ($MgSO_4$). The solvent was evaported and the residue was chromatographed on silica gel (eluent: hexane/EtOAc, 1:1) to give a 1:1 mixture of **5a** and (2*R*,5*S*)-1,5-bis(benzoyloxy)-2,6-hexanediol **(11)**; total yield: 93 mg (36%). The mixture of the products obtained was used without separation for further reaction.

Further chromatography on silica gel (eluent: hexane/EtOAc, 2:1) afforded **5a** as the first fraction and **11** as the second fraction. The ^1H NMR data for **11** are:

^1H NMR ($CDCl_3$, 90 MHz): δ = 1.83 [m, 4H, $(CH_2)_2$], 3.51 (dd, 1H, J = 12.0, 5.4 Hz, 1H of H-6), 3.78 (dd, 1H, J = 12.0, 4.0 Hz, 1H of 1H of H-6), 4.10 (m, 1H, H-2), 4.43 (m, 2H, H-1), 5.00 (br s, 1H, H-5), 7.28–8.12 (m, 10 H_{arom}).

(2*R*,5*R*)-1,2,5,6-Diepoxyhexane [(*R*,*R*)-2]:
From **7**: To a stirred solution of **7** (457 mg, 0.888 mmol) in a mixture of MeOH/THF (6 mL, 1:1) cooled to 0°C, was added 10 N NaOH (1 mL) and the mixture was stirred at this temperature for 1 h. To this mixture was added $CHCl_3$ (100 mL) and a white solid which separated was filtered through a pad of Celite. The filtrate was washed with H_2O (2 × 30 mL), dried ($MgSO_4$), and concentrated to leave an oil, which was purified by chromatography on silica gel (eluent: hexane/EtOAc, 4:1) followed by distillation to give (*R*,*R*)-**2**; yield: 80 mg (79%); bp 76°C (16 Torr); $[\alpha]_D^{26}$ + 26.8° (c = 5.03, $CHCl_3$) {Lit.[1] $[\alpha]_D^{26}$ + 18.5° (c = 2.22, $CHCl_3$)}.

^1H and ^{13}C NMR spectra of (*R*,*R*)-**2** are identical with those of the substance prepared previously.[1]

From **9**: Compound **9** (350 mg, 0.72 mmol) was dissolved in MeOH (5 mL) and hydrogenated over 10% Pd-C (100 mg) at r.t. for 2 h. The solution was filtered and concentrated to give (2*S*,5*S*)-2,5-bis(methylsulfonyloxy)-1,6-hexanediol as a colorless oil, which was without purification dissolved in a mixture of THF/MeOH (6 mL, 2:1). The solution was stirred and cooled at 0°C. To this was added 4 N NaOH (0.5 mL) and stirring was continued for 15 min. The mixture was diluted with $CHCl_3$ (100 mL), washed with H_2O (50 mL), dried ($MgSO_4$), and concentrated. The residue was purified by silica gel column chromatography (eluent: hexane/EtOAc, 4:1) to give (*R*,*R*)-**2**; yield: 78 mg (95%).

From the Mixture of **5a** *and* **11**: To a stirred solution of the 1:1 mixture (720 mg, 2.00 mmol) of **5a** and **11**, obtained from the disulfate **10**, in pyridine (10 mL) was added a solution of $MeSO_2Cl$ (575 mg, 5.00 mmol) in $CHCl_3$ (2 mL) at 0°C and stirring was continued for 30 min. The mixture was poured into an ice cold 10% aq HCl (100 mL) and extracted with $CHCl_3$ (3 × 100 mL). The extracts were washed with H_2O (100 mL), sat. aq $NaHCO_3$ (100 mL), and H_2O (50 mL), and dried ($MgSO_4$). Evaporation of the solvent gave crude products (1.00 g, 97%) of the corresponding 2,5- and 1,5-di-*O*-methanesulfonates as a pale yellow oil, which was

without purification dissolved in a mixture of MeOH/THF (3 mL, 2:1). The solution was cooled to 0 °C and 10 N NaOH (1 mL) was added. After being stirred at r.t. for 1 h, and diluted with $CHCl_3$ (100 mL), a white solid which separated was removed by filtration through a pad of Celite. The filtrate was washed with H_2O (2 × 30 mL), dried ($MgSO_4$), and concentrated. The residue was purified by a silica gel column (eluent: hexane/EtOAc, 4:1) to give (*R,R*)-**2**; *yield*: 187 mg (82%).

From **12**: To a stirred solution of **12** (589 mg, 1.85 mmol) and Et_3N (607 mg, 6.00 mmol) in $CHCl_3$ (6 mL) ice-cooled, was added a solution of $MeSO_2Cl$ (550 mg, 4.80 mmol) in $CHCl_3$ (2 mL) and stirring was continued for 15 min. The mixture was diluted with $CHCl_3$ (200 mL) and washed with H_2O (50 mL) and 10% aq HCl (50 mL). The solution was dried ($MgSO_4$) and concentrated to give (2*S*,5*S*)-2,5-bis(methylsulfonyloxy)-1,6-bis(pivaloyloxy)hexane as a colorless crude oil, which was solidified by cooling and was sufficiently pure for further conversion. Pure sample was obtained by recrystallization from Et_2O/hexane as white needles, mp 58–60 °C. The resulting bismethanesulfonate (850 mg, 1.79 mmol) was dissolved in a 2:1 mixture of THF/MeOH (6 mL) and cooled in an ice bath. To this solution was added 10 N NaOH (2 mL) and the mixture was stirred at r.t. for 1 h, and diluted with $CHCl_3$ (100 mL). A white solid which separated was removed by filtration through a pad of Celite. The filtrate was washed with H_2O (2 × 30 mL), dried ($MgSO_4$), and concentrated to dryness to give pure (*R,R*)-**2**; yield: 207 mg (98%).

(2*S*,5*S*)-1,6-Bis[(1-naphthylsulfonyl)oxy]-2,5-hexanediol (13):
A solution of **1** (300 mg, 2.00 mmol) and 1-naphthalenesulfonyl chloride (997 mg, 4.40 mmol) in pyridine (6 mL) was stirred at r.t. for 12 h. The mixture was poured into 10% aq HCl (50 mL) and extracted with EtOAc (3 × 50 mL). The combined extracts were washed with H_2O (100 mL), dried ($MgSO_4$), and concentrated. The residue was purified by chromatography on silica gel (eluent: $CHCl_3$/EtOAc, 5:1) to give **13** as a colorless gum; yield: 441 mg (42%); $[\alpha]_D^{26}$ + 5.59° (*c* = 0.59, $CHCl_3$).

$C_{26}H_{26}O_8S_2$	calc.	C 58.85	H 4.94
(530.6)	found	58.31	5.14

IR (film): ν = 3508 (br, OH), 3062, 2955, 1724, 1509, 1455, 1358, 1178, 1141, 966, 933, 840, 806, 771, 680 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.30 [m, 4 H, $(CH_2)_2$], 3.04 (br s, 2 H, 2 OH), 3.62 (m, 2 H, H-2, H-5), 3.74 (dd, 2 H, *J* = 10.2, 6.3 Hz, 2 H of H-1, H-6), 3.83 (dd, 2 H, *J* = 10.2, 3.9 Hz, 2 H of H-1, H-6), 7.49–8.56 (m, 14 H_{arom}).

^{13}C NMR ($CDCl_3$): δ = 28.45, 68.76, 73.66, 123.99, 124.52, 127.25, 128.13, 128.75, 128.88, 130.57, 133.98, 135.43.

MS (EI): *m/z* (%) = 322 (5, $M^+ - C_{10}H_8O_3S$), 291 (4), 210 (3), 209 (6), 208 (52), 191 (4), 135 (8), 134 (7), 128 (22), 127 (80), 126 (18), 116 (14), 115 (48), 102 (7), 101 (100).

1,2-Bis[(4*S*)-2-phenyl-1,3-dioxolan-4-yl]ethane (14):
A solution of **1** (4.13 g, 27.5 mmol), benzaldehyde (7.00 g, 66.0 mmol), and $TsOH \cdot H_2O$ (10 mg, 0.05 mmol) in toluene (45 mL) was refluxed for 5 h. The reaction mixture was diluted with Et_2O (200 mL) and washed with sat. aq $NaHCO_3$ (50 mL) and H_2O (50 mL). The solution was dried ($MgSO_4$) and the solvent was evaporated to give a brown oily residue, which was purified by silica gel chromatography (eluent: hexane/EtOAc, 6:1) to furnish **14** as a yellowish oil; yield: 8.66 g (96%).

$C_{20}H_{22}O_4$	calc.	C 73.60	H 6.79
(326.4)	found	73.40	6.84

IR (film): ν = 3063, 3035, 2935, 2880, 2760, 1495, 1456, 1403, 1311, 1294, 1220, 1067, 1027, 970, 916, 850 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.66–2.02 [m, 4 H, $(CH_2)_2$], 3.63–3.78 (m, 2 H, H-1, H-6), 4.11–4.37 (m, 4 H, H-1, H-2, H-5, H-6), 5.84, 5.95, 5.97 (3 s, total 2 H in 2.6:1:1 ratio, 2 PhCH for 2 diastereomers), 7.38–7.54 (m, 10 H_{arom}).

MS (EI): *m/z* (%) = 326 (3, M^+), 325 (6), 220 (4), 219 (10), 205 (5), 203 (8), 149 (12), 114 (30), 105 (100).

(2*S*,5*S*)-1,2,5,6-Diepoxyhexane [(*S,S*)-2]:
From **13**: To an ice-cooled solution of **13** (207 mg, 0.390 mmol) in THF (4 mL) was added 4 N NaOH (0.5 mL) and the mixture was stirred at r.t. for 15 min. The mixture was diluted with Et_2O (50 mL), washed with H_2O (30 mL), and dried ($MgSO_4$). Evaporation of the solvent and short column chromatography on silica gel (eluent: hexane/EtOAc, 4:1) and distillation afforded (*S,S*)-**2** as a colorless oil; yield: 41 mg (92%); bp 76 °C (16 Torr) [Lit.[1] bp 75–80 °C (42 Torr)]; $[\alpha]_D^{26}$ − 26.4° (*c* = 1.86, $CHCl_3$) {Lit.[1] $[\alpha]_D^{26}$ − 19.0° (*c* = 1.26, $CHCl_3$)}.

^1H and ^{13}C NMR spectra of (*S,S*)-**2** are identical with those of the substance prepared previously.[1]

From **14**: A solution of **14** (8.66 g, 26.5 mmol) and NBS (10.38 g, 58.3 mmol) in CCl_4 (50 mL) was stirred at r.t. for 24 h. The resulting suspension was filtered and the filtrate was washed with sat. aq $NaHCO_3$ (50 mL) and brine (50 mL). Drying ($MgSO_4$) and evaporation of the solvent gave (2*S*,5*S*)-2,5-bis(benzoyloxy)-1,6-dibromohexane (**15**) as a pale yellow oil, which was used without purification. Thus, crude **15** obtained was dissolved in a mixture of THF/MeOH (60 mL, 2:1) and cooled to 0 °C. To this solution was added 10 N NaOH (25 mL) and the mixture was stirred at r.t. for 1 h. The reaction mixture was diluted with $CHCl_3$ (600 mL) and a white solid which separated was removed by filtration through a pad of Celite and the filtrate was washed with H_2O (2 × 200 mL), and dried ($MgSO_4$). Evaporation of the solvent followed by purification by silica gel chromatography (eluent: hexane/EtOAc, 4:1) afforded (*S,S*)-**2** as a colorless oil; yield: 2.72 g (90%).

From **1** *via* **17**: To a cold 30% AcOH solution of HBr (4 mL) was added **1** (300 mg, 2.00 mmol), and the mixture was stirred at r.t. for 20 h. The mixture was poured into cold H_2O (100 mL), neutralized with Na_2CO_3, and extracted with CH_2Cl_2 (3 × 50 mL). The combined extracts were washed with H_2O (50 mL), dried ($MgSO_4$), and concentrated to give (2*S*,5*S*)-2,5-diacetoxy-1,6-dibromohexane (**17**)[8] as a pale yellow oil, which was used without purification; yield: 712 mg (99%).

Compound **17** (712 mg, 1.98 mmol) was dissolved in a mixture of THF/MeOH (6 mL, 2:1). To this solution cooled to 0 °C, was added 10 N NaOH (1.6 mL) and the mixture was stirred at r.t. for h. The reaction mixture was diluted with $CHCl_3$ (100 mL) and a white solid which separated was removed by filtration. The filtrate was washed with H_2O (2 × 30 mL), dried ($MgSO_4$), and concentrated to give pure (*S,S*)-**2** as a colorless oil; yield: 217 mg (96%).

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