Selective Manipulation of Hydroxy Groups in (2*S*,3*S*)-Threitol

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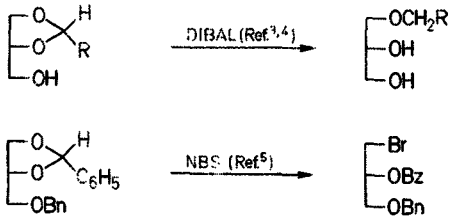
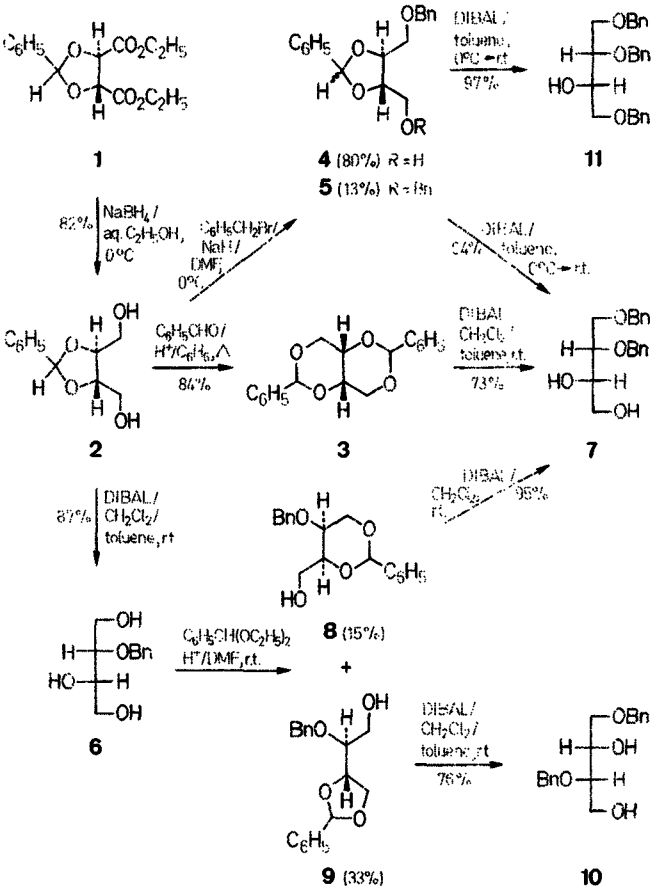
Systematic transformation of diethyl (2*R*,3*R*)-tartrate into a number of protected or functionalized derivatives of threitol, which are important precursors for many natural products, is carried out employing reductive and oxidative cleavage reactions of benzylidene acetal bond.

Optically active threitol would have greater utility in the syntheses of natural products and physiologically active compounds provided that selective protection or functionalization among the hydroxy groups could be possible. Although some investigations leading to the selective modification of optically active threitol have been known[1], we disclose here some new results affording the selectively protected or functionalized threitols in conjunction with our recent synthetic efforts using chiral glycerol building blocks[2]. We reported two cleavage reactions for the regioselective modification of two contiguous hydroxy groups of glycerol *via* 1,2-*O*-benzylidene derivatives, one by reductive cleavage using diisobutylaluminum hydride[3,4] and the other by oxidative cleavage using *N*-bromosuccinimide[5].



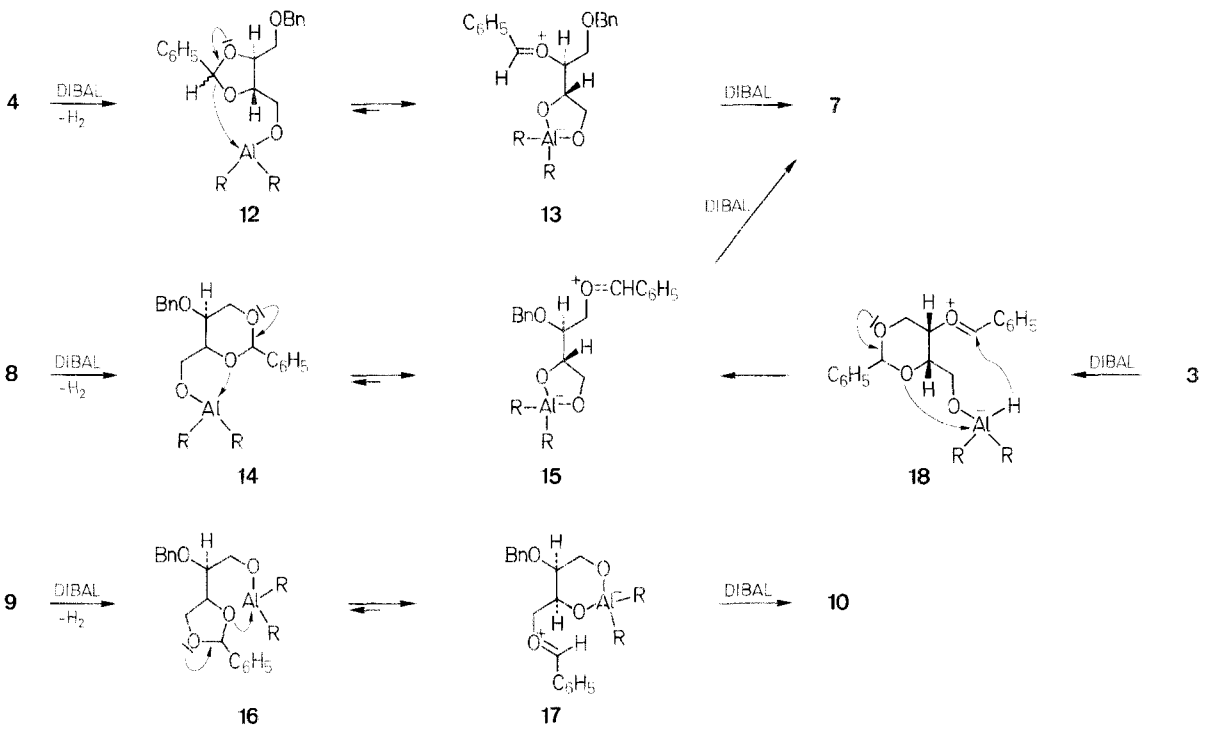
Our key starting material (2*S*,3*S*)-2,3-*O*-benzylidenethreitol (**2**) was prepared in 82% yield from diethyl (2*R*,3*R*)-2,3-*O*-benzylidenetartrate (**1**)[6] by reduction with sodium borohydride in ethanol[7]. Treatment of **2** with benzaldehyde in refluxing benzene in the presence of a catalytic amount of *p*-toluenesulfonic acid yielded 1,3-:2,4-di-*O*-benzylidenethreitol (**3**)[8] in 77% yield as a single epimer *via* concomitant benzylidenation and rearrangement. On the other hand, **2** was treated with one equivalent of benzyl bromide in the presence of sodium hydride to give 1-*O*-benzyl-2,3-*O*-benzylidenethreitol (**4**) in 80% yield accompanied by 1,4-di-*O*-benzyl-2,3-*O*-benzylidenethreitol (**5**)[6] in 13% yield. The latter was also prepared in 90% yield by using more than five equivalents of the alkylating agent. As shown in Scheme **A**, first, we applied the reductive cleavage using diisobutylaluminum hydride (DIBAL) to the benzylidene acetals of threitol to give the corresponding benzyl ethers[3,4]. The compound **2**, upon treatment with five equivalents of DIBAL in dichloromethane, underwent smooth cleavage to give 2-*O*-benzylthreitol[9,10] (**6**) in 87% yield which was further converted into two isomeric *O*-benzylideneacetals **8** and **9**, in 15 and 33% yield respectively. Although **6** has been obtained directly from **1** by using a large excess of DIBAL[4] or an excess of a mixture of lithium aluminum hydride and aluminum chloride[12,13], the present synthesis proved to be more practical for a large scale preparation.



Scheme A

Interestingly, highly regioselective cleavage occurred in variably at proximal position to the hydroxy group when the benzylidene acetals possessing a hydroxy group, **4**, **8**, and **9**, were exposed to DIBAL under the same conditions. Thus, **4** and **8** afforded the same product, 1,2-di-*O*-benzylthreitol (**7**) in 94 and 95% yield, respectively, while **9** afforded 1,3-di-*O*-benzylthreitol (**10**) in 76% yield. Moreover, the bis-benzylidene acetal (**3**) selectively furnished **7** in 73% under the same reduction conditions. 1,2,3-Tri-*O*-benzylthreitol (**11**) could be obtained from 1,4-di-*O*-benzyl-2,3-*O*-benzylidenethreitol (**5**) without difficulty on treatment with two equivalents of the hydride reagent.

As shown in Scheme **B**, we reasoned that the remarkable regioselectivity observed in the reaction of the compounds, **4**, **8**, and **9** may be directed by initial aluminum-oxygen bond formation at the primary hydroxy group followed by complexation at proximal acetal oxygen leading to the corresponding betaines **13**, **15**, and **17**, *via* the aluminum alkoxides **12**, **14**, and **16**. The former two gave the same benzyl ether **7** and the latter afforded the isomeric benzyl ether **10** as end products, respectively. The bis-acetal **3**, on the other hand, may also interact at the primary oxygen to

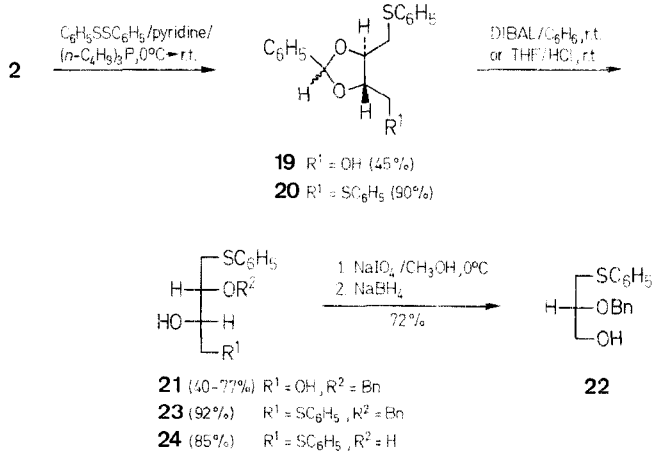


Bn = benzyl
R = *i*-butyl

Scheme B

form the betain **18**, which may be sequentially reduced, rearranged, and reduced again to give 1,2-di-*O*-benzylthreitol (**7**) *via* the same intermediate **15** generated from **8**.

Scheme C shows the conversion of 2,3-*O*-benzylidenethreitol (**2**) to the phenylthiothreitols employing the reductive cleavage reaction. Reaction of **2** with each one equivalent of diphenyl disulfide and tri-*n*-butylphosphine[11,14] gave 2,3-*O*-benzylidene-1-phenylthiothreitol (**19**) and 2,3-*O*-benzylidene-1,4-diphenylthiothreitol (**20**), in 45 and 15% yield respectively. The yield of **20** could be increased to 90% yield using three equivalents of diphenyl disulfide and tri-*n*-butylphosphine. Treatment of **19** with DIBAL gave a single product selectively in 77% yield which was shown to be 2-*O*-benzyl-1-phenylthiothreitol (**21**), as it gave 2-*O*-benzyl-1-phenylthioglycerol (**22**) in 72% overall yield by sequential treatment with sodium periodate and sodium borohydride. Under the same reduction conditions, **20** afforded 2-*O*-benzyl-1,4-diphenylthiothreitol (**23**) in 92% yield. On acid hydrolysis, **20** gave 1,4-diphenylthiothreitol (**24**) in 85% yield.

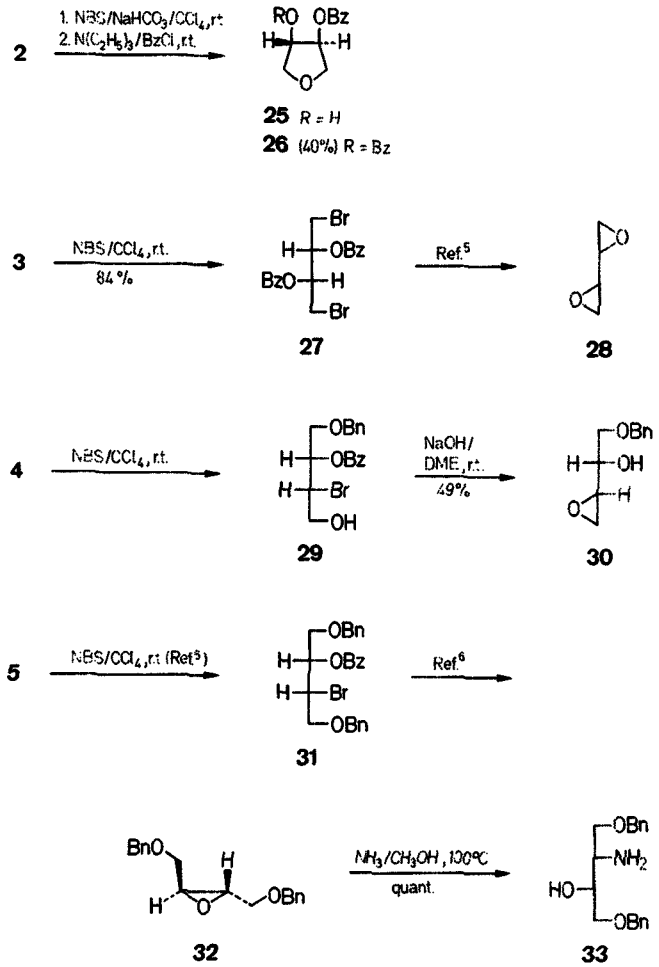


Bn = benzyl
DIBAL = diisobutylaluminum hydride

Scheme C

Reaction of *N*-bromosuccinimide (NBS) with cyclic sugar derivatives possessing benzylidene acetal moiety has been extensively investigated, especially by Hanessian and co-workers[13–17]. The cleavage has been found to be greatly affected by stereochemical environment, however, effect of neighboring hydroxy group in the cleavage reaction has not been fully investigated. Thus, treatment of **2** with one equivalent of NBS in carbon tetrachloride furnished *trans*-3-benzoyloxy-4-hydroxytetrahydrofuran (**25**) as an unstable oil which was immediately treated with benzoyl chloride to give *trans*-3,4-dibenzoyloxytetrahydrofuran (**26**) in 40% overall yield (Scheme **D**). On the same oxidative treatment **3** gave 2,3-dibenzoyloxy-1,4-dibromobutane (**27**) in 84% yield indicating selective cleavage at less substituted and less hindered position. Conversion of **27** into 1,2; 3,4-diepoxybutane (**28**)[18] was attempted by the same basic conditions which have been successfully applied to convert 2-benzoyloxy-3-benzyloxypropyl bromide into *O*-benzylglycidol in good yield[5]. However, high volatility and high water solubility of the product **28** did not allow us its isolation from the reaction mixture in satisfactory yield though clean formation of the epoxide **28** could be detected chromatographically.

Regioselective cleavage at the proximal position to the hydroxy group was observed when **4** was exposed to NBS under the same conditions to give rise to 3-benzoyloxy-4-benzyloxy-2-bromo-1-butanol (**29**) as an unstable oil which was immediately converted into 1-benzyloxy-3,4-epoxy-2-butanol (**30**) in 49% overall yield by treating with sodium

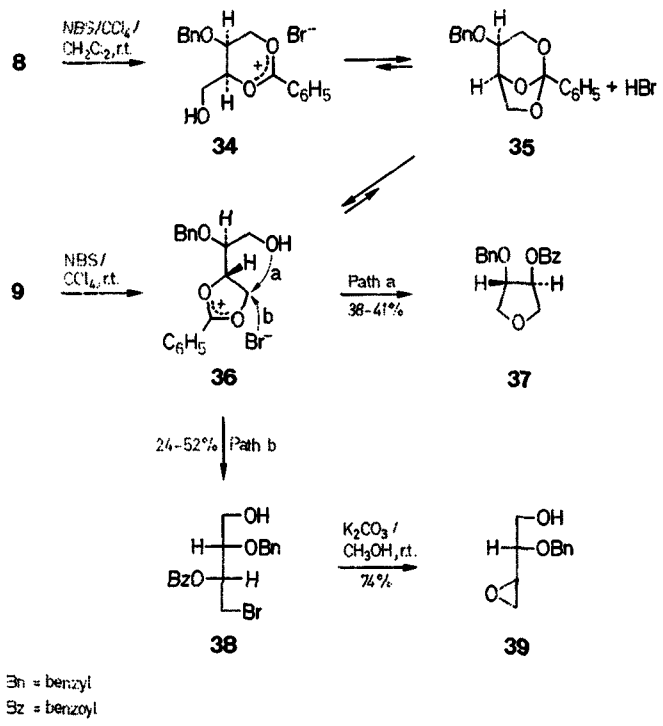


Scheme D

hydroxide in dimethoxyethane[5] (Scheme D). This compound has been already obtained in more lengthy sequence of reactions from optically active tartrate[19].

Conversion of **5** into the epoxide **32** *via* the bromobenzoate **31** has been already reported by using the same NBS conditions[6]. The epoxide **32** thus obtained was heated with methanolic ammonia in a sealed tube to give 2-amino-1,4-di-*O*-benzylthreitol **(33)** in quantitative yield (Scheme D).

When both of the isomeric **8** and **9** were exposed to NBS under the same conditions, they furnished a mixture of the same products, *trans*-3-benzoyloxy-4-benzyloxytetrahydrofuran **(37)** and 3-*O*-benzoyl-2-*O*-benzyl-4-bromo-1-butanol **(38)** respectively, suggesting the intervention of the same intermediate **(35)**, *via* **34** and **35** from the former **(8)** and directly from the latter **(9)**, which in turn was collapsed to either **37** via route *a* or **38** via route *b* (Scheme E). The structure of **38** could be deduced by its facile conversion into 2-benzyloxy-3,4-epoxy-1-butanol **(39)** in 74% yield under basic conditions. A similar rearrangement may also be involved under the NBS cleavage conditions in the formation of **25** from **2** though we could not isolate any bromide corresponding to **38**. The sulfide **19** and **20**, however, did not give any isolable material on the same treatment with NBS presumably owing to instability of the sulfur group under these conditions.



Scheme E

In conclusion a number of protected or functionalized threitol derivatives have been systematically prepared from diethyl (2*R*,3*R*)-tartrate by employing two cleavage reactions of benzylidene acetal bond, one by reductive with diisobutylaluminum hydride and the other by oxidative with *N*-bromosuccinimide.

All reactions were carried out under argon. IR spectra were measured with a JASCO A-102 spectrophotometer. ^{1}H-NMR spectra were recorded on a JEOL-PMX 60 and a FX 100 spectrometers. Mass spectra were measured with a JEOL-OISG-2 instrument. Optical rotations were measured with a JASCO-DIP-4 *automatic polarimeter.*

(2*S*,3*S*)-2,3-*O*-Benzylidenethreitol (2):
Diethyl (2*R*,3*R*)-2,3-*O*-Benzylidenetartrate **1**[6]; (60.0 g, 0.2 mol) in *ethanol (400 ml) is added to a stirred solution* of sodium borohydride (11.4 g, 0.3 mol) in ethanol (300 ml) at 0°C. After stirring for 2.5 h at 0°C, the mixture is evaporated *in vacuo*. The residue is taken into ethyl acetate (500 ml) and the solution is washed with saturated brine (3 × 100 ml), dried with sodium sulfate, and evaporated *in vacuo*. The crude product is distilled under vacuum to give pure **2** as a viscous oil; yield: 35.3 g (82%); b.p. 135°C/0.02 torr; $[\alpha]_D^{23}$ + 10.1° (*c* 1.20, $CHCl_3$) [Lit.[6], $[\alpha]_D^{20}$ + 7.4° (*c* 1.0, $CHCl_3$).

(2*S*,3*S*)-1,3:2,4-Di-*O*-Benzylidenethreitol (3):
A solution of **2** (1.0 g, 4.76 mmol) and benzaldehyde (556 mg, 5.24 mmol) in benzene (25 ml) is refluxed for 2.5 h in the presence of *p*-toluenesulfonic acid (10 mg) with removal of water using a Dean-Stark trap. After cooling the separating crystals are collected by suction filtration and the filtrate is washed with saturated aqueous sodium hydrogen carbonate (20 ml), dried with sodium sulfate, and evaporated *in vacuo* to give a crystalline solid. The combined crystalline materials are recrystallized from benzene to give **3** as colorless needles; yield: 1.20 g (84%); m.p. 218–220°C (Lit.[8], m.p. 217–218°C); $[\alpha]_D^{23}$ + 79.0° (*c* 0.61, $CHCl_3$).

^{1}H-NMR ($CDCl_3$/TMS_{int}): δ = 3.86–4.42 (m, 6H); 5.58 (s, 2H); 7.16–7.42 (m, 6H); 7.42–7.64 ppm (m, 4H).

MS (70 ev): *m/e* = 298 (M^+), 105 (100%).

(2*S*,3*S*)-1-*O*-Benzyl-2,3-*O*-benzylidenethreitol (4) and (2*S*,3*S*)-1,4-Di-*O*-benzyl-2,3-*O*-benzylidenethreitol (5):
To a stirred suspension of sodium hydride (60% in oil, 411 mg, 10.3 mmol), in dimethylformamide (14.5 ml) is added **2** (2.0 g,

9.51 mmol) in dimethylformamide (11.5 ml) dropwise at −20 °C followed by benzyl bromide (1.71 g, 10 mmol) at the same temperature and the stirring is continued for 2 h at 0 °C. After the reaction is quenched by addition of water (20 ml), the mixture is extracted with dichloromethane (3 × 50 ml). The extract is washed with saturated brine (20 ml), dried with magnesium sulfate, and evaporated *in vacuo*. The residual oil is purified by chromatography on silica gel column (80 g) using a mixture of *n*-hexane and ether (4:1 to 1:1 v/v) as eluent to give **5**; yield: 490 mg (13%); $[\alpha]_D^{18}$ + 8.7° (*c* 1.00, $CHCl_3$) [Lit.[6], $[\alpha]_D^{20}$ + 10.1° (*c* 1.4, $CHCl_3$)]; and **4** yield: 2.30 g (81%), both as pale yellow oil.

4:

$C_{18}H_{20}O_4$	calc.	C 71.98	H 6.71
(300.3)	found	71.73	6.59

IR (Film): ν = 3420 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS_{int}): δ = 2.02–2.52 (m, 1H, exchangeable with D_2O); 3.28–4.32 (m, 6H); 4.50 (s, 2H); 5.87 (s, 1H); 7.15–7.62 ppm (m, 10H).

MS (70 ev): *m/e* = 300 (M^+), 91 (100%).

5: Spectral data are identical with those reported[6].

(2*S*,3*S*)-2-*O*-Benzylthreitol (6):

To a stirred solution of **2** (9.6 g, 46 mmol) in dichloromethane (200 ml) is added a solution of diisobutylaluminum hydride in toluene [152 ml (228 mmol) of 1.5 M solution] dropwise at 0 °C and the stirring is continued for 14 h at room temperature. Then, methanol (10 ml) followed by saturated aqueous ammonium chloride (30 ml) is added to the mixture at 0 °C and the mixture is stirred for 5 hours with dichloromethane (100 ml). The mixture is filtered through Celite and the organic layer is separated and evaporated *in vacuo*. The residue is taken into chloroform (200 ml) and insoluble material is removed by filtration. Evaporation of the solvent *in vacuo* gives practically pure **6** as colorless crystals which can be recrystallized from chloroform as colorless leaflets; yield: 8.4 g (87%); m.p. 74–75.5 °C (Lit.[10], m.p. 69–72 °C); $[\alpha]_D^{23}$ + 14.67° (*c* 2.00, CH_3OH) [Lit.[10], $[\alpha]_D^{23}$ + 15.7° (*c* 1.00, CH_3OH)]. Spectral data are identical with those reported[10].

Formation of (2*S*,3*S*)-1,3-*O*-Benzylidene-2-*O*-benzylthreitol (8) and (2*S*,3*S*)-1,2-*O*-Benzylidene-3-*O*-benzylthreitol (9) from 6:

A solution of **6** (1.0 g, 4.7 mmol) and benzaldehyde diethyl acetal (1.2 g, 6.6 mmol) in dimethylformamide (10 ml) is stirred in the presence of *p*-toluenesulfonic acid (9 mg) at room temperature. After 10 h, the mixture is diluted with ether (50 ml) and the mixture is washed with saturated aqueous sodium hydrogen carbonate (20 ml) and saturated brine (20 ml), dried with sodium sulfate, and evaporated *in vacuo*. The oily residue is purified by chromatography on silica gel column (60 g) using a mixture of ethyl acetate and *n*-hexane (1:3, v/v) as eluent to give **9** (473 mg, 33%) as less polar fraction as an epimeric mixture at benzylidene carbon and **8** (213 mg, 15%) as more polar fraction as a single epimer.

8; m.p. 108.5–110 °C; $[\alpha]_D^{18}$ + 63.9° (*c* 1.00, $CHCl_3$).

$C_{18}H_{20}O_4$	calc.	C 71.98	H 6.71
(300.3)	found	71.80	6.63

IR (Film): ν = 3300 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS_{int}): δ = 1.94 (br s, 1H); 3.38 (d, 1H, *J* = 2 Hz); 3.53–4.08 (m, 5H); 4.43 (d, 1H, *J* = 12 Hz); 4.80 (d, 1H, *J* = 12 Hz); 5.56 (s, 1H); 7.20–7.56 ppm (m, 10H).

MS (70 ev): *m/e* = 300 (M^+), 91 (100%).

9; b.p. 190–200 °C/0.42 torr. (Kugelrohr).

$C_{18}H_{20}O_4$	calc.	C 71.98	H 6.71
(300.3)	found	71.92	6.81

MS (High Resolution): *m/e* = 300.1351 (calc. 300.1352).

IR (Film): ν = 3452 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS_{int}): δ = 2.15 (br s, 1H); 3.42–3.78 (m, 8H); 6.75, 6.92 (2 s, each 1H), 7.20–7.56 ppm (m, 10H).

MS (70 ev): *m/e* = 300 (M^+), 91 (100%).

(2*R*,3*R*)-1,2-Di-*O*-benzylidenethreitol (7):

Method A, from **3**: To a stirred solution of **3** (5.0 g, 16.8 mmol) in dichloromethane (60 ml) is added a solution of diisobutylaluminum hydride in toluene [67 ml (100 mmol) of 1.5 M solution] dropwise at 0 °C and the stirring is continued for 5 h at room temperature. Then, methanol (10 ml) followed by saturated aqueous ammonium chloride (10 ml) is added to the mixture and the mixture is stirred for 24 hours with dichloromethane (100 ml). The mixture is filtered through Celite and the organic layer is separated, washed with saturated brine (50 ml), and evaporated *in vacuo*. The residue is taken into chloroform (150 ml) and insoluble material is removed by filtration. Evaporation of the solvent *in vacuo* followed by distillation gives pure **7** as a colorless oil; yield: 3.82 g (73%); b.p. 190–200 °C/0.6 torr (Kugelrohr); $[\alpha]_D^{20}$ + 35.32° (*c* 1.01, $CHCl_3$).

$C_{18}H_{22}O_4$	calc.	C 71.50	H 7.33
(302.4)	found	71.36	7.11

MS (High Resolution): *m/e* = 302.1514 (calc. 302.1516).

IR (Film): ν = 3420 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS_{int}): δ = 2.61 (s, 2H, exchangeable with D_2O); 3.60 (s, 6H); 4.37–4.82 (m, 4H); 7.25 ppm (s, 10H).

Method B, from **8**: To a stirred solution of **8** (247 mg, 0.82 mmol) in dichloromethane (3 ml) is added dropwise diisobutylaluminum hydride in dichloromethane [5.7 ml (5.7 mmol) of 1.0 M solution] at 0 °C and the stirring is continued for 24 h at room temperature. Then, methanol (few drops) followed by saturated aqueous ammonium chloride (5 ml) is added to the mixture and the mixture is stirred for several hours with dichloromethane (50 ml). The mixture is filtered through Celite and the organic layer is separated, and evaporated *in vacuo*. The residue is taken into chloroform (30 ml) and insoluble material is removed by filtration. Evaporation of the solvent *in vacuo* followed by distillation gives pure **7** as a colorless oil; yield: 235 mg (95%); b.p. 200–220 °C/0.5 torr (Kugelrohr); $[\alpha]_D^{20}$ + 33.20° (*c*, 0.99, $CHCl_3$). Spectral data are completely identical with those of **7** obtained from **3**.

Method C, from **4**: To a stirred solution of **4** (1.93 g, 6.4 mmol) in toluene (15 ml) is added diisobutylaluminum hydride in toluene [15.0 ml (22.5 mmol) of 1.5 M solution] dropwise at 0 °C and the stirring is continued for 4 h at the same temperature and for 1 h at room temperature. Then, saturated ammonium hydroxide (10 ml) and tetrahydrofuran (30 ml) is added to the mixture and is stirred for 33 h at room temperature. The mixture is filtered through Celite and the filtrate is evaporated *in vacuo*. The residue is extracted with ether (150 ml) and the extract is dried with magnesium sulfate, evaporated *in vacuo*, and purified by chromatography on silica gel column (40 g) using a mixture of chloroform and methanol (19:1 v/v) as eluent to give **7** as a pale yellow oil; yield: 1.82 g (94%); b.p. 240 °C/0.3 torr (Kugelrohr); $[\alpha]_D^{20}$ + 31.2° (*c* 1.03, $CHCl_3$), which is identical with the product obtained from **8**.

(2*S*,3*S*)-1,3-Di-*O*-benzylthreitol (10):

To a stirred solution of **9** (1.46 g, 4.87 mmol) in dichloromethane (10 ml) is added dropwise a solution of diisobutylaluminum hydride in toluene [16 ml (24.3 mmol) of a 1.5 M solution] at 0 °C and the stirring is continued for 3 h at room temperature. Then, methanol (20 ml) followed by saturated aqueous ammonium chloride (10 ml) is added to the mixture at 0 °C and the mixture is stirred for several hours with dichloromethane (100 ml). The mixture is filtered through Celite and the organic layer is separated, and evaporated *in vacuo*. The residue is taken into chloroform (50 ml) and insoluble material is removed by filtration. Evaporation of the solvent *in vacuo* gives a colorless solid which on recrystallization from a mixture of *n*-hexane and ether gives **10** as colorless needles; yield: 1.12 g (76%); m.p. 57–58 °C, $[\alpha]_D^{20}$ + 22.40° (*c* 1.00, $CHCl_3$).

$C_{18}H_{22}O_4$	calc.	C 71.50	H 7.33
(302.4)	found	71.44	7.27

IR (Film): ν = 3430 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS_{int}): δ = 2.55 (s, 2H, exchangeable with D_2O); 3.50–4.07 (m, 6H); 4.50 (s, 2H); 4.60 (s, 2H); 7.26 ppm (s, 10H).

MS (70 ev): *m/e* = 303 (M^+ + 1), 91 (100%).

(2*S*,3*S*)-1,2,4-Tri-*O*-benzylthreitol (11):
To a stirred solution of **5**[6] (2.0 g, 5.13 mmol) in toluene (15 ml) is added a solution of diisobutylaluminum hydride in toluene [8.55 ml (12.8 mmol) of 1.5 M solution] dropwise at 0 °C and the stirring is continued for 3.5 h at the same temperature. Then, saturated ammonium hydroxide (5 ml) and tetrahydrofuran (30 ml) is added to the mixture and the stirring is continued for 1.5 h at room temperature. The mixture is filtered through Celite and the filtrate is evaporated *in vacuo*. The residue is extracted with ether (150 ml) and the extract is dried with magnesium sulfate, evaporated *in vacuo*, and purified by chromatography on silica gel column (30 g) using a mixture of *n*-hexane and ether (1 : 1 v/v) as eluent to give **11** as a pale yellow oil; yield: 1.95 g (97%); $[\alpha]_D^{20}$ + 23.4° (*c* 1.01, $CHCl_3$).

$C_{25}H_{28}O_4$	calc.	C 76.50	H 7.19	
(392.5)	found	76.21	6.90	

MS (High Resolution): *m/e* = 392.1983 (calc. 392.1986)

IR (Film): ν = 3450 cm^{-1}.

^{1}H-NMR ($CDCl_3/TMS_{int}$): δ = 2.30 (br s, 1 H, exchangeable with D_2O); 3.43–4.13 (m, 6 H); 4.31–4.83 (m, 6 H); 7.03–7.58 ppm (m, 15 H).

MS (70 ev): *m/e* = 392 (M^+), 91 (100%).

(2*R*,3*S*)-2,3-*O*-Benzylidene-1-phenylthiothreitol (19):
To a stirred solution of **2** (1.60 g, 7.62 mmol) in pyridine (10 ml) is added diphenyl disulfide (1.74 g, 8.0 mmol) and tri-*n*-butylphosphine (1.99 ml, 8.0 mmol) at 0 °C and the stirring is continued for 16 h at room temperature. The reaction mixture is evaporated under vacuum and the residue is taken into ether (200 ml). The ether layer is washed successively with aqueous 15% sodium hydroxide, water, saturated brine (each 30 ml), and dried with magnesium sulfate. After evaporation of the solvent *in vacuo*, the residue is purified by chromatography on silica gel column (120 g) using a mixture of *n*-hexane and ether (9 : 1 v/v) as eluent to give **19** as a colorless oil as a mixture of epimers (1 : 1) at benzylidene carbon; yield: 1.03 g (45%).

$C_{17}H_{18}O_3S$	calc.	C 67.52	H 6.00	S 10.60
(302.4)	found	67.44	6.16	10.84

Each epimer is separated by using flash chromatography on silica gel column (24 g) using a mixture of *n*-hexane and ether (4 : 1 v/v) as eluent.

19a:

MS (High Resolution): *m/e* = 302.0998 (calc. 302.0977)

IR (Film): ν = 3325 cm^{-1}.

^{1}H-NMR ($CDCl_3/TMS_{int}$): δ = 1.75–2.22 (br s, 1 H, exchangeable with D_2O); 2.80–3.45 (m, 2 H); 3.45–4.00 (m, 2 H); 4.00–4.47 (m, 2 H); 5.97 (s, 1 H); 7.20–7.61 ppm (m, 10 H).

MS (70 ev): *m/e* = 302 (M^+), 149 (100%).

19b:

MS (High Resolution): *m/e* = 302.1020 (calc. 302.0977)

IR (Film): ν = 3300 cm^{-1}.

^{1}H-NMR ($CDCl_3/TMS_{int}$): δ = 1.73–2.08 (br m, 1 H, exchangeable with D_2O); 3.20–3.45 (m, 2 H); 3.70–4.40 (m, 4 H); 5.95 (s, 1 H); 7.12–7.80 ppm (m, 10 H).

MS (70 ev): *m/e* = 302 (M^+), 107 (100%).

(2*R*,3*R*)-2,3-*O*-Benzylidene-1,4-diphenylthiothreitol (20):
To a stirred solution of **2** (1.60 g, 7.62 mmol) in pyridine (10 ml) is added diphenyl disulfide (4.98 g, 22.86 mmol) and tri-*n*-butylphosphine (5.70 ml, 22.86 mmol) at 0 °C and the stirring is continued for 20 min at the same temperature and for 50 min at room temperature. The reaction mixture is evaporated under vacuum and the residue is taken into ether (200 ml). The ether layer is washed successively with each 30 ml of water, 15% aqueous sodium hydroxide, water, brine, and dried with magnesium sulfate. After evaporation of the solvent *in vacuo*, the residue is purified by chromatography on silica gel column (200 g) using a mixture of *n*-hexane and ether (7 : 1 v/v) as eluent to give **20** as a colorless oil; yield: 2.24 g (90%); $[\alpha]_D^{25}$ − 13.2° (*c* 1.11, CH_3OH).

$C_{23}H_{22}O_2S_2$	calc.	C 70.02	H 5.62	S 16.25
(394.5)	found	70.21	5.75	16.02

MS (High Resolution): *m/e* = 394.1079 (394.1062)

IR (Film): ν = 685 cm^{-1}.

^{1}H-NMR ($CDCl_3/TMS_{int}$): δ = 3.10–3.60 (m, 4 H); 4.08–4.54 (m, 2 H); 5.93 (s, 1 H); 7.18–7.60 ppm (m, 15 H).

MS (70 ev): *m/e* = 394 (M^+), 162 (100%).

2-*O*-Benzyl-1-phenylthiothreitol (21):
Method A, from **19a**: To a stirred solution of **19a** (128 mg, 0.424 mmol) in benzene (3 ml) is added a solution of diisobutylaluminum hydride in *n*-hexane [1.13 ml (1.70 mmol) of 1.5 M solution] dropwise at 0 °C and the stirring is continued 15 hr at room temperature. The reaction mixture is treated with 10% hydrochloric acid (1.5 ml) at 0 °C and extracted with ether (50 ml). The extract is washed with 10% hydrochloric acid, water, saturated brine, (each 10 ml), and dried with magnesium sulfate. After evaporation of the solvent *in vacuo*, the residue is purified by TLC on a silica gel plate (1 mm) using ether as eluent to give **21** as a pale yellow oil; yield: 51 mg (40%); $[\alpha]_D^{24}$ − 17.69° (*c* 0.29, CH_3OH).

$C_{17}H_{20}O_3S$	calc.	C 67.08	H 6.62	S 10.53
(304.4)	found	66.97	6.54	10.71

MS (High Resolution): *m/e* = 304.1109 (calc. 304.1087)

IR (Film): ν = 3300 cm^{-1}.

^{1}H-NMR ($CDCl_3/TMS_{int}$): δ = 1.94–2.72 (br m, 2 H, exchangeable with D_2O), 3.10–3.34 (m, 2 H), 3.38–4.10 (m, 4 H), 4.55 (2 H, ABq, 10 Hz), 7.02–7.48 ppm (m, 10 H).

MS (70 ev): *m/e* = 304 (M^+), 91 (100%).

Method B, from **19b**: **19b** (75 mg, 0.248 mmol) is treated as **19a** as described above to give **21**; yield: 58 mg (77%); $[\alpha]_D^{25}$ − 17.90° (*c* 0.32, CH_3OH). TLC behavior and spectral data are identical with those of **21** obtained from **19a**.

Method C, from an epimeric mixture of **19a** and **19b**: A mixture of **19a** and **19b** (1 : 1, 247 mg, 0.818 mmol) is treated as **19a** or **19b** as described above to give **21**; yield: 178 mg (72%); $[\alpha]_D^{25}$ − 15.93° (*c* 0.45, CH_3OH). TLC behaviour and spectral data are identical with those of **21** obtained from **19a** or **19b**.

2-*O*-Benzyl-1-phenylthioglycercol (22):
To a stirred solution of **21** (155 mg, 0.51 mmol) in 50% aqueous methanol (3 ml) is added sodium periodate (100 mg, 0.51 mmol) in water (1 ml) at 0 °C. After stirring for 25 min at the same temperature, the mixture is then treated with sodium borohydride (39 mg, 1.02 mmol) in methanol (1 ml) and the stirring is continued for 15 min. The mixture is extracted with dichloromethane (50 ml), washed with water (10 ml), saturated brine (10 ml), and dried with magnesium sulfate. After evaporation of the solvent *in vacuo*, the residue is purified by TLC on a silica gel plate (1 mm) to give **22** as a colorless oil; yield: 100 mg (72%); $[\alpha]_D^{25}$ − 46.96° (*c* 0.49, CH_3OH).

$C_{16}H_{18}O_2S$	calc.	C 70.04	H 6.61	S 11.69
(274.4)	found	69.94	6.84	11.76

MS (High Resolution): *m/e* = 274.0995 (calc. 274.0964).

IR (Film): ν = 3450 cm^{-1}.

^{1}H-NMR ($CDCl_3/TMS_{int}$): δ = 1.58–2.24 (m, 1 H, exchangeable with D_2O); 2.99–3.32 (m, 2 H); 3.45–4.04 (m, 3 H); 4.59 (dd, 2 H, *J* = 12, 12 Hz); 7.10–7.52 ppm (m, 10 H).

MS (70 ev): *m/e* = 274 (M^+), 91 (100%).

(2*R*,3*R*)-2-*O*-Benzyl-1,4-diphenylthiothreitol (23):
To a stirred solution of **20** (152 mg, 0.386 mmol) in benzene (7 ml) is added a solution of diisobutylaluminum hydride in *n*-hexane [0.59 ml (0.89 mmol) of 1.5 M solution] dropwise at 0 °C and the stirring is continued for 6 h at room temperature. The reaction mixture is treated with 10% hydrochloric acid (1.5 ml) at 0 °C and extracted with ether (20 ml). The extract is washed with 10% hyrochloric acid (5 ml), saturated aqueous sodium hydrogen carbonate (5 ml), brine (5 ml), and dried with magnesium sulfate. After evaporation of the solvent *in vacuo*, the residue is purified by TLC on

a silica gel plate (1 mm) using a mixture of *n*-hexane and ether (2:1 v/v) to give **23** as a colorless oil; yield: 146 mg (92%); $[\alpha]_D^{24}$ +88.1° (*c* 0.54, CH_3OH).

$C_{23}H_{24}O_2S_2$ (396.5) calc. C 69.66 H 6.10 S 16.17
found 69.57 6.30 16.31

MS (High Resolution): *m/e* = 396.1234 (calc. 396.1218).

IR (Film): ν = 3450 cm^{-1}.

^{1}H-NMR ($CDCl_3/TMS_{int}$): δ = 2.30–2.56 (m, 1H, exchangeable with D_2O); 3.04 (d, 2H, *J* = 9 Hz); 3.14 (d, 2H, *J* = 9 Hz); 3.57–4.02 (m, 2H); 4.48 (dd, 2H, *J* = 12, 12 Hz); 7.08–7.50 ppm (m, 10H).

MS (70 ev): *m/e* = 396 (M^+), 91 (100%).

(2*R*,3*R*)-1,4-Diphenylthiothreitol (24):
A solution of **20** (2.25 g, 5.71 mmol) in a mixture of tetrahydrofuran (50 ml) and 10% aqueous hydrochloric acid (50 ml) is stirred for 37 h at room temperature. After most of tetrahydrofuran is evaporated *in vacuo*, the residue is extracted with dichloromethane (200 ml) and the extract is washed with saturated aqueous sodium hydrogen carbonate (30 ml), saturated brine (30 ml), and evaporated *in vacuo* to leave a crystalline solid which is recrystallized from benzene to give **24** as colorless needles; yield: 1.49 g (85%); m.p. 117–118 °C; $[\alpha]_D^{24}$ +30.5° (*c* 1.04, $CHCl_3$).

$C_{16}H_{18}O_2S_2$ (306.4) calc. C 62.71 H 5.92 S 20.93.
found 62.59 5.64 20.83.

MS (High Resolution): *m/e* = 306.0743 (calc. 306.0746).

IR (Film): ν = 3250 cm^{-1}.

^{1}H-NMR ($CDCl_3/TMS_{int}$): δ = 2.58–2.83 (d, 2H, *J* = 5 Hz, exchangeable with D_2O); 3.00–3.40 (d, 4H, *J* = 6 Hz); 3.53–4.00 (m, 2H); 7.10–7.60 ppm (m, 10H).

MS (70 ev): *m/e* = 306 (M^+), 152 (100%).

***trans*-(3*S*,4*S*)-3,4-Dibenzoyloxytetrahydrofuran (26):**
To a stirred suspension of **2** (210 mg, 1 mmol) and sodium hydrogen carbonate (101 mg, 1.2 mmol) in carbon tetrachloride (10 ml) is added *N*-bromosuccinimide (178 mg, 1 mmol) portionwise at 0 °C and the stirring is continued for 4 h at room temperature in the dark. The mixture containing **25** is then treated with triethylamine (0.314 ml, 2.25 mmol) followed by benzoyl chloride (0.174 ml, 1.5 mmol) at 0 °C. After the stirring for 4 h at room temperature, the mixture is washed with, 5% hydrochloric acid (5 ml), saturated aqueous hydrogen carbonate (5 ml), saturated brine (5 ml), dried with magnesium sulfate, and evaporated *in vacuo*. The residue is purified by chromatography on silica gel column (30 g) using a mixture of *n*-hexane and dichloromethane (1:3 v/v) as eluent to leave a crystalline solid which is recrystallized from methanol to give **26** as colorless needles; yield: 96 mg (40%); m.p. 89–90 °C; $[\alpha]_D^{20}$ +174.2° (*c* 1.00, $CHCl_3$).

$C_{18}H_{16}O_5$ (312.3) calc. C 69.22 H 5.16
found 69.03 4.91

IR (Film): ν = 1710 cm^{-1}.

^{1}H-NMR ($CDCl_3/TMS_{int}$): δ = 3.92 (dd, 2H, *J* = 10, 2 Hz); 4.28 (dd, 2H, *J* = 10, 2 Hz); 5.43–5.63 (m, 2H); 7.23–7.70 (m, 6H); 7.87–8.13 ppm (m, 4H).

MS (70 ev): *m/e* = 313 (M^+ + 1), 105 (100%).

(2*R*,3*R*)-2,3-Dibenzoyloxy-1,4-dibromobutane (27):
To a stirred solution of **3** (2.5 g, 8.4 mmol) in carbon tetrachloride (50 ml) is added *N*-bromosuccinimide (3.3 g, 18.5 mmol) portionwise at 0 °C and the stirring is continued for 7 days at room temperature in the dark. The mixture is washed with saturated aqueous sodium hydrogen carbonate (2 × 10 ml), saturated brine (10 ml), dried with sodium sulfate, and evaporated *in vacuo*. The residue is purified by silica gel column (70 g) using a mixture of *n*-hexane and dichloromethane (1:2 v/v) as eluent to leave a crystalline solid which is recrystallized from a mixture of ether and *n*-hexane to give **27** as colorless prisms; yield: 3.21 g (84%; m.p. 95–96 °C; $[\alpha]_D^{25}$ −19.48° (*c* 1.00, $CHCl_3$).

$C_{18}H_{16}O_4Br_2$ (456.1) calc. C 47.38 H 3.53 Br 35.06
found 47.22 3.39 35.25

IR (Film): ν = 1710 cm^{-1}.

^{1}H-NMR ($CDCl_3/TMS_{int}$): δ = 4.70 (d, 4H, *J* = 5 Hz); 5.78 (m, 2H); 7.27–7.70 (m, 6H); 7.93–8.17 ppm (m, 4H).

MS (FD): *m/e* = 456 (M^+, 100%).

(2*S*,3*S*)-1-Benzyloxy-3,4-epoxy-2-butanol (30) from a *via* 3-Benzoyloxy-4-benzyloxy-2-bromo-1-butanol (29):
To a stirred solution of **4** (10.71 g, 35.66 mmol) in carbon tetrachloride (100 ml) is added *N*-bromosuccinimide (9.52 g, 53.5 mmol) portionswise at 0 °C and the stirring is continued for 6 h at room temperature in the dark. The reaction mixture is diluted with dichloromethane (250 ml) and washed with saturated aqueous sodium hydrogen carbonate (2 × 100 ml), saturated brine (50 ml), dried with magnesium sulfate, and evaporated *in vacuo* to give **29** (13.72 g, 101%) as a pale yellow oil which can be used for the following conversion without further purification.

To a stirred solution of **29** (13.72 g) in 1,2-dimethoxyethane (130 ml) is added sodium hydroxide (3.62 g, 90.5 mmol) at room temperature and the stirring is continued for 9.5 h at the same temperature. The mixture is diluted with saturated brine (100 ml) and is extracted with ether (300 ml). The extract is washed with saturated aqueous sodium hydrogen carbonate (80 ml), saturated brine (50 ml), dried with magnesium sulfate, and evaporated *in vacuo*. The residue is purified by chromatography on silica gel column (200 g) using a mixture of *n*-hexane-ether (2:3 v/v) as eluent to give **30** as a pale yellow oil; yield: 3.37 g (49% from **4**); b.p. 130 °/0.15 torr (Kugelrohr) (Lit.[19], 130 °C/0.01 torr), $[\alpha]_D^{29}$ +13.8° (*c* 1.02, $CHCl_3$) [Lit.[19], $[\alpha]_D^{25}$ +13.5° (*c* 1, $CHCl_3$)].

MS (High Resolution): *m/e* = 194.0913 (calc. 194.0943)

IR (Film): ν = 3440 cm^{-1}.

^{1}H-NMR ($CDCl_3/TMS_{int}$) is identical with the reported data[19].

MS (70 ev): *m/e* = 194 (M^+), 91 (100%).

(2*S*,3*S*)-2-Amino-1,4-di-*O*-benzylthreitol (33):
A solution of **32** (403 mg, 1.42 mmol) in methanol (7 ml) saturated with ammonia is heated at 100 °C in a sealed tube for 35 h. After evaporation of the solvent *in vacuo*, the residue is purified by chromatography on silica gel column (8 g) using a mixture of chloroform and methanol (24:1 v/v) as eluent to leave a crystalline solid which is recrystallized from ether to give **33** as colorless plates; yield: 427 mg (100%); m.p. 63.5°; $[\alpha]_D^{36}$ +3.2° (*c* 0.68, $CHCl_3$).

$C_{18}H_{23}O_3N$ (301.4) calc. C 71.73 H 7.69 N 4.65
found 71.60 7.77 4.55

IR (Film): ν = 3150 cm^{-1}.

^{1}H-NMR ($CDCl_3/TMS_{int}$): δ = 2.07 (s, 1H, exchangeable with D_2O); 2.83–3.40 (m, 2H); 3.57 (m, 6H); 4.48 (s, 2H); 4.50 (s, 2H); 7.27 ppm (s, 10H).

MS (70 ev) *m/e* = 301 (M^+), 91 (100%).

***trans*-(3*S*,4*S*)-3-Benzoyloxy-4-benzyloxytetrahydrofuran (37) and (2*S*,3*R*)-3-*O*-Benzoyl-2-*O*-benzyl-4-bromo-1-butanol (38).**
Method A, from **8**: To a stirred solution of **8** (750 mg, 2.5 mmol) in a mixture of carbon tetrachloride (10 ml) and dichloromethane (5 ml) is added *N*-bromosuccinimide (489.5 mg, 2.75 mmol) portionwise at 0 °C and the stirring is continued for 4 h at room temperature in the dark. The mixture is washed with saturated aqueous hydrogen carbonate (2 × 5 ml), saturated brine (5 ml), dried with sodium sulfate, and evaporated *in vacuo*. The residue is purified by chromatography on silica gel column (30 g) using a mixture of *n*-hexane and ether (5:1 v/v) as eluent to give **37** (285 mg, 38%) as a colorless oil from less polar fractions and **38** (490 mg, 52%) as a colorless oil from more polar fractions.

37; b.p. 175–185 °C/0.4 torr (Kugelrohr); $[\alpha]_D^{17}$ +34.06° (*c* 1.20, $CHCl_3$).

$C_{18}H_{18}O_4$ (298.3) calc. C 72.46 H 6.08
found 72.33 6.04

MS (High Resolution): *m/e* = 298.1200 (calc. 298.1203).

IR (Film): ν = 1720 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS_{int}): δ = 3.47–4.33 (m, 5H); 4.70 (d, 2H, J = 2 Hz); 5.33–5.57 (m, 1H); 7.30 (s, 4H); 7.30–7.48 (m, 4H); 7.90–8.17 ppm (m, 2H).

MS (70 ev): m/e = 299 (M^+ +1), 91 (100%).

38: $[\alpha]_D^{17}$ −22.96° (c 1.03, $CHCl_3$).

$C_{18}H_{19}O_4Br$	calc.	C 57.01	H 5.05	Br 21.07
(379.3)	found	57.05	5.13	20.94

MS (High Resolution): m/e = 378.0427 (calc. 378.0465).

IR (Film): ν = 3460, 1720 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS_{int}): δ = 2.23 (br s, 1H, exchangeable with D_2O); 3.62–4.03 (m, 5H); 4.64 (s, 2H); 5.33–5.65 (m, 1H); 7.25 (s, 4H); 7.05–7.63 (m, 4H); 7.97–8.13 ppm (m, 2H).

MS (70 ev): m/e = 379 (M^+ +1), 91 (100%).

Method B, from **9**: To a stirred solution of **9** (1.15 g, 3.82 mmol) in carbon tetrachloride (10 ml) is added *N*-bromosuccinimide (750 mg, 4.21 mmol) portionwise at 0 °C and the stirring is continued for 5.5 h at room temperature in the dark. The mixture is washed with saturated aqueous sodium hydrogen carbonate (2 × 5 ml), saturated brine (5 ml), dried with magnesium sulfate, and evaporated *in vacuo*. The residue is purified by chromatography on silica gel column (60 g) using a mixture of *n*-hexane and ether (4:1 v/v) as eluent to give **37**; yield: 469 mg (41%) and **38** yield: 352 mg (24%) whose TLC behaviour and spectral data (IR, ^{1}H-NMR and MS) are identical in all respects with those of the product obtained from **8**.

(2*S*,3*S*)-2-Benzyloxy-3,4-epoxy-1-butanol (39):

A suspension of **38** (240 mg, 0.63 mmol) and potassium carbonate (263 mg, 1.9 mmol) in methanol (6 ml) is stirred at room temperature for 30 min. The mixture is treated with saturated brine (10 ml) and extracted with dichloromethane (3 × 20 ml). The extract is washed with brine (10 ml), dried with magnesium sulfate, and evaporated *in vacuo*. The residue is purified by chromatography on silica gel column (6 g) using a mixture of *n*-hexane and ether (1:1 v/v) as eluent to give **39** as a colorless oil; yield: 91 mg (74%); b.p. 130–135 °C/0.5 torr (Kugelrohr); $[\alpha]_D^{30}$ +33.28° (c 1.16, $CHCl_3$).

$C_{11}H_{14}O_3$	calc.	C 68.02	H 7.27
(194.2)	found	67.80	7.46

IR (Film): ν = 3440 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS_{int}): δ = 2.42 (br s, 1H, exchangeable with D_2O), 2.47–2.67 (m, 1H); 2.77 (dd, 1H, J = 4, 4 Hz); 2.97–3.36 (m, 2H); 3.67 (br s, 2H); 4.73 (dd, 2H, J = 18, 12 Hz); 7.30 ppm (s, 5H).

MS (70 ev): m/e = 194 (M^+), 91 (100%).

Received: July 1, 1985
(Revised form: October 28, 1985)

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