## (2*S*,3*R*)-2-Benzyloxy-3,4-epoxybutan-1-ol; A Versatile Synthetic Building Block Formally Derived From (*u*)-Tartaric acid

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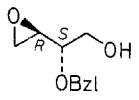
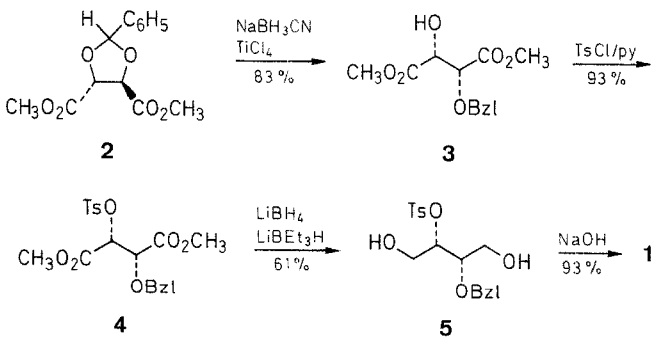
The title chiral $C_4$-building block[2] **1**, a *meso*-tartaric acid synthon, is prepared from dimethyl (*R*,*R*)-O,O'-benzylidenetartrate on a multigram scale. The key step is a tosylation- reduction sequence which leads to the diol **5**.

The (*u*)-1,2-dihydroxy-functionality[3] is often found in molecules occuring in nature, for example in macrolides[4] eicosanoids[5] and pheromones.[6] During our studies on the synthesis of macrolide antibiotics, we now developed[7] a short synthesis of the enantiomerically pure epoxy- alcohol **1**, a *meso*-tartaric acid synthon. After its conversion into the 1-bromo-derivative, this ambident electrophile can be used to introduce the (*u*)-dihydroxy moiety in EPC-syntheses.[2] This has been previously achieved[8-10] by starting from 2-deoxy-D-ribose[9] or by applying the *Sharpless* epoxidation.[10] However, since both enantiomers of a chiral building block should be equally readily available, and since the stereoselective epoxidation does not always give a single enantiomer or diastereoisomer, we believe that the tartaric acid approach competes very well with the previously published methods.



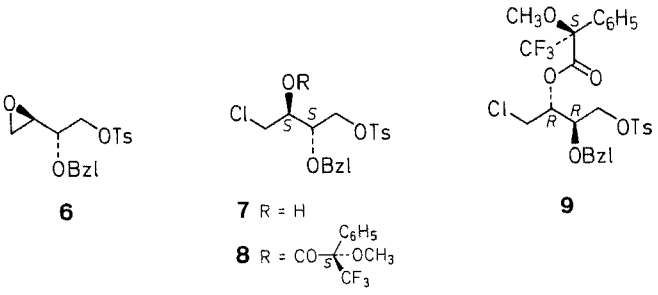

**1**

The preparation of **1** starts with the reduction (in 83% yield) of the commercially available benzylidene acetal **2** to the benzylether **3**, using sodium cyanoborohydride/titanium tetrachloride in acetonitrile. Most of the reported methods[11] to perform such reductive acetal ring openings are not applicable here because the ester groups would also be reduced. The hydroxydiester **3** is then converted to the corresponding diester-tosylate **4** [*p*-toluenesulfonyl chloride, pyridine, 4-pyrrolidinopyridine (cat.), 93%], which is reduced with lithium borohydride/lithium triethylborohydride[12] to afford the crystalline diol **5**, an erythritol derivative, in 61% yield. If lithium aluminum hydride or sodium borohydride was used instead, a complex mixture resulted, probably due to tosylate elimination and subsequent reactions. The epoxide-ring closure to **1** is then achieved by treatment of **5** with two equivalents of sodium hydroxide in methanol/dichloromethane (93%). Thus, the tartrate acetal **2** is converted to the epoxy-alcohol **1** in an overall yield of 45%.




**2** **3** **4** **5**

To determine the enantiomeric excess of the title compound **1**, we also prepared *ent*-**1** from the (*S*,*S*)-benzylidene acetal *ent*-**2** and converted the enantiomeric epoxy-alcohols into the corresponding *Mosher* (*S*)-esters.[13] Unfortunately, neither $^{19}$F- nor $^1$H-NMR measurements of these diastereoisomeric esters showed any significant difference. Also, $^1$H-NMR spectra of mixtures of different enantiomeric compositions (**1** and *ent*-**1**) in the presence of the chiral shift reagent[14] Eu(hfbc)$_3$ did not provide any useful seperation of the signals from the two enantiomers. We also tried to analyse these enantiomeric mixtures by a chiral HPLC column[15] without success. The problem of determining the enantiomeric excess of the chiral epoxy-alcohol **1** was finally solved by serendipity: we noticed that during acylations and tosylations (with acyl chlorides and tosyl chloride, respectively) of **1** the epoxide ring was opened to some extent, with formation of chlorohydrins such as **7**.




**6** **7** R = H **9**

**8** R = CO–C(C6H5)(OCH3)(CF3)

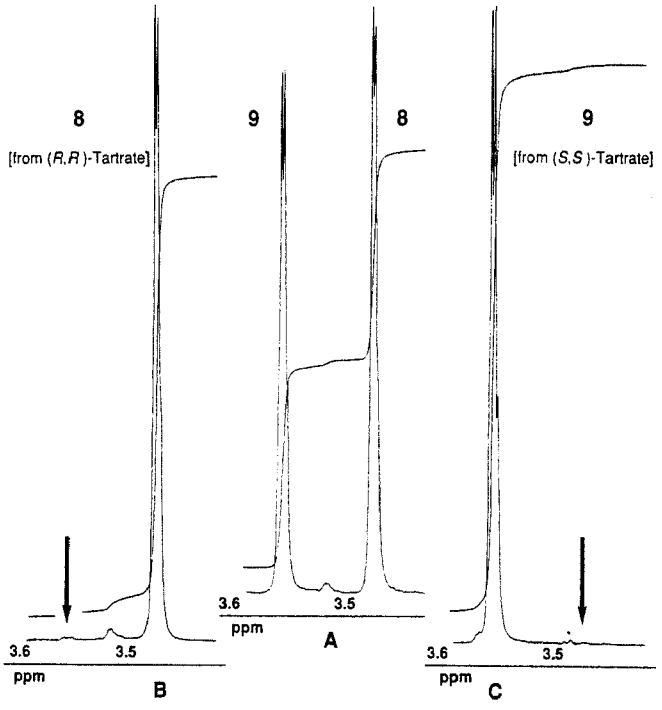



**Fig.** Methoxy signals in the 300 MHz $^1$H-NMR spectra of the *Mosher* esters **8** and **9**. **B** and **C**: Samples obtained from the dioxolane **2** of (*R*,*R*)-tartrate and *ent*-**2** of (*S*,*S*)-tartrate, respectively. **A**: Sample prepared by acylation of a 1:1 mixture of **7** and *ent*-**7** with (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride. The arrows in **B** and **C** indicate the positions of the signals from the respective diastereoisomers.

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Thus, under the usual tosylation conditions [dichloromethane, pyridine, tosyl chloride, 4-pyrrolidinopyridine (cat.)[16]], a ca. 2:1 mixture of the epoxytosylate **6** and the chlorotosylate **7** was formed. These could be readily separated and were fully characterised. The diastereoisomeric *Mosher* esters **8** (derived from **1**) and **9** (derived from *ent*-**1**) could easily be distinguished by $^1$H-NMR spectroscopy (see Fig.). We could thus establish that the enantiomeric excess of the hydroxy-tosylates **7** and *ent*-**7**, and, by the same token, of the two epoxy-alcohols **1** and *ent*-**1**, is > 99%.

Melting points (uncorrected) were measured using a Büchi 510 apparatus. Optical rotations were measured on a Perkin-Elmer 241 polarimeter at room temperature (22 °C). IR spectra were recorded on a Perkin-Elmer 297 spectrometer (film, $CHCl_3$) or on a Perkin-Elmer 287 spectrometer (KBr) (s = strong, m = medium, w = weak, br = broad). $^1$H-NMR spectra were obtained on a Bruker WM 300 spectrometer (300 MHz), with TMS as internal standard and $CDCl_3$ as solvent. MS spectra were recorded on a Hitachi-Perkin-Elmer spectrometer RMU-6M. For flash column chromatography, Merck silica gel 60 (230–400 mesh) was used.

**Dimethyl (2*R*,3*R*)-2-Benzyloxy-3-hydroxysuccinate (3):**
To a solution of **2** (26.60 g, 0.1 mol) and $NaBH_3CN$ (6.60 g, 0.1 mol) in $CH_3CN$ (200 mL) under argon at 0° is slowly added $TiCl_4$ (11 mL, 0.1 mol). The yellow suspension is stirred at room temperature for 3 h, then the solvent is evaporated and the resulting brown oil is dissolved in $CH_2Cl_2$. Water (150 mL) is added slowly to the ice-cold solution and, after separation of the layers, the aqueous phase is extracted with $CH_2Cl_2$ (2 × 150 mL). The combined organic layer is washed successively with aqueous 2 N NaOH (100 mL), water (100 mL), brine, and dried ($MgSO_4$). The solvent is removed and the resulting oil is chromatographed on silica gel using n-hexane/EtOAc (3:2) as eluent to afford **3** as a colourless solid; yield: 22.4 g (83%); m.p. 69.0–70.0 °C (ether) (Lit.[17] mp 68.5 °C); $[\alpha]_D$ + 91.7° (*c* = 1.0, $CHCl_3$) (Lit.[17] $[\alpha]_D$ + 91,5° (*c* = 1.0, $CHCl_3$). *ent*-**3**: mp 68.5–70 °C (ether); $[\alpha]_D$ – 87.7° (*c* = 1.0, $CHCl_3$).

**Dimethyl (2*R*,3*R*)-2-Benzyloxy-3-*p*-tolylsulfonyloxysuccinate (4):**
To a solution of **3** (22.40 g, 83.5 mmol), pyridine (16.20 mL, 0.2 mol) and a catalytic amount of 4-pyrrolidinopyridine in dry $CH_2Cl_2$ (250 mL) is added *p*-TsCl (31.73 g, 0.166 mol) at 0 °C over a period of 15 min. The mixture is stirred at room temperature for 70 h and then poured into 2 N HCl (150 mL). The layers are separated and the aqueous phase is extracted with $CH_2Cl_2$ (2 × 200 mL). The combined organic layer is washed with sat. aq. $CuSO_4$, water, and brine, and dried ($MgSO_4$). The solvent is removed, and the resulting oil chromatographed on silica gel using hexane/EtOAc (9:1 to 1:1) as eluent to afford **4** as a colourless, crystalline solid; yield: 32.81 g (93%); mp 71.0–72.0 °C (ether); $[\alpha]_D$ + 55.4° (*c* = 1.0, $CHCl_3$).

| | | | |
|---|---|---|---|
| $C_{20}H_{22}SO_8$ | calc. | C 56.86 | H 5.25 |
| (422.4) | found | 56.85 | 5.27 |

IR (KBr): *v* = 1760 (s), 1600 (w), 1500 (w), 1280 (s), 1210 (s), 1180 (s), 1150 (s), 1060 (s), 960 (m), 760 (m), 740 (m) $cm^{-1}$.

$^1$H-NMR (300 MHz): $\delta$ = 2.43 (s, 3 H, $ArCH_3$); 3.63 (s, 3 H, $CO_2CH_3$); 3.65 (s, 3 H, $CO_2CH_3$); 4.42 (1/2 AB, *J* = 11.8 Hz, 1 H, $CH_2C_6H_5$); 4.49 (d, *J* = 3.0 Hz, 1 H, $CHOCH_2$); 4.83 (1/2 AB, *J* = 11.8 Hz, 1 H, $CH_2C_6H_5$); 5.41 (d, *J* = 3.0 Hz, 1 H, CHOTS); 7.21–7.43 (m, 7 $H_{arom}$), 7.79–7.83 (m, 2 $H_{arom}$).

MS: *m/z* (%) = 423 (0.1, $[M + 1]^+$); 172 (100); 155 (48); 145 (98); 113 (65); 91 (98); 65 (63); 39 (15).

*ent*-**4**: mp 72.5–73.0 °C (ether); $[\alpha]_D$ – 58° (*c* = 1.51, $CHCl_3$).

**(2*S*,3*S*)-2-Benzyloxy-3-*p*-tolylsulfonyloxybutane-1,4-diol (5):**
A solution of **4** (24.50 g, 58.0 mmol) and $LiBH_4$ (2.78 g, 0.127 mol) in dry ether/THF (2:1, 210 mL) is prepared. To this solution is added, at 0 °C under argon, a 1 M THF solution of $LiBEt_3H$ (12.8 mmol, 12.8 mL). The mixture is stirred at room temperature for 60 h, then water (100 mL), MeOH (30 mL) and 6 N aq. HCl (10 mL) are carefully added to the ice-cold solution. The aqueous layer is extracted with $CH_2Cl_2$ (3 × 100 mL) and the combined organic layer is washed with water (100 mL) and brine. After drying ($MgSO_4$), the solvent is evaporated and the residue is chromatographed on silica gel using *n*-hexane/EtOAc (1:1) as eluent to afford the crystalline diol **5**; yield: 13.1 g (61%); mp 77.5–78.0 °C (ether); $[\alpha]_D$ – 5.3° (*c* = 1.05, $CHCl_3$).

| | | | |
|---|---|---|---|
| $C_{18}H_{22}SO_6$ | calc. | C 59.00 | H 6.05 S 8.75 |
| (366.4) | found | 59.10 | 6.02 8.56 |

IR (KBr): *v* = 3400 (br), 1350 (m), 1190 (m), 1175 (s), 1100 (w), 910 (m) $cm^{-1}$.

$^1$H-NMR (300 MHz): $\delta$ = 2.27–2.39 (br, 2 H, OH); 2.42 (s, 3 H, $ArCH_3$); 3.66–3.80 (m, 5 H, $CH_2OH$, $CHOCH_2$); 4.52 (1/2 AB, *J* = 11.8 Hz, 1 H, $CH_2C_6H_5$); 4.57 (1/2 AB, *J* = 11.8 Hz, 1 H, $CH_2C_6H_5$); 4.74 (app. q, 1 H, CHOTs); 7.22–7.36 (m, 7 $H_{arom}$); 7.77–7.80 (m, 2 $H_{arom}$).

MS: *m/z* = 366 (0.8, $M^+$); 173 (7.9); 155 (16); 107 (34); 91 (100); 70 (17); 65 (17); 39 (8).

*ent*-**5**: mp 76.0–76.5 °C (ether); $[\alpha]_D$ + 6.0° (*c* = 1.05, $CHCl_3$).

**(3*R*,2*S*)-2-Benzyloxy-3,4-epoxybutan-1-ol (1):**
NaOH (3.12 g, 78 mmol) is dissolved in MeOH/$H_2O$ (10:1, 220 mL) and a solution of the diol **5** (13.0 g, 34.5 mmol) in $CH_2Cl_2$ (200 mL) is added with vigorous stirring at 30 °C.

After 10 min, sat. aq. $NH_4Cl$ (50 mL) and $CH_2Cl_2$ (100 mL) are added and the layers are separated. The aqueous phase is extracted with $CH_2Cl_2$ (2 × 150 mL) and the combined organic layer is washed with brine and dried ($MgSO_4$). The solvent is evaporated and the residue is distilled to afford the epoxy alcohol **1** as a hygroscopic, colourless liquid; yield 6.2 g (93%); bp 100 °C/0.0004 mbar (Kugelrohr); $[\alpha]_D$ – 12.5° (*c* = 3,11, $CHCl_3$).

| | | | |
|---|---|---|---|
| $C_{11}H_{14}O_3$ | calc. | C 68.02 | H 7.27 |
| (194.2) | found | 67.98 | 7.49 |

IR (film): *v* = 3450 (br s), 3060 (m), 3030 (m), 2990 (m), 2920 (s), 2870 (s), 1490 (m), 1450 (s), 1390 (m), 1100 (m), 740 (s), 690 (s) $cm^{-1}$.

$^1$H-NMR (300 MHz): $\delta$ = 2.04 (t, *J* = 6 Hz, 1 H, OH); 2.71 (ABC, $J_{AB}$ = 5.2 Hz, $J_{AC}$ = 2.7 Hz, 1 H, H-4); 2.80 (ABC, $J_{AB}$ = 5.2 Hz, $J_{BC}$ = 3.9 Hz, 1 H, H-4); 3.03 (ABCX, $J_{AC}$ = 2.7 Hz, $J_{BC}$ = 3.9 Hz, $J_{CX}$ = 5.5 Hz, 1 H, H-3); 3.38 (dt, $J_{2,3}$ = 3.7 Hz, $J_{2,1}$ = 5.7 Hz, 1 H, H-2); 3.66–3.74 (m, 1 H, H-1); 3.78–3.85 (m, 1 H, H-1); 4.58 (1/2 AB, *J* = 11.6 Hz, 1 H, $CH_2C_6H_5$); 4.71 (1/2 AB, *J* = 11.6 Hz, 1 H, $CH_2C_6H_5$); 7.25–7.38 (m, 5 $H_{arom}$).

MS: *m/z* (%) = 194 (0.3, $M^+$); 107 (22); 91 (100); 65 (13); 31 (11.8).

*ent*-**1**: bp 100 °C/0.0004 mbar (Kugelrohr): $[\alpha]_D$ + 11.9° (*c* = 1.13, $CHCl_3$).

**(3*R*,2*S*)-2-Benzyloxy-3,4-epoxybutyl *p*-Toluenesulfonate (6) and (2*S*,3*S*) 1-Chloro-3-benzyloxy-4-*p*-tolylsulfonyloxybutane-2-ol (7):**
To a solution of the epoxy-alcohol **1** (0.595 g, 3.0 mmol) in $CH_2Cl_2$ (5 mL) and pyridine (0.48 mL, 6 mmol) under argon at 0 °C is added *p* TsCl (0.858 g, 4.5 mmol) and a few crystals of 4-pyrrolidinopyridine. The mixture is stirred at 0 °C for 2 h and then at room temperature for 15 h. Ether (50 mL) is added and the solution is washed with sat. aq. $CuSO_4$ (2 × 30 mL), water (30 mL), and brine. The organic layer is dried ($MgSO_4$), filtered and the solvent is evaporated. The resulting oil is chromatographed on silica gel using *n*-hexane/EtOAc (5:1) as eluent to afford the compounds **6** and **7** (in this order of elution).

**Epoxytosylat 6:** Oil, yield: 0.474 g (45%); $[\alpha]_D$ + 12.2° (*c* = 1.6, $CHCl_3$);

| | | | |
|---|---|---|---|
| $C_{18}H_{20}SO_5$ | calc. | C 62.05 | H 5.79 |
| (348.4) | found | 61.93 | 5.94 |

IR (film): *v* = 3060 (w), 3030 (w), 2990 (w), 2920 (w), 2860 (w), 1595 (w), 1490 (w), 1450 (w), 1360 (s), 1187 (s), 1175 (s), 1090 (s) $cm^{-1}$.

$^1$H-NMR (300 MHz): $\delta$ = 2.43 (s, 3 H, $ArCH_3$), 2.60 (ABC, $J_{AB}$ = 5.2 Hz, $J_{AC}$ = 2.6 Hz, 1 H, H-4); 2.72 (ABC, $J_{AB}$ = 5.2 Hz, $J_{BC}$ = 3.9 Hz, 1 H, H-4); 2.96 (ABCX, $J_{AC}$ = 2.6 Hz, $J_{BC}$ = 3.9 Hz, $J_{CX}$ = 5.4 Hz, 1 H, H-3); 3.48 (dt, $J_{2,3}$ = 3.8 Hz, $J_{2,1}$ = 5.8 Hz, 1 H, H-2); 4.13 (ABX, $J_{AB}$ = 10.6 Hz, $J_{AX}$ = 5.7 Hz, 1 H, $CH_2OTs$); 4.17 (ABX, $J_{AB}$ = 10.6 Hz, $J_{BX}$ = 3.8 Hz, 1 H, $CH_2OTs$); 4.54 (AB, *J* = 11.8 Hz, 1 H, $CH_2C_6H_5$); 4.59 (AB, *J* = 11.8 Hz, 1 H, $CH_2C_6H_5$); 7.24–7.34 (m, 7 $H_{arom}$); 7.76–7.79 (m, 2 $H_{arom}$).

MS: *m/z* (%) = 348 (0.2, $M^+$); 173 (11.8); 155 (18.2); 107 (20); 91 (100); 70 (17.8); 42 (7.4).

*ent*-**6**: $[\alpha]_D$ – 11.1° (*c* = 2.0, $CHCl_3$).

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**Chlorotosylate 7:** Colourless crystals, yield: 0.325 g (28 %); mp 71–73 °C (ether); $[\alpha]_D$ + 33.4° ($c$ = 1.38, $CHCl_3$).

$C_{18}H_{21}ClSO_5$ (384.9) calc. C 56.17 H 5.50 found 56.17 5.59

IR (KBr): $\nu$ = 3510 (br), 3030 (w), 2960 (w), 2920 (w), 1600 (m), 1455 (m), 1350 (s), 1190 (m), 1180 (s), 1170 (s), 1090 (s), 930 (s) $cm^{-1}$.

$^1$H-NMR (300 MHz): $\delta$ = 2.01 (br s, 1 H, OH); 2.44 (s, 3 H, $ArCH_3$); 3.62–3.67 (m, 1 H, CHOH); 3.68–3.78 (m, 2 H, $CH_2Cl$); 3.85–3.91 (m, 1 H, $CHOCH_2$); 4.24 (ABX, $J_{AB}$ = 11.0 Hz, $J_{AX}$ = 4.5 Hz, 1 H, $CH_2OTs$); 4.38 (ABX, $J_{AB}$ = 11.0 Hz, $J_{BX}$ = 2.7 Hz, $CH_2OTs$); 7.23–7.37 (m, 7 $H_{arom}$); 7.78–7.81 (m, 2 $H_{arom}$).

MS: $m/z$ (%) = 384 (0.9, $M^+$); 173 (6.5); 155 (10.5); 107 (23.6); 91 (100); 65 (7.3).

*ent*-**7:** mp 72.0–73.5 °C (ether); $[\alpha]_D$ – 32.1° ($c$ = 1.59, $CHCl_3$).

*G. A. thanks the Fond der chemischen Industrie (Germany) for a stipend. We thank Linda Behrend and Michele Ghisletta for technical assistance. Financial support by the Sandoz AG (Basel) is gratefully acknowledged.*

Received: 21 August 1987; revised: 25 January 1988

(1) Part of the projected Ph. D. Thesis of G. A., ETH-Zürich.
(2) For a review on building blocks from tartaric acid, see: Seebach, D., Hungerbühler, E., in: *Modern Synthetic Methods 1980*, Scheffold, R. (ed.), Verlag Saale + Sauerländer, Frankfurt, Aarau, 1980, pp. 93–171.
(3) *like/unlike*-Nomenclature for specification of configuration and steric course of reactions: Seebach, D., Prelog, V. *Angew. Chem.* **1982**, *94*, 696; *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 654.
(4) For a recently discovered new structure of this type, see: Trowitzsch, W., Borgschulte, K., Wray, V., Schomburg, D., Höfle, G. *Liebigs Ann. Chem.* **1986**, 1629.
(5) Isolation: Serhan, C.N., Hamberg, M., Samuelson, B. *Proc. Natl. Acad. Sci.* **1984**, *81*, 5335.
(6) See for example: Laurence, R.L., Pickett, J.A. *J. Chem. Soc. Chem. Commun.* **1985**, 59.
(7) Some years ago we published another, longer route to a differently protected derivative of **1**: Hunberbühler, E., Seebach, D., Wasmuth, D. *Angew. Chem.* **1979**, *91*, 1025; *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 958.
(8) Very recently, Mulzer and coworkers reported a multistep synthesis of both enantiomers of the 1-desoxy-derivative of **1**, starting from D-glucose and *R*-glyceraldehyde: Mulzer, J., Angermann, A., Münch, W., Schlichthörle, G., Hentzschel, A. *Liebigs Ann. Chem.* **1987**, 7.
(9) Morris, J., Wishka, D.G. *Tetrahedron Lett.* **1986**, *27*, 803.
(10) See, for example, Guo-giang, L., L., Hai-jain, X., Bi-chi, W., Guong-zhong, G., Wei-shan, Z. *Tetrahedron Lett.* **1985**, *26*, 1233.
(11) See, for instance, Tsumoda, T., Suzuki, M., Noyori, R. *Tetrahedron Lett.* **1979**, *20*, 4679, and literature cited therein.
(12) Brown, H.C., Narasimhan, S. *J. Org. Chem.* **1982**, *47*, 1604.
(13) Dale, J.A., Dull, D.L., Mosher, H.S. *J. Org. Chem.* **1969**, *34*, 2543.
(14) Fraser, R.R., Petit, M.A., Saunders, J.K. *J. Chem. Soc. Chem. Commun.* **1971**, 1450.
(15) Kinkel, J.N., Fraenkel, W., Blaschke, G. *Kontakte (Darmstadt)* **1987**, 3.
(16) Höfle, G., Steglich, W., Vorbrüggen, H. *Angew. Chem.* **1978**, *90*, 602; *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 569.
(17) Blarer, S.J. *Ph. D. Thesis*, ETH Zürich, Nr. 7188, 1982.

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