α-Chelation Controlled Nucleophilic Addition to Chiral α,β-Dialkoxy Carbonyl Compounds. Diastereoselective Preparation of L-*xylo* and L-*lyxo* Triols

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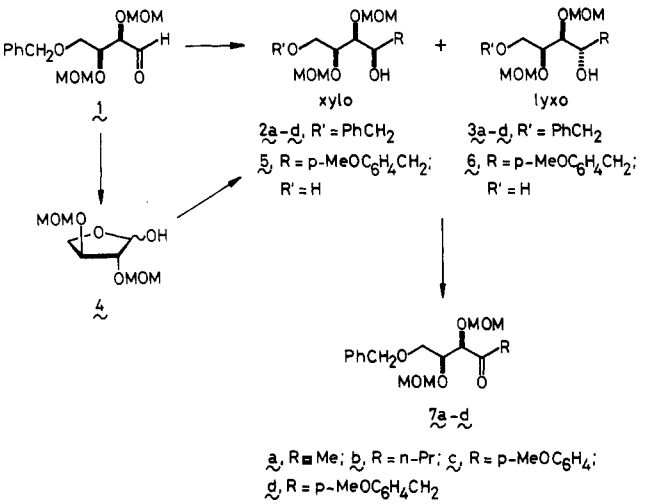
Received March 10, 1986

The Grignard reaction of 4-*O*-benzyl-2,3-*O*-bis(methoxymethyl)-L-threose (**1**) or 2,3-*O*-bis(methoxymethyl)-L-*threo*-furanose (**4**) with RMgX (R = Me, *n*-Pr, *p*-$MeOC_6H_4$, and *p*-$MeOC_6H_4CH_2$) provided the chromatographically separable mixtures of the *xylo* and *lyxo* alcohols, in 79–77:21–23 ratio favoring the *xylo* isomers in agreement with the prediction based on the α-chelation model. Swern oxidation of these diastereomeric mixtures of the *xylo* and *lyxo* alcohols **2a–d** and **3a–d** gave the corresponding ketones **7a–d** which were subjected to diastereoselective hydride addition using various metal hydride reagents. Thus employment of $NaBH_4$, vitride, and $Zn(BH_4)_2$ as hydride reagents led to the preponderant formation of the *lyxo* alcohols **3a–d** on the basis of the α-chelation control with diastereoexcess of 44–60, 72–90, and 86 to >98%, respectively. In striking contrast to this, reduction using L-Selectride resulted in the *xylo* alcohols as major isomers, probably predicted by the Felkin–Anh open-chain model, in 54–90% de.

The general problem of stereocontrolled reduction in acyclic carbonyl systems has been a prominent, current topic in organic chemistry. Numerous approaches of this general problem have focused on β-chelation controlled addition of hydride[1] to β-keto esters and β-hydroxy and β-alkoxy ketones in connection with synthetic studies of natural products such as polyether and polyene macrolide antibiotics because 1,3-diol functions often occur in these molecules. Other efforts have been focused on the investigations of stereoselective reduction via α-chelation controlled hydride addition.[2] However, these reactions are not always applicable to optically active substrates nor is the competition of these two chelation pathway addressed.

In the course of our studies directed toward use of the L-threose synthon **1** for natural product synthesis[3] we were faced with the problem of synthesizing both *xylo* and *lyxo* 1,2,3-triol derivatives. Our recent observations[3] on the α-chelation controlled Grignard reaction of this α,β-dialkoxy aldehyde leading to *xylo* alcohols has prompted us to assess whether the α- or β-chelation controls would predominate in the hydride addition to α,β-dialkoxy ketones and to examine efficient stereoselective routes to L-*xylo* and L-*lyxo* alcohols, the results of which are described in this paper.

Treatment of 4-*O*-benzyl-2,3-*O*-bis(methoxymethyl)-L-threose (**1**), easily available from the chiral pool (diethyl (*R,R*)-tartrate),[3] with methylmagnesium bromide in ether afforded a chromatographically separable mixture of the *xylo* **2a** and *lyxo* **3a** alcohols in 95% total yield and a 77:23 ratio favoring the *xylo* isomer. Similarly, addition of the *n*-propyl Grignard reagent to **1** gave a 78:22 mixture of the *xylo* **2b** and *lyxo* **3b** alcohols in 82% yield. The diastereofacial preference observed in these reactions is consistent with the results recently obtained in Grignard additions to **1** with (*p*-methoxyphenyl)magnesium bromide and to



4 derived from **1** with (*p*-methoxybenzyl)magnesium chloride leading to **2c**[3a] and **5**,[3b] respectively, as major isomers.

In all cases of the Grignard addition, the α,β-dialkoxy aldehydes **1** and **4** (in hemiacetal structure) showed a good diastereomeric bias in agreement with the prediction based on the α-chelate model[4] and not the β-chelate nor the Felkin[5] open chain models which both predict preferential formation of the *lyxo* isomers **3a–c** and **6**. These results are in marked contrast to the result obtained by Mukaiyama[6] in nucleophilic addition with organotin compounds to an analogue of **1** wherein the reaction is antiselective, affording *lyxo* isomers predicted by the Felkin model.

Encouraged by the above results, we next turned attention to the stereoselective synthesis of *lyxo* alcohols based on the α-chelate controlled hydride addition to α,β-dialkoxy ketones. Thus the diastereomeric mixture of the alcohols **2** and **3** from the Grignard reaction of **1** was subjected to Swern oxidation[7] to provide the ketone **7** in 83–99% yield. With the chiral α,β-dialkoxy ketones **7a–d** obtained, we examined, in some detail, diastereofacial selectivity in the nucleophilic hydride addition using

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(3) (a) Iida, H.; Yamazaki, N.; Kibayashi, C. *Tetrahedron Lett.* **1985**, *26*, 3255. (b) Iida, H.; Yamazaki, N.; Kibayashi, C. *J. Org. Chem.* **1986**, *51*, 1069.

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(5) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199.

(6) Mukaiyama, T.; Suzuki, K.; Yamada, T. *Chem. Lett.* **1982**, 929.

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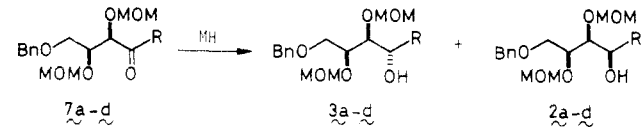
0022-3263/86/1951-3769$01.50/0

Table I. Hydride Reduction of α,β-Dialkoxy Ketones 7a–d

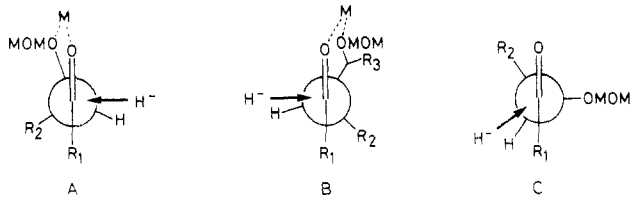


ketone	R	reducing agent	product	*lyxo*:*xylo* ratio[a]	yield, %
7a	Me	$NaBH_4$	**3a**/**2a**	79:21	94
7b	*n*-Pr	$NaBH_4$	**3b**/**2b**	80:20	93
7d[b]	*p*-$MeOC_6H_4CH_2$	$NaBH_4$	**3d**/**2d**	72:28	99
7a	Me	vitride	**3a**/**2a**	86:14	82
7b	*n*-Pr	vitride	**3b**/**2b**	95:5	87
7d	*p*-$MeOC_6H_4CH_2$	vitride	**3d**/**2d**	95:5	78
7a	Me	$Zn(BH_4)_2$	**3a**/**2a**	93:7	85
7b	*n*-Pr	$Zn(BH_4)_2$	**3b**/**2b**	95:5	95
7c	*p*-$MeOC_6H_4$	$Zn(BH_4)_2$	**3c**/**2c**	>99:1	78
7d	*p*-$MeOC_6H_4CH_2$	$Zn(BH_4)_2$	**3d**/**2d**	>99:1	91
7d	*p*-$MeOC_6H_4CH_2$	$LiAlH_4$	**3d**/**2d**	64:36	66
7a	Me	L-Selectride	**3a**/**2a**	23:77	75
7b	*n*-Pr	L-Selectride	**3b**/**2b**	8:92	75
7d	*p*-$MeOC_6H_4CH_2$	L-Selectride	**3d**/**2d**	5:95	74

[a] Determined on the basis of 400-MHz ^1H NMR spectrum. [b] Prepared from **2d** + **3d** according to ref 3b.

various metal hydride reagents. The results are presented in Table I.

Our results indicate that anti selectivity (affording the *lyxo* isomers **3a–d**) predicted by the α-chelation transition-state A is obtained without racemization when sodium borohydride, vitride, zinc borohydride, and lithium aluminum hydride are employed as hydride reagents. Thus



β-chelate B and Felkin–Anh[5,8] open chain C models both leading to the minor syn adducts (*xylo* isomers **2a–d**) should be disfavored in these cases examined. An increase in the anti selectivity was observed for the addition with zinc borohydride; this should be related to the high coordinating ability of zinc.

In striking contrast to these results, the reduction using L-Selectride leads to the syn isomers **2a–d** as major products with stereochemical outcome opposite to that predicted by the α-chelation model A. The syn selectivity seen in this case may be explained by assuming the Felkin–Anh open chain model C which should be favored by low complexing ability of L-Selectride.

In conclusion, these studies established an efficient means of controlled stereochemistry, which is governed by the α-chelate model, in the construction of either the L-*xylo* or the L-*lyxo* diastereomers from the common chiral synthon 1. Exploitation of these chiral 1,2,3-triols in stereoselective synthesis of natural products are in progress and will be reported in due course.

Experimental Section

Melting points are uncorrected. ^1H and ^{13}C NMR spectra were recorded at 400 and 100.6 MHz, respectively. Mass spectra were obtained at an ionizing potential of 70 eV. Optical rotations were measured at the sodium D line in a 0.05-dm cell at the designated concentration in grams per 100 mL. TLC was run on Wako precoated silica gel 70 FM plates. Column chromatography refers to flash chromatography on Merck silica gel 60 (230–400 mesh).

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Reaction of 4-*O*-Benzyl-2,3-*O*-bis(methoxymethyl)-L-threose (1) with Methylmagnesium Bromide. To a stirred, cooled (0 °C) ethereal solution of methylmagnesium bromide, prepared from 142 mg (5.84 mmol) of magnesium and 1.11 g (11.69 mmol) of bromomethane was added dropwise a solution of **1** (870 mg, 2.92 mmol) in ether (20 mL) under N_2 during 5 min. The reaction was allowed to warm to room temperature, stirred for 14 h, and quenched with water (3 mL). The organic layer was separated and the aqueous layer was extracted with ether (3 × 70 mL). The organic layers were dried ($MgSO_4$), the solvent was removed in vacuo, and the residue was chromatographed on silica gel (3:1 hexane/ethyl acetate) to give a mixture of the *xylo* and *lyxo* isomers **2a** and **3a** (77:23 by ^1H NMR spectrum) as a colorless oil (870 mg, 95%). A part of this oil was further separated on a silica gel column by using gradient elution (5:1 to 3:1 hexane/ethyl acetate) to give the pure *xylo* and *lyxo* isomers **2a** and **3a**.

(2*R*,3*S*,4*S*)-5-(Benzyloxy)-3,4-bis[(methoxymethyl)oxy]-2-pentanol (**2a**): $[\alpha]^{23}_D$ −2.2° (*c* 6.30, MeOH); ^1H NMR ($CDCl_3$) δ $CHCl_3$ 1.24 (3 H, d, *J* = 6.3 Hz), 3.19 (1 H, d, *J* = 3.7 Hz), 3.37 (3 H, s), 3.43 (3 H, s), 3.48 (1 H, dd, *J* = 5.6, 3.7 Hz), 3.60–3.70 (2 H, m), 3.89–4.00 (2 H, m), 4.53 (1 H, $^1/_2$ AB q, *J* 11.4 Hz), 4.55 (1 H, $^1/_2$ AB q, *J* = 11.4 Hz), 4.66 (1 H, $^1/_2$ AB q, *J* = 6.8 Hz), 4.71 (1 H, $^1/_2$ AB q, *J* = 6.6 Hz), 4.73 (1 H, $^1/_2$ AB q, *J* = 6.6 Hz), 4.78 (1 H, $^1/_2$ AB q, *J* = 6.8 Hz), 7.25–7.40 (5 H, m); mass spectrum, *m*/*e* 269 (1), 251 (1.3), 237 (10), 163 (28), 91 (100).

(2*S*,3*S*,4*S*)-5-(Benzyloxy)-3,4-bis[(methoxymethyl)oxy]-2-pentanol (**3a**): $[\alpha]^{23}_D$ −11.5° (*c* 2.18, MeOH); ^1H NMR ($CDCl_3$) δ $CHCl_3$ 1.23 (3 H, d, *J* = 6.4 Hz), 3.35–3.48 (1 H, unresolved; containing 2 × 3 H, 2 × s, at δ 3.40 and 3.41), 3.55–3.70 (3 H, m), 3.89 (1 H, sext, *J* = 6.1 Hz), 3.98 (1 H, dd, *J* = 5.4, 4.7 Hz), 4.54 (2 H, s), 4.65–4.82 (4 H, m), 7.25–7.41 (5 H, m); mass spectrum, *m*/*e* (relative intensity) 269 (1.2), 25 (0.9), 237 (10), 163 (24), 91 (100).

Reaction of 4-*O*-Benzyl-2,3-*O*-bis(methoxymethyl)-L-threose (1) with Propylmagnesium Bromide. To a stirred cooled (−10 °C) ethereal solution of propylmagnesium bromide, prepared from 176 mg (7.24 mmol) of magnesium and 980 mg (7.97 mmol) of 1-bromopropane, was added dropwise a solution of **1** (1.80 g, 6.03 mmol) in ether (10 mL) under N_2 during 5 min. The mixture was allowed to warm to room temperature and stirred for 14 h. Working up the resulting mixture in a similar manner to that described above afforded a mixture of the *xylo* and *lyxo* alcohols **2b** and **3b** (78:22 by ^1H NMR spectrum) as colorless oil (1.70 g, 82%). A part of this product was further separated by silica gel chromatography using gradient elution (5:1 to 3:1 hexane/ethyl acetate) to give the pure *xylo* and *lyxo* isomers **2b** and **3b**.

(2*S*,3*S*,4*R*)-1-(Benzyloxy)-2,3-bis[(methoxymethyl)oxy]-4-heptanol (**2b**): $[\alpha]^{22}_D$ −9.2° (*c* 6.63, MeOH); ^1H NMR ($CDCl_3$) δ $CHCl_3$ 0.94 (3 H, t, *J* = 6.9 Hz), 1.30–1.60 (4 H, m), 2.83 (1 H, d, *J* = 5.2 Hz), 3.37 (3 H, s), 3.41 (3 H, s), 3.57 (1 H, t, *J* = 4.4 Hz), 3.59–3.80 (3 H, m), 3.94 (1 H, q, *J* = 4.9 Hz), 4.53 (2 H, s), 4.67 (1 H, $^1/_2$ AB q, *J* = 6.8 Hz), 4.70 (1 H, $^1/_2$ AB q, *J* = 6.7 Hz),

4.74 (1 H, $^1/_2$ AB q, J = 6.7 Hz), 4.77 (1 H, $^1/_2$ AB q, J = 6.8 Hz), 7.26–7.39 (5 H, m); mass spectrum, m/e (relative intensity) 265 (4), 208 (4), 163 (15), 91 (100).

(2*S*,3*S*,4*S*)-1-(Benzyloxy)-2,3-bis[(methoxymethyl)oxy]-4-heptanol (**3b**): $[\alpha]^{22}_D$ −26.3° (*c* 7.53, MeOH); ^{1}H NMR ($CDCl_3$) δ $CHCl_3$ 0.92 (3 H, t, J = 7.1 Hz), 1.30–1.68 (4 H, m), 3.28 (1 H, d, J = 6.0 Hz), 3.39 (3 H, s), 3.41 (3 H, s), 3.54–3.77 (4 H, m), 4.02 (1 H, q, J = 4.9 Hz), 4.53 (1 H, $^1/_2$ AB q, J = 11.7 Hz), 4.55 (1 H, $^1/_2$ AB q, J = 11.7 Hz), 4.67 (1 H, $^1/_2$ AB q, J = 6.8 Hz), 4.70 (1 H, $^1/_2$ AB q, J = 6.8 Hz), 4.73 (1 H, $^1/_2$ AB q, J = 6.7 Hz), 4.81 (1 H, $^1/_2$ AB q, J = 6.7 Hz), 7.26–7.39 (5 H, m); mass spectrum, m/e (relative intensity) 265 (4), 208 (8), 163 (40), 92 (21), 91 (100).

(3*R*,4*S*)-5-(Benzyloxy)-3,4-bis[(methoxymethyl)oxy]pentan-2-one (7a). To a stirred −78 °C solution of oxalyl chloride (1.40 g, 11.03 mmol) in dichloromethane (9 mL) was added dropwise a solution of dimethyl sulfoxide (1.73 g, 22.15 mmol) in dichloromethane (8 mL) over 5 min, and the mixture was stirred for another 15 min at −78 °C. To this mixture was added dropwise a solution of a diastereomeric mixture of **2a** and **3a** (870 mg, 2.77 mmol), prepared by the Grignard reaction of **1**, in dichloromethane (7 mL) over a period of 5 min, and stirring was continued at −78 °C. After 1 h, triethylamine (3.36 g, 33.20 mmol) was added to the reaction mixture, and the reaction was allowed to warm to ambient temperature. After addition water (12 mL) the mixture was stirred for 15 min and extracted with dichloromethane (3 × 60 mL), and the extract was dried ($MgSO_4$). The solvent was removed and ether (80 mL) was added to the residue to separate triethylamine hydrochloride which was removed by filtration. The filtrate was evaporated to leave an oil, which was purified by chromatography on silica gel (4:1 hexane/ethyl acetate) to give **7a** (860 mg, 99%) as a colorless oil: $[\alpha]^{20}_D$ +33.5° (*c* 4.12, MeOH); ^{1}H NMR ($CDCl_3$) δ $CHCl_3$ 2.23, 3.28, 3.36 (each 3 H, s), 3.58–3.69 (2 H, m), 4.12–4.21 (1 H, m), 4.24 (1 H, d, J = 3.2 Hz), 4.49 (2 H, s), 4.56–4.76 (4 H, m), 7.21–7.39 (5 H, m); mass spectrum, m/e (relative intensity) 280 (0.2), 267 (1.4), 239 (1.4), 235 (1.0), 207 (1.0), 194 (1.4), 193 (1.7), 162 (14), 91 (100).

(5*R*,6*S*)-7-(Benzyloxy)-5,6-bis[(methoxymethyl)oxy]heptan-4-one (7b). Swern oxidation of a mixture of **2b** and **3b** (1.60 g, 4.67 mmol), prepared by the Grignard reaction of **1**, in a similar manner to that described above for the preparation of **7a** afforded **7b** (1.40 g, 88%) as a colorless oil: $[\alpha]^{21}_D$ +17.6° (*c* 4.90, MeOH); ^{1}H NMR ($CDCl_3$)[9] δ $CHCl_3$ 0.90 (3 H, t, J = 7.5 Hz), 1.58 (2 H, quint, J = 7.5 Hz), 2.55 (2 H, t, J = 7.5 H), 3.27 (3 H, s), 3.33 (3 H, s), 3.45–3.70 (2 H, unresolved), 4.00–5.00 (8 H, m), 7.30 (5 H, br s); mass spectrum, m/e (relative intensity) 263 (5), 239 (12), 207 (10), 194 (15), 193 (23), 191 (12), 190 (100), 189 (21), 187 (32), 163 (46); mass spectrum (isobutane CI), m/e (relative intensity) 341 (1), 309 (6), 265 (7), 190 (20), 187 (100).

(2*R*,3*S*)-4-(Benzyloxy)-2,3-bis[(methoxymethyl)oxy]-1-(4-methoxyphenyl)butan-1-one (7c). Swern oxidation of a mixture of **2c** and **3c** (2.22 g, 5.46 mmol), prepared by the Grignard reaction of **1**,[3a] in a similar manner to that described for the preparation of **7a** gave **7c** (1.84 g, 83%) as a colorless oil: $[\alpha]^{26}_D$ −2.0° (*c* 1.32, MeOH); IR ($CHCl_3$) 1670 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ $CHCl_3$ 3.19 (3 H, s), 3.27 (3 H, s), 3.56 (1 H, dd, J = 9.6, 5.0 Hz), 3.73 (1 H, dd, J = 9.6, 6.7 Hz), 3.82 (3 H, s), 4.20–4.27 (1 H, m), 4.45 (2 H, br s), 4.52 (1 H, $^1/_2$ AB q, J = 6.9 Hz), 4.63 (1 H, $^1/_2$ AB q, J = 6.9 Hz), 4.64 (1 H, $^1/_2$ AB q, J = 6.9 Hz), 4.73 (1 H, $^1/_2$ AB q, J = 6.9 Hz), 5.21 (1 H, d, J = 4.0 Hz), 6.89 (2 H, $^1/_2$ AB q, J = 8.9 Hz), 7.20–7.36 (5 H, m), 7.98 (2 H, $^1/_2$ AB q, J = 8.9 Hz); ^{13}C NMR ($CDCl_3$) δ $CDCl_3$ 55.36 (q), 55.59 (q), 55.94 (q), 69.15 (t), 73.35 (t), 76.71 (d), 77.96 (d), 96.64 (2 × t), 113.74 (4 × d), 127.59 (2 × d), 128.27 (d), 128.73 (s), 131.03 (2 × d), 137.76 (s), 163.61 (s), 196.32 (s); mass spectrum, m/e (relative intensity) 405 (0.1), 373 (1.7), 254 (6), 163 (13), 135 (100), 91 (74).

General Procedure for Reduction of Ketones 7. A. With $NaBH_4$. In a general experiment, to a stirred 0 °C solution of the ketone **7** (0.1 mmol) in ethanol (3 mL) was added $NaBH_4$ (0.2 mmol), and the mixture was stirred for 0.5–1 h. The solvent was removed in vacuo below 30 °C, water was added to the residue, and the resulting oil was taken up in ether (3 × 20 mL). The organic phase was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was subjected to preparative TLC on silica gel (1:1 hexane/ethyl acetate) to give two bands; the less polar fraction as the *lyxo* alcohol and the more polar fraction the *xylo* alcohol. Actually, these fractions were combined and the ratio of the diastereoisomers was determined by ^{1}H NMR analysis of this mixture.

B. With Vitride. To a stirred, cooled (−78 °C) solution of the ketone **7** (0.01 mmol) in toluene (0.7 mL) was added 0.03 mL (0.10 mmol) of 3.4 M vitride in toluene by using a microsyringe. The reaction mixture was stirred at −78 °C for 20 min and then at room temperature for 10 min. The reaction was quenched by addition of water (0.2 mL), and the resultant mixture was extracted with toluene (3 × 2 mL), dried ($MgSO_4$), and evaporated in vacuo. The residue was worked up in a similar manner to that described in A.

C. With $Zn(BH_4)_2$. To a stirred, cold (0 °C) solution of the ketone **7** (0.1 mmol) in ether (4 mL) was added 3.44 mL (0.5 mmol) of 0.145 M $Zn(BH_4)_2$ in ether by using a microsyringe. The reaction mixture was stirred at 0 °C for 10 min and at room temperature for 50 min. After addition of water (3 mL) and being stirred for 15 min, the mixture was extracted with ether (3 × 30 mL) and then treated in a similar manner to that described in A.

D. With L-Selectride. To a stirred, cooled (−78 °C) solution of the ketone **7** (0.1 mmol) in THF (4 mL) was added 0.2 mL (0.2 mmol) of 1 M L-Selectride in THF, and the mixture was stirred at −78 °C for 30 min. The reaction was quenched by addition of water (0.5 mL), and the reaction mixture was extracted with ether (3 × 30 mL) and worked up in a similar manner to that described in A.

Reduction of Ketone 7d with $LiAlH_4$. To a stirred cold (0 °C) mixture of $LiAlH_4$ (4 mg, 0.1 mmol) in ether (1 mL) was added to a solution of **7d** (5.6 mg, 0.0134 mmol) in ether (1 mL). The mixture was stirred at 0 °C for 30 min, quenched by addition of water (0.1 mL), and extracted with ether (3 × 10 mL). Removal of the solvent followed by preparative TLC on silica gel (2:1 hexane/ethyl acetate) afforded (2*S*,3*S*,4*S*)- and (2*R*,3*S*,4*S*)-5-(benzyloxy)-3,4-bis[(methoxymethyl)oxy]-1-(4-methoxyphenyl)-2-propanol (**3d** and **2d**)[3b] (3.7 mg, 66%) in a 64:36 ratio.

Registry No. 1, 99878-63-4; **2a**, 103499-48-5; **2b**, 103499-49-6; **2c**, 99878-64-5; **2d**, 100449-55-6; **3a**, 103616-05-3; **3b**, 103616-06-4; **3c**, 99945-48-9; **3d**, 100569-42-4; **7a**, 103499-50-9; **7b**, 103499-51-0; **7c**, 103499-52-1; **7d**, 100449-56-7; CH_3Br, 74-83-9; $BrCH_2CH_2CH_3$, 106-94-5.

(9) Recorded at 90 MHz.