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Note

Asymmetric reduction of ketones by using hydridoaluminate complexes of symmetrical, chiral, branched-chain alditol derivatives*

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Various asymmetric reactions have been reported using carbohydrates as the chiral influence[2], including markedly enantioselective reductions with lithium aluminium hydride complexed with carbohydrate diols[3]. In the latter class, the potential simplification of interpretation when using chiral diols which contain a C_2 axis of symmetry has been pointed out[4]. However, when symmetrical diols derived from D-mannitol and containing free secondary hydroxyl groups were used in this type of asymmetric reduction, the observed enantioselectivity was low[4]. We now report on similar asymmetric reductions, using a series of symmetrical, chiral diols containing tertiary alcohol groups and carrying alkyl groups of increasing steric bulk at the chiral centre.

Recently, chiral amino alcohols derived from amino acids have been used in highly enantioselective reductions[5]. In these reactions, the chiral ligands contain a tertiary alcohol group that is not a chiral centre. We also report our experience with a symmetrical tertiary diol in this class.

For synthesis of the desired bis-branched-chain mannitol derivatives, the potential strategy involving addition of a range of Grignard reagents to the corresponding diketone has been shown to be generally unsatisfactory[6]. For the synthesis of a more limited range of bis-branched derivatives, a convenient starting material was the di-epoxide 2,2′:5,5′-dianhydro-1,3:4,6-di-*O*-benzylidene-2,5-di-*C*-hydroxymethyl-D-mannitol[6] (**1**), which had been reduced[6] to the 2,5-di-*C*-methyl-diol **2**, the first member of the proposed series of tertiary diols. The reaction of **1** with methylmagnesium iodide gave the bis-iodomethyl derivative **3**. This reaction, involving epoxide opening by halide ion rather than by carbanion attack, is well known[7] and can be avoided with organocopper reagents[8]. Thus, with a mixture of

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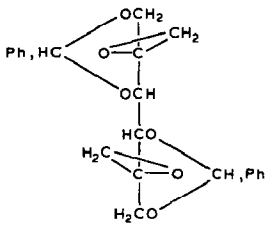

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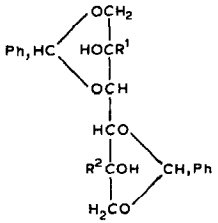
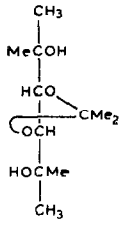


2 $R^1 = R^2 =$ Me
3 $R^1 = R^2 = CH_2I$
4 $R^1 = R^2 =$ Et
5 $R^1 = R^2 = CH_2Br$
6 $R^1 = CH_2Br, R^2 =$ Bn
7 $R^1 = R^2 =$ Bn
8 $R^1 = R^2 = H$



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methyl-lithium and cuprous iodide, the desired di-*C*-ethyl branched hexitol derivative **4** was obtained from the di-epoxide **1**. Reaction of **1** with phenyl-magnesium bromide gave a mixture of **5** and **6** resulting from epoxide opening by bromide ion and phenyl carbanion. Again, with phenyl-lithium and cuprous bromide, the reaction was more clear-cut and gave the di-*C*-benzyl-diol **7**. Thus, these reactions, together with the previous reduction, have afforded three bis-branched mannitol derivatives having methyl, ethyl, and benzyl branches. The constitution and configuration of these derivatives follows logically from their syntheses, since the nucleophilic attack occurs at the primary carbon atom and the *manno* configuration of the starting epoxide should not be changed during the above transformations.

The ability of these symmetrical, chiral, tertiary diols to influence asymmetric reductions of a number of representative ketones with lithium aluminium hydride was explored and compared with results obtained[4] using secondary diols (see Table I). The secondary diol 1,3:4,6-di-*O*-benzylidene-D-mannitol (**8**) can be considered to be the parent for this group of tertiary diols, since the latter can be formally obtained from **8** by replacement of two hydrogen atoms by alkyl groups. Asymmetric reduction of acetophenone conditioned by **8** had previously given[4] a 9.8% optical yield of the *S*-alcohol in ether–tetrahydrofuran. In contrast, in a similar reduction of acetophenone using the tertiary diol **2**, the selectivity was largely lost and the *R*-alcohol was obtained in ~0.2% optical yield. With the di-*C*-ethyl-diol **4** in ether–tetrahydrofuran, the selectivity was improved slightly, again favouring the *R*-alcohol. With the di-*C*-benzyl-diol **7**, acetophenone was reduced in ether–tetrahydrofuran to give preferentially the *S*-alcohol in 13.1% optical yield. Similarly, the optical yield was 11.7% when propiophenone was reduced under the same conditions.

Thus, in comparing results with **8** and **2**, the change from secondary to tertiary hydroxyl group caused a decrease in enantioselectivity and induced selective formation of the opposite enantiomer. The selectivity in reduction increased with increase in bulk of the alkyl group in the series of tertiary diols **2**, **4**, and **7**, and the selectivity again changed to preferential formation of the *S*-enantiomer with diol **7**. The optical yield with the tertiary diol **7** was not significantly better than with the secondary diol **2**.

When aliphatic ketones were reduced with complexes derived from these

TABLE I

ASYMMETRIC REDUCTIONS WITH CHIRAL DIOLATOHYDRIDOALUMINATE(III) COMPLEXES

Ketone	*Diol*	*Branching group*	*Solvent*[a]	*Yield (%)*	$[\alpha]_D$ *(degrees)*		*Optical yield (%)*	*Main isomer*
					Obs.	*Max.*[b]		
Acetophenone	**2**	Me	E	50	+0.764	+42.8(*R*)	1.8	*R*
	2	Me	E + T	47	+0.082		0.2	*R*
	4	Et	E	70	−0.876		2.0	*S*
	4	Et	E + T	60	+0.820		1.9	*R*
	7	$PhCH_2$	E + T	80	−5.463		13.1	*S*
	8	H	E + T	69	−4.174		9.8	*S*[c]
Propiophenone	**7**	$PhCH_2$	E + T	63	−3.230	−27.7(*S*)	11.7	*S*
	8	H	E + T	62	−1.512		5.6	*S*[c]
	9	Me	E	35	+0.67		2.4	*R*
3,3-Dimethylbutan-2-one	**2**	Me	E	54	+0.104	+7.8(*S*)	1.3	*S*
	2	Me	E + T	44	±0		0	
	4	Et	E + T	50	±0		0	
	7	$PhCH_2$	E + T	56	−0.013		0.2	*R*
4-Methylpentan-2-one	**7**	$PhCH_2$	E + T	40	+0.508	+20.5(*S*)	2.5	*S*
4,4-Dimethylpentan-2-one	**7**	$PhCH_2$	E + T	61	+0.463	+24.8(*S*)	1.9	*S*

[a]E, Diethyl ether; E + T, diethyl ether and tetrahydrofuran. [b]Values for maximum rotation and configuration taken from ref. 9. [c]Values taken from ref. 4.

tertiary diols, only **7** gave optically active products but with low enantioselectivity; in one case, the *R*-isomer was selectivitely formed, and in the other, the *S*-isomer preponderated. With aliphatic ketones, the enantioselectivity was lower than with the parent secondary diol. Two of the tertiary diols were sufficiently soluble to allow reduction in ether solvent. In the reactions studied, the enantioselectivity was slightly better compared with the above results with tetrahydrofuran. In the case of the reduction of acetophenone conditioned by **4**, the preponderant enantiomeric product changed on changing the solvent. These bewildering reversals in enantioselectivity with solvent and with steric bulk cannot be simply explained in terms of the transition-state models previously proposed[4]. Furthermore, the relatively low enantioselectivity observed serves to limit the practical utility of these asymmetric reductions.

The symmetrical, chiral tertiary diol 1,6-dideoxy-3,4-*O*-isopropylidene-2,5-di-*C*-methyl-L-*threo*-hexitol (**9**), which is readily obtainable from tartaric acid, has been used in asymmetric Grignard addition reactions[1]. The tertiary carbon atoms in **9** are not chiral centres, whereas they are in **2, 4**, and **7**; nevertheless, **9** should still induce asymmetric synthesis. When the dihydroaluminate complex of this diol was made in ether solution and used to reduce propiophenone and cyclohexyl phenyl ketone, the *R*-alcohol was selectively produced but the enantioselectivity was low (see Table I). Furthermore, the synthetic yields were also low. Consequently, asymmetric reductions conditioned by this diol also have limited practical utility.

EXPERIMENTAL

General methods. — Melting points are uncorrected. T.l.c. was performed on silica gel (Merck, 7731) with detection by iodine vapour or vanillin–sulphuric acid. Column chromatography was conducted on silica gel (Merck, 7734). Optical rotations were determined with a Perkin–Elmer 141 automatic polarimeter (1-dm tube) at 21°. N.m.r. spectra (internal Me_4Si) were recorded at 100 MHz with a Perkin–Elmer R14 spectrometer. Chemical shifts are given in p.p.m.

*1,3:4,6-Di-O-benzylidene-2,5-di-C-iodomethyl-*D*-mannitol* (**3**). — A solution of 2,2′:5,5′-di-*O*-benzylidene-2,5-di-*C*-hydroxymethyl-D-mannitol (**1**, 0.5 g) in dry ether (100 mL) was added to a solution of Grignard reagent made from magnesium (0.19 g) and iodomethane (1.13 g) in dry ether (50 mL). The solution was heated under reflux for 0.5 h and then poured into ice and water (50 mL). Conventional extraction with ether gave **3** (0.56 g, 67%), m.p. 145–146° (from chloroform–light petroleum), $[\alpha]_D$ −13° (*c* 1, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 2.63 (s, 2 H, 2 OH), 3.77, 3.88, 4.00, and 4.11 (ABq, 4 H, 2 CH_2I), 4.34, 4.46, 4.59, and 4.71 (ABq, 4 H, H-1,1,6,6), 4.40 (s, 2 H, H-3,4), 5.60 (s, 2 H, 2 PhC*H*), 7.4 (m, 10 H, 2 Ph) (Found: C, 41.7; H, 3.8; I, 40.0. $C_{22}H_{24}I_2O_6$ calc.: C, 41.4; H, 3.8; I, 39.8%).

Action of phenyl Grignard reagent on **1**. — A solution of **1** (0.5 g) in dry ether (100 mL) was added to a solution of Grignard reagent made from magnesium (96

mg) and bromobenzene (0.62 g) in dry ether (50 mL). The mixture was heated under reflux for 2 h and then poured into ice and water (50 mL). Conventional extraction with ether gave a red syrup (1.0 g), column chromatography of which on silica gel (100 g), using tetrachloromethane–ethyl acetate (4:1), gave, first, 2-*C*-benzyl-1,3:4,6-di-*O*-benzylidene-5-*C*-bromomethyl-D-mannitol (**6**; 41 mg, 6%), m.p. 135–136°. ^{1}H-N.m.r. data: δ 2.95–4.58 (5 ABq, 10 H, H-1,3,4,6,2′,5′), 5.61 and 5.65 (2 s, 2 H, 2 PhC*H*), 7.3 (m, 15 H, 3 Ph) (Found: Br, 15.1. $C_{28}H_{29}BrO_6$ calc.: Br, 14.8%).

Eluted second was 1,3:4,6-di-*O*-benzylidene-2,5-di-*C*-bromomethyl-D-mannitol (**5**; 37 mg, 5%), m.p. 148–149°. ^{1}H-N.m.r. data: δ 2.68 (s, 2 H, 2 OH), 3.57, 3.69, 4.40, and 4.52 (ABq, 4 H, H-1,6), 3.89, 4.00, 4.15, and 4.25 (ABq, 4 H, 2 CH_2Br), 4.4 (s, 2 H, H-3,4), 5.59 (s, 2 H, 2 PhC*H*), 7.4 (m, 10 H, 2 Ph) (Found: Br, 29.3. $C_{22}H_{24}Br_2O_6$ calc.: Br, 29.4%).

1,3:4,6-Di-O-benzylidene-2,5-di-C-ethyl-D-mannitol (**4**). — A suspension of cuprous iodide (20 g, 0.105 mol) in dry ether (100 mL) was stirred under nitrogen with cooling in a salt/ice bath. Methyl-lithium (0.21 mol) was added during 1 h followed by **1** (4.0 g). The mixture was stirred and allowed to attain room temperature overnight, and then poured into water (200 mL). Ether extraction gave a syrup, column chromatography of which on silica gel (130 g), using benzene–ether (4:1), gave a small amount of the di-iodide **3** and then **4** (3.03 g, 70%), m.p. 123–124°, $[\alpha]_D$ +2° (*c* 1, chloroform). ^{1}H-N.m.r. data: δ 0.97 (t, 6 H, 2 CH_2CH_3), 1.29–2.37 (m, 4 H, 2 CH_2CH_3), 3.40 (s, 2 H, 2 OH), 3.39, 3.52, 4.11, 4.24 (ABq, 4 H, H-1,1,6,6), 4.00 (s, 2 H, H-3,4), 5.52 (s, 2 H, 2 PhC*H*), 7.4 (m, 10 H, 2 Ph) (Found: C, 69.6; H, 7.1. $C_{24}H_{30}O_6$ calc.: C, 69.55; H, 7.3%).

2,5-Di-C-benzyl-1,3:4,6-di-O-benzylidene-D-mannitol (**7**). — A suspension of cuprous bromide (15.0 g, 0.105 mol) in dry ether (100 mL) was stirred under nitrogen with cooling in salt/ice, and phenyl-lithium (0.21 mol) was added during 1 h followed by **1** (4.0 g). The mixture was stirred and allowed to attain room temperature overnight, and then poured into water (200 mL), filtered, and extracted with ether (2 × 100 mL) to give the product (0.15 g, 12%). The above insoluble material was extracted with hot tetrahydrofuran (2 × 250 mL) to give, after crystallisation from benzene, **7** (5.0 g, 62%), m.p. 293–295°, $[\alpha]_D$ +99° (*c* 1, methyl sulphoxide). ^{1}H-N.m.r. data [$(CD_3)_2SO$]: δ 2.93, 3.06, 3.24, 3.39 (ABq, 4 H, H-1,1,6,6), 3.36, 3.47, 3.57, 3.68 (ABq, 4 H, 2 PhCH_2), 4.34 (s, 2 H, H-3,4), 5.25 (s, 2 H, 2 OH), 5.70 (s, 2 H, 2 PhC*H*), 7.3 (m, 20 H, 4 Ph) (Found: C, 75.9; H, 6.7. $C_{34}H_{34}O_6$ calc.: C, 75.8; H, 6.4%).

Reduction of ketones with lithium 2,5-di-C-alkyl-1,3:4,6-di-O-benzylidene-D-mannitolatodihydridoaluminate. — (*a*) A solution of **2** (3.6 g, 8.7 mmol) in dry ether (100 mL) was added to a dry solution (8.7 mL) of lithium aluminium hydride (8.7 mmol) in ether. The mixture was heated under reflux for 0.5 h and a solution of acetophenone (2.0 g, 16.6 mmol) in dry ether (20 mL) was then added. The mixture was heated for a further 2 h, water (15 mL) was added, the aqueous layer was extracted with ether (2 × 50 mL), and the combined ether layers were dried

($MgSO_4$) and concentrated. Column chromatography of the resulting syrup on silica gel (80 g), using benzene–ether (4:1), gave 1-phenylethanol (1.4 g, 70%), b.p. 98–102°/15 mmHg, $[\alpha]_D$ −0.876° (neat liquid), which was homogeneous by g.l.c. (PEGA, 150°).

(*b*) The reduction was performed as in (*a*) except that a solution of **2** in dry tetrahydrofuran (60 mL) was added. Chromatography and distillation gave 1-phenylethanol (1.2 g, 60%), b.p. 98–102°/15 mmHg, $[\alpha]_D$ +0.82° (neat liquid).

(*c*) The reaction was repeated essentially as in (*b*), using **7**. The organic residue was separated by trituration twice with hot ether to leave **7** (98%). The combined ether extract was concentrated under reduced pressure and the residue distilled to give 1-phenylethanol (80%), b.p. 98–102°/15 mmHg, $[\alpha]_D$ −5.46° (neat liquid), which was homogeneous by g.l.c. (PEGA, 150°).

(*d*) Several other ketones were reduced under the conditions described above, using **2, 4, 7**, or **9**. The results are summarised in Table I.

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