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Chiral β-Oxidofunctionalised Organolithium Compounds from Epoxides: EPC-Synthesis of 1,3-Diols

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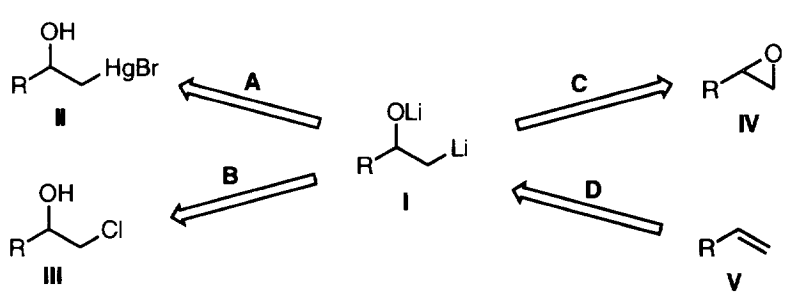
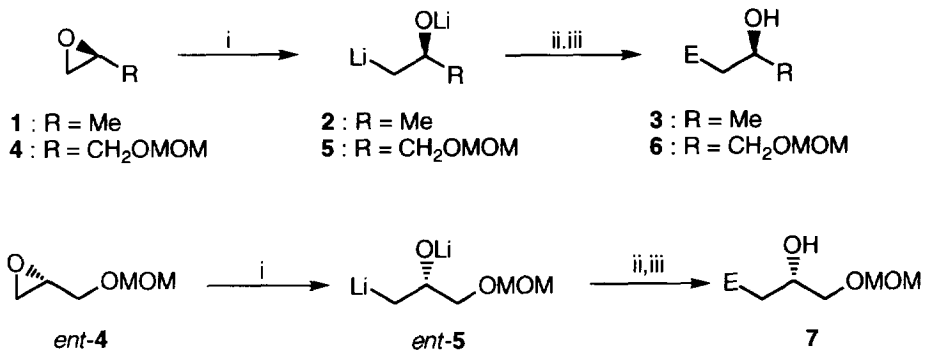
Abstract: The reductive opening of (*S*)-propylene oxide (**1**) with lithium powder and a catalytic amount of DTBB (5 mol %) in THF at -78°C followed by treatment with different carbonyl compounds [Bu^{t}CHO, PhCHO, $(CH_2)_5CO$ and PhCOMe] at the same temperature leads, after hydrolysis with water to the expected chiral 1,3-diols **3**. The same methodology applied to both (*R*) and (*S*) protected epoxyalcohols **4** yields the expected enantiomerically pure compounds **6** and **7**, wich are monoprotected 1,2,4-triols; carbonation of these last two starting materials affords hydroxyacids **6d** and **7d**.

Functionalised organolithium compounds[1] are interesting intermediates in synthetic organic chemistry because their ability to transfer the functionality to an electrophilic reagent giving, in general, polyfunctionalised structures. In the particular case of β-oxidofunctionalised derivatives of the type **I**, which can be considered as d^2 reagents following Seebach's nomenclature[2], three different routes have been reported for their preparation: (a) mercury-lithium transmetallation from hydroxymercurials **II**[3] (route A); (b) chlorine-lithium exchange from chlorohydrins **III**[4] (route B); (c) reductive ring opening of epoxides **IV**[5] (route C). Intermediates **I** are unstable species, which should be prepared and handled at low temperature (-78°C) in order to avoid decomposition, mainly by β-elimination giving olefins **V**[6] (route D). The chiral version of intermediates **I** has been achieved following route B[7], existing, to our best knowledge, only one example of application of route C to this purpose, namely in one of the steps of the synthesis of calcitriol lactone[8]. On the other hand, we discovered recently a very efficient method[9] to lithiate different oxygenated[10], nitrogenated[11] or sulfur-containing[12] substrates as well as saturated heterocycles[13] or polychlorinated materials[14] by using lithium powder and a catalytic amount of an arene, naphthalene or 4,4'-di-*tert*-butylbiphenyl (DTBB) being the most widely used. In this paper we describe the application of this methodology to the reductive opening of chiral epoxides, so chiral 1,3-diols[15] are prepared as a typical example of EPC-synthesis[16].

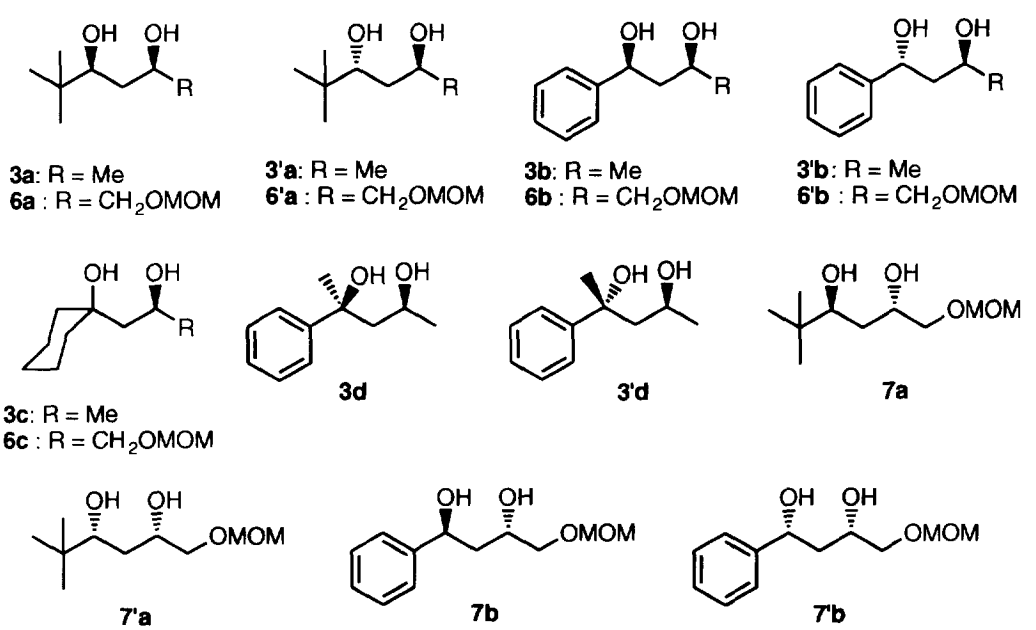


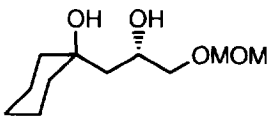
Scheme 1.

The reaction of commercially available (*S*)-propylene oxide (**1**)[17a] with an excess of lithium powder in the presence of a catalytic amount of DTBB (5 mol %) in THF at -78°C led to a solution of intermediate **2**, which after reaction with different electrophiles [Bu^{t}CHO, PhCHO, $(CH_2)_5CO$ and PhCOMe] at the same temperature followed by hydrolysis with water afforded the expected chiral compounds **3** (Scheme 2 and Table 1, entries 1-7). When the carbonyl compound was prochiral a *ca.* 1:1 diastereoisomers mixture (**3/3'**) was obtained, which could be separated by flash chromatography (silica gel, hexane/ethyl acetate), so both enantiomerically pure diastereoisomers **3** and **3'** were obtained in pure form[18].

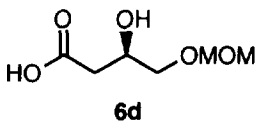


Scheme 2. *Reagents and conditions*: i, Li, DTBB cat. (5 mol %), THF, -78°C; ii, E^+ = Bu^{t}CHO, PhCHO, $(CH_2)_5CO$, PhCOMe, -78°C; iii, H_2O, -78 to 20°C.

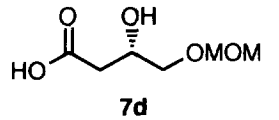




7c



6d



7d

Table 1. Preparation of Chiral 1,3-Diols **3**, **6** and **7**

Entry	Starting material	Intermediate	Electrophile E+	Product[a] No.	R_f[b] or mp[c]	$[\alpha]_D^{20}$[d]	Yield (%)[e]
1	**1**	**2**	ButCHO	**3a**	45°C	+7.2	63
2				**3'a**	85°C	+45.2	
3	**1**	**2**	PhCHO	**3b**	0.21	-33.2	64
4				**3'b**	0.27	+55.2	
5	**1**	**2**	$(CH_2)_5CO$	**3c**	0.45	+2.6	68
6	**1**	**2**	PhCOMe	**3d**	0.41	+31.2	62
7				**3'd**	0.34	-27.0	
8	**4**	**5**	ButCHO	**6a**	0.44	-10.2	67
9				**6'a**	0.30	+20.0	
10	**4**	**5**	PhCHO	**6b**	0.31	-22.6	69
11				**6'b**	0.24	+31.1	
12	**4**	**5**	$(CH_2)_5CO$	**6c**	0.32	-4.8	58
13	*ent*-**4**	*ent*-**5**	ButCHO	**7a**	0.30	-17.2	63
14				**7'a**	0.44	+12.0	
15	*ent*-**4**	*ent*-**5**	PhCHO	**7b**	0.24	-33.2	66
16				**7'b**	0.31	+26.4	
17	*ent*-**4**	*ent*-**5**	$(CH_2)_5CO$	**7c**	0.32	+4.0	60

[a] All products **3**, **6**, and **7** were >95% pure (GLC and 300 MHz ^1H NMR) and were fully characterised by spectroscopic means (IR, ^1H and ^{13}C NMR, and MS). [b] Silica gel, hexane/ethyl acetate: 2/1. [c] From hexane/ethyl acetate. [d] In dichloromethane, c=1.0. [e] Global yield of *ca.* 1:1 mixture of diastereoisomers.

The possibility of applying this methodology for the preparation of polyols[15] was explored starting from the protected epoxides **4**[19]. Following the same procedure described for epoxide **1** the expected chiral compounds **6** and **7** were obtained through the corresponding enantiomeric intermediates **5** and *ent*-**5** (Scheme 2 and Table 1, entries 8-17). Also in this case the reaction with pivalaldehyde and benzaldehyde afforded a *ca.* 1:1 diastereoisomers mixture (**6/6'** or **7/7'**), which was separated chromatographically allowing the preparation of enantiomerically pure diastereoisomers[18]. For starting materials **4** and *ent*-**4** the carbonation reaction was studied, so both enantiomeric hydroxyacids **6d** and **7d** were isolated in pure form with modest isolated yields (30 and 24%, respectively)[20].

The optical purity of the obtained compounds is related to the starting materials **1**, **4** and *ent*-**4**, since no racemisation has never been observed for this type of systems[7,8], so this procedure represents a typical example of EPC-synthesis[16]. Finally, we think that this methodology can potentially be applied for the synthesis of desoxysugars[21].

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16. See, for instance: Seebach, D.; Hungerbühler, E. In *Modern Synthetic Method*; Shefold, R., Ed.; Salle+Sauerländer Verlag: Aarau, 1980; pp. 91-171.
17. (a) This compound is available from Aldrich in 99% purity. (b) These compounds are available from Aldrich in 96% purity.
18. The stereochemistry of 1,3-diols described in this paper was determined by ^{1}H NMR experiments.
19. Both compounds **4** and *ent*-**4** were prepared from the corresponding epoxyalcohols by successive treatment with *n*-butyllithium in THF and chloromethyl methyl ether (-78 to 20°C) in 96% isolated yield. Compound **4**: R_f 0.16 (hexane); $[\alpha]_D^{20}$ -1.6 (c 1.1, CH_2Cl_2). Compound *ent*-**4**: R_f 0.16 (hexane); $[\alpha]_D^{20}$ +1.9 (c 1.2, CH_2Cl_2).
20. Compound **6d**: R_f 0.14 (hexane/ethyl acetate: 1/1); $[\alpha]_D^{20}$ +2.3 (c 1.0, CH_2Cl_2). Compound **7d**: R_f 0.14 (hexane/ethyl acetate: 1/1); $[\alpha]_D^{20}$ -2.7 (c 0.9, CH_2Cl_2).
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