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Chiral Epoxides as a Source of Chiral β-Oxidofunctionalised Organolithium Compounds: Reaction with Electrophiles†

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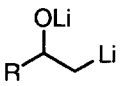
Abstract: The reductive opening of chiral epoxides **1**, **4**, **7** and **11** with lithium powder and a catalytic amount of DTBB (5 mol %) in THF at -78°C, followed by treatment with different electrophiles [Bu^{t}CHO, PhCHO, $(CH_2)_5CO$, PhCOMe, CO_2, H_2O, D_2O,] at the same temperature leads, after hydrolysis with water, to enantiomerically pure functionalised alcohols **3**, **6**, **9**, **10** and **13**. Monoprotected diols **6** and **10** give 1,2,4-triols **14** after treatment under acidic conditions in methanol, in almost quantitative yield. Copyright © 1996 Elsevier Science Ltd

INTRODUCTION

Among the different methodologies to prepare enantiomerically pure compounds[1] one of the most used take advantage of the chiral pool, that is the so called EPC-synthesis.[2] In this strategy the organic chemist uses easily available (commercially if possible) chiral molecules in order to transform them to prepare the target molecule. One of the possible starting materials to carry out the mentioned strategy are chiral epoxides, which are easily available from natural α-hydroxyacids. Although the most important reactivity of epoxides includes a nucleophilic opening of the three-membered ring under acidic or basic conditions,[3] ten years ago Bartmann reported[4] the arene-catalysed lithiation of epoxides, which allows the possibility of preparing β-oxidofunctionalised organolithium compounds **I** and the subsequent reaction with electrophiles, this process being complementary to the former nucleophilic opening of epoxides. Intermediates of type **I** have also been prepared following two alternative routes: chlorine/lithium exchange from chlorohydrins[5] or mercury/lithium transmetallation from hydroxymercurials.[6,7] In general, functionalised organolithium compounds[8] are interesting building blocks because by reaction with carbon electrophiles they produce together with the formation of a carbon-carbon bond the transference of the functionality to the electrophilic reagent, so polyfunctionalised molecules are prepared in only one reaction step. On the other hand, five years ago we discovered that a catalytic amount of an arene [naphthalene or 4,4'-di-*tert*-butylbiphenyl (DTBB) being mainly used][9] can accelerate very much the lithiation of chlorinated precursors at low temperature.[10] This arene catalysed lithiation can be used not only for chlorine-lithium exchange,[11] but also to open oxygen-, nitrogen-, or sulfur-containing heterocycles,[12] or to prepare polylithium synthons,[13] as well as for the development of new

† Dedicated to Professor Juan Bertrán on his 65th birthday

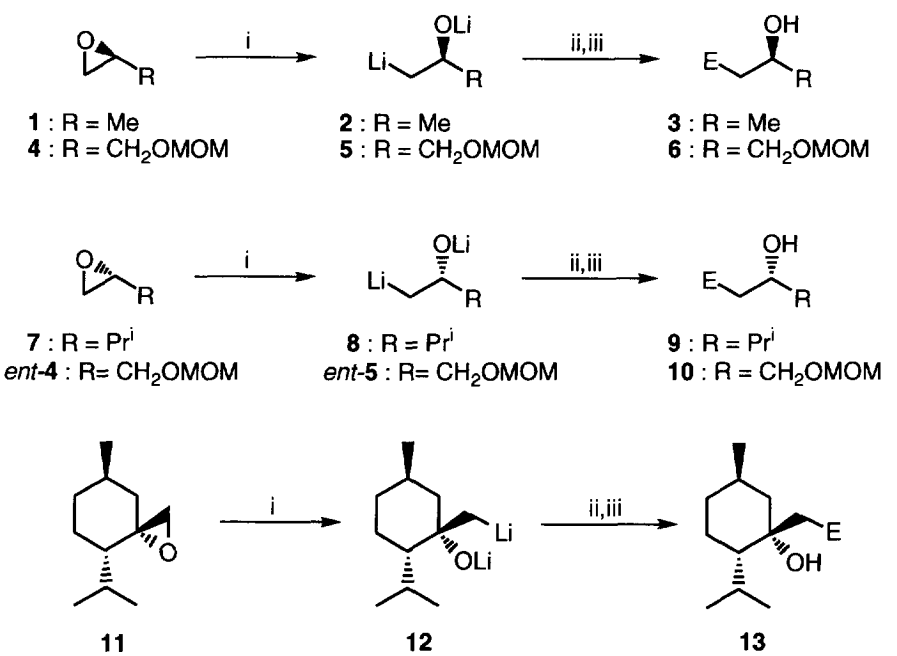
routes for organolithium intermediates.[14] In this paper we apply this methodology to the preparation of chiral organolithium compounds of the type **I**,[15] which have been achieved by chlorine/lithium exchange with lithium naphthalene from chiral chlorohydrins,[16] existing -to our best knowledge- only one example of opening of a chiral epoxide, using Bartmann's methodology, in one step of the synthesis of calcitriol lactone.[17,18]



I

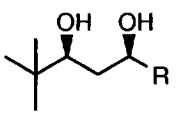
RESULTS AND DISCUSSION

Treatment of commercially available (*S*)-propylene oxide **1** with an excess of lithium powder in the presence of a catalytic amount of DTBB (5 mol %) in THF at -78°C[19] led to a solution of intermediate **2**, which after reaction with different electrophiles [Bu^{t}CHO, PhCHO, $(CH_2)_5CO$, PhCOMe] at the same temperature, followed by hydrolysis with water, afforded the expected chiral compounds **3**[20] (Scheme 1, Chart 1 and Table 1, entries 1-7). For prochiral carbonyl compounds 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, their corresponding stereochemistry being assigned by 300 MHz ^{1}H NMR experiments.

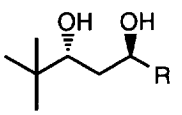


Scheme 1. *Reagents and conditions* : i, Li, DTBB cat. (5 mol %), THF, -78°C; ii, E$^+$= Bu^{t}CHO, PhCHO, $(CH_2)_5CO$, PhCOMe, CO_2, H_2O, D_2O, -78°C; iii, H_2O, -78 to 20°C.

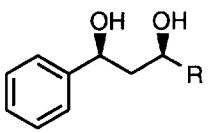
The same methodology was applied to both protected enantiomeric hydroxy epoxides **4** and *ent*-**4**[21] in order to explore the possibility of using this procedure to prepare polyols.[22] Thus, through intermediates **5** or *ent*-**5** the expected products **6** and **10** were, respectively, prepared (Scheme 1, Chart 1 and Table 1, entries 8-13 and 16-21). In both cases the reaction with carbon dioxide was studied giving the corresponding enantiomeric hydroxyacids **6e** and **10e** with modest yields (Table 1, entries 13 and 21). Also in the case when pivaldehyde or benzaldehyde were used as electrophiles a *ca.* 1:1 diastereoisomers mixture was obtained and separated chromatographically (see above).



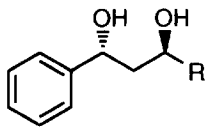
3a: R = Me
6a : R = CH_2OMOM



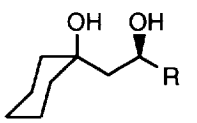
3'a: R = Me
6'a : R = CH_2OMOM



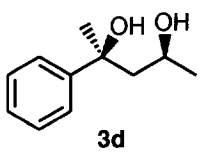
3b: R = Me
6b : R = CH_2OMOM



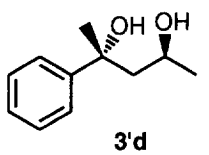
3'b: R = Me
6'b : R = CH_2OMOM



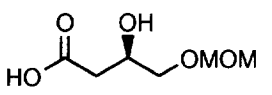
3c: R = Me
6c : R = CH_2OMOM



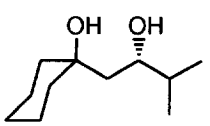
3d



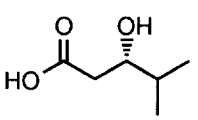
3'd



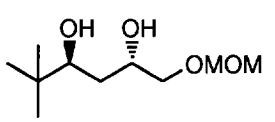
6e



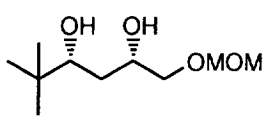
9c



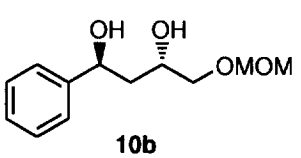
9e



10a



10'a



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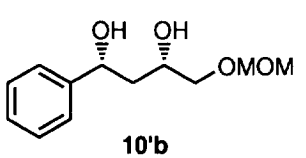
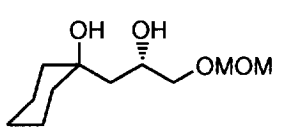
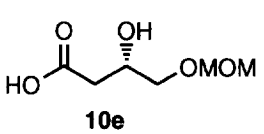


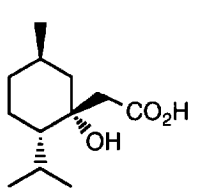
10'b



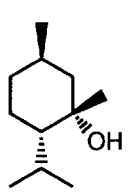
10c



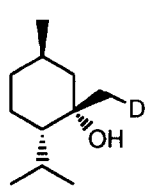
10e



13e



13f



13g

Chart 1.

Table 1. Preparation of Compounds **3**, **6**, **9**, **10** and **13**

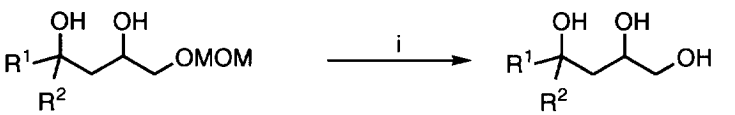
Entry	Starting material	Intermediate	Electrophile E+	Product[a] No.	R_f[b] or mp[c]	$[\alpha]_D^{20}$[d]	Yield(%)[e]
1	**1**	**2**	Bu^{t}CHO	**3a**	45°C	+7.2	63
2				**3'a**	85°C	+45.2	
3	**1**	**2**	PhCHO	**3b**	0.21	-33.2	64
4				**3'b**	0.27	+55.2	
5	**1**	**2**	$(CH_2)_5CO$	**3c**	0.45	+2.6	68
6	**1**	**2**	PhCOMe	**3d**	0.41	+31.2	62
7				**3'd**	0.34	-27.0	
8	**4**	**5**	Bu^{t}CHO	**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	**4**	**5**	CO_2	**6e**	0.14[f]	+2.3	30
14	**7**	**8**	$(CH_2)_5CO$	**9c**	0.56	-7.6[g]	69
15	**7**	**8**	CO_2	**9e**	0.31	-31.9[h]	80
16	*ent*-**4**	*ent*-**5**	Bu^{t}CHO	**10a**	0.30	-17.2	63
17				**10'a**	0.44	+12.0	
18	*ent*-**4**	*ent*-**5**	PhCHO	**10b**	0.24	-33.2	66
19				**10'b**	0.30[i]	+26.4	
20	*ent*-**4**	*ent*-**5**	$(CH_2)_5CO$	**10c**	0.32	+4.0	60
21	*ent*-**4**	*ent*-**5**	CO_2	**10e**	0.14[f]	-2.7[i]	24
22	**11**	**12**	CO_2	**13e**	0.53	-4.4[g]	78
23	**11**	**12**	H_2O	**13f**	0.30[j]	-4.6[k]	90
24	**11**	**12**	D_2O	**13g**	0.30[j]	-5.2[i]	70

[a] All products **3**, **6**, **9**, **10** and **13** were > 95% pure (GLC and 300 MHz ^{1}H NMR). [b] Silica gel, hexane/ethyl acetate: 2/1, unless otherwise stated. [c] From hexane/ethyl acetate. [d] In dichloromethane, c= 1.0, unless otherwise stated. [e] Global yield (*ca.* 1:1 diastereoisomers mixture for prochiral electrophiles) based on the starting epoxide **1**, **4**, **7** or **11**. [f] Silica gel, hexane/ethyl acetate: 1/1. [g] c= 1.10. [h] c= 0.65. [i] c= 0.90. [j] Silica gel, hexane/ethyl acetate: 20/1. [k] c= 1.25.

Branched epoxide **7** was obtained from (*S*)-valine by nitrosation, followed by reduction with $LiAlH_4$ and final basic hydrolysis (41% overall yield).[23] The tandem DTBB-catalysed opening of the epoxide-reaction with cyclohexanone or carbon dioxide as electrophiles led to the enantiopure compounds **9c** and **9e**, respectively, the carbonation occurring with good yield (Scheme 1, Chart 1 and Table 1, entries 14 and 15). Intermediate **8** is probably involved in this reaction.

Finally, we studied the reaction above described using a more congested epoxide such as **11**[24] [prepared from (-)-menthone by reaction with *in situ* generated chloromethyllithium[25]], which after reductive opening yielded the intermediate **12**. The final reaction of this species with different electrophiles (CO_2, H_2O, D_2O) afforded the corresponding products **13e-g**[26] (Scheme 1, Chart 1 and Table 1, entries 22-24).

In the last part of this study we performed the deprotection of representative protected diols **6** and **10** under acidic conditions in methanol, so the expected crude triols **14** were obtained in essentially pure form (Scheme 2 and Table 2).



6a/6'a, **10a/10'a**: R^1= H, R^2= Bu^t
6b/6'b, **10b/10'b**: R^1= H, R^2= Ph
6c, **10c**: R^1-R^2= $(CH_2)_5$

14/14', *ent*-**14**/*ent*-**14'**

Scheme 2. *Reagents and conditions* : i, 4N HCl-MeOH, 25°C, 4 h.

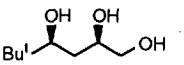
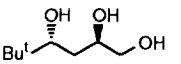
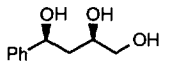
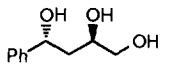
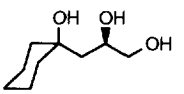
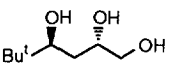
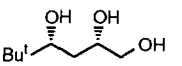
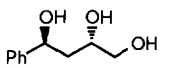
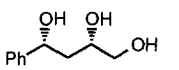
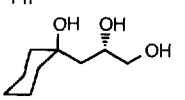
As a conclusion, we think that the here described methodology is a easy way to prepare diols or triols in an enantiomerically pure form (EPC-synthesis) starting from easily available materials. This strategy can be extended to the preparation of polyols related to carbohydrates.

EXPERIMENTAL PART

General.- For general information see reference 27. Starting material **1** was commercially available; the other chiral epoxides **4**,[28] *ent*-**4**,[28] **7**[23] and **11**[24] were prepared according to the literature procedures.

DTBB-Catalysed Lithiation of Chiral Epoxides **1**, **4**, ent-**4**, **7** *and* **11** *and Reaction with Electrophiles. Isolation of Compounds* **3**, **6**, **9**, **10** *and* **13**. *General Procedure.*- To a cooled (-78°C) blue suspension of lithium powder (0.100 g, 14.0 mmol) and a catalytic amount of 4,4'-di-*tert*-butylbiphenyl (0.040 g, 0.15 mmol) in THF (10 ml) was added the corresponding epoxide (1.5 mmol) under argon and the mixture was stirred at -78°C for 2 h. Then, the corresponding electrophile (1.6 mmol; 0.5 ml in the case of water or deuterium oxide; CO_2 was bubbled for 30 min) was added and the temperature was allowed to rise to 20°C overnight. The resulting mixture was hydrolysed with water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and evaporated (15 mmHg). The resulting residue was purified by column chromatography (silica gel, hexane/ethyl acetate) and/or recrystallised to yield pure products **3**, **6**, **9**, **10** and **13**. Yields and physical data (mp's or R_f values and especific rotations) are included in Table 1; analytical and espectroscopic data as well as literature references follow.

Table 2. Preparation of Triols **14**

Entry	Starting material	Product[a] Structure	No.	$[\alpha]_D$[b]	Yield(%)[c]
1	**6a**		**14a**	-11.6 (1.40)	>95
2	**6'a**		**14'a**	+6.2 (1.15)	>95
3	**6b**		**14b**	-19.2 (1.15)	>95
4	**6'b**		**14'b**	+19.4 (0.50)	>95
5	**6c**		**14c**	-2.6 (0.65)	>95
6	**10a**		*ent*-**14'a**	-7.1 (0.35)	>95
7	**10'a**		*ent*-**14a**	+11.0 (0.80)	>95
8	**10b**		*ent*-**14'b**	-21.3 (0.40)	>95
9	**10'b**		*ent*-**14b**	+21.8 (0.85)	>95
10	**10c**		*ent*-**14c**	+3.1 (0.85)	>95

[a] All products **14** were >95% pure (300 MHz ^{1}H NMR). [b] In dichloromethane; the corresponding concentration is given in parenthesis. [c] Isolated crude yield of essentially pure compounds (300 MHz ^{1}H NMR).

(2S,4S)-5,5-Dimethyl-2,4-hexanediol **3a** :[29] ν_{max} (KBr) 3500-3100 cm^{-1} (OH); δ_H 0.89 [9H, s, $(CH_3)_3C$], 1.20 (3H, d, *J*= 6.1, CH_3CH), 1.41 (1H, dt, *J*= 14.4, 10.0, C*H*H), 1.60 (1H, dt, *J*= 14.4, 2.1,CH*H*), 3.38 (1H, br s, 2xOH), 3.48 (1H, dd, *J*= 10.0, 2.1, CCH), 3.95-4.01 (1H, m, C*H*CH_3); δ_C 24.1 (CH_3CH), 25.5 [$(CH_3)_3C$], 34.7 [$(CH_3)_3C$], 38.6 (CH_2), 69.3 (CH_3CH), 80.9 (C*C*H); m/z 89 [M+-$(CH_3)_3C$, 57%], 87 (16), 84 (42), 71 (72), 69 (18), 57 (70), 45 (100), 43 (72). *(2S,4R)-5,5-Dimethyl-2,4-hexanediol* (**3'a**):[29] ν_{max} (KBr) 3450-3110 cm^{-1} (OH); δ_H 0.90 [9H, s, $(CH_3)_3C$], 1.25 (3H, d, *J*= 6.4, CH_3CH), 1.48-1.61 (2H, m, CH_2), 2.47 (2H, br s, 2xOH), 3.59 (1H, dd, *J*= 18.5, 4.0, CCH), 4.10-4.19 (1H, m, C*H*CH_3); δ_C 23.2 (CH_3CH), 25.8 [$(CH_3)_3C$], 34.6 [$(CH_3)_3C$], 38.8 (CH_2), 65.7 (CH_3CH), 75.9 (C*C*H); m/z 89 [M+-$(CH_3)_3C$, 40%], 87 (15), 84 (32), 71 (82), 69 (23), 57 (65), 45 (100), 43 (42).

(1S,3S)-1-Phenyl-1,3-butanediol **3b** :[30] ν_{max} (film) 3680-3090 cm^{-1} (OH); δ_H 1.16 (3H, d, *J*= 6.4, CH_3),

1.68 (1H, dt, *J*= 14.3, 3.0, C*H*H), 1.79 (1H, dt, *J*= 14.3, 10.0,CH*H*), 3.90 (2H, br s, 2xOH), 3.98-4.10 (1H, m, C*H*CH_3), 4.84 (1H, dd, *J*= 10.0, 3.0, CHAr), 7.24-7.36 (5H, m, ArH); δ_C 23.8 (CH_3), 46.8 (CH_2), 68.6 (CH_3*C*H), 75.0 (Ar*C*H), 125.6, 127.45, 128.3, 144.4 (ArC); m/z 166 (M+, 8%), 148 (19), 107 (100), 105 (61), 79 (73), 77 (66), 51 (26), 45 (20), 43 (25), 42 (26).

*(1*R,*3*S*)-1-Phenyl-1,3-butanediol* **3'b** :[30] ν_{max} (film) 3690-3085 cm^{-1} (OH); δ_H 1.15 (3H, d, *J*= 6.1, CH_3), 1.70-1.82 (2H, m, CH_2), 3.43 (2H, br s, 2xOH), 3.94-4.03 (1H, m, C*H*CH_3), 4.95 (1H, dd, *J*= 7.6, 4.0, CHAr), 7.24-7.36 (5H, m, ArH); δ_C 23.2 (CH_3), 46.1 (CH_2), 65.1 (CH_3*C*H), 71.3 (Ar*C*H), 125.5, 127.1, 128.2, 144.3 (ArC); m/z 166 (M+, 5%), 148 (32), 107 (100), 105 (46), 79 (38), 77 (56), 51 (23), 43 (27).

(S)-1-(2-Hydroxypropyl)cyclopentanol **3c** :[31] ν_{max} (film) 3600-3100 cm^{-1} (OH); δ_H 1.17 (3H, d, *J*= 6.1, CH_3), 1.45-1.83 (12H, m, 6xCH_2), 3.66 (2H, br s, 2xOH), 4.11-4.21 (1H, m, C*H*CH_3); δ_C 21.9 (CH_3), 22.1, 24.2, 25.6, 34.45, 35.6, 40.0 (6xCH_2), 64.6 (CH_3*C*H), 72.3 (COH); m/z 158 (M+, 7%), 115 (28), 102 (17), 99(68), 98 (58), 84 (14), 83 (13), 80 (18), 71 (54), 70 (31), 69 (50), 67 (17), 55 (100), 45 (42), 43 (63).

*(2*S,*4*S*)-2-Phenyl-2,4-pentanediol* **3d** :[32] ν_{max} (film) 3600-3100 cm^{-1} (OH); δ_H 1.09 (3H, d, *J*= 6.1, C*H*$_3$CH), 1.52 (3H, s, CH_3C), 1.98 (1H, dd, *J*= 14.6, 9.5, C*H*H), 2.00 (1H, dd, *J*= 14.6, 3.1, CH*H*), 2.33 3.66 (2H, br s, 2xOH), 3.61 (1H, ddq, *J*= 9.5, 6.1, 3.1, CH), 7.21-7.44 (5H, m, ArH); δ_C 24.3 (*C*H_3CH), 32.5 (*C*H_3C), 50.1 (CH_2), 66.3 (CH_3*C*H), 75.6 (Ar*C*), 124.8, 126.3, 128.1, 147.3 (ArC); m/z 180 (M+, 1%), 121 (56), 105 (48), 77 (23), 51 (11), 45 (10), 43 (100).

*(2*R,*4*S*)-2-Phenyl-2,4-pentanediol* **3'd** :[32] ν_{max} (film) 3650-3110 cm^{-1} (OH); δ_H 1.20 (3H, d, *J*= 6.1, C*H*$_3$CH), 1.67 (3H, s, CH_3C), 1.67-1.87 (2H, m, CH_2), 3.31 (2H, br s, 2xOH), 4.32 (1H, ddq, *J*= 9.5, 6.1, 3.0, CH), 7.24-7.48 (5H, m, ArH); δ_C 24.2 (*C*H_3CH), 28.0 (*C*H_3C), 50.9 (CH_2), 65.75 (CH_3*C*H), 75.0 (Ar*C*), 124.3, 126.7, 128.2, 149.1 (ArC); m/z 180 (M+, 1%), 121 (40), 105 (62), 77 (41), 43 (100).

*(2*R,*4*S*)-1-(Methoxymethoxy)-5,5-dimethyl-2,4-hexanediol* **6a** : ν_{max} (film) 3750-3010 cm^{-1} (OH); δ_H 0.91 [9H, s, (C2xH_3)$_3$C], 1.45 (1H, dt, *J*= 14.3, 10.1, CHC*H*HCH), 1.66 (1H, dt, *J*= 14.3, 2.1, CHCH*H*), 3.12 (2H, br s, OH), 3.40 (3H, s, OCH_3), 3.45 (1H, dd, *J*= 10.4, 5.8, CCH), 3.49-3.58 (1H, m, OC*H*HCH), 3.60 (1H, dd, *J*= 10.4, 3.7, OCH*H*CH), 3.98-4.06 (1H, m, CH_2C*H*CH_2), 4.66 (2H, s, OCH_2O); δ_C 25.9 [(*C*H_3)$_3$C], 33.5 [(CH_3)$_3$*C*], 34.75 (CHCH_2CH), 55.4 (CH_3O), 72.0 (CHCH_2O), 73.1, 80.2 (2xCH), 97.0 (OCH_2O); m/z 143 [M+-(H_2O+CH_2OCH_3), 2%], 87 (29), 69 (12), 57 (37), 45 (100), 43 (24), 41 (37).

*(2*R,*4*R*)-1-(Methoxymethoxy)-5,5-dimethyl-2,4-hexanediol* **6'a** : ν_{max} (film) 3700-3080 cm^{-1} (OH); δ_H 0.84 [9H, s, (CH_3)$_3$C], 1.40 (1H, ddd, *J*= 14.0, 10.7, 3.7, CHC*H*HCH), 1.56 (1H, ddd, *J*= 14.0, 8.2, 1.8, CHCH*H* CH), 2.30 (2H, br s, 2xOH), 3.32 (3H, s, OCH_3), 3.44 (1H, dd, *J*= 10.4, 7.6, CCH), 3.46-3.53 (1H, m, OC*H*HCH), 3.60 (1H, dd, *J*= 10.4, 3.0, OCH*H*CH), 3.99-4.10 (1H, m, CH_2C*H*CH_2), 4.63 (2H, s, OCH_2O); δ_C 25.5 [(*C*H_3)$_3$C], 33.9 [(CH_3)$_3$*C*], 34.6 (CH*C*H_2CH), 55.4 (CH_3O), 68.3 (CH*C*H_2O), 73.2, 75.6 (2xCH), 97.0 (OCH_2O); m/z 143 [M+-(H_2O+CH_2OCH_3), 3%], 87 (41), 69 (23), 57 (41), 45 (100), 43 (23), 41 (48).

(1S,3R)-4-(Methoxymethoxy)-1-phenyl-1,3-butanediol **6b** : ν_{max} (film) 3740-3200 cm^{-1} (OH); δ_H 1.76 (1H, dt, *J*= 14.3, 3.5, CHC*H*HCH), 1.86 (1H, dt, *J*= 14.3, 9.5, CHCH*H* CH), 2.86 (2H, br s, 2xOH), 3.36 (3H, s, OCH_3), 3.44 (1H, dd, *J*= 10.4, 6.7, OC*H*HCH), 3.55 (1H, dd, *J*= 10.4, 3.4, OCH*H*CH), 3.98-4.06 (1H, m, CH_2CHCH_2), 4.62 (2H, s, OCH_2O), 4.94 (1H, dd, *J*= 9.5, 3.5, ArCH), 7.23-7.38 (5H, m, ArH); δ_C 41.7 ($CHCH_2CH$), 55.4 (CH_3O), 71.0 ($CHCH_2O$), 72.9, 74.25 (2xCH), 96.9 (OCH_2O), 125.6, 127.5, 128.4, 144.2 (ArC); m/z 181 [M^+-(CH_2OCH_3), 5%], 105 (27), 79 (21), 77 (25), 45 (100), 43 (15). Anal. Calcd. for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.19; H, 7.64.

(1R,3R)-4-(Methoxymethoxy)-1-phenyl-1,3-butanediol **6'b** : ν_{max} (film) 3730-3250 cm^{-1} (OH); δ_H 1.82-1.93 (2H, m, $CHCH_2CH$), 3.12 (2H, br s, 2xOH), 3.37 (3H, s, OCH_3), 3.48 (1H, dd, *J*= 10.4, 7.3, OC*H*HCH), 3.63 (1H, dd, *J*= 10.4, 3.4, OCH*H*CH), 4.01-4.12 (1H, m, CH_2CHCH_2), 4.65 (2H, s, OCH_2O), 5.00-5.11 (1H, m, ArCH), 7.24-7.39 (5H, m, ArH); δ_C 41.1 ($CHCH_2CH$), 55.4 (CH_3O), 67.9 ($CHCH_2O$), 71.2, 73.0 (2xCH), 96.9 (OCH_2O), 125.5, 127.3, 128.4, 144.5 (ArC); m/z 181 [M^+-(CH_2O-CH_3), 4%], 105 (31), 79 (28), 77 (21), 45 (100), 43 (18).

(R)-1-[2-Hydroxy-3-(methoxymethoxy)propyl]cyclohexanol **6c** : ν_{max} (film) 3700-3060 cm^{-1} (OH); δ_H 1.43-1.88 (12H, m, 6xCH_2), 3.29 (2H, br s, OH), 3.40 (3H, s, 2xOCH_3), 3.49 (1H, dd, *J*= 10.4, 7.0, OC*H*HCH), 3.57 (1H, dd, *J*= 10.4, 3.7, OCH*H*CH), 4.16-4.24 (1H, m, CH_2CHCH_2), 4.67 (2H, s, OCH_2O); δ_C 22.0, 22.2, 25.7, 36.06, 39.7, 42.4 (6xCH_2), 55.3 (CH_3O), 67.7 ($CHCH_2O$), 71.6 (CH), 72.3 (COH), 96.9 (OCH_2O); m/z 186 [M+-(CH_3OH), 3%], 155 (20), 143 (17), 125 (26), 113 (26), 99 (58), 81 (65), 79 (21), 55 (60), 45 (100), 42 (33), 41 (59).

(R)-3-Hydroxy-4-(methoxymethoxy)butanoic Acid **6e** :[31] ν_{max} (film) 3700-2650 cm^{-1} (OH); δ_H 1.43-1.88 (2H, d, *J*= 6.4, O_2CCH_2), 3.39 (3H, s, OCH_3), 3.56 (1H, dd, *J*= 10.4, 6.1, OC*H*HCH), 3.64 (1H, dd, *J*= 10.4, 4.0, OCH*H*CH), 4.18-4.26 (1H, m, CH_2CHCH_2), 4.66 (2H, s, OCH_2O), 6.41 (2H, br s, 2xOH); δ_C 37.9 (CH_2), 55.5 (CH_3O), 67.1 ($CHCH_2O$), 71.5 (CH), 96.9 (OCH_2O), 176.6 (CO_2H); m/z 119 [M+-(CH_2OCH_3), 1%], 45 (100), 44 (12), 43 (20), 42 (17).

(S)-1-(2-Hydroxy-3-methylbutyl)cyclopentanol **9c** : ν_{max} (film) 3600-3120 cm^{-1} (OH); δ_H 0.90, 0.92 [6H, 2 d, *J*= 6.4, 6.1, $(CH_3)_2CH$], 1.29-1.79 [13H, m, $(CH_3)CH$, 6xCH_2], 3.30 (2H, br s, 2xOH), 3.74 (1H, ddd, *J*= 11.0, 5.5, 2.2, C*H*OH); δ_C 17.6, 18.2 (2xCH_3), 22.1, 22.3, 25.8, 34.2, 35.6, 40.4, 42.5 (CH_3CH, 6xCH_2), 72.3 (CHOH), 73.3 (COH); m/z 186 (M+, 1%), 143 (30), 125 (45), 107 (23), 99 (49), 81 (77), 71 (34), 70 (34), 69 (20), 57 (12), 55 (100), 43 (70), 42 (25), 41 (54).

(S)-3-Hydroxy-4-methylpentanoic Acid **9e** :[33] ν_{max} (film) 3710-2500 cm^{-1} (OH); δ_H 0.93, 0.96 [6H, 2 d, *J*= 7.3, 7.0, $(CH_3)_2CH$], 1.68-1.79 (1H, m, $(CH_3)_2CH$], 2.45-2.51 (1H, m, C*H*H), 2.56 (1H, dd, *J*= 16.3, 3.1, CH*H*), 3.79-3.85 (1H, m, C*H*OH), 7.22 (2H, br s, 2xOH); δ_C 17.7, 18.2 (2xCH_3), 33.1 (CH_2), 33.8 [$(CH_3)_2CH$], 72.8 (CHOH), 178.1 (CO_2H); m/z 85 [M^+-(H_2O+CH_3), 2%], 76 (100), 73 (67), 58 (42), 55 (53), 45 (24), 43 (79), 41 (66).

(2S,4R)-1-(Methoxymethoxy)-5,5-dimethyl-2,4-hexanediol **10a** : physical and spectrocopic data were found to be the same than for **6'a** .

(2S,4S)-1-(Methoxymethoxy)-5,5-dimethyl-2,4-hexanediol (**10'a**): physical and spectrocopic data were found to be the same than for **6a** .

(1R,3S)-4-(Methoxymethoxy)-1-phenyl-1,3-butanediol **10b** : physical and spectrocopic data were found to be the same than for **6'b** .

(1S,3S)-4-(Methoxymethoxy)-1-phenyl-1,3-butanediol **10'b** : physical and spectrocopic data were found to be the same than for **6b** .

(S)-1-[2-Hydroxy-3-(methoxymethoxy)propyl]cyclohexanol **10c** : physical and spectrocopic data were found to be the same than for **6c** .

(S)-3-Hydroxy-4-(methoxymethoxy)butanoic Acid **10e** : physical and spectrocopic data were found to be the same than for **6e** .

(1R,2S,5R)-(1-Hydroxy-2-isopropyl-5-methylcyclohexyl)acetic Acid **13e** : ν_{max} (film) 3600-2650 cm^{-1} (OH); δ_H 0.83 (3H, d, *J*= 6.1, CH_3CH), 0.91, 0.92 [6H, 2 d, *J*= 2.4, $(CH_3)_2CH$], 1.08-1.16 (2H, m, CH_2), 1.26-1.32 (2H, m, CH_2), 1.46-1.54 (2H, m, CH_2), 1.71-1.79 [2H, m, CH_3CH, $(CH)_2CH$], 2.01-2.10 (1H, m, CHCO), 2.35 (1H, d, *J*= 5.0, $CHHCO_2$), 2.90 (1H, d, *J*= 5.0, $CHHCO_2$), 8.31 (2H, br s, 2xOH); δ_C 17.9, 20.5, 22.2 ($3xCH_3$), 23.6, 26.4, 27.8, ($3xCH_2$), 35.0 (CH), 44.5 (CH_2CO_2), 47.0, 49.9 (2xCH), 74.0 (COH), 178.2 (CO_2H); m/z 214 (M+, 1%), 129 (71), 111 (34), 69 (83), 56 (31), 55 (70), 44 (29), 43 (70), 42 (30), 41 (100), 40 (66).

(1S,2S,5R)-2-Isopropyl-1,5-dimethylcyclohexanol **13f** :[34] ν_{max} (film) 3700-2600 cm^{-1} (OH); δ_H 0.86 (3H, d, *J*= 6.4, CH_3CH), 0.89, 0.91 [6H, 2 d, *J*= 4.6, 4.3, $(CH_3)_2CH$], 0.98-1.15 (2H, m, CH_2), 1.23 (3H, s, CH_3CO), 1.25-1.80 (6H, m, $2xCH_2$, 2xCH), 2.09-2.19 (1H, m, CHCO), 3.18 (1H, br s, OH); δ_C 18.2, 20.9, 22.3 ($3xCH_3$), 23.8, 26.1, 28.2 ($3xCH_2$), 28.8 (CH_3CO), 35.2, 50.5, 50.7 (3xCH), 73.1 (COH); m/z 170 (M+, 2%), 85 (100), 67 (16), 55 (21), 43 (73), 41 (51), 40 (14).

(1S,2S,5R)-1-Deuteriomethyl-2-isopropyl-5-methylcyclohexanol **13g** : ν_{max} (film) 3700-2600 cm^{-1} (OH); δ_H 0.85 (3H, d, *J*= 6.4, CH_3CH), 0.88, 0.90 [6H, 2 d, *J*= 4.6, 4.3, $(CH_3)_2CH$], 1.00-1.17 (2H, m, CH_2), 1.23 (2H, s, CH_2D), 1.26-1.86 (6H, m, $2xCH_2$, 2xCH), 2.11-2.23 (1H, m, CHCO), 3.00 (1H, br s, OH); δ_C 18.3, 20.8, 22.3 ($3xCH_3$), 23.6, 26.4, 28.1 ($3xCH_2$), 28.5 (t, J_{CD}= 18.9, CH_2D), 35.3, 50.4, 50.8 (3xCH), 73.2 (COH); m/z 171 (M+, 2%), 86 (100), 59 (10), 55 (14), 44 (47), 43 (24), 41 (30).

Deprotection of Diols **6** *and* **10**. *Isolation of Triols* **14**. *General Procedure.*- The corresponding diol was treated with a 4 M methanol solution of hydrogen chloride (4 ml) for 4 h at 25°C. After that the solvent was evaporated (15 mmHg) to give in quantitative yield and without further purification the title triols **14**. Yields and especific rotations are included in Table 2; analytical and espectroscopic data as well as literature references follow.

(2R,4S)-5,5-Dimethyl-1,2,4-hexanetriol **14a** : ν_{max} (film) 3600-3100 cm^{-1} (OH); δ_H 0.90 [9, s, $(CH_3)_3C$], 1.49 (1H, dt, *J*= 14.4, 10.4, CHC*H*HCH), 1.62 (1H, dt, *J*= 14.4, 1.8, CHCH*H*), 3.12 (3H, br s, 3xOH),

3.40 (3H, s, OCH_3), 3.48 (1H, dd, *J*= 11.0, 6.4, OC*H*H), 3.52 (1H, dd, *J*= 10.4, 1.8, OCH*H*), 3.64 (1H, dd, *J*= 1.0, 3.4, CCH), 3.90-3.97 (1H, m, CH_2CHCH_2); δ_C 25.4 [$(CH_3)_3C$], 33.1 [$(CH_3)_3C$], 34.9 ($CHCH_2CH$), 66.9 (CH_2O), 73.1, 80.6 (2xCH); m/z 131 (M+-CH_2OH, 4%), 95 (19), 87 (99), 71 (13), 69 (58), 61 (36), 57 (48), 45 (54), 43 (100), 41 (96). Anal. Calcd. for $C_8H_{18}O_3$: C, 59.23; H, 11.18. Found: C, 58.51; H, 10.53.

(2R,4R)-5,5-Dimethyl-1,2,4-hexanetriol **14'a** : ν_{max} (film) 3600-3000 cm^{-1} (OH); δ_H 0.91 [9H, s, $(CH_3)_3C$], 1.50 (1H, dt, *J*= 14.4, 9.8, CHC*H*HCH), 1.65 (1H, dt, *J*= 14.4, 2.1, CHCH*H* CH), 2.13 (3H, br s, 3xOH), 3.55 (1H, dd, *J*= 10.4, 6.4, OCH*H*), 3.59 (1H, dd, *J*= 10.4, 1.8, OCH*H*), 3.68 (1H, dd, *J*= 11.0, 3.6, CCH); δ_C 25.5 [$(CH_3)_3C$], 33.9 [$(CH_3)_3C$], 34.7 ($CHCH_2CH$), 66.8 (CH_2O), 70.1, 76.2 (2xCH); m/z 131 (M+-CH_2OH, 4%), 95 (19), 87 (99), 71 (13), 69 (58), 61 (36), 57 (48), 45 (54), 43 (100), 41 (96).

(2R,4S)-4-Phenyl-1,2,4-butanetriol **14b** : ν_{max} (film) 3640-3110 cm^{-1} (OH); δ_H 1.76 (1H, dt, *J*= 14.5, 2.4, CHC*H*HCH), 1.93 (1H, dt, *J*= 14.5, 10.0, CHCH*H*CH), 3.21 (3H, br s, 3xOH), 3.50 (1H, dd *J*= 10.7, 6.4, OC*H*H), 3.64 (1H, dd, *J*= 10.7, 3.2, OCH*H*), 3.96-4.08 (1H, m, CH_2CHCH_2), 4.98 (1H, dd, *J*= 10.0, 3.0, ArCH), 7.28-7.41 (5H, m, ArH); δ_C 41.4 ($CHCH_2CH$), 66.7 (CH_2O), 72.2, 74.3 (2xCH), 125.6, 127.7, 128.5, 144.1 (ArC); m/z 182 (M+, 2%), 133 (10), 108 (10), 107 (99), 105 (100), 97 (85), 78 (18), 77 (57), 51 (23).

(2R,4R)-4-Phenyl-1,2,4-butanetriol **14'b** :[35] ν_{max} (film) 3600-3100 cm^{-1} (OH); δ_H 1.64 (3H, br s, 3xOH), 1.85-1.92 (2H, m, $CHCH_2CH$), 3.50-3.56 (1H, m, OC*H*H), 3.61-3.70 (1H, m, OCH*H*), 3.93-3.99 (1H, m, CH_2CHCH_2), 5.06 (1H, dd, *J*= 4.5, 3.2, ArCH), 7.25-7.38 (5H, m, ArH); δ_C 40.9 ($CHCH_2CH$), 66.7 (CH_2O), 69.5, 71.6 (2xCH), 125.5, 127.6, 128.6, 144.2 (ArC); m/z 182 (M+, 2%), 133 (16), 107 (83), 105 (100), 97 (81), 78 (23), 77 (43), 51 (28).

(R)-1-(2,3-Dihydroxypropyl)cyclohexanol **14c** : ν_{max} (film) 3640-3150 cm^{-1} (OH); δ_H 1.46-1.84 (15H, m, 3xOH, 6xCH_2), 3.46 (1H, dd, *J*= 11.0, 6.7, OC*H*H), 3.63 (1H, dd, *J*= 11.0, 3.4, OCH*H*), 4.08-4.14 (1H, m, CH_2CHCH_2); δ_C 22.1, 22.2, 25.6, 35.8, 40.1, 42.3 (6xCH_2), 67.2 (CH_2O), 68.9 (CH), 72.5 (COH); m/z 174 (M+, 2%), 143 (35), 125 (20), 113 (39), 99 (57), 81 (100), 79 (26), 67 (25), 55 (95), 43 (94), 42 (35), 41 (66).

(2S,4S)-5,5-Dimethyl-1,2,4-hexanetriol *ent*-**14'a** : physical and spectrocopic data were found to be the same than for **14'a** .

(2S,4R)-5,5-Dimethyl-1,2,4-hexanetriol *ent*-**14a** : physical and spectrocopic data were found to be the same than for **14a** .

(2S,4S)-4-Phenyl-1,2,4-butanetriol *ent*-**14'b** : physical and spectrocopic data were found to be the same than for (**14'b**).

(2S,4R)-4-Phenyl-1,2,4-butanetriol *ent*-**14b** :[35] physical and spectrocopic data were found to be the same than for **14b** .

(S)-1-(2,3-Dihydroxypropyl)cyclohexanol *ent*-**14c** : physical and spectrocopic data were found to be the same than for **14c** .

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