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Enantiomerically pure γ-oxidofunctionalised organolithium compounds from chiral oxetanes †

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Abstract: The reductive opening of chiral oxetanes **1**, *ent*-**1**, **4** and **7** with lithium powder and a catalytic amount of DTBB (5 mol%) in THF at 0°C or −20°C, followed by treatment with different electrophiles [H_2O, D_2O, Bu^tCHO, PhCHO, Me_2CO, $(CH_2)_5CO$ and CO_2] at −78°C leads, after hydrolysis with water to functionalised alcohols **3**, *ent*-**3**, **6** and **9**. Monoprotected diols **6d** and **9d** give enantiomerically pure 1,2,5-triols **10** and *ent*-**10** or spirohydroxyethers **11** and *ent*-**11** under acidic conditions in methanol in almost quantitative yield. © 1997 Elsevier Science Ltd

Introduction

The main advantage of using functionalised organolithium compounds[1] of general type **I** as carbanionic intermediates in synthetic organic chemistry is centered on the fact that in the reaction of these species with electrophilic reagents polyfunctionalised molecules are formed in only one reaction step. Intermediates of the type **I** are, in general, unstable compounds due to their decomposition, even at low temperature, by elimination processes.[2] For n>1, we found some years ago[3] that the existence of a negative charge on the heteroatom (see **II**), which decreases its ability to act as a leaving group, allows the preparation, at low temperature, of this type of compound. In the case of γ-functionalised organolithium compounds (**II**, n=3; also called d^3-reagents following Seebach's nomenclature[4]) containing an oxygen,[5] nitrogen[6] or sulfur[7] functionality, they have been prepared by different routes: (a) chlorine–lithium exchange,[5a–d,q,6a,7a] (b) reductive heterocyclic ring opening,[5e,f,r,s,6b,7b] (c) sulfur–lithium exchange,[5g,h,t,u] (d) tin–lithium transmetallation[5i,v] and (e) other less general methodologies such as direct deprotonation[5j–n,6c] or addition of organolithium compounds to allylic systems.[5o,w,x,6d,e,f] However, to the best of our knowledge, chiral γ-functionalised organolithium compounds have been prepared following the routes (a),[5c,q] (c),[5u] (d)[5v] and (e).[5x,6f] In this paper we describe the preparation of these type of intermediates in an enantiomerically pure form by reductive opening of oxetanes[5e,f] [route (b)] using lithium and a catalytic amount of 4,4′-di-*tert*-butylbiphenyl (DTBB) as the electron carrier.[8] In recent years we have used this methodology for the new preparation of organolithium compounds starting from non-halogenated materials,[9a] as well as functionalised organolithium compounds (starting from chlorinated materials,[9b] heterocyclic precursors,[9c] or other systems[9d]) and polyfunctionalised synthons.[9e]

† This paper is dedicated to Professor E. Winterfeld on occasion of his 65th birthday.

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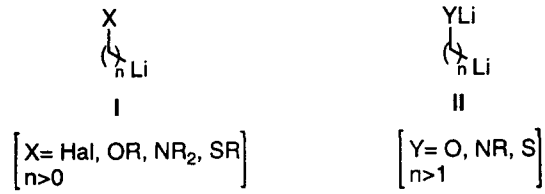
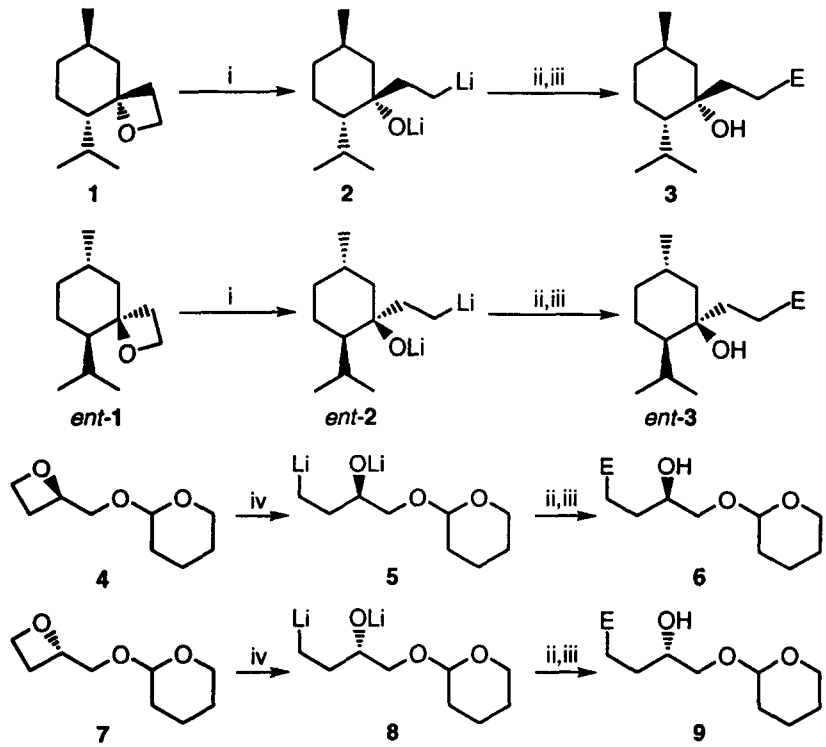


Results and discussion

The reaction of chiral oxetane **1** with an excess of lithium powder in the presence of a catalytic amount of DTBB (5 mol%) in THF at 0°C for 6 h, led to a solution of intermediate **2**, which after reaction with different electrophiles [D_2O, Bu^tCHO, PhCHO, Me_2CO, CO_2] at −78°C, followed by hydrolysis with water, afforded the expected chiral compounds **3** (Scheme 1, Figure 1 and Table 1, entries 1–7).



Scheme 1. *Reagents and conditions*: i, Li, DTBB cat. (5 mol%), THF, 0°C; ii, E^+=H_2O, D_2O, CO_2, Bu^tCHO, PhCHO, Me_2CO, $(CH_2)_5CO$, −78°C; iii, H_2O, −78 to 20°C; iv, Li, DTBB cat. (5 mol%), THF, −20°C.

In the case of using prochiral carbonyl compounds as electrophiles a *ca.* 2:3 and 3:2 (300 MHz ^1H NMR) diastereoisomers mixture was determined for pivaldehyde and benzaldehyde, respectively (Scheme 1, Figure 1 and Table 1, entries 2–5), which could be seperated by flash chromatography (silica gel, hexane/ethyl acetate), so both enantiomerically pure diastereoisomers **3** and **3′** were obtained in enantiomerically pure form. When carbon dioxide was used as the electrophile, spirolactone **3e** was the only reaction product isolated after acidic work-up (Scheme 1, Figure 1 and Table 1, entry 7). To prove the validity of this methodology in EPC-synthesis, we performed the same reactions indicated above starting from the enantiomeric oxetane *ent*-**1**, so through the corresponding intermediate *ent*-**2** the expected reaction products *ent*-**3** were isolated (Scheme 1, Figure 1 and Table 1, entries 8–12).

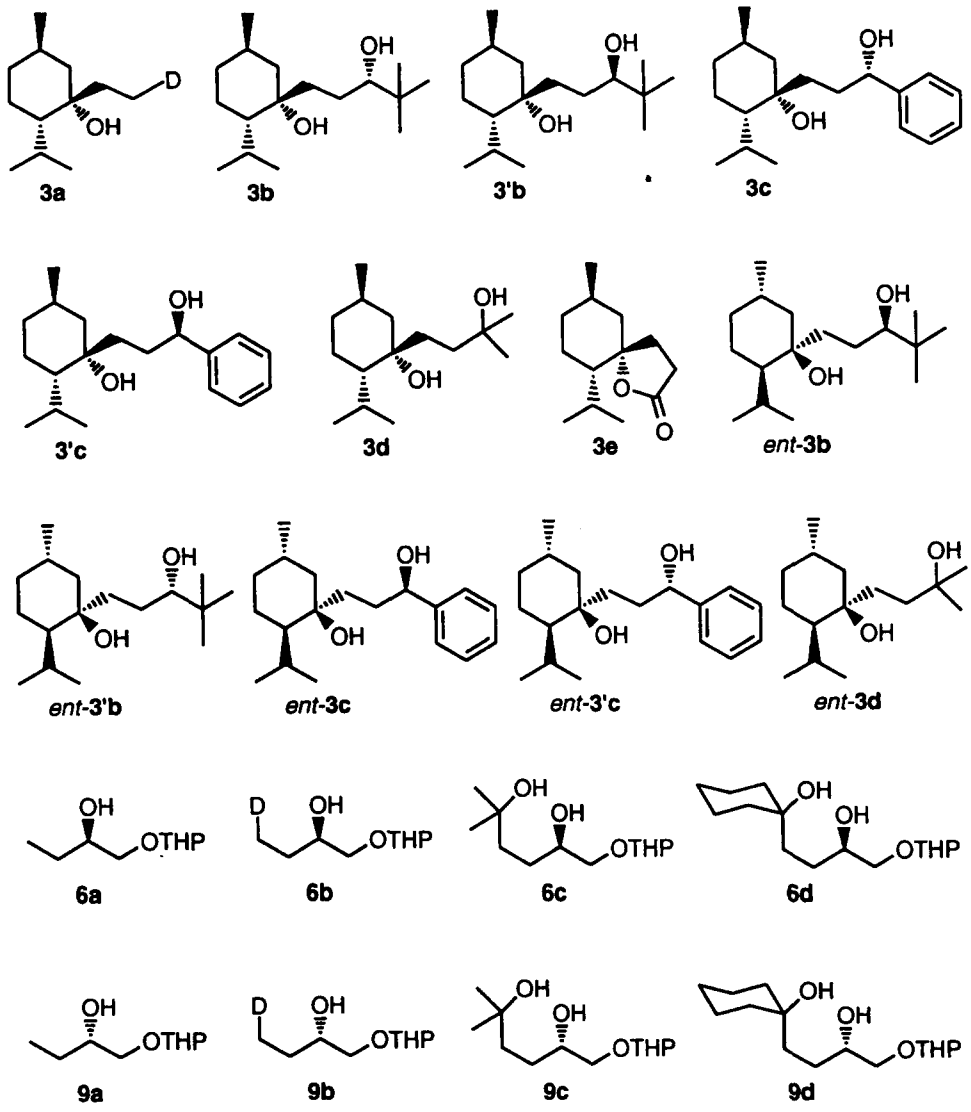


Figure 1.

The unequivocal assignment of the stereochemistry of diols **3b** and **3'b** was performed by single-crystal analysis of compound **3'b** (Figure 2);[10] for diols **3c** and **3'c** the structure was deduced by correlation with the X-ray analysis, the study of their NMR spectra and our previous experience in similar diols.[11]

Starting oxetanes **1** and *ent*-**1** were prepared by treatment of (−)- and (+)-menthone, respectively, with 6 equivalents of trimethylsulfoxonium ylide in *tert*-butanol at 50°C for 72 h (45% yield).[12] A similar methodology was applied to both protected hydroxyoxetanes **4** and **7**,[13] which can be used as chiral precursors of polyols. Thus, treatment of these chiral oxetanes with an excess of lithium powder in the presence of a catalytic amount of DTBB (5 mol%) in THF at −20°C for 3 h led to a solution of intermediates **5** or **8**, respectively, which by reaction with different electrophiles [H_2O, D_2O, Me_2CO, $(CH_2)_5CO$] and final hydrolysis yielded products **6** and **9**, respectively (Scheme 1, Figure 1 and Table 1, entries 13–20).

Table 1. Preparation of compounds **3**, **6** and **9**

Entry	Starting material	Intermediate	Electrophile E+	Product[a] No.	R_f[b] or mp[c]	$[\alpha]_D^{20}$ (c)[d]	Yield(%)[e]
1	**1**	**2**	D_2O	**3a**	0.73	+2.1 (1.6)	80
2	**1**	**2**	Bu^tCHO	**3b**	0.64	-18.4 (1.25)	59[f]
3				**3'b**	139-140	+9.8 (1.4)	
4	**1**	**2**	PhCHO	**3c**	159-160	-19.0 (0.5)	77[g]
5				**3'c**	142-143	+12.8 (0.8)	
6	**1**	**2**	Me_2CO	**3d**	0.43	-18.2 (1.3)	65
7	**1**	**2**	CO_2	**3e**	0.57	-43.0 (1.15)	75
8	*ent*-**1**	*ent*-**2**	Bu^tCHO	*ent*-**3b**	0.64	+20.4 (0.7)	61[f]
9				*ent*-**3'b**	139-140	-10.8 (1.35)	
10	*ent*-**1**	*ent*-**2**	PhCHO	*ent*-**3c**	159-160	+18.8 (0.65)	80[g]
11				*ent*-**3'c**	142-143	-11.7 (0.65)	
12	*ent*-**1**	*ent*-**2**	Me_2CO	*ent*-**3d**	0.43	+20.1 (1.15)	63
13	**4**	**5**	H_2O	**6a**	0.26	+7.6 (1.2)	98
14	**4**	**5**	D_2O	**6b**	0.26	+7.3 (1.1)	90
15	**4**	**5**	Me_2CO	**6c**	0.41[h]	-7.1 (1.4)	67
16	**4**	**5**	$(CH_2)_5CO$	**6d**	0.20	-4.4 (1.1)	62
17	**7**	**8**	H_2O	**9a**	0.26	-7.8 (1.75)	97
18	**7**	**8**	D_2O	**9b**	0.26	-8.0 (0.7)	91
19	**7**	**8**	Me_2CO	**9c**	0.41[h]	+6.1 (1.75)	65
20	**7**	**8**	$(CH_2)_5CO$	**9d**	0.20	+3.8 (1.4)	66

[a] All products **3**, **6** and **9** were > 95% pure (GLC and 300 MHz ^1H NMR). [b] Silica gel, hexane/ethyl acetate: 2/1, unless otherwise stated. [c] From hexane/chloroform, temperature given in °C. [d] In dichloromethane, c given in g/100 ml. [e] Global yield based on the starting oxetanes **1**, *ent*-**1**, **4** or **7**. [f] A *ca.* 2:3 diastereoisomers mixture (300 MHz ^1H NMR) was obtained. [g] A *ca.* 3:2 diastereoisomers mixture (300 MHz ^1H NMR) was obtained. [h] Silica gel, hexane/ethyl acetate: 1/2.

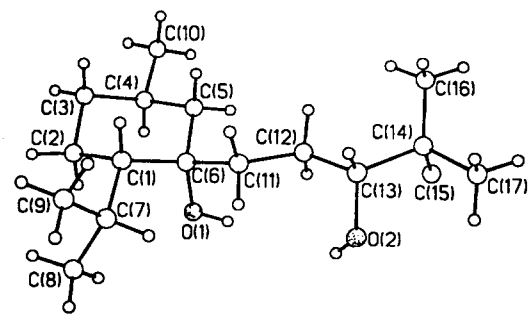
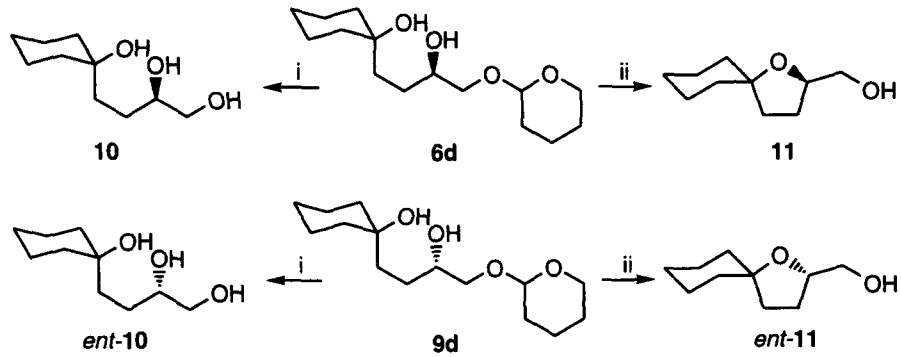


Figure 2. Ball-and-stick representation of the solid state structure **3'b**.

Oxetanes **4** and **7** were prepared by *O*-protection of commercially available chiral epoxides (*S*)- and (*R*)-glycidol respectively with dihydropyran in the presence of a catalytic amount of *p*-toluenesulfonic acid[14] followed by reaction with 3 equivalents of trimethylsulfoxonium ylide in *tert*-butanol at 50°C for 72 h (70% overall yield).[12]

In the last part of this study we carried out the deprotection of diols **6d** and **9d** in methanol under acidic conditions in order to prepare enantiomerically pure triols. Surprisingly these reactions showed a great dependency on the amount of *p*-toluenesulfonic acid. Thus, when the reaction was performed in methanol at 25°C in the presence of 5 mg of *p*-toluenesulfonic acid, the expected triols **10** and *ent*-**10** were isolated almost in quantitaive yield, but when around 15 mg of *p*-toluenesulfonic acid was used, spirohydroxyethers **11** and *ent*-**11** were the main reaction products (Scheme 2, Table 2).



Scheme 2. *Reagents and conditions*: i, *p*-TsOH (5 mg), MeOH, 25°C; ii, *p*-TsOH (15 mg), MeOH, 25°C.

From the results described in this paper we conclude that the reductive opening of chiral oxetanes allows the preparation of enantiomerically pure alcohols after reaction with different electrophiles. In the case of appropriate chiral oxetanes and after reaction with carbonyl compounds 1,4-diols, 1,2,5-triols and spirohydroxy-ethers can be obtained in enantiomerically pure forme. Chiral 1,4-diols, which are umpoled systems,[4] are interesting ligands for enantioselective catalytic addition of organometallics to carbonyl compound derivatives.[15]

Table 2. Preparation of compounds **10** and **11**

Entry	Starting material	Product[a]			
		No.	R_f	$[\alpha]_D$ (c)[b]	Yield(%)[c]
1	**6d**	**10**	0.32[d]	-4.9 (1.45)	>95
2	**9d**	*ent*-**10**	0.32[d]	+5.6 (1.2)	>95
3	**6d**	**11**	0.33[e]	-11.5 (0.6)	>95
4	**9d**	*ent*-**11**	0.33[e]	+12.6 (0.5)	>95

[a] All products **10** and **11** were >95% pure (GLC and 300 MHz ^{1}H NMR). [b] In dichloromethane; c given in g/100 ml. [c] Global yield based on the starting diols **6d** and **9d**. [d] Silica gel, hexane/ethyl acetate : 1/2. [e] Silica gel, hexane/ethyl acetate : 1/1.

Experimental part

General

For general information see Ref.[16] Chiral oxetanes **1**,[12] *ent*-**1**,[12] **4**[12,14] and **7**[12,14] were prepared according to the literature procedures. Yields are given in the text. Physical, analytical and spectroscopic data follow.

(4R,5S,8R)-5-Isopropyl-8-methyl-1-oxaspiro[3.5]nonane ***1***

R_f=0.23 (hexane/ethyl acetate, 20/1); ν_{max} (film) 1455, 1130 cm^{-1}; δ_H 0.87, 0.96, 1.04 [9H, 3d, *J*=6.7, $(CH_3)_2CH$, $(CH_3)CH$], 1.25–1.51 (4H, m, CH_2, 2×CH), 1.67–1.72 (3H, m, CH_2, CH), 2.05–2.24 (2H, m, CH_2), 2.39–2.49 (2H, m, CH_2), 4.31–4.48 (2H, m, CH_2O); δ_C 18.3, 20.35, 22.2 [$(CH_3)_2CH$, $(CH_3)CH$], 23.6 [$CH_2CHCH(CH_3)_2$], 23.8 ($CHCH_3$), 28.0 [$CH(CH_3)_2$], 30.0 (CH_2CH_2O), 34.9 (CH_2CHCH_3), 49.35 (CH_2CO), 49.95 (*C*HCO), 64.3 (CH_2O), 89.65 (CO); m/z 182 [M^+, 1%], 97 (100), 95 (24), 69 (43), 67 (23), 55 (54), 43 (54), 41 (77), 40 (80) (Found: M^+, 182.1665. $C_{12}H_{22}O$ requires M, 182.1670). $[\alpha]_D^{25}$=−19.8 [c=0.95 (CH_2Cl_2)].

(4S,5R,8S)-5-Isopropyl-8-methyl-1-oxaspiro[3.5]nonane ent-***1***

Physical and spectroscopic data were found to be the same than for **1**. Found: M^+, 182.1663. $C_{12}H_{22}O$ requires M, 182.1670). $[\alpha]_D^{25}$=+21.8 [c=1.05 (CH_2Cl_2)].

(2R)-2-(Tetrahydro-2H-2-pyranyloxymethyl)oxetane ***4***[17,18]

R_f =0.36[17] (hexane/ethyl acetate, 3/1); ν_{max} (film) 1435, 1095 cm^{-1}; δ_H 1.19–1.93 (6H, m, 3×CH_2), 2.41–2.75 (2H, m, CH_2), 3.38–3.69 (2H, m, $OCHCH_2O$), 3.82–3.92 (2H, m, $CH_2CH_2CH_2O$), 4.54–4.73 (3H, m, CH_2CHCH_2, $CH_2CH_2CH_2O$), 4.93–4.99 (1H, m, CHO_2); δ_C 19.2, 19.3, 23.55, 23.7, 25.35, 30.35, 30.5 (CH_2), 61.95, 62.05 ($CH_2CH_2CH_2O$), 68.8, 68.85, 70.05, 71.0 (CH_2O), 80.9, 80.95 (CHO), 98.85, 98.9 (CHO_2); m/z 143 (5%), 101 [$M^+-CH_2(C_3H_7O)$, 67%], 85 (C_5H_9O, 100), 84 (78), 83 (22), 71 (37), 70 (38), 67 (54), 57 (80), 56 (39), 55 (69), 54 (21), 44 (16), 43 (85), 42 (46). $[\alpha]_D^{25}$=−3.4 [c=1.2 (CH_2Cl_2)].

(2S)-2-(Tetrahydro-2H-2-pyranyloxymethyl)oxetane ***7***[17,18]

Physical and spectroscopic data were found to be the same than for **4**. $[\alpha]_D^{25}$=+2.5 [c=1.6 (CH_2Cl_2)].

DTBB-Catalysed lithiation of chiral oxetanes ***1***, ent-***1***, ***4*** *and* ***7***, *and reaction with electrophiles. Isolation of compounds* ***3***, ent-***3***, ***6*** *and* ***9***. *General procedure*

To a cooled (0°C for compounds **1** and *ent*-**1** or −20°C for compounds **4** and **7**) blue suspension of lithium powder (0.10 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 oxetane (1.5 mmol) under argon and the mixture was stirred at the same temperature for 6 h in the case of compounds **1** and *ent*-**1**, or for 3 h in the case of compounds **4** and **7**. 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 at −78°C 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**, *ent*-**3**, **6** and **9**. Yields and physical data (mps or R_f values and specific rotations) are included in Table 1; analytical and spectroscopic data follow.

(1S,2S,5R)-1-(2-Deuterioethyl)-2-isopropyl-5-methylcyclohexanol ***3a***[18]

ν_{max} (film) 3700–3200 (OH), 1420, 1100 cm^{-1}; δ_H 0.87, 0.90, 0.96 [9H, 3d, *J*=6.4, 7.0, $(CH_3)_2CH$, $(CH_3)CH$], 1.25–1.78 (10H, m, 4×CH_2, 2×CH), 2.01–2.29 (3H, m, CH, CH_2), 3.46 (1H, br s, OH); δ_C 8.1 (t, J_{CD}=19.2, CH_2D), 18.15, 20.5, 22.45 [$(CH_3)_2CH$, $(CH_3)CH$], 23.6 [$CH_2CHCH(CH_3)_2$], 25.35 ($CHCH_3$), 27.95 [$CH(CH_3)_2$], 33.55, 35.2 (2×CH_2), 46.05 (CH_2CO), 47.1 (*C*HCO), 75.4 (CO);

m/z 167 [M^+-H_2O, 1%], 155 (31), 137 (149), 100 (100), 99 (59), 85 (25), 81 (55), 69 (27), 58 (33), 57 (35), 55 (41), 44 (22), 43 (64), 41 (71).

(1S,2S,5R)-1-[(3S)-3-Hydroxy-4,4-dimethylpentyl]-2-isopropyl-5-methylcyclohexanol ***3b***[18]

ν_{max} (film) 3580–3080 (OH), 1470, 1130 cm^{-1}; δ_H 0.82–0.91 [9H, m, $(CH_3)_2CH$, $(CH_3)CH$], 0.92 [9H, s, $(CH_3)_3C$], 0.95–1.24 (2H, m, CH_2), 1.25–1.46 (4H, m, 2×CH_2), 1.50–1.87 (6H, m, 2×CH_2, 2×$CHCH_3$), 1.56 (2H, br s, 2×OH), 2.04–2.17 [1H, m, $CH(CH_3)_2$], 3.20 (1H, dd, J=10.2, 1.3, CHO); δ_C 18.15, 20.6, 22.45 [$(CH_3)_2CH$, $(CH_3)CH$], 23.65 [$CH_2CHCH(CH_3)_2$], 25.35, 25.45 [$CHCH_3$, $CH(CH_3)_2$], 25.75 [$(CH_3)_3C$], 28.1, 35.05 (2×CH_2), 35.1 [$C(CH_3)_3$], 38.45 (CH_2), 46.6 (CH_2CO), 48.75 (CHCO), 70.15 (CO), 80.5 (CHO); m/z 252 [M^+-H_2O, 2%], 167 (13), 123 (14), 95 (16), 83 (12), 69 (19), 57 (23), 55 (22), 44 (28), 43 (31), 41 (37), 40 (100).

(1S,2S,5R)-1-[(3R)-3-Hydroxy-4,4-dimethylpentyl]-2-isopropyl-5-methylcyclohexanol ***3'b***

ν_{max} (KBr) 3580–3080 (OH), 1470, 1130 cm^{-1}; δ_H 0.81–0.89 [9H, m, $(CH_3)_2CH$, $(CH_3)CH$], 0.91 [9H, s, $(CH_3)_3C$], 0.93–1.26 (5H, m, CH, 2×CH_2), 1.26–1.79 (7H, m, 2×CH_2, 2×OH, CH), 1.90–2.00 (2H, m, CH_2), 2.05–2.17 [1H, m, $CH(CH_3)_2$], 3.14 (1H, d, J=11.2, CHO); δ_C 18.15, 20.7, 22.45 [$(CH_3)_2CH$, $(CH_3)CH$], 23.7 [$CH_2CHCH(CH_3)_2$], 25.4, 25.45 [$CHCH_3$, $CH(CH_3)_2$], 25.75 [$(CH_3)_3C$], 28.0, 35.05 (2×CH_2), 35.1 [$C(CH_3)_3$], 38.6 (CH_2), 46.55 (CH_2CO), 48.8 (CHCO), 74.85 (CO), 80.9 (CHO); m/z 252 [M^+-H_2O, 3%], 167 (15), 123 (16), 95 (10), 83 (19), 69 (21), 57 (25), 55 (24), 44 (34), 43 (36), 41 (41), 40 (100) (Found: C, 75.37; H, 12.79. $C_{17}H_{34}O_2$ requires C, 75.50; H, 12.67).

(1S,2S,5R)-1-[(3S)-3-Hydroxy-3-phenylpropyl]-2-isopropyl-5-methylcyclohexanol ***3c***

ν_{max} (KBr) 3505–3150 (OH), 1430, 1100 cm^{-1}; δ_H 0.86, 0.92, 0.98 [9H, 3d, J=6.4, 6.7, $(CH_3)_2CH$, $(CH_3)CH$], 0.96–1.11 (2H, m, CH_2), 1.24–1.44 (2H, m, CH_2), 1.49–1.68 (5H, m, 2×CH_2, CH), 1.71–1.84 (3H, m, CH, CH_2), 2.06–2.13 [1H, m, $CH(CH_3)_2$], 2.19 (2H, br s, 2×OH), 4.69–4.73 (1H, m, CHO), 7.27–7.37 (5H, m, ArH); δ_C 18.1, 20.5, 22.4 [$(CH_3)_2CH$, $CH_3)CH$], 23.6 [$CH_2CHCH(CH_3)_2$], 25.45, 28.0 [$CHCH_3$, $CH(CH_3)_2$], 33.4, 35.0, 36.8 (3×CH_2), 46.5 (CH_2CO), 48.3 (CHCO), 74.8 (CO), 74.59 (CHO), 125.8, 127.5, 128.45, 144.75; m/z 272 [M^+-H_2O, 15%], 211 (22), 187 (96), 107 (22), 105 (25), 104 (29), 95 (22), 91 (54), 81 (36), 79 (21), 69 (65), 55 (68), 44 (100), 43 (71) (Found: C, 74.42; H, 9.94. $C_{19}H_{30}O_2.H_2O$ requires C, 73.98; H, 10.46).

(1S,2S,5R)-1-[(3R)-3-Hydroxy-3-phenylpropyl]-2-isopropyl-5-methylcyclohexanol ***3'c***

ν_{max} (KBr) 3600–3100 (OH), 1470, 1120 cm^{-1}; δ_H 0.85, [6H, d, J=6.7, $(CH_3)_2CH$], 0.87 (3H, d, J=6.4, CH_3CH), 0.99–1.10 (2H, m, CH_2), 1.07–2.03 (10H, m, 4×CH_2, 2×CH), 2.05–2.10 [1H, m, $CH(CH_3)_2$], 2.47 (2H, br s, 2×OH), 4.64–4.65 (1H, m, CHO), 7.22–7.36 (5H, m, ArH); δ_C 18.1, 20.6, 22.4 [$(CH_3)_2CH$, $(CH_3)CH$], 23.6 [$CH_2CHCH(CH_3)_2$], 25.4, 28.0 [$CHCH_3$, $CH(CH_3)_2$], 33.6, 35.0, 37.35 (3×CH_2), 46.5 (CH_2CO), 48.4 (CHCO), 74.8 (CO), 75.3 (CHO), 125.9, 127.55, 128.45, 144.8 (ArC); m/z 272 [M^+-H_2O, 7%], 211 (17), 187 (90), 107 (34), 105 (29), 104 (15), 95 (43), 91 (50), 81 (30), 79 (61), 69 (62), 55 (28), 44 (100), 43 (59) (Found: C, 76.20; H, 9.69. $C_{19}H_{30}O_2.1/2H_2O$ requires C, 76.21; H, 10.43).

(1S,2S,5R)-1-(3-Hydroxy-3-methylbutyl]-2-isopropyl-5-methylcyclohexanol ***3d***[18]

ν_{max} (film) 3630–3150 (OH), 1430, 1090 cm^{-1}; δ_H 0.87, 0.89, 0.91 [9H, d, J=6.7, $(CH_3)_2CH$, CH_3CH], 0.94–1.21 (3H, m, CH_2, CH), 1.23, 1.24 [6H, 2s, $(CH_3)_2C$], 1.26–1.35 (2H, m, CH_2), 1.37–1.78 (7H, m, 3×CH_2, CH), 2.06–2.17 (1H, m, $CH(CH_3)_2$], 2.21 (2H, br s, 2×OH); δ_C 18.1, 20.5, 22.45 [$(CH_3)_2CH$, $(CH_3)CH$], 23.6 [$CH_2CHCH(CH_3)_2$], 25.45, 28.0 [$CHCH_3$, $CH(CH_3)_2$], 28.9, 29.7 [$(CH_3)_2C$], 35.05, 35.25, 37.6 (3×CH_2), 46.6 (CH_2CO), 48.05 (CHCO), 70.8 [$OC(CH_3)_2$], 74.95 (CHCO); m/z 224 [M^+-H_2O, 2%], 155 (20), 139 (76), 95 (27), 81 (48), 69 (79), 59 (24), 55 (66), 43 (100), 41 (90), 40 (17).

(5S,6S,9R)-6-Isopropyl-9-methyl-1-oxaspiro[4,5]decan-2-one ***3e***[18]

ν_{max} (film) 3650–3090 (OH), 1770 (CO), 1455, 1140 cm^{-1}; δ_H 0.83, 0.87, 0.95 [9H, 3d, *J*=6.7, 7.0, $(CH_3)_2CH$, $(CH_3)CH$], 1.00–1.32 (4H, m, 2×CH_2), 1.42–1.60 (2H, m, CH_2), 1.74–1.86 (3H, m, CH, CH_2), 1.95–2.04 (1H, m, CH), 2.27–2.38 (1H, m, CH), 2.55 (2H, m, CH_2CO); δ_C 17.8, 21.7, 22.0 [$(CH_3)_2CH$, $(CH_3)CH$], 23.8 [$CH_2CHCH(CH_3)_2$], 26.3, 28.6 [$CHCH_3$, $CH(CH_3)_2$], 29.0, 31.2, 34.6 (3×CH_2), 49.3 (CH_2CO), 49.8 (CHCO), 89.4 (CHCO), 177.1 (CO_2); m/z 210 [M^+, 2%], 153 (10), 125 (100), 97 (11), 94 (10), 81 (17), 69 (15), 56 (15), 55 (44), 44 (34), 43 (22), 41 (50), 40 (62).

(1R,2R,5S)-1-[(3R)-3-Hydroxy-4,4-dimethylpentyl]-2-isopropyl-5-methylcyclohexanol ent-***3b***[18]

Physical and spectroscopic data were found to be the same than for **3b**.

(1R,2R,5S)-1-[(3S)-3-Hydroxy-4,4-dimethylpentyl]-2-isopropyl-5-methylcyclohexanol ent-***3'b***

Physical and spectroscopic data were found to be the same than for **3'b**. Found: C, 75.36; H, 12.74. $C_{17}H_{34}O_2$ requires C, 75.50; H, 12.67.

(1R,2R,5S)-1-[(3R)-3-Hydroxy-3-phenylpropyl]-2-isopropyl-5-methylcyclohexanol ent-***3c***

Physical and spectroscopic data were found to be the same than for **3c**. Found: C, 74.39; H, 9.96. $C_{19}H_{30}O_2 \cdot H_2O$ requires C, 73.98; H, 10.46.

(1R,2R,5S)-1-[(3S)-3-Hydroxy-3-phenylpropyl]-2-isopropyl-5-methylcyclohexanol ent-***3'c***

Physical and spectroscopic data were found to be the same than for **3'c**. Found: C, 76.40; H, 10.05. $C_{19}H_{30}O_2.1/2H_2O$ requires C, 76.21; H, 10.41.

(1R,2R,5S)-1-(3-Hydroxy-3-methylbutyl]-2-isopropyl-5-methylcyclohexanol ent-***3d***[18]

Physical and spectroscopic data were found to be the same than for **3d**.

(2R)-1-(Tetrahydro-2H-2-pyranyloxy)-2-butanol ***6a***[17,18]

ν_{max} (film) 3680–3100 (OH), 1460, 1200 cm^{-1}; δ_H 0.97 (3H, t, *J*=7.5, CH_3), 1.21–2.05 (8H, m, 4×CH_2), 2.77 (1H, br s, OH), 3.21–3.95 (5H, m, $OCHCH_2O$, CH_2CHCH_2, $CH_2CH_2CH_2O$), 4.56–4.65 (1H, m, CHO_2); δ_C 9.85, 9.9 (CH_3), 19.8, 19.85, 25.15, 25.2, 25.95, 26.1, 30.6, 30.7 (CH_2), 61.85, 63.0 ($CH_2CH_2CH_2O$), 71.8 (CHO)H, 72.5, 73.45 ($CHCH_2O$), 99.9, 100.0 (CHO_2); m/z 143 (2%), 85 (C_5H_9O, 100), 84 (36), 67 (21), 59 (42), 57 (36), 56 (37), 55 (76), 43 (70).

(2R)-4-Deuterio-1-(tetrahydro-2H-2-pyranyloxy)-2-butanol ***6b***[17,18]

ν_{max} (film) 3685–3120 (OH), 1450, 1180 cm^{-1}; δ_H 0.96 (2H, t, *J*=7.6, CH_2D), 1.22–2.11 (8H, m, 4×CH_2), 3.01 (1H, br s, OH), 3.23–3.99 (5H, m, $OCHCH_2O$, CH_2CHCH_2, $CH_2CH_2CH_2O$), 4.53–4.62 (1H, m, CHO_2); δ_C 9.6, 9.65 (2t, J_{CD}=19.2, CH_2D), 19.9, 19.85, 25.2, 25.3, 25.95, 26.2, 30.65, 30.7 (CH_2), 61.9, 63.1 ($CH_2CH_2CH_2O$), 71.9 (CHOH), 72.55, 73.6 ($CHCH_2O$), 99.8, 99.95 (CHO_2); m/z 145 [$M^+-CH_2CH_2D$), 0.8%], 85 (100), 84 (66), 79 (19), 67 (41), 60 (55), 59 (30), 58 (22), 57 (59), 55 (76), 44 (38), 43 (77), 42 (41).

(2R)-5-Methyl-1-(tetrahydro-2H-2-pyranyloxy)-2,5-hexanediol ***6c***[17,18]

ν_{max} (film) 3700–3040 (OH), 1430, 1130 cm^{-1}; δ_H 1.23 [6H, s, $(CH_3)_2C$], 1.26–1.85 (10H, m, 5×CH_2), 2.62 (2H, br s, OH), 3.36–3.92 (5H, m, $OCHCH_2O$, CH_2CHCH_2, $CH_2CH_2CH_2O$), 4.55–4.63 (1H, m, CHO_2); δ_C 19.8, 19.9, 25.1, 25.15, 26.85 (CH_2), 29.4, 29.45 [$(CH_3)_2C$], 30.55, 30.7 (CH_2), 39.6, 39.65 (CH_2COH), 62.9, 63.2 ($CH_2CH_2CH_2O$), 70.2, 70.25 (COH), 70.9 (CHOH), 72.7, 73.8, 99.95, 100.1 (CHO_2); m/z 159 (3%), 99 (30), 85 (93), 84 (28), 81 (33), 59 (46), 55 (81), 43 (100).

(2R)-4-(1-Hydroxycyclohexyl)-1-(tetrahydro-2H-2-pyranyloxy)-2-butanol ***6d***[17,18]

ν_{max} (film) 3700–3100 (OH), 1400, 1120 cm^{-1}; δ_H 1.25–1.82 (22H, m, 10×CH_2, 2×OH), 3.34–3.95 (5H, m, $OCHCH_2O$, CH_2CHCH_2, $CH_2CH_2CH_2O$), 4.56–4.65 (1H, m, CHO_2); δ_C 19.85, 19.95, 22.2, 22.25, 25.8, 25.85, 26.35, 26.6, 29.6, 29.65, 30.6, 30.8, 38.15 (CH_2), 63.0, 63.5 ($CH_2CH_2CH_2O$), 70.8,

70.9 (COH), 72.55, 73.6 ($CHCH_2O$), 72.85, 74.1 (CHOH), 100.05, 100.2 (CHO_2); m/z 252 (0.61%), 199 (1.6), 139 (17), 121 (19), 99 (12), 95 (12), 85 (63), 84 (30), 83 (21), 81 (22), 79 (15), 67 (27), 57 (28), 56 (25), 55 (100), 54 (22), 53 (17), 44 (15), 43 (41), 42 (13).

(2S)-1-(Tetrahydro-2H-2-pyranyloxy)-2-butanol ***9a***[17,18]

Physical and spectroscopic data were found to be the same than for **6a**.

(2S)-4-Deuterio-1-(tetrahydro-2H-2-pyranyloxy)-2-butanol ***9b***[17,18]

Physical and spectroscopic data were found to be the same than for **6b**.

(2S)-5-Methyl-1-(tetrahydro-2H-2-pyranyloxy)-2,5-hexanediol ***9c***[17,18]

Physical and spectroscopic data were found to be the same than for **6c**.

(2S)-4-(1-Hydroxycyclohexyl)-1-(tetrahydro-2H-2-pyranyloxy)-2-butanol ***9d***[17,18]

Physical and spectroscopic data were found to be the same than for **6d**.

Deprotection of diols ***6d*** *and* ***9d****. Isolation of triols* ***10*** *and hydroxyspiroethers* ***11****. General procedure*

To an ethanol solution (10 ml) of the corresponding diol (60 mg, 0.2 mmol) was added a catalytic amount of *p*-toluenesulfonic acid (5 mg when triols **10** were isolated and 15 mg when hydroxyspiroethers **11** were isolated) at 25°C for 5 h. After that the solvent was evaporated (15 mmHg). The resulting residue was hydrolysed with aqueous sodium bicarbonate solution and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and evaporated (15 mmHg) to give in quantitative yield and without further purification the title compounds **10** and **11**. Yields and specific rotations are included in Table 2; analytical and spectroscopic data follow.

(2R)-4-(1-Hydroxycyclohexyl)-1,2-butanediol ***10***[18]

ν_{max} (film) 3720–3020 (OH), 1070, 1035 cm^{-1}; δ_H 1.22–1.57 (17H, m, 7×CH_2, 3×OH), 3.48 (1H, dd, *J*=11.0, 7.0, C*H*HO), 3.61–3.68 (2H, m, CH*H*O, CHO); δ_C 22.25, 25.8, 26.3, 36.95 (CH_2), 66.5 (COH), 71.25 (CH_2OH), 72.6 (CHOH); m/z 170 [M^+-H_2O, 3.5%], 139 (27), 127 (35), 121 (46), 99 (64), 98 (16), 96 (10), 95 (31).

(2S)-4-(1-Hydroxycyclohexyl)-1,2-butanediol ent-***10***[18]

Physical and spectroscopic data were found to be the same than for **10**.

(2R)-2-Hydroxymethyl-1-oxaspiro[4.5]decane ***11***

ν_{max} (film) 3580–3110 (OH), 1120, 1015 cm^{-1}; δ_H 1.23–1.96 (15H, m, 7×CH_2, OH), 3.46 (1H, dd, *J*=11.3, 5.5, C*H*HO), 3.68 (1H, dd, *J*=11.3, 3.4, CH*H*O), 4.05–4.15 (1H, m, CHO); δ_C 23.7, 24.05, 25.6, 27.05, 36.0, 37.3, 38.3 (CH_2), 65.2 (CH_2OH), 78.05 (CHO), 83.4 (CO); m/z 170 (M^+, 6.5%), 139 (81), 12 7(53), 121 (100), 95 (47), 93 (37), 83 (58), 81 (73), 79 (44), 71 (37), 67 (56), 57 (56), 55 (90), 53 (25), 43 (56), 42 (25) (Found: M^+, 170.1308. $C_{10}H_{18}O_2$ requires M, 170.1307).

(2S)-2-Hydroxymethyl-1-oxaspiro[4.5]decane ent-***11***

Physical and spectroscopic data were found to be the same than for **11**. (Found: M^+, 170.1310. $C_{10}H_{18}O_2$ requires M, 170.1307).

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10. (a) A weakly diffracting crystal of approximate dimensions 0.45×0.22×0.22 mm was used for geometric and intensity data collection on a CAD-4 diffractometer.[10b] *Crystal data*: $C_{17}H_{34}O_2$, M=270.45; monoclinic, a=10.645 (11), b=18.040 (6), c=10.737 (10) Å, β=119.53 (7)°; U=1794 (3) Å^3; space group $P2_1$, Z=4, D_c=1.001 Mg.m^{-3}, λ=0.71073 Å, μ=0.063 mm^{-1}; F(000)=608. Data were measured at 297 K in the 2θ range 4.0–47.0°. Monitor reflections were used as a check on experimental stability and crystal orientation. Lp and absorption corrections were applied, although the absorption corrections were minimal. The structure was solved by direct methods[10c] and refined by full matrix least-squares,[10d] using all 2747 unique F^2_0. A restraint was used to fix the origin of the polar axis.[10e] The asymmetric unit consists of two molecules that form a loose dimer through hydrogen bonding among their -OH groups. Just 15 of the 68 unique hydrogen atoms were seen in

difference maps. For the final refinement, methyl group hydrogen atoms were located in local slant Fourier calculations for 9 of the 12 unique methyl groups. Three of the four hydroxyl hydrogen atoms were located in a similar procedure. All of the H atoms thus located were refined as riding atoms with variable torsion angles about the adjoining C–C or O–C bonds. The other methyl and OH hydrogen atoms were not found. All remaining hydrogen atoms were placed at calculated positions and refined as riding atoms. H atoms were assigned displacement parameters equal to 1.2 times the equivalent isotropic displacement parameters of their respective parent atoms. The final weighting scheme was $w^{-1}=[\sigma^2(F^2_0)+(0.2.P)^2]$, with $P=(\max(F^2_0,0)+2F^2_c)/3$. The convergent refinement (ave., max. $\Delta/\sigma=0.002, 0.021$) gave R1=0.1236, wR2=0.3337, and quality-of-fit=1.116. Twin models were tested for hypothetical two-fold twin axes along [100], [101], and [001], and for a hypothetical 3-fold twin axis along [010]. None of these models led to improvement of the agreement factors. The absolute configuration was established by the known stereochemistries at chiral carbon atoms C(1), C(4), C(21), and C(24). Detailed structural results have been deposited at the Cambridge Crystallographic Data Centre. (b) Diffractometer control program: CAD4-PC Version 2.0, ©1996, Delft Instruments X-ray Diffraction bv, Delft, The Netherlands. (c) Data were processed on an AlphaStation 200 4/166 (AlphaVMS V6.2), with the program XCAD4B (K. Harms, University of Marburg) and with the commercial package SHELXTL-PLUS Release 5.05/V: ©1996, Siemens Analytical X-ray Instruments, Inc., Madison, Wisconsin. Further calculations were done on a Hewlett-Packard 9000 Model 715/50 (HP-UX V9.05). (d) Shelxl-96 (Version beta 2): FORTRAN-77 program for the refinement of crystal structures from diffraction data: ©1996, George M. Sheldrick. (e) H. D. Flack and D. Schwarzenbach, *Acta Cryst. Section A* **1988**, *A44*, 499–506.

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