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Ketalised 3,4-Dihydroxybutyllithiums: New Intermediates to transfer Four-Carbon Diol Functionality to Electrophilic Reagents

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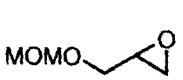
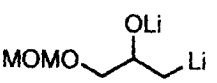
Abstract: The reaction of ketalised 1-chlorobutane-3,4-diol **1a,b** with lithium powder and a catalytic amount of 4,4'-di-*tert*-butylbiphenyl (DTBB, 4 mol %) in the presence of an electrophile [Pr^iCHO, Bu^tCHO, PhCHO, Pr^nCOMe, $(CH_2)_5CO$] at -78°C in THF (Method A: Barbier-type conditions) leads, after hydrolysis, to the formation of the corresponding ketalised reaction products **2aa-bf**. Alternatively, the reaction can be carried out in a two-step process (Method B), which implies first a DTBB-catalysed lithiation folowed by reaction with an electrophile [Me_3SiCl, Pr^iCHO, Bu^tCHO, PhCHO, Me_2CO, Et_2CO, Pr^nCOMe, $(CH_2)_5CO$, PhCOMe] both steps being performed at -78°C. When the starting materials are chiral, this methodology allows the preparation of chiral protected di or triols in a non-diastereoselective manner. Copyright © 1996 Elsevier Science Ltd

INTRODUCTION

Polyhydroxylated structures are important moieties in organic molecules, mainly in relation to the field of carbohydrates:[1] for this reason, in general, methodologies which allow the regio and stereoselective formation of polyols are welcome. In the last decade our group has been developing new carbon-carbon bond formation methods involving functionalised organolithium compounds;[2,3] using this type of reagents it is possible to transfer functionality from the carbanionic intermediate to the electrophilic reagent, so in one only step polyfunctionalised molecules are accessible. For instance, starting from the *O*-protected epoxyalcohol **I**, the reductive opening[4] using 4,4'-di-*tert*-butylbiphenyl (DTBB) as catalyst,[5] leads to the intermediate **II**, which by reaction with carbonyl compounds and final deprotection affords triols of the type **III**.[6] In this paper we apply this methodology, arene-catalysed lithiation at low temperature,[7] for the preparation of the anionic synthon 3,4-dihydroxybutyl **IV** in a racemic or enantiomerically pure form by a chlorine-lithium exchange, studying also its reactivity towards electrophiles to which the corresponding diol functionality is transferred.[8]



I



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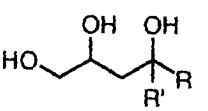
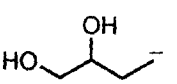


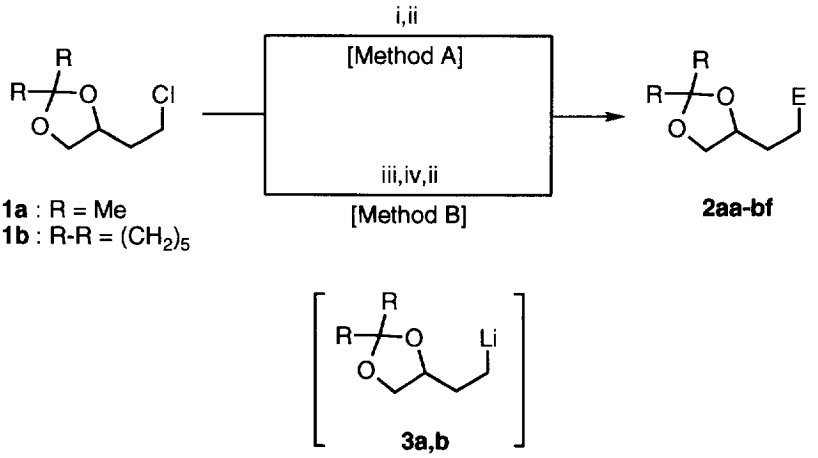
III



IV

RESULTS AND DISCUSSION

Treatment of an equimolecular mixture of chloroketal **1a** and a carbonyl compound [Pr^{i}CHO, Bu^{t}CHO, PhCHO, Pr^{n}COMe, $(CH_2)_5CO$] with a suspension of lithium powder (1:7 molar ratio) and a catalytic amount of DTBB (8:1 molar ratio, 4 mol %) in THF at -78°C led, after hydrolysis with water, to the expected products **2aa-ac**, **2ae** and **2af** [Method A (Barbier-type conditions); Scheme 1 and Table 1, entries 1, 3, 5, 8 and 10, respectively]. Alternatively, the process can be carried out in a two-step reaction, so after the catalytic lithiation as above, yielding the same intermediate of type **3**, the corresponding electrophile [Pr^{i}CHO, Bu^{t}CHO, PhCHO, Me_2CO, Et_2CO, Pr^{n}COMe, $(CH_2)_5CO$, PhCOMe, Me_3SiCl] was added, affording after hydrolysis the same type of reaction products **2aa-ag** (Method B; Scheme 1 and Table 1, entries 2, 4, 6, 7, 9, 11 and 12, respectively). In general, yields are better using Method B, probable due to the partial decomposition of the electrophile in the presence of active lithium (Method A). On the other hand, with prochiral carbonyl compounds (aldehydes or differently substituted ketones) the corresponding diastereoisomers mixture is obtained, the found ratios being between 1:1 and 1:2, so the process works with low diastereoselectivity. This behaviour can be explained considering the high reactivity of the intermediate **3a** involved in the reaction, which is not able to differentiate between both prochiral faces of the carbonyl moiety. The separation of both diastereoisomers was not possible by column chromatography (silica gel, hexane/ethyl acetate mixtures). For this reason we prepared the cyclohexanone derivative **1b** and used it as starting material;[9] applying Method B and using several carbonyl compounds as electrophiles [Bu^{t}CHO, PhCHO, Pr^{n}COMe, $(CH_2)_5CO$] the expected products **2bb-bf** were isolated in moderate yields (Scheme 1 and Table 1, entries 18-21, respectively). The stereoselectivity was also here low, in the same range than before, and both diastereoisomers could not be separated chromatographically under the tried conditions.



Scheme 1. *Reagents and conditions*: i, Li, DTBB cat. (4 mol %), E$^+$ = Pr^{i}CHO, Bu^{t}CHO, PhCHO, Pr^{n}COMe, $(CH_2)_5CO$, THF, -78°C; ii, H_2O; iii, Li, DTBB cat. (4 mol %), -78°C; iv, E$^+$ = Me_3SiCl, Pr^{i}CHO, Bu^{t}CHO, PhCHO, Me_2CO, Et_2CO, Pr^{n}COMe, $(CH_2)_5CO$, PhCOMe, -78°C.

Table 1. Preparation of compounds **2**

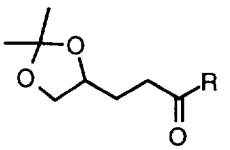
Entry	Starting material	Electrophile E+	Method	Product[a] No	R or RR	E	Yield(%)[b]	Diast.ratio[c]
1	**1a**	PriCHO	A	**2aa**	Me	PriCHOH	16	2:1
2	**1a**	PriCHO	B	**2aa**	Me	PriCHOH	36	2:1
3	**1a**	ButCHO	A	**2ab**	Me	ButCHOH	56	2:1
4	**1a**	ButCHO	B	**2ab**	Me	ButCHOH	30	2:1
5	**1a**	PhCHO	A	**2ac**	Me	PhCHOH	44	1:1
6	**1a**	PhCHO	B	**2ac**	Me	PhCHOH	41	1:1
7	**1a**	Me_2CO	B	**2ad**	Me	Me_2COH	71	---
8	**1a**	PrnCOMe	A	**2ae**	Me	PrnC(OH)Me	25	1:1
9	**1a**	PrnCOMe	B	**2ae**	Me	PrnC(OH)Me	72	1:1
10	**1a**	$(CH_2)_5CO$	A	**2af**	Me	$(CH_2)_5COH$	44	---
11	**1a**	$(CH_2)_5CO$	B	**2af**	Me	$(CH_2)_5COH$	54	---
12	**1a**	Me_3SiCl	B	**2ag**	Me	Me_3Si	58	---
13	(*S*)-**1a**	ButCHO	B	(*S*,*S**)-**2ab**	Me	ButCHOH	40	2:1
14	(*S*)-**1a**	PhCHO	A	(*S*,*S**)-**2ac**	Me	PhCHOH	20	1:1
15	(*S*)-**1a**	PhCHO	B	(*S*,*S**)-**2ac**	Me	PhCHOH	41	1:1
16	(*S*)-**1a**	Et_2CO	B	(*S*)-**2ah**	Me	Et_2COH	92	---
17	(*S*)-**1a**	PrnCOMe	B	(*S*,*S**)-**2ae**	Me	PrnC(OH)Me	72	1:1
18	**1b**	ButCHO	B	**2bb**	$(CH_2)_5$	ButCHOH	40	2:1
19	**1b**	PhCHO	B	**2bc**	$(CH_2)_5$	PhCHOH	30	1:1
20	**1b**	PrnCOMe	B	**2be**	$(CH_2)_5$	PrnC(OH)Me	45	1:1
21	**1b**	$(CH_2)_5CO$	B	**2bf**	$(CH_2)_5$	$(CH_2)_5COH$	30	---
22	(*S*)-**1b**	ButCHO	B	(*S*,*S**)-**2bb**	$(CH_2)_5$	ButCHOH	45	1:1
23	(*S*)-**1b**	PrnCOMe	B	(*S*,*S**)-**2be**	$(CH_2)_5$	PrnC(OH)Me	45	1:1

[a] All isolated products **2** were >94% pure (GLC and or 300 MHz, ^1H NMR). [b] Isolated yield after column chromatography (silica gel, hexane/ethyl acetate). [c] From ^{13}C NMR.

Starting material **1a** was prepared from commercially available 1,2,4-butanetriol by ketalisation with acetone and anhydrous copper(II) sulfate[8b] followed by chlorination of the remaining alcohol functionality with carbon tetrachloride and triphenyl phosphine.[10] The other ketal **1b** was prepared by transketalisation of compound **1a** with cyclohexanone in the presence of a catalytic amount of *p*-toluenesulfonic acid.

In the last part of this study we considered the use of enantiomerically pure chloroketals of the type **1** in order to prepare optically pure compounds of the type **2**. Thus, starting from chloroketals (*S*)-**1a** or (*S*)-**1b** and using almost in all cases Method B (see Table 1, entries 14 and 15) the expected products **2** were obtained as the corresponding 1:1 or 2:1 diastereoismers mixture except in the case of using 3-pentanone as electrophile (Table 1, entry 16), in which, as expected, the corresponding chiral compound (*S*)-**2ah** was isolated. Starting materials (*S*)-**1a** and (*S*)-**1b** were prepared following the same protocol as for the corresponding racemic compounds **1ab** and **1b**, respectively, using commercially (*S*)-1,2,4-butanetriol as the common precursor (see above).

Finally, and considering the difficulties found in the separation of diastereoisomers **2** when the electrophile was a carbonyl compound, we studied the transformation of aldehyde derivatives **2aa** and **2ab** into the corresponding ketones by oxidation. Thus, treatment of these compounds with lead tetraacetate in pyridine[11] yielded ketones **3aa** and **3ab**, respectively, so the way is opened to prepare chiral ketones of type **3** starting from the corresponding chiral alcohols of the type **2**, this process being a typical example of an EPC-synthesis.[12]



3aa : R = Pr^i
3ab : R = Bu^t

As a conclusion, we described here for the first time the preparation of organolithium intermediates bearing a masked diol functionality by a DTBB-catalysed lithiation of the corresponding easily available chlorinated material. The process, which is not diastereoselective (up to 2:1 diastereoisomers mixture) is applied to enantiomerically pure starting material, so chiral products are accessible by this methodology.

EXPERIMENTAL SECTION

General.- For general considerations see reference 13. FTIR spectra were determined with a Nicolet Impact 400D instrument. Mass spectra were measured with a Shimadzu QP-5000 Mass Spectrometer equiped with a GC-17A Gas Chromatograph. Specific rotations were determined with a Jasco DIP-1000 Digital Polarimeter.

Preparation of 4-(2-Chloroethyl)-2,2-dimethyl-1,3-dioxolane (**1a**).-[8b,10] A mixture of 1,2,4-butanetriol (1.06 g, 10 mmol) and anhydrous copper(II) sulfate (2.5 g, 16 mmol) in dry acetone (15 ml) was stirred for 24 h at room temperature. The resulting suspension was filtered off trough celite and the precipitate washed with acetone (2x10 ml). The resulting filtrate was evaporated at reduced pressure (15 Torr) giving an oily residue, which was dissolved in carbon tetrachloride (3 ml). To the resulting solution was added triphenylphosphine (2.89 g, 11 mmol) and the mixture was stirred for 48 h. Then, the solvent was evaporated (15 Torr) and the resulting residue was distilled *in vacuo* to give the pure title compound **1a** in 61% yield: bp 80°C/0.1 Torr.R_f 0.6 (hexane/diethyl ether: 3/1); ν (film) 1070 (C-O) and 850 cm^{-1} (C-Cl); δ_H 1.28 (3H, s, CH_3), 1.34 (3H, s, CH_3), 2.02 (2H, m, OCHCH_2), 3.45-3.50 (3H, m, C*H*HO and CH_2Cl), 4.02 (1H, dd, J= 6.1, 8.2, CH*H*O),

4.20 (1H, m, OCH); δ_C 25.5, 26.9 (2C, 2xCH_3), 36.7 (1C, OCH*C*H_2), 41.3 (1C, CH_2Cl), 69.0 (1C, CH_2O), 73.1 (1C, OCH) , 109.0 (1C, OCO); *m/z* 151 (M^+-CH_3+2, 18%), 149 (M^+-CH_3, 15), 89 (17), 72 (33), 61 (17), 59 (10), 43 (100), 42 (17), 41 (14).

Compound (*S*)-**1a**, which was prepared as **1a** (54 % yield), showed the same physical and spectroscopic data as **1a**: $[\alpha]_D^{25}$ -13.2 (c = 0.96, CH_2Cl_2).

Preparation of 3-(2-Chloroethyl)-1,4-dioxaspiro[4.5]decane (**1b**).- Compound **1a** (1.11 g, 6.75 mmol), cyclohexanone (0.70 ml, 6.75 mmol) and a catalytic amount of *p*-toluenesulfonic acid (0.06 g, 5 mol %) were dissolved in THF (5 ml) and the resulting mixture was stirred for 24 h. Then the solvent was evaporated (15 Torr) and cyclohexanone was distilled (75°C bath temperature, 0.1 Torr) leading a residue, which contained essentially pure compound **1b** (72% yield). R_f 0.4 (hexane/diethyl ether: 2/1); ν (film) 1163, 1103 and 1042 cm^{-1} (C-O); δ_H 1.40 (2H, s br, 1xring CH_2), 1.54-1.61 (8H, m, 4xring CH_2), 1.85-2.11 (2H, m, OCHCH_2), 3.59 (1H, dd, *J*= 7.9, 6.4, C*H*HO), 3.66 (2H, dd, *J*= 7.5, 6.0, CH_2Cl), 4.09 (1H, dd, *J*= 7.9, 6.4, CH*H*O), 4.22-4.31 (1H, m, OCH); δ_C 23.8, 24.0, 25.1, 35.0, 36.6, 37.0 (6C, 5xring CH_2 and CH_2), 41.4 (1C, CH_2Cl), 68.7 (1C, CH_2O), 72.7 (1C, OCH), 109.6 (1C, OCO); *m/z* 204 (M^+, 9%), 163 (31), 161 (100), 89 (10), 73 (10), 55 (56), 53 (18), 49 (11), 43 (14), 42 (29), 41 (51).

Compound (*S*)-**1b**, which was prepared as **1b** (60 % yield), showed the same physical and spectroscopic data as **1b**: $[\alpha]_D^{25}$ -1.7 (c = 1.25, CH_2Cl_2).

DTBB-Catalysed Lithiation of Chloroketals **1** *and Reaction with Electrophiles. Isolation of Compounds* **2**. *General Procedure: Method A*.- To a green suspension of lithium powder (100 mg, 14 mmol) and DTBB (26 mg, 0.1 mmol, 4 mol %) in THF (5 ml) was slowly added (*ca.* 1 h) with stirring a solution of the corresponding chloroketal **1** (1 mmol) and the electrophile (1 mmol) in THF (3 ml) at -78°C and the mixture was stirred for 30 additional min at the same temperature. Then, the resulting mixture was hydrolysed with water (5 ml) at -78°C and warming until room temperature it was extracted with ethyl acetate (3x10 ml), the organic layer dried over anhydrous Na_2SO_4 and the solvent evaporated (15 Torr). The resulting residue was then purified by column chromatography (silica gel, hexane/ethyl acetate) giving pure compounds **2**.

Method B.- Using the same amounts mentioned in the Method A, to the activated green lithium suspension in THF containing the DTBB catalyst was added the chloroketal **1** in THF (2 ml) at -78°C and the mixture was stirred at the same temperature for 30 min (the green colour was then recuperated). Then the corresponding electrophile was added in THF (2 ml) and the mixture stirred at the same temperature for *ca.* 20 min and hydrolysed and worked up as it was above described in Method A. Yields and diastereoisomeric ratios for compounds **2** are included in Table 1; physical, analytical and spectroscopic data, as well as literature references for known compounds, follow.

2,2-Dimethyl-4-(3-hydroxy-4-methylpentyl)-1,3-dioxolane (**2aa**): R_f 0.55 (hexane/diethyl ether: 3/1); ν (film) 3422 (OH) and 1059 cm^{-1} (C-O); δ_H 0.93 [12H, d, *J*= 7.0, 2x(CH_3)$_2$CH], 1.36, 1.42 [12H, 2s, 2x(CH_3)$_2$C], 1.45-1.83 [10H, m, 2xCH_2CH_2 and 2x(CH_3)$_2$C*H*], 3.28-3.42 (2H, m, 2xHOC*H*), 3.45-3.62 (2H, m, 2xC*H*HO), 4.03-4.15 (4H, m, 2xCH*H*O and 2xOCH); δ_C 17.3, 17.4, 18.75, 18.8, 25.6, 25.7, 26.85, 26.9 (8C, 8xCH_3), 30.0, 30.4, 30.45, 30.5 (4C, 4xCH_2), 33.6, 33.65 [2C, 2x(CH_3)$_2$*C*], 69.45, 69.5 (2C, 2xCH_2O), 76.2, 76.3, 76.6 (4C, 4xOCH), 108.9 (2C, 2xOCO); *m/z* 187 (M^+-CH_3, 6%), 109 (13), 101 (13), 83 (14), 72 (17), 69 (11), 59 (26), 57 (19), 55 (28), 43 (100), 41 (35).

2,2-Dimethyl-4-(4,4-dimethyl-3-hydroxypentyl)-1,3-dioxolane (**2ab**): R_f 0.47 (hexane/diethyl ether: 1/1); ν (film) 3470 (OH) and 1060 cm^{-1} (C-O); δ_H 0.90 [18H, s, 2x(CH_3)$_3$C], 1.36, 1.42 (12H, 2s, 4xCH_3), 1.56-1.74 (4H, m, CH_2CH_2), 1.76-1.89 (4H, m, CH_2CH_2), 3.19, 3.22 (2H, 2dd, *J*=7.6, 1.5, 2xOC*H*H), 3.52 (2H, 2t, *J*= 7.6, 7.3, 2xHOC*H*), 4.05 (2H, m, 2xOCH*H*), 4.09-4.18 (2H, m, 2xOCH); δ_C 25.7 [6C, 2x(*C*H_3)$_3$C], 26.8, 26.85 (4C, 4xCH_3), 27.7, 27.9, 30.9, 31.25 (4C, 2xCH_2CH_2), 34.9 [2C, 2x(CH_3)$_3$*C*], 69.4, 69.5 (2C, 2xCH_2O), 76.2, 76.3, 79.5, 79.9 (4C, 4xOCH), 108.8, 108.9 (2C, 2xOCO); *m/z* 201 (M^+-CH_3, 14%), 123 (23), 115 (12), 101 (100), 83 (59), 81 (17), 72 (39), 71 (12), 69 (15), 59 (51), 57 (58), 55 (29), 43 (86), 42 (11), 41 (45) (Found: M^+, 201.1501.$C_{12}H_{24}O_3$-CH_3 requires M, 201.1491).

2,2-Dimethyl-4-(3-hydroxy-3-phenylethyl)-1,3-dioxolane (**2ac**):[8a] R_f 0.30 (hexane/ethyl acetate: 8/2); ν (film) 3376 (OH), 3061, 3029 (ArH), 1705, 1603 and 1493 cm^{-1} (ArC and C=C); δ_H 1.34, 1.35 (12H, 2s, 4xCH_3),

1.59-1.92 (8H, m, 2xCH_2CH_2), 3.44-3.52 (2H, m, 2xOCHPh), 4.00-4.14 (4H, m, 2xCH_2O), 4.68-4.74 (2H, 2m, 2xOCH), 7.21-7.35 (10H, m, 2xArH); δ_C 25.7, 26.8 (4C, 4xCH_3), 29.5, 30.0, 35.2, 35.5 (4C, 4xCH_2), 69.4 (2C, 2xCH_2O), 74.0 , 74.3 (2C, 2xOCH), 75.9 (2C, 2xOCH), 108.8, 108.9 (2C, 2xOCO), 125.8, 126.9, 127.85, 128.1, 128.4, 144.4, 144.5 (12C, 2xArC); *m/z* 221 (M^+-CH_3, 6%), 143 (24), 117 (14), 115 (33), 107 (24), 105 (31), 91 (15), 79 (39), 77 (41), 72 (24), 59 (24), 43 (100), 42 (14), 41 (14).

2,2-Dimethyl-4-(3-methyl-3-hydroxybutyl)-1,3-dioxolane (**2ad**): R_f 0.69 (hexane/ethyl acetate: 8/2); ν (film) 3241 (OH), 1060 and 980 cm^{-1} (C-O); δ_H 1.23 (6H, s, 2xCH_3),1.36 (3H, s, CH_3), 1.42 (3H, s, CH_3), 1.25-1.70 (4H, m, CH_2CH_2), 3.53 (1H, dd, *J*= 6.4, 7.0, OC*H*H), 4.05-4.10 (2H, m, CH*H*O and OCH); δ_C 25.7, 26.9 (2C, 2xCH_3), 28.3 (1C, CCH_2), 29.2, 29.4 (2C, 2xCH_3), 39.7 (1C, OCHCH_2), 69.5 (1C, OCH_2), 70.3 (1C, HOC), 76.4 (1C, OCH), 108.9 (1C, OCO); *m/z* 173 (M^+-CH_3, 15%), 115 (13), 95 (28), 72 (23), 69 (14), 59 (52), 57 (10), 43 (100), 41 (19).

2,2-Dimethyl-4-(3-hydroxy-3-methylhexyl)-1,3-dioxolane (**2ae**): R_f 0.57 (hexane/ethyl acetate: 8/2); ν (film) 3450 (OH) and 1065 cm^{-1} (C-O); δ_H 0.93 (6H, t, *J*= 7.0, 2xCH_3CH_2), 1.16, 1.17 (6H, 2s, 2xCCH_3), 1.35, 1.42 (12H, 2s, 4xCH_3), 1.35-1.79 (16H, 2m, 8xCH_2), 3.53 (2H, t, *J*= 6.5, 2xC*H*HO), 4.03-4.11 (4H, m, 2xCH*H*O and 2xOCH); δ_C 14.6 (2C, 2xCH_3CH_2), 17.2 (2C, 2xCH_3CH_2), 25.7, 26.7, 26.8, 26.9 (6C, 6xCH_3), 28.0, 37.6, 37.7 (6C, 6xCH_3), 69.5 (2C, 2xCH_2O), 72.1, 72.2 (2C, 2xCOH), 76.4, 76.45 (2C, 2xOCH), 108.8, 108.85 (2C, 2xOCO); *m/z* 201 (M^+-CH_3, 11%), 123 (15), 115 (39), 97 (18), 87 (17), 81 (26), 72 (37), 71 (23), 69 (17), 59 (41), 57 (21), 55 (22), 45 (29), 43 (100), 42 (19), 41 (46) (Anal. Calc. for $C_{12}H_{24}O_3.0.3H_2O$: C, 65.00; H, 11.18. Found: C, 64.99; H, 11.29).

2,2-Dimethyl-4-[2-(1-hydroxycyclohexyl)ethyl]-1,3-dioxolane (**2af**): R_f 0.44 (hexane/ethyl acetate: 8/2); ν (film) 3440 (OH) and 1060 cm^{-1} (C-O); δ_H 1.18-1.70 (14H, m, 5xring CH_2 and CH_2CH_2), 1.35 (3H, s, CH_3), 1.41 (3H, s, CH_3), 3.44-3.55 (2H, m, CH_2O), 4.02-4.13 (2H, m, OCH and OH); δ_C 22.2, 26.9, 27.0, 37.4, 37.5 (7C, 5xring CH_2 and CH_2CH_2), 25.7, 25.8 (2C, 2xCH_3), 69.5 (1C, OCH_2), 70.8 (1C, OCH), 76.5 (1C, HCO), 108.8 (1C, OCO); *m/z* 213 (M^+-CH_3, 43%), 153 (14), 139 (50), 127 (48), 115 (38), 114 (25), 109 (12), 99 (31), 95 (13), 83 (13), 81(43), 79 (13), 72 (36), 71 (18), 67 (23), 59 (31), 57 (18), 55 (42), 43 (100), 42 (20), 41 (43).

2,2-Dimethyl-4-(2-trimethylsilylethyl)-1,3-dioxolane (**2ag**): R_f 0.59 (hexane); ν (film) 1064 (C-O) and 837 cm^{-1} (Si-C); δ_H 0.21 [9H, s, $(CH_3)_3Si$], 1.34, 1.40 (6H, 2s, 2xCH_3), 1.23-1.68 (4H, m, CH_2CH_2), 3.73 (1H, m, CH*H*O), 4.06 (2H, m, C*H*HO and OCH); δ_C -1.9 [3C, $(CH_3)_3Si$], 12.1 (1C, CH_2Si), 25.7, 26.9 (2C, 2xCH_3), 27.9 (1C, OCHCH_2), 69.3 (1C, CH_2O), 78.4 (1C, HOC), 108.7 (1C, OCO); *m/z* 187 (M^+-CH_3, 15%), 101 (31), 75 (24), 73 (86), 72 (22), 59 (22), 55 (44), 45 (21), 43 (100), 42 (16), 41 (17).

(4S,3S)-2,2-Dimethyl-4-(4,4-dimethyl-3-hydroxypentyl)-1,3-dioxolane* [(*S,S**)-**2ab**]. Physical and spectroscopic data were found to be the same than for compound **2ab**.

(4S,3S)-2,2-Dimethyl-4-(3-hydroxy-3-phenylethyl)-1,3-dioxolane* [(*R,S**)-**2ac**]. Physical and spectroscopic data were found to be the same than for compound **2ac**.

(4S)-4-(3-Ethyl-3-hydroxypentyl)-2,2-dimethyl-1,3-dioxolane [(*S*)-**2ah**]: R_f 0.73 (hexane/diethyl ether: 3/1), $[\alpha]_D^{25}$ +7.2 (c = 0.99, CH_2Cl_2); ν (film) 3502 (OH) and 1063 cm^{-1} (C-O); δ_H 0.85, 0.86 (6H, 2t, *J*= 7.5, 2xCH_3CH_2), 1.35, 1.41 [6H, 2s, $(CH_3)_2C$], 1.30-1.63 (8H, m, 2xCH_3CH_2 and CH_2CH_2), 3.50-3.62 (1H, m, C*H*HO), 3.93-4.13 (2H, m, CH*H*O and OCH); δ_C 7.7 (2C, 2xCH_3CH_2), 25.6, 26.8 (2C, 2xCH_3), 27.5, 30.7, 30.8, 34.1 (4C, 4xCH_2), 69.4 (1C, CH_2O), 74.0 (1C, COH), 76.4 (1C, OCH), 108.7 (1C, OCO); *m/z* 201 (M^+-CH_3, 28%), 129 (88), 123 (30), 115 (27), 111 (16), 87 (24), 85 (21), 83 (28), 81 (34), 73 (15), 72 (33), 71 (10), 69 (19), 67 (11), 59 (29), 57 (60), 55 (28), 45 (20), 43 (100), 42 (13), 41 (27) (Found: M^+, 201.1486. $C_{11}H_{21}O_3$ requires M, 201.1491).

(4S,3S)-2,2-Dimethyl-4-(3-hydroxy-3-methylhexyl)-1,3-dioxolane* [(*S,S**)-**2ae**]. Physical and spectroscopic data were found to be the same than for compound **2ae**.

3-(4,4-Dimethyl-3-hydroxypentyl)-1,4-dioxaspiro[4,5]decane (**2bb**): R_f 0.63 (hexane/diethyl ether: 1/1); ν (film) 3483 (OH) and 1104 cm^{-1} (C-O); δ_H 0.91 [18H, s, 2x$(CH_3)_3C$], 1.26-1.82 (28H, m, 4xCH_2 and

10xring CH_2), 1.93 (1H, s br, OH), 2.31 (1H, s br, OH), 3.22 (2H, t, *J*= 11.1, 2xHOC*H*), 3.52, 3.53 (2H, 2t, *J*= 7.5, 7.5, 2xC*H*HO), 4.02-4.16 (4H, m, 2xCH*H*O and 2xOCH); δ_C 23.9, 24.0, 25.1, 25.2, 27.8, 28.1, 30.1, 31.5, 34.9, 34.95, 35.25, 36.5, 36.6 (14C, 10xring CH_2 and 2xCH_2CH_2), 25.7, 25.8 [6C, 2x(CH_3)$_3$C], 35.3 [2C, 2x(CH_3)$_3$*C*], 69.2 (2C, 2xCH_2O), 75.8, 75.9 (2C, 2xOCH), 79.5, 79.9 (2C, 2xHOCH), 109.4, 109.5 (2C, 2xOCO); *m/z* 257 (M^++1, 1%), 256 (M^+, 6) 213 (17), 141 (15), 127 (12), 123 (64), 112 (15), 101 (69), 99 (29), 98 (17), 97 (18), 85 (17), 84 (12), 83 (71), 81 (59), 73 (10), 71 (25), 70 (17), 69 (43), 67 (22), 57 (70), 56 (14), 55 (99), 54 (11), 45 (15), 43 (93), 42 (46), 41 (100).

3-(3-Phenyl-3-hydroxypropyl)-1,4-dioxaspiro[4,5]decane (**2bc**): R_f 0.34 (hexane/diethyl ether: 1/1); ν (film) 3436 (OH), 3085, 3061, 3028 (ArH), 1601, 1485, 1450 (ArC) and 1017 cm^{-1} (C-O); δ_H 1.37-1.92 (28H, m, 4xCH_2 and 10xring CH_2), 3.49, 3.50 (2H, 2t, *J*= 7.6, 7.6, 2xC*H*OH), 4.01, 4.03 (2H, 2dd, *J*= 5.8, 3.2, 2xC*H*HO), 4.07-4.16 (2H, m, 2xCH*H*O), 4.69-4.77 (2H, m, 2xOCH), 7.26-7.35 (10H, m, 2xArH); δ_C 23.8, 24.0, 25.1, 29.5, 30.4, 35.2, 35.3, 35.9, 36.5 (14C, 10xring CH_2 and 2xCH_2CH_2), 69.0 (2C, 2xCH_2O), 73.9, 74.4, 75.6 (4C, 4xOCH), 109.6 (2C, 2xOCO), 125.8, 127.4, 128.4, 144.5, 144.6 (12C, 2xArC); *m/z* 277 (M^++1, 1%), 276 (M^+, 5) 215 (12), 161 (28), 160 (32), 147 (12), 144 (10), 143 (68), 141 (11), 128 (12), 118 (13), 117 (34), 114 (10), 112 (11), 107 (17), 105 (65), 104 (13), 98 (10), 91 (30), 81 (12), 79 (37), 77 (30), 69 (17), 55 (100), 54 (11), 43 (62), 42 (35), 41 (55).

3-(3-Hydroxy-3-methylhexyl)-1,4-dioxaspiro[4,5]decane (**2be**): R_f 0.41 (hexane/diethyl ether: 1/1); ν (film) 3446 (OH) and 1104 cm^{-1} (C-O); δ_H 0.93 (6H, t, *J*= 6.9, 2xCH_3CH_2), 1.16, 1.17 (6H, 2s, 2xCH_3), 1.26-1.88 (36H, m, 10xring CH_2 and 8xCH_2), 3.52 (2H, m, 2xC*H*HO), 4.02-4.10 (4H, m, 2xCH*H*O and 2xOCH); δ_C 14.6 (2C, 2x*C*H_3CH_2), 26.7 (2C, 2xOC*C*H_3), 17.2, 23.9, 25.1, 28.2, 35.2, 36.6, 37.8, 44.2, 44.6 (18C, 18xCH_2), 69.2 (2C, 2xOCH), 72.1 (2C, 2xCOH), 76.0, 76.1 (2C, 2xCH_2O), 109.5 (2C, 2xOCO); *m/z* 256 (M^+, 5%), 263 (10), 141 (17), 127 (12), 115 (46), 112 (10), 99 (13), 98 (12), 97 (22), 87 (11), 85 (19), 83 (17), 82 (12), 81 (52), 71 (19), 69 (25), 67 (18), 57 (16), 55 (73), 45 (31), 43 (100), 42 (24), 41 (57).

3[2-(1-Hydroxycyclohexyl)ethyl]-1,4-dioxaspiro[4,5]decane (**2bf**): R_f 0.6 (hexane/diethyl ether: 1/2); ν (film) 3443 (OH) and 1104 cm^{-1} (C-O); δ_H 1.19-1.92 (24H, m, 2xCy and CH_2CH_2), 3.52 (1H, m, C*H*HO), 4.02-4.13 (2H, m, CH*H*O and OCH); δ_C 22.2, 23.9, 24.0, 25.1, 25.8, 27.3, 35.2, 36.6, 37.6 (12C, 12xCH_2), 69.2 (1C, HOC), 70.8 (1C, CH_2O), 76.2 (1C, OCH), 109.5 (1C, OCO); *m/z* 269 (M^++1, 3%), 268 (M^+, 18) 225 (39), 170 (16), 153 (43), 152 (18), 141 (13), 139 (57), 136 (16), 135 (100), 134 (28), 128 (19), 127 (60), 121 (25), 119 (12), 114 (56), 112 (24), 109 (20), 108 (12), 107 (18), 99 (50), 98 (23), 97 (27), 96 (21), 95 (43), 94 (54), 93 (46), 92 (22), 91 (30), 84 (13), 83 (28), 82 (10), 81 (77), 80 (16), 79 (56), 77 (17), 73 (10), 71 (28), 70 (23), 69 (44), 68 (11), 67 (72), 57 (29), 56 (19), 55 (93), 54 (25), 53 (24), 43 (83), 42 (65), 41 (89) (Found: M^+, 268.2023. $C_{16}H_{28}O_3$ requires M, 268.2038).

(3S,3'S)-3-(4',4'-Dimethyl-3'-hydroxypentyl)-1,4-dioxaspiro[4,5]decane* [(*R,S**)-**2bb**]. Physical and spectroscopic data were found to be the same than for compound **2bb**.

(3S,3'S)-3-(3'-Hydroxy-3'-methylhexyl)-1,4-dioxaspiro[4,5]decane* [(*R,S**)-**2bd**]. Physical and spectroscopic data were found to be the same than for compound **2bd**.

Oxidation of Compounds **2aa** *and* **2ab**. *Isolation of Ketone* **3aa** *and* **3ab**. *General Procedure.*- A mixture of the corresponding alcohol **2** (1 mmol), lead tetraacetate (0.44 g, 1 mmol) and pyridine (5 ml) was stirred for 24 h at room temperature. The resulting mixture was cooled at 0°C and the precipitate formed was filtered off through celite, washing it with pyridine (2x5ml). Ethyl acetate (15 ml) was then added to the filtrate, which was washed with water (2x10 ml), the organic layer dried over anhydrous Na_2SO_4 and the solvent evaporated (15 Torr) to give the title compounds **3aa** [38% yield after column chromatography (silica geel, hexane/ethyl acetate) and **3ab** (80% crude yield of >95% pure compound). Physical and spectroscopic data follow.

2,2-Dimethyl-4-(4-methyl-3-oxopentyl)-1,3-dioxolane (**3aa**): R_f 0.36 (hexane/diethyl acetate: 9/1); ν (film) 1713 cm^{-1} (C=O); δ_H 1.11 [6H, d, *J*= 7.0, (CH_3)$_2$CH], 1.34, 1.40 (6H, 2s, 2xCH_3), 1.42-1.89 (3H, m, OCHCH_2 and C*H*CH_3), 2.50-2.69 (2H, m, CH_2CO), 3.48-3.56 (1H, m, OC*H*H), 4.01-4.10 (2H, m, OCH*H* and OCH); δ_C 18.2 [2C, (CH_3)$_2$C], 26.85 (2C, 2xCH_3), 27.4 (1C, OCH*C*H_2), 36.2 (1C, *C*H_2CO), 40.9 [1C, (CH_3)$_2$*C*], 69.2 (1C, OCH_2), 75.15 (1C, OCH), 108.85 (1C, OCO), 214.0 (1C, CO); *m/z* 185 (M^+-CH_3,

43%), 142 (23), 125 (18), 97 (17), 83 (12), 72 (55), 71 (94), 69 (10), 59 (22), 57 (17), 56 (17), 55 (50), 54 (11), 44 (15), 43 (100), 42 (54), 41 (75), 40 (11) (Found: M+, 185.1175. $C_{11}H_{20}O_3$-CH_3 requires M, 185.1177).

2,2-Dimethyl-4-(4,4-dimethyl-3-oxopentyl)-1,3-dioxolane (**3ab**): R_f 0.3 (hexane/diethyl acetate: 9/1); ν (film) 1705 cm-1 (C=O); δ_H 1.15 [9H, s, $(CH_3)_3C$], 1.34, 1.40 (6H, 2s, 2xCH_3), 1.65-1.92 (2H, m, OCHCH_2), 2.64 (2H, m, CH_2CO), 3.53 (1H, m, OC*H*H), 4.02-4.16 (2H, m, OCH and OCH*H*); δ_C 25.6 (1C, CH_2), 26.4 [3C, $(CH_3)_3C$], 26.9, 27.7 (2C, 2xCH_3), 32.6 (1C, CH_2CO), 44.1 [1C, $(CH_3)_3C$], 69.3 (1C, OCH_2), 75.3 (1C, OCH), 108.8 (1C, OCO), 215.4 (1C, CO); *m/z* 199 (M+-CH_3, 36%), 157 (18), 156 (29), 139 (17), 121 (13), 101 (11), 100 (11), 99 (99), 97 (15), 95 (11), 85 (29), 83 (10), 81 (14), 72 (56), 71 (72), 69 (21), 59 (35), 58 (17), 57 (92), 55 (52), 54 (14), 53 (11), 44 (15), 43 (38), 42 (100), 41 (86) (Found: M+, 199.1331. $C_{12}H_{22}O_3$-CH_3 requires M, 199.1334).

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