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Reductive Opening of 2-Phenyl-1,3-dioxolanes by a Naphthalene-Catalysed Lithiation: Synthetic Applications

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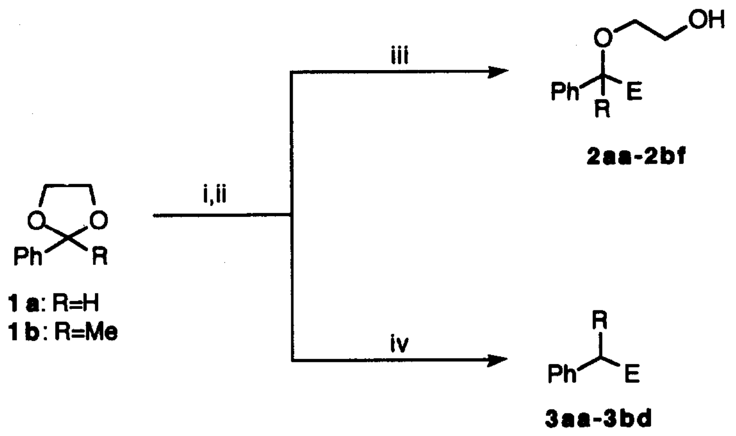
Abstract: The reaction of 2-phenyl-1,3-dioxolanes **1a,b** with an excess of lithium powder in the presence of a catalytic amount of naphthalene (4 mol %) in tetrahydrofuran at -40°C followed by successive reaction with an electrophile and final hydrolysis with water at the same temperature yields the corresponding monoprotected 1,2-diols **2aa-2bf**. The same process but allowing to rise the temperature to 20°C before the hydrolysis affords alcohols **3aa-3bd**. The use of 2,2-diphenyl-1,3-dioxolane **1d**, under similar reaction conditions as for compounds **2**, permits the isolation of 2,2-diphenylalcohols **11da-11dc**, resulting from the reaction with two different electrophiles. A mechanistic rationalization for all processes is given.

Introduction

Saturated heterocycles such as oxiranes[1], aziridines[2], oxetanes[3] and tetrahydrofurans[4] have been recently used as starting materials for the preparation of functionalized organolithium compounds[5] by reductive opening using a lithium-arene reagent[6] or more efficiently by an arene-catalysed lithiation using lithium powder[7]. However, to our best knowledge, the same process has not been applied to the reductive opening of 1,3-dioxolanes[8], which, on the other hand, have been used as protected carbonyl compounds in the preparation of masked lithium β–[9], γ–[7,10] and δ-enolates[7,11]. In the last two cases the dioxolane ring does not suffer reductive opening with lithium and a catalytic[12] or stoichiometric amount of an arene at -78°C[7,10,11]. In the present paper we study the naphthalene-catalysed lithiation of different 2-phenyl-1,3-dioxolanes and the application of the generated lithiated intermediates in organic synthesis.

Results and Discussion

The reaction of 1-phenylketals **1a,b**[13] with an excess of lithium powder (1:8 molar ratio) and a catalytic amount of naphthalene (1:0.08 molar ratio; 4 mol %) in tetrahydrofuran at -40°C[14] followed by treatment with an electrophile and final hydrolysis with water at the same temperature led to the corresponding products **2aa-2bf** (Scheme 1 and Table 1, entries 1-7). The maintenance of the reaction temperature is important in order to obtain exclusively products **2**; thus, when the temperature was allowed to rise to 20°C before the last hydrolysis compounds **3aa-3bd** were isolated as the only reaction products (Scheme 1 and Table 1, entries 8-12).



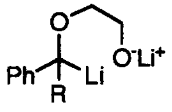
Scheme 1. *Reagents and conditions*: i, Li powder (1:8 molar ratio), $C_{10}H_8$ cat. (4 mol %), THF, -40°C, 45 min; ii, $E^+ = H_2O$, D_2O, Me_2CO, Et_2CO, $(CH_2)_4CO$, $(CH_2)_5CO$, $(CH_2)_7CO$, -40°C, 1 h; iii, H_2O, -40°C; iv, -40 to 20°C and then H_2O or D_2O.

Table 1. Obtention of Compounds **2** and **3**

Entry	Starting material	Electrophile E^+	Product[a] no.	R	E	yield (
1	**1a**	Me_2CO	**2aa**	H	Me_2COH	60
2	**1b**	H_2O	**2ba**	Me	H	81
3	**1b**	D_2O	**2bb**	Me	D	90
4	**1b**	Me_2CO	**2bc**	Me	Me_2COH	85
5	**1b**	Et_2CO	**2bd**	Me	Et_2COH	55
6	**1b**	$(CH_2)_4CO$	**2be**	Me	$(CH_2)_4COH$	60
7	**1b**	$(CH_2)_5CO$	**2bf**	Me	$(CH_2)_5COH$	60
8	**1a**	Me_2CO	**3aa**	H	Me_2COH	53
9	**1b**	Me_2CO	**3ba**	Me	Me_2COH	60 (
10	**1b**	Et_2CO	**3bb**	Me	Et_2COH	55
11	**1b**	$(CH_2)_4CO$	**3bc**	Me	$(CH_2)_4COH$	50
12	**1b**	$(CH_2)_7CO$	**3bd**	Me	$(CH_2)_7COH$	35

[a] All isolated compounds **2** and **3** were >95% pure (GLC and 300 Mz ^1H NMR). [b] Isolated y after flash chromatography (silica gel, hexane/ethyl acetate) based on the starting material **1**. [c] Y obtained under Barbier-type reaction conditions (see Scheme 1 and text).

A rationalization of the obtained results can be as follows: after the first reductive ring opening an intermediate of the type **4** is formed, which under these reaction conditions (-40°C) is stable and after addition of the electrophile reacts to give the alcoholate **5**. When the final hydrolysis is carried out at low temperature the corresponding compound **2** is obtained. But by warming till ambient temperature a second ether cleavage[8] yields a benzylic organolithium compound of the type **6**, which under these reaction conditions takes a proton from the reaction media[15] to give the obtained products **3**. The proton abstraction before the final hydrolysis with water is demonstrated by carrying out a deuteriolysis with deuterium oxide instead of the hydrolysis: no incorporation of deuterium was observed, resulting always products **3**.



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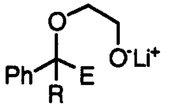

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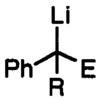
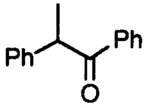


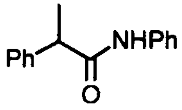
6

4-6	a	b	d
R	H	Me	Ph

In the case of using benzonitrile or phenyl isocyanate as electrophilic reagents compounds **3be** and **3bf** were obtained in 40% and 45% isolated yields, respectively, even performing the final hydrolysis at -40°C. We think that the easy transformation **5**→**6** is due, in this case, to the presence of a carbon-nitrogen double bond next to the benzylic carbon-lithium bond in the intermediate of the type **6**, which stabilizes the carbanionic centre.



3be

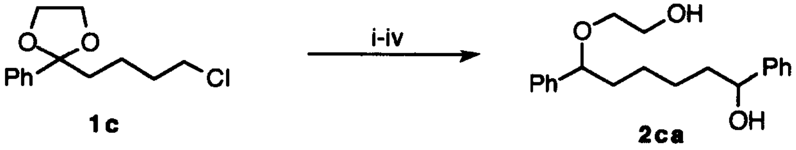


3bf

When the whole reaction indicated in Table 1, entry 4 was carried out at 0°C a mixture of compounds **2ba** (46%) and **3ba** (36%) was isolated. This result would mean that under these reaction conditions the intermediate **4b** initially formed can take a proton from the reaction media to give another intermediate of the type **5b** with E=H, and finally the product **2ba**. Another possibility is that the intermediate of the type **5b** with E=Me_2COLi suffers cleavage of the benzylic carbon-oxygen bond to give successively the species **6b** with E=Me_2COLi and, after hydrolysis, the product **3ba**, as it was described above.

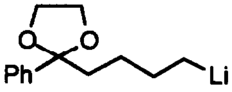
On the other hand a Barbier-type reaction does not improve the results indicated in Table 1. Thus, the obtention of compound **3ba** (Table 1, entry 9 and footnote c) carrying the lithiation in the presence of acetone as electrophile at -40°C afforded only a 44% isolated yield. When the reaction temperature was 0°C this process yielded a mixture of **2ba** (16%) and **3ba** (52%).

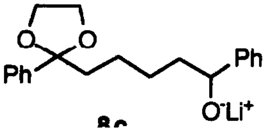
We tried to prepare a dilithiated intermediate starting from the chloroketal **1c**. The catalytic lithiation of this starting material at -78°C led to the expected masked lithium ε-enolate **7c**[11], which is stable at this temperature and reacted with benzaldehyde to give the corresponding alcoholate **8c**. When the temperature was then allowed to rise to -40°C (see above for compound **2**) the reductive opening of the dioxolane ring took place yielding the trianion **4c**, which after hydrolysis afforded the isolated product **2ca** in 43% as a *ca.* 1:1 mixture of diastereoisomers (75 MHz ^{13}C NMR) (Scheme 2).

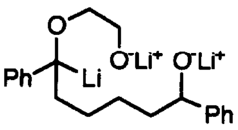


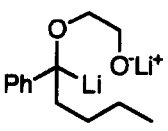
Scheme 2. *Reagents and conditions*: i,, Li powder (1:8 molar ratio), $C_{10}H_8$ cat. (4 mol %), THF, -78°C, 2 h; ii, PhCHO, -78°C, 2 h and then -78 to -40°C, 2 h; iii, H_2O, -40°C.

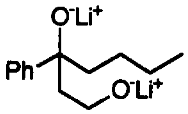
As it was already described[11] the intermediate **7c** decomposes by warming over -78°C, so once this species was prepared as above, the temperature was allowed to rise to 20°C: the dianion initially formed **4c'** (see Scheme 1) suffered a Wittig-type rearrangement[16] to give the dianion **9c** (instead of taking a proton from the reaction media), which after hydrolysis led to the diol **10c** in 42% isolated yield.

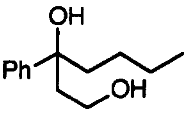

7c


8c

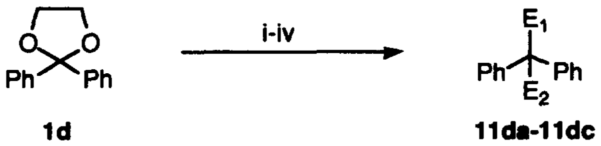

4c


4c'


9c


10c

The use of the ketal **1d** as starting material allows the obtention of compounds **11da-11dc** following the same methodology described in Scheme 1 for compounds **2**, except that two different electrophiles E_1^+ and E_2^+, were successively added at -40°C (Scheme 3 and Table 2). It is worthy to note that the reaction worked only when water or deuterium oxide were used as second electrophile E_2^+. In this case it seems that the reaction gives the same intermediate **6d** as for compound **3**, which is stabilized by the presence of both phenyl groups and can react with water or deuterium oxide to yield compounds **11**.



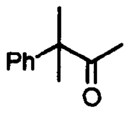
Scheme 3. *Reagents and conditions*: i, Li powder (1:8 molar ratio), $C_{10}H_8$ cat. (4 mol %), THF, -40°C, 45 min; ii, E_1^+=Pr^{i}CHO, Bu^{t}CHO, -40°C, 1 h; iii, E_2^+ =H_2O, D_2O, -40°C; iv, H_2O, -40 to 20°C.

Table 2. Obtention of Compounds **11**

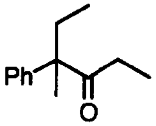
Entry	Electrophiles		Product[a]			
	E_1^+	E_2^+	no.	E_1	E_2	yield (%)[b]
1	Pr^{i}CHO	H_2O	**11da**	Pr^{i}CHOH	H	88
2	Pr^{i}CHO	D_2O	**11db**	Pr^{i}CHOH	D	86[c]
3	Bu^{t}CHO	H_2O	**11dc**	Bu^{t}CHOH	H	45

[a,b] See footnotes a and b in Table 1. [c] >95% deuterium incorporation by mass spectrometry.

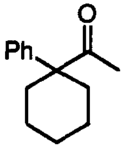
From the obtained compounds, the corresponding ones containing the structure **2** can be used as starting materials for a pinacolinic-type rearrangement. Thus, treatment of compounds **2bc**, **2bd** and **2bf** with phosphoric acid in toluene under reflux overnight gave the expected ketones **12bc** (75%), **12bd** (85%) and the mixture **12bf** (40%)+**12bf'** (50%), respectively.



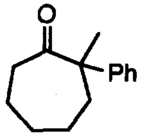
12bc



12bd

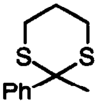


12bf

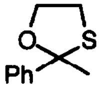


12bf'

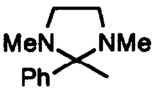
Finally, we studied the naphthalene-catalysed lithiation of other saturated heterocycles such as **13**, **14** and **15**. In the first two cases, the same process as for compounds **2** indicated in Scheme 1 and using acetone as electrophile and deuterium oxide in the quenching step at -40°C afforded compound **3ba** in 86% and 85% isolated yield, respectively; no deuterium incorporation was observed (for mechanistic considerations see above). In the case of the starting material **15** the lithiation process at -40°C did not take place after 7 h, compound **15** being the only one product isolated together with decomposition materials.



13



14



15

From the results described in this paper we conclude that 2-phenyl-1,3-dioxolane **1**, easily available from the corresponding phenones, are suitable starting materials to give, after an arene-catalysed lithiation, intermediates of the type **4** or **6** depending on the reaction conditions, which by reaction with electrophiles yield polifunctionalized structures of the type **2** and **3**. On the other hand, intermediates of the type **4** schould be consider as d^1 reagents with umpolung reactivity[17] of difficult access by other synthetic routes[18].

Experimental Part

General.- M.p.s (from hexane/ethyl acetate) are uncorrected and were measured on a Reichert thermovar apparatus. IR spectra were determined with a Pye Unicam SP3-200 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded in a Bruker AC-300 using $CDCl_3$ as solvent and $SiMe_4$ as internal standard; chemical shifts are given in δ (ppm) and the coupling constants (*J*) are measured in Hz. MS (EI) were recorded with a Hewlett Packard EM/CG HP-5988A spectrometer. The purity of volatile distilled products and the chromatographic analyses (GLC) were determined with a Konik Kromatix KNK 2000 equiped with a FID and a 2 m column (1/8 inch diam, Chromosorb Q 80/100, OV 17, 3% stationary phase), using nitrogen (40 ml/min) as the carrier gas, $T_{injector}$=325°C, T_{column}=80°C (3 min) and 80-320 (15°C/min); retention times (t_r) are given under these conditions. Thin layer chromatography (TLC) was carried out on Scheleicher & Schnell F1500/LS 254 plates coated with a 0.2 mm layer of silica gel, using a mixture of hexane/ethyl acetate as eluant; R_f values are given under these conditions. Microanalyses were performed by the Microanalyses Service of the University of Alicante. Solvents were dried by standard procedures[19]. Lithium powder, naphthalene, electrophiles and other reagents were commercially available (Aldrich, Fluka) and were used as received. Starting compounds **1a**[20], **1b**[20], **1c**[11], **1d**[20], **13**[21], **14**[22] and **15**[23] were prepared according to the literature procedures.

Catalytic Monolithiation of Compounds ***1a****,* ***1b*** *and* ***1c****. Isolation of Compounds* ***2****. General Procedure.*- To a green suspension of lithium (112 mg, 16 mmol) and naphthalene (20 mg, 0.16 mmol) in THF (5 ml) was added a solution of the corresponding precursor **1** (2 mmol) in THF (5 ml) at -40°C[24] under an argon atmosphere. The reaction mixture was stirred for *ca.* 45 min at the same temperature. Then the corresponding electrophile (2.1 mmol; 0.5 ml in the cases of H_2O or D_2O) was added and the mixture was stirred at the same temperature for a period of 1 h. Then, it was hydrolyzed with water (20 ml) at -40°C, neutralized with 2 N HCl and extracted with diethyl ether (2x20 ml). The organic layer was dried over anhydrous Na_2SO_4 and evaporated (15 Torr). The resulting residue was then purified by flash chromatography (silica gel, hexane/ethyl acetate) to afford the title compounds. Yields are included in Table 1 and text. Analytical, physical and spectral data follow.

1-(2-Hydroxyethoxy)-2-methyl-1-phenylpropan-2-ol (**2aa**): t_r=9.77 min, R_f=0.31 (hexane/ethyl acetate: 4/5), m.p. 68-70°C; ν_{max} (melted) 3440 (OH), 3040, 3020, 1490 (Ph), 1110 and 1060 cm^{-1} (C-O); δ_H 1.12, 1.17 (6 H, 2 s, $2xCH_3$), 2.90, 3.10 (2 H, 2 br s, 2xOH), 3.35-3.45, 3.50-3.60, 3.70-3.80 (1, 1 and 2 H respectively, 3 m, CH_2CH_2), 4.17 (1 H, s, CHO) and 7.20-7.40 (5 H, m, Ph); δ_C 23.95, 26.25, 61.85, 70.75, 73.1, 89.2, 127.85, 128.0 (2C), 128.1 (2C) and 138.2; *m/z* 195 (M^+-15, <1%), 152 (63), 107 (100), 105 (15), 92 (13), 91 (26), 79 (33), 77 (15), 59 (19) and 43 (10). Anal cald. for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 68.4; H, 8.5.

2-(1-Phenylethoxy)ethanol (**2ba**)[25]: t_r=8.37 min, R_f=0.34 (hexane/ethyl acetate: 4/1); ν_{max} (film) 3400 (OH), 3080, 3060, 3020, 1600 (Ph) and 1100 cm^{-1} (C-O); δ_H 1.43 (3 H, d, *J*=6.5, CH_3), 3.20-3.45, 3.55-3.80 (3 and 2 H respectively, 2 m, CH_2CH_2OH), 4.41 (1 H, q, *J*=6.5, CHO) and 7.00-7.50 (5 H, m, Ph); δ_C 23.7, 61.55, 69.6, 78.2, 125.9 (2C), 127.3, 128.25 (2C) and 143.2; *m/z* 166 (M^+, 13%), 151 (37), 121 (16), 107 (30), 105 (100), 103 (10), 79 (27) and 77 (17).

2-(1-Deuterio-1-phenylethoxy)ethanol (**2bb**): t_r=8.37 min, R_f=0.34 (hexane/ethyl acetate: 4/1); ν_{max} (film) 3400 (OH), 3080, 3060, 3020, 1600 (Ph) and 1100 cm^{-1} (C-O); δ_H 1.42 (3 H, s, CH_3), 3.20-3.50, 3.55-3.75 (3 and 2 H respectively, 2 m, CH_2CH_2OH) and 7.15-7.45 (5 H, m, Ph); δ_C 23.5, 61.4, 69.5, 77.65 (t, *J*=21.7), 125.85 (2C), 127.2, 128.15 (2C) and 143.1; *m/z* 167 (M^+, 11%), 152 (38), 122 (10), 108 (27), 107 (12), 106 (100), 105 (11), 80 (21), 78 (11) and 77 (11).

3-(2-Hydroxyethoxy)-2-methyl-3-phenylbutan-2-ol (**2bc**): t_r=10.42 min, R_f=0.34 (hexane/ethyl acetate: 4/5), m.p. 94-96°C; ν_{max} (melted) 3320 (OH), 3060, 3020, 1590 (Ph), 1120 and 1060 cm^{-1} (C-O); δ_H 1.08, 1.20 (6 H, 2 s, CH_3COCH_3), 1.65 (3 H, s, $\mathrm{PhCOC}\mathit{H}_3$), 2.58 (2 H, br s, 2xOH), 3.25-3.40, 3.40-3.55, 3.70-3.85 (1, 1 and 2 H respectively, 3 m, CH_2CH_2) and 7.25-7.45 (5 H, m, Ph); δ_C 19.15, 24.8, 24.9, 62.45, 63.85, 75.35, 83.75, 127.05, 127.6 (2C), 128.1 (2C) and 141.05; *m/z* 191 (M^+-33, <1%), 166 (40), 165 (28), 151 (10), 121 (100), 105 (15) and 43 (45). Anal cald. for $C_{13}H_{20}O_3$: C, 69.61; H, 8.98. Found: C, 69.3; H, 9.0.

3-Ethyl-2-(2-hydroxyethoxy)-2-phenylpentan-3-ol (**2bd**): t_r=11.24 min, R_f=0.46 (hexane/ethyl acetate: 4/5); ν_{max} (film) 3460 (OH), 3080, 3040 (Ph), 1110 and 1060 cm^{-1} (C-O); δ_H 0.79, 0.87 (6 H, 2 t, *J*=7.6 and 7.5 respectively, $2\mathrm{xCH_2C}\mathit{H}_3$), 1.46, 1.56 (4 H, 2 q, *J*=7.6 and 7.5 respectively, $2\mathrm{xC}\mathit{H}_2\mathrm{CH_3}$), 1.65 (3 H, s, CH_3CO), 2.30 (2 H, br s, 2xOH), 3.20-3.30, 3.40-3.50, 3.70-3.85 (1, 1 and 2 H respectively, 3 m, CH_2CH_2O) and 7.20-7.45 (5 H, m, Ph); δ_C 8.65, 8.95, 19.8, 26.5, 26.6, 62.4, 63.4, 78.0, 84.7, 127.0, 128.15 (2C), 128.2 (2C) and 141.5; *m/z* 205 (M^+-47, <1%), 166 (43), 165 (20), 161 (15), 151 (17), 121 (100), 105 (19), 91 (13), 87 (18), 57 (10), 45 (23) and 43 (68).

1-[1-(2-Hydroxyethoxy)-1-phenylethyl]cyclopentanol (**2be**): t_r=11.88 min, R_f=0.33 (hexane/ethyl acetate: 4/5), m.p. 103-105°C; ν_{max} (melted) 3360 (OH), 3040, 1500 (Ph), 1100 and 1070 cm^{-1} (C-O); δ_H 1.20-2.00 (8 H, m, $4\mathrm{xCH_2}$ ring), 1.69 (3 H, s, CH_3), 2.10, 2.55 (2 H, 2 br s, 2xOH), 3.29-3.36, 3.45-3.55, 3.70-3.85 (1, 1 and 2 H respectively, 3 m, OCH_2CH_2O), 7.25, 7.33 and 7.40 (1, 2 and 2 H respectively, t, t and d respectively, *J*=7.1, Ph); δ_C 19.75, 23.3, 23.6, 34.4, 34.85, 62.35, 63.65, 82.95, 87.15, 127.05, 127.7 (2C), 128.0 (2C) and 141.55; *m/z* 166 (M^+-84, 31%), 165 (15), 151 (16), 121 (100), 105 (23), 77 (17), 45 (11), 43 (89) and 41 (11). Anal cald. for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.0; H, 8.7.

1-[1-(2-Hydroxyethoxy)-1-phenylethyl]cyclohexanol (**2bf**): t_r=12.51 min, R_f=0.32 (hexane/ethyl acetate: 4/5), m.p. 110-112°C; ν_{max} (melted) 3410 (OH), 3040, 1490 (Ph) and 1060 cm^{-1} (C-O); δ_H 1.20-1.80 (10 H, m, $5\mathrm{xCH_2}$ ring), 1.62 (3 H, s, CH_3), 2.30, 3.00 (2 H, 2 br s, 2xOH), 3.20-3.30, 3.40-3.50, 3.70-3.80 (1, 1 and 2 H respectively, 3 m, OCH_2CH_2O) and 7.20-7.40 (5 H, m, Ph); δ_C 18.9, 21.55, 21.65, 25.65, 31.05, 31.3, 62.3, 63.6, 75.6, 84.15, 126.8, 127.4 (2C), 128.3 (2C) and 141.15; *m/z* 166 (M^+-98, 49%), 165 (12), 151 (16), 121 (100), 105 (18), 99 (21), 81 (20), 77 (10) and 43 (58). Anal cald. for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.6; H, 9.1.

6-(2-Hydroxyethoxy)-1,6-diphenylhexan-1-ol (**2ca**): t_r=19.23 min[26], R_f=0.25 (hexane/ethyl acetate: 3/2)[26]; ν_{max} (film) 3400 (OH), 3080, 3040, 1600 (Ph), 1120 and 1060 cm^{-1} (C-O); δ_H 1.25-1.95 (8 H, m, $(CH_2)_4$), 2.80 (2 H, br s, 2xOH), 3.18-3.30, 3.50-3.55 (4 H, 2 m, OCH_2CH_2O), 4.05-4.15, 4.45-4.55 (2 H, 2 m, 2xCHO) and 7.10-7.50(10 H, m, 2xPh); δ_C 25.35, 25.45, 25.6, 26.15, 37.75, 37.8, 38.7, 38.75, 61.75 (2C), 69.75 (2C), 74.1, 74.25, 82.55, 82.65, 125.7 (2C), 125.75 (2C), 125.8 (2C), 126.46 (2C), 126.9, 127.05, 127.25 (2C), 127.45 (2C), 127.8, 128.2, 128.25 (2C), 128.3 (2C), 138.25, 139.0, 142.25 and 144.8; *m/z* 252 (M$^+$-62), 151 (100), 146 (14), 117 (13), 107 (57), 104 (12), 91 (28), 79 (34) and 77 (18).

Catalytic Dilithiation of Compounds 1a, 1b and 1c. Isolation of Compounds 3 and 10c. General Procedure.- Once the intermediate of the type **4** was prepared as it was above described for compounds **2** (2 mmol), the corresponding electrophile (2.1 mmol)[27] was added and the mixture was stirred at the same temperature for a period of 1 h[28]. Then, the temperature was allowed to rise to 20°C overnight. The resulting mixture was then worked up as for compounds **2** to give the title compounds. Yields are included in Table 1 and text. Physical and spectral data follow.

2-Methyl-1-phenyl-2-propanol (**3aa**)[29]: t_r=6.84 min, R_f=0.48 (hexane/ethyl acetate: 4/1); ν_{max} (film) 3480 (OH), 3060, 3020, 1600 (Ph) and 900 cm^{-1} (C-O); δ_H 1.14 (6 H, s, $2xCH_3$), 1.30 (1 H, br s, OH), 2.68 (2 H, s, CH_2) and 7.10-7.30 (5 H, m, Ph); δ_C 29.1 (2C), 49.7, 70.7, 126.4 (2C), 128.1, 130.4 (2C) and 137.7; *m/z* 150 (M$^+$, 2%), 135 (10), 92 (100), 91 (51) and 59 (37).

2-Methyl-3-phenyl-2-butanol (**3ba**)[30]: t_r=6.76 min, R_f=0.58 (hexane/ethyl acetate: 4/1); ν_{max} (film) 3420 (OH), 3080, 3060, 3020, 1600 (Ph) and 930 cm^{-1} (C-O); δ_H 1.17 (6 H, s, $2xCH_3CO$), 1.34 (3 H, d, J=7.2, CH_3CH), 1.57 (1 H, br s, OH), 2.79 (1 H, q, J=7.2, $CHPh$) and 7.15-7.35 (5 H, m, Ph); δ_C 15.75, 26.9, 28.0, 50.35, 72.6, 126.45, 128.0 (2C), 128.95 (2C) and 143.3; *m/z* 164 (M$^+$, 1%), 149 (10), 106 (94), 105 (17), 91 (100), 78 (10), 77 (12), 58 (44) and 43 (12).

3-Ethyl-2-phenyl-3-pentanol (**3bb**): t_r=8.23 min, R_f=0.57 (hexane/ethyl acetate: 4/1); ν_{max} (film) 3460 (OH), 3060, 3040, 3020, 1600 (Ph) and 950 cm^{-1} (C-O); δ_H 0.82, 0.87 (6 H, 2 t, J=7.3, $2xCH_3CH_2$), 1.07 (1 H, br s, OH), 1.28 (3 H, d, J=7.1, CH_3CH), 1.37, 1.57 (4 H, 2 q, J=7.3, $2xCH_2$), 2.85 (1 H, q, J=7.1, $CHPh$) and 7.15-7.35 (5 H, m, Ph); δ_C 7.6, 7.95, 15.2, 27.25, 29.0, 45.4, 75.8, 126.25, 127.95 (2C), 129.1 (2C) and 143.6; *m/z* 163 (M$^+$-29, 35%), 107 (13), 106 (55), 105 (30), 91 (53), 87 (100), 79 (12), 77 (15), 69 (13), 57 (20), 45 (42) and 43 (15).

1-(1-Phenylethyl)cyclopentanol (**3bc**)[31]: t_r=8.86 min, R_f=0.61 (hexane/ethyl acetate: 4/1); ν_{max} (film) 3440 (OH), 3060, 3040, 3020, 1600 (Ph) and 910 cm^{-1} (C-O); δ_H 1.10 (1 H, br s, OH), 1.36 (3 H, d, J=7.1, CH_3), 1.55-1.85 (8 H, m, $4xCH_2$), 2.81 (1 H, q, J=7.1, $CHPh$) and 7.15-7.35 (5 H, m, Ph); δ_C 16.1, 23.45, 23.65, 37.8, 39.5, 48.75, 84.45, 126.4, 128.1 (2C), 128.25 (2C) and 144.1; *m/z* 190 (M$^+$, <1%), 106 (100), 105 (29), 91 (63), 85 (59), 79 (13), 78 (10), 77 (22), 67 (30), 57 (12), 55 (11), 43 (12) and 41 (16).

1-(1-Phenylethyl)cyclooctanol (**3bd**): t_r=11.26 min, R_f=0.59 (hexane/ethyl acetate: 4/1); ν_{max} (film) 3440 (OH), 3040, 3020, 1600 (Ph) and 950 cm^{-1} (C-O); δ_H 1.29 (3 H, d, J=7.2, CH_3), 1.25-1.80 (14 H, m, $7xCH_2$), 1.86 (1 H, br s, OH), 2.81 (1 H, q, J=7.2, $CHPh$) and 7.15-7.35 (5 H, Ph); δ_C 15.5, 22.0, 22.3, 25.15, 27.5, 28.85, 32.65, 36.75, 46.95, 76.0, 126.1, 127.9 (2C), 129.0 (2C) and 144.05; *m/z* 232 (M$^+$, <1%), 127 (100), 109 (28), 106 (22), 105 (30), 91 (23), 79 (13), 77 (16), 67 (35), 57 (10), 55 (26), 43 (17) and 41 (20).

2-Phenylpropiophenone (**3be**)[32]: t_r=10.50 min, R_f=0.48 (hexane/ethyl acetate: 9/1); ν_{max} (film) 3060, 3020, 1590 (Ph) and 1680 cm^{-1} (C=O); δ_H 1.50 (3 H, d, *J*=6.8, CH_3), 4.65 (1 H, q, *J*=6.8, CHCO), 7.0-7.25 (5 H, m, *Ph*CH), 7.29, 7.38 and 7.92 (2, 1 and 2 H respectively, t, t and d respectively, *J*=7.0, PhCO); δ_C 19.3, 47.65, 126.7, 127.7 (2C), 128.25 (2C), 128.55 (2C), 128.75 (2C), 132.55, 136.3, 141.3 and 200.05; *m/z* 210 (M^+, 3%), 105 (100) and 77 (21).

2-Phenylpropioanilide (**3bf**)[33]: t_r=12.37 min, R_f=0.64 (hexane/ethyl acetate: 3/2), m.p. 125-127°C; ν_{max} (melted) 3300 (NH), 3040, 3020, 1600 (Ph), 1650 and 1530 cm^{-1} (O=C-N); δ_H 1.59 (3 H, d, *J*=7.2, CH_3), 3.71 (1 H, q, *J*=7.2, CHCO), 7.13 (1 H, s, NH), 7.05, 7.25, 7.41 (1, 2 and 2 H respectively, t, t and d respectively, *J*=7.3, PhN), 7.45 (5 H, s, PhC); δ_C 18.55, 48.05, 119.65 (2C), 124.2, 127.55, 127.65 (2C), 128.85 (2C), 129.1 (2C), 137.8, 140.9 and 172.25; *m/z* 225 (M^+, 34%), 132 (24), 120 (13), 119 (10), 106 (60), 105 (100), 104 (14), 103 (15), 93 (53), 92 (13), 91 (31), 79 (20), 78 (11), 77 (43), 65 (15) and 51 (14).

3-Phenyl-1,3-heptanediol (**10c**): t_r=12.40 min, R_f=0.60 min (hexane/ethyl acetate: 2/3); ν_{max} (film) 3390 (OH), 3080, 3060, 3040, 1600 (Ph), 1060 and 1040 cm^{-1} (C-O); δ_H 0.80 (3 H, t, *J*=7.2, CH_3), 1.10-1.40, 1.70-2.20 (8 H, 2 m, $(CH_2)_3CCH_2$), 3.35-3.70 (2 H, m, CH_2O), 4.10 (2 H, br s, 2xOH) and 7.10-7.40 (5 H, m, Ph); δ_C 13.85, 22.9, 25.1, 42.7, 43.35, 59.75, 78.05, 125.2 (2C), 126.15, 127.94 (2C) and 145.75; *m/z* 208 (M^+, <1%), 163 (33), 151 (100), 133 (28), 105 (71) and 77 (23).

*Catalytic Dilithiation of Compound **1d**. Isolation of Compounds **11**. General Procedure*.- To a green suspension of lithium (112 mg, 16 mmol) and naphthalene (20 mg, 0.16 mmol) in THF (5 ml) was added a solution of the ketal precursor **1d** (2 mmol) in THF (5 ml) at -40°C under an argon atmosphere. The reaction mixture was stirred for *ca.* 1.5 h at the same temperature. Then the corresponding aldehyde (2.1 mmol) was added and the mixture was stirred at the same temperature for a period of 1 h. Then, the second electrophile (H_2O or D_2O, 0.5 ml) was added, the mixture was neutralized with 2 N HCl and extracted with diethyl ether (2x20 ml). The organic layer was dried over anhydrous Na_2SO_4 and evaporated (15 Torr). The resulting residue was then purified by flash chromatography (silica gel, hexane/ethyl acetate) to afford the title compounds. Yields are included in Table 2. Physical and spectral data follow.

1,1-Diphenyl-3-methyl-2-butanol (**11da**)[34]: t_r=11.24 min, R_f=0.50 (hexane/ethyl acetate: 4/1); ν_{max} (film) 3440 (OH), 3060, 3040, 3020, 1590 (Ph) and 990 cm^{-1} (C-O); δ_H 0.93, 0.99 (6 H, 2 d, *J*=6.8, $2xCH_3$), 1.47 (1 H, br s, OH), 1.60-1.75 (1 H, m, *CH*CH_3), 4,01 (1 H, d, *J*=8.7, *CH*Ph), 4.15 (1 H, dd, *J*=8.7, 3.8, CHO) and 7.10-7.45 (10 H, m, 2xPh); δ_C 15.15, 20.45, 29.7, 55.9, 78.1, 126.4, 126.7, 128.2 (2C), 128.6 (2C), 128.7 (2C), 128.85 (2C), 141.65 and 142.45; *m/z* 240 (M^+, <1%), 168 (49), 167 (100), 165 (28), 152 (13), 71 (10) and 43 (17).

1-Deuterio-1,1-diphenyl-3-methyl-2-butanol (**11db**): t_r=11.24 min, R_f=0.50 (hexane/ethyl acetate: 4/1); ν_{max} (film) 3440 (OH), 3060, 3040, 3020, 1590 (Ph) and 990 cm^{-1} (C-O); δ_H 0.93, 0.99 (6 H, 2 d, *J*=6.8, $2xCH_3$), 1.58 (1 H, br s, OH), 1.60-1.80 (1 H, m, CHCO), 4.15 (1 H, d, *J*=3.8, CHO) and 7.10-7.45 (10 H, 2xPh); δ_C 15.15, 20.45, 29.7, 55.45 (t, *J*=19.4), 78.05, 126.4, 126.7, 128.2 (2C), 128.6 (2C), 128.7 (2C), 128.85 (2C), 141.65 and 142.45; *m/z* 199 (M^+-42, <1%), 170 (43), 169 (100), 168 (75), 167 (22), 166 (39), 165 (14), 154 (12), 153 (19), 105 (11), 92 (19), 77 (11), 55 (14) and 43 (11).

3,3-Dimethyl-1,1-diphenyl-2-butanol (**11dc**): t_r=11.36 min, R_f=0.55 (hexane/ethyl acetate: 4/1); ν_{max} (film) 3560 (OH), 3060, 3040, 3020, 1600 (Ph) and 1000 cm^{-1} (C-O); δ_H 0.84 (9 H, s, $3xCH_3$), 1.57 (1 H, s, OH), 4.08 (1 H, d, *J*=6.5, *CH*Ph), 4.13 (1 H, d, *J*=6.5, CHO), 7.05-7.30 and 7.30-7.45 (10 H, 2 m, 2xPh); δ_C

27.0 (3C), 36.15, 54.75, 80.9, 126.2, 126.6, 128.25 (2C), 128.45 (2C), 128.6 (2C), 129.45 (2C), 141.95 and 144.3; *m/z* 197 (M^+-57, 2%), 169 (12), 168 (100), 167 (59), 166 (17), 165 (51), 153 (15), 152 (25), 105 (15), 91 (30), 87 (11), 77 (11), 59 (15), 57 (18) and 41 (30).

Treatment of Diols 2bc, 2bd and 2bf with Phosphoric Acid. Isolation of Compounds 12. General Procedure.- To a mixture of phosphoric acid (2.0 mmol) in toluene (10 ml) was added the corresponding purified diol (1.0 mmol) and the corresponding solution was refluxed for 14 h. After cooling the mixture was neutralized with a saturated solution of Na_2CO_3 and extracted with diethyl ether (2x20 ml). The organic layer was dried over anhydrous Na_2SO_4 and evaporated (15 Torr). The resulting residue was then purified by flash chromatography (silica gel, hexane/diethyl ether) to afford the title ketones. Yields are included in the text. Physical and spectral data follow.

3-Methyl-3-phenyl-2-butanone (**12bc**)[35]: t_r=6.72 min, R_f=0.37 (hexane/ethyl acetate: 9/1); ν_{max} (film) 3060, 3040, 3020, 1590 (Ph) and 1700 cm^{-1} (C=O); δ_H 1.48 (6 H, s, 2xCH_3C), 1.91 (3 H, s, CH_3CO) and 7.20-7.40 (5 H, m, Ph); δ_C 25.1 (2C), 25.5, 52.45, 125.9 (2C), 126.8, 128.7 (2C), 144.05 and 211.15; *m/z* 162 (M^+, 2%), 120 (12), 119 (100), 91 (87), 79 (10) and 77 (10).

4-Methyl-4-phenyl-3-hexanone (**12bd**)[36]: t_r=8.01 min, R_f=0.74 (hexane/ethyl acetate: 9/1); ν_{max} (film) 3040, 3020, 1590 (Ph) and 1700 cm^{-1} (C=O); δ_H 0.64 (3 H, t, J=7.5, CH_3CH_2C), 0.82 (3 H, t, J=7.3, CH_3CH_2C=O), 1.34 (3 H, s, CH_3C), 1.89 (2 H, q, J=7.5, CH_2C), 2.07 (2 H, q, J=7.3, CH_2CO) and 7.05-7.40 (5 H, m, Ph); δ_C 8.55, 8.65, 20.7, 29.9, 30.85, 55.84, 126.35 (2C), 126.6, 128.5 (2C), 143.2 and 213.7; *m/z* 190 (M^+, <1%), 133 (72), 105 (18), 92 (10), 91 (100) and 77 (11).

1-Acetyl-1-phenylcyclohexane (**12bf**)[37]: t_r=9.18 min, R_f=0.70 (hexane/ethyl acetate: 9/1); ν_{max} (film) 3060, 3040, 3020, 1590 (Ph) and 1700 cm^{-1} (C=O); δ_H 1.25-1.65, 1.80-1.90 (10 H, 2 m, 5xCH_2), 1.89 (3 H, s, CH_3) and 7.10-7.40 (5 H, m, Ph); δ_C 23.15 (2C), 25.5, 25.85. 33.55 (2C), 56.35, 126.45 (2C), 126.8, 128.75 (2C), 142.6 and 210.4; *m/z* 202 (M^+, 6%), 160 (10), 159 (94), 117 (14), 115 (12), 91 (100) and 81 (16).

2-Methyl-2-phenylcycloheptanone (**12bf'**)[37]: t_r=9.53 min, R_f=0.67 (hexane/ethyl acetate: 9/1); ν_{max} (film) 3060, 3040, 3020, 1590 (Ph) and 1700 cm^{-1} (C=O); δ_H 1.20-1.60, 1.80-2.35 (8 H, 2 m, $C(CH_2)_4$), 1.34 (3 H, s, CH_3), 2.55 (2 H, dd, J=11.3, 9.6, CH_2CO) and 7.15-7.40 (5 H, m, Ph); δ_C 24.35, 26.5, 26.95, 30.6, 36.6, 40.9, 55.8, 125.9 (2C), 126.6, 128.65 (2C), 144.9 and 215.0; *m/z* 202 (M^+, 36%), 159 (14), 131 (100), 118 (54), 117 (26), 115 (16), 105 (21), 103 (14), 91 (28) and 77 (14).

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