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Lithium 2-(2-Lithiomethylphenyl)ethanolate from Isochroman: Easy Preparation of Substituted Benzoxepines and Functionalised Arenes

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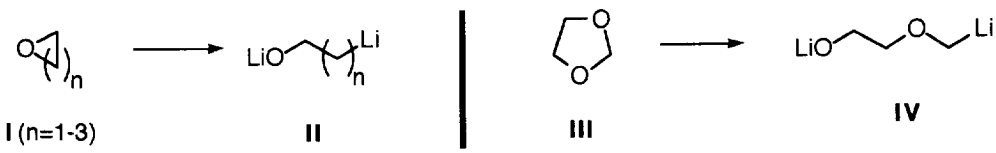
Abstract: The reaction of isochroman (**1**) with an excess of lithium powder and a catalytic amount of DTBB (2.5 mol %) in THF at 20°C yields the title intermediate, which by reaction with different electrophiles (H_2O, D_2O, CO_2 and carbonyl compounds) at temperatures ranging between -78 and 20°C yields, after hydrolysis, the corresponding products **3**. Diols **3h-m**, derived from benzaldehyde or ketones, give upon treatment with 85% phosphoric acid the corresponding benzoxepines **5h-m**. In the other cases, Friedel-Crafts products resulting from a rearrangement of the first carbenium ion formed, are obtained.

INTRODUCTION

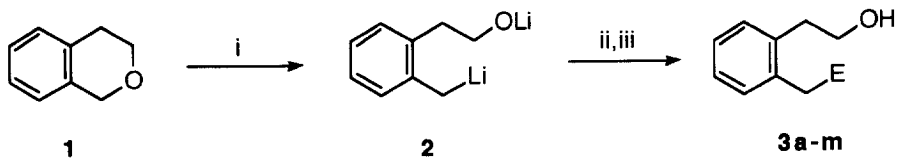
The interest of functionalised organolithium compounds[1] in synthetic organic chemistry is focused on their capability to transfer their functionality to an electrophilic reagent, so giving directly polyfunctionalised organic structures. This type of intermediates are generally prepared by the usual ways to generate organolithium compounds[2], namely deprotonation, halogen-lithium exchange and mercury- or tin-lithium transmetallation, as the most important methodologies. In the case of organolithium compounds bearing an alkoxide functionality a new possibility for their preparation consists in the reductive opening of cyclic ethers[3]. Thus, using activated lithium (with a stoichiometric[4] or catalytic[5] amount of an arene) epoxides[6], oxetanes[7], tetrahydrofurans[8], phthalan[9] or dioxolanes[10] (of the general type **I** or **III**) have been used as starting materials for the preparation of the corresponding oxygen-containing functionalised organolithium compounds (of the type **II** or **IV**). In this paper we describe for the first time the reductive opening of a six-membered cyclic ether, isochroman, using an arene-catalysed[5] lithiation and the application of this process in organic synthesis.



I (n=1-3) **II** **III** **IV**

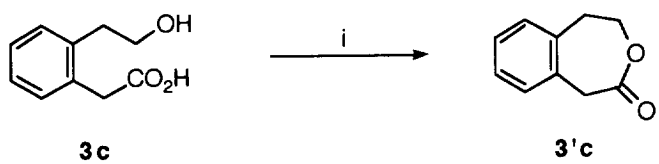
RESULTS AND DISCUSSION

When commercially available isochroman (**1**) was allowed to react with an excess of lithium powder (*ca.* 1:20 molar ratio) and a catalytic amount of 4,4'-di-*tert*-butylbiphenyl (DTBB; 1:0.05 molar ratio; 2.5 mol %) in THF at ambient temperature for 45 min, a solution of the corresponding dianionic intermediate **2** was prepared, which reacted with different electrophiles (H_2O, D_2O, CO_2 and carbonyl compounds) at temperatures ranging between -78 to 20°C for 2 h to give, after hydrolysis, the corresponding products **3** (Scheme 1 and Table 1). In the absence of the catalyst lithiation times were longer (*ca.* 3 h) and yields were considerably lower.



Scheme 1. *Reagents and conditions*: i, Li excess, DTBB cat. (2.5 mol %), THF, 20°C, 45 min; ii, E^+=H_2O, D_2O, CO_2, EtCHO, PrⁿCHO, BuⁱCHO, BuᵗCHO, PhCHO, Me_2CO, Et_2CO, $(CH_2)_4CO$, $(CH_2)_5CO$, PhCOMe, -78 to 20°C, 2 h; iii, H_2O, 20°C.

The hydroxyacid **3c** (Table 1, entry 3) was easily cyclised to the corresponding ε-lactone **3'c** (75% isolated) by means of a catalytic amount of *p*-toluenesulfonic acid at benzene reflux[9,11] (Scheme 2).



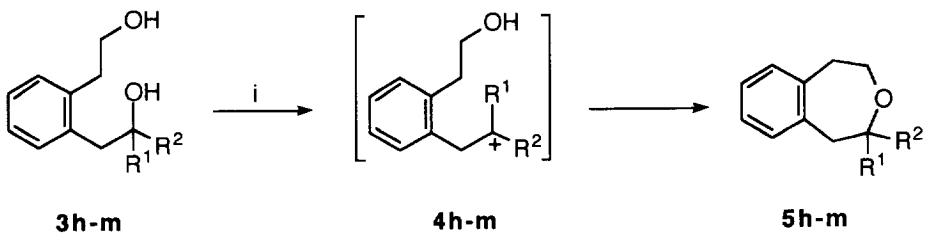
Scheme 2. *Reagents and conditions*: i, TsOH cat., PhH reflux, 2 h.

We consider specially interesting the diols **3d-m** as starting materials for the corresponding oxepanes by an intramolecular dehydration. However, we could prepare these heterocycles only with the diols **3h-m** derived from benzaldehyde or ketones. Thus, by treating these precursors with 85% phosphoric acid at toluene reflux[9,12] the corresponding benzoxepines **5h-m** were isolated (Scheme 3 and Table 2). When the more stable benzylic or tertiary carbenium ions **4h-m** are formed, they do not suffer a transposition reaction, and after nucleophilic attack of the remaining hydroxy group yield the corresponding products **5h-m**.

Table 1. Preparation of Compounds **3**

Entry	Electrophile E+	Product[a] No.	E	Yield (%)[b]	R_f[c]
1	H_2O	**3a**	H	89	0.35
2	D_2O	**3b**	D	86	0.35
3	CO_2	**3c**	CO_2H	74	0.19
4	EtCHO	**3d**	EtCHOH	68	0.24
5	PriCHO	**3e**	PriCHOH	80	0.28
6	BuiCHO	**3f**	BuiCHOH	82	0.33
7	ButCHO	**3g**	ButCHOH	59	0.56
8	PhCHO	**3h**	PhCHOH	65	0.36
9	Me_2CO	**3i**	Me_2COH	44	0.23
10	Et_2CO	**3j**	Et_2COH	55	0.41
11	$(CH_2)_4CO$	**3k**	$(CH_2)_4COH$	67	0.26
12	$(CH_2)_5CO$	**3l**	$(CH_2)_5COH$	53	0.35
13	PhCOMe	**3m**	PhC(OH)Me	44	0.38

[a] All products **3** were >95% pure (GLC and 300 MHz ^1H NMR). [b] Isolated yield after flash chromatography (silica gel, hexane/ethyl acetate) based on the starting material **1**. [c] Silica gel, hexane/ethyl acetate: 1:1.



Scheme 3. *Reagents and conditions*: i, H_3PO_4, PhMe reflux, 2 h.

However, in the other cases (diols **3d-g**) we obtained always products resulting from a rearrangement of the initially formed carbocation **4**. Thus, the diol **3d** upon the same treatment as shown in Scheme 3 gave the carbenium ion **4d**, which underwent transposition to the more stable benzylic one **4'd** and final cyclisation to the cyclic ether **6d** (49% isolated; Scheme 4). Diols **3e** and **3g** behaved differently: after generating the carbocations **4e,g**, they rearranged to the tertiary one **4'e,g** (preferred than the corresponding benzylic one),

which after a Friedel-Crafts type aromatic S_E reaction gave the final isolated products **7e** and **7g** in 76 and 86% isolated yields, respectively (Scheme 4). Finally, the diol **3f** yielded a mixture of the Friedel-Crafts product **8f** (resulting from the rearranged carbenium ion **4'f**) and the olefin **9f** in 66% overall isolated yield (2:1 molar ratio). It is strange that neither conjugated (from **4f**) or more substituted (from **4'f**) olefins were obtained instead of **9f** (Scheme 4).

Table 2. Preparation of Benzoxepines **5**

Entry	Starting material	Product[a]				
		No.	R^1	R^2	Yield (%)[b]	R_f[c]
1	**3h**	**5h**	Ph	H	67	0.37
2	**3i**	**5i**	Me	Me	72	0.28
3	**3j**	**5j**	Et	Et	79	0.49
4	**3k**	**5k**	$-(CH_2)_4-$		69	0.40
5	**3l**	**5l**	$-(CH_2)_5-$		68	0.44
6	**3m**	**5m**	Ph	Me	72	0.41

[a] All products **5** were >95% pure (GLC and 300 MHz ^{1}H NMR). Isolated yield after flash chromatography (silica gel, hexane/ethyl acetate) based on the starting diol **3**. [c] Silica gel, hexane/ethyl acetate: 10/1.

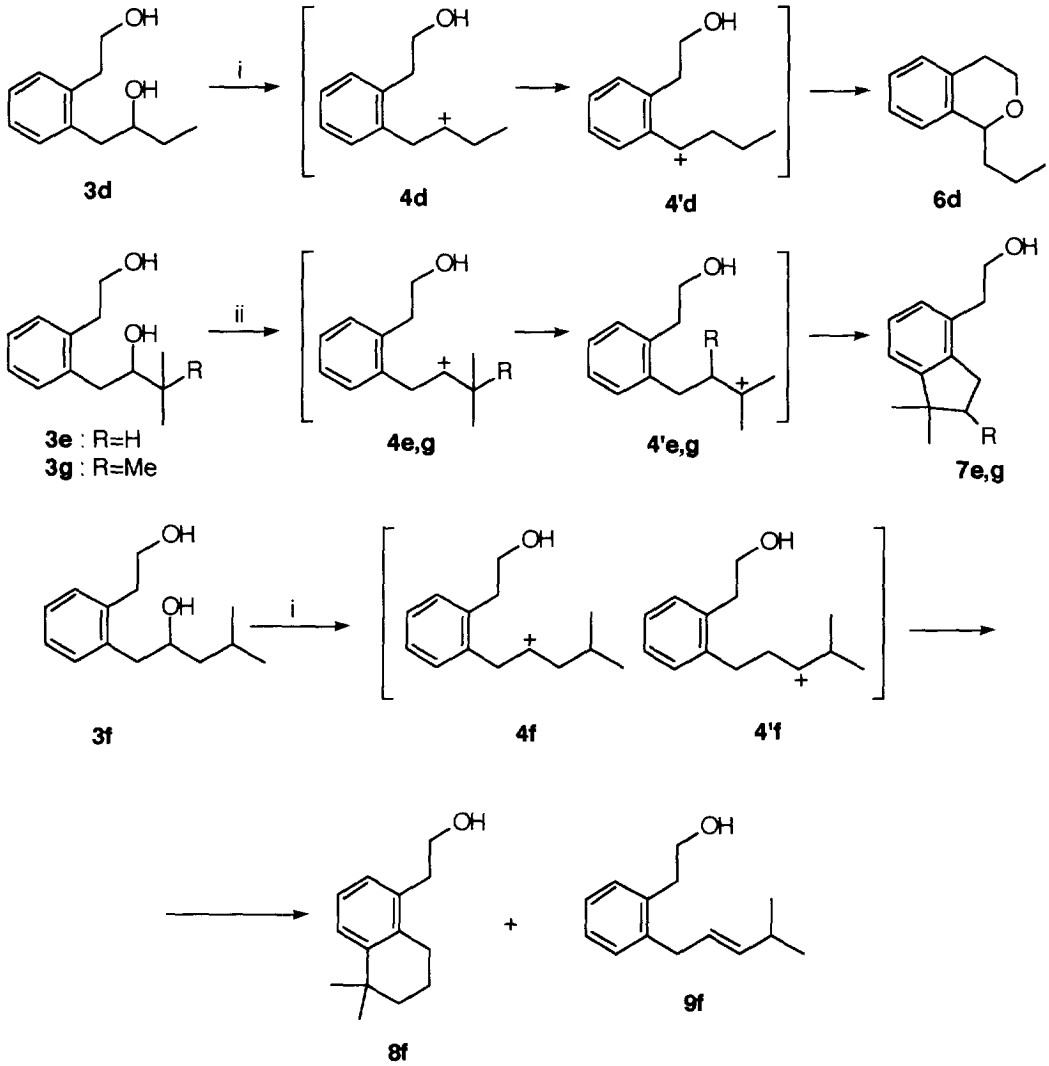
From the results described in this paper we conclude that commercially available isochroman is an adequate precursor for functionalised arenes of the type **3** and heterocycles such as benzoxepines **5**[13].

EXPERIMENTAL PART

General.- For general information see reference 9.

Preparation of Compounds **3**. *General Procedure.*- To a blue suspension of lithium powder (0.125 g, 18.0 mmol) and a catalytic amount of 4,4'-di-*tert*-butylbiphenyl (0.047 g, 0.18 mmol) in THF (10 ml) at 20°C was added the isochroman (**1**) (0.250 ml, 2.0 mmol) under argon and the mixture was stirred for 45 min at the same temperature. Then, the mixture was cooled at -78°C and the corresponding electrophile (3.0 mmol; 0.5 ml in the case of water or deuterium oxide; CO_2 was bubbled for 1.5 h) was added. The mixture was stirred at the same temperature for 1 h and was hydrolysed with water. The resulting mixture was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and evaporated (15 mmHg). The residue was then purified by column chromatography (silica gel; hexane/ethyl acetate) and/or recrystallised to yield pure products **3a-m**. When the electrophile was CO_2, after having hydrolysed the mixture with water at -78°C it was basified with 2.5 M sodium hydroxide and extracted with ethyl acetate. The aqueous layer was then acidified with 3 M hydrochloric acid and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and evaporated (15 mmHg). The resulting residue was compound **3c** [>95% pure (GLC and 300 MHz ^{1}H NMR)]. Yields and R_f values are included in Table 1; other physical, analytical and spectroscopic data follow.

2-(2-Methylphenyl)ethanol (**3a**): ν_{max} (film) 3640-3040 cm^{-1} (OH); δ_H 1.95 (1H, br s, OH), 2.31 (3H, s, CH_3), 2.86 (2H, t, J =6.9, $ArCH_2$), 3.78 (2H, t, J =6.9, CH_2OH), 7.08-7.21 (4H, m, ArH); δ_C 19.3 (CH_3),



Scheme 4. *Reagents and conditions*: i, H_3PO_4, PhMe reflux, 2 h; ii, as in step i but 10 h.

36.3 ($ArCH_2$), 62.5 (CH_2OH), 125.9, 126.5, 129.5, 130.3, 136.3, 136.4 (ArC); *m/z* 136 (M+, 26%), 106 (33), 105 (100), 103 (15), 91 (23), 79 (20), 77 (25) (Found: M+, 136.0881. $C_9H_{12}O$ requieres M, 136.0888).

2-(2-Deuteriomethylphenyl)ethanol (**3b**): ν_{max} (film) 3640-3080 cm^{-1} (OH); δ_H 1.92 (1H, br s, OH), 2.29 (2H, s, CH_2D), 2.85 (2H, t, *J* =6.9, $ArCH_2$), 3.77 (2H, t, *J* =6.9, C H_2OH), 7.07-7.19 (4H, m, ArH); δ_C 19.1 (t, J_{CD} =19.3, CH_2D), 36.3 ($ArCH_2$), 62.5 (CH_2OH), 125.9, 126.5, 129.5, 130.3, 136.3, 136.4 (ArC); *m/z* 137 (M+, 35%), 118 (11), 107 (36), 106 (100), 105 (16), 104 (14), 92 (15), 91 (15), 80 (14), 79 (11), 78 (18), 77 (11) (Found: M+, 137.0950. $C_9H_{11}DO$ requires M, 137.0951).

2-(2-Hydroxyethyl)phenylacetic Acid (**3c**)[14]: ν_{max} (film) 3680-2260 (COOH), 1700 cm^{-1} (C=O); δ_H 2.80 (2H, t, J=6.9, $ArCH_2$), 3.62 (2H, s, CH_2COOH), 3.72 (2H, t, J=6.9, CH_2OH), 7.05-7.21 (4H, m, ArH), 7.37 (2H, br s, COOH, OH); δ_C 35.4, ($ArCH_2$), 38.3 (CH_2COOH), 62.8 (CH_2OH), 126.7, 127.6, 130.0, 130.7, 132.5, 137.1 (ArC), 176.5 (C=O); *m/z* 162 (M^+-H_2O, 27%), 118 (33), 117 (100), 115 (23), 105 (10), 104 (69), 103 (20), 91 (25), 78 (24), 77 (23), 65 (10), 63 (22), 52 (11), 51 (19), 50 (16).

1-[2-Hydroxyethyl)phenyl]-2-butanol (**3d**)[14]: ν_{max} (film) 3680-3060 cm^{-1} (OH); δ_H 0.98 (3H, t, J=7.4, CH_3), 1.46-1.64 (2H, m, CH_3CH_2), 2.40-2.98 (6H, m, 2x$ArCH_2$, 2xOH), 3.60-3.86 (3H, m, CH_2OH, CHOH), 7.14-7.25 (4H, m, ArH); δ_C 10.1 (CH_3), 30.0 (CH_3CH_2), 35.5 (CH_2CH_2OH), 39.9 ($ArCH_2$), 63.3 (CH_2OH), 74.1 (CHOH), 126.5, 126.5, 129.9, 130.3, 137.4, 137.5 (ArC); *m/z* 136 (M^+-C_3H_6O, 60%), 119 (11), 118 (54), 117 (100), 115 (29), 106 (65), 105 (97), 104 (23), 103 (26), 91 (54), 79 (13), 78 (20), 77 (32), 65 (17), 59 (77), 57 (17), 51 (13), 43 (18), 41 (35).

1-[2-(2-Hydroxyethyl)phenyl]-3-methyl-2-butanol (**3e**)[14]: ν_{max} (film) 3700-3080 cm^{-1} (OH); δ_H 1.02 (6H, d, J=6.7, 2xCH_3), 1.75-1.86 [1H, m, $(CH_3)_2CH$], 1.98 (2H, br s, 2xOH), 2.73 (1H, dd, J=14.0, 9.8, HCHCHOH), 2.82-2.94 (2H, m, CH_2CH_2OH), 3.00 (1H, dd, J= 14.0, 6.5, HCHCHOH), 3.61 (1H, ddd, J=9.7, 5.2, 3.2, HCHOH), 3.79-3.94 (2H, m, HCHOH, CHOH), 7.16-7.23 (4H, m, ArH); δ_C 17.5, 18.7 (2xCH_3), 33.7 [$(CH_3)_2CH$], 35.5 (CH_2CH_2OH), 36.8 (CH_2CHOH), 63.4 (CH_2OH), 77.6 (CHOH), 126.5, 126.6, 130.0, 130.2, 137.6, 138.0 (ArC); *m/z* 147 (M^+-C_3H_7-H_2O, 6%), 136 (58), 119 (24), 118 (69), 117 (98), 115 (20), 106 (100), 105 (92), 104 (26), 103 (25), 92 (11), 91 (55), 79 (17), 78 (17), 77 (31), 73 (31), 65 (12), 57 (10), 55 (35), 51 (11), 45 (13), 43 (86), 41 (69).

1-[2-(2-Hydroxyethyl)phenyl]-4-methyl-2-pentanol (**3f**)[14]: ν_{max} (film) 3660-3080 cm^{-1} (OH); δ_H 0.91 (3H, d, J=6.5, CH_3CCH_3), 0.95 (3H, d, J=6.5, CH_3CCH_3), 1.29-1.38 (1H, m, HOCHHCHCH), 1.47-1.52 (1H, m, HOCHHCHCH), 1.75-1.92 [1H, m, $(CH_3)_2CH$], 2.20 (2H, br s, 2xOH), 2.75-2.96 (4H, m, 2x$ArCH_2$), 3.80-3.92 (3H, m, CHOH, CH_2OH), 7.18-7.26 (4H, m, ArH); δ_C 22.0, 23.4, 24.6 [$CH(CH_3)_2$], 35.6 (CH_2CH_2OH), 40.8 ($ArCH_2$), 46.5 [$CH_2CH(CH_3)_2$], 63.4 (CH_2OH), 70.8 (CHOH), 126.6, 126.6, 130.0, 130.4, 137.4, 137.5 (ArC); *m/z* 136 (M^+-C_5H_8-H_2O, 63%), 118 (62), 117 (47), 115 (22), 106 (71), 105 (87), 104 (23), 103 (18), 91 (38), 79 (12), 78 (12), 77 (21), 69 (24), 57 (15), 45 (17), 43 (100), 42 (16), 41 (90).

1-[2-(2-Hydroxyethyl)phenyl]-3,3-dimethyl-2-butanol (**3g**): mp 90-91°C (pentane/dichloromethane); ν_{max} (KBr) 3660-3040 cm^{-1} (OH); δ_H 1.00 [9H, s, $(CH_3)_3C$], 2.25 (2H, br s, 2xOH), 2.65 (1H, dd, J=13.9, 10.6, ArCHH), 2.79-2.88 (2H, m, CH_2CH_2OH), 2.96 (1H, dd, J= 13.9, 2.1, ArCHH), 3.44 (1H, dd, J=10.6, 2.1, CHOH), 3.74-3.90 (2H, m, CH_2OH), 7.15-7.25 (4H, m, ArH); δ_C 25.7 [$(CH_3)_3C$], 34.2 (CH_2CH_2OH), 35.1 [$(CH_3)_3C$], 35.4 ($ArCH_2$), 63.5 (CH_2OH), 80.7 (CHOH), 126.5, 126.6, 130.0, 130.2, 137.7, 138.5 (ArC); *m/z* 204 (M^+-H_2O, 1%), 136 (100), 129 (16), 119 (28), 118 (96), 117 (73), 115 (23), 106 (88), 105 (91), 104 (19), 103 (16), 92(10), 91 (51), 87 (23), 79 (18), 78 (15), 77 (30), 69 (27), 65 (14), 57 (43), 45 (21), 43 (29), 41 (67). Anal. Calcd. for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found : C, 75.41; H, 10.05.

2-[2-(2-Hydroxyethyl)phenyl]-1-phenylethanol (**3h**)[14]: ν_{max} (film) 3640-3080 cm^{-1} (OH); δ_H 2.57 (2H, br s, 2xOH), 2.74-2.90 (2H, m, CH_2CH_2OH), 2.94 (1H, dd, J=14.0, 4.6, ArHCH), 3.06 (1H, dd, J=14.0, 8.7, ArHCH), 3.66-3.79 (2H, m, CH_2OH), 4.83 (1H, dd, J=8.7, 4.6, CHOHPh), 7.11-7.34 (9H, m, ArH); δ_C 35.3 (CH_2CH_2OH), 42.3 ($ArCH_2$), 63.3 (CH_2OH), 75.2 (CHOH), 125.7, 126.4, 126.7, 127.5, 128.3, 129.9, 130.4, 136.8, 137.5, 144.1 (ArC); *m/z* 165 (M^+-C_6H_5, 3%), 136 (67), 118 (38), 117 (32), 115 (21), 107 (77), 106 (39), 105 (57), 104 (27), 103 (22), 91 (31), 79 (100), 78 (28), 77 (98), 51 (15).

1-[2-(2-Hydroxyethyl)phenyl]-2-methyl-2-propanol (**3i**)[14]: ν_{max} (film) 3680-3060 cm^{-1} (OH); δ_H 1.23 (6H, s, 2xCH_3), 2.55 (2H, br s, 2xOH), 2.85 (2H, s, CH_2COH), 2.97 (2H, t, J=6.7, CH_2CH_2OH), 3.80 (2H, t, J=6.7, CH_2OH), 7.12-7.26 (4H, m, ArH); δ_C 29.6 (2xCH_3), 35.5 ($ArCH_2$), 45.2 (CH_2COH), 63.2 (CH_2OH), 71.4 (COH), 125.9, 126.7, 129.7, 131.9, 136.4, 138.0 (ArC); *m/z* 161 (M^+-CH_3-H_2O, 5%),

143 (12), 136 (53), 118 (37), 117 (58), 115 (18), 106 (46), 105 (66), 104 (19), 103 (13), 91 (32), 79 (10), 78 (16), 77 (21), 65 (10), 59 (100), 43 (54), 41 (18).

2-Ethyl-1-[2-(2-hydroxyethyl)phenyl]-2-butanol (**3j**)[14]: ν_{max} (film) 3640-3080 cm^{-1} (OH); δ_H 0.92 (6H, t, J=7.5, 2xCH_3), 1.46 (2H, q, J=7.5, 1xCH_3CH_2), 1.55 (2H, q, J=7.5, 1xCH_3CH_2), 1.90 (2H, br s, 2xOH), 2.83 (2H, s, $ArCH_2$), 3.00 (2H, t, J=6.5, CH_2CH_2OH), 3.85 (2H, t, J=6.5, CH_2OH), 7.15-7.26 (4H, m, ArH); δ_C 8.0 (2xCH_3), 30.7 (2xCH_3CH_2), 35.6 (CH_2CH_2OH), 40.8 ($ArCH_2$), 63.4 (CH_2OH), 75.2 (COH), 125.9, 126.7, 129.7, 132.0, 136.1, 138.6 (ArC); *m/z* 193 (M^+-C_2H_5, 3%), 175 (13), 136 (50), 129 (13), 118 (41), 117 (43), 115 (18), 106 (47), 105 (18), 104 (12), 91 (30), 87 (100), 79 (11), 78 (11), 77 (18), 69 (18), 57 (62), 45 (80), 43 (24), 41 (28).

1-{[2-(2-Hydroxyethyl)phenyl]methyl}cyclopentanol (**3k**): mp 70-71°C (pentane/dichloromethane); ν_{max} (KBr) 3600-3060 cm^{-1} (OH); δ_H 1.60-1.81 (8H, m, 4xring CH_2), 2.27 (2H, br s, 2xOH), 2.98 (2H, s, CH_2COH), 2.99 (2H, t, J=6.6, $ArCH_2$), 3.83 (2H, t, J=6.6, CH_2OH), 7.13-7.26 (4H, m, ArH); δ_C 23.2, 35.7, 39.5 (4xring CH_2, $ArCH_2$), 42.5 (CH_2COH), 63.4 (CH_2OH), 82.9 (COH), 126.1, 126.7, 129.8, 131.4, 137.1, 138.0 (ArC); *m/z* 136 (M^+-C_5H_8O, 64%), 119 (10), 118 (56), 117 (69), 115 (26), 106 (73), 105 (70), 104 (21), 103 (20), 91 (42), 85 (100), 79 (12), 78 (20), 77 (22), 67 (53), 65 (14), 57 (27), 55 (42), 51 (12), 43 (29), 42 (27), 41 (73). Anal. Calcd. for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found : C, 75.81; H, 9.26.

1-{[2-(2-Hydroxyethyl)phenyl]methyl}cyclohexanol (**3l**): mp 104-105°C (pentane/dichloromethane); ν_{max} (KBr) 3600-3040 cm^{-1} (OH); δ_H 1.19-1.59 (10H, m, 5xring CH_2), 2.12 (2H, br s, 2xOH), 2.83 (2H, s, $ArCH_2COH$), 3.00 (2H, t, J=6.6, CH_2CH_2OH), 3.83 (2H, t, J=6.6, CH_2OH), 7.14-7.22 (4H, m, ArH); δ_C 21.9, 25.7, 35.7, 37.6 (5xring CH_2, CH_2CH_2OH), 44.9 (CH_2COH), 63.3 (CH_2OH), 71.7 (COH), 125.8, 126.7, 129.7, 132.1, 135.8, 138.3 (ArC); *m/z* 136 (M^+-$C_6H_{10}O$, 36%), 129 (15), 118 (35), 117 (42), 115 (20), 106 (55), 105 (35), 104 (30), 103 (17), 99 (100), 91 (35), 81 (84), 79 (21), 78 (18), 77 (26), 65 (12), 57 (13), 55 (47), 53 (14), 43 (34), 42 (16), 41 (57). Anal. Calcd. for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found : C, 76.11; H, 9.83.

1-[2-(2-Hydroxyethyl)phenyl]-2-phenyl-2-propanol (**3m**)[14]: ν_{max} (film) 3660-3080 cm^{-1} (OH); δ_H 1.59 (3H, s, CH_3), 2.40 (2H, br s, 2xOH), 2.84 (2H, t, J=6.5, CH_2CH_2OH), 3.14 (2H, s, CH_2COH), 3.78 (2H, t, J=6.5, CH_2OH), 6.88-7.40 (9H, m, ArH); δ_C 29.6 (CH_3), 35.3 (CH_2CH_2OH), 46.2 (CH_2COH), 63.4 (CH_2OH), 75.0 (COH), 124.9, 125.8, 126.6, 126.9, 128.0, 129.6, 131.9, 135.5, 138.3, 147.9 (ArC); *m/z* 178 (M^+-C_6H_6, 1%), 136 (14), 121 (58), 106 (10), 105 (13), 77 (15), 43 (100).

Preparation of Compound **3'c**.- A solution of the hydroxyacid **3c** (1mmol) in benzene (50 ml) in the presence of a catalytic amount of *p*-toluenesulfonic acid (0.001 g) was heated in a 120°C oil bath temperature at a Dean-Stark apparatus for 15 h, then the benzene was removed by distillation and the resulting residue was hydrolysed with a saturated solution of sodium carbonate and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and evaporated (15 mmHg). The residue was then purified by column chromatography (silica gel; hexane ethyl acetate) and recrystallised to yield the tittle compound **3'c** (75% yield). *4,5-Dihydro-3-benzoxepin-2(1H)-one* (**3'c**)[15]: mp 83-84°C (hexane/dichloromethane)[lit. mp 92°C]; ν_{max} (KBr) 1720 cm^{-1} (C=O); δ_H 3.29 (2H, t, J=5.5, $ArCH_2CH_2$), 4.03 (2H, s, $ArCH_2C$=O), 4.60 (2H, t, J=5.5, CH_2O), 7.07-7.22 (4H, m, ArH); δ_C 33.8 ($ArCH_2CH_2$), 40.3 (CH_2C=O), 65.7 (CH_2O), 126.9, 127.6, 128.5, 130.3, 130.8, 134.7 (ArC), 172.3 (C=O); *m/z* 162 (M^+, 56%), 118 (42), 117 (100), 115 (22), 105 (13), 104 (53), 103 (23), 91 (17), 78 (18), 77 (15), 63 (11), 51 (14).

Treatment of Diols **3d-m** *with Phosphoric Acid. Isolation of Compounds* **5-9**. *General Procedure.*- To a solution of the corresponding diol **3d-m** (1 mmol) in toluene (5 ml) was added 85% phosphoric acid (0.4 ml). The reaction mixture was heated at 110°C for 10 h, then the toluene was removed by distillation

and the resulting residue 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) to yield pure products **5-9**. Yields and physical data of compounds **5h-m** (R_f) are included in Table 2; analytical and spectroscopic data follow.

1,2,4,5-Tetrahydro-2-phenyl-3-benzoxepine (**5h**): ν_{max} (film) 3040, 3000, 1600, 750, 690 cm^{-1} (ArH); δ_H 2.76 (1H, dd, J= 15.2, 4.6, *H*CHCH$_2$O), 2.90 (1H, d, J=15.2, HC*H*CH$_2$O), 3.41 (1H, d, J=15.2, Ar*H*CH), 3.48 (1H, dd, J= 15.2, 9.8, ArHC*H*), 3.60-3.68 (1H, m, *H*CHO), 4.26-4.32 (1H, m, HC*H*O), 4.45 (1H, d, J=9.8, CHOPh), 7.10-7.43 (9H, m, ArH); δ_C 39.5 (*C*H$_2$CH$_2$O), 47.2 (*C*H$_2$CHOPh), 70.0 (CH$_2$O), 82.0 (CHO), 125.8, 126.4, 126.5, 127.4, 128.4, 129.3, 129.7, 140.1, 141.5, 143.7 (ArC); *m/z* 224 (M^+, 9%), 118 (73), 117 (100), 115 (23), 105 (11), 91 (21), 78 (11), 77 (20), 51 (13) (Found: M^+, 224.1196. $C_{16}H_{16}O$ requires M, 224.1201).

1,2,4,5-Tetrahydro-2,2-dimethyl-3-benzoxepine (**5i**): ν_{max} (film) 3040, 3000, 750 cm^{-1} (ArH); δ_H 1.16 (6H, s, 2xCH$_3$), 2.94 (2H, t, J=5.0, ArC*H*$_2$CH$_2$), 2.95 [2H, s, C*H*$_2$CO(CH$_3$)$_2$], 3.80 (2H, t, J=5.0, CH$_2$O), 6.98-7.15 (4H, m, ArH); δ_C 26.8 (2xCH$_3$), 38.9 (ArCH$_2$CH$_2$), 49.3 (*C*H$_2$CO), 62.6 (CH$_2$O), 73.0 (CO), 126.2, 126.4, 128.7, 130.0, 138.8, 140.9 (ArC); *m/z* 176 (M^+, 9%), 118 (34), 117 (100), 115 (23), 91 (22), 77 (12), 51 (12), 43 (34), 41 (11) (Found: M^+, 176.1207. $C_{12}H_{16}O$ requires M, 176.1201).

2,2-Diethyl-1,2,4,5-tetrahydro-3-benzoxepine (**5j**): ν_{max} (film) 3020, 3000, 750 cm^{-1} (ArH); δ_H 0.84 (6H, t, J=7.5, 2xC*H*$_3$), 1.33-1.50 (4H, m, 2xCH$_3$C*H*$_2$), 2.92 (2H, s, ArCH$_2$), 2.93 (2H, t, J=4.9, C*H*$_2$CH$_2$O), 3.77 (2H, t, J=4.9, CH$_2$O), 7.01-7.24 (4H, m, ArH); δ_C 7.5 (2xCH$_3$), 27.7 (2xCH$_3$CH$_2$), 38.9 (*C*H$_2$CH$_2$O), 45.6 (ArCH$_2$), 61.9 (CH$_2$O), 76.9 (CO), 126.1, 126.3, 128.7, 130.1, 138.5, 141.0 (ArC); *m/z* 204 (M^+, 6%), 119 (16), 118 (75), 117 (100), 115 (13), 91 (15), 57 (12) (Found: M^+, 204.1504. $C_{14}H_{20}O$ requires M, 204.1514).

Spirocyclopentane-2-[1,2,4,5-tetrahydro-3-benzoxepine] (**5k**): ν_{max} (film) 3040, 3000, 750 cm^{-1} (ArH); δ_H 1.43-1.74 (8H, m, 4xring CH$_2$), 2.95 (2H, t, J=4.8, C*H*$_2$CH$_2$O), 3.01 (2H, s, ArCH$_2$), 3.75 (2H, t, J=4.8, CH$_2$O), 7.00-7.23 (4H, m, ArH); δ_C 23.3, 36.6, 38.9, 47.3 (4xring CH$_2$, 2xArCH$_2$), 63.5 (CH$_2$O), 84.9 (CO), 126.1, 126.3, 128.7, 129.9, 139.2, 141.1 (ArC); *m/z* 202 (M^+, 5%), 119 (14), 118 (55), 117 (100), 115 (41), 103 (11), 91 (29), 78 (11), 67 (10), 55 (15), 41 (13) (Found: M^+, 202.1351. $C_{14}H_{18}O$ requires M, 202.1358).

Spirocyclohexane-2-[1,2,4,5-tetrahydro-3-benzoxepine] (**5l**): ν_{max} (film) 3040, 3000, 750 cm^{-1} (ArH); δ_H 1.23-1.62 (10H, m, 5xring CH$_2$), 2.91 (2H, s, ArCH$_2$), 2.93-2.96 (2H, m, C*H*$_2$CH$_2$O), 3.76-3.79 (2H, m, CH$_2$O), 6.99-7.13 (4H, m, ArH); δ_C 21.7, 25.9, 34.8, 39.0 (5xring CH$_2$, *C*H$_2$CH$_2$O), 48.2 (ArCH$_2$CO), 61.4 (CH$_2$O), 73.3 (CO), 126.1, 126.3, 128.7, 130.0, 138.3, 140.9 (ArC); *m/z* 216 (M^+, 19%), 119 (27), 118 (100), 117 (96), 115 (24), 91 (18), 41 (12) (Found: M^+, 216.1510. $C_{15}H_{20}O$ requires M, 216.1514).

1,2,4,5-Tetrahydro-2-methyl-2-phenyl-3-benzoxepine (**5m**): ν_{max} (film) 3020, 3000, 1590, 750, 700 cm^{-1} (ArH); δ_H 1.40 (3H, s, CH$_3$), 2.99-3.03 (2H, m, C*H*$_2$CH$_2$O), 3.22 (1H, d, J=14.8, *H*CHCO), 3.50 (1H, d, J= 14.8, HC*H*CO), 3.79-3.97 (2H, m, CH$_2$O), 7.01-7.51 (9H, m, ArH); δ_C 29.1 (CH$_3$), 38.1 (*C*H$_2$CH$_2$O), 47.9 (*C*H$_2$CO), 62.7 (CH$_2$O), 77.4 (CO), 125.8, 126.1, 126.5, 128.1, 128.9, 130.8, 137.7, 140.6, 146.4 (ArC); *m/z* 238 (M^+, 5%), 118 (49), 117 (100), 115 (19), 115 (19), 91 (19), 78 (12), 77 (17), 51 (12), 43 (17) (Found: M^+, 238.1364. $C_{17}H_{18}O$ requires M, 238.1358).

*3,4-Dihydro-4-propyl-*1H*-2-benzopyran* (**6d**): (49% yield) ν_{max} (film) 3020, 3000, 740 cm^{-1} (ArH); δ_H 0.96 (3H, t, J=7.3, CH$_3$), 1.49 (2H, sextet, J=7.3, CH$_3$C*H*$_2$), 1.73-1.90 (2H, m, ArCHC*H*$_2$), 2.68 (1H, dt, J=16.2, 3.8, *H*CHCH$_2$O), 2.97 (1H, ddd, J=16.2, 9.5, 5.4, HC*H*CH$_2$O), 3.76 (1H, ddd, J=11.2, 9.5, 3.8, CH$_2$*H*CHO), 4.13 (1H, ddd, J=11.2, 5.4, 3.8, CH$_2$HC*H*O), 4.75 (1H, dd, J= 7.9, 3.5, CHO), 7.05-7.19 (4H, m, ArH); δ_C 14.1 (CH$_3$), 18.5 (CH$_3$*C*H$_2$), 29.2 (CH*C*H$_2$), 38.1 (ArCH$_2$), 63.1 (CH$_2$O), 75.6

(CHO), 124.8, 126.0, 126.0, 128.8, 133.9, 138.6 (ArC); *m/z* 176 (M^+, 2%), 133 (100), 115 (12), 105 (15), 103 (10), 79 (10), 77 (17), 43 (13), 41 (22) (Found: M^+, 175.8951. $C_{12}H_{16}O$ requires M, 176.1201).

2,3-Dihydro-4-(2-hydroxyethyl)-1,1-dimethyl-1H-*indene* (**7e**): (76% yield) ν_{max} (film) 3680-3080 cm^{-1} (OH); δ_H 1.25 (6H, s, 2xCH_3), 1.74 (1H, br s, OH), 1.92 [2H, d, *J*=7.2, $C(CH_3)_2CH_2$], 2.82-2.88 (4H, m, 2x $ArCH_2$), 3.82 (2H, t, *J*=7.2, CH_2OH), 6.98-7.14 (3H, m, ArH); δ_C 28.4 [$C(CH_3)_2CH_2$], 28.7 (2xCH_3), 36.6, 40.9 (2x$ArCH_2$), 44.0 [$C(CH_3)_2$], 62.5 (CH_2OH), 120.2, 126.8, 126.9, 134.0, 141.7, 152.9 (ArC); *m/z* 190 (M^+, 42%), 176 (21), 175 (100), 159 (14), 157 (54), 143 (12), 142 (24), 141 (17), 130 (11), 129 (61), 128 (51), 127 (16), 117 (10), 115 (16), 91 (20), 77 (17), 65 (11), 63 (13), 51 (11), 41 (17) (Found: M^+, 190.1356. $C_{13}H_{18}O$ requires M, 190.1358).

2,3-Dihydro-4-(2-hydroxyethyl)-1,1,2-trimethyl-1H-*indene* (**7g**): (86% yield) ν_{max} (film) 3600-3080 cm^{-1} (OH); δ_H 0.95 (3H, s, CH_3CCH_3), 1.06 (3H, d, *J*=6.9, CH_3CH), 1.26 (3H, s, CH_3CHCH_3), 2.03-2.15 (1H, m, CH_3CH), 2.45 (1H, dd, *J*=15.5, 10.1, $ArHCHCHCH_3$), 2.83 (2H, t, *J*=6.8, CH_2CH_2OH), 2.96 (1H, dd, *J*= 15.5, 7.5, $ArHCHCHCH_3$), 2.97 (1H, br s, OH), 3.81 (2H, t, *J*=6.8, CH_2OH), 6.97-7.13 (3H, m, ArH); δ_C 13.9 (CH_3CH), 23.1, 26.6 [$(CH_3)_2C$], 36.6 (CH_2CH_2OH), 36.8 ($ArCH_2$), 45.0 (CH_3CH), 45.4 [$(CH_3)_2C$], 62.6 (CH_2OH), 120.5, 126.7, 126.8, 133.7, 140.9, 153.7 (ArC); *m/z* 204 (M^+, 33%), 189 (66), 172 (19), 171 (82), 157 (10), 156 (27), 143 (67), 142 (16), 141 (42), 130 (11), 129 (44), 128 (87), 127 (19), 115 (67), 105 (22), 91 (36), 79 (14), 78 (11), 77 (44), 65 (22), 63 (23), 55 (23), 53 (21), 52 (13), 51 (37), 45 (11), 43 (64), 41 (100) (Found: M^+, 204.1510. $C_{14}H_{20}O$ requires M, 204.1514).

1,2,3,4-Tetrahydro-5-(2-hydroxyethyl)-1,1-dimethylnaphthalene (**8f**): (44% yield) ν_{max} (film) 3640-3080 cm^{-1} (OH); δ_H 1.28 (6H, s, 2xCH_3), 1.63 [2H, t, *J*=5.8, $C(CH_3)_2CH_2$], 1.70 (1H, br s, OH), 1.73-1.86 (2H, m, $CH_2CH_2CH_2Ar$), 2.71 (2H, t, *J*=6.4, $ArCH_2$), 2.85 (2H, t, *J*=6.9, CH_2CH_2OH), 3.81 (2H, t, *J*=6.9, CH_2OH), 6.97 (1H, dd, *J*= 7.4, 1.2, 1xArH), 7.10 (1H, t, *J*=7.4, 1xArH), 7.25 (1H, dd, *J*= 7.4, 1.2, 1xArH); δ_C 19.5 ($CH_2CH_2CH_2Ar$), 27.3 [$C(CH_3)_2CH_2$], 32.0 (2xCH_3), 34.1 [$C(CH_3)_2$], 36.3, 38.7 (2x$ArCH_2$), 62.4 (CH_2OH), 125.3, 125.5, 126.7, 134.6, 135.9, 146.3 (ArC); *m/z* 204 (M^+, 41%), 190 (10), 189 (75), 173 (13), 172 (13), 171 (100), 159 (10), 156 (10), 148 (10), 143 (29), 142 (17), 141 (26), 131 (26), 130 (13), 129 (54), 128 (63), 127 (12), 119 (14), 117 (17), 115 (42), 105 (16) (Found: M^+, 204.1507. $C_{14}H_{20}O$ requires M, 204.1514).

(E)-2-[2-(4-Methyl-2-pentenyl)phenyl]ethanol (**9f**): (22% yield) ν_{max} (film) 3620-3080 cm^{-1} (OH); δ_H 0.97 (6H, d, *J*=6.7, 2xCH_3), 1.47 (1H, br s, OH), 2.13-2.35 [1H, m, $(CH_3)_2CH$], 2.91 (2H, t, *J*=6.9, CH_2CH_2OH), 3.36 (2H, d, *J*=5.6, CH_2CH=CH), 3.83 (2H, t, *J*=6.9, CH_2OH), 5.40 (1H, dd, *J*=15.5, 6.0, CH_2CH=CH), 5.50 (1H, dt, *J*=15.5, 5.6, CH_2CH=CH), 7.14-7.23 (4H, m, ArH); δ_C 22.5 (2xCH_3), 31.0 [$(CH_3)_2CH$], 35.8, 35.9 (2x$ArCH_2$), 63.2 (CH_2OH), 125.5, 126.2, 126.7, 129.8, 129.9, 136.3, 139.1, 139.3 (ArC, CH=CH); *m/z* 204 (M^+, 17%), 171 (13), 144 (13), 143 (100), 141 (10), 135 (15), 133 (12), 130 (21), 129 (37), 128 (51), 127 (14), 119 (17), 117 (63), 116 (13), 115 (59), 105 (23), 104 (17), 103 (12), 91 (43), 78 (15), 77 (19), 69 (17), 65 (17), 63 (11), 55 (15), 53 (11), 51 (15), 43 (20), 41 (56) (Found: M^+, 204.1516. $C_{14}H_{20}O$ requires M, 204.1514).

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