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SELECTIVE LITHIATION OF 4- AND 5-HALOPHTHALANS

Daniel García, Francisco Foubelo,* and Miguel Yus*

Department of Organic Chemistry, Faculty of Science, and Institut of Organic Synthesis (ISO), University of Alicante, Apdo. 99, 03080 Alicante, Spain

Abstract – The reaction of 4- and 5-halophthalans **5** with lithium and a catalytic amount of DTBB at -78 ºC leads to the formation of the corresponding functionalized organolithium intermediates **6** and **11**, which by reaction with carbonyl compounds give, after hydrolysis, the expected substituted phthalans **8** and **13**, respectively. When after reaction with the carbonyl compound the system is allowed to react at 0 ºC, a second lithiation occur: A reductive opening of the heterocycle takes place with some regioselectivity leading to new organolithium intermediates **9** and **14**/**15** that by reaction with electrophiles lead, after hydrolysis, to polyfunctionalized molecules **10** and **16**/**17**, respectively.

INTRODUCTION

Functionalized organolithium compounds[1] can be prepared following the same methodologies used for simple organolithium compounds. They are also accessible through the reductive ring opening of appropriate oxygen-, nitrogen- and sulfur-containing heterocycles,[2] such as strained heterocycles (three and four membered-rings) and heterocycles with activated bonds. In addition, suitable precursors are compounds bearing allylic[3] and benzylic[4] carbon-heteroatom bonds, and cyclic aryl ethers[5] and thioethers.[6] Among the lithiation reagents, the use of an excess of lithium in the presence of a catalytic amount of an arene[7] [naphthalene and 4,4'-di-*tert*-butylbiphenyl (DTBB)],[8] has shown to be very effective even at low temperatures for this purpose. More recently, polymer supported naphthalene, biphenyl[9] and also polyphenylene[10] have been used as electron transfer reagents in these processes.[11] As an example, phthalan (**1**; R = R' = H) can be easily opened with the above mentioned methodology to give the expected lithiated intermediate **2a/2b** (R = R' = H)[12] through a favoured reductive benzylic cleavage (Scheme 1). When the heterocyclic ring isn phthalan bears substituents (**1**; R = Me, *n*-Bu, Ph; R' = H),

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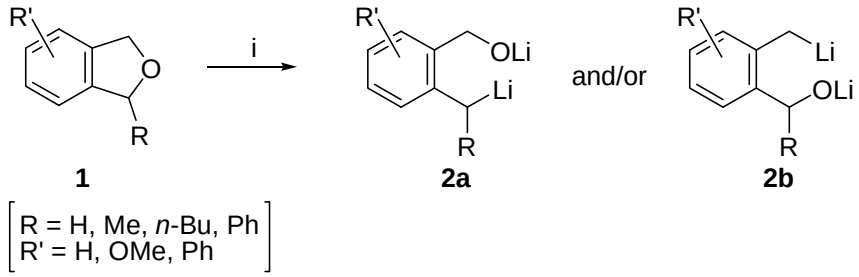
This paper is dedicated to Professor Emeritus Keiichiro Fukumoto on the occasion of his 75th birthday.

the opening takes place giving the most stable intermediate **2a** (R = Ph; R' = H) or **2b** (R = Me, *n*-Bu; R' = H) (Scheme 1).[13] In the case of non-symmetrically substituted phthalans possessing different groups attached to the aromatic ring (**1**; R = H; R' = OMe, Ph), the reductive opening leading to intermediates **2** occurs with high regioselectivity and it can be explained taking into account the electron density deduced by semiempirical PM3 calculations of either the anion or the radical-anion intermediate responsible of the reductive cleavage (Scheme 1).[14]

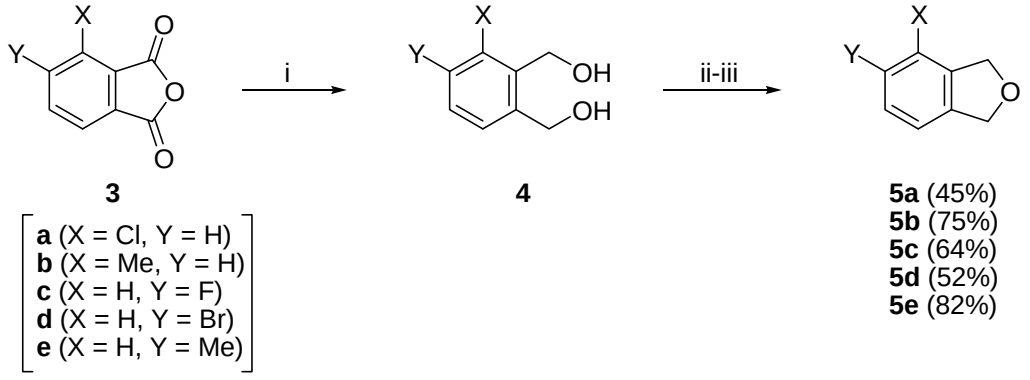


Scheme 1. Reagents and conditions: (i) Li, ArH (DTBB or $C_{10}H_8$), THF, -78, 0 or 20 °C, 4 h.

Continuing with our recent studies on the selective lithiation of substituted phthalans,[14] we report here the selective (chemo- and/or regioselective) lithiation of 4- and 5-halophthalans.

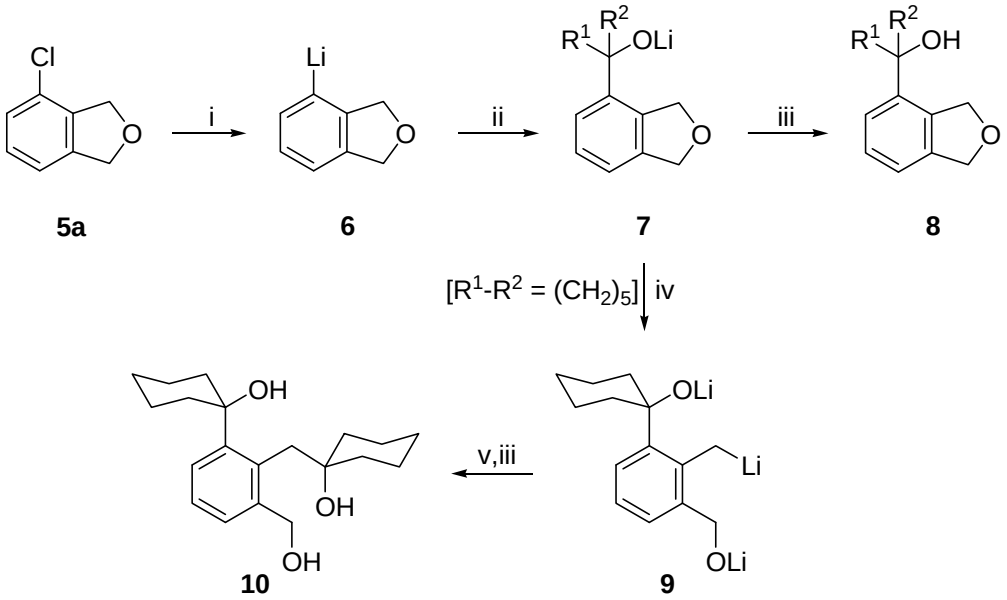
RESULTS AND DISCUSSION

Substituted phthalans **5** were prepared starting from the corresponding commercially available phthalic anhydrides **3** through a three-step process: first reduction with LAH in the presence of $ZnCl_2$ to give the corresponding diol **4**, followed by Swern oxidation and final cyclization of the resulting dialdehyde by treatment with Et_3SiH in the presence of Me_3SiOTf. The expected substituted phthalans **5** were obtained, in general, in good overall yields (Scheme 2).



Scheme 2. Reagents and conditions: (i) $LiAlH_4$, $ZnCl_2$, THF, 0 to 20 °C, 6 h; (ii) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, -60 to 20 °C, 2 h; (iii) Et_3SiH, Me_3SiOTf, CH_2Cl_2, 0 ºC, 4 h, then 20 ºC, 2 h.

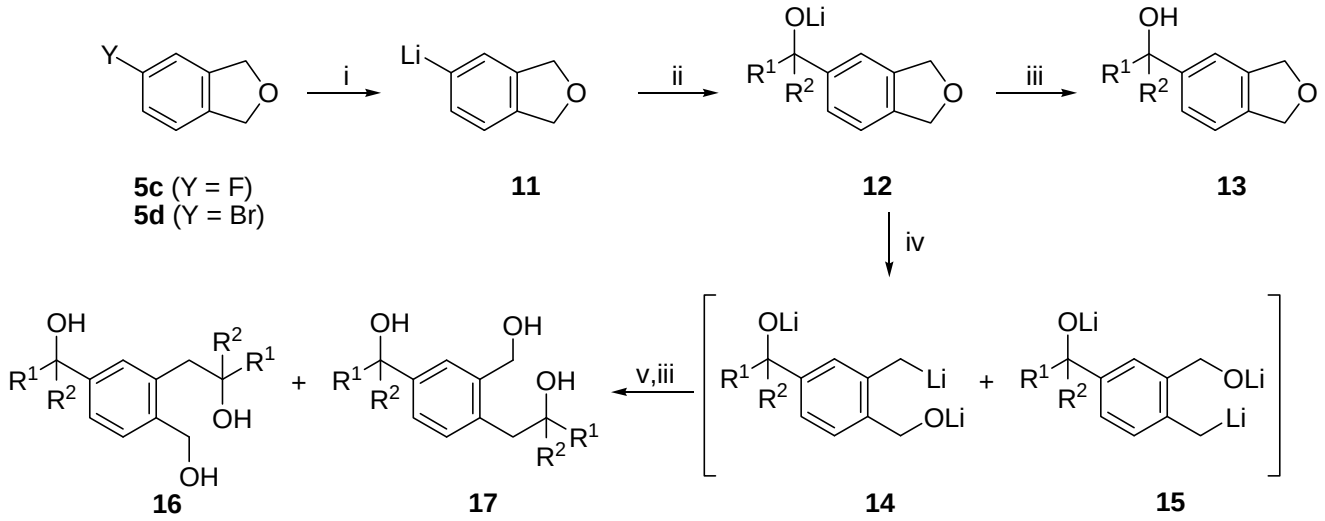
The reaction of 4-chlorophthalan (**5a**) with an excess of lithium powder (1:10 molar ratio) and a catalytic amount of DTBB (1:0.13 molar ratio; 7.0 mol %) in THF at -78 ºC for 2 h, led to a solution of the intermediate **6**, which by reaction with different carbonyl compounds as electrophiles [R^1R^2CO: PhCHO, $(CH_2)_5CO$] at -78 ºC gave, after hydrolysis with water at the same temperature, the corresponding alcohol **8** (Scheme 3, Table 1, entries 1 and 2).



Scheme 3. Reagents and conditions: (i) Li, DTBB (7.0 mol %), THF, -78 ºC, 2 h; (ii) R^1R^2CO: PhCHO, $(CH_2)_5CO$, -78 ºC; (iii) H_2O, -78 to 20 ºC; (iv) 0 ºC, 1 h; (v) $(CH_2)_5CO$, -78 ºC.

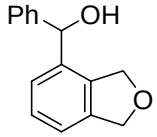
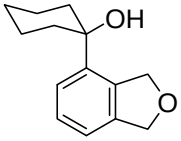
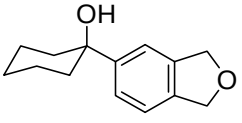
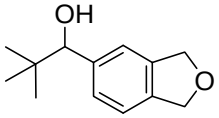
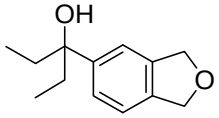
Lithiation of 5-fluorophthalan (**5c**) and 5-bromophthalan (**5d**) under the same reaction conditions as for 4-chlorophthalan (**5a**) in Scheme 3 led to organolithium intermediate **11** which upon reaction with different carbonyl compounds as electrophiles [R^1R^2CO: *t*-BuCHO, Et_2CO, $(CH_2)_5CO$] at -78 ºC gave, after hydrolysis with water at the same temperature, the corresponding substituted phthalan **13** (Scheme 4, Table 1, entries 3-5). In these processes, a chemoselective lithiation occurred: Carbon-halogen bonds are more reactive towards the lithiation reagent than the benzylic carbon-oxygen bond, so halogen/lithium exchange took place exclusively instead of the reductive opening of the heterocycle. The presence of a carbon-lithium bond in intermediates **6** and **11** prevents them for suffering a further reduction (reductive opening in this case) even if the process is performed at 0 ºC. Yields were considerably higher in the case of 5-halophthalans **5c**,**d**, due probably to the higher stability of the organolithium intermediate **11** compared to **6**.

From a synthetic point of view, an interesting variant of the monolithiation of the halophthalans **5** results when the second electrophile is introduced in the molecule. It happens when the alcoholates **7** [derived from 4-chlorophthalan (**5a**), Scheme 3] and **12** [derived from 5-bromophthalan (**5d**), Scheme 4] were stirred at 0 ºC for 1 h in the presence of the excess of lithium still present in the reaction medium. Under these reaction



Scheme 4. Reagents and conditions: (i) Li, DTBB (7.0 mol %), THF, -78 ºC, 2 h; (ii) R^1R^2CO: *t*-BuCHO, Et_2CO, $(CH_2)_5CO$, -78 ºC; (iii) H_2O, -78 to 20 ºC; (iv) 0 ºC, 1 h; (v) R^1R^2CO: Et_2CO, $(CH_2)_5CO$, -78 ºC.

Table 1. Preparation of compounds **8** and **13** through monolithiation of halophthalans **5a**, **5c** and **5d**

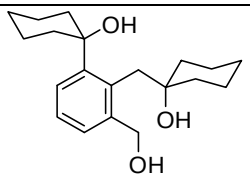
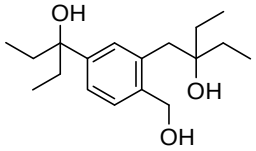
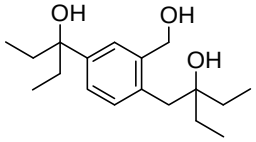
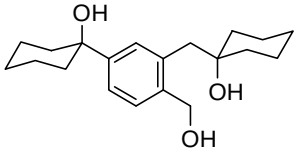
Entry	Starting phthalan	R^1R^2CO	Alcohols **8** and **13**[a]		
			No.	Structure	Yield (%)[b]
1	**5a**	PhCHO	**8a**		28
2	**5a**	$(CH_2)_5CO$	**8b**		37
3	**5c**	$(CH_2)_5CO$	**13a**		42
4	**5d**	*t*-BuCHO	**13b**		55
5	**5d**	Et_2CO	**13c**		61

[a] All products were >95% pure (GLC and/or 300 MHz ^{1}H RMN). [b] Isolated yield based on the starting material **5**.

conditions the reductive cleavage of the heterocycle took place and after addition of a new equivalent of the carbonyl compound as electrophile at -78 ºC, followed by hydrolysis with water, the triols **10** (Scheme 3) and **16**/**17** (Scheme 4) were obtained, respectively. The structure of these compounds was

elucidated using NOESY, HSQC and HMBC experiments. The solid triol **17a** [R = $Ph(CH)_2$] gave crystals suitable for single crystal X-ray analysis and the obtained structure (Chart 1)[15-18] was in total agreement with the NMR experiments. Apparently, in the case of alcoholate **7** [$R^1R^2 = (CH_2)_5$] a selective reductive cleavage took place leading to intermediate **9** exclusively (Scheme 3, Table 2, entry 1). However, in the case of alcoholates **12** derived from 5-bromophthalan (**5d**), a mixture of the two possible organolithium intermediates **14** and **15** were obtained, so leading to a mixture of triols **16** and **17** after reaction with the electrophile (Scheme 4, Table 2, entries 2 and 3). Yields were low in all cases.

Table 2. Preparation of compounds **10**, **16** and **17** through monolithiation of halophthalans **5a** and **5d**

Entry	Starting phthalan	R^1R^2CO	Alcohols **6** and **11**[a]		
			No.	Structure	Yield (%)[b]
1	**5a**	$(CH_2)_5CO$	**10**		21
2	**5d**	Et_2CO	**16a**		23
			17a		13
3	**5d**	$(CH_2)_5CO$	**16b**		28[c]

[a] All products were >95% pure (GLC and/or 300 MHz ^{1}H RMN). [b] Isolated yield based on the starting material **5**. [c] The other regioisomer was detected by GL-MS (<5%) but it was not isolated.

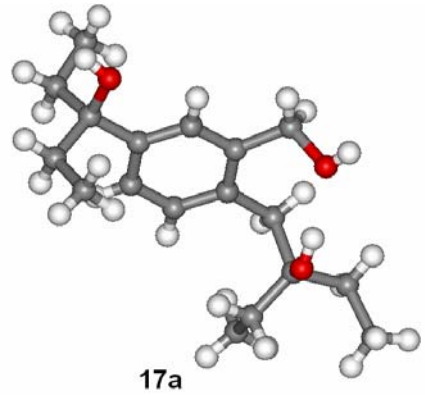
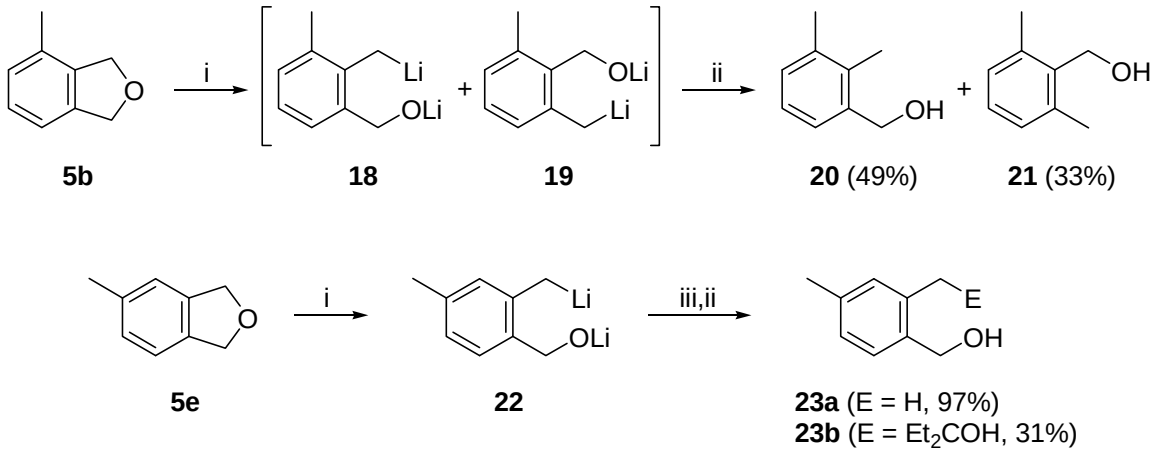


Chart 1

The lithiation of 4-methylphthalan (**5b**) and 5-methylphthalan (**5e**) was also studied in order to rationalize the experimental results of the reductive opening of alcoholates **7** and **12**, concerning the regiochemistry of the process. Lithiation of 4-methylphthalan (**5b**) under the same reaction conditions as previously described for other phthalan derivatives, followed by hydrolysis with water, gave a mixture of regioisomeric alcohols **20** and **21** in a 3:2 ratio. That means that the two possible reductive openings of **5b** took place leading to dianionic intermediates **18** and **19** (Scheme 5). Surprisinly, 2,4-dimethylbenzyl alcohol (**23a**) was the only reaction product in the case of starting from 5-methylphthalan (**5e**) and using water as electrophile. In the case of using 3-pentanone as electrophile, diol **23b** was isolated in 31% yield, 2,4-dimethylbenzyl alcohol (**23a**) being the major reaction product. So, under these reaction conditions reductive cleavage in **5e** leading to intermediate **22** took place exclusively. Since the regiochemistry of the reductive opening of 4- and 5-methyl substituted phthalans **5b** and **5e** was different to that of alcoholates **7** and **12**, it seems that the lithium alkoxide unit plays an important role in this process.



Scheme 5. Reagents and conditions: (i) Li, DTBB (7.0 mol %), THF, -78 ºC, 2 h; (ii) H_2O, -78 to 20 ºC; (iii) E^+: H_2O, Et_2CO, -78 ºC.

From the results described in this paper we can conclude that it is possible to lithiate selectively 4- and 5-halophthalans **5** using an excess of lithium in the presence of a catalytic amount of DTBB, halogen/lithium exchange taking place first. A second lithiation occurs only after the reaction of the resulting organolithium intermediates **6** and **11** with a carbonyl compound as electrophile. The new organolithium intermediates result from the reductive opening of the heterocycle that happens with some regioselectivity. The addition of a carbonyl compound as electrophile yields triols **10**, **16** and **17**.

EXPERIMENTAL

All reactions were performed in oven dried glassware under argon. All chemicals were commercially available (Acros, Aldrich). TLC was performed on Merck silica gel 60 F_{254}, using aluminum plates and

visualized with phosphomolybdic acid (PMA) stain. Chromatographic purification was performed by flash chromatography using Merck silica gel 60 (0.040-0.063 mm) and hexane/EtOAc as eluent. IR spectra were measured (film) with a Nicolet Impact 510 P-FT Spectrometer. Melting points were recorded on an OptiMelt (Stanford Research Systems) apparatus using open glass capillaries and reported without corrections. NMR spectra were recorded with a Bruker AC-400 using $CDCl_3$ as the solvent and TMS as internal standard. HRMS (EI) were recorded on a Finnigan MAT 95S.

Preparation of diols 4. General procedure.

To a suspension of $LiAlH_4$ (10 mmol, 380 mg) and $ZnCl_2$ (3 mmol, 408 mg) in THF (20 mL) under Argon was slowly added a solution of the corresponding phthalic anhydride **3** (5 mmol) in THF (2 mL) at 0 ºC. The resulting reaction mixture was strirred at 20 ºC for 6 h. After that it was hydrolyzed with water (10 mL) at 0 ºC, acidified with 2M HCl (20 mL), extrated with EtOAc (3 × 20 mL), dried over anhydrous $MgSO_4$ and evaporated (15 Torr). The residue was purified by column chromatography (silica gel, hexane/EtOAc) to give products **4** in almost quantitative yield. Physical and spectroscopic data as well as literature references for known compounds follow.

3-Chloro-2-(hydroxymethyl)benzyl alcohol (4a): White solid; mp 69-70 ºC (pentane/CH_2Cl_2); R_f = 0.29 (hexane/EtOAc: 1/1); IR ν (KBr) 3425-3455 (OH), 3057, 2971, 2892 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.61 (2H, br s, 2×OH), 4.77 (4H, s, 2×CH_2OH), 7.14-7.16 (2H, m, ArH), 7.26-7.27 (1H, m, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 59.1, 63.9 (CH_2), 128.3, 129.4, 129.5, 135.0, 136.1, 141.6 (ArC); LRMS (EI) *m/z* 156 (M^+-H_2O, 32%), 155 (41), 154 (98), 153 (100), 127 (12), 125 (34), 91 (44), 90 (10), 89 (27), 77 (28), 63 (10), 51 (11).

2-(Hydroxymethyl)-3-methylbenzyl alcohol (4b): Colorless oil; R_f = 0.21 (hexane/EtOAc: 1/1); IR ν (film) 3380-3295 (OH), 3069, 2965, 2897 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.33 (3H, s, CH_3), 4.11 (2H, br s, 2×OH), 4.48 (2H, s, CH_2OH), 4.53 (2H, s, CH_2OH), 7.04-7.11 (3H, m, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.3 (CH_3), 58.4, 65.8 (CH_2), 127.4, 128.0, 130.5, 137.2, 137.5, 139.8 (ArC); LRMS (EI) *m/z* 152 (M^+, 1%), 135 (10), 134 (100), 133 (82), 132 (16), 119 (12), 106 (37), 105 (88), 103 (29), 91 (73), 79 (24), 78 (18), 77 (43), 65 (11), 51 (18).

4-Fluoro-2-(hydroxymethyl)benzyl alcohol (4c): Colorless oil; R_f = 0.20 (hexane/EtOAC: 1/1); IR ν (film) 3405-3335 (OH), 2947, 2887 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.43 (2H, s, CH_2OH), 4.46 (2H, s, CH_2OH), 4.70 (2H, br s, 2×OH), 6.86-6.97 (2H, m, ArH), 7.13-7.18 (1H, m, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 62.2, 62.3 (CH_2), 114.2, 114.4, 115.4, 115.7, 130.1, 134.3, 141.5, 141.6, 160.7, 163.9 (ArC); LRMS (EI) *m/z* 138 (M^+-H_2O, 100%), 137 (98), 110 (13), 109 (81), 107 (11), 97 (15), 95 (10), 83 (16), 77 (11).

4-Bromo-2-(hydroxymethyl)benzyl alcohol (4d):[19] White solid; mp 69-70 ºC (pentane/CH_2Cl_2); R_f =

0.20 (hexane/EtOAc: 1/1); IR ν (KBr) 3320-3235 (OH), 2941, 2882 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.22 (2H, br s, 2×OH), 4.62 (2H, s, CH_2OH), 4.66 (2H, s, CH_2OH), 7.29-7.32 (1H, m, ArH), 7.39-7.43 (1H, m, ArH), 7.59 (1H, s, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 61.9, 62.1 (CH_2), 122.3, 130.1, 131.2, 131.3, 139.1, 142.8 (ArC); LRMS (EI) *m/z* 218 (M^+, 2%), 216 (2), 200 (94), 199 (89), 198 (100), 197 (82), 171 (28), 169 (29), 92 (13), 91 (69), 90 (35), 89 (45), 79 (10), 78 (24), 77 (41), 65 (17), 63 (24), 51 (22), 50 (12).

2-(Hydroxymethyl)-4-methylbenzyl alcohol (4e):[20] Colorless oil; R_f = 0.25 (hexane/EtOAc: 1/1); IR ν (film) 3355-3280 (OH), 3014, 2917, 2880 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.29 (3H, s, CH_3), 4.16 (2H, br s, 2×OH), 4.48 (4H, s, 2×CH_2OH), 7.03-7.06 (2H, m, ArH), 7.12 (1H, d, J = 7.7 Hz, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.0 (CH_3), 63.2, 63.5 (CH_2), 128.8, 129.6, 130.3, 136.2, 138.1, 139.1 (ArC); LRMS (EI) *m/z* 152 (M^+, 1%), 135 (10), 134 (100), 133 (97), 106 (11), 105 (49), 103 (13), 93 (11), 91 (53), 79 (17), 78 (11), 77 (37), 65 (11), 51 (11).

Preparation of phthalans 5. General procedure.

To a solution of oxalyl chloride (11.5 mmol, 1.450 g, 1.0 mL) in CH_2Cl_2 (45 mL) was added dimethylsulfoxide (25 mmol, 1.750 g, 1.8 mL) at -65 ºC. After 5 min at this temperature, a solution of the corresponding diol **4** (5 mmol) in CH_2Cl_2 (45 mL) was added and stirring continued for 15 min prior to the addition Et_3N (52 mmol, 5.252 g, 7.2 mL). After that, the cold bath was removed and stirring was manteined for 2 h at 20 ºC. The reaction mixture was hydrolyzed with 2M HCl (50 mL) and extrated with CH_2Cl_2 (3 × 40 mL). The organic layers were washed with water (3 × 50 mL), dried over anhydrous $MgSO_4$ and evaporated (15 Torr). The resulting dialdehyde was used without purification in the next step of the reaction. To a solution of the corresponding dialdehyde (4.50 mmol) in dry CH_2Cl_2 (15 mL) was successively added Et_3SiH (20 mmol, 2.32 g, 2.58 mL) and Me_3SiOTf (0.134 mml, 30 mg, 0.025 mL) at 0 ºC. The reaction mixture was stirred at the same temperature for 4 h and for 2 h at 20 ºC. After that the solvent was evaporated (15 Torr) and the resulting residue was purified by column chromatography (silica gel, hexane/EtOAc) to give products **5**. Overall yields are given in Scheme 2. Physical, and spectroscopic data as well as literature references for known compounds follow.

4-Chlorophthalan (5a): Yellow oil; R_f = 0.41 (hexane/EtOAc: 10/1); IR ν (film) 3155, 2917, 2855, 1456 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.12 (2H, s, CH_2O), 5.16 (2H, s, CH_2O), 7.10 (1H, t, J = 4.1 Hz, ArH), 7.21 (2H, d, J = 3.85 Hz, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 73.3, 74.5 (CH_2), 119.3, 127.4, 128.0, 129.2, 137.8, 141.3 (ArC); LRMS (EI) *m/z* 156 (M^+, 17%), 155 (20), 154 (52), 153 (48), 127 (26), 126 (28), 125 (75), 99 (10), 92 (10), 91 (100), 90 (18), 89 (44), 63 (24), 62 (11); HRMS (EI) calcd for C_8H_7ClO 154.0185, found 154.0200.

4-Methylphthalan (5b):[21] Yellow oil; R_f = 0.36 (hexane/EtOAc: 10/1); IR ν (film) 3027, 2916, 2855

cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.30 (3H, s, CH_3), 5.07 (2H, s, CH_2O), 5.12 (2H, s, CH_2O), 7.02-7.05 (2H, m, ArH), 7.10-7.19 (1H, m, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.8 (CH_3), 73.1, 74.1 (CH_2), 118.2, 127.6, 128.0, 130.3, 138.1, 138.7 (ArC); LRMS (EI) *m/z* 134 (M^+, 63%), 133 (43), 119 (16), 106 (56), 105 (100), 103 (29), 91 (71), 79 (25), 78 (15), 77 (38), 63 (11), 51 (20).

5-Fluorophthalan (5c): Yellowish oil; R_f = 0.32 (hexane/EtOAc: 10/1); IR ν (film) 3024, 1262 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.06 (4H, s, CH_2O), 6.90-6.97 (2H, m, ArH), 7.13-7.17 (1H, m, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 73.1, 73.4 (CH_2), 108.1, 108.5, 114.3, 114.6, 122.1, 122.2, 134.5, 141.4, 141.5, 161.1, 164.3 (ArC); LRMS (EI) *m/z* 138 (M^+, 43%), 137 (49), 110 (57), 109 (100), 107 (19), 83 (27), 57 (10).

5-Bromophthalan (5d): White solid; mp 41-42 ºC (pentane/CH_2Cl_2); R_f = 0.30 (hexane/EtOAc: 10/1); IR ν (KBr) 3074, 1051 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.09 (2H, s, CH_2O), 5.20 (2H, s, CH_2O), 7.15 (2H, d, J = 6.3 Hz, ArH), 7.35 (1H, dd, J = 6.3, 2.3 Hz, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 74.7 (CH_2), 115.9, 119.7, 129.2, 130.2, 139.8, 141.0 (ArC); LRMS (EI) *m/z* 200 (M^+, 35%), 199 (31), 198 (36), 197 (29), 172 (14), 171 (37), 170 (15), 169 (38), 118 (10), 91 (100), 89 (42), 88 (41), 63 (24), 62 (11).

5-Methylphthalan (5e):[22] Colorless oil; R_f = 0.39 (hexane/EtOAc: 10/1); IR ν (film) 3014, 2953, 2910, 2850 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.31 (3H, s, CH_3), 5.00 (4H, s, 2×CH_2O), 6.96 (1H, s, ArH), 6.99-7.06 (2H, m, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.0 (CH_3), 73.2 (CH_2), 120.4, 121.3, 127.9, 136.0, 136.7, 139.2 (ArC); LRMS (EI) *m/z* 134 (M^+, 65%), 133 (52), 119 (10), 106 (51), 105 (100), 103 (25), 91 (52), 79 (21), 78 (11), 77 (31), 63 (10), 51 (14).

Monolithiation of phthalans 5. Preparation of compounds 8, 13, 20, 21 and 23. General procedure.

To a blue suspension of lithium powder (72 mg, 10.4 mmol) and a catalytic amount of DTBB (34 mg, 0.13 mmol) in dry THF (3 mL) under argon was added dropwise a solution of the corresponding phthalan **5** (1 mmol) in THF (0.5 mL) at -78 ºC, and the resulting mixture was stirred for 2 h at the same temperature. Then the corresponding carbonyl compound was added dropwise (1.1 mmol) at -78 ºC and, after 20 min the reaction mixture was hydrolyzed with water (4 mL), extracted with EtOAc (3 × 15 mL), dried over anhydrous $MgSO_4$ and evaporated (15 Torr). The residue was purified by column chromatography (silica gel, hexane/ethyl acetate) to yield pure products **8**, **13**, **20**, **21** and **23**. Yields are given in Table 1 and Scheme 4. Physical, analytical and spectroscopic data as well as literature references for known compounds follow.

4-(1-Hydroxy1-phenylmethyl)phthalan (8a): Colorless oil; R_f = 0.11 (hexane/EtOAc: 5/1); IR ν (film) 3420-3355 (OH), 3069, 3032, 2928, 2855 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.60 (1H, br s, OH), 4.91 (1H, d, J = 12.9 Hz, C*H*HO), 4.96 (1H, d, J = 12.9 Hz, CH*H*O), 5.02 (2H, s, CH_2O), 7.13 (1H, d, J = 7.3 Hz, ArH), 5.74 (1H, s, C*H*OH), 7.24-7.33 (7H, m, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 72.8, 73.3 (CH_2),

75.0 (CH), 120.2, 125.1, 126.8, 127.8, 128.0, 128.7, 136.8, 137.6, 139.9, 142.5 (ArC); LRMS (EI) *m/z* 226 (M^+, 2%), 209 (17), 208 (100), 207 (72), 180 (19), 179 (23), 165 (34), 152 (11), 146 (17), 132 (11), 119 (36), 104 (19), 91 (38), 89 (18), 79 (10), 77 (30), 65 (12), 63 (12), 51 (10); HRMS (EI) calcd for $C_{15}H_{12}O$ [M^+-H_2O] 208.0883, found 208.0841.

4-(1-Hydroxycyclohexyl)phthalan (8b): Colorless oil; R_f = 0.14 (hexane/EtOAc: 5/1); IR ν (film) 3430-3365 (OH), 2918, 2849, 1037 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.68-1.80 (10H, m, 5×CH_2), 2.45 (1H, br s, OH), 5.06 (2H, s, CH_2O), 5.35 (2H, s, CH_2O), 7.12 (1H, d, J = 6.1 Hz, ArH), 7.20-7.25 (2H, m, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.3, 24.3, 25.6, 30.8, 35.7, 72.8, 74.5 (CH_2), 75.8 (CH), 119.5, 123.8, 127.6, 127.7, 130.5, 140.6 (ArC); LRMS (EI) *m/z* 218 (M^+, 7%), 201 (15), 200 (100), 199 (14), 185 (10), 171 (18), 167 (10), 159 (30), 157 (21), 147 (10), 145 (29), 144 (10), 143 (12), 141 (13), 119 (13), 115 (28), 104 (10), 91 (21); HRMS (EI) calcd for $C_{14}H_{16}O$ [M^+-H_2O] 200.1201, found 200.1233.

5-(1-Hydroxycyclohexyl)phthalan (13a): Yellow oil; R_f = 0.16 (hexane/EtOAc: 5/1); IR ν (film) 3475-3395(OH), 3069, 2933, 2855, 1035 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.70-1.85 (10H, m, 5×CH_2), 2.63 (1H, br s, OH), 5.10 (4H, br s, CH_2O), 7.21 (1H, d, J = 8.6 Hz, ArH), 7.40-7.42 (2H, m, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.3, 25.6, 39.2, 73.3, 73.5 (CH_2), 73.7 (CH), 117.3, 120.8, 124.0, 137.6, 139.3, 149.2 (ArC); LRMS (EI) *m/z* 218 (M^+, 28%), 188 (10), 175 (22), 162 (22), 147 (19), 146 (15), 145 (100), 133 (11), 119 (10), 105 (10), 104 (14), 91 (20), 55 (15); HRMS (EI) calcd for $C_{14}H_{18}O_2$ 218.1307, found 218.1305.

5-(1-Hydroxy-2,2-dimethylpropyl)phthalan (13b):[23] Colorless oil; R_f = 0.34 (hexane/EtOAc: 2/1); IR ν (film) 3460-3385 (OH), 3020 (ArH), 2953, 2892, 2867 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.92 [9H, s, $C(CH_3)_3$], 2.55 (1H, br s, OH), 4.40 (1H, s, C*H*OH), 5.08 (4H, br s, CH_2O), 7.13-7.26 (3H, m, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.0 (CH_3), 35.1 (C), 73.5, 73.6 (CH_2), 82.4 (CH), 120.0, 120.1, 127.1, 138.1, 138.6, 141.8 (ArC); LRMS (EI) *m/z* 206 (M^+, 6%), 150 (15), 149 (100), 93 (18), 91 (34); HRMS (EI) calcd for $C_{13}H_{18}O_2$ 206.1307, found 206.1292.

5-(1-Ethyl-1-hydroxypropyl)phthalan (13c): Colorless oil; R_f = 0.19 (hexane/EtOAc: 5/1); IR ν (film) 3465-3390 (OH), 2967. 2940, 2855 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.77 (6H, t, J = 7.4 Hz, 2×CH_3), 1.79-1.91 (4H, m, 2×C*H*$_2$CH$_3$), 5.10 (4H, br s, CH_2O), 7.19 (1H, d, J = 7.95 Hz, ArH), 7.25-7.29 (2H, m, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.0 (CH_3), 35.3, 73.5, 73.7 (CH_2), 77.5 (C), 118.2, 120.5, 124.8, 137.1, 139.1, 145.5 (ArC); LRMS (EI) *m/z* 206 (M^+, 1%), 178 (13), 177 (100), 175, 147 (11), 119 (10), 91 (11), 57 (50); HRMS (EI) calcd for $C_{13}H_{18}O_2$ 206.1307, found 206.1300.

2,3-Dimethylbenzyl alcohol (20):[24] ^1H NMR (400 MHz, $CDCl_3$) δ 1.75 (1H, br s, OH), 2.24 (3H, s, CH_3), 2.28 (3H, s, CH_3), 4.66 (2H, s, C*H*$_2$OH), 7.07-7.18 (3H, m, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.4 (CH_3), 64.2 (CH_2OH), 125.6, 125.8, 129.7, 135.0, 137.5, 138.1 (ArC); LRMS (EI) *m/z* 136 (M^+, 35%),

134 (37), 133 (36), 121 (21), 119 (21), 118 (100), 117 (47), 115 (10), 107 (14), 105 (52), 103 (23), 93 (30), 91 (73), 79 (19), 78 (12), 77 (44), 65 (13), 51 (15).

2,6-Dimethylbenzyl alcohol (21):[25] ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.75 (1H, br s, OH), 2.41 (6H, s, 2×CH_3), 4.70 (2H, s, CH_2OH), 7.01-7.19 (3H, m, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.5 (CH_3), 59.4 (CH_2OH), 128.1, 128.5, 136.6, 137.3 (ArC); LRMS (EI) *m/z* 136 (M^+, 35%), 134 (37), 133 (36), 121 (21), 119 (21), 118 (100), 117 (47), 115 (10), 107 (14), 105 (52), 103 (23), 93 (30), 91 (74), 79 (19), 78 (12), 77 (45), 65 (13), 51 (16).

2,4-Dimethylbenzyl alcohol (23a): Yellow oil; R_f = 0.27 (hexane/EtOAc: 6/1); IR ν (film) 3395-3320 (OH), 3006, 2959, 2917, 2849 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.85 (1H, br s, OH), 2.30 (6H, br s, 2×CH_3), 4.60 (2H, s, CH_2OH), 6.99 (2H, br s, ArH), 7.18-7.23 (1H, m, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.7, 21.1 (CH_3), 63.4 (CH_2), 126.7, 127.9, 131.3, 135.8, 136.2, 137.6 (ArC); LRMS (EI) *m/z* 136 (M^+, 52%), 135 (10), 134 (29), 133 (41), 121 (47), 119 (24), 118 (100), 117 (54), 115 (19), 107 (22), 105 (45), 103 (25), 93 (33), 91 (79), 79 (17), 78 (11), 77 (39), 65 (14), 51 (15).

3-[(2-Hydroxymethyl-5-methyl)phenyl]pentan-3-ol (23b): Yellow oil; R_f = 0.32 (hexane/EtOAc: 2/1); IR ν (film) 3340-3285 (OH), 2963, 2929, 2879 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (6H, t, J = 7.4 Hz, CH_3), 1.52-1.60 (4H, m, C$H_2$$CH_3$), 2.33 (3H, s, Ar$CH_3$), 2.82 (2H, s, Ar$CH_2$), 4.53 (2H, s, C$H_2$OH), 6.94 (1H, s, ArH), 7.02 (1H, d, J = 7.55 Hz, ArH), 7.21 (1H, d, J = 7.55 Hz, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.2, 21.3 (CH_3), 30.9, 40.6, 63.1 (CH_2), 74.3 (C), 127.7, 130.8, 132.8, 136.1, 137.3, 137.7 (ArC); LRMS (EI) *m/z* 204 [(M^+-H_2O) 2%], 186 (20), 184 (21), 175 (61), 171 (12), 169 (33), 157 (55), 153 (11), 143 (20), 142 (24), 141 (20), 128 (15), 119 (29), 118 (100), 117 (22), 115 (18), 91 (14), 57 (23); HRMS (EI) calcd for $C_{14}H_{20}O$ [M^+-H_2O] 204.1514, found 204.1494.

Double lithiation of phthalans 5. Preparation of compounds 10, 16 and 17. General procedure.

To a blue suspension of lithium powder (72 mg, 10.4 mmol) and a catalytic amount of DTBB (34 mg, 0.13 mmol) in dry THF (3 mL) under argon was added dropwise a solution of the corresponding phthalan **5** (1 mmol) in THF (0.5 mL) at -78 ºC, and the resulting mixture was stirred for 2 h at the same temperature. Then, the corresponding carbonyl compound was added dropwise (1.1 mmol) at -78 ºC and stirring was continued for 20 min. After that, the reaction mixture was allowed to rise to 0ºC and stirring was continued for 1 h at this temperature. Then, the reaction mixture was cooled down to -78 ºC and the carbonyl compound (1.1 mmol) was added dropwise. Finally it was hydrolyzed with water (4 mL), extracted with EtOAc (3 × 15 mL), dried over anhydrous $MgSO_4$ and evaporated (15 Torr). The residue was purified by column chromatography (silica gel, hexane/ethyl acetate) to yield pure products **10**, **16** and **17**. Yields are given in Table 2. Physical, analytical and spectroscopic data follow.

1-[2-(1-Hydroxycyclohexyl)-6-(hydroxymethyl)benzyl]cyclohexanol (10): White solid; mp 206-207 ºC

(pentane/CH_2Cl_2); R_f = 0.21 (hexane/EtOAc: 2/1); IR ν (KBr) 3420-3350 (OH), 3063, 3020, 2928, 2853, 1034 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.26-1.37 (4H, m, 2×CH_2), 1.38-1.93 (14H, m, 7×CH_2), 2.01-2.05 (2H, m, CH_2), 2.61 (2H, s, $ArCH_2$), 4.72 (2H, s, CH_2OH), 7.18 (1H, t, J = 7.7 Hz, ArH), 7.32 (1H, d, J = 7.0 Hz, ArH), 7.72 (1H, d, J = 8.0 Hz, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.7, 22.3, 25.6, 37.9, 64.3 (CH_2), 74.4, 77.4 (CH), 125.2, 125.6, 126.7, 135.4, 140.9, 146.5 (ArC); LRMS (EI) *m/z* 220 {M^+-[$(CH_2)_5$COH], 9%}, 202 (24), 159 (12), 150 (13), 149 (100), 147 (46), 143 (11), 129 (15), 128 (13), 114 (13), 91 (14), 77 (11), 55 (14); HRMS (EI) calcd for $C_{14}H_{20}O_2$ [M^+-$(CH_2)_5$COH] 220.1463, found 220.1457.

3-[3-(2-Ethyl-2-hydroxybutyl)-4-(hydroxymethyl)phenyl]pentan-3-ol (16a): White solid; mp 90-91 ºC (pentane/CH_2Cl_2); R_f = 0.37 (hexane/EtOAc: 1/1); IR ν (KBr) 3375-3300 (OH), 2964, 2937, 2878 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.76 (6H, t, J = 7.4 Hz, 2×$CH_2C\mathit{H}_3$), 0.94 (6H, t, J = 7.5 Hz, 2×$CH_2C\mathit{H}_3$), 1.43-1.62 (4H, m, 2×CH_2CH_3), 1.73-1.89 (4H, m, 2×CH_2CH_3), 2.88 (2H, s, $ArCH_2$), 4.57 (2H, s, CH_2OH), 7.15 (1H, d, J = 1.7 Hz, ArH), 7.21 (1H, dd, J = 8.4, 1.9 Hz, ArH), 7.30 (1H, d, J = 1.9 Hz, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.9, 8.2 (CH_3), 31.1, 35.0, 41.1, 63.1 (CH_2), 75.0, 77.3 (C), 124.2, 129.5, 130.5, 135.7, 138.5, 145.3 (ArC); LRMS (EI) *m/z* 247 [(M^+-Et-H_2O), 20%], 191 (15), 190 (85), 179 (12), 161 (57), 159 (12), 134 (15), 133 (34), 105 (10), 91 (11), 87 (16), 57 (100); HRMS (EI) calcd for $C_{16}H_{23}O_2$ [M^+-Et-H_2O] 247.1693, found 247.1702.

3-[4-(2-Ethyl-2-hydroxybutyl)-3-(hydroxymethyl)phenyl]pentan-3-ol (17a): White solid; mp 119-120 ºC (pentane/CH_2Cl_2); R_f = 0.27 (hexane/EtOAc: 1/1); IR ν (KBr) 3390-3310 (OH), 3027, 2966, 2938, 2879 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.76 (6H, t, J = 7.4 Hz, 2×CH_3), 0.95 (6H, t, J = 7.4 Hz, 2×CH_3), 1.50-1.64 (4H, m, 2×CH_2CH_3), 1.79-1.86 (4H, m, 2×CH_2CH_3), 2.86 (2H, s, $ArCH_2$), 4.60 (2H, s, CH_2OH), 7.11 (1H, d, J = 8.05 Hz, ArH), 7.24-7.26 (1H, m, ArH), 7.35-7.37 (1H, m, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.1, 8.2 (CH_3), 31.1, 34.8, 40.3, 63.9 (CH_2), 75.0, 77.4 (C), 125.0, 128.0, 131.9, 134.0, 140.2, 144.8 (ArC); LRMS (EI) *m/z* 247 [(M^+-Et-H_2O), 29%], 191 (15), 190 (100), 179 (24), 172 (11), 162 (12), 161 (84), 148 (10), 134 (18), 133 (41), 105 (14), 91 (13), 87 (22), 57 (98); HRMS (EI) calcd for $C_{16}H_{23}O_2$ [M^+-Et-H_2O] 247.1693, found 247.1689.

1-[5-(1-Hydroxycyclohexyl)-2-(hydroxymethyl)benzyl]cyclohexanol (16b): White solid; mp 166-167 ºC (pentane/CH_2Cl_2); R_f = 0.27 (hexane/EtOAc: 1/1); IR ν (KBr) 3390-3315 (OH), 2931, 2854, 1022 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.31-1.57 (10H, m, 5×CH_2), 1.71-1.85 (10H, m, 5×CH_2), 2.88 (2H, s, $ArCH_2$), 4.64 (2H, s, CH_2OH), 7.29-7.34 (3H, m, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.2, 26.7, 27.0, 38.7, 39.7, 63.5 (CH_2), 72.4, 73.8 (CO), 123.9, 129.8, 130.2, 136.9, 139.4, 150.0 (ArC); LRMS (EI) *m/z* 282 [(M^+-2H_2O), 22%], 264 (10), 202 (19), 185 (18), 184 (100), 155 (11), 141 (20), 129 (10), 128 (11); HRMS (EI) calcd for $C_{20}H_{26}O$ [M^+-2H_2O] 282.1984, found 282.1951.

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= 1.097 Mg m^{-3}; λ = 0.71073 Å; μ = 0.073 mm^{-1}; $F(000)$ = 1296; T = 23±1 °C. Data collection was performed on a Bruker Smart CCD diffractometer, based on three ω-scan runs (starting = -34°) at values ϕ =0°, 120°, 240° with the detector at 2θ =-32°. For each of these runs, 606 frames were collected at 0.3° intervals and 10 s per frame. An additional run at ϕ=0° of 100 frames was collected to improve redundancy. The diffraction frames were integrated using the program SAINT[16] and the integrated intensities were corrected for Lorentz-polarization effects with SADABS.[17] The structure was solved by direct methods[18] and refined to all 3247 unique F_o^2 by full matrix least squares.[18] All the hydrogen atoms were placed at idealized positions and refined as rigid atoms. Final $wR2$=0.1194 for all data and 393 parameters; $R1$=0.0436 for 2493 F_o>4σ(F_o).

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