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Regioselective reductive opening of substituted phthalans: synthetic applications

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Dedicated to Professors Ricardo Riguera and José Manuel Saá on occasion of their 60th birthday

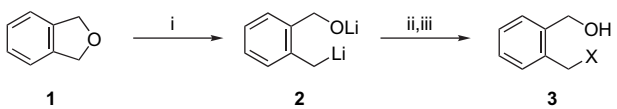
Abstract

The reductive opening of substituted phthalans **6**, **11**, **12**, **20**, **21** and **28** with lithium and a catalytic amount of DTBB leads to the formation of corresponding functionalised organolithium intermediates **8**, **15**, **16**, **23**, **25** and **29**+**30** in a regioselective manner. The further reaction of these dianions with different electrophiles, mainly carbonyl compounds, gives the expected functionalised benzylic alcohols **9**, **17**, **18**, **24**, **26** and **31**+**32**. The observed stereochemistry can be easily explained taking into account the values of the electron densities deduced by semiempirical PM3 calculations.

Keywords: Substituted phthalans; DTBB-catalysed lithiation; Reductive ring opening; S_E reaction

1. Introduction

For the generation of functionalised organolithium compounds,[1] besides the normal methodologies used to prepare simple organolithium,[2] some new procedures have been developed in the last few years.[3] Among them, the reductive ring opening of heterocycles[4] using an arene-catalysed lithiation[5] has been used extensively to prepare oxygen-, nitrogen- or sulfur-containing organolithium intermediates. As an example, phthalan (**1**) can be easily opened with the mentioned methodology to give the expected lithiated intermediate **2** through a favoured benzylic cleavage, which by reaction with electrophilic reagents gave, after hydrolysis, the corresponding functionalised benzyl alcohols **3** (Scheme 1).[6]

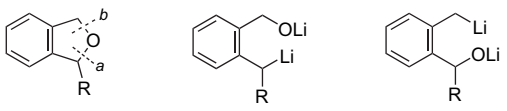


1 **2** **3**

Scheme 1. Reagents and conditions: (i) Li, DTBB cat., THF, rt; (ii) electrophile (E), −78 °C to rt; (iii) H_2O.

When the heterocyclic ring in phthalan itself bears substituents, its reductive ring opening can take place following two regiochemical ways. For instance in compounds **4**, depending on the nature of the group R, the opening takes place giving the most stable intermediate **5a** (cleavage *a* for R=Ph) or **5b** (cleavage *b* for R=Me, ^{n}Bu)[7] (Chart 1).

In this paper we study the regiochemistry of the reductive ring opening of non-symmetrically substituted phthalans possessing different groups attached to the aromatic ring, explaining the obtained experimental results in the basis of simple theoretical calculations on electron density for the intermediate radical-anions or dianions derived from the starting heterocycles.[8]



4 **5a** **5b**

Chart 1.

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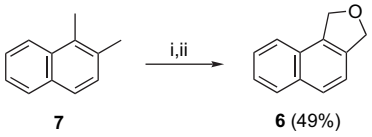
2. Results and discussion

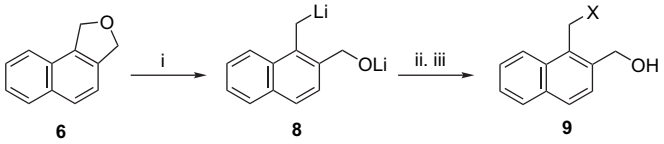
2.1. 1,3-Dihydronaphtho[2,1-c]furan (6)

The benzophthalan **6** was prepared in 49% overall yield starting from commercially available 1,2-dimethylnaphthalene **7** by successive radical bromination[9] and cyclisation under basic conditions[10] (Scheme 2).



Scheme 2. Reagents and conditions: (i) 2.2 equiv NBS, AIBN cat., $CHCl_3$ reflux; (ii) 5 M NaOH, 2,6-lutidine cat., dioxane reflux.

The lithiation of the benzophthalan **6** with an excess of lithium (1:10 molar ratio) and a catalytic amount of 4,4′-di-*tert*-butylbiphenyl (DTBB; 5 mol %) in THF at temperatures ranging from −78 to 50 °C for 3 h led to a solution of the corresponding intermediate **8**, which by reaction with different electrophiles [E=H_2O, ^{t}BuCHO, PhCHO, Me_2CO, Et_2CO, (n-$C_5H_{11})_2CO$, $(CH_2)_5CO$, $(EtO)_2CO$] at −78 °C gave, after hydrolysis with water, the corresponding products **9** (Scheme 3 and Table 1). Only when water was used as electrophile, the regioisomer **9a′** (involving the intermediate **8′**) was isolated in 14% yield (Chart 2 and Table 1, entry 1 and footnote b). In the other cases we never detected the corresponding regioisomers of type **9′** in the reaction crudes. The use of diethyl carbonate as electrophiles led, after work-up, to the direct formation of the corresponding δ-lactone **9h** (Chart 2 and Table 1, entry 8).



Scheme 3. Reagents and conditions: (i) Li excess (10 equiv), DTBB (5 mol %), THF, −78 to −50 °C; (ii) E=H_2O, ^{t}BuCHO, PhCHO, Me_2CO, Et_2CO, (n-$C_5H_{11})_2CO$, $(CH_2)_5CO$, $(EtO)_2CO$, −78 °C; (iii) H_2O, −78 °C to rt.

Table 1
Preparation of compounds **9**

Entry	Electrophile (E)	Product		
		Compound no.	X	Yield[a] (%)
1	H_2O	**9a**	H	85[b]
2	^{t}BuCHO	**9b**	^{t}BuCHOH	61
3	PhCHO	**9c**	PhCHOH	54
4	Me_2CO	**9d**	Me_2COH	50
5	Et_2CO	**9e**	Et_2COH	51
6	(n-$C_5H_{11})_2CO$	**9g**	(n-$C_5H_{11})_2COH$	42
7	$(CH_2)_5CO$	**9g**	$(CH_2)_5COH$	50
8	$(EtO)_2CO$	**9h**	—[c]	42

[a] Isolated yield after column chromatography (silica gel, hexane/ethyl acetate) based on the starting material **6**.
[b] Compound **9a′** was also obtained in 14% yield.
[c] See structure **9h** in Chart 2.

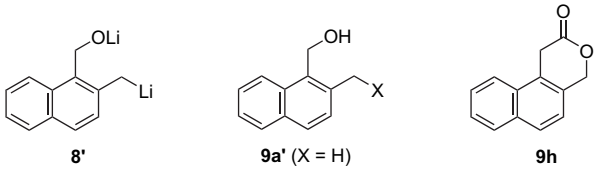


Chart 2.

Concerning the observed regioselectivity (cleavage at the C3−O bond), it can be easily explained considering the electron density in the aromatic systems of the resulting anionic intermediates (either in the radical-anion or the dianion) through a single electron transfer (SET) from the reduction reagent[11] to the substrate. The reductive cleavage at the benzylic carbon−oxygen bond takes place at the position bonded to the carbon atom of the aromatic ring with higher electron density in both the radical-anion and the dianion.[12] Thus, the almost exclusive generation of the intermediate **8** can be explained taking into account the values of the Mulliken charges for the mono or dianion species $[\mathbf{6}]^{2-(\cdot-)}$ deduced by semiempirical PM3 calculations. The favoured dianion of type $[\mathbf{6'}]^{2-}$ leads to the corresponding alkoxide **6″**, which after aromatisation gives the intermediate **8** (Chart 3 and Scheme 3).

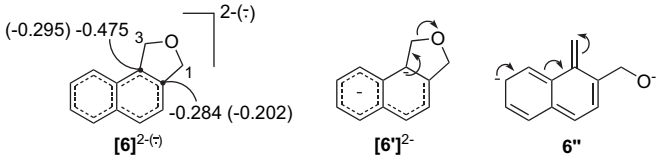
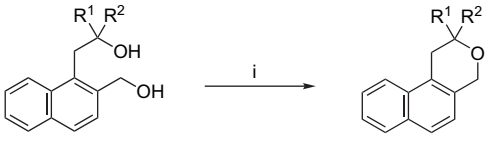


Chart 3.

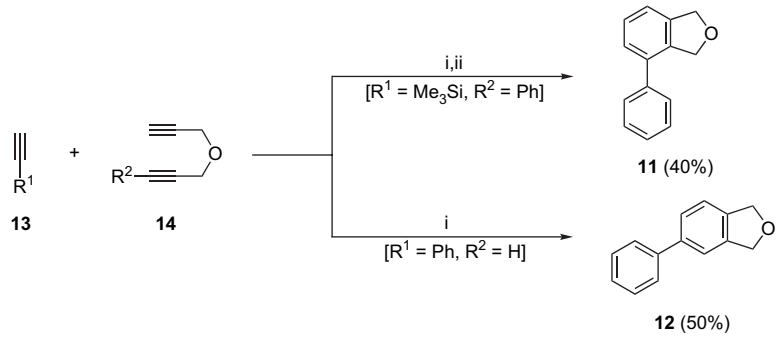
Diols of type **9** derived from carbonyl compounds (X=R^1R^2COH) could be good candidates for a new cyclisation by intramolecular dehydration. This reaction was exemplified treating diols **9c** and **9e** with 85% phosphoric acid under toluene reflux, so the expected six-membered cyclic ethers **10** were formed in good yields (Scheme 4).



Scheme 4. Reagents and conditions: (i) 85% H_3PO_4, PhMe reflux.

2.2. 4- and 5-Phenylphthalans (11, 12)

Starting phenyl substituted phthalans **11** and **12** were prepared according to variants of methodologies already described in the literature,[13] as shown in Scheme 5. Wilkinson's catalyst promoted cyclotrimerisation of alkynes **13** and diynes **14**,[14] which afforded the corresponding phenylated phthalans **11** and **12** with moderate yields (Scheme 5).



Scheme 5. Reagents and conditions: (i) $Rh(PPh_3)_3Cl$ cat., PhMe, 60 (for **11**) or 0 °C (for **12**); (ii) TFA, CH_2Cl_2, rt.

The lithiation of compounds **11** and **12** under the conditions described in Scheme 3 (but performing the lithiation at −78 °C) led to the intermediates **15** and **16**, respectively, also in a regioselective manner. After reaction with some electrophiles [E=H_2O, ^{t}BuCHO, PhCHO, Et_2CO, $(CH_2)_5CO$] and final hydrolysis with water, the corresponding functionalised benzylic alcohols **17** and **18**, respectively, were obtained (Scheme 6 and Table 2). As Table 2 shows, except for the hydrolysis (Table 2, entries 1 and 5), in the other cases yields are very modest, the main reaction product being **17a** and **18a**, resulting from a hydrogen abstraction of intermediates **15** and **16** from the reaction medium[15] under the assayed reaction conditions. In any case we could find in the reaction crudes any trace of the other possible regioisomers.[16]

Also in the case of reductive ring opening of phthalans **11** and **12** the experimental results concerning regiochemistry can be explained considering the electron density of the carbon atoms both in the radical-anion and in the dianion obtained by simple semiempirical PM3 calculations. Based on the theoretical data, both anions $[\mathbf{11}]^{2-(\cdot-)}$ and $[\mathbf{12}]^{2-(\cdot-)}$ should lead to cleavage of C3−O and C1−O bonds, respectively, so the most stable dianions $[\mathbf{11}']^{2-}$ and $[\mathbf{12}']^{2-}$ gave the dearomatised intermediates **11″** and **12″**, respectively, which after recovering the aromatisation afforded the real intermediates of the reaction, namely **15** and **16**, before reacting with the electrophiles (Chart 4).

Also in the case of compounds **18c** and **18d** we performed the corresponding cyclisation using the same protocol as for compounds **10** (Scheme 4: 85% H_3PO_4, PhMe reflux), so substituted isochromans **19c**,**d** were obtained (Chart 5).

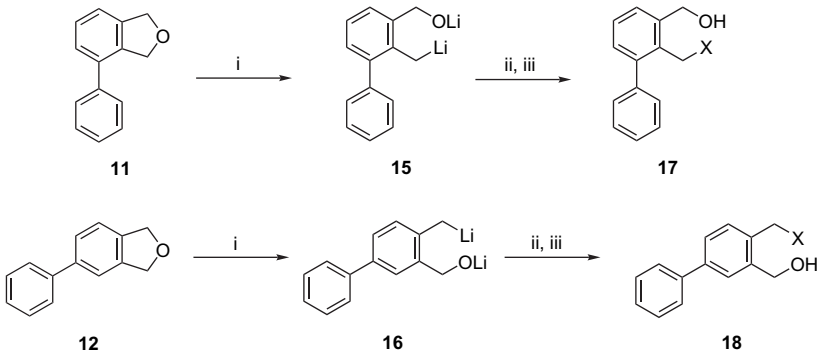
2.3. Alkoxy substituted phthalans (*20*, *21*)

4- and 5-Methoxyphthalans (**20**, **21**) were prepared from furfuryl alcohol (**22**) following the literature procedures.[14,17] For compound **20**, the starting alcohol **22** was transformed into its 5-dimethyl-*tert*-butylsilylated (TBS) derivative by successive treatment with ^{n}BuLi, TBSCl and pyridinium *p*-toluenesulfonate (PPTS); this compound was *O*-propargylated (propargyl bromide, NaH, DMF) and submitted to a $PtCl_2$-catalysed cyclisation[14] to give, after desilylation, 4-hydroxyphthalan, which was finally methylated (MeI, NaH).[18] In the case of the preparation of compound **21**, the furfuryl alcohol **22** was *O*-propargylated as above (to yield furfuryl propargyl ether) and then submitted to a $AuCl_3$-catalysed cyclisation[17] followed by final methylation as for the last step for compound **20** (Scheme 7).

Table 2
Preparation of compounds **17** and **18**

Entry	Starting material	Electrophile (E)	Product		
			Compound no.	X	Yield[a] (%)
1	**11**	H_2O	**17a**	H	95
2	**11**	^{t}BuCHO	**17b**	^{t}BuCHOH	25
3	**11**	PhCHO	**17c**	PhCHOH	32
4	**11**	$(CH_2)_5CO$	**17d**	$(CH_2)_5COH$	26
5	**12**	H_2O	**18a**	H	95
6	**12**	^{t}BuCHO	**18b**	^{t}BuCHOH	58
7	**12**	PhCHO	**18c**	PhCHOH	18
8	**12**	Et_2CO	**18d**	Et_2COH	25

[a] Isolated yield after column chromatography (silica gel, hexane/ethyl acetate) based on the starting materials **11** and **12**.



Scheme 6. Reagents and conditions: (i)−(iii) as in Scheme 3 but performing the step (i) at −78 °C.

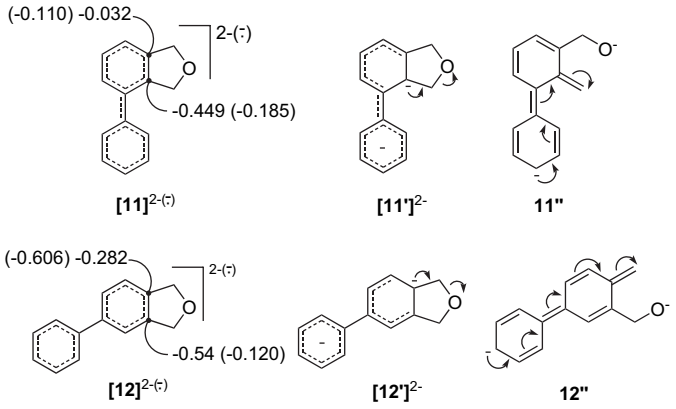


Chart 4.

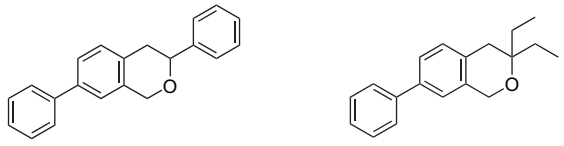
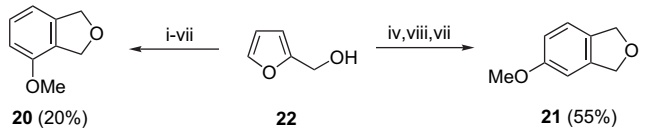


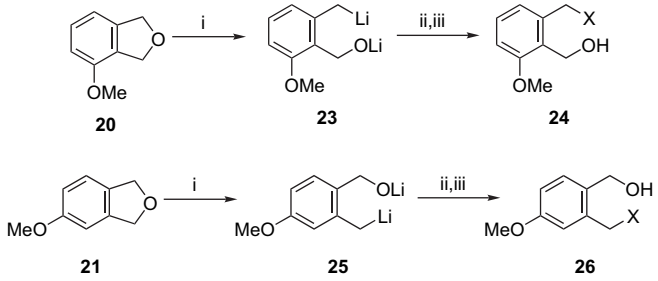
Chart 5.



Scheme 7. Reagents and conditions: (i) 2 ^{n}BuLi, −30 °C; (ii) 2 TBSCl, rt; (iii) PPTS, MeOH, 55 °C; (iv) HC≡CCH$_2$Br, NaH, DMF, rt; (v) $PtCl_2$ cat., MeCO, 60 °C; (vi) TFA, CH_2Cl_2, rt; (vii) NaH, MeI, 0 °C; (viii) $AuCl_3$ cat., MeOH, rt.

We then applied the DTBB-catalysed lithiation shown in Schemes 3 and 6 to the methoxy derivatives **20** and **21**. For the 4-substituted derivative (**20**) the cleavage took place at the C1−O bond giving the intermediate **23** and the final products **24**, after reaction with the electrophiles (E=HO, ^{t}BuCHO) and hydrolysis (Scheme 8 and Table 3, entries 1 and 2). The same reaction applied to compound **21** gave opening of the phthalan at the C3−O bond, so intermediate **25** was involved reacting with several electrophiles (E=H_2O, ^{t}BuCHO, PhCHO, Et_2CO) to give products **26** (Scheme 8 and Table 3, entries 3−6).

Semiempirical PM3 calculations of the Mulliken charge of radical-anions and dianions $[\mathbf{20}]^{2-(\cdot-)}$ and $[\mathbf{21}]^{2-(\cdot-)}$ gave us the values shown in Chart 6. Whereas for $[\mathbf{21}]^{2-(\cdot-)}$ the experimental regioselectivity is in agreement with calculations, undergoing cleavage of the C3−O bond and so giving intermediates $[\mathbf{21}']^{2-}$ and **21**″ before suffering aromatisation to afford the species **25**, in the case of both the dianion and the radical-anion of $[\mathbf{20}]^{2-(\cdot-)}$ the expected bond to be broken would be C3−O. However, the experimental result indicates that the only cleavage observed was C1−O, giving finally the intermediate **23** (trough species $[\mathbf{20a}']^{2-}$ and **20**″). The only explanation for this disagreement should be found in the fact that in the predicted (and not formed) intermediate $[\mathbf{20b}']^{2-}$ there is a strong steric repulsion between the negative charge at the 3a position and the electron lone pairs at the oxygen atom of the methoxy group, this effect working in opposite direction than the electron density resulting from the calculations.



Scheme 8. Reagents and conditions: (i)−(iii) as in Scheme 6.

Table 3
Preparation of compounds **24** and **26**

Entry	Starting material	Electrophile (E)	Product		
			Compound no.	X	Yield[a] (%)
1	**20**	H_2O	**24a**	H	80
2	**20**	^{t}BuCHO	**24b**	^{t}BuCHOH	45
3	**21**	H_2O	**26a**	H	90
4	**21**	^{t}BuCHO	**26b**	^{t}BuCHOH	38
5	**21**	PhCHO	**26c**	PhCHOH	55
6	**21**	Et_2CO	**26d**	Et_2COH	26

[a] Isolated yield after column chromatography (silica gel, hexane/ethyl acetate) based on the starting materials **20** and **21**.

The cyclisation of compounds of type **24** or **26** with X=R^1R^2COH was tested using compound **26d**. Its treatment under the same conditions as for compounds **10** or **19** (85% H_3PO_4, PhMe reflux) failed. However, the mesylation under basic conditions[19] gave directly the expected compound **27d** in moderate yield (Scheme 9).

In the final part of this study we considered the reductive double ring opening of the diphthalan **28**, easily prepared in 30% yield from commercially available 1,2,4,5-tetrakis(bromomethyl)benzene by basic treatment. Actually, we wanted to know the influence of the first ring opening in the second one. Thus, using the same lithiation procedure shown above, we observed always a mixture of products resulting from a mono or double ring opening, the second one working at the distant C−O bond respect to the first cleavage, so intermediates **29** and **30** were generated. Final reaction of these species with water or benzaldehyde gave, after hydrolysis, the corresponding mixture of compounds **31a**+**32a** (52%) and **31b**+**32b** (31%), respectively, the major component (**31**) being always the one resulting from a mono opening (Scheme 10).

3. Conclusions

From the results shown here we conclude that the reductive ring opening of different phthalan derivatives **6**, **11**, **12**, **20**, **21** and **28** with an excess of lithium and a catalytic amount of DTBB takes place in a regioselective manner. The observed regioselectivity can be explained taking into account the electron density of either the dianion or the radical-anion responsible for the reductive cleavage, in all cases studied except for the 4-methoxyphthalan **20** for which we observed the contrary

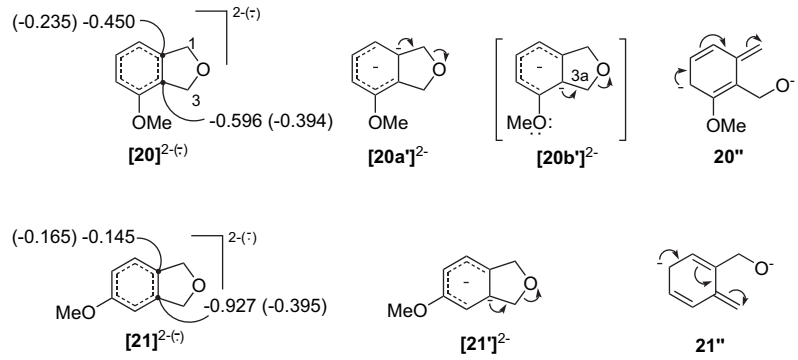
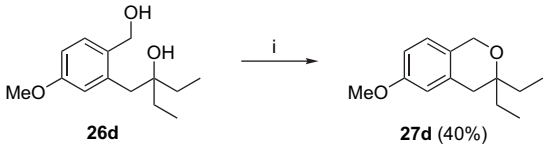
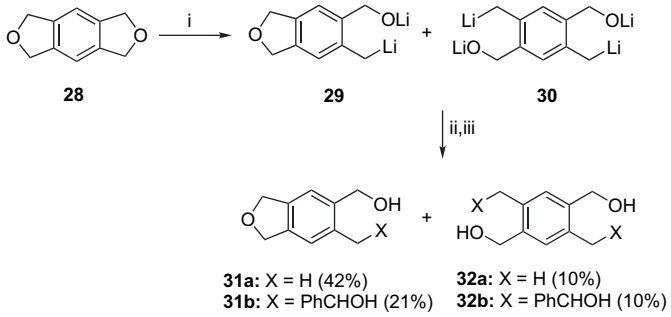


Chart 6.



Scheme 9. Reagents and conditions: (i) MsCl, Et_3N, CH_2Cl_2, 0 °C to rt.



Scheme 10. Reagents and conditions: (i)–(iii) as in Scheme 6 but performing step (i) at −78 to 0 °C.

regiochemistry, that can be explained considering the repulsion between the negative charge at the phthalan ring and the electron lone pairs at the methoxy group. The reaction of the resulting organolithium intermediates with different electrophiles allows the regioselective synthesis of a series of functionalised aromatic compounds **9**, **17**, **18**, **24**, **26**, **31** and **32**.

4. Experimental

4.1. General

For general experimental information, see Ref. 19. All commercially available reagents (Acros, Aldrich, Fluka) were used without further purification. Melting points were obtained with a Reichert Thermovar apparatus. The HRMS (EI) were performed by the Technical Services of the University of Alicante on a Finnigan MAT 95S apparatus.

4.2. Preparation of 1,3-dihydronaphtho[2,1-c]furan (*6*)

To a 1,2-dimethylnaphthalene (**7**, 1.092 g, 7.0 mmol) solution in chloroform (10 mL) was added *N*-bromosuccinimide (NBS, 3.026 g, 17.0 mmol). A small amount of azabisisobutyronitrile (AIBN, 5.0 mg) was added every 30 min to the reaction mixture, which was stirred at 80 °C for 6 h. After that the reaction mixture was allowed to cool down to room temperature and a white solid was removed by filtration. Chloroform was removed under vacuum (15 Torr) and the resulting residue was purified by column chromatography (silica gel, hexane) to yield pure 1,2-bis(bromomethyl)naphthalene (1.32 g, 60%): white solid; mp 147–148 °C (hexane/dichloromethane); R_f=0.32 (hexane/ethyl acetate 10:1); ν (KBr) 3088 (ArH), 1091 cm^{-1} (C–Br); δ_H 4.74 (2H, s, CH_2Br), 5.08 (2H, s, CH_2Br), 7.40 (1H, d, J=8.4 Hz, ArH), 7.49–7.54 (1H, m, ArH), 7.59–7.64 (1H, m, ArH), 7.78–7.84 (2H, m, ArH), 8.11 (1H, d, J=8.4 Hz, ArH); δ_C 25.4, 30.5 (CH_2), 123.6, 126.7, 127.3, 127.8, 128.7, 130.0, 131.4, 132.0, 133.8, 134.8 (ArC); *m/z* 316 (M^+, 5%), 314 (11), 235 (64), 233 (67), 155 (12), 154 (100), 153 (43), 152 (35), 151 (11), 77 (29), 76 (78), 75 (10).

To a 5 M aqueous NaOH solution (50 mL) was added a solution of 1,2-bis(bromomethyl)naphthalene (0.945 g, 3.0 mmol) in dioxane (5 mL). The resulting mixture was stirred at 80 °C for 15 h. After that the reaction mixture was allowed to cool down to room temperature, hydrolysed with 3 M HCl (90 mL), extracted with ethyl acetate (3×40 mL) and the organic layer was dried over anhydrous sodium sulfate and evaporated (15 Torr). The resulting residue was then purified by column chromatography (silica gel, hexane/ethyl acetate 20:1) to yield pure compounds **6** (0.408 g, 80%): colourless oil; R_f=0.33 (hexane/ethyl acetate 10:1); ν (film) 3056 cm^{-1} (ArH); δ_H 5.15 (2H, d, J=3.0 Hz, CH_2O), 5.33 (2H, d, J=3.0 Hz, CH_2O), 7.18 (1H, d, J=8.4 Hz, ArH), 7.30–7.42 (2H, m, ArH), 7.42 (3H, m, ArH), 7.61 (1H, d, J=8.4 Hz, ArH); δ_C 73.3, 74.7 (CH_2), 118.8, 123.6, 125.3, 126.4, 127.2, 127.9, 128.3, 132.6, 134.2, 135.7 (ArC); *m/z* 170 (M^+, 31%), 169 (13), 142 (37), 141 (100), 139 (17), 115 (29), 85 (11), 70 (20); HRMS: M^+, found: 170.0734, $C_{12}H_{10}O$ requires: 170.0732.

4.3. Lithiation of 1,3-dihydronaphtho[2,1-c]furan (*6*) and reaction with electrophiles. Isolation of compounds *9*: general procedure

To a cooled (−78 °C) blue suspension of lithium powder (72 mg, 10.4 mmol) and a catalytic amount of DTBB

(33.6 mg, 0.13 mmol) in THF (3 mL) was added dropwise a solution of compound **6** (118 mg, 0.7 mmol) in THF (0.5 mL) under argon and the mixture was stirred at temperatures ranging between −78 and −50 °C for 3 h. Then the corresponding electrophile was added dropwise (1.1 mmol, 0.5 mL in the case of H_2O) at −78 °C and, after 20 min at this temperature, the reaction mixture was hydrolysed with water (4 mL) allowing the temperature to rise to 20 °C, extracted with ethyl acetate (3×10 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 **9**. Yields are given in Table 1; physical, analytical and spectroscopic data as well as literature references for known compounds are as follows.

4.3.1. 2-Hydroxymethyl-1-methylnaphthalene (**9a**)[20]

Colourless oil; R_f=0.12 (hexane/ethyl acetate 10:1); ν (film) 3401 cm^{-1} (OH); δ_H 2.58 (3H, s, CH_3), 3.23 (1H, br s, OH), 4.78 (2H, s, CH_2OH), 7.34–7.44 (3H, m, ArH), 7.61 (1H, d, J=8.4 Hz, ArH), 7.71–7.74 (1H, m, ArH), 7.98 (1H, d, J=8.3 Hz, ArH); δ_C 13.9 (CH_3), 64.0 (CH_2OH), 124.1, 125.5, 126.0, 126.3, 126.4, 126.9, 128.4, 128.7, 135.3 (ArC); *m/z* 172 (M^+, 61%), 157 (16), 155 (20), 154 (100), 143 (18), 141 (24), 139 (13), 129 (48), 128 (49), 127 (15), 115 (30).

4.3.2. 1-Hydroxymethyl-2-methylnaphthalene (**9a′**)

White solid; mp 138–139 °C (hexane/dichloromethane); R_f=0.12 (hexane/ethyl acetate 10:1); ν (KBr) 3207 cm^{-1} (OH); δ_H 2.58 (3H, s, CH_3), 4.15 (1H, br s, OH), 5.13 (2H, s, CH_2OH), 7.31 (1H, d, J=8.4 Hz, ArH), 7.40–7.55 (2H, m, ArH), 7.71 (1H, d, J=8.40 Hz, ArH), 7.80 (1H, d, J=8.40 Hz, ArH), 8.17 (1H, d, J=8.4 Hz, ArH); δ_C 19.7 (CH_3), 58.4 (CH_2), 123.4, 124.9, 126.6, 128.5, 129.2, 132.3, 132.6, 132.7, 134.6 (ArC); *m/z* 172 (M^+, 100%), 157 (38), 155 (31), 154 (82), 153 (43), 152 (17), 143 (79), 141 (29), 129 (77), 128 (76), 115 (39), 77 (32), 76 (77), 70 (12).

4.3.3. 1-[2-(Hydroxymethyl)naphthalen-1-yl]-3,3-dimethylbutan-2-ol (**9b**)

Brown oil; R_f=0.43 (hexane/ethyl acetate 2:1); ν (film) 3364 (OH), 3053 cm^{-1} (ArH); δ_H 1.10 (9H, s, C(CH_3)$_3$), 3.12 (1H, dd, J=11.0, 3.3 Hz, ArC*H*H), 3.34 (2H, br s, OH), 3.52 (1H, dd, J=12.3, 1.9 Hz, C*H*OH), 3.63 (1H, dd, J=9.05, 2.0 Hz, ArCH*H*), 4.50 (1H, d, J=11.7 Hz, C*H*HOH), 4.95 (1H, d, J=11.7 Hz, CH*H*OH), 7.40–7.54 (3H, m, ArH), 7.69 (1H, d, J=8.4 Hz, ArH), 7.84 (1H, d, J=7.65 Hz, ArH), 7.97 (1H, d, J=8.1 Hz, ArH); δ_C 25.9 (CH_3), 29.9 (C), 36.0 (CH_2), 64.0 (CH_2OH), 78.7 (CHOH), 124.0, 125.6, 126.2, 127.3, 128.8, 129.1, 132.2, 134.0, 134.3, 137.8 (ArC); *m/z* 258 (M^+, 1%), 155 (28), 154 (100), 153 (13), 141 (11), 128 (10); HRMS: M^+-H_2O, found: 240.1474, $C_{17}H_{20}O$ requires: 240.1514.

4.3.4. 2-[2-(Hydroxymethyl)naphthalen-1-yl]-1-phenylethanol (**9c**)

Orange solid; mp 123–124 °C (hexane/dichloromethane); R_f=0.28 (hexane/ethyl acetate 2:1); ν (KBr) 3219 (OH), 3030, 3021 cm^{-1} (ArH); δ_H 1.59 (2H, br s, 2×OH), 3.54–3.61 (2H, m, CH_2CHOH), 4.62 (1H, t, J=11.0 Hz, C*H*OH), 5.06 (2H, dd, J=12.0, 3.0 Hz, CH_2OH), 7.30–7.60 (8H, m, ArH), 7.80 (1H, d, J=8.3 Hz, ArH), 7.90 (1H, d, J=7.95 Hz, ArH), 8.13 (1H, d, J=8.1 Hz, ArH); δ_C 38.4 (CH_2), 64.0 (CH_2OH), 74.1 (CH), 124.0, 125.7, 125.8, 126.5, 127.3, 127.9, 128.2, 128.4, 128.7, 129.0, 129.2, 132.2, 133.0, 134.0, 137.8, 144.7 (ArC); *m/z* 260 [(M^+-H_2O), 1%], 228 (100), 154 (70); HRMS: M^+-H_2O, found: 260.1216, $C_{19}H_{16}O$ requires: 260.1201.

4.3.5. 1-[2-(Hydroxymethyl)naphthalen-1-yl]-2-methylpropan-2-ol (**9d**)

Orange oil; R_f=0.12 (hexane/ethyl acetate 2:1); ν (film) 3355 (OH), 3064 cm^{-1} (ArH); δ_H 1.26 (6H, s, 2×CH_3), 1.84 (2H, br s, OH), 3.51 (2H, s, CH_2COH), 4.82 (2H, s, CH_2OH), 7.46–7.83 (5H, m, ArH), 8.09 (1H, d, J=6.3 Hz, ArH); δ_C 14.3 (CH_3), 31.2 (CH_2), 60.5 (CH_2OH), 71.9 (CHOH), 125.5, 125.8, 127.7, 128.8, 128.9, 131.0, 132.5, 133.5, 133.7, 138.4 (ArC); *m/z* 212 [(M^+-H_2O), 5%], 155 (17), 154 (100), 153 (19), 141 (11); HRMS: M^+-H_2O, found: 212.1215, $C_{15}H_{16}O$ requires: 212.1201.

4.3.6. 3-{[2-(Hydroxymethyl)naphthalen-1-yl]methyl}pentan-3-ol (**9e**)

White solid; mp 95–96 °C (hexane/dichloromethane); R_f=0.26 (hexane/ethyl acetate 2:1); ν (KBr) 3373 (OH), 3071, 3060 cm^{-1} (ArH); δ_H 0.91–1.03 (6H, m, 2×CH_3), 1.61–1.82 (6H, m, 2×CH_2CH$_3$, 2×OH), 3.44 (2H, s, CH_2CH), 4.74 (2H, s, CH_2OH), 7.25–7.53 (3H, m, ArH), 7.73 (1H, d, J=8.4 Hz, ArH), 7.81 (1H, dd, J=7.2, 2.3 Hz, ArH), 8.08 (1H, d, J=7.95 Hz, ArH); δ_C 8.2 (CH_3), 36.3 (CH_2), 63.9 (CH_2OH), 75.6 (COH), 125.4, 125.5, 125.8, 127.6, 128.8, 128.9, 132.3, 133.6, 133.8, 138.7 (ArC); *m/z* 240 [(M^+-H_2O), 11%], 211 (31), 155 (21), 154 (100), 153 (28), 57 (24); HRMS: M^+-H_2O, found: 240.1533, $C_{17}H_{20}O$ requires: 240.1514.

4.3.7. 6-{[2-(Hydroxymethyl)naphthalen-1-yl]methyl}undecan-6-ol (**9f**)

Orange oil; R_f=0.40 (hexane/ethyl acetate 2:1); ν (film) 3363 (OH), 3054 cm^{-1} (ArH); δ_H 0.85–0.91 (22H, m, 2×CH_3, 8×CH_2), 2.04 (2H, br s, 2×OH), 3.44 (2H, br s, CH_2COH), 4.70 (2H, br s, CH_2OH), 7.45–7.55 (3H, m, ArH), 7.75 (1H, d, J=8.3 Hz, ArH), 7.81 (1H, dd, J=7.5, 1.9 Hz, ArH), 8.08 (1H, d, J=8.0 Hz, ArH); δ_C 14.2 (CH_3), 22.8, 22.9, 29.6, 30.2, 36.9 (CH_2), 64.0 (CH_2OH), 75.5 (CHOH), 125.4, 125.5, 125.7, 127.7, 128.7, 128.9, 132.3, 133.7, 133.8, 138.8 (ArC); *m/z* 324 [(M^+-H_2O), 2%], 253 (16), 155 (17), 154 (100), 153 (10); HRMS: M^+-H_2O, found: 324.2469, $C_{23}H_{32}O$ requires: 324.2453.

4.3.8. 1-{[2-(Hydroxymethyl)naphthalen-1-yl]methyl}cyclohexanol (**9g**)

Pale yellow solid; mp 131–132 °C (hexane/dichloromethane); R_f=0.21 (hexane/ethyl acetate 2:1); ν (KBr) 3382 (OH), 3059 cm^{-1} (ArH); δ_H 1.50–1.71 (12H, m, 10×CH_2, 2×OH), 3.45 (2H, s, CH_2COH), 4.80 (2H, s, CH_2OH), 7.46–7.57 (3H, m, ArH), 7.79 (1H, d, J=10.0 Hz, ArH), 7.83 (1H, d, J=7.65 Hz, ArH), 8.13 (1H, d, J=8.1 Hz, ArH); δ_C 22.0, 25.7, 40.2 (CH_2), 64.1 (CH_2OH), 72.5 (CHOH), 125.5, 125.7, 127.7,

128.4, 128.7, 128.9, 129.0, 129.2, 132.0, 133.7, 138.7 (ArC); *m/z* 252 [(M^+-H_2O), 5%], 155 (17), 154 (100), 153 (15); HRMS: M^+-H_2O, found: 252.1508, $C_{18}H_{20}O$ requires: 252.1514.

*4.3.9. 1H-Benzo[f]isochroman-2(4H)-one (**9h**)*

Brown oil; R_f=0.36 (hexane/ethyl acetate 2:1); ν (film) 1715 (C=O), 1264 cm^{-1} (C–O); δ_H 2.70 (2H, s, CH_2CO), 4.91 (1H, s, OCH_2), 7.47–7.61 (3H, m, ArH), 7.72 (1H, d, *J*=8.4 Hz, ArH), 7.80–7.84 (1H, m, ArH), 7.90 (1H, d, *J*=8.1 Hz, ArH); δ_C 64.3, 70.7 (CH_2), 122.3, 124.3, 125.7, 126.5, 127.4, 128.6, 129.1, 130.2, 131.0, 133.3 (ArC), 177.5 (CO_2); *m/z* 198 (M^+, 55%), 154 (100), 153 (61), 141 (19), 114 (17), 76 (17); HRMS: M^+, found: 198.0670, $C_{13}H_{10}O_2$ requires: 198.0681.

*4.4. Cyclisation of diols **9c** and **9e**. Isolation of benzoisochromans **10c** and **10e**: general procedure*

To a solution of the corresponding diol **9** (0.2 mmol) in toluene (2 mL) was added 85% phosphoric acid (0.2 mL). The reaction mixture was heated at 110 °C for 4 h. Then toluene was removed by distillation and the resulting residue was hydrolysed with water (5 mL), extracted with ethyl acetate (3×10 mL), dried over anhydrous $MgSO_4$ and evaporated (15 Torr). The residue was purified by column chromatography (silica gel, hexane) to yield pure products **10**. Yields are given in Scheme 4; physical, analytical and spectroscopic data are as follows.

*4.4.1. 2-Phenyl-2,4-dihydrobenzo[f]isochroman (**10c**)*

Pale yellow oil; R_f=0.25 (hexane/ethyl acetate 30:1); ν (film) 3088, 3059, 3027 (ArH), 1095 cm^{-1} (COC); δ_H 3.21–3.28 (1H, m, ArC*H*HCH), 3.43 (1H, d, *J*=10.6 Hz, ArCH*H*CH), 4.74–4.90 (1H, m, C*H*OH), 5.09–5.18 (2H, m, CH_2O), 7.17–7.57 (7H, m, ArH), 7.73 (1H, d, *J*=6.2 Hz, ArH), 7.80–7.99 (1H, m, ArH); δ_C 33.2 (CH_2), 64.3 (CH_2O), 69.3 (CHO), 122.6, 125.6, 126.2, 126.7, 127.8, 128.0, 129.2, 129.3, 130.2, 131.9, 132.5, 136.4, 142.5 (ArC); *m/z* 260 (M^+, 4%), 155 (14), 154 (100), 153 (27), 152 (13); HRMS: M^+, found: 260.1209; $C_{19}H_{16}O$ requires: 260.1201.

*4.4.2. 2,2-Diethyl-2,4-dihydrobenzo[f]isochroman (**10e**)*

Yellow oil; R_f=0.29 (hexane/ethyl acetate 30:1); ν (film) 3057 (ArH), 1090 cm^{-1} (COC); δ_H 0.98 (6H, t, *J*=7.4 Hz, 2×CH_3), 1.54–1.61 (2H, m, C$H_2$$CH_3$), 1.77 (2H, q, *J*=7.1 Hz, C$H_2$$CH_3$), 2.99 (2H, s, C$H_2$CO), 4.87 (2H, s, CH_2O), 7.11 (1H, d, *J*=8.4 Hz, ArH), 7.46–7.53 (2H, m, ArH), 7.67 (1H, d, *J*=8.4 Hz, ArH), 7.83 (1H, d, *J*=8.0 Hz, ArH), 7.94 (1H, d, *J*=8.1 Hz, ArH); δ_C 7.9 (CH_3), 27.8, 32.6 (CH_2), 63.1 (CH_2O), 75.2 (CO), 122.4, 122.7, 125.3, 126.1, 126.2, 127.6, 128.8, 131.5, 132.5, 132.6 (ArC); *m/z* 240 (M^+, 10%), 211 (27), 155 (21), 154 (100), 153 (28), 152 (16), 57 (51); HRMS: M^+, found: 240.1518, $C_{17}H_{20}O$ requires: 240.1514.

*4.5. Preparation of 4-phenylphthalan (**11**)*

To a solution of tris(phenylphosphine)rhodium(I) chloride (81.6 mg, 0.088 mmol) in toluene (20 mL) were added dropwise trimethylsilylacetylene (**13**, R^1=Me_3Si; 651 mg, 7.0 mmol) and 3-phenylpropargyl propargyl ether (**14**, R^2=Ph; 340 mg, 2.0 mmol) under argon at 60 °C. The reaction mixture was stirred at the same temperature for 5 h. Then toluene was evaporated (15 Torr) and the resulting residue was dissolved in dichloromethane (10 mL) and trifluoroacetic acid (1 mL) was added at room temperature. The reaction mixture was stirred at this temperature overnight and after that it was hydrolysed with water (5 mL), extracted with ethyl acetate (3×10 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 product **11** (157 mg, 40%):[21] yellow oil; R_f=0.21 (hexane/ethyl acetate 10:1); ν (film) 3069 (ArH), 1056 cm^{-1} (C–O); δ_H 5.17 (2H, s, CH_2O), 5.20 (2H, s, CH_2O), 7.30–7.45 (8H, m, ArH); δ_C 73.4, 73.7 (CH_2O), 120.0, 127.3, 127.4, 127.8, 127.9, 128.6, 136.0, 137.0, 139.9, 140.1 (ArC); *m/z* 196 (M^+, 83%), 195 (51), 168 (58), 167 (100), 166 (24), 165 (77).

*4.6. Preparation of 5-phenylphthalan (**12**)*

To a solution of tris(phenylphosphine)rhodium(I) chloride (81.6 mg, 0.088 mmol) in toluene (20 mL) were added dropwise phenylacetylene (**13**, R^1=Ph; 714 mg, 7.0 mmol) and dipropargyl ether (**14**, R^2=H; 188 mg, 2.0 mmol) under argon at 0 °C. The reaction mixture was stirred at the same temperature for 5 h. Then toluene was evaporated (15 Torr) and the resulting residue was purified by column chromatography (silica gel, hexane/ethyl acetate) to yield pure product **12** (194 mg, 50%):[22] yellow oil; R_f=0.20 (hexane/ethyl acetate 10:1); ν (film) 3039 cm^{-1} (ArH); δ_H 5.16 (4H, s, CH_2O), 7.30 (1H, d, *J*=7.8 Hz, ArH), 7.36 (1H, d, *J*=7.0 Hz, ArH), 7.41–7.51 (4H, m, ArH), 7.57 (2H, d, *J*=7.2 Hz, ArH); δ_C 73.4, 73.5 (CH_2O), 119.7, 121.2, 126.5, 127.2, 127.3, 128.8, 138.2, 139.9, 140.7, 141.0 (ArC); *m/z* 197 [(M^++1), 12%], 196 (M^+, 75%), 168 (52), 167 (100), 166 (16), 165 (59), 153 (15), 152 (37), 115 (10).

*4.7. Lithiation of phenylphthalans **11** and **12** and reaction with electrophiles. Isolation of compounds **17** and **18**: general procedure*

To a cooled (−78 °C) blue suspension of lithium powder (72 mg, 10.4 mmol) and a catalytic amount of DTBB (33.6 mg, 0.13 mmol) in THF (3 mL) was added dropwise a solution of the corresponding phenylphthalan **11** or **12** (186 mg, 1.1 mmol) in THF (0.5 mL) under argon and the mixture was stirred at the same temperature for 3 h. Then the corresponding electrophile was added dropwise (1.1 mmol, 0.2 mL in the case of H_2O) at −78 °C and, after 20 min at this temperature, the reaction mixture was worked up as described above (Section 4.3) for compounds **9** to yield pure products **17** and **18**. Yields are given in Table 2; physical, analytical and spectroscopic data as well as literature references for known compounds are as follows.

*4.7.1. 3-Hydroxymethyl-2-methylbiphenyl (**17a**)*

Yellow solid; mp 59–60 °C (hexane/dichloromethane); R_f=0.10 (hexane/ethyl acetate 10:1); ν (KBr) 3384 (OH), 3059, 3014 cm^{-1} (ArH); δ_H 1.61 (1H, br s, OH), 2.24 (3H, s, CH_3), 4.78 (2H, s, CH_2OH), 7.19–7.24 (2H, m, ArH), 7.28–7.31

(2H, m, ArH), 7.33–7.37 (1H, m, ArH), 7.38–7.43 (3H, m, ArH); δ_C 16.0 (CH_3), 62.3 (CH_2O), 125.7, 126.9, 127.0, 128.2, 129.5, 129.7, 133.8, 139.3, 142.2, 143.0 (ArC); *m/z* 198 (M^+, 48%), 181 (10), 180 (51), 179 (30), 178 (14), 166 (20), 165 (100), 155 (23), 154 (11), 153 (13), 152 (22), 89 (11).

*4.7.2. 1-[3-(Hydroxymethyl)biphenyl-2-yl]-3,3-dimethylbutan-2-ol (**17b**)*

White solid; mp 111–112 °C (hexane/dichloromethane); R_f=0.34 (hexane/ethyl acetate 2:1); ν (KBr) 3322 (OH), 1362 cm^{-1} (CO); δ_H 0.59 (9H, s, $C(CH_3)_3$), 2.62–2.70 (1H, m, C*H*HCH), 2.99 (1H, d, *J*=10.4 Hz, CH*H*CH), 3.11 (1H, d, *J*=10.4 Hz, C*H*OH), 3.62 (2H, br s, 2×OH), 4.44 (1H, d, *J*=11.7 Hz, CH*H*OH), 4.88 (1H, d, *J*=11.7 Hz, C*H*HOH), 7.19–7.40 (8H, m, ArH); δ_C 25.2 (CH_3), 30.3 (CH_2), 35.0 (C), 64.0 (CH_2OH), 79.2 (CHOH), 126.4, 127.1, 128.3, 129.5, 130.1, 130.6, 136.7, 140.4, 142.2, 143.3 (ArC); *m/z* 266 (M^+-H_2O, 2%), 181 (37), 180 (100), 179 (21), 178 (15), 167 (14), 166 (20), 165 (63), 152 (11); HRMS: M^+-H_2O, found: 266.1675, $C_{19}H_{22}O$ requires: 266.1671.

*4.7.3. 2-[3-(Hydroxymethyl)biphenyl-2-yl]-1-phenylethanol (**17c**)*

Yellow oil; R_f=0.23 (hexane/ethyl acetate 2:1); ν (film) 3355 (OH), 1257 cm^{-1} (CO); δ_H 2.93–3.19 (2H, m, CH_2CH), 3.43 (2H, br s, 2×OH), 4.39–4.42 (1H, m, CH*H*OH), 4.66 (1H, br s, C*H*OH), 4.80–4.85 (1H, m, CH*H*OH), 6.76–7.46 (13H, m, ArH); δ_C 39.5, 39.7 (CH_2), 63.8, 63.9 (CH_2OH), 78.2, 79.2 (CHOH), 125.4, 126.7, 126.9, 127.1, 127.2, 127.4, 127.9, 128.2, 128.3, 128.4, 128.6, 128.7, 129.3, 129.4, 129.6, 130.7, 139.9, 140.0 (ArC); *m/z* 195 (M^+–PhCHO, 2%), 108 (99), 107 (100), 105 (11), 79 (88), 78 (11), 77 (57), 51 (12); HRMS: M^+-H_2O, found: 286.1354, $C_{21}H_{18}O$ requires: 286.1358.

*4.7.4. 1-{[3-(Hydroxymethyl)biphenyl-2-yl]methyl}-cyclohexanol (**17d**)*

White solid; mp 109–110 °C (hexane/dichloromethane); R_f=0.23 (hexane/ethyl acetate 2:1); ν (KBr) 3334 (OH), 1257 cm^{-1} (CO); δ_H 0.96–1.09 (2H, m, CH_2), 1.54–1.64 (8H, m, 4×CH_2), 2.87 (2H, br s, 2×OH), 3.13–3.23 (2H, m, CH_2), 4.70 (2H, s, CH_2OH), 7.19–7.20 (1H, m, ArH), 7.21–7.46 (7H, m, ArH); δ_C 21.9, 22.1, 22.2, 25.4, 25.7, 31.7 (CH_2), 64.1 (CH_2OH), 72.5 (COH), 126.6, 126.7, 126.8, 128.2, 128.4, 130.2, 130.4, 130.9, 133.6, 141.9, 143.2, 144.2 (ArC); *m/z* 278 (M^+-H_2O, 2%), 181 (17), 180 (100), 179 (20), 178 (14), 166 (12), 165 (54), 81 (10); HRMS: M^+-H_2O, found: 278.1669; $C_{20}H_{22}O$ requires: 278.1671.

*4.7.5. 3-Hydroxymethyl-4-methylbiphenyl (**18a**)[23]*

Brown oil; R_f=0.09 (hexane/ethyl acetate 10:1); ν (film) 3391 (OH), 3056, 3027 cm^{-1} (ArH); δ_H 2.05 (1H, br s, OH), 2.42 (3H, s, CH_3), 4.79 (2H, s, CH_2OH), 7.27 (1H, d, *J*=5.4 Hz, ArH), 7.36 (1H, t, *J*=9.3 Hz, ArH), 7.47 (2H, t, *J*=10.5 Hz, ArH), 7.63 (2H, d, *J*=9.8 Hz, ArH); δ_C 18.5 (CH_3), 63.7 (CH_2O), 126.4, 126.5, 127.1, 127.2, 128.9, 130.1, 135.3, 139.1, 139.2, 141.0 (ArC); *m/z* 198 (M^+, 62%), 181 (18), 180 (100), 179 (18), 178 (11), 165 (39), 155 (18), 154 (12), 153 (12), 152 (19), 89 (10).

*4.7.6. 1-[3-(Hydroxymethyl)biphenyl-4-yl]-3,3-dimethylbutan-2-ol (**18b**)*

White solid; mp 113–114 °C (hexane/dichloromethane); R_f=0.42 (hexane/ethyl acetate 2:1); ν (KBr) 3241 cm^{-1} (OH); δ_H 0.97 (9H, s, $C(CH_3)_3$), 2.68–2.82 (2H, m, CH_2CH), 3.33 (1H, dd, *J*=7.5, 2.5 Hz, C*H*OH), 3.74 (2H, br s, 2×OH), 4.38 (2H, d, *J*=11.8 Hz, CH*H*OH), 4.79 (2H, d, *J*=11.8 Hz, C*H*HOH), 7.21 (1H, d, *J*=8.3 Hz, ArH), 7.32–7.55 (5H, m, ArH), 7.56 (2H, dd, *J*=3.3, 1.4 Hz, ArH); δ_C 25.8 (CH_3), 33.7 (C), 35.4 (CH_2), 63.5 (CH_2OH), 81.4 (CHOH), 127.1, 128.8, 128.9, 130.7, 138.6, 139.4, 139.9, 140.8 (ArC); *m/z* 266 [(M^+-H_2O), 4%], 181 (60), 180 (100), 179 (12), 178 (11), 167 (15), 165 (24), 152 (12); HRMS: M^+-H_2O, found: 266.1666, $C_{19}H_{22}O$ requires: 266.1671.

*4.7.7. 2-[3-(Hydroxymethyl)biphenyl-4-yl]-1-phenylethanol (**18c**)*

White solid; mp 109–110 °C (hexane/dichloromethane); R_f=0.30 (hexane/ethyl acetate 2:1); ν (KBr) 3394 (OH), 3063, 3018 cm^{-1} (ArH); δ_H 3.08–3.16 (2H, m, CH_2CH), 3.72 (2H, br s, 2×OH), 4.52 (1H, d, *J*=8.9 Hz, CH*H*OH), 4.81 (1H, d, *J*=8.9 Hz, C*H*HOH), 4.89 (1H, dd, *J*=4.5, 2.4 Hz, C*H*OH), 7.25–7.45 (8H, m, ArH), 7.50–7.59 (5H, m, ArH); δ_C 42.1 (CH_2), 63.6 (CH_2OH), 75.7 (CHOH), 125.8, 127.2, 127.2, 127.4, 127.9, 128.7, 128.9, 129.0, 131.2, 136.5, 140.0, 140.7, 144.3 (ArC); *m/z* 286 [(M^+–18), 4%], 181 (17), 180 (100), 165 (11); HRMS: M^+-H_2O, found: 286.1362, $C_{21}H_{18}O$ requires: 286.1358.

*4.7.8. 3-{[3-(Hydroxymethyl)biphenyl-4-yl]methyl}pentan-3-ol (**18d**)*

Yellow oil; R_f=0.26 (hexane/ethyl acetate 2:1); ν (film) 3342 (OH), 3029 cm^{-1} (ArH); δ_H 0.97 (6H, t, *J*=7.5 Hz, 2×CH_3), 1.57–1.63 (4H, m, 2×CH_2CH$_3$), 2.92 (2H, s, ArCH_2COH), 3.37 (2H, br s, 2×OH), 4.67 (2H, s, CH_2OH), 7.22 (1H, d, *J*=7.9 Hz, ArH), 7.33–7.50 (4H, m, ArH), 7.58–7.61 (3H, m, ArH); δ_C 8.2 (CH_3), 31.1, 40.3 (CH_2), 63.7 (CH_2OH), 75.1 (COH), 126.3, 127.1, 127.4, 128.9, 129.5, 132.6, 135.2, 140.0, 140.7, 141.1 (ArC); *m/z* 266 [(M^+-H_2O), 2%], 237 (10), 181 (18), 180 (100), 165 (10); HRMS: M^+-H_2O, found: 266.1675, $C_{19}H_{22}O$ requires: 266.1671.

*4.8. Cyclisation of diols **18c** and **18d**. Isolation of phenylisochromans **19c** and **19d**: general procedure*

Reaction conditions were exactly the same as described in Section 4.7 for compounds **10**. Yields are given in Chart 5; physical, analytical and spectroscopic data are as follows.

*4.8.1. 3,7-Diphenylisochroman (**19c**)*

White solid; mp 105–106 °C (hexane/dichloromethane); R_f=0.25 (hexane/ethyl acetate 30:1); ν (KBr) 3088, 3069, 2033 (ArH), 1092 cm^{-1} (COC); δ_H 2.99–3.11 (2H, m, CH_2CH), 4.76 (1H, dd, *J*=6.7, 3.8 Hz, CHO), 5.07 (2H, s, CH_2O), 7.20–7.48 (11H, m, ArH), 7.58 (2H, d, *J*=9.2 Hz, ArH); δ_C 36.0 (CH_2), 69.0 (CH_2O), 77.1 (CHO), 123.0, 125.5, 126.1, 127.2, 127.4, 128.7, 128.9, 129.4, 132.8,

135.1, 139.5, 141.0, 142.2 (ArC); *m/z* 286 (M^+, 3%), 181 (16), 180 (100), 179 (12), 178 (15), 165 (12); HRMS: M^+, found: 286.1353, $C_{21}H_{18}O$ requires: 286.1358.

4.8.2. 3,3-Diethyl-7-phenylisochroman (**19d**)

Pale yellow oil; R_f=0.27 (hexane/ethyl acetate 30:1); ν (film) 3057, 3027 (ArH), 1081 cm^{-1} (COC); δ_H 0.93 (6H, t, J=7.6 Hz, 2×CH_3), 1.52 (2H, q, J=7.1 Hz, CH_2CH$_3$), 1.71 (2H, q, J=7.1 Hz, CH_2CH$_3$), 2.72 (2H, s, CH_2COH), 4.80 (2H, s, CH_2O), 7.16 (1H, d, J=8.0 Hz, ArH), 7.23 (1H, s, ArH), 7.26–7.45 (4H, m, ArH), 7.55–7.58 (2H, m, ArH); δ_C 7.8 (CH_3), 27.7, 36.1 (CH_2), 62.8 (CH_2O), 75.4 (CO), 122.7, 125.3, 127.1, 127.2, 128.9, 129.9, 132.2, 134.9, 138.9, 141.2 (ArC); *m/z* 266 (M^+, 4%), 237 (31), 181 (21), 180 (100), 179 (12), 178 (16), 57 (14); HRMS: M^+, found: 266.1663, $C_{19}H_{22}O$ requires: 266.1671.

4.9. Preparation of methoxyphthalans **20** and **21**: general procedure

To a stirred suspension of NaH (99%, 27 mg, 1.1 mmol) in dry DMF (1.2 mL) was added the corresponding hydroxyphthalan (116.6 mg, 0.857 mmol). The resulting reaction mixture was cooled down to 0 °C and methyliodide (150 mg, 1.1 mmol) was added dropwise. The mixture was stirred for 2 h at the same temperature and after that it was hydrolysed with water (4 mL), extracted with ethyl acetate (3×10 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 **20** and **21** in almost quantitative yield. Overall yields starting from furfuryl alcohol (**22**) are given in Scheme 7; physical, analytical and spectroscopic data are as follows.

4.9.1. 4-Methoxyphthalan (**20**)

Pale yellow oil; R_f=0.41 (hexane/ethyl acetate 10:1); ν (film) 3410 (OH), 1271 cm^{-1} (CO); δ_H 3.82 (3H, s, OCH_3), 5.11 (4H, s, CH_2O), 6.74 (1H, d, J=8.1 Hz, ArH), 6.82 (1H, d, J=7.3 Hz, ArH), 7.24 (1H, t, J=7.8 Hz, ArH); δ_C 55.3 (CH_3), 72.2, 74.2 (CH_2O), 108.8, 113.2, 127.0, 129.2, 141.2, 154.3 (ArC); *m/z* 150 (M^+, 77%), 149 (61), 122 (54), 121 (40), 107 (22), 106 (11), 105 (11), 92 (15), 91 (100), 90 (14), 89 (16), 78 (18), 77 (32), 65 (13), 63 (13), 51 (23); HRMS: M^+, found: 150.0672, $C_9H_{10}O_2$ requires: 150.0681.

4.9.2. 5-Methoxyphthalan (**21**)

Colourless oil; R_f=0.33 (hexane/ethyl acetate 10:1); ν (film) 1276 cm^{-1} (C–O); δ_H 3.81 (3H, s, OCH_3), 5.06 (2H, s, CH_2O), 5.07 (2H, s, CH_2O), 6.77 (1H, s, ArH), 6.82 (1H, dd, J=6.05, 2.05 Hz, ArH), 7.13 (1H, d, J=8.4 Hz, ArH); δ_C 55.5 (CH_3), 73.2, 73.5 (CH_2O), 106.2, 113.4, 121.6, 131.0, 140.7, 159.4 (ArC); *m/z* 150 (M^+, 76%), 149 (100), 122 (37), 121 (63), 107 (11), 91 (38), 77 (29), 51 (14); HRMS: M^+, found: 150.0671, $C_9H_{10}O_2$ requires: 150.0681.

4.10. Lithiation of methoxyphthalans **20** and **21** and reaction with electrophiles. Isolation of compounds **24** and **26**: general procedure

Reaction conditions were exactly the same as in Section 4.7. Yields are given in Table 3; physical, analytical and spectroscopic data as well as literature references for known compounds are as follows.

4.10.1. 2-Hydroxymethyl-3-methylanisole (**24a**)[24]

Colourless oil; R_f=0.32 (hexane/ethyl acetate 2:1); ν (film) 3355 (OH), 1265 cm^{-1} (CO); δ_H 2.33 (1H, br s, OH), 2.39 (3H, s, ArCH_3), 3.86 (3H, s, OCH_3), 4.76 (2H, s, CH_2OH), 6.76 (1H, d, J=8.2 Hz, ArH), 6.81 (1H, d, J=7.5 Hz, ArH), 7.13–7.26 (1H, m, ArH); δ_C 19.3 (CH_3), 55.6 (OCH_3), 57.7 (CH_2OH), 108.3, 123.2, 128.7, 129.2, 137.9, 158.3 (ArC); *m/z* 152 (M^+, 100%), 151 (10), 137 (50), 136 (12), 135 (29), 134 (51), 123 (23), 121 (27), 120 (23), 119 (59), 109 (13), 108 (15), 107 (24), 105 (30), 104 (29), 103 (13), 92 (11), 91 (81), 79 (19), 77 (35), 65 (25), 63 (11).

4.10.2. 1-(2-Hydroxymethyl-3-methoxyphenyl)-3,3-dimethylbutan-2-ol (**24b**)

White solid; mp 92–93 °C (hexane/dichloromethane); R_f=0.26 (hexane/ethyl acetate 2:1); ν (KBr) 3318 (OH), 1267 cm^{-1} (CO); δ_H 1.01 (9H, s, C$(CH_3)_3$), 2.74–2.86 (2H, m, CH_2CH), 3.07 (2H, br s, 2×OH), 3.36 (1H, dd, J=8.4, 2.0 Hz, C*H*OH), 3.84 (3H, s, OCH_3), 4.55 (1H, d, J=11.9 Hz, C*H*HOH), 4.91 (1H, d, J=11.9 Hz, CH*H*OH), 6.77 (1H, d, J=8.2 Hz, ArH), 6.81 (1H, d, J=7.7 Hz, ArH), 7.23 (1H, t, J=8.0 Hz, ArH); δ_C 25.8 (CH_3), 34.4 (CH_2), 35.4 (C), 55.5 (OCH_3), 55.8 (CH_2OH), 81.3 (CHOH), 108.6, 122.6, 128.3, 129.0, 140.1, 158.0 (ArC); *m/z* 220 (M^+-H_2O, 2%), 135 (31), 134 (100), 105 (12), 104 (17), 91 (13); HRMS: M^+-H_2O, found: 220.1460, $C_{14}H_{20}O_2$ requires: 220.1463.

4.10.3. 4-Hydroxymethyl-3-methylanisole (**26a**)[25]

Yellow oil; R_f=0.29 (hexane/ethyl acetate 2:1); ν (film) 3354 (OH), 1251 cm^{-1} (CO); δ_H 2.24 (1H, br s, OH), 2.37 (3H, s, ArCH_3), 3.80 (3H, s, OCH_3), 4.64 (2H, s, CH_2OH), 6.71 (1H, d, J=2.6 Hz, ArH), 6.74 (1H, d, J=2.6 Hz, ArH), 7.24 (1H, d, J=8.1 Hz, ArH); δ_C 19.1 (CH_3), 55.4 (OCH_3), 63.5 (CH_2OH), 110.9, 116.4, 129.7, 131.2, 138.3, 159.4 (ArC); *m/z* 152 (M^+, 100%), 151 (28), 137 (67), 135 (65), 123 (47), 121 (12), 109 (18), 108 (25), 91 (41), 79 (15), 77 (24), 65 (12).

4.10.4. 1-(2-Hydroxymethyl-5-methoxyphenyl)-3,3-dimethylbutan-2-ol (**26b**)

White solid; mp 113–114 °C (hexane/dichloromethane); R_f=0.23 (hexane/ethyl acetate 2:1); ν (KBr) 3309 (OH), 1261 cm^{-1} (CO); δ_H 0.99 (9H, s, C$(CH_3)_3$), 2.66–2.78 (2H, m, CH_2CH), 3.34 (1H, dd, J=7.5, 2.7 Hz, C*H*OH), 3.61 (2H, br s, 2×OH), 3.79 (3H, s, OCH_3), 4.31 (1H, d, J=11.9 Hz, C*H*HOH), 4.70 (1H, d, J=11.9 Hz, CH*H*OH), 6.70–6.72 (2H, m, ArH), 7.17 (1H, d, J=8.2 Hz, ArH); δ_C 25.8 (CH_3), 34.3 (CH_2), 35.4 (C), 55.3 (OCH_3), 62.8 (CH_2OH), 81.5 (CHOH), 111.41, 115.7, 131.6, 132.3, 141.2, 159.7 (ArC);

m/z 220 (M^+-H_2O, 2%), 163 (10), 135 (44), 134 (100); HRMS: M^+, found: 238.1568, $C_{14}H_{22}O_3$ requires: 238.1569.

*4.10.5. 2-(2-Hydroxymethyl-5-methoxyphenyl)-1-phenylethan-1-ol (**26c**)*

White solid; mp 87–88 °C (hexane/dichloromethane); R_f=0.13 (hexane/ethyl acetate 2:1); ν (KBr) 3363 (OH), 1258 cm^{-1} (CO); δ_H 2.90–3.05 (2H, m, CH_2CH), 3.72 (3H, s, OCH_3), 4.18 (2H, br s, 2×OH), 4.33 (1H, d, *J*=11.8 Hz, C*H*HOH), 4.61 (1H, d, *J*=11.8 Hz, CH*H*OH), 4.79 (1H, dd, *J*=5.08, 3.77 Hz, C*H*OH), 6.65 (1H, s, ArH), 6.72 (1H, dd, *J*=5.8, 2.5 Hz, ArH), 7.15 (1H, d, *J*=8.4 Hz, ArH), 7.13–7.31 (1H, m, ArH), 7.33 (4H, d, *J*=4.3 Hz, ArH); δ_C 42.6 (CH_2), 55.3 (OCH_3), 62.3 (CH_2OH), 75.2 (CHOH), 112.1, 116.0, 125.8, 127.7, 128.5, 131.6, 132.1, 139.1, 144.5, 159.5 (ArC); *m/z* 240 (M^+-H_2O, 8%), 209 (13), 207 (55), 178 (10), 152 (10), 135 (13), 134 (100), 107 (16), 105 (15), 91 (28), 79 (13), 77 (25); HRMS: M^+, found: 258.1246, $C_{16}H_{18}O_3$ requires: 258.1256.

*4.10.6. 3-[(2-Hydroxymethyl-5-methoxyphenyl)methyl]-pentan-3-ol (**26d**)*

Pale yellow oil; R_f=0.27 (hexane/ethyl acetate 2:1); ν (film) 3312 (OH), 1259 cm^{-1} (CO); δ_H 0.95 (6H, t, *J*=7.5 Hz, 2×CH_3), 1.50–1.63 (4H, m, 2×C$H_2$$CH_3$), 2.84 (2H, s, ArC$H_2$-COH), 3.80 (3H, s, OCH_3), 3.55 (2H, br s, 2×OH), 4.54 (2H, s, CH_2OH), 6.69 (1H, s, ArH), 6.76 (1H, dd, *J*=5.6, 2.6 Hz, ArH), 7.26 (1H, d, *J*=8.4 Hz, ArH); δ_C 8.2 (CH_3), 31.0, 40.8 (CH_2), 55.3 (OCH_3), 62.8 (CH_2OH), 74.9 (COH), 111.5, 118.1, 132.1, 133.2, 137.8, 158.9 (ArC); *m/z* 220 [(M^+-H_2O), 2%], 191 (23), 135 (22), 134 (100), 91 (12), 87 (10), 57 (18); HRMS: M^+, found: 238.1567, $C_{14}H_{22}O_3$ requires: 238.1569.

*4.11. Cyclisation of diol **26d**. Isolation of 3,3-diethyl-6-methoxyisochroman (**27d**)*

To a solution of diol **26d** (50 mg, 0.21 mmol) in dry dichloromethane (0.7 mL) under argon was added dropwise first methanesulfonyl chloride (51 mg, 0.46 mmol) and then triethylamine (45 mg, 0.30 mL, 0.46 mmol) at 0 °C. The reaction mixture was stirred for 4 h allowing the system to reach room temperature. The mixture was then hydrolysed with 2 M HCl (2 mL), the organic layer was neutralised with an aqueous saturated solution of NaHCO, washed with water (10 mL), extracted with ethyl acetate (3×10 mL), dried over anhydrous $MgSO_4$ and evaporated (15 Torr). The residue was purified by column chromatography (silica gel, hexane) to yield pure products **20** (18 mg, 40%): colourless oil, R_f=0.20 (hexane/ethyl acetate 30:1); ν (film) 3057 (ArH), 1121 cm^{-1} (CO); δ_H 0.90 (6H, t, *J*=7.6 Hz, 2×CH_3), 1.40–1.52 (2H, m, C$H_2$$CH_3$), 1.63–1.72 (2H, m, C$H_2$$CH_3$), 2.65 (2H, s, Ar$CH_2$CO), 3.79 (3H, s, OCH_3), 4.68 (2H, s, CH_2O), 6.63 (1H, s, ArH), 6.70–6.74 (1H, m, ArH), 6.91 (1H, d, *J*=8.4 Hz, ArH); δ_C 7.8 (CH_3), 27.7, 36.7 (CH_2), 55.4 (OCH_3), 62.4 (CH_2OH), 75.1 (CO), 112.1, 114.1, 125.0, 126.7, 134.3, 158.2 (ArC); *m/z* 220 (M^+, 13%), 192 (13), 191 (100), 163 (18), 135 (42), 134 (85), 92 (18), 57 (37); HRMS: M^+, found: 220.1443, $C_{14}H_{20}O_2$ requires: 220.1463.

*4.12. Preparation of 2,5-dihydrofuro[3,4-f]phthalan (**28**)*

To a solution of tetrakis(bromomethyl)benzene (2.367 g, 5.0 mmol) in 1,4-dioxane (20 mL) was added an aqueous solution of tetrabutylammonium hydroxide (55–60%, 10 mL). The resulting mixture was stirred at 90 °C for 4 h. After that the reaction mixture was allowed to cool down to room temperature, hydrolysed with 2 M HCl (20 mL), extracted with ethyl acetate (3×40 mL) and the organic layer was dried over anhydrous sodium sulfate and evaporated (15 Torr). The resulting residue was then purified by column chromatography (silica gel, hexane/ethyl acetane 20:1) to yield pure compounds **28** (0.243 g, 30%): white solid; mp 159–160 °C (hexane/dichloromethane); R_f=0.13 (hexane/ethyl acetate 10:1); ν (KBr) 1043 cm^{-1} (C–O); δ_H 5.09 (8H, s, CH_2O), 7.07 (2H, s, ArH); δ_C 73.2 (CH_2O), 113.6, 138.9 (ArC); *m/z* 163 [(M^++1), 8%], 162 (M^+, 76%), 162 (45), 134 (13), 133 (51), 132 (20), 105 (95), 104 (100), 103 (39), 91 (12), 79 (24), 78 (23), 77 (43), 63 (11), 51 (25).

*4.13. Lithiation of 2,5-dihydrofuro[3,4-f]phthalan (**28**) and reaction with electrophiles. Isolation of compounds **31** and **32**: general procedure*

Reaction conditions were the same as in Section 4.7 but performing the lithiation at temperatures ranging between −78 and 0 °C. Yields are given in Scheme 10; physical, analytical and spectroscopic data as well as literature references for known compounds are as follows.

*4.13.1. 5-Hydroxymethyl-6-methylphthalan (**31a**)*

Pale yellow solid; mp 105–106 °C (hexane/dichloromethane); R_f=0.19 (hexane/ethyl acetate 2:1); ν (KBr) 3411 cm^{-1} (OH); δ_H 2.35 (3H, s, CH_3), 4.69 (2H, s, CH_2OH), 5.05 (4H, s, CH_2OCH_2), 7.04 (1H, s, ArH), 7.24 (1H, s, ArH); δ_C 18.8 (CH_3), 63.3, 73.4, 73.5 (CH_2O), 120.0, 122.7, 135.3, 136.9, 138.2, 138.5 (ArC); *m/z* 164 (M^+, 100%), 163 (78), 146 (25), 135 (21), 133 (24), 118 (52), 106 (70), 105 (96), 103 (24), 91 (88), 79 (35), 77 (43), 65 (16), 51 (18); HRMS: M^+, found: 164.0832, $C_{10}H_{12}O_2$ requires: 164.0837.

*4.13.2. 5-(2-Hydroxy-2-phenylethyl)-6-hydroxymethylphthalan (**31b**)*

White solid; mp 289–290 °C (hexane/dichloromethane); R_f=0.23 (hexane/ethyl acetate 1:1); ν (KBr) 3350 (OH), 3034 cm^{-1} (ArH); δ_H 3.02–3.13 (2H, m, CH_2CH), 3.60 (2H, br s, 2×OH), 4.49 (1H, d, *J*=8.8 Hz, C*H*HOH), 4.80 (1H, d, *J*=8.8 Hz, CH*H*OH), 4.89 (1H, dd, *J*=4.5, 2.4 Hz, CHOH), 5.07 (4H, s, CH_2OCH_2), 7.10 (1H, s, ArH), 7.21 (1H, s, ArH), 7.29–7.41 (5H, m, ArH); δ_C 42.1 (CH_2), 63.0 (CH_2OH), 75.5 (CHOH), 122.7, 123.0, 125.8, 128.0, 128.7, 136.8, 138.1, 138.9, 139.6, 144.3 (ArC); *m/z* 252 [(M^+-H_2O), 8%], 146 (100), 118 (33), 117 (33), 115 (22), 91 (16), 77 (10); HRMS: M^+-H_2O, found: 252.1144, $C_{17}H_{16}O_2$ requires: 252.1150.

*4.13.3. 1,4-Bis(hydroxymethyl)-2,5-dimethylbenzene (**32a**)*[26]

White solid; mp 127–128 °C (hexane/dichloromethane); R_f=0.10 (hexane/ethyl acetate 2:1); ν (KBr) 3411 cm^{-1} (OH); δ_H 2.33 (6H, s, 2×CH_3), 4.67 (4H, s, 2×CH_2OH), 7.18 (2H, s, ArH); δ_C 18.3 (CH_3), 63.4 (CH_2OH), 130.0, 133.8, 138.2 (ArC); *m/z* 166 (M^+, 43%), 164 (21), 148 (82), 146 (28), 135 (38), 119 (49), 107 (77), 105 (74), 91 (100), 77 (57); HRMS: M^+, found: 166.0990, $C_{10}H_{14}O_2$ requires: 166.0994.

*4.13.4. 2-[4-(2-Hydroxy-2-phenylethyl)-2,5-bis(hydroxymethyl)phenyl]-1-phenylethan-1-ol (**32b**)*

Yellow oil; R_f=0.23 (hexane/ethyl acetate 1:2); ν (film) 3389 (OH), 3029 cm^{-1} (ArH); δ_H 2.94–3.03 (4H, m, 2×CH_2CH), 4.38 (2H, d, *J*=8.9 Hz, 2×CHHOH), 4.70 (2H, d, *J*=8.9 Hz, 2×CHHOH), 4.78 (2H, dd, *J*=4.8, 2.4 Hz, 2×CHOH), 7.24 (2H, s, ArH), 7.28–7.37 (10H, m, ArH); δ_C 42.3 (CH_2), 63.4, 73.5 (CH_2O), 75.8 (CHOH), 122.2, 125.8, 127.8, 128.6, 129.5, 132.5, 136.4, 136.8, 137.2, 137.7, 144.5 (ArC); *m/z* 254 [(M^+–PhCHO–H_2O), 1%], 148 (100), 130 (16), 119 (18), 105 (17), 91 (12), 79 (11), 77 (12); HRMS: M^+–H_2O–PhCHOH, found: 254.1306, $C_{17}H_{18}O_2$ requires: 254.1307.

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12. In a recent paper on the reductive cleavage of an alkyl naphthyl thioether, Donohoe, Compton and co-workers proved that at 20 °C the dissociation of alkyl carbon–sulfur bond occurs after the substrate accepts a single electron (radical-anion), however, at −78 °C the radical-anion is stabilised at sufficiently longer timescales to accept a second electron, leading to the corresponding dianion, which cleaves at the aryl-sulfur bond: Paddon, C. A.; Bhatti, F. L.; Donohoe, T. J.; Compton, R. G. *Chem. Commun.* **2006**, 3402–3404.
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14. Compounds **13** (R^1=Ph, Me_3Si) and **14** (R^2=H) were commercially available. Starting material **14** (R^2=H) was prepared from 3-phenylprop-2-yn-1-ol by propargylation with propargyl bromide (NaH, DMF, rt) following the general reported procedure. See, for instance: Martín-Matute, B.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. *J. Am. Chem. Soc.* **2003**, *125*, 5757–5766.
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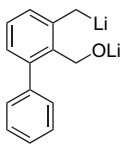
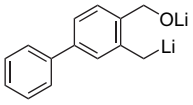
16. The other possible regioisomeric intermediates (**15′**, **16′**) would afford the corresponding final regioisomers of compounds **17** and **18**:



15'



16'

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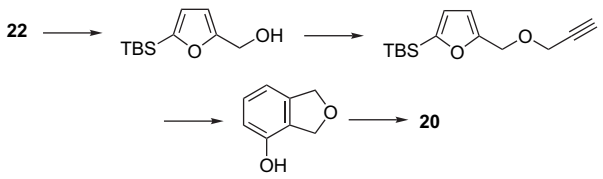
18. The sequence of compounds involved in the transformation of the starting material **22** into the product **20** performed according to the reported procedures[14,17] and shown in Scheme 6 is as follows:



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