Lithiophenylalkyllithiums: new dilithium reagents having both sp^2- and sp^3-hybridised remote carbanionic centres

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This paper is dedicated to Professor Pascual Royo on occasion of his 65th birthday

Abstract

The reaction of chloro-(2-chloroethyl)benzenes (**1**), 4-chloro-(3-chloropropyl)benzene (**3**) or 4-chlorophenyl chloromethyl ether (**5**) with lithium power using naphthalene as the electron shuttle (8 mol%) in the presence of different carbonyl compounds [Bu^{t}CHO, PhCHO, Me$_2$CO, Et$_2$CO, (CH$_2$)$_5$CO, PhCOMe] in THF at −78 to 20 °C gives, after hydrolysis with water, the expected diols **2**, **4** or **6**, respectively. Bromo-2-(chloroethyl)benzenes (**7**) are treated with *n*-BuLi in THF at −100 °C, so the corresponding bromine–lithium exchanges takes place giving an intermediate, which is trapped by treatment with benzaldehyde or cyclohexanone, affording intermediates **9**, which are submitted to a naphthalene-catalysed (8 mol%) lithiation with lithium power as above, followed by reaction with 3-pentanone and final hydrolysis with water, to give differently substituted diols **10**. Some diols **2** are transformed into either the corresponding oxepane **11** or dienes **12** under Mitsunobu type conditions or by acidic treatment, respectively.
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1. Introduction

The existence in Nature of a huge amount of polyfunctionalised organic compounds [1] prompts chemists to develop new methodologies to get these type of structures as easily and selectively as possible. One very useful methodology for this purpose consists in the use of organometallic intermediates [2], due to the versatility of these compounds in their reactivity with different reagents, especially making carbon–carbon bond formation reacting with electrophiles.

Concerning to the use of organometallic reagents in the construction of organic molecules, apart of the classical linear (one-directional homologation) or convergent (two separate one-directional synthesis, which are finally connected) syntheses [3], two new strategies have been recently recognised [4]: sequential (a real two-fold one-directional synthesis) or simultaneous (two extremes of molecule are elongated at the same time) two-directional syntheses. The last two cases, two-directional syntheses, are far less studied than the classical mentioned ways (linear or convergent syntheses), due to the difficulties to find reagents able to react independently at two different parts of the molecules. If the synthesis involves an organometallic reagent, it is useful to have two equal or different carbon–metal bonds in the structure in order to perform a simultaneous or sequential reaction with electrophiles. Among organometallic compounds, organolithium reagents [5] are very reactive, so the use of dilithiated species is not an easy task for a synthetic chemist. However, in the last few years, some dilithiated synthons [6] have been introduced as a helpful tool, some of them being prepared from the corresponding dichlorinated materials using an arene-catalysed lithiation [7–15] under Barbier-type reaction conditions (lithiation in the presence of the electrophile) [16]. Thus, for instance, intermediates **I** [17] and **II** [18] (Fig. 1) have been generated using the former procedure and used in the

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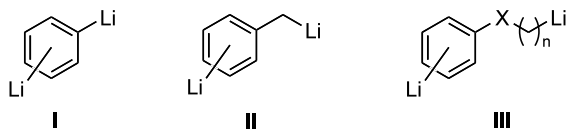
[1] www.ua.es/dept.quimorg

Fig. 1. Dilithiated intermediates **I**–**III**.

preparation of polyfunctionalised molecules by in situ reaction with different electrophiles. In this paper, we report the generation of intermediates of type **III** (Fig. 1; $Y = CH_2$, O; $n = 1$, 2) by a chlorine–lithium exchange and their reaction toward electrophiles. To the best of our knowledge only one example of an intermediate of type **III** [2-(2-lithiophenyl)ethyllithium] has been described in the literature [19], having been generated by lithiation of benzocyclobutene and chemically characterised by quenching with water. In our opinion, intermediates of type **III** having two different hybridised carbon–lithium bonds have the opportunity of being used in a two-directional synthetic approach.
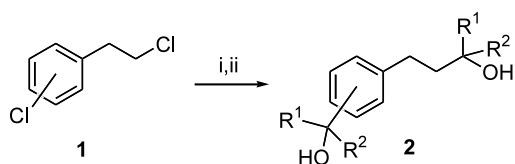
2. Results and discussion

2.1. Simultaneous two-directional homologation

The reaction of dichlorinated compounds **1** with an excess of lithium powder (1:7 molar ratio; stoichiometric amount: 1:4) and a catalytic amount of naphthalene (8 mol%) in the presence of the corresponding electrophile (R^1R^2CO) in THF at temperatures ranging from −78 to 20 °C gave, after hydrolysis with water, the expected diols **2a**–**n** (Scheme 1 and Table 1).

In the case of using prostereogenic carbonylic compounds (Bu^tCHO, PhCHO, PhCOMe), the expected mixture of diastereoisomers (1–2:1) was obtained (Table 1, entries 1, 4, 5, 7, 9, 10 and 13, and footnotes c, f and g), being in some cases chromatographically separable (Table 1, footnote d).

Alternatively, the reaction shown in Scheme 1 can be carried out in a two-step process. Thus, once the catalytic lithiation was completed (after 1 h, no starting material was found by GLC–MS of an aliquot hydrolysed with water), the reaction mixture was then treated with the corresponding electrophile giving, after hydro-

lysis with water, the corresponding products **2** (Table 1, footnote e). Actually, when the lithiation mixture was quenched with water after 1 h only ethylbenzene was found (resulting from a chlorine–hydrogen exchange), what is a clear proof that a dilithiated species of type **III** ($Y = CH_2$, $n = 1$) was involved in the process, so ruling out a double tandem lithiation-electrophilic substitution reaction process.

All attempts to lithiate regioselectively materials **1** under different reaction conditions, in order to introduce two different electrophiles, failed. It seems that under the assayed reaction conditions, the catalytic lithiation can not discriminate both carbon–chlorine atom bonds.

The application of the aforementioned methodology to the homologous starting materials **3** gave the expected result, affording compounds **4** in 52–65% isolated yield. Also here, the two alternatives (Barbier or two-step reaction process) can be applied with similar results (Fig. 2, footnotes a and b).

The reaction using compounds **1** and **3** as starting materials can be extended to the more sophisticated chloroether **5**. In this case, the lithiation must be performed under Barbier conditions in order to avoid the decomposition of the intermediate of type **IV**, which is a α-functionalised organolithium compound [12,20] with a great tendency to undergo α-elimination process, even at low temperatures (Fig. 3).

Starting dichlorinated materials **1** were prepared (86–91% yield) from the corresponding commercially available chlorinated homobenzylic alcohols by mesylation, followed by treatment with lithium chloride, according to the literature procedure [21]. Compounds **3** and **5** were commercially available.

2.2. Sequential two-directional homologation

Since it was not possible to discriminate both chlorine–carbon atom bonds in dichlorinated materials **1**, **3** and **5** (see above), we decided to use a different approach consisting in starting from a material having a bromine and a chlorine atom easier to be discriminate [22]. Thus, compounds **7** were treated with *n*-BuLi in THF at −100 °C, so the corresponding intermediates **8** were generated, which were allowed to react with an electrophile [PhCHO, $(CH_2)_4CO$] at the same temperature, being then submitted in situ to a naphthalene-catalysed lithiation under the reaction conditions (−78 °C) shown in Scheme 1, to give new functionalised intermediates **9**. Final treatment of these reagents with 3-pentanone, followed by hydrolysis with water, gave the differently substituted diols **10** (Scheme 2 and Table 2).

Starting materials **7** were prepared (73–91% yield) following the same procedure employed to obtain compounds **1** (see above) [21], starting from the

Scheme 1. Synthesis of diols **2**. Reagents and conditions: (i) Barbier procedure: Li powder (1.75 equivalents), C_8H_{10} (8%), $R^1COR^2=$ Bu^tCHO, PhCHO, Me_2CO, Et_2CO, PhCOMe, $(CH_2)_5CO$ (1.25 equivalents), THF, −78 °C, 4 h. Two-step procedure: Li powder (1.75 equivalents), C_8H_{10} (8%), THF, −78 °C, 1 h, then $R^1COR^2=$ Bu^tCHO (1.25 equivalents), THF, −78 °C, 4 h. (ii) H_2O.

Table 1
Simultaneous two-directional homologation

Entry	Starting material		Electrophile	Product [a]			
	Number	Substitution		Number	R^1	R^2	Yield (%) [b]
1	**1a**	1,2-	Bu^{t}CHO	**2a**	H	Bu^t	38 [c,d] (45) [c,e]
2	**1a**	1,2-	Et$_2$CO	**2b**	Et	Et	51
3	**1a**	1,2-	(CH$_2$)$_5$CO	**2c**	−(CH$_2$)$_5$−	−(CH$_2$)$_5$−	65
4	**1b**	1,3-	Bu^{t}CHO	**2d**	H	Bu^t	70 [f] (33) [e]
5	**1b**	1,3-	PhCHO	**2e**	H	Ph	68 [g]
6	**1b**	1,3-	Et$_2$CO	**2f**	Et	Et	76
7	**1b**	1,3-	PhCOMe	**2g**	Me	Ph	53 [f]
8	**1b**	1,3-	(CH$_2$)$_5$CO	**2h**	−(CH$_2$)$_5$−	−(CH$_2$)$_5$−	63
9	**1c**	1,4-	Bu^{t}CHO	**2I**	H	Bu^t	78 [g]
10	**1c**	1,4-	PhCHO	**2j**	H	Ph	60 [f]
11	**1c**	1,4-	Me$_2$CO	**2k**	Me	Me	60
12	**1c**	1,4-	Et$_2$CO	**2l**	Et	Et	85
13	**1c**	1,4-	PhCOMe	**2m**	Me	Ph	54 [f]
14	**1c**	1,4-	(CH$_2$)$_5$CO	**2n**	−(CH$_2$)$_5$−	−(CH$_2$)$_5$−	73

Synthesis of diols **2**.
[a] All compounds **2** were > 95% pure (300 MHz ^{1}H-NMR and/or GLC).
[b] Isolated yield after column chromatography (neutral silica gel, hexane−ethyl acetate) based on the starting compound **1**, unless otherwise stated.
[c] Diastereomeric ratio (ca. 1:1) (300 MHz 1H NMR of crude mixture).
[d] Both diastereoisomers were individually isolated.
[e] Yield obtained by sequential lithiation and electrophilic substitution process.
[f] Diastereomeric ratio (ca. 1:1) (HPLC of crude mixture).
[g] Diastereomeric ratio (ca. 2:1) (HPLC of crude mixture).

3

4a (R^1 = H, R^2 = Bu^t) [65%[a] (60%)[b]]
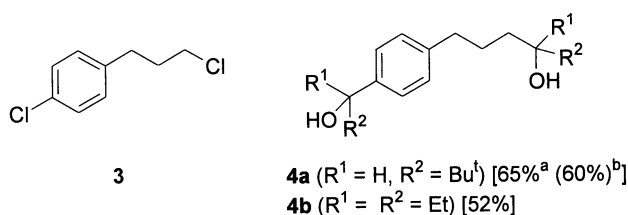**4b** (R^1 = R^2 = Et) [52%]

Fig. 2. Preparation of compounds **4**: (a) Barbier-type reaction; a ca. 1:1 diastereoisomeric ratio was obtained (HPLC of crude mixture). (b) Yield corresponding to the two-step reaction process.

corresponding commercially available brominated homobenzylic alcohols.

2.3. Dehydration of some diols 2

Some diols **2** were treated under dehydration conditions in order to study their possible cyclisation versus olefin formation process. Thus, under Mitsunobu-type conditions [23] compound (R*,S*)-**2a** (the more polar

diastereoisomer product isolated after column-chromatographic separation) gave the *cis*-oxepane **11** [24], so confirming the relative stereochemistry of the starting diol, which suffered an expected inversion process (Scheme 3). Surprisingly, the same procedure applied to the other less polar (R*,R*)-diastereoisomer gave a mixture of compounds containing mainly the starting diol. We do not have any reasonable explanation for this different behaviour.

The aforementioned Mitsunobu procedure was applied to the corresponding 1,2-derivative **2c**, but even performing the reaction under stronger conditions (3 days under reflux) only the starting material was recovered. For this reason, we studied the dehydration of diols **2c,h,m** with 85% phosphoric acid [25] at toluene reflux, so the corresponding diolefins **12** were isolated with excellent yields (Scheme 4). On the other hand, compounds of type **12** can be used as bidentated-diene ligands in the preparation of organometallic compounds [26].

5

6a (R^1 = R^2 = Et) [53%]
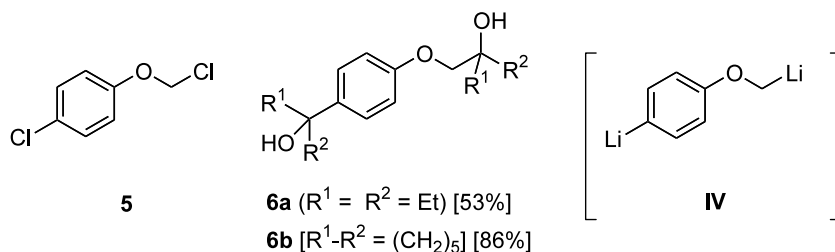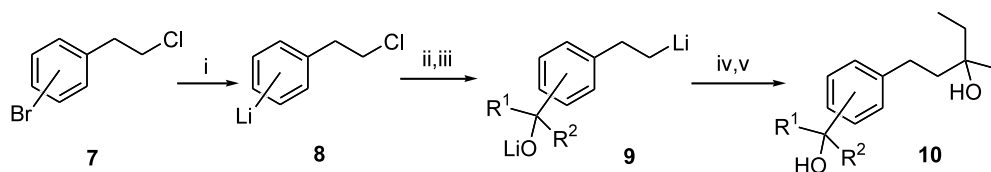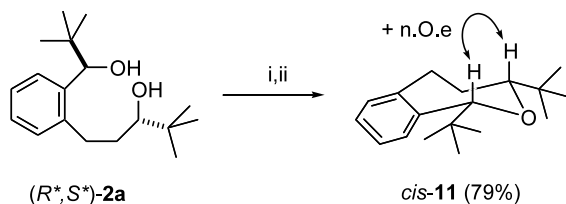**6b** [R^1-R^2 = (CH$_2$)$_5$] [86%]

IV

Fig. 3. Preparation of compounds **6**.

Scheme 2. Synthesis of diols **10**. Reagents and conditions: (i) *n*-BuLi (1.1 equivalents), THF, −100 °C, 5 min. (ii) RCOR′ (1.2 equivalents), 15 min. (iii) Li powder (seven equivalents), C_8H_{10} (8%), THF, −78 °C, 30 min. (iv) Et_2CO (1.3 equivalents), −78 °C, overnight. (v) H_2O.

Scheme 3. Synthesis of oxepane **11**. Reagents and conditions: (i) PPh_3 (2.4 equivalents), DIAD (2.4 equivalents), C_6H_6, 80 °C, 3 h. (ii) H_2O.
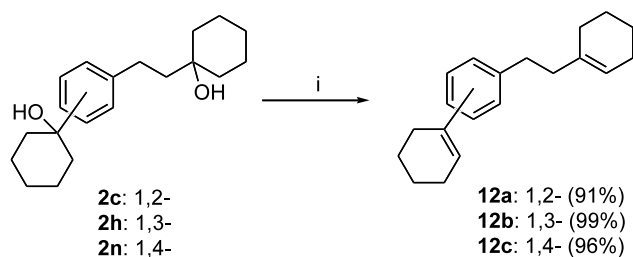
Scheme 4. Synthesis of dienes **12**. Reagents and conditions: (i) 85% H_3PO_4 (2.2 equivalents), toluene, 110 °C, 6 h.

3. Conclusions

From the results reported in this paper, we conclude that the use of dichlo (**1**, **3**, **5**) or bromochloro derivatives (**7**) in a tandem lithiation-electrophilic substitution reaction using carbonyl compounds as electrophiles, allows to carry out simultaneous or sequential double homologation processes giving diols, when carbonylic compounds are used as electrophiles. These remote functionalised molecules can be dehydrated

giving different compounds depending on the structure of starting diols.

4. Experimental

4.1. General

Full general statements were described elsewhere [27]. All reactions using organolithium compounds were carried out under nitrogen atmosphere using standard Schlenk techniques. Compound **3** was purchased from Maybridge, all other reagents were obtained from Aldrich and used without further purification.

4.2. Preparation of dihalogenated materials

According to the literature procedure [21], dihalogenated compounds **1** and **7** were prepared from the corresponding commercially available 2-(halophenyl)ethanol (20.0 mmol) by reaction with mesylchloride (3.0 ml, 30.0 mmol) and triethylamine (7.0 ml, 50 mmol) in dry toluene (40 ml) at 0 °C. After 1 h, dry DMF (40 ml) and LiCl (4.2 g, 100 mmol) were successively added at r.t. After 24 h, the mixture was washed with water (2 × 50 ml). The separated aqueous layer was extracted with ethyl acetate (3 × 40 ml). All combined organic layers were washed with brine (2 × 100 ml), and then dried over $MgSO_4$. Solvent was removed under reduced pressure (15 Torr) to yield the corresponding pure compound. Yields, as well as physical, spectroscopic and literature data follow.

Table 2
Sequential two-directional homologation

Entry	Starting material		Electrophile	Product [a]				
	Number	Substitution		Number	R^1	R^2	Yield (%) [b]
1	**7a**	1,2-	PhCHO	**10a**	H	Ph	55
2	**7a**	1,2-	$(CH_2)_5CO$	**10b**	$-(CH_2)_5-$	$-(CH_2)_5-$	64
3	**7b**	1,3-	PhCHO	**10c**	H	Ph	70
4	**7b**	1,3-	$(CH_2)_5CO$	**10d**	$-(CH_2)_5-$	$-(CH_2)_5-$	85
5	**7c**	1,4-	PhCHO	**10e**	H	Ph	50
6	**7c**	1,4-	$(CH_2)_5CO$	**10f**	$-(CH_2)_5-$	$-(CH_2)_5-$	45

Synthesis of diols **10**.
[a] All compounds **10** were >95% pure (300 MHz ^{1}H-NMR and/or GLC).
[b] Isolated yield after column chromatography (neutral silica gel, hexane–ethyl acetate) based on the starting compound **7**.

4.2.1. 1-Chloro-2-(2-chloroethyl)benzene (**1a**) [28]

Yield 91%; R_f (hexane–ethyl acetate: 4/1) 0.62; ν_{max} (liquid film) 3062, 3019, 1594 cm^{-1}; δ_H (300 MHz, CDCl$_3$) 7.35–7.30 and 7.25–7.10 (1 and 3H, respectively, 2m, ArH), 3.69 (2H, t, $J = 7.3$ Hz, CH$_2$Cl), 3.15 (2H, t, $J = 7.3$ Hz, C*H$_2$*CH$_2$Cl); δ_C (75 MHz, CDCl$_3$) 135.4, 133.85, 131.15, 129.45, 128.25, 126.7, 42.9, 36.7; m/z (EI) 178 (2, [M$^+$ +4]), 176 (9, [M$^+$ +2]), 174 (15, [M$^+$]), 127 (32), 125 (100), 89 (10), 77 (10), 51 (19), 50 (11).

4.2.2. 1-Chloro-3-(2-chloroethyl)benzene (**1b**) [29]

Yield 91%; R_f (hexane–ethyl acetate: 7/3) 0.69; ν_{max} (liquid film) 3063, 1599 cm^{-1}; δ_H (300 MHz, CDCl$_3$) 7.30–7.20 and 7.15–7.05 (3 and 1H, respectively, 2m, ArH), 3.70 (2H, t, $J = 7.3$ Hz, CH$_2$Cl), 3.04 (2H, t, $J = 7.3$ Hz, C*H$_2$*CH$_2$Cl); δ_C (75 MHz, CDCl$_3$) 140.0, 134.3, 129.75, 128.95, 127.05, 127.0, 44.45, 38.6; m/z (EI) 178 (5, [M$^+$ +4]), 176 (28, [M$^+$ +2]), 174 (42, [M$^+$]), 139 (10), 127 (60), 126 (16), 125 (100), 103 (16), 89 (25), 77 (23), 75 (18), 63 (15).

4.2.3. 1-Chloro-4-(2-chloroethyl)benzene (**1c**) [29]

Yield 86%; R_f (hexane–ethyl acetate: 7/3) 0.63; ν_{max} (liquid film) 3028, 1598 cm^{-1}; δ_H (300 MHz, CDCl$_3$) 7.30–7.25 and 7.15–7.10 (2 and 2H, respectively, 2m, ArH), 3.67 (2H, t, $J = 7.0$ Hz, CH$_2$Cl), 3.01 (2H, t, $J = 7.0$ Hz, C*H$_2$*CH$_2$Cl); δ_C (75 MHz, CDCl$_3$) 136.4, 132.6, 130.1 (2C), 128.6 (2C), 44.65, 38.25; m/z (EI) 178 (2, [M$^+$ +4]), 176 (12, [M$^+$ +2]), 174 (18, [M$^+$]), 127 (39), 125 (100), 89 (13), 77 (11), 51 (22), 50 (15).

4.2.4. 1-Bromo-2-(2-chloroethyl)benzene (**7a**) 22i

Yield 91%; R_f (hexane–ethyl acetate: 4/1) 0.71; ν_{max} (liquid film) 3058, 1591 cm^{-1}; δ_H (300 MHz, CDCl$_3$) 7.55–7.50, 7.30–7.25 and 7.15–7.10 (1, 2 and 1H, respectively, 3m, ArH), 3.73 (2H, t, $J = 7.3$ Hz, CH$_2$Cl), 3.20 (2H, t, $J = 7.3$ Hz, C*H$_2$*CH$_2$Cl); δ_C (75 MHz, CDCl$_3$) 137.2, 132.9, 131.3, 128.65, 127.5, 124.35, 43.15, 39.3; m/z (EI) 222 (8, [M$^+$ +4]), 220 (36, [M$^+$ +2]), 218 (27, [M$^+$]), 171 (82), 169 (100), 139 (11), 103 (17), 102 (11), 90 (28), 89 (21), 77 (26), 75 (11), 63 (19), 51 (33), 50 (26), 49 (11).

4.2.5. 1-Bromo-3-(2-chloroethyl)benzene (**7b**) [30]

Yield 91%; R_f (hexane–ethyl acetate: 7/3) 0.70; ν_{max} (liquid film) 3059, 1595 cm^{-1}; δ_H (300 MHz, CDCl$_3$) 7.40–7.35 and 7.25–7.10 (2 and 2H, respectively, 2m, ArH), 3.68 (2H, t, $J = 7.2$ Hz, CH$_2$Cl), 3.01 (2H, t, $J = 7.2$ Hz, C*H$_2$*CH$_2$Cl); δ_C (75 MHz, CDCl$_3$) 140.25, 131.8, 130.05, 130.0, 127.45, 122.5, 44.45, 38.5; m/z (EI) 222 (6, [M$^+$ +4]), 220 (28, [M$^+$ +2]), 218 (22, [M$^+$]), 171 (72), 170 (11), 169 (100), 104 (12), 103 (13), 90 (35), 89 (22), 77 (26), 75 (12), 63 (15), 51 (45), 50 (27).

4.2.6. 1-Bromo-4-(2-chloroethyl)benzene (**7c**) [29]

Yield 73%; R_f (hexane–ethyl acetate: 4/1) 0.66; ν_{max} (liquid film) 3027, 1595 cm^{-1}; δ_H (300 MHz, CDCl$_3$) 7.43 and 7.08 (2 and 2H, respectively, 2d, $J = 8.2$ Hz, ArH), 3.67 (2H, t, $J = 7.2$ Hz, CH$_2$Cl), 3.00 (2H, t, $J = 7.2$ Hz, C*H$_2$*CH$_2$Cl); δ_C (75 MHz, CDCl$_3$) 136.95, 131.6 (2C), 130.5 (2C), 120.7, 44.55, 38.35; m/z (EI) 222 (5, [M$^+$ +4]), 220 (28, [M$^+$ +2]), 218 (23, [M$^+$]), 171 (78), 169 (100), 90 (23), 89 (16), 77 (13), 51 (30), 50 (20).

4.3. Naphthalene-catalysed lithiation of dichlorinated materials **1**, **3** and **5** in the presence of electrophiles. Isolation of compounds **2**, **4** and **6**

4.3.1. General procedure

To a green suspension of lithium powder (ca. 100 mg, 14 mmol) and naphthalene (20 mg, 0.16 mmol) in THF (8 ml), under nitrogen atmosphere, was dropwise added a solution of dichlorinated material **1**, **3** or **5** (2.0 mmol) and the corresponding carbonylic compound (5 mmol) in THF (2 ml), at −78 °C. The mixture was stirred for ca. 4 h. Then, the reaction was quenched by subsequent addition of water (10 ml) and saturated solution of NH$_4$Cl (25 ml). The mixture was extracted with ethyl acetate (3 × 20 ml). The combined organic layers were dried over anhydrous MgSO$_4$. After evaporation of the solvents under reduced pressure (15 Torr), the resulting residue was purified by column chromatography (neutral silica gel, hexane–ethyl acetate) to yield the title pure compounds **2**, **4** or **6**. Yields, as well as physical, analytical and spectroscopic data follow.

4.3.1.1. (R*,R*)-1-[2-(1-Hydroxy-2,2-dimethylpropyl)phenyl]-4,4-dimethyl-3-pentanol [(R*,R*)-2a].
Yield 22%; R_f (hexane–ethyl acetate: 7/3) 0.68; ν_{max} (liquid film) 3435, 3062, 3023, 1603, 1077, 1040, 1006 cm^{-1}; δ_H (300 MHz, CDCl$_3$) 7.50–7.45 and 7.25–7.20 (1 and 3H, respectively, 2m, ArH), 4.86 (1H, s, CCHOC), 3.20–3.15 (1H, m, CC*H*OCH$_2$), 2.95–2.75 (2H, m, CCH$_2$), 1.90–1.80 and 1.65–1.50 (3 and 1H, respectively, 2m, CH$_2$COH, OH), 0.96 and 0.87 (9 and 9H, respectively, 2s, 6 × Me); δ_C (75 MHz, CDCl$_3$) 140.25, 140.2, 128.75, 127.7, 127.15, 125.35, 79.25, 76.75, 36.7, 34.95, 33.25, 29.8, 26.2 (3C), 25.65 (3C); m/z (EI) 278 (<1, [M$^+$]), 185 (11), 147 (13), 146 (14), 145 (100), 143 (29), 133 (11), 129 (17), 119 (17), 117 (41), 105 (10), 91 (33), 87 (35), 71 (13), 69 (19), 59 (67), 57 (66), 55 (10), 43 (49), 41 (57); HRMS (EI) [M$^+$], Found: 278.2259. C$_{18}$H$_{30}$O$_2$ requires 278.2246%.

4.3.1.2. (R*,S*)-1-[2-(1-Hydroxy-2,2-dimethylpropyl)phenyl]-4,4-dimethyl-3-pentanol [(R*,S*)-2a].
Yield 23%; R_f (hexane–ethyl acetate: 7/3) 0.62; ν_{max} (liquid film) 3439, 3061, 3022, 1602, 1074, 1040, 1005 cm^{-1}; δ_H (300 MHz, CDCl$_3$) 7.50–7.45 and 7.25–7.20 (1 and 3H, respectively, 2m, ArH), 4.85 (1H,

s, CCHOC), 3.25–3.20 (1H, m, CC*H*OCH$_2$), 3.15–3.05 and 2.65–2.55 (1 and 1H, respectively, 2m, CC*H*$_2$), 1.85–1.45 (4H, m, CH$_2$COH, OH), 0.97 and 0.88 (9 and 9H, respectively, 2s, 6 × Me); δ_C (75 MHz, CDCl$_3$) 140.35, 139.95, 129.15, 128.05, 127.1, 125.4, 79.75, 77.0, 36.7, 34.95, 33.55, 30.45, 26.2 (3C), 25.65 (3C); *m/z* (EI) 260 (< 1, [M$^+$ −18]), 185 (11), 147 (13), 146 (13), 145 (100), 143 (29), 133 (11), 129 (17), 119 (17), 117 (42), 105 (11), 91 (33), 87 (36), 71 (14), 69 (19), 59 (68), 57 (68), 43 (49), 41 (57); HRMS (EI) [M$^+$ −OH], Found: 261.2225. C$_{18}$H$_{29}$O requires 261.2218%.

4.3.1.3. 3-Ethyl-1-[2-(1-ethyl-1-hydroxypropyl)phenyl]-3-pentanol (2b). Yield 51%; R_f (hexane–ethyl acetate: 7/3) 0.54; ν_{max} (liquid film) 3423, 3058, 1600, 1184, 1156, 1127 cm^{-1}; δ_H (300 MHz, CDCl$_3$) 7.23 and 7.15–7.10 (1 and 3H, respectively, d and m, $J = 6.7$ Hz, ArH), 2.95–2.90 (2H, m, C*H*$_2$CH$_2$CO), 2.18 (2H, s, 2 × OH), 2.10–1.95, 1.90–1.80, 1.75–1.70 and 1.53 (2, 2, 2 and 4H, respectively, 3m and q, respectively, $J = 7.3$ Hz, 5 × CH$_2$CO), 0.89 and 0.79 (6 and 6H, respectively, 2t, $J = 7.3$ Hz, 4 × Me); δ_C (75 MHz, CDCl$_3$) 141.9, 141.5, 131.85, 127.4, 126.5, 125.05, 79.5, 74.75, 41.65, 34.55 (2C), 30.70 (2C), 28.15, 8.2 (2C), 7.85 (2C); *m/z* (EI) 249 (1, [M$^+$ −29]), 231 (11), 213 (22), 171 (30), 159 (14), 157 (19), 146 (12), 145 (100), 143 (39), 131 (14), 129 (27), 128 (16), 117 (46), 115 (13), 91 (31), 87 (80), 69 (14), 57 (68), 55 (21), 45 (39), 43 (53), 41 (35); HRMS (EI) [M$^+$ −Et], Found: 249.1860. C$_{16}$H$_{25}$O$_2$ requires 249.1855%.

4.3.1.4. 1-{2-[2-(1-hydroxycyclohexyl)phenyl]ethyl}-1-cyclohexanol (2c). Yield 65%; R_f (hexane–ethyl acetate: 7/3) 0.24; ν_{max} (liquid film) 3415, 3058, 3009, 1600, 1171, 1145, 1134 cm^{-1}; δ_H (300 MHz, CDCl$_3$) 7.33 and 7.25–7.05 (1 and 3H, respectively, d and m, $J = 7.3$ Hz, ArH), 3.05–3.00 (2H, m, C*H*$_2$Ar), 2.42 (2H, s, 2 × OH), 2.00–1.95, 1.85–1.20 (2 and 20H, respectively, 2m, 2 × (CH$_2$)$_5$ and ArCH$_2$C*H*$_2$); δ_C (75 MHz, CDCl$_3$) 145.7, 141.95, 132.0, 126.8, 125.3, 125.25, 74.5, 71.5, 45.2, 38.2 (2C), 37.6 (2C), 27.6, 25.85, 25.45, 22.3 (2C), 21.95 (2C); *m/z* (EI) 302 (1, [M$^+$]), 284 (11), 266 (19), 213 (43), 202 (15), 201 (100), 200 (13), 195 (16), 184 (20), 183 (57), 182 (15), 170 (20), 157 (12), 145 (39), 144 (11), 143 (37), 142 (22), 141 (42), 134 (16), 133 (15), 132 (11), 131 (21), 130 (35), 129 (47), 128 (19), 119 (28), 117 (22), 115 (19), 105 (14), 99 (30), 95 (11), 91 (41), 81 (47), 79 (17), 77 (14), 67 (13), 57 (14), 55 (77), 53 (11), 43 (45), 41 (57); HRMS (EI) [M$^+$ −H$_2$O], Found: 284.2115. C$_{20}$H$_{28}$O requires 284.2140%.

4.3.1.5. 1-[3-(1-Hydroxy-2,2-dimethylpropyl)phenyl]-4,4-dimethyl-3-pentanol (2d). Yield 70%; R_f (hexane–ethyl acetate: 7/3) 0.49; ν_{max} (liquid film) 3439, 3026, 1606, 1048, 1010 cm^{-1}; δ_H (300 MHz, CDCl$_3$) 7.25–7.10 (4H, m, ArH), 4.34 (1H, s, CCHOC), 3.20–3.15 (1H, m, CC*H*OCH$_2$), 2.90–2.85 and 2.65–2.55 (1 and

1H, respectively, 2m, CC*H*$_2$), 2.2 (2H, brs, 2 × OH), 1.85–1.75 and 1.60–1.55 (1 and 1H, respectively, 2m, CH$_2$CO) 0.90 and 0.86 (9 and 9H, respectively, 2s, 6 × Me); δ_C (75 MHz, CDCl$_3$) 142.3, 141.5, 127.75, 127.65, 127.45 (minor diastereoisomer), 127.4, 127.3 (minor diastereoisomer), 125.1, 125.0 (minor diastereoisomer), 82.25, 79.15, 79.05 (minor diastereoisomer), 35.5, 34.85, 33.3, 33.25 (minor diastereoisomer), 33.2, 25.9 (3C), 25.6 (3C); *m/z* (EI) 260 (5, [M$^+$ −18]), 227 (10), 203 (12), 172 (14), 160 (12), 159 (31), 157 (14), 147 (17), 145 (16), 143 (15), 133 (24), 129 (13), 128 (10), 120 (11), 119 (57), 117 (27), 115 (11), 105 (50), 91 (46), 83 (18), 77 (11), 71 (20), 69 (36), 57 (63), 55 (23), 44 (28), 43 (41), 41 (100), 40 (22); HRMS (EI) [M$^+$ −H$_2$O], Found: 260.2120. C$_{18}$H$_{28}$O requires 260.2140%.

4.3.1.6. 3-[3-Hydroxy(phenyl)methylphenyl]-1-phenyl-1-propanol (2e). Yield 68%; R_f (ethyl acetate) 0.73; ν_{max} (liquid film) 3373, 3085, 3060, 3028, 1603, 1493, 1039, 1023 cm^{-1}; δ_H (300 MHz, CDCl$_3$) 7.25–7.00 (14H, m, ArH), 5.60 (1H, s, CCHOC), 4.55–4.40 (1H, m, CC*H*OCH$_2$), 2.97 (2H, brs, 2 × OH), 2.60–2.50 (2H, C*H*$_2$CH$_2$CO), 1.95–1.80 (2H, m, CH$_2$CO); δ_C (75 MHz, CDCl$_3$) 144.35, 143.8, 141.85, 141.8, 128.2 (4C), 127.3, 127.2, 126.55, 126.45, 126.40 (2C), 126.35, 125.8 (2C), 124.05, 75.9, 73.45, 40.05, 31.8; *m/z* (EI) 318 (< 1, [M$^+$]), 301 (14), 300 (60), 196 (12), 194 (38), 193 (37), 181 (19), 180 (94), 179 (51), 178 (22), 166 (10), 165 (48), 119 (13), 117 (11), 115 (18), 107 (71), 105 (98), 92 (15), 91 (51), 79 (100), 78 (20), 77 (99), 51 (24); HRMS (EI) [M$^+$], Found: 318.1644. C$_{22}$H$_{22}$O$_2$ requires 318.1620%.

4.3.1.7. 3-Ethyl-1-[3-(1-ethyl-1-hydroxypropyl)phenyl]-3-pentanol (2f). Yield 76%; R_f (hexane–ethyl acetate: 1/2) 0.71; ν_{max} (liquid film) 3453, 3023, 1604, 1159 cm^{-1}; δ_H (300 MHz, CDCl$_3$) 7.25–7.15 and 7.05–7.00 (3 and 1H, respectively, 2m, ArH), 2.65–2.60 (2H, m, C*H*$_2$CH$_2$CO), 1.95 (2H, s, 2 × OH), 1.90–1.70 and 1.55–1.50 (6 and 4H, respectively, m and q, respectively, $J = 7.5$ Hz, 5 × CH$_2$CO), 0.89 and 0.75 (6 and 6H, respectively, 2t, $J = 7.5$ Hz, 4 × Me); δ_C (75 MHz, CDCl$_3$) 145.8, 142.1, 127.65, 125.9, 125.3, 122.75, 77.1, 77.4, 40.15, 34.55 (2C), 30.65 (2C), 29.9, 7.65 (4C); *m/z* (EI) 260 (4, [M$^+$ −18]), 242 (26), 231 (18), 213 (18), 160 (14), 159 (73), 157 (17), 147 (12), 143 (13), 131 (16), 129 (23), 128 (16), 117 (21), 115 (15), 91 (19), 87 (17), 83 (12), 57 (100), 55 (31), 45 (22), 43 (22), 41 (55); HRMS (EI) [M$^+$ −H$_2$O], Found: 260.2132. C$_{18}$H$_{28}$O requires 260.2140%.

4.3.1.8. 4-{[3-(1-Hydroxy-1-phenyl)ethyl]phenyl}-2-phenyl-2-butanol (2g). Yield 53%; R_f (ethyl acetate) 0.85; ν_{max} (liquid film) 3438, 3085, 3057, 3025, 1601, 1493, 1066, 1028 cm^{-1}; δ_H (300 MHz, CDCl$_3$) 7.40–7.10 and 7.00–6.95 (13 and 1H, respectively, 2m, ArH), 2.60–2.35 (3H, m, C*H*$_2$CH$_2$CO, OH), 2.15–2.05 (3H, m,

CH$_2$CO, OH), 1.86 and 1.52 (3 and 3H, respectively, 2s, 2 × Me); δ_C (75 MHz, CDCl$_3$) 148.0, 147.45, 142.0 (2C), 128.1 (4C), 128.0, 126.7 (2C), 126.5, 125.7 (2C), 125.65, 124.65 (2C), 123.35, 76.05, 74.55, 45.7, 30.7, 30.45, 30.25; m/z (EI) 328 (3, [M$^+$−18]), 310 (37), 217 (10), 208 (27), 207 (29), 206 (32), 205 (11), 193 (57), 192 (11), 191 (23), 179 (18), 178 (56), 165 (11), 130 (20), 129 (18), 121 (62), 115 (24), 103 (43), 91 (49), 77 (25), 51 (14), 43 (100); HRMS (EI) [M$^+$], Found: 346.1945. C$_{24}$H$_{26}$O$_2$ requires 346.1933%.

4.3.1.9. 1-{2-[3-(1-Hydroxycyclohexyl)phenyl]ethyl}-1-cyclohexanol (2h).

Yield 63%; m.p. 84–86 °C (ethyl acetate–hexane); R_f (hexane–ethyl acetate: 1/2) 0.71; ν_{max} (melted film) 3415, 3023, 1604, 1169, 1133 cm^{-1}; δ_H (300 MHz, CDCl$_3$) 7.35, 7.30–7.20 and 7.05–7.00 (1, 2 and 1H, respectively, s, m and m, respectively, ArH), 2.70–2.65 (2H, m, CH_2Ar), 1.98 (2H, s, 2 × OH), 1.70–1.25 (22H, m, 2 × (CH$_2$)$_5$ and ArCH$_2$CH_2); δ_C (75 MHz, CDCl$_3$) 149.55, 142.55, 128.0, 126.5, 124.55, 121.85, 72.95, 71.3, 44.2, 38.65 (2C), 37.3 (2C), 29.45, 25.7, 25.4, 22.15 (2C), 22.0 (2C); m/z (EI) 284 (20, [M$^+$−18]), 267 (16), 266 (83), 223 (11), 190 (15), 186 (14), 185 (19), 184 (47), 183 (18), 173 (15), 172 (68), 171 (100), 170 (19), 169 (12), 158 (11), 157 (22), 155 (15), 145 (18), 144 (12), 143 (34), 142 (20), 141 (35), 131 (12), 130 (26), 129 (59), 128 (47), 127 (12), 118 (12), 117 (29), 115 (32), 105 (27), 104 (22), 99 (27), 95 (37), 93 (13), 91 (45), 81 (62), 80 (24), 79 (41), 77 (28), 67 (39), 65 (13), 55 (77), 53 (29), 43 (33), 41 (85); Anal. Found: C, 79.38; H, 10.08. Calc. for C$_{20}$H$_{30}$O$_2$: C, 79.42; H, 10.00%.

4.3.1.10. 1-[4-(1-Hydroxy-2,2-dimethylpropyl)phenyl]-4,4-dimethyl-3-pentanol (2i).

Yield 78%; m.p. 112–114 °C (ethyl acetate–hexane); R_f (hexane–ethyl acetate: 7/3) 0.47; ν_{max} (melted film) 3439, 3088, 3048, 1614, 1511, 1048, 1009 cm^{-1}; δ_H (300 MHz, CDCl$_3$) 7.20–7.15 (4H, m, ArH), 4.34 (1H, s, CCHOC), 3.20–3.15, 2.95–2.85 and 2.65–2.55 (1, 1 and 1H, respectively, 3m, CH_2CH$_2$CHO), 1.90–1.75 and 1.60–1.55 (3 and 1H, respectively, 2m, CH$_2$CO, 2 × OH) 0.91 and 0.87 (9 and 9H, respectively, 2s, 6 × Me); δ_C (75 MHz, CDCl$_3$) 141.35, 139.65, 127.6 (4C), 82.15, 79.3, 35.55, 34.9, 33.35, 32.95, 25.9 (3C), 25.6 (3C); m/z (EI) 278 (< 1, [M$^+$]), 260 (15), 222 (10), 221 (73), 203 (18), 185 (12), 172 (52), 160 (17), 159 (100), 158 (11), 157 (26), 147 (22), 145 (18), 143 (23), 133 (56), 131 (13), 129 (27), 128 (15), 120 (27), 119 (73), 117 (48), 114 (16), 105 (86), 92 (11), 91 (91), 77 (11), 71 (22), 69 (40), 57 (77), 55 (15), 43 (28), 41 (81); Anal. Found: C, 77.61; H, 10.76. Calc. for C$_{18}$H$_{30}$O$_2$: C, 77.65; H, 10.86%.

4.3.1.11. 3-[4-Hydroxy(phenyl)methylphenyl]-1-phenyl-1-propanol (2j).

Yield 60%; m.p. 109–111 °C (ethyl acetate–hexane); R_f (hexane–ethyl acetate: 7/3) 0.18; ν_{max} (liquid film) 3543, 3369, 3085, 3060, 3028, 1602,

1511, 1493, 1058, 1035, 1024, 1016 cm^{-1}; δ_H (300 MHz, CDCl$_3$) 7.30–7.20 and 7.10–7.05 (13 and 1H, respectively, 2m, ArH), 5.72 (1H, s, CCHOC), 4.60–4.55 (1H, m, CCHOCH$_2$), 2.70–1.19 (6H, m, CH$_2$CH$_2$, 2 × OH); δ_C (75 MHz, CDCl$_3$) 144.4, 143.85, 141.35, 141.05, 128.45 (2C), 128.4 (2C), 128.35 (2C), 127.55, 127.35, 126.6 (2C), 126.4 (2C), 125.85 (2C), 75.9, 73.7, 40.25, 31.6; m/z (EI) 318 (< 1, [M$^+$]), 196 (11), 195 (15), 194 (72), 193 (40), 181 (17), 180 (100), 179 (15), 178 (16), 165 (15), 117 (12), 115 (14), 107 (80), 106 (11), 105 (80), 92 (12), 91 (36), 79 (46), 77 (51), 51 (10)); Anal. Found: C, 82.85; H, 6.91. Calc. for C$_{22}$H$_{22}$O$_2$: C, 82.99; H, 6.96%.

4.3.1.12. 4-[4-(1-Hydroxy-1-methylethyl)phenyl]-2-methyl-2-butanol (2k).

Yield 60%; R_f (hexane–ethyl acetate: 1/1) 0.37; ν_{max} (liquid film) 3371, 3088, 3052, 3023, 1613, 1510, 1212, 1169, 1146 cm^{-1}; δ_H (300 MHz, CDCl$_3$) 7.38 and 7.15 (2 and 2H, respectively, 2d, $J =$ 8.5 Hz, ArH), 2.70–2.65 (2H, m, CH_2CH$_2$CO), 2.18 (2H, s, 2 × OH), 1.80–1.75 (2H, m, CH$_2$CO), 1.55 and 1.26 (6 and 6H, respectively, 2s, 4 × Me); δ_C (75 MHz, CDCl$_3$) 146.55, 140.7, 127.95 (2C), 124.4 (2C), 72.2, 70.75, 45.55, 31.6 (2C), 30.1, 29.15 (2C); m/z (EI) 222 (< 1, [M$^+$]), 204 (13), 189 (33), 186 (32), 171 (19), 143 (22), 133 (11), 131 (74), 129 (18), 128 (11), 115 (15), 105 (10), 91 (21), 59 (41), 43 (100), 41 (15); HRMS (EI) [M$^+$], Found: 222.1615. C$_{14}$H$_{22}$O$_2$ requires 222.1620%.

4.3.1.13. 3-Ethyl-1-[4-(1-ethyl-1-hydroxypropyl)phenyl]-3-pentanol (2l).

Yield 85%; R_f (hexane–ethyl acetate: 7/3) 0.54; ν_{max} (liquid film) 3439, 3089, 3051, 3022, 1614, 1511, 1159 cm^{-1}; δ_H (300 MHz, CDCl$_3$) 7.3 and 7.16 (2 and 2H, respectively, 2d, $J =$ 7.9 Hz, ArH), 2.65–2.60 (2H, m, CH_2CH$_2$CO), 1.85–1.70 and 1.54 (7 and 5H, respectively, 2m, 5 × CH$_2$CO, 2 × OH), 0.90 and 0.75 (6 and 6H, respectively, 2t, $J =$ 7.3 Hz, 4 × Me); δ_C (75 MHz, CDCl$_3$) 143.15, 140.5, 127.8 (2C), 125.45 (2C), 77.2, 74.55, 40.1, 34.7 (2C), 30.9 (2C), 29.3, 7.8 (2C), 7.75 (2C); m/z (EI) 260 (< 1, [M$^+$−18]), 242 (18), 160 (13), 159 (100), 129 (13), 57 (17), 41 (21); HRMS (EI) [M$^+$], Found: 278.2210. C$_{18}$H$_{30}$O$_2$ requires 278.2246%.

4.3.1.14. 4-{[4-(1-Hydroxy-1-phenyl)ethyl]phenyl}-2-phenyl-2-butanol (2m).

Yield 54%; R_f (hexane–ethyl acetate: 1/1) 0.61; ν_{max} (liquid film) 3439, 3086, 3057, 3025, 1601, 1494, 1066 cm^{-1}; δ_H (300 MHz, CDCl$_3$) 7.45–7.10 and 7.05–7.00 (12 and 2H, respectively, 2m, ArH), 2.60–2.35 (3H, m, CH_2CH$_2$CO, OH), 2.20–2.00 (3H, m, CH$_2$CO, OH), 1.87 and 1.55 (3 and 3H, respectively, 2s, 2 × Me); δ_C (75 MHz, CDCl$_3$) 148.05, 147.45, 145.4, 140.8, 128.15 (2C), 127.95 (4C), 126.7, 126.55, 125.8 (2C), 125.7 (2C), 124.7 (2C), 75.95, 74.55, 45.7, 30.7, 30.3, 29.85; m/z (EI) 328 (3, [M$^+$−18]), 311 (11), 310 (44), 208 (15), 207 (25), 206 (12), 194 (17), 193

(100), 191 (12), 178 (31), 129 (13), 121 (40), 115 (17), 103 (34), 91 (27), 77 (16), 43 (81); HRMS (EI) [$M^+ - H_2O$], Found: 328.1823. $C_{24}H_{24}O$ requires 328.1827%.

4.3.1.15. 1-{2-[4-(1-Hydroxycyclohexyl)phenyl]ethyl}-1-cyclohexanol (2n).

Yield 73%; m.p. 114–116 °C (ethyl acetate–hexane); R_f (hexane–ethyl acetate: 7/3) 0.32; ν_{max} (melted film) 3394, 3022, 1613, 1513, 1147, 1133 cm^{-1}; δ_H (300 MHz, CDCl$_3$) 7.42 and 7.18 (2 and 2H, respectively, 2d, respectively, $J = 7.9$ Hz, ArH), 2.70–2.65 (2H, m, CH_2Ar), 1.80–1.25 (24H, m, 2 × (CH$_2$)$_5$, ArCH$_2$CH_2, 2 × OH); δ_C (75 MHz, CDCl$_3$) 146.85, 141.2, 128.15 (2C), 124.65 (2C), 72.95, 71.4, 44.25, 38.85 (2C), 37.5 (2C), 28.9, 25.8, 25.5, 22.25 (2C), 22.2 (2C); m/z (EI) 284 (4, [$M^+ - 18$]), 266 (34), 184 (15), 172 (17), 171 (100), 141 (15), 129 (16), 128 (16), 115 (15), 91 (22), 81 (15), 79 (10), 55 (14), 41 (26); Anal. Found: C, 79.28; H, 9.91. Calc. for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00%.

4.3.1.16. 6-[4-(1-Hydroxy-2,2-dimethylpropyl)phenyl]-2,2-dimethyl-3-hexanol (4a).

Yield 65%; R_f (hexane–ethyl acetate: 7/3) 0.57; ν_{max} (liquid film) 3416, 3091, 3046, 1614, 1514, 1068, 1049, 1007 cm^{-1}; δ_H (300 MHz, CDCl$_3$) 7.18 and 7.11 (2 and 2H, respectively, 2d, $J = 7.9$ Hz, ArH), 4.33 (1H, s, CCHOC), 3.20–3.15 (1H, m, CH$_2$CHO), 2.70–2.50 (2H, m, CCH$_2$), 1.95–1.90, 1.65–1.50, 1.35–1.20 (3, 2 and 1H, respectively, 3m, CH$_2$CH$_2$CO, 2 × OH), 0.90 and 0.86 (9 and 9H, respectively, 2s, 6 × Me); δ_C (75 MHz, CDCl$_3$) 141.4, 139.55, 127.45 (4C), 82.1, 79.65, 35.5, 35.45, 34.9, 31.05, 28.8, 25.9 (3C), 25.6 (3C); m/z (EI) 274 (13, [$M^+ - 18$]), 217 (24), 199 (20), 189 (14), 173 (13), 172 (81), 161 (13), 159 (29), 157 (35), 147 (16), 145 (13), 143 (19), 133 (48), 131 (68), 129 (31), 128 (15), 120 (10), 119 (50), 117 (18), 115 (12), 105 (51), 91 (75), 85 (18), 79 (14), 77 (11), 71 (17), 69 (63), 57 (67), 55 (24), 45 (12), 43 (61), 41 (100); HRMS (EI) [$M^+ - H_2O$], Found: 274.2283. $C_{19}H_{30}O$ requires 274.2297%.

4.3.1.17. 3-Ethyl-6-[4-(1-ethyl-1-hydroxypropyl)phenyl]-3-hexanol (4b).

Yield 52%; R_f (hexane–ethyl acetate: 7/3) 0.52; ν_{max} (liquid film) 3439, 3089, 3051, 3023, 1613, 1511, 1159, 1123 cm^{-1}; δ_H (300 MHz, CDCl$_3$) 7.27 and 7.14 (2 and 2H, respectively, 2d, $J = 7.9$ Hz, ArH), 2.59 (2H, t, $J = 7.3$ Hz, CH_2Ar), 1.90–1.75, 1.65–1.55 and 1.45–1.40 (4, 4 and 6H, respectively, 3m, 5 × CH$_2$CO, CH_2CH$_2$CO, 2 × OH), 0.85–0.70 (12H, m, 4 × Me); δ_C (75 MHz, CDCl$_3$) 143.05, 140.25, 127.85 (2C), 125.35 (2C), 77.15, 74.5, 37.55, 35.85, 34.7 (2C), 30.9 (2C), 25.25, 7.75 (2C), 7.6 (2C); m/z (EI) 274 (1, [$M^+ - 18$]), 245 (14), 172 (52), 159 (16), 143 (14), 117 (11), 57 (100), 55 (14), 45 (12), 43 (12), 41 (24); HRMS (EI) [$M^+ - H_2O$], Found: 274.2270. $C_{19}H_{30}O$ requires 274.2297%.

4.3.1.18. 2-Ethyl-1-[4-(1-ethyl-1-hydroxypropyl)phenoxy]-2-butanol (6a).

Yield 53%; R_f (hexane–ethyl acetate: 7/3) 0.27; ν_{max} (liquid film) 3465, 3038, 1609, 1510, 1175 cm^{-1}; δ_H (300 MHz, CDCl$_3$) 7.28 and 6.88 (2 and 2H, respectively, 2d, $J = 8.8$ Hz, ArH), 3.82 (2H, s CH$_2$O), 2.04 (1H, brs, OH), 1.90–1.75 and 1.70–1.60 (4 and 5H, respectively, 2m, respectively, 4 × CH_2CH$_3$, OH), 0.93 and 0.76 (6 and 6H, respectively, 2t, $J = 7.4$ Hz, 4 × Me); δ_C (75 MHz, CDCl$_3$) 157.25 138.25, 126.6 (2C), 114.0 (2C), 77.1, 73.95, 72.45, 34.85 (2C), 28.4 (2C), 7.8 (2C), 7.7 (2C); m/z (EI) 280 (2, [M^+]), 262 (27), 252 (10), 251 (62), 176 (32), 162 (53), 161 (17), 151 (80), 147 (32), 133 (76), 115 (13), 107 (11), 105 (18), 91 (20), 87 (86), 77 (16), 69 (15), 57 (100), 55 (27), 45 (84), 43 (58), 41 (61); HRMS (EI) [M^+], Found: 280.2037. $C_{17}H_{28}O_3$ requires 280.2038%.

4.3.1.19. 1-[4-(1-Hydroxycyclohexyl)phenoxy]methylcyclohexanol (6b).

Yield 86%; m.p. 129–131 °C (ethyl acetate–hexane); R_f (hexane–ethyl acetate: 7/3) 0.19; ν_{max} (KBr) 3581, 3436, 3062, 3038, 1607, 1511, 1170, 1038 cm^{-1}; δ_H (300 MHz, CDCl$_3$) 7.41 and 6.87 (2 and 2H, respectively, 2d, $J = 8.8$ Hz, ArH), 3.79 (2H, s CH$_2$O), 1.80–1.30 [22H, m, 2 × (CH$_2$)$_5$COH]; δ_C (75 MHz, CDCl$_3$) 157.55, 141.95, 125.8 (2C), 114.15 (2C), 75.35, 72.7, 70.75, 38.85 (2C), 34.3 (2C), 25.8, 25.5, 22.2 (2C), 21.7 (2C); m/z (EI) 286 (27, [$M^+ - 18$]), 188 (17), 175 (13), 174 (100), 173 (14), 159 (25), 146 (38), 145 (25), 131 (11), 129 (13), 128 (12), 115 (17), 107 (10), 99 (23), 91 (20), 81 (34), 80 (11), 79 (19), 77 (15), 67 (13), 55 (36), 53 (14), 43 (33), 41 (56); Anal. Found: C, 74.85; H, 9.19. Calc. for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27%.

4.4. Sequential lithiation of dihalogenated materials 7. Isolation of compounds 10

4.4.1. General procedure

To a solution of starting material **7** (2.0 mmol) in THF (5 ml), under nitrogen atmosphere, was dropwise added a solution of *n*-BuLi (1.3 ml, 2.1 mmol) in hexane at −100 °C. After 5 min at this temperature, the corresponding carbonylic compound (2.2 mmol) was added and the resulting solution was stirred during 15 min. Then, the aforementioned solution was transfer via cannula to a green suspension of lithium powder (ca. 100 mg, 14 mmol) and naphthalene (20 mg, 0.16 mmol) in THF (5 ml) at −78 °C. The mixture was stirred for ca. 30 min and 3-pentanone (4.5 mmol, 0.48 ml) was subsequently added. After additional 30 min, the reaction was quenched by subsequent addition of water (10 ml) and saturated solution of NH$_4$Cl (25 ml). The mixture was extracted with ethyl acetate (3 × 20 ml). The combined organic layers were dried over anhydrous MgSO$_4$. After evaporation of the solvents under reduce pressure (15 Torr), the resulting residue was purified by

column chromatography (neutral silica gel, hexane–ethyl acetate) to yield the title pure compounds **10**. Yields, as well as physical, analytical and spectroscopic data follow.

4.4.1.1. 3-Ethyl-1-[2-hydroxy(phenyl)methylphenyl]-3-pentanol (10a). Yield 55%; R_f (hexane–ethyl acetate: 7/3) 0.23; ν_{max} (liquid film) 3387, 3062, 3027, 1602, 1176, 1019 cm^{-1}; δ_H (300 MHz, CDCl$_3$) 7.40–7.15 (9 H, m, ArH), 6.10 (1H, s, CCHOC), 2.75–2.55 (2H, m, CH_2Ar), 1.70–1.40 (8H, m, 3 × CH$_2$CO, 2 × OH), 0.85–0.80 (6H, m, 2 × Me); δ_C (75 MHz, CDCl$_3$) 143.5, 140.95, 140.5, 129.6, 128.25 (2C), 127.7, 127.45, 127.25, 126.9 (2C), 126.0, 74.75, 72.8, 40.1, 30.6, 30.45, 26.05, 7.75 (2C); *m/z* (EI) 280 (1, [M$^+$ −18]), 251 (25), 196 (36), 195 (30), 194 (18), 193 (18), 179 (31), 178 (18), 116 (14), 115 (18), 105 (12), 91 (41), 187 (14), 77 (17), 57 (100), 45 (22), 43 (12), 41 (18); HRMS (EI) [M$^+$ −H$_2$O], Found: 280.1839. C$_{20}$H$_{24}$O requires 280.1827%.

4.4.1.2. 3-Ethyl-1-[2-(1-hydroxycyclohexyl)phenyl]-3-pentanol (10b). Yield 64%; m.p. 48–50 °C (ethyl acetate–hexane); R_f (hexane–ethyl acetate: 7/3) 0.39; ν_{max} (melted film) 3416, 3103, 3057, 3011, 1600, 1171, 1134 cm^{-1}; δ_H (300 MHz, CDCl$_3$) 7.37 and 7.20–7.10 (1 and 3H, respectively, d and m, respectively, $J = 6.7$ Hz, ArH), 3.00–2.95 (2 H, m, CH_2Ar), 2.05–1.60, 1.53 and 1.30–1.25 [13, 4 and 1H, respectively, m, q and m, respectively, $J = 7.5$ Hz, (CH$_2$)$_5$COH, 3 × CH$_2$CO, OH], 0.90 (6H, t, $J = 7.5$ Hz, 2 × Me); δ_C (75 MHz, CDCl$_3$) 145.7, 141.9, 132.05, 126.95, 125.45, 125.35, 74.8, 74.55, 41.8, 38.3 (2C), 30.75 (2C), 27.95, 25.5, 22.0 (2C), 7.9 (2C); *m/z* (EI) 272 (2, [M$^+$ −18]), 254 (16), 225 (24), 201 (49), 184 (18), 183 (100), 182 (17), 171 (29), 170 (30), 169 (15), 157 (11), 145 (19), 143 (35), 142 (21), 141 (47), 131 (15), 130 (28), 129 (91), 128 (27), 119 (11), 117 (28), 115 (26), 105 (15), 91 (39), 87 (25), 81 (18), 79 (10), 77 (12), 69 (12), 57 (43), 55 (53), 45 (42), 43 (39), 41 (59); Anal. Found: C, 78.57; H, 10.41. Calc. for C$_{19}$H$_{30}$O$_2$: C, 78.56; H, 10.42%.

4.4.1.3. 3-Ethyl-1-[3-hydroxy(phenyl)methylphenyl]-3-pentanol (10c). Yield 70%; R_f (hexane–ethyl acetate: 7/3) 0.20; ν_{max} (liquid film) 3371, 3058, 3027, 1602, 1487, 1179, 1149, 1031 cm^{-1}; δ_H (300 MHz, CDCl$_3$) 7.35–7.05 (9H, m, ArH), 5.77 (1H, s, CCHOC), 2.60–2.55 (2H, m, CH_2Ar), 2.02 (2H, brs, 2 × OH), 1.70–1.65 (2H, m, CH$_2$CH_2CO), 1.50 (4H, q, $J = 7.5$ Hz, 2 × CH_2CH$_3$) 0.86 (6H, t, $J = 7.5$ Hz, 2 × Me); δ_C (75 MHz, CDCl$_3$) 143.95, 143.85, 142.95, 128.45, 128.35 (2C), 127.45, 127.4, 126.5 (2C), 126.45, 124.0, 76.15, 74.65, 40.2, 30.8 (2C), 29.8, 7.75 (2C); *m/z* (EI) 280 (23, [M$^+$ −18]), 251 (37), 194 (29), 180 (20), 179 (98), 178 (18), 165 (23), 145 (47), 119 (33), 107 (100), 105 (46), 91 (51), 87 (44), 79 (48), 78 (12), 77 (57), 69 (14), 65 (12), 57 (24), 55 (16), 45

(59), 43 (25), 41 (31); HRMS (EI) [M$^+$ −H$_2$O], Found: 280.1826. C$_{20}$H$_{24}$O requires 280.1827%.

4.4.1.4. 3-Ethyl-1-[3-(1-hydroxycyclohexyl)phenyl]-3-pentanol (10d). Yield 85%; R_f (hexane–ethyl acetate: 7/3) 0.21; ν_{max} (liquid film) 3409, 3025, 1603, 1169, 1134 cm^{-1}; δ_H (300 MHz, CDCl$_3$) 7.35–7.25 and 7.10–7.05 (3 and 1H, respectively, 2m, ArH), 2.70–2.60 (2H, m, CH_2Ar), 1.85–1.50 (18H, m, (CH$_2$)$_5$COH, 3 × CH$_2$CO, OH), 0.91 (6H, t, $J = 7.3$ Hz, 2 × Me); δ_C (75 MHz, CDCl$_3$) 149.6, 142.6, 128.2, 126.65, 124.55, 121.95, 74.6, 73.1, 40.45, 38.8 (2C), 30.9 (2C), 30.1, 25.5, 22.15 (2C), 7.8 (2C); *m/z* (EI) 272 (17, [M$^+$ −18]), 254 (32), 225 (29), 186 (12), 172 (28), 171 (100), 169 (11), 157 (33), 145 (42), 143 (24), 142 (15), 141 (33), 131 (15), 130 (18), 129 (67), 128 (53), 127 (14), 118 (18), 117 (29), 115 (34), 105 (23), 103 (10), 99 (13), 91 (34), 87 (42), 83 (20), 81 (63), 79 (28), 77 (24), 69 (21), 67 (13), 65 (12), 57 (20), 55 (79), 53 (12), 45 (43), 43 (30), 41 (57); HRMS (EI) [M$^+$], Found: 290.2224. C$_{19}$H$_{30}$O$_2$ requires 290.2246%.

4.4.1.5. 3-Ethyl-1-[4-hydroxy(phenyl)methylphenyl]-3-pentanol (10e). Yield 50%; R_f (hexane–ethyl acetate: 7/3) 0.16; ν_{max} (liquid film) 3382, 3058, 3026, 1604, 1493, 1136, 1023 cm^{-1}; δ_H (300 MHz, CDCl$_3$) 7.40–7.25 and 7.20–7.15 (7 and 2H, respectively, 2m, ArH), 5.83 (1H, s, CCHOC), 2.65–2.60 (2H, m, CH_2Ar), 1.75–1.70 (2H, m, CH$_2$CH_2CO), 1.55–1.50 (6H, m, 2 × CH_2CH$_3$, 2 × OH) 0.89 (6H, t, $J = 7.5$ Hz, 2 × Me); δ_C (75 MHz, CDCl$_3$) 142.15, 141.3 (2C), 128.55, 128.5, 128.4 (3C), 127.5, 126.65 (2C), 126.45, 76.1, 74.55, 40.3, 30.9 (2C), 29.5, 7.8 (2C); *m/z* (EI) 280 (15, [M$^+$ −18]), 251 (22), 194 (14), 179 (10), 145 (35), 107 (95), 105 (100), 91 (53), 87 (31), 79 (29), 77 (39), 57 (23), 55 (12), 51 (11), 45 (61), 44 (19), 43 (29), 41 (36), 40 (12); HRMS (EI) [M$^+$ −H$_2$O], Found: 280.1829. C$_{20}$H$_{24}$O requires 280.1827%.

4.4.1.6. 3-Ethyl-1-[4-(1-hydroxycyclohexyl)phenyl]-3-pentanol (10f). Yield 45%; R_f (hexane–ethyl acetate: 7/3) 0.21; ν_{max} (liquid film) 3413, 3085, 1601, 1512, 1173, 1136 cm^{-1}; δ_H (300 MHz, CDCl$_3$) 7.40 and 7.20 (2 and 2H, respectively, 2d, $J = 8.2$ Hz, ArH), 2.65–2.60 (2H, m, CH_2Ar), 1.85–1.50 (18H, m, (CH$_2$)$_5$COH, 3 × CH$_2$CO, OH), 0.90 (6H, t, $J = 7.6$ Hz, 2 × Me); δ_C (75 MHz, CDCl$_3$) 146.85, 141.05, 128.1 (2C), 124.65 (2C), 74.55, 72.95, 40.25, 38.8 (2C), 30.9 (2C), 29.35, 25.5, 22.2 (2C), 7.8 (2C); *m/z* (EI) 272 (10, [M$^+$ −18]), 254 (32), 225 (32), 172 (17), 171 (100), 157 (26), 141 (14), 129 (19), 128 (11), 115 (11), 91 (23), 87 (17), 81 (14), 55 (12), 45 (21), 43 (10), 41 (21); HRMS (EI) [M$^+$], Found: 290.2231. C$_{19}$H$_{30}$O$_2$ requires 290.2246%.

4.5. Dehydration of diol (R*,S*)-2a. Synthesis of oxepane 11

To a solution of starting diol **2a** (0.112 g, 0.4 mmol) and triphenylphosphine (0.252 g, 0.96 mmol) in benzene (8 ml), under nitrogen atmosphere, was dropwise added diisopropyl azodicarboxylate (DIAD, 0.19 ml, 0.96 mmol) at r.t. The resulting solution is heated until refluxing in a Dean–Stark apparatus during 3 h. Then, the solvents were removed and the residue was treated with water (15 ml) and the resulting mixture was extracted with ethyl acetate (3 × 20 ml). The combined organic layers were dried over anhydrous MgSO$_4$. After evaporation of the solvents under reduce pressure (15 Torr), the resulting residue was purified by column chromatography (silica gel, hexane) to yield the title pure compounds cis-**11**. Yield, as well as physical, analytical and spectroscopic data follow.

4.5.1. cis-1,3-Di(tert-butyl)-1,3,4,5-tetrahydro-2-benzoxepine (cis-11)

Yield 79%; R_f (hexane) 0.47; v_{max} (liquid film) 3113, 3063, 3022, 1094, 1069 cm^{-1}; δ_H (300 MHz, CDCl$_3$) 7.50–7.45 and 7.20–7.15 (1 and 3H, respectively, 2m, ArH), 4.56 (1H, s, CHAr), 3.15–3.05 and 2.90–2.75 (1 and 2H, respectively, 2m, OCHCH$_2$CH$_2$), 1.80–1.70 (2H, m, CH$_2$CHO), 1.19 and 0.85 (9 and 9H, respectively, 2s, 6 × Me); δ_C (75 MHz, CDCl$_3$) 142.15, 136.2, 128.85, 127.75, 127.25, 125.65, 83.2, 79.7, 35.85, 35.05, 31.3, 28.05 (3C), 26.95, 26.65 (3C); m/z (EI) 203 (41, [M$^+$ −57]), 185 (14), 159 (10), 147 (20), 146 (14), 145 (100), 143 (32), 133 (13), 131 (13), 129 (20), 117 (52), 91 (30), 87 (32), 71 (10), 69 (15), 59 (61), 57 (65), 55 (11), 43 (59), 41 (59); HRMS (EI) [M$^+$ −Bu^t], Found: 203.1429. C$_{14}$H$_{19}$O requires 203.1436%.

4.6. Dehydration of diols 2c,h and n. Synthesis of dienes 12

4.6.1. General procedure

To a solution of starting diol **2** (0.104 g, 0.34 mmol) in benzene (2 ml) was dropwise added H$_3$PO$_4$ (85%, 0.050 ml, 0.74 mmol) at room temperature. The resulting solution is heated until refluxing during 6 h. Then, the resulting mixture was cooled down to room temperature, and a saturated solution of NaHCO$_3$ (15 ml) was added to the aforementioned solution. After extraction with ethyl ether (2 × 20 ml), the combined organic layers were dried over anhydrous MgSO$_4$. Finally, the solvents were removed under reduce pressure (15 Torr) to yield the title pure dienic compounds **12**. Yields, as well as physical, analytical and spectroscopic data follow.

4.6.1.1. 1-(1-Cyclohexenyl)-2-[2-(1-cyclohexenyl)ethyl]benzene (12a).

Yield 91%; R_f (hexane) 0.58; v_{max} (liquid film) 3021, 1600 cm^{-1}; δ_H (300 MHz, CDCl$_3$) 7.20–7.10 and 7.05–7.00 (3 and 1H, respectively, 2m, ArH), 6.10–6.05 (1H, m, CH=CAr), 5.60–5.55 (1H, m, CH$_2$CH=CCH$_2$), 2.70–2.65 (2H, m, CH$_2$Ar), 2.20–2.15 and 1.70–1.40 [4 and 14H, respectively, 2m, 2 × (CH$_2$)$_4$, CH$_2$CH$_2$Ar]; δ_C (75 MHz, CDCl$_3$) 144.35, 139.8, 138.6, 129.2 (2C), 128.65 (2C), 126.6, 125.6, 125.5, 44.75, 37.45 (2C), 31.1, 29.65, 25.8, 25.35, 23.15, 22.3, 22.15; m/z (EI) 266 (15, [M$^+$]), 184 (21), 183 (100), 182 (25), 171 (11), 170 (35), 143 (19), 142 (27), 141 (60), 130 (14), 129 (61), 128 (26), 117 (20), 115 (25), 99 (13), 91 (24), 81 (21), 79 (11), 77 (11), 67 (14), 55 (38), 53 (11), 43 (18), 41 (40); HRMS (EI) [M$^+$], Found: 266.1987. C$_{20}$H$_{26}$ requires 266.2034%.

4.6.1.2. 1-(1-Cyclohexenyl)-3-[2-(1-cyclohexenyl)ethyl]benzene (12b).

Yield 99%; R_f (hexane) 0.62; v_{max} (liquid film) 3023, 1602, 1484 cm^{-1}; δ_H (300 MHz, CDCl$_3$) 7.20–7.15 and 7.05–7.00 (3 and 1H, respectively, 2m, ArH), 6.10–6.05 (1H, m, CH=CAr), 5.45–5.40 (1H, m, CH$_2$CH=CCH$_2$), 2.70–2.65 (2H, m, CH$_2$Ar), 2.45–2.35, 2.25–2.20, 2.00–1.95 and 1.80–1.55 [2, 4, 4, and 8H, respectively, 4m, 2 × (CH$_2$)$_4$, CH$_2$CH$_2$Ar]; δ_C (75 MHz, CDCl$_3$) 142.65, 142.35, 137.35, 136.75, 128.0, 126.55, 125.05, 124.45, 122.35, 121.15, 40.1, 34.6, 28.5, 27.45, 25.85, 25.25, 23.05, 23.0, 22.55, 22.2; m/z (EI) 266 (64, [M$^+$]), 184 (15), 183 (11), 173 (20), 172 (80), 171 (100), 170 (13), 157 (14), 155 (11), 144 (14), 143 (31), 142 (13), 141 (24), 130 (18), 129 (47), 128 (40), 117 (12), 115 (25), 105 (25), 104 (23), 95 (46), 93 (14), 92 (10), 91 (37), 81 (20), 80 (18), 79 (30), 77 (22), 67 (34), 65 (13), 55 (35), 53 (23), 41 (58); HRMS (EI) [M$^+$], Found: 266.2041. C$_{20}$H$_{26}$ requires 266.2034%.

4.6.1.3. 1-(1-Cyclohexenyl)-4-[2-(1-cyclohexenyl)ethyl]benzene (12c).

Yield 96%; R_f (hexane) 0.65; v_{max} (liquid film) 3022, 1606, 1513 cm^{-1}; δ_H (300 MHz, CDCl$_3$) 7.30–7.25 and 7.15–7.10 (2 and 2H, respectively, 2m, ArH), 6.10–6.05 (1H, m, CH=CAr), 5.45–5.40 (1H, m, CH$_2$CH=CCH$_2$), 2.70–2.65 (2H, m, CH$_2$Ar), 2.40–2.35, 2.25–2.20, 2.00–1.95 and 1.80–1.55 [2, 4, 4 and 8H, respectively, 4m, 2 × (CH$_2$)$_4$, CH$_2$CH$_2$Ar]; δ_C (75 MHz, CDCl$_3$) 140.9, 140.05, 137.4, 136.35, 128.15 (2C), 124.75 (2C), 123.95, 121.15, 39.95, 34.05, 28.5, 27.35, 25.85, 25.25, 23.1, 23.05, 22.55, 22.2; m/z (EI) 266 (27, [M$^+$]), 172 (24), 171 (100), 143 (10), 129 (13), 128 (16), 115 (12), 91 (26), 41 (19); HRMS (EI) [M$^+$], Found: 266.2028. C$_{20}$H$_{26}$ requires 266.2034%.

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