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# Arene-promoted lithiation of 1,*n*-dihaloalkanes (*n*=2–6): a comparative study

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**Abstract**—The reaction of 1,*n*-dichloroalkanes **3a** (*n*=2–6) with an excess of lithium powder and a catalytic amount of 4,4′-di-*tert*-butylbiphenyl (DTBB; 2.5 mol %) in the presence of different carbonyl compounds [$Bu^tCHO$, PhCHO, $Et_2CO$, $(CH_2)_4CO$, $(CH_2)_5CO$, $(CH_2)_7CO$, (−)-menthone], in THF at −78 °C leads, after hydrolysis with water, to the expected 1,(*n*+2)-diols **4**, yields being <25% for *n*=2, 3 and in the range of 45–79% for *n*=4–6. When the same protocol is applied to 1,*n*-bromochloroalkanes **3b** and 1,*n*-dibromoalkanes **3c** (*n*=2–6), diols **4** are obtained in general with lower yields.


## 1. Introduction

From a synthetic point of view, the generation of dilithio compounds[1] of the type **1** (Chart 1) would be of great interest because their reaction with two molecules of an electrophile would allow the simultaneous introduction of two electrophilic fragments in the starting molecule through a single synthetic operation. The halogen–lithium exchange[2] is the most commonly used method to generate these intermediates, but this methodology cannot be applied in this case because the initially formed halogen-lithium compound **2** (Chart 1) is extremely unstable and suffers spontaneous elimination of lithium halide, thus preventing the second lithiation step.[3] Thus, **2** with *n*=1, the so-called lithium carbenoids, undergo α-elimination giving a carbene, which either decompose or can be trapped by an appropriate reagent.[4] Probably, the most dramatic situation appears for **2** with *n*=2, where the β-elimination affording an olefin occurs rapidly, even at very low temperatures (<−100 °C),[5] making impossible to prepare this type of intermediates and, consequently, the corresponding 1,2-dilithio compounds. In the case of *n*=3, it has been shown that the γ-elimination that gives a cyclopropane derivative works not so easily, so in some cases, the corresponding γ-functionalised organolithium compound can be trapped under mild reaction conditions.[6] For intermediates **2** with *n*=4–6 the elimination can be avoided partially under controlled reaction conditions,[7] which in general consist in performing the lithiation using an arene as electron carrier[8] at low temperature and in the presence of the corresponding electrophile (Barbier-type reaction conditions[9]). In the frame of our continuous interest on the lithiation of compounds of type **3**[10] (Chart 1) we report here the 4,4′-di-*tert*-butylbiphenyl (DTBB)-catalysed lithiation of different 1,*n*-dihaloalkanes **3a–c**[11] and their use as 1,*n*-dianionic synthetic equivalents in the reaction with different carbonyl compounds as electrophiles.

**1** **2** (X = Cl, Br, I) **3** [X = Hal (Cl, Br), RO, RS, $R_2N$]

**Chart 1**.

## 2. Results and discussion

### 2.1. Lithiation of 1,*n*-dihaloalkanes 3 under Barbier-type reaction conditions (Method A)

The reaction of commercially available 1,*n*-dichloroalkanes **3a** with an excess of lithium (1:10 molar ratio; theoretic 1:4 molar ratio) and a catalytic amount of DTBB (1:0.1 molar ratio, 2.5 mol %) in the presence of different carbonyl compounds (1:3 molar ratio) in THF at −78 °C for ca. 3 h, followed by hydrolysis with water at temperatures ranging between −78 °C and room temperature (Method A), led to the diols **4** (Scheme 1 and Table 1).

As expected, yields are low for compounds **4** with *n*=2, 3 due to the above commented elimination side reaction problems, which gave ethylene and cyclopropane, respectively (Table 1, entries 1–6). However, in the other cases (**4** with *n*=4–6) this problem was extensively overcome, so the

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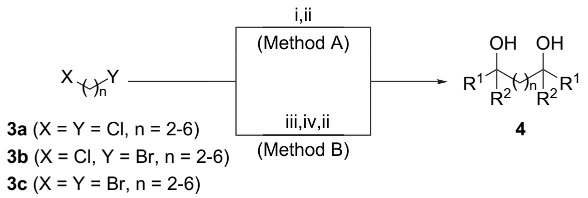


**Scheme 1**. Reagents and conditions: (i) Li, DTBB (2.5 mol %), $R^1R^2CO$, THF, −78 °C; (ii) $H_2O$, −78 to 20 °C; (iii) Li, DTBB (2.5 mol %), THF, −78 °C; (iv) $R^1R^2CO$, −78 °C.

expected diols were the main products isolated (Table 1, entries 7–17). When aldehydes were used as prochiral electrophiles, the corresponding ca. 1:1 mixtures of diastereomers (NMR) were obtained (Table 1, entries 1, 5, 7, 14 and 15, and footnote c). In the case of (−)-menthone, the attack of the organolithium intermediate to the upper less hindered face of the chiral electrophile[12] was exclusively observed, so the corresponding enantiomerically pure diol was the only reaction product obtained (Table 1, entries 4, 6, 10, 13 and 17, and footnote d).

Concerning a possible mechanistic pathway for the reaction shown in the Scheme 1, we think that after the first lithiation, the chloro-lithio intermediate **2** with X=Cl initially formed, which has a great tendency to undergo elimination of lithium chloride (see above, especially for $n$=2, 3), can also react with the electrophile present in the reaction medium to give the chloro-alkoxide **5**. This new intermediate then suffers a new chlorine–lithium exchange to afford the functionalised organolithium species **6**, which in the presence of the electrophile gives the corresponding dialkoxide **7**, precursor of the diols **4** by final hydrolysis (Chart 2). On the other hand, the participation of dilithium intermediates of the

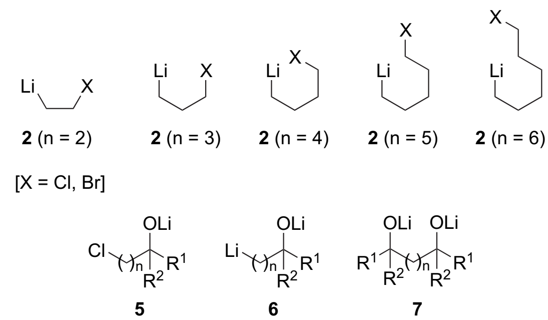
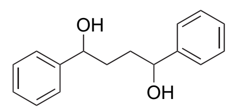
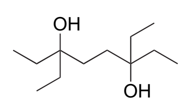
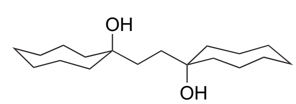
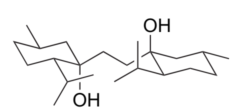
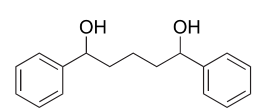
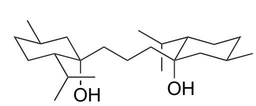
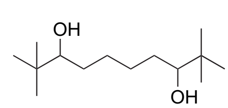
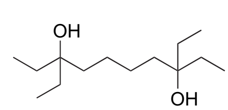


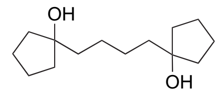
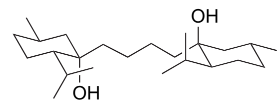
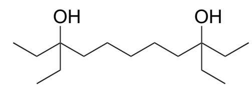
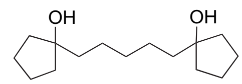
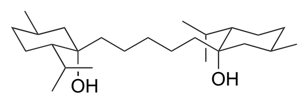
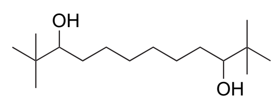
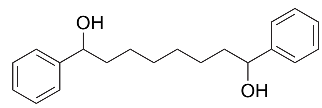
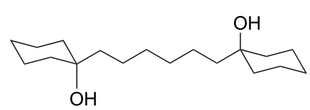
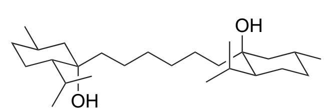
**Chart 2**.

**Table 1**. Double lithiation of 1,$n$-dichloroalkanes **3a** (preparation of compounds **4** (Method A))

| Entry | $n$ | Electrophile | Product[a] No. | Structure | Yield (%)[b] |
|---|---|---|---|---|---|
| 1 | 2 | PhCHO | **4a** |  | 23[c] |
| 2 | 2 | $Et_2CO$ | **4b** |  | 18 |
| 3 | 2 | $(CH_2)_7CO$ | **4c** |  | 9 |
| 4 | 2 | (−)-Menthone | **4d** |  | 25[d] |
| 5 | 3 | PhCHO | **4e** |  | 20[c] |
| 6 | 3 | (−)-Menthone | **4f** |  | 15[d] |
| 7 | 4 | Bu$^t$CHO | **4g** |  | 79[c] |
| 8 | 4 | $Et_2CO$ | **4h** |  | 45 |

(*continued*)

**Table 1**. (*continued*)

| Entry | *n* | Electrophile | Product[a] | | |
|---|---|---|---|---|---|
| | | | No. | Structure | Yield (%)[b] |
| 9 | 4 | $(CH_2)_4CO$ | **4i** |  | 62 |
| 10 | 4 | (−)-Menthone | **4j** |  | 67[d] |
| 11 | 5 | $Et_2CO$ | **4k** |  | 46 |
| 12 | 5 | $(CH_2)_4CO$ | **4l** |  | 57 |
| 13 | 5 | (−)-Menthone | **4m** |  | 63[d] |
| 14 | 6 | $Bu^t$CHO | **4n** |  | 64[c] |
| 15 | 6 | PhCHO | **4o** |  | 78[c] |
| 16 | 6 | $(CH_2)_5CO$ | **4p** |  | 65 |
| 17 | 6 | (−)-Menthone | **4q** |  | 72[d] |

[a] All products **4** were >95% pure (GLC and/or 300 MHz $^1$H NMR) and were fully characterised by spectroscopic means (IR, $^1$H and $^{13}$C NMR, and LR and HR mass spectrometry).
[b] Isolated yields of compounds **4** after column chromatography (silica gel, hexane/ethyl acetate).
[c] Obtained as a ca. 1:1 mixture of diastereomers (NMR).
[d] The diastereomer shown in this table was exclusively obtained (see text).

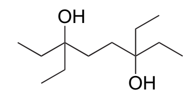
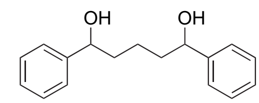
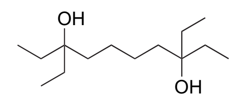
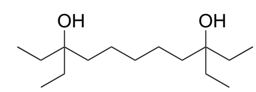
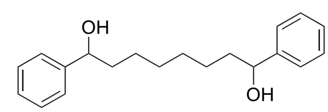
type **1** could be ruled out because the second lithiation of the already chlorinated organolithium intermediate is much more difficult than either the decomposition by elimination or the reaction with the electrophile present in the reaction medium.[13] The reaction conditions [(a) low temperature, (b) slow addition of the reagents (see Section 4.2) and (c) Barbier-type conditions] are essential for the preparation of diols **4** from the corresponding 1,*n*-dihaloalkane **3**.

The double lithiation under the same reaction conditions (Method A) of other starting materials, such as 1-bromo-*n*-chloroalkanes **3b** and 1,*n*-dibromoalkanes **3c** (both commercially available), was also studied. The results of this comparative study are summarised in Table 2. In general, yields are lower for compounds **3b** and **3c**, dichloro derivatives **3a** being the best substrates in this kind of processes. In the case of 1-bromo-*n*-chloroalkanes **3b**, we think that after the first lithiation, the choro-lithio intermediate **2** with X=Cl is formed due to the higher reactivity of the carbon–bromine bond towards the lithiation reagent. We have reported recently on the selective monolithiation of bromochloroalkanes (**2**, *n*=4, 5 and 6) (carbon–bromine bond undergoes reductive cleavage faster than carbon–chlorine bond) and also on the one-pot tandem introduction of two different electrophiles under careful reaction conditions.[7]

## 2.2. Lithiation of 1,*n*-dihaloalkanes 3 under Grignard-type reaction conditions (Method B)

In order to determine the stability of the intermediates **2** (X=Cl, Br; Chart 2), we studied the lithiation of compounds **3a–c** in the absence of the electrophile (Grignard-type

**Table 2**. Double lithiation of 1,*n*-dihaloalkanes **3a–c** (preparation of compounds **4**)

| Entry | Starting material [X–$(CH_2)_n$–Y] | | | | Electrophile | Product[a] | | | |
|---|---|---|---|---|---|---|---|---|---|
| | No. | X | Y | *n* | | Yield (%)[b] Method A | Yield (%)[b] Method B | No. | Structure |
| 1 | **3a** | Cl | Cl | 2 | | 18 | 0 | | |
| 2 | **3b** | Cl | Br | 2 | $Et_2CO$ | 12 | 0 | **4b** |   |
| 3 | **3c** | Br | Br | 2 | | 2[c] | 0 | | |
| 4 | **3a** | Cl | Cl | 3 | | 20 | 0 | | |
| 5 | **3b** | Cl | Br | 3 | PhCHO | 7 | 0 | **4e** |   |
| 6 | **3c** | Br | Br | 3 | | 23 | 0 | | |
| 7 | **3a** | Cl | Cl | 4 | | 45 | 3[c] | | |
| 8 | **3b** | Cl | Br | 4 | $Et_2CO$ | 31 | 2[c] | **4h** |   |
| 9 | **3c** | Br | Br | 4 | | 22 | 0 | | |
| 10 | **3a** | Cl | Cl | 5 | | 46 | 4[c] | | |
| 11 | **3b** | Cl | Br | 5 | $Et_2CO$ | 30 | 0 | **4k** |   |
| 12 | **3c** | Br | Br | 5 | | 16 | 0 | | |
| 13 | **3a** | Cl | Cl | 6 | | 78 | 23 | | |
| 14 | **3b** | Cl | Br | 6 | PhCHO | 67 | 17 | **4o** |   |
| 15 | **3c** | Br | Br | 6 | | 53 | 0 | | |

[a] All products **4** were >95% pure (GLC and/or 300 MHz $^{1}H$ NMR) and were fully characterised by spectroscopic means (IR, $^{1}H$ and $^{13}C$ NMR, and LR and HR mass spectrometry).
[b] Isolated yields of compounds **4** after column chromatography (silica gel, hexane/ethyl acetate).
[c] Yield determined by GLC analysis.

conditions). So, there would be a correlation between the yield of compounds **4** and the stability of the corresponding intermediates **2**. The reaction of compounds **3a–c** with an excess of lithium (1:10 molar ratio; theoretic 1:4 molar ratio) and a catalytic amount of DTBB (1:0.1 molar ratio, 2.5 mol %) in THF at −78 °C for 1 h, followed by addition of 2.2 equiv of a carbonyl compound at the same temperature and final hydrolysis with water at temperatures ranging between −78 °C and room temperature (Method B), would lead to the expected diols **4** (Scheme 1 and Table 2).

In the case of 1,2-dihalo derivatives **3a–c** (*n*=2, entries 1–3, Table 2), intermediates **2** (*n*=2) decomposed rapidly before a second lithiation took place, so, after the addition of 3-pentanone as electrophile, nothing of the expected diol **4b** was isolated or detected by tandem GC–MS analysis. This indicates, as previously commented, that intermediates of type **2** (*n*=2, 3) show a high tendency to undergo elimination. Such elimination takes place almost exclusively (Scheme 1, Table 2, entries 1–3) even in the presence of the electrophile (Barbier-type conditions), this probably being the main reason for the low yields. The possible participation of β-haloradicals in the synthesis of 1,4-diols **4** cannot be completely ruled out.

Intermediates **2** with *n*=3 seem to be also highly unstable because 1,5-diol **4e** was not observed after addition of benzaldehyde as electrophile (Table 2, entries 4–6).

Very low yield was also obtained from 1,4- and 1,5-dihaloalkanes **3a–c** (*n*=4, 5) when 3-pentanone was used as electrophile, the expected reaction products **4h** and **4k** not being isolated but detected by tandem GC–MS (Table 2, entries 7–9 and 10–12). This indicates that 4-halo- and 5-haloalkyllithium intermediates (**2**, *n*=4, 5, X=Cl, Br) were not stable species under these reaction conditions. Finally, when benzaldehyde was used as electrophile, low yields of diol **4o** were obtained from 1,6-dichloro- and 1-bromo-6-chlorohexanes **3a** and **3b** (*n*=6) (Table 2, entries 13 and 14), meanwhile, diol **4o** was not detected when starting from 1,6-dibromohexane (**3c**, *n*=6) (Table 2, entry 15). Paying attention to these experimental results, we can assume that the 6-chloro derivative (**2**, *n*=6, X=Cl) is more stable than the 6-bromoalkyllithium intermediate **2** (*n*=6, X=Br) under the commented reaction conditions. The best yields of 1,4-, 1,6-, 1,7- and 1,8-diols **4** were obtained from dichloroalkanes **3a** (*n*=2, 4, 5 and 6). The preparation of 1-chloro-4-lithiobutane[14] (**2**, *n*=4, X=Cl) and 1-chloro-6-lithiohexane[15] (**2**, *n*=6, X=Cl) by monolithiation of the corresponding *n*-chloro-1-iodoalkanes with butyllithium has been previously reported.

## 3. Conclusions

In conclusion, we report here for the first time the controlled lithiation of 1,*n*-dihaloalkanes under DTBB-promoted conditions, which allows the preparation of symmetrically substituted diols **4** by using carbonyl compounds as electrophiles. The reaction is especially of interest for *n*=2, 3 (even working with low yields in all cases)[16] due to the outstanding problems concerning the decomposition of the halogen-lithio intermediates by elimination, which are partially overcome in this study. The best yields are always obtained starting from 1,*n*-dichloroalkanes **3a**.

## 4. Experimental

### 4.1. General

All reactions were carried out under an atmosphere of argon in oven-dried glassware. All reagents were commercially available (Acros, Aldrich) and were used without further purification. Commercially available anhydrous THF (99.9%, water content≤0.006%, Acros) was used as solvent in all the lithiation reactions. IR spectra were measured (film) with a Nicolet Impact 400 D-FT spectrometer. NMR spectra were recorded with a Bruker AC-300 or a Bruker ADVANCE DRX-500 using $CDCl_3$ as the solvent. LRMS and HRMS were measured with Shimadzu GC/HS QP-5000 and Finingan MAT95 S spectrometers, respectively. The purity of volatile products and the chromatographic analyses (GLC) were determined with a flame ionisation detector and a 12 m capillary column (0.2 mm diameter, 0.33 μm film thickness), using nitrogen (2 mL/min) as carrier gas, $T_{injector}$=275 °C, $T_{detector}$=300 °C, $T_{column}$=60 °C (3 min) and 60–270 °C (15 °C/min), $P$=40 kPa. Specific rotations were determined with a Perkin–Elmer 341 digital polarimeter.

### 4.2. Double lithiation of compounds 3a–c in the presence of a carbonyl compound as electrophile (Barbier-type reaction conditions, Method A). Preparation of diols 4

**4.2.1. Isolation of compounds 4. Method A: general procedure.** To a blue suspension of lithium powder (0.070 g, 10 mmol) and a catalytic amount of DTBB (0.027 g, 0.1 mmol) in THF (3 mL), a solution of the corresponding 1,*n*-dihaloalkane **3a–c** (1.0 mmol) and the corresponding carbonyl compound ($R^1R^2CO$, 3.0 mmol) in THF (1.2 mL) was slowly added (ca. 3 h) at −78 °C. After the addition, the reaction mixture was stirred for 15 min at the same temperature. Then, it was hydrolysed with water (4 mL) and extracted with ethyl acetate (3×10 mL). The organic layer was dried over anhydrous magnesium sulfate and evaporated (15 Torr). The residue was purified by column chromatography (silica gel; hexane/ethyl acetate) to yield pure products **4**. Yields and structures are included in Tables 1 and 2. Physical and spectroscopic data as well as literature references follow.

**4.2.1.1. 1,4-Diphenylbutane-1,4-diol (4a).**[17] Diastereomeric mixture. Colourless oil; $R_f$ 0.19 (hexane/ethyl acetate: 2/1); $\nu$ (film) 3580–3170 (OH), 3060, 3029, 2935, 2875, 1460 $cm^{-1}$; $\delta_H$ 1.43 (2H, quintet, $J$=7.9 Hz, $CH_2CH_2CH_2$), 1.75–1.81 (4H, m, $CH_2CH_2$), 2.94 (2H, br s, 2×OH), 4.63–4.67 (2H, m, 2×C*H*OH), 7.23–7.31 (10H, m, ArH); $\delta_C$ 35.0, 35.9 ($CH_2$), 74.05, 74.45 (CHOH), 125.8, 127.35, 127.4, 128.35, 144.45 (ArC); *m/z* 224 ($M^+-H_2O$, 13%), 120 (73), 118 (100), 107 (38), 105 (22), 104 (16), 79 (48), 77 (44).

**4.2.1.2. 3,6-Diethyloctane-3,6-diol (4b).**[18] Colourless oil; $R_f$ 0.21 (hexane/ethyl acetate: 2/1); $\nu$ (film) 3520–3190 (OH), 2972, 2935, 2880, 1460 $cm^{-1}$; $\delta_H$ 0.86 (12H, t, $J$=7.5 Hz, 4×$CH_3$), 1.45 [4H, s, $(CH_2)_2$], 1.48 (8H, q, $J$=7.5 Hz, 2×$CH_3CH_2$), 1.75 (2H, br s, 2×OH); $\delta_C$ 7.8 ($CH_3$), 30.9, 31.3 ($CH_2$), 74.4 (COH); *m/z* 166 ($M^+-2H_2O$, 1%), 156 (11), 155 (100), 137 (52), 98 (33), 95 (18), 87 (56), 83 (26), 69 (31), 57 (91), 55 (30); HRMS: $M^+-H_2O$, found 184.1833. $C_{12}H_{24}O$ requires 184.1827.

**4.2.1.3. 1-[2-(1-Hydroxycyclooctyl)ethyl]cyclooctanol (4c).**[19] White solid; mp 118–119 °C (dichloromethane/hexane); $R_f$ 0.16 (hexane/ethyl acetate: 2/1); $\nu$ (KBr) 3470–3230 (OH), 2932, 2919, 2852, 1460 $cm^{-1}$; $\delta_H$ 1.25–1.78 (34H, m, 16×$CH_2$, 2×OH); $\delta_C$ 22.4, 25.0, 28.25, 34.2, 36.3 ($CH_2$), 74.65 (COH); *m/z* 264 ($M^+-H_2O$, 5%), 193 (42), 180 (29), 127 (100), 122 (46), 110 (54), 109 (56), 95 (29), 81 (63), 67 (51), 55 (59).

**4.2.1.4. (1*S*,2*S*,5*R*,1′*S*,2′*S*,5′*R*)-1-[2-(1′-Hydroxy-2′-isopropyl-5′-methylcyclohexyl)ethyl]-2-isopropyl-5-methylcyclohexanol (4d).** White solid; mp 122–123 °C (dichloromethane/hexane) (found: C, 77.96; H, 12.37. $C_{22}H_{42}O_2$ requires: C, 78.05; H, 12.50); $R_f$ 0.64 (hexane/ethyl acetate: 2/1); $\nu$ (KBr) 3510–3280 (OH), 2965, 2954, 2868, 1455, 1371 $cm^{-1}$; $\delta_H$ 0.85–1.00 (20H, m, 6×$CH_3$, 2×CH), 1.05–1.67 (13H, m), 1.70–1.81 (6H, m), 1.90–2.15 (3H, m); $\delta_C$ 18.1 ($CH_3$), 19.9 ($CH_3$), 20.4 ($CH_2$), 22.5, 23.5 ($CH_3$), 24.3 ($CH_2$), 24.7, 25.25, 25.3 (CH), 25.8 ($CH_2$), 28.0, 29.85 (CH), 33.9, 35.05, 46.8, 47.1 ($CH_2$), 47.4, 54.4 (CH), 75.2, 75.4 (COH); *m/z* 320 ($M^+-H_2O$, 8%), 236 (17), 235 (100), 217 (18), 166 (21), 155 (64), 150 (51), 138 (51), 136 (31), 123 (30), 109 (21), 108 (17), 95 (51), 81 (42), 69 (38), 55 (29). $[\alpha]_D^{20}$ −15.9 (*c* 0.80, dichloromethane).

**4.2.1.5. 1,5-Diphenylpentane-1,5-diol (4e).**[20] Diastereomeric mixture. Colourless oil; $R_f$ 0.19 (hexane/ethyl acetate: 2/1); $\nu$ (film) 3530–3180 (OH), 3062, 3029, 2980, 2938, 2865, 1454 $cm^{-1}$; $\delta_H$ 1.43 (2H, quintet, $J$=7.9 Hz, $CH_2CH_2CH_2$), 1.52–1.81 (4H, m, 2×$CH_2$CH), 2.56 (2H, br s, 2×OH), 4.58 (2H, t, $J$=7.3 Hz, 2×C*H*OH), 7.23–7.33 (10H, m, ArH); $\delta_C$ 22.05, 22.15, 38.6, 38.7 ($CH_2$), 74.1, 74.3 (CHOH), 125.8, 127.4, 128.35, 144.7 (ArC); *m/z* 238 ($M^+-H_2O$, 4%), 129 (22), 105 (20), 104 (100), 91 (18), 77 (21).

**4.2.1.6. (1*S*,2*S*,5*R*,1′*S*,2′*S*,5′*R*)-1-[3-(1′-Hydroxy-2′-isopropyl-5′-methylcyclohexyl)propyl]-2-isopropyl-5-methylcyclohexanol (4f).** Colourless oil; $R_f$ 0.71 (hexane/ethyl acetate: 2/1); $\nu$ (film) 3630–3340 (OH), 2952, 2868, 1464, 1373 $cm^{-1}$; $\delta_H$ 0.82–1.78 (42H, m), 2.06–2.11 (2H, m); $\delta_C$ 18.0 ($CH_2$), 18.15 ($CH_3$), 20.5 ($CH_2$), 22.4, 23.6 ($CH_3$), 25.5, 28.0 (CH), 35.1, 41.9, 46.7 ($CH_2$), 48.1 (CH), 75.0 (COH); *m/z* 334 ($M^+-H_2O$, 1%), 165 (15), 164 (100), 163 (18), 149 (26), 137 (25), 135 (35), 121 (27), 109 (38), 107 (17), 95 (53), 93 (26), 83 (17), 81 (58), 69 (48), 67 (34), 55 (56), 43 (56), 41 (58); HRMS: $M^+-H_2O$, found 334.3233. $C_{23}H_{42}O$ requires 334.3236. $[\alpha]_D^{20}$ +4.2 (*c* 1.07, dichloromethane).

**4.2.1.7. 2,2,9,9-Tetramethyldecane-3,8-diol (4g).**[10c] Diastereomeric mixture. White solid; mp 113–114 °C (dichloromethane/hexane) (found: C, 72.70; H, 13.39. $C_{14}H_{30}O_2$ requires: C, 72.99; H, 13.39); $R_f$ 0.44 (hexane/ethyl acetate: 2/1); $\nu$ (KBr) 3580–3220 (OH), 2972, 2865, 1470, 1390, 1371 $cm^{-1}$; $\delta_H$ 0.89 (18H, s, 6×$CH_3$), 1.26–1.54 (10H, m, 4×$CH_2$, 2×OH), 3.20 (2H, dd, $J$=8.3, 2.1 Hz, 2×C*H*OH); $\delta_C$ 25.6 ($CH_3$), 26.9, 27.1, 31.4 ($CH_2$), 34.9 (C), 79.7, 79.9 (CHOH); *m/z* 212 ($M^+-H_2O$, 1%), 155 (24), 137 (100), 99 (17), 97 (25), 95 (49), 83 (24), 81 (69), 71 (31), 69 (46), 67 (17), 57 (77), 55 (19).

**4.2.1.8. 3,8-Diethyldecane-3,8-diol (4h).**[21] White solid; mp 72–73 °C (dichloromethane/hexane); $R_f$ 0.25 (hexane/ethyl acetate: 2/1); ν (KBr) 3520–3230 (OH), 2963, 2943, 2878, 1461 $cm^{-1}$; $\delta_H$ 0.85 (12H, t, $J$=7.5 Hz, 4×$CH_3$), 1.27–1.40 [10H, m, $(CH_2)_4$, 2×OH], 1.46 (8H, q, $J$=7.5 Hz, 4×$CH_2$); $\delta_C$ 7.75 ($CH_3$), 24.0, 31.0, 38.15 ($CH_2$), 74.6 (COH); $m/z$ 194 ($M^+-2H_2O$, 1%), 183 (13), 165 (65), 109 (23), 97 (43), 95 (20), 87 (100), 85 (24), 69 (38), 57 (77), 55 (21).

**4.2.1.9. 1-[4-(1-Hydroxycyclopentyl)butyl]cyclopentanol (4i).**[22] White solid; mp 98–99 °C (dichloromethane/hexane) (found: C, 74.20; H, 11.75. $C_{14}H_{26}O_2$ requires: C, 74.29; H, 11.58); $R_f$ 0.13 (hexane/ethyl acetate: 2/1); ν (KBr) 3440–3180 (OH), 2957, 2869, 1434 $cm^{-1}$; $\delta_H$ 1.43–1.81 (26H, m, 12×$CH_2$, 2×OH); $\delta_C$ 23.7, 25.2, 39.55, 41.4 ($CH_2$), 82.4 (COH); $m/z$ 208 ($M^+-H_2O$, 1%), 121 (14), 113 (13), 108 (100), 95 (15), 93 (31), 85 (28), 79 (12), 67 (31), 55 (18).

**4.2.1.10. (1*S*,2*S*,5*R*,1′*S*,2′*S*,5′*R*)-1-[4-(1′-Hydroxy-2′-isopropyl-5′-methylacyclohexyl)butyl]-2-isopropyl-5-methylcyclohexanol (4j).** White solid; mp 56–57 °C (dichloromethane/hexane) (found: C, 78.21; H, 12.54. $C_{24}H_{46}O_2$ requires: C, 78.63; H, 12.65); $R_f$ 0.69 (hexane/ethyl acetate: 2/1); ν (KBr) 3610–3330 (OH), 2941, 2866, 1455, 1366 $cm^{-1}$; $\delta_H$ 0.83–0.98 (20H, m, 6×$CH_3$, 2×CH), 1.06–1.52 (17H, m), 1.60–1.77 (6H, m), 1.86–2.17 (3H, m); $\delta_C$ 18.1 ($CH_3$), 20.5 ($CH_2$), 22.4, 23.6 ($CH_3$), 24.7 ($CH_2$), 25.45, 28.0 (CH), 35.1, 41.3, 46.8 ($CH_2$), 47.7 (CH), 75.05 (COH); $m/z$ 348 ($M^+-H_2O$, 25%), 330 (12), 196 (18), 194 (19), 178 (78), 163 (27), 155 (78), 137 (100), 135 (49), 95 (46), 83 (15), 81 (54), 69 (49), 55 (30). $[\alpha]_D^{20}$ +6.1 ($c$ 0.84, dichloromethane).

**4.2.1.11. 3,9-Diethylundecane-3,9-diol (4k).** White solid; mp 82–83 °C (dichloromethane/hexane); $R_f$ 0.27 (hexane/ethyl acetate: 2/1); ν (KBr) 3450–3210 (OH), 2968, 2933, 2878, 1466 $cm^{-1}$; $\delta_H$ 0.85 (12H, t, $J$=7.5 Hz, 4×$CH_3$), 1.25–1.42 [12H, m, $(CH_2)_5$, 2×OH], 1.45 (8H, q, $J$=7.5 Hz, 4×$CH_2$); $\delta_C$ 7.7 ($CH_3$), 23.3, 30.9, 30.95, 38.1 ($CH_2$), 74.55 (COH); $m/z$ 208 ($M^+-2H_2O$, 2%), 197 (17), 179 (64), 123 (21), 111 (42), 109 (28), 97 (20), 95 (28), 87 (100), 85 (31), 69 (45), 57 (90), 55 (26).

**4.2.1.12. 1-[5-(1-Hydroxycyclopentyl)pentyl]cyclopentanol (4l).**[23] Colourless oil; $R_f$ 0.18 (hexane/ethyl acetate: 2/1); ν (film) 3530–3210 (OH), 2968, 2933, 2859, 1462 $cm^{-1}$; $\delta_H$ 1.26–1.82 (28H, m, 13×$CH_2$, 2×OH); $\delta_C$ 23.8, 24.6, 30.7, 39.65, 41.4 ($CH_2$), 82.6 (COH); $m/z$ 222 ($M^+-H_2O$, 1%), 204 (6), 136 (20), 135 (62), 123 (20), 122 (100), 121 (26), 108 (34), 95 (45), 93 (47), 85 (77), 81 (49), 80 (58), 67 (71), 57 (29), 55 (51).

**4.2.1.13. (1*S*,2*S*,5*R*,1′*S*,2′*S*,5′*R*)-1-[5-(1′-Hydroxy-2′-isopropyl-5′-methylcyclohexyl)pentyl]-2-isopropyl-5-methylcyclohexanol (4m).** White solid; mp 68–69 °C (dichloromethane/hexane) (found: C, 78.23; H, 12.60. $C_{25}H_{48}O_2$ requires: C, 78.88; H, 12.71); $R_f$ 0.74 (hexane/ethyl acetate: 2/1); ν (KBr) 3560–3390 (OH), 2949, 2866, 2840, 1469, 1368 $cm^{-1}$; $\delta_H$ 0.86–0.91 (18H, m, 6×$CH_3$), 1.03–1.11 (4H, m), 1.22–1.49 (18H, m), 1.62–1.77 (6H, m), 2.03–2.12 (2H, m); $\delta_C$ 18.1 ($CH_3$), 20.45 ($CH_2$), 22.45, 23.6 ($CH_3$), 23.9 ($CH_2$), 25.45, 28.0 (CH), 31.0, 35.1, 41.3, 46.8 ($CH_2$), 47.6 (CH), 75.1 (COH); $m/z$ 362 ($M^+-H_2O$, 14%), 344 (13), 319 (26), 208 (19), 165 (45), 155 (64), 137 (100), 123 (14), 109 (30), 97 (18), 95 (47), 81 (51), 69 (42), 55 (25). $[\alpha]_D^{20}$ +5.8 ($c$ 0.91, dichloromethane).

**4.2.1.14. 2,2,11,11-Tetramethyldodecane-3,10-diol (4n).**[7] Diastereomeric mixture. White solid; mp 104–105 °C (dichloromethane/hexane) (found: C, 74.99; H, 13.81. $C_{16}H_{34}O_2$ requires: C, 74.36; H, 13.26); $R_f$ 0.58 (hexane/ethyl acetate: 2/1); ν (KBr) 3580–3210 (OH), 2970, 2864, 1469, 1389, 1367 $cm^{-1}$; $\delta_H$ 0.89 (18H, s, 6×$CH_3$), 1.25–1.55 (14H, m, 6×$CH_2$, 2×OH), 3.18 (2H, dd, $J$=9.9, 2.0 Hz, 2×C*H*OH); $\delta_C$ 25.7 ($CH_3$), 27.1, 29.7, 31.4, 31.45 ($CH_2$), 34.9 (C), 79.9, 79.95 (CHOH); $m/z$ 240 ($M^+-H_2O$, 1%), 183 (22), 165 (29), 109 (100), 97 (23), 95 (62), 83 (58), 81 (22), 71 (29), 69 (39), 67 (17), 57 (74), 55 (24).

**4.2.1.15. 1,8-Diphenyloctane-1,8-diol (4o).**[7] Diastereomeric mixture. White solid; mp 83–84 °C (dichloromethane/hexane); $R_f$ 0.30 (hexane/ethyl acetate: 2/1); ν (KBr) 3520–3180 (OH), 3083, 3058, 3022 $cm^{-1}$ (ArH); $\delta_H$ 1.19–1.69 (14H, m, 6×$CH_2$, 2×OH), 4.54 (2H, dd, $J$=7.2, 6.1 Hz, 2×C*H*OH), 7.21–7.29 (10H, m, 2×ArH); $\delta_C$ 25.1, 28.8, 38.4 ($CH_2$), 73.9 (CHOH), 125.3, 126.8, 127.8, 144.3 (ArC); $m/z$ 280 ($M^+-H_2O$, 2%), 207 (37), 174 (64), 158 (15), 117 (52), 107 (100), 105 (26), 104 (83), 91 (30), 79 (61), 77 (36).

**4.2.1.16. 1-[6-(1-Hydroxycyclohexyl)hexyl]cyclohexanol (4p).**[23] White solid; mp 89–90 °C (dichloromethane/hexane) (found: C, 76.11; H, 12.36. $C_{18}H_{34}O_2$ requires: C, 76.54; H, 12.13); $R_f$ 0.35 (hexane/ethyl acetate: 2/1); ν (KBr) 3570–3240 (OH), 2945, 1442 $cm^{-1}$; $\delta_H$ 1.25–1.60 (34H, m, 16×$CH_2$, 2×OH); $\delta_C$ 22.2, 22.7, 25.8, 30.2, 37.3, 42.3 ($CH_2$), 71.3 (COH); $m/z$ 246 ($M^+-2H_2O$, 13%), 166 (26), 109 (21), 99 (100), 96 (39), 95 (20), 94 (21), 83 (17), 82 (17), 81 (59), 67 (24), 55 (35).

**4.2.1.17. (1*S*,2*S*,5*R*,1′*S*,2′*S*,5′*R*)-1-[6-(1′-Hydroxy-2′-isopropyl-5′-methylcyclohexyl)hexyl]-2-isopropyl-5-methylcyclohexanol (4q).** White solid; mp 54–55 °C (dichloromethane/hexane); $R_f$ 0.77 (hexane/ethyl acetate: 2/1); ν (KBr) 3590–3370 (OH), 2952, 2866, 1455, 1366 $cm^{-1}$; $\delta_H$ 0.86–0.91 (18H, m, 6×$CH_3$), 1.02–1.12 (4H, m), 1.22–1.49 (20H, m), 1.64–1.77 (6H, m), 2.05–2.10 (2H, m); $\delta_C$ 18.1 ($CH_3$), 20.4 ($CH_2$), 22.45, 23.6 ($CH_3$), 23.8 ($CH_2$), 25.4, 27.95 (CH), 30.2, 35.1, 41.3, 46.8 ($CH_2$), 47.5 (CH), 75.1 (COH); $m/z$ 376 ($M^+-H_2O$, 38%), 358 (18), 333 (65), 315 (18), 222 (13), 179 (36), 155 (81), 137 (100), 123 (20), 109 (30), 97 (21), 95 (49), 81 (55), 69 (43), 55 (25); HRMS: $M^+-H_2O$, found 376.3707. $C_{26}H_{48}O$ requires 376.3705. $[\alpha]_D^{20}$ +6.3 ($c$ 1.09, dichloromethane).

### 4.3. Double lithiation of compounds 3a–c followed by reaction with carbonyl compounds as electrophiles (Grignard-type reaction conditions, Method B). Preparation of diols 4

**4.3.1. Isolation of compounds 4. Method B: general procedure.** To a blue suspension of lithium powder (0.070 g, 10 mmol) and a catalytic amount of DTBB (0.027 g, 0.1 mmol) in THF (3 mL) was added the corresponding 1,*n*-difunctionalised alkane **3a–c** (1.0 mmol) at −78 °C. The reaction mixture was stirred for 1 h at the same temperature and after that, the corresponding carbonyl compound

(2.2 mmol) was added dropwise and after 15 min it was hydrolysed with water (4 mL) and extracted with ethyl acetate (3×10 mL). The organic layer was dried over anhydrous magnesium sulfate and evaporated (15 Torr). The residue was purified by column chromatography (silica gel; hexane/ethyl acetate) to yield pure products **4**. Yields and structures are included in Table 2. Physical and spectroscopic data as well as literature references are shown above.

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