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ScienceDirect
Tetrahedron 63 (2007) 6625–6634
Tetrahedron

Selective lithiation of 1,6-dihalohex-1-enes and 1,6-dihalohex-1-ynes

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Received 15 January 2007; revised 5 March 2007; accepted 16 March 2007
Available online 21 March 2007

Abstract—The lithiation of 1-choro- and 1-bromo-6-chlorohex-1-yne (**2**, **3**) with lithium naphthalene in the presence of benzaldehyde in THF at −78 °C leads after hydrolysis with water to the corresponding chloroalkynol (**5**) resulting from a regioselective lithiation at the alkynylic position. However, the lithiation of 1-chloro-6-iodohex-1-yne (**4**) under the same reaction conditions and using pentan-3-one as electrophile leads to the corresponding chloroalcohol (**6**) from the exclusive lithiation at the aliphatic carbon–iodine bond. Double lithiation of compounds **2** and **3** under Barbier conditions allows the isolation of diols (**9**), whereas the two-step process leads to differently substituted diols **13**. The monolithiation of (*E*)-1-bromo-6-chlorohex-1-ene (**14**) under the above conditions and using pentan-3-one as electrophile affords a mixture of chloroalcohols **15** and **16**, the process being not stereospecific. However, the lithiation of the same starting material with *t*-BuLi leads exclusively to a bromine–lithium exchange with retention of the configuration, so after treatment with pentan-3-one only compound **16** was isolated. Finally, whereas double lithiation of compound **14** under the conditions for compounds **9** gives the mixture of compounds **18** and **19**, the tandem process involving the *t*-BuLi-promoted bromine–lithium exchange as the first step followed by lithiation under DTBB-catalysed conditions allows the isolation of (*E*)-diols **19** as the only reaction products isolated.

1. Introduction

Organolithium compounds are nowadays probably the most useful class of organometallic compounds as a source of the corresponding carbanion intermediates.[1] Normally these types of molecules are generated by halogen–lithium exchange using lithium or in some cases an alkyllithium reagent, the Wurtz-type coupling being the non-desirable process to be overcome. For this reason, chlorinated precursors are in general preferred because they give fewer amounts of coupling products than brominated or iodinated materials. In the case of polyhalogenated compounds, their selective lithiation is more difficult because the discrimination of both halogens is very problematic even at low temperatures.

In the last few years we have been interested in the generation of dilithiated intermediates,[2] since they are able to react with two molecules of an electrophile giving polyfunctionalised molecules in which two electrophilic fragments are introduced in only one synthetic operation. For this purpose we have taken advantage of the different reactivity of the carbon–chlorine and the carbon–oxygen[3] or carbon–sulfur[4] bonds in the lithiation reaction, in order to choose the carbon–heteroatom bond to be selectively lithiated. In order to perform the lithiation under the mildest reaction conditions we have commonly used an arene-promoted lithiation either under stoichiometric[5] or catalytic[6] conditions. The last procedure, an arene-catalysed lithiation, has been shown to be especially useful for the generation of dilithium synthons[2,7] starting from sp^3-hybridised dichlorinated precursors, being necessary in many cases to work under Barbier-type conditions (performing the lithiation in the presence of the electrophile)[8] in order to avoid decomposition of the monolithiated intermediate initially formed.[9]

Continuing with our recent studies on the selective lithiation of aliphatic compounds containing two equal or different halogens,[10] we report here the selective (chemo- and/or regioselective) lithiation of dihalo compounds bearing different hybridisation at both carbon atoms attached to the halogen substituents.[11]

2. Results and discussion

2.1. Lithiation of 1,6-dihalohex-1-ynes

2.1.1. Preparation of 1,6-dihalohex-1-ynes 2, 3 and 4. Dihalo hexynes **2–4** were prepared from commercially available 6-chlorohex-1-yne **1**. Thus, the corresponding

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Keywords: Halogen–lithium exchange; Dilithium synthons; Selective lithiation; Arene-promoted lithiation; Lithium acetylides.
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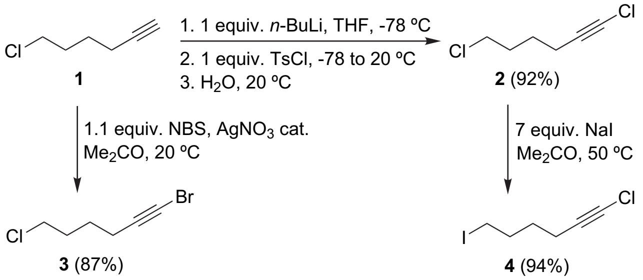
0040–4020/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2007.03.106

dichloro derivative **2** was obtained by deprotonation with *n*-BuLi at low temperature, followed by treatment with tosyl chloride, allowing the temperature to rise to 20 °C (Scheme 1).[12] On the other hand, silver-catalysed bromination of compound **1** with *N*-bromosuccinimide (NBS) at room temperature allowed the isolation of the chloro bromo derivative **3** (Scheme 1).[13] Finally, the chloro iodo compound **4** was easily prepared from the dichlorohexyne **2** by chlorine–iodine exchange under standard conditions (sodium iodide in acetone at 50 °C; Scheme 1).



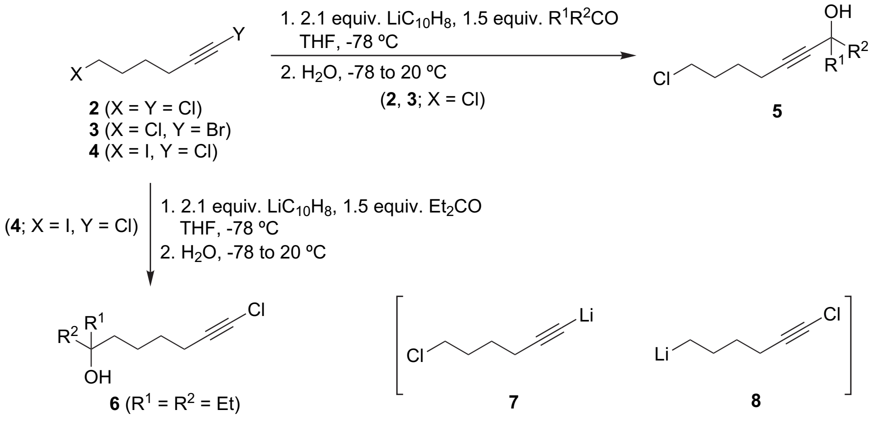
Scheme 1.

2.1.2. Monolithiation of 1,6-dihalohex-1-ynes 2, 3 and 4.

Compounds **2** and **3** could be regioselectively monolithiated using the stoichiometric version[5] of the arene-promoted lithiation. Thus, the lithiation of these starting materials with lithium naphthalene (1:2.1 M ratio) in the presence of benzaldehyde as electrophile in THF at −78 °C gave, after hydrolysis with water at temperatures ranging between −78 °C and room temperature, the corresponding chloroalcohol **5** (Scheme 2 and Table 1, entries 1 and 2). In this process, a regioselective (for compound **2**) or a chemoselective (for compound **3**) lithiation occurred involving the functionalised organolithium compound[9] **7**, which is the active species to be condensed with the electrophile present in the reaction medium (Barbier-type conditions).[8] Either the two-step process (lithiation followed by reaction with the electrophile: Grignard-type conditions) or the use of higher temperatures provoked the decomposition of the in situ generated intermediate **7**. Regioisomeric chlorohexynol **6** could be selectively obtained by using the same methodology to prepare the compound **5**: in this case the iodine–lithium exchange occurred preferentially; so using pentan-3-one as electrophile the corresponding compound **6** was the only product isolated with modest yield (Scheme 2 and Table 1, entry 3). In this case, it seems that the intermediate **8**, involved in the reaction as the organometallic component, is less stable than its corresponding isomer **7** and suffers extensive decomposition under the assayed reaction conditions.

2.1.3. Double lithiation of 1,6-dihalohex-1-ynes 2 and 3.

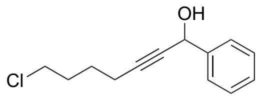
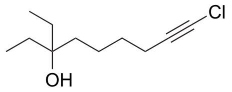
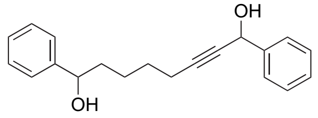
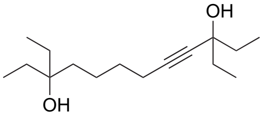
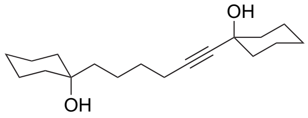
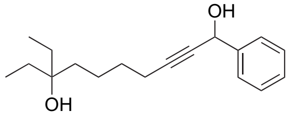
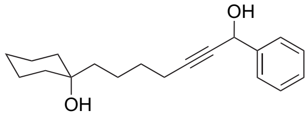
The double lithiation of compounds **2** and **3** was studied in order to introduce two (the same of different) electrophilic fragments in the starting molecules. When compounds **2** or **3** were allowed to react with an excess of lithium powder (1:10 M ratio; theoretical 1:4 M ratio) and a catalytic amount of 4,4′-di-*tert*-butylbiphenyl (DTBB; 1:0.1 M ratio; theoretical 1:4 M ratio; 2.5 mol %) in the presence of the corresponding electrophile (benzaldehyde, pentan-3-one, cyclohexanone) in THF at −78 °C, the expected unsaturated diols **9** were obtained after hydrolysis with water with concomitant warming till room temperature (Scheme 3 and Table 1, entries 4–9). In this case, and considering the results shown in Scheme 2 (conversion of compounds **2** and **3** into chloroalcohol **5**), the first lithiation gave the intermediate **7**, which reacts with the electrophile present in the reaction medium to give the alkoxides **10**. These compounds are then lithiated again to afford the new organolithium intermediates **11**, which condensed with a second molecule of the carbonyl compound to generate the corresponding dialkoxide, precursors of the obtained diols **9** after final hydrolysis. The introduction of two different electrophilic fragments was possible performing the regioselective monolithiation of the starting dichlorinated material **2** in the presence of benzaldehyde as the first electrophile as it is shown in Scheme 2. After the in situ generation of the intermediate of type **10** (R^1=H, R^2=Ph), lithium powder was added to the resulting reaction mixture; so a second lithiation took place (this situation simulates the arene-catalysed version of the lithiation promoted by an arene) giving the second lithiated species **11**. This intermediate is now ready to react with a second electrophile (pentan-3-one, cyclohexanone) to give the corresponding dialkoxides **12**, which after hydrolysis with water at temperatures between −78 °C and room temperature afforded the isolated mixed diols **13** (Scheme 3).



[R^1R^2CO = PhCHO, Et_2CO]

Scheme 2.

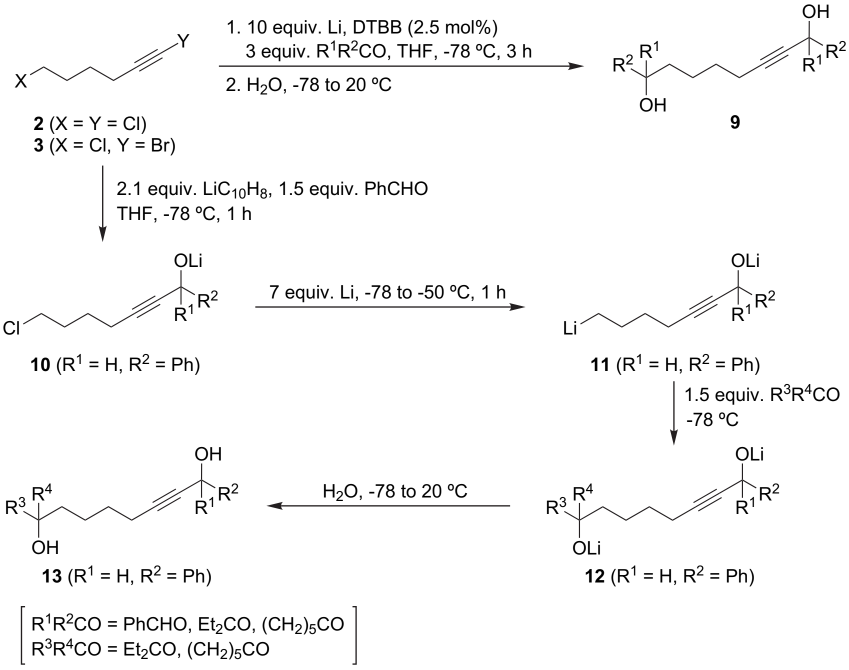
Table 1. Mono- and dilithiation of 1,6-dihalohex-1-ynes **2**, **3** and **4** (preparation of compounds **5**, **6**, **9** and **13**)

Entry	Starting material			R^1R^2CO	R^3R^4CO	Product[a]		
	No.	X	Y			No.	Structure	Yield[b] (%)
1	**2**	Cl	Cl	PhCHO	—	**5**		54
2	**3**	Cl	Br	PhCHO	—	**5**		69
3	**4**	I	Cl	Et_2CO	—	**6**		26
4	**2**	Cl	Cl	PhCHO	—	**9a**		56[c]
5	**3**	Cl	Br	PhCHO	—	**9a**		61[c]
6	**2**	Cl	Cl	Et_2CO	—	**9b**		42
7	**3**	Cl	Br	Et_2CO	—	**9b**		46
8	**2**	Cl	Cl	$(CH_2)_5CO$	—	**9c**		59
9	**3**	Cl	Br	$(CH_2)_5CO$	—	**9c**		54
10	**2**	Cl	Cl	PhCHO	Et_2CO	**13a**		39
11	**2**	Cl	Cl	PhCHO	$(CH_2)_5CO$	**13b**		36

[a] All products were >95% pure (GLC and/or 300 MHz ^1H NMR) and were fully characterised by spectroscopic means (IR, ^1H and ^{13}C NMR, and LR and HR mass spectrometry).

[b] Isolated yields of compounds **5**, **6**, **9** and **13** after column chromatography (silica gel, hexane/ethyl acetate).

[c] Obtained as a ca. 1:1 mixture of diastereomers (NMR).

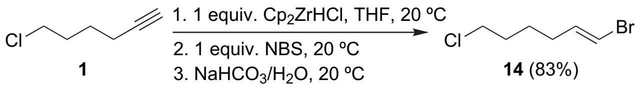


Scheme 3.

2.2. Lithiation of (*E*)-1-bromo-6-chlorohex-1-ene (14)

In the last part of this study we considered the lithiation of a compound having two different halogens attached to differently hybridised carbon atoms, such as the chlorinated bromo olefin **14**.

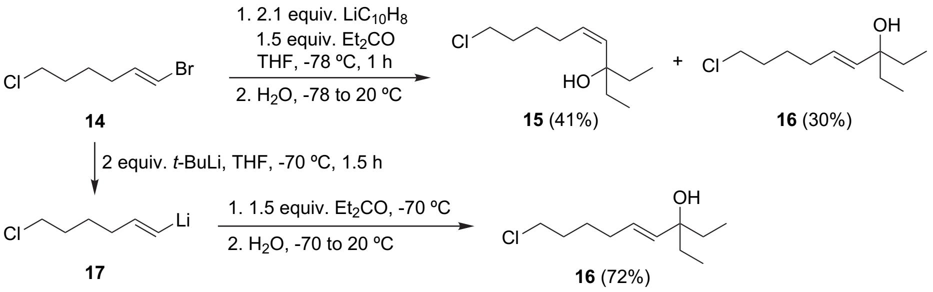
2.2.1. Preparation of (*E*)-1-bromo-6-chlorohex-1-ene (14). The desired dihalo compound **14** was prepared by a tandem hydrozirconiation–bromination of commercially available 6-chlorohex-1-yne (**1**).[14] Thus, treatment of this chloro alkyne with Cp_2ZrHCl in THF at room temperature followed by the addition of *N*-bromosuccinimide (NBS) under the same reaction conditions gave, after final basic treatment, the expected *E*-dihalo olefin **14** with total diastereoselectivity (Scheme 4).



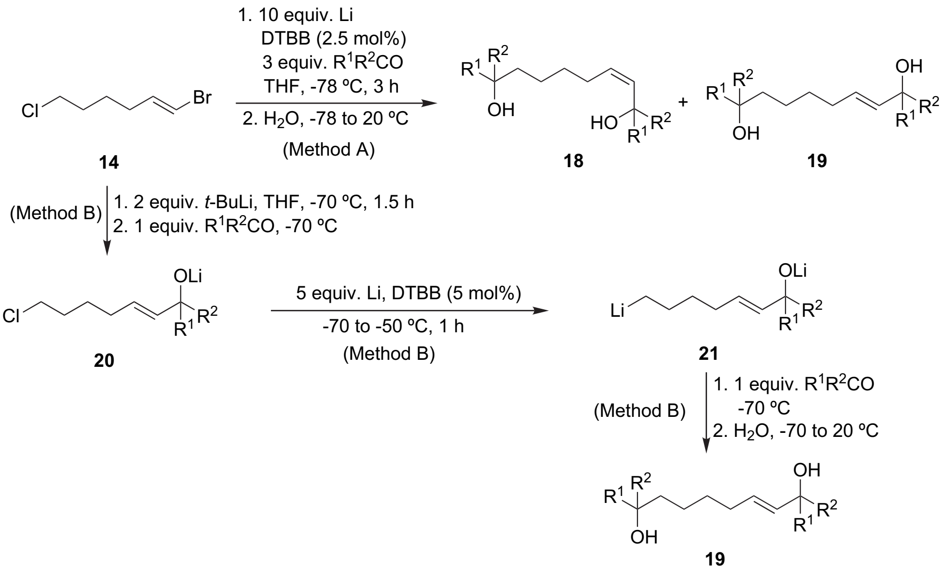
Scheme 4.

2.2.2. Monolithiation of (*E*)-1-bromo-6-chlorohex-1-ene (14). When diastereomerically pure compound **14** was lithiated with lithium naphthalene (1:2.1 M ratio) in the presence of an excess of pentan-3-one in THF at −78 °C, the final hydrolysis with water at temperatures between −78 °C and room temperature afforded a mixture of the corresponding unsaturated chloroalcohols **15** and **16**, which could be easily separated chromatographically (Scheme 5). From this result, and taking into account that the reaction of a vinylic organolithium intermediate with an electrophile works with retention in the configuration (see below) it is clear that the bromine–lithium exchange is not stereospecific; so both *Z*- and *E*-vinylic organolithiums of type **17** were generated (Scheme 5). On the contrary, the lithiation of the same starting material with *t*-BuLi generated only the corresponding *E*-intermediate **17** and therefore only the product **16** was obtained.[15]

2.2.3. Double lithiation of (*E*)-1-bromo-6-chlorohex-1-ene (14). The double lithiation of compound **14** was carried out following two protocols. As expected (see above), the use of lithium powder and a catalytic amount of DTBB (2.5 mol %) in the presence of the electrophile [PhCHO, Et_2CO, $(CH_2)_5CO$] in THF at −78 °C led, after hydrolysis with water, to the corresponding *Z*/*E*-mixture of unsaturated diols **18** and **19** (Method A, Scheme 6 and Table 2, entries 1–3). However, when the initial bromine–lithium exchange was performed with *t*-BuLi at −70 °C,[15] followed by reaction of the intermediate **17** with the same electrophiles than in Method A, only the alkoxide (*E*)-**20** was generated. The

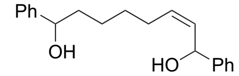
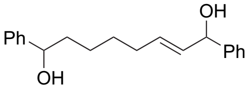
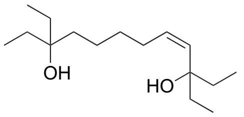
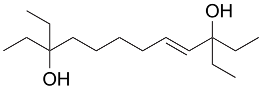
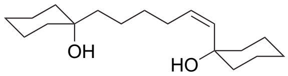
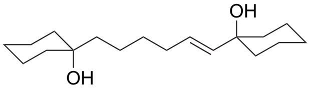
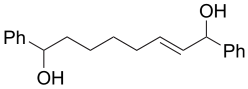
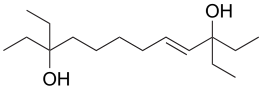
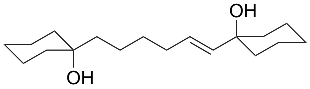


Scheme 5.



Scheme 6.

Table 2. Double lithiation of (*E*)-1-bromo-6-chlorohex-1-ene (**14**) (preparation of diols **18** and **19**)

Entry	R^1R^2CO	Method	Product[a]		
			No.	Structure	Yield[b] (%)
1	PhCHO	A	**18a**		44[c]
			19a		21[c]
2	Et_2CO	A	**18b**		40
			19b		22[c]
3	$(CH_2)_5CO$	A	**18c**		38
			19c		17
4	PhCHO	B	**19a**		54[c]
5	Et_2CO	B	**19b**		63
6	$(CH_2)_5CO$	B	**19c**		56

[a] All products **18** and **19** 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 **18** and **19** after column chromatography (silica gel, hexane/ethyl acetate) based on the starting material **14**.

[c] A ca. 4:1 mixture of diastereomers was obtained (75 MHz ^{13}C NMR).

second lithiation of this intermediate was performed by simply adding an excess of lithium powder (1:5 M ratio) and a catalytic amount of DTBB (5 mol%); so a new functionalised organolithium compound (*E*)-**21** was formed, which by treatment with the same electrophile than for the first step afforded, after hydrolysis with water, the diols **19** (Scheme 6, and Table 2, entries 4–6). This sequential procedure opens the possibilities of introducing two different electrophiles; so mixed diols of type **19** could be accessible.

3. Conclusions

From the results described in this paper we can conclude that it is possible to lithiate selectively halogenated compounds, concerning not only the different halogens but also the different hybridisation of two carbon–halogen bonds bearing equal or different halogens. Thus, sp-C–Cl or C–Br bonds can be lithiated exclusively in the presence of sp^3-C–Cl using lithium naphthalene as the lithiating agent. However, the sp^3-C–I bond can be selectively lithiated in the presence of a sp-C–Cl bond by using the same methodology. For sp^2-C–Hal bonds, we found that the sp^2-C–Br bond can be selectively lithiated in the presence of a sp^3-C–Cl bond, but the process is not stereospecific in an arene-promoted lithiation (either using the stoichiometric or the catalytic version), so a mixture of the corresponding vinylic organolithiums were generated. However, the lithiation of the same compound with *t*-BuLi allows the stereospecific bromine–lithium exchange with retention of the configuration. This last process has been shown to be adequate to the stereospecific introduction of two electrophiles in a molecule such as (*E*)-1-bromo-6-chlorohex-1-ene.

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 $\leq$0.006%, Acros) was used as a 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 AVANCE 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 diam., 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. Preparation of 1,6-dichlorohex-1-yne (2)

To a solution of 6-chlorohex-1-yne (**1**) (1.16 g, 10.0 mmol) in THF (20 mL) was added a hexane solution of *n*-BuLi (6.5 mL, 1.6 M, 10.4 mmol) at −78 °C under argon. The reaction mixture was stirred at the same temperature for 30 min and then a solution of *p*-toluenesulfonyl chloride (1.90 g, 10.0 mmol) in THF (10 mL) was added dropwise. The resulting reaction mixture was allowed to reach the room temperature, and it was hydrolysed with water (15 mL) and extracted with ethyl acetate (3×30 mL). The organic layer was dried over anhydrous magnesium sulfate and evaporated (15 Torr). The residue was purified by column chromatography (silica gel; hexane) to yield pure product **2** (1.39 g, 92% yield). Physical and spectroscopic data for this compound follow. Pale yellow liquid; R_f 0.20 (hexane); ν (film) 2953, 2864, 2240 cm^{-1} ($C\equiv C$); δ_H 1.62–1.69 (2H, m, CH_2), 1.84–1.91 (2H, m, CH_2), 2.23 (2H, t, J=6.8 Hz, $CH_2C\equiv C$), 3.55 (2H, t, J=6.6 Hz, CH_2Cl); δ_C 18.0, 25.5, 31.4, 44.4 (CH_2), 57.7, 68.7 ($C\equiv C$); *m/z* 150 (M^+, 4%), 124 (26), 122 (44), 101 (11), 88 (35), 87 (15), 86 (18), 79 (61), 77 (49), 75 (35), 73 (43), 65 (59), 53 (30), 51 (73), 50 (25), 49 (26), 41 (100); HRMS: M^+ found 149.9994. $C_6H_8Cl_2$ requires 150.0000.

4.3. Preparation of 1-bromo-6-chlorohex-1-yne (3)

To a solution of 6-chlorohex-1-yne (**1**) (1.16 g, 10.0 mmol) in dry acetone (20 mL) were added silver nitrate (0.15 g, 0.88 mmol) and NBS (1.96 g, 11.0 mmol). The reaction mixture was stirred at 20 °C for 3 h and after that hexane (90 mL) was added. The resulting reaction mixture was washed with water (3×80 mL). The aqueous layer was extracted with a 1:1 mixture of diethyl ether/hexane (3×30 mL). The combined organic layers were dried over anhydrous magnesium sulfate and evaporated (15 Torr). The residue was purified by column chromatography (silica gel; hexane) to yield pure product **3** (1.70 g, 87% yield). Physical and spectroscopic data for this compound follow. Orange liquid; R_f 0.52 (hexane); ν (film) 2955, 2870, 2217 cm^{-1} ($C\equiv C$); δ_H 1.65–1.72 (2H, m, CH_2), 1.84–1.91 (2H, m, CH_2), 2.27 (2H, t, J=6.9 Hz, $CH_2C\equiv C$), 3.57 (2H, t, J=6.5 Hz, CH_2Br); δ_C 18.9, 25.4, 38.4 ($\mathit{C}\equiv C$), 44.4 (CH_2), 79.4 ($C\equiv \mathit{C}$); *m/z* 196 (M^++2, 16%), 194 (M^+, 12), 168 (50), 166 (38), 134 (22), 132 (30), 119 (33), 117 (30), 87 (20), 79 (76), 77 (84), 66 (39), 65 (75), 53 (54), 51 (74), 41 (100).[16]

4.4. Preparation of 1-chloro-6-iodohex-1-yne (4)

To a solution of sodium iodide (3.0 g, 20 mmol) in dry acetone (10 mL) was added 1,6-dichlorohex-1-yne (**2**) (0.45 g, 3.0 mmol). The resulting mixture was stirred at 50 °C for 15 h. The solvent was removed (15 Torr) and the resulting residue was hydrolysed with water (10 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) to yield pure product **4** (0.68 g, 94% yield). Physical and spectroscopic data for this compound follow. Yellow liquid; R_f 0.63 (hexane); ν (film) 2950, 2928, 2858, 2242 cm^{-1} ($C\equiv C$); δ_H 1.57–1.67 (2H, m, CH_2), 1.87–1.97 (2H, m, CH_2), 2.22 (2H, t, J=6.9 Hz, $CH_2C\equiv C$), 3.20 (2H, t, J=6.9 Hz, CH_2I); δ_C 5.8, 17.7, 29.0, 32.25 (CH_2), 57.8, 68.7 ($C\equiv C$); *m/z* 242 (M^+, 5%), 127 (15), 80 (16), 79 (100), 77 (41), 75 (18), 73 (31), 51 (17); HRMS: M^+ found 241.9361. C_6H_8ClI requires 241.9359.

4.5. Monolithiation of 1,6-dihalohex-1-ynes 2–4. Preparation of compounds 5 and 6. General procedure

A THF solution of lithium/naphthalene (0.7 M, 3.0 mL, 2.1 mmol) was added dropwise at −78 °C over 1 h to a stirred THF solution (3 mL) of the corresponding 1,6-dihalohex-1-yne **2–4** (1.0 mmol) and a carbonyl compound (R^1R^2CO, 1.5 mmol). The reaction mixture was carefully hydrolysed with water (4 mL), and the system was allowed to reach room temperature. The reaction mixture was extracted with ethyl acetate (3×10 mL), 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 **5** and **6**. Yields are given in Table 1; physical and spectroscopic data for these compounds follow.

4.5.1. 7-Chloro-1-phenylhept-2-yn-1-ol (5). Pale yellow oil; R_f 0.17 (hexane/ethyl acetate: 10:1); ν (film) 3450–3190 (OH), 3088, 3033, 2953, 2865, 2232 cm^{-1} ($C\equiv C$); δ_H 1.64–1.71 (2H, m, CH_2), 1.84–1.91 (2H, m, CH_2), 2.28–2.32 (2H, m, $CH_2C\equiv C$), 2.38 (1H, br s, OH), 3.53 (2H, t, J=6.5 Hz, CH_2Cl), 5.41 (1H, s, $C\mathit{H}OH$), 7.28–7.38 (3H, ArH), 7.50 (2H, d, J=7.5 Hz, ArH); δ_C 18.0, 25.6, 31.4, 44.4 (CH_2), 64.6 (CHOH), 80.6, 86.4 ($C\equiv C$), 126.5, 128.1, 128.5, 141.0 (ArC); *m/z* 222 (M^+, 100%), 145 (78), 131 (48), 129 (27), 117 (33), 115 (48), 105 (50), 91 (33), 79 (32), 77 (47), 51 (15).[17]

4.5.2. 9-Chloro-3-ethylnon-8-yn-3-ol (6). Colourless oil; R_f 0.10 (hexane/ethyl acetate: 10:1); ν (film) 3500–3220 (OH), 2973, 2873, 2237 cm^{-1} ($C\equiv C$); δ_H 1.02 (6H, t, J=7.5 Hz, 2×CH_3), 1.29–1.67 (10H, m, 5×CH_2), 1.82 (1H, br s, OH), 2.19 (2H, t, J=6.8 Hz, $CH_2C\equiv C$); δ_C 8.6 (CH_3), 18.5, 28.6, 28.7, 34.6 (CH_2), 72.2 (COH), 82.6, 84.8 ($C\equiv C$); *m/z* 167 (M^+−Cl, 31%), 150 (11), 150 (11), 149 (100), 71 (15), 70 (14), 57 (22); HRMS: M^+−EtOH found 156.0696. $C_9H_{13}Cl$ requires 156.0706.

4.6. Double lithiation of 1,6-dihalohex-1-ynes 2 and 3. Preparation of diols 9. General procedure

A THF solution (3 mL) of the corresponding 1,6-dihalohex-1-yne **2** or **3** (1.0 mmol) and a carbonyl compound (R^1R^2CO, 3.0 mmol) was added to a green suspension of lithium (0.070 g, 10.0 mmol) and DTBB (0.027 g, 0.1 mmol) in dry THF (3 mL) over 3 h. The reaction mixture was carefully hydrolysed with water (4 mL), and the system was allowed to reach room temperature. The reaction mixture was extracted with ethyl acetate (3×10 mL), 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 **9**. Yields are given in Table 1; physical and spectroscopic data for these compounds follow.

4.6.1. 1,8-Diphenyloct-2-yne-1,8-diol (9a). Colourless oil; R_f 0.29 (hexane/ethyl acetate: 2:1); ν (film) 3525–3210 (OH), 3085, 3063, 3028, 2940, 2862, 2232, 2202 cm^{-1} ($C\equiv C$); δ_H 1.22–1.72 (6H, m, 3×CH_2), 2.16–2.19 (2H, m, $CH_2C\equiv C$), 2.81 (1H, br s, OH), 3.35 (1H, br s, OH), 4.52 (1H, t, J=6.6 Hz, $C\mathit{H}OHCH_2$), 5.32 (1H, s, $C\mathit{H}OHC\equiv C$), 7.20–7.46 (10H, m, ArH); δ_C 18.5, 24.7, 28.0, 38.1 (CH_2), 64.3, 74.1 (CHOH), 80.3, 86.9 ($C\equiv C$), 125.7, 126.5, 127.3, 127.8, 128.2, 128.3, 141.2, 144.5 (ArC); m/z 276 (M^+-H_2O, 4%), 170 (28), 169 (26), 155 (20), 142 (100), 141 (85), 129 (31), 128 (27), 115 (26), 107 (45), 105 (48), 91 (32), 79 (59), 77 (54); HRMS: M^+-H_2O found 276.1508. $C_{20}H_{20}O$ requires 276.1514.

4.6.2. 3,10-Diethyldodec-4-yne-3,10-diol (9b). Colourless oil; R_f 0.40 (hexane/ethyl acetate: 2:1); ν (film) 3540–3280 (OH), 2968, 2933, 2870, 2237 cm^{-1} ($C\equiv C$); δ_H 0.85 (6H, t, J=7.4 Hz, 2×CH_3), 1.01 (3H, t, J=7.5 Hz, 2×CH_3), 1.41–1.67 (16H, m, 7×CH_2, 2×OH), 2.23 (2H, t, J=6.7 Hz, $CH_2C\equiv C$); δ_C 7.7, 8.6 (CH_3), 18.5, 22.5, 29.2, 30.9, 34.5, 37.4 (CH_2), 72.1, 74.5 (COH), 82.8, 84.5 ($C\equiv C$); m/z 207 (M^+-H_2O–Et, 71%), 189 (19), 135 (41), 121 (32), 109 (18), 107 (13), 93 (28), 79 (21), 57 (100); HRMS: $M^+-EtOH-H_2O$ found 190.1714. $C_{14}H_{22}$ requires 190.1721.

4.6.3. 1-[6-(1-Hydroxycyclohexyl)hex-1-ynil]cyclohexanol (9c). Colourless oil; R_f 0.34 (hexane/ethyl acetate: 2:1); ν (film) 3510–3200 (OH), 2933, 2858, 2232 cm^{-1} ($C\equiv C$); δ_H 1.36–1.66 (26H, m, 12×CH_2, 2×OH), 1.84–1.87 (2H, m, CH_2), 2.23 (2H, t, J=6.3 Hz, $CH_2C\equiv C$); δ_C 18.4, 21.8, 22.1, 23.3, 25.1, 25.7, 29.0, 37.2, 40.0 (CH_2), 68.4, 71.3 (COH), 84.1, 84.2 ($C\equiv C$); m/z 260 (M^+-H_2O, 9%), 217 (31), 203 (28), 189 (30), 177 (16), 162 (35), 161 (51), 147 (42), 133 (47), 119 (38), 99 (46), 81 (100), 79 (73), 67 (42), 55 (72); HRMS: M^+-H_2O found 260.2122. $C_{18}H_{28}O$ requires 260.2140.

4.7. Double sequential lithiation of 1,6-dichlorohex-1-yne (2). Preparation of diols 13. General procedure

A THF solution of lithium–naphthalene (0.7 M, 3.0 mL, 2.1 mmol) was added dropwise at −78 °C over 1 h to a stirred THF solution (3 mL) of 1,6-dichlorohex-1-yne (**2**) (0.151 g, 1.0 mmol) and benzaldehyde (0.095 g, 0.9 mmol). After that, lithium powder (0.028 g, 4.0 mmol) was added and stirring was continued for one additional hour at temperatures ranging between −78 and −50 °C. The reaction mixture was cooled down to −78 °C and a second carbonyl compound (R^3R^4CO, 1.5 mmol) was added. After 15 min, the reaction mixture was hydrolysed with water (4 mL), and the system was allowed to reach room temperature. The reaction mixture was extracted with ethyl acetate (3×10 mL), 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 **13**. Yields are given in Table 1; physical and spectroscopic data for these compounds follow.

4.7.1. 8-Ethyl-1-phenyldec-2-yne-1,8-diol (13a). Colourless oil; R_f 0.31 (hexane/ethyl acetate: 2:1); ν (film) 3530–3190 (OH), 3088, 3063, 3032, 2968, 2938, 2878, 2227 cm^{-1} ($C\equiv C$); δ_H 0.83 (6H, t, J=7.6 Hz, 2×CH_3), 1.22–1.69 (10H, m, 5×CH_2), 2.26–2.32 (2H, m, $CH_2C\equiv C$), 2.55 (2H, br s, 2×OH), 5.43 (1H, br s, $C\mathit{H}OH$), 7.25–7.39 (3H, m, ArH), 7.50–7.55 (2H, m, ArH); δ_C 7.7 (CH_3), 18.6, 22.5, 28.8, 30.9, 37.5 (CH_2), 64.7 (CHOH), 74.7 (COH), 80.3, 87.2 ($C\equiv C$), 126.5, 128.1, 128.4, 141.2 (ArC); m/z 256 (M^+-H_2O, 7%), 238 (13), 227 (27), 209 (45), 207 (40), 181 (23), 169 (23), 167 (29), 155 (96), 154 (49), 146 (75), 145 (43), 142 (71), 141 (76), 131 (73), 129 (52), 128 (51), 115 (72), 105 (88), 91 (65), 87 (69), 77 (91), 57 (100); HRMS: M^+-H_2O found 256.1837. $C_{18}H_{24}O$ requires 256.1827.

4.7.2. 7-(1-Hydroxycyclohexyl)-1-phenylhept-2-yn-1-ol (13b). Colourless oil; R_f 0.36 (hexane/ethyl acetate: 2:1); ν (film) 3520–3200 (OH), 3083, 3058, 3030, 2930, 2858, 2232 cm^{-1} ($C\equiv C$); δ_H 1.22–1.57 (16H, m, 8×CH_2), 2.26–2.31 (2H, m, $CH_2C\equiv C$), 2.98 (2H, br s, 2×OH), 5.42 (1H, br s, $C\mathit{H}OH$), 7.26–7.38 (3H, m, ArH), 7.50–7.54 (2H, m, ArH); δ_C 18.6, 21.9, 22.1, 25.7, 28.8, 37.2 (CH_2), 64.6 (CHOH), 71.5 (COH), 80.4, 87.1 ($C\equiv C$), 126.6, 128.0, 128.4, 141.3 (ArC); m/z 268 (M^+-H_2O, 10%), 250 (11), 207 (16), 170 (24), 169 (32), 167 (16), 159 (25), 155 (39), 154 (40), 146 (46), 142 (100), 141 (93), 131 (41), 129 (45), 128 (44), 115 (47), 105 (50), 99 (56), 91 (58), 81 (59), 77 (55), 67 (26), 55 (41); HRMS: M^+-H_2O found 268.1823. $C_{19}H_{24}O$ requires 268.1827.

4.8. Preparation of (*E*)-1-bromo-6-chlorohex-1-ene (14)

A THF solution of $LiEt_3BH$ (1.0 M, 5.0 mL, 5.0 mmol) was added dropwise at 20 °C over 5 min to a stirred THF solution (40 mL) of Cp_2ZrCl_2. The reaction mixture was protected from light and stirred at the same temperature for 1 h. After that, 6-chlorohex-1-yne (**1**) (0.58 g, 5.0 mmol) was added dropwise and after 10 min, NBS (0.89 g, 5.0 mmol) was also added at once. Stirring was continued for another additional 10 min and the reaction mixture was hydrolysed with an aqueous saturated $NaHCO_3$ solution (150 mL), extracted with a 1:10 mixture of ethyl acetate/hexane (3×40 mL) and dried over anhydrous magnesium sulfate. The residue was filtrated through a Celite and silica gel path, and evaporated (15 Torr) to give pure compound **14** (0.82 g, 83% yield). Physical and spectroscopic data for this compound follow. Orange liquid; R_f 0.48 (hexane); ν (film) 3065, 2950, 2938, 2860, 1615 cm^{-1}; δ_H 1.53–1.61 (2H, m, CH_2), 1.82–1.91 (2H, m, CH_2), 2.05–2.12 (2H, m, CH_2), 3.40 (2H, t, J=6.5 Hz, CH_2Br), 6.03 (1H, dt, J=13.9, 1.2 Hz, $BrC\mathit{H}{=}CH$), 6.16 (1H, dt, J=13.9, 6.7 Hz, $BrCH{=}C\mathit{H}$); δ_C 27.0, 31.8, 31.9, 33.2 (CH_2), 104.8, 137.2 ($CH{=}CH$); m/z 240 (M^+, 8%), 163 (23), 161 (22), 134 (17), 121 (31), 119 (30), 81 (100), 55 (27), 53 (17).[16]

4.9. Monolithiation of (*E*)-1-bromo-6-chlorohex-1-ene (14) using lithium naphthalene as lithiating reagent. Preparation of alcohols 15 and 16

A THF solution of lithium/naphthalene (0.7 M, 3.0 mL, 2.1 mmol) was added dropwise at −78 °C over 1 h to a stirred THF solution (3 mL) of (*E*)-1-bromo-6-chlorohex-1-ene (**14**) (0.197 g, 1.0 mmol) and Et_2CO (0.129 g, 1.5 mmol). The reaction mixture was carefully hydrolysed with water (4 mL), and the system was allowed to reach room temperature. The reaction mixture was extracted with ethyl acetate (3×10 mL), dried over anhydrous magnesium sulfate and evaporated (15 Torr). The residue was purified by column chromatography (silica gel; hexane/ethyl acetate) to yield a 4:3 mixture of stereoisomeric pure products **15** and **16**. Yields are given in Scheme 5; physical and spectroscopic data for these compounds follow.

4.9.1. (*Z*)-9-Chloro-3-ethylnon-4-en-3-ol (15). Colourless oil; R_f 0.41 (hexane/ethyl acetate: 10:1); ν (film) 3600–3250 (OH), 2940, 2865, 1630 cm^{-1}; δ_H 0.90 (6H, t, J=7.5 Hz, 2×CH_3), 1.51–1.63 (7H, m, 3×CH_2, OH), 1.76–1.83 (2H, m, CH_2), 2.35–2.41 (2H, m, $CH_2C{=}C$), 3.55 (2H, t, J=6.8 Hz, CH_2Cl), 5.23 (1H, dt, J=12.1, 1.7 Hz, CH=C*H*COH), 5.36–5.43 (1H, dt, J=12.1, 7.4 Hz, CH=C*H*COH); δ_C 8.0 (CH_3), 27.2, 27.3, 32.2, 34.1, 47.25 (CH_2), 79.6 (COH), 131.4, 134.3 (CH=CH); *m/z* 186 ($M^+{-}H_2O$, 16%), 177 (32), 175 (100), 157 (14), 123 (10), 109 (18), 95 (15), 93 (12), 85 (73), 81 (32), 79 (19), 69 (14), 67 (34), 57 (51), 55 (23); HRMS: $M^+{-}H_2O$ found 186.1163. $C_{11}H_{19}Cl$ requires 186.1175.

4.9.2. (*E*)-9-Chloro-3-ethylnon-4-en-3-ol (16). Colourless oil; R_f 0.37 (hexane/ethyl acetate: 10:1); ν (film) 3602–3240 (OH), 2945, 2867, 1635 cm^{-1}; δ_H 0.85 (6H, t, J=7.5 Hz, 2×CH_3), 1.48–1.57 (7H, m, 3×CH_2, OH), 1.75–1.80 (2H, m, CH_2), 2.07–2.12 (2H, m, $CH_2C{=}C$), 3.54 (2H, t, J=6.7 Hz, CH_2Cl), 5.40 (1H, dt, J=15.6, 1.4 Hz, CH=C*H*COH), 5.36–5.43 (1H, dt, J=15.6, 6.7 Hz, CH=C*H*COH); δ_C 7.8 (CH_3), 26.6, 31.5, 32.0, 33.0, 47.9 (CH_2), 75.2 (COH), 128.0, 135.9 (CH=CH); *m/z* 186 ($M^+{-}H_2O$, 14%), 177 (30), 175 (100), 157 (10), 109 (15), 95 (10), 85 (65), 81 (19), 79 (12), 69 (10), 67 (21), 57 (34), 55 (16); HRMS: $M^+{-}H_2O$ found 186.1166. $C_{11}H_{19}Cl$ requires 186.1175.

4.10. Monolithiation of (*E*)-1-bromo-6-chlorohex-1-ene (14) using *tert*-butyllithium as lithiating reagent. Preparation of alcohol 16

A hexane solution of *t*-BuLi (1.7 M, 1.2 mL, 2.0 mmol) was added dropwise at −70 °C over 5 min to a stirred THF solution (4 mL) of (*E*)-1-bromo-6-chlorohex-1-ene (**14**) (0.197 g, 1.0 mmol). The reaction mixture was stirred at the same temperature for 1.5 h and after that Et_2CO (0.129 g, 1.5 mmol) was also added. The reaction mixture was hydrolysed with water (4 mL), and the system was allowed to reach room temperature. The reaction mixture was extracted with ethyl acetate (3×15 mL), dried over anhydrous magnesium sulfate and evaporated (15 Torr). The residue was purified by column chromatography (silica gel; hexane/ethyl acetate) to yield pure product **16**. Yield is given in Scheme 5; physical and spectroscopic data are given above.

4.11. Double lithiation of (*E*)-1-bromo-6-chlorohex-1-ene (14). Preparation of alcohols 18 and 19 (Method A). General procedure

A THF solution (3 mL) of (*E*)-1-bromo-6-chlorohex-1-ene (**14**) (0.197 g, 1.0 mmol) and a carbonyl compound (R^1R^2CO, 3.0 mmol) were added to a green suspension of lithium (0.070 g, 10.0 mmol) and DTBB (0.027 g, 0.1 mmol) in dry THF (3 mL) over 3 h. The reaction mixture was carefully hydrolysed with water (5 mL), and the system was allowed to reach room temperature. The reaction mixture was extracted with ethyl acetate (3×15 mL), 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 **18** and **19**. Yields are given in Table 2; physical and spectroscopic data for these compounds follow.

4.11.1. (*Z*)-1,8-Diphenyloct-2-ene-1,8-diol (18a). Colourless oil (diastereomeric mixture); R_f 0.30 (hexane/ethyl acetate: 2:1); ν (film) 3500–3250 (OH), 3087, 3060, 3027, 2929, 2858 cm^{-1}; δ_H 1.38–1.77 (8H, m, 3×CH_2, 2×OH), 1.95–2.06 (2H, m, $CH_2C{=}C$), 4.61–4.69 (1H, m, C*H*OHCH_2), 5.13 (1H, d, J=6.0 Hz, C*H*OHC=C), 5.61–5.71 (2H, m, CH=CH), 7.25–7.35 (10H, m, ArH); δ_C 25.2, 28.7, 28.8, 31.9, 31.95, 38.7, 38.8 (CH_2), 74.45, 74.55, 75.1 (CHOH), 125.7, 125.8, 125.9, 126.1, 127.5, 128.4, 132.3, 132.4, 143.3, 143.4 (CH=CH, ArC); *m/z* 278 ($M^+{-}H_2O$, 5%), 146 (11), 130 (100), 117 (41), 115 (22), 104 (60), 91 (34), 77 (16); HRMS: $M^+{-}2H_2O$ found 260.1563. $C_{20}H_{20}$ requires 260.1565.

4.11.2. (*Z*)-3,9-Diethyldodec-4-ene-3,9-diol (18b). Colourless oil; R_f 0.52 (hexane/ethyl acetate: 2:1); ν (film) 3560–3130 (OH), 2968, 2880, 1651 cm^{-1}; δ_H 0.82–0.92 (12H, m, 4×CH_3), 1.25–1.58 (16H, m, 7×CH_2, 2×OH), 2.32–2.38 (2H, m, $CH_2C{=}C$), 5.22 (1H, d, J=11.9 Hz, CH=C*H*COH), 5.35–5.45 (1H, m, C*H*=CHCOH); δ_C 7.75, 8.0 (CH_3), 22.8, 28.0, 30.6, 31.0, 34.0, 37.9 (CH_2), 74.5, 74.6 (COH), 132.2, 134.0 (CH=CH); *m/z* 238 ($M^+{-}H_2O$, 2%), 220 (10), 209 (18), 191 (80), 149 (20), 137 (41), 123 (39), 107 (99), 95 (69), 93 (69), 81 (68), 79 (50), 69 (38), 67 (53), 57 (100), 55 (74); HRMS: $M^+{-}2H_2O$ found 220.2195. $C_{16}H_{28}$ requires 220.2191.

4.11.3. (*Z*)-1-[6-(1-Hydroxycyclohexyl)hex-1-enyl]cyclohexanol (18c). Colourless oil; R_f 0.47 (hexane/ethyl acetate: 2:1); ν (film) 3500–3220 (OH), 2938, 2858, 1451 cm^{-1}; δ_H 1.31–1.70 (28H, m, 13×CH_2, 2×OH), 2.36–2.39 (2H, m, $CH_2C{=}C$), 5.30–5.39 (1H, m, C*H*=CHCOH), 5.45 (1H, d, J=12.7 Hz, CH=C*H*COH); δ_C 22.2, 22.3, 22.4, 25.4, 25.8, 28.2, 30.4, 37.4, 39.2 (CH_2), 71.5, 72.4 (COH), 132.3, 136.0 (CH=CH); *m/z* 262 ($M^+{-}H_2O$, 2%), 244 (45), 161 (62), 148 (100), 136 (40), 133 (43), 119 (32), 105 (35), 93 (57), 91 (90), 81 (70), 79 (99), 67 (75), 55 (53); HRMS: $M^+{-}2H_2O$ found 244.2191. $C_{18}H_{28}$ requires 244.2191.

4.11.4. (*E*)-1,8-Diphenyloct-2-ene-1,8-diol (19a). Colourless oil (diastereomeric mixture); R_f 0.28 (hexane/ethyl acetate: 2:1); ν (film) 3510–3230 (OH), 3085, 3062, 3030, 2932, 2864 cm^{-1}; δ_H 1.40–1.78 (8H, m, 3$\times$CH$_2$, 2$\times$OH), 1.93–2.08 (2H, m, CH$_2$C$=$C), 4.58 (1H, dd, J=7.2, 6.3 Hz, C*H*OHCH$_2$), 5.08 (1H, d, J=6.3 Hz, CH$=$CHC*H*OH), 5.58 (1H, ddt, J=15.3, 6.3, 1.1 Hz, CH$=$C*H*CHOH), 5.63–5.69 (1H, m, C*H*$=$CHCHOH), 7.22–7.31 (10H, m, ArH); δ_C 25.1, 25.15, 28.65, 28.7, 31.85, 31.9, 38.6, 38.7 (CH$_2$), 74.4, 75.0 (CHOH), 125.8, 126.0, 127.3, 128.3, 128.35, 132.2, 132.4, 143.3, 144.7 (CH$=$CH, ArC); *m*/*z* 278 (M$^+$$-H_2$O, 3%), 146 (13), 130 (100), 117 (39), 115 (24), 104 (58), 91 (35), 77 (15); HRMS: M$^+$$-$2H$_2$O found 260.1566. $C_{20}H_{20}$ requires 260.1565.

4.11.5. (*E*)-3,9-Diethyldodec-4-ene-3,9-diol (19b). Colourless oil; R_f 0.49 (hexane/ethyl acetate: 2:1); ν (film) 3550–3110 (OH), 2970, 2878, 1654 cm^{-1}; δ_H 0.84 (12H, t, J=7.4 Hz, 4$\times$CH$_3$), 1.36–1.52 (16H, m, 7$\times$CH$_2$, 2$\times$OH), 2.04–2.08 (2H, m, CH$_2$C$=$C), 5.37 (1H, dt, J=15.6, 1.4 Hz, CH$=$C*H*COH), 5.57 (1H, dt, J=15.6, 6.8 Hz, C*H*$=$CHCOH); δ_C 7.7, 7.8 (CH$_3$), 22.8, 30.0, 30.9, 32.3, 33.0, 37.9 (CH$_2$), 74.6, 75.2 (COH), 128.7, 135.3 (CH$=$CH); *m*/*z* 238 (M$^+$$-H_2$O, 1%), 220 (11), 209 (21), 191 (85), 149 (19), 137 (51), 136 (36), 135 (19), 124 (52), 123 (47), 121 (35), 113 (31), 109 (23), 107 (90), 99 (40), 95 (67), 93 (65), 87 (37), 85 (40), 81 (57), 79 (41), 69 (34), 67 (44), 57 (100), 55 (56); HRMS: M$^+$$-$2H$_2$O found 220.2194. $C_{16}H_{28}$ requires 220.2191.

4.11.6. (*E*)-1-[6-(1-Hydroxycyclohexyl)hex-1-enyl]cyclohexanol (19c). Colourless oil; R_f 0.45 (hexane/ethyl acetate: 2:1); ν (film) 3480–3230 (OH), 2940, 2856, 1464 cm^{-1}; δ_H 1.32–1.77 (28H, m, 13$\times$CH$_2$, 2$\times$OH), 2.02–2.07 (2H, m, CH$_2$C$=$C), 5.55 (1H, dt, J=15.3, 1.2 Hz, CH$=$C*H*COH), 5.64 (1H, dt, J=15.3, 6.2 Hz, C*H*$=$CHCOH); δ_C 22.2, 25.5, 25.8, 29.7, 32.2, 37.3, 38.0 (CH$_2$), 71.15, 71.4 (COH), 127.8, 137.8 (CH$=$CH); *m*/*z* 262 (M$^+$$-H_2$O, 1%), 244 (43), 161 (58), 148 (100), 136 (35), 133 (44), 119 (31), 105 (32), 93 (55), 91 (86), 81 (71), 79 (96), 67 (70), 55 (51); HRMS: M$^+$$-$2H$_2$O found 244.2190. $C_{18}H_{28}$ requires 244.2191.

4.12. Double sequential lithiation of (*E*)-1-bromo-6-chlorohex-1-ene (14). Preparation of alcohols 19 (Method B). General procedure

A hexane solution of *t*-BuLi (1.7 M, 1.2 mL, 2.0 mmol) was added dropwise at −70 °C over 5 min to a stirred THF solution (4 mL) of (*E*)-1-bromo-6-chlorohex-1-ene (**14**) (0.197 g, 1.0 mmol). The reaction mixture was stirred at the same temperature for 1.5 h and after that the corresponding carbonyl compound was added (R^1R^2CO, 1.0 mmol). After 15 min, lithium powder (0.035 g, 5.0 mmol) and DTBB (0.027 g, 0.1 mmol) were added and stirring was continued for one additional hour at temperatures ranging between −70 and −50 °C. The reaction mixture was cooled down to −70 °C and a second carbonyl compound (R^3R^4CO, 1.5 mmol) was added. After 15 min, the reaction mixture was hydrolysed with water (4 mL), and the system was allowed to reach room temperature. The reaction mixture was extracted with ethyl acetate (3$\times$15 mL), 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 **19**. Yields are given in Table 2; physical and spectroscopic data are given above.

Acknowledgements

This work was generously supported by the Spanish Ministerio de Educación y Ciencia (MEC; Grant no. CTQ2004-01261) and the Generalitat Valenciana (GV; Grants no. GRUPOS05/052 and GRUPOS05/058). A.A. thanks the University of Alicante for a predoctoral fellowship. We also thank MEDALCHEMY S.L. for a gift of chemicals, especially lithium powder.

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