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Preparation of α,*n*-dilithiotoluene equivalents. Synthesis of tamoxifen

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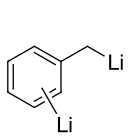
Abstract—The successive reaction of chlorobenzyl alcohols with *n*-butyllithium and lithium powder in the presence of a substoichiometric amount of 4,4′-di-*tert*-butylbiphenyl (DTBB) at −78°C yields the expected (lithiooxymethyl)phenyllithium derivative, which is trapped by reaction with different ketones. The subsequent arene-catalysed lithiation at 25°C permits the one-pot chemoselective lithiation of the primary benzyl alcoholate in the presence of a tertiary one. These new functionalised benzyllithium derivatives react with different electrophilic compounds, such as aldehydes, ketones and chlorotrimethylsilane, to give after hydrolysis the expected functionalised benzyl alcohols. Some of these alcohols are successfully transformed into mono- or di-olefins by acidic treatment. This whole strategy is applied to the preparation of anti-cancer drug tamoxifen. © 2003 Published by Elsevier Science Ltd.

1. Introduction

The huge amount of polyfunctionalised organic compounds present in Nature[1] has prompted chemists to develop new methodologies to obtain them as easily and selectively as possible. One very useful methodology consists in the application of organometallic intermediates[2] in their synthesis, and this is due to the versatility of these compounds in their reactivity with different reagents. Within this ample group, polylithiated equivalents[3] are a very interesting subclass due to their higher reactivity towards electrophilic compounds. In this way, the reaction of dilithiated species with two (equal or different) electrophiles allows the direct introduction of two electrophilic fragments in the molecule in only one synthetic step. This recently recognised strategy of construction of targets is divided in two groups:[4] (a) the simultaneous two-directional homologation, when the two electrophiles are the same or (b) the sequential two-directional homologation, when the two electrophiles are different. The great difficulty in a two-directional synthesis resides in the preparation of the appropriate intermediates having two carbon–lithium bonds with different reactivity.

Ones of the most simple dilithiated species having different hybridisation[5] are α,*n*-dilithiotoluenes (**1**). These intermediates were postulated in the reaction of toluene with a big excess of *n*-butyllithium-tetramethylethylendiamine in hexane, together with other products arising from a mono-, di- and tri-deprotonation process of any possible carbon–hydrogen bonds.[6]

An alternative to the direct metalation is the reductive lithiation of the corresponding dichlorinated materials,[7] using an arene as the electron shuttle.[8]



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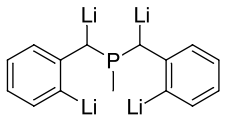

2

When at the benzylic position is a phosphorus atom, the stability of the intermediate is higher and the chemoselective polylithiation[9] is possible, yielding, for example, the compound **2**, which was characterised by X-ray analysis.[10] However, with this kind of intermediates the use of two different electrophiles for chemoselective reacting with the corresponding α,*n*-dilithiotoluene derivative is not possible.

In order to overcome this inconvenience and to be able to use α,2-dilithiotoluene equivalents in sequential two-directional synthesis, 1-bromo-2-[(trimethylstannyl)-methyl]benzene (**3**) was introduced.[11] The chemoselective lithiation of compound **3** using *tert*-butyllithium gave the corresponding aryllithium derivative, which was trapped by reaction with trimethylgermanium chloride. The further tin–lithium exchange must be conducted by a large excess of *tert*-butyllithium to give the expected benzyllithium derivative. The availability of compound **3**, as well as the

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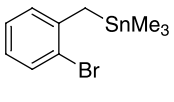
necessity of a large excess of alkyllithium reagent, limits the use of this reagent in synthesis.



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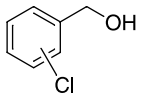

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In this paper we would like to introduce the commercially available chlorobenzyl alcohols (**4**) as ideal starting materials in the preparation of α,*n*-dilithiotoluene equivalents (**1**) and their use in sequential two-directional homologations. The one-pot sequential chemoselective lithiation of compounds **4** through a DTBB-catalysed lithiation process will take place depending on the reaction conditions, allowing to prepare and use synthetic equivalents of reagent **1**.

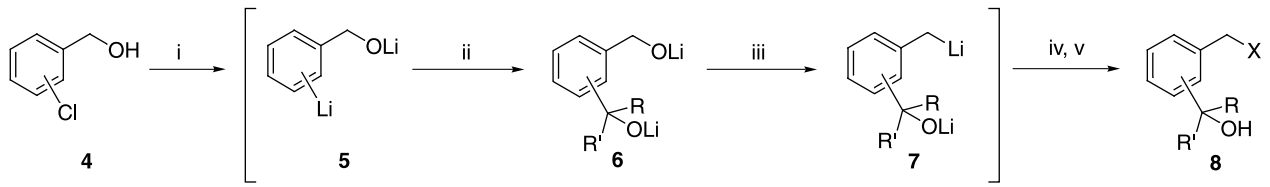
2. Results and discussion

The reaction of chlorobenzyl alcohols **4** with 1 equiv. of *n*-BuLi in THF gave the expected lithium alcoholate, which was then added to a solution of an excess of lithium powder and a substoichiometric amount of 4,4′-di-*tert*-butylbiphenyl (DTBB, 4% molar ratio) at −78°C to give after 1 h the corresponding functionalised organolithium[12] **5**. The same intermediate could be obtained when compounds **4** were added to a mixture of excess of lithium, DTBB (4% molar ratio) and *n*-BuLi. Arylithium derivatives[13] **5** were trapped by reaction with different ketones to give the corresponding alcoholate derivatives **6**. Then, the temperature reaction was allowed to rise from −78 to room temperature, so the chemoselective lithiation of the primary alcoholate[14] in the presence of the tertiary one took place, to lead to the benzyllithium derivatives **7**. The chemoselectivity found may be a consequence of the higher stability of primary organolithium compounds compared to the corresponding tertiary ones, and therefore it is based on thermodynamic considerations. Even for compounds **8b** and **8e** (derived from acetophenone), the postulate intermediate **7** (R=Me, R′=Ph) seems to be preferred compared to the corresponding tertiary one containing two phenyl groups. The final reaction of organolithiums **7** with different electrophiles, followed by hydrolysis, gave the functionalised benzyl alcohols **8** (see Scheme 1 and Table 1).

Global yields are variable, depending on both electrophiles used, being higher when cyclohexanone was used as the first electrophilic reagent. The relative position of substituents had also a great influence, and for example, using the *ortho*-chloroalcohol **4a** as starting material, the corresponding benzyl intermediate of type **7** could not be reacted with a second electrophile (benzaldehyde or cyclohexanone), giving in both cases the tolyl derivative **8** where X=H (see Scheme 1 and Table 1, entry 1). Probably, the *ortho*-intermediate **7** is very unstable and takes a proton for the reaction media, probably from the THF.[15]

The treatment of some benzylic alcohols **8** with phosphoric acid in toluene at room temperature gave the chemioselectively dehydration[16] to lead to the conjugate olefins **9** (see Table 2) with excellent yields.

In order to perform the full dehydration, the above diols **9** were submitted to the same acid conditions (phosphoric acid in toluene) but under a higher temperature. At toluene reflux the dehydration took place in 2 h, giving the expected diolefins **10** with excellent yields. It is worthy to note that in the case of the alcohol **9c** instead of the expected conjugate olefin of type **10a**,**b** the only isolated product was the compound **10c**. The reason for this behaviour must include



4 **5** **6** **7** **8**

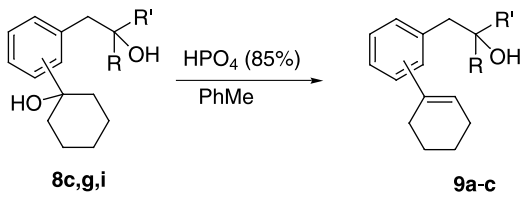
Scheme 1. *Reagents and conditions*: (i) *n*-BuLi (1 equiv.), −78°C, THF and then Li, DTBB (4 mol%) or Li, DTBB (4 mol%), *n*-BuLi (1 equiv.), THF, −78°C; (ii) $RCOR' = (CH_2)_5CO$, Et_2CO, PhCOMe; (iii) −78 to 25°C; (iv) E=Me_3SiCl, Bu^tCHO, PhCHO, Et_2CO, $(CH_2)_4CO$, THF, −40°C; (v) H_2O, −40 to 25°C.

Table 1. Preparation of compounds **8**

Entry	Starting material		E	Substituted benzyl alcohol				
	No.	Substitution		No.	R	R′	X	Yield (%)[a]
1	**4a**	1,2-	PhCHO	**8a**	$-(CH_2)_5-$		H	63
2	**4b**	1,3-	Me_3SiCl	**8b**	Me	Ph	Me_3Si	21
3	**4b**	1,3-	PhCHO	**8c**	$-(CH_2)_5-$		PhCHOH	52
4	**4b**	1,3-	Et_2CO	**8d**	$-(CH_2)_5-$		Et_2COH	48
5	**4c**	1,4-	Me_3SiCl	**8e**	Me	Ph	Me_3Si	35
6	**4c**	1,4-	Bu^tCHO	**8f**	Et	Et	Bu^tCHOH	18
7	**4c**	1,4-	PhCHO	**8g**	$-(CH_2)_5-$		PhCHOH	57
8	**4c**	1,4-	Et_2CO	**8h**	$-(CH_2)_5-$		Et_2COH	51
9	**4c**	1,4-	$(CH_2)_4CO$	**8i**	$-(CH_2)_5-$		$(CH_2)_4COH$	10

[a] Isolated yield (>95% from GLC and/or 300 MHz ^1H NMR) after column chromatography (silica gel, hexane/ethyl acetate).

Table 2. Preparation of olefins **9**

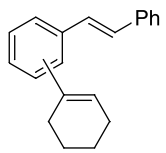


8c,g,i **9a-c**

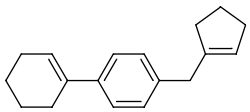
Entry	Diol		Product			
	No.	Position	No.	R	R′	Yield (%)[a]
1	**8c**	1,3-	**9a**	H	Ph	91
2	**8g**	1,4-	**9b**	H	Ph	97
3	**8i**	1,4-	**9c**	$-(CH_2)_4-$		90

[a] Isolated crude yield of pure product **9** (>95% from 300 MHz ^{1}H NMR).

the high torsional deformation of bond angles in overcrowded alkenes,[17] this steric hindrance being vanished in the case of the *endo*-cyclic olefin **10c**.



10a: 1,3- (95%)
10b: 1,4- (92%)



10c (88%)

This approach of lithiation of aryl- and benzyl derivatives using a arene-catalysed lithiation followed by dehydration was thought to be effective in the preparation of anticancer drug tamoxifen. (*Z*)-2-[4-(1,2-diphenyl-1-butenyl)-phenoxy]-*N*,*N*-dimethylethaneamine (tamoxifen, **14**) is a selective estrogen receptor antagonist, being used for the treatment for all stages of hormone-reponsive breast cancer.[18] The active metabolite of tamoxifen is the corresponding (*Z*)-4-hydroxytamoxifen. In vivo, the *Z*/*E*-mixture equilibrates very rapidly, so the isomeric mixture can be prescribed.[19] As far as the synthetic approaches are concerned, there are two general pathways to obtain tamoxifen derivatives: (a) the McMurry approach[20] which has the inconvenience of obtaining a mixture of the desired hetero-ketone coupling and the undesired homo-ketone coupling; (b) the use of organometallic nucleophiles (mainly organomagnesium reagents) to create carbon skeleton.[21] In our case, we followed the second approach, using phenyllithium and 1-lithio-1-phenylpropane as reagents. Thus, the naphthalene-catalysed lithiation of chlorobenzene[13a] (**11**) at −78°C gave the expected phenyllithium reagent, which was trapped by reaction with propanal, to give, after hydrolysis, the expected 1-phenyl-1-propanol.[22] This crude alcohol was transformed to the corresponding chlorinated material **12** with 82% isolated yield by nucleophilic substitution, using hydrochloric acid in hexane.[23] The other electrophilic component for this approach is 4-[2-(dimethylamino)ethoxy]benzophenone (**13**),[21b] which was easily prepared by alkylation of the corresponding 4-hydroxybenzophenone with 2-chloroethyldimethylamine under basic conditions.[20c,21b] The DTBB-catalysed lithiation of the chlorinated material **12** in the presence of the aforementioned benzophenone at low temperature gave, after hydrolysis, a mixture of the corresponding diastereomeric tertiary alcohol. The final dehydration using hydrochloric acid under reflux[21a] of ethanol gave a ca. 1/1 mixture of *Z*/*E* tamoxifen (**14**) with 51% isolated overall yield (see Scheme 2).

3. Conclusions

In conclusion, we have introduce here a simple method for the preparation of α-*n*-dilithiotoluene equivalents from commercial available chlorobenzyl alcohols. This strategy avoids the use of sophisticated starting materials, giving similar results. The arene-catalysed reductive lithiation of aryl and benzyl derivatives has been successfully used in the preparation of tamoxifen, the overall yield being similar to the best describes before using a similar strategy.

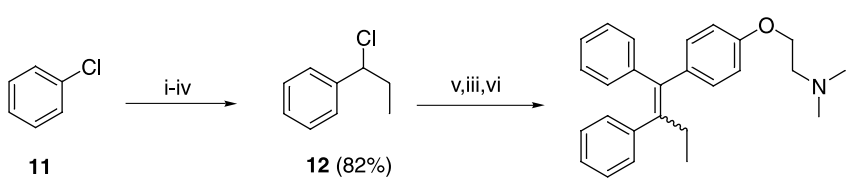
4. Experimental

4.1. General

Full general statements were described elsewhere.[24] All reactions using lithium powder were carried out under an argon atmosphere. 4-[2-(Dimethylamino)ethoxy]benzophenone (**13**)[21b] was prepared according to the reported procedure,[20c,21b] starting from the corresponding 4-hydroxybenzophenone by deprotonation using K_2CO_3 in a solution of H_2O/Me_2CO and final alkylation of the phenolate derivative with 2-chloroethyldimethylamine hydrochloride to give the expected product in 85% overall yield.

4.2. General procedure for the sequential chemoselective lithiation of chlorobenzyl alcohol. Isolation of compounds 8

To a turquoise-coloured suspension of lithium powder (0.20 g, 28 mmol) and DTBB (0.085 g, 0.32 mmol) in THF (5 mL) at −78°C was added a solution of *n*-buthyllithium (1.6 M, 1.25 mL). After 5 min, a solution of the corresponding



11 **12** (82%) **14** (51%)

Scheme 2. *Reagents and conditions*: (i) Li, $C_{10}H_8$ (4 mol%), THF, −78°C; (ii) EtCHO; (iii) H_2O, −78 to 25°C; (iv) HCl (35%), hexane, 25°C; (v) Li, DTBB (4 mol%), 4-($Me_2NCH_2CH_2O$)C_6H_4COPh (**13**), THF, −78°C; (vi) HCl (35%), EtOH, 80°C.

chlorobenzyl alcohol **4** (2 mmol) in THF (3 mL) was added. After 45 min, the corresponding ketone (2.2 mmol) was added, and after 15 min the temperature was allowed to rise to 25°C by removing of cooling bath. The reaction mixture was kept at this temperature for 4 h. Then, the mixture was cooled down to −40°C and the second electrophile (2.2 mmol) was added. After 1 h, the reaction mixture was successively quenched with H_2O (10 mL) and a saturated solution of NH_4Cl (25 mL). The resulting mixture was extracted with ethyl acetate (3×20 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and evaporated (15 Torr) to give a residue, which was purified by column chromatography, affording the pure title compounds **8**. Yields are included in Table 1. Physical and spectroscopic data, as well as the literature reference, follow.

4.2.1. 1-(2-Methylphenyl)-1-cyclohexanol 8a.[25] t_r 11.8; R_f 0.38 (hexane/ethyl acetate: 9/1); ν (film) 3451 (OH), 3104, 3057, 3014, 1608 (HC=C), 1171, 1132 cm^{-1} (CO); δ_H 1.20–2.00 [11H, m, $(CH_2)_5$ and OH], 2.61 (3H, s, Me), 7.10–7.25 and 7.40–7.45 (3 and 1H, respectively, 2m, ArH); δ_C 22.05 (2C), 22.3, 25.5, 37.25 (2C), 74.15, 125.2, 125.5, 126.8, 132.8, 136.45, 146.1; *m/z* 190 (M^+, 15%), 175 (10), 172 (10), 147 (62), 134 (18), 129 (17), 119 (100), 91 (38), 65 (10), 55 (40).

4.2.2. 1-Phenyl-1-(3-trimethylsilylmethylphenyl) ethanol 8b. t_r 14.7; R_f 0.64 (hexane/ethyl acetate: 7/3); ν (film) 3407 (OH), 3055, 3027, 1599 (HC=C), 1153 cm^{-1} (CO); δ_H 0.0 (9H, s, $SiMe_3$), 2.00 (3H, s, CMe), 2.12 (2H, s, CH_2), 2.20 (1H, broad s, OH), 6.90–6.95, 7.07 and 7.20–7.50 (1, 1 and 7H, respectively, m, s and m, respectively, ArH); δ_C −2.0 (3C), 27.1, 30.75, 76.2, 121.3, 125.8 (3C), 126.6, 126.8, 127.9, 128.0 (2C), 140.3, 147.75, 148.2; *m/z* 284 (M^+, <1%), 194 (42), 180 (10), 179 (66), 105 (12), 77 (10), 75 (15), 74 (11), 73 (100), 45 (37), 43 (50); HRMS: M^+ found 284.1576. $C_{18}H_{24}SiO$ requires 284.1596.

4.2.3. 1-[3-(2-Hydroxy-2-phenylethyl)phenyl]-1-cyclohexanol 8c. t_r 18.0; R_f 0.27 (hexane/ethyl acetate: 7/3); ν (film) 3405 (OH), 3061, 3028, 1604, 1493 (HC=C), 1043 cm^{-1} (CO); δ_H 1.55–1.75 [10H, m, $(CH_2)_5$], 2.12 (2H, broad s, 2×OH), 2.95–3.00 (2H, m, ArCH_2), 4.80–4.85 (1H, m, ArC*H*O), 7.05–7.10 and 7.20–7.30 (1 and 8H, respectively, 2m, ArH); δ_C 22.05 (2C), 25.4, 38.7 (2C), 46.2, 73.05, 75.25, 122.8, 125.9, 127.05, 127.45, 127.8, 128.2, 128.3 (2C), 137.8, 143.8, 149.5; *m/z* 278 (M^+-H_2O, 3%), 173 (14), 172 (100), 157 (20), 144 (13), 143 (17), 130 (12), 129 (30), 128 (18), 115 (16), 107 (80), 105 (27), 104 (23), 91 (19), 80 (16), 79 (89), 78 (10), 77 (54), 51 (16), 41 (12); HRMS: M^+-H_2O found 278.1656. $C_{20}H_{22}O$ requires 278.1671.

4.2.4. 1-[3-(2-Ethyl-2-hydroxybutyl)phenyl]-1-cyclohexanol 8d. t_r 16.0; R_f 0.27 (hexane/ethyl acetate: 7/3); ν (film) 3411 (OH), 3041, 3025, 1604 (HC=C), 1168, 1131 cm^{-1} (CO); δ_H 0.93 (6H, t, *J*=7.4 Hz, 2×Me), 1.45 (4H, q, *J*=7.4 Hz, 2×CH_2Me), 1.55–1.85 (12H, m, $(CH_2)_5$ and 2×OH), 2.75 (2H, s, ArCH_2), 7.10 and 7.25–7.40 (1 and 3H, respectively, d, *J*=7.3 Hz and m, respectively, ArH); δ_C 8.0 (2C), 22.1 (2C), 25.45, 30.3 (2C), 38.75 (2C), 44.95, 73.0, 74.55, 122.6, 126.95, 127.9, 128.8, 137.25, 149.3; *m/z* 258 (M^+-H_2O, <1%), 173 (16), 172 (100), 161 (10), 147 (13), 144 (19), 143 (46), 130 (11), 129 (14), 106 (12), 105 (12), 104 (47), 91 (19), 87 (48), 81 (25), 69 (12), 67 (13), 57 (38), 55 (41), 45 (85), 43 (32), 41 (43); HRMS: M^+-H_2O found 258.1962. $C_{18}H_{26}O$ requires 258.1984.

4.2.5. 1-Phenyl-1-(4-trimethylsilylmethylphenyl)-ethanol 8e. t_r 15.0; R_f 0.67 (hexane/ethyl acetate: 7/3); ν (film) 3466 (OH), 3079, 3056, 1605, 1507 (HC=C), 1155 cm^{-1} (CO); δ_H 0.0 (9H, s, $SiMe_3$), 1.84 (1H, s, OH), 1.94 (3H, s, CMe), 2.07 (2H, s, CH_2), 6.95–7.00 and 7.25–7.45 (2 and 7H, respectively, 2m, ArH); δ_C −1.0 (3C), 26.55, 30.9, 76.1, 125.7 (2C), 125.75 (2C), 126.7, 127.75 (2C), 128.05 (2C), 139.25, 143.4, 148.35; *m/z* 284 (M^+, 2%), 194 (55), 179 (20), 105 (15), 77 (11), 75 (10), 74 (12), 73 (100), 45 (39), 43 (55); HRMS: M^+ found 284.1614. $C_{18}H_{24}SiO$ requires 284.1596.

4.2.6. 1-[4-(2-Hydroxy-3,3-dimethylbutyl)phenyl]-3-pentanol 8f. t_r 14.4; R_f 0.38 (hexane/ethyl acetate: 7/3); ν (film) 3454 (OH), 1614 (C=C), 1159, 1069 cm^{-1} (CO); δ_H 0.76 (6H, t, *J*=7.4 Hz, 2×*Me*CH_2), 1.00 (9H, s, CMe_3), 1.50–1.70 (3H, m, 2×OH and CHO), 1.75–1.85 (4H, m, 2×CH_2Me), 2.90 and 3.44 (1 and 1 H, respectively, 2dd, *J*=2, 10.8 Hz, ArCH_2), 7.19 and 7.32 (2 and 2H, respectively, 2d, *J*=8.1 Hz, ArH); δ_C 7.85 (2C), 24.9, 25.85 (3C), 34.8, 34.85, 37.9, 77.3, 80.45, 125.75 (2C), 128.9 (2C), 137.65, 143.85; *m/z* 235 (M^+−Et, 100%), 166 (20), 149 (44), 104 (14), 91 (19), 87 (30), 69 (20), 57 (99), 45 (42), 43 (41), 41 (55); HRMS: $M^+-CH_3CH_2$ found 235.1672. $C_{15}H_{23}O_2$ requires 235.1698.

4.2.7. 1-[4-(2-Hydroxy-2-phenylethyl)phenyl]-1-cyclohexanol 8g. t_r 18.4; R_f 0.22 (hexane/ethyl acetate: 7/3); ν (film) 3403 (OH), 3061, 3028, 1604, 1512 (HC=C), 1037 cm^{-1} (CO); δ_H 1.60–1.85 [11H, m, $(CH_2)_5$ and OH], 2.11 (1H, broad s, OH), 2.90–3.05 (2H, m, ArCH_2), 4.85–4.90 (1H, m, ArC*H*O), 7.15–7.45 (9H, m, ArH); δ_C 22.1 (2C), 25.45, 38.75 (2C), 45.6, 72.95, 75.2, 124.75 (2C), 125.85 (2C), 127.55, 128.35 (2C), 129.25 (2C), 136.45, 143.85, 147.7; *m/z* 278 (M^+-H_2O, 2%), 173 (15), 172 (100), 171 (18), 157 (26), 144 (11), 129 (20), 128 (15), 115 (15), 107 (50), 105 (12), 104 (33), 91 (20), 79 (52), 77 (32), 51 (11); HRMS: M^+-H_2O found 278.1674. $C_{20}H_{22}O$ requires 278.1671.

4.2.8. 1-[4-(2-Ethyl-2-hydroxybutyl)phenyl]-1-cyclohexanol 8h. t_r 14.5; R_f 0.33 (hexane/ethyl acetate: 7/3); ν (film) 3400 (OH), 3087, 3053, 1613, 1510 (HC=C), 1146, 1128 cm^{-1} (CO); δ_H 0.91 (6H, t, *J*=7.4 Hz, 2×Me), 1.43 (4H, q, *J*=7.4 Hz, 2×CH_2Me), 1.60–1.80 [12H, m, $(CH_2)_5$ and 2×OH], 2.70 (2H, s, ArCH_2), 7.17 and 7.41 (2 and 2H, respectively, 2d, *J*=7.9 Hz, ArH); δ_C 7.9 (2C), 22.1 (2C), 25.45, 30.3 (2C), 38.7 (2C), 44.2, 72.8, 74.5, 124.35 (2C), 130.3 (2C), 135.65, 147.45; *m/z* 258 (M^+-H_2O, <1%), 173 (13), 172 (90), 157 (16), 147 (16), 144 (10), 143 (14), 134 (13), 129 (21), 128 (13), 105 (16), 104 (100), 99 (14), 91 (19), 87 (54), 81 (18), 69 (18), 57 (26), 55 (24), 45 (82), 43 (25), 41 (40); HRMS: M^+ found 276.2076. $C_{18}H_{28}O_2$ requires 276.2089.

4.2.9. 1-[4-(1-Hydroxycyclopentylmethyl)phenyl]-1-cyclohexanol 8i. t_r 17.5; R_f 0.24 (hexane/ethyl acetate:

7/3); ν (film) 3406 (OH), 1644 (C=C), 1086, 1021 cm^{-1} (CO); δ_H 1.55–1.80 [20H, m, $(CH_2)_5$, $(CH_2)_4$ and 2×OH], 2.86 (2H, s, ArCH_2), 7.21 and 7.43 (2 and 2H, respectively, 2d, J=8.5 Hz, ArH); δ_C 23.15 (2C), 24.45 (2C), 26.5, 39.8 (2C), 40.35 (2C), 47.55, 73.95, 83.1, 125.55 (2C), 131.0 (2C), 137.6, 148.55; m/z 274 (M^+, <1%), 190 (15), 173 (15), 172 (100), 147 (27), 134 (19), 129 (12), 119 (10), 105 (14), 104 (81), 91 (20), 85 (48), 81 (11), 67 (34), 57 (17), 55 (52), 43 (29), 41 (44); HRMS: M^+-H_2O found 256.1797. $C_{18}H_{24}O$ requires 256.1827.

4.3. General procedure for the chemoselective monodehydration. Isolation of compounds 9

To a solution of the corresponding diol **8** (0.13 mmol) in toluene was added H_3PO_4 (85%, 0.29 mmol) at 25°C and it was stirred during 8 h. Then, the reaction was quenched by addition of a solution of saturated $NaHCO_3$ (10 mL). The resulting mixture was extracted with ether (2×15 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and evaporated (15 Torr) to give the pure compounds **9**. Yields are included in Table 2. Physical and spectroscopic data are as follows.

4.3.1. 2-[3-(Cyclohex-1-en-1-yl)phenyl]-1-phenyl-1-ethanol 9a. t_r 17.8; R_f 0.55 (hexane/ethyl acetate: 7/3); ν (film) 3538, 3391 (OH), 3058, 3029, 1601 (HC=C), 1046 cm^{-1} (CO); δ_H 1.60–1.80 (4H, m, $CH_2(CH_2)_2CH_2$), 2.10 (1H, broad s, OH), 2.20–2.40 (4H, m, $CH_2(CH_2)_2CH_2$), 2.90–3.05 (2H, m, ArCH_2), 4.85–4.90 (1H, m, ArC*H*O), 6.05–6.10 (1H, m, CH_2CH=C), 7.05–7.35 (9H, m, ArH); δ_C 22.1, 23.0, 25.8, 27.35, 46.25, 75.25, 123.3, 124.9, 125.85, 126.15, 127.5, 127.6, 128.3 (2C), 128.35 (2C), 136.4, 137.7, 142.95, 143.8; m/z 278 (M^+, 3%), 216 (16), 173 (14), 172 (100), 157 (18), 144 (11), 143 (15), 141 (11), 130 (11), 129 (26), 128 (16), 115 (14), 107 (66), 105 (15), 104 (19), 91 (18), 80 (13), 79 (69), 77 (42), 51 (13), 41 (11); HRMS: M^+ found 278.1664. $C_{20}H_{22}O$ requires 278.1671.

4.3.2. 2-[4-(Cyclohex-1-en-1-yl)phenyl]-1-phenyl-1-ethanol 9b. t_r 18.4; R_f 0.60 (hexane/ethyl acetate: 7/3); ν (film) 3534, 3442 (OH), 3029, 1605 (HC=C), 1049 cm^{-1} (CO); δ_H 1.50–1.80 [5H, m, $CH_2(CH_2)_2CH_2$ and OH], 2.15–2.20 and 2.30–2.40 [2 and 2H, respectively, 2m, $CH_2(CH_2)_2CH_2$], 2.90–3.05 (2H, m, ArCH_2), 4.85–4.90 (1H, m, ArC*H*O), 6.10–6.15 (1H, m, CH_2CH=C), 7.10–7.35 (9H, m, ArH); δ_C 22.15, 23.0, 25.85, 27.3, 45.7, 75.25, 124.45, 125.0 (2C), 125.85 (2C), 127.55, 128.35 (2C), 129.3 (2C), 136.1 (2C), 141.0, 143.8; m/z 278 (M^+, 2%), 173 (15), 172 (100), 171 (17), 157 (25), 144 (10), 129 (18), 128 (13), 115 (13), 107 (47), 105 (11), 104 (30), 91 (18), 79 (47), 77 (26); HRMS: M^+ found 278.1664. $C_{20}H_{22}O$ requires 278.1671.

4.3.3. 1-[4-(Cyclohex-1-en-1-yl)benzyl]-1-cyclopentanol 9c. t_r 16.5; R_f 0.52 (hexane/ethyl acetate: 7/3); ν (film) 3429 (OH), 3022, 1644 (HC=C), 1013 cm^{-1} (CO); δ_H 1.55–1.80 [13H, m, $(CH_2)_4$, $(CH_2)_2CH_2C$=C and OH], 2.20–2.25 and 2.30–2.40 (2 and 2H, respectively, 2m, CH_2C=CHCH_2), 2.86 (2H, s, ArCH_2), 6.10–6.15 (1H, m, CH_2CH=C), 7.18 and 7.33 (2 and 2H, respectively, 2d, J=8.3 Hz, ArH); δ_C 22.15, 23.05, 23.45, 25.85, 27.3, 29.7, 39.35 (2C), 46.65, 82.15, 124.45, 124.75 (2C), 129.95 (2C), 136.15, 136.4, 140.8; m/z 256 (M^+, 4%), 238 (11), 173 (14), 172 (100), 171 (12), 157 (45), 144 (18), 129 (37), 128 (20), 115 (19), 104 (53), 91 (22), 85 (57), 80 (13), 79 (12), 67 (46), 57 (16), 55 (20), 43 (21), 41 (52); HRMS: M^+ found 256.1824. $C_{18}H_{24}O$ requires 256.1827.

4.4. General procedure for the dehydration of alcohols 9. Isolation of compounds 10

To a solution of the corresponding alcohol **9** (0.06 mmol) in toluene (1 mL) was added H_3PO_4 (85%, 0.5 mmol) at 25°C, and it was refluxed during 2 h. After cooling down to room temperature, the reaction was quenched by addition of a saturated solution of $NaHCO_3$ (5 mL). The resulting mixture was extracted with ether (2×10 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and evaporated (15 Torr) to give the pure compound **10**. Yields are included in the text. Physical and spectroscopic data are as follows.

4.4.1. (*E*)-1-[3-(Cyclohex-1-en-1-yl)phenyl]-2-phenyl-1-ethene 10a. t_r 18.3; R_f 0.30 (hexane); ν (film) 3025, 1599 cm^{-1} (HC=C); δ_H 1.80–1.95 [4H, m, $CH_2(CH_2)_2CH_2$], 2.30–2.40 and 2.50–2.60 (2 and 2H, respectively, 2m, CH_2C=CHCH_2), 6.25–6.35 (1H, m, CH_2CH=C), 7.25–7.50 and 7.60–7.65 (9 and 2H, respectively, 2m, ArCH=CHPh); δ_C 22.15, 23.05, 25.85, 27.5, 123.3, 124.4, 124.65, 125.1, 126.45 (2C), 127.55, 128.5, 128.65 (2C), 128.95, 129.0, 136.55, 137.1, 137.4, 143.15; m/z 260 (M^+, 100%), 217 (14), 215 (14), 203 (11), 202 (16), 180 (13), 179 (17), 178 (19), 165 (12), 153 (13), 141 (31), 129 (10), 128 (26), 115 (23), 108 (21), 101 (14), 91 (34), 77 (15), 51 (11), 41 (14); HRMS: M^+ found 260.1550. $C_{20}H_{20}$ requires 260.1565.

4.4.2. (*E*)-1-[4-(Cyclohex-1-en-1-yl)phenyl]-2-phenyl-1-ethene 10b. t_r 18.6; R_f 0.40 (hexane); ν (film) 3022, 1598 cm^{-1} (HC=C); δ_H 1.80–1.95 [4H, m, $CH_2(CH_2)_2CH_2$], 2.30–2.40 and 2.50–2.60 (2 and 2H, respectively, 2m, CH_2C=CHCH_2), 6.30–6.35 (1H, m, CH_2CH=C), 7.35–7.65 (11H, m, ArCH=CHPh); δ_C 22.15, 23.0, 25.95, 27.2, 124.9, 125.1 (2C), 126.35 (2C), 126.4 (2C), 127.45, 127.95, 128.45, 128.65 (2C), 135.55, 136.05, 137.45, 141.85; m/z 260 (M^+, 100%), 232 (12), 217 (12), 215 (11), 202 (14), 179 (11), 178 (16), 153 (13), 141 (25), 130 (11), 128 (25), 115 (19), 114 (10), 107 (12), 101 (11), 91 (25), 77 (15), 51 (10), 41 (13); HRMS: M^+ found 260.1566. $C_{20}H_{20}$ requires 260.1565.

4.4.3. 1-(Cyclohex-1-en-1-yl)-4-(cyclopent-1-en-1-ylmethyl)benzene 10c. t_r 15.4; R_f 0.28 (hexane); ν (film) 3047, 3024, 1601, 1511 cm^{-1} (HC=C); δ_H 1.65–1.85 [6H, m, $CH_2(CH_2)_2CH_2$ and C=CCH_2CH$_2CH_2CH$=C] 2.20–2.40 [8H, m, $CH_2(CH_2)_2CH_2$ and C=C$CH_2CH_2CH_2$-CH=C], 3.36 (2H, s, ArCH_2), 5.30–5.35 (1H, m, HC=CAr), 6.10–6.15 (1H, m, *H*C=CCH_2Ar), 7.10 and 7.34 (2 and 2H, respectively, 2d, J=8.2 Hz, ArH); δ_C 22.2, 23.5, 25.85, 27.35, 29.7, 32.45, 34.8, 37.55, 124.7 (2C), 125.25, 127.75, 128.6 (2C), 130.9, 136.3, 140.2, 143.9; m/z 238 (M^+, 100%), 171 (10), 170 (11), 157 (61), 155 (13), 142 (18), 141 (23), 130 (11), 129 (62), 128 (27), 115 (28), 91 (45), 81 (25), 80 (20), 79 (35), 77 (17), 67 (22), 65 (11), 53 (19), 41 (47); HRMS: M^+ found 238.1706. $C_{18}H_{22}$ requires 238.1721.

4.5. Synthesis of tamoxifen 14

4.5.1. Preparation of 1-phenyl-1-chloropropane 12.[26] To a green suspension of lithium powder (0.1 g, 14 mmol) and naphthalene (20 mg, 0.16 mmol) in THF (10 mL) at −78°C was added chlorobenzene (**11**, 0.2 mL, 2 mmol). After 45 min propionaldehyde (0.18 mL, 2.5 mmol) was added and the resulting mixture was stirred for 30 min being then quenched by subsequent addition of H_2O (1 mL) and a solution of saturated NH_4Cl (20 mL). The resulting mixture was extracted with ethyl acetate (3×20 mL), the combined organic layers were dried over anhydrous $MgSO_4$ and evaporated (15 Torr) to give 1-phenyl-1-propanol.[22] This alcohol was dissolved in hexane (20 mL) and to the resulting solution was added HCl (35%, 1 mL) at 25°C. The resulting mixture was stirred over 1 h and the reaction was quenched by addition of a saturated solution of $NaHCO_3$ (10 mL). The resulting mixture was extracted with ether (2×10 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and evaporated (15 Torr) to give the a residue which was distilled bulb to bulb (130°C, 0.1 Torr) to yield the title compound. Overall yield is included in Scheme 2: t_r 7.2; R_f 0.4 (hexane/ethyl acetate: 9/1); ν (film) 3063, 3031, 1600, 1491 cm^{-1} (HC=C); δ_H 0.99 (3H, t, J=7.3 Hz, Me), 2.00–2.20 (2H, m, CH_2), 4.77 (1H, t, J=7.2 Hz, CHCl), 7.25–7.40 (5H, m, ArH); δ_C 11.65, 33.2, 65.45, 126.95 (2C), 128.15, 128.55 (2C), 141.75; *m/z* 156 (M^++2, 8%), 154 (M^+, 23), 127 (20), 125 (62), 119 (69), 117 (11), 115 (11), 91 (100), 89 (14), 51 (11).

4.5.2. Preparation of tamoxifen. To a turquoise-coloured suspension of lithium powder (0.1 g, 14 mmol) and DTBB (0.042 g, 0.16 mmol) in THF (3 mL) at −78°C was slowly added (ca. 1 h) a solution of the chlorinated material **12** (0.23 g, 1.5 mmol) and 4-[2-(dimethylamino)ethoxy]-benzophenone (**13**, 0.86 g, 3.2 mmol)[21b] in THF (2 mL). After stirring for one additional hour at the same temperature, the reaction mixture was quenched by subsequent addition of H_2O (1 mL) and a solution of saturated NH_4Cl (20 mL). The resulting mixture was extracted with ethyl acetate (3×20 mL), the combined organic layers were dried over anhydrous $MgSO_4$ and evaporated (15 Torr) to give a residue which contains a ca. 1:1 diastereomeric mixture of expected alcohols. The crude product was dissolved in ethanol (1 mL) and HCl was added (35%, 0.2 mL). The resulting mixture was refluxed during 20 min, being then quenched by addition of a saturated solution of NaOH (3 M, 15 mL). The resulting mixture was extracted with ether (2×15 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and evaporated (15 Torr) to give a residue, which was purified by column chromatography (silica gel, hexane/ethyl acetate) to give a ca. 1:1 mixture of (*Z*/*E*)-*N*,*N*-dimethyl-2-[4-(1,2-diphenyl-but-1-en-1-yl)phenoxy]-1-ethylamine [(*Z*/*E*)-**14**]:[21b] t_r 20.2, 20.5; R_f 0.14 (ethyl acetate/methanol: 9/1); ν (melted) 3074, 3059, 3028, 1604 (HC=C), 1097, 1030 cm^{-1} (CO); δ_H 0.85–0.95 (6H, m, 2×*Me*CH_2), 2.28 and 2.35 (6 and 6H, respectively, 2s, 2×NMe_2), 2.65 and 2.75 (2 and 2H, respectively, 2t, J=5.8, 5.8 Hz, 2×CH_2N), 3.92 and 4.09 (2 and 2H, respectively, 2t, J=5.8, 5.8 Hz, 2×CH_2O), 6.55, 6.75 and 6.85–7.35 (2, 2 and 24H, respectively, 2d and m, respectively, J=8.7, 8.7 Hz, respectively, ArH); δ_C 13.5, 28.95, 29.65, 45.8 (2C), 45.85 (2C), 58.25, 58.35, 65.6, 65.85, 113.4 (2C), 114.1 (2C), 125.6, 125.95, 126.45 (2C), 127.25 (2C), 127.7, 127.8 (2C), 128.0 (2C), 128.15, 129.45 (2C), 129.65 (2C), 130.5 (2C), 130.75 (2C), 131.8 (2C), 135.55, 136.05, 138.25, 138.4, 141.3, 141.9, 142.4, 143.3, 143.8, 156.7, 157.55; *m/z* (first isomer) 371 (M^+, 4%), 72 (24), 58 (100); *m/z* (second isomer) 371 (M^+, 3%), 72 (24), 58 (100).

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