Stereoselective Reductive Opening of 2,3-Benzofuran − A Two-Step Synthesis of 2*H*-Chromenes Including Deoxycordiachromene

Miguel Yus,*[a] Francisco Foubelo,*[a] and José V. Ferrández[a]

Dedicated to the memory of Professor Angel Alberola

Keywords: Lithium / Lithiation / Carbanions / Heterocycles / Homogeneous catalysis

The reaction of 2,3-benzofuran (**1**) with lithium and a catalytic amount of 4,4′-di-*tert*-butylbiphenyl (TDBB, 5 mol %) in THF at 0 °C leads to the stereoselective ring opening of the heterocycle, yielding the (*Z*)-organolithium derivatives (**2**) which, by reaction with different electrophiles [H_2O, D_2O, *t*BuCHO, PhCHO, $Ph(CH_2)_2CHO$, Me_2CO, *n*PrCOMe, PhCOMe, $(CH_2)_4CO$] at −78 °C and final hydrolysis with water, give the expected (*Z*)-products **3**. Cyclisation of the products obtained by reaction with carbonyl compounds under acidic conditions affords the expected substituted 2*H*-chromenes **4**, including deoxycordiachromene **4j**.

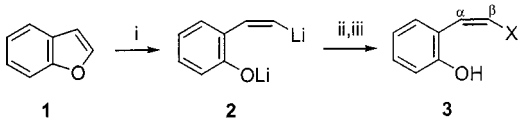
Introduction

Functionalised organometallic compounds[1] are of interest in synthetic organic chemistry due to their ability to transfer their functionality to electrophilic reagents, meaning that polyfunctionalised molecules are easily available in only one reaction step. In the case of polar functionalised organometallic intermediates, especially organolithium compounds,[2] their high reactivity makes these species more interesting because they can react with electrophiles under very mild reaction conditions, so giving rise to very selective processes. Apart from standard methods for the generation of functionalised organolithium compounds, including halogen−lithium exchange or metal−lithium transmetallation,[3,4] these intermediates can be generated by the reductive opening of different oxygen-, nitrogen- or sulfur-containing heterocycles.[5] Since most functionalised organolithium compounds are very unstable molecules, they have to be prepared at low temperatures in order to avoid decomposition processes, mainly elimination reactions or lithium−hydrogen exchange.[2] For that purpose, in the last few years[6] we have been using a methodology consisting of the use of an excess of lithium powder and a catalytic amount of an arene, naphthalene and 4,4′-di-*tert*-butylbiphenyl (DTBB) being the most commonly used,[7] as the lithiating agent.[8−10] This methodology has been used successfully in the ring opening of several heterocycles, mostly for benzylic carbon−heteroatom (oxygen, nitrogen or sulfur) cleavage, and always involving an sp^3-hybridised carbon atom.[11] In this communication we describe for the first time the reductive opening of 2,3-benzofuran using a DTBB-catalysed lithiation, which involves an sp^2-hybridised carbon−oxygen stereoselective cleavage.

[a] Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Alicante,
Apdo. 99, 03080 Alicante, Spain
Fax: (internat.) +34 965 903549
E-mail: yus@ua.es
URL: http//www.ua.es/dept.quimorg/

Results and Discussion

The reaction of 2,3-benzofuran (**1**) with an excess of lithium powder (1:10 molar ratio) and a catalytic amount of DTBB (1:0.1 molar ratio; 5 mol %) in THF at 0 °C led to a solution of the corresponding dilithiated intermediate **2** which, upon treatment with different electrophiles [H_2O, D_2O, *t*BuCHO, PhCHO, $Ph(CH_2)_2CHO$, Me_2CO, *n*PrCOMe, PhCOMe, $(CH_2)_4CO$] at −78 °C, afforded, after hydrolysis with water, the expected products **3** (Scheme 1 and Table 1). The ring opening takes place in a stereoselective manner, so the corresponding (*Z*)-products ($J_{H_\alpha H_\beta}$ = 9.7−12.2 Hz; see Table 1) were obtained as the only reaction products: no compounds **3** with an (*E*)-configuration were detected in the crude reaction products by ^1H NMR spectroscopy at 300 MHz.



Scheme 1. Preparation of compounds **3**: (i) Li, DTBB (5 mol %), THF, 0 °C; (ii) E = H_2O, D_2O, *t*BuCHO, PhCHO, $Ph(CH_2)_2CHO$, Me_2CO, *n*PrCOMe, PhCOMe, $(CH_2)_4CO$, −78 °C; (iii) H_2O, −78 to 0 °C

From a mechanistic point of view, we think that the reaction gives the *cis* radical-anion **I** after the first carbon−oxygen cleavage, and this has two possibilities of evolving depending on its stability. In our case, $k_1 >> k_2$, so the capture of a second electron to give the dianion **II** is faster than the isomerization to the radical anion **IV**

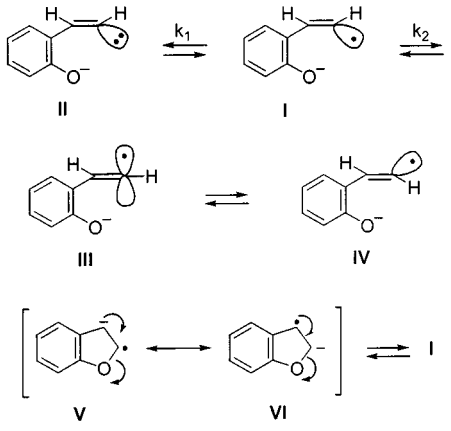
  1434−193X/01/0815−2809 $ 17.50+.50/0

Table 1. Preparation of compounds **3**

Entry	Electrophile E		X	Product **3**[a] Yield (%)[b]	R_f[c]	$J_{H_\alpha H_\beta}$ (Hz)
1	H_2O	**3a**	H	93	0.63	11.0[d]
2	D_2O	**3b**	D	94[e]	0.63	11.0
3	*t*BuCHO	**3c**	*t*BuCHOH	67	0.38	11.4
4	PhCHO	**3d**	PhCHOH	88	0.33	9.7
5	$Ph(CH_2)_2CHO$	**3e**	$Ph(CH_2)_2CHOH$	65	0.23	11.6
6	Me_2CO	**3f**	Me_2COH	45	0.25	12.2
7	*n*PrCOMe	**3g**	*n*PrC(OH)Me	58	0.38	12.2
8	PhCOMe	**3h**	PhC(OH)Me	56	0.45	12.2
9	$(CH_2)_4CO$	**3i**	$(CH_2)_4COH$	70	0.44	12.2

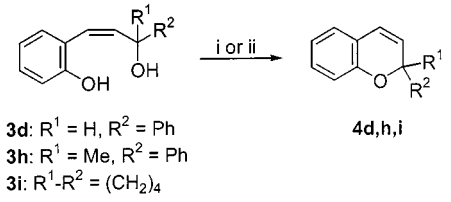
[a] All products **3** were ≥95% pure (300 MHz ^{1}H NMR and/or GC) and were characterised by spectroscopic means (IR, ^{1}H and ^{13}C NMR, and MS). – [b] Isolated yield after column chromatography (silica gel, hexane/ethyl acetate) based on the starting material **1**. – [c] Silica gel, hexane/ethyl acetate: 3:1. – [d] $J_{H_\alpha H_\beta}$ (*trans*) = 17.4 Hz. – [e] A ca. 75% deuterium incorporation was obtained from 75 MHz ^{13}C NMR spectroscopy.

(through the lineal species **III**), which would afford the corresponding *trans* dianion. Another possible pathway, which cannot be ruled out, would involve the radical anions **V/VI** resulting from the addition of one electron to the starting benzofuran **1** followed by a β-elimination to give the same radical anion **I**. Thus, in our opinion, either the ring opening or the corresponding reaction with the electrophile work with retention of the configuration (Scheme 2).[12]



Scheme 2

Compounds **3** are potential precursors of 2*H*-chromenes, this reaction being another proof of their (*Z*)-stereochemistry. Thus, as selected examples, compounds **3d**, **3h** and **3i** were cyclised either under acidic conditions (Method A: 85% H_3PO_4, toluene reflux)[13] or by means of zinc chloride (Method B: $ZnCl_2$, $ClCH_2CH_2Cl$, room temperature)[14] to give the expected substituted 2*H*-chromenes **4d**, **4h** and **4i** (Scheme 3 and Table 2).



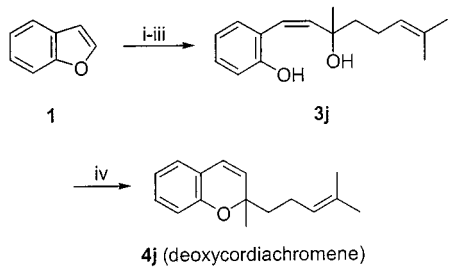
Scheme 3. Preparation of compounds **4**: (i) 85% H_3PO_4, PhMe reflux (Method A); (ii) $ZnCl_2$, $ClCH_2CH_2Cl$, 20 °C (Method B)

Table 2. Preparation of 2*H*-chromenes **4**

Entry	Starting Material	Method[a]	Product **4**[b] No.	R^1	R^2	Yield (%)[c]	R_f[d]
1	**3d**	A	**4d**	H	Ph	80	0.35
2	**3h**	A	**4h**	Me	Ph	85	0.39
3	**3i**	B	**4i**	$(CH_2)_4$		95	0.45

[a] Method A: 85% H_3PO_4, PhMe reflux; Method B: $ZnCl_2$, $ClCH_2CH_2Cl$, 20 °C. – [b] All products **4** were ≥97% pure (300 MHz ^{1}H NMR and/or GC) and were characterised by spectroscopic means (IR, ^{1}H and ^{13}C NMR, and MS). – [c] Isolated yield after column chromatography (silica gel, hexane) based on the starting material **3**. – [d] Silica gel, hexane/ethyl acetate: 20:1.

In the last part of this study we report the application of the methodology shown above to the two-step synthesis of deoxycordiachromene (**4j**).[15] Thus, once the ring opening of 2,3-benzofuran (**1**) took place as described above, the intermediate **2** was allowed to react with commercially available 6-methyl-5-hepten-2-one under the same reaction conditions as for compounds **3**, giving the expected product **3j** (45% isolated yield after column chromatography). Final cyclisation of this compound using either Method A or B gave deoxycordiachromene (**4j**) in about 60% isolated yield in both cases (Scheme 4).



Scheme 4. Preparation of deoxycordiachromene (**4j**): (i) Li, DTBB (5 mol %), THF, 0 °C; (ii) 6-methyl-5-hepten-2-one, −78 °C; (iii) H_2O, −78 to 20 °C; (iv) Method A or B

Conclusions

In conclusion, we have reported here a new methodology to give stereoselectively (*Z*)-organolithium compounds of type **2** bearing an *o*-phenoxide functionality. These are then able to react with different electrophiles giving final compounds **3** with the same (*Z*)-stereochemistry, both processes (lithiation and S_E reaction) working with retention of the configuration of the olefin. The easy cyclisation of some products **3** derived from carbonyl compounds gives the expected 2*H*-chromenes **4**, including deoxycordiachromene (**4j**).

Experimental Section

General: Melting points were obtained with a Reichert Thermovar apparatus. FT-IR spectra were obtained on a Nicolet Impact 400D spectrophotometer, NMR spectra were recorded on a Bruker AC-300 (300 MHz for ^{1}H and 75 MHz for ^{13}C) with $CDCl_3$ as solvent and TMS as internal standard; chemical shifts are given in ppm and coupling constants (*J*) are given in Hz. ^{13}C NMR assignments were made on the basis of DEPT experiments. Mass spectra (EI) were obtained at 70 eV on a Shimadzu QP-5000 spectrometer, fragment ions in *m*/*z* with relative intensities (%) in parentheses. High resolution mass spectra were obtained by the corresponding service at the University of Alicante using a Finnigan MAT 95 S apparatus. The purity of volatile products and the chromatographic analyses (GLC) were determined with a Hewlett−Packard HP-5890 instrument equipped 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_{column} = 60 °C (3 min.) and 60−270 °C (15 °C/min). Thin layer chromatography (TLC) was carried out on Schleicher & Schuell F1500/LS 254 plates coated with a 0.2 mm layer of silica gel; R_f values are given under these conditions. Column chromatography was performed using silica gel 60 of 35−70 mesh. All starting materials were commercially available (Acros, Aldrich, Fluka) of the best grade and were used without further purification. THF was dried over benzophenone ketyl under a nitrogen atmosphere and distilled before use.

DTBB-Catalysed Lithiation of 2,3-Benzofuran (1) and Reaction with Electrophiles. Isolation of Compounds 3. General Procedure: To a blue suspension of lithium powder (0.140 g, 20.0 mmol) and a catalytic amount of 4,4′-di-*tert*-butylbiphenyl (0.05 g, 0.19 mmol) in THF (4 mL) was added 2,3-benzofuran (**1**, 0.236 g, 0.22 mL, 2.0 mmol) under argon at 0 °C. After 45 min. stirring at the same temperature, the reaction mixture was cooled to −78 °C and the corresponding electrophile (2.4 mmol; 0.5 mL for H_2O or D_2O) was added to the resulting mixture. After 15 min. the reaction mixture was hydrolysed with water (5 mL), neutralised with 3 M hydrochloric acid and extracted with ethyl acetate (3 × 20 mL). The organic layer was dried over anhydrous sodium sulfate and the solvents evaporated (15 Torr) to give a residue, which was purified by column chromatography (silica gel, hexane/ethyl acetate (50:1 for **3a**, **b** and 10:1 for **3c**−**i**) to yield pure products **3**. Yields and R_f values for compounds **3a**−**3i** are included in Table 1. The yield for compound **3j** is given in the text. Other physical and spectroscopic data follow.

2-Vinylphenol (3a):[16] IR (film): $\tilde{\nu}$ = 3401, 3081, 3054, 3040, 1265 cm^{-1}. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.93 (br. s, 1 H, OH), 5.29 (dd, *J* = 11.0, 1.2 Hz, 1 H, ArCH=CH*H*), 5.67 (dd, *J* = 17.7, 1.2 Hz, 1 H, ArCH=C*H*H), 6.72 (dd, *J* = 7.9, 1.2 Hz, 1 H, ArH), 6.82−6.92 (m, 2 H, ArH, ArCH), 7.07 (td, *J* = 7.9, 1.2 Hz, 1 H, ArH), 7.31 (dd, *J* = 7.9, 1.4 Hz, 1 H, ArH). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 115.8, 115.9, 120.9, 124.8, 127.4, 128.9, 131.5, 152.8 (ArC, CH=CH_2). − GC-LRMS: *m*/*z* (%) = 120 (80) [M^+], 119 (26), 92 (17), 91 (100), 65 (24), 51 (23), 50 (15), 45 (17), 44 (11), 43 (14), 40 (15). − HRMS for C_8H_8O: calcd. 120.0575; found 120.0576 [M^+].

(*Z*)-2-(2-Deuteriovinyl)phenol (3b): IR (film): $\tilde{\nu}$ = 3401, 3081, 3054, 3040, 1265 cm^{-1}. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.02 (br. s, 1 H, OH), 5.27 (d, *J* = 11.0 Hz, 1 H, ArCH=C*H*), 6.71 (d, *J* = 7.9 Hz, 1 H, ArH), 6.81−6.88 (m, 2 H, ArH, ArCH), 7.03−7.09 (m, 1 H, ArH), 7.31 (d, *J* = 7.9 Hz, 1 H, ArH). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 115.6 (t, J_{CD} = 23.2 Hz, CHD), 120.9, 127.39, 127.4, 128.9, 131.4, 152.8 (ArC, *C*H=C). − GC-LRMS: *m*/*z* (%) = 121 (83) [M^+], 120 (29), 93 (21), 92 (100), 91 (27), 66 (22), 65 (15), 64 (12), 63 (16), 60 (17), 53 (12), 52 (15), 51 (25), 50 (19), 45 (16), 40 (28). − HRMS for C_8H_7DO: calcd. 121.0653; found 121.0640 [M^+].

(*Z*)-1-(2-Hydroxyphenyl)-4,4-dimethyl-1-penten-3-ol (3c): IR (film): $\tilde{\nu}$ = 3368, 3055, 1666, 1265 cm^{-1}. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.87 (s, 9 H, 3 CH_3), 3.94 (d, *J* = 9.9 Hz, 1 H, HOC*H*), 4.42 (br. s, 2 H, 2 OH), 5.91 (dd, *J* = 11.4, 9.9 Hz, 1 H, ArCH=C*H*), 6.54 (d, *J* = 11.4 Hz, 1 H, ArCH), 6.84−6.88, 7.07−7.15 (2 m, 4 H, ArH). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.4 [C(*C*H_3)], 34.5 [*C*(CH_3)], 75.7 (CHOH), 116.1, 120.2, 123.6, 128.1, 128.7, 130.0, 132.9, 152.8 (ArC, C=C). − GC-LRMS: *m*/*z* (%) = 188 (3) [M^+ − H_2O], 149 (32), 132 (11), 121 (21), 91 (13), 77 (19), 57 (26), 55 (27), 51 (11), 43 (18), 41 (30). − HRMS for $C_{13}H_{16}O$: calcd. 188.1201; found 188.1194 [M^+ − H_2O].

(*Z*)-3-(2-Hydroxyphenyl)-1-phenyl-2-propen-1-ol (3d): IR (film): $\tilde{\nu}$ = 3404, 3061, 3029, 1642, 1228 cm^{-1}. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.31 (br. s, 2 H, 2 OH), 5.78 (dd, *J* = 9.7, 3.4 Hz, 1 H, ArCH=C*H*), 5.91 (m, 1 H, HOC*H*), 6.52 (dd, *J* = 9.7, 1.8 Hz, 1 H, ArCH), 6.77−6.88, 6.98−7.13, 7.30−7.37 (3 m, 9 H, ArH). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 77.1 (CHOH), 116.0, 121.1, 121.3, 124.0, 124.8, 126.6, 127.0, 128.3, 128.6, 129.4, 140.8, 153.1 (ArC, C=C). − GC-LRMS: *m*/*z* (%) = 208 (68) [M^+ − H_2O], 207 (100), 178 (21), 131 (71), 89 (21), 77 (23), 76 (21), 63 (15), 51 (31), 50 (15). − HRMS for $C_{15}H_{12}O$: calcd. 208.0888; found 208.0893 [M^+ − H_2O].

(*Z*)-1-(2-Hydroxyphenyl)-5-phenyl-1-penten-3-ol (3e): IR (film): $\tilde{\nu}$ = 3330, 3084, 3061, 3026, 1265 cm^{-1}. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.79−1.98 (m, 2 H, HOCCH_2), 2.56−2.69 (m, 2 H, PhCH_2), 4.34 (dt, *J* = 9.6, 6.4 Hz, 1 H, HOC*H*), 4.82 (br. s, 2 H, 2 OH), 5.81 (dd, *J* = 11.6, 9.6 Hz, 1 H, ArCH=C*H*), 6.51 (d, *J* = 11.6 Hz, 1 H, ArCH), 6.82−7.00, 7.02−7.22 (2 m, 4 H, ArH). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 31.5, 38.7 (CH_2), 68.1 (COH), 116.1, 120.4, 123.4, 125.8, 126.9, 128.3, 128.9, 130.1, 135.8, 141.5, 152.8 (ArC, C=C). − GC-LRMS: *m*/*z* (%) = 236 (54) [M^+ − H_2O], 145 (34), 144 (14), 142 (11), 132 (17), 131 (100), 130 (17), 129 (68), 128 (30), 127 (17), 117 (20), 115 (38), 108 (14), 107 (20), 91 (52), 89 (14), 78 (10), 77 (33), 65 (22), 63 (19), 51 (25), 44 (11). − HRMS for $C_{17}H_{16}O$: calcd. 236.1201; found 236.1199 [M^+ − H_2O].

(*Z*)-4-(2-Hydroxyphenyl)-2-methyl-3-buten-2-ol (3f): IR (film): $\tilde{\nu}$ = 3341, 3054, 1265 cm^{-1}. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.25 (s, 6 H, 2 CH_3), 1.58 (br. s, 2 H, 2 OH), 5.84 (d, *J* = 12.2 Hz, 1 H, ArCH=C*H*), 6.24 (d, *J* = 12.2 Hz, 1 H, ArCH), 6.78−6.99, 7.01−7.09 (2 m, 4 H, ArH). − ^{13}C NMR (75 MHz, $CDCl_3$): δ =

30.4 (2 CH_3), 71.7 (COH), 120.3, 140.8, 116.8, 123.9, 124.9, 128.8, 129.8, 152.5 (ArC, C=C). − GC-LRMS: *m*/*z* (%) = 178 (0.5) [M^+], 145 (93), 115 (13), 91 (13), 51 (15), 43 (100), 41 (10). − HRMS for $C_{11}H_{14}O_2$: calcd. 178.0994; found 178.0988 [M^+].

(*Z*)-1-(2-Hydroxyphenyl)-3-methyl-1-hexen-3-ol (3g): IR (film): $\tilde{\nu}$ = 3372, 3054, 1265 cm^{-1}. − ^1H NMR (300 MHz, $CDCl_3$): δ = 0.73 (t, *J* = 7.3 Hz, 3 H, CH_2CH_3), 1.14 (s, 3 H, CCH_3), 1.16−1.25 (m, 2 H, CH_2CH_3), 1.35−1.42 (m, 2 H, CCH_2), 2.98 (br. s, 2 H, 2 OH), 5.79 (d, *J* = 12.2 Hz, 1 H, ArCH=C*H*), 6.28 (d, *J* = 12.2 Hz, 1 H, ArCH), 6.66−6.85, 6.99−7.35 (2 m, 4 H, ArH). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.4 (CH_2CH_3), 17.4 (CH_2CH_3), 28.4 (CCH_3), 45.5 (CCH_2), 74.3 (COH), 116.9, 120.4, 123.9, 128.4, 128.9, 129.6, 140.6, 152.5 (ArC, C=C). − GC-LRMS: *m*/*z* (%) = 188 (5) [$M^+ - H_2O$], 173 (10), 146 (10), 145 (100), 43 (12), 40 (12). − HRMS for $C_{13}H_{16}O$: calcd. 188.1201; found 188.1199 [$M^+ - H_2O$];.

(*Z*)-4-(2-Hydroxyphenyl)-2-phenyl-3-buten-2-ol (3h): IR (film): $\tilde{\nu}$ = 3352, 3085, 3059, 3027 cm^{-1}. − ^1H NMR (300 MHz, $CDCl_3$): δ = 1.61 (s, 3 H, CH_3), 4.33 (br. s, 2 H, 2 OH), 6.23 (d, *J* = 12.2 Hz, 1 H, CH=C*H*), 6.43 (d, *J* = 12.2 Hz, 1 H, C*H*=CH), 6.71−6.86, 7.02−7.40 (2 m, 9 H, ArH). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 31.6 (CH_3), 75.0 (COH), 116.4, 120.3, 124.4, 124.6, 124.8, 126.8, 128.1, 128.8, 129.5, 140.6, 147.1, 152.3 (ArC, C=C). − GC-LRMS: *m*/*z* (%) = 222 (8) [$M^+ - H_2O$], 208 (17), 207 (100), 178 (11), 145 (20). − HRMS for $C_{16}H_{14}O$: calcd. 222.1045; found 222.1036 [$M^+ - H_2O$].

(*Z*)-2-[2-(1-Hydroxycyclopentyl)vinyl]phenol (3i): IR (film): $\tilde{\nu}$ = 3318, 3070, 3005, 1231 cm^{-1}. − ^1H NMR (300 MHz, $CDCl_3$): δ = 1.62−1.77 (m, 8 H, CH_2), 3.05 (br. s, 2 H, 2 OH), 6.04 (d, *J* = 12.2 Hz, 1 H, CH=C*H*), 6.37 (d, *J* = 12.2 Hz, 1 H, C*H*=CH), 6.85−6.90, 7.06−7.25 (2 m, 4 H, ArH). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.3 (2 CH_2), 40.7 [HOC(CH_2)], 82.0 (COH), 117.0, 120.3, 124.9, 125.1, 128.8, 129.8, 139.0, 152.6 (ArC, C=C). − GC-LRMS: *m*/*z* (%) = 186 (65) [$M^+ - H_2O$], 185 (19), 158 (36), 157 (100), 128 (13), 115 (19), 107 (39), 91 (20), 82 (12), 79 (29), 77 (21), 65 (12), 63(11), 51 (18), 41 (14). − HRMS for $C_{13}H_{16}O_2$: calcd. 204.1150; found 204.1145 [M^+].

(*Z*)-1-(2-Hydroxyphenyl)-3,7-dimethyl-1,6-octadien-3-ol (3j): R_f = 0.43 (hexane/ethyl acetate, 3:1). − IR (film): $\tilde{\nu}$ = 3330, 3061, 1643 cm^{-1}. − ^1H NMR (300 MHz, $CDCl_3$): δ = 1.30 (s, 3 H, CH_3), 1.50−1.64 (m, 2 H, CH_2), 1.59 (s, 3 H, CH_3), 1.67 (s, 3 H, CH_3), 2.01−2.09 (m, 2 H, CH_2), 4.62 (br. s, 2 H, 2 OH), 5.06 (t, *J* = 6.7 Hz, 1 H, CH=C), 5.85 (d, *J* = 12.5 Hz, 1 H, CH=C*H*), 6.37 (d, *J* = 12.5 Hz, 1 H, C*H*=CH), 6.85−6.90 (m, 2 H, ArH), 7.07−7.16 (m, 2 H, ArH). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.6 (CH_3), 22.9 (CH_2), 25.6 (CH_3), 28.1 (CH_3), 42.9 (CH_2), 74.2 (CO), 116.9, 120.3, 123.9, 124.3, 125.0, 128.8, 129.7, 132.0, 139.8, 152.5 (ArC, C=C). − GC-LRMS: *m*/*z* (%) = 228 (3) [$M^+ - H_2O$], 146 (11), 145 (100), 41 (26). − HRMS for $C_{16}H_{20}O$: calcd. 228.1514; found 228.1526 [$M^+ - H_2O$].

Acidic Cyclisation of Diols 3. Preparation of 2*H*-Chromenes 4. Method A: 85% Phosphoric acid (0.3 mL) was added to a solution of the corresponding diol **3d**, **h**, **j** (0.5 mmol) in toluene (4 mL). The reaction mixture was heated at 110 °C for 4 h, then the toluene was evaporated (15 Torr) and the resulting residue was hydrolysed with water (5 mL) and extracted with ethyl acetate (3 × 15 mL). The organic layer was dried over anhydrous sodium sulfate and the solvents evaporated (15 Torr) to give a residue, which was purified by column chromatography (silica gel, hexane) to yield pure products **4**. The yields and R_f values for compounds **4d** and **4h** are included in Table 2. The yield for compound **4j** is given in the text. Other physical and spectroscopic data follow.

2-Phenyl-2*H*-chromene (4d): IR (film): $\tilde{\nu}$ = 1642, 1245 cm^{-1}. − ^1H NMR (300 MHz, $CDCl_3$): δ = 5.80 (dd, *J* = 9.8, 3.4 Hz, 1 H, ArCH=C*H*), 6.53 (dd, *J* = 9.8, 1.2 Hz, 1 H, ArCH), 6.77−6.88, 7.00−7.18, 7.30−7.46 (3 m, 10 H, ArH, CHO). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 77.1 (CO), 116.0, 121.2, 121.3, 124.0, 124.8, 125.6, 126.6, 127.0, 128.3, 128.6, 128.8, 129.4, 140.8 (ArC, HC=CH). − GC-LRMS: *m*/*z* (%) = 208 (65) [M^+], 207 (100), 178 (19), 131 (65), 89 (19), 77 (17), 76 (17), 63 (10), 51 (17). − HRMS for $C_{15}H_{12}O$: calcd. 208.0888; found 208.0891 [M^+].

2-Methyl-2-phenyl-2*H*-chromene (4h): IR (film): $\tilde{\nu}$ = 3058, 3035, 3027, 1642, 1245 cm^{-1}. − ^1H NMR (300 MHz, $CDCl_3$): δ = 1.76 (s, 3 H, CH_3), 5.92 (d, *J* = 9.8 Hz, 1 H, CH), 6.44 (d, *J* = 9.8 Hz, 1 H, CH), 6.73−7.38 (m, 9 H, ArH). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 29.3 (CH_3), 78.7 (CO), 116.3, 121.0, 122.8, 125.1, 126.5, 127.2, 128.2, 129.3, 129.6, 145.9 (ArC, HC=CH). − GC-LRMS: *m*/*z* (%) = 222 (8) [M^+], 208 (16), 207 (100), 178 (12), 145 (21), 103 (11), 51 (11). − HRMS for $C_{16}H_{14}O$: calcd. 222.1045; found 222.1053 [M^+].

Deoxycordiachromene (4j): R_f = 0.53 (hexane/ethyl acetate, 20:1). − IR (film): $\tilde{\nu}$ = 3405, 3055, 3040, 3025, 1640, 1260 cm^{-1}. − ^1H NMR (300 MHz, $CDCl_3$): δ = 1.39 (s, 3 H, CH_3), 1.57 (s, 3 H, CH_3), 1.61−1.75 (m, 2 H, CH_2), 1.66 (s, 3 H, CH_3), 2.07−2.17 (m, 2 H, CH_2), 5.10 (t, *J* = 7.3 Hz, 1 H, C=CH), 5.55, 6.34 (2 d, *J* = 10.1 Hz, 2 H, CH=CH), 6.75 (d, *J* = 7.9 Hz, 1 H, ArH), 6.78−6.83 (m, 1 H, ArH), 6.95 (d, *J* = 6.1 Hz, 1 H, ArH), 7.06−7.11 (m, 1 H, ArH). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.6 (CH_3), 22.7 (CH_2), 25.6 (CH_3), 26.5 (CH_3), 41.3 (CH_2), 78.4 (CO), 116.1, 120.4, 121.1, 122.8, 124.1, 126.3, 129.0, 129.6, 131.7, 153.2 (ArC, C=C). − GC-LRMS: *m*/*z* (%) = 228 (6) [M^+], 146 (13), 145 (100), 41 (24). − HRMS for $C_{16}H_{20}O$: calcd. 228.1514; found 228.1514 [M^+].

Acidic Cyclisation of Diols 3. Preparation of 2*H*-Chromenes 4. Method B: $ZnCl_2$ (0.065 g, 0.48 mmol) was added to a solution of the corresponding diol **3i**, **j** (0.5 mmol) in 1,2-dichloroethane (4 mL). The reaction mixture was stirred at 20 °C for 3 h, and was then hydrolysed with 1 M solution of sodium bicarbonate (10 mL) and extracted with ethyl acetate (3 × 15 mL). The organic layer was dried over anhydrous sodium sulfate and the solvents evaporated (15 Torr) to give a residue, which was purified by column chromatography (silica gel, hexane) to yield pure products **4**. The yield and R_f value for compound **4i** are included in Table 2. The yield for compound **4j** is given in the text and other physical and spectroscopic data were given previously. Spectroscopic data for compound **4i** follow.

2,2-Tetramethylene-2*H*-chromene (4i): IR (film): $\tilde{\nu}$ = 3060, 3036, 1640, 1242 cm^{-1}. − ^1H NMR (300 MHz, $CDCl_3$): δ = 1.26−2.39 (m, 8 H, 4 CH_2), 5.64 (d, *J* = 9.8 Hz, 1 H, CH=C*H*), 6.34 (d, *J* = 9.8 Hz, 1 H, C*H*=CH), 6.73−7.37 (m, 4 H, ArH). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.6, 39.4 (CH_2), 87.0 (CO), 116.3, 120.7, 123.1, 126.2, 128.5, 128.8, 129.8, 152.9 (ArC, HC=CH). − GC-LRMS: *m*/*z* (%) = 186 (18) [M^+], 158 (15), 157 (100), 115 (11). − HRMS for $C_{13}H_{14}O$: calcd. 186.1045; found 186.1051 [M^+].

Acknowledgments

This work was financially supported by the DGES of the Spanish Ministerio de Educación y Cultura (MEC) (Project no. PB97-0133).

[1] A. Boudier, L. O. Bromm, M. Lotz, P. Knochel, *Angew. Chem.* **2000**, *112*, 4584−4606; Angew. *Chem. Int. Ed.* **2000**, *39*, 4414-4435.
[2] [2a] C. Nájera, M. Yus, *Trends Org. Chem.* **1991**, *2*, 155-181. − [2b] C. Nájera, M. Yus, *Recent Res. Devel. Org. Chem.* **1997**, *1*, 67-96.
[3] B. Wakefield, *Organolithium Methods*, Academic Press, London, **1988**.
[4] For a review on the generation of organolithium reagents from non-halogenated materials, see: D. Guijarro, M. Yus, *Recent Res. Devel. Org. Chem.* **1998**, *2*, 713-744.
[5] [5a] For a review, see: M. Yus, F. Foubelo, *Rev. Heteroatom Chem.* **1997**, *17*, 73-107. See also: [5b] T. Cohen, F. Chen, T. Kulinski, S. Florio, V. Capriati, *Tetrahedron Lett.* **1995**, *36*, 4459-4462. − [5c] S. Florio, V. Capriati, A. Gallo, T. Cohen, *Tetrahedron Lett.* **1995**, *36*, 4463-4466.
[6] First account: M. Yus, D. J. Ramón, *J. Chem. Soc., Chem. Commun.* **1991**, 398-400.
[7] N. L. Holy, *Chem. Rev.* **1974**, *74*, 243-277.
[8] Reviews: [8a] M. Yus, *Chem. Soc. Rev.* **1996**, 155-161. − [8b] D. J. Ramón, M. Yus, *Eur. J. Org. Chem.* **2000**, 225-237.
[9] For a polymer-supported arene-catalysed version of this lithiation, see: [9a] C. Gómez, S. Ruiz, M. Yus, *Tetrahedron Lett.* **1998**, *39*, 1397-1400. − [9b] C. Gómez, S. Ruiz, M. Yus, *Tetrahedron* **1999**, *55*, 7017-7026.
[10] Mechanistic study: M. Yus, R. P. Herrera, A. Guijarro, *Tetrahedron Lett.* **2001**, *42*, 3455-3458.
[11] Last paper on this topic from our laboratory: M. Yus, F. Foubelo, *Tetrahedron Lett.* **2001**, *42*, 2469-2472.
[12] This behaviour has also been observed in other types of sp^2-hybridised functionalised organolithium compounds prepared by halogen−lithium exchange[12a,b] or tin−lithium transmetallation.[12c] See, for instance: [12a] J. Barluenga, J. R. Fernández, M. Yus, *J. Chem. Soc., Perkin Trans. 1* **1985**, 447-451. − [12b] V. Godebout, S. Lecomte, F. Levasseur, L. Duhamel, *Tetrahedron Lett.* **1996**, *37*, 7255-7258. − [12c] R. H. Wollenberg, K. F. Albizati, R. Peries, *J. Am. Chem. Soc.* **1977**, *99*, 7365-7367.
[13] See, for instance: J. Almena, F. Foubelo, M. Yus, *Tetrahedron* **1995**, *51*, 3351-3364.
[14] A. Arcadi, S. Cacchi, G. Fabrizi, F. Marinelli, P. Pace, *Eur. J. Org. Chem.* **2000**, 4099-4109.
[15] For a recent account on the synthesis of cordiachromene, see: S. Bouzbouz, J.-Y. Goujon, J. Deplanne, B. Kirschleger, *Eur. J. Org. Chem.* **2000**, 3223-3228.
[16] K. Kondo, M. Sodeoka, M. Shibasaki, *Tetrahedron: Asymmetry* **1995**, *6*, 2453-2464.

Received April 10, 2001
[O01173]