Reductive Ring Opening of Oxygen-Containing Benzo-Fused Heterocycles by an Arene-Catalysed Lithiation

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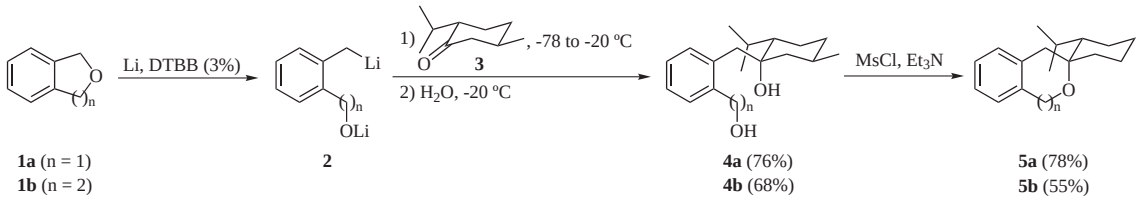
Received 29 December 2003

Abstract: The reductive ring opening of phthalan and isochroman in a 8 mmol scale process, using a small excess of lithium (1.35 equiv) and a substoichiometric amount of DTBB (3 mol%), leads to functionalised organolithium compounds, which after reaction with (–)-menthone as electrophile followed by hydrolysis with water, gives the corresponding diols in good yields with high stereoselectivity. Dehydration of these diols leads to the corresponding oxygen-containing heterocycles, which are homologous of the starting heterocycles.

Key words: functionalised organolithium compounds, stereoselective addition, reductive opening, lithiation



1a (n = 1) **2** **4a** (76%) **5a** (78%)
1b (n = 2) **4b** (68%) **5b** (55%)

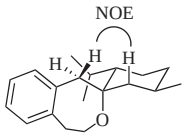
Scheme 1

Functionalised organolithium compounds[1] can be prepared following the same methodologies as for simple organolithium compounds and are of interest in synthetic organic chemistry because polyfunctionalised molecules are obtained in only one step by reaction with electrophilic reagents.[2] In the case of these functionalised intermediates, one of the most elegant and direct strategies consists in the reductive opening of appropriate oxygen-, nitrogen- and sulfur-containing heterocycles.[3] However, the following requirements should be accomplished in order to achieve the reductive opening of a heterocycle: (a) small heterocycles (three- and four-membered rings) due to release of strain energy[3] and (b) heterocycles with activated bonds that can be reductively broken by means of the lithiating reagent, as in the case of compounds bearing allylic[4] and benzylic[5] carbon–heteroatom bonds as well as cyclic aryl ethers[6] and thioethers.[7] Concerning the lithiation process, one potent lithiating mixture, which has shown to be very effective even at low temperatures, consists in the use of an excess of lithium in the presence of a catalytic amount of an arene,[8] naphthalene and 4,4′-di-*tert*-butylbiphenyl (DTBB), and these are most commonly used.[9] More recently, polymer supported naphthalene, biphenyl[10] and also polyphenylene[11] have been used as electron-transfer reagents in these processes.[12]

Benzylic carbon–oxygen bonds are susceptible of suffering reductive cleavage by means of lithium metal to generate benzylic organolithium compounds. Phthalan (**1a**) and isochroman (**1b**) are a special kind of cyclic benzyl ethers. These heterocycles are opened reductively with lithium and a catalytic amount of DTBB at 0 and 20 °C, respectively, to afford dianions **2** which have shown a wide use in organic synthesis.[13,14] The reaction of intermediates **2** with (–)-menthone (**3**) as electrophile at –78 °C gave the diols **4**, after hydrolysis with water at the same temperature (Scheme 1). Regarding the stereochemistry of these reaction products, the almost exclusive diastereomers are those resulting from the attack of dianions **2** to the less hindered face of the carbonyl group. The diastereomeric ratios were determined by the study of the ^{1}H NMR spectra of the crude reaction mixtures, being around 30:1 for phthalan derivative **4a** and 22:1 in the case of isochroman derivative **4b**. Finally, dehydration of diols **4** led to the homologous spiro heterocyclic compounds **5**. All attempts to perform the dehydration under acidic conditions gave always a mixture of diastereomers due to epimerisation of the new stereogenic center. However, total retention of the configuration was obtained when the diols **4** were treated with an excess of methanesulfonyl chloride in the presence of triethylamine in dichloromethane. The configuration of the new stereogenic center for the major isomers was confirmed by a NOESY experiment in compound **5b**. NOE is observed between one of the diastereotopic protons at benzylic position [2.35 ppm (d, J = 14.2 Hz)] and the axial proton next to

SYNTHESIS 2004, No. 7, pp 1115–1118
Advanced online publication: 12.02.2004
DOI: 10.1055/s-2004-815971; Art ID: Z19003SS

the new stereogenic center which appear at 0.44 ppm as a dd (J = 12.2, 12.35 Hz) (Figure 1).



5b

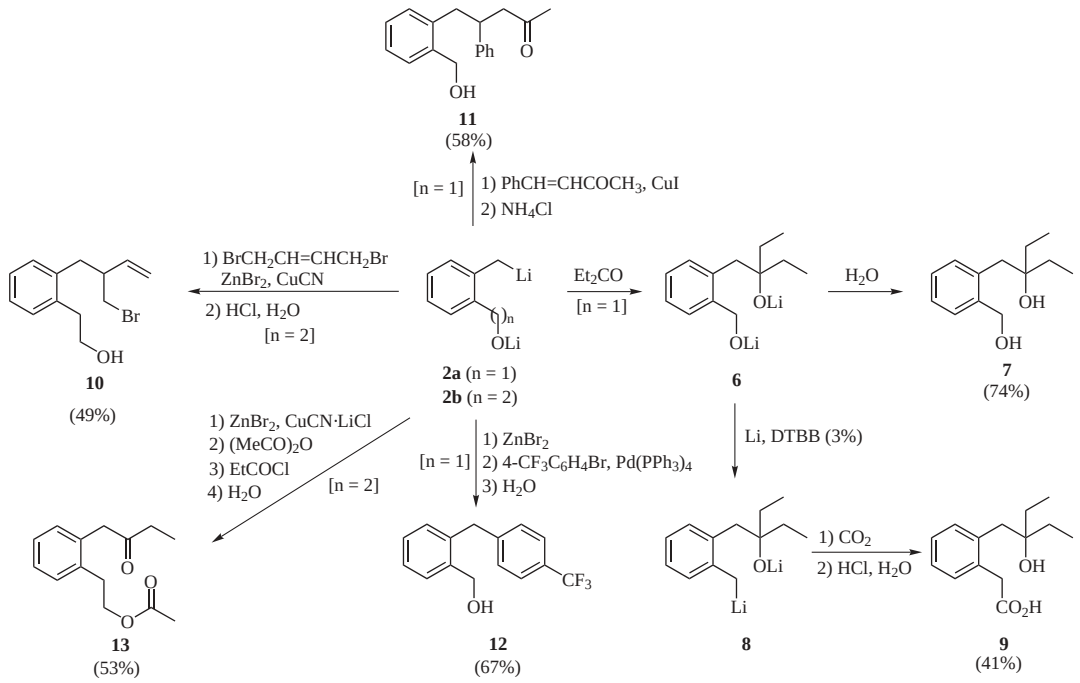
Figure 1 NOE enhancement for **5b**

At this point it is worthy to note the advantage of working on a larger scale (8 mmol) compared to the process performed at 1 mmol scale. Due to the low density of lithium powder in the reaction medium, in the small scale process an important amount of the metal is lost on the walls of the flask, so a large excess (ca. 15:1, lithium:substrate molar ratio) is needed. On the contrary for the 8 mmol scale, only a 2.5:1 molar ratio was necessary to carry out the lithiation step.

The lithiation of **1a** can be directed to the introduction of two different electrophiles at both benzylic positions in a sequential manner. Thus, if after addition of pentan-3-one as the first electrophile, the resulting alcoholate **6** is stirred in the presence of the excess of lithiating mixture at room temperature for four additional hours, a new organolithium intermediate **8** is formed, which by reaction with carbon dioxide as a second electrophile, yields, after acidic hydrolysis, the hydroxy acid **9**.[13] On the other hand, the hydrolysis of the dialcoholate **6** leads to the diol **7** (Scheme 2).[13] The use of keto derivatives of some protected monosaccharides (glucose, fructose),[15] as well as steroids (estrone and cholestanone)[16] gives the expected selectively functionalised natural products.

As commented above, the functionalised organolithium compounds **2** have been used extensively in organic synthesis. Thus, the reaction of the organolithium intermediate **2b** with equimolecular amounts of zinc bromide and copper cyanide, followed by treatment with 1,4-dibromobut-2-ene leads, after hydrolysis, almost exclusively to the corresponding alcohol **10** resulting from a S_N2' displacement, the process being highly regioselective (Scheme 2).[17] The reaction of **2a** with an electrophilic olefin such as benzylidenacetone in the presence of copper(I) salts and HMPA in THF at –78 °C leads, after hydrolysis with a saturated solution of ammonium chloride, to the hydroxy ketone **11**, resulting from a conjugate addition (Scheme 2).[18,19] The palladium-catalysed Negishi cross-coupling reaction can also be applied to the in situ generated functionalised organozinc reagent, which are easily prepared from functionalised organolithium **2a** by a lithium-zinc transmetallation process with zinc bromide. This reaction is not possible without the help of both the zinc and palladium components, the process working well for arylic and vinylic bromides, as well as with iodides. In the case of *p*-(trifluoromethyl)phenyl bromide, compound **12** is obtained in good yield (Scheme 2).[20,21] Finally, chemoselective acylation can be easily achieved using a tandem reaction of intermediate **2b** with acetic anhydride and propanoyl chloride, after generating the corresponding zinc-copper species, to give compound **13** (Scheme 2).[22]

All reactions were carried out under argon in oven-dried glassware. All reagents were commercially available and were used as received. THF was distilled from sodium benzophenone ketyl. IR spectra were measured (neat) with a Nicolet Impact 400 D-FT Spec-



Scheme 2

trometer. NMR spectra were recorded with a Bruker AC-300 using $CDCl_3$ as the solvent. ^{13}C NMR DEPT was used to assign the C atoms. 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 (GC) 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 N_2 (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.

(1*R*,2*S*,5*R*)-1-(2-Hydroxymethylbenzyl)-2-isopropyl-5-methylcyclohexanol (4a)

To a blue suspension of lithium powder (150 mg, 21.4 mmol) and a catalytic amount of DTBB (130 mg, 0.5 mmol; 3 mol%) in anhyd THF (25 mL) under argon was added dropwise phthalan (**1a**; 960 mg, 0.88 mL, 8.0 mmol) at 0 °C, and the resulting mixture was stirred for 6 h (monitored by GC) at the same temperature. Then, the temperature was cooled down to –78 °C and (–)-menthone (**3**; 1.23 g, 1.56 mL, 8.0 mmol) was added dropwise. After that, the reaction mixture was allowed to warm to –20 °C for around 3 h, hydrolysed with H_2O (10 mL), and extracted with EtOAc (3 × 40 mL). The combined organic layers were dried (Na_2SO_4) and evaporated (15 Torr). The residue was purified by column chromatography (hexane–EtOAc, 20:1, 85 g Merck silica gel 60, 0.063–0.200 mm) to give **4a** as a colourless oil (1.67 g, 76%); $[\alpha]_D^{20}$ –19.5 (*c* = 1.0, CH_2Cl_2); R_f 0.13 (hexane–EtOAc, 5:1).

IR (film): 3350, 2951, 2863, 1701, 1640, 1448 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.81 (d, *J* = 6.2 Hz, 3 H), 0.87–1.04 (m, 2 H), 0.98 (d, *J* = 7.02 Hz, 6 H), 1.21–1.51 (m, 4 H), 1.59–1.67 (m, 1 H), 1.73–1.78 (m, 1 H), 2.35–2.45 (m, 1 H), 2.43 (d, *J* = 13.9 Hz, 1 H), 2.71 (br s, 2 H), 3.61 (d, *J* = 13.9 Hz, 1 H), 4.42 (d, *J* = 11.9 Hz, 1 H), 4.81 (d, *J* = 11.9 Hz, 1 H), 7.14–7.27 (m, 3 H), 7.33–7.38 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.0 (CH_3), 21.0 (CH_2), 22.3 (CH_3), 23.8 (CH_3), 25.9 (CH), 28.0 (CH), 34.8 (CH_2), 42.4 (CH_2), 46.8 (CH_2), 51.1 (CH), 63.3 (CH_2), 74.7 (C), 126.9 (CH), 127.3 (CH), 130.6 (CH), 133.0 (CH), 136.0 (C), 140.5 (C).

MS (EI, 70 eV): *m*/*z* (%) = 258 [$M^+ – H_2O$, 3], 104 (100), 95 (11), 81 (29), 69 (21).

HRMS (EI): *m*/*z* calcd for $C_{18}H_{26}O$ (M – H_2O): 258.1984; found: 258.1971.

(1*R*,2*S*,5*R*)-1-[2-(2-Hydroxyethyl)benzyl]-2-isopropyl-5-methylcyclohexanol (4b)

To a blue suspension of lithium powder (150 mg, 21.4 mmol) and a catalytic amount of DTBB (130 mg, 0.5 mmol; 3 mol%) in anhyd THF (25 mL) under argon was added dropwise isochroman (**1b**; 1.07 g, 1.00 mL, 8.0 mmol) at 20 °C, and the resulting mixture was stirred for 4 h (monitored by GC) at the same temperature. Then, the temperature was cooled down to –78 °C and (–)-menthone (**3**; 1.23 g, 1.56 mL, 8.0 mmol) was added dropwise. After that, the reaction mixture was allowed to warm to –20 °C for around 3 h, hydrolysed with H_2O (20 mL), and extracted with EtOAc (3 × 40 mL). The combined organic layers were dried (Na_2SO_4) and evaporated (15 Torr). The residue was purified by column chromatography (hexane–EtOAc, 20:1, 85 g Merck silica gel 60, 0.063–0.200 mm) to yield **4b** as a colourless oil (1.57 g, 68%); $[\alpha]_D^{20}$ –29.2 (*c* = 1.1, CH_2Cl_2); R_f 0.37 (hexane–EtOAc, 2:1).

IR (film): 3375, 3060, 2946, 1722, 1596, 1454 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.76 (d, *J* = 6.55 Hz, 3 H), 0.82–0.95 (m, 1 H), 0.98 (d, *J* = 7.0 Hz, 3 H), 1.00 (d, *J* = 7.1, 3 H), 1.18–1.58 (m, 6 H), 1.71–1.75 (m, 1 H), 2.07 (br s, 2 H), 2.32–2.41 (m, 1 H), 2.50 (d, *J* = 13.7 Hz, 1 H), 2.93–3.10 (m, 2 H), 3.40 (d, *J* = 13.7 Hz, 1 H), 3.81–3.87 (m, 2 H), 7.11–7.25 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.0 (CH_3), 20.8 (CH_2), 22.3 (CH_3), 23.7 (CH_3), 26.0 (CH), 27.6 (CH), 35.0 (CH_2), 35.6 (CH_2), 42.3 (CH_2), 46.8 (CH_2), 50.7 (CH), 63.3 (CH_2), 75.2 (C), 125.8 (CH), 126.5 (CH), 129.6 (CH), 132.3 (CH), 136.6 (C), 138.2 (C).

MS (EI, 70 eV): *m*/*z* (%) = 272 [$M^+ – (H_2O)$, 1], 155 (57), 137 (34), 136 (32), 118 (36), 117 (22), 115 (11), 106 (25), 105 (21), 95 (41), 91 (20), 81 (100), 79 (10), 77 (13), 69 (44).

HRMS (EI): *m*/*z* calcd for $C_{19}H_{28}O$ (M – H_2O): 272.2140; found: 272.2116.

Spiro Compound 5a

To a solution of the diol **4a** (276 mg, 1.0 mmol) in anhyd CH_2Cl_2 (3 mL) under argon was added dropwise first methanesulfonyl chloride (252 mg, 0.17 mL, 2.2 mmol) and then Et_3N (222 mg, 0.30 mL, 2.2 mmol) at 0 °C. The reaction mixture was stirred for 4 h (monitored by GC) at the same temperature. The mixture was then hydrolysed with aq 2 M HCl (5 mL), the organic layer was neutralised with an aq sat. solution of $NaHCO_3$, washed with H_2O (10 mL), extracted with EtOAc (3 × 15 mL), and the organic layer was dried (Na_2SO_4) and evaporated (15 Torr). The residue was purified by column chromatography (hexane, 30 g Merck silica gel 60, 0.063–0.200 mm) to yield **5a** as a colourless oil (201 mg, 78%); $[\alpha]_D^{20}$ –29 (*c* = 0.42, CH_2Cl_2); R_f 0.39 (hexane).

IR (film): 2951, 2918, 2853, 1732, 1454, 1072 1363 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.67 (dd, *J* = 12.5, 14.0 Hz, 1 H), 0.81 (d, *J* = 6.7 Hz, 3 H), 0.87 (d, *J* = 6.9 Hz, 3 H), 0.93 (d, *J* = 7.0 Hz, 3 H), 1.17–1.32 (m, 2 H), 1.50–1.68 (m, 3 H), 1.70–1.82 (m, 1 H), 1.95–2.05 (m, 1 H), 2.16–2.22 (m, 1 H), 2.17 (d, *J* = 16.0 Hz, 1 H), 3.33 (d, *J* = 16.0 Hz, 1 H), 4.60–4.72 (m, 2 H), 6.99–7.02 (m, 1 H), 7.07–7.16 (m, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.3 (CH_3), 20.9 (CH_2), 22.3 (CH_3), 24.0 (CH_3), 26.2 (CH), 27.9 (CH), 35.5 (CH_2), 35.9 (CH_2), 42.0 (CH_2), 50.3 (CH), 62.0 (CH_2), 75.2 (C), 123.9 (CH), 125.4 (CH), 126.3 (CH), 129.2 (CH), 134.0 (C), 134.9 (C).

MS (EI, 70 eV): *m*/*z* (%) = 258 (M^+, 27), 173 (54), 146 (17), 145 (23), 117 (10), 105 (16), 104 (100), 103 (12), 78 (15), 69 (27).

HRMS (EI): *m*/*z* calcd for $C_{18}H_{26}O$ (M): 258.1984; found: 258.1978.

Spiro Compound 5b

To a solution of the diol **4b** (290 mg, 1.0 mmol) in anhyd CH_2Cl_2 (3 mL) under argon was added dropwise first methanesulfonyl chloride (252 mg, 0.17 mL, 2.2 mmol) and then Et_3N (222 mg, 0.30 mL, 2.2 mmol) at 0 °C. The reaction mixture was stirred for 1 h (monitored by GC) at the same temperature. The reaction mixture was then hydrolysed with aq 2 M HCl (5 mL), the organic layer was neutralised with an aq sat. solution of $NaHCO_3$, washed with H_2O (10 mL), extracted with EtOAc (3 × 15 mL), and the organic layer was dried (Na_2SO_4) and evaporated (15 Torr). The residue was purified by column chromatography (hexane, 30 g Merck silica gel 60, 0.063–0.200 mm) to yield **5b** as a colourless oil (149 mg, 55%); $[\alpha]_D^{20}$ –87.5 (*c* = 0.76, CH_2Cl_2); R_f 0.50 (hexane).

IR (film): 2940, 2864, 1733, 1493, 1454 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.44 (dd, *J* = 12.2, 12.35 Hz, 1 H), 0.71 (d, *J* = 6.5 Hz, 3 H), 0.79–0.89 (m, 1 H), 0.94 (d, *J* = 7.0 Hz, 3 H), 0.98 (d, *J* = 6.8 Hz, 3 H), 1.0–1.15 (m, 1 H), 1.39–1.73 (m, 5 H), 2.30–2.38 (m, 1 H), 2.35 (d, *J* = 14.2 Hz, 1 H), 2.60 (dd, *J* = 4.7 Hz, 15.0 Hz, 1 H), 3.16–3.26 (m, 1 H), 3.56 (t, *J* = 11.6 Hz, 1 H), 3.67 (d, *J* = 14.2 Hz, 1 H), 3.77–3.83 (m, 1 H), 6.97–7.25 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.4 (CH_3), 20.7 (CH_2), 22.4 (CH_3), 24.1 (CH_3), 25.9 (CH), 26.9 (CH), 35.5 (CH_2), 39.2 (CH_2),

39.6 (CH_2), 47.7 (CH_2), 53.7 (CH), 61.0 (CH_2), 76.1 (C), 126.0 (CH), 126.1 (CH), 128.5 (CH), 130.0 (CH), 139.5 (C), 140.9 (C).

MS (EI, 70 eV): *m*/*z* (%) = 272 (M^+, 13), 119 (40), 118 (100), 117 (82), 91 (10).

HRMS (EI): *m*/*z* calcd for $C_{19}H_{28}O$ (M): 272.2140; found: 272.2132.

Acknowledgement

This work was financially supported by the DGES from the Spanish Ministerio de Educación Cultura y Deporte (project no. PB-97-0133) and by the Generalitat Valenciana (project no. GV01-443). B.M. thanks the Spanish Ministerio de Ciencia y Tecnología for a predoctoral fellowship.

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