HETEROCYCLES, Vol. 74, 2007, pp. 507 - 519. © The Japan Institute of Heterocyclic Chemistry
Received, 13th August, 2007, Accepted, 4th October, 2007, Published online, 5th October, 2007. COM-07-S(W)29

CYCLIC ACETALS AS PRECURSORS OF SUBSTITUTED ISOCHROMANS AND NAPHTHOXEPINES

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Abstract – The reaction of 6,8-dioxabenzocycloheptenes **3** or 8,10-dioxacycloocta[*de*]naphthalenes **5** [easily prepared from the dibenzylic diols **1** and **4**, respectively, and a carbonyl compound] with an excess of lithium and a catalytic amount of DTBB (2.5 mol %) in THF at temperatures ranging between -78 and -60 ºC leads, after hydrolysis with water, to the corresponding homobenzylic alcohols **6** and **7**, respectively. Cyclization of compounds **6** and **7** under acidic conditions (85% H_3PO_4 for diols **6** and *p*-TsOH for diols **7**) affords the expected isochromans **8** and naphthoxepines **9**, respectively.

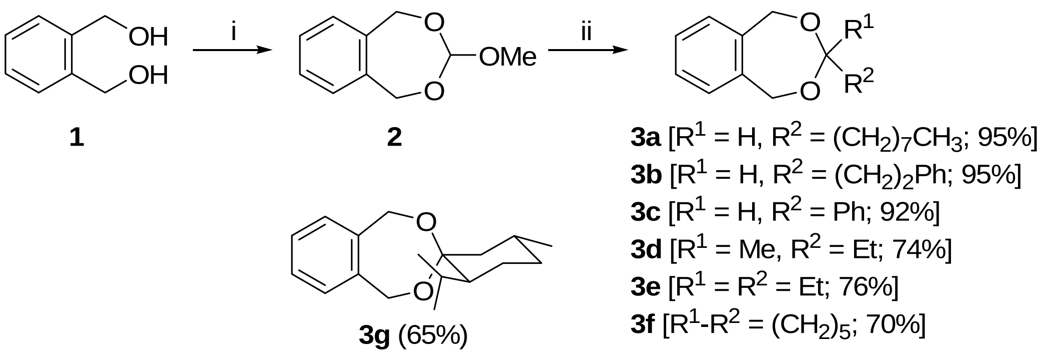
INTRODUCTION

Benzylic organolithium compounds can be prepared by carbon-oxygen bond cleavage from a benzyl ether by means of lithium metal, through a single electron transfer (SET) process.[1] In the case of cyclic benzyl ethers,[2] the reductive opening lithiation of the corresponding heterocycles[3] leads to a functionalized organolithium compounds. These intermediates show a wide applicability in organic synthesis[4] upon reaction with electrophiles, leading to polyfunctionalized molecules. The most commonly used lithiating reagents are lithium metal itself or in the presence of a stoichiometric or catalytic[5] amount of an arene, mainly naphthalene and 4,4'-di-*tert*-butylbiphenyl (DTBB). More recently, polymer supported naphthalene, biphenyl[6] and also polyphenylene[7] have been used as electron transfer reagents in these processes.[8] In this paper we report on the application of the mentioned arene-catalyzed lithiation methodology to the reductive ring opening of dibenzylic cyclic acetals and the study of the synthetic utility of the resulting functionalized organolithium compounds.

This paper is dedicated to Professor Dr. Ekkehard Winterfeldt on the occasion of his 75th birthday.

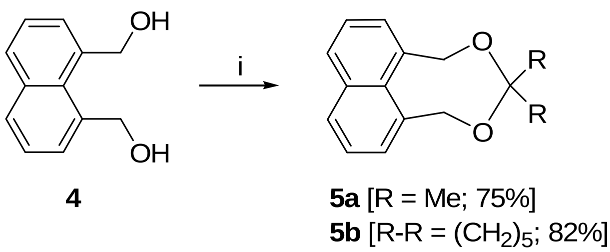
RESULTS AND DISCUSSION

Cyclic acetals **3** were prepared in a one-pot two steps process starting from commercially available 1,2-benzenedimethanol (**1**). Thus, the reaction of diol **1** with trimethyl orthoformate in the presence of a catalytic amount of *p*-toluenesulfonic acid for 5 h at room temperature in 1,2-dimethoxyethane (DME) led to the cyclic orthoester **2**. Further addition of a carbonyl compound [$R^1R^2C=O$: $CH_3(CH_2)_7CHO$, $Ph(CH_2)_2CHO$, PhCHO, EtCOMe, Et_2CO, $(CH_2)_5CO$, (-)-menthone] gave the expected cyclic acetals **3** in good yields (Scheme 1).[9]



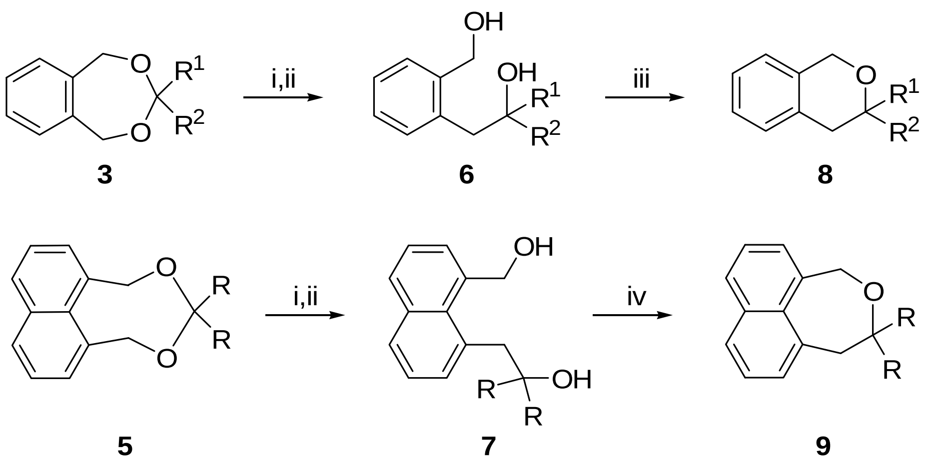
Scheme 1. Reagents and conditions: (i) $HC(OMe)_3$, TsOH (cat.), DME, 25 ºC, 5 h; (ii) R^1R^2CO, 25 ºC, 15 h.

It was not possible to prepare cyclic acetals **5** derived from 1,8-naphthalenedimethanol (**4**) by using the same methodology as for acetals **3**, because under those reaction conditions the cyclic ether resulting from the dehydration of diol **4** was the main reaction product. However, the desired 7*H*,11*H*-8,10-dioxacycloocta[*de*]naphthalenes **5** were prepared in good yields by treatment of diol **4** (easily prepared by reduction with $LiAlH_4$ in the presence of $ZnCl_2$ of commercially available 1,8-naphthalic anhydride)[10] with the dimethyl acetal[11] of the corresponding carbonyl compound [$R_2C(OMe)_2$: $Me_2C(OMe)_2$, $(CH_2)_5C(OMe)_2$] in the presence of a catalytic amount of *p*-toluenesulfonic acid in DME at room temperature for 5 h (Scheme 2).



Scheme 2. Reagents and conditions: (i) $R_2C(OMe)_2$, TsOH (cat.), DME, 25 ºC, 5 h.

The reaction of cyclic acetals **3** or **5** with an excess of lithium powder (1:14 molar ratio) and a catalytic amount of DTBB (1:0.1 molar ratio; 5.0 mol %) in THF at temperatures ranging between -78 and -60 ºC for 5 h led, after hydrolysis with water, in moderate yields to the corresponding diols **6** and **7**, respectively (Scheme 3 and Table 1).



Scheme 3. Reagents and conditions: (i) Li, DTBB (2.5 mol %), THF, -78 to -60 ºC, 5 h; (ii) H_2O, -78 to 25 ºC; (iii) H_3PO_4 (85%), PhMe, 115 ºC, 2-6 h; (iv) TsOH (cat.), MS 4 Å, PhMe, 110 ºC, 2 h.

Concerning a possible mechanistic pathway for the formation of compounds **6** and **7**, it could be possible that in the first step, a benzylic cleavage takes place giving dianionic intermediates of the type **I** and **IV**, respectively. These intermediates either could afford directly the dialcoholates **II** and **V** which are the precursors, after hydrolsys with water, of the final diols **6** and **7**, respectively, or could give complexes of type **III** and **VI** between a benzylic dianion and a carbonyl compound which is generated by elimination from intermediates **I** and **IV**, respectively (Chart 1).

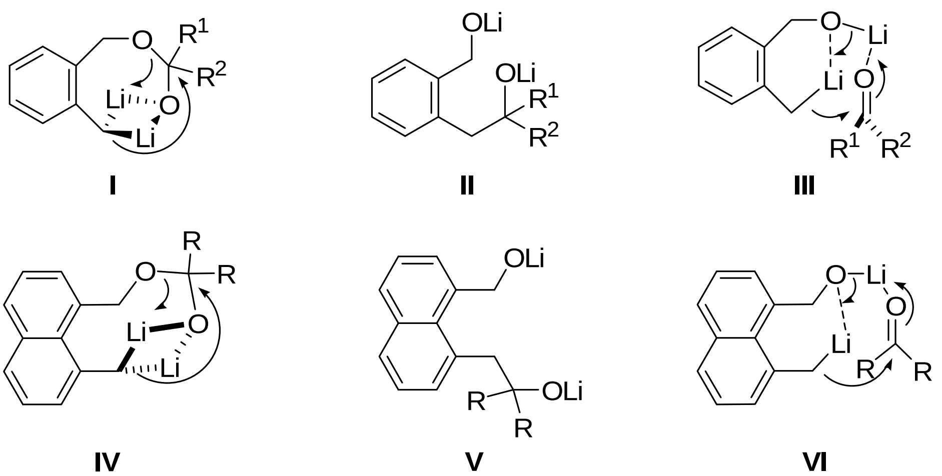
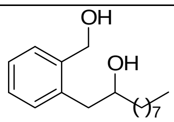
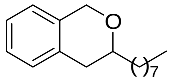
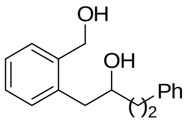
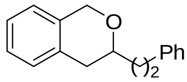
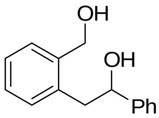
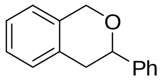
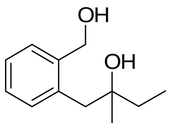
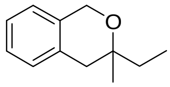
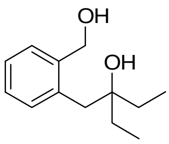
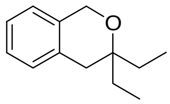
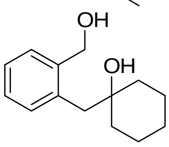
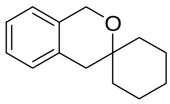
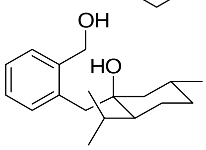
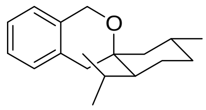
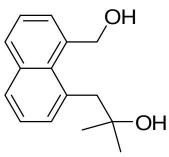
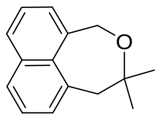
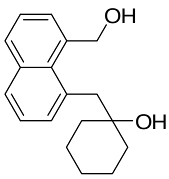
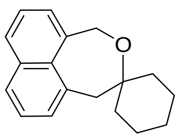


Chart 1.

Table 1. Preparation of diols **6** and **7** and oxygen containing heterocycles **8** and **9**

Entry	Starting acetal	Diols **6** and **7**[a] No.	Structure	Yield (%)[b]	Isochromans **8** and oxepines **9**[a] No.	Structure	Yield (%)[c]
1	**3a**	**6a**		62	**8a**		>95
2	**3b**	**6b**		43	**8b**		92
3	**3c**	**6c**		65	**8c**		90
4	**3d**	**6d**		51	**8d**		48
5	**3e**	**6e**		40	**8e**		83
6	**3f**	**6f**		74	**8f**		86
7	**3g**	**6g**		40[d]	**8g**		78[d,e]
8	**5a**	**7a**		45	**9a**		>95
9	**5b**	**7b**		48	**9b**		>95

[a] All products were >95% pure (GLC and 300 MHz ^{1}H RMN). [b] Yield based on the starting material **3** or **5**. [c] Yield based on the starting material **6** or **7**. [d] Only the shown diastereomer was obtained. [e] For cyclization conditions see reference 12.

The cyclization of diols **6** and **7** under acidic conditions was studied in the last part of this work. Thus, 3-substituted isochromans **8a-f** were obtained in high yields (except in the case of compound **8d**, for which some other by-products were also obtained; Table 1, entry 4) by treatment of diols **6a-f** with 85% phosphoric acid in refluxing toluene (Scheme 3, Table 1, entries 1-6).[2a] All attempts to perform the dehydration of diol **6g** (Table 1, entry 7) under acidic conditions gave a mixture of reaction products. However, spiro isochroman derivative **8g** (Table 1, entry 7) was obtained in moderate yield when diol **6g** was treated with an excess of methanesulfonyl chloride in the presence of triethylamine in CH_2Cl_2 at room temperature.[12] Finally, intramolecular dehydration of diols **7a**,**b** by treatment with a catalytic amount of *p*-toluenesulfonic acid in the presence of 4 Å molecular sieves in toluene at 110ºC gave the corresponding oxygen-containing seven membered heterocycles **9a**,**c** in very high yields (Scheme 3, Table 1, entries 8-9).[13]

In summary, we have described in this paper a methodology which allows the transformation of cyclic acetals **3** and **5** into diols **6** and **7**, respectively, through a DTBB-catalyzed lithiation. Moreover, these diols are cyclized under acidic conditions to give isochromans **8** and naphthoxepines **9**.

EXPERIMENTAL

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

Preparation of 5,9-dihydro-6,8-dioxabenzenecycloheptenes 3. General procedure.

To a solution of 1,2-benzenedimethanol (1.2 mmol, 168 mg) and TsOH (5 mg) in DME (1 mL) was added trimethyl orthoformate (1.3 mmol, 138 mg) at 25 ºC. After 5 h, the corresponding carbonyl compound (1.3 mmol) was added and the reaction mixture was stirred for 15 additional h. Then, all volatile compounds were evaporated (15 Torr). The resulting residue was purified by column chromatography (silica gel, hexane/EtOAc) to yield pure products **3**. Yields are given on Scheme 1. Physical and spectroscopic data as well as literature references follow.

7-Octyl-5,9-dihydro-6,8-dioxabenzocycloheptene (3a): White solid; R_f 0.33 (hexane/EtOAc: 30/1); mp 58-59 ºC (hexane/CH_2Cl_2); IR ν (KBr) 3027 (ArH), 1025 cm^{-1} (COC); ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (3H, t, J = 6.8 Hz, CH_3), 1.27-1.29 (10H, m, 5xCH_2), 1.40-1.42 (2H, m, $CHCH_2CH_2$), 1.68-1.73 (2H, m, $CHCH_2$), 4.84-4.89 (5H, m, CH_2O, CH), 7.15-7.21 (4H, m, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2 (CH_3), 22.8, 24.7, 29.4, 29.6, 29.7, 32.0, 34.7 (CH_2), 71.6 (CH_2O), 108.7 (CH), 127.4, 127.5, 139.4

(ArC); LRMS (EI) *m/z* 262 (M^+, 1%), 150 (10), 149 (100), 121 (24), 119 (11), 93 (17), 91 (35); HRMS (EI) calcd for $C_9H_9O_2$ (M^+-C_8H_{17}) 149.0603, found 149.0598.

7-(2-Phenylethyl)-5,9-dihydro-6,8-dioxabenzocycloheptene (3b): Colourless oil; R_f 0.25 (hexane/EtOAc: 30/1); IR ν (film) 3063, 3020 (ArH), 1129 cm^{-1} (COC); ^1H NMR (400 MHz, $CDCl_3$) δ 2.01-2.04 (2H, m, C*H*$_2$CH), 2.75 (2H, t, *J* = 8.0 Hz, CH_2Ph), 4.82-4.84 (5H, m, CH_2O, CH), 7.13-7.21 (7H, m, ArH), 7.25-7.29 (2H, m, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.9, 36.2 (CH_2), 71.8 (CH_2O), 107.8 (CH), 126.0, 127.5, 127.6, 128.5, 128.6, 139.3, 141.7 (ArC); LRMS (EI) *m/z* 254 (7%), 192 (44), 179 (5), 149 (34), 133 (10), 121 (28), 120 (10), 119 (22), 118 (14), 105 (57), 104 (83), 93 (30), 92 (23), 91 (100), 89 (10), 77 (22), 65 (17); HRMS (EI) calcd for $C_{17}H_{18}O_2$ 254.1307, found 254.1308.

7-Phenyl-5,9-dihydro-6,8-dioxabenzocycloheptene (3c)[14]: White solid; R_f 0.27 (hexane/EtOAc: 30/1); mp 78-79 ºC (hexane/CH_2Cl_2); IR ν (KBr) 3063, 3031 (ArH), 1109 cm^{-1} (COC); ^1H NMR (300 MHz, $CDCl_3$) δ 4.94 (4H, s, CH_2O), 5.92 (1H, s, (CHPh), 7.13-7.20 (4H, m, ArH), 7.21-7.53 (3H, m, ArH), 7.55 (2H, d, *J* = 6.4 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 70.2 (CH_2O), 105.0 (CH), 126.5, 127.1, 127.3, 128.3, 128.7, 138.9, 139.0 (ArC); LRMS (EI) *m/z* 226 (M^+, 7%), 120 (41), 119 (81), 105 (61), 104 (100), 92 (21), 91 (92), 89 (19), 77 (28), 65 (17), 51 (10).

7-Ethyl-7-methyl-5,9-dihydro-6,8-dioxabenzocycloheptene (3d)[9]: Colourless oil; R_f 0.29 (hexane/EtOAc: 30/1); IR ν (film) 3076 (ArH), 1088 cm^{-1} (COC); ^1H NMR (300 MHz, $CDCl_3$) δ 0.98 (3H, t, *J* = 7.6 Hz, CH_2C*H*$_3$), 1.42 (3H, s, CH_3CO), 1.83 (2H, q, *J* = 7.5 Hz, C*H*$_2$$CH_3$), 4.81 (2H, d, *J* = 15.3 Hz, 2xC*H*HO), 4.86 (2H, d, *J* = 15.3 Hz, 2xCH*H*O), 7.04-7.07 (2H, m, ArH), 7.15-7.18 (2H, m, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.8, 20.6 (CH_3), 29.0 (CH_2), 64.8 (CH_2O), 104.4 (C), 126.2, 126.8, 138.4 (ArC); LRMS (EI) *m/z* 192 (M^+, 1%), 164 (10), 163 (100), 121 (36), 120 (14), 119 (44), 93 (11), 92 (12), 91 (51).

7,7-Diethyl-5,9-dihydro-6,8-dioxabenzocycloheptene (3e)[9]: White solid; R_f 0.31 (hexane/EtOAc: 30/1); mp 77-78 ºC (hexane/CH_2Cl_2); IR ν (KBr) 3018 (ArH), 1054 cm^{-1} (COC); ^1H NMR (400 MHz, $CDCl_3$) δ 0.92 (6H, t, *J* = 7.5 Hz, 2xCH_3), 1.78 (4H, q, *J* = 7.5 Hz, 2xC*H*$_2$$CH_3$), 4.83 (4H, s, 2x$CH_2O$), 7.05-7.07 (2H, m, ArH), 7.15-7.26 (2H, m, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.4 (CH_3), 24.3 (CH_2), 64.5 (CH_2O), 106,5 (C), 126.2, 126.7, 138.6 (ArC); LRMS (EI) *m/z* 177 (M^+-Et, 100%), 120 (12), 119 (36), 91 (36), 57 (94).

Spiro[cyclohexane-1,7'-(5',9'-dihydro-6',8'-dioxabenzocycloheptene)] (3f)[9]: White solid; R_f 0.33 (hexane/EtOAc: 30/1); mp 83-84 ºC (hexane/CH_2Cl_2); IR ν (KBr) 3066, 3006 (ArH), 1115 cm^{-1} (COC); ^1H NMR (400 MHz, $CDCl_3$) δ 1.43-1.48 (2H, m, CH_2), 1.57-1.62 (4H, m, 2xCH_2), 1.79-1.82 (4H, m, 2xCH_2), 4.86 (4H, s, 2xCH_2O), 7.04-7.07 (2H, m, ArH), 7.14-7.24 (2H, m, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.3, 25.9, 32.6 (CH_2), 64.2 (CH_2O), 102.4 (C), 126.2, 126.7, 138.5 (ArC); LRMS (EI) *m/z* 218 (M^+, 53%), 175 (32), 131 (12), 119 (30), 105 (29), 104 (100), 91 (36), 78 (10), 55 (16).

(2*S*,5*R*)-2-Isopropyl-5-methylspiro[cyclohexane-1,7'-(5',9'-dihydro-6',8'-dioxabenzocycloheptene)] (3g): White solid; $[\alpha]^{22}_D$ +23.0 (*c* 0.62, CH_2Cl_2); R_f 0.40 (hexane/EtOAc: 30/1); mp 62-63 ºC (hexane/CH_2Cl_2); IR ν (KBr) 3069, 3027 (ArH), 1118 cm^{-1} (COC); ^1H NMR (400 MHz, $CDCl_3$) δ 0.93 (3H, d, *J* = 6.9 Hz, C*H*$_3$CH), 0.96 (3H, d, *J* = 6.6 Hz, C*H*$_3$CH), 1.01-1.05 (1H, m, CH), 1.11 (3H, d, *J* = 6.6 Hz, C*H*$_3$CH), 1.30-1.36 (1H, m, CH), 1.42-1.49 (1H, m, CH), 1.67-1.82 (4H, m, 4xCH), 1.86-1.95 (1H, m, CH), 1.96-2.03 (1H, m, CH), 4.57 (1H, d, *J* = 14.8 Hz, C*H*HO), 4.68 (1H, d, *J* = 15.1 Hz, CH*H*O), 4.97 (1H, d, *J* = 15.1 Hz, C*H*HO), 5.00 (1H, d, *J* = 14.8 Hz, CH*H*O), 7.07 (2H, s, ArH), 7.14-7.26 (2H, m, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.3, 22.4, 23.6 (CH_3), 25.3, 27.0, 29.5 (CH_2), 29.9, 36.2, 44.0 (CH), 63.9, 64.5 (CH_2O), 105.9 (C), 126.0, 126.3, 126.6, 126.8, 138.55, 138.6 (ArC); LRMS (EI) *m/z* 274 (M^+, 13%), 189 (20), 105 (15), 104 (100), 91 (12), 69 (14); HRMS (EI) calcd for $C_{18}H_{26}O_2$ 274.1933, found 274.1937.

Preparation of 7*H*,11*H*-8,10-dioxacycloocta[*de*]naphthalenes 5. General procedure.

To a solution of 1,8-naphthalenedimethanol (1.5 mmol, 282 mg) and TsOH (5 mg) in DME (4 mL) was added the dimethyl acetal of the corresponding carbonyl compound (1.1 mmol; 5 mmol, 504 mg in the case of the dimethyl acetal of acetone) at 25 ºC and the reaction mixture was stirred for 5 h at the same temperature. Then, all volatile compounds were evaporated (15 Torr). The resulting residue was purified by column chromatography (silica gel, hexane/EtOAc) to yield pure products **5**. Yields are given on Scheme 2. Physical and spectroscopic data follow.

9,9-Dimethyl-7*H*,11*H*-8,10-dioxacycloocta[*de*]naphthalene (5a): White solid; R_f 0.11 (hexane/EtOAc: 30/1); mp 109-110 ºC (hexane/CH_2Cl_2); IR ν (KBr) 3035, 2990, 2945, 2890 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.57 (6H, s, 2×CH_3), 5.01 (4H, s, 2×OCH_2), 7.37-7.42 (4H, m, ArH), 7.79-7.82 (2H, m, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.2 (CH_3), 66.8 (CH_2), 100.9 (CO_2), 125.2, 130.2, 130.3, 132.9, 134.8, 135.6 (ArC); LRMS (EI) *m/z* 228 (M^+, 43%), 171 (31), 170 (93), 169 (77), 155 (24), 142 (57), 141 (100), 139 (33), 115 (37); HRMS (EI) calcd for $C_{15}H_{16}O_2$ 228.1150, found 228.1143.

Spiro[cyclohexane-1,9'-(7'*H*,11'*H*-8',10'-dioxacycloocta[*de*]naphthalene)] (5b): White solid; R_f 0.18 (hexane/EtOAc: 30/1); mp 115-116 ºC (pentane/CH_2Cl_2); IR ν (KBr) 3045, 2935, 2855 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.44-1.47 (2H, m, CH_2), 1.50-1.61 (4H, m, 2×CH_2), 1.81-1.84 (4H, m, 2×CH_2), 4.94 (4H, s, 2×OCH_2), 7.32-7.37 (4H, m, ArH), 7.74-7.77 (2H, m, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.3, 25.8, 34.0 (CH_2), 65.7 (OCH_2), 101.0 (CO_2), 125.1, 130.1, 130.2, 132.7, 134.9, 135.5 (ArC); LRMS (EI) *m/z* 268 (M^+, 12%), 170 (100), 169 (49), 154 (23), 153 (66), 152 (21), 142 (59), 141 (74), 115 (34); HRMS (EI) calcd for $C_{18}H_{20}O_2$ 268.1463, found 268.1469.

Lithiation of cyclic acetals 3 and 5. Preparation of diols 6 and 7. General procedure.

To a blue suspension of lithium powder (100 mg, 14 mmol) and a catalytic amount of DTBB (27 mg, 0.1 mmol; 5 mol%) in dry THF (2.5 mL) under argon was added dropwise a solution of the corresponding acetal **3** or **5** (1 mmol) in THF (0.5 mL) at -78 ºC, and the resulting mixture was stirred for 5 h at temperatures ranging between -78 and -60 ºC. After that, the reaction mixture was hydrolyzed with water (4 mL), extracted with EtOAc (3 × 10 mL), dried over anhydrous $MgSO_4$ and evaporated (15 Torr). The residue was purified by column chromatography (silica gel, hexane/EtOAc) to yield pure products **6** and **7**. Yields are given in Table 1, physical, analytical and spectroscopic data follow as well as literature references follow.

1-(2-Hydroxymethylphenyl)decan-2-ol (6a): Colourless oil; R_f 0.25 (hexane/EtOAc: 2/1); IR ν (film) 3540-3140 (OH), 3020, 2950, 2925, 2854 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.89 (3H, t, *J* = 6.8 Hz, CH_3), 1.22-1.57 (14H, m, 7×CH_2), 2.71-2.79 (2H, m, ArC*H*$_2$CH), 3.55 (2H, br s, 2×OH), 3.70-3.77 (1H, m, C*H*OH), 4.41 (1H, d, *J* = 11.7 Hz, C*H*HOH), 4.69 (1H, d, *J* = 11.7 Hz, CH*H*OH), 7.16-7.21 (2H, m, ArH), 7.24-7.29 (2H, m, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2 (CH_3), 22.8, 25.9, 29.4, 29.7, 29.8, 32.0, 37.9, 39.8 (CH_2), 63.2 (CH_2OH), 73.2 (CHOH), 126.8, 128.4, 130.1, 130.5, 138.3, 139.5 (ArC); LRMS (EI) *m/z* 246 (M^+-H_2O, 3%), 207 (15), 133 (10), 105 (31), 104 (100); HRMS (EI) calcd for $C_{15}H_{16}O$ (M^+-H_2O) 246.1984, found 246.2005.

1-(2-Hydroxymethylphenyl)-4-phenylbutan-2-ol (6b)[15]: Colourless oil; R_f 0.31 (hexane/EtOAc: 2/1); IR ν (film) 3583-3120 (OH), 3060, 3024, 1494, 1453, 1015 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.91-1.97 (2H, m, CHC*H*$_2$CH$_2$), 2.59-2.80 (4H, m, 2×CH_2), 3.52 (2H, br s, 2×OH), 3.81-3.84 (1H, m, C*H*OH), 4.50 (1H, d, *J* = 11.7 Hz, C*H*HOH), 4.76 (1H, d, *J* = 11.7 Hz, CH*H*OH), 7.17-7.31 (9H, m, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.3, 39.4, 40.0 (CH_2), 63.5 (CH_2OH), 72.6 (CHOH), 126.1, 127.0, 128.5, 128.6, 130.1, 130.5, 137.9, 139.5, 141.9 (ArC); LRMS (EI) *m/z* 238 (M^+-H_2O, 2%), 117 (13), 106 (100), 105 (19), 91 (84), 77 (10).

2-(2-Hydroxymethylphenyl)-1-phenylethanol (6c)[2a]: White solid; R_f 0.44 (hexane/EtOAc: 1/1); mp 70-71 ºC (pentane/CH_2Cl_2); IR ν (KBr) 3600-3080 cm^{-1} (OH); ^1H NMR (300 MHz, $CDCl_3$) δ 2.95 (1H, dd, *J* = 14.0, 3.7 Hz, C*H*HCHOH), 3.05 (1H, dd, *J* = 14.0, 9.1 Hz, CH*H*CHOH), 3.75 (2H, br s, 2×OH), 4.37 (1H, d, *J* = 11.8 Hz, C*H*HOH), 4.68 (1H, d, *J* = 11.8 Hz, CH*H*OH), 4.78 (1H, dd, *J* = 9.1, 7.3 Hz, C*H*OH), 7.14-7.36 (9H, m, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 42.2 (CH_2), 63.1 (CH_2OH), 75.3 (CHOH), 125.7, 126.8, 127.5, 128.3, 128.4, 130.0, 130.5, 137.4, 139.4, 144.3 (ArC); LRMS (EI) *m/z* 210 (M^+-H_2O, 9%), 105 (11), 104 (100), 103 (11), 77 (10).

1-(2-Hydroxymethylphenyl)-2-methylbutan-2-ol (6d): Colourless oil; R_f 0.24 (hexane/EtOAc: 2/1); IR ν (film) 3470-3180 (OH), 3070, 3020, 2968, 2925, 2860 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.98 (3H, t, *J* = 7.2 Hz, C*H*$_3$CH$_2$), 1.17 (3H, s, CCH_3), 1.54-1.60 (2H, m, C*H*$_2$CH$_3$), 2.74 (1H, d, *J* = 13.9 Hz, C*H*HAr), 2.94 (1H, d, *J* = 13.9 Hz, CH*H*Ar), 3.68 (2H, br s, 2×OH), 4.49 (1H, d, *J* = 11.8 Hz, C*H*HOH), 4.61 (1H, d, *J* = 11.8 Hz, CH*H*OH), 7.12-7.32 (4H, m, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.5 (CH_3), 26.4 (CH_2), 35.5 (CH_3), 43.2 (CH_2), 63.3 (CH_2OH), 72.8 (COH), 126.9, 127.7, 130.7, 132.3, 136.4, 140.2 (ArC); LRMS (EI) *m/z* 176 (M^+-H_2O, 1%), 147 (13), 119 (13), 105 (21), 104 (100), 91 (19), 73 (25); HRMS (EI) calcd for $C_{12}H_{18}O_2$ (M^+-H_2O) 176.1201, found 176.1191.

2-Ethyl-1-(2-hydroxymethylphenyl)butan-2-ol (6e)[2a]: Colourless oil; R_f 0.31 (hexane/EtOAc: 2/1); IR ν (film) 3600-3060 cm^{-1} (OH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (6H, t, *J* = 7.5 Hz, 2×CH_3), 1.44-1.60 (6H, m, 2×OH, 2×C*H*$_2$CH$_3$), 2.83 (2H, s, ArCH_2), 4.52 (2H, s, C*H*$_2$OH), 7.10-7.31 (4H, m, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.0 (CH_3), 30.7, 40.5 (CH_2), 63.1 (CH_2OH), 74.5 (COH), 126.7, 127.5, 130.5, 131.9, 136.1, 140.3 (ArC); LRMS (EI) *m/z* 190 (M^+-H_2O, 9%), 161 (12), 105 (14), 104 (100), 91 (13), 87 (11), 77 (12), 57 (29), 45 (17), 41 (10).

1-[(2-Hydroxymethylphenyl)methyl]cyclohexanol (6f)[2a]: White solid; R_f 0.48 (hexane/EtOAc: 2/1); mp 70-71 ºC (pentane/CH_2Cl_2); IR ν (KBr) 3600-3060 cm^{-1} (OH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.19-1.61 (10H, m, 5×CH_2), 2.86 (2H, s, ArCH_2C), 3.45 (2H, br s, 2×OH), 4.56 (2H, s, C*H*$_2$OH), 7.12-7.34 (4H, m, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.1, 25.6, 37.9, 44.5 (CH_2), 63.3 (CH_2OH), 71.2 (COH), 126.8, 127.5, 130.5, 132.1, 135.8, 140.3 (ArC); LRMS (EI) *m/z* 202 (M^+-H_2O, 9%), 105 (11), 104 (100).

(1*R*,2*S*,5*R*)-2-Isopropyl-5-methyl-1-[(2-hydroxymethylphenyl)methyl]cyclohexanol (6g)[12]: Colourless oil; $[\alpha]^{22}_D$ -19.5 (*c* 1.0, CH_2Cl_2); R_f 0.13 (hexane/EtOAc: 5/1); IR ν (film) 3500-3180 cm^{-1} (OH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.81 (3H, d, *J* = 6.2 Hz, C*H*$_3$CH), 0.87-1.04 (2H, m, 2×CH), 0.98 [6H, d, *J* = 7.0 Hz, (C*H*$_3$)$_2$CH], 1.21-1.51 (4H, m, 2×CH_2), 1.59-1.67 (1H, m, CH), 1.73-1.78 (1H, m, CH), 2.35-2.45 (1H, m, CH), 2.43 (1H, d, *J* = 13.9 Hz, ArC*H*HC), 2.71 (2H, br s, 2×OH), 3.61 (1H, d, *J* = 13.9 Hz, ArCH*H*C), 4.42 (1H, d, *J* = 11.9 Hz, ArC*H*HOH), 4.81 (1H, d, *J* = 11.9 Hz, ArCH*H*OH), 7.14-7.27 (3H, m, ArH), 7.33-7.38 (1H, m, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.0 (CH_3), 21.0 (CH_2), 22.3, 23.8 (CH_3), 25.9, 28.0 (CH), 34.8, 42.4, 46.8 (CH_2), 51.1 (CH), 63.3 (CH_2OH), 74.7 (COH), 126.9, 127.3, 130.6, 133.0, 136.0, 140.5 (ArC); LRMS (EI) *m/z* 258 (M^+-H_2O, 3%), 104 (100), 95 (11), 81 (29), 69 (21), 57 (29), 45 (17), 41 (10); HRMS (EI) calcd for $C_{18}H_{26}O$ (M^+-H_2O) 258.1984, found 258.1971.

1-[(8-Hydroxymethyl)-1-naphthyl]-2-methylpropan-2-ol (7a)[13]: Colourless oil; R_f 0.14 (hexane/EtOAc: 2/1); IR ν (film) 3560-3275 (OH), 3055, 3033 (ArH), 1095 cm^{-1} (COC); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25 [6H, s, $(CH_3)_2C$], 2.17 (2H, br s, 2×OH), 3.57 (2H, s, C*H*$_2$COH), 5.18 (2H, s, C*H*$_2$OH), 7.33-7.45 (3H, m, ArH), 7.52-7.55 (1H, m, ArH), 7.78-7.83 (2H, m, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.5 (CH_3), 47.7 (CH_2), 66.5 (CH_2OH), 72.7 (COH), 124.6, 125.0, 129.2, 129.5, 130.5, 131.4, 132.6, 133.6, 135.8, 137.0 (ArC); LRMS (EI) *m/z* 212 (M^+-H_2O, 9%), 179 (18), 172 (22), 154 (92), 153 (100), 141 (17), 128 (27), 115 (17), 59 (47); HRMS (EI) calcd for $C_{15}H_{16}O$ (M^+-H_2O) 212.1201, found 212.1196.

1-{[(8-Hydroxymethyl)-1-naphthyl]methyl}cyclohexanol (7b)[13]: Colourless oil; R_f 0.36

(hexane/EtOAc: 2/1); IR ν (film) 3535-3140 (OH), 3058, 3036 (ArH), 1045 cm^{-1} (COC); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.27-1.93 (12H, m, 5×CH_2, 2×OH), 3.54 (2H, s, ArC*H*$_2$COH), 5.16 (2H, s, C*H*$_2$OH), 7.30 (1H, d, *J* = 5.9 Hz, ArH), 7.36-7.42 (2H, m, ArH), 7.52 (1H, d, *J* = 5.8 Hz, ArH), 7.76-7.80 (2H, m, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.0, 25.8, 37.4, 47.2 (CH_2), 66.3 (CH_2OH), 73.2 (COH), 124.4, 125.0, 129.1, 130.4, 131.6, 132.4, 132.5, 132.9, 135.7, 137.1 (ArC); LRMS (EI) *m/z* 252 (M^+-H_2O, 5%), 172 (19), 165 (20), 155 (15), 154 (100), 153 (75), 152 (36), 141 (12), 128 (19), 115 (15), 81 (18), 55 (30); HRMS (EI) calcd for $C_{18}H_{20}O$ (M^+-H_2O) 252.1514, found 252.1503.

Cyclization of diols 6. Preparation of isochromans 8. General procedure.

To a solution of the corresponding diol **6** (1 mmol) in toluene (5 mL) was added 85% phosphoric acid (0.4 mL). The reaction mixture was heated at 110 ºC for 4 h. Then toluene was removed by distillation and the resulting residue was hydrolyzed with water (5 mL), extracted with EtOAc (3 × 10 mL), dried over anhydrous Na_2SO_4 and evaporated (15 Torr). The residue was purified by column chromatography (silica gel, hexane) to yield pure products **8**. Compound **8g** was prepared according to reference 12. Yields are given in Table 1, physical, analytical and spectroscopic data follow as well as literature references follow.

3-Octylisochroman (8a): Colourless oil; R_f 0.31 (hexane/EtOAc: 30/1); IR ν (film) 3069, 3014, 2955, 2925, 2850 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (3H, t, *J* = 7.0 Hz, CH_3), 1.23-1.70 (14H, m, 7×CH_2), 2.70 (2H, d, *J* = 9.7 Hz, C*H*$_2$CH), 3.57-3.66 (1H, m, C*H*O), 4.80 (1H, d, *J* = 12.3 Hz, C*H*HO), 4.83 (1H, d, *J* = 12.3 Hz, CH*H*O), 6.96-6.99 (1H, m, ArH), 7.00-7.16 (3H, m, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1 (CH_3), 22.6, 25.5, 29.3, 29.5, 29.7, 31.8, 34.1, 36.0 (CH_2), 68.2 (CH_2O), 74.9 (CHO), 124.1, 125.8, 126.2, 128.8, 133.6, 134.9 (ArC); LRMS (EI) *m/z* 246 (M^+, 3%), 133 (12), 105 (39), 104 (100); HRMS (EI) calcd for $C_{17}H_{26}O$ 246.1984, found 246.2001.

3-(2-Phenylethyl)isochroman (8b): Colourless oil; R_f 0.20 (hexane/EtOAc: 30/1); IR ν (film) 3063, 3020 (ArH), 1129 cm^{-1} (COC); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.87-2.02 (2H, m, CH_2C*H*$_2$CH), 2.70-2.88 (4H, m, ArC*H*$_2$CHO, PhC*H*$_2$), 3.60-3.66 (1H, m, CHO), 4.79 (1H, d, *J* = 15.1 Hz, C*H*HO), 4.87 (1H, d, *J* = 15.1 Hz, CH*H*O), 7.00-7.31 (9H, m, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.8, 34.2, 37.7 (CH_2), 68.3 (CH_2O), 74.0 (CHO), 124.3, 125.9, 126.1, 126.5, 128.5, 128.6, 129.0, 133.5, 135.0, 142.1 (ArC); LRMS (EI) *m/z* 238 (M^+, 12%), 117 (16), 116 (60), 105 (66), 104 (100), 91 (30); HRMS (EI) calcd for $C_{17}H_{18}O$ 238.1358, found 238.1350.

3-Phenylisochroman (8c)[16,2a]: White solid; R_f 0.26 (hexane); mp 69-70 ºC (hexane/CH_2Cl_2); IR ν (KBr) 3040, 1600, 1500, 740, 700 cm^{-1} (ArH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.94 (1H, dd, *J* = 16.4, 3.6 Hz, C*H*HCHO), 3.06 (1H, dd, *J* = 16.4, 10.6 Hz, CH*H*CHO), 4.70 (1H, dd, *J* = 10.6, 3.6 Hz, CHO), 4.98 (2H, s, CH_2O), 7.00-7.45 (9H, m, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 36.0 (CH_2), 68.6 (CH_2O), 76.8 (CHO), 124.2, 125.8, 126.1, 126.4, 127.6, 128.4, 128.7, 133.4, 134.5, 142.1 (ArC); LRMS (EI) *m/z* 210 (M^+, 20%), 105 (11), 104 (100), 103 (16), 78 (15), 77 (12).

3-Ethyl-3-methylisochroman (8d): Colourless oil; R_f 0.24 (hexane/EtOAc: 30/1); IR ν (film) 3063, 3020, 2965, 2928, 2836 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.96 (3H, t, J = 7.5 Hz, CH_3CH$_2$), 1.21 (3H, s, CCH$_3$), 1.43-1.68 (2H, m, CH_2CH$_3$), 2.64 (1H, d, J = 16.1 Hz, C*H*HAr), 2.74 (1H, d, J = 16.1 Hz, CH*H*Ar), 4.76 (2H, s, CH$_2$O), 6.98-7.01 (1H, m, ArH), 7.06-7.09 (1H, m, ArH), 7.12-7.17 (2H, m, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.9 (CH$_3$), 22.5 (CH$_2$), 32.1 (CH$_3$), 38.0 (CH$_2$), 62.8 (CH$_2$O), 73.0 (CO), 123.8, 125.7, 126.3, 129.2, 132.9, 134.2 (ArC); LRMS (EI) *m/z* 176 (M^+, 1%), 147 (52), 119 (24), 105 (16), 104 (100), 78 (12); HRMS (EI) calcd for $C_{12}H_{16}O$ 176.1201, found 176.1206.

3,3-Diethylisochroman (8e)[2a]: Colourless oil; R_f 0.35 (hexane); IR ν (film) 3040, 3000, 1580, 740, 720 cm^{-1} (ArH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (6H, t, J = 7.5 Hz, 2×CH$_3$), 1.42-1.54 (2H, m, 2×C*H*HCH$_3$), 1.60-1.72 (2H, m, 2×CH*H*CH$_3$), 2.67 (2H, s, ArCH$_2$CO), 4.72 (2H, s, CH$_2$O), 6.96-7.15 (4H, m, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.6 (CH$_3$), 27.5, 36.1 (CH$_2$), 62.5 (CH$_2$O), 75.1 (CO), 123.8, 125.6, 126.3, 129.2, 132.8, 134.4 (ArC); LRMS (EI) *m/z* 190 (M^+, 2%), 162 (11), 161 (100), 105 (20), 104 (52), 57 (13).

(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylspiro[cyclohexane-1,3'-isochroman] (8f)[12]: Colourless oil; $[\alpha]^{22}_D$ -29.0 (*c* 0.42, CH_2Cl_2); R_f 0.39 (hexane); IR ν (film) 2951, 2918, 2853, 1732, 1454, 1072 1363 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.67 (1H, dd, J = 14.0, 12.5 Hz, CH), 0.81 (3H, d, J = 6.7 Hz, CH_3CH), 0.87 (3H, d, J = 6.9 Hz, CH_3CH), 0.93 (3H, d, J = 7.0 Hz, CH_3CH), 1.17-1.32 (2H, m, CH$_2$), 1.50-1.68 (3H, m, CH, CH$_2$), 1.70-1.82 (1H, m, CH), 1.95-2.05 (1H, m, CH), 2.16-2.22 (1H, m, CH), 2.17 (1H, d, J = 16.0 Hz, ArC*H*HC), 3.33 (1H, d, J = 16.0 Hz, ArCH*H*C), 4.60-4-72 (2H, m, ArCH$_2$O), 6.99-7.02 (1H, m, ArH), 7.07-7.16 (3H, m, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.3 (CH$_3$), 20.9 (CH$_2$), 22.3, 24.0 (CH$_3$), 26.2, 27.9 (CH), 35.5, 35.9, 42.0 (CH$_2$), 50.3 (CH), 62.0 (CH$_2$OH), 75.2 (CO), 123.9, 125.4, 126.3, 129.2, 134.0, 134.9 (ArC); LRMS (EI) *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) calcd for $C_{18}H_{26}O$ 258.1984, found 258.1978.

Cyclization of diols 7. Preparation of naphthoxepines 9. General procedure.

To a solution of the corresponding diol **7** (0.1 mmol) in toluene (1.5 mL) a catalytic amount of *p*-toluenesulfonic acid (30 mg) and 4 Å molecular sieves (30 mg) were added. The reaction mixture was heated at 110 ºC for 2 h. Then toluene was removed by distillation and the resulting residue was hydrolyzed with water (5 mL), extracted with EtOAc (3 × 10 mL), dried over anhydrous Na_2SO_4 and evaporated (15 Torr). The residue was purified by column chromatography (silica gel, hexane) to yield pure products **9**. Yields are given in Table 1, physical, analytical and spectroscopic data as well as literature references follow.

9,9-Dimethyl-9,10-dihydro-7*H*-8-oxacyclohepta[*de*]naphthalene (9a)[13]: Pale yellow oil; R_f 0.37 (hexane/EtOAc: 10/1); IR ν (film) 3054, 3035 (ArH), 1065 cm^{-1} (COC); ^1H NMR (300 MHz, $CDCl_3$) δ 1.34 [6H, s, $C(CH_3)_2$], 3.32 (2H, s, CH_2CO), 5.03 (2H, s, CH_2O), 7.16-7.40 (4H, m, ArH), 7.71 (2H, d, *J* = 8.4 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.6 (CH_3), 46.9 (CH_2), 67.2 (CH_2O), 77.5 (*C*OCH_2), 124.8, 124.9, 125.4, 125.5, 127.5, 128.2, 128.3, 135.1, 135.6, 139.6 (ArC); LRMS (EI) *m/z* 212 (M^+, 11%), 165 (12), 154 (71), 153 (100), 152 (32), 151 (11); HRMS (EI) calcd for $C_{15}H_{16}O$ 212.1201, found 212.1217.

Spiro[cyclohexane-1,9'-(9',10'-dihydro-7'*H*-8'-oxacyclohepta[*de*]naphthalene)] (9b)[13]: Pale yellow oil; R_f 0.46 (hexane/EtOAc: 10/1); IR ν (film) 3052, 3035 (ArH), 1064 cm^{-1} (COC); ^1H NMR (300 MHz, $CDCl_3$) δ 1.27-1.76 (10H, m, 5×CH_2), 3.29 (2H, s, CH_2CO), 5.05 (2H, s, CH_2O), 7.17-7.36 (4H, m, ArH), 7.68-7.72 (2H, m, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.4, 25.9, 36.1, 45.5 (CH_2), 66.7 (CH_2O), 78.0 (CO), 124.9, 125.3, 125.4, 127.4, 128.0, 128.1, 132.4, 135.1, 135.4, 140.0 (ArC); LRMS (EI) *m/z* 252 (M^+, 5%), 155 (15), 154 (100), 153 (63), 152 (21); HRMS (EI) calcd for $C_{18}H_{20}O$ 252.1514, found 252.1537.

ACKNOWLEDGEMENTS

This work was generously supported by the Spanish Ministerio de Educación y Ciencia (MEC; grants no. CSD2007-00006 and CTQ2004-01261). D.G. 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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