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Reaction of functionalized organolithium compounds with substituted oxiranes: useful methodology for 1,6- and 1,7-diols, and tetrahydrobenzoxepines

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This paper is dedicated to the memory of Professor Henry Rapoport

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Abstract—The reaction of dianions **2**, derived from the reductive opening of phthalan (**1a**) or isochroman (**1b**) with lithium and a catalytic amount of 4,4′-di-*tert*-butylbiphenyl (DTBB) at 0°C, with several epoxides **3** at the same temperature gave, after hydrolysis, 1,6- and 1,7-diols, respectively. Dehydration of 1,6-diols by treatment with $BF_3\cdot OEt_2$ in dichloromethane at temperatures ranging from −30 to 20°C gave tetrahydrobenzoxepines **5** in very good yields. Under the same reaction conditions 1,7-diols **4** did not undergo dehydration. © 2002 Elsevier Science Ltd. All rights reserved.

1. Introduction

Epoxides are important starting materials in synthetic organic chemistry.[1] They usually react with nucleophiles undergoing ring opening and acting as two-carbon homologation reagents. Among the possible nucleophiles, organolithium intermediates are adequate to produce primary alcohols when the simplest oxirane (ethylene oxide) is used as the nucleophilic component.[2] However, the corresponding reaction with substituted oxiranes is more susceptible to side-reactions, mainly those consequent on deprotonation giving labile lithiated epoxides,[3] α-functionalized organolithium compounds[4] (or d^1-reagents[5]), which undergo easy decomposition, for instance through rearrangement processes.[6] An additional problem arises when the organolithium intermediate is generated in situ because the residual amount of lithium reacts with the epoxide[7,8] giving a β-oxido functionalized organolithium compound.[4] This intermediate is very unstable and can decompose (by a β-elimination reaction[9] or abstracting a proton from the reaction medium, probably from the THF[10]) or compete with the organolithium reagent initially formed, depending on the reaction conditions used. In the last few years, we have been using an arene-catalyzed lithiation[11–15] to generate very reactive organolithium compounds under very mild reaction conditions, naphthalene and 4,4′-di-*tert*-butylbiphenyl (DTBB) being the electron-carriers most commonly used.[16] Thus, using this methodology we have been able (a) to prepare simple organolithium compounds starting from non-halogenated materials,[17] (b) to generate functionalized organolithium compounds,[4,8,18] (c) to generate dilithium synthons,[19] and (d) to activate other metals,[20] especially nickel.[21] In some cases, when the intermediates are too unstable (case (c)), it was necessary to perform the lithiation reaction in the presence of the electrophile (Barbier-type conditions[22]) in order to avoid decomposition of the corresponding lithium intermediate. In this paper we report the application of the mentioned arene-catalyzed lithiation to generate functionalized organolithium compounds by ring opening of phthalan[23] and isochroman[24] and to study the reaction of the generated intermediates with different substituted epoxides.

2. Results and discussion

The reaction of phthalan (**1a**)[23] or isochroman (**1b**)[24] with an excess of lithium powder (ca. 1:5 molar ratio) and a catalytic amount of DTBB (1:0.05 molar ratio; 2.5 mol%) in THF at 0°C led, after 45 min, to a solution of dianions **2**, which reacted with different epoxides **3** (1.5 equiv.) at the same temperature for 3 h yielding, after hydrolysis with water, the expected diols **4** (Scheme 1 and Table 1). The nucleophilic addition of organolithium compounds **2** takes place at the less hindered carbon atom of the epoxide ring in all cases, except for styrene oxide, where an almost 1/1 mixture of regioisomers was obtained, due to the competition between the benzylic and the terminal positions towards nucleophilic attack (Table 1, entries 4 and 9).

In the case of using the chiral epoxide **3g** as electrophile (easily prepared from D-fructose[25]), the enantiomerically

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Keywords: lithiation; oxiranes; lithium and compounds; diols; oxepanes.

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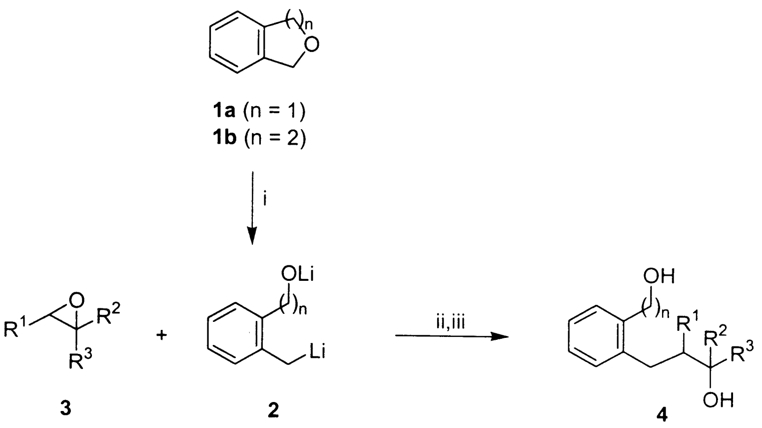


Scheme 1. *Reagents and conditions*: (i) Li, DTBB cat. (2.5 mol%), THF, 0°C, 45 min; (ii) 0°C, 3 h; (iii) H_2O, 0–20°C.

pure diol **4m** was obtained in moderate yield (Table 1, entry 11). In the same way, when we performed the reaction shown in Scheme 1 with (*S*)-propylene oxide (to yield diols **4a**′ from phthalan **1a** and **4g**′ from isochroman **1b**) and (*R*)-styrene oxide (to yield diols **4d**′+**4e**′ from phthalan **1a** and **4j**′+**4k**′ from isochroman **1b**), the corresponding enantiomerically pure diols (Fig. 1) being obtained in similar yields to those for racemic epoxides. For cyclohexene oxide, the *trans* diastereoisomers **4f** and **4l** were obtained as reaction products (Table 1, entries 5 and 10). The unequivocal assignment of the stereochemistry of these diols was performed by single-crystal analysis of compound **4f** (Fig. 2).[26]

We found diols **4** of interest because they can act as precursors of the corresponding oxygen-containing heterocycles by a dehydration process. Thus, treatment of compounds **4a–c**, **f**, derived from phthalan **1a**, with $BF_3 \cdot OEt_2$ in dichloromethane at temperatures ranging between −30 and 20°C[27] gave the corresponding tetrahydrobenzoxepines **5** in high yields (Scheme 2 and Table 2). For diol **4a**′, the process gave optically active compound **5a**′ (Fig. 3) with an optical purity >99.2% (determined by GLC with a chiral capillary column and compared with the chromatogram of racemic **5a**; see Section 4.1 for conditions and t_R values in Section 4.3). In the case of diol **4f**, we obtained **5f** (Table 2, entry 4) as a single diastereomer (^1H and ^{13}C NMR). We assume that the benzylic carbenium ion is the intermediate involved in the process, so the configuration of the stereogenic center (see below) is not modified along the cyclization.

The same mild dehydration reaction conditions failed for diols derived from isochroman **4g–i**, **l**, unreacted starting diol being recovered in all cases. Even dehydration to the desired eight-membered oxygen-containing heterocycles did not take place under Mitsunobu reaction conditions.[25] The presence of a hydroxyl group at benzylic position seems to be very important in the dehydration process, whether it takes place through an S_N2 reaction or through a carbocation intermediate. Finally, treatment of the mentioned diols with 85% phosphoric acid at toluene reflux gave complex mixtures of products resulting probably from rearrangement or elimination processes through the initially formed carbocations. Only in the case of diol **4l**, a significant amount of the spiro tetrahydrobenzoxepine **7** was obtained. Here, the initially formed secondary carbenium ion **6** undergoes transposition to the more stable tertiary one **6**′, which after final cyclization gave the corresponding product **7** (60% isolated; Scheme 3).

3. Conclusions

We reported here that substituted epoxides react efficiently with dianions derived from the reductive opening of phthalan **1a** and isochroman **1b**, to give 1,6- and 1,7-diols **4**, respectively. In the case of 1,6-diols, dehydration under

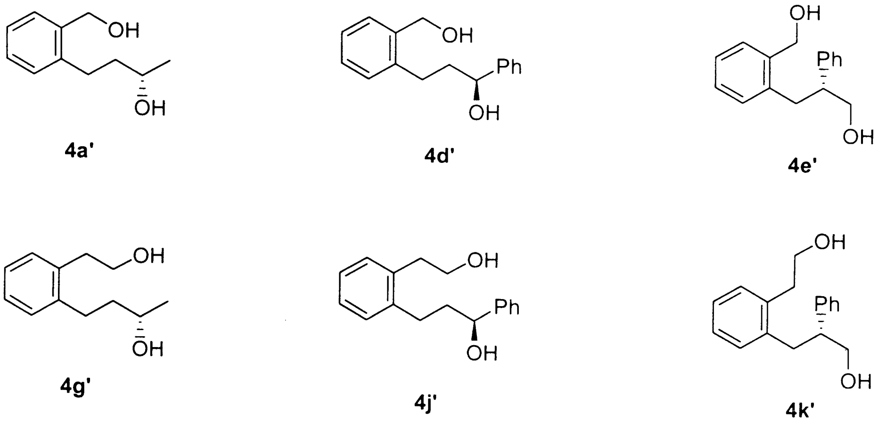
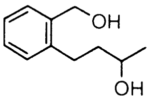
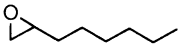
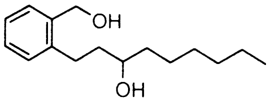
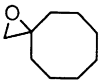
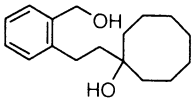
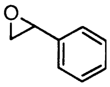
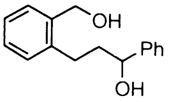
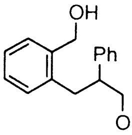
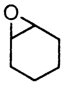
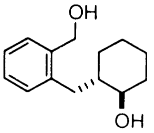
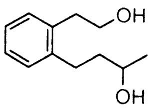
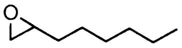
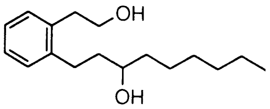
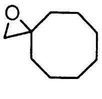
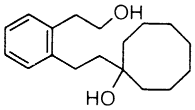
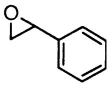
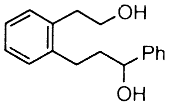
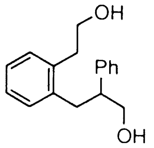
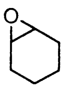
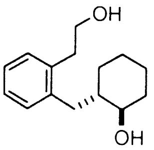
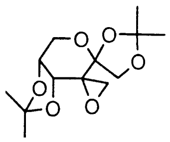
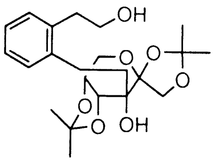


Figure 1.

Table 1. Preparation of diols **4**

Entry	Starting material **1**	Epoxide **3**		Product **4**			
		Structure	No.	Structure	No.	Yield (%)[a]	R_f[b]
1	**1a**		**3a**		**4a**	83	0.18 (1/1)
2	**1a**		**3b**		**4b**	52	0.10 (2/1)
3	**1a**		**3c**		**4c**	87	0.17 (2/1)
4	**1a**		**3d**		**4d**	80[c]	0.19 (2/1)
					**4e**		0.12 (2/1)
5	**1a**		**3f**		**4f**	89	0.07 (2/1)
6	**1b**		**3a**		**4g**	48	0.11 (1/1)
7	**1b**		**3b**		**4h**	75	0.14 (2/1)
8	**1b**		**3c**		**4i**	60	0.09 (2/1)
9	**1b**		**3d**		**4j**	83[c]	0.15 (2/1)
					**4k**		0.07 (2/1)
10	**1b**		**3f**		**4l**	79	0.09 (1/1)
11	**1b**		**3g**		**4m**	21	0.14 (2/1)

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[a] Isolated yield after column chromatography (silica gel, hexane/ethyl acetate) based on the starting material **1**.

[b] Silica gel, hexane/ethyl acetate ratio is given in parentheses.

[c] A ca. 1:1 mixture of regioisomers was obtained and separated by column chromatography.

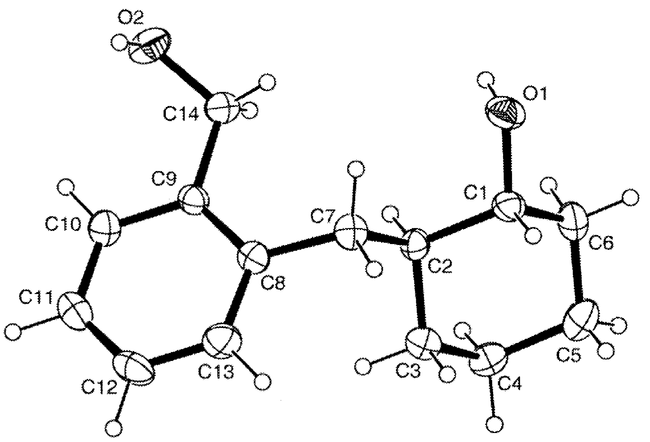
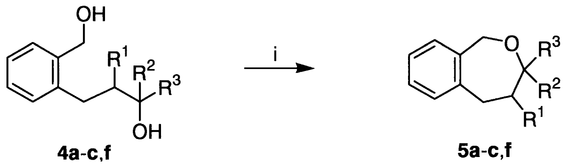
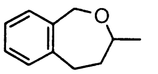
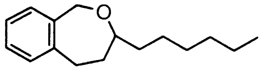
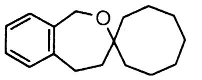
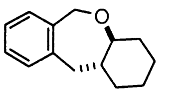


Figure 2.



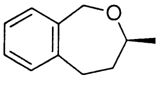
Scheme 2. *Reagents and conditions*: (i) $BF_3{\cdot}OEt_2$, CH_2Cl_2, −30 to 20°C.

Table 2. Preparation of benzoxepins **5** from diols **4**

Entry	Starting diol **4**	Product **5**			
		Structure	No.	Yield (%)[a]	R_f[b]
1	**4a**		**5a**	85	0.44
2	**4b**		**5b**	91	0.58
3	**4c**		**5c**	76	0.53
4	**4f**		**5f**	82	0.47

[a] Isolated yield after column chromatography (silica gel, hexane/ethyl acetate) based on the starting material **3**.

[b] Silica gel, hexane/ethyl acetate (10/1).



5a'

Figure 3.

mild reaction conditions with $BF_3{\cdot}OEt_2$ yields tetrahydrobenzoxepines **5**. This last methodology represents a bishomologation of the five-membered oxygen-containing heterocycle phthalan **1a**.

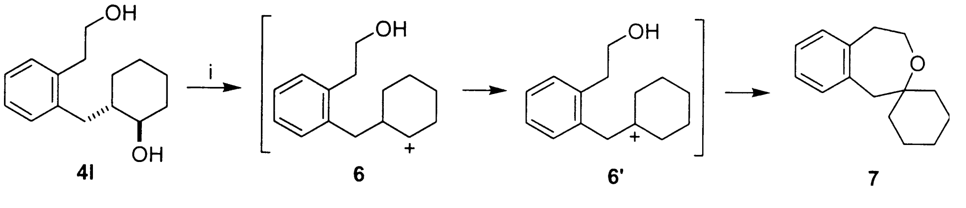
4. Experimental

4.1. General

All reactions were carried out under an atmosphere of nitrogen in oven-dried glassware. All reagents were commercially available and were used as received. THF was distilled from sodium benzophenone ketyl. Melting points were recorded in a Reichert Thermovar and are uncorrected. IR spectra were measured (neat) with a Nicolet Impact 400 D-FT Spectrometer. NMR spectra were recorded with a Bruker AC-300 using $CDCl_3$ as the solvent. LRMS and HRMS were measured with Shimadzu GC/MS QP-5000 and Finingan MAT95 S spectrometers, respectively. The purity of volatile products and the chromatographic analyses (GLC) were determined with a Hewlett-Packard HP-5890 instrument equipped with a flame ionization detector and a 12 m capillary column (0.2 mm diameter, 0.33 μm film thickness), using nitrogen (2 mL/min) as carrier gas, $T_{\text{injector}}=275°C$, $T_{\text{detector}}=300°C$, $T_{\text{column}}=80°C$ (3 min) and 80–270°C (15°C/min), $P=40$ kPa. The optical purity of compounds **5a** and **5a′** was determined with the aforementioned apparatus and a 50 m WCOT fused silica gel capillary column (0.25 mm diameter, 0.25 μm film thickness, FS-Lipodex-E) γ-CD, $T_{\text{injector}}=250°C$, $T_{\text{detector}}=260°C$, $T_{\text{column}}=110°C$ (5 min) and 110–180°C (1°C/min), $P=120$ kPa. Elemental analyses were performed by the Microanalyses Service at the University of Alicante. Specific rotations were determined with a Jasco DIP-1000 Digital Polarimeter. Single crystal analysis of **4f** was performed by the Crystallographic Service at the University of Santiago de Compostela.

4.2. Reductive lithiation of phthalan (1a) and isochroman (1b) and reaction with epoxides 3

Isolation of compounds **4**. *General procedure*. To a blue suspension of lithium powder (40 mg, 5.7 mmol) and a catalytic amount of DTBB (15 mg, 0.05 mmol; 2.5% molar) in THF (4 mL) was added phthalan (**1a**) or isochroman (**1b**) (1.0 mmol) at 0°C and the resulting mixture was stirred for 45 min at the same temperature. Then, the corresponding epoxide (**3**, 1.5 mmol) was added dropwise and stirring was continued for 3 h at 0°C. After that, the reaction mixture was hydrolyzed with water, extracted with ethyl acetate (3X20 mL) and the organic layer dried over anhydrous Na_2SO_4 and evaporated (15 Torr). The residue was purified



Scheme 3. *Reagents and conditions*: (i) H_3PO_4 (85%), $PhCH_3$, 110°C.

by column chromatography (silica gel, hexane/ethyl acetate) to yield pure products. Some yields and R_f values are given in Table 1, the rest of the yields as well as physical, analytical and spectroscopic data as follow.

4.2.1. 4-(2-Hydroxymethylphenyl)-2-butanol (4a). Colorless liquid; *ν* (film) 3677–3105 (OH), 3062, 3025 (ArH), 1135, 1006 cm^{-1} (CO); δ_H 1.11 (3H, d, *J*=6.2 Hz, C*H*$_3$CH), 1.66–1.73 (2H, m, C*H*$_2$CH), 2.73 (2H, t, *J*=7.3 Hz, ArC*H*$_2$CH$_2$), 3.60–3.66 (1H, m, C*H*OH), 4.12–4.14 (2H, m, 2×OH), 4.50 (1H, d, *J*=11.1 Hz, CH*H*OH), 4.60 (1H, d, *J*=11.1 Hz, C*H*HOH), 7.10–7.26 (4H, m, ArH); δ_C 23.7 (CH$_3$), 27.5 (*C*H$_2$CH), 40.1 (Ar*C*H$_2$), 62.7 (CH$_2$OH), 66.3 (CHOH), 125.8, 127.9, 129.1, 138.2, 140.5 (ArC); *m/z* 180 (M$^+$, 8%), 162 (17), 161 (12), 145 (13), 144 (51), 134 (19), 133 (22), 131 (11), 129 (62), 128 (11), 120 (56), 104 (24), 103 (14), 92 (34), 91 (93), 79 (25), 78 (19), 77 (49), 65 (25), 63 (11), 57 (19), 55 (12), 51 (25), 45 (78), 44 (32), 43 (74), 41 (19), 40 (46); HRMS: M$^+$−(H$_2$O) found 162.1027. $C_{11}H_{14}O$ requires 162.1045.

4.2.2. 1-(2-Hydroxymethylphenyl)-3-nonanol (4b). White solid, mp 53–54°C (pentane/dichloromethane); [Found: C, 76.41; H, 10.42. $C_{16}H_{26}O_2$ requires C, 76.75; H, 10.47]; *ν* (KBr) 3647–3121 (OH), 3064, 3020 (ArH), 1060, 1029 cm^{-1} (CO); δ_H 0.84–0.89 (3H, m, CH$_3$), 1.24–1.39 (10H, m, 5×CH$_2$), 1.61–1.70 (1H, m, C*H*H), 1.71–1.85 (1H, m, CH*H*), 2.79 (2H, t, *J*=7.5 Hz, ArC*H*$_2$CH$_2$), 3.46–3.48 (3H, m, C*H*OH, 2×OH), 4.55 (1H, d, *J*=12.2 Hz, ArC*H*HOH), 4.70 (1H, d, *J*=12.2 Hz, ArCH*H*OH), 7.12–7.28 (4H, m, ArH); δ_C 14.0 (CH$_3$), 22.5, 25.6, 27.4, 29.3, 31.7, 37.4, 38.3 (CH$_2$), 63.1 (CH$_2$OH), 70.4 (CHOH), 125.9, 128.0, 129.2, 129.3, 138.2, 140.7 (ArC); *m/z* 250 (M$^+$, 1%), 232 (12), 214 (32), 147 (23), 144 (12), 143 (18), 133 (31), 131 (12), 130 (35), 129 (100), 128 (20), 121 (12), 120 (99), 119 (62), 118 (97), 117 (98), 116 (17), 115 (21), 107 (11), 106 (11), 105 (99), 104 (25), 103 (11), 93 (15), 92 (37), 91 (84), 79 (16), 78 (12), 77 (37), 65 (13), 57 (23), 55 (68), 44 (12), 43 (89), 41 (64).

4.2.3. 1-[2-(2-Hydroxymethylphenyl)ethyl]cyclooctanol (4c). White solid, mp 105–106°C (dichloromethane/pentane); [Found: C, 77.31; H, 9.94. $C_{17}H_{26}O_2$ requires C, 77.82; H, 9.99]; *ν* (KBr) 3697–3015 (OH), 3007 (ArH), 1017 cm^{-1} (CO); δ_H 1.40–1.78 (16H, m, 7×CH$_2$, 2×OH), 2.74–2.77 (2H, m, CH$_2$C), 2.88–2.90 (2H, m, ArC*H*$_2$CH$_2$), 4.65–4.67 (2H, m, C*H*$_2$OH), 7.16–7.30 (4H, m, ArH); δ_C 22.3, 25.0, 26.0, 28.2, 36.0, 42.8 (CH$_2$), 63.1 (CH$_2$OH), 75.2 (COH), 125.9, 128.0, 129.0, 129.4, 138.1, 141.6 (ArC); *m/z* 244 [M$^+$−(H$_2$O), 4%], 226 (32), 169 (11), 160 (19), 155 (18), 145 (15), 143 (34), 142 (43), 141 (30), 131 (21), 130 (26), 129 (47), 128 (26), 127 (36), 121 (15), 120 (96), 119 (40), 118 (89), 117 (62), 116 (30), 115 (22), 109 (13), 105 (32), 104 (37), 93 (20), 91 (69), 83 (12), 81 (50), 79 (25), 78 (15), 77 (48), 69 (21), 67 (55), 65 (18), 57 (18), 55 (83), 53 (19), 51 (12), 43 (41), 42 (12), 41 (100).

4.2.4. 3-(2-Hydroxymethylphenyl)-1-phenyl-1-propanol (4d). White solid, mp 97–98°C (dichloromethane/pentane); [Found: C, 78.44; H, 7.41. $C_{16}H_{18}O_2$ requires C, 78.30; H, 7.49]; *ν* (KBr) 3682–3125 (OH), 3062, 3024 (ArH), 1039 cm^{-1} (CO); δ_H 2.02–2.11 (2H, m, C*H*$_2$CH), 2.27 (2H, br s, 2×OH), 2.83–2.88 (2H, m, C*H*$_2$CH$_2$), 4.59–4.61 (1H, m, C*H*), 4.60 (1H, d, *J*=12.2 Hz, C*H*HOH), 4.75 (1H, d, *J*=12.2 Hz, CH*H*OH), 7.19–7.31 (9H, m, ArH); δ_C 27.7 (*C*H$_2$CH), 40.3 (*C*H$_2$CH$_2$), 63.1 (CH$_2$OH), 72.7 (CH), 125.7, 126.1, 127.3, 128.1, 128.3, 129.1, 129.2, 138.3, 140.2, 144.4 (ArC); *m/z* 224 [M$^+$−(H$_2$O), 10%], 206 (46), 120 (39), 119 (24), 118 (74), 117 (100), 115 (26), 107 (21), 105 (37), 104 (17), 92 (12), 91 (66), 79 (38), 78 (14), 77 (47), 65 (14), 51 (19).

4.2.5. 3-(2-Hydroxymethylphenyl)-2-phenyl-1-propanol (4e). Colorless oil; *ν* (film) 3663–3125 (OH), 3062, 3024 (ArH), 1020 cm^{-1} (CO); δ_H 2.45 (2H, br s, 2×OH), 2.89 (1H, dd, *J*=14.0, 6.7 Hz, ArC*H*HCH), 2.98–3.11 (1H, m, CH), 3.28 (1H, dd, *J*=13.4, 7.9 Hz, ArCH*H*CH), 3.72 (1H, d, *J*=5.2 Hz, CHC*H*HOH), 4.51 (1H, d, *J*=12.2 Hz, ArC*H*HOH), 4.71 (1H, d, *J*=5.2 Hz, CHCH*H*OH), 4.74 (1H, d, *J*=12.2 Hz, ArCH*H*OH), 7.07–7.31 (9H, m, ArH); δ_C 34.1 (CH$_2$), 49.7 (CH), 63.3, 65.5 (CH$_2$O), 126.4, 126.8, 128.0, 128.6, 129.4, 130.1, 138.6, 138.65, 142.3 (ArC); *m/z* 242 (M$^+$, 0.2%), 224 (8), 206 (23), 194 (67), 193 (30), 191 (12), 180 (10), 179 (60), 178 (38), 165 (11), 133 (10), 121 (50), 120 (33), 119 (13), 116 (47), 115 (43), 105 (40), 104 (100), 103 (56), 93 (16), 92 (12), 91 (84), 89 (15), 79 (24), 78 (23), 77 (59), 65 (21), 51 (22), 44 (12), 43 (22), 40 (10); HRMS: M$^+$, found 242.1342. $C_{16}H_{18}O_2$ requires 242.1307.

4.2.6. (*R,*S**)-2-[(2-Hydroxymethylphenyl)methyl]-cyclohexanol (4f).** White solid, mp 128–129°C (dichloromethane/pentane); [Found: C, 75.72; H, 9.15. $C_{14}H_{20}O_2$ requires C, 76.33; H, 9.15]; *ν* (KBr) 3732–3040 (OH), 3021 (ArH), 1030 cm^{-1} (CO); δ_H 1.04–1.23 (4H, m, 2×CH$_2$), 1.53–2.04 (5H, m, 2×CH$_2$, CH), 2.32 (1H, dd, *J*=13.4, 8.5 Hz, ArC*H*H), 2.50 (2H, br s, 2×OH), 3.32–3.36 (2H, m, C*H*OH, ArCH*H*), 4.63 (1H, d, *J*=12.2 Hz, C*H*HOH), 4.81 (1H, d, *J*=12.2 Hz, CH*H*OH), 7.17–7.34 (4H, m, ArH); δ_C 24.9, 25.5, 31.2, 35.7, 35.9 (CH$_2$), 47.2 (*C*HCH$_2$), 63.5 (CH$_2$OH), 75.2 (CHOH), 126.2, 127.7, 129.4, 130.6, 138.5, 140.1 (ArC); *m/z* 220 (M$^+$, 4%), 202 (30), 201 (14), 184 (36), 169 (15), 155 (13), 145 (11), 143 (21), 142 (63), 141 (42), 133 (25), 131 (23), 130 (13), 129 (40), 128 (22), 121 (13), 120 (100), 119 (43), 118 (16), 117 (33), 116 (46), 115 (34), 105 (67), 104 (99), 103 (18), 93 (16), 92 (51), 91 (97), 81 (26), 79 (36), 78 (31), 77 (66), 69 (11), 67 (16), 65 (29), 57 (26), 55 (45), 53 (23), 51 (27), 44 (37), 43 (40), 42 (11), 41 (89), 40 (36).

4.2.7. 4-[2-(2-Hydroxyethyl)phenyl]-2-butanol (4g). Colorless liquid; *ν* (film) 3686–3108 (OH), 3059, 3015 (ArH), 1138, 1051 cm^{-1} (CO); δ_H 1.21 (3H, d, *J*=6.1 Hz, C*H*$_3$CH), 1.66–1.74 (2H, m, C*H*$_2$CH), 2.60–2.71 (1H, m, ArC*H*HCH$_2$CH), 2.75–2.87 (1H, m, ArCH*H*CH$_2$CH), 2.76 (2H, br s, 2×OH), 2.91 (2H, t, *J*=7.3 Hz, ArC*H*$_2$CH$_2$-OH), 3.80 (2H, t, *J*=7.3 Hz, C*H*$_2$OH), 3.83–3.86 (1H, m, C*H*OH), 7.14–7.16 (4H, m, ArH); δ_C 23.5 (CH$_3$), 28.75 (*C*H$_2$CH), 35.7, 40.5 (ArCH$_2$), 63.3 (CH$_2$OH), 67.5 (CHOH), 126.1, 126.6, 129.3, 129.8, 136.1, 140.6 (ArC); *m/z* 194 (M$^+$, 2%), 164 (23), 158 (39), 147 (10), 146 (24), 145 (20), 144 (12), 143 (59), 133 (27), 131 (49), 130 (17), 129 (40), 128 (14), 119 (16), 118 (46), 117 (81), 116 (19), 115 (37), 106 (30), 105 (100), 104 (68), 103 (22), 93 (13), 92 (19), 91 (82), 79 (20), 78 (21), 77 (38), 65 (17), 51 (21), 45 (57), 44 (26), 43 (61), 41 (17), 40 (34); HRMS: M$^+$−(H$_2$O) found 176.1199. $C_{12}H_{16}O$ requires 176.1201.

4.2.8. 1-[2-(2-Hydroxyethyl)phenyl]-3-nonanol (4h). Colorless oil; ν (film) 3615–3115 (OH), 3066, 3022 (ArH), 1054 cm^{-1} (CO); δ_H 0.85–0.87 (3H, m, CH$_3$), 1.21–1.44 (10H, m, 5×CH$_2$), 1.61–1.72 (2H, m, CH$_2$), 2.58–2.68 (1H, m, ArC*H*HCH$_2$CH), 2.81–2.90 (1H, m, ArCH*H*CH$_2$CH), 2.89 (2H, t, *J*=7.3 Hz, ArC*H*$_2$CH$_2$OH), 3.56–3.58 (3H, m, 2×OH, C*H*OH), 3.76 (2H, t, *J*=7.3 Hz, C*H*$_2$OH), 7.10–7.22 (4H, m, ArH); δ_C 13.9 (CH$_3$), 22.5, 25.6, 28.6, 29.2, 31.7, 35.7, 37.4, 38.8 (CH$_2$), 63.2 (CH$_2$OH), 71.4 (CHOH), 125.9, 126.4, 129.2, 129.7, 136.1, 140.7 (ArC); *m*/*z* 264 (M$^+$, 0.15%), 228 (15), 217 (10), 216 (22), 161 (14), 144 (14), 143 (69), 135 (13), 133 (31), 132 (15), 131 (41), 130 (39), 129 (38), 128 (13), 119 (46), 118 (65), 117 (92), 116 (14), 115 (29), 106 (33), 105 (100), 104 (66), 103 (18), 93 (13), 92 (19), 91 (73), 79 (15), 78 (12), 77 (20), 69 (18), 57 (26), 55 (50), 44 (29), 43 (75), 41 (60), 40 (15); HRMS: M$^+$−(H$_2$O) found 246.1992. $C_{17}H_{26}O$ requires 246.1984.

4.2.9. 1-{2-[2-(2-Hydroxyethyl)phenyl]ethyl}cyclooctanol (4i). Colorless oil; ν (film) 3639–3104 (OH), 3063, 3016 (ArH), 1045 cm^{-1} (CO); δ_H 1.26–1.81 (16H, m, 7×CH$_2$, 2×OH), 2.70–2.74 (2H, m, CH$_2$C), 2.91–2.95 (4H, m, 2×ArCH$_2$), 3.76–3.80 (2H, t, *J*=7.0 Hz, C*H*$_2$OH), 7.13–7.15 (4H, m, ArH); δ_C 22.3, 24.9, 26.4, 28.2, 35.9, 43.1 (CH$_2$), 63.3 (CH$_2$OH), 75.0 (COH), 125.9, 126.5, 129.4, 129.9, 136.1, 141.4 (ArC); *m*/*z* 258 [M$^+$−(H$_2$O), 9%], 227 (25), 207 (23), 169 (13), 155 (15), 143 (14), 141 (16), 135 (37), 133 (18), 131 (23), 130 (43), 129 (34), 128 (26), 123 (13), 119 (24), 118 (20), 117 (81), 116 (20), 115 (36), 105 (47), 104 (27), 103 (13), 96 (13), 95 (10), 93 (23), 91 (43), 82 (12), 81 (100), 79 (40), 78 (19), 77 (35), 69 (21), 67 (67), 65 (15), 55 (60), 53 (21), 51 (15), 44 (80), 43 (35), 41 (96), 40 (86); HRMS: M$^+$, found 276.2069. $C_{18}H_{28}O_2$ requires 276.2089.

4.2.10. 3-[2-(2-Hydroxyethyl)phenyl]-1-phenyl-1-propanol (4j). Colorless oil; ν (film) 3633–3109 (OH), 3063, 3022 (ArH), 1043 cm^{-1} (CO); δ_H 1.95–2.02 (2H, m, C*H*$_2$CH), 2.58–2.68 (1H, m, C*H*HCH$_2$CH), 2.74–2.85 (5H, m, CH*H*CH$_2$CH, C*H*$_2$CH$_2$OH, 2×OH), 3.68–3.73 (2H, t, *J*=7.0 Hz, C*H*$_2$OH), 4.61–4.66 (1H, m, C*H*OH), 7.11–7.30 (9H, m, ArH); δ_C 28.7, 35.7, 40.3 (CH$_2$), 63.2 (CH$_2$OH), 73.8 (CHOH), 125.8, 126.1, 126.6, 127.4, 128.4, 129.3, 129.8, 136.1, 140.3, 144.4 (ArC); *m*/*z* 256 (M$^+$, 1%), 221 (10), 220 (24), 208 (13), 207 (44), 206 (10), 205 (13), 193 (24), 191 (12), 133 (33), 131 (13), 130 (19), 129 (57), 128 (20), 120 (11), 118 (20), 117 (57), 116 (34), 115 (42), 107 (26), 106 (12), 105 (78), 104 (44), 103 (17), 92 (14), 91 (100), 79 (31), 77 (65), 75 (35), 65 (17), 51 (27), 44 (49), 43 (25), 40 (41); HRMS: M$^+$, found 256.1492. $C_{17}H_{20}O_2$ requires 256.1463.

4.2.11. 3-[2-(2-Hydroxyethyl)phenyl]-2-phenyl-1-propanol (4k). White solid, mp 59–60°C (dichloromethane/pentane); [Found: C, 78.74; H, 7.78. $C_{17}H_{20}O_2$ requires C, 78.65; H, 7.86]; ν (KBr) 3646–3095 (OH), 3064, 3027 (ArH), 1060, 1030 cm^{-1} (CO); δ_H 2.18 (2H, br s, 2×OH), 2.80–2.90 (3H, m, ArC*H*HCH, C*H*$_2$CH$_2$OH), 2.92–3.10 (1H, m, CH), 3.17 (1H, dd, *J*=13.7, 7.0 Hz, ArCH*H*CH), 3.75–3.83 (4H, m, 2×C*H*$_2$OH), 7.02–7.31 (9H, m, ArH); δ_C 35.3, 35.4 (CH$_2$), 49.7 (CH), 63.3, 66.1 (CH$_2$OH), 126.2, 126.3, 126.8, 128.0, 128.5, 129.7, 130.3, 135.4, 138.4, 142.0 (ArC); *m*/*z* 256 (M$^+$, 0.15%), 226 (23), 221 (16), 220 (24), 208 (17), 207 (24), 193 (18), 178 (19), 177 (12), 163 (10), 135 (30), 133 (22), 130 (11), 129 (33), 128 (12), 121 (38), 120 (26), 119 (12), 118 (22), 117 (63), 116 (17), 115 (33), 106 (14), 105 (54), 104 (100), 103 (48), 93 (13), 92 (13), 91 (95), 89 (12), 79 (24), 78 (20), 77 (47), 75 (20), 65 (15), 51 (17), 44 (29), 43 (41), 40 (26).

4.2.12. (*R,*S**)-2-{2-[2-(2-Hydroethyl)phenyl]ethyl}-cyclohexanol (4l).** White solid, mp 89–90°C (dichloromethane/pentane); [Found: C, 76.61; H, 9.61. $C_{15}H_{22}O_2$ requires C, 76.88; H, 9.46]; ν (KBr) 3669–3127 (OH), 3066, 3023 (ArH), 1049 cm^{-1} (CO); δ_H 0.90–1.04 (2H, m, CH$_2$), 1.23–1.29 (2H, m, CH$_2$), 1.42–1.46 (1H, m, C*H*H), 1.55–1.59 (1H, m, CH*H*), 1.65–1.70 (2H, m, CH$_2$), 1.98–2.04 (1H, m, C*H*CHOH), 2.11–2.19 (1H, m, ArC*H*HCH), 2.89–3.03 (2H, m, ArCH$_2$), 3.08–3.10 (2H, m, 2×OH), 3.29–3.31 (1H, m, C*H*OH), 3.40–3.45 (1H, m, ArCH*H*CH$_2$), 3.77–3.83 (2H, m, C*H*$_2$OH), 7.11–7.25 (4H, m, ArH); δ_C 25.0, 25.4, 30.3, 35.75, 35.8, 36.2 (CH$_2$), 46.6 (CH), 63.5 (CH$_2$OH), 75.1 (CHOH), 126.0, 126.1, 129.9, 130.9, 136.6, 139.4 (ArC); *m*/*z* 234 (M$^+$, 0.14%), 204 (12), 198 (47), 186 (26), 185 (19), 171 (11), 156 (12), 143 (23), 142 (11), 141 (14), 135 (15), 133 (17), 131 (12), 130 (28), 129 (45), 128 (19), 119 (18), 118 (73), 117 (90), 116 (22), 115 (33), 106 (45), 105 (100), 104 (57), 103 (16), 94 (12), 93 (12), 92 (15), 91 (67), 81 (41), 80 (22), 79 (30), 78 (16), 77 (27), 69 (11), 65 (14), 57 (20), 55 (36), 53 (14), 51 (11), 44 (20), 43 (29), 41 (57), 40 (22).

4.2.13. 3-*C*-[2-(2-Hydroxyethyl)phenyl]-1,2;4,5-di-*O*-isopropylidene-β-D-psicopyranose (4m). Colorless oil; ν (film) 3703–3137 (OH), 3063 (ArH), 1384, 1216, 1085 cm^{-1} (CO); δ_H 1.38, 1.41, 1.48, 1.63 (12H, 4s, 4×CH$_3$), 1.34–1.65 (2H, m, 2×OH), 1.82 (2H, t, *J*=8.5 Hz, C*H*$_2$COH), 2.83–2.99 (4H, m, 2×ArCH$_2$), 3.85 (2H, t, *J*=7.0 Hz, C*H*$_2$OH), 3.97 (1H, d, *J*=9.8 Hz, CC*H*HO), 4.08–4.29 (4H, m, C*H*C*H*C*H*$_2$), 4.37 (1H, d, *J*=9.8 Hz, CCH*H*O), 7.16–7.26 (4H, m, ArH); δ_C 25.4, 25.5, 26.0, 26.3 (CH$_3$), 26.7, 35.9, 37.5 (CH$_2$), 59.7 (CH$_2$OH), 63.4 (CH*C*H$_2$O), 71.5 (COH), 71.7 (CH), 72.3 (C*C*H$_2$O), 75.5 (CH), 107.1 (COH), 108.8, 112.3, 126.0, 126.7, 129.6, 129.8, 136.0, 141.3 (ArC); *m*/*z* 357 [M$^+$−(CH$_3$+2×H$_2$O), 0.63%], 253 (12), 251 (13), 57 (100), 43 (9), 41 (28); HRMS: M$^+$−(CH$_3$) found 393.1962. $C_{21}H_{29}O_7$ requires 393.1913; $[\alpha]_D^{20}$=−92.0 [*c*=0.88 (CH$_2$Cl$_2$)].

4.2.14. (*S*)-4-(2-Hydroxymethylphenyl)-2-butanol (4a′). Yield=78%; physical and spectroscopic data were found to be the same as for compound **4a**. $[\alpha]_D^{20}$=+41.1 [*c*=1.12 (CH$_2$Cl$_2$)].

4.2.15. (*S*)-3-(2-Hydroxymethylphenyl)-1-phenyl-1-propanol (4d′). Yield=37%; physical and spectroscopic data were found to be the same as for compound **4d**. $[\alpha]_D^{20}$=−26.9 [*c*=1.57 (CH$_2$Cl$_2$)].

4.2.16. (*S*)-3-(2-Hydroxymethylphenyl)-2-phenyl-1-propanol (4e′). Yield=35%; physical and spectroscopic data were found to be the same as for compound **4e**. $[\alpha]_D^{20}$=+53.1 [*c*=1.39 (CH$_2$Cl$_2$)].

4.2.17. (*S*)-4-[2-(2-Hydroxyethyl)phenyl]-2-butanol (4g′). Yield=57%; physical and spectroscopic data were found to be the same as for compound **4g**. $[\alpha]_D^{20}$=+20.9 [*c*=1.12 (CH$_2$Cl$_2$)].

4.2.18. (*S*)-3-[2-(2-Hydroxyethyl)phenyl]-1-phenyl-1-propanol (4j′). Yield=36%; physical and spectroscopic data were found to be the same as for compound **4j**. $[\alpha]_D^{20}=-14.1$ [*c*=1.50 (CH_2Cl_2)].

4.2.19. (*S*)-3-[2-(2-Hydroxyethyl)phenyl]-2-phenyl-1-propanol (4k′). Yield=41%; physical and spectroscopic data were found to be the same as for compound **4k**. $[\alpha]_D^{20}=+72.3$ [*c*=1.42 (CH_2Cl_2)].

4.3. Cyclization of diols 4

Isolation of compounds **5**. *General procedure*. Boron trifluoride etherate (87.6 mg, 0.076 ml, 0.6 mmol) was added dropwise to a solution of the corresponding diol **4** (0.5 mmol) in dichloromethane (5 mL) at −30°C. Stirring was continued for 10 h and the reaction mixture was allowed to reach ambient temperature. After that it was hydrolyzed with water, extracted with ethyl acetate (3×20 mL) and the organic layer dried over anhydrous Na_2SO_4 and evaporated (15 Torr). The residue was purified by column chromatography (silica gel, hexane/ethyl acetate) to yield pure products **5**. Some yields and R_f values are given in Table 2, other yields as well as physical, analytical and spectroscopic data follow.

4.3.1. 1,3,4,5-Tetrahydro-3-methyl-2-benzoxepin (5a). Colorless liquid, t_R 28.55 min (47.01%) and t_R 28.85 min (51.24%); ν (film) 3066, 3019 (ArH), 1099, 1003 cm^{-1} (CO); δ_H 1.25 (3H, d, *J*=6.1 Hz, C*H*$_3$CH), 1.50 (1H, ddd, *J*=12.2, 10.3, 1.8 Hz, C*H*HCH), 1.90 (1H, ddt, *J*=14.0, 6.7, 1.8 Hz, CH*H*CH), 2.85 (1H, ddd, *J*=15.3, 6.7, 1.8 Hz, ArC*H*HCH$_2$), 3.10 (1H, ddd, *J*=15.3, 12.2, 1.8 Hz, ArCH*H*CH$_2$), 3.85–3.95 (1H, m, C*H*O), 4.66 (1H, d, *J*=13.4 Hz, CH*H*O), 4.70 (1H, d, *J*=13.4 Hz, C*H*HO), 7.15–7.21 (4H, m, ArH); δ_C 22.8 (CH_3), 34.25, 36.5 (CH_2), 73.45 (CH_2O), 81.3 (CHO), 126.1, 127.8, 128.3, 128.9, 139.95, 142.3 (ArC); *m*/*z* 162 (M$^+$, 8%), 144 (33), 129 (11), 119 (10), 118 (47), 117 (100), 115 (21), 105 (14), 104 (12), 91 (37), 77 (11), 65 (17), 63 (12), 43 (24); HRMS: M$^+$ found 162.1034. $C_{11}H_{14}O$ requires 162.1044.

4.3.2. 3-Hexyl-1,3,4,5-tetrahydro-2-benzoxepin (5b). Colorless oil; ν (film) 3061, 3022 (ArH), 1088, 1031 cm^{-1} (CO); δ_H 0.88 (3H, t, *J*=6.7 Hz, CH_3), 1.25–1.59 (11H, m, 5×CH_2, ArCH$_2$C*H*H), 1.85–1.88 (1H, m, ArCH$_2$CH*H*), 2.86 (1H, ddd, *J*=14.7, 6.7, 1.8 Hz, ArCH*H*CH$_2$), 3.07 (1H, ddd, *J*=14.7, 12.2, 1.8 Hz, ArC*H*HCH$_2$), 3.65–3.73 (1H, m, C*H*O), 4.65 (1H, d, *J*=14.0 Hz, CH*H*O), 4.70 (1H, d, *J*=14.0 Hz, C*H*HO), 7.13–7.22 (4H, m, ArH); δ_C 14.05 (CH_3), 22.6, 25.8, 29.3, 31.8, 34.4, 35.0, 37.1 (CH_2), 73.6 (CH_2O), 85.4 (CHO), 126.05, 127.7, 128.3, 128.9, 140.1, 142.4 (ArC); *m*/*z* 232 (M$^+$, 1%), 147 (15), 129 (14), 119 (31), 118 (87), 117 (100), 115 (13), 105 (53), 91 (20), 55 (10), 43 (25); HRMS: M$^+$−(H_2O) found 214.1720. $C_{16}H_{22}$ requires 214.1721.

4.3.3. Spirocyclooctane-3-[1,3,4,5-tetrahydro-2-benzoxepin] (5c). Colorless oil; ν (film) 3068, 3017 (ArH), 1088 cm^{-1} (CO); δ_H 1.42–1.61 (12H, m, 6×CH_2), 1.73–1.77 (2H, m, ArCH$_2$C*H*$_2$), 1.84–1.91 (2H, m, CH_2), 2.82–2.86 (2H, m, ArC*H*$_2$CH$_2$), 4.57 (2H, s, ArCH$_2$O), 6.95–7.05 (4H, m, ArH); δ_C 22.0, 25.2, 28.4, 29.4, 32.4, 36.9 (CH_2), 64.5 (CH_2O), 79.8 (CO), 125.6, 126.9, 127.3, 129.3, 139.75, 140.8 (ArC); *m*/*z* 244 (M$^+$, 12%), 160 (29), 145 (15), 142 (16), 131 (16), 129 (16), 127 (11), 119 (21), 118 (100), 117 (92), 115 (20), 105 (30), 104 (34), 103 (12), 91 (30), 78 (12), 65 (12), 58 (15), 57 (16), 55 (60), 43 (22), 42 (13), 41 (62); HRMS: M$^+$ found 244.1817. $C_{17}H_{24}O$ requires 244.1827.

4.3.4. (*R,*S**)-4-Benzo-2-oxabicyclo[5.4.0]undec-4-ene (5f).** Colorless oil; ν (film) 3049, 3023 (ArH), 1082 cm^{-1} (CO); δ_H 1.26–1.39 (6H, m, 3×CH_2), 1.61–1.77 (2H, m, CH_2), 1.91–1.98 (1H, m, C*H*CHO), 2.56 (1H, d, *J*=14.0 Hz, ArCH*H*CH), 3.01 (1H, dd, *J*=14.0, 11.0 Hz, ArC*H*HCH), 3.33–3.41 (1H, m, CHO), 4.65 (1H, d, *J*=13.4 Hz, C*H*HO), 4.75 (1H, d, *J*=13.4 Hz, CH*H*O), 7.11–7.22 (4H, m, ArH); δ_C 25.1, 25.7, 33.5, 33.8, 43.2 (CH_2), 44.4 (*C*HCHO), 73.9 (CH_2O), 89.3 (CHO), 126.1, 127.85, 128.2, 129.1, 139.95, 141.8 (ArC); *m*/*z* 202 (M$^+$, 16%), 184 (39), 142 (40), 131 (18), 130 (11), 129 (29), 128 (18), 105 (71), 104 (100), 103 (19), 97 (15), 92 (30), 91 (45), 79 (12), 78 (33), 77 (23), 65 (18), 55 (16), 51 (15), 41 (47); HRMS: M$^+$ found 202.1346. $C_{14}H_{18}O$ requires 202.1357.

4.3.5. (*S*)-1,3,4,5-Tetrahydro-3-methyl-2-benzoxepin (5a′). Yield=84%; t_R 28.77 min (99.23%); physical and spectroscopic data were found to be the same as for compound **5a**. $[\alpha]_D^{20}=+19.3$ [*c*=1.40 (CH_2Cl_2)].

4.4. Cyclization of diol 4l

Isolation of compound **7**. To a solution of diol **4l** (0.117 g, 0.5 mmol) in toluene (5 mL) was added 85% phosphoric acid (0.3 mL). The reaction mixture was heated at 110°C for 4 h, then the reaction mixture was hydrolyzed with water and extracted with ethyl acetate (3×20 mL). The organic layer was dried over anhydrous Na_2SO_4 and evaporated (15 Torr). The resulting residue was purified by column chromatography (silica gel; hexane/ethyl acetate) to yield pure product **7**. Yield is given in the text. Spectroscopic data and literature reference follow.

4.4.1. Spirocyclohexane-2-[1,2,4,5-tetrahydro-3-benzoxepin] (7).[24] Colorless oil; ν (film) 3040, 3010 (ArH), 1030 cm^{-1} (CO); δ_H 1.23–1.62 (10H, m, 5×CH_2), 2.91 (2H, s, ArCH$_2$C), 2.93–2.96 (2H, m, ArC*H*$_2$CH$_2$), 3.76–3.79 (2H, m, CH_2O), 6.99–7.13 (4H, m, ArH); δ_C 21.7, 25.9, 34.8, 39.0, 42.8 (CH_2), 61.4 (CH_2O), 73.3 (CO), 126.1, 126.3, 128.7, 130.0, 138.3, 140.9 (ArC); *m*/*z* 216 (M$^+$, 19%), 119 (27), 118 (100), 117 (96), 115 (24), 91 (18), 41 (12).

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