Base-Mediated Ring Expansion Reactions, III[1]

A New Route from Dihydroisoquinolines to 2-Benzazepines

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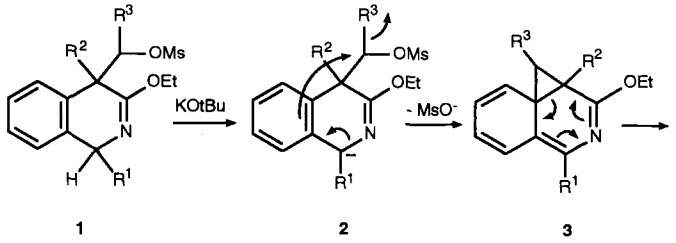
Received June 9, 1992

Key Words: 2-Benzazepines / Ring expansion

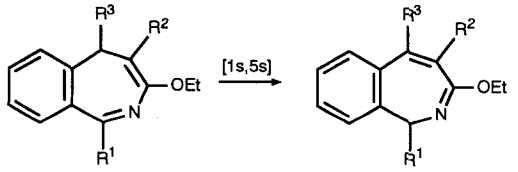
The substituted 2-benzazepines **4**, **5** and **12** were prepared by a base-mediated ring expansion reaction of mesylates **1a–e**, which were synthesized in 4 to 5 steps by starting from benzolactams **6**.

In the course of our investigations of base-mediated ring expansion reactions of 1,4-dihydroarenes[1,2], we were interested in the preparation of mesylates **1a–e**, which should form the 2-benzazepines **5a–e** upon treatment with potassium *tert*-butoxide in DMSO (Scheme 1).

Scheme 1



1 **2** **3**



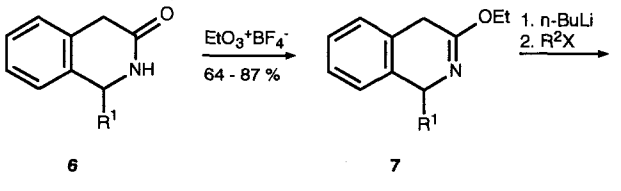
4 **5**

1-5	R^1	R^2	R^3
a	H	CH_3	H
b	C_6H_5	CH_3	H
c	C_6H_5	$CH_2C_6H_5$	H
d	H	CH_3	CH_3
e	C_6H_5	CH_3	CH_3

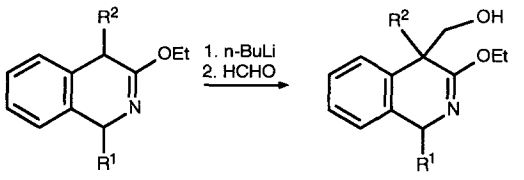
The synthesis of mesylates **1a–e** was accomplished in 4 to 5 steps starting from benzolactams **6a**, **b**[3]. After *O*-alkylation of lactams **6a**, **b** with triethyloxonium tetrafluoroborate, imino ethers **7a**, **b** were obtained. Lithiation and alkylation with methyl iodide afforded the substituted imino ethers **8a**, **b**, which were transformed into the primary alcohols **9a**, **b** by lithiation and hydroxymethylation with paraformaldehyde. The primary alcohol **9c** was prepared by the same method from imino ether **7b** by use of benzyl bromide for the alkylation step (Scheme 2).

The secondary alcohols **9d**, **e** were prepared in a different way. After lithiation and acylation of the imino ethers **8a** or **8b**, ketones **10a–d** were obtained. Reduction with sodium tetrahydroborate furnished the secondary alcohols **9d**, **e**, whereas **9f**, **g** underwent retro-aldol cleavage to yield imino ether **8a** and the corresponding aldehydes[4] (Scheme 3).

Scheme 2



6 **7**



8 **9**

6-9	R^1	R^2	yield of **8** (%)	yield of **9** (%)
a	H	CH_3	81	37
b	C_6H_5	CH_3	84	39
c	C_6H_5	$CH_2C_6H_5$	60	35

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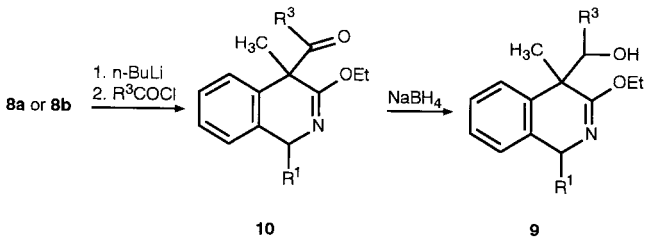
The alcohols **9a–e** were converted into the mesylates **1a–e** with methanesulfonyl chloride and triethylamine.

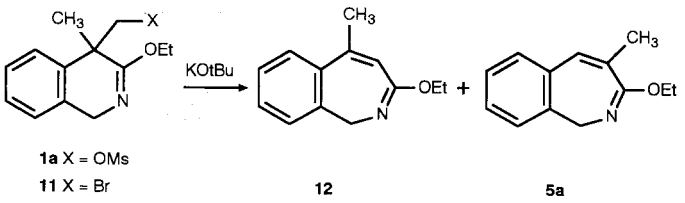
Scheme 3



8	9	10	R^1	R^3	yield of **10** (%)	yield of **9** (%)
a	d	a	H	CH_3	74	67
b	e	b	C_6H_5	CH_3	75	58
a	f	c	H	$C(CH_3)_3$	68	-
a	g	d	H	C_6H_5	80	-

After reaction of the mesylate **1a** with potassium *tert*-butoxide in DMSO, the 2-benzazepines **5a** and **12** were obtained in a 1:3 ratio (Scheme 4)[5].

Scheme 4

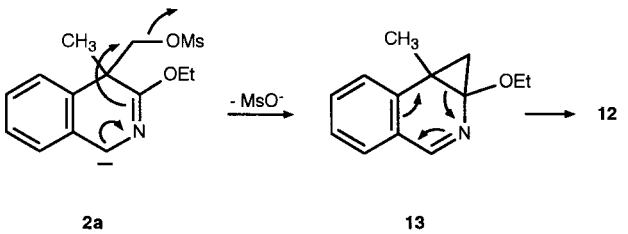


	X	yield of **12** (%)	yield of **5a** (%)
1a	OMs	71	23
11	Br	67	21

Formation of the major product **12** can be rationalized by ring expansion via the pathway indicated in Scheme 5, i.e. via the intermediate **13**, followed by the electrocyclic azanorcaradiene-azacycloheptene rearrangement[6] and a transannular [1s,5s] sigmatropic hydrogen shift[7]. This pathway has not been observed for ring expansion reactions of 2,5-dihydropyrazines to 2*H*-1,4-diazepines[8].

We assume that the minor product **5a** is formed via the expected pathway (Scheme 1). A change of the leaving group from mesylate to bromide[9] had no significant effect on either the ratio or the yield of the products (Scheme 4).

Scheme 5



The 1-phenyl-substituted dihydroisoquinolines **1b** and **1c** reacted exclusively via the usual pathway (Scheme 1). However, the phenyl substituent in position 1 apparently enhances the activation energy for the transannular [1s,5s] sigmatropic hydrogen shift reactions of **4b** and **4c**, possibly by stabilizing the conjugated C=N bond and consequently the ground state of the 2-benzazepines **4b** and **4c**. Thus, **1b** was converted into a 82:18 mixture of **4b** and **5b**, whereas the reaction of **1c** afforded exclusively **4c**.

As expected, the transannular [1s,5s] sigmatropic hydrogen shift reactions of **4b** and **4c** proceeded smoothly at higher temperatures[10]. Both compounds **4b** and **4c** were completely converted into the 2-benzazepines **5b** or **5c** by heating to 150°C for 10 min. The irreversible transannular [1s,5s] sigmatropic hydrogen shift of **4b** to **5b** was monitored kinetically[11] and proceeded with a rate constant of $k = (0.594 +/- 0.010) \cdot 10^{-4}\ s^{-1}$ at 85°C and $k = (2.448 +/- 0.027) \cdot 10^{-4}\ s^{-1}$ at 99°C. The rate for this [1s,5s] sigmatropic hydrogen shift is much faster than the analogous isomerization of the all-carbon analogue[2,12].

After reaction of the mesylates **1d, e** with potassium *tert*-butoxide in DMSO, the 2-benzazepines **5d, e** were obtained. Since $R^2 = R^3$ in **1d** and **1e**, both reactions pathways (Scheme 1 and Scheme 5) gave the same products. Which one of the two possible pathways prevails could not be determined by the available experimental data.

Financial support by the *Stiftung Volkswagenwerk* is gratefully acknowledged. We thank the *BASF AG*, the *Hoechst AG* and the *Degussa AG* for providing valuable starting materials. We thank Dr. *Thomas Gadek* and Dr. *Kirk Robarge*, Genentech Inc., for the correction of this manuscript.

Experimental

The benzolactams **6** were prepared according to ref.[3]. – Infrared (IR) spectra were obtained by using a Perkin-Elmer 298 spectrometer. – NMR spectra were obtained by using a Varian XL 200, a VXR 200 or a VXR 500 S spectrometer for ^1H and ^{13}C NMR. Chemical shifts are given in δ values by using tetramethylsilane as internal standard for ^1H and ^{13}C NMR. – Mass spectra were recorded with a Varian MAT 731 or 311a spectrometer. – Melting points are uncorrected. – TLC analyses were performed on Polygram Sil G/UV$_{254}$ silica gel plates. Silica gel (30–60 μm) from Baker was used for flash chromatography. – Combustion analyses were carried out by the microanalytical laboratory at the University of Göttingen. – All reagents were purified and dried if necessary prior to use. All reactions with metallorganic reagents were performed in anhydrous solvents under dry nitrogen.

Preparation of the Imino Ethers **7**. – *General Procedure:* A solution of the benzolactams **6** (0.1 mol) and triethyloxonium tetrafluoroborate (28.5 g, 0.15 mol) in dry dichloromethane (300 ml) was stirred for 2 d at 25°C. Then, a solution of $Na_2HPO_4 \cdot 2\ H_2O$ (53.4 g, 0.3 mol) and $NaH_2PO_4 \cdot 2\ H_2O$ (15.6 g, 0.1 mol) in water (250 ml) was added, and the organic layer was separated. The aqueous layer was reextracted with dichloromethane (3 portions of 50 ml each), and the combined organic layers were dried with $MgSO_4$. The solvent was removed in vacuo and the residue purified by flash chromatography on silica gel (150 g) with diethyl ether/petroleum ether (1:5).

3-Ethoxy-1,4-dihydroisoquinoline (**7a**): From 14.7 g of **6a** 11.2 g (64%) of **7a** was obtained; R_f = 0.29. – IR (neat): $\tilde{\nu}$ = 1680 cm^{-1} (C=N). – ^1H NMR ($CDCl_3$): δ = 1.30 (t, *J* = 7 Hz; 3H, CH_3), 3.37 (t, *J* = 3 Hz; 2H, 4-H_2), 4.15 (q, *J* = 7 Hz; 2H, OCH_2), 4.65 (t, *J* = 3 Hz; 2H, 1-H_2), 7.15 (s; 4H, arom. H). – ^{13}C NMR ($CDCl_3$): δ = 14.38 (CH_3), 30.19 (C-4), 51.16 (C-1), 60.85 (OCH_2), 125.31, 126.54 and 127.30 (arom. CH), 131.24 and 134.07 (arom. C), 163.07 (C=N). – MS (70 eV): *m/z* (%) = 175 (12) [M^+], 146 (5) [M^+ – C_2H_5], 118 (15) [M^+ – COC_2H_5], 104 (14) [M^+ – $NCOC_2H_5$], 91 (100) [$C_7H_7^+$].

$C_{11}H_{13}NO$ (175.2) Calcd. C 75.41 H 7.49
Found C 75.53 H 7.52

3-Ethoxy-1,4-dihydro-1-phenylisoquinoline (**7b**): From 22.3 g of **6b** 21.8 g (87%) of **7b** was obtained; R_f = 0.34. – IR (neat): $\tilde{\nu}$ = 1670 cm^{-1} (C=N). – ^1H NMR ($CDCl_3$): δ = 1.29 (t, *J* = 7 Hz; 3H, CH_3), 3.46 (d, *J* = 3 Hz; 2H, 4-H_2), 4.19 (q, *J* = 7 Hz; 2H, OCH_2), 5.76 (t, *J* = 3 Hz; 1H, 1-H), 7.05–7.25 (m; 9H, arom. H). – ^{13}C NMR ($CDCl_3$): δ = 14.36 (CH_3), 30.72 (C-4), 61.17 (OCH_2), 64.39 (C-1), 126.66, 126.74, 126.82, 127.34, 127.54 and 128.37 (arom.CH), 130.88, 137.43 and 143.95 (arom. C), 163.30 (C=N). – MS (70 eV): *m/z* (%) = 251 (100) [M^+], 222 (62) [M^+ – C_2H_5], 206 (15) [M^+ – OC_2H_5], 194 (24) [M^+ – COC_2H_5], 180 (18) [M^+ – $NCOC_2H_5$], 174 (51) [M^+ – C_6H_5], 91 (60) [$C_7H_7^+$], 77 (12) [$C_6H_5^+$].

$C_{17}H_{17}NO$ (251.3) Calcd. C 81.25 H 6.83
Found C 81.34 H 6.78

Alkylation of the Imino Ethers **7** *to Compounds* **8**. – *General Procedure:* To a stirred solution of the imino ether **6a** or **6b** (50 mmol) in THF (150 ml) a solution of *n*-butyllithium in hexane (1.6 N, 34.4 ml, 55 mmol) was added dropwise at –70°C. The solution was stirred at –70°C for 15 min and 53 mmol of the alkylating agent was added dropwise. Stirring was continued for 1 h at –70°C and for 10 min at room temp., and the solvent was removed in vacuo. The residue was dissolved in diethyl ether (100 ml) and washed with water (100 ml). The aqueous layer was reextracted with diethyl ether (3 portions of 50 ml each), and the combined organic layers were dried with $MgSO_4$. The solvent was removed in vacuo, and the crude product was purified by flash chromatography on silica gel (150 g) with diethyl ether/petroleum ether (1:5).

3-Ethoxy-1,4-dihydro-4-methylisoquinoline (**8a**): From 8.76 g of **7a** and 3.3 ml (53 mmol) of methyl iodide 7.7 g (81%) of **8a** was obtained; R_f = 0.31. – IR (neat): $\tilde{\nu}$ = 1670 cm^{-1} (C=N). – ^1H NMR ($CDCl_3$): δ = 1.28 (t, *J* = 7 Hz; 3H, CH_2CH_3), 1.35 (d, *J* = 10 Hz; 3H, 4-CH_3), 3.25–3.59 (m; 1H, 4-H), 4.13 (q, *J* = 7 Hz; 2H, OCH_2), 4.65 (d, *J* = 2 Hz; 2H, 1-H_2), 7.12 (s; 4H, arom. H). – ^{13}C NMR ($CDCl_3$): δ = 14.38 (CH_2CH_3), 19.58 (4-CH_3), 35.57 (C-4), 50.42 (C-1), 60.95 (OCH_2), 125.30, 126.33, 126.52 and 126.84 (arom. CH), 133.80 and 137.44 (arom. C), 166.55 (C=N). – MS (70 eV): *m/z* (%) = 189 (48) [M^+], 174 (4) [M^+ – CH_3], 160 (20) [M^+ – C_2H_5], 144 (15) [M^+ – OC_2H_5], 132 (12) [M^+ – COC_2H_5], 118 (100) [M^+ – $NCOC_2H_5$], 91 (16) [$C_7H_7^+$], 77 (12) [$C_6H_5^+$].

$C_{12}H_{15}NO$ (189.3) Calcd. C 76.13 H 8.00
Found C 76.17 H 7.96

3-Ethoxy-1,4-dihydro-4-methyl-1-phenylisoquinoline (**8b**): From 12.57 g of **7b** and 3.3 ml (53 mmol) of methyl iodide 11.2 g (84%) of **8b** was obtained as a 1:1 mixture of diastereomers; R_f = 0.51 and 0.57. – IR (neat): $\tilde{\nu}$ = 1670 cm^{-1} (C=N). – ^1H NMR ($CDCl_3$): δ = 1.28 (t, *J* = 7 Hz; 3H, CH_2CH_3), 1.42 and 1.46 (d, *J* = 7 Hz; 3H, 4-CH_3), 3.38–3.59 (m; 1H, 4-H), 4.18 and 4.17 (q, *J* = 7 Hz; 2H, OCH_2), 5.83 and 5.63 (d, *J* = 2 Hz; 1H, 1-H), 7.10–7.25 (m; 9H, arom. H). – ^{13}C NMR ($CDCl_3$): δ = 14.37 (CH_2CH_3), 20.97 and 19.08 (4-CH_3), 34.68 and 35.72 (C-4), 60.90 and 61.10 (OCH_2), 63.85 and 62.82 (C-1), 126.23, 126.28, 126.67, 126.76, 126.86, 127.54, 128.23 and 128.31 (arom. CH), 136.79, 137.14, 144.51 and 136.14, 137.48, 144.32 (arom. C), 165.89 and 165.38 (C=N). – MS (70 eV): *m/z* (%) = 265 (100) [M^+], 250 (14) [M^+ – CH_3], 236 (60) [M^+ – C_2H_5], 220 (7) [M^+ – OC_2H_5], 208 (25) [M^+ – COC_2H_5], 194 (11) [M^+ – $NCOC_2H_5$], 188 (43) [M^+ – C_6H_5], 91 (22) [$C_7H_7^+$], 77 (18) [$C_6H_5^+$].

$C_{18}H_{19}NO$ (265.4) Calcd. C 81.45 H 7.23
Found C 81.52 H 7.28

4-Benzyl-3-ethoxy-1,4-dihydro-1-phenylisoquinoline (**8c**): 12.57 g of **7b** and 6.5 ml (55 mmol) of benzyl bromide were used. After an extended reaction time of 12 h at –70°C and flash chromatography on silica gel (150 g) with diethyl ether/petroleum ether (1:10), 10.2 g (60%) of **8c** was obtained as a 1:1 mixture of diastereomers; R_f = 0.39 and 0.52. – IR (neat): $\tilde{\nu}$ = 1670 cm^{-1} (C=N). – ^1H NMR ($CDCl_3$): δ = 1.26 and 1.25 (t, *J* = 7 Hz; 3H, CH_3), 2.80–3.15 (m; 2H, $CH_2C_6H_5$), 3.58–3.92 (m; 1H, 4-H), 4.13 and 4.14 (q, *J* = 7 Hz; 2H, OCH_2), 4.19 and 5.82 (d, *J* = 2 Hz; 1H, 1-H), 6.65–7.28 (m; 14H, arom. H). – ^{13}C NMR ($CDCl_3$): δ = 14.39 and 14.38 (CH_3), 40.38 and 40.55 ($CH_2C_6H_5$), 43.57 and 42.20 (C-4), 61.00 (OCH_2), 62.39 and 63.69 (C-1), 126.23–130.86 (20 arom. CH), 134.68, 137.62, 138.98, 144.27 and 134.12, 136.41, 138.47, 144.40 (arom. C), 163.96 and 163.98 (C=N). – MS (70 eV): *m/z* (%) = 341 (5) [M^+], 312 (2) [M^+ – C_2H_5)], 264 (8) [M^+ – C_6H_5], 250 (100) [M^+ – $CH_2C_6H_5$], 91 (94) [$C_7H_7^+$], 77 (11) [$C_6H_5^+$].

$C_{24}H_{23}NO$ (341.5) Calcd. C 84.40 H 6.80
Found C 84.32 H 6.76

Preparation of the Primary Alcohols **9a–c**. – *General Procedure:* To a stirred solution of the substituted imino ether **8a**, **8b** or **8c** (20 mmol) in THF (100 ml) a solution of *n*-butyllithium in hexane (1.6 N, 13.8 ml, 22 mmol) was added dropwise at –70°C. After stirring for 15 min at this temp., paraformaldehyde (3.0 g, 100 mmol) was added and stirring was continued for 15 h at –40°C. The reaction mixture was poured into a solution of $NaH_2PO_4 \cdot 2\,H_2O$ (9.4 g, 60 mmol) and $Na_2HPO_4 \cdot 2\,H_2O$ (3.6 g, 20 mmol) in water (50 ml). The solvent was removed in vacuo, the residue dissolved in diethyl ether (50 ml) and washed with water (100 ml). The aqueous layer was reextracted with diethyl ether (3 portions of 30 ml each), and the combined organic layers were dried with $MgSO_4$. The solvent was removed in vacuo, and the crude product was purified by flash chromatography on silica gel (50 g) with diethyl ether/petroleum ether (2:1).

3-Ethoxy-1,4-dihydro-4-hydroxymethyl-4-methylisoquinoline (**9a**): From 3.79 g of **8a** 1.6 g (37%) of **9a** was obtained; R_f = 0.23. – IR (neat): $\tilde{\nu}$ = 3500–3200 (OH), 1670 cm^{-1} (C=N). – ^1H NMR ($CDCl_3$): δ = 1.31 (t, *J* = 7 Hz; 3H, CH_2CH_3), 1.43 (s; 3H, 4-CH_3), 2.30 (br.; 1H, OH), 3.72 and 3.98 (AB system, J_{AB} = 11 Hz; 2H, CH_2OH), 4.14 (q, *J* = 7 Hz; 2H, OCH_2), 4.70 (s; 2H, 1-H), 7.05–7.34 (m; 4H, arom. H). – ^{13}C NMR ($CDCl_3$): δ = 14.31 (CH_2CH_3), 21.79 (4-CH_3), 43.11 (C-4), 50.15 (C-1), 61.02 (OCH_2), 69.20 (CH_2OH), 124.84, 125.23, 126.54 and 127.02 (arom. CH), 134.35 and 136.85 (arom. C), 164.20 (C=N). – MS (70 eV): *m/z* (%) = 219 (6) [M^+], 202 (27) [M^+ – OH], 201 (35) [M^+ – H_2O], 188 (77) [M^+ – CH_2OH], 91 (16) [$C_7H_7^+$], 77 (16) [$C_6H_5^+$].

$C_{13}H_{17}NO_2$ (219.3) Calcd. C 71.20 H 7.83
Found C 71.29 H 7.78

3-Ethoxy-1,4-dihydro-4-hydroxymethyl-4-methyl-1-phenylisoquinoline (**9b**): From 5.31 g of **8b** 2.3 g (39%) of **9b** was obtained; R_f = 0.39. – IR (neat): $\tilde{\nu}$ = 3500–3200 (OH), 1670 cm^{-1} (C=N). – ^1H NMR ($CDCl_3$): δ = 1.27 (t, *J* = 7 Hz; 3H, CH_2CH_3), 1.52 (s; 3H, 4-CH_3), 1.95 (br.; 1H, OH), 3.78 and 4.07 (AB system, J_{AB} =

11 Hz; 2H, CH_2OH), 4.17 (q, J = 7 Hz; 2H, OCH_2), 5.82 (s; 1H, 1-H), 6.90–7.35 (m; 9H, arom. H). – ^{13}C NMR ($CDCl_3$): δ = 14.26 (CH_2CH_3), 23.35 (4-CH_3), 42.66 (C-4), 61.00 (OCH_2), 63.13 (C-1), 69.45 (CH_2OH), 124.83, 126.36, 126.79, 127.05, 127.18, 127.93 and 128.31 (arom. CH), 136.48, 137.04 and 145.15 (arom. C), 163.30 (C=N). – MS (70 eV): m/z (%) = 295 (4) [M^+], 278 (10) [M^+ – OH], 277 (22) [$M^+ - H_2O$], 264 (100) [$M^+ - CH_2OH$], 218 (9) [$M^+ - C_6H_5$], 91 (12) [$C_7H_7^+$], 77 (14) [$C_6H_5^+$].

$C_{19}H_{21}NO_2$ (295.4) Calcd. C 77.25 H 7.18
Found C 77.36 H 7.12

4-Benzyl-3-ethoxy-1,4-dihydro-4-hydroxy-1-phenylisoquinoline (**9c**): From 6.83 g of **8c** 2.6 g (35%) of **9c** was obtained; R_f = 0.42. – IR (neat): ṽ = 3500–3200 (OH), 1670 cm^{-1} (C=N). – ^1H NMR ($CDCl_3$): δ = 1.37 (t, J = 7 Hz; 3H, CH_3), 1.78 (br.; 1H, OH), 3.05 and 3.50 (AB system, J_{AB} = 13 Hz; 2H, $CH_2C_6H_5$), 3.80–4.37 (m; 4H, CH_2OH and OCH_2), 5.64 (s; 1H, 1-H), 6.08–6.25 and 6.67–7.54 (2 m; 14H, arom. H). – ^{13}C NMR ($CDCl_3$): δ = 14.45 (CH_3), 40.90 ($CH_2C_6H_5$), 48.90 (C-4), 60.81 (OCH_2), 63.29 (C-1), 70.73 (CH_2OH), 125.51, 126.49, 126.89, 127.68, 128.03, 128.08, 128.20 and 130.32 (arom. CH), 132.81, 136.95, 138.09 and 144.75 (arom. C), 159.88 (C=N). – MS (70 eV): m/z (%) = 91 (15) [$C_7H_7^+$], 77 (23) [$C_6H_5^+$].

$C_{25}H_{25}NO_2$ (371.5) Calcd. C 80.82 H 6.80
Found C 80.74 H 6.73

Acylation of the Imino Ethers **8a** *and* **8b** *to Compounds* **10**. – *General Procedure:* A solution of *n*-butyllithium in hexane (1.6 N, 13.8 ml, 22 mmol) was added to a stirred solution of the substituted imino ether **8a** or **8b** (20 mmol) in THF (60 ml) at –70°C. After stirring for 15 min, the mixture was added dropwise to a solution of the acyl chloride (100 mmol) in THF (30 ml) at –70°C. Stirring was continued for 1 h at this temp. and for 10 min at 25°C. The solvent was removed in vacuo, and the residue was dissolved in diethyl ether (100 ml) and washed with a 10% aqueous Na_2CO_3 solution (100 ml). The aqueous layer was reextracted with diethyl ether (3 portions of 30 ml each), and the combined organic layers were dried with $MgSO_4$. The solvent was removed in vacuo and the residue purified by flash chromatography on silica gel (100 g) with diethyl ether/petroleum ether (1:5).

4-Acetyl-3-ethoxy-1,4-dihydro-4-methylisoquinoline (**10a**): From 3.79 g (20 mmol) of **8a** and 7.9 g of acetyl chloride 3.42 g (74%) of **10a** was obtained; R_f = 0.25. – IR (neat): ṽ = 1720 (C=O), 1680 cm^{-1} (C=N). – ^1H NMR ($CDCl_3$): δ = 1.27 (t, J = 7 Hz; 3H, CH_2CH_3), 1.53 (s; 3H, 4-CH_3), 1.93 (s; 3H, $COCH_3$), 4.17 (q, J = 7 Hz; 2H, OCH_2), 4.83 (s; 2H, 1-H_2), 7.09–7.31 (m; 4H, arom. H). – ^{13}C NMR ($CDCl_3$): δ = 14.11 (CH_2CH_3), 22.45 (4-CH_3), 26.05 ($COCH_3$), 50.23 (C-1), 54.05 (C-4), 61.15 (OCH_2), 125.60, 125.73, 127.42 and 127.55 (arom. CH), 131.92 and 134.60 (arom. C), 161.91 (C=N), 203.59 (C=O). – MS (70 eV): m/z = 231 (31) [M^+], 188 (49) [$M^+ - COCH_3$], 160 (100) [$M^+ - NCOC_2H_5$], 91 (6) [$C_7H_7^+$], 77 (10) [$C_6H_5^+$].

$C_{14}H_{17}NO_2$ (231.3) Calcd. C 72.69 H 7.42
Found C 72.75 H 7.38

4-Acetyl-3-ethoxy-1,4-dihydro-4-methyl-1-phenylisoquinoline (**10b**): From 1.06 g (4 mmol) of **8b** and 1.57 g of acetyl chloride 0.93 g (75%) of **10b** was obtained; R_f = 0.36. – IR (neat): ṽ = 1720 (C=O), 1680 cm^{-1} (C=N). – ^1H NMR ($CDCl_3$): δ = 1.20 (t, J = 7 Hz; 3H, CH_2CH_3), 1.63 (s; 3H, 4-CH_3), 1.92 (s; 3H, $COCH_3$), 4.10 (q, J = 7 Hz; 2H, OCH_2), 5.86 (s; 1H, 1-H), 6.90–7.20 (m; 9H, arom. H).

$C_{20}H_{21}NO_2$ (307.2) Calcd. C 78.13 H 6.89
Found C 77.91 H 7.03

3-Ethoxy-1,4-dihydro-4-methyl-4-pivaloylisoquinoline (**10c**): From 3.79 g (20 mmol) of **8a** and 12.1 g of pivaloyl chloride 3.7 g (68%) of **10c** was obtained; R_f = 0.31. – IR (neat): ṽ = 1720 (C=O), 1680 cm^{-1} (C=N). – ^1H NMR ($CDCl_3$): δ = 0.99 [s; 9H, $C(CH_3)_3$], 1.28 (t, J = 7 Hz; 3H, CH_2CH_3), 1.49 (s; 3H, 4-CH_3), 3.85–4.35 (m; 2H, OCH_2), 4.83 (s; 2H, 1-H_2), 6.95–7.25 (m; 4H, arom. H). – ^{13}C NMR ($CDCl_3$): δ = 14.16 (CH_2CH_3), 26.71 (4-CH_3), 29.09 [$C(CH_3)_3$], 45.69 [$C(CH_3)_3$], 50.17 (C-1), 53.12 (C-4), 61.14 (OCH_2), 125.72, 125.93, 126.82 and 127.47 (arom. CH), 131.00 and 134.70 (arom. C), 162.56 (C=N), 211.31 (C=O). – MS (70 eV): m/z (%) = 273 (40) [M^+], 188 (25) [$M^+ - COC_4H_9$], 91 (5) [$C_7H_7^+$], 57 (100) [$C_4H_9^+$].

$C_{17}H_{23}NO_2$ (273.4) Calcd. C 74.68 H 8.50
Found C 74.76 H 8.43

4-Benzoyl-3-ethoxy-1,4-dihydro-4-methylisoquinoline (**10d**): From 3.79 g (20 mmol) of **8a** and 14.1 g of benzoyl chloride 4.7 g (80%) of **10d** was obtained; R_f = 0.22, m.p. 91°C. – IR (KBr): ṽ = 1670 cm^{-1} (C=O and C=N). – ^1H NMR ($CDCl_3$): δ = 0.89 (t, J = 7 Hz; 3H, CH_2CH_3), 1.15 (s; 3H, 4-CH_3), 3.73–4.15 (m; 2H, OCH_2), 4.92 (s; 2H, 1-H_2), 6.74–7.63 (m; 9H, arom. H). – ^{13}C NMR ($CDCl_3$): δ = 13.62 (CH_2CH_3), 24.87 (4-CH_3), 50.19 (C-1), 52.17 (C-4), 61.30 (OCH_2), 125.79, 125.98, 127.40, 127.58, 128.03, 128.78 and 131.96 (arom. CH), 130.77, 136.11 and 136.47 (arom. C), 164.11 (C=N), 196.41 (C=O). – MS (70 eV): m/z (%) = 293 (12) [M^+], 188 (4) [$M^+ - COC_6H_5$], 105 (100) [$COC_6H_5^+$], 77 (22) [$C_6H_5^+$].

$C_{19}H_{19}NO_2$ (293.4) Calcd. C 77.77 H 6.54
Found C 77.86 H 6.47

Preparation of the Secondary Alcohols **9d** *and* **9e**. – *General Procedure:* To a stirred solution of the ketones **10** (12 mmol) in ethanol (30 ml) sodium tetrahydroborate (0.45 g, 12 mmol) was added at 25°C. After stirring for 4 h at 25°C, the solvent was removed in vacuo. Water (50 ml) was added to the residue, and the aqueous layer was extracted with diethyl ether (3 portions of 50 ml each). The combined organic layers were dried with $MgSO_4$, the solvent was removed in vacuo, and the crude product was purified by flash chromatography on silica gel (50 g) with diethyl ether/petroleum ether (2:1).

3-Ethoxy-1,4-dihydro-4-(1-hydroxyethyl)-4-methylisoquinoline (**9d**): From 2.78 g of **10a** 1.9 g (67%) of **9d** was obtained as a mixture of diastereomers; R_f = 0.43 and 0.46. – IR (neat): ṽ = 3500–3200 (OH), 1670 cm^{-1} (C=N). – ^1H NMR ($CDCl_3$): δ = 1.00 and 0.97 (d, J = 7 Hz; 3H, $CHCH_3$), 1.28 and 1.32 (t, J = 7 Hz; 3H, CH_2CH_3), 1.61 (s; 3H, 4-CH_3), 2.55 (br.; 1H, OH), 3.80–4.34 (m; 3H, CHOH and OCH_2), 4.68 (s; 2H, 1-H_2), 7.05–7.42 (m; 4H, arom. H). – ^{13}C NMR ($CDCl_3$): δ = 14.34 and 14.41 (CH_2CH_3), 19.05 and 19.30 (4-CH_3), 20.75 and 21.83 ($CHCH_3$), 46.18 and 45.65 (C-4), 50.74 and 50.40 (C-1), 60.92 and 60.97 (OCH_2), 74.54 and 74.44 (CHOH), 124.98, 125.18, 125.57, 126.51, 126.55, 126.61 and 126.87 (arom. CH), 133.07, 134.55, 136.33 and 137.69 (arom. C), 164.51 and 163.61 (C=N). – MS (70 eV): m/z (%) = 233 (4) [M^+], 189 (100) [$M^+ - OC_2H_4$], 188 (25) [$M^+ - OC_2H_5$], 91 (9) [$C_7H_7^+$], 77 (10) [$C_6H_5^+$].

$C_{14}H_{19}NO_2$ (233.3) Calcd. C 72.07 H 8.23
Found C 72.14 H 8.29

3-Ethoxy-1,4-dihydro-4-(1-hydroxyethyl)-4-methyl-1-phenylisoquinoline (**9e**): From 0.92 g (3 mmol) of **10b** 0.54 g (58%) of **9e** was obtained; R_f = 0.55. – IR (neat): ṽ = 3500–3200 (OH), 1670 cm^{-1} (C=N). – ^1H NMR ($CDCl_3$): δ = 0.99 (d, J = 7 Hz; 3H, $CHCH_3$), 1.22 (t, J = 7 Hz; 3H, CH_2CH_3), 1.65 (s; 3H, 4-CH_3),

2.40 (br.; 1H, OH), 3.85–4.35 (m; 3H, C*H*OH and OCH_2), 5.82 (s; 2H, 1-H), 6.95–7.25 (m; 9H, arom. H).

$C_{20}H_{23}NO_2$ (309.4) Calcd. C 77.63 H 7.51
Found C 77.55 H 7.59

Preparation and Reactions of the Mesylates **1** *with Potassium tert-Butoxide/DMSO to Compounds* **4**, **5** *and* **12**. – *General Procedure:* a) To a stirred solution of the alcohols **9a–e** (7 mmol) in dichloromethane (50 ml) triethylamine (1.38 ml, 10 mmol) and methanesulfonyl chloride (0.62 ml, 8 mmol) were added dropwise at –10°C. The reaction mixture was stirred for 15 min at –5°C. The crude mixture was washed with 30 ml portions of ice-cold water, saturated $KHCO_3$ solution and saturated NaCl solution. The organic layer was dried with $MgSO_4$, and the solvent was removed in vacuo. The sensitive mesylates **1** were directly submitted to reaction with potassium *tert*-butoxide/DMSO without further purification.
b) To a stirred solution of the mesylates **1** in DMSO (30 ml), 1.1 equivalents of potassium *tert*-butoxide was added and stirring was continued for 30 min. The reaction mixture was poured into water (100 ml) and extracted with petroleum ether (3 portions of 30 ml each). The combined organic layers were dried with $MgSO_4$, the solvent was removed in vacuo, and the residue was purified by flash chromatography on silica gel (50 g).

Ring Expansion of **1a** *to Compounds* **5a** *and* **12**: From 1.54 g of **9a** 1.97 g (95%) of the crude mesylate **1a** was obtained. With potassium *tert*-butoxide (0.79 g, 7.0 mmol) in the subsequent reaction 907 mg (71%) of **12** and 292 mg (23%) of **5a** were obtained after flash chromatography with diethyl ether/petroleum ether (1:5).

3-Ethoxy-5-methyl-1H-2-benzazepine (**12**): R_f = 0.24. – IR (neat): $\tilde{\nu}$ = 1640 (C=N), 1620 cm^{-1} (C=C). – ^1H NMR ($CDCl_3$): δ = 1.23 (t, *J* = 7 Hz; 3H, CH_2CH_3), 2.30 (d, *J* = 1 Hz; 3H, 5-CH_3), 4.03 (q, *J* = 7 Hz; 2H, OCH_2), 4.18 (s; 2H, 1-H_2), 6.28 (d, *J* = 1 Hz; 1H, 4-H), 7.26–7.48 (m; 4H, arom. H). – ^{13}C NMR ($CDCl_3$): δ = 14.33 (CH_2CH_3), 23.52 (5-CH_3), 52.08 (C-1), 61.28 (OCH_2), 120.17 (C-4), 125.84, 127.15, 127.89 and 129.18 (arom. CH), 137.65, 139.03 and 146.96 (arom. C and C-5), 163.01 (C=N). – MS (70 eV): *m/z* (%) = 201 (34) [M^+], 186 (59) [$M^+ - CH_3$], 172 (6) [$M^+ - C_2H_5$], 156 (25) [$M^+ - OC_2H_5$], 144 (64) [$M^+ - COC_2H_5$], 130 (100) [$M^+ - NCOC_2H_5$], 91 (10) [$C_7H_7^+$], 77 (18) [$C_6H_5^+$].

$C_{13}H_{15}NO$ (201.3) Calcd. C 77.58 H 7.51
Found C 77.78 H 7.58

3-Ethoxy-4-methyl-1H-2-benzazepine (**5a**): R_f = 0.35. – IR (neat): $\tilde{\nu}$ = 1640 (C=N), 1615 cm^{-1} (C=C). – ^1H NMR ($CDCl_3$): δ = 1.24 (t, *J* = 7 Hz; 3H, CH_2CH_3), 2.16 (d, *J* = 1 Hz; 3H, 4-CH_3), 4.04 (q, *J* = 7 Hz; 2H, OCH_2), 4.17 (s; 2H, 1-H_2), 7.03 (d, *J* = 1 Hz; 1H, 5-H), 7.24–7.41 (m; 4H, arom. H). – ^{13}C NMR ($CDCl_3$): δ = 14.25 (CH_2CH_3), 20.97 (4-CH_3), 51.52 (C-1), 61.31 (OCH_2), 127.01, 127.37, 127.74 and 128.34 (arom. CH), 135.63 (C-5), 131.64, 135.92 and 138.03 (arom. C and C-4), 162.47 (C=N). – MS (70 eV): *m/z* (%) = 201 (62) [M^+], 186 (21) [$M^+ - CH_3$], 172 (18) [$M^+ - C_2H_5$], 156 (58) [$M^+ - OC_2H_5$], 144 (22) [$M^+ - COC_2H_5$], 130 (23) [$M^+ - NCOC_2H_5$], 91 (11) [$C_7H_7^+$], 77 (8) [$C_6H_5^+$].

$C_{13}H_{15}NO$ (201.3) Calcd. C 77.58 H 7.51
Found C 77.74 H 7.56

Ring Expansion of **1b** *to Compounds* **4b** *and* **5b**: From 2.06 g of **9b** 2.43 g (93%) of the crude mesylate **1b** was obtained. With potassium *tert*-butoxide (0.80 g, 7.2 mmol) in the subsequent reaction 1.24 g (69%) of **4b** and 0.27 g (15%) of **5b** were obtained after flash chromatography with diethyl ether/petroleum ether (1:10).

3-Ethoxy-4-methyl-1-phenyl-5H-2-benzazepine (**4b**): R_f = 0.35, m.p. 102°C. – IR (KBr): = 1640 (C=N), 1620 cm^{-1} (C=C). – ^1H NMR ($CDCl_3$): δ = 1.19 (t, *J* = 7 Hz; 3H, CH_2CH_3), 1.95 (s; 3H, 4-CH_3), 2.88 (s; 2H, 5-H_2), 3.95–4.15 (m; 2H, OCH_2), 7.17–7.83 (m; 9H, arom. H). – ^{13}C NMR ($CDCl_3$): δ = 15.32 (CH_2CH_3), 17.21 (4-CH_3), 37.50 (C-5), 63.79 (OCH_2), 106.03 (C-4), 124.95, 125.60, 128.09, 129.18, 129.63, 129.91 and 131.21 (arom. CH), 131.67, 140.53, 143.02 and 149.21 (arom. C and C-3), 165.50 (C=N). – MS (70 eV): *m/z* (%) = 277 (100) [M^+], 262 (31) [$M^+ - CH_3$], 248 (35) [$M^+ - C_2H_5$], 232 (18) [$M^+ - OC_2H_5$], 220 (23) [$M^+ - COC_2H_5$], 206 (68) [$M^+ - NCOC_2H_5$], 91 (18) [$C_7H_7^+$], 77 (22) [$C_6H_5^+$].

$C_{19}H_{19}NO$ (277.4) Calcd. C 82.28 H 6.91
Found C 82.41 H 6.85

Isomerization of **4b** *and* **4c** *to* **5b** *and* **5c**. – *General Procedure:* A solution of the 5H-2-benzazepines **4b** or **4c** (4.2 mmol) in DMSO (20 ml) was stirred for 10 min at 150°C. The solution was poured into water (100 ml) and extracted with petroleum ether (3 portions of 30 ml each). The combined organic layers were dried with $MgSO_4$, and the solvent was removed in vacuo. The residue – the crude compounds **5** – was purified by flash chromatography on silica gel (50 g) with diethyl ether/petroleum ether (1:50).

3-Ethoxy-4-methyl-1-phenyl-1H-2-benzazepine (**5b**): From 1.17 g of **4b** 1.07 g (92%) of **5b** was obtained; R_f = 0.38. – IR (neat): $\tilde{\nu}$ = 1640 (C=N), 1615 cm^{-1} (C=C). – ^1H NMR ($CDCl_3$): δ = 1.27 (t, *J* = 7 Hz; 3H, CH_2CH_3), 2.19 (d, *J* = 1 Hz; 3H, 4-CH_3), 4.15 and 4.22 (ABX_3 system, J_{AB} = 7 Hz, J_{AX} = J_{BX} = 7 Hz; 2H, OCH_2), 4.95 (br. s; 1H, 1-H), 6.59 (br. d, *J* = 7 Hz; 1H; 5-H), 7.08–7.68 (m; 9H, arom. H). – ^{13}C NMR ($CDCl_3$): δ = 14.30 (CH_2CH_3), 20.58 (4-CH_3), 61.33 (OCH_2), 62.37 (C-1), 125.89, 126.33, 126.89, 127.52, 128.18, 128.26 and 128.53 (arom. CH), 135.52 (C-5), 131.79, 135.34, 142.31 and 142.41 (arom. C and C-4), 160.43 (C=N). – MS (70 eV): *m/z* (%) = 277 (32) [M^+], 262 (6) [$M^+ - CH_3$], 248 (44) [$M^+ - C_2H_5$], 232 (34) [$M^+ - OC_2H_5$], 220 (10) [$M^+ - COC_2H_5$], 206 (14) [$M^+ - NCOC_2H_5$], 200 (12) [$M^+ - C_6H_5$], 186 (17) [$M^+ - CH_2C_6H_5$], 91 (25) [$C_7H_7^+$], 77 (12) [$C_6H_5^+$].

$C_{19}H_{19}NO$ (277.4) Calcd. C 82.28 H 6.91
Found C 82.17 H 6.84

Ring Expansion of **1c** *to 4-Benzyl-3-ethoxy-1-phenyl-5H-2-benzazepine* (**4c**): From 2.60 g of **9c** 2.95 g (94%) of the crude mesylate **1c** was obtained. With potassium *tert*-butoxide (0.81 g, 7.2 mmol) in the subsequent reaction 1.72 g (74%) of **4c** was obtained after flash chromatography with diethyl ether/petroleum ether (1:10); R_f = 0.47. – IR (neat): $\tilde{\nu}$ = 1640 (C=N), 1620 cm^{-1} (C=C). – ^1H NMR ($CDCl_3$): δ = 1.28 (t, *J* = 7 Hz; 3H, CH_2CH_3), 2.75–2.95 (m; 2H, 5-H_2), 3.63–3.86 (m; 2H, $CH_2C_6H_5$), 4.03–4.39 (m; 2H, OCH_2), 7.15–7.53 and 7.78–7.88 (2 m; 14H, arom. H). – ^{13}C NMR ($CDCl_3$): δ = 15.39 (CH_2CH_3), 34.88 ($CH_2C_6H_5$), 36.91 (C-5), 63.80 (OCH_2), 108.79 (C-4), 124.83, 125.84, 128.10, 128.15, 128.96, 129.08, 129.66, 130.06 and 131.16 (arom. CH), 131.69, 140.38, 143.38 and 149.86 (arom. C and C-3), 166.26 (C=N). – MS (70 eV): *m/z* (%) = 353 (28) [M^+], 324 (6) [$M^+ - C_2H_5$], 308 (4) [$M^+ - OC_2H_5$], 296 (3) [$M^+ - COC_2H_5$], 262 (100) [$M^+ - CH_2C_6H_5$], 91 (50) [$C_7H_7^+$], 77 (12) [$C_6H_5^+$].

$C_{25}H_{23}NO$ (353.5) Calcd. C 84.95 H 6.56
Found C 84.82 H 6.61

Isomerization of **4c** *to 4-Benzyl-3-ethoxy-1-phenyl-1H-2-benzazepine* (**5c**): From 1.48 g of **4c** 1.31 g (87%) of **5c** was obtained; R_f = 0.42. – IR (neat): $\tilde{\nu}$ = 1635 (C=N), 1615 cm^{-1} (C=C). – ^1H NMR ($CDCl_3$): δ = 1.22 (t, *J* = 7 Hz; 3H, CH_2CH_3), 3.73 and 4.42 (AB system, J_{AB} = 15 Hz; 2H, $CH_2C_6H_5$), 4.10 and 4.18 (ABX_3 system, J_{AB} = 8 Hz, J_{AX} = J_{BX} = 7 Hz; 2H, OCH_2), 4.96 (br. s; 1H, 1-H), 6.59 (br. d, *J* = 7 Hz; 1H, 5-H), 7.09–7.48 and 7.55–7.71 (2 m; 14H, arom. H). – ^{13}C NMR ($CDCl_3$): δ = 14.21 (CH_3), 40.60 ($CH_2C_6H_5$), 61.40 (OCH_2), 62.27 (C-1), 126.28, 126.37, 126.87, 127.78,

128.14, 128.44, 128.49, 128.54 and 128.94 (arom. CH), 136.07 (C-5), 134.99, 135.55, 139.45, 142.19 and 142.32 (arom. C and C-4), 159.52 (C=N). – MS (70 eV): *m/z* (%) = 353 (96) [M^+], 324 (52) [$M^+ - C_2H_5$], 308 (20) [$M^+ - OC_2H_5$], 296 (4) [$M^+ - COC_2H_5$], 262 (100) [$M^+ - CH_2C_6H_5$], 91 (79) [$C_7H_7^+$], 77 (13) [$C_6H_5^+$].

$C_{25}H_{23}NO$ (353.5) Calcd. C 84.95 H 6.56
Found C 84.99 H 6.42

Ring Expansion of **1d** *to 4,5-Dimethyl-3-ethoxy-1H-2-benzazepine* (**5d**): From 1.63 g of **9d** 1.98 g (91%) of the crude mesylate **1d** was obtained. With potassium *tert*-butoxide (0.79 g, 7.0 mmol) in the subsequent reaction 861 mg (63%) of **5d** was obtained after flash chromatography with diethyl ether/petroleum ether (1:5); R_f = 0.27. – IR (neat): $\tilde{\nu}$ = 1625 cm^{-1} (C=N and C=C). – ^1H NMR ($CDCl_3$): δ = 1.22 (t, *J* = 7 Hz; 3H, CH_2CH_3), 2.11 (s; 3H, 4-CH_3), 2.28 (s, 3H, 5-CH_3), 3.93 and 4.03 (ABX_3 system, J_{AB} = 10 Hz, $J_{AX} = J_{BX}$ = 7 Hz; 2H, OCH_2), 3.79 and 4.30 (AB system, J_{AB} = 11 Hz; 2H, 1-H_2), 7.22–7.43 (m; 4H, arom. H). – ^{13}C NMR ($CDCl_3$): δ = 14.27 (CH_2CH_3), 16.66 (4-CH_3), 20.05 (5-CH_3), 51.53 (C-1), 61.26 (OCH_2), 126.56, 126.75, 126.87 and 127.61 (arom. CH), 139.77, 140.05 and 140.38 (arom. C, C-4 and C-5), 163.79 (C=N). – MS (70 eV): *m/z* (%) = 215 (91) [M^+], 200 (74) [$M^+ - CH_3$], 186 (31) [$M^+ - C_2H_5$], 170 (25) [$M^+ - OC_2H_5$], 158 (31) [$M^+ - COC_2H_5$], 144 (57) [$M^+ - NCOC_2H_5$], 91 (17) [$C_7H_7^+$], 77 (15) [$C_6H_5^+$].

$C_{14}H_{17}NO$ (215.3) Calcd. C 78.10 H 7.96
Found C 77.95 H 8.03

Ring Expansion of **1e** *to 4,5-dimethyl-3-ethoxy-1-phenyl-1H-2-benzazepine* (**5e**): From 435 mg (1.4 mmol) of **9e** 488 mg (90%) of the crude mesylate **1e** was obtained. With potassium *tert*-butoxide (0.16 g, 1.4 mmol) in the subsequent reaction 184 mg (51%) of **5e** was obtained after flash chromatography with diethyl ether/petroleum ether (1:20); R_f = 0.38. – IR (neat): $\tilde{\nu}$ = 1625 cm^{-1} (C=N and C=C). – ^1H NMR ($CDCl_3$): δ = 1.28 (t, *J* = 7 Hz; 3H, CH_2CH_3), 2.18 (s; 3H, 4-CH_3), 2.39 (s; 3H, 5-CH_3), 4.14 and 4.24 (ABX_3 system, J_{AB} = 11 Hz, $J_{AX} = J_{BX}$ = 7 Hz; 2H, OCH_2), 4.94 (s; 1H, 1-H), 7.21–7.79 (m; 9H, arom. H). – ^{13}C NMR ($CDCl_3$): δ = 11.59, 14.02 and 23.05 (CH_2CH_3, 4-CH_3 and 5-CH_3), 62.08 (C-1), 62.36 (OCH_2), 122.18, 125.55, 126.30, 127.23, 128.09, 128.14, 128.18, 129.06 and 131.22 (arom. CH), 135.95, 138.09, 141.85 and 142.92 (arom. C), 156.11 (C=N). – MS (70 eV): *m/z* (%) = 291 (100) [M^+], 276 (21) [$M^+ - CH_3$], 262 (41) [$M^+ - C_2H_5$], 246 (27) [$M^+ - OC_2H_5$], 234 (24) [$M^+ - COC_2H_5$], 220 (31) [$M^+ - NCOC_2H_5$].

$C_{20}H_{21}NO$ Calcd. 291.1624 Found 291.1623 (MS)

4-Bromomethyl-3-ethoxy-1,4-dihydro-4-methylisoquinoline (**11**): To a stirred solution of the imino ether **8a** (3.8 g, 20 mmol) in THF (100 ml) a solution of *n*-butyllithium in hexane (1.6 N, 13.8 ml, 22 mmol) was added dropwise at –70°C. After stirring for 15 min at this temp. dibromomethane (1.4 ml, 200 mmol) was added. Stirring was continued for 12 h at –70°C and for 15 min at 25°C. The solvents were removed in vacuo, the residue was dissolved in diethyl ether (50 ml) and washed with water (100 ml). The aqueous layer was reextracted with diethyl ether (3 portions of 30 ml each), and the combined organic layers were dried with $MgSO_4$. After removal of the solvent in vacuo, the residue was purified by flash chromatography on silica gel (50 g) with diethyl ether/petroleum ether (1:10). 2.35 g (63%) of the starting material **8a** (R_f = 0.51) and 0.57 g (10%) of the bromomethyl derivative **11** were obtained; R_f = 0.25. – IR (neat): $\tilde{\nu}$ = 1680 cm^{-1} (C=N). – ^1H NMR ($CDCl_3$): δ = 1.31 (t, *J* = 7 Hz; 3H, CH_2CH_3), 1.58 (s; 3H, 4-CH_3), 3.58 and 3.97 (AB system, J_{AB} = 10 Hz; 2H, CH_2Br), 4.07 (q, *J* = 7 Hz; 2H, OCH_2), 4.72 (s; 2H, 1-H_2), 7.01–7.32 (m; 4H, arom. H). – ^{13}C NMR ($CDCl_3$): δ = 14.29 (CH_2CH_3), 25.67 (4-CH_3), 40.76 and 41.99 (C-4 and CH_2Br), 50.06 (C-1), 60.94 (OCH_2), 124.38, 125.02, 126.76 and 126.96 (arom.CH), 133.59 and 136.64 (arom. C), 161.91 (C=N). – MS (70 eV): *m/z* (%) = 281 and 283 (3) [M^+], 253 and 255 (4) [$M^+ - C_2H_5$], 203 (45) [$M^+ - Br$], 188 (26) [$M^+ - CH_2Br$], 91 (20) [$C_7H_7^+$].

$C_{13}H_{16}BrNO$ Calcd. 282.0415 Found 281.0415 (MS)

Ring Expansion of **11** *to Compounds* **5a** *and* **12**: To a stirred solution of **11** (280 mg, 1.0 mmol) in DMSO (5 ml), potassium *tert*-butoxide (123 mg, 1.1 mmol) was added at 25°C. Stirring was continued for 1 h, the reaction mixture was poured into water (50 ml) and extracted with diethyl ether (3 portions of 20 ml each). The combined organic layers were dried $MgSO_4$. The solvent was removed in vacuo, and the residue was purified by flash chromatography on silica gel (40 g) with diethyl ether/petroleum ether (1:5) to yield 135 mg (67%) of **12** and 43 mg (21%) of **5a**. – Spectroscopical data see above.

[1] For part II see: U. Groth, L. Richter, U. Schöllkopf, *Liebigs Ann. Chem.* **1992**, 199–202.

[2] U. Schöllkopf, J. Mittendorf, *Angew. Chem.* **1989**, *103*, 633–634; *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 613–614.

[3] [3a] L. Hazai, G. Deak, *Acta Chim. Hung.* **1986**, *121*, 237–242. – [3b] Y. Kamochi, Y. Watanabe, *Heterocycles* **1987**, *26*, 2385–2391.

[4] Under the reaction conditions, benzaldehyde and pivalaldehyde were further reduced to benzyl alcohol and 3,3-dimethyl-1-propanol, respectively.

[5] The structures of **5a** and **12** were established by NOE experiments.

[6] [6a] G. Maier, *Angew. Chem.* **1967**, *79*, 446–458; *Angew. Chem. Int. Ed. Engl.* **1967**, *6*, 402–414. – [6b] See ref.[1] and ref.[2].

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[8] After deprotonation of 2,5-dihydropyrazines at C-5 the electron pair always attacks the carbon of the imino ether group (see ref.[2]). An attack at the nitrogen according to Scheme 5 has not been observed for 2,5-dihydropyrazines.

[9] The bromomethyl imino ether **11** was obtained from **8a** by lithiation with *n*-butyllithium and subsequent alkylation with dibromomethane in 10% yield.

[10] C. W. Spangler, *Chem. Rev.* **1976**, *76*, 187–217.

[11] The mole fraction of **4b** was determined ^1H NMR spectroscopically as a function of time.

[12] C. B. Argo, J. T. Sharp, *J. Chem. Soc., Perkin Trans. 1*, **1984**, 1581–1587.

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CAS Registry Numbers

1a: 143265-92-3 / **1b**: 143266-15-3 / **1c**: 143266-16-4 / **1d**: 143266-18-6 / **1e**: 143266-17-5 / **4b**: 143266-09-5 / **4c**: 143266-11-9 / **5a**: 143265-93-4 / **5b**: 143266-10-8 / **5c**: 143266-12-0 / **5d**: 143266-13-1 / **5e**: 143266-14-2 / **6a**: 24331-94-0 / **6b**: 17507-05-0 / **7a**: 57023-99-1 / **7b**: 143266-01-7 / **8a**: 143265-94-5 / **8b**: 143265-99-0 / **8c**: 143266-00-6 / **9a**: 143265-95-6 / **9b**: 143266-02-8 / **9c**: 143266-03-9 / **9d**: 143266-07-3 / **9e**: 143266-08-4 / **10a**: 143265-96-7 / **10b**: 143266-04-0 / **10c**: 143266-05-1 / **10d**: 143266-06-2 / **11**: 143265-97-8 / **12**: 143265-98-9