SYNTHESIS AND CONFORMATIONAL ANALYSIS OF HEXAHYDROISOQUINO[3,2-*b*][3]BENZAZEPINES (iso-B-HOMOBERBINES)

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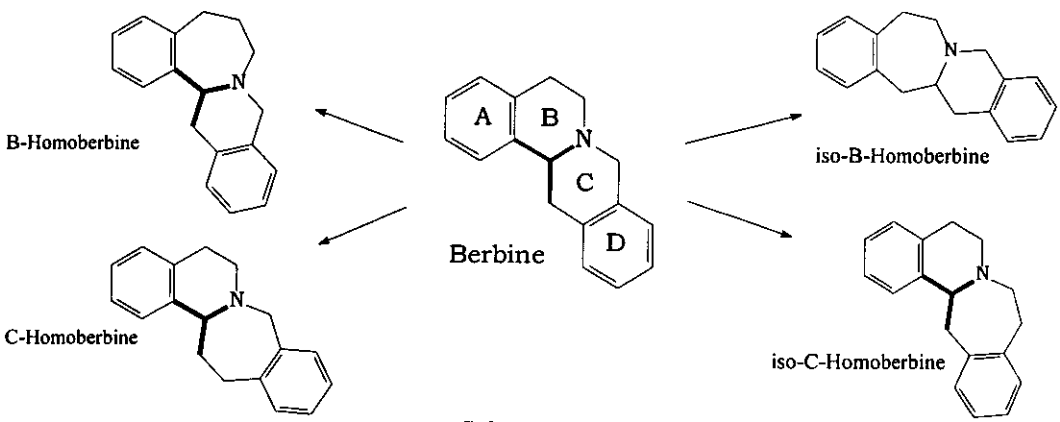
Abstract - A new simple synthetic approach to the hexahydroisoquino[3,2-*b*][3]-benzazepines has been developed. 3-Benzyl-2-tetralones (**3a-c**) were prepared in two different ways from 2-tetralone and 6-methoxy-2-tetralone. Regioselective methoxycarbonylation with dimethyl carbonate or with magnesium methyl carbonate gave the known ß-keto esters (**1**) or (**1'**), respectively, which could be alkylated to benzyl derivatives (**2**) and (**2'**), respectively. Demethoxycarbonylation using lithium iodide afforded the desired 3-benzyl-2-tetralones (**3a-c**), which furnished the lactams (**4a-c**) by submitting to the Schmidt reaction. Reduction using borane and a final Pictet-Spengler cyclization gave the title compounds (**6a-c**). NMR measurements indicated that iso-B-homoberbines exist as equilibrium mixture of the *cis* and *trans* conformers in $CDCl_3$ solution at room temperature, whereas the hydrochloride salt of **6b** adopts a *cis B*-fused conformation.

INTRODUCTION

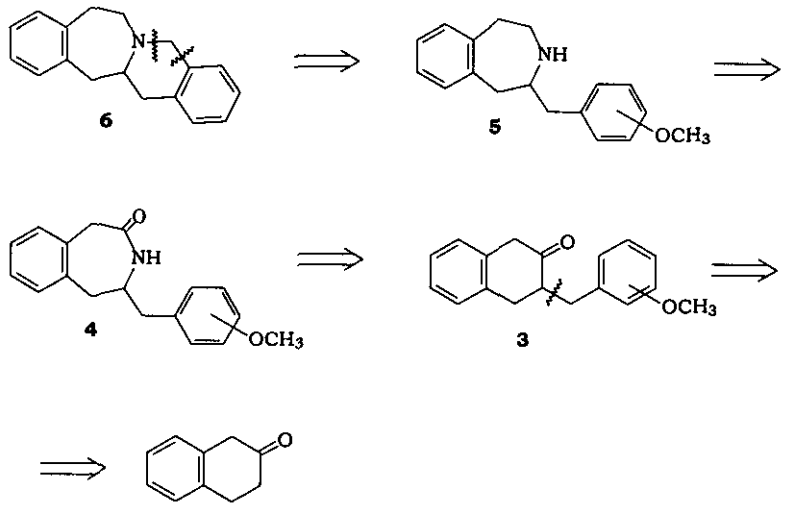


Scheme 1

The formal ring expansion of the berbine alkaloide framework leads to four different heterocyclic systems: the B-ring homologization provides B- and iso-B-homoberbines while the C ring-expansion affords C- and iso-C-homoberbines (Scheme 1). Recently, we have described the syntheses and conformational behaviours of B-, C- und iso-C-homoberbines.[1-3] Key steps involved a final construction of the ring B *via* Bischler-Napieralski cyclization.

In the case of iso-B-homoberbines, the benzazepine moiety (rings A/B) has to be built otherwise. Graftieaux *et al.*[4] reported the synthesis of a diastereomeric mixture of 2,3-dimethoxy-14-hydroxy-10,11-methylendioxy-iso-B-homoberbines using the intramolecular Vilsmeier reaction to close the ring B. In this new approach, the benzazepine part structure was constructed from the corresponding 2-tetralones by means of the Schmidt reaction. Our retrosynthetic analysis is shown in Scheme 2.

The title compounds (**6**) should be obtainable from the reduction of the lactams (**4**) to give the amines (**5**) followed by Pictet-Spengler ring closure. The key step in the synthesis involves the ring expansion of 3-benzyl-2-tetralones (**3**), which should be carried out either in the Schmidt reaction or in the Beckmann rearrangement of the corresponding oximes. Finally, the ketones (**3**) should be available from the regioselective benzylation of 2-tetralones at C-3.



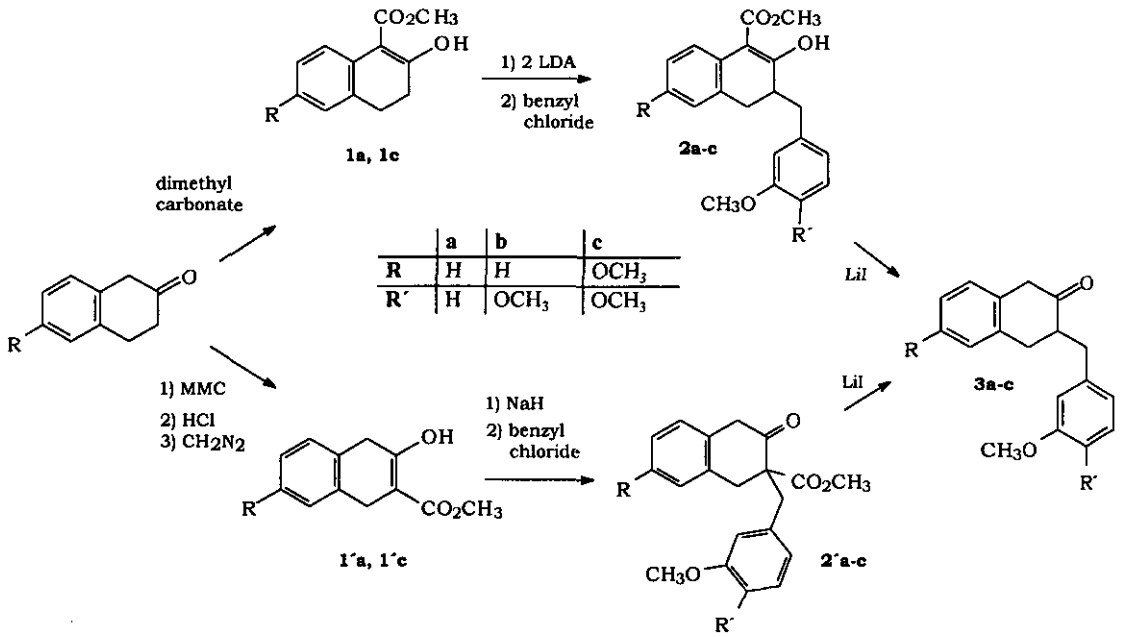
Scheme 2

RESULTS

Synthesis

3-Benzyl-2-tetralones (**3a-c**) were prepared in two different ways from 2-tetralone and 6-methoxy-2-tetralone. Regioselective methoxycarbonylation with dimethyl carbonate and with magnesium methyl carbonate (MMC) gave the known ß-keto ester (**1**) and (**1'**), respectively, which could be alkylated to the benzyl derivatives (**2**) and (**2'**). Demethoxycarbonylation of crude **2** or **2'** using the Krapcho

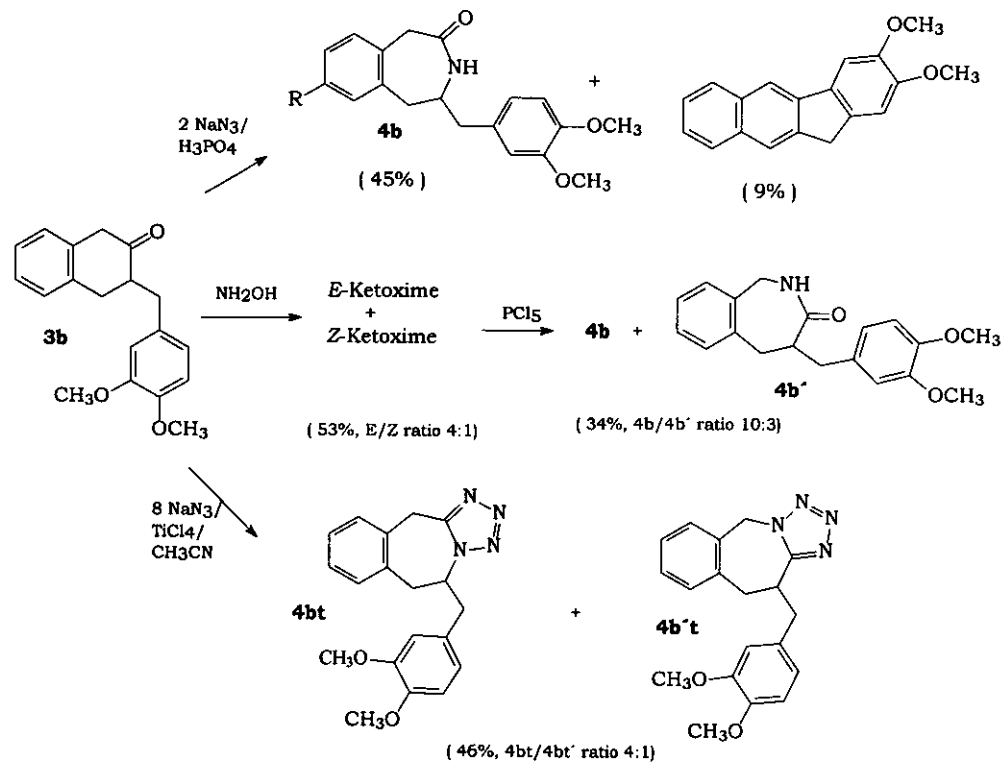
procedure[5] with lithium iodide afforded the desired tetralones (**3a-c**). The more convenient dianion approach *via* **1** and **2** proceeded in about 30 % overall yield.



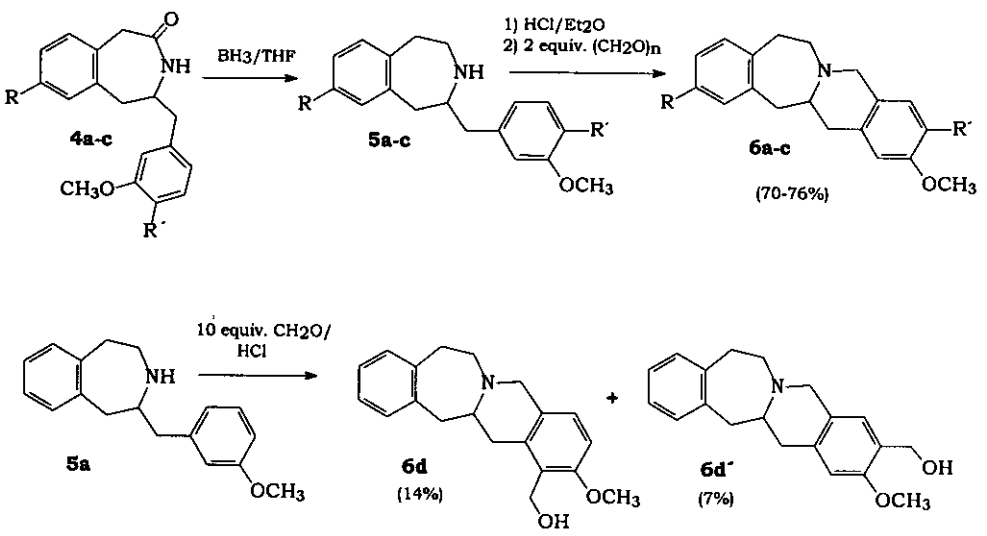
Scheme 3

The key step of the synthesis involves the NH insertion between the carbonyl group and the neighbouring tertiary alkyl group of **3** to give 3-benzazepine-2-on (**4**). Treatment of **3b** with sodium azide in phosphoric acid (Schmidt reaction) afforded the desired lactame (**4b**) in 45 % yield, together with some benzo[*b*]fluorene. Although 2 equiv. sodium azide were used, no tetrazole derivatives were obtained. However, if **3b** was treated with a large excess of sodium azide in the presence of titanium(IV) chloride in refluxing acetonitrile, two isomeric tetrazoles (**4bt**) and (**4bt'**) were yielded. When the Beckmann rearrangement was used instead, an isomeric mixture of **4b** and the undesired 2-benzazepine-3-on (**4b'**) was obtained. **3a** und **3c** provided under the Schmidt conditions **4a** and **4c** in 23% and 44 % yields, respectively (Scheme 4).

Reduction of the lactams (**4a-c**) with borane proceeded in quantitative yield to give the benzazepines (**5a-c**), which after converting to the hydrochloride salts underwent the Pictet-Spengler cyclization with paraformaldehyde to furnish the title compounds (**6a-c**) in about 70 % yield. When the benzazepine (**5a**) was refluxed with an excess of aqueous formaldehyde in 2M hydrochloric acid, a mixture of hydroxymethylated compounds (**6d**) and (**6d'**) was obtained (Scheme 5).



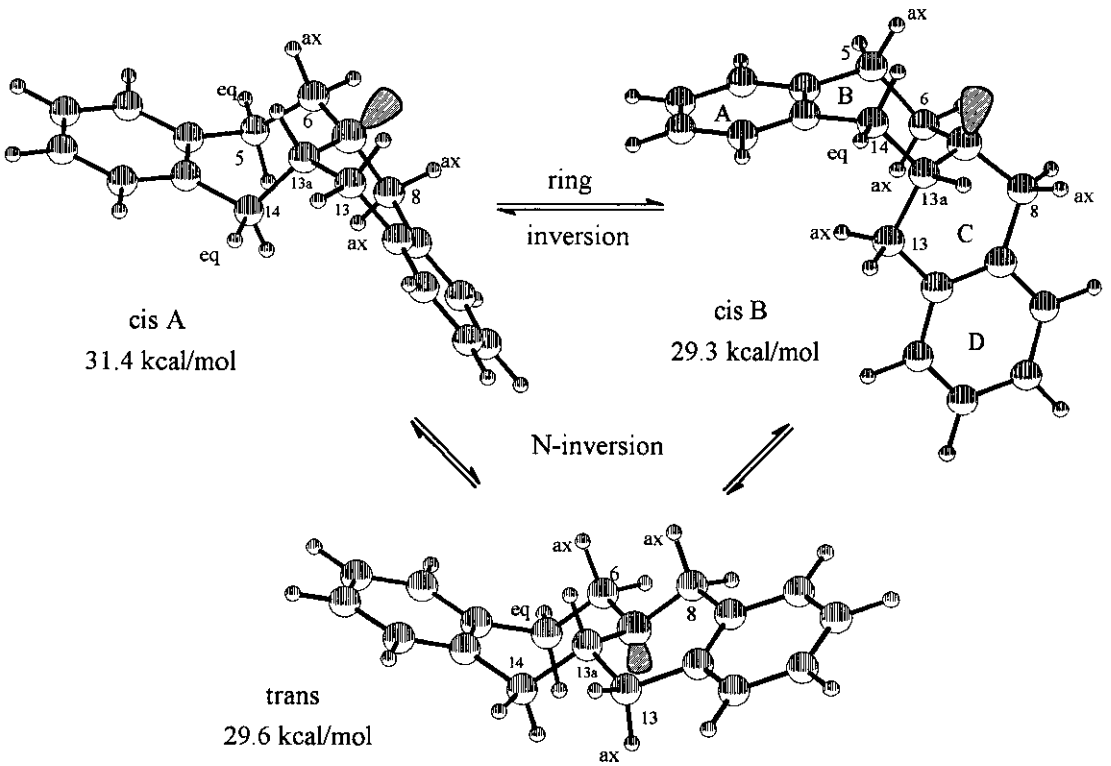
Scheme 4



Scheme 5

Conformational behaviour of iso-B-homoberbines

The iso-B-homoberbine ring system has, in principle, the possibility to exist in a *cis*-fused and/or a *trans*-fused conformation due to the conformationally mobile nitrogen. Furthermore, the *cis* isomer has, through ring inversion, two possible ring conformers, *cis A* (nitrogen lone pair equatorial to ring B) and *cis B* (nitrogen lone pair axial to ring B). The three conformers shown in Scheme 6 were calculated by means of the MMX force field of PC MODEL (Serena Software).



Scheme 6

IR spectra (KBr pellets) of the iso-B-homoberbines (**6a-d**) show clear Bohlmann bands at 2760 cm^{-1} which indicate the *trans* ring juncture in the solid state.[6] 300 MHz ^{1}H-NMR spectra of **6a-d** in $CDCl_3$ solution at room temperature show broad and strongly overlapping signals for all aliphatic protons, so that it was impossible to indicate the vicinal couplings between the angular proton 13a-H and the adjacent ones. 500 MHz NOE difference spectrum of **6b** (irradiation at the singlet of the C-8 protons) is consistent with all three conformations. The ^{13}C resonance signals of the carbons C-6 and C-13 are

strongly broadened. Accordingly, the free bases (**6a-d**) exist in solution as equilibrium mixture of the *cis* and *trans* conformers.

The NMR data for the hydrochloride salt of **6b** suggest that this molecule predominantly adopts a *cis B* conformation in solution. The 500 MHz ^{1}H NMR spectrum of **6b · HCl** in $CDCl_3/D_2O$ at room temperature shows separated signals for all aliphatic protons. The vicinal coupling constants $J_{13a\text{-}13^{ax}}$ = 12.5 Hz, $J_{13a\text{-}13^{eq}}$ = 3.0 Hz, $J_{13a\text{-}14^{ax}}$ = 5.5 Hz and $J_{13a\text{-}14^{eq}}$ < 1 Hz reflect the antiperiplanar orientation of the angular proton 13a-H and the axial proton 13-H as the only *trans* diaxial relation. This is in agreement with the *cis B* ring juncture only. Further evidence for the presence of the *cis B* form is given by the 500 MHz ROESY spectrum. It shows a strong *cis B* specific NOE effect between 13-H^{ax} and 6-H^{ax}

EXPERIMENTAL

Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. IR spectra were run on a Perkin Elmer PE-298 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Varian XL-300 or on a Bruker AMX-500 spectrometer. Proton chemical shifts (ppm) are referred to residual chloroform (δ 7.24 ppm), and carbon chemical shifts to the solvent ($^{13}CDCl_3$ = 77 ppm). The following abbreviations are used: s = singlet, d = doublet, dd = doublet of doublets, ddd = doublet of doublets of doublets, m = multiplet, br = broad, ax = axial, eq = equatorial. ^{1}H and ^{13}C NMR signals were assigned from 2D-COSY experiments of the following compounds: HH-COSY- **4b**, oxime mixture, **4b+4b′** mixture, tetrazole mixture, **5a**, **6b**, **6b · HCl**, **6d**; CH-COSY- **2b**, **3b**, **3c**, oxime mixture, **4b+4b′** mixture, tetrazole mixture, **4c**, **6b**, **6b · HCl**, **6c**, **6d**. Mass spectra were run on a Kratos MS-50. Elemental analyses were performed by the Institut für Organische Chemie und Biochemie der Universität Bonn on a Perkin-Elmer DIA-CHN RS and by Prof. Dr. H. Malissa and H. Reuter GmbH, Gummersbach. Analytical thin layer chromatography was performed by silica gel 60 F_{254} plates (0.2 mm thick) of Merck and visualized by uv light or by iodine adsorption. Except of the lactams (**4a-c**) all products were purified by column chromatography over Merck silica gel 60 (0.063-0.200 mm). All reactions were carried out under a nitrogen atmosphere.

Substitution pattern:

	R	R′
a	H	H
b	H	CH_3O
c	CH_3O	CH_3O

2-Tetralone has been synthetized by Birch reduction of ß-naphtyl methyl ether.[7]

6-Methoxy-2-tetralone has been prepared by a Friedel-Crafts reaction of 4-methoxyphenylacetyl chloride[8] with ethylene followed by intramolecular Michael addition.[9]

The known ß-keto esters (**1**) and (**1′**) have been prepared as in lit.[10-12] and purified by column chromatography.

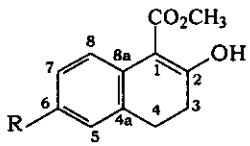
Table 1: Preparation Details of the β-Keto Esters (**1**) and (**1′**)

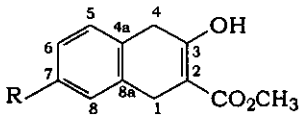
	lit.	yield	eluted with	
1a	10	96%	toluene	n_D^{21}=1.5780 (lit. n_D^{26}=1.5540)
1c	11	82%	toluene, recrystallized from methanol	mp. 48-49°C, (lit. n_D^{25}=1.5704)
1′a	12 *	45%	ethyl acetate-light petroleum 1:10	mp. 48-49°C, (lit. 49-50°C)
1′c	12 *	35%	ethyl acetate-light petroleum 1:10	mp. 98-99°C, (lit. 96-98°C)

* 0.17 mol of the corresponding 2-tetralone were heated for 4 h with the MMC solution generated from 15 g of Mg.

Table 2: The NMR Spectral Data of the ß-Keto Esters (**1**) and (**1′**) in $CDCl_3$

(**1a**, **1c**: approx. 80% enole form; **1′a**, **1′c**: 100 % enole form)





	^{1}H (300 MHz)		^{13}C (75 MHz)		^{1}H (300 MHz)		^{13}C (75 MHz)	
	1a	**1c**	**1a**	**1c**	**1′a**	**1′c**	**1′a**	**1′c**
1	-	-	99.68	99.50	3.65 s	3.53-3.62 m	28.19	28.45
2	-	-	178.12	176.59	-	-	95.47	95.14
3	2.86 t, 7.5 Hz	2.80 t, 7.5 Hz	29.45	29.47	-	-	169.36	169.70
4	2.58 t, 7.5 Hz	2.53 t, 7.5 Hz	27.67	28.20	3.65 s	3.53-3.62 m	33.68	32.85
4a	-	-	132.92	134.80	7.13-7.23 m	-	131.35	123.33
5	7.09-7.33 m	6.70 d, 3 Hz	126.18	113.19	"	7.03 d, 8.4 Hz	128.05	128.62
6	"	-	124.77	156.83	"	6.76 dd, 2.3, 8.4 Hz	126.37	112.52
7	"	6.75 dd, 9, 3 Hz	125.67	111.15	"	-	126.12	157.95
8	7.75 dd, 7.5, 0.9 Hz	7.62 d, 9 Hz	126.95	126.81	"	6.72 d, 2.3 Hz	127.80	112.52
8a	-	-	131.10	123.84	-	-	133.39	134.38
$\underline{C}O_2CH_3$	3.96 s	3.91 s	51.62	51.70	-	-	172.02	171.95
$CO_2\underline{C}H_3$	-	-	172.12	172.17	3.85 s	3.78 s	51.65	51.56
OCH_3	-	3.80 s	-	55.24	-	3.83 s	-	55.16
OH[a]	13.42 s	13.15 s	-	-	12.26 s	12.24 s	-	-

[a] exchangeable with D_2O; keto form of **1a**: δ = 3.76 (1-H), 59.93 (C-1), 37.48 (C-3); keto form of **1c**: δ = 3.72 (1-H), 59.33 (C-1), 37.57 (C-3).

Synthesis of 3-benzyl-1-methoxycarbonyl-2-tetralones (2a-c)

General procedure. A solution of the corresponding keto ester **(1a)** or **(1c)** (50 mmol) in 50 mL of dry THF was added dropwise to an ice-cooled and stirred 2M solution of LDA (50 mL, 100 mmol) in THF-ethylbenzene-n-heptane (*Aldrich*) over a period of 15 min. Stirring was continued for 20 min and the resulting yellow enolate suspension was treated with the corresponding benzyl chloride[13] (50 mmol) in 50 mL of dry THF. After removing the ice bath, stirring was continued for further 30 min. 20 mL of conc. HCl were added and the resulting mixture was extracted with ether (4 x 50 mL). The combined organic layers were washed with water and dried over $MgSO_4$. The solvents were removed *in vacuo* to give the crude products as reddish oils which were used without further purification.

Methyl 3,4-Dihydro-2-hydroxy-3-(3′-methoxybenzyl)naphthalene-1-carboxylate (2a). The crude product was obtained from **1a** and 3-methoxybenzyl chloride.

Methyl 3,4-Dihydro-3-(3′,4′-dimethoxybenzyl)-2-hydroxynaphthalene-1-carboxylate (2b). The crude product was obtained from **1a** and 3,4-dimethoxybenzyl chloride. An analytical sample was prepared by column chromatography (ethyl acetate-light petroleum 1:5) of 1 g of the crude product, followed by recrystallization from ether and light petroleum to give 0.33 g of **2b** as colourless crystals; mp 109-110°C; IR (KBr) 2960, 2840, 1660, 1600 cm^{-1}; MS (m/z, %) 354 (M^+, 16), 322 (8), 171 (14),152 (46), 151 (100); ^1H and ^{13}C NMR data see Table 3; Anal. Calcd for C, 71.17; H, 6.26. Found: C, 71.04; H, 6.36. HRMS m/z calcd for $C_{21}H_{22}O_5$: 354.1467; found: 354.1471.

Methyl 3,4-Dihydro-3-(3′,4′-dimethoxybenzyl)-2-hydroxy-6-methoxynaphthalene-1-carboxylate (2c). The crude product was obtained from **1c** and 3,4-dimethoxybenzyl chloride.

Synthesis of 3-benzyl-3-methoxycarbonyl-2-tetralones (2′a-c)

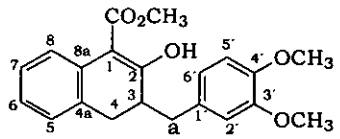
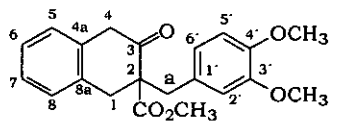
General procedure. 1.40 g of 60 % NaH suspension in oil was washed several times with dry toluene and the resulting NaH (36 mmol) was suspended in dry toluene. A solution of the corresponding keto ester **(1′a)** or **(1′c)** (36 mmol) in 50 mL of dry toluene was added with stirring over a period of 15 min. A vigorous hydrogen evolution was observed and the reaction mixture became slightly warm while the sodium enolate of the ß-keto ester separated as yellow paste. Stirring was continued for 30 min and then the corresponding benzyl chloride[13] (50 mmol) in 50 mL of dry toluene was rapidly added. The reaction mixture was refluxed for 2 h (in case of **2′c** for 1 h). After cooling, the mixture was washed with water and dried over $MgSO_4$. Evaporation yielded the crude products as yellow oils which were used without further purification.

Methyl 1,2,3,4-Tetrahydro-2-(3′-methoxybenzyl)-3-oxonaphthalene-2-carboxylate (2′a). The crude product was obtained from **1′a** and 3-methoxybenzyl chloride.

Methyl 1,2,3,4-Tetrahydro-2-(3′,4′-dimethoxybenzyl)-3-oxonaphthalene-2-carboxylate (2′b). The crude product was obtained from **1a** and 3,4-dimethoxybenzyl chloride. Treatment with methanol (100 mL) yielded 7.68 g (60 %) of **2′b** as colourless crystals; mp 139-140°C (methanol); IR (KBr) 2960, 1740, 1720, 1510 cm^{-1}; MS (m/z, %) 354 (M^+, 20), 152 (17), 151 (100); ^1H and ^{13}C NMR data see Table 3; Anal. Calcd for C, 71.17; H, 6.26. Found: C, 71.08; H, 6.38.

Methyl 1,2,3,4-Tetrahydro-2-(3′,4′-dimethoxybenzyl)-7-methoxy-3-oxonaphthalene-2-carboxylate (2′c). The crude product was obtained from **1c** and 3,4-dimethoxybenzyl chloride.

Table 3: The NMR Spectral Data of **2b** (100 % enole form) and **2′b** (100 % keto form) in $CDCl_3$

	2b 		**2′b** 	
	^1H (300 MHz)	^{13}C (75 MHz)	^1H (300 MHz)	^{13}C (75 MHz)
1	-	99.32	2.93 d, 15.5 Hz 3.35 d, 15.5 Hz	36.38
2	-	179.91	-	60.14
3	2.66-2.77 m	41.34	-	205.79
4	2.52 dd, 15.3, 3.5 Hz 2.85 dd, 15.3, 5.4 Hz	31.21	3.50 d, 20 Hz 3.76 d, 20 Hz	44.41
4a, 8a	-	131.11, 131.33	-	132.17, 134.15
5	7.12 dd, 7.3, 1.3 Hz	126.31	7.04-7.21 m	128.34
6,7	6.62-6.67 m, 7.19-7.27 m	125.08, 125.65	7.04-7.21 m	126.95, 127.06,
8	7.74 d, 7.3 Hz	128.10	7.04-7.21 m	127.64
a	2.33 dd, 13.6, 10.6 Hz 2.92 dd, 13.6, 5.1 Hz	34.49	3.13 d, 13.7 Hz 3.35 d, 13.7 Hz	38.56
1′	-	130.71	-	128.29
2′	6.62-6.67 m	112.19	6.65 d, 2 Hz	113.68
3′,4′	-	147.38, 148.65	-	147.99, 148.48
5′	6.81 d, 8 Hz	111.03	6.76 d, 8 Hz	110.90
6′	6.62-6.67 m	121.09	6.67 dd, 8, 2 Hz	122.68
OCH_3	3.87 s, 3.88 s	55.82, 55.88	3.83 s, 3.84 s	55.82, 55.84
$\underline{C}O_2CH_3$	-	172.52	-	171.25
$CO_2\underline{CH_3}$	3.94 s	51.86	3.55 s	52.49
OH	13.42	-	-	-

OH exchangeable with D_2O

Synthesis of 3-benzyl-2-tetralones (3a-c)

General procedure. The crude ß-keto ester **(2a-c)** (obtained from 50 mmol of **1a-c**) was dissolved in 250 mL of DMF and treated with 14.08 g of $LiI \cdot 3H_2O$ (75 mmol). Carbon dioxide evolution began

immediately. The resulting solution was refluxed for 3 h. After removal of the bulk of DMF *in vacuo* the residue was acidified with 50 mL of 2M HCl and extracted with ether (3 x 300 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution and with water, dried over $MgSO_4$ and concentrated *in vacuo* to give reddish oils, which were purified by column chromatography (**3a**: ethyl acetate-light petroleum 1:10; **3b** and **3c**: ethyl acetate-light petroleum 1:7). The following yields are based on the ß-keto esters **(1a-c).**

3-(3′-Methoxybenzyl)-2-tetralone (3a). Yield: 4.41 g (33 %); colourless oil; n_D^{20} = 1.5965; IR (neat) 3000, 2940, 2840, 1705, 1590 cm^{-1}; MS (m/z, %) 266 (M^+, 33), 159 (32), 145 (87),122 (100),121 (31); ^1H and ^{13}C NMR data see Table 4; Anal. Calcd for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81. Found: C, 80.43; H 6.79. HRMS m/z calcd for $C_{18}H_{18}O_2$: 266.1307; found 266.1314. Recovery of 2-tetralone: 0.92 g (13 %).

3-(3′,4′-Dimethoxybenzyl)-2-tetralone (3b). Yield: 4.47 g (30 %); colourless oil, which crystallized on freezing. Recrystallization from ether afforded colourless crystals; mp 50-51 °C; IR (KBr) 2920, 1700, 1590, 1510 cm^{-1}; MS (m/z, %) 296 (M^+, 34), 191 (7), 152 (28), 152 (27), 151 (100); ^1H and ^{13}C NMR data see Table 4; Anal. Calcd for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80. Found: C, 76.97; H, 7.02. Recovery of 2-tetralone: 1.64 g (22 %)

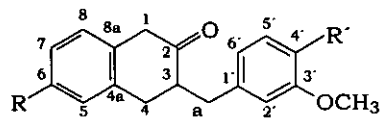
3-(3′,4′-Dimethoxybenzyl)-6-methoxy-2-tetralone (3c). Yield: 5.65 g (35 %); colourless oil, which crystallized on freezing. Recrystallization from ether afforded colourless crystals; mp 72-73 °C; IR (KBr) 2920, 2830, 1700, 1605, 1590, 1500 cm^{-1}; MS (m/z, %) 326 (M^+, 29), 191 (8), 175 (63), 174 (27), 152 (27), 151 (100); ^1H and ^{13}C NMR data see Table 4; Anal. Calcd for $C_{20}H_{22}O_4$: C, 73.60; H 6.79. Found: C, 73.43; H, 6.80. HRMS m/z calcd for $C_{20}H_{22}O_4$: 326.1518; found: 326.1514. Recovery of 6-methoxy 2-tetralone: 0.80 g (9 %)

Using the same general procedure for crude ß-keto esters **(2′a-c)** yielded identical samples of 3-benzyl-2-tetralones **(3a), (3b)** and **(3c)** in 55 %, 58% and 19 %, respectively.

Synthesis of lactams (4a-c)

General procedure. 17 mmol of the corresponding ketone **(3a-c)** were suspended in 150 mL of 85 % phosphoric acid and treated portionwise with 2.28 g (35 mmol) of sodium azide with vigourous stirring over a period of 1 h. During this time the reaction mixture was brought slowly to about 70°C. After stirring for further 2 h at 70°C, no more nitrogen evolution could be observed. The reaction mixture was allowed to cool to rt, then poured into cold water (200 mL) and extracted with chloroform (3 x 100 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution and with water, dried over $MgSO_4$ and evaporated *in vacuo.* The residual foam was recrystallized from ethyl acetate to give the lactams **(4a-c)** as colourless crystals.

Table 4: The NMR Spectral Data of **3a-c**



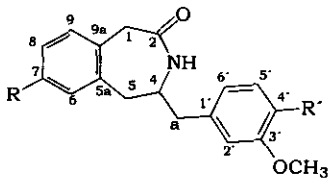
	^{1}H (300 MHz)			^{13}C (75 MHz)		
	3a	**3b**	**3c**	**3a**	**3b**	**3c**
1	3.60 d, 19.5 Hz 3.69 d, 19.5 Hz	3.57 d, 20 Hz 3.66 d, 20 Hz	3.51 d, 19.5 Hz 3.61 d, 19.5 Hz	44.75	44.74	43.74
2	-	-	-	210.70	210.70	210.81
3	2.68-2.76 m	2.63-2.72 m	2.63-2.72 m	48.99	49.12	48.92
4	2.78 dd, 14.7, 9.8 Hz 2.97 dd, 14.7, 4.2 Hz	2.77 dd, 15.5, 9.5 Hz 2.96 dd, 15.5, 4.5 Hz	2.73 dd, 14.5, 9.5 Hz 2.91 dd, 14.5, 4.5 Hz	33.22	33.09	33.22
4a	-	-	-	135.67	135.64	136.68
5	7.1-7.25 m	7.08-7.23 m	6.62-6.74 m	127.90	127.82	113.15
6	"	"	-	126.76	126.70	158.10
7	"	"	6.62-6.74 m	126.67	126.61	110.91
8	"	"	6.98 d, 8.2 Hz	127.87	127.80	128.56
8a	-	"	-	133.03	132.98	131.44
a	2.55 dd, 13.5, 9.4 Hz 3.25 dd, 13.5, 4 Hz	2.53 dd, 13.5, 9 Hz 3.17 dd, 13.5, 4 Hz	2.53 dd, 13.6, 9.5 Hz 3.17 dd, 13.6, 3.8 Hz	35.75	35.31	35.15
1′	-	-	-	140.78	135.64	136.68
2′	6.72-6.82 m	6.69 d, 1.5 Hz	6.62-6.74 m	114.76	112.11	112.14
3′	-	-	-	159.53	148.70	148.54
4′	6.72-6.82 m	-	-	111.57	147.37	147.20
5′	7.1-7.25 m	6.81 d, 8 Hz	6.77 d, 8.4 Hz	129.34	111.06	111.96
6′	6.72-6.82 m	6.70, dd, 8, 1.5 Hz	6.62-6.74 m	121.42	121.02	120.87
CH_3	3.81 s	3.86 s, 3.87 s	3.86 s, 3.87 s 3.78 s	55.16	55.79, 55.85	55.04, 55.62, 55.67

2,3,4,5-Tetrahydro-4-(3′-methoxybenzyl)-2-oxo-1*H*-3-benzazepine (4a). 1.09 g (23 %) was obtained from 4.78 g of **3a**; mp 139-140°C; IR (KBr) 3200, 3060, 2940, 1660, 1600 cm^{-1} ; MS (m/z, %) 281 (M^+, 13), 160 (74), 132 (100); ^{1}H and ^{13}C NMR data see Table 5; Anal. Calcd for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.69; H, 6.81; N, 4.73.

2,3,4,5-Tetrahydro-4-(3′,4′-dimethoxybenzyl)-2-oxo-1*H*-3-benzazepine (4b). 2.39 g (45 %) was obtained from 5.29 g of **3b**; mp 162-163°C; IR (KBr) 3210, 3060, 2940, 1660, 1590 cm^{-1}; MS (m/z, %) 311 (M^+, 13) 160 (27), 152 (77), 132 (100); ^{1}H and ^{13}C NMR data see Table 5; Anal. Calcd for $C_{19}H_{21}NO_3$: C, 73.28; H, 6.80; N, 4.50. Found: C, 73.03; H, 6.95; N, 4.32.

2,3,4,5-Tetrahydro-4-(3′,4′-dimethoxybenzyl)-7-methoxy-2-oxo-1*H*-3-benzazepine (4c). 2.58 g (44 %) was obtained from 5.54 g of **3c**; mp 155 °C; IR (KBr) 3210, 3070, 2930, 1660, 1610 cm^{-1}; MS (m/z, %) 341 (M^+, 13), 190 (30), 162 (100), 152 (100); ^1H and ^{13}C NMR data see Table 5; Anal. Calcd for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10. Found: C, 69.96; H, 6.85; N, 4.16. HRMS m/z calcd for $C_{20}H_{23}NO_4$: 341.1627; found: 341.1635.

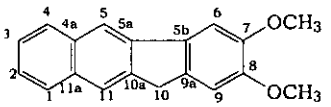
Table 5: The NMR Spectral Data of **4a-c** in $CDCl_3$.



	^1H (300 MHz)			^{13}C (75 MHz)		
	4a	**4b**	**4c**	**4a**	**4b**	**4c**
1	3.70 d, 15.4 Hz 3.89 d, 15.4 Hz	3.70 d, 15.4 Hz 3.87 d, 15.4 Hz	3.65 d, 15.4 Hz 3.79 d, 15.4 Hz	42.58	42.55	41.72
2	-	-	-	171.12	171.07	171.35
4	3.85-3.95 m	3.81-3.87 m	3.79-3.87 m,	55.17	54.96	55.31
5	3.03 dd, 15.3, 9.9 Hz 3.13 dd, 15.3, 3.8 Hz	3.02 dd, 15.3, 9.6 Hz 3.12 dd, 15.3, 3.8 Hz	3.03 dd, 15.3, 9.6 Hz 3.10 dd, 15.3, 3.9 Hz	37.81	37.74	38.10
5a		-	-	136.13	136.23	137.46
6	7.10-7.28 m	7.11-7.25 m	6.67-6.76 m	129.31	129.26	115.22
7	"	"	-	127.25	127.25	158.69
8	"	"	6.67-6.76 m	127.04	127.14	111.75
9	"	"	7.08 d, 8.2 Hz	129.23	129.14	130.32
9a	-	-	-	132.98	133.01	125.25
a	2.72 dd, 13.6, 8.2 Hz 2.86 dd, 13.6, 5.6 Hz	2.67 dd, 13.7, 8.3 Hz 2.83 dd, 13.7, 5.5 Hz	2.65 dd, 14.0, 8.8 Hz 2.84 dd, 14.0, 5.3 Hz	43.25	42.92	43.08
1′	-	-	-	138.23	129.10	129.03
2′	6.72-6.84 m	6.69 d, 2 Hz	6.67-6.76 m	112.17	111.45	111.46
3′	-	-	-	159.73	149.03	149.08
4′	6.72-6.84 m	-	-	114.96	147.94	148.01
5′	7.10-7.28 m	6.81 d,8.1 Hz	6.82 d, 8.1 Hz	129.77	112.19	112.10
6′	6.72-6.84 m	6.69 dd, 8.1, 2 Hz	6.67-6.76 m	121.39	121.27	121.28
NH	5.88-5.93 br	5.91-5.96 br	5.55-5.59 br	-	-	-
CH_3	3.79 s	3.85 s, 3.86 s	3.79 s, 3.86 s, 3.87 s	54.69	55.87, 55.90	54.87, 55.93, 55.96

NH with D_2O exchangeable

7,8-Dimethoxy-10H-benzo[*b*]fluorene.



The mother liquor of the lactam **(4b)** was evaporated and the residue chromatographed (ethyl acetate-light petroleum) yielding 0.4 g (9 %) of slight yellow solid; mp 158-159°C; IR (KBr) 3005, 2930, 1605 cm^{-1}; MS (m/z, %) 277 (21), 276 (M^+, 100), 261 (17), 245 (20), 233 (10), 215 (11), 202 (10), 189 (17), 138 (12); ^1H NMR (300 MHz): 8.05 (s, 1H, 11-H), 7.91 (m, 1H, 1-H), 7.90 (s, 1H, 5-H), 7.84 (dd, J = 7.5, 2.3 Hz, 1H, H-4), 7.42-7.48 (m, 2H, H-2 and H-3), 7.41 (s, 1H, H-6), 7.09 (s, 1H, H-9), 4.03 (s, 3H, CH_3), 3.97 (s, 3H, CH_3), 3.57 (s, 2H, H-10); ^{13}C NMR (75 MHz): 149.44, 148.87 (C-7, C-8), 140.88, 141.50 (C-5a, C-10a), 136.33 (C-9a), 133.46, 133.06, 132.21 (C-4a, C-5b, C-11a), 127.76, 127.70 (C-1, C-4), 125.26, 124.81 (C-2, C-3), 122.28 (C-11), 116.15 (C-5), 108.18 (C-9), 103.40 (C-6), 56.22, 56.18 (2 x CH_3), 36.29 (C-10); Anal. Calcd for $C_{19}H_{16}O_2$: C, 82.58; H, 5.84. Found: C, 81.09; H, 6.16. HRMS m/z calcd for $C_{19}H_{16}O_2$: 276.1150; found: 276.1144

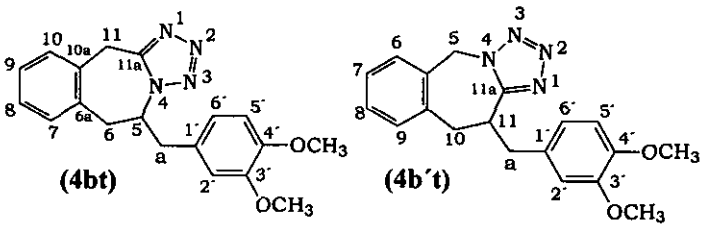
Mixture of **5,6-Dihydro-5-(3′,4′-dimethoxybenzyl)-11*H*-tetrazolo[5,1-*b*][3]benzazepine (4bt)** and **10,11-Dihydro-11-(3′,4′-dimethoxybenzyl)-5*H*-tetrazolo[1,5-*b*][2]benzazepine (4b′t)** in 4:1 ratio. To a stirred solution of $TiCl_4$ (0.57 g, 3 mmol) in dry acetonitrile (30 mL), 0.78 g (12 mmol) of sodium azide was added, followed by dimethoxybenzyl-2-tetralone **(3b)** (0.45 g, 1.5 mmol) in dry acetonitrile (30 mL). The mixture was heated under reflux for 4 h and diluted with 2M HCl (30 mL). Acetonitrile was removed *in vacuo* and the residue was extracted with chloroform (4 x 20 mL). The combined extracts were dried over $MgSO_4$ and evaporated. The residual red oil was chromatographed (ethyl acetate-light petroleum 1:2) to give a tetrazole mixture (0.23 g, 46 %, 4bt/4b′t ratio estimated by means of ^1H NMR spectrum) as a slightly yellow crystalline solid. Recrystallization from ether-light petroleum provided colourless crystals with the same 4bt/4b′t ratio; mp 157-158°C; IR (KBr) 2940, 2840, 1730, 1600, 1590 cm^{-1} ; MS (m/z, %) 337 (7), 336 (M+, 33), 157 (8), 152 (13), 151 (100); ^1H and ^{13}C NMR data see Table 6; Anal. Calcd for $C_{19}H_{20}N_4O_2$: C, 67.84; H, 5.99; N, 16.66. Found: C 67.55, H 6.05, N 16.44. HRMS m/z calcd for $C_{19}H_{20}N_4O_2$: 336.1586; found: 336.1584.

Mixture of **(*E*) and (*Z*)-3-(3′,4′-dimethoxybenzyl)-2-tetralone oxime (3b-oximes)** in 4:1 ratio.

A solution of **3b** (1.19 g, 4 mmol), hydroxylamine hydrochloride (0.56 g, 8 mmol) and sodium acetate (0.66g, 8 mmol) in ethanol (80 mL) and water (20 mL) was refluxed for 2 h. After cooling and adding of water (100 mL), a white precipitate was separated. The mixture was extracted with dichloromethane. The combined extracts were washed with water before drying over $MgSO_4$. Removal of the solvent left a foamy yellow residue which was chromatographed (ethyl acetate-light petroleum 1:2) to afford an oxime

mixture (0.66 g, 53 %, *E/Z* ratio 4:1 estimated by means of ^{1}H NMR spectrum) as colourless crystalline solid. Recrystallization from chloroform-light petroleum provided colourless crystals with the same *E/Z* ratio; mp 131°C; IR (KBr) 3260 , 3010, 2940, 2840, 1590, 1515 cm^{-1}; MS (m/z, %) 311 (M^+, 18), (295 15), 203 (8), 152 (23), 151 (100), 144 (27), 143 (22); ^{1}H and ^{13}C NMR data see Table 7; Anal. Calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.16; H, 6.80; N, 4.48. HRMS m/z calcd for $C_{19}H_{21}NO_3$: 311.1522; found: 311.1524.

Table 6: The NMR Spectral Data of **4bt** and **4b′t** in $CDCl_3$.

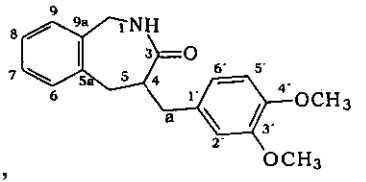


4bt			4b′t		
	^{1}H (300 MHz)	^{13}C (75 MHz)		^{1}H (300 MHz)	^{13}C (75 MHz)
11	4.17 d, 16.3 Hz 4.28 d, 16.3 Hz	29.14	5	5.45 d, 14.9 Hz 5.54 d, 14.9 Hz	51.00
11a	-	151.45	11a	-	155.47
5	4.93-5.03 m	60.45	11	3.65-3.75 m	37.68
6	3.15-3.26 m	33.27	10	3.03-3.15 m	32.50
6a	-	134.57	10a	-	137.63
7-10	7.15-7.35 m	130.11 128.46 127.81 127.71	6-9	7.15-7.35 m	130.06 129.27 128.36 127.18
10a	-	134.54	6a	-	132.73
a	3.08 dd, 13.9, 8.7 Hz 3.42 dd, 13.9, 3.4 Hz	40.56	a	2.90 dd, 13.8, 8.7 Hz 3.39 dd, 13.8, 3.4 Hz	39.74
1′	-	127.34	1′	-	129.63
2′	6.50 d, 1.8 Hz	111.95	2′	6.64 d, 1.8 Hz	111.95
3′	-	148.66	3′	-	148.60
4′	-	147.80	4′	-	147.50
5′	6.84 d, 8.1 Hz	111.01	5′	6.84 d, 8.1 Hz	110.90
6′	6.69 dd, 8.1, 1.8 Hz	121.45	6′	6.74 dd, 8.1, 1.8 Hz	121.23
OCH_3	3.81 s, 3.88 s	55.63, 55.63	OCH_3	3.82 s, 3.88 s	55.63, 55.63

Mixture of **4b** and **2,3,4,5-Tetrahydro-4-(3′,4′-dimethoxybenzyl)-3-oxo-1*H*-2-benzazepine (4b′)** in 10:3 ratio. The oxime mixture (0.47 g, 1.5 mmol) prepared above was dissolved in chloroform (50 mL) and cooled to -70°C using a dry ice-acetone bath. Phosphorus pentachloride (0.45 g, 2.2 mmol) was added portionwise with stirring so as to maintain the internal temperature at -50°C. The mixture was stirred for 1 h at -50°C, for 2 h at -25°C and after removal of the cooling bath for further 4 h. Water (100 mL) was added and the mixture was extracted with chloroform. The combined extracts were washed with water

and dried over $MgSO_4$. Removal of the solvent afforded a yellow oil which was chromatographed (ethyl acetate) to afford a lactam mixture (0.16 g, 34 %, 4b/4b′ ratio 10:3 estimated by means of 500 MHz ^{1}H NMR spectrum) as slightly yellow crystalline solid; mp 148-149°C; IR (KBr) 3200, 3050, 2950, 2830, 1650, 1590 cm^{-1}; MS (m/z, %) 311 (M^+,13), 160 (27), 152 (77), 132 (100).

The NMR spectral data of **4b′**



^{1}H NMR (500 MHz): 7.2 (d, J = 8.2 Hz, 1H, 5′-H), 7.05-7.25 (m, 4H , 6-H - 9-H), 6.75 (dd, J = 8.2, 1.8 Hz, 1H, 6′-H), 6.68 (d, J = 1.8 Hz, 1H, 2′-H), 6.50 (t, J = 6.1 Hz, 1H, NH), 4.65 (dd, J = 16.1, 5.8 Hz, 1H, 1-H^b), 4.04 (dd, J = 16.1, 6.2 Hz, 1H, 1-H^a), 3.87 (s, 3H, CH_3), 3.86 (s, 3H, CH_3), 3.22-3.29 (m, 1H, 4-H), 3.28 (dd, J = 14.0, 5.0 Hz, 1H, a-H^b), 2.84 (dd, J = 14.0, 5.5 Hz, 1H, a-H^a), 2.99 (dd, J = 16.4, 3.8 Hz ,1H, 5-H^b), 2.920 (dd, J = 16.4, 11.3; 1H, 5-H^a); ^{13}C NMR (75 MHz 176.68 (C-3), 148.65, 147.32 (C-3′, C-4′), 137.54, 135.65, 132.10 (C-9a, C-5a, C-1′), 130.32, 127.89, 127.08, 126.14 (C-6 - C-9), 121.17 (C-6′), 112.43, 111.05 (C-5′, C-1′), 55.90, 55.87 (2 x OCH_3), 45.75 (C-1), 43.72 (C-4), 37.40 (C-a).

Synthesis of benzazepines (5a-c)

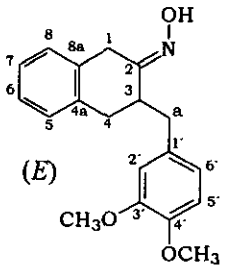
General procedure. The 1M diborane solution (20 mL, 20 mmol) in THF (*Aldrich*) was added dropwise to an ice-cooled and stirred solution of the corresponding lactam **(4a-c)** (4 mmol) in dry THF (100 mL) over a period of 15 min. The ice bath was removed and stirring was continued for further 60 min. After heating for another 2 h at 60 °C, the reaction mixture was allowed to cool to rt and then 2M HCl (100 mL) was slowly added with ice-cooling to destroy the excess diborane. The solution was heated for 30 min under reflux, made alkaline with 20 % NaOH (50 mL) with ice-cooling and extracted with chloroform (3 x 100 mL). The organic extract was washed with water and dried over $MgSO_4$. The solvent was removed *in vacuo* to give colourless oils shown by ^{1}H NMR to be pure amines **(5a-c)**

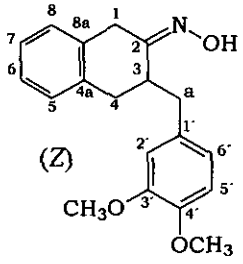
2,3,4,5-Tetrahydro-2-(3′-methoxybenzyl)-1*H*-3-benzazepine (5a). 1.03 g (96 %) was obtained from 1.13 g of **4a**; n_D^{21} = 1.5762; IR (neat) 3250 , 3005, 2900, 2840, 1580 cm^{-1}; MS (m/z, %) 268 (0.5), 267 (M^+, 1.7), 266 (1.8), 265 (1), 264 (0.8), 162 (8), 147 (27), 146 (100), 145 (4), 144 (6), 131 (6), 130 (7), 129 (11), 117 (20), 115 (12), 91 (18); ^{1}H and ^{13}C NMR data see Table 8; Anal. Calcd for $C_{18}H_{21}NO$: C, 80.86; H, 7.92; N, 5.24. Found: C, 80.93; H, 7.92; N 5.00.

2,3,4,5-Tetrahydro-2-(3′,4′-dimethoxybenzyl)-1*H*-3-benzazepine (5b). 1.15 g (97 %) was obtained from 1.24 g of **4b**; n_D^{21} = 1.5751; IR (neat) 3250, 3000, 2900, 2830, 1585 cm^{-1}; MS (m/z, %) 298 (0.2), 297 (M^+, 0.5), 296 (1.1), 295 (0.2), 147 (12), 146 (100), 145 (2), 144 (3), 131 (2), 130 (3), 129 (8), 117 (7), 115 (3), 91 (4); ^{1}H and ^{13}C NMR data see Table 8; Anal. Calcd for $C_{19}H_{23}NO_2$: C, 76.74; H, 7.80; N 4.71. Found: C, 74.95; H, 7.78; N, 4.50. HRMS m/z calcd for $C_{19}H_{23}NO_2$: 297.1729; found: 297.1738.

2,3,4,5-Tetrahydro-2-(3′,4′-dimethoxybenzyl)-8-methoxy-1*H*-3-benzazepine (5c). 1.30 g (99 %) was obtained from 1.37 g of **4c**; n_D^{21} = 1.5629; IR (neat) 3250, 3000, 2900, 2830, 1585 cm^{-1}; MS (m/z, %) 328 (0.2), 327 (M^+,0.2), 326 (0.5), 325 (0.8), 324 (0.5), 205 (5), 178 (12), 176 (100), 161 (2); 160 (1), 159 (2), 147 (3); ^1H and ^{13}C NMR data see Table 8; Anal. Calcd for $C_{20}H_{25}NO_3$: C, 73.37; H, 7.70; N, 4.28. Found: C, 72.08; H, 7.80; N, 4.10. HRMS m/z calcd for $C_{20}H_{25}NO_3$: 327.1835; found: 327.1838.

Table 7: The NMR Spectral Data of the **3b - oximes** in $CDCl_3$.





	(*E*)-3b-oxime		(*Z*)-3b-oxime	
	^1H (300 MHz)	^{13}C (75 MHz)	^1H (300 MHz)	^{13}C (75 MHz)
1	3.86 d, 21.9 Hz 3.96 d, 21.9 Hz	28.13	3.52 s	34.37
2	-	160.53	-	161.28
3	2.93-3.02 m	40.83	3.60-3.69 m	36.20
4	2.64 dd, 15.5, 5.5 Hz 2.86 dd, 15.5, 4.3 Hz	32.79	2.60-2.77 m	31.99
4a	-	135.02	-	136.33
5	7.05, d, 7 Hz	128.82	7.10-7.25 m	128.16
6-8	7.10-7.25 m	126.55 126.22 128.45	7.10-7.25 m	126.55 126.22 127.42
8a	-	132.78		134.31
a	2.49 dd, 12, 3.5 Hz 2.90-2.97 m	37.32	2.36 dd, 13.5, 10.3 Hz 3.12 dd, 13.5, 3.8 Hz	35.29
1′	-	131.76	-	131.97
2′	6.63 d, 1.9 Hz	112.21	6.71-6.83 m	112.33
3′	-	148.58	-	148.58
4′	-	147.28	-	147.28
5′	6.80 d, 8 Hz	111.02	6.71-6.83 m	112.19
6′	6.65 dd, 8, 1.9 Hz	121.02	6.71-6.83 m	121.19
OH	9.04-9.42 br	-	9.04-9.42 br	-
OCH_3	3.85 s, 3.87 s	55.77, 55.85	3.88 s, 3.87 s	55.77, 55.85

OH with D_2O exchangeable

Synthesis of isoquinobenzazepines (6a-c)

General procedure. The benzazepines **(5a-c)** (obtained from 4 mmol of **4a-c**) were dissolved in dichloromethane (20 mL) and treated with ether saturated with HCl gas (100 mL). The mixture was

concentrated to dryness and the resulting foamy hydrochlorides were taken up in boiling water (200 mL). Paraformaldehyde was added (0.36 g, 12 mmol). The reaction mixture was refluxed for 14 h and then made alkaline with 20 % NaOH with cooling on an ice bath. After extraction with chloroform (3 x 100 mL), the combined organic layers were washed with water and dried over $MgSO_4$. Evaporation yielded the crude products which were purified by column chromatography (**6a**: ethyl acetate-methanol 20:1, **6b** and **6c**: methanol).

5,6,8,13,13a,14-Hexahydro-11-methoxyisoquino[3,2-*b*][3]benzazepine (6a). 0.81 g (76 %) were obtained from 1.03 g of **5a** as colourless solid; mp 101-103°C. Recrystallization from isopropanol afforded colourless crystals; mp 103-104°C; IR (KBr) 2900, 2800, 2760, 1600, 1500 cm^{-1}; MS (m/z, %) 280 (16), 279 (83), 278 (M^+,100), 264 (7), 174 (23), 161 (12), 160 (9), 159 (6), 147 (10), 146 (7), 134 (26), 119 (24), 117 (12), 115 (8), 91 (15); ^1H and ^{13}C NMR data see Table 9; Anal. Calcd for $C_{19}H_{21}NO$: C, 81.68; H, 7.58; N, 5.01. Found: C, 81.68; H, 7.57; N, 5.04. HRMS m/z calcd for $C_{19}H_{21}NO$: 278.1545; found: 278.1528.

5,6,8,13,13a,14-Hexahydro-10,11-dimethoxyisoquino[3,2-*b*][3]benzazepine (6b). 0.84 g (70 %) were obtained from 1.15 g of **5b** as colourless, partly solidified oil. Recrystallization from ethyl acetate afforded colourless crystals; mp 112-113°C; IR (KBr) 2900, 2830, 2770, 1610, 1510 cm^{-1}; MS (m/z, %) 310 (10), 309 (M^+, 70), 308 (100), 294 (6), 205 (6), 204 (21), 191 (8), 190 (6), 189 (6), 176 (6), 165 (5), 164 (36), 149 (6), 119 (25), 117 (7), 91 (6); ^1H and ^{13}C NMR data see Table 9; Anal. Calcd for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49; N, 4.53. Found: C, 77.30; H, 7.60; N, 4.37.

5,6,8,13,13a,14-Hexahydro-2,10,11-trimethoxyisoquino[3,2-*b*][3]benzazepine (6c). 0.97 g (71 %) were obtained as colourless solid; mp 137-138°C. Recrystallization from isopropanol afforded colourless crystals; mp 139°C, IR (KBr) 3005, 2910, 2880, 2840, 2770, 1610, 1580 cm^{-1}; MS (m/z, %) 340(18), 339(M^+, 82), 338(100), 324(7),217(8), 205(11), 204(32) 189(12) 164(38), 149(65) 148(11),45(68); ^1H and ^{13}C NMR see Table 9; Anal. Calcd for $C_{21}H_{25}NO_3$: C, 74.31; H, 7.42; N, 4.13. Found: C, 73.80; H, 7.38; N, 4.12. HRMS m/z calcd for $C_{21}H_{25}NO_3$: 339.1834; found: 339.1828.

5,6,8,13,13a,14-Hexahydro-12-hydroxymethyl-11-methoxyisoquino[3,2-*b*][3]benzazepine (6d).

0.53 g (2 mmol) of **5a** was treated with 2M HCl (10 mL), followed by aqueous 30 % formaldehyde (2 mL, *ca.* 20 mmol). The mixture was refluxed for 2 h. After beeing cooled and basified with 20 % NaOH, the mixture was extracted with chloroform (3 x 50 mL). The combined organic layers were washed with water, dried over $MgSO_4$ and concentrated *in vacuo*. The white foamy residue was recrystallized from ethyl acetate yielding 0.07 g (11 %) of **6d** as colourless crystalls, mp 189°C; IR (KBr) 3260 , 3020, 3000, 2940 , 2900, 2830, 2760, 1600 cm^{-1}; MS (m/z, %) 310 (15), 309 (M^+, 88), 308 (100),

294 (14), 278 (11), 204 (32), 191 (12), 119 (63), 117 (23), 115 (20), 105 (10), 103 (11), 91 (23); ^{1}H and ^{13}C NMR see Table 9; Anal. Calcd for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49; N, 4.53. Found: C, 77.12; H, 7.35; N, 4.45. HRMS m/z calcd for $C_{20}H_{23}NO_2$: 309.1729; found: 309.1727.

0.06 g (10 %) of colourless solid separated from the mother liquor. This was shown by ^{1}H NMR to be a 1: 2.5 mixture of **6d** and **5,6,8,13,13a,14-Hexahydro-10-hydroxymethyl-11-methoxyisoquino-[3,2-*b*][3]benzazepine.**

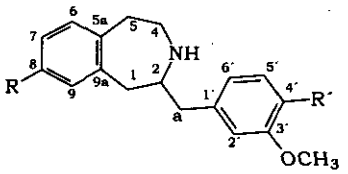


Table 8: The NMR Spectral Data of **5a-c** in $CDCl_3$.

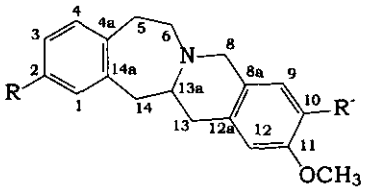
	^{1}H (300 MHz)			^{13}C (75 MHz)		
	5a	**5b**	**5c**	**5a**	**5b**	**5c**
1	2.82-3.01 m	2.76-2.90 m	2.72-2.92 m	44.83	44.85	44.88
2	2.87-2.95 m	2.76-2.90 m	2.72-2.92 m	58.80	59.09	59.14
4	2.65 ddd, 12.5, 10.5, 1.2 Hz 3.20 ddd, 12.5, 6.7, 1.7 Hz	2.57-2.69 3.19 ddd, 12.5, 6.6, 1.7 Hz	2.54-2.72 3.17 ddd, 12.5, 6.4, 1.8 Hz	48.01	48.18	48.49
5	2.76-2.85 m 3.07 ddd, 14.6, 10.5, 1.7 Hz	2.76-2.90 m 3.05 ddd, 14.6, 10.7, 1.6 Hz	2.72-3.03 m	38.81	38.80	37.76
5a	-	-	-	140.40	140.48	134.34
6	7.08-7.18 m	7.06-7.14 m	7.00 d, 8.8 Hz	129.45	129.45	129.90
7	"	"	6.62-6.67 m	126.12	126.19	112.08
8	"	"	-	126.00	126.05	157.73
9	"	"	6.62-6.67 m	128.93	129.00	115.72
9a	-	-	-	142.14	142.19	141.70
a	2.71 dd, 13.1, 8.6 Hz 2.82-2.93	2.57-2.69 m 2.95 dd, 13.9, 8.8 Hz	2.54-2.95 m	43.80		
1'	-	-	-	140.35	131.31	131.22
2'	6.77-6.87 m	6.73 d, 1.8 Hz	6.73 d, 2 Hz	114.55	111.18	111.17
3'	-	-	-	159.53	148.77	148.78
4'	6.77-6.87 m	-	-	111.87	147.44	147.45
5'	7.21-7.27 m	6.83 d, 7.9 Hz	6.82 d, 8.1 Hz	129.38	112.08	112.08
6'	6.77-6.87 m	6.76 dd, 7.9, 1.8 Hz	6.76 dd, 8.1, 2 Hz	121.43	121.09	121.09
NH	2.08-2.17 br	2.03-2.15 br	2.16-2.35 br	-	-	-
OCH_3	3.81 s	3.85 s, 3.87 s	3.78 s, 3.85 s, 3.86 s	55.07	55.79, 55.86	55.22, 55.80, 55.87

NH with D_2O exchangeable

5,6,8,13,13a,14-Hexahydro-10,11-dimethoxyisoquino[3,2-*b*][3]benzazepine hydrochloride (6b ·HCl). A solution of **6b** (0.31 g, 10 mmol) in chloroform (10 mL) was treated with ether saturated with HCl gas

(20 mL). After standing in a refrigerator for 48 h, **6b**·**HCl** (0.17 g, 49 %) was separated as colourless crystals; mp 220-222°C; IR (KBr) 3350, 2940, 2800, 2550, 1605 cm^{-1}; ^1H NMR (500 MHz): 13.23-13.44 (br, 1H, NH, exchangeable with D_2O), 7.11-7.26 (m, 4H, 1-H - 4-H), 6.51 (s, 1H, 9-H), 6.47 (s, 1H, 12-H), 4.09 (m, 1H, 13a-H), 4.78 (d, J = 15.8 Hz, 1H, 8-H^{ax}), 3.99 (d, J = 15.8 Hz, 1H, 8-H^{eq}), 4.26 (d, J = 16.5 Hz, 1H, 14-H^{ax}), 2.97 (dd, J = 16.5, 5.5 Hz, 1H, 14-H^{eq}), 3.42 (dd, J = 12.5, 5.6 Hz, 1H, 6-H^{eq}), 3.09 (dd, J = 22.2, 12.5 Hz, 1H, 6-H^{ax}), 3.78 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.92-4.01 (1H, 5-H^{ax}), 2.86 (dd, J = 16.3, 5.5 Hz, 1H, 5-H^{eq}); ^{13}C NMR data see Table 10; Anal. Calcd for $C_{20}H_{24}ClNO_2$: C, 69.45; H, 6.99; Cl, 10.25; N 4.05. Found: C, 69.05; H, 7.02; Cl, 9.99; N, 4.11.

Table 9: The ^1H NMR Spectral Data of **6a-c** in $CDCl_3$ and **6d** in $CDCl_3$ + CD_3OD.



	6a (300 MHz)	**6b** (500 MHz)	**6c** (300 MHz)	**6d** (300 MHz)
1	7.10-7.22 m	7.09-7.17 m	6.72 d, 2.8 Hz	7.01-7.11
2	"	"	-	"
3	"	"	6.67 dd, 8.1, 2.8 Hz	"
4	"	"	7.01 d, 8.1 Hz	"
5	2.85-2.95 m 3.15-3.23 m	2.95-3.04 m 3.11-3.18 m	2.81-2.96 m 3.00-3.15 m	2.79-2.97 m 3.01-3.17 m
6	2.52-2.60 m 3.11-3.20 m	2.57-2.64 m 3.11-3.18 m	2.49-2.58 m 3.00-3.15 m	2.38-2.48 m 3.01-3.17 m
8	3.74 d, 15.2 Hz 3.87 d, 15.2 Hz	3.80 br s	3.78 br s	3.59 d, 15 Hz 3.75 d, 15Hz
9	6.96 d, 8.4 Hz	6.51 s	6.50 s	6.89 d, 8.5 Hz
10	6.72 dd, 8.4, 2.5 Hz	-	-	6.67 d, 8.5 Hz
11	-	-	-	-
12	6.62 d, 2.5 Hz	6.53 s	6.53 s	-
13	2.70-2.79 m	2.63-2.73 m	2.59-2.73 m	2.64-2.75 m
13a	2.81-2.89 m	2.88-2.97 br	2.81-2.96 m	2.79-2.97 m
14	2.93-2.99 m 3.06-3.12 m	2.96-3.03 m 3.06-3.10 m	2.81-2.96 m 3.00-3.15 m	2.79-2.97 m 3.01-3.17 m
OCH_3	3.76 s	3.817 s, 3.822 s	3.79 s, 3.82 s, 3.82 s	3.76 s
CH_2OH	-	-	-	4.58 d, 11.8 Hz 4.63 d, 11.8 Hz

Table 10: The ^{13}C NMR Spectral Data of **6a-c** in $CDCl_3$ and **6d**, **6b** · **HCl** in $CDCl_3 + CD_3OD$.

	6a (75 MHz)	**6b** (75 MHz)	**6b** · **HCl** (125 MHz)	**6c** (75 MHz)	**6d** (75 MHz)
1	128.28	128.16	129.426	115.68	128.09
2	126.27[b]	126.13[b]	127.843	157.99	126.35[b]
3	126.55[b]	126.39[b]	127.995	110.77	126.42[b]
4	129.48	129.35	130.747	129.14	129.41
4a	142.26	142.10	138.438	140.56	141.82
5	35.31	35.47	32.489	34.51	34.65
6	54.73 br	54.43 br	49.172	54.62 br	55.07 br
8	58.25	58.51	57.035	58.47	58.63
8a	125.97	125.58[a]	117.175	125.59[a]	125.62[a]
9	126.91	108.77	109.366	108.81	126.57
10	112.14	147.12	149.316	147.22	108.79
11	157.95	147.38	148.733	147.47	156.40
12	112.65	110.86	111.176	110.89	133.44
12a	134.99	125.52[a]	121.643	125.64[a]	125.84[a]
13	34.94 br	33.85 br	26.331	33.46 br	32.28 br
13a	57.57	57.54	56.089	57.41	57.98
14	42.30	42.32	37.080	42.42	42.14
14a	139.26	139.17	135.411	134.44	138.88
OCH_3	55.18	55.83, 55.87	56.003, 56.157	55.18, 55.81, 55.84	55.45
CH_2OH	-	-	-	-	55.69

[a,b] interchangeable values

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8. 4-Methoxyphenylacetyl chloride was obtained by refluxing of the corresponding acid with thionyl chloride and catalytic amount of DMF in chloroform solution. After evaporating *in vacuo*, the red residue was distilled at *ca.* 0.2 torr.

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13. 3-Methoxy- and 3,4-dimethoxybenzyl chloride were obtained by refluxing of the corresponding benzyl alkohols with thionyl chloride in chloroform, followed by evaporation *in vacuo* and distillation at *ca.* 0.2 torr (3-methoxybenzyl chloride) or recrystallization from ether (dimethoxybenzyl chloride).

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