Synthesis of the tetracyclic skeleton of the galanthamine-type *Amaryllidaceae* alkaloids

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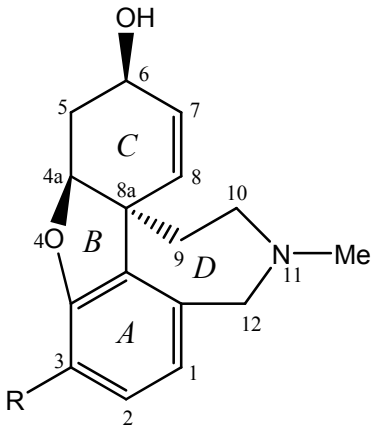
Abstract
The hexahydrobenzofurobenzazepine tetracycle characteristic of the principal galanthamine-type *Amaryllidaceae* alkaloids was synthesized from a methoxy substituted 2-tetralone *via* simple and convenient reaction steps.

Keywords: *Amaryllidaceae* alkaloids, galanthamine, tetracycle, benzofurobenzazepine

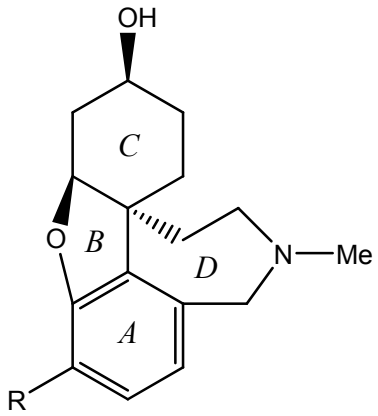
Introduction

(-)-Galanthamine (**1a**) and (-)-lycoramine (**2a**), alkaloids isolated from the bulbs of various species of the *Amaryllidaceae* family, contain a saturated benzofurobenzazepine tetracyclic skeleton consisting of four rings *A*-*D*.

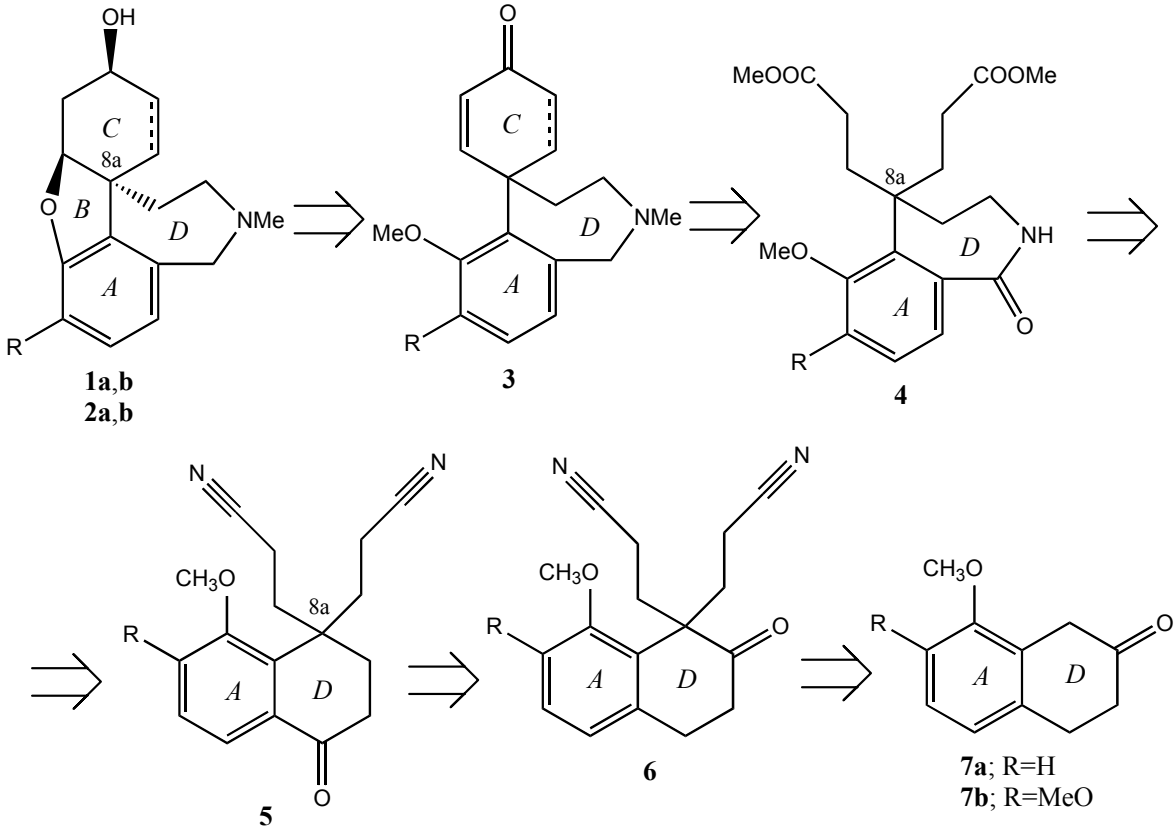
Galanthamine has an important role in the treatment of Alzheimer's disease as an acetylcholinesterase inhibitor[1] as well as a modulator of neuronal nicotinic receptors. Lycoramine has similar, but less potent activity. A number of total syntheses for galanthamine[2,3] and lycoramine[3-7] have been developed. These methods employ various approaches to building up the C-8a quaternary spiro carbon atom and the *A*-*D* rings. However, only few data can be found in the literature[8] on the chemistry and pharmacology of their demethoxy derivatives **1b** and **2b**. Recently[9] we established an efficient synthesis of benzazepines spiro-substituted with a cyclohexenone ring starting from an unsubstituted 2-tetralone. In the present paper we report an extension of that method for methoxy-substituted 2-tetralones according to the retrosynthetic route shown in Scheme 1.



Galanthamine, **1a**; R=OMe
Demethoxygalanthamine, **1b**; R=H



Lycoramine, **2a**; R=OMe
Demethoxylycoramine, **2b**; R=H



1a,**b**
2a,**b**

3

4

5

6

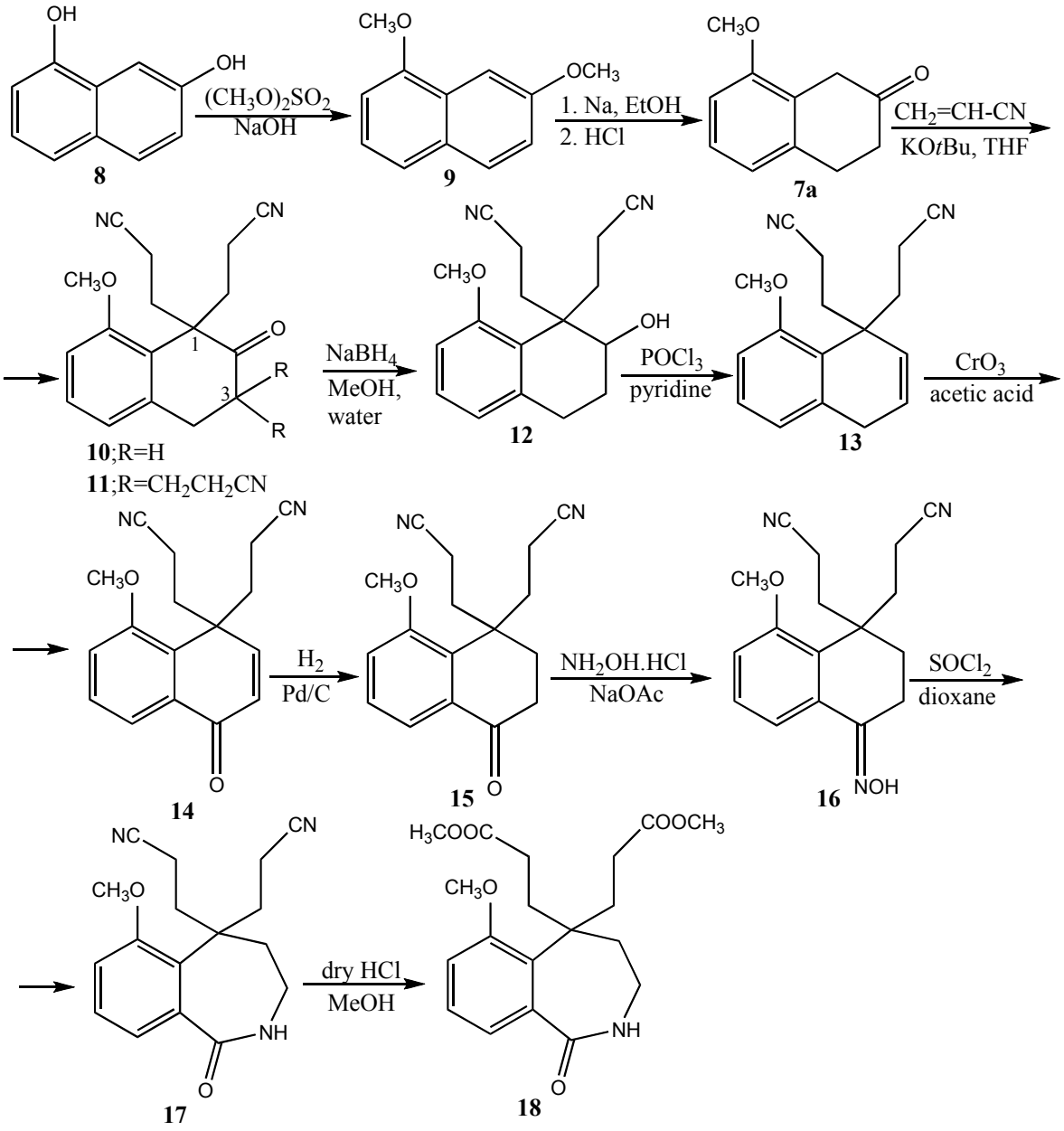
7a; R=H
7b; R=MeO

Scheme 1

The object of this work is the synthesis of the hexahydrobenzofurobenzazepine tetracycle characterising the galanthamine-type alkaloids. Our synthetic method started from 8-methoxy-2-tetralone and used simple reaction steps and inexpensive reagents. The C-8a spiro carbon atom was produced *via* a Dieckmann condensation.

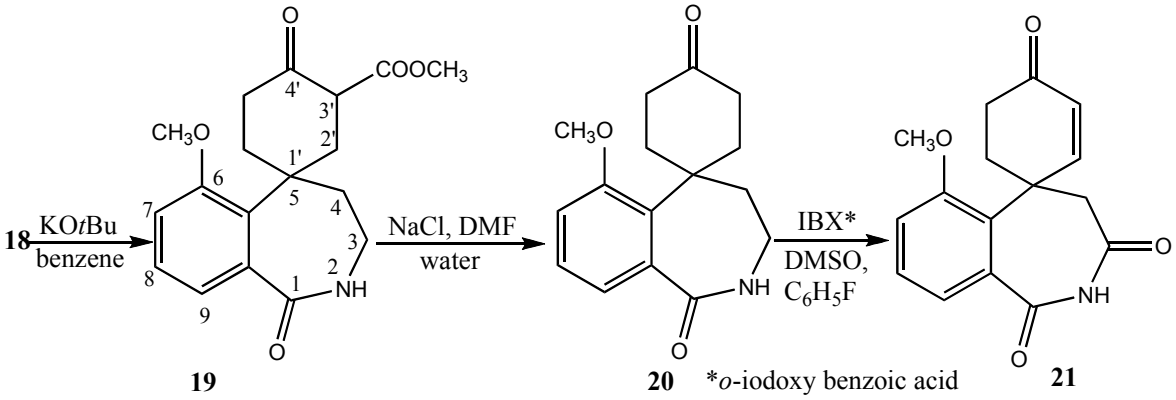
Results and Discussion

The starting material 8-methoxy-2-tetralone (**7a**) is not commercially available, but can be readily prepared from 1,7-dihydroxynaphthalene (**8**) using known methods (Scheme 2).[10,11] Compound **8** was methylated with dimethyl sulfate under alkaline conditions (93%) and the Birch reduction of the dimethoxy derivative **9** gave ketone **7a** in a good yield (86%).



Scheme 2

Cyanoethylation of tetralone **7a** at C-1 was carried out by reaction with acrylonitrile in THF and *t*-BuOH solution in 96% yield using potassium *tert*-butoxide as catalyst. The 1,3-tetra(cyanoethyl) derivative of **11** was also isolated in small amounts as a by-product. Ketone **10** was reduced (96%) and the corresponding alcohol **12** was quantitatively dehydrated by phosphorus oxychloride in refluxing pyridine. Oxidation of olefin **13** was achieved with chromium(VI) oxide and resulted in ketone **14** in 65% yield. Ketone **14** was catalytically hydrogenated in quantitative yield and compound **15** was converted to oxime **16** by a conventional method (91%). The Beckmann rearrangement of oxime **16** was accomplished in dioxane solution at 70 ^{o}C with thionyl chloride, giving the corresponding benzo[*c*]azepinone **17** in 52% yield. A Pinner reaction was used to convert the nitrile groups into ester substituents; **17** was treated with dry hydrogen chloride gas in refluxing methanol solution and product **18** was isolated in 96% yield. The Dieckmann condensation of diester **18** was carried out in benzene in the presence of potassium *tert*-butoxide forming the desired spiro structure **19** (Scheme 3).

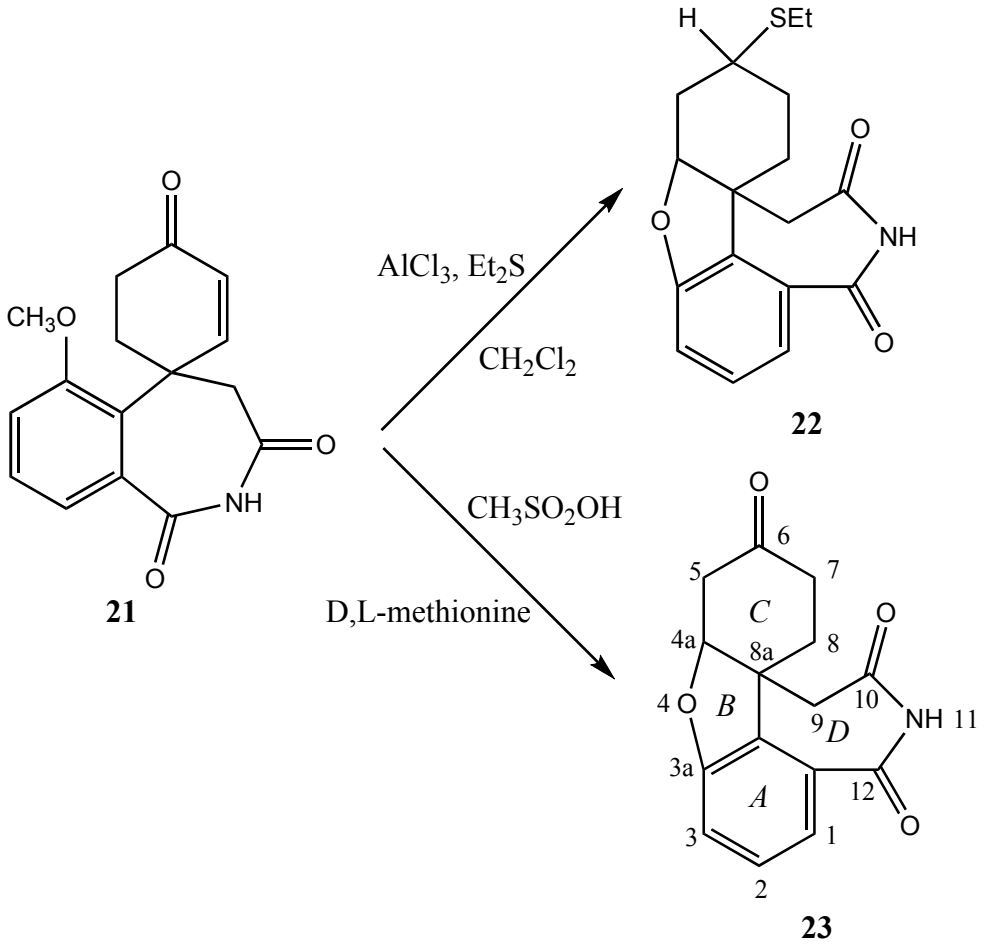


Scheme 3

Demethoxycarbonylation of **19** furnished spiro ketone **20** (62%), followed by formation of the carbon-carbon double bond in the cyclohexanone ring by the method of Nicolaou *et al*.[13] using IBX (*o*-iodoxy benzoic acid)[12] as oxidizing agent, giving the unsaturated key intermediate **21** in 62% yield.

Various reagent systems (boron tribromide, aluminium trichloride/diethyl sulfide, or thiocarbamide, boron trifluoride etherate) were investigated for the *O*-demethylation of imide **21** to initiate the intramolecular addition reaction forming the narwedine-like tetracyclic skeleton. The aluminium trichloride catalyzed reaction with diethyl sulfide in dichloromethane solution resulted in an unexpected product (Scheme 4) as a mixture of two diastereomers (**22**; 14%, D1:D2≈3:2); in reactions with the other reagents only decomposition products could be obtained. Formation of this type of ethylthio derivative in the demethylation reaction conditions, or similar examples, is unknown in the literature. However, using the methanesulfonic acid/D/L-methionine demethylating system, the tetracyclic ketone **23** was obtained almost quantitatively. Although the crude product isolated from the reaction mixture (93%) possessed satisfactory

quality for further reactions, the pure compound was obtained after chromatography in 23.5% yield.



Scheme 4

Conclusions

The successful preparation of the benzofurobenzazepine tetracycle **23** confirmed our synthetic strategy to build useful intermediates for preparing compounds like demethoxynarwedine or demethoxylycoraminone.

Experimental Section

General Procedures. Melting points are uncorrected. IR spectra were recorded on Zeiss IR 75 and 80 instruments. NMR spectra were recorded on a Varian INOVA 300, Varian INOVA 500

or a Varian VNMRS-500 spectrometer. Chemical shifts are given on the delta scale as parts per million (ppm) with tetramethylsilane (TMS) as the internal standard (0.00 ppm). Mass spectrometric measurements were performed on a VG-Trio-2 and a Finnigan MAT 95SQ mass spectrometer using EI (70 eV, 220 °C source temperature) and FIB (Cs^+, 3-nitrobenzyl alcohol matrix, 20 kV) ionization methods. High-resolution MS measurements were carried out on a Thermo LTQ FT Ultra mass spectrometer (ESI, 3.5-4.0 kV spray voltage, 275-300 °C capillary temperature, solvent: MeOH:H_2O 1:1 + 1 V/V% cc. AcOH). The protonated molecular ion peaks were fragmented by CID at a normalized collision energy of 35%. The relative abundance values of the fragment ions in the MS-MS spectrum are given in brackets. TLC was carried out using Kieselgel 60F_{254} (Merck) glass plates. 1,7-Dihydroxynaphthalene (**8**) was purchased from Aldrich. 1,7-Dimethoxynaphthalene[10,11] (**9**), 8-methoxy-2-tetralone[11] (**7a**) and IBX[12] were prepared by literature methods.

3,3′-(8-Methoxy-2-oxo-3,4-dihydronaphthalene-1,1(2*H*)-diyl)di(propanenitrile) (10). To a stirred solution of 8-methoxy-2-tetralone (**7a**) (4.0 g, 22.7 mmol) in *tert*-butanol (22 mL), acrylonitrile (2.7 mL, 2.13 g, 40.2 mmol) was added in THF (5.4 mL) under Ar. Then potassium *tert*-butoxide (550 mg, 4.9 mmol) was added is small portions (20-30 mg) over 10 min until the reaction temperature increased to 40-50 °C. The reaction mixture was then stirred for 20 min, poured into water (130 mL) and extracted with dichloromethane (3 × 130 mL). The combined organic layers were washed with water, dried ($MgSO_4$) and evaporated to dryness under reduced pressure. The residue was purified by column chromatography on silica gel (dichloromethane-methanol 50:1) to yield dinitrile **10 (**6.1 g (96%), mp 109-110 °C. TLC (CH_2Cl_2-MeOH 50:1) R_f 0.6; IR (KBr): 2220, 1705, 1575, 1460, 1250, 1050, 775, 750 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.88-2.10 (m, 4H), 2.43-2.63 (m, 4H, CH_2), 2.71 (t, 2H, CH_2), 3.07 (t, 2H, CH_2), 3.89 (s, 3H, OCH_3), 6.80-6.85 (m, 2H, 2 × ArH), 7.28 (t, 1H, ArH). HRMS: M+H: *m/z* 283.14451, calculated value for $C_{17}H_{19}N_2O_2$: 283.14410 (delta: 1.43 ppm). MS-MS of *m/z* 283 (%): *m/z* 266 (61), 255 (100), 249 (5), 242 (4), 238 (22), 229 (24), 224 (12), 200 (4), 173 (12).

A side product was also isolated (0.18 g, 2%) and was identified as the corresponding 1,3-tetracyanoethyl derivative (**11**); mp 132-133°C (dichloromethane-ethanol). TLC (CH_2Cl_2-MeOH 50:1) R_f 0.3; IR (KBr): 2230, 1700, 1580, 1480, 1270, 770 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.80-2.41 (m, 14H), 2.62-2.74 (m, 2H, CH_2), 3.00 (s, 2H, CH_2), 3.91 (s, 3H, OCH_3), 6.85 (dd, 1H, ArH), 6.95 (dd, 1H, ArH), 7.36 (d, 1H, ArH). MS (EI) *m/z* (%): 388(M^+, 30), 348(100), 334(66), 281(19), 254(21), 240(29), 212(23), 159(22), 115(30). Anal. Calcd for $C_{23}H_{24}N_4O_2$: C 71.11, H 6.23, N 14.42. Found C 70.94, H 6.22, N 14.36%.

3,3′-(2-Hydroxy-8-methoxy-3,4-dihydronaphthalene-1,1(2*H*)-diyl)di(propanenitrile) (12). Ketone **10 (**3.22 g, 11.4 mmol) was dissolved in a mixture of MeOH (222 mL) and water (3 mL) and sodium borohydride (1.2 g, 34.4 mmol) was added in small portions over 1.5 h at 0 °C with stirring. After stirring at 0 °C for 20 min the reaction mixture was acidified (pH 5) with acetic acid. The solvent was evaporated under reduced pressure, 10% aqueous sodium carbonate (50 mL) and water (50 mL) was added to the residue and the mixture was extracted with

dichloromethane (3 × 100 mL). The combined organic layers were washed with water (2 × 150 mL), dried ($MgSO_4$) and evaporated to dryness under reduced pressure to yield pure alcohol **12** (3.01 g, 96%), mp 82 °C. TLC (CH_2Cl_2-MeOH 50:1) R_f 0.43; IR(KBr) 3500, 2230, 1470, 1460, 1205 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.83-2.60 (m, 10H, CH_2), 2.75-2.95 (m, 2H, CH_2), 3.86 (s, 3H, OCH_3), 3.88-3.94 (m, 1H, OH), 6.73 (m, 2H, 2 × ArH), 7.18 (t, 1H, ArH). MS (EI) *m/z* (%): 284 (M^+, 100), 267 (39), 230 (27), 226 (32), 212 (36), 203 (44), 185 (21), 171 (32), 159 (24), 147 (18), 131 (44), 115 (85). Anal. Calcd for $C_{17}H_{20}N_2O_2$: C 71.81, H 7.09, N 9.85. Found C 71.58, H 7.14, N 9.76%.

3,3′-(8-Methoxynaphthalene-1,1(4*H*)-diyl)di(propanenitrile) (13). To a solution of hydroxy derivative **12** (2.0 g, 7.05 mmol) in dry pyridine (14 mL), phosphorus oxychloride (0.96 mL, 1.56 g, 10.17 mmol) was added with stirring. After refluxing for 3 h at 160 °C the reaction mixture was evaporated to dryness under reduced pressure, the residue was poured into ice and acidified with a mixture of water and *conc*. hydrochloric acid 1:1 to pH 1. The acidic mixture was then washed with dichloromethane (3 × 20 mL), the combined organic layers after drying ($MgSO_4$) were evaporated to dryness leaving oily product (**13**) (1.87 g, 99%) which spontaneously crystallized in a refrigerator, mp 108-110 °C. TLC (CH_2Cl_2-MeOH 50:1) R_f 0.8; IR (KBr) 2225, 1600, 1580, 1460, 1260, 1070, 790, 720 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.61-1.66 (m, 2H), 1.74-1.82 (m, 2H), 2.08-2.15 (m, 2H), 2.84-2.92 (m, 2H), 3.40 (m, 2H), 3.87 (s, 3H, OCH_3), 5.24 (dt, 1H, C-CH=CH), 6.15 (dt, 1H, CH=CH-CH_2), 6.75-6.78 (m, 2H, 2 × ArH), 7.22 (t, 1H, ArH). MS (EI) *m/z* (%): 266 (M^+, 21), 250 (6), 226 (10), 212 (84), 197 (7), 171 (100), 141 (20), 128 (17), 115 (26). Anal. Calcd for $C_{17}H_{18}N_2O$: C 76.66, H 6.81, N 10.52. Found C 76.38, H 6.81, N 10.38%.

3,3′-(8-Methoxy-4-oxonaphthalene-1,1(4*H*)-diyl)di(propanenitrile) (14). Unsaturated derivative **13** (2.6 g, 9.7 mmol) was dissolved in acetic acid (100 mL) and CrO_3 (3.6 g, 35.8 mmol) was added dropwise in acetic acid (50 mL)-water (5 mL) solution at 14-16 °C over 1 h under stirring. The reaction mixture was stirred at room temperature for 1 h and isopropanol (100 mL) was added dropwise under external ice-water cooling. After stirring for 1 h at room temperature the reaction mixture was evaporated to dryness in vacuum. The residue was suspended in water (160 mL) and extracted with dichloromethane (3 × 160 mL). The combined organic layers were washed with 10% aqueous sodium hydrogencarbonate (5 × 100 mL) and with brine (100 mL). After drying ($MgSO_4$), the solvent was evaporated to dryness under reduced pressure and the residue was purified by column chromatography on silica gel (dichloromethane-methanol 50:1) yielding of unsaturated ketone **14 (**2.35 g, 65%), mp 142-143 °C (petroleum ether [40-70]-THF). TLC (CH_2Cl_2-MeOH 50:1) R_f 0.27; IR (KBr) 2220, 1680, 1650, 1600, 1580, 1320, 1270, 1060, 810, 770 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.66-1.78 (m, 2H), 1.90-2.05 (m, 4H), 3.15-3.22 (m, 2H), 3.99 (s, 3H, OCH_3), 6.61 (d, 1H, CH=CH), 6.69 (d, 1H, CH=CH), 7.20 (dd, 1H, ArH), 7.53 (dd, 1H, ArH), 7.91 (dd, 1H, ArH). HRMS: M+H: *m/z* 281.12837, calculated value for $C_{17}H_{17}N_2O_2$: 281.12845 (delta: -0.30 ppm). MS-MS of *m/z* 281: *m/z* 264 (4), 250 (2), 240 (100), 227 (25).

3,3′-(8-Methoxy-4-oxo-3,4-dihydronaphthalene-1,1(2*H*)-diyl)di(propanenitrile) (15). Unsaturated ketone **14** (2.05 g, 7.33 mmol) was hydrogenated in a mixture of dichloromethane (93 mL) and ethanol (93 mL) in the presence of 10% palladium on charcoal (0.4 g) at room temperature under atmospheric pressure. The catalyst was filtered off, the filtrate was evaporated to dryness to give the saturated product **15 (**2.07 g, 100%), mp 105-107 °C. TLC (toluene-MeOH 7:1) R_f 0.42; IR (KBr) 2225, 1695, 1460, 1270 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.02-2.30 (m, 8H), 2.58-2.70 (m, 4H), 3.93 (s, 3H, OCH_3), 7.16 (dd, 1H, ArH), 7.40 (t, 1H, ArH), 7.76 (dd, 1H, ArH). MS (FIB) *m/z*: 283 (MH^+); MS-MS of *m/z* 283: 266 (100), 248 (77), 228 (53), 176 (35), 161 (20), 135 (11). Anal. Calcd for $C_{17}H_{18}N_2O_2$: C 72.32, H 6.42, N 9.92. Found C 72.30, H 6.40, N 9.77%.

3,3′-(4-Hydroxyimino-8-methoxy-3,4-dihydronaphthalene-1,1(2*H*)-diyl)di(propanenitrile) (16). To a solution of ketone **15** (1.33 g, 4.7 mmol) in ethanol (34 mL) was added hydroxylamine hydrochloride (0.5 g, 7.1 mmol) dissolved in water (34 mL) and then sodium acetate (0.39 g, 4.74 mmol) was added. The reaction mixture was refluxed for 3 h and then it was poured into water (30 mL). The mixture was extracted with dichloromethane (3 × 20 mL), the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The oily residue crystallized by treatment of a few drops of hexane to give product (**16**) (1.27 g, 91%), mp 120-121 °C. TLC (CH_2Cl_2-MeOH 40:1) R_f 0.4; IR (KBr) 3500, 2225, 1310, 1270, 960 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.78-1.82 (m, 2H), 1.86-2.02 (m, 2H), 2.16-2.24 (m, 4H), 2.50-2.60 (m, 2H) 2.80-2.86 (m, 2H), 3.89 (s, 3H, OCH_3), 6.94 (br, 1H, N-OH), 6.94 (dd, 1H, ArH), 7.26 (t, 1H, ArH), 7.64 (dd, 1H, ArH). MS (EI) *m/z* (%): 297 (M^+, 100), 282 (14), 243 (66), 225 (60), 210 (34), 198 (34), 183 (41), 171 (43), 156 (49), 146 (27), 128 (27), 115 (35). Anal. Calcd for $C_{17}H_{19}N_3O_2$: C 68.67, H 6.44, N 14.13. Found C 68.52, H 6.46, N 13.99%.

3,3′-(6-Methoxy-1-oxo-1,2,3,4-tetrahydro-2-benzazepin-5,5-diyl)di(propanenitrile) (17). Oxime **16** (7.3 g, 24.5 mmol) was dissolved in dioxane (134 mL) and thionyl chloride (9.2 mL, 15 g, 126 mmol) was added dropwise in dioxane solution (70 mL) at 70 °C with stirring. Then the reaction mixture was stirred at 70 °C for a further 2 h, poured into a mixture of saturated aqueous sodium carbonate (400 mL) and ice (pH must be maintained 9-10) and was extracted with dichloromethane (3 × 150 mL). The organic layers were combined, after drying ($MgSO_4$) the solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel (dichloromethane-methanol 40:1) to yield product (**17**) (3.8 g, 52%), mp 170-172 °C. TLC (CH_2Cl_2-MeOH 20:1) R_f 0.38; IR (KBr) 3400, 2220, 1650, 1570, 1450, 1250, 1045, 900, 750 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.96-2.02 (m, 2H), 2.08-2.24 (m, 6H), 2.38-2.48 (m, 2H), 3.17 (m, 2H, CH_2N), 3.84 (s, 3H, OCH_3), 7.02 (dd, 1H, ArH), 7.32 (brt, 1H, NH), 7.32 (t, 1H, ArH), 7.42 (dd, 1H, ArH). HRMS: M+H: *m/z* 298.15506, calculated value for $C_{17}H_{20}N_3O_2$: 298.15500 (delta: 0.19 ppm). MS-MS of *m/z* 298: *m/z* 280 (100), 269 (28), 263 (19), 226 (13), 212 (6), 200 (4).

Dimethyl 3,3′-(6-methoxy-1-oxo-1,2,3,4-tetrahydro-2-benzazepin-5,5-diyl)-di(propanoate) (18). Into a suspension of dinitrile **17** (3.84 g, 12.9 mmol) in methanol (60 mL), dry HCl gas was introduced for 1 h. Then the reaction mixture was refluxed for 1 h, and then it was poured into a

mixture of ice and saturated aqueous sodium carbonate solution (350 mL) and extracted with dichloromethane (3 × 130 mL). The combined organic layers were dried ($MgSO_4$), the solvent was evaporated to dryness under reduced pressure and the residue was treated with hexane to give of diester **18** (4.5 g, 96%), mp 121 °C. TLC (CH_2Cl_2-MeOH 20:1) R_f 0.43; IR (KBr) 1740, 1665, 1570, 1200, 1180, 990, 800 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 2.02-2.08 (m, 2H), 2.10-2.25 (m, 6H), 2.39-2.49 (m, 2H), 3.23 (m, 2H, CH_2N), 3.62 (s, 6H, 2 × $COOCH_3$), 3.83 (s, 3H, OCH_3), 6.86 (brm, 1H, NH), 7.03 (dd, 1H, ArH), 7.30 (t, 1H, ArH), 7.50 (dd, 1H, ArH). HRMS: M+H: *m/z* 364.17551, calculated value for $C_{19}H_{26}NO_6$: 364.17546 (delta: 0.13 ppm). MS-MS of *m/z* 364: *m/z* 332 (100), 314 (6).

Methyl 1,4′-dioxo-6-methoxy-1,2,3,4-tetrahydrospiro[2-benzazepine-5,1′-cyclohexane]-3′-carboxylate (19). To a solution of diester **18** (5.66 g, 15.6 mmol) in dry benzene (220 mL), potassium *tert*-butoxide (3.96 g, 35.3 mmol) was added and the reaction mixture was refluxed for 30 min. After cooling to room temperature the mixture was evaporated to dryness, water (100 mL) was added and the solution was acidified with 2N hydrochloric acid to pH 2 (22 mL). After extracting with dichloromethane (3 x 100 mL), the combined organic layers were dried ($MgSO_4$) and the solvent was evaporated to yield β-oxoester derivative **19** (4.4 g, 85%) as a foam. TLC (CH_2Cl_2-MeOH 20:1) R_f 0.5; IR (KBr) 1660, 1620, 1450, 1210, 1050 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) (in enolic form) δ 1.60-2.20 (m, 6H), 2.60-2.70 (m, 1H), 3.10-3.22 (m, 2H), 3.50-3.62 (d, 1H), 3.63 (s, 3H, $COOCH_3$), 3.82 (s, 3H, OCH_3), 6.70 (brm, 1H, NH), 6.98 (dd, 1H, ArH), 7.28 (t, 1H, ArH), 7.35 (dd, 1H, ArH), 11.93 (s, 1H, OH). HRMS: M+H: *m/z* 332.14937, calculated value for $C_{18}H_{22}NO_5$: 332.14925 (delta: 0.36 ppm). MS-MS of *m/z* 332: *m/z* 300.

6-Methoxy-3,4-dihydrospiro[2-benzazepine-5,1′-cyclohexane]-1(2*H*),4′-dione (20). To a solution of ketoester **19** (1.46 g, 4.4 mmol) in DMF (22 mL), water (0.15 mL) and sodium chloride (0.26 g, 4.4 mmol) were added. The reaction mixture was stirred at 150 °C for 3 h under argon, and then it was evaporated to dryness under vacuum. The residue was partitioned between dichloromethane (80 mL) and brine (50 mL), the organic phase was washed with dichloromethane (3 × 70 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated to dryness under reduced pressure. The residue was purified by preparative thin layer chromatography on silica gel (CH_2Cl_2-MeOH 20:1) to yield **20** (0.78 g, 65%), mp 213 °C. TLC (CH_2Cl_2-MeOH 20:1) R_f 0.4; IR (KBr) 3320, 1710, 1650, 1620, 1450, 1250, 760 cm^{-1}. ^1H-NMR (300 MHz, $CDCl_3$) δ 1.70-1.81 (m, 2H), 1.94-2.02 (m, 2H), 2.20-2.25 (m, 4H), 2.86-3.00 (m, 2H) 3.04-3.10 (m, 2H), 3.76 (s, 3H, OCH_3), 6.73 (brm, 1H, NH), 7.01 (dd, 1H, ArH), 7.28 (t, 1H, ArH), 7.33 (dd, 1H, ArH). HRMS: M+H: *m/z* 274.14381, calculated value for $C_{16}H_{20}NO_3$: 274.14377 (delta: 0.14 ppm). MS-MS of *m/z* 274: *m/z* 256 (100), 242 (30), 239 (18), 227 (47), 213 (20), 203 (26), 187 (20), 185 (12), 166 (11), 152 (9), 135 (45).

6-Methoxyspiro[2-benzazepine-5,1′-cyclohexan]-2′-ene-1,3(2*H*,4*H*),4′-trione (21). Lactam (**20**) (2.87 g, 10.5 mmol) was dissolved in a mixture of fluorobenzene (74 mL) and DMSO (37 mL) and *o*-iodoxybenzoic acid (11.46 g, 40.9 mmol)[12] was added. The reaction mixture was heated at 85 °C with stirring under argon for 77 h. Then the solvent was evaporated under vacuum, the residue was taken up in dichloromethane (500 mL), washed with saturated aqueous

sodium hydrogen carbonate (2 × 150 mL), with water (250 mL) and with saturated aqueous sodium chloride solution (2 × 150 mL). The organic layer was dried ($MgSO_4$) and evaporated to dryness under reduced pressure and the residue was treated with dichloromethane to yield 1.23 g of product. A further 377 mg of **21** was isolated from the mother liquor of dichloromethane by preparative thin layer chromatography on silica gel (CH_2Cl_2-MeOH 20:1) giving a total yield of **21** (1.61 g, 54%), mp 131-134 ^oC. TLC (CH_2Cl_2-MeOH 20:1) R_f 0.50; IR (KBr) 1705, 1665, 1650, 1630, 1300, 810, 740 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ 2.00-2.08 (m, 1H), 2.30-2.76 (m, 4H), 3.52 (d, 1H), 3.76 (s, 3H, OCH_3), 5.80 (d, 1H, CH), 7.00 (d, 1H, CH), 7.37 (dd, 1H, ArH), 7.47 (t, 1H, ArH), 7.95 (dd, 1H, ArH), 11.15 (brs, 1H, NH). HRMS: M+H: *m/z* 286.10740, calculated value for $C_{16}H_{16}NO_4$: 286.10738 (delta: 0.05 ppm). MS-MS of *m/z* 286: *m/z* 268 (100), 258 (20), 251 (9), 244 (34), 240 (35), 229 (16), 226 (43), 213 (37).

6-(Ethylsulfanyl)-5,6,7,8-tetrahydro-4a*H*-[1]benzofuro[3a,3,2-*ef*][2]benzazepine-10(9*H*),12(11*H*)-dione (22). To a mixture of dichloromethane (14 mL) and aluminium trichloride (431 mg, 3.2 mmol), diethyl sulfide (2 mL, 1.7 g, 19 mmol) and **21** (250 mg, 0.88 mmol) in dichloromethane (7 mL) solution was added with stirring at room temperature. After stirring for 4 h the reaction mixture was poured into a mixture of water (15 mL) and methanol (25 mL) and extracted with dichloromethane (3 × 20 mL). The combined organic layers were washed with brine (3 × 15 mL), dried ($NaSO_4$) and evaporated to dryness under reduced pressure. The residue was purified by preparative thin layer chromatography on silica gel (CH_2Cl_2-MeOH 10:1) to yield tetracycle **22** (39 mg, 14%) as an oil. TLC (CH_2Cl_2-MeOH 10:1) R_f 0.78; IR (KBr) 3450, 1710, 1695(br), 1675, 1610, 1310, 1250, 820, 760 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 1.26 (t, CH_3-D2), 1.28 (t, CH_3-D1), 1.41-1.51 (m, H-7ax-D1), 1.56-1.78 (m, H-8ax-D1, H-7eq-D2, H-5ax-D1, H-8eq-D2), 1.86-2.00 (m, H-7ax-D2, H-7eq-D1), 2.01-2.08 (m, H-8eq-D1), 2.09-2.15 (m, H-8ax-D2), 2.26 (ddd, H-5ax-D2), 2.46-2.52 (H-5eq-D2), 2.56 (q, CH_2S-D2), 2.62 (q, 2H, CH_2S-D1), 2.62-2.70 (m, H-5eq-D1), 2.94 (d, J_{gem} = 15.4 Hz, H-9A-D1), 2.96 (d, J_{gem} = 15.4 Hz, H-9A-D2), 2.94-3.02 (m, H-6ax-D1), 3.05 (d, J_{gem} = 15.4 Hz, H-9B-D2), 3.15 (d, J_{gem} = 15.4 Hz, H-9B-D1), 3.15-3.22 (m, H-6eq-D2), 4.33-4.36 (m, H_{eq}-4a-D1), 4.36-4.40 (m, H_{eq}-4a-D2), 7.09 (d, H-3-D1), 7.13 (d, H-3-D2), 7.33 (2×t, H-2-D2, H-2-D1), 7.73 (d, H-1-D2), 7.75 (d, H-1-D1), 8.25 (brs, NH). ^{13}C-NMR (125 MHz, $CDCl_3$) 14.6 (CH_3-D2), 15.0 (CH_3-D1), 24.2 (CH_2S-D1), 24.9 (C-7-D2), 26.1 (CH_2S-D2), 26.8 (C-8-D2), 27.4 (C-7-D1), 30.5 (C-5-D2), 30.8 (C-8-D1), 32.4 (C-5-D1), 36.7 (C-6-D1), 36.9 (C-6-D2), 41.4 (C-8a-D1), 41.9 (C-9-D1), 42.0 (C-8a-D2), 43.6 (C-9-D2), 86.8 (C-4a-D2), 88.2 (C-4a-D1), 115.7 (C-3-D1), 115.8 (C-3-D2), 124.1 (C-1-D2), 124.2 (C-1-D1), 125.1 (C-12a), 129.2 (C-2-D1), 129.3 (C-2-D2), 136.1 (C-12b-D2), 137.0 (C-12b-D1), 157.8 (C-3a-D1), 158.0 (C-3a-D2), 163.6 (CO-12-D1), 163.7 (CO-12-D2), 169.8 (CO-10-D1), 170.0 (CO-10-D2). HRMS: M+H: *m/z* 318.11588, calculated value for $C_{17}H_{20}NO_3S$: 318.11584 (delta: 0.12 ppm). MS-MS of *m/z* 318: *m/z* 301 (6), 276 (100), 259 (12), 214 (6).

7,8-Dihydro-4a*H*-[1]benzofuro[3a,3,2-*ef*][2]benzazepine-6(5*H*),10(9*H*),12(11*H*)-trione (23). Unsaturated spiroketone (**21**) (250 mg, 0.88 mmol) was dissolved in methanesulfonic acid (1.7 mL) and D,L-methionine (143 mg, 0.96 mmol) was added to the solution under stirring at room

temperature. After 10 h the reaction mixture was diluted with water (10 mL) and extracted with dichloromethane (5 × 30 mL). The combined organic layers were dried ($MgSO_4$), the solvent was evaporated under reduced pressure to yield tetracyclic compound **23 (**221 mg, 93%), which was pure enough for further reactions. After preparative thin layer chromatography on silica gel (benzene-MeOH 14:3) of **23** (56 mg, 23.5%) was obtained, mp 240 ^oC. TLC (benzene-MeOH 14:3) R_f 0.5; IR (KBr) 3290, 2920, 1730, 1690, 1605, 1355, 1300, 800, 750 cm^{-1}. ^1H-NMR (500 MHz, DMSO-d_6) δ 1.69-1.79 (m, 1H, H-7ax), 2.00-2.06 (m, 1H, H-8eq), 2.13-2.22 (m, 1H, H-8ax), 2.22-2.28 (m, 1H, H-7eq), 2.72 (dd, 1H, J_{gem} = 17.1 Hz, J = 3.5 Hz, H-5A), 3.03 (d, 1H, J_{gem} = 15.2 Hz, H-9A), 3.23 (dd, 1H, J_{gem} = 17.1 Hz, J = 2.4 Hz, H-5B), 3.34 (d, 1H, J_{gem} = 15.2 Hz, H-9B), 4.88-4.92 (m, 1H, H_{eq}-4a), 7.11 (d, 1H, H-3), 7.39 (t, 1H, H-2), 7.60 (d, 1H, H-1), 10.91 (s, 1H, NH). ^{13}C-NMR (125 MHz, DMSO-d_6) δ 29.2 (C-8), 34.8 (C-7), 40.1 (C-5), 41.7 (C-8a), 46.3 (C-9), 86.6 (C-4a), 114.0 (C-3), 123.8 (C-1), 127.0 (C-12a), 129.6 (C-2), 133.5 (C-12b), 158.1 (C-3a), 163.9 (CO-12), 170.8 (CO-10), 208.1 (CO-6). HRMS: M+H: *m/z* 272.09183, calculated value for $C_{15}H_{14}NO_4$: 272.09173 (delta: 0.35 ppm). MS-MS of *m/z* 272: *m/z* 254 (79), 244 (11), 237 (1), 230 (100), 227 (3), 213 (5), 202 (6).

Acknowledgements

The authors are grateful to Dr. H. Medzihradszky-Schweiger and her staff for the microanalyses, to Dr. G. Czira for providing some of the MS data, to A. Fürjes and I. Sinka for their NMR technical assistance and to OTKA (Hungarian Academic Research Found Grant K 68734) and to Richter Gedeon Rt for financial assistance.

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