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SYNTHESIS OF DEMETHOXY-LYCORAMINONE

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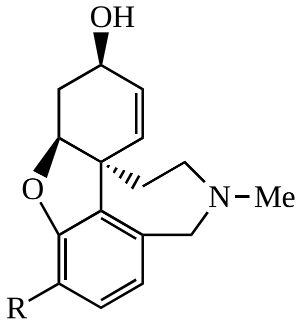
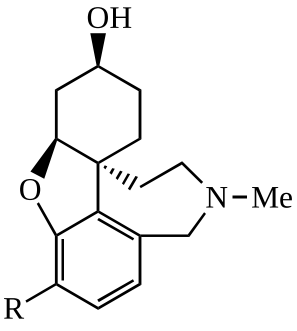
Abstract – Demethoxy-lycoraminone (**8**) was prepared in several steps starting from the appropriate benzo[*c*]azepine dione derivative (**9**). Ketone (**9**) was protected as a ketal group followed by methylation on the azepine nitrogen atom. After reduction of the imide carbonyl groups, deprotection, demethylation and ring closure were carried out as a one-pot reaction in methanesulfonic acid in the presence of racemic methionine.

INTRODUCTION

Galanthamine (**1**) (Nivalin, Razadyn, Reminyl, etc.) is a well-known alkaloid isolated from the *Amaryllidaceae* family,[1] and as an allosteric modulator of the neuronal nicotinic receptor as well as a selective acetylcholinesterase (AchE) inhibitor[2,3] it is used in the treatment of Alzheimer's disease and other memory disorders.[4-6]



1; R=OMe
2; R=H



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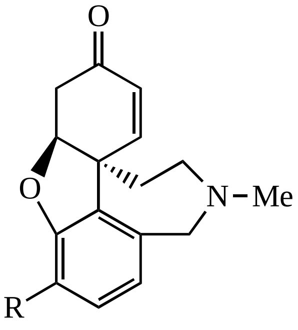
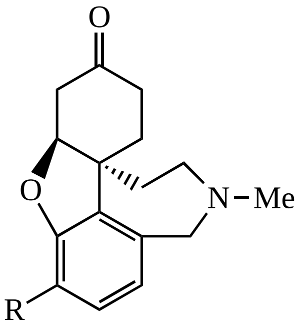
4; R=H



5; R=OMe
6; R=H



7; R=OMe
8; R=H

Lycoramine (**3**) is also a member of the galanthamine-type alkaloid family, however, has less potent AchE inhibitory activity.[7,8] Several total syntheses have been developed for galanthamine (**1**)[9-13] and lycoramine (**3**).[14-17] Most synthetic strategies utilized a biomimetic approach *via* intramolecular phenolic oxidative coupling to install the quaternary spiro carbon.[9] In this type of synthetic processes narwedine (**5**) can be considered not only the biogenetic precursor,[18] but the most important key intermediate for the synthesis of galanthamine (**1**). Similarly, reduction of lycoraminone (**7**) (dihydronarwedine) results lycoramine (**3**).[19] Demethoxy derivatives of galanthamine, lycoramine, **2** and **4**, respectively, are mentioned only in two patents[20,21] without any report on their pharmacological activity. Demethoxy-narwedine (**6**) was prepared by a biomimetic synthetic way,[22] demethoxy-lycoraminone (**8**), however, is un-known in the literature.

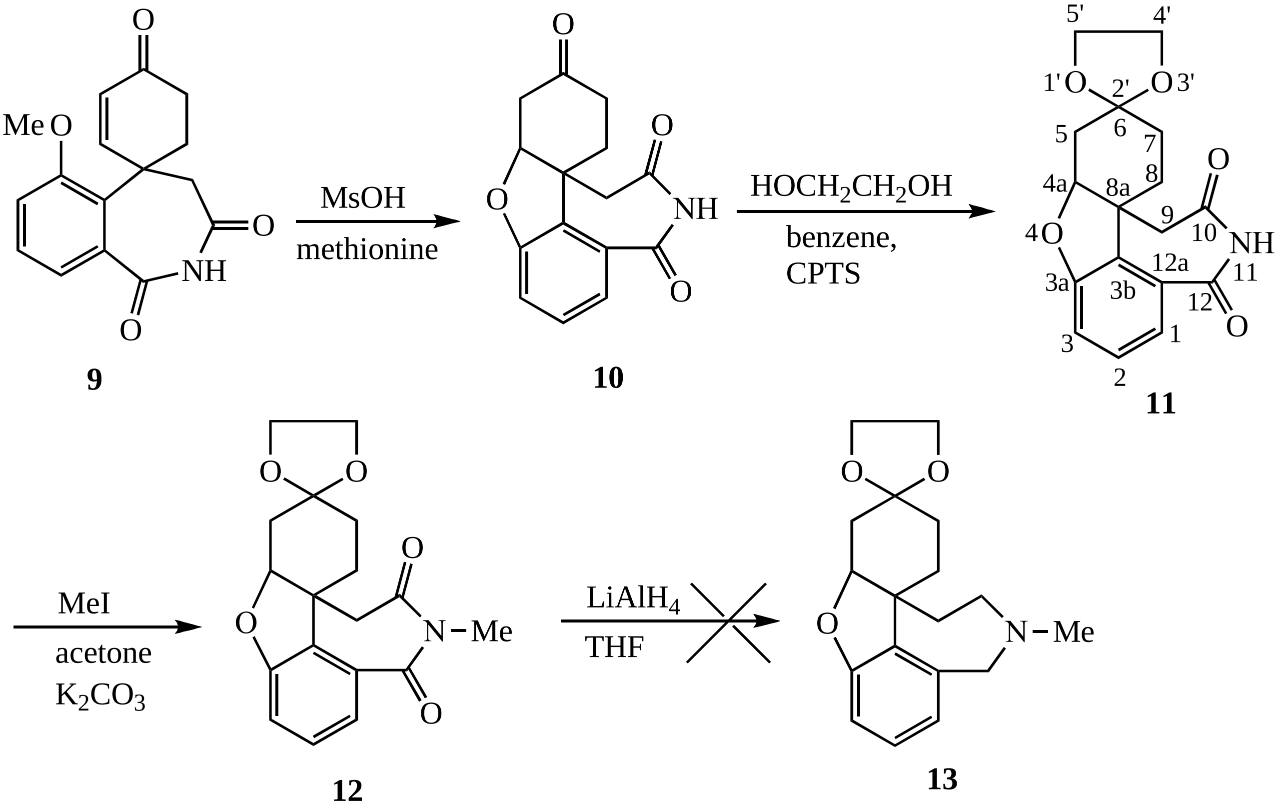
Recently, on the basis of an efficient retrosynthetic route Szántay and co-workers[23] developed a convenient synthesis for benzo[*c*]azepines spiro-substituted with a cyclohexenone ring. This method was then extended also for the synthesis of the methoxy substituted analogue **9** and the galanthamine-type hexahydrobenzofurobenzazepine tetracycle **10** (Scheme 1).[22] The *O*-demethylation and cyclisation as a one-pot reaction was carried out in methanesulfonic acid in the presence of D,L-methionine.

The object of this work was the synthesis of the demethoxy derivative of dihydronarwedine, namely demethoxy-lycoraminone (**8**) from the intermediates **9** and **10** previously prepared.

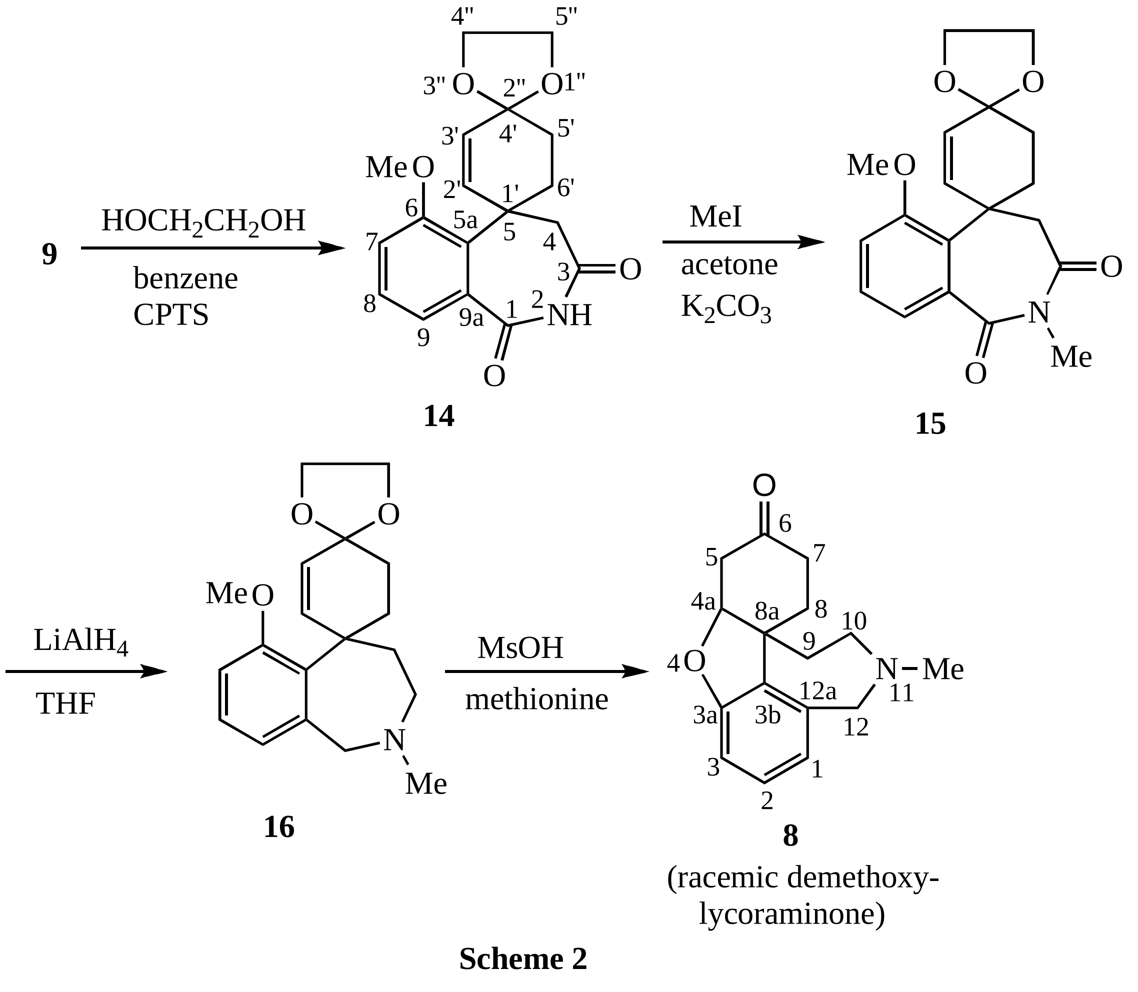
RESULTS AND DISCUSSION

Converting of the tetracycle **10** was first investigated (Scheme 1). Protection of the carbonyl group of the spiro ketone was achieved by reaction with ethylene glycol. The preparation of ketal **11** was carried out in dichloromethane solution in presence of boron trifluoride diethyl etherate at room temperature or in refluxing toluene using *p*-toluenesulfonic acid as catalyst with a rather low yield (10-30%). Eventually a reasonable yield (57%) for preparing ketal **11** was achieved in refluxing benzene using collidinium *p*-toluenesulfonate (CPTS). Omitting the protection of the ketone group, further reactions caused unexpected rearrangements on the tetracycle **10** and on the spiro-ketone **9**.[25]

Methylation of ketal **11** was conducted in the usual way. Thus the spiro ketal **11** was refluxed in dry acetone solution with methyl iodide in the presence of anhydrous potassium carbonate, and the *N*-methylated product **12** could be isolated in almost quantitative yield. The next task was to reduce the imide carbonyl groups using lithium aluminium hydride as before.[23] This reaction, however, proved to be unsuccessful; only decomposition products could be detected in the reaction mixture. Subsequently the benzazepinedione spiro-substituted with a cyclohexenone ring (**9**) was chosen as the starting material (Scheme 2).



Scheme 1



Scheme 2

First the protection of the ketone group of compound **9** was carried out as in the case of tetracycle **10**. Ketal **14** was prepared in refluxing benzene using CPTS as the catalyst in 77% yield. Methylation of ketal **14** was accomplished in refluxing dry acetone solution with methyl iodide in the presence of anhydrous potassium carbonate. The *N*-methyl azepinedione **15** was isolated in 50% yield. Reduction of the carbonyl groups of imide **15** succeeded in 93% yield in refluxing THF using lithium aluminium hydride as the reducing agent. Deprotection of the ketone group of ketal **16** in hydrochloric acid solution was unsuccessful. Eventually the deprotection reaction, *O*-demethylation and cyclisation were carried out in one-pot reaction in methanesulfonic acid in the presence of racemic methionine at room temperature similarly as presented earlier.[24] Racemic demethoxy-lycoraminone (**8**), as one of the most important key intermediates for the synthetic routes to different galanthamine-type *Amaryllidaceae* alkaloids, was isolated in 56% yield.

CONCLUSION

In conclusion a simple and convenient method was developed for the synthesis of demethoxy-lycoraminone (**8**) from benzo[*c*]azepinone (**9**) spiro-substituted with a cyclohexanone ring containing a carbon-carbon double bond in the α,ß-position.

EXPERIMENTAL

General procedures

Melting points are uncorrected. IR spectra were recorded on Zeiss IR 75 and 80 instruments. NMR spectra were recorded on a Varian VNMRS-500 (^{1}H: 499.9 MHz) and a Varian VNMRS-800 (^{1}H: 799.7 MHz) spectrometer, both equipped with a ^{13}C Enhanced HCN Cold Probe. Chemical shifts are given on the delta scale as parts per million (ppm) with tetramethylsilane (TMS) (^{1}H) or dimethylsulfoxide-d_6 (^{13}C) as the internal standard (0.00 ppm and 39.5 ppm, respectively). ^{1}H-^{1}H, direct ^{1}H-^{13}C, and long-range ^{1}H-^{13}C scalar spin-spin connectivities were established from 2D gDQFCOSY, gHSQCAD, and gHMBCAD experiments, respectively. All pulse sequences were applied by using the standard spectrometer software package. All experiments were performed at 298 K. High-resolution ESI-MS measurements were carried out on a Thermo LTQ FT Ultra mass spectrometer (4.8 kV source voltage, 280 °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 45%. The relative abundance values of the fragment ions in the MS-MS spectrum are given in brackets. High-resolution EI-MS measurements were carried out on a Finnigan MAT 95XP mass spectrometer, perfluorokerosene amine was used as a reference compound (220 °C source temperature, 70 eV). TLC was carried out using Kieselgel 60F_{254} (Merck) glass plates.

4a,5,7,8-Tetrahydro-spiro[[1]benzofuro[3a,3,2-*ef*][2]benzazepine-6,2'-[1,3]dioxolane]-10(9*H*),12-(11*H*)-dione (11)

To a solution of the tetracycle **10** (56 mg, 0.20 mmol) in dry benzene (3 mL) 1.05 mL (1.17 g, 18.9 mmol) of ethylene glycol and 18 mg (0.06 mmol) of CPTS were added. The two-phase reaction mixture was refluxed with stirring for 6 h using a Dean-Stark separator for 6 h. The upper benzene phase was then washed three times with water (3x10 mL), dried with magnesium sulfate and evaporated in vacuum to dryness. After preparative layer chromatography on silica gel (benzene-MeOH 14:3) we obtained 37 mg (57%) of the product (**11**) as a white solid, mp 214-215 ^{o}C (from Et_2O). TLC (benzene-MeOH 14:3) R_f 0.54. IR (KBr) 3274, 2885, 1691, 1677, 1602, 1458, 1356, 1304, 1244, 1096, 1028, 830, 792, 747 cm^{-1}. ^{1}H-NMR (499.9 MHz, DMSO-d_6) δ 1.52 (m, 1H, H_x-7), 1.64 (m, 1H, H_y-7), 1.72 (m, 2H, H_2-8), 2.17 (*ca.* dd, J = 15.7 Hz, J = 4.2 Hz, 1H, H_x-5), 2.25 (*ca.* ddd, J = 15.7 Hz, J = 2.7 Hz, J = 1.7 Hz, 1H, H_y-5), 3.05 (*ca.* d, J = 15.3 Hz, 1H, H_x-9), 3.20 (*ca.* d, J = 15.3 Hz, 1H, H_y-9), 3.77-3.94 (m, 4H, H_2-4', H_2-5'), 4.50 (dd, J = 4.2 Hz, J = 2.7 Hz, 1H, H-4a), 7.12 (dd, J = 8.0 Hz, J = 0.8 Hz, 1H, H-3), 7.34 (*ca.* t, J = 8.0 Hz, 1H, H-2), 7.56 (dd, J = 8.0 Hz, J = 0.8 Hz, 1H, H-1) ppm. ^{13}C-NMR (125.7 MHz, DMSO-d_6) δ 28.2 (C-8), 29.3 (C-7), 33.5 (C-5), 40.9 (C-8a), 42.5 (C-9), 63.2 (C-4'), 63.9 (C-5'), 87.5 (C-4a), 106.6 (C-6), 114.4 (C-3), 123.0 (C-1), 126.2 (C-12a), 128.9 (C-2), 136.4 (C-3b), 157.7 (C-3a), 164.0 (C-12), 171.0 (C-10) ppm. M+H (ESI): m/z 316.11813, calculated value for $C_{17}H_{18}O_5N$: 316.11795 (delta: 0.6 ppm). MS-MS of m/z 316: m/z 299(4), 298(3), 274(100), 272(23), 254(1), 230(2), 216(2), 212(2). Anal. Calcd for $C_{17}H_{17}NO_5$: C 64.75, H 5.43, N 4.44. Found C 64.65, H 5.46, N 4.66.

11-Methyl-4a,5,7,8-tetrahydro-spiro[[1]benzofuro[3a,3,2-*ef*][2]benzazepine-6,2'-[1,3]dioxolane]-10-(9*H*),12(11*H*)-dione (12)

Tetracyclic ketal **11** (90 mg, 0.29 mmol) was dissolved in dry acetone (3 mL), 49 mg (0.35 mmol) of anhydrous potassium carbonate and 0.4 mL (912 mg, 6.4 mmol) of methyl iodide were added and the reaction mixture was refluxed for 2 h with stirring. The solvent was then evaporated in vacuum and the residue was dissolved in a mixture of CH_2Cl_2 (20 mL) and water (20 mL). The water phase was washed with CH_2Cl_2 (2x20 mL), the combined organic phases were dried with magnesium sulfate and the solvent was evaporated to dryness in vacuum. The crude product was purified by preparative thin-layer chromatography (Kieselgel, benzene-MeOH 14:3), and 90 mg (96%) of the product (**12**) was isolated as a pale yellow solid, mp 173-175 ^{o}C. TLC (Kieselgel, benzene-MeOH 14:3) R_f 0.63. IR (KBr) 2893, 1691, 1650, 1603, 1450, 1419, 1339, 1108, 822, 751 cm^{-1}. ^{1}H-NMR (499.9 MHz, DMSO-d_6) δ 1.52 (m, 1H, H_x-7), 1.64 (m, 1H, H_y-7), 1.72 (m, 2H, H_2-8), 2.18 (*ca.* dd, J = 15.8 Hz, J = 4.3 Hz, 1H, H_x-5), 2.26 (*ca.* ddd, J = 15.8 Hz, J = 2.6 Hz, J = 1.5 Hz, 1H, H_y-5), 3.22 (*ca.* d, J = 14.8 Hz, 1H, H_x-9), 3.25 (s, 3H, $NC\underline{H}_3$-11), 3.27 (*ca.* d, J = 14.8 Hz, 1H, H_y-9), 3.77-3.94 (m, 4H, H_2-4', H_2-5'), 4.49 (dd, J = 4.3 Hz, J = 2.6 Hz, 1H, H-4a), 7.10 (dd, J = 8.0 Hz, J = 0.8 Hz, 1H, H-3), 7.33 (*ca.* t, J = 8.0 Hz, 1H, H-2), 7.65 (dd, *J* = 8.0 Hz, *J* = 0.8 Hz, 1H, H-1) ppm. ^{13}C-NMR (125.7 MHz, DMSO-d_6) δ 27.5 (C-8), 29.5 (C-7), 32.1 (N$\underline{C}H_3$-11), 33.6 (C-5), 40.4 (C-8a), 43.7 (C-9), 63.3 (C-4'), 63.9 (C-5'), 87.7 (C-4a), 106.7 (C-6), 114.1 (C-3), 123.8 (C-1), 126.7 (C-12a), 128.8 (C-2), 137.1 (C-3b), 157.5 (C-3a), 165.5 (C-12), 171.3 (C-10) ppm. *M*+H (ESI): *m*/*z* 330.13382, calculated value for $C_{18}H_{20}O_5N$: 330.13360 (delta: 0.7 ppm). MS-MS of *m*/*z* 330: *m*/*z* 299(1), 288(90), 286(100), 244(1), 230(12), 226(2). Anal. Calcd for $C_{18}H_{19}NO_5$: C 65.64, H 5.81, N 4.25. Found C 65.55, H 6.01, N 4.50.

6-Methoxydispiro[[2]benzazepine-5,1'-cyclohexane-4',2''-[1,3]dioxolane]-2'-ene-1,3(2*H*,4*H*)-dione (14)

To a solution of unsaturated ketone **9** (119 mg, 0.42 mmol) in dry benzene (14 mL), 2 mL (2.2 g, 36 mmol) of ethylene glycol and 34 mg (0.11 mmol) of CPTS were added. The two-phase reaction mixture was refluxed with stirring for 6 h using a Dean-Stark separator for 6 h. The upper benzene phase was then washed three times with water (3x10 mL), dried with magnesium sulfate and evaporated in vacuum to dryness. After preparative layer chromatography on silica gel (benzene-MeOH 14:3) we obtained 105 mg (77%) of the product (**14**) as a white solid, mp 180-182 °C (from Et_2O). TLC (benzene-MeOH 14:3) R_f 0.56. IR (KBr) 3446, 3199, 1707, 1654, 1570, 1372, 1306, 1268, 1096, 1028, 948 cm^{-1}. ^{1}H-NMR (499.9 MHz, DMSO-d_6) δ 1.78 (m, 1H, H_x-6'), 1.79 (m, 1H, H_x-5'), 1.93 (m, 1H, H_y-5'), 2.33 (m, 1H, H_y-6'), 2.55 (d, *J* = 14.5 Hz, 1H, H_x-4), 3.29 (d, *J* = 14.5 Hz, 1H, H_y-4), 3.71 (s, 3H, $C\underline{H}_3$O-6), 3.82-3.98 (m, 4H, H_2-4'', H_2-5''), 5.40 (dd, *J* = 10.2 Hz, *J* = 1.2 Hz, 1H, H-3'), 5.75 (dd, *J* = 10.1 Hz, *J* = 1.5 Hz, 1H, H-2'), 7.30 (dd, *J* = 8.1 Hz, *J* = 1.5 Hz, 1H, H-7), 7.40 (t, *J* = 8.1 Hz, 1H, H-8), 7.86 (dd, *J* = 8.1 Hz, *J* = 1.5 Hz, 1H, H-9), 11.02 (br, 1H, NH-2) ppm. ^{13}C-NMR (125.7 MHz, DMSO-d_6) δ 28.6 (C-6'), 29.8 (C-5'), 39.7 (C-5), 46.5 (C-4), 56.1 ($\underline{C}H_3$O-6), 63.7 and 63.8 (C-4'', C-5''), 104.0 (C-4'), 118.0 (C-7), 121.5 (C-3'), 125.9 (C-9), 127.8 (C-8), 132.1 (C-9a), 135.8 (C-5a), 140.7 (C-2'), 157.3 (C-6), 167.0 (C-1), 170.7 (C-3) ppm. *M*+H (ESI): *m*/*z* 330.13369, calculated value for $C_{18}H_{20}O_5N$: 330.13360 (delta: 0.3 ppm). MS-MS of *m*/*z* 330: *m*/*z* 313(16), 312(14), 295(3), 286(11), 285(8), 268(23), 240(10), 230(100), 226(61).

2-Methyl-6-methoxydispiro[[2]benzazepine-5,1'-cyclohexane-4',2''-[1,3]dioxolane]-2'-ene-1,3(2*H*, 4*H*)-dione (15)

Ketal **14** (107 mg, 0.32 mmol) was dissolved in dry acetone (3 mL), 59 mg (0.42 mmol) of anhydrous potassium carbonate and 0.32 mL (0.73 g, 5.1 mmol) of methyl iodide were added and the reaction mixture was refluxed for 2 h with stirring. The solvent was then evaporated in vacuum and the residue was dissolved in a mixture of CH_2Cl_2 (20 mL) and water (20 mL). The water phase was washed with CH_2Cl_2 (2x20 mL), the combined organic phases were dried with magnesium sulfate and the solvent was evaporated to dryness in vacuum. The crude product was purified by preparative thin-layer chromatography (Kieselgel, benzene-MeOH 14:3) and 55 mg (50%) of the product (**15**) was isolated as a pale yellow solid, mp 131-133 °C. TLC (Kieselgel, benzene-MeOH 14:3) R_f 0.77. IR (KBr) 2983, 1701, 1649, 1574, 1464, 1367, 1299, 1269, 1086, 1017, 978, 819, 756 cm^{-1}. ^{1}H-NMR (499.9 MHz, DMSO-d_6) δ 1.65 (m, 1H, H_x-6’), 1.82 (m, 1H, H_x-5’), 2.00 (td, J = 13.9 Hz, J = 3.5 Hz, 1H, H_y-5’), 2.47 (td, J = 13.8 Hz, J = 3.5 Hz, 1H, H_y-6’), 2.70 (d, 1H, J = 14.2 Hz, H_x-4), 3.11 (s, 3H, $NC\underline{H}_3$-2), 3.29 (d, J = 14.2 Hz, 1H, H_y-4), 3.73 (s, 3H, $C\underline{H}_3O$-6), 3.82-3.99 (m, 4H, H_2-4”, H_2-5”), 5.45 (dd, J = 10.0 Hz, J = 1.5 Hz, 1H, H-3’), 5.65 (dd, J = 10.0 Hz, J = 2.0 Hz, 1H, H-2’), 7.30 (dd, J = 8.0 Hz, J = 1.2 Hz, 1H, H-7), 7.41 (t, J = 8.0 Hz, 1H, H-8), 7.84 (dd, J = 8.0 Hz, J = 1.2 Hz, 1H, H-9) ppm. M+H (ESI): m/z 344.14944, calculated value for $C_{19}H_{22}O_5N$: 344.14925 (delta: 0.6 ppm). MS-MS of m/z 344: m/z 326(1), 313(1), 282(3), 254(3), 244(100), 240(16).

2-Methyl-6-methoxy-1,2,3,4-tetrahydrodispiro[[2]benzazepine-5,1’-cyclohexane-4’,2”-[1,3]dioxolane]-2’-ene (16)

To a suspension of 102 mg (2.66 mmol) of lithium aluminium hydride in THF (4 mL) a solution of 167 mg (0.48 mmol) of *N*-methylated ketal (**15**) was added in THF (10 mL) with stirring under argon. The reaction mixture was refluxed for 1 h and was then quenched with water (15 mL). After extraction with CH_2Cl_2 (25 mL) the water phase was washed further with CH_2Cl_2 (2x25 mL), the combined organic layers were dried with magnesium sulfate and the solvent was evaporated under vacuum to yield 143 mg (93%) of the pure product (**16**) as a pale yellow oil. TLC (benzene-MeOH 14:3) R_f 0.25. IR (KBr) 2933, 1575, 1452, 1261, 1092, 1020, 949, 800, 737 cm^{-1}. ^{1}H-NMR (799.7 MHz, DMSO-d_6) δ 1.77 (m, 1H, H_x-4), 1.79 (m, 1H, H_x-5’), 1.86 (ddd, J = 14.5 Hz, J = 13.7 Hz, J = 3.4 Hz, 1H, H_y-4), 2.04 (m, 1H, H_y-5’), 2.06 (m, 1H, H_x-6’), 2.27 (s, 3H, $NC\underline{H}_3$-2), 2.30 (m, 1H, H_y-6’), 2.34 (ddd, J = 11.2 Hz, J = 5.1 Hz, J = 3.4 Hz, 1H, H_x-3), 2.90 (*ca.* td, J = 11.2 Hz, J = 4.5 Hz, 1H, H_y-3), 3.55 (*ca.* d, J = 15.6 Hz, 1H, H_x-1), 3.62 (s, 3H, $C\underline{H}_3O$-6), 3.78 (*ca.* d, J = 15.6 Hz, 1H, H_y-1), 3.80-3.97 (m, 4H, H_2-5”, H_2-4”), 5.23 (dd, J = 10.2 Hz, J = 1.8 Hz, 1H, H-3’), 5.71 (dd, J = 10.2 Hz, J = 1.8 Hz, 1H, H-2’), 6.63 (dd, J = 7.5 Hz, J = 1.3 Hz, 1H, H-9), 6.81 (dd, J = 8.1 Hz, J = 1.3 Hz,, 1H, H-7), 7.05 (dd, J = 8.1 Hz, J = 7.5 Hz, 1H, H-8) ppm. ^{13}C-NMR (201.1 MHz, DMSO-d_6) δ 28.5 (C-6’), 30.2 (C-4), 34.6 (C-5’), 41.9 (C-5), 45.7 ($N\underline{C}H_3$-2), 54.0 (C-3), 55.3 ($\underline{C}H_3O$-6), 59.5 (C-1), 63.5 and 63.6 (C-4”, C-5”), 104.7 (C-4’), 111.4 (C-7), 119.8 (C-3’), 122.4 (C-9), 126.4 (C-8), 134.7 (C-5a), 140.6 (C-9a), 144.1 (C-2’), 158.5 (C-6) ppm. M (EI): m/z 315.18226, calculated value for $C_{19}H_{25}O_3N$: 315.18290 (delta: -2.0 ppm). m/z (%): 315(M^+, 5), 300(2), 284(100), 270(8), 256(70), 242(6), 226(11), 174(25).

11-Methyl-7,8,9,10,11,12-hexahydro-4a*H*-[1]benzofuro[3a,3,2-*ef*][2]benzazepine-6(5*H*)-one; racemic demethoxy-lycoraminone (8)

To a solution of 95 mg (0.3 mmol) of the reduced azepine derivative **16** in methanesulfonic acid (1 mL), 48 mg (0.32 mmol) of racemic methionine was added and the reaction mixture was stirred at room temperature for 10 h, then poured into water (10 mL) and extracted with CH_2Cl_2 (2x5 mL). The combined organic layers were washed with saturated aqueous sodium hydrogencarbonate solution (2x5 mL), dried with magnesium sulfate and the solvent was evaporated in vacuum. The crude product was purified by preparative thin-layer chromatography (Kieselgel, benzene-MeOH 14:3) and 43 mg (56%) of the product (**8**) was isolated as a pale yellow solid, mp 273-275 °C. TLC (Kieselgel, benzene-MeOH 14:3) R_f 0.28. IR (KBr) 3397, 2956, 1662, 1583, 1470, 1446, 1255, 1093, 990, 900, 792 cm^{-1}. ^{1}H-NMR (799.7 MHz, DMSO-d_6) δ 1.65 (m, 2H, H_{ax}-7, H_x-9), 1.88 (*ca.* td, *J* = 14.2 Hz, *J* = 3.3 Hz, 1H, H_{ax}-8), 2.09 (*ca.* td, *J* = 13.4 Hz, *J* = 2.9 Hz, 1H, H_y-9), 2.19 (*ca.* dt, *J* = 18.0 Hz, *J* = 3.3 Hz, 1H, H_{eq}-7), 2.24 (s, 3H, H_3-11), 2.27 (*ca.* dt, *J* = 14.2 Hz, *J* = 3.8 Hz,, 1H, H_{eq}-8), 2.67 (dd, *J* = 17.2 Hz, *J* = 3.6 Hz, 1H, H_x-5), 2.97 (*ca.* dt, *J* = 14.3 Hz, *J* = 3.0 Hz, H_x-10), 2.99 (dd, *J* = 17.2 Hz, *J* = 2.5 Hz, 1H, H_y-5), 3.14 (ddd, *J* = 14.3 Hz, *J* = 12.9 Hz, *J* = 1.4 Hz, H_y-10), 3.59 (*ca.* d, *J* = 15.1 Hz, 1H, H_x-12), 4.11 (*ca.* d, *J* = 15.1 Hz, 1H, H_y-12), 4.70 (dd, *J* = 3.6 Hz, *J* = 2.5 Hz, 1H, H-4a), 6.64 (d, *J* = 7.9 Hz, 1H, H-3), 6.68 (d, *J* = 7.5 Hz, 1H, H-1), 7.04 (dd, *J* = 7.9 Hz, *J* = 7.5 Hz, 1H, H-2) ppm. ^{13}C-NMR (201.1 MHz, DMSO-d_6) δ 28.4 (C-8), 34.4 (C-9), 35.1 (C-7), 40.4 (C-5), 41.3 (C-11), 46.5 (C-8a), 53.3 (C-10), 59.2 (C-12), 87.4 (C-4a), 108.2 (C-3), 121.7 (C-1), 128.3 (C-2), 131.3 (C-3b), 138.3 (C-12a), 158.2 (C-3a), 209.4 (C-6) ppm. *M* (EI): *m*/*z* 257.14075, calculated value for $C_{16}H_{19}O_2N$: 257.14103 (delta: -1.1 ppm). *m*/*z* (%): 257(M^+, 100), 256(83), 242(3), 228(14), 214(10), 200(28), 188(48), 186(23), 172(22), 171(20), 158(35), 157(40), 144(16), 128(16), 115(23).

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