

A Novel Synthetic Approach to (±)-Desoxynoreseroline

by Maged K. G. Mekhael^{a)}^{b)1)} and Heinz Heimgartner^{*a)}

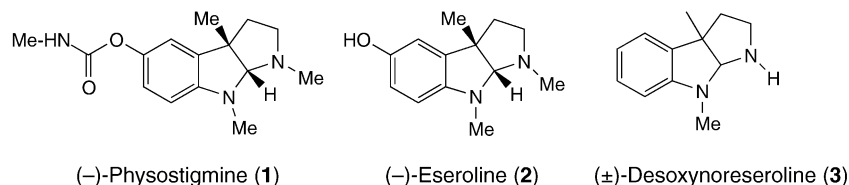
^{a)} Organisch-chemisches Institut der Universität Zürich, Winterthurerstrasse 190, CH-8057 Zürich

^{b)} Mubarak City for Scientific Research and Technological Applications, Alexandria, Egypt

(±)-Desoxynoreseroline (**3**), the basic ring structure of the pharmacologically active alkaloid physostigmine (**1**), was synthesized starting from 3-allyl-1,3-dimethyloxindole (**9**). The latter was prepared from the corresponding 2*H*-azirin-3-amine **6** by a BF₃-catalyzed ring enlargement *via* an amidinium intermediate **7** (Scheme 1). An alternative synthesis of **9** was also carried out by the reaction of *N*-methylaniline with 2-bromopropanoyl bromide (**12**), followed by intramolecular *Friedel–Crafts* alkylation of the formed anilide **13** to give *Julian's* oxindole **11**. Further alkylation of **11** with allyl bromide in the presence of LDA gave **9** in an excellent yield (Scheme 3). Ozonolysis of **9**, followed by mild reduction with (EtO)₃P, gave the aldehyde **14**, whose structure was chemically established by the transformation to the corresponding acetal **15** (Scheme 4). Condensation of **14** with hydroxylamine and hydrazine derivatives, respectively, gave the corresponding imine derivatives **16a–16d** as a mixture of *syn*- and *anti*-isomers. Reduction of this mixture with LiAlH₄ proceeded by loss of ROH or RNH₂ to give racemic **3** (Scheme 5).

Introduction. – (–)-Physostigmine (**1**), the major alkaloid of *Physostigma venenosum* (BALF.) seeds (Calabar beans) [1–3], is a highly potent acetylcholinesterase inhibitor and has been used medically in the treatment of glaucoma [4], myasthenia gravis [5], and as an antidote against organophosphorous poisoning. More recently, the therapeutic properties of **1** towards *Alzheimer's* disease [6] and the improved pharmacological activity exhibited by some analogues bearing different carbamate side chains [7] have prompted a renewed interest in this alkaloid [8].

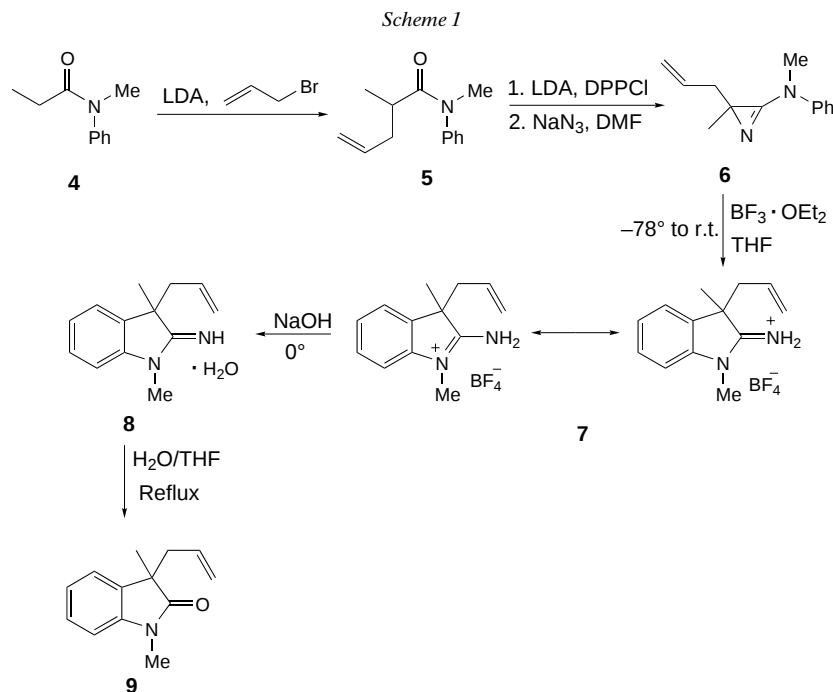
Furthermore, (–)-eseroline (**2**), a major metabolite of **1**, is known to possess an analgesic effect similar to that of morphine [9]. As a consequence, many syntheses of compounds of this class have been reported. The last ones are those of (±)-physostigmine [8] and the enantioselective preparation of (–)-physostigmine (**1**) [10].



In the present paper, a new synthetic approach to (±)-desoxynoreseroline (**3**), the basic ring structure of (–)-physostigmine (**1**), is described.

¹⁾ Part of the Ph.D. thesis of M. K. G. M., Universität Zürich, 2003.

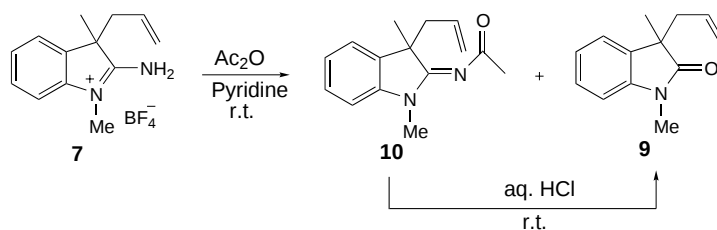
Results and Discussion. – The previously described success to synthesize 1,3,3-trimethyloxindole from the corresponding *N*,2,2-trimethyl-*N*-phenyl-2*H*-azirin-3-amine [11] prompted us to apply this protocol to the synthesis of 3-allyl-1,3-dimethyloxindole (**9**). It was assumed that **9** will be a versatile starting material for the synthesis of desoxynoreseroline (**3**). Alkylation of *N*-methyl-*N*-phenylpropanamide (**4**) with allyl bromide afforded **5** [12] which was subsequently converted to the corresponding azirine **6** according to the method developed by *Villalgorido* and *Heimgartner* [13]. Treatment of **6** with $\text{BF}_3 \cdot \text{OEt}_2$ in THF proceeded smoothly to give the corresponding amidinium salt **7**, which bears the allyl substituent at C(3). This salt was converted to the 3-allyl substituted oxindole **9** by the reaction of **7** with aqueous NaOH to give the hydrate **8**, followed by reflux in a $\text{H}_2\text{O}/\text{THF}$ mixture (*Scheme 1*).



Alternatively, the reaction of **7** with Ac_2O in pyridine gave **9** together with its *N*-Ac derivative **10**. It was established that **10** could easily be converted to **9** by refluxing in 10% aqueous HCl solution (*Scheme 2*) [11].

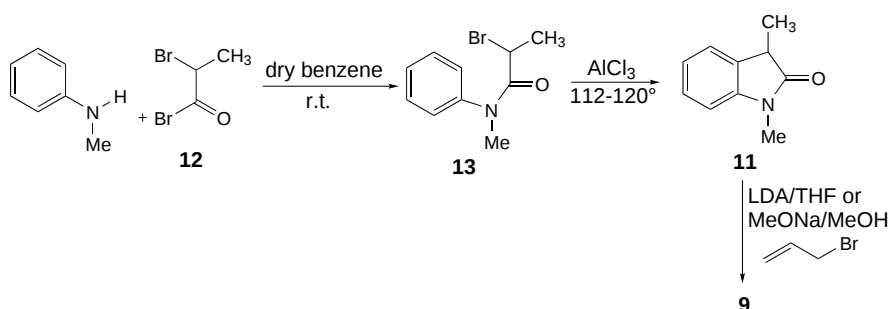
An alternative method for the synthesis of **9** was developed by the allylation of *Julian's* oxindole **11** [14]. The reaction of *N*-methylaniline with 2-bromopropanoyl bromide (**12**), followed by addition of sublimed AlCl_3 to the formed anilide **13**, gave **11** in 94% yield (*Scheme 3*). In analogy to the reported alkylation of **11** with ClCH_2CN and reduction of the nitrile formed to yield desoxynoreseroline **3** [14], we treated **11** with MeONa in MeOH to form the corresponding enolate, which, after addition of allyl bromide, gave 3-allyloxindole **9** in 99% yield. As an alternative, **9** was obtained in the

Scheme 2



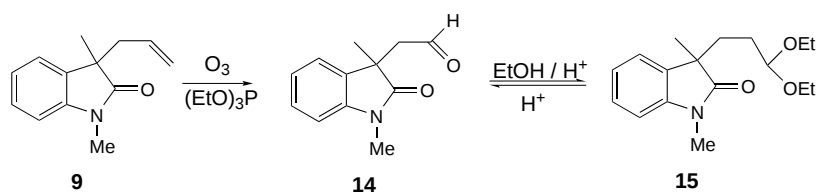
same yield by LDA deprotonation of **11** in THF at -78° (*cf.* [12]) and addition of allyl bromide.

Scheme 3



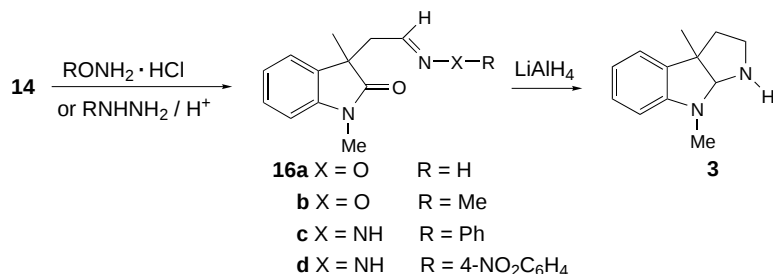
Ozonolysis of **9** in CH_2Cl_2 at -78° and reduction of the ozonide formed under mild conditions by addition of $(\text{EtO})_3\text{P}$ at -78° , followed by slow warming to r.t., provided the aldehyde **14** as a colorless oil in 88% yield (*Scheme 4*). Dimethyl sulfide has also been reported as a convenient reagent to effect reduction of ozonides (*cf.* [15]). The structure of **14** was established by the spectroscopic data as well as chemically by preparing the corresponding acetal **15**, which was obtained in 91% yield by the reaction of **14** with EtOH in the presence of HCl. The hydrolysis of **15** with aqueous HCl or TsOH in toluene/ H_2O afforded **14** in 84 and 91% yield, respectively (*Scheme 4*).

Scheme 4

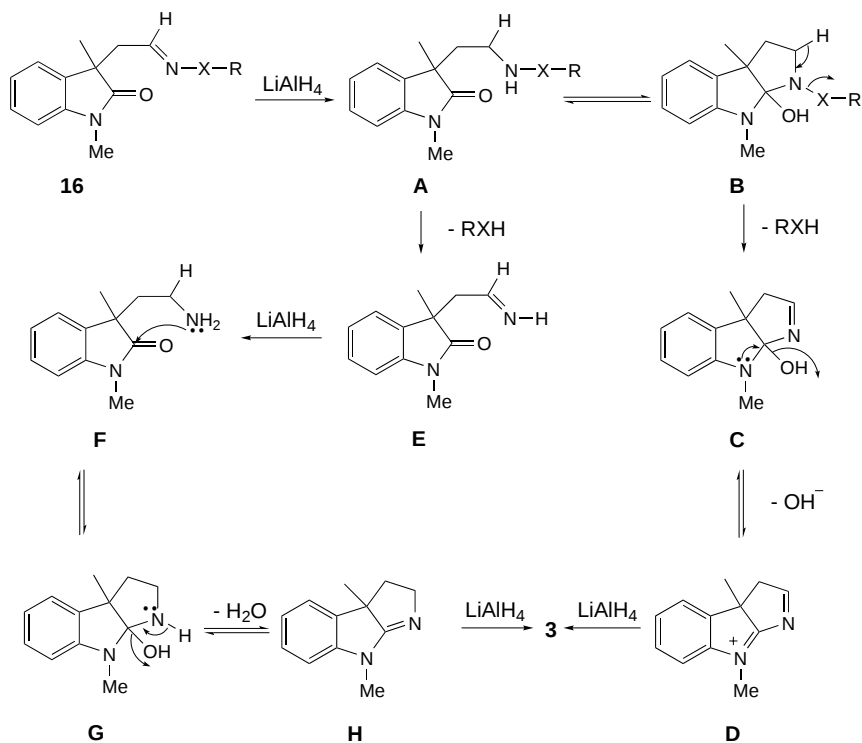


The reported condensation of a 5-MeO-substituted derivative of **14** with $\text{MeNH}_2 \cdot \text{HCl}$, followed by LiAlH_4 reduction to form the basic ring structure of physostigmine and physovenine [16], encouraged us to react **14** with hydroxylamine and phenylhydrazine derivatives. It was assumed that the high nucleophilicity of such compounds

will facilitate the condensation reaction. The oximes and phenyl hydrazones **16a–16d** were obtained as mixtures of the corresponding *syn*- and *anti*-isomers (*Scheme 5*). Reduction of these mixtures of isomers with LiAlH_4 proceeded by loss of ROH or RNH_2 to give ($\pm$)-desoxynoreseroline **3** as a pale brown oil in up to 64% yield.

Scheme 5

Reaction mechanisms proposed for the reductive cyclization $\mathbf{16} \rightarrow \mathbf{3}$ are depicted in *Scheme 6*. The $\text{C}=\text{N}$ group of **16** is reduced by LiAlH_4 to give the hydroxylamine or hydrazine **A**, which undergoes a nucleophilic attack on the lactam C-atom to give **B**,

Scheme 6

followed by elimination of an alcohol or amine leading to **C**. Loss of OH^- gives **D**, which, in turn, is reduced by excess LiAlH_4 to yield **3**. As another possibility, elimination of RXH in **A** leads to imine **E**, which is reduced to give the primary amine **F**. As in the synthesis of **3** described in [14], intramolecular nucleophilic attack of the NH_2 group on the lactam C-atom gives **G**, which undergoes elimination of H_2O to give **H**. The latter is further reduced to yield **3**.

In conclusion, it has been shown that 3-allyl-1,3-dimethyloxindole (**9**) can be prepared conveniently by the novel ring enlargement of 2*H*-azirin-3-amine **6** or by allylation of oxindole **11**. By standard reactions, **9** was transformed into ($\pm$)-desoxynoreseroline (**3**) in high yield. The latter is proved to be the basic ring skeleton of (–)-physostigmine (**1**), as it could be easily methylated to give ($\pm$)-desoxyeseroline [14]. Recently, (–)-desoxyeseroline has been transformed to (–)-eseroline (**2**) and (–)-physostigmine (**1**) [17].

We thank the analytical sections of our institute for spectra and analyses, and *F. Hoffmann-La Roche AG*, Basel, for financial support. *M. K. G. M.* thanks the *Swiss Federal Government* for the provision of a National Scholarship for Foreign Students.

Experimental Part

General. The *N*-methyl-*N*-phenylpropanamide (**4**) was synthesized according to standard procedures from propanoyl chloride and *N*-methylaniline; *N*,2-dimethyl-*N*-phenylpent-4-enamide (**5**) was prepared by alkylation of **4** with allyl bromide [12].

Solvents were purified by standard procedures. TLC: *Merck* TLC aluminium sheets, silica gel 60 F_{254} . Column chromatography (CC): *Uetikon-Chemie* 'Chromatographiegel' *C-560*. High-performance liquid chromatography (HPLC): *Varian-590*, *Nucleosil 100-7*; detection at λ 254 nm. Ozonolysis: *Fischer* ozone generator 502 (3–5 g O_3/h). M.p.: *Mettler-FP-5* apparatus or *Büchi 510* apparatus; uncorrected. IR Spectra: *Perkin-Elmer-781* spectrophotometer or *Perkin-Elmer-1600-FT-IR* spectrophotometer; absorptions in cm^{-1} . ^1H - (300 MHz) and ^{13}C -NMR (75.5 MHz) Spectra: in CDCl_3 , *Bruker ARX-300* instrument; at 300 K; δ in ppm, coupling constants J in Hz; ^{13}C -signal multiplicity from DEPT spectra. MS: *Finnigan SSQ-700* or *MAT-90* instrument for CI (NH_3); m/z (rel. %).

N,2-Dimethyl-*N*-phenyl-2-(prop-2-enyl)-2*H*-azirin-3-amine (**6**) [13]. To a soln. of **5** (1.126 g, 5.54 mmol) in dry THF (27 ml) at 0° under Ar was added LDA (ca. 6.32 mmol), and, after 1 h, the amide enolate formed was treated with diphenylphosphoryl chloride (DPPCl; 1.71 ml, 8.32 mmol) also at 0° . Under Ar, the suspension was filtered into a suspension of NaN_3 (900 mg, 13.8 mmol) in 2.8 ml of DMF to give, after stirring for 3–4 d at r.t., **6** (920 mg, 83%).

2-Amino-1,3-dimethyl-3-(prop-2-enyl)-3*H*-indolium Tetrafluoroborate (**7**). To a stirred soln. of **6** (400 mg, 2.0 mmol) in THF at -78° , $\text{BF}_3 \cdot \text{OEt}_2$ (ca. 48% BF_3 in Et_2O ; 0.54 ml, 2.1 mmol) was added. Then, the soln. was allowed to warm slowly to r.t. and was stirred for 12 h. After addition of Et_2O and filtration, the crude product was purified by CC ($\text{MeOH}/\text{CH}_2\text{Cl}_2$ 0.5 : 10) to yield 403 mg (70%) of **7**. Pale yellow viscous oil, which solidifies in h.v. IR (KBr): 3220s, 2862w, 1685m, 1471s, 1195s, 1113m, 931w, 884m, 799s, 676m, 646s. ^1H -NMR: 8.54, 8.31 (2 br. s, NH_2); 7.45–7.34 (m, 2 arom. H); 7.32–7.25 (*t*-like, 1 arom. H); 7.18 (*d*-like, 1 arom. H); 5.22–5.05 (m, $-\text{CH}=\text{}$); 4.96–4.89 (m, $=\text{CH}_2$); 3.58 (s, MeN); 2.90–2.72 (m, CH_2); 1.62 (s, Me). ^{13}C -NMR: 175.0 (s, $\text{C}=\text{N}$); 141.6, 133.8 (2s, 2 arom. C); 129.9 (*d*, $\text{CH}=\text{}$); 129.0, 125.7, 122.8, 110.6 (4*d*, 4 arom. CH); 120.8 (*t*, $=\text{CH}_2$); 52.0 (s, C(3)); 42.2 (*t*, CH_2); 29.1 (*q*, MeN); 22.7 (*q*, Me). CI-MS: 202 (19), 201 (97, $[\text{M} - \text{BF}_4]^+$), 159 (13), 102 (32).

2,3-Dihydro-2-imino-1,3-dimethyl-3-(prop-2-enyl)-1*H*-indole Hydrate (**8**). A soln. of **7** (47 mg, 0.16 mmol) in the least amount of H_2O was cooled to 0° , and 30% aq. NaOH (4.7 ml) was added. The cooled mixture (ice bath) was stirred for 5 h. After extraction with CH_2Cl_2 , the org. phase was washed with brine and dried (Na_2SO_4). Evaporation of the solvent gave 24 mg (68%) of **8**. Colorless viscous oil. IR (film): 3304m, 3056w, 2926m, 1725w, 1646s, 1608s, 1496s, 1468s, 1390m, 1308m, 1262w, 1227w, 1123m, 1083m, 1020m, 996m, 964w, 919w, 747m. ^1H -NMR: 7.21 (*t*-like, 1 arom. H); 7.11 (*d*-like, 1 arom. H); 6.93 (*t*-like, 1 arom. H); 6.71 (*d*-like, 1 arom. H); 5.53–5.37 (m, $-\text{CH}=\text{}$); 5.02–4.91 (m, $=\text{CH}_2$); 4.15 (br. s, NH_2); 3.22 (s, MeN); 2.51–2.35 (m, CH_2); 1.36 (s, Me). ^{13}C -NMR: 175.3 (s, $\text{C}=\text{N}$); 145.0, 133.7 (2s, 2 arom. C); 132.4 (*d*, $-\text{CH}=\text{}$); 127.8, 122.4, 120.5, 106.6 (4*d*,

4 arom. CH); 118.7 (t , $=\text{CH}_2$); 48.4 (s , C(3)); 44.5 (t , CH_2); 26.9 (q , MeN); 24.7 (q , Me). CI-MS: 202 (15), 201 (100), $[\text{M} - \text{NH}_3]^+$ or $[\text{M} - \text{OH}]^+$.

2,3-Dihydro-1,3-dimethyl-3-(prop-2-enyl)-1H-indol-2-one (9) and **N-[2,3-Dihydro-1,3-dimethyl-3-(prop-2-enyl)-1H-indol-2-yliden]acetamide (10)**. A soln. of **7** (100 mg, 0.35 mmol) in pyridine/ Ac_2O (1 ml each) was stirred at r.t. for 16 h. Then, the solvent was evaporated, and the residue was dissolved in CHCl_3 , washed with H_2O and brine, and dried (Na_2SO_4). After filtration, evaporation, and CC (Et_2O /hexane 3:10), two products **9** (9 mg, 13%) and **10** (34 mg, 40%) were isolated.

Data of 9 (minor product): Pale yellow oil. IR (film): 2927s, 2856s, 1724s, 1615m, 1493m, 1469s, 1378s, 1350m, 1274s, 1124s, 1074m, 995w, 920w, 753m, 742m, 703w, 653w. $^1\text{H-NMR}$: 7.28 (t -like, 1 arom. H); 7.20 (d -like, 1 arom. H); 7.05 (t -like, 1 arom. H); 6.83 (d -like, 1 arom. H); 5.52–5.38 (m , $-\text{CH}=\text{}$); 5.02–4.89 (m , $=\text{CH}_2$); 3.20 (s , MeN); 2.55–2.49 (m , CH_2); 1.38 (s , Me). $^{13}\text{C-NMR}$: 180.1 (s , $\text{C}=\text{O}$); 143.1, 133.5 (2s, 2 arom. C); 132.5 (d , $-\text{CH}=\text{}$); 127.6, 122.8, 122.2, 107.8 (4d, 4 arom. CH); 118.5 (t , $=\text{CH}_2$); 48.1 (s , C(3)); 42.3 (t , CH_2); 26.0 (q , MeN); 22.6 (q , Me). GC/EI-MS: 201 (15, M^+), 161 (12), 160 (100), 145 (5), 132 (15), 130 (10), 117 (17). Anal. calc. for $\text{C}_{13}\text{H}_{15}\text{NO}$ (201.26): C 77.58, H 7.51, N 6.96; found: C 77.38, H 7.46, N 7.16.

Data of 10 (major product): White solid. M.p. 84.5–85.0°. IR (KBr): 3068w, 2960m, 2927m, 1671s, 1644s, 1605s, 1494s, 1467m, 1382s, 1353m, 1288m, 1221s, 1203s, 1126m, 1101m, 1004m, 939m, 929m, 808m, 759s, 719m, 637w, 600m. $^1\text{H-NMR}$: 7.26 (t -like, 1 arom. H); 7.15 (d -like, 1 arom. H); 7.04 (t -like, 1 arom. H); 6.79 (d -like, 1 arom. H); 5.45–5.32 (m , $-\text{CH}=\text{}$); 5.01–4.85 (m , $=\text{CH}_2$); 3.19 (s , MeN); 2.82–2.72, 2.62–2.53 (2m, CH_2); 2.29 (s , MeCO); 1.51 (s , Me). $^{13}\text{C-NMR}$: 181.8 (s , $\text{C}=\text{O}$); 165.1 (s , $\text{C}=\text{N}$); 143.3, 134.6 (2s, 2 arom. C); 132.6 (d , $-\text{CH}=\text{}$); 127.8, 122.2, 122.0, 107.7 (4d, 4 arom. CH); 118.5 (t , $=\text{CH}_2$); 51.1 (s , C(3)); 43.7 (t , CH_2); 28.4, 27.3 (2q, MeCO, MeN); 24.3 (q , Me). GC/EI-MS: 242 (17, M^+), 227 (15), 215 (15), 201 (9), 186 (19), 160 (17), 159 (100), 143 (13), 132 (13), 117 (12). Anal. calc. for $\text{C}_{15}\text{H}_{18}\text{N}_2\text{O}$ (242.32): C 74.35, H 7.49, N 11.56; found: C 74.36, H 7.62, N 11.38.

Hydrolysis of Compounds 8 and 10. A soln. of **8** (30 mg, 0.14 mmol) in H_2O /THF (4.5 ml each) was heated to reflux for 3 d and then extracted with Et_2O . The org. phase was washed with brine and dried (Na_2SO_4). Evaporation of the solvent, followed by CC (Et_2O /hexane 3:10), gave 20.5 mg (74%) of **9**.

A soln. of **10** (50 mg, 0.21 mmol) in 10% aq. HCl (5 ml) was stirred at r.t. overnight and then extracted with Et_2O . The org. phase was washed with aq. NaHCO_3 soln. and brine, and dried (Na_2SO_4). Evaporation of the solvent, followed by CC (Et_2O /hexane 3:10), gave 54 mg (82%) of **9**.

Synthesis of 9 via Allylation of 1,3-Dimethyloxindole 11. **2-Bromo-N-methyl-N-phenylpropanamide (13)** [14]. To a well-cooled soln. of *N*-methylaniline (24.7 ml, 0.23 mol) in 100 ml of dry benzene, 2-bromopropanoyl bromide (**12**; 11.2 ml, 0.11 mol) was added, and the mixture was stirred overnight at r.t. The formed *N*-methylaniline hydrobromide was filtered off, and the filtrate was washed several times with 2% aq. HCl and then dried (Na_2SO_4). The solvent was evaporated, and the residue was dried in h.v. to give 23 g (95%) of **13**. Colorless oil. IR (film): 3050w, 2924w, 1668s, 1596s, 1496s, 1448s, 1389s, 1270m, 1192m, 1121s, 1065m, 1032m, 978w, 774m, 700s, 647w. $^1\text{H-NMR}$: 7.50–7.40 (m , 3 arom. H); 7.32–7.27 (m , 2 arom. H); 4.32–4.23 (q , CH); 3.30 (s , MeN); 1.74 (d , $J = 6.7$, Me). $^{13}\text{C-NMR}$: 169.6 (s , $\text{C}=\text{O}$); 143.0 (s , 1 arom. C); 130.0, 128.5, 127.2 (3d, 5 arom. CH); 38.1 (q , MeN); 32.1 (d , CHBr); 21.9 (q , Me). GC/EI-MS: 243 (34, M^+) for Br^{81} , 241 (34, M^+) for Br^{79} , 162 (20), 134 (55), 119 (7), 107 (100), 106 (71), 91 (5), 77 (54).

2,3-Dihydro-1,3-dimethyl-1H-indol-2-one (11) [14]. To **13** (23 g, 0.17 mol), sublimed AlCl_3 (26 g, 0.19 mol) was added in small portions under cooling. The mixture was heated to 112°, where HBr gas evolved. When the gas evolution ceased, the mixture was heated to 120° for 15 min, then cooled to r.t., poured onto ice, and extracted with Et_2O . The org. phase was washed with 2% aq. HCl and sat. NaHCO_3 soln., and dried (Na_2SO_4). The solvent was evaporated, and the residue was dried in h.v. to give 15.1 g (94%) of **11** ([14]: 92%). Colorless oil. IR (film): 3055w, 2972m, 2933m, 1714s, 1614s, 1493s, 1471s, 1420m, 1376s, 1346s, 1310m, 1257s, 1219w, 1130m, 1091m, 1063w, 1043w, 1018m, 982m, 929w, 890w, 807w, 751s, 729w, 701w. $^1\text{H-NMR}$: 7.30 (t -like, 1 arom. H); 7.24 (d -like, 1 arom. H); 7.06 (t -like, 1 arom. H); 6.84 (d -like, 1 arom. H); 3.49–3.39 (q , CH); 3.22 (s , MeN); 1.49 (d , $J = 7.6$, Me). $^{13}\text{C-NMR}$: 178.6 (s , $\text{C}=\text{O}$); 143.9, 130.5 (2s, 2 arom. C); 127.8, 123.4, 122.3, 107.9 (4d, 4 arom. CH); 40.5 (d , CH); 26.1 (q , MeN); 15.3 (q , Me). GC/EI-MS: 161 (83, M^+), 146 (40), 132 (21), 118 (100), 117 (17), 103 (5), 91 (20), 77 (11), 65 (5).

2,3-Dihydro-1,3-dimethyl-3-(prop-2-enyl)-1H-indol-2-one (9). *a*) To a cooled soln. (ice bath) of EtONa in EtOH (0.12 g in 2 ml EtOH), a mixture of **11** (420 mg, 2.61 mmol) and allyl bromide (0.47 ml, 5.56 mmol) was added dropwise. After complete addition, the solvent was evaporated, and Et_2O was added. The Et_2O phase was washed with 2% aq. HCl, sat. NaHCO_3 soln., and brine, and dried (Na_2SO_4). CC (AcOEt /hexane 1:2) yielded 520 mg (99%) of **9**. Pale yellow oil.

b) To a stirred soln. of (i-Pr)₂NH (0.43 ml, 3.03 mmol) in THF (10 ml) at –20°, BuLi (2M soln. in pentane, 1.5 ml, 3 mmol) was added under Ar, the soln. was warmed to 0° for 15 min, and then cooled to –78°. A soln. of **11** (420 mg, 2.61 mmol) in THF (2 ml) was added dropwise. After 30 min, allyl bromide (0.25 ml, 2.96 mmol) was added. The mixture was stirred for 30 min at –78°, then warmed to r.t., sat. NaHCO₃ soln. was added, and the mixture was extracted with Et₂O. The org. phase was washed with sat. NaHCO₃ soln. and brine, dried (MgSO₄), and evaporated to give 521 mg (99%) of **9**.

2,3-Dihydro-1,3-dimethyl-2-oxo-1H-indol-3-acetaldehyde (14). A flow of ozonoid oxygen was bubbled (G2 frit) through a soln. of **9** (313 mg, 1.56 mmol) in dry CH₂Cl₂ (60 ml) at –78° until the appearance of blue color indicated an excess of O₃. After blowing out the excess of O₃ with dry N₂, (EtO)₃P (0.50 ml, 2.87 mmol) was added at –78°, and the mixture was allowed to warm to r.t. and stirred for 1 h at r.t. Then, the solvent was evaporated, and the residue was purified by CC (AcOEt/hexane 1:2) to yield 278 mg (88%) of **14**. Colorless oil. IR (film): 3056m, 2970s, 2930m, 2889m, 2834m, 2733m, 1714s, 1652m, 1614s, 1495s, 1472s, 1453s, 1422m, 1379s, 1351s, 1309s, 1250s, 1159m, 1127s, 1067m, 1032s, 1019m, 986w, 905w, 756s, 700m. ¹H-NMR: 9.51 (*t*-like (ABX), *J*_{AX} ≈ *J*_{BX} = 1.6, CHO); 7.29 (*t*-like, 1 arom. H); 7.19 (*d*-like, 1 arom. H); 7.05 (*t*-like, 1 arom. H); 6.88 (*d*-like, 1 arom. H); 3.27 (*s*, MeN); 3.01–2.89 (*m* (ABX), *J*_{AB} ≈ 15.7, *J*_{AX} ≈ *J*_{BX} = 1.6, CH₂); 1.41 (*s*, Me). ¹³C-NMR: 198.6 (*d*, CH=O); 179.4 (*s*, C=O); 143.1, 132.7 (2s, 2 arom. C); 128.2, 122.5, 122.3, 108.2 (4d, 4 arom. CH); 50.4 (*t*, CH₂); 44.9 (*s*, C(3)); 26.3 (*q*, MeN); 23.8 (*q*, Me). CI-MS: 205 (14), 204 (100, [*M* + 1]⁺), 203 (2, *M*⁺).

3-(3,3-Diethoxypropyl)-2,3-dihydro-1,3-dimethyl-1H-indol-2-one (15). To a soln. of **14** (57.8 mg, 0.284 mmol) in abs. EtOH (15 ml), 2 drops of conc. HCl were added. The mixture was heated to reflux for 1 h, the solvent was evaporated, and CH₂Cl₂ was added. The org. phase was washed with 10% aq. HCl, sat. NaHCO₃ soln., and brine, and dried (Na₂SO₄). CC (AcOEt/hexane 3:10) gave 71.6 mg (91%) of **15**. Colorless oil. IR (film): 3055m, 2974s, 2927s, 2897s, 1714s, 1613s, 1494s, 1471s, 1452s, 1426m, 1378s, 1349s, 1310m, 1266m, 1248m, 1158s, 1123s, 1060s, 1019s, 1005s, 958w, 918w, 853w, 754s, 742s, 702m, 644w. ¹H-NMR: 7.26 (*t*-like, 1 arom. H); 7.19 (*d*-like, 1 arom. H); 7.04 (*t*-like, 1 arom. H); 6.82 (*d*-like, 1 arom. H); 4.17–4.12 (*m*, CHO₂); 3.51–3.40, 3.32–3.25, 3.11–2.99 (3m, 2 CH₂O); 3.21 (*s*, MeN); 2.51–2.42, 2.07–1.99 (2m, CH₂); 1.35 (*s*, Me); 1.05–1.01, 1.01–0.93 (2t, 2 Me). ¹³C-NMR: 180.2 (*s*, C=O); 143.3, 133.3 (2s, 2 arom. C); 127.6, 122.7, 122.0, 107.7 (4d, 4 arom. CH); 99.7 (*d*, CHO₂); 61.0, 60.0, 45.6 (3t, 3 CH₂); 40.7 (*s*, C(3)); 26.0 (*q*, MeN); 25.0, 15.0, 14.7 (3q, 3 Me). GC/EI-MS: 277 (11, *M*⁺), 232 (11), 174 (24), 159 (63), 161 (100), 130 (13), 117 (34), 103 (26), 89 (8), 75 (24).

Hydrolysis of 15. *a*) A soln. of **15** (70 mg, 0.25 mmol) in 10 ml of 5% aq. HCl was heated to reflux for 4 h, then extracted with CH₂Cl₂, and the org. phase was washed with sat. NaHCO₃ soln. and brine, and dried (Na₂SO₄) to give 43 mg (84%) of **14**.

b) To a soln. of **15** (30 mg, 0.11 mmol) in toluene (10 ml), TsOH · H₂O (23 mg, 0.12 mmol) was added, and the mixture was heated to reflux for 2 h. Then, the solvent was evaporated, CH₂Cl₂ was added, and the org. phase was washed with sat. NaHCO₃ soln. and brine, and dried (Na₂SO₄) to give 20 mg (91%) of **14**.

Preparation of Oximes 16a and 16b, and phenylhydrazones 16c and 16d.

General Procedure A (GPA). To a soln. of **14** in 10 ml of THF, NH₂OR · HCl was added, and the mixture was heated to reflux for 2 h and evaporated to dryness. After addition of Et₂O, the soln. was washed with 10% aq. HCl, sat. NaHCO₃ soln., and sat. NaCl soln., and dried (Na₂SO₄) to give **16** as a mixture of *syn*- and *anti*-isomers.

2,3-Dihydro-1,3-dimethyl-2-oxo-1H-indol-3-acetaldehyde Oxime (16a). According to the GPA, **14** (47.5 mg, 0.23 mmol) and NH₂OH · HCl (32 mg, 0.46 mmol). Yield: 35.5 mg (70%) of **16a**. Colorless oil. Mixture of isomers (1:0.8, ¹H-NMR). *Isomer 1*: ¹H-NMR: 7.20 (*t*-like (ABX), *J*_{AX} ≈ *J*_{BX} = 6.8, CH=N); 7.25 (*t*-like, 1 arom. H); 7.18 (*d*-like, 1 arom. H); 7.05 (*t*-like, 1 arom. H); 6.87 (*d*-like, 1 arom. H); 3.21 (*s*, MeN); 2.72–2.57 (*m* (ABX), *J*_{AB} ≈ 14.3, CH₂); 1.41 (*s*, Me). ¹³C-NMR: 179.4 (*s*, C=O); 147.4 (*d*, CH=N); 142.8, 132.6 (2s, 2 arom. C); 128.1, 122.7, 122.6, 108.2 (4d, 4 arom. CH); 46.9 (*s*, C(3)); 37.3 (*t*, CH₂); 26.2 (*q*, MeN); 22.9 (*q*, Me). *Isomer 2*: ¹H-NMR: 6.49 (*t*-like (ABX), *J*_{AX} ≈ *J*_{BX} = 5.5, CH=N); 7.26 (*t*-like, 1 arom. H); 7.17 (*d*-like, 1 arom. H); 7.04 (*t*-like, 1 arom. H); 6.82 (*d*-like, 1 arom. H); 3.23 (*s*, MeN); 2.96–2.81 (*m* (ABX), *J*_{AB} ≈ 16.1, CH₂); 1.43 (*s*, Me). ¹³C-NMR: 179.5 (*s*, C=O); 147.4 (*d*, CH=N); 142.8, 133.0 (2s, 2 arom. C); 128.2, 122.8, 122.6, 108.2 (4d, 4 arom. CH); 45.9 (*s*, C(3)); 32.6 (*t*, CH₂); 26.1 (*q*, MeN); 22.9 (*q*, Me).

GC: Two isomers were detected. EI-MS (mixture): 218 (12, *M*⁺), 161 (14), 160 (100), 130 (9), 117 (8), 77 (5).

2,3-Dihydro-1,3-dimethyl-2-oxo-1H-indol-3-acetaldehyde O-Methylxime (16b). According to the GPA, **14** (75 mg, 0.37 mmol) and NH₂OMe · HCl (31 mg, 0.37 mmol). Yield: 81.6 mg (87%) of **16b**. HPLC: AcOEt/hexane 3:10, 0.5 ml/min, 13 atm. Colorless oil. Mixture of isomers (1:0.74, ¹H-NMR). IR (film, mixtures of isomers): 3056m, 2967s, 2937s, 2900s, 2820m, 1715s, 1614s, 1493s, 1471s, 1453s, 1423s, 1378s, 1350s, 1309s, 1252s, 1159m, 1125s, 1102s, 1085s, 1060s, 1041s, 1020s, 951m, 907m, 884m, 855s, 755s, 744s, 700m, 686w, 656w, 637w.

Isomer 1: $^1\text{H-NMR}$: 7.16 (*t*-like (*ABX*), $J_{AX} \approx J_{BX} = 6.4$, $\text{CH}=\text{N}$); 7.27 (*t*-like, 1 arom. H); 7.18 (*d*-like, 1 arom. H); 7.07 (*t*-like, 1 arom. H); 6.87 (*d*-like, 1 arom. H); 3.72 (*s*, MeO); 3.22 (*s*, MeN); 2.70–2.56 (*m* (*ABX*), $J_{AB} \approx 14.5$, CH_2); 1.41 (*s*, Me). $^{13}\text{C-NMR}$: 179.4 (*s*, $\text{C}=\text{O}$); 145.9 (*d*, $\text{CH}=\text{N}$); 142.9, 132.7 (2*s*, 2 arom. C); 128.1, 122.9, 122.5, 108.1 (4*d*, 4 arom. CH); 61.2 (*q*, MeO); 46.7 (*s*, C(3)); 37.3 (*t*, CH_2); 26.1 (*q*, MeN); 22.9 (*q*, Me). *Isomer 2*: $^1\text{H-NMR}$: 6.41 (*t*-like (*ABX*), $J_{AX} \approx J_{BX} = 5.5$, $\text{CH}=\text{N}$); 7.28 (*t*-like, 1 arom. H); 7.17 (*d*-like, 1 arom. H); 7.06 (*t*-like, 1 arom. H); 6.83 (*d*-like, 1 arom. H); 3.80 (*s*, MeO); 3.23 (*s*, MeN); 2.90–2.77 (*m* (*ABX*), $J_{AB} \approx 16.1$, CH_2); 1.43 (*s*, Me). $^{13}\text{C-NMR}$: 179.5 (*s*, $\text{C}=\text{O}$); 146.2 (*d*, $\text{CH}=\text{N}$); 142.9, 132.8 (2*s*, 2 arom. C); 128.2, 122.8, 122.5, 108.1 (4*d*, 4 arom. CH); 61.5 (*q*, MeO); 46.0 (*s*, C(3)); 33.3 (*t*, CH_2); 26.1 (*q*, MeN); 22.9 (*q*, Me). GC: Two isomers were detected. EI-MS (mixture): 232 (12, M^{+}), 201 (4), 160 (100), 145 (4), 130 (9), 117 (8), 77 (6). CI-MS (mixture): 234 (13), 233 (100, $[M+1]^+$).

2,3-Dihydro-1,3-dimethyl-2-oxo-1H-indol-3-acetaldehyde N-Phenylhydrazone (16c). A mixture of phenylhydrazine (0.06 ml, 0.61 mmol), **14** (50 mg, 0.25 mmol), and 2 drops of AcOH in 5 ml of EtOH was heated to reflux for 2 h. The solvent was evaporated, and CH_2Cl_2 was added. The org. phase was washed with 5% NaHCO_3 soln. and brine, and dried (Na_2SO_4). CC ($\text{MeOH}/\text{CH}_2\text{Cl}_2$ 0.1:40) gave 72 mg (100%) of **16c**. Colorless oil. Mixture of isomers (1:0.57, $^1\text{H-NMR}$). *Isomer 1*: $^1\text{H-NMR}$: 7.32–7.18 (*m*, 5 arom. H); 7.08 (*t*-like, 1 arom. H); 7.02 (*t*-like (*ABX*), $J_{AX} \approx J_{BX} = 6.4$, $\text{CH}=\text{N}$); 6.91–6.76 (*m*, 3 arom. H); 3.22 (*s*, MeN); 2.87–2.69 (*m* (*ABX*), $J_{AB} \approx 14.9$, CH_2); 1.42 (*s*, Me). $^{13}\text{C-NMR}$: 179.9 (*s*, $\text{C}=\text{O}$); 145.0 (*s*, 1 arom. C); 143.1, 133.7 (2*s*, 2 arom. C); 135.5 (*d*, $\text{CH}=\text{N}$); 129.1, 119.6, 112.6 (3*d*, 5 arom. CH); 127.9, 122.8, 122.6, 108.1 (4*d*, 4 arom. CH); 47.3 (*s*, C(3)); 39.8 (*t*, CH_2); 26.3 (*q*, MeN); 23.5 (*q*, Me). *Isomer 2*: $^1\text{H-NMR}$: 7.32–7.14 (*m*, 5 arom. H); 7.08 (*t*-like, 1 arom. H); 6.91–6.76 (*m*, 3 arom. H); 6.12 (*t*-like (*ABX*), $J_{AX} \approx J_{BX} = 5.2$, $\text{CH}=\text{N}$); 3.18 (*s*, MeN); 2.92–2.55 (*m* (*ABX*), $J_{AB} \approx 14.9$, CH_2); 1.49 (*s*, Me). $^{13}\text{C-NMR}$: 181.0 (*s*, $\text{C}=\text{O}$); 145.0 (*s*, 1 arom. C); 143.1, 133.7 (2*s*, 2 arom. C); 135.5 (*d*, $\text{CH}=\text{N}$); 129.1, 119.8, 113.1 (3*d*, 5 arom. CH); 127.9, 122.8, 122.6, 108.2 (4*d*, 4 arom. CH); 47.2 (*s*, C(3)); 34.7 (*t*, CH_2); 26.3 (*q*, MeN); 23.5 (*q*, Me).

2,3-Dihydro-1,3-dimethyl-2-oxo-1H-indol-3-acetaldehyde N-(4-Nitrophenyl)hydrazone (16d). To a soln. of (4-nitrophenyl)hydrazine hydrochloride (125 mg, 0.67 mmol) and AcONa (200 mg, 2.44 mmol) in 0.12 ml of H_2O , a soln. of **14** (50 mg, 0.25 mmol) in 5 ml of EtOH was added. The mixture was heated to reflux for 1 h, extracted with CH_2Cl_2 , and the org. phase was washed with 5% NaHCO_3 soln. and brine, and dried (MgSO_4). CC ($\text{MeOH}/\text{CH}_2\text{Cl}_2$ 0.1:10) gave 0.81 g (98%) of **16d**. Yellow viscous oil. GC: Two isomers were detected (ratio 1:0.1, $^1\text{H-NMR}$). IR (film, mixture of isomers): 3322*s*, 3050*m*, 2909*m*, 1693*s*, 1598*s*, 1471*s*, 1380*m*, 1300*s*, 1277*s*, 1175*s*, 1108*s*, 1000*m*, 837*s*, 751*s*, 693*m*, 668*w*, 632*w*. *Isomer 1*: $^1\text{H-NMR}$: 8.32 (*br.s*, NH); 8.03 (*AA'* of *AA'BB'*, 2 arom. H); 7.30 (*t*-like, 1 arom. H); 7.22 (*d*-like, 1 arom. H); 7.08 (*t*-like, 1 arom. H); 7.05 (*t*-like (*ABX*), $J_{AX} \approx J_{BX} = 6.4$, $\text{CH}=\text{N}$); 6.89 (*d*-like, 1 arom. H); 6.78 (*BB'* of *AA'BB'*, 2 arom. H); 3.21 (*s*, MeN); 2.91–2.73 (*m* (*ABX*), $J_{AB} \approx 14.9$, CH_2); 1.42 (*s*, Me). $^{13}\text{C-NMR}$: 179.9 (*s*, $\text{C}=\text{O}$); 149.9, 139.5 (2*s*, 2 arom. C of $\text{C}_6\text{H}_4\text{NO}_2$); 142.8, 133.3 (2*s*, 2 arom. C); 139.9 (*d*, $\text{CH}=\text{N}$); 128.0, 122.7, 122.5, 108.2 (4*d*, 4 arom. CH); 125.9, 111.1 (2*d*, 4 arom. CH of $\text{C}_6\text{H}_4\text{NO}_2$); 47.0 (*s*, C(3)); 39.6 (*t*, CH_2); 26.2 (*q*, MeN); 23.7 (*q*, Me). *Isomer 2*: $^1\text{H-NMR}$: 8.70 (*br.s*, NH); 8.03 (*AA'* of *AA'BB'*, 2 arom. H); 7.29 (*t*-like, 1 arom. H); 7.22 (*d*-like, 1 arom. H); 7.07 (*t*-like, 1 arom. H); 6.88 (*d*-like, 1 arom. H); 6.78 (*BB'* of *AA'BB'*, 2 arom. H); 6.27 (*t* (*ABX*), $J_{AX} \approx J_{BX} = 5.2$, $\text{CH}=\text{N}$); 3.17 (*s*, MeN); 3.07–2.62 (*m* (*ABX*), $J_{AB} \approx 14.9$, CH_2); 1.49 (*s*, Me). $^{13}\text{C-NMR}$: 181.0 (*s*, $\text{C}=\text{O}$); 150.3, 140.0 (2*s*, 2 arom. C of $\text{C}_6\text{H}_4\text{NO}_2$); 142.2, 132.0 (2*s*, 2 arom. C); 138.8 (*d*, $\text{CH}=\text{N}$); 128.6, 123.3, 122.7, 108.8 (4*d*, 4 arom. CH); 125.9, 111.9 (2*d*, 4 arom. CH of $\text{C}_6\text{H}_4\text{NO}_2$); 47.2 (*s*, C(3)); 34.7 (*t*, CH_2); 26.2 (*q*, MeN); 24.0 (*q*, Me). CI-MS (mixture): 340 (18), 339 (86, $[M+1]^+$), 252 (10), 212 (11), 211 (99), 203 (33), 197 (15), 195 (12), 194 (100).

LiAlH_4 Reduction of Oximes and Hydrazones. General procedure B (GP B). To a soln. of **16** (1 equiv.) in THF, LiAlH_4 (10 equiv.) was added. The mixture was heated to reflux for 1.5 h. After cooling to r.t., excess LiAlH_4 was decomposed by adding 15 ml of AcOEt dropwise, then, sat. NaHCO_3 soln. was added, the phases were separated, and the aq. layer was extracted with AcOEt. The combined org. extracts were washed with brine and dried (MgSO_4). CC ($\text{MeOH}/\text{CH}_2\text{Cl}_2$ 1:5) gave ($\pm$)-*desoxynereseroline* (**3**) in 41–64% yield as a pale brown oil.

a) According to the GP B, **16a** (19.3 mg, 0.09 mmol) in THF (10 ml) and LiAlH_4 (33.6 mg, 0.88 mmol). Yield: 10.3 mg (62%) of **3**.

b) According to the GP B, **16b** (17.3 mg, 0.07 mmol) in THF (10 ml) and LiAlH_4 (28.3 mg, 0.74 mmol). Yield: 9.4 mg (64%) of **3**.

c) According to the GP B, **16c** (76.4 mg, 0.26 mmol) in THF (20 ml) and LiAlH_4 (100 mg, 2.64 mmol). Yield: 23 mg (47%) of **3**.

d) According to the GP B, **16d** (63.2 mg, 0.19 mmol) in THF (20 ml) and LiAlH_4 (70 mg, 1.84 mmol). Yield: 14.5 mg (41%) of **3**.

Data of 1,2,3,3a,8,8a-Hexahydro-3a,8-dimethylpyrrolo[2,3-b]indole (3; cf. [14]). IR (film): 3325m, 3051m, 3024m, 2925s, 1714s, 1607s, 1494s, 1450s, 1378s, 1349s, 1298s, 1240m, 1201m, 1156m, 1121s, 1062s, 1021s, 985m, 920m, 899m, 858m, 740s, 656w. ¹H-NMR: 7.08 (*t*-like, 1 arom H); 7.02 (*d*-like, 1 arom. H); 6.64 (*t*-like, 1 arom. H); 6.33 (*d*-like, 1 arom. H); 4.53 (*s*, CH); 3.11–3.03, 2.81–2.72, 2.09–2.00, 1.88–1.77 (4m, CH₂CH₂); 2.84 (*s*, MeN); 2.58–2.52 (br. *s*, NH); 1.46 (*s*, Me). ¹³C-NMR: 150.8, 135.5 (2s, 2 arom. C); 127.7, 122.4, 116.8, 105.0 (4d, 4 arom. CH); 92.2 (*d*, CH); 52.1 (*s*, C(3a)); 45.9, 42.5 (2d, 2 CH₂); 31.8 (*q*, MeN); 26.1 (*q*, Me). CI-MS: 190 (14), 189 (100, [M+1]⁺). GC/EI-MS: 188 (100, M⁺), 187 (8), 173 (6), 159 (20), 158 (61), 145 (50), 144 (76), 130 (15), 115 (8), 91 (5), 77 (11).

REFERENCES

- [1] M. F. Roberts, M. Wink, 'Alkaloids: Biochemistry, Ecology, and Medicinal Applications', Plenum Press, New York, 1998, p. 38.
- [2] S. Takano, K. Ogasawara, in 'The Alkaloids', Ed. A. Brossi, Academic Press, New York, 1989, Vol. 36, p. 225–251.
- [3] J. Jobst, O. Hesse, *Ann. Chem. Pharm.* **1864**, 129, 115.
- [4] U. Axelsson, *Acta Ophthalmol., Suppl.* **1969**, 102, 1.
- [5] M. B. Walker, *Proc. Royal. Soc. Med.* **1934**, 1, 1200.
- [6] A. Brossi, X.-F. Pei, N. H. Greig, *Aust. J. Chem.* **1996**, 49, 171.
- [7] a) J. E. Christie, A. Shering, J. Ferguson, A. I. M. Glen, *Br. J. Psychiatry* **1981**, 138, 46; b) K. L. Davis, R. C. Mohs, *Am. J. Psychiatry* **1982**, 139, 1421; c) K. L. Davis, R. C. Mohs, B. M. Davis, W. G. Rosen, B. S. Greenwald, M. I. Levy, T. B. Horvath, *New England J. Med.* **1983**, 308, 721; d) L. J. Thal, P. A. Fuld, *New England J. Med.* **1983**, 308, 720; e) L. J. Thal, P. A. Fuld, D. M. Masur, N. S. Sharpless, *Ann. Neurol.* **1983**, 13, 491; f) R. C. Mohs, B. M. Davis, B. S. Greenwald, A. A. Mathé, C. A. Johns, T. B. Horvath, K. L. Davis, *J. Am. Geriatr. Soc.* **1985**, 33, 749.
- [8] P. F. Santos, P. S. Almeida, A. M. Lobo, S. Prabhakar, *Heterocycles* **2001**, 55, 1029.
- [9] a) A. Galli, G. Renzi, A. Bartolini, R. Bartolini, P. Malmberg-Aiello, *J. Pharm. Pharmacol. Commun.* **1979**, 31, 784; b) A. Bartolini, G. Renzi, A. Galli, P. Malmberg-Aiello, R. Bartolini, *Neurosci. Lett.* **1981**, 25, 179; c) S. Fürst, T. Friedmann, A. Bartolini, R. Bartolini, P. Malmberg-Aiello, A. Galli, G. T. Somogyi, J. Knoll, *Eur. J. Pharmacol.* **1982**, 83, 233; d) M. F. Siddiqui, A. I. Levey, *Drugs Future* **1999**, 24, 417.
- [10] M. Kawahara, A. Nishida, M. Nakagawa, *Org. Lett.* **2000**, 2, 675.
- [11] M. K. G. Mekhael, R. J. Smith, S. Bienz, A. Linden, H. Heimgartner, *Z. Naturforsch.* **2002**, 57b, 444.
- [12] A. D. Hughes, D. A. Price, N. S. Simpkins, *J. Chem. Soc., Perkin Trans.* **1999**, 10, 1295.
- [13] J. M. Villalgordo, H. Heimgartner, *Helv. Chim. Acta* **1993**, 76, 2830.
- [14] P. L. Julian, J. Píkl, D. Boggess, *J. Am. Chem. Soc.* **1934**, 56, 1797.
- [15] M. J. Martin, F. Bermejo, *Tetrahedron Lett.* **1995**, 36, 7705; J. J. Pappas, W. P. Keaveney, E. Gancher, M. Berger, *Tetrahedron Lett.* **1966**, 36, 4273; J. E. Baldwin, W. J. Norris, R. T. Freeman, M. Bradley, R. M. Adlington, S. Long-Fox, C. J. Schofield, *J. Chem. Soc., Chem. Commun.* **1988**, 1128.
- [16] T. Matsuura, L. E. Overman, D. J. Poon, *J. Am. Chem. Soc.* **1998**, 120, 6500.
- [17] A. Ashimori, B. Bachand, M. A. Calter, S. P. Govek, L. E. Overman, D. J. Poon, *J. Am. Chem. Soc.* **1998**, 120, 6488.

Received April 1, 2003