A Novel Synthetic Approach to (±)-Desoxynoreseroline

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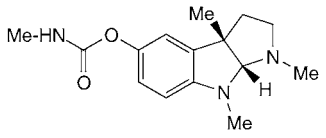
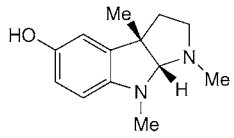
(±)-Desoxynoreseroline (**3**), the basic ring structure of the pharmacologically active alkaloid physostigmine (**1**), was synthesized starting from 3-allyl-1,3-dimethyloxindole (**9**). The latter was prepared from the corresponding 2*H*-azirin-3-amine **6** by a BF_3-catalyzed ring enlargement *via* 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 $LiAlH_4$ proceeded by loss of ROH or RNH_2 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].

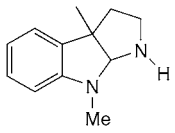
Furthermore, (−)-eseroline (**2**), a major metabolite of **1**, is known to possess an analgesic effect similar to that of morphine [9]. As a consequence, many syntheses of compounds of this class have been reported. The last ones are those of (±)-physostigmine [8] and the enantioselective preparation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



(–)-Physostigmine (**1**)



(–)-Eseroline (**2**)



(±)-Desoxynoreseroline (**3**)

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

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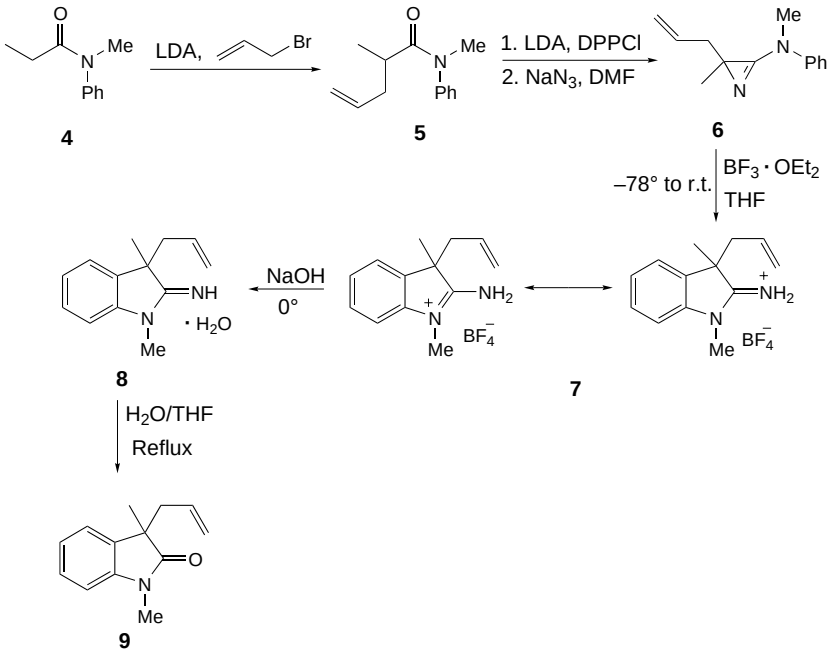
[1]) Part of the Ph.D. thesis of *M. K. G. M.*, Universität Zürich, 2003.

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 *Villalgordo* and *Heimgartner* [13]. Treatment of **6** with $BF_3 \cdot OEt_2$ 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 H_2O/THF mixture (*Scheme 1*).

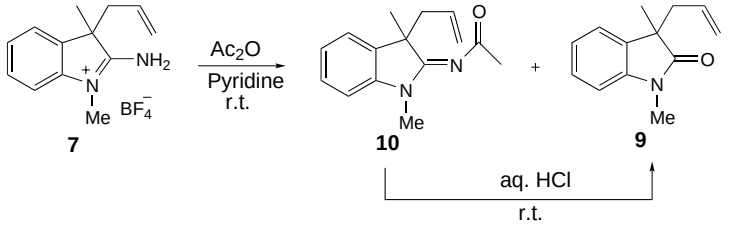
Scheme 1



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].

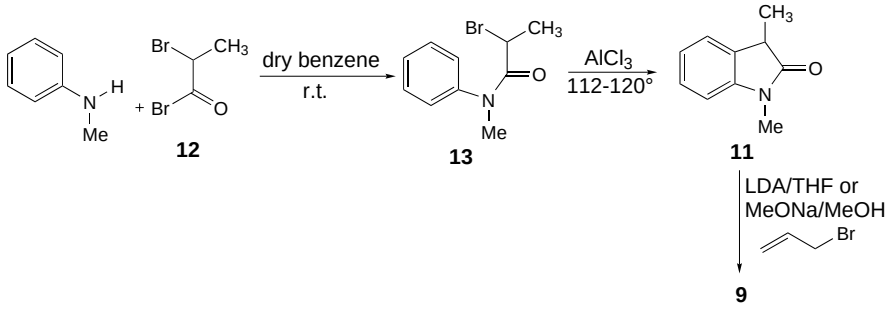
An alternative method for the synthesis of **9** was developed by the allylation of *Julian*'s oxindole **11** [14]. The reaction of *N*-methylaniline with 2-bromopropanoyl bromide (**12**), followed by addition of sublimed $AlCl_3$ to the formed anilide **13**, gave **11** in 94% yield (*Scheme 3*). 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



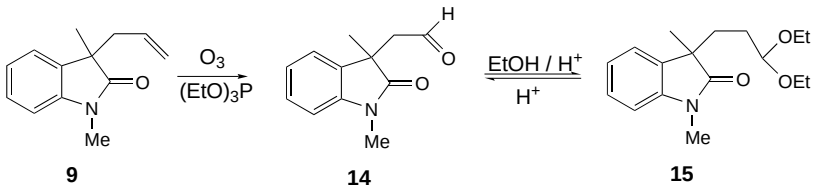
same yield by LDA deprotonation of **11** in THF at $-78°$ (*cf.* [12]) and addition of allyl bromide.

Scheme 3



Ozonolysis of **9** in CH_2Cl_2 at $-78°$ and reduction of the ozonide formed under mild conditions by addition of $(EtO)_3P$ 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*).

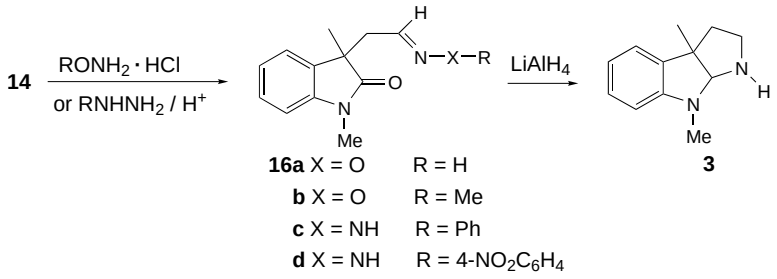
Scheme 4



The reported condensation of a 5-MeO-substituted derivative of **14** with $MeNH_2 \cdot HCl$, 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

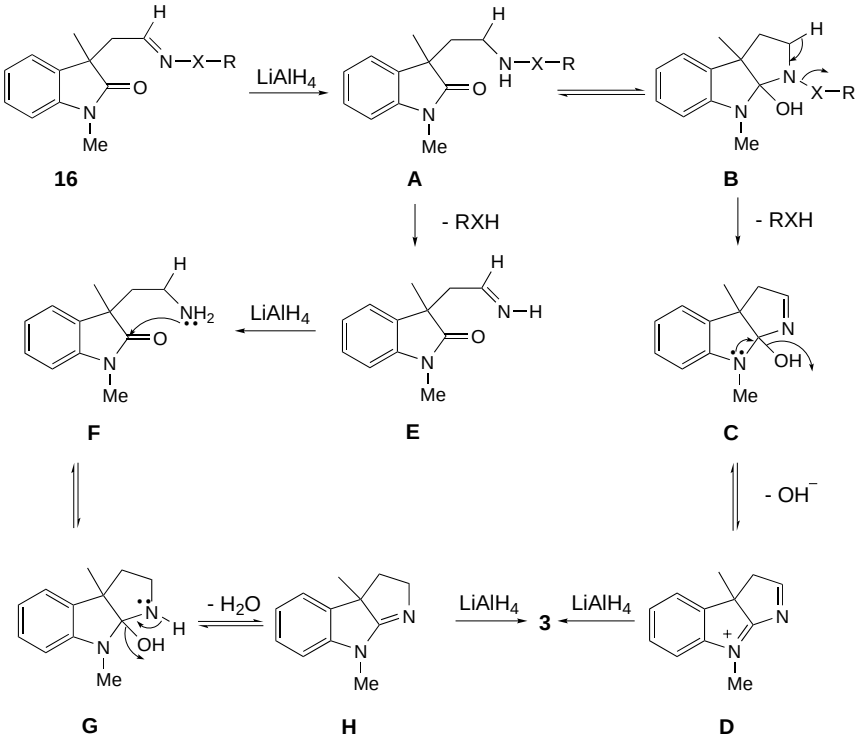
will facilitate the condensation reaction. The oximes and phenyl hydrazones **16a**–**16d** were obtained as mixtures of the corresponding *syn*- and *anti*-isomers (*Scheme 5*). Reduction of these mixtures of isomers with $LiAlH_4$ proceeded by loss of ROH or RNH_2 to give (±)-desoxynoreseroline **3**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

Scheme 5



Reaction mechanisms proposed for the reductive cyclization **16** → **3** are depicted in *Scheme 6*. The C=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 (±)-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 (±)-desoxyeseroline [14]. Recently, (−)-desoxyeseroline has been transformed to (−)-eseroline (**2**) and (−)-physostigmine (**1**) [17].

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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}. ^{1}H-(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°, $BF_3 \cdot OEt_2$ (*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 (MeOH/CH_2Cl_2 0.5 : 10) to yield 403 mg (70%) of **7**. Pale yellow viscous oil, which solidifies in h.v. IR (KBr): 3220*s*, 2862*w*, 1685*m*, 1471*s*, 1195*s*, 1113*m*, 931*w*, 884*m*, 799*s*, 676*m*, 646*s*. ^{1}H-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*, −CH=); 4.96–4.89 (*m*, =CH_2); 3.58 (*s*, MeN); 2.90–2.72 (*m*, CH_2); 1.62 (*s*, Me). ^{13}C-NMR: 175.0 (*s*, C=N); 141.6, 133.8 (2*s*, 2 arom. C); 129.9 (*d*, CH=); 129.0, 125.7, 122.8, 110.6 (4*d*, 4 arom. CH); 120.8 (*t*, =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, $[M - BF_4]^+$), 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): 3304*m*, 3056*w*, 2926*m*, 1725*w*, 1646*s*, 1608*s*, 1496*s*, 1468*s*, 1390*m*, 1308*m*, 1262*w*, 1227*w*, 1123*m*, 1083*m*, 1020*m*, 996*m*, 964*w*, 919*w*, 747*m*. ^{1}H-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*, −CH=); 5.02–4.91 (*m*, =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*, C=N); 145.0, 133.7 (2*s*, 2 arom. C); 132.4 (*d*, −CH=); 127.8, 122.4, 120.5, 106.6 (4*d*,

4 arom. CH); 118.7 (*t*, $=CH_2$); 48.4 (*s*, C(3)); 44.5 (*t*, CH_2); 26.9 (*q*, MeN); 24.7 (*q*, Me). CI-MS: 202 (15), 201 (100, $[M-NH_3]^+$ or $[M-OH]^+$).

*2,3-Dihydro-1,3-dimethyl-3-(prop-2-enyl)-1*H*-indol-2-one* (**9**) and N-*[2,3-Dihydro-1,3-dimethyl-3-(prop-2-enyl)-1*H*-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): 2927*s*, 2856*s*, 1724*s*, 1615*m*, 1493*m*, 1469*s*, 1378*s*, 1350*m*, 1274*s*, 1124*s*, 1074*m*, 995*w*, 920*w*, 753*m*, 742*m*, 703*w*, 653*w*. ^{1}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*, −CH=); 5.02–4.89 (*m*, $=CH_2$); 3.20 (*s*, MeN); 2.55–2.49 (*m*, CH_2); 1.38 (*s*, Me). ^{13}C-NMR: 180.1 (*s*, C=O); 143.1, 133.5 (2*s*, 2 arom. C); 132.5 (*d*, −CH=); 127.6, 122.8, 122.2, 107.8 (4*d*, 4 arom. CH); 118.5 (*t*, $=CH_2$); 48.1 (*s*, C(3)); 42.3 (*t*, CH_2); 26.0 (*q*, MeN); 22.6 (*q*, Me). GC/EI-MS: 201 (15, $M^{+\cdot}$), 161 (12), 160 (100), 145 (5), 132 (15), 130 (10), 117 (17). Anal. calc. for $C_{13}H_{15}NO$ (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): 3068*w*, 2960*m*, 2927*m*, 1671*s*, 1644*s*, 1605*s*, 1494*s*, 1467*m*, 1382*s*, 1353*m*, 1288*m*, 1221*s*, 1203*s*, 1126*m*, 1101*m*, 1004*m*, 939*m*, 929*m*, 808*m*, 759*s*, 719*m*, 637*w*, 600*m*. ^{1}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*, −CH=); 5.01–4.85 (*m*, $=CH_2$); 3.19 (*s*, MeN); 2.82–2.72, 2.62–2.53 (2*m*, CH_2); 2.29 (*s*, MeCO); 1.51 (*s*, Me). ^{13}C-NMR: 181.8 (*s*, C=O); 165.1 (*s*, C=N); 143.3, 134.6 (2*s*, 2 arom. C); 132.6 (*d*, −CH=); 127.8, 122.2, 122.0, 107.7 (4*d*, 4 arom. CH); 118.5 (*t*, $=CH_2$); 51.1 (*s*, C(3)); 43.7 (*t*, CH_2); 28.4, 27.3 (2*q*, *Me*CO, MeN); 24.3 (*q*, Me). GC/EI-MS: 242 (17, $M^{+\cdot}$), 227 (15), 215 (15), 201 (9), 186 (19), 160 (17), 159 (100), 143 (13), 132 (13), 117 (12). Anal. calc. for $C_{15}H_{18}N_2O$ (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): 3050*w*, 2924*w*, 1668*s*, 1596*s*, 1496*s*, 1448*s*, 1389*s*, 1270*m*, 1192*m*, 1121*s*, 1065*m*, 1032*m*, 978*w*, *774m*, 700*s*, 647*w*. ^{1}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}C-NMR: 169.6 (*s*, C=O); 143.0 (*s*, 1 arom. C); 130.0, 128.5, 127.2 (3*d*, 5 arom. CH); 38.1 (*q*, MeN); 32.1 (*d*, CHBr); 21.9 (*q*, Me). GC/EI-MS: 243 (34, $M^{+\cdot}$) for Br^{81}, 241 (34, $M^{+\cdot}$) for Br^{79}, 162 (20), 134 (55), 119 (7), 107 (100), 106 (71), 91 (5), 77 (54).

*2,3-Dihydro-1,3-dimethyl-1*H*-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): 3055*w*, 2972*m*, 2933*m*, 1714*s*, 1614*s*, 1493*s*, 1471*s*, 1420*m*, 1376*s*, 1346*s*, 1310*m*, 1257*s*, 1219*w*, 1130*m*, 1091*m*, 1063*w*, 1043*w*, 1018*m*, 982*m*, 929*w*, 890*w*, 807*w*, 751*s*, 729*w*, 701*w*. ^{1}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}C-NMR: 178.6 (*s*, C=O); 143.9, 130.5 (2*s*, 2 arom. C); 127.8, 123.4, 122.3, 107.9 (4*d*, 4 arom. CH); 40.5 (*d*, CH); 26.1 (*q*, MeN); 15.3 (*q*, Me). GC/EI-MS: 161 (83, $M^{+\cdot}$), 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)-1*H*-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 $(i\text{-Pr})_2NH$ (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. $NaHCO_3$ soln. was added, and the mixture was extracted with Et_2O. The org. phase was washed with sat. $NaHCO_3$ soln. and brine, dried ($MgSO_4$), and evaporated to give 521 mg (99%) of **9**.

*2,3-Dihydro-1,3-dimethyl-2-oxo-1*H*-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 CH_2Cl_2 (60 ml) at $-78°$ until the appearance of blue color indicated an excess of O_3. After blowing out the excess of O_3 with dry N_2, $(EtO)_3P$ (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): 3056*m*, 2970*s*, 2930*m*, 2889*m*, 2834*m*, 2733*m*, 1714*s*, 1652*m*, 1614*s*, 1495*s*, 1472*s*, 1453*s*, 1422*m*, 1379*s*, 1351*s*, 1309*s*, 1250*s*, 1159*m*, 1127*s*, 1067*m*, 1032*s*, 1019*m*, 986*w*, 905*w*, 756*s*, 700*m*. ^{1}H-NMR: 9.51 (*t*-like (*ABX*), $J_{AX} \approx J_{BX} = 1.6$, 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*), $J_{AB} \approx 15.7$, $J_{AX} \approx J_{BX} = 1.6$, CH_2); 1.41 (*s*, Me). ^{13}C-NMR: 198.6 (*d*, CH=O); 179.4 (*s*, C=O); 143.1, 132.7 (2*s*, 2 arom. C); 128.2, 122.5, 122.3, 108.2 (4*d*, 4 arom. CH); 50.4 (*t*, CH_2); 44.9 (*s*, C(3)); 26.3 (*q*, MeN); 23.8 (*q*, Me). CI-MS: 205 (14), 204 (100, $[M+1]^+$), 203 (2, $M^{+\cdot}$).

*3-(3,3-Diethoxypropyl)-2,3-dihydro-1,3-dimethyl-1*H*-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 CH_2Cl_2 was added. The org. phase was washed with 10% aq. HCl, sat. $NaHCO_3$ soln., and brine, and dried (Na_2SO_4). CC (AcOEt/hexane 3:10) gave 71.6 mg (91%) of **15**. Colorless oil. IR (film): 3055*m*, 2974*s*, 2927*s*, 2897*s*, 1714*s*, 1613*s*, 1494*s*, 1471*s*, 1452*s*, 1426*m*, 1378*s*, 1349*s*, 1310*m*, 1266*m*, 1248*m*, 1158*s*, 1123*s*, 1060*s*, 1019*s*, 1005*s*, 958*w*, 918*w*, 853*w*, 754*s*, 742*s*, 702*m*, 644*w*. ^{1}H-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*, CHO_2); 3.51–3.40, 3.32–3.25, 3.11–2.99 (3*m*, 2 CH_2O); 3.21 (*s*, MeN); 2.51–2.42, 2.07–1.99 (2*m*, CH_2); 1.35 (*s*, Me); 1.05–1.01, 1.01–0.93 (2*t*, 2 Me). ^{13}C-NMR: 180.2 (*s*, C=O); 143.3, 133.3 (2*s*, 2 arom. C); 127.6, 122.7, 122.0, 107.7 (4*d*, 4 arom. CH); 99.7 (*d*, CHO_2); 61.0, 60.0, 45.6 (3*t*, 3 CH_2); 40.7 (*s*, C(3)); 26.0 (*q*, MeN); 25.0, 15.0, 14.7 (3*q*, 3 Me). GC/EI-MS: 277 (11, $M^{+\cdot}$), 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 CH_2Cl_2, and the org. phase was washed with sat. $NaHCO_3$ soln. and brine, and dried (Na_2SO_4) to give 43 mg (84%) of **14**.

b) To a soln. of **15** (30 mg, 0.11 mmol) in toluene (10 ml), $TsOH \cdot H_2O$ (23 mg, 0.12 mmol) was added, and the mixture was heated to reflux for 2 h. Then, the solvent was evaporated, CH_2Cl_2 was added, and the org. phase was washed with sat. $NaHCO_3$ soln. and brine, and dried (Na_2SO_4) to give 20 mg (91%) of **14**.

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

General Procedure A (*GP A*). To a soln. of **14** in 10 ml of THF, $NH_2OR \cdot HCl$ was added, and the mixture was heated to reflux for 2 h and evaporated to dryness. After addition of Et_2O, the soln. was washed with 10% aq. HCl, sat. $NaHCO_3$ soln., and sat. NaCl soln., and dried (Na_2SO_4) to give **16** as a mixture of *syn*- and *anti*-isomers.

*2,3-Dihydro-1,3-dimethyl-2-oxo-1*H*-indol-3-acetaldehyde Oxime* (**16a**). According to the *GP A*, **14** (47.5 mg, 0.23 mmol) and $NH_2OH \cdot HCl$ (32 mg, 0.46 mmol). Yield: 35.5 mg (70%) of **16a**. Colorless oil. Mixture of isomers (1:0.8, ^{1}H-NMR). *Isomer 1:* ^{1}H-NMR: 7.20 (*t*-like (*ABX*), $J_{AX} \approx J_{BX} = 6.8$, 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*), $J_{AB} \approx 14.3$, CH_2); 1.41 (*s*, Me). ^{13}C-NMR: 179.4 (*s*, C=O); 147.4 (*d*, CH=N); 142.8, 132.6 (2*s*, 2 arom. C); 128.1, 122.7, 122.6, 108.2 (4*d*, 4 arom. CH); 46.9 (*s*, C(3)); 37.3 (*t*, CH_2); 26.2 (*q*, MeN); 22.9 (*q*, Me). *Isomer 2:* ^{1}H-NMR: 6.49 (*t*-like (*ABX*), $J_{AX} \approx J_{BX} = 5.5$, 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*), $J_{AB} \approx 16.1$, CH_2); 1.43 (*s*, Me). ^{13}C-NMR: 179.5 (*s*, C=O); 147.4 (*d*, CH=N); 142.8, 133.0 (2*s*, 2 arom. C); 128.2, 122.8, 122.6, 108.2 (4*d*, 4 arom. CH); 45.9 (*s*, C(3)); 32.6 (*t*, CH_2); 26.1 (*q*, MeN); 22.9 (*q*, Me).

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

*2,3-Dihydro-1,3-dimethyl-2-oxo-1*H*-indol-3-acetaldehyde* O*-Methyloxime* (**16b**). According to the *GP A*, **14** (75 mg, 0.37 mmol) and $NH_2OMe \cdot HCl$ (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, ^{1}H-NMR). IR (film, mixtures of isomers): 3056*m*, 2967*s*, 2937*s*, 2900*s*, 2820*m*, 1715*s*, 1614*s*, 1493*s*, 1471*s*, 1453*s*, 1423*s*, 1378*s*, 1350*s*, 1309*s*, 1252*s*, 1159*m*, 1125*s*, 1102*s*, 1085*s*, 1060*s*, 1041*s*, 1020*s*, 951*m*, 907*m*, 884*m*, 855*s*, 755*s*, 744*s*, 700*m*, 686*w*, 656*w*, 637*w*.

Isomer 1: ^{1}H-NMR: 7.16 (*t*-like (*ABX*), $J_{AX} \approx J_{BX} = 6.4$, CH=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}C-NMR: 179.4 (*s*, C=O); 145.9 (*d*, CH=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}H-NMR: 6.41 (*t*-like (*ABX*), $J_{AX} \approx J_{BX} = 5.5$, CH=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}C-NMR: 179.5 (*s*, C=O); 146.2 (*d*, CH=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, $M^{+\cdot}$), 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-1*H*-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 (MeOH/CH_2Cl_2 0.1:40) gave 72 mg (100%) of **16c**. Colorless oil. Mixture of isomers (1:0.57, ^{1}H-NMR). *Isomer 1:* ^{1}H-NMR: 7.32–7.18 (*m*, 5 arom. H); 7.08 (*t*-like, 1 arom. H); 7.02 (*t*-like (*ABX*), $J_{AX} \approx J_{BX} = 6.4$, CH=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}C-NMR: 179.9 (*s*, C=O); 145.0 (*s*, 1 arom. C); 143.1, 133.7 (2*s*, 2 arom. C); 135.5 (*d*, CH=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}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*), $J_{AX} \approx J_{BX} = 5.2$, CH=N); 3.18 (*s*, MeN); 2.92–2.55 (*m* (*ABX*), $J_{AB} \approx 14.9$, CH_2); 1.49 (*s*, Me). ^{13}C-NMR: 181.0 (*s*, C=O); 145.0 (*s*, 1 arom. C); 143.1, 133.7 (2*s*, 2 arom. C); 135.5 (*d*, CH=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-1*H*-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 (MeOH/CH_2Cl_2 0.1:10) gave 0.81 g (98%) of **16d**. Yellow viscous oil. GC: Two isomers were detected (ratio 1:0.1, ^{1}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}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*), $J_{AX} \approx J_{BX} = 6.4$, CH=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}C-NMR: 179.9 (*s*, C=O); 149.9, 139.5 (2*s*, 2 arom. C of $C_6H_4NO_2$); 142.8, 133.3 (2*s*, 2 arom. C); 139.9 (*d*, CH=N); 128.0, 122.7, 122.5, 108.2 (4*d*, 4 arom. CH); 125.9, 111.1 (2*d*, 4 arom. CH of $C_6H_4NO_2$); 47.0 (*s*, C(3)); 39.6 (*t*, CH_2); 26.2 (*q*, MeN); 23.7 (*q*, Me). *Isomer 2:* ^{1}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*), $J_{AX} \approx J_{BX} = 5.2$, CH=N); 3.17 (*s*, MeN); 3.07–2.62 (*m* (*ABX*), $J_{AB} \approx 14.9$, CH_2); 1.49 (*s*, Me). ^{13}C-NMR: 181.0 (*s*, C=O); 150.3, 140.0 (2*s*, 2 arom. C of $C_6H_4NO_2$); 142.2, 132.0 (2*s*, 2 arom. C); 138.8 (*d*, CH=N); 128.6, 123.3, 122.7, 108.8 (4*d*, 4 arom. CH); 125.9, 111.9 (2*d*, 4 arom. CH of $C_6H_4NO_2$); 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 (MeOH/CH_2Cl_2 1:5) gave (±)*-desoxynoreseroline* (**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): 3325*m*, 3051*m*, 3024*m*, 2925*s*, 1714*s*, 1607*s*, 1494*s*, 1450*s*, 1378*s*, 1349*s*, 1298*s*, 1240*m*, 1201*m*, 1156*m*, 1121*s*, 1062*s*, 1021*s*, 985*m*, 920*m*, 899*m*, 858*m*, 740*s*, 656*w*. ^{1}H-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 (4*m*, CH_2CH_2); 2.84 (*s*, MeN); 2.58–2.52 (br. *s*, NH); 1.46 (*s*, Me). ^{13}C-NMR: 150.8, 135.5 (2*s*, 2 arom. C); 127.7, 122.4, 116.8, 105.0 (4*d*, 4 arom. CH); 92.2 (*d*, CH); 52.1 (*s*, C(3a)); 45.9, 42.5 (2*d*, 2 CH_2); 31.8 (*q*, MeN); 26.1 (*q*, Me). CI-MS: 190 (14), 189 (100, $[M+1]^+$). GC/EI-MS: 188 (100, $M^{+\cdot}$), 187 (8), 173 (6), 159 (20), 158 (61), 145 (50), 144 (76), 130 (15), 115 (8), 91 (5), 77 (11).

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