Application of a Tandem Electrocyclic [3,3]Sigmatropic Reaction of *o*-Quinodimethane to the Synthesis of Calabar Bean Alkaloids. Part 2.[1] First Total Synthesis of (±)-Geneserine[2,†]

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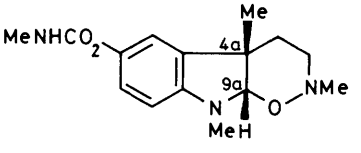
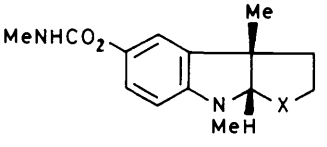
The first total synthesis of the Calabar bean alkaloid geneserine (**1**) starting with 1-cyano-5-methoxybenzocyclobutene (**7**) has been accomplished *via* a 16-step sequence in 27% overall yield. The key step in the synthetic strategy involves the tandem electrocyclic [3,3]sigmatropic reaction of the *o*-quinodimethane generated *in situ* by thermolysis of the benzocyclobutene (**4**), which affords quantitatively the isochroman-3-one (**5**). After the conversion of (**5**) into the oxindole (**6**), the pivotal intermediate for our strategy, differential functionalisation of this system provides the hydroxylamine (**19**) which has finally been converted into (±)-geneserine by treatment with di-isobutylaluminium hydride.

The alkaloid geneserine was first isolated by Polonovski[3] from the seeds of the Calabar bean (*Physostigma venenosum*). Although the related alkaloids physovenine (**2**)[4] and physostigmine (**3**)[5] have comparable antiacetylcholinesterase activities, the activity of geneserine is much lower.[6] The structure of geneserine was identified as the *N*-oxide of physostigmine in 1925 by Polonovski[7] on the basis of its chemical properties such that the alkaloid is reduced by zinc and acetic acid to (**3**), which in turn can be oxidized by hydrogen peroxide to geneserine,[8] and this assignment has long been accepted. In 1969, however, the structure was corrected to (**1**) by careful considerations of the mass spectral data, its non-hygroscopic character, its low water solubility, and the ^{1}H n.m.r. spectral data by Hootelé.[9] The revised chemical structure of geneserine incorporates as a key feature an unusual hexahydro-1,2-oxazino[5,6-*b*]indole ring system. The efficient synthesis of such a functionalized ring system presents a formidable synthetic challenge. Although the conversion of physostigmine (**3**) into (**1**) *via* a Meisenheimer-type rearrangement has already been established,[8b,10] no total synthesis has been accomplished so far.



(**1**)



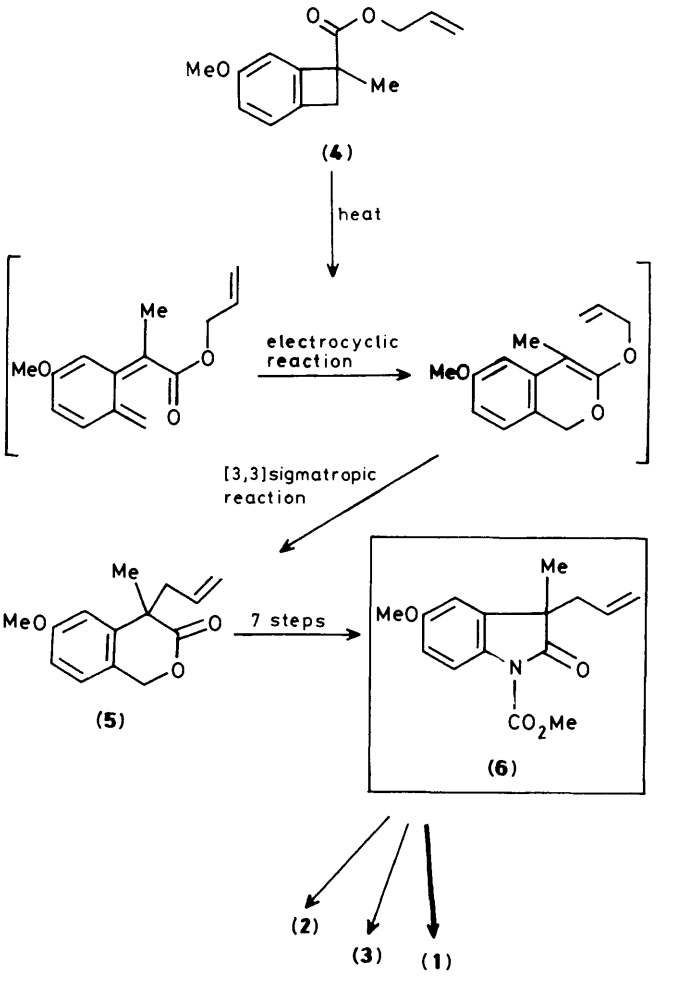
(**2**) X = O

(**3**) X = NMe

Recently, we described the total syntheses of (±)-physovenine (**2**) and physostigmine (**3**)[1] based on the newly developed tandem electrocyclic [3,3]sigmatropic reaction[11] of *o*-quinodimethane generated *in situ* by thermolysis of the benzocyclobutene (**4**). In the total synthesis, the oxindole (**6**), derived uneventfully from the thermolysis product (**5**), was a common and pivotal intermediate for both alkaloids (Scheme 1).

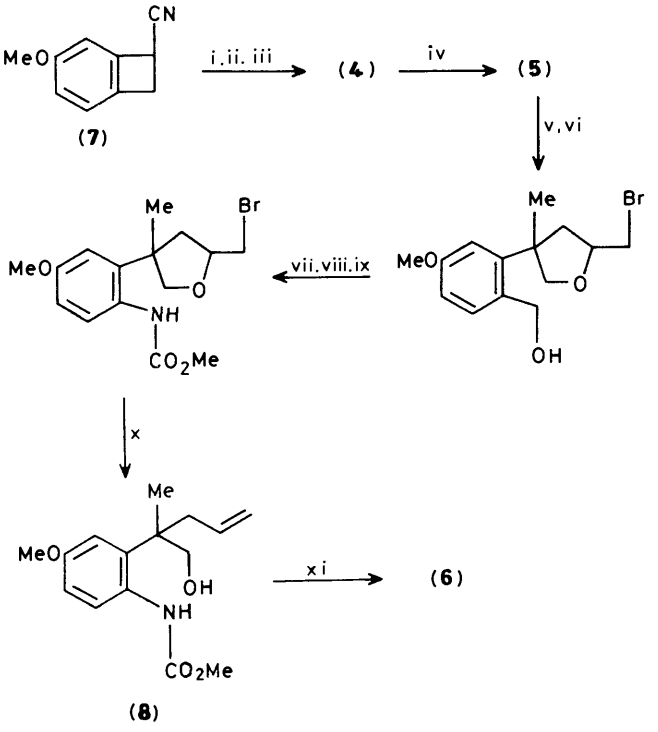
In this article, we now report the details of the further application of the strategy in an efficient route to (±)-geneserine (**1**).

Our total synthesis also commenced with the oxindole (**6**) which was prepared from 1-cyano-5-methoxybenzocyclobutene



Scheme 1.

† All compounds in this paper are racemic. For convenience, only one enantiomer is shown.



Scheme 2. *Reagents:* i, LDA, MeI, HMPA, THF, 98%; ii, KOH, EtOH, 100%; iii, allyl alcohol, DCC, 4-DMPA, 87%; iv, 180 °C, *o*-dichlorobenzene, 100%; v, $LiAlH_4$, 100%; vi, NBS, THF, H_2O, 100%; vii, Jones oxidation, 97%; viii, $NaClO_2$, NH_2SO_3H, Bu^{t}OH, H_2O, 84%; ix, $(PhO)_2PON_3$, NEt_3, benzene, reflux, then MeOH, reflux, 100%; x, Zn(Cu), NH_4Cl, 95%; xi, PDC, DMF, 79%

(7) in 52% overall yield by the 11-step sequence of the reactions depicted in Scheme 2.[1]

Lemieux oxidation[12] of the double bond in (**6**) with sodium metaperiodate in the presence of a catalytic amount of osmium tetraoxide gave the aldehyde which, without purification, was immediately treated with methylhydroxylamine and sodium cyanoborohydride at pH 5—6[13] to afford the hydroxylamine (**9**). Construction of the desired hexahydro-1,2-oxazino[5,6-*b*]indole ring system was accomplished by employing the following 2-step sequence. First, the C-2 carbonyl in the oxindole was chemoselectively reduced by treatment with sodium borohydride after which the resulting hemiacetal was exposed to boron trifluoride–ether at room temperature for 10 min to furnish the tricyclic compound (**11**) as a sole product in 29% yield from (**6**). This conversion is thought to proceed *via* the formation of an intermediate acyliminium salt (**10**), from which stereodirected cyclization occurs. The structural assignment of (**11**) rested on the ^1H n.m.r., ^{13}C n.m.r., and mass spectra. The relative configuration at the B/C ring juncture was shown to have *cis* geometry by nuclear Overhauser effect difference spectroscopy. Namely, irradiation of the 4a-methyl proton at δ_H 1.13 gave a 12.8% enhancement of the 9a-methine proton at δ_H 5.54. Alternatively, (**11**) could also be prepared stereoselectively from (**8**) by the following sequence of the reactions. Swern oxidation[14] of the alcohol (**8**), the precursor for (**6**), gave a hemiacetal which upon treatment with trimethyl orthoformate and a catalytic amount of toluene-*p*-sulphonic acid afforded the acetal (**12**) as a mixture of diastereoisomers. Lemieux oxidation of (**12**) and subsequent reductive hydroxylamination gave (**13**) which was then treated with boron trifluoride–ether to afford (**11**), identical with a sample prepared by the above procedure, in 63% overall yield from (**8**).

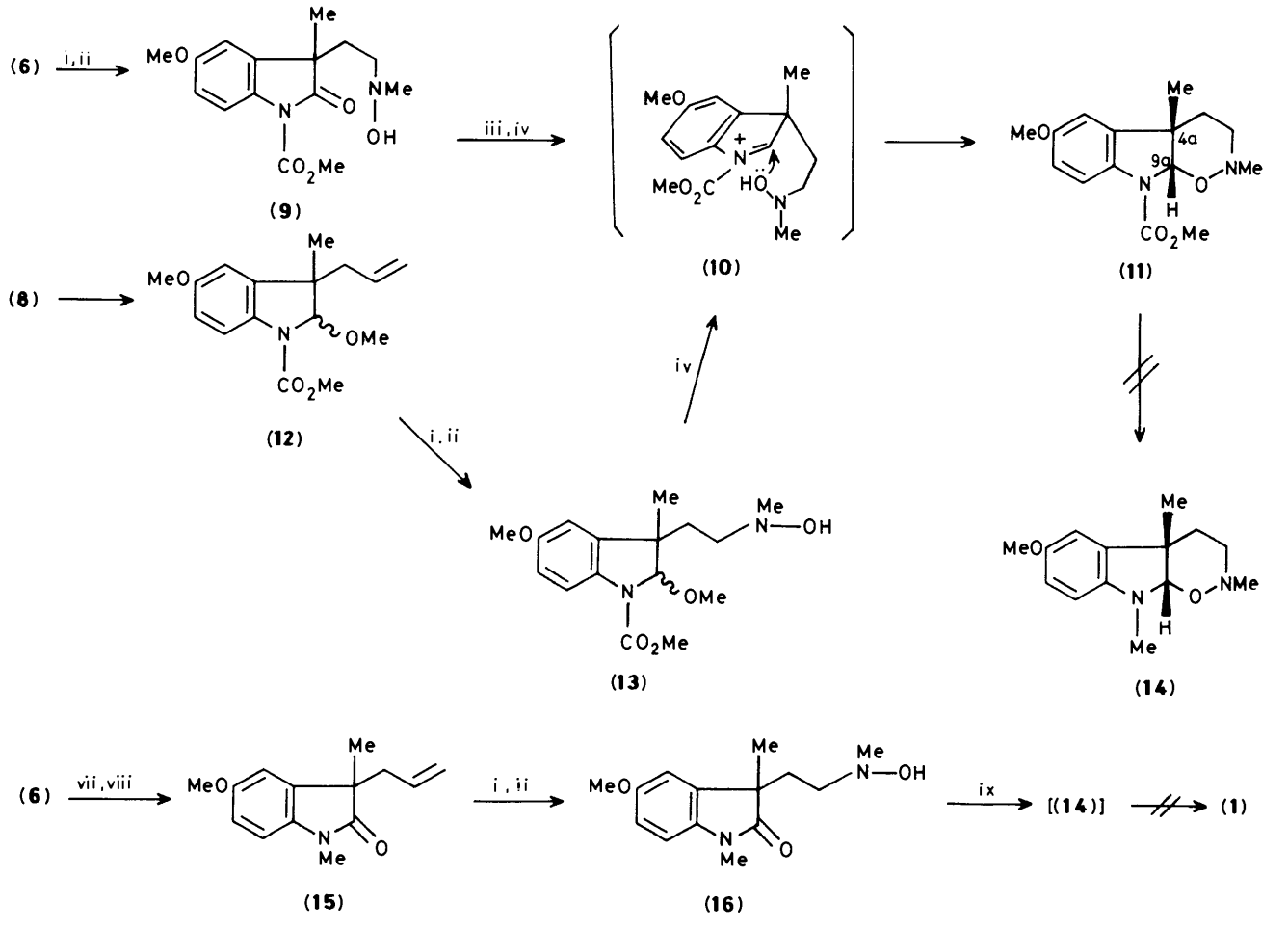
The stage was now set for us to examine the feasibility of the conversion into geneserine. Attempted transformation of the carbamate functionality to an *N*-methyl group gave unsatisfactory results, presumably because of the lability of the remaining functional groups in the molecule to the conditions necessary for cleavage of the *N*-methoxycarbonyl group (*e.g.* $LiAlH_4$,[1] Me_2S–$AlBr_3$,[15] *etc.*). These results suggested that chemoselective demethoxycarbonylation was desirable at the earliest stage. Thus, treatment of compound (**6**) under the conditions described by Fujita[15] employing dimethyl sulphide and aluminium tribromide followed by a standard methylation with methyl iodide and sodium hydride afforded (**15**) in 98% yield. Sequential Lemieux oxidation and reductive hydroxylamination provided (**16**) which was then cyclized by exposure to di-isobutylaluminium hydride in tetrahydrofuran at −72 to −15 °C for 1 h to furnish the crude tricycle (**14**) whose ^1H n.m.r. spectrum showed four singlet methyl signals at δ_H 1.23, 2.56, 2.84, and 3.75 and a singlet signal for the 9a methine proton at δ_H 4.67. Without further purification, the crude compound (**14**) was immediately submitted to the conditions for cleavage of the aryl methyl ether; all attempts, however, were unsuccessful owing to the lability of the molecule for the reaction conditions.

From these unsuccessful attempts, it was clear that the two chemoselective functional group transformations should be conducted in the order demethoxycarbonylation/*N*-methylation followed by phenolic methyl ether cleavage/carbamate formation. Thus, exposure of the oxindole (**15**) to boron tribromide[16] in methylene dichloride at 0 °C for 1 h produced the corresponding phenol (**17**) which was directly treated with methyl isocyanate in the presence of sodium hydride to afford the carbamate (**18**). The olefin function in (**18**) was then manipulated in the customary fashion to furnish the hydroxylamine (**19**) in 70% yield from (**15**). Completion of the synthesis of racemic geneserine (**1**) was accomplished in 75% yield by treating (**19**) with di-isobutylaluminium hydride in dimethoxyethane at −75 °C for 0.5 h. The identity of the synthetic sample of (**1**) was confirmed by careful comparison of the ^1H n.m.r., i.r., and mass spectroscopic properties as well as t.l.c. mobility (three-solvent systems) with those of an authentic sample of geneserine prepared from the commercial physostigmine according to the procedure of Nakagawa.[10]

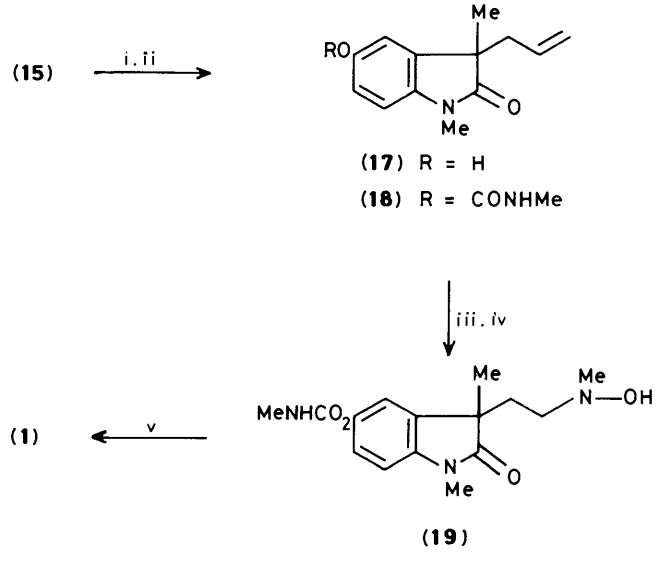
In conclusion, we have described the first 16-step total synthesis of (±)-geneserine in 27% overall yield from (**7**) that demonstrates the further utility of the tandem electrocyclic [3,3]sigmatropic technology for the synthesis of the Calabar bean alkaloids.

Experimental

General Methods.—M.p.s were determined on a Yanagimoto MP-22 apparatus and are uncorrected. I.r. spectra were measured with a Hitachi 260-10 recording spectrophotometer, u.v. spectra with Hitachi 320 spectrophotometer, and n.m.r. spectra with JEOL JNM-PMX-60, JEOL JNM-FX100, and JEOL JNM-FX-90A spectrometers. Chemical shifts are reported as δ_H values relative to internal $SiMe_4$. Ordinary mass spectra were measured with a Hitachi M-52G spectrometer, while high resolution mass spectroscopy was performed on a JEOL TMS-OISG-2 spectrometer. All reactions were carried out under an atmosphere of dry argon or nitrogen. Column chromatography was carried out with silica gel (Wako gel C-200). Thin-layer chromatography (t.l.c.) was carried out with E. Merck Silica gel 60 F-254 (0.25 mm thickness) pre-coated t.l.c. plates and preparative thin-layer chromatography (prep. t.l.c.) was performed on 20 × 20 cm plates coated with 1-mm thickness of Merck Kieselgel 60 containing PF 254 indicator.



Scheme 3. *Reagents:* i, $NaIO_4$, OsO_4; ii, MeNHOH·HCl, $NaCNBH_3$; iii, $NaBH_4$; iv, BF_3·OEt_2; v, $(COCl)_2$, DMSO, NEt_3; vi, $CH(OMe)_3$, *p*-TsOH; vii, Me_2S, $AlBr_3$; viii, NaH, MeI; ix, Bu^i_2AlH



Scheme 4. *Reagents:* i, BBr_3; ii, MeNCO, NaH; iii, $NaIO_4$, OsO_4; iv, MeNHOH·HCl, $NaCNBH_3$; v, Bu^i_2AlH

The phrase 'residue upon work-up' refers to the residue when the organic layer was separated, dried over $MgSO_4$, and the solvent was evaporated under reduced pressure. All new compounds described in this Experimental section were homogeneous on t.l.c.

Methyl 3-[2-(N-*Hydroxy*-N-*methylamino*)*ethyl*]-5-*methoxy*-3-*methyl*-2-*oxo*-2,3-*dihydroindole*-1-*carboxylate* (**9**).—Sodium metaperiodate (407 mg, 1.90 mmol) was added to a stirred solution of the oxindole (**6**)[1] (54.6 mg, 0.199 mmol) and osmium tetraoxide (2.5 mg, 9.83 μmol) in a mixture of diethyl ether (2.2 ml) and water (2.2 ml) at room temperature. After the reaction mixture had been stirred for 3 h, the organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic phases were washed with saturated brine and the residue upon work-up was taken up in methanol (2.5 ml). The methanol solution was added to a solution of *N*-methylhydroxylamine hydrochloride (23.2 mg, 0.278 mmol) in methanol (0.5 ml) and the resulting solution was adjusted to pH 6 using 5% potassium hydroxide in methanol. After the addition of sodium cyanoborohydride (15.0 mg, 0.239 mmol), the mixture was further adjusted to pH 5—6 using 5% hydrochloric acid in methanol and the stirring was continued for 50 min. After removal of the solvent, water was added to the residue and the resulting mixture was extracted with ethyl acetate. The extract was washed with saturated brine and the residue upon work-up was chromatographed using chloroform as an eluant to afford the *hydroxylamine* (**9**) (34.5 mg, 56%) as needles after recrystallization from benzene–hexane, m.p. 110—111 °C, $\nu_{max.}(CHCl_3)$ 3 500, 1 785, and 1 730 cm^{-1}; $\lambda_{max.}$(EtOH) 289, 248, and 233 nm (ε 1 093, 3 365, and 12 276); δ_H(100 MHz;

$CDCl_3$), 1.38 (3 H, s), 2.28 (3 H, s), 3.82 (3 H, s), 3.99 (3 H, s), 6.72 (1 H, dd, *J* 9.0 and 3.0 Hz), 6.86 (1 H, d, *J* 3.0 Hz), and 7.83 (1 H, d, *J* 9.0 Hz); δ_C(25 MHz; $CDCl_3$) 26.067 (q), 36.106 (t), 47.673 (q), 48.025 (s), 53.602 (q), 55.598 (t), 56.890 (q), 108.732 (d), 112.428 (d), 116.186 (d), 132.451 (s), 133.507 (s), 157.109 (s), and 180.058(s) (Found: M^+, 308.1371. $C_{15}H_{20}N_2O_5$ requires *M*, 308.1371).

Methyl 3-*Allyl*-2,5-*dimethoxy*-3-*methyl*-2,3-*dihydroindole*-1-*carboxylate* (**12**).—Dimethyl sulphoxide (84 mg, 1.08 mmol) was added to a stirred solution of oxalyl chloride (60 mg, 0.54 mmol) in methylene dichloride (1.4 ml) at −78 °C and the stirring was continued for 5 min. A solution of the alcohol (**8**)[1] (137 mg, 0.49 mmol) in methylene dichloride (1.36 ml) was then added dropwise to the solution at −78 °C. The mixture was stirred at the same temperature for 15 min, after which triethylamine (247 mg, 2.46 mmol) was added dropwise; stirring was continued at −78 °C for 5 min and then the reaction temperature was gradually elevated to room temperature during 1 h. The reaction mixture was diluted with water and extracted with methylene dichloride. The extract was washed with saturated brine and the residue upon work-up was taken up with methanol (12.4 ml). Trimethyl orthoformate (65 mg, 0.61 mmol) and a catalytic amount of toluene-*p*-sulphonic acid were added to the solution and the resulting mixture was heated under reflux for 1.5 h. After removal of the solvent, the residue was extracted with methylene dichloride and the extract was washed with saturated brine. The residue upon work-up was chromatographed using hexane–ethyl acetate (9:1, v/v) as an eluant to afford the *acetal* (**12**) (136 mg, 95%), a mixture of diastereoisomers, as an oil (Found: C, 66.15; H, 7.4; N, 4.85. $C_{16}H_{21}NO_4$ requires C, 65.95; H, 7.25; N, 4.8%); $\nu_{max.}$($CHCl_3$) 1 700 cm^{-1}; δ_H(60 MHz; $CDCl_3$) 1.33 (3 H, br s), 3.43 (3 H, br s), 3.77 (3 H, s), 3.85 (3 H, s), 4.73—6.00 (4 H, m), 6.62—6.83 (2 H, m), and 7.47 (1 H, br d, *J* 9.0 Hz); *m/z* 291 (M^+) and 250 (100%).

Methyl 3-[2-(N-*Hydroxy*-N-*methylamino*)*ethyl*]-2,5-*dimethoxy*-3-*methyl*-2,3-*dihydroindole*-1-*carboxylate* (**13**).—According to the procedure described for compound (**9**), the acetal (**12**) (187 mg, 0.64 mmol) was converted into the *hydroxylamine* (**13**) (157 mg, 75%), a mixture of diastereoisomers, as an oil after column chromatography using hexane–ethyl acetate (7:3, v/v) as an eluant, $\nu_{max.}$($CHCl_3$) 3 570 and 1 700 cm^{-1}; δ_H(100 MHz; $CDCl_3$) 1.25 (3 H, s), 1.40—1.78 (2 H, m), 2.04—2.50 (2 H, m), 2.43 (3 H, s), 3.36 (3 H, s), 3.68 (3 H, s), 3.77 (3 H, s), 5.12 (1 H, br s), 6.42 (1 H, br s, D_2O exchangeable), 6.52 (1 H, d, *J* 2.0 Hz), 6.60 (1 H, dd, *J* 10.8 and 2.0 Hz), and 7.34 (1 H, br m) (Found: M^+, 324.1681. $C_{16}H_{24}N_2O_5$ requires *M*, 324.1683).

rel-(4a*S*,9a*S*)-*Methyl* 2,3,4,4a,9,9a-*Hexahydro*-6-*methoxy*-2,4a-*dimethyl*-1,2-*oxazino*[5,6-b]*indole*-1-*carboxylate* (**11**).—*From compound* (**9**). Sodium borohydride (7.5 mg, 0.20 mmol) was added to a stirred solution of the hydroxylamine (**9**) (12.2 mg, 0.04 mmol) in methanol (0.6 ml) at 0 °C. After being stirred at room temperature for 20 min, the mixture was evaporated to give a residue which was treated with water and then extracted with ethyl acetate. The extract was washed with saturated brine and the residue upon work-up was taken up in methylene dichloride (0.4 ml). A catalytic amount of boron trifluoride–ether was added to the solution and the resulting mixture was stirred at room temperature for 10 min. After dilution with water, the organic layer was separated and the aqueous layer was extracted with methylene dichloride. The combined organic phases were washed with saturated brine and the residue upon work-up was chromatographed using hexane–ethyl acetate (4:1, v/v) as eluant to afford the *tricyclic compound* (**11**) (5.9 mg, 51%) as needles after recrystallization from diethyl ether–hexane, m.p. 122—123 °C (Found: C, 61.9; H, 6.75; N, 9.8. $C_{15}H_{20}N_2O_4$ requires C, 61.65; H, 6.9; N, 9.6%); $\nu_{max.}$($CHCl_3$) 1 710 cm^{-1}; δ_H(100 MHz; $CDCl_3$) 1.13 (3 H, s), 2.53 (3 H, s), 3.79 (3 H, s), 3.85 (3 H, s), 5.54 (1 H, s), 6.66 (1 H, d, *J* 2.0 Hz), 6.72 (1 H, dd, *J* 9.0 and 2.0 Hz), and 7.58 (1 H, br m); δ_C(25 MHz; $CDCl_3$) 27.946 (q), 31.175 (t), 41.273 (s), 46.205 (q), 52.780 (q), 53.544 (5), 55.598 (q), 94.697 (d), 108.905 (d), 111.371 (d), 115.659 (d), 134.855 (s), 138.322 (s), 153.525 (s), and 156.170 (s); *m/z* 292 (M^+) and 234 (100%).

From compound (**13**). Boron trifluoride–ether (12 mg, 0.08 mmol) was added dropwise to a stirred solution of the hydroxylamine (**13**) (31 mg, 0.097 mmol) in methylene dichloride (1.6 ml) at room temperature. After being stirred for 10 min, the mixture was diluted with water and extracted with methylene dichloride. The extract was washed with saturated brine and the residue upon work-up was chromatographed to afford compound (**11**) (25 mg, 89%) which was identical with a sample prepared from (**9**).

3-*Allyl*-5-*methoxy*-1,3-*dimethylindol*-2(3H)-*one* (**15**).—A solution of the oxindole (**6**) (0.27 g, 0.97 mmol) in methylene dichloride (2.2ml) at room temperature was added dropwise to a stirred solution of aluminium tribromide (0.78 g, 2.92 mmol) in dimethyl sulphide (2.45 g, 39.6 mmol). After being stirred for 15 min, the mixture was poured into water (10 ml) and the resulting solid mass was acidified with 1M-hydrochloric acid. The acidic solution was extracted with chloroform, the extract was washed with saturated brine and the residue upon work-up was taken up with anhydrous tetrahydrofuran (THF) (5 ml). Methyl iodide (0.69 g, 4.86 mmol) was added to the solution which was then added dropwise to a suspension of sodium hydride (60% in oil; 0.16 g, 3.89 mmol) in anhydrous THF (3 ml) at 0 °C. After being stirred at the same temperature for 1 h, the reaction mixture was diluted with diethyl ether and quenched with saturated aqueous ammonium chloride. After removal of the solvent, the residue was extracted with chloroform and the extract was washed with saturated brine. The residue upon work-up was chromatographed using hexane–ethyl acetate (4:1, v/v) as eluant to afford the *title compound* (**15**) (0.22 g, 98%) as prisms after recrystallization from diethyl ether–hexane, m.p. 56—58 °C (Found: C, 72.35; H, 7.65; N, 6.05. $C_{14}H_{17}NO_2$ requires C, 72.7; H, 7.4; N, 6.05%); $\nu_{max.}$($CHCl_3$) 1 695 cm^{-1}; δ_H (100 MHz; $CDCl_3$) 1.35 (3 H, s), 2.49 (2 H, d, *J* 8.0 Hz), 3.16 (3 H, s), 3.78 (3 H, s), 4.71—5.68 (3 H, m), and 6.52—6.84 (3 H, m); *m/z* 231 (M^+) and 190 (100%).

3-[2-(N-*Hydroxy*-N-*methylamino*)*ethyl*]-1,3-*dimethylindol*-2(3*H*)-*one* (**16**).—According to the described procedure for compound (**9**), the oxindole (**15**) (57 mg, 0.25 mmol) was converted into the *hydroxylamine* (**16**) (42 mg, 65%) as an oil after column chromatography using diethyl ether as an eluant, $\nu_{max.}$($CHCl_3$) 3 400 and 1 680 cm^{-1}; δ_H(60 MHz; $CDCl_3$) 1.33 (3 H, s), 2.33 (3 H, s), 3.15 (3 H, s), 3.80 (3 H, s), 5.55 (1 H, br s, D_2O exchangeable), and 6.75 (3 H, s) (Found: M^+, 264.1514. $C_{14}H_{20}N_2O_3$ requires *M*, 264.1474).

3-*Allyl*-5-*hydroxy*-1,3-*dimethylindol*-2(3H)-*one* (**17**) *and* 3-*Allyl*-1,3-*dimethyl*-5-(N-*methylcarbamoyloxy*)*indol*-2(3H)-*one* (**18**).—Boron tribromide (199 mg, 0.79 mmol) was added dropwise to a stirred solution of the oxindole (**15**) (127 mg, 0.55 mmol) in methylene dichloride (4 ml) at 0 °C. After being stirred at 0 °C for 1 h, the reaction mixture was quenched with saturated aqueous sodium hydrogen carbonate and extracted with ethyl acetate. The extract was washed with saturated brine and the residue upon work-up was taken up with anhydrous THF (3 ml). The solution was added dropwise to a stirred suspension of sodium hydride (60% in oil; 33 mg, 0.82 mmol) in anhydrous THF (2 ml) at 0 °C. The mixture was stirred at the

same temperature for 10 min, after which methyl isocyanate (0.67 g, 11.7 mmol) was added; the resulting solution was then further stirred at room temperature for 4 h. It was then quenched with water and the solvent evaporated to give a residue which was acidified with 1M-hydrochloric acid. The acidic mixture was extracted with ethyl acetate and the extract was washed with saturated brine and the residue upon work-up was chromatographed using hexane–diethyl ether (1:4, v/v) as eluant to afford the *phenol* (**17**) (12 mg, 10%) as needles after recrystallization from hexane–ethyl acetate, m.p. 179—180 °C, $\nu_{max.}$(KBr) 3 180 and 1 670 cm^{-1}; δ_H(90 MHz; $CDCl_3$) 1.36 (3 H, s), 2.49 (1 H, d, *J* 6.8 Hz), 3.17 (3 H, s), 4.79—5.44 (3 H, m), and 6.67—7.14 (4 H, m) (Found: M^+, 217.1116. $C_{13}H_{15}NO_2$ requires *M*, 217.1104). From the fractions using hexane–diethyl ether (1:5, v/v) as eluant, the *carbamate* (**18**) [132 mg, 91% based on the consumed phenol (**17**)] was obtained as an oil (Found: C, 65.4; H, 6.95; N, 9.9. $C_{15}H_{18}N_2O_3$ requires C, 65.65; H, 6.6; N, 10.2%); $\nu_{max.}$($CHCl_3$) 3 460, 1 735, and 1 700 cm^{-1}; δ_H (100 MHz; $CDCl_3$) 1.36 (3 H, s), 2.48 (2 H, d, *J* 8.0 Hz), 2.89 (3 H, d, *J* 5.0 Hz), 3.17 (3 H, s), 4.68—5.69 (4 H, m), 6.75 (1 H, d, *J* 10.0 Hz), and 7.01 (2 H, m); *m/z* 274 (M^+) and 177 (100%).

3-[2-(N-*Hydroxy*-N-*methylamino*)*ethyl*]-1,3-*dimethyl*-5-(N-*methylcarbamoyloxy*)*indol*-2-(3H)-*one* (**19**).—According to the described procedure for compound (**9**), the carbamate (**18**) (164 mg, 0.60 mmol) was converted into the *hydroxylamine* (**19**) (143 mg, 78%) as needles after recrystallization from ethyl acetate–hexane, m.p. 133—135 °C, $\nu_{max.}$($CHCl_3$) 3 350 and 1 710 cm^{-1}; δ_H(100 MHz; $CDCl_3$) 1.33 (3 H, s), 2.28 (3 H, s), 2.89 (3 H, d, *J* 5.0 Hz), 3.16 (3 H, s), 6.68 (1 H, d, *J* 9.0 Hz), and 7.01 (2 H, m) (Found: M^+, 307.1508. $C_{15}H_{21}N_3O_4$ requires *M*, 307.1531).

(±)-*Geneserine* (**1**).—Di-isobutylaluminium hydride (1.0M solution in hexane; 0.37 ml, 0.37 mmol) was added dropwise to a stirred solution of the hydroxylamine (**19**) (11.3 mg, 0.037 mmol) in anhydrous dimethoxyethane (1 ml) at −75 °C. The mixture was stirred at the same temperature for 0.5 h after which it was diluted with water (0.37 ml) and filtered through Celite. The filtered slurry was washed well with ethyl acetate. The combined filtrates were dried ($MgSO_4$) and evaporated to give a residue which was submitted to prep. t.l.c. using diethyl ether–methanol–ammonium hydroxide (25% aqueous solution) (30:2:1, v/v/v) as a developing solvent system to afford the starting hydroxylamine (**19**) (6.5 mg) (R_F = 0.38) and (±)-geneserine (**1**) (3.4 mg, 75% based on the consumed starting material) (R_F = 0.60) as an oil, $\nu_{max.}$($CHCl_3$) 3 450 and 1 720 cm^{-1}; δ_H(100 MHz; $CDCl_3$) 1.19 (3 H, s), 2.54 (3 H, s), 2.84 (3 H, s), 2.86 (3 H, d, *J* 4.0 Hz), 4.69 (1 H, s), 4.84 (1 H, br s), 6.37 (1 H, d, *J* 8.8 Hz), and 6.60—6.88 (2 H, m) (Found: M^+, 291.1577. $C_{15}H_{21}N_3O_3$ requires *M*, 2291.1582).

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