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TOTAL SYNTHESES OF CLAVINE ALKALOIDS BY AN INTRAMOLECULAR NITRONE–OLEFIN CYCLOADDITION REACTION

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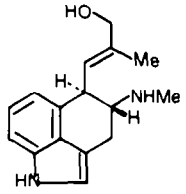
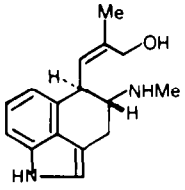
Abstract—The racemic ergot alkaloids chanoclavine I (**1**) and 6,7-secoagroclavine (**4**) have been synthesized stereoselectively from indole-4-carboxaldehyde (**7**) in overall yields of 14 and 13%, respectively. Further syntheses of isochanoclavine I (**2**), paliclavine (**5**) and costaclavine (**6**), *via* the same isoxazolidine **18** are described. The key step **16**→**18** (Scheme 4) involves a transient nitrone **17** which undergoes a kinetically controlled, regio- and stereoselective intramolecular cycloaddition to a 1,2-disubstituted olefinic bond.

The ergolines, many of which exhibit diverse pharmacodynamic properties,[1] present a formidable challenge to organic synthesis. The isolation and structural elucidation of clavine-type members of the ergot alkaloid class, e.g. **1**–**6**, has been stimulated particularly by the pioneering work at Sandoz Ltd, Basel.[1] Thus, chanoclavine I (**1**), first isolated from *Claviceps purpurea* together with its olefinic stereoisomer isochanoclavine I (**2**) and its C-10-epimer chanoclavine II (**3**),[2] occurs also in the higher plant family *Convolvulaceae*.[3] Structure **4**[4] has been established for 6,7-secoagroclavine, which is produced by *Claviceps purpurea*[4] and by systemic fungi from toxic pasture grasses,[5] and structure **5**[6] for paliclavine, a metabolite of *Claviceps paspali*.[6] Costaclavine, obtained from cultures of Agropyrum[7] or *Penicillium*[8] type fungi, has been assigned formula **6**.[9,10] Chanoclavine I (**1**) is of particular interest regarding its role as a biosynthetic precursor of the tetracyclic ergolines paspalic and lysergic acids.[11]



1
Chanoclavine I



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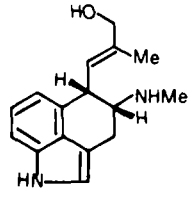
Isochanoclavine I



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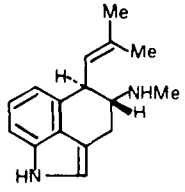
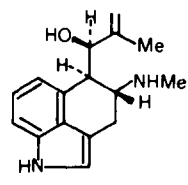
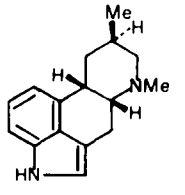
Chanoclavine II



4
6,7-Secoagroclavine



5
Paliclavine



6
Costaclavine

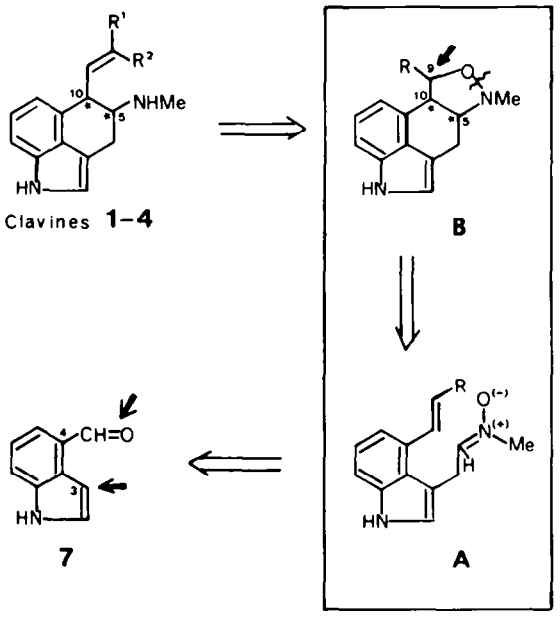
In terms of total synthesis the clavine type ergot alkaloids have received increasing attention during the last few years.

(±)-Chanoclavine I (**1**) was first synthesized in 1976 by Plieninger *et al.*[12] and, more recently, by our[13] and other[14] laboratories using various new routes. Syntheses of (±)-6,7-secoagroclavine (**4**),[15] (+)-paliclavine (**5**)[16] and (±)-costaclavine (**6**)[10] were also reported recently.[17]

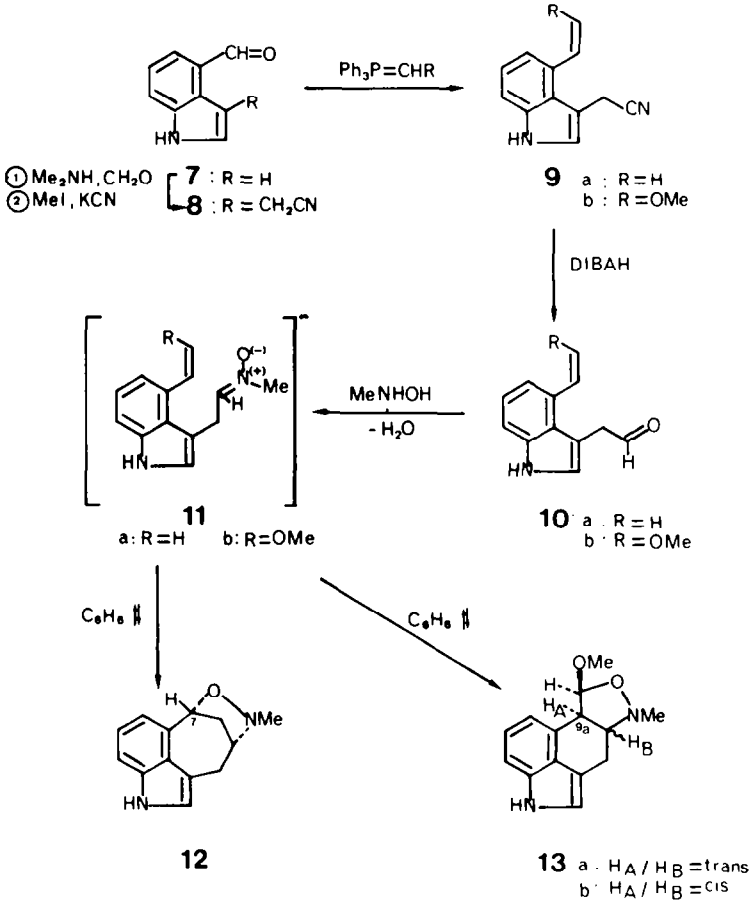
We wish to present here in detail direct and selective syntheses of (±)-chanoclavine I (**1**) and (±)-isochanoclavine I (**2**), described previously in preliminary form.[13] Moreover, the versatility of our approach is further illustrated by syntheses of (±)-6,7-secoagroclavine (**4**), (±)-paliclavine (**5**) and (±)-costaclavine (**6**). The cornerstone of our strategy (Scheme 2) is the closure of the bond C-5/C-10[18] by a nitrone/olefin cycloaddition **A**→**B**. Exploiting the accessibility of 4-substituted indoles by the Batcho–Leimgruber method,[19] we chose the aldehyde **7** as a bifunctional starting material which permits the elaboration of the dipolarophile at the aldehyde group and the introduction of the dipole chain at position 3. Thus, the indole nucleus is kept intact throughout the synthesis, in contrast to earlier syntheses of ergolines.[12,20] This concept parallels the biogenetic pathway from tryptophan to chanoclavine I insofar as the latter also involves C-5/C-10-bond formation of a 3,4-disubstituted indole intermediate.[21]

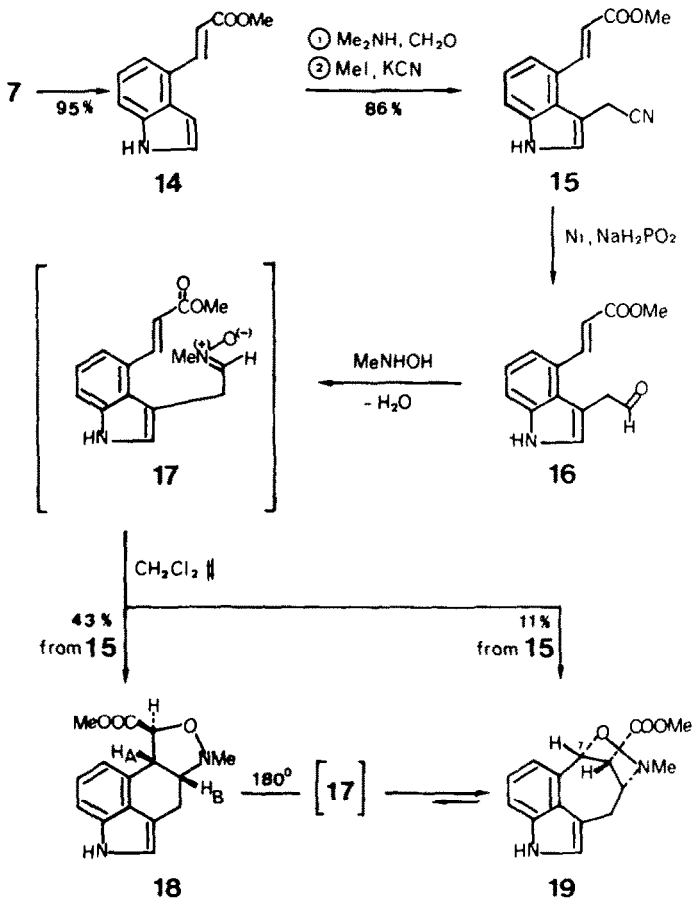
Regiochemical substituent effects on intramolecular nitrone/vinylindole-additions (Scheme 3)

In the initial phase of this work aldehyde **7** was



subjected to a conventional Mannich reaction followed by N-methylation and cyanide displacement giving the nitrile **8** (31–45%). Wittig methylenation of **8** provided vinylindole **9a** (77%). Reduction of nitrile **9a** with diisobutylaluminium hydride gave the unstable olefinic aldehyde **10a** which was immediately condensed with N-methylhydroxylamine in benzene. Heating the resulting solution of the transient nitrone **11a** under reflux for 12 hr gave the bridged cycloadduct **12** as the only isolable product in 56% overall yield from **9a**. Structure **12** follows readily from the ^{1}H-NMR-signal of H-C-7 at δ 5.45 ppm and from the low-field ^{13}C-NMR-doublet of C-7 at δ 80.2 ppm. The undesired regioselectivity of the addition **11a**→**12** is not surprising in view of the orientational bias of the aryl-substituent on the near end of the alkene unit in **11a**.[22] Placing either an electron-donating or withdrawing group R at the terminal of the vinyl moiety should direct the regiochemistry[23] towards the desired annelated isoxazolidines **B**. Indeed, this proved to be the case: the enolether **9b**, prepared from **8** and methoxymethylenetriphenylphosphorane (75%, 5:1-(*Z*)/(*E*)-mixture) gave on reduction/condensation **9b**→**10b**→**11b** followed by nitrone cycloaddition a mixture of the two annelated isoxazolidines **13a** and **13b** (57% overall from **9b**). After separation by medium pressure chromatography the structures of **13a** (30%) and **13b** (16%) were readily assigned. Thus, the H_A-NMR signals of **13a** and **13b** appear at δ 3.82 (J(AB) = 11 Hz) and at δ 4.18 ppm (J(AB) = 5 Hz), respectively. The corresponding ^{13}C-NMR-spectra reveal the C-**9a**-doublet at δ 68.5 (**13a**) and δ 64.0 ppm (**13b**).



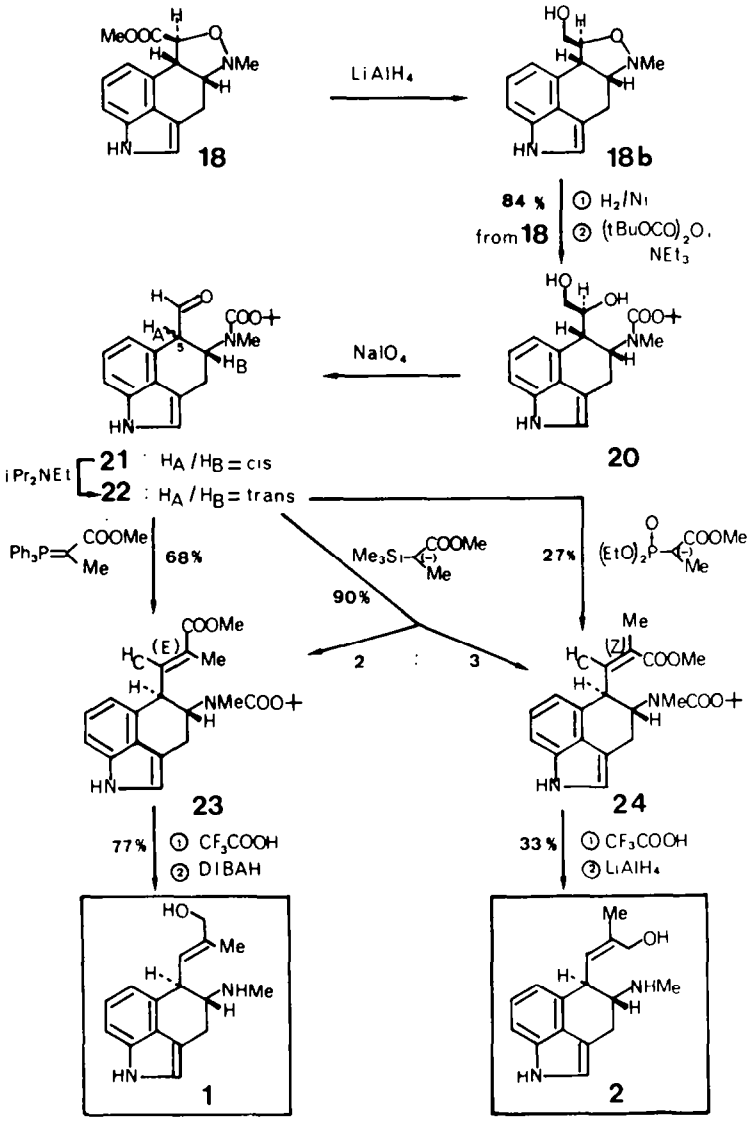


Preparation of the cis-fused isoxazolidine **18** (*Scheme* 4)

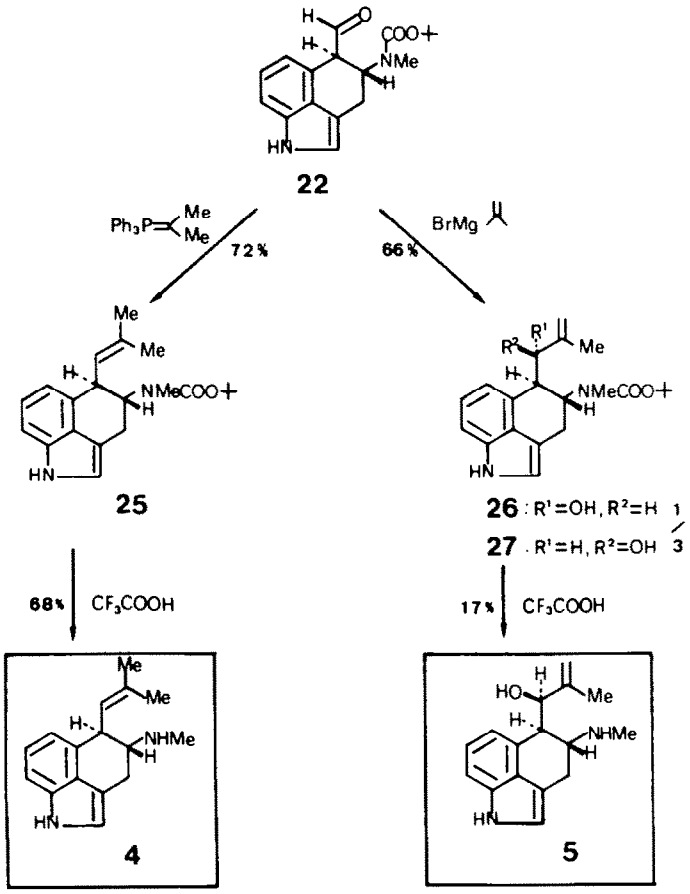
For the actual synthesis of chanoclavine I (**1**) we chose the carbomethoxy group to direct the regiochemistry in the cycloaddition. The Horner–Emmons reaction of the aldehyde **7** with the anion prepared from methyl dimethylphosphonoacetate gave the (*E*)-ester **14** (95%). C-3-Functionalisation of **14** by successive treatment with dimethylamine/formaldehyde and methyl iodide/potassium cyanide furnished the crystalline, stable 3-cyanomethylpropenoate **15** (m.p. 172–174°, 86%). Alternatively, **15** was obtained by Horner–Emmons reaction of the 3-cyanomethyl-aldehyde **8** in 95% yield. Selective reduction of the nitrile group in **15** with an excess of Raney nickel and sodium hypophosphite in pyridine/acetic acid/water 2:1:1[24] gave the unstable aldehyde **16** which was subjected *in situ* to the crucial condensation/cycloaddition sequence. Thus, treatment of **16** with N-methylhydroxylamine-hydrochloride/sodium methoxide in toluene/CH_2Cl_2/MeOH, and subsequent heating of the mixture at 70° with azeotropic removal of water furnished the regioisomeric isoxazolidines **18** and **19** in a ratio of 4:1 (^{1}H-NMR). Chromatography and crystallisation provided the pure *cis*-fused isoxazolidine **18** (m.p. 176–178°, ^{1}H-NMR: J(AB) = 7 Hz, 40% from **15**) and the slightly more polar bridged cycloadduct **19** (m.p. 227–229°, 2% from **15**). Isomer **19** shows NMR-signals analogous to those of **12** (^{1}H-NMR: H-C-7 at δ 5.65 ppm (*s*); ^{13}C-NMR: C-7 at δ 82.8 ppm (*d*)). It is interesting to note that each of the isolated isoxazolidines **18** or **19** gave the same equilibrium mixture 18/19 = 1:4 in dichlorobenzene at reflux, presumably *via* cycloreversion **18**→**17**←**19**. In contrast, pure **18** was not even partially converted to **19** on heating in boiling benzene. It thus follows that the cycloaddition of the intermediate nitrone **17** may be directed either to the kinetically preferred, annelated adduct **18**, or to the thermodynamically favored, bridged isoxazolidine **19** by simple alteration of the reaction temperature. This finding, analogous to results of a former study, targeted towards histrionicotoxin,[25] may be of general value in synthesis.

Conversion of the isoxazolidine **18** *to* (±)-*chanoclavine I* (**1**) *and to* (±)-*isochanoclavine I* (**2**) (*Scheme* 5)

Reduction of the ester **18** with $LiAlH_4$ gave the unstable crude alcohol **18b** which underwent smooth hydrogenolysis of the N,O-bond in the presence of Raney nickel. Selective protection of the resulting methylamine using di-*t*-butyl dicarbonate afforded the relatively stable diol carbamate **20** in 84% overall yield from **18**. Oxidative cleavage of the diol **20** in aqueous methanol at 0° yielded initially the *cis*-aldehyde **21** (^{1}H-NMR: J(AB) = 4 Hz) which epimerized slowly on standing to the more stable *trans*-isomer **22**. Complete epimerization of **21** by



treatment with ethyldiisopropylamine in chloroform at 20° furnished the crystalline *trans*-aldehyde **22** (dec at 200–210°, ^{1}H-NMR: J(AB) = 11 Hz, 99% from **20**). Wittig reaction of **22** using crystalline (α-carbomethoxyethylidene) triphenylphosphorane in dichloromethane at 60° for 2 days afforded selectively the crystalline, pure (*E*)-olefin **23** (m.p. 218–221°, ^{1}H-NMR: δ H_C = 6.87 ppm,[26] *d*, *J* = 10 Hz, 68% from **20**). No (*Z*)-ester **24** was found in the crude reaction mixture (TLC, ^{1}H-NMR). Analogous Wittig reaction of the *cis*-aldehyde **21** gave the same *trans*-substituted (*E*)-olefin **23**, indicating epimerization at C-5 under the basic reaction conditions. Removal of the *t*-butoxycarbonyl group by treatment of **23** with trifluoroacetic acid in chloroform at 0° and subsequent reduction of the ester group with diisobutylaluminium hydride gave, after crystallization, pure (±)-chanoclavine-I(**1**) (m.p., sealed capillary, 185–186° (dec), 77% from **23**). The synthetic alkaloid (±)-**1** was identified by comparison (UV, IR, ^{1}H-NMR) with natural (−)-chanoclavine-I. We were pleased to find that a Horner–Emmons reaction of the *trans*-aldehyde **22** with the anion prepared from methyl (diethyl-α-phosphono) propionate and sodium hydride in tetrahydrofuran at 0° for 18 hr furnished after chromatography and crystallization the pure (*Z*)-olefin **24** (m.p. 192–194°, ^{1}H-NMR: δ H_C = 6.02 ppm,[26] *d*, *J* = 10 Hz, 27% from **20**). Apart from a more polar product, lacking the ^{1}H-NMR-signals of the ester group, no (*E*)-isomer **23** was found in the crude reaction mixture. The observed (*Z*)-selectivity in the transformation **22**→**24** agrees with independent studies of Horner–Emmons reactions of aldehydes, particularly those using trimethyl α-phosphonopropionate.[27] Subjecting the aldehyde **21** to analogous reaction conditions led neither to **23** nor to **24**. On the other hand, Peterson olefination of recrystallized **22** using the anion of methyl 2-trimethylsilylpropionate[28] proceeded smoothly at −78° to give a 2:3-mixture of **23** and **24** in 90% yield. Consecutive treatment of the pure (*Z*)-N-*t*-butoxycarbonyl ester **24** with trifluoroacetic



acid and $LiAlH_4$, followed by chromatography and crystallization afforded (±)-isochanoclavine I (**2**) (m.p. 162–167°, 33% from **24**) identified by spectral comparison (UV, IR, ^{1}H-NMR, MS) with natural isochanoclavine I.

Conversion of the trans-*aldehyde* **22** *to* (±)-6,7-*seco-agroclavine* (**4**) *and to* (±)-*paliclavine* (**5**) (*Scheme* 6)

The synthetic versatility of our approach was further demonstrated by the transformation of *trans*-aldehyde **22** to the clavine alkaloids (±)-**4** and (±)-**5**: Wittig reaction of **22** with isopropylenetriphenylphosphorane afforded the crystalline olefin carbamate **25** (m.p. 221°, 72% from **20**) which on removal of the N-t-butoxycarbonyl group with trifluoroacetic acid gave (±)-6,7-secoagroclavine (**4**) (m.p. 202–203°, 68%), identified by spectral comparison with the natural alkaloid **4**.

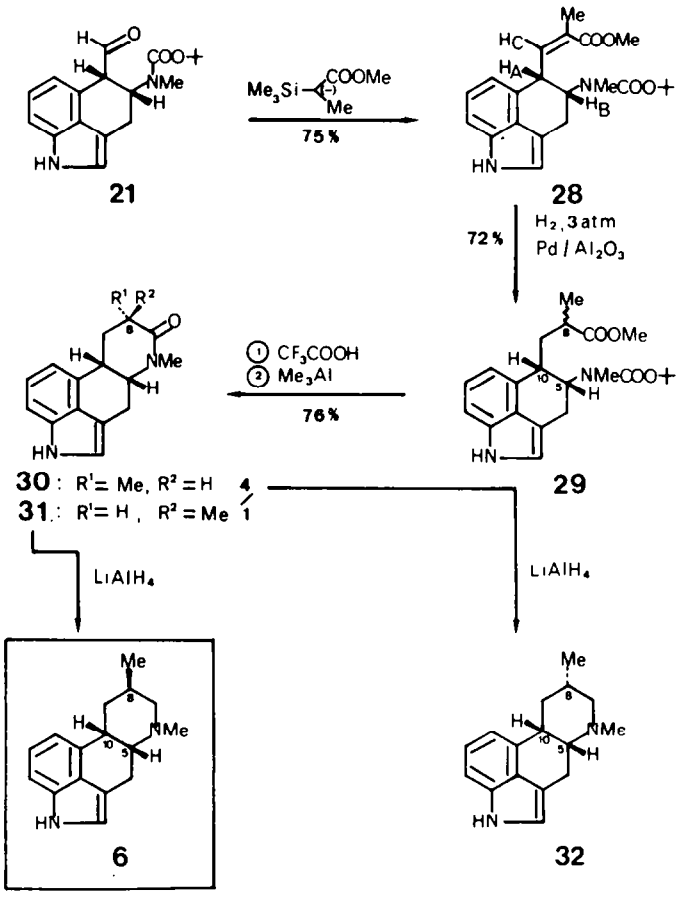
Furthermore, addition of isopropenylmagnesium bromide to **22** furnished the two epimeric alcohols **26** and **27** (66% from **20**) in a ratio of 1:3. The major epimer **27** gave on N-deprotection with trifluoroacetic acid (±)-paliclavine (**5**) (m.p. 175–177°, 17%), showing IR, ^{1}H-NMR and mass spectra identical to those of a natural sample.

Conversion of the cis-*aldehyde* **21** *to* (±)-*costaclavine* (**6**) (*Scheme* 7)

We then focused our attention on the possibility of functionalizing the *cis*-aldehyde **21** without concomitant epimerization at C-5 in order to synthesize clavine alkaloids containing a *cis*-substituted ring C. Indeed, Peterson olefination of **21** (prepared *in situ* from **20**) with lithiated methyl 2-trimethylsilylpropionate was complete within 10 min at −78° to give selectively the *cis*-substituted (*Z*)-ester **28** (75% from **20**). The stereochemical assignment of **28** follows from its ^{1}H-NMR-spectrum showing the signal of the olefinic proton at δ 5.95 ppm[26] (*Z*-olefin) and the spin-spin coupling constant $J(AB) = 4$ Hz ($H_A/H_B = cis$). In order to synthesize (±)-costaclavine (**6**), olefin **28** was hydrogenated (3 atm H_2, Pd/Al_2O_3) to give a non-separable mixture of the two diastereoisomers **29**. Cleavage of the N-*t*-butoxycarbonyl group of **29** with trifluoroacetic acid, followed by cyclization of the resulting amine using trimethylaluminium,[29] gave a mixture of the C-8-epimeric lactams **30** and **31** (76% from **29**) which were separated by medium-pressure chromatography. Treatment of the major lactam **30** with $LiAlH_4$ provided (±)-8-epi-costaclavine **32** (m.p. 149°, 74%), whereas reduction of the minor lactam **31** gave (±)-costaclavine (**6**) (subliming at 182–183°, 78% m.p. 222–224°, sealed capillary, m.p. lit.: 183–185°.[10]) Both (±)-8-epi-costaclavine (**32**) and (±)-costaclavine (**6**) exhibit IR, ^{1}H-NMR and mass spectra identical to those of racemic **32** and **6**, prepared by an independent synthesis.[10]

CONCLUSION

In summary, this work illustrates once more the synthetic potential of intramolecular nitrone-olefin



additions in regio- and stereochemical terms.[30] Thus, starting from 4-indole carboxaldehyde (7) (±)-chanoclavine I and (±)-6,7-secoagroclavine have been obtained in overall yields of 14% and 13%, respectively, by direct routes which compare very favorably with other syntheses of racemic **1** and **4**. Stereoselectivity was achieved throughout the syntheses of (±)-isochanoclavine I and (±)-paliclavine, whereas the preparation of (±)-costaclavine involved configurational control of centers C-5 and C-10 only.

EXPERIMENTAL

General. All reactions were carried out under argon. "Usual work-up" means pouring the mixture into sat NH_4Claq, extraction with ether or CH_2Cl_2, washing the combined organic layers successively with sat $NaHCO_3aq$ and sat NaClaq, drying with solid Na_2SO_4 and removal of solvent by distillation *in vacuo* using a rotatory evaporator. Column chromatography was carried out on SiO_2 (Merck, Kieselgel 60, 0.05–0.20). TLC were carried out on Merck SiO_2-plates. For medium-pressure liquid chromatography prepacked columns (Merck, Li Chro Prep Si 60) were used. Melting points (m.p.) were determined on a Kofler hot stage, unless otherwise specified, and are uncorrected. Temps are expressed as degrees Celsius. UV spectra: MeOH, unless otherwise specified, λ_{max} in nm ($\log \epsilon$). IR, spectra: $CHCl_3$, $\tilde{\nu}_{max}$ in cm^{-1}. NMR spectra in $CDCl_3$, ^{1}H-NMR at 100 MHz, unless otherwise specified, standard TMS δ (ppm) = 0, abbreviations: *s* = singlet, *d* = doublet, *t* = triplet, *qa* = quadruplet, *qi* = quintuplet, *m* = multiplet, *J* = spin-spin coupling constant (Hz), irr. = position of decoupling irradiation. Mass spectra (MS): signals are given in *m/e* (rel%).

Indole 4-carboxaldehyde (7). The procedure of Troxler *et al.*[31] was followed. Raney Ni (Fluka, water suspension, 10 g) was added to a soln of 4-cyanoindole (15 g, 0.105 mole), and sodium hypophosphite (30 g) in 2:1:1 pyridine:AcOH:water (440 ml). The mixture was vigorously mechanically stirred at 45–50° for 1.5–2 hr, until TLC (CH_2Cl_2) showed no starting material. The soln was filtered through *Celite* and the cake washed with water and EtOAc. Usual work-up of the filtrate, and recrystallisation of the crude product ($HCCl_3$) gave 7 (13.5–13.9 g, 88–91%), m.p. 140–142° (lit.[31] 140–142°), IR: 3470, 2810, 2730, 1685, 1615, 1578, 1350, 1268, 1115. ^{1}H-NMR: 7.4 (*m*, 3H); 7.7 (*m*, 2H); 8.7 (broad, 1H); 10.32 (*s*, 1H). MS: 145 ($C_9H_7NO^+$, 100), 144 (55), 116 (54), 89 (30), 63 (13).

4-Formylindole-3-acetonitrile (**8**). A Mannich reagent was formed by addition of Me_2NH (4.5 g of 40% aq. soln, 40 mmol) and formaldehyde (3.4 g of 35% aqueous soln, 40 mmol) to AcOH (20 ml) at 0°. 7 (5 g, 34.5 mmol) was then added and the mixture shaken at room temp until it became homogeneous. The soln was stirred 3–4 hr at room temp, then diluted with water (30 ml) and washed with ether (30 ml). The aqueous phase was basified with 3M NaOH and extracted with $CHCl_3$, the organic phases washed with sat NaClaq and dried (K_2CO_3): evaporation gave crude 3-dimethylaminomethyl indole-4-carboxaldehyde as a red gum. This was dissolved in i-PrOH (70 ml), a sat KCNaq (9.2 g, 0.12 mol) was added, followed by careful addition of MeI (17 g, 0.12 mole) at 0°. The stirred mixture was allowed to come to room temp overnight, filtered, and the cake washed with hot EtOAc. The filtrate was evaporated and partitioned between hot EtOAc and water. Washing of the

organic phases with sat NaClaq, drying (Na_2SO_4) and evaporation yielded a pale yellow solid which was filtered through a silica gel column (EtOAc) and recrystallised (EtOAc) to give **8** (1.95–2.8 g, 31–45%), m.p. 166–168°. IR: 3460, 2840, 2730, 2250, 1690, 1610, 1565, 1440, 1355, 1160, 1115, 1032. ^{1}H-NMR (DMSO d^6): 4.3 (*s*, 2H); 7.2–8.0 (4H), 10.2 (*s*, 1H); 11.8 (broad, 1H). MS: 184 ($C_{11}H_8ON_2^+$, 90), 155(50), 129 (100).

4-*Vinylindole*-3-*acetonitrile* (**9a**). A THF soln of methylenetriphenylphosphorane (from methyltriphenylphosphonium bromide (2.35 g, 6.6 mmol) and n-BuLi (6 ml of 1.15 M, 6.9 mmol)) was cooled to −78° and a soln of **8** (552 mg, 3 mmol) in THF was added. The pale brown cloudy soln was allowed to warm to 0° for 0.5 hr, then poured onto sat NH_4Claq and submitted to the usual work-up followed by chromatography (CH_2Cl_2) to give **9a** (417 mg, 77%). Recrystallisation from ether/pentane gave 352 mg (65%) of pure **9a**, m.p. 126–128°, UV: 217 (4.36), 295 (3.91). IR: 3460, 3000, 2245, 1615, 1410, 1345, 1155, 1108, 1050, 980, 920. ^{1}H-NMR: 4.03 (*d*, *J* = 1, 2H, irr. at 7.3→*s*); 5.48 (*d* × *d*, *J* = 11 and 1.5, 1H, irr. at 7.3→*d*, *J* = 1.5); 5.77 (*d* × *d*, J = 17 and 1.5, 1H, irr. at 7.3→*d*, *J* = 1.5); 7.3 (*m*, 4H); 7.38 (*d* × *d*, *J* = 17 and 11, 1H); 8.3 (broad, 1H). MS: 182 ($C_{12}H_{10}N_2^+$, 65), 154 (100), 127 (17).

5 - *Methyl* - 4,7 - *methano* - 3H - [1,3]*oxacino*[5,6,7 - cd] *indole* (**12**). Diisobutylaluminium hydride (0.8 ml of 1.2 M toluene soln. 0.95 mmol) was added to a soln of 4 - vinylindole - 3 - acetonitrile (80 mg, 0.44 mmol) in dry toluene (4 ml) at −78°. Stirring of the mixture at −78° for 1 hr, followed by quenching with sat sodium potassium tartrate aq and the usual work-up furnished the crude **10a**. A freshly prepared methanolic soln of N-methylhydroxylamine (from N-methylhydroxylamine hydrochloride, and NaOMe, each 1.6 mmol) was added to the soln of crude **10a** in benzene (50 ml). Heating the mixture under reflux for 15 hr with azeotropic water removal (3 Å molecular sieves), followed by filtration, evaporation and chromatography (EtOAc) gave the bridged **12** (m.p. 186–188° (dec) from $CHCl_3$–hexane) as the only isolable product (53 mg, 56%). UV: 222 (4.57), 287 (3.95). IR: 3470, 3010, 2950, 1615, 1440, 1360, 1340, 1177, 1115, 1060, 1040, 1015, 955. ^{1}H-NMR: 2.46 (*d*, *J* = 12, 1H); 2.84 (*s*, 3H); 2.9–3.5 (3H); 3.68 (*d* × *t*, *J* = 9 and 3.5, 1H); 5.45 (*d*, *J* = 8, irr. at 3.1→*s*, 1H); 6.9–7.4 (4H); 8.4 (broad, 1H). ^{13}C-NMR (DMSO d^6): 135.8 (*s*), 134.1 (*s*), 124.2 (*s*), 122.4 (*d*), 119.4 (*d*), 117.0 (*d*), 111.0 (*s*), 110.8 (*d*), 80.2 (*d*), 64.1 (*d*), 46.3 (*qa*), 38.7 (*t*), 31.1 (*t*). MS: 214 ($C_{13}H_{14}N_2O^+$, 32), 195 (12), 168 (100).

(Z) - 4 - (2 - *Methoxyethenyl*)*indole* - 3 - *acetonitrile* (**9b**). s-BuLi (1.87 ml of 1.23 M, 2.3 mmol) was added to a suspension of methoxymethyltriphenylphosphonium chloride (Aldrich) (786 mg, 2.3 mmol) in dry THF (40 ml) at −78°. After stirring for 1 hr at −78°, **8** (184 mg, 1 mmol) in THF (3 ml) was added to the deep red soln. Stirring the mixture for 15 min at −78°, then 1.5 hr at room temp, subsequent quenching with sat NH_4Claq, usual work-up and chromatography (CH_2Cl_2) yielded **9b** as a gum which solidified on standing (159 mg, 75%), m.p. 90–93°. UV: 220 (4.36), 299 (4.07), 316 (3.88). IR: 3470, 3010, 2930, 2250, 1650, 1605, 1460, 1415, 1350, 1280, 1160, 1100, 1045, 1005. ^{1}H-NMR: 3.76 (*s*, 3H); 4.01 (*d*, *J* = 1, 2H), 5.75 (*d*, *J* = 7, 1H); 6.34 (*d*, *J* = 7, 1H); 7.2–7.6 (4H); 8.2 (broad, 1H), (small doublets at 6.40, 6.94 (J = 12) showed presence of *trans* isomer, ratio *cis* : *trans* = 5:1). MS: 212 ($C_{13}H_{12}N_2O^+$, 100), 197 (69), 170 (40), 157 (46), 115 (25). When the reaction was performed with sodium t-amylate as the base (toluene, RT, 1 hr), **9b** was obtained in 44% yield, ratio *cis* : *trans* 2:1 by ^{1}H-NMR.

6aR*,9S,9aR* - 9 - *Methoxy* - 7 - *methyl* - 4,6,6*a*,7,9,9*a*-*hexahydroindole*[4,3 - *e*,*f*][2,1]*benzisoxazole* (**13a**) *and* 6aR*,9R*,9aS*,9 - *methoxy* - 7 - *methyl* - 4,6,6*a*,7,9,9*a* - *hexahydroindolo*[4,3 - *e*,*f*][2,1]*benzisoxazole* (**13b**). Diisobutylaluminium hydride (6 ml of 1.2 M soln in toluene, 7.2 mmol) was added to a soln of **9b** (708 mg, 3.33 mmol) in dry toluene (25 ml) at −78°. Stirring the mixture at −78° for 1 hr, then quenching with sat sodium potassium tartrate aq at −78° and the usual work-up furnished the crude aldehyde. The crude aldehyde was stirred in benzene (110 ml) with a soln of N-methylhydroxylamine (from N-methylhydroxylamine, hydrochloride, 835 mg, 10 mmol, and NaOMe, 670 mg, 12 mmol, in MeOH, 5 ml) and then heated under reflux with azeotropic water removal for 3 hr. Filtration, evaporation and chromatography (EtOAc) gave the mixture of adducts as a gum (465 mg, 57%). The isomers were separated by medium-pressure chromatography ($CHCl_3$:THF 9:1) to give the (6aR*, 9aR*) isomer **13a** (R_f 0.42, 245 mg, 30%) m.p. 160–163° (dec) (from $CHCl_3$–hexane), UV: 221 (4.55), 279 (3.86), 289 (3.75). IR: 3620, 3470, 3010, 2970, 1615, 1600, 1445, 1160, 1128, 1100, 1078, 1045, 970, 955. ^{1}H-NMR: 3.00 (*s*, 3H); 2.7–3.4 (3H); 3.54 (*s*, 3H); 3.82 (*d* × *d*, *J* = 11 and 4.5, 1H, irr. at 5.50→*d*, *J* = 11); 5.50 (*d*, *J* = 4.5, 1H); 6.8–7.4 (4H); 8.25 (broad, 1H). ^{13}C-NMR (DMSO-d^6): 133.0 (*s*), 127.5 (*s*), 127.0 (*s*), 121.4 (*d*), 119.1 (*d*), 113.7 (*d*), 109.2 (*s*), 108.7 (*d*), 100.3 (*d*), 68.5 (*d*), 53.8 (*qa*), 53.0 (*d*), 46.3 (*qa*), 25.6 (*t*). MS: 244 ($C_{14}H_{16}N_2O_2^+$, 84), 227 (35), 198 (100), 183 (42), 169 (22), 154 (43) and the (6aR*, 9aS*) isomer **13b** (R_f 0.35, 135 mg, 16%) m.p. 221–224 (dec) (from $CHCl_3$–hexane), UV: 222 (4.50), 280 (3.82), 291 (3.74); IR: 3470, 3020, 2970, 2920, 2830, 1620, 1610, 1445, 1345, 1120, 1072, 1055, 955. ^{1}H-NMR: 2.94 (*s*, 3H); 3.0–3.4 (2H); 3.23 (*s*, 3H); 3.5 (*m*, 1H); 4.18 (*t*, *J* = 5, 1H, irr. at 5.40→*d*, *J* = 5); 5.40 (*d*, *J* = 5, 1H; irr. at 4.18→*s*); 6.8–7.4 (4H); 8.05 (broad, 1H). ^{13}C-NMR (DMSO d^6): 133.1 (*s*), 127.2 (*s*), 124.6 (*s*) 121.3 (*d*), 118.5 (*d*), 116.1 (*d*), 109.8 (*s*), 108.7 (*d*), 103.9 (*d*), 64.0 (*d*), 54.2 (*qa*), 46.5 (*qa*), 46.2 (*d*), 25.6 (*t*). MS: 244 ($C_{14}H_{16}N_2O_2^+$, 100), 227 (49); 198 (43), 195 (22), 184 (61), 183 (70), 169 (80), 154 (79), 127 (30), 115 (30).

Preparation of the annelated isoxazolidine **18** (*Scheme* 4)

(E) - *Methyl* - 3 - (4 - *indolyl*)*propenoate* (**14**). Trimethylphosphonoacetate (4.85 ml, 30 mmol) was added to NaH (1.32 g of 60% dispersion, washed with pentane, 33 mmol), in THF (100 ml) at 0°. The thick white suspension was stirred at r.t. for 30 min, then recooled to 0°, and indole-4-carboxaldehyde (4.1 g, 28.3 mmol) in THF (50 ml) was added. The pale yellow clear soln was stirred at r.t. for 1.5 hr, then quenched by addition of sat NH_4Claq. The usual workup followed by recrystallisation (EtOAc) gave **14** (5.4 g, 95%), m.p. 125–126°, IR: 3470, 3020, 2950, 1710, 1632, 1610, 1440, 1360, 1345, 1320, 1280, 1170, 1158, 1112, 975. ^{1}H-NMR: 3.85 (*s*, 3H); 6.64 (d, J = 16, 1H); 6.85 (m, 1H); 7.1–7.5 (4H); 8.14 (*d*, *J* = 16, 1H); 8.5 (broad, 1H). MS: 201 ($C_{12}H_{11}NO_2^+$, 100), 170 (32), 143 (7), 142 (11), 141 (13), 115 (15).

(E) - *Methyl* 3 - (3 - *cyanomethyl* - 4 - *indolyl*)*propenoate* (**15**)

Method A. A Mannich reagent was prepared from Me_2NH (40% aqueous soln, 4.5 g, 40 mmol) and formaldehyde (35% aqueous soln, 3.4 g, 40 mmol) in AcOH (30 ml) at 0°. (*E*)-**14** (7 g, 35 mmol) was added, and the mixture shaken until the solid has dissolved, then stirred 18 hr at r.t. Addition of 3N NaOH to pH = 9 followed by the usual work-up gave the crude Mannich product, which was dissolved in i-PrOH (160 ml), and sat KCNaq (5.2 g, 80 mmol) added, followed by 6.8 ml (100 mmol) of MeI at 0°. The stirred mixture was allowed to come to r.t., stirred at r.t. for 72 hr and then evaporated. The residue was partitioned between refluxing EtOAc and water, the EtOAc washed with sat NaClaq, dried and evaporated, and the residue recrystallised to give 7.22 g (86%) of **15**, m.p. 172–174°. UV: 207 (4.46), 233 (4.21), 350 (3.92). IR: 2360, 2990, 2940, 1705, 1630, 1610, 1430, 1340, 1160, 1110, 1040, 970. ^{1}H-NMR ($CDCl_3$ + DMSO d^6): 3.85 (*s*, 3H), 4.06 (*d*, *J* = 1, 2H), 6.47 (*d*, *J* = 16, 1H); 7.1–7.7 (4H); 8.34 (*d*, *J* = 16, 1H). MS: 240 ($C_{14}H_{12}N_2O_2^+$, 46), 208 (100), 179 (74), 169 (14), 154 (29), 127 (20), 77 (19).

Method B. NaH (120 mg of 60% dispersion, washed with pentane, 3 mmol) in THF (30 ml) at 0° was treated with

trimethylphosphonoacetate (0.49 ml, 3 mmol). After 0.5 hr at r.t., the reaction was cooled to 0° and **8** (0.5 g, 2.7 mmol) in THF (10 ml) was added and stirred for 0.5 hr at r.t. After addition of sat NH_4Claq and the usual work-up, recrystallisation (EtOAc–hexane) gave the ester as a pale yellow solid (620 mg, 95%), m.p. 172–174°, identical with **15**, prepared by Method A.

Methyl (6a**R***,9**S***,9a**S***) - 4,6,6a,7,9,9a - *hexahydro* - 7 - *methylindolo*[4,3 - ef][2,1]*benzisoxazole* - 9 - *carboxylate* (**18**) *and methyl* 5 - *methyl* - 4,7 - *methano* - 3H - [1,3]*oxacino*[5,6,7 - cd]*indole* - 11 - *carboxylate* (**19**). A mixture of **15** (2.16 g, 9 mmol), sodium hypophosphite (4.26 g) and Raney Ni (2.5 g) in pyridine/AcOH/water 2:1:1 was mechanically stirred at 60°. After 1.5 hr at 60° more Raney Ni (1 g) was added and the mixture stirred at 60° for 4 hr until TLC (hexane/EtOAc 1:1) showed no more **15**. Then the mixture was filtered through Celite and the cake washed with water (150 ml) and ether/toluene (1:1, 100 ml). Shaking the filtrates with water (300 ml) and CH_2Cl_2, washing of the organic phase with water (until disappearance of green color in the aq. phase) and sat NaClaq followed by drying (solid Na_2SO_4) gave a soln of the unstable aldehyde **16** which was used directly to prepare **18** and **19** as described below. For its characterization a sample of the pure **16** was obtained by chromatography: IR: 3470, 3020, 2950, 1720, 1635, 1610, 1440, 1355, 1115, 1050, 975. ^{1}H-NMR (60 MHz): 3.80 (*s*, 3H); 4.05 (*s*, broad, 2H); 6.40 (*d*, *J* = 15, 1H); 7.1–7.7 (4H); 8.33 (*d*, *J* = 15, 1H); 8.7 (broad, 1H); 9.9 (*t*, *J* = 1, 1H). N-Methylhydroxylamine (prepared from N-methylhydroxylamine hydrochloride, 0.75 g, 9 mmol in dry MeOH (12 ml) and NaOMe (Fluka, 0.49 g, 9 mmol) in MeOH (12 ml)) was added slowly to the above described soln of the crude **16**. The mixture was heated at 70° for 2 hr with removal of 20 ml portions of azeotrope every 15 min using a Dean–Stark trap and then left at r.t. for 16 hr. The usual work-up furnished a crude mixture (2.0 g) which according to ^{1}H-NMR analysis contained the regioisomeric **18** and **19** in a ratio of 79:21. Chromatography (neutral Al_2O_3, activity II-III, EtOAc/hexane 1:1) furnished unchanged **15** (100 mg, 5%), followed by the annelated **18** (1.04 g, 43%). Crystallization (EtOAc) of chromatographically pure **18** furnished crystalline **18** (968 mg, 40%), m.p. 167–169°. UV: 222 (4.49), 280 (3.84), 291 (3.77). IR: 3470, 3040, 2970, 2850, 1745, 1620, 1610, 1465. ^{1}H-NMR: 2.9–3.2 (2H); 2.96 (*s*, 3H); 3.6 (*m*, 1H); 3.90 (*s*, 3H); 4.35 (*t*, *J* = 7, 1H, irr. at 3.6→*d*, *J* = 7, irr. at 3.1: no change); 4.59 (*d*, *J* = 7, 1H, irr. at 3.1 or 3.6: no change); 6.9–7.4 (4H); 8.1 (broad, 1H. ^{13}C-NMR (DMSO d^6): 171.8 (*s*), 133.3 (*s*), 126.6 (*s*), 125.0 (*s*), 121.6 (*d*), 119.0 (*d*), 115.3 (*d*), 109.0 (*d*), 107.9 (*s*), 80.7 (*d*), 65.7 (*d*), 51.8 (*qa*), 47.2 (*qa*), 44.5 (*d*), 22.1 (*t*). MS: 272 ($C_{15}H_{16}N_2O_3^+$, 100), 255 (55), 226 (27), 223 (25), 183 (35), 169 (25), 154 (95), 127 (20), 115 (26). Further elution afforded the more polar, bridged isoxazolidine **19** which was crystallized (EtOAc) to give crystalline **19** (40 mg, 2%), m.p. 227–229°. UV: 220 (3.57), 287 (2.97). IR (Nujol): 1730, 1285, 1223, 1000, 740. ^{1}H-NMR (360 mHz): 2.90 (*s*, 3H); 3.08 (*d*, *J* = 16, 1H, irr. at 3.34→*s*); 3.34 (*d* × *d*, *J* = 16 and 4, 1H, irr. at 3.1→broad *s*, irr. at 4.09→*d*, *J* = 16); 3.59 (*s*, 1H); 3.85 (*s*, 3H); 4.09 (broad *s*, 1H, irr. at 3.34→sharp *s*); 5.68 (*s*, 1H); 7.05–7.4 (4H); 8.2 (broad *s*, 1H). ^{13}C-NMR (90.561 MHz): 172.6 (*s*), 136.1 (s), 131.4 (*s*), 124.7 (*s*), 123.1 (*d*), 119.8 (*d*), 118.6 (*d*), 111.6 (*s*), 110.4 (*d*), 82.8 (*d*), 66.0 (*d*), 58.2 (*d*), 52.1 (*qa*), 45.3 (*qa*), 29.6 (*t*). MS: 272 ($C_{15}H_{16}N_2O_3^+$, 100), 255 (71), 226 (46), 223 (46), 195 (31), 167 (43), 154 (40).

Thermal equilibration of the regioisomeric isoxazolidines **18** *and* **19**. (a) The annelated **18** (50 mg) was heated under reflux (argon) in freshly distilled 1,2-dichlorobenzene for 1 hr. Evaporation of the solvent at 0.05 torr gave according to ^{1}H-NMR analysis a 17:83-mixture (50 mg) of **18** and **19**. (b) Heating of the bridged **19** (20 mg) under identical conditions furnished according to ^{1}H-NMR analysis also a 1:5-mixture (120 mg) of **18** and **19**. (c) After heating a soln of **18** in benzene under reflux for 4.5 hr followed by evaporation of the solvent no **19** could be found in the residue (^{1}H-NMR).

Conversion of the isoxazolidine **18** *to* (±)-*chanoclavine* I *and to* (±)-*isochanoclavine* I (*Scheme 5*)

t-Butyl N - [(4**R***,5**S***,1′**S***) - 5 - (1′,2′ - *dihydroxyethyl*)-1,3,4,5 - *tetrahydrobenz*[cd]*indol* - 4 - *yl*]N - *methylcarbamate* (**20**). The ester **18** (413 mg, 1.52 mmol) in THF (22 ml) was added slowly to a suspension of $LiAlH_4$ (186 mg, 0.65 mmol) in THF (25 ml) at r.t. After stirring the mixture at r.t. for 14 min addition of sat Na_2SO_4aq and work-up furnished **18b** as a colorless solid (356 mg, 96%) which darkened rapidly on attempted crystallization and thus was transformed directly to the more stable carbamate **20** as described below. Crude **18b** showed the following properties: m.p. 65–70°. IR: 3600, 3470, 3400 (broad), 3020, 2950, 1620, 1608, 1450, 1345, 1155, 1070. ^{1}H-NMR: 2.1 (broad, 1H, disappears with D_2O); 2.9 (*s*, 3H); 3.0–3.2 (2H); 3.4 (*m*, 1H); 3.8–4.1 (3H); 6.95 (*m*, 2H); 7.1–7.4 (3H); 8.1 (broad, 1H, disappears with D_2O). MS: 244 ($C_{14}H_{16}N_2O_2^+$, 100), 227 (21), 209 (32), 197 (17), 183 (26), 168 (36), 154 (55). The crude **18b** was stirred with Raney Ni (50 mg) in MeOH (80 ml) under H_2 (1 atm) until TLC (EtOAc) showed no more **18b** to be present. The filtered (Celite) soln was partially evaporated to 40 ml. After addition of NEt_3 (0.43 ml) di-*t*-butyl-dicarbonate (668 mg, 3 mmol) in THF (24 ml) was added dropwise at r.t. The mixture was stirred at r.t. for 16 hr, then submitted to the usual work-up and chromatography (EtOAc/toluene 3:1) to give **20** as a colorless solid which decomposes on heating (435 mg, 84% from **18**), m.p. 80–83° (dec). IR: 3600–3300 (broad), 3470, 3030, 2930, 1680, 1370, 1150. ^{1}H-NMR: 1.48 (*s*, 9H); 2.2, (broad, 1H, disappears with D_2O): 2.88 (*s*, 3H); 3.1 (*d* × *d*, *J* = 15 and 5, 1H); 3.3–3.7 (4H); 3.8 (broad, disappears with D_2O); 4.10 (*m*, 1H); 4.45 (*m*, 1H); 6.9–7.4 (4H); 8.1 (broad, 1H). ^{1}H-NMR (360 MHz, pyridine-d^5): 1.52 (*s*, 9H); 3.03 (*d* × *d*, *J* = 14 and 4.5, 1H, irr. at 3.63→*d*, *J* = 4.5); 3.25 (*s*, 3H); 3.63 (*t*, *J* = 14, 1H, irr. at 3.03→*d*, *J* = 14); 3.95 (*d* × *d*, *J* = 11 and 8, 1H, irr. at 4.55→*d*, *J* = 11); 4.04 (*d* × *d*, *J* = 11 and 3, 1H, irr. at 4.55→*d*, *J* = 11); 4.22 (*t*, *J* = 5, 1H, irr. at 4.55→*d*, *J* = 5); 4.55 (*m*, 1H); 5.04 (*m*, 1H); 5.5 (broad, 2H); 7.15–7.45 (4H); 11.55 (*s*, 1H). MS: 346 ($C_{19}H_{26}N_2O_4^{+\cdot}$, 4), 215 (11), 197 (28), 155 (57), 154 (100), 57 (26).

t - Butyl cis - N(5 - *formyl* - 1,3,4,5 - *tetrahydrobenz*[cd]*indo*-4 - *yl*)N - *methylcarbamate* (**21**). $NaIO_4$ (135 mg, 0.85 mmol) in water (5 ml) was added to a stirred soln of **20** (200 mg, 0.58 mmol) in MeOH (10 ml) at 0°. Stirring of the mixture at 0° for 15 min, filtration and work-up of the filtrate yielded the unstable *cis*-**21** (181 mg, 100%) as a colorless gum which without purification was converted either to its *trans*-**22** or to **28**. On standing or on chromatography **21** isomerized partially to its *trans*-**22**. The crude *cis*-**21** shows the following spectra: IR: 3470, 3030, 2990, 1720, 1688, 1610, 1450, 1400, 1370, 1240, 1150. ^{1}H-NMR: 1.50 (*s*, 9H); 2.98 (*s*, 3H); 3.1 (*m*, 1H); 3.64 (*qi* × *d*, *J* = 11 and 2, 1H); 4.22 (*t*, *J* = 4, 1H, irr. at 9.87→*d*, *J* = 4); 4.66 (*d* × *t*, *J* = 11 and 4, 1H, irr. at 3.6→*t*, *J* = 4); 6.9–7.4 (4H); 8.15 (broad, 1H); 9.87 (*d*, *J* = 4, 1H, irr. at 4.22→*s*, 1H).

t-Butyl trans - N(5 - *formyl* - 1,3,4,5 - *tetrahydrobenz*[cd]*indol* - 4 - yl)N - *methylcarbamate* (**22**). A mixture of the *cis*-**21** (181 mg, 0.58 mmol) and ethyldiisopropylamine (0.3 ml) in dry $CHCl_3$ (5 ml) was kept at r.t. for 3 hr. Evaporation of the soln *in vacuo* afforded the *trans*-aldehyde (180 mg, 99%) as a solid (dec at 200–210°) which was used in the work described below without further purification. A chromatographed (toluene/EtOAc 3:1) sample of **22** shows the following spectra: IR: 3610, 3470, 3020, 2970, 1725, 1685, 1450, 1395, 1370, 1350, 1145, 1045, 880. ^{1}H-NMR: 1.48 (*s*, 9H); 2.91 (*s*, 3H); 3.0–3.2 (2H); 4.06 (*d* × *d*, *J* = 11 and 5, 1H, irr. at 9.66→*d*, *J* = 11, irr. at 5.1→*d*, *J* = 5); 5.1 (*m*, 1H); 6.75 (*d* × *t*, *J* = 6 and 1.5, 1H); 6.98 (*m*, 1H); 7.1–7.4 (2H); 8.1 (broad, 1H); 9.68 (*d*, *J* = 5, irr. at 4.06→s, 1H). MS: 314 ($C_{18}H_{22}N_2O_3^{+\cdot}$, 0.2), 285 (2), 241 (2), 183 (65), 155 (27), 154 (100).

Methyl (E) - (4R*,5R*) - 3 - [4 - (*t* - *butoxycarbonyl*)*methylamino* - 1,3,4,5 - *tetrahydrobenz*[cd]*indol* - 5 - *yl*]-2 - *methylphropenoate* (**23**). A soln of the crude *trans*-**22** (180 mg, 0.58 mmol) and crystalline (α-carbomethoxyethylidene)triphenylphosphorane[32] (623 mg, 1.8 mmol) in dry CH_2Cl_2 (30 ml) was heated at 60° (sealed tube) for 2 days. Evaporation of the soln and chromatography of the residue (toluene/EtOAc 3:1) gave crude **23** containing no (*Z*)-**24** according to TLC and ^{1}H-NMR evidence. Crystallisation of crude **23** (hexane/EtOAc) furnished the pure (*E*)-**23** (152 mg, 68% from **20**), m.p. 218–221° (dec). TLC (toluene/EtOAc 9:1): $R_f = 0.22$. IR: 3470, 3020, 1720–1680 (broad), 1605, 1445, 1400, 1370, 1350, 1295, 1145, 1075. ^{1}H-NMR: 1.47 (*s*, 9H); 2.06 (*d*, *J* = 1.4, 3H); 2.89 (*s*, broad, 3H); 2.8–3.4 (2H); 3.78 (*s*, 3H); 4.30 (*t*, *J* = 10, 1H, irr. at 6.86→*d*, *J* = 10); 4.4–4.7 (1H); 6.67 (*d*, *J* = 7, 1H); 6.87 (*d*, *J* = 10, 1H, irr. at 4.52→*s*); 6.93 (*m*, 1H); 7.0–7.2 (2H); 8.05 (broad, 1H). MS: 384 ($C_{22}H_{28}N_2O_4^+$, 3), 328 (2), 311 (12), 284 (34), 283 (31), 253 (100), 221 (36), 155 (38), 91 (22). See also the preparation of a mixture of the (*E*)-**23** and the (*Z*)-**24** by Peterson olefination of **22** as described further below.

(±)-*Chanoclavine I* (**1**). Trifluoroacetic acid (0.8 ml) was added to a soln of the (*E*)-**23** (100 mg, 0.26 mmol) in dry $CHCl_3$ (8 ml) at 0°. After stirring the mixture at 0° for 3 hr it was poured into sat. $NaHCO_3$aq to give after usual work-up and chromatography the methyl (*E*) - (4R*,5R*) 3 - (4 - methylamino - 1,2,3,4,5 - tetrahydrobenz[cd]indolyl-5 - yl) - 2 - methylpropenoate (70 mg, 94%), IR: 3470, 3400 (broad), 3030, 2950, 2800, 1715, 1605, 1445, 1295, 1255, 1130, 1105. ^{1}H-NMR: 1.6 (broad *s*, 1H); 2.15 (*d*, *J* = 1, 3H, irr. at 6.83→*s*); 2.56 (*s*, 3H); 2.7–3.5 (3H); 3.81 (*s*, 3H); 4.15 (*d* × *d*, *J* = 10 and 7, 1H, irr. at 6.83→*d*, *J* = 7); 6.83 (*d* × *qa*, *J* = 10 and 1, 1H, irr. at 4.15→broad *s*); 6.75 (*m*, 1H); 6.98 (*m*, 1H); 7.1–7.3 (2H); 8.15 (broad s, 1H). MS: 384 ($C_{17}H_{20}N_2O_2^+$, 60), 197 (31), 182 (26), 168 (64), 155 (100), 83 (48). 1.2N Diisobutylaluminium hydride in toluene (0.15 ml, 0.18 mmol) was added to a soln of the thus obtained ester (10 mg, 0.035 mmol) in THF (3 ml). Stirring of the mixture at r.t. for 2 hr, followed by addition of 3N NaOH, workup and chromatography ($CHCl_3$/MeOH/25% aq. NH_4OH 9:1:0.01) and crystallisation (acetone) gave pure (±)-**1** (7.4 mg, 82%), m.p. 185–186° (dec, sealed capillary). TLC ($CHCl_3$/n-BuOH/25% NH_4OHaq 2:1:0.02): $R_f = 0.43$. UV: 222 (4.46), 281 (3.87), 291 (3.78). IR (KBr): 3250, 3050, 2870, 2810, 1620, 1605, 1482, 1450, 1420, 1380, 1340, 1260, 1220, 1138, 1070, 1021, 975, 920, 875, 855, 830, 811, 749, 635, 600, 562. ^{1}H-NMR. (360 MHz pyridine d^5): 2.03 (*d*, *J* = 1, 3H, irr. at 5.87→s); 2.41 (s, 3H); 2.90 (*d* × *d* × *d*, *J* = 15, 9 and 1.5, 1H, irr. at 3.40→*d* × *d*, *J* = 9 and 1.5); 3.02 (*t* × *d*, *J* = 8 and 3, 1H, irr. at 3.40→*t*, *J* = 8, irr. at 4.19→*d* × *d*, *J* = 8 and 3); 3.40 (*d* × *d*, *J* = 15 and 3, 1H); 4.19 (*d* × *d*, *J* = 9 and 8, 1H, irr. at 5.87→*d*, *J* = 8); 4.43 (*s*, 2H); 5.87 (*d* × *d*, *J* = 9 and 1, 1H, irr. at 4.19→broad *s*); 7.01 (*d*, *J* = 7, 1H); 7.21 (broad, 1H); 7.24 (*t*, *J* = 7, 1H); 7.40 (*d*, *J* = 7, 1H); 11.50 (broad, 1H). MS: 256 ($C_{16}H_{20}N_2O^+$, 100), 237 (32), 223 (11), 206 (10), 196 (26), 183 (5), 181 (9), 168 (38), 167 (32), 155 (60), 108 (13), 101 (26). (−)Chanoclavine of natural origin showed TLC-behaviour, UV, IR, ^{1}H-NMR and mass spectra identical with those quoted above for synthetic (±)-**1**.

Methyl (Z) - (4R*,5R*) - 3 - [4 - *t* - *butoxycarbonyl*)*methylamino* 1,3,4,5 - *tetrahydrobenz*[cd]*indol* - 5 - *yl*] - 2 - *methylpropenoate* (**24**). The crude *trans*-**22** (35 mg (0.113 mmol) in THF (1 ml) was added to a soln of the anion prepared from methyl (diethyl-α-phosphono)propionate (56 mg, 0.25 mmol) and NaH (10 mg, 0.25 mmol) in THF (5 ml). The mixture was stirred at 0° for 18 hr, then poured into sat NH_4Claq to give after work-up and chromatography (toluene/EtOAc 9:1) the crude (*Z*)-**24** which according to TLC and ^{1}H-NMR evidence does not contain the (*E*)-**23**. Crystallisation (ether/pentane) furnished pure **24**, m.p. 192–194° (12 mg, 27% from **20**). TLC (toluene/EtOAc 9:1): $R_f = 0.26$. IR: 3470, 3020, 2970, 1720, 1685, 1605, 1450, 1410, 1370, 1295, 1140, 890. ^{1}H-NMR (signals doubled presumably because of hindered rotation): 1.45 (*s*, 9H); 2.06 (*s*, 3H); 2.82, 2.88 (2 × *s*, 3H); 2.9–3.1 (2H); 3.75 (s, 3H); 4.5 (*m*, 1H); 5.01, 5.11 (2 × *t*, *J* = 10, 1H); 5.96, 6.02 (2 × *d*, *J* = 10, 1H); 6.75 (*m*, 1H), 6.9 (*m*, 1H); 7.2 (*m*, 2H); 8.06 (broad, 1H). MS: 384 ($C_{22}H_{28}N_2O_4^+$, 3), 311 (8), 280 (27), 253 (100), 233 (60), 221 (73), 169 (37), 155 (33), 89 (70), 73 (93). Further elution afforded only more polar material lacking the ^{1}H-NMR signals of the ester group.

Peterson-olefination of the trans-aldehyde **22**. Methyl 2-trimethylsilylpropionate[28] (87 mg, 0.54 mmol) in THF (0.5 ml) was added dropwise at −78° to a soln of lithium diisopropylamide, freshly prepared from diisopropylamine (0.082 ml, 0.58 mmol) and BuLi (0.55 mmol) in THF/hexane (1.3 ml, 3:1). After 10 min at −78° recrystallised (EtOAc) *trans*-**22** (41 mg, 0.136 mmol) in THF (2.5 ml) was added at −78°. The mixture was stirred at −78° for 45 min, then poured into sat NH_4Claq to give after work-up and chromatography (toluene/EtOAc 3:1) a 2:3-mixture of the (*E*)- and (*Z*)**23** and **24** (47.3 mg, 90%), identified by TLC and ^{1}H-NMR comparison with pure **23** and **24**.

(±)-*Isochanoclavine I* (**2**). A mixture of the (*Z*)-**24** (18 mg, 0.047 mmol), trifluoroacetic acid (0.5 ml) and $CHCl_3$ (3 ml) was stirred at 0° for 2 hr, then poured into sat $NaHCO_3$aq to give after work-up and chromatography ($CHCl_3$/MeOH/25% NH_4OHaq 100:2:1) crude (*Z*)-(4R*,5R*) - 5 - (2 - methoxycarbonyl - 1 - propenyl) - 4 - (N - methylamino)- 1,3,4,5 - tetrahydrobenz[c,d]indole (12 mg, 90%), IR: 3470, 3030, 2970, 2800, 1710, 1605, 1455, 1445, 1365, 1245, 1130, 1100, 1070, 800. ^{1}H-NMR (60 MHz): 1.96 (*s*, 3H); 2.40 (*s*, 3H); 2.6–3.2 (3H); 3.7 (*s*, 3H); 4.6 (*m*, 1H); 5.8 (*d*, *J* = 10, 1H); 6.7–7.4 (4H); 7.9 (broad, 1H). This crude ester was dissolved in dry ether (5 ml). After addition of $LiAlH_4$ (4 mg, 0.1 mmol) at 0° the mixture was stirred at 0° for 2 hr, then quenched with 3N NaOH to give after workup and chromatography ($CHCl_3$/MeOH/25% NH_4OHaq 19:1:0.01) (±)-**2** (4 mg, 33%), m.p. 162–167°. TLC ($CHCl_3$/n-BuOH/25% NH_4OHaq 2:1:0.02): $R_f = 0.48$. IR: 3400–3300, broad, 2900 broad, 1615, 1605, 1560, 1470, 1445, 1380, 1340, 1290, 1230, 1180, 1140, 1100, 1080, 1040, 1030, 1010, 965, 900, 780, 750, 665, 630 identical with the published IR, of natural **2**.[2] ^{1}H-NMR (360 mHz, pyridine d^5): 2.13 (d, J = 1, 3H); 2.43 (s, 3H); 2.86 (*d* × *d*, *J* = 14 and 9, 1H); 2.95 (*t* × *d*, *J* = 9 and 4, 1H); 3.42 (*d* × *d*, *J* = 14 and 4, 1H); 4.29 (*t*, *J* = 9, 1H); 4.56 (*d*, *J* = 12, 1H); 4.70 (*d*, *J* = 12, 1H); 4.85 (broad, 2H); 5.47 (*d*, *J* = 9, 1H); 7.05 (*d*, *J* = 7, 1H); 7.22 (m, 1H); 7.27 (*t*, *J* = 7, 1H); 7.40 (*d*, *J* = 7, 1H); 11.53 (broad, 1H). MS: 256 ($C_{16}H_{20}N_2O^+$, 100), 237 (63), 223 (19), 196 (24), 183 (77), 168 (32), 155 (66), 108 (21), 101 (27). The TLC-behaviour, ^{1}H-NMR and mass spectra described above for synthetic (±)-**2** are identical to those of naturally derived isochanoclavine I.

Conversion of the trans-*aldehyde* **22** *to* (±) - 6,7 - *seco* - *agroclavine* (**4**) *and to* (±)-*paliclavine* (**5**) (*Scheme* 6)

t-Butyl (4R*,5S*)-N-[5-(2-*methyl*-1-*propenyl*)-1,3,4,5-*tetrahydrobenz*[cd]*indol* - 4 - *yl*]N - *methylcarbamate* (**25**). 2.1N PhLi in benzene/ether 7:3 (1.15 ml, 2.42 mmol) was added with stirring to isopropyltriphenylphosphonium iodide (1.06 g, 2.45 mmol) in THF (20 ml), at r.t. After 1 hr at r.t. a soln of the crude **22** (prepared *in situ* from **20**, 211 mg, 0.615 mmol) in THF (25 ml) was added to the red ylid soln. Stirring of the mixture at r.t. for 1 hr, subsequent addition of sat NH_4Claq, work-up and chromatography (toluene/EtOAc 3:1) gave **25** (151 mg, 72% from **20**), m.p. 221° (ether/CH_2Cl_2). IR: 3480, 3020, 2940, 1683, 1605, 1483, 1450, 1405, 1372, 1356, 1295, 1150, 1078, 908, 875. ^{1}H-NMR: 1.48 (*s*, broad, 9H); 1.82 (*d*, *J* = 2, 3H); 1.88 (*d*, *J* = 2, 3H); 2.75–3.2 (5H); 4.04 (*qa*, *J* = 10.5, 1H); 4.40 (*m*, 1H); 5.20 (*m*, 1H); 6.7–7.0 (2H); 7.0–7.3 (2H); 7.99 (broad, 1H). MS: 340 ($C_{21}H_{28}N_2O_2^+$, 18), 284 (3), 267 (6), 239 (14), 209 (100), 194 (13).

(±) - 6,7 - *Seco* - *agroclavine* (**4**). Trifluoroacetic acid (1.2 ml) was added to a soln of **25** (44 mg, 0.13 mmol) in

CH_2Cl_2 (3.7 ml) at 0°. After 10 min at 0° the mixture was poured into sat $NaHCO_3$aq to give after work-up and chromatography (EtOAc/MeOH 1:1) (±)-**4** (21 mg, 68%), m.p. 202–203 (EtOAc, lit.[15]: 202–205°). UV (EtOH): 218 (4.32), 279 (3.84). IR: 3485, 3320, 3005, 2940, 2920, 2860, 2800, 1608, 1475, 1442, 1415, 1375, 1338, 1285, 1148, 1105, 1072, 1002, 964, 873, 820. ^{1}H-NMR: 1.88 (*d*, *J* = 1.5, 3H); 1.91 (*d*, *J* = 1.5, 3H); 2.25 (broad *s*, 1H, disappears with D_2O); 2.55 (*s*, 3H); 2.66–2.98 (2H); 3.34 (broad *d*, *J* = 11, 1H); 3.90 (*m*, 1H); 5.16 (*d*, *J* = 10, 1H); 6.80 (*m*, 1H); 6.93 (broad *s*, 1H); 7.18 (*m*, 2H); 8.01 (broad, disappears with D_2O). ^{1}H-NMR (360 MHz): 1.73 (*s*, 1H, disappears with D_2O); 1.86 (*d*, *J* = 1.5, 3H); 1.90 (**d**, *J* = 1.5, 3H); 2.54 (*s*, 3H); 2.72 (*d* × *d*, *J* = 15 and 10, 1H, irr. at 3.32→*d*, *J* = 10); 2.83 (*d* × *t*, *J* = 4 and 9, 1H, irr. at 3.32→*t*, *J* = 9, irr. at 3.88→*d* × *d*, *J* = 9 and 4); 3.32 (*d* × *d*, *J* = 15 and 4, 1H, irr. at 2.72→*d*, *J* = 4); 3.88 (*d* × *d*, *J* = 10 and 8, 1H, irr. at 5.15→*d*, *J* = 8, irr. at 2.83→*d*, *J* = 10); 5.15 (*d*, *J* = 10, 1H, irr. at 3.88→*s*); 6.78 (*d*, *J* = 6.5, 1H); 6.91 (*s*, 1H); 7.10–7.22 (2H); 7.96 (broad *s*, 1H, disappears with D_2O). MS: 240 ($C_{16}H_{20}N_2^+$, 37), 225 (5), 207 (5), 197 (11), 194 (12), 184 (33), 168 (67), 155 (100). The UV, IR, ^{1}H-NMR and mass spectra of synthetic (±)-**4** as described above are identical to those of naturally derived 6,7-seco-agroclavine.

t-Butyl (4R*,5S*,1'S*) - N - [5 - (2' - *methyl* - 2' - *propen*-1'*ol*) - 1,3,4,5 - *tetrahydrobenz*[cd]*indol* - 4 - *yl*]N - *methylcarbamate* (**26**) *and t-butyl* (4R*,5S*,1'R*) - N - [5 - (2' - *methyl* - 2' - *propen* - 1'*ol*) - 1,3,4,5 - *tetrahydrobenz*[cd]*indolyl*]N - *methylcarbamate* (**27**). The crude aldehyde **22**, prepared *in situ* from **20** (128 mg, 0.37 mmol) in THF (3 ml) was added at r.t. to a soln of 2-propenylmagnesium bromide (prepared from Mg (121 mg, 5 mmol) and 2-bromopropene (0.43 ml, 5 mmol)) in THF (1.5 ml). After 15 min at r.t. addition of sat NH_4Claq, work-up and chromatography (toluene/EtOAc 3:1) gave a 1:3-mixture of **26** and **27** (87 mg, 66% from **20**). Separation of this mixture (31 mg) by medium pressure chromatography (toluene/EtOAc 5:1) furnished the less polar, minor isomer **26** (7 mg), m.p. 159–162° (ether). IR: 3600–3300, 3480, 3040–2850, 1680, 1450, 1370, 1150. ^{1}H-NMR: 1.51 (*s*, 9H); 1.98 (*s*, 3H); 2.64 (*s*, 3H); 3.05–3.25 (2H); 3.47 (1H); 4.22 (*m*, 1H); 4.74 (*m*, 1H); 5.01 (broad *s*, 1H); 5.26 (broad *s*, 1H); 6.93 (broad *s*, 1H); 7.14–7.4 (3H); 8.0 (broad *s*, 1H). MS: 356 ($C_{21}H_{28}N_2O_3^+$, 5), 338 (5), 181 (23), 229 (50), 207 (27), 194 (29), 185 (29), 154 (100). Further elution furnished the more polar major isomer **27** (19 mg), m.p. 186° (ether). 3600–3300, 3480, 3050–2850, 1675, 1450, 1372, 1150. ^{1}H-NMR: 1.51 (*s*, 9H); 1.88 (*s*, 3H); 2.46 (*s*, 3H); 3.0–3.8 (4H); 4.58 (*m*, 1H); 4.85–5.15 (2H); 6.9 (broad *s*, 1H); 6.95–7.3 (3H); 8.02 (broad *s*, 1H). MS: 356 ($C_{21}H_{28}N_2O_3^+$, 5), 338 (5), 281 (18), 229 (49), 207 (25), 194 (30), 185 (30), 144 (100).

(±)-*Paliclavine* (**5**). Trifluoroacetic acid (0.52 ml) was added to a soln of the major **27** (44.6 mg, 0.12 mmol) in CH_2Cl_2 (3 ml) at 0°. After 15 min at 0° the mixture was poured into sat $NaHCO_3$aq to give after work-up and preparative TLC ($CHCl_3$/MeOH/NH_3, 92:7:1) (±)-**5** as the major isolable product (5.2 mg, 17%), m.p. 175–177° (acetone). IR: 3600, 3480, 3350 broad, 3030, 2945, 1608, 1450, 1340, 1265, 1225, 1150, 1100, 1032, 910. ^{1}H-NMR (360 MHz): 1.70 (broad *s*, disappears with D_2O); 1.86 (*s*, 3H); 2.40 (*s*, 3H); 3.05 (*d* × *d*, *J* = 16 and 2, 1H); 3.17 (*d* × *d*, *J* = 16 and 2, 1H); 3.37 (*d* × *d*, *J* = 8 and 2, 1H, irr. at 4.21→*d*, *J* = 2); 3.56 (*m*, 1H); 4.21 (*d*, *J* = 8, 1H); 4.86 (*s*, 1H); 4.91 (*s*, 1H); 6.90 (*d*, *J* = 7, 1H); 6.97 (*s*, 1H); 7.13 (*d* × *d*, *J* = 8 and 7, 1H); 7.22 (*d*, *J* = 8, 1H); 8.98 (broad *s*, 1H, disappears with D_2O). MS: 256 ($C_{16}H_{20}N_2O^+$, 2), 238 (7), 237 (8), 198 (3), 197 (3), 196 (3), 187 (24), 186 (36), 185 (36), 170 (17), 156 (56), 155 (100), 154 (34). The IR, ^{1}H-NMR and mass spectra of (±)-**5** described above are identical to those of natural paliclavine.

Conversion of the cis*-aldehyde* **21** *to* (±)*-costaclavine* (**6**) *and to* (±)*-8-epi-costaclavine* (**32**) (*Scheme* 7)

Methyl (Z) - (4R*,5S*) - 3 - [4 - (*t* - *butoxycarbonyl*)*methylamino* - 1,3,4,5 - *tetrahydrobenz*[cd]*indol* - 5 - *yl*]-2 - *methylpropenoate* (**28**). Methyl 2-trimethylsilylpropionate[28] (200 mg, 1.25 mmol) in THF (1 ml) was added dropwise at −78° to a soln of lithium diisopropylamide, freshly prepared from diisopropylamine (0.19 mg, 1.35 mmol) and n-BuLi (1.25 mmol) in THF/hexane (2.7 ml, 3:1). After 10 min at −78° the crude *cis*-**21**, prepared *in situ* from **20** (107 mg, 0.31 mmol) in THF (1.5 ml) was added at −78°. The mixture was stirred at −78° for 45 min, then poured onto sat NH_4Claq to give after work-up and rapid chromatography the *cis*-fused (*Z*)-**28** (93 mg, 75% from **20**), m.p. 194° (ether). IR: 3485, 3010–2860, 1715, 1682, 1608, 1443, 1392, 1368, 1355, 1190, 1150. ^{1}H-NMR: 1.40 (*s*, 9H); 1.82 (*d*, *J* = 2, 3H); 2.71 (*s*, 3H); 2.92 (*d* × *d*, *J* = 15.5 and 5, 1H, irr. at 4.64→*d*, *J* = 15.5); 3.20 (*m*, 1H, irr. at 4.64 *d* × *d*, *J* = 15.5 and 2); 3.75 (*s*, 3H); 4.64 (*qi*, *J* = 5, 1H); 5.04 (*d* × *d*, *J* = 11 and 4.5, 1H, irr. at 5.95→*d*, *J* = 4.5); 5.95 (*d* × *d*, *J* = 11 and 2, 1H); 6.75–7.15 (4H); 7.95 (broad s, 1H). MS: 384 ($C_{22}H_{28}N_2O_4^+$, 7), 301 (7), 284 (22), 283 (22), 254 (100), 221 (48), 197 (13), 183 (11), 168 (15), 155 (26).

Methyl (4R*,5S*) - 3 - [4 - (*t* - *butoxycarbonyl*)*methylamino* - 1,3,4,5 - *tetrahydrobenz*[cd]*indol* - 5 - *yl*]-2 - *methylpropionates* (**29**). A soln of the *cis*-fused (*Z*)-28 (350 mg, 0.91 mmol) in MeOH (17 ml) was shaken with 10%Pd/Al_2O_3 under H_2 (3 atm) at r.t. for 16 hr. Successive filtration, evaporation and chromatography (hexane/EtOAc 3:1) of the mixture furnished a non-separable mixture of the two diastereoisomers **29** (254 mg, 72%), IR: 3485, 3020–2850, 1730, 1680, 1618, 1607, 1480, 1450, 1393, 1370, 1290, 1255, 1150. ^{1}H-NMR: major signals. 1.12 (*d*, *J* = 7, 3H); 1.5 (*s*, 9H); 1.9–2.4 (2H); 2.5–3.7 (4H); 2.98 (*s*, 3H); 3.77 (*s*, 3H); 4.50 (*m*, 1H); 6.8–7.3 (4H); 8.32 (broad *s*, 1H). MS: 386 ($C_{22}H_{30}N_2O_4^+$, 46), 285 (16), 255 (100), 195 (29), 167 (55).

(5R*,8S*,10S*) - 6,8 - *Dimethylergolin* - 7 - *one* (**30**) *and* (5R*,8R*,10S*) - 6,8 - *dimethylergolin* - 7 - *one* (**31**). Trifluoroacetic acid (5 ml) was added at 0° to a soln of **29** (176 mng, 0.46 mmol) in CH_2Cl_2 (15 ml). After 15 min at 0° the mixture was poured onto sat $NaHCO_3$aq to give after work-up an amorphous residue which was dissolved in CH_2Cl_2 (10 ml). After addition of Me_3Al (0.51 ml, 25% in hexane) the mixture was stirred at r.t. for 1 hr. Addition of sat NH_4Claq at −78° followed by work-up and medium-pressure chromatography (EtOAc/CH_2Cl_2 1:1) furnished the less polar **30** (46 mg), and the more polar **31** (13 mg) and fractions containing both **30** and **31** (29 mg); (overall yield of **30** and **31** = 88 mg, 76% from **29**). The main isomer **30** shows the following spectra: IR: 2390, 3060–2870, 1620. ^{1}H-NMR: 1.30 (d, J = 7, 3H); 1.82 (broad d, J = 12, 1H); 2.15 (m, 1H); 2.5–3.0 (2H); 3.13 (s, 3H); 3.3–3.65 (2H); 3.80 (m, 1H); 6.8–7.35 (4H); 8.24 (broad s, 1H). The minor **31** shows the following spectra: IR: 3480, 3000–2940, 1620. ^{1}H-NMR (360 MHz): 1.49 (*d*, *J* = 7, 3H); 1.77 (*d* × *m*, *J* = 15, 1H); 2.24 (*t* × *d*, *J* = 15 and 7, 1H); 2.69 (*m*, 1H); 2.82 (*d* × *d*, *J* = 15 and 11, 1H); 3.10 (*s*, 3H); 3.40 (*d* × *d*, *J* = 15 and 5, 1H); 3.56 (*d* × *t*, *J* = 13 and 4, 1H); 3.78 (*m*, 1H); 6.94 (*m*, 2H); 7.15–7.35 (2H); 8.04 (broad *s*, 1H).

(±)-8-*Epi-costaclavine* (**32**). A soln of the major lactam **30** (43 mg, 0.18 mmol) in THF (2 ml) was added at r.t. to a suspension of $LiAlH_4$ (13 mg, 0.18 mmol) in THF (1 ml). After 1.5 hr at r.t. addition of sat Na_2SO_4aq, followed by work-up and chromatography (EtOAc/MeOH 2:1) afforded (±)-**32** (30 mg, 74%), m.p. 194° (ether). IR: 3490, 3062, 3010–2800, 1620, 1612, 1480, 1462, 1445, 1420, 1385, 1345, 1315, 1291, 1275. ^{1}H-NMR: 0.92 (*d*, *J* = 7, 3H); 1.30 (*t*, *J* = 12, 1H); 1.73–2.20 (2H); 2.38 (*t*, *J* = 11, 1H); 2.62 (*s*, 3H); 2.70 (*m*, 1H); 3.00 (*d*, *J* = 8, 2H); 3.17–3.60 (2H); 6.90 (*m*, 2H); 7.2 (*m*, 2H); 8.19 (broad *s*, 1H). ^{1}H-NMR (360 MHz): 0.91 (*d*, *J* = 7, 3H, irr. at 2.04→*s*); 1.28 (*m*, 1H); 1.85 (*d* × *t*, *J* = 13 and 3, 1H); 2.04 (*m*, 1H); 2.33 (*t*, *J* = 12, 1H, irr. at 2.04→*d*, *J* = 12); 2.57 (*s*, 3H); 2.67 (*d* × *d*, *J* = 12 and 4, 1H, irr. at 2.04→*d*, *J* = 12); 2.99 (*d*, *J* = 8, 2H, irr. at 3.41→*s*); 3.27 (*d* × *t*, *J* = 13 and 4, 1H, irr. at

3.41→$d \times d$, J = 13 and 4, irr. at 1.35→broad s); 3.41 (m, 1H, irr. at 3.27→t, J = 6); 6.88 (m, 2H); 7.16 (m, 2H); 8.21 (broad s, 1H). MS: 240 ($C_{16}H_{20}N_2^+$, 100), 225 (6), 197 (20), 182 (6), 167 (11), 154 (21), 144 (33), 127 (10), 120 (23). The IR, ^{1}H-NMR and mass spectra are identical to those of (±)-**32** obtained by an independent synthesis.[10]

(±)-*Costaclavine* (**6**). The soln of the minor lactam **31** (13 mg, 0.05 mmol) in THF (5 ml) was added at r.t. to a suspension of $LiAlH_4$ (4 mg, 0.10 mmol) in THF (1 ml). After 1.5 hr at r.t. quenching of the mixture with sat Na_2SO_4aq, followed by work-up, and chromatography (EtOAc/MeOH 1:1) gave (±)-**6**, 9.6 mg m.p. 222–224° (sealed capillary). IR: 3499, 3070, 3005–2760, 1620, 1610, 1560, 1508, 1465, 1455, 1445, 1420, 1388, 1360, 1352, 1333, 1328, 1295, 1278, 1242, 1198, 1180, 1160, 1130, 1105, 1072, 1039, 990. ^{1}H-NMR (360 MHz): 0.95 (d, J = 6, 3H); 1.45 (m, 1H); 1.87 (m, 2H); 2.27 (s, 3H); 2.5 (m, 1H); 2.67 (broad s, 1H); 2.75 (d, J = 8, 1H); 2.90 (broad d, J = 16, 1H); 3.30 ($d \times d$, J = 16 and 3, 1H); 3.37 (broad s, 1H); 6.9–7.35 (4H); 7.77 (broad s, 1H). MS: 240 ($C_{16}H_{20}N_2^+$, 100), 225 (4), 197 (16), 182 (5), 167 (8), 154 (15), 144 (21), 127 (6), 120 (11). The IR, ^{1}H-NMR (100 MHz), and mass spectra of (±)-**6** are identical to those of (±)-costaclavine, prepared by an independent synthesis.[10]

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