

178. Stereoselective Total Syntheses of (\pm)-Chanoclavine I and (\pm)-Isochanoclavine I by an Intramolecular Nitron-Olefin/Cycloaddition¹⁾

Preliminary communication

by **Wolfgang Oppolzer** and **J. Ian Grayson**

Département de Chimie Organique, Université de Genève, CH-1211 Genève, Switzerland

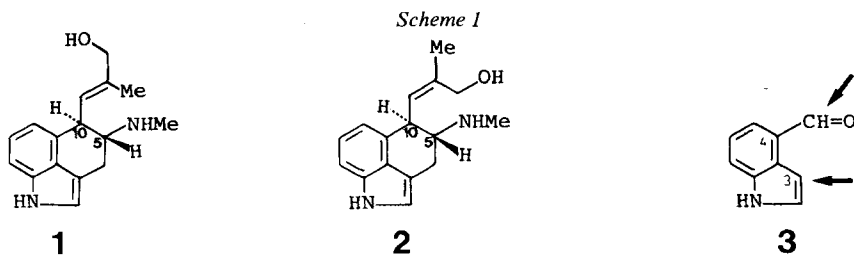
(6. VIII. 80)

Summary

The racemic alkaloids chanoclavine I (**1**) and isochanoclavine I (**2**) have been synthesized stereoselectively from indole-4-carbaldehyde (**3**) by a sequence of 11 operations in overall yields of 14% and 2.4%, respectively. The key step **6** \rightarrow **8** (*Scheme 2*) involves a transient nitron **7** which undergoes a regio- and stereoselective intramolecular cycloaddition to a 1,2-disubstituted olefinic bond.

Intramolecular additions of *C*-alkenyl- and *N*-alkenyl-nitrones have received increasing attention in the field of natural product synthesis in recent years²⁾. Continuing earlier work on analogous additions to styrenes [6], we have now exploited an intramolecular cycloaddition of a nitron to a 4-vinylindole for the synthesis of the ergot alkaloids chanoclavine I and isochanoclavine I.

Chanoclavine I and its olefinic stereoisomer isochanoclavine I, isolated from *Claviceps purpurea* at Sandoz Ltd., Basel, have been assigned structures **1** and **2** (*Scheme 1*) [7]. The racemic alkaloid **1** was first synthesized by a multistep approach

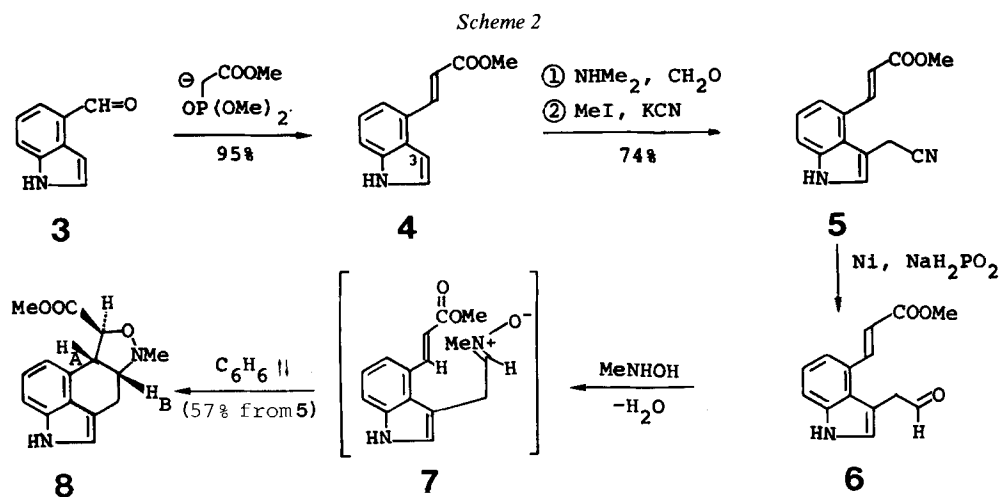


¹⁾ Presented at the 6th Symposium on Heterocyclic Chemistry, Mulhouse, July 3, 1980.

²⁾ Reviews: [1]. For the first observation of an intramolecular *C*-alkenyl nitron addition see [2]. For pertinent applications see the use of *C*-alkenyl nitrones in the synthesis of (\pm)-bisabolol [3a] and (\pm)-biotin [3b], and of *N*-alkenyl nitrones in the synthesis of (+)-luciduline [4a] and (\pm)-cocaine [4b]; for a systematic regiochemical study see [5].

from 5-nitro-2-naphthol in about 0.3% overall yield [8]³⁾. We chose the known [10] and readily available⁴⁾ aldehyde **3** as a bifunctional starting material which allows the elaboration of the dipolarophile at the aldehyde group and the introduction of the dipole chain at C(3). Thus in contrast to most other syntheses of ergolines⁵⁾ the unprotected indole nucleus is to be carried intact throughout the synthesis⁶⁾. *Horner-Emmons* reaction of the aldehyde **3** (1.06 mol-equiv. of the anion prepared from methyl dimethylphosphonoacetate and NaH, THF, 0° then +20°, 1.5 h) gave after crystallization (ethyl acetate) the ester **4**⁷⁾ (m.p. 125–126°, 95%). Functionalization of **4** at C(3) by the following sequence: 1) *Mannich* reaction with 1.14 mol-equiv. of 40% aq. Me₂NH-solution, 1.14 mol-equiv. of 34% aq. CH₂O-solution, HOAc, 0° then +25°, 18 h; 2) alkaline work-up and treatment of the crude *Mannich* product with an excess of sat. aq. KCN-solution and MeI in 2-propanol 0° → +20°, 18 h, furnished after crystallization (hexane/ethyl acetate) the nitrile **5**⁷⁾ (m.p. 172–174°, 74%). Selective reduction of the nitrile group in **5** with an excess of *Raney* nickel and sodium hypophosphite in pyridine/acetic acid/water 2:1:1 (45°, 1.5 h) [14] gave the crude aldehyde **6**⁷⁾ in high yield.

Now the stage was set for the crucial cycloaddition step. Consecutive condensation of the crude aldehyde **6** with *N*-methylhydroxylamine (2 mol-equiv.) in benzene/methanol 10:1 and heating the resulting solution of the transient nitron **7** for 2.5 h at reflux with azeotropic removal of water furnished after crystallization (hexane/THF) the pure *cis*-fused isoxazolidine **8**⁷⁾⁸⁾ (m.p. 176–178°, ¹H-NMR.:



³⁾ After completion of this work another multi-step synthesis of chanoclavine I was published [9].

⁴⁾ For the preparation of 4-cyanoindole see [11].

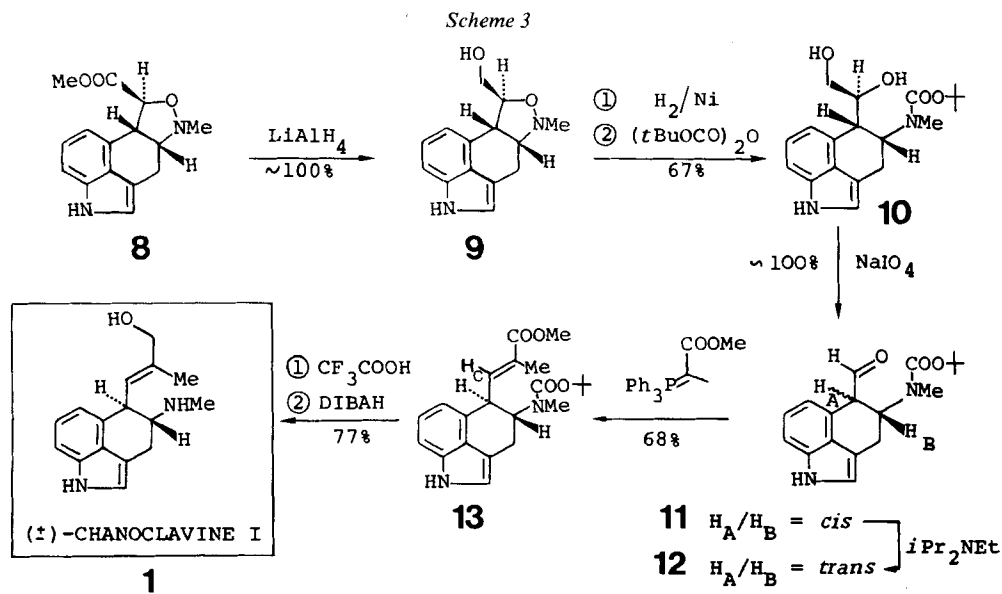
⁵⁾ E.g. [8] or the reported syntheses of lysergic acid [12].

⁶⁾ This strategy parallels the biosynthesis of **1** insofar as it starts from tryptophan and involves C(5),C(10)-bond formation of a 3,4-disubstituted indole intermediate [13].

⁷⁾ UV., IR., ¹H-NMR. and MS. are in full agreement with the assigned structure.

⁸⁾ The ¹³C-NMR. agrees with the assigned structure.

$J(AB)=7$ Hz, 57% yield from the nitrile **5**). Conversion of the key cycloadduct **8** to the racemic forms of the alkaloids **1** and **2** was accomplished as follows (Schemes 3 and 4). Reduction of **8** with an excess of LiAlH_4 (THF, 20° , 1 h) gave the alcohol **9**⁷ (solid, m.p. $65-70^\circ$, darkens rapidly on attempted crystallization, 95%) which underwent smooth hydrogenolysis of the N,O-bond (Raney nickel/ H_2 , MeOH, 20° , 40 min); selective protection of the crude methylamine (1.4 mol-equiv. of di-*t*-butyl dicarbonate [15], 1.4 mol-equiv. of 1N NaOH in THF/ H_2O 2:1, 20° , 2.5 h) gave, after chromatography (SiO_2 , ethyl acetate), the diol carbamate **10**⁷ (solid, m.p. $80-83^\circ$ (dec.), 67% from **9**). Oxidative cleavage of the diol **10** with NaIO_4 (1.1 mol-equiv., MeOH/ H_2O 2:1, 0° , 15 min) yielded initially the *cis*-aldehyde **11**⁷ (gum, $^1\text{H-NMR}$.: $J(AB)=4$ Hz) which epimerized slowly on standing to the more stable *trans*-isomer **12**. Complete epimerization of **11** by treatment with ethyl-diisopropylamine in CHCl_3 at 20° furnished the *trans*-aldehyde **12** (solid, dec. at $200-210^\circ$ without melting, $^1\text{H-NMR}$.: $J(AB)=11$ Hz, 99% from **10**). Wittig reaction of **12** using crystalline (*a*-carbomethoxyethylidene)triphenylphosphorane [16] in CH_2Cl_2 at 60° for 2 days yielded after crystallization (hexane/ethyl acetate) the pure (*E*)-olefin **13**⁹ (m.p. $218-221^\circ$, $^1\text{H-NMR}$.: $\delta_{\text{HC}}=6.87$ ppm, *d*, $J=10$ Hz, 68% from **10**). Mild removal of the *t*-butoxycarbonyl group by treatment of **13** with an excess of trifluoroacetic acid in CHCl_3 at 0° for 3 h and subsequent reduction of the ester group (excess of diisobutylaluminium hydride, THF, 20° , 2 h) gave, after chromatography (SiO_2 , 1% sat. aq. NH_4OH in $\text{CHCl}_3/\text{MeOH}$ 9:1), and crystallization (acetone), (\pm)-chanoclavine I (**1**) (m.p., sealed capillary $185-186^\circ$ (dec.), 77% from **13**). The crystalline racemic alkaloid **1** shows UV. (MeOH), IR.

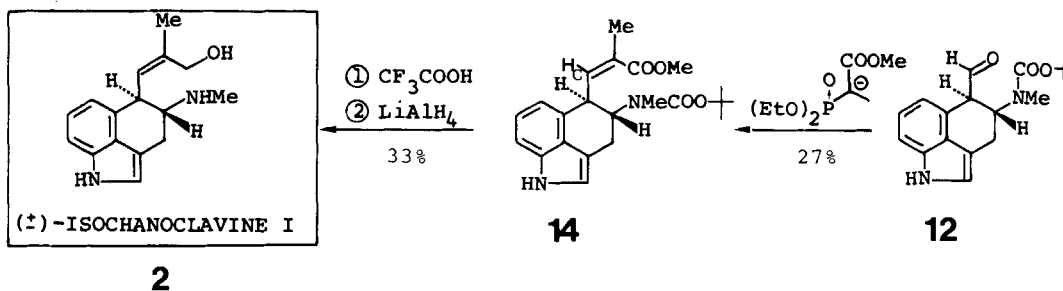


⁹) No (*Z*)-ester **14** could be detected in the crude reaction mixture (TLC.).

(KBr), $^1\text{H-NMR}$. (360 MHz, (D_5) pyridine) and MS. identical to those of natural chanoclavine I.

We were also pleased to find that *Horner-Emmons* reaction of the aldehyde **12** with the anion prepared from methyl (diethyl-*a*-phosphono)propionate and NaH in THF at 0° for 18 h furnished after chromatography (SiO_2 , toluene/ethyl acetate 9:1) and crystallization (pentane/ether) the (*Z*)-olefin **14**¹⁰⁾ (m.p. 192–194°, $^1\text{H-NMR}$.: $\delta_{\text{HC}} = 6.02$ ppm, *d*, $J = 10$ Hz, 27%). Consecutive treatment of the protected ester **14** with trifluoroacetic acid and an excess of LiAlH_4 in ether at 0° for 2 h, followed by chromatography (SiO_2 , 1% sat. aq. NH_3 -solution in $\text{CHCl}_3/\text{MeOH}$ 9:1) gave (\pm)-isochanoclavine I (**2**) (m.p. 162–167°, 33% from **14**) identified by spectral comparison¹¹⁾ with a sample of natural origin.

Scheme 4



In summary, the above routes lead to the otherwise not easily accessible alkaloid (\pm)-**1** in 14% overall yield from **3** and for the first time to its even scarcer isomer isochanoclavine I (**2**). Work is in progress to extend this and related approaches to the enantioselective syntheses of ($-$)-**1**, ($-$)-**2** and other ergot alkaloids.

Financial support of this work by the *Swiss National Science Foundation*, *Sandoz Ltd*, Basel and *Givaudan S.A.*, Vernier is gratefully acknowledged. We are indebted to *Sandoz Ltd*, Basel for a generous supply of 4-cyanoindole and a sample of natural chanoclavine I and are grateful to Professor *D. Arigoni* for kindly providing a sample of natural isochanoclavine I. Our thanks are due to Mr. *J. P. Saulnier* and to Mrs. *F. Klöti* for carrying out the NMR. and MS. measurements.

¹⁰⁾ Apart from another non-identified side product no (*E*)-isomer **13** was found in the crude reaction mixture. For predominant formation of (*Z*)-olefins in the *Horner-Emmons* reaction of aldehydes depending on the structure of the reaction partners, counter ion, solvent and temperature see [17] and a recent review [18].

¹¹⁾ UV. (MeOH), IR. (KBr), $^1\text{H-NMR}$. (360 MHz, (D_5) pyridine) and MS.

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