Tetrahedron Letters,Vol.27,No.35,pp 4165-4168,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

ERGOLINE PRECURSORS 2. AN EFFICIENT SYNTHESIS OF C RING BY PALLADIUM (0) CATALYZED REACTIONS

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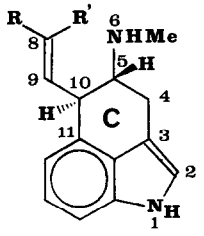
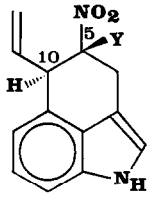
Abstract : A six step synthesis of the tricyclic ergoline synthon **2** is described from indole 4-carboxaldehyde (**3**) in 38-43% overall yield without protection of the indole nucleus. Selective Pd(0)-catalyzed cyclization of functionalized allylic nitro derivatives **6** , **7** and **8** provides **2** with the proper functionality for further elaboration into ergot alkaloids of biological interest.

Ergolines **1** are a group of biologically active compounds which exhibit diverse pharmacodynamic properties and present a formidable challenge to biosynthesis studies[1] and organic synthesis.[2] The simplest clavine system[3] and the well-known lysergic acid have received increasing attention during the last few years. Two main strategies for elaboration of the C ring have been developed. Initially more attention was focused on **C-10/C-11**[4] carbon-carbon bond formation.[2,5] Recently, a very elegant methodology involving **C-5/C-10** ring closure has been proposed via the synthesis of isoxazolidines intermediates[3,6] and intramolecular Diels-Alder reaction.[7]



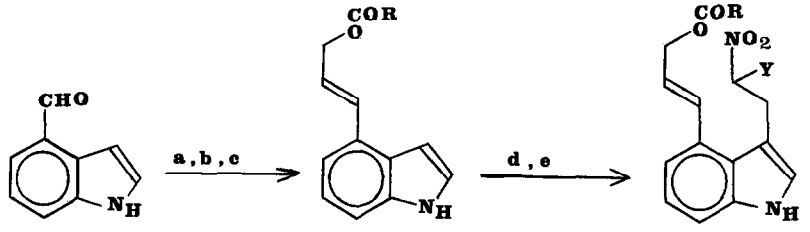


1 **Chanoclavine I** : R=CH_2OH, R'=CH_3
Isochanoclavine R=CH_3, R'=CH_2OH
Secoagroclavine R=R'= CH_3

2 **a** : Y=CO_2Et
b : Y=H

We have previously reported[8] on the intermolecular palladium allylation of nitroacetic esters. We wish to present here a facile synthesis of the ergoline synthon **2**. The key step of our strategy involves **C-5/C-10** intramolecular alkylation of allylic nitro compounds **6**, **7** and **8**.[9]

For the elaboration of the desired substrates we chose the aldehyde 3[10], as a bifunctional starting material which allows their preparation by conventional methods. The Horner-Emmons reaction of this aldehyde with ethyl diethylphosphinoacetate with potassium carbonate as base [11] in refluxing THF gave the unsaturated E ester. Reduction of this ester with $LiAlH_4$ in THF gave the allylic alcohol, which by acylation (Ac_2O in CH_2Cl_2,NEt_3) gave 4. Treatment with ethyl chloroformate in CH_2Cl_2,NEt_3 afforded the corresponding carbonate 5 in 73% overall yield. Classical C-3 functionalization of 4 by treatment with dimethylamine/formaldehyde in acetic acid[12a] gave the gramine derivatives(85%). Conversion of these compounds by treatment with ethyl nitroacetate[13] (1eq) in benzene at reflux gave the expected nitroacetate 6. Under the same conditions methyl nitroacetate in toluene at 100°C gave an adduct which underwent decarbomethoxylation to produce the nitro derivatives 7. Alternatively this compound was obtained directly from 4 and nitroethylene[14], but in lower yield (25%).



3

4 : R = Me
5 : R = OEt

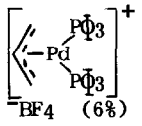
6 : R = Me Y = CO_2Et
7 : R = Me Y = H
8 : R = OEt Y = CO_2Et

(a)$(EtO)_2OPCH_2CO_2Et$,K_2CO_3,24h,THF,reflux;b)$LiAlH_4$,0°C,3h,Et_2O;c)Ac_2O,NEt_3, 0°C,4h,CH_2Cl_2 or $ClCO_2Et$,NEt_3;d)HCHO,$HNMe_2$,AcOH,0°C,4h;e)$NO_2CH_2CO_2Et$, benzene reflux,18h or $NO_2CH_2CO_2Me$,toluene,100°C;50% overall yield.

The palladium (O)-catalyzed cyclization, compounds 6-8 to 2, was examined next.[7,8] Treatment of 6 with Pd (O) catalyst in presence or absence of base under mild conditions in THF afforded regioselective alkylation to give the key synthon 2 in good yield (Table 1).

The success of this cyclization with 6 depends to some extend on the catalyst, cationic palladium catalysts being more efficient (compare entries 1,2) . The cyclization which requires formation of the anion with the allylic acetate, was achieved by organic bases such as NEt_3 or DBU. However 2b was obtained in higher yield by treating the nitroethyl derivative 4 with Pd/KF-alumina.[8b] More interestingly, the same cyclization was performed in good yield under neutral conditions[16] using the carbonate 8 (entry 6).

Table I : Palladium (O) catalyzed cyclization of nitro derivatives 6-8[a]

Entry	Substrate	Catalyst	Base	Temp °C	Time (hr)	Product	Yields%[b]
1	**6**	$Pd(dppe)_2$ (6%)	NEt_3	45	10	**2a**[c]	30
2	**6**	 (6%)	NEt_3	20	15	**2a**	75
3	**7**	$Pd(dppe)_2$ (7%)	DBU or DABCO	20	5	**2b**[c]	20-40
4	**7**	$Pd(dppe)_2$ (7%)	KF/Alumina	20	22	**2b**	80
5	**7**	"	"	65	3	**2b**	85
6	**8**	$Pd(dppe)_2$	none	20	20	**2a**	75

a) all reactions were run in dry THF under argon. b) yields not optimized ; chromatographed purification on silica gel, eluant ether/hexane (1:1), some starting material(10-25%) was recovered in runs 1-3 . c) Products were characterized by IR, ^1H NMR, Mass Spectrometry. The trans stereochemistry was assigned to **2b**.[15]

In summary, we have described here a facile synthesis of ergoline synthon **2** in six steps from aldehyde **3** (38-43% overall yield). This synthetic sequence proceeds without the need for a protecting group. Compounds **2** possess the proper functionality (nitro and vinyl side chains at C_5 and C_{10}, respectively) for further elaboration into natural products. This approach parallels the biosynthetic pathway from tryptophane[1] to this potential precursor of clavines and ergot alkaloids.

Acknowledgments : S.G. thanks Centre National de la Recherche Scientifique (C.N.R.S) and Roussel UCLAF (R.U) for a grant (1984-1987). We are indebted to C.N.R.S and Université Pierre et Marie Curie for their support of this investigation.We also acknowledge Dr L. Nedelec (R.U) for valuable discusions and a generous gift of indole-4-carboxaldehyde and T. Mottay for her technical contribution. We also thank Professor J.Crandall (University of Indiana) for his help with this manuscript.

References and Notes

1) Review : H.G. Floss, Tetrahedron 32, 873 (1976).

2) Reviews : a) A.P. Kozikowski, Heterocycles, 267 (1981) ; b) D.C. Horwell, Tetrahedron, 36, 3123 (1980) ; c) J.E. Saxton, Natural Products, 2, 53 (1985).

3) W. Oppolzer, J.I. Grayson, H. Wegmann and M. Urrea, Tetrahedron, 39, 3695 (1983).

4) The numbering of the ergoline skeleton is used here.

5) a) J. Rebek,Jr, D.F. Tai and Y.K. Shue, J.Am.Chem.Soc., 106, 1813 (1984) and references cited therein ; b) P.J. Harrington and L.S. Hegedus, J.Org.Chem., 49, 2657 (1984) ; c) M.D. Meyer and L. I. Kruse, J.Org.Chem., 49, 3195 (1984) ; d) ibid, J.Org.Chem., 49, 4761 (1984).

6) a) A.P. Kozikowski and H. Ishida, J.Am.Chem.Soc., 102, 4265 (1980) ; b)A.P. Kozikowski and P.D. Stein, J.Am.Chem.Soc., 107, 2569 (1985) ; c) M. Somei, F. Yamada, Y. Karasawa and C. Kaneko, Chemistry Lett., 615 (1981).

7) W. Oppolzer, E. Francotte and K. Battig, Helv.Chem.Acta., 64, 478 (1981)

8) a) J.P. Genêt and D. Ferroud, Tetrahedron Letters, 25, 3579 (1984) ; b) D. Ferroud, J.P. Genêt and J. Muzart, Tetrahedron Letters, 25, 4379 (1984).

9) The intramolecular alkylation of tertiary allylic alcohols catalyzed by $ZnBr_2$ proceeds in poor yields (17%).[6c]

10) A.P. Kozikowski, H. Ischida and Y.Y. Chen, J.Org.Chem., 45, 3350 (1980). For general synthesis see references cited in 2a and 3. We thank Roussel UCLAF for gifts of this material.

11) According to the procedure developed by Z. Mouloungui, A. Gaset and M. Delmas, Synth.Comm., 14, 701 (1984).

12) a) H. Plieninger, C. Wagner, H. Immel, Liebigs Ann.Chem., 743, 95 (1971) ; b) The recent procedure using preformed N,N-dimethyl (methylene) ammonium chloride, A.P. Kozikowski and H. Ishida, Heterocycles, 14, 55 (1980) gave in our hands poor yields and mixture of products.

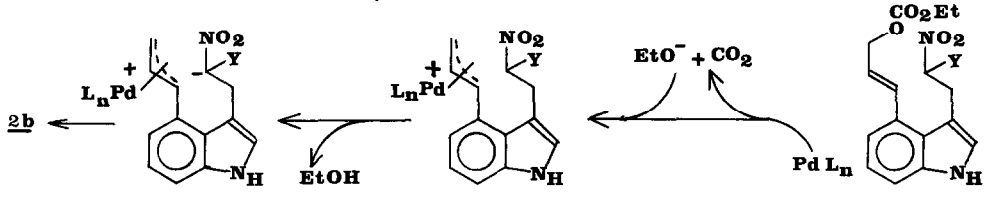
13) D.A. Lyttle and D.I. Weisblat, J.Am.Chem.Soc., 69, 2118 (1947).

14) W.E. Noland and P.J. Hartman, J.Am.Chem.Soc., 76, 3227 (1954).

15) **2a** oil (mixture of diastereoisomers distinguished by ^1H NMR). IR (KBr)1720,1530,1440,1270cm^{-1};^1H NMR ($CDCl_3$,80MHz):8.1(br s,1H);7.25 (m,2H); 7.0(m,2H);5.15(m,1H);4.85(d,J=10Hz,1H);4.35 and 4.1(two q,J=8Hz,2H);3.85 (s,2H);1.3 and 1.05(two t,J=8Hz,3H).

2b white solid, mp=190°C. IR(KBr):3380,1525,1440,1290cm^{-1};^1H NMR ($CDCl_3$,500MHz):8.60(br s,1H);7.15(m,2H);6.98(m,2H);5.88(d.d.d,J=9,10 and 17Hz,1H);5.4(dd,J=1.5 and 10Hz,1H);5.36(d.d,J=1.55 and 17Hz,1H) ; 4.87(d.t=5.5 and 9.5Hz,1H);4.28(d.d,J=9 and 9.5Hz,1H);3.55(m,2H). The assignment of the trans stereochemistry is based on the coupling constant between the C_5 proton and the C_{10} proton(J=9Hz).

16) During this cyclization under neutral conditions (**8** → **2**) the electrophilic intermediate η^3- allyl species **9** gave smooth ring closure at C_{10}.



(Received in France 4 June 1986)