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ASYMMETRIC SYNTHESIS. AN ENTRY INTO TRICYCLIC NITRO ERGOLINE SYNTHON.[§]

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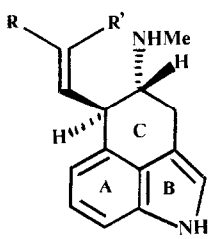
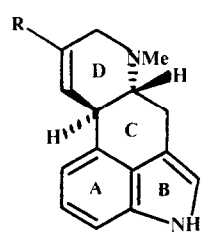
Abstract : A facile and short procedure for optically active tricyclic nitro ergoline synthon **6** (up to 70 % ee) is described. The key step involves enantioselective Pd(o) catalyzed carbocyclization of nitro acetate derivative **4** using chiral ligands on the metal.

The ergot alkaloids represent an important class of compounds which exhibit interesting biological properties, giving rise to clinically useful agents for the treatment of hypertension, migraine attacks, Parkinson's disease etc ...[1] These powerful biological effects of alkaloids based on the ergoline skeleton **1**, **2**, **3** have stimulated biosynthetic investigations[2] and extensive synthetic activity in the last decade.[3,4] Although several elegant routes towards the total synthesis of ergot derivatives have been designed, methods for their enantioselective preparation have been inefficient [4j,4l] and quite limited.[4u]



1 Chanoclavine I R = CH_2OH ; R' = CH_3

2 Secoagroclavine R = R'= CH_3



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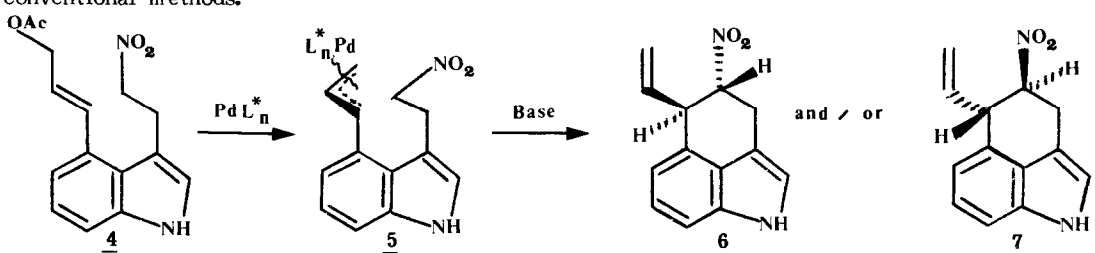
We have been developing the intermolecular palladium catalyzed alkylation of nitroacetic esters[5] and its facile intramolecular version for the synthesis of the C ring of ergoline synthons.[6] In this paper we wish to present an asymmetric synthesis of the nitro ergoline **6** or **7**. The preparation of these chiral synthons was achieved by Palladium - enantioselective carbocyclization of the bifonctional nitroacetate **4**. The derivative **4** has already been synthesized from 4 - indole carboxyaldehyde by conventional methods.[6]



Scheme I

[§] Presented at the "4th International Conference on Chemistry and Biotechnology of Biologically Active Natural Products" August 10, 1987, Budapest, (Hungaria) and at the Royal Chemical Society meeting July 10, 1987, Cambridge, (U.K.).

We felt that palladium(o) complexes modified with chiral ligands might cyclize 4 with high selectivity.[7,8] The rate at which the two catalytic diastereomeric n^3-allyl species 5 react (Scheme I), will determine the enantioselectivity between 6 and 7. In this study the carbocyclisation of 4, was performed with catalysts bearing different chiral ligands on the palladium. The reaction conditions and results are summarized in table I.

Table I: Asymmetric Palladium cyclization of 4 by Palladium Chiral ligand complexes[a]

Entry	Ligand	Conditions time (h)	T (°C)	solvent	base	$[\alpha]_D^{20}$	Yield (%)[b]	ee (%)
1	(+) DIOP	24	25	THF	LDA	+27°	19	37
2	(+) DIOP	20	20	THF	KF-Alumina	+28°	41	39
3	(-) DIOP	20	20	THF	KF-Alumina	-29°	45	39.2
4	(-) NORPHOS	20	20	THF	"	19°	20	26
5	(-)CHIRAPHOS	20	20	THF	"	-46°	35	62.2
6	(-)CHIRAPHOS	3	65	THF	NaH	-14°	30	19
7	(-)DIPAMP	3	65	THF	KF-Alumina	-29°	54	40
8	(+)BINAP	3	65	THF	$K_2CO_3(H_2O)$	+35°	32	47.3
9	(-)CHIRAPHOS	3	65	THF	"	-51°	65	68.9
10	(-)CHIRAPHOS	24	20	DME	KF-Alumina	-52°	28	70.2
11	(-)CHIRAPHOS	2	65	THF	K_2CO_3 (anhydrous)	-49°	62	66.2

a) $Pd(dba)_2$ (7 %) with the appropriate chiral ligand (13 %) is added dropwise, under argon, at the desired temperature, to the nitroacetate 4 mixed with KF-Alumina (200 mg/mmol) or K_2CO_3 (1.5 equiv.) in THF or DME.

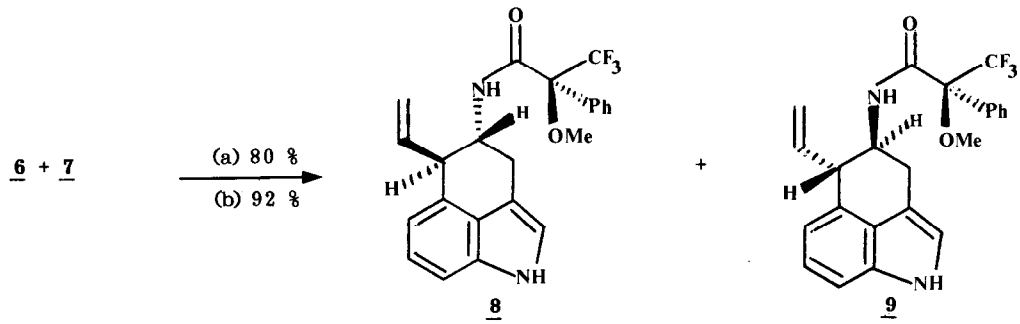
b) Isolated yields after flash chromatography on silica gel (ether/hexane : 1/1).

The palladium promoted carbocyclization of the lithio or sodio nitronates derived from 4 gave poor yields (19-30 %) with 19-37 % ee. (entries 1,6). In comparison, generation **in situ** of the nitronate with heterogeneous bases (e.g. KF-Alumina or K_2CO_3, solid) led to acceptable chemical yields (40-65 %) with substantial enrichment (39-69 % ee) (entries 2,3,7,9,11).

Among the different Pd-chiral phosphines[9] used, we found that Pd-CHIRAPHOS was the most efficient system giving 62-70.2 % ee (entries 5, 10). The ligands BINAP, DIPAMP, NORPHOS and DIOP were less efficient giving moderate ee (26-47 %) (entries 2,3,7,8). Surprisingly[10] in this intramolecular carbocyclization Pd-DIPAMP gave substantial enrichments up to 40 % ee. $Pd(dba)_2$ as the procatalyst using (-) or (+) DIOP produced the two ergoline enantiomeric synthons 6 or 7 (45 % yield) with 39 % ee (entries 2,3).

Finally, on exposing compound 4 to Pd-CHIRAPHOS with K_2CO_3 as the base, we are able to isolate on a practical scale the chiral derivative 6 with an acceptable level of optical purity (69 % ee) entry 9).

In this study, tentative determination of the enantiomeric purity using HPLC with Pirkle column[11] gave unsatisfactory separation of the two enantiomers. Howewer optical purity of 6 and 7 was determined by ^1H-NMR analysis (500 MHz) of 8 and 9. These derivatives were obtained after reduction of 6 and 7 with Zn(Hg), HCl (80 % yield) followed by derivatization (92 % yield) of the primary amine with Mosher reagent[13] methoxy-α-trifluoromethylphenylacetic acid (MTPA) (scheme II). The high field assigment of the absolute configuration has also been possible by NMR from a detailed investigation of MTPA derivatives.[13]



a) Zn(HCl), MeOH, HCl ; b) ClCO - C(CF3)(Ph)(OMe) , NEt_3 in CH_2Cl_2.

Scheme II

In summary this **catalytic** enantioselective Pd(O) promoted C - 5, C - 10 ring closure provides a simple, direct and versatile synthesis of chiral ergoline compounds. Because both enantiomers of the chiral phosphine ligands are available, this method yields to either chiral synthon **6** or **7**. From an economic and quantitative stand point this methodology is the most desirable to synthesize chiral products. This strategy could in principle led to an efficient chiral approach to natural ergoline derivatives such work is presently in progress.

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12 - ^{1}H - NMR ($CDCl_3$, 500 mHz) of **8** (major with (-)chiraphos) and **9** : 8.10 (2s, 1H) ; 7.5 - 6.8 (m) ; 5.87 (m) ; 5.75 (m) ; 5.30 - 4.95 (m) ; 4.68 (m) ; 4.56 (m) ; 3.90 (d,d, J = 9 Hz and 5 Hz) ; 3.80 (m) ; 3.40 - 3.25 (m + 2s) ; 3.15 - 3.03 (m) ; 2.94 - 2.79 (m).

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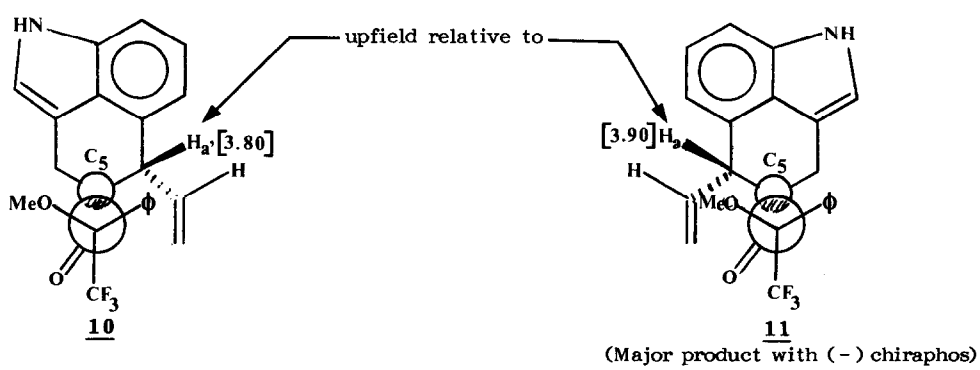
14 - According to the useful NMR configurational correlation scheme developed by Dale and Mosher see reference 13 and Asymmetric Synthesis, Ed. J.D. Morrison, Acad. Press. N.Y., vol. 1, p. 125 - 138, **1983.** This scheme allows the configurational assignment of (R) - MTPA derivatives prepared form partially active amine **7.** It has been concluded that a preferred conformation has the α-CF_3 and carbonyl group of the MTPA moiety eclipsed with the amide carbonyl. Thus, as shown in scheme III the ^{1}H - NMR signal due to H_a in structure **11** appears at lower field (3.90) than that of $H_{a'}$ (3.80) in structure **10.**



10 **11**

(Major product with (-) chiraphos)

Scheme III

(Received in France 12 February 1988)