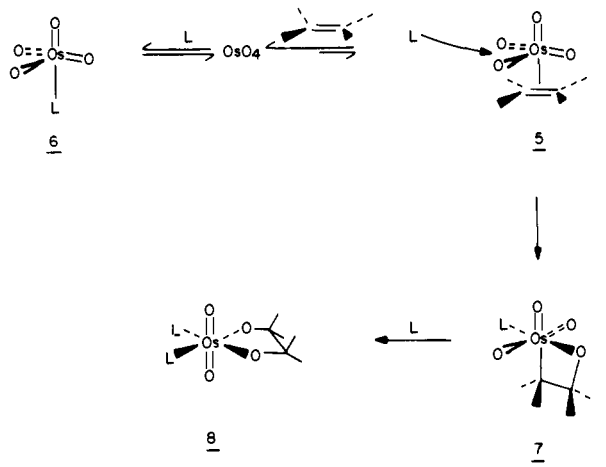
Scheme I



with a second ligand induces formation of the final product **8**, again an 18-electron complex.[17]

Following Scheme I, the stereoselectivity, when L is a chiral ligand, can be seen to arise in the conversion of **5** into **7**. Coordination of a prochiral olefin, such as a symmetrical trans olefin, to OsO_4 gives a pair of enantiomeric intermediates **9** and **10**.[18] Reaction of **9** and **10** with a chiral ligand would be

expected to proceed with different rates owing to differential steric interactions in the pair of diastereomeric transition states. The source of this steric effect may be in the interaction of the methoxy quinoline moiety of **3** and **4** with the olefin substituents.[19] Through examination of molecular models we have been able to rationalize the stereochemical outcome of this reaction, including the opposite stereoselectivities exhibited by **3** and **4**. Although the mechanism is still speculative[20] we have found that this mechanism can at least provide a useful model for prediction of the absolute configuration of the diol products.[21]

In our continuing studies, we are extending the reaction to a wider variety of olefins and alkaloid derivatives and also examining possible catalytic schemes.[22]

Acknowledgment. We are grateful to the National Institutes of Health (GM24551-01) for financial support and to Professor Harry S. Mosher for many helpful discussions.

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(8) Evidence for coordination through the quinuclidine nitrogen was obtained by comparison of the colors of solutions containing OsO_4 (0.14 M) and an equimolar amount of a ligand in toluene. Solutions made with **2**, **3**, or **4** are all a very similar red-orange color, whereas solutions made with quinoline are bright yellow.

(9) Examination of the oxo-stretch region (Os=O) of the IR spectrum of a toluene solution containing 0.14 M OsO_4 and 0.14 M **2** reveals that the 1:1 adduct **6** (L = **2**) is the predominant species (98%). Similarly, a toluene solution containing 0.10 M OsO_4 and the more sterically hindered **3** (0.10 M) contains a mixture (~1:1) of the adduct **6** (L = **3**) and free OsO_4. In contrast, solutions of OsO_4 and **1** give no evidence for complex formation (<5%). However, **1** apparently does coordinate to the metal center at some point along the reaction pathway, since chiral diols are obtained in reactions of olefins with OsO_4 in the presence of **1**.

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(16) Griffith, W. P.; Skapski, A. C.; Woode, K. A.; Wright, M. J. *Inorg. Chim. Acta* **1978**, *31*, L413. As shown in Scheme I, the structure of **6** (L = **2**) is a distorted trigonal bipyramid.

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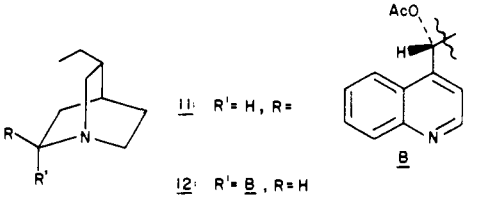
(18) Unsymmetrical prochiral olefins give rise to two diastereomeric sets of enantiomers upon coordination to OsO_4.

(19) In preliminary experiments, we have observed that dihydrocinchonine acetate (**11**) and dihydrocinchonidine acetate (**12**) give rise to optically



active diols with enantiomeric purities substantially lower than those obtained with **3** and **4**. This indicates that the methoxy group of **3** and **4** is of some importance in determining stereoselectivity.

(20) Although we favor the mechanism shown in Scheme I, we have not eliminated the possibility that intermediate **7** is formed by reaction of **6** with the olefin via a direct [2 + 2] cycloaddition.

(21) A more detailed discussion of this stereochemical model will be given in a forthcoming publication.

(22) In preliminary work, we have found that the presence of **3** during the reaction of *t*-$BuNOsO_3$ with styrene results in production of an optically active vicinal amino alcohol with unknown enantiomeric excess.

(23) NSF Predoctoral Fellow, 1976–1979.

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Intramolecular [3 + 2] Cycloaddition Reactions in the Indole Series "The Nitrile Oxide Route to the Ergot Alkaloids". 1. Chanoclavine I

Sir:

The application of dipolar cycloaddition reactions to the synthesis of complex natural products has recently come to be recognized as a very powerful synthetic tool, one equally akin

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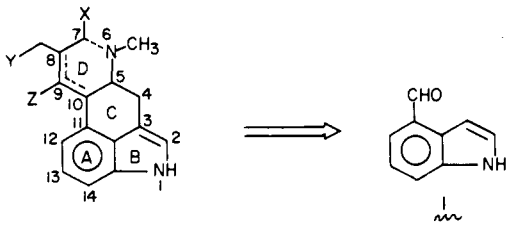
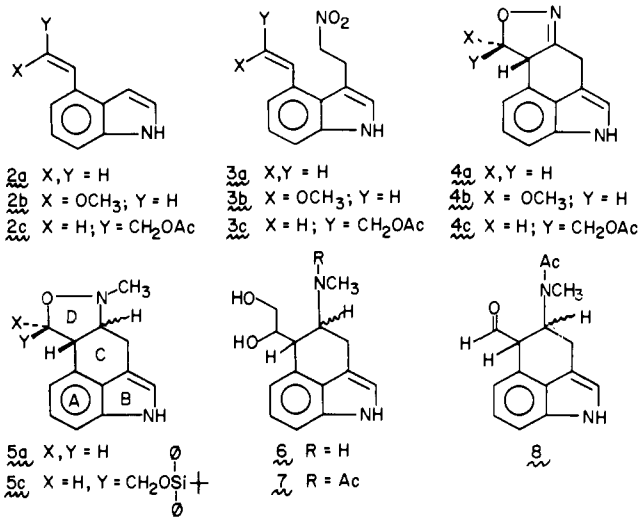
to the Diels–Alder cycloaddition reaction in its potential scope of application.[1]

We have previously detailed a highly efficient method for preparing 4-substituted indoles from substituted *o*-nitrotoluenes.[2] In this communication we now present a strategy for assembling from indole-4-carboxaldehyde, via an intramolecular [3 + 2] cycloaddition reaction, tetracyclic compounds possessing suitably functionalized C rings for elaboration to a diverse number of ergot alkaloids. A total synthesis of chanoclavine I accomplished by this chemistry and described below constitutes just one example of the many products which can be generated through this scheme or variations of it.[3] Our retrosynthetic analysis of the ergoline system takes cognizance of the fact that the strategic bond to consider making in developing a "totally new route" to these products is that linking carbon atoms 5 and 10.



Indole-4-carboxaldehyde (**1**) was thus reacted with methylenetriphenylphosporane and methoxymethylenetriphenylphosphorane to provide the vinylindoles **2a** and **2b,** respectively, or with the anion of ethyl diethylphosphonoacetate to yield, after reduction (AlH_3) and O-acetylation, the indole **2c.**[2] These



products could be converted readily into their respective grammine derivatives in accordance with our newly introduced procedure by exposure to *N,N*-dimethyliminium chloride in methylene chloride for several minutes at room temperature.[4] Reaction of the grammine compounds with excess nitromethane and dimethyl acetylenedicarboxylate in THF at 0 °C for 2 h led to the "key" 3,4-disubstituted indoles **3a–c**.[5] Such materials contained the necessary functionality required for conversion into nitrile oxides with intramolecular interception of the reactive dipole by a neighboring unsaturated linkage.[6] Using a procedure developed by Mukaiyama for the conversion of nitro groups into nitrile oxides, the indoles **3a–c** were accordingly stirred at room temperature with phenyl isocyanate in the presence of a trace of triethylamine.[7] After 24 h, the isoxazolines **4a–c** were isolated in high yield (70–90%). No side products resulting from reaction of the dipole with the electron rich indole nucleus were detected.

The isoxazoline nuclei could in turn be cleanly reduced to the corresponding isoxazolidines. This operation required prior protection of the indole nitrogen by N-acetylation (*N*-acetylimidazole). The moderately basic nitrogen of the isoxazoline was now N-methylated using Meerwein's reagent in nitromethane (0 °C → room temperature), and the intermediate salt was reduced with sodium borohydride in absolute ethanol (10 h, room temperature).[8] Compound **4a** was thus transformed to an 1:1 mixture of the cis- and trans-fused products **5a** (mp 160.5–161 °C) in 60% overall yield. No attempt has presently been made to control the stereoselectivity of this reduction process through the use of more hindered reducing agents. When the standard reduction procedure was applied to isoxazoline **4c,** the acetate group was found to interfere with this conversion. The hydroxyl group was accordingly deprotected (0.5 M K_2CO_3, EtOH–H_2O) and then reprotected as its *tert*-butyldiphenylsilyl ether. Reduction then proceeded cleanly to generate **5c,** also as a 1:1 mixture of cis and trans isomers (mp 143–146 °C). The stereochemistry of this reduction was, as we shall see, of little consequence to the present synthesis efforts.

The isoxazolidines **5a** and **5c,** which should themselves possess interesting biological properties as a consequence of the presence of the phenethylamine network,[9] contain all the functionality necessary for conversion to a host of ergot alkaloids.

From the isoxazolidine **5c,** a synthesis of racemic chanoclavine I is now described. Desilylation ($Bu_4N^+F^-$, THF) of the hydroxyl group and scission of the nitrogen–oxygen bond by hydrogenation over palladium on carbon (MeOH, 6 h) afforded the aminodiol 6 in 94% overall yield. Triacetylation of this compound (Ac_2O, pyridine) followed by selective O-deacetylation with 0.125 M aqueous potassium carbonate in MeOH–H_2O afforded **7** (78% overall). Periodate cleavage of the free diol led to the sensitive key aldehyde **8.** Reaction of aldehyde **8** with the stabilized Wittig reagent, ethyl 2-(triphenylphosphoranylidene)propionate (50 °C, THF, 2 h), afforded the unsaturated ester **9** (mp 220–221.5 °C, 50% overall yield from **7**) of entirely *E* configuration as judged by ^1H NMR analysis. N-Deacetylation was effected by treatment with triethyloxonium fluoroborate in the presence of sodium carbonate in methylene chloride followed by hydrolysis at 0 °C with a 3% aqueous acetic acid solution (80% yield after chromatography on alumina).[10] Completion of the synthesis of (±)-chanoclavine I was accomplished by reducing the unsaturated ester to allylic alcohol by treatment with aluminum hydride in THF (78% yield).

Because of the relative insolubility of this alcohol in most NMR solvents, comparison of the synthetic material with natural chanoclavine I was made through the N,O-diacetylation products. Treatment of racemic chanoclavine I with acetic anhydride–pyridine gave a single, pure crystalline derivative (mp 165–167 °C) which was identical by TLC, IR, ^1H NMR, and MS with the corresponding derivative prepared from natural chanoclavine I.[11] None of the corresponding cis compound, chanoclavine II, could be detected in our synthetic material at this stage. An epimerization at C-10 had thus occurred during the transformation of 6 to **10.** This epimerization could be traced back to intermediate **8,** which needs only to undergo a favorable tautomerization to convert the cis material into the trans compound.

In summary, our scheme is noteworthy for the fact that the

majority of the synthetic operations reported can be carried out in the presence of the unprotected indole nucleus, thus attesting to the mildness of the reaction conditions employed. There exists no need to reduce indole to indoline and then to regenerate the indole nucleus at a latter stage by oxidation as was deemed necessary, for example, in the Kornfeld–Woodward synthesis of lysergic acid.[12]

Further studies being carried out in our laboratories should greatly streamline the scheme presented. The application of this nitrile oxide cycloaddition chemistry to the construction of the rugulovasines and lysergic acid as well as other ergots is presently in progress and will be reported in separate accounts.[13]

Acknowledgments. We are grateful to Dr. John Cassady of Purdue University for the authentic sample of chanoclavine I. This work was supported by the National Institutes of Health through Grant HL 20579-04. We are also indebted to the National Science Foundation, Grant CHE-79-05-185, for providing funds to purchase the 300-MHz Bruker NMR instrument used in these studies. We thank Anthony Ames for acquiring the high-field spectra.

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(13) All new compounds reported had spectral properties and high resolution mass spectral data fully compatible with the assigned structures. Melting points are uncorrected.
(14) Fellow of the Alfred P. Sloan Foundation.

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Binding of 5-Fluoro-L-tryptophan to Human Serum Albumin

Sir:

The rate of synthesis of 5-hydroxytryptamine (serotonin) in the brain appears to be determined by the concentration of tryptophan in the brain[1] which, in turn, is related to concentration levels of this amino acid in the blood plasma.[2,3] It has been demonstrated that tryptophan interacts strongly and stereospecifically with plasma albumin[4] and recently several ^{1}H NMR studies of the complexes formed between albumin and tryptophan have been reported.[5-7] These NMR experiments have not directly addressed the question of the number of binding sites for tryptophan on this protein and have generally been interpreted in terms of exhange rates between free and bound forms of the amino acid that are rapid. By using ^{19}F NMR spectroscopy to examine complexes formed between albumin and 5-fluorotryptophan, we have been able to establish that (1) there are at least two distinct binding loci for tryptophan on human albumin and (2) 5-fluorotryptophan at one of these sites is in slow exchange with the bulk amino acid.

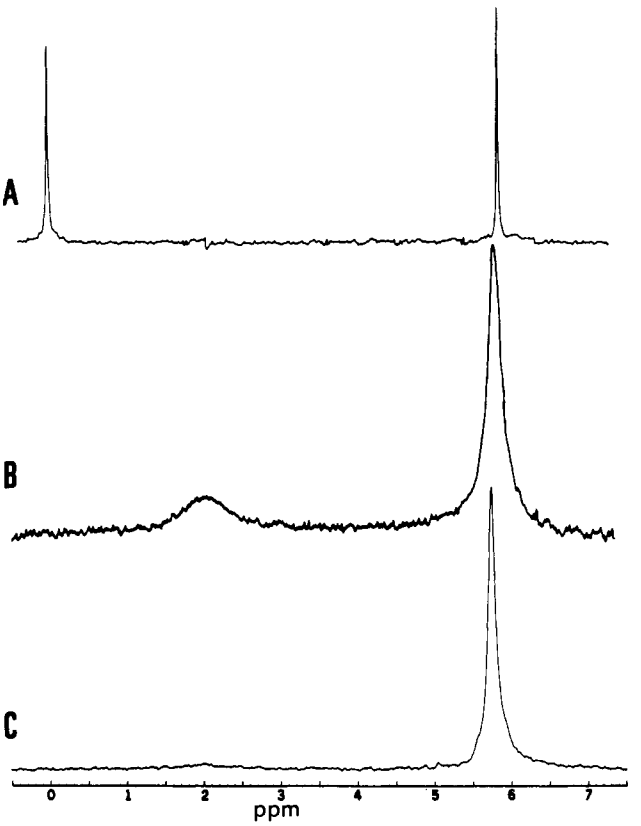

Figure 1. ^{19}F NMR spectra of 5-fluoro-L-tryptophan: trace A, 6 mM 5-fluorotryptophan (proton decoupled); trace B, 3.06 mM 5-fluoro-L-tryptophan and 1.03 mM human serum albumin (proton decoupling gated on during acquistion of the free induction decay); trace C, 3.06 mM 5-fluoro-L-tryptophan, 1.03 mM human serum albumin, and 4.00 mM L-tryptophan (gated proton decoupling). All spectra were recorded using a Varian Associates XL-100 spectrometer operating at 94.14 MHz. Sample temperatures were controlled at 25 ± 1 °C. The reference peak at 0 ppm was derived from a capillary containing a solution of *p*-fluorotoluene in toluene.

Commercial 5-fluorotryptophan (Aldrich) was resolved via its methyl ester by chymotryptic hydrolysis following the procedure of Tong et al.[8] The L isomer (mp 255–258 °C) showed a specific rotation $[\alpha]_D$ −19.5° at pH 5.9. Fatty acids were removed from crystallized human albumin (Schwartz-Mann) by Chen's procedure[9] and the protein had <0.15 mol of fatty acid/mol after this treatment. Chromatographic and electrophoretic experiments showed that the protein used for the NMR experiments was >80% monomeric. Samples for NMR spectroscopy were made up in a solvent containing 0.15 M NaCl, 0.05 M phosphate buffer, 1 mM EDTA, and 5% deuterium oxide and were adjusted to pH 7.4.

Some results are shown in Figure 1. Under conditions of complete proton decoupling the fluorine spectrum of 5-fluoro-L-tryptophan consists of a sharp singlet 5.843 ppm upfield from the reference signal provided by a capillary containing a 10% solution of 4-fluorotoluene in toluene (trace A). When human albumin is present at a concentration ratio of 1:3, the signal at 5.8 ppm is broadened substantially and a new resonance with a line width of ~60 Hz appears at 2.06 ppm (trace B). Experiments with glycerol solutions of the fluoroamino acid confirmed that the line widths were not due to sample viscosity. When L-tryptophan is added to a mixture of 5-fluoro-L-tryptophan and albumin two effects are noted: (1) the intensity of

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