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THE INTRAMOLECULAR NITRILE OXIDE CYCLOADDITION (INOC) ROUTE TO THE ERGOT ALKALOIDS: USE OF THE ISOXAZOLINE TO γ-AMINO ALCOHOL CONVERSION IN THE TOTAL SYNTHESIS OF (+)-PALICLAVINE

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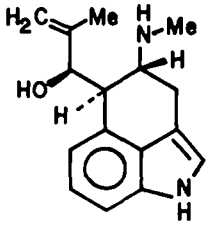
Abstract - A total synthesis of the ergot alkaloid paliclavine (20) in optically active form is described. The synthesis scheme is based on the intramolecular dipolar cycloaddition reaction of a nitrile oxide to a neighboring olefinic appendage bearing an allylic asymmetric center. The extent of diastereofacial selection in the intramolecular nitrile oxide cycloaddition (INOC) reaction was found to be marginal. A single-crystal X-ray analysis has established the complete stereostructure of the isoxazoline 15 prepared from the "major" INOC product. The dependence of the reduction stereochemistry of the isoxazolinium salt 15a on the nature of the reducing agent is discussed.



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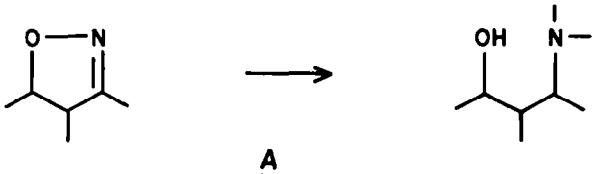
In this article we report in part our efforts to synthesize various members of the ergot alkaloid family.[1] Specifically, we shall focus on the utilization of the intramolecular nitrile oxide cycloaddition reaction to key formation of the crucial C_5 - C_{10} bond of the ergot alkaloid paliclavine.[2] In the context of the total synthesis, the ability of an isoxazoline to serve as a masked γ-amino alcohol will be amply demonstrated.[3]

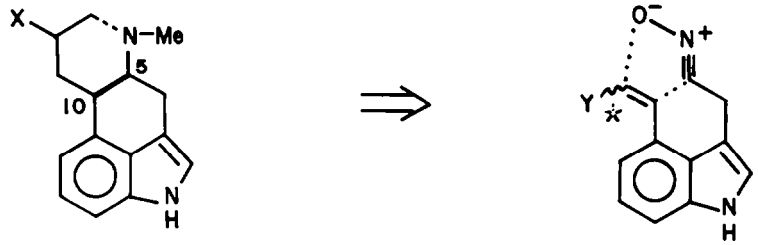


A

While many varied ergot structures are known, and a few of these compounds have been prepared by total synthesis and many more by semi-synthesis, no immediately general strategy capable of encompassing all of the known structures in an efficient manner has actually evolved to date.[4]

At the onset of our work in this area, we believed that the development of an efficient means for linking the C_5 - C_{10} bond of the C-ring of these structures constituted the key to a

general synthesis strategy. After considerable experimentation and thought, it was realized that formation of this carbon-carbon bond might be effected under very mild conditions through use of a reactive dipole, a nitrile oxide. The nitrile oxide strategy envisioned would allow us to not only make the C_5 - C_{10} bond under mild conditions but, moreover, it would locate a nitrogen atom

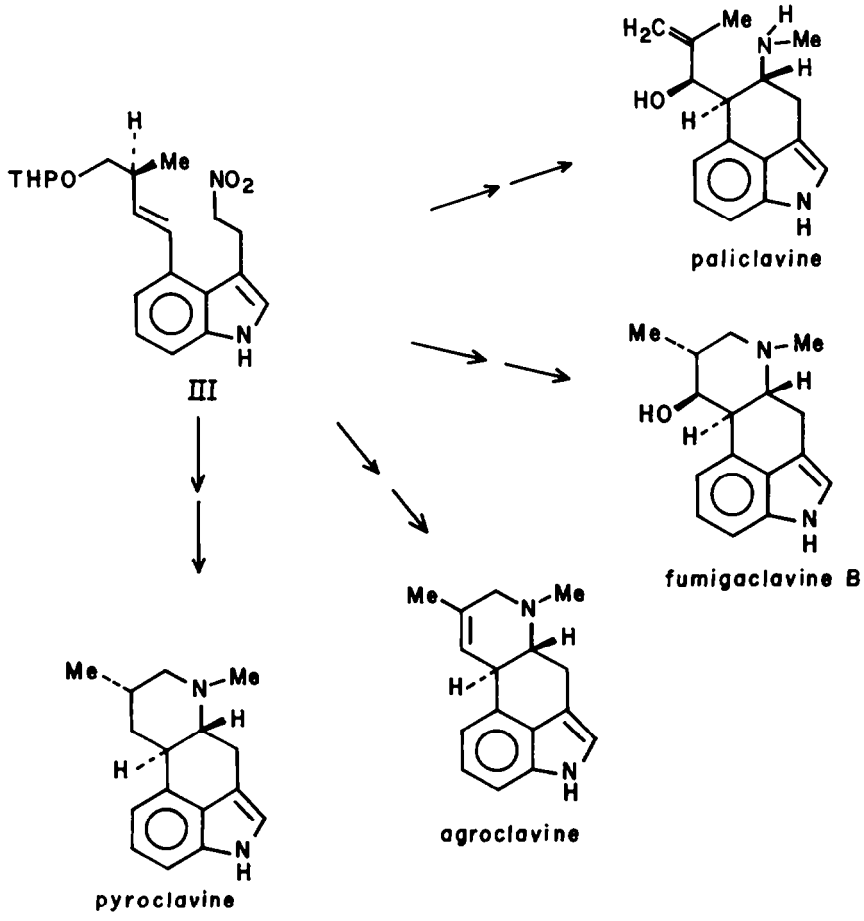


I II

at the correct position required for elaboration to an ergot alkaloid. Since some of these compounds do possess a hydroxyl group at C_9, the oxygen functionality introduced at the starred position in II is also valuable. Additionally, such functionality could prove useful in chemical manipulations involving elongation of this C-ring appendage.

Our first successful implementation of the strategy described above was directed toward the total synthesis of chanoclavine I. In further exploring various aspects of this strategy, we decided to select a target whose synthesis would pass through an intermediate which might itself serve as a precursor to a wide variety of other ergot products. Our second generation synthesis thus focussed on paliclavine via intermediate III, a product which might also serve as a precursor to fumigaclavine B, agroclavine and pyroclavine to name but a few. In this article then, the

SCHEME I. A General Ergot Precursor



synthesis of paliclavine in optically active form is described. Since the methods and techniques developed for the chanoclavine I synthesis are similar to those utilized in the paliclavine synthesis, we shall make no further mention of the earlier work other than to point out that a communication describing this effort was published in 1980.[5]

Results and Discussion

The key starting material in all of our ergot directed studies has been indole-4-carboxaldehyde, a compound readily synthesized from the ester of 2-methyl-3-nitrobenzoic acid by the Leimgruber-Batcho method as described by us.[6] Since the first step involved in the elaboration of the indole-4-aldehyde to paliclavine required that we elongate the aldehyde group via a trans-selective Wittig reaction, the indole nitrogen was N-tosylated in order to insure a high yield of condensation product. We had hoped that the chirality present in the C_4-appendage might control diastereofacial selection in the INOC reaction. The *R,S* nature of the phosphonium salt required for this elongation process was thus selected on the basis of theoretical calculations which support the operation of the anti-periplanar effect in the addition of nitrile oxides to olefins.[7] This effect suggests that a preference exists for the addition of an electrophile anti to the larger substituent present at the allylic asymmetric center. Thus, we made the assumption that

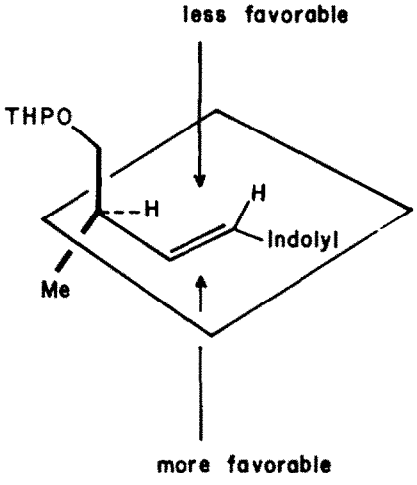
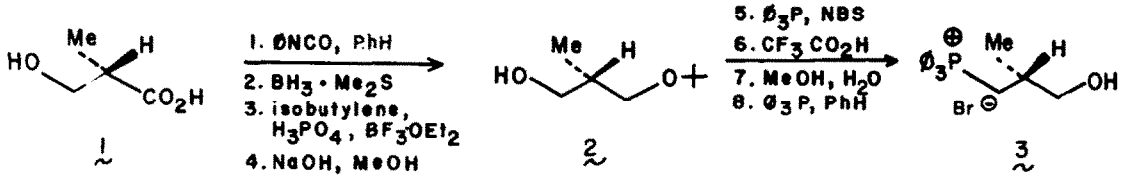


Figure 1. The direction of approach of nitrile oxide to an olefin containing an allylic asymmetric center.

the (tetrahydropyranyloxy)methyl group would function as the larger group and that cycloaddition would occur through the allylic conformation depicted in Figure 1.[8] The foregoing analysis required that we prepare the *R*-phosphonium salt 3. This was easily accomplished by starting with optically active 3-hydroxy-2-methylpropionic acid, available from the oxidative fermentation of isobutyric acid.[9] The hydroxy group of the acid was protected as its carbanilate and the carboxyl group was reduced with the borane-dimethyl sulfide complex. Protection of the new hydroxyl group as its tert-butyl ether, base hydrolysis of the carbanilate, transformation of alcohol 2 to bromide, cleavage of the tert-butyl group with trifluoroacetic acid and hydrolysis

SCHEME 2. Synthesis of an Optically Active γ-hydroxyphosphonium Salt



of the trifluoroacetate gave the corresponding bromoalcohol [$[\alpha]_D^{25}$ = -8.1° (c 21.0, $CHCl_3$)]. On refluxing this bromide with triphenylphosphine in benzene, the required phosphonium salt 3 formed in 98% yield [$[\alpha]_D^{25}$ = +0.098° (c 10.2, DMSO)].[10]

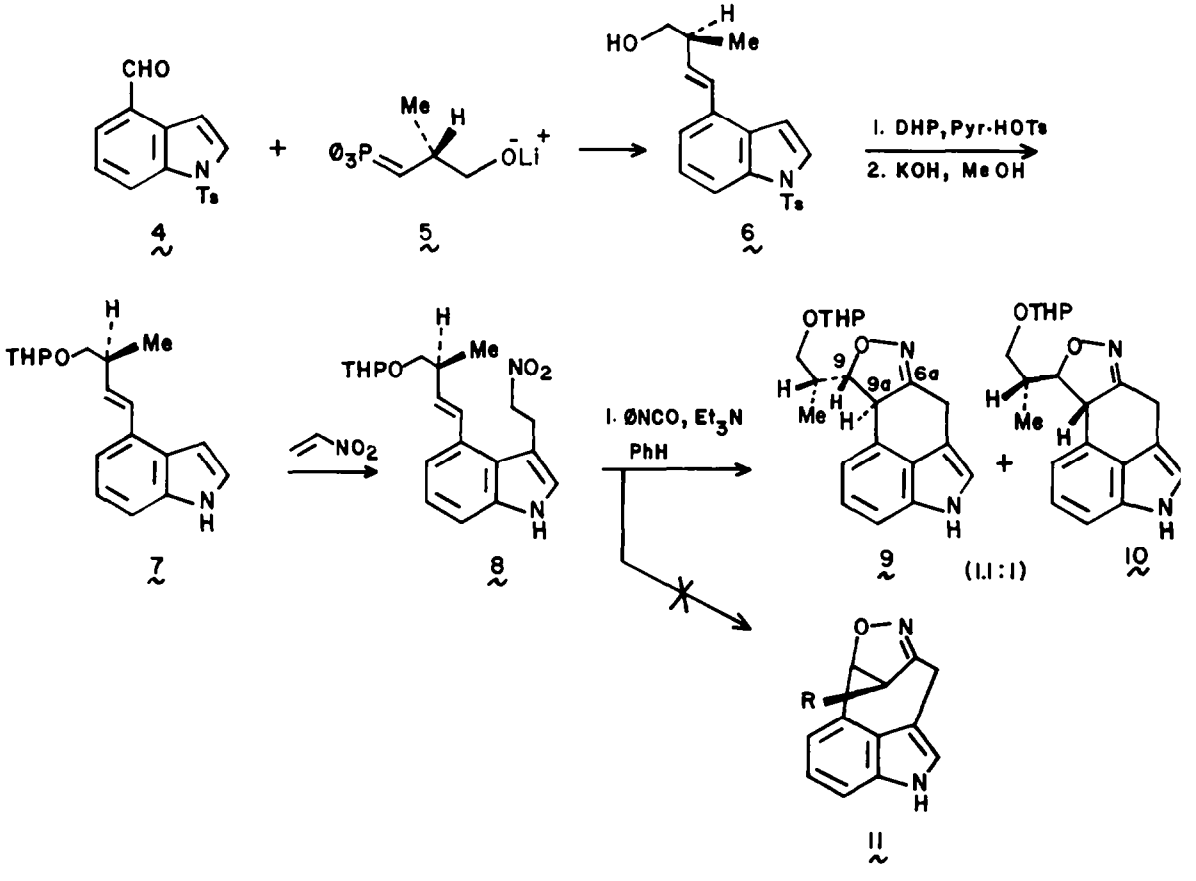
Phosphonium salt 3 was treated dropwise with two equivalents of n-butyllithium at -78°C in tetrahydrofuran and the reaction mixture slowly brought to room temperature. The red solution of phosphorane was then cooled to -78°C and treated with a tetrahydrofuran solution of the N-tosylindole 4.

After warming to room temperature over 2 h, workup in the normal fashion yielded a 12:1 mixture of the trans- and cis-olefin isomers. Thus, in this case, as in all previous examples studied in our laboratories, the γ-oxido ylide reagent reacts with the aromatic aldehyde 4 to generate predominantly trans-olefin 6. While it has been suggested that such selectivity may result from the operation of an intrinsic Schlosser mechanism, recent experimental evidence indicates that the polar end group may instead influence the manner in which aldehyde and ylid initially come together, or more importantly control the rates of dissociation and elimination.[12] Irregardless of the actual mechanistic details of this process, the high trans-selectivity was extremely desirable for the present synthetic undertaking.

After chromatographic separation of the cis- and trans-isomers, the hydroxyl group of the pure trans compound 6 was protected as its tetrahydropyranyl ether. Protection of the hydroxyl group by either silylation or acetate formation was found unsuitable, for these groups were unable to withstand either the base conditions required for removal of the N-tosyl group, or the subsequent Meerwein's salt reaction[5] needed to effect N-methylation of the isoxazoline nitrogen.

The N-tosyl group was cleaved by the action potassium hydroxide in methanol in order to permit incorporation of the C_3-nitroethyl group. In previous work, this group was generally

SCHEME 3. Construction of an Appropriately Functionalized Tetracycle



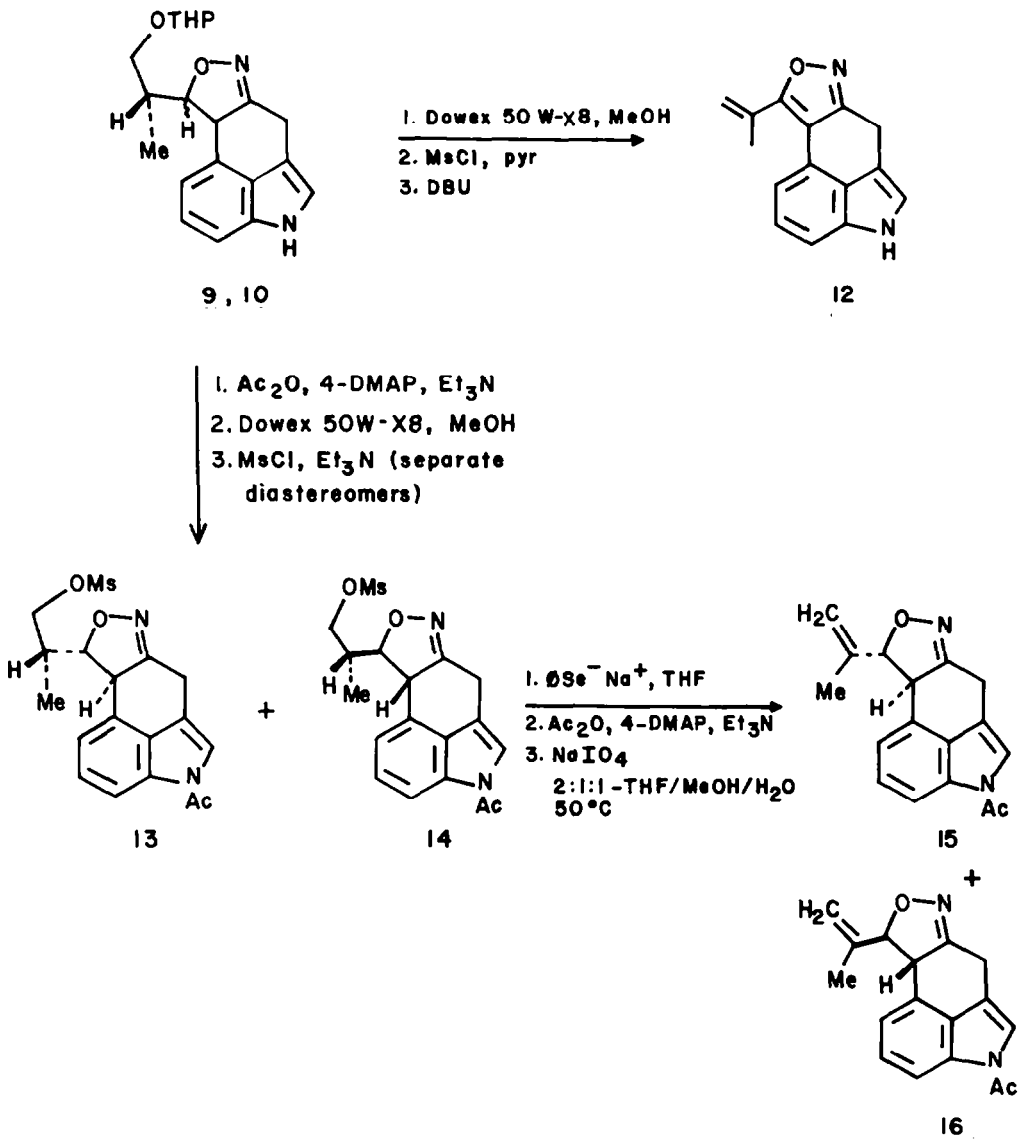
introduced by a two step procedure which required gramine formation (N,N-dimethyliminium chloride)[13] followed by the dimethyl acetylenedicarboxylate promoted addition of nitromethane to the indole derivative.[5] In the present instance, however, nitroethylene was found to behave as a suitable Michael acceptor towards the indole derivative 7.[14]

To a 1 M solution of 7 in benzene was added 1/2 - 1 equiv of nitroethylene (1.74 M in benzene) each day for a period of six days. A reasonable yield of the monoaddition product 8 (44%) together with the bis-addition product (13%) was generated as long as the reaction was run in the dark.

On subjecting the 3,4-disubstituted indole 8 to phenyl isocyanate/triethylamine, the desired intramolecular cycloaddition reaction occurred in high yield to afford isoxazolines 9 and 10 as a 1.1:1 mixture of diastereomers. Formation of the alternative regioisomer 11 is, of course, impossible in this case because of geometric constraints.

Dehydration of the hydroxyl containing side-chain was now required. The original plan called for removal of the THP group (Dowex 50 W-X8)[15] and conversion of the alcohol to its mesylate so that a base-promoted elimination reaction could be tried. While generation of this mesylate was

SCHEME 4. Manipulations of the C9 appendage



quite facile, its exposure to 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) in tetrahydrofuran led not to the desired elimination product, but to the aromatized isoxazole derivative 12 instead as verified by its ^{1}H NMR and high resolution mass spectra. Such a product is, of course, of little value to a paliclavine synthesis, for the crucial stereochemistry at C_9 and C_{9a} has been lost (see structure 9 for numbering scheme).

A somewhat more circuitous route was thus examined in order to prepare the desired isoxazoline structure. The indole nitrogen of 9/10 was first N-acetylated in order to produce a more organic solvent-soluble derivative. Removal of the THP group was carried out as described earlier. Conversion of the free hydroxyl group to its mesylate now gave a chromatographically separable mixture of the diastereomeric products 13 and 14. Each mesylate was reacted separately with sodium phenylselenide[16] to provide the corresponding seleno-indoles. Since the N-acetyl group was lost from each isomer during this displacement reaction, the products were next re-acetylated and then subjected to oxidative elimination in order to remove the superfluous center of asymmetry. The enantiomers 15 and 16 so generated possessed indistinguishable infrared, 90 MHz ^{1}H NMR and mass spectral data. Their melting points, and the absolute values of their specific optical rotations also matched closely.

The less polar mesylate which showed negative rotation was latter found (vide infra) to possess the stereochemistry required to synthesize (+)-paliclavine. The absolute configuration of this elimination product was also confirmed independently by an X-ray structure analysis (Figure 2).[17]

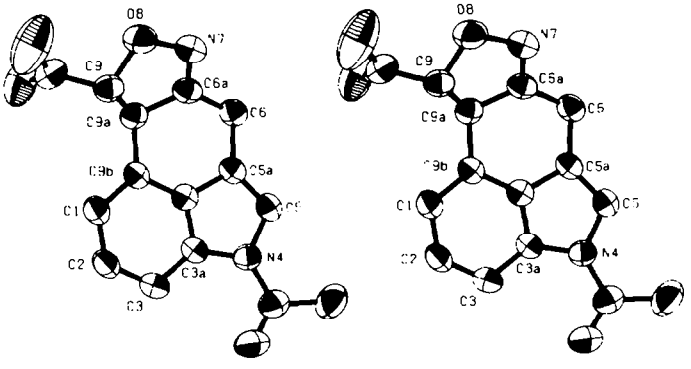


Figure 2. An X-ray structure of 15 with the hydrogen atoms omitted for clarity.

Completion of the paliclavine synthesis required reduction of the C-N double bond of the isoxazoline and N-methylation of its nitrogen atom. From our previous work on chanoclavine, we had found that Meerwein's salt in nitromethane was the preferred reagent to effect conversion of the isoxazoline to isoxazolinium salt. Since the methylation reaction could not be carried out in the presence of other reactive functionalities, such as ester, acetal, or tetrahydropyranyl groups, this was the prime reason for carrying out the dehydration of the hydroxyalkyl appendage prior to manipulation of the isoxazoline ring.

Thus, N-methylation of the (-)-indole 15 by Meerwein's salt in nitromethane, followed by removal of the solvent and reduction of the isoxazolinium salt by sodium borohydride in absolute ethanol gave an isoxazolidine of unspecified stereochemistry at C_{6a}. Scission of the N-O bond of the isoxazolidine 17 was achieved easily by treatment with aluminum amalgam in wet tetrahydrofuran.[18]

Diacetylation of the resulting 1,3-aminoalcohol 18 with acetic anhydride and pyridine gave a material whose mass spectrum matched that for the diacetate prepared from natural paliclavine.[19] Unfortunately, however, the ^{1}H NMR of the synthetic material was quite different from that of the natural diacetate.

An examination of Dreiding models reveals that the isoxazolinium salt 15a (figure 3) does, in fact, possess an envelope like shape. Attack of hydride should thus take place on the convex surface of the molecule so as to deliver the cis-fused C,D-ring system. While the analogous trans-fused compound must certainly be more strained than the cis-compound, it should nonetheless be possible to generate this structure under a different set of reaction conditions.

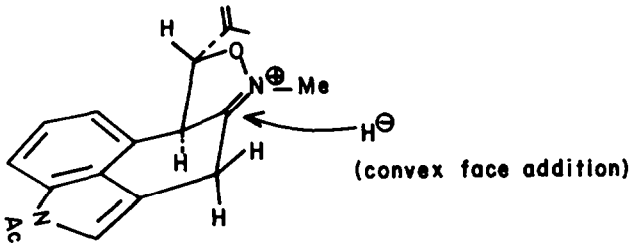


Figure 3. Structure of the isoxazolinium salt 15a.

While a number of different ways of influencing the stereochemical outcome of the reduction were envisioned, we felt that a change in the nature of the reducing agent would perhaps offer the simplest solution. While any mild reducing agent, ($NaBH_4$) or extremely reactive but bulky reducing agent (L-selectride) was anticipated to selectively reduce the isoxazolinium salt from the convex surface, it did seem feasible that a smaller, reactive reducing agent capable of coordinating with the isoxazoline ring might begin to "feel" the presence of the isopropenyl group. Thus, while a reagent like borohydride might be envisioned as effecting reduction through a more "remote" transition state which recognizes only the convex/concave surface of the molecule, lithium aluminum hydride, which can coordinate to the oxygen atom of the isoxazolinium ring through its lithium atom (thus positioning aluminum and hydride above the nitrogen-carbon double bond) might show some concave face selectivity in order to avoid steric interaction with the isopropenyl group.[20] Indeed, on employing lithium aluminum hydride in tetrahydrofuran, a 3:1

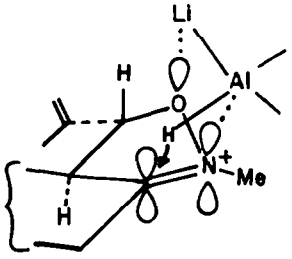
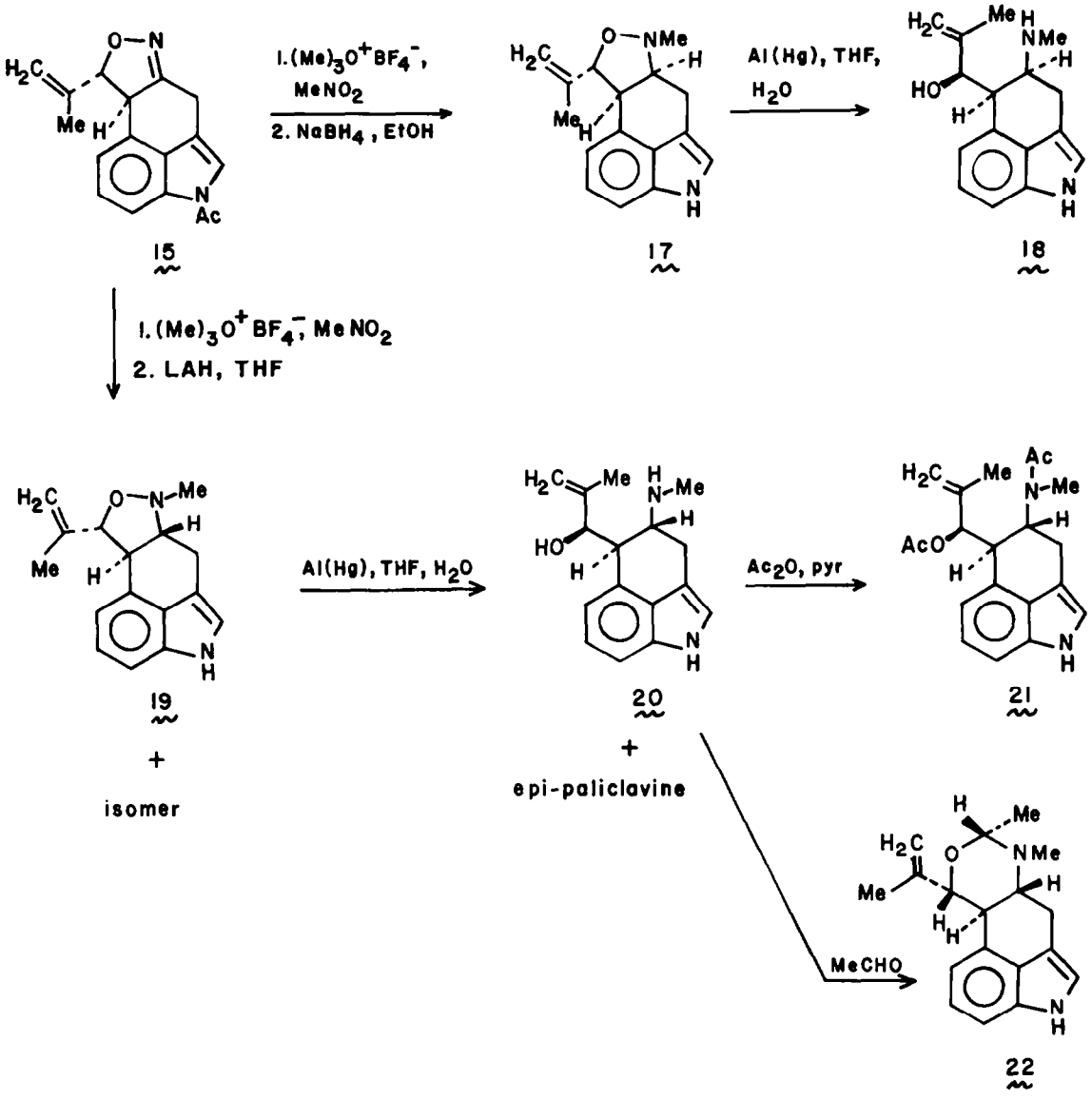


Figure 4.

mixture of the cis/trans-stereoisomers was formed. While this mixture of isomers could not be separated, the ^{1}H NMR did reveal the presence of a slightly larger coupling interaction between the C_9 and C_{9a} protons (J = 10 Hz) than was found for the cis-isomer (J = 7 Hz). Models do reveal that the dihedral angle between the C_9 and C_{9a} protons should be larger for the trans-C,D-ring fused product.

The inseparable mixture of isomers was reacted with aluminum amalgam in wet tetrahydrofuran to yield a mixture of (+)-paliclavine and epi-paliclavine. These were easily separated by silica gel chromatography (5:10:100-diethylamine/methanol/ethyl acetate). The less polar compound was identified as epi-paliclavine and the more polar compound as (+)-paliclavine. Since

SCHEME 5. Completion of the Paliclavine Synthesis



(+)-paliclavine exhibits poor solubility in volatile deuterated solvents,[21] it was converted to its more soluble diacetate derivative 21. Spectral data for both the synthetic and natural diacetates of (+)-paliclavine were recorded and compared. The 300 MHz ^{1}H NMR, MS and IR data were identical. Their specific rotations as measured in pyridine were also quite close. This latter result indicates that the separation of the diastereomers resulting from the INOC reaction at the stage of their mesylates was quite efficient. In essence then, the chiral phosphonium salt does function as an efficient (non-recoverable) resolving agent. Since the reaction of (+)-paliclavine with acetaldehyde has been reported to yield (+)-paspaclavine (22), the synthesis of paliclavine does also constitute a total synthesis of the latter ergot alkaloid as well.[21]

With the synthesis of paliclavine thus completed, it is of interest to review the fact that while some diastereoselection was observed in the [3+2] reaction, and that this diastereoselection was in the direction predicted by theory, the extent of such diastereoselection was not remarkable.[7] Indeed, in hindsight, there really is little to distinguish between the methyl and the (tetrahydropyranyloxy)methyl groups on either a steric or electronic basis. Only by, for example, replacing one of the carbon substituents by a polar oxygen substituent (or other heteroatom)[8,22] could one hope to achieve a better degree of diastereoselection. Such a situation constitutes the focus of future work in these laboratories.[23]

EXPERIMENTAL

General Methods. Melting points were determined on either a Fisher-Johns or Thomas Hoover melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 137, 247 or 700 infrared spectrophotometer using the polystyrene absorption at 1601 cm^{-1} as a reference. The infrared spectra of solid samples were measured using potassium bromide wafers. The ^1H NMR spectra were recorded at the frequency indicated on the following instruments: 60 MHz-Varian EM-360, T-60, and T-60A; 90 MHz-Varian EM-390; 300 MHz-Bruker WH-300. Chemical shifts are reported in parts per million (δ) relative to internal tetramethylsilane. Coupling constants are reported in cycles per second. Low resolution mass spectra were recorded on a LKB 9000A gas chromatograph-mass spectrometer. High resolution mass spectra were obtained on a Varian MAT CH-5DF mass spectrometer. Elemental analyses were performed by Gailbraith Laboratories, Knoxville, TN. Thin-layer chromatography was performed on Brinkman MN polygram 0.25 mm silica gel sheets with G/UV_{254} inorganic phosphor fluorescent indicator. Preparative thick layer chromatography was performed on Merck or Analtech silica gel plates with PF_{254} fluorescent indicator. E. Merck 0.063-0.200 mm silica gel was employed for gravity column chromatography, and ICN-Woelm 0.032-0.063 mm silica gel for flash chromatography.

(R)-(-)-3-Bromo-2-methylpropyl Trifluoroacetate. (R)-(-)-3-tert-butoxy-2-methyl-1-bromopropane[9] (22.5 g, 108 mmol) was dissolved in 350 mL of trifluoroacetic acid at 0°C. The resulting solution was stirred at 0°C in a cold room overnight, and then fractionally distilled at water aspirator pressure (50°C) to remove the excess trifluoroacetic acid. A sample of the residue was dissolved in chloroform-*d* and its ^1H NMR spectrum was measured using tetramethylsilane as the internal standard. The ^1H NMR spectrum showed that the crude product was entirely the trifluoroacetate of 3-bromo-2-methyl-1-propanol. This product was used directly for saponification without purification, and the yield was not ascertained: IR (film) 3000, 1780 (C=O), 1470, 1410, 1390, 1360, 1250 (s), 1180 (s), 990, 800, 780, 750 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 4.36 (d, 2 H, J = 6 Hz), 3.42 (d, 2 H, J = 6 Hz), 2.33 (m, 1 H), 1.09 (d, 3 H, J = 6 Hz); mass spectrum (15 eV), m/z 169, 168, 136, 134 (M^+-HBr); $[\alpha]_D^{25} = -0.22°$ (c 11.8, $CHCl_3$). Exact mass calcd for $C_6H_8BrF_3O_2$-HBr 168.0398; found 168.0398.

(R)-(-)-3-Hydroxy-2-methyl-1-bromopropane. The above bromoester (33.6 g, 135 mmol) was added dropwise to a solution of potassium carbonate (22.36 g, 161 mmol) in a mixture of methanol (45 mL) and water (194 mL). The resulting solution was stirred for another 1 h at room temperature, and then 1 L of distilled water and an excess of sodium chloride were added to make a saturated solution. The saturated solution was extracted four times with ethyl acetate (400 mL x 4). The combined organics were dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was fractionally distilled, and the fraction boiling at 73-74°C/9mm was collected to yield 13 g of the title bromoalcohol (62.9%): IR (film) 3333, 2940, 2860, 1450, 1430, 1370, 1330, 1250, 1230, 1030 (s), 980 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 3.61 (d, 2 H, J = 6 Hz), 3.50 (d, 2 H, J = 6 Hz), 2.04 (m, 1 H), 1.72 (s, 1 H), 1.03 (d, 3 H, J = 6 Hz); mass spectrum (15 eV), m/z 72 (M^+-HBr).

(R)-(+)-(3-Hydroxy-2-methyl-1-propyl)triphenylphosphonium Bromide (3). This phosphonium salt was prepared by refluxing a solution of the above bromoalcohol (12 g, 7.42 mmol) and triphenylphosphine (25.7 g, 98.03 mmol) in 23 mL of benzene for 72 h. The precipitated product was then filtered, washed with benzene, and dried under vacuum (0.2 mm Hg) at 50°C to yield 29.1 g of phosphonium salt (+)-3 (89.3%): m.p. 181-182°C. Mass spectrum (70 eV, 135°C), m/z 333 (M^+-H_2Br); $[\alpha]_D^{25} = +0.098°$ (c 10.2, DMSO). Exact mass calcd for $C_{22}H_{24}BrOP$-H_2Br 333.1408; found 333.1406.

Synthesis of 4-Formyl-1-[(4-methylphenyl)sulfonyl]-1H-indole (4). 4-Methoxycarbonyl-1-[(4-methylphenyl)sulfonyl]-1H-indole. To a stirred solution of 4-carbomethoxy-1H-indole (11.86 g, 67.7 mmol) in 320 mL of 2-butanone was added successively 48.4 g (350 mmol) of potassium carbonate and 32.5 g (170 mmol) of p-toluenesulfonyl chloride. The resulting mixture was heated to reflux for 24 h. Without cooling, the inorganic precipitate was filtered, and the filter cake was washed with 100 mL of 2-butanone. The combined filtrate and washings were evaporated under vacuum to remove the excess 2-butanone. The solid residue was further dissolved in ethyl acetate and washed with distilled water. The organic layer was separated, dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was chromatographed on silica gel with 25% ethyl acetate-hexanes as eluent to yield 20.6 g (92.4%) of the title compound: m.p. 145-146°C ^1H NMR (60 MHz, $CDCl_3$) δ 7.00-8.40 (m, 9 H), 3.97 (s, 3 H), 2.33 (s, 3 H); mass spectrum (15 eV, 50°C), m/z 329 (M^+), 155.

4-(Hydroxymethyl)-1-[(4-methylphenyl)sulfonyl]-1H-indole. To a cooled stirred suspension of lithium aluminum hydride (1.98 g, 49.4 mmol) in 50 mL of anhydrous tetrahydrofuran was added slowly a tetrahydrofuran solution (125 mL) of the above indole ester (11.4 g, 34.6 mmol) at 0°C. The time required for addition of the ester solution was about 30 min, and the reaction temperature was carefully controlled between 0-5°C. Stirring was continued for an additiona 15 min. The reaction was quenched by the addition of concentrated sodium sulfate until the evolution of gas ceased. The final suspension was then filtered, and the filter cake was washed with tetrahydrofuran. The combined tetrahydrofuran solutions were dried over anhydrous sodium sulfate, filtered and concentrated to give 8.9 g of pure alcohol (85.3%). This material was suitable as such for the subsequent oxidation step. A pure chromatographed sample had the following properties: m.p. 128-129°C; ^{1}H NMR (60 MHz, $CDCl_3$) δ 6.60-8.00 (m, 9 H), 4.47 (br s, 2 H), 2.27 (s, 3 H), 1.77 (br s, 1 H): mass spectrum (15 eV, 50°C), m/z 301 (M^+), 155, 129, 118.

4-Formyl-1-[(4-methylphenyl)sulfonyl]-1H-indole (4). The 4-(hydroxymethyl)-1-[(4-methylphenyl)sulfonyl]-1H-indole (10 g, 33.2 mmol) dissolved in 100 mL of dichloromethane was added dropwise to a mechanically stirred mixture of pyridinium chlorochromate (28.6 g, 132.7 mmol) and sodium acetate (8.2 g, 0.1 mmol) in 200 mL of dichloromethane at room temperature. Stirring was continued for a period of 2.5 h after the addition was completed. The gummy brown residue was allowed to precipitate, the dichloromethane layer was decanted, and the residue was triturated with additional dichloromethane. The combined organics were diluted with 1.5 L of ether, and the entire mixture was filtered through a column of Florisil. The crude product obtained on concentration of the filtrate was chromatographed on silica gel with 25% ethyl acetate-hexanes as eluent to afford 9.6 g (96.6%) of the desired aldehyde 4. Recrystallization of this material from benzene and petroleum ether provided an analytical sample: m.p. 142°C. IR (KBr) 3120, 2850, 2810, 2750, 1680 (C=O), 1580, 1430, 1360, 1280, 1230, 1170, 1140, 1120, 1090, 960, 880, 820, 780, 710, 680, 640 cm^{-1}; ^{1}H NMR (60 MHz, $CDCl_3$) δ 10.10 (s, 1 H, -CHO), 8.20 (br d, 1 H, J = 8 Hz), 7.00-7.90 (m, 8 H), 2.30 (s, 3 H). Anal. calcd for $C_{16}H_{13}NO_3S$: C, 64.20; H, 4.38. Found: C, 64.34; H, 4.44.

[3S-(E)]-4-(4-Hydroxy-3-methyl-1-butenyl)-1-[(4-methylphenyl)sulfonyl]-1H-indole (6). To a suspension of (+)-(3-hydroxy-2-methyl-1-propyl)triphenylphosphonium bromide (3) (7.5 g, 18 mmol) in 100 mL of dry tetrahydrofuran cooled to -78°C was added dropwise 23 mL (36 mmol) of a 1.6 M solution of *n*-butyllithium in hexane under an atmosphere of argon. The reaction was brought to room temperature and stirred for 3 h. The red homogeneous solution was then cooled to -78°C, and a solution of 4-formyl-1-[(4-methylphenyl)sulfonyl]-1H-indole (4, 4.5 g, 15 mmol) in 50 mL of tetrahydrofuran was added. The reaction mixture was slowly warmed to room temperature over 2 h and then poured in 200 mL of a saturated solution of ammonium chloride. The mixture was extracted with ethyl acetate (200 mL x 2), and the combined organics were dried over anhydrous sodium sulfate and concentrated by rotary evaporation. The crude product was chromatographed on silica gel with 25% ethyl acetate-hexanes to afford 3.96 g (74.3%) of (-)-trans-olefin 6: IR (film) 3520, 3320, 3120, 3020, 2920, 2860, 1590, 1520, 1470, 1440, 1420, 1360, 1290, 1180, 1130, 1100, 1040, 970 (trans-olefin), 920, 820, 780 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ 6.60-8.05 (m, 10 H), 6.20 (d of d, 1 H, J = 16, 7 Hz), 3.56 (d, 2 H, J = 7 Hz), 2.20 (s, 3 H), 2.53 (m, 1 H), 2.40 (br s, 1 H, -OH), 1.07 (d, 3 H, J = 7 Hz); mass spectrum (15 eV, 55°C), m/z 355 (M^+), 324 (M^+-CH_2OH); $[\alpha]_D^{25}$ = -22.1° (c 8.0, $CHCl_3$). Exact mass cald for $C_{20}H_{21}NO_3S$ 355.1242; found 355.1242.

A small amount of the cis-olefin (0.33 g, 6.2%) was also isolated: m.p. 110-115°C. IR (film) 3520, 3320, 3120, 2930, 2860, 1590, 1520, 1480, 1460, 1420, 1360, 1290, 1180, 1130, 1100, 1040, 920, 820, 780 cm^{-1}; ^{1}H NMR (60 MHz, $CDCl_3$) δ 7.00-8.00 (m, 8 H), 6.65 (d, 1 H, J = 11 Hz), 6.63 (d, 1 H, J = 4 Hz), 5.53 (d of d, 1 H, J = 11, 10 Hz), 3.43 (d, 2 H, J = 7 Hz), 2.60-3.20 (m, 1 H), 2.27 (s, 3 H), 1.80 (br s, 1 H, -OH), 0.97 (d, 3 H, J = 6 Hz); mass spectrum (70 eV, 135°C), m/z 355 (M^+), 324 (M^+-CH_2OH).

[3-S-(E)]-4-[3-Methyl-4-[(tetrahydro-2H-pyran-2-yl)oxy]-1-butenyl]-1-[(4-methylphenyl)sulfonyl]-1H-indole. Alcohol 6 (3.24 g, 9.1 mmol), redistilled dihydropyran (0.91 mL, 10 mmol) and a catalytic amount of pyridinium *p*-toluenesulfonate were dissolved in 44 mL of dry dichloromethane and stirred overnight at room temperature. The solution was concentrated, and the crude product was chromatographed on silica gel with 15% ethyl acetate-hexanes as eluent to afford 4 g (100%) of the desired (-)-indole. IR (film) 2920, 2860, 1690, 1530, 1480, 1450, 1430, 1360, 1280, 1170, 1130, 1070, 1030, 980 (trans-olefin), 920, 880, 830, 770, 690 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ 6.65-8.01 (m, 10 H), 6.30 (d of d, 1 H, J = 16, 6 Hz), 4.63 (m, 1 H), 4.20 (m, 4 H), 2.70 (m, 1 H), 2.33 (s, 3 H), 1.61 (m, 6 H), 1.16 (d, 3 H, J = 7 Hz); mass spectrum (15 eV, 75°C), m/z 439 (M^+), 355 (M^+-dihydropyran), 339, 297. Exact mass calcd for $C_{25}H_{29}NO_4S$ 439.1817; found 439.1808.

[3S-(E)-4-[3-Methyl-4-[(tetrahydro-2H-pyran-2-yl)oxy]-1-butenyl]-1H-indole (7). The above N-tosylindole (4.0 g, 9.1 mmol) was refluxed under an argon atmosphere for 3 h in a solution of potassium hydroxide (5.9 g, 9.1 mmol) dissolved in 100 mL of absolute methanol. Upon cooling the reaction mixture was concentrated, diluted with 250 mL of distilled water, and extracted twice with 250 mL of diethyl ether. The combined extracts were dried over anhydrous magnesium sulfate, concentrated by rotary evaporation, and chromatographed on 70 g of silica gel with 20% ethyl acetate-hexanes as eluent to afford 2.52 g (97.4%) of (-)-indole 7: IR (film) 3400, 3300, 2920, 2850, 1400, 1340, 1110 (s), 1060 (s), 1020 (s), 960 (s), 890, 860, 800, 740, 710 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ 8.37 (br s, 1 H), 6.60-7.40 (m, 6 H), 6.41 (d of d, 1 H, J = 16, 7 Hz), 4.70 (br t, 1 H), 3.25-4.30 (m, 4 H), 2.76 (m, 1 H), 1.30-2.00 (m, 6 H), 1.20 (d, 3 H, J = 6 Hz); mass spectrum (15 eV), m/z 285 (M^+), 201 (M^+-dihydropyran); $[\alpha]_D^{25}$ = -14.9° (c 13.9, $CHCl_3$). Exact mass calcd for $C_{18}H_{23}NO_2$ 285.1729; found 285.1725.

[3S-(E)]-4-[3-Methyl-4-[(tetrahydro-2H-pyran-2-yl)oxy]-1-butenyl]-3-(2-nitroethyl)-1H-indole (8). To a stirred benzene solution (6 mL) of indole 7 (2.69, 9.1 mmol) stored in a dark room was added 2.64 mL of a 1.74 M solution of nitroethylene in benzene each day. The reaction was monitored by thin-layer chromatography and after ~6 days the reaction was complete. The black solution was concentrated, and the tar-like residue was purified by silica gel column chromatography with 20% ethyl acetate-hexanes to afford 1.43 g (43.8%) of the desired nitroindole (-)-8: m.p. 103-107°C; IR (film) 3400, 2950, 2860, 1550 (s, $-NO_2$), 1430, 1380, 1350, 1280, 1130, 1120, 1075, 1060, 1030 (s), 970 (trans-olefin), 900, 860, 810, 780, 740 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 8.58 (br s, 1 H), 6.85-7.45 (m, 5 H), 6.14 (br d of d, 1 H, J = 16, 7 Hz), 4.67 (m, 1 H), 4.56 (t, 2 H, J = 7 Hz), 3.30-4.40 (m, 4 H), 3.49 (t, 2 H, J = 7 Hz), 2.71 (m, 1 H), 1.58 (m, 6 H), 1.13 (d, 3 H, J = 6 Hz); mass spectrum (15 eV, 90°C), m/z 358 (M^+), 274, 258, 227; $[\alpha]_D^{25}$ = -12.1° (c 20.1, $CHCl_3$). Exact mass calcd for $C_{20}H_{26}N_2O_4$ 358.1893; found 358.1890.

A considerable amount of dinitro-compound (0.51 g, 13%) produced by the second addition of nitroethylene to the nitroethyl side chain of indole 8 was also isolated. IR (film) 3400, 3300, 2950, 2850, 1550 ($-NO_2$), 1440, 1380, 1340, 1140, 1110, 1060, 1020, 970 (trans-olefin) cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 8.60 (br s, 1 H), 6.90-7.40 (m, 5 H), 6.19 (two d of d, 1 H, J = 16, 7 Hz), 4.93 (m, 1 H), 4.67 (m, 1 H), 4.30 (t, 2 H, J = 7 Hz, $-CH_2NO_2$), 3.00-4.15 (m, 6 H), 2.77 (m, 1 H), 2.47 (q, 2 H, J = 7 Hz), 1.60 (m, 6 H), 1.20 (d, 3 H, J = 7 Hz); mass spectrum (15 eV, 75°C) 431 (M^+), 347, 331, 316, 289, 182.

[9R-[9α(R),9aα]] and [9S-[9β(R*),9aβ]]-4,6,9,9a-Tetrahydro-9-[1-methyl-2-[(tetrahydro-2H-pyran-2-yl)oxy]ethyl]indolo[4,3-ef][2,1]benzisoxazole (9 and 10).* To a 25 mL benzene solution of 8 (1.39 g, 3.88 mmol) was added phenyl isocyanate (1.7 mL, 15.51 mmol) and a catalytic amount of triethylamine (0.10 mL). The reaction mixture was stirred at room temperature until the consumption of starting material was complete (approximately 24 h). The precipitated urea side product was removed by filtration, and the filtrate was concentrated. The crude product was purified by silica gel column chromatography with 25% ethyl acetate-hexanes as eluent to afford 1.1 g (83.3%) of the cycloadducts 9 and 10: IR (film) 3290, 2910, 2840, 1600, 1440 (br), 1350, 1130, 1070, 1030, 870, 760 (s) cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 8.64 (br s, 1 H), 6.70-7.70 (m, 4 H), 4.67 (m, 3 H), 4.40 (m, 6 H), 2.43 (m, 1 H), 1.62 (m, 6 H), 1.20-1.22 (two d, 3 H, J = 7 Hz); mass spectrum (70 eV, 160°C), m/z 340 (M^+), 256, 197. Exact mass calcd for $C_{20}H_{24}N_2O_3$ 340.1787; found 340.1788.

[9R-[9α(R),9aα]] and [9S-[9β(R*),9aβ]]-4-Acetyl-4,6,9,9a-tetrahydro-9-[1-methyl-2-[(tetrahydro-2H-pyran-2-yl)oxy]ethyl]indolo[4,3-ef][2,1]benzisoxazole.* A dichloromethane solution of the diastereomeric indoles 9 and 10 (1.1 g, 3.23 mmol) was refluxed with acetic anhydride (1.22 mL, 12.93 mmol) and triethylamine (1.8 mL, 12.93 mmol) in the presence of a catalytic amount of 4-N,N-dimethylaminopyridine (158 mg, 1.29 mmol) overnight. The reaction mixture was cooled and concentrated, and the crude isolated product was chromatographed on silica gel with 40% ethyl acetate-hexanes as eluent to afford 1.13 g (91%) of the title compounds: IR (film) 2950, 2900, 1700 (C=O), 1440, 1400, 1340, 1280, 1160, 1140, 1080, 1040, 980, 920, 890, 780 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 8.33 (d, 1 H, J = 7 Hz), 7.10-7.60 (m, 3 H), 4.76 (m, 3 H), 3.40-4.20 (m, 6 H), 2.68 (s, 3 H, -OAc), 2.43 (m, 1 H), 1.63 (m, 6 H), 1.10-1.23 (two d, 3 H, J = 7 Hz); mass spectrum (70 eV, 160°C), m/z 382 (M^+), 298 (M^+-dihydropyran), 239, 197, 85 ($M^+-C_3H_7O$ and dihydropyran). Exact mass calcd for $C_{22}H_{26}N_2O_4$ 382.1893; found 382.1872.

[9R-[9α(R),9aα]] and [9S-[9β(R*),9aβ]]-4-Acetyl-4,6,9,9a-tetrahydro-β-methylindolo[4,3-ef][2,1]benzisoxazole-9-ethanol.* To a stirred solution of the diastereomeric mixture of the above indoles (1.13 g, 2.94 mmol) in 30 mL of absolute methanol was added 2 g of Dowex 50W-X8 cation resin. (This cation resin was activated by washing successively with 6 N hydrochloric acid, distilled water until neutral, and then with absolute methanol.) The mixture was allowed to stir overnight and filtered. The filtrate was concentrated, and the crude product was purified by silica gel column chromatography with 40% ethyl acetate-hexanes to afford 0.735 g (84%) of a diastereomeric mixture of the title indoles: IR (film) 3370 (-OH), 2960, 2920, 2870, 1770 (C=O), 1440, 1390, 1340, 1270, 1160, 1040, 990, 880, 770 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 8.11 (d, 1 H, J = 8 Hz), 6.90-7.45 (m, 3 H), 3.40-4.90 (m, 6 H), 3.00 (br s, 1 H, -OH), 2.57 (s, 3 H, -OAc), 2.20 (m, 1 H), 1.14-1.15 (two d, 3 H, J = 7 Hz); mass spectrum (20 eV, 100°C), m/z 298 (M^+), 239 ($M^+-C_3H_7O$). Exact mass calcd for $C_{17}H_{18}N_2O_3$ 298.1317; found 298.1322.

[9R-[9α(R),9aα]] and [9S-[9β(R*),9aβ]]-4-Acetyl-4,6,9,9a-tetrahydro-9-[1-methyl-2-[(methanesulfonyl)oxy]ethyl]indolo[4,3-ef][2,1]benzisoxazole (13) and (14).* To a cooled (0°C) stirred solution of the diastereomeric mixture of the above indoles (0.592 g, 1.984 mmol) in 6 mL of dichloromethane was added successively triethylamine (0.55 mL, 3.96 mmol) and methanesulfonyl chloride (0.39 mL, 3.96 mmol). The solution was allowed to stir for 15 min and then concentrated by rotary evaporation. The two diastereomers were separated cleanly by flash column chromatography using silica gel 60 (230-400 mesh) and 40% ethyl acetate-hexanes as eluent to afford a less polar mesylate 13 (344 mg, 46%) and a more polar mesylate 14 (316 mg, 42.3%).

Less Polar isomer (9R)-13: IR (film) 3030, 2980, 2950, 1700 (C=O), 1440, 1400, 1340 (s, -OMs), 1270, 1180 (s, -OMs), 980, 880, 840, 780 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 8.22 (d, 1 H, J = 8 Hz), 7.20-7.55 (m, 2 H), 7.03 (d, 1 H, J = 8 Hz), 4.81 (d of d, 1 H, J = 10, 3 Hz, C_9 - H), 4.54 (br d, 1 H, J = 10 Hz, C_{9a} - H), 4.36 (d, 2 H, J = 6 Hz, $-CH_2OMs$), 4.00 (br d, 1 H, J = 18 Hz, C_6 - H), 3.63 (br d, 1 H, J = 18 Hz, C_6 - H), 3.08 (s, 3 H, $-OSO_2CH_3$), 2.63 (s, 3 H, -NAc), 1.21 (d, 3 H, J = 7 Hz).

More Polar Isomer (9S)-14: IR (film) 3030, 2980, 2950, 1700 (C=O), 1440, 1400, 1340 (s, -OMs), 1270, 1180 (s, -OMs), 980, 880, 840, 780 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 8.21 (d, 1 H,

J = 8 Hz), 7.20-7.55 (m, 2 H), 7.03 (d, 1 H, J = 8 Hz), 4.35-4.80 (m, 4 H), 4.02 (br d, 1 H, J = 18 Hz, C_6 - H), 3.64 (br d, 1 H, J = 18 Hz, C_6 - H), 3.08 (s, 3 H, $-OSO_2CH_3$), 2.63 (s, 3 H, -NAc), 1.32 (d, 3 H, J = 7 Hz); mass spectrum (70 eV, 75°C), m/z 376 (M^+), 239, 197, 168.

[9R-[9α(S),9aα]]-4,6,9,9a-tetrahydro-9-[1-methyl-2-(phenylseleno)ethyl]indolo[4,3-eβ][2,1]benzisoxazole.* A 0.406 M solution of sodium phenyl selenide was prepared by first dissolving diphenyl diselenide (634 mg, 2.03 mmol) in 10 mL of absolute ethanol. To the cooled (0°C) diselenide solution was added sodium borohydride (162 mg, 4.06 mmol). The reaction was complete when the yellow color of the diselenide disappeared. This reagent is suitable for storage for several weeks without much decomposition.

To the solution of the required indole 13 (344 mg, 0.91 mmol) in 15 mL of dry tetrahydrofuran was added 7.5 mL of the phenyl selenide solution (3.05 mmol) at room temperature. The solution was allowed to stir for 24 h and then concentrated. The organic residue was taken up with chloroform and washed once with concentrated ammonium chloride solution. After separation, drying over anhydrous magnesium sulfate, and concentration of the chloroform layer, the crude product obtained was further purified by silica gel chromatography (20 g of silica gel with 40% ethyl acetate-hexanes as eluent) to afford 320 mg of the title indole (88.6%): IR (film) 3400, 3060, 2980, 2900, 1600, 1580, 1480, 1440 (s), 1350, 1220, 1080, 1030, 920, 880 (s), 760 (s), 700 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 8.32 (br s, 1 H), 6.55-7.75 (m, 9 H), 4.87 (d of d, 1 H, J = 10, 3 Hz, C_9 - H), 4.40 (br d, J = 10 Hz, C_{9a} - H), 4.03 (br d, 1 H, J = 18 Hz, C_6 - H), 3.67 (br d, 1 H, J = 18 Hz, C_6 - H), 3.11 (AB of ABX, 2 H, J = 12, 8, 6 Hz, $-CH_2SePh$), 2.31 (m, 1 H), 1.26 (d, 3 H, J = 7 Hz); $[\alpha]_D^{25}$ = -213.1° (c 13.9, $CHCl_3$).

[9R-[9α(S),9aα]]-4-Acetyl-4,6,9,9a-tetrahydro-9-[1-methyl-2-(phenylseleno)ethyl]indolo[4,3-eβ][2,1]benzisoxazole.* To a stirred solution of the above selenoindole (320 mg, 0.809 mmol) in 3 mL of dichlormethane was added triethylamine (0.451 mL, 3.24 mmol), acetic anhydride (0.31 mL, 3.24 mmol) and a catalytic amount of 4-N,N-dimethylaminopyridine (40 mg, 0.324 mmol). The resultant mixture was stirred at room temperature for 24 hours. After concentration the crude product was purified by silica gel column chromatography (40% ethyl acetate-hexanes) to afford 352 mg of the title indole (quantitative yield): IR (film) 3000, 2900, 1700 (s, C=O), 1580, 1480, 1440, 1400, 1370, 1340, 1280, 1170, 1000, 900, 770 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 8.19 (d, 1 H, J = 9 Hz), 7.10-7.70 (m, 7 H), 6.82 (d, 1 H, J = 9 Hz), 4.84 (d of d, 1 H, J = 10, 3 Hz, C_9 - H), 4.37 (br d, 1 H, J = 10 Hz, C_{9a} - H), 3.97 (br d, 1 H, J = 18 Hz, C_6 - H), 3.53 (br d, 1 H, J = 18 Hz, C_6 - H), 3.11 (AB of ABX, 2 H, J = 12, 7, 6 Hz, $-CH_2SePH$), 2.57 (s, 3 H), 2.30 (m, 1 H), 1.24 (d, 3 H, J = 7 Hz); $[\alpha]_D^{25}$ = -203.2° (c 14.6, $CHCl_3$).

[9R-cis]-4-Acetyl-4,6,9,9a-tetrahydro-9-[1-methylethenyl]indolo[4,3-eβ][2,1]benzisoxazole (15). To a stirred solution of the above (-)-selenoindole (352 mg, 0.805 mmol) in 35 mL of a 4:2:1 mixture of tetrahydrofuran/methanol/water was added sodium periodate (345 mg, 1.610 mmol). The reaction mixture was kept at 50°C for 24 h. The solution was then concentrated, and the residue was chromatographed on silica gel with 35% ethyl acetate-hexanes as eluent. The product was further recrystallized from absolute ethanol to afford 152 mg of (-)-indole 15 as yellow shiny needles (67.4%): m.p. 179°C; IR (film) 1700 (s, C=O of amide), 1440, 1400, 1370, 1340, 1280, 1160, 990, 930, 880, 680 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 8.19 (d, 1 H, J = 7 Hz), 7.20-7.50 (m, 2 H), 7.04 (d, 1 H, J = 7 Hz), 5.37 (br s, 1 H), 5.24 (m, 1 H), 4.91 (br d, 1 H, J = 12 Hz, C_9 - H), 4.54 (br d, 1 H, J = 12 Hz, C_{9a} - H), 4.00 (br d, 1 H, J = 18 Hz, C_6 - H), 3.60 (d of m, 1 H, J = 18 Hz, C_6 - H), 2.61 (s, 3 H), 1.98 (m, 3 H); $[\alpha]_D^{25}$ = -184.8° (c 7.1, $CHCl_3$). Anal. calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75. Found: C, 72.69; H, 5.93.

[9S-[9β(S),9aβ]]-4,6,9,9a-Tetrahydro-9-[1-methyl-2-(phenylseleno)ethyl] indolo[4,3-eβ][2,1]benzisoxazole.* This (+)-selenoindole was obtained in a similar operation by the treatment of the required mesylate (316 mg, 0.83 mmol) with 7.5 mL of a 0.406 M solution of sodium phenyl selenide (3.05 mmol). After purification 303 mg of the (+)-selenoindole was obtained (91.3%): IR (film) 3400, 3060, 2980, 2900, 1600, 1580, 1480, 1440 (s), 1350, 1220, 1080, 1030, 920, 880 (s), 760 (s), 700 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 8.42 (br s, 1 H), 6.65-7.75 (m, 9 H), 4.67 (d of d, 1 H, J = 8, 7 Hz, C_9 - H), 4.40 (br d, 1 H, J = 8 Hz, C_{9a} - H), 4.00 (br d, 1 H, J = 18 Hz, C_6 - H), 3.62 (br d, 1 H, J = 18 Hz, C_6 - H), 3.42 (d of d, 1 H, J = 12, 3 Hz, $-CH_2SePh$), 2.89 (d of d, 1 H, J = 12, 9 Hz, $-CH_2SePh$), 2.23 (m, 1 H), 1.27 (d, 3 H, J = 7 Hz; $[\alpha]_D^{25}$ = +253.7° (c 15.5, $CHCl_3$).

[9S-[9β(S),9aβ]]-4-Acetyl-4,6,9,9a-tetrahydro-9-[1-methyl-2-(phenylseleno)ethyl]indolo[4,3-eβ][2,1]benzisoxazole.* To a stirred solution of the above (+)-selenoindole (303 mg, 0.766 mmol) in 3 mL of dichloromethane was added triethylamine (0.43 mL, 0.307 mmol), acetic anhydride (0.29 mL, 3.07 mmol) and a catalytic amount of 4-N,N-dimethylaminopyridine (37 mg, 0.307 mmol). The resultant mixture was stirred at room temperature for 24 hours. After concentration the crude product was purified by silica gel column chromatography (30 g of silica gel and 40% ethyl acetate-hexanes as eluent) to afford 303 mg of the title indole (90.4%): IR (film) 3000, 2900, 1700 (s, C=O), 1580, 1480, 1440, 1400, 1370, 1340, 1280, 1170, 1000, 900, 770 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 8.17 (d, 1 H, J = 9 Hz), 7.15-7.75 (m, 7 H), 6.94 (d, 1 H, J = 7 Hz), 4.62 (d of d J = 9, 6 Hz, C_9 - H), 4.40 (br d, J = 9 Hz, C_{9a} - H), 3.94 (br d, 1 H, J = 18 Hz, C_6 - H), 3.54 (br d, 1 H, J = 18 Hz, C_6 - H), 3.41 (d of d, 1 H, J = 12, 4 Hz, $-CH_2SePh$), 2.90 (d of d, 1 H, J = 12, 8 Hz, $-CH_2SePh$), 2.28 (m, 1 H), 1.27 (d, 3 H, J = 7 Hz); $[\alpha]_D^{25}$ = +250.5° (c 20.9, $CHCl_3$).

[9S-cis]-4-Acetyl-4,6,9,9a-tetrahydro-9-[1-methylethenyl]indolo[4,3-eβ][2,1]benzisoxazole (16). To a stirred solution of the above (+)-selenoindole (303 mg, 0.693 mmol) in 35 mL of a 4:2:1 mixture of tetrahydrofuran/methanol/water was added sodium periodate (296 mg, 1.39 mmol). The reaction mixture was kept at 50°C for 24 h. The solution was then concentrated, and the

residue was chromatographed on silica gel with 35% ethyl acetate-hexanes as eluent. The product was further recrystallized from absolute ethanol to afford 142 mg of the (+)-indole 16 as shiny needles (73.1%): m.p. 179°C; IR (film) 1700 (s, C=O of amide), 1440, 1400, 1370, 1340, 1280, 1160, 990, 930, 880, 680 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 8.19 (d, 1 H, J = 7 Hz), 7.20-7.50 (m, 2 H), 7.04 (d, 1 H, J = 7 Hz), 5.37 (br s, 1 H), 5.24 (m, 1 H), 4.91 (br d, 1 H, J = 12 Hz, C_9 - H), 4.54 (br d, 1 H, J = 12 Hz, C_{9a} - H), 4.00 (br d, 1 H, J = 18 Hz, C_6 - H), 3.60 (d of m, 1 H, J = 18 Hz, C_6 - H), 2.61 (s, 3 H), 1.98 (m, 3 H); $[\alpha]_D^{25}$ = +185.8 (c 6.8, $CHCl_3$). Anal calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75. Found: C, 72.69; H, 5.93.

[6aR-(6aα,9β,9aβ)]- and [6aS-(6aβ,9β,9aβ)]-4,6,6a,7,9,9a-Tetrahydro-7-methyl-9-[1-methylethenyl]indolo[4,3-ef][2,1]benzisoxazole. To a cooled (0°C) stirred solution of (-)-indole 15 (44 mg, 0.157 mmol) in 4 mL of nitromethane was added trimethyloxonium tetrafluoroborate (24 mg, 10.65 mmol) under an atmosphere of argon. The solution was brought to room temperature, stirred for 2 h, concentrated, and dried under an atmosphere of argon. Dry tetrahydrofuran (6 mL) and lithium aluminum hydride (100 mg, 2.64 mmol) were added sequentially to the residue. The reaction mixture, which became homogeneous after a few minutes, was stirred overnight, and the excess hydride was destroyed by the addition of 12 mL of a 10% sodium hydroxide solution. The mixture was extracted with ethyl acetate, and the extracts were dried over anhydrous sodium sulfate, filtered, and concentrated. The crude product was purified by preparative thick layer chromatography (silica gel) using 50% ethyl acetate-hexanes as the developing solvent to yield 28 mg of a mixture of 17 and 19. This mixture was subjected directly to the aluminum amalgam reduction reaction.

The cis-isomer 17 exhibits the following characteristic peaks in its ^1H NMR spectrum: (90 MHz, $CDCl_3$) δ 5.07 (s, 2 H), 4.47 (d, 1 H, J = 7 Hz). For the trans-isomer 19 these are as follows: δ 5.37 (m, 1 H), 5.17 (m, 1 H), 4.83 (d, 1 H, J = 10 Hz).

(+)-Paliclavine. [4R-[4α,5β[R]]]-1,3,4,5-tetrahydro-4-(methylamino)-α-(1-methylethenyl)benz-[cd]indole-5-methanol (20).* Aluminum amalgam (prepared by treating aluminum foil sequentially with a 10% sodium hydroxide solution and a 2% mercuric chloride solution followed by washing with water)[18] was added to a solution of the isomeric mixture of indoles 17 and 19 in 11 mL of a 9:1 mixture of tetrahydrofuran-water. The reaction mixture was stirred overnight, and the inorganic salts were removed by filtration. The filtrate was concentrated, and the residue was separated by chromatography on silica gel with a 1:2:20 mixture of diethylamine/methanol/ethyl acetate as eluent to afford 6 mg (21.3%) of (+)-paliclavine and 12 mg (42.6%) of epi-paliclavine. Due to the insolubility of these substances in most common organic solvents, they were immediately derivatized as their N,O-diacetates from which all comparisons of physical and spectral data were made.

(-)-Paliclavine Diacetate (21). (+)-Paliclavine (20, 6 mg) was stirred with 30 μL of acetic anhydride in 0.2 mL of dry pyridine under an atmosphere of argon overnight at room temperature. The solvent was removed under high vacuum, and the residue was purified by preparative thin-layer chromatography using ethyl acetate as the developing solvent to yield (-)-paliclavine diacetate 21 (quantitative yield): IR ($CHCl_3$) 3250, 2925, 1730 (s, C=O of acetate), 1620, (s, C=O of amide), 1440, 1400, 1370, 1240 (s, C=O of acetate), 1110, 750 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ two broad NH peaks (total 1 H) 8.10, 8.03; aromatic protons: 7.27 (m, 2 H), 6.91-6.99 (m, 2 H); olefinic protons (total 2 H): 5.53 (d, J = 5.7 Hz), 5.41 (m); 4.61-5.00 (total 2 H): 4.99 (br s), 4.93 (br s), 4.81 (br s), 4.64 (q, J = 5.4 Hz); C_4 - H: 3.48 (m, 1 H); 2.90-3.08 (total 1 H): 3.04 (d of d, J = 16.7, 4.1 Hz), 2.95 (d of d, J = 17, 3.2 Hz); 2.48 (br s, 3 H); 1.77-2.26 (total 9 H): 2.25 (s), 2.02 (s), 1.95 (s), 1.86 (s), 1.80 (s), 1.77 (s); mass spectrum (15 eV, 90°C), m/z 280, 267, 227, 208, 154; $[\alpha]_D^{25}$ = -48.4° (c 0.64, pyridine) (synthetic); $[\alpha]_D^{25}$ = -49.6° (c 0.5, pyridine) (natural). Exact mass calcd for $C_{20}H_{24}N_2O_3$-$C_2H_4O_2$ 280.1576; found 280.1576.

(+)-epi-Paliclavine Diacetate. This compound was prepared in an identical fashion as described above for paliclavine diacetate: ^1H NMR (300 MHz, $CDCl_3$) δ 8.30 (br s, 1 H), 6.90-7.50 (m, 4 H), 5.70 (d, J = 7 Hz), 5.00-5.60 (m), 3.97 (d of d, J = 7, 3 Hz), 3.20 (d, J = 6 Hz), 2.67 (br s, 3 H), 2.03 (s, 3 H), 2.00 (s, 3 H), 1.70 (br s, 3 H); mass spectrum (15 eV, 55°C), m/z 340 (M^+), 267, 227, 208, 154; $[\alpha]_D^{25}$ = +81° (c 0.7, $CHCl_3$).

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