Synthesis of Ergot Alkaloids from Tryptophan

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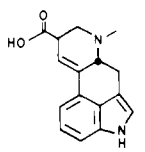
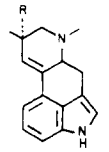
Abstract: The first total syntheses of lysergine and setoclavine are described, as well as a new and efficient synthesis of lysergic acid. The starting material for these syntheses is tryptophan, protected as its dihydro, dibenzoyl derivative. This material is dehydrated to the corresponding azlactone, which undergoes stereoselective intramolecular Friedel–Crafts acylation to give a tricyclic ketone intermediate. Reformatsky reaction with ethyl α-(bromomethyl)acrylate introduces the remaining four carbons and leads to a spiro methylene lactone that represents the branching point of the three syntheses. The high selectivity of the reactions described permits the synthesis of optically active ergot alkaloids from L-tryptophan.

Ergot alkaloids possess a range of biological activity, and a number of ailments are currently treated with ergoline derivatives.[1] The parent structure of these agents, lysergic acid (**1**), has been



1 Lysergic acid



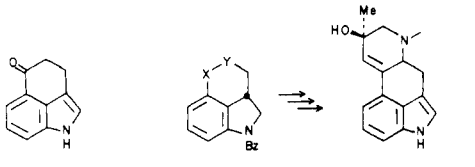
2 R = H, Lysergine
3 R = OH, Setoclavine

seminal in the origin of psychopharmacology and its abuse as the diethylamide made LSD a household term in the 1960s. The significance of **1** as a synthetic target may be weighed by the fact that of the six total syntheses,[2-7] three have appeared during the last 2 years. The position of lysergic acid among the ergot alkaloids is more than symbolic. It provides the starting material for the formal syntheses[8] of several other ergolines such as lysergine (**2**) and setoclavine (**3**), both of which were unknown in racemic form before our synthetic work.

Synthetic approaches to the ergot alkaloids have been compiled in an extensive, recent review[9] which concludes that chemical synthesis is not yet able to compete with fermentation processes for access to these substances. The central intermediate in several successful syntheses has been Uhle's ketone[10] **4**, (Scheme I) either as the protected derivative **5** or its carbonyl transposition[11a] product **6**. The former was involved in both Kornfeld's[2] and Ramage's[4] synthesis of lysergic acid as well as Kornfeld's[12] synthesis of isosetoclavine (**7**). The latter is encountered in Ninomiya's[6] synthesis of **1** and is a key intermediate in the synthesis of cis-fused dihydroisolysergyl derivatives.[11b]

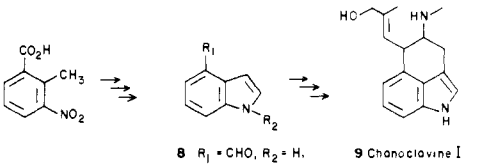
The alternative to Uhle's ketone has been the preparation of 4-substituted indoles[13] as in Scheme II. For example, **8** has been

Scheme I



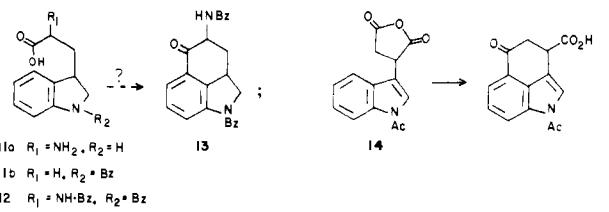
4 (Uhle's Ketone)
5 X = CO, Y = CH_2
6 X = CH_2, Y = CO
7 Isosetoclavine

Scheme II



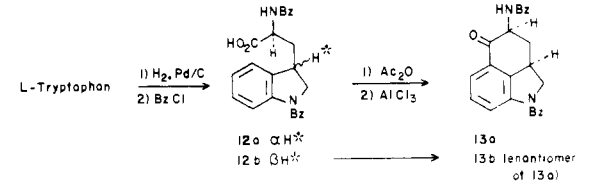
8 R_1 = CHO, R_2 = H.
10 R_1 = CH_2OH, R_2 = Tos
9 Chanoclavine I

Scheme III



11a R_1 = NH_2, R_2 = H
11b R_1 = H, R_2 = Bz
12 R_1 = NH-Bz, R_2 = Bz
13
14

Scheme IV



12a αH☆
12b βH☆
13a
13b (enantiomer of 13a)

converted[14] to chanoclavine-I (**9**), while **10**[15] is an intermediate in a lysergic acid synthesis.[5] Both of these syntheses go to great lengths to accommodate intramolecular cycloaddition strategies. An indole of this type has also been converted to dihydrosetoclavine.[16]

It was our premise that synthetic access to these alkaloids had been limited by the selection of starting materials, *a situation that could be remedied through the use of the biosynthetic precursor tryptophan.* Why tryptophan had been avoided is puzzling. By 1967 Witkop[17] had deescribed the hydrogenation product **11a** and

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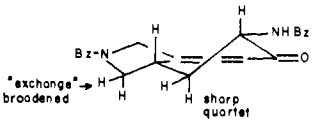


Figure 1.

its dibenoyl derivative **12** (Scheme III). The intramolecular Friedel–Crafts acylation shown had ample precedent in Kornfeld's lysergic acid synthesis from **11b** and was further suggested by a report[18] of a related cyclization of an anhydride, **14**, in 1964. While it is well-known that acyl amino acids form azlactones on treatment with dehydrating agents, it was also reported in 1963 that azlactones were quite suitable acylating agents in *intermolecular* Friedel–Crafts reactions.[19] These auguries, combined with the additional possibility of a chiral synthesis from L-tryptophan, made this inexpensive amino acid an irresistable starting material for ergot synthesis.

Dihydrotryptophans. We repeated the hydrogenation of L-tryptophan in 1 N HCl with 10% Pd/C as described by Witkop.[17] Upon treatment of the product solution with NH_4OH a precipitate is obtained at pH ~7.5. This substance, when benzoylated (Scheme IV) gave **12a** (25% overall), while the more soluble isomer can be benzoylated in situ to give **12b** (33% overall). Low solubility precluded comparison of the specific rotation with the figure reported by Witkop, although **12a** showed the same melting point as the single isomer previously described.[17] The homogeneity of these isomers was confirmed by conversion with CH_2N_2 to the corresponding methyl esters, which showed different OMe singlets in their NMR spectra. Additional measures of purity were obtained in subsequent reaction products with shift reagents. The *absolute* stereochemistry at the new center was established only when **12b** was ultimately converted to a substance (**41**) obtainable from natural sources but is anticipated in the reaction scheme. In the racemic series, **12** was obtained in 70% overall yield and was composed of roughly equal amounts of the racemates of **12a** and **12b**.

Conversion of any of these dibenzoyl dihydrotryptophans to the corresponding azlactones was accomplished by brief heating with Ac_2O. When the crude azlactone was added to a suspension of $AlCl_3$ in dichloroethane, cyclization occurred to give the corresponding tricyclic ketones **13** in 60% overall yield. *Invariably a single isomer was obtained.* Thus the diastereomeric **12a** and **12b** gave the enantiomers **13a** and **13b**, respectively. The relative stereochemistry was deduced from NMR as that involving a cis 1,3 diaxial relationship between the tertiary hydrogens. This result was most apparent in the multiplicity of the most upfield signal, a sharp quartet (even at 600 MHz), J = 12 Hz, for the axial proton at C_3 (Figure 1). Decoupling experiments established that this quartet resulted from equivalent coupling of this proton to the two adjacent methines and to the geminal equatorial proton. This quartet persisted in all of the compounds at the indoline oxidation state. The second general diagnostic feature of compounds in this series was the broadened (at 300 or 600 MHz) signal for the equatorial proton of the indoline ring, centered at δ 4.5. Intermediate rotation rates of the neighboring benzoyl function are the likely cause of this broadening.

That a single isomer was obtained in the Friedel–Crafts reaction *established the feasibility of preparing either enantiomer of ergot alkaloids from* L-*tryptophan.* Hydrogenation introduces the stereochemistry at the γ-carbon of the diastereomers. This center now fixes the stereochemistry of the α-carbon, C_4, in the tricyclic ketone. The rapid racemization of azlactones (a bane of peptide synthesis) assures a supply of the proper arrangement for the cyclization step. This α-carbon represents an asymmetric center in all of these alkaloids, but which diastereomer of dihydro-L-tryptophan leads to the natural series was determined only later.

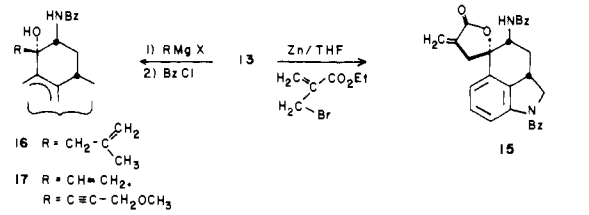
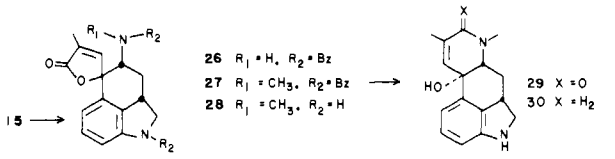


Figure 2.

Since Uhle's ketone had already been shown[20] to undergo clean Reformatsky reaction with ethyl α-(bromomethyl)acrylate, the parallel reaction with **13** was expected to be facile. That a single isomer was obtained (Figure 2) was not unexpected, given the ability of α-amido carbonyl compounds such as peptides to act as chelating ligands to divalent metals. Such behavior predicts a cis relationship between product heteroatoms as shown in **15**. Again, proof of the stereochemistry had to await comparison with natural substances. The clean reaction extends to Grignard reagents as well; **16** and **17** were obtained in high yield from the reaction of **13** with appropriate (excess) reagents. Here, however, some cleavage of the tertiary amide invariably occurred, requiring a rebenzoylation step in the workup.

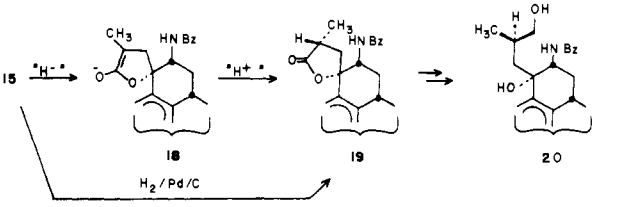
Removal of the remaining benzoyl was accomplished by the method of Uskokovic[22] (Dibal·H) in 73% yield and its replacement with a methyl group ($H_2CO/NaBH_3CN$[23]) led to racemic lysergine, mp 227–229 °C, in 71% yield.

(±)-Setoclavine. The isomerization of the methylene lactone **15** to the butenolide **26** was cleanly mediated by $RhCl_3 \cdot 3H_2O$, as described by Grieco.[24] Alkylation with MeI gave **27** which



was deblocked at both nitrogens by alkylation ($Et_3O^+BF_4^-$) followed by mild hydrolysis.[25] The amine **28** was obtained in 57% overall yield from **15**. The rearrangement of **28** to the lactam **29** was induced by brief treatment with base (NaOMe/MeOH). Subsequent reduction (LAH) gave **30** from which the indole **31** could be obtained by MnO_2 oxidation (45% from **28**).

(±)-Lysergine. The methylene lactone **15** represents the branching point of these syntheses. It resembles lysergic acid in oxidation state, but requires some reduction for either lysergine or setoclavine. Accordingly, $NaBH_4$ in MeOH was used to reduce **15** to the saturated diol **20** in high yield (80%) and high stereoselectivity (> 10:1). The stereochemistry observed corresponds to protonation of the enolate **18** by solvent from the exterior face



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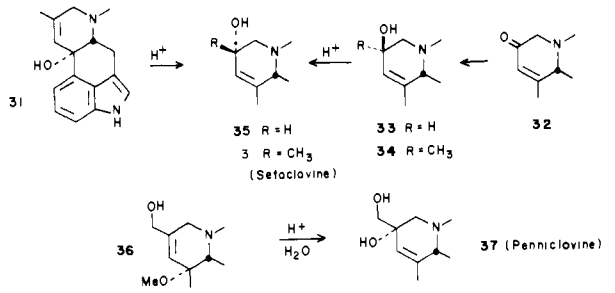
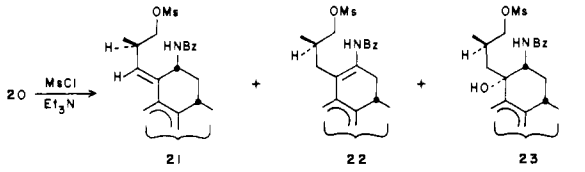
Scheme V



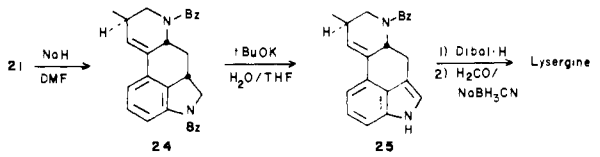
(rather than intramolecular protonation by the benzamido group), followed by reduction of the carbonyl group. Some deterioration of the stereoselectivity was observed in larger scale reactions, probably because of epimerization of **19** which is competitive with reduction. Hydrogenation of **15** with Pd/C gave **19** with even higher stereoselectivity, (>30:1). Reduction of **19** with Vitride preserved this stereochemistry and provided the diol **20**, whereas reduction of **19** with BH_4^- showed considerable epimerization. In either route to **20** some cleavage of the tertiary amide was observed. Benzoylation during workup was again the solution to this problem; up to 88% yields of **20** were obtained from **15**.

Elimination of the tertiary alcohol proved to be the least satisfactory step of the lysergine synthesis. Treatment of **20** with mesyl chloride/Et_3N gave a mixture of the mesylate olefins **21**



(30%) and **22** (20%) along with mesyl alcohol **23** (5%). Attempts to improve this situation were unsuccessful; for example, the use of more hindered bases merely led to more **23** at the expense of the desired **21**.

The cyclization of **21** with NaH in dry DMF led cleanly to the tetracyclic **24**, the structure of which was confirmed by the special (retroDiels–Alder) fragmentation pattern of its mass spectrum. Mild cleavage of the indoline benzoyl followed by MnO_2 oxidation afforded the indole **25**, but a much more efficient method involved

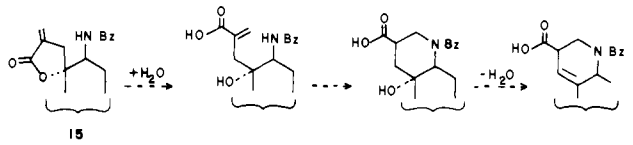


the Gassman[21] procedure for tertiary amide cleavage (*t*-BuOK/H_2O/THF). These conditions, intended to remove both benzoyls, gave **25** directly in >90% yield. Perhaps the indole here arises by loss of H^- under the dint of aromatization, but the alternative possibility of air oxidation cannot be excluded.

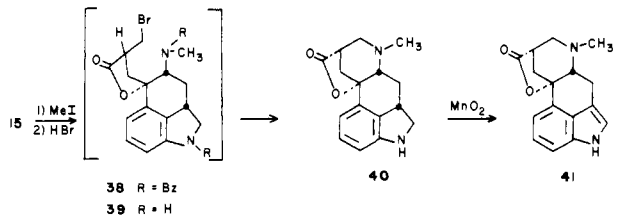
That this substance would rearrange to setoclavine on mild acid treatment was suggested by a number of facts (Scheme V). First, Kornfeld[12,26] had shown that the ketone **32** reacted with nucleophiles (MeLi or $NaBH_4$) on the α-face. Moreover, solvolysis[26] of the related ether **36** gave the rearranged α-alcohol **37**, and, finally, acid treatment[12] of **33** resulted in isomerization to **35**. When **31** was exposed to dilute HCl, (±)-setoclavine was indeed generated. A sample of (±)-isosetoclavine (**34**), kindly provided by Dr. Kornfeld, likewise gave setoclavine under the same conditions.

Lysergic Acid. As mentioned earlier, the methylene lactone **15** bears the oxidation state and functionality appropriate for lysergic acid; all that is lacking is a low-energy pathway for the rearrangement outlined in Scheme VI. Of course, several attemps

Scheme VI



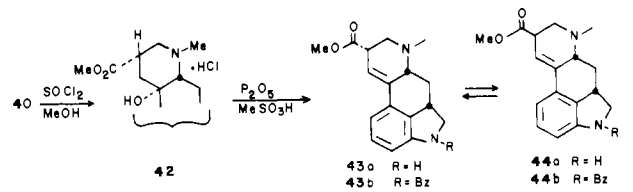
Scheme VII



were made to effect this rearrangement directly. None succeeded. A less dramatic sequence, sanctioned[27] by stereoelectronic considerations, proved workable.

Alkylation of **15** with MeI/NaH followed by treatment with HBr in CH_2Cl_2 afforded the addition product **38** (Scheme VII). While this could be isolated and characterized, it was more practical to subject it to the benzoylectomy sequence previously described[25] because this gave the pentacyclic indoline **40** directly (44% from **15**). It appears that the intermediate product **39** cyclizes spontaneously to **40** during workup. This event permitted the long-awaited reckoning of the absolute stereochemistry of the dihydrotryptophans, since oxidation (MnO_2) gave *an indole which could be related to one derived from natural products.* Thus, starting with the levorotatory form of **13**, the sequence described above led to a dextrorotatory form of **41** whose properties compared well with that described by Bernardi[28] for the "lumilactone" of isolysergic acid.

Though the stereochemical thread had been spliced, the synthetic one had not, since **41** had not been converted to lysergic acid. This proved to be possible for **40** by opening the lactone with $SOCl_2$/MeOH to the ester **42**, which, as its hydrochloride



was dehydrated (P_2O_5/$MeSO_3H$) to the methyl ester of dihydroisolysergic acid (**43a**) (95% from **40**). This substance had already been described by Ramage[4] and it is partly converted to the dihydrolysergic acid stereochemistry on benzoylation. Oxidation of **43a** led to a mixture of methyl isolysergate and methyl lysergate. The latter was identical with the substance prepared by the action of CH_2N_2 on lysergic acid, a sample of which was kindly provided by Professor J. Cassady.

Conclusions

We have confirmed the feasibility and practicality of ergoline synthesis from tryptophan. In doing so the first syntheses of (±)-setoclavine and (±)-lysergine have been recorded; these are intended to complement the several formal syntheses[29] involving lysergic acid. In addition, the availability of *either enantiomer* of these alkaloids from L-tryptophan has been established through the high selectivity of the reactions involved. Our exploitation

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(29) See, for example: Nakahara, Y.; Niwaguchi, T.; Ishii, H. *Chem. Pharm. Bull.* **1977**, *25*, 1756–1763. Schreier, E. *Helv. Chim. Acta* **1958**, *41*, 1984–1997.

of this development is described in the sequel.

Experimental Section

Hydrogenation and Benzoylation of Tryptophan. A solution of 15.7 g of L-tryptophan in 260 mL of 1 N HCl containing 3 g of 10% Pd/C was shaken under 30 psi of H_2 for 16 h. The catalyst was removed by filtration and the filtrate was treated at 0 °C with concentrated NH_3. When the pH reached 7.5–8, a white solid precipitated, ca. 7.5 g. After recrystallization from H_2O, rotations varied widely, e.g., from −6 to +37 with different crops. The rotation reported by Witkop, $[\alpha]^{20}_D = -10.7 \pm 2.0$ (*c* 0.28, 1 N NaOH) was never achieved. Nonetheless the initial precipitate was benzoylated as described by Witkop to give ca. 15 g of crude material. Three recrystallizations from aqueous MeOH gave 7.5 g (25%) of **12a**: mp 200–201 °C; $[\alpha]^{20}_D = -46$ (*c* 0.25, MeOH).

The filtrate from the neutralized hydrogenation mixture was treated with 4 g of NaOH and likewise benzoylated to give 14 g of crude material. Recrystallization from MeOH gave 10 g (33%) of **12b**: mp 222–223 °C; $[\alpha]^{20}_D = -4$ (*c* 0.25, MeOH).

Neither isomer showed sufficient solubility in $CHCl_3$ to obtain a rotation that could be compared with the reported[17] value. Esterification with CH_2N_2 gave the methyl ester of **12a**, δ 3.72, and the methyl ester of **12b**, δ 3.74.

From DL-tryptophan a mixture of diastereomeric dibenzoyl derivatives were obtained in 70% yield. Esterification with CH_2N_2 showed that racemic **12b** (55%) and racemic **12a** (45%) were present in the product.

1-Benzoyl-4-benzamido-5-oxo-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole (13). A solution of compound **12a** (206 mg, 0.5 mmol) in 1 mL of acetic anhydride was heated at 100 °C for 15 min with stirring. This was cooled to room temperature and the Ac_2O–AcOH mixture was completely evaporated in vacuo at a water temp <50 °C for 4 h. The resulting pale yellow oil was redissolved in 1 mL of anhydrous dichloroethane and was added over 5 min to a suspension of $AlCl_3$ (266 mg, 2 mmol) in 1 mL of dichloroethane under N_2 in an ice bath. After the addition, the ice bath was removed and the reaction mixture was heated at reflux for 30 min. This was cooled to room temperature, added to 20 mL of ice water, and extracted with $CHCl_3$ (3 × 30 mL). The organic phase was washed with saturated brine and dried over sodium sulfate. After evaporation of the volatiles, the resulting crude yellow-brown solid was chromatographed on 20 g of silica gel (Et_2O:Hexane = 1:4) to give 112 mg (57%) of pale yellow ketone, mp 199–200 °C. Racemic **13** was prepared from the mixture of diastereomers in an identical fashion. The product was recrystallized from ethyl acetate, mp 191–193 °C (rotations are reported in Scheme IV): mass spectrum (70 eV) 396 M^+ (100), 291 (45), 275 (90), 169 (20); IR ($CDCl_3$) 3400, 1685, and 1650 cm^{-1}; *m/e* calcd for $C_{25}H_{20}N_2O_3$, 396.1474; found, 396.1469; NMR 600 MHz ($CDCl_3$) 1.93 (q, 1 H, *J* = 12 Hz), 3.16 (dt, 1 H, *J* = 12 Hz, *J* = 5 Hz), 3.81 (t, 1 H, *J* = 10.5 Hz), 3.82–3.92 (m, 1 H), 4.30–4.55 (br s, 1 H), 4.87 (dt, 1 H, *J* = 12 Hz, *J* = 5 Hz), 7.33 (d, 1 H, *J* = 5 Hz), 7.12–7.97 (m, 13 H). Anal. Calcd for $C_{25}H_{20}N_2O_3$: C, 75.74; H, 5.09; N, 7.06. Found: C, 75.75; H, 5.17, N, 7.07.

1-Benzoyl-4-benzamido-1,2,2a,3,4,5-hexahydro-5-hydroxy-α-methylenebenz[*cd*]indole-5-propionic Acid, γ-Lactone (15). A solution of tricyclic ketone **13** (480 mg, 1.2 mmol) in 20 mL of anhydrous THF was treated with activated zinc (204 mg, 3.12×10^{-3} mol) and I_2 catalyst (15 mg). A solution of ethyl α-(bromomethyl)acrylate (482 mg, 2.5 mmol) in 2 mL of THF was added to the above mixture over 20 min. The temperature was maintained at 0 °C during the addition. After the addition the reaction mixture was heated to 50 °C over 20 min and was kept at that temperature for 14 h. The reaction mixture was cooled to room temperature and poured into 100 mL of an ice cold dilute HCl solution. A white solid formed which was collected by filtration. From racemic **13** the product was recrystallized from ethanol to give 460 mg (83%) of a white solid, mp 265–267 °C. Optically active **15** was prepared from **13a** or **13b** in an identical fashion. The product was recrystallized from ethyl acetate, mp 254–255 °C. From **13a**: $[\alpha]^{25}_D$ −81° (*c* 0.5, $CHCl_3$). From 13b: $[\alpha]^{25}_D$ +82° (*c* 0.5, $CHCl_3$). Mass spectrum (70 eV) 464 M^+ (100), 317 (95); IR ($CHCl_3$) 1754, 1639 cm^{-1}; NMR (300 MHz, $CDCl_3$) 1.97 (q, 1 H, *J* = 12 Hz), 2.15–2.27 (br s, 1 H), 3.45 (br s, 2 H), 3.50–3.65 (m, 1 H), 3.75 (t, 1 H, *J* = 9.5 Hz), 4.22–4.50 (br s, 1 H), 4.86 (dt, 1 H, *J* = 12 Hz, 5 Hz), 5.70 (s, 1 H), 6.25 (s, 1 H), 6.38 (d, 1 H, *J* = 9.5 Hz), 7.00 (m, 1 H), 7.40–7.75 (m, 12 H). Anal. Calcd for $C_{29}H_{24}N_2O_4$: C, 74.98; H, 5.21; N, 6.03. Found: C, 74.75; H, 5.43; N, 5.80.

1-Benzoyl-4-benzamido-1,2,2a,3,4,5-hexahydro-5-hydroxy-5-methallylbenz[*cd*]indole (16). The method described by Pirrung[30] was used. Into a 500-mL 3-neck round bottom flask equipped with an addition funnel, reflux condenser, and serum stopper was placed magnesium (5.4 g, 0.22 mol) and 10 mL of THF. Into the addition funnel was placed 2-methyl-3-chloropropene (10.6 mL, 0.11 mol) and a few drops were added to the flask with vigorous stirring. After initiation was complete, the reaction was diluted with 100 mL of THF and the remainder of the halide was added over ca. 1 h. After addition was complete, the reaction mixture was stirred at room temperature for 1 h. A solution of racemic tricyclic ketone **13** (1 g, 2.52 mmol) in 50 mL of anhydrous THF was added to the above Grignard reagent (100 mL, excess) at 0 °C with vigorous stirring and the reaction kept at this temperature for 30 min. The reaction mixture was poured into 100 mL of a saturated aqueous ammonium chloride solution and extracted with chloroform. The organic solvent was evaporated and the residue redissolved in 60 mL of THF and treated with 0.6 mL of pyridine and 0.6 mL of benzoyl chloride at 0 °C. This was stirred at 0 °C for 15 min and then added to 50 mL of a 3% ice cold aqueous HCl solution. The product was extracted with $CHCl_3$ and dried over Na_2SO_4. The organic solvent was removed under reduced pressure. Filtration through silica gel (EtOAc:hexane = 1:1) gave a white solid, mp 193–194 °C, in quantitative yield: NMR 300 MHz ($CDCl_3$) 1.46 (s, 3 H), 1.52 (q, 1 H, *J* = 12 Hz), 2.37 (br s, 1 H), 2.81, 2.84 (ABq, 2 H, *J* = 3.7 Hz), 3.44–3.50 (m, 1 H), 3.61 (t, 1 H, *J* = 11.1 Hz), 4.0–4.4 (br s, 1 H), 4.54 (dt, 1 H, *J* = 5.8 Hz, 5Hz), 4.65 (br s, 1 H), 4.82 (br s, 1 H), 7.08 (d, 1 H, *J* = 7.5 Hz), 7.20–7.90 (m, 13 H).

1-Benzoyl-4-benzamido-1,2,2a,3,4,5-hexahydro-5-hydroxy-5-(3-hydroxy-2-methylpropyl)benz[*cd*]indole (20). A suspension of methylene lactone **15** (60 mg, 0.13 mmol) in 9 mL of methanol was treated with sodium borohydride (380 mg, 10 mmol) at room temperature with vigorous stirring and occasional cooling for 2 h. The reaction mixture was added to 10 mL of a cold 3% HCl solution and extracted with $CHCl_3$. TLC and NMR experiments showed some of the indoline benzoyl was lost under these conditions. After evaporation of the organic solvent, the residue was rebenzoylated with 0.1 mL benzoyl chloride and 0.1 mL of pyridine in 5 mL of MeOH at 0 °C. Purification on silica gel (EtOAc:hexane = 1:1, then EtOAc) gave 52 mg (88%) of pure diol with an isomer ratio of 10/1. Efforts to separate the isomers were proven to be impractical, and the mixture was used in the next step without further purification.

Preparation of the Saturated Lactone, 19. A solution of α-methylene lactone **15** (10 mg, 0.022 mmol) in 5 mL of absolute ethanol was shaken overnight under a hydrogen atmosphere in the presence of a catalytic amount of 10% palladium on charcoal. After the catalyst was separated by filtration, evaporation of the ethanol gave a residue which was purified on 2 g of silica gel using EtOAc:hexane = 1:1 as eluent. The saturated lactone **19** was obtained in quantitative yield with an isomer ratio of 15:1: NMR 300 MHz ($CDCl_3$) 1.26 (d, *J* = 7.0 Hz, 3 H), 1.92 (q, 1 H, *J* = 11.7 Hz), 2.18–2.32 (br, 1 H), 2.34 (dd, 1 H, *J* = 9.5 Hz, *J* = 11.7 Hz), 2.93 (dd, 1 H, *J* = 9.5 Hz), 3.11–3.25 (m, 1 H), 3.47–3.60 (m, 1 H), 3.72 (t, 1 H, *J* = 11.5 Hz), 4.10–4.50 (br, 1 H), 4.76 (dt, 1 H, *J* = 2.5, *J* = 11.7 Hz), 6.52 (d, 1 H, *J* = 8 Hz), 7.01 (br, 1 H), 7.40–7.80 (m, 12 H).

Alternative Preparation of 20. To a solution of saturated lactone **19** (20 mg, 0.04 mmol) in 1 mL of anhydrous THF at 0 °C was added a 1.4 M solution (0.5 mL) of sodium bis(2-methoxyethoxy)aluminum hydride. The mixture was stirred at this temperature for 2 h. The mixture was then added to 5 mL of a 10% citric acid solution and the pH was adjusted to 8.0 with NaOH. This was followed by extraction into chloroform, drying over sodium sulfate, and evaporation of the organic solvent. The crude product was rebenzoylated with benzoyl chloride and pyridine in methanol as previously described. The product was purified on silica gel with EtOAc:hexane = 1:2 to give the diol (15 mg, 75%) with an isomer ratio of 30:1. The physical and spectral properties (TLC, NMR) of diol **20** obtained in this fashion were identical with those of the materials obtained via sodium borohydride reduction.

1-Benzoyl-4-benzamido-1,2,2a,3,4,5-hexahydro-5-[2-methyl-3-((methylsulfonyl)oxy)propylidene]benz[*cd*]indole (21). Diol **20** (200 mg, 0.42 mmol) was dissolved in 15 mL of dry THF and cooled to −10 °C under N_2 with vigorous stirring. This was treated with triethylamine (1.4 mL, 10 mmol) followed by dropwise addition of methanesulfonyl chloride (0.5 mL, 6.5 mmol). The triethylamine hydrochloride precipitate formed immediately and stirring was continued for 30 min below 0 °C and then for 1 h at room temperature. To this was added 60 mL of a 1% ice cold HCl solution followed by extraction with $CHCl_3$ (3 × 40 mL). The organic phase was dried over sodium sulfate. Evaporation of the organic solvent and purification on MPLC (EtOAc:hexane = 1.5:1) gave 70 mg (30%) of mesylate **21**, mp 183–184 °C, 51 mg of mesylate **22** (21%), and 10 mg of monomesylate **23** (4%).

Mesylate **21**: NMR (300 MHz, $CDCl_3$) 1.05 (d, 3 H, *J* = 8 Hz), 1.38 (q, 1 H, *J* = 12 Hz), 2.75–2.90 (m, 1 H), 3.00 (s, 3 H), 3.04–3.19 (m, 1 H), 3.25–3.45 (m, 1 H), 3.69 (t, 1 H, *J* = 11 Hz), 4.02–4.15 (overlapping dd, 2 H), 4.15–4.70 (br s, 1 H), 5.40–5.50 (m, 1 H), 5.98 (br d, 1 H, *J* = 7 Hz), 6.29 (br d, 1 H), 7.10–7.60 (m, 11 H), 7.20–7.28 (m, 2 H). Anal. Calcd for $C_{30}H_{30}N_2O_5S$: C, 67.90; H, 5.70; N, 5.28. Found: C, 67.70; H, 5.79; N, 5.19.

(30) Pirrung, M. J. *J. Am. Chem. Soc.* **1981**, *103*, 82–87.

4,7-Dibenzoyl-9-methyl-4,5,5a,6a,6,7,8,9-octahydroindolo[4,3-*fg*]quinoline 24. A solution of mesylate **21** (110 mg, 0.2 mmol) in 6 mL of dry DMF was added to a suspension of NaH (50% oil dispersion, 1 g, 20.8 mmol) in 2 mL of dry DMF with cooling under a nitrogen atmosphere. After stirring at 0 °C for 40 min the reaction mixture was poured into 50 mL of an ice cold dilute HCl solution and extracted with $CHCl_3$. After drying over Na_2SO_4 and evaporation of the organic solvent, the residue was purified on silica gel (EtOAc:hexane = 1:2) to give 80 mg (88%) of a pure white solid: mp 217–218 °C; mass spectrum 434 M^+ (28), 329 (11), 301 (11); NMR (300 MHz, $CDCl_3$) at 60 °C 1.05 (d, 3 H, J = 6.9 Hz), 1.74 (q, 1 H, J = 11 Hz), 2.40–2.55 (br m, 2 H), 3.20 (dd, 1 H, J = 12.7 Hz, 3 Hz), 3.57–3.68 (m, 2 H), 3.73 (t, 1 H, J = 11 Hz), 4.32 (br s, 1 H), 5.11 (br d, 1 H, J = 11 Hz), 6.48 (br d, 1 H, J = 5.0 Hz), 7.05 (t, 1 H, J = 7.5 Hz), 7.21 (d, 1 H, J = 7.5 Hz), 7.30–7.50 (m, 9 H), 7.51–7.61 (m, 2 H). Anal. Calcd for $C_{29}H_{26}N_2O_2$: C, 80.16; H, 6.03; N, 6.45. Found: C, 79.96; H, 6.19; N, 6.27.

8-Methyl-6-benzoyl-9,10-dehydroergoline (25). A solution of tetracyclic compound **24** (20 mg, 0.046 mmol) in 3 mL of dry THF was treated with a 0.2 M *t*-BuOK/THF solution (12 mL, 2.4 mmol) and distilled water (15 μL, 0.8 mmol) at 0 °C under N_2 and stirred at ambient temperature for 1 h. The reaction mixture was added to 10 mL of distilled water and the pH was adjusted to 8.0. After extraction with $CHCl_3$ (4 × 15 mL) and drying over sodium sulfate, the organic solvent was removed. Recrystallization from ethanol gave 14 mg (92%) of a pure white solid: mp 262–266 °C dec; mass spectrum (15 eV) 328 M^+ (30), 195 (100); NMR (300 MHz, $CDCl_3$) at 70 °C 1.14 (d, 3 H, J = 7.5 Hz), 2.46–2.57 (br s, 1 H), 2.99 (t, 1 H, J = 12 Hz), 3.25–3.42 (m, 2 H), 3.83–4.03 (br s, 1 H), 5.12–5.30 (br s, 1 H), 6.45 (br d, 1 H, J = 5 Hz), 6.84 (br s, 1 H), 7.08–7.20 (m, 3 H), 7.31–7.51 (m, 5 H), 7.84 (br s, 1 H). (At ambient temperature broadened spectra were observed for both **24** and **25** due to rotation of the 6-benzoyl function).

Debenzoylation of 25 and Its Conversion to Lysergine (2). To a solution of compound **25** (14 mg, 0.07 mmol) in 2 mL of dry THF at −78 °C was added a 20% solution (1 mL) of diisobutylaluminum hydride. The mixture was stirred at this temperature for 40 min then warmed to −45 °C for 20 min. The mixture was then added to 5 mL of a 10% citric acid aqueous solution, and the pH adjusted to 8.0, followed by extraction with ethyl acetate. After drying over Na_2SO_4 and evaporation of the organic solvent, the product was purified on silica gel (EtOAc then EtOH) to give 7 mg (73%) of the free amine: NMR (300 MHz, $CDCl_3$) 1.08 (d, 3 H, J = 7 Hz), 2.57 (t, 1 H, J = 9 Hz), 2.61 (br s, 1 H), 2.72 (dt, 1 H, J = 11 Hz, 2 Hz), 3.21–3.36 (m, 2 H), 3.80–3.90 (m, 1 H), 6.33 (br s, 1 H, $W_{1/2}$ = 6 Hz), 6.90 (br s, 1 H), 7.15–7.28 (m, 3 H), 7.90 (br s, 1 H).

This material was converted to lysergine without further purification. NaH_3BCN (90 mg) was added to a stirred solution of the above amine (7 mg, 0.03 mmol) and 0.6 mL of 37% aqueous formaldehyde in 3 mL of acetonitrile. Stirring was continued for 45 min with glacial acetic acid being added occasionally to maintain neutral pH. The reaction mixture was added to 5 mL of a saturated $NaHCO_3$ solution and extracted with $CHCl_3$. Evaporation of the organic solvent and recrystallization from EtOAc gave 5 mg (71%) of racemic lysergine as a white solid: mp 227–229 °C; mass spectrum (70 eV) 238 M^+ (100), 195 (50), 181 (50); UV $\lambda_{max}^{CHCl_3}$ 309, 244 nm; NMR (300 MHz, $CDCl_3$) 1.09 (d, 3 H, J = 7.1 Hz), 2.20 (t, 1 H, J = 11 Hz), 2.60 (s, 3 H), 2.76 (ddd, 1 H, J = 14 Hz, 11 Hz, 1.8 Hz), 2.77 (m, 1 H), 3.08 (dd, 1 H, J = 11 Hz, 5.2 Hz), 3.20–3.29 (m, 1 H), 3.55 (dd, 1 H, J = 14 Hz, 5.5 Hz), 6.34 (br s, 1 H, $W_{1/2}$ = 6.25 Hz), 6.91 (m, 1 H), 7.17–7.21 (m, 3 H), 7.95 (br s, 1 H); m/e calcd for $C_{16}H_8N_2$, 238.1470; found, 238.1467.

1-Benzoyl-4-benzamido-1,2,2a,3,4,5-hexahydro-5-hydroxy-α-methylbenz[*cd*]indole-5-acrylic Acid, γ-Lactone (26). A solution of methylene lactone **15** (400 mg, 0.86 mmol) in 30 mL of $CHCl_3$, 15 mL EtOH, and 2 mL of H_2O was treated with $RhCl_3 \cdot 3H_2O$ (90 mg, 0.34 mmol). After carefully evacuating the air, the suspension was heated at reflux for 14 h under N_2. The reaction mixture was cooled to room temperature, poured into 30 mL of saturated $NaHCO_3$ solution, extracted with $CHCl_3$, and dried over Na_2SO_4. The organic solvent was removed under reduced pressure. Filtration through silica gel (EtOAc:Hexane = 1:1) gave a white solid which was recrystallized from ethyl acetate to give 300 mg (75%) of a pure white solid, mp >275 °C. Optically active **26** was prepared from (−) **15** in identical fashion. The product was recrystallized from ethyl acetate: mp 242–243 °C; optical rotation of (+)-**26** from (−)-**15** $[\alpha]^{25}_D$ +42° (*c* 0.55, $CHCl_3$); mass spectrum (70 eV) 464 M^+ (25), 317 (100); IR (KBr) 3350, 1731, 1631 cm^{-1}; NMR (300 MHz, $CDCl_3$) 1.93 (d, 3 H, J = 1.5 Hz), 1.99 (q, 1 H, J = 12 Hz), 2.25–2.38 (br s, 1 H), 3.52–3.67 (m, 1 H), 3.79 (t, 1 H, J = 11 Hz), 4.20–4.60 (br s, 1 H), 4.92 (dt, 1 H, J = 3.2 Hz, J = 11.7 Hz), 7.12 (d, 1 H, J = 1.5 Hz), 6.32 (d, 1 H, J = 8 Hz), 7.40–7.70 (m, 13 H). Anal. Calcd for $C_{29}H_{24}N_2O_4$: C, 74.98; H, 5.21; N, 6.03. Found: C, 74.83; H, 5.34; N, 5.89.

1-Benzoyl-4-(*N*-methylbenzamido)-1,2,2a,3,4,5-hexahydro-5-hydroxy-α-methylbenz[*cd*]indole-5-acrylic Acid, γ-Lactone (27). A solution of butenolide **26** (156 mg, 0.336 mmol) in 5 mL of DMF was added to a suspension of NaH (50% oil dispersion, 528 mg, 11.1 mmol) in 5 mL of anhydrous DMF with cooling under a nitrogen atmosphere followed by the addition of CH_3I (0.27 mL, 4.32 mmol). After the addition, the ice bath was removed and the reaction mixture was allowed to warm to room temperature over a 20 min period. After 1 h at room temperature, the reaction mixture was poured into 50 mL of an ice cold dilute HCl solution and then extracted with chloroform. After drying over Na_2SO_4, evaporation of the organic solvent gave a pale yellow solid which was recrystallized from ethyl acetate to give 143 mg (90%) of racemic **27** as a white solid, mp 251–252 °C. (+)-**27** was prepared in an identical fashion from (+)-**26**. The product was recrystallized from a mixture of ethanol and hexane: mp 164–165 °C; optical rotation of (+)-**27** $[\alpha]^{25}_D$ +61° (*c* 0.5, $CHCl_3$); IR (KBr) 1754, 1635, 1623 cm^{-1}; NMR (300 MHz, $CDCl_3$) 2.05 (d, 3 H, J = 1.2 Hz), 2.23 (q, 1 H, J = 12.5 Hz), 2.20–2.36 (br s, 1 H), 2.98 (s, 3 H), 3.56–3.70 (m, 1 H), 3.85 (t, 1 H, J = 10.5 Hz), 4.20–4.65 (br s, 1 H), 5.40 (dd, J = 12.5 Hz, 3.3 Hz), 6.74 (br s, 1 H), 7.23 (d, J = 1.2 Hz), 7.24–7.64 (m, 12 H). Anal. Calcd for $C_{30}H_{26}N_2O_4$: C, 75.30; H, 5.48; N, 5.85. Found: C, 75.39; H, 5.56; N, 5.70.

Debenzoylation Procedure, Preparation of 28. A solution of *N*-methylbutenolide **27** (240 mg, 0.5 mmol) in 25 mL of CH_2Cl_2 was treated with 100 mg of dry Na_2CO_3 and excess $Et_3O^+BF_4^-$ at room temperature under N_2 for 2 h. The reaction mixture was treated with 200 mL of a N HCl solution and, after 15 min, neutralized with saturated $NaHCO_3$. Extraction into $CHCl_3$, drying over Na_2SO_4, and evaporation of the volatiles gave 115 mg (85%) of product. This was recrystallized from EtOAc: mp 194 °C; mass spectrum (70 eV) 270 (8), 241 (16), 203 (100), 204 (14), 170 (15); IR 1740, 1620, 1600 cm^{-1}; NMR (300 MHz, $CDCl_3$) 1.55 (q, 1 H, J = 11.7 Hz), 2.06 (d, 3 H, J = 1.6 Hz), 2.47 (s, 3 H), 2.53 (dt, 1 H, J = 11.7 Hz, J = 1.4 Hz), 2.96 (dd, 1 H, J = 2.7 Hz, J = 11.7 Hz), 3.15 (m, 2 H), 3.72 (t, 1 H, J = 6.1 Hz), 6.59 (d, 1 H, J = 7.5 Hz), 6.38 (d, 1 H, J = 7.9 Hz), 6.95 (d, 1 H, J = 1.6 Hz), 6.99 (t, 1 H, J = 7.7 Hz); m/e calcd for $C_{16}H_{18}N_2O_2$, 270.1368; found, 270.1369.

2,3-Dihydro-7-oxo-8,9-dehydro-10-hydroxyergoline (29). A solution of butenolide indoline **28** (135 mg, 0.5 mmol) in 10 mL of absolute methanol was added to a sodium methoxide solution (2.3 g of NaOMe in 10 mL of methanol). The reaction mixture was refluxed for 1 h, cooled, extracted with chloroform, and dried over Na_2SO_4, and the organic solvent was removed to give a brown solid: 100 mg (75%); NMR (300 MHz, $CDCl_3$) 1.93 (d, 3 H, J = 1.4 Hz), 1.99 (q, 1 H, J = 12.5 Hz), 2.42 (dd, 1 H, J = 2.6 Hz, 12.5 Hz), 3.07 (s, 3 H), 3.1–3.2 (m, 2 H), 3.66 (t, 1 H, J = 5.3 Hz), 3.87 (dd, 1 H, J = 2.6 Hz, 12.5 Hz), 6.58 (d, 1 H, J = 7.5 Hz), 6.88 (d, 1 H, J = 7.5 Hz), 6.96 (s, 1 H), 7.09 (t, 1 H, J = 7.5 Hz).

2,3-Dihydro-8,9-dehydro-10-hydroxyergoline (30). A solution of lactam **29** (135 mg, 0.5 mmol) and lithium aluminum hydride (200 mg, 6 mmol) in 50 mL of THF was stirred at room temperature for 4 h. The reaction mixture was then cautiously poured into 100 mL water and filtered. The filtrate was extracted with $CHCl_3$ then dried over Na_2SO_4. Evaporation of the solvent gave **30**: 102 mg (80%); mp 192–197 °C; mass spectrum (70 eV) 256 M^+ (100), 238 (30), 198 (100), 184 (100), 144 (60); IR ($CDCl_3$) 1620, 1600 cm^{-1}; NMR (300 MHz, $CDCl_3$) 1.73 (s, 3 H), 1.74 (q, 1 H, J = 10.5 Hz), 2.28 (dd, 1 H, J = 2 Hz, 10.5 Hz), 2.45 (s, 3 H), 2.54 (dd, 1 H, J = 2 Hz, 10.5 Hz), 2.84 (d, 1 H, J = 17 Hz), 3.1–3.22 (m, 2 H), 3.27 (d, 1 H, J = 17 Hz), 3.66 (t, 1 H, J = 6.3 Hz), 6.29 (s, 1 H), 6.59 (d, 1 H, J = 7.7 Hz), 6.98 (d, 1 H, J = 7.7 Hz), 7.10 (t, 1 H, J = 7.7 Hz).

8,9-Dehydro-10-hydroxyergoline (31). A solution of **30** (51 mg, 0.2 mmol) in 10 mL of CH_2Cl_2 was treated with 0.6 g of Attenburrow[31] MnO_2 and stirred at room temperature for 2 h. The solids were separated by filtration and evaporation of the solvent gave 37 mg (75%) of **31**: mp 150–160 °C; mass spectrum (70 eV) 254 M^+ (60), 236 (100), 219 (40), 170 (30), 154 (40); IR ($CDCl_3$) 3480, 1620, 1600 cm^{-1}; NMR 300 MHz ($CDCl_3$) 1.78 (s, 3 H), 2.51 (s, 3 H), 2.63 (m, 1 H), 2.54 (d, 1 H, J = 17 Hz), 2.94 (t, 1 H, J = 13.4 Hz), 3.10–3.15 (m, 2 H), 3.28 (d, 1 H, J = 17 Hz), 6.48 (s, 1 H), 6.94 (s, 1 H), 7.18–7.30 (m, 3 H), 7.98 (s, 1 H). This material was used in the next step without further purification.

Setoclavine (3). A solution of compound **31** (25 mg, 0.1 mmol) in 10 mL of 1 N HCl was stirred for 1 h and then added to 50 mL of a saturated $NaHCO_3$ solution. Extraction with chloroform, drying over Na_2SO_4, and evaporation of the solvent gave a yellow solid: 20 mg (80%); mp 206 °C; mass spectrum (70 eV) 254 M^+ (100), 236 (30), 201

(31) Jansen, A. B. A.; Johnson, J. M.; Surtees, J. R. *J. Chem. Soc.* **1964**, 5573–5577.

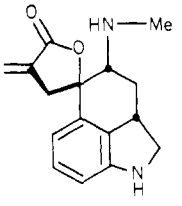
(40), 196 (50), 181 (40), 168 (45), 154 (100); IR ($CDCl_3$) 3480, 1615, 1600 cm^{-1}; NMR (300 MHz, $CDCl_3$) 1.36 (s, 3 H), 2.53 (d, 1 H, J = 13 Hz), 2.58 (s, 3 H), 2.68 (dt, 1 H, J = 1.4 Hz, J = 12.5 Hz), 2.81 (dd, 1 H, J = 1.4 Hz, J = 13 Hz), 3.07 (ddd, 1 H, J = 2 Hz, 5.7 Hz, 12.5 Hz), 3.55 (dd, 1 H, J = 5.7 Hz, 14.5 Hz), 6.41 (s, 1 H), 6.92 (t, 1 H, J = 2 Hz), 7.15–7.3 (m, 3 H), 7.90 (s, 1 H).

Rearrangement of Isosetoclavine (34) to Setoclavine (3). A solution of isosetoclavine (**34**) (12 mg, 0.05 mmol) in 10 mL of 1 N HCl was stirred for 1 h and then added slowly to a well stirred solution of saturated $NaHCO_3$. Extraction into $CHCl_3$ and evaporation of the solvent gave setoclavine, 7 mg (60%), identical with that described above.

Alkylation of 15. The method used to alkylate **26** → **27** was used. This resulted in a pale yellow solid which was recrystallized from EtOAc to give the racemic *N*-methyl derivative (80%) as a pure white solid, mp 232–234 °C. Alkylation of (+)-**15** gave its derivative: mp 217 °C; $[\alpha]^{25}_D$ +120 (c 0.5, $CHCl_3$); mass spectrum (70 eV) 478 M^+ (10), 343 (15), 317 (60), 212 (40), 105 (100); IR ($CDCl_3$) 1760, 1638, 1600, 1580 cm^{-1}; NMR (300 MHz, $CDCl_3$) 2.12–2.18 (m, 2 H), 2.96 (s, 3 H), 3.42 (d, 1 H, J = 18 Hz), 3.56–3.70 (m, 1 H), 3.75 (d, 1 H, J = 18 Hz), 3.80 (t, 1 H, J = 11 Hz), 4.10–4.70 (br, 1 H), 5.47 (t, 1 H, J = 7.5 Hz), 5.76 (t, 1 H, J = 2.0 Hz), 6.35 (t, 1 H, J = 2 Hz), 7.01 (br, 1 H), 7.29–7.63 (m, 12 H).

10α-Hydroxy-2,3,9,10-tetrahydroisolysergate, γ-Lactone (40). A solution of the *N*-methyl derivative of **15** (240 mg, 0.5 mmol) in 20 mL of CH_2Cl_2 saturated with dry HBr was stirred for 3 h at room temperature under N_2. The reaction mixture was evaporated to dryness to give a 3:1 ratio of the isomers of **38**. Without separation, the mixture was treated with anhydrous Na_2CO_3 (100 mg) and excess triethyl oxonium salt in CH_2Cl_2 solution for 2 h at room temperature under N_2. The reaction mixture was then treated with 100 mL of 1N HCl and stirred for 10 min. Neutralization with saturated $NaHCO_3$, extraction into $CHCl_3$, and drying over Na_2SO_4 followed by chromatography on silica gel (60% ethyl acetate/hexane followed by ethyl acetate) gave a white solid, which was recrystallized from EtOAc to give racemic **40**: 74 mg (55%); mp 220 °C dec. (+)-**40** was prepared in an identical fashion from the (+)-*N*-methyl derivative of **15**: mp 176 °C dec; $[\alpha]^{25}_D$ +80 (c 0.5, $CHCl_3$); mass spectrum (70 eV) 270 M^+ (100), 225 (18), 213 (10), 152 (20); IR ($CDCl_3$) 1772, 1625, 1608, 1580 cm^{-1}; NMR (300 MHz $CDCl_3$) 1.53 (q, 1 H, J = 11.5 Hz), 1.95 (d, 1 H, J = 11 Hz), 2.36–2.51 (m, 3 H), 2.49 (s, 3 H), 2.95–3.33 (m, 5 H), 3.708 (t, 1 H, J = 7 Hz), 6.64 (d, 1 H, J = 7 Hz), 6.83 (d, 1 H, J = 7 Hz), 7.12 (t, 1 H, J = 7 Hz); m/e calcd for $C_{16}H_{18}N_2O_2$, 270.1368; found, 270.1369.

Further elution of the column with acetone gave 39 mg (30%) of the *debenzoylated* derivative of the methylene lactone, i. This substance



i

apparently results from elimination from the other isomer of the HBr addition product.

10α-Hydroxy-9,10-dihydroisolysergate, γ-Lactone (41). A solution of indoline **40** (135 mg, 0.5 mmol) in 20 mL of anhydrous methylene chloride was treated with 1.1 g of Attenburrow manganese dioxide and stirred at room temperature for 2 h. MnO_2 was separated by filtration and washed thoroughly with $CHCl_3$. Evaporation of the solvent gave a pale yellow solid which was recrystallized from CH_2Cl_2 to give 100 mg (75%) of **41** as a white solid, mp 190 °C dec. (+)-**41** was prepared in an identical fashion from (+)-**40**: mp 203 °C dec; $[\alpha]^{25}_D$ +67 (c 1.37, pyridine) [lit.[29] $[\alpha]^{25}_D$ +69 (c 1.3, pyridine); NMR (300 MHz, $CDCl_3$) 1.94 (d, 1 H, J = 11.7 Hz), 3.18 (s, 3 H), 2.60 (d, 1 H, J = 10 Hz), 2.65 (dd, 1 H, J = 4.7, 11 Hz), 2.84 (dt, 1 H, J = 1.6 Hz, J = 11 Hz), 2.99 (t, 1 H, J = 4.5 Hz), 3.26 (ddd, 1 H, J = 2 Hz, 5.5 Hz, J = 11.7 Hz), 3.31–3.41 (m, 2 H), 6.98 (s, 1 H), 7.24–7.48 (m, 3 H), 8.11 (br s, 1 H); m/e calcd for $C_{16}H_{16}N_2O_2$, 268.1212; found, 268.1215; mass spectrum (70 eV) 268 M^+ (100), 223 (50).

Methyl 10α-Hydroxy-2,3,9,10-dihydroisolysergate (42). A solution of the pentacyclic lactone **40** (54 mg, 0.2 mmole) in 20 mL of MeOH was treated with $SOCl_2$ (1 mL). After stirring at room temperature for 4 h under N_2, the reaction mixture was evaporated to dryness. For isolation of the free base **42**, 5 mL of ice water was added to the salt, followed by neutralization with $NaHCO_3$ solution. Extraction with $CHCl_3$, drying over Na_2SO_4, and evaporation afforded 60 mg (100%) of hydroxymethyl ester **42**: mass spectrum (70 eV) 302 (70), 270 (45), 244 (40), 223 (25), 172 (30), 154 (40), 146 (80), 130 (60), 118 (100); IR ($CDCl_3$) 1720, 1615, 1600 cm^{-1}; NMR (300 MHz, $CDCl_3$) 1.57 (q, 1 H, J = 11.5 Hz), 1.81 (dd, 1 H, J = 7 Hz, J = 14 Hz), 2.24 (dd, 2 H, J = 2.2 Hz, J = 10.7 Hz), 2.35 (dd, 1 H, J = 4.5 Hz, J = 11 Hz), 2.45 (s, 3 H), 2.70 (t, 1 H, J = 4.5 Hz), 3.12 (d, 1 H, J = 14 Hz). 3.10–3.2 (m, 2 H), 3.46 (d, 1 H, J = 11.7 Hz, 3.66 (t, 1 H, J = 7 Hz), 3.77 (s, 3 H), 6.58 (d, 1 H, J = 7.4 Hz), 6.90 (d, 1 H, J = 7 Hz), 7.07 (t, 1 H, J = 7.4 Hz).

For direct conversion to **43a** the salt was treated with 10 mL of a P_2O_5/methanesulfonic acid solution at room temperature for 3 h. Neutralization with $NaHCO_3$ solution, extraction with $CHCl_3$, drying over Na_2SO_4, and evaporation of the solvent afforded 54 mg (95%) of a brown solid, which isomerized and decomposed, and was used without further purification: mass spectrum (70 eV) 284 M^+ (100), 241 (16), 225 (15), 223 (16), 182 (45), 168 (20), 167 (20); IR ($CDCl_3$) 1728, 1615, 1600 cm^{-1}; NMR (300 MHz, $CDCl_3$) 1.42 (q, 1 H, J = 11.5 Hz), 2.49 (s, 3 H), 2.52 (d, 1 H, J = 5 Hz), 2.57 (dd, 1 H, J = 4.7 Hz, J = 12 Hz), 2.90 (br dd, 1 H, J = 2.5 Hz, J = 11.5 Hz), 3.10–3.31 (m, 3 H), 3.44 (d, 1 H, J = 12 Hz), 3.67 (t, 1 H, J = 7 Hz), 3.72 (s, 3 H), 6.49–6.53 (m, 2 H), 6.96–7.06 (m, 2 H).

These spectroscopic features are in agreement with those reported by Ramage,[4] however the HPLC retention time using $MeCN/CH_2Cl_2$ reported by these workers was attained by us only when $MeOH/CH_2Cl_2$ was the eluent. For further characterization this substance was benzoylated.

Methyl 1-Benzoyl-2,3-dihydrolysergate (44b) and Methyl 1-Benzoyl-2,3-dihydroisolysergate (43b). A solution of **43a** (14 mg, 0.05 mmol) in 5 mL of MeOH containing 0.05 mL of pyridine was treated with 0.05 mL of BzCl at room temperature. Chromatography on silica gel (EtOAc/hexane 1:1 then acetone) gave 17 mg (80%) of two isomers which could be separated by HPLC (microporasil, Me_2CO/hexane 3:2).

44b: IR ($CDCl_3$) 1728, 1640, 1602, 1585, 1580 cm^{-1}; NMR (300 MHz, $CDCl_3$) 1.40, (q, 1 H, J = 11.7 Hz), 2.50 (s, 3 H), 2.50–2.65 (m, 1 H), 2.70 (t, 1 H, J = 12.5 Hz), 3.05 (br dd, 1 H, J = 2.8 Hz, J = 11.7 Hz), 3.28 (dd, 1 H, J = 5.5 Hz, J = 12.5 Hz), 3.35–3.50 (m, 1 H), 3.60–3.76 (m, 2 H), 3.76 (s, 3 H), 4.1–4.6 (br, 1 H), 6.55 (s, 1 H), 6.9–7.10 (br 1 H), 7.27–7.61 (m, 7 H). These values are in agreement with those reported by Ramage,[4] and this substance was also an intermediate in Ninomiya's[6] synthesis.

43b: IR ($CDCl_3$) 1733, 1640, 1605, 1580 cm^{-1}; NMR (300 MHz, $CDCl_3$) 1.41 (q, 1 H, J = 11.7 Hz), 2.48 (s, 3 H), 2.51 (d, 1 H, J = 6.8 Hz), 2.58 (dd, 1 H, J = 5 Hz, 11.7 Hz), 2.89 (br dd, 1 H, J = 2 Hz, 11.7 Hz), 3.18 (br t, 1 H), 3.30–3.45 (m, 1 H), 3.45 (d, 1 H, J = 11.7 Hz), 3.67 (t, 1 H, J = 11 Hz), 4.1–4.6 (m, 1 H), 6.55[32] (d, 1 H, J = 3.2 Hz), 6.9–7.15 (br, 1 H), 7.27–7.61 (m, 7 H).

Either isomer gave the same (equilibrium) mixture on heating in MeOH; the ratio **44b**:**43b** ≐ 3:1 was observed.

Methyl Lysergate and Methyl Isolysergate. A solution of **43a** (28 mg, 0.1 mmol) in 5 mL of anhydrous methylene chloride was treated with 220 mg MnO_2 and stirred at room temperature for 1 h. The solids were separated by filtration and washed thoroughly with $CHCl_3$. Chromatography on silica gel gave 12 mg (45%) of ester in a 3:2 ratio of isomers which were separated by HPLC.

Methyl lysergate: NMR (300 MHz, $CDCl_3$) 2.63 (s, 3 H), 2.68–2.80 (m, 2 H), 3.18–3.35 (m, 2 H), 3.53 (dd, 1 H, J = 6 Hz, J = 14 Hz), 3.53 (m, 1 H), 3.79 (s, 3 H), 6.61 (br s, 1 H), 6.93 (br s, 1 H), 7.16–7.25 (m, 3 H), 7.92 (br s, 1 H); mass spectrum (70 eV) 282 M^+ (100), 266 (45), 231 (30), 224 (30), 207 (30), 149 (22).

Methyl isolysergate: NMR (300 MHz, $CDCl_3$) 2.62 (s, 3 H), 2.58–2.62 (m, 1 H), 2.70–2.92 (m, 2 H), 3.30–3.58 (m, 3 H), 3.74 (s, 3 H), 6.57 (d, 1 H, J = 4 Hz), 6.92 (s, 1 H), 7.16–7.25 (m, 3 H), 7.92 (br s, 1 H).

A suspension of natural lysergic acid (2 mg) in 5 mL of benzene was treated with 1 mL of CH_2N_2/Et_2O solution at 0 °C for 2 h. Evaporation of the solvents gave the methyl ester of lysergic acid, the 300 MHz NMR spectrum of which was identical with that described above.

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Registry No. 1, 82-58-6; (±)-**1** (methyl ester), 88636-21-9; (±)-*iso*-**1** (methyl ester), 88636-22-0; (±)-**2**, 82359-58-8; (±)-**2** (*N*-demethyl), 88636-16-2; (±)-**3**, 86194-81-2; (±)-**7**, 34964-90-4; **12a**, 88636-10-6; (±)-**12a**, 88668-84-2; **12b**, 88636-11-7; (±)-**12b**, 88668-83-1; (±)-**13**,

(32) This value reported[4] as 6.19.

74644-93-2; **13a**, 88668-85-3; **13b**, 74606-97-6; (+)-**15**, 86783-97-3; (−)-**15**, 88668-86-4; (±)-**15**, 74606-93-2; (+)-**15** (*N*-methyl), 86749-47-5; (±) **15** (*N*-methyl), 88668-95-5; (±)-**16**, 88636-12-8; (±)-**19** (isomer 1), 88636-13-9; (±)-**19** (isomer 2), 88668-88-6; (±)-**20** (isomer 1), 82359-56-6; (±)-**20** (isomer), 88668-87-5; (±)-**21**, 82359-57-7; (±)-**22**, 88636-14-0; (±)-**23**, 88636-15-1; (±)-**24**, 82359-60-2; (±)-**25**, 82359-59-9; (+)-**26**, 88668-89-7; (±)-**26**, 74606-94-3; (+)-**27**, 88668-90-0; (±)-**27**, 74606-95-4; (±)-**28**, 88668-91-1; (±)-**29**, 88668-92-2; (±)-**30**, 88668-93-3; (±)-**31**, 88668-94-4; (±)-**38** (isomer 1), 88668-96-6; (±)-**38** (isomer 2), 88668-97-7; (+)-**40**, 86749-46-4; (±)-**40**, 88636-17-3; (+)-**41**, 3623-44-7; (±)-**41**, 88668-98-8; (±)-**42**, 88636-20-8; (±)-**42** (base), 88636-19-5; (±)-**43a**, 62592-63-6; (±)-**43b**, 62592-69-2; (±)-**44b**, 62630-94-8; i, 88636-18-4; CH_2=$C(CH_2Br)CO_2Et$, 17435-72-2; CH_2=$C(CH_3)CH_2Cl$, 563-47-3; L-tryptophan, 73-22-3; DL-tryptophan, 54-12-6.

Antimicrobial Metabolites from a Pacific Sponge, *Agelas* sp.

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Contribution from Scripps Institution of Oceanography, A-012F La Jolla, California 92093.
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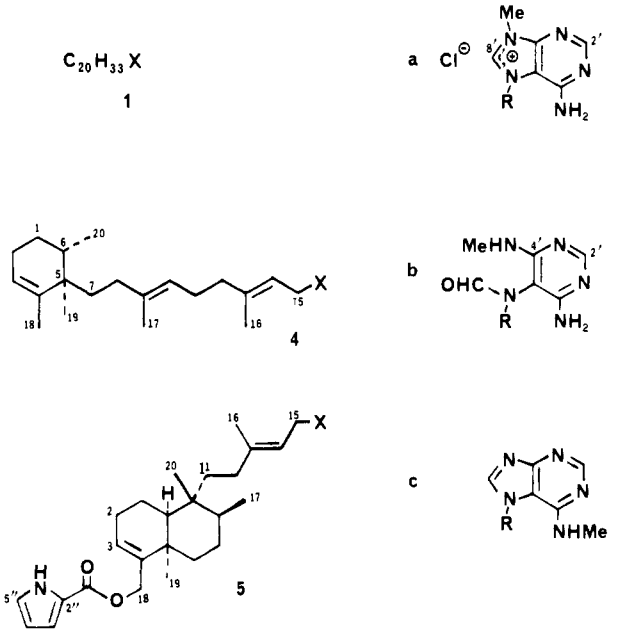
Abstract: Three novel antimicrobial metabolites have been isolated from the Pacific sponge *Agelas* sp. Two of the metabolites, ageline A (**4a**) and ageline B (**5a**), are quarternary 9-methyladenine salts of diterpenes. The third and minor metabolite was shown to be agelasidine A (**6**), a sesquiterpenoid derivative of taurocyamine. The structures of ageline A and ageline B were elucidated by interpretation of spectral data with particular emphasis on ^{13}C NMR correlations. The agelines are mild ichthyotoxins and show moderate antimicrobial activities.

In 1975, Cullen and Devlin[1] reported that *Agelas dispar* contained agelasine (**1a**), a 9-methyladenine derivative of an unidentified diterpene.[2] This report was in sharp contrast to all other studies[3] of *Agelas* species that described brominated pyrrole derivatives, such as oridin (**2**)[3a] and sceptrin (**3**),[3b] as the typical metabolites of the genus. From an unidentified *Agelas* species collected at Palau, Western Caroline Islands, we have isolated three novel metabolites, two of which were quarternary 9-methyladenine derivatives of diterpenes while the third was agelasidine A (**6**), a sesquiterpene derivative of taurocyamine, recently described by Nakamura et al.[4] In this paper, we report the structural elucidation of ageline A (**4a**) and ageline B (**5a**).

The material from the methanolic extract of the sponge was triturated with dichloromethane and then methanol to obtain two fractions that showed activity against *Bacillus subtilis*, *Staphylococcus aureus*, *Candida albicans*, and the marine bacterium B-392. With use of antimicrobial activity to follow the separations, the dichloromethane fraction was repeatedly chromatographed on Sephadex LH-20 first with methanol and then with 1:1 dichloromethane/methanol as eluants and then on silica gel with 6:3:1 chloroform/methanol/ammonia as eluant to obtain agelasidine A (**6**, 0.16% dry weight) and a white solid. The white solid was separated into four fractions by reversed-phase LC, but each of the fractions equilibrated on standing. The four fractions represented pairs of isomers of the two formamides **4b** (1.28% dry weight) and **5b** (0.21% dry weight).



Although the formamides **4b** and **5b** had retained sufficient antimicrobial activity to allow a bioassay-directed fractionation, these metabolites were not present in the crude dichloromethane or methanol extracts. Examination of the ^1H NMR spectra revealed that the formamides were artifacts produced during chromatography on silica gel. The same transformation had been observed by Cullen and Devlin,[1] who obtained the formamide **1b** by hydrolysis of agelasine (**1a**) with aqueous sodium carbonate solution. We were able to isolate a pure sample of ageline A (**4a**, 0.11% dry weight) together with 2:1 mixture of ageline A (**4a**) and ageline B (**5a**) by fractional crystallization of the methanol-soluble fraction from acetonitrile. Since hydrolysis of the 2:1 mixture of **4a** and **5a** gave a 2:1 mixture of **4b** and **5b**, the

(1) Cullen, E.; Devlin, J. P. *Can. J. Chem.* **1975**, *53*, 1690.
(2) The data presented in ref 1 indicated that the diterpene portion of the molecule was probably based on a labdane, kolevane, or related bicyclic skeleton. Devlin (personal communication) has reported that the diterpene portion was not homogeneous.
(3) (a) Minale, L.; Cimino, G.; De Stefano, S.; Sodano, G. *Prog. Chem. Nat. Prod.* **1976**, *33*, 1 and references cited therein. (b) Walker, R. P.; Faulkner D. J.; Van Engen, D.; Clardy, J. *J. Am. Chem. Soc.* **1981**, *103*, 6772. (c) Chevolot, L.; Padua, S.; Ravi, B. N.; Blyth, P. C.; Scheuer, P. J. *Heterocycles* **1977**, *7*, 891.
(4) Nakamura, H.; Wu, H.; Kobayashi, J.; Ohizumi, Y.; Hirata, Y.; Higashijima, T.; Miyazawa, T. *Tetrahedron Lett.* **1983**, *24*, 4105.

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