AN ATTEMPTED TOTAL SYNTHESIS OF LYSERGIC ACID *VIA* AN ALKENE/*N*-SULFONYLIMINE CYCLIZATION

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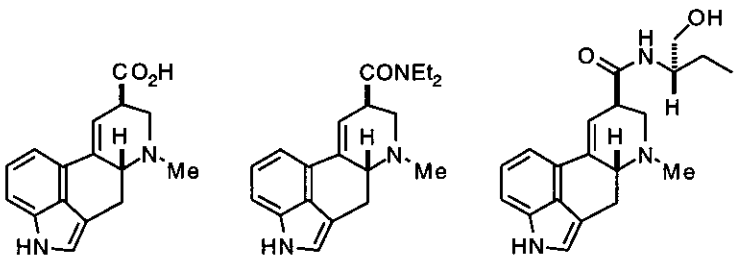
Abstract - Lewis acid-promoted cyclization of the *N*-tosylimine derived from aldehyde alkene (**18**) affords an interesting rearranged seven-membered ring tricycle (**21**) rather than the expected intermediate containing the lysergic acid skeleton.

The *Ergot* alkaloids represent an important subgroup of indole alkaloids because of their wide range of biological activity.[1,2] Many *Ergot* alkaloids and their derivatives have been reported to produce such diverse effects as uterotonic action, increase or decrease in blood pressure, induction of hypothermia and emesis, and control of the secretion of pituitary hormones. These biological responses are primarily mediated by noradrenaline, serotonin, or dopamine receptors.

One of the most important compounds in this class is lysergic acid (**1**). Various derivatives of lysergic acid, particularly carboxamides, show remarkable pharmacological effects. For example, lysergic acid diethylamide (LSD) (**2**) is one of the most potent hallucinogenic drugs known. Another derivative, methysergide (**3**), is a highly effective substance for the prevention of migraine attacks.

Lysergic acid has long been a target for chemical synthesis. The first reported synthesis was by Woodward and workers at the Eli Lilly Company in 1954.[1] To date, total syntheses of lysergic acid have been achieved by eight groups, and these successes have been recently reviewed.[1]

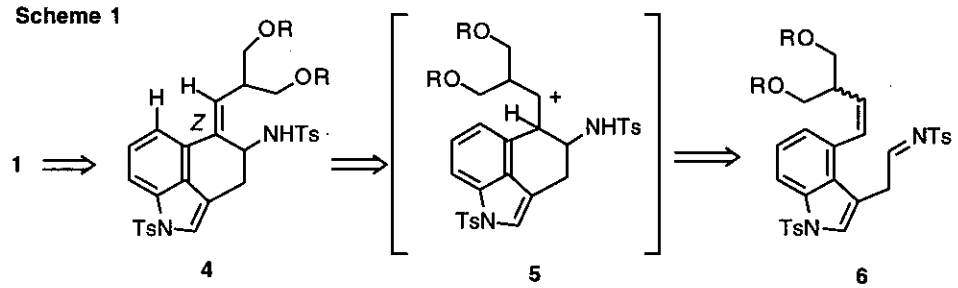
During the past several years, we have been actively investigating the scope and utility of *N*-sulfonyl imines,[3,4] prepared via the Kresze reaction of *N*-sulfinyl sulfonamides with aldehydes,[5] in synthesis of a variety of heterocycles and alkaloids. We hoped to apply the previously discovered[3] intramolecular cyclization of an *N*-sulfonylaldimine with an olefin as the key step in an efficient new approach to lysergic



(1) lysergic acid (2) LSD (3) methysergide

acid (**1**). Our intended strategy was to synthesize (**1**) *via* a tricyclic intermediate (**4**) which was to be prepared by cyclization of alkene *N*-sulfonylimine (**6**), presumably involving an intermediate cation (**5**) (Scheme 1). A critical requirement for a successful approach to the alkaloid using this general plan is that

Scheme 1



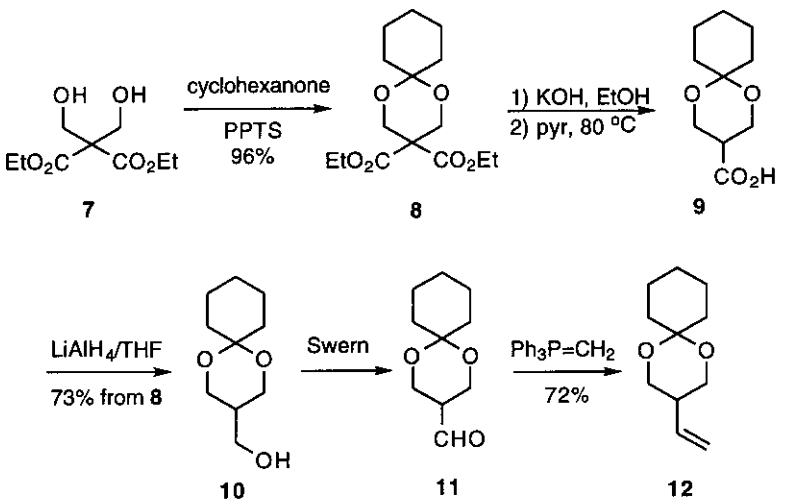
4 **5** **6**

cyclization product (**4**) have the *Z* alkene double bond geometry. Molecular mechanics calculations indicated that the *Z* compound is approximately 3 kcal/mole more stable than the *E*, probably due to a destabilizing *peri* interaction between an aromatic hydrogen and the bulky olefin substituent in the latter isomer. We hoped that the *Z* isomer (**4**) could be formed either directly or upon olefin equilibration subsequent to cyclization.

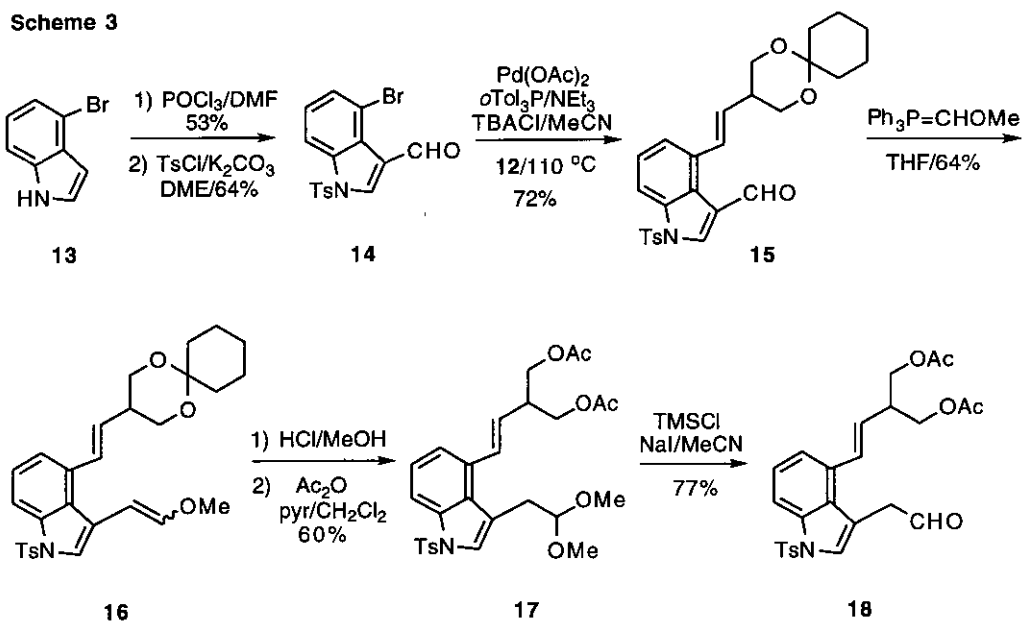
The requisite substrate (*cf***6**) for the pivotal cyclization step was synthesized *via* a short, convergent route. Thus, commercially available diethyl *bis*(hydroxymethyl)malonate (**7**) was converted to ketal (**8**), which was then decarboxyated to afford monoacid (**9**) (Scheme 2).[6] Hydride reduction of this acid yielded primary alcohol (**10**), and subsequent Swern oxidation provided aldehyde (**11**). Wittig olefination of (**11**) yielded the desired terminal olefin (**12**).

The indole moiety was constructed from readily available bromo compound (**13**).[7] Formylation of (**13**) using Vilsmeier-Haack conditions[8] provided the indole-3-aldehyde, which was *N*-tosylated giving (**14**) (Scheme 3). Using methodology related to that described by Hegedus and coworkers,[9] it was possible to

Scheme 2



Scheme 3

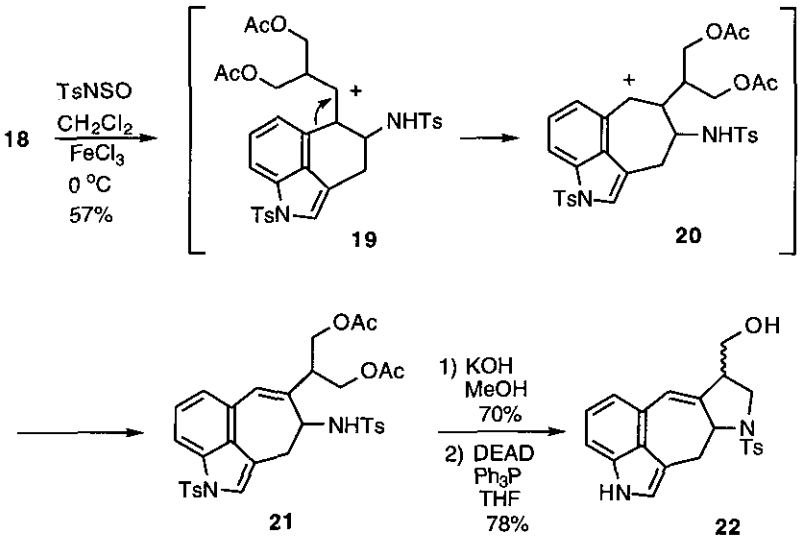


effect a Heck reaction between bromoindole (**14**) and alkene (**12**) to generate coupled product (**15**) as the *E*-olefin isomer. Homologation of the formyl group was effected by Wittig chemistry giving enol ether (**16**). However, the enol ether moiety proved rather difficult to hydrolyze cleanly to the corresponding aldehyde.[10] In addition, it was also subsequently found that a ketal protecting group for the 1,3-diol was not compatible with the Lewis acid catalysts required for the key cyclization step (*vide infra*) and therefore a sequence was eventually developed leading to the optimally protected cyclization substrate (**18**).[10] Thus, enol ether (**16**) was treated with methanolic HCl, affording a diol dimethyl acetal, which was acetylated to

yield diacetate acetal (**17**). Cleavage of the dimethyl acetal using *in situ*-generated TMSI then afforded the desired olefin aldehyde (**18**).[11]

With aldehyde (**18**) in hand, extensive studies were conducted to determine how to best generate the requisite *N*-sulfonylimine.[10] It was found that treatment of **18** with *N*-sulfinyl-*p*-toluenesulfonamide[12] in methylene chloride at room temperature under neutral conditions[13,14] for 25 minutes gave the *N*-sulfonylimine. Addition of anhydrous $FeCl_3$ at 0°C then led to formation of a cyclization product in 57% yield (Scheme 4). Other Lewis acids such as $ZnCl_2$, $TiCl_4$ and BF_3-etherate gave significantly lower

Scheme 4

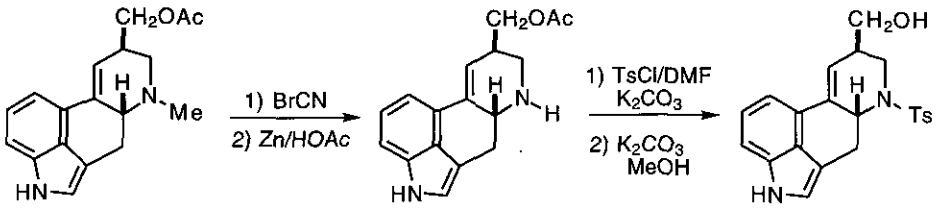


yields of product. It was eventually established that in fact this material had the interesting and unexpected rearranged structure (**21**) containing a seven-membered ring (*vide infra*).

Although the spectral data for this cyclization product were generally compatible with the desired lysergic acid intermediate (*cf* **4**, R=Ac), a firm assignment of structure could not be made, and therefore it was decided to chemically correlate our synthetic material with the natural alkaloid. Thus, known *O*-acetyl-lysergol (**23**)[15] (Scheme 5) was demethylated using a von Braun degradation[16] to afford secondary amine (**24**). Tosylation of the indole nitrogen of **24** and acetate methanolysis led to hydroxy sulfonamide (**25**).

The tricyclic product (**21**) could be further cyclized by a Mitsunobu protocol[17] into a chromatographically separable 1:1 mixture of diastereomeric tetracyclic alcohols (**22**) (Scheme 4). Comparison of the spectral

Scheme 5



23 **24** **25**

data for both isomers of **22** with lysergol-derived compound (**25**) indicated that they were not identical. These surprising results prompted reinvestigation of the structure of synthetic intermediate (**21**) by *X*-ray crystallography. An ORTEP drawing of the crystal structure is shown in the Figure.[18]

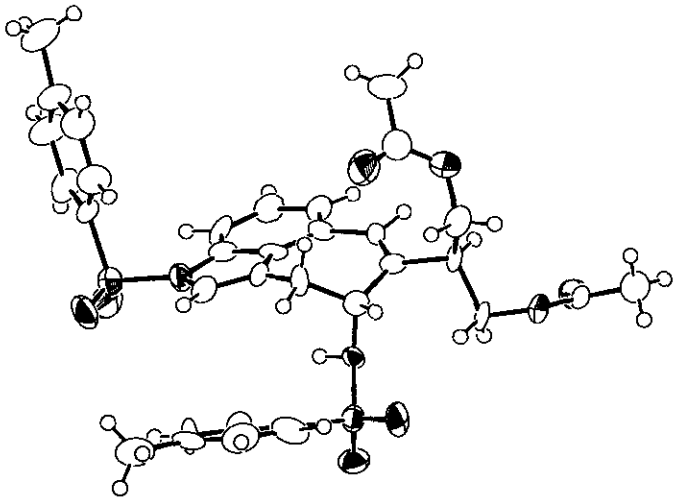


Figure. ORTEP drawing of tetracyclic intermediate (**21**)

As can be seen, compound (**21**) proved to be an undesired ring expanded product. We believe this material forms *via* initial *N*-sulfonylimine/alkene cyclization as expected to produce carbonium ion (**19**) (Scheme 4) which then undergoes 1,2-aryl migration to yield benzyl cation (**20**). Proton loss from **20** then provides seven membered olefin (**21**). Although a number of attempts were made to suppress this undesired rearrangement by varying reaction conditions and *O*-protecting groups, only small amounts of the requisite six-membered ring cyclization product could ever be produced. We are planning to modify our basic strategy to avoid this unanticipated rearrangement problem, and future studies in this area will be reported in due course.

EXPERIMENTAL

Preparation of Ketal Diester (8). *p*-Toluenesulfonic acid (5.1g, 0.027 mol) was added to a vigorously stirred solution of diethyl *bis*(hydroxymethyl)malonate (**7**) (60.0 g, 0.272 mol) and cyclohexanone (42.0 ml, 0.410 mol) in 300 ml of pentane and the mixture was refluxed for 48 h. During this heating period, 5.0 ml of water was separated from the condensate using a Dean-Stark trap. The reaction mixture was cooled to room temperature and concentrated *in vacuo*. The crude brown oil was dissolved in 500 ml of ethyl acetate and the solution washed two times with 200 ml portions of saturated $NaHCO_3$ solution. The organic extract was washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. Vacuum distillation of the residual yellow oil afforded 78.0 g (96%) of ketal diester (**8**) as a colorless oil: bp 120°C (0.1 Torr); ir (film) 2945, 2865, 1735, cm^{-1}; ^1H nmr (300 MHz, $CDCl_3$) δ 4.24 (4 H, s), 4.18 (4 H, q, J=7.1 Hz), 1.75-1.65 (4 H, m), 1.52-1.40 (4 H, m), 1.39-1.30 (2 H, m), 1.25-1.18 (6 H, t, J=7.1 Hz); ^{13}C nmr (75 MHz, $CDCl_3$) δ 168.0, 98.4, 61.8, 53.8, 32.2, 25.5, 22.4, 13.9; ms, m/z (relative intensity) 300 (M^+, 26), 271 (11), 258 (15), 257 (100), 127 (38).

Synthesis of Ketal Acid (9). Diester (**8**) (30.0 g., 0.999 mmol) in 50 ml of ethanol was added in one portion to a solution of KOH (30.0 g, 53.4 mmol) in 250 ml of ethanol and the resulting viscous mixture was heated at reflux for 8 h. The reaction mixture was cooled to room temperature, diluted with 200 ml of water and acidified to pH 4 with 5% HCl solution. The resulting mixture was extracted four times with ethyl acetate and the combined extracts were washed twice with brine, dried (Na_2SO_4), and evaporated *in vacuo* to afford a light brown solid (173 g). The crude material was used in the next step without purification. A small sample of diacid was purified by washing three times with ethyl acetate to yield the diacid as a white solid: mp 136-138°C; IR (film) 3350, 2950, 1710 cm^{-1}; ^1H nmr (300 MHz, CD_3CN) δ 4.19 (4 H, s), 1.69-1.65 (4 H, m), 1.49-1.37 (6 H, m); ^{13}C nmr (75 MHz, CD_3CN) δ 169.3, 99.0, 62.1, 53.9, 32.9, 26.0, 23.1; ms, m/z (relative intensity) 244 (M^+, 6), 215 (4), 281 (37), 157 (37), 139 (10), 99 (10), 98 (32), 85 (30), 70 (13), 69 (21), 55 (100); HRms calcd for $C_{11}H_{16}O_6$: 244.0946. Found: 244.0939.

A solution of the above dicarboxylic acid (23.0 g, 0.094 mol) in 40 ml of anhydrous pyridine was refluxed for 2.5 h. The reaction mixture was cooled to room temperarture and the solvent removed *in vacuo*. The oily brown residue was dissolved in 300 ml of ethyl acetate and the solution was washed with two 100 ml portions of aqueous 5% HCl and one 100 ml portion of brine. The solution was dried (Na_2SO_4), and the

solvent removed *in vacuo* to afford monocarboxylic acid (**9**) (17.0 g) as a light brown solid which was used in the next step without further purification. A small sample of acid (**9**) was purified by washing the solid with three portions of cold ethyl acetate: mp 92-94°C; ir (film) 3300-2500, 1700 cm^{-1}; ^1H nmr (300 MHz, $CDCl_3$) δ 4.14-3.99 (4 H, m), 2.82-2.74 (1 H, m), 1.80-1.68 (4 H, m), 1.55-1.38 (6 H, m); ^{13}C nmr (75 MHz, $CDCl_3$) δ 176.9, 98.4, 59.6, 40.0, 34.2, 30.7, 25.5, 22.4, 22.3; ms, m/z (relative intensity) 208 (M^+,14) 271 (10), 156 (9), 98 (14), 85 (38), 69 (10), 55 (39); HRms calcd for $C_{10}H_{16}O_4$: 200.1049. Found: 200.1052.

Reduction of Carboxylic Acid (9). A solution of acid (**9**) (16.9 g, 0.084 mol) in 100 ml of anhydrous ether was added dropwise to an ice-cold suspension of lithium aluminum hydride (8.0 g, 0.21 mol) in 150 ml of anhydrous ether and the mixture was stirred for 12 h at room temperature. The reaction was quenched by the consecutive addition of 33 ml of ethyl acetate, 17 ml of 15% NaOH solution, 17 ml of H_2O and 40 ml of saturated NH_4Cl solution. The mixture was filtered and the salts washed with ether and ethyl acetate. The combined filtrate was washed with brine, dried (Na_2SO_4), and rotary evaporated to give a yellow oil which was purified by vacuum distillation to afford 12.8 g (73% from diester (**8**)) of alcohol (**10**), bp 105°C (0.1 Torr); ir (film) 3400, 2940, 2865 cm^{-1}; ^1H nmr (300 MHz, $CDCl_3$) δ 3.98 (2 H, dd, J=12.0, 4.1 Hz), 3.77-3.70 (4 H, m), 2.40-2.35 (1 H, OH, br) 1.81-1.67 (5 H, m), 1.58-1.38 (6 H, m); ^{13}C nmr (75 MHz, $CDCl_3$) δ 98.1, 61.7, 60.4, 36.6, 33.4, 31.8, 25.6, 22.4, 23.0; ms, m/z (relative intensity) 186 (M^+, 21), 185 (12), 162 (18), 98 (7), 81 (17), 80 (11), 79 (11), 69 (11), 67 (11), 55 (42).

Preparation of Cyclohexylidene Aldehyde (11). Oxalyl chloride (1.13 ml, 0.013 mol) in 35 ml of CH_2Cl_2 was cooled to -78°C and DMSO (2.02 ml, 0.028 mol) was slowly added so as to keep the temperature of the solution below -50°C. The reaction mixture was stirred for 10 min and alcohol (**10**) (2.20 g, 0.012 mol) in 15 ml of CH_2Cl_2 was added dropwise. The reaction mixture was stirred for 1.5 h at -78°C, and then triethylamine (8.23 ml, 0.059 mol) was added. After 45 min, H_2O was added, and the reaction mixture was allowed to warm to room temperature. The mixture was extracted with ethyl acetate, the organic layer was washed with 5% HCl solution, dried over Na_2SO_4 and concentrated. The residue was purified by Kugelrohr distillation (75°C, 0.2 Torr) to give 1.75 g (80%) of aldehyde (**11**) as a yellow oil. ^1H Nmr (200 MHz, $CDCl_3$) δ 9.87 (1 H, s), 4.17-4.15 (4 H, d, J = 4.2 Hz), 2.39-2.28 (1 H, m), 1.85-1.27 (10 H, m); ^{13}C nmr (75 MHz, $CDCl_3$) δ 202.3, 98.1, 60.1, 57.9, 46.5, 34.7, 30.1, 25.4,

22.3, 22.2; ir (film) 2920, 2845, 1715 cm^{-1}; ms, m/z (relative intensity) 184 (22), 155 (16), 14 (100), 69 (31), 55 (52), 43 (16), 41 (25); HRms calcd for $C_{10}H_{16}O_3$: 184.1099. Found: 184.1101.

Preparation of Cyclohexylketal Alkene (12). *n*-Butyllithium (1.6 M in hexanes, 11.72 ml, 0.018 mol) was added dropwise to a solution of methyltriphenylphosphonium bromide (6.69 g, 0.018 mol) in 50 ml of THF at 0°C. The red solution was warmed to room temperature and was stirred for 45 min. Aldehyde (**11**) (2.30 g, 0.012) in 5 ml of THF was added dropwise to the solution at 0°C. After the reaction mixture was stirred for 5 h at room temperature, H_2O was added, and the mixture was extracted with ethyl acetate. The organic layer was dried over Na_2SO_4 and concentrated. Purification of the residue by Kugelrohr distillation (75°C, 0.2 Torr) gave 1.63 g (72%) of (**12**) as a yellow oil which was contaminated with a small amount (~5%) of triphenylphosphine. ^1H Nmr (200 MHz, $CDCl_3$) δ 5.68-5.51 (1 H, m), 5.14-5.04 (2 H, m), 4.05-3.63 (4 H, m), 2.65-2.43 (1 H, m), 1.87-1.31 (10 H, m); ^{13}C nmr (90 MHz, $CDCl_3$) δ 134.9, 117.1, 97.4, 63.3, 63.0, 39.1, 36.7, 28.5, 25.6, 22.4, 22.3; ir (film) 2920, 2840 cm^{-1}; ms, m/z (relative intensity) 182 (31), 153 (16), 139 (96), 98 (18), 86 (86), 84 (100), 67 (25), 54 (63), 48 (37), 35 (20); HRms calcd for $C_{11}H_{18}O_2$: 182.1307. Found: 182.1308.

***N*-Tosylindole Aldehyde (14).** Phosphorus oxychloride (2.62 ml, 0.028 mol) was added dropwise to DMF (9.36 ml) at 0°C. The reaction mixture was warmed to room temperature and was stirred for 1 h. Bromoindole (**13**)[7] (5.0 g, 0.025 mol) in 50 ml of DMF was added slowly to the solution at 0°C. The reaction mixture was warmed to room temperature and was stirred for 16 h. The viscous solution was brought to 0°C and H_2O was added. After 2h, the reaction mixture was thoroughly extracted with ethyl acetate. The organic layers were dried over Na_2SO_4 and concentrated to give 3.04 g (53%) of aldehyde as a gray solid. ^1H Nmr (200 MHz, $CDCl_3$) δ 10.90 (1 H, s), 9.15 (1 H, br s), 7.50-7.41 (2 H, m), 7.24-7.08 (1 H, m); ^{13}C nmr (75 MHz, $CDCl_3$) δ 186.6, 138.1, 131.1, 126.7, 124.9, 124.0, 118.5, 113.5, 111.2; ir (film) 1630, 1370, 1180 cm^{-1}; ms, m/z (relative intensity) 224 (100), 223 (93), 222 (95), 196 (17), 194 (16), 115 (39), 89 (27), 88 (21), 63 (18), 44 (15); HRms calcd for C_9H_6NOBr: 222.9633. Found: 222.9624.

Potassium carbonate (11.6 g, 84.0 mmol) and *p*-toluenesulfonyl chloride (1.76 g, 9.28 mmol) were added to a stirred solution of the above indole-3-aldehyde (1.89 g, 8.44 mmol) in 25 ml of DME. The reaction mixture was stirred for 20 h at room temperature, diluted with H_2O, and extracted with ethyl acetate. The

organic layer was washed with 5% HCl solution, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (10% ethyl acetate/hexanes to 50% ethyl acetate/hexanes) to give 2.05 g (64%) of aldehyde (**14**) as a tan solid (mp 167°C). ^{1}H Nmr (200 MHz, $CDCl_3$) δ 10.91 (1 H, s), 8.41 (1H, s), 8.00-7.96 (1 H, d, J=9.1 Hz), 7.84-7.80 (2 H, d, J=8.5 Hz), 7.55-7.52 (1 H, d, J=8.4 Hz), 7.31-7.18 (3 H, m), 2.35 (3 H, s); ^{13}C nmr (75 MHz, $CDCl_3$) δ 185.6, 145.9, 135.5, 133.5, 131.5, 129.9, 128.3, 126.7, 126.4, 125.6, 121.4, 113.3, 112.3, 21.1; ir (film) 1665, 1370, 1165, 975, 670 cm^{-1}; ms, m/z (relative intensity) 377 (28), 155 (67), 91 (100), 65 (17); HRms calcd for $C_{16}H_{12}NO_3BrS$: 376.9722. Found: 376.9753. Anal. Calcd for $C_{16}H_{12}NO_3BrS$: C, 50.93; H, 3.18. Found: C, 50.90, H, 3.35.

Formation of Heck Product (15). *N*-Tosyl bromoindole (**14**) (0.05 g, 1.32 mmol), alkene (**12**) (0.040 g, 2.21 mmol), palladium acetate (0.089 g, 0.37 mmol), tri-*o*-tolylphosphine (0.11 g, 0.37 mmol), tetrabutylammonium chloride (0.51 g, 1.85 mmol) and triethylamine (0.33 ml, 2.39 mmol) were added to 10 ml of acetonitrile in a sealable tube. The system was thoroughly degassed using the freeze-thaw method and sealed under vacuum (0.2 Torr). The reaction mixture was heated at 110°C for 20 h, cooled to room temperature and filtered through Celite. The filtrate was concentrated, and the residue purified by flash chromatography on neutral alumina (30% ethyl acetate/hexanes) to give 0.45 g (72%) of *E*-olefin (**15**) as a yellow viscous oil. ^{1}H Nmr (200 MHz, $CDCl_3$) δ 10.05 (1 H, s), 8.32 (1 H, s), 7.93-7.62 (3 H, m), 7.48-7.21 (5 H, m), 6.15-5.96 (1 H, dd, J=15.9, 7.5 Hz), 4.11-3.73 (4 H, m), 2.89-2.71 (1 H, m), 2.35 (3 H, s), 1.95-1.27 (10 H, m); ^{13}C nmr (90 MHz, $CDCl_3$) δ 184.4, 146.3, 139.1, 136.4, 134.2, 133.3, 131.7, 130.4, 129.3, 127.4, 126.3, 124.2, 121.9, 112.3, 97.8, 63.5, 60.5, 38.6, 36.4, 29.3, 25.8, 22.7, 22.5, 21.7, 14.3; ir (film) 2910, 2840, 1670 cm^{-1}; ms, m/z (relative intensity) 479 (1), 351 (47), 208 (21), 196 (83), 168 (61), 141 (21), 91 (100), 55 (40), 41 (19); HRms calcd for $C_{27}H_{29}NO_5S$: 479.1766. Found: 479.1728.

Synthesis of Enol Ether (16). Phenyllithium (1.8 M in cyclohexane/ether, 1.69 ml, 3.05 mmol) was added dropwise to a solution of methoxymethyltriphenylphosphonium chloride (0.99 g, 2.89 mmol) in 5 ml of THF at 0°C. The dark red solution was stirred for 45 min. Aldehyde (**15**) (0.73 g, 1.52 mmol) in 1 ml of THF was added dropwise to the solution at 0°C. After the reaction mixture was stirred for 1 h, water was added, and the mixture was extracted with ethyl acetate. The organic layer was dried over Na_2SO_4,

and concentrated. Purification of the residue by flash chromatography on neutral alumina (10% to 30% ethyl acetate/hexanes) gave 0.49 g (64%) of enol ether (**16**) as a 5:3 mixture of geometric isomers. ^{1}H Nmr (360 MHz, $CDCl_3$) δ 8.12-7.68 (4 H, m), 7.45-7.09 (4 H, m), 6.79-6.72 (1 H, d, J=12.7 Hz, major isomer), 6.25-6.23 (1 H, d, J=6.7 Hz, minor isomer), 5.96-5.78 (2 H, m), 5.63-5.60 (1 H, d, J=6.7 Hz, minor isomer), 3.91-3.84 (4 H, m), 3.71 (1 H, s, major isomer), 3.70 (1 H, s, minor isomer), 3.02-2.95 (1 H, m, minor isomer), 2.83-2.69 (1 H, m, major isomer), 2.32 (3 H, s), 1.93-1.26 (10 H, m); ir (film) 2910, 2820, 1620 cm^{-1}; ms, m/z (relative intensity) 507 (43), 364 (15), 353 (20), 254 (20), 224 (30), 194 (44), 180 (35), 168 (22), 91 (67); HRms calcd for $C_{29}H_{33}NO_5S$: 507.2079. Found: 507.2060.

Conversion of Enol Ether (16) to Acetal Diacetate (17). Methanolic HCl (1.15 M, 0.46 ml, 0.53 mmol) was added to a solution of enol ether (**16**) (0.090 g, 0.18 mmol) in 2 ml of methanol at room temperature. After the reaction mixture was stirred for 2 h, sat. $NaHCO_3$ was added, and the mixture was extracted with ethyl acetate. The organic layer was dried over Na_2SO_4 and concentrated to yield 0.061 g (75%) of the diol dimethyl acetal as a viscous oil. The crude oil was judged by tlc and ^{1}H nmr to be of sufficient purity to be used in the next step. An analytical sample was purified by preparative tlc (ethyl acetate). ^{1}H Nmr (200 MHz, $CDCl_3$) δ 7.93-7.88 (1 H, m), 7.75-7.71 (2 H, d, J=7.3 Hz), 7.47 (1 H, s), 7.27-7.13 (5 H, m), 6.08-5.91 (1 H, dd, J= 15.8, 7.9 Hz), 4.62-4.59 (1 H, t, J=5.4 Hz), 3.86-3.82 (4 H, d, J=6.8 Hz), 3.29-3.28 (6 H, s), 3.10-3.08 (2 H, d, J=5.4 Hz), 2.77-2.59 (1 H, m), 2.29 (3 H, s); ^{13}C nmr (90 MHz, $CDCl_3$) δ 143.5, 134.6, 133.7, 131.3, 130.9, 130.1, 129.9, 128.5, 127.4, 126.5, 125.1, 124.0, 123.4, 120.8, 117.1, 111.8, 102.5, 63.5, 52.1, 45.8, 30.1, 20.2; ir (film) 3400, 2910, 2215, 1680, 1580 cm^{-1}; ms, m/z (relative intensity) 459 (3), 91 (11), 75 (100); HRms calcd for $C_{24}H_{29}NO_6S$: 459.1715. Found: 459.1705.

Acetic anhydride (0.17 ml, 1.75 mmol) was added to a solution of the above crude acetal diol (0.20 g, 0.44 mmol) and pyridine (0.28 ml, 3.50 mmol) in 2 ml of CH_2Cl_2 at room temperature. After the mixture was stirred for 24 h, the solution was diluted with 5% HCl and was extracted with ethyl acetate. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography on neutral alumina (30% to 50% ethyl acetate/hexanes) to give 0.15 g (60% from enol ether (**16**)) of **17** as a yellow oil. ^{1}H Nmr (200 MHz, $CDCl_3$) δ 7.93-7.88 (1 H, d, J=9.3 Hz), 7.74-7.70 (2 H, d, J=8.4 Hz), 7.48 (1 H, s), 7.26-7.10 (5 H, m), 5.96-5.84 (1 H, dd, J=15.8, 8.1 Hz), 4.66-4.60 (1 H, t, J=5.5 Hz), 4.18-4.14 (4 H, m), 3.29 (6 H, s), 3.07-3.03 (2 H, d, J=5.6 Hz), 2.92-2.88 (1 H, m), 2.28 (3 H, s),

2.00 (6 H, s); ^{13}C nmr (90 MHz, $CDCl_3$) δ 170.9, 144.9, 135.6, 135.2, 132.0, 130.9, 129.8, 129.7, 129.4, 128.0, 127.6, 126.8, 125.1, 124.7, 121.8, 118.1, 113.1, 103.6, 76.7, 64.0, 53.1, 41.7, 31.2, 21.6, 21.0, 20.9; ir (film) 2920, 1725, 1585 cm^{-1}; ms, m/z (relative intensity) 543 (1), 75 (100), 43 (20); HRms calcd for $C_{28}H_{33}NO_8S$: 543.1927. Found: 543.1938.

Preparation of Aldehyde (18). Chlorotrimethylsilane (0.063 ml, 0.49 mmol) was added to a solution of acetal diacetate (**17**) (0.090 g, 0.016 mmol) and NaI (0.12 g, 0.83 mmol) in 2 ml of acetonitrile at 0°C. The reaction mixture was stirred for 1 h at 0°C, diluted with sat. $NaHCO_3$ and extracted with ethyl acetate. The organic layer was washed with sat. $NaHSO_3$, dried over Na_2SO_4 and concentrated. The crude oil was purified by preparative tlc (50% ethyl acetate/hexanes) and 0.063 g (77%) of pure aldehyde (**18**) was obtained as an oil. ^1H Nmr (200 MHz, $CDCl_3$) δ 9.74-9.72 (1 H, t, J=2.0 Hz), 7.94-7.89 (1 H, d, J=7.9 Hz), 7.77-7.73 (2 H, d, J=8.3 Hz), 7.53 (1 H, s), 7.30-7.19 (4 H, m), 6.95-6.87 (1 H, d, J=15.7 Hz), 5.94-5.86 (1 H, dd, J=15.7, 15.7 Hz), 4.18-4.13 (4 H, dd, J=6.2 Hz), 3.82 (2 H, br s), 2.93-2.81 (1 H, m), 2.30 (3 H, s), 2.00 (6 H, s); ir (film) 2920, 1715, 1585 cm^{-1}; ms, m/z (relative intensity) 497 (27), 377 (39), 363 (23), 222 (100), 208 (51), 194 (68), 181 (23), 167 (33), 155 (39), 92 (27); HRms calcd for $C_{26}H_{27}NO_7S$: 497.1508. Found: 497.1490.

Synthesis of Cyclized Product (21). *N*-Sulfinyl-*p*-toluenesulfonamide (0.012 g, 0.055 mmol) was added *via* a Pasteur pipet to the aldehyde (**18**) (0.016 g, 0.032 mmol) in 10 ml of CH_2Cl_2 at room temperature. After 25 min, the yellow solution was cooled to 0°C and anhydrous $FeCl_3$ (0.010 g, 0.064 mmol) was added. The reaction mixture turned a deep red color and was stirred at 0°C for 45 min. At 0°C, sat. $NaHCO_3$ was added, and the mixture was extracted with ethyl acetate, dried over Na_2SO_4 and concentrated. The residue was purified by preparative tlc (6:40:1 hexanes/ether/methanol) to give 0.012 g (57%) of tricycle (**21**). ^1H Nmr (200 MHz, $CDCl_3$) δ 7.85-7.81 (1 H, d, J=8.9 Hz), 7.73-7.69 (2 H, d, J=8.4 Hz), 7.60-7.56 (2 H, d, J=8.3 Hz), 7.31-7.20 (5 H, m), 7.01-6.97 (1 H, d, J=7.3 Hz), 6.82 (1 H, s), 6.31 (1 H, s), 4.43-4.09 (6 H, m), 2.93-2.64 (3 H, m), 2.47 (3 H, s), 2.30 (3 H, s), 1.99 (3 H, s), 1.97 (3 H, s); ^1H Nmr (300 MHz, d_6-benzene) δ 7.91-7.89 (1 H, d, J=8.3 Hz) , 7.48-7.42 (2 H, d, J=8.3 Hz), 7.40-7.37 (2 H, d, J=8.2 Hz), 6.88-6.83 (1 H, m), 6.71-6.68 (4 H, m), 6.53-6.51 (1 H, d, J=7.7 Hz), 6.40-6.37 (1 H, d, J=8.5 Hz), 5.97 (1 H, s), 4.34-4.28 (2 H, m), 4.04-3.80 (4 H, m), 2.88-2.81 (1 H, dd, J=15.4, 5.5 Hz), 2.57-2.53 (1 H, t, J=6.6 Hz), 2.44-2.39 (1 H, d, J=15.4 Hz), 1.92 (3

H, s), 1.48 (3 H, s), 1.43 (3 H, s), 1.42 (3 H, s); ir (film) 3500, 2940, 1730, 1590 cm^{-1}; ^{13}C nmr (90 MHz, $CDCl_3$) δ 171.2, 146.0, 144.8, 143.5, 139.4, 138.6, 134.8, 134.2, 129.5, 129.3, 129.2, 127.3, 126.5, 126.3, 126.0, 124.9, 124.7, 124.3, 116.8, 112.9, 76.7, 62.7, 62.6, 59.9, 52.5, 46.7, 30.5, 21.2, 20.4; ms, m/z (relative intensity) 650 (3), 375 (20), 222 (28), 196 (31), 167 (30), 155 (45), 139 (26), 91 (62), 65 (68), 43 (100); HRms calcd for $C_{33}H_{34}N_2O_8S_2$: 650.1756. Found: 650.1717.

Preparation of Tetracycles (22). The tricyclic product (**21**) (0.25 g, 0.038 mmol) was treated with aqueous 3M KOH (0.25 ml, 0.77 mmol) in methanol (2 ml), and the mixture was heated at reflux. After 16 h, the mixture was cooled to room temperature, diluted with H_2O and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4 and concentrated. The crude mixture was purified by preparative tlc (ethyl acetate) to afford 0.011 g (70%) of diol. ^1H Nmr (200 MHz, $CDCl_3$) δ 8.16 (1 H, s), 7.67-7.63 (2 H, d, J=8.3 Hz), 7.31-7.11 (3 H, m), 6.95-6.91 (1 H, d, J=7.1 Hz), 6.64 (1 H, s), 6.47 (1 H, s), 4.84-4.79 (1 H, d, J=10.0 Hz), 4.51-4.41 (1 H, m), 3.87-3.74 (4 H, m), 2.87-2.85 (2 H, m), 2.67-2.60 (1 H, m), 2.44-2.40 (3 H, s); ^{13}C nmr (90 MHz, $CDCl_3/CD_3OD$) δ 143.1, 139.6, 137.9, 135.6, 129.8, 129.1, 127.9, 126.6, 123.7, 123.0, 122.5, 121.0, 110.5, 109.8, 62.8, 53.2, 52.9, 30.8, 21.0; ir (film) 3300, 2900, 1590 cm^{-1}; ms, m/z (relative intensity) 412 (29), 210 (48), 209 (100), 193 (48), 167 (48), 91 (78), 28 (65); HRms calcd for $C_{22}H_{24}N_2O_4S$: 412.1457. Found: 412.1482.

The above diol (0.020 g, 0.048 mmol) in 2 ml of THF was treated with triphenylphosphine (0.019 g, 0.073 mmol) and DEAD (0.012 ml, 0.073 mmol). The mixture was stirred for 1 h, diluted with H_2O and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4 and concentrated. The crude product was purified by preparative tlc (50% ethyl acetate/hexanes) to afford 0.015 g of **22** as a 1:1 mixture of two diastereomeric compounds (78% yield). Ir (film) 3350, 2900 cm^{-1}. The mixture was separated by preparative tlc (30:1:1 $CHCl_3$/acetone/hexanes).

Less polar isomer: ^1H Nmr (300 MHz, $CDCl_3$) δ 8.07 (1 H, s), 7.70-7.67 (2 H, d, J=8.2 Hz), 7.24-7.22 (2 H, m), 7.25-7.07 (3 H, m), 6.87-6.84 (1 H, d, J=7.4 Hz), 6.47 (1 H, s), 4.27-4.21 (1 H, m), 3.89-3.83 (1 H, dd, J=14.1, 2.8 Hz), 3.74-3.68 (1 H, m), 3.41-3.36 (1 H, m), 3.30-3.28 (1 H, m), 3.10-3.00 (3 H, m), 2.35 (3 H, s); ^{13}C nmr (90 MHz, $CDCl_3$) δ 143.5, 141.9, 135.5, 134.1, 129.8, 128.5, 127.3, 125.2, 123.4, 122.1, 121.9, 121.1, 113.1, 110.3, 63.1, 62.5, 50.0, 46.8, 34.1, 21.1; ms, m/z (relative intensity) 394 (31), 239 (100), 209 (60), 207 (56), 180 (31), 91 (72), 41 (30); HRms calcd for $C_{22}H_{22}N_2O_3S$: 394.1351. Found: 394.1313.

More polar isomer: ^{1}H Nmr (300 MHz, $CDCl_3$) δ 8.12 (1 H, s), 7.68-7.66 (2 H, d, J=8.1 Hz), 7.34-7.11 (5 H, m), 6.89-6.86 (1 H, d, J=7.1 Hz), 6.50 (1 H, s), 4.09-4.00 (2 H, m), 3.78-3.65 (3 H, m), 3.33-3.27 (1 H, m), 3.06-2.98 (1 H, m), 2.84-2.73 (1 H, m), 2.38 (3 H, s); ^{13}C nmr (90 MHz, $CDCl_3$) δ 145.0, 143.6, 142.1, 135.1, 132.0, 129.8, 127.8, 127.3, 123.4, 122.8, 122.1, 120.9, 113.1, 110.5, 64.8, 63.9, 51.1, 46.2, 34.5, 21.3; ms, m/z (relative intensity) 394 (35), 240 (23), 239 (100), 238 (26), 209 (61), 207 (56), 180 (30), 91 (66), 65 (21); HRms calcd for $C_{22}H_{22}N_2O_3S$: 349.1351. Found: 394.1356.

Demethylation of *O*-Acetyllysergol (23). *O*-Acetyllysergol (**23**) (0.13 g, 0.44 mmol) was added to a solution of cyanogen bromide (0.070 g, 0.66 mmol) in 2 ml of CH_2Cl_2. The reaction mixture was refluxed for 5 h, brought to room temperature, diluted with water, and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4 and concentrated. The crude material was purified by preparative tlc (ethyl acetate) to give 0.071 g (55%) of the desired nitrile. ^{1}H Nmr (300 MHz, $CDCl_3$) δ 8.30 (1 H, s), 7.22-7.19 (1 H, d, J=8.5 Hz), 7.15-7.10 (1 H, m), 7.06-7.03 (1 H, d, J=7.1 Hz), 6.88 (1 H, s), 6.18 (1 H, s), 4.20-4.15 (1 H, dd, J=11.1, 4.9 Hz), 4.09-4.04 (1 H, m), 4.01-3.95 (1 H, dd, J=11.0, 8.6 Hz), 3.57-3.41 (2 H, m), 3.21-3.14 (1 H, dd, J=12.6, 7.4 Hz), 2.97-2.88 (2 H, m), 2.06 (3 H, s); ^{13}C nmr (90 MHz, $CDCl_3$) δ 170.2, 134.8, 133.8, 126.6, 125.9, 123.1, 119.1, 119.0, 116.8, 112.0, 110.5, 108.4, 64.2, 55.5, 48.2, 34.5, 27.3, 20.7; ir (film) 3600, 2825, 2200, 1715 cm^{-1}; ms, m/z (relative intensity) 307 (18), 247 (100), 192 (47), 167 (15), 154 (13), 43 (56); HRms calcd for $C_{18}H_{17}N_3O_2$: 307.1321. Found: 307.1313.

The amine (**24**) was obtained by adding zinc dust (0.39 g, 5.99 g atoms) to a solution of the above nitrile (0.23 g, 0.75 mmol) in 2 ml of 80% aqueous acetic acid. The reaction mixture was heated at 100°C for 5 h, cooled to room temperature, diluted with sat. $NaHCO_3$ and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography on neutral alumina (20% methanol/ethyl acetate to 100% methanol) to give 0.017 g (81%) of the demethylated lysergol derivative (**24**). ^{1}H Nmr (300 MHz, $CDCl_3$) δ 8.01 (1 H, s), 7.25-7.11 (3 H, m), 6.91 (1 H, s), 6.37-6.35 (1 H, d, J=6.0 Hz), 4.13-4.10 (2 H, m), 3.92-3.86 (1 H, m), 3.44-3.38 (1 H, dd, J=12.1, 5.3 Hz), 3.33-3.26 (1 H, dd, J=14.6, 5.8 Hz), 2.94-2.82 (1 H, m), 2.80-2.59 (2 H, m), 2.11 (3 H, s); ^{13}C nmr (90 MHz, $CDCl_3$) δ 171.4, 135.7, 134.1, 126.3, 122.8, 119.3, 118.7, 111.6, 110.2, 110.1, 108.7, 65.7, 54.1, 45.2, 34.8, 28.4, 20.6; ir (film) 3300, 2900, 1720, 1580 cm^{-1}; ms, m/z (relative intensity) 282

(100), 252 (23), 207 (29), 192 (69), 152 (23), 43 (97); HRms calcd for $C_{17}H_{18}N_2O_2$: 282.1368. Found 282.1367.

***N*-Tosyllysergol Derivative (25).** *p*-Toluenesulfonyl chloride (0.12 g, 0.061 mmol) was added to a solution of potassium carbonate (0.28 g, 2.02 mmol) and lysergol derivative (**24**) (0.057 g, 0.20 mmol) in 1 ml of anhydrous DMF, and the reaction mixture was stirred at room temperature. After 48 h, the mixture was diluted with water and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by preparative tlc (ethyl acetate) to afford 0.028 g (32%) of *N*-tosylated compound. ^{1}H Nmr (300 MHz, $CDCl_3$) δ 8.04 (1 H, s), 7.76-7.73 (2 H, d, J=8.3 Hz), 7.26-7.24 (2 H, d, J=8.3 Hz), 7.21-7.10 (2 H, m), 7.02-7.00 (1 H, d, J=7.0 Hz), 6.85 (1 H, s), 6.18-6.16 (1 H, d, J=6.1 Hz), 4.82-4.77 (1 H, m), 4.06-4.01 (1 H, dd, J=11.1, 4.6 Hz), 3.96-3.91 (1 H, d, J=13.5 Hz), 3.45-3.36 (2 H, m), 3.27-3.22 (1 H, m), 3.05-2.95 (1 H, m), 2.64-2.61 (1 H, m), 2.40 (3 H, s), 2.01 (3 H, s); ^{13}C nmr (75 MHz, $CDCl_3$) δ 170.6, 143.4, 137.9, 137.2, 133.6, 129.6, 129.2, 127.7, 127.0, 125.8, 123.0, 119.3, 118.9, 111.5, 110.4, 110.1, 63.3, 54.3, 39.7, 37.8, 35.5, 28.5, 21.4, 20.8; ir (film) 3375, 2920, 1720, 1591 cm^{-1}; ms, m/z (relative intensity) 436 (4), 296 (100), 254 (52), 223 (22), 221 (26), 192 (42), 154 (24), 28 (43); HRms calcd for $C_{24}H_{24}N_2O_4S$: 436.1457. Found: 436.1439. Potassium carbonate (0.044 g, 0.32 mmol) was added to a solution of the above *N*-tosyllysergol acetate (0.028 g, 0.064 mmol) in 1 ml of methanol. The reaction mixture was stirred for 16 h, diluted with water and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4 and concentrated to give 0.020 g (80%) of alcohol (**25**) as a solid. ^{1}H Nmr (300 MHz, $CDCl_3$) δ 7.94 (1 H, s), 7.81-7.78 (2 H, d, J=8.3 Hz), 7.34-7.31 (2 H, d, J=8.1 Hz), 7.21-7.05 (3 H, m), 6.83 (1 H, s), 6.32-6.30 (1 H, d, J=6.2 Hz), 4.94-4.88 (1 H, dd, J=12.4, 4.7 Hz), 4.13-4.09 (1 H, d, J=15.4 Hz), 3.70-3.53 (2 H, m), 3.16-3.04 (2 H, m), 2.88-2.79 (1 H, m), 2.60-2.52 (1 H, m), 2.44 (3 H, s); ^{13}C nmr (75 MHz, $CDCl_3$) δ 143.3, 138.5, 136.4, 134.4, 129.7, 129.3, 127.7, 126.7, 125.6, 123.1, 120.9, 118.8, 111.5, 110.2, 109.9, 61.6, 54.1, 39.9, 38.7, 37.9, 27.7, 21.5; ir ($CHCl_3$) 3350, 2900, 1585 cm^{-1}; ms, m/z (relative intensity) 394 (57), 239 (100), 207 (36), 194 (23), 91 (27), 28 (45); HRms calcd for $C_{22}H_{22}N_2O_3S$: 394.1351. Found: 394.1367.

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#Author to be contacted concerning X-ray structure determination.

REFERENCES

1. For a recent review of *Ergot* alkaloids, see: I. Ninomiya and T. Kiguchi, "The Alkaloids," Brossi, A., Ed.; Academic Press, San Diego, 1990; Vol. **38**, Chapter 1, p.1.
2. For a review on the pharmacology of *Ergot* alkaloids, see: P.A. Stadler and K.A. Gigar, "Natural Products and Drug Development," P. Krogsgaard-Larsen, S.B. Christensen and H. Koffod, Eds.; Munksgaard, Copenhagen, 1984; p. 463. J.M. Cassady and H.G. Floss, *Lloydia*, 1977, **40**, 90. J.P. Cannon, *Prog. Drug Res.*, 1985, **29**, 303.
3. M.J. Melnick, A.J. Freyer, and S.M. Weinreb, *Tetrahedron Lett.*, 1988, **29**, 3891.
4. For a survey of the chemistry of *N*-sulfonylimines, see: S.M. Weinreb, *Top Curr. Chem.*, in press.
5. R. Albrecht, G. Kresze, and B. Mlakar, *Chem. Ber.*, 1964, **97**, 483. R. Albrecht and G. Kresze, *Chem. Ber.*, 1965, **98**, 1431.
6. E.L. Eliel and H.D. Banks, *J. Am. Chem. Soc.*, 1972, **94**, 171.
7. M.P. Moyer, J.F. Shiurba, and H. Rapoport, *J. Org. Chem.*, 1986, **51**, 5106.
8. M. Somei, F. Yamada, M. Kunimoto, and C. Kaneko, *Heterocycles*, 1984, **22**, 797. F. Yamada and M. Somei, *Heterocycles*, 1987, **26**, 1173.
9. L.S. Hegedus, J.L. Toro, and P.J. Harrington, *J. Org. Chem.*, 1987, **52**, 3319. P.J. Harrington, L.S. Hegedus, and K.F. McDaniel, *J. Am. Chem. Soc.*, 1987, **109**, 4335.
10. a) P.M. Scola, Ph.D. Thesis, The Pennsylvania State University, 1993. b) J.L. Ralbovsky, Ph.D. Thesis, The Pennsylvania State University, 1993.
11. T. Morita, Y. Okamoto, and H. Sakurai, *J. Chem. Soc., Chem. Comm.*, 1978, 874.
12. T. Hori, S.P. Singer, and K.B. Sharpless, *J. Org. Chem.*, 1978, **43**, 1456.
13. *cf* J. Sisko and S.M. Weinreb, *J. Org. Chem.*, 1990, **55**, 393.
14. Aldehyde (**18**) appears to polymerize rapidly in the presence of Lewis acids and thus the *N*-sulfonylimine needed to be generated prior to addition of $FeCl_3$.[13] *N*-Sulfonyl imine formation can be easily monitored by ^1H nmr.
15. E. Eich, *Arch. Pharm.* (Weinheim), 1983, **316**, 303.
16. T. Fehr, P.A. Stadler, and A. Hoffmann, *Helv. Chim. Acta*, 1970, **53**, 2197.

17. J.R. Henry, L.R. Marcin, M.C. McIntosh, P.M. Scola, G.D. Harris, Jr., and S.M. Weinreb, *Tetrahedron Lett.*, 1989, **30**, 5709.

18. X-Ray data has been deposited with the Cambridge Crystallographic Data Centre.

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