Registry No. 1, 23560-25-0; **3**, 89486-33-9; **7**, 76069-04-0; **8**, 61057-05-4; **9**, 52890-26-3; **10**, 89486-34-0; **11**, 76069-03-9; **13**, 89486-35-1; **14**, 89486-36-2; **15**, 89486-37-3; **16**, 61057-08-7; **17**, 61057-09-8; 3-$ClC_6H_4NPh^-$, 78525-46-9; $(4\text{-}BrC_6H_4)_2N^-$, 79990-95-7; $PhCON(Ph)CH_2Ph$, 19672-91-4; $m\text{-}CF_3C_6H_4CH_2Cl$, 705-29-3; $PhCH_2Cl$, 100-44-7; Ph_2NCH_2Ph, 606-87-1; 3-chlorocarbazole anion, 80010-03-3; 3,6-dibromocarbazole anion, 79990-92-4; 2-chlorophenothiazine anion, 79990-93-5; 3,7-dibromophenothiazine anion, 79990-94-6; *N*-benzylphenoxazine, 89486-38-4; *N*-(*m*-(trifluoromethyl)benzyl)carbazole, 89486-39-5; *N*-benzylphenothiazine, 58478-75-4.

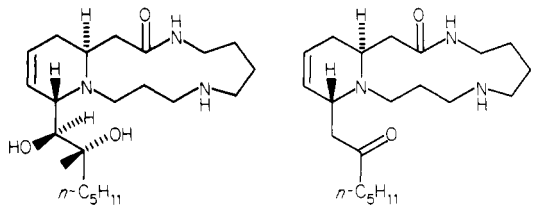
Total Synthesis of Anhydrocannabisativene

Thomas R. Bailey, Ravi S. Garigipati, Judith A. Morton, and Steven M. Weinreb*

Contribution from the Department of Chemistry, The Pennsylvania State University, University Park, Pennsylvania 16802. *Received November 25, 1983*

Abstract: A stereoselective total synthesis of the macrocyclic spermidine alkaloid anhydrocannabisativene (**2**) has been executed in approximately 17 steps starting from pentadienylsilane **6**. The pivotal step in construction of the tetrahydropyridine ring and for establishing the relative stereochemistry of the alkaloid involved an intramolecular imino Diels–Alder cycloaddition. An intramolecular sulfonamide alkylation was subsequently used to generate the 13-membered macrocyclic lactam ring of **2**.

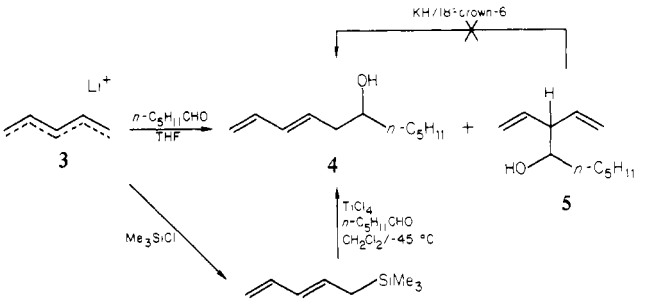
The common marijuana plant *Cannabis sativa* is the source of several non-cannabinoid nitrogeneous compounds including the interesting spermidine alkaloids cannabisativene (**1**) and anhydrocannabisativene (**2**).[1,2] In recent years there has been considerable interest in developing synthetic routes to such macrocyclic spermine- and spermidine-derived alkaloids.[3,4] We have previously described some model studies involving intramolecular Diels–Alder reactions of imino dienophiles which allow ready construction of *trans*-2,6-disubstituted tetrahydropyridines related to **1** and **2**.[5,6] We now describe the application of this methodology to an efficient stereospecific total synthesis of racemic anhydrocannabisativene.



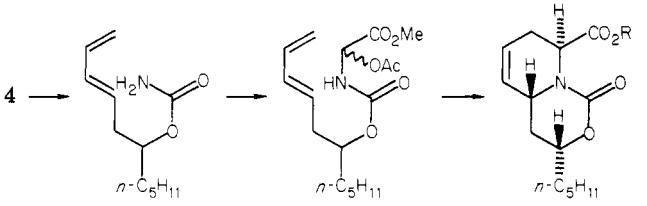
1 2

The required starting material for our imino Diels–Alder approach to **2** was diene alcohol **4**. Initially this compound was prepared by addition of pentadienyllithium (**3**)[7,8] to *n*-hexanal, but this procedure was unattractive in that it afforded a 1:1 mixture of the desired diene alcohol **4** and the unwanted isomer **5** (Scheme I). Attempts to convert **5** to **4** via an anion-accelerated [1,3]-sigmatropic rearrangement using the conditions described by Wilson et al.[9] were unsuccessful. A much better route to **4** was eventually developed using the pentadienylsilane **6** recently described by Seyferth[10a] and Sakurai.[10b] This compound, which is readily prepared from **3** by treatment with trimethylsilyl chloride, reacted with 1-hexanal in the presence of titanium tetrachloride to produce *only* the desired conjugated diene alcohol **4** (69%).[10]

Scheme I



Scheme II



7 8 9, R = Me; 10, R = H

This alcohol was next transformed to the corresponding carbamate **7** by using the cyanate procedure of Loev and Kormendy[11] (Scheme II) in 95% yield. The carbamate reacted with anhydrous

(1) (a) Lotter, H. L.; Abraham, D. J.; Turner, C. E.; Knapp, J. E.; Schiff, P. L.; Slatkin, D. J. *Tetrahedron Lett.* **1975**, 2815. (b) Turner, C. E.; Hsu, M.-F. H.; Knapp, J. E.; Schiff, P. L.; Slatkin, D. J. *J. Pharm. Sci.* **1976**, *65*, 1084.

(2) Elsohly, M. A.; Turner, C. E.; Phoebe, C. H.; Knapp, J. E.; Schiff, P. L.; Slatkin, D. J. *J. Pharm. Sci.* **1978**, *67*, 124.

(3) (a) Hesse, M.; Schmid, H. In "International Review of Science, Organic Chemistry, Series Two"; Wiesner, K., Ed.; Butterworths: London, 1976; Vol. 9, "Alkaloids", p 265. (b) Wasserman, H. H.; Wu, J. S. *Heterocycles* **1982**, *17*, 581.

(4) (a) Trost, B. M.; Cossy, J. *J. Am. Chem. Soc.* **1982**, *104*, 6881. (b) Ogawa, M.; Nakajima, J.; Natsume, M. *Heterocycles* **1982**, *19*, 1247. (c) Wasserman, H. H.; Robinson, R. P.; Carter, C. G. *J. Am. Chem. Soc.* **1983**, *105*, 1697.

(5) (a) Nader, B.; Franck, R. W.; Weinreb, S. M. *J. Am. Chem. Soc.* **1980**, *102*, 1153. (b) Nader, B.; Bailey, T. R.; Franck, R. W.; Weinreb, S. M. *Ibid.* **1981**, *103*, 7573.

(6) For reviews of the imino Diels–Alder reaction, see: (a) Lora-Tomayo, M. In "1,4-Cycloaddition Reactions"; Hamer, J., Ed.; Academic Press: New York, 1967; pp 127–142. (b) Weinreb, S. M.; Levin, J. I. *Heterocycles* **1979**, *12*, 949. (c) Weinreb, S. M.; Staib, R. R. *Tetrahedron* **1982**, *38*, 3087.

(7) Bates, R. B.; Gosselink, D. W.; Kaczynski, J. A. *Tetrahedron Lett.* **1967**, 199.

(8) Wilson, S. R.; Jernberg, K. M.; Mao, D. T. *J. Org. Chem.* **1976**, *41*, 3209.

(9) Wilson, S. R.; Mao, D. T.; Jernberg, K. M.; Ezmirly, S. T. *Tetrahedron Lett.* **1977**, 2559.

(10) (a) Seyferth, D.; Pornet, J. *J. Org. Chem.* **1980**, *45*, 1721. (b) Hosomi, A.; Saito, M.; Sakurai, H. *Tetrahedron Lett.* **1980**, *21*, 3783.

(11) Loev, B.; Kormendy, M. R. *J. Org. Chem.* **1963**, *28*, 3421.

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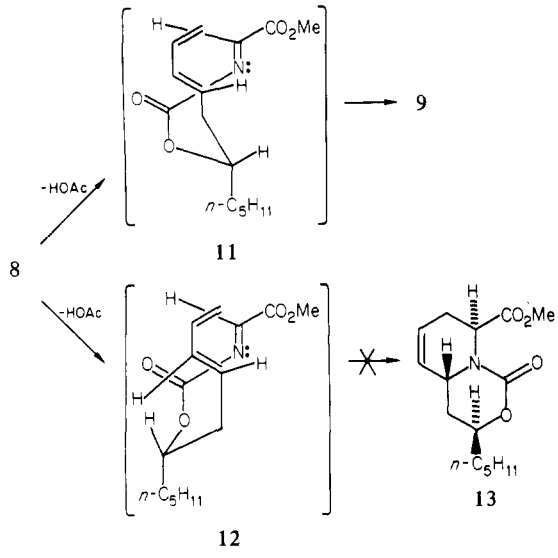
Scheme III



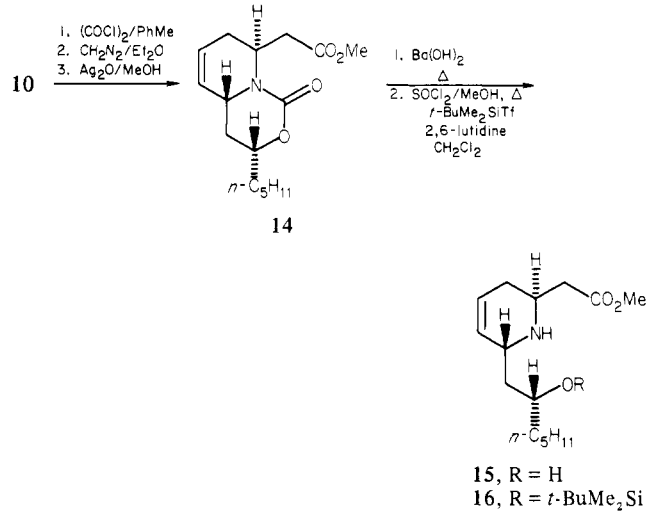
methyl glyoxylate[12] in refluxing acetone to give an intermediate methylol, which without purification was acetylated to afford methylol acetate **8** as a mixture of stereoisomers (97%). This material, upon heating in toluene containing an equivalent of Hunig's base in a sealed tube at 215 °C for 3 h, afforded a single bicyclic adduct **9** (83%).[14,15] The structure and relative stereochemistry of **9** were unambiguously established by a single-crystal X-ray analysis of acid **10**, produced by mild basic hydrolysis of the methyl ester (96%).[13]

The formation of **9** can be rationalized if one assumes that **8** thermally loses acetic acid to produce an intermediate *N*-acylimine, which subsequently undergoes an intramolecular Diels–Alder reaction.[6] On the basis of previous model studies, we anticipated that a trans relationship of the hydrogens flanking nitrogen would be produced in the cycloadduct.[5] This relative stereochemistry is probably generated from an *E* acyl imine in a Diels–Alder transition state having the nitrogen carbonyl group endo to the diene moiety (Scheme III).

More surprising was the high stereoselectivity with which the remote chiral center of **9** was established. Thus, the cycloaddition must be occurring via the conformation shown in **11** in which the bridging atoms assume a quasi-boat and the large pentyl group is quasi-equatorial. The related quasi-chair conformation **12** would afford the stereoisomeric adduct **13**, which was not detected in the cycloaddition. The primary difference between these two conformations readily detectable from inspection of molecular models is a nonbonded "flagpole" hydrogen interaction present in **12** but absent in **11**. We recently described a related intramolecular imino Diels–Alder cycloaddition that produced a 6/6-ring system like **9**. This reaction also showed total stereoselectivity with respect to the substituent on the bridging chain.[14] In addition, an analogous intramolecular Diels–Alder reaction that formed a carboyclic 6/6 system has been found to also proceed largely through a reacting *quasi*-boat conformer like **11**.[16] It is quite likely that the preference for a boat conformation **11** rather than a chair **12** may be a general phenomenon in intramolecular Diels–Alder reactions that generate 6/6-fused-ring systems. We are currently investigating this point in other heterocyclic systems.

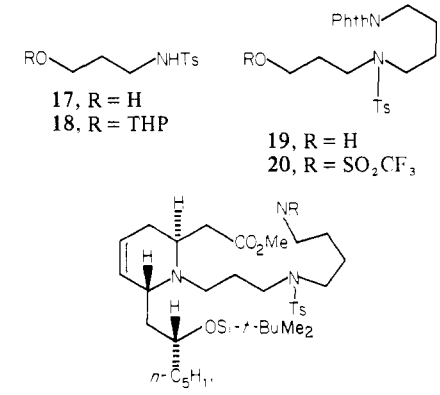
(12) Kelly, T. R.; Schmidt, T. E.; Haggerty, J. G. *Synthesis* **1972**, 544.
(13) We thank M. Bernheim and Dr. R. Whittle for their assistance in this structure determination.
(14) Taber, D. F.; Gunn, B. P. *J. Am. Chem. Soc.* **1979**, *101*, 3992.
(15) (a) Bremmer, M. L.; Weinreb, S. M. *Tetrahedron Lett.* **1983**, *24*, 261. (b) Bremmer, M. L.; Khatri, N. A.; Weinreb, S. M. *J. Org. Chem.* **1983**, *48*, 3661.
(16) (a) Weinreb, S. M.; Khatri, N. A.; Shringarpure, J. *J. Am. Chem. Soc.* **1979**, *101*, 5073. (b) Schmitthenner, H. F.; Weinreb, S. M. *J. Org. Chem.* **1980**, *45*, 3372. (c) Khatri, N. A.; Schmitthenner, H. F.; Shringarpure, J.; Weinreb, S. M. *J. Am. Chem. Soc.* **1981**, *103*, 6387. (d) Gobao, R. A.; Bremmer, M. L.; Weinreb, S. M. *Ibid.* **1982**, *104*, 7065.

Scheme IV



The tetrahydropyridine nucleus of **2** was further elaborated as shown in Scheme IV. Acid **10** was efficiently homologated by an Arndt–Eistert sequence to give ester **14** (78%).[5] Hydrolysis of the carbamate functionality of **14** afforded an amino acid that was re-esterified to provide **15** (87%). In order to prove that epimerization had not occurred on hydrolysis of **14**,[4b] amino alcohol **15** was treated with carbonyldiimidazole, regenerating cyclic carbamate **14**. Protection of the alcohol group of **15** as the *tert*-butyldimethylsilyl ether gave amine **16** (91%).

Annulation of a 13-membered macrocyclic lactam ring onto **16** proved considerably more difficult than originally anticipated. Initially, it was our plan to generate the lactam bond of the alkaloid in the penultimate step of the synthesis. Toward this end, 3-aminopropanol was monotosylated (TsCl, Et_3N, CH_2Cl_2; 79%) to give alcohol **17**, which was protected as its tetrahydropyran (THP) ether **18** (DHP, *p*-TsOH, Et_2O; 95%). N-Alkylation of



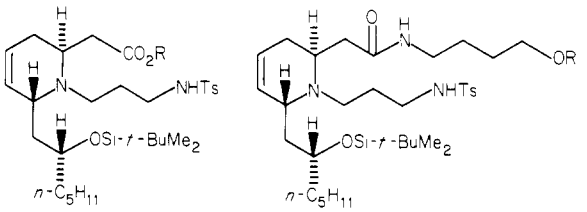
sulfonamide **18** with *N*-(4-bromobutyl)phthalimide (KH, DMF) followed by treatment of the crude product with methanolic HCl afforded alcohol **19** (71%).

Several attempts were made to alkylate amine **16** with the iodide and mesylate derived from alcohol **19**, but in all cases the starting materials were recovered unchanged. However, triflate **20** did react cleanly with **16** (i-Pr_2NEt, CH_2Cl_2) to afford tertiary amine **21** (70%). Despite a considerable amount of effort it was not possible to remove the phthalimide protecting group of **21** to produce the requisite primary amine **22**. A variety of standard deprotection procedures were attempted,[17,18] but at best **22** could be isolated in only very low (<30%) yield. We were also com-

(17) Greene, T. W. "Protective Groups in Organic Synthesis"; Wiley: New York, 1981; p 265.
(18) Bailey, T. R. Ph.D. Thesis, The Pennsylvania State University, University Park, 1983.

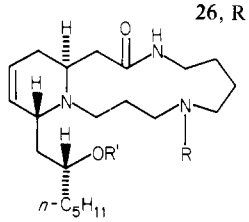
pletely unsuccessful in preparing compounds like **21** having other more easily removable nitrogen protecting groups.[18] It thus became necessary to develop an alternative strategy for construction of the macrocyclic ring of the alkloid.

Alkylation of tetrahydropyridine **16** with the triflate prepared from alcohol **17** gave amino ester **23** in 99% yield, which was hydrolyzed (LiOH, $MeOH/H_2O$) to the corresponding acid **24**



23, R = Me
24, R = H

25, R = H
26, R = Ms



27, R = Ts; R′ = t-$BuMe_2Si$
28, R = H; R′ = t-$BuMe_2Si$
29, R = R′ = H

(100%). This acid was activated as the 2,4,5-trichlorophenyl ester,[19] which upon treatment with 4-aminobutanol in DMF gave amide alcohol **25** (82%). Standard chemistry was used to convert **25** to mesylate **26** (80%).

Cyclization of this compound could be effected by refluxing a dilute solution of **26** in acetonitrile containing excess suspended potassium carbonate, affording the desired lactam **27** (58%). The *N*-tosyl protecting group of **27** was cleanly removed with sodium in liquid ammonia[4b] to give the secondary amine **28** (90%). The *tert*-butyldimethylsilyl group of **28** proved resistant to cleavage with fluoride ion. However, treatment of **28** with boron trifluoride etherate gave the amino alcohol **29**. Finally, oxidation of **29** with Jones reagent afforded racemic anhydrocannabisativene (**2**) (54% from **28**). This material was identical in TLC, MS, ^1H NMR, and IR with an authentic sample of the alkaloid.[20] Thus, we have developed a stereoselective total synthesis of **2** in approximately 17 steps starting from silylpentadiene **6**.

Experimental Section

(*E*)-1,3-Undecadien-6-ol (4). A solution of 2.5 g (25 mmol) of 1-hexanal in 30 mL of dry methylene chloride at −41 °C under a nitrogen atmosphere was treated with 1 mL (10 mmol) of $TiCl_4$. Silyl diene **6** (3.1 g, 22 mmol) was added dropwise to this mixture and the resulting solution was allowed to warm to room temperature over 5 min. The mixture was poured into saturated sodium bicarbonate solution (30 mL) and was extracted with ether. The organic phase was concentrated in vacuo, and the crude reaction mixture was chromatographed on 100 g of silica gel eluting with 19:1 hexane/ethyl acetate affording 2.6 g (69%) of diene alcohol **4** as a colorless liquid: IR (film) 3400, 2940, 1460, 1000, 970, 895, 840 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 0.89 (t, 3 H, J = 8.0 Hz), 1.20–1.60 (m, 8 H), 2.03–2.42 (m, 3 H), 3.62–3.67 (m, 1 H), 5.01 (d, 1 H, J = 10.0 Hz), 5.13 (d, 1 H, J = 16.8 Hz), 5.71 (dt, 1 H, J = 15.0, 7.3 Hz), 6.13 (dd, 1 H, J = 15.1, 10.5 Hz), 6.32 (dt, 1 H, J = 16.8, 10.3 Hz); mass spectrum, m/z 168 [M^+], 150, 149, 68, 55, 41.

(*E*)-1-Pentyl-3,5-hexadienyl Carbamate (7). A solution of 0.66 g (3.9 mmol) of diene alcohol **4**, 0.55 g (8.0 mmol) of NaOCN, and 0.8 mL (8.0 mmol) of trifluoroacetic acid in 5 mL of dry ether was sealed in a 250-mL glass pressure bottle (Fisher Scientific) and the solution was stirred vigorously for 24 h. The crude reaction mixture was poured into 25 mL of water, and the solution was extracted with ether. The extract was washed with saturated sodium bicarbonate solution (25 mL), and the etheral phase was dried. The solvent was removed in vacuo, and the crude product was chromatographed on 20 g of silica gel eluting with 9:1 hexane/ethyl acetate, affording 0.79 g (95%) of carbamate **7** as an oil. Distillation of this material (80 °C (0.1 torr)) gave a white solid: mp 56–58 °C; IR (film) 3300, 2940, 2860, 1710, 1600, 1390, 1325, 1040, 1005, 900, 780 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.6–1.0 (m, 3 H), 1.1–1.6 (m, 9 H), 2.3 (t, 2 H, J = 6 Hz), 4.5–6.5 (m, 7 H); mass spectrum, m/z (relative intensity) 211 [M^+] (2.5), 151 (12.1), 150 (92.2), 101 (23.3), 94 (20.4), 93 (26.3), 83 (48.2), 80 (100), 79 (96.5), 78 (30.4), 68 (40.7), 67 (35.3), 55 (66.1), 41 (47.6).

Methyl (Acetyloxy)[[[(1-pentyl-3,5-hexadienyl)oxy]carbonyl]amino]-acetate (8). To a solution of 0.75 g (3.5 mmol) of carbamate **7** in 50 mL of reagent grade acetone was added 1.10 g (12.6 mmol) of methyl glyoxylate[12] freshly distilled from P_2O_5. The mixture was refluxed under nitrogen for 3 days and was concentrated in vacuo. The residue was extracted with CH_2Cl_2 and was washed with water (2 × 50 mL), and the organic phase was dried. After concentration of the solution under vacuum, the crude product was chromatographed on 20 g of silica gel eluting with 2:1 hexane/ethyl acetate, yielding 0.87 g (82%) of the intermediate methylol as a colorless oil: IR (film) 3350, 2960, 2930, 1755, 1710, 1510, 1440, 1220, 1040, 1000, 900, 795, 775 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.8–1.8 (m, 12 H), 2.3 (t, 2 H, J = 6 Hz), 3.8 (s, 3 H), 4.1 (br s, 1 H), 4.5–6.6 (m, 7 H).

To a solution of 0.87 g (2.9 mmol) of the crude methylol in 50 mL of acetic anhydride was added 2 drops of pyridine, and the mixture was stirred under nitrogen for 12 h. The solvent was removed in vacuo, and the crude product was chromatographed on 16 g of silica gel eluting with 1:1 hexane/ethyl acetate, affording 0.94 g (97%) of acetate **8** as a light yellow oil: IR (film) 3350, 2960, 2930, 2860, 1735, 1510, 1435, 1220, 1000, 900, 775, 725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.9–1.7 (m, 12 H), 2.1 (s, 3 H), 2.3 (t, 2 H, J = 6 Hz), 3.8 (s, 3 H), 4.6–6.5 (m, 7 H); mass spectrum, m/z (relative intensity) 341 [M^+] (0.7), 282 (3.0), 281 (6.2), 222 (3.2), 178 (12.5), 166 (7.6), 151 (14.0), 150 (66.6), 144 (17.6), 109 (4.3), 95 (6.6), 94 (6.4), 93 (7.7), 81 (9.6), 80 (32.3), 79 (22.8), 67 (27.5), 55 (12.9), 45 (12.3), 44 (10.9), 43 (52.3), 42 (11.2), 41 (17.6), 32 (21.5).

Methyl (3α,4aβ,8β)-4,4a,7,8-Tetrahydro-1-oxo-3-pentyl-1*H*,3*H*-pyrido[1,2-*c*][1,3]oxazine-9-carboxylate (9). A solution of 0.91 g (2.7 mmol) of methylol acetate **8** and 0.35 g (2.7 mmol) of diisopropylethylamine in 20 mL of toluene sealed in a thick-walled glass tube was heated at 215 °C for 3 h. After cooling, the reaction mixture was diluted with CH_2Cl_2. The solution was washed with 40 mL of water, dried, and concentrated in vacuo. The crude product was chromatographed on 19 g of silica gel eluting with 2:1 hexane/ethyl acetate to yield 0.62 g (83%) of oily ester **9** as a colorless oil: IR (film) 3040, 2950, 2860, 1745, 1690, 1420, 1305, 1270, 1210, 1130, 1070, 1020, 970, 925, 905, 850, 765, 730, 695, 655 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.90 (t, 3 H, J = 6.3 Hz), 1.23–1.79 (m, 8 H), 2.04–2.17 (m, 2 H), 2.46–2.73 (m, 2 H), 3.73 (s, 3 H), 4.31–4.40 (m, 2 H), 5.42 (d, 1 H, J = 6.3 Hz), 5.54 (d, 1 H, J = 10.3 Hz), 5.79–5.85 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 13.08, 21.61, 23.41, 25.33, 30.71, 33.33, 34.35, 49.15, 50.58, 51.44, 75.62, 122.63, 125.96, 152.60, 170.29; mass spectrum, m/z (relative intensity) 281 [M^+] (2.0), 222 (8.6), 208 (6.8), 194 (7.8), 178 (48.0), 176 (13.1), 166 (10.8), 120 (10.6), 106 (12.9), 94 (23.5), 93 (14.5), 86 (19.6), 84 (32.2), 81 (16.2), 80 (100), 79 (17.4), 67 (16.8), 57 (11.2), 55 (31.0), 53 (26.9), 47 (11.4), 43 (36.2), 42 (10.7), 41 (59.5), 39 (23.8).

(3α,4aβ,8β)-4,4a,7,8-Tetrahydro-1-oxo-3-pentyl-1*H*,3*H*-pyrido[1,2-*c*][1,3]oxazine-8-carboxylic Acid (10). To a solution of 0.19 g (0.68 mmol) of methyl ester **9** in 10 mL of methanol was added 1 mL of 5% NaOH solution. After 2 h at room temperature, the mixture was acidified with 5% aqueous HCl. The solvent was removed under vacuum and the residue was extracted with ethyl acetate. The extract was washed twice with 30 mL of water, and the organic phase was dried and concentrated. The resulting yellow oil was crystallized from ether/hexane, affording 0.18 g (96%) of acid **10** as white plates: mp 107–109 °C; IR (KBr) 3600–2700, 2940, 2860, 1735, 1650, 1430, 1200, 1130, 865, 760, 730, 690, 660 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.90 (t, 3 H, J = 6.4 Hz), 1.18–1.78 (m, 8 H), 2.06–2.14 (m, 2 H), 2.57–2.73 (m, 2 H), 4.31–4.42 (m, 2 H), 5.47 (d, 1 H, J = 5.1 Hz), 5.56 (d, 1 H, J = 10.3 Hz), 5.80–6.13 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 13.88, 22.42, 24.19, 26.05, 31.50, 34.12, 35.08, 49.92, 51.42, 76.59, 123.78, 126.46, 154.06, 175.10; mass spectrum, m/z (relative intensity) 268 [M^+ + 1] (1.3), 267 [M^+] (9.2), 224 (1.1), 223 (5.9), 222 (9.6), 221 (2.0), 196 (6.8), 194 (6.9), 183 (5.1), 182 (1.1), 1.81 (3.6), 180 (20.3), 178 (50.0), 176 (16.8), 166 (14.4), 152 (41.8), 124 (30.4), 106 (17.0), 94 (39.3), 80 (100), 79 (16.3), 67 (15.9), 55 (21.3), 53 (19.7), 43 (14.0), 41 (30.8). Anal. Calcd for $C_{14}H_{21}NO_4$: C, 62.90; H, 7.92. Found: C, 62.75; H, 8.06.

Methyl (3α,4aβ,8β)-4,4a,7,8-Tetrahydro-1-oxo-3-pentyl-1*H*,3*H*-pyrido[1,2-*c*][1,3]oxazine-8-acetate (14). To a solution of 0.080 g (0.099

(19) Pless, J.; Boissonnas, R. A. *Helv. Chim. Acta* **1963**, *46*, 1607.
(20) We are grateful to Dr. M. A. Elsohly (University of Mississippi) for a sample and spectra of anhydrocannabisativene.
(21) The XRAY67 crystal structure determination program was designed by: Stewart, J. M., Computer Science Center, University of Maryland, College Park, 1967.

mmol) of carboxylic acid **10** in 2 mL of toluene was added 0.08 mL (0.224 mmol) of oxalyl chloride. The mixture was stirred under nitrogen at room temperature for 3 h, and the solvent was removed in vacuo. The resulting acid chloride was dissolved in 3 mL of dry ether, and an excess of ethanol-free diazomethane in ether was added. The mixture was allowed to stand at room temperature for 1 h, and the solvent was removed in vacuo. The diazo ketone was dissolved in 10 mL of dry methanol to which a catalytic amount of freshly prepared Ag_2O was added. The mixture was stirred for 12 h and was filtered through a Celite pad, and the solvent was removed under vacuum. Flash chromatography of the crude product (1:1 hexane/ethyl acetate) afforded 0.068 g (78%) of ester **14** as a pale yellow oil: IR (film) 3040, 2960, 2940, 2860, 1740, 1690, 1420, 1280, 1125, 1065, 1040, 760, 715 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 0.89 (t, 3 H, J = 6.4 Hz), 1.23–1.68 (m, 10 H), 1.93–2.15 (m, 2 H), 2.52 (dd, 1 H, J = 7.0, 14.3 Hz), 2.63 (dd, J = 8.5, 14.3 Hz), 3.68 (s, 3 H), 4.05–4.26 (m, 2 H), 5.17 (dd, 1 H, J = 7.0, 14.3 Hz), 5.54–5.60 (m, 1 H); mass spectrum, m/z (relative intensity) 295 [M^+] (3.2), 281 (2.0), 222 (8.6), 208 (6.8), 194 (7.8), 180 (18.2), 178 (48.0), 176 (13.1), 174 (7.0), 166 (10.8), 120 (10.6), 117 (6.3), 106 (12.9), 94 (23.5), 93 (14.5), 86 (19.6), 84 (32.2), 81 (16.2), 80 (100), 79 (17.4), 78 (8.4), 77 (9.9), 67 (16.8), 57 (11.2), 55 (31.0), 53 (26.9), 47 (11.4), 43 (36.2), 42 (10.7), 41 (59.5), 39 (23.8), 32 (13.1), 29 (61.5); high-resolution mass spectrum calcd for $C_{16}H_{25}NO_4$ 295.1783, found 295.1786.

Methyl (2α,6β)-1,2,3,6-Tetrahydro-6-(2-hydroxyheptyl)-2-pyridineacetate (15). To a solution of 39 mg (0.13 mmol) of ester **14** in 2 mL of glyme and 1.5 mL of water was added 165 mg (0.52 mmol) of barium hydroxide octahydrate. After refluxing under nitrogen for 48 h, the mixture was cooled to room temperature, and CO_2 gas was bubbled through the solution to precipitate the barium salts. Filtration of the mixture and concentration in vacuo afforded a colorless amino acid, which was dissolved in 15 mL of reagent grade methanol and 13 drops of thionyl chloride were carefully added. The mixture was refluxed under nitrogen for 12 h, and the solvent was removed in vacuo. The residue was dissolved in methylene chloride, and the solution was washed with dilute sodium bicarbonate. After drying of the solution, the organic phase was concentrated to afford 31 mg (87%) of amino alcohol **15** as an unstable brown oil of sufficient purity for use in the next step: IR (film) 3300, 3030, 2940, 2860, 1735, 1590, 1440, 820, 800, 760, 710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.7–1.1 (m, 3 H), 1.2–1.7 (m, 10 H), 1.8–2.2 (m, 2 H), 2.3–2.7 (m, 2 H), 3.7 (s, 3 H), 3.8–4.0 (m, 2 H), 5.6–5.8 (m, 2 H).

Methyl (2α,6β)-1,2,3,6-Tetrahydro-6(*S)-[2-(*tert*-butyldimethylsiloxy)heptyl]-2-pyridineacetate (16).** To a solution of 0.200 g (0.743 mmol) of amino alcohol **15** in 5 mL of CH_2Cl_2 were added 0.17 mL (1.49 mmol) of 2,6-lutidine and 0.26 mL (1.11 mmol) of *tert*-butyldimethylsilyl triflate[22] at 0 °C, and the reaction mixture was stirred for 4 h. The mixture was diluted with CH_2Cl_2 and was washed with cold 5% HCl and brine. The organic extract was dried and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (5% MeOH/$CHCl_3$) to give 0.260 g (91%) of silyl ether **16** as an unstable brown oil. IR (film) 3030, 2960, 2940, 2860, 1740, 1460, 1435, 1360, 1255, 1200, 1005, 835, 810, 775, 700 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 0.08 (s, 6 H), 0.86–0.90 (m, 12 H), 1.10–1.60 (m, 10 H), 1.81–1.90 (m, 2 H), 2.04–2.18 (m, 2 H), 2.40–2.51 (m, 2 H), 3.48–3.58 (m, 1 H), 3.81–3.90 (m, 1 H), 3.88 (s, 3 H), 5.70–5.73 (m, 2 H); high-resolution mass spectrum calcd for $C_{21}H_{41}NO_3Si$ 383.2856, found 383.2866.

4-Methyl-*N*-(3-hydroxypropyl)benzenesulfonamide (17). A solution of 1.26 g (6.6 mmol) of tosyl chloride in 20 mL of CH_2Cl_2 was added dropwise to a solution of 0.50 g (6.6 mmol) of 3-aminopropanol and 1.00 g (13.3 mmol) of Et_3N in 25 mL of CH_2Cl_2 at 0 °C. The mixture was stirred at 0 °C for 15 min after addition was complete. The reaction mixture was washed twice with 50 mL of water, and the organic layer was dried. Chromatography of the crude oil on 25 g of silica gel eluting with 2:3 hexane/ethyl acetate afforded 1.21 g (79%) of alcohol **17** as a clear, viscous oil: IR (film) 3500, 3260, 2950, 2880, 1600, 1430 (br), 1320, 1160, 1095, 820, 665 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.4–1.9 (m, 2 H), 2.4 (s, 3 H), 2.7–3.3 (m, 3 H), 3.5–3.9 (m, 2 H), 5.5–5.9 (m, 1 H), 7.3 (d, J = 8 Hz, 2 H), 7.8 (d, J = 8 Hz, 2 H).

4-Methyl-*N*-[3-[(tetrahydro-2*H*-pyran-2-yl)oxy]propyl]benzenesulfonamide (18). A solution of 1.21 g (5.29 mmol) of the alcohol **17**, 0.67 g (7.94 mmol) of dihydropyran, and 0.050 g of *p*-TsOH·H_2O in 75 mL of dry ether was stirred under nitrogen for 3 h. The reaction mixture was washed twice with 50 mL of saturated sodium bicarbonate solution, and the organic layer was dried. Chromatography of the resulting crude oil on 15 g of silica gel eluting with 1:1 hexane/ethyl acetate afforded 1.58 g (95%) of THP ether **18** as a colorless oil: IR (film) 3300, 2950, 2875, 1600, 1330, 1260, 1095, 1085, 1035, 1020, 990, 905, 870, 815, 665 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.2–2.0 (m, 8 H), 2.4 (s, 3 H), 2.8–4.0 (m, 6 H), 4.4–4.6 (m, 1 H), 5.2–5.4 (br s, 1 H), 7.2 (d, J = 8 Hz, 2 H), 7.8 (d, J = 8 Hz, 2 H).

N-[4-(1,3-Dihydro-1,3-dioxo-2*H*-isoindol-2-yl)butyl]-*N*-(3-hydroxypropyl)-4-methylbenzenesulfonamide (19). To a solution of 0.420 g (1.3 mmol) of sulfonamide **18** in 25 mL of dry DMF was added 0.040 g (2.4 mmol) of 25% KH in mineral oil. After cessation of gas evolution, the mixture was heated to 50 °C, and 380 mg (1.3 mmol) of *N*-(4-bromobutyl)phthalimide was added to the stirred solution under nitrogen. After heating the mixture for 2.5 h 50 °C, the solvent was removed in vacuo. The residue was diluted with CH_2Cl_2, and the solution was washed with 20 mL of water. The organic layer was dried and concentrated, and the residue was dissolved in a saturated methanolic HCl solution. The solution was stirred at room temperature for 1.5 h, and the solvent was removed in vacuo. The crude product was chromatographed on 9 g of silica gel eluting with 1:1 hexane/ethyl acetate yielding 411 mg (71%) of alcohol **19** as a clear oil, which crystallized upon standing: mp 79–82 °C; IR (film) 3500 (br), 2940, 2875, 1770, 1710, 1465, 1435, 1395, 1330, 1155, 1085, 1040, 910, 815, 720, 655 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.4–1.9 (m, 6 H), 2.3 (s, 3 H), 2.8–3.4 (m, 5 H), 3.4–3.8 (m, 4 H), 7.2 (d, 2 H, J = 8 Hz), 7.4–7.8 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 27.23, 27.31, 27.47, 33.12, 37.58, 38.71, 46.75, 50.01, 60.39, 124.67, 128.54, 130.89, 131.12, 133.50, 135.42, 144.73, 169.79; mass spectrum, m/z (relative intensity) 431 [M^+ + 1] (0.2), 430 [M^+] (0.1), 386 (5.9), 385 (24.8), 276 (30.8), 275 (91.4), 257 (28.0), 245 (13.2), 242 (15.5), 231 (38.7), 224 (37.2), 218 (11.6), 217 (73.9), 202 (37.2), 200 (45.2), 199 (76.3), 198 (86.2), 184 (12.8), 172 (41.5), 161 (32.0), 160 (89.5), 155 (90.2), 133 (20.3), 130 (35.1), 128 (23.1), 124 (34.5), 109 (15.0), 105 (19.7), 104 (20.2), 92 (44.2), 91 (100), 90 (10.1), 84 (28.4), 83 (22.3), 82 (25.7), 77 (30.3), 71 (20.1), 70 (89.8), 68 (26.0), 65 (33.5), 57 (41.5), 56 (39.1), 55 (25.3).

N-[4-(1,3-Dihydro-1,3-dioxo-2*H*-isoindol-2-yl)butyl]-*N*-[3-[(trifluoromethylsulfonyl)oxy]propyl]-4-methylbenzenesulfonamide (20). A solution of 0.135 g (0.31 mmol) of alcohol **19** in 5 mL of dry CH_2Cl_2 was added dropwise to a solution of 0.05 mL (0.31 mmol) of trifluoromethanesulfonic anhydride and 2 drops of pyridine in 10 mL of dry CH_2Cl_2 at 0 °C. After addition was complete, the reaction mixture was stirred for an additional 15 min and was poured into 20 mL of water. The mixture was extracted with CH_2Cl_2 (50 mL), washed twice with 20 mL of water and once with 20 mL of saturated brine, and dried over anhydrous Na_2SO_4. Concentration of the solution in vacuo yielded 0.68 g (95%) of triflate **20** as unstable yellow oil of sufficient purity for subsequent reactions: IR (film) 3075 (br), 2950, 2860, 1775, 1715, 1600, 1440, 1400, 1340, 1225, 1160, 1030, 925, 820, 725, 655, 640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.4–1.8 (m, 6 H), 2.4 (s, 3 H), 3.0–3.9 (m, 6 H), 4.6 (t, 2 H, J = 6 Hz), 7.2 (d, 2 H, J = 8 Hz), 7.4–7.9 (m, 6 H).

Methyl [2α,6β(*S)]-1-[3-[[4-(1,3-Dihydro-1,3-dioxo-2*H*-isoindol-2-yl)butyl][(4-methylphenyl)sulfonyl]amino]propyl]-6-[2-[[(1,1-dimethylethyl)dimethylsilyl]oxy]heptyl]-1,2,3,6-tetrahydro-2-pyridineacetate (21).** To a stirred solution of 2 mL of dry CH_2Cl_2, 2 drops of diisopropylethylamine, and 0.019 g (0.049 mmol) of amino ester **16** was added 0.052 g (0.095 mmol) of triflate **20** at room temperature. The solution was stirred under nitrogen for 13 h, and the solvent was removed in vacuo. The crude product was purified by preparative TLC eluting with 1:1 hexane/ethyl acetate to afford 0.028 g (70%) of **21** as a yellow oil: IR (film) 3025, 2960, 2940, 2860, 1775, 1740, 1715, 1600, 1465, 1435, 1395, 1370, 1340, 1255, 1210, 1155, 1090, 1040, 840, 775, 720, 650 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.04 (s, 6 H), 0.86 (s, 12 H), 1.25–1.91 (m, 16 H), 2.28–2.48 (m, 10 H), 2.39 (s, 3 H), 3.03–3.17 (m, 3 H), 3.65 (s, 3 H), 3.66–3.73 (m, 2 H), 5.63–5.70 (m, 2 H), 7.25–7.29 (m, 2 H), 7.66–7.87 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 14.05, 18.11, 21.45, 22.68, 24.82, 25.86, 26.00, 26.68, 27.95, 29.71, 32.13, 36.93, 37.38, 41.79, 44.44, 46.67, 47.47, 49.75, 51.49, 54.86, 69.92, 75.89, 76.29, 77.80, 123.18, 124.29, 127.20, 129.28, 129.57, 132.22, 133.85, 137.22, 142.89, 168.21, 168.21, 172.67; mass spectrum, m/z (relative intensity) 797 [M^+ + 2] (0.1), 796 [M^+ + 1] (0.3), 795 [M^+] (0.4), 794 (0.2), 781 (0.6), 780 (1.0), 739 (1.6), 738 (3.0), 725 (2.7), 724 (6.0), 723 (4.4), 722 (8.5), 665 (2.2), 664 (5.0), 663 (3.3), 620 (3.4), 606 (3.7), 590 (4.4), 568 (11.6), 567 (33.5), 566 (80.7), 552 (7.7), 544 (3.1), 509 (3.7), 508 (10.6), 494 (13.3), 493 (21.2), 492 (59.0), 482 (3.9), 426 (7.0), 413 (4.0), 412 (4.9), 395 (13.5), 383 (11.0), 382 (37.2), 365 (10.4), 338 (5.1), 291 (12.8), 278 (40.3), 264 (32.3), 259 (10.3), 257 (16.5), 245 (18.6), 231 (20.8), 216 (12.1), 215 (55.4), 202 (19.5), 200 (10.5), 192 (10.0), 169 (10.3), 168 (61.4), 161 (5.9), 160 (45.8), 159 (13.5), 155 (52.3), 154 (14.9), 149 (12.9), 120 (9.7), 119 (4.2), 118 (7.2), 115 (16.4), 96 (14.1), 95 (10.7), 94 (28.3), 93 (17.1), 92 (10.8), 91 (71.8), 89 (11.1), 84 (12.3), 77 (13.1), 76 (13.2), 75 (100), 74 (13.9), 73 (85.6), 70 (39.2), 57 (13.4), 56 (16.1), 55 (11.2), 44 (11.5), 43 (19.5), 41 (16.4); high-resolution mass spectrum calcd for $C_{43}H_{67}N_3O_7SSi$ 795.4312, found 795.4328.

Methyl [2α,6β(*S)]-1-[3-[[(4-Methylphenyl)sulfonyl]amino]propyl]-6-[2-[[(1,1-dimethylethyl)dimethylsilyl]oxy]heptyl]-1,2,3,6-tetrahydro-2-pyridineacetate (23).** Trifluoromethanesulfonic anhydride (0.130 mL,

(22) Stewart, R. F.; Miller, L. L. *J. Am. Chem. Soc.* **1980**, *102*, 4999.

0.782 mmol) was added to a solution of 3-(tosylamino)-1-propanol (**17**, 0.120 g, 0.521 mmol) and pyridine (0.078 mL, 0.913 mmol) in CH_2Cl_2 (3 mL) at −30 °C. The reaction mixture was warmed to 0 °C over 20 min, diluted with CH_2Cl_2, and washed with water. The organic phase was dried and concentrated to yield the triflate, which was used immediately in the next step.

To a solution of amine **16** (0.100 g, 0.261 mmol) in dry CH_2Cl_2 (2 mL) were added diisopropylethylamine (0.159 mL, 0.913 mmol) and a solution of the above triflate in CH_2Cl_2 (5 mL). The mixture was stirred at room temperature for 4 h and was diluted with CH_2Cl_2. The solution was washed with saturated $NaHCO_3$ solution and brine. The organic phase was dried and concentrated in vacuo. Flash chromatography (4% MeOH/$CHCl_3$) of the crude product afforded **23** (0.155 g, 99%) as a colorless oil. IR (film) 3300, 3040, 2960, 2940, 2850, 1740, 1600, 1470, 1440, 1330, 1260, 1210, 1170, 1100, 1070, 1040, 1010, 840, 820, 780, 710, 670, 610 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.01 (s, 3 H), 0.03 (s, 3 H), 0.84 (s, 9 H), 0.86 (br t, 3 H), 1.22–1.91 (m, 14 H), 2.33–2.50 (m, 4 H), 2.40 (s, 3 H), 2.96–3.06 (m, 3 H), 3.04 (m, 1 H), 3.06 (s, 3 H), 3.67 (m, 1 H), 5.63–5.70 (m, 2 H), 6.30 (m, 1 H), 7.27 (d, J = 8.4 Hz, 2 H), 7.74 (d, J = 8.4 Hz, 2 H); mass spectrum, m/z (relative intensity) 595 [M^+ + 1] (0.7), 594 [M^+] (1.3), 537 (12.1), 521 (5.0), 462 (6.4), 391 (2.2), 389 (2.0), 382 (30.4), 379 (4.2), 369 (2.1), 366 (25.1), 365 (100), 291 (57.8), 278 (15.8), 215 (28.9), 184 (9.4), 168 (16.3), 155 (31.0), 91 (40.1); high-resolution mass spectrum calcd for $C_{31}H_{54}N_2O_5SSi$ 594.3522, found 594.3523.

[2α,6β(S*)]-1-[3-[[(4-Methylphenyl)sulfonyl]amino]propyl]-6-[2-[[(1,1-dimethylethyl)dimethylsilyl]oxy]heptyl]-1,2,3,6-tetrahydro-2-pyridineacetic Acid (24). To a solution of ester **23** (0.047 g, 0.079 mmol) in methanol (1.5 mL) was added an aqueous solution of 1 N lithium hydroxide (0.35 mL) at 0 °C, and the mixture was stirred at room temperature for 15 h. The reaction mixture was carefully neutralized to pH 7 with 5% HCl at 0 °C and was extracted with chloroform. The organic extract was dried and concentrated in vacuo. The crude product was purified by preparative TLC (10% MeOH/$CHCl_3$) to afford acid **24** (0.045 g, 100%). IR ($CHCl_3$) 3500–2400 (br), 2970, 2940, 2870, 1600 (br), 1460, 1440, 1330, 1260, 1180, 1100, 1010, 980, 920, 840 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.04 (s, 3 H), 0.07 (s, 3 H), 0.86 (br s, 12 H), 1.20–1.49 (m, 10 H), 1.87–2.13 (m, 6 H), 2.40 (s, 3 H), 2.58 (m, 3 H), 2.80–3.25 (m, 3 H), 3.56–3.82 (m, 3 H), 5.73 (m, 1 H), 5.86 (m, 1 H), 7.28 (d, J = 8.0 Hz, 2 H), 7.75 (d, J = 8.0 Hz, 2 H).

[2α,6β(S*)]-N-(4-Hydroxybutyl)-1-[3-[[(4-methylphenyl)sulfonyl]amino]propyl]-6-[2-[[(1,1-dimethylethyl)dimethylsilyl]oxy]heptyl]-1,2,3,6-tetrahydro-2-pyridineacetamide (25). To a solution of carboxylic acid **24** (0.100 g, 0.172 mmol) in anhydrous methylene chloride (8 mL) was added 2,4,5-trichlorophenol (0.068 g, 0.345 mmol) and 1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide metho-*p*-toluenesulfonate (0.145 g, 0.345 mmol). The mixture was stirred for 45 h, diluted with CH_2Cl_2, washed with water, and dried. Concentration of the solution in vacuo gave the trichlorophenyl ester, which was used immediately without purification.

To a solution of the trichlorophenyl ester in anhydrous DMF (3.5 mL) was added 4-aminobutanol (0.16 mL, 1.723 mmol) at −20 °C, and the mixture was stirred for 18 h at −20 °C. The solvent was removed in vacuo and the crude product was purified by preparative TLC (10% MeOH in $CHCl_3$) to yield the amide alcohol **25** (0.092 g, 82%): IR (film) 3380, 3300, 3040, 2960, 2940, 2860, 1650, 1600, 1550, 1460, 1440, 1360, 1330, 1310, 1260, 1190, 1160, 1100, 1070, 980, 840, 820, 780, 710, 660 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.06 (s, 3 H), 0.07 (s, 3 H), 0.85–0.88 (br s, 12 H), 1.25 (s, 9 H), 1.34–2.30 (m, 20 H), 2.43 (s, 3 H), 2.54–2.59 (m, 1 H), 2.88–3.01 (m, 1 H), 3.22–3.40 (m, 2 H), 3.67 (m, 1 H), 5.75 (q, 2 H), 7.30 (d, J = 8.2 Hz, 2 H), 7.73 (d, J = 8.2 Hz, 2 H), 7.92 (NH, 1 H); mass spectrum, m/z (relative intensity) 652 [M^+ + 1] (0.41), 651 [M^+] (0.77), 636 (0.35), 594 (2.61), 581 (2.73), 580 (7.00), 521 (1.55), 463 (1.63), 439 (4.36), 437 (1.40), 423 (0.79), 422 (0.73), 389 (1.59), 369 (1.73), 366 (1.18), 365 (1.21), 355 (1.10), 343 (1.56), 323 (1.20), 321 (1.68), 313 (1.10), 309 (2.44), 308 (7.60), 307 (3.88), 306 (1.22), 305 (2.94), 294 (1.50), 292 (8.57), 291 (44.01), 282 (20.39), 267 (2.68), 253 (2.35), 250 (2.40), 240 (6.85), 239 (10.76), 215 (14.53), 204 (2.01), 185 (4.78), 184 (27.24), 178 (13.07), 172 (4.67), 159 (5.84), 155 (69.75), 149 (5.79), 139 (4.95), 131 (6.03), 94 (11.66), 92 (3.41), 86 (33.14), 84 (53.36); high-resolution mass spectrum calcd for $C_{34}H_{61}N_3O_5SSi$ 651.4101, found 651.4092.

[2α,6β(S*)]-N-[4-[(Methylsulfonyl)oxy]butyl]-1-[3-[[(4-methylphenyl)sulfonyl]amino]propyl]-6-[2-[[(1,1-dimethylethyl)dimethylsilyl]oxy]heptyl]-1,2,3,6-tetrahydro-2-pyridineacetamide (26). To a solution of alcohol **25** (0.022 g, 0.034 mmol) in anhydrous CH_2Cl_2 (1 mL) were added triethylamine (15 μL, 0.101 mmol) and methanesulfonyl chloride (8 μL, 0.101 mmol) at −15 °C, and the mixture was stirred for 1 h with gradual warming to 5 °C. The reaction mixture was diluted with CH_2Cl_2 and was washed with water. The organic phase was dried and concentrated in vacuo. Purification of the crude product by preparative TLC (10% MeOH in $CHCl_3$) afforded the mesylate **26** as a light yellow oil (0.0198 g, 80%): IR (film) 3400, 3300, 3040, 2960, 2940, 2870, 1650, 1600, 1550, 1460, 1380, 1330, 1260, 1180, 1160, 1090, 980, 960, 840, 810, 780, 710, 660 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.04 (s, 3 H), 0.07 (s, 3 H), 0.87 (s, 12 H), 1.18–2.25 (m, 13 H), 2.43 (s, 3 H), 3.03 (s, 3 H), 2.92–3.02 (m, 1 H), 3.19–3.40 (m, 4 H), 3.69–3.75 (m, 1 H), 4.26 (t, J = 6.2 Hz, 3 H), 5.70 (q, 2 H), 7.31 (d, J = 8.1 Hz, 2 H), 7.66 (NH, 1 H), 7.74 (d, J = 8.1 Hz, 2 H).

Synthesis of Lactam 27. To a solution of mesylate **26** (0.018 g, 0.025 mmol) in anhydrous acetonitrile (150 mL) was added anhydrous potassium carbonate (2 g), and the mixture was refluxed for 24 h. The reaction mixture was cooled, and the inorganic salts were removed by filtration. Removal of the solvent in vacuo and purification of the crude product by preparative TLC (10% MeOH in $CHCl_3$) yielded lactam **27** as a colorless oil (0.009 g, 58%): IR (film) 3400, 3310, 3040, 2960, 2940, 2875, 1680, 1600, 1550, 1460, 1440, 1340, 1290, 1250, 1180, 1090, 1070, 990, 920, 840, 820, 780, 760, 730, 710, 680 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.01 (s, 3 H), 0.03 (s, 3 H), 0.78 (s, 9 H), 0.87 (t, J = 6.9 Hz, 3 H), 0.90–2.00 (m, 18 H), 2.25–2.35 (m, 3 H), 2.43 (s, 3 H), 2.63 (m, 1 H), 2.90 (m, 1 H), 3.06 (t, J = 7.3 Hz, 2 H), 3.12–3.71 (m, 6 H), 5.74–5.76 (m, 2 H), 7.29 (d, J = 8.2 Hz, 2 H), 7.66 (d, J = 8.2 Hz, 2 H), 8.02 (NH, 1 H); ^{13}C NMR ($CDCl_3$) δ 0.84, 13.80, 17.81, 21.26, 22.46, 24.35, 24.61, 25.22, 25.72, 25.79, 25.97, 31.90, 37.90, 38.79, 43.52, 45.97, 48.70, 49.45, 56.35, 69.59, 125.60, 127.15, 128.26, 129.51, 142.96, 171.30; mass spectrum, m/z (relative intensity) 634 [M^+ + 1] (1.31), 633 [M^+] (2.81), 618 (2.21), 576 (14.02), 562 (18.58), 501 (8.02), 478 (9.72), 446 (12.03), 405 (27.96), 404 (96.74), 362 (11.35), 350 (9.85), 346 (18.12), 265 (18.77), 264 (100), 250 (10.62), 218 (16.10), 215 (13.97), 204 (12.23), 191 (6.17), 190 (7.80), 178 (10.04), 176 (37.86), 155 (19.51), 149 (16.11), 133 (13.12), 112 (24.59), 97 (97.69), 94 (36.49), 88 (43.85); high-resolution mass spectrum calcd for $C_{34}H_{59}N_3O_4SSi$ 633.3995, found 633.3980.

Reductive Cleavage of Sulfonamide 27. Lactam **27** (0.040 g, 0.063 mmol) was dissolved in anhydrous THF (2 mL) and the solution was cooled to −60 °C. Ammonia (~8 mL) was condensed into the solution, and small pieces of sodium were added until a blue color persisted. The reaction mixture was refulxed for 20 min, and the ammonia was evaporated. The residue was carefully dissolved in water (4 mL) and was extracted with ethyl acetate (3 × 6 mL). The organic phase was dried and concentrated in vacuo. Purification of the crude product by preparative TLC ($CHCl_3$/MeOH/NH_4OH, 90:9:1) yielded the amine **28** (0.027 g, 90%): IR (film) 3300, 3025, 2960, 2940, 2850, 1650, 1550, 1470, 1440, 1370, 1250, 1050, 840, 810, 780, 630 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.06 (s, 6 H), 0.88 (s, 12 H), 1.1–2.1 (m, 21 H), 2.27–2.47 (m, 2 H), 2.60–2.80 (m, 3 H), 2.90–3.01 (m, 2 H), 3.23–3.50 (m, 3 H), 3.72 (m, 1 H), 5.72 (m, 2 H), 9.51 (NH, 1 H); ^{13}C NMR ($CDCl_3$) δ 0.85, 13.95, 18.06, 22.66, 24.75, 25.94, 26.61, 26.85, 27.43, 27.63, 32.16, 37.70, 39.19, 40.10, 41.29, 42.54, 47.49, 50.32, 50.71, 53.12, 70.09, 125.47, 128.56, 172.01; mass spectrum, m/z (relative intensity) 480 [M^+ + 1] (6.30), 479 (15.91), 465 (2.03), 464 (5.90), 423 (9.99), 422 (30.79), 408 (24.59), 308 (11.31), 265 (28.60), 264 (22.67), 250 (59.10), 222 (12.62), 215, (20.85), 208 (100.0), 171 (27.83), 112 (24.28); high-resolution mass spectrum calcd for $C_{27}H_{53}N_3O_2Si$ 479.3907, found 479.3911.

(±)-Anhydrocannabisativene (2). To a solution of lactam **28** (0.010 g, 0.021 mmol) in dry CH_2Cl_2 (1.5 mL) was added boron trifloride etherate (40 μL, 0.31 mmol). The mixture was stirred at room temperature for 1 h and was diluted with CH_2Cl_2. The solution was washed with saturated $NaHCO_3$ and brine, dried, and concentrated in vacuo to yield alcohol **29**.

To a solution of this alcohol in acetone (1 mL) was added 6 drops of Jones reagent, and the mixture was stirred at room temperature for 30 min. The reaction mixture was poured into saturated $NaHCO_3$ solution and was extracted with ethyl acetate. The organic phase was washed with brine, dried, and concentrated in vacuo to yield essentially pure racemic anhydrocannabisativene (**2**)[2] (0.004 g, 54%), which was identical with an authentic sample[20] (^1H NMR, IR, mass spectrum, TLC). Attempted further purification of the alkaloid by chromatography resulted in extensive decomposition.

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Registry No. (±)-**2**, 89617-63-0; (±)-**4**, 89578-60-9; **6**, 72952-73-9; (±)-**7**, 89578-61-0; **7** (methylol), 89578-63-2; (±)-**8** (isomer 1), 89578-62-1; (±)-**8** (isomer 2), 89578-84-7; (±)-**9**, 89578-64-3; (±)-**10**, 89578-

65-4; (±)-**10** (acid chloride), 89578-67-6; (±)-**10** (diazo ketone), 89578-81-4; (±)-**14**, 89578-66-5; (±)-**15**, 89578-68-7; (±)-**15** (acid), 89578-69-8; (±)-**16**, 89578-70-1; **17**, 13379-98-1; **17** (triflate), 89578-82-5; **18**, 89578-71-2; **19**, 89578-72-3; **20**, 89578-73-4; **21**, 89596-61-2; (±)-**23**, 89578-74-5; (±)-**24**, 89578-75-6; (±)-**24** (2,4,5-trichlorophenol), 89578-83-6; (±)-**25**, 89578-76-7; (±)-**26**, 89578-77-8; (±)-**27**, 89578-78-9; (±)-**28**, 89578-79-0; (±)-**29**, 89578-80-3; methyl glyoxylate, 922-68-9; 3-aminopropanol, 156-87-6; *N*-(4-bromobutyl)phthalimide, 5394-18-3; trifluoromethanesulfonic anhydride, 358-23-6; 4-aminobutanol, 13325-10-5.

Supplementary Material Available: Complete X-ray data for compound **10** (12 pages). Ordering information is given on any current masthead page.

A General Procedure for Preparing α-Lithiosilanes. Generalization of the Peterson Olefination[1]

Theodore Cohen,* James P. Sherbine, James R. Matz, Robert R. Hutchins, Barry M. McHenry, and Paul R. Willey

Contribution from the Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260. *Received June 23, 1983*

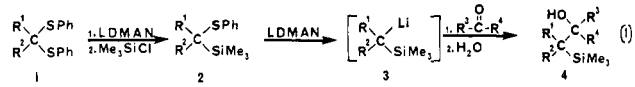
Abstract: A particularly convenient method for the preparation of α-lithiosilanes consists of the reductive lithiation of diphenyl thioacetals or thioketals with lithium 1-(dimethylamino)naphthalenide, treatment of the resulting anion with trimethylsilyl chloride, and reductive lithiation, with the same reducing agent, of the resulting α-(phenylthio)silane. The generality of the procedure is demonstrated by the preparation of α-lithiosilanes in which the negatively charged carbon atom is secondary, tertiary, vinylic, or part of a cyclopropyl ring. These species react with aldehydes and ketones to produce alcohols which, in all cases except the allylic alcohol produced from the vinylic α-lithiosilane, could be induced to form an olefin by loss of the elements of trimethylsilanol upon treatment with potassium hydride or acid.

The Peterson olefination,[2,3a] involving the reaction of an α-lithiosilane[3b] with an aldehyde or ketone followed by elimination of the hydroxide and silicon functions, is a potentially powerful alternative to the Wittig olefination, particularly because of the fact that the elimination step can usually be directed in either a syn or an anti manner.[4] However, the method has had the serious limitation that except in special cases α-lithiosilanes have not been readily available.[1a,3] Since early 1980[5], we have been studying the feasibility of preparing these organometallics by reductive lithiation, using lithium 1-(dimethylamino)naphthalenide[6] (LDMAN), of α-(phenylthio)silanes, a class of compounds two members of which we have reported to be available by reductive lithiation with lithium naphthalenide[7] or LDMAN[6] of diphenyl thioacetals followed by silylation; in addition to conventional procedures[8] for preparing such thioacetals, simple and versatile methods for preparing a variety of cyclopropanone thioketals[9] and ketene thioacetals[10] have recently been developed in our laboratory.

Results and Discussion

Preparation of α-Lithiosilanes. We now report that this method is completely general for the production of α-lithiosilanes (eq 1 and Table I).

We have found LDMAN to be far superior to lithium naphthalenide in the reductive lithiation steps for it obviates the necessity to separate the naphthalene byproduct from the neutral products; the 1-(dimethylamino)naphthalene is simply washed out with dilute acid.[11-13] We have found that even very acid sensitive groups can withstand this treatment.[14]



(1)

The reductive lithiation method is the only general one for the prepation of α-lithiosilanes containing no additional functionality.[15] An alternative procedure for the production of secondary α-lithiosilanes **3** ($R^1 \neq H$; $R^2 = H$) involves lithium–selenium exchange, but the yields are not entirely satisfactory and the method is not applicable to tertiary α-lithiosilanes (**3**, R^1 and $R^2 \neq H$)[16] except for the special case of 1-(lithiocyclopropyl)trimethylsilane.[17,18] The required α-(phenylthio)silane can be

(1) Taken in part (a) from the M.S. thesis of Paul R. Willey, University of Pittsburgh, 1981, and (b) from the Ph.D. thesis of James R. Matz, University of Pittsburgh, 1981.
(2) Peterson, D. J. *J. Org. Chem.* **1968**, *33*, 780.
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(4) Hudrlik, P. F.; Peterson, D. *Tetrahedron Lett.* **1974**, 1133; *J. Am. Chem. Soc.* **1975**, *97*, 1464. Hudrlik, P. F.; Peterson, D.; Rona, R. J. *J. Org. Chem.* **1975**, *40*, 2263.
(5) Many of the results reported here were discussed by T.C. in various lectures during 1981 and late 1980 in the United States and Europe; see footnote 3 of ref 17.
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(11) (a) Ager[12] has recently reported an analogous sequence for a specific subclass of **1**, namely diphenylthioacetals in which $R^1 = H$ and R^2 = phenyl or alkyl, using lithium naphthalenide rather than LDMAN. However, no mention was made of the problem of separating the α-silyl thioether from the naphthalene, one that has caused us and others[13] great grief before the LDMAN reagent was developed.[6] Also in this paper[12] it is implied that treatment of the α-lithiosilane with ketones or aldehydes yields olefins directly; no details are given. This does not correspond to our experience; as indicated, we found it necessary to treat the alcohols **4** with KH or with acid to effect elimination. (b) Paquette[13] prepared **3** ($R^1R^2 = CH_2CH_2$) from **2** ($R^1R^2 = CH_2CH_2$) using reductive lithiation with lithium naphthalenide, but the method was abandoned when the chromatography required to separate the alcohols (**4**, $R^1R^2 = CH_2CH_2$) from the naphthalene caused dehydration of the tertiary alcohols. Paquette also claimed that LDMAN gave incomplete reduction; we have found this not to be the case.
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(13) (a) Paquette, L. A.; Horn, K. A.; Wells, G. J. *Tetrahedron Lett.* **1982**, *23*, 259. (b) Paquette, L. A.; Wells, G. J.; Horn, K. A.; Yau, T. H. *Tetrahedron* **1983**, *39*, 913.
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(18) A still less general method involves the addition of an alkyllithium to a triorganylvinylsilane. Cason, L. F.; Brooks, H. G. *J. Org. Chem.* **1954**, *19*, 1278. Chan, T.-H.; Chang, E.; Vinokur, E. *Tetrahedron Lett.* **1970**, 1137. See also ref 4.

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