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A TOTAL SYNTHESIS OF (±)-ANHYDROCANNABISATIVINE.

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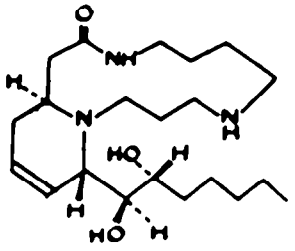
Abstract: Racemic anhydrocannabisativine has been efficiently synthesized starting with a β-lactam-imino ether coupling reaction. A key step in the formation of the tetrahydropyridine moiety of anhydrocannabisativine is a stereoselective intramolecular conjugate addition of the N-11 amino group to a Z,E-dienone.

Cannabisativine 1 and anhydrocannabisativine 2 are macrocyclic spermidine alkaloids isolated in small amounts from the roots and leaves of the common marijuana plant, Cannabis sativa.[1] Recently,[2] Natsume has reported a synthesis of 1 using the photooxygenation of a dihydropyridine to form the suitably functionalized starting material, while Weinreb[3] has prepared 2 through an intramolecular imino Diels Alder route. During the course of our studies on the formation of macrocyclic spermidine alkaloids,[4,5,6] we have developed a general route to both of these large ring lactams which allows for good synthetic flexibility and convergent pathways. We now report full details of the use of this process in a total synthesis of racemic anhydrocannabisativine. An important element in this synthesis was the construction of the macrocyclic lactam via the β-lactam imino-ether coupling reaction. This was followed by elaboration of the carbocyclic framework of the tetrahydropyridine ring.



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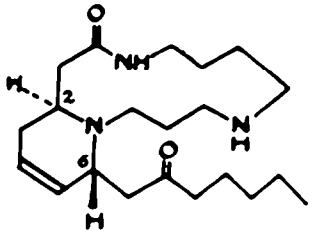

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Our plan for formation of the tetrahydropyridine ring involved conjugate addition of the secondary amino group to a Z,E dienone system as outlined in Fig. 1. Additionally, the trans relationship of centers C-2 and C-6 would require stereoselectivity in this cyclization. In earlier studies, Natsume[2] has found that aldehyde 3a readily undergoes complete cis to trans conversion of stereochemistry at centers C-2 and C-6 to give 3b (Fig. 2) and has interpreted these results in terms of a reversible addition of the nitrogen to the α,β-unsaturated aldehyde. Thus, there is reasonable precedent favoring a trans stereochemistry in forming the tetrahydropyridine system in this setting.

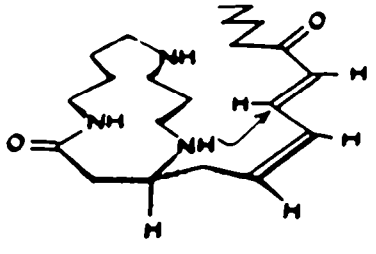


Figure 1

Dedicated to Professor Edward C. Taylor on the occasion of his 65th birthday

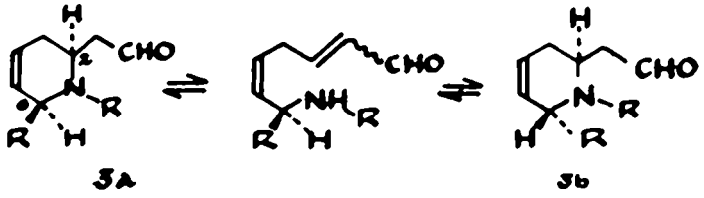
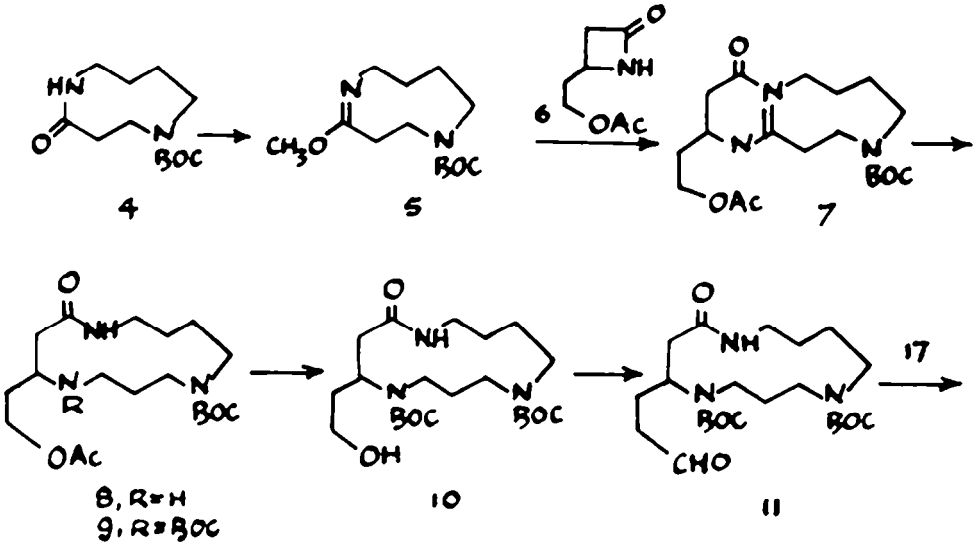
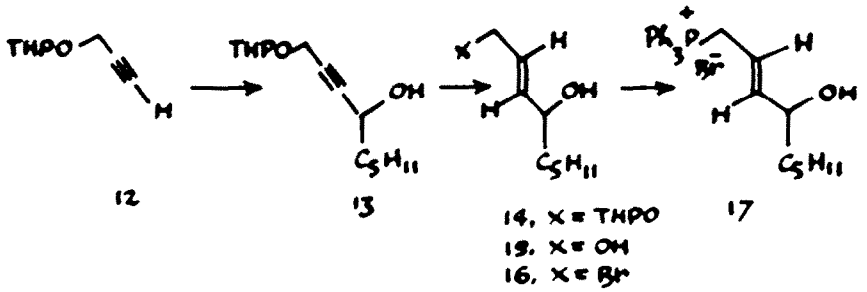


Figure 2

A key unit in our synthesis of anhydrocannabisativine was the protected nine-membered lactam 4 which we previously employed in the synthesis of the alkaloids cheenorhine[4], verbascenine[5], and dihydropalustrine.[6] As outlined in our report on dihydropalustrine, we converted 4 to the imino ether 5 and coupled this derivative with β-lactam 6 in warm mesitylene (145°C) to form the fused-ring amidine 7. The β-lactam 6 was readily available from the condensation of N-chlorosulfonyl isocyanate with 1-acetoxybutadiene by the Merck procedure.[7] Reduction of amidine 7 with $NaCNBH_3$ in acetic acid then yielded 8.[8] The secondary amino group in 8 was protected as its tert-butoxycarbonyl derivative 9 (82%), and deacetylation of 9 was accomplished with sodium methoxide in methanol to afford alcohol 10 (100%). Attempts to oxidize alcohol 10 under the acidic conditions of the Swern Oxidation failed, presumably due to accompanying N-deprotection. However, the use of Moffat conditions[9] (DMSO/DCC) gave excellent yields (82%) of the aldehyde 11.

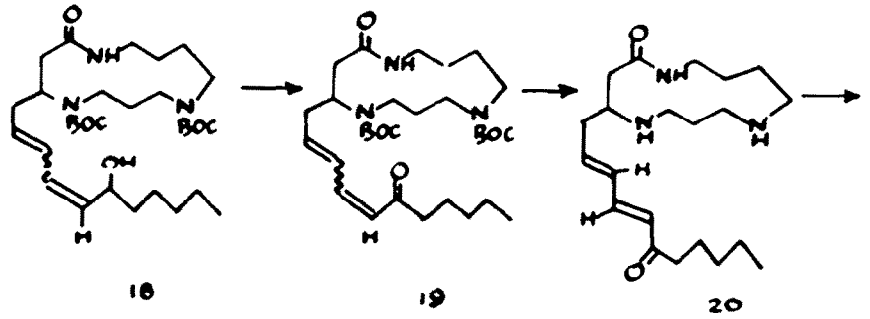


The side chain of anhydrocannabisativine was attached by means of a Wittig olefination involving aldehyde 11 and the phosphonium ylide 17. This salt was prepared by conventional methods from the THP protected propargyl alcohol 12[10]. Thus, the acetylide anion formed from 12 at -78°C upon reaction with n-butyllithium in THF was added to hexanal yielding alcohol 13 (93%). Reduction of this acetylenic alcohol 13 with sodium in liquid ammonia afforded the trans olefin 14 (59%),[11] which with pyridinium tosylate in refluxing methanol underwent deprotection to the diol 15 (84%). Selective bromination of 15 with triphenylphosphonium dibromide gave the desired primary bromide 16 (84%), which underwent reaction with triphenylphosphine in DMF at 78 C for 16 h to yield the desired triphenylphosphonium salt 17 (92%).



12 13 14, X = THPO 17
15, X = OH
16, X = Br

The Wittig-type coupling of aldehyde 11 and phosphonium salt 17 proceeded smoothly on treatment of a mixture of these compounds in THF at -5°C with potassium tert-butoxide. A mixture of the Z,E and E,E dienols 18 (90%) was obtained after workup and chromatography. Allylic oxidation of the dienol mixture 18 with manganese dioxide in ether gave the corresponding mixture of the Z,E and E,E dienones 19 (75%). Removal of the BOC protecting groups from 19 was accomplished by treatment with neat trifluoroacetic acid at room temperature generating the N-deprotected-(E,E)-dienone 20 as the exclusive product. As noted below, formation of the E,E-product with stereochemistry unfavorable for cyclization posed a temporary obstacle to the completion of the synthesis.



18 19 20

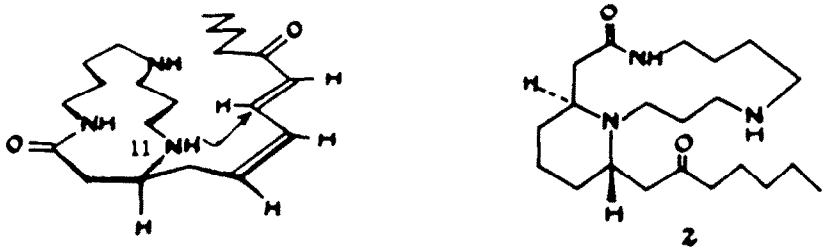


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Figure 3

Our plan for fusing the tetrahydropyridine ring to the 13-membered amino lactam depended on addition of the (N-11) secondary amino group to the dienone by intramolecular conjugate reaction to the Z,E system shown in Figure 3. We found, however, that the E,E-dienone 20 was resistant towards thermal isomerization and cyclization (up to 260°C) with or without added amine catalysts. Fortunately, the stereochemical problem involved in the cyclization could be solved by irradiation of 20 at 254 nm in ethanol. Under these conditions, isomerization of the E,E dienone to the desired Z,E isomer took place, followed by conjugate addition-cyclization to give (±)-anhydrocannabisativine 2 (93% from 18).[12] It was apparent from TLC and NMR analysis (500 MHz) of this cyclization product that only one diastereomer is formed in this reaction. Since, in principle, reversibility in the conjugate addition should be possible, it is reasonable to assume that the trans-stereochemistry found in the natural product is thermodynamically favored. Our synthetic product, formed in an overall yield of 25% from the 9-membered lactam 3, was identical in every respect (TLC, ^{1}HNMR, IR, Mass Spec) with the natural material.[14]

Experimental Section

Melting points were obtained in a Mel-temp melting point apparatus with an open capillary tube and are uncorrected. Boiling points are uncorrected. The IR spectra were determined with a Perkin-Elmer Model 700A infrared recording spectrophotometer or a Nicolet 5-SX FTIR instrument. The ^1H NMR spectra were determined at 90 MHz with a Varian EM-390 NMR spectrometer or at 250, 500 MHz with Bruker Model WM-250, WM-500 NMR spectrometers. The chemical shift values are expressed in δ values (ppm) relative to a Me_4Si standard. The mass spectra were obtained with an HP 5985 GC-MS system. High resolution mass spectra were determined by Mr. Mervin Thompson (University of Connecticut). Elemental analyses were performed by Atlantic Microlab Inc., Atlanta, Georgia.

2-(4-Hydroxy-2-nonynyloxy)-tetrahydro-2H-pyran (13)

To a solution of 2-(2-propynyloxy)-tetrahydro-2H-pyran 12, [10] (MW 140, 15g, 0.107 mole) in dry ether (250 mL) under nitrogen at -78°C (IPrOH-CO_2) was added n-butyllithium (1.55 M in hexanes, 76 mL, 0.12 mole). The solution formed a white precipitate after several min and was stirred for an additional 30 min at -78°C. Freshly distilled hexanal [12] (MW 100, 11.78 g, 14.13 mL, 0.12 mole) was added to the lithio-acetylene giving a clear solution. The mixture was stirred at -78°C for 90 min, then warmed to room temperature. The solution was quenched with saturated aq. NH_4Cl, poured into water and the aqueous layer extracted into ether. The ether extracts were dried (aq. NaCl, Na_2SO_4) and evaporated to a colorless oil. Shortpath distillation afforded 13 as a viscous, colorless oil, bp 128-133° C/0.05 mm (MW 240, 21.2 g, 0.088 mmole, 83%).

IR(Neat) 3460, 2970, 2890, 1460, 1350, 1120, 1025, 900 cm^{-1}. NMR ($CDCl_3$, 90 MHz) 4.80 (br s, 1H), 4.43(br d, 1H), 4.31(s, 2H), 3.37-4.03(m, 2H), 1.14-1.94(m, 16 H), 0.90(t, 3H).

Anal. Calcd. for $C_{14}H_{24}O_3$, 240.346, C 69.96, H 10.07

Found:C 69.81, H 10.08.

2-(4-Hydroxy-E-2-nonenyloxy)-tetrahydro-2H-pyran (14)

Sodium metal (MW 23, 2.76 g, 120 mmole) was added in small chunks to a dry solution of ammonia (175 mL) under nitrogen at -78°C(IPrOH-CO_2). After 5 min, a THF solution (25 mL) of 13 (MW 240, 9.60 g, 40 mmole) was added to the dark blue ammonia mixture. The blue color persisted for 50 min at which time the solution was stirred an additional 10 min, then quenched with 3 g of solid NH_4Cl. Methanol (5 mL) was added and the ammonia was evaporated. The material was poured into water (500 mL) and the aqueous layer extracted with ether (4 x 100 mL). The organic layers were dried (aq. NaCl, K_2CO_3) and evaporated to an oil. The desired alcohol 14 (MW 242, 5.66 g, 23 mmole, 59%) was obtained after shortpath distillation, bp 123°C/0.05 mm. This material was contaminated by a small amount of 13 which could be removed by careful flash chromatography (10-20% Et_2O in hexanes).

IR(Neat) 3470, 2970, 2890, 1470, 1205, 1115, 1015, 910 cm^{-1}

NMR($CDCl_3$, 90 MHz) 5.77(m, 2H), 4.63(br s, 1H), 4.12(m, 2H), 3.34-4.00(m, 2H), 1.09-1.86(m, 16H), 0.89(t, 3H).

Anal Calcd. for $C_{14}H_{26}O_3$, 242.362; C 69.38, H 10.81.

Found: C 69.14, H 10.82.

(E)-2-Nonene-1,4-diol (15)

A methanol solution (40 mL) of 14, (MW 242, 3.1 g, 12.8 mmole) and pyridinium tosylate [11] (MW 251, 150 mg, 0.6 mmole) was heated to reflux for 30 min, cooled, and poured into water (40 mL). The mixture was extracted with ether (3 x 40 mL), and the organic layers were dried (aq. NaCl, Na_2SO_4). Evaporation of the ether gave a viscous oil which was purified by flash chromatography (4:1 hexanes: ether). The diol was identified as the most polar component by TLC (1:1 hexanes

ether) and gave a dark blue stain upon vanillin spray development.[13] This procedure gave (E)-2-nonene-1,4-diol (15), (MW 158, 1.7 g, 10.8 mmole, 84%) as a colorless, very viscous oil. Kugelrohr distillation (100 C/0.1 mm) of the purified material gave the diol which slowly solidified on standing, mp 45–47° C.

IR(Neat) 3360, 2980, 2890, 1470, 1020, 975 cm^{-1}.

NMR ($CDCl_3$, 90 MHz) 5.78(m, 2H), 4.16(m, 3H), 1.30–1.80 (m, 10 H), 0.89(t, 3H).

Anal Calcd. for $C_9H_{18}O_2$, 158.243, C 68.31, H 11.47

Found: C 68.29, H 11.52.

1-Bromo-4-hydroxy-(E)-2-nonene (16)

Triphenylphosphonium bromide was prepared by the addition of bromine (MW 159.8, 4.52 mmole, 0.23 mL) to a methylene chloride solution (10 mL) of triphenylphosphine (MW 262, 4.52 mmole, 1184 mg) at -5°C(iPrOH-ice). The mixture of triphenylphosphonium bromide was added to a methylene chloride solution (4 mL) of 15 (MW 158, 4.52 mmole, 714 mg) and triethylamine (MW 101, 4.75 mmole, 0.67 mL) at -78°C ($iPrOH-CO_2$). The mixture was slowly warmed to room temperature over 1 h, then poured into water. The aqueous layer was extracted with fresh methylene chloride and the organic layers were dried (Na_2SO_4). Evaporation of the solvent left an oil which was purified by flash chromatography (4:1 hexanes:ether). Bromide 16 (MW 221, 840 mg, 3.80 mmole, 84%) was recovered as a colorless oil. Kugelrohr distillation (bp 95–100 C/0.1 mm) provided an analytical sample.

IR(Neat) 3390, 2960, 2890, 1470, 1205, 965 cm^{-1}.

NMR ($CDCl_3$, 90 MHz) 5.83(m, 2H), 4.14 (d of d, 1H), 3.95(d, 2H), 1.26–1.83(m, 9H), 0.89(t, 3H).

Anal. Calcd. for $C_9H_{17}BrO$, 221.144, C 48.88, H 7.75, Br 36.13.

Found: C48.71, H 7.78, Br 36.19.

4-Hydroxy-1-triphenylphosphonium-non-(E)-2-ene Bromide (17)

A mixture of 16 (MW 221, 840 mg, 3.8 mmole) and triphenylphosphine (MW 262, 1992 mg, 7.6 mmole) were heated under nitrogen at ~78° C for 16 h in a solution of dimethylformamide (1 mL). The dimethylformamide was removed under vacuum and the crude product was purified by flash chromatography (EtOAc, then 1:20 MeOH:EtOAc). The phosphonium salt 17 obtained in this manner was a colorless hygroscopic foam, (MW 483, 1696 mg, 3.51 mmole, 92%).

NMR ($CDCl_3$, 90 MHz) 7.51–8.00(m, 15H), 5.43–6.17(m, 2H), 4.56, 4.73(d of d, 2H), 4.09(br s, 1H), 1.00–1.40(m, 9H), 0.69(t, 3H).

1-Methoxy-7-tert-butoxycarbonyl-2,7-diazacyclononene (5)

A solution of 4[5] (MW 242, 2 g, 8.26 mmole) in methylene chloride was dried over activated 4A molecular sieves under nitrogen for 18 h. Trimethyloxonium tetrafluoroborate (MW 148, 1476 mg, 9.91 mmole) was added to the dry methylene chloride solution under nitrogen in a dry box apparatus. The mixture was stirred for 6 h at room temperature under nitrogen, then filtered into an aqueous solution of sodium bicarbonate. The product was extracted into fresh methylene chloride, and the organic layers were collected and dried over K_2CO_3. Evaporation of the solvent gave essentially pure 4 (MW 256, 1074 mg, 8.10 mmole, 98%) as a colorless oil which was used directly in the next reaction.

9-tert-Butoxycarbonyl-4-(2-acetoxyethyl)-1,5,9-triazabicyclo [4.7.0] tridec-6-ene-2-one (7)

A mixture of 4-(2-acetoxyethyl)-2-azetidinone (6)[6] (MW 157, 648 mg, 4.13 mmole) and 5 (MW 256, 1.06 g, 4.13 mmole) were heated under nitrogen in a solution of mesitylene (1 mL) for 15 h at 145°C. The mesitylene was removed by trituration of the brown oil several times with pentane. Flash chromatography (1:1 Et_2O:EtOAc, then 7:3 EtOAc:Et_2O) of the crude material afforded 7 (MW 381, 950 mg, 2.49 mmole, 60%) as a colorless oil.

7-tert-Butoxycarbonyl-12-(2-acetoxyethyl)-2,7,11-triazatridecanone (8)

An acetic acid solution (20 mL) of 8 (MW 381, 1.47 g, 3.86 mmole) and sodium cyanoborohydride (MW 63, 729 mg, 11.57 mmole) was stirred under nitrogen for 30 min at room temperature, then 16 h at 50°C, and finally an additional 16 h at room temperature. The acetic acid was stripped off under vacuum, and the crude material was dissolved in methylene chloride. The organic layer was washed with saturated sodium bicarbonate and dried over Na_2SO_4. Evaporation of the solvent gave a crude sample of 8 (MW 385, 1.49 g, 3.87 mmole, 100%).

7, 11-bis-tert-Butoxycarbonyl-12-(2-Acetoxyethyl)-2,7,11-triazatridecanone (9)

Amine 8 (MW 385, 1445 mg, 3.75 mmole) was dissolved in 20 mL of dry tetrahydrofuran under nitrogen. Di-tert-butyl dicarbonate (MW 218, 1060 mg, 4.86 mmole) was added, and the mixture was heated to 50°C for 15 h. The tetrahydrofuran was removed under vacuum, and the crude material was purified by flash chromatography (ether, then 4:1 ether:ethyl acetate) to give 9 (MW 485, 1468 mg, 3.03 mmole, 81%) as a colorless foam.

IR($CDCl_3$) 3005, 2970, 1740, 1685, 1375, 1170 cm^{-1}.

NMR($CDCl_3$, 250 MHz) 5.67(br s, 1H), 4.12(p, 1H), 2.06(s 3H), 1.47(s, 9H), 1.44(s, 9H), remaining hydrogens, 1.4-4.0(br m, 20 H). MS(EI, 20 ev) 486 (3.2), 485(11.7), 385(22.4), 384(45.6), 328(9.8), 312(4.3), 284(100), 266(4.4), 224(8.5), 198(8.9) amu.

Anal. Calcd. for $C_{24}H_{43}N_3O_7$, MW 485.626, C 59.36, H 8.93, N 8.65.

Found: C 59.19, H 8.97, N 8.58.

7,11-Bis-tert-Butoxycarbonyl-12-(2-hydroxyethyl)-2,7,11-triazatridecanone (10)

To a solution of anhydrous methanol (40 mL) was added 9 (MW 485, 1311 mg, 2.70 mmole) and sodium methoxide (MW 54, 44 mg, 0.81 mmole. The mixture was stirred at room temperature under nitrogen until the starting material was gone as judged by TLC (1:1 ether:ethyl acetate), ca. 3.5 h. Acetic acid (MW 60, 0.11 mL, 2 mmole) was added, and the methanol solution was poured into water. The product was extracted into ether, and the organic layers were dried (aq. NaCl, Na_2SO_4). Evaporation of the solvent gave a crude material that was purified by flash chromatography (1:20 methanol:ethyl acetate) to give 10 (MW 443, 1203 mg, 2.71 mmole, 100%). Recrystallization from ether-pentane afforded white crystals, mp 164-165 C.

IR($CDCl_3$) 2995, 2960, 1680, 1370, 1170 cm^{-1}.

NMR ($CDCl_3$, 250 MHz), 5.70 (br s, 1H), 2.32 (br d, 1H), 1.48 (s, 9H), 1.44 (s, 9H), remaining hydrogens 1.3-4.0 (br m, 21 H). MS (EI,20 eV) 444(3.6), 443(11.5), 342(51.6), 286(12.2), 270(25.4), 242(100), 217(11.9), 198(15.6), 173(12.6), 169(15.0), 157(10.5), 155(14.5) amu.

Anal. Calcd. for $C_{22}H_{41}N_3O_6$, 443.589, C 59.57, H 9.32, N 9.47.

Found: C 59.43, H 9.37, N 9.43.

7,11-Bis-tert-Butoxycarbonyl-12-(2-formylmethyl)-2,7,11-triazatridecanone (11)

A mixture of toluene (4 mL), dry dimethylsulfoxide (4 mL), trifluoroacetic acid (MW 114, 0.104 mL, 1.35 mmole) and pyridine (MW 79, 0.22 mL, 2.7 mmole) was stirred under nitrogen at room temperature. Alcohol 10 (MW 443, 1203 mg, 2.7 mmole) was added to the mixture followed by freshly distilled dicyclohexylcarbodiimide (MW 206, 1678 mg, 8.1 mmole). After stirring for 15 h at room temperature, an equal volume of ether was added to the toluene solution, and the insoluble dicyclohexylurea was removed by filtration. The toluene was removed under aspirator vacuum, and the crude material was taken up into ether and washed with water, satd. $NaHCO_3$ solution and dried (Na_2SO_4). Flash chromatography of the crude oil (1:1 ethyl acetate:hexanes) provided 11 (MW 441, 980 mg, 2.2 mmole, 82%). Recrystallization from ether-pentane afforded white crystals mp 132-135°C.

IR($CDCl_3$) 2995, 2960, 1730, 1680, 1370, 1170 cm^{-1}.

NMR($CDCl_3$, 250 MHz), 9.77(s, 1H), 5.69(br d, 1H), 2.25(d of d, J=14.6, 2.6Hz, 1H), 1.46(s, 9H), 1.44(s, 9H), remaining hydrogens, 1.3–4.3(br m, 18H), MS(EI, 20 eV), 442(1.3), 441(5.3), 385(3.7), 340(72.7), 323(20.3), 284(43.0), 268(61.1), 240(65.1), 222(53.1), 215(25.6), 212(36.9), 198(30.9), 195(78.9), 57(100) amu.

Anal. Calcd. for $C_{22}H_{39}N_3O_6$, 441.573, C 59.84, H 8.90, N 9.52.
Found: C 59.89, H 8.93, N 9.50.

7,11-Bis-tert-Butoxycarbonyl-12-(6-hydroxy-undec-2,4-diene)-2,7,11 -triazatridecanone (18)

A mixture of 11 (MW 441, 800 mg, 1.81 mmole) and 17 (MW 483, 964 mg, 2 mmole) in dry tetrahydrofuran (50 mL) under nitrogen was cooled to -5°C (IPrOH- ice). Potassium t-butoxide (MW 112, 265 mg, 2.37 mmole) was added to the THF solution giving rise to a deep red color which gradually faded over the period of 90 min at -5°C. Acetic acid (MW 60, 0.16 mL, 2.72 mmole) was added and the mixture was poured into water. The product was extracted into methylene chloride and the organic layers were dried (Na_2SO_4). Evaporation of the solvent left a crude solid that was purified by flash chromatography (hexanes: ethyl acetate, 3:1). A foam was recovered from chromatography, 1339 mg, which consisted of a mixture of triphenylphosphine oxide and the desired olefin. This material was rechromatographed using a different eluent (2% MeOH/$CHCl_3$) which gave complete separation of product from the triphenylphosphine oxide. Pure 18 (MW 565, 919 mg, 1.63 mmole, 90%) was recovered from the chromatographic column as a colorless foam.

IR($CDCl_3$) 2970, 1680, 1370, 1170 cm^{-1}.

NMR ($CDCl_3$, 250 MHz), 6.45(br t, 11.7 Hz, 1H), 6.08(m, 1H), 5.70(d of d, J=15.4, 7.3 Hz, 1H), 5.65 (br s, 1H), 5.37(br q, J=9.2 Hz, 1H), 2.29(br d, 1H), 1.47(s, 9H), 1.43(s, 9H), 0.89(t, 3H), remaining hydrogens, 1.3–4.2(br m, 28H). MS(EI, 20 eV) 565(1), 547(1), 465(4), 398(7.9), 298(11.7), 198(100, 129(5) amu.

Anal. Calcd. For $C_{31}H_{55}N_3O_6$, 565.801, C 65.81, H 9.80, N 7.43
Found: C 65.62, H 9.85, N 7.34.

7,11-Bis-tert-Butoxycarbonyl-12-(undec-2,4-diene-6-one)-2,7,11- triazatridecanone (19)

To an ether solution (20 mL) of 18 (MW 565, 300 mg, 0.53 mmole) was added 3 g of activated manganese dioxide. The suspension was stirred for 5 h at which time TLC (5% MeOH in $CHCl_3$) showed the reaction to be complete. The mixture was then filtered through celite, and the celite was washed well with dichloromethane. The organic solutions were evaporated to give essentially pure 19 (MW 563, 170 mg, 0.30mmole, 57%). A 75% yield of the ketone was obtained on a 0.1 mmole scale using the same procedure. Flash chromatography (1% MeOH in $CHCl_3$) provided an analytical sample of 19 as a pale yellow foam.

IR($CDCl_3$) 3005, 2970, 1685, 1375, 1175 cm^{-1}

NMR ($CDCl_3$, 250 MHz), 7.45(E, E), 7.21(Z, E), (d of d, J=12.1, 15.7Hz (E,E), 9.9, 15.7Hz (Z, E), 1H), 6.32(m, 2H), 5.85(q, J=8.1Hz, 1H), 5.66(br s, 1H), 2.55(t, J=7.3Hz, 2H), 2.99(br d, J=13.5Hz, 1H), 1.63(t, J=7Hz), 1.43(s, 18H), 0.90(t, J=7.5Hz, 3H), remaining hydrogens, 1.3–4.0(br m, 24H).

MS(EI, 20eV) 563(1), 469(2.4), 463(2.1), 398(2.4), 363(2.1), 298(5.6), 242(2.1), 198(100), 129(8.7) amu.

HRMS Calcd. for $C_{31}H_{53}N_3O_6$, 563.3957, Observed Mass 563.3941

12-(Undec-2,4-diene-6-one)-2,7,11-triazatridecanone (20)

The di-tert-butoxycarbonyl derivative 19 (MW 563, 162 mg, 0.288 mmole) was dissolved in trifluoroacetic acid (3 mL) and stirred at room temperature for 15 min. The trifluoroacetic acid was removed under vacuum and the crude material was taken up into a methylene chloride solution. The organic layers were washed with satd. $NaHCO_3$ solution and dried (Na_2SO_4). Evaporation of the solvent left a crude yellow foam of 19 (MW 363, 128 mg). The crude material

could be purified by flash chromatography if necessary (MeOH, then3% NH_4OH in MeOH) to give 20 as a pale yellow foam.

NMR($CDCl_3$, 250 MHz), 8.59(br s, 1H), 7.12(d of d, J=9.2, 15.8 Hz, 1H), 6.26(m, 3H), 2.55, 1.64, 0.90(t, J=7.0 Hz), remaining hydrogens, 1.2-4.0(br m, 32 H).

(±)-Anhydrocannabisativine (2)

An ethanol solution (30 mL) of 20 (128 mg) obtained directly from the previous reaction, was photolyzed at 254 nm through a quartz tube under nitrogen using a portable UV lamp. The reaction progress was monitored by TLC (4% NH_4OH in MeOH) and was found to be complete after 20 h. The crude material was flash chromatographed (silica gel, 1:1 EtOAc:MeOH) giving 115 mg of a yellow foam. The foam was taken up into dichloromethane (1 mL), and pentane (5 mL) was added, causing a yellow gum to precipitate. The pentane solution was decanted and set aside. The gum was triturated with additional dichloromethane, leaving behind a residue (19 mg) which was insoluble in dichloromethane. The organic fractions were combined and evaporated to give pure anhydrocannabisativine 2 (MW 363, 97 mg, 0.267 mmole, 93% from 20 as a pale yellow solid. The synthetic material was identical to the natural sample by TLC (4% NH_4OH in MeOH), NMR ($CDCl_3$, 250 and 500 MHz), IR($CHCl_3$, FT) and mass spectroscopy (EI, 20 eV).

IR($CHCl_3$, FT) 2959, 2971, 1709, 1651, 1466, 1129 cm^{-1}.

NMR($CDCl_3$, 500 MHz), 9.68(br s, 1H), 5.82(d of d, J=5.1, 10.2Hz, 1H), 5.50(br d, J=10.2Hz, 1H), 3.72(br s, 1H), 3.44(br s, 2H), 2.28(br d, J=14.7Hz), 2.08(d, J=13.4Hz), 0.89(t, J=6.9Hz, 3H), remaining hydrogens, 1.2-3.0(br m, 28H). MS(EI, 20 eV), 364(11.0), 363(29.4), 345(5.9), 334(3.7), 320(7.3), 305(4.0), 304(5.2), 292(4.8), 264(45.1), 250(28.8), 248(7.6), 235(10.4), 234(12.1), 222(22.1), 208(49.2), 198(53.2), 192(100), 112(68.8) amu.

HRMS Calcd. for $C_{21}H_{37}N_3O_2$ 363.2886, Observed Mass 363.2897.

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13. Prepared by the addition of 1.5 mL of conc. H_2SO_4 to 50 mL of abs. ethanol, followed by addition of this solution to a mixture of vanillin (3 g) in 50 mL of ethanol. The TLC plates were sprayed with this reagent followed by heating.
14. Crude samples of natural anhydrocannabisativine were kindly supplied by Professor Steven Weinreb (Pennsylvania State University) and Dr. Mahmoud Elsohly (University of Mississippi), and were purified by flash chromatography (2% NH_4OH in MeOH).