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A TOTAL SYNTHESIS OF (±)-ANHYDROCANNABISATIVINE.

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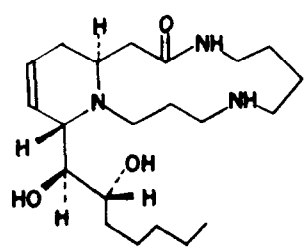
Abstract: Racemic anhydrocannabisativine has been efficiently synthesized by employing a β-lactam-imino ether coupling reaction. The key to the formation of the tetrahydropyridine moiety of the natural alkaloid is a stereoselective intramolecular conjugate addition of a secondary amino group to a Z,E 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 key 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, we have developed a general route to these large ring lactams using β-lactam-imino ether coupling which allows for good synthetic flexibility and convergent routes.[4,5,6] We now report the use of this process in a total synthesis of racemic anhydrocannabisativine .



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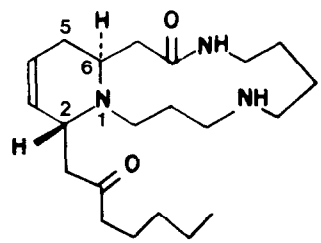

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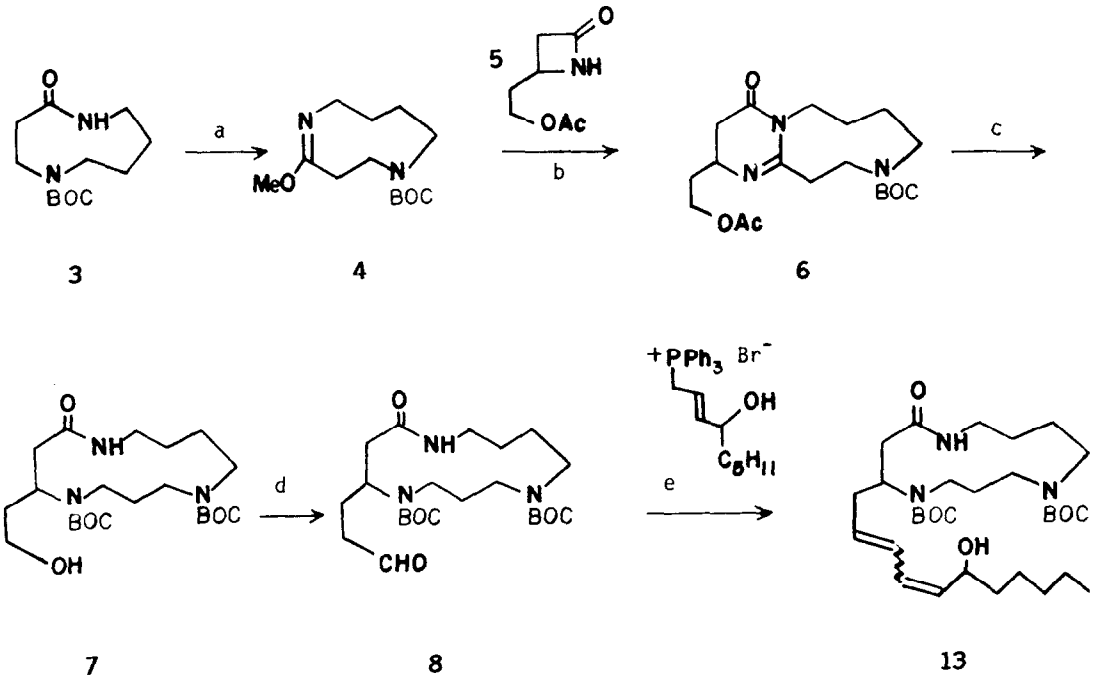
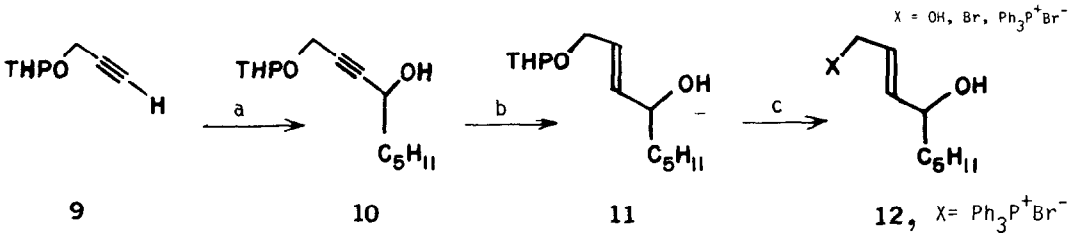
Our synthesis began with the protected nine-membered lactam 3 which we have previously employed in the synthesis of the alkaloids chaenorhine[4], verbascenine[5], and dihydropalustrine.[6] Formation of the imino ether 4, reaction with the β-lactam 5[7] and reduction of the amidine 6 proceeded as described for the synthesis of dihydropalustrine.[6] After protection of the secondary amine as the BOC derivative (82%), treatment with $NaOCH_3/CH_3OH$ yielded the alcohol 7 (100%). Moffat oxidation of 7 [8] gave the aldehyde 8 (82%).



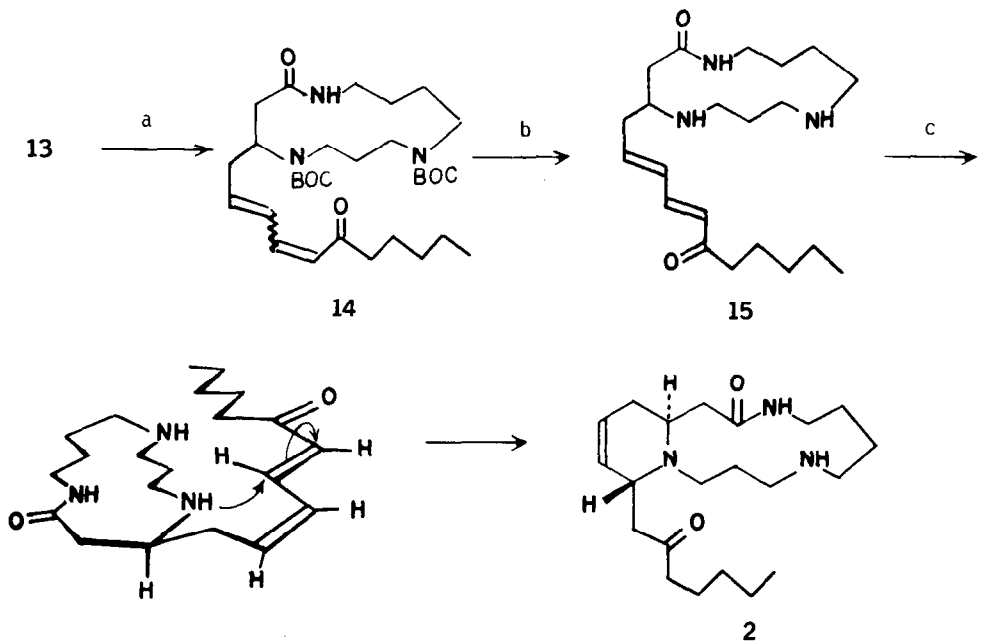
(a) $Me_3O^+BF_4^-$;(b) 145°C, 15h;(c) $NaCNBH_3$, HOAc; $(BOC)_2O$, 50°C, 15h; NaOMe, MeOH; (d) DMSO, DCC, TFA, Pyr;(e) tBuOK, THF.

We then proceeded to attach the anhydrocannabisativine side chain by a Wittig olefination of aldehyde 8 with the phosphonium ylide derived from salt 12. The latter was prepared from the THP-protected propargyl alcohol 9 [9] according to the following procedure: the acetylide anion, added to hexanal, gave alcohol 10 (93%), which was reduced in Na/NH_3 to the trans olefin 11 (59%).[10] Treatment of 11 with pyridinium tosylate in refluxing methanol gave the diol (84%), convertible by selective bromination with triphenylphosphine dibromide to the desired primary bromide (84%). Reaction of the bromide with triphenylphosphine in DMF at 78 °C for 16 h gave the triphenylphosphonium salt 12 (92%).



(a) nBuLi, $C_5H_{11}CHO$; (b) Na, NH_3; (c) pyridinium p-toluenesulfonate, MeOH; $Ph_3P{\cdot}Br_2$; Ph_3P, DMF.

The Wittig-type coupling of aldehyde 8 and phosphonium salt 12 proceeded smoothly with potassium tert-butoxide in THF at -5 °C, yielding a mixture of the Z,E and E,E dienols 13 (90%). Allylic oxidation of the dienols 13 with manganese dioxide in ether gave 14 (75%) as a mixture of Z,E and E,E dienones. At this stage, treatment of 14 with neat trifluoroacetic acid at room temperature in order to remove the protecting BOC groups gave the N-deprotected-(E,E)-dienone 15 exclusively.



(a) MnO_2, Ether; (b) CF_3CO_2H; (c) hν, EtOH

Since our synthetic plan called for an intramolecular addition of the secondary amino group to a Z,E-dienone to form the desired tetrahydropyridine ring, the preference shown by 15 for the E,E configuration posed a temporary stumbling block. Thus, compound 15 showed resistance toward thermal cyclization up to 260 °C with or without added amine catalyst. However, the desired conjugate addition occurred cleanly and in high yield under conditions of ultraviolet irradiation (with accompanying isomerization) at 254 nm in ethanol, yielding ±-anhydrocannabisativine as the sole product (93% from 14). Our synthetic product was indistinguishable (TLC, ^{1}HNMR, IR, mass spec) from the natural material.[11,12] It is noteworthy that in the photoisomerization-cyclization, only one diastereomer was formed corresponding to the natural configuration. The mechanistic aspects of this addition will be considered more fully in our further studies.

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11. 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).

12. All new compounds gave satisfactory IR, NMR, mass spectroscopic and/or combustion analysis.

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