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A TOTAL SYNTHESIS OF (±)-CANNABISATIVINE

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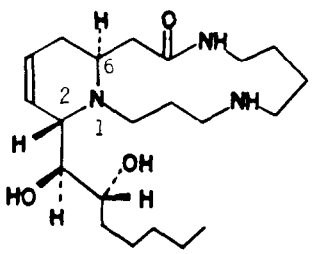
Abstract: A synthesis of racemic cannabisativine is reported. Intramolecular opening of an erythro-acetoxy epoxide by a secondary amino group provided the side chain containing the desired stereochemistry.

The alkaloid cannabisativine (1) isolated from the marijuana plant, Cannabis sativa is a member of a family of polyamine lactams containing spermidine residues.[1,2] Recent synthetic investigations have explored new methods for forming this system (Natsume)[3] and the related anhydro derivative (Weinreb).[4] Our own studies in this field have focused on methods for effecting expansion of smaller heterocyclic rings to larger units, and have led to syntheses of several members of this class,[5-10] including anhydrocannabisativine[10] and dihydropalustrine (2).[11]



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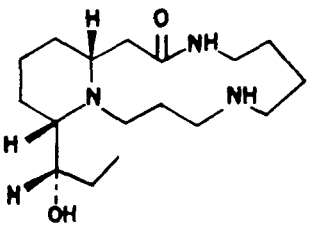

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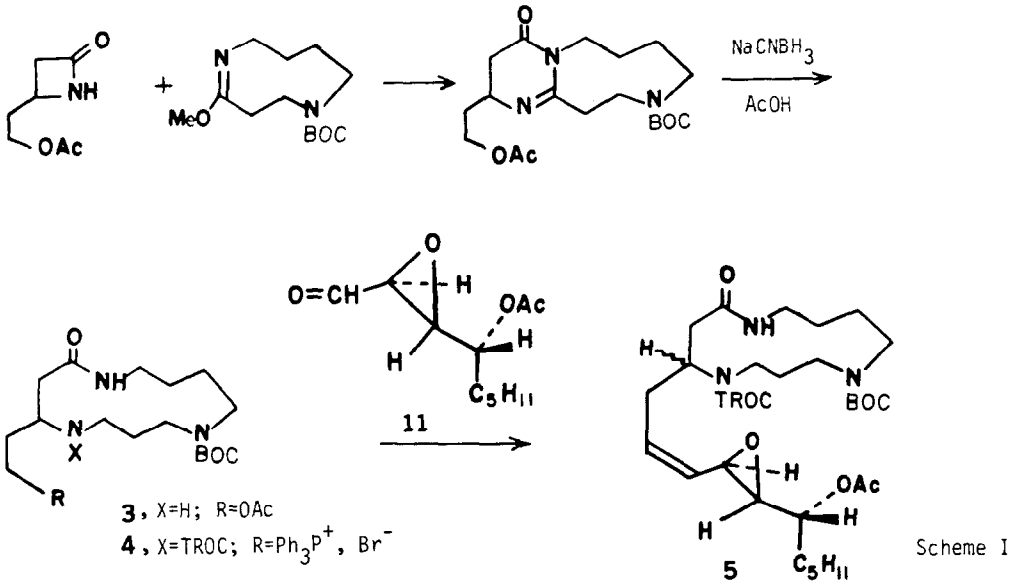
We now report the total synthesis of (±)-cannabisativine (1). As outlined below, our route permits stereochemical control in the assembly of the three adjacent chiral centers at the 2-position of the molecule.

The key starting material in the synthesis was a protected acetoxy diamino lactam 3 prepared as in our earlier work[11] by the coupling of an acetoxyethyl β-lactam with a nine-membered imino ether, followed by reduction (Scheme I). The thirteen-membered lactam 3 could be converted to the differentially protected triphenylphosphonium salt 4 as described in the synthesis of dihydropalustrine,[11] and allowed to react with the

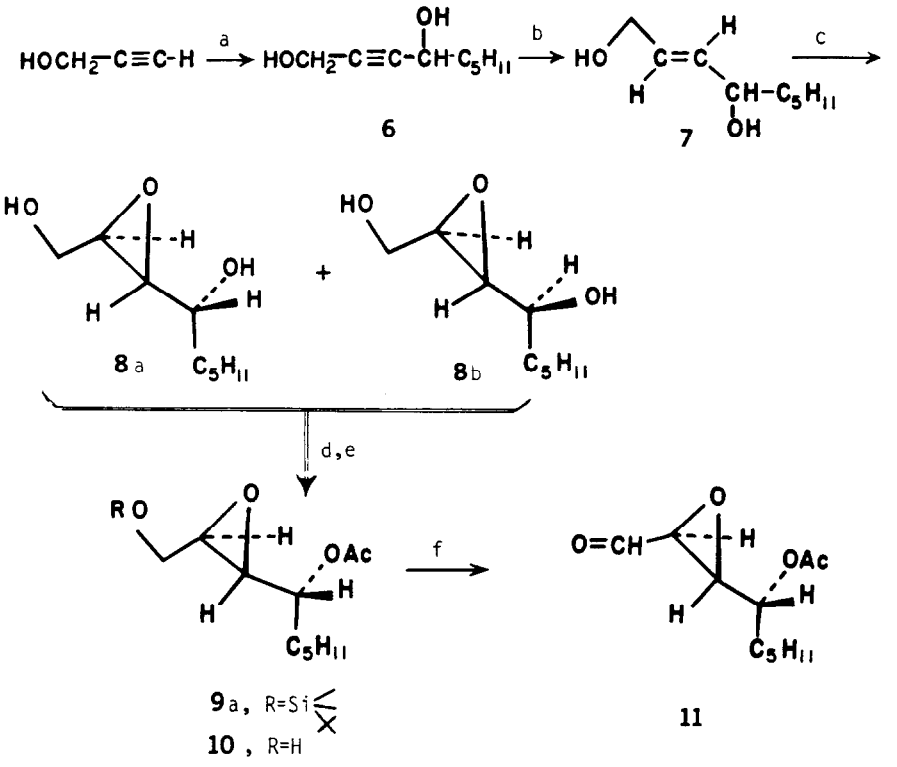


Scheme I

acetoxy epoxy aldehyde 11 (NaH, DMSO/THF) generating the cis-unsaturated epoxide 5. This coupling served to introduce the double bond and the epoxide in the desired location for formation of the tetrahydropyridine ring.

To form the aldehydic component 11, the dianion of propargyl alcohol was added to hexanal to give the diol 6 (93%) which was reduced ($LiAlH_4$) to the trans-allylic diol 7 (79%) (Scheme II). This alcohol was then epoxidized (t-BuOOH/$VO(acac)_2$) to form 8a,b (90%) as a 3:1 mixture of diastereomers. Since this catalyst is known to produce the erythro-epoxide preferentially,[12] the major isomer was assigned structure 8a. The primary alcohols in the mixture were selectively protected (TBDMSCl, DMAP), and the secondary alcohols acylated (Ac_2O, DMAP) without isolation of the intermediate. At this stage, the two diastereomers 9a,b could be separated by flash chromatography giving 9a (50%) as the less polar isomer. Cleavage of the silyl ether was accomplished smoothly (Bu_4NF/THF) to give the primary alcohol 10 (90%). Oxidation with dimethyl sulfoxide activated with oxalyl chloride[13] gave the required aldehyde 11 (67%) as a single diastereomer.

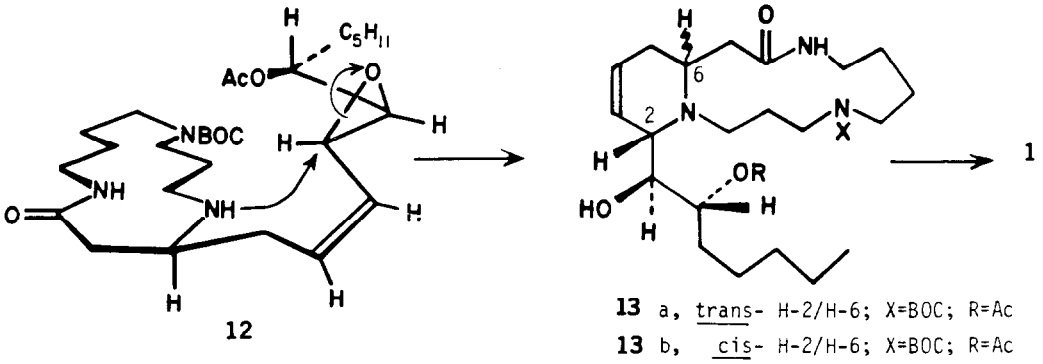
With the Wittig reaction product 5 in hand, the complete assembly of the alkaloid framework required only the removal of the trichloroethoxycarbonyl protecting group, freeing the secondary amino group in 12 for intramolecular epoxide opening. This deprotection-cyclization sequence was carried out in one operation with Zn in THF/H_2O at



Scheme II*

*(a) n-BuLi, THF, -78°C, then, n-$C_5H_{11}CHO$; (b) $LiAlH_4$, Et_2O, reflux; (c) $VO(acac)_2$, 0.02 eq, TBHP, CH_2Cl_2, 0°C, 24h; (d) TBDMSCl, DMAP, CH_2Cl_2, 0°C, then Ac_2O, DMAP, 22°C; (e) n-Bu_4NF, THF, 0°C; (f) DMSO, $(COCl)_2$, CH_2Cl_2, -78°C.

pH=5, yielding 13a,b (62%). The two diastereomers (ca., 1:1)could be separated by flash chromatography. The more polar compound was assigned the trans H-2/H-6 configuration 13a by analogy with palustrine.[11] Cleavage of the acetyl group of 13a (MeONa, MeOH, 80%) followed by removal of the BOC group (HCl/CH_2Cl_2) gave pure (±)-cannabisativine (1) (70%) identical in all respects (250-MHz ^1H NMR, IR, TLC) with the natural product.[1]



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14. All new compounds gave satisfactory NMR, IR and mass spectral or analytical data.

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