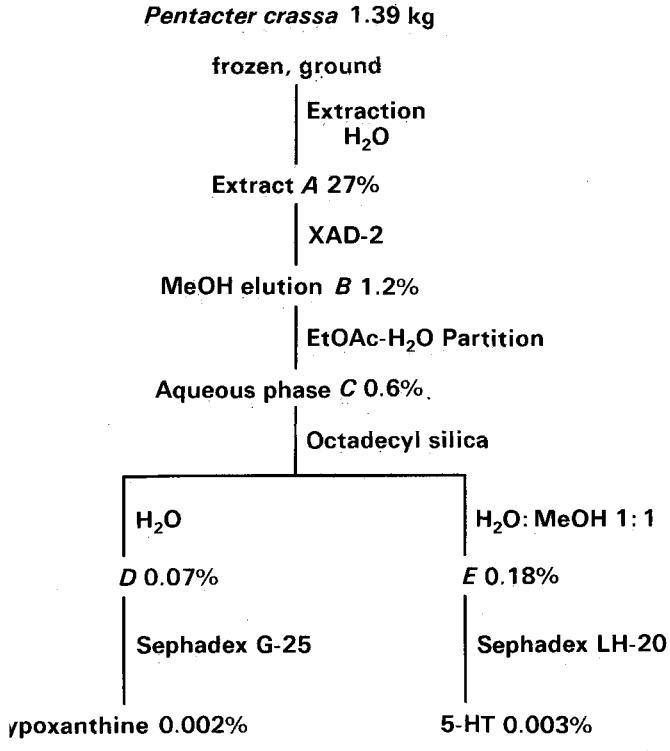
shown to be hypoxanthine by comparison (HRMS, ^{13}C NMR) with an authentic sample. Elution of the octadecyl silica column with water: methanol (1:1) afforded an active fraction E (2.5 g) which was chromatographed on Sephadex LH-20 in methanol to yield potent material at V_R/V_M 2.20–2.53. Rechromatography on Sephadex LH-20 afforded the active constituent (44 mg) which was shown to be identical with 5-HT by ^{13}C NMR, ^1H NMR and bioassay. The pure material caused the well known triphasic response on blood pressure after i.v. administration and this effect was abolished by predosing with methysergide[12], a specific inhibitor of 5-HT. The concentration of 5-HT present (30 µg/1 g dry organism) in *P. crassa* was confirmed by HPLC analysis of butanol extracts of whole organisms.

Aqueous extracts of the holothurians *Thelenota ananus* Jaeger (1833) and *Stichopus chloronatus* Brandt (1835) almost certainly contain 5-HT as they exhibited very similar hypotensive activities, which were abolished by methysergide, to the *P. crassa* extract. Although we were unable to examine neuronal tissue of these holothurians, the isolation of 5-HT from *P. crassa*, and its apparent presence in *T. ananus* and *S. chloronatus*, means that 5-HT should be of primary importance when considering the neurotransmitters, and cardiovascular effects, of holothurians.



Separation scheme for the isolation of the anti-hypertensive constituent from the holothurian, *Pentacter crassa*.

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Hashish: Synthesis of (±)-2′,11-dihydroxy-Δ^9-tetrahydrocannabinol (THC), a metabolite of Δ^9-THC[1]

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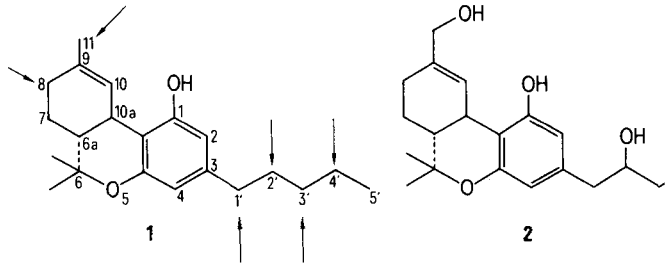
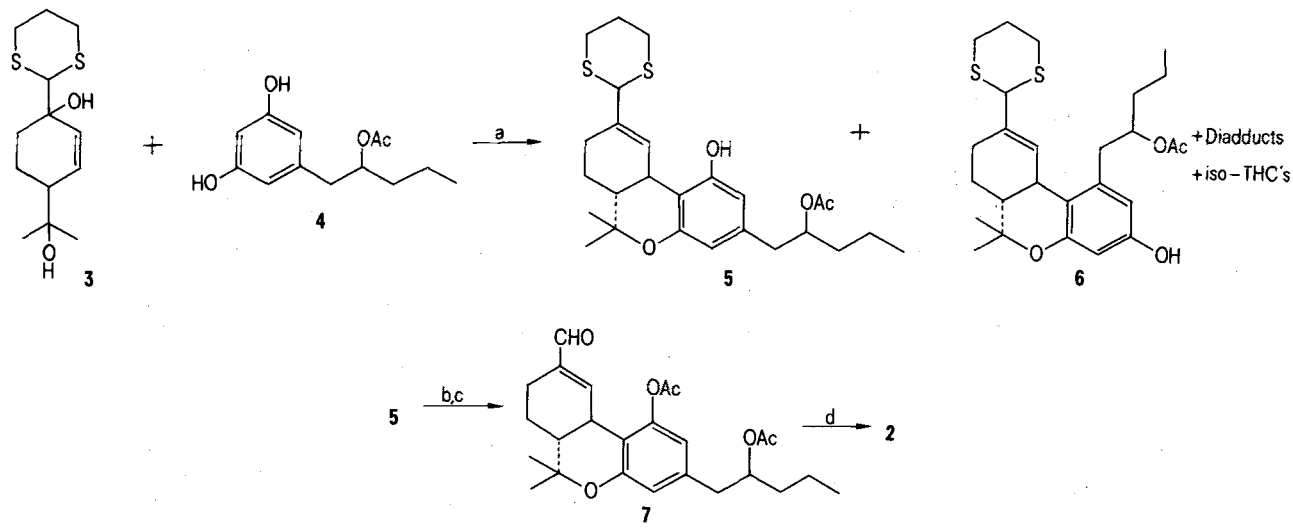
SISA Institute for Research, Inc., 763D Concord Ave., Cambridge (MA 02138, USA), 15 December 1980

Summary. The synthesis of (±)-2′,11-dihydroxy-Δ^9-THC, a difunctionalized metabolite of Δ^9-THC, is presented.

In recent years a great deal of attention has been focused on the biotransformation of cannabinoids. Metabolism has been studied in several species: man, mouse, monkey, rabbit and guinea-pig among others[2–4]. In the case of Δ^9-THC, the active constituent of marihuana, these studies have identified primary metabolites that are hydroxylated within the terpene portion at the allylic positions, C-8 and C-11 and/or the aromatic side chain as shown in **1**. Some of these metabolites are pharmacologically equi-active with Δ^9-THC, and still others are active to greater and lesser degrees. This has complicated the understanding of marihuana activity in man[2,3].

Synthetic methods have been developed which have provided metabolites of Δ^9-THC functionalized either in the terpene portion[5] or the aromatic side chain[6–9]. Until now, the metabolites with a functionalization both in the terpene portion and the aromatic side chain have not been synthesized. In this communication we wish to report the synthesis of (±)-2′,11-dihydroxy-Δ^9-THC **(2)**, the first example of a metabolite belonging to this class. Compound **2** was shown by Harvey et al.[10] by GC-MS to be a major metabolite of Δ^9-THC in the guinea-pig, although it does not appear to be a major metabolite in man.





Scheme. a, pTSA, PhH; b, Ac_2O, Pyr.; c, HgO, $BF_3 \cdot Et_2O$, H_2O-THF; d, $LiAlH_4$.

The synthesis of **2** was achieved by utilizing the general procedure we developed for 11-substituted Δ^9-THC's from the novel synthon **3**[5d]. This further extends the versatility of our procedure for the synthesis of different types of metabolites.

The terpene synthon **3**[5d] was added to an excess of (±)-2-acetoxyolivetol **4**[11] in refluxing benzene with a catalytic amount of dry p-toluenesulfonic acid (p-TSA). After 15 min the reaction was quenched with aqueous sodium carbonate, worked-up by extraction and the oily residue separated by flash chromatography (silica gel 60, 230–400 mesh, 4/1 hexane/EtOAc) yielding approximately equal amounts of n-adduct, **5**, (16%) [NMR (CCl_4) δ: 0.87 (t, ω-CH_3), 1.37 (s, 6H, *gem* CH_3's), 1.98 (s, 3H, 2'-OAc), 2.75 (br band, 6H SCH_2 and H-1'), 4.52 (s, 1H, 2-dithiane H), 5.05 (br s, 1H, H-2'), 6.10 (s, 2H, H-2 and H-4) and 6.93 (br s, 1H, H-10)] and abn-isomer, **6**, (17%) [NMR (CCl_4) δ: 0.90 (t, ω-CH_3), 1.27 and 1.37 (s, 3H, *gem* CH_3's), 1.95 (s, 3H, 2'-OAc), 2.32 (br s, 2H, H-1'), 2.80 (br band, 4H, SCH_2), 3.50 (br s, 1H, H-10a) 4.47 (s, 1H, 2-dithiane H), 517 (br s, 1H, H-2'), 6.07 (s, 1H, H-2) and 6.23 (br s, 2H, H-4 and H-10) ppm] as well as diadducts and iso-THC's. After first protecting the phenol as its acetate (Ac_2O/Pyr., rt, overnight), the dithiane masking group was hydrolyzed with red mercury oxide and boron trifluoride etherate in wet (15%) tetrahydrofuran[5d]. The aldehyde **7** was purified by multiple development preparative TLC (silica, 30% EtOAc/hexane); yield 84%. NMR (CCl_4) δ: 0.88 (t, ω-CH_3), 1.12 and 1.40 (s, 3H, *gem* CH_3's), 1.93 (s, 3H, 2'OAc), 2.25 (s, 3H, 1-OAc), 2.70 (d, 1H, J 6 Hz, H-1'), 3.30 (br s, 1H, H-10a), 4.97 (br s, 1H, H-2'), 6.38 (s, 1H, H-2), 6.52 (s, 1H, H-4), 7.25 (br s, 1H, H-10) and 9.38 (s, 1H, *CHO*) ppm; M calc.: 428.21989, M^+ 428.22054.

The aldehyde and both acetate groups were reduced with lithium aluminum hydride in THF at rt for 4 h which, after work-up and purification (preparative TLC on silica developed with ether), produced (±)-2',11-dihydroxy-Δ^9-THC as a clear gum in 71% yield; NMR [$(CD_3)_2CO$] δ: 0.87 (t, ω-CH_3), 1.06 and 1.37 (s, 3H, *gem* CH_3's), 2.52 (d, 1H, J 6 Hz, H-1'), 3.33 (br s, 1H, H-10a) 3.60 (br s, 1H, H-2'), 3.93 (br s, 2H, H-11), 6.18 (d, 1H, J 2 Hz, H-2), 6.33 (d, 1H, J 2 Hz, H-4) and 6.77 (br s, 1H, H-10) ppm. Mass spectrum (70 eV) m/e (relative intensity): 346 (33), 315 (100), 259 (10), 247 (16) and 175 (43); ν_{max} (CH_2Cl_2): 3600 and 3450 cm^{-1}.

1 Acknowledgment. This work was carried out with the support of NIDA Grant No. DA 00574. We are grateful to Mr. J. Coe for assistance with some of the experiments. Author for correspondence R.K. Razdan.

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