Tetrahedron Letters No. 8, pp 681 - 684. 0040-4039/79/0215-0681$02.00/0

HASHISH[1]: SYNTHESIS OF (-)-Δ^9-TETRAHYDROCANNABINOL (THC) AND ITS BIOLOGICALLY POTENT METABOLITE 3'-HYDROXY-Δ^9-THC.

G. R. Handrick, D. B. Uliss, H. C. Dalzell and R. K. Razdan*
Sheehan Institute for Research, Inc., 767B Concord Avenue, Cambridge, MA 02138

In continuation of our search for various synthons[2] for the synthesis of Δ^9-THC and its metabolites, we now report the use of the readily available monoterpene p-menth-2-ene-1,8-diol[3] (1) in the synthesis of (-)-Δ^9-THC. The general utility of this synthon for the preparation of the side-chain-hydroxylated metabolite of Δ^9-THC is illustrated by the synthesis of 3'-hydroxy-Δ^9-THC (6c). The latter is one of the two side-chain-hydroxylated metabolites of Δ^9-THC, formed in the perfused dog-lung preparation and isolated by Widman, et al.[4] These authors assigned the structure of this metabolite on the basis of mass spectral data alone.

Recently Pitt et al.[5] have reported without details (NMR, etc.) the synthesis of 6c by building up the side chain after forming the THC ring system. Our product was synthesized and characterized independently of this work.

The preparation of (-)-Δ^9-THC from p-menth-2-ene-1,8-diol (1) and olivetol (2) was studied using a variety of catalysts [$BF_3 \cdot Et_2O$, p-toluenesulfonic acid (p-TSA), $ZnCl_2$, $ZnBr_2$, Dowex acid-ion-exchange resin, $SnCl_4$] and solvents (CH_2Cl_2, benzene, ether, etc.). In an experiment giving the best yield of n-Δ^9-THC and least by-products, a mixture of 21.69 g (0.12 mol) of olivetol and 37.8 g (0.277 mol) of anhydrous $ZnCl_2$ in 500 ml of dry CH_2Cl_2 was refluxed under N_2 with stirring, while a solution of 3.4 g (0.02 mol) of 1 in 250 ml of CH_2Cl_2 was added dropwise during 3 hr. Heating and stirring were continued for a total reaction time of 5 hr. After workup, the residual red oil was taken up in ether and the excess olivetol was recovered (19.5 g, 98%) by extraction with 5 x 100 ml of 8% NaOH solution. The ether solution provided 5.99 g (95%) of a resin containing 51% of Δ^9-THC (GLC). This crude resin was fractionated by a single pass through a Waters Prep LC/500 system with one cylinder of silica (325 g), using 6 liters of 1:0.6:98.4 Et_2O/CH_3CN/isooctane, followed by 680 ml of Et_2O as a sweep wash, to give 1.0 g (17%) of (-)-Δ^9-THC (purity > 90% by GLC).

The fractions assaying 40-90% Δ^9-THC (2.0 g) were combined and rechromatographed using two cylinders of silica with 11.2 liters of solvent, from which an additional 0.9 g of 3 was obtained. The total recovery was 1.9 g (28% of theory) of (-)-Δ^9-THC identical in all respects with an authentic sample; $[\alpha]_D$ -161° (1%, $CHCl_3$), lit. -174° ($CHCl_3$)[6]; assay 95% (GLC). The by-products that were isolated and identified[7] (GLC, NMR, and comparison with authentic samples)

from this reaction were diadducts (6%), n-5(12)-isoTHC 8 (2%), abn-Δ^9-THC (14%), and a new isoTHC (4).[8]

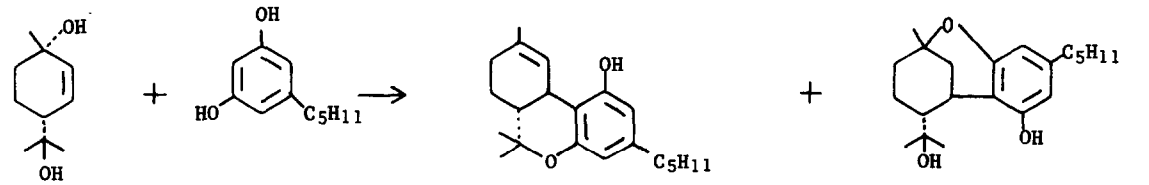
The resorcinol derivative 5[9] was used for the synthesis of the metabolite 6c. A solution of 0.52 g (2.2 mmol) of 5 in 10 ml of dry CH_2Cl_2 was efficiently stirred at 25° with 3.0 g of fused anhydrous $ZnCl_2$ for 10 min under N_2, and then a solution of 0.37 g (2.2 mmol) of p-menth-2-en-1,8-diol in a mixture of 2 ml of dry THF and 10 ml of dry CH_2Cl_2 was added during 15 min. After 2 hr the reaction was worked up and the residue (0.81 g) was separated by column chromatography (silica gel 60, 230-400 mesh, eluted by 20:80 EtOAc/hexane) into fractions consisting of diadducts (17% of the charge), n-THCs (30%), abn-THCs (13%), unchanged 5 (10%), and an unidentified slow-moving component (25%). The fraction of n-THC was an 80:20 mixture (GLC) of n-3'-acetoxy-Δ^9- and -Δ^8-THCs (6a, 7a).

Mixtures of 6a and 7a were separated by high-pressure liquid chromatography (HPLC) as the diacetoxy derivatives 6a and 7b (Ac_2O/pyridine, 3 hr at 23°C) using μPorasil and eluting with 5:95 Et_2O/isooctane, k'=15.9 for 6b. The 6b thus obtained [>90% (GLC); NMR (CCl_4) δ: 6.47 (d, J=2Hz, 2-CH); 6.30 (d, J=2Hz, 4-CH); 5.95 (br s, 10-CH); 4.79 (m, 1H, 3'-CH); 2.98 (br d, 1H, 10a-CH); 2.22 (s, 1-C-OCOCH_3); 1.96 (s, 3'-C-OCOCH_3); 1.66 (s, 9-C-CH_3); 1.35, 1.07 (2s, 6-C-(CH_3)$_2$); 0.88 (tr, 5'-CH_3); GLC (2% OV-17, column 280°): rentention time 3.40 min; TLC (silica F-254): R_f 0.54 (3:7 EtOAc/hexane), 0.40 (1:4 EtOAc/hexane)] was quantitatively hydrolyzed in 2% KOH in MeOH at room temperature to give 6c of >90% (GLC); NMR (CCl_4) δ: 6.35 (br s, 10-CH); 6.08 (s, 2H, aryl); 3.48 (m, 3'-CH); 2.50 (m, 1'-CH_2); 1.65 (s, 9-C-CH_3); 1.31, 1.02 (2s, 6-C-(CH_3)$_2$); 0.88 (m, 5'-CH_3); 2 exchangeable OH; GLC (2% OV-17, column 280°) retention time, 3.73 min; THC (silica F-254, 1:4 EtOAc/hexane) R_f 0.06; mass spectrum M/e calcd. for $C_{21}H_{30}O_3$: (M+) 330.2194; Found: 330.2160. Peak (%) 330 (49), 315 (16), 258 (100), 247 (48).

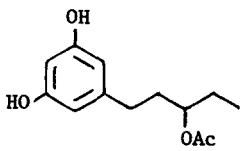
In a comparison of the present procedure using 1 for the synthesis of Δ^9-THC over the use of p-mentha-2,8-dien-1-ol as described by us[2c] and by Petrzilka and co-workers,[10] the former has the advantage that iso-THCs are a very minor product of the reaction and diadducts from the condensation can be greatly suppressed under the proper reaction conditions. With Zn halides the reaction stopped at the cannabidiol stage with p-menthadienol, but proceeded to the THC stage with 1, with apparently no isomerization of Δ^9- to Δ^8-THC, even during an extended reaction time.

3'-Hydroxy-Δ^9-THC (6c), tested in mice for overt symptomatology, produced mild catatonia at 0.1-0.2 mg/kg (iv) and thus was more potent than Δ^9-THC (0.5 mg/kg).

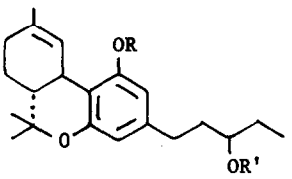
Acknowledgment: This work was carried out with the support of NIDA Grant No. DA-00574-04. We are grateful to Dr. J. Howes for carrying out the biological testing and to Prof. John C. Sheehan for helpful discussions.



1 2 3 4 + other products



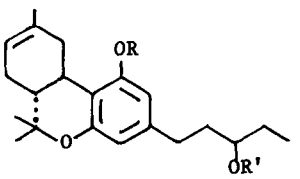
5



6a R = H, R' = $COCH_3$

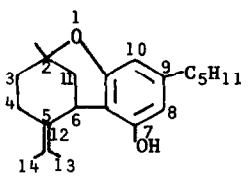
6b R = R' = $COCH_3$

6c R = R' = H



7a R = H, R' = $COCH_3$

7b R = R' = $COCH_3$



8

References

1. Part 24. For part 23, see D. B. Uliss, G. R. Handrick, H. C. Dalzell, R. K. Razdan, Tetrahedron, 34, 1885 (1978).
2. (a) D. B. Uliss, G. R. Handrick, H. C. Dalzell, R. K. Razdan, J. Am. Chem. Soc., 100, 2929 (1978); (b) R. K. Razdan, G. R. Handrick, H. C. Dalzell, Experientia, 31, 16 (1975); (c) R. K. Razdan, H. C. Dalzell, G. R. Handrick, J. Am. Chem. Soc., 96, 5860 (1974); (d) R. K. Razdan and G. R. Handrick, ibid., 92, 6061 (1970).
3. R. S. Prasad and Sukh Dev, Tetrahedron, 32, 1440 (1976) and references cited therein.
4. (a) M. Widman, M. Nordqvist, C. T. Dollery, R. H. Briant, J. Pharm. Pharmacol., 27, 842 (1975); (b) M. Binder, Helv. Chim. Acta, 59, 1674 (1976).
5. C. G. Pitt, H. H. Seltzman, Y. Sayed, C. E. Twine, Jr., D. L. Williams, Tetrahedron Lett., 37 (1978).
6. Arthur D. Little, Inc., Technical Report 3, to National Institute of Mental Health, January 1972, p. 39. Contract PH-43-68-1339.

7. All compounds gave appropriate NMR's. They were further characterized by retention times of their unsilated and silated forms and by comparison with authentic samples.
8. The structure of 4 was assigned on the basis of NMR spectrum (CCl_4) δ: 6.20, 6.15 (2d, 2H, aryl); 3.13 (br s, 6-CH); 2.42 (tr, benzylic CH_2); 1.40 (s, 2-C-CH_3); 1.20 (s, 5-C-$(CH_3)_2$); 0.88 (m, ω-CH_3); 8.52, 4.23 (2 br, 2 exchangeable OH), and from the fact that it was converted cleanly to n-5(12)-isoTHC (8) (NMR, GLC) when it was heated with a catalytic amount of p-TSA in benzene solution at reflux for 45 min. This hydroxy-isoTHC is the likely source of the n-5(12)-isoTHC recovered in the experiment described.
9. Resorcinol 5 was synthesized in 9 steps from 3,5-dihydroxybenzoic acid in an overall yield of 40%. The hydroxyl groups of the methyl ester were protected by conversion to the bis(methoxymethoxy) ether, and the side chain was extended in the steps $-COOCH_3 \rightarrow CH_2OH \rightarrow -CHO \rightarrow -CH{=}CHCOCH_2CH_3 \rightarrow -CH_2CH_2COCH_2CH_3 \rightarrow -CH_2CH_2CH(OH)CH_2CH_3 \rightarrow -CH_2CH_2CH(OAc)CH_2CH_3$. The MOM groups were then removed by hydrolysis in MeOH with the cation exchange resin DOWEX-50W-4X. NMR of 5 ($CDCl_3$) δ: 6.30 (s, 3H, aryl); 4.87 (m, 3'-CH); 2.47 (m, 1'-CH_2); 2.03 (s, 3'-C-OCOCH_3); 0.83 (tr, 5'-CH_3); GLC (3% OV-17, column 220°): retention time 4.91 min; TLC (silica F-254, 1:1 EtOAc/hexane); R_f 0.36.
10. T. Petrzilka, W. Haefliger, C. Sikemeier, Helv. Chim. Acta, 52, 1102 (1969).

(Received in USA 22 November 1978)