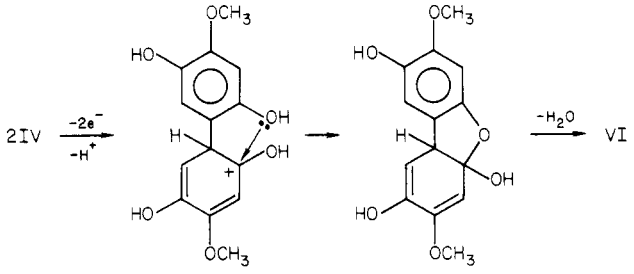

Similar anodic de-*tert*-butylation processes have been previously observed.[8]

Further applications of $FeCl_3/SiO_2$ as an oxidant will be reported at a later date.

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Registry No. I, 494-99-5; II, 19254-82-1; III, 52711-85-0; IV, 824-46-4; V, 7323-63-9; VI, 72442-70-7; VII, 72428-45-6; ferric chloride, 7705-08-0; 2,2'-dimethyl-4,4',5,5'-tetramethoxydiphenyl, 62012-51-5; 2,7-dimethoxy-4,5,9,10-tetrahydropyrene, 19254-83-2; 9,10-dihydro-10a-methyl-2-ethoxy-6,7-dimethoxy-3(10a*H*)-phenanthrone, 52711-88-3.

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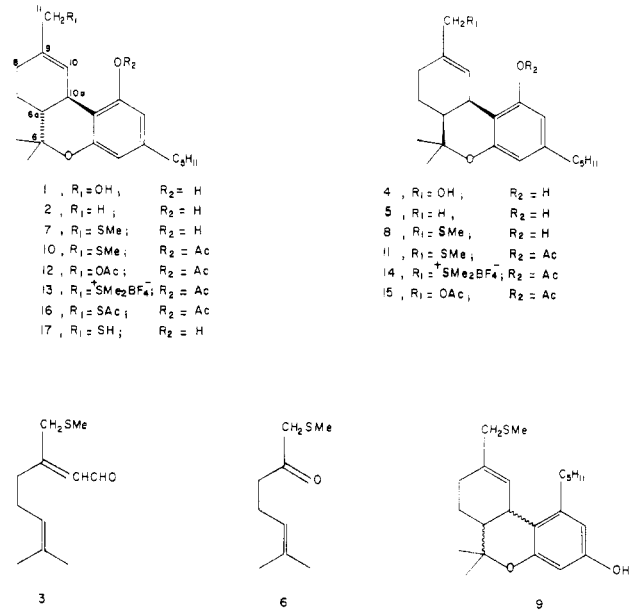
Synthesis of (±)-11-Hydroxy-Δ⁹-6a,10a-*trans*-tetrahydrocannabinol and Other 11-Substituted Δ⁹-Tetrahydrocannabinoids

Summary: 11-Substituted Δ⁹-tetrahydrocannabinoids, including the racemate of the biologically important 11-hydroxy-Δ⁹-6a,10a-*trans*-tetrahydrocannabinol (1) and the corresponding 11-mercapto analogue, are synthesized via condensation of olivetol with the terpenoid synthon 3 prepared from 6-methylhept-5-en-2-one.

Sir: The 11-hydroxy derivative (1) of (−)-Δ⁹-6a,10a-*trans*-tetrahydrocannabinol [(−)-Δ⁹-THC] is a major, pharmacologically important metabolite of (−)-Δ⁹-THC (2), the principal psychoactive component of *Cannabis sativa*.[1] Its formation is significant in man,[1] animals,[1] and certain fungi.[2] Previous preparations of this key metabolite (1)



in racemic or chiral form have involved the introduction of oxygen into an intact tetrahydrocannabinoid skeleton or condensation of olivetol with a functionalized monoterpenoid synthon. The former approach requires either Δ⁹- or Δ⁸-THC and is relatively inefficient whether it is carried out chemically[3] or biologically.[2,4] Cyclic monoterpenoid synthons for the second type of approach have been prepared in several steps from acyclic precursors[5] or from *p*-mentha-1,8-dien-7-al.[6] We present here an alternative route to racemic 11-OH-Δ⁹-THC (1), in which an acyclic terpenoid synthon (3) is prepared from readily available 6-methylhept-5-en-2-one and then condensed with olivetol. The synthesis also yields the corresponding racemic 6a,10a-cis isomer of 11-hydroxy-Δ⁹-tetrahydrocannabinol (4). This isomer (in chiral form) is of interest as a potential mammalian metabolite of Δ⁹-6a,10a-*cis*-tetrahydrocannabinol (5) which has recently been recognized[7] in certain phenotypes of *Cannabis sativa*.

6-Methyl-1-methylthiohept-5-en-2-one [6, bp 71 °C (0.1 mm)] was prepared (72%) from the *N,N*-dimethylhydrazone of 6-methylhept-5-en-2-one by reaction[8] of the regiospecifically generated anion (1 equiv of *n*-BuLi, THF, −78 °C, 40 min) with dimethyl disulfide (−78 °C, 1 h, then warmed to 25 °C) and hydrolysis[9] of the hydrazone on wet (10% H_2O) silica gel (CH_2Cl_2, room temperature 24 h). Formylmethylenation of the ketone 6 by reaction with the lithium salt of diethyl 2-(cyclohexylamino)vinylphosphonate[10] (10 equiv, THF, reflux 24 h) and hydrolysis [two phase, 20% aqueous HOAC–petroleum ether (40–60 °C), 15 min] gave the required synthon (3, 78%) as a

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(2) Christie, R. M.; Rickards, R. W.; Watson, W. P. *Aust. J. Chem.* **1978**, *31*, 1799.

(3) (a) Ben-Zvi, Z.; Mechoulam, R.; Burstein, S. H. *Tetrahedron Lett.* **1970**, 4495. (b) Pitt, C. G.; Hauser, F.; Hawks, R. L.; Sathe, S.; Wall, M. E. *J. Am. Chem. Soc.* **1972**, *94*, 8578. (c) Razdan, R. K.; Uliss, D. B.; Dalzell, H. C. *Ibid.* **1973**, *95*, 2361. (d) Pitt, C. G.; Fowler, M. S.; Sathe, S.; Srivastava, S. C.; Williams, D. L. *Ibid.* **1975**, *97*, 3798.

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mixture of cis and trans isomers.[11] This mixture (3) was reacted with olivetol in the presence of boron trifluoride diethyl etherate[12] (0.4 equiv of BF_3, 1% (v/v) in CH_2Cl_2, 0 °C, then room temperature for 25 min) to afford 11-(methylthio)-Δ^9-tetrahydrocannabinol (23%) as a 1:1 mixture of the trans and cis isomers 7 and 8, separable by column chromatography [medium-pressure N_2, 230–400 mesh SiO_2, 1:3 Et_2O–petroleum ether (40–60 °C)] from the expected trans–cis mixture of regioisomers (9, 18%) formed by condensation at the 4-position of olivetol.[13] It is notable that the double bond retains its original position in all these products (7, 8, and 9) in agreement with our own[2] and other[5] observations on the stability of sulfur-containing Δ^9-tetrahydrocannabinoids toward Lewis acids.

The trans and cis isomers (7 and 8) of 11-(methylthio)-Δ^9-tetrahydrocannabinol were separated by column chromatography [medium-pressure N_2, 230–400 mesh SiO_2, 1:6 Et_2O–petroleum ether (40–60 °C)] as their acetates (10 and 11)[14] (3 equiv of Ac_2O–pyridine, room temperature, 1 h), obtained in 10 and 8% overall yield, respectively, from the terpenoid synthon 3. Conversion of the methylthio function in the trans isomer 10 into the acetoxy function of 12 was effected via the sulfonium tetrafluoroborate 13 formed with trimethyloxonium tetrafluoroborate (1.1 equiv, CH_3NO_2, room temperature, 25 min). Displacement at the allylic sulfonium center with acetate anion (3 equiv of n-$Bu_4N^+OAc^-$,[15] acetone, reflux, 30 min) completed the conversion in 95% overall yield. Ammonolysis (NH_3–MeOH, room temperature, 48 h) of the diacetate 12 gave *trans*-11-OH-Δ^9-THC (1, 92%), identified by comparison (NMR, IR, and mass spectra) with authentic material.

cis-11-OH-Δ^9-THC (4)[16] was similarly prepared from the *cis*-11-methylthio isomer 11 via the salt 14 and the diacetate 15. The mass spectra and R_F values on TLC of the *cis* and *trans* isomers (4 and 1) of 11-OH-Δ^9-THC and the retention times on GLC of their corresponding bis(trimethylsilyl) ethers are extremely similar and could be misleading in metabolic studies where both isomers of the parent Δ^9-THC compounds are involved. ^{1}H NMR spectra ($(CD_3)_2CO$), however, distinguish these two 11-hydroxy isomers. The *cis* isomer 4 shows the geminal methyl singlets at δ 1.17 and 1.26 and the multiplets of C10a H and C10 H at δ 3.48 and 6.47, whereas the corresponding resonances in the *trans* isomer 1 are at δ 1.00, 1.31, 3.18 (J_{trans} = 11 Hz), and 6.70, respectively. The *cis* and *trans* isomers (5 and 2) of Δ^9-THC itself show similar features.[17]

The terpenoid synthon 3 affords access to a variety of 11-substituted Δ^9-tetrahydrocannabinoids. Retention of the methylthio function until the cannabinoid skeleton is formed not only controls the double bond position but its subsequent displacement also permits the introduction of various nucleophiles at C11. For example, reaction of the sulfonium tetrafluoroborate 13 with thioacetate anion (2 equiv of n-$Bu_4N^+SAC^-$,[18] acetone, room temperature, 15 min) gives the diacetate 16. Subsequent reduction[19] of both esters (30 equiv of $NaBH_4$, EtOH, room temperature, 20 h) then yields *trans*-11-SH-Δ^9-THC (17),[20] the 11-mercapto analogue of 11-OH-Δ^9-THC (1). Alternatively, condensation of the terpenoid synthon 3 with suitably substituted resorcinols[2,21] would lead to metabolites of Δ^9-THC hydroxylated both at C11 and in the alkyl side chain.[2,22]

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Registry No. 1, 28623-60-1; 2, 3556-79-4; 3, cis isomer, 72377-96-9; 3, trans isomer, 72377-97-0; 4, 72402-25-6; 5, 6087-73-6; 6, 72377-98-1; 7, 72377-99-2; 8, 72378-00-8; 9, cis isomer, 72378-01-9; 9, trans isomer, 72378-02-0; 10, 72390-08-0; 11, 72378-03-1; 12, 72402-26-7; 13, 72378-05-3; 14, 72378-07-5; 15, 72402-27-8; 16, 72378-08-6; 17, 72378-09-7; olivetol, 500-66-3; diethyl [2-(cyclohexylamino)vinyl]-phosphonate lithium salt, 72378-10-0.

(11) Data: bp 85 °C (0.03 mm) (Kugelrohr); cis/trans ratio 47:53; NMR ($CDCl_3$) δ 1.64, 1.70 (2 s, 6, Me_2C=), 2.01 and 2.03 (2 s, 3, SMe), 2.0–2.5 (m, 2, CH_2CH=), 2.75 (t, 2, J = 7 Hz, $CH_2C(CH_2SMe)$=), 3.24 and 3.61 (2 s, 2, CH_2SMe), 5.12 (br m, 1, $W_{1/2}$ = 16 Hz, CH=CMe_2), 5.90 and 6.30 (2 d, 1, J = 8 Hz, trans and cis =CHCHO), 9.96 (d, 1, J = 8 Hz, CHO); IR (film) 1670 (C=O), 1620 (C=C) cm^{-1}. The mixture had a satisfactory C, H, and S analysis.

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(13) Petrzilka, T.; Haefliger, W.; Sikemeier, C. *Helv. Chim. Acta* **1969**, *52*, 1102.

(14) The trans isomer 10 was the first to elute: NMR (CCl_4) δ 0.92 (t, 3, J = 6 Hz, CH_2Me), 1.09 (s, 3, Me), 1.38 (s, 3, Me), 1.92 (s, 3, SMe), 2.20 (s, 3, ArOCOMe), 2.60 (t, 2, J = 7 Hz, $ArCH_2$), 2.98 (br s, 2, SCH_2C=) superimposed upon 3.08 (m, 1, C10a H), 6.11 (m, 1, C10 H), 6.30 and 6.45 (2 m, 2, ArH); IR (film) 1763 (C=O), 1623, 1563 cm^{-1}; mass spectrum, m/z (relative intensity) 402 (21) (high resolution, 402.2229; calcd for $C_{24}H_{34}O_3S$, 402.2228), 313 (100). Cis isomer 11: NMR (CCl_4) δ 0.90 (t, 3, J = 6 Hz, CH_2Me), 1.25 (s, 3, Me), 1.36 (s, 3, Me), 1.87 (s, 3, SMe), 2.25 (s, 3, ArOCOMe), 2.48 (t, 2, J = 7 Hz, $ArCH_2$), 2.96 (br s, 2, SCH_2C=), 3.48 (m, 1, C10a H), 5.98 (d, 1, J = 5 Hz, C10 H), 6.28 and 6.42 (2 m, 2, ArH); IR (film) 1765 (C=O), 1668, 1625, 1565 cm^{-1}; mass spectrum, m/z (relative intensity) 402 (18) (high resolution, 402.2223; calcd for $C_{24}H_{34}O_3S$, 402.2228), 313 (100).

(15) Baker, R.; Hudec, J.; Rabone, K. L. *J. Chem. Soc. C* **1969**, 1605.

(16) Cis isomer 4: NMR ($(CD_3)_2CO$) δ 0.80 (t, 3, J = 6 Hz, CH_2Me), 1.17 (s, 3, Me), 1.26 (s, 3, Me), 2.34 (t, 2, J = 7.5 Hz, $ArCH_2$), 3.32 (t, 1, J = 6 Hz, CH_2OH), 3.48 (m, 1, C10a H), 3.82 (dm, 2, CH_2OH), 5.99 and 6.15 (2 m, 2, ArH), 6.47 (m, 1, C10 H), 7.95 (br s, 1, ArOH); IR (CCl_4) 3610 (OH), 3350 (OH), 1625 cm^{-1}; mass spectrum, m/z (relative intensity) 330 (30) (high resolution, 330.2197; calcd for $C_{21}H_{30}O_3$, 330.2195), 312 (19), 299 (100). The bis(trimethylsilyl) ether of 4 showed the following: mass spectrum, m/z (relative intensity) 474 (5), 459 (4), 413 (2), 403 (3), 384 (4), 371 (100); GLC (2% OV-17 on Gaschrom Q, 250 °C) retention time 1.82 relative to the derivative of (-)-Δ^9-THC (2); cf. 1.88 for the derivative of the *trans* isomer 1.

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(18) Prepared by neutralization of n-$Bu_4N^+OH^-$ with HSAc as described[15] for n-$Bu_4N^+OAc^-$ and recrystallized from EtOAc.

(19) Brown, M. S.; Rapoport, H. *J. Org. Chem.* **1963**, *28*, 3261.

(20) NMR (CCl_4) δ 3.19 (m, 2, CH_2SH), otherwise very similar to that of 1, δ 3.90 (m, 2, CH_2OH); mass spectrum, m/z (relative intensity) 346 (17) (high resolution, 346.1966; calcd for $C_{21}H_{30}O_2S$, 346.1966), 331 (17), 313 (100), 312 (15), 299 (43), 297 (11).

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(22) Wall, M. E.; Brine, D. R., p 51 in ref 1d.

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Efficient Enantioselective Synthesis of the Antitumor Agent Sarkomycin

Summary: An efficient total synthesis of (±)-sarkomycin (1) is described via bicyclic lactone 8. Preparation of a key precursor (*R*)-(+)-6 via an asymmetric Diels–Alder reaction affords the correct enantiomer for the preparation of natural (*R*)-(-)-sarkomycin (1) in high optical yield.

Sir: The antibiotic (*R*)-(-)-sarkomycin (1), discovered by Umezawa et al in 1953,[1] was subsequently shown to have substantial inhibitory effect on Erlich ascites tumors in mice.[2] Further pharmacological studies[3] led to the mar-

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