A Convenient Synthesis of (−)-11-Nor-Δ^9-tetrahydrocannabinol-9-methanol

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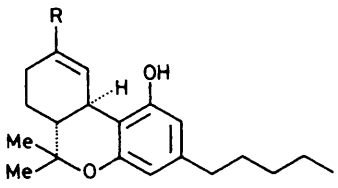
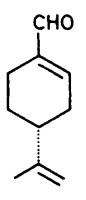
A convenient enantiospecific total synthesis of (−)-11-nor-Δ^9-tetrahydrocannabinol-9-methanol, a human urinary metabolite of Δ^9-tetrahydrocannabinol, has been accomplished in six steps from (*R*)-(+)-perillaldehyde.

Synthetic routes to Δ^9-tetrahydrocannabinol (Δ^9-THC) and its metabolites were pioneered by the research teams of Razdan, Mechoulam, and others.[1] The early motivation for this work was to confirm the structures of the metabolites and to provide material for the evaluation of their biological activity.[2] More recently there has been a need for the metabolites of Δ^9-THC as analytical standards in the calibration of assays for the accurate detection of cannabinoids in urine.[3] Although several approaches to the synthesis of (−)-11-nor-Δ^9-THC-9-methanol (**1**) and (−)-nor-Δ^9-THC-9-carboxylic acid (**2**) have been described, each of the published syntheses has either been long,[4] has produced racemic products,[4,5] or has given low yields.[6] Our work is an attempt to address these shortcomings.

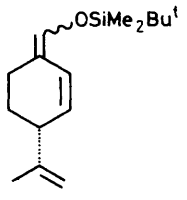
We chose to adopt a strategy which would provide the enantiomerically pure product. The first problem was to identify an available terpene which would provide the carbon atoms for the *A*-ring and would establish the absolute sense of symmetry of the final product. (*R*)-(+)-Perillaldehyde[7] (**3**) proved to be a good choice. Treatment of (**3**) with a small excess of t-butyldimethylsilyl trifluoromethanesulphonate[8] and triethylamine in dichloromethane at 0 °C provided silyl enol ether (**4**). Without purification, (**4**) was allowed to react with *m*-chloroperoxybenzoic acid in a two-phase mixture of ether and saturated aqueous sodium hydrogen carbonate at 25 °C. The intermediate epoxy silyl ether (**5**) formed reacted further to give hydroxyacetal (**6**). The unpurified material was dissolved in anhydrous tetrahydrofuran (THF), cooled to



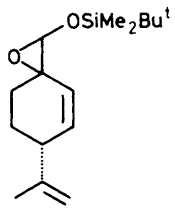
(**1**) R = CH_2OH
(**2**) R = CO_2H



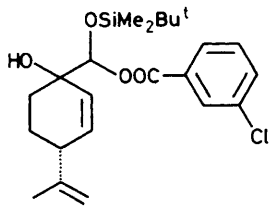
(**3**)



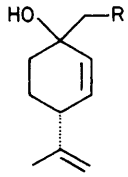
(**4**)



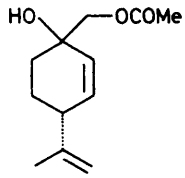
(**5**)



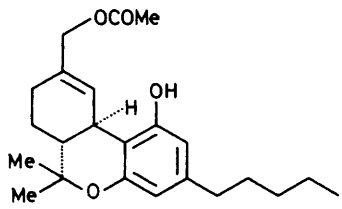
(**6**)



(7a) R = OH
(7b) R = H



(8)



(9)

0 °C, and treated with a THF solution of lithium aluminium hydride (LAH). Work-up with sodium fluoride followed by water produced diol (**7a**) as a mixture of diastereoisomers which were purified (but not separated) by flash chromatography on silica gel. The overall yield of (**7a**) from perillaldehyde (**3**) was 66%.

Since the total synthesis of Δ^9-THC from the acid catalysed condensation of olivetol with *p*-mentha-2,8-dien-1-ol (**7b**) has been reported,[1a] it seemed reasonable to expect that the Lewis acid catalysed cyclization of (**7a**) with olivetol would lead to (**1**). In the event, low yields of (**1**) were isolated from the reaction of (**7a**) with olivetol under a wide variety of conditions. The difference in reactivity between (**7a**) and (**7b**) may be attributed to the destabilizing inductive effect of the primary hydroxy group upon the putative cationic intermediate. Fortunately, the monoacetate (**8**) proved to be a suitable substrate for the cationic cyclization. Anchimeric assistance of the ionization of the tertiary allylic hydroxy group through an acetoxonium ion intermediate accounts for the pronounced difference in reactivity between (**7a**) and (**8**). The methyl carbonate of (**7a**) would be a particularly interesting substrate for the cyclization. The conversion of (**8**) to (**9**) was accomplished by exposure of a dichloromethane solution of olivetol and (**8**) to freshly distilled boron trifluoride–diethyl ether at 0 °C for 2 h. The yield of monoacetate (**9**) was *ca.* 30%. Exposure of this material to LAH in THF, followed by flash chromatography on silica gel, provided (−)-11-nor-Δ^9-THC-9-methanol (**1**) in 94% yield from (**9**) [19% overall yield from (**8**)]. The identity of the product was proved by the conversion of (**9**) to (−)-nor-Δ^9-THC-9-carboxylic acid (**2**) in four steps: (i) protection of the phenol as the t-butyldimethylsilyl ether; (ii) reductive cleavage of acetate with LAH; (iii) Swern oxidation;[9] (iv) oxidation with sodium chlorite in the presence of 2-methylbut-2-ene.[10] The material obtained from (**9**) through this sequence of reactions was identical to a sample of (**2**), which was prepared from Δ^9-THC.[6]

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References

1 (a) R. K. Razdan, H. C. Dalzell, and G. R. Handrick, *J. Am. Chem. Soc.*, 1974, **96**, 5860; (b) R. K. Razdan in 'The Total Synthesis of Natural Products,' ed. J. ApSimon, vol. 4, pp. 185—262, Wiley, New York, 1981; (c) G. R. Handrick, D. B. Uliss, H. C. Dalzell, and R. K. Razdan, *Tetrahedron Lett.*, 1979, 681; (d) R. Mechoulam, P. Braun, and Y. Gaoni, *J. Am. Chem. Soc.*, 1972, **94**, 6159; (e) R. Mechoulam, H. Varconi, Z. Ben-Zvi, H. Ederly, and Y. Grunfeld, *ibid.*, 1972, **94**, 7930; (f) T. Petrzilka, W. Haefliger, C. Sikemeier, G. Ohloff, and A. Eschenmoser, *Helv. Chim. Acta*, 1967, **50**, 719; (g) T. Petrzilka, W. Haefliger, and C. Sikemeier, *ibid.*, 1969, **52**, 1102; (h) R. W. Rickards and H. Ronneberg, *J. Org. Chem.*, 1984, **49**, 572; (i) W. E. Childers, Jr., and H. W. Pinnick, *ibid*, 1984, **49**, 5276; (j) A. Schwartz and P. Madan, *ibid.*, 1986, **51**, 5463.

2 R. A. Archer, P. Stark, and L. Lemberger in 'Cannabinoids as Therapeutic Agents,' ed. R. Mechoulam, pp. 85—103, CRC Press, Boca Raton, Florida, 1986.

3 J. D. Whiting and W. W. Manders, *J. Anal. Toxicol.*, 1982, **6**, 49.

4 K. E. Fahrenholtz, M. Lurie, and R. W. Kierstead, *J. Am. Chem. Soc.*, 1967, **89**, 5934.

5 D. B. Uliss, G. R. Handrick, H. C. Dalzell, and R. K. Razdan, *J. Am. Chem. Soc.*, 1978, **100**, 2929.

6 C. G. Pitt, M. S. Fowler, S. Sathe, S. C. Srivastava, and D. L. Williams, *J. Am. Chem. Soc.*, 1975, **97**, 3798.

7 M. A. Tius and M. A. Kerr, *Synth. Commun.*, in the press.

8 R. F. Stewart and L. L. Miller, *J. Am. Chem. Soc.*, 1980, **102**, 4999.

9 A. J. Mancuso, S.-L. Huang, and D. Swern, *J. Org. Chem.*, 1978, **43**, 2481.

10 R. Pellegata, P. Ventura, and M. Villa, *Synth. Commun.*, 1985, **15**, 165.