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Synthesis of Optically Active (−)-11-Nor-Δ^9-Tetrahydrocannabinol-9-Carboxylic Acid

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BAEK, S.-H., M. SZIRMAI AND M. M. HALLDIN. *Synthesis of optically active (−)-11-nor-Δ^9-tetrahydrocannabinol-9-carboxylic acid.* PHARMACOL BIOCHEM BEHAV **40**(3) 487–489, 1991.—Synthesis of optically active (−)-11-nor-Δ^9-tetrahydrocannabinol-9-carboxylic acid, the major acidic metabolite in the urine of man, was achieved involving an improved condensation reaction between an optically active monoterpene synthon and olivetol.

Cannabis Marijuana Chiral synthesis Metabolites (−)-11-Nor-Δ^9-tetrahydrocannabinol-9-carboxylic acid

Δ^9-TETRAHYDROCANNABINOL (Δ^9-THC), the principal psychoactive constituent in *Cannabis sativa* L., is extensively metabolized in man via allylic oxidation before being excreted mainly as 11-nor-Δ^9-tetrahydrocannabinol-9-carboxylic acid (**1**) (13). Different routes for the synthesis of this and other acidic metabolites of Δ^9-THC have been proposed, involving condensation between a monoterpene synthon and a suitable olivetol derivative, or by synthesis from Δ^9-THC (1–5, 7, 9–12). However, most of these procedures will give the metabolites as racemic mixtures, and since the psychotomimetic effect of Δ^9-THC and some of its metabolites is selective for the naturally occurring (−)-form, the recent synthetic efforts have focused on more appropriate chiral synthetic reactions. Recently, a procedure to get the (−)-enantiomer of 11-hydroxy-Δ^9-THC, using an optically active terpene synthon was published by Siegel et al. (7). In analogy with their findings, we now present a somewhat modified and improved reaction sequence for the synthesis of acidic metabolites of Δ^9-THC.

Synthesis

The aim of our approach was to achieve a higher yield in the critical condensation reaction between the terpene and aromatic moiety than previously reported for the synthesis of Δ^9-THC metabolites. The key intermediate in the synthesis of optically active terpene synthons is 4-isopropenyl-2-cyclohexen-1-one (**4**). Different synthetic approaches have been suggested in the literature; however, the most convenient way to obtain optically active **4** starts from the commercially available (+)-limonene oxide. (R)-(+)-Perillaldehyde (**2**), obtained from (+)-limonene oxide using essentially the same reaction conditions reported by Tius and Kerr (10), was converted into the alcohol before epoxidation using a vanadium-hydroperoxide system giving a mixture of diastereomeric epoxides, Scheme 1 (6). The epoxides were opened according to the procedure of Stevens and Albizati (8) with a mixture of diphenyldiselenide and sodium borohydride in ethanol to give the diols **3** in high overall yield (about 80%). Oxidative cleavage of compound **3** finally gave the key intermediate **4**, which upon addition of the lithium ion of 1,3-dithiane gave a racemic mixture of the desired monoterpene synthon **5**.

Razdan et al. (7,12) have previously shown that the condensation reaction between a racemic or an optically active terpene synthon (with a hydroxy-isopropyl side chain) and olivetol, gave Δ^9-THC derivatives [e.g., **7**] in about 20% yield. They also reported that the condensation with optically active **5** only gave a 3–4% yield using various acidic conditions (7). However, we were able to increase the yield to about 40% allowing the terpene synthon to react with olivetol at −63°C for 1 h in the presence of boron trifluoride etherate and anhydrous magnesium sulfate as dehydrating agent, Scheme 2. Deprotection through hydrolysis, using a mixture of mercury(II)chloride and mercury(II)oxide in aqueous acetonitrile, gave the aldehyde (**8**) which upon oxidation formed the desired (−)-11-nor-Δ^9-THC-9-carboxylic acid (**1**).

The chiral synthesis of two other important urinary metabolites of Δ^9-THC; 4′,5′,11-trisnor-Δ^9-THC-3′,9-dioic acid and 4′-hydroxy-11-nor-Δ^9-THC-9-oic acid, are now under investigation in our laboratories.

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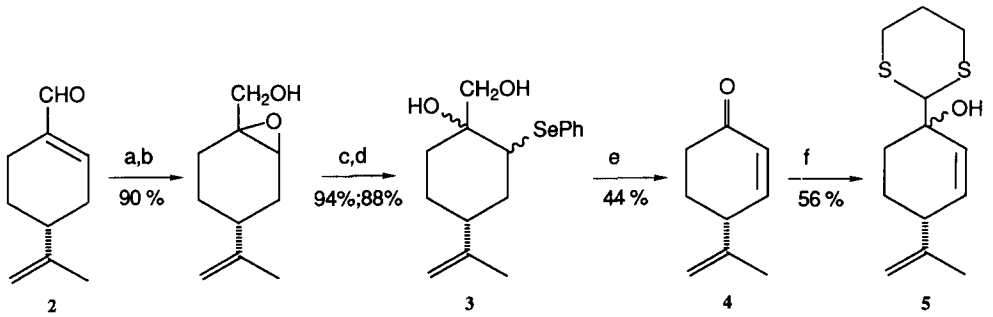
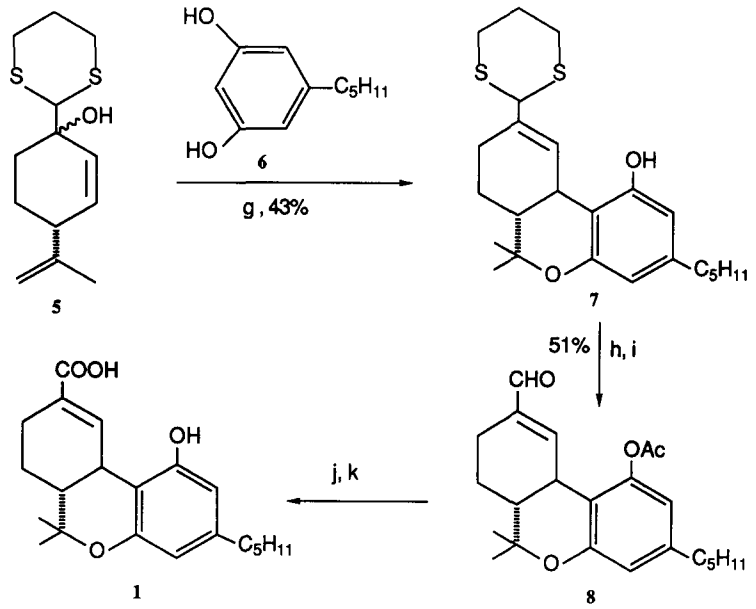


Scheme 1. Synthetic route for the (+)-monoterpene synthon (**5**). Reagents: a) $LiALH_4$/diethyl ether, 1 h, RT; b) $Vo(AcAc)_2$, t-BuOOH/toluene, 2 h, RT; c) Ac_2O/pyridine, overnight, RT; d) Ph_2Se_2, $NaBH_4$/EtOH, 24 h, RT; e) $NaIO_4$/aq. CH_3CN, 2 h, RT; f) 1,3-dithiane, BuLi/THF, 45°C.



Scheme 2. Synthesis of (−)-11-nor-Δ^9-THC-9-carboxylic acid (**1**). Reagents: g) BF_3-Et_2O, anh. $MgSO_4/CH_2Cl_2$, 1 h, −63°C; h) Ac_2O/pyridine, overnight, RT; i) $HgCl_2$, HgO/aq. CH_3CN, 1.5 h, reflux; j) NaCN, MnO_2, CH_3COOH/MeOH; k) KOH/aq. EtOH.

REFERENCES

1. Huffman, J. W.; Zhang, X.; Wu, M. -J.; Joyner H. H. Regioselective synthesis of (±)-11-nor-9-carboxy-Δ^9-THC. J. Org. Chem. 54: 4741–3; 1989.
2. Magó, E.; Szirmai, M.; Ohlsson, A.; Agurell, S. An alternative route for the synthesis of unlabelled and labelled delta-1-tetrahydrocannabinol-7-oic acid. In: Harvey, D. J., ed. Marihuana '84. Proceedings of the Oxford symposium on cannabis. Oxford: IRL Press; 1985:191–5.
3. Razdan, R. K. The total synthesis of cannabinoids. In: ApSimon J., ed. The total synthesis of natural products. vol 4. New York: John Wiley and Sons; 1981:185–262.
4. Razdan, R. K. Chemistry and structure-activity relationships of cannabinoids: An overview. In: Agurell, S.; Dewey, W. L.; Willette, R. E., eds. The cannabinoids: Chemical, pharmacologic, and therapeutic aspects. Orlando, FL: Academic Press; 1984:63–78.
5. Razdan, R. K.; Dalzell, H. C.; Handrick, G. R. Hashish. A simple one-step synthesis of (−)-tetrahydrocannabinol (THC) from *p*-mentha-2-,8-dien-1-ol and olivetol. J. Am. Chem. Soc. 96:5860–5865; 1974.
6. Sharpless, K. B.; Michaelson, R. C. High stereo- and regioselectivities in the transition metal catalyzed epoxidations of olefinic alcohols by *tert.*-butyl hydroperoxide. J. Am. Chem. Soc. 95:6136–7; 1973.
7. Siegel, C.; Gordon, P. M.; Razdan, R. K. An optically active terpenic synthon for Δ^9-cannabinoids: Synthesis of (−)-11-hydroxy-Δ^9-tetrahydrocannabinol (THC) and its 1′,1′-dimethylheptyl analogue. J. Org. Chem. 54:5428–30; 1989.
8. Stevens, R. V.; Albizati, K. F. Synthetic approach to the amphilectane diterpenes: The use of nitriles as terminators of carbocation-olefin cyclizations. J. Org. Chem. 50:632–40; 1985.
9. Szirmai, M.; Magó, E.; Ohlsson, A.; Halldin, M. M.; Agurell, S. Synthesis of two acidic urinary metabolites of Δ^1-tetrahydrocanna-

inol (Δ^1-THC): 4″,5″-Bisnor-Δ^1-THC-7,3″-dioic acid and 4″-hydroxy-Δ^1-THC-7-oic acid. In: Chesher, G.; Consroe, P.; Musty R., eds. Marijuana: An international research report. National Campaign Against Drug Abuse, Monograph Series No. 7. Canberra: Australian Government Publishing Service; 1988:303–8.

10. Tius, M. A.; Gu, X.-Q.; Kerr, M. A. A convenient synthesis of (−)-11-nor-Δ^9-tetrahydrocannabinol-9-methanol. J. Chem. Soc., Chem. Commun. 62–3; 1989.
11. Tius, M. A.; Kerr, M. A. A convenient synthesis of (R)-(+)-perillaldehyde. Synth. Commun. 18:1905–11; 1988.
12. Uliss, D. B.; Handrick, G. R.; Dalzell, H. C.; Razdan, R. K. A terpenic synthon for Δ^1-cannabinoids. J. Am. Chem. Soc. 100: 2929–30; 1978.
13. Widman, M.; Halldin, M. M.; Agurell, S. Metabolism of Δ-1-tetrahydrocannabinol in man. In: Barnette, G.; Chiang, C. N., eds. Pharmacokinetics and pharmacodynamics of psychoactive drugs. Foster City, CA: Biomedical Publications; 1985:415–26.