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Synthesis of a Primary Metabolite of Cannabidiol

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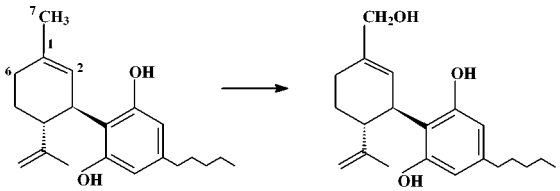
ABSTRACT



CBD **7-OH-CBD**

Cannabidiol 1 is the major nonpsychotropic, neutral constituent in most cannabis preparations. It is devoid of the psychoactive properties typical of cannabis; however, it produces numerous, potentially therapeutic pharmacological effects, some of which may be due to its metabolites. We report now the first total synthesis of 7-hydroxycannabidiol 2, a primary metabolite of cannabidiol, in an eight-step procedure.

Cannabidiol (CBD, **1**) is the major nonpsychotropic cannabinoid in most cannabis preparations, such as hashish and marihuana. It was isolated from marihuana by Adams[1a] and from hashish by Todd[1b] in the early 1940s. Its structure and absolute stereochemistry were elucidated only about two decades later.[2] The racemate of CBD was synthesized in 1965,[3a] the natural enantiomer was prepared in 1967,[3b] and the unnatural one was reported in 1982.[3c]

CBD does not cause any of the psychotropic effects typical of Δ^9-tetrahydrocannabinol (Δ^9-THC), the psychoactive constituent of cannabis. It does not bind to the known cannabinoid receptors CB_1 or CB_2 and therefore does not cause the central or peripheral effects mediated by these receptors. However, it has been shown in in vitro assays, in animal tests, and in human preliminary trials to produce numerous pharmacological effects. Thus, recent reports describe in vitro effects of CBD on immune cells[4a] and as a neuroprotective antioxidant.[4b] These in vitro studies lend support to earlier reports on analgesic and antiinflammatory effects in animals.[4c] Recently it was shown that CBD, through its combined immunosuppressive and antiinflammatory actions, has a potent antiarthritic effect in collagen-induced arthritis in mice. [4d] CBD also has anxiolytic activity in rats [4e] and mice. [4f]

CBD has been found to produce several, potentially therapeutic, effects in patients with neurological diseases,[5a] in particular with epilepsy[5b] and possibly with psychosis.[5c] CBD also reduces experimentally evoked anxiety in volunteers.[5d]

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(3) (a) Mechoulam, R.; Gaoni, Y. *J. Am. Chem. Soc.* **1965**, *87*, 3273. (b) Petrzilka, T.; Haefliger, W.; Sikemeier, C.; Ohloff, G.; Eschenmoser, A. *Helv. Chim. Acta* **1967**, *50*, 719. (c) Leite, J. R.; Carlini, E. A.; Lander, N.; Mechoulam, R. *Pharmacol.* **1982**, *124*, 141.

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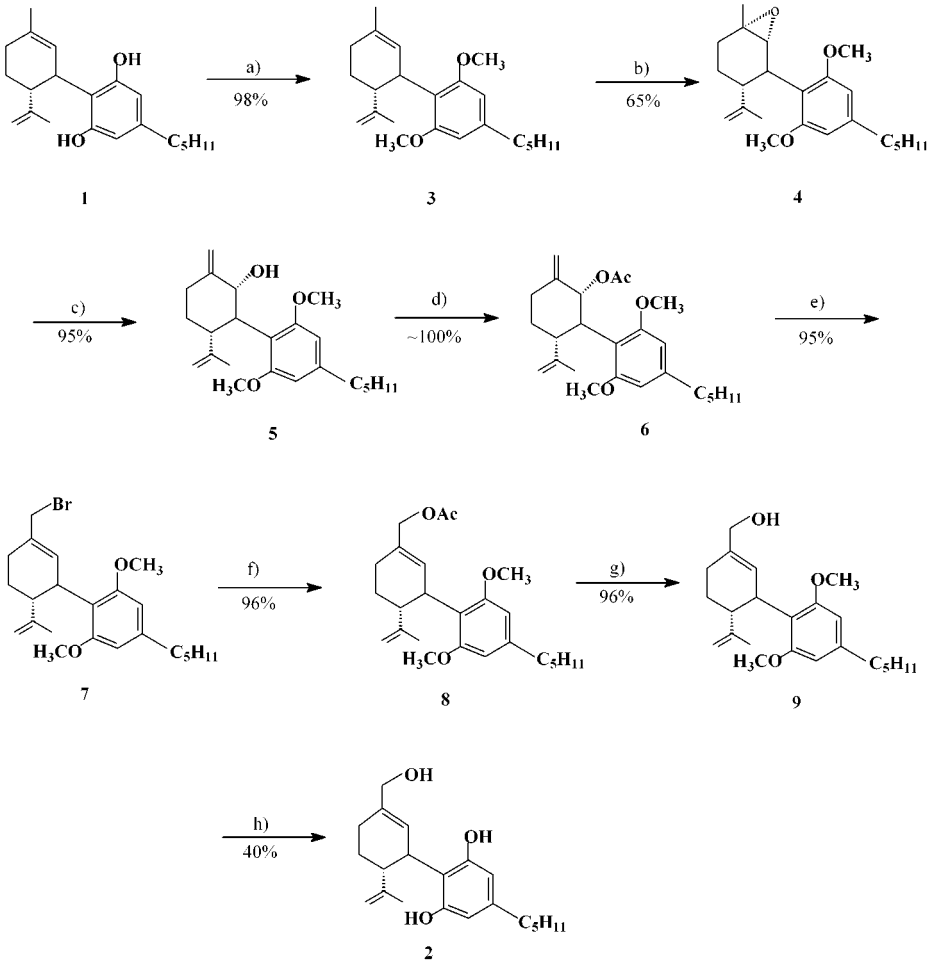
Scheme 1[a]



[a] (a) CH_3I, K_2CO_3 in DMF; (b) 3-Cl-perbenzoic acid in CH_2Cl_2; (c) methylmagnesium *N*-cyclohexylisopropylamide in toluene; (d) Ac_2O in pyridine; (e) TMSBr in CH_2Cl_2; (f) $(^nBu)_4NH_4OAc$ in acetone; (g) NaOH aq; (h) CH_3MgI at 200 °C.

In view of the encouraging results with CBD in in vivo experiments[4] and in clinical trials,[5d] it is surprising that its metabolites have not been investigated for their pharmacological properties, as the probability exists that some of the effects observed are due to active metabolites rather than to CBD. Indeed prolongation of barbiturate sleeping time caused by CBD has been shown to be due to an unidentified metabolite.[6]

The metabolism of CBD is well established. In numerous species, including man,[7a,b] the first step is hydroxylation, mostly on C-7, leading to 7-hydroxy-CBD **2**, followed by further oxidations. None of the CBD metabolites have been synthesized. We have previously described the synthesis of the unnatural enantiomer of 7-hydroxy-CBD in miniscule yields.[7c]

We report now the synthesis of 7-hydroxy-CBD **2**. CBD **1** was converted into its dimethyl ether **3** which was then reacted with 1 mol of 3-chloroperbenzoic acid to give the epoxide **4** (Scheme 1). Epoxidation, an electrophilic reaction, takes place preferably on the ring double bond rather than on the terminal olefinic group, as the electron density on the latter is lower than in the former. The epoxide presumably is *trans* to the aromatic ring, on the basis of related previous NMR studies.[2a] Ring opening with methylmagnesium *N*-cyclohexylisopropyl amide in toluene led to **5**.[8] The use of methyl ether as protective group was found necessary for the ring opening of the epoxide. Every attempt to change it with a different easier to remove group, such as methoxyethoxymethyl (MEM) or methoxymethyl (MOM) ether, led to compounds in which the ring opening of the epoxide could not be achieved. Acetylation of **5** gave **6**, which with *tert*-butyldimethylsilyl bromide (TMSBr)[9] gave the allylic bro-

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mide **7**. The bromide was converted into the corresponding allylic acetate diether **8** with tetrabutylammonium acetate. The ether blocking groups were removed by heating with methylmagnesium iodide at 200 °C,[3a] leading to 7-hydroxy-cannabidiol **2**, a primary CBD metabolite, in a total 21% yield.[10]

(10) **2:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.20 (2H, s, Ar), 5.82 (1H, s, olefin), 4.62 (1H, s, olefin), 4.52 (1H, s, olefin), 4.07 (2H, s, CH_2OH), 3.96−3.92 (1H, m, benzyl), 2.57−2.48 (1H, td, J = 13.3, 2.7 Hz, allyl), 2.43−2.38 (2H, t, J = 7.5 Hz, benzyl), 1.88−1.73 (2H, m), 1.66 (6H, s. allyl CH_3), 1.58−1.49 (2H, m), 1.28−1.25 (6H, m), 0.87−0.84 (3H, t, J = 6.3 Hz, terminal CH_3); IR 3300, 2900, 1620, 1580, 1440, 1240, 1020, 730 cm^{-1}; $[\alpha]_D$ −67.3° (*c* 19.51 mg/mL, $CHCl_3$); MS *m*/*z* (relative intensity) 330 (M^+, 10), 312 (44), 299 (53), 284 (44), 244 (100), 231(56), 187 (29), 147 (13); mass calcd for $C_{21}H_{30}O_3$ 330.21949, found 330.2211.

As the total synthesis of CBD has previously been reported,[3] the sequence described above represents the first total synthesis of a CBD metabolite.

The results of cannabinoid receptor binding and of pharmacological assays will be described separately.

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Supporting Information Available: Experimental details and physical and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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