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A Biomimetic Synthesis of Δ^1-Tetrahydrocannabinol

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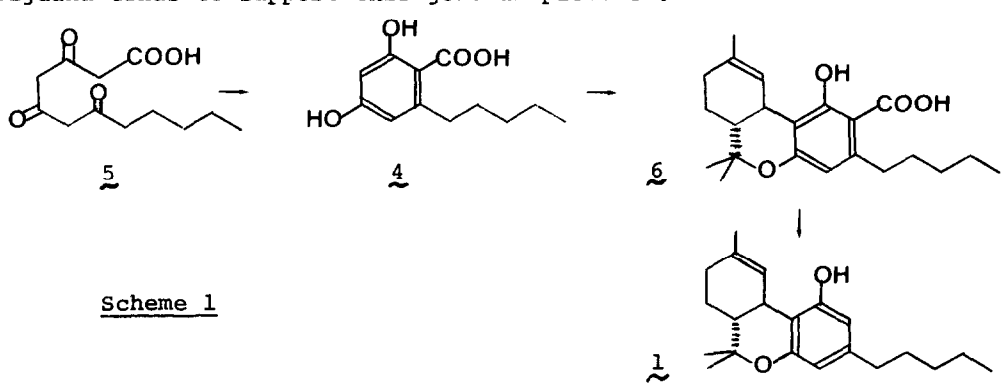
Abstract *Condensation of 1,3-bis(trimethylsiloxy)-1-methoxybutadiene with the acid chloride 12 gave methyl olivetolate (13). Condensation of 13 with (+)-p-mentha-2,8-dien-1-ol gave methyl Δ^1-tetrahydrocannabinolate (14) in 55% isolated yield. Alkaline hydrolysis of 14 gave Δ^1-tetrahydrocannabinol (1, Δ^1-THC). The synthesis is patterned after the biogenesis of 1.*

There have been several syntheses of Δ^1-tetrahydrocannabinol (1, Δ^1-THC), the active psychotomimetic component of marijuana[1]. They have in common as the critical step the condensation of a monoterpene with olivetol (2) which is generally synthesized from an aromatic precursor such as 3,5-dihydroxybenzoic acid[2]. Even with the best synthesis[3] to date, 1 can only be obtained in 25-31% isolated yield after careful chromatography of the complicated mixture from the acid-catalysed condensation of 2 with (+)-trans-p-mentha-2,8-dien-1-ol (3).

Although the biogenesis of Δ^1-THC has not been examined extensively, it is likely to follow the broad sequence outlined in scheme 1[4]. Olivetolic acid (4), derived from cyclisation of the poly-β-carbonyl compound 5 or its equivalent, condenses with a monoterpene (e.g. geraniol) to give Δ^1-tetrahydrocannabinolic acid (6) which then decarboxylates to give Δ^1-THC. The presence of 6 in marijuana tends to support this general picture[5].



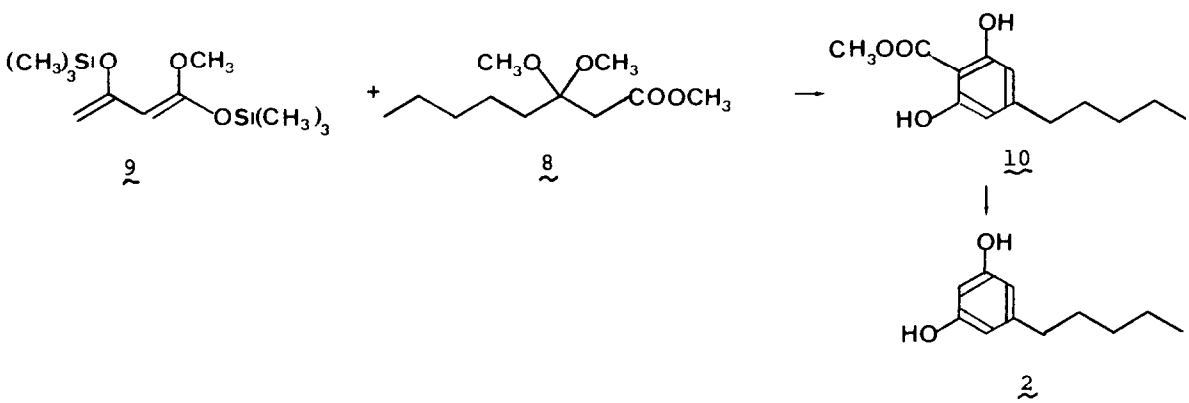
5 4 6 1

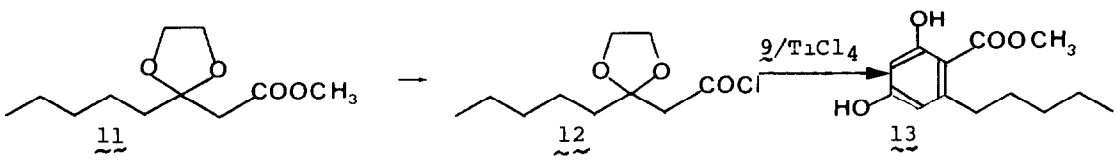
Scheme 1

We have recently suggested a novel cycloaromatisation reaction based on the condensation of enol silyl ethers with various poly-β-carbonyl equivalents[6]. The reaction has been used in a biomimetic synthesis of sclerin[7] relying on the regiocontrolled cyclisation of a penta-β-carbonyl unit. We thus became interested in the controlled condensation of 5 to 4, and thence the synthesis of 1.

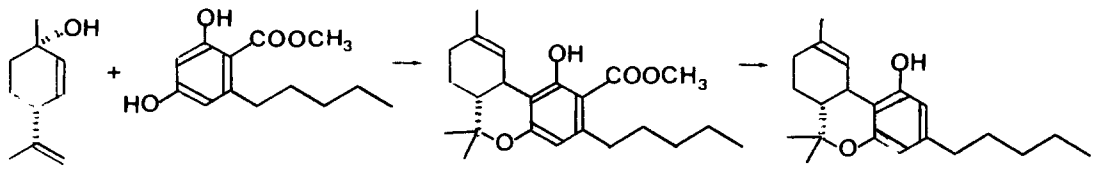
Condensation of the dimethyl ketal 8 of methyl 3-oxo-octanoate (7) with 1,3-bis-(trimethylsiloxy)-1-methoxybutadiene (9)[6] and titanium tetrachloride gave the aromatic product 10 in 72% yield. The structure of 10 (m.p. 29-30°) was evident from the ^{1}H nmr where only one type of phenolic hydrogen was observed at 9.7 ppm. Alkaline hydrolysis (NaOH in MeOH/H_2O) converted 10 to olivetol (2). While this constitutes a new and convenient synthesis of olivetol, it is clear that the regiochemistry of the cycloaromatisation reaction must be reversed in order to give the olivetolate 13.

The ethylene ketal 11 was hydrolysed by base (NaOH in MeOH/H_2O) to give the carboxylic acid which, without purification, was converted quantitatively to the acid chloride 12 with oxalyl chloride in benzene. Condensation of 12 with 9 and titanium tetrachloride, in CH_2Cl_2 gave methyl olivetolate (13), m.p. 65-68°, in 55% isolated yield. The regiocontrol of the aromatisation is based on the reactivity order of acid chloride > ketal > ester, and appears to be perfect in that neither 10 nor 13 are contaminated by one another





Condensation of 13 with an equivalent of (+)-trans-p-mentha-2,8-dien-1-ol[8] under strictly controlled conditions[9,10] gave as the major product methyl tetrahydrocannabinolate (14), m.p. 120-124° $[\alpha]_D$ = -188.4°($CHCl_3$), which was easily purified in 55% isolate yield with flash chromatography[11]. Alkaline hydrolysis (25% NaOH in MeOH/H_2O) of 14 gave Δ^1-THC, $[\alpha]_D$ = -170°($CHCl_3$), in ~78% yield with spectroscopic data identical to those reported in the literature[1,2a].



3 13 14 1

Several features of the present synthesis are of interest. The condensation of 9 with 12 (or 8) represents a controlled condensation of a tetra-β-carbonyl unit and can be regarded as a general way to construct natural products with resorcinol skeleton. Secondly, the condensation of 13 with 3 gave, as far as we could detect, chromenylation only at the carbon ortho to the two hydroxy groups. This is contrary to the reaction of olivetol where chromenylation also occurs at the carbon between the OH and the alkyl side chain. It seems that the carbomethoxy group does play a role in directing the site of chromenylation, in accordance with a suggestion put forward by Mechoulam[1d]. Last but not least, the present biomimetic synthesis, constitutes a convenient and efficient synthesis of Δ^1-THC competitive with those previously reported.

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Footnotes and References

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(7) T.H. Chan and P. Brownbridge, J.C.S. Chem. Comm., 20 (1981).

(8) We thank Firminish Co. and Prof. V. Sniekus for the supply of this compound.

(9) Reaction conditions were similar to those used by Razdan et. al[3]. To a mixture of 13 (0.149 g) and 3 (0.100 g) in 15 ml CH_2Cl_2 was added anhydrous magnesium sulfate (0.107 g) and stirred for 20 min. The mixture was cooled to 0° and 0.060 ml of BF_3-etherate was added and stirred at 0° for 1.5 h. To the mixture, 0.298 g of anhydrous sodium bicarbonate was added. Stirring continued until the brown color faded. The mixture was filtered and evaporated to give a colorless gum (0.209 g). The crude mixture was purified with flash chromatography on silica gel (230-400 mesh) with CCl_4-CH_2Cl_2 (4:1) as eluent to give pure 14, in 55% yield.

(10) Condensation of 13 and 3 was investigated previously under acidic conditions to give methyl cannabidiolate[2a]. L. Crombie, W.M.L. Crombie, R. Forbes and Whitaker, J. Chem. Res., (S), 114 (1977), (M) 1301 (1977).

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