# Novel Synthesis of (-)-*trans*-$\Delta^{9,11}$-Tetrahydrocannabinol



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Addition of hydrogen chloride gas to a solution of $\Delta^8$-tetrahydrocannabinol in dry dichloromethane at -60° in the presence of zinc chloride results in the formation of a higher concentration of 9-$\alpha$-chlorohexahydrocannabinol (75%) than the thermodynamically more stable 9-$\beta$-chlorohexahydrocannabinol (25%). The two isomers can be separated by reverse-phase hplc. Elimination of hydrogen chloride from 9-$\alpha$-chlorohexahydrocannabinol using potassium *t*-amylate under anhydrous conditions gives exclusively $\Delta^{9,11}$-tetrahydrocannabinol in overall yield of 65%.

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In recent years the growing interest in cannabinoids as potential therapeutic agents and attempts to understand the mechanism by which these compounds interact with cellular membranes have created a need for new methods in cannabinoid synthesis. Our involvement in cannabinoid chemistry is connected with our interest in understanding the mechanism with which these drug molecules affect cellular membranes [2,3]. To date, our studies have focused on three structurally related cannabinoids, namely $\Delta^8$-tetrahydrocannabinol ($\Delta^8$-THC), $\Delta^9$-tetrahydrocannabinol ($\Delta^9$-THC) and $\Delta^{9,11}$-tetrahydrocannabinol ($\Delta^{9,11}$-THC). Of these, $\Delta^9$-THC is the most active constituent of marijuana and also the cannabinoid most commonly used for pharmacological studies (Figure 1). $\Delta^8$-THC, although physiologically active, is less potent than $\Delta^9$-THC [4], while $\Delta^{9,11}$-THC is a synthetic analog that differs from the other two by having a double bond exocyclic to ring C. Due to its inactivity, $\Delta^{9,11}$-THC is used as a control in cannabinoid binding assays [5] as well as for studies dealing with *in vivo* distribution of cannabinoids. It also provides a key intermediate for introduction of new functionalities at either the C-9 or C-11 positions of THCs.

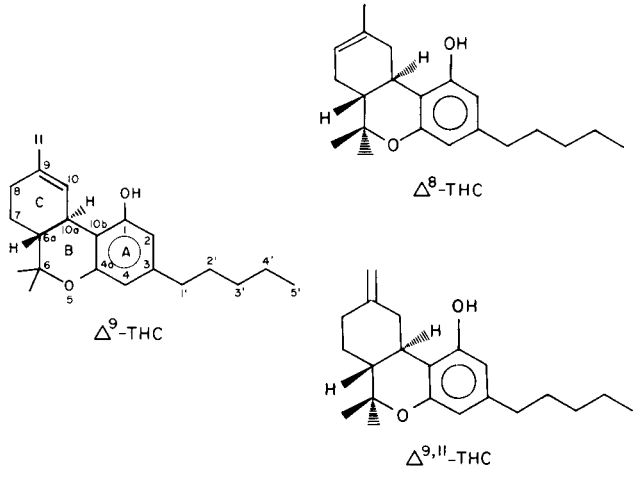



Figure 1

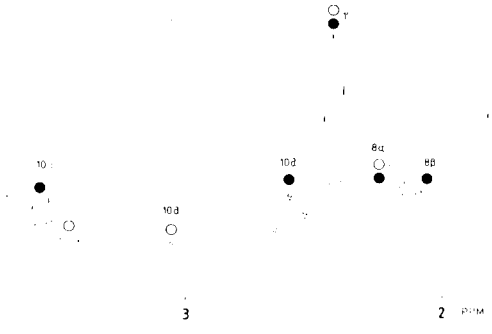



Figure 2. Partial $^1$H nmr (200 MHz) spectrum of 9-$\alpha$-(●) and 9-$\beta$-Cl-HHC (○).

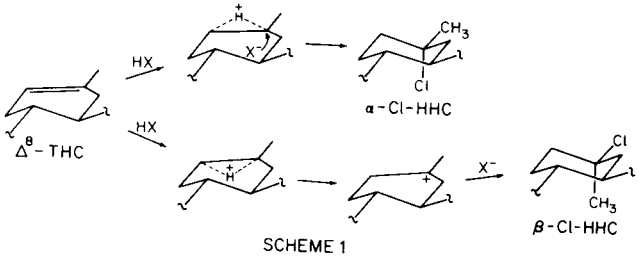
The synthesis of racemic as well as optically active (-)-*trans*-$\Delta^{9,11}$-THC has been reported by different investigators. A commonly used method for the preparation of this compound involves uv irradiation of the corresponding $\Delta^8$-THC [6]. This method lacks selectivity since a number of other products are also formed and the final yield is below 30%. Another method described for the synthesis of this compound [7] involves the addition of hydrogen chloride gas to $\Delta^8$-THC-1-methyl ether at 0°. The thermodynamically controlled sole intermediate, 9-$\beta$-chlorohexahydrocannabinol (9-$\beta$-Cl-HHC) was then treated with a bulky base (potassium tricyclopentylcarbinolate) followed by demethylation of the phenol to afford $\Delta^{9,11}$-THC in a yield of less than 30%. This method not only requires multi-step chemistry but also lacks selectivity since by-products such as $\Delta^8$- and $\Delta^9$-THC are always formed. In view of the fact that our studies required the availability of $\Delta^{9,11}$-THC specifically $^2$H labeled in different positions of the molecule [8], we sought to develop improved procedures for the synthesis of this compound.

We would like to report here on a simple and very effective method for obtaining $\Delta^{9,11}$-THC from its more accessible isomer, $\Delta^8$-THC. The method involves the addition of hydrogen chloride gas to $\Delta^8$-THC at low temperatures, isolation of the kinetically favored product 9-$\alpha$-chlorohexahydrocannabinol (9-$\alpha$-Cl-HHC), and quantitative hydrogen chloride elimination to yield $\Delta^{9,11}$-THC as the

only product.

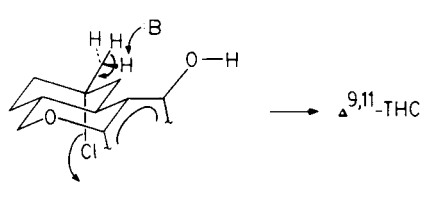
Synthesis.

Addition of hydrogen chloride gas to a solution of $\Delta^8$-THC at temperatures below -20° leads to formation of 9-α-Cl-HHC as the major product (75%) with the 9-β-Cl-HHC isomer forming in smaller quantities. Formation of the two hydrogen chloride addition products, can be rationalized by assuming that attack of hydrogen chloride on the double bond may occur from either face of the tetrahydrocannabinol molecule. Attack from the β face results into a *trans* diaxial hydrogen chloride addition presumably through the formation of a bridged cation followed by a *trans* attack of a chloride anion to give the 9-α-Cl-HHC. On the other hand, protonation from the α face leads to the formation of a carbonium ion at C-9 followed by chloride attack from the least hindered equatorial side giving 9-β-Cl-HHC (Scheme 1). Subsequently, we used hplc and a water/acetonitrile/tetrahydrofuran mixture as the eluent to obtain pure 9-α-Cl-HHC in quantitative yield.




SCHEME 1

When 9-α-Cl-HHC is treated with potassium *t*-amylate under anhydrous conditions, $\Delta^{9,11}$-THC is the exclusive product. Presumably, this occurs because the 11-methyl protons present the best choice for a *trans* diaxial elimination by the bulky base. It appears that the base is initially directed towards the phenolic group and is positioned to abstract either the 10β proton (axial) or one of the three 11-methyl protons. Of these, the methyl protons are sterically more accessible, resulting in the exclusive formation of the exocyclic isomer (Scheme 2). The mechanistic details of this reaction will be discussed elsewhere.




SCHEME 2

## EXPERIMENTAL

Proton nmr spectra were obtained on a 200 MHz IBM WP-200SY spectrometer using tetramethylsilane as internal reference. Chromatography was performed on a Waters Associate hplc system equipped with a Model 590 Programmable Solvent Delivery Module, a U6K injector and a recycling manifold. The reverse-phase column used was a μBondapak C18 column (Waters Assoc. Part No. 84176, Serial No. P62231A01) packed with 10 μm irregularly shaped particles and had dimensions of 30 cm x 7.8 mm i.d.. Solvents used in chromatography were purchased from Fisher Scientific Co.. Hydrogen chloride gas was purchased from Matheson Gas Products Inc.. Glassware was flame dried. $\Delta^8$-THC was prepared in our laboratories according to literature procedures [9].

Preparation of 9α-Chlorohexahydrocannabinol as the Precursor for the Synthesis of $\Delta^{9,11}$-THC.

Dry hydrogen chloride gas was added through a gas dispersion tube to a solution of $\Delta^8$-THC (200 mg) in 20 ml of dichloromethane containing anhydrous zinc chloride (70 mg) and kept at -60°. The addition was allowed to proceed under strictly anhydrous conditions with continuous stirring for 2 hours, after which the reaction was quenched with a 10% sodium carbonate/water solution (10 ml) and allowed to warm to room temperature. The organic layer was then washed with water (2 x 20 ml) and dried over anhydrous sodium sulfate. Removal of the solvent gave a quantitative yield of a mixture of 9-α- and 9-β-Cl-HHC as a pale yellow oil. Proton nmr spectra (deuteriochloroform) showed a 3:1 ratio for 9-α-Cl-HHC and 9-β-Cl-HHC respectively (Figure 2).

Purification.

Two hundred mg of the above sample was dissolved in 1 ml acetonitrile and applied to hplc. Elution with a ternary solvent system water/acetonitrile/tetrahydrofuran of volume ratio 50/35/15, respectively, and at a flow rate of 3 ml/minute results in separation of the two isomers after 120 minutes. The organic solvents were then removed on a rotary evaporator and 9-α-Cl-HHC was extracted from the remaining aqueous phase using dichloromethane. The extract was dried over anhydrous sodium sulfate and evaporated to give 130 mg of the pure 9-α-Cl-HHC (65% yield); $^1$H nmr (deuteriochloroform): δ (ppm) 6.24 (s, H4), 6.05 (s, H2), 4.69 (s, OH), 3.55 (dt, H10α), 2.58 (td, H10a), 2.41 (t, 2H, 1'$CH_2$), 2.22 (dd, br, H8α), 2.09 (td, H8β), 1.76 (s, 3H, 9$CH_3$), 1.5-1.57 (m, br, 2H, 2'$CH_2$), 1.44 (td, H6a), 1.23-1.33 (m, br, 5H, 3', 4' $(CH_2)_2$, H10β), 1.36 (s, 3H, 6β$CH_3$), 1.06 (s, 3H, 6α$CH_3$), 0.86 (t, 3H, 5'$CH_3$).

*Anal.* Calcd. for $C_{21}H_{30}ClO_2$: C, 72.08; H, 8.64. Found: C, 72.23; H, 8.67.

Elimination of Hydrogen Chloride for the Preparation of $\Delta^{9,11}$-THC.

9-α-Cl-HHC (100 mg) was dissolved in dry benzene (3 ml) and cooled to 0° under a nitrogen atmosphere. Freshly prepared potassium *t*-amylate (1 ml of 1*M* solution in benzene) was then added and the mixture stirred for 30 minutes. The mixture was warmed to 70° and stirred for 3 hours after which tlc (10% ether in petroleum ether) showed the completion of the reaction. The mixture was subsequently cooled to room temperature, diluted with benzene (10 ml) and neutralized with dry ice to *p*H 7. It was then extracted with ether (2 x 5 ml), washed with water (20 ml), aqueous sodium bicarbonate (5 ml) and again with water (20 ml). The organic layer was dried over anhydrous sodium sulfate and evaporated under vacuum to give exclusively $\Delta^{9,11}$-THC in a quantitative yield; $^1$H nmr (deuteriochloroform): δ (ppm) 6.15 (s, H4), 6.03 (s, H2), 4.80 (s, H11a), 4.61 (s, OH), 3.62 (dt, H10α), 2.41 (td, H10a), 2.38 (m, 2H, 1'$CH_2$), 2.10 (td, H8α), 1.87 (m, H8β), 1.75 (t, H10β), 1.58 (td, H6a), 1.51 (t, 2H, 2'$CH_2$), 1.31 (s, 3H, 6β$CH_3$), 1.20 (m, 4H, 3', 4' $(CH_2)_2$), 1.17 (m, 2H, H7α, 7β), 0.99 (s, 3H, 6α$CH_3$), 0.79 (t, 3H, 5'$CH_3$).

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