The Total Synthesis of Cannabinoids

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1. INTRODUCTION

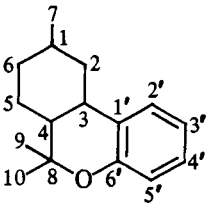
The illicit use of marijuana, which started in a substantial way in the early 1960s, has continued to increase. By 1975 over 36 million Americans had tried the drug, and among the 20-24 age group over 10% were using it on a daily basis. This has caused grave concern to society, and marijuana has become the subject of intense sociopolitical controversy. However, the recent use of marijuana and its active constituent Δ^1-THC for glaucoma and as an antinauseant in patients undergoing cancer chemotherapy has revived public interest in its therapeutic potential. In other cultures, particularly Chinese, Indian, and Middle Eastern, the therapeutic use of cannabis preparations has been well documented for centuries, and folklore has recorded its use in insomnia, neuralgia, migraine pain, rheumatism, asthma, bronchitis, loss of appetite, and gynecological and obstetrical problems such as dysmenorrhea. Even today its use is widely practiced in the Ayurvedic and Tibbi systems of Indian medicine. The recent discovery of its use in the treatment of glaucoma and as an antinauseant was serendipitous and came out of the drug culture. It was well known among drug users that while "high" on marijuana one could chop onions without the eyes watering. Encouraged by anecdotes like this, ophthalmologists Hepler and Frank[1] in 1971 found that smoking marijuana did indeed decrease lacrimation and also decreased the intraocular pressure (IOP) of the eye. This led to clinical trials with smoked marijuana or Δ^1-THC in glaucomatous patients.

Similarly, "pot" smokers who had cancer and were undergoing cancer chemotherapy noticed a relief from the nausea that traditionally accompanies this treatment. This was clinically confirmed by Sallan and co-workers[2] in 1975. These therapeutic aspects are being vigorously pursued at present.

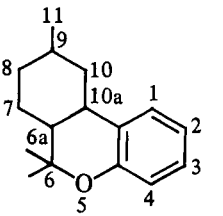
It is unlikely that the natural material marijuana itself will become a marketable product because it is a complex mixture of over 35 known cannabinoids, various terpenes, nitrogen bases, phenolic compounds, sugars, etc. It is possible that its main active constituent Δ^1-THC could become a viable drug, but it is most likely that the marketable products will come from the synthetic analogs, where the undesirable side effects and physical characteristics of Δ^1-THC have been modified or eliminated.

The term "cannabinoids" is used for the typical C_{21} groups of compounds present in *Cannabis sativa* L. (family Moraceae) and includes their analogs and transformation products.

The following two different numbering systems, dibenzopyran and monoterpenoid, are generally used for cannabinoids. The former is used by *Chemical Abstracts*. In the present article the monoterpenoid numbering system will be used, as it can be most easily adapted for ring-opened cannabidiol derivatives and isotetrahydrocannabinols (iso-THCs).



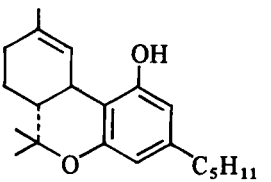
Monoterpenoid



Dibenzopyran

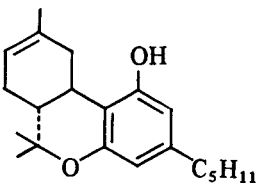
(−)-Δ^1-3,4-*trans*-Tetrahydrocannabinol (THC)[3] is the main physiologically active constituent of hashish or charas, which is the resinous exudate from the female flowers of *Cannabis sativa* L. Numerous preparations of *Cannabis* are known, and they are given different names depending on the country of origin and their mode of preparation. Thus the most potent preparation is the unadulterated resin, which is known as hashish in the Middle East and charas in India. Marijuana (pot, grass), mostly used in the United States, refers to the dried flowering tops of the plant, which are smoked in a pipe or a cigarette. Bhang, which is used in India, is a concoction made with milk and water from the flowering tops of the plant and is ingested by mouth.

(−)-Δ^1-3,4-*trans*-THC (1) is a resin that is optically active and is generally referred to as Δ^1-THC. It is also known as Δ^9-THC based on dibenzopyran numbering system. The other physiologically active isomer is Δ^6-THC (2; alternate name Δ^8-THC) and is found only in a few varieties of the plant. The isomers with a 3,4-*cis* ring junction are *cis*-Δ^1-THC (3) and *cis*-Δ^6-THC (4) both of which have been synthesized, but only 3 has been found in the plant so far. On theoretical grounds the *trans* compounds (1 and 2) are expected to be more thermodynamically stable compared to the *cis* compounds 3 and 4. In the *trans* series Δ^6-THC (2) is more stable than Δ^1-THC (1), since 1 is easily isomerized to (2) on treatment with acids. The main interest pharmacologically therefore centers around the thermodynamically less stable *trans*-Δ^1-THC (1) and its various derivatives and metabolites. This has posed many synthetic problems because during chemical reactions the more stable derivatives of *trans*-Δ^6-THC (2) are mostly formed.



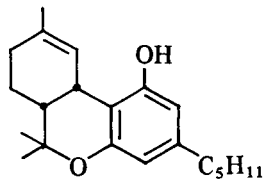
Δ^1-THC

1



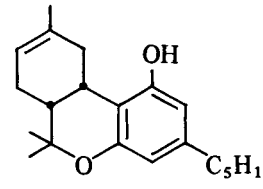
Δ^6-THC

2



cis-Δ^1-THC

3



cis-Δ^6-THC

4

With this background let us now examine the various syntheses for (−)-Δ^1- and Δ^6-THCs (1 and 2). No attempt is made to cover the subject exhaustively in this chapter. The examples are chosen to illustrate the strategy used in the synthesis of various cannabinoids.

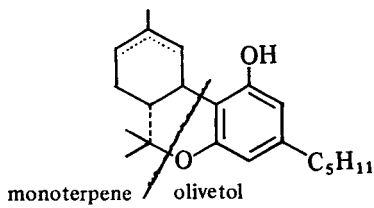
2. STRATEGY IN THE SYNTHESIS OF (−)-Δ^1- AND Δ^6-THCS AND THEIR METABOLITES

A. Synthesis of Δ^1- and Δ^6-THCs

The syntheses under discussion may be divided into two main categories: stereospecific syntheses and other approaches.

Stereospecific Syntheses

Since the structure of Δ^1-THC is not complex, the basic strategy can be envisioned as joining of the aromatic and the alicyclic parts of the molecule (as shown) by condensation of olivetol with an optically active monoterpene. Mainly, it is the selection of the monoterpene and the reaction conditions that dictate or control the position of the double bond in the Δ^1- or Δ^6- position in the final product.



From Verbenols

In 1967 Mechoulam et al.[4] described a synthesis of (−)-Δ^6-THC (2) from a pinane derivative, verbenol (5) and olivetol (6) in the presence of acid catalysts

(Chart 1.1). They visualized that the attack by the resorcinol will be favored from the side opposite the bulky dimethylmethylene bridge in verbenol and will thus provide stereochemical control of the reaction to give mainly *trans* products. Thus in the presence of $BF_3 \cdot Et_2O$, (−)-*cis*- or (−)-*trans*-verbenol (**5**) condensed with olivetol (**6**) to give (−)-Δ^6-THC (**2**) in 44% yield. The purification of this material proved to be tedious. A better procedure was found to be a two-step sequence. When **5** was allowed to react with **6** in the presence of *p*-toluenesulfonic acid (*p*-TSA) in CH_2Cl_2, a mixture containing **7** (60%), **8**, and **9** was formed from which **7** was isolated by chromatography. Treatment of **7** with $BF_3 \cdot Et_2O$ in CH_2Cl_2 cleanly formed **2** in 80% yield.

The final conversion of Δ^6-THC (**2**) to Δ^1-THC (**1**) was achieved by the addition of gaseous hydrochloric acid to the double bond of **2** to form **10** followed

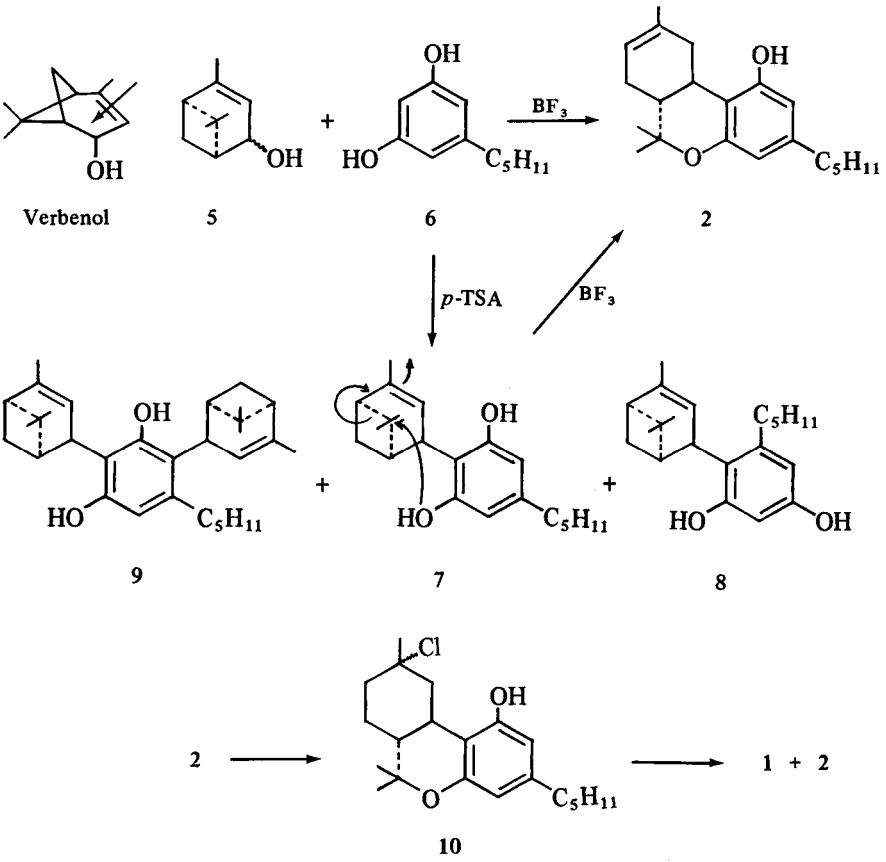


Chart 1.1

by dehydrochlorination with sodium hydride in THF. A mixture of 1 and 2 was thus obtained, which was separated by careful chromatography.

Following the same sequence of reactions the unnatural (+)-Δ^6-THC and (+)-Δ^1-THC were similarly prepared from (+)-verbenol.[5] Both the isomers were found to be relatively inactive compared to (−)-Δ^1- and (−)-Δ^6-THCs in monkeys[6] and dogs.[7]

Utilizing this procedure various side-chain homologs of (−)-Δ^1- and (−)-Δ^6-THC's were synthesized including deuterium-labeled [3-^{2}H]-Δ^6-THC, [3-^{2}H]-Δ^1-THC,[4] and other cannabinoids[8] with tritium labeled at unspecified positions.

From Chrysanthenol

It is apparent that the mechanism of the verbenol route (Chart 1.1) is likely to involve a common allylic cation, since both *cis*- and *trans*-verbenols give the same products. However, on mechanistic grounds Razdan et al.[9] reasoned that, by virtue of the position of the double bond, verbenol can lead only to Δ^6-THC, since the double bond has to migrate into that position during the ring opening of the cyclobutane ring. On the other hand, on the basis of similar arguments they thought chrysanthenol should lead directly to Δ^1-THC. This was indeed found to be the case albeit the yield was moderate[9] (Chart 1.2). Thus (−)-verbenone, on irradiation in cyclohexane gave (−)-chrysanthenone,[10,11] which on $LiAlH_4$ reduction formed the (+)-*cis*-chrysanthenol.[10,12] Treatment with equimolar quantity of olivetol (6) in the presence of 0.1% $BF_3 \cdot Et_2O$ in methylene chloride gave a resin containing ~25% [gas-liquid chromatography (GLC)] Δ^1-THC, which was separated by chromatography and was found to be identical to the natural material in all respects. The direct synthesis from chrysanthenol

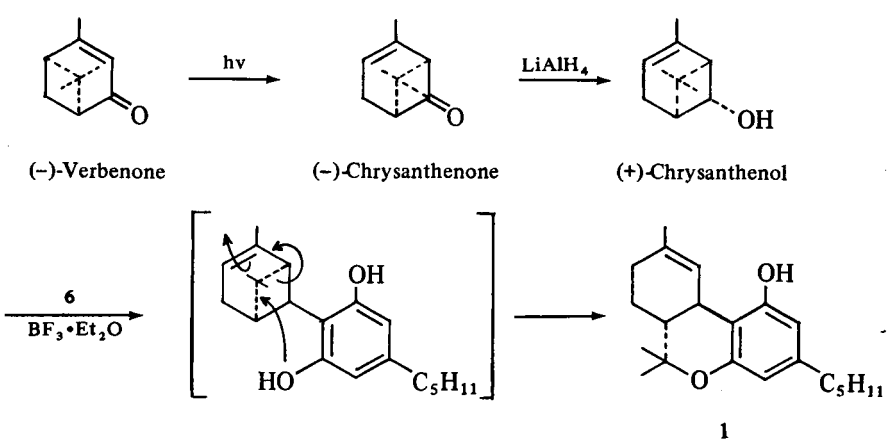


Chart 1.2

has some biogenetic implications, especially since chrysanthenone and chrysanthenyl acetate[12] have been found to occur naturally, and many publications report[13] the complete absence of cannabidiol in *Cannabis sativa*. It is therefore suggested that an alternative biogenetic scheme proceeding via the "pinane route"[14] might be operative in certain subspecies of *Cannabis*.

From p-*Mentha-2,8-dien-1-ol*

About the same time when Mechoulam et al.[4] reported their synthesis of (−)-Δ^6-THC from verbenol, Petrzilka et al.[15] in 1967 demonstrated a facile entry into cannabinoids utilizing (+)-*cis*- or *trans*-*p*-mentha-2,8-dien-1-ol (**11**). By condensing with olivetol (**6**) in the presence of weak and strong acids they obtained (−)-cannabidiol (**12**) and (−)-Δ^6-THC (**2**), respectively (Chart 1.3). The yield of **12** was 25%, but with a strong acid, *p*-TSA, no cannabidiol (**12**) was isolated, and Δ^6-THC (**2**) was obtained in 53% yield. Presumably **2** was being formed via the intermediates cannabidiol → Δ^1-THC → Δ^6-THC, since both cannabidiol and Δ^1-THC are known to yield Δ^6-THC in nearly quantitative yields on treatment with *p*-TSA. The enhanced yield of **2** was rationalized on the postulate that abnormal cannabidiol (*abn*-CBD, **14**), which always accompanies cannabidiol (**12**), undergoes a "retrocondensation" to give "ion *c*," which in turn forms more cannabidiol and hence Δ^6-THC.

The Δ^6-THC obtained by this procedure is accompanied by many by-products, which is typical of all THC syntheses and was purified by very careful column chromatography. Conversion to Δ^1-THC was carried out by the usual procedure of addition and elimination of HCl (Chart 1.1). But these authors improved the yield of Δ^1-THC in the dehydrochlorination step, previously reported by Fahrenholtz et al.[16] in the synthesis of *dl*-THCs (NaH/THF) and later applied by Mechoulam et al.[4] in their synthesis of (−)-Δ^1-THC by the verbenol route. By using potassium-*t*-amylate in benzene, Petrzilka and co-workers[15] reported a 100% yield of **1** from the chloro compound **10**.

Because of the commercial availability of the starting terpene, (+)-*cis*/*trans*-*p*-mentha-2,8-dien-1-ol (**11**), this route was further developed by Razdan and co-workers[17] for the preparation of kilogram quantities of **1** and **2** at Arthur D. Little, Inc., Cambridge, Massachusetts for the National Institutes of Health. They reported that the dehydrochlorination procedure was very sensitive to reaction conditions and showed (GLC) that under the best conditions a mixture of 95% **1** and 5% (−)-$\Delta^{1(7)}$-THC (**13**) was always obtained. This new THC (**13**) was completely chracterized[18] by isolation from this mixture by chromatography on silver nitrate-silica gel.

Based on the observation that cannabidiol (**12**) gives mainly Δ^1-THC (**1**) on treatment with $BF_3 \cdot Et_2O/CH_2Cl_2$, whereas under the same conditions **11** and **6** give Δ^6-THC (**2**), Razdan and co-workers concluded that the formation of **2** and not **1** must be due to the acid being generated from a mole of H_2O and

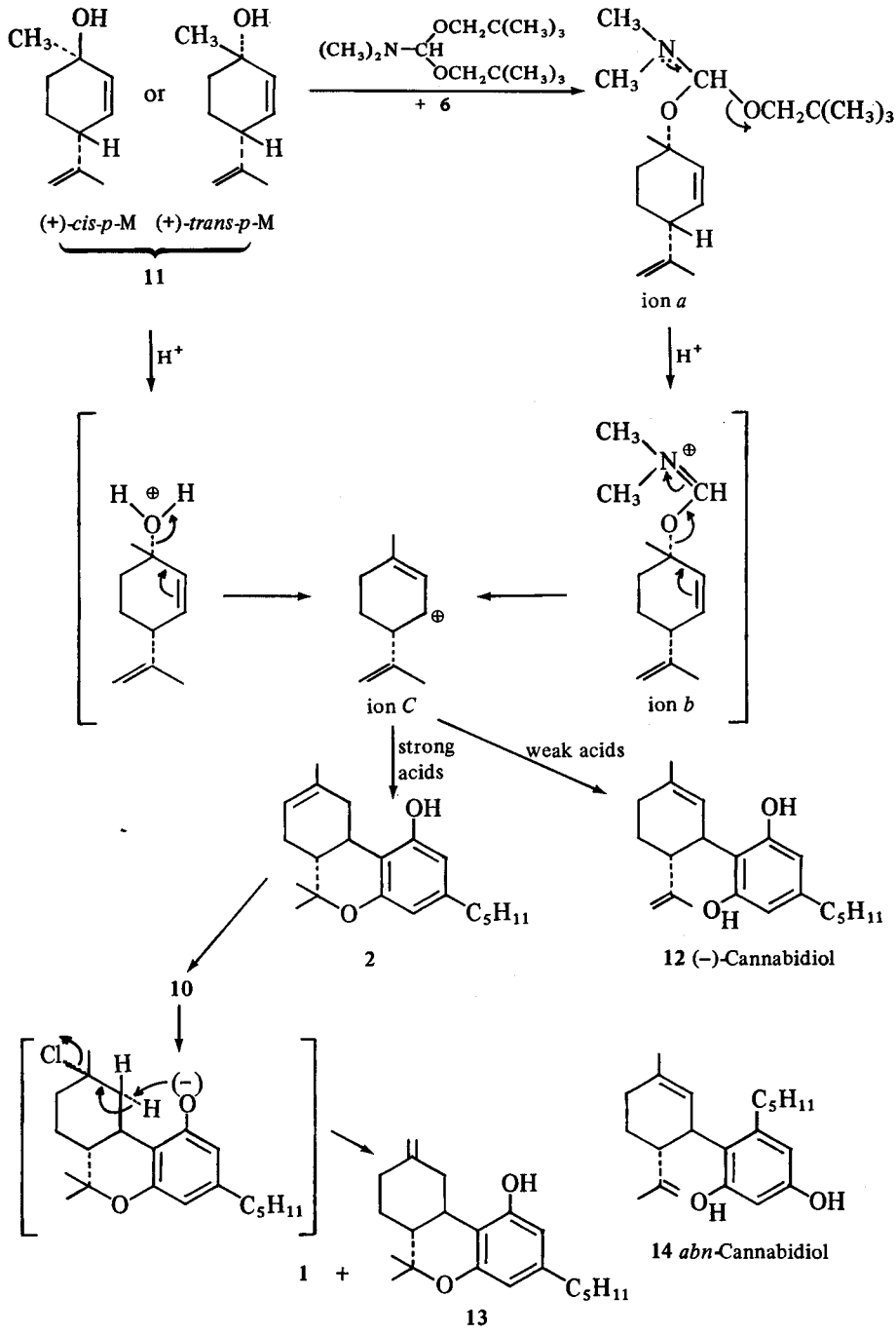

OH
CH3
or
H
(+)-cis-p-M
(+)-trans-p-M
11
(CH3)2N–CH
OCH2C(CH3)3
OCH2C(CH3)3
+ 6
CH3
N
CH3
CH
O
OCH2C(CH3)3
ion a
H+
H+
H
O
H
ion C
ion b
strong acids
weak acids
OH
C5H11
2
12 (–)-Cannabidiol
10
Cl
H
(–)
O
C5H11
1 +
13
14 abn-Cannabidiol

Chart 1.3

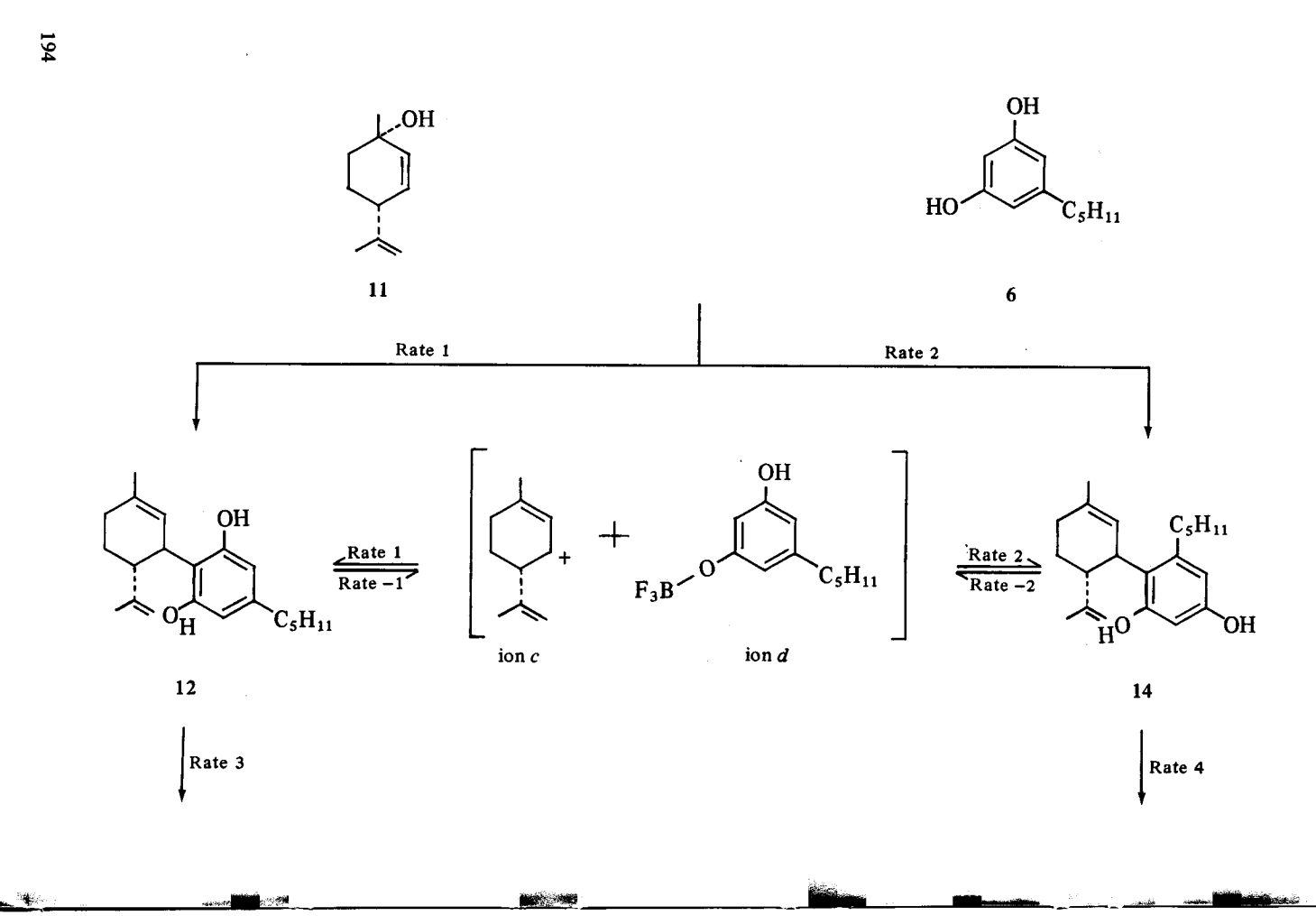
$BF_3 \cdot Et_2O$ in the reaction mixture. With this reasoning Razdan et al.[19] developed a modification of Petrzilka's cannabinoid synthesis utilizing $BF_3 \cdot Et_2O/CH_2Cl_2$ in the presence of $MgSO_4$ as the dehydrating agent. By this process Δ^1-THC (**1**) of very high optical purity was formed in a simple one-step synthesis in 50% yield (GLC) and was isolated in 31% yield after a simple and quick column chromatography.[19] The purity of Δ^9-THC was >96% by GLC and in contrast to Petrzilka's process no Δ^8-THC (**2**) is formed under the new conditions. Furthermore, by a slight change in the reaction conditions of the new process, (−)-cannabidiol (**12**) was obtained on a preparative scale.

On studying this reaction in greater detail, Razdan et al.[19] found (Chart 1.4) that normal cannabidiol (*n*-CBD, **12**) and abnormal cannabidiol (*abn*-CBD, **14**) were formed first and in a ratio of 1:2. The reaction stopped at this stage if <0.5% $BF_3 \cdot Et_2O$ or wet *p*-TSA was used. This was followed by conversion of cannabidiols **12** and **14** into normal and abnormal THC's (**1** and **16**) and iso-THCs (**15** and **17**). Significantly, the ratio of normal to abnormal products was now greater than 3:1, indicating that apparent transformation of *abn*-CBD (**14**) to normal products was taking place. To elucidate the mechanism they studied the conversion of individual compounds with $BF_3 \cdot Et_2O$ under the reaction conditions and arrived at the following interpretation of their results: (1) reaction rate 2 = twice rate 1, since **12** and **14** are formed in a ratio of 1:2; (2) reaction rate −2 ≥ rate 4 because *abn*-CBD (**14**) is converted into more normal than abnormal products; (3) rate −1 << rate −2 because **14** gives 50% normal products, whereas **12** gives no abnormal products and only a small amount of olivetol; and (4) rate 1 > rate 3 and rate 2 > rate 4, since the reaction can give cannabidiols **12** and **14** exclusively.

The different behavior of cannabidiols **12** and **14** can be explained on steric grounds. An examination of Dreiding models shows that in **14**, unlike **12**, ring closure to abnormal THC **16** results in a large steric interaction between the benzylic methylene of the C_5H_{11} group and the C-2 vinylic proton. This interaction retards the formation of compound **16** and also increases the propensity of **14** to undergo cleavage, probably by forcing a larger contribution of *trans*-diaxial conformation of the cyclohexene ring substituents. This conformation favors ring closure to compound **17** or cleavage to ion c and ion **d**.

The importance of the steric effect of the 5-alkylresorcinol side chain has been further illustrated by the observation that when the n-C_5H_{11} chain in **6** was substituted by a more sterically hindered $CH(CH_3)CH(CH_3)C_5H_{11}$ group, the reaction gave a 3:1 normal to abnormal cannabidiol ratio and subsequent ring closure gave only traces of abnormal products.

The above discussion provides an understanding of the formation of Δ^1-THC (**1**) as the main product from **11** and **6**.


OH
11
OH
HO
C_5H_{11}
6
Rate 1
Rate 2
OH
OH
C_5H_{11}
12
Rate 1
Rate −1
+
OH
F_3B
O
C_5H_{11}
ion c
ion d
Rate 2
Rate −2
C_5H_{11}
H
O
OH
14
Rate 3
Rate 4

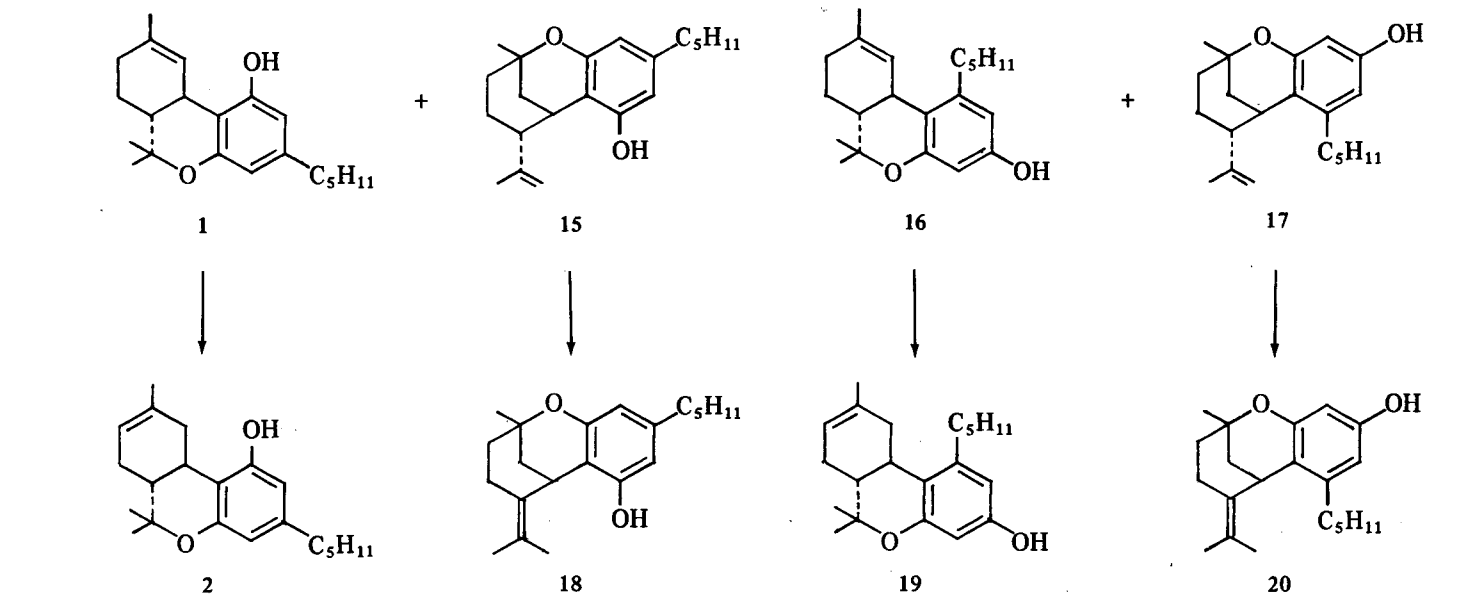

OH
O
C_5H_{11}
1
+
O
C_5H_{11}
OH
15
C_5H_{11}
O
OH
16
+
O
OH
C_5H_{11}
17
OH
O
C_5H_{11}
2
O
C_5H_{11}
OH
18
C_5H_{11}
O
OH
19
O
OH
C_5H_{11}
20

Chart 1.4

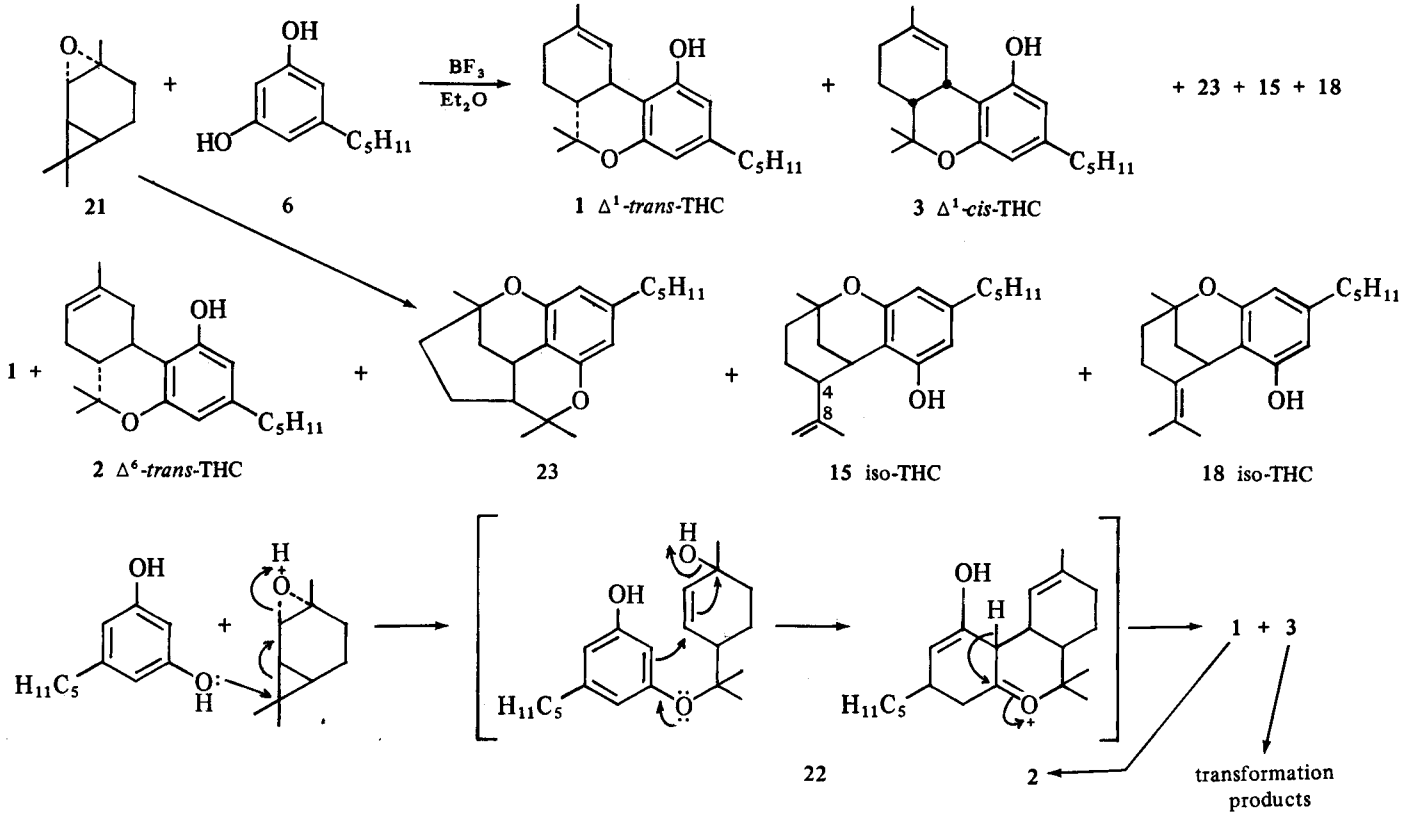

BF3
Et2O
+ 23 + 15 + 18
21
6
1 Δ1-trans-THC
3 Δ1-cis-THC
2 Δ6-trans-THC
23
15 iso-THC
18 iso-THC
22
2
1 + 3
transformation products

Chart 1.5

From Carene Epoxides

In 1970 Razdan and Handrick[20] reported an entry into cannabinoids from carane derivatives. Treatment of (+)-*trans*-2-carene epoxide (**21**) and **6** (Chart 1.5) in the presence of $BF_3 \cdot Et_2O$ gave mainly a mixture of (−)-Δ^1-*trans*-THC and (−)-Δ^1-*cis*-THC (**3**) from which the former was isolated by preparative gas chromatography. As expected, other transformation products like iso-THCs were also formed during this reaction, but no cannabidiol (**12**) was detected. Similar results were obtained by using *p*-TSA when the molar ratio of **21** was increased. However an equimolar quantity of **21** and olivetol (**6**) in the presence of *p*-TSA gave mainly the expected transformation products of Δ^1-*trans*- and Δ^1-*cis*-THCs, that is, Δ^6-*trans*- (**2**) and iso-THCs. These results were intrepreted as suggesting that the mechanism is different from the *p*-menthadienol route and that *trans*- and *cis*-Δ^1-THCs are first formed (Chart 1.5) and are then converted into their transformation products **2** and **23** → **15** → **18**, respectively.

Recently, Montero has reported in a thesis[21] that (+)-3-carene epoxide (**24**) and olivetol (**6**) give Δ^6-THC (**2**) and the corresponding diadduct, on refluxing in benzene with *p*-TSA for 12 hours. He did not isolate any other product from this reaction and postulated the mechanism as proceeding via ion *c*, which seems reasonable under the conditions he carried out the reaction (Chart 1.6).

From p-*Menth-2-ene-1,8-diol*

Handrick et al.[22] (Chart 1.7) have recently used another readily available monoterpene *p*-menth-2-ene-1,8-diol[23] (**25**) in the synthesis of (−)-Δ^1-THC (**1**). This

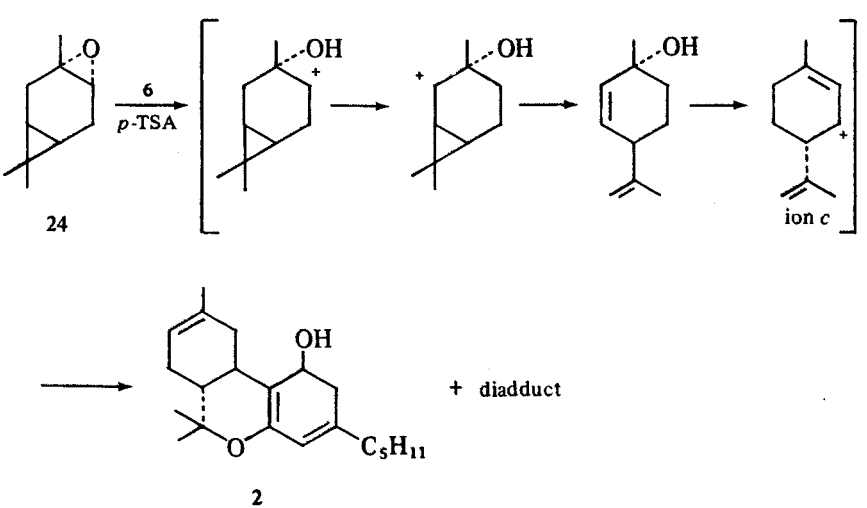


Chart 1.6

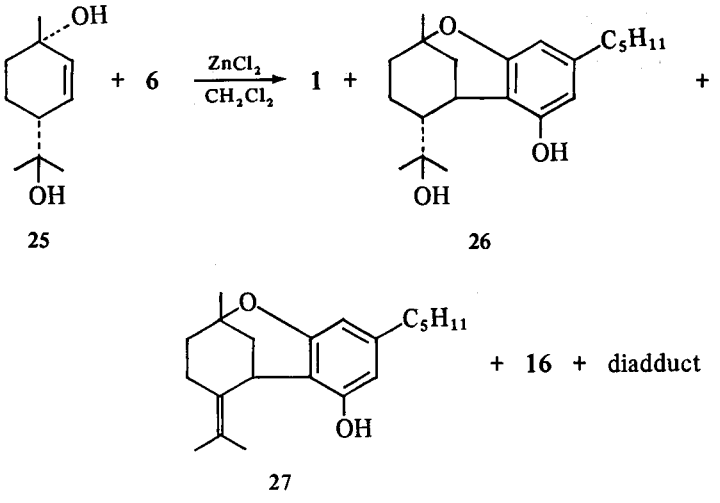


Chart 1.7

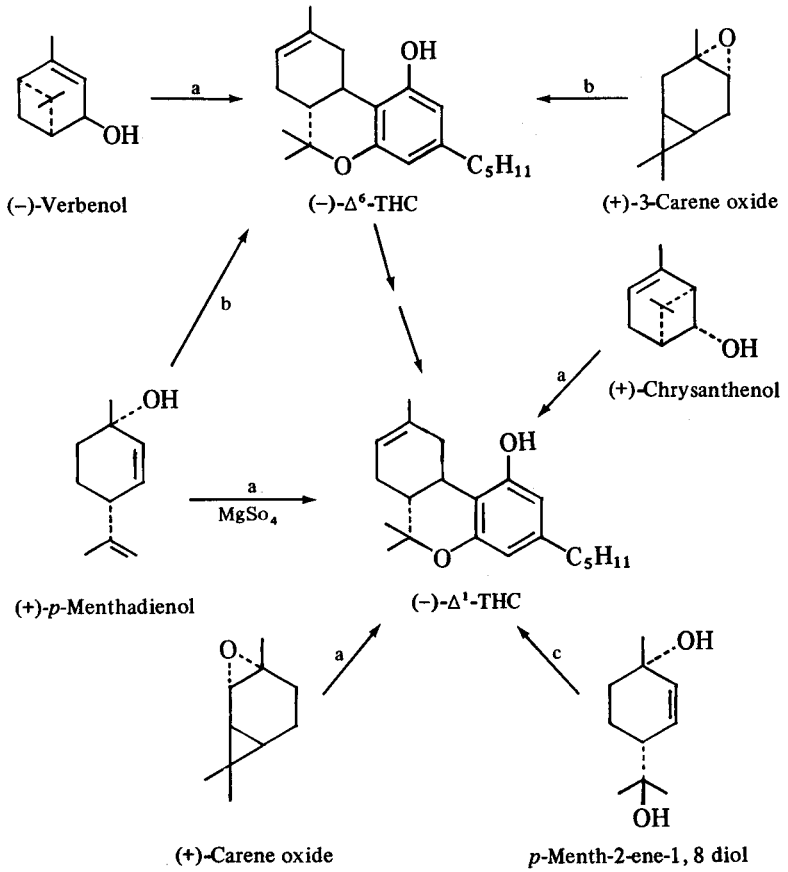
synthon was selected to facilitate the ring formation at C-8 by the presence of a hydroxyl group rather than a double bond as in *p*-mentha-2,8-diene-1-ol (**11**). A variety of catalysts were studied, and the best yield of **1** with the least amount of by-products was found to be with anhydrous $ZnCl_2/CH_2Cl_2$. The material was purified by preparative high-pressure liquid chromatography (HPLC). Although the quality of **1** was excellent, the isolated yield provided no advantage over the *p*-mentha-2,8-dien-1-ol route. It is interesting to note that with Zn halides the reaction stopped at the cannabidiol (**12**) stage with **11** but proceeded to the THC stage with **25** with apparently no isomerization of Δ^1- to Δ^6-THC, even during an extended reaction time.

Of all the procedures described above, as stated earlier, Petrzilka's process as developed by Razdan and co-workers[17] is presently used in the large-scale preparation of Δ^1-THC. Modification of Petrzilka's process ($BF_3 \cdot Et_2O/MgSO_4$) by Razdan et al.[19] has also been developed[24] to produce 50 g lots of **1** of very high purity. The purification is simplified by using Prep HPLC thus avoiding large-scale column chromatography.

Chart 1.8 summarizes the various monoterpenes that have been used for the synthesis of **1** and **2**.

Other Approaches

Various other approaches have been used for the synthesis of Δ^1- and Δ^6-THCs and some of these are described below to illustrate this objective.



Reagents: (a) $BF_3 \cdot Et_2O$ (b) *p*-TSA (c) $ZnCl_2$

Chart 1.8

Diels-Alder Reaction

An entirely different approach, which utilized a Diels-Alder reaction on an appropriately substituted cinnamic acid derivative (Chart 1.9), was developed by Jen et al.[25] This approach was originally reported by Adams and co-workers[26] but was later abandoned presumably because they failed to demethylate **29**. Jen et al.[25] deduced the *anti* configuration of **28** from its mode of preparation (Knoevenagel reaction of malonic acid with the corresponding aldehyde) and confirmed it by NMR. Based on the rule governing the retention of configuration of the dienophile constituents in the Diels-Alder reaction, compound **29**

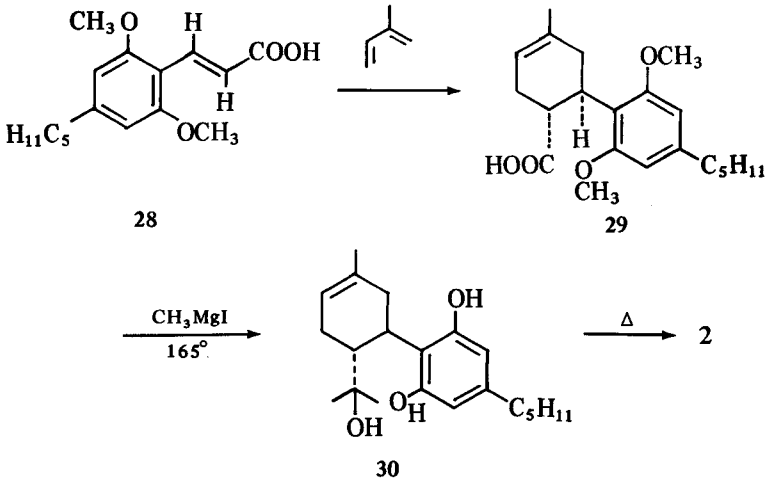


Chart 1.9

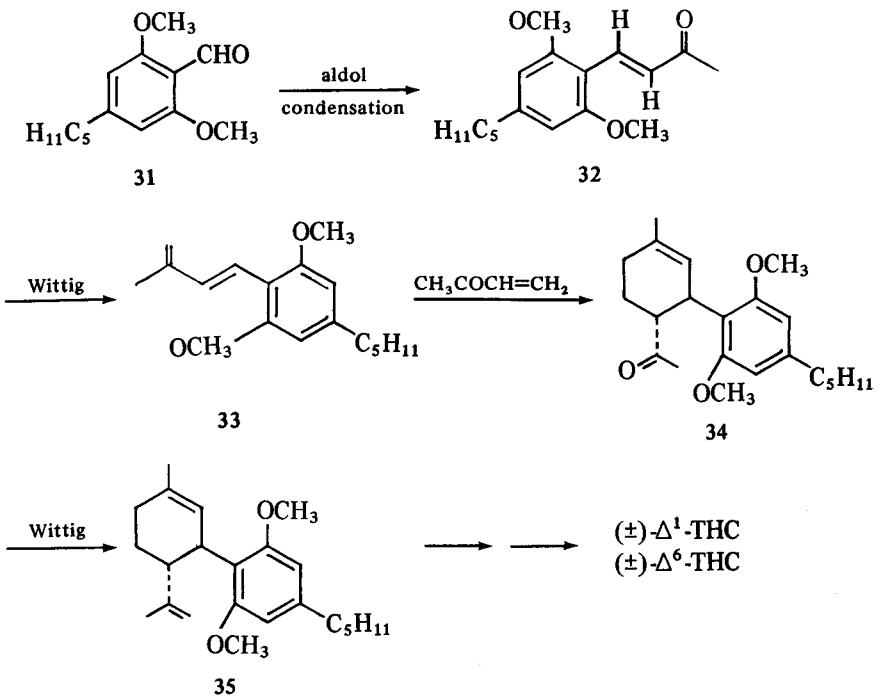


Chart 1.10

showed the *trans* configuration analogous to that found in THCs. After resolution of racemic **29** and treatment with excess CH_3MgI at 165°, the dimethoxy groups were successfully removed and the carboxyl was converted to a 2-hydroxypropyl group to give the triol **30**. Distillation furnished (−)-Δ^6-THC (**2**). Similarly the (+)-isomer was also prepared.

Another variation[27,28] on the Diels-Alder approach is shown in Chart 1.10.

From Citral

A synthesis of (±)-THCs, which is of historical interest and patterned along the suggested biogenetic pathway, was published by Mechoulam and Gaoni[29] (Chart 1.11). It was the first synthesis of (±)-Δ^1-THC and was achieved from citral (**36**) and the lithium derivative of olivetol dimethyl ether (**37**). A mixture was obtained that was tosylated to yield (±)-**35**. The success of the synthesis was due to the fact that **35** could be demethylated under near-neutral conditions to give **12**, since it is known that **12** is sensitive to both acidic and strongly basic conditions. As described earlier (Chart 1.9) the same procedure was used by Jen et al.[25] in their synthesis. Acid treatment of **12** gave **1** and **2**.

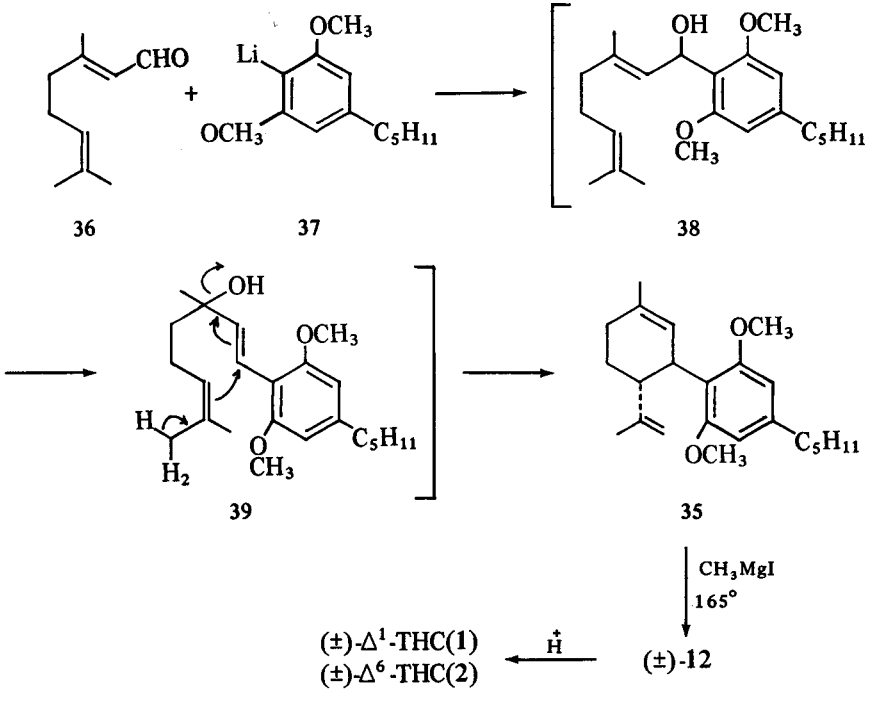


Chart 1.11

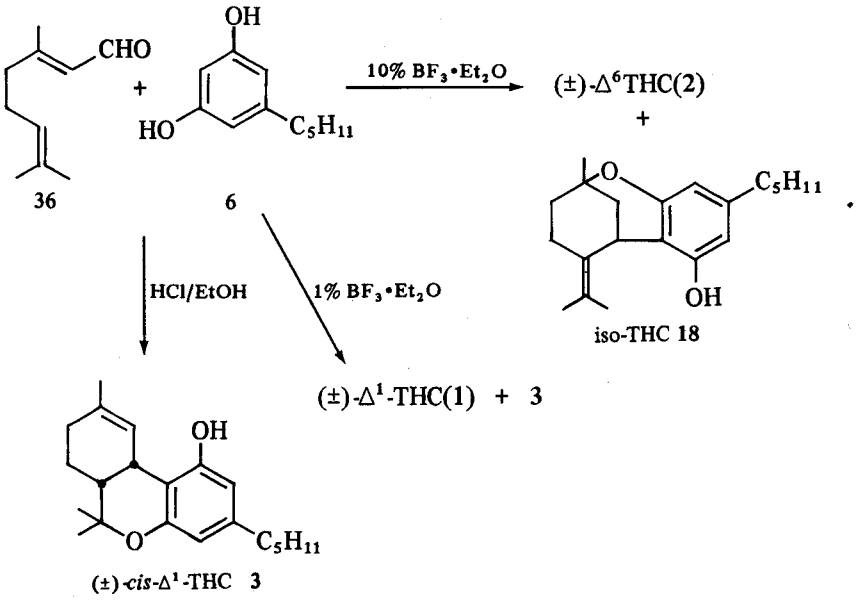


Chart 1.12

A very facile synthesis and somewhat related to the above synthesis of (±)-THCs was reported by Taylor et al.[30,31] In their approach olivetol (6) and citral were condensed with 10% $BF_3 \cdot Et_2O$ (Chart 1.12). These authors also found that with 0.0005 *N* HCl/C_2H_5OH, (±)-*cis*-Δ^1-THC (3) was formed in about 12% yield together with small amounts of (±)-*trans*-Δ^1-THC (1). Mechoulam et al.[29] later improved the yield of 1 to 20% by using 1% $BF_3 \cdot Et_2O$ in CH_2Cl_2. The mechanism of formation of these compounds has not yet been clearly established.

Pechmann Condensation

A very versatile route based on Von Pechmann condensation was developed by Fahrenholtz et al.[16] By this sequence (Chart 1.13) they prepared racemic Δ^1-, Δ^6-, and $\Delta^{1(7)}$-THCs. In addition the synthesis of (±)-*cis*-Δ^1-THC and (±)-*cis*-$\Delta^{1(7)}$-THC (48) was achieved from 46. The Li/NH_3 reduction of 43 gave both the *cis*- and *trans*-ketones 46 and 44, respectively, which were separated. The major product was the *trans*-isomer as expected. The *cis*-ketone 46 was also prepared by catalytic reduction (Raney nickel) under high pressure and temperature of the ketal of 42 followed by treatment with CH_3MgI and acid hydrolysis.

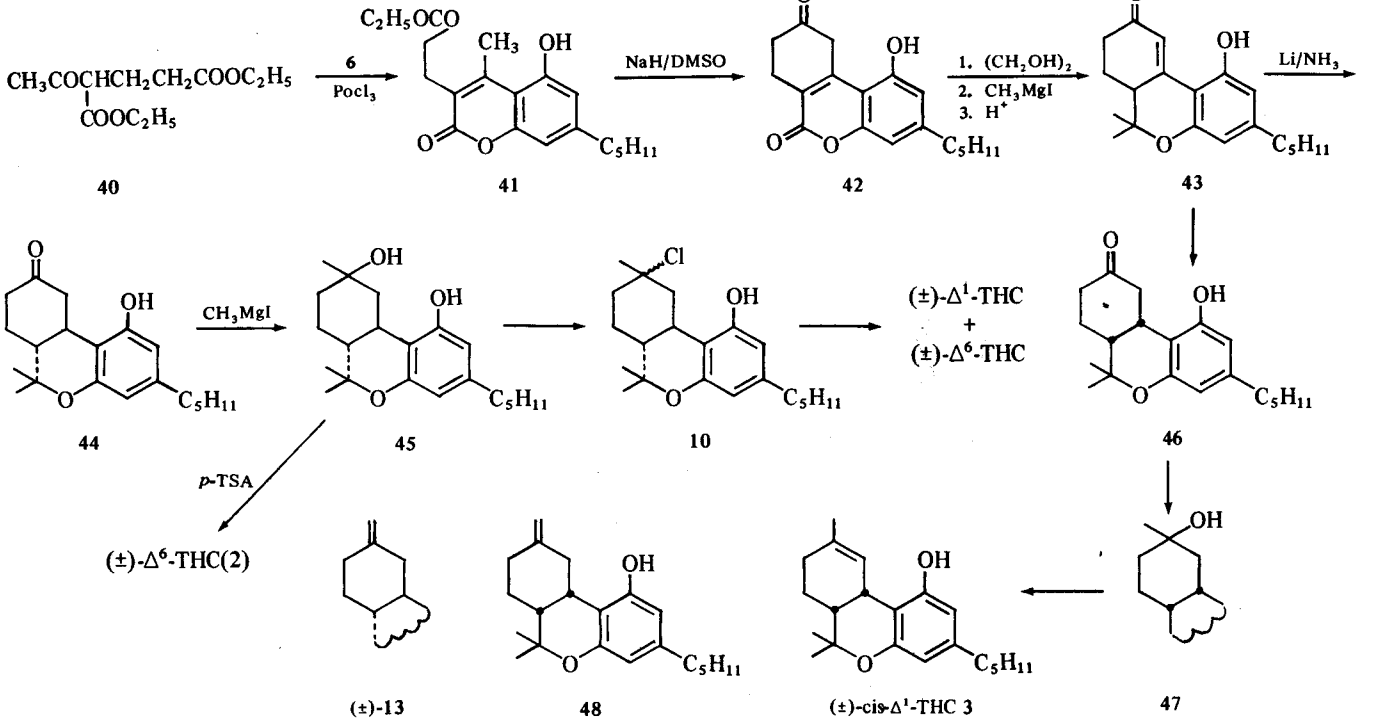
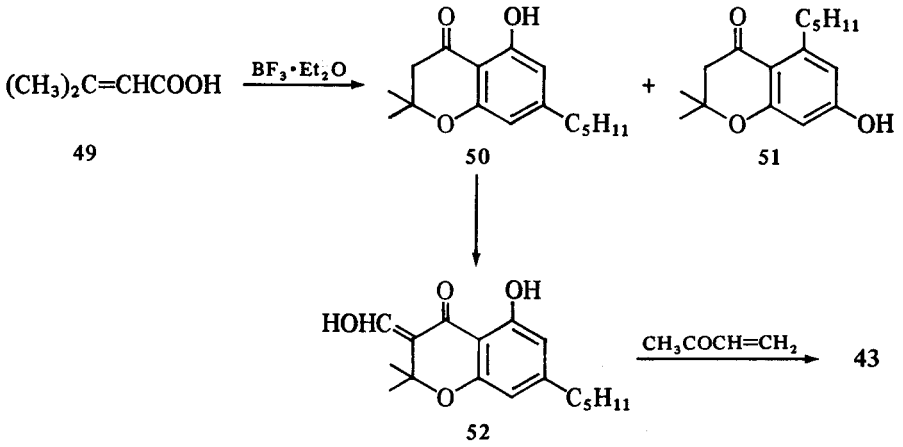

CH3COCHCH2CH2COOC2H5
COOC2H5
40
6
POCl3
C2H5OCO
CH3
OH
C5H11
41
NaH/DMSO
42
1. (CH2OH)2
2. CH3MgI
3. H+
43
Li/NH3
CH3MgI
44
45
Cl
10
(±)-Δ1-THC
+
(±)-Δ6-THC
46
p-TSA
(±)-Δ6-THC(2)
(±)-13
48
(±)-cis-Δ1-THC 3
47

Chart 1.13



49 50 51 52

Chart 1.14

Alternatively the key intermediate **43** was also prepared from **49** (Chart 1.14). The alicyclic ring was built by using the standard Robinson annelation procedure.

B. Synthesis of *cis*-THCs

Of the two *cis*-isomers, that is, *cis*-Δ^1-THC (**3**) and *cis*-Δ^6-THC (**4**) only **3** has been found in the plant and that only recently.[32] The Δ^1-isomer **3** is more thermodynamically stable than the Δ^6-isomer **4**. The former is well characterized, and its formation was observed during some synthetic sequences such as from citral-olivetol reaction (Chart 1.12) as reported by Taylor et al.[30] the carene oxide synthesis (Chart 1.5) by Razdan and Handrick[20] and a total synthesis by Fahrenholtz et al.[16] (Chart 1.13). Recently another synthesis, utilizing olivetol bis(tetrahydropyranyl ether) homocuprate and dehydrolinalool acetate, has been reported by Luteijn and Spronck.[32a]

In contrast, the *cis*-Δ^6-isomer **4** has had a confusing history. The earlier claims[30] regarding its synthesis has not been substantiated,[31] since at one time $\Delta^{4,8}$-iso-THC **18** was erroneously regarded as *cis*-Δ^6-THC (**4**).

*Synthesis of (±)-*cis-Δ^6*-THC*

In 1975 the synthesis of authentic (±)-**4** by three routes was achieved by Uliss et al.[33]

In the first synthesis they utilized the stereospecific intramolecular epoxide cleavage by phenolate anion.[34] Thus (Chart 1.15) epoxidation with *m*-chloroperbenzoic acid at 0° formed **54** from the acetate of (±)-*cis*-Δ^1-THC **53**. Under

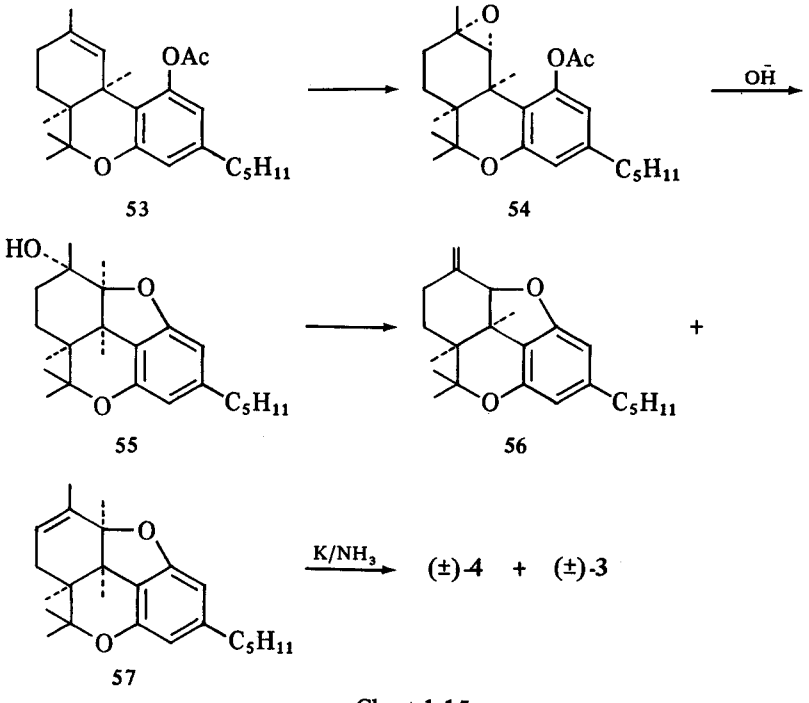


Chart 1.15

basic hydrolytic conditions **54** gave the benzofuran **55** in 90% yield. Dehydration with HMPA (240°, 0.25 h) gave a 3:2 mixture of **57** and **56**. Treatment of this mixture with K/NH_3 gave a mixture of the two *cis*-THCs, which were separated as their acetates by HPLC and subsequently hydrolyzed to give (±)-**4**.

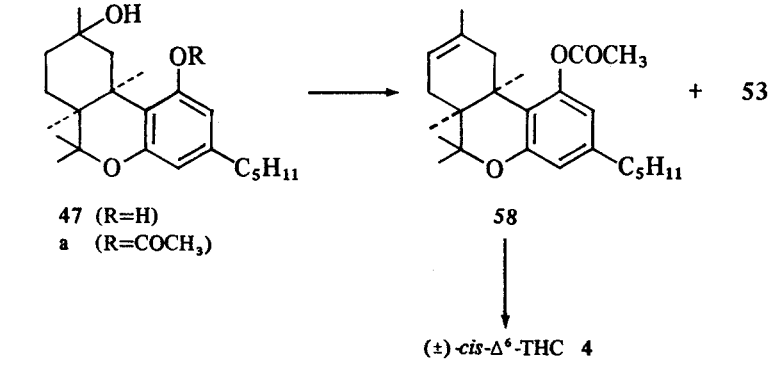


Chart 1.16

In a second synthesis (Chart 1.16), acetylation of the known *cis*-tertiary alcohol **47**[16] gave compound **47a**. Treatment of **47a** with thionyl chloride/pyridine furnished a mixture of **58** and **53** (2:3 by GLC), which was separated by HPLC. **58** was then hydrolyzed to yield (±)-**4**.

It was found that Δ^1-*cis*-THC acetate (**53**) under acid catalysis (*p*-TSA in boiling benzene) provided substantial quantities of the thermodynamically less stable **58** at equilibrium (ratio of 77:23, respectively). This is contrary to results reported in the literature[31b] and constitutes on hydrolysis the third synthesis of (±)-**4**.

*Synthesis of (+)-*cis-Δ^1- *and* Δ^6-*THC's*

Razdan and Handrick[20] had earlier reported a one-step stereospecific synthesis of (−)-Δ^1-THC (**1**) from a carene derivative. In this reaction (Chart 1.5) (+)-*trans*-2-carene oxide (**21**) and olivetol (**6**) in the presence of $BF_3 \cdot Et_2O$ gave a complex mixture containing optically active *trans*- and *cis*-Δ^1-THCs (**1** and **3**). Since separation of these two isomers proved difficult by chromatography on a preparative scale, a chemical reaction sequence was carried out (Chart 1.17) which allowed the separation of the *cis*-isomers from the *trans*-products. It takes advantage of the observation that *trans*-compounds do not undergo the stereospecific intramolecular epoxide cleavage by phenolate anion because of ring strain. On this basis Uliss et al.[35] acetylated the crude mixture and allowed it to react with *m*-chloroperbenzoic acid to presumably give a mixture containing optically active epoxides **54** and **59**. Hydrolysis with base was accompanied by an intramolecular opening of the epoxide ring (as in the racemic case, Chart 1.15), which occurred exclusively with the *cis*-isomer **54**, resulting in the dihydrofuran derivative **55**. After base treatment **55** was easily isolated as a neutral fraction and was then dehydrated, reductively cleaved and purified to give pure (+)-*cis*-Δ^1-THC and (+)-*cis*-Δ^6-THC. The natural *cis*-Δ^1-THC (**3**) has the opposite configuration to Δ^1-THC at C_4.[32]

C. Metabolites of Tetrahydrocannabinols

Extensive literature[3b,3c,36] has appeared in recent years describing the various metabolites of THC's isolated from *in vivo* or *in vitro* studies. These have been carried out on a wide variety of animal species and in some cases different animal organ homogenates have been utilized. Important sites of metabolism of Δ^1- and Δ^6-THCs are shown in Chart 1.18 with a listing of some specific metabolites. The hydroxylation at the 7-position appears to be the major initial point of attack in nearly every species tested including man. This metabolite, 7-hydroxy-Δ^1-THC, is pharmacologically equiactive with Δ^1-THC, and still others are active to different degrees. This has complicated the understanding of

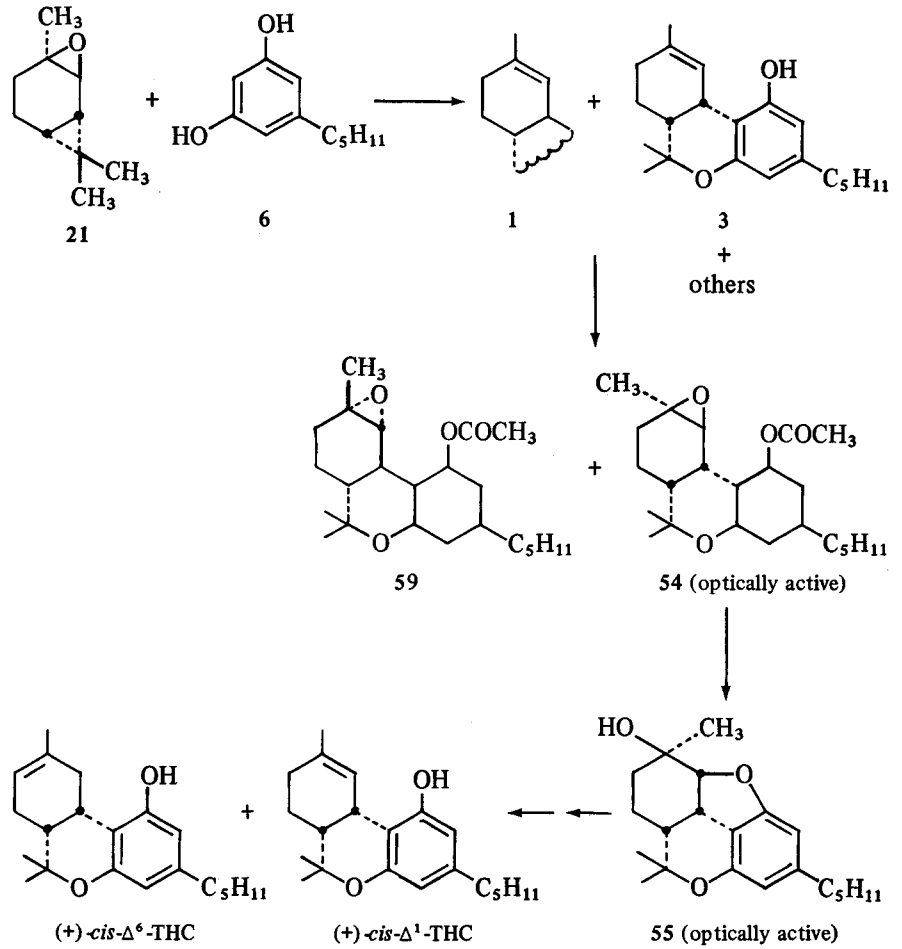
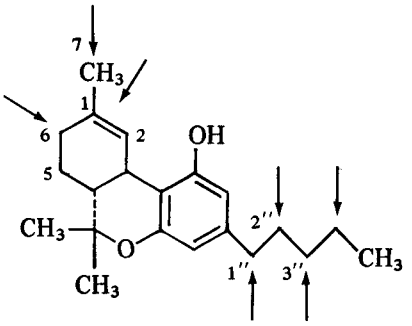


Chart 1.17

marijuana activity in man. The metabolites of Δ^1-THC so far identified in man[37] are shown in Chart 1.19.

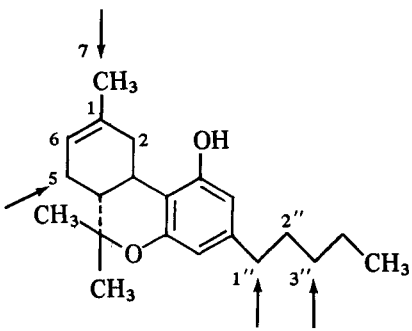
D. Metabolites Functionalized in the Alicyclic Ring

The most important memeber of this class is the 7-hydroxy-Δ^1-THC because it is pharmacologically equiactive with Δ^1-THC. The problems associated with the synthesis of these metabolites in the Δ^1-series are somewhat similar to those



Δ^1-THC

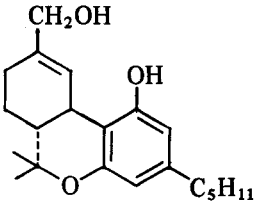
7-hydroxy-Δ^1-THC
6β-hydroxy-Δ^1-THC
6α-hydroxy-Δ^1-THC
6α, 7-dihydroxy-Δ^1-THC
6-keto-Δ^1-THC
1, 2-epoxy-Δ^1-THC
7-carboxy-1''-hydroxy-Δ^1-THC
7-carboxy-2''-hydroxy-Δ^1-THC



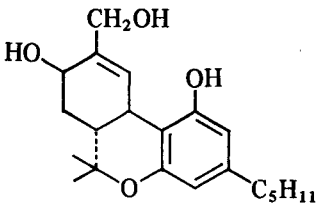
Δ^6-THC

7-hydroxy-Δ^6-THC
5β-hydroxy-Δ^6-THC
5α-hydroxy-Δ^6-THC
5β, 7-dihydroxy-Δ^6-THC
5α, 7-dihydroxy-Δ^6-THC
5-keto-Δ^6-THC
1''-hydroxy-Δ^6-THC
3''-hydroxy-Δ^6-THC

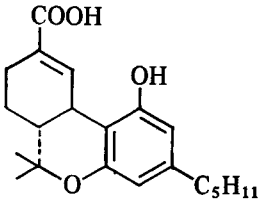
Chart 1.18

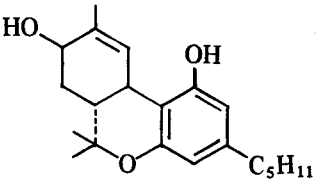


equiactive with Δ^1-THC



6α inactive
6β





6α 1/10th activity
6β 1/4 th activity

Chart 1.19

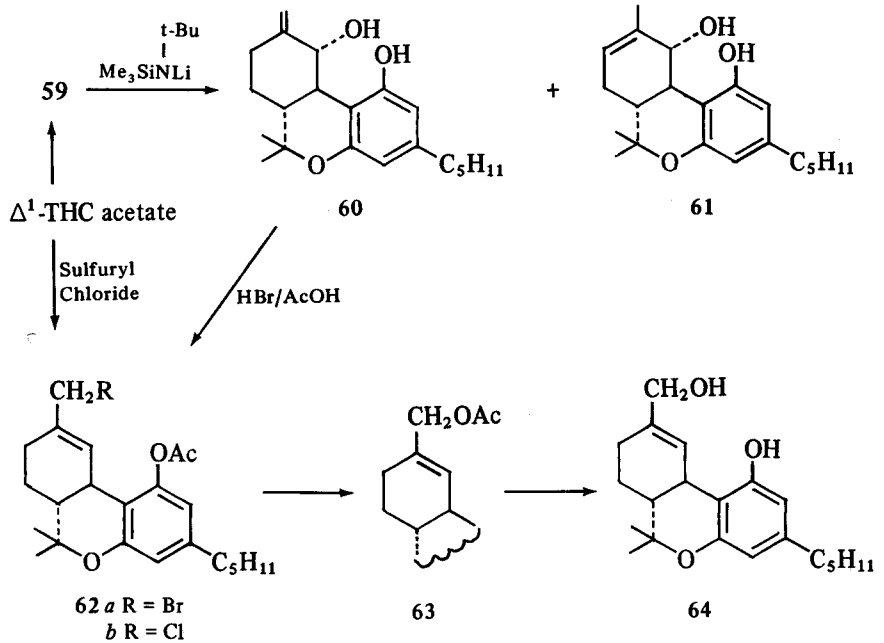
encountered in the synthesis of Δ^1-THC itself as has already been discussed in the Introduction. Thus a number of synthetic procedures that work satisfactorily in the Δ^6 series prove to be inadequate in the Δ^1 series.

7-Substituted Metabolites

A detailed discussion of the Δ^1-metabolites, which result from the natural material Δ^1-THC, is appropriate. Therefore various approaches to the synthesis of 7-hydroxy-Δ^1-THC, the most important member of this class, are described, and in addition some examples in the Δ^6-series are included to illustrate other synthetic strategies.

Δ^1-*Derivatives*

Pitt et al.[38] have developed a regioselective route to some of these metabolites by a base induced epoxide-allylic alcohol rearrangement followed by SN′ displacement. This procedure provides a new method of derivatizing the allylic 7-methyl group of Δ^1-THC and the synthetic sequence to 7-hydroxy-Δ^1-THC **64** from Δ^1-THC (**1**) is shown in Chart 1.20. Δ^1-THC acetate was converted to the known α-epoxide **59** which was isomerized to a mixture of the allylic alcohols **60** and **61** in excellent yield by treatment with the lithium salt of an amine in



62 *a* R = Br
b R = Cl

63

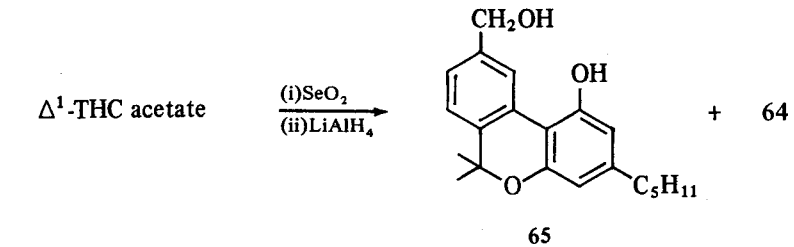
64

Chart 1.20

ether. The ratio of **60**/**61** was controlled by the size of the substituent on the amine. Thus the use of Me_3SiNH-*t*-Bu gave the best yield of **60**, which was converted to **62a** by 5% HBr/AcOH taking advantage of the thermodynamically controlled SN′ isomerization of allylic bromides. Acetolysis with tetramethyl ammonium acetate in acetone followed by reduction with $LiAlH_4$ converted **62a** to the desired metabolite **64** in ∿20% yield. In an alternative procedure[38] the phenol in **60** was selectively protected as ethoxymethyl ether and then treated with $SOCl_2$/Py to give the corresponding 7-chloro derivative. Acetolysis as before, followed by acid-catalyzed removal of the acetyl and ethoxymethyl groups formed the metabolite **64**. The yield was not as good as in the other procedure.

Direct allylic halogenation or oxidation of Δ^1-THC acetate has also been carried out, but the yields have been unsatisfactory mainly because of the lack of selectivity of attack at the primary and secondary allylic sites of Δ^1-THC. Pitt et al.[39] reported that treatment of Δ^1-THC acetate with sulfuryl chloride (Chart 1.20) gave a mixture containing **62b**, which, with silver acetate in acetic acid followed by hydrolysis with base, formed **64** albeit in poor yield (5%). The other metabolite 6β-hydroxy-Δ^1-THC was also isolated (14%) from this synthesis. Reagents like *N*-chloro- and *N*-bromosuccinimide, predominantly halogenate in the C-6 position, and these have been utilized in the synthesis of various 6-substituted metabolites.

Ben-Zvi et al.[40] reported the SeO_2 oxidation of Δ^1-THC acetate (Chart 1.21) followed by reduction with $LiAlH_4$ to give **64** in poor yield (1%), the main product being 7-hydroxycannabinol (**65**). This procedure has proved more successful in Δ^6-series (Chart 1.25).



65

Chart 1.21

In a different approach, Razdan et al.[41] (Chart 1.22) oxidized the exocyclic double bond of (−)-$\Delta^{1(7)}$-THC acetate (**66**) with *m*-chloroperbenzoic acid to the epoxide **67**, which was hydrolyzed (basic conditions were used to avoid forming the Δ^6-dehydration products) with 0.3N KOH/DMSO to form the triol **68**. After acetylation, the diacetate alcohol **69** was treated with $SOCl_2$/Py to give a

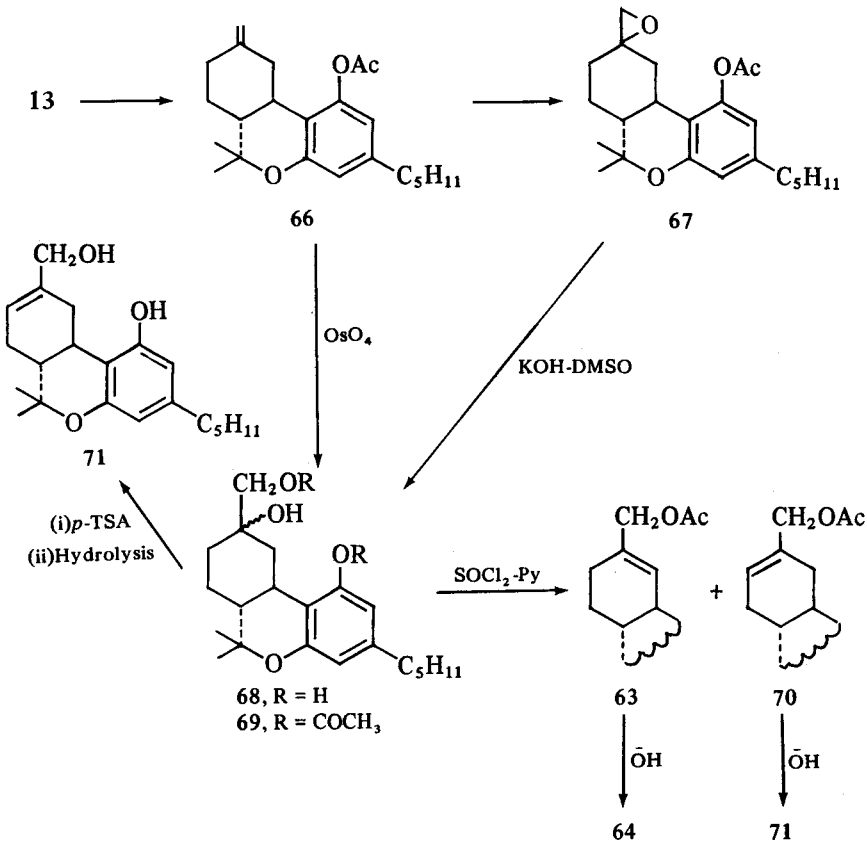


Chart 1.22

mixture of the two metabolites as their diacetates **63** and **70**. These were separated by HPLC and then hydrolyzed with base to yield 7-hydroxy-Δ^1-THC (**64**). The overall yield of **64** from $\Delta^{1(7)}$-THC (**13**) was 13%. Alternatively **69** was obtained from **66** by hydroxylation of the exocyclic double bond with OsO_4 in ether followed by acetylation. These syntheses were developed because **13** became available in large quantities from the kilogram synthesis of Δ^1-THC (see Chart 1.3).[17,18] The intermediate **69** also provided a facile route to the 7-hydroxy-Δ^6-THC **71**.[42] This was achieved by treatment with *p*-TSA followed by hydrolysis in an overall yield of 75% from **13**.

Uliss et al.[43] have recently reported a versatile route to 7-substituted Δ^1-THCs from the novel synthons **75a** and **75b**. This scheme (Chart 1.23) is based on the principal of reversal of reactivity of carbonyl compounds when masked as dithioacetals (i.e., umpolung). Interestingly, this route has resulted in the synthesis of

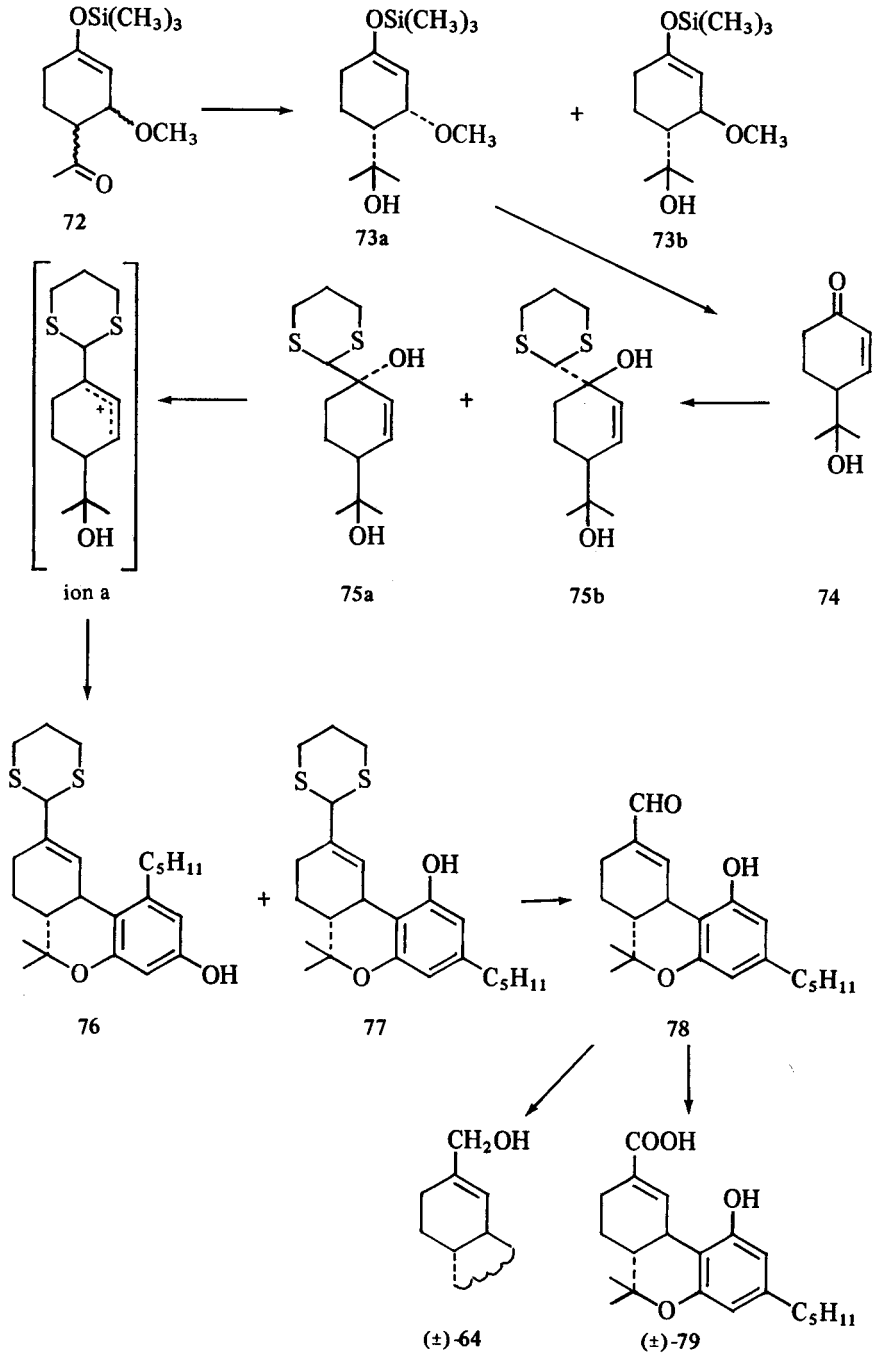
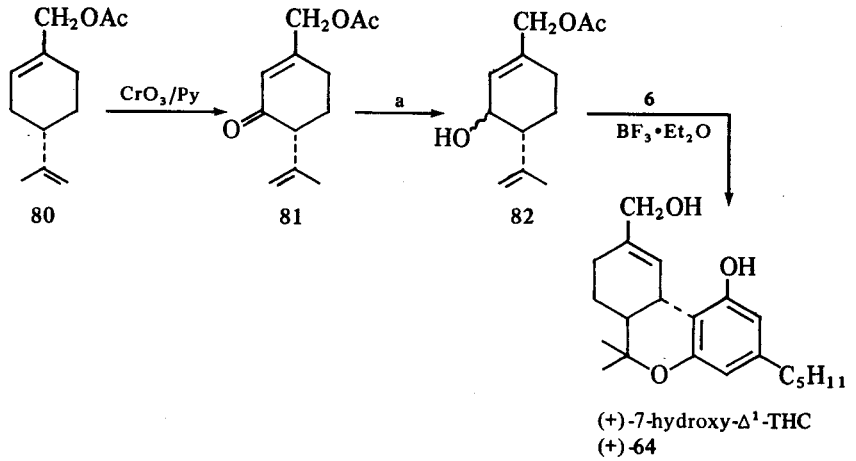

OSi(CH3)3
OCH3
O
72
OSi(CH3)3
OCH3
OH
73a
+
OSi(CH3)3
OCH3
OH
73b
O
OH
74
S
S
OH
75a
+
S
S
OH
75b
S
S
+
OH
ion a
S
S
C5H11
OH
76
+
S
S
OH
C5H11
77
CHO
OH
C5H11
78
CH2OH
(±)-64
COOH
OH
C5H11
(±)-79

Chart 1.23

Δ^1-derivatives specifically, since by introduction of the dithiane moiety into the THC structure, isomerization of the normally labile Δ^1 unsaturation to the Δ^6 isomer is effectively inhibited. The synthons **75a** and **75b** were readily obtained by carrying out a Grignard reaction on the Diels-Alder adduct **72**, thus extending the usefulness of Danishefsky's novel Diels-Alder diene.[44] This was followed by hydrolysis of the mixture (**73a** + **b**) to **74** with CCl_3COOH and addition of the Li anion of 1,3-dithiane to **75**. Treatment with olivetol (**6**) in the presence of *p*-TSA gave a mixture of Δ^1-compounds **76** and **77**, which was separated. The dithiane masking group in **77** was readily removed by $HgO/BF_3 \cdot Et_2O$ to give the metabolite (±)-**78**.[45] This was converted by $LiAlH_4$ reduction to the metabolite (±)-**64** or oxidized with MnO_2/CH_3OH containing acetone cyanohydrin, to the metabolite (±)-**79**.[38]

(−)-Perillyl aldehyde was converted into perillyl alcohol acetate (**80**) and then to **82** via **81**. On condensation with olivetol Lander et al.[46] obtained the (+)-7-hydroxy-Δ^1-THC (Chart 1.24) in low yield.



80 81 82

(+)-7-hydroxy-Δ^1-THC
(+)-**64**

Reagents: (a) lithium hydridotri-*t*-butoxyaluminate

Chart 1.24

Δ^6-Derivatives

In the case of 7-substituted Δ^6- derivatives the syntheses in general are more straightforward. Thus as described earlier (Chart 1.22) 7-hydroxy-Δ^6-THC (**71**) is prepared[41] in excellent yield from $\Delta^{1(7)}$-THC (**13**). Oxidation of Δ^6-THC acetate (Chart 1.25) with SeO_2 under controlled conditions followed by acetylation gives directly the 7-acetoxy-Δ^6-THC acetate (**70**), which on reduction provides the metabolite **71**.[40] By slightly changing the oxidation conditions and

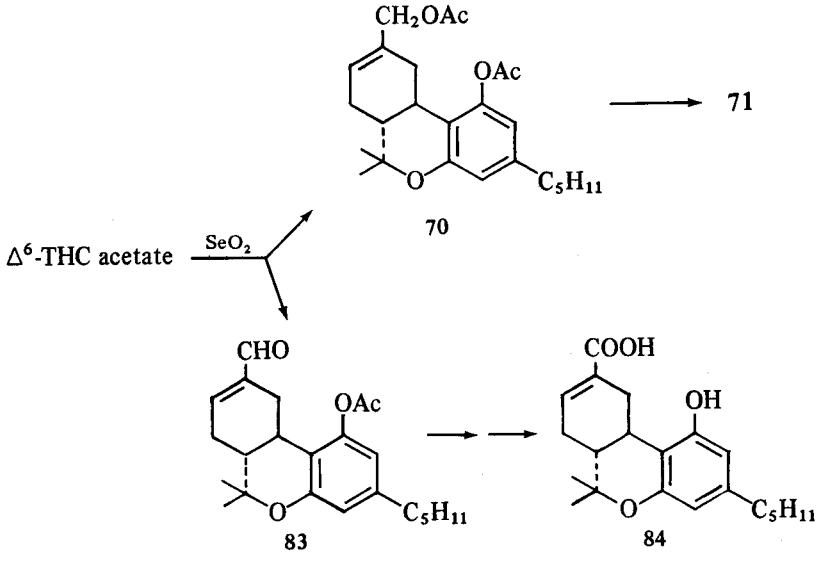


Chart 1.25

refluxing Δ^6-THC acetate with SeO_2 for a prolonged period in ethanol, the aldehyde **83** is isolated.[47,48] On further oxidation with MnO_2/NaCN in CH_3OH followed by hydrolysis **83** was converted to the metabolite **84**.[47] These reactions of Δ^6-THC acetate with SeO_2 are in contrast to similar oxidation of Δ^1-THC acetate (cf. Chart 1.21).

In other syntheses of 7-hydroxy-Δ^6-THC (**71**), the epoxide **85** of Δ^6-THC acetate with $HClO_4$ gave **86** (Chart 1.26), which after acetylation and dehydration ($SOCl_2$/Py) formed **87**. After hydrolysis and allylic rearrangement **87** was converted to the metabolite **71**.[3b]

The base-induced epoxide-allylic alcohol rearrangement was applied by Petrzilka and Demuth[49] on **88** to give a mixture of allylic alcohols **89** (Chart 1.27). These were acetylated after removal of the tetrahydropyranyl (THP) protecting group to give **87** and then subjected to allylic rearrangement and reduction to form **71**. The allylic alcohols **89** were also obtained from Δ^6-THC acetate by a photochemical rearrangement followed by reduction.

A direct conversion of $\Delta^{1(7)}$-THC acetate **66** to 7-bromo-Δ^6-THC acetate (**90**) was achieved by Weinhardt et al.[50] by using *N*-bromoacetamide in the presence of 70% $HClO_4$. Treatment with silver acetate/AcOH gave **70**, which on alkaline hydrolysis furnished **71** (Chart 1.28).

The metabolites **84** and **71** were also synthesized by Pitt et al.[39] from **91** (Chart 1.29), which has been previously prepared by Wildes et al.[51] The morpho-

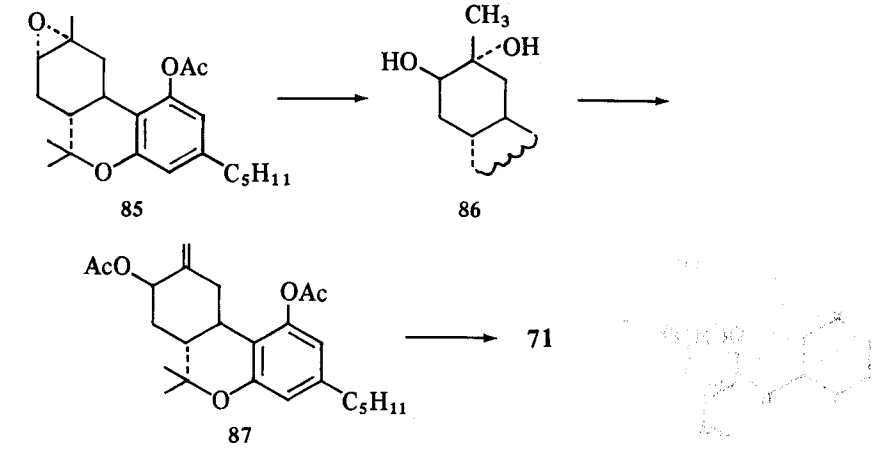
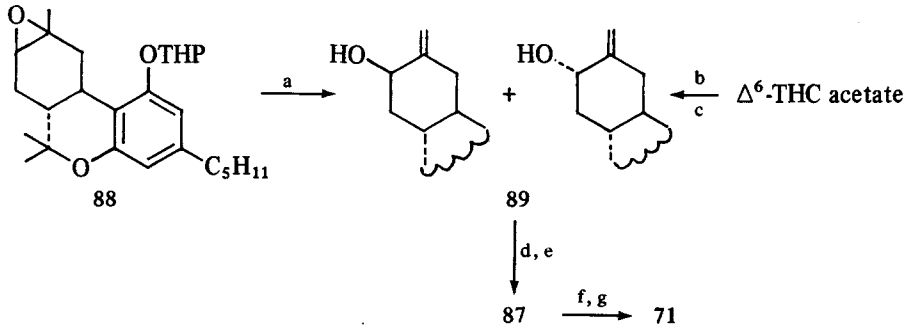


Chart 1.26



Reagents: (a) BuLi (b) irradiation, O_2-sensitizer (c) $NaBH_4$
(d) H^+ (e) Ac_2O-Py (f) Δ, 290°C (g) $LiAlH_4$

Chart 1.27

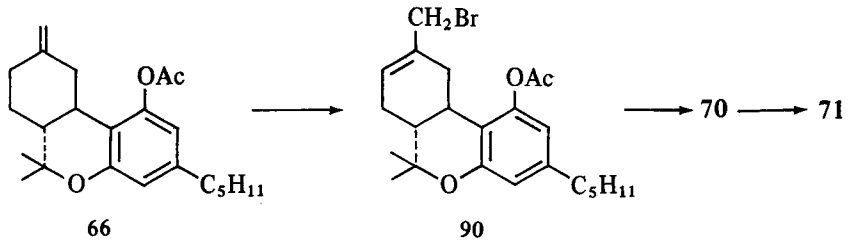


Chart 1.28

linoenamine of **91** treated with CCl_3COOH gave the α-chloramide **92**. After removal of the benzyl protecting group and conversion to the phenoxide anion to eliminate HCl, only the Δ^6-amide **93** was obtained. Saponification of **93** gave the metabolite **84**, which was reduced with $LiAlH_4$ to **71**.

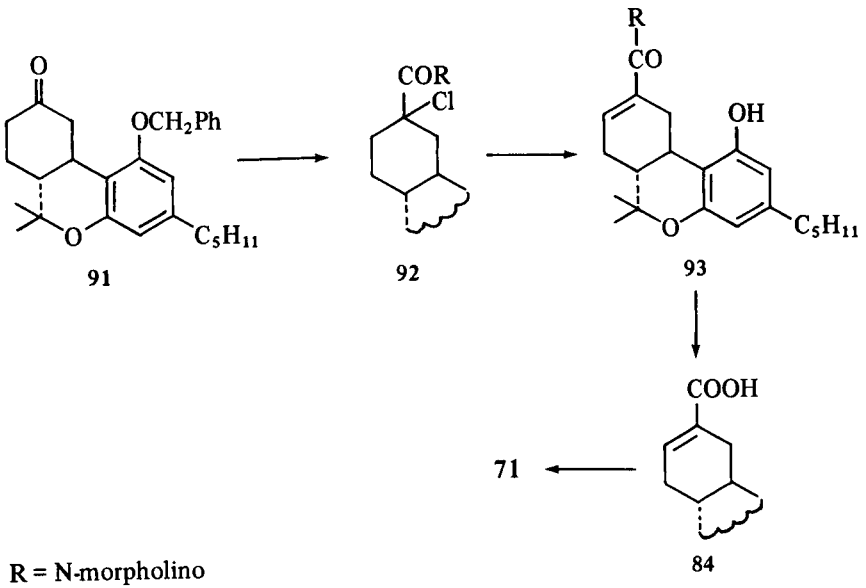


Chart 1.29

6-Substituted Metabolites

The 6α- and 6β-hydroxy-Δ^1-THC's are two metabolites that have been identified in man. The latter, **95**, was directly prepared (Chart 1.30) by bromination of Δ^1-THC acetate with *N*-bromosuccinimide[38] or sulfuryl chloride[39] followed by acetolysis and hydrolysis. The 6α-metabolite **97** was prepared[38] from **95** by selective acetylation of the phenolic group and MnO_2 dioxide oxidation to **96** followed by $LiAlH_4$ reduction to **97**. It is interesting to note that **96** was also obtained[52] by SeO_2 oxidation of Δ^1-THC acetate (cf. Chart 1.21).

5-Substituted Metabolites

The metabolites[53] known in this class were synthesized[52] from Δ^6-THC acetate as shown in Chart 1.31. Oxidation with *t*-butylchromate gave **98**. It was reduced with $LiAlH_4$ to give a mixture of the 5α- and 5β-hydroxy-Δ^6-THCs, **99** and **100**, respectively. These were isolated by chromatography.

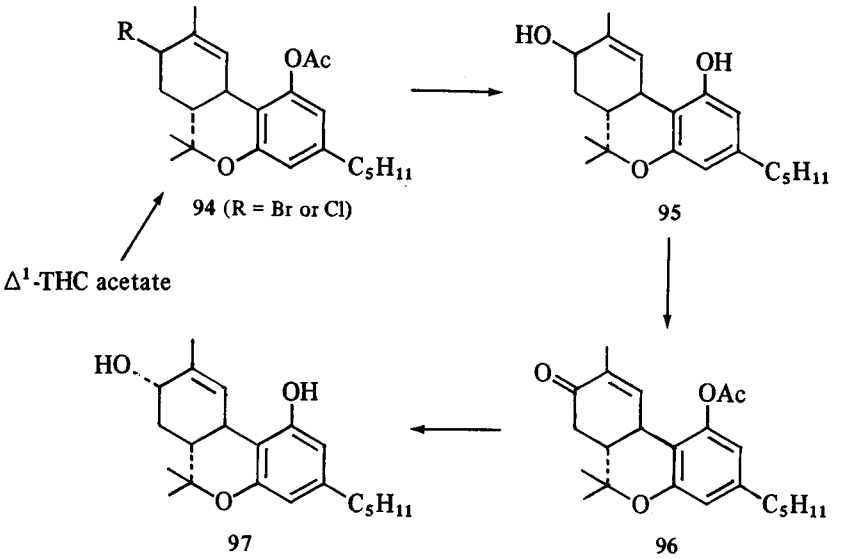


Chart 1.30

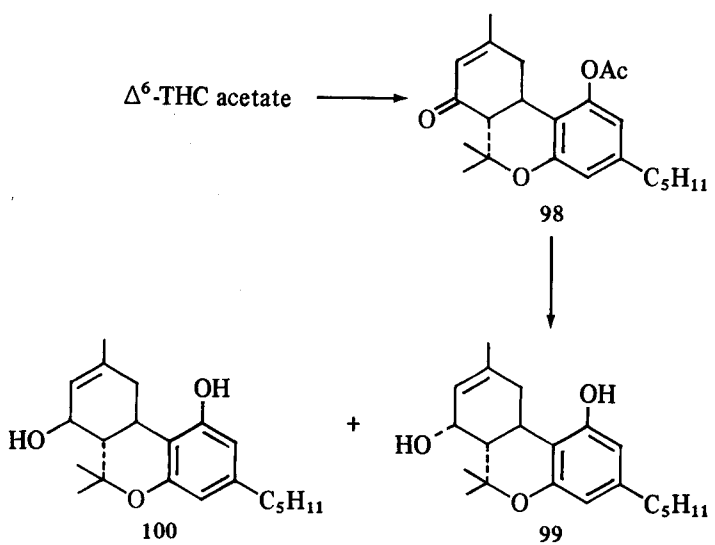


Chart 1.31

Other Metabolites

The two dihydroxy metabolites **103** and **104** have been found in humans[37a] and were synthesized by Pitt et al.[38] Δ^6-THC epoxide **85** (Chart 1.32) on treatment with BuLi rearranged to **101** as a 1:1 mixture of epimers at C-6. Diacetylation of **101** and treatment with OsO_4 gave **102** (R = H). Acetylation of the primary 7-hydroxyl group of **102**, dehydration with $SOCl_2$/Py followed by saponification gave **103** and a lesser amount of **104**. The latter was obtained in much better yield by using the same hydroxylation-dehydration sequence with 7-hydroxy-Δ^6-THC (**71**).[38]

Gurney et al.[53] reported the isolation of 1,2-epoxyhexahydrocannabinol as a metabolite from an *in vitro* preparation of squirrel monkey tissue. It was synthesized from Δ^1-THC acetate by epoxidation with *m*-chloroperbenzoic acid.[52,53] This metabolite has also been identified in *in vitro* preparations of dog tissue.[54]

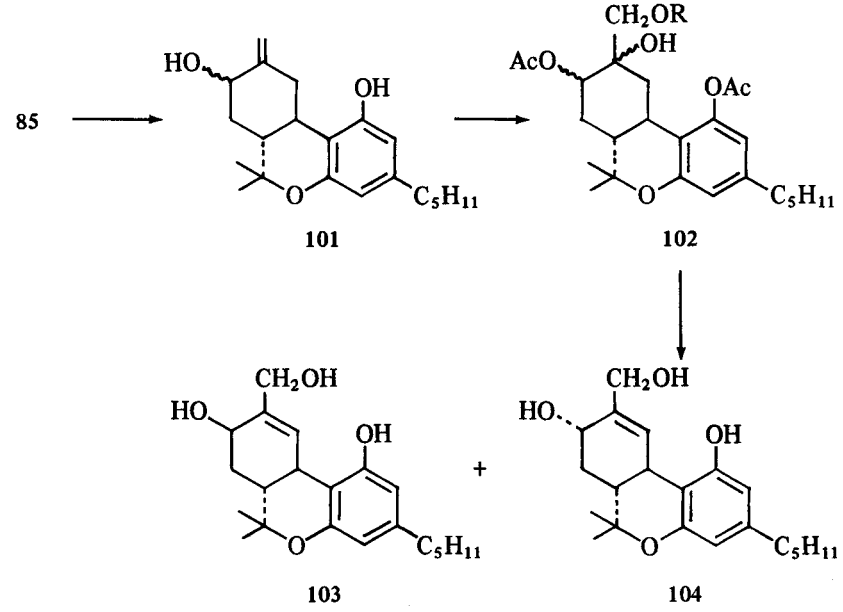


Chart 1.32

E. Metabolites Functionalized in the Aromatic Ring

The *n*-pentyl side chain of the aromatic ring is the main site of metabolic attack.[55] Thus Δ^1-THC, cannabidiol, and cannabinol give microsomal hydroxylations at carbons 1″-5″. In addition carboxylic acid metabolites, formed by oxidative cleavage of the side chain, have also been identified.[56]

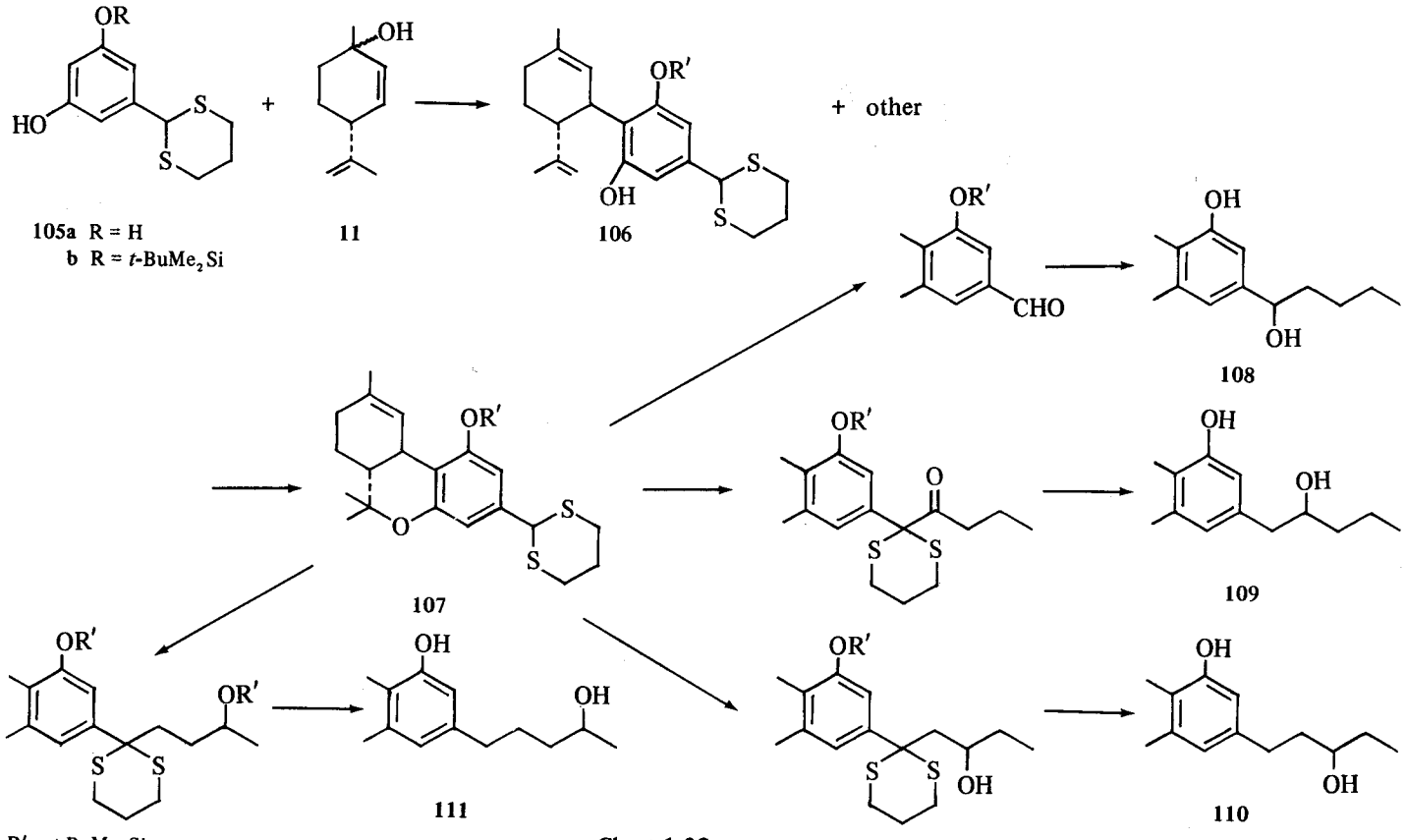
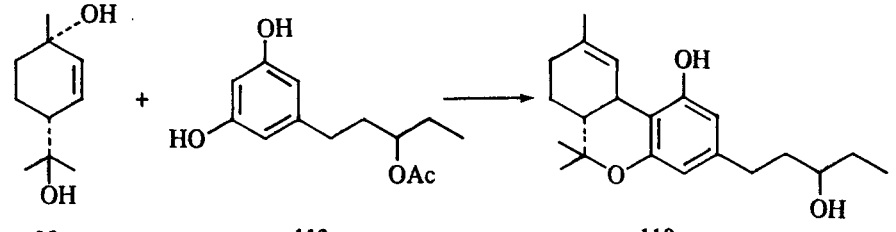

OR
HO
S
S
+
OH
OR′
OH
S
S
+ other
105a R = H
b R = t-BuMe2Si
11
106
OR′
CHO
OH
OH
108
OR′
O
S
S
OH
OH
109
107
OR′
OR′
S
S
OH
OH
111
OR′
S
S
OH
OH
110
R′ = t-BuMe2Si

Chart 1.33

Until very recently none of the Δ^1-THC metabolites hydroxylated at the *n*-pentyl side chain had been synthesized. Pitt et al.[57] have now reported an elegant general synthesis of side-chain derivatives of Δ^1-THC as shown in Chart 1.33. The poorly soluble resorcinol derivative **105a** was made more soluble in organic solvents by converting it to **105b**. This was best achieved by quantitative conversion to the diether and then selective monodesilylation with fluoride ion. Condensation of **105b** with *p*-mentha-2,8-dien-1-ol (**11**) in $CH_2Cl_2/BF_3 \cdot Et_2O/MgSO_4$, using the procedure of Razdan et al.[19] (Chart 1.4), the cannabidiol analog **106** was obtained together with other compounds. Treatment of this mixture with $BF_3 \cdot Et_2O/CH_2Cl_2$ at $-20°$ for 48 h gave the Δ^1-analog **107**, which was purified by chromatography. This key intermediate **107** was then converted to the various side-chain hydroxylated Δ^1-THCs.

It is interesting to note that Razdan et al.[58] had previously reported the reaction of the five-membered heterocyclic analog of **105a** [i.e., 2-(3′,5′-dihydroxyphenyl)-1,3-dithiolane] with **11** in benzene/*p*-TSA and found that the Δ^6-analog was formed (see Chart 4.4). It appears that the reaction products are very sensitive to structure and/or reaction conditions in cannabinoids.

The specific synthesis of the metabolite **110** was also achieved (Chart 1.34) recently by Handrick et al.[22] by the preparation and condensation of 3′-acetoxyolivetol (**112**) with the monoterpene *p*-menth-2-ene-1,8-diol (**25**). They essentially demonstrated the usefulness of this synthon (**25**, Chart 1.7) for the synthesis of Δ^1-THC and its metabolites by preparing **110**. 3″-Hydroxy-Δ^1-THC (**110**) was also reported to be about 3 times more active than Δ^1-THC in preliminary pharmacological tests in mice.[22] Christie et al.[58a] reported the synthesis of (±)-**110** by condensing 1-(3,5-dihydroxyphenyl)pentan-3-one ethylene thioacetal with citral in the presence of $BF_3 \cdot Et_2O$ followed by removal of the thioacetal and reduction with $NaBH_4$.



25 112 110

Chart 1.34

The synthesis in the Δ^6-series is generally carried out (Chart 1.35) by condensing the appropriate resorcinol or a suitable thioketal derivative thereof, with the monoterpene *p*-menthadienol[59] **11** or verbenol[55a] **5**. The direct coupling of

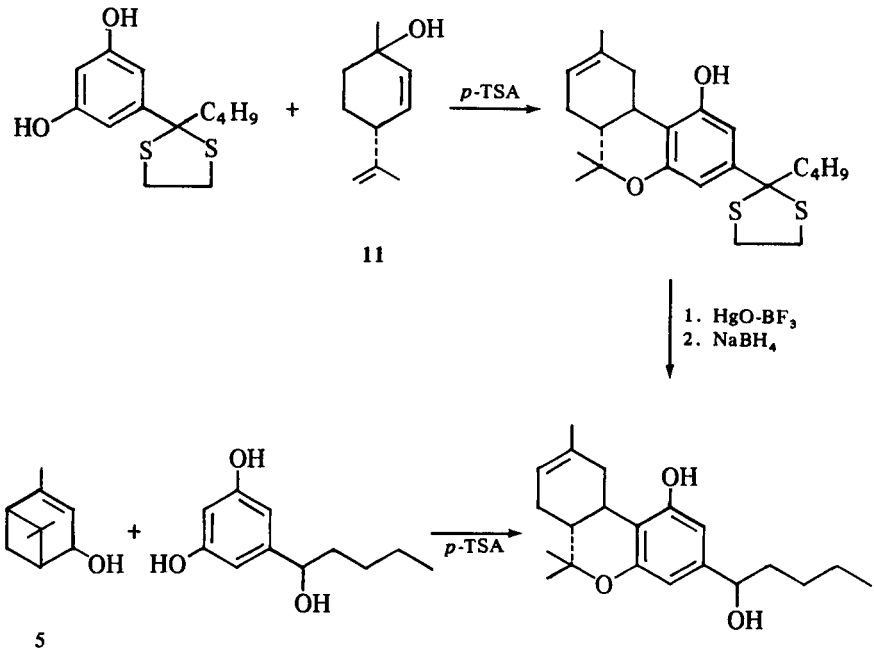


Chart 1.35

1′- or 3′-hydroxyolivetol or 1′- or 3′-oxoolivetol with **11** failed but worked as their thioketal derivatives.[59]

Recently Lotz et al.[60] have reported that resorcylalkyl esters directly condense with *p*-menthadienol **11** to give the corresponding Δ^6-THC derivatives. These on $LiAlH_4$ reduction provide Δ^6-THC analogs with a hydroxyl group, substituted on the terminal carbon of the aromatic side chain. The 5″-hydroxy-Δ^6-THC was synthesized using this procedure.

In the Δ^6-THC series the biological activity has been shown to vary with the position of the hydroxyl group in the pentyl side chain. The order of activity[55] is 3″- > 4″- > 2″- > 1″-hydroxy-Δ^6-THC. Full details of this work have now been published.[55a]

3. SYNTHESIS OF OTHER THCS AND RELATED CANNABINOIDS

In this section the synthetic approaches to some of the "unnatural" THC's and the important cannabinoids that occur in the plant *Cannabis sativa* L. will be discussed.

A. "Unnatural" THCs

(-)-$\Delta^{1(7)}$-THC (**13**, Chart 1.3) was isolated during Petrzilka's dehydrochlorination procedure by Razdan et al.[18] It was also produced by photoisomerization of Δ^6-THC[42] and by dehydrochlorination of 1-chlorohexahydrocannabinol methyl ether with a bulky base followed by demethylation of the ether with potassium thiophenoxide.[51]

Cardillo et al.[61] reported a synthesis (Chart 2.1) of cannabidiol (**12**) from *p*-mentha-1,8-dien-3-ol (**113**) and olivetol (**6**) in aqueous acid. These mild condensation conditions were applied in the preparation of "unnatural" Δ^4-THC derivatives. Thus *p*-menth-4-en-3-ol (**114**) and olivetol gave **115**, which formed the novel cannabinoid **116**. This procedure led to the synthesis of Δ^4-THC (**118**) by the condensation of olivetol with *p*-menth-4-ene-3,8-diol (**117**).[62]

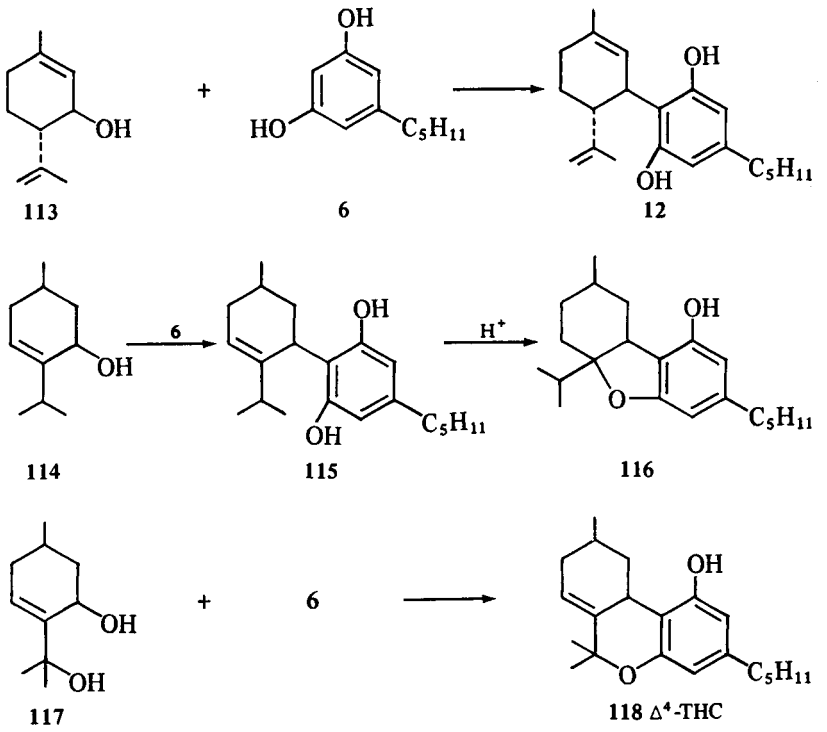
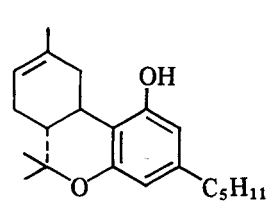
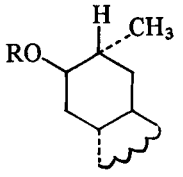


Chart 2.1

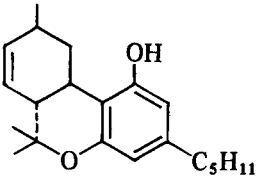
Δ^5-THC (**120**), another "unnatural" THC, was synthesized[63] (Chart 2.2) by hydroboration of Δ^6-THC to give **119a**, which was tosylated to **119b** and then treated with K-*t*-butoxide in benzene.



Δ^6-THC

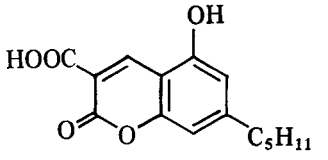


119a R = H
b R = Ts

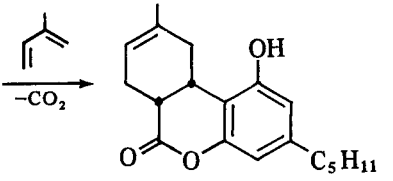


120 Δ^5-THC

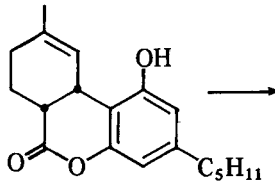
Chart 2.2



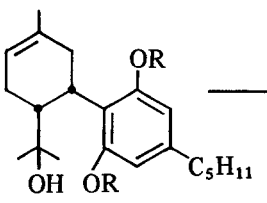
121



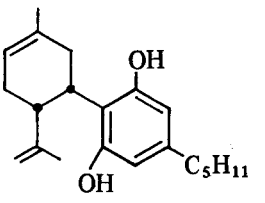
122



123

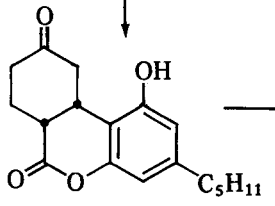


124a, R = H
b, R = Ac



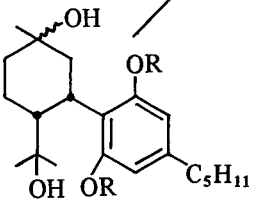
125

42

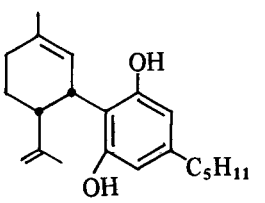


127

1. $SOCl_2$-Py
2. $\bar{O}H$



128a R = H
b R = Ac



126

Chart 2.3

B. Cannabidiols

(-)-Cannabidiol (12, Chart 1.3) is one of the major constituents of the plant. The natural material has a 3,4-*trans* ring junction with a double bond at the Δ^1 position. As discussed earlier, it was synthesized from *p*-menthadienol **11** by the Petrzilka procedure[15] (Chart 1.3) or by the modification of Razdan et al.[19] of Petrzilka's procedure (Chart 1.4). It is also prepared as shown in Chart 2.1 and by condensing **11** and olivetol in the presence of wet *p*-TSA.[19] For the synthesis of (±)-cannabidiol see Charts 1.10 and 1.11.

The Δ^6-isomer of cannabidiol is not known. The two Δ^1- and Δ^6-cannabidiols with a 3,4-*cis* junction are "unnatural" and were synthesized (Chart 2.3) recently by Handrick et al.[64] Thus lactone **122** was prepared from isoprene and **121** by a Diels-Alder reaction accompanied by decarboxylation.[64,65] Reaction of **122** with CH_3MgI gave the triol **124a**; its diacetate **124b** was dehydrated with $SOCl_2$/Py and then saponified to give (±)-Δ^6-3,4-*cis*-cannabidiol **125**. The Δ^1-isomer **126** was obtained by equilibrating the lactone **122** to a 1:1 mixture of **122** and **123**. The identical procedure then gave a mixture of Δ^6- and Δ^1-*cis*-cannabidiol diacetates. These were easily separated by HPLC and the Δ^1-isomer was saponified to give **126**. In an alternative synthesis by Handrick et al.[64] the keto lactone **42** (Chart 1.14) was ketalized, reduced with Raney nickel at high pressure,[16] and hydrolyzed to give **127**. Reaction with CH_3MgI furnished the tetrol **128a**. Its acetate **128b** was dehydrated and then saponified to form **125**.

C. Cannabinol

This was one of the first cannabinoids to be synthesized in early 1940, as it established the basic skeleton of the THC structure. Δ^1-THC is readily oxidized to cannabinol on exposure to air.[18]

The first synthesis (Chart 2.4) by Adams et al.[66] condensed **129** with dihydroolivetol **130** to form the pyrone **131** which on dehydrogenation gave **132**. Grignard reaction followed by acid treatment furnished cannabinol **136**. It is interesting to note that a similar reaction of **129** with olivetol (**6**) formed the "abnormal" isomer of **132** resulting from an attack on the 4 position of olivetol.[67]

In a different approach, based on Pechmann condensation, both the British[68] and American groups[69] independently arrived at the synthesis of cannabinol using the same sequence. Thus the keto ester **133** and olivetol formed the pyrone **134**, which on treatment with CH_3MgI, followed by acid treatment, gave Δ^3-THC (**135**). Sulfur dehydrogenation converted **135** to cannabinol. Both groups discovered that the physiological activity of Δ^3-THCs was similar to the natural material. The American group led by Roger Adams carried out extensive structure activity work in this series, which formed the basis for drug develop-

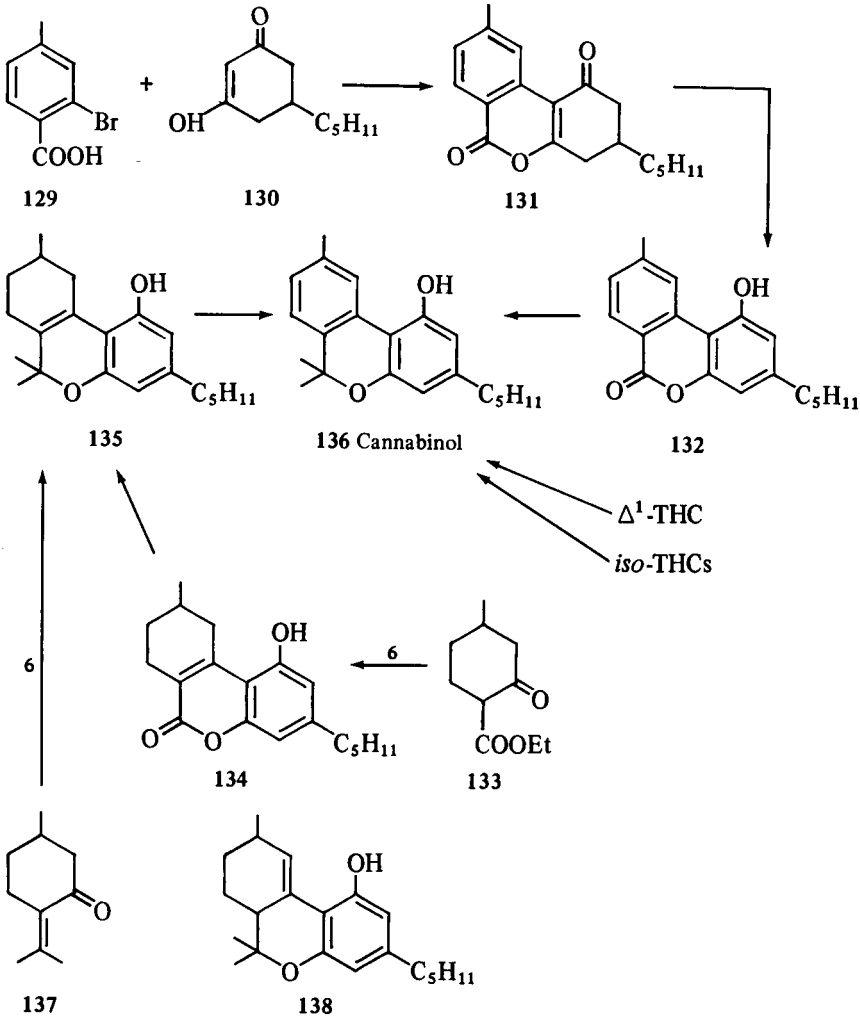


Chart 2.4

ment in cannabinoids during the late 1960s. This particular aspect will be discussed in a later section. The Pechmann condensation was reinvestigated by Claussen and Korte[70] and they isolated from this reaction the other isomer Δ^2-THC (138).

Another synthesis of cannabinol was achieved from pulegone (137) by both Adams et al.[71] and Ghosh et al.[72] (Chart 2.4). Cannabinol is also formed easily

by chloranil dehydrogenation of Δ^1-THC.[73] In contrast, Δ^6-THC and *cis*-Δ^1-THC do not form cannabinol. This has been explained on the basis of stereoelectronic factors.[73] The various iso-THCs are easily converted to **136**.[31b]

D. Cannabinoid Acids[3]

They form an important group of compounds present in the plant.[3] These acids are inactive by themselves but are readily decarboxylated on heating (smoking) or on GLC to the parent active THCs. The two methods which have been developed for their synthesis are shown in Chart 2.5. Methyl magnesium carbonate (MMC) carboxylated Δ^1-THC. Similarly cannabidiolic acid and cannabigerolic acid were synthesized. Petrzilka's procedure[15] was used to prepare **141**, but the acid itself could not be isolated, as during hydrolysis it decarboxylated to give **12**.

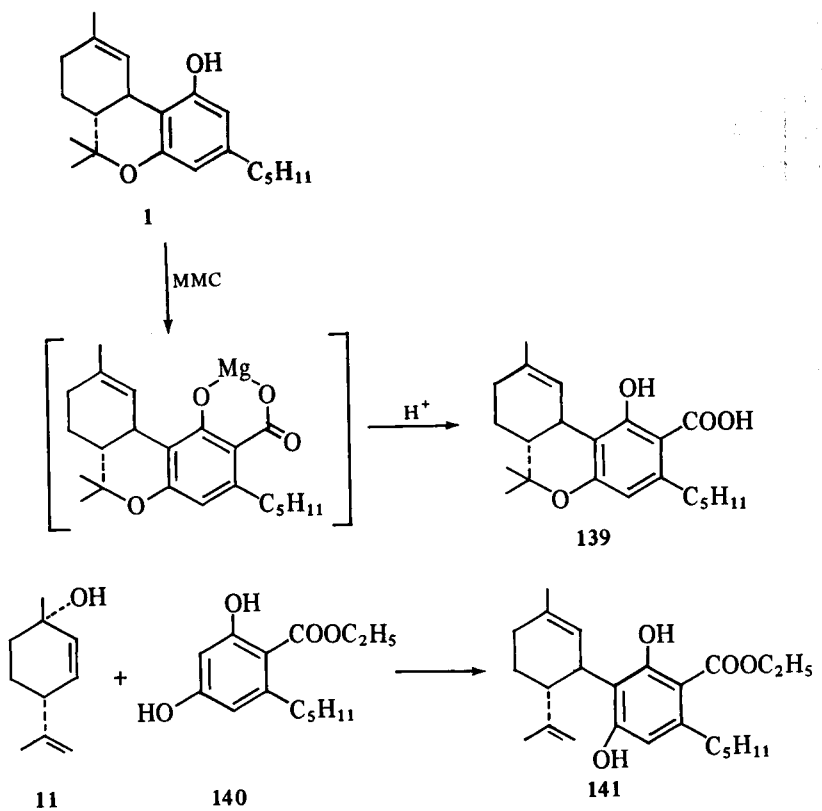
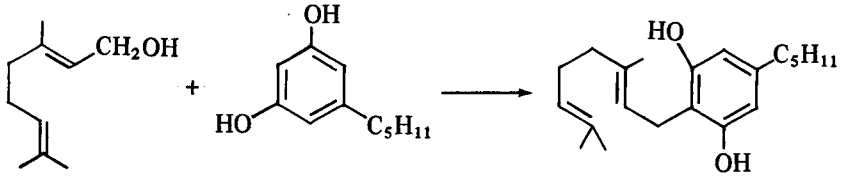


Chart 2.5

E. Cannabigerol

It is a minor constituent of the plant and was synthesized by condensation of geraniol with olivetol in the presence of *p*-TSA in CH_2Cl_2.[75] It was also prepared by a direct aklylation of ethoxycarbonyl olivetol with geranyl bromide followed by hydrolysis.[76]



Geraniol Olivetol Cannabigerol
142

F. Cannabichromene

It was previously considered to be a minor constituent of the plant, but recent advances in analytical techniques have established that it is no longer a minor cannabinoid. In fact in some variants it is more abundant that cannabidiol.[77] Two main approaches to the synthesis of cannabichromene have been reported (Chart 2.6). One is based on the dehydrogenation of cannabigerol (**142**) with chloranil[73] or dichlorodicyanobenzoquinone.[76] With both these reagents the reaction probably proceeds via hydride abstraction but the *O*-quinone methide intermediate **143** has also been proposed.[76] The other synthesis of **144** was simultaneously and independently reported by Crombie and Ponsford[78] and Kane and Razdan.[79] These two groups achieved a one-step total synthesis of cannabichromene **144** and cannabicyclol (**148**) by heating citral (**36**) and olivetol (**6**) in the presence of pyridine. From this reaction the tetracyclic ether (**147**, also called "cannabicitran") and iso-THCs were also isolated. They showed that the reaction between substituted resorcinols or phloroglucinol and citral in pyridine to form ethers of type **147** is a general one which leads to substituted iso-THC derivatives.[78b,79b] The most likely mechanism[78b,80] for the pyridine catalyzed reaction appears to be the initial condensation to **145** followed by cyclization to cannabichromene (**144**). This can either form cannabicyclol (**148**) or proceed via an intramolecular [2 + 4] cycloaddition within a quinone-methide tautomer **146** of the phenol, to **147**. The mechanism of the cyclization of **144** to **147** was previously considered to be ionic but Crombie and co-workers[81] have now shown it to be electrocyclic.

The yield of cannabichromene from citral reaction has been improved by using *t*-butylamine in place of pyridine and refluxing the mixture in toluene.[82]

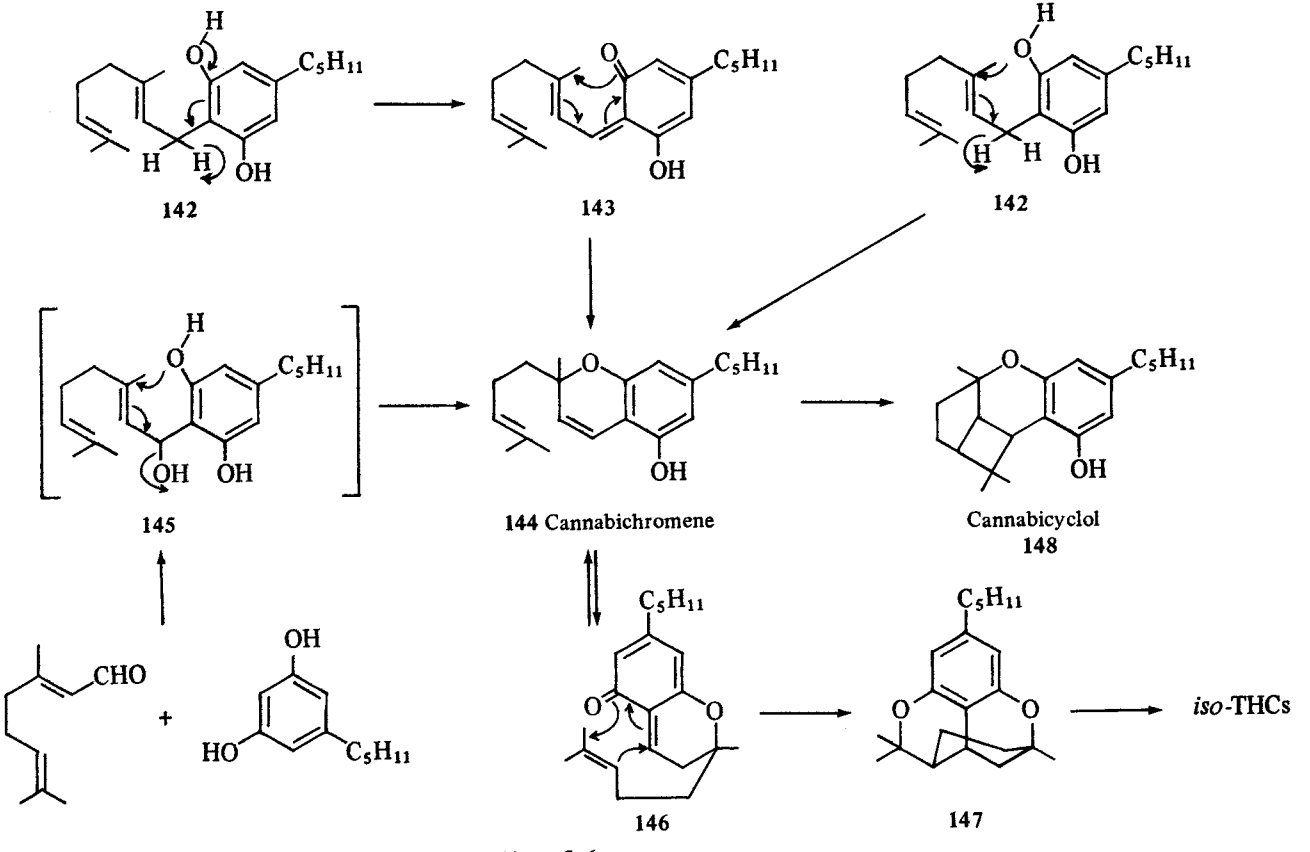

142
143
142
145
144 Cannabichromene
Cannabicyclol
148
146
147
iso-THCs

Chart 2.6

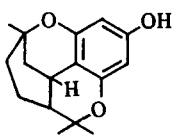
G. Cannabicyclol

It is a very minor compound of the plant and was initially assigned structure **149**. Crombie and Ponsford[78a] revised the structure to **148** mainly on the basis of NMR spectrum where the C-3 proton appears as a doublet being coupled to one proton only. This structure has since been firmly established on the basis of X-ray results published by Begley et al.[83] However, reading their paper gives the incorrect impression that we (Kane and Razdan)[79a] preferred the original structure **149** for cannabicyclol in spite of conclusive evidence. These authors placed our work completely out of context and ignored the fact that most of the evidence they gave appeared after the publication of our paper.[79a] This clarification* is necessary, as it can be misleading, particularly to those unfamiliar with the field.

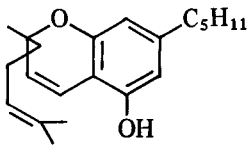
The first synthesis of cannabicyclol was achieved by the pyridine catalyzed condensation of citral and olivetol as described before (Chart 2.6). Treatment of **144** with either $BF_3 \cdot Et_2O$[84] or photolysis in the presence of a sensitizer[85] (*t*-butanol-acetone) also formed cannabicyclol.

*In 1968 when Crombie and Ponsford's paper[78a] appeared, in which they had suggested a revision of cannabicyclol structure from **149** to **148**, our paper[79a] had already been submitted and in a footnote we suggested "that in the absence of further experimental data the structure and stereochemistry as suggested by Korte and Mechoulam should not be discarded *at the present time*." In our subsequent paper[79b] in early 1969, we depicted structures **149** and **148** for cannabicyclol as either of the structures were acceptable to us in the absence of more definitive evidence. We based our position on the fact that we were unable to convert cannabichromene to cannabicyclol with pyridine, in contrast to Crombie and Ponsford's results.[78a] The conversion of cannabichromene to cannabicyclol by heat was not mentioned in the reference quoted by these authors and conversion under acid conditions appeared much later. The photochemical conversion in the presence of a sensitizer (*tert*-butanol-acetone) supported structure **148** but did not prove it unequivocally.

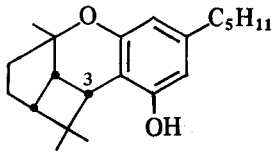
Furthermore, the NMR in this series of compounds is very complex particularly in the region where the benzylic proton appears and heavy reliance on this data can sometimes be misleading, e.g., the benzylic proton in



shows up as a sharp singlet (220 Mc/s, $CDCl_3$ 2500 Hz sweep width) at 2.8 ppm. However, at a 1000 Hz sweep width it shows signs of an ill-resolved multiplet.[24] Another example is the case of iso-THC[31] which was previously misinterpreted as Δ^6-3,4-*cis*-THC. Yet another example is the wrong assignment of the benzylic protons in Δ^6-THC [Archer et al. *J. Am. Chem. Soc.* 92, 5200 (1970)]. It was with this background that at the time we had indicated both the structures for cannabicyclol in the absence of definite proof such as now provided by X-ray.

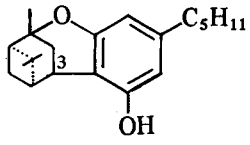


$BF_3 \cdot Et_2O$ or hv



Cannabichromene

148 Cannabicyclol



149

H. Novel Cannabinoids

Cannabielsoic acids (**151a, b**), which have been isolated from hashish,[86] represent a novel cannabinoid structure. The decarboxylation product of these naturally occurring consitutents is cannabielsoin (**152**), which is also the major product obtained by pyrolysis[87] of cannabidiol in air at 70°C. The synthesis of cannabielsoic acid A (**151a**) was achieved by Shani and Mechoulam[86] from cannabidiolic acid (**150**) by a novel photooxidative cyclization process (Chart 2.7). A mixture of **151a** and its isomer at C-1 was obtained.

Uliss et al.[34] reported (Chart 2.7) a stereochemically unambiguous synthesis of cannabielsoin (**152**) from the epoxide **156**. Thus cannabidiol diacetate **153** gave a mixture of epoxides **154**, **155**, and **156** when allowed to react with *m*-chloroperbenzoic acid. These were separated and the assignment of an α-configuration to the endocyclic epoxides in **155** and **156** was established. Treatment with base at room temperature converted **156** to **152**. This transformation involves an intramolecular trans diaxial cleavage of the α-epoxide at its less hindered site, which fixes the stereochemistry of the fused furan ring at C-2 and C-3 as *cis* and the configuration of the C-1 hydroxyl group as α (axial). This established the stereochemistry of cannabielsoin at C-1 so as to conform to structure **152**. Independently Shani and Mechoulam[86] arrived at similar conclusions while working on the cannabielsoic acid series. Similar treatment with base gave the novel cannabinoids **157** and **158** from **154** and **155**, respectively. These studies[34] have also suggested that the entropy of ring formation is the major factor in determining the product of an intramolecular epoxide cleavage. (−)-8β-Hydroxymethyl-Δ^1-THC (**157**)[88] is equiactive with Δ^1-THC in biological potency and represents the first example of functionalization in the geminal methyl part of the molecule of Δ^1-THC.

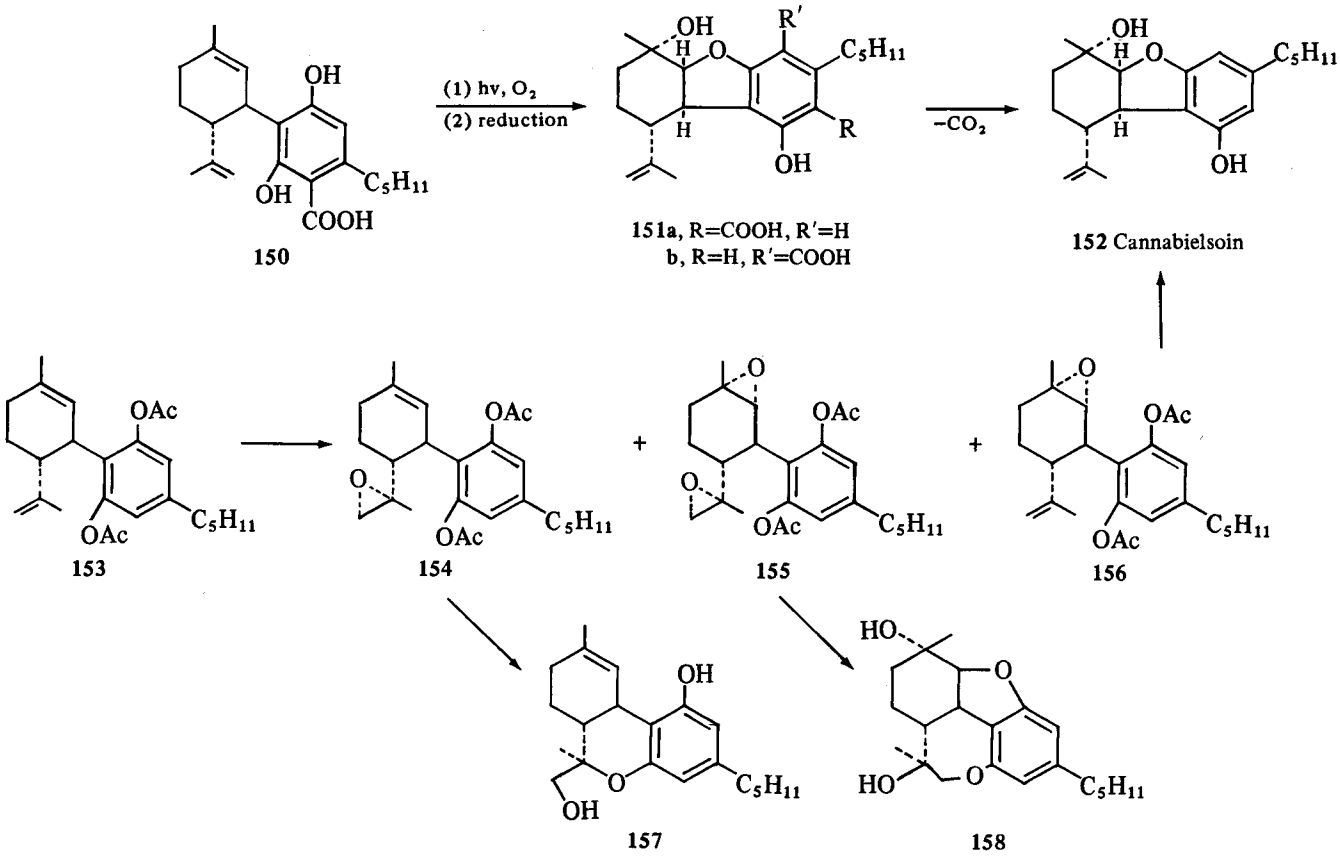

OH
OH
C_5H_{11}
COOH
150
(1) hv, O_2
(2) reduction
OH
H
O
R′
C_5H_{11}
H
R
OH
151a, R=COOH, R′=H
b, R=H, R′=COOH
$-CO_2$
OH
H
O
C_5H_{11}
H
OH
152 Cannabielsoin
OAc
OAc
C_5H_{11}
153
OAc
O
OAc
C_5H_{11}
154
+
O
O
OAc
OAc
C_5H_{11}
155
+
O
OAc
OAc
C_5H_{11}
156
OH
O
C_5H_{11}
OH
157
HO
O
HO
O
C_5H_{11}
158

Chart 2.7

During their studies on cannabielsoin (**152**) Uliss et al.[89] also synthesized (Chart 2.8) a novel cannabinoid **159** containing a 1,8-cineole moiety. It was formed in quantitative yield from **152** by an intramolecular cyclization on treatment with a catalytic amount of *p*-TSA. This conversion serves as confirmatory evidence for the stereochemical assignment of the C-1 hydroxyl group as α (axial) in **152**.

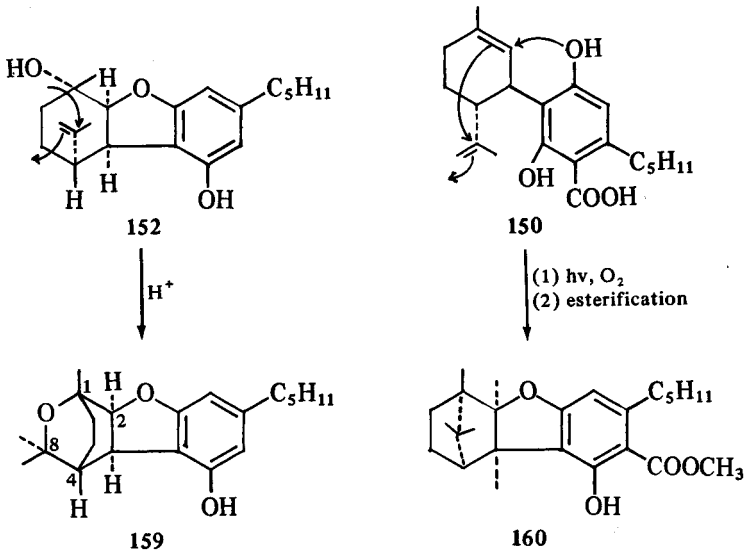


Chart 2.8

Another cannabinoid containing a camphane moiety **160** was synthesized by Kirtany and Paknikar[90] by irradiation of **150** in the presence of oxygen followed by esterification (Chart 2.8).

Ciommo and Merlini[91] reported the synthesis (Chart 2.9) of cannabinoid-like benzoxocinols **163** and **164** by condensing *p*-menth-3-en-8-ol (**161**) or *p*-mentha-3,8-diene (**162**) with olivetol (**6**) in the presence of HCOOH. It was shown that the reaction between **161** and **6** proceeds via dehydration of **161** to **162**.

Compound **163** was also synthesized (Chart 2.9) by Houry et al.[92] from carvone and olivetol using $POCl_3$ followed by reduction. They also prepared **164** from limonene or pinene. Compound **163** was reported to be biologically active.[92]

Citronellal and phloroacetophenone were condensed in the presence of pyridine to give hexahydrocannabinoid analogs.[93] This reaction is a variation of the citral-olivetol-pyridine reaction discussed earlier (see Section 3F; Chart 2.6).

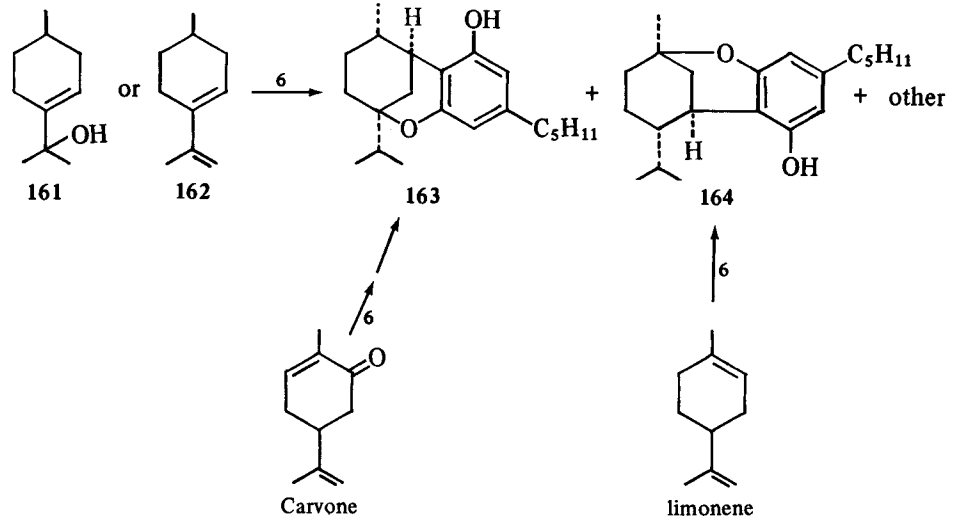


Chart 2.9

In recent years interest has focused on 1-ketocannabinoids because nabilone,[94] a member of this class, has been undergoing clinical trials as an antinausea and antiglaucoma agent. Wilson and May[95] oxidized the exocyclic double bond of (−)-$\Delta^{1(7)}$-THC (**13**) with OsO_4 and then cleaved it with $NaIO_3$ to give (−)-**167** (R = C_5H_{11}). Archer et al.[94] prepared nabilone [**167**, R = $C(CH_3)_2C_6H_{13}$] from the corresponding $\Delta^{1(7)}$-THC by ozonolysis. Since the overall yield was low they developed a different route to 1-ketocannabinoids (Chart 2.10). The known (+)-apoverbenone (**166**)[96] was prepared from β-pinene via ozonolysis to nopinone (**165**) followed by bromination and dehydrobromination. Reaction of **166** with the appropriate resorcinol in the presence of anhydrous $AlCl_3$ gave (−)-nabilone. Alternatively, **165** was converted to the enol acetate **168**,[97] which on oxidation with lead tetraacetate in refluxing benzene for 2 h gave **170**. If the reflux time was extended to 18 h, **169** was isolated. Either of them on condensation with the resorcinol derivative and *p*-TSA formed **171**. Stannic chloride treatment converted **171** to **167**. On the other hand, **171** on treatment with *p*-TSA gave the optically active *cis*-ketone **172**. The transformation of *cis*-**172** to *trans*-**167** was accomplished by treatment with $AlCl_3$ at 0°C.

For the preparation of racemic 1-keto cannabinoids the known optically inactive diene **173**[98] was condensed with olivetol or the other appropriate resorcinol in the presence of acid catalysts (Chart 2.11). The products of the reaction varied with the nature of the catalyst, solvent, temperature, and reaction time. Compounds **174** and **175** appear to be intermediates in the formation of the *cis*-ketone **172** following the sequence **174** → **175** → **172**. Since **167**[16]

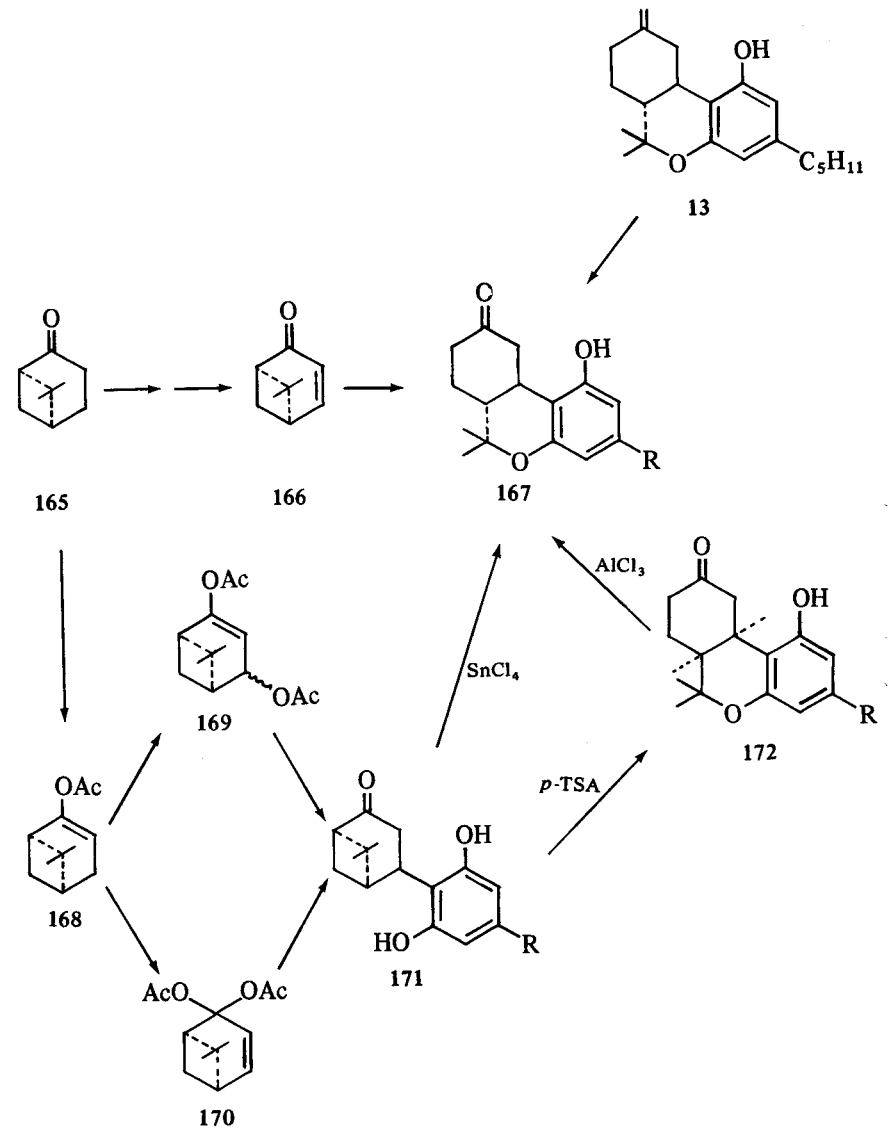
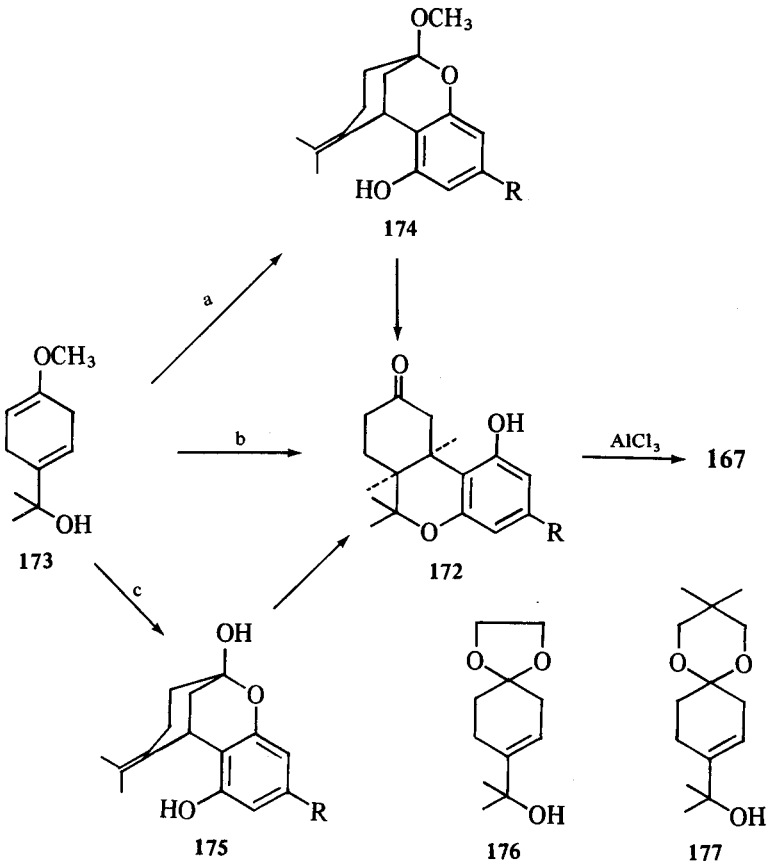


Chart 2.10

has been previously converted into (±)-Δ^1-THC (Chart 1.13) this represents a new synthesis of THCs.

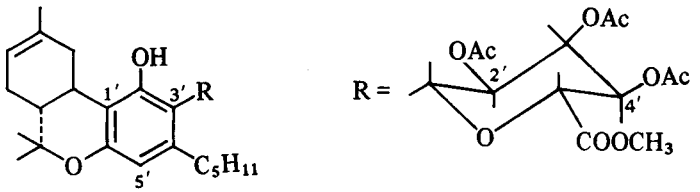
A variation of this scheme included the use of "masked ketones" such as **176** and **177** instead of the diene **173**. Both formed **167** (R= C_5H_{11}) in 80% yield.



Reagents: (a) $BF_3 \cdot Et_2O/C_6H_6$, RT, 6h; (b) $SnCl_4/CH_2Cl_2$, O°C, 7h; (c) $BF_3 \cdot Et_2O/CH_2Cl_2$, O°C, 7h.

Chart 2.11

The *C*-glucosidation of Δ^6-THC in the 3′-position has been reported[99] previously by treating Δ^6-THC with β-glucose pentaacetate in benzene containing $BF_3 \cdot Et_2O$. The formation of a *C*-glucoside in the presence of a phenolic group was unexpected but is not surprising in view of the reactivity of THCs toward electrophilic attack on the aromatic ring (e.g., formation of THC acids using methylmagnesium carbonate; Chart 2.5). Using the same procedure, the *C*-glucuronide of Δ^6-THC in the 3′-position was prepared.[100] On the basis of the large coupling constant observed (J = 10 Hz) for the C-1′ H in the sugar moiety it was considered to be a β-glucuronide.



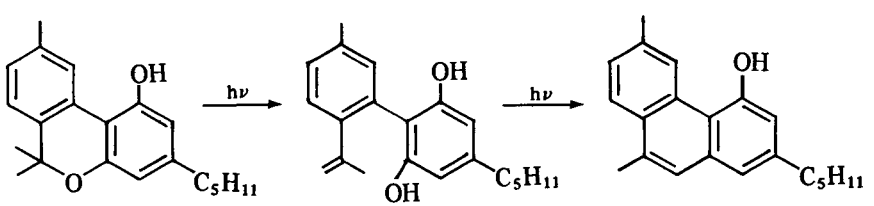
Δ^6-THC-C-3'-glucuronide methyl ester triacetate

4. NEW CANNABINOID TRANSFORMATIONS

Many interesting isomerizations and transformations have been observed in cannabinoids, due to the presence of double bonds, free phenolic groups and *cis* or *trans* ring junctions. The isomerizations and interconversions in the presence of acid catalysts of Δ^1- to Δ^6-THCs in the *trans* series and *cis*-THCs → tetracyclic ether (cannabictran, **147**) → iso-THCs in the *cis* series, are well established and have been discussed in detail in previous articles.[3] In this section some new transformations, which have since appeared, are described.

A. Photochemical

Bowd et al.[101] carried out the ultraviolet irradiation of cannabinol (**136**) in ethanol and showed (Chart 3.1) that cannabinodiol (**178**), a minor constituent of cannabis, is first formed by a photoinduced ring opening and hydrogen



136 **178** **179**

Chart 3.1

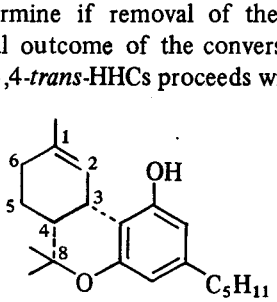
transfer. This in turn undergoes a photoinduced dehydration and ring closure to give the highly fluorescent hydroxyphenanthrene **179**. The conversion of **136** to **178** is analogous to a previously reported[102] photochemical transformation of 2,2-disubstituted chromenes.

B. cis → trans Conversion

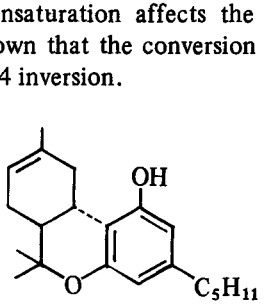
Uliss et al.[103] have elucidated the mechanism of the conversion of 3,4-*cis*- to 3,4-*trans*-cannabinoids. In 1969 Razdan and Zitko[104] reported the first example of the conversion of a *cis*- to a *trans*-THC. They found that (±)-Δ^1-3,4-*cis*-THC (**3**) was converted to (±)-Δ^6-3,4-*trans*-THC (**2**) on treatment with BBr_3. In a more recent example Archer et al.[94] have reported the conversion of a 3,4-*cis*-1-ketocannabinoid to its *trans* counterpart using $AlCl_3$ (Chart 2.10).

At the time Razdan and Zitko[104] had proposed that this transformation involved cleavage of the ether bond followed by probable inversion at C-4 rather than at C-3. With the recent availability[35] of (+)-Δ^1-3,4-*cis*-THC (**3**) of known absolute configuration (3*S*, 4*R*) by synthesis from 1*S*, 2*S*, 3*R*, 6*R*-carene-2-oxide (**21**, Chart 1.17) and olivetol, the conversion of *cis* to *trans* was reinvestigated. Inasmuch as the products formed by epimerization of **3a** at C-3 (Δ^6-3*R*, 4*R*-THC, **2b**) and at C-4 (Δ^6-3*S*, 4*S*-THC, **2a**) are enantiomers, preference for epimerization at either site will be reflected in the sign and magnitude of the optical rotation of the product. Hence a sample of **3a** of known optical purity was subjected to BBr_3 treatment and from the rotation of the product (Δ^6-*trans*-THC, 33% yield) it was found that it corresponds to a mixture of 24% enantiomer **2b** and 76% enantiomer **2a**. It was thus shown that epimerization at C-4 is the favored process and is accompanied by a lesser amount of C-3 epimerization or racemization. Supportive evidence was also provided, which indicates that the first step is cleavage of the pyran ring (Chart 3.2). The resulting equilibrium is driven to the relatively stable isomer **2a** via epimerization at C-4. Friedal-Crafts cleavage of the C-3-C-1′ bond in **126a** or **180a** followed by recombination leads to C-3 epimerization in the former and racemization of the latter.

Similar studies on *cis*-hexahydrocannabinols (HHCs) were also undertaken[103] to determine if removal of the carbocyclic unsaturation affects the stereochemical outcome of the conversion. It was shown that the conversion of 3,4-*cis*- to 3,4-*trans*-HHCs proceeds with exclusive C-4 inversion.



3a –(+)–3S, 4R*
3b –(–)–3R, 4S



2a –(+)–3S, 4S
2b –(–)–3R, 4R

*The **a** refers to the compound shown and **b** to its enantiomer.

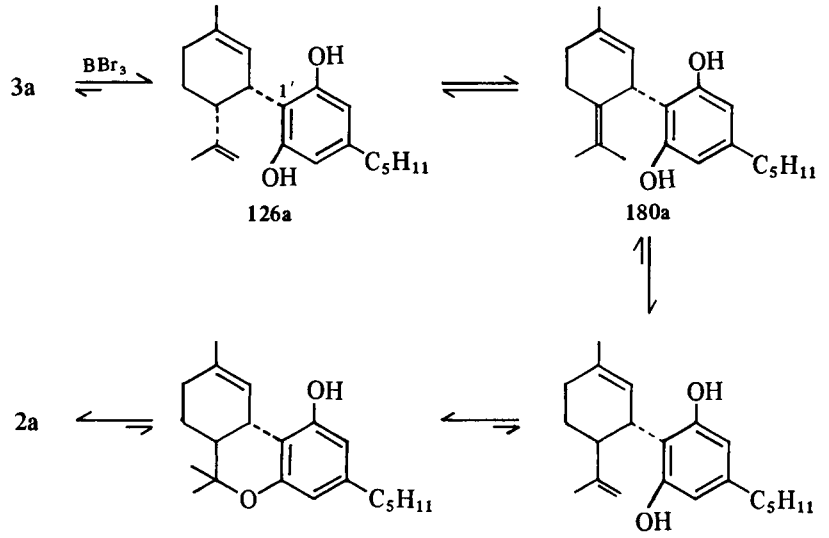


Chart 3.2

C. Pyrolysis

Since cannabis is generally ingested by smoking, the products formed on pyrolysis of cannabinoids are of general interest. Salemink and co-workers[105] have studied the pyrolysis of cannabidiol in detail and have isolated several

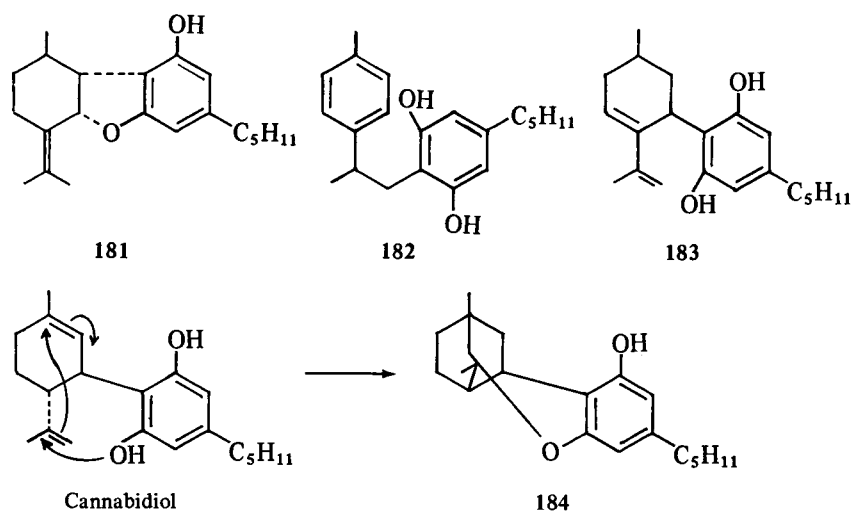


Chart 3.3

transformation products. They have observed that the nature of the gas phase considerably influences the nature of the pyrolytic products and have identified Δ^1-THC, cannabinol, several aromatic compounds, for example, olivetol, 2-methylolivetol and 2-ethylolivetol; *abn*-cannabidiol (14); cannabielsoin (152);[105a] a dibenzofuran 181[105d] in which there has been a rearrangement of the carbon skeleton (Chart 3.3); 182;[105e] a new cannabidiol isomer 183[105b] and the bicyclic cannabinoid 184.[105b] The structures of 183 and 184 were based on their mass spectral fragmentations only. Supportive NMR evidence was provided for 181 whereas 182 was confirmed by synthesis.[105f] In addition the isolation of 4-hydroxy-6-pentylbenzofuran and 2,2-dimethyl-5-hydroxy-7-pentylchromene were reported and confirmed by synthesis.[105f]

5. SYNTHESIS OF THC ANALOGS[106]

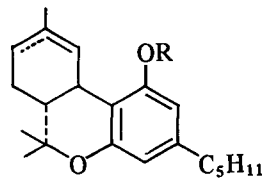
The cannabis plant, being a complex mixture, is unlikely to be used as a marketable drug; therefore, the future of therapeutic agents from cannabinoids undoubtedly lies in the synthetics.

This has led to intense interest in structural modification of Δ^1-THC and synthetic Δ^3-THCs. In addition a large variety of heterocyclic analogs have been prepared. All these modifications have resulted in a series of novel THC derivatives and analogs, which show a wide variety of enhanced activities such as antiglaucoma, antinausea, analgesic, tranquilizer, antihypertensive, etc. Like morphine, lysergic acid diethylamide, and cocaine, which have structurally related analgesics, oxytoxics, and local anaesthetics, respectively, the socially abused cannabinoids may now be on the verge of generating a family of safer and more useful therapeutic agents.

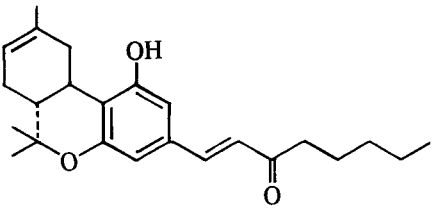
A. Carbocyclic Analogs

Compounds Related to Δ^1- and Δ^6-THCs

Some of these compounds are shown in Chart 4.1. Apart from the various metabolites of Δ^1- and Δ^6-THCs that have been synthesized, efforts have been directed to modify the THC structure to make water soluble derivatives. This is deemed necessary, since Δ^1- and other THCs are resinous materials completely insoluble in water, and to carry out pharmacological studies these materials have to be administered in various solvents such as polyethylene glycol, Tween, triton, and alcohol, which are themselves not without pharmacological activity. An aminoalkyl ester derivative of THCs is an obvious choice, but until recently conventional methods of esterification were not successful in its preparation. Razdan and co-workers[107] have shown that water-soluble esters of Δ^1- and other THCs can be easily prepared with carbodiimide as the condensing agent (Chart



185a, R = $CO(CH_2)_3$–N⟨O⟩
b, R = $CH_2CH_2N(C_2H_5)_2$
c, R = PO_3H_2



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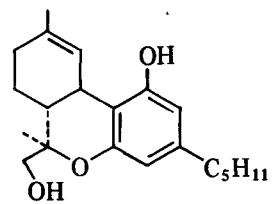

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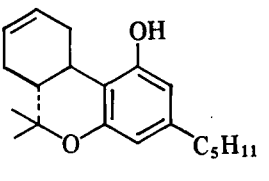

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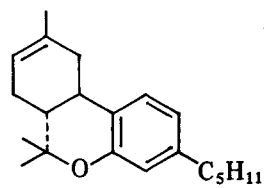

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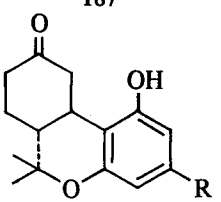
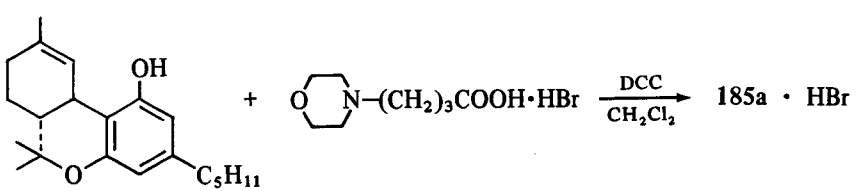


167

Chart 4.1

4.2). Thus the γ-morpholinobutyric ester (**185a**·HBr) of Δ^1-THC is a solid, freely soluble in water and is equiactive with Δ^1-THC in various pharmacological tests. In contrast, the ether derivative **185b**[107a] is quite different and does not show the pharmacological profile of Δ^1-THC.



Δ^1-THC

Chart 4.2

A biologically active, water-soluble phosphate ester of Δ^6-THC (185c as the sodium salt) has also been reported[108] recently. It was synthesized (Chart 4.3) by treating Δ^6-THC with phosphoryl chloride in pyridine followed by mild hydrolysis with water. Treatment with alcoholic sodium hydroxide gave the sodium salt of **185c**.

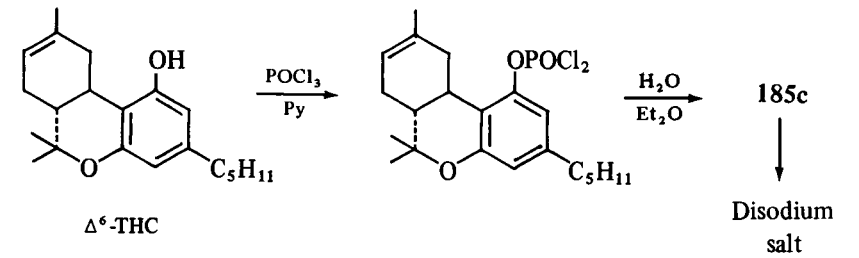


Chart 4.3

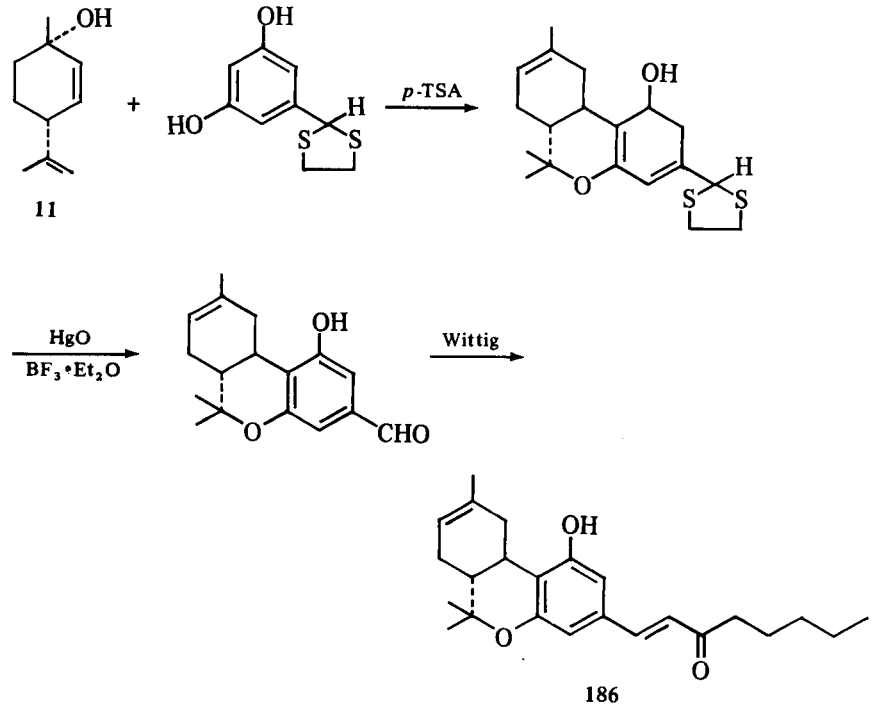
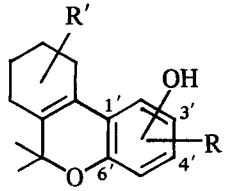


Chart 4.4



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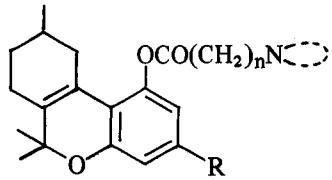

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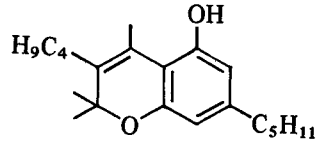

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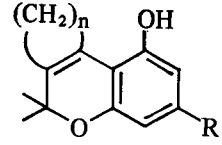
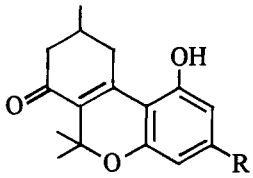


192a, n = 3
b, n = 5



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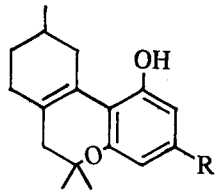

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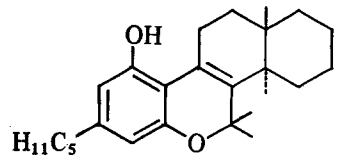

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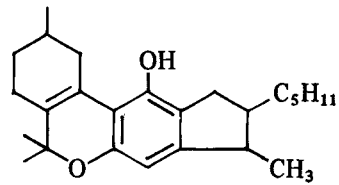

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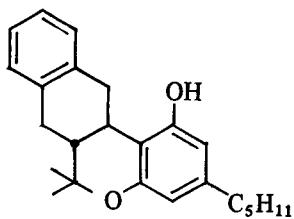

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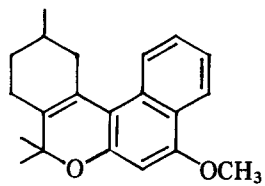

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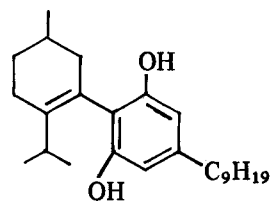

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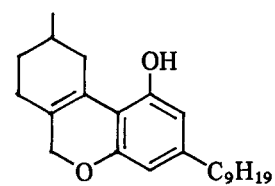


200

Chart 4.5

The potent analog **186** was synthesized by Razdan et al.[58] as shown in Chart 4.4. The resorcinol thioketal was prepared from the corresponding aldehyde.

As described earlier (Section 3H; Chart 2.7) the potent Δ^1-THC analog **157** was synthesized[34] from cannabidiol diacetate.

The Δ^6-THC analog **187** was synthesized[95] from the 1-keto compound **167** (R = C_5H_{11}) by reduction and dehydration with *p*-TSA. This compound was shown to be equiactive with Δ^6-THC.[95] Compound **188** was prepared[109] from Δ^6-THC by treatment with $C\ell PO(OC_2H_5)_2$ followed by cleavage with Li/NH_3.

The synthesis of 1-keto analog **167** has already been described in detail (see Section 3H; Charts 2.10 and 2.11).

Compounds Related to Δ^3-THC

Some examples of this type are shown in Chart 4.5. These compounds differ from the natural THCs **1** and **2** in the relative position of the double bond and show typical marijuana-like activity in rodents and dogs. They were discovered[106] independently by two groups, Adams and co-workers in the United States, and Todd and co-workers in Great Britain, in the course of their work on the structure elucidation of the active constituents of hashish and marijuana. Todd and Adams in particular carried out extensive structure-activity relationship (SAR) studies in Δ^3-THCs. Some of these are depicted by the general formula **189**, **191**, and **192** and have been reviewed in detail by Mechoulam[3b,c] and Pars et al.[106a] They were synthesized according to the general scheme shown in Chart 4.6. A Pechmann condensation between the appropriate keto ester and

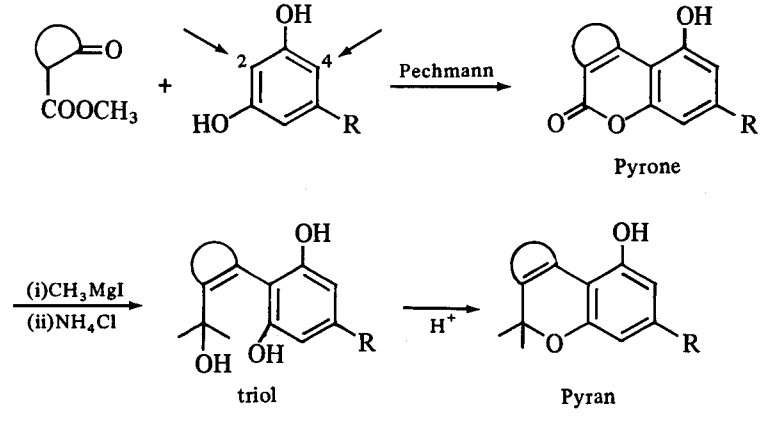


Chart 4.6

the resorcinol formed the pyrone. Generally the major product was formed by attack on the 2-position of the resorcinol. The isomers (attack on the 4-position) are also formed and their amount depends on the reaction conditions and the

nature of the substituent R in the resorcinol. Treatment of the pyrone with excess CH_3MgI gives the triol, which on treatment with catalytic amounts of acids (e.g., *p*-TSA) ring closes to the pyran.

Various water-soluble aklyl amino esters of type **190** and of the cyclopenteno derivative **192a** were prepared[107b] from the pyrans by using the appropriate acid and carbodiimide, as in the case of Δ^1-THC. Compounds of type **193** were prepared by oxidation of the pyrane as its acetate, with ceric ammonium nitrate.[110]

The novel cannabinoids with a homopyran ring of type **194** were reported by Matsumoto et al.[111] Their synthesis is shown in Chart 4.7. The pyrone **201** was reduced with Red-Al to the triol **202a**. Under mild alkaline conditions it was converted to the dibenzyl derivative **202b**. After bromination with PBr_3 and further treatment with NaCN/DMSO it formed the nitrile, which was debenzylated under mild hydrogenation conditions to **203**. Conversion of nitrile **203** to the ester **204** proceeded smoothly with HCl/EtOH. Grignard reaction with CH_3MgBr followed by treatment with ethanolic HCl gave the oxepin **194**. Some other related oxepins were also prepared by these authors.

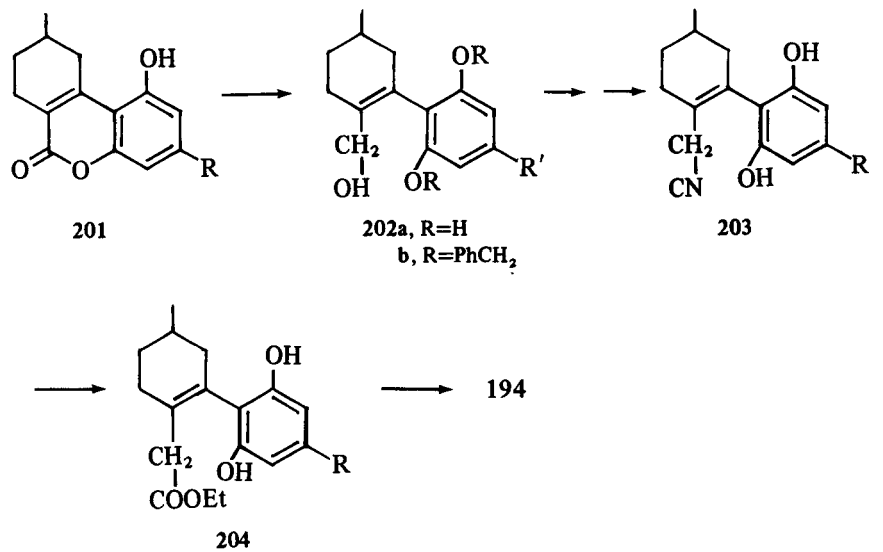


Chart 4.7

Razdan et al.[112] synthesized the steroidal analog **195**. They also prepared **196**.[113] Both these analogs were prepared using the general scheme shown in Chart 4.6. Similarly the analogs **197** and **198** were synthesized by Malik et al.[114] In the case of **197**, the corresponding pyrone was first reduced with Li/NH_3 to

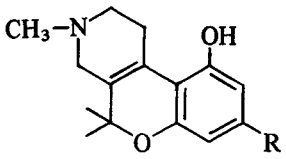
avoid aromatization of the alicyclic ring. Grignard reaction and ring closure with acid gave the desired pyran **197**.

The ring-opened analog **199** was prepared by Razdan et al.[115] by Li/NH_3 treatment of the corresponding pyran. The ring opening was unexpected as no reduced pyrans were formed. It shows a very low extinction coefficient in the UV spectrum, λ_{max}^{EtOH} 275 nm (ϵ 1600), in spite of the conjugation present, indicating that the alicyclic ring is out of plane from the aromatic ring. It has potent marijuana-like activity unlike other ring-opened cannabinoids, for example, cannabidiol.

Loev et al.[116] prepared the analog **200** by $LiAlH_4$ reduction of the corresponding pyrone to the allylic alcohol **202a** ($R' = C_9H_{19}$) followed by ring closure with *p*-TSA. The biologically active benzoxocinols **163**, **164** have already been discussed (section 3H; Chart 2.9).

B. Heterocyclic Analogs

Interest in preparing nitrogen analogs of THCs was stimulated by the observation that THC is one of the very few potent drugs that act on the central nervous system (CNS) yet has no nitrogen in its structure. As long ago as 1946 Anker and Cook[117] synthesized the nitrogen analog **205** and its dihydro derivative and found them to be without analgesic activity. Other types of CNS activity were not mentioned in their report. They prepared **205** by following the general scheme as used for the synthesis of Δ^3-THCs (Chart 4.6).



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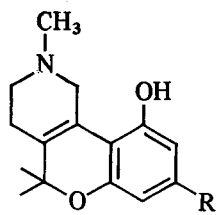


206

In 1966 Pars et al.[118] reported the synthesis of the nitrogen analog **206**, which showed marijuana-like pharmacological profile. Since that time various nitrogen analogs,[106, 107b, 119, 120] type **205**, **207** to **212** (Chart 4.8), and sulfur analogs[106, 120-122] (Chart 4.10), all showing varying amounts of CNS activity in laboratory animals, have been synthesized.

The sequence of reactions for the synthesis of **207** ($R = C_9H_{19}$), shown in Chart 4.9, illustrates the general procedure used in the preparation of *N*-substituted nitrogen analogs of type **207**. The synthetic scheme is an adaptation of the general scheme used for the synthesis of Δ^3-THCs (Chart 4.6). The pyrone

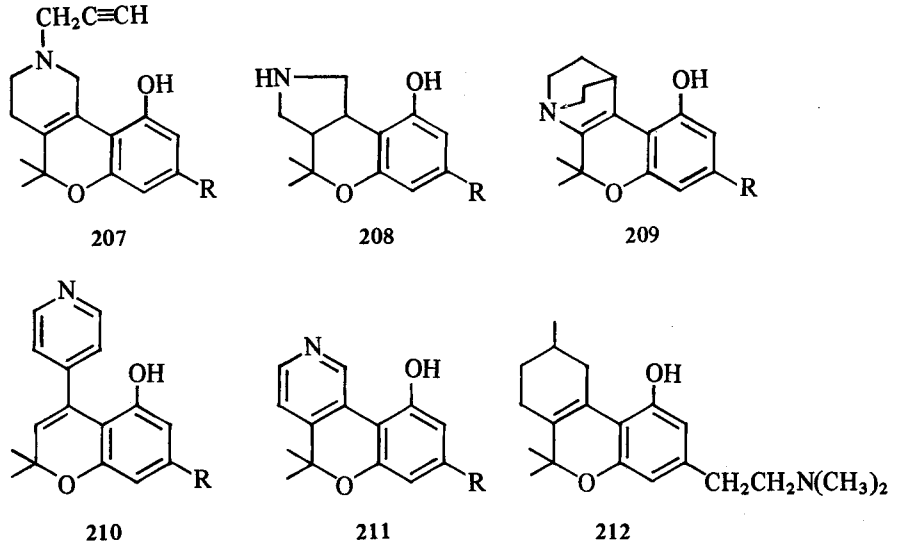


Chart 4.8

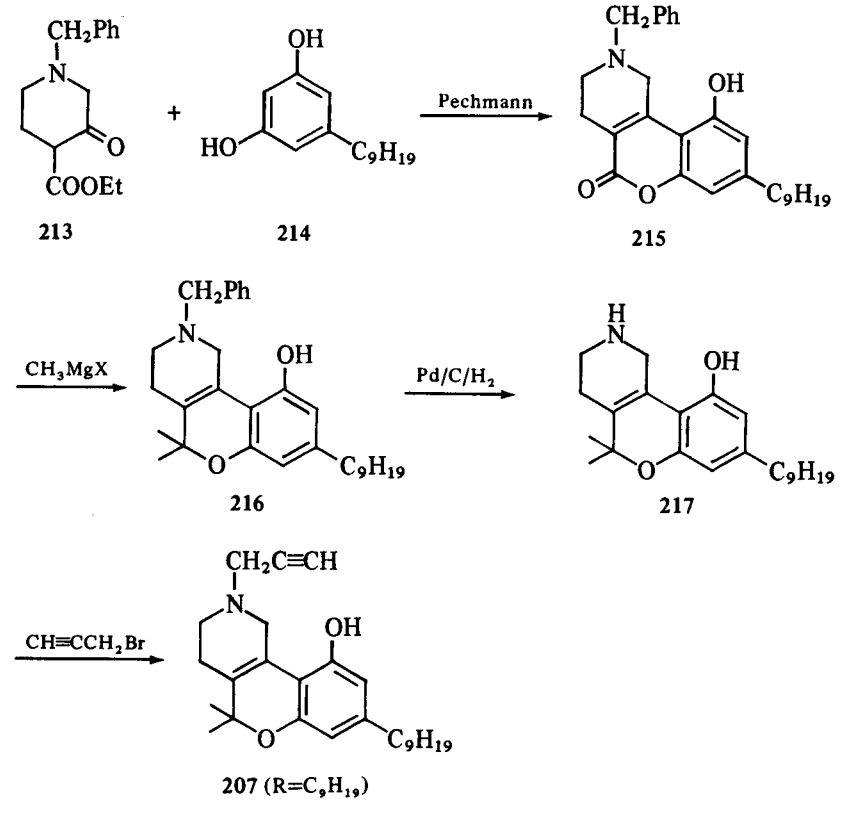
215 was obtained from the keto ester **213** and the resorcinol **214**. Best results in this Pechmann condensation were obtained by using a mixture of $POCl_3$/H_2SO_4. The Grignard addition was carried out in anisole and during workup the pyran **216** was formed. Debenzylation of **216** with Pd/C and H_2 formed the nor-base **217**. Alkylation with propargyl bromide-Na_2CO_3 in EtOH furnished the desired compound **207**. A similar sequence was used for the synthesis of analogs **208**, except that during the debenzylation step the double bond was also reduced.

Compounds **209**, **210**, and **212** were prepared following the general scheme in Chart 4.6. Compound **211** was prepared by dehydrogenation of **207** (R = C_9H_{19}) with 10% Pd/C in xylene.[123]

Surprisingly, all these nitrogen analogs as their acid addition salts were not very water soluble. Hence, like the carbocyclic analogs, they were made water soluble by making their alkylamino ester derivatives. A large number of water-soluble derivatives were prepared and studied by Razdan et al.[107b]

The sulfur analogs[121,122] **218** to **222** (Chart 4.10) were prepared according to the general scheme in Chart 4.6. In the sulfur series the Pechmann reaction was best carried out in the presence of HCl/EtOH. The sulfur analog **223** was prepared from **218** by dehydrogenation.

Recently Cushman and Castagnoli[124] reported the synthesis (Chart 4.11) of biologically active nitrogen analogs **230** having a *trans* ring fusion similar to that

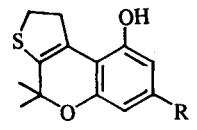


$C_9H_{19} = CH(CH_3)CH(CH_3)C_5H_{11}$

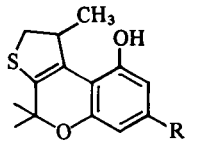
Chart 4.9

found in the natural THCs **1** and **2**. Their novel approach to the synthesis of these analogs untilizes the condensation of the Schiff base **225** with glutaric anhydride to give predominantly the *trans*-piperidone **226a**. The ester **226b** on Grignard treatment followed by demethylation with BBr_3 and subsequent dehydrohalogenation, afforded the olefin **227**. After ring closure with $BF_3 \cdot Et_2O$, compound **228** was treated with CH_3MgBr and then dehydrated to form the enamine **229**. Catalytic reduction of **229** gave a diastereomeric mixture of amines **230**. Preliminary pharmacological results showed the mixture to be active.

Several other nitrogen analogs have been prepared, and in most cases their biological activity has not been reported.



218



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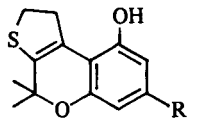

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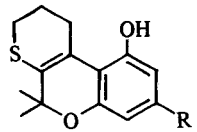

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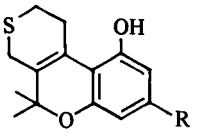

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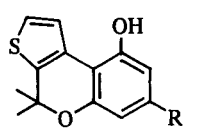
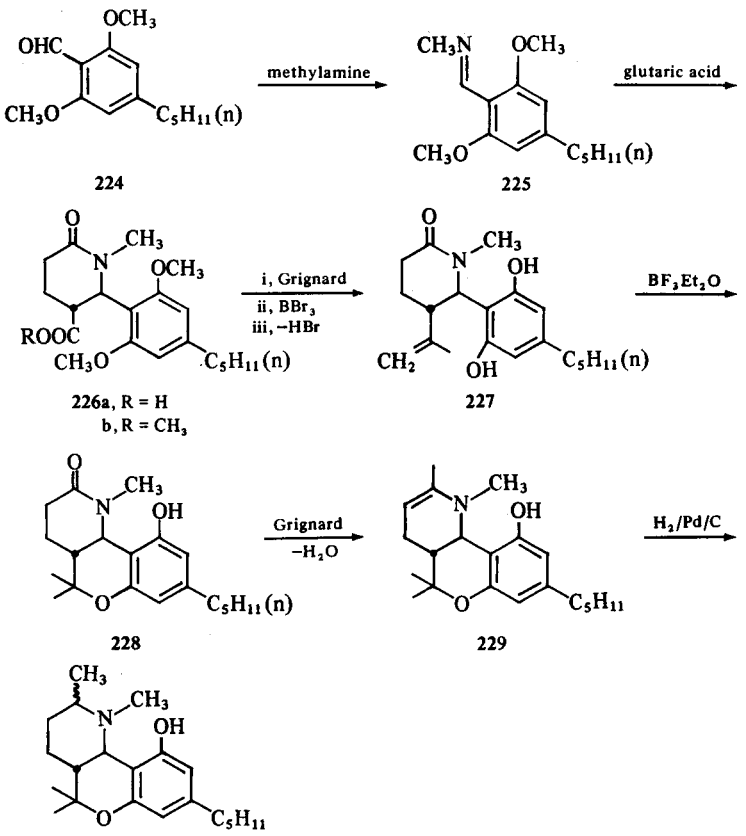


223

R = $CH(CH_3)CH(CH_3)C_5H_{11}$

Chart 4.10



224 225

226a, R = H
b, R = CH_3

227

228 229

230 diastereomeric mixture

Chart 4.11

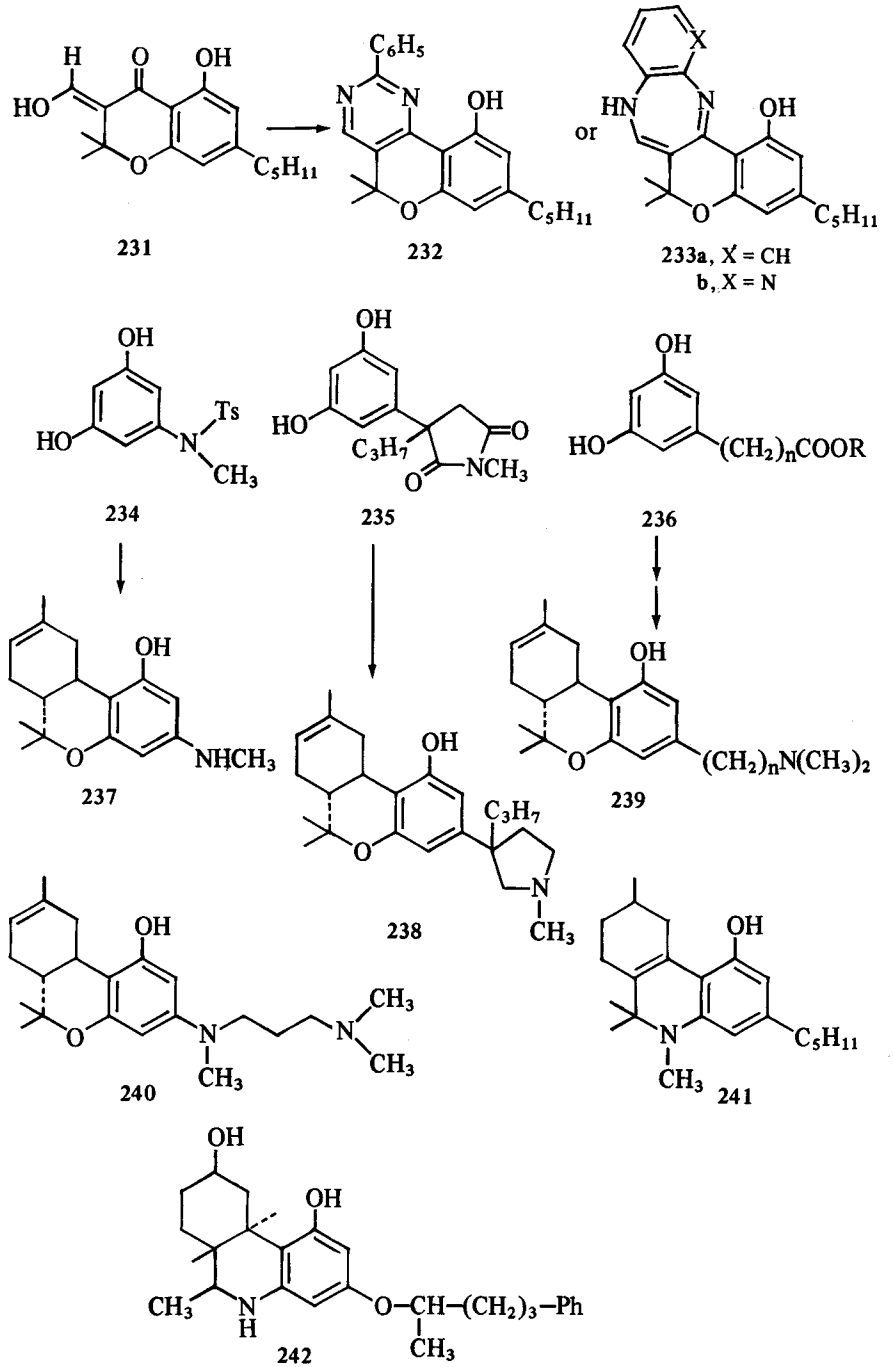
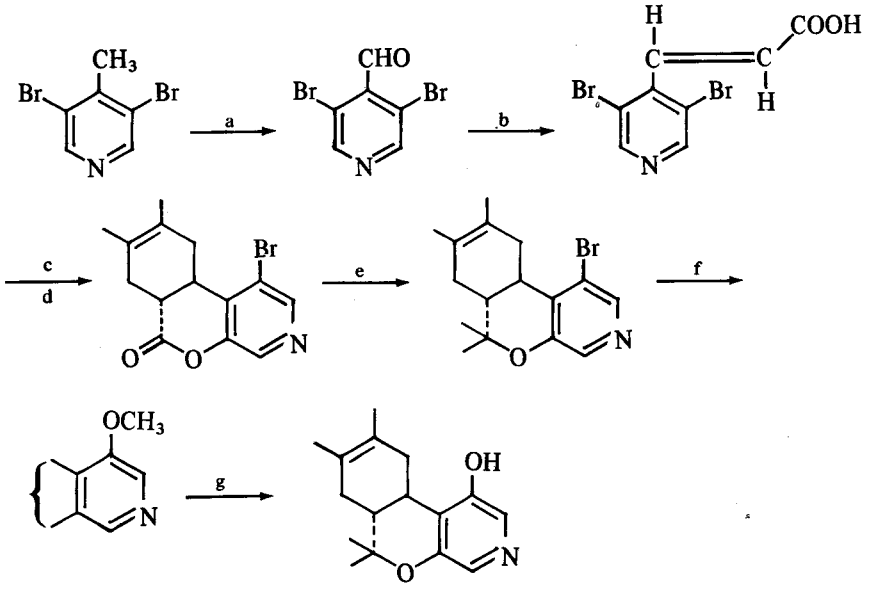


Chart 4.12

Condensation of **231** (Chart 4.12) with benzamidine furnished **232**, whereas condensation with the appropriate diamine followed by thermal ring closure in vacuum gave **233**.[125] The resorcinols **234** and **235** were condensed with *p*-menthadienol **11** and then reduced to yield **237**[126] and **238**,[127] respectively. Similarly **236** (R = CH_3 or C_2H_5) condensed with **11** to give the corresponding ester, which on treatment with dimethylamine followed by $LiAlH_4$ reduction formed the analogs **239** (*n* = 2 to 5).[128] The analog **240**[126] was obtained from **237** on treatment with dimethylaminopropyl chloride in the presence of butyllithium. No biological data were reported for any of these compounds.

Another nitrogen analog **241** (Chart 4.12), where the pyran oxygen is replaced by NCH_3, was synthesized and reported to be inactive.[129] However, a related analog **242** has been reported[130] to be very active biologically, but no details of its synthesis have been described.

The novel analog **243** was synthesized[131] according to the scheme in Chart 4.13. The Diels-Alder reaction is used to give the *trans* ring junction as in the synthesis of Δ^6-THC (see Chart 1.9).



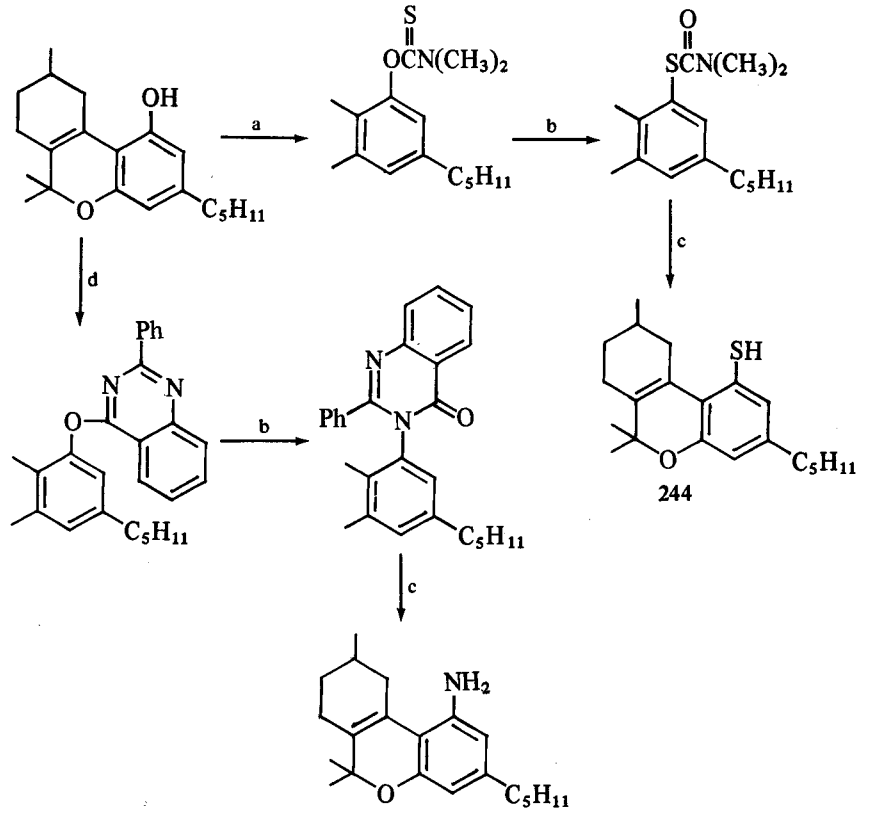
243

Reagents: (a) SeO_2-DMSO (b) $CH_2(COOH)_2$ (c) CH_3OH/H^+ (d)  , Dioxan at 120°C (e) CH_3MgI, Δ (f) $NaOCH_3/CH_3OH$ /DMF/CuI g, $NaSC_2H_5$/DMF, H^+

Chart 4.13

The analogs where the phenolic hydroxy group is replaced by SH (244) or NH_2 (245) were synthesized by Matsumoto et al.[132] (Chart 4.14). They showed that the amino analogs retained pharmacological activity, but the sulfur analogs were relatively inert.

Other sulfur analogs include 247, 248, and 249. They were prepared[133] from pulegone (137) by a base-catalyzed reaction with the thiophenol (Chart 4.15) followed by the ring closure to 246. Demethylation of the methoxyl gave 247, which on dehydrogenation gave the cannabinol analog 248. Sulfones 249 were also prepared by *m*-chloroperbenzoic acid oxidation of 246. No biological data were reported.



Reagents: (a) $(CH_3)_2NCS\,Cl$ (b) Δ (c) NaOH (d)

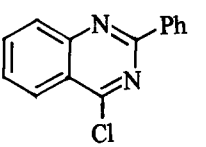
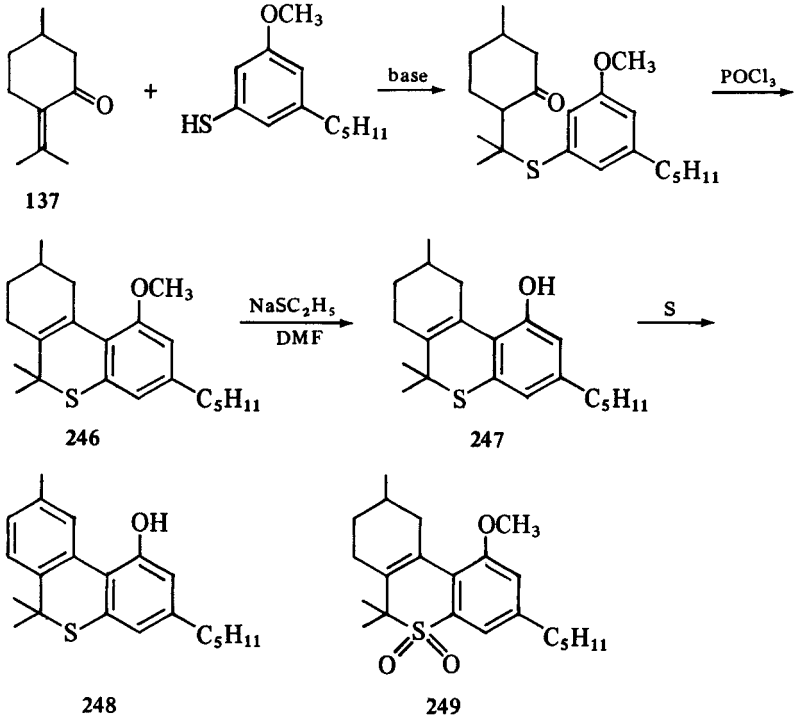


Chart 4.14



137 246 247 248 249

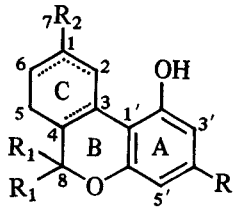
Chart 4.15

6. OVERALL STRUCTURE-ACTIVITY RELATIONSHIPS IN CANNABINOIDS

In various animals Δ^1-THC and other synthetic THCs show predominantly central nervous system (CNS) depression and ataxia, which lasts from several hours to days, depending on the dose administered. The characteristic effect of THCs, which distinguishes them from all other pyschoactive drugs, is a postural arrest phenomenon with relaxed staring and associated hypersensitivity to external stimuli.[134] For example, when Δ^1-THC is given at a dose of 0.2-0.5 mg/kg (i.v.) to dogs, they stand in a trancelike state, sway from side to side, pitch forward and backward, and overreact to a swinging object. When aroused, ataxia is evident for 3 to 4 hours after the injection. It is characteristic for the dogs to urinate and defecate soon after receiving the drug and sleep a great deal for the next 24 hours.

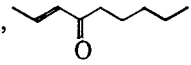
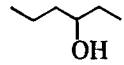
The synthesis and demonstration of CNS activity for a wide variety of cannabinoids has resulted in an expansion of the structure-activity (SAR) conclu-

sions originally put forth by Roger Adams and co-workers.[135] By using dog ataxia as the basis for THC activity, Adams found that the potency is increased when R is a highly branched alkyl with the 1,2-dimethylheptyl (C_9H_{19}) showing optimum activity. He also showed that when R_1 is methyl the activity is greater than when these (R_1) substituents are higher alkyls. Reduction of the double bond in the C-ring retained activity, and the C-ring could be contracted, expanded or even opened without entirely eliminating activity.
eliminating activity.



Recent studies of various metabolites and other synthetics have expanded these SAR observations. Thus based on CNS pharmacological profiles in laboratory animals, the SAR picture can be summarized as follows.

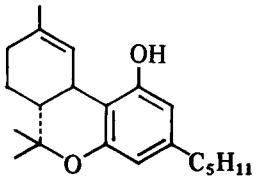
1. Essentially a benzopyran structure with an aromatic hydroxyl group at 2′-position and an alkyl or alkoxyl group on the 4′-position are a requirement for activity.
2. The position and the environment around the aromatic hydroxyl group are very important for the activity, viz.;
   a. The OH at position C-2′ is in itself necessary for CNS activity.
   b. Esterification of the phenol retains activity and in some carbocyclic and heterocyclic benzopyrans, can lead to greater selectivity of action. Etherification of the phenol eliminates activity. Replacement of the OH by NH_2 retains, whereas by SH, eliminates activity.
   c. Methyl substituents at C-2 in the C-ring significantly alter the activity of both carbocyclic and (C-ring) heterocyclic benzopyrans particularly in the case of planar five-membered C-rings.
3. Substitution in the aromatic ring by electronegative groups like carboxyl, carbomethoxyl, acetyl eliminates activity, whereas alkyl groups in C-3′ position retain, and in C-5′ position reduce, activity.
4. A minimum length of the aromatic side chain is necessary to elicit activity. The branching of the alkyl side chain increases potency. Thus 1,2-dimethylheptyl or 1,1-dimethylheptyl gives the most potent compounds. Similarly *p*-fluorphenyl alkyl and side chains as shown give good activity.

$-O-CH(CH_3)(CH_2)_3Ph$,  and 

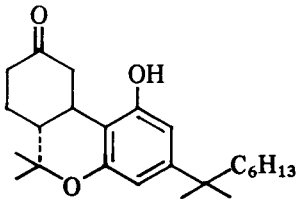
5. On ring B the *gem*-dimethyl group at C-8 (R_1) is optimum for activity. Replacement of one of the R_1 substituents on the B ring with a hydroxymethyl group retains activity. Replacement of pyran O by N and ring expansion of ring B by one carbon can retain activity.
6. In the alicyclic ring C, compounds with the double bond in the Δ^1-, Δ^6-, or Δ^3-position are active. A 3,4-*trans* junction increases and a *cis* junction decreases activity. The natural THCs are active in the 3*R*, 4*R* series only. A methyl at C-1 increases activity, but metabolism to the 7-hydroxymethyl is not a prerequisite for THC activity.
7. The C-ring can be substituted by a variety of nitrogen and sulfur-containing rings without loss of CNS activity. With the nitrogen and sulfur analogs the most active CNS agents are obtained when the heteroatom is in a phenethyl orientation, e.g., inserted in place of C-1 or C-5.
8. Planarity of the C ring is not a necessary criterion for activity. See, for example, the quinuclidine analog (**209**, chart 4.8) and the benzoxocine compounds (**163**, **164**; Chart 2.9).
9. In both carbocyclic and heterocyclic analogs, opening the pyran ring generally decreases activity. An exception is compound **199** (Chart 4.5), which is approximately equiactive with Adams DMHP (Chart 6.1).

7. THERAPEUTIC INDICATIONS AND POTENTIAL OF NEW DRUGS FROM CANNABINOIDS[136]

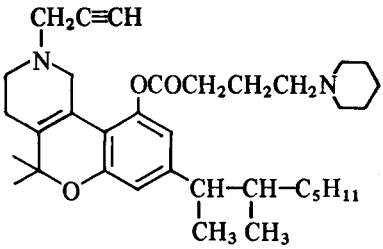
As discussed in the Introduction, the main therapeutic indications for Δ^1-THC have emerged from folklore anecdotes. The use of Δ^1-THC, as an antinauseant to patients undergoing cancer chemotherapy, and its utility as an antiglaucoma agent, is now well established clinically. In many states in the United States and in some foreign countries, a strong movement in favor of legalizing the use of Δ^1-THC for these purposes has developed. This is mainly because Δ^1-THC is more effective in controlling nausea than presently available drugs. In the case of glaucoma where patients tend to become refractory to the drug in use, the addition of a new class of drug which presumably acts by a novel mechanism is of great interest. The clinical activity of Δ^1-THC in these two fields has led investigators to use synthetics for these indications. Presently three such drugs are being actively pursued in the clinic. These are shown in Chart 6.1; a carbocyclic 1-ketocannabinoid, Nabilone,[137] and two nitrogen analogs, Nabitan,[107b, 138] a water-soluble derivative, and A-41988.[139, 140]



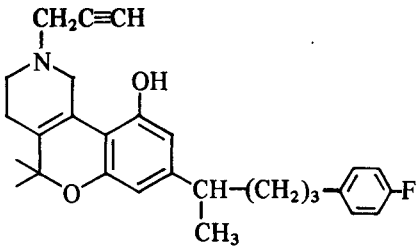
Δ^1-THC



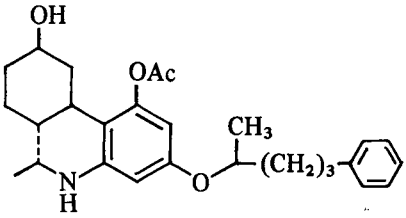
Nabilone (Lilly)



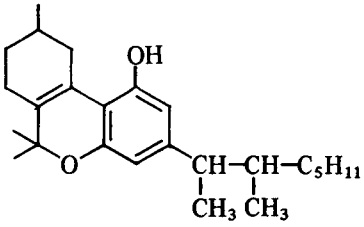
Nabitan (SP-106) (Burroughs Wellcome)



A-41988 (Abbott)



CP-44001-1 (Pfizer)



DMHP

Chart 6.1

Animal studies to date, both in heterocyclic and carbocyclic analogs, clearly point to therapeutic potential as analgesics. Preliminary studies in man have already given some indication of analgesic potential for both Δ^1-THC[141] and Nabitan (SP-106).[142-144] Since establishment of a new type of analgesic in the clinic is not simple due to subjective and placebo effects, the studies with Nabitan are continuing and as such the place of cannabinoids as analgesics has not yet been firmly established. Recently another nitrogen analog CP-44001-1 (Nantradol) has been reported[130] to be a potent analgesic in animals and is presently undergoing clinical trials.

The recent finding[145, 146] that DMHP, a carbocyclic analog originally synthesized by Roger Adams in the 1940s, shows hypotensive effects at doses where no CNS effects occur, is noteworthy and, it is hoped, will open up a fruitful area for

cardiovascular drugs. In addition a preliminary study has indicated the use of Nabilone as a tranquilizing agent.[137b]

Based on a few clinical studies with Δ^1-THC there are indications of its use as an antiasthmatic[147] and as an appetite stimulant.[148]

A recent survey[149] suggests a high incidence of marijuana use among young epileptics. Their observations of its efficacy in alleviating their symptoms, like those of the glaucoma and cancer patients, may point to another area where clinical utility should be focused. There is already some indication clinically[150, 151] to supprot this view and animal studies clearly point to thereapeutic potential in this area.

Other areas of interest, supported by animal pharmacology, are antiinflammatory, antipyretic, antitussive, antispasmodic, antidiarrheal, sedative-hypnotic, antidepressant, anticancer, and treatment of alcoholism and narcotic addiction.

It is obvious that Δ^1-THC and analogs display a wide range of pharmacological action. The future development of drugs from this area will undoubtedly depend on the success achieved by structural changes to provide selectivity of pharmacological action. However, it should be emphasized that the concept of drug development from THCs and cannbinoids is based on very sound foundations, since Δ^1-THC has a remarkably low toxicity in animals and humans. In addition, it has practically no respiratory-depressant activity, no or very low physical dependence liability and finally has a unique pharmacological profile compared to other psychoactive drugs.

On reflection, it is surprising that drug development from cannabinoids did not take place sooner.

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