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Synthesis of cannabidiol stereoisomers and analogs as potential anticonvulsant agents

Shah, Vibhakar Jayantilal, Ph.D.

The University of Arizona, 1988

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300 N. Zeeb Rd.
Ann Arbor, MI 48106

SYNTHESIS OF CANNABIDIOL STEREOISOMERS AND ANALOGS AS POTENTIAL ANTICONVULSANT AGENTS

BY

VIBHAKAR JAYANTILAL SHAH

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In Partial fulfillment of the Requirements

For the Degree of

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In the Graduate College

THE UNIVERSITY OF ARIZONA

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THE UNIVERSITY OF ARIZONA
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As members of the Final Examination Committee, we certify that we have read the dissertation prepared by Vibhakar J. Shah

entitled Synthesis of Cannabidiol stereoisomers and analogs as potential anticonvulsant agents.

and recommend that it be accepted as fulfilling the dissertation requirement for the Degree of Doctor of Philosophy.

Arnold Martin	8/30/88 Date
William A. Remers	8/30/88 Date
	8-30-88 Date
	8-30-88 Date
Eugene A. Mash Jr	8-30-88 Date

Final approval and acceptance of this dissertation is contingent upon the candidate's submission of the final copy of the dissertation to the Graduate College.

I hereby certify that I have read this dissertation prepared under my direction and recommend that it be accepted as fulfilling the dissertation requirement.

Arnold Martin — Dissertation Director

8/30/88 — Date

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SIGNED: Vibhakar Shah

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ABSTRCT

Anticonvulsant activity of cannabidiol (**CBD**) has been well documented in various laboratory animal species and also in man. As part of our continuing effort to study and to define the structure anticonvulsant relationship several analogs of **CBD** were synthesized wherein its structural units, namely, the terpene ring, aryl ring and/or side chain were systematically modified. These analogs include the: 1) unnatural (+)-Cannabidiol (**1b**), 2) Delta-3-carenyl analog-(+)-carenadiol (**45a**), its diacetate (**45b**) and its 1",1"-dimethylheptyl side chain analog (**45c**), and 3) unnatural 7-acetoxycannabidiol (**46b**).

(+)-Cannabidiol (**1b**) was synthesized in about 20-25%yield from olivetol (**51**) and two different p-menthadienols (**67** and **70**) as monoterpenoid synthons. (-)-p-Mentha-1,8-dien-3-ol (**67**) was prepared from (-)-limonene (**65**) by chromium trioxide-pyridine complex oxidation followed by cerium trichloride assisted sodium borohydride reduction of the obtained ketone (**66a**). (-) p-Mentha-2,8-dien-1-ol (**70**) was synthesized from 1:1 mixture of cis- (**69a**) and trans-epoxide (**68a**) of limonene (**65**) in about 35% yield. The reaction involves phenylselenide anion mediated stereospecific trans-diaxial opening of the epoxide ring to give the required alcohol (**70**) along with its regioisomer (**71**) as the major product (79%).

The delta-3-carenyl analog (+)-carenadiol (**45a**) was synthesized from car-4-en-3β-ol (**80**) and olivetol (**51**) in about 20% yield. Car-4-en-3β-ol (**80**) was prepared in about 90-95% yield from the corresponding 3β,4β-epoxy carane (**77**) by following the same methodology described for (**70**).

Attempts to synthesize (+)-7-hydroxycannabidiol (**46a**) met with little success. A variety of different reaction conditions were tried but none of them were suitable to avoid cyclization to THCs. The required monoterpenoid alcohol synthon p-mentha-2,8-dien-1,7-diol (**101**) was synthesized for the first time as a separable diastereomeric mixtures in 55%

yield in seven steps from commercially available (4S)-(-)-perillyl alcohol (**89**) utilizing the same approach described for (**70**) and (**80**).

The compounds were evaluated for anticonvulsant activity in seizure susceptible (**AGS**) rats and for neurotoxicity in the rotorod (**ROT**) test. A general lack of stereoselectivity for the anti-AGS and ROT neurotoxic effects was observed for CBD and its derivatives. Thus (-)-CBD (**1a**) was marginally more potent than (+)-CBD (**1b**). But the CBD analog derived from (+)-car-3-ene (**72**), i.e., (+)-carenadiol (**45a**), is of interest because of its high protective index (PI= 5.1) and is therefore comparable to (**1b**) (to which it is stereochemically related) in potency. On the other hand the 1",1"-dimethylheptyl derivative [(+)-**45b**], could not separate anticonvulsant activity from neurotoxicity.

From time immemorial mankind has sought cure for its pain, agony and diseases in nature. Mixtures of natural herbs,roots and plants possessing certain pharmacological properties have been the source of folklore medicines in different cultures around the world up to the present time. Most of these folklore medicines evolved not only due to the religious beliefs and social traditions but also from the therapeutic knowledge of practicing physicians of plantlore, keen observations, experiments and clinical trials. It is only during the 20th century that our understanding of biological sciences and human physiology has advanced to a point where novel synthetic therapeutic agents have played a major role in the treatment of variety of diseases. The development of many such modern synthetic therapeutic agents relates to structural modification of biologically active natural products which can be traced back to folklore medicines as their origin. Numerous examples of such synthetic therapeutic agents are known in the history of medicine. Penicillin from *Penicillium notatum*, digitoxin from the *Digitalis purpurea*, reserpine from *Rawulfia serpentina*, are the striking examples of such developments which have benefitted all mankind.

Marihuana or *Cannabis sativa L.*, one of the oldest plants grown by man, is an ideal example of a natural product which has been used by folklore for its therapeutic potential. For centuries man has used *Cannabis sativa* for the fiber in its stem, the oil in its seeds, and has used its various preparations for psychotomimetic and perported medicinal effects. The Chinese were the first to describe the medicinal properties of cannabis about 2000 years ago (Li, 1974). In India cannabis was widely used to treat a wide variety of ailments such as for relief of pain, muscle spasms, and convulsions occuring in tetanus, rabies, rheumatism, and/or epilepsy. Cannabis and its preparations were introduced for such a wide spectrum of medicinal uses to western medicine by an Irish physician practicing in India, William O'Shaughnessy (1842). Also the Indian Hemp Commission Report (1893) cited

Cannabis indica as one of the most important drugs of Indian Materia Medica. Following O'Shaughnessy's report Cannabis indica was widely used in Europe and America for the treatment of wide variety of ailments including migraine, depression, rheumatism, epilepsy, excessive menstrual bleedings, ulcers, menstrual cramps, childbirth psychosis, cough, insomnia, withdrawals from opiates, and relief of pain especially of neuralgic character.These applications made tincture of cannabis an official entry to British Pharmacopoeia as well as the United States Pharmacopoeia and National Formulary. Towards the end of the 19th century and by 1940, the developing pharmaceutical industry attempted to purify the constituents of cannabis and develop totally synthetic isomers and homologs of its active principle However most of these early attempts met with little success as (The La Guardia Report , 1939-1944).

In spite of all its medicinal promise the use and investigations with cannabis and synthetic cannabinoids began to decline by the late 1930s.Cannabis and its preparations were eliminated from British Pharmacopoaeia by 1932 and from the United States Pharmacopoaeia and National Formulary by 1942. The decline in use of cannabis as a therapeutic agent could perhaps be attributed to the : a) general lack of specificity of the therapeutic action; b) extreme variation in potency of different lots of cannabis preparations and hence difficulty in establishing the reproducible and reliable clinical effects; c) lack of solubility in water; and d) increasing availability of more specific medicinal agents of known potency for the same symptoms.or diseases.

In the early 1960s the illicit use of marihuana as an intoxicant spread with alarming growth among the youth and this caused a grave social concern. This, in addition to the early pioneering chemical research of Adams (1941-42), Todd (1946) and the pharmacological research of Loewe (1950), regenerated world wide interest on the chemical, pharmacological and toxicological aspects of marihuana.and its constituents.

CHEMICAL CONSTITUENTS OF *CANNABIS SATIVA*

The understanding of the pharmacology and biogenesis of a biologically active natural product can be achieved only when the chemistry has been well established and the pure compounds of known structure and stereochemistry are available for scientific use.

Consequently efforts were geared towards the isolation,and characterization of the chemical constituents of cannabis in the second half of the 20th century. Cannabinoids was the general term coined for the compounds, possessing cannabis activity which could be either isolated from cannabis or synthetic analogs. After the isolation and characterization of delta-9-tetrahydrocannabinol (**delta-9-THC, 3**), Mechoulam and his coworkers (Gaoni and Mechoulam, 1964; Mechoulam and Gaoni, 1965) synthesized delta-9-THC and proved beyond doubt that it was the major psychoactive component, of *Cannabis sativa L.* Another major nonpsychoactive component, cannabidiol (**CBD**) was isolated by Adams et al. (1940), but its structure was determined later in 1960s by Mechoulam and Shvo (1963) following several incorrect structural assignments. Since then seventeen other different classes of chemical compounds in addition to cannabinoids have been isolated and characterized during last two decades. Table 1 shows the classes of chemical constituents isolated thus far from *Cannabis sativa*.. At present, over 61 naturally occuring cannabinoids have been characterized (Turner et al., 1980). Many of these compounds are present in very low concentrations and play little or no part in the pharmacological profile of the plant. The most abundant natural cannabinoids isolated are shown in Fig 1. The relative abundance of these constituents varies considerably with both the source and generic strain of the plant.Cannabidiol (**CBD, 1**), and delta-9-THC (**2**) and cannabinol (**CBN, 5**) are usually the most abundant although cannabichromene(**CBC, 7**) can be the second most abundant cannabinoid in certain plants rich in delta-9-THC.

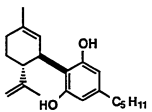
TABLE 1. CHEMICAL CONSTITUENTS OF CANNABIS@

CHEMICAL CLASSES	NO. KNOWN
Cannabinoids	61
Cannabigerol (CBG)	6
Cannabichromene (CBC)	4
Cannabidiol (CBD)	7
Delta-9-tetrahydrocannabidiol (Δ^9-THC)	9
Delta-8-tetrahydrocannabidiol (Δ^8-THC)	2
Cannabicyclol (CBL)	3
Cannabielsoin (CBE)	3
Cannabinol (CBN)	6
Cannabinodiol (CBND)	2
Cannabitriol (CBT)	6
Other cannabinoids	13
Nitrogenous compounds	20
Quarternary bases	5
Amides	1
amines	12
Spermidine alkaloids	2
Amino acids	18
Proteins, glycoproteins, enzymes	9
Sugar and related compounds	34
monosaccharides	13
Disaccharides	2
Polysaccharides	5
Cyclitols	12
Aminosugars	2
Hydrocarbons	50
Simple alcohols	7
Simple aldehydes	12
Simple ketones	13
Simple acids	20

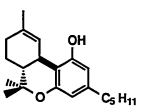
TABLE 1 CHEMICAL CONSTITUENTS OF CANNABIS (contd.)

CHEMICAL CLASSES	NO. KNOWN
Fatty acids	12
Simple esters and lactones	13
Steroids	11
Terpenes	103
Monoterpenes	58
Sesquiterpenes	38
Diterpenes	1
triterpenes	2
Miscellaneous Compounds of terpenoid origin	4
Noncannabinoid Phenols	16
Flavanoid glycosides	19
Vitamins	1
Pigments	2
Total	421

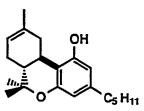
@ Reproduced from Turner et al. (1980).



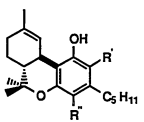
1a. Cannabidiol (CBD)



2. Delta-9-THC

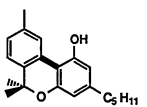


3. Delta-8-THC

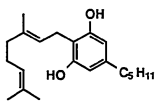


4a. Delta-9-THC acid A
R'= COOH, R"= H

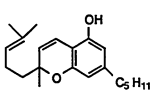
4b. Delta-9-THC acid B
R'= H, R"= COOH



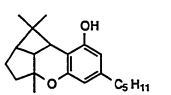
5. Cannabinol (CBN)



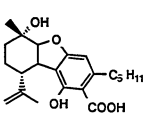
6. Cannabigerol (CBG)



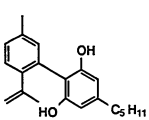
7. Cannabichromene (CBC)



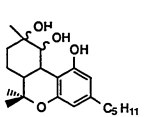
8. Cannabicyclol (CBL)



9. Cannabielsoic acid A

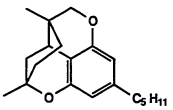


10. Cannabinodiol (CBND)

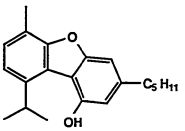


11. Cannabitriol

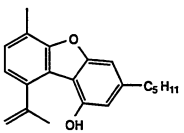
Fig. 1. Natural cannabinoids



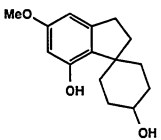
12. Cannabicitran



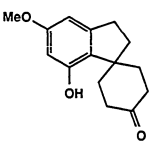
13a. Cannabifuranne



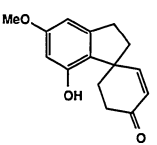
13b. Dehydrocannabifuranne



14. Cannabispirol



15. Cannabispirone



16. Cannabispirenone

Fig. 1 (contd.). Natural Cannabinoids

The total number of compounds known to occur in *Cannabis* is 421, with new compounds constantly being discovered and added to the list.

Cannabinoids were defined by Mechoulam and Gaoni (1967b) as "the group of C_{21} compounds typical of and present in *Canabis sativa*, their carboxylic acids, analogs, and transformation products." Cannabinoids belong to the chemical class of terpeno-phenolics, which are widely distributed in nature. However, cannabinoids as such are only found naturally in *Cannabis sativa.*

NUMBERING SYSTEMS OF CANNABINOIDS

Five numbering systems have been used in the literature for the cannabinoids (Fig 2a, Eddy 1965) but two of these, namely the monoterpene numbering based on p-cymene and dibenzopyran numbering, are used most commonly.

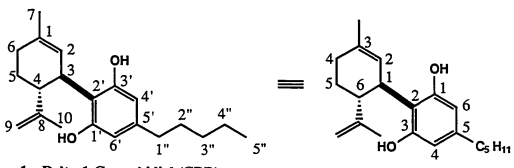
According to the dibenzopyran system the major psychoactive cannabinoid is designated as delta-9-THC (**2**) and this system is used mainly in North America. The only disadvantage of this system is that it can not be applied to the cannabinoids lacking a pyran ring such as cannabidiol (**CBD 1**, Fig 2b). Neverthless the dibenzopyran system has been adopted by several referencing sources including Chemical Abstract Services.

On the other hand the monoterpene system, which is most preferred in Europe can accomodate cannabinoids lacking a pyran ring such as CBD. In this system the benzene ring and the side-chain are numbered separately. Accordingly delta-9-THC is redesignated as delta-1-THC (**2**, Fig 2b).

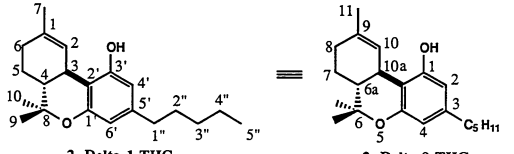
Throughout this manuscript the monoterpene numbering system has been used for CBD like compounds and benzopyran numbering has been used for THC like compounds. In experimental section Chemical Abstract nomenclature has been used, followed by the commonly accepted trivial name wherever possible.

Monoterpene
(based on p-Cymene)
Used in this Text
for CBD type compds.

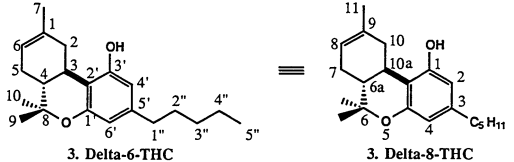
Dibenzopyran
(Adopted by CAS)
Used in this Text
for THC type compds.



1a. Delta-1-Cannabidiol (CBD) **1a. Delta-1-Cannabidiol (CBD)**

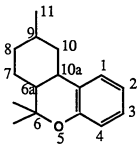


2. Delta-1-THC **2. Delta-9-THC**



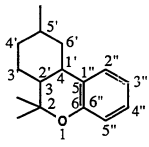
3. Delta-6-THC **3. Delta-8-THC**

Fig. 2b. Commonly used numbering systems for cannabinoids

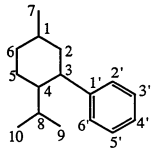


I. Dibenzopyran

(Adopted by **CAS**)
Used in this Text

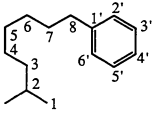


II. Used by **Todd**

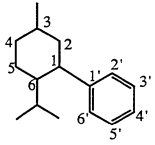


III. Monoterpene

(based on p-Cymene)
Used in this Text



IV. Monoterpene



V. Diphenyl

Fig. 2a. Numbering systems used for cannabinoids

CANNABINOIDS AS THERAPEUTIC AGENTS

As mentioned earlier several therapeutic applications have been claimed over the centuries for crude cannabis preparations. Out of all these purported medicinal uses only analgetic, antiasthamatic, anticonvulsive, sedative,hypnotic, antirheumatic, antidiarrheal, antibiotic, appetite stimulant, and antipyretic have received some substantiation in the last two decades. But from a modern point of view marihuana or these crude cannabis preparations could not be used as a drug in the treatment of specific ailment. The reasons being: a) they are known to cause unpleasant and occasionally alarming reactions (Abel, 1980; Rubin, 1975); b) it is difficult to obtain uniform and reliable preparations and dosage forms since cannabis contains over 421 different chemical compounds in variable proportions and most of them have never been pharmacologically evaluated; c) like other natural products it lacks specificity.

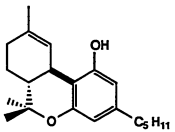
One of the objectives of pharmaceutical sciences is to extract therapeutically useful compounds from the crude material and to make them available in pure form to pharmacologists for their systematic therapeutic evaluations. Most of the therapeutic applications attributed to cannabis have been attributed to the effect of its major psychoactive constituent delta-9-THC (**2**) and to a lesser extent to the other major nonpsychoactive constituent, cannabidiol (**CBD, 1**).

DELTA-9-THC AS THERAPEUTIC AGENT

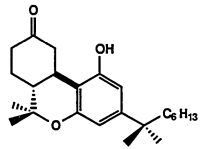
After its isolation and structure elucidation, delta-9-THC was the most thoroughly investigated cannabinoid for its pharmacological effects in experimental animals and in man (Cohen and Stillman, 1976). At present delta-9-THC has been extensively studied experimentally as an analgesic, antidepressant, anticonvulsant, hypnotic, tranquilizer, antiemetic, and as a treatment for glaucoma and for withdrawal symptoms (Razdan and Howes, 1983;

Nahas,1984; Mechoulam, 1986). As a result of such exhaustive research, delta-9-THC (Dronabinol®; Marinol®; Unimed Inc.) has emerged as a very effective drug for controlling nausea and vomiting in patients undergoing cancer chemotherapy. But due to its chemical instability, poor oral bioavailability (6-15%), and psychic as well as cardiovascular side effects, delta-9-THC is not the drug of choice. However some of the synthetic analogs of delta-9-THC, especially, nabilone (**17**), levonantradol (**18**), nabitan (**19b**),and naboctate (**23**), as shown in Fig 3ab, have also shown efficacy either as an antiemetic or antiglaucoma agent. These newer agents appears to be less toxic than delta-9-THC. Also many of these analogs are crystalline, and thus more readily absorbed after oral administration. Nabilone (Caesamet®; Eli Lilly Co.) is currently available in United States and many other countries including Canada and Switzerland. Levonantradol (Milne et al., 1980) is a very potent compound with analgetic and antiemetic activity (Cronin et al., 1981; and Diasio et al., 1981) but due to its marked cannabis-like side effects its use in clinical trials has been abandoned from 1982. From the clinical data obtained so far, naboctate given orally appears to be effective in normotensive subjects with no major side-effects and is superior to nabitan. This drug is under development for the treatment of glaucoma.

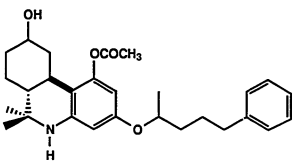
Another most significant therapeutic application of cannabinoids is in the management of epileptic seizures which has been discussed below.



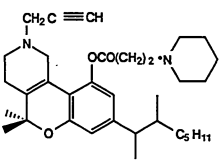
2. Delta-9-THC



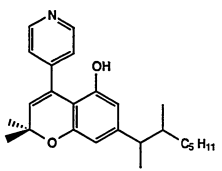
17. Nabilone



18. Levonentradol

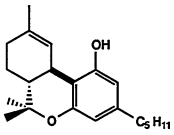


19b. Nabitan

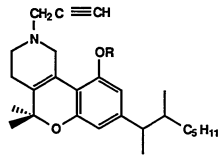


20. BRL 4664

Fig. 3a.. Antiemetic cannabinoids



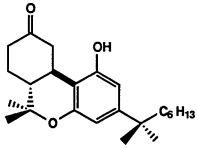
2. Delta-9-THC



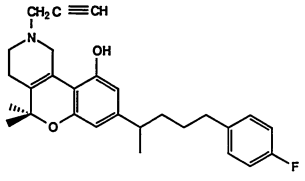
19a. SP-1, R= H

b. Nabitan, R= $CO(CH_2)_3N$ HCl

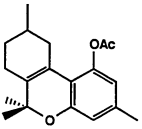
c. SP-204, R= $COCH(CH_3)CH_2CH_2N$ 2HCl



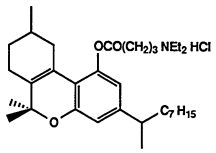
17. Nabilone



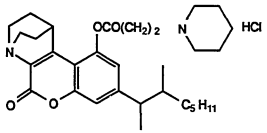
21. A-41988



22. Piranabine



23. Naboctate



24. SPA-229

Fig. 3b. Cannabinoids as antiglaucoma agents

AN OVERVIEW OF SEIZURE DISORDERS (Consroe and Snider, 1986).

Epilepsy is of great sociomedical importance. It is one of the most prevalent neurological disorders: about 1% of population are affected (Juul-Jensen and Foldspang, 1983), 3% have had a recurrent seizure disorder at some time in their life, and 9% have experienced at least one epileptic seizure.Epilepsy most commonly begin in early childhood but can appear at any time. It tends to last for life, and may have profound medical, economic, social, and legal consequences for the affected individuals.

An epileptic seizure is a paroxysmal event that consists of a transient distortion of normal electral activity in the brain and some alteration of normal motor, sensory, autonomic,or psychic function. Epileptic disorders can be considered either primary which can be characterized as conditions of intrinsic, nonprogressive, and presumably hereditary cerebral hyperexcitability with seizures as the only manifestation of disordered brain function or secondary in which epileptic attacks are symptomatic of some known pathogenic process affecting the brain.

Epileptic seizures can be classified under two major headings based upon the clinical manifestations of the attack and the pattern of the electroencephalogram (EEG) as defined by the Commission on Classification and Terminology of the International League Against Epilepsy (Dreifuss, 1981).

1) Partial seizures originate in and are largely restricted to one region or focus of cerebral tissue. These are the most commonly occuring attacks and are further subdivided as: a) simple partial (cortical focal), and b) complex partial(temporal lobe or psychomotor) seizures.

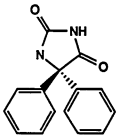
2) Generalized seizures involve diffuse, usually bilateral, areas of brain. Some of the common type of the primary generalized seizures are: a) grand mal (tonic-clonic and clonic-tonic-clonic), b) myoclonic, and c) absence (petit mal) seizures. Mixed

seizure types may also be present at the begining or evolve during the course of the illness.

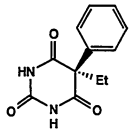
Symptomatic epilepsy may result from head trauma, neoplasma, cerebral vascular disorders, infection, metabolic derangement and high fever in young children. The cause(s) of idiopathic epilepsy is (are) unknown, but genetic factors are involved in many cases.

The molecular bases of epileptogenesis are still unknown but research has shown that abnormalities of central neurotransmitters such as gamma aminobutyric acid (**GABA**) may be involved (Fariello and Ticku, 1983). In addition to deficient GABA, deficient neurotransmission or function of taurine, norepinephrine, and serotonin, and/or excessive neurotransmission or function of aspartate and glutamate also may play contributing role (Emson, 1978; Jobe and Laird,1981).

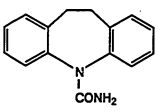
Clinical trials together with many years of experience have provided general therapeutic guidelines for different seizure types, however there is no firm evidence for which drug is more suitable for which seizure type (Gram et al., 1982). Antiepileptic drugs (Fig 4), phenytoin (**PHT, 25**), phenobarbital (**PB, 26**), carbamazepine(**CBZ, 27**), and primidone (**28**) are the four primary drugs used to treat partial seizures (Delgado-Escueta et al., 1983; Porter, 1983).Valproic acid (**29**) has been recommended as a first choice in addition to PHT or CBZ in the treatment of primary generalized seizures of the grand mal type (Delgado-Escueta et al., 1983; Porter, 1983). Ethosuximide (**ESM, 30**) is generally considered the first chioce for generalized absence seizure, but valproic acid and clonazepam (**31**), also are effective in many cases. Valproic acid is also used to treat some forms of generalized myoclonic seizures (Delgado-Escueta et al., 1983; Porter, 1983).



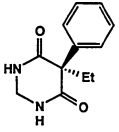
25. Phenytoin (PHT)



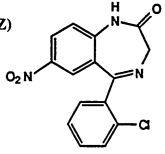
26. Phenobarbital (PB)



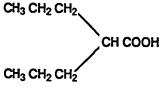
27. Carbamazepine (CBZ)



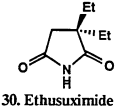
28. Primidone



31. Clonazepam



29. Valproic acid (Valproate)



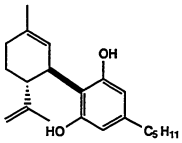
30. Ethusuximide

Fig. 4. Standard antiepileptic drugs (commercial)

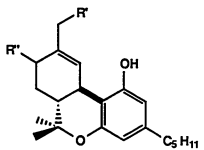
Even though these antiepileptic drugs are the mainstay of the seizure treatment, the problems and limitations associated with them are: a) lack of effective long term control of seizures, and/or b) drug toxicity e.g., adverse effects on arousal, motor performance, mood and other body functions. It has been estimated that 20 to 30% of epileptics are not adequately controlled with the currently available drugs used alone or in combination. Since the introduction of carbamazepine, clonazepam, and valproic acid in the United States in the 1960's there have been no new drugs for epilepsy. Taken together, there is a need for more effective and safe drugs to treat this common and debilitating conditions.

CANNABINOIDS IN SEIZURE DISORDERS

The folkloric use and numerous anecdotal accounts of the antiseizure activity of cannabis preparations (O'Shaughnessy,1842; Loewe and Goodman, 1947; Davis and Ramsey, 1949) provided the initial lead for the systematic investigation and evaluation of cannabinoids for anticonvulsant properties. As a result since 1971 numerous reports have confirmed that marihuana, its constituents, and related congeners have anticonvulsant properties. Followed by their isolation and availability as pure compounds via chemical synthesis, four major cannabinoids, delta-9-THC (2) (Garriott et al., 1968;Sofia et al., 1971a,b, McCaughran et al. 1973), delta-8-THC (**3**), (Consroe et al., 1973; Consroe and Mann, 1973), cannabidiol (**CBD, 1a**) (Carlini et al., 1973; Izquierdo and Tannhauser, 1973; Izquierdo et al., 1973; Karler et al. 1973,1974b; and Turkanis et al., 1974) and cannabinol (**CBN, 5**) (Karler et al. 1973) were found to have anticonvulsant properties in several species of laboratory animals such as mice, rats, and frog. In addition 11-hydroxy and 8,11-dihydroxy-delta-9-THCs, important metabolites of delta-9-THC also showed anticonvulsant activity against in the rat and frog (Karler et al., 1974a,c) (Fig 5).



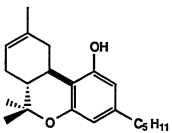
1. CBD



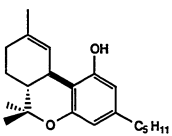
2. Delta-9-THC, R"= R"= H

32. 11-OH-delta-9-THC, R'= OH, R"= H

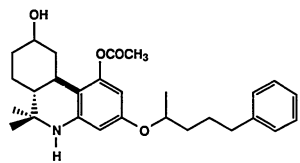
33. 8,11-Dihydroxy-delta-9-THC, R'=R"= OH



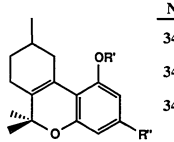
3. Delta-8-THC



4. CBN



18. Levonentradol



34. Delta-3-THCs

No.	Name	R'	R"
34a.	Delta-3-THC,	H	C_5H_{11}
34b.	Synhexyl,	H	C_5H_{11}
34c.	DMHP, (Dimethylheptylpyran)	H	$C(Me)_2C_6H_{13}$
34d.	SP-175	$CO(CH_2)_3N$	$C(Me)_2C_6H_{13}$

Fig. 5. Cannabinoids of interest as anticonvulsants

In general most anticonvulsant studies were focused on delta-9-THC because of its distinction as being the major psychoactive constituent of marihuana and its availability in pure form. A review of the reported effects of delta-9-THC in laboratory animals for a variety of experimentally-induced seizure paradigms has been published(Consroe et al., 1976) and updated (Consroe and Snider, 1986).Although the spectrum of anticonvulsant activity of delta-9-THC resemble, in many respects, to that of the standard antiepileptic drug, phenytoin (**25**) (Consroe et al., 1976; Sofia et al., 1976; and Turkanis et al., 1974), there are several disturbing findings which limit its usefulness as potential anticonvulsant. In laboratory animals delta-9-THC and its closely related analogs exhibit a narrow separation between anticonvulsant and neurotoxic properties (Consroe and Walkin, 1977; Karler and Turkanis, 1979), exhibit anticonvulsant tolerance (Fried and McIntyre, 1973; Karler et al., 1974d; Karler and Turkanis,1976a,b, 1981), and actually can produce convulsions in some seizure susceptible animals (Consroe et al., 1976; Martin and Consroe, 1976; Feeney et al. 1976; Feeney, 1979; Craigmill,1979; Chiu et al., 1979; Turkanis and Karler, 1981; and Consroe et al., 1982). In humans, delta-9-THC elicits well known psychoactive, cardiotoxic and other undesirable effects (Perez-Reyes et al. 1973; Hollister, 1974; Hollister and Gillespie, 1975; and Jones, 1983). Similar findings of psychoactivity, cardiac effects, relatively low anticonvulsant potency and specificity and/or anticonvulsant tolerance also limit the therapeutic potential of most other cannabinoids, e.g., delta-8-THC (**3**), 11-hydroxy- (**32**), 8,11-dihydroxy-THC (**33**), CBN (**5**), and delta-3-THCs (**34**) (Consroe and Man, 1973; Karler et al., 1974c, 1976a,b.)

CANNABIDIOL IN SEIZURE DISORDERS

However of all natural cannabinoids studied so far, cannabidiol (**CBD**) is the only major neutral nonpsychoactive cannabinoid of *Cannabis sativa* which appears to have an

excellent potential as an anticonvulsant. Numerous reports (Carlini et al., 1973; Izquierdo and Tannhauser, 1973; Izquierdo et al., 1973; Karler et al. 1973, 1974b; and Turkanis et al., 1974) have confirmed its ability to prevent various kind of seizures in laboratory animals. Consroe et al.(1981) have summarized the anticonvulsant effects of CBD for variety of experimental seizure paradigms in laboratory animals. In general CBD has dose-response anticonvulsant activity in variety of seizure tests across species of laboratory animals. CBD has good selectivity of anticonvulsant action relative to neurotoxicity. Unlike the THCs CBD does not produce anticonvulsant tolerance. Moreover CBD is devoid of THC-like CNS excitatory effects including convulsions in seizure susceptible animals and in fact can prevent THC-induced seizures (Consroe et al.,1977). All these findings have demonstrated that anticonvulsant profile of CBD especially with respect to potency, efficacy, and lack of anticonvulsant tolerance is comparable with the classical anticonvulsants phenytoin, phenobarbital, carbmazepine and ethosuximide (Karler and Turkanis, 1981), that are useful for the treatment of partial seizures, and generalized seizures of the grand mal type.

In normal man, CBD, given acutely or chronically, does not produce typical THC-like cognitive, psychomotor and cardiovascular effects and so far, is devoid of any significant side effects. (Perez-Reyes et al., 1973;Hollister, 1973, 1974; Karniol et al., 1974; Wall et al.,1976; Dalton et al., 1976; Cunha and Carlini, 1981; Benowitz and Jones, 1981). A clinical trial of CBD (given daily for up to 4-5 months) in human epileptic patients, produced a reduction of clinical seizures and no significant side effects (Cunha et al.,1980).

These preliminary experimental results in laboratory animals together with the preliminary results in humans suggest that: a) CBD can be a very useful anticonvulsant agent in the treatment of grand mal and psychomotor seizures; b) has potency comparable to that

of phenytoin, and phenobarbitol; and c) can augment the anticonvulsant effects of phenytoin phenobarbitol and some other anticonvulsant drugs (Karler and Turkanis, 1976a; Turkanis et al., 1974; Consroe and Wolkin,1977).

CANNABIDIOL IN MOVEMENT DISORDRES

Recently it has been suggested that CBD may also have efficacy for human movement disorders. The term 'movement disorder' is used for a group of clinical syndromes that have in common a deficit in nonpyramidal motor function and usually one or more of the nonepileptic, abnormal involuntary movements (Marsden et al. 1984). The parkinsonism syndrome of bent posture, slowness of movement, and tremors of the hands is the best known example. However movement disorders may be found in at least 100 neurological, psychiatric, drug-induced, and other type of medical conditions (Yung, 1983). A review of the potential therapeutic effects of cannabinoids in movement disorders has been published. (Consroe and Snider,1986). It was proposed that CBD may have therapeutic value in patients with hyperkinetic movement disorders (dystonia, essential tremors, and drug induced dyskinesia) in chronic doses that are not associated with any significant side-effects. Most recently, preliminary clinical trials of CBD in dystonia (Consroe et al., 1986) and in Huntington's chorea (Sandyk et al., 1988) were carried out. Results of these investigations suggested that CBD reduced the abnormal movements (dystonia, and chorea) and produced no side-effects.

CANNABIDIOL AS AN ANTIANXIOLYTIC AGENT

CBD also has been investigated for its possible anxiolytic properties in laboratory animals (Musty, 1984; and Musty et al., 1984). The authors have demonstrated that CBD: 1) reduces tremor and seizure activity associated with withdrawal from alcohol dependence,

2) facilitates the acquisition of an active avoidance behavior, 3) reduces the suppression of a punished response, and 4) reduces the development of stress induced ulcers. They have concluded that CBD produces pharmacological effects which are similar to drugs that have been established as having anxiolytic properties in both animals and man,e.g.,clonidine (Tseng et al., 1975; Lipman and Spencer, 1978; Goldet al. 1978) and diazepam (Miczek, 1973a,b; and Rickels,1981).

METABOLISM OF CANNABIDIOL

Extensive literature has been published in recent years elucidating the major bio-transformation pathways involved in the metabolism of the cannabinoids (Mechoulam et al 1976;Harvey et al 1978). Metabolism has been studied in a wide variety of laboratory animal species including rats, mice, rabbits, dogs, guinea-pigs and rhesus monkeys, but less is known about metabolism by man. For example the metabolism of CBD has been studied in vitro in the rat (Nilsson et al 1971; Martin et al., 1976, 1977) and found to yield wide variety of metabolites hydroxylated both in the monoterpene moiety and in all five positions in the side-chain ; and the metabolism of CBD is similar to that of delta-9-THC (2) (Agurell et al, 1976). The important sites of metabolism in CBD are shown in Fig 7. As with delta-9-THC (Wall et al 1976), delta-8-THC (Burstein et al 1970), and CBN (widman et al 1971), 7-hyhdroxylation (Fig 6) has been established as the major route of metabolism in the rats and rabbits (Agurell et al., 1976) and in man (Wall et al., 1976) for CBD. In THC series 7-hydroxylation (Truitt, 1971; and Christenssen etal., 1971) as well as side chain hydroxylation enhance pharmacological activity. By analogy with the THC series the anticonvulsant activity of CBD could be enhanced by hydroxylation in these positions. Moreover 7-hydroxy CBD (**37**) may turn out to be of considerable clinical importance in elucidating the mode of action of CBD.

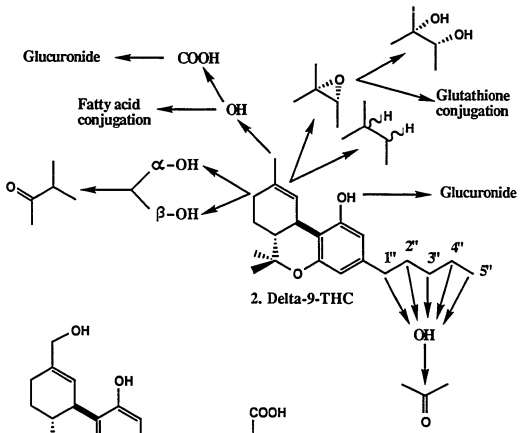


Fig 6. Metabolic sites and important metabolites of THC in man

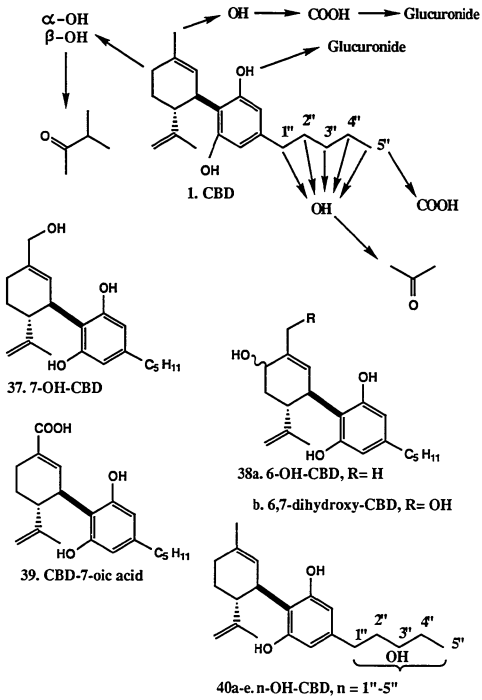


Fig. 7. Metabolic sites and important metabolites of CBD

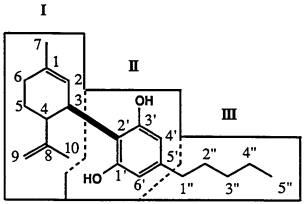
However, no data are available on the potential anticonvulsant or any pharmacological effects of these CBD metabolites as of this time.

RATIONALE AND STRUCTURE ANTICONVULSANT ACTIVITY RELATIONSHIP OF CBD AND ITS ANALOGS

The potential usefulness of CBD as an anticonvulsant indicates the significance of additional studies that can delineate structure anticonvulsant relationship (**SAR**) by synthesizing a wide variety of CBD analogs and evaluating them for the anticonvulsant activity.

In order to delineate anticonvulsant SAR of CBD, our approach was to envisage the CBD molecule as composed of 3 principal units: 1) the terpene moiety, 2) aromatic ring, and 3) alkyl side chain (Fig 8) and to systematically modify each unit using classical SAR techniques. The techniques employed were:1) isosteric replacement of atoms and functional groups (Thronber, 1979); 2) homologation of rings and side chains; 3) synthesis of potential prodrugs derivatives (Sinkula,1975); 4) blockade of known (or potential) sites of biotransformation; 5) modification of stereochemistry at asymmetric centers; and 6) design of conformationally restricted analogs. In addition we also followed the lead from the previous SAR studies with delta-9-THC and congeners carried out by others (Mechoulam and Gaoni, 1967; Mechoulam et al., 1976; Razdan, 1973, 1986; Pars et al., 1977; Wilson and may, 1975; Archer et al., 1977; Johnson and Milne, 1980; Apsimon et al.,1982; Gardner and miller, 1984; Melvin et al., 1984).

Before our group got involved in this field, there was only one report published (Carlini et al., 1975) on the anticonvulsant effects of four terpene ring oxygenated putative CBD metabolites (Table 2). All of them were found active in mice against maximal electroshock seizures (MES) but none of them was found to be more effective than CBD.



1. Delta-1-Cannabidiol (CBD)

I. Terpenyl Unit

II. Aryl Unit

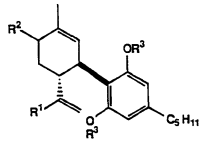
III. Side Chain

Fig. 8. CBD molecule from SAR point of view

Table 2.

SAR data of CBD analogs in MES test in mice[a]

I. Modification within the terpene ring:



41

Compd.No.	R^1	R^2	R^3	E/F[b]	comments
1a	Me	H	H	2.8	most active at high concentration.
41a	CHO	H	Ac	3.9	toxic, no protection
41b	Me	=O	Ac	2.8	as active as CBD at high concentration.
41c	Me	AcO	Ac	5.1	toxic at low concentration
41d	CH2OAc	H	Ac	4.1	less active than CBD

[a]Data taken in part from Carlini et al., 1975.

[b]E/F = Extension to Flexion ratio.

Since then several CBD analogs have been synthesized and have been evaluated for their anticonvulsant profile by us (Consroe et al. 1981, 1985; Martin et al., 1987a,b) and others (Leite et al. 1982; Martin et al., 1984) in laboratory animals.

These analogs represents alteration in: 1) stereochemistry of CBD; 2) terpene moiety; 3) aryl moiety; and 4) alkyl side chain. The results have been presented in Table 3.

Based on these results following conclusions concerning the structure-anticonvulsant activity relationships among cannabidiol analogs could be drawn.

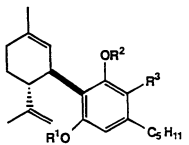
1. Both phenolic hydroxyl groups have to be free or esterified for anticonvulsant action.
2. Acetate ester groups are apparently hydrolyzed in vivo.
3. Substitution at C-4' in aryl unit results in loss of activity.
4. Change in the position of phenolic groups (e.g., abn-CBD) also results in loss of activity.
5. Oxidation in terpenyl moiety [e.g., 6- and 9-oxo derivatives (putative metabolites) retains the activity with toxicity.
6. Hydroxylation in terpenyl moiety (e.g., 6- and 10-hydroxy) does not improve activity over CBD.
7. The addition of N-ethyl or GABA functional group does not appear to impart greater activity.
8. CBD-like anticonvulsant activity appears to be nonstereoselective.
9. CBD like anticonvulsant activity might be conformationally dependant (e.g. pinenyl derivatives).
10. Side chain branching at C-1" position increases anticonvulsant potency and (usually) neurotoxicity.

Table 3

Protective Index (PI) data of standard anticonvulsants and CBD analogs in ROT and AGS tests[a].

Compd. No.	Protective Index (PI)
25. Phenytoin (PHT)	1.6
26. Phenobarbitol (PB)	2.7
27. Carbamazepine (CBZ)	2.7

L (-)-CBD Aryl Ring Modifications:

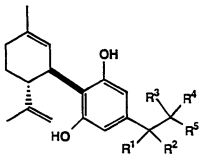


42

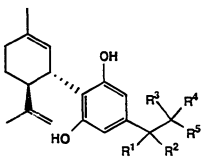
Compd. No.	R^1	R^2	R^3	PI/Comments
1a.	H	H	H	2.1
42a.	Ac	Ac	H	4.2
42b.	H	Ac	Ac	inactive
42c.	Me	Me	H	inactive
42d.	Me	H	H	inactive

Table 3 (continued)

II. (-)-CBD. Side Chain Modifications:



(-)-43

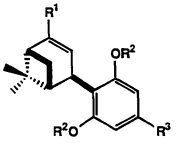


(+)-43

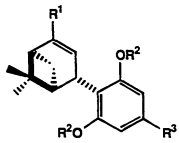
Compd. No.	R^1	R^2	R^3	R^4	R^5	PI/Comment
(-)-43a.	Me	Me	H	H	n-pentyl	0.6
43b.	Me	Et	H	H	n-pentyl	-
43c.	Me	n-allyl	H	H	n-pentyl	inactive
(-)-43d.	Me	Me	H	H	n-butyl	-
43e.	Me	Et	H	H	n-butyl	-
43f.	Me	n-allyl	H	H	n-butyl	-
43g.	H	H	Me	Me	n-pentyl	-
(+)-43a.	Me	Me	H	H	n-pentyl	potent but toxic

Table 3 (continued)

III. (-)- and (+)-Pinenyl analogs (conformationally restricted)



(-)-44



(+)-44

Compd. No.	R^1	R^2	R^3	PI/Comments
(-)-44a.	Me	H	n-pentyl	-
44b.	Me	H	1,1-DMH	1.8
44c.	CH2OAc	H	1,1-DMH	1.0
44d.	CH2OAc	Ac	1,2-DMH	-
44e.	CH2OPv	H	1,1-DMH	-
(+)-44a.	Me	H	n-pentyl	-
44b.	Me	H	1,1-DMH	2.7
44d.	CH2OAc	Ac	1,2-DMH	-
44e.	CH2OPv	H	1,1-DMH	-
44f.	CH2OAc	Ac	1,1-DMH	-

[a]Data taken, in part from Martin et al., 1986.

Chemical abbreviations: Ac= acetyl, Pv= pivaloyl, and

1,2-DMH= dimethylheptyl.

11. Maximum anticonvulsant potency and neurotoxicity are seen with 1",1"-dimethylheptyl side chain.

12. Optimal therapeutic index is seen with 1"-methyl,.1"-ethylheptyl side chain.

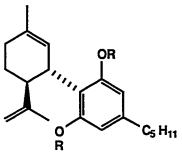
In general it seems that the aryl unit and the side chain of CBD are highly sensitive to structural modification. On the other hand structural changes within the CBD-terpene unit (limonenyl) appears to be relatively insensitive compared to its substitution with new terpenoid. Also there is a general lack of stereoselectivity associated with the terpene unit.

For the above SAR a novel animal model audiogenic seizure (**AGS**) susceptible rat model of epilepsy (Dailey and Jobe,1985), also known as the genetically epilepsy prone rat or GEPR was used to assess anticonvulsant activity, and the rotorod (**ROT**) paradigm (Dunham and Miya, 1957) was used to assess differential neurotoxicity (i.e., reflecting mainly sedation and/or incoordination) in our laboratory. The CBD analogs, suspended in vehicle of 10% polysorbate and 90% distilled water, were injected intravenously (iv) and rats were tested 15 minutes later (a peak-effect time for both the tests). In AGS test, responses to sound were recorded as the presence or absence of seizure (i.e., generalized clonus or clonus and generalized flexion). In the ROT test, effects were measured as the ability or inability (i.e., neurotoxicity) of trained rats to remain on a revolving drum (rotorod) for 60 seconds. Protective indexes (PI) were calculated as a ratio of ROT-TD_{50} to AGS-ED_{50}.

OBJECTIVE

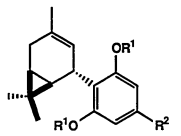
On the basis of the results known so far the objective of the present study was to further investigate the requirement for structure anticonvulsant activity of CBD and design potential anticonvulsant agents with aim to optimize anticonvulsant activity as a function of structure. The Fig 9 shows the proposed target analogs.

1. (-)- Cannabidiol analogs.



No.	R	
1b.	H	(+)- Cannabidiol
1d.	Ac	

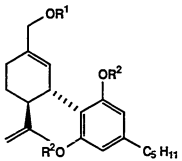
45. (+)- Delta-3-Caryl analogs.



No.	R^1	R^2
45a.	H	n-pentyl
b.	Ac	n-pentyl
c.	H	1",1"- DMH

DMH = Dimethylheptyl

46. (+)- 7-Hydroxy-CBD analogs.



No.	R^1	R^2
46a.	H	H
b.	Ac	H
c.	Ac	Ac

Fig. 9. Proposed CBD analogs

SYNTHESIS OF CANNABIDIOL

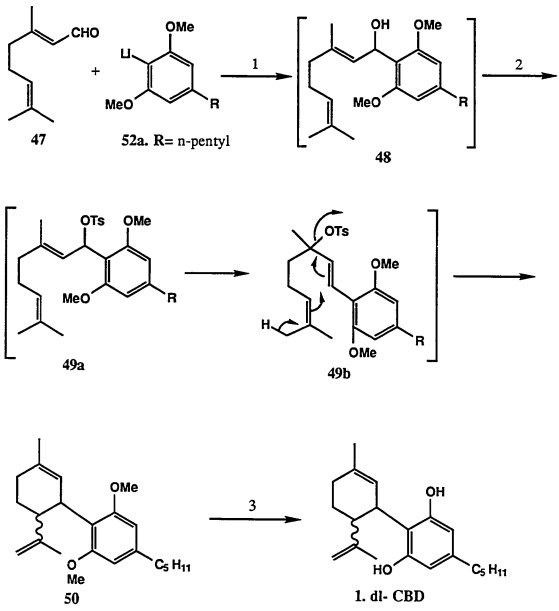
(-)-Cannabidiol (**CBD, 1a**) is a major neutral cannabinoid of the plant *Cannabis sativa*. It was first isolated in the early 1940's (Adams, Baker, and Wearn, 1940). Its structure was elucidated (Mechoulam and Shvo, 1963; Mechoulam and Gaoni,1967) and was confirmed by X-ray crystallography (Jones et al. 1977, and Ottersen et al., 1977). This natural material has a 3,4-trans ring substitution with a double bond at C-1.

SYNTHESES OF RACEMIC CBD (1)

The first total synthesis of racemic CBD (**1**) which is of historical interest and patterned eloquently along the suggested biogenetic pathway (Mechoulam, 1970) was published by Mechoulam and Gaoni from citral (**47**) and the lithiated olivetol dimethyl ether (**52a**) as shown in Scheme 1 (Mechoulam and Gaoni, 1965; Mechoulam, Braun, and Gaoni ,1972). The mechanism of the condensation-cyclization reaction is not entirely clear. It was postulated by the authors that the condensation product (**48**) after tosylation undergoes cyclization involving cis-trans isomerization of the double bond. Thus the hypothetical geranyl-tosylate (**49a**) can isomerize through internal return to linalyl-tosylate (**49b**),which can then undergo cyclization to CBD dimethyl ether (**50**).The key step in the synthesis was the successful demethylation under near basic condition to give racemic CBD (**1**), since it is known that CBD is sensitive to both acidic and strongly basic conditions.

An entirely different synthetic approach based on the idea of Adams, utilizing the Diels-Alder reaction is shown in Scheme 2 (Korte, Dlugosch, and Claussen 1966; Kochi and Matsui 1967). Adams et al. (Adams and Carlin 1943; Adams and Bockstahler 1952) presented this approach for the synthesis of delta-8-THC (**3**), however it remained unsuccessful, presumably due to their inability to find a suitable demethylating reagent.

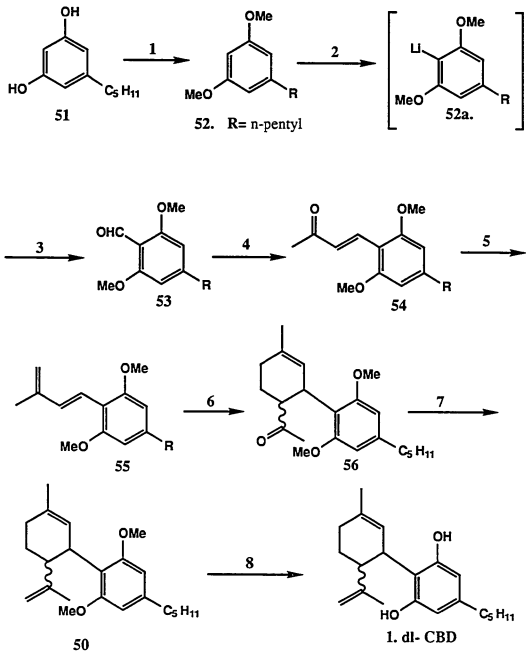
SCHEME 1



47 52a. R= n-pentyl 48 49a 49b 50 1. dl- CBD

Reagents: 1) room temp.; 2) TsCl/Pyr; 3) MeMgI, 160°C

SCHEME 2



51 52. R= n-pentyl 53 54 55 56

Reagents: 1) DMS/K_2CO_3; 2) n-BuLi; 3) N-methylformanilide; 4) aldol with acetone; 5) wittig with $Ph_3P{=}CH_2$; 6) DA with methylvinyl ketone; 7) $Ph_3P{=}CH_2$; 8) MeMgI, 160°C.

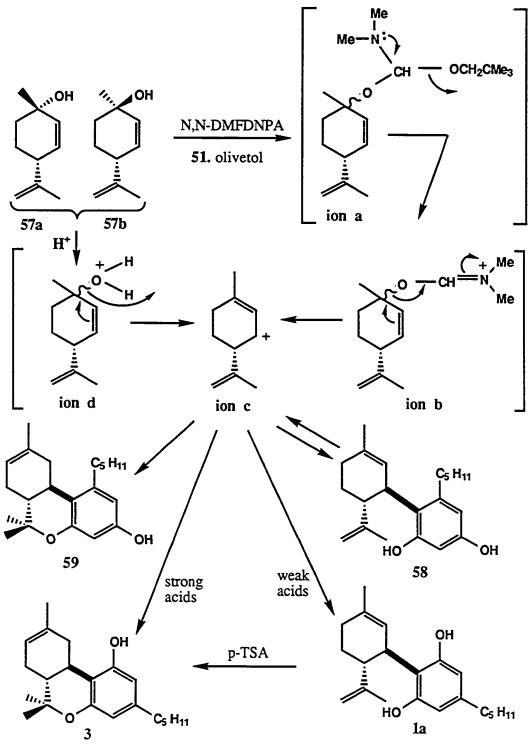
Korte et al.(1966) converted the lithiated olivetol dimethyl ether (**52a**) to the aromatic aldehyde (**53**), which on aldol condensation with acetone gave α,β-unsaturated ketone (**54**). The ketone (**54**) was converted to the diene (**55**)via Wittig reaction with triphenylphosphine-methylene. A Diels-Alder condensation of the diene (**55**) with methyl vinyl ketone as dienophile formed the adduct (**56**), which on a second Wittig reaction gave CBD dimethyl ether (**50**). The overall yield of CBD (**1**) after demethylation (Mechoulam and Gaoni, 1965) was 9.5%. Kochi and Matsui's synthesis (1967) differed only in the preparation of diene (**55**), which was achieved by a Grignard reaction on α,β-unsaturated ketone (**54**), followed by dehydration.

STEREOSPECIFIC SYNTHESES OF (-)-CANNABIDIOL (1a)

The basic strategy in most of the stereospecific synthetic methods was to envision the CBD molecule as a condensation product of the aromatic and alicyclic units. Thus condensation of olivetol (aromatic unit) with an appropiate optically active monoterpene (alicyclic unit) has been the key concept to obtain optically active CBD until the present time. The condensation reaction is catalyzed by weak or strong acids as well as Lewis acids. Proper selection of reaction condition and the acid reagent have played an important role in the formation of CBD preferentially.

Petrzilka et al. (1967, 1969) were the first to report the synthesis of (-)-CBD (**1a**), in 25% yield from (+)-cis- or trans-p-mentha-2,8-diene-1-ol (**57a,b**) and olivetol (**51**) in the presence of N,N-dimethylformamide dineopentylacetal (**DMFDNPA**) as a condensing agent. A putative mechanistic pathway is shown in the Scheme 3. Mild acids such as oxalic, picric or maleic acid, were also found suitable as the condensing agents. In all these instances isomer abn-CBD (**58**)was the predominant product (35%), in addition to (-)-CBD(**1a**) (Petrzilka et al., 1969).

SCHEME 3


N,N-DMFDNPA
51. olivetol
57a
57b
ion a
ion d
ion c
ion b
59
58
3
1a
strong acids
weak acids
p-TSA

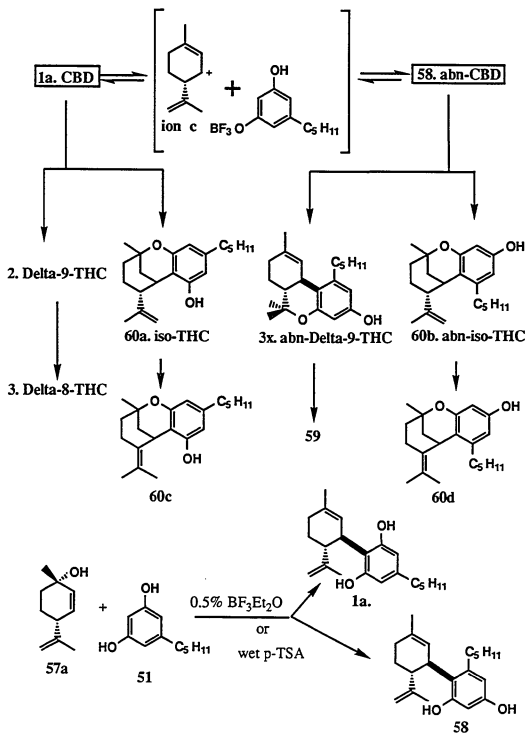
On the other hand when strong acids such as p-toluene sulfonic (p-TSA), trifluoroacetic or hydrochloric acid were used as the catalyst no CBD (**1a**) was isolated, instead delta-8-THC (**3**) was obtained as the major product (53% yield) along with abn-delta-8-THC (**59**) (13%yield). It is presumed that the formation of delta-8-THC (**3**) could be via intermediates CBD (**1a**)--> delta-9-THC (**2**)--> delta-8-THC (**3**), since both CBD and delta-9-THC (**2**) are known to yield delta-8-THC (**3**) in quantitative yield on treatment with p-TSA.This dramatic difference in yields of CBD (**1a**) and delta-8-THC (**3**) was rationalized on the postulate that abn-CBD (**58**) which accompanies CBD (**1a**), undergoes a "retrocondensation"to give "ion c", which in turn forms more CBD and hence delta-8-THC (**3**).

Razdan et al. (1974) studied this reaction in greater detail and found that normal cannabidiol (**n-CBD, 1a**) and abnormal cannabidiol (abn-CBD, 58) were formed first in a ratio of 1:2, followed by their conversion to n-THCs (**2, 3**) and abn-THC (**3x, 59**), and iso-THCs (**60a-d**). The reaction could be stopped at the n-CBD (**1a**) and abn-CBD (**58**) stage if <0.5% BF_3·Et $_2O$, or wet p-TSA was used as condensing agent.

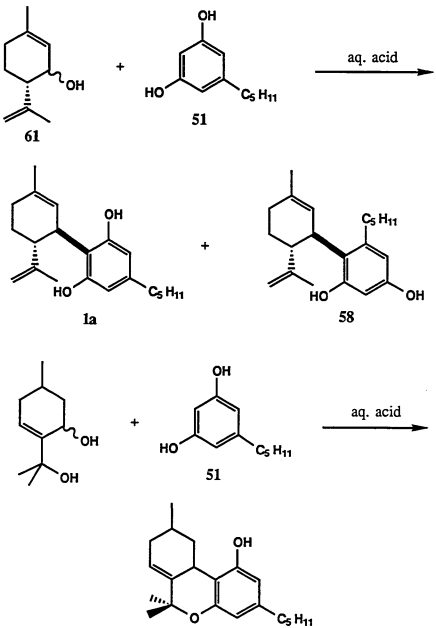
Thus Razdan et al. by minor variation of Petrzilka's procedure provided a less time consuming method for the synthesis of (-)-CBD (**1a**). They isolated (-)-CBD (**1a**, 16%) and abn-CBD (**58**, 32%) with wet p-TSA whereas with BF_3·Et $_2O$ (0.05%) they were able to obtain (-)-CBD (**1a**, 28%) and (-)-abn-CBD (**58**, 47%; Scheme 3).

Cardillo et al. (1972) utilized menthadiene-3-ols and menthen-3-ols as the monoterpenoid allylic alcohols to alkyalte 5-alkylresorcinols in aqueous acid medium to synthesize (-)- CBD and its analogs. As shown in Scheme 4, p-mentha-1,8-diene-3-ol (**61**, isopiperitenol) with olivetol in aqueous 5% citric acid provided (-)-CBD (**1a**) and (-)-abn-CBD (**58**) in 10% yield.

SCHEME 3 (Contd.)



SCHEME 4



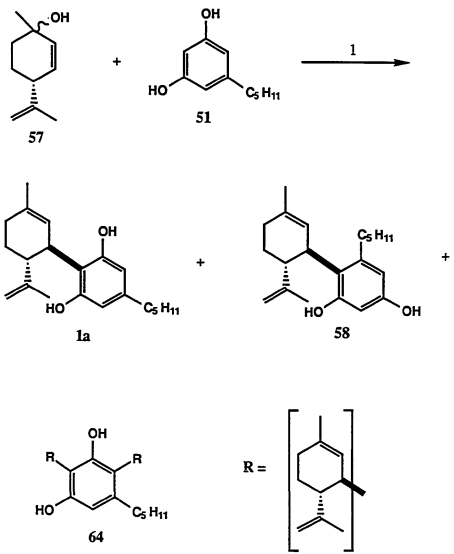
63. Delta-6a-THC or Delta-4-THC

Even though the yields were very poor, this approach also made a facile entry into the preparation of "unnatural" delta-6a-THC (**63**) and its analogs (Arnone et al.,1962).

The synthetic methods discussed so far suffer one or more drawbacks as outlined : a) mediocre yields of CBD; b) inability to control the formation of unnatural isomer, abn-CBD (**58**) in considerably larger amount than that of CBD; c) considerable longer reaction time; d) difficulty in isolation of products. The abn-CBD may be converted to CBD with BF_3·Et $_2O$ by a retro-Friedel-Crafts reaction followed by recombination. However with this reagent the reaction proceeds further causing cyclization to delta-9-THC (**2**) and iso-THCs (**60**) (Mechoulam and Gaoni, 1971).

Mechoulam et al. (Baek, Srebnik, and Mechoulam 1985) reported an improved synthesis of cannabidiol from (+)-p-mentha-2,8-diene-1-ol (**57**) and olivetol (**51**) in presence of boron trifluoride etherate on alumina - a modified Lewis acid reagent as a condensing agent (Scheme 5). They could isolate (-)-CBD (**1a**) as the major product in 55% yield as pure oil or 41% yield as crystalline material. No cyclization was observed. The formation of abn-CBD (**58**) was considerably decreased (14%). The bis adduct (**64**) being much less polar than CBD, was separated with ease in about 6% yield. The yields of CBD either as an oil (46%) or crystalline material (37%) were comparable even on a larger scale (100 mmol).

SCHEME 5



Reagents: 1) BF_3 • etherate on alumina (basic)/ CH_2Cl_2 , reflux 1 min.

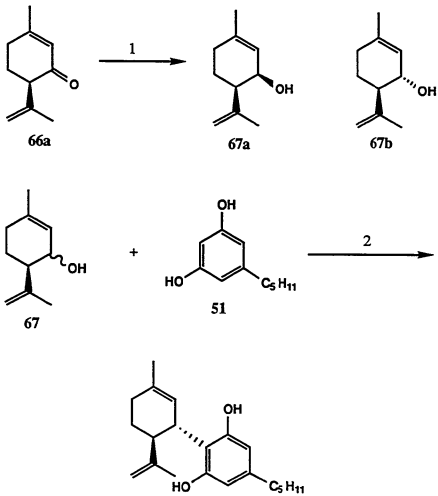
SYNTHESIS OF (+)-CANNABIDIOL

The strategy to synthesize the unnatural (+)- cannabidiol (**1b**) remains the same as for (-)-CBD (**1a**), that is condensation of an appropriate optically active monoterpenoid alcohol with olivetol (**51**). Leite et al. (1982) published the first synthesis of (+)-CBD (**1b**, Scheme 6). Although they followed Cardillo's route (Cardillo et al., 1972), their experimental conditions were quite different. They used $BF_3 \cdot Et_2O$ as a condensing agent at low temperature (-10°C).

The basic concept of our synthesis of (+)-CBD (**1b**) was also the same as described by Cardillo et al. (1972); however the experimental conditions used were different (Scheme 7). We opted for N,N-dimethylformamide dineopentylacetal (DMFDNPA) as a condensing agent for the following reasons: a) it is known to stop the reaction at the CBD stage; b) it avoids further cyclization to THC; c) it has never been used with p-menthadiene-3-ols.Thus condensation of (-)-cis- and trans-p-mentha-1,8-diene-3-ol (**67**) and olivetol (**51**) in the presence of N,N-dimethylformamide dineopentylacetal (DMFDNPA) at RT for 60-63 h. provided (+)-CBD (1b) in 20-25% yield. It can be presumed that DMFDNPA associates with p-menthadiene-3-ol (**67**) to generate carbocationic species (ion a), which in turn alkylates olivetol (**51**) at the ortho carbons to give (+)-CBD (**1b**). The (-)-cis- and trans-p-mentha-1,8-diene-3-ol (**67**) were prepared from (-)-isopiperitenone (**66a**) by sodium borohydride reduction in presence of cerium trichloride heptahydrate (Luche et al., 1978). (-)-Isopiperitenone (**66a**) was synthesized by allylic oxidation of (-)-limonene (**65**) with chromium trioxide-pyridine complex (Dauben et al., 1969).

The few drawbacks of the above described synthesis were the cumbersome preparation, and the separation of (-)-isopiperitenone (**66a**) from its isomer (**66b**). Moreover the yield of (**66a**) was low.

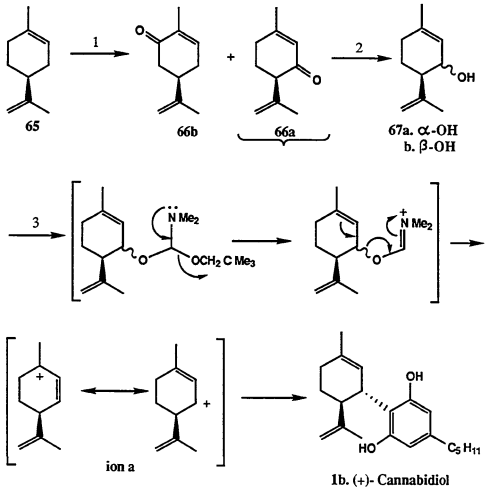
SCHEME 6



1b. (+)- Cannabidiol

Reagents: 1) $NaBH_4$; 2) BF_3• etherate, -10°C.

SCHEME 7



1b. (+)- Cannabidiol

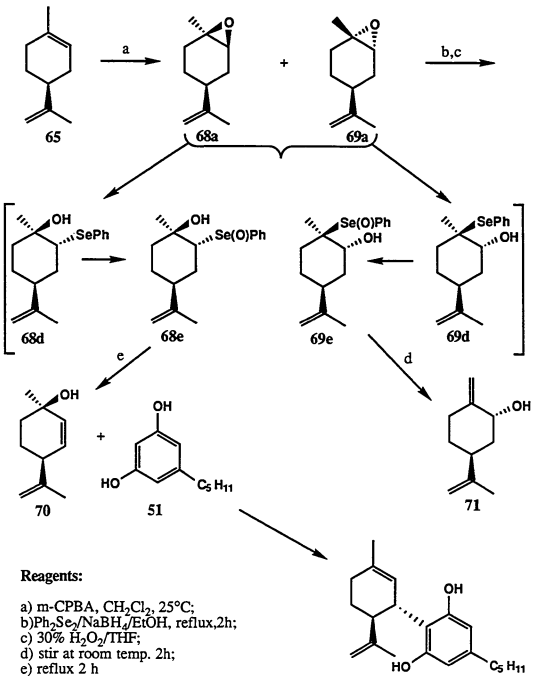
Reagents: 1) CrO_3/Py; 2) $NaBH_4$, $CeCl_3 \cdot 7H_2O$/MeOH;
3) DMFDNPA, olivetol, CH_2Cl_2, room temp., 63 h

Hence our options were either to find new methodology to improve its yield or to try a new cyclic monoterpenoid allylic alcohol with suitable chirality at the isopropenyl junction to establish (S) chirality at C-4 (C-6') in the final product. The later option seemed more feasible than the first one. The obvious choice of the monoterpenoid alcohol would be either diastereomer of (-)-cis- or trans-p-mentha-2,8-diene-1-ols (**70**). But both of these (-)-cis (not shown) or trans-p-mentha-2,8-diene-1-ol (**70**) are unnatural and not available commercially. The task became to synthesize either of these diastereomeric alcohols.

Our approach to the synthesis of these alcohols was conceived from the methodology published by Sharpless and Lauer (1973) for the conversion of epoxides to allylic alcohols via an organoselenium reagent. The selenium anion being an excellent nucleophile easily opens the epoxide to the hydroxyselenide.The hydroxyselenide on oxidative work-up with hydrogen peroxide gives an unstable selenoxide which on elimination of phenylselenic acid provides an allylic alcohol.

By following the lead of Rickards and Watson (1980) who also had used a similar approach to synthesize the commercially available (+)-(1S,4R)-p-mentha-2,8-diene-1-ol (**57b**) from (+)-(4R)-limonene, we synthesized (-)-(1R,4S)-p-mentha-2,8-diene-1-ol (**70**) from (-)-(4S)-limonene (**65**, Scheme 8). Epoxidation of (-)-(4S)-limonene (**65**) with m-chloroperbenzoic acid according to a modified procedure (Knoll and Tamm, 1975) gave a 1:1 mixture of cis- and trans-(-)-epoxides (**69a**, **68a**). When treated with sodium phenylselenide in situ, each epoxide (**68a**) and (**69a**) undergoes trans diaxial opening with complete regiospecificity. Thus the (1R,2S)-epoxide (**68a**) affords the secondary selenide (**68d**), whereras the (1S,2R)-epoxide (**69a**),affords tertiary selenide (**69d**). This can be rationalized as follows. There are many possible conformations for each epoxide. It is expected that the most favoured conformation will be one in which the isopropylidine group is equatorial.

SCHEME 8



Reagents:

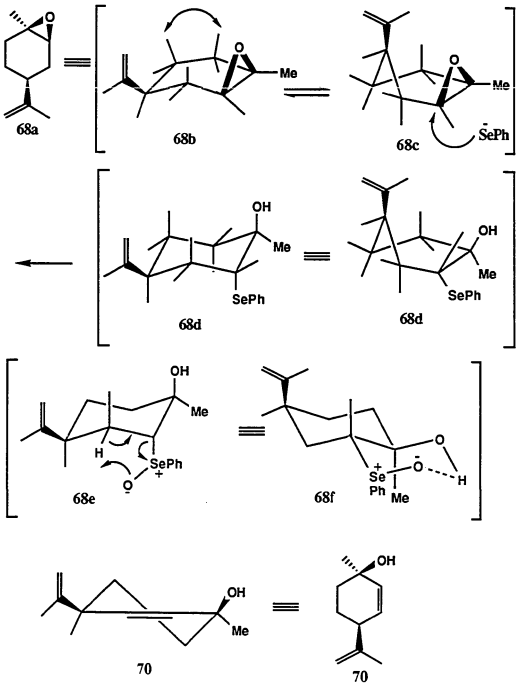
a) m-CPBA, CH_2Cl_2, 25°C;
b)$Ph_2Se_2/NaBH_4/EtOH$, reflux,2h;
c) 30% H_2O_2/THF;
d) stir at room temp. 2h;
e) reflux 2 h

1b. (+)- Cannabidiol

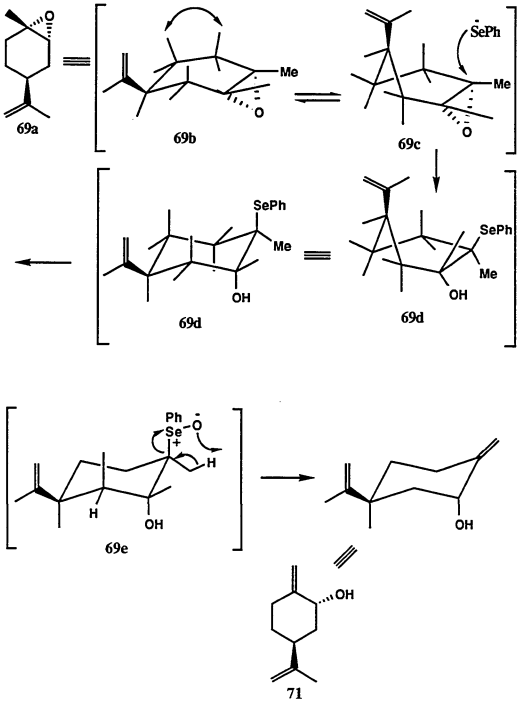
But the Dreiding model of each such conformation (**68a** and **69b**) revealed that there is considerable eclipsing of the C-5 and C-6 hydrogen atoms. Hence these conformations have to flip to avoid such interaction. Conformations (**68c**) and (**69c**) in which the isopropylidine group has flipped into the less preferred axial orientation are devoid of such interaction. Thus the conformation (**68c**) of (1R,2S)-epoxide (**68a**) accounts for an attack of phenylselenide anion at less hindered site C-2 to give secondary selenide (**68d**). In contrast, the conformation (**69c**) for (1S,2R)-epoxide (**69a**) favors phenylselenide attack at C-1 instead at C-2, since the attack at the latter site is hindered by 2,4-diaxial interaction from the isopropylidine group and hence explains the formation of tertiary selenide (**69d**). The mixture of selenides (**68d**) and (**69d**) is oxidized directly with hydrogen peroxide to the corresponding selenoxides (**68e**) and (**69e**). The tertiary selenoxide (**69e**) undergoes regiospecific elimination of phenylselenic acid at RT to generate exocyclic methylene of (-)-(2R,4S)-p-mentha-1(7),8-diene-2-ol (**71**). The secondary selenoxide (**68e**) is expected to be stable at room temperature as is its enantiomer (Rickards and Watson 1980), but no attempts were made to isolate or identify it. Its stability could be reasoned through a conformation (**68f**) in which the selenium substituent occupies an equatorial orientation and is hydrogen bonded to the neighboring hydroxyl group.Thermolysis of this selenoxide in ethanol-free chloroform provided the required terpenoid synthon (-)-(1R,4S)-p-mentha-2,8-diene-1-ol (**70**) in moderate yield. The overall yield of (**70**) from (-)-limonene (**65**) was 35%.

Condensation of (-)-(1R,4S)-p-mentha-2,8-diene-1-ol (**70**) with olivetol (**51**) in the presence of DMFDNPA afforded (+)-CBD (**1b**) in 20-25% yield. The specific rotation, IR, PMR, CMR, and MS were in agreement with the values reported by Leite et al. (1982).

SCHEME 8 (Contd.)



SCHEME 8 (Contd.)



SYNTHESIS OF CONFORMATIONALLY RESTRICTED CBD ANALOGS

SYNTHESIS OF (+)-CARENADIOL (45a)

As a result of our previous SAR studies (Consroe, Martin, and Singh, 1981; Consroe, Martin, and Fish, 1982; Consroe, Martin, and Mechoulam, 1984) attempting to define structure anticonvulsant efficacy it was found that CBD derivatives with conformational restriction in the terpene unit, i.e. pinenyl analogs [**(+)-44a-e**] and [**(-)-44a-f**] in which the isopropylidine appendage is a part of the cyclobutane ring, had retained the anticonvulsant activity in most of the cases.However they were more neurotoxic than (-)-CBD (**1a**). These findings prompted us to explore new conformationally restricted and stereochemically equivalent cyclohexenyl moieties in which the isopropylidine substituent is a part of a fused ring. As a result we synthesized new caryl-CBD analogs in which the isopropylidine substituent was a part of a cyclopropane ring.

Our approach was the same as described earlier for (+)-CBD (1b), namely, prepare the appropriate optically active allylic alcohol and to condense it with 5-alkylresorcinols. We decided to use commercially available (+)-Car-3-ene (**72**) which is stereochemically related to (+)-CBD (**1b**) and convert it to allylic alcohol car-4-en-3-ol according to Sharpless's procedure (1973). Thus synthesis of car-4-en-3α-ol (**75**) or car-4-en-3β-ol (**80**) can be accomplished via phenylselenide mediated trans-diaxial ring opening of the corresponding 3α,4α-epoxy carane (**73**) and 3β,4β-epoxycarane (**77**) respectively, followed by hydrogen peroxide work-up.

Uzarewicz and Zientek (1977) were the first to use this approach for the synthesis of car-4-en-3-ols. They were able to synthesize both the alcohols(**75**) and (**80**) from the corresponding epoxides (**73**) and (**77**) respectively, but they found a dramatic difference in their yields.

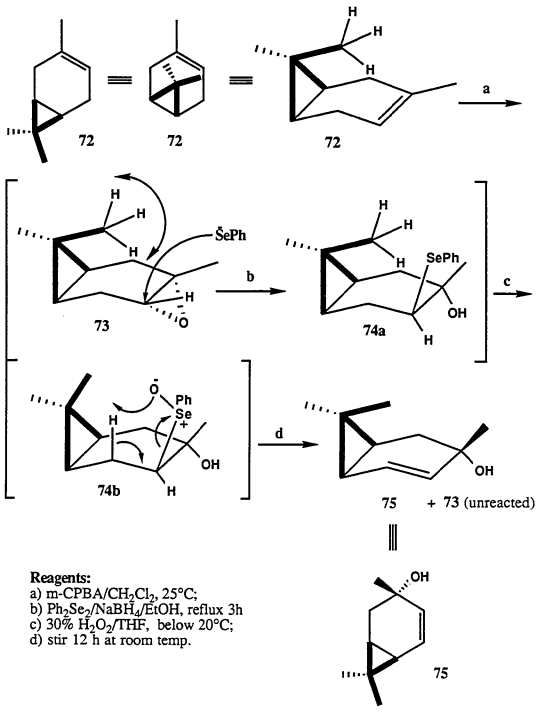
The yield of car-4-en-3α-ol (**75**) was poor (35%) compared to car-4-en-3β-ol (**80**, 90%). This poor yield of car-4-en-3α-ol (**75**) can be explained on the basis of steric hindrance rendered by the gem-dimethyl and C-3 methyl groups to the phenylselenide ion attack on the α-epoxide (**73**) from the top face, i.e. β-face, as shown in the Scheme 9. On the other hand, β-epoxide (**77**) is devoid of such steric hindrance because of the fact that the phenylselenide ion attack has to occur from face opposite the gem-dimethyl bearing cyclopropane ring, i.e. α-face, as shown in Scheme 10.

Following the lead of Uzarewicz and Zientek (1977) we decided to prepare car-4-en-3β-ol (**80**) from 3β,4β-epoxycarane (**77**). 3β,4β-epoxy carane was prepared according to the method of Cocker and Grayson (1969). As shown in Scheme 10, (+)-car-3-ene (**72**) on treatment with N-bromosuccinimide in aqueous dioxane containing calcium carbonate gave bromohydrin (**76**), which on treatment with potassium t-butoxide in t-butanol afforded (-)-3β,4β-epoxy carane (**77**) in 55% overall yield from car-3-ene (**72**). The bromohydrin, being unstable on exposure to air and on atmospheric distillation,was used for the subsequent reaction without further purification. The IR and NMR of (**77**) were in agreement with the literature values (Gollnick et al., 1965).

As shown in Scheme 10 the β-epoxide (**77**) on treatment with phenylselenide underwent diaxial opening of the epoxide ring with complete stereospecificity and regio-specificity to afford secondary selenide (**78**), which on subsequent oxidative elimination of phenylselenic acid and work-up provided the desired optically active synthon car-4-ene-3β-ol (**80**) in 90-95% yield. The IR and PMR parameters were identical to those reported by Uzrewicz and Zientek (1977).

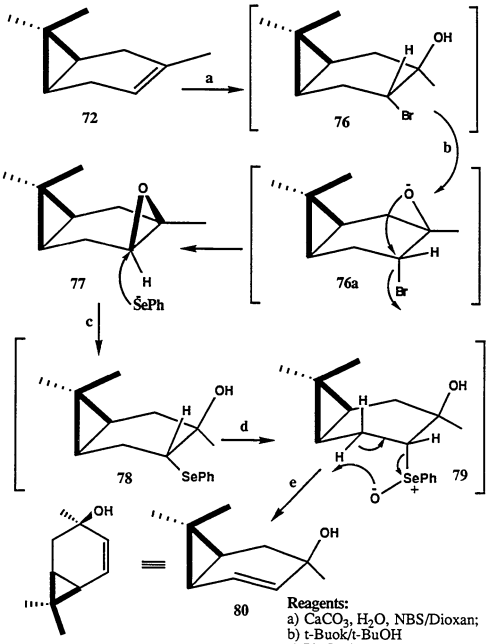
(+)-Carenadiol (**45a**) was obtained in 20% yield by condensing car-4-en-3β-ol (**80**) and olivetol (**51**) in the presence of DMFDNPA at RT and under nitrogen. It was identified by IR, PMR, CMR, MS and elemental analysis.

SCHEME 9



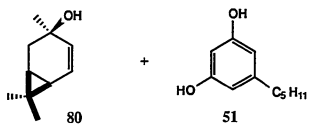
Reagents:
a) m-CPBA/CH_2Cl_2, 25°C;
b) $Ph_2Se_2/NaBH_4/EtOH$, reflux 3h
c) 30% H_2O_2/THF, below 20°C;
d) stir 12 h at room temp.

SCHEME 10

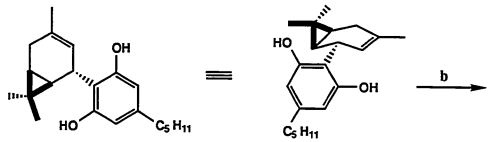


Reagents:
a) $CaCO_3$, H_2O, NBS/Dioxan;
b) t-Buok/t-BuOH
c) $Ph_2Se_2/NaBH_4$/EtOH, reflux 3h
d) 30% H_2O_2/THF, below 20°C;
e) stir 20 h at room temp.

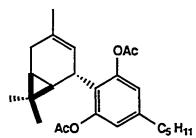
SCHEME 10 (Contd.)



80 51



45a. (+)- Carenadiol



45b. (+)- Carenadiol diacetate

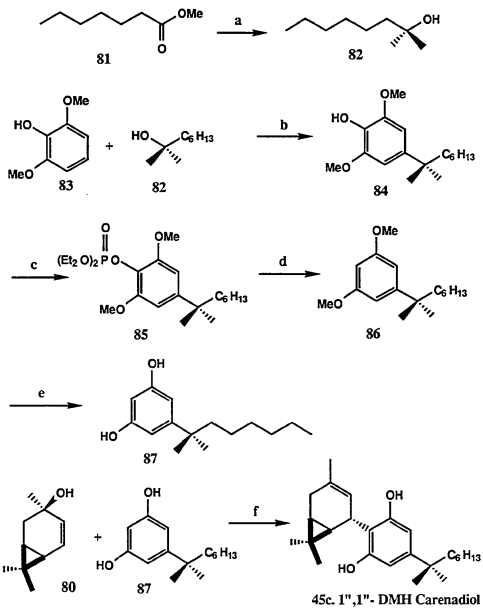
Reagents:
a) DMFDNPA/CH_2Cl_2, room temp., 63 h;
b) Ac_2O/Py, room temp., 12 h.

A diacetate of (+)-carenadiol (**45a**) was also prepared by standard acetylation procedure using pyridine as a base and acetic anhydride as an acylating agent at RT (Scheme 10). The diacetate (**45b**) was obtained in 85% yield. It was characterized by IR, PMR, CMR and elemental analysis.

It is known that side-chain branching at the C-1" position in the CBD molecule increases the anticonvulsant potency and neurotoxicity. Maximum anticonvulsant potency and neurotoxicity are seen with the 1",1"-dimethylheptyl side-chain as is evident in the case of pinenyl analogs [**(+)-44a-e**] and [**(-)-44a-e**].We decided to synthesize a caryl analog with the 1",1"-dimethylheptyl side chain. The synthesis of the required intermediate 5-(1,1-dimethylheptyl)resorcinol (**87**) could be accomplished by known methods (Adams et al., 1948; Petrzilka et al., 1969; Marmor, 1978; Matsumoto and Meister, 1977; Dominianni et. al, 1977; Singh et al., 1981; Reetz and Westermann, 1982). We followed Dominianni's procedure to synthesize (**87**). This synthesis was based upon the finding that alkylation of 2,6-dimethoxyphenol with tertiary carbonium precursors occurs predominantly, if not exclusively, para to the hydroxyl group.

As shown in Scheme 11, methyl enanthate (methylheptanoate, **81**) on treatment with methyl magnesium bromide provided tertiary alcohol (**82**). Thus treatment of dimethoxyphenol (**83**) with tertiary alcohol (**82**) in methanesulfonic acid at 50°C afforded a 98% crude yield of 5-(1,1-dimethyl)-2,6-dimethoxyphenol (**84**), which without further purification was converted to a crystalline phosphate ester (**85**) with diethyl phosphonate, carbon tetrachloride and triethylamine in 85% yield. Treatment of phosphate ester (**85**) with lithium in liq ammonia, followed by demethylation of the product (**86**) with trimethylsilyl iodide, provided crystalline 5-(1,1-dimethylheptyl)resorcinol (**87**) in 60% yield. The MP, IR, PMR, and CMR parameters of the product were identical with the reported values (Dominianni et al., 1977).

SCHEME 11



Reagents: a) MeMgBr (2 equiv)/THF; b) $MeSO_3H$, 50°C, 6 h, room temp, 12 h;
c) Diethylphosphate/CCl_4/Triethyl amine; d) Li/NH_3, -50°C;
e) Trimethylsilyliodide/$CHCl_3$/Py, reflux, 60 h;
f) DMFDNPA/CH_2Cl_2, room temp., 60-63 h.

Car-4-en-3β-ol (**80**), on condensation with 5-(1',1'-dimethyl heptyl)resorcinol (**87**) in the presence of DMFDNPA (Petrzilka et. al, 1969) provided the 1",1"-dimethylheptyl side-chain analog (**45c**) in 20% yield. It was characterized by IR, PMR, CMR, MS, and elemental analysis.

The dose-response data of (+)-carenadiol (**45a**), its 1",1"-dimethylheptyl analog (**45b**) along with (+)-CBD (**1b**) have been compared with (-)-CBD (**1a**), and standard anti-convulsant drugs in ROT and AGS tests and have been presented in Table 4.

Table 4

Dose-Response data of standard anticonvulsants and CBD analogs in ROT and AGS Tests[a].

Compound	ROT-TD_{50}	AGS-ED_{50}	(PI)
25. Phenytoin	23.9	14.7	1.6
26. Phenobarbital	28.9	10.8	2.7
27. Cabamazepine	33.9	12.8	2.7
1a. (-)-CBD	30.7	14.9	2.1
1b. (+)-CBD	39.7	16.2	2.54
5a. (+)-Carenadiol	99.8	18.1	5.5
45b. (+)-1",1"-DMH analog	3.7	3.4	1.1

[a]Data taken, in part from Martin et al., 1980.

AGS-TD_{50}= Median effective dose (mg/Kg) to block audiogenic seizures.

ROT-TD_{50}= Median toxic dose (mg/Kg) causing rotorod neurotoxicity.

PI= Protective Index= ROT-TD_{50}/AGS-ED_{50}.

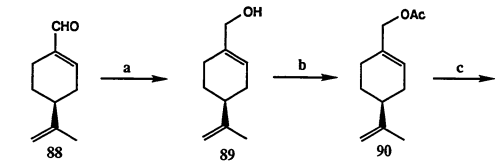
DMH= Dimethylheptyl

SYNTHESIS OF (+)-7-HYDROXY CANNABIDIOL

As mentioned earlier in the THC series 7-hydroxylation as well as side-chain hydroxylation enhance pharmacological activity. By analogy with the THC series the anti-convulsant activity of CBD might be enhanced by hydroxylation in these positions. Moreover, 7-hydroxy CBD may turn out to be of considerable clinical importance in elucidating the mode of action of CBD.

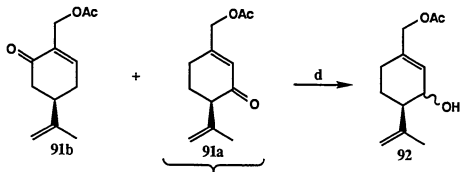
Lander et al. (1976) reported the first total synthesis of unnatural (+)-7-hydroxy CBD (**46a**) from 7-acetoxy-p-mentha-1,8-dien-3-ol (**92**) and olivetol (**51**) utilizing Cardillo's (1973) approach as shown in Scheme 12. The condensation step is known to result in poor yield in most of the synthetic CBD type cannabinoids. But in their synthesis even the yield of the monoterpenoid synthon (**92**) was very poor (9%).Consequently the overall yield starting from 7-acetoxy-p-mentha-1,8-diene (**90**) was miserable (0.6%). Therefore there was a need to design a synthesis of 7-hydroxy CBD in practical yield to meet the needs for studies of its mechanism of action and pharmacology. Initially our efforts were focused towards a practical synthesis for an appropriate monoterpenoid allylic alcohol as a synthon for the final condensation with olivetol (**51**). Our strategy was to synthesize (+)- or (-)-p-mentha-2,8-diene-1,7-diol (**101**) and then to condense it with olivetol (**51**) in the presence of DMFDNPA as per Petrzilka's method (1967). The ideal choice of starting material would be commercially available (-)-(4S)-p-mentha-1,8-diene-7-ol (Perillyl alcohol, **89**) or its rare enantiomer (+)-(4R)-p-mentha-1,8-diene-7-ol [(+)-**89**]. The former should lead to the unnatural (+)-7-hydroxy CBD (**46a**), whereas the latter should lead to the natural (-)-7-hydroxy CBD[(-)-**46a**]. The rare enantiomer (+)-(4R)-p-mentha-1,8-diene-7-ol [(+)-**89**] could be synthesized by Buchi's method (1969). However we initially decided to use the commercially available optical isomer [(-)-**89**].

SCHEME 12

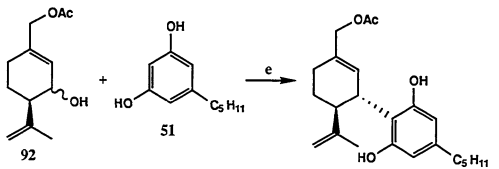


88 89 90

(-)-(4S)- Perillaldehyde (-)-(4S)- Perillyl alcohol



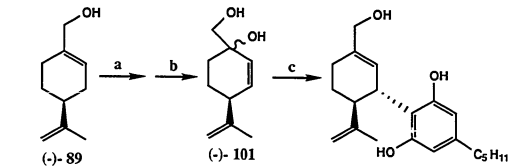
91b 91a 92



92 51 46b. (+)- 7-OAc-Cannabidiol

Reagents: a) LAH reduction; b) Ac_2O/ Py; c) CrO_3/ Py;
d) Lithium hydridotri-t-Butoxy aluminate/ THF;
e) BF_3• etherate, -5°C.

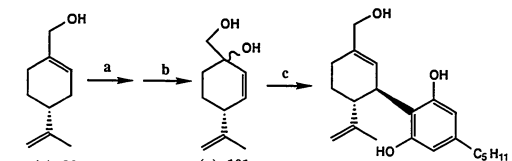
SCHEME 13



(-)- 89
Commercially available

(-)- 101

46a. (+)-7-OH-CBD



(+)- 89
Commercially not available

(+)- 101

46a. (-)-7-OH-CBD

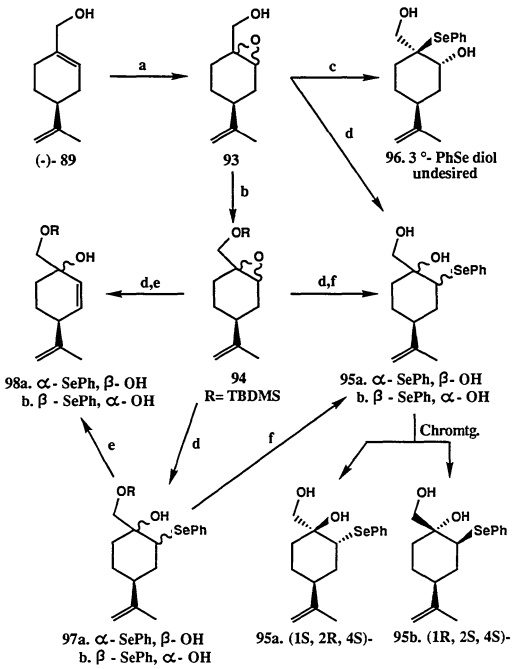
Reagents:

a) epoxidation;
b) Sharpless methodology;
c) condensation with olivetol

We decided to utilize Sharpless's methodology (1973),that is, epoxidation of perillyl alcohol (**89**), and its one pot conversion to the required synthon (**101**), via phenylselenide mediated diaxial opening of the epoxide followed by oxidative elimination. This should serve as a short and practical synthesis (Scheme 13). But this did not occur quite as well as expected.

Preliminary work on our synthetic approach (Scheme 14)was accomplished by Stevens and Albizati (1985) for a different purpose. Epoxidation of perillyl alcohol (**89**) by the Sharpless reagent (Sharpless and Verhoeven 1979) afforded an essentially 1:1 mixture of inseparable diastereomeric epoxy alcohols (**93**). Knowing that direct opening of this epoxy alcohols by sodium phenylselenide, the reagent generated from diphenyl diselenide and sodium borohydride in ethanol, lacks the regiospecificity and results in an inseparable mixture of required diols (**95a,b**) and useless diol (**96**), we converted the epoxy alcohol (**93**) to a bulky t-butyldimethylsilyl derivative (**94**) so as to achieve regiospecificity in epoxide opening. As predicted the steric hindrance offered by such a bulky silyl group caused epoxide opening to occur regeospecifically at the tertiary carbon to give the desired silyloxy phenylselenides (**97a** and **97b**). The subsequent oxidation-elimination which was carried out with 30% hydrogen peroxide without isolation of intermediates met with little success. The reaction gave a multicomponent mixture. By repeated chromatography we were able to isolate and characterize both diastereomeric allylic alcohols as silylated derivatives(**98a,b**). The yields were very poor. We thought if the oxidative-elimination is carried out on isolated silyloxy phenylselenides (**97a**) and (**97b**) it may improve the yield. Both silyloxy phenyl-selenide (**97a**) and (**97b**) were isolated (Stevens and Albizati, 1985) and treated independently with hydrogen peroxide. A multicomponent reaction mixture was obtained with very poor yields of the corresponding silyloxy alcohol (**98a**) and (**98b**). The reason for the poor yield of (**98a**) and (**98b**) is not clear to us.

SCHEME 14



Reagents: a) t-BuooH/ $VO(AcAc)_2$/ Toluene; b) t-$BuMe_2SiCl$/ Imidazole/ CH_2Cl_2
c) Ph_2Se_2/ $NaBH_4$/ EtOH, 25°C, 0.5 h; d) Ph_2Se_2/ $NaBH_4$/ EtOH, reflux, 24 h;
e) 30% H_2O_2, stir at room temp., 1-6 h; f) n-$Bu_4N^+F^-$/ THF, room temp., 12 h.

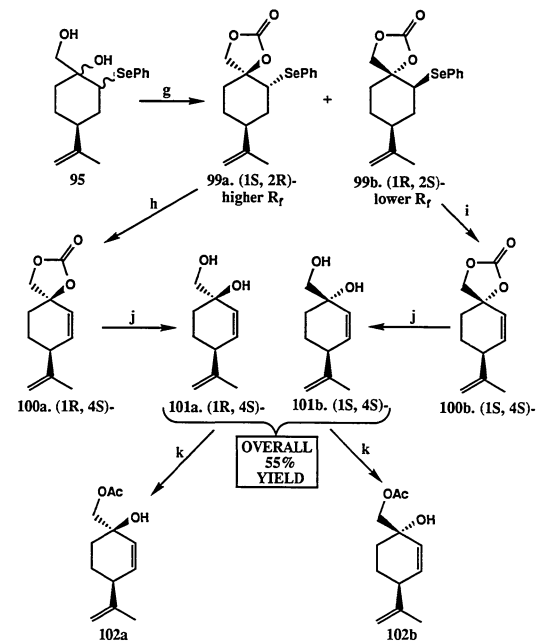
It is quite possible that the tertiary 1-hydroxy- or 7-t-butyldimethylsilyloxy may act as a leaving group. The former would leave a stable tertiary carbonium ion which could trigger subsequent rearrangement reactions. To eliminate this remote possibility we felt it necessary to reprotect the 7-hydroxy and protect the 1-hydroxy simultaneously.

The desilylation of the diastereomeric mixture of silyloxy phenylselenides (**97a**) and (**97b**) with tetra-n-butylammonium fluoride in THF provided a diastereomeric mixture of inseparable diol phenylselenides (**95a**) and (**95b**) in almost quantitative yield. The diol phenylselenides (**95**) were converted to cyclic carbonates (**99a**) and (**99b**) on treatment with N',N'-carbonyldiimidazole (Kutney and Ratcliffe 1975) in 85% combined yield. Both the carbonates were isolated and characterized by IR, PMR, and CMR.

Each carbonates (**99a**) and (**99b**) was subjected to the oxidation-elimination reaction with hydrogen peroxide independently. The higher R_f diastereomeric carbonate [(**1S,2R**)-, **99a**] went through the oxidative-elimination at RT within an hour to give the product carbonate [(**1R,4S**)-,**100a**] in 85% yield, where as the lower R_f diastereomeric carbonate [(**1R,2S**)-, **99b**] required refluxing in THF to undergo oxidation-elimination when reacted with hydrogen peroxide to yield the product carbonate [(**1S,4R**)-, **100b**] in 73%yield. Decarbonylation of these two carbonates with 2M NaOH provided the required monoterpenoid allylic alcohols (-)-(1R,4S)-p-mentha-2,8-diene-1,7-diol (**101a**) and its diastereomer (-)-(1S,4S)-p-mentha-2,8-diene-1,7-diol (**101b**) each in 95% yield.

Thus starting from perillyl alcohol (**89**) we were able to synthesize the required monoterpenoid synthon (-)-p-mentha-2,8-diene-1,7-diol (**101**) as separable diastereomers in about 55% combined yield over seven steps. These diastereomers (**101a** and **101b**) could be used either individually or as a mixture for the condensation with olivetol (**51**) since the stereochemistry at C-1 is destroyed during the course of condensation.

SCHEME 14 (Contd.)



Reagents: g) N',N'-Carbonyldiimidazole/ Toluene, reflux, 3 h;
h) 30% H_2O_2/ THF, stir, room temp., 1 h; i) 30% H_2O_2/ THF, reflux, 1 h;
j) 2M NaOH/ THF, room temp., 1 h;
k) Ac_2O/ TEA/ DMAP, room temp, 3 h.

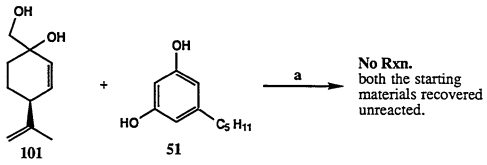
The next major hurdle was to find suitable reaction conditions for the condensation of menthadiene diols (**101**) with olivetol (**51**) so as to avoid cyclization to THCs. The first condensation attempt using Petrzilka's procedure (1967) proved unsuccessful (Scheme 15). Both the starting materials (**101a** or **101b**) and (**51**) were recovered unreacted. This may be due to the inability of the reagent DMFDNPA to associate with tertiary hydroxyl group at C-1 and eventually to form the carbonium ion at C-3.

The next attempt was carried out using boron trifluoride supported on basic alumina as the condensing reagent (Baek, Srebnik, and Mechoulam, 1985). The tlc of the reaction mixture showed two major spots along with several others. Both these spots were isolated by column chromatography and purified by repeated prep tlcs. Neither of these products (**103a**, 22% and **103b**, 17%) has not been fully characterized, but neither is the desired product 7-hydroxy CBD (**46a**). They seem to be isomers of each other, since the mass spectra showed m/z = 318. The elemental analysis supported this molecular weight and fit $C_{21}H_{18}O_2$ for both products. It seems that the 7-hydroxy CBD might have formed but must have lost a water molecule during the course of reaction to give eliminated or re-arranged product whose structure is unclear. But from the spectral information and personal communication with Mechoulam, cannabielsoic type of structures (**103**) can not be ruled out.

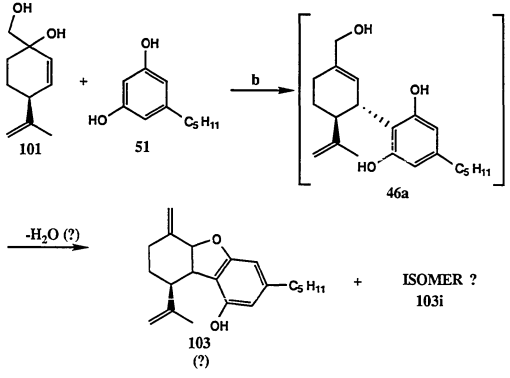
With this ambiguity on mind we thought that the 7-acetate of diol (**101**) might be worth condensing with olivetol (**51**). As this might overcome the problem of elimination as described earlier and 7-acetoxy CBD might be a major product. The diols (**101a,b**) was converted to its 7-acetate (**102a,b**) by a routine literature procedure. We carried out this reaction with acetate (102) under similar reaction condition and isolated two major products (**104**, 20% and **46b**, < 5%). To our surprise (**104**) turned out to be a known acetate of the major metabolite of delta-9-THC, 7-acetoxy-delta-9-THC (Lander et al., 1976).

SCHEME 15

I.



II.



Reagents: a) DMFDNPA/ CH_2Cl_2, room temp., stir 60-63 h;
b) BF_3·etherate/basic alumina/ CH_2Cl_2, stir 15 min, room temp., reflux 1 min, quench with satd. $NaHCO_3$ in 30 s.

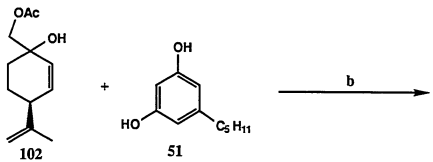
The product **46b** was the desired unnatural 7-acetoxy CBD which was characterized by spectral data and comparision with literature values (Lander et al., 1976).

To avoid this cyclization to THC we decided to use olivetyl dimethyl ether (**52**) instead of olivetol (**51**) and carry out the condensation followed by demethylation to obtain 7-hydroxy CBD. Indeed this change helped us in obtaining 7-acetoxycannabidiol dimethylether (**46d**) in 15% yield. It has been characterized by spectral data. The demethylation of (**46d**) under near neutral conditions by trimethylsilyl iodide was a total failure. The reaction mixture did not show any trace of unreacted starting material (**102**) or the demethylated product (**46b**). This result suggested that a new demethylating reagent needs to be tried.

From all these results it is clear that the condensation step is the yield-limiting step. We did obtain the desired product (**46b**) but the yields were extremely poor. A thorough investigation to find suitable condensing agent and reaction conditions will prove to be a major contribution to cannabidiol research.

SCHEME 15 (Contd.)

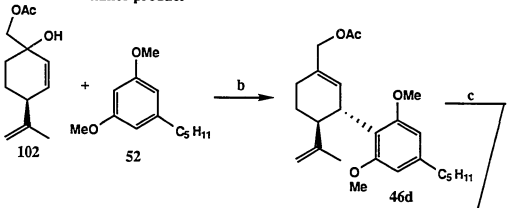
III.



46b. (+)-7-OAc-CBD
minor product

104. (+)-11-OH-Delta-9-THC
major product

IV.



complex Rxn. Mixt.
no trace of demethylated
product 46b.

Reagents:

b) BF_3·etherate/basic alumina/ CH_2Cl_2, stir 15 min, room temp., reflux 1 min, quench with satd. $NaHCO_3$ in 30 s;
c) Me_3SiI/ $CHCl_3$/ Py, reflux, 60-72 h.

EXPERIMENTAL

General

Thin layer chromatography was carried out on precoated 0.25 mm layer thickness silica gel and alumina plates, supplied by Analtech Co. Preparative thin layer plates were coated with 1.5 mm layer thickness silica gel GF-254 (60 mesh ASTM). Column Chromatography was carried out using silica gel (70-230 mesh ASTM), supplied by E. Merck. Melting points were taken on an Electrothermal apparatus and are uncorrected.Infrared spectra were recorded on Beckman IR-33 or 1100 FT-IR spectrophotometers with samples prepared as potassium bromide pellets or as thin film on NaCl plates. NMR spectra were recorded on a Varian EM-360 (60 MHz), Jeol FX-90Q (90 MHz), Brucker WM-250 (250 MHz) or Brucker WM-500 (500 MHz) spectrometer using tetramethylsilane as internal standard in deuterochloroform. Mass spectra were recorded on a Varian MAT 311A double focusing mass spectrometer or Varian MAT 90. Optical rotations were measured in a 1-dm cell at 23°C at the sodium D line on a Perkin-Elmer polarimeter, Model 241 MC.Elemental analyses were performed by Desert Analytics, Tucson,Arizona.

All the chemical reactions requiring inert atmosphere were carried out under Nitrogen or Argon in oven- or flame-dried glassware using septum techniques. All solvents were distilled prior to use. Diethyl ether (ether) and tetrahydrofuran (THF) were dried over calcium hydride and distilled from lithium aluminium hydride. Benzene and toluene were distilled from metallic sodium. Pyridine and triethylamine (TEA) were distilled from calcium hydride.Chloroform and dichloromethane (DCM) were predried over anhydrous calcium chloride and distilled from phosphorus pentoxide. N,N-dimethylformamide (DMF) was dried over 3°A molecular sieves and distilled under reduced pressure.Chemicals were

used as supplied from the commercial sources.

2-Cyclohexen-1-one, 3-methyl-6-(1-methylethenyl)-, (6S)-: [(-)- Isopiperitenone, (66a)].

In a 3 neck 3L flask, equipped with a mercury sealed mechanical stirrer, dry DCM (140 ml) and dry pyridine (100 mmol, 7.9 g) were placed. This solution was cooled to 10°C with an ice bath. To this solution chromium(VI) oxide powder (50 mmol, 25 g, dried over P_2O_5) was added in small portions over a period of 5 min. with constant stirring. The rxn. mixt.turned pink . To this pink rxn. mixt. celite (30 g), followed by (-)- limonene (**65**) (5 mmol, 0.68 g) in DCM were added. The rxn. mixt. was stirred at room temp. (RT) for 24 h. The rxn. mixt. was filtered and the filter cake was thoroughly washed with DCM (3x50 ml). The filtrate was washed with saturated Na_2CO_3 solution (3x100 ml), followed by saturated $CuSO_4$ solution (3x100 ml). The DCM filtrate was dried ($MgSO_4$) and evaporated at reduced pressure (< 40°C) to yield a lemon yellow oil. This oil showed 4 spots on tlc in 10% ethylacetate/hexane (EA/hex). The title product (66a) was isolated in about 31% yield (0.14 g) from the oil by column chromatography using 4% EA/hexane. The yield was reproducible on a larger scale (1 moler). IR (film): 3095,2940, 1670, 1435, 1375, 1200, 1020, 885, 790 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$): δ 5.88 (br m, 1H, =CH/C-2), 4.95 and 4.93 (br s,2H, $=CH_2$/C-9), 2.94 (br t, J=8 Hz, 1H, -CH/C-4), 2.36-2.01 (m, overlapping resonances, 4H, -CH2s'/C-5, C-6), 1.96 (br s, 3H,CH_3/C-7), 1.75 (s, 3H, CH3/C-10).

2-Cyclohexen-1-ol, 3-methyl-6-(1-methylethenyl)-, mixt. of(1R)- and (1S)- isomers: [(-)-Isopiperitenol, (67)]

To a 50 ml flask, a solution of $CeCl_3 \cdot 7H_2O$ (0.95 mmol) in MeOH (10 ml) and a solution of compound (**66a**, 1 mmol, 150 mg) in MeOH (5 ml) were added. This solution

was cooled to 10°C with an ice bath. To this solution $NaBH_4$ (1.1 mmol, 42 mg) was added gradually with stirring. The rxn. mixt. was stirred at room temp. for 5 min. and quenched with water (5 ml). It was then extracted with ether (2x25 ml). The ether extract was dried ($MgSO_4$) and evaporated to leave an oil which showed a single spot on tlc with the same R_f value as the starting material (-)-isopiperitenone (**66a**) in 10% EA/hex. The reduced product isopiperitenol (**67**) was isolated in 80% yield (120 mg) by column chromatography using the 4% EA/hex. IR (film): 3200, 3050, 3000-2900, 1645, 1670, 1445, 1375, 950,800 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$): δ 5.64-5.62 (br 2d, J = 5Hz, 1H, =CH), 4.94 (br d, 2H, $=CH_2$), 4.1 [br m, 1H, -CH(OH)],2.14-1.51 (m, overlapping resonances, 5H, CH_2s' and CH), 1.79(s, 3H, CH_3), 1.69 (s, 3H, CH_3).

1,3-Benzenediol, 2-[3-methyl-6-(1-methylethenyl)-2-cyclohexen-1-yl]-5-pentyl-, (1S, trans)-,; [(+)-Cannabidiol, (1b)]

In a 25 ml flask, to a solution of olivetol (**51**, 1 mmol, 180 mg) and isopiperitenol (**67**, 1.1 mmol, 167.5 mg) in dry DCM(25 ml) N,N-dimethylformamide dineopentyl acetal (1.3 mmol,300 mg) was added via syringe under nitrogen. A dark brown precipitation was observed. The flask was covered with aluminium foil and the rxn. mixt. was stirred under nitrogen and at RT for 63 h. Tlc of the rxn. mixt. showed no trace of starting materials. The rxn. mixt. was poured into chilled water (25 ml). The aqueous layer after separating from the organic layer was washed thoroughly with DCM (2x25 ml). These DCM washings were combined with the organic layer and dried ($MgSO_4$). Evaporation of dichloromethane provided a dark brown oil which showed several spots on tlc (10% EA/hex). The title compound (**1b**, R_f =0.3875/10% EA/hex) was isolated by column chromatography in about 20% yield (65 mg) using 1% EA/hex. $[\alpha]_D^{23}$= +80.3° (13.26 mg/ml, EtOH); IR (film): 3630, 3480, 3080, 3000-2850, 1635, 1585, 1515, 1450, 1210,

885 cm^{-1}; ^1H NMR (90 MHz,$CDCl_3$): δ 6.2 (br s, 2H, aromatic), 5.55 (br m, 1H, =CH),4.62-4.53 (br 2s, 2H, $=CH_2$), 3.85 (br m, 1H, -CH); 2.4 (t, 2H,-CH_2), 2.3-1.08 (m, overlapping resonances, 5H, -CH2s'), 2.1(br m, 1H, -CH), 1.65 (s, 3H, CH_3), 1.26 (s, 3H, CH_3), 0.87(t, 3H, CH_3); ^{13}C NMR (500 MHz, $CDCl_3$): δ 156.311, 154.211,149.635, 143.335, 140.349, 124.435, 114.069, 111.144, 110.039,108.327, 46.482, 37.536, 35.775, 31.794, 30.932, 30.702,28.723, 23.965, 22.836, 20.784, 14.351.

7-Oxabicyclo[4.1.0]heptane, 1-methyl-4-(1-methylethenyl)-, [(mixt of (1R,2S,4S)- and (1S,2R,4S)- isomers]: [(-)-Limonene 1,2-epoxide, (68a, 69a)]

In a 500 ml flask, to a solution of (-)-limonene (**65**, 100 mmol, 13.62 g) in dry DCM (100 ml), a solution of m-CPBA (110 mmol, 19 g) in dry DCM (150 ml) was added gradually with vigorous stirring over 10 min under nitrogen and at RT. The rxn. mixt. was stirred at RT for 2 h. Tlc showed that the rxn. had almost gone to the completion, leaving traces of (-)- limonene unreacted. The stirring was stopped and excess peracid was destroyed by treating the rxn. mixt. with 10% sodium sulfite solution till it gave negative test with starch iodide paper. The organic layer was washed thoroughly with saturated sodium bicarbonate solution (3x100 ml), water (3x50 ml) and saturated sodium chloride solution(100 ml). The aqueous layer was reextracted with DCM (2x50 ml) and these DCM washings were combined with the organic layer and dried ($MgSO_4$). An yellow oil was obtained on evaporation of the solvent which showed 3 major spots in 20% EA/hex. The desired (-)-Limonene epoxide (68a, 69a) was isolated in 66% yield (10 g).$[\alpha]_D^{23}$= -53°; IR (film): 3080, 2930, 1645, 1434, 1378,1250, 1120, 1040, 880, 840, 760, 670 cm^{-1}; ^1H NMR (90 MHz,CDCl3): δ 4.72-4.7 (br m, 2H, $=CH_2$), 3.04-2.95 (t, J_{aa} = 5.28Hz, J_{ae} = 2.64 Hz, 1H, CH-O), 2.16-1.2 (m, 7H, overlapping resonances, CH, CH2s'),

1.68-1.67 (2s, 3H, CH_3-C-O), 1.31-1.3(2s, 3H, CH_3-C=C).

2-Cyclohexen-1-ol, 1-methyl-4-(1-methylethenyl)-, (1R,4S)-: [trans-(-)-p-Mentha-2,8-dien-1-ol, (70)],

Sodium borohydride (12.3 mmol, 467.5 mg) was added in portions to a continuously stirred yellow suspension of diphenyl diselenide (5.6 mmol, 1.75 g) in absolute dry EtOH(5 ml/mmol, 30 ml) below 15°C and under argon. The suspension was stirred till it turned colorless solution (30 min). A 1:1 cis and trans stereoisomeric mixt. of (-)-limonene epoxides (**68a, 69a**; 10 mmol,1.52 g) was added dropwise under argon via syringe.The resulting solution was heated at reflux for 3 h. It was cooled to RT and THF (25 ml) was added, followed by dropwise addition of 30% H_2O_2 solution (11.7 mmol, 3.975 g, 13.25 ml) maintaining the rxn. temp. below 20°C. The rxn.mixt. was stirred for 5 h. between 15-20°C. The reddish yellow solution turned to a colorless on completion of the rxn. The solution was diluted and washed with water (3x50 ml). The organic layer was separated,combined with DCM extract of the aqueous phase, and washed successively with aqueous 10% Na_2CO_3, and saturated brine.Evaporation of the solvent after drying provided a viscous oil. Extraction of this oil with petroleum ether (PE) caused yellowish precipitation. The mother liquor after evaporation of PE provided a yellow oil, which was further purified by column chromatography to give the 2° alcohol [(**71**, Cyclohexenol, 2-methylene-5-(1-methylethenyl)-,(2R,4S)-] in about 79% yield (600 mg). IR and ^1H NMR were in agreement with the values reported for its enantiomer (Rickards and Watson,1980).

The yellow precipitates were dissolved in dry chloroform and the resulting yellow solution was heated at reflux for 30 min. under nitrogen . After cooling and evaporating the solvent, the 3° alcohol was extracted from the residue by ether. Concentration of the ether extract, followed by column chromatography provided the title product 3° alcohol (**70**,

R_f=0.52/15% EA/PE) as pure colorless oil in about 53%yield (405 mg). $[\alpha]_D^{23} = -89$ 60.526° (C = 15.2 mg/ml EtOH); IR (film): cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$): δ 5.662 (br s, 2H,2 =CH), 4.775 (br s, 2H, $=CH_2$), 2.63 (br m, $J_{3,4}$ = 5.7Hz, 1H,CH), 2.1-1.1 (m, overlapping resonances, 4H, CH2s'), 1.732 (s,3H, CH_3=C), 1.28 (s, 3H, CH_3-C-OH), ^{13}C NMR (90 MHz, $CDCl_3$):δ 148.113, 134.027, 131.969, 110.515, 67.393, 43.447, 36.73,29.47, 24.811, 20.803.

1,3-Benzenediol, 2-[3-methyl-6-(1-methylethenyl)-2-cyclohexen-1-yl]-5-pentyl-, (1S, trans)-, : (+)-Cannabidiol, (1b)

As per the procedure described earlier a solution of olivetol (**51**, 1 mmol, 180 mg), and trans-(-)- p-mentha-2,8-dien-1-ol (**70**, 1.1 mmol,167.5 mg) in dry DCM (25 ml) in the presence of N,N-dimethylformamide dineopentyl acetal (1.3 mmol, 300 mg) provided the title compound (**1b**, R_f =0.3875/10% EA/hex) in about 20% yield (65 mg). $[\alpha]_D^{23}$= +80.3° (13.26 mg/ml, EtOH); IR (film): 3630, 3480, 3080,3000-2850, 1635, 1585, 1515, 1450, 1210, 885 cm^{-1}; ^1H NMR (500 MHz,$CDCl_3$): δ 6.0458 (br s, 2H, aromatic CH), 5.396 (br s, 1H, =CH), 4.5166-4.3625 (br 2s, 2H, $=CH_2$), 3.6687 (br m, 1H, -CH); 2.275 (t, 2H, benzylic CH_2), 2.23 (dd, 1H, benzylic CH), 2.1-1.0687 (m, overlapping resonances, 5H, CH, CH2s'), 1.6078 (s, 3H, CH_3), 1.4833 (s, 3H, CH_3), 0.7166 (t, 3H, CH_3); ^{13}C NMR (500 MHz, $CDCl_3$): δ 156.311, 154.211, 149.635, 143.335,140.349, 124.435, 114.069, 111.144, 110.039, 108.327, 46.482,37.536, 35.775, 31.794, 30.932, 30.702, 28.723, 23.965,22.836, 20.784, 14.351.

4-Oxatricyclo[5.1.0.0^{3,5}]octane, 3,8,8-trimethyl-, [1R-(1α,3β,5β,7α)-]: [Carane, 3,4-epoxy-, (1S,3R,4S,6R)-(-)-, (77)]

Dry powdered calcium carbonate (100 mmol, 10 g), water (50 ml), purified dioxane (100 ml), and N-bromosuccinimide (200 mmol, 35.6 g) were added in this order

to (+)-3-carene (**72**, 100 mmol, 13.623 g). The resulting rxn. mixt. was stirred at RT for 2 h. Initially the temp. started rising to 50°C but the mixt.was cooled to RT by an ice bath. The mixt. was poured into water (250 ml), filtered, the solid residue was washed thoroughly with ether and the aqueous filtrate was extracted with ether (3x100 ml). The combined extract was washed with water (3x250 ml), followed by 5% sodium thiosulphate solution (100 ml) and evaporated to give a brown oil which rapidly solidified on standing (20 g). This intermediate bromohydrin (**76**) being unstable to air and distillation at atmospheric pressure was immediately used for the ensuing rxn. without any further purification. Potassium t-butoxide (170 mmol, 19.75 g) in t-butanol (170 ml, 1 ml/mmol) was added to a solution of the bromohydrin (85 mmol, 19.75 g) in t-butanol (215 ml, 2.5 ml/mmol). The rxn.mixt. was left at RT for 2 h. with continuous stirring and then poured into water (1.5 L, 9 ml/mmol of t-BuOK). It was extracted with ether (1:1) and the extract was thoroughly washed with water, dried ($MgSO_4$) and the solvent evaporated to give an oil which on distillation at 55°C/2.75 mm Hg afforded pure β-epoxide in overall 55% yield (7.1 g).It was identical in glc, ir, and nmr with the literature values.(Gollnick et al. 1965); IR (film): 3010-2880, 1450, 1425, 1375, 1305, 1215, 1060, 1055 835, 760 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$): δ 2.89-2.84 (br 2s, J = 5.28 Hz, 1H, CH-O), 2.34-1.55 (m, overlapping resonances, 4H, CH2s'), 1.295 (s, 3H, CH_3-C-O), 0.96 (s, 3H, CH_3-C), 0.924 (s, 3H, CH_3-C), 0.6-0.4 (br m, 2H, CHs').

<u>Bicyclo[4.1.0]hept-4-en-3-ol, 3,7,7-trimethyl-, [1S-(1α,3α,6α)]-; [4-Caren-3-ol, (1S,3S,6R)-(-)-, (80)]</u>

Sodium borohydride (30.75 mmol, 1.17 g) was added in portions to a continuously stirred yellow suspension of diphenyl diselenide (14 mmol, 4.375 g) in absolute dry EtOH (70 ml, 5 ml/mmol) at RT and under argon. The suspension was stirred till it turned to

colorless solution (30 min). (-)- 3β,4β-Carane epoxide(**77**, 25 mmol, 3.82 g) was added dropwise under argon via syringe. The resulting solution was heated at reflux for 3 h. It was cooled and stirred at RT for 12 h. The rxn. mixt was cooled to 0°C and THF (45 ml) was added, followed by dropwise addition of 30% H_2O_2 solution (441 mmol, 15 g, 50 ml) maintaining the rxn. temp. below 20°C.The rxn. mixt. was stirred for 20 h. at RT. The reddish yellow solution turned to a colorless on completion of the rxn. The solution was poured into water (200 ml). The organic layer was separated, combined with the ether extract (4x50 ml) of the aqueous phase and washed successively with aqueous 10% Na_2CO_3, and saturated brine. After drying ($MgSO_4$) the solvent was removed to give a yellow oil in 93% yield (3.55 g). The tlc of this oil (R_f= 0.39/10%EA/PE) seemed to be pure enough for the further reaction. About 250 mg of this oil was purified by prep. tlc using 20% EA/PE. IR, and PMR were in agreement with the values reported (Uzarewicz and Zientek, 1977). IR(film): 3270, 3020-2890, 1715, 1650, 1460, 1380, 1330, 1295,1255, 1210, 1160, 1125, 1105, 1055, 1000, 985, 960, 915, 790,720 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$): δ 5.762 (br d, J = 9.89 Hz, 1H, =CH-C-OH), 5.52 (t of d, J = 9.85 Hz, J = 1.98 Hz, J = 1.21 Hz, 1H, =CH-C), 2.32 (br s, 1H, exchangeable with D_2O,OH), 2.22-1.4 (m, 2H, CH_2), 1.32 [s, 3H, CH_3-C(OH)], 1.09 (s, 3H, CH_3-C), 1.0-0.8 (m, overlapping resonances, 2H, CH-C); ^{13}C NMR (90 MHz, $CDCl_3$): δ 138.97, 124.45, 70.06, 36.145, 29.21,27.58, 25.42, 22.17, 20.867, 15.13.

1,3-Benzenediol, 2-(bicyclo[4.1.0]hept-3-en-3,8,8-trimethyl-1-yl)-5-pentyl-, (1S, trans): [(+)- Carenadiol, (45a)]

(+)-Carenadiol (**45a**) was obtained in about 15% yield from a solution of olivetol (5 mmol, 900 mg), (-)-4-caren-3β-ol (**80**, 5 mmol, 761 mg) in dry DCM 100 ml in the presence of N,N-dimethylformamide dineopentyl acetal (6.5 mmol, 1.5 g,1.8 ml) by

following the same procedure described earlier for (+)-cannabidiol. $[\alpha]_D^{23}$ = (+) 166.20 (c = (#), EtOH), IR (film): 3450, 3010-2840, 1630, 1585, 1515, 1445, 1370, 1332,1305, 1275, 1230, 1218, 1165, 1090, 1065, 1025, 920-900, 850,830, 725 cm^{-1}.; ^1H NMR (90 MHz, $CDCl_3$): δ 6.22 (br s, 2H, CH, aromatic), 5.81 (br s, 2H, OH, aromatic), 5.31 (br m, 1H,CH=C), 3.85 (br unresolved m, J = 1.1 Hz, 1H, CH, benzylic and allylic), 2.4 (br t, J = 6.8 Hz, 2H, CH_2, benzylic), 2.3-0.5(m, overlapping resonances, 10H, 2 CH and 4 CH_2), 1.64 (br s,3H, CH_3-C=C), 0.998 (s 3H, CH_3), 0.861 (s, 6H, 2 CH_3); ^{13}C NMR(90 MHz, CDCl3): d 155.101, 142.912, 134.298, 122.38, 115.283,108.457, 35.538, 31.583, 30.716, 29.687, 28.116, 27.737,26.762, 24.649, 23.511, 22.699, 22.536,, 18.473, 17.66,13.977, 13.164; MS: m/e 314.2 (M^+), 315.3 (M^++1); Anal. calcd for $C_{21}H_{30}O_2$: C 80.2091, H 9.6153. Found: C 79.68, H 9.49.

Diacetate of (+)-Carenadiol (45b):

Pyridine (100 mmol, 7.9 g, 8 ml), and acetic anhydride (10 mmol, 1.02 g, 0.95 ml) were added in this order to (+)-Carenadiol (**45a**, 1 mmol, 314 mg) at RT. The solution was stirred at RT for 12 h. The solution was poured into water (15 ml) and it was then extracted with ether (3x25 ml). This ether layer was thoroughly washed with aqueous 1% HCl solution followed by brine and dried ($MgSO_4$). Evaporation of the solvent at reduced pressure offered reddish yellow oil as crude product in 90% yield (360 mg) which on further purification by chromatography provided the diacetate in overall 85% yield (340 mg). IR (film): 2980-2830, 1765 (ester C=O), 1620, 1570, 1420, 1310, 1205-1175, 1120, 1090, 1025,880, 850, 765, 730 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$): δ 6.737 (brs, 2H, aromatic CH), 5.103 (br s, 1H, =CH), 3.2 (br s, 1H,benzylic CH), 2.566 (t, J = 7.92 Hz, 2H, benzylic CH_2), 2.208(br s, 6H, CH_3-CO), 1.8-0.5 (m, overlapping resonances, 10H,CH and CH2s'), 1.629 (br s, 3H, CH_3-C=C), 1.01 (s, 3H, CH_3-C), 0.799 (s, 6H,

CH3s'); ^{13}C NMR (90 MHz, $CDCl_3$): δ 169.132,149.521, 142.153, 130.885, 128.285, 121.892, 120.646, 35.213,31.475, 30.446, 28.712, 27.845, 24.757, 23.457, 22.861,22.428, 20.694, 18.581, 16.902, 13.922, 13.489; Anal. calcd for $C_{25}H_{34}O_4$: C 75.3435, H 8.5985.; Found C 75.50, H 8.60.

2-Methyloctane-2-ol (82):

Methyl magnesium bromide (250 mmol, 29.75 g, 86.25 ml/2.9 M etheral solution) was added dropwise to a solution of methyl enanthate (**81**, 100 mmol, 14.4 g, 16.4 ml) in dry THF (100 ml) under nitrogen and with stirring. The rxn. mixt. was heated gradually at reflux for 3 h., then cooled down and stirred at RT for 12 h. The excess of MeMgBr was hydrolyzed by dropwise addition of satd. NH_4Cl solution followed by water (100 ml). The organic layer was combined with the ether extract of the aqueous phase and dried (MgSO4). Evaporation of the solvent provided a reddish yellow oil which on distillation at 35-37°C/0.3 mm Hg afforded the product (**82**, R_f= 0.39/20% EA/hex) in 85% yield (12.25g). IR and ^1H NMR were in agreement with the values reported by Dominianni et al. (1977). ^1H NMR (90 MHz, $CDCl_3$): δ 2.6 (br s, 1H, OH), 1.6-1.0 (m, overlapping resonances, 10H, CH2s'), 1.18 (s, 6H,CH3s'), 0.888 (unresolved t, 3H, CH_3).

4-(1',1'-Dimethylheptyl)-2,6-dimethoxyphenol, (84):

To a mixt. of 2-methyloctane-2-ol (**82**, 100 mmol, 14.4 g) and 2,6-dimethoxyphenol (**83**, 100 mmol, 15.4 g) methanesulfonic acid (300 mmol, 20 ml, 98%) was added. The resulting reddish yellow solution was stirred at 50°C for 6 h. and then at RT for 12 h. The rxn. mixt. was poured into ice (100 g) and extracted with DCM (4x50 ml). The DCM extract was washed with water, satd $NaHCO_3$, brine and dried ($MgSO_4$). Evaporation of solvent afforded an oil in 98%yield (27.5 g). Tlc (20% EA/hex) showed

that this crude product was pure enough to be used directly for the next step. The product (84, R_f= 0.525/20% EA/hex) was isolated in 95% yield (26.6 g) by column chromatography using 10% EA/hex. IR and ^1H NMR, were in agreement with reported values (Dominianni, Ryan, and Dearmitt, 1977). IR (film): 3540,3460, 3000-2860, 1610, 1520, 1455, 1415, 1355, 1325, 1240,1210, 1110, 1025, 905, 820, 765 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$):δ 6.536 (s, 2H, CH, aromatic), 5.397 (s, 1H, OH), 3.876 (s,6H, CH_3O-), 1.66-0.925 (m, overlapping resonances, 16H, CH_2s'), 0.848 (s, 3H, CH_3); ^{13}C NMR (90 MHz, $CDCl_3$): δ 146.56,141.088, 132.745, 103.274, 56.306, 44.659, 37.616, 31.657,29.922, 29.110, 24.559, 22.555, 13.944

4-(1',1'-dimethylheptyl)-2,6-dimethoxyphenyl diethylphosphate (85):

To a cooled (< 5°C) solution of crude 4-(1',1'-dimethylheptyl)-2,6-dimethoxyphenol (**84**, 100 mmol, 28.04 g) in CCl_4 (15 ml), diethyl phosphite (117.2 mmol, 16.18 g, 15.1 ml) was added, followed by dropwise addition of triethylamine (117.2 mmol, 11.86 g, 16.34 ml). The rxn. mixt. was stirred at 0°C for 1 h and then at RT for 12 h. The mixture was then diluted with DCM (50 ml), washed (water, 4N NaOH, water, 1N HCl, water, brine), filtered to remove a trace of solid, and dried ($MgSO_4$). Evaporation of the solvent provided a viscous red oil which solidified on cooling. This crude solid on repeated recrystallization from benzene/PE provided the phosphate ester (**85**, R_f= 0.2/20% EA/hex) in 85% yield (35.4 g). MP, IR, and ^1H NMR, were in agreement with reported values (Dominianni, Ryan, and Dearmitt, 1977): mp 61-64°C, IR (KBr): 2925-2860, 1595, 1520, 1460, 1415, 1358, 1340, 1290,1265, 1245, 1225, 1185, 1130, 1105, 1065, 1015, 980, 965, 925,905, 815, 775 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$): δ 6.531 (s, 2H,CH, aromatic), 4.3 (2q, 4H, CH_2O), 3.847 (s, 6H, CH_3O), 1.65-1.0 (m, overlapping resonances, 16H, CH_2s', CH_3s'), 1.25 (s,6H, CH_3s'), 0.84 (t, 3H, CH_3).

1-(1',1'-Dimethylheptyl)-3,5-dimethoxybenzene (86):

A solution of the phosphate ester (**85**, 100 mmol, 41.64 g) in ether (80 ml) and THF (20 ml) was added dropwise to a mixt of lithium (0.18 g-atom, 1.25 g) in liq ammonia (225 ml) at -50°C, maintaining the deep blue color of the rxn. mixt. The rxn. mixt. was stirred at -50°C for 1 h and then brought to RT. The excess lithium was destroyed by dropwise addition of satd NH_4Cl. The rxn. mixt. was diluted with ether (115 ml) and ammonia was allowed to evaporate. The rxn. mixt. was washed with water and the layers were separated. The organic layer was washed (4N NaOH, water, brine), dried ($MgSO_4$) and evaporated to give an oil in 95% yield (25.11 g) which on further purification by column chromatography (10%EA/hex) afforded the product (**86**, Rf= 0.75/20% EA/hex) in 90% yield overall (23.8 g). IR, ^1H NMR, were in agreement with reported values (Dominianni, Ryan, and Dearmitt, 1977).; ^1H NMR (90 MHz, $CDCl_3$): δ 6.484 (d, J = 2.19 Hz, 2H, aromatic), 6.286 (t, J = 2.2 Hz, 1H), 3.773 (s, 6H, CH_3O),1.7-0.95 (m, overlapping resonances, 10H, CH_2s'), 1.251 (s, 6H, CH_3s'), 0.839 (t, 3H, CH_3).

5-(1',1'-Dimethylheptyl)resorcinol (87):

To a solution of (**86**, 100 mmol, 26.4 g) in dry $CHCl_3$ (250 ml), pyridine (200 mmol, 15.82 g, 16.2 ml) followed by iodotrimethylsilane (600 mmol, 120 g, 85.4 ml) were added under nitrogen atmosphere. A yellow precipitation was observed. The rxn. mixt. was heated at reflux for 60 h. By this time the rxn had almost gone to completion. The rxn. mixt. was cooled to RT and excess iodotrimethylsilane was destroyed by dropwise addition of anhydrous MeOH (50 ml). The rxn. mixt.was evaporated to yield an oil which on dilution with ether (250 ml) precipitated pyridinium hydroiodide. The ppts were filtered off and thoroughly washed with ether. The ether layer combined with ether

washings was washed with 5M NaOH solution.The aqueous layer was acidified with conc HCl and then extracted with ether. The combined ether extract was washed with water, brine and dried (MgSO4). Evaporation of the solvent provided red oil which on purification by column chromatography (20% EA/hex) afforded pure product (**87**) in 95% yield (22.45 g). Recrystallization from benzene/PE offered fine needles (R_f= 0.19/20% EA/hex). MP, IR, and ^1H NMR, were in agreement with reported values (Dominianni, Ryan and Dearmitt, 1977). mp 98°C; ^1H NMR (90 MHz,$CDCl_3$): δ 6.381 (d, J = 2 Hz, 2H, aromatic), 6.18 (t, J = 2Hz, 1H, aromatic), 4.9 (br s, 2H, OH, exchangable with D_2O),1.7- 1.0 (m, overlapping resonances, 10H, CH_2s'), 1.216 (s, 6H, CH_3s'), 0.844 (t, 3H, CH_3); ^{13}C NMR (90 MHz, $CDCl_3$): δ 156.185, 153.693, 106.073, 100.06, 44.477, 37.759, 31.8,30.012, 28.82, 24.649, 22.644, 14.031.

1,3-Benzenediol, 2-(bicyclo[4.1.0]hept-3-en-3,8,8-trimethyl-1-yl)-, 5-(1",1"-dimethylheptyl)-, (1S, trans)-, (45c):

A solution of 5-(1',1'dimethyl-heptyl)resorcinol (**87**, 5 mmol,1.18 g), (-)- 4-Caren-3β-ol (**80**, 5 mmol, 761 mg) in dry DCM (100 ml) and N,N-dimethylformamide dineopentyl acetal (6.5 mmol, 1.5 g, 1.8 ml) as catalyst provided the product (**45c**, R_f= 0.55/10% EA/Hex) in about 18% yield (300 mg). IR (film): 3438, 2955-2864, 1629, 1581,1432, 1376, 1302,1232, 1218, 1180, 1027, 861, 840, 757, 670 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 6.233 (br s, 2H, aromatic CH), 5.34 (br s, 1H,=CH), 3.829 (br s, 1H, benzylic CH), 2.45 (t, J = 6.25 Hz, 2H,CH_2), 2.4 (dd, J = 6.25 Hz, 15.62 Hz, 2H, CH_2), 2.0 (dd, J =6.25 Hz, 15.62 Hz, 1H, CH), 1.65-0.8 (m, overlapping resonances, 14H, CHs, CH_2s, and CH_3), 1.58 (s, 3H, CH_3), 1.05 (s, 3H, CH_3), 0.9 (s, 9H, CH_3s), 0.683 (d, J = 6.25 Hz, 1H,CH); ^{13}C NMR (500 MHz, $CDCl_3$): δ 150.312, 134.578, 122.236,114.828, 107.026, 105.731, 44.5, 37.412, 31.866, 30.091, 28.810,

28.126, 26.801, 24.706, 24.633, 23.57, 22.755, 22.581,18.432, 17.676, 14.124, 13.193; Anal Calcd for $C_{25}H_{38}O_2$: C 81.02, H 10.34; Found: C 81.14, H 10.55.

7-Oxabicyclo[4.1.0]heptane-1-methanol, 4-(1-methylethenyl)-,; [p-Mentha-8-ene-7-ol, 1,2-epoxy, (93)]

(S)-(-)-Perillyl alcohol (**89**, 100 mmol, 15.22 g) and $VO(acac)_2$ (0.46 g) were dissolved in dry toluene (150 ml). To the resulting purple blue solution, freshly distilled 3.34 M t-butyl hydroperoxide in toluene (130 mmol, 11.7 g, 39 ml) was added dropwise with stirring and cooling to keep the rxn. mixt.below 5°C. The dark brown rxn. mixt. was allowed to warm up to RT and then stirred for 10 h. The rxn. mixt. was diluted with ether (350 ml), washed with 10% aqueous Na_2SO_3(3x100), brine and dried ($MgSO_4$). Evaporation of ether provided crude product as an orange yellow oil which was sufficiently pure for the subsequent rxn. The epoxy alcohol (**93**) was purified by distillation at 100-110°C at 0.2 mm Hg to give colorless oil in 90% yield (15.14 g). IR, ^1H NMR, ^{13}C NMR are in agreement with literature values (Stevens and Albizati, 1985). IR (film): 3404, 3081, 2926, 2867, 1643,1449, 1377, 1060, 1038, 959, 944, 888, 848, 765 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$): δ 4.68 (br s, 2H, $=CH_2$), 3.62 [br s, 2H,CH_2(OH)], 3.336 (br s, 1H, CH-O-), 2.91, (br s, 1H, CH), 2.38-1.0 (m, overlapping resonances, 6H, CH), 1.692 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 148.654, 109.215, 64.756, 60.133, 56.883,55.908, 40.847, 36.838, 30.229, 29.362, 25.895, 24.595,23.836, 20.911, 20.152.

7-Oxabicyclo[4.1.0]heptane, 1-[[[(1,1-dimethylethyl)-dimethylethylsilyl]oxy]methyl]-4-(1-methylethenyl)-, : [p-Mentha-8-ene-7-silyloxy, 1,2-epoxy, (94).

Epoxy alcohol (**93**, 100 mmol, 16.82 g) was dissolved in dry DMF (85 ml). Imidazole (215 mmol, 14.65 g) followed by t-butyldimethylsilyl chloride (110 mmol, 16.6 g) were added and the resulting pale yellow solution was stirred at RT for 12 h. It was diluted with ether (415 ml). The organic layer was washed with water (3x150 ml), brine and dried ($MgSO_4$). Evaporation of ether left a yellow oil which was passed through a short silica gel column (5% EA/PE) to afford a colorless liquid in quantitative yield (28.25 g). IR, ^1H NMR, ^{13}C NMR are in agreement with the reported values (Stevens and Albizati, 1985). IR (film): 3060, 2940, 2840,1635, 1445, 1439, 1370, 1310, 1240, 1100, 1070, 870, 835, 740,675 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$): δ 4.67 (br s, 2H, $=CH_2$), 3.633 and 3.375 (2 s, 2H, CH_2-O), 3.175 (br m, 1H, CH), 2.47-1.2 (m, overlapping resonances, 7H, CH_2s' and CH), 1.67 (s, 3H, CH_3), 0.9 (s, 9H, t-Bu), 0.1 (s, 6H, CH_3-Si); ^{13}C NMR (90 MHz, $CDCl_3$): δ 148.92, 109.05, 67.17, 67.07, 57.59, 56.233,36.89, 30.66, 29.69, 26.17, 26.06, 25.9, 24.43, 23.99, 20.965,20.2.

Cyclohexanol, 1[[[(1,1-dimethylethyl)dimethylethylsilyl]oxy]methyl]-4-(1-methylethenyl)-2-(phenylseleno)-, [mixt of [(1R)-1α,2β,4β]-, (97a) and [(1S)-1α,2β,4α]-, (97b)]:

Sodium borohydride (125 mmol, 4.75 g) was added in portions to a continuously stirred yellow suspension of diphenyl diselenide (55 mmol, 17.17 g) in absolute dry EtOH (275 ml, 5 ml/mmol) at RT and under argon. The suspension was stirred till it turned to a colorless solution (30 min). Silyloxy epoxide (**94**, 100 mmol,28.25 g) was added dropwise under argon via syringe. The resulting solution was heated at reflux for 24 h. The rxn. mixt. was diluted with aqueous satd $NaHCO_3$ (225 ml), stirred for 15 min and extracted with ether (5x100 ml).The ether extracts were washed with brine, dried ($MgSO_4$)

and evaporated to leave reddish yellow oil which was passed through a short silica gel column and eluted with 2.5% EA/hex to offer a mixt of major products (**97a**) and (**97b**) in 92% yield (44.36 g). A small sample (250 mg) of this mixt. was purified by prep tlc and both the diastereomers were isolated as pure colorless oils. The IR and ^1H NMR of these two diastereomers were in agreement with the reported values (Stevens and Albizati, 1985).

The higher R_f diastereomer [(1S,2R,4S)-, (97a)]:

R_f= 0.47/5% EA/PE; IR (film): 3540, 3065, 2920, 2830,1635, 1570, 1480, 1455, 1435, 1250, 1075, 1050, 1000, 890,850, 830, 770, 750, 685, 660 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$): δ 7.54 (m, 2H, Ar H), 7.23 (m, 3H, Ar H), 4.7 (br s, 2H, CH_2=C), 3.84 (d, J = 10 Hz, 1H, CH-OSi), 3.49 (d, overlapped on m, J= 10 Hz, 2H, CH-OSi, and CH-SePh), 2.73 (br s, OH), 2.5-1.5(m, overlapping resonances, 7H, CH's and CH_2s'), 1.69 (s, 3H, CH_3), 0.875 (s, 9H, t-Bu), 0.075 (s, 6H, CH_3-Si).

The lower R_f diastereomer [(1R,2S,4S)-, (97b)]:

R_f= 0.31/5% EA/PE; IR (film): 3530, 3085, 2930, 2860,1640, 1575, 1470, 1435, 1400, 1325, 1250, 1100, 1000, 950,880, 835, 775, 735, 695, 685, 660 cm^{-1}; ^1H NMR (60 MHz,$CDCl_3$): δ 7.6 (m, 2H, aromatic H), 7.23 (m, 3H, aromatic H),4.63 (br s, CH_2=C), 3.9 (d, J = 10 Hz, 1H, CH-OSi), 3.55 (d,overlapped on m, J = 10 Hz, 1H, CH-OSi and CH-SePh), 3.45-3.1(m, overlapping resonances, 2H, OH and CH-SePh), 2.33-1.13 (m,overlapping resonances, 7H, CH's and CH_2s'), 1.63 (s, 3H,CH_3=C), 0.93 (s, 9H, t-Bu), 0.15 (s, 6H, CH_3-Si).

Cyclohexanemethanol, 1-hydroxy-4-(1-methylethenyl)-2-(phenylseleno)-, [mixt of [(1R)-1α,2β,4β]-, (95a) and [(1S)-1α,2 β,4α]-, (95b)]:

The crude mixt of silyloxy phenylselenides (**97**, 100 mmol,43.95 g) was dissolved in dry THF (500 ml), and while stirring to this lemon yellow solution at RT a 1.0 M solution of tetra-n-butylammonium fluoride in THF (110 ml) was added under nitrogen. The resulting solution was stirred for 6 h at RT and then diluted with ether (500 ml). The diluted rxn. mixt. was washed with water (250x4), brine and dried ($MgSO_4$). Evaporation of the solvent provided a reddish yellow oil which was passed through a short silica gel column and eluted with 10-20% EA/PE to give a quantitative yield (32.53 g) of an inseparable mixt. of diastereomeric diolselenides (**95a**, R_f= 0.368/35% EA/PE) and (**95b**, R_f= 0.312/35% EA/PE). This mixt was used as such for the ensuing rxn. IR (film): 3327, 3059,2959, 2930, 2890, 2858, 1641, 1585, 1475, 1449, 1434, 1377,1254, 1190, 1118, 1047, 1000, 950, 916, 896, 882, 735, 692 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$): δ 7.58 (m, 2H, Ar H), 7.26 (m, 3H,Ar H), 4.67 (br s, 2H, CH_2=C), 3.73 (br s, overlapped with m, 2H, CH_2-OH and CH-SePh), 3.5-2.6 (m, overlapping resonances, 3H, CH-SePh and OHs'), 2.5-1.2 (m, overlappinng resonances,7H, CH and CH_2s'), 1.66 (s, 3H, CH_3); ^{13}C NMR (90 MHz, $CDCl_3$): δ 148.004, 134.244, 130.05, 129.152, 127.635, 109.324, 74.219,64.467, 56.45, 46.265, 37.813, 34.346, 28.062, 20.694.

1,3-Dioxaspiro[4.5]decan-2-one, 8-(1-methylethenyl)-6-(phenylseleno)-,[mixt of [(1R)-1α,2β,4β]-, (99a)] and [(1S)-1α,2β,4α]-, (99b)]:

N,N-Carbonyldiimidazole (200 mmol, 32.43 g) was dissolved in dry THF (100 ml) and diluted with dry toluene(300 ml). To this colorless solution, a mixt of diol selenides (**95**, 100 mmol, 32.53 g) in dry toluene (100 ml) was added under nitrogen. The resulting yellow solution was refluxed gently for 3 h. The rxn. mixt. was cooled to RT,

diluted with ether (500 ml), washed with water (2x250ml) followed by brine and dried ($MgSO_4$). Evaporation of the solvent afforded a viscous yellow oil. Tlc (20% EA/hex) of this oil showed two distinct spots for the isomers. The isomers were separated by column chromatography in 85% combined yield.

The higher Rf diastereomer [(1S,2R,4S)-, (99a)] was isolated (8-10% EA/hex) in 30% yield (10.55 g). R_f= 0.475/20% EA/PE; IR (film): 3072, 2933, 2864, 1802, 1643, 1580, 1478, 1439,1379, 1218, 1203, 1122, 1057, 1023, 969, 890, 769, 742, 691,643 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$): δ 7.54 (m, J = 3.52 Hz, 2.64 Hz, 2H, Ar H), 7.32 (m, J = 2.64 Hz, 3H, Ar H), 4.76 (br s, 2H, CH_2=C), 4.377 and 4.15 (2 d, overlapped on m, J = 8.79 Hz,9.24 Hz, 2H, CH_2-O); 4.27 (m, J = 14.07 Hz, 14.95 Hz, J = 5.2 Hz, 6.16 Hz, 1H, CH-SePh), 3.48 (br s, 1H, CH), 2.5-1.5 (m,overlapping resonances, 6H, CH_2s'), 1.74 (s, 3H, CH_3); ^{13}C NMR (90 MHz, $CDCl_3$): δ 154.07, 147.896, 134.027, 129.585, 128.393,128.068, 109.865, 84.512, 74.327, 50.6, 39.44, 34.35, 32.613,25,787, 20.803.

The lower R_f diastereomer [(1R,2S,4S)-, (99b)] was isolated (10% EA/hex) in 55% yield (19.3 g). R_f= 0.35/20% EA/PE; IR(film): 3060, 2939, 2864, 1807, 1656, 1642, 1579, 1477, 1450,2388, 1300, 1267, 1188, 1153, 1091, 1070, 1023, 893, 761, 742,693 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$): δ 7.64 (m, J = 3.52 Hz, 2H,Ar H), 7.29 (m, J = 3.52 Hz, 2.64 Hz, 3H, Ar H), 4.73 and 4.66 (2 s, 2H, CH_2-O), 3.39 (dd, J = 16 Hz, 4 Hz, 1H, CH-SePh),2.6-1.0 (m, overlapping resonances, 7H, CH's and CH_2s'), 1.68 (s, 3H CH_3); ^{13}C NMR (90 MHz, $CDCl_3$): δ 154.07, 146.921,135.544, 129.26, 128.393, 127.96, 110.082, 84.728, 70.86,50.924, 44.856, 37.163, 36.73, 27.52, 20.911.

1,3-Dioxaspiro[4.5]dec-6-en-2-one, 8-(1-methylethenyl)-,[(1R,4S)-, (100a)]:

To a solution of phenylselenide carbonate (**99a**, 25 mmol, 8.8 g) in THF (125 ml), a 31% solution of hydrogen peroxide (250 mmol, 27.5 ml) was added. It was stirred for 1 hr at RT and then diluted with ether (125 ml). The rxn. mixt. was washed with water (2x100 ml), aqueous satd Na_2CO_3 (2x100 ml), and brine. The ether extract of the aqueous layer was combined with the organic layer and dried ($MgSO_4$). Evaporation of the solvent left an orange oil. The elimination product (**100a**) was isolated by column chromatography (10% EA/hex) in 85% yield (4.45 g). R_f= 0.3/20% EA/PE; IR (Film): 3076, 2933, 2921, 2866, 1798,1642, 1451, 1377, 1246, 1223, 1178, 1156, 111221, 1059, 963,897, 771, 751, 727 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$): δ 6.05 (dd,J = Hz, 1H, CH=C), 5.75 (d, J = Hz, 1H, CH=C), 4.84 and 4.77 (2 s, 2H, CH_2=C), 4.22 (s, 2H, CH_2-O), 2.74 (m, 1H, CH), 2.31-1.6 (m, overlapping resonances, 4H, CH_2s'), 1.75 (s, 3H,CH_3=C); ^{13}C NMR (90 MHz, $CDCl_3$): δ 154.05, 146.216, 138.957,125.468, 111.978, 80.178, 74.38, 42.58, 32.233, 24.053, 20.857.

1,3-Dioxaspiro[4.5]dec-6-en-2-one, 8-(1-methylethenyl)-,[(1S,4R)-, (100b)]:

To a solution of phenylselenide carbonate (**99b**, 25 mmol,8.8 g) in THF (125 ml) a 31% solution of hydrogen-peroxide (250 mmol, 27.5 ml) was added. It was heated to reflux for 1 hr, cooled to RT, and diluted with ether (125 ml). The rxn. mixt. was worked up as described in the previous procedure. The elimination product (**100b**) was isolated by column chromatography (10% EA/hex)in 73% yield (3.55 g). R_f= 0.425/20% EA/PE; IR (Film): 3076,2933, 2921, 2866, 1798, 1642, 1451, 1377, 1246, 1223, 1178,1156, 111221, 1059, 963, 897, 771, 751, 727 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$): δ 6.05 (dd, J = Hz, 1H, CH=C), 5.75 (d, J = Hz,1H, CH=C), 4.83 and 4.66 (2 s, 2H, CH_2=C), 4.2 (s, 2H, CH_2-O), 2.85 (m, 1H, CH), 2.2- 1.2 (m, overlapping resonances,CH_2s'), 1.746

(s, 3H, CH_3=C); ^{13}C NMR (90 MHz, $CDCl_3$): δ 154.614, 145.837, 137.928, 126.01, 111.761, 81.1, 74.056,41.714, 31.367, 24.053, 21.182.

General method for decarbonylation:

The carbonate (**100**, 10 mmol, 1.94 g) was dissolved in THF (100 ml) and 2M NaOH solution (200 mmol, 8 g, 100 ml) was added to it with stirring and chilling. The rxn. mixt. was stirred at RT for 1 h. Tlc showed that rxn had gone to completion. The aqueous layer was extracted with ether (3x100 ml), the ether extract combined with the THF layer was washed with brine and dried ($MgSO_4$). Evaporation of the solvent provided a yellow oil which was passed through a short column and eluted with 25% EA/hex to afford 95% yield (1.6 g) of the product diol (**101**).

2-Cyclohexen-1-ol, 1-methanol, 4-(1-methylethenyl)-, [(1R,4S)-, (101a)]:

R_f= 0.35 (50% EA/hex); IR: 3355-3282, 2968, 2933,2865, 1640, 1450, 1220, 1046, 990, 890, 740 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$): δ 5.7 (m, 2H, CH=CH), 4.76 and 4.69 (2 s, 2H,CH_2=C), 3.42 (br d, 2H, CH_2-O), 2.73, (br m, 1H, CH), 2.3-1.19(m, overlapping resonances, 4H, CH_2s'), 1.68 (s, 3H, CH_3); ^{13}C NMR (90 MHz, $CDCl_3$): δ 147.1, 133.7, 129.9, 111.17, 70.92,68.77, 42.85, 30.5, 24.43, 21.18.

2-Cyclohexen-1-ol, 1-methanol, 4-(1-methylethenyl)-, [(1S,4S)-, (101b)]:

R_f= 0.30 (50% EA/hex); IR: 3355-3282, 2968, 2933,2865, 1640, 1450, 1220, 1046, 990, 890, 740 cm^{-1}, ^1H NMR (60 MHz, $CDCl_3$): δ 5.7 (m, 2H, CH=CH), 4.76 and 4.69 (2 s, 2H,CH_2=C), 3.42 (br d, 2H, CH_2-O), 2.73, (br m, 1H, CH), 2.3-1.19 (m, overlapping resonances, 4H, CH_2s'), 1.68 (s, 3H, CH_3); ^{13}C NMR (90 MHz, $CDCl_3$): δ 147.029, 133.756, 129.91, 111.057,70.914, 68.747, 42.852, 30.5, 24.43, 21.182.

General procedure for monoacetylation of diol (101):

To a solution of diol (**101**, 5 mmol, 0.85 g) in dry pyridine (25 mmol, 1.98 g, 2 ml), acetic anhydride (10 mmol,1.02 g, 1 ml) was added. The solution was stirred for 3 h at RT and then poured into water (25 ml). The aqueous solution was extracted with ether (4x25 ml). The ether extract was washed with water (2x25 ml), 1% HCl (2x25 ml), brine and dried ($MgSO_4$). Evaporation of ether left a yellow oil which on column chromatography (10% EA/hex) afforded a 90% yield (1.9 g) of pure acetate (**102**).

2-Cyclohexen-1-ol, 1-[(1-acetyloxy)methyl]-4-(1-methyl-ethenyl)-, [(1R,4S)-, (102a)]:

R_f= 0.49 (25% EA/hex); IR (film): 3461, 3432, 3091,2939, 2889, 2869, 1740, 1727, 1643, 1450, 1375, 1247, 1115,1094, 1040, 895, 833, 750 cm^{-1}, ^1H NMR (90 MHz, $CDCl_3$): δ 5.75(m, J = 2.64 Hz, 2H, CH=CH), 4.79 and 4.67 (2 s, 2H, CH_2=C), 2.8 (br s, 1H, CH), 2.38 (br s, 1H, OH), 2.105 (s, 3H, CH_3-CO), 2.05-1.45 (m, overlapping resonances, 4H, CH_2s'), 1.74(s, 3H, CH_3=C), ^{13}C NMR (90 MHz, $CDCl_3$): δ 171.083, 147.679, 135.111, 128.664, 110.95,70.86, 68.53, 43.664, 31.854, 23.945, 20.803.

2-Cyclohexen-1-ol, 1-[(1-acetyloxy)methyl]-4-(1-methyl-ethenyl)-, [(1S,4S)-, 102b]:

Rf: 0.4 (25% EA/hex); IR (film): 3461, 3432, 3091,2939, 2889, 2869, 1740, 1727, 1643, 1450, 1375, 1247, 1115, 1094, 1040, 895, 833, 750 cm^{-1}, ^1H NMR (90 MHz, $CDCl_3$): δ 5.75 (m, J = 2.64 Hz, 2H, CH=CH), 4.79 and 4.67 (2 s, 2H, CH2=C), 2.8 (br s, 1H, CH), 2.38 (br s, 1H, OH), 2.105 (s, 3H, CH_3-CO), 2.05-1.45 (m, overlapping resonances, 4H, CH_2s'), 1.74(s, 3H, CH_3=C); ^{13}C NMR (90 MHz, $CDCl_3$): δ 171.083, 146.596, 134.136, 129.26, 111.274, 70.101, 69.343, 42.472, 30.771, 24.053, 21.236, 20.803.

Condensation of diol (101) and olivetol (51):

Method-1: Diol (**101**, 1 mmol, 168 mg) and olivetol (**51**, 1 mmol, 180 mg) were dissolved in dry DCM and N,N-dimethylformamide dineopentyl acetal was added to the above yellow solution under nitrogen atmosphere. A yellowish white precipitate was observed. The flask was covered with aluminium foil and stirred at RT for 72 h.

Tlc showed both the reactants unchanged and no trace of the expected product 1,3-Benzenediol, 2-[1-methanol-6-(1-methylethenyl)-2-cyclohexen-1-yl]-5-pentyl-,(1S-trans)-,(46a,7-hydroxycannabidiol).

Method-2: BF_3•etherate (3 mmol, 425 mg, 0.37 ml) was added via syringe to a stirring suspension of basic alumina (25 mmol,2.55 g, Brockman grade-1) in dry DCM (25 ml) under nitrogen. The rxn. mixt. was stirred at RT for 15 min and then heated to reflux for 1 min. To this boiling suspension a mixt of diol (**101**, 1 mmol, 168 mg) and olivetol (**51**, 1.25 mmol, 225 mg) in DCM (10 ml) was added under nitrogen. A dark brown suspension formed and the mixt. was quenched with 10% aqueous Na_2CO_3 (10 ml) within 10 sec. The resulting yellow suspension was diluted with 10% aqueous Na_2CO_3. The separated aqueous layer was extracted with ether. The organic layer combined with the ether extract was washed with brine, dried ($MgSO_4$) and evaporated to give a yellow oil which on purification by column chromatography followed by ptlc gave two isomeric products (**103**, **103i**).

Product (103) 22% yield (80 mg, R_f = 0.642/10% EA/hex); ^1H NMR (90 MHz, $CDCl_3$): δ 6.2 (br d, 2H, aromatic), 5.49 (br hump, 1H, OH), 5.15 (br, 2H, $=CH_2$/C-7), 4.8-4.5 (m,overlapping resonance, 3H, of CH/C-2 on 2H of $=CH_2$/C-9), 3.02 (dd, 1H, CH/C-3), 2.6-1.0 (m, overlapping resonances, 13H,CH_2s' and CHs'), 1.72 (s, 3H, CH_3), 0.88 (t, 3H, CH_3); ^{13}C NMR (90 MHz, $CDCl_3$): δ 160.42, 156.1, 152.185, 146.5, 143.92, 141.5,124.2, 116.5, 113.663, 108.604, 96.0, 88.0, 49.0, 45.2, 33.5,

33.3, 30.54, 22.8, 20.0, 14.044; MS: m/e 312.2 (M^+); Anal. calcd.for $C_{21}H_{28}O_2$: C 80.7262, H 9.03267. Found: C 80.83, H 9.29.

Isomeric Product (103i) 17% yield (60 mg, R_f = 0.444/10% EA/hex). ^1H NMR (90 MHz, $CDCl_3$): δ 6.3 (br d, 2H, aromatic), 5.4 [(s, 1H, OH(?)], 5.2 (br, 2H, $=CH_2$/C-7), 5.05 (s, 2H, ?,), 4.85-4.7 (2s, 2H, of $=CH_2$/C-9), 3.25 (dd, 1H, CH/C-3), 2.6-1.0 (m, overlapping resonances, 12H, CH_2s' and CHs'), 1.85 (s, 3H, CH_3), 0.89 (t, 3H, CH_3); ^{13}C NMR (90 MHz, $CDCl_3$); δ 160.42, 152.944, 152.185, 145.192,143.192, 116.972, 115.997, 111.663, 109.604, 103.212, 86.418,48.387, 45.788, 36.037, 31.593, 30.943, 22.6, 14.044; MS: m/e=312.2 (M^+); Anal. calcd. for $C_{21}H_{28}O_2$: C 80.7262, H 9.03267. Found:C 80.83, H 9.08.

Condensation of acetate (102) and olivetol (51):

By following the same procedure as method-2, acetate(**102**, 1 mmol, 210 mg), and olivetol (**51**, 1.25 mmol, 225 mg) in presence of BF_3•etherate on basic alumina gave two products which were moving together on tlc (R_f = 0.494, and R_f = 0.444,25% EA/PE). Repeated purification by ptlc gave two identifiable products. The major product was the 11-acetoxytetrahydrocannabinol (**104**, yield = 20%) and the minor product was the desired 7-acetoxycannabidiol (**46b**, yield = < 5%).

7-Acetoxycannabidiol (46b):

Reddish yellow oil, R_f= 0.59/20% EA/PE; IR (film): 3433,2953, 2928, 2872, 1735, 1713, 1624, 1582, 1431, 1374, 1262,1246, 1048, 1024, 859, 891, 848, 756 cm^{-1}; ^1H NMR (250 MHz,$CDCl_3$): δ 6.22 (m, 2H, Ar H), 5.86 (br s, 1H, CH=C), 4.64-4.54(2 s overlapped on s, 4H, CH_2=C and CH_2-OH), 3.95 (m, 1H,CH), 2.43 (t, J = 7.564 Hz, 7.97 Hz, 2H, benzylic CH_2), 2.3-1.0 (m, overlapping resonances, 11H, CH and CH_2s'), 2.087(s, 3H, CH_3-CO), 1.66 (s, 3H, CH_3=C), 0.875 (t, J = 6.698 Hz,6.88 Hz,

3H, CH_3); ^{13}C NMR (90 MHz, $CDCl_3$): δ 170.974, 155.20, 148.546, 143.237, 137.061, 128.176, 113.333, 111.057, 109.107, 67.718, 46.048, 36.73, 35.43, 31.53, 30.554, 29.687, 28.062, 26.328, 22.536, 20.80, 20.044, 13.977.

7-Acetoxytetrahydrocannabinol (104):

Red oil, R_f= 0.5/20% EA/PE; IR (film): 3374, 2951, 2930, 2871, 1738, 1721, 1718, 1612, 1591, 1449, 1378, 1323, 1263, 1246, 1149, 1132, 1022, 959, 838, 754 cm^{-1}; ^1H NMR (90 MHz,$CDCl_3$): δ 6.2 (dd, 2H, aromatic), 5.5 (br s, 1H, =CH), 4.4 (s, 2H, CH_2-OAc), 3.18 (br m, 1H, benzylic CH), 2.58 (t, 2H, benzylic CH_2), 2.4-0.99 (m, overlapping resonances, 11H, CH and CH_2s'), 2.05 (s, 3H, CH_3-CO), 1.32 (s, 6H, gem dimethyl), 0.85 (t, 3H, CH_3); ^{13}C NMR (90 MHz, $CDCl_3$): δ 171.255, 155.219, 154,786, 143.192, 132.791, 131.924, 115.022, 109.171, 102.02, 76.774, 68.432, 46.762, 34.845, 33.112, 31.811, 30.943, 27.476, 26.826, 24.66, 22.6, 20.975, 18.7, 14.152.

Condensation of acetate (102) and olivetol dimethyl ether (52):

As per the procedure described in method-2, acetate(**102**, 1 mmol, 210 mg), and olivetol dimethyl ether (**52**, 1.25 mmol, 225 mg) in presence of BF_3•etherate on basic alumina gave two products which were isolated by column chromatography (1-1.5% EA/hex) and purified by ptlc.

7-Acetyloxycannabidiol dimethyl ether (46d):

R_f = 0.454 (5% EA/PE), 15% yield (50 mg); IR(film): cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$): δ 6.315 (br s, 2H , aromatic), 5.6 (br, 1H, =CH), 4.47 (br s, 2H, $=CH_2$), 3.79-3.6 (br s, overlapping resonance of OCH_3 and CH_2-0Ac, 8H), 2.537 (br t, 1H, benzylic CH), 2.2-1.0 (m, overlapping resonance of CH and CH2s', 13H), 2.05 (s, 3H, CH_3), 1.60 (br s, 3H, CH_3) 0.89 (br t, 3H, CH_3); ^{13}C NMR (90 MHz, $CDCl_3$): δ 171.083, 158.731, 148.763, 142.262, 131.752, 130.018, 117.883, 110.082, 104.773, 68.909,

55.799, 45.398, 36.513, 35.971, 31.746, 30.987, 29.145, 26.545, 22.536, 21.019, 18.961, 14.085; MS: m/e = 400.2 (M^+).

Demethylation of dimethyl ether (46d):

To a solution of 7-acetyloxycannabidiol dimethyl ether (**46d**, 0.25 mmol, 100 mg) in dry CHCl3 (25 ml), pyridine (1.25 mmol, 98 mg, 0.1 ml) followed by trimethylsilyliodide (2.5 mmol, 500 mg, 0.36 ml) were added under nitrogen. The resulting yellow solution was heated to reflux for 72 h. The tlc did not show a spot for the product even though there was no trace of the starting material left unreacted.

Olivetol dimethyl ether (52):

To a suspension of potassium carbonate (250 mmol, 34.55 g) in dry acetone (250 ml), olivetol (**51**, 50 mmol, 9 g) followed by dimethyl sulfate (200 mmol, 25.23 g, 18.9 ml) were added under nitrogen and with continuous stirring.The resulting dark reddish brown rxn. mixt. was heated to reflux for 24 h. The rxn. mixt. was cooled to RT, filtered to remove potassium carbonate and the filter cake was washed with ether (4x25 ml). The mother liquor combined with ether washings was evaporated to give a red viscous oil. It was diluted with ether (200 ml), washed with 2M NaOH (2x100 ml), water(2x100 ml), brine and dried ($MgSO_4$). Evaporation of ether gave a red oil which after column chromatography (1-2% EA/PE) afforded the product (**52**) in 80% yield (8.35 g). IR (film): 1596, 1462, 1205, 1060 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$): δ 6.31 (br s, 3H, aromatic), 3.71 (s, 6H, OCH3), 2.52 (t, J=2Hz, 2H, benzylic CH_2), 1.58-1.26 (m, overlapping resonance of CH_2s', 6H), 0.88 (t, J=6 Hz, 3H, CH_3).

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