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Part I. New synthetic approaches to cannabinoids and their analogs. Part II. Benzoannelation of ketones

Kannangara, Gallage Sriyant, Ph.D.

University of Hawai'i, 1994
To Mohan and my parents
ACKNOWLEDGEMENTS

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ABSTRACT

Part I: New Synthetic Approaches To Cannabinoids And Their Analogs

New synthetic approaches to several tetrahydrocannabinoids (THC) and their analogs are described. The synthesis of 11-hydroxy-Δ8-THC and (-)-11-nor-Δ8-THC-9-carboxylic acid methyl ester proceed through a common intermediate obtained from the addition of a mixed higher-order cuprate derived from bis-2-ethoxyethyl ether of olivetol to (+)-apoverbenone in the presence of BF3·Et2O. The cuprate addition is stereospecific and takes place trans to the geminal dimethyl bearing bridge of (+)-apoverbenone. Further, it provides an efficient solution to the regiochemistry problem encountered in some of the earlier cannabinoid syntheses. Another interesting reaction in the synthetic sequence for (-)-11-nor-Δ8-THC-carboxylic acid methyl ester is the cationic cyclization of the vinyl triflate derived from cuprate adduct with excess BF3·Et2O in CH2Cl2. The relief of ring strain attending the cleavage of four-membered ring of the pinane skeleton is assumed to be the driving force of the reaction. The palladium catalyzed carbonylation of the Δ8-THC-cyclohexenyl triflate thus obtained led to (-)-11-nor-Δ8-THC-9-carboxylic acid methyl ester.

The synthesis of 5′-(2H3)-(−)-11-nor-9-carboxy-Δ9-THC methyl ester methyl ether was accomplished from the α-bromoeneone derived from noppinone. The halogen substituent at Cl0 acts as a control element to generate the thermodynamically less stable unsaturation of the Δ9-series. It was necessary to use an oxygen protecting group on olivetol which would be robust enough to survive the acid-catalyzed conditions for the cleavage of
the cyclobutane ring. Hence, bismethoxy olivetol ether was used in the cuprate reaction. The key steps in the synthesis are the stereocontrolled ring opening of the cuprate adduct and formation of the benzopyran ring using iodo trimethylsilane in chloroform leading to the \( \Delta^9 \)-THC-cyclohexenyl triflate.

A convenient synthesis of several bicyclic and tricyclic fluoro- and iodo analogs of cannabinoids has also been reported. A new, mild synthetic methodology for the synthesis of vinyl fluorides from vinylstannanes has been demonstrated. These C9 halo-functionalized cannabinoid analogs, along with (−) and (+)-\( \Delta^9 \)-THC carboxylic acids, have been screened for anti-inflammatory activity in the mouse ear edema assay. It is interesting to find that both enantiomers of \( \Delta^9 \)-THC carboxylic acid were moderately active as anti-inflammatories. The bicyclic vinyl iodide also showed appreciable anti-inflammatory activity.

Part II: Benzoannelation of Ketones

Benzoannelation procedures, the elaboration of aromatic rings from non-aromatic precursors have offered several advantages such as synthesis of highly substituted aromatic rings and substitution patterns not easily accessible through conventional approaches. The synthetic methodology described herein provides a highly practical route for the benzoannelation of ketones. The efficacy of the method is demonstrated by its application to both cyclic and acyclic, \( \alpha \)-unsubstituted ketones. Both the methallylmagnesium chloride reaction and the cyclization take place cleanly. There is no need to purify the intermediate and the aromatic compounds are obtained in high overall yield.
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<td>Å</td>
<td>angstrom</td>
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<tr>
<td>Ac</td>
<td>acetyl</td>
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<td>DME</td>
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<td>HETCOR</td>
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<thead>
<tr>
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<td>J</td>
<td>coupling constant</td>
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<tr>
<td>KHMDS</td>
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<td>LDA</td>
<td>lithium diisopropylamide</td>
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<td>meta-chloroperoxybenzoic acid</td>
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<td>N-bromosuccinimide</td>
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<td>PDC</td>
<td>pyridinium dichromate</td>
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<td>PET</td>
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<td>Ph</td>
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<tr>
<td>PMA</td>
<td>phorbol-12-myristate-13-acetate</td>
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PPTS  pyridinium \textit{para}-toluene sulfonate
\textit{p-TSA}  \textit{para}-toluenesulfonic acid
\textit{pyr.}  pyridine
\textit{q}  quartet
\textit{Rf}  retention factor
\textit{s}  singlet
\textit{SAR}  structure activity relationship
\textit{sat'd}  saturated
\textit{t}  triplet
\textit{tert-Bu}  tertiary butyl
\textit{TBDMS}  tertiary-butyldimethylsilyl
\textit{TEA}  triethylamine
\textit{TFA}  trifluoroacetic acid
\textit{TFAA}  trifluoroacetic anhydride
\textit{THC}  tetrahydrocannabinol
\textit{THF}  tetrahydrofuran
\textit{TIPS}  triisopropylsilyl
\textit{tlc}  thin-layer chromatography
\textit{TMS}  trimethylsilyl
\textit{TMSOTf}  trimethylsilyl trifluoromethanesulfonate
\textit{Ts}  toluenesulfonyl
\textit{UV}  ultraviolet
\textit{U. S.}  United States

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INTRODUCTION

A. Pharmacohistory of Cannabis sativa

Cannabis sativa L. is one of the oldest and most extensively used plants by man for fiber, food, medicine and social and religious rituals. It is a fast-growing, herbaceous annual, propagated by seed. Cannabis sativa is normally a dioecious plant of which two varieties exist, namely indica and non indica or typica. The cannabis fiber, better known as "hemp" comes from the stem. The flowers are small and typically green, greenish yellow or white. The leaves are distinctive, commonly with five, seven, nine, or other odd numbers of saw-toothed leaflets arranged palmately. The flowering tops of the female plant are covered with glandular hairs which secrete a resin. The resin formation usually becomes abundant late in the plant's development and it is commonly believed that the function of the resin is to prevent desiccation of the seeds and to protect them during the ripening period. The choice of cannabis plant parts as drug products and the method of preparation vary from place to place. In the United States, the two main drug products from Cannabis sativa are known as marijuana and hashish. "Marijuana" consists of any part of the plant that has been crudely prepared for smoking, primarily by drying. "Hashish" essentially is resin from the plant.

Cannabis has been quite prominent as a folk medicine in different cultures since ancient times. The Greek historian Herodotus (ca. 300 B.C.) reported use of cannabis as an intoxicant by the Scythians which had also played a central role in their religious rites. A Chinese treatise, about 2000
years old, has recorded the use of cannabis mixed with wine as an anesthetic in surgery.\textsuperscript{4} Externally, cannabis was used as a poultice, or as a constituent of various ointments for swellings and bruises. Crushed seeds, either as a drink or in food, were prescribed for depression. Cannabis fumes were a medication to alleviate arthritis pain. The plant extracts were used in Europe for a long period of time for chronic headaches and certain psychosomatic disorders. It is still quite popular in indigenous medicine especially in India (referred to as bhang, ganja, Indian hemp etc.) and is used as a spasmolytic, hypnotic, analgesic and also to increase body resistance to severe physical stress.\textsuperscript{5} Further, cannabis derived drugs were used in various parts of India as appetite promoters and a general tonic to improve both the physical and mental state of the user. Cannabis was also used with considerable success in dysentery and cholera.

Although the folkloric use of cannabis as a medicine has been around for a long period of time, it was largely during the 19th century that the preparations of cannabis were assimilated into the standard medical practice. In the 1840s the British scientist and physician O'Shaugnessy meticulously carried out research on various cannabis preparations and observed that cannabis was a potent antivomiting agent.\textsuperscript{6} Encouraging results were also reported when ethanolic extracts (tincture) of cannabis resin were administered to patients with rheumatism, tetanus, rabies and infantile convulsions. For example, the painful, tonic muscular spasms of tetanus and rabies were attenuated.

Despite the widespread long pharmacohistory and the therapeutic potential of cannabis, its acceptance as a medicine declined in the early
decades of the 20th century. The main reason for this was the unavailability of the constituents of cannabis in pure form. Crude extracts or preparations of cannabis whose contents were known to vary widely were used instead, and this resulted in low reproducibility of the clinical results. Another factor was the unavailability of a reliable animal test which paralleled the activity in humans and the lack of controlled clinical experiments. The development of more conveniently administered and more uniform alternative drugs therefore hampered the biological work and medical use of cannabis.

Interest in cannabis was renewed in the early 1940s as a result of the identification of the basic structural features and synthesis of compounds with cannabimimetic activity by Adams and Todd. The most widely tested compound was synhexyl (1). Although initial trials with synhexyl reported efficacy as an antidepressant and as a treatment for alcohol or opiate withdrawal, subsequent evaluations proved negative.

In 1964, the modern era of cannabinoid research began with the isolation and structure elucidation of \((-\Delta^9\text{-THC})\), the primary psychoactive constituent of cannabis, by Mechoulam and Gaoni in Israel. This coincided with an explosion in
marijuana use as a drug of leisure by large numbers of young individuals and evidence of serious health hazards. In 1967, the U. S. Federal government, responding to the rising concern over the use of marijuana, launched its first intensive research program on cannabis through the National Institute of Mental Health. The cannabis preparations once accepted as therapeutically useful drugs were subjected to strict controls of the U. S. Drug Enforcement Administration under the Controlled Substances Act (1970). Today, hashish and marijuana, the best known cannabis preparations, have become the most widely used illicit drugs in the world. Ironically, the psychoactive effects that are responsible for its abuse are the same properties that limit its medical use. Since 1964 an enormous number of research publications on the chemistry, pharmacology and behavioral effects and metabolism of both natural and synthetic cannabinoids have appeared. Efforts have also been directed toward the design of analogs that may serve as probes for identifying the mechanisms responsible for the behavioral effects of the cannabinoids.

B. Nomenclature of the cannabinoids

Two different numbering systems for cannabinoids with a dibenzo­pyran ring appear in the literature (Figure 1). Most of the American publications use the dibenzopyran numbering system while most researchers in Europe use the monoterpenoid numbering system. In this dissertation, dibenzopyran ring nomenclature will be used for tricyclic cannabinoids.
In 1973, Mechoulam and Edery formulated tentative rules for cannabimimetic structure-activity relationships (SAR)\textsuperscript{11} based on the results of pharmacological studies carried out following the identification of the primary active constituent of cannabis in 1964. Most of these rules were consistent with the observed SARs for both natural and synthetic cannabinoids.\textsuperscript{12} The term "cannabimimetic" refers to cannabinoids that produce human subjective effects in common with (\textit{\textendash})\textsuperscript{\textgreek{Delta}}\textsuperscript{9}-\textit{THC}, or that produce (\textit{\textendash})\textsuperscript{\textgreek{Delta}}\textsuperscript{9}-\textit{THC}-like activity in laboratory animals that parallels the human activity.\textsuperscript{13} Some of the commonly used animal behavioral measures\textsuperscript{14} for assessing the psychoactive component of cannabinoids are dog ataxia, spontaneous activity and hypothermia in rats and mice, overt behavior in Rhesus monkeys and baboons, drug discrimination behavior in rodents, pigeons or in monkeys, and the mouse ring test. But on the basis of these tests, it is not possible to quantify the extent of separation of psycho-
active and other side effects from therapeutic effects. In more recent
years, synthetic compounds with structures apparently unrelated to
the classical cannabinoids, referred to as nonclassical cannabinoids, have
shown promise in SAR studies. Although the structural requirements
for cannabimimetic activity have been reasonably well established, the
stereochemical requirements need further investigation. The main
reason for the difficulties in establishing the stereochemical requirements
was that the cannabinoids are very often oily compounds which cannot be
recrystallized and obtained in absolute enantiomeric purity.

Considerable effort has been devoted to the SAR of the cannabinoids
in order to develop agents with a selective spectrum of pharmacological
effects. Depending on the specific structural modifications, potency
differences among compounds were substantial, i.e., ranging from hundreds
of times that of (−)-Δ⁹-THC to being completely devoid of cannabimimetic
activity. The dihydropyran-type structure, with a hydroxyl group at C1 and
an alkyl group at C3 appeared in most of the psychoactive cannabinoids.
When the dihydropyran ring of Δ⁹-THC was opened and the oxygen was
converted to a free hydroxyl group on the aromatic ring, the bicyclic structure
so obtained was the naturally occurring cannabidiol (CBD, 3a) and was
completely devoid of cannabimimetic activity and most other major activities
characteristic of Δ⁹-THC except anticonvulsant activity. However, several
major exceptions have been found. The studies of Wilson and May using the
9-nor-9β-hydroxyhexahydrocannabinol (HHC, 4) and the epimeric 9-nor-9α-
HHC (5) led to research in the nonclassical cannabinoid field. Their
findings demonstrated that both isomers of HHC produced cannabimimetic
activity but only the β-isomer exhibited enhanced analgesic activity in
rodents, with potency equal to morphine.\textsuperscript{18a,b} These results represented a significant step forward in the search for a nonnarcotic, potent analgesic structurally unrelated to morphine.

In an attempt to delineate the minimum structural requirements of HHC needed to produce analgesia, it was found that the dihydropyran ring of HHC was not necessary for activity.\textsuperscript{19} For example, the bicyclic analogs CP-47,497 (6)\textsuperscript{20} and CP-55,940 (7)\textsuperscript{21} exhibited potent analgesic activity. A wide variety of analogs were developed based on this simplified cannabinoid structure to define the pharmacophore of cannabinoid activity.\textsuperscript{22a,b} In fact, the tritium-labeled nonclassical cannabinoid CP-55,940 was used to identify a unique cannabinoid receptor in rat brain membranes.\textsuperscript{22c} Autoradiography of
tritiated CP-55,940 binding in brain sections from several mammalian species, including man, revealed a unique and conserved distribution of the presumptive cannabinoid receptor. Recently, Matsuda and co-workers have reported their results of cloning and expressing the gene which codes for the cannabinoid receptor.

Structure-activity relationship studies revealed that the phenolic hydroxyl group at Cl has to be free or esterified. Blocking of the hydroxyl group as an ether has led to either elimination or considerable reduction of activity. It is possible that the esters were actually inactive but undergo hydrolysis \textit{in vivo} to the free phenols. Further, it was shown that the orientation of the lone pairs of electrons on the oxygen plays an important role in the mediation of at least some of the behavioral effects of the cannabinoids. Adams and co-workers have reported that the replacement of the n-pentyl side chain of cannabinoids by higher and branched homologs significantly increases biological activity. The removal of the alkyl side chain at C3 eliminates pharmacological activity. The optimum pharmacological activity was achieved with 1,1-dimethylheptyl and 1,2-dimethylheptyl side chains. It has also been reported that the 9-methyl substituent of $\Delta^8$-THC might not be essential for activity. Accordingly, 9-nor-$\Delta^8$-THC was synthesized and its pharmacological activity was evaluated. It was found that the profile of biological activity of 9-nor-$\Delta^8$-THC is very similar to that of $\Delta^8$-THC and the two materials are of equal potency.

The synthesis of natural and synthetic cannabinoid enantiomeric pairs in high optical purity made possible the comparison of their biological and pharmacological activities. In most cases, the natural trans-(6aR,10aR)-(−)-cannabinoids showed significant cannabimimetic activity. In general, the (+)-
enantiomers exhibited either no activity or very little activity compared to the
(−)-compounds.28 The high enantioselectivity and the degree of potency
demonstrated for (−)-enantiomers were consistent with the existence of a
specific receptor for the cannabinoids. However, there is evidence to suggest
that some of the pharmacological properties, such as the anticonvulsant
activity of both enantiomers of CBD,29 are produced through nonspecific
membrane interactions.

The recent identification of a cannabinoid receptor in the rat brain22
was a major step forward in the understanding of cannabinoid mechanism(s).
This receptor was shown to be more responsive to the psychoactive
cannabinoids than the nonpsychoactive derivatives. The first successful
photoaffinity receptor probe, 5'-azido-Δ8-THC (8) was developed by
Makriyannis and co-workers30 and was used to covalently label the
cannabinoid receptor. The photoaffinity labeling of a receptor provides useful
information on receptor distribution and molecular weights of amino acid
residues at or near the active site. The discovery of the cannabinoid receptor
has also led to a search for its endogenous ligand(s). More recently,
arachidonylethanolamide (9), an arachidonic acid derivative in porcine brain,
has been identified as a natural ligand for the cannabinoid receptor.31 This
compound, whose structure is totally unrelated to both classical and

8 (−)-5'-N3-Δ8-THC

9 Arachidonylethanolamide (anandamide)
nonclassical cannabinoids, has been characterized by mass spectrometry and nuclear magnetic resonance spectroscopy and has been confirmed by synthesis.

D. Some common natural cannabinoids

Cannabis is a complex mixture of about 426 compounds, including at least 62 cannabinoids. The most important of these cannabinoids are shown in Figure 2. Among cannabinoids, (-)-Δ⁹-THC (2) is the major psychoactive component present in the plant with its content ranging from 2-14% among plant varieties. The cannabinoids were defined by Mechoulam and Gaoni "as the compounds unique to the cannabis plant with 21 carbon atoms, their carboxylic acids, analogs and transformation products." These exist in several homologous series characterized by side chains containing 1, 2, 3, 4, or 5 carbon atoms. The n-pentyl side chain is by far the most important followed by the n-propyl sidechain. Naturally occurring cannabinoids not only occur as neutral substances but also as carboxylic acid derivatives substituted at positions 2 or 4. However, these acidic cannabinoids are unstable and undergo slow spontaneous decarboxylation to the neutral form. This process is rapid and complete when the material is smoked. The concentration of cannabinoids in the plant seems to depend both on climatic factors and on the botanical variety. It is generally accepted that the resin of Cannabis sativa grown in temperate climates contains more cannabidiol (3a) and also probably cannabidiolic acid (3b) and less THC and cannabinol (13) than the resin formed in subtropical and tropical regions.
Figure 2: Some of the Representative Natural Cannabinoids
E. Metabolism of cannabinoids

The metabolism of (-)-Δ⁹-THC (2), (-)-Δ⁸-THC (12) and the non-psychoactive cannabinoid, (-)-CBD (3a) and several other major natural cannabinoids has been investigated in detail, and numerous reviews are available.³⁴ The major metabolic pathway for Δ⁹-THC when marijuana is smoked involves cytochrome P-450 catalyzed oxidation at the C-11 position giving rise to the 11-hydroxy-Δ⁹-THC (18).³⁵ This metabolite was first characterized in 1970 and was shown to have a pharmacological profile very similar to that of Δ⁹-THC.³⁶ Allylic hydroxylation also occurs at C-8 (in Δ⁹-THC) to give both 8α- and 8β-hydroxy-Δ⁹-THC and at C-7 (in Δ⁸-THC) to give 7α- and 7β-hydroxy-Δ⁸-THC. The relative amounts of these stereoisomers showed marked species specificity. Comparable metabolic pathways are followed for CBD and other natural cannabinoids. Further oxidation of the monohydroxy metabolites gives rise either to the carbonyl compound or, in the case of primary alcohols, to the carboxylic acid. The secondary metabolism involves glucuronidation of the carboxylic acid to give 19.³⁷

![Chemical structures](image)

18 R = CH₂OH
20 R = COOH
19 Glucuronide of 11-nor-Δ⁹-THC-9-carboxylic acid
glucuronide has also been detected in human urine. The major urinary metabolite of \(\Delta^9\)-THC, 11-nor-\(\Delta^9\)-THC-9-carboxylic acid (20), has received much attention as an internal reference in a number of immunological screening tests\(^3^8\) which have been developed to ascertain whether an individual has used marijuana.

**F. Therapeutic potential of cannabinoids and synthetic analogs**

Although cannabis preparations have been known to produce beneficial effects in humans, clinical experiences in the early 1900s using crude extracts of the cannabis plant were not encouraging. This was mainly because of the complexity and variability of active constituents of the plant itself and the different methods of preparation of drug products. In the 1960s the identification of the active principal component of cannabis and the widespread usage of marijuana as a major recreational drug led to chance observations concerning some of the beneficial effects. These observations together with the historical accounts on the medicinal properties of cannabis therefore provided an impetus for modern investigations on the effects and potential therapeutic uses of natural cannabinoids and their analogs.

\((-\Delta^9\text{-THC})\) (2) has a broad pharmacological spectrum consisting of anticonvulsant, analgesic, ocular hypotensive, bronchodilator and antiemetic effects in animals and humans\(^3^9\). Both \((-\Delta^9\text{-THC})\) and the synthetic analog, nabilone (21),\(^4^0\) demonstrated efficacy and safety as oral antiemetics in cancer chemotherapy and are commercially available as Dronabinol (Unimed, Inc.) and Cesamet (Eli Lilly and Company) respectively.\(^4^1\) Very recently, it has
been clinically observed that considerably higher doses of Δ8-THC (12) can be given as an antiemetic to children undergoing cancer chemotherapy. The side effects observed in this case were negligible.

\[
\text{Nabilone}
\]

(−)-Δ9-THC was also evaluated for its antispasmodic and antitremor effects in patients with multiple sclerosis. Additionally, CBD (3a) was tried experimentally for epilepsy and, more recently, on patients with other neurological conditions such as Huntington’s chorea and dystonia. The fact that CBD lacks cannabimimetic activity and possesses only antiepileptic effects has made it a very attractive candidate for a potential drug. There are several other nonclassical cannabinoids, Levonantradol (22), (−)-CP 55,940 (7) and (−)-HU-210 (23) for example, that are being evaluated for their anticonvulsant, analgesic and cannabinoid receptor binding activities.

Another promising therapeutic area for (−)-Δ9-THC and possibly some other analogs, is in the treatment of glaucoma, which is one of the leading causes of blindness in the United States. It is a condition characterized by an increase in intraocular pressure that progressively impairs vision and may lead to absolute blindness. The psychoactive properties of (−)-Δ9-THC and its
inability to penetrate the human eye when administered topically have been listed as principal deficiencies associated with the drug. The latter property is related to the fact that THCs are extremely hydrophobic, thus presenting problems with proper formulation.

It is obvious that the realization of the pharmacological potential of cannabinoids and their analogs will depend on the ability to eliminate undesirable psychotropic side effects. There are several recent reports on the separation of cannabimimetic from therapeutic activity in synthetic molecules, in particular enantiomers, and this discovery may revitalize the development of cannabinoid related drugs.

G. Previous synthetic approaches to cannabinoids and analogs

There is a huge body of published research on synthetic efforts directed toward cannabinoids and their analogs. In reviewing some of the past synthetic research on these compounds, it will, of course be worthwhile to emphasize some of the important contributions to this field. The synthetic
schemes will be discussed briefly, showing only the key reactions and the intermediates.

Since the identification of the structure of Δ⁹-THC, many hundreds of analogs of Δ⁹-THC and of other natural and unnatural cannabinoids have been synthesized. The motivation for the early synthetic work in this area was to confirm the structures of metabolites and to provide materials for the evaluation of biological activity. More recently, the interest in these compounds was driven by the commercial need for metabolites of Δ⁹-THC as analytical standards in the calibration of assays for the accurate detection of cannabinoids in urine. Further, much emphasis has also been placed on designing analogs that may serve as probes for understanding the mechanisms responsible for cannabinoid drug action in man. In this regard, a large number of cannabinoid agonists, active and inactive metabolites, and related structures have been used to characterize the pharmacology of the receptor. The development of a novel, easily available radiolabeled cannabinoid type ligand with very high binding affinity to the receptor is necessary for further work in this field.

A large number of synthetic procedures for cannabinoids show that most efforts have been focused on reactions of olivetol (24) with an appropriately functionalized monoterpene derivative. Some of the drawbacks encountered in previous syntheses of THCs will be discussed. Firstly, the conjunction of olivetol with an appropriate monoterpene under cationic cyclization conditions led to a ca. 1/1 mixture of regioisomers derived from substitution at both C2 and C4 of olivetol (eq. 1). The byproduct, in which hydroxyl and n-pentyl groups are formally transposed, is often referred to as the "abnormal" cannabinoid. This lack of regiospecificity compromises
the efficacy of the synthesis and would lead to unacceptable loss of material if expensive labeled olivetol derivatives were utilized.

\[
\begin{align*}
&\text{HO}_2 \text{R} + \text{OH} \text{C}_3\text{H}_{11} \quad \rightarrow \quad \text{OH} \text{C}_3\text{H}_{11} + \quad \text{"abnormal"} \\
&\text{R} = \text{CH}_3, \text{CH}_2\text{OCOCH}_3, \quad \text{(eq. 1)}
\end{align*}
\]

When the 1',1'-dimethylheptyl analog of olivetol (25) was condensed with monoterpane derivative 26 using \(p\)-TSA in benzene at 45 °C, the reaction proceeded smoothly to give the cyclized cannabinoid 27 in 43% yield (eq. 2).49 There was no appreciable formation of the other regioisomer. This is presumably due to the steric effect provided by the 1',1'-dimethyl group, which suppresses the attack of the resorcinol at C4.
The chiral cyclic monoterpenoids which have been used to synthesize Δ⁹-THC include cis and trans-\(p\)-mentha-2,8-dien-1-ol,\(^{50}\) (+)-trans-2,3-epoxy-carane,\(^{51}\) (−)-cis- or (−)-trans-verbenol,\(^{52}\) and (−)-(1R,4R)-\(p\)-menth-2-ene-1,8-diol.\(^{53}\) Of these, cis and trans-\(p\)-mentha-2,8-dien-1-ol and (+)-(1R,4R)-\(p\)-menth-2-ene-1,8-diol appear to offer advantages in terms of fewer byproducts in the preparation of Δ⁹-THC. It should also be emphasized that these cationic condensations are promoted by Lewis acids, and their regiochemical course is critically sensitive to reaction conditions. The cyclization often results in a mixture of trans- and cis-THCs which are quite difficult to separate. When the reaction was carried out with cis/trans-\(p\)-mentha-2,8-dien-1-ol and olivetol in strong acids (\(p\)-TSA, CF₃COOH), the thermodynamically more stable Δ⁸-THC (12) was formed which requires isomerization\(^{54}\) to Δ⁹-THC by the addition and elimination of hydrogen chloride. These processes thus require three steps and involve at least two very tedious and careful chromatographic separations. Treatment of equimolar quantities of cis/trans-\(p\)-mentha-2,8-dien-1-ol and olivetol with 1% BF₃·Et₂O and MgSO₄ in CH₂Cl₂ at 0 °C produced Δ⁹-THC as the major product and practically no Δ⁸-THC was formed.\(^{49}\) Another interesting synthesis of (−)-Δ⁹-THC was reported by Rickards and Ronneberg,\(^{55}\) wherein a BF₃·Et₂O catalyzed arylation of (1S,4R)-\(p\)-mentha-2,8-dien-1-yl acetate (28) with the homocuprate derived from lithiated olivetol dimethyl ether proceeded efficiently with high regio- and stereospecificity (Scheme 1). Attempts to effect concomitant demethylation and dihydropyran ring formation by treatment of 29 with boron tribromide gave a complex mixture containing Δ⁹-THC only in low yield. It was necessary to protect the terpenoid double bonds from the Lewis acid to obtain Δ⁹-THC in good yield.
The dihydrobromide 30 was prepared through treatment with a saturated solution of hydrogen bromide in CH₂Cl₂ at -20 °C. Surprisingly, when the reaction was left at room temperature for ca. 5 h, the extremely unstable bis-bromo adduct 30 underwent monodemethylation and dihydropyran ring

**SCHEME 1**

Reagents: (a) homocuprate (2 equiv.) of dimethyl ether of olivetol, BF₃·Et₂O (3.5 equiv.), ether, -76 °C; (b) HBr-saturated CH₂Cl₂, -20 °C; (c) warm up to room temperature; (d) BBr₃, CH₂Cl₂; (e) potassium tert-butoxide
formation to yield 31 in quantitative yield. It is worthy of note that olivetol dimethyl ether itself was unaffected by HBr under above conditions, therefore the formation of 31 was attributed to the crowding of the vicinal substituents in the dihydrobromide 30. Demethylation was completed by reaction of 31 with boron tribromide to afford 32. The bromide 32 was subjected to regiospecific dehydrobromination with potassium tert-butoxide to give (-)-Δ⁹-THC in 59% overall yield from the acetate 28.

Another, very ingenious method for overcoming the problem of non-specific condensation at C2 and C4 of resorcinol has been described by Chan, wherein 4-carbomethoxyolivetol (33) was used in place of olivetol (eq. 3). The aromatic carbomethoxy group blocked the undesired cyclization. However, the introduction of carbomethoxy group and its subsequent removal from the product detracts somewhat from the overall efficiency.

![Chemical diagram](image)

Reagents: (a) Anhydrous MgSO₄, CH₂Cl₂, BF₃·Et₂O, 0 °C, 1.5 h.

A problem often encountered with the purification of cannabinoids is that these compounds are more often than not difficult to crystallize and are sensitive to oxidation, particularly in basic media. In recent years, several additional synthetic strategies for Δ⁹- and Δ⁸-THC have been reported. These
address most of the problems encountered in earlier work. A very elegant synthesis of Δ⁸-THC was reported by Kowalski and Sankar Lal (Scheme 2), wherein a Diels-Alder reaction between isoprene and ketoester 34 in the presence of catalytic Lewis acid (TiCl₄) afforded the adduct 35, which was converted to the silyloxyacetylene 36. The homologation and rearrangement reaction central to this step proceeded with retention of stereochemistry to afford the trans-substituted product. Heating a mixture of silyloxyacetylene and 3-pentyl-cyclobutenone in toluene at 80 °C smoothly gave rise to the desired resorcinol product 37, which was conveniently cyclized to Δ⁸-THC.

Scheme 2

Reagents: (a) TiCl₄, CH₂Cl₂; (b) MeLi, -98 °C, THF; LiCHBr₂; BuLi, RT; TIPSCI; TMSCI; (c) 3-pentyl-cyclobutenone, toluene, 80 °C; (d) HCl, EtOH.
This novel four-step synthesis, proceeding in 29% overall yield from the ester 34 provides an easy access to $\Delta^8$-THC.

A recent synthetic approach to $\Delta^9$-THC involves the condensation of olivetol with cis-p-menth-2-ene-1,8-diol using p-TSA in CH$_2$Cl$_2$ to give ring opened intermediate 38 in 68% yield (Scheme 3). The purification of 38 was achieved through crystallization. It is of interest to note that purification of this intermediate eliminated most of the byproducts which otherwise contaminate the target molecule and create separation problems. Subsequent ring closure of 38 with ZnBr$_2$ in CH$_2$Cl$_2$ in the presence of 3Å molecular sieves afforded $\Delta^9$-THC (2) in 72% yield.

SCHEME 3

cis-p-menth-2-ene-1,8-diol

Reagents: (a) p-TSA, CH$_2$Cl$_2$; (b) ZnBr$_2$, CH$_2$Cl$_2$, 3Å molecular sieves.
In the synthesis of Δ⁹-THC metabolites, it was necessary to identify an available terpene that would provide the carbon atoms for the C-ring and would establish the absolute sense of asymmetry in the final product. A convenient synthesis of (-)-11-nor-Δ⁹-THC-9-carboxylic acid (20) was reported in our laboratory by Tius, Gu and Kerr in 1989.59 The conversion of (+)-limonene oxide (39) to (R)-(+)−perillaldehyde (40) was accomplished in 4 steps (overall yield 34%) by Tius and Kerr.60 The diol 41 was prepared in 3 steps from 40 as follows: treatment of 40 with a small excess of TBDMSOTf and triethylamine in CH₂Cl₂ at 0 °C provided the silyl enol ether. The crude silyl enol ether was treated with m-CPBA in a two-phase mixture of ether and saturated sodium bicarbonate resulting in the consumption of the starting material. The unpurified reaction mixture was dissolved in THF, and was treated with a THF solution of lithium aluminum hydride (LAH) to produce diol 41 as a mixture of diastereomers which was purified (but not separated) by silica gel column chromatography. The overall yield of diol 41 from 40 was 66%. It was thought that the condensation of olivetol with 41 would proceed in a manner similar to the reported reaction with p-mentha-2,8-dien-1-ol. In the event, the acid catalyzed condensation of 41 with olivetol under a
variety of conditions led to a very low yield of 11-hydroxy-Δ⁹-THC (18). The difference in reactivity between 41 and p-menth-2,8-dien-1-ol was attributed to the destabilizing inductive effect of the primary hydroxy group upon the putative cationic intermediate. The acetate 42 obtained from the monoacetylation of the primary hydroxyl group proved to be a suitable substrate for the condensation with olivetol (Scheme 4). The conversion of 42 to 43 was accomplished by exposure of CH₂Cl₂ solution of 42 and olivetol (24) to freshly distilled BF₃·Et₂O at 0 °C. The yield of the reaction was ca. 30%. This material was converted to (−)-11-hydroxy-Δ⁹-THC (18) and to the

![Scheme 4](image)

Reagents: (a) BF₃·Et₂O, CH₂Cl₂; (b) LAH, THF
corresponding carboxylic acid 20 in good yield. The shortcomings of this synthetic route were the lack of regiocontrol during the cyclization step and the difficulty in obtaining the optically active starting material, (R)-(+) perillaldehyde (40), from a commercial source.

A convenient synthesis of racemic Δ⁹-cis-(6a,10a)-THC-9-carboxylic acid has also been accomplished in our laboratory by Tius and Gu in 1989 (eq. 4). The key intermediate 44 of the synthetic sequence was treated with TFA in CHCl₃ at 0 °C to produce 45 in 69% yield as a mixture of ring junction isomers (cis/trans: 6/1). The preferred formation of the cis ring fusion isomer was attributed to a kinetically controlled intramolecular cycloaddition of an o-quinone methide. Under the mild conditions for this reaction, acid-catalyzed opening of the dihydropyran ring, followed by reclosing to the thermodynamically favored trans ring fusion, did not take place. It is of interest to note that the kinetically controlled cyclizations of saturated cannabinoids, under conditions which preclude ring junction isomerization through reversible opening of the pyranoid ring, gave rise to trans ring fused products. With C8-C9 unsaturated cannabinoids, the same reaction conditions produced cis ring fused products.
Continued interest in the synthesis of C9 functionalized cannabinoids has resulted in several efficient procedures. The problem of regiospecificity has been addressed elegantly by Huffman and co-workers (Scheme 5)\textsuperscript{64} wherein the bis-MOM ether of olivetol was lithiated with n-butyllithium and subsequently was reacted with (+)-apoverbenone (46) to give 47. Allylic oxidation and rearrangement of 47 gave 48 in excellent overall yield. The cyclization of 48 was carried out by refluxing in \(p\)-TSA in CHCl\(_3\) or CHCl\(_3\) to which small amount of ethanol had been added. The yield of 49 was 86\%. When dried CHCl\(_3\) (4Å molecular sieves followed by distillation) was

\begin{equation}
\text{trans/cis} = 3/1
\end{equation}
used, the cation obtained by opening of the cyclobutane ring underwent deprotonation rather than reaction with the phenolic hydroxyl. Therefore, it is probable that the cation formed during the ring opening is trapped by an external nucleophile such as ethanol and then undergoes cyclization via an intramolecular S_N1 reaction to yield 49. Racemization probably would have occurred through the formation of an achiral enol during the prolonged heating (ca. 26 h) with acid which was needed to effect rearrangement. The major disadvantage in this scheme was the non-stereospecific nature of the reduction of cyclized enone 49 which produced a 3/1 ratio of trans/cis ring junction isomers. Furthermore, this isomeric mixture was inseparable by chromatography. The mixture of cyclohexenyl triflate isomers was subjected to palladium catalyzed carbonylation to yield a mixture of diastereomeric acids. A pure sample of acid 20 was obtained in modest yield through recrystallization. The problem of racemization in scheme 5 was subsequently solved by using less stringent conditions (3 equiv. of AlCl3 in CH2Cl2 at 22°C) to afford optically active 53 in 68% yield (Scheme 6). However, the formation of the ring junction isomers during the reduction of double bond could not be avoided. It is worthy of note that the phenol 52 was obtained through a nucleophilic ether cleavage of 51 using sodium thiopropoxide. The carbon atom at the C11 position was introduced via a one-carbon homologation reaction on the cyclohexenyl triflate 50. Although cyclohexenyl triflates are promising intermediates for the labeled cannabinoids, the lack of stereospecificity and the resulting diminution of the chemical yield does not appeal for such syntheses.
Lately, attention has been focused on development of improved synthetic methods for the chiral monoterpenoids which could be used in the condensation reaction with olivetol to afford Δ⁹-THC metabolites. For example, Razdan and co-workers have reported an improved and updated version of work done in 1978. However, it is disappointing to note that these synthetic schemes still use the conventional acid-catalyzed condensation reaction which gave rise to a substantial amount of the "abnormal" cannabinoid product.
RESULTS AND DISCUSSION

Our synthetic strategy was aimed at a methodology for the Δ^8-THC and Δ^9-THC metabolites that would be short, efficient and general enough to be applied to cannabinoid analogs as well. The cyclohexenyl triflates corresponding to Δ^8- and Δ^9-THC were envisioned as potential precursors to C11 oxidized metabolites because these not only avoid the difficult oxidation step for the conversion of the corresponding C11 alcohol and/or aldehyde to acid, but also might provide access to cannabinoids labeled at C11. It is of considerable interest to develop a synthetic method that would utilize easily accessible optically active starting materials and would also eliminate the formation of regioisomers during the cyclization reaction.

A. Stereo- and regiospecific condensation of olivetol diether with (+)-apoeverbenone

The starting material for the synthesis, (+)-apoeverbenone (46), was prepared from cheap and readily available (-)-β-pinene (54) according to Grimshaw's method via ozonolysis of (-)-β-pinene to nopinone (55), followed by bromination and dehydrobromination. Recently, a more reliable method for the synthesis of (+)-apoeverbenone from (-)-β-pinene has been reported by Huffman and co-workers.

\[ \text{54 (-)-β-pinene} \rightarrow \text{55 nopinone} \rightarrow \text{46 (+)-apoeverbenone} \]
Olivetol (24) was converted to its bis-2-ethoxyethyl ether (56) in 77-80% yield by treatment with a small excess of ethyl vinyl ether in the presence of catalytic p-TSA in diethyl ether (eq. 5). The bis-2-ethoxyethyl ether of olivetol (56) can be deprotonated selectively using n-butyllithium in THF at 25 °C.

\[
\text{Olivetol (24)} \xrightarrow{p\text{-TSA, EVE}} \text{bis-2-ethoxyethyl ether (56)} \quad (\text{eq. 5})
\]

The lithiated bis-2-ethoxyethyl ether of olivetol was converted to the mixed higher-order cuprate by transferring to a solution of lithium-2-thienylcyanocuprate\textsuperscript{70} in THF at -78 °C. The lithium-2-thienylcyanocuprate solution was initially purchased from Aldrich Chemical Company and later was prepared according to the published procedure\textsuperscript{71} by Lipshutz and co-workers (Scheme 7). The mixed higher-order cuprate solution was next treated with a

**SCHEME 7**

\[
\begin{align*}
\text{Thiophene} & \xrightarrow{n\text{-BuLi/THF, -78 °C, 30 min}} \text{thiophene-Li} \\
\text{thiophene-Li} & \xrightarrow{\text{CuCN/THF, -78 °C}} \text{thiophene-CuCNLi}
\end{align*}
\]

"Mixed higher-order cuprate"
THF solution of (+)-apoverbenone and BF3·Et2O (1/1) at -78 °C (eq. 6). The progress of the reaction can be monitored by tlc. After 2 h, the reaction was quenched with a solution of saturated NH4Cl/NH4OH (9/1) and the product was purified by silica gel column chromatography. The yield of the cuprate adduct 57 was 66%. Lately, this step has been scaled up in our group to afford 3 g of the cuprate adduct. It is of interest to note that in the absence of BF3·Et2O there was no appreciable formation of cuprate adduct.

Reagents: (a) Mixed higher-order cuprate (see text), BF3·Et2O, THF, -78 °C

The cuprate reaction takes advantage of the steric shielding that steers conjugate arylation of apoverbenone away from the territory dominated by the geminal dimethyl substituent. This in turn, determines the ring junction stereochemistry of the final product. Therefore, it not only provided an efficient solution to the stereochemical problem but also addressed the lack of regiochemistry discussed in section G. It should, of course, be emphasized that the conjugate addition strategy has been used very successfully by others in the past, for both the synthesis of natural,55 as well as nonclassical cannabinoids.72 The adduct 57 can be envisioned as a promising precursor to both Δ8- and Δ9-THC series.
B. Synthesis of 11-hydroxy-\(\Delta^8\)-tetrahydrocannabinol

a. Retrosynthesis of 11-hydroxy-\(\Delta^8\)-THC

An attractive method for the formation of allylic alcohol A in Figure 3, would be through the rearrangement of the cis- or trans-spiroepoxide. Cis-spiroepoxide B could be obtained from methylenation of the cuprate adduct C and trans-spiroepoxide could be obtained from a two-step procedure involving the epoxidation of the exo-methylene group derived from C.

![Chemical Structures](image)

Figure 3. Retrosynthesis of 11-hydroxy-\(\Delta^8\)-THC.
b. Formation of spiroepoxides

Cuprate adduct 57 was converted to cis-spiroepoxide 58 by treatment with dimethylsulfonium methylide\textsuperscript{73} in THF at 0 °C (eq. 7). Attempts to catalyze the rearrangement of 58 with BF\textsubscript{3}·Et\textsubscript{2}O in ether afforded a mixture of products. The \textsuperscript{1}H NMR spectrum of the product mixture indicated the presence of an aldehyde as the major product. Similar reactivity has been reported for the cis-spiroepoxide derived from (−)-β-pinene.\textsuperscript{74} The mechanism for the formation of aldehyde can be thought of as a concerted cleavage of the oxirane C-O bond with hydride migration.\textsuperscript{74}

\[
\begin{align*}
\text{Reagents: (a) Dimethylsulfonium methylide, THF, 0 °C}
\end{align*}
\]

Since the desired rearrangement to the allylic alcohol was postulated to be stereoelectronically favored for the trans-spiroepoxide,\textsuperscript{75} its synthesis was undertaken. The bridge bearing the geminal dimethyl group in 57 had directed the entry of the methylide leading to cis-spiroepoxide 58, so it seemed logical that epoxidation of an exo-methylene group would provide the trans-spiroepoxide. Cuprate adduct 57 was treated with triphenylmethylene phosphorane which was generated from freshly sublimed potassium-\textit{tert-}
butoxide and methyltriphenylphosphonium iodide in ether at ca. 45 °C to produce exo-methylene product 59 in 80% yield (Scheme 8). Since the epoxide rearrangement required acidic conditions, the acid labile ethoxyethyl protecting groups were first removed by treatment in methanol with PPTS to produce resorcinol 60 in 85% yield. Acetylation of the hydroxy groups in 60 was carried out in CH2Cl2 with acetic anhydride and pyridine in the presence of catalytic DMAP to afford 61 in 80% yield. Exposure of 61 to a two-phase reaction mixture of m-CPBA in CH2Cl2/ether (1/1) and aqueous saturated NaHCO3 resulted in 62 as a single diastereomer in 85% yield.

SCHEME 8

Reagents: (a) tert-BuO-K+, Ph3PCH3+I−, ether, 45 °C; (b) PPTS, methanol; (c) Ac2O, pyr., cat. DMAP, CH2Cl2; (d) m-CPBA, CH2Cl2/ether/sat’d. NaHCO3
c. Epoxide ring opening to form the allylic alcohol

The rearrangement of 62 was surprisingly challenging, and a number of reaction conditions which have been used for the epoxide ring opening of β-pinene oxide were examined. Treatment of 62 with HgCl₂ in aqueous acetone, or aqueous acetone which had been saturated with CO₂, led to no detectable reaction. The reaction with WCl₆ in THF at -78 °C or with trichloroacetic acid in 1,2-dichloroethane in the presence of Zeolite A-4 produced complicated mixtures of aldehydes along with modest quantities (15-35% yield) of the desired allylic alcohol 63. The best conditions for the rearrangement of 62 were those disclosed by Delay. Exposure of 62 to ammonium nitrate in nitromethane at 25 °C led to the allylic alcohol 63 (eq. 8). The rather low solubility of the ammonium salt in the reaction solvent was suspected to be responsible for the slow rate of conversion of 62 to 63, however sonication of the reaction mixture did not result in an appreciable rate acceleration. Examination of the crude reaction mixture by ¹H NMR spectroscopy after 3 days indicated the presence of 63 and unreacted starting material. The yield of 63 was 35-37% and 8-10% of recovered 62.

In an attempt to improve the yield for this reaction, 62 was converted to

![Reaction diagram]

Reagents: (a) ammonium nitrate, nitromethane, 25 °C
monoacetate 64 by exposure to solid powdered potassium carbonate in methanol at 25 °C in quantitative yield (eq. 9). Since the reactions of 64 were similar to those of 62, this avenue was not pursued.

\[ \text{62} \xrightarrow{\text{K}_2\text{CO}_3, \text{methanol}} \text{64} \] (eq. 9)

**d. Formation of the dihydropyran ring from triol**

Exposure of 63 to methanolic potassium carbonate for 3 h at 25 °C gave 65, which was cyclized conveniently with catalytic p-TSA in benzene at 25 °C.
to produce 11-hydroxy-Δ⁸-THC (66) in 65% overall yield from 63 (Scheme 9).
Comparison of the spectral data for 66 obtained from this sequence of
reactions with those obtained in an earlier synthesis⁷⁸ of 11-hydroxy-Δ⁸-THC
confirmed the structural assignment.

C. Synthesis of (-)-11-nor-Δ⁸-THC-9-carboxylic acid methyl ester⁷⁹

a. Formation of Δ⁸-cyclohexenyl triflate

The ketone 57 was converted to 67 by consecutive treatment in THF
with KHMDS or LDA followed by phenyl triflimide⁸⁰ (Scheme 10). The

Reagents; (a) KHMDS or LDA, THF, 0 °C then PhN(SO₂CF₃)₂; (b) PPTS,
methanol; (c) BF₃·Et₂O, CH₂Cl₂
ethoxyethyl groups in 67 were removed by treatment in methanol with PPTS at 25 °C to give diol 68 in 65% overall yield from 57. The cyclohexenyl triflate 68 was robust, as expected, and exposure to a solution of excess BF₃·Et₂O in CH₂Cl₂ produced 69 in 87% yield following flash column chromatography on silica gel. The reaction proceeded smoothly and progress was easily monitored by tlc. Transposition of the double bond during cyclization led specifically to the Δ⁸-series. This cyclization reaction is without precedent and is undoubtedly a stepwise process which is facilitated by the relief of ring strain attending the cleavage of the four-membered ring.

b. Palladium catalyzed carbonylation of Δ⁸-cyclohexenyl triflate

The one-carbon homologation of cyclohexenyl triflate was carried out with a solution of 69 in methanolic THF with 10 mol% of PdCl₂(PPh₃)₂, potassium carbonate and a static atmosphere of carbon monoxide at 25 °C to give methyl ester 70 in 72% yield as a crystalline solid (mp 142 °C) following flash column chromatography (eq. 10). In preliminary experiments to optimize the palladium-catalyzed carbonylation reaction, a strongly UV-absorbing byproduct was obtained when the ratio of THF-methanol was 6:1.

![Chemical structure](image)

Reagents: (a) PdCl₂(PPh₃)₂ 10 mol%, K₂CO₃, CO, methanol, THF, 25 °C
This byproduct was assigned oxalate structure 71 based on spectroscopic evidence. No attempt was made to optimize the formation of 71. When the proportion of methanol in the solvent mixture was reduced, 70 was the only product observed. The ester 70 has been conveniently hydrolyzed by Schwartz and Madan\textsuperscript{82} using methanolic aqueous NaOH to afford 11-nor-Δ⁸-THC-9-carboxylic acid (72) in quantitative yield (eq. 11). The spectroscopic data reported therein for 11-nor-Δ⁸-THC-9-carboxylic methyl ester is consistent with that obtained for 70 through this synthetic scheme. Alternatively, through the use of ammonium formate in the palladium-catalyzed reaction, acid 72 can be prepared directly from 69.\textsuperscript{65}
D. Synthesis of (-)-11-nor-Δ⁹-THC acid methyl ester methyl ether

a. Retrosynthesis of 11-nor-Δ⁹-THC-9-carboxylic acid

Our synthetic strategy for the Δ⁹-THC metabolites involved the Δ⁹-cyclohexenyl triflate (A) as a potential precursor. There are two approaches to the formation of subunit A (Figure 4). The first was through the regiospecific enolization of cyclized ketone B (\(X = H\)) leading specifically to the Δ⁹-series. Cyclic ketone B can be envisioned to arise from the cationic cyclization of resorcinol C (\(X = H\)) which in turn can be prepared through the use of a mixed higher-order cuprate as described in Section I. Since the Δ⁸- cannabinoids represent the thermodynamically more stable isomer series, it was evident that the formation of the Δ⁹-enolate with specificity would be difficult.

Figure 4: Retrosynthesis of Δ⁹-cyclohexenyl triflate
However, the apparent simplicity and directness of the approach suggested that enolization of $B$ ($X = H$) was worth examining under both kinetic and thermodynamic enolization conditions. The second was to utilize a heteroatomic substituent ($X = \text{halogen, alkoxy}$) at C10 of ketone $B$ as a control element to generate the unsaturation leading to the $\Delta^9$-series. The substitution at C10 could be introduced either through the use of the substituted apoverbenone ($D; X = \text{halogen, alkoxy}$) in the cuprate reaction or by intercepting the enolate formed from the apoverbenone ($D; X = H$) with a heteroatomic electrophile.

b. Formation of $(-)$-11-nor-9-ketohexahydrocannabinol

Hydrolytic cleavage of the ethoxyethyl groups in the cuprate adduct $57$ was carried out with PPTS in methanol to afford $73$ as a single isomer in 78% yield. Treatment of $73$ with stannic chloride in anhydrous CHCl$_3$ at 25 °C produced optically active ketone $74$ in 72% yield (eq. 12). These conditions are analogous to those described by Archer and co-workers in the synthesis of nabilone (21).\textsuperscript{40a} In Archer's report, the conjunction of substituted resorcinols with $+\text{-}$apoverbenone was accomplished under acidic conditions. Phenol functionality in $74$ was protected either as the ethoxyethyl ether (EVE,}

\begin{center}
\begin{tikzpicture}
  \node[draw] (A) at (0,0) {73};
  \node[draw] (B) at (2,0) {74};
  \draw (A) -- (B);
  \node at (1,0.5) {SnCl$_4$, CHCl$_3$};
  \node at (1,-0.5) {25 °C};
\end{tikzpicture}
\end{center}
cat. p-TSA, ether) or as the tert-butyldimethylsilyl ether (Imidazole, DMF, TBDMSI). The enolization of these two protected ketones with variety of bases (LDA, KHMD, Et3N, diisopropylaminomagnesium bromide, 2,4,6-trimethyl pyridine) followed by trapping the enolate either as the silyl ether or as the triflate in all cases resulted in Δ⁸-enol ether with no detectable formation of the Δ⁹-isomer.

c. **Mixed higher-order cuprate reaction with α-bromoenone**

Attention was next focused on the alternative strategy for the Δ⁹-cyclohexenyl triflate. (+)-Nopinone (55), readily obtainable in large quantities by ozonolysis of (-)-β-pinene, was brominated with excess NBS in CCl₄ at 75 °C in the presence of catalytic benzoyl peroxide (Scheme 11). Bis-bromo-nopinone (75) was formed along with mono-bromonopinone as a 3:2 mixture and was separated by flash column chromatography on silica gel. The dehydrobromination was carried out in DMF with lithium carbonate and lithium bromide at 130 °C to afford the α-bromoenone 76 as pale yellow

**SCHEME 11**

![Scheme 11](image)

Reagents: (a) NBS, cat. (PhCO₂)₂, CCl₄, 75 °C; (b) Li₂CO₃, LiBr, DMF, 130 °C
crystals in 76% yield. Attempts to carry out the dehydrobromination reaction with DBU in CH₂Cl₂ and potassium tert-butoxide in THF at varying temperatures resulted in a mixture of products and a lower yield of 76.

The initial synthetic strategy envisioned that the ethoxyethyl ether would serve as a protecting group for olivetol during cuprate addition. Regio-specific lithiation of olivetol bis-2-ethoxyethyl ether with n-butyllithium in THF at 22 °C followed by transfer to lithium-2-thienylcyanocuprate in THF at -78 °C afforded the mixed higher-order cuprate solution. After 1.5 h at -78 °C, cuprate solution was treated with 76 and BF₃·Et₂O (1/1) in THF to furnish 77 in 55-60% yield (Scheme 12). The ¹H NMR spectrum of 77 indicated a mixture of diastereoisomers, due to the asymmetric center on each of the ethoxyethyl ether protecting groups. Hydrolytic removal of the ethoxyethyl ether with catalytic PPTS in methanol produced resorcinol 78.
as a single isomer in 90% yield. Attack of the cuprate took place trans to the geminal dimethyl bridge, which was confirmed by reduction of the bromine substituent in 78 with sodium dithionite (Na$_2$S$_2$O$_4$) in aqueous DMF$^{87}$ to yield 73, with known stereochemistry. The chemical shift assignments of the protonated carbons in compound 78 were made using 2D NMR (HMOC, HMBC) techniques. It was interesting to note that the proton on the carbon bearing the bromine substituent was highly deshielded (δ = 6.30 ppm), and was coupled to the benzylic proton at δ 4.28 ppm (d, J = 8.7 Hz). The magnitude of the vicinal coupling constant suggests a trans diaxial relationship between these protons.

d. Attempted cyclization of the bromo ketone

The next phase involved the cyclization of 78, the crucial step in the synthetic sequence. A number of methods were investigated to effect cyclization of 78 unsuccessfully, including treatment with stannic chloride in CHCl$_3$$^{40a}$ or aqueous CH$_2$Cl$_2$, BF$_3$-Et$_2$O in CH$_2$Cl$_2$, perchloric acid in aqueous trifluoroethanol, lithium perchlorate in ether$^{88}$ and zinc bromide in ether in the presence of lithium bromide. These conditions resulted in no detectable reaction at lower temperatures (-78 °C to 22 °C) and partial
decomposition of 78 at elevated temperatures (60 °C to 110 °C). When the reaction was carried out with excess TiCl4 in CHCl3 at 60 °C, 79 was isolated as the major product in 42% yield (unoptimized). The stereochemistry of the dihydrofuran derivative 79 was established through n.O.e experiments. Attempted cyclization of 78 with p-TSA in CHCl3 in either ethanol or methanol provided the corresponding ketal 80 and 81 in good yield. These ketal s could not be converted to the cyclized ketone with stannic chloride in CH2Cl2, although the conversion of the corresponding non-halogenated cannabinoid methyl ketal to the cyclized ketone with cis ring junction has been reported.40a Apparently the electronic effect of the bromine substituent adversely influences the cationic cyclization process.

The electrophile-initiated cyclobutane ring cleavage of 3-methyl nopenone has been carried out with iodotrimethylsilane.89 When 78 was treated in acetonitrile with iodotrimethylsilane in the hope of cleaving the cyclobutane ring, a facile reduction of the bromine substituent took place instead, giving rise to 73 (eq. 13). This type of reduction of a halogen

\[ \text{79} \]

\[ \text{80} \quad \text{R} = \text{Et} \]
\[ \text{81} \quad \text{R} = \text{Me} \]
substituent α to the keto group is well preceded.\textsuperscript{90} Cyclobutane ring opening of 3-methyl-nopinone has been achieved by Yoshikishi and co-workers\textsuperscript{91} using BF\textsubscript{3}·Et\textsubscript{2}O in the presence of zinc acetate in acetic anhydride. Treatment of 78 with similar reaction conditions led to acetylation of the hydroxyls on the aromatic ring.

\begin{equation}
\begin{array}{c}
\text{TMSI/CHCl}_3 \\
78 \xrightarrow{} \text{} \xrightarrow{} \text{73 (eq. 13)}
\end{array}
\end{equation}

\textbf{e. Formation of the α-alkoxyenones}

The difficulties encountered with 78 suggested that an α-alkoxy substituent be examined. The formation of 1,2-diketones via ozonolysis of α-hydroxymethylene ketones is preceded.\textsuperscript{92} Treatment of (+)-nopinone with ethyl formate and sodium hydride in ether in the presence of catalytic ethanol produced the salt of the α-hydroxymethylene ketone\textsuperscript{93} which was acidified carefully with 1N HCl and extracted with ether to afford 82 in 73\% yield (Scheme 13). Ozonolysis of 82 in CH\textsubscript{2}Cl\textsubscript{2}:pyridine (v/v 1:1) at -78 °C gave a bright yellow solution which was treated with methyl sulfide to afford 83 in 56\% yield. Enones 84 and 85 were prepared from 83 by trapping the enolate formed with potassium \textit{tert}-butoxide in THF at -50 °C with methyl iodide and acetic anhydride respectively. The cuprate addition to enone 84 was first studied using methyl homocuprate and mixed cyanocuprate in ether.
These studies revealed that prior activation of the enone 84 with TMSCl was necessary to effect complete addition of the cuprate. On the other hand, the enone 85, which would serve as a better Michael acceptor than 84, underwent reaction with the methyl cuprates in the absence of any Lewis acids. However, the mixed higher-order cuprate reaction of bis-2-ethoxyethyl ether of olivetol with either 84 or 85 was unsuccessful even in the presence of monodentate and bidentate Lewis acids such as boron trifluoride etherate or stannic chloride, respectively.

f. Reevaluation of the retrosynthesis

These failures prompted a rethinking of the chemistry outlined in Figure 4. Ketals 80 and 81 presumably arise from intramolecular attack of the phenolic oxygen on the carbonyl carbon. To avoid the ketal formation, it was therefore necessary to use an oxygen protecting group on olivetol which would be robust enough to survive the acid-catalyzed conditions for the cleavage of the cyclobutane ring of the cuprate adduct. 5′-[(2H3)-Olivetol
dimethyl ether (86)\textsuperscript{94} was metalated with n-butyllithium in THF at 25 °C and was converted to the mixed higher-order cuprate as before,\textsuperscript{79} by transferring to an equivalent of lithium-2-thienylcyanocuprate in THF -78 °C. The cuprate solution was next treated with a solution of α-bromoenone 76 in the presence of BF\textsubscript{3}·Et\textsubscript{2}O (1/1) in THF to produce 87 in 83% yield (eq. 14).

\[
\begin{align*}
\text{OCH}_3 & \quad \text{a} \quad \text{OCH}_3 \\
\text{CH}_3\text{O} & \quad \text{CD}_3
\end{align*}
\]

86 \quad 87 (eq. 14)

Reagents: (a) Mixed higher-order cuprate, BF\textsubscript{3}·Et\textsubscript{2}O, THF, -78 °C

g. Stereospecific ring opening of cuprate adduct

The stereospecific ring opening of 87 was carried out with excess 1,2-bis(trimethylsilyloxy)ethane in CH\textsubscript{2}Cl\textsubscript{2} at 22 °C using an equivalent of TMSOTf to give 88 in 65% yield (eq. 15). When the reaction was carried out with catalytic TMSOTf,\textsuperscript{95} initial ketalization took place, followed by

\[
\begin{align*}
\text{O} & \quad \text{a} \quad \text{O} \\
\text{Br} & \quad \text{OCH}_3 \\
\text{CH}_3\text{O} & \quad \text{CD}_3
\end{align*}
\]

87 \quad 88 (eq. 15)

Reagents: (a) 1,2-bis(trimethylsilyloxy)ethane, TMSOTf, CH\textsubscript{2}Cl\textsubscript{2}
cyclobutane ring opening to 88 upon addition of more TMSOTf. A related rearrangement of a pinane with ethylene glycol and p-TSA in benzene at 100 °C has also been reported. Exposure of 87 to these conditions produced traces of 88. It is worthy of note that ketalization and cyclobutane ring opening of α-bromonopinone (89) formed 2-bromo-4-isopropylidene cyclohexan-1-ethylene ketal (90) exclusively; none of the isopropenyl isomer could be detected. The formation of the isopropenyl substituent in the case of 88 is due to a stereoelectronic effect by the aryl substituent at C4: in the carbocationic intermediate 91, the steric bulk of the aryl group prevents the alignment of the 2p orbital on C6 with the C6a-H bonding orbital. Consequently, proton loss takes place from the methyl group in 92, leading to the isopropenyl group of the product.
h. Regiospecific formation of the cyclohexenyl triflate followed by Palladium-catalyzed carbonylation

Hydrolysis of ketal 88 with 50% aqueous perchloric acid in acetone\textsuperscript{97} at 40 °C gave ketone 93 in 66-71% yield (Scheme 14). Formation of the double bond corresponding to the Δ\textsuperscript{9}-THC series was achieved through the reductive debromination of 93 with lithium dimethylcuprate in ether\textsuperscript{98} at 0 °C followed by trapping of the enolate with N-phenyltriflimide in freshly distilled DME to produce 94 in 75-81% yield. Palladium-catalysed carbonylation of 94 gave the methyl ester 95 in 80% yield.\textsuperscript{65}

SCHEME 14

Reagents: (a) 50% aqueous HClO\textsubscript{4}, acetone; (b) lithium dimethylcuprate, ether, 0 °C, then N-phenyltriflimide, DME, 0 °C; (c) Et\textsubscript{3}N, Pd(OAc)\textsubscript{2}, triphenylphosphine, methanol, DMF, CO.
i. Attempted cleavage of methyl ether

The next task was to cleave the methyl ether groups in 95 and form the dihydrobenzopyran ring. As anticipated, cleavage of the methyl ester to the corresponding carboxylate took place rapidly. When 95 was fused with pyridine hydrochloride at 200 °C, a clean reaction took place leading to 96, the carboxy analog of cannabifuran. Other reaction conditions for the cleavage of the methyl ether groups, such as boron tribromide in CH₂Cl₂ at -78 °C followed by warming to 0 °C were accompanied by isomerization of isopropenyl to isopropylidene. Attempted cleavage of the methyl ether of 88 with sodium thioethoxide in DMF at 120 °C gave only the dihydrobenzofuran derivative 97 and 98. The stereochemistry of these dihydrobenzofuran derivatives was established by n.O.e experiments.

![Chemical Structures](image)

96

97 R = H

98 R = CH₃

j. Formation of benzopyran ring and carbonylation of cyclohexenyl triflate

Cyclohexenyl triflates are chemically robust, and it was gratifying to note that 94 was a suitable substrate for the demethylation and cyclization. Treatment of 94 with excess iodotrimethylsilane (purchased from Aldrich Chemical Co.) in anhydrous CHCl₃ at 22 °C, followed by purification by flash
column chromatography, gave a mixture of trans (99) and cis stereoisomers in the approximate ratio of 17:1 (by $^1$H NMR spectral integration of the proton at C10) in 47% yield (Scheme 15). The vinylic proton at C10 for the trans- stereoisomer appeared at $\delta$ 6.78 ppm, whereas in the cis-stereoisomer it is slightly shielded ($\delta = 6.65$ ppm). Attempts to improve the yield using various methods for in situ generation of iodotrimethysilane, such as sodium iodide or lithium iodide and trimethylchlorosilane in acetonitrile, allylsilane$^{100}$ or hexamethyldisilane$^{101}$ and iodine, gave either lower yields of 99 or a higher percentage of the cis stereoisomer. The cis isomer probably arises from acid-catalyzed isomerization of the isopropenyl to the isopropylidene followed by cyclization. The major reaction byproduct,

**SCHEME 15**

![Scheme 15](image)

Reagents: (a) iodotrimethylsilane, CHCl$_3$, 22 $^\circ$C; (b) Et$_3$N, Pd(OAc)$_2$, triphenylphosphine, methanol, DMF, CO
5'-(2H3)olivetol dimethyl ether (86), presumably arises from initial transfer of a proton to the electron-rich aromatic ring of 94, followed by carbon-carbon bond cleavage with generation of allylic carbocation 100. It is interesting that the presence of the electron-withdrawing triflate group on 94 is not sufficient to inhibit this cleavage reaction. Both the side reaction leading to 86 as well as the cyclization to 99 apparently require catalysis by HI because the conversion of 94 to 99 did not proceed when iodotrimethylsilane was used in the presence of an acid scavenger, such as pyridine or methylcyclohexene, or when excess allylsilane or hexamethyldisilane and iodine were used to form iodotrimethylsilane in situ. Cyclohexenyl triflate 99 and the cis isomer were treated with carbon monoxide and methanol under palladium catalysis to afford trans- (101) and cis- unsaturated methyl esters in 82% combined yield. The trans isomer was separated and purified by HPLC (Phenomenex Ultracarb 5 ODS 30 column, 250x10 mm, flow rate 2.5 ml/min, methanol). The specific rotation for 101 was \([\alpha]^{21}_D = -237^\circ\) (c = 0.005 g/ml, ethanol) and the \(^1\)H NMR spectral data closely paralleled those of the racemic, undeuterated 101 reported earlier. The benzylic proton at C10a in 101 appeared at \(\delta 3.31\) ppm as a doublet of doublets (J = 11.4, 1.5 Hz), as expected for a trans relationship of the C6a and C10a protons.
E. Synthesis of halogenated cannabinoids

The discovery of the non-classical cannabinoids and the early recognition of their activities have shed light on the structural requirements for activity. The essential features associated with pharmacological activity appear to be the aromatic ring, an unsubstituted phenolic hydroxyl group, the n-pentyl or 7 carbon aliphatic side chain with small alkyl groups at 1' and 2' positions and a B/C trans ring fusion. The substitution of the C ring with hydroxyl groups has also resulted in enhancement of activity. However, there is very little information on the synthesis of halogen substituted cannabinoids or the effect of halogen substitution on cannabinoid activity. Very recently, the pharmacological activities and relative cannabinoid receptor site(s) binding affinities of (-)-Δ⁸-THC analogs with a halogen substituent at C11 and C5' have been described. Another analog with a ¹⁸F substituent at the C5' has been used to study the biodistribution of cannabinoids in primate brain by positron emission tomography (PET). Because of the low binding affinity of (-)-5'-¹⁸F-Δ⁸-THC (102), the PET experiment was unable to distinguish between the specific and the non-specific binding sites for cannabinoids. Further, (-)-2-iodo-Δ⁸-THC (103)
was found to be an interesting probe which exhibited the greatest separation between antinociceptive and sedative cannabinoid properties.\textsuperscript{105c} The presence of a hydroxy group either at C9 or at C11 in the C ring is a significant feature in determining the activity.\textsuperscript{104} Therefore, it would be useful to prepare halogen substituted THC derivatives because unlike the oxygen substituted cannabinoids, in which the hydroxyl can act as a donor or an acceptor of a hydrogen bond, halogens act only as hydrogen bond acceptors. The steric and electronic effects of halogen substitution on cannabinoid SARs can be dissected by using fluoro- and iodo substituents.

It should be pointed out that some of the reactions in the synthesis of halogenated cannabinoids, namely the formation of 106 and 108 from 104, the reduction of ketones 104 and 116 to yield their respective alcohols 109 and 117 and fluorination reactions using methyl-DAST were carried out by Dr. Michael A. Kerr of this group.

a. Bis-fluorination of ketones using methyl-DAST

The fluorination of ketones and alcohols with dialkylaminosulfur trifluoride (DAST) and its analogs is well precedented.\textsuperscript{107} Therefore, (–)-11-nor-9-keto-hexahydrocannabinol (74) was an ideal starting material for 9-fluoro-hexahydrocannabinol analogs. The phenolic hydroxyl in 74 was protected as the acetate (pyr., cat. DMAP, acetic anhydride, CH\textsubscript{2}Cl\textsubscript{2}) to afford 104 in 83% yield (Scheme 16). Treatment of 104 with excess dimethylaminosulfur trifluoride (methyl-DAST) in CH\textsubscript{2}Cl\textsubscript{2} under nitrogen at ambient temperature for 2 days afforded bis-fluoride 105 in excellent yield along with a trace of vinyl fluoride. Acetate hydrolysis in 105 with potassium carbonate in methanol at 22 °C gave 106 in 80% yield. The \textsuperscript{13}C NMR spectrum of 106
Reagents: (a) pyr., cat. DMAP, Ac₂O; (b) methyl-DAST, CH₂Cl₂, 22 °C, 2 days; (c) K₂CO₃, methanol.

proved interesting. Fluorine-bearing carbon C9 at δ = 123.6 ppm, showed not only the expected coupling to the fluorine atoms (t, J = 240.7 Hz) but also two- and three-bond coupling to C8, C10 (t, J = 24.4 Hz) and C7, C10a (d, J = 10.4 Hz) respectively. Examination of Drieding models indicated that both C7 and C10a form dihedral angles of 180° and 90° with the equatorial and axial fluorine respectively. This observation proved to be useful for the assignment of stereochemistry at C9 for monofluoro hexahydrocannabinols.

b. Formation of vinyl-fluoride from bis-fluoride

The formation of trace amount of vinyl fluoride 107, during the bis-fluorination of ketones was presumed to occur through the loss of an α-hydrogen from the fluoro-carbocation. Therefore, the use of polar solvents was expected to stabilize the polar fluoro-carbocation intermediate which would eventually increase the yield of vinyl fluoride. However, all attempts
to increase the ratio of vinyl fluoride 107 to 105 during the fluorination of 104 by using a polar solvent, such as THF, DME or N-methylpyrrolidone were unsuccessful. Therefore, a two step procedure for the synthesis of 107 was envisioned. Elimination of hydrogen fluoride from 105 using neutral activated alumina at 120 °C in a sealed tube for two days afforded vinyl fluoride 108 in 37% yield (eq. 16). It should be noted that hydrolysis of the acetate also took place during the elimination reaction. The formation of the Δ8-isomer is not surprising as it is thermodynamically more stable than the Δ9-isomer.

**c. Formation of 9-nor-9α-fluoro-hexahydrocannabinol**

In order to prepare 9-nor-9α-fluoro-hexahydrocannabinol (112), ketone 104 was reduced with sodium borohydride in a 9:1 mixture of THF and
isopropanol at 22 °C to afford 9-nor-9β-hydroxy-hexahydrocannabinol (109) in 80% yield (eq. 17).27 Fluorination of the alcohol 109 with methyl-DAST in CH₂Cl₂ at -78 °C gave 42% yield of the desired axial monofluoride acetate 110 along with 21% of alkene 111 (Scheme 17).¹⁰⁹ The hydrolysis of 110 with potassium carbonate in methanol produced phenol 112 in 88% yield.

**SCHEME 17**

\[
\begin{align*}
\text{H₂O} & \quad \text{F₂H} \\
\text{OCOCH₃} & \quad \text{OR} \\
\text{109} & \quad \text{110} \quad \text{R=COCH₃} \\
\text{112} & \quad \text{R=H} \\
\end{align*}
\]

Reagents: (a) methyl-DAST, CH₂Cl₂, -78 °C; (b) K₂CO₃, methanol.

The stereochemistry at the fluorine-bearing carbon in 112 was determined by examination of the ¹⁹F spectrum which showed vicinal coupling to each of the trans diaxial hydrogens. Furthermore, the absence of 3-bond coupling of C7 and C10a to the fluorine atom in the ¹³C NMR spectrum is consistent with an axial fluorine substituent. Attempts to synthesize the other isomer, 9-nor-9β-fluoro-hexahydrocannabinol, from 9-nor-9α-OH-hexahydrocannabinol acetate using methyl-DAST under identical conditions resulted in a mixture of products. Studies have shown that cyclic alcohols which possess an axial hydroxyl group and a neighboring anti-periplanar hydrogen often undergo
facile elimination reactions and/or rearrangements to give rise to a mixture of products.\textsuperscript{110}

d. Formation of 3-[4-pentyl-2,6-bis(acetoxy)phenyl]-4-isopropenyl-cyclohexan-1-one and attempted fluorination with methyl-DAST

Bicyclic C9 halogen substituted cannabinoids were the next targets for synthesis. Ketone 114 was obtained from the reaction between racemic enone 113 and the mixed higher-order cuprate derived from the bis-2-ethoxyethyl ether of olivetol (56) and lithium-2-thienylcyanocuprate (Scheme 18).\textsuperscript{70}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{scheme18}
\caption{SCHEME 18}
\end{figure}

Reagents: (a) mixed higher-order cuprate, THF, - 78 °C; (b) \textit{p}-TSA, wet THF to form 115 (R = H); (c) pyr., cat. DMAP, Ac\textsubscript{2}O

59
Enone 113 was prepared from commercially available racemic perillaldehyde according to Razdan's procedure.\textsuperscript{68c} The fluorination of 114 with methyl-DAST was not successful, perhaps due to the acid-labile ethoxyethyl ether protecting groups. Hydrolysis of the ethoxyethyl ether groups with PPTS in methanol gave the methyl ketal (115; R = CH\textsubscript{3}) cleanly. The use of catalytic p-TSA in wet THF gave the hemiketal (115; R = H) which was subsequently rearranged and protected using pyridine and acetic anhydride in CH\textsubscript{2}Cl\textsubscript{2} in the presence of catalytic DMAP to afford bis acetate 116 in 80\% yield. The formation of the hemiketal, though unexpected, was not surprising as such acid catalyzed reactions are known.\textsuperscript{83} Fluorination of 116 with methyl-DAST failed to give the desired geminal difluoride. Instead, a complicated mixture was produced from which no identifiable products were isolated. Fluorination of the alcohol 117 which was obtained from the reduction of 116 with sodium borohydride afforded only 9\% of monofluoride 118 with an approximately equal amount of the elimination product 119 (eq. 18).

\begin{equation}
\begin{array}{c}
\text{H} \\
\text{a} \\
\text{CH}_3\text{COO} \text{CH}_3\text{COO} \\
\text{OCOCH}_3
\end{array}
\end{equation}

\begin{align*}
117 & \rightarrow \begin{array}{c}
\text{F} \\
\text{H} \\
\text{OCOCH}_3 \\
\text{CH}_3\text{COO} \\
\text{OCOCH}_3 \\
\text{C}_5\text{H}_{11}
\end{array} + \begin{array}{c}
\text{C}_5\text{H}_{11} \\
\text{OCOCH}_3 \\
\text{C}_5\text{H}_{11} \\
\text{CH}_3\text{COO}
\end{array}
\end{align*}

(eq. 18)

Reagents: (a) methyl-DAST, CH\textsubscript{2}Cl\textsubscript{2}, -78 \textdegree C.
e. Formation of vinyl stannanes

The difficulty which we encountered in our attempts to prepare these fluoro analogs in acceptable yield, and the limitations of methyl-DAST as a fluorination agent for these systems, provided the impetus for the development of a mild alternative method for the introduction of fluorine.

Exposure of vinyltrimethylstannanes to xenon difluoride in the presence of silver(I) salts leads to the rapid, stereospecific replacement of tin by fluorine. Recent work in our laboratory by Tius and Kawakami has led to significant improvement in the yield of this process. This methodology appeared to be ideal for the synthesis of fluorovinyl cannabinoids. Treatment of ketone 114 with LDA in THF at 0 °C followed by N-phenyltriflimide in freshly distilled DME gave cyclohexenyl triflate 120 (Scheme 19). The position of the double bond was determined by 2D-NMR (HMQC, HMBC) correlations. Hydrolytic cleavage of the ethoxyethyl protection groups with PPTS in methanol afforded 121 in 57% overall yield from 114. Palladium(0)

\[ \text{Reagents: (a) PPTS, methanol; (b) anhydrous Li}_2\text{CO}_3, \text{ LiCl, cat. (PPh}_3\text{)}_4\text{Pd, hexamethyldistannane, THF, 60 °C, 12 h; (c) pyr., cat. DMAP, Ac}_2\text{O, CH}_2\text{Cl}_2. \]
catalyzed stannylation of the cyclohexenyl triflate 121 with hexamethyl-
distannane in the presence of lithium carbonate and lithium chloride
produced 122 in 73% yield.\textsuperscript{112} The phenolic hydroxyls in 122 were protected
as the acetates to give 123 in 65% yield.

f. Fluorination of vinyl stannanes

The conversion of vinyl stannane 123 to vinyl fluoride 124\textsuperscript{113} was
carried out with silver triflate formed \textit{in situ} from silver carbonate and
trifluoromethanesulfonic acid (triflic acid),\textsuperscript{114} and xenon difluoride in
CH\textsubscript{2}Cl\textsubscript{2} at 22 °C (Scheme 20).\textsuperscript{115} Fluorination was fast (ca. 3 min) and gave
rise to a mixture of vinyl fluoride 124 and alkene (5:1 ratio) respectively. The
separation of 124 from alkene using flash column chromatography on
silica gel was difficult. Separation of the free resorcinols was much easier.
Hydrolysis of the acetates in the mixture followed by purification using flash
column chromatography produced 125 contaminated with traces of alkene in

\begin{center}
\textbf{SCHEME 20}
\end{center}

\begin{center}
\[ \text{Reagents: (a) XeF}_2, \text{Ag}_2\text{CO}_3, \text{triflic acid, CH}_2\text{Cl}_2, 22 ^\circ\text{C}; (b) K}_2\text{CO}_3, \text{methanol.} \]
\end{center}
57% overall yield. The fluorination of 122 took place in lower yield (ca. 30%), and the product mixture in this case contained a number of polar byproducts. Nonetheless, the remarkable fact that 125 could be isolated from the reaction demonstrates the utility of the method. The survival of the electron rich resorcinol in the presence of xenon difluoride is unusual and testifies to the mildness of the method.116

g. Formation of (−)-9-fluoro-Δ8-THC

This methodology was next applied to 69 (Scheme 21). Stannylation of 69 and protection of the phenolic hydroxyl as the acetate gave 127 in 60% overall yield from 69. The fluorination of 127 using xenon difluoride in the

SCHEME 21

Reagents: (a) Li2CO3, LiCl, hexamethyldistannane, cat. Pd(PPh3)4 THF, 60 °C, 12 h; (b) pyr., cat. DMAP, Ac2O; (c) XeF2, Ag2CO3, triflic acid, CH2Cl2.
presence of silver carbonate and trifluormethanesulfonic acid in CH2Cl2 followed by hydrolysis gave (−)-9-fluoro-Δ⁸-THC (128) and the corresponding alkene as a 5:1 mixture in 62% yield.

h. Formation of vinyl iodo cannabinoids

Vinyl stannanes 122 and 126 are excellent starting materials for the preparation of vinyl iodides via a metal halogen exchange. Treatment of vinyl stannanes 122 and 126 separately with a dilute solution of iodine in CH2Cl2 at 0 °C gave rise to 129 (78% yield) and 130 (83% yield) respectively.

F. Anti-inflammatory activity of several cannabinoids

Burstein has suggested that (−)-11-nor-Δ⁹-THC-9-carboxylic acid (20) may act as a non-steroidal anti-inflammatory agent. In order to learn whether other C9-functionalized cannabinoids share this activity, and in particular whether the halogenated analogs act as anti-inflammatory agents, several were evaluated in the mouse ear edema assay. The mouse ear edema assay was performed by Ms. Krista J. S. Grace in Prof. Jacob's research group, at University of California, Santa Barbara. The results are summarized in Table 1, and confirm that (−)-11-nor-Δ⁹-THC-9-carboxylic acid (20) is in fact
active. It is interesting that \textit{131,119} the enantiomer of \textit{20}, was active at approximately same level. This insensitivity to molecular chirality may suggest the cell membrane as the drug target, rather than the cannabinoid receptor which would presumably discriminate between the two enantiomers. Iodo cannabinoid \textit{129} also showed appreciable activity in this assay.

Table 1. Effect of Topical Application of Various Cannabinoid Analogs on Phorbol-12-myristate-13-acetate-induced Edema of the Mouse Ear\textsuperscript{a}

<table>
<thead>
<tr>
<th>Compound</th>
<th>Percent Inhibition of Inflammation</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>52%</td>
</tr>
<tr>
<td>131</td>
<td>69%</td>
</tr>
<tr>
<td>130</td>
<td>15%</td>
</tr>
<tr>
<td>112</td>
<td>17%</td>
</tr>
<tr>
<td>106</td>
<td>19%</td>
</tr>
<tr>
<td>129</td>
<td>45%</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Compounds were topically applied in acetone to the inside pinnae of the ears of mice in a solution containing phorbol-12-myristate-13-acetate (PMA). PMA alone (2 \(\mu\)g/ear) or in combination with 50 \(\mu\)g/ear of test compound was applied to the left ears and acetone was applied to all right ears. After 3 hours 20 minutes incubation, the mice were sacrificed, the ears removed, bores taken and the difference in weight between the two ears recorded. Per cent inhibition of inflammations relative to the PMA control were calculated and the mean values were based on 5 mice.
CONCLUSION

In conclusion, the design and execution of new synthetic approaches to several cannabinoids and analogs have been described. The key step in these synthetic schemes is the conjunction of olivetol ether with the appropriate monoterpenes using a mixed higher-order cuprate reaction. Some of the features of the cuprate reaction are noteworthy and are listed below:

(1) (+)-Apoverbenone (46), the starting material for the cuprate reaction, is derived in high yield from cheap and readily available, (−)-β-pinene (Aldrich Chemical Company, 92% optical purity) through ozonolysis to nopinone (55), followed by introduction of the double bond through oxidation. The optical purity of 46 can be enhanced by recrystallization of reduction product, followed by re-oxidation to 46. The optically active form of enone 113, on the other hand, can be prepared through the use of a commercially available, enantiomerically pure terpene, (+)-limonene oxide.

(2) The mixed higher-order cuprate utilizes one equivalent of the olivetol ether as the transfer ligand with thiophene acting as the "dummy" ligand. This is a significant improvement to the earlier homocuprates, and an important factor that has to be taken into consideration, especially when an expensive, alkylresorcinol is employed. Also, the fact that lithium-2-thienylcyanocuprate solution can be prepared conveniently in the laboratory adds to the utility of the reaction.

(3) Modification of the cannabidiol (CBD) structure has led to analogs with unique pharmacological profiles. The cuprate adduct 114 is an ideal precursor for the synthesis of CBD analogs with structural modifications in the isopropenyl substituent. If the conjunction of olivetol with a ring opened
monoterpene derivative were carried out under acid catalysis, it could have
resulted in products containing a dihydrobenzopyran ring.

(4) The regiospecificity problem encountered in most of the earlier
cannabinoid syntheses is completely avoided by using the cuprate reaction
to join the olivetol derivative to the monoterpene fragment. An alternative,
elegant approach to cannabinoids has been developed by Huffman and
co-workers which addresses the lack of regiospecificity. According to
their procedure, the synthesis of natural (−)-cannabinoids requires
(−)-apoverbenone, which is obtained from (−)-β-pinene. (−)-β-Pinene is
commercially unavailable and is prepared from the isomerization of
(−)-α-pinene. Further, Huffman's procedure cannot be applied to the ring
opened enone 113.

(5) The cuprate attack is stereospecific and took place trans to the geminal
dimethyl bridge of 46. This is an important factor because the stereochemistry
of the cuprate addition determines the ring junction stereochemistry of the
final product.

Apart from the mixed higher-order cuprate reaction, it is worthy of note
that some of the other reactions and products obtained through these
synthetic schemes can be employed towards the synthesis of cannabinoid
analogs.

A convenient synthesis of optically active, cyclized ketone 74 has been
accomplished in high yield. It should be emphasized that 74 is a very
versatile intermediate. Recently, analogs of 74 have been prepared in our
laboratory with either dimethyl heptyl or with an unsaturated sidechain.

The synthetic sequence for 11-nor-Δ8-THC-carboxylic acid methyl ester
constitutes one of the shortest enantioselective routes to Δ8-cannabinoids and
their analogs. An interesting reaction in scheme 10 is the opening of the cyclobutane ring in 68 followed by transposition of the double bond during cyclization leading specifically to the Δ8-series. The cyclohexenyl triflates 69 and 121 were key intermediates in the synthesis of vinyl fluoro- and vinyl iodo- cannabinoids and could also be envisioned as ideal precursors for the synthesis of radio-labeled cannabinoids.

The synthesis of a deuterium-labeled Δ9-THC derivative 101 that is of interest as a standard for GC-MS analysis of urine samples has also been accomplished. Of particular interest was the formation of the isopropenyl substituent during the ring opening reaction of 87 due to a stereoelectronic effect exerted by the aryl substituent at C4. In our group, this result has led to the synthesis of CBD structural variants from pinane-type intermediates. The good site selectivity observed in the formation of the thermodynamically less stable Δ9-unsaturation is also remarkable. Cleavage of methyl ether in both 95 and 101 without altering the rest of the THC skeleton was challenging. Attempted cleavage of the methyl ether groups of 88 with sodium thioethoxide in DMF at 120 °C resulted in dihydrobenzofuran derivative 97 which can be envisioned as an intermediate for the synthesis of Δ9-THC-carboxylic acid.
EXPERIMENTAL SECTION

General:

\(^1\text{H} \text{NMR and } ^{13}\text{C} \text{NMR spectra were recorded at } 300 \text{ MHz } ^1\text{H} (75.5 \text{ MHz } ^{13}\text{C}) \text{ or } 500 \text{ MHz } ^1\text{H} (125.8 \text{ MHz } ^{13}\text{C}) \text{ in either deuteriochloroform (CDCl}_3) \text{ with chloroform (7.26 ppm } ^1\text{H, 77.00 ppm } ^{13}\text{C}) \text{ or deuteriobenzene (C}_6\text{D}_6) \text{ with benzene (7.15 ppm } ^1\text{H, 128.00 ppm } ^{13}\text{C}) \text{ as an internal reference. } ^{19}\text{F NMR spectra were recorded on a Nicolet NT-300 instrument, and chemical shifts are reported upfield from fluorotrichloromethane (0.00 ppm) as an external standard. Chemical shifts are given in } \delta; \text{ multiplicities are indicated as br (broadened), s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet); coupling constants (J) are reported in hertz (Hz). Infrared spectra were recorded on a Perkin-Elmer IR 1430 spectrometer. Electron impact mass spectra were performed on a VG-70 SE mass spectrometer.}

Thin-layer chromatography (tlc) was performed on EM Reagents percoated silica gel 60 F-254 analytical plates (0.25 mm). Flash column chromatography was performed on Brinkmann silica gel (0.040-0.063 mm).

Tetrahydrofuran (THF), diethyl ether, 1,2-dimethoxyethane (DME) were distilled from sodium-benzophenone ketyl, N,N-dimethylformamide (DMF), triethylamine (Et\textsubscript{3}N) and boron trifluoride-etherate (BF\textsubscript{3}-Et\textsubscript{2}O) from calcium hydride, carbon tetrachloride (CCl\textsubscript{4}), dichloromethane (CH\textsubscript{2}Cl\textsubscript{2}) from phosphorus pentoxide. Other reagents were obtained commercially and used as received unless otherwise specified.

All moisture sensitive reactions were performed under a static nitrogen or argon atmosphere in flame-dried glassware. The purity and homogeneity of the products on which the high resolution mass spectral data are reported were determined on the basis of 300 MHz \(^1\text{H} \text{NMR and multiple elution tlc analysis, respectively.}

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Procedure:

To a solution of olivetol (1g, 5.55 mmol) in ether (20 mL) at 0 °C was added ethyl vinyl ether (1.35 mL, 13.88 mmol), followed by a catalytic amount (ca. 50 mg) of p-TSA in ether. The reaction mixture was stirred at 0 °C and the progress of the reaction was monitored by tlc. After 7 h, the reaction mixture was diluted with ether, washed with sat'd aqueous NaHCO₃, followed by brine, and was dried (Na₂SO₄). Solvent evaporation in vacuo gave the crude bis-2-ethoxyethyl olivetol which was purified by flash column chromatography on silica gel eluting with 5% ethyl acetate in hexanes. The yield of the reaction was 77-80%.
Bis-2-ethoxyethyl olivetol (56):

$^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 6.49-6.47 (br s, 2H), 5.35 (q, $J = 5.1$ Hz, 2H), 3.81-3.73 (m, 2H), 3.59-3.49 (m, 2H), 2.52 (t, $J = 7.5$ Hz, 2H), 1.61-1.56 (m, 2H), 1.49 (d, $J = 5.4$ Hz, 6H), 1.33-1.27 (m, 4H), 1.21 (t, $J = 6.9$ Hz, 6H), 0.89 (t, $J = 6.3$ Hz, 3H) ppm.

$^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 157.8, 145.3, 110.8, 103.8, 99.5, 61.5, 36.1, 31.4, 30.9, 22.5, 20.3, 15.2, 13.9 ppm.

IR (neat): 2990, 2920, 2850, 1590, 1450, 1380, 1150, 1110, 1080, 1050 cm$^{-1}$
Procedure:

To a solution of 311 mg (0.956 mmol) of bis-2-ethoxyethyl olivetol (56) in THF (15 mL) at 0 °C was added n-butyllithium solution in hexane (0.85 mL, 1.150 mmol) during 20 min. The mixture was stirred at 0 °C for 10 min and then at 25 °C for 2.5 h. In a separate flask 3.85 mL (0.956 mmol) of a solution of lithium 2-thienylcyanocuprate\textsuperscript{71} in THF was cooled to -78 °C. The lithiated olivetol ether was transferred by cannula to the cuprate solution over a 20-min period. Following addition, the reaction mixture was placed in an ice bath for 10 min, cooled to -78 °C, and stirred for 1.5 h. To the pale yellow cuprate solution was added a mixture of 100 mg (0.735 mmol) of (+)-apoverbenone (46) and 0.10 mL (0.735 mmol) of BF\textsubscript{3}·Et\textsubscript{2}O in 1.5 mL of THF at -78 °C. The mixture was stirred at -78 °C until tlc (10% ethyl acetate in hexane) showed the disappearance of the starting material (1-2 h). The reaction was diluted with ether (30 mL), washed with concentrated NH\textsubscript{4}OH/sat'd NH\textsubscript{4}Cl (1/9) solution, extracted with ether, and dried (MgSO\textsubscript{4}). Evaporation of the solvent in vacuo and purification of the crude product by flash column chromatography on silica gel eluting with 5% ethyl acetate in hexane produced 225 mg (66% yield) as a mixture of diastereomers due to the asymmetric center on each of the two ethoxyethyl protecting groups.
4-[4-n-Pentyl-2,6-bis(2-ethoxyethyl)phenyl]-6,6-dimethyl-2-nopinone (57):

$^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 6.59 (s, 1H), 6.55 (s, 1H), 5.46-5.39 (m, 2H), 4.16-4.09 (m, 1H), 3.74-3.64 (m, 2H), 3.57-3.46 (m, 2H), 3.38-3.29 (m, 1H), 2.56-2.45 (m, 6H), 2.22 (br s, 1H), 1.61-1.56 (m, 4H), 1.48 (d, $J = 5.1$ Hz, 6H), 1.35 (s, 3H), 1.33-1.31 (m, 2H), 1.22-1.16 (m, 6H), 0.98 (s, 3H), 0.89 (t, $J = 6.7$ Hz, 3H) ppm.

IR (neat): 2975, 2925, 2860, 1710, 1605, 1570, 1430, 1380, 1071, 1050 cm$^{-1}$.
Procedure:

To a suspension of freshly sublimed potassium tert-butoxide (275 mg, 2.46 mmol) in 20 mL of ether was added methyltriphenylphosphonium iodide (989 mg, 2.46 mmol) in a single portion. The reaction mixture immediately turned bright yellow and was heated to gentle reflux. After 15 min, ketone 57 (225 mg, 0.49 mmol) in 5 mL of ether was added and stirring was continued until tlc indicated the complete disappearance of starting material (ca. 6 h). The reaction was quenched with water, extracted with ether and was dried over MgSO₄. Solvent evaporation in vacuo and purification of the crude product by flash column chromatography on silica gel eluting with 5% ethyl acetate in hexanes produced 193 mg (80% yield) of 59 as a colorless oil.
Exo-methylene 59:

$^1$H NMR (CDCl$_3$, 300 MHz): δ 6.56 (s, 1H), 6.53 (s, 1H), 5.43-5.36 (m, 2H), 4.68 (s, 1H), 4.61 (s, 1H), 4.02-3.95 (m, 1H), 3.76-3.66 (m, 2H), 3.59-3.47 (m, 2H), 2.92-2.79 (m, 1H), 2.51 (dd, $J = 7.8, 7.5$ Hz, 2H), 2.46-2.25 (m, 4H), 1.99 (t, $J = 5.4$ Hz, 1H), 1.61-1.58 (m, 2H), 1.48 (dd, $J = 5.2, 2.7$ Hz, 6H), 1.34-1.30 (m, 4H), 1.28 (s, 3H), 1.20 (d, $J = 1.8$ Hz, 3H), 1.18 (d, $J = 1.8$ Hz, 3H), 0.89 (t, $J = 6.9$ Hz, 3H), 0.86 (s, 3H) ppm.

IR (CCl$_4$): 2960, 2920, 2840, 1600, 1570, 1430, 1375, 1070, 1040 cm$^{-1}$.
Procedure:

To a solution of 193 mg (0.42 mmol) of 59 in 30 mL of methanol was added ca. 15 mg of PPTS. The mixture was stirred at 25 °C until tlc indicated that both ethoxyethyl groups have been removed (ca. 5 h). The reaction mixture was diluted with ether, washed with brine and was dried over MgSO₄. Evaporation of the solvent in vacuo and purification of the crude product by flash chromatography eluting with 5% ethyl acetate in hexanes produced 110 mg (85% yield) of 60 as a white foam.
Resorcinol 60:

\(^{1}\text{H NMR (CDCl}_3, 300 \text{ MHz): } \delta \ 6.16 (s, 2H), 4.74 (s, 2H, exchangeable with D}_2\text{O), 4.71 (s, 1H), 4.63 (s, 1H), 3.78 (dd, } J = 9.3, 8.7 \text{ Hz, 1H), 2.81-2.71 (m, 1H), 2.61-2.44 (m, 3H), 2.41 (dd, } J = 7.8, 7.5 \text{ Hz, 2H), 2.19-2.12 (m, 2H), 1.58-1.48 (m, 2H), 1.30 (s, 3H), 1.28-1.22 (m, 4H), 0.87 (s, 3H), 0.86 (t, } J = 7.5 \text{ Hz, 3H) ppm.}

\(^{13}\text{C NMR (CDCl}_3, 75 \text{ MHz): } \delta \ 154.8, 150.9, 142.3, 115.5, 108.7, 106.7, 51.1, 45.3, 42.1, 35.2, 31.5, 30.9, 30.8, 30.7, 26.5, 26.2, 22.5, 21.7, 14.0 \text{ ppm.}

\text{IR (neat): 3410, 2900, 2830, 1620, 1580, 1430, 1020 cm}^{-1}.\)
Procedure:

To a solution of 150 mg (0.46 mmol) of resorcinol 60 in 20 mL of CH₂Cl₂ at 0 °C was added 0.20 mL (2.50 mmol) of pyridine and a catalytic amount of DMAP. After 15 min, 0.12 mL (1.30 mmol) of acetic anhydride was added. The reaction stirred at 0 °C for 1 h at which time tlc indicated the complete consumption of starting material. The reaction mixture was diluted with ether, washed with sat'd aqueous NaHCO₃, followed by brine. The organic phase was dried (MgSO₄) and evaporated. Purification of the residue by flash column chromatography eluting with 15% ethyl acetate in hexanes produced 153 mg (84%) of 61 as a colorless oil.
**Diacetate 61:**

\(^1\)H NMR (CDCl\(_3\), 300 MHz): \(\delta\) 6.71 (s, 2H), 4.72 (s, 1H), 4.64 (s, 1H), 3.46 (dd, \(J = 10.5, 7.5\) Hz, 1H), 2.65-2.58 (m, 1H), 2.54 (dd, \(J = 8.1, 7.5\) Hz, 2H), 2.49-2.36 (m, 3H), 2.29 (s, 6H), 2.05 (t, \(J = 5.7\) Hz, 1H), 1.99 (d, \(J = 9.6\) Hz, 1H), 1.61-1.54 (m, 2H), 1.33-1.30 (m, 4H), 1.28 (s, 3H), 0.88 (t, \(J = 6.9\) Hz, 3H), 0.81 (s, 3H) ppm.

\(^{13}\)C NMR (CDCl\(_3\), 75 MHz): \(\delta\) 169.4, 150.1, 149.6, 141.9, 126.9, 120.8, 107.3, 50.6, 44.9, 41.9, 34.9, 32.1, 31.4 (two coincident signals), 30.3, 26.4, 26.3, 22.4, 21.3, 21.2, 13.9 ppm.

IR (CCl\(_4\)): 2920, 2850, 1765, 1565, 1185, 1025 cm\(^{-1}\).

Mass spectrum (70 ev, m/e): 398 (M\(^+\)), 289, 247, 205, 139 (100%), 111, 75, 57.

HRMS: for C\(_{25}\)H\(_{34}\)O\(_4\) calculated 398.2457, found 398.2479.
Procedure:

To a solution of 200 mg (0.51 mmol) of 61 in 25 mL of CH$_2$Cl$_2$ at 0 °C was added a sat'd aqueous solution of NaHCO$_3$ (7 mL). A solution of 152 mg (0.88 mmol) of $m$-CPBA in CH$_2$Cl$_2$/ether (1/1) was added slowly at 0 °C and the two-phase mixture was stirred vigorously until tlc indicated the disappearance of starting material (ca. 8 h). The excess oxidant was quenched with aqueous sat'd NaHSO$_3$ and the reaction mixture was extracted with ether. The ether extracts were dried (MgSO$_4$) and the solvent was evaporated in vacuo. Flash column chromatography of the residue on silica gel eluting with 5% ethyl acetate in hexanes produced 176 mg (85% yield) of epoxide 62 as a single diastereomer.
Epoxide 62:

$^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 6.73 (s, 2H), 3.49 (dd, J = 10.5, 8.1 Hz, 1H), 2.81 (d, J = 4.8 Hz, 1H), 2.65 (d, J = 4.8 Hz, 1H), 2.54 (t, J = 7.8 Hz, 2H), 2.42-2.37 (m, 2H), 2.32 (s, 6H), 2.28-2.22 (m, 2H), 2.03 (t, J = 5.4 Hz, 1H), 1.77 (dd, J = 14.7, 7.8 Hz, 1H), 1.63-1.52 (m, 2H), 1.32-1.28 (m, 4H), 1.29 (s, 3H), 1.01 (s, 3H), 0.88 (t, J = 6.3 Hz, 3H) ppm.

$^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 169.3, 149.6, 142.3, 126.1, 120.9, 60.6, 55.9, 48.2, 45.3, 41.9, 35.0, 31.4, 31.1, 30.3, 29.9, 26.4, 24.7, 22.4, 21.2, 20.7, 13.9 ppm.

IR (CCl$_4$): 2920, 2850, 1770, 1620, 1425, 1365, 1180, 1025 cm$^{-1}$.

Mass spectrum (70 ev, m/e): 414 (M$^+$), 370, 312, 285, 247, 219, 193 (100%).

HRMS: for C$_{25}$H$_{34}$O$_5$ calculated 414.2406, found 414.2397.
Procedure:

To a solution of ca. 15 mg of ammonium nitrate in nitromethane (10 mL) at 25 °C was added 100 mg (0.24 mmol) of epoxide 62. The solution was stirred at 25 °C and was sonicated intermittently until tlc indicated the disappearance of most of the starting material (ca. 3 d). The reaction mixture was diluted with ether (20 mL), washed with sat’d aqueous NaHCO₃ and brine, and was dried over MgSO₄. Solvent evaporation in vacuo and purification of the crude product by flash column chromatography on silica gel provided the allylic alcohol 63 in 38% yield.
Allylic alcohol 63:

Note: Some signals in $^1$H NMR and $^{13}$C NMR are broadened due to the hindered rotation of substituted aryl group.\(^{120}\)

$^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 6.76 (br s, 2H), 5.75 (s, 1H), 4.62 (s, 1H), 4.57 (s, 1H), 3.99 (s, 2H), 3.05 (dt, J = 11.4, 5.4 Hz, 1H), 2.94-2.85 (m, 1H), 2.54 (dd, J = 8.1, 7.5 Hz, 2H), 2.30 (s, 6H), 2.18-2.85 (m, 3H), 1.65-1.56 (m, 4H), 1.53 (s, 3H), 1.32-1.25 (m, 4H), 0.88 (t, J = 6.3 Hz, 3H) ppm.

$^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 168.9, 149.3, 146.9, 142.1, 137.0, 124.9, 121.5, 121.1-119.8 (br m), 111.7, 66.4, 45.1, 35.9, 35.2, 32.1, 31.5, 31.4, 30.2, 22.4, 21.3 (br s), 18.6, 13.9 ppm.

IR (CCl$_4$): 3495, 2920, 2850, 1770, 1365, 1195, 1175, 1030 cm$^{-1}$.

Mass spectrum (70 ev, m/e): 414(M$^+$), 396, 354, 312, 231, 193 (100%), 91, 69.

HRMS: for C$_{25}$H$_{34}$O$_5$ calculated 414.2406, found 414.2401.
Procedure:

To a suspension of 100 mg of K₂CO₃ in 10 mL of methanol at 25 °C was added 30 mg (0.07 mmol) of 63. The reaction mixture was stirred for ca. 3h at 25 °C until tlc indicated the disappearance of starting material. The reaction mixture was diluted with ether, washed with brine and dried over MgSO₄. Solvent evaporation in vacuo produced the crude triol. The crude product of 65 was pure enough (by ¹H NMR) to be used in the cyclization reaction without any further purification.
Triol 65:

$^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 6.11 (s, 2H), 5.77 (s, 1H), 4.73 (s, 1H), 4.69 (s, 2H, exchangeable with D$_2$O), 4.54 (s, 1H), 4.04 (s, 2H), 3.39 (dt, $J = 11.4$, 5.4 Hz, 1H), 3.18 (dt, $J = 10.8$, 5.7 Hz, 1H), 2.73-2.63 (m, 1H), 2.41 (dd, $J = 8.1$, 7.5 Hz, 2H), 2.22-2.12 (m, 3H), 1.59 (s, 3H), 1.38-1.25 (m, 6H), 0.88 (t, $J = 6.6$ Hz, 3H) ppm.

$^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 154.6 (br s), 148.8, 142.2, 137.4, 122.8, 114.6, 110.4, 108.5, 67.2, 44.4, 35.3, 34.4, 32.0, 31.6, 30.8, 30.5, 22.5, 18.5, 14.0 ppm.

IR (CCl$_4$): 3350, 2920, 2850, 1620, 1580, 1430, 1025 cm$^{-1}$.
Procedure:

To the product 65 of the preceding reaction in 10 mL of benzene was added catalytic p-TSA monohydrate. The solution was stirred for ca. 15 h at 25 °C. The reaction mixture was diluted with ether (20 mL), washed with sat'd aqueous NaHCO₃ followed by brine, and dried over MgSO₄. Solvent evaporation in vacuo and purification of the crude product by flash column chromatography eluting with 10% ethyl acetate in hexanes produced 15 mg of pure 66. The overall yield of 66 from 63 was 65%.
11-Hydroxy-Δ⁸-tetrahydrocannabinol (66):

¹H NMR (CDCl₃, 300 MHz): δ 6.27 (s, 1H), 6.11 (s, 1H), 5.74 (d, J = 4.2 Hz, 1H), 4.91 (br s, 1H, exchangeable with D₂O), 4.06 (s, 2H), 3.39 (dd, J = 15.6, 3.9, 1H), 2.71 (dt, J = 10.8, 4.5 Hz, 1H), 2.44 (dd, J = 8.4, 6.9, 2H), 2.26-2.16 (m, 1H), 1.92-1.83 (m, 2H), 1.61-1.51 (m, 3H), 1.38 (s, 3H), 1.32-1.25 (m, 4H), 1.11 (s, 3H), 0.88 (t, J = 6.6 Hz, 3H) ppm.

¹³C NMR (CDCl₃, 75 MHz): δ 154.9, 154.7, 142.8, 138.2, 121.3, 110.1, 109.9, 107.7, 76.4, 67.1, 45.0, 35.5, 31.6 (two coincidental peaks), 31.4, 30.6, 27.6, 27.5, 22.5, 18.4, 14.0 ppm.

IR (CCI₄): 3340, 2950, 2840, 1620, 1570, 1425, 1260, 1180, 1040 cm⁻¹.

Mass spectrum (70 ev, m/e): 330 (M⁺), 297, 269, 231 (100%), 214, 193, 69.

HRMS: for C₂₁H₃₀O₃ 330.2195, found 330.2195.
Procedure:

To a solution of 1.302 mmol of potassium hexamethyldisilylamide in 8 mL of THF at 0 °C was added a solution of 200 mg (0.434 mmol) of 57 in 2 mL of THF. The solution was stirred for 1h at 0 °C, and 465 mg (1.303 mmol) of solid phenyl triflimide was added to the reaction mixture. The progress of the reaction was monitored by tlc (ca. 2 h). The reaction mixture was diluted with ether (20 mL), washed with brine, and dried (MgSO₄). Evaporation of the solvent produced the crude vinyl triflate. Separation of the product from the excess reagent was difficult as both had nearly identical chromatographic mobilities. The mixture containing the reagent and the product which was obtained from flash column chromatography, eluting with 5% ethyl acetate in hexane was used in the next reaction.
Vinyl triflate (67):

$^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 6.63-6.58 (m, 2H), 5.82-5.75 (br m, 1H), 5.42-5.37 (m, 2H), 4.15 (t, J = 2.6 Hz, 1H), 3.73-3.64 (m, 2H), 3.57-3.49 (m, 2H), 2.51 (t, J = 7.6 Hz, 2H), 2.41-2.33 (br m, 2H), 2.09-2.05 (m, 1H), 1.97-1.94 (m, 1H), 1.60-1.56 (m, 2H), 1.47 (d, J = 5.4 Hz, 6H), 1.33 (s, 3H), 1.32-1.25 (m, 4H), 1.19 (t, J = 8.2 Hz, 6H), 1.07 (s, 3H), 0.89 (t, J = 6.9 Hz, 3H) ppm.

IR (CHCl$_3$): 2990, 2920, 1610, 1585, 1425, 1210, 1150, 1080, 1050, 1040, 930, 865 cm$^{-1}$.

Mass spectrum (70 ev, m/e): 595 (M$^+$, weak), 448, 405, 315, 234, 193, 109, 73(100%).

HRMS: for C$_{29}$H$_{43}$SO$_7$F$_3$ 592.2682, found 595.2730.
Procedure:

To the product 67 from the proceeding reaction in 15 mL of methanol was added ca. 15 mg of PPTS. The reaction mixture was stirred vigorously at 25 °C until tlc indicated that both ethoxyethyl groups have been removed (ca. 6 h). The reaction mixture was diluted with ether (20 mL), washed with brine, and dried (MgSO₄). Solvent evaporation gave the crude diol 68, which was purified by flash column chromatography on silica gel, eluting with 5% ethyl acetate in hexane. The overall yield from 57 was 125 mg (65% yield).
Resorcinol of the vinyl triflate (68):

$^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 6.21 (s, 2H), 5.94 (s, 1H), 5.20 (s, 2H, exchangeable with D$_2$O), 4.12 (incomplete t, $J = 2.4$ Hz, 1H), 2.54-2.41 (m, 4H), 2.28 ($t, J = 5.6$ Hz, 1H), 1.76 (d, $J = 9.3$ Hz, 1H), 1.61-1.51 (m, 2H), 1.38 (s, 3H), 1.32-1.26 (m, 4H), 1.08 (s, 3H), 0.89 ($t, J = 6.9$ Hz, 3H) ppm.

$^1$H NMR (C$_6$D$_6$, 300 MHz): $\delta$ 5.84 (s, 2H), 5.56 (s, 1H), 4.71 (s, 2H, exchangeable with D$_2$O), 4.05 (br s, 1H), 2.34 ($t, J = 7.2$ Hz, 2H), 2.22-2.16 (m, 2H), 2.11-2.04 (m, 1H), 1.86 (d, $J = 7.2$ Hz, 1H), 1.51 (br $t, J = 7.2$ Hz, 2H), 1.28-1.24 (m, 4H), 0.98 (s, 3H), 0.89 (s, 3H), 0.87 (t, partially obscured by the peak at 0.89 ppm, $J = 6.9$ Hz, 3H) ppm.

$^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 156.5, 154.8, 143.7, 113.8, 111.0, 108.7, 47.0 (two coincidental peaks), 42.4, 35.5, 35.4, 31.5, 30.6, 28.6, 25.3, 22.5, 20.7, 13.9 ppm.

$^{13}$C NMR (C$_6$D$_6$, 75 MHz): $\delta$ 155.6, 155.4, 143.3, 114.8, 111.7, 108.9, 47.4, 47.2, 42.2, 35.8, 35.7, 31.7, 31.1, 28.7, 25.2, 22.9, 20.6, 14.2 ppm.

IR (CHCl$_3$): 3005, 2960, 2860, 1630, 1580, 1420, 1250, 1220, 1140, 1060, 1025 cm$^{-1}$.

Mass spectrum (70 ev, m/e): 448 (M$^+$), 405, 315, 233 (100%), 193, 109, 83.

HRMS: for C$_{21}$H$_{27}$SO$_5$F$_3$ 448.1531, found 448.1523.

Specific rotation: [$\alpha$]$^{24}_D = -79.74^\circ$ (c = 0.38, ethanol)
Procedure:

To a solution of 125 mg (0.279 mmol) of diol 68 in 8 mL of anhydrous CH$_2$Cl$_2$ was added 0.32 mL (2.601 mmol) of boron trifluoride etherate at 25 °C. The reaction mixture was stirred at 25 °C for 8 h, at which time tlc indicated the complete consumption of starting material. The reaction mixture was diluted with ether (20 mL), washed with brine, and dried (MgSO$_4$). Solvent evaporation produced the crude product, which was purified by flash column chromatography on silica gel, eluting with 10% ethyl acetate in hexane, to produce 106 mg (87% yield) of cyclic 69.
(-)-trans-6a,7,10,10a-Tetrahydro-1-hydroxy-6,6-dimethyl-3-pentyl-6H-dibenzo[b,d]-pyran-9-yl-trifluoromethanesulfonate (69):

$^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 6.28 (s, 1H), 6.10 (s, 1H), 5.81 (br s, 1H), 4.76 (s, 1H, exchangeable with D$_2$O), 3.67 (dd, $J = 8.2, 4.5$ Hz, 1H), 2.86 (dt, $J = 11.1, 4.8$ Hz, 1H), 2.44 (t, $J = 7.8$ Hz, 2H), 2.39-2.18 (br m, 2H), 2.05-1.93 (br m, 1H), 1.86 (dt, $J = 9.9, 3.6$ Hz, 1H), 1.56-1.52 (m, 2H), 1.41 (s, 3H), 1.32-1.28(m, 4H), 1.12 (s, 3H), 0.84 (t, $J = 6.3$ Hz, 3H) ppm.

$^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 154.5 (two coincidental peaks), 149.4, 143.6, 116.5, 110.1, 108.3, 107.7, 76.3, 43.6, 35.4, 33.2, 31.6, 31.5, 30.5, 27.5, 25.8, 22.5, 18.3, 13.9 ppm.

$^{13}$C NMR (C$_6$D$_6$, 75 MHz): $\delta$ 155.3, 155.2, 149.4, 143.5, 116.9, 110.5, 108.6, 107.8, 75.9, 43.5, 35.9, 33.4, 31.9, 31.8, 31.1, 27.5, 25.5, 22.9, 18.3, 14.2 ppm.

IR (CHCl$_3$): 3400, 2960, 2925, 2850, 1625, 1585, 1420, 1250, 1210, 1140, 1050 cm$^{-1}$.

Mass spectrum (70 ev, m/e): 448(M$^+$), 392, 231, 193, 109, 69(100%).

HRMS: for C$_{21}$H$_{27}$SO$_5$F$_3$ 448.1531, found 448.1514.

Specific rotation: $[\alpha]^{24}_{D} = -206.13^\circ$ (c = 0.31, ethanol)
Procedure:

A solution of 7 mg (0.01 mmol) of PdCl$_2$(PPh)$_3$ in 2.00 mL of THF and 0.12 mL of methanol, containing 42 mg (0.31 mmol) of potassium carbonate, was purged with carbon monoxide at 25 °C for 5 min. A solution of 45 mg (0.10 mmol) of cyclohexenyl triflate 69 in 2 mL of THF was added, and purging was continued for an additional 10 min. The reaction mixture was stirred at 25 °C under an atmosphere of carbon monoxide until tlc indicated complete disappearance of starting material (ca. 8 h). The reaction mixture was diluted with water and extracted with ether. The ether layers were concentrated and dried (MgSO$_4$). Solvent evaporation gave the crude product, which was purified by flash column chromatography on silica gel, eluting with 10% ethyl acetate in hexane. The yield of 70 was 26 mg (72% yield).
(-)-11-Nor-Δ⁸-tetrahydrocannabinol-9-carboxylic acid methyl ester (70):

$^1$H NMR (CDCl₃, 300 MHz): δ 7.02 (br s, 1H), 6.25 (s, 1H), 6.14 (s, 1H), 5.49 (s, 1H, exchangeable with D₂O), 3.85 (dd, $J = 8.7, 3.3$ Hz, 1H), 3.76 (s, 3H), 2.67 (dt, $J = 16.2, 4.5$ Hz, 1H), 2.43 (t, $J = 7.8$ Hz, 2H), 2.41-2.36 (m, partially obscured by the peak at 2.43 ppm, 1H) 2.06-1.92 (br m, 3H), 1.82 (dt, $J = 11.7, 4.2$ Hz, 1H), 1.58-1.53 (m, 2H), 1.39 (s, 3H), 1.32-1.26 (br m, 4H), 1.12 (s, 3H), 0.88 (t, $J = 6.9$ Hz, 3H) ppm.

$^{13}$C NMR (CDCl₃, 75 MHz): δ 168.2, 155.3, 154.6, 142.9, 138.1, 130.9, 109.6, 109.4, 107.7, 76.0, 51.8, 44.2, 35.5, 31.5, 31.2, 30.6, 30.1, 28.5, 27.5, 22.5, 18.3, 13.9 ppm.

IR (CHCl₃): 3405, 2960, 2940, 2860, 1715, 1695, 1630, 1580, 1440, 1270, 1190, 1075 cm⁻¹.

Mass spectrum (70 ev, m/e): 358 (M⁺, 100%), 302, 283, 231, 193, 69.

HRMS: for C₂₂H₃₀O₄ 358.2144, found 358.2165

Specific rotation: $\left[\alpha\right]^{23}_D = -219^o$ (c = 1.5, ethanol)

Literature $^{82}$ $\left[\alpha\right]_D = -302^o$ (ethanol)
Oxalate (71):

$^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 7.04 (br s, 1H), 6.27 (s, 1H), 6.12 (s, 1H), 4.94 (s, 1H, exchangeable with D$_2$O), 3.91 (br d, 1H, partially obscured by the peak at 3.89 ppm), 3.89 (s, 3H), 2.67 (dt, $J = 11.1$, 4.2 Hz, 1H), 2.59-2.48 (m, 1H), 2.45 (t, $J = 6.3$ Hz, 2H), 2.19-2.05 (m, 1H), 1.98-1.82 (m, 2H), 1.61-1.52 (m, 2H), 1.40 (s, 3H), 1.35-1.21 (m, 4H), 1.13 (s, 3H), 0.88 (t, $J = 6.6$ Hz, 3H) ppm.

$^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 187.4, 164.8, 154.8, 154.6, 147.0, 143.3, 136.8, 110.0, 109.0, 107.8, 75.8, 52.5, 44.1, 35.4, 31.5, 30.8, 30.6, 29.4, 28.2, 27.5, 22.5, 18.3, 14.0 ppm.

IR (CHCl$_3$): 3480, 2960, 2860, 1745, 1675, 1590, 1440, 1265, 1190, 1170, 1020 cm$^{-1}$.

Mass spectrum (70 ev, m/e): 386 (M$^+$), 330, 231, 205, 85, 71, 57(100%).

HRMS: for C$_{23}$H$_{30}$O$_5$ 386.2093, found 386.2092.
Procedure:

A solution of (+)-nopinone (2.00 g, 14.49 mmol) in CCl₄ (10 mL) was added to a stirred solution of recrystallized N-bromosuccinimide (7.74 g, 43.48 mmol) and benzoyl peroxide (0.36 g, 1.49 mmol) in CCl₄ (20 mL) in a nitrogen atmosphere. The resulting solution was heated at reflux, and the progress of the reaction was monitored by tlc. After 2 days, tlc indicated the formation of both mono- and bis-bromonopinone (ca. 2:3 ratio). The reaction mixture was cooled, diluted with water, and extracted with CH₂Cl₂. The combined CH₂Cl₂ extracts were washed successively with sat'd aqueous NaHCO₃ and brine, dried (MgSO₄), and concentrated under reduced pressure. Bis-bromonopinone (75) was separated from mono-bromonopinone by flash column chromatography on silica gel, eluting with 5% ethyl acetate in hexane to afford 2.35 g (55% yield).
3,3-Dibromo-6,6-dimethylbicyclo[3.1.1]-heptan-2-one (75):

$^1$H NMR (300 MHz, CDCl$_3$): δ 3.57 (dd, J = 15.9, 4.2 Hz, 1H), 3.39 (d, J = 15.9 Hz, 1H), 2.99 (t, J = 5.7 Hz, 1H), 2.75-2.68 (m, 1H), 2.60 (d, J = 1.1 Hz, 1H), 2.27-2.22 (m, 1H), 1.43 (s, 3H), 0.96 (s, 3H) ppm.

$^{13}$C NMR (75 MHz, CDCl$_3$): δ 199.1, 59.6, 57.3, 48.9, 44.3, 42.3, 25.7, 25.4, 23.8 ppm.

IR (CHCl$_3$): 2980, 2960, 2920, 1730, 1450 cm$^{-1}$.

Mass spectrum (70 ev, m/e): 296(M$^+$, weak), 217, 215, 173, 136, 110, 95, 83(100%).

HRMS: for C$_9$H$_{12}$OBr (M$^+$-Br) 215.0071, found 215.0063.
Procedure:

To a suspension of anhydrous lithium carbonate (1.77 g, 23.89 mmol), anhydrous lithium bromide (1.45 g, 16.74 mmol) in freshly distilled DMF (20 mL) under nitrogen, equipped with a reflux condenser at 100 °C, was added a solution of bis-bromonopinone (75) (2.35 g, 7.96 mmol) in DMF (10 mL) by cannula. The reaction mixture was stirred at 130 °C for 6 h, at which time tlc indicated the complete consumption of starting material. The reaction mixture was cooled, diluted with water (50 mL) and extracted with ether. The combined ether extracts were washed with brine and dried (MgSO₄). Solvent evaporation produced the crude product, which was purified by flash column chromatography on silica gel, eluting with 5% ethyl acetate in hexane, to afford 1.29 g (76% yield) of the α-bromoenone 76.
3-Bromo-6,6-dimethylbicyclo[3.1.1]hept-3-en-2-one (76):

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.83 (d, $J = 7.2$ Hz, 1H), 2.93 (dd, $J = 12.6$, 6.0 Hz, 1H), 2.87 (dd, $J = 15.0$, 5.4 Hz, 1H), 2.65 (dd, $J = 12.6$, 6.9 Hz, 1H), 2.23 (d, $J = 9.3$ Hz, 1H), 1.52 (s, 3H), 1.03 (s, 3H) ppm.

$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 195.9, 156.3, 119.8, 58.3, 56.3, 45.9, 41.6, 26.3, 22.5 ppm.

IR (CHCl$_3$): 2960, 1695, 1580, 1460, 1305, 1240 cm$^{-1}$.

Mass spectrum (70 ev, m/e): 216, 214, 201, 199, 176, 174, 135, 83(100%).
Procedure:

To a solution of the bis-2-ethoxyethyl olivetol (56) (650 mg, 2.20 mmol) in anhydrous THF (30 mL) was added n-butyllithium in hexane solution (1.45 mL, 2.20 mmol) at 0 °C during 20 min. The reaction mixture was stirred at 0 °C for 10 min and then at 25 °C for 2.5 h. In a separate flask, a solution of lithium-2-thienylcyanocuprate⁷¹ (22.00 mL, 2.20 mmol) was cooled to -78 °C. The lithiated olivetol diether was transferred via cannula to the cuprate solution over a 15 min period. Following addition, the reaction mixture was placed in an ice bath for 10 min, cooled to -78 °C, and stirred for 1.5 h. To this mixed higher-order cuprate solution at -78 °C was added 76 (268 mg, 1.25 mmol) mixed with BF₃·Et₂O (0.15 mL, 1.25 mmol) in THF (2 mL). The mixture was stirred at -78 °C until tlc showed the disappearance of starting material (5-6 h). The reaction was diluted with ether (30 mL), washed with concentrated NH₄OH/sat’d NH₄Cl (1/9) solution, extracted with ether, and dried (MgSO₄). Evaporation of the solvent followed by purification by flash column chromatography on silica gel eluting with 5% ethyl acetate in hexane produced 375 mg (56% yield) of 77 as a mixture of ethoxyethyl diastereomers.
3-Bromo-4-[4-pentyl-2,6-bis(2-ethoxyethyl)phenyl]-6,6-dimethylbicyclo[3.1.1]hept-2-one (77):

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 6.59 (br s, 2H), 6.27 (d, $J = 9.0$ Hz, 1H), 5.56-5.35 (br m, 2H), 4.42 (d, $J = 9.0$ Hz, 1H), 3.81-3.65 (br m, 2H), 3.59-3.51 (br m, 2H), 2.83 (dd, $J = 6.3$, 5.4 Hz, 1H), 2.61-2.43 (br m, 2H), 2.53 (t, $J = 6.9$ Hz, 2H), 2.14-2.11 (m, 1H), 1.58-1.56 (m, 2H), 1.49 (d, $J = 2.7$ Hz, 6H), 1.37 (s, 3H), 1.35-1.30 (m, 4H), 1.18 (t, $J = 6.9$ Hz, 6H), 1.01 (s, 3H), 0.88 (t, $J = 6.6$ Hz, 3H) ppm.

IR (CCl$_4$): 2960, 2920, 2870, 1725, 1605, 1580, 1440, 1380, 1350, 1080, 1050 cm$^{-1}$. 
Procedure:

To a solution of 77 (375 mg, 0.69 mmol) in methanol (20 mL) was added PPTS (ca. 35 mg). The reaction was stirred vigorously at 22 °C until tlc indicated that both ethoxy ethyl groups have been removed (ca. 8 h). The reaction mixture was extracted with ether, and the combined ether extracts were washed with brine and dried (MgSO₄). Solvent evaporation, followed by purification by flash column chromatography on silica gel eluting with 10% ethyl acetate in hexane afforded 246 mg (90% yield) of the resorcinol 78.
3-Bromo-4-[(2,6-dihydroxy-4-pentyl)phenyl]-6,6-dimethylbicyclo[3.1.1]-hept-2-one (78):

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 6.30 (d, $J = 8.7$ Hz, CHBr, 1H), 6.24 (s, 2H), 5.66 (br s, 2H, exchangeable with D$_2$O), 4.28 (d, $J = 8.7$ Hz, 1H), 2.84 (dd, $J = 5.4$, 5.2 Hz, 1H), 2.62 (d, $J = 11.1$ Hz, 1H), 2.49-2.47 (m, 1H), 2.42 (t, $J = 7.8$ Hz, 2H), 2.20 (t, $J = 5.7$ Hz, 1H), 1.59-1.50 (m, 2H), 1.36 (s, 3H), 1.32-1.24 (m, 4H), 1.01 (s, 3H), 0.88 (dd, $J = 6.9$, 6.3 Hz, 3H) ppm.

$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 208.7, 155.2, 143.4, 110.8, 108.9, 57.7, 52.6, 48.9, 44.1, 42.2, 35.3, 31.5, 30.5, 25.5, 23.7, 22.5, 22.5, 13.9 ppm.

IR (CHCl$_3$): 3400, 2960, 2940, 2850, 1710, 1620, 1590, 1430, 1350, 1260 cm$^{-1}$.

Mass spectrum (70 ev, m/e): 396(2%), 394(2%), 314, 258, 231, 204, 148, 83(100%).

HRMS: for C$_{20}$H$_{27}$O$_3$Br 394.1140, found 394.1144.
Selected long-range connectivities observed in the HMBC experiment

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<td>8</td>
<td>25.5</td>
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<td>1'</td>
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Correlation of $^1$H and $^{13}$C Resonances, from HMQC Experiment

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<td>2.20 (t, 1H)</td>
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Procedure:

To a solution of the 5'-($^2$H$_3$)olivetol dimethyl ether (86) (1.20 g, 5.77 mmol) in anhydrous THF (50 ml) was added n-butyllithium in hexane (4.50 mL, 7.21 mmol) at 0 °C during 20 min. The reaction mixture was stirred at 0 °C for 10 min and then at 25 °C for 1.5 h. In a separate flask, a solution of lithium-2-thienylcyanocuprate (75.00 mL, 7.50 mmol) was cooled to -78 °C. The lithiated olivetol diether was transferred via cannula to the cuprate solution over a 15 min period. Following addition, the reaction mixture was placed in an ice bath for 10 min, cooled to -78 °C, and stirred for 1.5 h. To this mixed higher-order cuprate solution at -78 °C was added a mixture of 76 (770 mg, 3.60 mmol) and BF$_3$·Et$_2$O (0.80 mL, 6.50 mmol) in THF (5 mL). The mixture was stirred at -78 °C until tlc showed the disappearance of starting material (3-4 h). The reaction was diluted with ether, washed with concentrated NH$_4$OH/sat'd NH$_4$Cl (1/9) solution, extracted with ether, and dried (MgSO$_4$). Evaporation of the solvent followed by purification by flash column chromatography on silica gel eluting with 5% ethyl acetate in hexane produced 1.27 g (82% yield) of cuprate adduct 87.
3-Bromo-4-[(2,6-dimethoxy-4-(5′-(2H3)pentyl)phenyl)-6,6-dimethylbicyclo[3.1.1]hept-2-one (87):

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 6.41 (s, 2H), 6.14 (d, $J = 9.0$ Hz, -CHBr, 1H), 4.37 (d, $J = 9.0$ Hz, 1H), 3.80 (s, 6H), 2.84-2.81 (m, 1H), 2.57 (dd, $J = 8.1, 7.5$ Hz, 2H), 2.46 (dd, $J = 4.5, 3.0$ Hz, 2H), 2.09 (br t, $J = 4.5$ Hz, 1H), 1.65-1.58 (m, 2H), 1.41-1.25 (m, 4H), 1.37 (s, 3H), 1.01 (s, 3H) ppm.

$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 206.9, 158.6, 143.4, 113.7, 104.7, 57.6, 55.7, 52.9, 48.9, 43.8, 41.2, 36.3, 31.5, 30.9, 25.4, 23.7, 22.4, 22.2 ppm.

IR (CCl$_4$): 2920, 2850, 1725, 1605, 1575, 1450, 1420, 1120 cm$^{-1}$.

Mass specturm (70 ev, m/e): 427(4%), 425(5%), 346, 250, 224, 137, 95, 83(100%).

HRMS: for C$_{22}$H$_{28}$O$_3$D$_3$Br 425.1600, found 425.1606.
Procedure:

To a solution of 1,2-bis(trimethylsilyloxy)ethane (5.75 mL, 23.64 mmol) in CH$_2$Cl$_2$ (2 mL) at 22 °C was added trimethylsilyl trifluoromethanesulfonate (TMSOTf, 0.25 mL, 1.26 mmol). After 15 min, a solution of 87 (500 mg, 1.18 mmol) in CH$_2$Cl$_2$ (5 mL) was added and stirred vigorously at 22 °C. The progress of the reaction was monitored by tlc. After 60 h, the tlc indicated nearly complete disappearance of the starting material. The reaction mixture was extracted with CH$_2$Cl$_2$, and the combined CH$_2$Cl$_2$ extracts were washed successively with sat'd aqueous NaHCO$_3$, brine, and dried (MgSO$_4$). Solvent evaporation, followed by separation of the product from the unreacted starting material by flash column chromatography, eluting with 2% ethyl acetate in hexane afforded 360 mg (65% yield) of ketal 88.
2-Bromo-3-[(2,6-dimethoxy-4-(5'-(2H3)pentyl))phenyl]-4-isopropenyl-
cyclohexan-1-ethylene ketal (88):

$^1$H NMR (300MHz, CDCl$_3$): $\delta$ 6.32 (s, 1H), 6.30 (s, 1H), 5.11 (d, $J = 12.0$ Hz, 1H), 4.42 (s, 1H), 4.37 (s, 1H), 4.33-4.29 (m, 1H), 4.25-4.16 (m, 1H), 4.06-3.99 (m, 2H), 3.92 (dd, $J = 12.0$, 11.4 Hz, 1H), 3.79 (s, 3H), 3.76 (s, 3H), 2.97 (ddd, $J = 11.4$, 11.1, 3.0 Hz, 1H), 2.53 (dd, $J = 8.1$, 7.5 Hz, 2H), 2.04-1.99 (m, 1H), 1.83-1.71 (m, 2H), 1.63-1.56 (m, 3H), 1.55 (s, 3H), 1.32-1.29 (m, 4H) ppm.

$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 158.6, 158.3, 147.8, 142.6, 115.4, 110.6, 108.3, 104.1, 66.2, 65.4, 61.9, 56.0, 55.1, 48.4, 43.8, 36.5, 35.4, 31.6, 30.8, 28.5, 22.3, 18.7 ppm.

IR (CCl$_4$): 2920, 2850, 1605, 1575, 1450, 1120 cm$^{-1}$.

Mass spectrum (70 ev, m/e): 471(4%), 469(5%), 388, 308, 224, 154, 99, 86(100%).

HRMS: for C$_{24}$H$_{32}$D$_3$O$_4$Br 469.1907, found 469.1879.
Correlation of $^1$H and $^{13}$C Resonances, from HMQC Experiment

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<td>C5</td>
<td>1.83-1.71 (m, 1H)</td>
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<td>C3&quot;</td>
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<td>C6</td>
<td>2.04-1.99 (m, 1H)</td>
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<td>C1&quot;</td>
<td>2.53 (dd, 2H)</td>
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<td>43.8</td>
<td>C3</td>
<td>3.92 (dd, 1H)</td>
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<td>C4</td>
<td>2.97 (ddd, 1H)</td>
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<td>55.1</td>
<td>C6&quot; or C7&quot;</td>
<td>3.76 (s, 3H)</td>
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<td>56.0</td>
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### Correlation of $^1$H and $^{13}$C Resonances, from HMQC Experiment (Cont'd)

<table>
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<th>Assignment</th>
<th>$^1$H NMR (δ)</th>
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<td>C1</td>
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<td>115.4</td>
<td>C1'</td>
<td>-</td>
</tr>
<tr>
<td>142.6</td>
<td>C4'</td>
<td>-</td>
</tr>
<tr>
<td>147.8</td>
<td>C9</td>
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<tr>
<td>158.3</td>
<td>C2' or C6'</td>
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</tr>
<tr>
<td>158.6</td>
<td>C2' or C6'</td>
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Selected long-range connectivities observed in the HMBC Experiment

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<thead>
<tr>
<th>Position</th>
<th>$^{13}$C NMR ($\delta$)</th>
<th>Correlations</th>
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<td>H3, H4, H6</td>
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<td>48.4</td>
<td>H2, H3, H5, H6, H10, H11</td>
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<td>H3, H4, H6</td>
</tr>
<tr>
<td>6</td>
<td>35.4</td>
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<td>2', 6'</td>
<td>158.3, 158.6</td>
<td>H3, H3', H5', H6&quot;, H7&quot;</td>
</tr>
<tr>
<td>4'</td>
<td>142.6</td>
<td>H3', H5', H1&quot;, H2&quot;</td>
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</table>
Procedure:

To a solution of 88 (250 mg, 0.53 mmol) in acetone (100 mL) was added 50% aqueous perchloric acid (10 mL). The reaction mixture was stirred vigorously at 40 °C, and the progress of the reaction was monitored by tlc. After 48 h, the reaction mixture was cooled to room temperature and neutralized carefully with sat'd aqueous NaHCO$_3$, extracted with ether, and dried (MgSO$_4$). Evaporation of the solvent followed by purification by flash column chromatography on silica gel eluting with 5% ethyl acetate in hexane produced 160 mg (71% yield) of ketone 93.
2-Bromo-3-[(2,6-dimethoxy-4-(5′-(2H3)pentyl))phenyl]-4-isopropenyl-cyclohexan-1-one (93):

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 6.33 (s, 2H), 5.48 (d, $J = 11.4$ Hz, -CHBr, 1H), 4.51 (s, 1H), 4.45 (s, 1H), 3.98 (dd, $J = 11.4$, 11.1 Hz, 1H), 3.83 (s, 3H), 3.73 (s, 3H), 3.33 (ddd, $J = 11.7$, 11.4, 4.2 Hz, 1H), 2.77 (ddd, $J = 14.1$, 3.6, 3.1 Hz, 1H), 2.62 (dd, $J = 13.5$, 6.6 Hz, 1H), 2.54 (dd, $J = 8.1$, 7.5 Hz, 2H), 2.03-1.82 (br m, 2H), 1.63-1.57 (m, 2H), 1.52 (s, 3H), 1.32-1.29 (m, 4H) ppm.

$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 201.9, 158.2, 157.9, 146.2, 143.4, 114.5, 111.6, 104.4, 104.1, 60.1, 55.9, 55.1, 48.1, 47.0, 40.2, 36.4, 31.5, 30.8, 30.6, 22.2, 18.5 ppm.

IR (CCl$_4$): 2920, 2850, 1725, 1605, 1580, 1450, 1420, 1230, 1120 cm$^{-1}$.

Mass spectrum (70 ev, m/e): 427(11%), 425(12%), 346(100%), 317.

HRMS: for C$_{22}$H$_{28}$O$_3$D$_3$Br 425.1600, found 425.1631.
Procedure:

A solution of methyllithium (0.59 mL, 0.71 mmol) was added dropwise to a suspension of anhydrous cuprous iodide (68 mg, 0.36 mmol) in ether (6 mL) at 0 °C. The reaction mixture was stirred at 0 °C 10 min. A solution of ketone 93 (105 mg, 0.25 mmol) in ether (4 mL) was added to the lithium dimethylcuprate solution at 0 °C during 30 sec. The reaction mixture turned bright yellow after ca. 10 sec. A solution of N-phenyltriflimide (176 mg, 0.49 mmol) in freshly distilled DME (3 mL) was added immediately after the appearance of the bright yellow color. The solution was stirred at 0 °C for 5 h. The reaction was diluted with ether, washed with sat’d NH₄Cl concentrated NH₄OH (9/1) solution, extracted with ether, and dried (MgSO₄). Evaporation of the solvent followed by purification by flash column chromatography on silica gel by eluting with 5% ethyl acetate in hexane produced 90 mg (76% yield) of the cyclohexenyl triflate 94.
3[(2,6-dimethoxy-4-(5'-(2H3)pentyl))phenyl]-4-isopropenyl-1-((trifluoromethyl)sulfonyl)oxy)-cyclohex-1-ene (94):

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 6.32 (s, 2H), 5.67 (dd, $J = 2.3, 2.1$ Hz, 1H), 4.49 (dd, $J = 2.9, 1.5$ Hz, 1H), 4.39 (br d, $J = 1.5$ Hz, 1H), 4.15 (dm, $J = 10.1$ Hz, 1H), 3.74 (s, 6H), 2.84 (dd, $J = 15.5, 7.8$ Hz, 1H), 2.67-2.58 (br m, 1H), 2.54 (dd, $J = 7.9, 7.7$ Hz, 2H), 2.37 (dm, $J = 15.5$ Hz, 1H), 1.91-1.86 (br m, 2H), 1.62-1.58 (br m, 2H), 1.61 (s, 3H), 1.34-1.30 (m, 4H) ppm.

$^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 158.5, 158.4, 147.1, 146.9, 143.1, 124.0, 115.1, 103.9, 55.5, 44.5, 36.5, 34.8, 31.6, 31.0, 28.8, 28.1, 22.3, 18.8 ppm.

IR (CHCl$_3$): 2920, 2860, 1605, 1580, 1450, 1420, 1210, 1150, 1120, 1050, 980 cm$^{-1}$.

Mass spectrum (70 ev, m/e): 479(M$^+$), 411, 329, 278(100%), 224, 205, 190, 152, 119.

HRMS: for C$_{23}$H$_{28}$D$_3$F$_3$O$_5$S 479.2033, found 479.2061.
Correlation of $^1$H and $^{13}$C Resonances, from HMQC Experiment

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<th>Assignment</th>
<th>$^1$H NMR ($\delta$)</th>
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<td>3.74 (s, 6H)</td>
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Correlation of $^1$H and $^{13}$C Resonances, from HMQC Experiment (Cont'd)

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<td>C2' or C6'</td>
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Selected long-range connectivities observed in the HMBC Experiment

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<td>4'</td>
<td>143.1</td>
<td>H3', H5', H1''</td>
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Procedure:

To a solution of 94 (100 mg, 0.21 mmol) in distilled CHCl₃ (10 mL) was added iodotrimethylsilane (purchased from Aldrich Chemical Co., 0.45 mL, 3.14 mmol) at 22 °C. After stirring for 12 h at 22 °C, more iodotrimethylsilane (0.45 mL, 3.14 mmol) was added as the tlc of the reaction mixture indicated the presence of starting material. After 10 h, the reaction was quenched with sat'd aqueous sodium sulfite, and extracted with CH₂Cl₂. The combined CH₂Cl₂ extracts were washed successively with sat'd aqueous NaHCO₃, brine and dried (MgSO₄). The solvent was evaporated and the crude product was purified by flash column chromatography on silica gel eluting with 2% ethyl acetate in hexane to afford 46 mg (47% yield) of cyclized enol triflate. The major by-product was 5'-({H₃)-olivetol dimethyl ether. Examination of the ¹H NMR spectrum of the product showed the presence of both trans (99) and cis ring junction isomers (trans:cis, 17:1). The mixture was used in the succeeding step without further separation.
1-Methoxy-3-(5'-(2H3)pentyl)-6a,7,8,10a-tetrahydro-6,6-dimethyl-9-((trifluoromethyl)sulfonyl)oxy)-6H-dibenzo[b,d]-pyran (99):

$^{1}$H NMR (500 MHz, CDCl$_3$): $\delta$ 6.78 (br s, 1H), 6.32 (s, 1H), 6.27 (s, 1H), 3.82 (s, 3H), 3.39 (dd, $J = 10.9$, 2.1 Hz, 1H), 2.56-2.52 (m, 2H), 2.51 (dd, $J = 8.1$, 7.5 Hz, 2H), 2.06 (br d, $J = 12.6$ Hz, 1H), 1.78 (dt, $J = 11.7$, 2.1 Hz, 1H), 1.61-1.49 (m, 3H), 1.43 (s, 3H), 1.31-1.28 (m, 4H), 1.09 (s, 3H) ppm.

$^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 157.9, 154.2, 148.5, 143.6, 122.5, 110.3, 107.4, 102.9, 76.6, 55.1, 44.3, 36.0, 32.9, 31.5, 30.8, 28.3, 27.6, 24.3, 22.3, 19.1 ppm.

IR (CDCl$_3$): 2920, 2850, 1615, 1570, 1410, 1205, 1140 cm$^{-1}$.

Mass spectrum (70 ev, m/e): 465(M$^+$), 406, 332, 211, 152(100%), 69.

HRMS: for C$_{22}$H$_{26}$D$_3$F$_3$O$_5$S 465.1876, found 465.1890.
Correlation of $^1$H and $^{13}$C Resonances, from HMQC Experiment

<table>
<thead>
<tr>
<th>$^{13}$C NMR (δ)</th>
<th>Assignment</th>
<th>$^1$H NMR (δ)</th>
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<tbody>
<tr>
<td>19.1</td>
<td>C12 or C13</td>
<td>1.09 (s, 3H)</td>
</tr>
<tr>
<td>22.3</td>
<td>C4'</td>
<td>1.31-1.28 (m, 2H)</td>
</tr>
<tr>
<td>24.3</td>
<td>C7</td>
<td>2.06 (br d, 1H)</td>
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<td></td>
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<td>1.61-1.49 (m, 1H)</td>
</tr>
<tr>
<td>27.6</td>
<td>C8</td>
<td>2.56-2.52 (m, 2H)</td>
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<tr>
<td>28.3</td>
<td>C12 or C13</td>
<td>1.43 (s, 3H)</td>
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<tr>
<td>30.8</td>
<td>C2'</td>
<td>1.61-1.49 (m, 2H)</td>
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<td>31.5</td>
<td>C3'</td>
<td>1.31-1.28 (m, 2H)</td>
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<tr>
<td>32.9</td>
<td>C10a</td>
<td>3.39 (br d, 1H)</td>
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<td>36.0</td>
<td>C1'</td>
<td>2.51 (dd, 2H)</td>
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<td>44.3</td>
<td>C6a</td>
<td>1.78 (dt, 1H)</td>
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<td>55.1</td>
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<td>3.82 (s, 3H)</td>
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<tr>
<td>76.6</td>
<td>C6</td>
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Correlation of $^1$H and $^{13}$C Resonances, from HMQC Experiment (Cont'd)

<table>
<thead>
<tr>
<th>$^{13}$C NMR ($\delta$)</th>
<th>Assignment</th>
<th>$^1$H NMR ($\delta$)</th>
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<td>102.9</td>
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<td>107.4</td>
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<td>110.3</td>
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<td>122.5</td>
<td>C10</td>
<td>6.78 (br s, 1H)</td>
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<tr>
<td>143.6</td>
<td>C3</td>
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<td>148.5</td>
<td>C9</td>
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<td>154.2</td>
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<tr>
<td>157.9</td>
<td>C1</td>
<td>–</td>
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Selected long-range connections observed in the HMBC Experiment

<table>
<thead>
<tr>
<th>Position</th>
<th>$^{13}$C NMR ($\delta$)</th>
<th>1H Assignment</th>
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<tr>
<td>1</td>
<td>157.9</td>
<td>H2, H6'</td>
</tr>
<tr>
<td>2</td>
<td>102.9</td>
<td>H4, H1'</td>
</tr>
<tr>
<td>3</td>
<td>143.6</td>
<td>H2, H4, H1', H2'</td>
</tr>
<tr>
<td>4</td>
<td>110.3</td>
<td>H2, H1'</td>
</tr>
<tr>
<td>4a</td>
<td>154.2</td>
<td>H4, H10a</td>
</tr>
<tr>
<td>6</td>
<td>76.7</td>
<td>H7, H6a, H12, H13</td>
</tr>
<tr>
<td>6a</td>
<td>44.3</td>
<td>H7, H8, H10, H10a, H12, H13</td>
</tr>
<tr>
<td>7</td>
<td>24.3</td>
<td>H6a, H8, H10a</td>
</tr>
<tr>
<td>8</td>
<td>28.3</td>
<td>H6a, H7, H10</td>
</tr>
<tr>
<td>10</td>
<td>122.5</td>
<td>H6a, H8, H10a</td>
</tr>
<tr>
<td>10a</td>
<td>32.9</td>
<td>H6a, H7</td>
</tr>
<tr>
<td>1'</td>
<td>36.0</td>
<td>H2, H4, H2', H3'</td>
</tr>
<tr>
<td>2'</td>
<td>30.8</td>
<td>H1', H3', H4'</td>
</tr>
<tr>
<td>3'</td>
<td>31.5</td>
<td>H1', H2', H4'</td>
</tr>
<tr>
<td>4'</td>
<td>22.3</td>
<td>H2', H3'</td>
</tr>
</tbody>
</table>
Procedure:

A solution of 46 mg (0.10 mmol) of the mixture of trans (99) and cis ring junction isomers of the cyclohexenyl triflate, 0.03 mL of Et3N, 1.0 mg of Pd(OAc)2, 2.0 mg of triphenylphosphine, 0.2 mL of methanol in 0.5 mL of DMF was purged with carbon monoxide for 5 min. and then stirred under a carbon monoxide atmosphere. The progress of the reaction was monitored by tlc. After 12 h, the reaction mixture was poured into water, and extracted with ether. The ether extracts were dried (MgSO4) and solvent was evaporated. The purification of the crude product by flash column chromatography on silica gel eluting with 5% ethyl acetate in hexane afforded 30 mg of a mixture of trans (101) and cis methyl esters. These stereoisomers were separated by HPLC (Phenomenex Ultracarb 5 ODS 30 column, 250 x 10 mm, flow rate 2.5 mL/min, methanol).
(-)-trans-1-methoxy-3-(5'-(2H3)pentyl)-6a,7,8,10a-tetrahydro-6,6-dimethyl-9-carbomethoxy-6H-dibenzo[b,d]-pyran (101):

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.81 (br s, 1H), 6.31 (s, 1H), 6.28 (s, 1H), 3.87 (s, 3H), 3.73 (s, 3H), 3.31 (dd, J = 11.4, 1.5 Hz, 1H), 2.59-2.53 (br m, 1H), 2.50 (dd, J = 8.1, 7.2 Hz, 2H), 2.47-2.39 (m, 1H), 2.00 (dd, J = 12.6, 7.5 Hz, 1H), 1.71 (ddd, J = 12.6, 11.4, 1.8 Hz, 1H), 1.63-1.54 (br m, 2H), 1.43 (s, 3H), 1.41-1.36 (m, 1H), 1.33-1.28 (br m, 4H), 1.09 (s, 3H) ppm.

$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 168.2, 158.2, 154.4, 143.3, 143.2, 128.9, 110.3, 108.2, 102.9, 77.6, 55.3, 51.5, 44.5, 36.0, 34.6, 31.5, 30.8, 27.5, 25.4, 24.4, 22.3, 18.9 ppm.

IR (CHCl$_3$): 2980, 2915, 2860, 1720, 1620, 1575, 1420, 1120, 1100 cm$^{-1}$.

Mass spectrum (70 ev, m/e): 375(M$^+$), 360, 356, 316, 272, 258, 229, 210(100%), 185.

HRMS: for C$_{23}$H$_{29}$D$_3$O$_4$ 375.2489, found 375.2492.

Specific rotation: $[\alpha]^{21}_D = -237^\circ$ (c = 0.005 g/ml, ethanol).
Procedure:

To a solution of the bis-2-ethoxyethyl olivetol (56, 765 mg, 2.35 mmol) in anhydrous THF (30 mL) was added n-butyllithium in hexane (1.5 mL, 2.21 mmol) at 0 °C during 20 min. The reaction mixture was stirred at 0 °C for 10 min and then at 25 °C for 2.5 h. In a separate flask, a solution of lithium-2-thienylcyanocuprate (23.5 mL, 2.35 mmol) was cooled to -78 °C. The lithiated olivetol diether was transferred via cannula to the cuprate solution over 15 min. Following addition, the reaction was placed in an ice bath for 10 min, cooled to -78 °C, and stirred for 1.5 h. To this mixed higher-order cuprate solution at -78 °C, was added a mixture of 113 (200 mg, 1.47 mmol) and BF3·Et2O (0.2 mL, 1.63 mmol) in THF (3 mL). The progress of the reaction was monitored by tlc. After 4 h, the reaction mixture was diluted with ether, washed with concentrated NH4OH/sat'd NH4Cl (1/9) solution, extracted with ether, and dried (MgSO4). Evaporation of the solvent followed by purification by flash chromatography on silica gel eluting with 10% ethyl acetate in hexane produced 500 mg (74% yield) of 114 as a mixture of diastereomers due to the asymmetric center on each of the two ethoxyethyl protecting groups.
Procedure:

To a solution of ketone 114 (60 mg) in THF (5 mL) and H2O (1 mL) at 23 °C was added catalytic p-TSA and was stirred at 23 °C until tlc showed complete consumption of starting material (10 h). The reaction mixture was diluted with ether, washed with sat'd aqueous NaHCO3, and dried (MgSO4). Evaporation of the solvent followed by purification by flash chromatography on silica gel eluting with 10% ethyl acetate in hexane produced the hemiketal 115 (97% yield):
Hemiketal 115:

$^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 6.29 (s, 1H), 6.15 (s, 1H), 5.01 (s, 1H), 4.94 (s, 1H), 4.73 (s, 1H, exchangeable with D$_2$O), 3.62 (br s, 1H), 2.83 (s, 1H, exchangeable with D$_2$O), 2.46 (dd, $J = 7.8, 7.5$ Hz, 2H), 2.34 (br s, 1H), 2.09 (t, $J = 12.6$ Hz, 1H), 2.05-1.91 (br m, 2H), 1.88 (s, 3H), 1.67-1.52 (m, 4H), 1.35-1.26 (m, 5H), 0.88 (dd, $J = 6.9, 6.6$ Hz, 3H) ppm.

$^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 156.4, 152.2, 145.4, 143.2, 111.1, 110.5, 107.6, 106.8, 98.7, 42.7, 35.7, 35.3, 31.5, 31.2, 30.8, 30.4, 22.5, 21.6, 14.0 ppm.

IR (neat): 3470, 2950, 2920, 2850, 1625, 1585, 1435, 1140, 1070 cm$^{-1}$

Mass spectrum (70 ev, m/e): 316(M$^+$), 248, 233(100%), 204, 150.

HRMS: for C$_{20}$H$_{28}$O$_3$ 316.2038, found 316.2013.
Procedure:

To a solution of hemiketal 115 (130 mg, 0.41 mmol) in CH₂Cl₂ (20 mL) at 0 °C was added pyridine (0.10 mL, 1.23 mmol), catalytic DMAP and acetic anhydride (0.10 mL, 1.03 mmol). The reaction mixture was stirred at 0 °C for 30 min and warmed to ambient temperature. The progress of the reaction was monitored by tlc for the disappearance of the starting material (5 h). The reaction was diluted with CH₂Cl₂, washed with brine, and dried (MgSO₄). Evaporation of the solvent and purification of the crude product by flash chromatography on silica gel eluting with 5% ethyl acetate in hexane gave 116 in 80% yield.
3-[4-Pentyl-2,6-bis(acetoxy)phenyl]-4-isopropenyl-cyclohexan-1-one (116):

Note: Some of the peaks in $^1$H NMR and $^{13}$C NMR are broadened due to hindered rotation of the aryl substituent.$^{120}$

$^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 6.78 (br s, 2H), 4.62 (s, 1H), 4.59 (s, 1H), 3.25 (td, $J = 12.0, 4.8$ Hz, 1H), 2.96 (td, $J = 11.4, 3.3$ Hz, 1H), 2.76 (t, $J = 14.4$ Hz, 1H), 2.54 (dd, $J = 8.1, 7.8$ Hz, 2H), 2.51-2.39 (m, 2H), 2.32 (br s, 6H), 2.10-2.02 (m, 1H), 1.78 (qd, $J = 13.2, 4.8$ Hz, 1H), 1.63-1.57 (m, 1H), 1.54 (s, 3H), 1.32-1.25 (m, 6H), 0.88 (t, $J = 6.6$ Hz, 3H) ppm.

$^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 209.7, 168.5 (br s), 149.3 (br s), 145.5, 142.8, 123.0, 120.9, 119.9, 112.4, 47.4, 45.0, 41.4, 39.1, 35.2, 31.6, 31.5, 30.2, 29.7, 29.4, 22.4, 19.2, 14.0 ppm.

IR (neat): 2920, 2850, 1765, 1720, 1570, 1195, 1175 cm$^{-1}$.

Mass spectrum (70 ev, m/e): 400(M$^+$), 341, 298, 272, 231, 206, 150, 117(100%).

HRMS: for C$_{24}$H$_{32}$O$_5$ 400.2250, found 400.2234.
Procedure:

To a solution of 57 (150 mg, 0.33 mmol) in 25 mL of methanol was added ca. 25 mg of PPTS. The reaction mixture was stirred at 25 °C until tlc indicated that both ethoxyethyl groups had been removed (ca. 5-8 h). The reaction mixture was diluted with ether, washed with brine and was dried over MgSO₄. Evaporation of the solvent followed by flash chromatography eluting with 15% ethyl acetate in hexane produced 80 mg (78% yield) of 73 as a single isomer.
Resorcinol (73):

$^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 6.17 (s, 2H), 5.13 (s, 2H, exchangeable with D$_2$O), 3.95 (t, $J$ = 8.1 Hz, 1H), 3.47 (dd, $J$ = 18.9, 7.8 Hz, 1H), 2.68-2.39 (m, 5H), 2.30 (t, $J$ = 5.4 Hz, 1H), 1.36 (s, 3H), 1.31-1.26 (m, 4H), 0.99 (s, 3H), 0.89 (t, $J$ = 6.9 Hz, 3H) ppm.

$^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 217.2, 155.3, 142.6, 113.7, 108.6, 57.9, 46.8, 42.3, 37.9, 35.2, 31.5, 30.6, 29.5, 26.2, 24.4, 22.5, 22.1, 14.0 ppm.

IR (CCl$_4$): 3350, 2950, 2850, 1680, 1620, 1590, 1430, 1265, 1020 cm$^{-1}$

Mass spectrum (70 eV, m/e): 316 (M$^+$), 310, 273, 247, 235 (100%), 219, 206, 193, 150, 83, 69, 57.

Specific rotation: $[\alpha]^{24}_D = +69.1^\circ$ (c = 0.4, ethanol)
Procedure:

To a solution of 125 mg (0.40 mmol) of resorcinol 73 in anhydrous CHCl₃ (12 mL) was added 0.42 mL (3.60 mmol) of stannic chloride at 25 °C. The resulting mixture was stirred at 25 °C for ca. 24 h at which time tlc (double elution using 10% ethyl acetate in hexanes) indicated the complete consumption of the starting material. The reaction mixture was poured onto ice and extracted with ether. The combined ether extracts were washed with a sat'd aqueous solution of NaHCO₃ followed by brine, dried (MgSO₄), and concentrated in vacuo. The purification of the crude product by flash column chromatography eluting with 10% ethyl acetate in hexane produced 90 mg (72% yield) of 74 as a white foam.
(-)-trans-3-Pentyl-6,6a,7,8,10,10a-hexahydro-1-hydroxy-6,6-dimethyl-9H-dibenzo[b,d]pyran-9-one (74):

$^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 6.26 (1H), 6.22 (s, 1H, exchangeable with D$_2$O), 6.18 (s, 1H), 3.99 (br d, $J = 15.0$ Hz, 1H), 2.88 (ddd, $J = 11.7, 11.4, 3.0$ Hz, 1H), 2.64-2.48 (m, 2H), 2.44 (dd, $J = 8.1, 7.5$ Hz, 2H), 2.18-2.09 (m, 3H), 1.96 (t, $J = 12.3$ Hz, 1H), 1.59-1.53 (m, 2H), 1.47 (s, 3H), 1.31-1.26 (m, 4H), 1.12 (s, 3H), 0.88 (t, $J = 6.7$ Hz, 3H) ppm.

$^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 214.7, 155.3, 154.5, 143.6, 109.1, 107.9, 107.8, 76.4, 47.3, 44.9, 40.8, 35.5, 34.8, 31.6, 30.7, 27.8, 26.9, 22.5, 18.9, 14.0 ppm.

IR (CCl$_4$): 3260, 2940, 2920, 2840, 1685, 1615, 1570, 1420, 1350, 1250, 1175, 1090, 1030 cm$^{-1}$.

Mass spectrum (70 ev, m/e): 316(M$^+$), 301, 273, 260, 245, 233 (100%), 150, 95, 83, 69, 57.

HRMS: for C$_{20}$H$_{28}$O$_3$ 316.2038, found 316.2034.

Specific rotation: $[\alpha]_D^{25} -43.7^\circ$ (c = 2.40, CHCl$_3$)
Procedure:

To a solution of cyclized ketone 74 (150 mg, 0.48 mmol) in CH$_2$Cl$_2$ (5 mL) at 0°C was added pyridine (0.06 mL, 0.72 mmol), catalytic DMAP and acetic anhydride (0.06 mL, 0.63 mmol). The reaction mixture was stirred at 0°C for 30 min and warmed to ambient temperature. The progress of the reaction was monitored by tlc for the disappearance of the starting material (4 h). The reaction was diluted with CH$_2$Cl$_2$, washed with brine, and dried (MgSO$_4$). Evaporation of the solvent and purification of the crude product by flash chromatography on silica gel eluting with 5% ethyl acetate in hexane gave 104 in quantitative yield.
(-)-trans-3-Pentyl-6,6a,7,8,10,10a-hexahydro-1-acetoxy-6,6-dimethyl-9H-
dibenzo-[b,d]-pyran-9-one (104):

$^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 6.58 (s, 1H), 6.41 (s, 1H), 3.28 (dt, $J = 14.7$, 2.7 Hz, 1H), 2.71 (td, $J = 11.6$, 3.3 Hz, 1H), 2.60-2.54 (m, 1H), 2.49 (t, $J = 7.8$ Hz, 2H), 2.45-2.36 (m, 1H), 2.32 (s, 3H), 2.29-2.11 (m, 3H), 1.95 (td, $J = 12.0$, 2.4 Hz, 1H), 1.60-1.49 (m, 2H), 1.47 (s, 3H), 1.36-1.25 (m, 4H), 1.11 (s, 3H), 0.88 (t, $J = 6.6$ Hz, 3H) ppm.

$^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 209.6, 169.0, 154.3, 149.3, 143.7, 115.4, 114.6, 114.0, 76.4, 47.5, 45.9, 40.6, 35.4, 34.9, 31.5, 30.4, 27.7, 26.7, 22.5, 21.2, 18.8, 14.0 ppm.

IR (neat): 2940, 2910, 2840, 1760, 1705, 1620, 1560, 1420, 1360, 1195, 1175 cm$^{-1}$.

Mass spectrum (70 ev, m/e): 358(M$^+$), 316(100%), 299, 260, 233, 206, 150, 69.

HRMS: for C$_{22}$H$_{30}$O$_4$ 358.2144, found 358.2113.
Procedure:

To a solution of ketone 104 (12 mg, 0.033 mmol) in dry CH$_2$Cl$_2$ under a static atmosphere of nitrogen was added methyl-DAST (0.04 mL, 0.330 mmol) and the mixture was stirred at ambient temperature. The progress of the reaction was monitored by tlc. Upon complete disappearance of the starting material (1-2 d), water was added and the reaction was stirred for a few minutes. The organic layer was separated and the aqueous layer was extracted with several portions of CH$_2$Cl$_2$. The combined organic extracts were washed once with distilled water and dried (MgSO$_4$). Evaporation of the solvent gave the crude product of 105 which was purified by flash column chromatography on silica gel eluting with 2-5% ethyl acetate in hexane. The yield of the reaction was 12 mg (96%).
9-Nor-9,9-bis-fluoro-hexahydrocannabinol acetate (105):

$^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 6.56 (s, 1H), 6.41 (s, 1H), 3.12-2.99 (m, 1H), 2.62 (t, $J = 11.4$ Hz, 1H), 2.50 (t, $J = 8.1$ Hz, 2H), 2.32 (s, 3H), 2.30-2.23 (m, 1H), 1.93-1.69 (m, 2H), 1.60-1.49 (m, 4H), 1.41 (s, 3H), 1.35-1.25 (m, 5H), 1.08 (s, 3H), 0.88 (t, $J = 6.6$ Hz, 3H) ppm.

$^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 168.8, 154.6, 149.5, 143.5, 123.1 (t, $J = 241.4$ Hz), 115.4, 114.5, 113.7, 76.9, 47.9, 38.6 (t, $J = 23.1$ Hz), 35.4, 34.1 (t, $J = 24.0$ Hz), 32.3 (d, $J = 11.1$ Hz), 31.5, 30.4, 27.6, 24.2 (d, $J = 11.1$ Hz), 22.5, 21.0, 18.9, 13.9 ppm.

$^{19}$F NMR (CDCl$_3$, 283 MHz): $\delta$ -91.1 (d, $J = 236.6$ Hz), -99.1 (dm, $J = 238.0$ Hz).
Procedure:

A stream of argon was bubbled through a solution of 105 (7 mg, 0.018 mmol) in methanol (5 mL) at 23 °C (15 min) followed by rapid addition of powdered potassium carbonate. The reaction mixture was stirred at ambient temperature for 15 min during which time tlc showed complete disappearance of starting material. The mixture was filtered into a separatory funnel with ether (20 mL), washed with 1N HCl (2x10 mL) and sat'd aqueous NaHCO₃ before drying over MgSO₄. Evaporation of the solvent in vacuo followed by purification by flash chromatography on silica gel with 5% ethyl acetate in hexane gave 5 mg (80% yield) of 106.
9-Nor-9,9-bisfluoro-hexahydrocannabinol (106):

$^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 6.26 (d, $J = 1.3$ Hz, 1H), 6.08 (d, $J = 1.3$ Hz, 1H), 4.73 (s, 1H, exchangeable with D$_2$O), 3.66-3.59 (m, 1H), 2.77 (tt, $J = 11.5$, 2.6 Hz, 1H), 2.43 (td, $J = 7.1$, 2.2 Hz, 2H), 2.20-2.23 (m, 1H), 1.92-1.87 (m, 1H), 1.81 (dtt, $J = 35.7$, 13.4, 4.9 Hz, 1H), 1.59-1.26 (series of multiplets, 9H), 1.41 (s, 3H), 1.10 (s, 3H), 0.88 (t, $J = 6.3$ Hz, 3H) ppm.

$^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 155.0, 154.4, 143.3, 123.6 (t, $J = 240.7$ Hz), 110.2, 108.0, 107.7, 76.6, 47.7, 37.9 (t, $J = 24.4$ Hz), 35.4, 34.3 (t, $J = 24.4$ Hz), 32.0 (d, $J = 10.4$ Hz), 31.5, 30.5, 27.8, 24.2 (d, $J = 10.5$ Hz), 22.5, 19.0, 13.9 ppm.

$^{19}$F NMR (CDCl$_3$, 283 MHz): $\delta$ -91.4 (d, $J = 238.1$ Hz), -99.8 (dm, $J = 247.7$ Hz) ppm.

IR (neat): 3390, 2950, 2920, 2870, 2850, 1620, 1575, 1425, 1365, 1090 cm$^{-1}$

Mass spectrum (70 ev, m/e): 338(M$^+$), 318, 295, 282(100%), 262, 235, 193.

HRMS: for C$_{20}$H$_{28}$F$_2$O$_2$ 338.2057, found 338.2063.
Procedure:

To a solution of LDA at 0 °C, prepared from 0.37 mL (2.60 mmol) of diisopropylamine, 2.43 mmol of n-butyllithium and 20 mL of THF, was added a solution of 400 mg (0.87 mmol) of 114 in 5 mL of THF. The solution was stirred at 0 °C for 45 min and treated with N-phenyltriflimide (930 mg, 2.60 mmol) in DME (4 mL). After stirring at 0 °C for 30 min, the reaction mixture was diluted with ether (15 mL) and washed with sat'd aqueous NaHCO₃, and extracted with ether. The organic layer was dried (MgSO₄) and concentrated to give crude 120, in which the ethoxyethyl groups were removed hydrolytically by treatment with catalytic PPTS in methanol at 23 °C. The crude diol 121 was purified by flash column chromatography on silica gel, eluting with 7% ethyl acetate in hexane. The overall yield of 121 from 114 was 57%. 

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4-[2,6-Dihydroxy-4(pentyl)phenyl]-5-isopropenyl-2-(((trifluoromethyl)sulfonyl)-oxy)-cyclohex-1-ene (121):

$^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 6.10 (s, 2H), 5.82 (br s, 1H), 4.74 (s, 1H), 4.62 (s, 2H, exchangeable with D$_2$O), 4.56 (s, 1H), 3.58 (td, J = 11.3, 5.4 Hz, 1H), 3.24 (td, J = 11.3, 5.4 Hz, 1H), 3.06 (br t, J = 12.6 Hz, 1H), 2.41 (dd, J = 8.1, 7.5 Hz, 2H), 2.34-2.17 (br m, 3H), 1.57 (s, 3H), 1.54-1.52 (m, 2H), 1.31-1.25 (m, 4H), 0.89 (dd, J = 6.9, 6.6 Hz, 3H) ppm.

$^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 154.7 (br s), 148.5, 146.9, 143.0, 117.7, 112.5, 111.6, 108.5, 43.1, 35.3, 34.4, 31.9, 31.5, 30.5, 29.9, 22.5, 18.3, 14.0 ppm.

IR (CCl$_4$): 3450, 2960, 2920, 2850, 1620, 1590, 1410, 1240, 1205, 1140, 1035 cm$^{-1}$.

Mass spectrum (70 ev, m/e): 448(M$^+$), 392, 299, 247, 231, 193(100%), 149, 109, 81.

HRMS: for C$_{21}$H$_{27}$F$_3$O$_5$S 448.1531, found 448.1522.
Procedure:

To a suspension of anhydrous lithium carbonate (0.22 mmol) and lithium chloride (1.56 mmol) in THF (5 mL) under a static nitrogen atmosphere, was added a solution of 121 (0.22 mmol) in THF (2 mL). The mixture was heated to a gentle reflux. After 30 min, hexamethyldistannane (0.22 mmol) in THF (2 mL) was added via cannula followed by catalytic tetrakis(triphenylphosphine)palladium(0) in THF (1 mL). The reaction mixture was heated at 60 °C for 12 h, during which time tlc indicated the complete consumption of starting material. The reaction was diluted with ether (20 mL), washed with sat'd aqueous NaHCO₃ and dried (Na₂SO₄). Solvent evaporation produced the crude product, which was purified by flash chromatography on silica gel eluting with ethyl acetate: hexane:triethyl amine (86:10:4 ratio) to give 122 (73% yield).
4-[2,6-Dihydroxy-4-(pentyl)phenyl]-5-isopropenyl-2-trimethylstannyl-cyclohex-1-ene (122):

$^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 6.13 (s, 2H), 5.93 (br s, 1H), 4.72 (s, 1H), 4.54 (s, 1H), 3.38 (td, J = 11.1, 5.1 Hz, 1H), 3.18 (td, J = 11.1, 5.1 Hz, 1H), 2.83-2.71 (m, 2H), 2.42 (dd, J = 8.1, 7.5 Hz, 2H), 2.34-2.13 (br m, 3H), 1.59 (s, 3H), 1.55-1.50 (m, 2H), 1.31-1.25 (m, 4H), 0.89 (dd, J = 6.9, 6.6 Hz, 3H), 0.08 (s, 9H) ppm.

$^{13}$C NMR (C$_6$D$_6$, 75 MHz): $\delta$ 149.1, 141.7, 140.6, 136.7, 115.3, 110.8, 108.5 (br s), 44.9, 36.8, 35.8, 35.7, 34.8, 31.9, 31.0, 22.9, 18.8, 14.2, −10.4 ppm.

IR (CCl$_4$): 3450, 2960, 2920, 2850, 1620, 1585, 1425 cm$^{-1}$. 

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Procedure:

To a solution of 122 (230 mg, 0.50 mmol) in CH$_2$Cl$_2$ at 0 °C was added pyridine (0.14 mL, 1.75 mmol), catalytic DMAP and acetic anhydride (0.14 mL, 1.50 mmol). The reaction mixture was stirred at 0 °C for 30 min and warmed to ambient temperature. The progress of the reaction was monitored by tlc for the disappearance of the starting material (4 h). The reaction was diluted with CH$_2$Cl$_2$, washed with brine, and dried (Na$_2$SO$_4$). Evaporation of the solvent and purification of the crude product by flash chromatography on silica gel eluting with ethyl acetate:hexane:triethylamine (86:10:4 ratio) gave 123 in 87% yield.
4-[4-Pentyl-2,6-bis(acetoxy)phenyl]-5-isopropenyl-2-trimethylstannyln-cyclohex-1-ene (123):

\[ \text{1H NMR (C}_6\text{H}_6, 300 MHz)}: \delta 6.98 (br s, 1H), 6.77 (br s, 1H), 5.98 (s, 1H), 4.95 (s, 1H), 4.73 (s, 1H), 3.38 (td, J = 10.5, 6.6 Hz, 1H), 3.21 (td, J = 10.5, 5.7 Hz, 1H), 2.74-2.66 (m, 2H), 2.42-2.31 (m, 2H), 2.28 (dd, J = 8.1, 7.2 Hz, 2H), 1.79 (br s, 6H), 1.69 (s, 3H), 1.39-1.32 (m, 2H), 1.12-1.08 (m, 4H), 0.77 (t, J = 6.3 Hz, 3H), 0.09 (s, 9H) ppm.

\[ \text{IR (CCL}_4\): 2960, 2920, 2840, 1765, 1195, 1175 \text{ cm}^{-1}.\]
Procedure:

To a suspension of silver carbonate (20 mg, 0.072 mmol) in CH2Cl2 (2.0 mL) under a static atmosphere of nitrogen at 22 °C was added triflic acid (trifluoromethanesulfonic acid, 16 mg, 1.5 equiv., ca. 8.7 mg/drop) and stirred for 30 min. The solution of vinyl stannane 123 (38 mg, 0.059 mmol) in CH2Cl2 (2.0 mL) and an equimolar amount of xenon difluoride (12 mg) in CH2Cl2 [115] (1.0 mL) was added in rapid succession via cannula using positive nitrogen pressure. The progress of the reaction was monitored by tlc for the complete disappearance of starting material (ca. 3 min). The reaction mixture was diluted with CH2Cl2 and washed with saturated aqueous NaHCO3. The organic layer was dried (MgSO4) and filtered through a short pad of silica gel. After solvent evaporation, the product was purified by flash chromatography on silica gel eluting with 2% ethyl acetate in hexane to give 57% yield (16 mg) of 124.
4-[2,6-Bis(acetoxy)-4(pentyl)phenyl]-5-isopropenyl-2-fluoro-cyclohex-1-ene (124):

$^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 6.78 (br s, 2H), 5.25 (td, $J = 16.5, 1.8$ Hz, 1H), 4.63 (s, 1H), 4.58 (s, 1H), 3.15 (td, $J = 11.4, 5.7$ Hz, 1H), 2.86 (td, $J = 11.1, 6.6$ Hz, 1H), 2.55 (dd, $J = 8.1, 7.5$ Hz, 2H), 2.52-2.45 (m, 1H), 2.33 (s, 6H), 2.31-2.24 (m, 1H), 2.14-2.12 (m, 2H), 1.63-1.58 (m, 2H), 1.52 (s, 3H), 1.33-1.25 (m, 4H), 0.88 (dd, $J = 6.9, 6.6$ Hz, 3H) ppm.

$^{19}$F NMR (CDCl$_3$, 283 MHz): $\delta$ -104.04 (m) ppm.

IR (CCl$_4$): 2920, 2850, 1770, 1370, 1200, 1180 cm$^{-1}$.

Mass spectrum (70 ev, m/e): 402($M^+$), 384, 360, 318, 263, 235, 193(100%).

HRMS: for C$_{24}$H$_{31}$FO$_4$ 402.2206, found 402.2202.
Procedure:

A stream of argon was bubbled through a solution of 124 (16 mg) in methanol (3 mL) at 23 °C followed by rapid addition of powdered potassium carbonate. The reaction mixture was stirred at ambient temperature for 15 min during which time tlc showed complete disappearance of starting material. The mixture was filtered into a separatory funnel with ether, washed with 1N HCl and sat'd aqueous NaHCO₃ before drying over MgSO₄. Evaporation of the solvent in vacuo followed by purification by flash chromatography on silica gel with 5% ethyl acetate in hexane gave 10 mg of 125 in quantitative yield.
4-[2,6-Dihydroxy-4(pentyl)phenyl]-5-isopropenyl-2-fluoro-cyclohex-1-ene (125):

$^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 6.11 (s, 2H), 5.25 (dd, $J = 16.5, 5.4$ Hz, 1H), 4.73 (s, 1H), 4.62 (s, 2H, exchangeable with D$_2$O), 4.54 (s, 1H), 3.52 (td, $J = 11.7, 5.7$ Hz, 1H), 3.18 (td, $J = 11.1, 5.1$ Hz, 1H), 2.89 (br t, $J = 14.4$ Hz, 1H), 2.42 (dd, $J = 8.1, 7.5$ Hz, 2H), 2.28-2.05 (br m, 3H), 1.57 (s, 3H), 1.55-1.51 (m, 2H), 1.31-1.26 (m, 4H), 0.89 (dd, $J = 6.9, 6.0$ Hz, 3H) ppm.

IR (CCl$_4$): 3420, 2960, 2920, 2840, 1620, 1580, 1430, 1120 cm$^{-1}$.

Mass spectrum (70 ev, m/e): 319, 318, 300, 263, 231(100%), 199.

HRMS: for C$_{20}$H$_{27}$F$_2$O$_2$ 318.1995, found 318.2005.
Procedure:

To a suspension of anhydrous lithium carbonate (5 mg, 0.07 mmol) and lithium chloride (20 mg, 0.49 mmol) in THF (5 mL) under a static nitrogen atmosphere, was added a solution of 69 (30 mg, 0.07 mmol in THF (5 mL). The mixture was heated to a gentle reflux. After 30 min, a solution of hexamethyldistannane (23 mg, 0.07 mmol) in THF (1 mL) was added via cannula followed by catalytic tetrakis(triphenylphosphine)palladium(0) in THF (1 mL). The reaction mixture was heated at 60 °C for 6 h, during which time tlc indicated the complete consumption of starting material. The reaction was diluted with ether (5 mL), washed with sat'd aqueous NaHCO₃ and dried (Na₂SO₄). Solvent evaporation produced the crude product, which was purified by flash chromatography on silica gel eluting with ethyl acetate:hexane:triethylamine (86:10:4) to give 126 78% (25 mg) yield.
1-Hydroxy-6a,7,10,10a-tetrahydro-6,6-dimethyl-9-trimethylstannyl-6H-dibenzo[b,d]-pyran (126):

$^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 6.27 (s, 1H), 6.10 (s, 1H), 5.87 (br s, 1H), 4.67 (s, 1H, exchangeable with D$_2$O), 3.50 (br d, $J = 16.2$ Hz, 1H), 2.70 (td, $J = 10.5$, 4.2 Hz, 1H), 2.43 (dd, $J = 8.1$, 6.9 Hz, 2H), 2.26-2.20 (m, 1H), 2.06-1.81 (br m, 3H), 1.58-1.52 (m, 2H), 1.36 (s, 3H), 1.32-1.25 (m, 4H), 1.09 (s, 3H), 0.88 (t, $J = 6.9$ Hz, 3H), 0.10 (s, 9H) ppm.
Procedure:

To a solution of cyclized ketone 126 (115 mg, 0.25 mmol) in CH₂Cl₂ at 0 °C was added pyridine (0.14 mL, 0.85 mmol), catalytic DMAP and acetic anhydride (0.06 mL, 0.75 mmol). The reaction mixture was stirred at 0 °C for 30 min and warmed to ambient temperature. The progress of the reaction was monitored by tlc for the disappearance of the starting material. The reaction was diluted with CH₂Cl₂, washed with brine, and dried (Na₂SO₄). Evaporation of the solvent and purification of the crude product by flash chromatography on silica gel with ethyl acetate:hexane:triethylamine (86:10:4 ratio) gave 127 in 80% yield.
1-Acetoxy-6a,7,10,10a-tetrahydro-6,6-dimethyl-9-trimethylstannyl-6H-bibenzo[b,d]-pyran (127):

$^1$H NMR (C$_6$D$_6$, 300 MHz): $\delta$ 6.87 (d, $J = 1.5$ Hz, 1H), 6.58 (d, $J = 1.5$ Hz, 1H), 5.78 (s, 1H), 3.25 (dd, $J = 17.1$, 2.1 Hz, 1H), 2.76 (td, $J = 10.8$, 4.5 Hz, 1H), 2.39 (dd, $J = 7.9$, 7.5 Hz, 2H), 2.14-2.03 (m, 1H), 1.93 (s, 3H), 1.86-1.76 (m, 2H), 1.65-1.60 (m, 1H), 1.53-1.43 (m, 2H), 1.25 (s, 3H), 1.19-1.14 (m, 4H), 1.03 (s, 3H), 0.79 (t, $J = 6.9$ Hz, 3H), 0.15 (s, 9H) ppm.

$^{13}$C NMR (C$_6$D$_6$, 75 MHz): $\delta$ 168.0, 155.4, 150.7, 143.0, 140.3, 135.5, 116.7, 115.8, 114.9, 76.4, 45.2, 37.3, 35.7, 33.0, 31.7, 31.0, 30.4, 27.4, 22.8, 20.8, 18.5, 14.2, -10.5 ppm.

IR (C$_6$D$_6$): 2950, 2920, 2850, 1765, 1620, 1565, 1420, 1365, 1200, 1175 cm$^{-1}$. 
Procedure:

To a suspension of silver carbonate (0.042 mmol) in CH$_2$Cl$_2$ (1 mL) under a static atmosphere of nitrogen at 22 °C was added trifluoromethanesulfonic acid (0.059 mmol) and stirred for 30 min.$^{114}$ The solution of vinyl stannane 127 (0.039 mmol) in CH$_2$Cl$_2$ (1.5 mL) and an equimolar amount of xenon difluoride in CH$_2$Cl$_2$$^{115}$ (1.0 mL) was added in rapid succession via cannula using positive nitrogen pressure. The progress of the reaction was monitored by tlc for the complete disappearance of starting material (ca. 3 min). The reaction mixture was diluted with CH$_2$Cl$_2$ and washed with sat’d aqueous NaHCO$_3$. The organic layer was dried (MgSO$_4$) and filtered through a short pad of silica gel. After solvent evaporation, the products were purified by flash chromatography on silica gel eluting with 2% ethyl acetate in hexane gave a mixture of 107 and alkene (5:1 ratio based on $^1$H NMR integration of the vinylic protons). The hydrolysis of the ester group in 107 according to the procedure described for the preparation of 125 followed by purification using flash chromatography on silica gel eluting with 5% ethyl acetate in hexane gave 128 contaminated with a small amount of alkene (17:1).
1-Hydroxy-6\textsubscript{a},7,10,10\textsubscript{a}-tetrahydro-6,6-dimethyl-9-fluoro-6\textsubscript{H}-dibenzo[\textit{b,d}]pyran (128):

\textsuperscript{1}\text{H} NMR (CDCl\textsubscript{3}, 500 MHz): \textit{\delta} 6.28 (d, \textit{J} = 1.3 Hz, 1H), 6.09 (d, \textit{J} = 1.6 Hz, 1H), 5.23 (ddt, \textit{J} = 16.1, 5.7, 2.0 Hz, 1H), 4.69 (s, 1H, exchangeable with D\textsubscript{2}O), 3.50 (ddddd, \textit{J} = 16.7, 8.1, 4.8, 1.6 Hz, 1H), 2.83 (td, \textit{J} = 11.3, 5.2 Hz, 1H), 2.44 (td, \textit{J} = 7.5, 3.2, 2H), 2.22-2.17 (m, 1H), 2.12-2.05 (m, 1H), 1.90-1.85 (m, 1H), 1.80 (td, \textit{J} = 11.5, 3.9 Hz, 1H), 1.59-1.53 (m, 2H), 1.40 (s, 3H), 1.34-1.25 (m, 4H), 1.12 (s, 3H), 0.88 (t, \textit{J} = 7.0 Hz, 3H) ppm.

\textsuperscript{13}\text{C} NMR (CDCl\textsubscript{3}, 125 MHz): \textit{\delta} 159.5 (d, \textit{J} = 255.3 Hz), 154.4, 154.2, 142.9, 109.7, 108.8, 107.2, 99.7 (d, \textit{J} = 16.7 Hz), 76.1, 43.9, 35.0, 31.1, 31.0, 30.9 (d, \textit{J} = 16.7 Hz), 30.2, 27.3, 24.1 (d, \textit{J} = 9.7 Hz), 22.2, 18.1, 13.6 ppm.

\textsuperscript{19}\text{F} NMR (CDCl\textsubscript{3}, 283 MHz): \textit{\delta} -103.1 (m).

IR (neat): 3399, 2957, 2930, 2871, 2856, 1706, 1625, 1580, 1427, 1366, 1257, 1185, 1132, 1129, 1081, 1007, 811 cm\textsuperscript{-1}.

Mass spectrum (70 ev, m/e): 319, 318(M\textsuperscript{+}, 100%), 275, 262, 246, 231, 193.

HRMS: for C\textsubscript{20}H\textsubscript{27}F\textsubscript{2}O\textsubscript{2} 318.1995, found 318.1982.
Correlation of $^1$H and $^{13}$C Resonances, from HMQC Experiment

<table>
<thead>
<tr>
<th>$^{13}$C NMR(δ)</th>
<th>Assignment</th>
<th>$^1$H NMR(δ)</th>
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<tr>
<td>159.5</td>
<td>C9</td>
<td>–</td>
</tr>
<tr>
<td>154.4</td>
<td>Cl</td>
<td>–</td>
</tr>
<tr>
<td>154.2</td>
<td>C4a</td>
<td>–</td>
</tr>
<tr>
<td>142.9</td>
<td>C3</td>
<td>–</td>
</tr>
<tr>
<td>109.7</td>
<td>C4 or C2</td>
<td>6.28 (d, 1H)</td>
</tr>
<tr>
<td>108.8</td>
<td>C10b</td>
<td>–</td>
</tr>
<tr>
<td>107.2</td>
<td>C4 or C2</td>
<td>6.09 (d, 1H)</td>
</tr>
<tr>
<td>99.7</td>
<td>C8</td>
<td>5.23 (ddt, 1H)</td>
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<tr>
<td>76.1</td>
<td>C6</td>
<td>–</td>
</tr>
<tr>
<td>43.9</td>
<td>C6a</td>
<td>1.80 (td, 1H)</td>
</tr>
<tr>
<td>35.0</td>
<td>C1'</td>
<td>2.44 (td, 2H)</td>
</tr>
<tr>
<td>31.1</td>
<td>C3'</td>
<td>1.34-1.25 (m, 2H)</td>
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Correlation of $^1$H and $^{13}$C Resonances, from HMOC Experiment (Cont'd)

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<th>$^{13}$C NMR ($\delta$)</th>
<th>Assignment</th>
<th>$^1$H NMR ($\delta$)</th>
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<tr>
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<td>2.83 (td, 1H)</td>
</tr>
<tr>
<td>30.9</td>
<td>C10</td>
<td>3.50 (dddd, 1H)</td>
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<td>2.12-2.05 (m, 1H)</td>
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<tr>
<td>30.2</td>
<td>C2'</td>
<td>1.59-1.53 (m, 2H)</td>
</tr>
<tr>
<td>27.3</td>
<td>C12 or C13</td>
<td>1.40 (s, 3H)</td>
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<tr>
<td>24.1</td>
<td>C7</td>
<td>2.22-2.17 (m, 1H)</td>
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<td>1.90-1.85 (m, 1H)</td>
</tr>
<tr>
<td>22.2</td>
<td>C4'</td>
<td>1.34-1.25 (m, 2H)</td>
</tr>
<tr>
<td>18.1</td>
<td>C12 or C13</td>
<td>1.12 (s, 3H)</td>
</tr>
<tr>
<td>13.6</td>
<td>C5'</td>
<td>0.88 (t, 3H)</td>
</tr>
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</table>
Procedure:

To a solution of ketone 104 (0.06 mmol) in THF and isopropanol (9:1) at ambient temperature under a static atmosphere of nitrogen was added sodium borohydride (1.05 mmol) portionwise and the mixture was stirred for 10 min, during which time tlc indicated the complete consumption of starting material. The reaction was quenched with water, acidified carefully with 1N HCl and extracted with ether. The combined ether extracts were washed once with 1N HCl, sat'd aqueous NaHCO₃, and brine and dried (MgSO₄). Evaporation of the solvent gave the crude alcohol which was purified by flash chromatography on silica gel eluting with 20% ethyl acetate in hexane to give the alcohol 109 as a single isomer (9β-hydroxy isomer).
9-Nor-9β-hydroxy-hexahydrocannabinol acetate (109):

$^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 6.55 (s, 1H), 6.38 (s, 1H), 3.74 (tt, $J = 11.4, 4.2$ Hz, 1H), 2.90 (br d, $J = 12.3$, 1H), 2.49 (t, $J = 7.8$ Hz, 2H), 2.37 (td, $J = 11.7, 2.4$ Hz, 1H), 2.30 (s, 3H), 2.16 (br d, $J = 9.9$ Hz, 1H), 1.88 (dd, $J = 12.6, 3.0$ Hz, 1H), 1.62-1.42 (m, 5H), 1.38 (s, 3H), 1.35-1.09 (m, 6H), 1.06 (s, 3H), 0.88 (t, $J = 6.6$ Hz, 3H) ppm.

IR (neat): 3388, 2932, 2871, 2860, 1767, 1626, 1426, 1371, 1208, 1184, 1136, 1052, 1038 cm$^{-1}$.

Mass spectrum (70 ev, m/e): 360(M$^+$), 342, 319, 318(100%), 300, 262, 257, 193.

HRMS: for C$_{22}$H$_{32}$O$_4$ 360.2300, found 360.2304.
To the solution of 109 (0.05 mmol) in CH₂Cl₂ (3 mL) under a static atmosphere of nitrogen at -78 °C was added methyl-DAST (5.10 mmol) and was stirred at -78 °C. The reaction was monitored by tlc. Upon completion of the reaction (ca. 4h), water was added and reaction mixture was warmed to 23 °C. The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂. The combined organic extracts were washed once with distilled water and dried (MgSO₄). Evaporation of the solvent followed by purification by flash chromatography on silica gel eluting with 5% ethyl acetate in hexane gave 2:1 mixture of 110 (42% yield) and elimination product 111 (21% yield).
9-Nor-9α-fluoro-hexahydrocannabinol acetate (110):

$^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 6.55 (d, $J = 1.5$ Hz, 1H), 6.39 (d, $J = 1.5$ Hz, 1H), 4.95 (d, $J = 46.5$ Hz, 1H), 3.04-2.94 (m, 1H), 2.79-2.71 (m, 1H), 2.49 (t, $J = 7.5$ Hz, 2H), 2.30 (s, 3H), 2.23-2.14 (m, 1H), 1.74-1.66 (m, 1H), 1.64-1.41 (m, 5H), 1.39 (s, 3H), 1.32-1.27 (m, 5H), 1.09 (s, 3H), 0.88 (t, $J = 6.6$ Hz, 3H) ppm.

$^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 169.2, 154.8, 149.5, 143.0, 115.3, 115.1, 114.3, 89.0 (d, $J = 168.4$ Hz), 77.2, 48.6, 35.7 (d, $J = 19.7$ Hz), 35.4, 31.5, 31.2 (d, $J = 21.1$ Hz), 30.4, 29.7, 27.3, 22.9, 22.5, 21.0, 18.9, 14.0 ppm.

$^{19}$F NMR (CDCl$_3$, 283 MHz): $\delta$ -181.4 (br q, $J = 44.2$ Hz) ppm.

IR (neat): 2932, 2872, 2858, 1769, 1568, 1427, 1367, 1206 cm$^{-1}$.

Mass spectrum (70 ev, m/e): 362(M$^+$), 343, 342, 321, 320, 300(100%), 283, 257, 244, 231.

HRMS: for C$_{22}$H$_{31}$FO$_3$ 362.2257, found 362.2197.
9-Nor-9α-fluoro-hexahydrocannabinol (112):

Hydrolysis of the ester group was carried out according to the procedure described for 124.

$^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 6.26 (s, 1H), 6.08 (s, 1H), 4.98 (br d, $J$ = 47.4 Hz, 1H), 4.70 (s, 1H, exchangeable with D$_2$O), 3.55-3.45 (m, 1H), 2.91 (td, $J$ = 10.9, 2.7 Hz, 1H), 2.43 (t, $J$ = 7.2 Hz, 2H), 2.24-2.16 (m, 1H), 1.74-1.69 (m, 1H), 1.61-1.51 (m, 4H), 1.39 (s, 3H), 1.32-1.26 (m, 6H), 1.10 (s, 3H), 0.88 (t, $J$ = 6.6 Hz, 3H) ppm.

$^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 155.2, 154.5, 142.8, 110.2, 109.3, 107.7, 89.4 (d, $J$ = 167.3 Hz), 76.6, 48.6, 35.4, 35.2 (d, $J$ = 21.1 Hz), 31.5, 31.4 (d, $J$ = 22.6 Hz), 30.4, 29.4, 27.5, 22.8, 22.4, 19.0, 13.9 ppm.

$^{19}$F NMR (CDCl$_3$, 283 MHz): $\delta$ -180.7 (qt, $J$ = 46.6, 11.3 Hz) ppm.

IR (neat): 3532, 3410, 2932, 2858, 1624, 1578, 1427, 1133, 1039 cm$^{-1}$.

Mass spectrum (70 ev, m/e): 320(M$^+$), 300, 281(100%), 257, 244, 231.

HRMS: for C$_{20}$H$_{29}$FO$_2$ 320.2151, found 320.2184.
3-[4-Pentyl-2,6-bis(acetoxy)phenyl]-4-isopropenyl-1β-hydroxy-cyclohexane (117):

Reduction of the ketone in 116 was carried out according to the procedure described for 104.

$^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 6.79 (s, 1H), 6.69 (s, 1H), 4.58-4.47 (m, 2H), 3.68-3.58 (m, 1H), 2.80 (td, $J = 11.9$, 3.0 Hz, 1H), 2.61-2.41 (m, 1H), 2.53 (t, $J = 8.4$ Hz, 2H), 2.34 (s, 3H), 2.30 (s, 3H), 2.11-1.96 (m, 2H), 1.83-1.25 (m, 11H), 1.51 (s, 3H), 0.88 (t, $J = 6.6$ Hz, 3H) ppm.

IR (neat): 3489, 3348, 2954, 2932, 2859, 1770, 1645, 1624, 1573, 1450, 1370, 1201, 1180, 1029, 888 cm$^{-1}$.

Mass spectrum (70 ev, m/e): 402 (M$^+$), 384, 360, 342, 318, 300, 261, 219, 193, 150, 118, 83 (100%).

HRMS: for C$_{24}$H$_{34}$O$_5$ 402.2407, found 402.2384.
Alcohol 117, when subjected to the same conditions employed for the synthesis of 110, afforded 118 in poor yield (9%) along with an approximately equivalent amount of alkene.

\[ \begin{align*}
1^1H \text{ NMR (CDCl}_3, 500 MHz): & \delta 6.78 (br s, 1H), 6.71 (br s, 1H), 4.90 (br d, J = 48.7 Hz, 1H), 4.58 (s, 1H), 4.53 (m, 1H), 3.25 (td, J = 12.3, 3.6 Hz, 1H), 2.65 (tm, J = 11.8 Hz, 1H), 2.54 (t, J = 8.7 Hz, 2H), 2.33 (s, 6H), 2.17-2.12 (m, 1H), 2.08-2.02 (m, 1H), 1.87-1.72 (m, 2H), 1.64-1.57 (m, 3H), 1.56 (s, 3H), 1.31-1.25 (m, 5H), 0.88 (t, J = 6.5 Hz, 3H) ppm. \\
1^3C \text{ NMR (CDCl}_3, 125 MHz): & \delta 169.4, 168.5, 149.7, 149.2, 147.4, 142.2, 124.7, 121.0, 119.7, 111.1, 88.6 (d, J = 169. Hz), 48.0, 35.4 (d, J = 23.8 Hz), 35.2, 33.1, 31.5, 31.0 (d, J = 20.6 Hz), 30.2, 26.9, 22.5, 20.8, 19.0, 14.0 ppm. \\
1^9F \text{ NMR (CDCl}_3, 283 MHz): & \delta -186.1 (qt, J = 47.8, 9.6 Hz) ppm. \\
IR (neat): & 3075, 2952, 2930, 2856, 1771, 1646, 1625, 1574, 1457, 1440, 1429, 1368, 1199, 1181, 1033 \text{ cm}^{-1}. \\
Mass \text{ spectrum (70 ev, m/e):} & 404(M^+), 384, 362, 342, 341, 320, 299, 277. \\
HRMS: & \text{for C}_{24}\text{H}_{33}\text{FO}_4 \text{ 404.2363, found 404.2380.}
\end{align*} \]
Procedure:

To a solution of vinyl stannane 122 in CH₂Cl₂ (5 mL) under a static nitrogen atmosphere at 0 °C was added a dilute solution of iodine in CH₂Cl₂ dropwise with vigorous stirring until a permanent light pink color remained in the reaction mixture. The reaction mixture was diluted with CH₂Cl₂ and washed with sat'd aqueous NaHCO₃ followed by brine and dried (Na₂SO₄). Solvent evaporation produced the crude product, which was purified by flash chromatography on silica gel eluting with 2% ethyl acetate in hexane to give 129 in 78% yield.
4-[2,6-Dihydroxy-4-(pentyl)phenyl]-5-isopropenyl-2-iodo-cyclohex-1-ene (129):

$^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 6.37 (br s, 1H), 6.09 (s, 2H), 4.72 (s, 1H), 4.64 (s, 2H, exchangeable with D$_2$O), 4.54 (s, 1H), 3.58 (td, $J = 11.1$, 5.1 Hz, 1H), 3.26 (td, $J = 11.1$, 5.1 Hz, 1H), 3.14 (m, 1H), 2.61 (dd, $J = 17.1$, 4.2 Hz, 1H), 2.40 (dd, $J = 8.1$, 7.5 Hz, 2H), 2.34-2.24 (m, 1H), 2.17-2.05 (m, 1H), 1.57 (s, 3H), 1.56-1.51 (m, 2H, partially obscured by the peak at 1.57 ppm), 1.30-1.26 (m, 4H), 0.88 (dd, $J = 6.9$, 6.3 Hz, 3H) ppm.

$^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 155.0, 147.9, 142.7, 136.8, 122.9, 113.3, 111.1, 108.6, 95.7, 43.9, 42.9, 36.9, 35.5, 35.3, 31.5, 30.5, 22.5, 18.4, 14.0 ppm.

IR (CCl$_4$): 3450, 2950, 2920, 2840, 1620, 1580, 1420 cm$^{-1}$.

Mass spectrum (70 ev, m/e): 426(M$^+$), 370, 299, 231, 193, 71, 69(100%).

HRMS: for C$_{20}$H$_{27}$I0$_2$ 426.1056, found 426.1025.
Iodination of 126 was carried out according to the procedure described for 122 to give 130 in 83% yield.

$^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 6.36 (br s, 1H), 6.26 (s, 1H), 6.09 (s, 1H), 4.79 (s, 1H, exchangeable with D$_2$O), 3.87 (td, $J$ = 17.7, 4.2 Hz, 1H), 2.89 (td, $J$ = 10.8, 4.5 Hz, 1H), 2.43 (dd, $J$ = 8.4, 6.9 Hz, 2H), 2.36-2.28 (m, 1H), 2.27-2.16 (m, 1H), 1.99-1.72 (m, 2H), 1.57-1.53 (m, 2H), 1.36 (s, 3H), 1.31-1.28 (m, 4H), 1.09 (s, 3H), 0.88 (dd, $J$ = 6.0, 6.9 Hz, 3H) ppm.

IR (CCl$_4$): 3390, 2950, 2920, 2850, 1620, 1570, 1425 cm$^{-1}$.

Mass spectrum (70 ev, m/e): 426(M$^+$), 370, 300, 231, 169, 111, 69(100%).

HRMS: for C$_{20}$H$_{27}$IO$_2$ 426.1056, found 426.1040.
APPENDIX 1: SPECTRA FOR SELECTED COMPOUNDS IN PART I

$^1$H NMR Spectrum/CDCl$_3$

$^{13}$C NMR spectrum/CDCl$_3$
$^1$H NMR Spectrum/CDCl$_3$

Infra-red spectrum
$^1$H NMR Spectrum/CDCl$_3$
$^{1}\text{H NMR Spectrum/CDCl}_3$

$^{13}\text{C NMR spectrum/CDCl}_3$
$^{1}H$ NMR Spectrum/CDCl$_3$

$^{13}C$ NMR spectrum/CDCl$_3$
$\text{H NMR Spectrum/CDCl}_3$

$\text{C NMR spectrum/CDCl}_3$
$\text{\textsuperscript{1}H NMR Spectrum/CDCl}_3$

$\text{\textsuperscript{13}C NMR spectrum/CDCl}_3$
Infra-red spectrum
$^1$H NMR Spectrum/CDCl$_3$

$^{13}$C NMR spectrum/CDCl$_3$
$^{1}H$ NMR Spectrum/CDCl$_3$

Infra-red spectrum
$^1H$ NMR Spectrum/C$_6$D$_6$

$^1H$ NMR Spectrum/CDCl$_3$
$^{13}$C NMR spectrum/$\text{C}_6\text{D}_6$

$^{13}$C NMR spectrum/$\text{CDCl}_3$
QSOP3

![Chemical Structure](image)

$^1$H NMR Spectrum/CDCl$_3$

![1H NMR Spectrum](image)

$^{13}$C NMR spectrum/CDCl$_3$

![13C NMR Spectrum](image)
Infra-red spectrum

Mass spectrum

RT0: 16-48 x 1 8gd = 5 13-06-89 14:40-0:12.43 79-SE E1-
BpR=1 I=1.2 Savg Hm=0 TIC=14902000
KAM=0 H=4-11 C21H27O5SFS 448
100 69 211
382 448

100 169 133 283
10. 150 200 250 300 350 400 450
50 100 150 200 250 300 350 400 450
M ASS
$^1$H NMR Spectrum/CDCl$_3$

$^{13}$C NMR spectrum/CDCl$_3$
$^{1}$H NMR Spectrum/CDCl$_3$

$^{13}$C NMR spectrum/CDCl$_3$
Mass spectrum

Infra-red spectrum
$^{1}H$ NMR spectrum/CDCl$_3$

$^{13}C$ NMR spectrum/CDCl$_3$
$\text{Br}$

$\text{Br}$

$\text{Br}$

$\text{Br}$

1H NMR Spectrum/CDCl₃

$\text{Br}$

$\text{Br}$

$\text{Br}$

$\text{Br}$

13C NMR spectrum/CDCl₃
Mass spectrum

Infra-red spectrum

Chemical Structure:

- Molecular Weight: 286
- Formula: 

Mass Spectrum Details:

- Mass Spectrum Number: 12-SEP-91 16:24·0:02:47
- System: E1-
- Sample: MUB800
- Cal: PFK860
- Mass Range: 80-300
- Peaks:
  - 83
  - 95
  - 110
  - 136
  - 173
  - 215

Wavenumber (cm⁻¹):

- TIC: 22193008
- Acquisition Time: 0.0847545024

202
76

$^1\text{H NMR Spectrum/CDCl}_3$

$^{13}\text{C NMR spectrum/CDCl}_3$
$^{1}H$ NMR spectrum/CDCl$_3$

$^{13}C$ NMR spectrum/CDCl$_3$
Mass spectrum

Infra-red spectrum
HMOCQ Experiment
CSCM experiment

78
$^{1}H$ NMR spectrum/CDCl$_3$

$^{13}C$ NMR spectrum/CDCl$_3$
n.O.e
HMOC Experiment
HMBC Experiment
$^{1}$H NMR spectrum/CDCl$_3$

$^{13}$C NMR spectrum/CDCl$_3$
\[ \text{IH NMR spectrum/CDCl}_3 \]

\[ \text{13C NMR spectrum/CDCl}_3 \]
HMOCQ Experiment
HMBC Experiment
$^1\text{H NMR spectrum/CDCl}_3$

$^{13}\text{C NMR spectrum/CDCl}_3$
HMBC Experiment
$^{1}$H NMR spectrum/CDCl$_3$
1H NMR spectrum / C₆D₆

13C NMR spectrum / CDCl₃
Infra-red spectrum

Mass spectrum
n.O.e
1H NMR spectrum/CDCl₃

13C NMR spectrum/CDCl₃
$^{1}H$ NMR spectrum/CDCl$_3$

$^{13}C$ NMR spectrum/CDCl$_3$
Mass spectrum

104

Mass spectrum

Infra-red spectrum

TRANSMISSION (%)
$^{1}H$ NMR spectrum/CDCl$_3$

$^{13}C$ NMR spectrum/CDCl$_3$
$\text{1H NMR spectrum/CDCl}_3$

Infra-red spectrum
Mass spectrum

EI+ 350 ~ 0 29 10

Bod=29 TIC=24732088

P1 = 8°
1H NMR spectrum/CDCl₃

13C NMR spectrum/CDCl₃
$^{1}H$ NMR spectrum/CDCl$_3$

Mass spectrum

MT0518247  x1  Bgd=4  10-MAY-91  16:34+0:02:33  70-SE
Bp=0  I=11mvs  Ha=0  TIC=165705000  Rent:  
MK-20-89 C20H29F02 320  PT= 0°
Infra-red spectrum

13C NMR spectrum/CDCl₃
$^{19}F$ NMR spectrum
$^{1}H$ NMR spectrum/CDCl$_3$

$^{13}$C NMR spectrum/CDCl$_3$
1H NMR spectrum/CDCl₃

13C NMR spectrum/CDCl₃
$^1$H NMR spectrum/CDCl$_3$

Infra-red spectrum
Mass spectrum

MT05211#22  x1  Bgd=13  21-MAY-91  15:06-0:06:18  70-SE  EI+
Bpm=0  I=102mv  Hm=0  TIC=662060992
KERR MK2891  402  C24H34O5 (REALLY)

PT= 0°
$^1$H NMR spectrum/CDCl$_3$

$^{13}$C NMR spectrum/CDCl$_3$
ACYCLIC MONOFUORIDE

Infra-red spectrum

Mass spectrum

Mass spectrum data:
- Date: 28-MAY-91
- Time: 18:17+0:04:46
- Instrument: 70-SE EI+
- Sample: KERR MK-20-87C2H34O6 402
- Conditions: Bp=8, I=11mv, Hm=0
- TIC=41879816
- Retention time: 70-SE EI+
- PT= 0°
Infra-red spectrum

Mass spectrum

MT05214411 x1 Dpd=6 21-MAY-91 16:24+0:04:03 70-SE EI-
Dpd=8 I=2.2ms Ha=0 TIC=3847088 Rent:
KAMARI KK-VII-95 C21H27O5F3 448
193 231
160 90 60 40 30 20 10
162 168 180 200 250 300 350 400 450
MASS

259
HMBC Experiment
Infra-red spectrum

![Infra-red spectrum](image)
$^{1}H$ NMR spectrum/CDCl$_3$

Infra-red spectrum
$^{1}H$ NMR spectrum/CDCl$_3$

Infra-red spectrum
Mss spectrum

![Mss spectrum diagram]

BP=80, I=12, Ha=0, TIC=82063000, Acet.: 1:5:0:0.6:0.8, EI+++ Sys: MAB750

KK: 150-30 C22H27O2F 310

189156888

186 183 119 169 149 169 203 300

MSS

186 183 119 169 149 169 203 300
$^{1}H$ NMR spectrum/CD$_6$

$^{13}C$ NMR spectrum/CD$_6$
$^{1}$H NMR spectrum/CDCl$_3$

$^{13}$C NMR spectrum/CDCl$_3$
Infra-red spectrum

Mass spectrum

269
1H NMR spectrum/CDCl₃

13C NMR spectrum/CDCl₃
$^1$H NMR spectrum/CDCl$_3$

Mass spectrum
Infra-red spectrum
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8. Todd, A. R. Experientia, 1946, 2, 55.


274


(c) Also see references 11 and 13.


(d) Harvey, D. J.; Samara, E.; Mechoulam, R. *J. Chromatogr.* 1991, 562, 299.


280


(b) Jones, S. E.; Durant, J. R.; Greco, A.; Roberstone, A. *Cancer Treat. Rev.* 1982, 9, 45.
(c) Levitt, M. *Cancer Treat. Rev.* 1982, 9, 49.


71. The solution of the cuprate was prepared according to Lipshutz's procedure: Lipshutz, B. H.; Koerner, M.; Parker, D. A. *Tetrahedron Lett.* 1987, 28, 945.


    (b) Nomura, M; Fujihara, Y. *Nippon Kagaku Kaishi*, 1985, 990.


94. A sample of 5'-{(2H3)olivetol dimethyl ether prepared previously according to the published procedure (Girard, M.; Moir, D. B.; ApSimon, J. W. *Can. J. Chem.* 1987, 65, 189) was used in this project.
98. Alkylation of α-bromo ketones and α,α'-dibromo ketones by treatment with lithium dialkylcuprate followed by trapping of the enolate with an alkyl halide had been reported.


104. (a) Hollister, L. E. Pharmacology, 1974, 11, 3.
(b) Wilson, R. S. J. Med. Chem. 1979, 22, 879.
(c) Watanabe, K.; Yamamoto, I.; Oguri, K.; Nishikami, J.; Yamamoto, I.; Yoshimura, H. European J. Pharmcol. 1980, 63, 1


109. The majority of the nonfluorination side reactions are dehydrations to olefins. These accompany conversion of alcohols into fluorides and may become the only reaction in certain hydroxy compounds.


111. (a) Tius, M. A.; Kawakami, J. K. Synthetic Commun. 1992, 22(10), 1461.
   See also, Hodson, H. F.; Madge, D. J.; Widdowson, D. A. Synlett, 1992, 831.


113. The conditions for the fluorination have been improved by Joel K. Kawakami and will be published in the near future.

114. The flask was covered with aluminum foil to prevent decomposition of silver carbonate and silver triflate.

115. Xenon difluoride was weighed in a glove box, and dissolved in CH2Cl2 using sonication.


119. We thank Dr. Xue-qin Gu for providing a sample of (+)-11-nor-Δ⁹-THC-9-carboxylic acid (131) which had been prepared according to the published procedure (reference 59) using (S)-(−)-perillaldehyde.

120. A similar rotational non-equivalence of carbon resonances as a function of the temperature has been reported earlier for the ¹³C nmr of cannabidiol. Kane, V. V.; Martin, A. R.; Jaime, C.; Osawa, E. Tetrahedron, 1984, 40, 2919.
INTRODUCTION

The classical approach to the synthesis of functionalized aromatic compounds has been to start with a commercially available, cheap aromatic hydrocarbon(s) and make use of traditional substitution reactions to introduce appendages and functionality. This strategy has served well, but it is limiting for multistep organic synthesis because it normally requires that the aromatic substitutions (nucleophilic and/or electrophilic) be carried out at the very beginning of a sequence. Further, these substitution strategies generally require protecting/deprotecting sequences which result in diminution of overall yield. The formation of aromatic rings from non-aromatic precursors, aromatic annelation, is therefore an important objective in organic synthesis. The use of annelation procedures has advantages, such as the synthesis of highly substituted aromatic rings in relatively few steps and the formation of compounds with substitution patterns not easily accessible through conventional routes. Also, the greater availability of labeled acyclic precursors would provide easy access to labeled aromatic compounds.

General methods for the preparation of phenols, pyridines and substituted benzene rings from non-aromatic precursors have been reported. The two most commonly employed methods for the construction of six-membered rings, the Robinson annelation and the Diels-Alder reaction, involve the union of a two-carbon unit with a four-carbon fragment. Another approach involving the condensation of two three-carbon units, one with two nucleophilic sites and the other containing two electrophilic sites has been reported. The regiochemistry of the reaction was controlled by the
differential reactivities of nucleophilic and electrophilic sites. G. S. Krishna Rao and co-workers have reported a one-pot general procedure for benzoannelation of homoallylic alcohols using the Vilsmeier reagent to afford biphenyls and dihydrophenanthrenes.

Studies on benzoannelation of non-aromatic precursors by Tius and co-workers have led to the elaboration of α-unsubstituted ketones into phenols, catechol monoethers, pyridines, hydroxy-p-quinones, m-terphenyls, 2,3-disubstituted naphthalenes and phenanthrenes and unsymmetrical biphenyls (Figure 5). The substituted biphenyls whose preparation through classical methodology is often not straightforward are potentially useful materials for liquid crystal synthesis.

![Figure 5: Aromatic compounds obtained from α-unsubstituted ketones](image-url)
Further, an efficient general procedure for the synthesis of methyl-substituted aromatic compounds from ketones was reported by Tius and Ali in 1982. This synthetic sequence involves three steps: addition of the methallylmagnesium chloride in ether at 0 °C to trimethylsilyl vinylogous ester 1, dehydration to form the β-methallylic unsaturated aldehyde 2 and acid-catalyzed intramolecular Prins reaction and dehydration to yield the methyl-substituted aromatic compound 3. The cyclization of 2 has been carried out using p-TSA in refluxing benzene (Scheme 21). The mechanism for the cyclization is believed to involve a cationic intermediate, a view supported by the need for a cation stabilizing substituent (methyl group in the above reaction). In the absence of a cation stabilizing group at C-2 of the Grignard reagent, the yield of the cyclization is low. A similar effect has been

**SCHEME 21**

Reagents: (a) methallylmagnesium chloride, ether, 0 °C and then 1N aqueous HCl, 3 h; (b) p-TSA, benzene, reflux.
observed by Junjappa and co-workers in related work. Unsubstituted, benzoannelated products are nevertheless accessible from cyclization of the adducts of [2-(trimethylsilyl-2-propenyl]magnesium chloride. Further, the conditions for the cationic cyclization step have been modified (PPTS in benzene at 23 °C for 12 h) to accommodate acid-sensitive functionality.

This benzoannelation methodology is general enough to be applied to both cyclic and acyclic ketones. In order to submit a large-scale (10 g of 3,4-cyclododeceno-1-methylbenzene) experimental procedure to *Organic Syntheses*, it was necessary to identify potentially hazardous steps in the published procedure and any safety measures taken during the reaction. Further, it was desirable to avoid as much as possible the handling of large quantities of potentially dangerous or carcinogenic materials.
RESULTS AND DISCUSSION

The sodium salt of 2-hydroxymethylene ketone 5 was prepared by mixing an ether solution of ethyl formate and cyclododecanone (4) with a suspension of sodium hydride in ether in the presence of a small amount of methanol as a catalyst. Sodium hydride was washed with hexane to remove mineral oil and ethyl formate was distilled from phosphorus pentoxide. On large-scale, stirring of the heterogeneous reaction mixture required the use of a mechanical stirrer. A pressure-equalizing dropping funnel was used to ease the addition of large volumes of reagents. The salt obtained was washed once with ether to remove unreacted ketone and residual mineral oil. Careful acidification of the sodium salt with 1N HCl to pH 6 afforded 5, which was used in the next reaction without purification.

\[
\begin{align*}
\text{O} & \quad \text{OH} \\
\text{4} & \quad \xrightarrow{a} \quad \text{5}
\end{align*}
\]

Reagents: (a) $\text{HCO}_2\text{CH}_2\text{CH}_3$, sodium hydride, ether, cat. methanol

The Grignard reagent, methallylmagnesium chloride, was prepared from methallyl chloride\textsuperscript{17} and magnesium turnings\textsuperscript{18} in anhydrous ether at 0 °C. This reaction was exothermic and care should be exercised to add the methallyl chloride at a moderate rate with adequate stirring and cooling of
the reaction mixture. In a separate flask, 5 was treated with a 1/1 (v/v) mixture of chlorotrimethylsilane and triethylamine to produce the hydrolytically labile trimethylsilyl vinylogous ester 6 which was immediately added to an excess of methallylmagnesium chloride at 0 °C. The reaction mixture was quenched by slow addition of saturated brine until the reaction mixture becomes clear. The ether layer was decanted from the sodium salt and unreacted magnesium. The crude product 7 which was obtained after drying over magnesium sulfate, followed by concentration, was used in the cyclization step without purification.

\[ \text{Reagents: (a) methallylmagnesium chloride, ether, 0 °C, then sat'd. brine} \]

It was necessary to find conditions for the cyclization of 7 which did not utilize large amounts of carcinogenic solvents, such as benzene. During the benzoannelation reaction, a highly UV-active product was observed by thin-layer chromatography (tlc) which underwent conversion to the final product 9 on standing. The \(^1\)H NMR spectrum of the UV-active product revealed that it was the \(\beta\)-methallylic unsaturated aldehyde 8. When catalytic
BF₃·Et₂O was used in CH₂Cl₂ at low temperatures (-78 °C), the product mixture consisted primarily of 8. The use of one equivalent of BF₃·Et₂O at 0 °C for 20 min afforded a moderate yield of 9. The best conditions for the reaction were obtained through the use of p-TSA (0.4 equiv. with respect to 5) in toluene at 80 °C for 3 h. The overall yield of the reaction was 86% from 5.

Several related methods for benzoannelation have been reported. Most provide aromatic sulfides or phenols that require additional manipulation. The efficacy of the present benzoannelation methodology has been demonstrated (Entries 1-7, Table 2) by its application to both cyclic and acyclic ketones with one methylene group flanking the carbonyl. This

Reagents: (a) p-TSA, toluene, 80 °C, 3 h.
method is not limited to the preparation of methyl-substituted aromatics. By using benzylmagnesium bromide instead of methallyl Grignard reagent, a naphthalene can be appended onto the ketone.\textsuperscript{10} Similarly, phenanthrenes\textsuperscript{10} and \textit{m}-terphenyls\textsuperscript{9} have been obtained conveniently and in high yield.
Table 2: Benzoannelation of Ketones

<table>
<thead>
<tr>
<th>Entry</th>
<th>2-Hydroxymethylene ketone</th>
<th>Product</th>
<th>Overall yield (%)</th>
</tr>
</thead>
<tbody>
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<td>1</td>
<td>![Image](2-Hydroxymethylene ketone 1)</td>
<td>![Image](Product 1)</td>
<td>52</td>
</tr>
<tr>
<td>2</td>
<td>![Image](2-Hydroxymethylene ketone 2)</td>
<td>![Image](Product 2)</td>
<td>76</td>
</tr>
<tr>
<td>3</td>
<td>![Image](2-Hydroxymethylene ketone 3)</td>
<td>![Image](Product 3)</td>
<td>79</td>
</tr>
<tr>
<td>4</td>
<td>![Image](2-Hydroxymethylene ketone 4)</td>
<td>![Image](Product 4)</td>
<td>74</td>
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</table>
Table 2: Benzoannelation of Ketones (Cont'd)

<table>
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<th>Entry</th>
<th>2-Hydroxymethylene ketone</th>
<th>Product</th>
<th>Overall yield (%)</th>
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</thead>
<tbody>
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<td><img src="image8" alt="Chemical Structure" /></td>
<td>86</td>
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</table>

298
CONCLUSION

This preparation describes a highly practical and efficient method for the synthesis of structurally diverse aromatic compounds from non-aromatic precursors. It is applicable to a wide variety of ketones and gives rise to high yields of benzoannelated products. It is worthy of note that there are no intermediate purification steps; both the nucleophilic addition of methallylmagnesium chloride and the aromatic cyclization take place cleanly. The cyclization process is fast and avoids the use of benzene as a solvent. The ease of the reactions, the high yields, and the convenience recommend its use.
A. General Procedure for the preparation of 2-(hydroxymethylene)ketone:

To a 1-L, three-necked, round-bottomed flask equipped with a septum inlet, mechanical stirrer, nitrogen inlet, and pressure equalizing dropping funnel was added 92 mmol of sodium hydride (obtained from Aldrich Chemical Company, Inc.). The mineral oil was removed from the sodium hydride by washing with hexane, ether was added (250 mL) and the reaction mixture cooled to 0 °C. A mixture of 77 mmol of ketone and 85 mmol of ethyl formate (obtained from Aldrich Chemical Company, Inc., and distilled from phosphorus pentoxide) in ether (75 mL) was added through the dropping funnel over 45 min. Next methanol (4 mL) was cautiously added. After 30 min the reaction became heterogenous. Further addition of methanol (4 mL) allowed stirring to take place. The reaction mixture was then stirred of 4 h at 0 °C. The cooling bath was removed and stirring was continued for 8 h at 23 °C. The reaction was worked up by collecting the solid and dissolving it in water (150 mL). The aqueous layer was washed once with ether to remove unreacted ketone and residual mineral oil. Careful acidification with 1N hydrochloric acid to pH 6 was followed by extraction with ether (6 x 50 mL). The ether extracts were washed with brine (2 x 50 mL), dried (MgSO4) and concentrated to produce 2-(hydroxymethylene)ketone, which was used in the next step without purification.
B. Reaction of methallylmagnesium chloride with trimethylsiloxyhydroxymethylene ketone:

A dry, 2-L, three-necked, round-bottomed flask connected to a nitrogen bubbler and equipped with a mechanical stirrer with ground shaft and bearing a 100-mL pressure equalizing dropping funnel and a septum inlet was charged with 1.89 mol of magnesium turnings and flushed for 5 min with nitrogen. Anhydrous ether (450 mL) was added and the flask was cooled to 0 °C in an ice bath. Methallyl chloride (0.65 mol) was added dropwise from the addition funnel to the stirred magnesium turnings during 45 min. The reaction is exothermic and care must be exercised to add the methallyl chloride at a moderate rate with adequate stirring and cooling of the reaction mixture. During this time the reaction mixture turns to a gray heterogeneous slurry. Stirring was continued at 0 °C for 1.5 h and at 22 °C for 1.5 h.

In a separate, dry, 1-L, two-necked, round-bottomed flask fitted to a nitrogen bubbler and equipped with a magnetic stirring bar and a septum inlet was added a solution of 2-(hydroxymethylene)ketone in anhydrous ether (500 mL). The stirred ethereal solution of the hydroxymethylene ketone was treated at 22 °C with a freshly prepared mixture (1/1, v/v) of chlorotrimethylsilane and triethylamine. An immediate reaction took place with deposition of a white precipitate. The mixture was stirred thoroughly at 22 °C for 15 min to insure complete conversion to the silyl enol ether.

The heterogeneous mixture of the silyl ether and triethylamine hydrochloride was transferred to the solution of the Grignard reagent at 0 °C by means of a large cannula during 5 min. The efficient transfer of the silyl enol ether was accomplished with the aid of nitrogen pressure. The flask containing the silyl enol ether was rinsed with 50 mL of ether and was
transferred to the Grignard solution. Stirring at 0 °C was continued for 15 min. The reaction was then quenched by slow addition of saturated aqueous sodium chloride solution until the reaction mixture becomes clear. The septa were removed from the flask in order to vent the pressure. The solution was allowed to warm to 22 °C and the ether layer was decanted from the magnesium salt and the unreacted magnesium. The residue was diluted with saturated aqueous sodium chloride solution (100 mL) and extracted with ether (3 x 50 mL). The combined ether extracts were washed with saturated aqueous sodium chloride solution (2 x 50 mL), dried over anhydrous magnesium sulfate and concentrated at reduced pressure. The product that was obtained was used in the cyclization reaction without purification.

C. Cyclization of 1-(2-methallyl)-2-(trimethylylsiloxy)methylene alcohol to the methyl-substituted aromatic compound:

A 1-L, two-necked, round-bottomed flask equipped with a reflux condenser, septum inlet, and a magnetic stirring bar is fitted to a nitrogen bubbler. The flask is charged with 200 mL of toluene and 24 mmol of p-toluenesulfonic acid monohydrate. The solution is warmed to 80 °C in a heating mantle. Tertiary alcohol from the preceding step is dissolved in 150 mL of toluene and transferred to the flask by cannula. The progress of the reaction was monitored by silical gel tlc. After 3 h, the reaction mixture was cooled to 22 °C and washed with saturated aqueous sodium bicarbonate (2 x 100 mL). The aqueous phase was extracted with ether (4 x 100 mL) and the combined organic extracts were dried (MgSO4). The solvents were removed under reduced pressure and the residue was purified by flash column chromatography on silica gel eluting with hexane.
3,4-Cyclopenteno-1-methylbenzene (10):

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.13-6.94 (m, 3H), 2.87 (t, $J = 7.5$ Hz, 4H), 2.33 (s, 3H), 2.06 (q, $J = 7.5$ Hz, 2H) ppm.

$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 144.3, 141.1, 135.5, 126.7, 125.1, 124.1, 32.8, 32.4, 25.6, 21.2 ppm.

IR (neat): 3000, 2950, 2820, 1490, 1430, 800 cm$^{-1}$.

Mass spectrum (70 eV, m/e): 132 ($M^+$), 117 (100%), 91, 131.

HRMS: for C$_{10}$H$_{12}$ 132.0939, found 132.0957

Physical appearance: colorless oil.
3,4-(4'-tert-butylcyclohexeno)-1-methylbenzene (11):

\[
\begin{align*}
\text{CH}_3 \\
\text{t-Bu}
\end{align*}
\]

\[\text{t-Bu}\]

\[
\begin{align*}
\text{3,4-(4'-tert-butylcyclohexeno)-1-methylbenzene (11):} \\
^1\text{H NMR (300 MHz, CDCl}_3\text{): } & \delta 7.02-6.92 (m, 3H), 2.82-2.69 (m, 3H), 2.57-2.47 (m, 1H), 2.31 (s, 3H), 2.03-1.97 (m, 1H), 1.52-1.26 (m, 2H), 0.96 (s, 9H) \text{ ppm.} \\
^13\text{C NMR (75 MHz, CDCl}_3\text{): } & \delta 136.8, 134.7, 134.5, 129.2, 129.1, 126.2, 44.9, 32.4, 30.6 (2 coincidental peaks), 27.3, 24.6, 20.9 \text{ ppm.} \\
^13\text{C NMR (75 MHz, C}_6\text{D}_6\text{): } & \delta 136.8, 134.6, 134.5, 129.6, 129.5, 126.7, 45.2, 32.4, 30.9, 30.8, 27.3, 25.0, 21.2 \text{ ppm.} \\
\text{IR (neat): } & 2960, 2870, 1500, 1470, 1430, 1390, 1360, 800 \text{ cm}^{-1}. \\
\text{Mass spectrum (70 eV, m/e): } & 202(M^+), 187, 159, 145(100\%), 131, 118, 105. \\
\text{HRMS: for C}_{15}\text{H}_{22} \text{calculated 202.1722, found 202.1732.} \\
\text{Physical appearance: colorless oil}
\end{align*}
\]
3,4-Cyclohepteno-1-methylbenzene (12):

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.00-6.89 (m, 3H), 2.77-2.74 (m, 4H), 2.29 (s, 3H), 1.87-1.79 (m, 2H), 1.65-1.63 (m, 4H) ppm.

$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 143.2, 140.3, 135.2, 129.9, 128.9, 126.4, 36.7, 36.2, 32.8, 28.5, 28.4, 20.9 ppm.

IR (neat): 3000, 2920, 2840, 1500, 1450, 810 cm$^{-1}$.

Mass spectrum (70 eV, m/e): 160(M$^+$, 100%), 145(100%), 131, 118, 105, 91, 77

HRMS: for C$_{12}$H$_{16}$ 160.1252, found 160.1244.

Physical appearance: light yellow crystalline solid.
3-(4'-Chlorophenyl)-1,4-dimethylbenzene (13):

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.39 (d, $J = 8.4$ Hz, 2H), 7.26 (d, $J = 8.4$ Hz, 2H), 7.19-7.03 (m, 3H), 2.36 (s, 3H), 2.23 (s, 3H) ppm.

$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 140.5, 135.3, 132.7, 132.1, 130.5, 130.3, 128.2, 128.1, 20.9, 19.9 (2 peaks coincidental in the aromatic region) ppm.

$^{13}$C NMR (75 MHz, DMF-d$_7$): $\delta$ 141.4, 140.9, 135.9, 132.8, 132.5, 131.6, 131.1, 130.8, 129.0, 128.9, 20.7, 19.9 ppm.

IR (neat): 3020, 3000, 2960, 2920, 2860, 1480, 1450, 1390, 1090, 1010, 830 cm$^{-1}$.

Mass spectrum (70 eV, m/e): 216(M$^+$, 100%), 210, 181, 165, 89, 76.

HRMS: for C$_{14}$H$_{13}$Cl 216.0706, found 216.0713.

Physical appearance: light yellow oil.
3-(4'-Methylphenyl)-1-methylbenzene (14):

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.54-7.17 (br m, 8H), 2.45 (s, 3H), 2.43 (s, 3H) ppm.

$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 141.1, 138.4, 138.2, 136.9, 129.4, 128.6, 127.7, 127.6, 126.9, 124.1, 21.5, 21.1 ppm.

IR (neat): 3100, 2920, 2860, 1600, 1510, 1480, 1450, 820 cm$^{-1}$.

Mass (70 eV, m/e): 182 ($M^+$, 100%), 167, 152, 90, 76, 40, 28.

HRMS: for C$_{14}$H$_{14}$ 182.1096, found 182.1099.

Physical appearance: light yellow oil.
3-Ethyl-1,4-dimethylbenzene (15):

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.05-6.91 (m, 3H), 2.60 (q, J = 7.5 Hz, 2H), 2.31 (s, 3H), 2.27 (s, 3H), 1.21 (t, J = 7.5 Hz, 3H) ppm.

$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 142.1, 135.3, 132.5, 129.9, 128.7, 126.3, 26.2, 20.9, 18.7, 14.5 ppm.

IR (neat): 2960, 2920, 2870, 1460, 1380, 1360, 1130 cm$^{-1}$.

Mass spectrum (70 eV, m/e): 134 ($M^+$), 119 (100%), 105, 91.

HRMS: for C$_{10}$H$_{14}$ 134.1096, found 134.1103.

Physical appearance: light yellow oil.
3-Methyl-7-methoxy-9,10-dihydrophenanthrene (16):

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.68 (d, $J = 8.4$ Hz, 1H), 7.51 (s, 1H), 7.11 (d, $J = 7.5$ Hz, 1H), 7.00 (d, $J = 7.5$ Hz, 1H), 6.86-6.78 (m, 2H), 3.85 (s, 3H), 2.83 (s, 4H), 2.39 (s, 3H) ppm.

$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = 158.9, 139.1, 136.3, 134.2, 133.5, 127.9, 127.5, 127.2, 124.8, 123.7, 113.5, 112.3, 55.2, 29.7, 28.6, 21.4 ppm.

IR (CCl$_4$): 3000, 2930, 2830, 1610, 1500, 1430, 1270, 1240, 1105, 1040, 1030, 860, 810 cm$^{-1}$.

Mass spectrum (70 eV, m/e): 224(M$^+$, 100%), 209, 194, 178, 165.

HRMS: for C$_{16}$H$_{16}$O 224.1201, found 224.1194.

Physical appearance: Light yellow crystalline solid
3,4-Cyclododeceno-1-methylbenzene (9):

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.09-6.93 (m, 3H), 2.62 (t, J - 7.5 Hz, 4H), 2.29 (s, 3H), 1.76-1.65 (m, 4H), 1.54-1.51 (m, 4H), 1.44-1.39 (m, 8H) ppm.

$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 140.8, 137.9, 134.9, 130.2, 129.5, 126.5, 30.0, 29.9, 29.3, 28.9, 26.3, 26.3, 26.2, 25.6, 22.9, 20.9 ppm.

Note: 2 peaks are coincidental in the aliphatic region.

IR (neat): 2940, 2880, 1510, 1475, 1450, 830, 810 cm$^{-1}$.

Mass spectrum (70 eV, m/e): 230 (M$^+$), 215, 173, 159, 145, 119 (100%), 105, 91, 40.

HRMS: for C$_{17}$H$_{26}$ 230.2035, found 230.2026.

Physical appearance: light yellow oil.
APPENDIX II: SPECTRA FOR SELECTED COMPOUNDS IN PART II

1H NMR spectrum/CDCl₃

13C NMR spectrum/CDCl₃
Infra-red spectrum

Mass spectrum
$^1$H NMR spectrum/CDCl$_3$

$^{13}$C NMR spectrum/CDCl$_3$
Infra-red spectrum
1H NMR spectrum/CDCl₃

13C NMR spectrum/CDCl₃
1H NMR spectrum/CDCl₃

13C NMR spectrum/CDCl₃
Mass spectrum
$^1$H NMR spectrum/CDCl$_3$

$^{13}$C NMR spectrum/CDCl$_3$
Mass spectrum
$^{1}H$ NMR spectrum/CDCl$_3$

$^{13}C$ NMR spectrum/CDCl$_3$
Infra-red spectrum

Mass spectrum

[Graph showing mass spectrum with peaks at 111, 165, 176, 194, and 203]
REFERENCES


17. Methallyl chloride obtained from Aldrich Chemical Company, Inc., was distilled (bp 71-72 °C) from phosphorus pentoxide.
18. Magnesium turnings (98%) from Aldrich Chemical Company, Inc., were used after drying in a beaker at 110 °C overnight. The Grignard reaction took place without need of an initiator.
19. Chlorotrimethylsilane obtained from Aldrich Chemical Company, Inc., and triethylamine (Aldrich Chemical Company, Inc.,) were mixed in equal volumes in dry, stoppered tubes. These were centrifuged briefly and the supernatant was transferred through a septum by syringe.
20. A suitable cannula was made by filing the ends of a 45-cm long aluminum tube of 2-mm internal diameter to points.

21. The reaction was most easily monitored by noting the disappearance of the highly UV absorbing unsaturated aldehyde intermediate by tlc.

22. Reagent grade toluene (Fisher Scientific Company) was degassed with a nitrogen stream.


and also see references 4 and 1(k).