THE TOTAL SYNTHESIS OF C1'-AZACYCLOALKYL HEXAHYDROCANNABINOIDs
THE TOTAL SYNTHESIS OF 3-OXAADAMANTYL HEXAHYDROCANNABINOIDs
THE SYNTHESIS OF BICYCLIC 3-ADAMANTYL CANNABINOIDs

A DISSERTATION SUBMITTED TO THE GRADUATE DIVISION OF THE
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CHEMISTRY

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By

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We certify that we have read this dissertation and that, in our opinion, it is satisfactory in scope and quality as a dissertation for the degree of Doctor of Philosophy in Chemistry.

DISSERTATION COMMITTEE

__________________________________  Chairperson

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Chapter 1. A brief background on the discovery and pharmacology of cannabinoids and of cannabinoid receptors was described. Also, SAR and earlier synthesis approaches to tricyclic cannabinoids were reviewed.

Chapter 2. The total synthesis of three series of C1'-azacycloalkyl 9β-hydroxy hexahydrocannabinoids: 2,2-disubstituted pyrrolidine, 3,3-disubstituted azetidine, and 2,2-disubstituted azetidine cannabinoids are described. The key steps in the synthesis for each series were the Liebeskind cross coupling, the Pd-catalyzed decarboxylative cross coupling, and the titanium enolate addition to Ellman's imine. 3,3-Disubstituted N-methyl azetidine and 2,2-disubstituted N-methyl pyrrolidine cannabinoids exhibited high binding affinities for CB1 and CB2 receptors that are similar to (-)-Δ⁹-THC while evaluation of binding affinities of 2,2-disubstituted azetidine cannabinoid is in progress.

Chapter 3. The total synthesis of a series of 3'-functionalized 3-oxaadamantyl 9β-hydroxy hexahydrocannabinoids is described. The key steps in the synthesis were the nucleophilic addition of aryllithium to epoxide ketone to prepare an 3-oxaadamantyl resorcinol, condensation of resorcinol with a mixture of optically active diacetates followed by cyclization to construct the tricyclic cannabinoid nucleus, and functional group manipulation. It is noteworthy that no functional group protection was employed in the synthesis. Ligands with -CH₂NCS and -CH₂N₃ as functional groups have affinities for CB1 and CB2 receptors at nanomolar or subnanomolar levels, and they can be used for LAPS studies in the group of Professor Makriyannis.

Chapter 4. The synthesis of two series of cannabinoids: the bicyclic 3-adamantyl cannabinoids and the 3'-functionalized 3-oxaadamantyl 9β-hydroxymethyl hexahydrocannabinoids are described. In the synthesis of bicyclic 3-adamantyl cannabinoids, the
challenging step, oxidation of bicyclic hydroxy isothiocyanate to bicyclic keto isothiocyanate, was accomplished with PDC with the preservation of the phenolic hydroxy groups. Evaluation of binding affinities for receptors of bicyclic cannabinoids are currently in progress. In the other series, the synthesis related to conversion of the 9-keto group to 9β-hydroxymethyl and 3′-functional groups. Ligands in this series with \(-\text{CH}_2\text{NCS}\) and \(-\text{CH}_2\text{N}_3\) have affinities for CB1 and CB2 at nanomolar and subnanomolar levels, and they are also used for LAPS studies.
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<tr>
<td>[α]</td>
<td>specific rotation</td>
</tr>
<tr>
<td>Å</td>
<td>Angstrom</td>
</tr>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>AIDS</td>
<td>acquired immunodeficiency syndrome</td>
</tr>
<tr>
<td>aq</td>
<td>aqueous</td>
</tr>
<tr>
<td>BC</td>
<td>Before Christ</td>
</tr>
<tr>
<td>br</td>
<td>broadened</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>BINAP</td>
<td>2,2'-bis(diphenylphosphino)-1,1'-binaphthyl</td>
</tr>
<tr>
<td>ca.</td>
<td>circa (approximately)</td>
</tr>
<tr>
<td>cAMP</td>
<td>cyclic adenosine monophosphate</td>
</tr>
<tr>
<td>calcd</td>
<td>calculated</td>
</tr>
<tr>
<td>cat.</td>
<td>catalytic</td>
</tr>
<tr>
<td>°C</td>
<td>degrees Celsius</td>
</tr>
<tr>
<td>CB1</td>
<td>cannabinoid receptor 1</td>
</tr>
<tr>
<td>CB2</td>
<td>cannabinoid receptor 2</td>
</tr>
<tr>
<td>log</td>
<td>logarithm</td>
</tr>
<tr>
<td>cm⁻¹</td>
<td>reciprocal centimeters</td>
</tr>
<tr>
<td>CNS</td>
<td>central nervous system</td>
</tr>
<tr>
<td>δ (ppm)</td>
<td>chemical shift (parts per million)</td>
</tr>
<tr>
<td>d</td>
<td>day(s) (length of reaction time)</td>
</tr>
<tr>
<td>d</td>
<td>doublet</td>
</tr>
<tr>
<td>dba</td>
<td>dibenzylideneacetone</td>
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<tr>
<td>dd</td>
<td>doublet of doublets</td>
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<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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</tr>
<tr>
<td>ddd</td>
<td>doublet of doublet of doublets</td>
</tr>
<tr>
<td>DPPA</td>
<td>diphenylphosphoryl azide (diphenylphosphorazidate)</td>
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<td>dppf</td>
<td>1,1’-bis(diphenylphosphino)ferrocene</td>
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<td>DMAP</td>
<td>4-(dimethylamino)pyridine</td>
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<td>DMF</td>
<td>N,N-dimethylformamide</td>
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<td>DMP</td>
<td>Dess-Martin periodinane</td>
</tr>
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<td>DMSO</td>
<td>dimethyl sulfoxide</td>
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<tr>
<td>dr</td>
<td>diastereomeric ratio</td>
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<tr>
<td>EDCI</td>
<td>1-ethyl-3-(3-dimethylaminopropyl) carbodiimide</td>
</tr>
<tr>
<td>EI</td>
<td>electron impact</td>
</tr>
<tr>
<td>e.g.</td>
<td>exempli gratia (for the sake of example)</td>
</tr>
<tr>
<td>ESI</td>
<td>electrospray ionization</td>
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<tr>
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<td>ethyl acetate</td>
</tr>
<tr>
<td>g</td>
<td>gram(s)</td>
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<tr>
<td>GPCR(s)</td>
<td>G-protein-coupled receptor(s)</td>
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<td>GPR55</td>
<td>G-protein-coupled receptor 55</td>
</tr>
<tr>
<td>GPR119</td>
<td>G-protein-coupled receptor 119</td>
</tr>
<tr>
<td>h</td>
<td>hour(s)</td>
</tr>
<tr>
<td>HHC</td>
<td>hexahydrocannabinol(s)</td>
</tr>
<tr>
<td>HMPA</td>
<td>hexamethylphosphoric acid triamide</td>
</tr>
<tr>
<td>HOBT</td>
<td>1-hydroxybenzotriazole</td>
</tr>
<tr>
<td>HPLC</td>
<td>high performance liquid chromatography</td>
</tr>
<tr>
<td>HRMS</td>
<td>high resolution mass spectrum</td>
</tr>
<tr>
<td>Hz</td>
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<td>Symbol</td>
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<td>--------</td>
<td>-------------</td>
</tr>
<tr>
<td><em>i-</em></td>
<td>iso</td>
</tr>
<tr>
<td>IBX</td>
<td><em>o</em>-iodoxybenzoic acid</td>
</tr>
<tr>
<td>IC&lt;sub&gt;50&lt;/sub&gt;</td>
<td>half maximal inhibitory concentration</td>
</tr>
<tr>
<td>IR</td>
<td>infrared</td>
</tr>
<tr>
<td>Pr</td>
<td>propyl</td>
</tr>
<tr>
<td><em>J</em></td>
<td>coupling constant</td>
</tr>
<tr>
<td><em>K</em>&lt;sub&gt;i&lt;/sub&gt;</td>
<td>absolute inhibition constant</td>
</tr>
<tr>
<td><em>K</em>&lt;sub&gt;D&lt;/sub&gt;</td>
<td>dissociation constant</td>
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<td><em>L</em>&lt;sub&gt;-&lt;/sub&gt;</td>
<td>levorotation</td>
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<tr>
<td>LAPS</td>
<td>ligand-assisted protein structure</td>
</tr>
<tr>
<td>LC</td>
<td>liquid chromatography</td>
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<td>LDA</td>
<td>lithium diisopropylamide</td>
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<tr>
<td><em>m</em></td>
<td>multiplet</td>
</tr>
<tr>
<td><em>m-</em></td>
<td>meta</td>
</tr>
<tr>
<td><em>m</em>-CPBA</td>
<td>meta chloroperbenzoic acid</td>
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<td>M</td>
<td>molar (concentration)</td>
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<td>M+</td>
<td>molecular ion</td>
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<td>MHz</td>
<td>megahertz</td>
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<td>minute(s)</td>
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<td>mm Hg</td>
<td>millimeters of mercury</td>
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<td>milligram(s)</td>
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<td>mL</td>
<td>milliliter(s)</td>
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<td>millimole(s)</td>
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<td>MOM</td>
<td>methoxymethyl</td>
</tr>
<tr>
<td>mp</td>
<td>melting point</td>
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<tr>
<td>Ms</td>
<td>methanesulfonyl</td>
</tr>
<tr>
<td>Symbol</td>
<td>Definition</td>
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<td>------------</td>
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<tr>
<td>µL</td>
<td>microliter(s)</td>
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<tr>
<td>MS</td>
<td>mass spectrometry; or molecular sieves</td>
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<td>m/z</td>
<td>mass to charge ratio</td>
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<tr>
<td>n-</td>
<td>normal</td>
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<tr>
<td>NaHMDS</td>
<td>sodium bis(trimethylsilyl)amide</td>
</tr>
<tr>
<td>NAG</td>
<td>northern aliphatic group</td>
</tr>
<tr>
<td>nm</td>
<td>nanometers</td>
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<tr>
<td>nM</td>
<td>nanomolar</td>
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<tr>
<td>N</td>
<td>normal (concentration)</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
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<tr>
<td>Ns</td>
<td>2-nitrobenzenesulfonyl</td>
</tr>
<tr>
<td>o-</td>
<td>ortho</td>
</tr>
<tr>
<td>O.N.</td>
<td>overnight</td>
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<tr>
<td>p-</td>
<td>para</td>
</tr>
<tr>
<td>p-TsOH·H₂O</td>
<td>p-toluenesulfonic acid monohydrate</td>
</tr>
<tr>
<td>PCC</td>
<td>pyridinium chlorochromate</td>
</tr>
<tr>
<td>PDC</td>
<td>pyridinium dichromate</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
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<tr>
<td>PH</td>
<td>phenolic hydroxyl</td>
</tr>
<tr>
<td>PhNTf₂</td>
<td>N-phenylbistrifluoromethanesulfonimide</td>
</tr>
<tr>
<td>PMHS</td>
<td>polymethylhydrosiloxane</td>
</tr>
<tr>
<td>Pyr</td>
<td>pyridine</td>
</tr>
<tr>
<td>q</td>
<td>quartet</td>
</tr>
<tr>
<td>R</td>
<td>rectus</td>
</tr>
<tr>
<td>rac</td>
<td>racemic</td>
</tr>
<tr>
<td>rt</td>
<td>room temperature</td>
</tr>
</tbody>
</table>
s  second(s)
s  singlet
s-  secondary
S  sinister
SAH  southern aliphatic hydroxyl
SAR  structure – activity relationships
SC  side chain
SM  starting material
t-  tertiary
TFAA  trifluoroacetic anhydride
TBS  t-butyldiphenylsilyl
td  triplet of doublets
TEA  triethylamine
Tf  trifluoromethanesulfonyl
THC  tetrahydrocannabinol
THF  tetrahydrofuran
TLC  thin layer chromatography
TMS  trimethylsilyl
Ts  toluenesulfonyl
UV  ultraviolet
wt.  weight
CHAPTER 1. INTRODUCTION
1.1. Cannabinoids: Discovery and Pharmacology

*Cannabis sativa L.* is one of the first plants used by man for fibre, food and medicine, and in social and religious rituals. One of the first evidence for the use of cannabis in medicine probably comes from China circa 2600 BC when cannabis, known as *ma-fen*, was recommended for malaria, constipation, female disorders, childbirth, rheumatic pains, and other treatments, and was mixed with wine as a surgical analgesic. In Assyria (circa 800 BC), cannabis was listed in the pharmacopoeia as one of the important drugs under the name *gan-zi-gun-nu* which means "the drug that takes away the mind". Over the millennia, its use spread into India and other Asian countries, the Middle East, South Africa and South America as a drug mostly for pain, inflammation, epilepsy, and various other neurological diseases. During the 19th century, cannabis became a mainstream medicine in Western Europe, particularly in England, whereas in France it was mostly known as a "recreational" drug.

Research for the active component of *Cannabis sativa* commenced around the turn of the 19th century, however, there was not much progress due to the complexity of many closely related compounds, their instability, and the rudimentary techniques for separation and identification of organic molecules. In 1899, Wood and co-workers isolated the first component of *Cannabis*, cannabinol, which was analysed as C$_{21}$H$_{26}$O$_2$, however, the structure was only partially elucidated by Cahn in 1932 and it was not the active principal of *Cannabis*. In the early 1940s, the Todd group in the UK and independently the Adams group in the USA synthesized various cannabinol isomers, which were suggested by Cahn's partial structure, and put more effort in the isolation of natural active constituents. These groups elucidated the correct structure of cannabinol (2), isolated cannabidiol, another inactive component of *Cannabis*, although its structure was assigned incorrectly, and unexpectedly found racemic Δ$_{6a,10a}$-tetrahydrocannabinol (synhexyl, 4) to be active in animal tests.
In the early 1960s, the correct structure and stereochemistry of cannabidiol (3) was established with the assistance of advances in chromatography and NMR spectroscopy. Most importantly, the major psychoactive constituent of Cannabis sativa, Δ⁹-tetrahydrocannabinol (Δ⁹-THC), was isolated for the first time in pure form and its structure was elucidated by Gaoni and Mechoulam in 1964, followed by the synthesis of the natural active (–)-Δ⁹-THC enantiomer (1) in 1967. Since that time, research into the chemistry, pharmacology, as well as the metabolism and clinical aspects of cannabinoids has flourished. To date, more than 480 natural components have been found in the cannabis plant, of which 70 have been classified as cannabinoids, and more than 10,000 publications on all aspects of cannabinoids have appeared. The term "cannabinoid" was classically defined as "the group of C₂₁ compounds typical of and present in Cannabis sativa, their carboxylic acids, analogs and transformation products". This term which referred only to natural, plant derived cannabinoids, has been extended currently to a larger number of compounds such as synthetic analogs, endogenous cannabinoids and their congeners.
These advances led on to the clinical use of $\Delta^9$-THC (Dronabinol, or Marinol, Solvay Pharmaceuticals, Brussels, Belgium) and its synthetic analogues, nabilone (5, Cesamet, Valeant Pharmaceuticals, Aliso Viejo, CA, USA) in 1980s for the suppression of nausea and vomiting from chemotherapy, of Marinol for the stimulation of appetite in AIDS patients in 1992, and, in 2005, of cannabidiol in a 1:1 mixture with $\Delta^9$-THC (Nabiximols, or Sativex, GW Pharmaceuticals, UK) for the alleviation of neuropathic pain associated with multiple sclerosis patients and cancer patients. In spite of their strong therapeutic potential, the use of cannabinoids in medicine still faces limits due to serious adverse effects on the respiratory, digestive, and urinary systems and especially on the central nervous system. Cannabinoid abuse causes addiction, aggression, anxiety, sedation, depression and even suicide. To the question “Should Marijuana be a medical option?”, Raphael Mechoulam, the founding father of modern scientific research in cannabinoids, responded that "My answer is 'yes', but as with any other potent drug, its use should be regulated".
1.2. Cannabinoid Receptors

Initially, it was believed that the actions of cannabinoids proceed through non-specific interactions with membrane lipids.\(^{23}\) This concept was developed from the highly lipophilic nature of cannabinoids, and was supported by experimental evidence that there was a correlation between the ability of certain cannabinoids to change the physical properties of artificial membranes containing only cholesterol and phospholipid and their psychoactive potency.\(^ {24}\) In the mid-1980s, in the context of Gilman and Casey's mechanism of signal transduction by G-protein-coupled receptors having been widely accepted,\(^ {25}\) Howlett and co-workers provided a series of reports that psychotropic cannabinoids have in common an ability to inhibit adenylate cyclase by acting through pertussis toxin-sensitive G\(_{i/o}\) proteins.\(^ {26}\) In 1988, by the use of radiolabelled \(^{3}\)H]-CP-55,940 (6), Devane detected the presence of high affinity binding sites for this ligand in rat brain membranes. Since the ability of unlabelled cannabinoids to displace \(^{3}\)H]-CP-55,940 from these sites and to induce G\(_{i/o}\) mediated inhibition of adenylate cyclase \textit{in vitro} is comparable to the analgetic activity of these compounds \textit{in vivo}, this was convincing evidence that cannabinoids acted on a receptor and that this receptor was G-protein coupled.\(^ {27}\)

![\(^{3}\)H]-CP-55,940, 6

**Figure 2.** Cannabinoid ligand \(^{3}\)H]-CP-55,940.

The existence of cannabinoid receptors was confirmed by the cloning of rat CB\(_1\) receptor by Matsuda in 1990,\(^ {28}\) and of the human CB1 receptor by Gerard in 1991,\(^ {29}\) followed by the cloning of the CB\(_2\) receptor by Munro in 1993.\(^ {30}\) At present, two types of cannabinoid receptors, CB1 and CB2, have been identified and characterized, which are distinguished by their tissue distribution, their amino acid sequence, their signaling mechanisms, and the structural
requirements of ligands for their activation. The existence of other putative non-CB1/CB2 receptors, such as GPR18, GPR55, and GPR119 has also been suggested from experiments of CB1 and CB2 knock out mice, however, there has been no report on the cloning of these receptors so far.

CB₁ and CB₂ receptors are integral-membrane proteins of the class-A (rhodopsin-like) G-protein coupled receptors (GPCRs) that are comprised of seven transmembrane α-helices (TMHs) connected by alternating intracellular and extracellular loops in addition to the extracellular N-terminus and intracellular C-terminus.

Figure 3. Helical-net representations of the human CB1 and CB2 sequences. For simplicity, the first amino acids from the N termini and the last amino acid from the C termini have been omitted, Onaivi et al. 2006.

In humans, the CB1 and CB2 receptors are constituted of 472 and 360 amino acids respectively, and share 44% amino acid sequence homology throughout the total protein, and 68% homology within the transmembrane domains. Autoradiography and positron emission tomography experiments revealed that the CB1 receptors are predominant in the brain with the highest density in the hippocampus, cerebellum and striatum, that correlates well with the observed effects of cannabinoids on cognitive and motor functions. Outside the central nervous system (CNS), CB1 receptors have been identified in various peripheral tissues including the gastrointestinal (GI) tract, pancreas, liver, kidney, prostate, testis, uterus, eye, lungs, adipose
tissue and heart, in which it relates to energy balance, metabolism, nociception, and cardiovascular health.\textsuperscript{38} In contrast, the CB2 cannabinoid receptors are distributed in the periphery, particularly in the immune system.\textsuperscript{39} However, it can also be expressed in both CNS (perivascular microglial cells) and peripheral tissues under inflammatory conditions.\textsuperscript{40}

Generally, activation of cannabinoid receptors inhibits adenylate cyclase, which produces cyclic adenosine monophosphate (cAMP) from adenosine triphosphate (ATP), and activates mitogen-activated protein (MAP) kinases (\textbf{Figure 4}).\textsuperscript{36,41} MAP kinases are a family of serine/threonine kinases that regulate cell growth, division, differentiation and apoptosis.\textsuperscript{42} cAMP levels in the cell regulate the phosphorylation of key enzymes and proteins, which is supposed to relate to the physiological and psychological effects of cannabinoids although the mechanism has remained unclear. In addition, while the activation of CB2 receptors does not modulate ion channel function, the activation of CB1 receptors affects several ion channels: it stimulates potassium channels, but inhibits N- and P/Q- type calcium channels, which play a key role in neurotransmission modulation by endogenous cannabinoids. Furthermore, cannabinoid receptors are able to interact with other receptor systems, such as opioid, vanilloid TRPV1, serotonin (5-HT), N-methyl-D-aspartate (NMDA), and nicotinic acetylcholine receptors.\textsuperscript{36a}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{cannabinoid_receptors.png}
\caption{Signalling-transduction of cannabinoid receptor, Rukwied \textit{et al.} 2005.\textsuperscript{41b}}
\end{figure}
Understanding of mode(s) of interactions between ligands and target proteins has been a powerful tool for drug discovery and design. The methodology of structure-based drug design usually uses information from direct experimental structural analysis either by NMR or X-ray crystallography of target proteins as a useful source of data. However, structural analysis of GPCRs such as CB1 and CB2 is prevented because of the heterogeneity of conformations as well as the rapid denaturation outside the membrane environment of integral-membrane proteins. As a result, except for the reported 1H NMR spectra of the CB1 receptor, crystal structures of the CB1 and CB2 receptors have not been obtained. Under these circumstances, the development of suitably designed molecules to probe the structure−activity relationships (SAR) becomes the key strategy to obtain information about the structural requirements for ligand-receptor interactions.
1.3. Bioassay Techniques

Among the various current quantitative behavioral assays that are used to determine the modes of action of CNS drugs, several typical ones that proved to be successful for cannabinoids are 'static ataxia' in dogs, 'overt behavior' in monkeys, and recently the 'mouse tetrad'. In vitro assays for cannabinoids have also been developed, including radioligand binding assays, inhibition of cAMP production, [\(^{35}\text{S}\)]Guanosine-5'-O-(3-thiotriphosphate) (or [\(^{35}\text{S}\)]GTP\(\gamma\)S) binding assay, and inhibition of electrically evoked contractions of isolated smooth muscle preparations. In this part of dissertation, the radioligand binding assay, which is used for our receptor-ligand binding affinity measurements, and the recently developed technique of ligand-assisted protein structure, LAPS, are briefly described. Some of compounds that we have prepared were to support LAPS studies of CB1 and of CB2.

1.3.1. Ligand Binding Assay

Competitive binding assays are widely used to assess the binding affinity between a ligand and its receptor binding sites.

\[
\text{[\(^{3}\text{H}\)]-CP-55,940, 6} \quad \text{[\(^{3}\text{H}\)]-WIN-55,212-2, 7} \quad \text{[\(^{3}\text{H}\)]-SR-141716A, 8}
\]

**Figure 5.** Tritium labelled non-classical cannabinoids used in binding assays.

The novel ligand, or inhibitor, is tested for its ability to compete for the binding of a radiolabelled ligand, or substrate, such as [\(^{3}\text{H}\)]-CP-55,940, \(^{3}\text{H}\)]-WIN-55212-2 (7), or [\(^{3}\text{H}\)]-SR-141716A (8), at a range of concentrations in a buffered solution containing artificial membranes or tissues that are known to contain either CB1 or CB2 receptors. The concentration
of the inhibitor at which 50% of the substrate is displaced is determined to be the IC$_{50}$ value for the inhibitor.

![Graph showing competitive radioligand binding assay](image)

**Figure 6.** Example of competitive radioligand binding assay: displacement of $[^3]$H-SR-141716A binding to CB1 receptor in mouse brain homogenates by AM-2233 and WIN-55212-2, Deng, H. *et al.* 2005.$^{40}$

In order to describe the binding affinity of the ligand to its receptors in a way that is independent of the concentration of radioligand used in the assays, the absolute inhibition constant K$_i$ is determined using the Cheng-Prusoff equation: $K_i = IC_{50} / (1 + [L]/K_D)$, in which [L] is the fixed concentration of radioligand and dissociation constant K$_D$ is the concentration of radioligand that results in half maximal activation of the receptor.$^{50}$ This equation can only used if inhibitor and substrate bind to receptor in a competitive manner.$^{51}$

**1.3.2. Ligand-Assisted Protein Structure**

Ligand-assisted protein structure is an experimental approach, developed by the group of Dr. Makriyannis,$^{52}$ to obtain information about the key amino acid residues involved in ligand-receptor interactions. LAPS is especially useful in the case of membrane-bound receptors like CB1 and CB2 that cannot be crystallized in the presence of their respective ligands. The LAPS experiment requires access to high-affinity ligands that are functionalized to interact covalently with specific amino acids within the receptor binding domain. Enzymatic degradation
of the receptor-ligand covalent complex is then followed by analysis and sequencing of the fragments by mass spectrometry to identify the sites of interaction of the ligand with specific amino acids. The location of the receptor pocket can then be deduced from the known primary amino acid sequence. Site-directed protein mutations can then be used to obtain additional data to support the location of the binding site. The information revealed from these experiments can be used to construct computer models of the ligand-protein complex, which forms the basis for rational drug design.
1.4. Tricylic Cannabinoids and Structure – Activity Relationships

1.4.1. Nomenclature of Classical Cannabinoids

Two different numbering systems, dibenzopyran and monoterpenoid, are generally used for cannabinoids. These are shown in Figure 7.

![Figure 7. Numbering systems in (−)-Δ⁹-THC.](image)

In this dissertation, the dibenzopyran ring nomenclature will be used for tricylic cannabinoids.

1.4.2. Categorization of Cannabinoids

The structural classification of cannabinoids includes: (i) classical cannabinoids; (ii) nonclassical cannabinoids; (iii) hybrid cannabinoids; (iv) arachidonic acid based endocannabinoids and their analogs; (v) diarylpyrazole compounds, aminoalkylindole compounds, and other cannabinoids.

![Figure 8. Pharmacophores in (−)-Δ⁹-THC and (−)-CP-55,940.](image)
Classical cannabinoids are natural or synthetic cannabinoids structurally related to (−)-Δ⁹-THC (1). This class contains ABC-tricyclic terpenoid compounds bearing a benzopyran moiety. Three pharmacophores associated with cannabinoid activity are the northern aliphatic group (NAG), the phenolic hydroxyl (PH), and the lipophilic side chain (SC).

Nonclassical cannabinoids were initially developed by Pfizer in an effort to simplify the classical cannabinoid structure while maintaining or improving biological activity. These ligands are characterized by AC bicyclic (e.g. (−)-CP-55,940, 9) or ACD tricyclic (e.g. (−)-CP-55,244, 10) structures lacking the pyran B-ring of classical cannabinoids, but containing an additional pharmacophore: the southern aliphatic hydroxyl group (SAH), which is trans to the aromatic ring. (−)-CP-55,940 is a cannabinoid agonist that is considerably more potent than (−)-Δ⁹-THC in both behavioral tests and receptor binding assays.⁵⁵

![Chemical structures of cannabinoids](image)

**Figure 9.** Some cannabinoids that illustrate their structural classification (Note: m = mouse).
Hybrid cannabinoids, introduced by Makriyannis and Tius in 1994, combine features of classical and nonclassical cannabinoids (e.g. AM-4030, 11). One distinguishing characteristic is that the C-6 equatorial β-hydroxyethyl analog (12) has higher affinity for CB1 than its α-axial epimer (13).

Endogeneous cannabinoid ligands were first reported by Mechoulam in 1992 with the discovery of N-arachidoylethanolamine (anandamide, 14) from porcine brain. The structure of endogeneous ligands and of their synthetic analogs can be divided into two fragments: the polar head group (e.g. ethanolamido in anandamide) and the hydrophobic arachidonyl chain, which includes four non-conjugated cis double bonds.

Other classes of canabinoids include compounds structurally distinct from the classical cannabinoids, such as diarylpyrazole compounds (e.g. SR-141716A, 15), aminoalkyl indole compounds (e.g. WIN-55,212-2, 16), diarylsulfonyl ester compounds (e.g. BAY-38-7271), diarylmethyleneazetidine compounds, and others. Recently, Makriyannis and co-workers have reported replacement of the C-ring in the classical THC structure with a hydrolyzable seven-membered lactone (AM-4809, 17) as a novel cannabinergic chemotype. AM-4890 can undergo enzymatic hydrolysis by plasma esterases to give the respective acid metabolite, which is inactive at the CB receptors. This was developed in order to provide a short-acting cannabinoid, which becomes inactive after its desired biological role has been achieved, thus limiting the undesirable side effects of the long-acting compounds.
1.4.3. Structure – Activity Relationships of Tricyclic Cannabinoids

In 1971, Mechoulam reported that hexahydrocannabinol, in which the C-ring is fully saturated, with an equatorial methyl group at C9 (18) has similar psychoactivity in the rhesus monkey as tetrahydrocannabinol, (−)-Δ⁹-THC (20), and that the axial epimer (19) was nearly 20 times less active. In 1975 and 1976, Wilson and May reported that incorporation of a hydroxyl group at the northern aliphatic position increases potency in the analgesia test in mice: 21 and 22 were nearly 5 times more active than (−)-Δ⁹- and (−)-Δ⁷-THC respectively, and that 23, with a C9 equatorial hydroxyl, was found to be a potent analgetic in rodents while 24, in which the C9 hydroxyl is axial, was found to be in active.

![Chemical structures](image)

Figure 10. Cannabinoids illustrating the NAG.

The equatorial northern aliphatic hydroxyl group is a structural feature that is shared by high potency and affinity cannabinoids, including classical cannabinoids such as AM-906 (25) and non-classical cannabinoids such as CP-55,940 (9), and levonantradol (26). Moreover, the
introduction of a carbonyl group into C9 position, (e.g. nabilone, 5) also potentiates the activity.\(^{68}\) Also, the (6aR, 10aR) stereochemistry is a preferred for cannabinoid activity. As an illustration, while HU-210 (28) is one of the most potent classical cannabinoids, its (6aS, 10aS) enantiomer, HU-211 (27), is inactive with CB1 and CB2.\(^{69}\)

The second pharmacophore, the phenolic hydroxyl group at C1, is essential for CB1 affinity. When it is replaced by a methoxy (e.g. 29 vs. 30), hydrogen (e.g. 20 vs. 31),\(^{70}\) or fluorine atom (e.g. 32 vs. 33),\(^{71}\) CB1 affinity is strongly diminished while lesser effects on CB2 are observed. These characteristics serve as the basis for the synthesis of CB2 selective cannabinoids.\(^{72}\)

![Cannabinoids illustrating the PH.](image)

**Figure 11.** Cannabinoids illustrating the PH.

The C3 aliphatic side chain is the most studied pharmacophore within the tricyclic cannabinoid template. In 1947-1948, Adam and coworkers reported that cannabinoids with 1',1'-dimethylheptyl, 1'-methylloctyl, and 1',2'-dimethylheptyl side chains have optimal affinity: 3-((1',1'-dimethylheptyl)-\(\Delta^{6a,10a}\))-tetrahydrocannabinol (34) is 20 times, and a mixture of isomeric 3-((1',2'-dimethylheptyl)-\(\Delta^{6a,10a}\))-tetrahydrocannabinols (35) is 512 times more potent than the n-pentyl analogue (36).\(^{73}\) Among all isomers of 3-(1',2'-dimethylheptyl) cannabinoids, the (1'S,2'R) (37) and (1'R,2'S) are considerably more potent than the other isomers.\(^{74}\) Although the 3-(1',2'-
dimethylheptyl) cannabinoids are extremely potent, the 3-(1',1'-dimethylheptyl) analogs have been investigated more extensively because their precursor 1,3-dimethoxy-5-(1,1-dimethylheptyl)benzene, is readily available from synthesis, and there is no requirement for control of the stereochemistry of additional chiral centers. Subsequently, 3-(1',1'-dimethylheptyl)-Δ⁸-THC (29) was synthesized and was found to have very high affinity in vivo that is comparable with the isomers of 3-(1',2'-dimethylheptyl)-Δ⁸-THC (e.g. 37, the most potent diastereomer in vivo). Thus, the dimethylheptyl side chain has been widely incorporated into highly potent cannabinoids. For example, HU-210, JWH-051, CP-55940, and nabilone, which contain the 3-(1',1'-dimethylheptyl) side chain, exhibit nanomolar or sub-nanomolar affinities for both cannabinoid receptors. It is notable that the length of the side chain can also affect the CB1/CB2 selectivity. Cannabinoids with shorter side chains such as ethyl, propyl, or butyl exhibited enhanced CB2 selectivity, whereas analogs with longer seven- or eight- carbon side chains were shown to prefer CB1. For example, 1',1'-dimethylethyl-Δ⁸-THC (CB1, Kᵢ = 14.0 nM), 1',1'-dimethylbutyl-Δ⁸-THC (CB1, Kᵢ = 10.9 nM), 1',1'-dimethypentyl-Δ⁸-THC (38) (CB1, Kᵢ = 3.9 nM), 1',1'-dimethylheptyl-Δ⁸-THC (29) (CB1, Kᵢ = 0.77 nM) exhibit an increase in CB1 affinity. Another example is that JWH-133 (39) shows high affinity and better CB2 selectivity compared to its C1-deoxy analogs that have 5 to 9 carbon atoms in their side chains.

![Figure 12. Cannabinoids illustrating the SC.](image-url)
Another study of the stereochemical requirements of the side chain involved blocking C1'-C2' bond rotation through the introduction of a multiple bond. Cannabinoids with a double or triple C1'-C2' bond (e.g. 25, 40, 41), show higher affinity for CB1 than analogs with a saturated C1'-C2' bond (e.g. 42), particularly the *cis*-alk-1-ene (AM-906, 25) that shows better CB1/CB2 selectivity than other analogs.\(^{66}\)

**Figure 13.** Cannabinoids illustrating the SC.

When the position of the double bond is modified by introduction of a 1'-methylene group into the heptyl side chain (e.g. 43), the high affinity is maintained but the selectivity for CB1 is limited. However, when a ketone or a hydroxy group (e.g. 44) was introduced at C1', affinities for CB1 and CB2 dropped significantly.\(^{79}\) These results indicate that a hydrophobic group at the benzylic position tends to increase affinities for both cannabinoid receptors. Consistent with this trend is the observation that 1',1'-dithiolane analog (AMG-3, 45) exhibits high affinities for both CB1 and CB2 receptors with *K*\(_i\) values at subnanomolar levels.\(^{79,80}\)
Further probes with various ring sizes of the C1'-cycloalkyl side chain showed that the C1'-cyclopropyl (e.g. 47) and C1'-cyclopentyl (e.g. 49) are optimal pharmacophores for both receptors. The C1'-cyclobutyl (48) was close in CB1 affinity, but much better in CB1/CB2 selectivity than the 3- and 5-membered rings. The C1'-cyclohexyl (e.g. 50) had reduced affinities for both CB1 and CB2.\(^1\) This structural feature has been developed by the Makriyannis group in the synthesis of AM-2389 (51), which is a highly potent CB1 agonist \emph{in vitro} and \emph{in vivo} with a relatively very long duration of action.\(^2\)

In addition to the C1'-\emph{tert}-alkyl or C1'-alicyclic side chain substituents, bulky substituents at C3, such as C1'-2-bornyl (\emph{endo}), \emph{-2-isobornyl (exo)},\(^3\) \emph{-adamantyl},\(^4\) or \emph{-heteroadamantyl}\(^5\) can easily be tolerated within the CB1/CB2 binding sites. Furthermore, the relative orientation of these bulky groups with respect to the tricyclic cannabinoid structure strongly affects the CB1/CB2 affinity and selectivity. For example, AM-411 (52) with the 3-(1-adamantyl) group's
orientation within a spherical space in the direct proximity of the aromatic ring was shown to have high affinity and selectivity for CB1. In contrast with AM-411, the adamantyl substituents in AM-744 (53) and AM-755 (54) occupy a much larger volume by virtue of rotation about the C3-C1' bond, and exceed the space preference for CB2 selectivity. AM-4054 (55) that shares the favorable C1 attachment of the adamantyl substituent with AM-411 has high CB1 affinity and a full agonist profile.86

Figure 15. Cannabinoids illustrating the SC.

Substitution at the terminal carbon atom of the side chain with bulky halogen75,87 such as Br, I or with a cyano group88 slightly enhances CB1 affinity. However when an azido or an isothiocyanate group is introduced to the terminus of the side chain, affinities are enhanced dramatically89 because of covalent interactions with amino acid residues within the receptors.90 For example, AM-841 (56) exhibited exceptionally potent "megagonist" activity at hCB2 because this ligand can covalently interact with a critical cysteine residue in the receptor's transmembrane helix 6.91

Figure 16. Cannabinoids illustrating the property of covalent binding or of water solubility.
Finally, one uncommon modification in the structure of cannabinoid ligand is the enhancement of water solubility. For example, O-1057 (57) behaves as an agonist at both receptor subtypes with high potency at CB1 matching that of (−)-CP-55,940.⁹²
The first synthesis of cannabinoids was initiated in the early 1940s with reports on the synthesis of cannabinol (2) and some of its isomers in the laboratories of Rodger Adams in the US and Lord Todd in the UK. However, it was not until 1967 that the first stereospecific synthesis of cannabinoids was reported by Raphael Mechoulam, the synthesis of (−)-Δ⁹-THC, the major psychoactive constituent of *Cannabis sativa*, and its isomer (−)-Δ⁸-THC. The structure of tricyclic cannabinoids such as Δ⁹-THC and Δ⁸-THC can be envisioned as being composed of an aromatic part and an alicyclic part, therefore they were first constructed by the condensation of olivetol with a monoterpenes, such as verbenol. The distinction of the Mechoulam synthesis is that the bulky dimethylmethylene bridge of verbenol provided stereochemical control of the reaction to give exclusively the *trans* products; and because optically pure α-pinene is readily available in both the (+) and (−) modifications, this approach can lead to the natural (−) and unnatural (+) series. The details of Mechoulam's pioneering synthesis are summarized in Scheme 1. (−)-*Cis* and (−)-*trans*-verbenols were condensed with olivetol (59) in the presence of BF₃·Et₂O to give (−)-Δ⁸-THC (20) (44% yield), but purification was tedious. When *p*-TsOH was used, the abnormal byproduct 61 (15%) and the bis-substituted compound 62 (11%) were formed along with the major product 60 (60%), however, this is the better and higher yielding approach because treatment of 60 with BF₃·Et₂O cleanly formed (−)-Δ⁸-THC (20) in 80% yield. Since the reaction of either *cis-* or *trans*-verbenol
gave the same product, it seems that these reactions proceed through a mechanism that involves the same allylic cation. (−)-\(\Delta^9\)-THC (1) was obtained by hydrochlorination followed by dehydrochlorination from (−)-\(\Delta^8\)-THC (20) in this approach.

Reagents and conditions: (a) BF\(_3\)-Et\(_2\)O, CH\(_2\)Cl\(_2\), rt, 44%; (b) p-TsOH, CH\(_2\)Cl\(_2\), 60 (60%), 61 (15%), 62 (11%); (c) BF\(_3\)-Et\(_2\)O, CH\(_2\)Cl\(_2\), rt, 80%; (d) HCl, ZnCl\(_2\) cat, toluene, -15 °C; (e) NaH, THF, reflux.

**Scheme 1.** Synthesis of (−)-\(\Delta^9\)-THC and (−)-\(\Delta^8\)-THC by Mechoulam, Mechoulam *et al.* 1967.

Also in 1967, Petrzilka reported the total synthesis of only the natural (−) series from (+)-cis/trans-\(p\)-mentha-2,8-dien-1-ol (Scheme 2). This soon became the most common and scalable approach for the preparation of tricyclic cannabinoids.\(^{94}\) It is notable that when strong protic acids are used in the condensation/cyclization reaction, the thermodynamically more stable (−)-\(\Delta^8\)-THC is formed from which additional steps were required to yield the desired (−)-\(\Delta^9\)-THC.
Scheme 2. Synthesis of (−)-Δ⁸-THC and (−)-Δ⁹-THC by Petrzilka, Petrzilka et al. 1967.¹⁴

Based on the same principle, various optically active monoterpenes (Figure 18) including (+)-cis-chrysanthlenol,⁵⁵a (+)-trans-2-carene epoxide,⁵⁵b and (+)-(1R, 4R)-p-menth-2-ene-1,8-diol⁶⁶ have been used to synthesize optically active natural THC's.

Figure 18. Some optically active monoterpenes used to prepare THC.

In 1977, Archer and coworkers developed the total synthesis of optically active 9-ketocannabinoid nabilone 5 by condensation of resorcinol with the mixture of diacetates 67a and 67b (Scheme 3).⁹⁷ Remarkably, the undesired abnormal cannabinoid byproduct was not formed, which is presumably due to steric hindrance of the bulky 1',1'-dimethylheptyl group. The undesired cis-ketone 70 was obtained by treatment 69 with p-TsOH·H₂O, however, it could be isomerized to trans-5 by treatment with anhydrous AlCl₃ in CH₂Cl₂.
Reagents and conditions: (a) isopropenyl acetate, \( p\)-TsOH-H\(_2\)O, reflux; (b) Pb(OAc)\(_4\), benzene, reflux, 39% over 2 steps; (c) \( p\)-TsOH-H\(_2\)O, CHCl\(_3\), rt, 70%; (d) SnCl\(_4\), CHCl\(_3\), rt, 84%; (e) \( p\)-TsOH-H\(_2\)O, CHCl\(_3\), reflux, 61% (and 31% of compound 5); (f) AlCl\(_3\), CH\(_2\)Cl\(_2\), rt, 70%.

**Scheme 3.** Total synthesis of nabilone, Archer *et al.* 1977.\(^{97}\)

This approach has been used in the Tius group for construction of the tricyclic ring system in the synthesis of hexahydrocannabinoids. Other approaches, such as Michael addition of the resorcinol fragment to apoverbenone\(^{66,98}\) have been explored and an intramolecular hetero-Diels–Alder cycloaddition\(^{56d,99}\) has been described. Recent work in our lab has focused on modifying the pharmacophores of cannabinoid ligands. For example, the NAG has been probed with halogen,\(^{100}\) C9-methyl carboxylate ester,\(^{98}\) equatorial C9-hydroxyl or -hydroxymethyl\(^{56c,d,66}\) groups, the SAH in hybrid cannabinoids with substituents at C6 position.\(^{56}\) Especially, the SC has been explored with unsaturation,\(^{56}\) functionalization (NCS, N\(_3\), Br, I),\(^{99}\) or substitution with bulky groups such as 1',1'-dimethylalkyl,\(^{56d,99b}\) adamantyl, oxazaadamantyl,\(^{101}\) heteroadamantyl,\(^{85}\) heteroaroyl.\(^{102}\)
CHAPTER 2

THE TOTAL SYNTHESIS OF

C1'-AZACYCLOALKYL 9β-HYDROXY HEXAHYDROCANNABINOIDS
2.1. Introduction

The aliphatic side chain of tricyclic cannabinoids plays a key role in determining the ligand's affinity for cannabinoid receptors as well as the pharmacological potency. It is known that cannabinoids with the C1'-tert-alkyl side chain have high affinities for CB1 and CB2. Recent studies with various ring sizes of a C1'-cycloalkyl side chain (47-50, Figure 19) in the Makriyannis group suggested that small ring sizes (three- to five-membered) potentiate receptor binding affinity and that cannabinoids with the C1'-cyclobutyl side chain have high CB1/CB2 selectivity.81

![Figure 19. Some C1'-cycloalkyl cannabinoids.](image)

In order to improve the water solubility of tricyclic cannabinoids as well as to explore the space within the receptor, heteroatoms capable of H-bonding can be introduced into the hydrophobic side chain. This part of the dissertation focuses on the construction of the series of C1'-azacycloalkyl cannabinoids with the four- and five-membered rings as well as their ammonium salts (Figure 20). These tricyclic cannabinoids are featured with the equatorial 9-hydroxy, the (6aR, 10aR) absolute stereochemistry, the phenolic hydroxy group, as well as the 1',1'-disubstituted n-heptyl side chain, which are all required for the high CB1 and CB2 affinity.
Figure 20. General structure of C1'-azacycloalkyl cannabinoids and intermediate triflate 78.

The synthesis of these hexahydrocannabinoids was designed from a common starting material, triflate 78 that has been prepared from (−)-β-pinene following the procedure developed by Dr. Darryl Dixon in our group. Herein, the non-diastereoselective synthesis of 2,2-disubstituted pyrrolidine, the synthesis of 3,3-disubstituted azetidine, and the diastereoselective synthesis of 2,2-disubstituted azetidine cannabinoids, and their evaluation in the receptor binding assays will be described.
2.2. Synthesis of Advanced Intermediate Triflate

Aryl triflate 78 was obtained from commercially available (-)-β-pinene 71 in acceptable yields in 10 steps, following the procedure that has been developed in our group (Scheme 4).

Reagents and conditions: (a) i. O₃, CH₃OH/CH₂Cl₂, -78 °C, ii. Me₂S, -78 °C to rt, 89%; (b) isopropenyl acetate, p-TsOH·H₂O, reflux, 6 h; (c) Pb(OAc)₄, benzene, reflux, 2.5 h, 71% from 65; (d) p-TsOH·H₂O, CHCl₃/(CH₃)₂CO, 0 °C to rt, 2 h, rt, 4 h; (e) Ac₂O, Pyr, DMAP, CH₂Cl₂, rt, 12 h, 67% from 67; (f) KOH, CH₃OH, 0 °C, 2 h, 96%; (g) TMSOTf, CH₂NO₂, 0 °C, 2.5 h, 83%; (h) PhNTf₂, Et₃N, CH₂Cl₂, rt, 14 h, 84%; (i) NaBH₄, CH₃OH, -5 °C, 1 h, 90%; (j) CH₃OCH₂Cl, i-Pr₂NEt, CH₂Cl₂, 0 °C, 45 min, rt, 2 h, 89%.


The key step in the total synthesis is the condensation of phloroglucinol derivative 72 with a mixture of optically active terpene-derived diacetates 67, followed by rearrangement-cyclization to construct the tricyclic cannabinoid nucleus. In order to obtain the (6aR, 10aR) absolute configuration of the tricyclic cannabinoid nucleus, the mixture of chiral diacetates 67 was synthesized from the (-)-β-pinene via ozonolysis to nopinone 65, followed by enol acetylation to 66 and oxidation with lead (IV) acetate to 67a and 67b according to the procedure...
described by Archer and co-workers. The procedure of Archer and co-workers for the condensation step in the synthesis of nabilone works beautifully in chloroform. Phloroglucinol has limited solubility in chloroform, therefore our group had attempted the condensation reaction of 67 with phloroglucinol in other solvents but the yields of 73 were poor, suggesting that chloroform appears to be the best solvent for this process. In response to this challenge, former group members devised a simple modification by using acetone/chloroform and masking the phenolic hydroxyl groups with trimethylsilyl ethers. Condensation of persilylated phloroglucinol 72, which was generated in situ from the reaction of phloroglucinol with trimethylsilyl chloride in the presence of triethylamine, with a mixture of diacetates 67 in chloroform/acetone in the presence of p-TsOH·H₂O afforded bicyclic compound 73. The separation of 73 from unreacted phloroglucinol by silica gel column chromatography was difficult, therefore the crude mixture of 73 and phloroglucinol was peracetylated to give pure triacetate 74 in ca. 70% yield from 67 following column chromatography. Hydrolysis of 74 with KOH in methanol regenerated pure 73 in almost quantitative yield. Rearrangement-cyclization of 73 promoted by TMSOTf in nitromethane gave tricylic ketocannabinoid 75 in ca. 80% yield. Treatment of 75 with 1.0 eq of N-phenyl triflimide provided monotriflate 76 regioselectively. The 9β-hydroxy cannabinoids generally have higher affinities for CB1 and CB2 receptors than the 9α-hydroxy diastereomers, therefore ketone 76 was reduced with sodium borohydride to give the equatorial alcohol 77, followed by methoxymethylation of the phenolic and the aliphatic hydroxyl groups to give intermediate triflate 78 in high yields. The details of the total synthesis of intermediate triflate 78 can be found in Dixon et al., 2010.
**2.3. Non-diastereoselective Synthesis of 2,2-Disubstituted Pyrrolidine Cannabinoids**

**Synthesis design**

The synthesis of 2,2-disubstituted pyrrolidine cannabinoids was designed starting from the common intermediate triflate 78. The pyrrolidine ring was introduced via desulfitative carbon–carbon cross coupling of pyrrolidine-2-thione with arylboronic acid 80, which was obtained from triflate 78 via Miyaura borylation followed by hydrolysis of arylboronic acid pinacol ester. The n-hexyl group of 83 was introduced via nucleophilic addition to cyclic imine 81. The details of these reactions will be discussed in what follows.

![Scheme 5. Retrosynthesis of 2,2-disubstituted pyrrolidine HHC.](image)

**Details**

The details of the synthesis of 2,2-disubstituted pyrrolidine cannabinoids are summarized in **Scheme 6**.
Reagents and conditions: (a) AcOK, PdCl$_2$(dppf), DMF, 90 °C, 3.5 h, 84%; (b) NaIO$_4$, NH$_4$OAc, (CH$_3$)$_2$CO/H$_2$O, rt, 20 h; (c) CuTC, Pd$_2$(dba)$_3$-CHCl$_3$, PPh$_3$, THF, microwaves, 100 °C, 2 h, 62% from 79; (d) i. LiCl, THF, rt, 30 min, ii. n-C$_6$H$_{13}$Li, -10 °C to rt, 2 h, 92%; (e) Sc(OTf)$_3$, 1,3-propanediol, CH$_3$CN, reflux, 48 h, 91%; (f) i. (HCHO)$_n$, Ti(OiPr)$_4$, diglyme, 60 °C, 30 min, rt, 30 min, ii. NaBH$_4$, rt, 3 h, 60 °C, 3 h, 80%.

**Scheme 6.** Synthesis of 2,2-disubstituted pyrrolidine cannabinoids.

Palladium-catalyzed coupling of aryl triflate 78 and commercially available bis(pinacolato)diboron provided aryl boronic ester 79 in 84% yield.$^{105}$ PdCl$_2$(dppf), which has been reported to be an effective catalyst for the borylation reactions of arylhalogenates as well as of *pseudohalogen* substrates like triflates, was used in 4 mol %. Pd(PPh$_3$)$_4$ was not used because of an earlier report that had mentioned the formation of an undesired byproduct from the coupling with a phenyl group on the triphenylphosphine.$^{106}$ The undesired biaryl byproduct from the Suzuki cross-coupling of aryl boronic ester 79 with triflate 78 was not detected. The critical factor for the success of the Miyaura borylation reaction is the base.$^{106}$ It was reported by Miyaura that KOAc is the appropriate base to give a high yield borylation reaction. This is because it not only accelerates the transmetalation step due to the high reactivity of the Pd-O
bond in the acetoxopalladium (II) intermediate, which consists of a soft acid and a hard base combination, as well as due to the high oxophilicity of the boron atom toward acetate, but also because it disfavors the formation of the biaryl byproduct. Stronger bases such as K₃PO₄ and K₂CO₃ have been reported to promote the undesired coupling reaction to the biaryl byproduct by activation of the boron atom of the aryl boronic ester product, therefore they are not used for this reaction.

Model studies on the cross-coupling reactions of phenylboronic acid, pinacol phenylboronate, or potassium trifluoro(phenyl)borate with pyrrolidine-2-thione have shown that only the boronic acid gave the desired product, suggesting that boronic ester 79 would need to be hydrolysed to boronic acid 80. The hydrolysis of boronic ester 79 was unexpectedly challenging. Conventional hydrolysis methods of pinacol arylboronates under strongly acidic conditions, such as HCl, BBr₃ as well as transesterification with diethanolamine followed by acidic hydrolysis were avoided because the methoxymethyl ether groups as well as the benzopyran ring in 79 and 80 are susceptible to acidic conditions. Using a different set of conditions, the conversion of boronic ester 79 with potassium bifluoride to potassium trifluoroborate 85 was successful, however, the attempted purification of 85 did not give a satisfactory result. As a consequence, the structural assignment for 85 could not be confirmed. Further in situ hydrolysis of 85 with bases such as K₂CO₃, LiOH, or with fluorophiles such as TMSCl or water–silica gel did not provide a clean sample of boronic acid 80 (Scheme 7).

Reagents and conditions: (a) KHF₂, CH₃OH/H₂O, rt, 30 min; (b) TMSCl, H₂O, CH₃CN, rt, 1 h; (c) K₂CO₃, CH₃CN/H₂O, rt, 20 h; (d) LiOH, CH₃CN/H₂O, rt, 20 h; (e) water–silica gel, rt, 24 h.

Scheme 7. Hydrolysis of boronic ester 79.
Boronic acid 80 was unstable and decomposed during hydrolysis under these conditions as well as during purification. It was reported by Kuivila and co-workers that under basic conditions boronic acids can undergo protodeboronation (Scheme 8, left).\textsuperscript{111} Analysing the Hammett rho value of the aqueous protodeboronation, Kuivila suggested the equilibrium-generated boronate undergoes a direct protonolysis rather than a cleavage via a Wheland intermediate. Also, Lennox and Lloyd-Jones have reported that boronic acids in anhydrous media tend to form trimeric anhydrides (boroxines), which are stabilized by their aromatic character in an entropically favored process that liberates 3.0 equivalents of water (Scheme 8, right).\textsuperscript{112,113}

Scheme 8. Base catalysed protodeboronation of arylboronic acid (left). Dehydration of boronic acid to form aromatic boroxines (right), Lennox and Lloyd-Jones 2014.\textsuperscript{113}

The hydrolysis of pinacol boronic ester 79 was complicated by the instability of boronic acid 80 as well as by the high propensity of the liberated diol to regenerate the pinacol boronic ester.\textsuperscript{113} Therefore, a strategy was used to drive the equilibrium in the forward direction by removing the pinacol. Oxidative cleavage of the pinacol boronic ester 79 by sodium metaperiodate in aqueous ammonium acetate and acetone gave boronic acid 80 in a very clean reaction.\textsuperscript{114} The driving force for the hydrolysis toward boronic acid is the oxidation of pinacol to acetone.\textsuperscript{115} The boronic acid 80 from the oxidative cleavage reaction after work up, extraction, and partial concentration was used for the next step without further purification.

Palladium(0)-catalyzed, copper(I)-mediated desulfitative carbon–carbon cross coupling of crude arylboronic acid 80 with pyrrolidine-2-thione in THF in a microwave reactor at 100 °C in 2 h gave cyclic imine 81 in 62% yield from boronic ester 79.\textsuperscript{116} It is noteworthy that the
Liebeskind-Srogl coupling reaction of 80 under conventional reflux conditions in THF or in dioxane proceeded very slowly (ca. 3 days) with high catalyst loading (10 mol% of Pd$_2$(dba)$_3$) and gave cyclic imine 81 in only 35-46% yield from 79, whereas microwave-assisted coupling reaction of 80 was complete in a shorter time, led to product in higher yield, and with only 4 mol% of Pd$_2$(dba)$_3$. Microwave irradiation is believed to produce efficient internal heating by directly acting on molecules. This probably prevents the formation of alternative products that would have arisen through competing pathways from gradual heating of the reaction mixture.\textsuperscript{117}

The mechanism, originally proposed by Prokopcova, for the desulfitative coupling reaction of boronic acid 80 is illustrated in Scheme 9. According to Prokopcova, copper (I) exchange of pyrrolidine-2-thione with Cu(I)-thiophene-2-carboxylate (CuTC) gave intermediate 86. This intermediate either undergoes Pd insertion to the C-S bond (oxidative addition) to form 87, followed by complexation with another equivalent of CuTC and combination with boronic acid 80 or undergoes a reversed process via 88, to give the key intermediate 89.

\textbf{Scheme 9.} Mechanism for the desulfitative thioamide–boronic acid cross-coupling, Prokopcova \textit{et al. 2007}.\textsuperscript{116}
CuTC as a cofactor polarizes the Pd-S bond through coordination of S to Cu(I) and simultaneously activates the boron atom through coordination of the carboxylate to the boron atom in the intermediate 89, leading to the base-free transmetalation with extrusion of Cu$_2$S. Reductive elimination of 90 provides cyclic imine 81 and regenerates the Pd(0) catalyst. CuTC was prepared from commercially available thiophene-2-carboxylic acid and Cu$_2$O in 80% yield according to the procedure described by Allred and Liebeskind.$^{118}$ Pyrrolidine-2-thione was prepared by treatment of pyrrolidin-2-one with 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane 2,4-disulfide (Lawesson reagent) in 90% yield.$^{119}$

The next important step in the synthesis of 2,2-disubstituted pyrrolidine cannabinoids is the nucleophilic addition of an organometallic nucleophile to cyclic imine 81 (Scheme 6). In the model reactions with 5-phenyl-3,4-dihydro-2H-pyrrrole, n-hexylmagnesium bromide did not provide the desired product. Also, no significant amount of desired mode of addition was observed when n-BuLi was used in a stoichiometric amount with 81 in a control experiment. Excess n-BuLi (3.0-8.0 equivalents) led to the desired nucleophilic addition product in ca. 40% yield. The use of TMSOTf as a Lewis acid to activate the imine$^{120}$ did not provide a better result. Surprisingly, addition of anhydrous LiCl into the reaction mixture resulted in a very clean reaction. This information was applied in the reaction of the real system. Treatment of cyclic imine 81 with 4.0 equivalents of anhydrous LiCl in THF for 30 min, followed by the addition of n-hexyllithium, which was generated in situ from the lithium–iodine exchange reaction of t-BuLi/pentane and n-hexyl iodide/Et$_2$O,$^{121}$ at -10 °C to room temperature gave cyclic amine 82 in 92% yield. The nucleophilic addition reaction did not occur or was too slow at temperatures lower than -30 °C. When Et$_2$O was used in the place of THF, the reaction mixture was not homogeneous due to the limited solubility of LiCl leading to a lower yield of product (ca. 65%). The precise role of LiCl is not certain. The lithium cation may act as a Lewis acid to activate cyclic imine 81, or in THF, a Lewis basic solvent, lithium cation may increase the reactivity of
the organometallic nucleophile by deaggregating oligomeric forms of \( n \)-hexyllithium.\textsuperscript{122} The nucleophilic addition has worked well under the above described procedure, therefore further experiments to confirm the role of LiCl were not explored. It is worth mentioning that the reaction mixture may have contained more than 4.0 equivalents of lithium cation. Although most of the LiI that was formed during the metal–halogen exchange reaction that was used to prepare the \( n \)-hexyllithium precipitated in ether, it is possible that a small amount was transferred via cannula into the reaction mixture containing imine \textsuperscript{81}. It should be noted that the lithium–halogen exchange reaction was not successful when \( n \)-hexyl bromide was used in the place of \( n \)-hexyl iodide, therefore \( n \)-hexyl iodide was prepared via a Finkelstein reaction in 86\% yield by treatment of \( n \)-hexyl bromide with potassium iodide in acetone at reflux.\textsuperscript{123} The preparation of \( n \)-hexyllithium following Gilman's procedure, in which \( n \)-hexyl bromide and lithium metal were refluxed in Et\(_2\)O, was tried but was found to be less effective (20\% in yield, determined by titration) mainly due to the undesired Wurtz coupling and the difficulty of maintaining anhydrous conditions for the duration of the reaction (\textit{ca.} 3 h).\textsuperscript{124}

Deprotection of the methoxymethyl ether groups in \textsuperscript{82} was predicted to be challenging. A Bronsted acid, which is usually used for the cleavage of the methoxymethyl ether, can protonate the benzylic amine, and the decomposition to form a benzylic cation may take place in competition with the desired process. Therefore a mild condition using a Lewis acid was selected for this reaction. Cleavage of the methoxymethyl protecting groups of amine \textsuperscript{82} with a stoichiometric amount of scandium (III) triflate in the presence of excess 1,3-propanediol in acetonitrile at reflux provided amine \textsuperscript{83} in 91\% yield.\textsuperscript{125} Catalytic amounts of Sc(OTf)\(_3\) or lower temperatures did not drive the reaction to completion while more than 3.0 equivalents of Sc(OTf)\(_3\) led to small amounts of decomposition product. The reaction at high concentration proceeded faster than at low concentration. The more 1,3-propanediol was used, the faster the reaction proceeded. However, when too much 1,3-propanediol was used, it was difficult to wash
this diol out from 83 because both compounds have high solubility in water and are also difficult to separate by conventional silica gel column chromatography due to the fact that they have similar mobilities on the column. Therefore, the use of 5.0 equivalents of 1,3-propanediol was optimal to drive the reaction to completion without causing difficulty for the purification of the desired product. Because amine 83 has appreciable water solubility in acid or base (because of the formation of the phenoxide), the minimum amount of pH 7 buffer was used to work up the reaction.

The last challenging step in the synthesis of 2,2-disubstituted pyrrolidine cannabinoids is the N-methylation of secondary amine 83. The classical Eschweiler-Clarke conditions, using formalin and formic acid at reflux,126 as well as the popular method of using formaldehyde-cyanoborohydride in acidic medium,127 were avoided due to the instability of 83 and 84 to strong acid. In a modification of the reductive amination for acid-sensitive compounds, Bhattacharyya reported that that titanium (IV) isopropoxide functions as a Lewis acid as well as an excellent water scavenger to generate either an iminium ion or a stable dialkylaminomethanolato titanium complex which can be reduced in a non-protic medium.128 Also, these mild conditions were expected to work well without protection of the hydroxy groups, and to tolerate steric hindrance from the nearby quaternary center. Accordingly reductive methylation of secondary amine 83 by treatment with paraformaldehyde in diglyme in the presence of titanium (IV) isopropoxide, followed by sodium borohydride reduction gave tertiary N-methylamine 84 in 80% yield.

Treatment of secondary amine 83 with 1.0 equivalent of succinic acid, L-(+-)tartaric acid, or hydrochloric acid gave ammonium hemisuccinate 91, hemitartrate 92, or chloride 93, respectively. Also, treatment of tertiary amine 84 with 1.0 equivalent of succinic acid or hydrochloric acid gave ammonium hemisuccinate 94 or chloride 95, respectively (Scheme 10).
Reagents and conditions: (a) succinic acid, CH$_3$OH, rt, 12 h, 91 or 94; (b) L-(+)-tartaric acid, CH$_3$OH, rt, 12 h, 92; (c) HCl, (CH$_3$)$_2$CO, rt, 12 h, 93 or 95.

**Scheme 10.** Salts preparation of 2,2-disubstituted pyrrolidine cannabinoids.
2.4. Synthesis of 3,3-Disubstituted Azetidine Cannabinoids

Synthesis design

The synthesis of 3,3-disubstituted azetidine cannabinoids was designed starting from the common intermediate triflate 78. The azetidine ring can be constructed by reductive cyclization of α-tosyloxymethyl nitrile 98. The aliphatic side chain can be introduced to triflate 78 via palladium-catalyzed decarboxylative coupling to form nitrile 96, followed by aldol condensation with paraformaldehyde.

![Chemical structures showing the synthesis process.]

Scheme 11. Retrosynthesis of 3,3-disubstituted azetidine HHC.

Details

The details of the synthesis of 3,3-disubstituted azetidine cannabinoids are summarized in Scheme 12.
Reagents and conditions: (a) [PdCl(C\textsubscript{3}H\textsubscript{5})\textsubscript{2}], Xantphos, xylene, 130 °C, 16 h, 82%; (b) (HCHO)\textsubscript{n}, 40% Triton B/CH\textsubscript{3}OH, toluene, 60 °C, 26 h, 95%; (c) p-TsCl, Et\textsubscript{3}N, DMAP, CH\textsubscript{2}Cl\textsubscript{2}, rt, 4 h, 94%; (d) LiAlH\textsubscript{4}, THF, rt, 3 h; (e) i. 37% HCHO\textsubscript{(aq)}, CH\textsubscript{3}OH, rt, 2 h, ii. NaBH\textsubscript{4}, rt, 2 h, 62% from 98; (f) Sc(OTf)\textsubscript{3}, C\textsubscript{2}H\textsubscript{5}OH, CH\textsubscript{3}CN, reflux, 12 h, 89%; (g) succinic acid, CH\textsubscript{3}OH, rt, 12 h, ∼99%.

**Scheme 12.** Synthesis of 3,3-disubstituted azetidine cannabinoids.

The introduction of the aliphatic side chain into the tricyclic cannabinoid nucleus was initially explored with the Buchwald–Hartwig palladium-catalyzed α-arylation. However, coupling triflate 78 with ethyl cyanoacetates did not give the desired products even though the conditions had been demonstrated successfully for 4-bromoanisole in a model study (Scheme 13). Most examples of the Buchwald–Hartwig palladium-catalyzed α-arylation have been reported with aryl bromides or aryl chlorides, but not with aryl triflates.\textsuperscript{129}
Conditions and reagents: (a) NaHMDS/THF, Pd(OAc)\(_2\), rac-BINAP, toluene, 100 °C, 20 h; (b) Na\(_3\)PO\(_4\), Pd\(_2\)Cl\(_2\)(C\(_3\)H\(_5\))\(_2\), (t-Bu)\(_3\)PHBF\(_4\), toluene, 70 °C, 5-20 h.

**Scheme 13.** Palladium-catalyzed α-arylation of 4-bromoanisole and of intermediate triflate 78.

Consequently, an alternative coupling reaction developed by Liu and co-workers was employed. Palladium-catalyzed decarboxylative coupling of potassium 2-cyanoctanoate with aryl triflate 78 provided a diastereomeric mixture of α-aryl nitriles 96 in 82% yield (Scheme 12).\(^{130}\)

Potassium 2-cyanoctanoate was prepared in two steps: monoalkylation of ethyl 2-cyanoacetate with 1.0 equivalent of 1-bromohexane in the presence of K\(_2\)CO\(_3\) in DMF at 85 °C gave ethyl 2-cyanoctanoate in 85% yield, and hydrolysis of the ester with 1.0 equivalent of potassium tert-butoxide in a combination with 1.0 equivalent of water in EtOH at 60 °C gave anhydrous potassium carboxylate in nearly quantitative yield. It is noteworthy that no extra base was required for the palladium-catalyzed decarboxylative cross coupling reaction. The reaction worked well in the temperature range of 120–130 °C, but a slightly higher reaction temperature (145 °C) led to the decomposition of triflate 78. The separation of 96 from 78 by conventional silica gel column chromatography is very difficult due to the fact that they have the same mobility on the column; luckily the reaction proceeded to completion facilitating the purification of the product. The mechanism, originally proposed by Jiang in the Liu group,\(^ {131}\) for the palladium-catalyzed decarboxylative coupling reaction of 78 is illustrated in **Scheme 14.**

According to Jiang, the catalyst [PdCl(C\(_3\)H\(_5\))]\(_2\) is reduced *in situ* and then combines with
Xantphos to generate Pd(0) complex. Oxidative addition of Pd(0) to aryl triflate 78, followed by metathesis with potassium 2-cyanoctanoate led to palladium carboxylate 103.

Scheme 14. Mechanism for the Pd-catalyzed decarboxylative α-arylation, Jiang et al. 2012.131

The most interesting step in the catalytic cycle is the decarboxylation. It has been reported by Tsuji132 and by Tunge133 that palladium is directly involved in the decarboxylation to form a metalated nitrile (see examples in Scheme 15).

Scheme 15. Palladium-catalyzed decarboxylation, Tunge et al. 2009.133

Also, anions of nitriles are known to be able to coordinate to a metal through the α-carbon or through the cyano nitrogen or to bridge two metals in a $\mu^2-C,N$ fashion.134 Therefore intermediate 103 (Scheme 14) is assumed to undergo decarboxylation under the effect of
palladium catalyst prior to reductive elimination to form the desired product. The other possibility (Scheme 16), not mentioned in the literature, in which the ketenimine form of 103 undergoes rearrangement from Pd-O to Pd-C bonding, followed by reductive elimination prior to decarboxylation is less attractive because it does not express the role of the palladium catalyst in the decarboxylation step.

Scheme 16. Alternative mechanism for decarboxylative coupling reaction.

The next step in the synthesis of 2,2-disubstituted azetidine cannabinoids is the introduction of a hydroxymethyl group at the α-position of nitrile 96. Condensation of α-aryl nitrile 96 with excess paraformaldehyde in the presence of Triton B (benzyltrimethylammonium hydroxide, 40% solution of CH₃OH) in toluene at 60 °C in a resealable sealed tube gave diastereomeric alcohols 97 in excellent yield (Scheme 12).¹³⁵

Treatment of alcohol 97 with p-TsCl and excess Et₃N in the presence of a stoichiometric amount of DMAP formed tosylate 98 in 94% yield.¹³⁶ Reduction of cyanotosylate 98 with excess LiAlH₄ in THF at room temperature and spontaneous substitution/cyclization of the intermediate amino derivative through displacement of the tosylate afforded 3,3-disubstituted azetidine 99.¹³⁷ Reductive methylation of crude secondary amine 99 by treatment with 37% aqueous formaldehyde in methanol, followed by sodium borohydride reduction of the iminium ion led to tertiary N-methylamine 100 in 62% yield from 98.¹³⁸ Cleavage of the methoxymethyl protecting groups of amine 100 using a stoichiometric amount of scandium triflate as before in the presence of excess ethanol provided amine 101 in 89% yield.¹²⁵ It was surprising that excess
ethanol worked well in the place of 5.0 equivalents of 1,3-propanediol for this reaction. The use of ethanol solved the problem of the separation of the desired amino alcohol product from 1,3-propanediol because ethanol can be easily removed by evaporation. Treatment of tertiary amine 101 with 1.0 equivalent of succinic acid gave ammonium hemisuccinate 102.
2.5. Diastereoselective Synthesis of 2,2-Disubstituted Azetidine Cannabinoids

Synthesis Design

The synthesis of 2,2-disubstituted azetidine cannabinoids was designed starting from the common intermediate triflate 78.

The initial proposal was for a nondiastereoselective synthesis. Introduction of the aliphatic side chain was planned to take place through nucleophilic addition to cyclic imine 112 in the same way in which 2,2-disubstituted pyrrolidine 82 had been prepared (Scheme 6). The plan was to prepare cyclic imine 116 from aryl nitrile 113 via Kulinkovich reaction to form cyclopropylamine 114, followed by diazo transfer and thermal rearrangement (Scheme 17). The model study using benzonitrile as the starting material provided 2-butyl-2-phenylazetidine in satisfactory yield. However, in the real system the Kulinkovich reaction of nitrile 113 gave a complicated mixture which was assumed to be a consequence of the instability of the benzopyran ring as well as of the methoxymethyl groups in the presence of BF3·Et2O.

Scheme 17. Nondiastereoselective synthesis of 2,2-disubstituted azetidine via Kulinkovich reaction and nucleophilic addition to cyclic imine.

In another nondiastereoselective synthesis, the synthesis of the azetidine ring was planned to take place by S$_{N}$2 cyclization of carbamate 120 or the corresponding primary amine...
(Scheme 18). Curtius rearrangement of carboxylic acid 119, which was to have been prepared from nitrile 96 via alkylation and hydrolysis would lead to carbamate 120. However, hydrolysis of sterically hindered nitrile 117 to either carboxylic acid 119 or its derivative amide failed under a number of conditions while attempted reduction of the nitrile to the aldehyde with DIBAL followed by oxidation to the carboxylic acid led to the cyclic imine 122. Displacement of the chloride probably took place with the intermediate aluminum salt. In an alternative approach, alkylation of the dianion derived from carboxylic acid 118 gave five-membered ring lactone 123 whereas alkylation of the dianion of 118 with protected 2-bromoethanol gave desired product 124 in only 30% yield.

Scheme 18. Nondiastereoselective synthesis of 2,2-disubstituted azetidine via Curtius rearrangement and S_N2 cyclization.
Since the nondiastereoselective synthesis of the 2,2-disubstituted azetidines had failed, we considered that we might have better success with an alternative, diastereoselective strategy. We considered that the azetidine ring could be constructed from β-amino ester 107 via condensation to azetidinone 108, followed by reduction. The desired highly diastereoselective preparation of β-amino ester 107 from ketone 104 was based on the elegant work developed by Ellman using the N-tert-butanesulfinyl group as a chiral auxiliary for the enolate addition to the derived imine. Ketone 104 was prepared from common intermediate triflate 78 via palladium catalyzed decarboxylative coupling followed by oxidative decyanation. The retrosynthesis according to these precepts is illustrated in Scheme 19.

Scheme 19. Diastereoselective retrosynthesis of 2,2-disubstituted azetidine cannabinoids.

Details

The details of the synthesis of 2,2-disubstituted azetidine cannabinoids are summarized in Scheme 20.
Reagents and conditions: (a) i. NaHMDS, THF, rt, 30 min, ii. O\(_2\) (gas), -78 °C, 30 min, iii. Na\(_2\)SO\(_3\) (aq), 0 °C, 30 min, 74%; (b) Ti(OMe)\(_4\), THF, reflux, 19 h, 92%; (c) CH\(_3\)COOC\(_2\)H\(_5\), LDA, TiCl(OMe)\(_3\), THF, -78 °C, 1 h, 81%; (d) HCl/1,4-dioxane, CH\(_3\)OH, 10 °C, 2 h, 85%; (e) CH\(_3\)MgBr, Et\(_2\)O, rt, 1.5 h, 78%; (f) LiBF\(_4\), CH\(_3\)CN, H\(_2\)O, 72 °C, 18 h, 87%; (g) LiAlH\(_4\), THF, 65 °C, 24 h; (h) i. 37% HCHO (aq), CH\(_3\)OH, rt, 3 h, ii. NaBH\(_4\), rt, 2 h, 70% from 108; (i) Dowex 50W-X8, CH\(_3\)OH, rt, 30 h, 77%.

**Scheme 20.** Diastereoselective synthesis of 2,2-disubstituted azetidine cannabinoids.

Oxidation of α-aryl nitrile 96 with molecular oxygen (gas tank) in the presence of sodium bis(trimethylsilyl)amide in THF at -78 °C, followed by reduction of intermediate sodium α-cyanohydroperoxide with aqueous sodium sulfite and spontaneous decyanation provided
ketone 104 in 74% yield. The mechanism for the oxidative decyanation of α-aryl nitrile 96, which was originally proposed by Watt et al., is illustrated in Scheme 21.

Scheme 21. Mechanism for the oxidative decyanation of α-aryl nitrile.

How molecular oxygen oxidizes the nitrile carbanion 125 is not certain and has not been discussed in detail in earlier reports. Nitrile carbanion 125 probably transfers an electron to molecular oxygen to form nitrile radical 126, followed by oxidation to nitrile peroxide anion 127. Reduction of α-hydroperoxynitrile 128 with aqueous sodium sulfite followed by spontaneous decyanation led to ketone 104. This reaction provides an effective way to prepare ketone 104 from intermediate triflate 78 in two high yielding steps: palladium-catalyzed decarboxylative coupling followed by oxidative decyanation. The synthesis of ketone 104 according to earlier work in our group by Dr. Darryl Dixon and Dr. Naoyuki Shimada required a larger number of steps. The details of this approach are summarized in Scheme 22. Palladium-catalyzed cyanation of triflate 78 with zinc cyanide in the presence of PMHS led to nitrile 130, followed by DIBAL reduction to gave aldehyde 131. Nucleophilic addition of n-hexylmagnesium bromide to 131 followed by oxidation of the resulting alcohol 132 with manganese dioxide provided ketone 104 in high yields.
Reagents and conditions: (a) Zn(CN)$_2$, Pd(PPh$_3$)$_4$, PMHS, DMF, 60 °C, 8 h; 96% (Dr. Dixon's result); (b) DIBAL, CH$_2$Cl$_2$, toluene, -78 °C, 1 h, 89% (Dr. Shimada's result); (c) $n$-C$_6$H$_{13}$MgBr, Et$_2$O, 0 °C, 1 h, 96%; (d) MnO$_2$, CH$_2$Cl$_2$, rt, 2 d, 92%.

Scheme 22. Original approach for the synthesis of ketone 104.

The diastereoselective synthesis of 2,2-disubstituted azetidine cannabinoids started with well-designed work developed by Ellman. Titanium (IV)-mediated condensation of the chiral auxiliary (R)-(+) tert-butanesulfinamide with ketone 104 in THF at reflux gave N-sulfinyl imine 105 in 92% yield (Scheme 20). The undesired deprotection of methoxymethyl groups or the aldol condensation of ketone did not occur under the influence of Ti(OEt)$_4$. Also, ketimine 105 was resistant to hydrolysis during aqueous work up and conventional purification. Approximately 2.0-3.0 equivalents of Ti(OEt)$_4$ and a small excess of tert-butanesulfinamide (1.1-1.3 equivalents) provided an excellent yield of imine 105. The reaction was slow and was not complete with a stoichiometric amount of Ti(OEt)$_4$, while too much reagent created difficulty during aqueous work up due to the formation of titanium oxide in hard cake form. Ellman and co-workers reported that only the E isomers were observed for N-tert-butanesulfinyl ketimines derived from methylphenyl ketone or n-butylphenyl ketone. (Note: The E assignment by the Ellman group is made by analogy to p-toluenesulfinyl imines, whose conformations were determined from X-ray crystal structures). In fact, the $^1$H NMR and $^{13}$C NMR spectra of
ketimine 105 in CDCl₃ showed only one geometric isomer. Nucleophilic addition of the titanium enolate which was generated in situ from transmetalation of the lithium enolate of ethyl acetate with TiCl(Oi-Pr)₃ to N-tert-butanesulfinyl imine 105 furnished ester 106 in 81% yield, dr = 9:1.¹⁴⁵ The stereochemical outcome of the reaction was rationalised by the Zimmerman–Traxler-type six-membered chair-like transition state that is stabilized by a four-membered metallocycle (Scheme 23). This had originally been proposed by David and co-workers for the asymmetric addition of lithium enolates to N-p-toluenesulfinyl imines¹⁴⁶ as well as later by the Ellman group for titanium enolate addition to N-tert-butanesulfinyl imines.¹⁴⁷

Scheme 23. Rationalization of the diastereoselectivity in asymmetric enolate addition to imine 105.

Transmetalation of the lithium enolate to a more covalent titanium enolate is very important for obtaining high diastereoselectivity in the reaction of enolate to sulfinimine. According to Ellman, addition in THF of the lithium enolate of methyl acetate with the N-tert-butylsulfinyl aldimine derived from benzaldehyde led to moderate diastereoselectivity (dr = 83:17), while the use of 2.0 equivalents of ClTi(Oi-Pr)₃ for transmetalation from lithium enolate to titanium enolate led to excellent diastereoselectivity (dr = 98:2). Similar excellent diastereoselectivities
were also observed in the addition of titanium enolates to N-tert-butylsulfinyl ketimines. The use 2.0 equivalents or more of ClTi(Oi-Pr)\textsubscript{3} is believed to favor the formation of the titanium enolate that is in equilibrium with a lithium enolate and a lithium–titanium–ate complex\textsuperscript{148} because 1.0 equivalent of ClTi(Oi-Pr)\textsubscript{3} was not effective to increase diastereoselectivity.\textsuperscript{145} Another early interesting example by Fujisawa and co-workers is that the addition of lithium enolate to p-toluenesulfinimine 135 in THF with HMPA, in which the counterion effect was negated by metal-coordinating HMPA solvent, gave product 136 via a non-chelation transition state 137, whereas chelation with titanium enolate in a Zimmerman–Traxler-type six-membered chair-like transition state containing a four-membered metallocycle 139, and/or even a seven-membered counterpart 140, gave the other diastereomer 138 (Scheme 24).\textsuperscript{149}

Scheme 24. Diastereoselectivity in the addition to imine via non chelation and chelation-control, Fujisawa \textit{et al.} 1996.\textsuperscript{149}

Applying these concepts to the reaction of N-tert-butanesulfinyl imine 105, the titanium enolate of ethyl acetate was prepared by treatment of the lithium enolate with ca. 2.0 equivalents of TiCl(Oi-Pr)\textsubscript{3}, which was prepared from TiCl\textsubscript{4} and Ti(Oi-Pr)\textsubscript{4} in toluene. The lithium enolate was generated \textit{in situ} from freshly prepared LDA and ethyl acetate in THF at -78 °C for 30 min. Addition of imine 105 as a THF solution at -78 °C to ca. 2.0-3.0 equivalents of titanium enolate at -78 °C for 1 h provided ester 106 in 70-81% yield. However, it was interesting that when
excess titanium enolate (ca. 6.0 equivalents) was used a Claisen condensation byproduct 141 was observed in ca. 30% yield (Scheme 25). The proportion of byproduct increased when the reaction was allowed to proceed for a longer time or at higher temperatures in the presence of excess titanium enolate.

Scheme 25. Claisen reaction of ester 104 with titanium enolate of ethyl acetate.

Cleavage of the tert-butylsulfinyl group of ester 106 by treatment of a methanolic solution with hydrochloric acid (4 N in dioxane) at 10 °C gave β-amino ester 107 in 85% yield (Scheme 20). It should be noted that temperature and reaction time strongly affected the course of the acidic methanolysis: the ratio (after work up with aqueous NaHCO₃) of starting material 106 to desired product 107 to undesired product in which one methoxymethyl protecting group was lost was ca. 2/3/0 at 0 °C after 4 h and 1/3/1 at room temperature after 1 h, nevertheless a good yield of 107 could be obtained at 10 °C after 2 h. The other diastereomer of 106 can be easily obtained by the same approach using the enantiomeric chiral auxiliary (S)-(−)-tert-butanesulfinamide.

The next important step is the construction of the four-membered ring from β-amino ester 107. One of the conventional approaches is reduction of the β-amino ester 107 to a γ-amino alcohol 142 with LAH followed by Mitsunobu ring closure with PPh₃ and DEAD (Scheme 26). The purification of the γ-amino alcohol 142 may be not convenient to due to its high polarity, and the Mitsunobu cyclization with free amino alcohol may take place in low
yield. Fukuyama's methodology, in which aminoalcohol is sulfonated (-Ns or -p-Ts), may give a high yield in the cyclization, but requires two extra steps.


We followed a different strategy for the construction of the azetidine ring which was originally developed by Testa intramolecular condensation/cyclization of the β-amino ester, followed by reduction of the azetidinone. Base-promoted lactamation of β-amino ester 107 with ca. 3.0 equivalents of methylmagnesium bromide in Et₂O at room temperature afforded 108 in 78% yield (Scheme 20). The precise mechanism for the reaction is not certain and has, to my knowledge, not been discussed in the literature. Undesired products derived from nucleophilic addition of the Grignard reagent to the carbonyl group of ester 107 as well as to the amide group of 108 groups did not take place to a significant extent because the deprotonation occurred faster than the nucleophilic addition (Scheme 27). The cyclization probably takes place by means of an indirect process that involves the initial formation of the ester enolate (pKa EtOAc 29.5 in DMSO). The amine is less acidic than the ester (pKa MeNH₂ ca. 41 in DMSO) therefore the equilibrium that is established through proton transfer from the amine to the enolate must greatly favor the enolate. Even so, the small amount of deprotonated amine can attack the nearby ester.
carbonyl group to form lactam 108. Rapid loss of a proton from the now much more acidic (pKa MeCONH$_2$ 25.5 in DMSO) amide nitrogen atom by the second equivalent of Grignard reagent protects the lactam from nucleophilic attack.

Scheme 27. Proposed mechanism for the Grignard reagent-promoted lactamization.

Another mechanism is that amino ester 107 can undergo kinetic deprotonation to 146 without process via intermediate 145. This is explained by the lone pair electron on the nitrogen atom of the -NH$_2$ group coordinates to the magnesium atom of the Grignard reagent that facilitates the deprotonation. To confirm the precise mechanism, the use of deuterium labeled ethylacetate to prepare deuterium labeled amino ester 107 from the precursor N-tert-butanesulfinyl imine 105 can be proposed.

Reduction of azetidinone 108 with LiAlH$_4$ in THF at 65 °C gave azetidine 110 in a clean reaction (Scheme 20).$^{155}$ Undesired amino alcohol was not detected in the reaction (Scheme 28), which is consistent with earlier reports by Testa that the reduction with LiAlH$_4$ of 2,2-disubstituted azetidinones (R$_1$ = phenyl, R$_2$ = ethyl, 84%) took place in high yield; a small amount of ring-opened amino alcohol product was observed with 2-monosubstituted azetidinones (R$_1$ = isopropyl, R$_2$ = H).$^{153}$
Scheme 28. Pathways for reduction of azetidinone with LAH, Jackson et al. 1983.\textsuperscript{156b}

The crude extract of amine 110 (after work up with Na\textsubscript{2}SO\textsubscript{4} paste, and drying with solid K\textsubscript{2}CO\textsubscript{3}) was used for the next step without further purification. Diborane in THF as well as alane in Et\textsubscript{2}O have been reported to give high yields for this type of reduction,\textsuperscript{156} but there was no need to explore other reductants since the results with LAH were satisfactory. Reductive methylation of crude secondary amine 110 by treatment with 37% aqueous formaldehyde in methanol, followed by sodium borohydride reduction led to tertiary N-methylamine 111 in 70% yield from 108 (Scheme 20).\textsuperscript{138}

Unlike the 2,2-disubstituted pyrrolidine and 3,3-disubstituted azetidine cannabinoids, the cleavage of methoxymethyl protecting groups of 2,2-disubstituted azetidinone 108 or 2,2-disubstituted azetidine 111 with Sc(OTf)\textsubscript{3} gave complicated reaction mixtures. Thiols as strong nucleophiles in combination with ZnBr\textsubscript{2} were examined for the methoxymethyl ether cleavage.\textsuperscript{157a,b} This combination of reagents was developed by Rawal and co-workers, and has proven to be effective by other members of our research group.\textsuperscript{85} Ethanethiol or butanethiol did not lead to a satisfactory result. One major compound observed in the reaction of EtSH with 108 has equal molecular weight (detected by HRESI) to the sum of the molecular weights of EtSH and of the desired product 109, which may indicate the addition of EtSH to the carbonyl group of azetidinone or to the quaternary carbon atom of the benzopyran ring. Accordingly, a less reactive nucleophile was used in the place of EtSH. Removal of the methoxymethyl protecting groups from 108 and 111 and with ZnBr\textsubscript{2} and benzyl mercaptan gave 109 and 112 in \textit{ca.} 70 and
80% yield (TLC yield and TLC scale), respectively. To refine methods for demethoxymethylation without using thiols due to their toxicity, Dowex 50W-X8 resin (H+ form) in methanol at room temperature converted 111 to 112 in 77% yield.\textsuperscript{157c} Unfortunately, desired tertiary amine 112 was not highly stable (the \textsuperscript{1}H NMR and ESI MS supports that a tertiary amine N-oxide was generated), therefore this compound will not be explored for the receptor binding studies. Unlike the case of amine 111, demethoxymethylation of lactam 108 with Dowex 50W-X8 gave a complicated mixture. This can be explained that amine 111 was absorbed on the surface of the resin easier than lactone 108 while the decomposition of the azetidinone ring of 108 probably occurred along with the demethoxymethylation. Alternatively, LiBF\textsubscript{4} in CH\textsubscript{3}CN/water at 72 °C converted 108 to 109 in 87% yield, in which LiBF\textsubscript{4} was known to disproportionate to LiF and BF\textsubscript{3} upon heating (Scheme 20).\textsuperscript{157d} Compound 108 will be evaluated in receptor binding affinities for CB1 and CB2.
2.6. Receptor Binding Studies

The affinities for CB1 and CB2 were determined by our collaborators in the group of Professor Makriyannis at Northeastern University. CB2 receptor-ligand binding affinities were measured for both mouse and human receptors because of species variation in CB2 while CB1 receptor-ligand binding affinities were measured only in rat because no significant variation in CB1 between rat and human receptors has been observed.86 Ligand affinities ($K_i$) of C1'-azacycloalkyl 9β-hydroxy hexahydrocannabinoids are displayed in Table 1.

Table 1. Ligand affinities ($K_i$) of C1'-azacycloalkyl 9β-hydroxy hexahydrocannabinoids.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Structure</th>
<th>$K_i$ (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>rCB1</td>
</tr>
<tr>
<td>AM-996 (83)</td>
<td><img src="image" alt="Structure" /></td>
<td>~900 nM</td>
</tr>
<tr>
<td>AM-997 (91)</td>
<td><img src="image" alt="Structure" /></td>
<td>&gt;1,000 nM</td>
</tr>
<tr>
<td>AM-998 (92)</td>
<td><img src="image" alt="Structure" /></td>
<td>~890 nM</td>
</tr>
<tr>
<td>Compound</td>
<td>Structure</td>
<td>$K_i$ (nM)</td>
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<tr>
<td>------------</td>
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<td>------------</td>
</tr>
<tr>
<td></td>
<td></td>
<td>rCB1</td>
</tr>
<tr>
<td>AM-999 (93)</td>
<td></td>
<td>~740 nM</td>
</tr>
<tr>
<td>AM-10500 (84)</td>
<td></td>
<td>68.2 nM</td>
</tr>
<tr>
<td>AM-10501 (94)</td>
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<td>15.6 nM</td>
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<tr>
<td>AM-10502 (95)</td>
<td></td>
<td>33.9 nM</td>
</tr>
<tr>
<td>AM-10505 (101)</td>
<td></td>
<td>22.4 nM</td>
</tr>
<tr>
<td>AM-10506 (102)</td>
<td></td>
<td>19.2 nM</td>
</tr>
</tbody>
</table>
Structure – activity relationships of C1'-azacycloalkyl 9β-hydroxy hexahydrocannabinoids, especially on C3- side chain with its C1'-azacycloalkyl substituents can be summarized as follows:

(1) The 2,2-disubstituted N-methyl pyrrolidine cannabinoid has significantly higher affinities for both CB1 and CB2 than the corresponding secondary pyrrolidine cannabinoids. The corresponding salts of these amines retain their binding affinities as their parent amines do, therefore these salts may be useful to improve pharmaceutical potency because their water solubilities are better than that of their parent amines.

(2) 3,3-Disubstituted N-methyl azetidine and 2,2-disubstituted N-methyl pyrrolidine cannabinoids have similar affinities for CB1 and CB2 and these ligands can bind well to both CB1 and CB2 at concentrations comparable to (−)-Δ9-THC (hCB1 = 40.7 nM, hCB2 = 36.4 nM). Binding affinities of these compounds were slightly less than those of the corresponding C1'-cyclobutyl, C1'-cyclopentyl cannabinoids (compound 48, 49, and 51) or of the 1',1'-dithiolane analog (compound 45). This suggests that a hydrophilic element (nitrogen atom) in the C1'-cycloalkyl position decreases binding affinities for both receptors, which is consistent with an earlier hypothesis by the group of Professor Makriyannis that the introduction of a hydrophobic element to this position increases binding affinities. 79,80

(3) The 2,2-disubstituted N-methyl azetidine cannabinoid was not evaluated for binding affinities due to its low stability. Evaluation of binding affinities of the diastereomeric 2,2-disubstituted azetidinone cannabinoid is in progress. This compound is expected to provide a
useful probe for determining the deactivation of cannabinergic ligands because it is expected to be susceptible to enzymatic hydrolysis by plasma esterases, in which case the hydrolysed form of 108 would behave differently in receptor binding assays.
2.7. Experimental Section - chapter 2

General

$^1$H NMR and $^{13}$C NMR spectra were recorded at 500 MHz ($^1$H) and 126 MHz ($^{13}$C). Chemical shifts are reported in parts per million (δ) and are referenced to the solvent, i.e. 7.26/77.0 for CDCl$_3$. Multiplicities are indicated as br (broadened), s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), or m (multiplet). Coupling constants (J) are reported in Hertz (Hz). Thin layer chromatography (TLC) was performed on glass plates 250 µm, particle size 5-17 µm, pore size 60 Å. Flash column chromatography was performed on silica gel, 200-400 mesh, or premium silica gel, 60 Å, 40-75 µm. All moisture sensitive reactions were performed under a static atmosphere of nitrogen or argon in oven-dried or flame-dried glassware. Purity and homogeneity of all materials was determined to be at least 95% from TLC, $^1$H NMR, $^{13}$C NMR, and LC–MS. All optical rotations were measured on a JASCO digital polarimeter in a 0.1 dL cell.
**Intermediate triflate 78**

![Chemical structure](image)

2-((1R,2R,5R)-6,6-dimethyl-4-oxobicyclo[3.1.1]heptan-2-yl)benzene-1,3,5-triy1 triacetate (74)

To a suspension of anhydrous benzene-1,3,5-triol (3.78 g, 0.03 mol) in CH$_2$Cl$_2$ (250 mL) under a nitrogen atmosphere at 0 °C was slowly added Et$_3$N (16.7 mL, 0.12 mol) followed by dropwise addition of TMSCl (15.0 mL, 0.12 mol). (Note. A higher concentration, using less CH$_2$Cl$_2$, led to difficulty in stirring). After completion of addition, the reaction mixture was stirred at 0 °C for an additional 20 min, then at room temperature for 2 h. The solid was removed via filtration (Celite pad). The filtrate was washed with ice cold water (100 mL × 3), dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure at 22 °C to afford 1,3,5-tris((trimethylsilyl)oxy)benzene 72 as a dark pink oil. To a solution of crude 72 in CHCl$_3$/acetone (300 mL, 4/1) under a nitrogen atmosphere at 0 °C was added a solution of diacetates 67 (2.98 g, 12.5 mmol; 4.80 g of material containing 62% pure diacetates 67) and p-TsOH·H$_2$O (3.08 g, 16.2 mmol) in CHCl$_3$/acetone (100 mL, 4/1) dropwise via an addition funnel. After completion of addition (ca. 1.5-2 h), the reaction mixture was slowly warmed to room temperature, and stirred for an additional 4 h. The reaction was quenched with a minimum amount of saturated aqueous NaHCO$_3$ (until pH ~ 8), and stirred for 45 min under nitrogen. (Note. Too much NaHCO$_3$ led to difficulty in later extraction of product from aqueous layer). The organic layer was separated while the aqueous layer was extracted with EtOAc until most product was absent in the aqueous layer as judged by TLC. The combined organic layer was
dried over MgSO₄ and concentrated under reduced pressure to give crude phenol 73. To a mixture of crude 73 and DMAP (76 mg, 0.63 mmol) in CH₂Cl₂ (150 mL) under a nitrogen atmosphere at 0 °C was slowly added pyridine (8.9 mL, 0.11 mol), resulting in a homogeneous solution, followed by dropwise addition of Ac₂O (10.5 mL, 0.11 mol), and the reaction mixture was stirred for 12 h. The reaction was quenched with ice cold water, and the organic material was washed with 1 M aqueous HCl, brine, dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with EtOAc/hexane (3/7) as eluent to afford triacetate 74 (3.25 g, 67% yield from 67) as a white solid.

(1R,4R,5R)-6,6-dimethyl-4-(2,4,6-trihydroxyphenyl)bicyclo[3.1.1]heptan-2-one (73)

To a solution of triacetate 74 (6.76 g, 17.4 mmol) in CH₃OH at 0 °C was added KOH (3.42 g, 60.9 mmol) at once under nitrogen, and the reaction mixture was stirred at this temperature for 2 h. The reaction was quenched under nitrogen atmosphere at 0 °C with 1M aqueous HCl (until pH ~ 2) through a syringe. The solution was partially concentrated under reduced pressure, and the organic material was extracted with EtOAc. The combined organic layer was washed with brine, dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (a short column) with EtOAc/hexane (1/1 → 4/1) as eluent to afford 73 (4.39 g, 96% yield) as an off-white foam that typically contains 10-20% ethyl acetate.
(6aR,10aR)-1,3-dihydroxy-6,6-dimethyl-7,8,10,10a-tetrahydro-6H-benzo[c]chromen-9(6aH)-one (75)

To a solution of 73 (589 mg, 2.25 mmol; 693 mg of material containing 85% pure 73 and 15% EtOAc) in CH$_3$NO$_2$ (150 mL) under a nitrogen atmosphere at 0 °C was added TMSOTf (1.0 mL, 5.63 mmol) slowly over 20 min, and the reaction mixture was stirred at 0 °C for an additional 2.5 h. The reaction was quenched with solid K$_2$CO$_3$ and the heterogeneous mixture was stirred for 45 min under nitrogen at room temperature. The solids were filtered off and the solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (a short column) with EtOAc/hexane (1/1) as eluent to afford 75 (489 mg, 83% yield) as an white foam that typically contains 10-20% ethyl acetate.

(6aR,10aR)-1-hydroxy-6,6-dimethyl-9-oxo-6a,7,8,9,10,10a-hexahydro-6H-benzo[c]chromen-3-yl trifluoromethanesulfonate (76)

To a solution of phenol 75 (2.62 g, 0.01 mol; 3.25 g of material containing 81% pure 75 and 19% EtOAc) in CH$_2$Cl$_2$ (100 mL) under a nitrogen atmosphere at 0 °C was added Et$_3$N (4.2 mL, 0.03 mmol) followed by dropwise addition of a solution of N-phenyltrifluoromethanesulfonylimide (3.93 g, 0.011 mmol) in CH$_2$Cl$_2$ (100 mL) via an addition funnel. After completion of addition, the reaction mixture was stirred at ambient temperature for 14 h. The reaction was quenched with 1 M aqueous HCl, and the organic material was extracted with CH$_2$Cl$_2$. The combined organic layer was washed with water, brine, dried over MgSO$_4$, and concentrated to afford 76 (4.03 g, 85% yield) as a yellow oil.
filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with EtOAc/hexane (1/4 → 2/3) as eluent to afford monotriflate 76 (3.31 g, 84% yield) as a white semisolid.

(6aR,9R,10aR)-1,9-dihydroxy-6,6-dimethyl-6a,7,8,9,10,10a-hexahydro-6H-benzo[c]chromen-3-yl trifluoromethanesulfonate (77)

To a solution of ketone 76 (2.72 g, 6.90 mmol) in CH₂OH (70 mL) at -5 °C (ice–salt bath) was added NaBH₄ (1.31 g, 34.5 mmol) in 3 portions over 5 min, and the reaction mixture was stirred at this temperature for 1 h. The reaction was quenched by dropwise addition of 1 M aqueous HCl at 0 °C, and the organic material was diluted and extracted with EtOAc. The combined organic layer was washed with brine, dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with EtOAc/hexane (2/3) as eluent to afford alcohol 77 and the minor 9α-hydroxy diastereomer (2.46 g, 90% combined yield, dr = 94:6) as a white foam. The 9α-hydroxy diastereomer was well separated by column chromatography after the subsequent methoxymethyl ether protection.

(6aR,9R,10aR)-1,9-bis(methoxymethoxy)-6,6-dimethyl-6a,7,8,9,10,10a-hexahydro-6H-benzo[c]chromen-3-yl trifluoromethanesulfonate (78)

To a solution of alcohol 77 (2.29 g, 5.78 mmol) in CH₂Cl₂ (60 mL) under a nitrogen atmosphere at 0 °C was added N,N-diisopropylethylamine (6.0 mL, 34.7 mmol), followed by dropwise
addition of chloro(methoxy)methane (2.6 mL, 34.7 mmol). The reaction mixture was stirred at 45 °C for 45 min, then at room temperature for 2 h. The reaction was quenched with saturated aqueous NaHCO₃, and the organic material was extracted with Et₂O. The combined organic layer was washed with CuSO₄ (until no more precipitate formed), brine, dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with EtOAc/hexane (1/9 → 1/4) as eluent to afford intermediate triflate 78 (2.48 g, 89% yield) as a clear, colorless oil.

The spectral data of intermediate 78 and its precursors were identical to those reported in the literature, *J. Med. Chem.* 2010, 53, 5656–5666.
2,2-Disubstituted pyrrolidine cannabinoids

\[
\text{To a mixture of triflate } 78 \text{ (485 mg, 1.0 mmol), diboron pinacol ester (305 mg, 1.20 mmol), KOAc (295 mg, 3.0 mmol), and PdCl}_2(dppf) \text{ (30 mg, 0.04 mmol) under an argon atmosphere at room temperature was added DMF (10 ml), and the reaction mixture was stirred at 90 °C for 3.5 h. After the mixture was cooled to room temperature, water was added, and the organic material was extracted with benzene/Et}_2O (1/1). The combined organic layer was washed with water, brine, dried over MgSO}_4, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography with EtOAc/hexane (1/4) as eluent to afford pinacol boronic ester } 79 \text{ (387 mg, 84% yield) as a light yellow amorphous solid.}
\]

\[\begin{align*}
\text{1H NMR (500 MHz, CDCl}_3 \text{) } &\delta 6.97 (d, J = 1.0 \text{ Hz, 1H}), 6.95 (d, J = 1.0 \text{ Hz, 1H}), 5.28 – 5.17 (m, 2H), 4.77 – 4.69 (m, 2H), 3.75 (tt, J = 11.1, 4.5 \text{ Hz, 1H}), 3.51 (s, 3H), 3.46 – 3.40 (m, 1H), 3.38 (s, 3H), 2.49 (td, J = 11.3, 2.6 \text{ Hz, 1H}), 2.23 – 2.14 (m, 1H), 1.93 – 1.86 (m, 1H), 1.57 – 1.49 (m, 1H), 1.49 – 1.39 (m, 1H), 1.37 (s, 3H), 1.30 (s, 6H), 1.29 (s, 6H), 1.18 – 1.04 (m, 2H), 1.02 (s, 3H). \\
\text{13C NMR (126 MHz, CDCl}_3 \text{) } &\delta 156.0, 154.4, 128.3, 118.3, 117.3, 110.5, 94.6, 94.4, 83.6, 76.5, 75.6, 56.4, 55.1, 48.6, 36.4, 34.2, 33.1, 27.7, 26.1, 24.8, 24.7, 18.7. \\
\text{11B NMR (160 MHz, CDCl}_3 \text{) } &\delta 31.6 \text{ (external reference BF}_3\text{Et}_2O). IR (thin film, cm}^{-1}: 3048, 2940, 2878, 1558, 1365, 1141, 1042, 979, 856, 740. HRMS ((+)ESI) m/z caled for C}_{25}H_{46}BO_7 \text{ [M+H]}^+, 463.2862; found 463.2888. [\alpha]^{23}_D -46.8^\circ \text{(c 3.0, CH}_2\text{OH).}
\end{align*}\]
Pyrrolidine-2-thione

A flask containing pyrrolidone (0.85 g, 0.01 mol) and 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane 2,4-disulfide) (2.02 g, 0.005 mol) was purged with nitrogen and moved to a pre-heated oil bath at 80 °C and stirred. When the reaction mixture became partially liquid (ca. 5 min), toluene (40 mL) was added slowly during 10 min via syringe. The reaction mixture was stirred at this temperature until it became homogeneous (ca. 5 min), and at that time the \(^1\)H NMR spectra showed that most of pyrrolidine was consumed. After the mixture was cooled to room temperature, Celite was added, and solvent was removed under reduced pressure. The residue was purified by flash silica gel column chromatography with EtOAc/hexane (2/3 \(\rightarrow\) 1/1) as eluent to afford thiopyrrolidone (0.91 g, 90%) as a white solid. Spectral data were identical to those reported in the literature, *Tetrahedron* **2009**, 65, 2484–2496.

\[
\begin{array}{c}
\text{O} \\
\text{N} \\
\rightarrow \\
\text{S} \\
\text{N}
\end{array}
\]

(Thiophene-2-carbonyl)oxy)copper

A flask containing thiophene-2-carboxylic acid (4.99 g, 39.0 mmol), Cu\(_2\)O (1.38 g, 9.75 mmol), and toluene (16 mL), outfitted with a Dean-Stark trap with activated 4Å molecular seives and a condenser was purged with nitrogen. The reaction mixture was refluxed for 18 h with azeotropic removal of water. The yellow/brown suspension was cooled to 60 °C and the product was collected on a medium pore fritted-glass funnel. Under a stream of nitrogen the filter cake was washed with CH\(_3\)OH (15 mL) to remove excess acid, followed with Et\(_2\)O until the eluent was colorless, and finally with a small amount of hexane. The product was dried on the fritted-glass funnel under a flow of nitrogen, transferred to a round bottom-flask, and further dried under vacuum to give copper (I) thiophene carboxylate (5.95 g, 80%) as a tan powder. The preparation

\[
\begin{array}{c}
\text{S} \\
\text{C} \text{O} \text{C} \text{H} \\
\rightarrow \\
\text{S} \\
\text{C} \text{O} \text{C} \text{Cu}
\end{array}
\]
followed the procedure that was described in the literature, *J. Am. Chem. Soc.* 1996, **118**, 2748–2749.

![Chemical Structures](image)

5-((6aR,9R,10aR)-1,9-Bis(methoxymethoxy)-6,6-dimethyl-6a,7,8,9,10,10a-hexahydro-6H-benzo[c]chromen-3-yl)-3,4-dihydro-2H-pyrrrole (81)

To a solution of pinacol boronic ester 79 (231 mg, 0.50 mmol) in acetone/water (10 mL, 1/1) was subsequently added NaIO₄ (320 mg, 1.50 mmol) and NH₄OAc (135 mg, 1.75 mmol). After flushing with nitrogen, the thick suspension was stirred at room temperature until most of 79 was consumed as judged by TLC (ca. 20 h). Solvent was partially removed under reduced pressure at 23 °C and the organic material was extracted with EtOAc. The combined organic layer was washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure at 23 °C. Toluene was added in aliquots during concentration to avoid the decomposition of boronic acid 80. The crude concentrated toluene solution (ca. 1 mL) of 80 was immediately diluted with THF (10 mL) and the solution was added to a microwave process vial containing thioamide (51 mg, 0.50 mmol), CuTC (285 mg, 1.50 mmol), Pd₂dba₃·CHCl₃ (21 mg, 0.02 mmol), and PPh₃ (21 mg, 0.08 mmol) under an argon atmosphere. The mixture was heated in a microwave reactor at 100 °C for 2 h. After cooling to room temperature, the mixture was concentrated under reduced pressure. CHCl₃ (120 mL) was added, and the organic layer was washed with 25% aqueous ammonia (40 mL × 3). The aqueous layer was back extracted with CHCl₃ (40 mL × 3). The combined organic layer was dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column
chromatography with EtOAc/hexane (2/3) as eluent to afford imine 81 (126 mg, 62% yield from 79) as a light yellow oil.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.29 (d, $J = 1.6$ Hz, 1H), 6.81 (d, $J = 1.6$ Hz, 1H), 5.32 – 5.20 (m, 2H), 4.76 – 4.68 (m, 2H), 4.07 – 3.96 (m, 2H), 3.80 – 3.68 (m, 1H), 3.49 (s, 3H), 3.44 – 3.35 (m, 4H), 2.98 – 2.83 (m, 2H), 2.49 (td, $J = 11.3$, 2.6 Hz, 1H), 2.23 – 2.14 (m, 1H), 2.06 – 1.96 (m, 2H), 1.93 – 1.84 (m, 1H), 1.57 – 1.50 (m, 1H), 1.48 – 1.34 (m, 4H), 1.18 – 1.01 (m, 5H). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 173.9, 156.4, 154.6, 133.1, 117.0, 112.0, 103.9, 94.7, 94.5, 77.1, 75.5, 60.6, 56.5, 55.1, 48.4, 36.3, 34.8, 34.1, 33.0, 27.6, 26.0, 22.3, 18.7. IR (neat, cm$^{-1}$): 3055, 2940, 2878, 1612, 1566, 1427, 1350, 1265, 1150, 1041, 987, 918, 740. HRMS ((+)-ESI) $m/z$ calcd for C$_{23}$H$_{33}$NNaO$_5$ [M+Na]$^+$, 426.2251; found 426.2230. $[\alpha]_{D}^{23}$ $-42.3^o$ (c 2.0, CH$_3$OH).

1-Iodohexane

A mixture of 1-bromohexane (1.64 g, 0.01 mol) and KI (2.49 g, 0.015 mol) in acetone (35 mL) was refluxed for 3 h under a nitrogen atmosphere. After the mixture was cooled to room temperature, water was added, and the organic material was immediately extracted with hexane. The combined organic layer was washed with water, dried over MgSO$_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with hexane as eluent to afford 1-iodohexane (1.82 g, 86% yield) as a colorless oil. Spectral data were identical to those reported in the literature, Tetrahedron Lett. 2008, 49, 2638–2641.
To a solution of 1-iodohexane (318 mg, 1.50 mmol) in Et₂O (3.0 mL) under an argon atmosphere at -78 °C was added a 0.9 M solution of t-BuLi in pentane (3.0 mL, 2.70 mmol) dropwise. The reaction mixture was stirred at -78 °C for an additional 30 min, warmed up to room temperature over 20 min, and stirred at room temperature for an additional 1 h, at which time the mixture became a cloudy suspension. In another flask, a mixture of imine 81 (202 mg, 0.50 mmol), freshly azeotroped with benzene, and anhydrous LiCl (84 mg, 2.0 mmol) in THF (20 mL) under an argon atmosphere was stirred at room temperature for 30 min. The homogeneous solution was then cooled to -10 °C, followed by dropwise addition of n-hexyllithium via cannula. The reaction mixture was slowly warmed up from -10 °C to room temperature over 2 h. A solution of pH 7 phosphate buffer (3 mL) was added via syringe and the organic material was extracted with Et₂O. The combined organic layer was dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with NH₄OH(aq)/CH₃OH/CH₂Cl₂ (1/5/94) as eluent to afford amine 82 (225 mg, 92% yield) as a mixture of diastereoisomers at C1' (brown oil). Interpretation of the ¹H and ¹³C NMR spectra was rendered difficult by the presence of the two diastereomers that led to overlapping signals.

¹H NMR (500 MHz, CDCl₃) δ 6.78 – 6.74 (m, 1H), 6.48 – 6.43 (m, 1H), 5.34 – 5.18 (m, 2H), 4.77 – 4.68 (m, 2H), 3.73 (tt, J = 11.1, 4.5 Hz, 1H), 3.49 (s, 3H), 3.45 – 3.27 (m, 5H), 3.16 – 3.03 (m, 1H), 2.48 – 2.40 (m, 1H), 2.35 – 2.24 (m, 1H), 2.23 – 2.13 (m, 1H), 2.02 – 1.78 (m, 6H), 1.60 – 1.40 (m, 2H), 1.38 (s, 3H), 1.35 – 1.04 (m, 9H), 1.04 (s, 3H), 0.92 – 0.82 (m, 1H),
0.80 (t, J = 6.8 Hz, 3H). $^1$C NMR (126 MHz, CDCl$_3$) δ 156.55, 154.61, 140.82, 113.00, 108.92, 103.78, 94.84, 94.65, 75.56, 71.16, 63.02, 56.49, 55.13, 53.39, 48.46, 44.02, 40.31, 36.31, 33.77, 33.13, 32.74, 31.48, 29.31, 27.72, 26.09, 24.77, 22.49, 18.84, 13.99. IR (neat, cm$^{-1}$): 3471, 3055, 2940, 2878, 1612, 1574, 1419, 1265, 1157, 1042, 918, 740. HRMS ((+)-ESI) m/z calcd for C$_{29}$H$_{48}$NO$_5$ [M+H]$^+$, 490.3527; found 490.3548.

(6aR,9R,10aR)-3-(2-Hexylypyrrolidin-2-yl)-6,6-dimethyl-6a,7,8,9,10,10a-hexahydro-6H-benzo[c]chromene-1,9-diol (83)

To a mixture of amine 82 (49 mg, 0.10 mmol) and 1,3-propanediol (38 mg, 0.50 mmol) in CH$_3$CN (10 mL) at room temperature was added Sc(OTf)$_3$ (49 mg, 0.10 mmol). After flushing with nitrogen, the reaction mixture was refluxed for 48 h. CH$_3$CN was removed under reduced pressure, and a minimum amount of pH 7 phosphate buffer (0.5 mL) was added and the reaction mixture was stirred for 10 min. The organic material was extracted with Et$_2$O, dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with NH$_4$OH (aq)/CH$_3$OH/CH$_2$Cl$_2$ (1/5/94 $\rightarrow$ 1/9/90) as eluent to afford amine 83 (36 mg, 91% yield) as a mixture of diastereoisomers at C1' (brown amorphous solid). Interpretation of the $^1$H and $^{13}$C NMR spectra was rendered difficult by the presence of the two diastereomers that led to overlapping signals.

$^1$H NMR (500 MHz, CD$_3$OD): δ 6.31 – 6.26 (m, 2H), 3.74 (tt, J = 11.0, 4.5 Hz, 1H), 3.53 – 3.46 (m, 1H), 3.45 – 3.38 (m, 1H), 3.29 – 3.24 (m, 1H), 2.47 (td, J = 11.3, 5.7 Hz, 1H), 2.39 – 2.05 (m, 5H), 1.99 – 1.83 (m, 3H), 1.49 – 1.15 (m, 11H), 1.12 – 0.80 (m, 10H). $^{13}$C NMR (126 MHz, CD$_3$OD): δ 158.6, 156.9, 139.4, 114.0, 107.3, 105.8, 78.4, 73.8, 71.2, 50.0, 44.6, 39.6, 38.9,
36.6, 34.9, 32.5, 30.2, 29.4, 28.1, 27.1, 25.3, 23.5, 22.9, 19.2, 14.3. IR (thin film, cm\(^{-1}\)): 3184–3584 (br), 3055, 2936, 2870, 1620, 1582, 1421, 1265, 1174, 1029, 741, 704, 638. HRMS ((+) ESI) \(m/z\) calcd for C\(_{25}\)H\(_{40}\)NO\(_3\) [M+H]\(^+\), 402.3003; found 402.2991.

(6a\(R\),9\(R\),10a\(R\))-3-(2-Hexyl-1-methylpyrrolidin-2-yl)-6,6-dimethyl-6a,7,8,9,10,10a-hexahydro-6\(H\)-benzo[c]chromene-1,9-diol (84)

To a mixture of secondary amine 83 (ca. 10 mg, 0.025 mmol) and paraformaldehyde (ca. 3 mg) under an argon atmosphere at room temperature was added a 0.05 M solution of Ti(Oi-Pr\(_4\)) in freshly distilled diglyme (1 mL, 0.05 mmol). The reaction mixture was stirred at 60 °C for 30 min, then at room temperature for an additional 30 min. NaBH\(_4\) (ca. 20 mg, 0.53 mmol) was added and the resulting mixture was stirred at room temperature for 3 h, then at 60 °C for an additional 3 h. After the mixture was cooled to 0 °C, a 2 M aqueous solution of ammonia (1.5 mL) was added slowly during 15 min, and the organic material was extracted with Et\(_2\)O. The combined organic layer was dried over Na\(_2\)SO\(_4\), filtered, and concentrated under reduced pressure at 60 °C (to remove diglyme). The residue was purified by silica gel column chromatography with NH\(_3\)OH\(_{aq}\)/CH\(_3\)OH/CH\(_2\)Cl\(_2\) (1/5/94) as eluent to afford tertiary amine 84 (ca. 8 mg) as a mixture of diastereoisomers at C1’ (light pink oil). Interpretation of the \(^1\)H and \(^13\)C NMR spectra was rendered difficult by the presence of the two diastereomers that led to overlapping signals.

\(^1\)H NMR (500 MHz, CD\(_3\)OD): \(\delta\) 6.32 – 6.26 (m, 1H), 6.24 – 6.19 (m, 1H), 3.73 (tt, \(J = 11.0, 4.4\) Hz, 1H), 3.57 – 3.45 (m, 1H), 3.08 – 2.94 (m, 1H), 2.64 – 2.51 (m, 1H), 2.47 (td, \(J = 11.3, 2.6\) Hz, 1H), 2.43 – 2.37 (m, 1H), 2.29 – 2.07 (m, 5H, NMe and 2CH), 2.04 – 1.85 (m, 4H), 1.54 – 1.13 (m, 12H), 1.14 – 0.83 (m, 10H). \(^13\)C NMR (126 MHz, CD\(_3\)OD): \(\delta\) 157.6, 156.0, 137.9,
112.8, 109.7, 108.1, 78.0, 71.7, 71.3, 54.4, 50.1, 39.7, 36.6, 35.9, 34.9, 32.8, 32.7, 31.0, 29.7, 28.2, 27.2, 26.4, 23.7, 19.2, 14.4. IR (neat, cm$^{-1}$): 3192–3584 (br), 3051, 2933, 2868, 1618, 1573, 1413, 1364, 1265, 1139, 1053, 897, 733, 703, 677. HRMS ((+)-ESI) $m/z$ calcd for C$_{26}$H$_{42}$NO$_3$ [M+H]$^+$, 416.3159; found 416.3165.

$2$-((6$a$R,9$R$,10$a$R)$\text{-}1,9$\text{-}$Dihydroxy$\text{-}6,6$-dimethyl$\text{-}6a,7,8,9,10,10a$-hexahydro$\text{-}6H$-benzo[c]chromen$\text{-}3$-yl)$\text{-}2$-hexylpyrrolidin$\text{-}1$-ium 3-carboxypropanoate (91)

To amine 83 (ca. 8 mg, 0.02 mmol) under a nitrogen atmosphere was added a 0.02 M solution of succinic acid in CH$_3$OH (1 mL, 0.02 mmol), and the mixture was stirred at room temperature for 12 h. CH$_3$OH was removed under reduced pressure to give ammonium hemisuccinate 91 (ca. 10 mg) as a mixture of diastereoisomers at C1'. Interpretation of the $^1$H and $^{13}$C NMR spectra was rendered difficult by the presence of the two diastereomers that led to overlapping signals.

$^1$H NMR (500 MHz, CD$_3$OD): $\delta$ 6.34 – 6.24 (m, 2H), 3.74 (tt, $J = 11.1, 4.4$ Hz, 1H), 3.53 – 3.46 (m, 1H), 3.46 – 3.37 (m, 1H), 3.29 – 3.23 (m, 1H), 2.55 (s, 4H, succinate), 2.47 (td, $J = 11.2, 2.4$ Hz, 1H), 2.39 – 2.05 (m, 5H), 1.97 – 1.84 (m, 3H), 1.48 – 1.15 (m, 11H), 1.11 – 0.76 (m, 10H).

$^{13}$C NMR (126 MHz, CD$_3$OD): $\delta$ 176.2, 158.5, 156.9, 139.4, 113.9, 107.3, 105.8, 78.4, 73.8, 71.2, 50.0, 44.6, 39.6, 38.9, 36.6, 34.9, 32.5, 30.2, 29.9, 29.4, 28.1, 27.1, 25.3, 23.5, 22.9, 19.2, 14.3. IR (neat, cm$^{-1}$): 3165–3584 (br), 3053, 2936, 2870, 1714, 1620, 1581, 1421, 1265, 1174, 1030, 739, 704, 638. HRMS ((+)-ESI) $m/z$ calcd for C$_{26}$H$_{40}$NO$_3$ [M+H]$^+$, 402.3003; found 402.2995.
2-((6aR,9R,10aR)-1,9-Dihydroxy-6,6-dimethyl-6a,7,8,9,10,10a-hexahydro-6H-benzo[c]chromen-3-yl)-2-hexylpyrrolidin-1-ium (2R,3S)-3-carboxy-2,3-dihydroxypropanoate (92)

To amine 83 (ca. 8 mg, 0.02 mmol) under a nitrogen atmosphere was added a 0.02 M solution of L-(2R,3R)-(+-)tartratic acid in CH₃OH (1 mL, 0.02 mmol), and the mixture was stirred at room temperature for 12 h. CH₃OH was removed under reduced pressure to give ammonium hemitartrate 92 (ca. 11 mg) as a mixture of diastereoisomers at C1'. Interpretation of the ¹H and ¹³C NMR spectra was rendered difficult by the presence of the two diastereomers that led to overlapping signals.

¹H NMR (500 MHz, CD₃OD): δ 6.34 – 6.26 (m, 2H), 4.54 (s, 2H, tartrate), 3.74 (tt, J = 11.1, 4.7 Hz, 1H), 3.53 – 3.47 (m, 1H), 3.47 – 3.39 (m, 1H), 3.30 – 3.24 (m, 1H), 2.47 (td, J = 11.3, 2.4 Hz, 1H), 2.39 – 2.03 (m, 5H), 1.98 – 1.84 (m, 3H), 1.51 – 1.12 (m, 11H), 1.11 – 0.81 (m, 10H).

¹³C NMR (126 MHz, CD₃OD): δ 174.9, 158.5, 156.9, 139.4, 113.9, 107.3, 105.8, 78.4, 73.8, 73.4, 71.2, 50.0, 44.6, 39.6, 38.9, 36.6, 34.9, 32.5, 30.2, 29.4, 28.1, 27.1, 25.3, 23.5, 22.9, 19.2, 14.3. IR (neat, cm⁻¹): 3167–3584 (br), 3062, 2936, 2870, 1732, 1620, 1581, 1423, 1273, 1170, 1029, 739, 638. HRMS ((+-ESI) m/z calcd for C₂₅H₄₀NO₃ [M+H]⁺, 402.3003; found 402.3015.
To amine 83 (ca. 8 mg, 0.02 mmol) under a nitrogen atmosphere was added a 0.02 M solution of HCl in acetone (1 mL, 0.02 mmol), prepared from concentrated 37.4% HCl and acetone, and the mixture was stirred at room temperature for 12 h. Solvent was removed under reduced pressure to give ammonium chloride 93 (ca. 9 mg) as a mixture of diastereoisomers at C1'. Interpretation of the $^1$H and $^{13}$C NMR spectra was rendered difficult by the presence of the two diastereomers that led to overlapping signals.

$^1$H NMR (500 MHz, CD$_3$OD): $\delta$ 6.33 – 6.25 (m, 2H), 3.74 (tt, $J = 11.0$, 4.4 Hz, 1H), 3.53 – 3.47 (m, 1H), 3.46 – 3.38 (m, 1H), 3.29 – 3.25 (m, 1H), 2.47 (td, $J = 11.3$, 5.8 Hz, 1H), 2.36 – 2.06 (m, 5H), 1.97 – 1.83 (m, 3H), 1.49 – 1.15 (m, 11H), 1.11 – 0.78 (m, 10H). $^{13}$C NMR (126 MHz, CD$_3$OD): $\delta$ 158.5, 156.9, 139.4, 113.9, 107.3, 105.8, 78.4, 73.8, 71.2, 50.0, 44.6, 39.6, 38.9, 36.6, 34.9, 32.5, 30.2, 29.5, 28.1, 27.1, 25.3, 23.5, 22.9, 19.2, 14.3. IR (neat, cm$^{-1}$): 3165–3584 (br), 3055, 2953, 2870, 1614, 1582, 1423, 1360, 1246, 1172, 1030, 843, 737, 702, 638. HRMS ((+-ESI) m/z calcd for C$_{25}$H$_{40}$NO$_3$ [M+H]$^+$, 402.3003; found 402.2992.
2-((6aR,9R,10aR)-1,9-Dihydroxy-6,6-dimethyl-6a,7,8,9,10,10a-hexahydro-6H-benzo[c]chromen-3-yl)-2-hexyl-1-methylpyrrolidin-1-ium 3-carboxypropanoate (94)

To amine 84 (ca. 8 mg, 0.019 mmol) under a nitrogen atmosphere was added a 0.019 M solution of succinic acid in CH$_3$OH (1 mL, 0.019 mmol), and the mixture was stirred at room temperature for 12 h. CH$_3$OH was removed under reduced pressure to give ammonium hemisuccinate 94 (ca. 10 mg) as a mixture of diastereoisomers at C1'. Interpretation of the $^1$H and $^{13}$C NMR spectra was rendered difficult by the presence of the two diastereomers that led to overlapping signals.

$^1$H NMR (500 MHz, CD$_3$OD): δ 6.47 – 6.35 (m, 2H), 3.74 (tt, $J = 11.1, 4.4$ Hz, 1H), 3.64 – 3.54 (m, 1H), 3.24 – 3.09 (m, 1H), 2.69 – 2.59 (m, 1H), 2.57 – 2.53 (m, 3H, NMe), 2.53 – 2.46 (m, 5H, succinate and 1CH), 2.32 – 2.16 (m, 4H), 2.14 – 2.09 (m, 1H), 1.93 – 1.87 (m, 1H), 1.85 – 1.73 (m, 1H), 1.51 – 1.42 (m, 1H), 1.42 – 1.14 (m, 11H), 1.13 – 0.83 (m, 10H). $^{13}$C NMR (126 MHz, CD$_3$OD): δ 178.5, 158.7, 156.9, 134.8, 114.8, 109.6, 107.6, 78.4, 77.4, 71.2, 54.8, 49.9, 39.5, 36.6, 36.0, 34.9, 32.6, 32.5, 32.0, 30.5, 29.6, 28.1, 27.1, 25.9, 23.6, 21.3, 19.2, 14.3. IR (neat, cm$^{-1}$): 3176–3584 (br), 3503, 2934, 2870, 1714, 1576, 1418, 1265, 1057, 737, 704. HRMS ((+)-ESI) $m/z$ calcd for C$_{26}$H$_{42}$NO$_3$ [M+H]$^+$, 416.3159; found 416.3153.
2-((6aR,9R,10aR)-1,9-Dihydroxy-6,6-dimethyl-6a,7,8,9,10,10a-hexahydro-6H-benzo[c]chromen-3-yl)-2-hexyl-1-methylpyrrolidin-1-ium chloride (95)

To amine 84 (ca. 6 mg, 0.015 mmol) under a nitrogen atmosphere was added a 0.015 M solution of hydrochloric acid in acetone (1 mL, 0.015 mmol), prepared from concentrated 37.4% HCl and acetone, and the mixture was stirred at room temperature for 12 h. Solvent was removed under reduced pressure to give ammonium chloride 95 (ca. 7 mg) as a mixture of diastereoisomers at C1'. Interpretation of the $^1$H and $^{13}$C NMR spectra was rendered difficult by the presence of the two diastereomers that led to overlapping signals.

$^1$H NMR (500 MHz, CD$_3$OD): δ 6.41 – 6.27 (m, 2H), 3.73 (tt, J = 11.1, 4.4 Hz, 1H), 3.59 – 3.50 (m, 1H), 3.14 – 3.03 (m, 1H), 2.75 – 2.58 (m, 1H), 2.53 – 2.47 (m, 3H, NMe), 2.38 – 2.04 (m, 6H), 1.93 – 1.88 (m, 1H), 1.88 – 1.79 (m, 1H), 1.49 – 1.42 (m, 1H), 1.40 – 1.22 (m, 11H), 1.09 – 0.79 (m, 10H). $^{13}$C NMR (126 MHz, CD$_3$OD): δ 158.6, 157.0, 133.7, 115.3, 110.1, 107.9, 78.5, 77.0, 71.2, 54.5, 49.9, 39.5, 37.3, 36.6, 34.9, 32.5, 32.2, 30.4, 29.5, 28.1, 27.1, 26.0, 23.5, 20.9, 19.2, 14.3. IR (neat, cm$^{-1}$): 3194–3584 (br), 3053, 2931, 2870, 1620, 1579, 1418, 1360, 1265, 1144, 1057733, 704. HRMS (+(+)-ESI) m/z calcd for C$_{20}$H$_{22}$NO$_3$ [M+H]$^+$, 416.3159; found 416.3156.
Disubstituted azetidine cannabinoids

**Ethyl 2-cyanoctanoate**

To a mixture of ethyl 2-cyanoacetate (3.39 g, 30.0 mol) and K₂CO₃ (6.21 g, 45.0 mol) in DMF (30 mL) under a nitrogen atmosphere at room temperature was added 1-bromohexane (4.4 mL, 31.3 mol). The reaction mixture was stirred at 85 °C for 12 h. After the mixture was cooled to room temperature, water was added, and the organic material was extracted with Et₂O. The combined organic layer was washed with water, brine, dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with Et₂O/hexane (5/95 → 1/9) as eluent to afford ethyl 2-cyanoctanoate (5.0 g, 85% yield) as a colorless oil.

¹H NMR (500 MHz, CDCl₃): δ 4.26 (q, J = 7.1 Hz, 2H), 3.48 (t, J = 6.5, 1H), 1.94 (td, J = 8.2, 6.5 Hz, 2H), 1.55 – 1.42 (m, 2H), 1.41 – 1.24 (m, 9H), 0.89 (t, J = 7.1 Hz, 3H). ¹³C NMR (126 MHz, CDCl₃): δ 166.2, 116.6, 62.7, 37.6, 31.3, 29.9, 28.4, 26.7, 22.4, 14.0, 13.9. IR (neat, cm⁻¹): 2930, 2860, 2249, 1742, 1468, 1369, 1250, 1196, 858, 725. HRMS ((+)-ESI) m/z calcd for C₁₁H₁₉NNaO₂ [M+Na]⁺, 220.1308; found 220.1299.

**Potassium 2-cyanoctanoate**

To a mixture of ethyl 2-cyanoctanoate (3.94 g, 0.02 mol), water (360 mg, 0.02 mol), and EtOH (40 mL) under a nitrogen atmosphere at 60 °C was added a solution of t-BuOK (2.24 g, 0.02 mol) in EtOH (24 mL) dropwise over 30 min, and the mixture was stirred at this temperature for an additional 1.5 h. Solvent was removed under reduced pressure at 30 °C, and Et₂O (80 mL) was added. The resulting solid was collected by filtration, washed subsequently with Et₂O/EtOH
(10 mL, 1/1) and Et₂O (10 mL x 2), and dried under vacuum at room temperature for 2 h to give potassium 2-cyanoctanoate (3.73 g, 90% yield).

¹H NMR (500 MHz, CD₃OD): δ 3.33 (dd, J = 8.0, 6.1 Hz, 1H), 1.93 – 1.80 (m, 2H), 1.54 – 1.27 (m, 8H), 0.90 (t, J = 6.9 Hz, 3H). ¹³C NMR (126 MHz, CD₃OD): δ 172.6, 121.1, 41.8, 32.7, 31.9, 29.8, 28.4, 23.6, 14.3. IR (neat, cm⁻¹): 2918, 2853, 2232, 1605, 1470, 1373, 1265, 903, 737, 648. HRMS ((–)ESI) m/z calcd for C₉H₁₄NO₂ [M]⁺, 168.1030; found 168.1034.

2-((6aR,9R,10aR)-1,9-Bis(methoxymethoxy)-6,6-dimethyl-6a,7,8,9,10,10a-hexahydro-6H-benzo[c]chromen-3-yl)octanenitrile (96)

To a mixture Pd₂(allyl)₂Cl₂ (18 mg, 0.05 mmol), Xantphos (116 mg, 0.20 mmol), and potassium 2-cyanoctanoate (311 mg, 1.50 mmol) under an argon atmosphere was added a solution of triflate 78 (484 mg, 1.0 mmol) in dry (4Å molecular seives), deoxygenated (argon bubbling) xylene (20 mL). The reaction mixture was stirred at room temperature for 15 min, then moved to a preheated oil bath at 130 °C. Upon completion of the reaction (ca. 16 h), the mixture was cooled to room temperature, Celite was added, and xylene was removed under reduced pressure at 50 °C. The residue was purified by silica gel column chromatography with EtOAc/hexane (1/4) as eluent to afford nitrile 96 (377 mg, 82% yield) as a mixture of diastereoisomers at C1' (light yellow oil). Interpretation of the ¹H and ¹³C NMR spectra was rendered difficult by the presence of the two diastereomers that led to overlapping signals.

¹H NMR (500 MHz, CDCl₃): δ 6.60 – 6.41 (m, 2H), 5.24 – 5.11 (m, 2H), 4.77 – 4.68 (m, 2H), 3.73 (tt, J = 11.1, 4.5 Hz, 1H), 3.65 – 3.56 (m, 1H), 3.49 (s, 3H), 3.42 – 3.34 (m, 4H), 2.45 (td, J = 11.3, 2.6 Hz, 1H), 2.24 – 2.14 (m, 1H), 1.94 – 1.76 (m, 3H), 1.54 – 1.39 (m, 3H), 1.38 (s, 3H), 1.33 (s, 3H), 1.24 (s, 3H), 1.11 (s, 3H).
1.34 – 1.21 (m, 7H), 1.18 – 1.05 (m, 2H), 1.04 (s, 3H), 0.87 (t, J = 6.8 Hz, 3H). \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 156.9, 155.1, 135.7, 120.9, 113.7, 110.4, 105, 94.8, 94.6, 77.1, 75.6, 56.3, 56.1, 48.4, 37.2, 36.3, 35.4, 33.8, 33.1, 31.4, 28.6, 27.7, 27.1, 26.0, 22.5, 18.8, 14.0. IR (neat, cm\(^{-1}\)): 2930, 2872, 2239 \((\text{CN})\), 1614, 1574, 1558, 1431, 1404, 1369, 1337, 1153, 1103, 1057, 922, 737, 625. HRMS ((+)-ESI) \text{m/z calcd for } C_{27}H_{41}NNaO_{5} [M+Na]^+, 482.2877; found 482.2869.

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\begin{align*}
\text{96} & \rightarrow \\
\text{97}
\end{align*}
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2-((6a\text{R},9\text{R},10a\text{R})\text{-1,9-Bis(methoxymethoxy)-6,6-dimethyl-6,7,8,9,10,10a-hexahydro-6H-benzo[\text{c}]chromen-3-yl)-2-(hydroxymethyl)octanenitrile (97)}

To a suspension of nitrile 96 (322 mg, 0.70 mmol) and paraformaldehyde (315 mg) in toluene (70 mL) in a resealable sealed tube was added Triton B/CH\(_3\)OH 40\% (1.0 mL) dropwise. The resealable tube was sealed, and the reaction mixture was stirred at ambient temperature for 3 min, then at 60 °C for 26 h. After the reaction mixture was cooled to room temperature, saturated aqueous NaHCO\(_3\) (25 mL) was added, and the organic material was extracted with EtOAc. The combined organic layer was dried over MgSO\(_4\), filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with EtOAc/hexane (2/3) as eluent to afford alcohol 97 (325 mg, 95% yield) as a mixture of diastereoisomers at C1’ (light yellow foam). Interpretation of the \(^1\)H and \(^{13}\)C NMR spectra was rendered difficult by the presence of the two diastereomers that led to overlapping signals.

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 6.66 – 6.64 (m, 1H), 6.55 – 6.53 (m, 1H), 5.22 – 5.13 (m, 2H), 4.76 – 4.69 (m, 2H), 3.85 – 3.79 (m, 2H), 3.72 (tt, J = 11.0, 4.4 Hz, 1H), 3.48 (s, 3H), 3.41 – 3.37 (m, 4H), 2.45 (td, J = 11.4, 2.6 Hz, 1H), 2.22 – 2.16 (m, 1H), 2.16 (br s, OH), 2.06 – 1.94 (m, 1H), 1.93 – 1.85 (m, 1H), 1.85 – 1.75 (m, 1H), 1.54 – 1.39 (m, 3H), 1.38 (s, 3H), 1.32 – 1.19
(m, 7H), 1.18 – 1.06 (m, 2H), 1.04 (s, 3H), 0.84 (t, J = 6.6 Hz, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$): δ 157.0, 155.1, 135.7, 121.5, 114.0, 109.5, 104.1, 94.7, 94.7, 77.2, 75.6, 69.2, 56.3, 56.1, 50.9, 48.3, 36.2, 35.3, 33.7, 33.0, 31.4, 29.1, 27.6, 26.0, 24.8, 22.5, 18.9, 14.0. IR (neat, cm$^{-1}$): 3447 (br), 2930, 2872, 2237 (CN), 1614, 1574, 1558, 1465, 1423, 1402, 1385, 1334, 1265, 1153, 1157, 921, 736, 660. HRMS ((+)-ESI) m/z calcd for C$_{28}$H$_{43}$NNaO$_6$ [M+Na]$^+$, 512.2983; found 512.3001.

$^{13}$C NMR ($^{125}$MHz, CDCl$_3$): δ 157.0, 155.1, 135.7, 121.5, 114.0, 109.5, 104.1, 94.7, 94.7, 77.2, 75.6, 69.2, 56.3, 56.1, 50.9, 48.3, 36.2, 35.3, 33.7, 33.0, 31.4, 29.1, 27.6, 26.0, 24.8, 22.5, 18.9, 14.0. IR (neat, cm$^{-1}$): 3447 (br), 2930, 2872, 2237 (CN), 1614, 1574, 1558, 1465, 1423, 1402, 1385, 1334, 1265, 1153, 1157, 921, 736, 660.

2-((6aR,9R,10aR)-1,9-Bis(methoxymethoxy)-6,6-dimethyl-6a,7,8,9,10,10a-hexahydro-6H-benzo[c]chromen-3-yl)-2-cyanoctyl 4-methylbenzenesulfonate (98)

To a solution of alcohol 97 (295 mg, 0.60 mmol) in CH$_2$Cl$_2$ (60 mL) was added $p$-TsCl (345 mg, 1.80 mmol), Et$_3$N (1.0 mL, 7.17 mmol), and DMAP (88 mg, 0.72 mmol), and the reaction mixture was stirred at room temperature for 4 h. Saturated aqueous NaHCO$_3$ (10 mL) was added, and the organic material was extracted with EtOAc. The combined organic layer was dried over MgSO$_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with EtOAc/hexane (3/7) as eluent to afford tosylate 98 (362 mg, 94%) as a mixture of diastereoisomers at C1' (light yellow foam). Interpretation of the $^1$H and $^{13}$C NMR spectra was rendered difficult by the presence of the two diastereomers that led to overlapping signals.

$^1$H NMR (500 MHz, CDCl$_3$): δ 7.74 (dd, J = 8.3, 4.2 Hz, 2H), 7.32 (dd, J = 8.3, 2.0 Hz, 2H), 6.61 – 6.54 (m, 1H), 6.48 – 6.42 (m, 1H), 5.18 – 5.08 (m, 2H), 4.76 – 4.68 (m, 2H), 4.17 – 4.04 (m, 2H), 3.72 (tt, J = 11.2, 4.5 Hz, 1H), 3.47 (s, 3H), 3.41 – 3.44 (m, 4H), 2.49 – 2.38 (m, 4H), 2.23 – 2.15 (m, 1H), 2.08 – 1.98 (m, 1H), 1.94 – 1.86 (m, 1H), 1.83 – 1.74 (m, 1H), 1.54 – 1.31
(m, 6H), 1.31 – 1.05 (m, 9H), 1.03 (s, 3H), 0.86 – 0.81 (m, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$): δ 157.0, 155.1, 145.2, 133.8, 132.1, 129.9, 128.0, 119.5, 114.5, 109.7, 104.0, 94.7, 94.7, 77.3, 75.5, 72.8, 56.3, 56.1, 48.3, 47.7, 36.2, 35.5, 33.7, 33.0, 31.3, 28.9, 27.6, 26.0, 24.5, 22.4, 21.6, 18.9, 13.9. IR (neat, cm$^{-1}$): 2930, 2872, 2243 (CN), 1610, 1573, 1558, 1454, 1423, 1402, 1362, 1179, 1057, 1042, 841, 814, 737, 663. HRMS ((+)-ESI) m/z calcd for C$_{35}$H$_{50}$NO$_8$S [M+H]$^+$, 644.3252; found 644.3236.

3-((6aR,9R,10aR)-1,9-Bis(methoxymethoxy)-6,6-dimethyl-6a,7,8,9,10,10a-hexahydro-6H-benzo[c]chromen-3-yl)-3-hexyl-1-methylazetidine (100)

To a stirred suspension of LiAlH$_4$ (65 mg, 1.74 mmol) in THF (5.0 mL) under a nitrogen atmosphere at 0 °C was added a solution of cyanotosylate 98 (110 mg, 0.17 mmol) in THF (12 mL) slowly, and the reaction mixture was stirred at room temperature for 3 h. (Note: more LiAlH$_4$ was used on smaller scale to reduce most of starting material within 3-4 h). The reaction mixture was quenched with a minimum amount of Na$_2$SO$_4$ paste (ca. 100 µL), which was prepared by cooling hot saturated aqueous Na$_2$SO$_4$, diluted with Et$_2$O, and stirred at room temperature for 30 min. The organic material was taken up with Et$_2$O, dried over solid K$_2$CO$_3$, filtered, and concentrated under reduced pressure to give crude azetidine 99 as a colorless oil. To a solution of amine 99 in CH$_3$OH (17 mL) was slowly added a 37% formaldehyde in aqueous solution (1.0 mL), and the reaction mixture was stirred at room temperature for 2 h. NaBH$_4$ (40 mg, 1.06 mmol) was added in many portions at 0 °C, and the reaction mixture was stirred at 0 °C for 5 min, then at ambient temperature for 2 h. Solvents were carefully removed under reduced pressure to give a white solid, followed by addition of a small amount of aqueous 10 M NaOH.
(ca. 100 µL), diluted with CH₂Cl₂, and stirred for 5 min. The organic material was extracted with CH₂Cl₂, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with CH₃OH/CH₂Cl₂ (5/95) as eluent to afford N-methylazetidine 100 (52 mg, 62% yield from 98) as a colorless foam.

¹H NMR (500 MHz, CDCl₃): δ 6.23 (s, 1H), 6.13 (s, 1H), 5.18 – 5.08 (m, 2H), 4.76 – 4.68 (m, 2H), 3.91 (d, J = 8.1 Hz, 2H), 3.72 (t, J = 11.1, 4.4 Hz, 1H), 3.61 (d, J = 8.1 Hz, 2H), 3.47 (s, 3H), 3.40 – 3.35 (m, 4H), 2.57 (s, 3H, NMe), 2.43 (td, J = 11.3, 2.6 Hz, 1H), 2.22 – 2.14 (m, 1H), 2.04 – 1.92 (m, 2H), 1.92 – 1.84 (m, 1H), 1.53 – 1.38 (m, 3H), 1.37 (s, 3H), 1.26 – 0.99 (m, 12H), 0.80 (t, J = 6.7 Hz, 3H). ¹³C NMR (126 MHz, CDCl₃): δ 156.7, 154.6, 144.9, 112.2, 108.6, 103.1, 94.7, 94.6, 77.1, 75.6, 65.5, 56.2, 55.1, 48.4, 44.2, 42.2, 40.6, 36.4, 33.7, 33.1, 31.6, 29.2, 27.7, 26.0, 24.4, 22.5, 18.9, 14.0. IR (neat, cm⁻¹): 2930, 2857, 1614, 1568, 1557, 1447, 1402, 1366, 1361, 1153, 1103, 1057, 922, 737, 702, 660. HRMS ((+)-ESI) m/z calcd for C₂₉H₄₈NO₅ [M+H]⁺, 490.3527; found 490.3540. [α]²³D –39.0º (c 0.5, CH₃OH).

(6aR,9R,10aR)-3-(3-Hexyl-1-methylazetidin-3-yl)-6,6-dimethyl-6a,7,8,9,10,10a-hexahydro-6H-benzo[c]chromene-1,9-diol (101)

To a mixture of amine 100 (30 mg, 0.06 mmol) and ethanol (220 mg, 4.78 mmol) in CH₃CN (6.0 mL) at room temperature was added Sc(OTf)₃ (30 mg, 0.06 mmol). After flushing with nitrogen, the reaction mixture was refluxed for 12 h. CH₃CN was removed under reduced pressure, and a minimum amount of pH 7 phosphate buffer (300 µL) was added and stirred for 10 min. The organic material was extracted with Et₂O, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with
NH₄OHₓaq/CH₃OH/CH₂Cl₂ (2/5/93) as eluent to afford amine 101 (22 mg, 89%) as a colorless amorphous solid.

¹H NMR (500 MHz, CD₃OD): δ 6.04 (d, J = 1.7 Hz, 1H), 5.99 (d, J = 1.7 Hz, 1H), 3.72 (tt, J = 11.0, 5.5 Hz, 1H), 3.54 – 3.48 (m, 1H), 3.48 – 3.41 (m, 4H), 2.44 (td, J = 11.3, 2.6 Hz, 1H), 2.34 (s, 3H), 2.16 – 2.06 (m, 1H), 1.98 – 1.80 (m, 3H), 1.47 – 1.35 (m, 2H), 1.34 (s, 3H), 1.29 – 1.13 (m, 8H), 1.08 – 0.99 (m, 4H), 0.99 – 0.88 (m, 1H). ¹³C NMR (126 MHz, CD₃OD): δ 157.7, 156.1, 147.0, 111.2, 107.4, 105.9, 77.8, 71.3, 67.4, 50.3, 45.8, 43.1, 42.5, 39.9, 36.7, 34.9, 32.9, 30.6, 28.1, 27.2, 25.7, 23.6, 19.2, 14.4. IR (thin film, cm⁻¹): 3092–3582 (br), 2930, 2857, 1614, 1418, 1362, 1184, 1138, 1057, 737, 691, 660. HRMS ((+)-ESI) m/z calcd for C₂₅H₄₀NO₃ [M+H]+, 402.3003; found 402.3012. [α]₂⁰D = −30.0° (c 0.3, CH₂OH).

3-((6aR,9R,10aR)-1,9-Dihydroxy-6,6-dimethyl-6a,7,8,9,10,10a-hexahydro-6H-benzo[c]chromen-3-yl)-3-hexyl-1-methylazetidin-1-ium 3-carboxypropanoate (102)

To amine 101 (ca. 10 mg, 0.025 mmol) under a nitrogen atmosphere was added a 0.025 M solution of succinic acid in CH₃OH (1 mL, 0.025 mmol), and the mixture was stirred at room temperature for 12 h. CH₃OH was removed under reduced pressure to give ammonium hemisuccinate 102 (ca. 13 mg).

¹H NMR (500 MHz, CD₃OD): δ 6.06 (s, 1H), 6.06 (s, 1H), 4.15 (s, 4H), 3.73 (tt, J = 10.9, 4.3 Hz, 1H), 3.54 – 3.46 (m, 1H), 2.80 (s, 3H, NMe), 2.50 (s, 4H, succinate), 2.45 (td, J = 11.3, 2.2 Hz, 1H), 2.15 – 2.07 (m, 1H), 1.98 – 1.85 (m, 3H), 1.47 – 1.40 (m, 1H), 1.40 – 1.31 (m, 4H), 1.28 – 1.13 (m, 8H), 1.09 – 0.99 (m, 4H), 0.98 – 0.87 (m, 1H), 0.84 (t, J = 6.8 Hz, 3H). ¹³C
NMR (126 MHz, CD$_3$OD): $\delta$ 179.5, 158.3, 156.5, 143.8, 112.2, 107.2, 105.5, 78.0, 71.2, 66.4, 50.2, 43.2, 42.7, 41.7, 39.8, 36.6, 34.9, 32.9, 32.7, 30.3, 28.2, 27.2, 25.3, 23.6, 19.2, 14.4. IR (neat, cm$^{-1}$): 3208–3610 (br), 2926, 2855, 1712, 1645, 1556, 1418, 1277, 1184, 1076, 922, 840, 737. HRMS ((+)-ESI) $m/z$ calcd for C$_{25}$H$_{40}$NO$_3$ [M+H]$^+$, 402.3003; found 402.3014. $[\alpha]^{23}_D$ $-56.0^\circ$ (c 1.0, CH$_3$OH).
2,2-Disubstituted azetidine cannabinoids

1-((6aR,9R,10aR)-1,9-Bis((methoxymethoxy)-6,6-dimethyl-6a,7,8,9,10,10a-hexahydro-6H-benzo[e]chromen-3-yl)heptan-1-one (104)

To a solution of nitrile 96 (230 mg, 0.50 mmol) in THF (10 mL) under a nitrogen atmosphere at room temperature was added a 2.0 M solution of NaHMDS in THF (1 mL, 2.0 mmol) dropwise over 10 min, and the reaction mixture was stirred at room temperature for an additional 20 min. A stream of dry oxygen gas (from tank) was bubbled through the mixture over 30 min at -78 °C. An 1.0 M aqueous solution of sodium sulfite (5.0 mL) was added and the mixture was stirred at 0 °C for 30 min. The organic material was extracted with Et₂O, and the combined organic layer was washed with brine, dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with EtOAc/hexane (1/4) as eluent to afford ketone 104 (166 mg, 74% yield) as a light yellow oil.

¹H NMR (500 MHz, CDCl₃) δ 7.19 (d, J = 1.6 Hz, 1H), 7.07 (d, J = 1.6 Hz, 1H), 5.29 – 5.17 (m, 2H), 4.78 – 4.67 (m, 2H), 3.75 (tt, J = 11.0, 4.5 Hz, 1H), 3.50 (s, 3H), 3.44 – 3.39 (m, 1H) 3.38 (s, 3H), 2.86 (t, J = 7.4 Hz, 2H), 2.50 (td, J = 11.3, 2.6 Hz, 1H), 2.24 – 2.16 (m, 1H), 1.95 – 1.89 (m, 1H), 1.72 – 1.65 (m, 2H), 1.62 – 1.23 (m, 11H), 1.19 – 1.07 (m, 2H), 1.04 (s, 3H), 0.87 (t, J = 6.9 Hz, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 199.9, 156.6, 154.7, 136.7, 119.2, 111.9, 104.2, 94.7, 94.4, 77.3, 75.5, 56.4, 55.2, 48.4, 38.5, 36.2, 34.2, 33.1, 31.6, 29.0, 27.6, 26.0, 24.4, 22.5, 18.8, 14.0. IR (neat, cm⁻¹): 3055, 2932, 2870, 1682 (C=O), 1574, 1466, 1366, 1157, 1042, 918, 740. HRMS ((+)-ESI) m/z calcd for C₂₆H₄₁O₆ [M+H]⁺, 449.2898; found 449.2898. [α]D²⁵ +61.0° (c 1.0, CH₃OH).
(R,E)-N-(1-((6aR,9R,10aR)-1,9-Bis(methoxymethoxy)-6,6-dimethyl-6a,7,8,9,10,10a-hexahydro-6H-benzo[c]chromen-3-yl)heptylidene)-2-methylpropane-2-sulfinamide (105)

To a solution of ketone 104 (318 mg, 0.71 mmol) and (R)-2-methylpropane-2-sulfinamide (95 mg, 0.78 mmol) in THF (3.0 mL) was added Ti(OEt)$_4$ (ca. 0.45 mL, 2.13 mmol), and the mixture was refluxed under nitrogen atmosphere for 19 h. After cooling to 0 °C, the reaction mixture was quenched with saturated aqueous NaCl, diluted with CH$_2$Cl$_2$, and stirred at 0 °C for 15 min. The mixture was filtered and the filter cake was washed with CH$_2$Cl$_2$. The combined organic layer was separated, washed with brine, dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with EtOAc/hexane (1/4) as eluent to afford ketimine 105 (359 mg, 92% yield) as a light yellow oil.

$^1$H NMR (500 MHz, CDCl$_3$) δ 7.19 (s, 1H), 6.90 (s, 1H), 5.21 – 5.12 (m, 2H), 4.75 – 4.63 (m, 2H), 3.71 (tt, $J$ = 11.0, 4.5 Hz, 1H), 3.46 (s, 3H), 3.41 – 3.33 (m, 4H), 3.17 – 2.97 (m, 2H), 2.47 (td, $J$ = 11.3, 2.5 Hz, 1H), 2.22 – 2.13 (m, 1H), 1.92 – 1.83 (m, 1H), 1.66 – 1.57 (m, 2H), 1.55 – 1.47 (m, 1H), 1.46 – 1.34 (m, 6H), 1.31 – 1.25 (m, 13H), 1.17 – 1.04 (m, 2H), 1.02 (s, 3H), 0.85 – 0.82 (m, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 179.5, 156.5, 154.6, 137.3, 117.7, 110.8, 104.7, 94.7, 94.5, 77.2, 75.5, 57.3, 56.1, 55.0, 48.3, 36.1, 34.0, 32.4, 31.3, 29.5, 28.8, 27.5, 25.9, 22.5, 22.4, 18.7, 13.9. IR (neat, cm$^{-1}$): 3055, 2932, 2870, 1728, 1612, 1558, 1458, 1334, 1157, 1042, 918, 732. HRMS ((+)-ESI) m/z calcd for C$_{30}$H$_{49}$NNaO$_6$ [M+Na]$^+$, 574.3173; found 574.3158. [$\alpha$]$^D_{23}$ –49.0° (c 0.5, CH$_3$OH).
(3S)-Ethyl 3-((6aR,9R,10aR)-1,9-bis(methoxymethoxy)-6,6-dimethyl-6a,7,8,9,10,10a-hexahydro-6H-benzo[c]chromen-3-yl)-3-(1,1-dimethylethylsulfinamido)nonanoate (106)

To a solution of diisopropylamine (1.20 mmol) in THF (5 mL) under an argon atmosphere at -10 °C (ice–salt bath) was added over 10 min a 2.0 M solution of n-BuLi in hexane (0.6 mL, 1.20 mmol), and the solution was stirred at -10 °C for an additional 10 min. The solution was then cooled to -78 °C and a solution of EtOAc (1.20 mmol) in THF (1 mL) was added slowly over 5 min, and the reaction mixture was stirred at -78 °C for 30 min. To this solution was added a solution of TiCl(Oi-Pr)₃ (2.50 mmol) in THF/toluene (2 mL, 1/1) dropwise, and the yellow solution was stirred for 20 min at -78 °C. (Note: the solution of TiCl(Oi-Pr)₃ was prepared from 1.0 eq of TiCl₄ and 3.0 eq of Ti(Oi-Pr)₄ in toluene at -10 °C, and diluted with THF). After that time, a solution of N-sulfinyl imine 105 (330 mg, 0.60 mmol) in THF (2 mL) was added slowly, and the reaction mixture was stirred at -78 °C for 1 h. Saturated aqueous NH₄Cl (4 mL) was added and the mixture was warmed to 0 °C, and stirred for 15 min, and the organic material was extracted with Et₂O. The combined organic layer was washed with brine, dried over NaSO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with EtOAc/hexane (3/7 → 2/3) as eluent to afford ester 106 (310 mg, 81% yield) as a colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 6.66 (d, J = 1.8 Hz, 1H), 6.37 (d, J = 1.9 Hz, 1H), 5.49 (s, NH), 5.15 – 5.07 (m, 2H), 4.75 – 4.70 (m, 2H), 3.98 (q, J = 7.1 Hz, 2H), 3.72 (tt, J = 11.1, 4.5 Hz, 1H), 3.45 (s, 3H), 3.40 – 3.37 (m, 4H), 3.21 (d, J = 16.7 Hz, 1H), 3.02 (d, J = 16.7 Hz, 1H), 2.42 (td, J = 11.3, 2.6 Hz, 1H), 2.22 – 2.09 (m, 2H), 1.93 – 1.84 (m, 1H), 1.83 – 1.73 (m, 1H), 1.53 – 1.41 (m, 2H), 1.41 – 1.35 (m, 4H), 1.32 (s, 9H), 1.27 – 1.03 (m, 12H), 1.02
(s, 3H), 0.81 (t, J = 7.0 Hz, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 172.0, 156.4, 154.4, 144.2, 112.5, 108.6, 104.2, 94.8, 94.7, 77.2, 76.9, 75.7, 61.4, 60.3, 56.2, 56.0, 55.1, 48.5, 45.4, 39.9, 36.4, 33.8, 33.1, 31.4, 29.1, 27.7, 26.1, 23.0, 22.4, 18.8, 14.0, 13.9. IR (neat, cm$^{-1}$): 3279, 3055, 2940, 2870, 1721 (C=O), 1612, 1574, 1458, 1334, 1265, 1157, 1042, 740. HRMS (+(+)ESI) m/z calcd for C$_{34}$H$_{57}$NNaO$_8$ [M+Na]$^+$, 662.3697; found 662.3706. [$\alpha$]$^{23}$D $-$48.0° (c 1.0, CH$_3$OH).

(S)-Ethyl 3-amino-3-((6aR,9R,10aR)-1,9-bis(methoxymethoxy)-6,6-dimethyl-6a,7,8,9,10,10a-hexahydro-6H-benzo[c]chromen-3-yl)nonanoate (107)

To a solution of N-tert-butan sulfinyl β-amino ester 106 (200 mg, 0.31 mmol) in CH$_3$OH (10 mL) at 0 °C was added a 4.0 M solution of HCl in 1,4-dioxane (1 mL, 4.0 mmol) dropwise. The resulting mixture was stirred at ca.10 °C until most of the starting material was consumed as judged by TLC (ca. 2 h). The mixture was cooled to 0 °C then quenched with cold saturated aqueous NaHCO$_3$. The organic material was extracted with Et$_2$O, and the combined organic layer was washed with brine, dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with CH$_3$OH/CH$_2$Cl$_2$ (3/97) as eluent to afford β-amino ester 107 (141 mg, 85% yield) as a colorless oil.

$^1$H NMR (500 MHz, CD$_3$OD) δ 6.62 (d, J = 2.0 Hz, 1H), 6.46 (d, J = 2.0 Hz, 1H), 5.25 – 5.17 (m, 2H), 4.71 (s, 2H), 4.04 (qd, J = 7.1, 1.4 Hz, 2H), 3.72 (tt, J = 11.3, 4.6 Hz, 1H), 3.50 – 3.43 (m, 4H), 3.36 (d, J = 2.0 Hz, 3H), 3.01 (d, J = 15.9 Hz, 1H), 2.79 (d, J = 16.0 Hz, 1H), 2.48 (td, J = 11.3, 2.7 Hz, 1H), 2.22 – 2.15 (m, 1H), 1.98 – 1.77 (m, 2H), 1.52 – 1.29 (m, 6H), 1.27 – 1.07 (m, 12H), 1.04 – 0.96 (m, 4H), 0.89 – 0.82 (m, 3H). $^{13}$C NMR (126 MHz, CD$_3$OD) δ 172.4,
158.1, 156.2, 143.2, 114.8, 109.6, 104.4, 96.0, 95.9, 78.2, 77.3, 61.8, 59.7, 56.8, 55.5, 50.1, 45.0, 42.6, 38.0, 35.0, 34.3, 32.8, 30.4, 28.1, 27.1, 24.2, 23.5, 19.1, 14.4. IR (neat, cm⁻¹): 3302, 3156, 2932, 2870, 1728 (C=O), 1612, 1574, 1465, 1334, 1265, 1157, 1041, 918, 740.

HRMS ((+)-ESI) m/z calcd for C₃₀H₅₀NO₇ [M+H]^+ 536.3582; found 536.3601. [α]²³D -76.0° (c 1.5, CH₃OH).

(S)-4-((6aR,9R,10aR)-1,9-Bis(methoxymethoxy)-6,6-dimethyl-6a,7,8,9,10,10a-hexahydro-6H-benzo[c]chromen-3-yl)-4-hexylazetidin-2-one (108)

To a solution of β-amino ester 107 (107 mg, 0.20 mmol) in Et₂O (20 mL) under a nitrogen atmosphere at room temperature was added a 1.0 M solution of CH₃MgBr in THF/toluene (0.6 mL, 0.60 mmol) dropwise and the mixture was stirred at room temperature for 1.5 h. The reaction mixture was quenched with saturated aqueous NH₄Cl, and stirred until the two layers became clear. The organic material was extracted with Et₂O. The combined organic layer was dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with EtOAc/hexane (3/2) as eluent to afford azetidinone 108 (76 mg, 78% yield) as a colorless oil.

¹H NMR (500 MHz, CDCl₃) δ 6.47 (br s, NH), δ 6.47 (d, J = 1.6 Hz, 1H), 6.37 (d, J = 1.6 Hz, 1H), 5.19 – 5.13 (m, 2H), 4.76 – 4.70 (m, 2H), 3.73 (tt, J = 10.6, 4.5 Hz, 1H), 3.48 (s, 3H), 3.43 – 3.35 (m, 4H), 3.07 – 2.93 (m, 2H), 2.45 (td, J = 11.3, 2.6 Hz, 1H), 2.23 – 2.15 (m, 1H), 2.07 – 1.99 (m, 1H), 1.93 – 1.79 (m, 3H), 1.56 – 1.35 (m, 5H), 1.28 – 1.07 (m, 9H), 1.05 (s, 3H), 0.84 (t, J = 6.8 Hz, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 167.5, 156.7, 154.5, 142.9, 112.7, 108.4, 93.
103.0, 94.7, 94.6, 77.1, 75.6, 59.7, 56.2, 55.1, 50.8, 48.5, 40.7, 36.4, 33.8, 33.1, 31.5, 29.2, 27.7, 26.1, 24.7, 22.5, 18.9, 14.0. IR (neat, cm\(^{-1}\)): 3433, 3055, 2932, 2870, 1751 (C=O), 1612, 1574, 1420, 1265, 1157, 1041, 918, 741. HRMS (+(+)ESI) m/z calcd for C\(_{28}\)H\(_{43}\)NNaO\(_6\) [M+Na]\(^+\), 512.2983; found 512.2980. \([\alpha]_{D}^{23}\) -48.0\(^o\) (c 0.5, CH\(_3\)OH).

(S)-2-(((6aR,9R,10aR)-1,9-Bis(methoxymethoxy)-6,6-dimethyl-6a,7,8,9,10,10a-hexahydro-6H-benzo[c]chromen-3-yl)-2-hexyl-1-methylazetidine (111)

To a stirred suspension of LiAlH\(_4\) (ca. 50 mg, 1.31 mmol) in THF (1.5 mL) under a nitrogen atmosphere at 0 °C was added a solution of azetidinone 108 (10 mg, 0.02 mmol) in THF (1.5 mL) dropwise. The reaction mixture was heated at 68 °C (oil bath) for 24 h. After cooling to 0 °C, the reaction mixture was quenched with a minimum amount of Na\(_2\)SO\(_4\) paste, diluted with Et\(_2\)O, and stirred at room temperature for 30 min. The organic material was taken up with Et\(_2\)O, dried over solid K\(_2\)CO\(_3\), filtered, and concentrated under reduced pressure to give crude azetidine 110 as a colorless oil (ca. 10 mg). To a solution of amine 110 in CH\(_3\)OH (2 mL) was slowly added a 37% formaldehyde in aqueous solution (ca. 80 µL), and the reaction mixture was stirred at room temperature for 3 h. NaBH\(_4\) (ca. 50 mg, 1.31 mmol) was added in many portions at 0 °C, and the reaction mixture was stirred at 0 °C for 5 min, then at ambient temperature for 2 h. Solvents were carefully removed under reduced pressure to give a white solid, followed by addition of a minimum amount of aqueous 10 M NaOH, diluted with CH\(_2\)Cl\(_2\), and stirred for 5 min. The organic material was extracted with CH\(_2\)Cl\(_2\), dried over Na\(_2\)SO\(_4\), filtered, and concentrated under reduced pressure. The residue was purified by silica gel column
chromatography with CH$_3$OH / CH$_2$Cl$_2$ (6/94) as eluent to afford N-methyl azetidine 111 (ca. 7 mg) as a colorless oil.

$^1$H NMR (500 MHz, CD$_3$OD) δ 6.57 (d, $J = 1.8$ Hz, 1H), 6.43 (d, $J = 1.8$ Hz, 1H), 5.32 – 5.19 (m, 2H), 4.71 (s, 2H), 3.84 – 3.78 (m, 1H), 3.73 (tt, $J = 10.7, 4.5$ Hz, 1H), 3.67 – 3.58 (m, 1H), 3.50 – 3.42 (m, 4H), 3.36 (s, 3H), 2.96 – 2.84 (m, 1H), 2.62 (s, 3H), 2.52 (td, $J = 11.3, 2.5$ Hz, 1H), 2.42 – 2.33 (m, 1H), 2.31 – 2.16 (m, 2H), 2.14 – 2.04 (m, 1H), 1.97 – 1.85 (m, 2H), 1.66 – 1.55 (m, 1H), 1.54 – 1.46 (m, 1H), 1.41 – 1.20 (m, 11H), 1.08 – 0.93 (m, 4H), 0.86 (t, $J = 6.6$ Hz, 3H). $^{13}$C NMR (126 MHz, CD$_3$OD) δ 158.2, 156.5, 141.1, 115.7, 109.8, 104.1, 96.0, 95.6, 78.4, 77.5, 77.2, 56.7, 55.5, 51.5, 50.0, 37.9, 36.7, 35.9, 35.1, 34.3, 32.7, 30.4, 28.1, 27.8, 27.0, 24.5, 23.7, 19.1, 14.5. HRMS ((+)-ESI) m/z calcd for C$_{29}$H$_{48}$NO$_5$ [M+H]$^+$, 490.3527; found 490.3519. IR (neat, cm$^{-1}$): 2931, 2858, 1612, 1567, 1440, 1261, 1155, 920, 736. [α]$^2_D$ −52.0° (c 0.5, CH$_3$OH).

(S)-4-((6aR,9R,10aR)-1,9-Dihydroxy-6,6-dimethyl-6a,7,8,9,10,10a-hexahydro-6H-benzo[c]chromen-3-yl)-4-hexylazetidin-2-one (109)

To a solution of azetidinone 108 (ca. 7 mg, 0.014 mmol) in CH$_3$CN (2.0 mL) and water (0.2 mL) at room temperature was added LiBF$_4$ (40 mg, 0.43 mmol). After flushing with nitrogen, the reaction mixture was heated at 72 °C for 18 h. CH$_3$CN was removed under reduced pressure, then pH 7 phosphate buffer (2 mL) was added, and the organic material was extracted with EtOAc. The combined organic layer was washed with brine, dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column
chromatography with EtOAc/hexane (4/1) as eluent to afford azetidinone 109 (ca. 5 mg) as a light yellow amorphous solid.

$^1$H NMR (500 MHz, CD$_3$OD) $\delta$ 6.21 (d, $J = 1.9$ Hz, 1H), 6.18 (d, $J = 1.9$ Hz, 1H), 3.73 (tt, $J = 11.0, 4.4$ Hz, 1H), 3.55 – 3.48 (m, 1H), 2.98 (d, $J = 14.6$ Hz, 1H), 2.83 (d, $J = 14.6$ Hz, 1H), 2.45 (td, $J = 11.3, 2.6$ Hz, 1H), 2.16 – 2.06 (m, 1H), 2.06 – 1.96 (m, 1H), 1.93 – 1.85 (m, 1H), 1.84 – 1.73 (m, 1H), 1.49 – 1.40 (m, 1H), 1.40 – 1.32 (m, 4H), 1.30 – 1.09 (m, 9H), 1.03 (s, 3H), 1.00 – 0.91 (m, 1H), 0.89 – 0.82 (t, $J = 7.1$ Hz, 3H). $^{13}$C NMR (126 MHz, CD$_3$OD) $\delta$ 170.7, 158.0, 156.1, 143.9, 112.1, 106.9, 105.4, 78.0, 71.3, 60.5, 51.1, 50.2, 42.0, 39.8, 36.6, 34.9, 32.8, 30.4, 28.2, 27.2, 25.8, 23.6, 19.1, 14.4. HRMS ((–)-ESI) m/z calcd for C$_{24}$H$_{34}$NO$_4$ [M-H]$^-$, 400.2488; found 400.2474. IR (thin film, cm$^{-1}$): 3369, 2930, 2859, 1723 (C=O), 1622, 1580, 1421, 1274, 1142, 1056, 738. $[\alpha]_{D}^{23}$ –67.0° (c 1.0, CH$_3$OH).

$^{(6aR,9R,10aR)-3-((S)-2-Hexyl-1-methylazetidin-2-yl)-6,6-dimethyl-6a,7,8,9,10,10a-hexahydro-6H-benzo[c]chromene-1,9-diol (112}$

To a solution of amine 111 (ca. 4 mg, mmol) in CH$_3$OH (0.5 mL) at room temperature was added Dowex 50W-X8 (H$^+$ form) (ca. 250 mg, excess). (Note: Dowex 50W-8X had been previously washed with distilled water, 1 M aqueous NaOH, distilled water, 1 M aqueous HCl, and distilled water before it was used). After flushing with nitrogen, the reaction mixture was stirred vigorously at room temperature for 30 h. (Note: the reaction was not clean without flushing with nitrogen). The reaction was quenched with a minimum amount of saturated aqueous NaHCO$_3$ (until pH ~ 8). The organic material was extracted with Et$_2$O, dried with Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel
column chromatography with CH$_3$OH/CH$_2$Cl$_2$ (1/4) as eluent to afford amine 112 (ca. 2.5 mg) as a colorless amorphous solid.

$^1$H NMR (500 MHz, CD$_3$OD) $\delta$ 6.23 (d, $J = 1.9$ Hz, 1H), 6.20 (d, $J = 1.9$ Hz, 1H), 3.73 (tt, $J =$ 10.8, 5.2 Hz, 1H), 3.54 – 3.39 (m, 3H), 2.77 – 2.64 (m, 1H), 2.50 – 2.41 (m, 4H), 2.26 – 2.18 (m, 1H), 2.16 – 2.04 (m, 2H), 2.01 – 1.84 (m, 3H), 1.47 – 1.41 (m, 1H), 1.41 – 1.34 (m, 4H), 1.34 – 1.10 (m, 8H), 1.02 (s, 3H), 0.99 – 0.89 (m, 1H), 0.85 (t, $J = 6.7$ Hz, 3H). HRMS (+(E)-ESI) $m/z$ calcd for C$_{25}$H$_{40}$NO$_3$ [M+H]$^+$, 402.3003; found 402.2987.
CHAPTER 3

THE TOTAL SYNTHESIS OF

3-OXAADAMANTYL 9β-HYDROXY HEXAHYDROCANNABINOIDS
3.1. Introduction

The side chain of tricyclic cannabinoids plays a key role in determining the ligand's affinity for cannabinoid receptors as well as the pharmacological potency. Recent studies with compound AM-411 (52) and its 2-adamantyl analog in the Makriyannis group suggested that the bulky adamantyl group at the C3 position can be tolerated by both CB1 and CB2 receptor binding sites, and that the receptor subtype selectivity can be modulated by varying the relative orientation of that group with respect to the tricylic nucleus.\textsuperscript{84} To extend this work, the Tius group has introduced a series of functional groups at the C3' position of the adamantane structure. Some of these cannabinoids, such as compound 148 and its azide analog, exhibited remarkably high affinities for CB1 and CB2. Another structural modification brought about by introducing heteroatoms on the ring resulted in oxaadamantyl 149 that exhibited high affinity for both CB1 and CB2 (Figure 21).\textsuperscript{85}

![AM-411, 52](image)

**Figure 21.** Some adamantyl and oxaadamantyl cannabinoids

Although compound 148 and its 3'-functional group analogs have high affinities for CB1 and CB2, the synthesis of these adamantyl cannabinoids, as reported by Mr. Go Ogawa, is somewhat difficult due to a series of low yielding steps that require specific and narrowly defined conditions, such as the reductive cleavage of the phenolic hydroxy group under Birch conditions (Na\textsuperscript{0} and NH\textsubscript{3}(l)) and the Friedel-Crafts adamantylation in neat methanesulfonic acid. Alternatively, the oxaadamantyl series is expected to be relatively ease to prepare and to have similar binding affinities for CB1 and CB2 compared to the adamantyl series.
In this part of the dissertation, the preparation of a series of 3'-functionalized oxaadamantyl cannabinoids (Figure 22) and their evaluation in the receptor binding assays will be described. This study focused on the 9β-hydroxy compounds, which are more active than the 9α-hydroxy diastereomers.

**Figure 22.** General structure of 3'-functionalized oxaadamantyl cannabinoids
3.2. Total Synthesis of 3-Oxaadamantyl 9β-Hydroxy Hexahydrocannabinoids

3.2.1. Synthesis Design

The structure of tricyclic cannabinoids can be considered as being composed of an aromatic part and an alicyclic part. For a stereospecific construction of the tricyclic nucleus, tricyclic cannabinoids are generally constructed by joining of an achiral resorcinol fragment and a chiral non-racemic terpene derivative. The synthesis of a series of 3'-functionalized oxaadamantyl cannabinoids was developed following the strategy that is detailed in what follows. Introduction of the oxaadamantyl fragment into the resorcinol was done first, then construction of the tricyclic cannabinoid nucleus, and finally functional group manipulation. The oxaadamantyl resorcinol 155 was developed from commercially available 1,3-adamantanediol 150 and 1-bromo-3,5-dimethoxybenzene 161. The tricyclic cannabinoid nucleus was constructed by condensation/cyclization between oxaadamantyl resorcinol 155 and an optically active mixture of diacetates 67a and 67b, following the general approach developed by Archer and coworkers for the synthesis of nabilone. No protecting groups were needed for the functional group conversions. To obtain cannabinoids with high affinity for CB1 and CB2, the equatorial 9-hydroxy as well as the (6aR, 10aR) absolute stereochemistry are required. The retrosynthesis of 3-oxaadamantyl-9β-hydroxy hexahydrocannabinoids according to these precepts is illustrated in Scheme 29.

Scheme 29. Retrosynthesis of 3-oxaadamantyl-9β-hydroxy HHC.
An alternative approach for the synthesis of these cannabinoids follows the reverse sequence of operations. The tricyclic cannabinoid ring is constructed first, with the adamantyl fragment introduced subsequently (Scheme 30). Although the construction of the tricyclic nucleus (e.g. intermediate triflate 78) has been optimized in our group by Dr. Darryl Dixon, the design of the adamantyl part as nucleophile for the cross coupling reaction may be problematic due to the presence of an oxygen atom on the bridge of the adamantyl fragment. Metallation of the oxaadamantyl group leads to a carbenoid that is likely to have one or more pathways available for its decomposition.

**Scheme 30.** Retrosynthesis of 3-oxaadamantyl-9β-hydroxy HHC via intermediate 78

### 3.2.2. Synthesis of resorcinol 155

The details of the synthesis of oxaadamantyl resorcinol 155 are summarized in Scheme 31.
Reagents and conditions: (a) p-TsCl, benzene/Pyr, 75 °C, 40 h, 81%; (b) m-CPBA, NaHCO₃, CH₂Cl₂/H₂O, rt, 3 h, 85%; (c) CeCl₃, -50 °C, 1 h, 0 °C, 30 min, 83%; (d) Jones reagent, (CH₃)₂CO, 0 °C, 2 h, 87%; (e) 47% HI(aq), 120 °C, 21 h, 92%.

Scheme 31. Synthesis of resorcinol 155.

Following the procedure described in earlier reports, Grob fragmentation of commercially available 1,3-adamantanediol 150 by treatment with p-TsCl in a mixture of benzene and pyridine at 75 °C gave 7-methylenebicyclo[3.3.1]nonan-3-one 151 in 81% yield (Scheme 31). The use of benzenesulfonyl chloride instead of p-TsCl, as had been reported by Dr. Darryl Dixon, gave a similar yield of 151. Although 1,3-adamantanediol 150 is commercially available, it is quite expensive (308 USD/5 g, ≥ 99% GC, Sigma-Aldrich), therefore we had an incentive to prepare 150 from cheap (25.7 USD/5 g, 99% GC, Sigma-Aldrich) 1-adamantanol. Oxidation of 1-adamantanol with catalytic ruthenium trichloride and 2.2 equivalents of NaIO₄ led to 150 in 80% yield on 5.9 gram scale, as reported by Dr. Xiaojun Huang, a former member of our group.

Epoxidation of 151 with m-CPBA in a CH₂Cl₂-aqueous Na₂CO₃ biphasic system led to the formation of 7-exo-epoxymethylenebicyclo[3.3.1]nonane-3-one 152 in 85% yield (Scheme 31). It has been reported that treatment of 151 with peracids such as H₂O₂ in benzonitrile, m-CPBA (p-TsOH cat.) in CHCl₃, or monoperphthalic acid in CHCl₃ yielded exo-epoxide 152 stereoselectively as the only product, and that no lactone was observed. This can be explained by the steric hindrance due to the preferred twin chair conformation that prevents the
formation of *endo*-butterfly transition state in the Prilezhaev reaction, as well as the back-side steric hindrance that prevents the formation of the tetrahedral Criegee intermediate in the Baeyer Villiger reaction. Epoxidation in CH$_2$Cl$_2$ yielded only 70-75% of the desired product. Buffering the biphasic reaction with Na$_2$CO$_3$ to prevent acid catalyzed epoxide opening resulted in a slightly cleaner process, suggesting that although the reactivity of peracid was slightly diminished in the aqueous biphasic media, the system was still sufficiently reactive enough to epoxidize the relatively unreactive disubstituted alkene 151.$^{162}$

Nucleophilic addition of 3,5-dimethoxyphenyllithium, which was generated in situ from bromine/lithium exchange of 1-bromo-3,5-dimethoxybenzene and n-BuLi,$^{163}$ to epoxy ketone 152 in the presence of anhydrous CeCl$_3$, followed by transannular cyclization led to 3-(3,5-dimethoxyphenyl)-2-oxaadamantan-1-ylmethanol 153 in 83% yield (Scheme 31). In the absence of anhydrous CeCl$_3$, the reaction led to recovered epoxy ketone 152 (~ 30%), abnormal byproduct (~ 50%), which was assumed to be compound 156 (Scheme 32), and no significant amount of the desired addition product was detected. The generation of compound 156 is consistent with the earlier report of Mlinaric-Majerski that compound 157 was dominant (69% yield) over the desired product 158 (10% yield) in the reaction of epoxy ketone 152 and MeLi without CeCl$_3$.\(^{164}\)

![Scheme 32](image)

**Scheme 32.** Enolization and alkylation of epoxy ketone 152 by an organometallic reagent.

In the presence of CeCl$_3$, the reaction proceeded very slowly at -78 °C (less than ca. 20% consumption of starting material after 4 h), but was complete at -50 °C in less than 1 h. These
results were in agreement with earlier reports of Imamoto that CeCl₃ can inhibit enolization of ketones as well as other abnormal reactions such as reduction or pinacol coupling that sometimes compete with the nucleophilic addition of Grignard or organolithium reagents to ketones.¹⁶⁵ Organocerium reagents are known to have attenuated basicity and very high nucleophilicity although the exact structure of these species in solution remains unclear.¹⁶⁶ It is noteworthy that the quality of anhydrous CeCl₃ significantly affects the yield of reactions because CeCl₃·7H₂O is easily hydrolyzed to CeOCl during heating and because CeCl₃·H₂O is difficult to dehydrate completely.¹⁶⁷ Addition of ketone 152 to a mixture of aryllithium and CeCl₃ gave a significantly lower yield of product than the alternative procedure in which a solution of the aryllithium was added to a mixture of ketone 152 and CeCl₃. The superiority of the second method was reported in several reactions similar to ours,¹⁶⁴,¹⁶⁸ and was explained by the decomposition of the organometallic reagent on contact with cerium chloride. Alternatives for the use of CeCl₃ are the use of lanthanum (III) chloride¹⁶⁹ or zinc (II) chloride¹⁷⁰ that have not been explored for this reaction. The use of the Grignard reagent prepared from the reaction of 3,5-dimethoxybromobenzene and magnesium turnings at 55 °C in THF catalysed by Mel,¹⁷¹ in combination with CeCl₃ at room temperature also gave product 153, however, the yield was lower (ca. 40%, 0.5 mmol scale) and the reaction was not easily reproducible on small scale.

The next task was to convert the hydroxymethyl group in 153 to the carboxylic acid. Oxidation of a derivative of alcohol 153 which incorporates methoxymethyl ether groups in place of methoxy groups by Swern oxidation, followed by Pinnick oxidation gave a derivative of carboxylic acid 154 in high yield (Scheme 34), as reported by Mr. Kahoano Wong, a former member of our group. In a successful effort to shorten the synthesis, Jones oxidation of 153 led to 3-(3,5-dimethoxyphenyl)-2-oxaadamantane-1-carboxylic acid 154 directly in 87% yield (Scheme 31).¹⁷² We chose a more direct approach to the oxidation (vide infra).
Removal of the phenolic methyl groups was unexpectedly challenging. Methyl aryl ethers are generally difficult to demethylate under mild conditions. Our concern was that harsh conditions would cleave the benzylic C-O bond within the oxaadamantyl fragment. Demethylation of the second methoxy group in 154 is rendered more difficult because of coordination of the oxygen atom on the first methoxy group to the electrophilic reagent, typically an aluminum or boron halide, deactivates the aromatic ring, thereby diminishing nucleophilicity of the oxygen atom on the second methoxy group. In fact, while demethylation of compound 159 with BBr₃ yielded the corresponding resorcinol 160 in 85% yield,¹⁴ demethylation of 154 was not a clean reaction, as reported by Dr. Xiaojun Huang and Dr. Joe Mullins, former members of our group (Scheme 33).

Scheme 33. Demethylation with BBr₃.

An alternative approach for the synthesis of 155 had been proposed initially via the methoxymethyl (MOM) group protection, which was easier to remove (Scheme 34).
Reagents and conditions: (a) BBr₃, CH₂Cl₂, -78 °C to rt, O.N., 93%; (b) MeOCH₂Cl, (i-Pr)₂NEt, CH₂Cl₂, 0 °C to rt, O.N., 86%; (c) Mg turnings, CeCl₃, epoxide 152, THF, rt, O.N., ca. 70%; (d) Swern oxidation, 98%; (e) Pinnick oxidation, 89%; (f) p-TsOH-H₂O, CH₃OH, rt, 3 h, 98%.

*Results reported by Mr. Kahoano Wong in our group.*

**Scheme 34.** An alternative approach for the synthesis of resorcinol 155.

However, this initial approach is less attractive because the synthesis of 155 following this strategy is too long. Phenol 162 is not commercially available, therefore methoxymethyl ether 163 must be prepared from commercially available 161 in two additional steps. Moreover, the Jones reagent, which directly oxidizes alcohol to carboxylic acid, cannot be used in this approach because of the instability of the methoxymethyl groups to the strongly acidic conditions. Also, once the methoxymethyl ethers are cleaved, the free phenolic hydroxy groups are oxidized and the compound is destroyed. For these reasons, the use of methoxy ether 161 directly (Scheme 31) is a better choice providing the methyl ether cleavage can be accomplished. The fact that carboxylic acid 154 could be obtained from alcohol 153 via Jones oxidation (Scheme 31) in high yield suggested that the -COOH group as well as the oxadamantyl fragment can tolerate strongly acidic conditions. Therefore, demethylation was approached in a modified way: exposure of 154 to a protic acid with strongly nucleophilic counterion. Treatment of 154 with excess 47% aqueous HI under reflux (ca. 120 °C) gave
resorcinol 155 in almost quantitative yield.\textsuperscript{173} The option of protecting the resorcinol as the bismethoxymethyl ether was consequently abandoned in favor of this better approach.

### 3.2.3. Condensation/cyclization to construct the tricyclic cannabinoid nucleus

The tricylic 9-ketocannabinoid nucleus was constructed by condensation/cyclization of resorcinol 155 with a mixture of optically active terpene-derived diacetates 67. The synthesis of a mixture of diacetates 67 was described earlier in chapter 2 (Scheme 4), in which \((\text{--})\)-\(\beta\)-pinene 71 was used as the starting material to obtain the \((6aR, 10aR)\) absolute configuration of the tricyclic cannabinoid nucleus.

![Scheme 35](image)

Reagents and conditions: (a) \(p\)-TsOH-H\(_2\)O, \((\text{CH}_3)_2\text{CO}/\text{CHCl}_3\), 50 °C, 22 h, 52%; (b) TMSOTf, \(\text{CH}_3\text{NO}_2\), 0 °C to rt, 3 h, 87%.

**Scheme 35.** Condensation and cyclization steps in synthesis of oxaadamantyl cannabinoids

Friedel-Crafts alkylation of resorcinol 155 with the mixture of diacetates 67 in chloroform/acetone at 50 °C in the presence of 1.0 equivalent of \(p\)-TsOH-H\(_2\)O afforded the desired condensation product 167 in 52% yield. (Scheme 35). As mentioned earlier in chapter 2, the procedure of Archer and co-workers works beautifully for Nabilone, but any deviation from the conditions for the condensation of the diacetates with the resorcinol, especially solvent, results in a poor reaction. However, the reaction of resorcinol 155 with the mixture of diacetates 67 in chloroform, which is the solvent used by the Archer group, did not give desired product 167 in a clean reaction due to the limited solubility of resorcinol 155 in chloroform. Following a simple modification of the experimental procedure by our group involving the use of a minimum
amount of acetone as a co-solvent, desired product 167 was obtained in a satisfactory yield. A low concentration of 155 resulted in a long reaction time and product that was accompanied by undesired byproducts, therefore addition of a minimum amount of acetone as a cosolvent was necessary. No reaction (or a very slow reaction) was observed at room temperature while byproduct formation became the major pathway at temperatures higher than 60 °C. Addition of diacetates 67 and p-TsOH in aliquots did not improve the yield significantly. It is noteworthy that excess p-TsOH (1.7 equivalents) or excess diacetates 67 (2.5 equivalents) led to a complicated reaction mixtures, in which undesired byproducts were not isolated.

Rearrangement-cyclization of 167 promoted by TMSOTf in dry CH$_3$NO$_2$ gave tricyclic ketocannabinoid 168 in 87% yield (Scheme 35). Treatment of 167 with less than 3.0 equivalents of TMSOTf yielded only a trace of cyclization product 168, while approximately 5.0 equivalents of TMSOTf gave a clean reaction. From an earlier report, it was not clear whether triflic acid or trimethylsilyl triflate is the catalytically active species. The erosion of stereochemical integrity at C-6, which led to the cis-(6aS, 10aR) tricyclic product was not observed in this cyclization. The use of SnCl$_4$ as the Lewis acid leads to the formation of emulsions during work up that erodes the isolated yield.

3.2.4. Functional group conversions

In order to obtain C9-β-hexahydrocannabinoids, ketone 168 was reduced with excess NaBH$_4$ in 94% yield to give a ca. 95/5 mixture of C9-β (equatorial) alcohol 169 and its C9-α (axial) diastereomer (Scheme 36, Figure 23).
Figure 23. Structure of 9β-hydroxy isomer 169 and its 9α-hydroxy diastereomer

The $^1$H NMR spectral data of 9β-hydroxy 169 and its 9α-hydroxy diastereomer were compared. The -CHOH methine proton in the 9β-hydroxy isomer is shielded by the axial protons at C7 and C10a and appears as an upfield signal at 3.76-3.69 ppm (m, broader signal), while the -CHOH methine proton in the 9α-hydroxy isomer is not shielded and thus appears as a downfield signal at 4.12-4.08 ppm (m, narrower signal). The chemical shift trends were consistent with earlier reports in comparing 9β-hydroxy and 9α-hydroxy cannabinoids.

Compound 169 was converted to a series of oxaadamantyl hexahydrocannabinoids via functional group conversions. Our goals were to make cannabinoids with -CONH$_2$, -CN, -CH$_2$N, and -CH$_2$NCS groups at the C3' position. The reactive groups will be used for LAPS studies in the Makriyannis lab. The details of the functional group transformations are summarized in Scheme 36. It is noteworthy that no protecting groups were used for any of the steps.
Reagents and conditions: (a) NaBH₄, CH₃OH, -5 °C, 3 h, 94%; (b) i. HOBT, EDCI, THF, rt, 16 h, ii. NH₄OH (aq), rt, 1 h, 81%; (c) i. TFAA, Pyr, 1,4-dioxane, rt, 16 h, ii. K₂CO₃, CH₃OH, rt, 16 h, 84%; (d) BH₃·Me₂S, THF, 0 °C, 30 min, rt, 3 h, 81%; (e) TfN₃, Et₃N, CuSO₄, CH₂Cl₂/CH₃OH/H₂O, rt, 14 h, 74%. (f) i. CS₂, Et₃N, THF, 0 °C, 2 h, ii. p-TsCl, 0 °C to rt, 1.5 h, 82%.

**Scheme 36.** Functional group transformations of oxaadamantyl cannabinoids.

Amidation of carboxylic acid 169 in the presence of NH₃, EDCI and HOBT afforded 170 in 81% yield (Scheme 36). Dehydration of amide 170 with trifluoroacetic anhydride-pyridine in dioxane, followed by hydrolysis of trifluoroacetate ester intermediate 175 with potassium carbonate in methanol led to nitrile 171 in 84% yield from 170 (Scheme 36, 37).

**Scheme 37.** Preparation of nitrile 171 from amide 170.
Reduction of amide 170 with excess BH₃-Me₂S in THF led to the formation of amine 172 in 81% yield (Scheme 36). Azide 173 was prepared from amine 172 following the methodology that was originally developed by Cavender and Shiner as well as later by the Wong group. Copper (II) catalyzed diazo transfer of amine 172 with triflyl azide, freshly prepared from triflic anhydride and sodium azide at 0 °C, led to azide 173 in 74% yield (Scheme 36). The presence of triflic acid may be deleterious for both starting material and product, therefore sodium azide was used in excess in order to consume all triflic anhydride and the crude triflyl azide product in CH₂Cl₂ was washed with cold saturated aqueous NaHCO₃ prior to use. The homogeneity of the CH₂Cl₂/CH₃OH/H₂O solvent system, that depends on the relative ratio, significantly affected the yield of the diazo transfer reaction, thus it was carefully optimized to 6/6/1. Excess triflic azide (more than 5.0 equivalents) or too much base (more than 10 equivalents) led to a complicated reaction mixture. It is worthy of note that the use of copper (II) sulfate in a stoichiometric amount contributed to decomposition of the product, whereas the reaction was very clean with 4% copper (II) sulfate. Treatment of primary amine 172 with CS₂ in the presence of TEA in THF, followed by p-TsCl mediated decomposition of in situ generated dithiocarbamate gave isothiocyanate 174 in 82% yield (Scheme 36, 38).

Scheme 38. Preparation of isothiocyanate 174.
The use of excess carbon disulfide to improve the yield of isothiocyanate has been reported.\textsuperscript{180} More than 3.0 equivalents of triethylamine was required to consume amine 172 completely while more than 10 equivalents of triethylamine (with excess $p$-TsCl) increased the proportion of undesired products, including phenol tosylate 176, and traces of several other compounds that were not isolated. Approximately 2.0 equivalents of $p$-TsCl in 1.5 h was suitable to decompose dithiocarbamate salt to desired product 174 in high yield while more than 5.0 equivalents of this reagent for a longer time (8-12 h) formed undesired product 176 in a significant proportion.

3.2.5. A Dimeric 3-Oxaadamantyl 9\textbeta-Hydroxy Cannabinoid

**Introduction**

In the evaluation of ligands in the receptor binding assays, the Makriyannis lab mistakenly identified our compound isothiocyanate 174 as an agonist at CB1 and a CB2 inverse agonist. The mystery compound was interesting because it was also an allosteric agonist. The Makriyannis group had very little of the original sample, and could not identify the presumed impurity that (they thought) had led to the very unusual spectrum of activity. Consequently, we tried to guess the structure of an impurity that might form from 174 on storage or that might have formed during its preparation (Scheme 38). Finally, the mystery compound because known to be one of the compounds in their lab. Even so, since the synthesis of thioureas was interesting, it will be described in a small part of this chapter.

**Chemistry**

The likely generation of byproducts derived from isothiocyanate 174 was narrowed down to the hydrolysis of compound 174 due to the electrophilicity of the central heterocumulene carbon atom in the isothiocyanate group. Aminolysis of isothiocyanates usually produces $N,N'$-disubstituted thioureas. According to J. L. J. Blanco,\textsuperscript{181a} nucleophilic addition of water to the central carbon atom of -NCS 177 resulted in thiocarbamic acid 178. This unstable
compound undergoes loss of COS to give the corresponding amine 179 that is trapped by a second isothiocyanate molecule 177 to produce the symmetric $N,N'$-disubstituted thiourea 181. In the presence of base the thiocarbamate species can be stabilized and can have a half-life that is long enough for it to react directly with another isothiocyanate molecule to gave thiocarbamic anhydride 180. This anhydride is unstable and easily loses COS to gave the symmetric thiourea 181 too. These transformations are illustrated in Scheme 39.

Scheme 39. Hydrolysis pathways of isothiocyanate, Blanco et al. 1999

The thiocarbamic acid, its thiocarbamate salt, as well as thiocarbamic anhydride are expected to be unstable, and are thus not likely to correspond to the unknown allosteric compound. For this reason, the symmetric thiourea 182 which was prepared from isothiocyanate 174 was considered to be the likeliest candidate for the "mystery compound" (Scheme 40). Heating isothiocyanate 174 in pyridine/water (10/1) at 60 °C for 5 days led to symmetric $N,N'$-disubstituted thiourea 182 in 80% yield.181
Reagents and conditions: (a) Pyr/H₂O (10/1), 60 °C, 5 d, 80%; (b) Et₃N/H₂O, DMSO, 60 °C, 5 d, 70%.

**Scheme 40.** Synthesis of symmetric thiourea 182 and unexpected product 183.

Isothiocyanate 174 showed no tendency to react in wet DMSO at room temperature to 40 °C in the absence of base while phenyl isothiocyanate in a model study gave symmetric N,N'-diphenyl thiourea in high yield under the same conditions. Unexpectedly, the addition of triethylamine to the solution of isothiocyanate 174 in wet DMSO at 40 °C slowly led to unsymmetrical thiourea 183. The reaction was optimized by using a large excess of triethylamine in aqueous DMSO at 60 °C for 5 d. Under these conditions 183 was isolated in 70% yield (**Scheme 40**). A similar reaction has been reported by Blanco and co-workers in the synthesis of N,N'-disubstituted symmetric thiourea 185 by self-condensation of 2,3,4,6-tetra-O-acetyl β-D-glucopyranosyl isothiocyanate 184. The byproduct N,N-diethyl N'-alkyl thiourea 186 was discovered and was rationalized by the mechanism illustrated in **Scheme 41**. It is remarkable that diethylamine was assumed to have been generated from triethylamine via nucleophilic displacement of one of the ethyl groups in triethylammonium ion by the postulated thiocarbamate anion. The nucleophilic diethylamine, thus generated, reacted with isothiocyanate to give the corresponding thiourea. The exact mechanism for the generation of unsymmetric thiourea 183 is not completely certain because we did not perform further experiments to confirm it. However, the isolation of ethyl thiocarbamate 187 was reported by Blanco, in which the spectral data of 187 was reported.
to be identical with earlier report on the preparation of 187 from the reaction of isothiocyanate with ethanol and diethylamine.

![Scheme 41. Reaction generating unsymmetric thiourea and mechanism proposed by Blanco et al. 2009.](image)

\[ R - N\equiv C\equiv S + \text{HOEt}_2N \rightarrow R\text{-N\equiv C\equiv O} + \text{CH}_2\text{CH}_2\text{NH}_2 + \text{N}_2\text{Et}_2 \]
3.3. Receptor Binding Studies

The affinities for CB1 and CB2 were determined by our collaborators in the group of Professor Makriyannis. Ligand affinities ($K_i$) of 3-oxadamantyl 9β-hydroxy hexahydrocannabinoids are displayed in Table 2.

Table 2. Ligand affinities ($K_i$) of 3-oxadamantyl 9β-hydroxy hexahydrocannabinoids.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Structure</th>
<th>$K_i$ (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>rCB1</td>
</tr>
<tr>
<td>AM-1057</td>
<td></td>
<td>180-200 nM</td>
</tr>
<tr>
<td>(170)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AM-1058</td>
<td></td>
<td>90-130 nM</td>
</tr>
<tr>
<td>(171)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AM-1059</td>
<td></td>
<td>1-10 nM</td>
</tr>
<tr>
<td>(173)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AM-1054</td>
<td></td>
<td>4.9 nM</td>
</tr>
<tr>
<td>(174)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>183</td>
<td></td>
<td>in progress</td>
</tr>
</tbody>
</table>
Structure – activity relationships of 3-oxaadamantyl 9β-hydroxy hexahydrocannabinoids, especially of C3'-functional group variations can be summarized as follows:

(1) Binding affinities of these ligands for CB1 and CB2 receptors are comparable to those of the corresponding adamantyl analogs.

(2) Compounds with -CH2N3, and -CH2NCS groups at C3'-position have affinities at a nanomolar or sub-nanomolar level. Compound with -CN group has the best mCB2 selectivity and its affinity for CB2 was at the nanomolar level. These important compounds will also be used for LAPS studies in the group of Professor Makriyannis.

(3) Compounds with the -CONH2 group had lower affinities for both CB1 and CB2 while evaluation of binding affinities of the urea compounds is in progress.
3.4. Experimental Section - Chapter 3

LC–MS purity of final compounds

<table>
<thead>
<tr>
<th>Compounds</th>
<th>LC-MS Purity, %</th>
<th>UV absorbance</th>
</tr>
</thead>
<tbody>
<tr>
<td>170 (-CONH₂)</td>
<td>98.6</td>
<td>230 nm</td>
</tr>
<tr>
<td>172 (-CH₂NH₂)</td>
<td>96.2</td>
<td>230 nm</td>
</tr>
<tr>
<td>174 (-CH₂NCS)</td>
<td>&gt;99%</td>
<td>230 nm</td>
</tr>
<tr>
<td>171 (-CN)</td>
<td>98.0</td>
<td>230 nm</td>
</tr>
<tr>
<td>173 (-CH₃N₃)</td>
<td>96.6</td>
<td>230 nm</td>
</tr>
<tr>
<td>211 (-NHCSNH-)</td>
<td>95.0</td>
<td>254 nm</td>
</tr>
</tbody>
</table>

Table 3. LC–MS purity of final compounds

7-Methylenebicyclo[3.3.1]nonan-3-one (151)

A mixture of 1,3-adamantanediol (10.1 g, 0.06 mol) and p-TsCl (28.6 g, 0.15 mol) in benzene-pyridine (260 mL, 5/8) was stirred under a nitrogen atmosphere at 75 °C for 40 h. After cooling to 0 °C, the reaction mixture was poured into H₂O, and the organic material was extracted with cold Et₂O. The combined organic layer was washed with brine, dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude product was recrystallized in hexane in 3 crops to afford 151 (7.29 g, 81% yield) as a white solid. Spectral data were identical to those reported in the literature, J. Am. Chem. Soc. 2006, 128, 8412–8413.

¹H NMR (500 MHz, CDCl₃) δ 4.65 (d, J = 1.7 Hz, 2H), 2.33 – 2.31 (m, 2H), 2.29 – 2.20 (m, 6H), 2.17 – 2.11 (m, 2H), 1.87 – 1.75 (m, 2H). ¹³C NMR (126 MHz, CDCl₃) δ 210.4, 141.4, 114.2, 47.0, 41.1, 31.7, 30.5. IR (thin film, cm⁻¹): 3053, 2926, 1699 (C=O), 1651 (C=C), 1442,
To a mixture of alkene 151 (9.01 g, 0.06 mol) in CH₂Cl₂ (600 mL) and 0.5 M aqueous NaHCO₃ (180 mL, pH 8.3) at room temperature was added m-CPBA (17.8 g, 70% purity, 0.072 mol) in small portions over 5 min. The reaction mixture was vigorously stirred at room temperature for 3 h. The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (100 mL). The combined organic layer was washed successively with 1 M aqueous KOH (180 mL x 2), then water (180 mL x 2), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude product was recrystallized in toluene/hexane (1/1) in 3 crops to afford epoxyketone 152 (8.47 g, 85% yield) as white crystals. Spectral data were identical to those reported in the literature, *Tetrahedron Lett.* 1970, 28, 2419–2420.

¹H NMR (500 MHz, CDCl₃) δ 2.59 (s, 2H), 2.46 (dd, J = 15.5, 5.9 Hz, 2H), 2.35 (s, 2H), 2.29 (dd, J = 15.5, 1.2 Hz, 2H), 2.08 (dd, J = 13.1, 3.8 Hz, 2H), 1.94 – 1.85 (m, 1H), 1.78 – 1.70 (m, 1H), 1.17 (dd, J = 13.1, 1.2 Hz, 2H). ¹³C NMR (126 MHz, CDCl₃) δ 210.4, 58.2, 53.8, 47.4, 39.5, 32.4, 31.6. IR (thin film, cm⁻¹): 3053, 2987, 1699 (C=O), 1440, 1398, 1265, 1091,745. HRMS (EI) m/z calcd for C₁₀H₁₄O₂ [M+], 166.0994; found, 166.0990. EI+ (amu): 166 (M+, 19), 136 (13), 109 (100), 108 (33), 91 (13), 79 (30), 77 (14). Mp. 258–260 °C.
3-(3,5-Dimethoxyphenyl)-2-oxaadamantan-1-yl)methanol (153)

A solution of THF (150 mL) was added in once via cannula to the flask containing anhydrous CeCl₃, prepared from CeCl₃·7H₂O (27.9 g, 0.075 mol), at 0 °C with vigorous stirring, and the mixture was stirred under an argon atmosphere at 0 °C for 10 min, then sonicated for 2 h at room temperature with intermittent shaking. *(Note: introduction of THF to anhydrous CeCl₃ without either cooling or vigorous stirring led to the formation of a hard cake.)* To this milky suspension at 0 °C, a solution of epoxyketone 152 (5.0 g, 0.03 mol) in THF (50 mL) at 0 °C was added, and the mixture was stirred for 10 min, then cooled to -50 °C. To another flask containing 1-bromo-3,5-dimethoxybenzene (13.0 g, 0.06 mol) in THF (100 mL) under an argon atmosphere at -78 °C was added a 2.4 M solution of n-BuLi in hexane (27.5 mL, 0.066 mmol) dropwise over 30 min, and the reaction mixture was stirred at -78 °C for an additional 1 h. The generated aryllithium at -78 °C was transferred into the flask, containing the vigorously stirred mixture of 152 and CeCl₃ at -50 °C, via cannula. The resulting yellow suspension was stirred at -50 °C for 1 h, then warmed to 0 °C over 30 min. Water (100 mL) was added and the mixture was allowed to warm to room temperature. The organic material was extracted with EtOAc, and the combined organic layer was washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with EtOAc/hexane (3/7) as eluent to afford alcohol 153 (7.61 g, 83% yield) as a colorless oil.

¹H NMR (500 MHz, CDCl₃) δ 6.59 (d, J = 2.2 Hz, 2H), 6.33 (dd, J = 2.2 Hz, 1H), 3.77 (s, 6H), 3.41 (s, 2H), 2.57 (br s, OH), 2.32 – 2.27 (m, 2H), 1.96 – 1.79 (m, 8H), 1.49 (d, J = 13.1 Hz, 2H). ¹³C NMR (126 MHz, CDCl₃) δ 160.4, 150.0, 102.5, 97.9, 73.3, 72.9, 70.3, 55.0, 41.2, 35.8, 34.7, 27.6. IR (neat, cm⁻¹): 3441 (br), 2929, 2848, 1589, 1446, 1323, 1199, 1153, 1061, 833, 694.
HRMS (EI) m/z calcd for C_{18}H_{24}O_{4} [M+], 304.1675; found, 304.1678. EI+ (amu): 304 (M+, 100), 273 (50), 180 (61), 165 (32), 152 (11), 124 (10).

**Preparation of anhydrous CeCl$_3$**

A round-bottom flask containing CeCl$_3$·7H$_2$O at 3-5 mm Hg was gradually warmed from room temperature to 90 °C over 30 min, and heated at 90-100 °C for 4 h with vigorous stirring to give CeCl$_3$·H$_2$O as a white powder. The flask was then gradually warmed to 160 °C at 3-5 mmHg over 1 h, and heated at this temperature for an additional 7 h to give anhydrous CeCl$_3$ as a fine, white powder. Flame drying under vacuum removed traces of water on the neck of the flask.

![Chemical structure](image)

**3-(3,5-Dimethoxyphenyl)-2-oxaadamantane-1-carboxylic acid (154)**

To a solution of alcohol 153 (6.08 g, 0.02 mol) in acetone (200 mL) at 0 °C was added a 2.7 N solution of Jones reagent dropwise until the reddish orange color persisted (ca. 16 mL). After the reaction mixture was stirred at 0 °C for 2 h, 2-propanol (ca. 10 mL) was added slowly with vigorous stirring. The resulting mixture was stirred at 0-5 °C for an additional 30 min, and then filtered through a Celite pad with EtOAc. The filtrate was partially concentrated under reduced pressure at 25 °C. The remaining solution (ca. 150 mL) was washed with water, brine, dried over Na$_2$SO$_4$, and concentrated under reduced pressure. The crude product was recrystallized in toluene/hexane (1/4, ca. 500 mL) to afford carboxylic acid 154 (5.51 g, 87% yield).

$^1$H NMR (500 MHz, CDCl$_3$) δ 6.58 (d, $J = 2.2$ Hz, 2H), 6.38 (dd, $J = 2.2$ Hz, 1H), 3.80 (s, 6H), 2.41–2.38 (m, 2H), 2.10 (dd, $J = 12.4$, 1.6 Hz, 2H), 2.01–1.90 (m, 8H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 174.7, 160.8, 148.5, 102.7, 98.6, 75.9, 75.0, 55.3, 40.6, 36.4, 33.7, 27.5. IR (thin film, cm$^{-1}$): 3398 (br), 3053, 2985, 1773 (C=O), 1597, 1423, 1265, 1155, 896, 736, 704. HRMS (EI)
To a flask of 154 (3.18 g, 0.01 mol) at room temperature was added HI (47 wt.% in water, 50 mL) in one portion. The reaction mixture was purged with argon 3 times, then refluxed at 118 °C for 21 h. Aqueous HI was fully removed by evaporation under reduced pressure at 70 °C. After cooling to room temperature, the mixture was diluted with EtOAc, washed with 1 M aqueous Na₂S₂O₃ until no more precipitate was observed. The aqueous layer was back extracted with EtOAc, and the combined organic layer was washed with brine, dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with EtOAc/hexane (4/1 → 1/0) as eluent to afford resorcinol 155 (2.66 g, 92% yield).

1H NMR (500 MHz, THF-d₈) δ 10.76 (br s, COOH), 7.88 (br s, 2OH), 6.36 (d, J = 2.2 Hz, 2H), 6.01 (dd, J = 2.2 Hz, 1H), 2.30 – 2.24 (m, 2H), 1.97 – 1.89 (m, 8H), 1.79 (d, J = 13.0 Hz, 2H).

13C NMR (126 MHz, THF-d₈) δ 174.5, 159.4, 150.6, 103.2, 101.4, 75.1, 74.8, 42.2, 38.0, 35.1, 29.1. IR (neat, cm⁻¹): 3329 (br), 2933, 2852, 1708 (C=O), 1607, 1456, 1373, 1219, 945, 840.

HRMS (EI) m/z calcd for C₁₆H₁₈O₅ [M+], 290.1154; found, 290.1167. EI+ (amu): 290 (M+, 74), 245 (100), 187 (20), 152 (74), 137 (22), 128 (16), 91 (13), 77(12), 64 (12).

m/z calcd for C₁₈H₂₂O₅ [M+], 318.1467; found, 318.1461. EI+ (amu): 318 (M+, 100), 273 (83), 180 (45), 165 (15), 152 (16), 68 (11).
3-(4-((1R,2R,5R)-6,6-Dimethyl-4-oxobicyclo[3.1.1]heptan-2-yl)-3,5-dihydroxyphenyl)-2-oxaadamantane-1-carboxylic acid (167)

To a mixture of resorcinol 155 (580 mg, 2.0 mmol) and diacetates 67 (1.24 g, 50% purity, 2.60 mmol) was added acetone/chloroform (8.0 mL, 1/3). The reaction mixture was stirred under an argon atmosphere at room temperature for 5 min, then moved to a preheated oil bath at 50 ºC. After 5 min, a solution of p-TsOH·H2O (380 mg, 2 mmol) in acetone/chloroform (7.0 mL, 1/3) was added in one portion under an argon atmosphere. When most of 155 was consumed as judged by TLC (ca. 22 h), the reaction mixture was cooled to room temperature, diluted with Et2O, and washed with 1 M aqueous HCl. The aqueous layer was back extracted with Et2O, and the combined organic layer was washed with brine, dried over MgSO4, filtered, and concentrated under reduced pressure. The residue was absorbed onto Celite, and purified by silica gel column chromatography with acetone/hexane (1/4 → 1/1) as eluent to afford 167 (444 mg, 52% yield).

1H NMR (500 MHz, CD3OD) δ 6.45 (s, 2H), 4.01 (t, J = 8.1 Hz, 1H), 3.72 (dd, J = 18.7, 7.6 Hz, 1H), 2.63 – 2.57 (m, 1H), 2.48 – 2.45 (m, 2H), 2.41 (dd, J = 18.7, 8.7 Hz, 1H), 2.31 – 2.28 (m, 2H), 2.17 – 2.14 (m, 1H), 2.03 – 1.95 (m, 3H), 1.94 – 1.90 (m, 5H), 1.83 (d, J = 12.5 Hz, 2H), 1.35 (s, 3H), 0.95 (s, 3H). 13C NMR (126 MHz, CD3OD) δ 219.8, 177.2, 157.5, 147.9, 115.4, 104.4, 75.8, 75.5, 59.3, 48.6, 43.2, 42.0, 38.5, 38.1, 35.1, 30.4, 29.1, 26.9, 25.0, 22.5. IR (neat, cm⁻¹): 3347 (br), 2965, 2851, 1759 (C=O), 1713 (C=O), 1614, 1587, 1456, 1377, 1039, 947, 721. HRMS (EI) m/z calcd for C25H30O6 [M+], 426.2042; found, 426.2058. EI+ (amu): 426 (M+, 2), 290 (60), 245 (100), 187 (41), 152 (85), 91 (64), 77 (46). [α]D23 +11.5º (c 1.0, CH3OH).
3-((6aS,10aR)-1-Hydroxy-6,6-dimethyl-9-oxo-6a,7,8,9,10,10a-hexahydro-6H-
benzo[c]chromen-3-yl)-2-oxaadamantane-1-carboxylic acid (168)

To a solution of 167 (724 mg, 1.70 mmol) in CH₃NO₂ (300 mL) under a nitrogen atmosphere at 0 °C was added TMSOTf (1.55 mL, 8.50 mmol) dropwise over 20 min, and the reaction mixture was stirred at 5-10 °C for 2.5 h, then at room temperature for 30 min. The reaction was quenched with 1 M aqueous HCl, and the mixture was stirred for 10 min. The mixture was concentrated under reduced pressure and the organic material was extracted with Et₂O. The combined organic layer was washed again with 1 M aqueous HCl, brine, dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with acetone/hexane (1/4 → 2/3) as eluent to afford 168 (630 mg, 87 % yield) as a light yellow amorphous solid.

¹H NMR (500 MHz, CDCl₃) δ 6.52 (d, J = 1.8 Hz, 1H), 6.41 (d, J = 1.8 Hz, 1H), 4.04 (ddd, J = 15.1, 3.6, 2.0 Hz, 1H), 2.91 (ddd, J = 12.8, 11.2, 3.6 Hz, 1H), 2.67 – 2.59 (m, 1H), 2.52 – 2.42 (m, 1H), 2.42 – 2.35 (m, 2H), 2.22 – 2.08 (m, 4H), 2.01 – 1.87 (m, 9H), 1.59 – 1.51 (m, 1H), 1.49 (s, 3H), 1.13 (s, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 213.2, 174.5, 155.5, 154.7, 146.3, 109.9, 105.3, 103.5, 77.0, 76.1, 75.1, 47.3, 44.9, 40.7, 40.3, 36.4, 34.7, 33.7, 27.8, 27.5, 26.8, 18.9. IR (thin film, cm⁻¹): 3367 (br), 3053, 2983, 2927, 2856, 1772 (C=O), 1722 (C=O), 1622, 1419, 1265, 1134, 1045, 740, 794. HRMS (EI) m/z calcd for C₂₅H₃₀O₆ [M+], 426.2042; found, 426.2032. EI+ (amu): 426 (M+, 1), 279 (16), 167 (42), 149 (100), 113 (15), 97 (14), 83 (18), 71 (34). [α]²⁰D = -16.5° (c 1.0, CH₃OH).
3-((6aS,9R,10aR)-1,9-Dihydroxy-6,6-dimethyl-6a,7,8,9,10,10a-hexahydro-6H-benzo[c]chromen-3-yl)-2-oxaadamantane-1-carboxylic acid (169)

To a solution of 168 (418 mg, 0.98 mmol) in CH$_3$OH (20 mL) at -5 °C (ice–salt bath) was added NaBH$_4$ (730 mg, 0.02 mol) in 3 portions over 5 min. The reaction mixture was stirred at this temperature for 3 h and then quenched by dropwise addition of 1 M aqueous HCl (until pH = 2). The organic material was extracted with EtOAc and the combined organic layer was washed with brine, dried over MgSO$_4$, filtered, and concentrated under reduced pressure. The residue was absorbed onto Celite, and purified by silica gel column chromatography with acetone/hexane (1/1 → 7/3) as eluent to afford 169 (395 mg, 94% yield) as an off-white amorphous solid.

$^1$H NMR (500 MHz, CD$_3$OD) δ 6.48 (d, $J = 1.8$ Hz, 1H), 6.37 (d, $J = 1.8$ Hz, 1H), 3.72 (tt, $J = 10.8, 5.4$ Hz, 1H), 3.54 – 3.47 (m, 1H), 2.43 (td, $J = 11.2, 2.6$ Hz, 1H), 2.32 – 2.30 (m, 2H), 2.05 – 1.81 (m, 12H), 1.46 – 1.26 (m, 5H), 1.24–1.12 (m, 1H), 1.02 (s, 3H), 0.98 – 0.87 (m, 1H).$^{13}$C NMR (126 MHz, CD$_3$OD) δ 182.2, 157.5, 155.8, 148.6, 111.7, 106.2, 104.9, 77.7, 77.2, 75.3, 71.3, 50.4, 42.3, 39.9, 38.7, 36.6, 35.5, 35.0, 29.5, 28.2, 27.2, 19.1. IR (thin film, cm$^{-1}$): 3375 (br), 2924, 2852, 1742 (C=O), 1456, 1373, 1263, 1018, 742. HRMS ((–)-ESI) m/z calcd for C$_{25}$H$_{31}$O$_6$ [M-H], 427.2121; found 427.2108. $[\alpha]^{23}_{D} -22.5^\circ$ (c 1.0, CH$_3$OH).
3-((6aS,9R,10aR)-1,9-Dihydroxy-6,6-dimethyl-6a,7,8,9,10,10a-hexahydro-6H-benzo[c]chromen-3-yl)-2-oxaadamantane-1-carboxamide (170)

To a solution of carboxylic acid 169 (120 mg, 0.28 mmol) in THF (24 mL) at room temperature was added HOBT (76 mg, 0.56 mmol), and the mixture was stirred for 5 min. EDCI-HCl (140 mg, 0.73 mmol) was added, and the resulting suspension was stirred for 16 h. Aqueous 29.6% NH₄OH (0.8 mL) was added over 5 min, and the reaction mixture was stirred for 1 h and then quenched by dropwise addition of 1 M aqueous HCl (until pH ~ 3). The organic material was extracted with EtOAc, and the combined organic layer was washed with pH 7 phosphate buffer, brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was absorbed onto Celite, and purified by silica gel column chromatography with CH₂Cl₂/CH₃OH (94/6) as eluent to afford amide 170 (97 mg, 81% yield) as an off-white amorphous solid.

¹H NMR (500 MHz, CD₃OD) δ 6.44 (d, J = 1.8 Hz, 1H), 6.33 (d, J = 1.8 Hz, 1H), 3.73 (tt, J = 11.0, 4.4 Hz, 1H), 3.55 – 3.49 (m, 1H), 2.44 (td, J = 11.2, 2.4 Hz, 1H), 2.32 – 2.26 (m, 2H), 2.10 (d, J = 9.8 Hz, 1H), 2.07 – 1.72 (m, 1H), 1.48 – 1.35 (m, 2H), 1.34 (s, 3H), 1.22 – 1.12 (m, 1H), 1.02 (s, 3H), 0.98 – 0.89 (m, 1H). ¹³C NMR (126 MHz, CD₃OD) δ 180.3, 157.6, 155.9, 148.1, 111.8, 105.6, 104.3, 77.8, 76.4, 75.9, 71.3, 50.2, 42.1, 39.9, 38.0, 36.6, 34.9, 29.2, 28.2, 27.2, 19.2. IR (thin film, cm⁻¹): 3478, 3341 (br), 3053, 2986, 2928, 1672 (C=O), 1622, 1577, 1420, 1265, 1055, 894, 740, 704. HRMS (EI) m/z calcd for C₂₅H₃₃NO₅ [M⁺], 427.2359; found, 427.2338. EI+ (amu): 427 (M+, 1), 279 (23), 167 (42), 149 (100), 97 (38), 83 (40), 71 (52). [α]²³Դ −35.0° (c 1.0, CH₃OH).
To a solution of amide 170 (30 mg, 0.07 mmol) in 1,4-dioxane (9.0 mL) under a nitrogen atmosphere at room temperature was added pyridine (ca. 0.23 mL, 2.80 mmol), and the mixture was stirred for 10 min. Trifluoroacetic anhydride (ca. 0.20 mL, 1.40 mmol) was added and the reaction mixture was stirred at room temperature for 16 h. The reaction was quenched with pH 7 phosphate buffer, and the organic material was extracted with Et₂O. The combined organic layer was washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was dissolved in CH₃OH (15 mL), followed by addition of K₂CO₃ (386 mg, 2.80 mmol), and the reaction mixture was stirred under a nitrogen atmosphere at room temperature for 16 h. The reaction was quenched with 1 M aqueous HCl, and the organic material was extracted with Et₂O. The combined organic layer was washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with EtOAc/hexane (2/3 → 1/1) as eluent to afford nitrile 171 (24 mg, 84% yield) as a colorless amorphous solid.

¹H NMR (500 MHz, CD₃OD) δ 6.42 (d, J = 1.9 Hz, 1H), 6.26 (d, J = 1.9 Hz, 1H), 3.72 (tt, J = 11.0, 4.5 Hz, 1H), 3.59 – 3.44 (m, 1H), 2.44 (td, J = 11.3, 2.6 Hz, 1H), 2.38 – 2.27 (m, 2H), 2.25 – 2.17 (m, 2H), 2.15 – 2.02 (m, 3H), 2.01 – 1.83 (m, 7H), 1.47 – 1.26 (m, 5H), 1.23 – 1.12 (m, 1H), 1.02 (s, 3H), 0.97 – 0.90 (m, 1H). ¹³C NMR (126 MHz, CD₃OD) δ 157.6, 155.9, 147.2, 121.9, 112.0, 105.5, 104.2, 77.8, 76.0, 71.3, 70.1, 50.3, 41.5, 39.9, 39.8, 36.7, 35.0, 34.3, 28.7, 28.2, 27.2, 19.2. IR (thin film, cm⁻¹): 3304 (br), 3053, 2983, 2931, 1622, 1577, 1419, 1265,
1047, 736. HRMS (EI) m/z calcd for C_{25}H_{31}NO_{4} [M+], 409.2253; found, 409.2267. EI+ (amu): 409 (M+, 8), 279 (15), 167 (48), 149 (100), 119 (79), 91 (55), 71 (25), 64 (35). [α]^{23}_{D} -13.5^\circ (c 1.0, \text{CH}_3\text{OH}).

(6aS,9R,10aR)-3-(3-(Aminomethyl)-2-oxadamantan-1-yl)-6,6-dimethyl-6a,7,8,9,10,10a-hexahydro-6H-benzo[c]chromene-1,9-diol (172)

To a solution of amide 170 (26 mg, 0.06 mmol) in THF (1.5 mL) under an argon atmosphere at 0 °C was added excess BH$_3$·S(CH$_3$)$_2$ (0.20 mL, 2.0 mmol, 10 M in THF). The reaction mixture was stirred at 0 °C for an additional 30 min, then at room temperature for 3 h. EtOH (1.0 mL) was added slowly and carefully at 0 °C, then the mixture was stirred at 70 °C for 14 h. Solvent was removed under reduced pressure, followed by addition of a minimum amount of pH 7 phosphate buffer (ca. 50 µL). The organic material was extracted with EtOAc, absorbed onto Celite, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with NH$_4$OH$_{aq}$/CH$_3$OH/CH$_2$Cl$_2$ (2.5/7.5/90) as eluent to afford amine 172 (20 mg, 81% yield) as a clear glass.

$^1$H NMR (500 MHz, CD$_3$OD) δ 6.41 (d, $J = 1.8$ Hz, 1H), 6.33 (d, $J = 1.8$ Hz, 1H), 3.72 (tt, $J = 11.0, 4.5$ Hz, 1H), 3.54 – 3.48 (m, 1H), 2.64 – 2.59 (m, 2H), 2.43 (td, $J = 11.3, 2.6$ Hz, 1H), 2.30 – 2.26 (m, 2H), 2.10 (d, $J = 13.0$ Hz, 1H), 1.95 – 1.86 (m, 5H), 1.82 – 1.73 (m, 4H), 1.56 (d, $J = 12.2$ Hz, 2H), 1.45 – 1.38 (m, 1H), 1.38 – 1.27 (m, 4H), 1.22 – 1.11 (m, 1H), 1.01 (s, 3H), 0.98 – 0.86 (m, 1H). $^{13}$C NMR (126 MHz, CD$_3$OD) δ 157.5, 155.8, 148.6, 111.6, 105.7, 104.4, 77.7, 74.6, 73.2, 71.3, 52.0, 50.3, 42.3, 39.9, 38.0, 36.6, 35.7, 35.0, 29.3, 28.2, 27.2, 19.2. IR (thin film, cm$^{-1}$): 3358 (br), 3285, 3173, 2931, 1612, 1544, 1462, 1377, 1149, 1051, 721. HRMS (EI)
m/z calcd for C_{25}H_{35}NO_{4} [M+], 413.2566; found, 413.2564. EI+ (amu): 413 (M+, 1), 279 (20), 167 (41), 149 (100), 97 (45), 83 (45), 71 (66). [α]^{23}_D -23.5^\circ (c 1.0, CH_{3}OH).

(6aS,9R,10aR)-3-(3-(Azidomethyl)-2-oxaadamantan-1-yl)-6,6-dimethyl-6a,7,8,9,10,10a-hexahydro-6H-benzo[c]chromene-1,9-diol (173)

To a solution of primary amine 172 (14 mg, 0.034 mmol), CuSO_{4} (0.0015 mmol), Et_{3}N (0.10 mmol) in CH_{2}Cl_{2}/CH_{3}OH/H_{2}O (2.5 mL, 2/2/1) was added a 0.2 M solution of trifluoromethanesulfonfyl azide (TfN_{3}) in CH_{2}Cl_{2} (300 µL, ca. 0.06 mmol) dropwise at 0 °C. Additional CH_{2}Cl_{2} (1.7 mL) was slowly added, followed by CH_{3}OH (2.0 mL) resulting in a homogeneous solution. The reaction mixture was stirred at room temperature for 14 h, and the organic material was extracted with CH_{2}Cl_{2}. The combined organic layer was washed with pH 7 phosphate buffer (10 mL × 2), brine (10 mL), dried over Na_{2}SO_{4}, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with EtOAc/hexane (2/3) as eluent to afford azide 173 (11 mg, 74% yield) was a light yellow amorphous solid.

{\textsuperscript{1}}H NMR (500 MHz, CD_{3}OD) δ 6.41 (d, J = 1.8 Hz, 1H), 6.36 (d, J = 1.8 Hz, 1H), 3.72 (tt, J = 10.9, 4.5 Hz, 1H), 3.53 – 3.47 (m, 1H), 3.13 (d, J = 1.8 Hz, 2H), 2.43 (td, J = 11.2, 2.5 Hz, 1H), 2.31 – 2.25 (m, 2H), 2.10 (d, J = 12.2 Hz, 1H), 2.01 – 1.76 (m, 9H), 1.58 (d, J = 13.2 Hz, 2H), 1.44 – 1.35 (m, 2H), 1.33 (s, 3H), 1.21 – 1.15 (m, 1H), 1.01 (s, 3H), 0.97 – 0.90 (m, 1H). {\textsuperscript{13}}C NMR (126 MHz, CD_{3}OD) δ 157.3, 155.9, 148.5, 111.6, 106.0, 104.6, 77.7, 75.0, 74.5, 71.4, 61.6, 50.3, 42.3, 40.0, 38.2, 36.7, 35.6, 35.0, 29.4, 28.2, 27.2, 19.2. IR (thin film, cm\textsuperscript{-1}): 3327 (br), 2926, 2855, 2100 (N\textsubscript{3}), 1620, 1568, 1265, 1136, 1053, 912, 823, 736. HRMS (EI) m/z calcd
for C_{25}H_{33}N_{3}O_{4} [M^{+}], 439.2471; found, 439.2463. EI+ (amu): 439 (M^{+}, 6), 232 (20), 188 (33), 163 (86), 99 (31), 80 (97), 69 (100). [\alpha]^{23}_{D} -58.5^o (c 1.0, CH_{3}OH).

(6aS,9R,10aR)-3-(3-(Isothiocyanatomethyl)-2-oxaadamantan-1-yl)-6,6-dimethyl-6a,7,8,9,10,10a-hexahydro-6H-benzo[c]chromene-1,9-diol (174)

To a solution of primary amine 172 (17 mg, 0.04 mmol) in THF (4.0 mL) under a nitrogen atmosphere at 0 °C was added Et_{3}N (ca. 50 µL, 0.36 mmol) slowly, and the mixture was stirred for 3 min. CS\textsubscript{2} (ca. 80 µL, 1.36 mmol) was added slowly over 5 min and the reaction mixture was stirred at 0 °C for 30 min, then additional CS\textsubscript{2} (ca. 80 µL, 1.36 mmol) was added and the reaction mixture was stirred at 0 °C for an additional 1.5 h. p-TsCl (15 mg, 0.08 mmol) was added in one portion and the reaction mixture was allowed to warm gradually from 0 °C to room temperature over 1.5 h. The reaction was quenched with pH 7 phosphate buffer, and the organic material was extracted with Et\textsubscript{2}O. The combined organic layer was washed with brine, dried over Na\textsubscript{2}SO\textsubscript{4}, filtered, and concentrated under reduced pressure at 22 °C. The residue was purified by silica gel column chromatography with acetone/hexane (1/4 \rightarrow 3/7) as eluent to afford isothiocyanate 174 (14 mg, 82% yield) as a colorless amorphous solid.

\textsuperscript{1}H NMR (500 MHz, CD\textsubscript{3}OD) δ 6.41 (d, J = 1.8 Hz, 1H), 6.36 (d, J = 1.8 Hz, 1H), 3.72 (tt, J = 10.8, 4.5 Hz, 1H), 3.54 – 3.48 (m, 1H), 3.47 (s, 2H), 2.44 (td, J = 11.2, 2.4 Hz, 1H), 2.35 – 2.30 (m, 2H), 2.10 (d, J = 9.5 Hz, 1H), 1.98 – 1.74 (m, 9H), 1.67 (d, J = 10.7 Hz, 2H), 1.46 – 1.36 (m, 1H), 1.34 (s, 3H), 1.33 – 1.27 (m, 1H), 1.22 – 1.12 (m, 1H), 1.02 (s, 3H), 0.98 – 0.87 (m, 1H).

\textsuperscript{13}C NMR (126 MHz, CD\textsubscript{3}OD) δ 157.4, 155.9, 148.3, 133.0, 111.7, 105.9, 104.4, 77.7, 75.2, 73.7, 71.4, 55.8, 50.3, 42.1, 39.9, 37.9, 36.7, 35.3, 35.0, 29.4, 28.2, 27.2, 19.2. IR (thin film, cm\textsuperscript{-1})
1): 3358 (br), 2926, 2197 (br, NCS), 2104 (br, NCS), 1622, 1574, 1417, 1265, 1138, 1053, 961, 910, 737. HRMS (EI) m/z calcd for C_{26}H_{33}NO_{4}S [M+] 455.2130; found, 455.2110. EI+ (amu): 455 (M+, 1), 279 (17), 167 (49), 149 (100), 113 (9), 83 (8), 71 (15).

$[\alpha]^{23}_D$ $-43.5^\circ$ (c 1.0, CH_{3}OH).

1,3-Bis((3-((6aS,9R,10aR)-1,9-dihydroxy-6,6-dimethyl-6a,7,8,9,10,10a-hexahydro-6H-benzo[c]chromen-3-yl)-2-oxaadamantan-1-yl)methyl)thiourea (182)

A solution of isothiocyanate 174 (ca. 5 mg) in pyridine-water (2.0 mL, 10/1) was stirred at 60 °C for 5 days. Solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography with CH_{2}Cl_{2}/CH_{3}OH (95/5) as eluent to afford thiourea 182 (ca. 4 mg).

^1H NMR (500 MHz, CD_{3}OD) $\delta$ 6.38 (br s, 4H), 3.71 (tt, J = 10.8, 5.3 Hz, 2H), 3.55 (s, 4H), 3.50 – 3.45 (m, 2H), 2.42 (td, J = 11.2, 2.6 Hz, 2H), 2.26 – 2.23 (m, 4H), 2.09 (d, J = 12.1 Hz, 2H), 1.94 – 1.63 (m, 18H), 1.55 (d, J = 12.2 Hz, 4H), 1.43 – 1.27 (m, 10H), 1.20 – 1.10 (m, 2H), 0.99 (s, 6H), 0.97 – 0.86 (m, 2H). ^13C NMR (126 MHz, CD_{3}OD) C=S (not shown up) $\delta$ 157.3, 155.9, 148.4 (weak), 111.8, 106.1, 104.7, 77.8, 74.8, 74.6 (weak), 71.4, 55.3, 50.3, 42.1, 40.0, 38.3, 36.7, 35.7, 35.0, 29.3, 28.3, 27.2, 19.3. IR (thin film, cm$^{-1}$): 3434 (br), 2973, 2925, 1617, 1577, 1419, 1383, 1138, 1053, 957, 737. HRMS ((+)-ESI) m/z calcd for C_{51}H_{68}N_{3}O_{8}SNa [M+Na]^+$, 891.4594; found 891.4579. $[\alpha]^{23}_D$ $-4.5^\circ$ (c 1.0, CH_{3}OH).
3-((3-((6aS,9R,10aR)-1,9-Dihydroxy-6,6-dimethyl-6a,7,8,9,10,10a-hexahydro-6H-benzo[c]chromen-3-yl)-2-oxaadamantan-1-yl)methyl)-1,1-diethylthiourea (183)

To a solution of isothiocyanate 174 (ca. 5 mg, 0.011 mmol) in DMSO (2.0 mL) was added Et₃N (ca. 140 µL, 1.0 mmol) and water (ca. 20 µL, 1.0 mmol). The reaction mixture was stirred at 60 °C for 5 days. After cooling to room temperature, the reaction was quenched with brine, and the organic material was extracted with EtOAc. The combined organic layer was washed again with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with EtOAc/hexane (3/2) as eluent to afford thiourea 183 (ca. 3.5 mg).

¹H NMR (500 MHz, CD₃OD) δ 6.37 (d, J = 1.8 Hz, 1H), 6.35 (d, J = 1.8 Hz, 1H), 3.72 – 3.66 (m, 7H), 3.53 – 3.48 (m, 1H), 2.44 (td, J = 11.3, 2.6 Hz, 1H), 2.31 – 2.26 (m, 2H), 2.10 (d, J = 12.3 Hz, 1H), 1.93 – 1.87 (m, 5H), 1.82 – 1.74 (m, 4H), 1.67 – 1.63 (m, 2H), 1.45 – 1.36 (m, 2H), 1.34 (s, 3H), 1.22 – 1.13 (m, 7H), 1.02 (s, 3H), 0.96 – 0.88 (m, 1H). ¹³C NMR (126 MHz, CD₃OD) δ 181.2, 157.6, 156.1, 148.3, 111.8, 105.8, 104.3, 77.7, 74.8, 74.5, 71.3, 56.3, 50.3, 46.2, 42.3, 39.9, 38.6, 36.7, 35.7, 35.0, 29.3, 28.3, 27.2, 19.2, 13.1. IR (thin film, cm⁻¹): 3413 (br), 2976, 2930, 1622, 1577, 1418, 1383, 1266, 1054, 957, 738. HRMS ((+)-ESI) m/z calcd for C₃₀H₄₄N₂O₄SNa [M+Na]^+ , 551.2919; found 551.2904. [α]D²³ = -38.0° (c 0.5, CH₃OH).
CHAPTER 4

THE SYNTHESIS OF
BICYCLIC 3-ADAMANTYL CANNABINOIDS
AND 3-OXAADAMANTYL 9β-HYDROXYMETHYL HEXAHYDROCANNABINOIDS
4.1. Synthesis of Bicyclic 3-Adamantyl Cannabinoids

**Introduction**

CB2 selective agonists are potential therapeutic targets for the treatment of peripheral and neuropathic pain and inflammation without the undesired CNS side effects mediated by CB1.\(^{396,182}\) Recent studies in the Makriyannis group with bicyclic ketocannabinoids (e.g. compounds 188, 189, Figure 24) have revealed that these nonclassical cannabinoids tend to be CB2 selective.\(^{183}\) The high potency of ketocannabinoids may be due to their presumptive C9-carbinol metabolites. These compounds have longer plasma half-life than the parent ketocannabinoids, for example nabilone. Of the bicyclic ketocannabinoids reported by Makriyannis and co-workers, compound 188 exhibited high affinity for CB2 and a relative large difference in CB2 and CB1 selectivity (ca. 119). Moreover, this compound can be modified easily to further increase CB2 selectivity by removing or masking the phenolic hydroxyl group, as in the case of HU-308, compound 190.\(^{184}\) Therefore bicyclic ketocannabinoids, particularly derivatives of 188, have a promising future for the development of CB2 selective agonists.

**Figure 24.** Structures of bicyclic cannabinoids.

In this part of the dissertation, the preparation of bicyclic 3'-functionalized 3-adamantyl ketocannabinoids and the evaluation of these ligands in the receptor binding assays will be described. The desired functional groups on the adamantyl ring are -CN, -CH\(_2\)NCS, and these compounds will be used for LAPS studies in the Makriyannis lab.
Chemistry

The synthesis of bicyclic 3'-functionalized 3-adamantyl ketocannabinoids was designed with adamantane-carboxylic acid 198 as a starting material. Functional group conversions were used to access the series of functionalized ketocannabinoids shown in Scheme 42.

Scheme 42. Retrosynthesis of bicyclic cannabinoids.

Starting material 198 was provided by Mr. Go Ogawa, a former member of our group.

The details of the synthesis of 198 are summarized in Scheme 43.

Reagents and conditions: (a) MsOH, 50 ºC, >99%; (b) i. TMSCHN₂, benzene, CH₃OH, rt, ii. Tf₂NPh, Et₃N, DMAP (cat.), CH₂Cl₂, reflux, 91%; (c) PdCl₂(PPh₃)₂, dppp, n-Bu₃N, HCOOH, PMHS (cat.), DMF, reflux, 89%; (d) BBr₃, CH₂Cl₂, 0 ºC to rt, 89%; (e) p-TsOH·H₂O, (CH₃)₂CO/CHCl₃, 55 ºC, 78%.

Scheme 43. Synthesis of compound 198 by Mr. Go Ogawa.
In this part of the dissertation the transformation of 198 to bicyclic 3-adamantyl ketocannabinoids 3'-functionalized with -CONH₂, -CN, and -NCS will be described. The details of the synthesis of these cannabinoids are summarized in Scheme 44.

Reagents and conditions: (a) i. HOBT, EDCI, THF, rt, 21 h, ii. NH₄OH (aq), rt, 1.5 h, 86%; (b) i. TFAA, Pyr, 1,4-dioxane, rt, 16 h, ii. K₂CO₃, CH₃OH, rt, 16 h, 88%. (c) BH₃·Me₂S, THF, 0 °C, 30 min, rt, 3.5 h; (d) i. CS₂, Et₃N, THF, 0 °C, 2 h, ii. p-TsCl, 0 °C to rt, 1.5 h, 54% from 199; (e) PDC, Pyr, rt, 2 h, 78%.

Scheme 44. Synthesis of bicyclic adamantyl cannabinoids.

Amidation of carboxylic acid 198 in the presence of NH₃, EDCI and HOBT in THF afforded 199 in 86% yield. Dehydration of amide 199 with excess trifluoroacetic anhydride-pyridine in dioxane, followed by hydrolysis of bis-trifluoroacetate ester intermediate with potassium carbonate in methanol led to nitrile 200 in 88% yield. These functional group transformations are similar to the reactions used for the synthesis of 3'-functionalized 3-oxaadamantyl 9β-hydroxy cannabinoids that have been described in chapter 3 of this dissertation.

Reduction of ketoamide 199 with excess BH₃·Me₂S in THF gave aminoalcohol 201. Reduction of the keto group in 199 during this step to the α-hydroxy represents an undesired
side reaction. Treatment of 201 with CS$_2$ in the presence of TEA in THF, followed by $p$-TsCl mediated decomposition of the *in situ* generated dithiocarbamate gave hydroxylisothiocyanate 202 in 54% yield from 199. The stereochemistry of the 9-hydroxyl group in compounds 201 and 202 was assigned based on the $^1$H NMR spectral data of compound 202. The high polarity of amine 201 made its purification difficult, and it was not possible to obtain clean NMR spectral data for this compound. Therefore, the stereochemistry of the alcohol was determined in 202. Hydroxylisothiocyanate 202 was a 93/7 mixture of C9-$\alpha$ (axial) alcohol 202 and its C9-$\beta$ (equatorial) diastereomer. The stereochemistry of C9 was determined as follows (Figure 25).

The $^1$H NMR spectral data of the 9$\alpha$-hydroxy 202 and its 9$\beta$-hydroxy diastereomer were compared. The axial C9 proton in the 9$\beta$-hydroxy isomer is shielded by the axial C6 methyl and by the axial C10a proton and appears as an upfield signal at 4.14-4.17 ppm, while the corresponding equatorial proton in 9$\alpha$-hydroxy isomer 202 is deshielded and thus appears as a downfield signal at 4.39-4.42 ppm. Irradiation of the C9 methine signal at 4.39-4.42 ppm of 9$\alpha$-hydroxy 202 resulted in strong NOE enhancements of the signals for the *endo* C7 proton at 1.81 ppm, and for the axial C10 proton at 2.89 ppm, while no NOE enhancements of the signals for the C10a methine at 3.97 ppm or for the C6 methyl group at 1.23 ppm were observed.

**Figure 25.** Structures of 9$\alpha$-hydroxy 202 and its 9$\beta$-hydroxy diastereomer.
The preference for the 9α-hydroxy isomer 201 in the reduction with borane can be explained by noting that the 1,3-diaxial interaction between the endo(pseudoaxial)-methyl group at C6 and the reagent affects the direction of hydride delivery more strongly than the 1,2-torsional strain does. Similar metal hydride reductions of the nopinone system have been reported (Scheme 45), in which a strong preference for the axial alcohol isomer was observed.  

Scheme 45. Examples for the reduction of nopinone and a nopinone derivative.

The last step in the synthesis that is summarized in Scheme 44 is the oxidation of secondary alcohol 202 to bicyclic ketocannabinoid 203. This step was predicted to be very challenging because the unprotected phenolic hydroxyl groups in 202 and 203 can be very easily oxidized, the isothiocyanate group is susceptible to nucleophilic attack, such as hydrolysis, and rearrangement/cyclization to the tricyclic cannabinoid is rapid under acidic conditions. Several common methods for the oxidation of secondary alcohols were considered. For example, Swern oxidation or other related methods based on activated DMSO have not been explored for the oxidation of 202 because methylthiomethyl ethers may be formed, as reported in an reaction similar to ours (Scheme 46). Also, alkyl isothiocyanates (e.g. methyl isothiocyanate) have been reported to be highly reactive with oxalyl chloride at room temperature to give 3-alkyl-2,2-dichlorothiazolidine-4,5-diones, which are highly reactive with nucleophiles such as alcohols, amines, or water. Another approach, hypervalent iodine species, such as IBX or DMP, were also not explored because these reagents have been reported to easily oxidize phenols to o-quinones (Scheme 46).
Scheme 46. Some examples for oxidation with Swern, IBX, and DMP.

The Corey-Schmidt reagent, which is mild and neutral, was used successfully for the oxidation of 202 to 203.\textsuperscript{188} Also, in the rigid cyclic system, the chromium-based reagents generally favor the oxidation of axial alcohols because the rate determining breakdown of the metal ester intermediate is accompanied by the relief of 1,3-diaxial interactions.\textsuperscript{189} Accordingly, oxidation of 9-hydroxylisothiocyanate 202 with pyridinium dichromate in pyridine at room temperature formed 9-keto isothiocyanate 203 in 78% yield.\textsuperscript{190} The reaction was very clean with ca. 0.7 equivalent of PDC after 2 h, but excess pyridinium dichromate and longer reaction times led to a complicated reaction mixture.\textsuperscript{191} One minor drawback of this reaction is the formation of emulsions during aqueous work up. However, addition of silica gel to the work up allowed the chromium-derived byproducts to be absorbed on the silica gel surface, giving a clear organic layer. Alternative work-up manipulations, such as using of aqueous oxalic acid/ammonium oxalate to remove residual chromium (III) salts in the form of a ligand-metal complex, have not been explored.\textsuperscript{186} A similar reaction has been reported by Benchikh and co-workers, in which the chromium-based reagent, PCC, was used for the oxidation of alcohol to ketone in the presence of phenolic hydroxy group (Scheme 47).\textsuperscript{190a}
Scheme 47. Example for oxidation with chromium-based reagent, Benchikh et al. 2013.\textsuperscript{190a}
4.2. Synthesis of 3-Oxaadamantyl 9\(\beta\)-Hydroxymethyl Hexahydrocannabinoids

**Introduction**

9\(\beta\)-Hydroxymethyl cannabinoids (e.g. AM-4054, 55) generally have higher binding affinities for both CB1 and CB2 receptors than the 9\(\alpha\)-hydroxymethyl diastereomers (e.g. 204) or the corresponding 9\(\beta\)-hydroxy cannabinoids (e.g. 205) (Figure 26). The results from the evaluation in the receptor binding assays of 3'-functionalized 3-oxaadamantyl cannabinoids (see chapter 3) as well as the 3'-functionalized 3-adamantyl series (compounds of Mr. Go Ogawa) suggested that cannabinoids that were functionalized at the C3' position with -CH\(_2\)NCS (148) and -CH\(_2\)N\(_3\) groups exhibited very high affinity for CB1 and CB2.

![Chemical structures](image)

**Figure 26.** Some adamantyl cannabinoids with variations in the NAG.

As mentioned in **chapter 3**, we have focused on the synthesis of the oxaadamantyl series because of their relative ease of preparation compared to the adamantyl series. In this part of the dissertation, the preparation of 3-oxaadamantyl 9\(\beta\)-hydroxymethyl cannabinoids functionalized with -CONH\(_2\), -CH\(_2\)NCS and -CH\(_2\)N\(_3\) groups and their evaluation in the receptor binding assays will be described. Cannabinoids with reactive groups will be used for LAPS studies in the Makriyannis lab.
Chemistry

The synthesis of 3'-functionalized 3-oxaadamantyl 9β-hydroxymethyl cannabinoids started from intermediate ketone 168, which was prepared during the synthesis 3'-functionalized 3-oxaadamantyl 9β-hydroxy cannabinoids in 7 steps from 1,3-adamantanediol 150 (see chapter 3). The desired products were obtained by stereospecific introduction of the 9β-hydroxymethyl group from the C9 ketone, followed by functional group transformations of the 3'-carboxyl group to -CONH₂, -CH₂NCS, and -CH₂N₃. The retrosynthesis of 3-oxaadamantyl 9β-hydroxymethyl cannabinoids is illustrated in Scheme 48.


The first task in this synthesis is the stereospecific introduction of the 9β-hydroxymethyl group. This conversion was reported by our group several years ago.⁵⁶b,⁶⁶ The details of an example are illustrated in Scheme 49.
Reagents and conditions: (a) $t$-Bu(CH$_3$)$_2$SiCl, imidazole, DMF, 25 °C, 92%; (b) Ph$_3$PCH$_2$OCH$_3$Cl, Na tert-amylate, benzene, 70 °C, 1.5 h; (c) Cl$_3$CCO$_2$H, H$_2$O, CH$_2$Cl$_2$, 25 °C; (d) K$_2$CO$_3$, EtOH, 25 °C, 85% from 207; (e) NaBH$_4$, EtOH, 0 °C; (f) $n$-Bu$_4$NF, THF, 0 °C, 95% from 208.

**Scheme 49.** An earlier approach in our group for introduction of the 9β-hydroxymethyl group, Busch-Peterson et al. 1996.$^{66}$

The 9-keto group in 206 was converted to the equatorial aldehyde via a Wittig reaction with (methoxymethylene)triphenylphosphorane, followed by hydrolysis of the methyl enol ether, and isomerization to the β-equatorial C9 aldehyde 208. Reduction with NaBH$_4$ led to the equatorial 9-hydroxymethyl group. It was notable that because benzene had been used as the solvent in the Wittig reaction, the low solubility of the phenolate led to the recovery of unreactive parent phenol 206. Therefore, protecting the phenolic hydroxy group as the tert-butyldimethylsilyl ether was necessary. Recently, a similar reaction in which THF was used as the solvent for the Wittig reaction has been reported by the Makriyannis group, allowing the use of the unprotected resorcinol as starting material.$^{86}$

The synthesis of 9β-hydroxymethyl 212 from ketone 168 was executed based on the chemistry described above. Wittig reaction of ketone 168 and excess
(methoxymethylene)triphenylphosphorane, which was generated \textit{in situ} from (methoxymethyl)triphenylphosphonium chloride and potassium \textit{tert}-butoxide in THF at room temperature gave a very clean mixture of methyl enol ether geometric isomers 209. Commercially available potassium \textit{tert}-butoxide\textsuperscript{192} could be used effectively in the place of \textit{n}-BuLi,\textsuperscript{86} or sodium \textit{tert}-amylylate, which was prepared from sodium hydride and \textit{tert}-amyl alcohol in benzene.\textsuperscript{193} Hydrolysis of crude 209 with wet trichloroacetic acid in DCM afforded the diastereomeric mixture of aldehydes 210. Epimerization the mixture of aldehydes 210 with potassium carbonate in methanol led to the more stable equatorial aldehyde 211 as the major diastereomer. This was followed by sodium borohydride reduction \textit{in situ} to provide 9\textbeta-hydroxymethyl intermediate 212 in 77\% yield from ketone 168, accompanied by ca. 3\% of the 9\alpha-hydroxymethyl diastereomer. The details of the synthesis of 9\textbeta-hydroxymethyl 212 are summarized in Scheme 50. It is noteworthy that 212 could be obtained from 168 in high yield in only 4 steps without purification of intermediates 209, 210, and 211 by silica gel column chromatography and without the use of protecting groups.

Reagents and conditions: (a) Ph$_3$PCH$_2$OCH$_2$Cl, \textit{t}-BuOK, THF, rt, 1.5 h; (b) CCl$_3$COOH, H$_2$O, CH$_2$Cl$_2$, rt, 45 min; (c) K$_2$CO$_3$, CH$_3$OH, rt, 4 h; (d) NaBH$_4$, CH$_3$OH, rt, 30 min, 77\% from 168.

\textbf{Scheme 50.} Synthesis of 9\textbeta-hydroxymethyl 212 from ketone 168
The $^1$H NMR spectral data of 9β-hydroxymethyl 212 and its 9α-hydroxymethyl diastereomer were compared. The -CH$_2$OH methylene protons in the 9β-hydroxymethyl isomer are strongly shielded by the nearby protons at C8 and C10, resulting in an upfield signal at 3.35-3.44 ppm (m, broader signal), whereas the -CH$_2$OH methylene protons in the 9α-hydroxymethyl are not shielded, thus the downfield signal at 3.68-3.71 ppm (m, narrower signal) (Figure 27). The chemical shift trends were consistent with earlier reports in comparing 9β-hydroxymethyl and 9α-hydroxymethyl cannabinoids.$^{56d, 66, 86}$

Figure 27. Structures of 9β-hydroxymethyl 212 and its 9α-hydroxymethyl diastereomer.

To complete the synthesis of this series of compounds, conversion of the carboxylic acid group in 212 to the azide and the isothiocyanate group was necessary. The details of the functional group transformations are summarized in Scheme 51.
Reagents and conditions: (a) i. HOBT, EDCI, THF, rt, 16 h, ii. NH₄OH (aq), rt, 1 h, 80%; (b) BH₃·Me₂S, THF, 0 °C, 30 min, rt, 3 h, 80%; (c) TfN₃, K₂CO₃, CuSO₄, CH₂Cl₂/CH₃OH/H₂O, rt, 18 h 74%; (d) i. CS₂, Et₃N, THF, 0 °C, 2 h, ii. p-TsCl, 0 °C to rt, 2 h, 82%.

Scheme 51. Functional group transformations in the synthesis of 9β-hydroxymethyl oxaadamantyl cannabinoids.

Amidation of carboxylic acid 212 in the presence of NH₃, EDCI and HOBT afforded 213 in 80% yield. Reduction of amide 213 with excess BH₃·Me₂S in THF led to amine 214 in 80% yield. Copper (II) catalyzed diazo transfer of amine 214 with triflyl azide formed to azide 215 in 74% yield. Treatment of primary amine 214 with CS₂ in the presence of TEA in THF, followed by p-TsCl mediated decomposition of the dithiocarbamate that was generated in situ gave isothiocyanate 216 in 82% yield. These conversions are similar to the functional group transformations that have been described in the synthesis of 9β-hydroxy oxaadamantyl cannabinoids in chapter 3 (Scheme 36).
4.3. Receptor Binding Studies

The affinities for CB1 and CB2 were determined by our collaborators in the group of Professor Makriyannis. These are displayed in Table 4.

Table 4. Ligand affinities ($K_i$) of 3-adamantyl cannabinoids and 3-oxadamantyl 9β-hydroxymethyl hexahydrocannabinoids.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Structure</th>
<th>$K_i$ (nM)</th>
<th>rCB1</th>
<th>mCB2</th>
<th>hCB2</th>
</tr>
</thead>
<tbody>
<tr>
<td>200</td>
<td><img src="image1" alt="Structure" /></td>
<td>in progress</td>
<td>in progress</td>
<td>in progress</td>
<td></td>
</tr>
<tr>
<td>203</td>
<td><img src="image2" alt="Structure" /></td>
<td>in progress</td>
<td>in progress</td>
<td>in progress</td>
<td></td>
</tr>
<tr>
<td>213</td>
<td><img src="image3" alt="Structure" /></td>
<td>70-100 nM</td>
<td>$K_i = 34.9$ nM</td>
<td>170-220 nM</td>
<td></td>
</tr>
<tr>
<td>215</td>
<td><img src="image4" alt="Structure" /></td>
<td>1-10 nM</td>
<td>$K_i = 0.74$ nM</td>
<td>1-10 nM</td>
<td></td>
</tr>
</tbody>
</table>
Receptor binding studies of these compounds are in progress. Current results, provided from the group of Professor Makriyannis, have revealed that 3-oxadamantyl 9β-hydroxymethyl hexahydrocannabinoids have very high binding affinities for both CB1 and CB2, especially compounds with -CH₂NCS and -CH₂N₃ as functional groups that have affinities at nanomolar or sub-nanomolar levels.
4.4. Experimental Section - Chapter 4

LCMS purity of final compounds

<table>
<thead>
<tr>
<th>Compounds</th>
<th>LC-MS Purity, %</th>
<th>UV absorbance</th>
</tr>
</thead>
<tbody>
<tr>
<td>199 (-CONH₂)</td>
<td>96.8</td>
<td>230 nm</td>
</tr>
<tr>
<td>200 (-CN)</td>
<td>98.8</td>
<td>230 nm</td>
</tr>
<tr>
<td>203 (-CH₂NCS)</td>
<td>96.0</td>
<td>230 nm</td>
</tr>
<tr>
<td>205 (-CH₂NCS)</td>
<td>97.1</td>
<td>230 nm</td>
</tr>
<tr>
<td>204 (-CH₂N₃)</td>
<td>97.6</td>
<td>230 nm</td>
</tr>
</tbody>
</table>

Table 5. LC–MS purity of final compounds

Bicyclic adamantyl cannabinoids

![Chemical Structure]

3-(4-(1R,2R,5R)-6,6-Dimethyl-4-oxobicyclo[3.1.1]heptan-2-yl)-3,5-dihydroxyphenyl)adamantane-1-carboxamide (199)

To a solution of carboxylic acid 198 (57 mg, 0.134 mmol) in THF (12 mL) at room temperature was added HOBT (36 mg, 0.266 mmol), and the mixture was stirred for 5 min. EDCI-HCl (70 mg, 0.365 mmol) was added and the resulting suspension was stirred at room temperature for 21 h. Aqueous 29.6% NH₄OH solution (0.4 mL) was added over 5 min, and the resulting homogenous solution was stirred at room temperature for 1.5 h. The reaction was quenched by dropwise addition of 1 M aqueous HCl until pH ~ 3. The organic material was extracted with EtOAc, and the combined organic layer was washed with pH 7 phosphate buffer, brine, dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by
silica gel column chromatography with CH₂Cl₂/CH₃OH (95/5) as eluent to afford amide 199 (49 mg, 86% yield) as a white amorphous powder.

¹H NMR (500 MHz, CD₃OD) δ 6.32 (s, 2H), 3.99 (t, J = 8.1 Hz, 1H), 3.72 (dd, J = 18.8, 7.6 Hz, 1H), 2.64 – 2.57 (m, 1H), 2.51 – 2.45 (m, 2H), 2.41 (dd, J = 18.8, 8.7 Hz, 1H), 2.23 – 2.12 (m, 3H), 1.94 – 1.70 (m, 12H), 1.36 (s, 3H), 0.95 (s, 3H). ¹³C NMR (126 MHz, CD₃OD) δ 219.9, 183.8, 157.6, 150.9, 114.6, 105.0, 59.3, 49.5, 45.6, 43.3, 43.2, 42.9, 39.6, 38.5, 37.3, 36.8, 30.4, 30.3, 26.6, 24.9, 22.4. HRMS ((–)-ESI) m/z calcd for C₂₆H₃₂NO₄ [M-H]⁻, 422.2337; found 422.2358. IR (thin film, cm⁻¹): 3398 (br), 1653 – 1635 (CO and CONH₂), 1456, 1265, 737. [α]²⁵_D +33.3° (c 0.3, CH₃OH).

3-(4-((1R,2R,5R)-6,6-Dimethyl-4-oxobicyclo[3.1.1]heptan-2-yl)-3,5-dihydroxyphenyl)adamantane-1-carbonitrile (200)

To a solution of amide 199 (12 mg, 0.028 mmol) in 1,4-dioxane (2.5 mL) under a nitrogen atmosphere at room temperature was added pyridine (ca. 150 µL, 1.86 mmol), and the mixture was stirred for 10 min. Trifluoroacetic anhydride (ca. 130 µL, 0.92 mmol) was added, and the mixture was stirred at room temperature for 19 h. The reaction mixture was quenched with pH 7 phosphate buffer, and the organic material was extracted with Et₂O. The combined organic layer was washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was dissolved in CH₃OH (10 mL), followed by addition of K₂CO₃ (330 mg, 2.39 mmol) and stirred under nitrogen atmosphere at room temperature for 16 h. The reaction mixture was quenched with aqueous 1 M HCl until pH ~ 3, and the organic material was extracted with Et₂O. The combined organic layer was washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column
chromatography with acetone/hexane (3/7) as eluent to afford nitrile 200 (10 mg, 88% yield) as an off-white powder.

$^1$H NMR (500 MHz, CD$_3$OD) $\delta$ 6.29 (s, 2H), 4.00 (t, $J = 7.9$ Hz, 1H), 3.71 (dd, $J = 18.8, 7.6$ Hz, 1H), 2.63 – 2.57 (m, 1H), 2.51 – 2.45 (m, 2H), 2.41 (dd, $J = 18.8, 8.7$ Hz, 1H), 2.21 – 2.13 (m, 3H), 2.11 – 2.00 (m, 7H), 1.90 – 1.71 (m, 5H), 1.36 (s, 3H), 0.95 (s, 3H). $^{13}$C NMR (126 MHz, CD$_3$OD) $\delta$ 219.7, 157.8, 149.6, 126.0, 115.0, 104.8, 59.3, 48.6, 46.1, 43.2, 42.6, 40.3, 38.5, 36.6, 36.0, 32.7, 30.4, 29.5, 26.6, 25.0, 22.5. IR (thin film, cm$^{-1}$): 3410 (br), 3055, 2924, 2854, 2237 (CN), 1720 (C=O), 1573, 1419, 1265, 894, 740. HRMS ((-)-ESI) m/z calcd for C$_{26}$H$_{30}$NO$_3$ [M-H], 404.2226; found 404.2185. [$\alpha$]$_D^{23}$ +28.0º (c 0.5, CH$_3$OH).

2-((1R,2R,4R,5R)-4-Hydroxy-6,6-dimethylbicyclo[3.1.1]heptan-2-yl)-5-(3-(isothiocyanatomethyl)adamantan-1-yl)benzene-1,3-diol (202)

To a solution of amide 199 (24 mg, 0.057 mmol) in THF (1.5 mL) at 0 °C under a nitrogen atmosphere was added excess BH$_3$·S(CH$_3$)$_2$ (0.25 mL, 2.50 mmol, 10 M in THF), and the reaction was stirred at 0 °C for 30 min, then at room temperature for 3.5 h. EtOH (1.0 mL) was added slowly, and the mixture was gently refluxed for 22 h. Solvent was removed under reduced pressure, and a minimal amount of pH 7 phosphate buffer (ca. 50 µL) was added, followed by Et$_2$O (4 mL). The mixture was stirred for 10 min, then Celite was added. After concentration by evaporation, the residue was purified by silica gel column chromatography with NH$_4$OH(aq)/CH$_3$OH/CH$_2$Cl$_2$ (1/5/45) as eluent to afford amine 201 (ca. 15 mg). HRMS ((+)-ESI) m/z calcd for C$_{26}$H$_{38}$NO$_3$ [M+H]$^+$, 412.2846; found 412.2827. This amine (not completely pure as showed on NMR) was used for the next step with out repurification. To a solution of amine
201 (ca. 15 mg, 0.036 mmol) in THF (4.0 mL) under a nitrogen atmosphere at 0 °C was added Et₃N (ca. 50 µL, 0.36 mmol) slowly, and the mixture was stirred for 3 min. CS₂ (ca. 80 µL, 1.36 mmol) was added slowly over 3 min at 0 °C. After stirring for 30 min, additional CS₂ (ca. 80 µL, 1.36 mmol) was added. The mixture was stirred at 0 °C for an additional 1.5 h. p-TsCl (14 mg, 0.073 mmol) was then added in one portion, and the mixture was stirred for an additional 1.5 h while gradually warming to room temperature. The reaction was quenched with pH 7 phosphate buffer, extracted with Et₂O, washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with acetone/hexane (3/7) as eluent to afford isothiocyanate 202 (14 mg, 54% yield from 199) as a white amorphous powder.

¹H NMR (500 MHz, CD₃OD) δ 6.28 (s, 2H, H-Ar), 4.41 (dt, J = 9.2, 3.5 Hz, 1H, H-C9), 4.01 – 3.93 (m, 1H, H-C10a), 3.26 (s, 2H, -CH₂NCS), 2.89 (ddd, J = 14.9, 9.2, 5.6 Hz, 1H, Haxial-C10), 2.20 – 2.17 (m, 2H), 2.10 – 1.99 (m, 2H), 1.90 – 1.94 (m, 1H), 1.90 – 1.82 (m, 4H), 1.80 – 1.67 (m, 4H), 1.64 – 1.55 (m, 6H), 1.23 (s, 3H, equatorial -CH₃), 1.20 (s, 3H, axial -CH₃). ¹³C NMR (126 MHz, CD₃OD) δ 157.3, 150.0, 131.3, 117.6, 105.0, 74.0, 57.7, 49.1, 48.6, 46.4, 43.5, 40.7, 40.1, 37.4, 37.0, 37.0, 32.6, 32.0, 30.4, 28.5, 27.2, 23.0. IR (thin film, cm⁻¹): 3426 (br), 3055, 2916, 2854, 2183 (br, NCS), 2106 (br, NCS), 1620, 1419, 1265, 1018, 740. HRMS ((-)ESI) m/z calcd for C₂₇H₃₄NO₃S [M-H], 452.2259; found 452.2248. [α]D²³ +31.0° (c 0.5, CH₃OH).
(1R,4R,5R)-4-(2,6-Dihydroxy-4-(3-(isothiocyanatomethyl)adamant-1-yl)phenyl)-6,6-
dimethylbicyclo[3.1.1]heptan-2-one (203)

To a solution of hydroxyisothiocyanate 202 (ca. 5 mg, 0.011 mmol) in pyridine (200 µL) at
room temperature was added a solution of PDC (ca. 3 mg, 0.008 mmol) in pyridine (800 µL),
and the reaction mixture was stirred for 2 h. Saturated aqueous NaCl was then added and the
organic material was diluted with EtOAc. Silica (ca. 20 mg) was added to the resulting
emulsion, and the mixture was stirred until the organic layer became clear (ca. 3 min). The
organic layer was separated (using pipette), then washed again with brine, dried over Na₂SO₄,
filtered, and concentrated under reduced pressure. The residue was purified by silica gel column
chromatography with acetone/hexane (1/4) as eluent to afford keto isothiocyanate 203 (ca. 3.8
mg) as a colorless oil.

¹H NMR (500 MHz, CD₃OD) δ 6.32 (s, 2H), 4.00 (t, J = 8.2 Hz, 1H), 3.71 (dd, J = 18.8, 7.6 Hz,
1H), 3.27 (s, 2H), 2.63 – 2.58 (m, 1H), 2.50 – 2.45 (m, 2H), 2.41 (dd, J = 18.8, 8.7 Hz, 1H), 2.21
– 2.14 (m, 4H), 1.90 – 1.73 (m, 4H), 1.65 – 1.56 (m, 7H), 1.36 (s, 3H), 0.95 (s, 3H). ¹³C NMR
(126 MHz, CD₃OD) δ 219.9, 157.7, 150.9, 131.3, 114.6, 105.0, 59.3, 57.6, 49.5, 46.4, 43.5, 43.2,
40.1, 38.6, 37.5, 37.0, 36.9, 30.4, 30.4, 26.6, 25.0, 22.5. IR (neat, cm⁻¹): 3350 (br), 3057, 2918,
2850, 2178 (br, NCS), 2101 (br, NCS), 1701 (CO), 1618, 1420, 1265, 1026, 736. HRMS ((-)ESI) m/z calcd for C₂₇H₃₃NO₃S [M-H]⁻, 450.2103; found 450.2089. [α]₂₃° +36.0° (c 0.5,
CH₃OH).
9β-Hydroxymethyl oxaadamantyl cannabinoids

3-((6aS,9R,10aR)-1-Hydroxy-9-(hydroxymethyl)-6,6-dimethyl-6a,7,8,9,10,10a-hexahydro-6H-benzo[c]chromen-3-yl)-2-oxaadamantane-1-carboxylic acid (212)

To a suspension of (methoxymethyl)triphenylphosphonium chloride (2.47 g, 7.20 mmol) in THF (20 mL) under a nitrogen atmosphere at room temperature was added t-BuOK (1.13 g, 10.0 mmol) in one portion. After 15 min, a solution of 168 (256 mg, 0.60 mmol) in THF (5.0 mL) was added via cannula. The reaction mixture was stirred at room temperature for 1.5 h, then water was added to quench and dilute the mixture. The aqueous solution was washed with Et₂O, then acidified with 1 M aqueous HCl. The organic material was extracted with Et₂O, and the combined organic extract was washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude enol ethers were dissolved in CH₂Cl₂ (50 mL), followed by addition of wet trichloroacetic acid (1.18 g, 7.2 mmol, dissolved in 0.5 mL water), and the reaction mixture was stirred at room temperature for 45 min. The mixture was washed with water, brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude aldehydes were dissolved in CH₃OH (50 mL), followed by addition of K₂CO₃ (1.0 g, 7.2 mmol), and the light yellow suspension (pH ~ 9) was stirred at room temperature for 4 h. NaBH₄ (455 mg, 12.0 mmol) was added in 3 portions over 5 min, and the reaction mixture was stirred at room temperature for 30 min. The reaction was quenched by dropwise addition of 1 M aqueous HCl (until pH = 2), and the organic material was extracted with EtOAc. The combined organic layer was washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced
pressure. The residue was purified by silica gel column chromatography with acetone/hexane (1/4 → 1/1) as eluent to afford 212 (204 mg, 77% yield over 4 steps) as an amorphous solid.

$^1$H NMR (500 MHz, CD$_3$OD) $\delta$ 6.48 (d, $J = 1.9$ Hz, 1H), 6.35 (d, $J = 1.9$ Hz, 1H), 3.45 – 3.34 (m, 2H), 2.44 (td, $J = 11.1$, 2.7 Hz, 1H), 2.31 – 2.29 (m, 2H), 2.03 – 1.91 (m, 12H), 1.84 (d, $J = 11.5$ Hz, 2H), 1.44 – 1.38 (m, 1H), 1.33 (s, 3H), 1.20 – 1.05 (m, 2H), 1.03 (s, 3H), 0.70 – 0.60 (m, 1H). $^{13}$C NMR (126 MHz, CD$_3$OD) $\delta$ 177.7, 157.7, 155.8, 148.0, 112.4, 105.8, 104.5, 77.7, 76.0, 75.5, 68.7, 51.2, 42.0, 41.8, 38.2, 36.7, 35.1, 34.5, 31.2, 29.2, 28.7, 28.1, 19.2. IR (thin film, cm$^{-1}$): 3379 (br), 3053, 2983, 2927, 2856, 1762 (C=O), 1622, 1576, 1420, 1265, 839, 739. HRMS (EI) m/z calcd for C$_{26}$H$_{34}$O$_6$ [M+], 442.2355; found, 442.2368. EI+ (amu): 442 (M+, 1), 279 (10), 216 (61), 201 (100), 183 (9), 167 (18), 149 (42), 83 (73). $[\alpha]_{D}^{23}$ −23.0° (c 1.0, CH$_3$OH).

![Chemical Structure](image)

3-((6aS,9R,10aR)-1-Hydroxy-9-(hydroxymethyl)-6,6-dimethyl-6a,7,8,9,10,10a-hexahydro-6$H$-benzo[c]chromen-3-yl)-2-oxaadamantane-1-carboxamide (213)

To a solution of carboxylic acid 212 (30 mg, 0.068 mmol) in THF (6.0 mL) at room temperature was added HOBT (18 mg, 0.13 mmol), and the mixture was stirred for 5 min. EDCI·HCl (35 mg, 0.18 mmol) was added, and the suspension was stirred for 16 h. Aqueous 29.6% NH$_4$OH (0.2 mL) was added over 5 min, and the reaction mixture was stirred for 1 h and then quenched by dropwise addition of 1 M aqueous HCl (until pH = 3). The organic material was extracted with EtOAc, and the combined organic layer was washed with pH 7 phosphate buffer, brine, dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The residue was absorbed onto Celite, and purified by silica gel column chromatography with CH$_2$Cl$_2$/CH$_3$OH (94/6) as eluent to afford amide 213 (24 mg, 80% yield) as an off-white amorphous solid.
$^1$H NMR (500 MHz, CD$_3$OD) δ 6.44 (d, $J = 1.8$ Hz, 1H), 6.32 (d, $J = 1.8$ Hz, 1H), 3.46 – 3.35 (m, 2H), 2.45 (td, $J = 11.0$, 2.6 Hz, 1H), 2.32 – 2.28 (m, 2H), 2.05 (d, $J = 11.9$ Hz, 2H), 2.01 – 1.64 (m, 12H), 1.46 – 1.37 (m, 1H), 1.34 (s, 3H), 1.18 – 1.07 (m, 2H), 1.04 (s, 3H), 0.71 – 0.61 (m, 1H). $^{13}$C NMR (126 MHz, CD$_3$OD) δ 180.3, 157.8, 155.9, 145.0, 112.5, 105.6, 104.3, 77.9, 76.4, 75.9, 68.7, 51.2, 42.2, 41.8, 38.1, 36.7, 35.0, 34.5, 31.2, 29.2, 28.7, 28.1, 19.2. IR (thin film, cm$^{-1}$): 3439–3053 (br), 2922, 2855, 1670 (C=O), 1418, 1265, 1136, 957, 737. HRMS (EI) m/z calcd for C$_{26}$H$_{35}$NO$_5$ [M+], 441.2515; found, 441.2502. EI+ (amu): 441 (M+, 1), 279 (20), 201 (21), 167 (50), 149 (100), 97 (12), 83 (31). [$\alpha$]$^\circ$$_{23}$D $-22.5$° (c 1.0, CH$_3$OH).

(6aS,9R,10aR)-3-(3-(Aminomethyl)-2-oxaadamantan-1-yl)-9-(hydroxymethyl)-6,6-dimethyl-6a,7,8,9,10,10a-hexahydro-6H-benzo[c]chromen-1-ol (214)

To a solution of amide 213 (40 mg, 0.09 mmol) in THF (2.0 mL) under an argon atmosphere at 0 °C was added excess BH$_3$·S(CH$_3$)$_2$ (0.3 mL, 3.0 mmol, 10 M in THF). The reaction mixture was stirred at 0 °C for an additional 30 min, then at room temperature for 3 h. EtOH (1.0 mL) was added slowly and carefully at 0 °C, then the mixture was stirred at 70 °C for 14 h. Solvent was removed under reduced pressure, followed by addition of a minimum amount of pH 7 phosphate buffer (ca. 70 µL). The organic material was extracted with EtOAc, absorbed onto Celite, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with NH$_4$OH$_{aq}$/CH$_3$OH/CH$_2$Cl$_2$ (2.5/7.5/90) as eluent to afford amine 214 (31 mg, 80% yield) as a clear glass.

$^1$H NMR (500 MHz, CD$_3$OD) δ 6.42 (d, $J = 1.7$ Hz, 1H), 6.30 (d, $J = 1.7$ Hz, 1H), 3.48 – 3.34 (m, 2H), 2.54 (s, 2H), 2.43 (td, $J = 11.0$, 2.4 Hz, 1H), 2.31 – 2.24 (m, 2H), 2.02 – 1.64 (m, 12H),
1.53 (d, J = 12.0 Hz, 2H), 1.45 – 1.36 (m, 1H), 1.33 (s, 3H), 1.22 – 1.06 (m, 2H), 1.03 (s, 3H), 0.71 – 0.59 (m, 1H). ¹³C NMR (126 MHz, CD₃OD) δ 157.7, 155.8, 148.7, 112.3, 105.7, 104.4, 77.7, 74.4, 73.6, 68.7, 52.7, 51.2, 42.5, 41.8, 38.1, 36.7, 35.9, 34.5, 31.2, 29.4, 28.7, 28.2, 19.2. IR (thin film, cm⁻¹): 3390 (br), 3053, 2926, 2857, 1622, 1519, 1417, 1265, 1136, 956, 736. HRMS (EI) m/z calcd for C₂₆H₃₇NO₄ [M+], 427.2723; found, 427.2735. EI+ (amu): 427 (M+, 4), 279 (10), 167 (20), 149 (54), 83 (13), 71 (100), 69 (14). [α]²³D −43.0° (c 1.0, CH₃OH).

(6aS,9R,10aR)-3-(3-(Azidomethyl)-2-oxaadamantan-1-yl)-9-(hydroxymethyl)-6,6-dimethyl-6a,7,8,9,10,10a-hexahydro-6H-benzo[c]chromen-1-ol (215)

To a solution of amine 214 (ca. 5 mg, 0.012 mmol) in CH₂Cl₂/CH₃OH (2.0 mL, 1/1) was added a 0.07 M aqueous solution of K₂CO₃ (0.26 mL, 0.018 mmol), a 0.002 M aqueous solution of CuSO₄ (0.25 mL, 0.0005 mmol), followed by dropwise addition of a 0.2 M solution of trifluoromethanesulfonyl azide (TfN₃) in CH₂Cl₂ (100 µL, ca. 0.02 mmol) at 0 °C. Additional CH₂Cl₂ (1.9 mL) was slowly added, followed by CH₃OH (2.0 mL) resulting in a homogeneous solution. The reaction mixture was stirred at room temperature for 18 h, and the organic material was extracted with CH₂Cl₂. The combined organic layer was washed with pH 7 phosphate buffer (3 mL x 2), brine (3 mL), dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with EtOAc/hexane (2/3) as eluent to afford azide 215 (ca. 3.9 mg) was a colorless amorphous solid.

¹H NMR (500 MHz, CD₃OD) δ 6.40 (d, J = 1.8 Hz, 1H), 6.34 (d, J = 1.8 Hz, 1H), 3.45 – 3.34 (m, 2H), 3.13 (d, J = 2.4 Hz, 2H), 2.43 (td, J = 11.0, 2.5 Hz, 1H), 2.31 – 2.26 (m, 2H), 2.03 – 1.63 (m, 12H), 1.59 (d, J = 12.1 Hz, 2H), 1.44 – 1.37 (m, 1H), 1.33 (s, 3H), 1.21 – 1.05 (m, 2H),
1.02 (s, 3H), 0.70 – 0.61 (m, 1H). $^{13}$C NMR (126 MHz, CD$_3$OD) δ 157.6, 155.8, 148.4, 112.3, 105.9, 104.5, 77.7, 75.0, 74.5, 68.8, 61.5, 51.3, 42.2, 41.8, 38.1, 36.7, 35.6, 34.5, 31.2, 29.4, 28.8, 28.1, 19.2. IR (thin film, cm$^{-1}$): 3315 (br), 3053, 2926, 2857, 2102 (N=), 1612, 1419, 1265, 1194, 1028, 737. HRMS (EI) m/z calcd for C$_{26}$H$_{35}$N$_{3}$O$_{4}$ [M+], 453.2628; found, 453.2644. EI+ (amu): 453 (M+, 1), 279 (23), 167 (44), 149 (100), 83 (17), 71 (18), 69 (11). $[\alpha]^2_{D} -31.5^\circ$ (c 1.0, CH$_3$OH).

**Preparation of TfN$_3$:** To an aqueous solution of NaN$_3$ (1.0 mL, 5.6 mmol) at 0 °C was added CH$_2$Cl$_2$ (1.0 mL), followed by dropwise addition of Tf$_2$O (ca. 100 µL, 0.6 mmol) with vigorous stirring at 0 °C. After 2 h, the organic layer was separated, and the aqueous layer was extracted with CH$_2$Cl$_2$ (1 mL x 1). The combined organic layer (ca. 2 mL) was washed with saturated aqueous NaHCO$_3$ (4 mL) at 0 °C, then diluted with cold CH$_2$Cl$_2$ to give ca. 3 mL solution of TfN$_3$ (ca. 0.6 mmol, 0.2 M).

(6aS,9R,10aR)-9-(Hydroxymethyl)-3-(3-(isothiocyanatomethyl)-2-oxaadamantan-1-yl)-6,6-dimethyl-6a,7,8,9,10,10a-hexahydro-6H-benzo[c]chromen-1-ol (216)

To a solution of amine 214 (22 mg, 0.05 mmol) in THF (5.0 mL) under a nitrogen atmosphere at 0 °C was added Et$_3$N (ca. 65 µL, 0.45 mmol) slowly, and the mixture was stirred for 3 min. CS$_2$ (ca. 100 µL, 1.70 mmol) was added slowly over 5 min and the reaction mixture was stirred at 0 °C for 30 min, then additional CS$_2$ (ca. 100 µL, 1.70 mmol) was added and the reaction mixture was stirred at 0 °C for an additional 1.5 h. p-TsCl (19 mg, 0.1 mmol) was added in one portion and the reaction mixture was allowed to warm gradually from 0 °C to room temperature over 1.5 h. The reaction was quenched with pH 7 phosphate buffer, and the organic material was
extracted with Et₂O. The combined organic layer was washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure at 22 °C. The residue was purified by silica gel column chromatography with acetone/hexane (2/8–3/7) as eluent to afford isothiocyanate 216 (14 mg, 82% yield) as a colorless amorphous solid.

¹H NMR (500 MHz, CD₃OD) δ 6.41 (d, J = 1.7 Hz, 1H), 6.35 (d, J = 1.7 Hz, 1H), 3.47 (s, 2H), 3.45–3.34 (m, 2H), 2.44 (td, J = 11.0, 2.6 Hz, 1H), 2.36 – 2.28 (m, 2H), 2.08 – 1.56 (m, 14H), 1.45 – 1.39 (m, 1 Hz, 1H), 1.33 (s, 3H), 1.20 – 1.08 (m, 2H), 1.03 (s, 3H), 0.71 – 0.59 (m, 1H).

¹³C NMR (126 MHz, CD₃OD) δ 157.6, 155.8, 148.2, 133.1, 112.5, 105.9, 104.5, 77.7, 75.2, 73.7, 68.8, 55.8, 51.3, 42.2, 41.9, 37.9, 36.7, 35.3, 34.5, 31.2, 29.4, 28.8, 28.1, 19.2. IR (thin film, cm⁻¹): 3416–3050 (br), 2924, 2855, 2197 (br, NCS), 2104 (br, NCS), 1622, 1418, 1265, 1136, 1026, 737. HRMS (EI) m/z calcd for C₂₇H₃₅NO₄S [M⁺], 469.2287; found, 469.2292. EI+ (amu): 469 (M+, 71), 279 (23), 167 (43), 149 (100), 91 (41), 83 (53), 71 (47), 69 (55). [α]²³D –43.5° (c 1.0, CH₃OH).

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CONCLUSION

The total synthesis of some series of cannabinoids has been accomplished. These ligands have been evaluated in the receptor binding studies for CB1 and CB2 and some of them have been used for LAPS studies by collaborators in the group of Professor Makriyannis at Northeastern University.

Chapter 2 describes the total synthesis of three series of C1'-azacycloalkyl 9β-hydroxy hexahydrocannabinoids: 2,2-disubstituted pyrrolidine, 3,3-disubstituted azetidine, and 2,2-disubstituted azetidine cannabinoids. The synthesis of these series was designed from the common tricyclic intermediate triflate. The key step in the non-diastereoselective synthesis of 2,2-disubstituted pyrrolidine cannabinoids are the Liebeskind coupling reaction of aryl boronic acid to a cyclic imine followed by nucleophilic addition of n-hexyllithium. The key step in the synthesis of 3,3-disubstituted azetidine cannabinoids is the palladium-catalyzed decarboxylative cross coupling that introduced the side chain into the aromatic ring, and the symmetric azetidine ring was constructed by the reductive cyclization of α-tosyloxymethyl nitrile. The key step in the diastereoselective synthesis of 2,2-disubstituted azetidine cannabinoids is the diastereoselective synthesis of the amino ester from the corresponding ketone using Ellman chemistry, and base-promoted cyclization to construct the azetidine ring. Tricyclic cannabinoids with N-methyl azetidine as well as N-methyl pyrrolidine with improvements in water solubility showed comparable binding affinities (in vitro) to (-)-Δ⁹-THC, the major psychoactive constituent of Cannabis sativa. Evaluation in binding affinities of diastereomeric 2,2-disubstituted azetidinone cannabinoid is in progress.

Chapter 3 describes the total synthesis of a series of 3'-functionalized 3-oxaadamantyl 9β-hydroxy hexahydrocannabinoids. These compounds were designed as an alternative for
analogs of 3-adamantyl cannabinoids due to difficulties in the synthesis of 3-adamantyl cannabinoids. The synthesis of 3-oxaadamantyl cannabinoids was conducted by the introduction of the oxaadamantyl fragment into the aromatic ring first, then construction of the tricyclic cannabinoid nucleus, and finally functional group manipulation. The connection of the oxaadamantyl fragment with the aromatic ring was conducted by nucleophilic addition of aryllithium to epoxide ketone in the presence of anhydrous cerium chloride, followed by transannular cyclization. The construction of tricyclic nucleus by condensation of the derived resorcinol with a mixture of optically active diacetates followed by Lewis acid-catalyzed cyclization were adapted from the chemistry that has been developed by the Archer group. It was valuable that no protecting groups were employed for the functional group conversions in the final steps. The synthesis of these compounds was easier than that of the 3-adamantyl analogs, and these ligands exhibit high affinities for CB1 and CB2 which are similar to those of the 3-adamantyl analogs. Especially, compounds with -CN, -CH₂N₃, and -CH₂NCS at the C3' position have affinities at nanomolar or sub-nanomolar levels, and they will be used for LAPS studies in the group of Professor Makriyannis.

Chapter 4 describes the synthesis of two series of cannabinoids: the bicyclic 3-adamantyl cannabinoids and the 3'-functionalized 3-oxaadamantyl 9β-hydroxymethyl hexahydrocannabinoids. The series of bicyclic 3-adamantyl cannabinoids was designed for the development of high CB2 selectivity ligands and LAPS studies. The synthesis of bicyclic 3-adamantyl cannabinoids required functional group conversions from the intermediate bicyclic keto carboxylic acid to the desired bicyclic keto isothiocyanate. The challenging step, oxidation of bicyclic hydroxy isothiocyanate to bicyclic keto isothiocyanate was accomplished with PDC without affecting the phenolic hydroxy group or isothiocyanate group as well as without leading to undesired cyclization. And no protecting groups were used during these conversions. Evaluation of binding affinities of these ligands is in progress. The other series, the 3'-
functionalized 3-oxaadamantyl 9β-hydroxymethyl hexahydrocannabinoids was designed for ligands with high affinities for CB1 and CB2. The synthesis focused on the conversion of the 9-keto group to 9β-hydroxymethyl, then functional group manipulation similar to what was described in chapter 2. Current results from receptor binding studies showed that ligands with -CH$_2$NCS and -CH$_2$N$_3$ at the C3’ position have extremely high affinities (at nanomolar or sub-nanomolar levels). Compounds of these two series will also be used for LAPS studies in the group of Professor Makriyannis.
Appendix I

THE SYNTHESIS AND SOLUTION STRUCTURES OF

α-LITHIATED VINYL ETHERS
5.1. Introduction

α-Lithiated alkoxy vinyl ethers, initially developed by Schollkopf\textsuperscript{194a} and Baldwin,\textsuperscript{194b} are useful acyl anion equivalents since their reactions with with electrophiles led to adducts that can be hydrolyzed to acetyl derivatives. For example, the nucleophilic addition of an α-lithiovinyl nucleophile to a ketone has been used in our group to prepare 3-pentadienol, a precursor for the Nazarov cyclization for the synthesis of difluorocyclopentenones (Scheme 53), which have been very difficult to obtain by alternative means.\textsuperscript{195}

\begin{center}
\begin{align*}
\text{Scheme 53. Preparation of difluorocyclopentenone, Harrington et al. 1999.}
\end{align*}
\end{center}

It is generally known that alkyl lithium reagents exist as oligomeric species in solution, in which the state of aggregation depends on solvent, concentration, temperature, as well as additives of a coordinating cation (Lewis acid) such as LiCl or of a metal-coordinating solvent such as HMPA, and that the smaller the aggregate size under the reaction conditions the more active the lithiated species. In an earlier report,\textsuperscript{196} our group described that 1-methoxyallenyllithium (its acetal allenyllithium analogs were used by our group for the Nazarov cyclization)\textsuperscript{197} exists in a dimer–tetrramer equilibrium in THF solution (NMR experiments) while in the gas phase this species is aggregated as a hexamer (computational results) (Figure 28).

\begin{center}
\begin{align*}
\text{Figure 28. Structure of some oligomers of 1-methoxyallenyllithium, Dixon et al. 2009.}\textsuperscript{196}
\end{align*}
\end{center}
In this appendix the synthesis of (1-(methoxymethoxy)vinyl)lithium, (2,2-difluoro-1-(methoxymethoxy)vinyl)lithium and (1-butoxyvinyl)lithium as well as their structures will be described on the basis of their low temperature NMR spectra.

5.2. Synthesis of α-lithiated vinyl ethers

Generally, a α-lithiated vinyl ether can be obtained by lithiation, or deprotonation, of the parent vinyl ether with an alkyllithium. The regioselective α-lithiation can be explained by the fact that the acidity of the α-vinyl hydrogen is greater than of the β-vinyl hydrogen due to the presence of the electronegative oxygen atom and because the vinyl ether oxygen atom can precoordinate the alkyllithium and direct it to the adjacent α-hydrogen atom rather than to the β-one.\textsuperscript{198} It has also been reported that alkyl vinyl ethers, such as methyl vinyl ether or ethyl vinyl ether, are most readily metalated with $t$-BuLi, while the methoxymethyl vinyl ethers can be deprotonated with s-BuLi or n-BuLi\textsuperscript{199} because the chelation of the oxygen atom of the methoxymethyl group to the lithium atom of the alkyllithium makes the deprotonation more favorable, as illustrated in Scheme 54.

Scheme 54. Chelation of the MOM group facilitates lithiation.\textsuperscript{198}

The α-lithiation to prepare (1-(methoxymethoxy)vinyl)lithium 220, (2,2-difluoro-1-(methoxymethoxy)vinyl)lithium 225, and (1-butoxyvinyl)lithium 228 was executed based on the chemistry described above. The details of the synthesis of α-lithiated vinyl ethers are summarized in Scheme 55.
Reagents and conditions: (a) CH₃OCH₂OCH₃, P₂O₅, 0 ºC, 10 min, rt, 12 h, 63%; (b) pellet KOH, TDA-1, 140 ºC, 27 h, 61%; (c) sec-BuLi/cyclohexane (1.0 eq), d⁸-THF, -78 ºC, 2.5 h, NMR exp.; (d) CH₃OCH₂OCH₃, P₂O₅/Celite (1/1 wt.), 0 ºC, 15 min, rt, 6 h, 42%; (e) i. n-BuLi/hexane (2.2 eq), THF, -78 ºC, 2 h, ii. n-Bu₃SnCl, -78 ºC to rt, 2 h, 77%; (f) n-BuLi/hexane (1.0 eq), d⁸-THF, -78 ºC, 30 min, NMR exp.; (g) i. tert-BuLi/pentane (1.0 eq), Et₂O, -78 ºC, 0 ºC, 3 min, ii. n-Bu₃SnCl, -78 ºC to rt, 2 h, 68%; (h) n-BuLi/hexane (1.0 eq), d⁸-THF, -40 ºC, 45 min, NMR exp.

Scheme 55. Synthesis of α-lithiated vinyl ethers.

**Synthesis of (1-(methoxymethoxy)vinyl)lithium**

The precursor, (methoxymethoxy)ethene 219, was prepared from commercially available 2-bromoethanol 217 in two steps, following the procedure that has been reported by Tamao and co-workers for the synthesis of this material.²⁰⁰ Methoxymethylation of 2-bromoethanol 217 with 6.0 equivalents of dimethoxymethane in the presence of 0.5 equivalents of phosphorous pentoxide at room temperature led to 1-bromo-2-(methoxymethoxy)ethane 218 in 63% yield (distilled). Dehydrobromination of 218 with one pellet of KOH in the presence of catalytic tris[2-(2-methoxyethoxy)ethyl]amine (TDA-1) provided (methoxymethoxy)ethene 219 in 61% yield (distilled).

α-Deprotonation of (methoxymethoxy)ethene 219 was explored with various alkylolithiums, in a series of experiments in which the lithiated species was trapped with a
stoichiometric amount of benzaldehyde. The reaction with s-BuLi/cyclohexane was cleaner than with n-BuLi/hexane or with t-BuLi/pentane. Accordingly, NMR spectra (1H, 13C, 6Li) of (1-(methoxymethoxy)vinyl)lithium 220 were recorded at -100, -90, -80, -60, -40 °C after treatment of (methoxymethoxy)ethene 219 with a stoichiometric amount of s-BuLi/cyclohexane in THF-d8 in a flame sealed NMR tube. The 1H NMR showed that α-lithiation was complete after storage at -78 °C for 2.5 hours.

**Synthesis of (2,2-difluoro-1-(methoxymethoxy)vinyl)lithium**

1,1,1-Trifluoro-2-(methoxymethoxy)ethane 222 was initially prepared using a similar procedure to the one used for the synthesis of 1-bromo-2-(methoxymethoxy)ethane 218. The reaction mixture from treatment of 2,2,2-trifluoroethanol 221 with 6.0 equivalents of dimethoxymethane in the presence of 0.5 equivalents of phosphorous pentoxide was unexpectedly very difficult to stir due to the high viscosity of the reaction mixture. As a result, only 56% of 221 was able to convert to 222 after 18 h (as determined from the 1H NMR of the crude reaction mixture) and yielded 23% of 222 after fractional distillation through a Vigreux column. Another disadvantage of this reaction was the difficulty of separating 222 (bp. ca. 57 °C, 760 mmHg) from dimethoxymethane (bp. 42 °C, 760 mmHg). Using less dimethoxymethane simplifies the separation but leads to low conversion even after much longer reaction times (the magnetic bar stopped stirring). This problem was solved by using Celite® in combination with P2O5 (1:1 wt.) making the reaction mixture less viscous and much easier to stir. The reaction was complete in 6 h with 3.0 equivalents of dimethoxymethane and yielded 42% of pure product 222 after fractional distillation. It should be mentioned that the conventional methods for methoxymethylation of alcohols by treatment with methoxymethyl chloride and bases, such as DIPEA, NaH, or even n-BuLi, in solution or neat with a Lewis acid such as Al2O3 did not give a satisfactory result due to the weak nuclephilicity of 2,2,2-trifluoroethanol. Less than 55 %
conversion was observed in all cases as well as difficulty in separation of the product from solvents of the reaction.

The (2,2-difluoro-1-(methoxymethoxy)vinyl)lithium 225 was obtained by directly treatment of 1,1,1-trifluoro-2-(methoxymethoxy)ethane 222 with 2.0 equivalents of n-BuLi/hexane in THF-\textit{d}_8 at -78 °C for 2 hours in a flame sealed NMR tube. However, this reaction generates LiF, and the lithium cation can affect the state of the aggregation of the vinyllithium. To avoid the presence of LiF, it is better to deprotonate 1,1-difluoro-2-(methoxymethoxy)ethene 223 with stoichiometric n-BuLi/hexane. The synthesis of alkene analogs of 223 with -MEM, OBn, or -OTs as the ether protecting groups have been reported, see Scheme 56.

Scheme 56. Examples of the preparation of difluoroethene analogs.

However, it was challenging to obtain pure alkene 223 because its boiling point (55 °C, predicted by ChemBioDraw Ultra 2012) is expected to be very close to that of alkane 222 (57 °C, 760 mmHg) and to solvents that are usually used for the reaction, such as THF, or to solvents that are used for the storage of commercially available n-BuLi, such as hexane. Our attempts to monodehydrofluorinate 222 to 223 completely did not gave a satisfactory result. For example, neat or in ethylene glycol, solid KOH or t-BuOK did not consume the starting material. Reaction in solution with an alkyllithium such as MeLi/Et\textsubscript{2}O or t-BuLi/pentane which contain low boiling point solvent, led to either no reaction (MeLi) or formed 1-fluoro-2-(methoxymethoxy)ethyne (MeLi in the presence of catalytic NH\textsubscript{2}Pr\textsubscript{2}, or t-BuLi). The use of high boiling point solvents, such as dioxane or diglyme for the reaction failed due to their high melting points (both were solids at -78 °C) while at higher temperatures 225 may be instable, as its analog (2,2-difluoro-1-
((2-methoxyethoxy)methoxy)vinyl)lithium decomposes at -65 °C. The use of toluene or heptane as co-solvents solved the problem with the melting point but led to low conversion to the desired product. To circumvent these issues, it was more practical to prepare (2,2-difluoro-1-(methoxymethoxy)vinyl)lithium \( 225 \) by transmetalation of tributyl(2,2-difluoro-1-(methoxymethoxy)vinyl)stannane \( 224 \) with a stoichiometric amount of \( n \)-BuLi/hexane. Tributyl(2,2-difluoro-1-(methoxymethoxy)vinyl)stannane \( 224 \) was prepared in 77% yield by treatment of 1,1,1-trifluoro-2-(methoxymethoxy)ethane \( 222 \) with 2.0 equivalents of \( n \)-BuLi/hexane in THF at -78 °C, followed by in situ trapping the lithium species with tributyltin chloride, prepared by Mr. Zhe Zhou, a current member in our group. The NMR spectra \( (^{1}H, ^{13}C, ^{6}Li, ^{19}F) \) of (2,2-difluoro-1-(methoxymethoxy)vinyl)lithium \( 225 \) were recorded at -100, -90, -80, -70 °C after treatment of tributyl(2,2-difluoro-1-(methoxymethoxy)vinyl)stannane \( 224 \) with stoichiometric \( n \)-BuLi/hexane in THF-\( d_8 \) in a flame sealed NMR tube. The \( ^{1}H \) NMR showed that \( \alpha \)-lithiation was complete after storage at -78 °C for 30 min.

**Synthesis of (1-butoxyvinyl)lithium**

(1-Butoxyvinyl)lithium was initially prepared following the original procedure developed by Baldwin for the synthesis of (1-methoxyvinyl)lithium, in which 1-(vinyloxy)methane was treated with \( t \)-BuLi at -65 °C and was subsequently warmed to 0 °C. The \( ^{1}H \) NMR spectra of (1-butoxyvinyl)lithium \( 228 \) in the experiment in which 1-(vinyloxy)butane \( 226 \) was treated with stoichiometric \( t \)-BuLi/pentane in THF-\( d_8 \) showed that the reaction did not occur at temperatures lower than -40 °C while at higher temperatures (-20 °C to 0 °C), along with the major (1-butoxyvinyl)lithium \( 228 \), small amounts of several undesired byproducts (ca. 20%) were detected whose structures were not determined. This was consistent with an earlier report by Soderquist and co-workers that the deprotonation of methylvinyl ether or of ethylvinyl ether with \( t \)-BuLi generated small amounts (ca. 7%) of dilithioacetylene by the elimination of alkoxide. The mechanism is illustrated in Scheme 57. Soderquist reported that \( \beta \)-
deprotonation of methylvinyl ether (pathway B) is more likely than the decomposition of (1-methoxyvinyl)lithium to vinylidene intermediate (pathway A) because the preparation of (1-methoxyvinyl)lithium via transmetalation from the corresponding tin compound, followed by trapping with chlorotrimethylsilane, did not form 1,2-bis(trimethylsilyl)ethyne.

![Scheme 57. Pathways to explain the formation of dilithioacetylene, Sodequist et al. 1982](image)

Therefore, an alternative approach via transmetalation of (1-butoxyvinyl)tributylstannane with n-BuLi/hexane was used. (1-Butoxyvinyl)tributylstannane was prepared in 68% yield by treatment of (vinyloxy)butane with t-BuLi/pentane in Et₂O, followed by in situ trapping the lithium species with tributyltin chloride. NMR spectra (¹H, ¹³C, ⁶Li) of (1-butoxyvinyl)lithium were recorded at -100, -90, -80, -70 ºC after treatment of (1-butoxyvinyl)tributylstannane with a stoichiometric amount of n-BuLi/hexane in THF-d₈ in a flame sealed NMR tube. The ¹H NMR showed that α-lithiation was complete after storage at -40 ºC for 45 min.

5.3. Solution structure of α-lithiated vinyl ethers

The solution structures of the α-lithiated vinyl ethers determined from the NMR spectra will be compared with results from computational studies by Professor Pratt at the City University of New York. From the NMR spectra of α-lithiated vinyl ethers in solution, it is probable that CF₂=CLiOMOM was observed in two different aggregation states, whereas CH₂=CLiOMOM and CH₂=CLiOC₄H₉ were observed in more than two states of aggregation. Professor Pratt’s computational results may support or disprove our conclusions.
5.4. Experimental Section - Appendix 1

$^{19}$F NMR chemical shifts were referenced to a CF$_3$COOH (in THF) external standard (-76.5 ppm). $^6$Li NMR chemical shifts were referenced to a LiCl (in THF) external standard (0 ppm).

Preparation of α-lithiated vinyl ethers in NMR tube reactions

\[
\text{O} = \text{O} \quad \rightarrow \quad \text{O} = \text{O} \quad \text{Li}^{220}
\]

(1-(Methoxymethoxy)vinyl)lithium (220)

To a 1.08 M solution of sec-BuLi in cyclohexane (200 µL, 0.216 mmol) in an oven dried NMR tube connected to an ampule sealing apparatus under an argon atmosphere at -78 °C was added a solution of (methoxymethoxy)ethene 219 (19 mg, 0.215 mmol) in $d_8$-THF (600 µL) dropwise via syringe. The reaction was allowed to proceed for 30 min at -78 °C before being flame sealed under vacuum. The $^1$H NMR showed that lithiation was complete after storage at -78 °C for an additional 2 h. The $^1$H NMR (500 MHz), $^6$Li NMR (74 MHz), and $^{13}$C NMR (126 MHz) of 220 were recorded at 173, 183, 193, 213, and 233 K. $^6$Li NMR spectra and $^{13}$C NMR spectra were broadband, proton decoupled.

\[
\text{O} = \text{O} \quad \rightarrow \quad \text{O} = \text{O} \quad \text{Li}^{225}
\]

(2,2-Difluoro-1-(methoxymethoxy)vinyl)lithium (225)

To a 1.15 M solution of n-BuLi in hexane (200 µL, 0.23 mmol) in an oven dried NMR tube connected to an ampule sealing apparatus under an argon atmosphere at -78 °C was added a solution of tributyl(2,2-difluoro-1-(methoxymethoxy)vinyl)stannane 224 (95 mg, 0.23 mmol) in $d_8$-THF (600 µL) dropwise via syringe, then the NMR tube was flame sealed under vacuum. The $^1$H NMR showed that lithiation was complete after storage at -78 °C for 30 min. The $^1$H NMR (500 MHz), $^6$Li NMR (74 MHz), $^{19}$F NMR (471 MHz), and $^{13}$C NMR (126 MHz) of 225 were
recorded at 173, 183, 193, and 203 K. $^6$Li NMR spectra and $^{13}$C NMR spectra were broadband, proton decoupled.

(1-Butoxyvinyl)lithium (228)

To a 1.10 M solution of $n$-BuLi in hexane (200 µL, 0.22 mmol) in an oven dried NMR tube connected to an ampule sealing apparatus under an argon atmosphere at -78 °C was added a solution of (1-butoxyvinyl)tributylstannane 227 (78 mg, 0.20 mmol) in $d_8$-THF (600 µL) dropwise via syringe, then the NMR tube was flame sealed under vacuum. The $^1$H NMR showed that lithiation was complete after storage at -40 °C for 45 min. The $^1$H NMR (500 MHz), $^6$Li NMR (74 MHz), and $^{13}$C NMR (126 MHz) of 228 were recorded at 173, 183, 193, and 203 K. $^6$Li NMR spectra and $^{13}$C NMR spectra were broadband, proton decoupled.

Preparation of starting materials

(Methoxymethoxy)ethene (219)

To a solution of 2-bromoethanol (12.5 g, 0.10 mol) in dimethoxymethane (53 mL, 0.60 mol) under an argon atmosphere at 0 °C was added P$_2$O$_5$ (7.12 g, 0.05 mol) in one portion with vigorous stirring. The reaction mixture was stirred at 0 °C for 10 min, then at room temperature for 12 h during which time the viscosity of the mixture decreased. The reaction was quenched with water, and the organic material was extracted with Et$_2$O. The combined organic layer was washed again with water, then saturated aqueous Na$_2$CO$_3$, dried over MgSO$_4$, filtered, and carefully concentrated under reduced pressure (20-30 mmHg) at room temperature. The residue was distilled under reduced pressure (40 mmHg) at 80 °C to give 1-bromo-2-(methoxymethoxy)ethane 218 (10.6 g, 63%) as a colorless liquid.
A round-bottomed flask containing 218 (8.40 g, 0.05 mol), KOH pellets (5.61 g, 0.1 mol), and tris[2-(2-methoxyethoxy)ethyl]amine (TDA-1) (0.81 g, 0.25 mmol) was equipped with a reflux condenser that was attached through a rubber tube to a clean cold trap (-78 °C), whose outlet is equipped with a CaCl₂ drying tube. The reaction mixture was heated to reflux at 140 °C for 27 h. The crude product containing water was collected in the cold trap. Water was removed by a syringe. The crude product was distilled at atmospheric pressure into an ice-cooled receiver to give pure methoxymethyl vinyl ether 219 (2.68 g, 61%, bp 68 °C) as a colorless oil. Traces of water were then removed using 4Å molecular sieves.

Spectral data of 1-bromo-2-(methoxymethoxy)ethane and of methoxymethyl vinyl ether were identical to those reported in the literature, *Organic Syntheses, 1998, 9, 539–547.*

![Diagram](image)

**(1-Butoxyvinyl)tributylstannane (227)**

To a 0.9 M solution of t-BuLi in pentane (3.1 mL, 2.80 mmol) diluted with Et₂O (3 mL) under an argon atmosphere at -78 °C was added a solution of 1-(vinyloxy)butane 226 (0.28 g, 2.80 mmol) in Et₂O (2 mL) dropwise over 3 min. After completion of addition, the reaction mixture was warmed to 0 °C for 3 min, then cooled back to -78°C. Tributyltin chloride (0.7 mL, 2.50 mmol) was added, and the reaction mixture was allowed to warm up to room temperature over 2 h. The reaction was quenched with aqueous saturated NH₄Cl, and the organic material was extracted with EtOAc. The combined organic layer was washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with hexane as eluent to afford (1-butoxyvinyl)tributylstannane 227 (0.74 g, 68% yield) as a viscous colorless oil. Spectral data were identical to those reported in the literature, *J. Label. Compd. Radiopharm., 1994, 34, 557–563.*
1,1,1-Trifluoro-2-(methoxymethoxy)ethane (222)

To a solution of 2,2,2-trifluoroethanol (20 g, 0.20 mol) in dimethoxymethane (53 mL, 0.60 mol) under an argon atmosphere at 0 °C was added a mixture of P₂O₅ (14.2 g, 0.10 mol) and Celite (14.0 g) in one portion with vigorous stirring. The reaction mixture was stirred at 0 °C for 15 min, then at room temperature until the ¹H NMR showed that most of starting material was converted to product (ca. 6 h). The reaction was quenched with water, and the organic material was extracted with Et₂O. The combined organic layer was washed again with water, then saturated aqueous Na₂CO₃, dried over MgSO₄, filtered, and carefully concentrated with a rotary evaporator under reduced pressure (180 mmHg) at room temperature. The residue was fractionally distilled at atmospheric pressure using a Vigreux column to give 1,1,1-trifluoro-2-(methoxymethoxy)ethane 222 (12.2 g, 42%, bp 57 °C) as a colorless liquid. Traces of water were then removed using 4Å molecular sieves.

¹H NMR (500 MHz, THF-d₈) δ 4.65 (s, 2H), 3.94 (q, ³J_H,F = 9.1 Hz, 2H), 3.33 (s, 3H). ¹³C NMR (126 MHz, THF-d₈) δ 125.4 (q, ¹J_C,F = 278 Hz, CF₃), 97.4 (s, CH₂), 64.8 (q, ²J_C,F = 34 Hz, CH₂), 55.6 (s, CH₃). ¹⁹F NMR (471 MHz, THF-d₈) δ -75.1 (t, ³J_H,F = 9.1 Hz).

Tributyl(2,2-difluoro-1-(methoxymethoxy)vinyl)stannane (224)

To a 2.5 M solution of n-BuLi in hexane (8.8 mL, 22.0 mmol) diluted with THF (30 mL) under an argon atmosphere at -78 °C was added a solution of 1,1,1-trifluoro-2-(methoxymethoxy)ethane 222 (1.44 g, 10.0 mmol) in THF (10 mL) dropwise over 10 min. After completion of addition, the reaction mixture was stirred at -78°C for 2 h. Tributyltin chloride (2.6 mL, 9.50 mmol) was added, and the reaction mixture was allowed to warm up to room
temperature over 2 h. The reaction was quenched with aqueous saturated NH₄Cl, and the organic material was extracted with EtOAc. The combined organic layer was washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with hexane as eluent to afford tributyl(2,2-difluoro-1-(methoxymethoxy)vinyl)stannane 224 (3.19 g, 77% yield) as a viscous colorless oil.

¹H NMR (500 MHz, CDCl₃) δ 4.66 (s, 2H), 3.41 (s, 3H), 1.57 – 1.45 (m, 6H), 1.36 – 1.29 (m, 6H), 1.09 – 0.97 (m, 6H), 0.89 (t, J = 7.4 Hz, 9H). ¹³C NMR (126 MHz, CDCl₃) δ 159.6 (dd, ¹JC,F = 317 Hz, ¹JC,F = 267 Hz, CF₂), 115.8 (dd, ²JC,F = 72 Hz, ²JC,F = 11 Hz), 97.2, 56.0, 28.8, 27.2, 13.5, 10.2. ¹⁹F NMR (282 MHz, CDCl₃) δ -85.1 (d, ²JF,F = 67 Hz), δ -110.0 (d, ²JF,F = 67 Hz).
Appendix II

SPECTRA FOR SELECTED COMPOUNDS IN CHAPTER 2
$^1$H NMR, (500 MHz, CD$_3$OD)

$^{13}$C NMR, (126 MHz, CD$_3$OD)
$^1$H NMR, 500 MHz, CD$_3$OD

$^{13}$C NMR, 120 MHz, CD$_3$OD
$^1$H NMR. (500 MHz, CD$_3$OD)

$^{13}$C NMR. (126 MHz, CD$_3$OD)

(mixture of diastereomers)

(mixture of diastereomers)
$^1$H NMR, (500 MHz, CD$_3$OD)

$^{13}$C NMR, (120 MHz, CD$_3$OD)

(mixture of diastereomers)
$^1$H NMR (500 MHz, CDCl$_3$)

$^{13}$C NMR (125 MHz, CDCl$_3$)
$^1$H NMR (600 MHz, CDCl$_3$)

$^1^3$C NMR (126 MHz, CDCl$_3$)
Appendix III

SPECTRA FOR SELECTED COMPOUNDS IN CHAPTER 3
$^1$H NMR (500 MHz, CDCl$_3$)

$^1$C NMR (125 MHz, CDCl$_3$)
$^1$H NMR (500 MHz, THF-"d$_6$")

$^1$C NMR (125 MHz, THF-"d$_6$")
Appendix IV

SPECTRA FOR SELECTED COMPOUNDS IN CHAPTER 4
^1H NMR (500 MHz, CD$_3$OD)

^13C NMR (125 MHz, CD$_3$OD)
REFERENCES & NOTES


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