Novel Cannabidiol and Anandamide Analogs

Thesis Presented

by

Marsha Rebecca D’Souza

to

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in Partial Fulfillment of the Requirements for the Degree of Doctor of Philosophy in
Medicinal Chemistry

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BOSTON, MASSACHUSETTS

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Signature page 1

Northeastern University
Bouvé Graduate School of Health Sciences

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Author: Marsha Rebecca D’Souza

Program: Medicinal Chemistry

Approval for thesis requirement of the Doctor of Philosophy in Medicinal Chemistry

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Director of the Graduate School ___________________________ Date _________

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Abstract

Part I

Delta-9-tetrahydrocannabinol (Δ⁹-THC) and (-)-cannabidiol (CBD) are the major constituents of Cannabis sativa (marijuana). (-)-CBD shares many of Δ⁹-THC’s therapeutic properties without inducing negative psychotropic effects. These include potential medicinal uses for anti-inflammation, neuroprotection, anxiolytic, anti-nausea and anti-cancer that are all of great therapeutic importance. The clinical potential of (-)-CBD has been realized with the recent approval of Sativex® in Canada, a drug consisting of a 1:1 mixture of Δ⁹-THC and (-)-CBD for relief of neuropathic and cancer-related pain. Nonetheless, the levorotatory (-)-CBD natural product binds with low affinity to the two principal cannabinoid (CB) G protein-coupled receptors, CB1R and CB2R, whereas the synthetic dextrorotatory (+)-CBD enantiomer binds to both with high (nanomolar) affinity. However, little is known regarding (+)-CBD ligand-binding and functional domains at these receptors, and structure-activity relationship (SAR) data around (+)-CBD is sparse. In this dissertation, a number of high-affinity (+)-CBD analogs have been synthesized in order to explore the SAR. The SAR focused on the side-chain, northern-end, and phenolic hydroxyl pharmacophores of the (+)-CBD prototype. In vitro leads were selected based on their high binding affinity, selectivity as CB2R agonists or CB1R partial agonists, drug-like physicochemical properties, and modulation of in vitro pharmacological activity (cAMP, β-arrestin assays). These leads were profiled in a panel of rodent paradigms for in vivo cannabinergic activity (hypothermia, catalepsy and tail-flick tests). AM9200 was demonstrated to have a longer duration of action as compared to its metabolite, AM9201, whereas (+)-CBD analogs AM9217 and AM9248 were
(weak) partial agonists active in vivo. AM9252 and AM 9222 showed potent analgesic and hypothermic effects in mice and rats, suggesting agonist activity at both CB1R and CB2R. AM 9252 was also shown to have analgesic effects comparable to synthetic Δ9-THC analog (AM 4054) in non-human primates. Also, in order to obtain structural information regarding the binding site of (+)-CBD analogs with these membrane-bound proteins, pharmacologically active (+)-CBD analogs designed as covalent probes to wild-type and mutant CB1R and CB2R are being profiled to help characterize their binding site(s).

Part II

Anandamide (AEA) and 2-arachidonyl glycerol (2-AG) are the two key endocannabinoids that act at CB1R and CB2R to modulate physiological and pathological processes including nociception, inflammation, neuroprotection, feeding behavior, anxiety, memory, and cell proliferation. They are produced “on demand,” are rapidly inactivated by enzymatic hydrolysis, and serve as substrates for oxidative metabolism by cyclooxygenases and lipoxygenases, making it difficult to study directly their in vivo physiology and pharmacology. For the development of novel endocannabinoid templates with potential resistance to hydrolytic and oxidative metabolism, we targeted the methylation of the bis-allylic carbons of the arachidonoyl skeleton. Towards this end, the synthesis and preliminary biological data for the (13S)-methyl-anandamide analog were recently disclosed from our laboratory. This compound was found to have the highest CB1 binding affinity among anandamide analogs to date. Based on this discovery, this dissertation reports the total synthesis of the (10S)- and (10R)-methyl-counterparts. The synthetic approach used was stereospecific, efficient, and
provided the chiral analogs without the need for resolution. Biological testing showed that (10S)- and (10R)-methyl anandamide analogs bound to CB1 and CB2 with moderate affinity.

To explore the binding motifs of the novel (13S)-methyl-substituted arachidonoyl template, the respective tail-modified covalent probes (at C-20) were synthesized and profiled. The covalent probes bound to the CB1R and CB2R with low nanomolar affinity and are currently being tested for their ability to covalently label the CB receptors.
Acknowledgements

I am very excited to have successfully completed my doctorate. This journey has been possible mainly because of my Lord and Savior Jesus, who has been by my side through all my trials and successes. There is nothing that I can do without him.

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<td>Δ⁹-THC</td>
<td>Δ⁹-Tetrahydrocannabinol</td>
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<tr>
<td>DMH- Δ⁹-THC</td>
<td>Dimethylheptyl-Delta-9-tetrahydrocannabinol</td>
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<td>CBD</td>
<td>Cannabidiol</td>
</tr>
<tr>
<td>CBN</td>
<td>Cannabinol</td>
</tr>
<tr>
<td>CNS</td>
<td>Central Nervous System</td>
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<td>CB</td>
<td>Cannabinoid</td>
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<td>GPCRs</td>
<td>G-protein coupled receptors</td>
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<td>AEA</td>
<td>Anandamide</td>
</tr>
<tr>
<td>AA</td>
<td>Arachadonic acid</td>
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<td>2-AG</td>
<td>2-arachidonoyl glycerol</td>
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<td>NADA</td>
<td>N-arachidonoyldopamine</td>
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<td>PI3K</td>
<td>Phosphoinositide 3-kinase</td>
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<td>TRPV1</td>
<td>Transient receptor potential vanilloid</td>
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<td>MAPK</td>
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<td>FAAH</td>
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<td>cAMP</td>
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<td>Guanosine triphosphate</td>
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<td>GDP</td>
<td>Guanosine diphosphate</td>
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<td>NTE</td>
<td>Neuropathy target esterase</td>
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<tr>
<td>H-S</td>
<td>Heat sensitive</td>
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<tr>
<td>SAR</td>
<td>Structure activity relationship</td>
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<td>Structure Property relationship</td>
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<td>NAH</td>
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<td>CA1</td>
<td>Carbonic anhydrase 1</td>
</tr>
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<td>CIA</td>
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<td>MGL</td>
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<td>LD&lt;sub&gt;50&lt;/sub&gt;</td>
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CHAPTER 1: THE CANNABINOID REALM

BACKGROUND

Cannabis

Preparations from the Cannabis *sativa* L. hemp plant have been used for therapeutic, ritualistic, and recreational purposes long before the identification of its psychoactive constituent, $\Delta^9$-tetrahydrocannabinol ($\Delta^9$-THC). $\Delta^9$-THC has been the object of scientific research since its isolation and structural elucidation by Gaoni and Mechoulam in 1964.\textsuperscript{1} Due to its psychotropic and medicinal effects, the cannabis plant (marijuana) continues to be controversial in everyday life. Medicinally, this plant was used for indications such as cough, seizures, tetanus, rheumatism, migraines, asthma, as well as an anxiolytic, anti-convulsive, analgesic, and anti-emetic agent.\textsuperscript{2} Despite the plant’s several beneficial effects,\textsuperscript{3} the psychotropic and abuse potential associated with its use led to its decline as a medicine. The Controlled Substances Act of the United States Congress classifies marijuana as a Schedule I drug. It is the world’s most widely used illegal recreational drug and the third most commonly abused drug after alcohol and cigarettes. A number of countries such as UK, Germany, Spain, Canada and some states in the USA allow treatment with medical marijuana for multiple disorders.

Synthetic analogs of $\Delta^9$-THC such as Dronabinol (Marinol®) and Nabilone (Cesamet®) are available as prescription drugs in several countries. Marinol® has been approved by the FDA as an appetite stimulant for anorexic AIDS patients and as an anti-emetic medicine for patients undergoing cancer chemotherapy. Nabilone® also inhibits nausea and vomiting associated with chemotherapy and is used for neuropathic pain relief.
Legalized use of medical marijuana has become a national debate due to its abuse potential and has not been successful at the national level. Apart from its therapeutic use as an analgesic and anti-emetic, marijuana use is associated with several negative side effects such as dry mouth, red eyes, impaired motor skills and impaired concentration. Marijuana use in general can be linked to several adverse effects such as irritability, nervousness, depression, anxiety, restlessness, severe changes in appetite and interrupted sleep. Its use also has negative effects on the cardiovascular, respiratory, and immune systems that make it unsuitable for people with some pre-existing medical conditions.

In light of the numerous therapeutic effects associated with the cannabis plant, researchers all over the world have been involved in the design, synthesis, and development of cannabinoid analogs that are devoid of psychoactive effects.

**Chemical Constituents of Cannabis**

Marijuana is the crude drug derived from the plant *Cannabis sativa*. It belongs to the ‘Cannabaceae’ family, within the ‘Cannabis’ genus and the highly variable ‘sativa’ species. The plant contains around 500 compounds that mainly consist of cannabinoïds and terpenes. Other minor constituents include sugars, hydrocarbons, steroids, flavonoids, nitrogenous compounds and amino acids, among others as listed in Table 1.1.
The $C_{21}$ groups of compounds present in Cannabis *sativa* L. are classified as cannabinoids and are characterized by a monoterpenoid fused with a substituted resorcinol. Of the many plant cannabinoids (phytocannabinoids), the psychoactive (-)-$\Delta^9$-THC is present in the highest amounts. The natural $\Delta^9$-THC exists in two isomeric forms, (-)-$\Delta^9$-THC and (-)-$\Delta^8$-THC that differ in the position of double bond in the C-ring, as shown in Figure 1.1. (-)-$\Delta^9$-THC and its positional isomer, (-)-$\Delta^8$-THC, are pharmacologically equipotent, but the latter is chemically more stable. Both isomers are extracted from cannabis and have the (6a$R$, 10a$R$) absolute configuration. The opposite synthetic enantiomer (+)-(6a$S$, 10a$S$) is inactive at CB receptors. Based on pharmacological tests,
the (-)-trans-isomer is 6-100 times more potent than the (+)-trans-isomer, which confirms the stereoselectivity of their interactions with CB receptors.\textsuperscript{9} Cannabidiol (CBD) and cannabinol (CBN) are the two other pharmacologically important phytocannabinoids that are devoid of psychoactive effects. The identification of the active constituents of cannabis laid the foundation for understanding their pharmacological effects and opened a new door for novel cannabinoid chemistry.

**Figure 1.1: Structure of phytocannabinoids**
Cannabinoid receptors

Following the isolation and structural elucidation of Δ⁹-THC, the next milestone in cannabinoid research was the discovery of the CB receptors. This paved the way for enormous research that led to the discovery of a multitude of cannabimimetic ligands. Cannabinoids produce their pharmacological effects by interacting with CB receptors that belong to the class 1A rhodopsin-like G-protein-coupled receptors (GPCRs). The two receptor subtypes are cannabinoid receptor 1 (CB1) and cannabinoid receptor 2 (CB2). They have been isolated, cloned, and expressed from mammalian tissue. The human CB1 and CB2 receptors share an overall amino acid sequence homology of only 44%, with a 68% homology in their transmembrane helical domains. The CB1 receptor is more conserved across species as compared to the CB2 receptors, which are more divergent. There is a 97.3% sequence homology (100% trans-membrane sequence homology) between the rat and human CB1 receptor, which contain 472 amino acid residues and differ only in 13 residues, mainly at the N-terminus. The CB2 receptors, on the other hand, have appreciable sequence differences across species. Human and rat CB2 receptors share 81% amino acid sequence homology, whereas the rat and mouse are more homologous, sharing 93% amino acid identity. There is also evidence of the existence of a third CB receptor. The GPR55 orphan receptor, although not definitely classified as CB3, is activated by cannabidiols, Δ⁹-THC and endocannabinoids.
Structure and distribution of cannabinoid receptors

GPCRs are among the largest and most diverse protein families. They are targets for ~40% of all modern medicinal drugs. The cannabinoid receptors belong to this family of receptors, and an understanding of the precise molecular interactions and functional properties of these receptors is vital for the design of ligands that possess high affinity and selectivity to them. Cannabinoid receptors are comprised of seven transmembrane α-helices (TMH) with an extracellular amino terminal and an intracellular C-terminus. The 7 transmembrane helices are connected by 3 extracellular, and 3 intracellular loops.

The distinctive tissue distribution of the CB1 and CB2 receptors in the body helps account for their different pharmacologic effects when activated. The CB1 receptor is expressed abundantly in the brain. High densities of CB1 receptors are found in the cerebellum and basal ganglia, regions of the brain that control movement. They are also found in the hippocampus and cerebral cortex that are involved in memory and cognition respectively. The memory impairment, delusions and altered consciousness due to marijuana use are a consequence of Δ⁹-THC activation of CB1 receptors in these brain regions. Like dopamine receptors, CB1 receptors are also found in regions such as the striatum and nucleus accumbens that are involved in mediating reward. The lack of lethality of cannabis is due to the low densities of CB1 receptors in the brain stem that is involved in controlling heart rate and respiration. CB1 receptors are also found in areas of the brain that are associated with pain processing such as periaqueductal gray (PAG), rostral ventromedial medulla, thalamus, dorsal root ganglia (DRG), amygdala, and cortex. Other effects include sedation, hypothermia, catalepsy and lack of cognitive function. CB1 receptors are also expressed in some peripheral organs such as heart, vas

6
deferens, testis, sperm, liver, uterus, and small intestine. CB1 activation in the periphery induces appetite-stimulation, analgesia, anti-emesis and decreases intra-ocular pressure.\textsuperscript{25} The antiemetic property of $\Delta^9$-THC might be due to the presence of CB1 receptor in cholinergic nerve terminals of the myentric and submucosal plexus of the stomach and duodenum.\textsuperscript{26} In contrast, the CB2 receptor is almost exclusively expressed in the immune system in tissues like the spleen, tonsils, lymph nodes and macrophages, B and T lymphocytes.\textsuperscript{27,28} CB2 receptor is reported to be present neuronally in species like mice and rats in regions such as DRG,\textsuperscript{29} brainstem,\textsuperscript{30} cerebellum.\textsuperscript{31} The CB2 levels in these sites are only present at low levels under basal conditions, but in neuropathic inflammatory conditions, an upregulation of CB2 mRNA was observed.\textsuperscript{32}

**Activation of CB receptor**

GPCRs are activated on agonist binding that result in downstream signaling events. They are coupled to the $G_{i/o}$-protein subtype.\textsuperscript{33} Figure 1.\textsuperscript{24}\textsuperscript{34} depicts the activation of CB receptors. In the inactive state the G proteins exist as a $\alpha\beta\gamma$ heterotrimer with the $G_\alpha$ sub-unit bound to GDP. Upon receptor activation, through agonist binding, a conformational change takes place in the receptor that promotes the exchange of GDP for GTP. This triggers dissociation of the heterotrimer from the receptor into the $G_\alpha$-GTP and $G_{\beta\gamma}$ dimer which then modulate downstream effectors. The signaling stops when the GTPase activity of the $G_\alpha$ subunit hydrolyses GTP to GDP, thereby allowing the $G_\alpha$ subunit to return to its resting conformation and reassociate with the $G_{\beta\gamma}$.\textsuperscript{34}
Since cannabinoid receptors are $G_{i/o}$ protein coupled, their activation inhibits adenylyl cyclase, which results in reduced production of cAMP. Stimulation of MAPK, inhibition of voltage-activated Ca$^{2+}$ channels and stimulation of inward rectifying K$^+$ channels\(^{35}\) are some of the other pathways that are affected by agonist binding to the CB1 receptor. The pharmacological mode of action to affect the efficacy of cannabnergic ligands (agonists, antagonists, inverse agonists and partial agonists) can be determined by monitoring changes in cellular levels of cAMP\(^{36}\) and GTP$\gamma$S assay (agonists stimulate the binding of [$^{35}$S]GTP$\gamma$S to G-proteins in the presence of excess GDP.\(^{37,38}\)

The dissociation of the heterotrimer also promotes the signaling by other messenger systems, such as those involving the second messengers GTP, diacylglycerol and calcium.\(^{39}\) Activated GPCRs are phosphorylated by GPCR kinases (GRKs) on the Ser/Thr residues of cytoplasmic loops and tails of the receptors, which results in termination of signaling.\(^{40}\) This occurs by the recruitment of arrestins (β-arrestin 1/β-arrestin 2) and
consequent desensitization followed by internalization into clathrin-coated pits. Figure 1.3\textsuperscript{34} depicts this β-arrestin mediated termination of signaling.

**Figure 1.3*: β-arrestin mediated termination of GPCR signaling

*Source: Cannabinoid CB(1) receptor-interacting proteins: novel targets for central nervous system drug discovery? Br. J. Pharmacol. - Page 459,\textsuperscript{34}

Initially, it was thought that only the heterotrimeric G proteins mediate signal transduction via the receptor, whereas β-arrestins were involved in receptor desensitization and internalization. However, the ability of β-arrestins to also act as adaptor proteins by signaling through multiple mediators such as MAPKs, nuclear factor-κB (NF-κB) and phosphoinositide 3-kinase (PI3K)\textsuperscript{41} has been recognized. This has led to the development of a new 7-TM signaling model (Figure 1.4)\textsuperscript{41} that also involves the β-arrestin pathway. In this model, both G proteins and β-arrestins interact and recruit intracellular signaling molecules, with desensitization of the receptor mediated by β-arrestins.\textsuperscript{41} The ability of some receptor–ligand systems to display a bias towards one pathway over the other has lead to the concept of functional selectivity biased agonism,
i.e., receptors preferentially signal through either the G-protein or β-arrestin-mediated pathway.\textsuperscript{42} Biased agonism towards either G protein or β-arrestin signaling can have important implications for the design of GPCR targeted drugs, since signaling through these parallel pathways has different consequences at molecular and functional levels. For example, drugs could act as agonists of G protein-mediated functions, but may have differing effects on β-arrestin-mediated signaling.\textsuperscript{41} It is also possible that a drug does not activate the G-protein pathway, but can act by activating the β-arrestin pathway. Thus compounds can be designed to modulate selectively certain cell signaling pathways and still produce the desired pharmacological effect. Understanding the physical and functional relationships between CB receptors and β-arrestin interacting proteins could thus provide new targets for drug discovery.

CB1 receptors heterologously expressed in cell lines undergo endocytosis (internalization) when activated by agonists.\textsuperscript{43} CB1 receptors can also undergo clathrin-coated endocytosis by either pits or caveolae.\textsuperscript{44,45} 

**Figure 1.4*: G-protein and β-arrestin mediated signaling**

\*Source: Teaching old receptors new tricks: biasing seven-transmembrane receptors. Nat Rev Drug Disc - Page 374.\textsuperscript{41}
Classes of cannabinoid receptor ligands

Cannabinoid receptor ligands are classified based on their chemical structure and pharmacological actions. They include the endocannabinoids, classical cannabinoids, non-classical cannabinoids, hybrid cannabinoids, aminoalkylindoles, and diarylpyrazoles.

Endogenous cannabnergic and endocannabinoids system

After the discovery and expression of CB receptors in the early 1990s, the discovery of endogenous ligands for these receptors was not surprising. Two key endogenous cannabinoid ligands (endocannabinoids - Figure 1.5) were discovered;\textsuperscript{46} $N$-arachidonoylethanolamide (AEA) or anandamide and 2-arachidonylglycerol (2-AG). Other endocannabinoids produced in lesser amounts include virodhamine, noladin ether, $N$-arachidonoylserine, oleamide, and $N$-arachidonoyldopamine (NADA).

Figure 1.5: Structures of endocannabinoids

![Structures of endocannabinoids](image-url)
AEA and 2-AG are the most intensively studied and best characterized endocannabinoids. They are highly lipophilic compounds with four non-conjugated cis-double bonds and an n-pentyl tail, similar to the lipophilic side chain of the classical cannabinoids. AEA is a partial agonist at the CB1 receptor with a binding affinity of 61 nM for rat CB1 receptor and 240 nM for human CB1 receptor. It is a weak agonist at the CB2 receptors with affinity of 440 nM for rat and 1930 nM for human CB2 receptors. 2-AG, on the other hand, is a full agonist at both the CB1 and CB2 receptors but binds with low affinity (472 nM for CB1 and 1400 nM for CB2). AEA is also known to interact with the vanilloid subtype 1 (TRPV1) channel. Endocannabinoids are sensitive to enzymatic oxidation, hydrolysis and in vitro oxidation.

Unlike some neurotransmitters, endocannabinoids are not stored in vesicles but instead produced and released from neurons upon demand. They are enzymatically synthesized from pools of membrane phospholipids as shown in Figure 1. When Ca$^{2+}$ channels on neurons are inhibited by CB1 activation, a neurotransmitter is released. The endocannabinoids are then released postsynaptically in response to the neurotransmitter stimuli and activate CB1 receptors on presynaptic neurons (“retrograde transmission”).
Figure 1.6*: Synthesis of AEA and 2-AG

The biological activity of AEA and 2-AG are terminated by a transport mechanism and enzymatic deactivation.\textsuperscript{50,51} AEA is metabolized enzymatically by fatty acid amide hydrolase (FAAH) into arachadonic acid (AA) and ethanolamine, whereas 2-AG is metabolized by monoacylglycerol lipase (MGL) to AA and glycerol (\textit{Figure 1.7}).\textsuperscript{52} FAAH is abundantly expressed in neurons post-synaptic\textsuperscript{53} to CB1 receptor, and MGL is localized in pre-synaptic neurons.\textsuperscript{54} Four other hydrolases are also involved in generating AA from 2-AG, but to a lesser extent than MGL. These include α/βhydrolase-6 (ABHD6), α/βhydrolase-12 (ABHD4), neuropathy target esterase (NTE), and hormone sensitive lipase (H-S lipase).\textsuperscript{49} Due to AEA and 2-AG inactivation by these enzymes, they have only weak and transient in vivo capabilities to activate the cannabinoid receptors.
An attractive alternative to take advantage of the desirable effects of cannabinoid activation, while avoiding the negative effects of CB1 stimulation, is to potentiate endocannabinoid signaling by inhibiting FAAH and MGL. FAAH and MGL are drug targets as their inhibitors elevate tissue AEA and 2-AG, thereby prolonging and potentiating their biological effects. Thus psychotropic effects associated with the use of exogenous CB1 receptor agonists can be reduced.

The AA generated from the action of FAAH and MGL can also act as a second messenger and undergo various reactions such as oxygenation, epoxidation or hydroxylation catalyzed by COX, LOX, epoxygenase or other hydroxylases to generate fatty acid derivatives (prostaglandins, leukotrienes, eicosanoids, prostacyclin, thromboxane). AEA and 2-AG can be directly oxygenated by COX. COX-1 is not very effective in catalyzing oxidative endocannabinoid metabolism compared to COX-2,
which might be due to their difference in regulation and tissue distribution.\textsuperscript{56} 2-AG is a substrate for COX-2\textsuperscript{57}, both 2-AG and COX-2 is found in the same regions of the brain and immune cells. 2-AG and AEA are also metabolized by LOX and cytochrome P\textsubscript{450}, leading to oxygenated products\textsuperscript{58} as shown in Figure 1.\textsuperscript{7} The involvement of COX oxidative metabolism in the endocannabinoid system demonstrates that there is cross talk between these two systems.

**SAR of Endocannabinoids**

Endocannabinoids have a wide range of biological effects with therapeutic implications. They participate as neuromodulators in various physiological and pathological processes\textsuperscript{59} including inflammation,\textsuperscript{60} anxiety,\textsuperscript{61} feeding,\textsuperscript{62} cell proliferation,\textsuperscript{63} memory,\textsuperscript{64} and pain,\textsuperscript{65} as well as in the functioning of the cardiovascular, respiratory and gastrointestinal systems. During the past two decades, a number of AEA and 2-AG analogs have been synthesized in an effort to develop potent, metabolically stable analogs. The structure of anandamide consists of a polar ethanolamido head group, a non-conjugated four \textit{cis} double bonds, and a \textit{n}-pentyl chain. Most of the SAR modifications were performed at the \textit{N}-hydroxyethyl group, amide group, \textit{cis}-double bonds and the \textit{n}-pentyl group. A limitation of AEA is its facile in vivo (FAAH) enzymatic degradation and instability in vitro. (\textit{R})-methanandamide (AM 356) discovered by the Makriyannis group is a metabolically stable analog with a higher affinity for CB1 ($K_i$: 20±1.6 nM) than anandamide, and is resistant to hydrolysis by FAAH.\textsuperscript{66} However, (\textit{S})-methanandamide exhibits lower potency ($K_i$: 173±26 nM) and is less resistant to FAAH-mediated hydrolysis.\textsuperscript{66}
**Classical cannabinoids**

Classical cannabinoids are ABC-tricylic compounds derived from the structure of $\Delta^9$-THC. These include the naturally occurring $\Delta^8$-THC, other phytocannabinoids and synthetic analogs *(Figure 1.8).*

**Figure 1.8:** Examples of classical cannabinoids

![Examples of classical cannabinoids](image)

Many classical cannabinoids have been extensively synthesized, and SAR studies have recognized four pharmacophores: phenolic hydroxyl (PH), lipophilic side chain (SC), southern aliphatic hydroxyl (SAH) and northern aliphatic hydroxyl (NAH). The PH group is important for CB1 affinity, since the replacement of the PH group with a methoxy, hydrogen, or fluorine atom diminishes CB1 affinity, but has less affinity for CB2. Variations in the SC of $\Delta^8$-THC, the most critical pharmacophore, have led to a wide range of analogs varying in potency and selectivity. Optimal activity is obtained with a seven or eight carbon chain length bearing 1', 1'-dimethylheptyl or 1', 2'-dimethyldimethylheptyl side chains. 1', 1'-cylic moieties have also been synthesized.
and exhibit high affinity for the cannabinoid receptors. Oxygen atoms, unsaturations within side chain as well as terminal substitutions (halogen, CN, N3, NCS) are well tolerated. The introduction of a hydroxyl group at C-9 or C-11 NAH position led to analogs with high affinities and potencies. Δ⁹-THC and endocannabinoids, AEA and 2-AG share common structural features like the polar head group and a hydrophobic chain with a pentyl moiety.

**Non-classical Cannabinoids**

Other cannabinergic classes are the non-classical cannabinoids, the hybrid classical/non-classical (CC/NC), the aminoalkylindoles and the diarylpyrazoles. Representative examples from each of these classes are shown in *Figure 1.9*. 
Figure 1.9: Other classes of non-classical cannabinoids

Non-classical cannabinoids

(-)-CP-55940

Ki = 0.6 nM (CB1)
Ki = 0.7 nM (CB2)

HU-308

Ki = 10,000 nM (hCB1)
Ki = 22.7 nM (hCB2)

Hybrid cannabinoids

AM919

Ki = 2.2 nM (CB1)
Ki = 3.4 nM (CB2)

AM938

Ki = 1.2 nM (CB1)
Ki = 0.3 nM (CB2)

Aminoalkylindoles

R(+)-WIN-55,212-2

Ki = 1.9 nM CB1
Ki = 0.3 nM CB2

AM630

Ki = 5152 nM CB1
Ki = 31.2 nM CB2

Diarylpyrazoles

SR141716A

Ki = 11.5 nM (CB1)
Ki = 1640 nM (CB2)

AM251

Ki = 7.5 nM (CB1)
Ki = 2290 nM (CB2)
Cannabidiol

Within the classical cannabinoid class, the phytocannabinoid (-)-\(\Delta^9\)-THC (1- *Figure 1.10*) has been the main focus since its isolation and synthesis in the 1960’s. Although \(\Delta^9\)-THC is generally accepted as the main component responsible for the psychobehavioral effects of cannabis, several studies have demonstrated that other phytocannabinoids present in the plant might also be responsible for some of its pharmacological activity. One of these is the non-psychoactive (-)-cannabidiol (2- *Figure 1.10*) that has recently gained interest due to its high potential for immune suppression, anti-anxiety, anti-convulsant, and antineoplastic therapeutic uses.\(^{141}\) It constitutes ~40% of cannabis extracts and was first isolated in 1940 by Roger Adams from Mexican marijuana and by Alexander Todd from Indian charas.\(^{137}\) However, the exact structure was determined only in 1963, and its absolute stereochemistry in 1967.\(^{73}\) The cannabidiol molecule is chiral, and the (3\(R\), 4\(R\))-(-)-enantiomer is the isomer present in cannabis.\(^{73}\) The \(\Delta^9\)-THC (1) and CBD (2) extracted from cannabis is derived from the C-2 and C-4 carboxylic acids of \(\Delta^9\)-THC (1) or the C'3/C'5 carboxylic acid of CBD (2), which undergoes decarboxylation when the plant material is heated or stored.\(^{74}\)
**Figure 1.10:** Structure of $\Delta^9$-THC and cannabidiol derivatives.

$\Delta^9$-THC exerts its pharmacological action by binding to CB1 and CB2 receptors. However, cannabidiols exhibit distinct binding affinities to these receptors. Current knowledge about the pharmacological actions of cannabidiol is limited, but it is well established that $(-)$-CBD (2) is pharmacologically active.

**Mechanisms of cannabidiol action**

$(-)$-CBD does not produce psychotropic effects that tricyclic cannabinoids such as $(-)$-$\Delta^9$-THC produce. Their mechanism of action is thus speculated to be different from those of the tricyclic cannabinoids. Recent pharmacological and biological experiments with $(-)$-CBD have helped elucidate some of the possible mechanisms of $(-)$-CBD action.
i. Stereospecificity of CBD Action

Cannabidiols exist as two enantiomers, the natural levorotary (-)-cannabidiol (2) and the synthetic dextrorotatory (+)-cannabidiol (4). (-)-CBD binds weakly to the cannabinoid receptors, whereas (+)-CBD binds to the cannabinoid receptors in the nanomolar range.\(^{146}\) However, it is not known if (+)-CBD actually activates the cannabinoid receptors to produce its pharmacological effect. The stereospecificity of its action may indicate that it acts through some other receptor.\(^{138}\) This has led to the hypothesis that cannabidiol might bind to the orphan GPCR, GPR55,\(^{75}\) or possess allosteryism at some other receptor(s).\(^{76}\)

A series of (-)-CBD and (+)-CBD analogs has been tested for in vivo central and peripheral effects.\(^{77,78}\) Central “tetrad” tests are a series of assays used to measure central cannabimimetic effects. The (-)-CBD analogs did not have any effect in the in vivo “tetrad” central tests. On the other hand, most of the (-)-CBD analogs inhibited intestinal motility in the periphery. From these tests, it was suggested that (-)-CBD analogues might inhibit intestinal motility through a non-CB1, non-CB2 receptor-mediated mechanism.\(^{77}\)

On testing the (+)-CBD analogs, only (+)-7-OH-CBD-DMH (9) showed central activity while the other (+)-CBD analogs potently inhibited defecation over a prolonged period (3h) without inducing hypothermia. It was speculated that (+)-CBD analogs that were not centrally active in the hypothermia test might not cross the blood-brain barrier. These analogs were thought to have antagonist, partial agonist/antagonist properties in the central nervous system while acting as agonists in the peripheral nervous system. Since most of the (+)-CBD and (-)-CBD compounds were peripherally acting, Hanus et al.
speculated that these analogs might be developed as drugs for peripheral conditions including cholera-induced diarrhea, inflammatory pain, Chron’s disease and cystic fibrosis.\textsuperscript{78}

\textbf{ii. Allosterism}

In order to study the allosterism of cannabidiols at the $\mu$ and $\delta$ opioid receptors, kinetic binding studies with $^3$H-DAMGO (synthetic opioid peptide with high $\mu$-opioid receptor specificity) and $^3$H-naltrindole (opioid antagonist) were performed.\textsuperscript{76} In the experiment, the dissociation of the radioligand from the orthosteric binding site is induced by a high concentration of an orthosteric ligand, a presumptive and an assumed allosteric ligand alters the velocity of dissociation.\textsuperscript{79} The experiment concluded that (-)-CBD was found to be an allosteric modulator at $\mu$ and $\delta$ opioid receptors.\textsuperscript{76}

The 5-HT$_3$ serotonin receptor is a member of the ligand gated ion channel family, which is involved in pain transmission, mood disorders and drug abuse. The 5-HT$_3$ receptor antagonists and cannabinoids produce similar pharmacological effects such as non-opioid receptor-mediated analgesia and antiemesis.\textsuperscript{80} (-)-CBD was found to be an allosteric antagonist at the serotonin 5-HT$_3$ receptors expressed in X. laevis oocytes, an action that is relevant to (-)-CBD’s physiological role in the modulating nociception and emesis.\textsuperscript{81}

\textbf{iii. Enhancer of adenosine signaling}

The release of adenosine is an endogenous mechanism of immunosuppression induced during cellular stress and inflammation.\textsuperscript{82} The uptake of adenosine is the main mechanism for terminating adenosine signaling, and thus adenosine uptake inhibitors increase endogenous activity at adenosine receptors. Anti-inflammatory effects of
adenosine agonists and uptake inhibitors are similar to the cannabinoids. Treatment with a low dose of (-)-CBD is known to decreased TNF-α production in lipopolysaccharide (LPS)-treated mice.\textsuperscript{83} (-)-CBD also inhibits $[^3]$H-thymidine incorporation into a murine microglial cell line.\textsuperscript{82}

iv. **An antioxidant**

Phenols and resorcinols are known to be potent anti-oxidants. Plant cannabinoids (monophenols) and resorcinols (as CBD) are also potent antioxidants. Antioxidant properties of (-)-CBD have been reported. It was shown that (-)-CBD prevented hydrogen peroxide (H$_2$O$_2$)-induced oxidative damage better than ascorbate (vitamin C) and tocopherol (vitamin E).\textsuperscript{84}

v. **Inhibition of anandamide transporter**

Studies have investigated the interaction of (-)-CBD with proteins of the ‘endocannabinoid signaling system’ other than the CB1 and CB2 receptors.\textsuperscript{146} These proteins include FAAH and the putative “anandamide membrane transporter” (AMT), thought to facilitate the transport of anandamide across the cell membrane and subsequently for its intracellular degradation.\textsuperscript{85} (+)-CBD has been shown to block anandamide uptake and (-)-CBD inhibits anandamide enzymatic hydrolysis.\textsuperscript{146} The (+)-5’-DMH-CBD and (+)-7-hydroxy-5’DMH-CBD were found to be as potent as the AMT inhibitor, AM404\textsuperscript{86} (IC$_{50}$= 10.0, 7.0 and 8.1 μM for the two compounds and AM404 respectively).
vi. Effect of CBD on the vanilloid receptor (VR1)

The VR1 receptor (TRPV2) is a ligand, heat-and proton-activated non-specific cation channel involved in nociceptive stimulus. The pharmacological actions of (-)CBD were found to be similar to those of natural (capsaicin) and synthetic agonists of VR1. The effect of (-)CBD was terminated by the VR1 receptor antagonist capsazepine, which strongly suggests that (-)CBD might stimulate the VR1 receptors (EC\textsubscript{50}= 3.5 ± 0.3 μM, max. effect 64.1 ± 3.1%).

vii. Effect of CBD on FAAH

Among CBD analogs tested for FAAH inhibition, (+)-CBD, (-)-CBD and (-)-7-hydroxy-CBD exhibited IC\textsubscript{50}'s < 100 μM. The (-)-enantiomer was found to be more potent than the (+)-enantiomer as a FAAH inhibitor, with (-)-CBD being the most potent (IC\textsubscript{50}= 27.5 μM).

viii. Interaction of CBD with Δ\textsuperscript{9}-THC

Co-administration of (-)-CBD potentiates the therapeutic effects of Δ\textsuperscript{9}-THC and attenuates some Δ\textsuperscript{9}-THC negative effects. (-)-CBD may reduce the psychoactive effects of Δ\textsuperscript{9}-THC by interfering with Δ\textsuperscript{9}-THC’s metabolism. A mixture of (-)-CBD with Δ\textsuperscript{9}-THC (0.5 mg/kg) significantly reduced psychobehavioral effects induced by Δ\textsuperscript{9}-THC in healthy volunteers.
Therapeutic aspects of cannabidiols

The phytocannabinoid, (-)-CBD (cannabidiol), shares many of Δ9-THC’s therapeutic properties without inducing negative psychotropic effects. The following uses are some examples that highlight (-)-CBD preclinical therapeutic effects, and thus might suggest its therapeutic potential in man.

i. Neuroprotection

Cannabidiols provide neuroprotection against toxicity caused by 6-hydroxydopamine in a rat Parkinson disease model. In other reports, oral doses of (-)-CBD (100-600 mg/kg over a 6-week period) led to a dose-related improvement (20 to 50%) in Parkinson’s patients.

Similarly, the neuroprotective mechanism of (-)-CBD has been studied in Alzheimer disease models. In rat PC12 cells exposed to β-amyloid peptide (1 μg/ml), a significant reduction in cell survival was observed that was associated with several effects such as the appearance of caspase-3, DNA fragmentation and increased intracellular calcium.

The treatment of cells with (-)-CBD prior to amyloid-peptide exposure significantly improved cell survival and decreased reactive oxygen species (ROS) production, lipid peroxidation, caspase-3 levels, DNA fragmentation, and intracellular calcium, indicating that CBD has neuroprotective, anti-oxidantant, and anti-apoptotic effects against β-amyloid-peptide toxicity.

(-)-CBD was also investigated for its efficacy against multiple sclerosis (MS), an autoimmune demyelinating disease. (-)-CBD is a major component of Sativex®, a MS drug consisting of THC and CBD. Beneficial results were obtained in placebo-controlled
trials when *Sativex®* was administered as an add-on MS therapy. Other trials confirmed that *Sativex®* is well tolerated and is able to reduce pain and sleep disturbance in patients with MS-related central neuropathic pain.\(^9^3\)

ALS (amyotrophic lateral sclerosis) is another neurodegenerative disease where (-)-CBD was beneficial in alleviating pain. This terminal disease is characterized by loss of motor neurons in the cortex, brain stem and spinal cord. (-)-CBD slowed the progression and prolonged survival of mice in a transgenic model of ALS.\(^9^4\)

Prion diseases are transmissible neurodegenerative diseases that are characterized by the accumulation of protease resistant protein (PrPres), a misfolded protein.\(^9^5\) (-)-CBD inhibited PrPres accumulation in both mouse and sheep scrapie-infected cells. A peripheral injection of (-)-CBD restricted the cerebral accumulation of PrPres in mice infected with murine scrapie.\(^9^5\)

(-)-CBD also exerts anti-inflammatory and neuroprotective effects by blocking oxidative stress and activation of p38 MAPK and microglia in retinal inflammation, uveitis and glaucoma.\(^9^6\)

**ii. Cerebral ischemia**

(-)-CBD was investigated for its ability to prevent damage caused by ischemia.\(^9^7\) (-)-CBD (1.25-20 mg/kg) was administered to gerbils after a bilateral carotid artery occlusion. Seven days after the ischemia, (-)-CBD antagonized electroencephalographic flattening, and histological examination showed live and healthy CA1 neurons.\(^9^7\)
iii. Type-1 diabetes

When CBD was given to non-obese diabetic (NOD) mice before the development of diabetes, (-)-CBD reduced the incidence of type-1 diabetes from 86% in the non-treated control mice to 30% in (-)-CBD treated mice. (-)-CBD treatment also resulted in reduction of pro-inflammatory cytokines, IFN-α and TNF-α and pancreatic inflammation.

iv. Anxiety

CBD is clinically effective in reducing anxiety has been measured by using SPECT (Single Photon-Emission-Computed Tomography). Human subjects were given either oral dose of (-)-CBD (400 mg) or placebo in a double-blind procedure. SPECT images were taken 90 minutes after drug ingestion. On comparing regional cerebral blood flow in the subjects, CBD was shown to decrease significantly anxiety and increase mental sedation in patients, compared to placebo.

v. Rheumatoid arthritis

The effect of (-)-CBD was examined in a rheumatoid arthritis (RA) model in which DBA/1 mice were immunized with type-II collagen in complete Freund’s adjuvant, resulting in classical acute or chronic relapsing collagen-induced arthritis (CIA). CBD administered orally (25 mg/kg) or i.p (5 mg/kg) after the onset of RA symptoms effectively blocked RA progression. There was also a decrease in IFN-γ from lymph node cells and a decrease in TNF-α from synovial cells in the CBD-treated mice.
vi. Cancer

CBD at a concentration of 8 µg/ml caused apoptosis of 61% of human myeloblastic leukemia cells and sensitized cells to γ-radiation-induced apoptosis.101 One of the resistance mechanisms of cancer cells is the over expression of the ATP-binding transporter, P-glycoprotein (P-gp), which effluxes several anticancer drugs from the brain. CBD at a concentration of 1 µM reduced the expression of P-gp by 50%.102

vii. Anti-nausea and anti-emetic

Both THC (dronabinol) and nabilone® are clinically approved antinausea drugs for chemotherapy cancer patients but have negative side effect such as tolerance and dependence. The house musk (Sunctus murinus) that vomits and shows signs of nausea was injected with LiCl to induce vomiting. The conditioned retching reaction was completely suppressed by pretreatment with (-)-CBD.99

viii. Antipsychotic effects

(-)-CBD produces antipsychotic effects in animal models that were induced with psychosis. (-)-CBD at a dose of 15-480 mg/kg reduced signs of psychotic behavior induced by apomorphine.103

ix. Anti-convulsant

(-)-CBD shows anti-convulsant activity in several in vivo epilepsy models.104,105 It can prevent convulsions induced in mice or rats by electroshock, sound or convulsants such as pentylenetetrazol. Unlike Δ⁹-THC, which produces both pro- and anti-convulsant effects in animals, (-)-CBD has only anti-convulsant properties.138
In view of the above pre-clinical therapeutic effects, cannabidiols may prove to have numerous clinical applications in the future, e.g., in the control of epilepsy and certain other central motor disorders, the treatment of anxiety and psychotic illnesses, and the reduction of inflammation.

**Metabolism of CBD**

The primary pathway of (-)-CBD metabolism is the hydroxylation at the C-7, leading to (-)-7-hydroxy-CBD followed by further oxidation to (-)-carboxy-CBD.\(^{106}\) (-)-CBD can also undergo multiple hydroxylations, β-oxidation, conjugation and epoxidation.\(^{107}\) (-)-CBD is eliminated in the urine, both in the free state and as a glucuronide conjugate with a half-life of 9 h.\(^{108}\) In vitro metabolism of (-)-CBD by human liver microsomes generates eight different metabolites\(^{109}\) (6α-OH-, 6β-OH-, 7-OH-, 1″-OH-, 2″-OH-, 3″-OH-, 4″-OH-, and 5″-OH-CBDs) produced by CYP enzymes (CYP1A1, CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, and CYP3A5).

**Pharmacokinetics of CBD**

When orally delivered and after the first-pass effect, (-)-CBD bioavailability ranges between 13-19%, thus making intravenous administration a better option.\(^{110}\) On injection of (-)-CBD, it gets rapidly distributed and passes easily through the blood-brain barrier (BBB), because of its lipohilicity (ClogP = 6.64), which results in a prolonged elimination.\(^{110}\)
Safety studies

Due to cannabidiols lack of psychotropic effects and in view of its potential therapeutic applications, efforts are being made to understand its safety profile. Acute (-)-CBD administration by the oral, inhalation or intravenous route does not induce any significant toxic effects in humans.\textsuperscript{111} Chronic administration of CBD for 30 days to healthy volunteers at daily doses from 10 mg to 400 mg also did not induce any significant toxic effects.\textsuperscript{111} (-)-CBD exhibited and LD\textsubscript{50} of 212 mg/kg when it was intravenously injected into the rhesus monkey.\textsuperscript{112} (-)-CBD also does not show teratogenic and mutagenic activities.\textsuperscript{113} Thus, from the available data, (-)-CBD can be safely administered over a wide dose range.

SIGNIFICANCE

Pain is a debilitating symptom associated with many disease states, with millions suffering from either acute or chronic pain. Pain takes a tremendous toll on health care costs, personal productivity, and causes emotional and financial burdens. Acute pain is a normal sensation triggered in the nervous system when a person is exposed to strong mechanical, chemical or thermal stimulation. Chronic pain is persistent and of two general types: nociceptive and neuropathic. The latter is treatment-resistant and reflects peripheral nerve injury, toxic insults and diseases (e.g. diabetes, MS).\textsuperscript{22} Most of the conventional first-line medications to treat neuropathic pain, like tricyclic antidepressants, 5\% lidocaine patch, gabapentin, amitriptyline, tramadol hydrochloride and opioid analgesics are not safe.\textsuperscript{114} For instance, even though opioid analgesics relieve pain symptoms, they are not ideal due to adverse effects like constipation, sedation,
cognitive impairment and addiction potential. Opioid-induced hyperalgesia can also develop due to long-term opioid use (both chronic and acute) in the treatment of chronic pain.

Cannabinoids suppress neuropathic pain in animal models of surgically-induced traumatic nerve or nervous system injury.\textsuperscript{115,116,117} Clinical studies have also shown that cannabinoids suppress neuropathic pain in humans.\textsuperscript{118,119} Cannabis-based medicines are attractive because of the relatively favorable safety profile of cannabis. There have been no reported deaths directly due to cannabis overdose.\textsuperscript{120} However, the psychoactive effects of centrally-acting cannabinoid agonists remain a challenge for analogs that activate CB1 receptors in the brain. There is a need for discovery of THC analogs that have limited adverse effects. Some of the current directions in the cannabinoid therapeutic field include targeting CB2 receptors, peripheral CB1 receptors and FAAH and MGL.

**Marijuana Abuse in the United States**

The most commonly used pain killers such as marijuana, and opioid drugs (oxycodone, morphine, fentanyl, and meperidine) result in dependence and addiction. Drug abuse and addiction have a tremendous negative impact on society. The overall cost of drug abuse in the US, including productivity, health and crime related costs exceed $600 billion annually.\textsuperscript{121}

The long-term use of marijuana can lead to addiction. In 2010 of the estimated 7.1 million Americans classified as abusers of illegal drugs, almost 4.5 million were dependent on marijuana.\textsuperscript{121} The addiction risk is greater (1 in 6) in people who started
using it as adolescents. For example, the use of marijuana has exceeded cigarette use in high school students. In 2011, 22.6% of high school seniors used marijuana in the past 30 days compared with 18.7% who smoked cigarettes.\textsuperscript{121} This survey also identified the use of synthetic “marijuana”, K2 ("Spice"), among high school seniors for the first time with almost 1 in 9, or 11.4%, of these seniors reporting use of Spice in the past year.\textsuperscript{121} Even though there is no currently available pharmacotherapeutic marijuana medications, recent research on the cannabinoid system offers hope for the development of medications to alleviate withdrawal symptoms, reduce the intoxicating effects of marijuana, and avert relapse.

Thus, CB1 agonist ligands that activate CB1 receptors in the brain to produce central effects need to be avoided. On the other hand, drugs acting as partial agonists at CNS receptors have become an attractive target for drug discovery since they can be used for the treatment of substance abuse. For example, varenicline is a nicotine receptor partial agonist used to combat nicotine addiction.\textsuperscript{122} By maintaining moderate levels of dopamine to counter withdrawal symptoms (acting as an agonist) and reducing drug satisfaction (acting as an antagonist), partial agonists can help substance abusers decrease their addiction towards drugs of abuse. Another example of this concept is the use of buprenorphine, a partial agonist at $\mu$-opiate receptors.\textsuperscript{123} It is given in combination with the opioid antagonist naloxone for treatment of heroin addiction. Compounds acting as partial agonists at dopamine\textsuperscript{124} and nicotinic receptors\textsuperscript{125} are also being extensively investigated in animal models and humans to evaluate their potential utility in inhibiting drug-seeking behavior and addiction.
Thus, the promise in cannabinoid based therapeutics lies in designing customized medications, developed from the active components of marijuana (phytocannabinoids), and to develop them to have better risk/benefit profiles. Scientists are actively engaged in this quest with the hopes of developing safe and effective medications that are devoid of unfavorable effects of smoked marijuana.

**Review of Current Cannabinoid-Based Medications**

The two THC based medications; nabilone and dronabinol have significant antiemetic efficacy, usually equivalent or superior to that of first-generation antiemetic drugs. Unfortunately, their use is declining due to the emergence of other more potent and less toxic drugs in the market. They also suffer from undesirable physiochemical properties that include poor bioavailability properties. The high lipophilicity of THC results in large volume of distribution ($V_d$), deposition in fat tissues (“depot effect”), and high (> 97 %) plasma protein binding. Cannabis is usually taken by smoking or ingestion. Using the inhalatory route, the bioavailability of THC varies from 18 to 50%, it has a rapid onset of action of 3–5 min, reaches its maximal effects in 30–60 min and euphoria lasts around 2–4 h. However, when cannabis is given orally, the bioavailability ranges from 6 to 20%, the onset of action is slow (30–60 min), euphoria is less prominent but the effects last longer.\textsuperscript{126} To increase the efficacy and reduce the toxic effects of THC, new formulations such as oral inhalers (aerosols), sublingual preparations, nasal sprays, transdermal patches and rectal suppositories have been developed. Since cannabinoids are insoluble in water, they can not be used intravenously.\textsuperscript{126}
Currently there are no effective treatment options for marijuana addiction and dependance. Patients undergoing treatment with marijuana-based medication often become addicted after treatment is stopped. One of the current strategies to prevent cannabis dependence and addiction is to administer low oral doses of Δ⁹-THC. For example, an oral dose of 30 mg THC per day reduced withdrawal symptoms.¹²⁷ Dronabinol is in phase-II clinical trials for treatment of marijuana addiction¹²⁶ and for its use as an adjunct therapy in combination with naltraxone to treat opioid addiction.¹²⁸ However, such treatments are not reliable since addicts can ingest more than required. The novel (+)-CBD analogs designed in this project as partial agonists can be used for marijuana or opioid addiction/dependence.

In order to avoid the psychoactive effects of THC based medications, CB2 selective agonists or peripheral acting agonists are attractive. Ligands that can selectively activate the CB2 receptor are expected to be devoid of psychotropic side effects associated with the activation of CB1 receptors. Such ligands can be potentially useful for the treatment of pain, inflammation, and other conditions related to cannabinoid physiology. Our lab has synthesized CB2-agonists (AM 1710, AM 1241) that are currently tested in various in-vivo pain models.¹²⁹,¹³⁰ By limiting the BBB penetrability of CB1/CB2 agonists one can target the CB receptors in the periphery. Despite the substantial interest for such ligands, very few low brain penetrant CB1 receptor agonists have been reported so far in the literature.¹³¹,¹³²,¹³³

Based on the above poor properties of THC and its synthetic analogs, there is a clear unmet medical need for novel cannabinoid based medications. These problems have
encouraged us to pursue the design and development of novel cannabidiol ‘agonist/partial agonist-based’ medications with improved ‘druggability’.
CHAPTER 2: DESIGN AND SYNTHESIS OF (+)-CANNABIDIOLS

OBJECTIVE AND SPECIFIC AIMS

The major psychoactive constituent of marijuana ($\Delta^9$-THC) has been extremely effective for the treatment of pain. However, its long-term usefulness in modern medicine is limited by the development of tolerance and physical dependence. The pharmacological effects of $\Delta^9$-THC have been attributed to the activation of CB1 and CB2 receptors,$^{134,135,136}$ which makes these targets attractive for the development of ligands. The unwanted psychobehavioral side effects of $\Delta^9$-THC are due to the activation of CB1 receptors in the brain. CB1 agonists also have effects like dysphoria, dizziness, motor coordination defects and memory loss which limit their use as drugs. In order to take advantage of the therapeutic potential of cannabimimetic compounds, a valid alternative would be the use of some other non-psychotropic phytocannabinoid.$^{142}$

In addition to $\Delta^9$-THC, another constituent of the marijuana plant, (-)-CBD,$^{137,138}$ produces beneficial pharmacological properties similar to those of $\Delta^9$-THC. Cannabidiol has gained tremendous attention in the past few years because of its lack of psychotropic effects.$^{139,140}$ Recent studies on (-)-CBD has revealed a plethora of beneficial preclinical and clinical effects,$^{141}$ such as anti-inflammation,$^{142}$ neuro-protection,$^{90,92,93}$ anti-anxiety,$^{143}$ anti-nausea,$^{95}$ anticancer,$^{101}$ etc. The therapeutic efficacy of (-)-CBD was further validated by the recent Canadian approval of Sativex®, a drug consisting of a 1:1 combination of $\Delta^9$-THC and (-)-CBD in an oral spray, which is used for the relief of neuropathic pain in MS$^{142}$ and as an adjunctive treatment of moderate to severe cancer pain.$^{144}$ Cannador® is another CBD- based drug, a preparation containing a 2:1 ratio of
Δ⁹-THC and (-)-CBD that has been clinically tested for reduction of muscle stiffness, spasms and pain in MS, for anorexia in cancer patients and for post-operative pain management.¹⁴⁵ These therapeutic applications have created a demand for CBD analogs to be synthesized for further clinical applications. In an effort to evaluate the biological properties of cannabidiols, it is important to develop suitable and convenient synthetic procedures for these compounds.

Since cannabidiols do not produce the psychotropic effects that tricyclic cannabinoids (Δ⁹-THC) do, their mechanism of action is thought to be different from those of the tricyclic cannabinoids. It is known that (4, (+)-CBD) binds to the CB1 and CB2 receptors with nanomolar affinity¹⁴⁶ as compared to (2, (-)-CBD) that binds CB receptors with micromolar affinity.¹⁴⁶ However, it is not known if (+)-CBD or (-)-CBD actually activate the cannabinoid receptors to produce their pharmacological effects. Despite cannabidiols broad therapeutic potential, the mechanism of action and molecular target of cannabidiols remain unknown.

Currently, there is very limited side-chain SAR¹⁴⁷ on (-)-CBD and no SAR on (+)-CBD. There is also very limited in vivo pharmacological data on (+)-CBD.⁷⁷ The in vivo properties of (+)-CBD haven’t been sufficiently explored and the development of a SAR will help in selecting leads to accomplish this goal. The objective of this thesis project is to design and synthesize a series of (+)-CBD analogs by a convenient synthetic procedure and to develop thereby an SAR for (+)-CBD in order to explore the binding site of cannabidiols with the CB1 and CB2 receptors. The pharmacophoric requirements of binding of cannabidiols to the CB receptors are not known, and a SAR will help in establishing this.
The strategy (Figure 2.1) for the synthesis of this project began with a rational design of analogs based on known SAR studies from classical tricyclic cannabinoids, and was
followed by the synthesis of (+)-CBD analogs. The binding affinities of the synthesized analogs for rat CB1R, mouse CB2R, and human CB2R were determined and evaluated to identify attractive pharmacophores of the (+)-CBD template. *In vitro* leads were selected based on their high binding affinity, selectivity as CB2R agonists or CB1R partial agonists, drug-like physicochemical properties, and modulation of *in vitro* pharmacological activity (cAMP, β-arrestin assays). These leads were profiled in a panel of rodent paradigms for *in vivo* cannabinergic activity (hypothermia, catalepsy and tail-flick tests). The resulting data enabled pharmacophore identification that aided the design of (+)-CBD analogs as covalent CB-receptor probes. During this iterative process, alterations to structures were performed to optimize compound physicochemical properties, CB1R/CB2R selectivity, and *in vivo* bioavailability/metabolic profiles. Furthermore, the SAR of cannabidiols and tricyclic cannabinoids were compared to indirectly determine if they share the same binding pocket to the cannabinoid receptors.

The SAR focused on the following parts of the cannabidiol template (*Figure 2.2*).

a) Side-chain variation: homologation and end carbon substitution

b) Modification of the B ring by isoteric replacement of the terpenoid ring

c) Modification of the northern end

d) Modification of phenolic group
The high-resolution 3-D structure of the CB receptors as well as identification of the receptors binding domain would provide a good starting point for rational drug design of (+)-CBD analogs. Since CB receptors are GPCR’s, it is tremendously difficult to isolate and obtain crystal structures of these native membrane proteins. The binding site of (+)-CBD to the CB receptors is not known. An understanding of the binding site will help in the development of selective and potent compounds and will help in understanding the difference in binding between the two CBD enantiomers. Additionally, it might also explain the lingering question of why (-)-cannabidiols do not possess the psychoactive properties of Δ⁹-THC. During the past decade, high affinity covalent probe ligands have been used to characterize the binding site of cannabinoids. This procedure (Ligand-Assisted Protein Structure, LAPS) involves the use of probes that form a covalent bond with amino acid residues within the binding site of the receptor or in its immediate vicinity.¹⁴⁸ The use of high-affinity ligands such as AM 841 has provided some
experimental three dimensional structural information of the cannabinoid receptor and has identified amino acid residues critical to ligand binding and recognition.\textsuperscript{149} Thus, in order to study the binding motifs of cannabinoids to the cannabinoid receptors, analogs with photoactivatable and electrophilic functional groups on the side chain pharmacophore of (+)-CBD were synthesized. Photoactivatable probes consist of chemically less reactive groups like azides, which on activation by UV, get transformed into highly reactive nitrenes\textsuperscript{150} and covalently react by insertion reactions with adjacent amino acid residues at the receptor site. Similarly, the electrophilic isothiocyanato group reacts with amino acids residues (primarily the free thiol of cysteines at physiological pH) that have a nucleophilic group near the binding domain of the receptors. In this thesis, we report the design and synthesis of high affinity covalent probes to pursue our goal.

**Design of cannabidiol (literature route)**

The first preparation of the natural (2, (-)-CBD), unnatural (4, (+)-CBD), dimethyl heptyl analogs (3, 5) and the metabolites of CBD (6, (-)-7-hydroxy-CBD),(8, (+)-7-hydroxy-CBD), (7, (-)-7-hydroxy-CBD-DMH), (9, (+)-7-hydroxy-CBD-DMH) have been reported by Mechoulam et al. as shown in Figure 2.3\textsuperscript{151,152} This was done by condensing (-)-\textit{p}-mentha-1,8-diene-3-ol and olivetol or dimethyl heptyl resorcinol with boron trifluoride etherate absorbed on basic alumina, to obtain 2 and 3 in 44% and 55% yields respectively.\textsuperscript{152}
Using 2 and 3 as starting points, the metabolites 6 and 7 were synthesized in 8 steps. In another reported procedure, the coupling reaction is the second step in the synthesis and
from there on, modification is made on the cannabidiol template in six other steps until the desired metabolite is produced.$^{153}$

These procedures do not allow for the easy synthesis of analogs and for the functionalization of side chains because the coupling of the terpene unit and the resorcinol is done at the beginning of the synthesis. Thus, an SAR profile would be difficult to develop if these procedures are followed. Although these products have been synthesized before, the synthetic route that we designed gave access to (+)-CBD analogs in a remarkably concise fashion with high yield features and contributed to developing a SAR.
CHEMISTRY

In order to synthesize (+)-CBD analogs, a retrosynthetic analysis was performed on the (+)-CBD template. The (+)-CBD analog, represented by the general structure 26, served as a starting point. Its synthesis requires the chiral terpene synthon 16 and resorcinols 25 (Scheme 2.1).

**Scheme 2.1: Retrosynthetic analysis of (+)-cannabidiol template (26)**

Starting with the commercially available (S)-perillyl alcohol 10, the terpene 16 was synthesized in six steps as shown in Scheme 2.2. (S)-(−)-Perillyl alcohol was epoxidized by the Sharpless reagent\(^{154}\) tert-butyl hydroperoxide (TBHP) and vanadyl acetylacetonate to give a 1:1 mixture of inseparable diastereomeric epoxides\(^ {155}\) 11; the VO(acac)\(_2\)-TBHP system exclusively epoxidizes the double bond of the allylic alcohol. The primary hydroxyl group of 11 was protected with tert-butyldimethyl silyl chloride to give 12.\(^ {155}\) Epoxide ring opening of 12 was accomplished by the phenylselenide anion, which was generated *in situ* by the reduction of diphenyl diselenide with sodium borohydride in ethanol,\(^ {156}\) and gave a mixture of diastereomers 13a, 13b and 13c. All three diastereomers were separated by flash column chromatography and 13a was isolated as the major product (46% yield). This is due to the presence of the bulky TBDMS group that directs the attack of the phenylselenide anion at the secondary carbon atom as compared to the
tertiary carbon atom. Desilylation of 13a with TBAF\textsuperscript{155} gave 14 as a white solid in 95\% yield. The primary hydroxyl group of intermediate selenide 14 was protected as the acetate using acetic anhydride\textsuperscript{157} to give 15 (98\% yield). Oxidation of the latter with \( \text{H}_2\text{O}_2 \) in pyridine\textsuperscript{157} and THF led to the required terpene 16 (53\% yield). The presence of pyridine and heat was essential for selenoxide elimination. In the absence of pyridine, the resultant acidity of phenylselenic acid causes an allylic rearrangement leading to a mixture of products.\textsuperscript{158} The synthesis of terpene 16 has been reported before.\textsuperscript{157} However, some of the reactions weren’t reproducible in our hands and some reactions were low yielding. Thus we utilized chemistry from other papers for the synthesis of terpene 16.\textsuperscript{155,158,159}

**Scheme 2.2: Synthesis of Chiral Terpene 16**

![Scheme 2.2: Synthesis of Chiral Terpene 16](image-url)
Reagents and conditions: (a) VO(acac)$_2$, HOOOC(CH$_3$)$_3$, toluene, r t, 3 h, 80%, 1:1 dr; (b) imidazole, TBDMSCl, DMF, r t, 14 h, 96%; (c) Ph$_2$Se$_2$, NaBH$_4$, EtOH, reflux, overnight, 46% (13a), 18% (13b), 16.7% (13c); (d) (n-Bu)$_4$N$^+$F$, THF, r t, 4 h, 98%; (e) acetic anhydride, pyridine, CH$_2$Cl$_2$, r t, 4 h, 98%; (f) 30% H$_2$O$_2$, pyridine, THF, 3 h r t, then 3 h reflux, 53%.

Similarly, the enantiomeric terpene 24 was synthesized in seven steps (Scheme 2.3) starting with the commercially available (R)-perillyl aldehyde 17 from which NaBH$_4$ reduction of the aldehyde group gave compound 18 in 94% yield. The subsequent steps are analogous to the preparation of the (S)-terpene 16 in Scheme 2.2. Terpene 24 has been synthesized previously by Tuis et al.$^{159}$

**Scheme 2.3: Synthesis of Chiral Terpene 24**
Reagents and conditions: (a) NaBH₄, CH₃OH, r t, 1 h, 93%; (b) VO(acac)₂, HOOOC(CH₃)₃, toluene, r t, 3 h, 79%; (c) imidazole, TBDMSCl, DMF, r t, 14 h, 97%; (d) Ph₂Se₂, NaBH₄, EtOH, reflux, overnight, 54% (21a), 20% (21b), 18% (21c); (e) (n-Bu)₄N⁺F⁻, THF, r t, 4 h, 95%; (f) acetic anhydride, pyridine, CH₂Cl₂, r t, 4 h, 98%; (g) 30% H₂O₂, pyridine, THF, r t, 3 h then 3 h reflux, 54%.

**Scheme 2.4**: Synthesis of resorcinol 25g

![Scheme 2.4](image)

Reagents and Conditions: (a) 4-phenoxybutyl magnesium bromide, THF, reflux, 33% (b) TiCl₄, Zn(CH₃)₂, -40 °C to -10 °C, 45% (c) BBr₃, CH₂Cl₂, -5 °C -23 °C, 84%.

The synthesis of resorcinol 25g is shown in *Scheme 2.4*. The Grignard reagent prepared from 4-bromo phenoxybutane in THF was added to nitrile 28 to give ketone 29 which on treatment with dimethylzinc and TiCl₄ gave compound 30 in 45% yield. Demethylation and replacement of the phenoxy group by bromine took place using the BBr₃ reagent and led to resorcinol 25g in 84% yield. This scheme was not followed for the synthesis of the 6-C (25l) and 7-carbon (25c) resorcinols, due to the modest yields of the Grignard reaction and the geminal dimethylation reaction and the highly pyrophoric nature of the Zn(CH₃)₂ reagent.
Scheme 2.5 was therefore utilized to make the 5-carbon 25g, 6-carbon 25l and 7-carbon 25c bromoresorcinols. Sequential deprotonation of 3,5-dimethoxypheny acetonitrile 31 using NaH, followed by geminal dimethylation with iodomethane produced 32 in a very good yield of 97%. The cyano group was subsequently reduced with DIBAL-H\textsuperscript{162,163} and hydrolyzed to give aldehyde 33. Wittig olefination of 33 with the respective phosphonium salt (Scheme 2.5) using n-BuLi as base afforded the olefins 34a, 34b and 34c, all favoring the trans isomer (trans: cis = 97:3 by \textsuperscript{1}H-NMR). The phosphonium salts were obtained by reacting their respective phenoxy alkyl bromides with PPh\textsubscript{3} in toluene for two days under reflux conditions.\textsuperscript{164} 5-Phenoxy pentyl bromide was synthesized by coupling phenol with 1, 5-dibromopentane in the presence of K\textsubscript{3}CO\textsubscript{3} in acetonitrile.\textsuperscript{170} Catalytic hydrogenation of 34a, 34b and 34c led to their respective dimethyl ethers 35a, 35b and 35c.\textsuperscript{163} These were converted to resorcinols 25g, 25l and 25c with BBr\textsubscript{3} at –78 °C\textsuperscript{165,163} in 85%, 96% and 93% yields respectively. The synthesis of 25g and 25c has been reported before by a different approach using different starting materials.\textsuperscript{161,173} One of the synthesis\textsuperscript{173} used to produce 25g and 25c uses Al(CH\textsubscript{3})\textsubscript{3}, another pyrophoric reagent. The synthesis also involved a low yielding Grignard step and resulted in the formation of alkene elimination byproducts. We thus decided to use a safer and high yielding approach for the synthesis of resorcinols. The methodology reported in Scheme 2.5 for the synthesis of 25g and 25c has not been reported, however it parallels the one developed in our laboratory for the synthesis of C1' cycloalkyl resorcinols.\textsuperscript{169,170,166}
Scheme 2.5: Synthesis of resorcinol 25g, 25l and 25c

Reagents and Conditions: (a) CH₃I, NaH, DMF, 0 °C to r t, 2 h, 97%; (b) DIBAL-H, CH₂Cl₂, -78 °C, 0.5 h, 75%; (c) Br⁻P(Ph₃(CH₂)ₙO)Ph, n-BuLi, THF, -78 °C to R.T, 93% (34a), 92% (34b), 87% (34c); (d) H₂, 10% Pd on C, EtOH, r t, overnight, 89% (35a), 89% (35b), 96% (35c); (e) BBr₃, CH₂Cl₂, -78 °C to r t, 1 day, 85% (25g), 96% (25l), 93% (25c).

Rescorcinol 25m (Scheme 2.6) was synthesized to investigate the role of a heterocycle at the C1' position. Increase in binding affinities of heteratom substituted analogs might indicate the close proximity of polar amino acid residues within the binding pocket. The hitherto unknown resorcinol 25m bearing C1'-tetrahydropyran ring substituent was synthesized in eight steps from 3,5-dimethoxyphenyl acetonitrile 31 by following a new methodology developed in our laboratory. The methoxymethyl groups of 31 were demethylated with BBr₃¹⁶⁵ to give 36. It is important to note the sequence of quenching in this reaction for obtaining high yields. If the reaction mixture is poured into cold aqueous saturated NaHCO₃ the desired product is obtained in 85% yield, while if cold aqueous
NaHCO$_3$ is added into reaction mixture, the yield of the product is reduced drastically (25%). If the latter procedure is followed, the aqueous nature of NaHCO$_3$ produces HBr and boronic acid that hydrolyses the nitrile to carboxylic acid. This was indicated by the presence of a polar spot at the bottom of the TLC plate. The phenolic hydroxyls of 36 were then protected as ethoxyethyl ethers$^{167}$ using ethyl vinyl ether in the presence of $p$-toluene sulfonic acid, leading to 37. Again, it is noteworthy to mention the quenching process in this reaction$^{167}$. Due to the low stability of the ethoxy ethyl group under acidic conditions, the crude reaction mixture was added into aqueous saturated NaHCO$_3$, so that the excess NaHCO$_3$ would maintain an alkaline environment during quenching. Following this procedure, the yield of the reaction was 95%, while if aqueous saturated NaHCO$_3$ was added into the reaction mixture, the yield of the reaction was significantly less (10%). Cyclo-bis-alkylation of 37 using 2-bromoethyl ether, after sequential deprotonation with potassium bis(trimethylsilyl) amide, gave tetrahydropyranyl carbonitrile 38. It should be noted that, during the column chromatography purification of compounds 37 and 38, the column was equilibrated with 2% triethylamine to neutralize the acidic silica gel. The ethoxy ethyl groups were then removed with $p$-toluenesulfonic acid to give 39 and the resulted phenolic hydroxyl groups were protected as TBDMS ethers 40. The nitrile group of compound 40 was reduced with DIBAL-H to give aldehyde 41 in 51% yield.$^{162,163}$ The reduction of compound 38 with DIBAL-H led to low yields perhaps because the ethoxy ethyl group as well as the oxygen atom in tetrahydropyran ring might coordinate with DIBAL-H reagent. Treatment of commercially available $n$-pentyldiphenylphosphonium bromide with potassium bis(trimethylsilyl) amide and coupling of the generated phosphorane with 41 at 0 °C,
produced intermediate alkene 42 in 72% yield.\textsuperscript{168,169,170} On the basis of $^1$H NMR analysis, this Wittig olefination reaction afforded exclusively the Z-olefin with coupling constant ($J_{2H-3H}$) of 12.0 Hz. Finally, desilylation of 42 with TBAF gave resorcinol 25m in 97% yield. Resorcinol 25m was a novel resorcinol that was synthesized using a new developed synthetic procedure.

**Scheme 2.6:** Synthesis of C1' tetrahydropyranyl resorcinol 25m

Reagents and Conditions : (a) BBr\textsubscript{3}, CH\textsubscript{2}Cl\textsubscript{2}, -78 °C to r t, 2 days, 85%; (b) H\textsubscript{2}CCHOCH\textsubscript{2}CH\textsubscript{3}, p-TSA, Et\textsubscript{2}O, 0 °C, 1 h, 95%; (c) (Me\textsubscript{3}Si)$_{2}$N$^{+}$K\textsuperscript{-}, Br(CH\textsubscript{2})\textsubscript{2}O(CH\textsubscript{2})\textsubscript{2}Br, THF, 0 °C, 1 h, 98%; (d) p-TSA, CH\textsubscript{3}OH, 25 °C, 0.5 h, 91%; (e) imidazole, TBDMSCl, DMF, r t, 2 h, 91%; (f) DIBAL-H, CH\textsubscript{2}Cl\textsubscript{2}, -78 °C, 2.5 h, 51%; (g) CH\textsubscript{3}(CH\textsubscript{2})\textsubscript{4}PPh\textsubscript{3}Br, (Me\textsubscript{3}Si)$_{2}$N$^{+}$K\textsuperscript{-}, THF, 0 °C, 0.5 h, then 13, 0 °C, 10 min, 72%; (h) (n-Bu)$_{4}$N$^{+}$F\textsuperscript{-}, r t, THF, 1 h, 98%
Scheme 2.7: Products of coupling terpene 16 with Olivetol 25b

Reagents and conditions: (a) p-TSA, CH$_2$Cl$_2$, -10 °C to 25 °C, 26b (12%), 44 (6%), 45 (6%); (b) BF$_3$:Et$_2$O, 0 °C, CH$_2$Cl$_2$, 98%; (c) K$_2$CO$_3$, CH$_3$OH, r t, 74%.

Before beginning the synthesis of (+)-CBD analogs, we performed a model reaction using terpene 16 and commercially available resorcinol olivetol 25b, which involved a stepwise Fridel-Crafts alkylation and cyclization (Scheme 2.7). Terpene 16 was coupled with olivetol 25b (-10 °C to 25 °C) leading to three major products; normal cannabidiol product 26b, abnormal cannabidiol 45 and the tricyclic product 44 as it was reported previously for a closely related terpenic alcohol.$^{171}$ Absence of the C1’ substituent led to the abnormal product 45. Cannabidiol 26b can be further cyclized to the tricyclic product...
44 on treatment with BF$_3$Et$_2$O at 0 °C. Abnormal cannabidiol 45 was hydrolyzed to 46 by K$_2$CO$_3$ to examine its binding affinity for the CB receptors.

**Scheme 2.8:** Example of coupling reaction

Reagents and Conditions: (a) p-TsOH, -10 °C to 25 °C, CH$_2$Cl$_2$, 4 h, 55% (26a), 20% (43)

It is important to mention that in order to obtain high yields of the cannabidiol analogs, the temperature of the reaction must be below 0 °C. An increase in the reaction temperature to 25 °C results in the respective tricyclic analogs as outlined in *Scheme 2.8.* Tricyclic analogs have already been reported in previous work from our group.$^{67}$

**Scheme 2.9:** Synthesis of (1S, 6S) - dimethylheptyl enantiomer
Reagents and Conditions: (a) p-TsOH, -10 °C, CH₂Cl₂, 4 h, 55% (26a), (b) K₂CO₃, CH₃OH, r t, 2 h, 72%, (27a).

**Scheme 2.10:** Synthesis of (1R, 6R) - dimethylheptyl enantiomer

In order to compare the binding affinities of the cannabinoid enantiomers, (1SR,6S)-7-OH-DMH-CBD (27a) and (1R,6R)-7-OH-DMH-CBD (70) were synthesized (Scheme 2.9 and 2.10). The structure of 70 was established using 1D H-NMR spectra as well as ¹³C-NMR, COSY, HSQC, HMBC, and NOESY correlations (Appendix 2).

Interestingly, the signal corresponding to the aromatic protons of AM 9200 (26a) in the ¹H-NMR spectrum (Figure 2.4) appear as a broad singlet indicating some restriction of rotation about the C₂-C₃ bond at 25 °C. Based on this result, a temperature experiment was performed at 3 °C. At low temperature, the free rotation about the bond slows down and aromatic protons become clearly magnetically non-equivalent and differentiated into singlets.
Figure 2.4: $^1$H NMR spectrum of AM 9200 as a function of temperature

From the $^1$H-NMR of 70 (AM 9242- Appendix 2), the aromatic protons show as sharper signal as compared to AM 9200 (Figure 2.4). This is because the bulk of OH group is less than the acetate and thus free rotation is accelerated at 25 °C for 70 and thus resulting in a sharper peak for the aromatic protons.

After optimizing the reaction conditions and the thorough structural elucidation of AM 9242, the synthesis of (+)-CBD analogs were undertaken. As shown in Scheme 2.11, coupling of terpene alcohol 16 with resorcinols 25 in the presence of anhydrous $p$-TSA led to the ester intermediates 26. Subsequent base hydrolysis of the ester group with K$_2$CO$_3$ or reduction with DIBAL-H led to the required cannabidiol analogs 27. The
synthesis of (+)-CBD depicted in Scheme 2.11 represents a new methodology for the synthesis of (+)-CBD analogs in a concise high-yielding way.

**Scheme 2.11:** General scheme for the coupling of terpene alcohol 16 with resorcinols (25)

Reagents and Conditions: (a) \( p \)-TsOH, -10 °C, \( \text{CH}_2\text{Cl}_2 \), 4 h; (b) DIBAL-H, -78 °C, \( \text{CH}_2\text{Cl}_2 \), 0.5 h or \( \text{K}_2\text{CO}_3 \), \( \text{CH}_3\text{OH} \), r t.

**Figure 2.5:** R groups
The following R groups in Figure 2.5 represent the different resorcinols that were coupled to the terpene 16. (Note- some resorcinols were provided by other lab members).

Following this methodology cannabidiol ester intermediates 26a-26n (24-80% yields) and final cannabidiol analogs 27a-27n (52-81% yields) bearing different substituents at the C1' position and with different side chain lengths were synthesized.

**Side chain Modifications**

**Scheme 2.12**: Synthesis of side chain homologated cyano analogs

Reagents and conditions: (a) NaCN, DMSO, r t, 24 h.

Schemes 2.12 illustrates the transformation of the bromo analogs to cyano counterparts. Cyanide displacement of bromides of 27i, 27g, 27l and 27c with sodium cyanide in dimethyl sulfoxide led to cyano substituted analogs 53, 48, 52, 47. (Yields 37-74%).
Scheme 2.13: Synthesis of morpholino analog 49

Reagents and conditions: (a) Et₃N, morpholine, CH₃CN, r t, 48 h, 23%.

Morpholino analog 49 was synthesized in 23% yield by first converting the bromide 27g to cyano 48, then reacting 27g with morpholine in triethylamine and acetonitrile (Scheme 2.13). The cyano and morpholino groups were chosen as they can impose favorable physiochemical properties such as polarity to drug molecules. Also, morpholino-substituted analogs can be transformed to water-soluble salts.

Scheme 2.14: Synthesis of Cl' cyclobutyl tail modified analogs
Reagents and conditions: (a) K$_2$CO$_3$, CH$_3$OH, r t, 75%; (b) NaCN, DMSO, r t, 24 h; (c) K$_2$CO$_3$, CH$_3$OH, r t, 61%.

In order to synthesize the cyano analog 51 (*Scheme 2.14*), the bromo compound 26h was first converted to intermediate acetate 50 by nucleophilic cyanide displacement of the bromide group, and then to 51 by base catalyzed hydrolysis in 61% yield. 26h was also converted to 27h by saponification.

**Modifications of the phenolic group**

In order to explore the SAR of cannabidiols on ring A, analogs bearing OCH$_3$ groups in place of the phenolic group were synthesized. An increase in binding affinity might suggest that the hydrogen donor ability of OH is not necessary for binding. The hydrogen accepting ability is still retained with this change.

*Scheme 2.15*: Modification of phenolic group of C1' dimethylheptyl side chain analogs

Reagents and conditions: (a) CH$_3$I, K$_2$CO$_3$, CH$_3$COCH$_3$, 50 °C, 56%; (b) K$_2$CO$_3$, CH$_3$OH, r t, 61%; (c) NaCN, DMSO, r t, 24 h.
Modifications of the phenolic hydroxyls with methoxy groups were accomplished by reacting 26c and 26g with methyl iodide and potassium carbonate in acetone to yield ester intermediates 54 and 57 in 56% and 76% yields, respectively. This was followed by alkaline hydrolysis of 54 and 57 to yield final cannabidiols 55 and 58 in 73% and 76% yields, respectively (Schemes 2.15 and 2.16). Displacement of the bromide groups of 55 and 58 with NaCN in DMSO led to analogs 56 and 59. Morpholino analog 60 was synthesized by nucleophilic displacement of bromide 58 with morpholine to give 60 in 33%

Reagents and conditions: (a) CH₃I, K₂CO₃, CH₃COCH₃, 50 °C, 76%; (b) K₂CO₃, CH₃OH, r t, 76%; (c) NaCN, DMSO, r t, 24 h, 67%; (d) Et₃N, morpholine, CH₃CN, r t, 48 h, 33%.
Scheme 2.17: Synthesis of northern end modified analogs

Reagents and Conditions: (a) Imidazole, TBDMSCl, DMF, r t, overnight, 98%; (b) DIBAL-H, -78 °C, CH₂Cl₂, 0.5 h, 76%; (c) Imidazole, PPh₃, I₂, benzene, 50 °C, reflux, 1 h, 87%; (d) Bu₄N⁺N₃⁻, CH₂Cl₂, 24 h, 91%; (e) (n-Bu₄)N⁺F⁻, THF, r t, 4 h, 45%; (f) PPh₃, benzene, 50 °C, 6 h, then CS₂, 50 °C, 6 h, 32%.

In order to synthesize northern end (+)-CBD analogs, new synthethic approaches were developed as depicted in Scheme 2.17. Protection of the phenolic hydroxyl groups of 26a with TBDMSCl gave 61 in 98% yield. This was followed by DIBAL-H reduction of the ester group to the allylic alcohol intermediate 62. Reaction of 62 in the presence of imidazole, triphenylphosphine and iodine₁⁷³ resulted in intermediate 63 in 87% yield.
Iodo compound 63 was converted to the azide 64 by displacement of iodide with tetrabutylammonium azide (91% yield). Deprotection of 64 in the presence of TBAF led to azido analog 65. Exposure of 65 first to triphenylphosphine, then to carbon disulfide converted the azide to isothiocyanate leading to 66 in 32% yield.

Scheme 2.18: Deprotection of AM 9232

Interestingly, exposure of 63 to TBAF reagent (Scheme 2.18) does not give the cannabidiol 67 but, instead led to the formation of AM 9257 (68), a cis-fused ring tricyclic compound. The structure of AM 9257 was determined by $^1$H-NMR, $^{13}$C-NMR and a complete set of 2-D NMR experiments (NOESY, COSY and HSQC- Appendix I). All protons were assigned and coupling constants were calculated. Coupling constant, $J_{9a-5a}$ was found to be 6.5 Hz confirming a cis ring fusion (Page 291- Appendix I). This $J_3$ coupling constant is consistent with the dihedral angle (Karplus equation) shown in Figure 2.6 (A), where the 5a, 9a protons are cis-oriented. Conversely, when the cyclohexane ring is trans-fused to the furan ring (Figure 2.6 (B)), the dihedral angle is
larger and does not match with the obtained $^3J$ coupling constant. The NOESY experiment also shows NOE interactions between 12-H and OH, and 10-H and 5a-H (Page 300- Appendix I).

**Figure 2.6:** Low energy conformers for the cis- and trans-fused isomers of AM 9257

![Image of conformers](image)

**Scheme 2.19:** Potential mechanism for the formation of AM 9257

![Image of mechanism](image)

The mechanism of formation of AM 9257 (*Scheme 2.19*) might be by 5-exo trig favored ring closure according to Baldwin’s rules.
Isosteric replacement of the terpenoid ring B

In order to synthesize isosteric analogs, enantiomeric pure forms of terpenes 71 and 73 were provided by Dr. Spyros Nikas.

Scheme 2.20: Synthesis of (1R, 4S, 5S) analogs

Reagents and Conditions: (a) p-TSA, CH₂Cl₂, 0 °C, 2 h.

Isosteric replacement of the terpenoid ring (Scheme 2.20) was accomplished by coupling (+)-cis-verbenol 71 with resorcinols 25 and led to bicyclic analogs 72 in 48-87% yields.
Scheme 2.21: Synthesis of (1S,4R,5R) analogs

Reagents and Conditions: (a) p-TSA, CH\textsubscript{2}Cl\textsubscript{2}, 0 °C, 2 h.

In order to compare enantiomers, (-)-cis-verbenol 73 was coupled with resorcinols shown in Scheme 2.21 to produce bicyclic analogs 74 in 49-60% yields.

**Physicochemical property CB2 selectivity manipulation**

AM 8119 (Figure 2.7) was recently developed in our laboratory and it was found to be a CB2-selective compound ($K_i$ hCB2 = 0.8 nM, rCB1 = 47.2 nM- Dr. Spyros Nikas, Unpublished results). CB2-selective compounds are known to produce analgesic effects comparable to that of morphine without inducing psychotropic effects.\textsuperscript{174} In order to restrict permeability of CB1 agonists into the brain, the physicochemical properties can be manipulated to target them to the periphery. The CLogP and total polar surface area (tPSA) are two important parameters that are manipulated in such cases. Compounds with tPSA above 70 will not likely cross the BBB and compounds with tPSA over 150 will not be absorbed.\textsuperscript{175} tPSA values between 70 and 120 tend to favor compounds that non-CNS penetrant and orally active. Compounds with CLogP in the 3-5 range would
most likely be non-CNS penetrant. Chemdraw generated ClogP and tPSA values of AM 8219 (*Figure* 2.7) shows ClogP value of 7.1 and a tPSA of 57.5. This compound would likely have a high passive brain penetration. Also the structure of AM 8119 suggests that the presence of a six-membered tetrahydropyranyl ring at the C1' position of the cannabidiol template might result in CB2 selective analogs. Thus in order to lower the ClogP, analogs 27m, 76 and 78 (*Figure* 2.7) were synthesized. In vivo tetrad tests and BBB studies will be required to confirm our predictions of 27m, 76 and 78 being non-brain penetrant.

*Figure* 2.7: Chemdraw generated ClogP and tPSA values of side chain and B-ring modified cannabidiol derivatives.

Coupling of enantiomeric terpene diacetates (*Scheme* 2.22 and 2.23, 75 and 77 were provided by Dr. Spyros Nikas) with resorcinol 25m in the presence of p-toluene sulfonic
acid monohydrate in wet chloroform led to bicyclic analog enantiomers 76 and 78 in 41% and 48% yields respectively. The synthesis of the optically pure enantiomeric terpenes are reported in a patent form our group.\textsuperscript{176}

**Scheme 2.22:** Synthesis of C1’ tetrahydropyranyl bicyclic analog 76

\[
\begin{align*}
\text{Reagents and Conditions: (a) } & p\text{-TSA.H}_2\text{O, CHCl}_3, 0 \degree \text{C to r t, 3 days, 41%.}
\end{align*}
\]

**Scheme 2.23:** Synthesis of C1’ tetrahydropyranyl bicyclic analog 78

\[
\begin{align*}
\text{Reagents and Conditions: (a) } & p\text{-TSA.H}_2\text{O, CHCl}_3, 0 \degree \text{C to r t, 3 days, 48%}.
\end{align*}
\]
RESULTS AND DISCUSSION

Figure 2.8: Summary of the SAR

a) C1’ substitution with cycloalkyl groups and heterocyclic rings.

b) Isosteric replacements of the terpenoid B ring.

c) Modification at the northern end of B ring included acetate, hyrdoxyl, iodo, azido and isothiocynato groups.

d) Modification of the A ring involved methylation and silylation of the phenolic groups.

e) Side chain variation included homologation and end carbon substitution. The chain length varied from 4 to 7 carbons, while the terminal carbons were substituted with bromo, cyano, morpholino, azido and isothiocynato groups.
Our SAR study (Figure 2.8) focused on chemical synthesis to explore the pharmacophoric chemical space of (+)-CBD. In vitro profiling of the novel (+)-CBD was performed in the following assays:

- Competitive radioligand binding assay for CB1 and CB2 receptors (performed in-house).
- β-arrestin assay (performed at Duke University).
- Cyclic adenosine monophosphate (cAMP) assay (performed in-house by Dr. Aneetha Halikhedkar).

The binding affinities of (+)-CBD were determined for the CB1 receptor (rat brain membranes) and membrane preparations from HEK293 cells expressing human (hCB2) and mouse (mCB2) CB2 receptors. Displacement of [3H]-CP-55,940 from these membranes was used to determine IC$_{50}$ values in competition radioligand assays. [3H]-CP-55,940 was used as the competing ligand as it is nonselective with has high affinity for both CB1 and CB2 receptors. Despite the availability of other tritiated radioligands from other cannabinoid classes, [3H]-CP-55,940 was used for the purpose of consistency to allow for comparison of analogs. Also Ki values are subject to considerable variability depending on the radioligand used in the binding assays as well as on other experimental conditions (e.g., albumin concentration). Thus it is best to compare groups of compounds that have been tested under identical set of conditions. Ki values calculated from the respective displacement curves are listed in the following tables (See experimental procedure for detailed description).
Compounds that show high binding affinity and selectivity towards the CB2 receptor were sought after. On the other hand, compounds that exhibit binding affinity in the low nanomolar range, but are not functionally active at the CB receptors, are not ideal. Cannabinoid ligands are known to affect several downstream signaling pathways like the adenyl cyclase, β-arrestin, MAPK pathways, certain voltage-gated calcium channels and inward rectifying potassium channels.\textsuperscript{33,35,40} It is usually desired that compounds activate only a single signaling pathway (biased agonism) in order to limit undesired effects. But most compounds are not selective and activate more than one downstream signaling pathway. In order to determine the intrinsic efficacy of our key analogs, β-arrestin and cAMP assays were performed. Description of both assays can be found in the experimental procedures section. In the cAMP assay, the percent efficacy and IC\textsubscript{50} values of the analogs tested were compared to \([^3\text{H}]\) CP-55,940.

\textbf{rCB1 - [\textsuperscript{3}\text{H}] CP-55,940}, EC\textsubscript{50} = 4.0 ± 1.9 nM, % Efficacy = 62.0 ± 9.9 (Mean ±SD)

\textbf{hCB2 - [\textsuperscript{3}\text{H}] CP-55,940}, EC\textsubscript{50} = 9.1 ± 0.5 nM, % Efficacy = 78.0 ± 4.0 (Mean ±SD)

We designed libraries of compounds based on the known SAR studies from our laboratory on tricyclic and bicyclic cannabinoids. For tri-cyclic and bicyclic compounds, the 7-C alkyl side chain with cyclic moieties at the C1' position are well tolerated.\textsuperscript{67,177,168} Thus the SAR studies were started with the comparision of analogs containing a 7-C side chain, analogous to the known dimethyl heptyl (+)-CBD. In order to explore the effects of substituents at the C1' position of (+)-CBD, analogs shown in Table 2.1 were synthesized.
Table 2.1: Affinities of C1' substituted (+)-CBD’s

<table>
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<tr>
<th>AM#</th>
<th>R</th>
<th>$K_i$(nM)*</th>
<th>rCB1 (brain)</th>
<th>mCB2 (HEK)</th>
<th>hCB2 (HEK)</th>
<th>rCB1/mCB2</th>
<th>rCB1/hCB2</th>
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<td>2.3±0.6</td>
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<td></td>
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<td></td>
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<tr>
<td>27f</td>
<td></td>
<td></td>
<td>15.6±0.6</td>
<td>14.5±0.2</td>
<td>14.4±0.6</td>
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<tr>
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<tr>
<td>27m</td>
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<td>81.9±3.6</td>
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<td>27k</td>
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<td>410±80</td>
<td>25.3±0.7</td>
<td>160±88</td>
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<tr>
<td>27n</td>
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<td>24.0±2.6</td>
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*K_i values were obtained from three independent experiments run in triplicate and are expressed as the mean±SD.
For the substituted C1' side chains, the dimethyl heptyl side chain analog, AM 9201 (27a), showed the highest binding affinity for the CB1 and CB2 receptors, which was followed by the cyclopropyl side chain analog AM 9214 (27f). Cyclopropyl analog AM 9212 (27e), and thiolane analog AM9210 (27d) showed almost equal binding affinity for CB1. The bulky adamantyl analog side chain, AM 9238 (27k), showed reduced binding affinity for the CB1 receptor. Thus, there is a progressive loss in affinity for CB1 with bulky substituents such as cyclopentyl, thiolane, tetrahydropyranyl and adamantyl groups. Introduction of the C2'-C3' cis-double bond in the side chain of the cyclopentyl congener (27n) resulted in binding affinities that were better than its congener (27e) carrying a fully saturated side chain.

The smaller substituents, dimethyl (27a) and cyclopropyl (27f), have no significant selectivity between the two receptors, nor is there a species difference between the mouse and human CB2 receptors. In general, the bulkier substituents, cyclopentyl (27e), thiolane (27d) and adamantyl (27k) show a slight preference for mCB2 and hCB2 over rCB1. Noteworthy is the tetrahydropyran analog (27m), which exhibits a significant selectivity for CB2 over CB1 receptor. Thus, comparison of the binding data of analogs in Table 2.1 suggests that the presence of the two C1' methyl groups enhanced the ligands affinity for both the CB1 and CB2 receptors. The results of this table indicate that, the size of the substituent at C1' position has an effect on the affinities of the analogs for both the CB1 and CB2 receptors. For the CB2 receptor, this effect is optimized in the C1' tetrahydropyran analog (27m), which shows a significant preference for mouse and human CB2 over rat CB1 (34- and 16-fold respectively).
Comparison of SAR of (+)-CBD with SAR of tri-cyclic cannabinoids

The side chain of tri-cyclic cannabinoids is the most critical pharmacophore. Extension of the \( n \)-pentyl group side chain of natural cannabinoids from five to seven carbons with the \( 1', 1' \)-dimethyl group led to enhancement of CB receptor binding. This trend was also seen when \( n \)-pentyl group was replaced with \( 1', 1' \)-dimethyl heptyl group for (+)-CBD’s. Side chains bearing \( 1', 1' \)-cyclic moieties in classical tri-cyclic cannabinoids\(^{169} \) also had high affinities for the CB1 and CB2 receptors as observed with (+)-CBD’s. Unsaturation within the side chain was also tolerated in classical cannabinoids and was also observed with (+)-CBD. Interestingly, the adamantyl group in tri-cyclic cannabinoids results in analogs that are CB1 selective whereas in SAR of (+)-CBD’s, the adamantyl group resulted in selectivity towards the mouse CB2 receptor.\(^67 \)

Table 2.2: Affinities of (+)-CBD’s with bromo-substituted \( 1',1' \)-dimethylalkyl side chains

![Side chain structure](image)

Table 2.2 (a): Affinities of Br-substituted terminal side-chain carbon (+)-CBD’s

<table>
<thead>
<tr>
<th>AM #</th>
<th>R</th>
<th>( K_i ) (nM)</th>
<th>rCB1 (brain)</th>
<th>mCB2 (HEK)</th>
<th>hCB2 (HEK)</th>
<th>rCB1/mCB2</th>
<th>rCB1/hCB2</th>
</tr>
</thead>
<tbody>
<tr>
<td>27a</td>
<td>( r' )</td>
<td>2.3±0.6</td>
<td>4.1±1.4</td>
<td>4.6±0.2</td>
<td>0.6</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>AM9201</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Our optimization strategy for synthesis of CB-2 selective and peripheral acting agonists was centered on decreasing brain penetration (by increasing tPSA and lowering ClogP) while maintaining affinity and potency. Thus polar groups such as cyano and morphalino were incorporated, the length of the lipophilic side chain was reduced and heterocyclic groups containing oxygen was added to the C1’ position.

Table 2.2a summarizes the data obtained for different length C1' dimethyl side chains, terminally substituted with bromide. This was performed in order to explore the pharmacophoric limits of the side chain length. The bromide group also enables functionalization of the terminal side chain carbon by nucleophilic displacement reactions. As seen in analog (27c), substitution of the terminal side chain methyl group of the heptyl side chain (27a) with Br results in good affinity for both the CB1 and CB2 receptors. The shorter 6-C Br side chain AM 9250 (27l) also retained nM affinity for both receptors. Reduction of the chain length to 4-C resulted in loss in affinity (27g). The 5-C (27g) and the 4-C (27i) analogs showed mCB2 and hCB2 selectivity over CB1, respectively. In summary, our results indicate that in analogs bearing a bromo substituent

<table>
<thead>
<tr>
<th></th>
<th>Structure</th>
<th>K&lt;sub&gt;i&lt;/sub&gt;</th>
<th>K&lt;sub&gt;i&lt;/sub&gt;</th>
<th>K&lt;sub&gt;i&lt;/sub&gt;</th>
<th>K&lt;sub&gt;i&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>27c</td>
<td>AM9208</td>
<td>1.4±0.3</td>
<td>0.9±0.7</td>
<td>1.6±0.6</td>
<td>1.5</td>
</tr>
<tr>
<td>27l</td>
<td>AM9250</td>
<td>1.5±0.8</td>
<td>2.5±0.7</td>
<td>2.9±0.4</td>
<td>0.6</td>
</tr>
<tr>
<td>27g</td>
<td>AM9216</td>
<td>33.3±10.3</td>
<td>5.8±3.8</td>
<td>7.4±1.4</td>
<td>5.7</td>
</tr>
<tr>
<td>27i</td>
<td>AM9227</td>
<td>378.0±31</td>
<td>79.2±12</td>
<td>106±9.6</td>
<td>4.7</td>
</tr>
</tbody>
</table>

*K<sub>i</sub> values were obtained from three independent experiments run in triplicate and are expressed as the mean±SD.
at the terminal carbon, the order of decreasing affinity for the CB1 receptor was 7 carbons = 6 carbons > 5 carbons > 4 carbons. The shorter 5-C and 4-C analogs were more CB2-selective.

**Table 2.2 (b):** Affinities of CN-substituted terminal side-chain carbon (+)-CBD’s

<table>
<thead>
<tr>
<th>AM #</th>
<th>R</th>
<th>(K_i) (nM)</th>
<th>rCB1 (brain)</th>
<th>mCB2 (HEK)</th>
<th>hCB2 (HEK)</th>
<th>rCB1/mCB2</th>
<th>rCB1/hCB2</th>
</tr>
</thead>
<tbody>
<tr>
<td>27a</td>
<td><img src="image1.png" alt="Image of AM9201" /></td>
<td>2.3±0.6</td>
<td>4.1±1.4</td>
<td>4.6±0.2</td>
<td>0.6</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>47</td>
<td><img src="image2.png" alt="Image of AM9234" /></td>
<td>0.9±0.8</td>
<td>4.1±1.0</td>
<td>2.6±0.07</td>
<td>0.3</td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td>52</td>
<td><img src="image3.png" alt="Image of AM9252" /></td>
<td>1.2±0.6</td>
<td>2.1±0.1</td>
<td>0.9±0.8</td>
<td>0.6</td>
<td>1.3</td>
<td></td>
</tr>
<tr>
<td>48</td>
<td><img src="image4.png" alt="Image of AM9217" /></td>
<td>30.4±2.1</td>
<td>12.3±1.7</td>
<td>9.5±1.3</td>
<td>2.4</td>
<td>3.1</td>
<td></td>
</tr>
<tr>
<td>53</td>
<td><img src="image5.png" alt="Image of AM9228" /></td>
<td>596±70.5</td>
<td>49.7±8.2</td>
<td>41.1±18.4</td>
<td>120</td>
<td>14.5</td>
<td></td>
</tr>
</tbody>
</table>

*Ki* values were obtained from three independent experiments run in triplicate and are expressed as the mean±SD.

Based on the binding affinity of the bromo analogs, the CN group was incorporated to explore the role of a polar group at the terminal carbon and to eliminate potential toxicity of the alkyl bromide functionality. The nitrile group in drugs is quite prevalent, with
around 30 drugs currently on the market. The nitrile group is fairly robust and not metabolized readily.\textsuperscript{180} In most nitrile-containing drugs, the nitrile group is passed through the body unchanged. The C≡N unit is around eight times smaller than a methyl group. Crystal structures have shown that the nitrile group projects into narrow clefts to make polar interactions or hydrogen bonds in sterically packed areas.\textsuperscript{178} Nitriles also act as hydrogen bond acceptors.\textsuperscript{179} Several crystal structures have shown hydrogen bonding between the nitrile nitrogen and amino acids (serine or arginine) or water. The strong dipole of the C≡N group also facilitates polar interactions and it can act as an isostere of hydroxyl or carboxyl groups.\textsuperscript{180}

The effect of the cyano substitution on the terminal carbon is shown in \textit{Table 2.2b}. Substitution of the terminal methyl groups with a cyano group resulted in high-affinity ligands AM 9234 (47) and AM9252 (52). The 6-C analog (52) had marginal higher binding affinity towards the hCB2 and mCB2 receptor compared to the 7-C analog (47). Thus 6-C and 7-C lengths are optimal for CB binding with little selectivity between CB1 and CB2 receptors. Compared to the bromo analogs in \textit{Table 2.2a}, the 5-C analog (48) and the 4-C analog (53) were more CB2 selective. The CN group adds polarity to a compound which is attested by the tPSA and ClogP values of analogs AM 9227 (tPSA = 60.7, ClogP = 4.9) and AM 9228 (tPSA = 84.5, ClogP = 3.4).
Table 2.3: Affinities of 1',1',6'-chain substituted (+)-CBD’s

![Chemical structure](attachment:image.png)

<table>
<thead>
<tr>
<th>AM #</th>
<th>R</th>
<th>$K_i$ (nM)</th>
<th>rCB1/mCB2</th>
<th>rCB1/ hCB2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>rCB1 (brain)</td>
<td>mCB2 (HEK)</td>
<td>hCB2 (HEK)</td>
</tr>
<tr>
<td>27l</td>
<td>AM9250</td>
<td>1.5±0.8</td>
<td>2.5±0.7</td>
<td>2.9±0.4</td>
</tr>
<tr>
<td>27j</td>
<td>AM9231</td>
<td>16.6±7.3</td>
<td>5.1±1.1</td>
<td>11.1±4.4</td>
</tr>
<tr>
<td>27h</td>
<td>AM9219</td>
<td>14.0±1.8</td>
<td>10.8±2.1</td>
<td>17.5±2.2</td>
</tr>
<tr>
<td>52</td>
<td>AM9252</td>
<td>1.2±0.6</td>
<td>2.1±0.1</td>
<td>0.9±0.8</td>
</tr>
<tr>
<td>51</td>
<td>AM9222</td>
<td>8.6±0.05</td>
<td>5.5±1.7</td>
<td>10.3±3.3</td>
</tr>
<tr>
<td>84</td>
<td>AM9251</td>
<td>1.4±0.6</td>
<td>1.7±0.2</td>
<td>1.4±0.0</td>
</tr>
<tr>
<td>81</td>
<td>AM9220</td>
<td>21.6±1.7</td>
<td>7.2±1.4</td>
<td>10.0±0.9</td>
</tr>
</tbody>
</table>

*$K_i$ values were obtained from three independent experiments run in triplicate and are expressed as the mean±SD.

Based on previous results generated from the SAR study in Tables 2.1, 2.2a, and 2.2b, the 6-C and 7-C length side chains appeared optimal for CB receptor binding. Thus in
order to probe the size and nature of the C1' substitution in terminally 6-C functionalized side chain, analogs in Table 2.3 were synthesized. When comparing the 6-C bromo analogs, our results indicate that the order of binding affinity towards the CB1 receptor is dimethyl (27l) > cyclobutyl (27h) ≈ cyclopentyl (27j). However for the CB2 receptors, the binding affinities follows dimethyl (27l) > cyclopentyl (27j) > cyclobutyl (27h). When comparing the 6-C cyano analogs, the dimethyl heptyl analog (52) shows higher binding affinities for both the CB1 and CB2 receptors compared to the cyclobutyl analog (51). The same effect is seen for the azido analogs 81 and 84. Thus, the general trend observed is that the C1'-dimethyl hexyl side chains have good binding affinity for both the CB1 and CB2 receptors as compared to the C1’ cycloalkyl with 6-C substitution. Also as observed earlier with non-substituted side chains, bulky substituents at C1' position show slight preference for CB2.

Comparison of SAR of (+)-CBD with SAR of tri-cyclic cannabinoids

Terminal substitution of carbon with halogens, cyano, azido and isothicyanato groups were well tolerated in tri-cyclic cannabinoids. This trend was also visualized in the SAR of (+)-CBD’s. Decrease in side chain length from 7-C and 6-C to 5-C and 4-C in tri-cyclic cannabinoids led to compounds that were CB2-selective. This SAR trend was also visualized in the (+)-CBD’s.
**Table 2.4:** Affinities of phenolic hydroxyl and terminal carbon side chain substituted (+)-CBD’s

![Chemical Structure](image)

<table>
<thead>
<tr>
<th>AM#</th>
<th>R₁</th>
<th>R₂</th>
<th>Kᵢ (nM)</th>
<th>rCB1/ mCB2</th>
<th>rCB1/ hCB2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>rCB1 (brain)</td>
<td>mCB2 (HEK)</td>
<td>hCB2 (HEK)</td>
</tr>
<tr>
<td>62 AM9229</td>
<td>OTBS</td>
<td>&gt;1000</td>
<td>&gt;1000</td>
<td>&gt;1000</td>
<td>-</td>
</tr>
<tr>
<td>58 AM9245</td>
<td>OCH₃</td>
<td>194±32</td>
<td>59±13.4</td>
<td>20.2±4.5</td>
<td>3.3</td>
</tr>
<tr>
<td>60 AM9247</td>
<td>OCH₃</td>
<td>70.4±16</td>
<td>16.0±4</td>
<td>18.1±2.7</td>
<td>4.4</td>
</tr>
<tr>
<td>59 AM9246</td>
<td>OCH₃</td>
<td>739±53</td>
<td>262±37</td>
<td>20±16</td>
<td>2.8</td>
</tr>
<tr>
<td>55 AM9239</td>
<td>OCH₃</td>
<td>3.4±1.0</td>
<td>5.4±1.6</td>
<td>1.0±0.8</td>
<td>0.6</td>
</tr>
<tr>
<td>56 AM9254</td>
<td>OCH₃</td>
<td>11.9±0.8</td>
<td>4.5±0.6</td>
<td>13.7±1.4</td>
<td>2.6</td>
</tr>
</tbody>
</table>

*Kᵢ values were obtained from three independent experiments run in triplicate and are expressed as the mean±SD.
From the SAR results in Table 2.1, 2.2 (b), 2.2 (c), and 2.3, addition of dimethyl heptyl group at the C1’ position led to compounds with high affinity to the CB receptors as well as selectivity for the CB2 receptor. Thus we retained the side chain pharmacophore of dimethyl pentyl and heptyl side chains and investigated the role of modifying the phenolic hydroxyl group.

Table 2.4 summarizes the data obtained for the phenyl ring hydroxyl modified compounds. As seen for AM 9229 (62), protection of the phenolic group with the bulky TBDMS group resulted in complete loss of binding affinity for both the CB1 and CB2 receptors. This suggests that the bulky TBDMS group is too large to fit into the receptor’s binding pocket region into where the –OH groups fit. In all compounds containing R1=OCH₃, 55, 58, 59, and 60, a general CB2 selectivity trend can be seen. All compounds showed a slight preference for hCB2 over mCB2 with the exception of AM 9254 (56) and AM 9247 (60), which was equally selective for both the CB2 receptors. The mouse CB2 receptor exhibits only 82% sequence identity with the human CB2 receptors.¹¹ This divergent nature of mCB2 and hCB2 receptors might be a reason why species-based differences in affinity are sometimes seen. The best compounds in terms of over all CB1 and CB2 binding affinity are AM 9239 (55) and AM9254 (56). This implies that the hydrogen-donating ability of the OH group is not necessary for binding. The morpholino analog 60 can be made into a salt for oral formulation.¹⁸¹,¹⁸²,¹⁸³
Comparison of SAR of (+)-CBD with SAR of tri-cyclic cannabinoids

Replacement of phenolic hydroxyl by methoxy in tri-cyclic cannabinoids led to loss of activity.\textsuperscript{184,185} In some cases binding is retained and favored CB2-selectivity.\textsuperscript{186} However, in the SAR of (+)-CBD, analogs were found to have CB2 selectivity.

**Table 2.5:** Affinities of northern-end (+)-CBD analogs

<table>
<thead>
<tr>
<th>AM#</th>
<th>X</th>
<th>$K_i$ (nM)</th>
<th>rCB1 (brain)</th>
<th>mCB2 (HEK)</th>
<th>hCB2 (HEK)</th>
<th>rCB1/ mCB2</th>
<th>rCB1/ hCB2</th>
</tr>
</thead>
<tbody>
<tr>
<td>26a AM9200</td>
<td>OCOCH$_3$</td>
<td>25.0±9.2</td>
<td>26.6±6.7</td>
<td>51.6±10.7</td>
<td>0.9</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>27a AM9201</td>
<td>OH</td>
<td>2.3±0.6</td>
<td>4.1±1.4</td>
<td>4.6±0.2</td>
<td>0.6</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>65 AM9258</td>
<td>N$_3$</td>
<td>26.4±2.5</td>
<td>22.9±0.3</td>
<td>27.5±2.5</td>
<td>1.1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>66 AM9236</td>
<td>NCS</td>
<td>42.4±11</td>
<td>117±29</td>
<td>92±3.6</td>
<td>0.4</td>
<td>0.4</td>
<td></td>
</tr>
</tbody>
</table>

*$K_i$ values were obtained from three independent experiments run in triplicate and are expressed as the mean±SD.*
Retaining the dimethyl heptyl side chain and phenolic hydroxyl pharmacophore, the northern end of the (+)-CBD template was modified to select the northern end pharmacophore.

Table 2.5 summarizes the binding data from the northern end modified analogs. Replacement of the allylic alcohol with acetate (26a), azido (65) and isothiocyanate (66) groups all decreased binding affinities for the CB1 and CB2 receptors compared to AM 9201(27a). Interestingly, a significant loss of binding affinity is observed when OH is substituted with NCS. This result demonstrates that the hydrogen donor and accepting ability of the OH group is necessary for optimal binding of 27a to the CB receptor. Northern end modifications did not affect selectivity drastically for the CB1 and CB2 receptors, nor did it affect relative binding affinities between mouse and human CB2 receptors. Thus free hydroxyl is the optimal group for low nanomolar binding affinity.

**Comparison of SAR of (+)-CBD with SAR of tri-cyclic cannabinoids**

The hydroxyl group at the C-11 position of tri-cyclic cannabinoids led to a significant enhancement in affinity and potency for the cannabinoid receptors. This trend was also seen in (+)-CBD, where the northern end hydroxyl group was optimal for binding. 67
Table 2.6: cAMP and β-arrestin data of (+)-CBD analogs

![Chemical structure]

cAMP of $[^3H]$ CP-55,940

rCB1 EC$_{50}$ = 4.0 ± 1.9 nM, % Efficacy = 62.0 ± 9.9 (Mean ±SD)

hCB2 EC$_{50}$ = 9.1 ± 0.5 nM, % Efficacy = 78.0 ± 4.0 (Mean ±SD)

<table>
<thead>
<tr>
<th>AM#/compound#</th>
<th>R1</th>
<th>R2</th>
<th>R3</th>
<th>cAMP* nM/%efficacy</th>
<th>β-arrestin* hCB1 nM</th>
<th>hCB2 nM</th>
</tr>
</thead>
<tbody>
<tr>
<td>26a 9200</td>
<td>OCOCH$_3$</td>
<td>OH</td>
<td></td>
<td>9.4- 45% n.d</td>
<td>9.6- 56%</td>
<td>n.d</td>
</tr>
<tr>
<td>27a 9201</td>
<td>OH</td>
<td>OH</td>
<td></td>
<td>16.8- 61% n.d</td>
<td>16.0- 39%</td>
<td>1660</td>
</tr>
<tr>
<td>26c 9207</td>
<td>OCOCH$_3$</td>
<td>OH</td>
<td>Br</td>
<td>20.4- 62% n.d</td>
<td>0.8- 45%</td>
<td>n.d</td>
</tr>
<tr>
<td>27c 9208</td>
<td>OH</td>
<td>OH</td>
<td>Br</td>
<td>0.8- 32% 2.4- 53%</td>
<td>4.6- 39%</td>
<td>n.d</td>
</tr>
<tr>
<td>27d 9210</td>
<td>OH</td>
<td>OH</td>
<td></td>
<td>267- 84% n.d</td>
<td>292</td>
<td>379</td>
</tr>
<tr>
<td>27e 9212</td>
<td>OH</td>
<td>OH</td>
<td></td>
<td>176- 81% n.d</td>
<td>267</td>
<td>9.3</td>
</tr>
<tr>
<td>27f 9214</td>
<td>OH</td>
<td>OH</td>
<td></td>
<td>1.6- 58% n.d</td>
<td>1820</td>
<td>5.5</td>
</tr>
<tr>
<td>27g 9216</td>
<td>OH</td>
<td>OH</td>
<td>Br</td>
<td>20.9- 91% n.d</td>
<td>1690</td>
<td>2.3</td>
</tr>
<tr>
<td>48 9217</td>
<td>OH</td>
<td>OH</td>
<td>CN</td>
<td>13.1- 67.5% n.d</td>
<td>3080</td>
<td>238</td>
</tr>
<tr>
<td></td>
<td>9218</td>
<td>OCOCH₃</td>
<td>OH</td>
<td>![Chemical Structure]</td>
<td>n.d</td>
<td>5600</td>
</tr>
<tr>
<td>---</td>
<td>--------</td>
<td>---------</td>
<td>----</td>
<td>-----------------------</td>
<td>------</td>
<td>--------</td>
</tr>
<tr>
<td>26h</td>
<td>9219</td>
<td>OH</td>
<td>OH</td>
<td>![Chemical Structure]</td>
<td>16.4-79% n.d</td>
<td>No response</td>
</tr>
<tr>
<td>27h</td>
<td>9219</td>
<td>OH</td>
<td>OH</td>
<td>![Chemical Structure]</td>
<td>3.2-83% n.d</td>
<td>n.d 5900</td>
</tr>
<tr>
<td>51</td>
<td>9222</td>
<td>OH</td>
<td>OH</td>
<td>![Chemical Structure]</td>
<td>n.d n.d</td>
<td>n.d 7510</td>
</tr>
<tr>
<td>83</td>
<td>9225</td>
<td>OH</td>
<td>OH</td>
<td>![Chemical Structure]</td>
<td>n.d n.d</td>
<td>n.d 266000</td>
</tr>
<tr>
<td>53</td>
<td>9228</td>
<td>OH</td>
<td>OH</td>
<td>![Chemical Structure]</td>
<td>53.3-80% n.d 10.7-34%</td>
<td>n.d 24.9</td>
</tr>
<tr>
<td>47</td>
<td>9234</td>
<td>OH</td>
<td>OH</td>
<td>![Chemical Structure]</td>
<td>2.2-86% n.d 2.3-46%</td>
<td>7300 457</td>
</tr>
<tr>
<td>70</td>
<td>9242 (-)-CBD</td>
<td>OH</td>
<td>OH</td>
<td>![Chemical Structure]</td>
<td>389-61% n.d n.d</td>
<td>288 0.14</td>
</tr>
<tr>
<td>58</td>
<td>9245</td>
<td>OH</td>
<td>OCH₃</td>
<td>![Chemical Structure]</td>
<td>523-60% n.d n.d</td>
<td>n.d</td>
</tr>
<tr>
<td>59</td>
<td>9246</td>
<td>OH</td>
<td>OCH₃</td>
<td>![Chemical Structure]</td>
<td>n.d 86.0-26% 100.0-31%</td>
<td>n.d</td>
</tr>
<tr>
<td>60</td>
<td>9247</td>
<td>OH</td>
<td>OCH₃</td>
<td>![Chemical Structure]</td>
<td>50.4-51% n.d 6.7-28%</td>
<td>n.d</td>
</tr>
<tr>
<td>49</td>
<td>9248</td>
<td>OH</td>
<td>OH</td>
<td>![Chemical Structure]</td>
<td>1.4-88% n.d 0.4-42%</td>
<td>84.7 0.03</td>
</tr>
<tr>
<td>27i</td>
<td>9250</td>
<td>OH</td>
<td>OH</td>
<td>![Chemical Structure]</td>
<td>14.1-81% n.d 2.5-44%</td>
<td>0.1 0.008</td>
</tr>
<tr>
<td>84</td>
<td>9251</td>
<td>OH</td>
<td>OH</td>
<td>![Chemical Structure]</td>
<td>8.6-64% n.d 0.3-62%</td>
<td>0.2 0.002</td>
</tr>
<tr>
<td>52</td>
<td>9252</td>
<td>OH</td>
<td>OH</td>
<td>![Chemical Structure]</td>
<td>0.08-25% 0.9-61% n.d</td>
<td>0.1 0.00004</td>
</tr>
<tr>
<td>85</td>
<td>9253</td>
<td>OH</td>
<td>OH</td>
<td>![Chemical Structure]</td>
<td>6.4-90% n.d 1.4-41%</td>
<td>1390 0.3</td>
</tr>
</tbody>
</table>
The functional potency of cannabidiol analogs tested in cAMP and β-arrestin assays are tabulated in Table 2.6. None of the compounds tested were antagonists in either the cAMP or the β-arrestin assay for CB1 or CB2 receptors. The functional potency of the analogs was compared to the agonist WIN-55212 in the β-arrestin assay and CP-55,940 in the cAMP assay. AM 9252 is a potent partial agonist at the CB1 receptor (EC₅₀ = 0.08 nM, 25% efficacy) and agonist at the mCB2 receptor (EC₅₀ = 0.9 nM, 61% efficacy) in the cAMP assay. It is also a highly potent agonist at the CB2 receptor in the β-arrestin assay (EC₅₀ = 0.00004 nM). The azido probe AM 9251 was also a potent agonist at the hCB2 receptor in the β-arrestin assay (EC₅₀ = 0.002 nM). The functional data suggest that the analogs in Table 2.6 do not show biased agonism i.e., they activate both downstream signaling pathways.
Figure 2.9: Binding affinity and cAMP data for AM 9257

![Chemical structure of AM 9257](image)

**AM 9257 (68)**

<table>
<thead>
<tr>
<th>Receptor</th>
<th>IC&lt;sub&gt;50&lt;/sub&gt; Value (nM)</th>
<th>Efficacy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>rCB1</td>
<td>18.5 ± 4.3</td>
<td>81</td>
</tr>
<tr>
<td>mCB2</td>
<td>19.0 ± 2.6</td>
<td></td>
</tr>
<tr>
<td>hCB2</td>
<td>28.8 ± 1.6</td>
<td></td>
</tr>
</tbody>
</table>

(Expressed as mean ± S.D)

cAMP

<table>
<thead>
<tr>
<th>Receptor</th>
<th>IC&lt;sub&gt;50&lt;/sub&gt; Value (nM)</th>
<th>Efficacy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>rCB1</td>
<td>30.9</td>
<td>81</td>
</tr>
<tr>
<td>hCB2</td>
<td>38.9</td>
<td>74</td>
</tr>
</tbody>
</table>

It is worthy to note the binding affinity and cAMP results of AM 9257 (68) (Figure 2.9). The ability of AM 9257 to activate the rat CB1 and human CB2 receptors was assessed in the functional cAMP assay using HEK-293 cells expressing recombinant cannabinoid receptors. In both the rat CB1 and human CB2 receptors, AM 9257 showed a concentration-dependent inhibition of forskolin-induced cAMP accumulation with an IC<sub>50</sub> value of 30.9 nM (maximum inhibition of 81%) and an IC<sub>50</sub> value of 38.9 nM (maximum inhibition of 74%). Interestingly, this tricyclic cis-fused ring compound also binds with good nanomolar affinity to the CB receptors.
Scheme 2.24: Cyclization of (+)-CBD

Cyclization of (+)-CBD (Scheme 2.24) under BF$_3$-etherate conditions leads to tricyclic (+)-$\Delta^9$-THC that does not bind to the cannabinoid receptors with high affinity.$^{187}$ However, the cyclization of (+)-AM9232 (63) under TBAF conditions (Scheme 2.18-Page 62) led to a tricyclic compound that binds to the cannabinoid receptors and activates them as an agonist. This was an unexpected discovery and a good starting point for the development of a new class of cannabergic analogs where the classical pyran ring is replaced by a furan ring (ring contraction).

Figure 2.10: Comparison of 7-OH-dimethyl heptyl CBD enantiomers

<table>
<thead>
<tr>
<th>Enantiomer</th>
<th>$K_i$ (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>rCB1</td>
<td>2.3 ± 0.6</td>
</tr>
<tr>
<td>mCB2</td>
<td>4.1 ± 1.4</td>
</tr>
<tr>
<td>hCB2</td>
<td>4.6 ± 0.2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Enantiomer</th>
<th>$K_i$ (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>rCB1</td>
<td>83.2 ± 21.5</td>
</tr>
<tr>
<td>mCB2</td>
<td>57.1 ± 11.1</td>
</tr>
<tr>
<td>hCB2</td>
<td>70.6 ± 8.2</td>
</tr>
</tbody>
</table>
Binding results in *Figure 2.10* indicate that, (1S,6S)-7-OH-dimethyl heptyl CBD (27a) binds to the CB receptors in the low-nanomolar range, whereas the (1R,6R)-7-OH-dimethyl heptyl CBD (70), binds moderately to the CB receptors (*Figure 2.10*), is in sharp contrast to the literature binding data.\(^{137,141,146}\) (CB1 = 4.4 µM, CB2 = 0.67 µM for 70). This discrepancy might be due to different assay conditions under which the testing was performed ([\(^3\)H]-HU-243 was used as the radioligand and COS-2 cells were used for transfection of CB2 cDNA in the literature).

**Figure 2.11:** cAMP concentration-response curves of AM 9201 for rCB1 and hCB2

![cAMP concentration-response curves of AM 9201 for rCB1 and hCB2](image)

According to the cAMP results (*Figure 2.11* and *Table 2.6*), AM 9201 showed a concentration-dependent inhibition of forskolin-induced cAMP accumulation with an IC\(_{50}\) value of 16.8 nM (maximum inhibition of 61%) at the CB1 receptor and an IC\(_{50}\) value of 16.0 nM (maximum inhibition of 39%) at hCB2 receptor. Thus AM 9201 is equipotent at both receptors but acts as an agonist at the rCB1 and a partial agonist at the hCB2 receptor. It is also an agonist at CB1 and CB2 receptors in the β-arrestin assay (*Table 2.6*). AM 9242, on the other hand is a potent agonist at CB2 receptor in the β-
arrestin assay with EC$_{50}$ of 0.14 nM. However in the cAMP assay it was not as potent for the rCB1 compared to its enatiomer AM 9201 (IC$_{50}$ value of 389.2 nM, maximum inhibition of 61%).

**Figure 2.12**: Binding affinities for C1' tetrahydropyranyl bicyclic analogs

Replacement of cyclohexane ring of AM 8119 with the tetrahydropyranyl ring in AM 9259 resulted in a more (85-fold) hCB2 selective compound (**Figure 2.12**). Enantiomers AM 9259 and AM 9260 were selective for hCB2 receptor. Interestingly, both AM 9259 and AM 9260 are antagonists at the CB1 receptors but agonists at the CB2 receptors (**Figure 2.13, 2.14**) in the β-arrestin assay. The cAMP results of AM 9260 also confirm the antagonist behavior of AM 9260 at rCB1, as an agonist response was not obtained (data not shown). This result is highly desirable, as CB1 antagonists do not produce the psychotrophic side effects that CB1 agonists produce and thus the CB2 agonist effect can be taken advantage for the development of CB2 analgesic ligands. Several studies have
established that CB2 selective ligands modulate/reduce pain (acute and neuropathic) and do not produce psychoactive effects associated with CB1 receptor activation. CB2 agonists can also show therapeutic potential for suppressing neuropathic pain without producing tolerance.

**Figure 2.13:** β-arrestin curve of AM 9259 showing CB1 antagonism

**Figure 2.14:** β-arrestin curve of AM 9260 showing CB2 agonism
Table 2.7: Comparison of binding affinities of enantiomeric (1R,4S,5S) and (1S,4R,5R) verbenol analogs

<table>
<thead>
<tr>
<th></th>
<th>AM 9256 (72g)</th>
<th>AM 9267 (74g)</th>
<th>AM 9262 (72n)</th>
<th>AM 9261 (74n)</th>
<th>AM 9271 (72a)</th>
<th>AM 9272 (74a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>rCB1</td>
<td>19.5 ± 0.2 nM</td>
<td>18.1 ± 0.7 nM</td>
<td>12.6 ± 0.6 nM</td>
<td>45.1 ± 3.1 nM</td>
<td>5.7 ± 0.5 nM</td>
<td>46.9 ± 5.2 nM</td>
</tr>
<tr>
<td>mCB2</td>
<td>4.6 ± 1.6 nM</td>
<td>4.8 ± 0.8 nM</td>
<td>1.7 ± 0.5 nM</td>
<td>24.9 ± 4.5 nM</td>
<td>2.4 ± 0.4 nM</td>
<td>23.7 ± 7.2 nM</td>
</tr>
<tr>
<td>hCB2</td>
<td>3.5 ± 0.5 nM</td>
<td>16.6 ± 4.3 nM</td>
<td>4.5 ± 1.2 nM</td>
<td>20.4 ± 3.2 nM</td>
<td>2.8 ± 0.7 nM</td>
<td>29.8 ± 4.1 nM</td>
</tr>
</tbody>
</table>

*Values were obtained from three independent experiments run in triplicate and are expressed as the mean±SD.

Binding affinities of enantiomeric (1R,4S,5S) and (1S,4R,5R) analogs in Table 2.7 showed that the (1R,4S,5S) enantiomer (compounds 72g, 72n and 72a) bound with higher affinity to CB receptors compared to the (1R,4S,5S) enantiomer (compounds 74g, 74n, 74a). Most of the analogs were also slightly CB2-selective with the exception of AM 9267.
**Table 2.8:** Binding affinity of (1R,4S,5S) verbenol analogs

<table>
<thead>
<tr>
<th>Analog</th>
<th>rCB1</th>
<th>mCB2</th>
<th>hCB2</th>
<th>R</th>
</tr>
</thead>
<tbody>
<tr>
<td>AM 9268 (72o)</td>
<td>10.9 ± 1.5 nM</td>
<td>1.9 ± 0.2 nM</td>
<td>2.6 ± 0.4 nM</td>
<td>Br</td>
</tr>
<tr>
<td>AM 9269 (72d)</td>
<td>19.2 ± 3.1 nM</td>
<td>4.4 ± 1.7 nM</td>
<td>6.7 ± 0.07 nM</td>
<td>S</td>
</tr>
<tr>
<td>AM 9270 (72h)</td>
<td>4.5 ± 0.4 nM</td>
<td>2.1 ± 0.8 nM</td>
<td>6.7 ± 0.07 nM</td>
<td>Br</td>
</tr>
<tr>
<td>AM 9273 (72k)</td>
<td>619 ± 200.0 nM</td>
<td>8.0 ± 2.1 nM</td>
<td>114.0 ± 16.0 nM</td>
<td></td>
</tr>
</tbody>
</table>

*K* values were obtained from three independent experiments run in triplicate and are expressed as the mean±SD.

Based on the results in **Table 2.7**, analogs in the (1R,4S,5S) series were synthesized and evaluated for CB receptor binding (**Table 2.8**). These analogs show slight preference to the CB2 receptor with the exception of AM 9273. This compound exhibited some species selectivity (more selective for the mCB2 receptor compared to hCB2).
Table 2.9: Functional evaluation of verbenol analogs

<table>
<thead>
<tr>
<th>AM #</th>
<th>cAMP IC$_{50}$(nM), % maximal efficacy</th>
<th>β-arrestin (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>rCB1</td>
<td>hCB2</td>
</tr>
<tr>
<td>72g</td>
<td>9256</td>
<td>1.8–42%</td>
</tr>
<tr>
<td>72n</td>
<td>9262</td>
<td>n.d</td>
</tr>
<tr>
<td>74g</td>
<td>9267</td>
<td>16.1–59%</td>
</tr>
<tr>
<td>72o</td>
<td>9268</td>
<td>3.5–89%</td>
</tr>
<tr>
<td>72d</td>
<td>9269</td>
<td>20.8–38%</td>
</tr>
<tr>
<td>72h</td>
<td>9270</td>
<td>8.7–38%</td>
</tr>
<tr>
<td>72a</td>
<td>9271</td>
<td>32.5–116%</td>
</tr>
<tr>
<td>74a</td>
<td>9272</td>
<td>2.5–64%</td>
</tr>
</tbody>
</table>

*Data from single experiment done in triplicate

All verbenol analogs in Table 2.9 were found to be agonists or partial agonists in cAMP and β-arrestin assays for the CB1 and CB2 receptors.

Evaluation of lead compounds

Another aspect of developing a successful SAR is to correlate structure and biological activity (in vitro and in vivo). Many highly potent and efficacious drugs from SAR studies often have poor PK properties. It is essential to ensure that efforts during the development of SAR are concentrated in weeding out compounds with poor properties (e.g. low solubility and permeability, short half-life and low bioavailability). According to many drug databases most successful drugs usually have ‘drug-like properties’. This concept of drug likeness is used as a tool in drug design. At the in vivo level, drug likeness is related to safety and PK. These in vivo properties result from an interaction of physicochemical and structural properties, such as solubility, permeability and stability,
which can be studied in vitro. Molecular properties such as hydrogen bonding, polarity and molecular weight are categorized under Lipinski’s Rule of five and are profiled in silico. Most pharmaceutical small molecule oral drugs on the market have a molecular weight less than 500 g, less than 5 hydrogen bond donors, less than 10 hydrogen bond acceptors and a ClogP of less than 5 (Lipinski’s Rule of 5). Even though this rule has limitations, it serves as a guide in designing drug-like compounds. Since viable drug candidates require both activity and drug-like properties, it is important to test drug-like properties during early discovery in order to avoid development failures during later stages. An overall evaluation is necessary to determine modification to the structure that will optimize the overall activity of the drug. The design of drugs using drug-like properties, termed ‘structure-property relationships’ (SPR), complements SAR. These two strategies together will help in identifying poor candidates.

Four lead analogs were selected for further evaluation based on the binding affinities to the cannabinoid receptor, physicochemical properties (ClogP and tPSA), and synthetic chemical amenability. Molecular properties of compounds can affect biodistribution and thus ClogP and tPSA were used as the first approach criteria for ‘drugability’. AM 9201 was selected as the lipophilic lead, whereas AM 9217, AM 9248 and AM 9252 were the polar lead analogs. The depot effect exhibited by lipophilic drug analogs can be modulated by manipulating the polarity of the compound by the addition of groups such as cyano, morpholino and imidazole. Polar drugs are likely to diffuse rapidly from the lipophilic tissue to the blood when compared to drugs with high lipophilicity, which tend to remain in the fatty tissues for long periods. Lipophilic drugs also have high cell
permeability, protein binding and volume of distribution, and tend to decrease solubility and renal elimination.192

Evaluation of AM 9217 (48)

Figure 2.15: Structure of AM 9217

![Structure of AM 9217](image)

Table 2.10: $K_i$ values and cAMP data of AM 9217

<table>
<thead>
<tr>
<th>$K_i$ (nM)</th>
<th>cAMP ($EC_{50}$ % maximal efficacy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>rCB1 = 30.4 ± 2.1</td>
<td>1.3 nM (68%) - agonist</td>
</tr>
<tr>
<td>mCB2 = 12.3 ± 1.7</td>
<td>n.d</td>
</tr>
<tr>
<td>hCB2 = 9.5 ± 1.3</td>
<td>1.1 nM (35%) – partial agonist</td>
</tr>
</tbody>
</table>

AM 9217 (Figure 2.15) was found to be an agonist at CB1 receptor and a partial agonist at hCB2 receptor in the cAMP assay (Table 2.10) and β-arrestin assays (Figure 2.16). Some compounds that are active in vitro are not therapeutically active in vivo and, in contrast, some compounds show better therapeutic effects in vivo. In order to investigate the in vivo efficacy of AM 9217, it was tested in rats and mice.
Figure 2.16: β-arrestin curves of WIN-55212 and AM 9217 for the CB1 and CB2 receptor

The central tetrad test is a set of behavioral tests that is used to screen drugs that induce CB1 receptor-mediated (cannabimimetic) effects in rodents. The test involves behavioral experiments to determine catalepsy, hypothermia, and analgesia. Catalepsy is determined by the rota-rod bar test. After the test drug is given, the time that the rodent remains immobile on a bar is measured. Analgesia is usually determined by the hot plate or tail immersion test. In the tail-flick test for analgesia, the rodent’s tail is placed on a heated plate, and the time elapsed before it flicks its tail from the hot plate is measured. Similarly, in the tail immersion test, the rodent tail is placed into a warm water bath, and
the time taken for the mouse to remove its tail from the water bath is measured. Hypothermia is determined by with a rectal probe to measure body temperature. CB1 agonists such as CP-55,940 and WIN-55,2122 show these tetrad test effects. On the other hand, CB antagonists or peripheral acting ligands don’t show effects in the tetrad tests.

**Figure 2.17:** Effects of AM 9217 in the rat hypothermia and tail-flick tests

![Graphs showing effects of AM 9217](image)

The *in vivo* potency of the polar analog AM 9217 was explored in the hypothermia test and tail flick tests (*Figure 2.17*) in rats. Rats were dosed s.c in a vehicle solution of 20% ethanol, 20% alkamuls, and 60% saline. In the hypothermia assay (*Figure 2.17-left*), body temperature was measured in rats over a 6 h period following drug injection. AM 9217 at a dose of 1 mg/kg did not significantly decrease core body temperature. At a higher dose of 3 mg/kg and 10 mg/kg, the onset of the drug effect occurred within 60-90 minutes after injection, with a more pronounced effect (1.5 °C drop in temperature) seen after 180 minutes, and the effect is seen until the 6th hour. The drop in temperature is not large enough to confirm that AM 9217 is an agonist. Thus from *Figure 2.17*, we can infer that AM 9217 might be a partial agonist at the CB1 receptor or it may be a peripherally acting ligand (binding to CB receptors in the periphery which is not visualized in this
Antinociception (*Figure 2.17-right*) was measured using a tail-flick procedure over a 6 hour period after drug injection. The average baseline tail-flick latency was between 1.2-2.6 seconds prior to the administration of AM 9217. At a dose of 10 mg/kg, AM 9217 produced a nociceptive effect of around 35-40% at the 180 minute.

Thus AM 9217 did not show significant hypothermia at the highest dose tested (10 mg/kg). AM 9217 had a brain to plasma ratio of 0.3 in the BBB barrier screen that was performed and this suggests that compound AM 9217 is predisposed to act in the periphery. Additionally, AM 9217 has a CLog P of 3.93 and tPSA of 84.48. All these preliminary data might suggest that this compound might be a weak partial agonist at the CB1 receptors at the highest dose tested.

Since AM 9217 produced some analgesic effect at 10 mg/kg, it would be interesting to examine the effects of AM 9217 in rodent neuropathic pain models to evaluate its potency. Research has shown that antinociceptive effects of cannabinoids are mediated via a spinal and supraspinal site of action by inhibiting hyperalgesia and allodynia in neuropathic models in rat. In order to determine if AM 9217 is peripheral acting, in vivo tests that measure peripheral activity should be performed. One such test is the ‘gastrointestinal motility test’ in rodents. The ability of a compound to inhibit defecation rate suggests that the cannabinoid analog acts peripherally.
**Figure 2.18:** Effect of AM 4054 on AM 9217

In *Figure 2.18*, agonist AM 4054 was dosed along with AM 9217. AM 4054 is a potent tricyclic cannabinoid agonist that shows central effects. At a dose of 10 mg/kg (AM 9217) and 0.3 mg/kg (AM 4054), AM 9217 attenuated the hypothermic effects produced by AM 4054, i.e. it was able to antagonize slightly the effect of AM 4054 (curve shifts towards the right). This might suggest that AM 9217 is acting as a partial agonist. AM 9217 is currently undergoing further evaluation, in order to characterize it as a partial agonist or a peripheral restricted analog.
In-vitro metabolic stability of AM 9217

Figure 2.19: Plot of % drug (AM 9217) remaining vs. time

Many good compounds exhibit low bioavailability because of high rates of metabolism by cytochrome P$_{450}$ in phase 1 oxidation reactions and phase 2 conjugation reactions. Metabolism by such enzymes tends to decrease the concentration of circulating drug and increase its elimination. Thus, testing the metabolic stability of a compound is important. These assays are usually performed with liver microsomes, hepatocytes, plasma or the S9 fraction.

To understand the preliminary PK properties of AM 9217, it was subjected to cytochrome P$_{450}$ in vitro metabolism using human liver microsomes (Courtsey of Dr. Dustin Smith). Liver microsomes contain CYP$_{450}$ oxidizing enzymes and flavin-containing monooxygenases. The concentration of AM 9217 was quantified by LC-MS/MS and the rate of compound disappearance was used to determine the compound’s metabolic stability and half-life. AM 9217 was found to have a $t_{1/2}$ of 5.34 minutes and a clearance rate of 233.6 ml/min/kg of body weight (Figure 2.19). The polar groups on this
compound (two phenolic and one primary hydroxyl) are sites for phase 2 reactions such as glucoronidation, which might explain the short $t_{1/2}$ and extensive clearance rate. In order to increase the $t_{1/2}$ of this compound, the allylic alcohol can be converted to allylic ester to increase its duration of action.

**Figure 2.20:** Structures of AM 9217 and AM 9234

Blood brain barrier (BBB) screening is an important aspect to determine if compounds enter the brain. To investigate the permeability and plasma levels of some of the (+)-CBDs that were synthesized, AM 9217 and AM 9234 (*Figure 2.20*) were given intravenously (0.25 mg/kg, two mice) and orally (2 mg/kg, four mice), and the levels of compounds were measured in the plasma and brain (Dr. Jodi Wood). For intravenous plasma, AM 9217 had a concentration of 0.04±0.01 ng/µl and AM 9234 had a concentration of 0.08±0.01 ng/µl. Thus, AM 9234 has a longer-half life than AM 9217. For IV brain, AM 9217 had a concentration of 0.01±0.003 ng/µg and AM 9234 had a concentration of 0.03±0.001 ng/µg. Thus, AM 9234 might pass through the BBB more efficiently. This may be due to AM 9234 being more lipophilic than AM 9217.

For oral plasma, AM 9217 had a concentration of 0.001±0.0005 ng/µl after 60 minutes and AM 9234 had a concentration of 0.00028±0.0008 ng/µl after 60 minutes. For oral brain, AM 9217 had a concentration of 0.001±0.0005 ng/µg after 60 minutes and AM
9234 had a concentration of 0.00038±0.00014 ng/µg after 60 minutes. The predicted oral bioavailability was similar for both compounds, ~ 0.4-0.5%. These studies may imply that IV route leads to higher levels of compound in the plasma and brain.

**Evaluation of AM 9248**

**Figure 2.21:** Structure of AM 9248

![Structure of AM 9248](image)

<table>
<thead>
<tr>
<th></th>
<th>tPSA: 73.2</th>
<th>CLGAP: 4.5</th>
</tr>
</thead>
</table>

**Table 2.11:** $K_i$ values, cAMP and β-arrestin data of AM 9248

<table>
<thead>
<tr>
<th>(K$_i$ - nM)</th>
<th>cAMP (EC$_{50}$/ % maximal efficacy)</th>
<th>β-arrestin</th>
</tr>
</thead>
<tbody>
<tr>
<td>rCB1 = 5.6 ± 2.1</td>
<td>1.4 nM (88%)- agonist</td>
<td>0.8 nM (hCB1)</td>
</tr>
<tr>
<td>mCB2 = 2.9 ± 0.4</td>
<td>n.d</td>
<td>n.d</td>
</tr>
<tr>
<td>hCB2 = 6.0 ± 0.3</td>
<td>0.4 nM (42%)- partial agonist</td>
<td>0.03 nM (hCB2)</td>
</tr>
</tbody>
</table>
Figure 2.22: β-arrestin curves of AM 9248 and WIN55212 for the hCB1 and hCB2 receptor

AM 9248 showed β-arrestin mediated biased-agonism for the hCB2 receptor (Figure 2.22). In the cAMP assay AM 9248 showed partial-agonism for the hCB2 receptor.
Figure 2.23: Effects of AM 9248 in rats in the hypothermia and tail-flick tests

Rats were dosed s.c. in a vehicle solution of 20% ethanol, 20% alkamuls, and 60% saline. The polar morpholino analog AM 9248 hardly showed any hypothermia at 3 mg/kg (**Figure 2.23**) with only a 1.5 °C drop in temperature. At a dose of 10 mg/kg, AM 9248 had around a 50% antinociceptive effect. The onset of this effect began at 60 minute and stabilized at the 180 minute. Thus this compound might be partially peripherally restricted. BBB screening of this analog is currently underway. The in vitro pharmacological effects of AM 9248 (*Table 2.11*) do not correlate with its in vivo effects. PK properties might be responsible for this discrepancy.

**Evaluation of AM 9252**

**Figure 2.24:** Structure of AM 9252

![Structure of AM 9252](image)

tPSA: 84.5
CLogP: 4.5
Table 2.12: $K_i$ values and cAMP data of AM 9252

<table>
<thead>
<tr>
<th></th>
<th>cAMP ($EC_{50}$ % maximal efficacy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>rCB1</td>
<td>$1.2 \pm 0.6$</td>
</tr>
<tr>
<td>mCB2</td>
<td>$2.1 \pm 0.1$</td>
</tr>
<tr>
<td>hCB2</td>
<td>$0.9 \pm 0.8$</td>
</tr>
<tr>
<td></td>
<td>0.08 nM (25%) - partial agonist</td>
</tr>
<tr>
<td></td>
<td>n.d</td>
</tr>
<tr>
<td></td>
<td>0.86 nM (61%) - agonist</td>
</tr>
</tbody>
</table>

Figure 2.25: cAMP curves of AM 9252 for rCB1 and hCB2 receptors

Figure 2.26: β-arrestin curves of AM 9252 and WIN55212 for the hCB1 and hCB2 receptor
AM 9252 had different functional outcomes in the cAMP and β-arrestin assays (Figures 2.25 and 2.26). In the cAMP assay (Figure 2.25), AM 9252 was a highly potent partial agonist, whereas it was an agonist at hCB2 receptor when compared to CP-55,940. In the β-arrestin assay (Figure 2.26), AM 9252 was very potent agonist at hCB1 receptor and an extremely potent agonist at the hCB2 receptor when compared to WIN-55,212. Thus AM 9248 showed β-arrestin mediated biased agonism for the hCB1 receptor.

**Figure 2.27:** Effects of AM 9252 in rat hypothermia and tail-flick tests
In order to test if the in vitro data correlate with the in vivo data, the hypothermia and tail-flick tests were carried out. Rats were dosed s.c. in a vehicle solution of 20% ethanol, 20% alkamuls, and 60% saline. As seen in Figure 2.27 (left), AM 9252 reduced core body temperature by 3.5 °C at a dose of 3 mg/kg. In the tail-flick tests Figure 2.27 (right), higher doses were tested, and AM 9252 had a maximum possible antinociceptive effect of around 90% at 10 mg/kg. The onset of the antinociceptive effect occurred between 60 and 180 minutes after injection. This compound thus had a slow onset and long duration of action and was a potent agonist in both the hypothermia and tail-flick tests. Since hypothermia and anti-nociception are centrally CB1-receptor mediated, the in vivo data of AM 9252 correlates with the β-arrestin data (potent agonists at the CB1 receptor). However, the in vivo data does not agree with the partial agonist CB1 cAMP data of AM 9252 (Table 2.12). β-arrestin and cAMP are not the only signaling pathways that determine agonist activity, they are several other signaling pathways (MAPK, ER, JAK etc.) that can affect the biochemical activity of ligands.

**Drug-Discrimination studies**

Drug discrimination is used to test the in vivo effects of a potential psychoactive drug. The technique involves establishing the effects of a training drug (with known abuse liability) as a cue for performing a specific behavioral response. In this procedure rats or non-human primates are trained daily during short sessions, in which lever pressing is reinforced by presentation of a reward (food pellets). Each day, they are injected with either the training drug or its vehicle (saline), and are then put in the training chamber and allowed to choose between two levers. Responses on one lever (the 'drug-appropriate'
lever) are reinforced during drug sessions, and responses on the other lever (the 'vehicle-appropriate' lever) are reinforced during vehicle sessions.\textsuperscript{196}

**Figure 2.28:** Discriminative-stimulus effects of AM 9252 in AM 4054-trained squirrel monkeys.

Effects of cumulative i.m. doses of AM 9252 (0.0032-0.1 mg/kg) administered prior to sequential components of the test session. AM 4054 and AM 9252 served as the discriminative stimuli (*Figure 2.28*). The effects of i.m. AM 4054, the training drug are shown for comparison. The squirrel monkeys (n=4) identified 0.3-1.0 mg/kg, i.m. of AM 9252 as producing the same discriminative-stimulus effects as the CB1 full agonist AM
AM 4054 was more potent compared to AM 9252. Note that doses of AM 4054 and AM 9252 that produce full substitution for the training stimulus (0.01 mg/kg AM 4054, i.m.) do not produce decreases in rates of responding.

**Figure 2.29:** Summary of hypothermic and antinociception effects of AM 9217, AM 9248 and AM 9252

![Graph](image)

Among the lead analogs (AM 9217, AM 9248 and AM 9252), AM 9252 was the most potent centrally acting ligand based on the results obtained from the hypothermia and tail-flick tests in rats (*Figure 2.29*). For AM 9252, peak hypothermic and antinociceptive effects occurred over the same dose range (1-3 mg/kg) and time course (60-180 minutes). AM 9248 and AM 9217 did not show significant hypothermia or antinociceptive effects at the highest dose tested. These two analogs might possibly be partial agonists at the CB1 receptor or perhaps their PK parameters i.e. short half-lives, might play a role in these in vivo effects. PK studies have yet to be run on these two lead analogs.
Comparison of in vivo effects of AM 9217 and AM 9248 with (-)-Δ⁹THC

Figure 2.30: Bar test - cumulative dosing of AM 9217 and AM 9248 in mice

The two polar lead analogs, AM 9217 and AM 9248, were tested in the ‘bar-test’ to monitor catalepsy (Figure 2.30) in mice, and their effects were compared to that of Δ⁹-THC (for methods, see experimental procedures). Mice were dosed i.p. in a solution of ethanol: emulphor: saline (1:1:18). Both AM 9217 (ED₅₀~5 mg/kg) and AM 9248 (ED₅₀~7 mg/kg) were more potent in producing catalepsy than Δ⁹-THC. There was a dose dependent immobility effect from a cumulative dose of 1 mg/kg to 100 mg/kg. Thus based on the catalepsy test in mice, AM 9217 and AM 9248 produced immobility at the dose tested.
AM 9217 and AM 9248 were tested in the ‘tail withdrawal warm water’ tetrad test (Figure 2.31) in mice, and their effects were compared to that of Δ⁹-THC (for methods, see experimental procedures). Mice were dosed i.p. in a solution of ethanol: emulphor: saline (1:1:18). Similar to the results obtained in the catalepsy test, AM 9217 (ED₅₀~5mg/kg) and AM 9248 (ED₅₀~9 mg/kg) were more potent compared to Δ⁹-THC. For AM 9217, there was a sharp increase in antinociception at a cumulative dose of 3 mg/kg to 10 mg/kg. Thus both analogs produced antinociception in mice.

AM 9217 had similar relative potencies in the catalepsy and analgesia test whereas AM 9248 was more potent in the catalepsy test (ED₅₀~7 mg/kg) compared to the analgesia test (ED₅₀~9 mg/kg).
The ability of AM 9217 and AM 9248 to decrease body temperature was tested in the hypothermia assay in mice (for methods, see experimental procedures). Mice were dosed i.p. in a solution of ethanol: emulphor: saline (1:1:18). As seen in Figure 2.32, there was a dose dependent decrease in body temperature after both AM 9217 and AM 9248 administration. At the highest cumulative dose tested (30 mg/kg), there was an 8 ºC drop in temperature with AM 9217 and 6 ºC drop in temperature with AM 9248. In all three tetrad tests, AM 9217 and AM 9248 were more potent that the partial agonist Δ⁹-THC. It would be interesting to compare the efficacies of these analogs along with that of AM 4054 (CB1 potent agonist).
Comparision of in vitro and in vivo effects of AM 9201 and AM 9217

Table 2.13: $K_i$ values, cAMP and β-arrestin data of AM 9217 and AM 9201

<table>
<thead>
<tr>
<th></th>
<th>cAMP (EC$_{50}$/ % maximal efficacy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AM 9217 - ($K_i$ - nM)</td>
<td></td>
</tr>
<tr>
<td>rCB1 = 30.4 ± 2.1</td>
<td>1.3 nM (68%) - agonist</td>
</tr>
<tr>
<td>mCB2 = 12.3 ± 1.7</td>
<td>n.d</td>
</tr>
<tr>
<td>hCB2 = 9.5 ± 1.3</td>
<td>1.1 nM (35%) - partial agonist</td>
</tr>
<tr>
<td>AM 9201 - ($K_i$ - nM)</td>
<td></td>
</tr>
<tr>
<td>rCB1 = 2.3 ± 0.6</td>
<td>16.9 nM (61%) - agonist</td>
</tr>
<tr>
<td>mCB2 = 4.1 ± 1.4</td>
<td>n.d</td>
</tr>
<tr>
<td>hCB2 = 4.6 ± 0.2</td>
<td>16.0 nM (39%) - partial agonist</td>
</tr>
</tbody>
</table>

Figure 2.33: Hypothermic effect of AM 9201 and AM 9217 in mice

The in vivo effects of AM 9201 and AM 9217 were compared in the hypothermia test at the 10 mg/kg dose (Figure 2.33). AM 9217 did not show significant hypothermia, where
as AM 9201 had a quick onset of action with a 6 °C drop in temperature within 60 minutes and a relatively short duration of action, as the temperature returned to baseline at the 240 minute.

The in vivo hypothermia result of AM 9217 differs in Figure 2.32 and Figure 2.33. Both the test where done in mice. Mice in the Figure 2.32 experiment were dosed using a cumulative dosing regimen whereas mice were dosed with a set amount of drug (10 mg/kg) in Figure 2.33. Cumulative dosing can result in accumulation of compound in tissues (adipo effect) and thus might produce a greater hypothermic effect compared to a fixed amount of drug.

The in vitro cAMP data of both AM 9201 and AM 9217 showed that there are potent agonists at the CB1 receptor but as seen in Table 2.13 only the cAMP data of AM 9201 correlates with its agonist in vivo effects. AM 9217 showed partial agonism in the hypothermia test (Figure 2.33). This result might be due to the polar nature of AM 9217, which might partially restrict it to the periphery and hence it won’t be able to fully activate the CB1 receptors in the brain or it might be due to PK effects.
Figure 2.34: Antinociceptive effect of AM 9217 in tail-flick test in mice

* (Mean = 1.0175; SEM = ±0.1657 sec latency). Cut-off = 10 sec; n=8 CD-1 mice; cumulative dosing, i.e., 3 mg/kg + 7 mg/kg = 10 mg/kg + 20 mg/kg = 30 mg/kg)

The antinociceptive effects of AM 9217 were tested in the tail-flick test in mice. Mice were dosed cumulatively as shown in Figure 2.34. The onset of antinociception was observed at 3 mg/kg, and the antinociceptive response steadily rose in a dose-dependent manner. At the highest dose (30 mg/kg), AM 9217 showed greatest tail-flick latency (~9 sec) and an antinociception of 90%. This result is in contrast to that from when the tail-flick test in rats (Figure 2.17- showed weaker response in rats). AM 9217 might have different ADME properties in mice and rats (mice weigh less than rats).
Evaluation of AM 9222

Figure 2.35: Hypothermic effects of AM 9222 in mice

Based on in vivo results from AM 9217, AM 9222 was tested in the hypothermia test in mice with the hypothesis that it would act similarly to AM 9217. However, as seen in Figure 2.35, AM 9222 resulted in significant hypothermia. There was a 5 °C drop in temperature within 20 minutes and at the 180th minute there was a drop in 11 °C. This compound was thus a highly potent agonist in the hypothermia test. Thus a change in side
chain length from 5-C (AM 9217) to 6-C (AM 9222) had a significant effect in the potency of analogs in the hypothermia test. Thus the lipophilic analog AM 9222 (ClogP = 4.6) produced more hypothermia compared to AM 9217 (ClogP = 3.9).

(+)- CBD Prodrug-metabolite studies

Prodrugs are chemically modified versions of a pharmacologically active drug that undergo in vivo enzymatic metabolism to release the active drug. The prodrug strategy is very well established to improve the physicochemical and pharmacokinetic properties of pharmacologically potent compounds and thereby helps in the development of potentially useful drugs.\textsuperscript{197,198} For example, a prodrug strategy is used to tackle problems in drug formulation and delivery of compounds with poor aqueous solubility, chemical instability, poor membrane permeability, insufficient oral absorption, rapid pre-systemic metabolism, inadequate brain penetration, bad taste, short duration of action, toxicity and local irritation.\textsuperscript{199} Some of the functional groups that are amenable to prodrug design are esters, amides and carbamates. Ester prodrugs are most commonly used to increase lipophilicity and thereby increasing membrane permeability. Once the ester prodrug enters the systemic circulation, the ester bond is rapidly hydrolysed by ubiquitous esterases\textsuperscript{200} found in the blood, liver and other organs and tissues. Some prodrugs have been designed that are activated by other in vivo metabolic reactions such as $N$-demethylation, decarboxylation and hydrolysis of amides and phosphates.\textsuperscript{200}
Scheme 2.25: Enzymatic hydrolysis of AM 9200

Table 2.14: $K_i$ binding values and cAMP data for AM 9200

<table>
<thead>
<tr>
<th>(K_i - nM)</th>
<th>cAMP (EC_{50} % maximal efficacy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>rCB1 = 25.0 ± 9.2</td>
<td>9.4 nM (45%) – partial agonist</td>
</tr>
<tr>
<td>mCB2 = 26.2 ± 6.7</td>
<td>n.d</td>
</tr>
<tr>
<td>hCB2 = 51.6 ± 10.7</td>
<td>9.6 nM (56%) - partial agonist</td>
</tr>
</tbody>
</table>

Figure 2.36: Hypothermic effects of AM 9200 and AM 9201
Prodrugs are designed with the goal of converting to the active drug, thus prolonging drug activity. Allylic ester AM 9200 and its metabolite AM 9201 (Scheme 2.25) were tested in the hypothermia assay in mice to visualize how the in vivo effects of these analogs differ from each other. As seen in Figure 2.36, the ester had a longer duration of action compared to metabolite AM 9201. AM 9200 also showed a greater hypothermic effect with a 9 °C drop in temperature.

The absorption, distribution, metabolism, excretion (ADME) and pharmacokinetic properties of prodrugs have to be thoroughly understood to ensure that the prodrug is effectively converted to the active drug once it has been absorbed in the blood. Instability in plasma can be unfavorable as the concentration of compound in vivo will rapidly decline and will affect in vivo efficacy.

In some cases, when lipophilic compounds such as THC get deposited in fatty tissues ("depot effect"), susceptibility to plasma esterases is preferred so that the compound does not have an excessive half-life and lengthy duration of action. Also at the drug discovery stage, when drug candidates are screened against biological targets, compounds need to have sufficient stability in the assay buffers for enzyme, receptor, or cell-based assays to be assigned for biological activity. Some compounds may exhibit interspecies differences in their stability in plasma, and it is important to determine this in early stages.

The plasma stability assay was used to screen for prodrug stability. The active metabolite (AM 9201) was tested, and the disappearance of compound (AM 9200) and appearance of the active compound (AM 9201) were monitored simultaneously. This was performed by incubating prodrug AM 9200 and its metabolite AM 9200 in mouse plasma, rat
plasma and human plasma. The stability at 37 °C in TME buffer, gastric juices and acetonitrile were also determined. Test compounds were diluted (200 μM) and incubated at 37 °C for 2 hours under the respective test conditions. Samples were taken at various times and diluted to a 20% suspension in acetonitrile and centrifuged to precipitate the plasma proteins; the resulting analyte was analyzed by HPLC. For plasma conditions, the t_{1/2} of AM 9200 was determined (Performed by Jodi Wood and Andrew Pham).

**Figure 2.37:** Stability of AM 9200 in mouse, rat, human plasmas and TME buffer
Different half lives (Figure 2.37) were obtained for mouse (7.6 minutes), rat (104 minutes) and human plasmas (6 hours). For human plasma, prodrug (AM 9200) conversion to metabolite (AM 9201) started to take place after an hour. However, in rat and mice plasma, the plasma esterase hydrolysis is rapid. These results suggest that prodrug AM 9200 was relatively stable in human plasma. A main challenge with ester prodrugs is the difficulty in predicting their rates of bioconversion in different species due to the variability in the types of esterases and differences in their respective substrate specificities. The prodrug was found to be stable in TME buffer with 0.1% BSA, standard vitro testing conditions.

**Figure 2.38:** Stability of AM 9200 in gastric juice and acetonitrile

The stability of AM 9200 was tested in artificial gastric juice and acetonitrile at 37 °C (body temperature). It was found to be stable in acetonitrile, but had some solubility issues in artificial gastric juices (Figure 2.38).
The metabolite AM 9201 was found to be stable in mouse and rat plasmas (Figure 2.39).

AM 9201 was stable in human plasma, but had some solubility issues in TME buffer (Figure 2.40).
Figure 2.41: Stability of AM 9201 in gastric juice and acetonitrile

AM 9201 also had solubility issues in gastric juices but was stable in acetonitrile (Figure 2.41).

From the above plasma stability studies, both AM 9200 and AM 9201 are relatively stable in human plasma.
CANNABIDIOLS AS COVALENT PROBES

Between the years 2000-2007, the only crystal structure of a GPCR that was available was that of bovine rhodopsin. Since then, the crystal structures of six other GPCR’s have been published. In spite of recent advancements in crystallization procedures, it is still tremendously difficult to obtain crystal structures of unmodified, functional membrane proteins. Since cannabinoid receptors are integral membrane proteins that are dynamically flexible, obtaining a purified form of the receptor is not easy. Thus we can not use NMR experiments and X-ray crystallography to gain structural information on the native cannabinoid halo receptors. Our lab has concentrated efforts to characterize the ligand-binding domain of the cannabinoid receptor by using ligand-binding docking experiments and mutagenesis. This experimental approach termed “ligand-assisted protein structure” (LAPS) allows for the direct identification of important amino acid residues that interact with or very near the ligand binding site. Over the past years, a number of covalent tricyclic ligands with both photoactivable and electrophilic groups have been used as CB-receptor probes. The LAPS approach involves four main steps: a) the use of high affinity and pharmacologically active covalent probes to react with specific amino acids at or near the receptor binding site; b) the introduction of point mutations in the receptor to determine how the mutated receptor effects probe binding and pharmacological activity; c) the use of computer modeling to understand probe-receptor interactions; and d) the identification of the sites of covalent ligand attachment by MS-based proteomics. Information obtained from these experiments has led to the identification C6.47(355) in helix 6 of hCB2 that interacts with AM 841, a high-affinity NCS covalent probe. This probe has also unprecedented ability to activate
the hCB2 receptor with a 40-fold greater potency compared to the AM841 analog with out the NCS. Under the experimental conditions followed during the covalent binding experiements, the NCS group only reacts with the cysteine. Other amino acids such as lysine are protonated at physiological pH and are therefore weak nucleophiles.

It is not known how cannabidiols interact with the cannabinoid receptors to activate it. Information of the amino acid ligand-interaction site(s) of the binding regions of the CB receptors can help in the design of receptor selective (+)-CBD analogs. It will be also interesting to learn if cannabidiols and tricylic cannabinoids share the same binding site. In order to pursue this goal, covalent ligands with the photoactivable and electrophilic probes were designed. Our design incorporates the photoactivable azido (N\textsubscript{3}) and the electrophilic isothiocynato (NCS) groups on the side chain and on the northern end of the CBD template. This may help determine the amino acid residues and the transmembrane helix(es) involved in the binding of (+)-CBD.

**Chemistry**

As shown in *Schemes 2.26, 2.27 and 2.28*; azides 81, 83, and 85 were synthesized in yields 75%, 59% and 39% respectively by reacting bromides with tetrabutylammonium azide.
Scheme 2.26: Synthesis of the C1' cyclobutyl side chain azide probe

Reagents and conditions: (a) Bu₄N⁺N₃⁻, CH₂Cl₂, r t, 24 h, 66%; (b) p-TSA, CH₂Cl₂, -10°C; 30%; (c) K₂CO₃, CH₃OH, r t, 3 h, 75%.

In addition, as depicted in Scheme 2.22 and 2.28, representative isothiocyanates (83, 85) were synthesized (33, 39% yields) by reacting the corresponding azides with triphenylphosphine and carbon disulfide.²⁰⁷

Scheme 2.27: Synthesis of dimethyl heptyl side chain covalent (+)-CBD probes

Reagents and conditions: (a) n-Bu₄N⁺N₃⁻, CH₂Cl₂, r t, 24 h, 59%; (b) PPh₃, benzene, 50 °C, 6 h, then CS₂, 50 °C, 6 h, 33%.
Scheme 2.28: Synthesis of dimethyl hexyl side chain covalent (+)-CBD covalent probes

Reagents and conditions: (a) \(n\)-Bu\(_4\)N\(^+\)N\(_3\)\(^-\), CH\(_2\)Cl\(_2\), r t, 24 h, 38%; (b) PPh\(_3\), benzene, 50 °C, 6 h, then CS\(_2\), 50 °C, 6 h, 39%.

Results and Discussion

After determining the apparent K\(_i\)'s for the covalent ligands by radioligand displacement assays, they were evaluated for their abilities to label irreversibly the rCB1, mCB2 and the hCB2 receptors through formation of a covalent bond. The rat, mouse and human membranes were equilibrated with concentrations (10-fold the K\(_i\)'s) of the respective ligand for 1 hour followed by the termination of the reaction by centrifugation (performed by Han Zhou). For azide analogs, the ligands were photoirradiated with UV light (254 nM), which was followed by determination of the ligand occupancy of the receptors with saturation binding assay. For control experiments, membranes were photoirradiated in the absence of ligands. For the electrophilic covalent labeling experiment, the control experiment was performed by not treating the membranes with electrophilic ligands prior to determining specific binding. The ability of the test ligand to
label irreversibly the receptor was determined by comparing the specific binding of the test compound with that of the control ligand ([³H] CP-55,940). (See experimental procedures for assay protocol). The percent covalent labeling of all covalent probes synthesized is summarized in Table 2.15.

Table 2.15: Binding affinities and % covalent binding of (+)-CBD probes

<table>
<thead>
<tr>
<th>AM #</th>
<th>R</th>
<th>Apparent $K_i$ (nM)</th>
<th>% labeling (10 fold the $K_i$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>rCB1</td>
<td>mCB2</td>
</tr>
<tr>
<td>81</td>
<td>AM9220</td>
<td>21.6±1.7</td>
<td>7.2±1.4</td>
</tr>
<tr>
<td>82</td>
<td>AM9224</td>
<td>2.3</td>
<td>3.9</td>
</tr>
<tr>
<td>83</td>
<td>AM9225</td>
<td>20.1</td>
<td>21.8</td>
</tr>
<tr>
<td>84</td>
<td>AM9251</td>
<td>1.4±0.6</td>
<td>1.7±0.2</td>
</tr>
<tr>
<td>85</td>
<td>AM9253</td>
<td>7.7±0.4</td>
<td>6.2±2.2</td>
</tr>
</tbody>
</table>

*K_i values were obtained from three independent experiments run in triplicate and are expressed as the mean±S.D.
(+)-Cannabidiol analogs in Table 2.15 with side chains bearing 6, and 7 carbons with either an azido or the isothiocyano group at the terminal carbon were synthesized. Binding affinity values of the novel ligands for the rat CB1, mouse CB2 and human CB2 receptors were determined and selectivity evaluated. All covalent ligands in Table 2.15 had apparent $K_i$ values below 22 nM and thus were appropriate to be tested for covalent binding.

Based on SAR previously developed in this project, the gem-dimethyl group at C1' position was chosen as the optimal substituent for binding affinity. Summarized in Table 2.15, our results indicate that substitution of an azido group at the terminal carbon of the side chain led to ligands exhibiting high affinity, but no selectivity, towards the receptors tested. The 6-carbon azido analog 84 with a dimethyl at C1' had higher covalent binding towards the receptors as compared to 81, that had a cyclobutyl ring at C1'. The 6-C azido probe 81 did not bind covalently to any of the receptors.

Among the side-chain analogs, the dimethyl heptyl and the dimethyl hexyl side-chain showed high binding affinity, and thus covalent probes AM 9224, AM 9225 AM9251 and AM9253 were synthesized, and covalent binding studies were carried out. The probes 82-85 had different percentages of covalent labeling for cannabinoid receptors as seen in the Table 2.15. Further mutation study experiments as well as MS analysis will be required to identify amino acid residue(s) to which these covalent ligands attach in the cannabinoid receptors.
Table 2.16: Apparent Kᵢ values, cAMP and β-arrestin data for AM 9251

<table>
<thead>
<tr>
<th>(Kᵢ - nM)</th>
<th>cAMP (EC₅₀/ % maximal efficacy)</th>
<th>β-arrestin</th>
</tr>
</thead>
<tbody>
<tr>
<td>rCB1 = 1.4 ± 0.1</td>
<td>8.6 nM (64%) agonist</td>
<td>0.2 nM (hCB1)</td>
</tr>
<tr>
<td>mCB2 = 1.7 ± 0.2</td>
<td>n.d</td>
<td>n.d</td>
</tr>
<tr>
<td>hCB2 = 1.4 ± 0</td>
<td>0.29 nM (62%) agonist</td>
<td>0.002 nM (hCB2)</td>
</tr>
</tbody>
</table>

Table 2.17: Kᵢ values, cAMP and β-arrestin data of AM 9253

<table>
<thead>
<tr>
<th>(Kᵢ - nM)</th>
<th>cAMP (EC₅₀/ % maximal efficacy)</th>
<th>β-arrestin</th>
</tr>
</thead>
<tbody>
<tr>
<td>rCB1 = 7.7 ± 0.4</td>
<td>6.4 (90%) agonist</td>
<td>1.4 μM (hCB1)</td>
</tr>
<tr>
<td>mCB2 = 6.2 ± 2.2</td>
<td>n.d</td>
<td>n.d</td>
</tr>
<tr>
<td>hCB2 = 11.2 ± 2.9</td>
<td>1.4 (41%) partial agonist</td>
<td>0.3 nM (hCB2)</td>
</tr>
</tbody>
</table>

The functional efficacy of AM 9251 and AM 9253 probe analogs was evaluated in cAMP and β-arrestin assays (Table 2.16 and 2.17), which revealed that they were agonists. AM 9253 was a partial agonist for the hCB2 receptor in cAMP assay and a potent agonist for the hCB2 receptor in β-arrestin assay.
**Figure 2.42:** cAMP curve of AM 9258

![AM 9258 structure](image)

**Table 2.18:** $K_i$ values, cAMP and β-arrestin data of AM 9258

<table>
<thead>
<tr>
<th></th>
<th>cAMP (EC$_{50}$/ % maximal efficacy)</th>
<th>% Covalent binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>rCB1</td>
<td>26.4 ± 2.5</td>
<td>27.5 nM (74%) agonist</td>
</tr>
<tr>
<td>mCB2</td>
<td>22.9 ± 0.3</td>
<td>n.d</td>
</tr>
<tr>
<td>hCB2</td>
<td>27.5 ± 2.5</td>
<td>n.d</td>
</tr>
</tbody>
</table>

Northern end covalent probe analog (AM 9258) bound to CB1 and CB2 receptors with no selectivity (*Table 2.18*). It also had a very high percentage of covalent binding (72%) to the rCB1 receptor.
CONCLUSIONS

The main goal of this thesis project was to develop a suitable synthetic procedure to synthesize (+)-cannabidiol analogs and to thereby build up SAR data for (+)-cannabidiols. This goal was fulfilled with the generation of analogs that resulted from the modification of the (+)-CBD template. This was possible due to the approach of synthesizing a terpene (16) and resorcinols (25) followed by coupling them with p-toluene sulfonic acid in ~45-80% yields. The novel terpene was synthesized in six high-yielding steps using known chemistry for closely related terpenes. This thesis also reports the synthetic procedure for the synthesis of a novel tetrahydropyranyl resorcinol (25m).

Other C1'-dimethyl alkyl resorcinols were also synthesized using a new synthetic route reported for C1'-cyclo alkyl resorcinols. The SAR included side chain, northern end, phenolic hydroxyl, and analogs designed from isosteric replacement of the terpene ring. The side chain length was varied from pentyl to butyl, hexyl and heptyl. Terminal substitutions to the end carbon of the side chain were made by nucleophilic substitution reactions of the bromide group. Modifications to the C1' position of the side chain was incorporated by addition of dimethyl and cycloalkyl groups. A new synthetic route was also developed for the synthesis of northern end analogs.

Following the synthesis of (+)-CBD analogs, the binding affinities and pharmacological (cAMP, β-arrestin) of these analogs for the rCB1, mCB2 and hCB2 receptors were determined. Among the analogs synthesized, the dimethyl heptyl (AM 9201, AM 9208, AM 9234, AM 9224 and AM 9225) and hexyl (AM 9250, AM 9252, AM 9251 and AM 9253) side chain analogs had high binding affinity to the CB receptors with no selectivity between CB1 and CB2 receptors. Analogs of the shorter dimethyl pentyl (AM 9216, AM
9217 and AM 9248) and butyl (AM 9227 and AM 9228) side chain were found to be more CB2 selective. The SAR data generated by the modification of the phenolic hydroxyl to methoxy group showed that the hydrogen-donating ability of the OH group was not necessary for binding. Modification of the northern end allylic alcohol to groups such as (N₃, OCOCH₃ and NCS) led to analogs with decreased affinities for the CB receptors, which implied that the OH group is necessary for optimal binding. A CB2 selective analog, AM 9266 with tetrahydropyranyl group at the Cl' position was discovered to be a CB2-selective compound. AM 9238 and AM 9273, two adamantyl analogs, exhibited species selectivity for the mCB2 receptor when compared to the hCB2. The SAR data of the isosteric verbenol analogs concluded that the (1R,4S,5S) enantiomer bound with higher affinity to the CB receptor compared to the (1S,4R,5R) enantiomer. The in vitro cAMP and β- arrestin data of the analogs showed that all (+)-CBD’s tested were agonists or partial agonist activity at the CB receptors with the exception of bicyclic analogs, AM 9259 and AM 9260 that were antagonists at CB1 receptor and agonists at the CB2 receptors. From the SAR studies of (+)-CBD’s, we noticed a lot of common SAR features to that of tri-cyclic cannabinoids. This might suggest that there is a high level of congruency between the binding sites of these two classes of compounds. The current SAR study contributed to our understanding of the key interactions of (+)-CBD’s with the cannabinoid receptors, and it is a good starting point for the development of second-generation, more subtype-selective analogs.

The results of the covalent binding experiments demonstrate that the photoactivatable probes AM 9224 and AM 9220 did not have sufficient covalent binding to the CB receptors, suggesting that their interaction with the binding domain is different from
those of tricyclic classical cannabinoids. However, the azido analog, AM9251, and the isothiocyanate analogs, AM 9225 and AM9253, had significant covalent binding to the CB receptors, and these analogs are currently being pursued in further receptor mapping studies. LAPS studies will help in identifying if (+)-CBD’s and tri-cyclic cannabinoids share similar binding sites.

Among the lead analogs that were selected and tested in vivo, AM 9200 had a longer duration of action compared to its metabolite AM 9201. Pro-drug stability studies in rat, mouse and mouse plasma were also performed on AM 9200. Analogs AM 9217 and AM 9248 were found to be weak partial agonists based on the results of the tetrad tests. AM 9252 and AM 9222 on the other hand had potent analgesic and hypothermic effects in mice and rats. There was a drastic change of in vivo activity (hypothermia and analgesia) between the 6-C side chain analogs AM 9252 and AM 9222 compared to the 5-C side chain analogs AM 9217 and AM 9248.

**FUTURE DIRECTIONS**

The fulfilment of the goals of this thesis has opened up several doors for the continuation of this project. The SAR studies have provided lead analogs that can be profiled in a number of different in vivo and in vitro experiments. Extensive PK studies need to be done for the lead analogs to determine if they can be progressed into the pre-clinical phase of the drug discovery. For example, solubility, permeability, CYP450 inhibition, CYP450 induction, plasma-protein binding, BBB studies, Pgp substrate studies, metabolite screening, drug-drug interactions studies, multiple receptor screening are some in vitro tests that need to be run. Ongoing and future efforts include evaluating
compounds AM 9217 and AM 9248 as partial agonists or peripherally acting ligands. AM 9217 and AM 9248 are currently being evaluated in the impedance assay for functional efficacy. They are also currently undergoing evaluation in chronic constriction injury (CCI) model to evaluate its potency in reducing neuropathic pain. The ability of these compounds to inhibit peripheral inflammation, might suggest that these analogs act peripherally. It will also give us an idea about which cannabinoid receptor is involved in producing the therapeutic effect. It is important to run more extensive BBB studies or to perform ‘gastrointestinal motility studies’ on AM 9217 to determine if it is peripheral restricted. AM 9248 and AM 9252 are in line for BBB screening. The discrepancy obtained with the ‘tetrad’ data with AM 9217 and AM 9248 in mice and rats can be probably extended to higher species like primates. In order to determine the in vivo functional efficacy of the lead analogs, those compounds need to be tested in parallel with other CB1 agonists or antagonists. It will also be interesting to compare the effects of these (+)-cannabidiol analogs along with (-)-CBD in an in vivo central and peripheral activity assay. Since (-)- CBD’s are known to bind to the vanilloid, adenosine and the GPR-55 receptors, some of the (+)-CBD analogs will be sent to collaborators who will perform those tests.

AM 9257, the serendipitously discovered iodo analog that had moderate binding and agonist activity towards the CB receptors, should be pursued in a separate SAR project. Similar to the studies performed with prodrug analog (AM 9200) and its metabolite (AM 9201), other allylic ester (+)-CBD’s should be synthesized and evaluated in in vitro and in vivo tests to investigate the duration of actions of these prodrugs. Ester groups can also be added on the side chain of (+)-CBD to manipulate its duration of action.
The covalent (+)-cannabidiol probe analogs AM 9225, AM 9251 and AM 9253 should be pursued in mutation studies with the CB receptors to obtain information on the binding site of cannabidiols and to find out if their binding site differs from tricyclic cannabinoids.

**EXPERIMENTAL PROCEDURES**

Radioligand binding assay (Pusheng Fan, Othman Benchama, SriKrishnan Mallipeddi, Yan Peng, Girija Rajarshi, Shivagi Joshi)

Synaptosomal forebrain membranes prepared from frozen rat brains by the method described by Dodd et al.\(^\text{208}\) were used to assess the affinities of the novel analogues for the CB1 receptor. Membrane preparations from HEK293 cells expressing human CB2 (hCB2) receptor and mouse CB2 (mCB2) were used to assess the affinities of representative analogs for hCB2 and mCB2.\(^\text{209}\) The displacement of \(^{3}\text{H}\)-CP-55,940 from these membranes was used to determine the IC\(_{50}\) values for the test compounds. The assay was conducted in a 96-well microfilter plate. The samples were filtered using a Packard Filtermate harvester and Whatman GF/B Unifilter-96 plates, and 0.5% BSA was incorporated into the wash buffer. Radioactivity was detected using MicroScint 20 scintillation cocktail added to the dried filter plates and was counted using a Packard Top Count. Data were collected from three independent experiments between 100% and 0% specific binding for \(^{3}\text{H}\) CP-55,940, determined using 0 and 100 nM CP-55,940. The normalized data from three independent experiments were combined and analyzed using a four-parameter logistic equation to yield IC\(_{50}\) values that were converted to \(K_i\) values using the assumptions of Cheng and Prusoff.\(^\text{210}\)
cAMP assay (Dr. Aneetha Halikhedkar-CDD)

HEK-293 cells transfected with rCB1 or hCB2 receptors were used for the cAMP assays. The cells were grown for 24 to 48 h and harvested using the non-enzymatic cell dissociation reagent Versene. They were washed once with HBSS and resuspended in stimulation buffer. The assays were carried out in 384-well plates with 1000-1500 cells/well using PerkinElmer’s Lance ultra cAMP kit. The test compounds (5 µl) in forskolin (2 µM)-containing stimulation buffer were added to the plate followed by the cell suspension (5 µl). The cells were stimulated for 30 min at room temperature. Then Eu-cAMP tracer working solution (5 µl) and Ulight-anti-cAMP working solution (5 µl) were added to the plate and incubated at room temperature for 1h. The plates were read on PerkinElmer Envision, and the data were analyzed using GraphPad Prism software.

β-arrestin assay (Duke University- Dr. Larry Barak)

The translocation of β-arrestin 2 was examined in both agonist and antagonist modes using U2OS cells permanently expressing human CB1 or human CB2 and rat beta-arrestin 2-GFP. Cells were placed in serum free medium for 3-4 hrs, and treated with varying concentrations of test compounds (0.1 nM to 100 µM) to obtain a concentration response. After 45 min of treatment at 37 °C, cells were fixed with 1% PFA overnight at 4 °C. Each of two independent experiments was performed in duplicate at each concentration of compound. WIN55212 was used for antagonist assays at a concentration of 1 M for CB1 and 0.1 M for CB2, respectively. The readout was formation or loss of (agonist/antagonist respectively) fluorescent intracellular aggregates containing cannabinoid receptor/beta-arrestin-GFP complexes. Duplicate points were collected for
each concentration to enable determination of a concentration response curve. Image-based wavelet analysis was performed using the Duke Batchmode computer software to assess the response at each point. Concentration response data were fit by nonlinear regression analysis using GraphPad Prism to determine potency and efficacy of the compounds.

**Covalent binding assay (Han Zhou)**

**Photoaffinity Covalent Labeling** - The respective membranes (rat, mouse, human) were pretreated with 0.15 mM PMSF for 10 min on ice twice and then washed 3 times with 0.1% BSA in TME to remove the excess PMSF. The pretreated membranes were incubated with various concentrations of azido ligands (10 Ki) at 30 °C for 1 hour in the dark, followed by centrifugation at 27200g for 4 min. The pellets were resuspended in ice-cold TME containing 0.1% BSA and exposed to UV (254 nm) for 1 minute to activate the ligand. Unbound excess azide was washed out with 1% BSA in TME 3 times by centrifugation, followed by three washes with TME without BSA.

**Electrophilic covalent labeling** - The respective membranes (rat, mouse, human) were pretreated with PMSF as described above and incubated with various concentrations of isothiocyanate ligands (10Ki) at 30 °C for 1 hour. Unbound excess ligand was washed out with 1% BSA in TME 3 times by centrifugation, followed by three washes with TME.

**Preliminary distribution in brain/plasma and drug oral bioavailability (Dr. Jodi Wood)**

Mice (CD-1, weighing 25-30 g) are injected intravenously or orally with 0.1-2 mg/kg of the compound mixture. Fifteen minutes post-IV injection, or 30 and 60 minutes post-oral
administration, the animals are sacrificed by decapitation followed by blood collection (~500 µL) and tissue dissection; samples are flash frozen with liquid nitrogen to prevent post-mortem degradation of the compounds. Tissues (plasma or brain) are extracted following published procedures and analyzed using a Thermo-Finnigan Quantum Ultra triple quadrupole mass spectrometer in SRM mode with an Agilent 1100 HPLC front-end with internal standards used for quantification.

**In Vivo hypothermia and tail-Flick tests (Dr. Carol Paronis, Joe Anderson)**

Female Sprague–Dawley rats (n = 5–6/group), weighing between 200 and 350 g (Charles River, Wilmington MA), were used. Rats were tested repeatedly with at least three days intervening between drug sessions. Experiments occurred at roughly the same time (10:00 a.m.–5:00 pm) during the light portion of the daily light/dark cycle. Outside of experimental sessions, rats were group housed (2/cage) in a climate controlled vivarium, and they had unrestricted access to food and water except during the 6 h test sessions.

**Procedure**

Temperature was recorded using a thermistor probe (model 401, Measurement Specialties, Inc., Dayton, OH) inserted to a depth of 6 cm and secured to the tail with micropore tape. Rats were minimally restrained and isolated in 38 cm × 50 cm × 10 cm plastic stalls. Temperature was read to the nearest 0.01 °C using a thermometer (model 4000A, Measurement Specialties, Inc.). Two baseline temperature measures were recorded at 15 min intervals, and drugs were injected immediately after the second baseline was recorded. After injection, temperature was recorded every 30 min for 3 h and every hour thereafter for a total of 6 h. The change in temperature was determined for
each rat by subtracting temperature readings from the average of the two baseline measures.

Antinociception was measured using modified version of the tail-flick procedure of D’Amour and Smith. Radiant heat from a halogen lamp was focused on the tail using a commercial tail-flick apparatus (model LE7106, Harvard Apparatus, Holliston, MA); movement of the tail activated a photocell, turning off the lamp and a reaction timer. The lamp intensity was adjusted to yield baseline values of 1.2–2.6 s, and a maximum latency of 6.0 s was imposed to avoid damage to the tail. Two baseline tail-flick latencies were obtained in each rat at 10 min intervals, and drugs were injected immediately after the second baseline was recorded. Tail-flick responses were recorded at 30, 60, 120, 180, and 360 min after injection.

Drugs

Compounds AM 9217, AM 9248 and AM 9252 were initially dissolved in a solution of 20% ethanol, 20% alkamuls, and 60% saline, and was further diluted with saline. Injections were administered sc in a volume of 1.0 mL/kg, and drug doses are expressed as the weight of the free base.

Data Analysis

For each rat, the two baseline values recorded prior to drug injection were averaged to obtain a single baseline value. Temperatures recorded after drug injection were expressed as a change from baseline, calculated for each animal by subtracting the baseline temperature from the temperatures recorded postinjection. Tail-flick responses are expressed as a percentage of the maximum possible effect (%MPE) calculated according
to the equation: $100 \times \frac{\text{test latency} - \text{baseline latency}}{(6-\text{baseline latency})}$, where 6 represents the cutoff latency. Dose–effect functions were constructed using the maximum effect recorded in each rat at a given dose of drug. Group means and SEM were calculated and time-effect functions were analyzed using two-way repeated measures ANOVA procedures followed by Bonferroni’s posthoc test; dose–effect functions were analyzed using one-way repeated measures ANOVA procedures followed by Dunnett’s multiple comparison $t$ test; $p$ was set at $<0.05$, and statistical analyses were performed using GraphPad Prism 5.03 (GraphPad Software, San Diego, CA).

**Hypothermia test – (Dr. Torbjorn Jarbe, Sherrica Tai)**

Mice- C57BL/6 J mice (Charles River Breeding Laboratories, Wilmington, MA, USA) weighing 30 to 35 g were group housed five to a cage, in a temperature-controlled (20 °C) animal facility. Mice were habituated to the animal facility for at least 1 week prior to experiments with a 12-h light/dark cycle (lights on at 7:00AM). Mice were given free access to food and water. Experimentally naïve mice were used for each dose condition, and the mice were tested during the light phase.

**Procedure**

Rectal temperature was measured in mice using a rectal probe of a digital laboratory thermometer, RET-3-ISO, type T thermocouple (Physitemp Instruments Inc, Clifton, NJ). The lubricated probe was inserted approximately 2.0 cm into the rectum for approximately 30 sec, prior to each recording.212 Rectal temperature recording were taken from each mouse prior to dosing along with 20, 60, 180, 240, 360 and 1440-min post injection.
Aron Lichtman Collaboration – Tetrax Testing

Mice- C57BL6/J mice (Jackson Laboratories, Bar Harbor Maine) were single housed at least 1 h before start of experiment. Food and water are removed immediately before the first injection. The cumulative dose-response curves for AM9217 and AM9248 were based on 9 mice for each drug.

Drugs - AM9217 and AM9248 were dissolved in a solution of ethanol:emulphor: saline (1:1:18) in concentrations of 0.01 mg/ml (i.e. 0.1 mg/kg), 0.02 mg/ml, (i.e. 0.2 mg/kg), 0.07 mg/ml (i.e. 0.7 mg/kg), and 0.2 mg/ml (i.e. 2 mg/kg), 0.7 mg/ml (i.e. 7 mg/kg), and 2 mg/ml (i.e. 20 mg/kg), which will resulted in cumulative doses of 0.1, 0.3, 1, 3, 10 and 30 mg/kg. Δ⁹-THC was dissolved in a solution of ethanol: emulphor: saline (1:1:18) in concentrations of 0.3 mg/ml (i.e. 3 mg/kg), 0.7 mg/ml, (i.e. 7 mg/kg), 2 mg/ml (i.e. 20 mg/kg), and 7 mg/ml (i.e. 70 mg/kg), which resulted in cumulative doses of 3, 10, 30, and 100 mg/kg. Route of administration = i.p. Volume = 1 mL / 100 g body weight.

Dependent Measures (Taken in this order)

1. Catalepsy: Bar test (bar 0.7 cm in diameter that is 4.5 cm from the bench top)
   a. Two timers are used.
   b. The mouse's forepaws are placed on the bar.
   c. Timer #1 and Timer #2 are turned on when the mouse is first exhibiting catalepsy on the bar. Timer #2 is then started/stopped to record time when mouse is not moving, except for slight movements to breath or whisker/body twitches.
   d. If the mouse moves off the bar, it is placed back on in the original position. The assay ends when either Timer #1 reaches 60 s or when the mouse moves off the
bar on attempt #4. (If the mouse “popcorns” it should be noted on the data sheet
and each time the mouse pops off the bar it is counted towards the 4 tries. If
mouse popcorns each of 4 attempts, catalepsy for this mouse is excluded from
final data set.)

e. The catalepsy time is recoded as the amount of time on Timer #2.

2. Tail withdrawal test: 52 °C water bath (use bags)
   a. Bag is made of stapled surgery sheets to form a small pocket the size of a mouse
   b. Mouse should be placed head first into bag gently and the bag should be pinched
      securely to ensure the mouse does not turn around, but not forceful enough to be
      squeezing the mouse
   c. The tip mouse’s tail is dipped into the warm water, with 1 cm submerged.
   d. Time for the mouse to flick its tail or exhibit a gross tail movement such that it is
      no longer submerged is recorded; gross body movements are not considered a tail-
      flick

3. Rectal temperature: thermocouple probe dipped in mineral oil inserted 2 cm into the
   rectum. Method for holding mouse at experimenter’s discretion

**Procedure**

Pre-injection (baseline) values were determined for catalepsy, tail withdrawal latency and
rectal temperature. Subjects were tested 30 min after each injection and injections were
given every 40 min. * The order of behavioral tests was: bar test, tail immersion test, and
rectal temperature (from least invasive to most invasive).
**Materials for Chemical Synthesis**

All reagents and solvents were purchased from Aldrich Chemical Company, Alfa Aesar or Acros unless otherwise specified, and used without further purification. All anhydrous reactions were performed under a static argon atmosphere in flame-dried glassware using scrupulously dry solvents. Flash column chromatography employed silica gel 60 (230-400 mesh). All compounds were demonstrated to be homogeneous by analytical TLC on pre-coated silica gel TLC plates, (Merck, 60 F254 on glass, layer thickness 250 µm), and chromatograms were visualized by phosphomolybdic acid staining, unless otherwise specified. Melting points were determined on a micro-melting point Fisher Scientific apparatus and are uncorrected. IR spectra were recorded on a Perkin Elmer Spectrum One FT-IR spectrometer. $^1$H NMR spectra were recorded on a Varian INOVA-500. All NMR spectra were recorded in CDCl$_3$ unless otherwise stated and chemical shifts are reported in units of $\delta$ relative to internal TMS. Multiplicities are indicated as br (broadened), s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and coupling constants ($J$) are reported in hertz (Hz). $^{13}$C NMR spectra were recorded on a Bruker Ultra Shield 400 WB plus ($^1$H NMR at 400 MHz, $^{13}$C at 100 MHz). Low and high-resolution mass spectra were performed in School of Chemical Sciences, University of Illinois at Urbana-Champaign. Mass spectral data are reported in the form of m/z (intensity relative to base = 100). Purity (confirming ≥ 95% purity) was evaluated by LCMS (Waters ZQ) with Waters 2525 pump coupled to a photodiode array (Waters 2996) and ELS (Waters 2424) detector using a X Terra MS C18 5 µm, 4.6 mm x 50 mm column; flow rate 1.5 mL/min; using (Method A)- 5 to 100% water-acetonitrile; (Method B)- 20 to 100% water-acetonitrile, over 10 min.
(S)-1,2- Epoxy-8-p-menthen-7-ol (11). To an ice cooled solution of 10 (10 g, 65.70 mmol) and VO(acac)$_2$ (300 mg, 1.13 mmol) in anhydrous toluene (100 mL) was added tert-butyl hydroperoxide in tert-butyl alcohol (14 mL, 72.20 mmol) dropwise over 15 min. The reaction was allowed to stir at room temperature for 3 hours. On completion, the reaction was quenched with 20% aqueous Na$_2$SO$_3$ and extracted with diethyl ether. The ether extract was then washed with brine and dried over MgSO$_4$ and concentrated. The crude residue was purified by flash chromatography on silica gel column eluting with 10-30% ethyl acetate in hexanes to yield 8.87 g of diastereomeric mixture 11 as colorless oil in 80% yield. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ as a diastereomeric mixture 4.74 (m as t, $J = 1.4$ Hz, 1H, =CH$_2$), 4.68 (s, 1H, =CH$_2$), 3.76-3.56 (m, 2H, -CH$_2$OH), 3.35 (m, 1H, -CH$_2$CHOC-), 2.2-2.0 (m, 1H, -CH$_2$CHCH$_2$-), 1.71 (s, 3H, =CCH$_3$), 2.0-1.6 (m, 6H).

(S)-tert-Butyldimethyl[(4-(prop-1-en-2-yl)-7-oxa-bicyclo[4.1.0]heptan-1-yl)methoxy]silane (12). To a solution of 11 (7.5 g, 44.61 mmol) in DMF (100 mL) was added imidazole (6 g, 89.22 mmol). After stirring for 10 minutes, TBDMSCl (7.39 g, 49.07 mmol) was added and the mixture was stirred for 14 hours. The reaction was quenched with water and extracted with diethyl ether. The ethereal layer was washed with brine, dried over MgSO$_4$ and concentrated. The crude residue was purified by flash column chromatography on silica gel column (1-5% diethyl ether in hexanes) to give 7.2 g of 12 as colorless oil in 96% yield. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ as a diastereomeric mixture 4.73 (m as t, $J = 1.4$ Hz, 1H, =CH$_2$), 4.68 (s, 1H, =CH$_2$), 3.62 (br s, 1H), 3.56 (d, $J = 5.0$ Hz, 2H, -CH$_2$O-), 3.13 (br s, 1H), 1.90-2.12 (m, 4H), 1.70-1.20 (m, 6H), 0.88 (s,
9H, C(CH$_3$)$_3$), 0.83 (d, $J = 6.0$ Hz, 3H, CHCH$_3$), 0.82 (d, $J = 6.0$ Hz, 3H, CHCH$_3$), 0.04 (s, 3H, -OSiCH$_3$ C(CH$_3$)$_3$), 0.03 (s, 3H -OSiCH$_3$ C(CH$_3$)$_3$).

(1R,2S,4S)-1-((tert-Butyldimethylsilyloxy)methyl)-2-(phenylselanyl)-4-(prop-1-en-2-yl)cyclohexanol (13a)$^{155}$. Diphenyl diselenide (1 g, 3.54 mmol) was dissolved in anhydrous ethanol (25mL) and while stirring at room temperature, solid sodium borohydride (535 mg, 14.16 mmol) was added in portions. After stirring for about an hour, 12 (2.2 g, 7.08 mmol) was added and the reaction was refluxed overnight at 65 ºC. The reaction mixture was quenched with sodium bicarbonate, and extracted with diethyl ether. The organic phase was washed with brine, dried over MgSO$_4$ and concentrated to yield a yellow semisolid material. Flash column chromatography on silica gel (5% diethyl ether in hexanes) gave 13a, 0.71 g (46%), 13b, 0.28 g (18%) and 13a, 0.26 g (17) % yield as oils. 13a: $^1$H NMR (500 MHz, CDCl$_3$) δ 7.61 (m, 2H, 3-H, 5-H, -SePh), 7.26 (m, 3H, 2-H, 4-H, 6-H, -SePh), 4.68 (m as qt, $J = 1.5$ Hz, 1H, >C=CH$_2$), 4.66 (m, 1H, >C=CH$_2$), 3.90 (d, $J = 10.0$ Hz, 1H, -CH$_2$-O-), 3.60 (d, $J = 10.0$ Hz, 1H, -CH$_2$-O-), 3.34 (s, 1H, OH), 3.31 (dd, $J = 13.0$ Hz, 1H, >CH-C(CH$_3$)=CH$_2$), 2.19-2.13 (m, 1H), 2.08-2.04 (m, 1H), 2.0-1.92 (m,1H), 1.80-1.72 (m, 2H), 1.67 (s, 3H, >CH-C(CH$_3$)=CH$_2$), 1.57-1.50 (m, 1H), 1.34-1.24 (m, 1H), 0.95 (s, 9H, -C(CH$_3$)$_3$), 0.14 (s, 3H, -OSiCH$_3$C(CH$_3$)$_3$), 0.13 (s, 3H -OSiCH$_3$C(CH$_3$)$_3$); 13b: $^1$H NMR (500 MHz, CDCl$_3$) δ 7.53 (m, 2H, 3-H, 5-H, -SePh), 7.23 (m, 3H, 2-H, 4-H, 6-H, -SePh), 4.69 (m as d, $J = 1.0$ Hz, 1H, >C=CH$_2$), 4.69 (m as qt, $J = 1.5$ Hz, 1H, >C=CH$_2$), 3.80 (d, $J = 9.5$ Hz, 1H, -CH$_2$O-), 3.53-3.48 (m as d, $J = 8.5$ Hz, 2H, -CH$_2$O-), 2.74 (s, 1H, OH), 2.42-2.34 (m, 1H), 2.26-2.19 (m, 1H), 1.85-1.80 (m,1H), 1.74-1.58 (m and s overlapping, 6H,
especially 1.70, s, >CH-C(CH₃)=CH₂, 1.57-1.50 (m, 1H), 1.34-1.24 (m, 1H), 0.86 (s, 9H, -C(CH₃)₃), 0.04 (s, 3H -OSiCH₂C(CH₃)₃), 0.03 (s, 3H -OSiCH₃C(CH₃)₃).

(1R,2S,4S)-1-(Hydroxymethyl)-2-(phenylselanyl)-4-(prop-1-en-2-yl)cyclohexanol (14)¹⁵⁵ To a stirred solution of 13a (10.5 g, 23.88 mmol) in THF (150 mL) was added tetra-n-butylammonium fluoride (17.2 mL, 59. mmol, 1M solution in THF. On completion after 4 hours, the reaction was quenched with water, diluted with diethyl ether and the organic phase was separated. The aqueous layer was extracted with diethyl ether, the combined organic phase was washed with water and brine, dried (MgSO₄) and concentrated. The residue was purified by flash column chromatography on silica gel (20-45% ethyl acetate in hexanes) to give 8.5 g of white solid (14), (m.p = 66-68 °C) in 98% yield. H NMR (500 MHz, CDCl₃) δ 7.60 (m, 2H, 3-H, 5-H, -SePh), 7.29 (m, 3H, 2-H, 4-H, 6-H, -SePh), 4.70 (m as qt, J = 1.5 Hz, 1H, >C=CH₂), 4.68 (m, 1H, >C=CH₂), 3.73 (s, 2H, -CH₂OH), 3.36 (dd, J = 13.0 Hz, 1H, >CH-C(CH₃)=CH₂, axial), 2.97 (s, 1H, OH), 2.28 – 2.24 (m, 1H), 2.23- 2.18 (m, 1H), 2.06- 1.98 (m, 1H), 1.79- 1.71 (m, 2H), 1.68 (s, 3H, >CH-C(CH₃)=CH₂), 1.48-1.33 (m, 2H).

[(1R,2S,4S)-1-Hydroxy-2-(phenylselanyl)-4-(prop-1-en-2-yl)cyclohexyl]methylacetate (15)¹⁵⁷ To a stirred and ice-cooled solution of 14 (8.43 g, 25.9 mmol) in anhydrous pyridine (12 mL) and CH₂Cl₂ (40 mL) was added acetic anhydride (22 mL, 233.1 mmol). The reaction was stirred for 3 hours at room temperature and then quenched with ice water. The mixture was diluted with ethyl acetate, the organic phase separated, and the aqueous phase was extracted with ethyl acetate. The combined organic layer was washed successively with 0.5 N HCl, water and brine and (MgSO₄). The crude residue was purified by flash column chromatography on silica gel (20-35%
ethylacetate in hexanes) to give 9.4 g of colorless oil (15) in 98% yield. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.61 (m, 2H, -3-H, -5-H, -SePh), 7.29 (m, 3H, 2-H, 4-H, 6-H, -SePh), 4.70 (m as qt, \(J = 1.5\) Hz, 1H, >C=CH\(_2\)), 4.69 (m as d, \(J = 1.0\) Hz, 1H, >C=CH\(_2\)), 4.40 (d, \(J = 12.0\) Hz, 1H, -CH\(_2\)O-), 4.20 (d, \(J = 12.0\) Hz, 1H, -CH\(_2\)O-), 3.33 (dd, \(\Sigma J = 17.5\) Hz, 1H, >CH-C(CH\(_3\))=CH\(_2\)) axial), 3.02 (s, 1H, OH), 2.25-2.20 (m, 1H), 2.19-2.14 (m and s overlapping, 4H, especially 2.16, s, 3H, -OCOCH\(_3\)), 2.05-1.98 (m, 1H), 1.81-1.74 (m, 2H), 1.68 (s, 3H, >CH-C(CH\(_3\))=CH\(_2\)), 1.55-1.50 (m, 1H), 1.41-1.31 (m, 1H).

\[ (1S,4S)-1-Hydroxy-4-(prop-1-en-2-yl)cyclohex-2-enyl]methyl acetate \] (16). To a stirred and ice-cooled solution of 15 (1 g, 2.72 mmol) in a mixture of THF (20 mL) and pyridine (1.5 mL) was added 35% H\(_2\)O\(_2\) (1.4 mL, 43.52 mmol). The reaction was stirred for 3 hours at room temperature. After the completion of the formation of the intermediate, the reaction was heated for 3 hours at 65 ºC. On completion, the reaction mixture was diluted with ethyl acetate and hexane, washed with water and brine, dried (MgSO\(_4\)) and concentrated under vacuo. The crude residue was purified by flash chromatography on silica gel (20-45% ethylacetate in hexanes) to give 300 mg of 16 as a pale orange oil in 53% yield. \([\alpha]\)_D\(^{26} = -798.75^\circ\) (c = 0.492 g/100 mL in CHCl\(_3\)); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 5.82 (dd, \(J = 10.0\) Hz, \(J = 3.0\)Hz, 1H), 5.69 (dd, \(J = 10.0\) Hz, \(J = 2.0\)Hz, 1H), 4.80 (m as t, \(J = 1.5\)Hz, 1H), 4.66 (br s, 1H), 4.08 (d, \(J = 11.0\) Hz, 1H, -CH\(_2\) OCOCH\(_3\)), 4.00 (d, \(J = 11.0\) Hz, 1H, -CH\(_2\) OCOCH\(_3\)), 2.82-2.76 (m, 1H), 2.12 (s, 3H, -OCOCH\(_3\)), 2.05 (s, 1H), 1.96-1.90 (m, 1H), 1.85 (dt, \(J = 9.0\) Hz, \(J = 2.5\) Hz, 1H), 1.74 (s, 3H, >CH-C(CH\(_3\))=CH\(_2\)), 1.64 (dt, \(J = 8.5\) Hz, \(J = 2.5\) Hz, 1H), 1.60-1.52 (m, 1H); \(^1\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 148.
MHz, CDCl$_3$) $\delta$ 171.24 (C=O), 146.75 (>C=C<), 134.38 (>C=C<), 129.29 (>C=C<), 111.44 (>C=C<), 70.22, 69.51, 42.60, 30.80, 24.07, 21.41, 20.99.

(R)-2-[4-(prop-1-en-2-yl)cyclohex-1-enyl]acetaldehyde (18). To a stirred solution of (R)-perillyl aldehyde (17) (4.75 g, 31.60 mmol) in methanol (95 mL) was added NaBH$_4$ (46 mg, 1.22 mmol) in small portions and the reaction was stirred for 1 hour. On completion the reaction was quenched with dilute 1 N HCl and diluted with ethyl acetate. The combined organic layer was separated and the aqueous layer was extracted thrice with ethyl acetate. The combined organic layer was then washed with brine, dried over MgSO$_4$, and concentrated under vacuo to give 4.5 g of (18) as a colorless oil in 93% yield.

(R)-1,2- Epoxy-8-p-menthen-7-ol (19)$^{157}$. The synthesis was carried out as described for 10 using 18 (3.2 g, 21.02 mmol), vanadyl acetyl acetonate (37 mg, 0.15 mmol) and tert-butyl hydroperoxide in tert-butyl alcohol (4.5 mL, 23.12 mmol) to give 2.78 g of a colorless oil 19 in 79% yield. The $^1$H NMR (500 MHz, CDCl$_3$) was identical to that of 11.

(R)-tert-Butyldimethyl[(4-(prop-1-en-2-yl)-7-oxa-bicyclo[4.1.0]heptan-1-yl) methoxy]silane (20). The synthesis was carried out as described for 11 using 19 (1.5 g, 8.92 mmol), imidazole (1.21 g, 17.80 mmol) and TBDMSCl (1.47 g, 9.81 mmol) to give 2.44 g of 20 as a colorless oil in 97% yield. The $^1$H NMR (500 MHz, CDCl$_3$) was identical to that of 12.

(1S,2R,4R)-1-((tert-Butyldimethylsilyloxy)methyl)-2-(phenylselanyl)-4-(prop-1-en-2-yl)cyclohexanol (21a). The synthesis was carried out as described for 12 using 20 (2.59
g, 9.16 mmol), diphenyl diselenide (5.72 g, 18.33 mmol) and NaBH₄ (1.38 g, 36.64 mmol) in anhydrous ethanol (30 mL) to give 21a (1.78 g 54%), 21b (800 mg, 20%) and 21c (725 mg, 18%) as oils. The ¹H NMR (500 MHz, CDCl₃) spectra of 21a and 21b were identical to those of 13a and 13b.

(1S,2R,4R)-1-(Hydroxymethyl)-2-(phenylselanyl)-4-(prop-1-en-2-yl)cyclohexanol (22). The synthesis was carried out as described for 13a using 21a (1.78 g, 4.04 mmol) and 1 M TBAF (2.93 mL, 10.12 mmol) in THF (40 mL) to give 1.24 g of 22 in 95% yield as a white solid, (m.p = 66-68 ºC). The ¹H NMR (500 MHz, CDCl₃) was identical to that of 14.

[(1R,2S,4S)-1-Hydroxy-2-(phenylselanyl)-4-(prop-1-en-2-yl)cyclohexyl]methyl acetate (23)¹⁵⁷. The synthesis was carried out as described for 15 using 22 (1.1 g, 3.38 mmol), acetic anhydride (2.87 mL, 30.42 mmol) and pyridine (2 mL) in CH₂Cl₂ (30 mL) and gave 1.07 g of 23 as colorless oil in 98% yield. The ¹H NMR (500 MHz, CDCl₃) was identical to that of 15.

[(1R,4R)-1-Hydroxy-4-(prop-1-en-2-yl)cyclohex-2-enyl]methyl acetate (24)⁷⁰. The synthesis was carried out as described for 16 using 23 (1.3 g, 3.54 mmol), pyridine (1.95 mL, 24.7 mmol) and 35% H₂O₂ (1.92 mL, 56.64 mmol) and gave 401 mg of 24 (54%). ¹H NMR (500 MHz, CDCl₃) was identical to that of 16.

1-(3,5-dimethoxyphenyl)-5-phenoxypentan-1-one (29). To a grignard solution prepared from 4-phenoxybutyl bromide (4 g, 1.44 mmol) and Mg turnings (550 mg, 22.67 mmol) in anhydrous THF (150 mL) was added 3,5-dimethoxybenzonitrile (28) (2.84 g, 17.4 mmol) and CuBr. The reaction mixture was heated under reflux overnight
and then quenched with 10% H₂SO₄. The reaction mixture was diluted with water, extracted with diethyl ether, washed with NaHCO₃ and brine and dried (MgSO₄). Solvent evaporation and purification by flash chromatography on silica gel gave 1.78 g 29 as viscous oil in 33% yield. ¹H NMR (500 MHz, CDCl₃) δ 7.27 (m as t, J = 7.5 Hz, 2H, 3-H, 5-H, OPh), 7.09 (m as d, J = 7.5 Hz, 2H, 2-H, 6-H, OPh), 6.93 (m as t, J = 7.5 Hz, 1H, 4-H, OPh), 6.88 (d, J = 2.5 Hz, 2H, 2-H, 6-H, ArH) 6.65 (t, J = 2.5 Hz, 1H, 4-H, ArH), 4.01 (t, 2H, 5′-H), 3.83 (s, 6H, -OCH₃), 3.02-3.00 (m, 2H, 2′-H), 1.97-1.84 (m, 4H, 3′-H, 4′-H).

1-[5-(3,5-dimethoxyphenyl)-5-methylhexyloxy]benzene (30). To a dry flask was added CH₂Cl₂ (30 mL) which was cooled to -40 °C. A 1.0 M solution of TiCl₄ in CH₂Cl₂ (14.2 mL, 14.28 mmol) was then added to the cold solution maintaining the temperature at -40 °C. The solution was cooled to -50 °C and then a 2.0 M solution of Zn(CH₃)₂ in toluene (6.8 mL, 14.28 mmol) was added rapidly, maintaining the temperature between -40 °C to -50 °C. Upon complete addition, the viscous orange solution was stirred vigorously for 10 min, after which a solution of 29 (750 mg, 2.38 mmol) in dry CH₂Cl₂ was added maintaining the temperature between -40 °C and -50 °C. The temperature was then allowed to rise slowly to -10 °C over 2 hours with constant stirring. The reaction mixture was poured into ice/water and the aqueous layer was separated and extracted with CH₂Cl₂. The combined organic layer was washed with saturated NaHCO₃, water and brine, dried (MgSO₄) and concentrated. The residue was purified by flash chromatography on silica gel (0-15% diethyl ether in hexanes) to yield pure 350 mg of 30 in 45 % yield. ¹H NMR (500 MHz, CDCl₃) δ 7.25 (m as t, J = 7.5 Hz, 2H, 3-H, 5-H, OPh), 6.91 (m as t, J = 7.5 Hz, 1H, 4-H, OPh), 6.85 (m as d, J = 7.5 Hz, 2H, 2-H, 6-H,
OPh), 6.49 (d, J = 2.5 Hz, 2H, 2-H, 6-H, ArH) 6.29 (t, J = 2.5 Hz, 1H, 4-H, ArH), 3.87 (t, 2H, 5′-H), 3.78 (s, 6H, -OCH₃), 1.73-1.66 (m, 2H, 2′-H), 1.65-1.62 (m, 2H, 3′-H), 1.28 (s, 6H, -C(CH₃)₂-), 1.25-1.21 (m, 2H, 4′-H).

5-(6-bromo-2-methylhexan-2-yl)benzene-1,3-diol (25g). A solution of 30 (200 mg, 0.608 mmol) in CH₂Cl₂ was cooled to -5 °C and then a 1.0 M solution of BBr₃ in CH₂Cl₂ (2.5 mL, 2.5 mmol) was added dropwise and the reaction was allowed to stir for 24 hours. On completion, the reaction mixture was poured into ice-water and the aqueous layer separated and extracted with diethyl ether. The combined organic layer was washed with NaHCO₃, water and brine and dried (MgSO₄). Solvent evaporation and purification by flash column chromatography on silica gel (15-35% ethyl acetate in hexanes) gave 147 mg of 25g in 84% yield. ¹H NMR (500 MHz, CDCl₃) δ 6.38 (d, J = 2.0 Hz, 2H, 2-H, 6-H, ArH) 6.18 (t, J = 2.0 Hz, 1H, 4-H, ArH), 4.88 (br s, 2H, -OH), 3.33 (t, J = 7.0 Hz, 2H, 5′-H), 1.79-1.73 (m, 2H, 2′-H), 1.56-1.52 (m, 2H, 3′-H), 1.25-1.21 (s and m overlapping, 8H, -C(CH₃)₂- and 4′-H, especially, 1.24, s, -C(CH₃)₂-); Mass spectrum (ESI) m/z (relative intensity) 289 (M⁺+H+2, 100), 287 (M⁺+H, 100), 213 (32), 207 (30), 181 (61), 130 (10), 79 (20). Exact mass (ESI) calculated for C₁₃H₂₀O₂Br (M⁺+H), 287.0647; found, 287.0646.

2-(3,5-dimethoxyphenyl)-2-methylpropanenitrile (32). A mixture of 3,5-dimethoxyphenyl acetonitrile (31) (10 g, 56.43 mmol) and methyl iodide (10.5 mL) in anhydrous DMF (280 mL) under an argon atmosphere was added dropwise (via canula) to a cooled solution of sodium hydride (4.06 g, 169.20 mmol) in 30 mL DMF at 0 °C. The mixture was warmed to room temperature and stirred for 1.5 hours. Upon completion, the reaction was quenched by the addition of saturated aqueous NH₄Cl. The
organic layer was separated and the aqueous phase was extracted with diethyl ether. The combined organic layer was washed with brine and dried (MgSO₄) and the solvent was evaporated under pressure. The residue was purified on a silica gel (10-30% ethyl acetate in hexanes) to afford 11.3g of compound 32 as an oil in 98% yield. ¹H NMR (500 MHz, CDCl₃) δ 6.61(d, J = 2.0 Hz, 2H, 2-H, 6-H, ArH), 6.27 (t, J = 2.0 Hz, 1H, 4-H, ArH), 3.81 (s, 6H, OMe), 1.70 (s, 6H, -C(CH₃)₂C); Mass spectrum (ESI) m/z (relative intensity) 207 (M⁺+H+1, 18), 206 (M⁺+H, 100), 179 (M⁺-CN, 31), 139 (17), 115 (20). Exact mass (ESI) calculated for C₁₂H₁₆O₂N (M⁺+H), 206.1181; found, 206.1177.

2-(3,5-dimethoxyphenyl)-2-methylpropanal (33). To a solution of 32 (7.67 g, 37.36 mmol) in anhydrous CH₂Cl₂ (373 mL) at –78 °C, under an argon atmosphere was added 1M solution of DIBAL-H in toluene (93.5 mL). The reaction mixture was stirred for 20 min and then quenched by dropwise addition of potassium sodium tartarate (10% solution in water) at –78 °C. Following the addition, the mixture was warmed to room temperature, stirred for an additional 50 minutes and then diluted with ethyl acetate. The organic phase was separated and the aqueous phase extracted with ethyl acetate. The combined organic layer was washed with brine, dried (MgSO₄), and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography on silica gel (10-35% ethyl acetate in hexane) to give 5.85 g of 33 as viscous oil in 75% yield. ¹H NMR (500 MHz, CDCl₃) δ 9.46 (s, 1H, -CHO), 6.40 (d, J = 2.0 Hz, 2H, 2-H, 6-H, ArH), 6.39 (t, J = 2.0 Hz, 1H, 4-H, ArH), 3.78 (s, 6H, OMe), 1.43 (s, 6H, -C(CH₃)₂-); Mass spectrum (EI) m/z (relative intensity) 208 (M⁺, 25), 196 (16), 179 (M⁺-CHO), 165 (25), 151 (14), 139 (39), 91 (20), 77 (20). Exact mass (EI) calculated for C₁₂H₁₆O₃ (M⁺), 208.10995; found, 208.11077.
(3-Phenoxypropyl)triphenylphosphonium bromide. A mixture of 3-phenoxypropyl bromide (11.3 g, 52.5 mmol) and triphenylphosphine (16.5 g, 63.0 mmol) in anhydrous toluene (65 mL) was refluxed for two days under argon. The reaction mixture was cooled to room temperature, and the precipitating product was isolated by filtration under reduced pressure as a white microcrystalline solid, (m.p = 154-156 °C) in 85% yield (21.37 g). ¹H NMR (500 MHz, CDCl₃) δ 7.87 (dd, J = 12.5 Hz, J = 7.5 Hz, 6H, -PPh₃), 7.79 (td, J = 7.5 Hz, J = 2.0 Hz, 3H, -PPh₃), 7.69 (td, J = 7.5 Hz, J = 3.5 Hz, 6H, -PPh₃), 7.24 (t, J = 7.5 Hz, 2H, 5-H, -OPh), 6.92 (t, J = 7.5 Hz, 1H, 4-H, -OPh), 6.85 (d, J = 9.0 Hz, 2H, 3-H, -OPh), 4.33 (t, J = 5.5 Hz, 2H, -CH₂OPh), 4.10 (dt, J = 13.0 Hz, J = 7.5 Hz, 2H, -CH₂PPh₃), 2.27-2.19 (m, 2H); Mass spectrum (ESI) m/z (relative intensity) 398 (M⁺+H-Br, 30), 397 (M⁺-Br, 100). Exact mass (ESI) calculated for C₂₇H₂₆O₃P (M⁺-Br), 397.1721; found, 397.1715.

(4-Phenoxybutyl)triphenylphosphonium bromide. The synthesis was carried out analogous to the preparation of (3-Phenoxypropyl)triphenylphosphonium bromide, using 4-phenoxybutyl bromide, (5.0 g, 21.82 mmol) and triphenylphosphine (6.86 g, 26.18 mmol) in anhydrous toluene (27 mL) and gave 6.6 g of white microcrystalline solid, (m.p = 185-186 °C) in 62 % yield. ¹H NMR (500 MHz, CDCl₃) δ 7.86 (dd, J = 13.0 Hz, J = 7.5 Hz, 6H, -PPh₃), 7.77 (td, J = 7.5 Hz, J = 2.0 Hz, 3H, -PPh₃), 7.67 (td, J = 7.5 Hz, J = 3.5 Hz, 6H, -PPh₃), 7.25 (t, J = 8.0 Hz, 2H, 3-H, -OPh), 6.92 (t, J = 8.0 Hz, 1H, 4-H, -OPh), 6.82 (d, J = 8.0 Hz, 2H, 2-H, -OPh), 4.09 (t, J = 5.3 Hz, 2H, -CH₂OPh), 4.01 (dt, J = 12.6 Hz, J = 8.1 Hz, 2H, -CH₂PPh₃), 2.25 (qt, J = 6.5 Hz, 2H), 1.93-1.85 (m, 2H); Mass spectrum (ESI) m/z (relative intensity) 412 (M⁺+H-Br, 37), 411 (M⁺-Br, 100). Exact mass (ESI) calculated for C₂₈H₂₈O₃P (M⁺-Br), 411.1878; found, 411.1880.
(5-phenoxypentyl)triphenylphosphonium bromide. The synthesis was carried out analogous to the preparation of (3-phenoxypropyl)triphenylphosphonium bromide using 5-phenoxypentyl bromide (4.73 g, 19.33 mmol) and triphenylphosphine (6 g, 23.19 mmol) in anhydrous toluene (60 mL) and gave 6.6 g of white microcrystalline solid, (m.p = 174-176 °C) in 74% yield. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.86 (dd, $J = 12.7$ Hz, $J = 8.3$ Hz, 6H, -PPh$_3$), 7.78 (td, $J = 8.3$ Hz, $J = 1.0$ Hz, 3H, -PPh$_3$), 7.68 (td, $J = 8.3$ Hz, $J = 3.5$ Hz, 6H, -PPh$_3$), 7.24 (t, $J = 8.0$ Hz, 2H, 3-H, 5-H, -OPh), 6.91 (t, $J = 8.0$ Hz, 1H, 4-H, -OPh), 6.78 (d, $J = 8.0$ Hz, 2H, 2-H, 6-H, -OPh), 3.96-3.86 (t and dt overlapping, 4H, -CH$_2$OPh, -CH$_2$PPh$_3$), 1.90-1.79 (m, 4H), 1.77-1.69 (m, 2H); Mass spectrum (ESI) m/z (relative intensity) 426 (M$^+$+H-Br, 38), 425 (M$^+$-Br, 100). Exact mass (ESI) calculated for C$_{29}$H$_{30}$OP (M$^+$-Br), 425.2034; found, 425.2027.

(Z)-3,5-Dimethoxy-1-(2-methyl-6-phenoxyhex-3-en-2-yl) benzene (34a). To a stirred suspension of (3-phenoxypropyl)triphenylphosphonium bromide (13.7 g, 28.8 mmol) in dry THF (90 mL) at -78 °C, under an argon atmosphere was added n-butyl lithium (11.5 mL, 28.8 mmol, 2.5 M in hexanes). The mixture was stirred for 30 minutes to ensure complete formation of the orange phosphorane. A solution of aldehyde 33 (4 g, 19.20 mmol) in 5 mL THF was added dropwise to the resulting slurry, at -78 °C. The reaction was stirred for 2 hours and upon completion was quenched by the addition of saturated aqueous NH$_4$Cl. The organic layer was seperated and the aqueous phase was extracted with diethyl ether. The combined organic layer was washed with brine and dried (MgSO$_4$) and the solvent was evaporated under reduced pressure. The residue was purified on a silica gel (5-15 % ethyl acetate in hexanes) to give 5.82 g compound 34a as colorless oil in 93% yield. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.22 (m as t, $J = 7.5$ Hz, 2H, 3-
H, 5-H OPh), 6.89 (m as t, J = 7.5 Hz, 1H, 4-H, OPh), 6.76 (m as d, J = 7.5 Hz, 2H, 2-H, 6-H, OPh), 6.57 (d, J = 2.8 Hz, 2H, 2-H, 6-H, ArH), 6.28 (t, J = 2.8 Hz, 1H, 4-H, ArH), 5.78 (dt, J = 11.0 Hz, J = 1.5 Hz, 1H, 2'-H), 5.42 (dt, J = 11.0 Hz, J = 7.5 Hz, 1H, 3'-H), 3.75 (s, 6H, OCH3), 3.73 (t, J = 7.0 Hz, 2H, 5'-H), 2.14 (q, J = 7.0 Hz, 2H, 4'-H), 1.43 (s, 6H, -C(CH3)2C); 13C NMR (125 MHz, CDCl3) δ 161.22 (>C=C(-)-O-), 159.33 (>C=C(-)-O-), 153.33 (>C=C<), 142.01 (>C=C<), 129.58 (>C=C<), 126.34 (>C=C<), 121.02 (>C=C<), 114.23 (>C=C<), 105.03 (>C=C<), 97.44 (>C=C<), 67.32 (-CH2-O-), 55.73 (-OCH3), 40.07, 31.83, 28.72; Mass spectrum (ESI) m/z (relative intensity) 349 (M+Na, 5), 328 (M+H+1, 25), 327 (M+H, 100), 233 (M+H-OPh, 64), 177 (9), 165 (15), 151 (15).

Exact mass (ESI) calculated for C21H27O3 (M+H+), 327.1960; found, 327.1954.

(Z)-3,5-Dimethoxy-1-(2-methyl-7-phenoxyhept-3-en-2-yl) benzene (34b). The synthesis was carried out as described for 34a using (4-phenoxybutyl)triphenylphosphonium bromide (7 g 14.4 mmol), 33 (2 g, 9.60 mmol), n-butyl lithium (5.7 mL, 14.4 mmol, 2.5 M in hexanes) in anhydrous THF (45 mL). The crude product obtained after work up was purified by flash column chromatography on silica gel (5-15 % ethyl acetate in hexanes) to give 3 g of compound 34b as a colorless oil in 92% yield. 1H NMR (500 MHz, CDCl3) δ 7.25 (m as t, J = 7.0 Hz, 2H, 3-H, 5-H, OPh), 6.90 (m as t, J = 7.0 Hz, 1H, 4-H, OPh), 6.81 (m as d, J = 7.0 Hz, 2H, 2-H, 6-H, OPh), 6.56 (d, J = 2.5 Hz, 2H, 2-H, 6-H, ArH), 6.28 (t, J = 2.5 Hz, 1H, 4-H, ArH), 5.69 (d t, J = 11.0 Hz, J = 1.5 Hz, 1H, 2'-H), 5.31 (dt, J = 11.0 Hz, J = 7.8 Hz, 1H, 3'-H), 3.76 (s, 6H, OMe), 3.70 (t, J = 6.5 Hz, 2H, 6'-H), 1.83 (dtd, 2H, 4'-H), 1.64 (m, 2H, 5'-H), 1.34 (s, 6H, -C(CH3)2C-); Mass spectrum (ESI) m/z (relative intensity) 342 (M+H+1, 25), 341
(M^+H, 85), 248 (M^+H+1-OPh, 25), 247 (M^+H-OPh, 100), 205 (12), 191 (55), 165 (13). Exact mass (ESI) calculated for C_{22}H_{29}O_{3} (M^+H), 341.2117; found, 341.2109.

(Z)-3,5-Dimethoxy-1-(2-methyl-8-phenoxyoct-3-en-2-yl) benzene (34c). The synthesis was carried out as described for 34a using (5-phenoxybutyl)triphenylphosphonium bromide (14.5 g, 28.8 mmol), 33 (4 g, 19.2 mmol), n-butyl lithium (11.5 mL, 28.8 mmol, 2.5 M in hexanes) anhydrous THF (95 mL). The crude product obtained after work up was purified by flash column chromatography on silica gel (5-15 % ethyl acetate in hexanes) to give compound 8 g of 34c as a colorless oil in 87% yield. ^1H NMR (500 MHz, CDCl₃) δ 7.26 (m as t, J = 7.5 Hz, 2H, 3-H, 5-H, OPh), 6.91 (m as t, J = 7.5 Hz, 1H, 4-H, OPh), 6.83 (m as d, J = 7.5 Hz, 2H, 2-H, 6-H, OPh), 6.55 (d, J = 2.5 Hz, 2H, 2′-H, ArH), 6.27 (t, J = 2.5 Hz, 1H, 4-H, ArH), 5.65 (d t, J = 11.0 Hz, J = 1.5 Hz, 1H, 2′-H), 5.29 (dt, J = 11.0 Hz, J = 7.8 Hz, 1H, 3′-H), 3.79-3.73 (t and s overlapping, 8H, OMe and 7′-H), 1.71 (dtd, 2H, 4′-H), 1.56 (qt, 2H, 5′-H), 1.39 (s, 6H, -C(CH₃)₂-), 1.31 (qt, 2H, 6′-H); Mass spectrum (ESI) m/z (relative intensity) 377 (M^+Na, 5), 356 (M^+H, 30), 355 (M^+H+100), 261 (M^+H-OPh, 30), 205 (20), 191 (8), 165 (10), 115 (8). Exact mass (ESI) calculated for C_{21}H_{29}O_{3} (M^+H), 329.2117; found, 329.2109.

3,5-Dimethoxy-1-(2-methyl-6-phenoxyhexan-2-yl)benzene (35a). To a solution of 34a (5.85 g, 17.92 mmol) in EtOH (20 mL) was added 10% Pd/C (3 g, 17% w/w) and the resulting suspension stirred vigorously under hydrogen atmosphere, overnight at room temperature. The catalyst was removed by filtration through celite, and the filtrate was evaporated under reduced pressure to afford 5.2 g of the crude product 35a as colorless oil, in 89% yield which was used in the next step without further purification. ^1H NMR (500 MHz, CDCl₃) δ 7.25 (m as t, J = 7.5 Hz, 2H, 3-H, 5-H, OPh), 6.91 (m as t, J = 7.5
Hz, 1H, 4-H, OPh), 6.85 (m as d, $J = 7.5$ Hz, 2H, 2-H, 6-H, OPh), 6.49 (d, $J = 2.5$ Hz, 2H, 2-H, 6-H, ArH) 6.29 (t, $J = 2.5$ Hz, 1H, 4-H, ArH), 3.87 (t, 2H, 5-H, ArH), 3.78 (s, 6H, -OCH$_3$), 1.73-1.66 (m, 2H, 2'-H), 1.65-1.62 (m, 2H, 3'-H), 1.28 (s, 6H, -C(CH$_3$)$_2$C), 1.25-1.21 (m, 2H, 4'-H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 160.47 (C3 and C5 of Ph(OMe)$_2$), 159.09 (C1 of OPh), 152.34 (C1 of Ph(OMe)$_2$), 129.36 (C3 and C5 of OPh), 120.42 (C4 of OPh), 114.49 (C2 and C6 of OPh), 104.68 (C2 and C6 of Ph(OMe)$_2$), 96.60 (C2 of Ph(OMe)$_2$), 67.82 (C5'), 55.21 (-OMe), 44.40 (C2'), 37.97 (-C(CH$_3$)-), 29.17 (-C(CH$_3$)-), 28.96 (-C(CH$_3$)-), 26.72 (C4' or C3'), 24.48 (C3' or C4'); Mass spectrum (ESI) m/z (relative intensity) 330 (M$^+$+H+1, 25), 329 (M$^+$+H, 100), 235 (M$^+$+H-OPh, 20). Exact mass (ESI) calculated for C$_{21}$H$_{29}$O$_3$ (M$^+$+H), 329.2117; found, 329.2109.

3,5-Dimethoxy-1-(2-methyl-7-phenoxyheptan-2-yl)benzene (35b). The synthesis was carried out as described for 35a using 34b (1.36 g, 4.0 mmol) and 10% Pd/C (680 mg, 17% w/w) in EtOH (33 mL) and gave 1.21 g of product 35b as a colorless oil in 89% yield which was used in the next step without further purification. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.25 (m as t, $J = 7.5$ Hz, 2H, 3-H, 5-H, OPh), 6.91 (m as t, $J = 7.5$ Hz, 1H, 4-H, OPh), 6.86 (m as d, $J = 7.5$ Hz, 2H, 2-H, 6-H, OPh), 6.49 (d, $J = 2.5$ Hz, 2H, 2-H, 6-H, ArH) 6.30 (t, $J = 2.5$ Hz, 1H, 4-H, ArH), 3.88 (t, $J = 7.0$Hz, 2H, 6'-H), 3.78 (s, 6H, OMe), 1.74-1.68 (m, 2H, 2'-H), 1.62-1.57 (m, 2H, 3'-H), 1.4-1.33 (m, 2H, 4'-H), 1.26 (s, 6H, -C(CH$_3$)$_2$C), 1.17-1.11 (m, 2H, 5'-H); Mass spectrum (ESI) m/z (relative intensity) 344 (M$^+$+H+1, 35), 343 (M$^+$+H, 100). Exact mass (ESI) calculated for C$_{22}$H$_{31}$O$_3$ (M$^+$+H), 343.2273; found, 343.2274.

3,5-Dimethoxy-1-(2-methyl-8-phenoxyoctan-2-yl)benzene (35c). The synthesis was carried out as described for 35a using 34c (8 g, 22.5.0 mmol) and 10% Pd/C (3.83 mg,
17% w/w) in EtOH (188 mL) and gave 7.7 g of 35c as a colorless oil in 96% yield which was used in the next step without further purification. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.25 (m as t, $J$ = 8.0 Hz, 2H, 3-H, 5-H, OPh), 6.92 (m as t, $J$ = 8.0 Hz, 1H, 4-H, OPh), 6.86 (m as d, $J$ = 8.0 Hz, 2H, 2-H, 6-H, OPh), 6.49 (d, $J$ = 1.5 Hz, 2H, 2-H, 6-H, ArH), 6.30 (t, $J$ = 1.5 Hz, 1H, 4-H, ArH), 3.90 (t, $J$ = 6.0 Hz, 2H, 7′-H), 3.79 (s, 6H, OMe), 1.75-1.68 (m, 2H, 2′H), 1.59-1.53 (m, 2H, 3′-H), 1.43-1.35 (m, 2H, 4′-H), 1.30-1.22 (m and s overlapping, 8H, 5′-H and -C(CH$_3$)$_2$-), 1.12-0.60 (m, 2H, 6′-H); Mass spectrum (ESI) m/z (relative intensity) 358 (M$^+$+H+1, 30), 357 (M$^+$+H, 100), 281 (8), 263 (M$^+$+H-OPh, 5). Exact mass (ESI) calculated for C$_{23}$H$_{33}$O$_3$ (M$^+$+H), 357.2430; found, 357.2427.

5-(6-bromo-2-methylhexan-2-yl) resorcinol (25g)$^{173}$. To a stirred solution of 35a (5.2 g, 15.83 mmol) in dry CH$_2$Cl$_2$ (500 mL), at -78 °C, under an argon atmosphere, was added boron tribromide (6 mL, 63.3 mmol). Following the addition, the reaction mixture was gradually warmed to room temperature and the stirring was continued at that temperature until completion of the reaction (12 h). The reaction mixture was then poured into ice-water, warmed to room temperature and volatiles were removed in vacuo. The residue was diluted with ethyl acetate and was washed with saturated NaHCO$_3$ solution, water and brine. The organic layer was dried over MgSO$_4$, filtered and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (40% ethyl acetate in hexanes) afforded 3.84 g of 25g as a white foam in 85% yield. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 6.38 (d, $J$ = 2.0 Hz, 2H, 2-H, 6-H, ArH) 6.18 (t, $J$ = 2.0 Hz, 1H, 4-H, ArH), 4.85 (s, 2H, -OH), 3.33 (t, $J$ = 7.0 Hz, 2H, 5'-H), 1.79-1.73 (m, 2H, 2'-H), 1.56-1.52 (m, 2H, 3'H), 1.25-1.16 (s and m overlapping, 8H, -C(CH$_3$)$_2$C and 4'-H, especially, 1.23, s, -C(CH$_3$)$_2$-); Mass spectrum (ESI) m/z (relative intensity) 289 (M$^+$+H+2, 100), 287
Exact mass (ESI) calculated for C_{13}H_{20}O_{2}Br (M^{+}+H), 287.0647; found, 287.0646.

5-(7-bromo-2-methylhept-2-yl) resorcinol (25l). The synthesis was carried out as described for 25g using 35b (625 mg, 1.82 mmol) and boron tribromide (4.5 mL, 1M solution in CH_{2}Cl_{2}) in anhydrous CH_{2}Cl_{2}(75 mL). The crude product obtained after work up was purified by flash column chromatography on silica gel (50% ethyl acetate in hexane) to give 527 mg of pure 25l as a slightly brown viscous oil in 96% yield. \(^{1}\)H NMR (500 MHz, CDCl_{3}) \(\delta\) 6.38 (d, \(J = 2.0\) Hz, 2H, 2-\(H\), 6-\(H\), ArH) 6.18 (t, \(J = 2.0\) Hz, 1H, 4-H, ArH), 5.15 (br s , 2H, -OH), 3.34 (t, \(J = 7.0\) Hz, 2H, 6′-H) 1.80-1.75 (m, 2H, 2′-H), 1.55-1.50 (m, 2H, 3-H), 1.35-1.28 (m, 2H, 4′-H), 1.23 (s, 6H, -C(CH_{3})_{2}−), 1.10-1.02 (m, 2H, 5′-H); Mass spectrum (ESI) m/z (relative intensity) 303 (M^{+}+H+2, 100), 301 (M^{+}+H, 100), 221 (22), 193 (12), 191 (15), 181 (10), 165 (10), 111 (20). Exact mass (ESI) calculated for C_{14}H_{22}O_{2}Br (M^{+}+H), 301.0803; found, 301.0808.

5-(8-bromo-2-methyloct-2-yl) resorcinol (25c)\(^{173,155}\). The synthesis was carried out as described for 25g using 35c (8 g, 22.44 mmol) and boron tribromide (8.5 mL, 89.76 mmol) in anhydrous CH_{2}Cl_{2} (350 mL). The crude product obtained after work up was purified by flash column chromatography on silica gel (50% ethyl acetate in hexanes) to give 6.57 g of pure 25c as a slightly brown viscous oil in 93% yield. \(^{1}\)H NMR (500 MHz, CDCl_{3}) \(\delta\) 6.38 (d, \(J = 2.0\) Hz, 2H, 2-H, 6-H, ArH) 6.18 (t, \(J = 2.0\) Hz, 1H, 4-H, ArH), 4.69 (br s , 2H, -OH), 3.35 (t, \(J = 7.0\) Hz, 2H, 7′-H) 1.82-1.75 (m, 2H, 2′-H), 1.55-1.50 (m, 2H, 3′H), 1.40-1.33 (m, 2H, 4′-H), 1.23 (s and m overlapping, 8H, -C(CH_{3})_{2}−, -CH_{2}−of the side chain, especially 1.23, s, -C(CH_{3})_{2}−), 1.10-1.02 (m, 2H, -CH_{2}−of the side chain); Mass spectrum (ESI) m/z (relative intensity) 317 (M^{+}+H+2, 100), 315 (M^{+}+H,
100), 235 (10), 207 (8). Exact mass (ESI) calculated for C_{15}H_{24}O_{2}Br (M^{+}+H), 315.0960; found, 315.0952.

**2-(3,5-Dihydroxyphenyl)acetonitrile (36).** To a stirred solution of 31 (2.0 g, 11.28 mmol) in dry CH_{2}Cl_{2} (125 mL), at -78 °C, under an argon atmosphere, was added boron tribromide (3.75 ml, 39.48 mmol). Following the addition, the reaction mixture was gradually warmed to room temperature and the stirring was continued at that temperature until completion of the reaction (2 days). The reaction mixture was then poured into aqueous saturated NaHCO_{3} solution, and few pieces of ice were added. The reaction mixture was warmed to room temperature and volatiles were removed in vacuo. The residue was diluted with ethyl acetate and washed with saturated NaHCO_{3} solution, water and brine. The organic layer was dried over MgSO_{4}, filtered and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (40% ethyl acetate in hexanes) afforded 1.42 g of 36 as a white solid, (m.p = 144-146°C) in 85% yield. {\textsuperscript{1}}H NMR (500 MHz, CDCl_{3}/DMSO-d_{6}) δ 8.69 (s, 2H, OH), 6.34 (m, 1H, 2-H), 6.33 (m, 2H, 4-H, 6-H), 3.59 (s, 2H, -CH_{2}CN); Mass spectrum (EI) m/z (relative intensity) 149 (M^{+}, 100), 122 (15), 94 (20), 84 (10). Exact mass (EI) calculated for C_{8}H_{7}O_{2}N (M^{+}), 149.04768; found, 149.04848.

**2-[3,5-bis(1-ethoxyethoxy)phenylacetonitrile] (37).** To a solution of pre-dried 36 (2.6 g, 17.43 mmol) and p-toluene sulfonic acid (120 mg, 4 mol %), in anhydrous diethyl ether (65 mL) at 0 °C, under an argon atmosphere, was added a solution of ethyl vinyl ether (9.2 mL, 95.86 mmol) in anhydrous diethyl ether (10 mL). The reaction mixture was stirred at 0 °C for 1 h and then poured into a vigorously stirring saturated aqueous NaHCO_{3} at 0 °C. The organic phase was separated and the aqueous phase was extracted
with diethyl ether. The combined organic phase was washed with brine and dried (MgSO$_4$). Solvent evaporation followed by purification by flash column chromatography on silica gel (15% ethyl acetate and 2% triethyl amine in hexanes) gave 4.86 g of 37 in 95% yield. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 6.64 (m, 1H, 4-H), 6.61 (m, 2H, 2-H, 6-H), 5.37 (q, 2H, $J$ = 5.5 Hz, -OCH(CH$_3$)CH$_2$-), 3.76 (m as quintet, 2H, $J$ = 7.0 Hz, -OCH(CH$_3$)CH$_2$-), 3.67 (s, 2H, -CH$_2$CN), 3.55 (m as quintet, 2H, $J$ = 7.0 Hz, -OCH(CH$_3$)CH$_2$-), 1.49 (d, $J$ = 5.5 Hz, 6H, -CH$_2$CH$_3$); Mass spectrum (EI) m/z (relative intensity) 293 (M$^+$, 15), 248 (8), 221 (30), 204 (M$^+$-OEE, 2), 176 (52), 149 (100), 122(18), 94 (34), 73 (100). Exact mass (EI) calculated for C$_{16}$H$_{23}$O$_4$N (M$^+$), 293.16271; found, 293.16079.

4-[3,5-Bis(1-ethoxyethoxy)phenyl]tetrahydro-2H-pyran-4-carbonitrile (38). To a solution of 37 (4.9 g, 16.7 mmol) in dry THF (120 mL) at -16 °C, under an argon atmosphere, was added potassium bis-(trimethylsilyl)amide (10 g, 50.1 mmol). The mixture was stirred at the same temperature for 5 min, and then a solution of 2-bromoethyl ether (2.5 mL, 20.0 mmol) in dry THF (10 mL) was added over a period of 5 min. Following the addition, the reaction was stirred for 1h at -16 °C and then quenched by the addition of saturated aqueous NH$_4$Cl. The mixture was diluted with EtOAc, the organic layer separated, and the aqueous phase extracted with EtOAc. The combined organic layer was washed with brine and dried (MgSO$_4$) and the solvent evaporated under reduced pressure. Purification by flash column chromatography (30% ethyl acetate in hexanes) afforded 6 g of the compound 38 as a colorless oil in 98% yield. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 6.77 (d, $J$ = 2.5 Hz, 2H, 2-H, 6-H), 6.68 (dd, $J$ = 2.5 Hz, $J$ = 2.5 Hz, 1H, 4-H), 5.38 (q, 2H, $J$ = 5.5 Hz, -OCH(CH$_3$)CH$_2$-), 4.07 (dd, $J$ = 14.0 Hz, $J$ = 4.0 Hz,
2H, -CH₂O-, equatorial), 3.89 (ddd, J = 14.0 Hz, J = 12.0 Hz, J = 2.0 Hz, -CH₂O-, axial),
3.81-3.72 (m, 2H, -OCH(CH₃)CH₂-), 3.61-3.52 (m, 2H, -OCH(CH₃)CH₂-), 2.14-2.06 (m,
2H, -CH₂CH₂O-, axial), 2.05-2.0 (m as d, J = 11.5 Hz, 2H, -CH₂CH₂O-, equatorial), 1.51
(d, J = 5.0 Hz, 6H, -OCH(CH₃)CH₂-), 1.22 (t, J = 7.0 Hz, 6H, -CH₂CH₃); Mass spectrum
(EI) m/z (relative intensity) 363 (M⁺, 2), 318 (3), 291 (9), 246 (11), 219 (32), 175 (55),
73 (100). Exact mass (EI) calculated for C₂₀H₂₉O₅N (M⁺), 363.20457; found, 363.20604.

4-(3, 5-Dihydroxyphenyl)tetrahydro-2H-pyran-4-carbonitrile (39). Compound 38
(3.26 g, 8.96 mmol) was dissolved in methanol (44 mL), and p-toluenesulfonic acid (61.6
mg, 4 mol %) was added. The reaction mixture was stirred at 25 °C for 0.5 h. The
methanol was removed in vacuo, and the residue was dissolved in ethyl acetate and
washed with NaHCO₃/brine (1:1). The aqueous phase was extracted twice with ethyl
acetate. The combined organic phase was washed with brine and dried over MgSO₄.
Solvent evaporation followed by purification by flash column chromatography (30%
ethyl acetate in hexanes) gave 1.78 g of 39 as a white solid, (m.p = 210-212 °C ) in 91%
yield. ¹H NMR (500 MHz, CDCl₃/DMSO-d₆) δ 8.51 (s, 2H, OH), 6.49 (d, J = 1.5 Hz,
1H, 2-H), 6.33 (m, 2H, 4-H, 6-H), 4.04 (dd, J = 12.0 Hz, J = 4.0 Hz, 2H, -CH₂O-,
equatorial), 3.86 (ddd, J = 12.0 Hz, J = 12.0 Hz, J = 1.2 Hz, 2H, -CH₂O-, axial), 2.09 (td,
J = 12.0 Hz, J = 4.5 Hz, 2H, -CH₂CH₂O-, axial), 2.20-1.97 (m as d, J = 12.5 Hz, 2H, -
CH₂CH₂O-, equatorial); Mass spectrum (EI) m/z (relative intensity) 219 (M⁺, 25),
175(100), 162 (40), 135 (12), 91 (10), 84 (13). Exact mass (EI) calculated for C₁₂H₁₃O₃N
(M⁺), 219.08955; found, 219.08884.

4-[3,5-Bis[tert-butyldimethylsilyloxy]phenyl]tetrahydro-2H-pyran-4-carbonitrile
(40). To a solution of 39 (1.32 g, 6.02 mmol) in DMF (30 mL) was added imidazole (3.1
After 10 minutes, TBDMSCl (5.45 g, 36.12 mmol) was added and the mixture was stirred for 2 h. The reaction was quenched with water and extracted with diethyl ether. The ethereal layer was washed with brine and dried over MgSO₄. Solvent evaporation followed by flash column chromatography on a silica gel column, eluting with gradient 10-25% ether in hexane, afforded 2.45 g of compound 40 as a white solid, (m.p = 122-123 °C) in 91% yield. ¹H NMR (500 MHz, CDCl₃) δ 6.57 (d, J = 2.0 Hz, 2-H, 6-H), 6.29 (t, J = 2.0 Hz, 1H, 4-H), 4.06 (ddd, J = 14.0 Hz, J = 12.5 Hz, J = 4.5 Hz, 2H, -CH₂O-, equatorial), 3.88 (ddd, J =14.0 Hz, J = 12.5 Hz, J = 2.5 Hz, 2H, -CH₂O-, axial), 2.11-2.03 (m as td, J = 13.0 Hz, J = 4.5 Hz, 2H, -CH₂CH₂O-, axial), 2.20-1.97 (m as d, J = 13.0 Hz, 2H, -CH₂CH₂O-, equatorial), 0.98 (s, 18H, Si(CH₃)₂C(CH₃)₃), 0.18 (s, 12H, Si(CH₃)₂C(CH₃)₃); Mass spectrum (El) m/z (relative intensity) 447 (M⁺, 70), 390 (98), 363 (100), 333 (68), 73 (65). Exact mass (El) calculated for C₂₄H₄₁O₃NSi₂ (M⁺), 447.26251; found, 447.26185.

4-{3,5-Bis[tert-butyldimethylsilyloxy]phenyl}tetrahydro-2H-pyran-4-carboxaldehyde (41). To a solution of 40 (0.428 g, 0.955 mmol) in anhydrous CH₂Cl₂ (9.5 mL) at −78 °C, under an argon atmosphere was added 1M solution of DIBAL-H in toluene (2.57 mL). The reaction mixture was stirred for 2.5 h and then quenched by dropwise addition of potassium sodium tartarate (10% solution in water) at – 78 °C. Following the addition, the mixture was warmed to room temperature, stirred for an additional 50 minutes and then diluted with ethyl acetate. The organic phase was separated and the aqueous phase extracted with ethyl acetate. The combined organic layer was washed with brine, dried over MgSO₄, and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography on silica gel (0-10%
diethyl ether in hexanes) to give 41 as white foam in 51% yield. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 9.35 (s, 1H, CHO), 6.37 (d, $J = 2.5$ Hz, 2H, 6-H), 6.27 (t, $J = 2.5$ Hz, 1H, 4-H), 3.89 (ddd, $J = 13.5$ Hz, $J = 4.0$ Hz, $J = 4.0$ Hz, 2H, -CH$_2$O-, equatorial), 3.57 (ddd, $J = 13.5$ Hz, $J = 12.0$ Hz, $J = 2.5$ Hz, 2H, -CH$_2$O-, axial), 2.32-2.26 (m as d, $J = 13.5$ Hz, 2H, -CH$_2$CH$_2$O-, equatorial), 2.02 (ddd, $J = 13.5$ Hz, $J = 10.5$ Hz, $J = 4.5$ Hz, 2H, -CH$_2$CH$_2$O-, axial), 0.96 (s, 18H, Si(CH$_3$)$_2$C(CH$_3$)$_3$), 0.18 (s, 12H, Si(CH$_3$)$_2$C(CH$_3$)$_3$); Mass spectrum (EI) m/z (relative intensity) 450 (M$^+$, 67), 422 (92), 393 (100), 363 (90), 335 (51), 307 (18), 133 (18). Exact mass (EI) calculated for C$_{24}$H$_{42}$O$_4$Si$_2$ (M$^+$), 450.26217; found, 450.26352.

3,5-[Bis(tert-butyldimethylsilyl)oxy]-1-[4-(1,2-cis-hexen-1-yl)tetrahydro-2H-pyran-4-yl]-benzene (42). To a stirred suspension of pentyl triphenylphosphonium bromide (1.58 g, 3.82 mmol) in dry THF (9.5 mL) at 0 °C, under an argon atmosphere was added potassium bis(trimethylsilyl)amide (7.01 g, 35.6 mmol). The mixture was warmed to 10 °C and stirred for an additional 30 min to ensure complete formation of the orange (butylmethylene)triphenylphosphorane. To the resulting slurry, at the same temperature, was added dropwise a solution of 41 (0.245 g, 0.555 mmol) in dry THF (2 mL). The reaction was stirred for 10 min and upon completion was quenched by the addition of saturated aqueous NH$_4$Cl. The organic layer was separated, and the aqueous phase was extracted with diethyl ether. The combined organic layer was washed with brine and dried over MgSO$_4$, and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (5-25 % diethyl ether in hexanes) and gave compound 42 as colorless oil in 72% yield. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 6.46 (d, $J = 2.0$ Hz, 2H, 2-H, 6-H), 6.17 (t, $J = 2.0$ Hz, 1H, 4-H), 5.71 (dt, $J =$
12.0 Hz, \( J = 1.5 \) Hz, 1H, 2'-H), 5.42 (dt, \( J = 12.0 \) Hz, \( J = 7.5 \) Hz, 1H, 3'-H), 3.83 (ddd, \( J = 13.5 \) Hz, \( J = 4.0 \) Hz, 2H, -CH\(_2\)O-, equatorial), 3.73 (ddd, \( J = 13.5 \) Hz, \( J = 11.0 \) Hz, \( J = 2.0 \) Hz, 2H, -CH\(_2\)O-, axial), 2.04-1.96 (m, 2H, -CH\(_3\)CH\(_2\)O-, axial), 1.88-1.82 (m, 2H, -CH\(_3\)CH\(_2\)O-, equatorial), 1.64 (dt, \( J = 7.5 \) Hz, 2H, 4'-H), 1.12-1.06 (m, 4H, 5'-H, 6'-H), 0.96 (s, 18H, Si(CH\(_3\))\(_2\)C(CH\(_3\))\(_3\)), 0.75 (t, \( J = 7.0 \) Hz, 3H, 7'-H), 0.17 (s, 12H, Si(CH\(_3\))\(_2\)C(CH\(_3\))\(_3\)); Mass spectrum (EI) m/z (relative intensity) 504 (M\(^+\), 100), 461 (32), 447 (60), 421 (95), 352 (42), 133 (12). Exact mass (EI) calculated for C\(_{29}\)H\(_{52}\)O\(_3\)Si\(_2\) (M\(^+\)), 504.34551; found, 504.34630.

5-[4-(1,2-cis-hexen-1-yl)tetrahydro-2\(H\)-pyran-4-yl] resorcinol (25m). To a stirred solution of 42 (248 mg, 0.491 mmol) in THF (13 mL) was added tetra-\(n\)-butylammonium fluoride (0.568 mL, 1.96 mmol, 1M solution in THF). The reaction was stirred for 0.5 h and on completion; it was quenched with water and extracted with diethyl ether. The organic phase was washed with water and brine, dried (MgSO\(_4\)) and concentrated. Purification by flash column chromatography on silica gel (30-45% ethyl acetate in hexanes) gave 134 mg of white solid 25m (m.p = 104-105 °C) in 98% yield. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 6.43 (d, \( J = 2.0 \) Hz ,2H, 2-H, 6-H), 6.18 (t, \( J = 2.0 \) Hz, 1H, 4-H), 5.70 (dt, \( J = 11.5 \) Hz, \( J = 1.2 \) Hz, 1H, 2'-H), 5.46 (dt, \( J = 11.5 \) Hz, \( J = 7.5 \) Hz, 1H, 3'-H), 4.85 (br s, 2H, OH), 3.86 (ddd, \( J = 12.0 \) Hz, \( J = 3.5 \) Hz, \( J = 3.5\)Hz, 2H, -CH\(_2\)O-, equatorial), 3.75 (ddd, \( J = 12.0 \) Hz, \( J = 12.0 \) Hz, \( J = 1.5 \) Hz, 2H, -CH\(_2\)O-, axial), 2.10-1.97 (m as td, \( J = 12.0 \) Hz, \( J = 4.5 \) Hz, 2H, -CH\(_2\)CH\(_2\)O-, axial), 1.86-1.82 (m as d, \( J = 12.0 \) Hz, 2H, -CH\(_2\)CH\(_2\)O-, equatorial), 1.63 (dt, \( J = 7.3 \) Hz, 2H, 4'-H), 1.14-1.06 (m, 4H, 5'-H, 6'-H), 0.75 (t, \( J = 7.0 \) Hz, 3H, 7'-H); Mass spectrum (ESI) m/z (relative intensity)
278 (M^+H+1, 20), 277 (M^+H, 100), 259 (45), 233 (40), 179 (13), 149 (13). Exact mass (ESI) calculated for C_{17}H_{25}O_{3} (M^+H), 277.1804; found, 277.1796.

2-[(1S,6S)-3-(Acetoxymethyl)-6-(1-methylethenyl)-2-cyclohexen-1-yl]-5-(1,1-dimethylheptyl) resorcinol (26a). To a solution of resorcinol 25a (60 mg, 0.25 mmol) in anhydrous CH$_2$Cl$_2$ at -10 °C under an argon atmosphere was added p-toluenesulfonic acid (9.5 mg, 0.05 mmol), and a solution of terpene 16 (74 mg, 0.304 mmol) in anhydrous CH$_2$Cl$_2$. The reaction mixture was allowed to warm to 25 ºC over 4 hours, at which time TLC indicated the complete consumption of starting material. The reaction mixture was diluted with diethyl ether, and washed with saturated NaHCO$_3$ solution, water, and brine. The organic layer was dried over MgSO$_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (30% diethyl ether in petroleum ether) afforded 60 mg of 26a as colorless viscous oil in 55% yield. [$\alpha$]$_D^{26.5}$ = 194.83° (c = 0.214 g/100 mL in CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) δ 6.36 (br s, 2H, ArH), 5.89 (s, 1H, >C=CH$-$), 5.50 (br s, 1H, OH), 4.64 (br s, 1H, OH), 4.61 (m as t, J =1.5 Hz, 1H, >C=CH$_2$), 4.56 (d, J = 13.0 Hz, 1H, half of an AB system, -CH$_2$-O$-$), 4.54 (d, J = 13.0 Hz, 1H, half of an AB system, -CH$_2$-O$-$), 4.53 (br s, 1H, >C=CH$_2$), 3.91 (m as br d, J = 10.3 Hz, 1H, >C=CH-CH$<$), 2.48 (ddd, J = 10.1 Hz, J = 9.9 Hz, J = 3.1 Hz, 1H, >CH-C(CH$_3$)=CH$_2$), 2.32-2.14 (m, 2H, -CH$_2$-C(CH$_2$OCOCH$_3$)=C$<$), 2.09 (s, 3H, -OCOCH$_3$), 1.92-1.86 (m, 1H, -CH$_2$-CH$_2$-C(CH$_2$OCOCH$_3$)=C$<$, equatorial), 1.84-1.75 (m, 1H, -CH$_2$-CH$_2$-C(CH$_2$OCOCH$_3$)=C$<$, axial), 1.64 (s, 3H, >CH-C(CH$_3$)=CH$_2$), 1.48 (m, 2H, -C(CH$_3$)$_2$-CH$_2$-), 1.24-1.14 (m and s overlapping, 12 H, -C(CH$_3$)$_2$- and -CH$_2$-CH$_2$-CH$_2$-CH$_3$, -CH$_2$-CH$_2$-CH$_2$-CH$_3$, especially 1.20, s and 1.21, s, -C(CH$_3$)$_2$-), 1.14-0.96 (m, 2H, -C(CH$_3$)$_2$-CH$_2$-CH$_2$-), 0.84 (t, J = 6.5 Hz, 3H, -CH$_2$CH$_3$);
$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 171.42 (C=O), 155.82 (brs, ArC1 or ArC3), 154.19 (brs, ArC3 or ArC1), 150.59 (ArC5), 148.87 (C8), 137.44 (C3), 128.38 (C2), 113.19 (ArC2), 111.231 (C9), 108.04 (brs, ArC4 or ArC6), 106.08 (brs, ArC6 or ArC4), 68.05 (C7), 46.29 (C6), 44.78 (C2'), 37.65 (-C(CH$_3$)$_2$-), 37.08 (C1), 32.04 (C5'), 30.21 (C4'), 28.88 (-C(CH$_3$)$_2$-), 28.25 (C5), 26.55 (C4), 24.91 (C3'), 22.89 (C6'), 21.13 (-OCOCH$_3$), 20.50 (10-Me), 14.25 (C7')

Mass spectrum (ESI) m/z (relative intensity) 451 (M$^+$+Na, 35), 429 (M$^+$+H, 73), 369 (M$^+$-OCOCH$_3$, 100). Exact mass (ESI) calculated for C$_{27}$H$_{41}$O$_4$ (M$^+$+H), 429.3005; found, 429.3017; LCMS (ES+) retention time, 6.07 min (Method B); purity (100%).

2-[(1S,6S)-3-(Hydroxymethyl)-6-(1-methylethenyl)-2-cyclohexen-1-yl]-5-(1,1-dimethylheptyl) resorcinol (27a). To a solution of 26a (10 mg, 0.023 mmol) in anhydrous CH$_2$Cl$_2$ at –78°C, under an argon atmosphere was added 1M solution of DIBAL-H in toluene (1.4 mL). The reaction mixture was stirred for 20 min and then quenched by dropwise addition of potassium sodium tartrate (10% solution in water) at –78°C. Following the addition, the mixture was warmed to room temperature, stirred for an additional 50 minutes and then diluted with ethyl acetate. The organic phase was separated and the aqueous phase extracted with ethyl acetate. The combined organic layer was washed with brine, dried (MgSO$_4$), and the solvent was evaporated under pressure. The crude product was purified by flash chromatography on silica gel (20-40% ethyl acetate in hexane) to give pure 27a as viscous oil in 72% yield (6.5 mg). $[\alpha]_D^{26.6} = 224.34^\circ$ ($c = 0.221$ g/100 mL in CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 6.34 (br s, 2H, ArH), 5.87 (s, 1H, >C=CH-), 5.57 (br s, 1H, OH), 4.71 (br s, 1H, OH), 4.66 (m as t, $J = 1.5$ Hz, 1H, >C=CH$_2$), 4.55 (br s, 1H, >C=CH$_2$), 4.14 (d, $J = 14.0$ Hz, 1H, -CH$_2$-O-),
4.09 (d, J = 14.0 Hz, 1H, -CH$_2$-O-), 3.91 (m as br d, J = 10.2 Hz, 1H, >C=CH-CH<H), 2.47 (ddd, J = 10.1 Hz, J = 9.9 Hz, J = 3.1 Hz, 1H, >CH-C(CH$_3$)=CH$_2$), 2.28-2.22 (m, 2H, CH$_2$-C(CH$_2$OH)=C<H), 1.94-1.87 (m, 1H, -CH$_2$-CH$_2$-C(CH$_2$OH)=C<H, equatorial), 1.85-1.75 (m, 1H, -CH$_2$-CH$_2$-C(CH$_2$OH)=C<H, axial), 1.65 (s, 3H, >CH-C(CH$_3$)=CH$_2$), 1.48 (m, 2H, -C(CH$_3$)$_2$-CH$_2$), 1.24-1.14 (m and s overlapping, 12 H, -C(CH$_3$)$_2$- and –C(CH$_3$)$_2$-), 1.14-0.96 (m, 2H, -C(CH$_3$)$_2$-CH$_2$-CH$_2$-), 0.84 (t, J = 6.5 Hz, 3H, -CH$_2$CH$_3$); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 155.82 (brs, ArC1 or ArC3), 154.02 (brs, ArC3 or ArC1), 150.65 (ArC5), 149.27 (C8), 142.28 (C3), 125.61 (C2), 113.44 (ArC2), 111.27 (C9), 107.88 (brs, ArC4 or ArC6), 106.36 (brs, ArC6 or ArC4), 66.77 (C7), 46.68 (C6), 44.93 (C2'), 37.71 (-C(CH$_3$)$_2$-), 37.24 (C1), 32.15 (C5'), 30.29 (C4'), 29.04 (-C(CH$_3$)$_2$-), 29.00 (-C(CH$_3$)$_2$-), 28.54 (C5), 26.34 (C4), 24.96 (C3'), 22.95 (C6'), 20.70 (10-Me), 14.43 (C7'); Mass spectrum (ESI) m/z (relative intensity) 409 (M$^+$+Na, 13), 387 (M$^+$+H, 90), 369 (M$^+$-OH, 100). Exact mass (ESI) calculated for C$_{25}$H$_{39}$O$_3$ (M$^+$+H), 387.2899; found, 387.2898; LCMS (ES+) retention time, 5.92 min (Method A); purity (100%).

**Reaction of terpene 16 with Olivetol 25b in the presence of p-toluene sulfonic acid**

2-[(1S,6S)-3-(Acetoxymethyl)-6-(1-methylethenyl)-2-cyclohexen-1-yl]-5-pentylresorcinol (26b). To a solution of olivetol 25b (61 mg, 0.34 mmol) in anhydrous CH$_2$Cl$_2$ at -10 °C under an argon atmosphere was added p-toluenesulfonic acid (13 mg, 0.067 mmol), and a solution of terpene 16 (100 mg, 0.475 mmol in CH$_2$Cl$_2$. The reaction mixture was stirred at -10 °C to 20 °C for 4 hours, at which time TLC indicated the complete consumption of olivetol. The reaction mixture was diluted with diethyl ether, and washed sequentially with saturated NaHCO$_3$ solution, water and brine. The organic
layer was dried (MgSO₄), filtered and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (diethyl ether in hexanes) gave in order of elution: **26b** (15 mg, 12%, viscous oil), **44** (7 mg, 6%, viscous oil) and **45** (8 mg, 6%, colorless gum). **26b**: ^1^H NMR (500 MHz, CDCl₃) δ 6.24 (br s, 2H, ArH), 5.87 (s, 1H, >C=CH-), 5.48 (br s, 1H, OH), 4.65 (br s, 1H, OH), 4.64 (m as t, J = 1.5 Hz, 1H, >C=CH₂), 4.57-4.49 (d, d, br s, overlapping, 3H, -CH₂-O-, >C=CH₂), 3.94 (m as br d, J = 10.3 Hz, 1H, >C=CH-CH), 2.49 (ddd, J = 10.1 Hz, J = 9.9 Hz, J = 3.1 Hz, 1H, >CH-C(CH₃)=CH₂), 2.44 (m as t, J = 8.0 Hz, 2H, Ar-CH₂-), 2.30-2.13 (m, 2H, CH₂-C(CH₂OCOCH₃)=C<), 2.09 (s, 3H, -OCOCH₃), 1.92-1.86 (m, 1H, -CH₂-CH₂-C(CH₂OCOCH₃)=C<, equatorial), 1.84-1.75 (m, 1H, -CH₂-CH₂-C(CH₂OCOCH₃)=C<, axial), 1.66 (s, 3H, >CH-C(CH₃)=CH₂), 1.59-1.52 (m, 2H, Ar-CH₂-CH₂-), 1.35-1.24 (m, 4H, Ar-CH₂-CH₂-CH₂-CH₂-), 0.84 (t, J = 7.0 Hz, 3H, -CH₂CH₃); Mass spectrum (ESI) m/z (relative intensity) 373 (M^+H, 45), 313 (M^+-OCOCH₃, 100). Exact mass (ESI) calculated for C₂₃H₃₃O₄ (M^+H), 373.2379; found, 373.2366.

**(6aS,10aS)-6a,7,8,10a-Tetrahydro-1-hydroxy-6,6-dimethyl-3-pentyl-6H-dibenzo[b,d]pyran-9-methanol acetate (44)**. ^1^H NMR (500 MHz, CDCl₃) δ 6.75 (m as d, J = 1.0 Hz, 1H, 10-H), 6.27 (d, J = 1.5 Hz, 1H, ArH), 6.12 (d, J = 1.5 Hz, 1H, ArH), 4.78 (s, 1H, OH), 4.48 (m, AB system, 2H, -CH₂-O-), 3.27 (br d, J = 11.0 Hz, 1H, 10a-H), 2.43 (td, J = 8.0 Hz, J = 2.5 Hz, 2H, 1'-H), 2.33-2.16 (m, 2H, 8-H), 2.07 (s, 3H, -OCOCH₃), 2.00-1.94 (dddd, J = 12.5 Hz, J = 7.0 Hz, J = 3.0 Hz, J = 1.5 Hz, 1H, 7-H), 1.73 (ddd, J = 11.0 Hz, J = 10.5 Hz, J = 2.5 Hz, 1H, 6a-H), 1.59-1.52 (m, 2'-H), 1.49-1.38 (m and s overlapping, 4H, 6-Me, 7-H, especially 1.42, s, 6-Me), 1.34-1.24 (m, 4H, 3’-H, 4’-H), 1.10 (s, 3H, 6-Me), 0.88 (t, J = 7.0 Hz, 3H, 5'-H); Mass spectrum (ESI) m/z
(relative intensity) 373 (M$^+$+H, 100), 313 (65). Exact mass (ESI) calculated for C$_{23}$H$_{33}$O$_4$ (M$^+$+H), 373.2379; found, 373.2377.

4-[(1S,6S)-3-(Acetoxymethyl)-6-(1-methylethenyl)-2-cyclohexen-1-yl]-5-pentyl-resorcinol (45). $^1$H NMR (500 MHz, CDCl$_3$) δ 6.23 (d, $J = 2.5$ Hz, 1H, half of an AB system, ArH), 6.22 (d, $J = 2.5$ Hz, 1H, half of an AB system, ArH), 5.80 (br s, >C=CH-$\cdot$), 5.57 (br s, 1H, OH), 4.79 (br s, 1H, OH), 4.66 (m as t, $J = 1.5$ Hz, 1H, >C=CH$_2$), 4.54 (m, 2H, -CH$_2$O-), 4.48 (s, 1H, >C=CH$_2$), 3.56 (m as br d, $J = 10.3$ Hz, 1H, >C=CH-$\cdot$), 2.64-2.53 (m, 2H), 2.32-2.21 (m, 2H), 2.20-2.13 (m, 1H), 2.08 (s, 3H, -OCOCH$_3$), 1.93-1.87 (m, 1H, -CH$_2$-CH$_2$-CH$_2$OOCOCH$_3$=C$\cdot$, equatorial), 1.85-1.74 (m, 1H, -CH$_2$-CH$_2$-CH$_2$OOCOCH$_3$=C$\cdot$, axial ), 1.53 (s, 3H, >CH-$\cdot$C(CH$_3$)=CH$_2$), 1.47 (quintet, $J = 6.3$ Hz, 2H, 2'-H), 1.37-1.25 (m, 4H, 3'-H and 4'-H), 0.89 (t, $J = 7.0$ Hz, 3H, -CH$_2$CH$_3$); Mass spectrum (ESI) m/z (relative intensity) 373 (M$^+$+H, 43), 313 (M$^+$-OCOCH$_3$, 100). Exact mass (ESI) calculated for C$_{23}$H$_{33}$O$_4$ (M$^+$+H), 373.2395; found, 373.2379.

Cyclization of cannabidiol acetate 26b catalyzed by BF$_3$:Et$_2$O

(6aS,10aS)-6a,7,8,10a-Tetrahydro-1-hydroxy-6,6-dimethyl-3-pentyl-6H-dibenzo[b,d]pyran-9-methanol acetate (44). To a solution of 26b (8.2 mg, 0.019 mmol) in anhydrous CH$_2$Cl$_2$ at 0 °C under an argon atmosphere was added boron trifluoride etherate (6.79 mg, 0.0478 mmol) and the mixture was stirred at 0 °C for 2 h. The reaction was quenched by the addition of saturated NaHCO$_3$ solution and diluted with diethyl ether and the organic layer was separated. The aqueous phase was extracted with diethyl ether and the combined organic layer was washed with water and brine and dried (MgSO$_4$). Solvent evaporation and purification by preparative TLC (30% diethyl ether in
hexanes) afforded 8 mg (98% yield) of compound 44 as a colorless gum. $^1$H NMR (500 MHz, CDCl$_3$) and HRMS reported above.

**4-[(1S,6S)-3-(Hydroxymethyl)-6-(1-methylethenyl)-2-cyclohexen-1-yl]-5-pentyl-resorcinol (46).** To a stirred solution of 45 (100 mg, 0.268 mmol) in methanol at room temperature, under an argon atmosphere was added K$_2$CO$_3$ (26 mg, 0.187 mmol). The reaction was stirred for 3 hours and then water was added. The mixture was extracted with diethyl ether, and the organic phase was washed with brine and dried (MgSO$_4$). Solvent evaporation and purification by flash column chromatography on silica gel (30-45% ethyl acetate in hexanes) gave 46 as white foam in 74% yield (65 mg). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 6.21 (d, $J = 2.5$ Hz, 1H, half of an AB system, ArH), 6.20 (d, $J = 2.5$ Hz, 1H, half of an AB system, ArH), 5.81 (br s, >C=CH-$\text{-}$), 5.72 (br s, 1H, OH), 4.66 (m as t, $J = 1.5$ Hz, 1H, >C=CH$_2$), 4.62 (br s, 1H, OH), 4.47 (s, 1H, >C=CH$_2$), 4.13 (m, 2H, -CH$_2$O-), 3.57 (m as br d, $J = 10.3$ Hz, 1H, >C=CH-$\text{-}$CH$_2$), 2.64-2.54 (m, 2H), 2.32-2.21 (m, 3H), 1.95-1.88 (m, 1H, -CH$_2$-CH$_2$-C(OH)=C<, equatorial), 1.84-1.75 (m, 1H, -CH$_2$-CH$_2$-C(OH)=C<, axial), 1.53 (s, 3H, >CH-C(CH$_3$)=CH$_2$), 1.47 (quintet, $J = 6.3$ Hz, 2H, 2'H), 1.37-1.25 (m, 4H, 3'-H and 4'-H), 0.89 (t, $J = 7.0$ Hz, 3H, -CH$_2$CH$_3$); Mass spectrum (EI) m/z (relative intensity) 330 (M$^+$, 5), 312 (35), 299 (31), 284 (40), 244 (100), 231 (30), 187 (32), 91 (21). Exact mass (EI) calculated for C$_{21}$H$_{30}$O$_3$ (M$^+$), 330.2195; found, 330.2202.

**2-[(1S,6S)-3-(Acetoxymethyl)-6-(1-methylethenyl)-2-cyclohexen-1-yl]-5-(8-bromo-2-methyloct-2-yl)resorcinol (26c).** The synthesis was carried out analogous to the preparation of 26a by using terpene 16 (344.8 mg, 1.64 mmol), resorcinol 25c (397.8 mg, 1.262 mmol) and p-toluenesulfonic acid and (48.0 mg, 0.252 mmol) in anhydrous CH$_2$Cl$_2$
and gave 402 mg of 26c as a viscous oil in 63% yield. $^1$H NMR (500 MHz, CDCl$_3$) δ 6.38 (br s, 2H, ArH), 5.89 (s, 1H, >C=CH-), 5.52 (br s, 1H, OH), 4.70 (br s, 1H, OH), 4.64 (m as t, $J = 1.5$ Hz, 1H, >C=CH$_2$), 4.56 (d, $J = 13.0$ Hz, 1H, half of an AB system, -CH$_2$-O-), 4.53 (d, $J = 13.0$ Hz, 1H, half of an AB system, -CH$_2$-O-), 4.52 (br s, 1H, >C=CH$_2$), 3.92 (m as br d, $J = 10.3$ Hz, 1H, >C=CH-C), 3.36 (t, $J = 6.5$ Hz, -C(CH$_3$)$_2$Br), 2.47 (ddd, $J = 10.1$ Hz, $J = 9.9$ Hz, $J = 3.1$ Hz, 1H, >CH-C(CH$_3$)=CH$_2$), 2.23-2.22 (m, 1H, >CH$_2$-C(CH$_2$OCOCH$_3$)=C<), 2.09 (s, 3H, -OCOCH$_3$), 1.91-1.86 (m, 1H, >CH-C(CH$_3$)=CH$_2$), 1.49 (m, 2H, 2'H), 1.37-1.30 (m, 2H, -CH$_2$- of the side chain), 1.16-1.23 (m, s and s overlapping, 8H, -C(CH$_3$)$_2$ and -CH$_2$- of the side chain especially 1.21 s and 1.20 s, -C(CH$_3$)$_2$ ), 1.05-0.98 (m, 2H, -CH$_2$- of the side chain); Mass spectrum (ESI) m/z (relative intensity) 509 (M$^+$+2+H, 100), 507 (M$^+$+H, 100), 449 (100, M$^+$+2 - OCOCH$_3$), 447 (M$^+$-OCOCH$_3$, 100). Exact mass (ESI) calculated for C$_{27}$H$_{40}$O$_4$Br (M$^+$+H), 507.2110; found, 507.2102; LCMS (ES+) retention time, 6.38 min (Method A); purity (100%).

2-[(1S,6S)-3-(Hydroxymethyl)-6-(1-methylethenyl)-2-cyclohexen-1-yl]-5-(8-bromo-2-methyloct-2-yl)resorcinol (27c). The synthesis was carried out as described for 46 using 26c (157 mg, 0.309 mmol) and K$_2$CO$_3$ (30 mg, 0.216 mmol) in anhydrous methanol (4 mL) and gave 115 mg of 27c as a viscous oil in 80% yield. $^1$H NMR (500MHz, CDCl$_3$) δ 6.34 (br s, 2H, ArH), 5.88 (s, 1H, >C=CH-), 5.52 (br s, 1H, OH), 4.60 (br s, 1H, OH), 4.67 (m as t, $J = 1.5$ Hz, 1H, >C=CH$_2$), 4.55 (br s, 1H, >C=CH$_2$), 4.13 (d, $J = 13.5$ Hz, 1H, half of an AB system, -CH$_2$-O-), 4.09 (d, $J = 13.5$ Hz, 1H, half of an AB system, -
CH$_2$-O-), 3.92 (m as br d, $J = 10.2$ Hz, 1H, >C=CH-CH<), 3.37 (t, 2H, $J = 6.5$ Hz, -CH$_2$Br ) 2.47 (ddd, $J = 10.1$ Hz, $J = 9.9$ Hz, $J = 3.1$ Hz, 1H, >CH-C(CH$_3$)=CH$_2$), 2.28-2.22 (m, 2H, CH$_2$-C(CH$_2$OH)=C<), 1.93-1.87 (m, 1H, -CH$_2$-CH$_2$-C(CH$_2$OH)=C<, equatorial), 1.84-1.74 (m, 3H, especially 1H, -CH$_2$-CH$_2$-C(CH$_2$OH)=C<, axial and -CH$_2$-CH$_2$-Br of the side chain), 1.66 (s, 3H, >CH-C(CH$_3$)=CH$_2$), 1.50-1.49 (m, 2H, -C(CH$_3$)$_2$-CH$_2$-), 1.34 (m, $J = 7.3$ Hz, 2H, -CH$_2$-, of the side chain), 1.23-1.16 (m and s overlapping, 8H, -C(CH$_3$)$_2$ and -CH$_2$- of the side chain); Mass spectrum (ESI) m/z (relative intensity) 489 (M$^+$+2+Na, 13), 487 (M$^+$+Na, 13), 467 (M$^+$+2+H, 100), 465 (M$^+$+H, 100). Exact mass (ESI) calculated for C$_{25}$H$_{38}$O$_3$Br (M$^+$+H), 465.2004; found, 465.1993; LCMS (ES+) retention time, 6.82 min (Method A); purity (96%).

2-[(1S,6S)-3-(Acetoxymethyl)-6-(1-methylethenyl)-2-cyclohexen-1-yl]-5-(2-hexyl-1,3-dithiolane-2-yl) resorcinol (26d). The synthesis was carried out as described for 26a by using terpene 16 (197 mg, 0.938 mmol) and resorcinol 25d (200 mg, 0.67 mmol). The reaction was completed in 4 hours and purification by flash column chromatography on silica gel (30-50% diethyl ether in hexanes) afforded 92 mg of 26d in 28% yield. $^1$H NMR (500 MHz, CDCl$_3$) δ 6.73 (br s, 2H, ArH), 5.85 (s, 1H, >C=CH-), 5.56 (br s, 1H, OH), 4.69 (br s, 1H, OH), 4.61 (m as t, $J = 1.5$ Hz, 1H, >C=CH$_2$), 4.56 (d, $J = 13.0$ Hz, 1H, half of an AB system, -CH$_2$-O-), 4.53 (d, $J = 13.0$ Hz, 1H, half of an AB system, -CH$_2$-O-), 4.49 (br s, 1H, >C=CH$_2$), 3.94 (m as br d, $J = 10.3$ Hz, 1H, >C=CH-CH<), 3.38-3.30 (m, 2H, -S-CH$_2$-), 3.26-3.18 (m, 2H, -S-CH$_2$-), 2.48 (ddd, $J = 10.1$ Hz, $J = 9.9$ Hz, $J = 3.1$ Hz, 1H, >CH-C(CH$_3$)=CH$_2$), 2.29-2.22 (m, 3H, -CH$_2$-C(CH$_2$OH)=C<, (-S)$_2$C-CH$_2$-), 2.20-2.14 (m, 1H, -CH$_2$-C(CH$_2$OH)=C<), 2.09 (s, 3H, -OCOCH$_3$), 1.92-1.86
(m, 1H, -CH\textsubscript{2}-CH\textsubscript{2}-C(CH\textsubscript{2}OOC\textsubscript{3})=C<, equatorial), 1.84-1.75 (m, 1H, -CH\textsubscript{2}-CH\textsubscript{2}-C(CH\textsubscript{2}OOC\textsubscript{3})=C<, axial), 1.65 (s, 3H, >CH-C(CH\textsubscript{3})=CH\textsubscript{2}). 1.27-1.14 (m, 8H, -CH\textsubscript{2}-CH\textsubscript{2}-CH\textsubscript{2}-CH\textsubscript{2}-CH\textsubscript{3}, -CH\textsubscript{2}-CH\textsubscript{2}-CH\textsubscript{2}-CH\textsubscript{2}-CH\textsubscript{2}-CH\textsubscript{3}, -CH\textsubscript{2}-CH\textsubscript{2}-CH\textsubscript{2}-CH\textsubscript{2}-CH\textsubscript{2}-CH\textsubscript{3}). 0.83 (t, \(J = 7.5\) Hz, 3H, -CH\textsubscript{2}CH\textsubscript{3}); Mass spectrum (ESI) m/z (relative intensity) 491 (M\textsuperscript{+}+H, 62), 431 (100). Exact mass (ESI) calculated for C\textsubscript{27}H\textsubscript{39}O\textsubscript{4}S\textsubscript{2} (M\textsuperscript{+}+H), 491.2290; found, 491.2308; LCMS (ES+) retention time, 6.87 min (Method B); purity (100%).

2-[(1S,6S)-3-(Hydroxymethyl)-6-(1-methylethenyl)-2-cyclohexen-1-yl]-5-(2-hexyl-1,3-dithiolane-2-yl) resorcinol (27d). The synthesis was carried out as described for 27a using 26d (90 mg, 0.183 mmol) and 1 M DIBAL-H in toluene (1.1 mL, 1.1 mmol) to give 53 mg of 27d as a colorless viscous oil 63% yield; \(^{1}\)H NMR (500 MHz, CDCl\textsubscript{3}) \(\delta\)

6.73 (br s, 2H, ArH), 5.85 (s, 1H, >C=CH\textsubscript{2}), 5.63 (br s, 1H, OH), 4.75 (br s, 1H, OH), 4.63 (m as t, \(J = 1.5\) Hz, 1H, >C=CH\textsubscript{2}), 4.51 (br s, 1 H, >C=CH\textsubscript{2}), 4.14 (d, \(J = 9.0\) Hz, 1H, half of an AB system, -CH\textsubscript{2}-O-), 3.94 (m as br d, \(J = 10.2\) Hz, 1H, >C=CH-CH<), 3.38-3.30 (m, 2H, -S-CH\textsubscript{2}-), 3.26-3.18 (m, 2H, -S-CH\textsubscript{2}-), 2.48 (ddd, \(J = 10.1\) Hz, \(J = 9.9\) Hz, \(J = 3.1\) Hz, 1H, >CH-C(CH\textsubscript{3})=CH\textsubscript{2}), 2.29-2.20 (m, 4H, -CH\textsubscript{2}-C(CH\textsubscript{2}OH)=C<, (-S)\textsubscript{2}C-CH\textsubscript{2}-), 1.94-1.87 (m, 1H, -CH\textsubscript{2}-CH\textsubscript{2}-C(CH\textsubscript{2}OH)=C<, equatorial), 1.85 -1.75 (m, 1H, -CH\textsubscript{2}-CH\textsubscript{2}-C(CH\textsubscript{2}OH)=C<, axial), 1.66 (s, 3H, >CH-C(CH\textsubscript{3})=CH\textsubscript{2}), 1.26-1.13 (m, 8H, -CH\textsubscript{2}-CH\textsubscript{2}-CH\textsubscript{2}-CH\textsubscript{2}-CH\textsubscript{2}-CH\textsubscript{3}, -CH\textsubscript{2}-CH\textsubscript{2}-CH\textsubscript{2}-CH\textsubscript{2}-CH\textsubscript{2}-CH\textsubscript{3}, -CH\textsubscript{2}-CH\textsubscript{2}-CH\textsubscript{2}-CH\textsubscript{2}-CH\textsubscript{2}-CH\textsubscript{3}). 0.84 (t, \(J = 7.5\) Hz, 3H, -CH\textsubscript{2}CH\textsubscript{3}); \(^{13}\)C NMR (100 MHz, CDCl\textsubscript{3}) \(\delta\) 156.04 (brs, ArC1, ArC3), 148.51 (C8), 145.41 (ArC5), 142.36 (C3), 124.73 (C2), 114.80 (ArC2), 111.15 (C9), 108.31 (brs, ArC4, ArC6), 73.79 (-S-CH\textsubscript{2}-), 66.39 (-O-CH\textsubscript{2}-), 46.33, 45.77, 38.97, 36.74, 31.58, 29.26, 28.09, 27.77, 25.98, 22.50, 20.12, 14.04; Mass spectrum (ESI) m/z (relative
intensity) 471 (M⁺+Na, 100), 449 (M⁺+H, 17). Exact mass (ESI) calculated for C₂₅H₃₇O₃S₂ (M⁺+H), 449.2184; found, 449.2183; LCMS (ES+) retention time, 5.77 min (Method A); purity (95%).

2-[(1S,6S)-3-(Acetoxymethyl)-6-(1-methylethenyl)-2-cyclohexen-1-yl]-5-(1-hexyl-1-cyclopentyl) resorcinol (26e). The synthesis was carried out as described for 26a by using terpene 16 (224 mg, 1.067 mmol), resorcinol 25e (200 mg, 0.762 mmol) and p-toluenesulfonic acid (29 mg, 0.152 mmol) in anhydrous CH₂Cl₂ to give 123 mg of 26e as a viscous oil in 36% yield. ¹H NMR (500 MHz, CDCl₃) δ 6.33 (br s, 2H, ArH), 5.90 (s, 1H, >C=CH₂), 5.51 (br s, 1H, OH), 4.69 (br s, 1H, OH), 4.63 (m as t, J = 1.5 Hz, 1H, >C=CH₂), 4.56 (d, J = 13.0 Hz, 1H, >C=CH₂), 4.56 (d, J = 13.0 Hz, 1H, half of an AB system, -CH₂-O-), 4.53 (d, J = 13.0 Hz, 1H, half of an AB system, -CH₂-O-), 4.51 (br s, 1H, >C=CH₂), 3.91 (m as br d, J = 10.3 Hz, 1H, >C=CH(CH₃)=CH₂), 2.48 (ddd, J = 10.1 Hz, J = 9.9 Hz, J = 3.1 Hz, 1H, >CH-C(CH₃)=CH₂), 2.31-2.21 (m, 1H), 2.21-2.14 (m, 1H), 2.09 (s, 3H, -OCOCH₃), 1.92-1.79 (m, 4H, -CH₂-CH₂-C(CH₂OCOCH₃)=C<, equatorial, -CH₂-CH₂-C(CH₂OCOCH₃)=C<, axial and cyclopentane ring overlapping), 1.73-1.58 (m and s overlapping, 9H, >CH-C(CH₃)=CH₂ and cyclopentane ring, especially 1.65 s, 3H, >CH-C(CH₃)=CH₂), 1.47 (m, 2H, 2'-H), 1.24-1.10 (m, 6H, 4'-H, 5'-H, 6'-H), 0.92 (m, 2H, 3'-H), 0.82 (t, J = 7.1 Hz, 3H, 7'-H); Mass spectrum (ESI) m/z (relative intensity) 477 (M⁺+Na, 27), 455 (M⁺+H, 83), 395 (M⁺-OCOCH₃, 100). Exact mass (ESI) calculated for C₂₉H₄₃O₄ (M⁺+H), 455.3161; found, 455.3165; LCMS (ES+) retention time, 5.88 min (Method B); purity (100%).

2-[(1S,6S)-3-(Hydroxymethyl)-6-(1-methylethenyl)-2-cyclohexen-1-yl]-5-(1-hexyl-1-cyclopentyl) resorcinol (27e). The synthesis was carried out as described for 27a using
27e (60 mg, 0.131 mmol) and 1M DIBAL-H in toluene (0.8 mL, 0.8 mmol) to give 777 mg of 27e as a colorless viscous oil in 75% yield. $^1$H NMR (500 MHz, CDCl$_3$) δ 6.29 (br s, 2H, ArH), 5.87 (s, 1H, >C=CH-), 5.57 (br s, 1H, OH), 4.71 (br s, 1H, OH), 4.65 (m as t, J = 1.5 Hz, 1H, >C=CH$_2$), 4.53 (br s, 1H, >C=CH$_2$), 4.14 (d, J = 14.0 Hz, 1H, >C=CH$_2$), 4.53 (br s, 1H, >C=CH$_2$), 4.14 (d, J = 14.0 Hz, 1H, >C=CH$_2$), 4.14 (d, J = 14.0 Hz, 1H, >C=CH$_2$), 3.91 (m as br d, J = 10.2 Hz, 1H, >C=CH-CH$_3$), 2.47 (ddd, J = 10.1 Hz, J = 9.9 Hz, J = 3.1 Hz, 1H, >CH-C(CH$_3$)=CH$_2$), 2.28-2.22 (m, 2H, >CH$_2$-C(CH$_2$OH)=C<), 1.93-1.77 (m, 4H, -CH$_2$-CH$_2$-C(CH$_2$OH)=C<, equatorial, -CH$_2$-CH$_2$-C(CH$_2$OH)=C<, axial and cyclopentane ring overlapping), 1.73-1.57 (m and s overlapping, 9H, >CH-C(CH$_3$)=CH$_2$ and cyclopentane ring, especially 1.64 s, 3H, >CH-C(CH$_3$)=CH$_2$), 1.48 (m, 2H, 2’-H), 1.23-1.09 (m, 6H, 4’-H, 5’-H, 6’-H), 0.92 (m, 2H, 3’-H), 0.82 (t, J = 7.2 Hz, 3H, 7’-H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 155.63 (brs, ArC1 or ArC3), 153.83 (brs, ArC3 or ArC1), 149.70 (ArC5 or C8), 149.14 (C8 or ArC5), 142.20 (C3), 125.42 (C2), 113.19 (ArC2), 111.06 (C9), 108.60 (ArC4 or ArC6), 107.20 (ArC6 or ArC4), 66.60 (CH$_2$OH), 50.92, 46.55, 42.11, 37.72, 37.64, 37.17, 31.96, 30.07, 28.35, 26.20, 25.37, 23.41, 22.75, 20.57, 14.24; Mass spectrum (ESI) m/z (relative intensity) 435 (M$^+$Na, 14), 413 (M$^+$+H, 100), 395 (M$^+$-OH, 98). Exact mass (ESI) calculated for C$_{27}$H$_{41}$O$_3$ (M$^+$+H), 413.3056; found, 413.3043; LCMS (ES+) retention time, 6.25 min (Method A); purity (100%).

2-[(1S,6S)-3-(Acetoxymethyl)-6-(1-methylethenyl)-2-cyclohexen-1-yl]-5-(1-hexyl-cyclopropyl) resorcinol (26f). The synthesis was carried out as described for 26a by using terpene 16 (251 mg, 1.194 mmol), resorcinol 25f (200 mg, 0.853 mmol) and p-toluenesulfonic acid (32 mg, 0.17 mmol) in anhydrous CH$_2$Cl$_2$ to give 88 mg of 26f as a viscous oil in 24% yield. $^1$H NMR (500 MHz, CDCl$_3$) δ 6.32 (br s, 2H, ArH), 5.87 (s, 1H,
>C=CH-), 5.51 (br s, 1H, OH), 4.70 (br s, 1H, OH), 4.64 (m as t, J = 1.5 Hz, 1H, >C=CH2), 4.62-4.49 (AB system and br s overlapping, 3H, -CH2-O-, >C=CH2), 3.92 (m as br d, J = 10.3 Hz, 1H, >C=CH-C<), 2.82-2.13 (m, 2H, >C=CH2), 2.09 (s, 3H, -OCOCH3), 1.50-1.42 (m, 2H, 2'-H), 1.25-1.14 (m, 8H, 3'-H, 4'-H, 5'-H, 6'-H), 0.84 (t, J = 7.0 Hz, 3H, 7'-H), 0.72 (m, half of a AA'BB' system, 2H of the cyclopropane ring), 0.58 (m, half of a AA'BB' system, 2H of the cyclopropane ring); Mass spectrum (ESI) m/z (relative intensity) 449 (M+Na, 13), 427 (M+H, 74), 367 (M+OCOCH3, 100).

Exact mass (ESI) calculated for C27H39O4 (M+H), 427.2848; found, 427.2834; LCMS (ES+) retention time, 5.97 min (Method B); purity (100%).

2-[(1S,6S)-3-(Hydroxymethyl)-6-(1-methylethenyl)-2-cyclohexen-1-yl]-5-(1-hexyl-cyclopropyl) resorcinol (27f). The synthesis was carried out as described for 27a using 26f (80 mg 0.187 mmol) and 1 M DIBAL-H in toluene (1.12 mL, 1.2 mmol) to give 54 mg of 27f as a viscous oil in 75% yield. 1H NMR (500 MHz, CDCl3) δ 6.31 (br s, 2H, ArH), 5.85 (s, 1H, >C=CH-), 5.58 (br s, 1H, OH), 4.72 (br s, 1H, OH), 4.65 (m as t, J = 1.5 Hz, 1H, >C=CH2), 4.55 (br s, 1H, >C=CH2), 4.13 (d, J = 13.5 Hz, 1H, half of an AB system, -CH2-O-), 4.09 (d, J = 13.5 Hz, 1H, half of an AB system, -CH2-O-), 3.92 (m as br d, J = 10.2 Hz, 1H, >C=CH-C<), 2.48 (ddd, J = 10.1 Hz, J = 9.9 Hz, J = 3.1 Hz, 1H, >CH-C(CH3)=CH2), 2.28-2.19 (m, 2H, CH2-C(CH2OH)=C<), 1.93-1.87 (m, 1H, -CH2-CH2-C(CH2OH)=C<, equatorial), 1.84-1.74 (m, 1H, -CH2-CH2-C(CH2OH)=C<, axial), 1.66 (s, 3H, >CH-C(CH3)=CH2), 1.50-1.42 (m, 2H, 2'-H), 1.25-1.14 (m, 8H, 3'-H, 4'-H, 5'-H, 6'-H), 0.84 (t, J = 7.0 Hz, 3H, 7'-H), 0.72 (m, 2H of the cyclopropane ring), 0.58 (m, 2H of the cyclopropane ring); 13C NMR (100 MHz, CDCl3) δ 155.32 (brs,
ArC1, ArC3), 148.89 (ArC5), 145.87 (C8), 142.17 (C3), 125.13 (C2), 113.59 (ArC2), 111.00 (C9), 109.87 (brs, ArC4 or ArC6), 108.29 (brs, ArC6 or ArC4), 66.43 (-CH2OH), 46.36, 39.97, 36.89, 31.84, 29.42, 28.20, 27.15, 25.98, 25.14, 20.34, 140.8, 13.31(-CH2 of the cyclopropyl ring), 13.25 (-CH2 of the cyclopropyl ring); Mass spectrum (ESI) m/z (relative intensity) 407 (M+Na, 12), 385 (M+H, 74), 367 (M+OH, 100).

Exact mass (ESI) calculated for C25H37O3 (M+H), 385.2743; found, 385.2737; LCMS (ES+) retention time, 5.82 min (Method A); purity (100%).

2-[(1S,6S)-3-(Acetoxymethyl)-6-(1-methylethenyl)-2-cyclohexen-1-yl]-5-(6-bromo-2-methylhexan-2-yl)resorcinol (26g). The synthesis was carried out as described for 26a by using terpene 16 (360 mg, 1.713 mmol), resorcinol 25g (350 mg, 1.22 mmol) and p-toluenesulfonic acid (51 mg, 0.26 mmol) in anhydrous CH2Cl2 to give 200 mg of 26g as a viscous oil in 34% yield. 1H NMR (500 MHz, CDCl3) δ 6.35 (br s, 2H, ArH), 5.83 (s, 1H, >C=CH-), 5.51 (br s, 1H, OH), 4.77 (br s, 1H, OH), 4.65 (m as t, J=1.5 Hz, 1H, >C=CH2), 4.55 (d, J= 13.0 Hz, 1H, half of an AB system, -CH2-O-), 4.54 (d, J= 13.0 Hz, 1H, half of an AB system, -CH2-O-), 4.49 (br s, 1H, >C=CH2), 3.91 (m as br d, J=10.3 Hz, 1H, >C=CH-H), 3.31 (t, 2H, J= 6.5 Hz, -CH2Br ), 2.45 (ddd, J= 10.1 Hz, J = 9.9 Hz, J = 3.1 Hz, 1H, >CH-C(CH3)=CH2), 2.31-2.12 (m, 2H, >CH2-C(CH2OCOCH3)=C<), 2.09 (s, 3H, -OCOCH3), 1.92-1.86 (m, 1H, -CH2-CH2-C(CH2OCOCH3)=C<, equatorial), 1.85-1.70 (m, 3H, -CH2-CH2-C(CH2OCOCH3)=C<, axial and -CH2- of the side chain), 1.65 (s, 3H, >CH-C(CH3)=CH2), 1.52 (m, 2H, -C(CH3)2-CH2-), 1.24-1.14 (m and s overlapping, 8 H, -C(CH3)2- and -CH2- of side chain especially 1.20, s and 1.21, s, -C(CH3)2-), 1.21-1.14 (m, 2H, -CH2- of side chain); Mass spectrum (ESI) m/z (relative intensity) 503 (M+2+Na, 17), 501 (M+Na, 17), 481
(M^+ + 2+H, 75), 479 (M^+ + H, 75), 421 (M^+ + 2-OCOCH₃, 100), 419 (M^+ - OCOCH₃, 100).

Exact mass (ESI) calculated for C₂₅H₃₆BrO₄ (M^+), 479.1797; found, 479.1789; LCMS (ES+) retention time, 5.49 min (Method B); purity (100%).

2-[((1S,6S)-3-(Hydroxymethyl)-6-(1-methylethenyl)-2-cyclohexen-1-yl]-5-(6-bromo-2-methylhexan-2-yl)resorcinol (27g). The synthesis was carried out as described for 27a using 26g (190 mg, 0.398 mmol) and 1 M DIBAL-H in toluene (2.39 mL, 2.39 mmol) to give 90 mg of 27g as viscous oil in 52% yield. ¹H NMR (500 MHz, CDCl₃) δ 6.34 (br s, 2H, ArH), 5.86 (s, 1H, >C=CH-), 5.61 (br s, 1H, OH), 4.78 (br s, 1H, OH), 4.66 (m as t, J = 1.5 Hz, 1H, >C=CH₂), 4.55 (br s, 1H, >C=CH₂), 4.13 (d, J = 13.5 Hz, 1H, half of an AB system, -CH₂-O-), 3.92 (m as br d, J = 10.2 Hz, 1H, >C=CH₂), 3.31 (t, J = 7.0 Hz, 2H, -CH₂Br), 2.47 (ddd, J = 10.1 Hz, J = 9.9 Hz, J = 3.1 Hz, 1H, >CH-C(CH₃)=CH₂, 2.28-2.22 (m, 2H, CH₂-C(CH₂OH)=C<), 1.94-1.87 (m, 1H, -CH₂-CH₂-C(CH₂OH)=C<, equatorial), 1.85-1.70 (m, 3H, -CH₂-CH₂-C(CH₂OH)=C<, axial and -CH₂- of the side chain), 1.66 (s, 3H, >CH-C(CH₃)=CH₂), 1.53 (m, 2H, -C(CH₃)₂-CH₂-), 1.24-1.14 (m, s and s overlapping, 8 H, -C(CH₃)₂- and -CH₂- of side chain especially 1.20, s and 1.21, s, -C(CH₃)₂- and 1.20-1.14, m, 2H, -CH₂- of side chain); Mass spectrum (ESI) m/z (relative intensity) 461 (M^+ + 2+Na, 11), 459 (M^+ + Na, 11), 439 (M^+ + 2+H, 89), 437 (M^+ + H, 89), 421 (M^+ + 2-OH, 100), 419 (M^+ - OH, 100). Exact mass (ESI) calculated for C₂₃H₃₄BrO₃ (M^+), 437.1691; found, 437.1705; LCMS (ES+) retention time, 4.85 min (Method B); purity (96%).

2-[((1S,6S)-3-(Acetoxymethyl)-6-(1-methylethenyl)-2-cyclohexen-1-yl]-5-(5-bromopentyl)cyclobutyl resorcinol (26h). The synthesis was carried out as described for 26a by using terpene 16 (240 mg, 1.14 mmol), resorcinol 25h (250 mg, 1.14 mmol)
and p-toluenesulfonic acid and (35 mg, 0.228 mmol) in anhydrous CH$_2$Cl$_2$ to give 141 mg of 26h as a viscous oil in 35% yield. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 6.14 (br s, 2H, ArH), 5.89 (s, 1H, >C=CH-), 5.53 (br s, 1H, OH), 4.71 (br s, 1H, OH), 4.64 (m as t, $J$ =1.5 Hz, 1H, >C=CH$_2$), 4.56 (d, $J$ = 13.0 Hz, 1H, half of an AB system, -CH$_2$-O-), 4.53 (d, $J$ = 13.0 Hz, 1H, half of an AB system, -CH$_2$-O-), 4.52 (br s, 1H, >C=CH$_2$), 3.93 (m as br d, $J$ = 10.3 Hz, 1H, >C=CH-$\text{-CH}<$), 3.32 (t, $J$ = 10.0 Hz, -CH$_2$Br), 2.48 (ddd, $J$ = 10.1 Hz, $J$ = 9.9 Hz, $J$ = 3.1 Hz, 1H, >CH-C(CH$_3$)=CH$_2$), 2.32-2.20 (m, 3H, >C=CH$_2$-C(CH$_2$OCOCH$_3$)=C$<$ and –CH$_2$- of the cyclobutane ring), 2.09 (s, 3H, -OCOCH$_3$), 2.04-1.94 (m, 3H, cyclobutane ring), 1.92-1.86 (m, 1H, cyclobutane ring), 1.85-1.72 (m, 4H, >CH$_2$-CH$_2$-C(CH$_2$OCOCH$_3$)=C$<$ equatorial, >CH$_2$-CH$_2$-C(CH$_2$OCOCH$_3$)=C$<$, axial and -CH$_2$- of the side chain), 1.71-1.67 (m, 2H, 2'H), 1.66 (s, 3H, >CH-C(CH$_3$)=CH$_2$), 1.35-1.28 (quintet, $J$ = 7.0 Hz, 2H, -CH$_2$- of the side chain), 1.02-0.94 (m, 2H, -CH$_2$- of the side chain); $^{13}$C (100 MHz, CDCl$_3$) 171.02 (-OC(O)-), 155.75 (brs, ArC1 or ArC3), 155.62 (br s, ArC1 or ArC3), 150.73 (ArC5), 148.67 (C8), 137.36 (C3), 128.01 (C2), 112.89 (ArC2), 111.06(C9), 107.65 (brs, ArC4 or ArC6), 105.54 (brs, ArC4 or ArC6), 67.75 (-CH$_2$O-), 48.19, 42.20, 36.86, 33.94, 32.78, 32.67, 32.59, 28.50, 27.96, 26.29, 23.81, 20.91, 20.26, 15.80; Mass spectrum (ESI) m/z (relative intensity) 527 (M$^+$+2+Na, 29), 529 (M$^+$+Na, 29), 507 (M$^+$+2+H, 86), 505 (M$^+$+H, 86), 447 (M$^+$+2-OCOCH$_3$, 100), 445 (M$^+$-OCOCH$_3$). Exact mass (ESI) calculated for C$_{27}$H$_{38}$O$_4$Br (M$^+$+H), 505.1953; found, 505.1966; LCMS (ES+) retention time, 4.88 min (Method A); purity (96.7%).

2-[(1S,6S)-3-(Hydroxymethyl)-6-(1-methylethenyl)-2-cyclohexen-1-yl]-5-[(5-bromopentyl)cyclobutyl) resorcinol (27h). The synthesis was carried out as described
for 27a using 26h (140 mg, 0.277 mmol) and 1M DIBAL-H in toluene (1.6 mL, 1.6 mmol) and gave 96 mg of 27h as a viscous oil 75% yield. \(^1\)H NMR (500 MHz, CDCl₃) δ 6.12 (br s, 2H, ArH), 5.87 (s, 1H, >C=CH-), 5.62 (br s, 1H, OH), 4.70 (br s, 1H, OH), 4.66 (m as t, \(J = 1.5\) Hz, 1H, >C=CH₂), 4.55 (br s, 1H, >C=CH₂), 4.14 (d, \(J = 14.0\) Hz, 1H, half of an AB system, -CH₂-O-), 3.91 (m as br d, \(J = 10.2\) Hz, 1H, >C=CH-CH₂<), 3.32 (t, \(J = 6.5\) Hz, 2H, -CH₂-Br), 2.48 (ddd, \(J = 10.1\) Hz, \(J = 9.9\) Hz, \(J = 3.1\) Hz, 1H, >CH-C(CH₃)=CH₂), 2.30-2.22 (m, 4H, >CH₂-C(CH₂OH)=C< and -CH₂- of the cyclobutane ring), 2.40-1.96 (m, 3H, cyclobutane ring), 1.93-1.87 (m, 1H, cyclobutane ring), 1.85-1.72 (m, 4H, -CH₂-CH₂-C(CH₂OH)=C< and -CH₂- of the 5-bromopentyl group), 1.69 (m, 2H, 2'-H), 1.66 (s, 3H, >CH-C(CH₃)=CH₂), 1.31 (quintet, \(J = 7.0\) Hz, 2H, -CH₂- of the 5-bromopentyl group), 1.02-0.94 (m, 2H, -CH₂- of the 5-bromopentyl group); Mass spectrum (ESI) m/z (relative intensity) 487 (M⁺+2+Na, 8), 485 (M⁺+Na, 8), 465 (M⁺+2+H, 73), 463 (M⁺+H, 73), 447 (M⁺+2-OH, 100), 445 (M⁺-OH, 100). Exact mass (ESI) calculated for C₂₅H₃₆O₃Br (M⁺+H), 463.1848; found, 463.1855; LCMS (ES+) retention time, 5.75 min (Method A); purity (100%).

2-[(1S,6S)-6-(Acetoxymethyl)-6-(1-methylethenyl)-2-cyclohexen-1-yl]-5-(5-bromo-2-methypentan-2-yl)resorcinol (26i). The synthesis was carried out analogous to the preparation of 26a by using terpene 16 (431 mg, 2.05 mmol), resorcinol 25i (400 mg, 1.46 mmol) and p-toluenesulfonic acid (55 mg, 0.292 mmol) in anhydrous CH₂Cl₂ and gave 67 mg of 26i as a viscous oil 61% yield. \(^1\)H NMR (500 MHz, CDCl₃) δ 6.37 (br s, 2H, ArH), 5.88 (s, 1H, >C=CH-), 5.55 (br s, 1H, OH), 4.78 (br s, 1H, OH), 4.65 (m as t, \(J = 1.5\) Hz, 1H, >C=CH₂), 4.55 (d, \(J = 13.0\) Hz, 1H, half of an AB system, -CH₂-O-), 4.54
(d, \( J = 13.0 \) Hz, 1H, half of an AB system, -CH\(_2\)-O-), 4.52 (br s, 1H, >C=CH\(_2\)), 3.92 (m as br d, \( J = 10.3 \) Hz, 1H, >C=CH-CH<), 3.27 (t, 2H, \( J = 6.5 \) Hz, -CH\(_2\)Br), 2.47 (ddd, \( J = 10.1 \) Hz, \( J = 9.9 \) Hz, \( J = 3.1 \) Hz, 1H, >CH-C(CH\(_3\))=CH\(_2\)), 2.32-2.22 (m, 1H, CH\(_2\)-C(CH\(_2\)OOCOCH\(_3\))=C<), 2.19 (m, 1H, CH\(_2\)-C(CH\(_2\)OOCOCH\(_3\))=C<, equatorial), 2.15 (s, 3H, >CH-C(CH\(_3\))=CH\(_2\)), 1.93-1.75 (m, 4H, -C(CH\(_3\))\(_2\)-CH\(_2\)-CH\(_2\)), 1.23 (s, 6H, -C(CH\(_3\))\(_2\)), Mass spectrum (ESI) m/z (relative intensity) 489 (M\(^+\)+2+Na, 8), 487 (M\(^+\)+Na, 8), 467 (M\(^+\)+2+H, 100), 465 (M\(^+\)+H, 100), 407 (M\(^+\)-OCOCH\(_3\), 95), 405 (M\(^+\)-OCOCH\(_3\), 95). Exact mass (ESI) calculated for C\(_{24}\)H\(_{34}\)BrO\(_4\) (M\(^+\)), 465.1640; found, 465.1632; LCMS (ES+) retention time, 5.28 min (Method B); purity (100%).

2-[(1S,6S)-3-(Hydroxymethyl)-6-(1-methylethenyl)-2-cyclohexen-1-yl]-5-(5-bromo-2-methypentan-2-yl) resorcinol (27i). The synthesis was carried out as described for 46 using 26i (280 mg, 0.6 mmol) and K\(_2\)CO\(_3\) (58.2 mg, 0.42 mmol) in methanol (6mL) and gave 65 mg of 27i as a viscous oil in 26% yield; \(^1\)H NMR (500MHz, CDCl\(_3\)) \( \delta \) 6.34 (br s, 2H, ArH), 5.87 (s, 1H, >C=CH-), 5.61 (br s, 1H, OH), 4.71 (br s, 1H, OH), 4.66 (m as t, \( J = 1.5 \) Hz, 1H, >C=CH\(_2\)), 4.55 (br s, 1H, >C=CH\(_2\)), 4.13 (d, \( J = 13.5 \) Hz, 1H, half of an AB system, -CH\(_2\)-O-), 4.09 (d, \( J = 13.5 \) Hz, 1H, half of an AB system, -CH\(_2\)-O-), 3.92 (m as br d, \( J = 10.2 \) Hz, 1H, >C=CH-CH<), 3.27 (t, 2H, \( J = 6.5 \) Hz, -CH\(_2\)Br), 2.47 (ddd, \( J = 10.1 \) Hz, \( J = 9.9 \) Hz, \( J = 3.1 \) Hz, 1H, >CH-C(CH\(_3\))=CH\(_2\)), 2.28-2.22 (m, 2H, CH\(_2\)-C(CH\(_2\)OH)=C<), 1.93-1.87 (m, 1H, -CH\(_2\)-CH\(_2\)-C(CH\(_2\)OH)=C<, equatorial), 1.84-1.75 (m, 1H, -CH\(_2\)-CH\(_2\)-C(CH\(_2\)OH)=C<, axial), 1.61-1.55 (m and s overlapping, 7H, >CH-C(CH\(_3\))=CH\(_2\) and -CH\(_2\)- of the side chain, especially, 1.66, s, >CH-C(CH\(_3\))=CH\(_2\)), 1.23
(s, 6H, -C(CH₃)₂-); Mass spectrum (ESI) m/z (relative intensity) 425 (M⁺+2+H, 100), 423 (M⁺+H, 100), 407 (M⁺+2-OH, 23), 405 (M⁺-OH, 23); Exact mass (ESI) calculated for C₂₂H₃₂O₃Br (M⁺+H), 423.1535; found, 423.1535; LCMS (ES+) retention time, 4.65 min (Method B); purity (100%).

2-[(1S,6S)-3-(Acetoxymethyl)-6-(1-methylethenyl)-2-cyclohexen-1-yl]-5-[(5-bromopentyl)cyclopentyl] resorcinol (26j). The synthesis was carried out analogous to the preparation of 26a by using terpene 16 (167 mg, 0.795 mmol), resorcinol 25j (200 mg, 0.61 mmol) and p-toluenesulfonic acid (23.2 mg, 0.122 mmol) in anhydrous CH₂Cl₂ and gave 83 mg of 26j as a viscous oil in 26% yield; ¹H NMR (500 MHz, CDCl₃) δ 6.34 (br s, 2H, ArH), 5.90 (s, 1H, >C=CH₂), 5.51 (br s, 1H, OH), 4.69 (br s, 1H, OH), 4.64 (m as t, J =1.5 Hz, 1H, >C=CH₂), 4.58 (d, J = 13.0 Hz, 1H, half of an AB system, -CH₂-O-), 4.54 (d, J = 13.0 Hz, 1H, half of an AB system, -CH₂-O-), 4.51 (br s, 1H, >C=CH₂), 3.91 (m as br d, J = 10.3 Hz, 1H, >C=CH-CH<), 3.30 (t, J = 7.0 Hz, 2H, -CH₂-Br), 2.48 (ddd, J = 10.1 Hz, J = 9.9 Hz, J = 3.1 Hz, 1H, >CH-C(CH₃)=CH₂), 2.29-2.22 (m, 1H, >CH₂-C(CH₂OOCOH₃)=C<), 2.20-2.14 (m, 1H, >CH₂-C(CH₂OOCOH₃)=C<), 2.09 (s, 3H, -OOCOH₃), 1.92-1.77 (m, 4H, -CH₂-CH₂-C(CH₂OOCOH₃)=C<, equatorial, -CH₂-CH₂-C(CH₂OOCOH₃)=C<, axial and 2H of cyclopentyl ring ), 1.75-1.58 (m and s overlapping, 11H, cyclopentane ring, >CH-C(CH₃)=CH₂, -CH₂- of the side chain, especially 1.64s, 3H, >CH-C(CH₃)=CH₂), 1.52-1.47 (m, 2H, 2'H), 1.30-1.24 (m, 2H, -CH₂- of the side chain), 0.98-0.93 (m, 2H, -CH₂- of the side chain); LCMS (ES+) retention time, 6.0 min (Method B); purity (95.6%).

2-[(1S,6S)-3-(Hydroxymethyl)-6-(1-methylethenyl)-2-cyclohexen-1-yl]-5-[(5-bromopentyl)cyclopentyl] resorcinol (27j). The synthesis was carried out as described
for 46 using 26j (77 mg, 0.148 mmol) and K$_2$CO$_3$ (14.3 mg, 0.103 mmol) in methanol and gave 52 mg of 27j as a viscous oil in 74% yield. $^1$H NMR (500 MHz, CDCl$_3$) δ 6.29 (br s, 2H, ArH), 5.87 (s, 1H, >C=CH-), 5.60 (br s, 1H, OH), 4.75 (br s, 1H, OH), 4.65 (m as t, J = 1.5 Hz, 1H, >C=CH-_), 4.53 (br s, 1H, >C=CH$_2$), 4.14 (br s, 1H, >C=CH$_2$), 4.09 (d, J = 14.0 Hz, 1H, -CH$_2$-O-_), 3.91 (m as br d, J = 10.2 Hz, 1H, >C=CH), 3.30 (t, 2H, J = 7.0 Hz, 1H, -CH$_2$-O-), 2.47 (ddd, J = 10.1 Hz, J = 9.9 Hz, J = 3.1 Hz, 1H, >CH-C(CH$_3$)=CH$_2$), 2.28-2.22 (m, 2H, CH$_2$-C(CH$_2$OH)=C<), 1.94-1.78 (m, 4H, -CH$_2$-CH$_2$-C(OH)=C<, equatorial, -CH$_2$-CH$_2$-C(OH)=C<, axial and 2H of cyclopentyl ring), 1.75-1.58 (m and s overlapping, 11H, cyclopentane ring, >CH-C(CH$_3$)=CH$_2$, -CH$_2$- of the side chain, especially 1.64s, 3H, >CH-C(CH$_3$)=CH$_2$), 1.52-1.47 (m, 2H, 2'H), 1.30-1.24 (quintet, J= 6.3 Hz, 2H, -CH$_2$- of the side chain), 0.99-0.94 (m, 2H, -CH$_2$- of the side chain); $^{13}$C NMR (CDCl$_3$, 125 MHz): δ 155.82 (brs, ArC1 or ArC3), 154.03 (brs, ArC1 or ArC3), 149.44 (ArC5 or C8), 149.28 (C8 or ArC5), 142.49 (C3), 125.33 (C2), 113.40 (ArC2), 111.19 (C9), 108.66 (brs, ArC4 or ArC6), 107.10 (ArC6 or ArC4), 66.65 (C7), 50.95, 46.66, 41.89, 37.77, 37.73, 37.23, 34.26, 32.98, 28.94, 28.41, 26.28, 24.71, 23.45, 20.67; Mass spectrum (ESI) m/z (relative intensity) 479 (M$^+$+2+H, 78), 477 (M$^+$+H, 78), 461 (M$^+$+2-OH, 100), 459 (M$^+$-OH, 100). Exact mass (ESI) calculated for C$_{26}$H$_{38}$O$_3$Br (M$^+$+H), 477.2004; found, 477.2016; LCMS (ES+) retention time, 5.87 min (Method A); purity (99%).

2-[(1S,6S)-3-(Acetoxymethyl)-6-(1-methylethenyl)-2-cyclohexen-1-yl]-5-(1-adamantyl)resorcinol (26k). The synthesis was carried out as described for 26a by using terpene 16 (168 mg, 0.79 mmol), resorcinol 25k (150 mg, 0.61 mmol) and p-toluenesulfonic acid (23.2 mg, 0.122 mmol) and gave 120 mg of 26k in 45% yield. $^1$H
NMR (500 MHz, CDCl\textsubscript{3}) \(\delta\) 6.40 (br s, 2H, ArH), 5.87 (s, 1H, >C=CH-), 5.47 (br s, 1H, OH), 4.70 (br s, 1H, OH), 4.66 (m as t, \(J = 1.5\) Hz, 1H, >C=CH\textsubscript{2}), 4.56 (d, \(J = 13.0\) Hz, 1H, half of an AB system, -CH\textsubscript{2}O-), 4.49 (br s, 1H, >C=CH\textsubscript{2}), 3.93 (m as br d, \(J = 10.2\) Hz, 1H, >C=CH-CH<), 2.49 (ddd, \(J = 10.1\) Hz, \(J = 9.9\) Hz, \(J = 3.1\) Hz, 1H, >CH-C(CH\textsubscript{3})=CH\textsubscript{2}), 2.30-2.22 (m, 1H, CH\textsubscript{2}-C(CH\textsubscript{2}OCOCH\textsubscript{3})=C<), 2.07-2.03 (m, 3H, 1-adamantyl group), 1.94-1.87 (m, 3H, -CH\textsubscript{2}-CH\textsubscript{2}-C(CH\textsubscript{2}OCOCH\textsubscript{3})=C<, equatorial), 1.85-1.79 (m and s overlapping, 7H, 6H of the 1-adamantyl group and -CH\textsubscript{2}-CH\textsubscript{2}-C(CH\textsubscript{2}OCOCH\textsubscript{3})=C<, axial), 1.69-1.66 (m, 4H from 1-adamantyl group), 1.66 (s, 3H, >CH-C(CH\textsubscript{3})=CH\textsubscript{2}); Mass spectrum (ESI) m/z (relative intensity) 437 (M\textsuperscript{+}+H\textsubscript{1}, 60), 377 (100, M\textsuperscript{+} - COOCH\textsubscript{3}), 163 (31). Exact mass (ESI) calculated for C\textsubscript{28}H\textsubscript{37}O\textsubscript{4} (M\textsuperscript{+}+H), 437.2692; found, 437.2693.

2-[(1S,6S)-3-(Hydroxymethyl)-6-(1-methylethenyl)-2-cyclohexen-1-yl]-5-(1-adamantyl)resorcinol (27k). The synthesis was carried out as described for 46 using 25k (120 mg, 0.275 mmol) and K\textsubscript{2}CO\textsubscript{3} (26.6 mg, 0.192 mmol). The crude mixture was purified on a silica gel column (30-45% ethyl acetate in hexanes) and gave 85 mg of 27k as oil in 78 % yield. \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \(\delta\) 6.38 (br s, 2H, ArH), 5.86 (s, 1H, >C=CH-), 5.54 (br s, 1H, OH), 4.71 (br s, 1H, OH), 4.67 (m as t, \(J = 1.5\) Hz, 1H, >C=CH\textsubscript{2}), 4.58 (br s, 1H, >C=CH\textsubscript{2}), 4.14 (d, \(J = 14.0\) Hz, 1H, -CH\textsubscript{2}O-), 4.09 (d, \(J = 14.0\) Hz, 1H, -CH\textsubscript{2}O-), 3.92 (m as br d, \(J = 10.2\) Hz, 1H, >C=CH-CH<), 2.49 (ddd, \(J = 10.1\) Hz, \(J = 9.9\) Hz, \(J = 3.1\) Hz, 1H, >CH-C(CH\textsubscript{3})=CH\textsubscript{2}), 2.28-2.22 (m, 2H, CH\textsubscript{2}-C(CH\textsubscript{2}OH)=C<), 2.10-2.03 (m, 3H, 1-adamantyl group), 1.94-1.87 (m, 1H, -CH\textsubscript{2}-CH\textsubscript{2}-C(CH\textsubscript{2}OH)=C<, equatorial), 1.84 (s, 6H of the 1-adamantyl group), 1.84-1.79 (m, 1H, -
2-[(1S,6S)-3-(Acetoxymethyl)-6-(1-methylethenyl)-2-cyclohexen-1-yl]-5-(7-bromo-2-methylheptan-2-yl)resorcinol (26l). The synthesis was carried out analogous to the preparation of 26a by using terpene 16 (1.2 g, 6 mmol), resorcinol 25l (1.4 g, 4.64 mmol) and p-toluenesulfonic acid (176 mg, 0.93 mmol) in anhydrous CH$_2$Cl$_2$ to give 1.1 g of 26l as a viscous oil 56% yield. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 6.38 (br s, 2H, ArH), 5.87 (s, 1H, >C=CH$_2$), 5.52 (br s, 1H, OH), 4.70 (br s, 1H, OH), 4.64 (m as t, $J = 1$ Hz, 1H, >C=CH$_2$), 4.56 (d, $J = 13$ Hz, 1H, half of an AB system, -CH$_2$-O-), 4.53 (d, $J = 13$ Hz, 1H, half of an AB system, -CH$_2$-O-), 4.52 (br s, 1H, >C=CH$_2$), 3.92 (m as br d, $J = 10$ Hz, 2H, -CH$_2$Br), 2.47 (ddd, $J = 10$ Hz, 1H, >C=CH$_2$), 2.21-2.13 (m, 1H, CH$_2$-C(=CH$_2$)=C<), 2.21-2.13 (m, 1H, CH$_2$-C(=CH$_2$)=C<), 2.09 (s, 3H, -OCOCH$_3$), 1.91-1.86 (m, 1H, -CH$_2$-CH$_2$-C(=CH$_2$)=C<, equatorial), 1.85-1.73 (m, 3H, especially 1H, -CH$_2$-CH$_2$-C(=CH$_2$)=C<, axial and -CH$_2$-CH$_2$-Br of the side chain), 1.65 (s, 3H, >CH-C(CH$_3$)=CH$_2$), 1.50 (m, 2H, 2'H), 1.36-1.28 (m, 2H, -CH$_2$- of the side chain), 1.16-1.23 (m, s and s overlapping, 8H, -C(CH$_3$)$_2$- and -CH$_2$- of the side chain, especially 1.20, s and 1.21, s, -C(CH$_3$)$_2$-), 1.05-0.98 (m, 2H, -CH$_2$- of the side chain); Mass spectrum (ESI) m/z (relative intensity) 495 (M$^+$+2H, 72), 493 (M$^+$+H, 72), 435 (100, M$^+$+2-OCOCH$_3$), 433(100, M$^+$-OCOCH$_3$). Exact mass (ESI) calculated for
C_{26}H_{38}O_{4}Br (M^{+}+H), 493.1953; found, 493.1963; LCMS (ES+) retention time, 6.13 min (Method A); purity (99%).

2-[(1S,6S)-3-(Hydroxymethyl)-6-(1-methylethenyl)-2-cyclohexen-1-yl]-5-(7-bromo-2-methylheptan-2-yl)resorcinol (27l). The synthesis was carried out as described for 46 using 26l (1.1 g, 2.22 mmol) and K_{2}CO_{3} (215 mg, 1.56 mmol) in anhydrous methanol to give 1 g of 27l as a viscous oil in 77% yield. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 6.34 (br s, 2H, ArH), 5.86 (s, 1H, >C=CH\(-\)), 5.62 (br s, 1H, OH), 4.80 (br s, 1H, OH), 4.65 (m as t, \(J = 1.5\) Hz, 1H, >C=CH\(_2\)), 4.54 (br s, 1 H, >C=CH\(_2\)), 4.12 (d, \(J = 13.5\) Hz, 1H, half of an AB system, \(-\)CH\(_2\)-O-), 4.10 (d, \(J = 13.5\) Hz, 1H, half of an AB system, -CH\(_2\)-O-), 3.91 (m as br d, \(J = 10.2\) Hz, 1H, >C=CH\(_2\)), 3.33 ( t, 2H, \(J = 6.5\) Hz, -CH\(_2\)Br), 2.47 (ddd, \(J = 10.1\) Hz, \(J = 9.9\) Hz, \(J = 3.1\) Hz, 1H, >CH-C(CH\(_3\))=CH\(_2\)), 1.93-1.87 (m, 1H, -CH\(_2\)-CH\(_2\)-C(CH\(_2\)OH)=C\(<\), equatorial), 1.84-1.74 (m, 3H, especially 1H, -CH\(_2\)-CH\(_2\)-C(CH\(_2\)OH)=C\(<\), axial and -CH\(_2\)-CH\(_2\)-Br of the side chain), 1.66 (s, 3H, >CH-C(CH\(_3\))=CH\(_2\)), 1.52-1.47 (m, 2H, 2'H), 1.31 (quintet, \(J = 7.3\) Hz, 2H, -CH\(_2\)-, of the side chain), 1.23-1.16 (m, s and s overlapping, 8H, -C(CH\(_3\))\(_2\)) and -CH\(_2\)- of the side chain especially 1.21, s and 1.20 s, -C(CH\(_3\))\(_2\)-), 1.05-0.98 (m, 2H, -CH\(_2\)- of the side chain); Mass spectrum (ESI) m/z (relative intensity) 489 (M\(^{+}\)+2+Na, 13), 487 (M\(^{+}\)+Na, 13), 453 (M\(^{+}\)+2+H, 70), 451 (M\(^{+}\)+H, 70), 435 (M\(^{+}\)+2-OH, 100), 433 (M\(^{+}\)-OH, 100). Exact mass (ESI) calculated for C\(_{24}\)H\(_{36}\)O\(_3\)Br (M\(^{+}\)+H), 451.1848; found, 451.1851; LCMS (ES+) retention time, 5.62 min (Method A); purity (96.4%).

2-[(1S,6S)-3-(Acetoxymethyl)-6-(1-methylethenyl)-2-cyclohexen-1-yl]-5-[1-(1,2-cis-hexen-1-yl)- tetrahydro-2H-pyran-4-yl]resorcinol (26m). The synthesis was carried out analogous to the preparation of 26a by using terpene 16 (99 mg, 0.47 mmol),
resorcinol **25m** (100 mg, 0.362 mmol) and *p*-toluenesulfonic acid (12.4 mg, 0.724 mmol) in anhydrous CH$_2$Cl$_2$ to give 38 mg of **26m** as a viscous oil 25% yield. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 6.41 (br s, 2H, ArH), 5.87 (s, 1H, >C=CH-), 5.69 (dt, $J = 11.3$ Hz, $J = 1.5$ Hz, 1H, 2'H), 5.41 (dt, $J = 11.3$ Hz, $J = 7.5$ Hz, 1H, 3'H), 4.80 (br s, 1H, OH), 4.62 (m as t, $J = 1.5$ Hz, 1H, >C=CH$_2$), 4.55 (d, $J = 13.0$ Hz, 1H, half of an AB system, -CH$_2$-O-), 4.52 (d, $J = 13.0$ Hz, 1H, -CH$_2$CH$_2$O-, equatorial), 3.73 (ddd, $J = 12.0$ Hz, $J = 12.0$ Hz, $J = 1.5$ Hz, 2H, -CH$_2$CH$_2$O-, axial), 2.48 (ddd, $J = 10.1$ Hz, $J = 9.9$ Hz, $J = 3.1$ Hz, 1H, >CH-C(CH$_3$)=CH$_2$), 2.31-2.21 (m, 1H, CH$_2$-C(CH$_2$OCOCH$_3$)=C<), 2.20-2.14 (m, 1H, CH$_2$-C(CH$_2$OCOCH$_3$)=C<), 2.09 (s, 3H, OCOCH$_3$), 2.05-1.97 (m, 3H, -CH$_2$CH$_2$O-, axial, 1H of terpene), 1.86-1.82 (m, 3H, -CH$_2$CH$_2$O-, equatorial, 1H of terpene), 1.73-1.60 (m and s overlapping, 5H, >CH-C(CH$_3$)=CH$_2$ and 4'H), 1.14-1.06 (m, 4H, 5'H, 6'H), 0.76 (t, $J = 7.0$ Hz, 3H, -CH$_2$-CH$_3$); Mass spectrum (ESI) m/z (relative intensity) 468 (M$^+$, 5), 408 (M$^+$-OCOCH$_3$, 100), 380 (25), 340 (27), 352 (49), 307 (25). Exact mass (EI) calculated for C$_{29}$H$_{40}$O$_5$ (M$^+$), 468.28757; found, 468.28621; LCMS (ES+) retention time, 5.35 min (Method B); purity (95.8%).

2-[(1S,6S)-3-(Hydroxymethyl)-6-(1-methylethenyl)-2-cyclohexen-1-yl]-2-cyclohexen-1-yl-5-[1-(1,2-cis-hexen-1-yl)- tetrahydro-2H-pyran-4-yl]resorcinol (**27m**). The synthesis was carried out as described for **46** using **26m** (28 mg, 0.059 mmol) and K$_2$CO$_3$ (5.8 mg, 0.042 mmol) in anhydrous methanol to give 15 mg of **27m** as a viscous oil in 59% yield. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 6.41 (br s, 2H, ArH), 5.87 (s, 1H, >C=CH-), 5.69 (dt, $J = 11.3$ Hz, $J = 1.5$ Hz, 1H, 2'H), 5.41 (dt, $J = 11.3$ Hz, $J = 7.5$ Hz, 1H, 3'H), 4.76 (br s, 1H, OH), 4.55 (d, $J = 13.0$ Hz, 1H, -CH$_2$-O-, equatorial), 3.73 (ddd, $J = 12.0$ Hz, $J = 12.0$ Hz, $J = 1.5$ Hz, 2H, axial), 2.48 (ddd, $J = 10.1$ Hz, $J = 9.9$ Hz, $J = 3.1$ Hz, 1H, >CH-C(CH$_3$)=CH$_2$), 2.31-2.21 (m, 1H, CH$_2$-C(CH$_2$OCOCH$_3$)=C<), 2.20-2.14 (m, 1H, CH$_2$-C(CH$_2$OCOCH$_3$)=C<), 2.09 (s, 3H, OCOCH$_3$), 2.05-1.97 (m, 3H, -CH$_2$CH$_2$O-, axial, 1H of terpene), 1.86-1.82 (m, 3H, -CH$_2$CH$_2$O-, equatorial, 1H of terpene), 1.73-1.60 (m and s overlapping, 5H, >CH-C(CH$_3$)=CH$_2$ and 4'H), 1.14-1.06 (m, 4H, 5'H, 6'H), 0.76 (t, $J = 7.0$ Hz, 3H, -CH$_2$-CH$_3$); Mass spectrum (ESI) m/z (relative intensity) 468 (M$^+$, 5), 408 (M$^+$-OCOCH$_3$, 100), 380 (25), 340 (27), 352 (49), 307 (25). Exact mass (EI) calculated for C$_{29}$H$_{40}$O$_5$ (M$^+$), 468.28757; found, 468.28621; LCMS (ES+) retention time, 5.35 min (Method B); purity (95.8%).
4.64 (m as t, J = 1.5 Hz, 1H, >C=CH₂), 4.53 (br s, 1H, >C=CH₂), 4.14 (d, J = 14.0 Hz, 1H, half of an AB system, -CH₂-O-), 4.11 (d, J = 14.0 Hz, 1H, half of an AB system, -CH₂-O-), 3.91 (m as br d, J = 10.2 Hz, 1H, >C=CH-<), 3.87-3.79 (m as br d, J = 12.0 Hz, 2H, -CH₂CH₂O-, equatorial), 3.73 (ddd, J = 12.0 Hz, J = 12.0 Hz, J = 1.5 Hz, 2H, -CH₂CH₂O-, axial), 2.47 (ddd, J = 10.1 Hz, J = 9.9 Hz, J = 3.1 Hz, 1H, >CH-C(CH₃)=CH₂), 2.28-2.22 (m, 2H, -CH₂-C(CH₂OH)=C<), 2.13-1.78 (m, 6H, 2H of terpene and -CH₂CH₂O-, axial, -CH₂CH₂O-, equatorial), 1.73-1.60 (m and s overlapping, 5H, >CH-C(CH₃)=CH₂ and 4'H), 1.14-1.06 (m, 4H, 5'H, 6'H), 0.76 (t, J = 7.0 Hz, 3H, 7'H); Mass spectrum (ESI) m/z (relative intensity) 426 (M⁺, 15), 408 (M⁺-H₂O, 100), 380 (25), 365 (22), 340 (24), 325 (48), 297 (20), 255 (22), 105 (15), 91 (22). Exact mass (EI) calculated for C₂₇H₃₈O₄ (M⁺), 426.27701; found, 426.27622; LCMS (ES+) retention time, 4.68 min (Method B); purity (95.7%).

2-[(1S,6S)-3-(Acetoxymethyl)-6-(1-methylethenyl)-2-cyclohexen-1-yl]-5-[1-(1,2-cis-hexen-1-yl)cyclopent-1-yl]resorcinol (26n). The synthesis was carried out analogous to the preparation of 26a by using terpene 16 (51 mg, 0.24 mmol), resorcinol 25n (49 mg, 0.188 mmol) and p-toluenesulfonic acid (6.4 mg, 0.037 mmol) in anhydrous CH₂Cl₂ to give 28 mg of 26n as a viscous oil 33 % yield. ¹H NMR (500 MHz, CDCl₃) δ 6.40 (br s, 2H, ArH), 5.87 (s, 1H, >C=CH-), 5.66 (dt, J = 11.3 Hz, J = 1.5 Hz, 1H, 2'H), 5.46 (br s, 1H, OH), 5.25 (dt, J = 11.3 Hz, J = 1.5 Hz, 1H, 3'H), 4.62 (m as t, J = 1.5 Hz, 1H, >C=CH₂), 4.56 (d, J = 13.0 Hz, 1H, half of an AB system, -CH₂-O-), 4.53 (d, J = 14.0 Hz, 1H, half of an AB system, -CH₂-O-), 4.51 (br s, 1H, >C=CH₂), 3.91 (m as br d, J = 10.2 Hz, 1H, >C=CH-<), 2.48 (ddd, J = 10.1 Hz, J = 9.9 Hz, J = 3.1 Hz, 1H, >CH-C(CH₃)=CH₂), 2.31-2.21 (m, 1H), 2.21-2.14 (m, 1H), 2.09 (s, 3H, OCOCH₃), 1.98-1.77
(m, 8H, -CH<sub>2</sub>-CH<sub>2</sub>-C(CH<sub>2</sub>OCOCH<sub>3</sub>)=C<sub>&lt;</sub>, equatorial, -CH<sub>2</sub>-CH<sub>2</sub>-C(CH<sub>2</sub>OCOCH<sub>3</sub>)=C<sub>&lt;</sub>, axial, 4'H and cyclopentane ring overlapping), 1.73-1.57 (m and s overlapping, 9H, >CH-C(CH<sub>3</sub>)=CH<sub>2</sub> and cyclopentane ring, especially 1.64 s, 3H, >CH-C(CH<sub>3</sub>)=CH<sub>2</sub>), 1.23-1.09 (m, 4H, 5'-H, 6'-H), 0.78 (t, J = 7.2 Hz, 3H, 7'-H); Mass spectrum (EI) m/z (relative intensity) 452 (M<sup>+</sup> 5), 392 (M<sup>+</sup>-OCOCH<sub>3</sub>, 100), 364 (38), 349 (40), 309 (80), 297 (22), 267 (28). Exact mass (EI) calculated for C<sub>29</sub>H<sub>40</sub>O<sub>4</sub> (M<sup>+</sup>), 452.29266; found, 452.29148.

2-[(1S,6S)-3-(Hydroxymethyl)-6-(1-methylethenyl)-2-cyclohexen-1-yl]-5-[1-(1,2-cis-hexen-1-yl)-cyclopent-1-yl]resorcinol (27n) The synthesis was carried out as described for 46 using 26n (15 mg, 0.033 mmol) and K<sub>2</sub>CO<sub>3</sub> (3.2 mg, 0.023 mmol) in anhydrous methanol to give 5 mg of 27n as a viscous oil in 37% yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ  6.36 (br s, 2H, ArH), 5.85 (s, 1H, >C=CH-), 5.66 (dt, J = 11.3 Hz, J = 1.5 Hz, 1H, 2'H), 5.55 (br s, 1H, OH), 5.25 (dt, J = 11.3 Hz, J = 1.5 Hz, 1H, 3'H), 4.63 (m as t, J = 1.5 Hz, 1H, >C=CH<sub>2</sub>), 4.53 (br s, 1H, >C=CH<sub>2</sub>), 4.14 (d, J = 14.0 Hz, 1H, -CH<sub>2</sub>-O-), 4.09 (d, J = 14.0 Hz, 1H, -CH<sub>2</sub>-O-), 3.91 (m as br d, J = 10.2 Hz, 1H, >C=CH-CH<sub>&lt;</sub>), 2.47 (ddd, J = 10.1 Hz, J = 9.9 Hz, J = 3.1 Hz, 1H, >CH-C(CH<sub>3</sub>)=CH<sub>2</sub>), 2.28-2.22 (m, 2H, >CH<sub>2</sub>-C(CH<sub>2</sub>OH)=C<sub>&lt;</sub>), 1.93-1.77 (m, 6H, -CH<sub>2</sub>-CH<sub>2</sub>-C(CH<sub>2</sub>OH)=C<sub>&lt;</sub>, equatorial, -CH<sub>2</sub>-CH<sub>2</sub>-C(CH<sub>2</sub>OH)=C<sub>&lt;</sub>, axial, and cyclopentane ring overlapping), 1.73-1.60 (m and s overlapping, 9H, >CH-C(CH<sub>3</sub>)=CH<sub>2</sub>, 4'H and cyclopentane ring, especially 1.64 s, 3H, >CH-C(CH<sub>3</sub>)=CH<sub>2</sub>), 1.13-1.09 (m, 4H, 5'-H, 6'-H), 0.78 (t, J = 7.2 Hz, 3H, 7'-H); Mass spectrum (EI) m/z (relative intensity) 410 (M<sup>+</sup> 15), 392 (M<sup>+</sup>-H<sub>2</sub>O, 100), 364 (41), 349 (43), 324 (46), 309 (88), 297 (25), 267 (30), 105 (15), 91 (26). Exact mass (EI) calculated for C<sub>27</sub>H<sub>38</sub>O<sub>3</sub> (M<sup>+</sup>), 410.2821; found, 410.28049; LCMS (ES+) retention time, 5.5 min (Method B); purity (100%).
Side Chain Modifications

2-[(1S,6S)-3-(Hydroxymethyl)-6-(1-methylethenyl)-2-cyclohexen-1-yl]-5-(8-cyano-2-methyloct-2-yl)resorcinol (47). To a stirred solution of 27c (107 mg, 0.23 mmol) in anhydrous DMSO (3 mL) was added NaCN (56.4 mg, 1.15 mmol) and stirring was continued overnight. On completion, the reaction was quenched with brine and extracted with diethyl ether. The organic layer was washed with brine, dried over MgSO₄ and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (40-55% ethyl acetate in hexanes) gave 35 mg of 47 as a viscous oil in 37% yield; [α]D²⁴ = 731.68º (c = 0.064 g/100 mL in CHCl₃). IR (neat) 3426 (br, OH), 2929, 2251 (s, CN), 1708, 1623, 1583, 1417, 1374, 1148, 885, 840 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 6.33 (br s, 2H, ArH), 5.87 (s, 1H, >C=CH), 5.60 (br s, 1H, OH), 4.85 (br s, 1H, >C=CH₂), 4.64 (m as t, J = 1.5 Hz, 1H, >C=CH₂), 4.54 (br s, 1H, >C=CH₂), 4.13 (d, J = 13.5 Hz, 1H, half of an AB system, -CH₂-O-), 4.09 (d, J = 13.5 Hz, 1H, half of an AB system, -CH₂-O-), 3.92 (m as br d, J = 10.2 Hz, 1H, >C=CH(CH₃)=CH₂), 2.29 (t, 2H, J = 5.0 Hz, -CH₂CN), 2.28-2.22 (m, 2H, CH₂-C(CH₂OH)=C<), 1.93-1.87 (m, 1H, -CH₂-CH₂-C(CH₂OH)=C<, equatorial), 1.84-1.74 (m, 1H, -CH₂-CH₂-C(CH₂OH)=C<, axial), 1.66 (s, 3H, >CH-C(CH₃)=CH₂), 1.56 (quintet, 2H, J = 6.5 Hz, -CH₂- of the side chain), 1.50 (m, 2H, -CH₂- of the side chain), 1.36 (m, quintet, 2H, J = 6.2 Hz, -CH₂- of the side chain), 1.28-1.19 (m and s overlapping, 8H, -C(CH₃)₂ and -CH₂- of the side chain), 1.07-0.96 (m, 2H, -CH₂- of the side chain); Mass spectrum (ESI) m/z (relative intensity) 434 (M⁺+Na, 13), 412 (M⁺+H, 95), 394 (M⁺-OH, 100). Exact mass (ESI) calculated for C₂₆H₃₈NO₃
(M\(^+\)+H), 412.2852; found, 412.2856; LCMS (ES+) retention time, 5.2 min (Method A); purity (95.4%).

2-[(1S,6S)-3-(Hydroxymethyl)-6-(1-methylethenyl)-2-cyclohexen-1-yl]-5-(6-cyano-2-methylhexane-2-yl)resorcinol (48). To a stirred solution of 27g in anhydrous DMSO (5 mL) was added NaCN (31 mg, 0.64 mmol) and stirring was continued overnight. On completion, the reaction was quenched with brine and extracted with diethyl ether. The organic layer was washed with brine, dried over MgSO\(_4\) and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (40-55% ethyl acetate in hexanes) gave 45 mg of pure 48 as viscous oil in 73% yield; IR (neat) 3394(br, OH), 2928, 2251 (s, CN), 1622, 1583, 1417, 1375, 1246, 1148, 885, 838 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 6.34 (br s, 2H, ArH), 5.86 (s, 1H, >C=CH\(-\)), 5.63 (br s, 1H, OH), 4.91 (br s, 1H, OH), 4.65 (m as t, \(J = 1.5\) Hz, 1H, >C=CH\(_2\)), 4.53 (br s, 1H, >C=CH\(_2\)), 4.13 (d, \(J = 13.5\) Hz, 1H, half of an AB system, -CH\(_2\)-O-), 4.09 (d, \(J = 13.5\) Hz, 1H, half of an AB system, -CH\(_2\)-O-), 3.92 (m as br d, \(J = 10.2\) Hz, 1H, >C=CH-CH\(<\), 2.48 (ddd, \(J = 10.1\) Hz, \(J = 9.9\) Hz, \(J = 3.1\) Hz, 1H, >CH-C(CH\(_3\))=CH\(_2\)), 2.28-2.21 (m and t overlapping, 4H, >CH\(_2\)-C(CH\(_3\))=O=CH\(_2\)CN, especially 2.18, t, \(J = 7.0\) Hz, -CH\(_2\)CN\(_2\)), 1.93-1.87 (m, 1H, -CH\(_2\)-CH\(_2\)-C(CH\(_3\))=O=CH\(_2\)CN, equatorial), 1.84-1.75 (m, 1H, -CH\(_2\)-CH\(_2\)-C(CH\(_3\))=O=CH\(_2\)CN, axial), 1.66 (s, 3H, >C=CH-C(CH\(_3\))=CH\(_2\)), 1.56-1.50 (m, 4H, -CH\(_2\)- of the side chain), 1.24-1.14 (m, and s overlapping, 8 H, -C(CH\(_3\))\(_2\)- and -CH\(_2\)- of side chain especially 1.21, s, -C(CH\(_3\))\(_2\)- and 1.24-1.14, m, 2H, -CH\(_2\)- of side chain); \(^{13}\)CNMR (100 MHz, CDCl\(_3\)) \(\delta\) 155.68 (brs, ArC1, ArC3), 149.36 (ArC5), 148.99 (C8), 142.29 (C3), 124.96 (C2), 119.77 (CN), 113.48 (ArC2), 110.97 (C9), 107.26 (brs, ArC4, ArC6), 66.38 (C7), 46.41 (C6), 43.52 (C2\(_2\)), 37.30, 36.91, 28.64, 28.19, 26.00, 25.86,
24.00, 20.37, 17.06; Mass spectrum (ESI) m/z (relative intensity) 406 (M^+Na, 12), 384 (M^+H, 40), 366 (M^+-OH, 100). Exact mass (ESI) calculated for C_{24}H_{34}NO_{3} (M^+H), 384.2539; found, 384.2552.

2-[(1S,6S)-3-(hydroxymethyl)-6-(1-methylethenyl)-2-cyclohexen-1-yl]-5-(6-morphalino-2-methylhexane-2-yl)resorcinol (49). To a stirred solution of 27g (200 mg, 0.457 mmol) in dry acetonitrile (12 mL) was added triethylamine (138 mg, 1.37 mmol) followed by morpholine (398 mg, 4.47 mmol). The reaction was stirred for 2 days at room temperature. On completion, it was quenched with water and diluted with ethyl acetate. The organic layer was separated and the aqueous phase was extracted with ethyl acetate. The combined organic layer was washed with brine and dried over MgSO_{4}. Solvent evaporation and purification under flash column chromatography on silica gel column gave 46 mg of 49 as viscous oil in 23% yield. ^1H NMR (500 MHz, CDCl_3) δ 6.25 (br s, 2H, ArH), 5.85 (s, 1H, >C=CH-), 4.60 (br s, 1H, OH), 4.59 (m as t, J = 1.5 Hz, 1H, >C=CH_2), 4.49 (br s, 1 H, >C=CH_2), 4.13 (d, J = 13.5 Hz, 1H, half of an AB system, -CH_2-O-), 4.08 (d, J = 13.5 Hz, 1H, half of an AB system, -CH_2-O-), 3.96 (m as br d, J = 10.2 Hz, 1H, >C=CH-CH<), 3.72 (t, 4H, J = 5.0 Hz, -CH_2O- of the morpholine ring), 2.48 (ddd, J = 10.1 Hz, J = 9.9 Hz, J = 3.1 Hz, 1H, >CH-C(CH_3)=CH_2), 2.45 (brs, 4H, -CH_2N< of the morpholine ring), 2.31-2.20 (m and m as t overlapping, 4H, -CH_2N< and -CH_2-C(CH_2OH)=C< especially 2.27, m as t, J = 8.5Hz, -CH_2N< of the side chain), 1.92-1.86 (m, 1H, -CH_2-CH_2-C(CH_2OH)=C<, equatorial), 1.66 (s, 3H, >CH-C(CH_3)=CH_2), 1.83-1.74 (m, 1H, -CH_2-CH_2-C(CH_2OH)=C<, axial ), 1.18 (s, 3H, >CH-C(CH_3)=CH_2), 1.50-1.44 (m, 2H, 2'H), 1.43-1.33 (m, 2H, -CH_2- of the side chain), 1.19 (s, 6H -C(CH_3)_2), 1.04-0.96 (m, 2H, -CH_2- of the side chain); ^13C NMR (100 MHz, CDCl_3) δ
155.47 (brs, ArC1, ArC3), 149.45 (ArC5), 148.40 (C8), 141.32 (C3), 125.81 (C2), 113.83 (ArC2), 110.02 (C9), 106.27 (brs, ArC4, ArC6), 66.53 (C7), 59.44 (-CH2O<), 53.80 (-CH2N<), 46.54 (C6), 44.80 (C2'), 37.42, 36.37, 28.84, 28.70, 28.64, 26.74, 26.21, 22.91, 19.91; Mass spectrum (ESI) m/z (relative intensity) 444 (M^+H, 100). Exact mass (ESI) calculated for C_{27}H_{42}NO_{4} (M^+H), 444.3114; found, 444.3104.

2-[(1S,6S)-3-(Acetoxymethyl)-6-(1-methylethenyl)-2-cyclohexen-1-yl]-5-[(5-cyanopentyl)cyclobutyl] resorcinol (50). The synthesis was carried out as described for 48 using 26h (200 mg, 0.395 mmol) and NaCN (77 mg, 1.58 mmol) in DMSO (4 mL). The reaction was completed in 24 hours and gave 150 mg of 50 as viscous oil in 84% yield. ^1H NMR (500 MHz, CDCl₃) δ 6.16 (br s, 2H, ArH), 5.89 (s, 1H, >C=CH-), 5.54 (br s, 1H, OH), 4.78 (br s, 1H, OH), 4.63 (m as t, J =1.5 Hz, 1H, >C=CH₂), 4.53 (d, J = 13.0 Hz, 1H, half of an AB system, -CH₂-O-), 4.53 (d, J = 13.0 Hz, 1H, half of an AB system, -CH₂-O-), 4.51 (br s, 1H, >C=CH₂), 3.94 (m as br d, J = 10.3 Hz, 1H, >C=CH-CH<), 2.48 (ddd, J = 10.1 Hz, J = 9.9 Hz, J = 3.1 Hz, 1H, >CH-C(CH₃)=CH₂), 2.31-2.22 (m and t overlapping, 5H, >CH₂-C(CH₂OCOCH₃)=C<, -CH₂- of the cyclobutane ring and -CH₂CN, especially 2.41, t, J = 6.7 Hz, 2H, -CH₂-CN), 2.21-2.14 (m, 1H, >CH₂-C(CH₂OCOCH₃)=C< ), 2.09 (s, 3H, -OCOCH₃), 2.01-1.95 (m, 3H, cyclobutane ring), 1.92-1.87 (m, 1H, cyclobutane ring), 1.86-1.75 (m, 2H, >CH₂-CH₂-C(CH₂OCOCH₃)=C<, equatorial and >CH₂-CH₂-C(CH₂OCOCH₃)=C<, axial), 1.72-1.68 (m, 2H, 2'H), 1.67 (s, 3H, >CH-C(CH₃)=CH₂), 1.59-1.52 (quintet, J = 6.7 Hz, 2H, -CH₂- of the side chain), 1.33 (quintet, J = 6.7 Hz , 2H, -CH₂- of the side chain), 1.03- 0.95 (m, 2H, -CH₂- of the side chain); Mass spectrum (ESI) m/z (relative intensity) 474 (M^+Na, 19), 452 (M^+H,
26), 392 (M⁺-OCOCH₃, 100). Exact mass (ESI) calculated for C₂₈H₃₈NO₄ (M⁺+H), 452.2801; found, 452.2800.

2-[(1S,6S)-3-(Hydroxymethyl)-6-(1-methylethenyl)-2-cyclohexen-1-yl]-5-[(5-cyanopentyl)cyclobutyl] resorcinol (51). The synthesis was carried out as described for 46 using 50 (164 mg, 0.364 mmol) and K₂CO₃ (35 mg, 0.254 mmol) in methanol (3 mL) and gave 90 mg of 51 as a viscous oil in 61% yield; IR (neat) 3366 (br, OH), 2927, 2252 (s, CN), 1622, 1582, 1374, 1241, 1051, 1021, 882, 835 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 6.13 (br s, 2H, ArH), 5.87 (s, 1H, >C=CH₂), 5.62 (br s, 1H, OH), 4.73 (br s, 1H, >C=CH₂), 4.53 (br s, 1H, >C=CH₂), 4.13 (d, J = 14.0 Hz, 1H, >C=CH₂), 4.11 (d, J = 14.0 Hz, 1H, >C=CH₂), 3.93 (m as br d, J = 10.2 Hz, 1H, >C=CH-C), 2.48 (ddd, J = 10.1 Hz, J = 9.9 Hz, J = 3.1 Hz, 1H, >CH-C(CH₃)=CH₂), 2.32-2.22 (m and t overlapping, 6H, 2H of the cyclobutyl ring, 2H of CH₂-C(CH₂OH)=C< and especially 2.24, t, J = 5.0 Hz, -CH₂-CN), 2.02-1.95 (m, 3H, cyclobutylring), 1.93-1.87 (m, 1H, -CH₂-CH₂-C(CH₂OH)=C<, equatorial), 1.86-1.75 (m, 2H, cyclobutyl ring and 1H, -CH₂-CH₂-C(CH₂OH)=C<, axial), 1.72-1.68 (m, 2H, 2'H), 1.67 (s, 3H, >CH-C(CH₃)=CH₂), 1.59-1.52 (m, 2H, -CH₂- of the side chain), 1.34 (quintet, J = 6.7Hz , 2H, -CH₂- of the side chain), 1.15- 0.95 (m, 2H, -CH₂- of the side chain); Mass spectrum (ESI) m/z (relative intensity) 432 (M⁺+Na, 17), 410 (M⁺+H, 26), 392 (M⁺-OH, 100). Exact mass (ESI) calculated for C₂₆H₃₆NO₃ (M⁺+H), 410.2695; found, 410.2692; LCMS (ES+) retention time, 4.52 min (Method B); purity (96.2%).

2-[(1S,6S)-3-(hydroxymethyl)-6-(1-methylethenyl)-2-cyclohexen-1-yl]-5-(7-cyano-2-methylheptan-2-yl)resorcinol (52). The synthesis was carried out as described for 48 using 271 (0.36 g, 0.79 mmol) and NaCN (156 mg, 3.19 mmol) in anhydrous DMSO to
give 212 mg of 52 as a viscous oil in 67% yield; [α]D\textsubscript{25} = 3588.26° (c = 0.073 g/100 mL in CHCl₃). IR (neat) 3394(br, OH), 2929, 2249 (s, CN), 1623, 1583, 1375, 1246, 1148, 1020, 882, 838 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl₃) δ 6.34 (br s, 2H, ArH), 5.85 (s, 1H, >C=CH\textsubscript{-}), 5.64 (br s, 1H, OH), 5.0 (br s, 1H, OH), 4.64 (m as t, J = 1.5 Hz, 1H, >C=CH\textsubscript{-}), 4.53 (br s, 1H, >C=CH\textsubscript{-}), 4.12 (d, J = 13.5 Hz, 1H, half of an AB system, -CH\textsubscript{2}-O-), 4.10 (d, J = 13.5 Hz, 1H, half of an AB system, -CH\textsubscript{2}-O-), 3.92 (m as br d, J = 10.2 Hz, 1H, >C=CH-C\textsubscript{H} <), 2.48 (ddd, J = 10.1 Hz, J = 9.9 Hz, J = 3.1 Hz, 1H, >CH\textsubscript{-}C(CH\textsubscript{3})=CH\textsubscript{2}), 2.29-2.18 (m and t overlapping, 4H, CH\textsubscript{2}-C(CH\textsubscript{2}OH)=C\textsubscript{<}, -CH\textsubscript{2}CN, especially 2.25, t, J = 7.5 Hz -CH\textsubscript{2}CN), 1.93-1.87 (m, 1H, -CH\textsubscript{2}-CH\textsubscript{2}-C(CH\textsubscript{2}OH)=C\textsubscript{<}, equatorial), 1.84-1.74 (m, 1H, -CH\textsubscript{2}-CH\textsubscript{2}-C(CH\textsubscript{2}OH)=C\textsubscript{<}, axial), 1.66 (s, 3H, >CH\textsubscript{-}C(CH\textsubscript{3})=CH\textsubscript{2}), 1.60-1.53 (m, 2H, -CH\textsubscript{2}- of the side chain), 1.53-1.47 (m, 2H, 2'-H), 1.37-1.30 (m, 2H, CH\textsubscript{2}- of the side chain), 1.21 (s, 6H, -C(CH\textsubscript{3})\textsubscript{2}), 1.07-0.96 (m, 2H, -CH\textsubscript{-} of the side chain); \(^13\)C NMR (100 MHz, CDCl₃) δ 154.92 (brs, ArC1, ArC3), 149.69 (ArC5), 149.01 (C8), 141.81 (C3), 125.43 (C2), 120.06 (CN), 113.68 (ArC2), 111.03 (C9), 106.61 (brs, ArC4, ArC6), 66.55 (C7), 46.56 (C6), 44.24 (C2'), 37.51, 36.79, 29.24, 28.90, 28.41, 26.21, 25.27, 23.94, 20.25, 17.10; LCMS (ES+) retention time, 5.03 min (Method A); purity (100%).

2-[(1S,6S)-3-(Hydroxymethyl)-6-(1-methylethenyl)-2-cyclohexen-1-yl]-5-(5-cyano-2-methypentan-2-yl)resorcinol (53). The synthesis was carried out as described for 48 using 27i (59 mg, 0.14 mmol) and NaCN (27 mg, 0.55 mmol) in anhydrous DMSO and gave 34 mg of 53 as a viscous oil in 74% yield; IR (neat) 3332(br, OH), 2925, 2249 (s, CN), 1622, 1583, 1375, 1248, 1049, 1017, 882, 837 cm\(^{-1}\); \(^1\)H NMR (500MHz, CDCl₃) δ 6.33 (br s, 2H, ArH), 5.86 (s, 1H, >C=CH\textsubscript{-}), 5.66 (br s, 1H, OH), 4.95 (br s, 1H, OH),
4.66 (m as t, \( J = 1.5 \) Hz, 1H, >C=CH\(_2\)), 4.52 (br s, 1 H, >C=CH\(_2\)), 4.13 (d, \( J = 13.5 \) Hz, 1H, half of an AB system, -CH\(_2\)-O-), 4.09 (d, \( J = 13.5 \) Hz, 1H, half of an AB system, -CH\(_2\)-O-), 3.92 (m as br d, \( J = 10.2 \) Hz, 1H, >C=CH\(_2\)-C\(\text{H}_2\))<), 2.47 (ddd, \( J = 10.1 \) Hz, \( J = 9.9 \) Hz, \( J = 3.1 \) Hz, 1H, >CH-C(CH\(_3\))=CH\(_2\)), 2.28-2.22 (m, 2H, CH\(_2\)-C(CH\(_2\)OH)=C<), 2.18 (t, 2H, \( J = 7.2 \) Hz, -CH\(_2\)CN), 1.93-1.87 (m, 1H, -CH\(_2\)-CH\(_2\)-C(CH\(_2\)OH)=C<, equatorial), 1.84-1.75 (m, 1H, -CH\(_2\)-CH\(_2\)-C(CH\(_2\)OH)=C<, axial), 1.70-1.62 (m and s overlapping, 5H, >CH-C(CH\(_3\))=CH\(_2\) and -CH\(_2\)- of the side chain, especially, 1.67, s, >CH-C(CH\(_3\))=CH\(_2\)), 1.43-1.35 (m, 2H, -CH\(_2\)- of the side chain), 1.26 (s, 6H, -C(CH\(_3\))\(_2\)-); Mass spectrum (EI) m/z (relative intensity) 369 (M\(^+\), 5), 368 (M\(^+\)+H, 10), 351 (M\(^+\)-H\(_2\)O, 23), 323 (12), 283 (100), 215 (83). Exact mass (EI) calculated for C\(_{23}\)H\(_{31}\)NO\(_3\) (M\(^+\)), 369.23040; found, 369.23063; LCMS (ES+) retention time, 4.07 min (Method B); purity (100%).

2-[(1S,6S)-3-(Acetoxymethyl)-6-(1-methylethenyl)-2-cyclohexen-1-y1]-5-(8-bromo-2-methylcyclooctane-2-yl)-1,3-dimethoxy-benzene (54). To a solution of 26c in anhydrous acetone was added K\(_2\)CO\(_3\) (82 mg, 0.591 mmol), followed by iodomethane (209 mg, 1.47 mmol). The reaction mixture was stirred overnight at 50 °C. The precipitate obtained was filtered and washed with acetone. The acetone filtrate was evaporated and the crude obtained was then partitioned between water and diethyl ether. The aqueous layer extracted twice with diethyl ether. The combined organic layer was then washed with brine and dried over MgSO\(_4\). Solvent evaporation and purification by flash column chromatography (5-15% diethyl ether in hexanes) gave 33 mg of 54 as a viscous oil in 49% yield. \(^1\)H NMR (500 MHz, CDCl\(_3\)) δ 6.44 (s, 2H, ArH), 5.61 (s, 1H, >C=CH-), 4.52 (d, \( J = 13.0 \) Hz, 1H, half of an AB system, -CH\(_2\)-O-), 4.45 (d, \( J = 13.0 \) Hz, 1H, half of an AB system, -CH\(_2\)-O-), 4.35 (m as t, \( J = 1.5 \) Hz, 1H, >C=CH\(_2\)), 4.35 (m, 1H,
>C=CH₂), 4.01 (m as br d, J = 10.3 Hz, 1H, >C=CH-CH<), 3.72 (s, 6H, -OCH₃), 3.15 (t, 2H, J = 7.0 Hz, -CH₂Br), 2.81 (ddd, J = 10.1 Hz, J = 9.9 Hz, J = 3.1 Hz, 1H, >CH-C(CH₃)=CH₂), 2.25-2.17 (m, 1H, CH₂-C(CH₂OCOCH₃)=CH<), 2.16-2.10 (m, 1H, CH₂-C(CH₂OCOCH₃)=CH<), 2.09 (s, 3H, -OCOCH₃), 1.84-1.79 (m, 1H, -CH₂-CH₂-C(CH₂OCOCH₃)=CH<, equatorial), 1.77-1.70 (m and quintet overlapping, 3H, -CH₂-CH₂-C(CH₂OCOCH₃)=CH<, axial, -CH₂- of the side chain especially, 1.75, quintet, J = 6.5 Hz, -CH₂- of the side chain), 1.60 (s, 3H, >CH-C(CH₃)=CH₂), 1.56-1.50 (m, 2H, 2'-H), 1.34-1.28 (quintet, J = 6.2 Hz, 2H, -CH₂- of the side chain), 1.26 (s, 6H, -C(CH₃)₂-), 1.24-1.16 (quintet, J = 6.2 Hz, 2H, -CH₂- of the side chain), 1.07-0.99 (m, 2H, -CH₂- of the side chain).

2-[(1S,6S)-3-(Hydroxymethyl)-6-(1-methylethenyl)-2-cyclohexen-1-yl]5-(8-bromo-2-methylpropane-2-yl)-1,3-dimethoxy-benzene (55). The synthesis was carried out as described for 46 using 54 (6 mg, 0.0112 mmol) and K₂CO₃ (1 mg, 0.00784 mmol). The crude mixture was purified on a silica gel column with 30-45% ethyl acetate in hexanes to yield 4 mg of 55 as a viscous oil in 73% yield. ¹H NMR (500 MHz, CDCl₃) δ 6.44 (s, 2H, ArH), 5.53 (s, 1H, >C=CH-), 4.44 (m as t, J = 1.5 Hz, 1H, >C=CH₂), 4.37 (m, 1H, >C=CH₂), 4.05-3.95 (m, 3H, >C=CH-CH< and -CH₂-O), 3.73 (s, 6H, -OCH₃), 3.15 (t, J = 7.0 Hz, 2H, -CH₂Br), 2.85 (ddd, J = 10.1 Hz, J = 9.9 Hz, J = 3.1 Hz, 1H, >CH-C(CH₃)=CH₂), 2.30-2.15 (m, 2H, CH₂-C(CH₂OH)=CH<), 1.84-1.79 (m, 1H, -CH₂-CH₂-C(CH₂OH)=CH<, equatorial), 1.77-1.70 (m, 3H, especially 1H, -CH₂-CH₂-C(CH₂OH)=CH<, axial and -CH₂- of the side chain), 1.61 (s, 3H, >CH-C(CH₃)=CH₂), 1.56-1.50 (m, 2H, 2'-H), 1.39-1.18 (m and s overlapping, 10H, -C(CH₃)₂- and -CH₂- of the side chain, especially 1.26, s, -C(CH₃)₂-), 1.07-0.99 (m, 2H, -CH₂- of the side chain);
Mass spectrum (ESI) m/z (relative intensity) 495 (M⁺+2H, 100), 493 (M⁺+H, 100), 477 (M⁺+2-OH, 58), 475 (M⁺-OH, 58), 413 (30), 381 (30). Exact mass (ESI) calculated for C₂₆H₃₈NO₂S (M⁺+H), 493.2317; found, 493.2312.

2-[(1S,6S)-3-(Acetoxymethyl)-6-(1-methylethenyl)-2-cyclohexen-1-yl]-5-(6-bromo-2-methylhexane-2-yl)-1,3-dimethoxy-benzene (57). To a solution of 26g in anhydrous acetone was added K₂CO₃ (344 mg, 2.49 mmol), followed by iodomethane (0.24 mL, 4.16 mmol) and the reaction mixture was stirred overnight at 50 °C. The precipitate obtained was filtered and washed with acetone. The acetone filtrate was evaporated and the crude obtained was then partitioned between water and diethyl ether. The aqueous layer extracted twice with diethyl ether. The combined organic layer was then washed with brine and dried over MgSO₄. Solvent evaporation and purification by flash column chromatography (5-15% diethyl ether in hexanes) gave 176 mg of 57 as viscous oil in 84% yield. ¹H NMR (500 MHz, CDCl₃) δ 6.44 (s, 2H, ArH), 5.60 (s, 1H, >C=CH₂), 4.52 (d, J = 13.0 Hz, 1H, half of an AB system, -CH₂-O-), 4.44 (d, J = 13.0 Hz, 1H, half of an AB system, -CH₂-O-), 4.43 (m as t, J = 1.0 Hz, 1H, >C=CH₂), 4.35 (m, 1H, >C=CH₂), 4.01 (m as br d, J = 10.3 Hz, 1H, >C=CH-CH<), 3.72 (s, 6H, -OCH₃), 3.12 (t, J = 7.0 Hz, 2H, -CH₂Br), 2.81 (ddd, J = 10.1 Hz, J = 9.9 Hz, J = 3.1 Hz, 1H, >CH₂=C(CH₃)=CH₂), 2.25-2.17 (m, 1H, -CH₂=C(CH₃OCOCH₃)=C<), 2.16-2.10 (m, 1H, CH₂=C(CH₃OCOCH₃)=C<), 2.06 (s, 3H, -OCH₃), 1.84-1.79 (m, 1H, -CH₂-CH₂=C(CH₃OCOCH₃)=C<, equatorial), 1.77-1.70 (m and quintet overlapping, 3H, -CH₂-CH₂=C(CH₃OCOCH₃)=C<, axial, -CH₂- of the side chain especially, 1.75, quintet, J = 6.5 Hz, -CH₂- of the side chain), 1.60 (s, 3H, >CH-C(CH₃)=CH₂), 1.56-1.52 (m, 2H, 2'H), 1.28 (s, 6H, -C(CH₃)₂-), 1.18- 1.11 (m, 2H, -CH₂- of the side chain); Mass spectrum (ESI)
m/z (relative intensity) 507 (M⁺+H, 10), 495 (100), 447 (M⁺+H-OCOCH₃, 8). Exact mass (ESI) calculated for C₂₇H₄₀O₄Br (M⁺+H), 507.2110; found, 507.2100; LCMS (ES+) retention time, 7.53 min (Method B); purity (100%).

2-[(1S,6S)-3-(Hydroxymethyl)-6-(1-methylethenyl)-2-cyclohexen-1-yl]-5-(6-bromo-2-methylhexane-2-yl)-1,3-dimethoxy-benzene (58). The synthesis was carried out as described for 46 using 57 (155 mg, 0.305 mmol) and K₂CO₃ (30 mg, 0.213 mmol) in methanol to give 111 mg of 58 as a viscous oil in 76% yield. ¹H NMR (500 MHz, CDCl₃) δ 6.44 (s, 2H, ArH), 5.53 (s, 1H, >C=CH-), 4.44 (m as t, J = 1.5 Hz, 1H, >C=CH₂), 4.37 (m, 1H, >C=CH₂), 4.05-3.95 (m , 3H, >C=CH-C< and –C₂H₂-O), 3.74 (s, 6H, -OCH₃), 3.11 (t, 2H, J = 7.0 Hz, -CH₂Br), 2.85 (ddd, J = 10.1 Hz, J = 9.9 Hz, J = 3.1 Hz, 1H, >CH-C(CH₃)=CH₂), 2.30-2.15 (m, 2H, CH₂-C(CH₂OH)=C<), 1.86-1.81 (m, 1H, -CH₂-CH₂-C(CH₂OH)=C<, equatorial), 1.78-1.68 (m, 3H, especially 1H, -CH₂-CH₂-C(CH₂OH)=C<, axial and –CH₂- of the side chain), 1.60 (s, 3H, >CH-C(CH₃)=CH₂), 1.58-1.53 (m, 2H, 2'H), 1.28 (s, 6H, -C(CH₃)₂-), 1.18-1.12 (m, 2H, -CH₂- of the side chain); LCMS (ES+) retention time, 6.62 min (Method B); purity (95.6%).

2-[(1S,6S)-3-(Hydroxymethyl)-6-(1-methylethenyl)-2-cyclohexen-1-yl]-5-(6-cyano-2-methylhexane-2-yl)-1,3-dimethoxy-benzene (59). The synthesis was carried out as described for 48 using 58 (142 mg, 0.305 mmol) and NaCN (60 mg, 1.22 mmol) in DMSO (3mL) to give 78 mg of 59 as a viscous oil in 67% yield; IR (neat) 3437(br, OH), 2932, 2247 (s, CN), 1606, 1626, 1574, 1410, 1239, 884, 832 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 6.43 (s, 2H, ArH), 5.32 (s, 1H, >C=CH-), 4.44 (m as t, J = 1.5 Hz, 1H, >C=CH₂), 4.37 (br s, 1 H, >C=CH₂), 4.02 (m, 3H, -CH₂-O- and >C=CH(CH₂)<), 3.74 (s, 6H, -OCH₃), 2.85 (ddd, J = 10.1 Hz, J = 9.9 Hz, J = 3.1 Hz, 1H, >CH-C(CH₃)=CH₂),
2.28-2.15 (m and t overlapping, 4H, -CH₂-C(CH₂OH)=C< and -CH₂CN, especially 2.24, t , J = 7.5 Hz, -CH₂CN), 1.87-1.80 (m, 1H, -CH₂-CH₂-C(CH₂OH)=C<, equatorial), 1.78-1.70 (m, 1H, -CH₂-CH₂-C(CH₂OH)=C<, axial), 1.60 (s, 3H, >CH-C(CH₃)=CH₂), 1.59-1.52 (m, 2H, 2'-H), 1.28 (s, 6H, -C(CH₃)₂-), 1.26-1.14 (m, 4H, 3'-H and 4'-H); Mass spectrum (ESI) m/z (relative intensity) 434 (M⁺+Na, 40), 394 (M⁺+H-H₂O, 100), 274 (48). Exact mass (ESI) calculated for C₂₆H₃₇NO₃Na (M⁺+Na), 434.2671; found, 434.2658; LCMS (ES+) retention time, 5.42 min (Method B); purity (100%).

2-[(1S,6S)-3-(Hydroxymethyl)-6-(1-methylethenyl)-2-cyclohexen-1-yl]-5-(6-morphalino-2-methylhexane-2-yl)-1,3-dimethoxy-benzene (60). The synthesis was carried out as described for 49 using 58 (110 mg, 0.236 mmol), triethylamine (72 mg, 0.708 mmol) and morpholine (0.205g, 2.36 mmol) in acetonitrile (6mL) to give 37 mg of 60 in 33 % yield; ¹H NMR (500MHz, CDCl₃) δ 6.43 (s, 2H, ArH), 5.52 (s, 1H, >C=CH-), 4.44 (m as t, J = 1.5 Hz, 1H, >C=CH₂), 4.37 (br s, 1 H, >C=CH₂), 4.01 (m, 3H, -CH₂O- and >C=CH-CH<), 3.73 (s, 6H, -OCH₃), 3.69 (t, 4H, J = 5.0 Hz, -CH₂O- of the morpholine ring), 2.85 (ddd, J = 10.1 Hz, J = 9.9 Hz, J = 3.1 Hz, 1H, >CH-C(CH₃)=CH₂), 2.38 (brs, 4H, -CH₂N< of the morpholine ring), 2.26-2.22 (m as t, 2H, J = 7.0Hz, -CH₂N<), 2.21-2.14 (m, 2H, -CH₂-C(CH₂OH)=C<),1.86-1.80 (m, 1H, -CH₂-CH₂-C(CH₂OH)=C<, equatorial), 1.79-1.68 (m, 1H, -CH₂-CH₂-C(CH₂OH)=C<, axial ), 1.60 (s, 3H, >CH-C(CH₃)=CH₂), 1.58-1.54 (m, 2H, 2'-H), 1.42-1.35 (quintet, J = 7.5Hz, 2H, -CH₂- of the side chain), 1.26 (m, 6H -C(CH₃)₂, 1.08-0.80 (m, 2H, -CH₂- of the side chain); Mass spectrum (ESI) m/z (relative intensity) 472 (M⁺+H, 100). Exact mass (ESI) calculated for C₂₉H₄₆NO₄ (M⁺+H), 472.3427; found, 472.3429.
2-[(1S,6S)-3-(Acetoxymethyl)-6-(1-methylethenyl)-2-cyclohexen-1-yl]-1,3-[bis(tert-butyldimethylsilyloxy)-5-(1,1-dimethylheptyl)-benzene (61). To a stirred solution of 26a (92 mg, 0.214 mmol) and TBDMSCl (193 mg, 1.28 mmol) in anhydrous DMF under argon atmosphere, was added imidazole (110.7 mg, 1.62 mmol). The reaction mixture was stirred at room temperature for 24 hours, and on completion the reaction mixture was quenched with water and diluted with ethyl acetate. The organic phase was separated, the aqueous phase extracted with ether and combined organic layer was washed with brine, dried over MgSO₄ and concentrated. The crude mixture was purified on a silica gel column, eluting with 0-15% ethyl acetate in hexanes and gave 138 mg of 61 as a viscous oil in 98% yield. 

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\begin{align*}
\text{1H NMR (500 MHz, CDCl}_3\text{)} & \delta 6.38 (s, 2H, ArH), 5.61 (s, 1H, \text{ >C=CH-}), 4.48 (s, >C=CH_2), 4.47 (s, >C=CH_2), 4.45 (d, J = 12.0 Hz, 1H, half of an AB system, -CH_2-O-), 4.43 (d, J = 12.0 Hz, 1H, half of an AB system, -CH_2-O-), 3.94 (m as br d, J = 10.3 Hz, 1H, >C=CH-CH<), 2.99 (ddd, J = 10.1 Hz, J = 9.9 Hz, J = 3.1 Hz, 1H, >CH-C(CH_3)=CH_2), 2.20-2.13 (m, 2H, CH_2-C(CH_2OCOCH_3)=C<, equatorial), 1.79-1.69 (m, 1H, -CH_2-CH_2-C(CH_2OCOCH_3)=C<, equatorial), 1.55 (s, 3H, >CH-C(CH_3)=CH_2), 1.52-1.46 (m, 1H, half of an AB system, 2'H), 1.46-1.40 (m, 1H, half of an AB system, 2'H), 1.24-1.14 (m, s and s overlapping, 12H, -C(CH_3)₂- and –CH₂- of the side chain, especially 1.90 s and 1.87 s, -C(CH_3)₂-, 1.12- 0.95 (m and s overlapping, 20H, -Si(CH_3)₂C(CH_3)₃ and –CH₂- of the side chain especially, 0.99 s, -Si(CH_3)₂C(CH_3)₃), 0.84 (t, J = 6.5 Hz, 3H, -CH₂CH₃), 0.22 (s, 12H, -Si(CH_3)₂C(CH_3)₃); ¹³C NMR (100 MHz, CDCl₃) \delta 171.55 (–OC(O)-), 154.95 (brs, ArC3, ArC1), 148.99 (C8 or ArC5), 148.01(ArC5 or C8), 132.29(C3), 129.63(C2), 120.75(ArC2), 109.88(C9), 109.63(brs, ArC4, ArC6), 68.89(-CH₂O-), 58.89(-CH₂O-)
\end{align*}
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444.79, 43.75, 37.52, 37.27, 31.81, 29.95, 29.38, 28.97, 28.63, 26.61, 26.16(-C(CH$_3$)$_3$), 224.61, 22.56 21.02, 20.00, 14.07, -3.75 (-Si(CH$_3$)$_2$-); Mass spectrum (ESI) m/z (relative intensity) 657 (M$^+$+H, 100), 543 (25), 441 (35), 419 (46). Exact mass (ESI) calculated for C$_{39}$H$_{69}$O$_4$Si$_2$ (M$^+$+H), 657.4734; found, 657.4730.

2-[(1S,6S)-3-(Hydroxymethyl)-6-(1-methylethenyl)-2-cyclohexen-1-yl]-1,3-[bis(tertbutyldimethylsilyloxy]-5-(1,1-dimethylheptyl)-benzene (62). The synthesis was carried out as described for 27a using 61 (120 mg, 0.18 mmol) and 1M DIBAL-H in toluene (1.0 mL). The reaction afforded 85 mg of 62 in 76% yield; $^1$H NMR (500 MHz, CDCl$_3$) δ 6.33 (s, 2H, ArH), 5.53 (s, 1H, >C=CH), 4.48 (s, 1H, >C=CH$_2$), 4.47 (m, 1H, >C=CH$_2$), 3.99 (m, 2H, -CH$_2$OH-), 3.94 (m as br d, $J = 10.3$ Hz, 1H, >CH-C(CH$_3$)=CH$_2$), 2.99 (ddd, $J = 10.1$ Hz, $J = 9.9$ Hz, $J = 3.1$ Hz, 1H, >CH-C(CH$_3$)=CH$_2$), 2.28-2.11 (m, 2H, CH$_2$-C(CH$_2$OH)=C<), 1.89-1.83 (m, 1H, -CH$_2$-CH$_2$-C(CH$_2$OH)=C<, equatorial), 1.78-1.67 (m, 1H, -CH$_2$-CH$_2$-C(CH$_2$OH)=C<, axial), 1.55 (s, 3H, >CH-C(CH$_3$)=CH$_2$), 1.52-1.46 (m, 1H, half of an AB system, 2'H), 1.46-1.40 (m, 1H, half of an AB system, 2'H), 1.24-1.14 (m, s and s overlapping, 12H, -C(CH$_3$)$_2$- and -CH$_2$- of the side chain, especially 1.90 s and 1.87 s, -C(CH$_3$)$_2$-, 0.98 (m and s overlapping, 20H, -Si(CH$_3$)$_2$C(CH$_3$)$_3$) and -CH$_2$- of the side chain), 0.84 (t, $J = 6.5$ Hz, 3H, -CH$_2$CH$_3$), 0.22 (s, 12H, -Si(CH$_3$)$_2$C(CH$_3$)$_3$); Mass spectrum (ESI) m/z (relative intensity) 615 (M$^+$+H, 100). Exact mass (ESI) calculated for C$_{37}$H$_{67}$O$_3$Si$_2$ (M$^+$+H), 615.4629; found, 615.4619.

2-[(1S,6S)-3-(Iodomethyl)-6-(1-methylethenyl)-2-cyclohexen-1-yl]-1,3-[bis(tert-
butyldimethylsilyloxy]-5-(1,1-dimethylheptyl)-benzene (63). To a solution of benzene containing imidazole (22 mg, 0.325 mmol) was added 62 (50 mg, 0.081 mmol). To the resulting solution was added PPh$_3$ (42.49 mg, 0.162 mmol) and the solution was heated to
50 °C which was followed by a dropwise addition of iodine (41 mg, 0.162 mmol) in benzene (1.5 mL) through canula. The reaction mixture was stirred at 50 °C for 2 hours and then quenched with a solution of sodium sulfite and diluted with diethyl ether. The ether layer was washed with brine and dried over MgSO₄. Solvent evaporation and purification by flash column chromatography on a silica gel column eluting with 0-15% ethyl acetate/hexanes to afford 51 mg of 63 in 86% yield. ¹H NMR (500 MHz, CDCl₃) δ 6.33 (s, 2H, ArH), 5.83 (s, 1H, >C=CH), 4.48 (m, 2H, >C=CH₂), 3.99 (d, J = 8.5 Hz, half of an AX system, -CH₂I-), 3.83 (d, J = 8.5 Hz, half of an AX system, -CH₂I-), 3.75 (m as br d, J = 10.3 Hz, 1H, >C=CH-CH<), 2.96 (ddd, J = 10.1 Hz, J = 9.9 Hz, J = 3.1 Hz, 1H, >CH-C(CH₃)=CH₂), 2.48-2.40 (m, 1H, CH₂-C(CH₃)=C<), 2.28-2.17 (m, 1H, -CH₂-C(CH₂I)=C<, axial), 1.55 (s, 3H, >CH-C(CH₃)=CH₂), 1.52-1.46 (m, 1H, half of an AB system, 2'H), 1.46-1.40 (m, 1H, half of an AB system, 2'H), 1.22-1.14 (m, s and s overlapping, 12H, -CH₂-CH₂= and -CH₂- of the side chain, especially 1.19s and 1.18 s, -CH₂-CH₂=, 0.98 (m and s overlapping, 20H, -Si(CH₃)₂C(CH₃)₃ and -CH₂- of the side chain), 0.84 (t, J = 6.5 Hz, 3H, -CH₂CH₃), 0.82 (s, 12H, -Si(CH₃)₂C(CH₃)₃); Mass spectrum (ESI) m/z (relative intensity) 725 (M⁺+H, 20), 705 (98), 359 (100). Exact mass (ESI) calculated for C₃₇H₆₆O₂Si₂I (M⁺+H), 725.36646; found, 725.3671.

2-[(1S,6S)-3-(Azidomethyl)-6-(1-methylethenyl)-2-cyclohexen-1-yl]-1,3-[bis(tert-butyldimethylsilyloxy)-5-(1,1-dimethylheptyl)-benzene (64). The synthesis was carried out as described for 74 using 63 (150 mg, 0.206 mmol) to which tetrabutylammonium azide (589 mg, 2.06 mmol) was added. The reaction was completed in 24 hours to afford 120 mg of 64 as viscous oil in 91% yield. ¹H NMR (500 MHz,
CDCl$_3$ δ 6.34 (s, 2H, ArH), 5.60 (s, 1H, >C=CH), 4.48 (m, 2H, >C=CH$_2$), 4.01 (m as br d, $J = 10.3$ Hz, 1H, >C=CH CH<), 3.78 (d, $J = 13.0$ Hz, half of an AX system, -CH$_2$N$_3$), 3.47 (d, $J = 13.0$ Hz, half of an AX system, -CH$_2$N$_3$), 2.99 (ddd, $J = 10.1$ Hz, $J = 9.9$ Hz, $J = 3.1$ Hz, 1H, >CH-C(CH$_3$)=CH$_2$), 2.28-2.11 (m, 2H, -CH$_2$N$_3$=CH<), 1.91-1.83 (m, 1H, -CH$_2$-CH$_2$=C(CH$_2$N$_3$)=CH<, equatorial), 1.80-1.72 (m, 1H, -CH$_2$-CH$_2$=C(CH$_2$N$_3$)=CH<, axial), 1.56 (s, 3H, >CH-C(CH$_3$)=CH$_2$), 1.50-1.46 (m, 1H, half of an AB system, 2'H), 1.46-1.42 (m, 1H, half of an AB system, 2'H), 1.24-1.12 (m, s and s overlapping, 12H, -C(CH$_3$)$_2$- and –CH$_2$- of the side chain, especially 1.19 s and 1.18 s, -C(CH$_3$)$_2$-, 0.98 (m and s overlapping, 20H, -Si(CH$_3$)$_2$C(CH$_3$)$_3$ and –CH$_2$- of the side chain), 0.84 (t, $J = 6.5$ Hz, 3H, -CH$_2$CH$_3$), 0.22 (s, 12H, -Si(CH$_3$)$_2$C(CH$_3$)$_3$); Mass spectrum (ESI) m/z (relative intensity) 640 (M$^+$+H, 82), 615 (100), 394 (64). Exact mass (ESI) calculated for C$_{37}$H$_{66}$N$_3$O$_2$Si$_2$ (M$^+$+H), 640.4694; found, 640.4697.

2-[(1S,6S)-3-(Azidomethyl)-6-(1-methylethenyl)-2-cyclohexen-1-yl]-5-(1,1-dimethylheptyl) resorcinol (65). The synthesis was carried out as described for 14 using 64 (120 mg, 0.187 mmol) and 1M TBAF in THF (0.176 mL, 0.749 mmol) to afford 35 mg of 65 in 45% yield as a white foam. $^1$H NMR (500 MHz, CDCl$_3$) δ 6.33(br s, 2H, ArH), 5.88 (s, 1H, >C=CH-), 5.25 (br s, 1H, OH), 4.64 (m as t, $J = 1.8$ Hz, 1H, >C=CH$_2$), 4.63 (br s, 1H, OH), 4.54 (br s, 1H, >C=CH$_2$), 3.96 (m as br d, $J = 10.5$ Hz, 1H, >C=CH(CH$_3$)=CH<), 3.82 (d, $J = 13.5$ Hz, 1H, half of an AB system, -CH$_2$N$_3$), 3.77 (d, $J = 13.5$ Hz, 1H, half of an AB system, -CH$_2$N$_3$), 2.52 (ddd, $J = 10.1$ Hz, $J = 9.9$ Hz, $J = 3.1$ Hz, 1H, >CH-C(CH$_3$)=CH$_2$), 2.35-2.26 (m, 1H, -CH$_2$-CH$_2$=C(CH$_2$N$_3$)=CH<), 2.34-2.22 (m, 2H, -CH$_2$-CH$_2$=C(CH$_2$N$_3$)=CH<), 1.95-1.90 (m, 1H, -CH$_2$-CH$_2$=C(CH$_2$N$_3$)=CH<, equatorial), 1.86-1.78 (m, 1H, -CH$_2$-CH$_2$=C(CH$_2$N$_3$)=CH<, axial), 1.65 (s, 3H, >CH-C(CH$_3$)=CH$_2$), 206
1.51-1.45 (m, 2H, 2'-H), 1.30-1.14 (m and s overlapping, 12 H, -C(CH₃)₂- and -CH₂- of the side chain especially 1.20, s and 1.21, s, -C(CH₃)₂-), 1.12-0.96 (m, 2H, -CH₂-of the side chain), 0.84 (t, J = 7.0 Hz, 3H, -CH₂CH₃); Mass spectrum (EI) m/z (relative intensity) 411 (M⁺, 5), 383 (M⁺-N₂, 39), 366 (100), 340 (10), 314 (13), 299 (24), 249 (10), 91 (9). Exact mass (EI) calculated for C₂₅H₃₇N₃O₂ (M⁺), 411.28858; found, 411.28674; LCMS (ES+) retention time, 6.38 min (Method B); purity (95.7%).

2-[(1S,6S)-3-(Isothiocyanatomethyl)-6-(1-methylethenyl)-2-cyclohexen-1-yl]-5-(1,1-dimethylheptyl) resorcinol (66). The synthesis was carried out as described for 83 using 65 (30 mg, 0.728 mmol), Ph₃P (28.0 mg, 0.109 mmol) and CS₂ (0.087 mL, 1.45 mmol) in anhydrous benzene to afford 10 mg of 64 in 32 % yield. IR (neat) 3465 (br, OH), 2956, 2927, 2076 (s, NCS), 1708, 1626, 1581, 1417, 1329, 1246, 1048, 1021, 889, 839 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 6.33 (br s, 2H, ArH), 5.88 (s, 1H, >C=CH₂), 4.85 (br s, 1H, >C=CH₂), 4.54 (br s, 1H, >C=CH₂), 4.12 (s, 2H, -CH₂-NCS), 3.93 (m as br d, J = 10.5 Hz, 1H, >C=CH₂<), 2.55 (ddd, J = 10.1 Hz, J = 9.9 Hz, J = 3.1 Hz, 1H, >CH-C(CH₃)=CH₂), 2.35-2.26 (m, 1H, -CH₂-CH₂-C(CH₂NCS)=C<), 2.24-2.22 (m, 1H, -CH₂-CH₂-C(CH₂NCS)=C<, equatorial), 1.82 (ddd, J = 24.0 Hz, J = 12.0 Hz, J = 5.5 Hz, 1H, -CH₂-CH₂-C(CH₂NCS)=C<, axial), 1.65 (s, 3H, >CH-C(CH₃)=CH₂), 1.48 (m, 2H, -C(CH₃)₂-CH₂-<), 1.32-1.14 (m and s overlapping, 12 H, -C(CH₃)₂- and -CH₂-CH₂-CH₂-CH₃, -CH₂-CH₂-CH₂-CH₃, especially 1.20, s and 1.21, s, -C(CH₃)₂-), 1.12-0.96 (m, 2H, -C(CH₃)₂-CH₂-CH₂-), 0.84 (t, J = 7.0 Hz, 3H, -CH₂CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 154.60 (brs, ArC₁, ArC₃), 150.55 (ArC₅), 148.27 (C₈), 134.51 (C₃), 132.67 (NCS), 128.97 (C₂), 112.56 (ArC₂), 111.20 (C₉), 106.85 (burs, ArC₄, ArC₆), 50.68 (-
(5aR,9S,9aS)-6-methylene-3-(2-methyloctan-2-yl)-9-(prop-1-en-2-yl)-5a,6,7,8,9,9a-hexahydrodibenzo[b,d]furan-1-ol (68). The synthesis was carried out as described for 14 using 63 (25 mg, 0.034 mmol) and 1M TBAF (0.036 mL, 0.137 mmol) to give 68 as a colorless viscous oil in 93% yield. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 6.46 (d, \(J = 1.4\) Hz, 1H, ArH), 6.40 (d, \(J = 1.4\) Hz, 1H, ArH), 5.39 (s, 1H, OH), 5.23 (t, \(J = 1.5\) Hz, 1H, 10-H), 5.18 (t, \(J = 1.5\) Hz, 1H, 10-H), 5.07-5.06 (m, 2H, 12-H), 4.83 (d, \(J = 7.0\) Hz, 1H, 5a-H), 3.27 (dd, \(J = 11.0\) Hz, \(J = 7.0\) Hz, 1H, 11a-H), 2.43 (ddd, \(J = 14.0\) Hz, \(J = 3.5\) Hz, \(J = 3.5\) Hz, 7-H), 2.39-2.30 (m, 1H, 7-H), 2.13 (ddd, \(J = 12.0\) Hz, \(J = 12.0\) Hz, 1H, 9-H), 1.84 (s, 3H, 13-Me), 1.81 (dddd, \(J = 12.0\) Hz, \(J = 3.5\) Hz, \(J = 3.5\) Hz, \(J = 3.5\) Hz, 1H, 8-H), 1.52-1.49 (m, 2H, 2’H), 1.34 (dddd, \(J = 12.0\) Hz, \(J = 11.0\) Hz, \(J = 11.0\) Hz, \(J = 3.5\) Hz, 1H, 8-H), 1.26-1.16 (m and s overlapping, 12H, -C(CH\(_3\))\(_2\)- and 4’H, 5’H, 6’H, especially 1.20, s and 1.21, s, -C(CH\(_3\))\(_2\)-), 1.08-1.03 (m, 2H, 3’H), 0.84 (t, \(J = 7.0\) Hz, 3H, -CH\(_2\)CH\(_3\)). \(^{13}\)C NMR (175 MHz, CDCl\(_3\)) \(\delta\) 160.16, 152.98, 152.49, 151.70, 143.06, 117.04 (ArC6), 115.52 (C10), 111.60 (C12), 107.35 (ArC2 or ArC4), 100.95 (ArC4 or ArC2), 86.26 (C5a), 48.15 (C9), 45.64 (C9a), 44.62 (C’), 37.89 (C1’), 31.79 (C5’ or C4’), 31.43 (C8), 30.73 (C7), 30.00 (C4’ or C5’), 28.99 (-C(CH\(_3\))\(_2\)-), 24.65 (C3’), 22.67 (C13-Me), 22.59 (C6’), 14.09 (C7’); Mass spectrum (ESI) m/z (relative intensity) 370 (M\(^{+}\)+H+1, 20),
Exact mass (ESI) calculated for C\textsubscript{25}H\textsubscript{37}O\textsubscript{2} (M\textsuperscript{+}+H), 369.2794; found, 369.2794.

2-[(1R,6R)-3-(Acetoxymethyl)-6-(1-methylethenyl)-2-cyclohexen-1-yl]-5-(1,1-dimethylheptyl)resorcinol (69). Colorless viscous oil; yield: 30%; \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) identical to that of 26a; Mass spectrum (ESI) m/z (relative intensity) 451 (M\textsuperscript{+}+Na, 8), 429 (M\textsuperscript{+}+H, 100), 430 (M\textsuperscript{+}+H+1, 40), 369 (M\textsuperscript{+}+H-OCOCH\textsubscript{3}, 88). Exact mass (ESI) calculated for C\textsubscript{25}H\textsubscript{41}O\textsubscript{4} (M\textsuperscript{+}+H), 429.3005; found, 429.3001.

2-[(1R,6R)-3-(Hydroxymethyl)-6-(1-methylethenyl)-2-cyclohexen-1-yl]-5-(1,1-dimethylheptyl)resorcinol (70). Colorless viscous oil; yield: 42%. [\alpha]\textsubscript{D}\textsuperscript{26.6} = -224.34\degree (c = 0.221 g/100 mL in CHCl\textsubscript{3}). \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) identical to that of 27a. Mass spectrum (ESI) m/z (relative intensity) 409 (M\textsuperscript{+}+Na, 10), 387 (M\textsuperscript{+}+H, 100), 388 (M\textsuperscript{+}+H+1, 37), 369 (M\textsuperscript{+}+H-H\textsubscript{2}O, 78). Exact mass (ESI) calculated for C\textsubscript{25}H\textsubscript{39}O\textsubscript{3} (M\textsuperscript{+}+H), 387.2899; found, 387.2904.

(+)-2-[(1R,4S,5S)-2,6,6-trimethylbicyclo[3.1.1]hept-2-en-4-yl]-5-[2-methyloctyl]resorcinol (72a). To a stirred solution of 25a (30 mg, 0.126 mmol) and p-TSA (2.2 mg, 0.013 mmol) in dry CH\textsubscript{2}Cl\textsubscript{2} (4 mL) at 0 ºC under an argon atmosphere was added a solution of (+)-cis-verbenol (71) (21 mg, 0.14 mmol) in CH\textsubscript{2}Cl\textsubscript{2} over a period of 15 minutes. The reaction mixture was allowed to warm to room temperature and stirred for an additional 2 hours. The reaction was quenched by addition of NaHCO\textsubscript{3}, the aqueous phase was separated and extracted with CH\textsubscript{2}Cl\textsubscript{2} and the combined organic layer was washed with brine and dried over MgSO\textsubscript{4}. Solvent evaporation and purification of crude by flash column chromatography (0-15% diethyl ether in hexanes) afforded 40 mg
of 72a in 85% yield as a white gum. $^1$H NMR (500 MHz, CDCl$_3$) δ 6.31 (s, 2H, ArH), 5.71 (br s, 1H, 3-H), 3.91 (m as quintet, $J = 2.5$ Hz, 1H, -CH$_2$Br), 3.36 (m, 4H, -CH$_2$-), 2.32 (tt, $J = 10.0$ Hz, $J = 5.5$ Hz, 1H), 2.27 (tt, $J = 5.5$ Hz, $J = 2.5$ Hz, 1H), 2.19 (m as td, $J = 5.5$ Hz, $J = 1.0$ Hz, 1H), 1.86 (dd, $J = 2.0$ Hz, $J = 1.6$ Hz, C$_2$-CH$_3$), 1.52-1.48 (m and d overlapping, 3H, -C(CH$_3$)$_2$- and 7β-H, especially, 1.49, d, $J = 10.0$ Hz, 7β-H), 1.32 (s, 3H, C$_6$-CH$_3$), 1.24-1.18 (s and m overlapping, 12H, -C(CH$_3$)$_2$- and -CH$_2$- of the side chain, especially, 1.20, s, -C(CH$_3$)$_2$-), 1.11-1.04 (m, 2H, -CH$_2$- of the side chain), 0.97 (s, 3H, C$_6$-CH$_3$), 0.85 (t, $J = 7.5$ Hz, -CH$_2$-CH$_3$); Mass spectrum (ESI) m/z (relative intensity) 372 (M$^+$+H+1, 28), 371 (M$^+$+H, 100). Exact mass (ESI) calculated for C$_{25}$H$_{39}$O$_2$ (M$^+$), 371.2950; found, 371.2951.

(+)-2-[(1R,4S,5S)-2,6,6-trimethylbicyclo[3.1.1]hept-2-en-4-yl]-5-(2-hexyl-1,3-dithiolane-2-yl)resorcinol (72d). The synthesis was carried out as described for 72a using (+)-cis-verbenol (25 mg, 0.16 mmol), resorcinol 25d (45 mg, 0.15 mmol) and p-toluenesulfonic acid (2.6 mg, 0.015 mmol). The reaction was completed in 1 hour and purification by flash column chromatography on silica gel (0-15% diethyl ether in hexanes) afforded 90 mg of 72d in 65% yield as a white solid. $^1$H NMR (500 MHz, CDCl$_3$) δ 6.69 (s, 2H, ArH), 5.69 (br s, 1H, 3-H), 3.91 (m, 1H, 4-H), 3.38-3.30 (m, 2H, -S-CH$_2$-), 3.27-3.20 (m, 2H, -S-CH$_2$-), 2.35-2.24 (m, 4H, 7α-H, 5-H, 2'H), 2.19 (m as td, $J = 5.5$ Hz, $J = 1.0$ Hz, 1H, 1-H), 1.86 (dd, $J = 2.0$ Hz, $J = 1.6$ Hz, C$_2$-CH$_3$), 1.48 (d, $J = 10.0$ Hz, 1H), 1.32 (s, 3H, C$_6$-CH$_3$), 1.30-1.18 (m, 8H, 3'-H, 4'-H, 5'-H, 6'-H), 0.96 (s, 3H, C$_6$-CH$_3$), 0.85 (t, $J = 7.0$ Hz, 3H, 7'-H); Mass spectrum (EI) m/z (relative intensity) 432 (M$^+$, 16), 347 (100), 389 (15). Exact mass (EI) calculated for C$_{25}$H$_{36}$O$_2$S$_2$ (M$^+$),
432.21568 found, 432.21439; LCMS (ES+) retention time, 7.15min (Method B); purity (100%).

2-[(1R,4S,5S)-2,6,6-Trimethylbicyclo[3.1.1]hept-2-en-4-yl]-5-(6-bromo-2-methylhexyl)-resorcinol (72g). To a stirred solution of resorcinol 25g (54 mg, 0.188 mmol) and p-TSA in dry CH$_2$Cl$_2$ (4 mL) at 0 °C under an argon atmosphere was added a solution of (+)-cis-verbenol (71) in CH$_2$Cl$_2$ over a period of 15 minutes. The reaction mixture was allowed to warm to room temperature and stirred for an additional 2 hours. The reaction was quenched by addition of NaHCO$_3$, the aqueous phase was separated and extracted with CH$_2$Cl$_2$ and the combined organic layer was washed with brine and dried over MgSO$_4$. Solvent evaporation and purification of crude by flash column chromatography (30% diethyl ether in hexanes) afforded 64 mg of 72g as a colorless viscous oil in 81% yield. $^1$H NMR (500 MHz, CDCl$_3$) δ 6.31 (s, 2H, ArH), 5.71 (br s, 1H, 3-H), 3.91 (m as quintet, $J = 2.5$ Hz, 1H, 4-H), 3.36 (m, 2H, -CH$_2$Br), 2.32 (tt, $J = 10.0$ Hz, $J = 5.5$ Hz, 1H), 2.27 (tt, $J = 5.5$ Hz, $J = 2.5$ Hz, 1H), 2.19 (m as td, $J = 5.5$ Hz, $J = 1.0$ Hz, 1H), 1.86 (dd, $J = 2.0$ Hz, $J = 1.6$ Hz, C$_2$-CH$_3$), 1.77 (quintet, $J = 7.0$ Hz, 2H, -CH$_2$- of the side chain), 1.49 (d, $J = 10.0$ Hz, 1H), 1.32 (s, 3H, C$_6$-CH$_3$), 1.24-1.20 (s and m overlapping, 8H, -C(CH$_3$)$_2$- and -CH$_2$- of the side chain, especially, 1.22, s, -C(CH$_3$)$_2$-), 0.97 (s, 3H, C$_6$-CH$_3$); Mass spectrum (EI) m/z (relative intensity) 422 (M$^+$+2, 60), 420 (M$^+$, 60), 379 (60), 377 (60), 341 (M$^+$-Br, 100), 325 (40), 297 (56), 286 (91), 257 (63), 241 (38), 97 (85). Exact mass (EI) calculated for C$_{23}$H$_{33}$O$_2$Br (M$^+$), 420.16639; found, 420.16550.

(+)-2-[(1R,4S,5S)-2,6,6-trimethylbicyclo[3.1.1]hept-2-en-4-yl]-5-[(5-bromopentyl)cyclobutyl]resorcinol (72h). The synthesis was carried out as described
for 72a using (+)-cis-verbenol (13.3 mg, 0.09 mmol), resorcinol 25h (25 mg, 0.08 mmol) and p-toluenesulfonic acid (1.3 mg, 0.008 mmol). The reaction was completed in 1 hour and purification by flash column chromatography on silica gel (0-15% diethyl ether in hexanes) afforded 17 mg of 72h as colorless viscous oil in 48% yield. 1H NMR (500 MHz, CDCl3) δ 6.09 (s, 2H, ArH), 5.71 (br s, 1H, 3-H), 3.91 (m as quintet, J = 2.0 Hz, 1H, 4-H), 3.34 (t, J = 7.0 Hz, 2H, -CH2-Br), 2.36-2.24 (m, 4H, 7α-H, 5-H, 2H of the cyclobutane ring), 2.18 (t, J = 5.5 Hz, 1H, 1-H), 2.05-1.95 (m, 3H, cyclobutane ring), 1.86 (br s, 3H, C2-CH3), 1.84-1.75 (m, 3H, 1H of the cyclobutane ring, 5'-H), 1.70 (m, 2H, 2'-H), 1.50 (d, J = 10.0 Hz, 1H, 7β-H), 1.37-1.28 (m and s overlapping, 5H, C6-CH3, 4'-H, especially 1.32 s, C6-CH3), 1.09-1.03 (m, 2H, 3'-H), 0.97 (s, 3H, C6-CH3); Mass spectrum (EI) m/z (relative intensity) 448 (M+2, 100), 446 (M+, 100), 422 (30), 420 (30), 405 (40), 403 (40), 379 (80), 377 (80), 311 (92), 299 (32), 297 (32), 213 (52), 93 (48). Exact mass (EI) calculated for C25H35O2^81Br (M+2), 448.1800; found, 448.17866; LCMS (ES+) retention time, 7.03 min (Method B); purity (100%).

(+)-2-[(1R,4S,5S)-2,6,6-trimethylbicyclo[3.1.1]hept-2-en-4-yl]-5-[1-(adamantyl)]resorcinol (72k). The synthesis was carried out as described for 68a using (+)-cis-verbenol (24 mg, 0.157 mmol), resorcinol 25k (35 mg, 0.143 mmol) and p-toluenesulfonic acid (2.4 mg, 0.014 mmol). The reaction was completed in 1 hour and purification by flash column chromatography on silica gel (0-25% diethyl ether in hexanes) afforded 47 mg of 72k as a white solid (m.p = 190-193 °C) in 87% yield. 1H NMR (500 MHz, CDCl3) δ 6.36 (br s, 2H, ArH), 5.70 (br s, 1H, 3-H), 3.91 (m as q, J = 2.5 Hz, 1H, 4-H), 2.32 (ddd, J = 10.0 Hz, J = 5.5 Hz, J = 5.5 Hz, 1H, 7a-H), 2.27 (tt, J = 5.5 Hz, J = 5.5 Hz, 1H, 1-H), 2.17 (td, J = 5.5 Hz, J = 1.0 Hz, 1H, 1-H), 2.10-2.03 (m,
3H, 1-adamantyl group), 1.85-1.82 (m and s overlapping, 9H, C₂-CH₃ and 6H of adamantyl group especially 1.86 br s, C₂-CH₃), 1.78-1.68 (m, 4H of the 1-adamantyl group), 1.49 (d, J = 10.0 Hz, 1H, 7β-H), 1.32 (s, 3H, C₆-CH₃), 0.96 (s, 3H, C₆-CH₃);

Mass spectrum (ESI) m/z (relative intensity) 380 (M⁺+H+1, 30), 379 (M⁺+H, 100), 135 (5). Exact mass (ESI) calculated for C₂₆H₅₅O₂ (M⁺), 379.2637; found, 379.2624.

(+)-2-[(1R,4S,5S)-2,6,6-trimethylbicylc[3.1.1]hept-2-en-4-yl]-5-[1-(1,2-cis-hexen-1-yl)-cyclopent-1-yl]resorcinol (72n). The synthesis was carried out as described for 72a using (+)-cis-verbenol (21 mg, 0.138 mmol), resorcinol 25n (33 mg, 0.126 mmol) and p-toluenesulfonic acid (2.3 mg, 0.014 mmol). The reaction was completed in 1 hour and purification by flash column chromatography on silica gel (0-15% diethyl ether in hexanes) afforded 25 mg of 72n 50% yield. [α]D²⁴ = 362.69º (c = 0.087 g/100 mL in CHCl₃). ¹H NMR (500 MHz, CDCl₃) δ 6.35 (br s, 2H, ArH), 5.71 (m, 1H, 3'-H), 5.63 (dt, J = 11.3 Hz, J = 1.5 Hz, 1H, 2'-H), 5.27 (dt, J = 11.3 Hz, J = 7.5 Hz, 1H, 3'-H), 3.90 (m as q, J = 2.5 Hz, 1H, 4-H), 2.29 (ddd, J = 10.0 Hz, J = 5.5 Hz, J = 5.5 Hz, 1H, 7α-H), 2.24 (tt, J = 5.5 Hz, J = 2.5 Hz, 1H, 5-H), 2.17 (td, J = 5.5 Hz, J = 1.0 Hz, 1H, 1-H), 1.98-1.92 (m, 2H of the cyclopentane ring), 1.91-1.82 (m and dd overlapping, 5H, cyclopentane ring and C₂-CH₃, especially 1.85, dd, J = 2.0 Hz, J = 1.6 Hz, C₂-CH₃), 1.79-1.65 (m, 6H, 4H of the cyclopentane ring, 4'-H), 1.49 (d, J = 10.0 Hz, 1H, 7β-H), 1.32 (s, 3H, C₆-CH₃), 1.13-1.08 (m, 4H, 5'-H, 6'-H), 0.96 (s, 3H, C₆-CH₃), 0.75 (t, J = 7.0 Hz, 3H, 7'-H); Mass spectrum (EI) m/z (relative intensity) 394 (M⁺, 75), 379 (9), 351 (79), 337 (19), 311 (100), 273 (35), 95 (43). Exact mass (EI) calculated for C₂₇H₃₈O₂ (M⁺), 394.28718; found, 394.28834.
(+)-2-[(1R,4S,5S)-2,6,6-trimethylbicyclo[3.1.1]hept-2-en-4-yl]-5-[(5-bromobutyl)cyclobutyl]resorcinol (72o). The synthesis was carried out as described for 72a using (+)-cis-verbenol (17 mg, 0.113 mmol), resorcinol 25o (31 mg, 0.104 mmol) and p-toluenesulfonic acid (2 mg, 0.011 mmol). The reaction was completed in 1 hour and purification by flash column chromatography on silica gel (0-15% diethyl ether in hexanes) afforded 38 mg of 72o in 85% yield as a white foam. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta 6.10\) (s, 2H, ArH), 5.71 (br s, 1H, 3-H), 3.91 (m as quintet, \(J = 2.0\) Hz, 1H, 4-H), 3.33 (t, \(J = 7.0\) Hz, 2H, -CH\(_2\)-Br), 2.36-2.24 (m, 4H, 7α-H, 5-H, 2H of the cyclobutane ring), 2.19 (t, \(J = 5.5\) Hz, 1H, 1-H), 2.06-1.96 (m, 3H, cyclobutane ring), 1.86 (br s, 3H, C\(_2\)-CH\(_3\)), 1.84-1.75 (m, 3H, 1H of the cyclobutane ring, -CH\(_2\)- of the side chain), 1.71 (m, 2H, 2'-H), 1.50 (d, \(J = 10.0\) Hz, 1H, 7β-H), 1.33 (s, 3H, C\(_6\)-CH\(_3\)), 1.22-1.16 (m, 2H, -CH\(_2\)- of the side chain), 0.97 (s, 3H, C\(_6\)-CH\(_3\)); Mass spectrum (ESI) m/z (relative intensity) 435 (M\(^+\)+H+2, 100), 433(M\(^+\)+H, 100), 353 (5). Exact mass (ESI) calculated for C\(_{24}\)H\(_{34}\)O\(_2\)Br (M\(^+\)+H), 433.1742; found, 433.1732.

(+)-2-[(1S,4R,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-2-en-4-yl]-5-[2-methyloctyl]resorcinol (74a). The synthesis was carried out as described for 72a using (-)-cis-verbenol (176 mg, 1.16 mmol), resorcinol (25g) (250 mg, 1.06 mmol) and p-toluenesulfonic acid (18 mg, 0.106 mmol). The reaction was completed in 1 hour and purification by flash column chromatography on silica gel (0-15% diethyl ether in hexanes) afforded 318 mg of 74a in 60% yield as a white gum. \(^1\)H NMR (500 MHz, CDCl\(_3\)) is identical to that of 72a; Mass spectrum (ESI) m/z (relative intensity) 372 (M\(^+\)+H+1, 28), 371 (M\(^+\)+H, 100). Exact mass (ESI) calculated for C\(_{25}\)H\(_{39}\)O\(_2\) (M\(^+\)+H), 372.2324; found, 372.2322.
371.2950; found, 371.2948; LCMS (ES+) retention time, 7.03 min (Method B); purity (100%).

(+)-2-[(1S,4R,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-2-en-4-yl]-5-[(5-bromobutyl)dimethyl]resorcinol (74g). The synthesis was carried out as described for 72a using (-)-cis-verbenol (29 mg, 0.19 mmol), resorcinol (25g) (45 mg, 0.172 mmol) and p-toluenesulfonic acid (3.2 mg, 0.019 mmol). The reaction was completed in 1 hour and purification by flash column chromatography on silica gel (0-15% diethyl ether in hexanes) afforded 44 mg of 74g in 60% yield. \( \alpha \) \( \text{D} \)\( ^{26} \) = -460.32º (c = 0.087 g/100 mL in CHCl\(_3\)). \(^1\)H NMR (500 MHz, CDCl\(_3\)) is identical to that of 72g; Mass spectrum (EI) m/z (relative intensity) 422 (M\(^+\)+2, 50), 420 (M\(^+\), 50), 379 (68), 377 (68), 341 (M\(^+\)-Br, 42), 287 (66), 285 (66), 241 (43), 201 (63), 97 (100). Exact mass (EI) calculated for C\(_{23}\)H\(_{33}\)O\(_2\)Br (M\(^+\)), 420.16639; found, 420.16563.

(-)-2-[(1S,4R,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-2-en-4-yl]-5-[1-(1,2-cis-hexen-1-yl)cyclopentyl-1-yl] resorcinol (74n). The synthesis was carried out as described for 72a using (-)-cis-verbenol (32 mg, 0.211 mmol), resorcinol (25n) (50 mg, 0.192 mmol) and p-toluenesulfonic acid (3.6 mg, 0.02 mmol). The reaction was completed in 1 hour and purification by flash column chromatography on silica gel (0-15% diethyl ether in hexanes) afforded 37 mg of 74n in 49% yield. \( \alpha \) \( \text{D} \)\( ^{24} \) = -362.69º (c = 0.087 g/100 mL in CHCl\(_3\)). \(^1\)H NMR (500 MHz, CDCl\(_3\)) is identical to that of 72n; Mass spectrum (EI) m/z (relative intensity) 394 (M\(^+\), 75), 351 (100), 311 (90), 273 (43), 95 (45). Exact mass (EI) calculated for C\(_{27}\)H\(_{38}\)O\(_2\) (M\(^+\)), 394.28718; found, 394.28641.
(4S)-4-[(4-(1,2-cis-hexen-1-yl)tetrahydro-2H-pyran-4-yl)-2,6-dihydroxyphenyl]-6,6-dimethyl-2-norpinanone (76). To a degassed solution of 25m and p-TSA.H₂O (28 mg, 0.15 mmol) in wet chloroform at 0 °C under an argon atmosphere was added the mixture of diacetates 75 (36 mg, ca. 72% pure by ¹H NMR, 0.152 mmol) in CHCl₃. The mixture was warmed to room temperature and stirred for 3 days to ensure complete formation of the product. The reaction mixture was diluted with diethyl ether and washed sequentially with water, saturated NaHCO₃, and brine. The organic phase was dried over MgSO₄, and the solvent removed under reduced pressure. The crude residue was purified using flash column chromatography on silica gel (30-65% diethyl ether in hexanes) and gave 18 mg of 76 as a white foam in 41% yield. ¹H NMR (500 MHz, CDCl₃) δ 6.33 (s, 2H, ArH), 5.68 (dt, J = 11.5 Hz, J = 1.3 Hz, 1H, 2'H), 5.49 (dt, J = 11.5 Hz, J = 7.3 Hz, 1H, 3'H), 5.04 (br s, 2H, OH), 3.95 (t, J = 8.2 Hz, 1H, 4-H), 3.86 (m as br d, J = 11.5 Hz, 2H, -CH₂O-, equitorial), 3.73 (ddd, J = 11.5 Hz, J = 11.5 Hz, J = 1.0 Hz, 2H, -CH₂O-, axial), 3.51 (dd, J = 18.8 Hz, J = 7.8 Hz, 1H, 3α-H), 2.59 (dd, J = 18.9 Hz, J = 8.7 Hz, 1H, 3β-H), 2.58 (t, J = 5.0 Hz, 1H, 1-H), 2.50 (m, 1H, 7α-H), 2.47 (d, J = 10.5 Hz, 1H, 7β-H), 2.28 (t, J = 5.2 Hz, 1H, 5-H), 2.02-1.94 (m, 2H, -CH₂CH₂O- axial), 1.83 (m as br d, J = 12.0 Hz, 2H, -CH₂CH₂O-, equitorial), 1.69 (m as dt, J = 7.3 Hz, J = 7.3 Hz, 2H, 4'H), 1.37 (s, 3H, 6-Me), 1.13-1.06 (m, 4H, 5'-H, 6'-H), 1.01 (s, 3H, C₆-CH₃), 0.73 (t, J = 7.5 Hz, 3H, 7'-H); Mass spectrum (EI) m/z (relative intensity) 412 (M⁺, 48), 369 (19), 329 (100), 313 (25), 175 (32), 83 (50). Exact mass (EI) calculated for C₂₆H₃₆O₄ (M⁺), 412.26136; found, 412.26309.

(4R)-4-[(4-(1,2-cis-hexen-1-yl)tetrahydro-2H-pyran-4-yl)-2,6-dihydroxyphenyl]-6,6-dimethyl-2-norpinanone (78). The synthesis was carried out as described for 76
using the same amount of reagents to afford 21 mg of 78 in 48% yield. \( ^1H \) NMR identical is to that of 76; Mass spectrum (EI) m/z (relative intensity) 412 (M\(^+\), 60), 369 (20), 329 (100), 313 (25), 201 (27), 175 (32), 83 (43). Exact mass (EI) calculated for C\(_{26}\)H\(_{36}\)O\(_4\) (M\(^+\)), 412.26136; found, 412.26049.

5-(1-(5-Azidopentyl)cyclobutyl)benzene-1,3-diol (79). To a stirred solution of resorcinol 25h (300 mg, 0.95 mmol) in anhydrous CH\(_2\)Cl\(_2\) at room temperature, under an argon atmosphere was added tetrabutyl ammonium azide (1 g, 3.83 mmol) and stirring was continued for 1 day. On completion, the reaction was quenched with water and diluted with CH\(_2\)Cl\(_2\). The organic phase was washed with brine, dried over MgSO\(_4\) and concentrated in vacuo. Purification by flash column chromatography on silica gel (25-40% diethyl ether in hexanes) gave 173 mg of 79 as viscous yellow oil in 66% yield. \( ^1H \) NMR (500 MHz, CDCl\(_3\)) \( \delta \) 6.15 (s, 3H, ArH), 4.52 (br s, 2H, OH), 3.19 (t, \( J = 6.7 \) Hz, 2H, -CH\(_2\)N\(_3\)), 2.31-2.24 (m, 2H of the cyclobutane ring), 2.07-1.97 (m, 3H of the cyclobutane ring), 1.84-1.77 (m, 1H of the cyclobutane ring), 1.74-1.68 (m, 2H, 2'-H), 1.52 (quintet, \( J = 7.0 \) HZ, 5-azido-pentyl group), 1.26 (quintet, \( J = 7.0 \) Hz, 5-azido-pentyl group), 1.07-0.98 (m, 2H, 5-azido-pentyl group).

2-[(1S,6S)-3-(Acetoxymethyl)-6-(1-methylene)-2-cyclohexen-1-yl]-5-[(5-azidopentyl)cyclobutyl] resorcinol (80). The synthesis was carried out analogous to the preparation of 26a by using terpene 16 (182 mg, 0.86 mmol), resorcinol 79 (170 mg, 0.617 mmol) and \( p \)-toluenesulfonic acid and (23.3 mg, 0.123 mmol) in anhydrous CH\(_2\)Cl\(_2\) and gave 85 mg of 80 as a viscous oil in 30% yield.
2-[(1S,6S)-3-(Hydroxymethyl)-6-(1-methylethenyl)-2-cyclohexen-1-yl]-5-[(5-azidopentyl)cyclobutyl] resorcinol (81). The synthesis was carried out as described for 27a using 80 (75 mg, 0.16 mmol) and 1 M DIBAL-H (1.0 mL, 1.0 mmol) in toluene and gave 51 mg of 81 viscous oil in 75% yield. $^1$H NMR (500 MHz, CDCl$_3$) δ 6.14 (br s, 2H, ArH), 5.87 (s, 1H, >C=CH-), 5.62 (br s, 1H, OH), 4.73 (br s, 1H, OH), 4.66 (m as t, J = 1.5 Hz, 1H, >C=CH$_2$), 4.55 (br s, 1H, >C=CH$_2$), 4.13 (d, J = 14.0 Hz, 1H, >C=CH$_2$), 4.11 (br s, 1H, >C=CH$_2$), 3.93 (m as br d, J = 10.2 Hz, 1H, >C=CH-CH<), 3.17 (t, J = 7.5Hz, -CH$_3$N$_3$) 2.48 (ddd, J = 10.1 Hz, J = 9.9 Hz, J = 3.1 Hz, 1H, >CH-C(CH$_3$)=CH$_2$), 2.32-2.22 (m, 4H, 2H of the cyclobutyl ring, CH$_2$-C(CH$_2$OH)=C< ), 2.01-1.95 (m, 3H, cyclobutyl ring), 1.93-1.87 (m, 1H, -CH$_2$-CH$_2$-C(CH$_2$OH)=C<, equatorial), 1.86-1.75 (m, 2H, 1H cyclobutyl ring and 1H, -CH$_2$-CH$_2$-C(CH$_2$OCOCH$_3$)=C<, axial), 1.72-1.68 (m, 2H, 2'-H), 1.66 (s, 3H, >CH-C(CH$_3$)=CH$_2$), 1.53-1.47 (m, 2H, -CH$_2$- of the side chain), 1.30-1.22 (m, 2H, -CH$_2$- of the side chain), 1.03- 0.95 (m, 2H, -CH$_2$- of the side chain); Mass spectrum (ESI) m/z (relative intensity) 426 (M$^+$+H, 31), 408 (M$^+$-OH, 100). Exact mass (ESI) calculated for C$_{25}$H$_{36}$N$_3$O$_3$ (M$^+$+H), 426.2757; found, 426.2764. LCMS (ES+) retention time, 5.08 min (Method B); purity (95.6%).

2-[(1S,6S)-3-(Hydroxymethyl)-6-(1-methylethenyl)-2-cyclohexen-1-yl]-5-(8-azido-2-methyloct-2-yl)resorcinol (82). To a stirred solution of 27c (37 mg, 0.079 mmol) in anhydrous CH$_2$Cl$_2$ at room temperature, under an argon atmosphere was added tetrabutylammonium azide (224 mg, 0.79 mmol) and stirring was continued for 1 day. On completion, the reaction was quenched with water and diluted with CH$_2$Cl$_2$. The organic phase was washed with brine, dried over MgSO$_4$ and concentrated in vacuo. Purification by flash column chromatography on silica gel (20-35% diethyl ether in hexanes) yielded 218
20 mg of 82 as a viscous oil in 59% yield. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 6.34 (br s, 2H, ArH), 5.87 (s, 1H, >C=CH-), 5.60 (br s, 1H, OH), 4.71 (br s, 1H, OH), 4.66 (m as t, \(J = 1.4\) Hz, 1H, >C=CH\(_2\)), 4.55 (br s, 1H, >C=CH\(_2\)), 4.14 (m as t, \(J = 1.4\) Hz, 1H, >C=CH\(_2\)), 3.91 (m as br d, \(J = 10.2\) Hz, 1H, >C=CH\(_2\)), 3.87 (m, 2H, -CH\(_2\)-N\(_3\)), 2.68-2.62 (m, 4H, -CH\(_2\)-CH\(_2\)-CH\(_2\)-OH), 2.00-1.90 (m, 4H, -CH\(_2\)-CH\(_2\)-CH\(_2\)-OH), 1.29-1.20 (m, 8H, -CH\(_3\)- and -CH\(_2\)- of the side chain, especially 1.29, s and 1.20, s and 1.21, s, -C(CH\(_3\))\(_2\)-), 1.12-0.96 (m, 2H, -C(CH\(_3\))\(_2\)-CH\(_2\)-CH\(_2\)-OH); Mass spectrum (ESI) m/z (relative intensity) 450 (M\(^+\)+Na, 11), 428 (M\(^+\)+H, 52), 410 (M\(^+\)-OH, 100). Exact mass (ESI) calculated for C\(_{25}\)H\(_{38}\)N\(_3\)O\(_3\) (M\(^+\)+H), 428.2913; found, 428.2908.

2-[(1S,6S)-3-(Hydroxymethyl)-6-(1-methylethenyl)-2-cyclohexen-1-yl]-5-(8-isothiocyanato-2-methyloct-2-yl)resorcinol (83). To a solution of 82 (15 mg, 0.035 mmol) in anhydrous benzene was added triphenyl phsophine (13.8 mg, 0.0526 mmol) in a single portion at room temperature. The reaction mixture was stirred at 50 °C for 6 hours and was subsequently cooled to room temperature. Carbon disulfide (53 mg, 0.7 mmol) was added dropwise to the mixture and the reaction mixture was stirred for an additional 10 hours at 50 °C. After completion, the reaction mixture was concentrated under pressure and purified by flash column chromatography on silica gel (10-40% ethyl acetate in hexanes) and gave 5 mg of 83 as viscous oil in 33% yield. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 6.34 (br s, 2H, ArH), 5.87 (s, 1H, >C=CH-), 5.60 (br s, 1H, OH), 4.71 (br s, 1H,
OH), 4.66 (m as t, \( J = 1.4 \) Hz, 1H, >C=CH\(_2\)), 4.55 (br s, 1H, >C=CH\(_2\)), 4.14 (d, \( J = 14.0 \) Hz, 1H, half of an AB system, -CH\(_2\)-O-), 4.09 (d, \( J = 14.0 \) Hz, 1H, half of an AB system, -CH\(_2\)-O-), 3.92 (m as br d, \( J = 10.3 \) Hz, 1H, >C=CH-CH\(_2\)<), 3.46 (t, \( J = 7.0 \) Hz, 2H, -CH\(_2\)-NCS), 2.47 (ddd, \( J = 10.1 \) Hz, \( J = 9.9 \) Hz, \( J = 3.1 \) Hz, 1H, >CH-C(CH\(_3\))=CH\(_2\)), 2.28-2.22 (m, 2H, CH\(_2\)-C(CH\(_2\)OH)=C<), 1.94-1.87 (m, 1H, -CH\(_2\)-CH\(_2\)-C(CH\(_2\)OH)=C<, equatorial), 1.85-1.75 (m, 1H, CH\(_2\)-CH\(_2\)-C(CH\(_2\)OH)=C<, axial), 1.66 (s, 3H, >CH-C(CH\(_3\))=CH\(_2\)), 1.64-1.54 (m, 2H, -CH\(_2\)- of the side chain), 1.50 (m, 2H, -C(CH\(_3\))\(_2\)-CH\(_2\)-), 1.35-1.16 (m, and s overlapping, 10H, -C(CH\(_3\))\(_2\)- and -CH\(_2\)- of the side chain, especially 1.20, s, -C(CH\(_3\))\(_2\)-), 1.12-0.96 (m, 2H, -CH\(_2\)- of the side chain); Mass spectrum (ESI) m/z (relative intensity) 466 (M\(^+\)+Na, 8), 444 (M\(^+\)+H, 34), 426 (M\(^+\)-OH, 100). Exact mass (ESI) calculated for C\(_{26}\)H\(_{38}\)NO\(_3\)S (M\(^+\)+H), 444.2572; found, 444.2573.

2-[(1S,6S)-3-(Hydroxymethyl)-6-(1-methylethenyl)-2-cyclohexen-1-yl]-5-(7-azido-2-methylheptan-2-yl)resorcinol (84). The synthesis was carried out as described for 82 using 27l (400 mg, 0.88 mmol) and (2 g, 7.08 mmol) tetrabutyl ammonium azide in CH\(_2\)Cl\(_2\) (15 mL) to give 140 mg of 84 as a viscous oil in 38% yield; IR (neat) 3394 (br, OH), 2929, 2094 (s, N\(_3\)), 1621, 1582, 1416, 1374, 1246, 1150, 887, 843 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 6.36 (br s, 2H, ArH), 5.86 (s, 1H, >C=CH-), 5.61 (br s, 1H, OH), 4.75 (br s, 1H, OH), 4.66 (m as t, \( J = 1.4 \) Hz, 1H, >C=CH\(_2\)), 4.54 (br s, 1H, >C=CH\(_2\)), 4.13 (d, \( J = 14.0 \) Hz, 1H, half of an AB system, -CH\(_2\)-O-), 4.11 (d, \( J = 14.0 \) Hz, 1H, half of an AB system, -CH\(_2\)-O-), 3.91 (m as br d, \( J = 10.2 \) Hz, 1H, >C=CH-CH\(_2\)<), 3.18 (t, \( J = 6.5.0 \) Hz, 2H, -CH\(_2\)-N\(_3\)), 2.47 (ddd, \( J = 10.1 \) Hz, \( J = 9.9 \) Hz, \( J = 3.1 \) Hz, 1H, >CH-C(CH\(_3\))=CH\(_2\)), 2.28-2.22 (m, 2H, -CH\(_2\)-C(CH\(_2\)OH)=C<), 1.94-1.87 (m, 1H, -CH\(_2\)-CH\(_2\)-C(CH\(_2\)OH)=C<, equatorial), 1.85-1.75 (m, 1H, -CH\(_2\)-CH\(_2\)-C(CH\(_2\)OH)=C<, axial), 1.66
(s, 3H, >CH-C(CH₃)=CH₂), 1.54-1.47 (m, 4H, 2'-H and -CH₂- of the side chain), 1.29-1.24 (m, 2H, -CH₂- of the side chain), 1.23 (s, 6H, -C(CH₃)₂-), 1.12-0.98 (m, 2H, -CH₂- of the side chain); Mass spectrum (ESI) m/z (relative intensity) 436 (M⁺+Na, 18), 414 (M⁺+H, 52), 396 (100, M⁺-OH). Exact mass (ESI) calculated for C₂₃H₃₆N₃O₃ (M⁺+H), 414.2757; found, 414.2753; LCMS (ES+) retention time, 4.98 min (Method B); purity (99.2%).

2-[(1S,6S)-3-(Hydroxymethyl)-6-(1-methylethenyl)-2-cyclohexen-1-yl]-5-(7-isothiocyanato-2-methylheptan-2-yl)resorcinol (85). The synthesis was carried out as described for 83 using 84 (125 mg, 0.302 mmol), triphenyl phospine (118 mg, 0.453 mmol) and carbon disulfide (0.36 mL, 6.04 mmol) in anhydrous benzene and gave 51 mg of 85 as a viscous oil in 39% yield; IR (neat) 3344(br, OH), 2929, 2097 (s, NCS), 1623, 1582, 1417, 1345, 1050, 1148, 885, 838 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 6.33 (br s, 2H, ArH), 5.86 (s, 1H, >C=CH₂), 5.62 (br s, 1H, OH), 5.04 (br s, 1H, OH), 4.64 (m as t, J= 1.4 Hz, 1H, >C=CH₂), 4.53 (br s, 1H, >C=CH₂), 4.12 (d, J = 14.0 Hz, 1H, half of an AB system, -CH₂-O-), 4.10 (d, J = 14.0 Hz, 1H, half of an AB system, -CH₂-O-), 3.93 (m as br d, J = 10.3 Hz, 1H, >C=CH(CH₃)<), 3.42 (t, J = 7.0 Hz, 2H, -CH₂-NCS), 2.47 (ddd, J = 10.1 Hz, J = 9.9 Hz, J = 3.1 Hz, 1H, >CH-C(CH₃)=CH₂), 2.28-2.22 (m, 2H, CH₂-C(CH₂OH)=C<), 1.94-1.87 (m, 1H, -CH₂-CH₂-C(CH₂OH)=C<, equatorial), 1.85-1.75 (m, 1H, CH₂-CH₂-C(CH₂OH)=C<, axial), 1.66 (s, 3H, >CH-C(CH₃)=CH₂), 1.64-1.56 (quintet, 2H, -CH₂- of the side chain), 1.54-1.58 (m, 2H, 2'H), 1.33-1.24 (m, 2H, -CH₂- of the side chain), 1.21 (s, 6H, -C(CH₃)₂-), 1.08-0.99 (m, 2H, -CH₂- of the side chain); ¹³C NMR (100 MHz, CDCl₃) δ 155.68 (brs, ArC1, ArC3), 149.42 (ArC5), 148.78 (C8), 142.75 (C3), 129.92 (NCS), 125.31 (C2), 113.87 (ArC2), 110.85 (C9), 108.53 (brs,
ArC4, Ar6), 66.44 (C7), 45.82, 44.87, 43.33, 37.92, 36.63, 29.84, 28.32, 27.73, 26.65, 25.54, 24.13, 20.05; Mass spectrum (ESI) m/z (relative intensity) 452 (M\(^+\)+Na, 13), 430 (M\(^+\)+H, 44), 412 (M\(^+\)-OH, 100]). Exact mass (ESI) calculated for C\(_{25}\)H\(_{36}\)NO\(_3\)S (M\(^+\)+H), 430.2416; found, 430.2407; LCMS (ES+) retention time, 5.13 min (Method B); purity (95.5%).
CHAPTER 3: PART A
(10S) - AND (10R) - METHYL SUBSTITUTED ANANDAMIDE ANALOGS: STEREOSPECIFIC SYNTHESIS, BIOLOGICAL EVALUATION AND COMPARISON WITH THE (13S)-ISOMER

Introduction

The endogenous arachidonic acid (Ia) derivatives N-arachidonoylethanolamine (AEA, anandamide, Ib) and 2-arachidonoyl glycerol (2-AG, Ic, Figure 3A.1) are synthesized on demand in response to elevations of intracellular calcium, and are the two key lipid modulators that act on CB1 and CB2 cannabinoid receptors. Both CB1 and CB2 are members of the superfamily of G-protein-coupled receptors and they are implicated in a wide array of patho-physiological processes including inflammation, nociception, neuroprotection, memory, anxiety, feeding, and cell proliferation. Following their synthesis and release, the endocannabinoids AEA and 2-AG are removed from their sites of action by cellular uptake and degraded by enzymes. In most tissues, fatty acid amide hydrolase (FAAH) is the enzyme responsible for AEA hydrolysis, and monoacylglycerol lipase (MGL) is the major metabolizing enzyme for 2-AG. In addition to hydrolysis, the presence of an arachidonoyl moiety in both AEA and 2-AG suggests the conspicuous possibility that endocannabinoids may be metabolized by the plethora of oxygenases that act on arachidonic acid. Investigations into this possibility have shown that a subset of oxidative enzymes of the arachidonate cascade, such as lipoxygenases (LOX), cyclooxygenase-2 (COX-2), and cytochrome P450 catalyze the biotransformation of AEA and 2-AG into eicosanoid-related metabolites. Apart from the hydrolytic deactivation of AEA and 2-AG, the alternative COX-2 oxidative
deactivation becomes important when FAAH or MGL are inhibited and when endocannabinoid biosynthesis is activated following tissue damage. Also, in platelets, which lack significant COX-2 and FAAH activity a lipoxidative pathway of AEA deactivation predominates.

**Figure 3A.1:** Structure of endocannabinoid analogs

As a part of our ongoing projects in endocannabinoid SAR, we focused on the development of novel endocannabinoid prototypes that possess CB receptor binding affinity as well as metabolic stability to the action of COX-2 and LOX. The novel analogs can enhance our understanding regarding the stereoelectronic requirements for CB receptor binding and aid in the discovery of more potent and selective cannabinergic drug candidates and fatty acid oxygenase (e.g. COX-2 and LOX) inhibitors. They can also serve as biochemical/pharmacological tools to explore the connection between the
endocannabinoid and the COX-2 and LOX systems, and to define the physiological significance of the oxidative metabolism of endocannabinoids.\cite{221}

**Figure 3A.2: Mechanism of LOX action**\cite{222}

![Mechanism of LOX action](image)

Earlier work from our laboratory has shown that one of the most successful and convenient ways to "shut off" the enzymatic hydrolysis of AEA is the addition of a methyl substituent near the metabolic hot spot of the substrate (e.g. \((R)-\)methanandamide, \(\text{Id}\)).\cite{223,224} It has also been shown that COX-2 and LOX mediated (Figure 3A.2) metabolism of arachidonic acid and its derivatives begins with abstraction of a hydrogen radical from the bis-allylic carbons 7, 10, or 13 (Figure 3A.1).\cite{225,226} Therefore, we considered that introduction of a methyl group at the bis-allylic positions might preserve cannabinoid activity while blocking the oxidative metabolism by COX-2 and LOX enzymes. In this regard, we recently described the synthesis and preliminary biological evaluation of \((13S)-\)methyl anandamide (\(\text{Ie}\)).\cite{227} With the aim of exploring all three bis-allylic positions and establishing structure-activity relationships for the hitherto unknown, methyl-substituted arachidonoyl chain, we report here the stereospecific
synthesis of the (10S)- and (10R)-counterparts along with their affinities for cannabinoid receptors and their comparison with the (13S)-methyl-analog.

**Chemistry**

Our retrosynthetic analysis involves methyl esters 2a and 2b as the key precursors from which (10S)- and (10R)-methylanandamides (1a and 1b respectively) would be produced through peptide coupling (*Figure 3A.3*). Retrosynthetic disconnection at the double bonds adjacent to the chiral center provides four convergent fragments: the phosphonium salts 5 and 6, and the chiral aldehydes 3 and 4 that possess the S and R configuration corresponding to the C10 stereogenic centers of 1a and 1b respectively. The synthetic direction could be completed through Wittig olefination reactions.

*Figure 3A.3*: Retrosynthetic analysis of (10S)- and (10R)-methyl-anandamides
Synthesis of chiral aldehyde 3 was carried out by following our recently reported procedures (Scheme 3A.1). Briefly, silylation of commercially available methyl ester 7 gave the TBDPS ether 8 (95% yield) which upon reduction with diisobutylaluminum hydride led to aldehyde 3 (60% yield) and alcohol 9 (38% yield). Oxidation of 9 with Dess-Martin periodinane produced 3 in 88% yield. Similarly, the enantiomeric aldehyde 4 was synthesized from Roche ester 10.

**Scheme 3A.1: Synthesis of chiral aldehydes 3 and 4**

![Scheme 3A.1](image)

Reagents and conditions: (a) TBDPSCI, imidazole, CH₂Cl₂, 0 °C to r t, 1.5 h, 95-98%; (b) DIBAL-H, CH₂Cl₂, -110 °C to -90 °C, 20 min, 60-61% for 3, 4 and 38-35% for 9, 12; (c) Dess-Martin periodinane, CH₂Cl₂, 0 °C to r t, 45 min, 88-90%.

Construction of the required alkenyl phosphonium salt 5 is summarized in Scheme 3A.2. Protection of the acetylenic alcohol 13 afforded terminal alkyne 14 (95% yield), which
was metallated with \( n\text{-BuLi} \) and quenched with excess ethylene oxide to give the two carbon homologated alcohol 15 in 75% yield. As reported earlier,\textsuperscript{229} we also observed that ethylene oxide opening with lithium acetylides (e.g. TBDPSO(CH\(_2\))\(_4\)C≡CLi) in the presence of boron trifluoride etherate has low reproducibility, especially on large scale, and requires freshly distilled catalyst. Use of hexamethylphosphoramide,\textsuperscript{230} which strongly coordinates to lithium cations, is a robust alternative to carry out this conversion.

Partial hydrogenation of alkyne 15 over P-2 nickel catalyst afforded the corresponding Z alkene 16 in 86% yield (\( ^3J_{3H-4H} = 10.5 \text{ Hz} \)). Treatment of this material with the PPh\(_3\)/CBr\(_4\) system gave bromide 17 (81% yield). However, deprotection with TBAF at 0 °C produced the desirable bromide 18 (\( R_f = 0.32, 30\% \text{ AcOEt in hexane, 41}\% \text{ yield} \)) along with significant amounts of the elimination byproduct 19 (\( R_f = 0.27, 30\% \text{ AcOEt in hexane, 32}\% \text{ yield} \)). We also observed that large excess of TBAF reagent and elevated temperature favor the formation of 19. After our experimental exercise, the problem was solved by carrying out the reaction in the presence of acetic acid at 0 °C. Under these neutral conditions, 18 was produced in 83% yield without any contamination with 19.

Oxidation of the primary alcohol 18 to the carboxylic acid 20 employing Zhao’s method,\textsuperscript{231} followed by TMSCHN\(_2\) esterification gave methyl ester 21\textsuperscript{232,233} in 77% yield over two steps. A lower overall yield (63%) was obtained when conversion of 18 to 20 was carried out using Jones oxidation. Heating of 21 (72-75 °C) with triphenylphosphine in dry acetonitrile for four days furnished phosphonium salt\textsuperscript{232} 5 in 91% yield after purification.
Scheme 3A.2: Synthesis of alkenyl phosphonium salt 5

Reagents and conditions: (a) TBDPSCI, imidazole, CH₂Cl₂, 0 °C to r t, 2 h, 95%; (b) n-BuLi, THF, HMPA, -78 °C to 0 °C, 1.5 h, then ethylene oxide, 0 °C, 5 hours, 75%; (c) Ni(OAc)₂, NaBH₄, ethylenediamine, H₂, MeOH, r t, 2 h, 86%; (d) CBr₄, Ph₃P, CH₂Cl₂, 0 °C to r t, 3 h, 81%; (e) TBAF, CH₃COOH, THF, 0 °C, 12 h, 83%; (f) H₅IO₆, CrO₃, CH₃CN, H₂O, 0 °C, 3.5 h, 85%. (g) TMSCHN₂, MeOH, Et₂O, 0 °C, 20 min, 91%; (h) Ph₃P, CH₃CN, 72-75 °C, 4 days, 91%.

Similarly the requisite C12-C20 fragment 6 was synthesized in two steps and high overall yield (Scheme 3A.3) through conversion of alcohol 22 to bromide 23 (94% yield) and reaction with triphenylphosphine in refluxing acetonitrile for seven days (72% yield).

Our attempts to minimize the reaction time during the preparation of phosphonium salts 5 and 6 using microwave heating resulted in reduction of the purity of the products.
**Scheme 3A.3:** Synthesis of alkenyl phosphonium salt 6

```
HO-\(\rightarrow\)Br \quad \text{a} \quad \text{Br-PH}_3 \rightarrow \text{Br-PH}_3 \rightarrow 6
```

Reagents and conditions: (a) CBr₄, Ph₃P, CH₂Cl₂, 0 °C to r t, 3 h, 94%; (b) Ph₃P, CH₃CN, 72-75 °C, 7 days, 72%.

The assembly of the phosphonium salts 5 and 6 with chiral aldehyde 3 into (10S)-methyl-anandamide 1a is outlined in *Scheme 3A.4*. Treatment of 5 with KHMDS at -78 °C to -60 °C and coupling of the resulting ylide with aldehyde 3 at -115 °C gave TBDPS ether 24 (46% yield). Based on ¹H NMR analysis (see supporting information), this Wittig reaction afforded the Z olefin exclusively with \(3J_{8H-9H} = 10.5 \text{ Hz}\). Cleavage of the silyl ether 24 with TBAF produced alcohol 25 in 92% yield. Interestingly, in the ¹H NMR spectrum of 25, all four double bond protons are well separated with coupling constants \(3J_{5H-6H}\) and \(3J_{8H-9H}\) equal to 10.5 Hz (see supporting information), which confirms a Z relationship between the hydrogen atoms of the 5H-6H and 8H-9H spin systems.

Exposure of 25 to Dess-Martin periodinane delivered aldehyde 26 which was used immediately, without purification, in a Wittig reaction with phosphonium bromide 6, under salt free conditions, to give (10S)-methyl-arachidonate 2a (39% yield from 25).

Saponification of 2a with lithium hydroxide in THF/H₂O led to acid 27 (86% yield), which was coupled with 2-(tert-butyldiphenylsilyloxy)ethanamine (29) to give amide 30 (74% yield) by using the carbonyldiimidazole activation procedure. Desilylation of 30 with TBAF produced the requisite (10S)-methyl-anandamide (1a) in 83% yield. The structure of 1a was established using 1D and 2D NMR experiments (COSY, HSQC and
NOESY, given under supporting information). NOESY interactions between 10H and 13H confirm the Z stereochemistry for the C11═C12 double bond which was installed earlier in the arachidonate structure during the synthesis of the methyl ester 2a.

**Scheme 3A.4:** Synthesis of (10S)-methyl-anandamide 1a

![Scheme 3A.4](image-url)

Reagents and conditions: (a) (Me₃Si)₂N⁻K⁺, THF, -78 °C to -60 °C, 45 min, then 3, -115 °C to -20 °C, 3 h, 46%; (b) TBAF, THF, 0 °C to r t, 2 h, 92%; (c) Dess-Martin periodinane, CH₂Cl₂, 0 °C to r t, 1.5 h; (d) 6, (Me₃Si)₂N⁻K⁺, THF, 0 °C, 30 min, then addition of 26, -78 °C, 1 h, 39% from alcohol 25; (e) LiOH, THF/H₂O, r t, 24 h, 86%; (f) TBDPSCl, imidazole, CH₃CN, 0 °C, 30 min, 95%; (g) carbonyldiimidazole, THF, r t, 2 h, then 29, r t, 1 h, 74%; (h) TBAF, THF, 0 °C to r t, 1 h, 83%.

The enantiomer (10R)-methyl-anandamide 1b was synthesized in a similar fashion (Scheme 3A.5). Thus, Wittig olefination of aldehyde 4 with phosphonium bromide 5 gave the Z product 31. Deprotection with TBAF followed by oxidation with Dess-Martin periodinane led to intermediate aldehyde 33 which was used immediately in the next step. Combination of 33 and the ylide derived from 6 and KHMDS, resulted in the formation of the methyl ester precursor 2b. The synthesis of 1b was completed by following: a)
methyl ester hydrolysis, b) coupling with protected ethanolamine 29 and c) desilylation using TBAF.

**Scheme 3A.5: Synthesis of (10R)-methyl-anandamide 1b**

Reagents and conditions: (a) (Me₃Si)₂N⁻K⁺, THF, -78 °C to -60 °C, 45 min, then 4, -115 °C to -20 °C, 3 h, 48%; (b) TBAF, THF, 0 °C to rt, 2 h, 90%; (c) Dess-Martin periodinane, CH₂Cl₂, 0 °C to rt, 1.5 h; (d) 6, (Me₃Si)₂N⁻K⁺, THF, 0 °C, 30 min, then addition of 33, -78 °C, 1h, 40% from alcohol 32; (e) LiOH, THF/H₂O, rt, 24 h, 86%; (f) TBDPSCl, imidazole, CH₃CN, 0 °C, 30 min, 95%; (g) carbonyldiimidazole, THF, rt, 2 h, then 29, rt, 1 h, 83%; (h) TBAF, THF, 0 °C to rt, 1 h, 85%.
Results and Discussion

**Table 3A.1:** Binding affinities of anandamide, C13 and C10-Methyl anandamide analogs

<table>
<thead>
<tr>
<th>Compound</th>
<th>CB1 ($K_i$) with PMSF</th>
<th>CB1 ($K_i$)</th>
<th>mCB2 ($K_i$)</th>
<th>hCB2 ($K_i$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anandamide$^a$</td>
<td>61 nM</td>
<td>5810 nM</td>
<td>1930 nM</td>
<td>n.d</td>
</tr>
<tr>
<td>13(S)-Methyl Anandamide AMG 113$^b$</td>
<td>4.8±1.3 nM</td>
<td>n.d</td>
<td>137±22 nM</td>
<td>n.d</td>
</tr>
<tr>
<td>10(R)-Methyl Anandamide AM 9277</td>
<td>1.68 μM</td>
<td>1.82 μM</td>
<td>9.21 μM</td>
<td>8.0 μM</td>
</tr>
<tr>
<td>10(S)-Methyl Anandamide AM 9278</td>
<td>6.62 μM</td>
<td>7.77 μM</td>
<td>11.97 μM</td>
<td>11.22 μM</td>
</tr>
</tbody>
</table>

*a* $^{49}$, *b* $^{227}$

Flexible compounds such as anandamide are capable of several bond rotations. The hydrophobic backbone of anandamide is capable of taking a number of conformations in solution like the hairpin (U shaped), partially extended (J shaped) and the fully extended form. The U- and the J-shaped conformations are responsible for CB recognition. $^{236,237}$ Increasing the steric bulk with a methyl group at the C13 position...
increased the binding affinity of 13(S)-methyl anandamide towards the CB receptors. However, the addition of the methyl group at the C10 position led to a drastic decline in binding affinity towards the CB receptors. It is possible that the extra bulk of the methyl group at the C10 position in both the R and the S enantiomers caused the backbone of the two ligands to adopt a conformation that was not recognized by the CB receptors and hence led to a decrease in binding affinity.

**Experimental Procedures**

**General:** All reagents and solvents were purchased from Aldrich Chemical Company, unless otherwise specified, and used without further purification. All anhydrous reactions were performed under a static argon or nitrogen atmosphere in flame-dried glassware using scrupulously dry solvents. Flash column chromatography employed silica gel 60 (230-400 mesh). All compounds were demonstrated to be homogeneous by analytical TLC on pre-coated silica gel TLC plates (Merck, 60 F254 on glass, layer thickness 250 μm), and chromatograms were visualized by phosphomolybdic acid or KMnO4 staining. Melting points were determined on a micro-melting point apparatus and are uncorrected. Optical rotations were recorded on a Perkin Elmer 341 digital polarimeter. NMR spectra were recorded in CDCl3, unless otherwise stated, on a Bruker Ultra Shield 400WB plus (1H at 400 MHz, 13C at 100 MHz), or on a Varian 500 (1H at 500 MHz, 13C at 125 MHz), or on a Bruker Ultra Shield 700WB plus (1H at 700 MHz, 13C at 175 MHz) spectrometers and chemical shifts are reported in units of δ relative to internal TMS. Multiplicities are indicated as br (broadened), s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and coupling constants (J) are reported in hertz (Hz). Low and high-resolution mass spectra were performed in School of Chemical Sciences, University of Illinois at Urbana-
Champaign. Mass spectral data are reported in the form of m/z (intensity relative to base = 100).

(2S)-3-[(tert-Butyldiphenylsilyl)oxy]-2-methyl-propionic methyl ester (8). To a stirred solution of (2S)-3-hydroxy-2-methylpropionic methyl ester (7) (2.00 g, 16.94 mmol) and dried imidazole (1.5 g, 22 mmol) in anhydrous CH$_2$Cl$_2$ (22 mL) at 0 °C under an argon atmosphere, was added tert-butyldiphenylsilyl chloride (5.12 g, 18.64 mmol) dropwise. Stirring was continued for 1 h at 0 °C and for 30 min at room temperature. The reaction mixture was quenched by the addition of saturated aqueous NaHCO$_3$ and extracted with CH$_2$Cl$_2$. The combined organic extracts were washed with brine, dried (MgSO$_4$) and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (10-15% diethyl ether in hexane) gave 8 (5.74 g, 95% yield) as a colorless oil. $^1$H NMR (600 MHz, CDCl$_3$) δ 7.64 (d, J = 7.8 Hz, 4H, 2-H, 6-H, PhH) 7.42 (t, J = 7.8 Hz, 2-H, PhH), 7.38 (t, J = 7.8 Hz, 4H, 3-H, 5-H, PhH), 3.82 (dd, J = 10.2 Hz, J = 7.2 Hz, 1H, -CH$_2$-OTBDPS), 3.72 (dd, J = 10.2 Hz, J = 5.7 Hz, 1H, -CH$_2$-OTBDPS), 3.68 (s, 3H, -COOCH$_3$), 2.72 (tq, J = 7.2 Hz, J = 7.1 Hz, 1H, >CH-CH$_3$), 1.16 (d, J = 7.1 Hz, 3H, >CH-CH$_3$), 1.03 (s, 9H, -C(CH$_3$)$_3$).

(2S)-3-[(tert-Butyldiphenylsilyl)oxy]-2-methyl-propanal (3). To a stirred solution of 8 (1.5 g, 4.21 mmol) in dry CH$_2$Cl$_2$ (42 mL) at -110 °C, under an argon atmosphere, was added diisobutylaluminum hydride (9.3 mL, 1 M solution in hexanes) dropwise. The reaction mixture warmed to -90 °C over a 20 min period and then quenched by dropwise addition of potassium sodium tartrate (10% solution in water). The mixture was allowed to warm to room temperature and was then partitioned between water and ethyl acetate. The organic phase was separated, the aqueous phase was extracted with ethyl acetate, and
the combined organic layer was washed with brine and dried (MgSO₄). Solvent evaporation and purification by flash column chromatography on silica gel (10-40% diethyl ether in hexane) gave 822 mg (60% yield) of aldehyde 3 as a white solid (m.p. = 61-62 °C, lit.1 61-62 °C, white solid) and 523 mg (38% yield) of alcohol 9 as a viscous liquid. 

(2S)-3-[(tert-Butyldiphenylsilyloxy)-2-methyl-propanal (3): ¹H NMR (600 MHz, CDCl₃) δ 9.76 (d, J = 1.8 Hz, 1H, -CHO), 7.64 (d, J = 7.2 Hz, 4H, 2-H, 6-H, PhH), 7.44 (t, J = 7.2 Hz, 2H, 4-H, PhH), 7.39 (t, J = 7.2 Hz, 4H, 3-H, 5-H, PhH), 3.90 (dd, J = 10.2 Hz, J = 5.0 Hz, 1H, -CH₂-OTBDPS), 3.84 (dd, J = 10.2 Hz, J = 6.6 Hz, 1H, -CH₂-OTBDPS), 2.57 (dtq, J = 7.2 Hz, J = 6.7 Hz, J = 1.8 Hz, 1H, >CH-CH₃), 1.09 (d, J = 7.2 Hz, 3H, >CH-CH₃), 1.04 (s, 9H, -C(CH₃)₃). (2S)-3-[(tert-Butyldiphenylsilyloxy)-2-methyl-propan-1-ol (9): ¹H NMR (600 MHz, CDCl₃) δ 7.67 (d, J = 7.2 Hz, 4H, 2-H, 6-H, PhH), 7.44 (t, J = 7.2 Hz, 2H, 4-H, PhH), 7.40 (t, J = 7.2 Hz, 4H, 3-H, 5-H, PhH), 3.72 (dd, J = 10.2 Hz, J = 4.8 Hz, 1H, -CH₂OTBDPS), 3.67 (t, J = 5.4 Hz, 2H, CH₂OH), 3.59 (dd, J = 10.2 Hz, J = 7.8 Hz, 1H, -CH₂OTBDPS), 2.52 (t, J = 5.4 Hz, 1H, -CH₂OH), 1.99 (m, 1H, >CH-CH₃), 1.06 (s, 9H, -C(CH₃)₃), 0.83 (d, J = 7.2 Hz, 3H, >CH-CH₃).

Dess-Martin Periodinane (DMP) oxidation of alcohol 9 to aldehyde 3: To a solution of alcohol 9 (400 mg, 1.21 mmol) in wet CH₂Cl₂ (25 mL) at 0 °C under an argon atmosphere was added DMP (974 mg, 2.31 mmol) and the resulting suspension was warmed up to room temperature and stirred for 45 min. The reaction mixture was quenched by adding a mixture of Na₂S₂O₃ (10% in H₂O) and saturated NaHCO₃ (1:1) and diluted with diethyl ether. The slurry was filtered through Celite, the organic phase separated and the aqueous phase was extracted with diethyl ether. The combined organic layer was washed with saturated NaHCO₃, brine, and dried (MgSO₄). Solvent
evaporation and purification by flash column chromatography on silica gel (10% diethyl ether in hexane) afforded 513 mg (88% yield) of aldehyde 3.

(2R)-3-[(tert-Butyldiphenylsilyl)oxy]-2-methyl-propionic methyl ester(11)$^{228}$. The synthesis was carried out as described for 8 and gave the title compound in 98% yield. The $^1$H NMR spectrum was identical to that of the enantiomer 8.

(2R)-3-[(tert-Butyldiphenylsilyl)oxy]-2-methyl-propanal (4)$^{228}$. The synthesis was carried out analogous to the preparation of 3 and gave aldehyde 4 and alcohol 12 in 61% and 35% yields respectively. The $^1$H NMR spectra were identical to those of the enantiomers 3 and 9. The Dess-Martin periodinane oxidation of alcohol 12 was carried out as described for 9 and gave aldehyde 4 in 90% yield.

6-[(tert-Butyldiphenylsilyl)oxy]hex-1-yne (14)$^{238}$. To a solution of 5-hexyn-1-ol (13) (14.2 g, 144.7 mmol) and dried imidazole (12.8 g, 188.1 mmol) in anhydrous CH$_2$Cl$_2$ (180 mL) at 0 °C under an argon atmosphere, was added a solution of tert-butyldiphenylsilyl chloride (43.8 g, 159.2 mmol) in 10 mL CH$_2$Cl$_2$ dropwise. The reaction mixture was stirred for 1 hour at 0 °C and 1 hour at room temperature. On completion, the reaction was quenched with saturated aqueous sodium bicarbonate solution and extracted with CH$_2$Cl$_2$. The combined organic extracts were washed with brine, dried (MgSO$_4$) and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (10-20% diethyl ether in hexanes) gave 44.1 g (95% yield) of 14 as a colorless oil. $^1$H NMR (500 MHz, CDCl$_3$) $^\delta$ 7.68 (d, $J$ = 7.2 Hz, 4H, 2-H, 6-H, Ph), 7.42 (t, $J$ = 7.2 Hz, 2H, 4-H, Ph), 7.38 (t, $J$ = 7.2 Hz, 4H, 3-H, 5-H, Ph), 3.68 (t, $J$ = 6.0 Hz, 2H, -CH$_2$O-), 2.19 (td, $J$ = 7.0 Hz, $J$ = 2.5 Hz, 2H, -CH$_2$-C≡CH),
1.93 (t, J = 2.5 Hz, 1H, -CH₂-C≡CH), 1.71-1.60 (m, 4H, -CH₂-CH₂-), 1.05 (s, 9H, -C(CH₃)₃-). ¹³C NMR (100 MHz, CDCl₃) δ 135.78 (Ph), 134.21 (=C(Si)-), 129.77 (Ph), 127.82 (Ph), 84.74 (C=CH), 68.51 (=CH), 63.54 (-CH₂O-), 31.78, 27.21 (-C(CH₃)₃), 25.71, 19.45, 18.41. Mass spectrum (ESI) m/z (relative intensity) 359 (M⁺+Na, 37), 337 (M⁺+H, 100), 239 (95), 135 (42). Exact mass (ESI) calculated for C₂₂H₂₉OSi (M⁺+H), 337.1988; found, 337.1992.

8-[( tert-Butyldiphenylsilyl)oxy]oct-3-yn-1-ol (15). To a stirred solution of 14 (5.0 g, 15.6 mmol) in dry THF (78 mL) at -78 °C under an argon atmosphere, was added n-BuLi (12.5 mL, 31.2 mmol, 2.5 M solution in hexanes) dropwise followed by the addition of HMPA (previously dried over 4Å molecular sieves). The reaction temperature was raised to 0°C and stirring was continued for 1.5 hours. Ethylene oxide (7.7 mL, 156 mmol) was added at the same temperature and the reaction mixture was stirred for an additional 5 hours. On completion, the mixture was quenched by the addition of saturated aqueous NH₄Cl at -78 °C, then warmed at room temperature, and extracted with diethyl ether. The combined organic extracts were washed with brine, dried (MgSO₄), and concentrated under reduced pressure at 30 °C. Purification by flash column chromatography on silica gel (20-50% diethyl ether in hexanes) afforded 4.45 g (75% yield) of 15 as a colorless oil.

¹H NMR (500 MHz, CDCl₃) δ 7.66 (d, J = 7.2 Hz, 4H, 2-H, 6-H, Ph), 7.42 (t, J = 7.2 Hz, 2H, 4-H, Ph), 7.38 (t, J = 7.2 Hz, 4H, 3-H, 5-H, Ph), 3.67 (t, J = 6.0 Hz, 2H, -CH₂OH or -CH₂OTBDPS), 3.66 (t, J = 6.0 Hz, 2H, -CH₂OTBDPS or -CH₂OH), 2.42 (tt, J = 6.5 Hz, J = 2.5 Hz, 2H, -CH₂-C≡C-), 2.17 (tt, J = 6.5 Hz, J = 2.5 Hz, 2H, -C≡C-CH₂-), 1.72 (t, J = 6.5 Hz, 1H, OH), 1.68-1.56 (m, 4H, -CH₂-CH₂-), 1.05 (s, 9H, -C(CH₃)₃-). ¹³C NMR (100 MHz, CDCl₃) δ 135.79 (Ph), 134.25 (=C(Si)-), 129.76 (Ph), 127.82 (Ph),
84.51 (-C=CH), 77.23 (≡CH), 63.65 (-CH₂O-), 61.59 (-CH₂O-), 31.96, 27.10 (-C(CH₃)₃), 25.64, 23.41, 19.45, 18.72. Mass spectrum (ESI) m/z (relative intensity) 403 (M⁺+Na, 100), 303 (15). Exact mass (ESI) calculated for C₂₄H₃₂O₂NaSi (M⁺+Na), 403.2069; found, 403.2068.

(Z)-8-[(tert-Butyldiphenylsilyl)oxy]oct-3-en-1-ol (16). To a stirred solution of Ni(OAc)₂ (2.24 g, 9.0 mmol) in dry MeOH (178 mL) at room temperature under an argon atmosphere, was added NaBH₄ (0.4 g, 10.6 mmol) portionwise. Following the addition, the argon atmosphere was replaced with hydrogen. To the black suspension was added ethylenediamine (0.9 mL), stirring was continued for 5 min and then a solution of 15 (2.0 g, 5.3 mmol) in dry MeOH (20 mL) was added. The reaction mixture was hydrogenated until the TLC analysis indicated total consumption of the starting material (2 hours). The catalyst was filtered off through Celite pad, and the filtrate was diluted with diethyl ether and brine. The organic phase was separated and the aqueous phase extracted 5 times with diethyl ether, and the combined organic layer was washed with brine. Then, the aqueous phases were reextracted with diethyl ether and the ethereal layer was washed with brine. The combined organic phase was dried (MgSO₄) and evaporated under reduced pressure at 38°C. The residue was again diluted with diethyl ether/brine and the organic phase was separated. The aqueous phase was extracted with diethyl ether and the combined organic layer was washed with brine, dried (MgSO₄) and concentrated in vacuo (38 °C). Purification by flash column chromatography on silica gel (10-30% diethyl ether in hexanes) afforded 1.73 g (86% yield) of 16 as a colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 7.66 (d, J = 7.2 Hz, 4H, 2-H, 6-H, Ph), 7.42 (t, J = 7.2 Hz, 2H, 4-H, Ph), 7.38 (t, J = 7.2 Hz, 4H, 3-H, 5-H, Ph), 5.54 (dtt, J = 10.5 Hz, J = 7.0 Hz, J = 1.5 Hz, 1H,
=CH(CH₂O)-), 5.36 (dt, J = 10.5 Hz, J = 7.0 Hz, J = 1.5 Hz, 1H, -CH=), 3.66 (t, J = 6.5 Hz, 2H, -CH₂O-), 3.62 (t, J = 6.5 Hz, 2H, -CH₂OH), 2.30 (dt, J = 7.0 Hz, J = 7.0 Hz, 2H, -CH₂CH₂OH), 2.05 (dt, J = 7.0 Hz, J = 7.0 Hz, 2H, -CH₂-), 1.57 (quintet, J = 6.5 Hz, 2H, -CH₂-), 1.44 (quintet, J = 6.5 Hz, 2H, -CH₂-), 1.04 (s, 9H, -C(CH₃)₃-).

**13C NMR (100 MHz, CDCl₃)** δ 135.80 (Ph), 134.32 (=C(Si)-), 133.49 (-CH=CH-), 129.73 (Ph), 127.81 (Ph), 125.44 (-CH=CH-), 64.04 (-CH₂O-), 62.59 (-CH₂O-), 32.44, 31.05, 27.28, 27.10 (-C(CH₃)₃), 26.10, 19.52. Mass spectrum (ESI) m/z (relative intensity) 405 (M⁺+Na, 100). Exact mass (ESI) calculated for C₂₄H₃₄O₂NaSi (M⁺+Na), 405.2226; found, 405.2229.

**(Z)–[(8-Bromo-oct-5-en-1-yl)oxy](tert-butyl)diphenylsilane (17).** To a solution of 16 (1.64 g, 4.3 mmol) and carbon tetrabromide (2.85 g, 8.6 mmol) in dry CH₂Cl₂ (21 mL) at 0°C under an argon atmosphere, was added dried triphenylphosphine (2.25 g, 8.6 mmol) portionwise. The reaction mixture was stirred for 1 hour at 0°C and for 2 hours at room temperature. On completion, the solvent was removed under reduced pressure at 30°C and the residue was purified by flash column chromatography on silica gel (1-2% diethyl ether in hexanes) to give 1.54 g (81% yield) of 17 as a colorless oil. **1H NMR (500 MHz, CDCl₃)** δ 7.66 (d, J = 7.2 Hz, 4H, 2-H, 6-H, Ph), 7.42 (t, J = 7.2 Hz, 2H, 4-H, Ph), 7.38 (t, J = 7.2 Hz, 4H, 3-H, 5-H, Ph), 5.51 (dtt, J = 10.5 Hz, J = 7.0 Hz, J = 1.5 Hz, 1H, =CH(CH₂Br), 5.36 (dtt, J = 10.5 Hz, J = 7.0 Hz, J = 1.5 Hz, 1H, -CH=), 3.66 (t, J = 6.3 Hz, 2H, -CH₂O-), 3.35 (t, J = 6.3 Hz, 2H, -CH₂Br), 2.58 (dt, J = 7.0 Hz, J = 7.0 Hz, 2H, -CH₂Br), 2.03 (dt, J = 7.0 Hz, J = 7.0 Hz, 2H, -CH₂-), 1.57 (quintet, J = 6.5 Hz, 2H, -CH₂-), 1.44 (quintet, J = 6.5 Hz, 2H, -CH₂-), 1.05 (s, 9H, -C(CH₃)₃-). **13C NMR (100 MHz, CDCl₃)** δ 135.79 (Ph), 134.29 (=C(Si)-), 133.15 (-CH=CH-), 129.73 (Ph),
127.81 (Ph), 126.20 (-CH=CH-), 63.91 (-CH$_2$O-), 32.75, 32.34, 31.03, 27.33, 27.09 (-C(CH$_3$)$_3$), 25.95, 19.44. Mass spectrum (EI) m/z (relative intensity) 389 (M$^+$+2-C(CH$_3$)$_3$, 22), 387 (M$^+$-C(CH$_3$)$_3$, 22), 263 (25), 261 (25), 109 (100). Mass spectrum (ESI) m/z (relative intensity) 469 (M$^+$+2+Na, 100), 467 (M$^+$+Na, 100). Exact mass (ESI) calculated for C$_{24}$H$_{33}$BrOSiNa (M$^+$+Na), 467.1382; found, 467.1396.

(Z)-8-Bromo-oct-5-en-1-ol (18). To a solution of 17 (1.5 g, 3.36 mmol) in dry THF (67 mL) at 0 °C, under an argon atmosphere, was added acetic acid (1.78 mL, 31.2 mmol), followed by tetra-n-butylammonium fluoride (4.37 mL, 1M solution in THF) dropwise. The reaction mixture was stirred at 0 °C until completion of the reaction (12 hours) and then it was quenched with saturated aqueous NH$_4$Cl, and extracted with diethyl ether. The combined organic extracts were washed with brine, dried (MgSO$_4$) and the solvent was evaporated under reduced pressure at 33 °C. The residue was purified by flash column chromatography on silica gel (20-40% ethyl acetate in hexanes) to give 578 mg of 18 as a colorless oil in 83% yield. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 5.53 (dtt, J = 10.5 Hz, J = 7.0 Hz, J = 1.5 Hz, 1H, =C(CH$_2$)$_2$Br), 5.38 (dtt, J = 10.5 Hz, J = 7.0 Hz, J = 1.5 Hz, 1H, =CH=), 3.66 (t, J = 6.5 Hz, 2H, -CH$_2$OH), 3.37 (t, J = 7.0 Hz, 2H, -CH$_2$Br), 2.63 (dt, J = 7.0 Hz, J = 7.0 Hz, 2H, -CH$_2$CH$_2$Br), 2.09 (dt, J = 7.0 Hz, J = 7.0 Hz, 2H, -CH$_2$-CH=), 1.59 (m as quintet, J = 7.0 Hz, 2H, -CH$_2$-), 1.46 (m as quintet, J = 7.0 Hz, 2H, -CH$_2$-). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 132.77 (-CH=CH-), 126.42 (-CH=CH-), 62.96 (-CH$_2$O-), 32.60, 32.47, 30.99, 27.28, 25.81. Mass spectrum (Cl) m/z (relative intensity) 207 (M$^+$+H, 2%), 189 (M$^+$-OH, 5%), 188 (3), 187 (3), 127 (M$^+$+H-Br, 10), 109 (100). Exact mass (ESI) calculated for C$_8$H$_{16}$BrO (M$^+$+H), 207.0385; found, 207.0395.
When the above procedure was carried out without acetic acid, two major compounds were isolated and identified: a) (Z)-8-bromooct-5-en-1-ol (18, 41% yield, \( R_f = 0.32 \), 30% AcOEt in hexane) and b) (Z)-octa-5,7-dien-1-ol \(^{239} \) (19, 32% yield, \( R_f = 0.27 \), 30% AcOEt in hexane). (Z)-Octa-5,7-dien-1-ol (19) \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 6.63 (ddd, \( J = 16.5 \) Hz, \( J = 11.0 \) Hz, \( J = 10.5 \) Hz, 1H, 7-H), 6.02 (dd, \( J = 11 \) Hz, \( J = 10.5 \) Hz, 1H, 6-H), 5.45 (ddt, \( J = 10.5 \) Hz, \( J = 8.0 \) Hz, \( J = 1.0 \) Hz, 1H, 5-H), 5.18 (dd, \( J = 16.5 \) Hz, \( J = 1.5 \) Hz, 1H, 8-H), 5.09 (d, \( J = 10.5 \) Hz, 1H, 8-H), 3.65 (t, \( J = 6.5 \) Hz, 2H, -CH\(_2\)-O-), 2.23 (dt, \( J = 8.0 \) Hz, \( J = 7.5 \) Hz, 2H, 4-H), 1.65-1.57 (m, 2H, -CH\(_2\)-), 1.51-1.42 (m, 2H, -CH\(_2\)-).

(Z)-8-Bromooct-5-enoic acid (20). To a stirred mixture of 18 (512 mg, 2.5 mmol) in acetonitrile (9 mL) and water (3 mL) at 0 °C was added 1 mL of Zhao’s reagent every 30 min until completion of reaction (3.5 hours). A stock solution of Zhao’s reagent was prepared by dissolving 0.63 g H\(_5\)IO\(_6\) and 1.27 g CrO\(_3\) in 1.9 mL H\(_2\)O and 4.4 mL CH\(_3\)CN. The reaction was quenched with Na\(_2\)HPO\(_4\) (20 mg in 1mL H\(_2\)O) and diluted with diethyl ether. The organic phase was separated and the aqueous phase extracted with diethyl ether. The combined organic layer was washed with brine, dried (MgSO\(_4\)) and the solvent was evaporated under reduced pressure at 33 °C. Purification by flash column chromatography on silica gel (30-40% ethyl acetate in hexanes) gave 464 mg (85% yield) of 20\(^{233,232} \) as an oil. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 5.53 (dtt, \( J = 11.0 \) Hz, \( J = 7.0 \) Hz, \( J = 1.5 \) Hz, 1H, -CH(CH\(_2\))\(_2\)Br), 5.38 (dtt, \( J = 11.0 \) Hz, \( J = 7.0 \) Hz, \( J = 1.5 \) Hz, 1H, -CH=), 3.37 (t, \( J = 7.0 \) Hz, 2H, -CH\(_2\)Br), 2.63 (dt, \( J = 7.0 \) Hz, \( J = 7.0 \) Hz, 2H, -CH\(_2\)CH\(_2\)Br), 2.38 (t, \( J = 7.0 \) Hz, \( J = 7.0 \) Hz, 2H, -CH\(_2\)-COOH), 2.12 (dt, \( J = 7.0 \) Hz, \( J = 7.0 \) Hz, 2H, -CH\(_2\)-CH=), 1.73 (quintet, \( J = 7.0 \) Hz, 2H, -CH\(_2\)-CH\(_2\)-COOH). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 179.68 (-COOH), 131.68 (-CH=CH-), 127.45 (-CH=CH-), 33.52, 32.64, 30.96, 26.84,
24.58. Mass spectrum (EI) m/z (relative intensity) 222 (M⁺+2, 0.2), 220 (M⁺, 0.2), 204 (M⁺+2-H₂O, 1), 202 (M⁺-H₂O, 1), 176 (M⁺+2-H₂O-CO, 2), 174 (M⁺-H₂O-CO, 2), 162 (M⁺+2-H₂O-CO-CH₂, 18), 160 (M⁺-H₂O-CO-CH₂, 18), 140 (M⁺-Br, 86), 123 (39), 81 (100). Mass spectrum (ESI) m/z (relative intensity) 245 (M⁺+2+Na, 100), 243 (M⁺+Na, 100), 127 (45), 125 (45). Exact mass (ESI) calculated for C₈H₁₃BrO₂Na (M⁺+Na), 242.9997; found, 243.0004.

(5Z)-8-Bromo-5-octenoic methyl ester (21). To a stirred solution of 20 (0.35 g, 1.58 mmol) in 1:4 mixture of methanol (4 mL) and diethyl ether (16 mL) at 0 ºC under an argon atmosphere, was added trimethylsilyldiazomethane (1.02 mL, 2.05 mmol, 2.0 M solution in hexane). After 20 minutes, the reaction was quenched with saturated aqueous NH₄Cl and diluted with diethyl ether. The organic phase was separated and the aqueous layer was extracted with diethyl ether. The combined organic layer was washed with brine, dried (MgSO₄) and concentrated under reduced pressure at 25 ºC. Purification by flash column chromatography on silica gel (0-10% diethyl ether in hexanes) afforded 338 mg (91% yield) of 21 as a colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 5.50 (dtt, J = 11.0 Hz, J = 7.0 Hz, J = 1.5 Hz, 1H, =CH(CH₂)₂Br), 5.42 (dtt, J = 11.0 Hz, J = 7.0 Hz, J = 1.5 Hz, 1H, -CH=), 3.68 (s, 3H, -COOCH₃), 3.39 (t, J = 7.0 Hz, 2H, -CH₂Br), 2.61 (dt, J = 7.0 Hz, J = 7.0 Hz, 2H, -CH₂CH₂Br), 2.33 (t, J = 7.5 Hz, 2H, -CH₂-COO-), 2.10 (dt, J = 7.0 Hz, J = 7.0 Hz, 2H, -CH₂=), 1.71 (quintet, J = 7.0 Hz, 2H, -CH₂-CH₂-COO-). ¹³C NMR (100 MHz, CDCl₃) δ 174.11 (>C=O), 131.82 (-CH=CH-), 127.22 (-CH=CH-), 51.70 (-OCH₃), 33.55, 32.60, 30.93, 26.89, 24.81. Mass spectrum (EI) m/z (relative intensity) 236 (M⁺+2, 1), 234 (M⁺, 1), 205 (M⁺+2-MeO, 5), 204 (M⁺+2-MeOH, 3), 203 (M⁺-MeO, 5), 202 (M⁺-MeOH, 3), 176 (M⁺+2-MeOH-CO, 4), 174 (M⁺-MeOH-CO, 4),
162 (M$^+$+2-MeOH,-CO,-CH$_2$, 11), 160 (M$^+$-MeOH,-CO,-CH$_2$, 11), 160 (M$^+$-MeOH,-CO,-CH$_2$, 11), 155 (M$^+$+H-Br, 42), 154 (M$^+$-Br, 32), 123 (M$^+$-Br,-OMe, 79), 74 (100).

Exact mass (ESI) calculated for C$_9$H$_{15}$BrO$_2$(M$^+$), 234.0255; found, 234.0244.

[(3Z)-8-Methoxy-8-oxo-3-octen-1-yl]triphenylphosphonium bromide (5). A stirred mixture of 21 (300 mg, 1.27 mmol) and dried triphenylphosphine (667 mg, 2.54 mmol) in anhydrous acetonitrile (6 mL) was heated (72-75 °C) for four days under argon. Solvent evaporation and purification by flash column chromatography on silica gel (0-15% methanol in methylene chloride) gave 576 mg (91% yield) of 5$^{232}$ as a colorless gum. The product was rigorously dried in high vacuo for 6 hours at 40-42 °C, and used in the next step.$^1$H NMR (500 MHz, CDCl$_3$) δ 7.88 (m as dd, J = 12.6 Hz, J = 7.8 Hz, 6H, 2-H, 6-H, -PPh$_3$), 7.81 (m as td, J = 7.8 Hz, J = 1.8 Hz, 3H, 4-H, -PPh$_3$), 7.71 (m as td, J = 7.8 Hz, J = 4.2 Hz, 6H, 3-H, 5-H, -PPh$_3$), 5.65 (dtt, J = 11.0 Hz, J = 7.0 Hz, J = 1.5 Hz, 1H, =CH(CH$_2$)$_2$P$^+$Ph$_3$), 5.37 (dtt, J = 11.0 Hz, J = 7.0 Hz, J = 1.5 Hz, 1H, -CH=), 3.96 (dt, J = 12.0 Hz, J = 8.0 Hz, 2H, -CH$_2$P$^+$Ph$_3$), 3.61 (s, 3H, -COOCH$_3$), 2.48-2.46 (m, 2H, -CH$_2$-CH$_2$P$^+$Ph$_3$), 2.21 (t, J = 7.5 Hz, 2H, -CH$_2$-COO-), 1.87 (dt, J = 7.0 Hz, J = 7.0 Hz, J = 1.5 Hz, 2H, -CH$_2$-CH=), 1.58 (quintet, J = 7.5 Hz, 2H, -CH$_2$-CH$_2$-COO-). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 174.12 (>C=O), 135.24 (C4', Ph), 134.10 (d, J = 9.2 Hz, C2', C6', Ph), 131.31 (-CH=CH-(CH$_2$)$_2$P Ph$_3$), 130.70 (d, J = 11.5 Hz, C3', C5', Ph), 127.52 (d, J = 13.8 Hz, -CH=CH-(CH$_2$)$_2$P), 118.65 (d, J = 85.5 Hz, C1', Ph), 51.68 (-OCH$_3$), 33.51, 26.76, 24.69, 23.03 (d, J = 49 Hz, -CH$_2$P), 20.69. Mass spectrum (ESI) m/z (relative intensity) 417 (M$^+$-Br, 100). Exact mass (ESI) calculated for C$_{27}$H$_{30}$O$_2$P(M$^+$-Br), 417.1983; found, 417.1973.
(3Z)-1-Bromo-3-nonene (23). To a stirred solution of (3Z)-3-nonen-1-ol (5 g, 35.15 mmol) and carbon tetrabromide (11.6 g, 35.15 mmol) in dry CH$_2$Cl$_2$ (170 mL) at 0 °C under an argon atmosphere, was added dried triphenylphosphine (9.17 g, 35.15 mmol) portionwise. The reaction mixture was stirred for 1 hour at 0 °C and for 2 hours at room temperature. On completion, the solvent was removed under reduced pressure at 30 °C and the residue was purified by flash column chromatography on silica gel (1-2% diethyl ether in hexanes) to give 6.8 g (94% yield) of 23 as a colorless oil. $^1$H NMR (500 MHz, CDCl$_3$) δ 5.53 (dtt, J = 10.5 Hz, J = 7.0 Hz, J = 1.5 Hz, 1H, 3-H), 5.36 (dtt, J = 10.5 Hz, J = 7.0 Hz, J = 1.5 Hz, 1H, 4-H), 3.36 (t, J = 7.0 Hz, 2H, -CH$_2$Br), 2.61 (dt, J = 7.0 Hz, J = 7.0 Hz, 2H, -CH$_2$-CH$_2$Br), 2.03 (dt, J = 7.0 Hz, J = 7.0 Hz, 2H, =CH-CH$_2$-(CH$_2$)$_3$-CH$_3$), 1.40-1.24 (m and sextet overlapping, 6H, 6-H, 7-H, 8-H, especially 1.36 sextet, J = 7.0 Hz, 2H), 0.89 (t, J = 7.5 Hz, 3H, -CH$_2$CH$_3$); Mass spectrum (ESI) m/z (relative intensity) 205 (M$^+$+H, 15), 163 (15), 123 (92), 55 (100). Exact mass (EI) calculated for C$_7$H$_{17}$Br(M$^+$), 204.0514; found, 204.0504.

[(3Z)-3-Nonen-1-yl]triphenylphosphonium bromide (6). A stirred mixture of 23 (5 g, 24.37 mmol) and dried triphenylphosphine (12.78 g, 48.74 mmol) in anhydrous acetonitrile (48 mL) was heated (72-75 °C) for 7 days under argon. Solvent evaporation and purification by flash column chromatography on silica gel (3% methanol in methylene chloride) gave 8.2 g (72% yield) of 6 as a colorless gum. The product was rigorously dried in high vacuo for 6 hours at 40-42 °C, and used in the next step. $^1$H NMR (500 MHz, CDCl$_3$) δ 7.88 (m as dd, J = 12.5 Hz, J = 7.5 Hz, 6H, 2-H, 6-H, -PPh$_3$), 7.80 (m as td, J = 7.5 Hz, J = 1.8 Hz, 3H, 4-H, -PPh$_3$), 7.70 (m as td, J = 7.5 Hz, J = 4.2 Hz, 6H, 3-H, 5-H, -PPh$_3$), 5.57 (dtt, J = 11.0 Hz, J = 7.0 Hz, J = 1.5 Hz, 1H, 3-H, 4-H, -PPh$_3$), 5.36 (dtt, J = 10.5 Hz, J = 7.0 Hz, J = 1.5 Hz, 1H, 4-H, -PPh$_3$), 3.36 (t, J = 7.0 Hz, 2H, -CH$_2$Br), 2.61 (dt, J = 7.0 Hz, J = 7.0 Hz, 2H, -CH$_2$-CH$_2$Br), 2.03 (dt, J = 7.0 Hz, J = 7.0 Hz, 2H, =CH-CH$_2$-(CH$_2$)$_3$-CH$_3$), 1.40-1.24 (m and sextet overlapping, 6H, 6-H, 7-H, 8-H, especially 1.36 sextet, J = 7.0 Hz, 2H), 0.89 (t, J = 7.5 Hz, 3H, -CH$_2$CH$_3$); Mass spectrum (ESI) m/z (relative intensity) 205 (M$^+$+H, 15), 163 (15), 123 (92), 55 (100). Exact mass (EI) calculated for C$_7$H$_{17}$Br(M$^+$), 204.0514; found, 204.0504.
=CH(CH₂)₂P⁺Ph₃), 5.39 (dtt, J = 11.0 Hz, J = 7.0 Hz, J = 1.5 Hz, 1H, -CH=), 3.95 (dt, J = 12.0 Hz, J = 8.0 Hz, 2H, -CH₂P⁺Ph₃), 2.49-2.41 (m, 2H, -CH₂-CH₂-P⁺Ph₃), 1.75 (quintet, J = 7.0 Hz, 2H, -CH=CH-CH₂-), 1.26-1.17 (m, 4H, -CH₂-), 1.16-1.10 (m, 2H, -CH₂-), 0.84 (t, J = 7.0 Hz, 3H, -CH₃); Mass spectrometry (ESI) m/z (relative intensity) 387 (M⁺-Br, 100). Exact mass (ESI) calculated for C₂₇H₃₂P(M⁺-Br), 387.2242; found, 387.2249.

(10R, 5Z, 8Z)-11-[(tert-Butyldiphenylsilyl)oxy]-10-methyl-undeca-5,8-dienoic methyl ester (24). To a solution of 5 (415 mg, 0.834 mmol) in dry THF (4 mL) at -78 °C under an argon atmosphere was added potassium bis(trimethylsilyl)amide (0.79 mL, 1.0 M solution in THF) dropwise. The mixture was stirred at -78 °C to -60 °C for 45 min, to ensure complete formation of the orange ylide, and then it was cooled to -115 °C. Subsequently, a solution of aldehyde 3 (136 mg, 0.417 mmol) in dry THF (1 mL) was added dropwise. The reaction mixture was stirred for 15 min at -115 °C, and then it was warmed to -20 °C over a period of 2.5 hours. The reaction mixture was then cooled to -78 °C and quenched with a saturated aqueous sodium bicarbonate solution. The mixture was warmed to room temperature, extracted with diethyl ether and the combined organic extracts were washed with brine, dried (MgSO₄) and concentrated in vacuo. Purification by flash column chromatography on silica gel (5-7% diethyl ether in hexane) gave 24 as colorless oil in 46% yield (89 mg). [α]D²⁶ = -17.48° (c = 0.2 g/100 mL in CHCl₃). ¹H NMR (500 MHz, CDCl₃) δ 7.66 (d, J = 7.8 Hz, 4H, 2-H, 6-H, Ph), 7.44 (t, J = 7.2 Hz, 2H, 4-H, Ph), 7.37 (t, J = 7.2 Hz, 4H, 3-H, 5-H, Ph), 5.37-5.28 (m, 3H, 5-H, 6-H, 8-H), 5.19 (tdd, J = 10.5 Hz, J = 9.5 Hz, J = 1.0 Hz, 1H, 9-H), 3.66 (s, 3H, -COOCH₃), 3.46 (dd, J = 10.0 Hz, J = 6.0 Hz, 1H, 11-H), 3.46 (dd, J = 10.0 Hz, J = 7.0 Hz, 1H, 11-H),
2.81-2.73 (m, 1H, 10-H), 2.72-2.64 (m, 2H, 7-H), 2.30 (t, J = 7.5 Hz, 2H, 2-H), 2.07 (dt, J = 6.5 Hz, J = 6.5 Hz, 2H, 4-H), 1.69 (quintet, J = 7.5 Hz, 2H, 3-H), 1.05 (s, 9H, -C(CH₃)₃), 1.00 (d, J = 6.5 Hz, 3H, >CH-CH₃). ¹³C NMR (100 MHz, CDCl₃) δ 174.23 (>C=O), 135.88, 134.25, 133.29, 129.74, 129.49, 128.91, 128.27, 127.77, 68.79, 51.64, 35.03, 33.70, 27.15, 26.79, 26.12, 25.03, 19.52, 17.69; Mass spectrum (ESI) m/z (relative intensity) 465 (M⁺+H, 23), 387 (M⁺-Ph, 100). Exact mass (ESI) calculated for C₂₉H₄₁O₃Si (M⁺+H), 465.2825; found, 465.2827.

(10R, 5Z, 8Z)-11-Hydroxy-10-methyl-undeca-5,8-dienoic methyl ester (25). To a stirred solution of 24 (85 mg, 0.183 mmol) in dry THF (3 mL), under an argon atmosphere at 0 °C, was added TBAF (0.25 mL, 0.25 mmol, 1M solution in THF) dropwise. Stirring was continued for 10 min at 0 °C and for 1.5 hours at room temperature. The reaction mixture was quenched with a saturated aqueous NH₄Cl solution at 0 °C and extracted with AcOEt. The combined organic extracts were washed with brine, dried (MgSO₄) and concentrated under reduced pressure at 37 °C. The crude material was purified by flash column chromatography on silica gel (15-45% ethyl acetate in hexane) to afford 25 (38 mg, 92% yield) as a colorless viscous liquid. [α]D²⁶ = 83.11° (c = 0.139 g/100 mL in CHCl₃). ¹H NMR (500 MHz, CDCl₃) δ 5.49 (dtd, J = 10.5 Hz, J = 7.5 Hz, J = 1.2 Hz, 1H, 8-H), 5.40 (td, J = 10.5 Hz, J = 7.0 Hz, 1H, 6-H or 5-H), 5.35 (td, J = 10.5 Hz, J = 7.0 Hz, 1H, 5-H or 6-H), 5.16 (tdd, J = 10.5 Hz, J = 10.0 Hz, J = 1.5 Hz, 1H, 9-H), 3.67 (s, 3H, -COOCH₃), 3.49 (ddd, J = 12.0 Hz, J = 8.0 Hz, J = 4.5 Hz, 1H, 11-H), 2.83 (dd, J = 7.5 Hz, J = 7.5 Hz, 2H, 7-H), 2.73 (m as septet, J = 6.5 Hz, 1H, 10-H), 2.33 (t, J = 7.0 Hz, 2H, 2-H), 2.11 (dt, J = 7.5 Hz, J = 7.5 Hz, 2H, 4-H), 1.70 (quintet, J = 7.5 Hz, 2H, 3-
H), 1.51 (dd, $J = 6.0$ Hz, $J = 4.5$ Hz, 1H, OH), 0.96 (d, $J = 6.5$ Hz, 3H, >CH-CH$_3$). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 174.15 (>C=O), 132.85 (C-9 or C-8), 130.36 (C-8 or C-9), 129.38 (C-6 or C-5), 129.17 (C-5 or C-6), 68.09 (CH$_2$OH), 51.83 (OCH$_3$), 35.41, 33.86, 27.02, 26.43, 25.10, 17.37; Mass spectrum (ESI) m/z (relative intensity) 249 (M$^+$+Na, 100). Exact mass (ESI) calculated for C$_{13}$H$_{22}$O$_3$Na (M$^+$+Na), 249.1465; found, 249.1468.

(10R, 5Z, 8Z)-10-Methyl-11-oxo-undeca-5,8-dienoic methyl ester (26). To a solution of alcohol 25 (38 mg, 0.168 mmol) in dry CH$_2$Cl$_2$ (3.5 mL) at 0 ºC under an argon atmosphere, was added Dess-Martin periodiane (DMP) (142 mg, 0.336 mmol) and the resulting suspension was warmed to room temperature and stirred for 45 min. An additional amount of DMP (21 mg, 0.05 mmol) was added at 0 ºC and stirring was continued for 30 min at room temperature to ensure total consumption of alcohol 25. The reaction mixture was quenched by adding a mixture of Na$_2$S$_2$O$_3$ (10% in H$_2$O) and saturated NaHCO$_3$ (1:1) and diluted with diethyl ether. The slurry was filtered through Celite, the organic phase separated and the aqueous phase was extracted with diethyl ether. The combined organic layer was washed with saturated NaHCO$_3$, brine, and dried (MgSO$_4$). Solvent evaporation under reduced pressure at 36-40 ºC provided the sensitive crude product 26 as a colorless oil which was used in the next step immediately. $^1$H NMR (500 MHz, CDCl$_3$) δ 9.53 (d, $J = 1.5$ Hz, 1H, -CHO), 5.64 (dtd, $J = 10.5$ Hz, $J = 7.5$ Hz, $J = 1.2$ Hz, 1H, 8-H), 5.42-5.34 (m, 2H, 6-H, 5-H), 5.25 (ttd, $J = 10.5$ Hz, $J = 10.0$ Hz, $J = 1.5$ Hz, 1H, 9-H), 3.67 (s, 3H, -COOCH$_3$), 3.37 (m as quintet, $J = 8.0$ Hz, 1H, 10-H), 2.86-2.78 (m, 2H, 7-H), 2.33 (t, $J = 7.0$ Hz, 2H, 2-H), 2.11 (dt, $J = 7.5$ Hz, $J = 7.5$ Hz, 2H, 4-H), 1.71 (quintet, $J = 7.5$ Hz, 2H, 3-H), 1.19 (d, $J = 6.5$ Hz, 3H, >CH-CH$_3$); Mass
spectrum (ESI) m/z (relative intensity) 247 (M^+Na, 100), 225 (M^+H, 10), 175 (34). Exact mass (ESI) calculated for C_{13}H_{20}O_{3}Na (M^+Na), 247.1310; found, 247.1309.

(10S, 5Z, 8Z, 11Z, 14Z)-10-Methyl-eicosa-5,8,11,14-tetraenoic methyl ester (2a). To a stirred solution of phosphonium bromide 6 (395 mg, 0.845 mmol) in dry THF (4 mL) at 0°C under an argon atmosphere, was added potassium bis(trimethylsilyl)amide (0.83 mL, 1.0 M solution in THF) dropwise. The mixture was stirred for 30 min at 0 °C to ensure complete formation of the orange ylide and then it was cooled to -78 °C. A solution of crude aldehyde 26 in dry THF (1 mL) was added dropwise, the reaction mixture was stirred for 1 hour at -78 °C and then it was quenched by the addition of saturated aqueous sodium bicarbonate. The mixture was warmed to room temperature, extracted with diethyl ether, and the combined organic extracts were washed with brine, dried (MgSO_4) and concentrated in vacuo. Purification by flash column chromatography on silica gel (0-8% diethyl ether in hexane) gave 21 mg (39% yield from alcohol 25) of ester 2a as a colorless oil. [α]_D^{25.7} = 351.92° (c = 0.087 g/100 mL in CHCl_3). \(^1\)H NMR (500 MHz, CDCl_3) δ 5.43-5.31 (m, 4H, -CH=CH-), 5.31-5.21 (m, 4H, -CH=CH-), 3.67 (s, 3H, -COOCH_3), 3.49 (ddq as sextet, J = 6.5 Hz, 1H, 10-H), 2.88-2.75 (m, 4H, 7-H, 13-H), 2.32 (t, J = 7.0 Hz, 2H, 2-H), 2.11 (dt, J = 7.0 Hz, J = 7.0 Hz, 2H, 4-H), 2.05 (dt, J = 7.5 Hz, J = 7.5 Hz, 2H, 16-H), 1.71 (quintet, J = 7.5 Hz, 2H, 3-H), 1.39-1.24 (m, 6H, 18-H, 19-H, 17-H), 1.02 (d, J = 7.0 Hz, 3H, >CH-C=H), 0.89 (t, J = 7.0 Hz, 3H, 20-H). \(^1\)C NMR (100 MHz, CDCl_3) δ 174.18 (>C=O), 134.99 (-CH=), 134.68 (-CH=), 130.68 (-CH=), 129.27 (-CH=), 129.11 (-CH=), 127.93 (-CH=), 126.61(-CH=), 126.23(-CH=), 51.63 (OCH_3), 33.68, 31.72, 30.77, 29.92, 29.51, 27.44, 26.77, 26.04, 25.02, 22.76, 22.14, 14.20 (C-20); Mass spectrum (ESI) m/z (relative intensity) 355 (M^+Na, 100), 333
(M^+H, 72). Exact mass (ESI) calculated for C_{22}H_{36}O_2Na (M^+Na), 355.2613; found, 355.2618, and calculated for C_{22}H_{37}O_2 (M^+H), 333.2794; found, 333.2797.

(10S, 5Z, 8Z, 11Z, 14Z)-10-Methyl-eicosa-5,8,11,14-tetraenoic acid (27). To a stirred solution of 2a (15 mg, 0.045 mmol) in dry THF (1 mL) at room temperature, under an argon atmosphere, was added 1 M aqueous LiOH solution (0.09 mL). Stirring was continued for 24 h, and then the reaction mixture was acidified with 5% HCl to pH 3, and lipophilic products were extracted with Et_2O. The combined organic extracts were washed with brine and dried (MgSO_4). Solvent evaporation under reduced pressure at 37-40 °C gave pure acid 27 (12.4 mg, 86% yield) as a colorless oil which was used in the next step without further purification. \(^1\)H NMR (500 MHz, CDCl_3) \(\delta\) 5.43-5.31 (m, 4H, \(-\text{CH}=\text{CH}-\)), 5.31-5.21 (m, 4H, \(-\text{CH}=\text{CH}-\)), 3.48 (ddq as sextet, \(J = 6.5\) Hz, 1H, 10-H), 2.88-2.76 (m, 4H, 7-H, 13-H), 2.38 (t, \(J = 7.5\) Hz, 2H, 2-H), 2.13 (dt, \(J = 7.5\) Hz, \(J = 7.5\) Hz, 2H, 4-H), 2.05 (dt, \(J = 7.0\) Hz, \(J = 7.0\) Hz, 2H, 16-H), 1.72 (quintet, \(J = 7.5\) Hz, 2H, 3-H), 1.39-1.24 (m, 6H, 18-H, 19-H, 17-H), 1.03 (d, \(J = 7.0\) Hz, 3H, \(>\text{CH}-\text{CH}_3\)), 0.89 (t, \(J = 7.0\) Hz, 3H, 20-H); Mass spectrum (ESI) m/z (relative intensity) 341 (M^+Na, 100), 319 (M^+H, 45). Exact mass (ESI) calculated for C_{21}H_{34}O_2Na (M^+Na), 341.2457; found, 341.2456, and calculated for C_{21}H_{35}O_2 (M^+H), 319.2637; found, 319.2638.

2-[(tert-Butyldiphenylsilyl)oxy]ethanamine (29). To a solution of ethanolamine (28) (1 g, 16.4 mmol) and dried imidazole (2.44 mg, 36.1 mmol) in anhydrous CH_3CN (80 mL) at 0 °C under an argon atmosphere, was added tert-butyldiphenylsilyl chloride (4.95 mg, 18.0 mmol) dropwise. The reaction mixture was stirred for 30 min at 0 °C and then quenched with a saturated aqueous sodium bicarbonate solution, diluted with water and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried
(MgSO₄) and concentrated in vacuo. The crude oil was purified by flash column chromatography on silica gel (10% MeOH in CH₂Cl₂) to afford 29 (4.64 g, 95%) as a colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 7.68 (d, J = 7.2 Hz, 4H, 2-H, 6-H, PhH), 7.43 (t, J = 7.2 Hz, 2H, 4-H, PhH), 7.39 (t, J = 7.2 Hz, 4H, 3-H, 5-H, PhH), 3.70 (t, J = 5.4 Hz, 2H, -CH₂-OTBDPS), 2.83 (t, J = 5.4 Hz, 2H, -CH₂-NH-). 2.41 (br s, 2H, -NH₂), 1.07 (s, 9H, -C(CH₃)₃).

(10S, 5Z, 8Z, 11Z, 14Z)-10-Methyl-eicosa-5,8,11,14-tetraenoic acid N-{2-[(tert-butyldiphenylsilyl) oxy]ethyl}amide (30). A mixture of acid 27 (10 mg, 0.031 mmol), and fresh carbonyldiimidazole (15 mg, 0.093 mmol) in dry THF (1 mL) at room temperature under an argon atmosphere, was stirred for 2 hours and then protected ethanolamine 29 (37 mg, 0.125 mmol) in THF (0.5 mL) was added. The reaction mixture was stirred for 1 hour and then diluted with water and ethyl acetate. The organic phase was separated and the aqueous phase extracted with AcOEt. The combined organic layer was washed with brine, dried (MgSO₄) and concentrated in vacuo. The crude product obtained after work up was purified by flash column chromatography on silica gel (15-25% acetone in hexane), and gave 14 mg (74% yield) of 30 as a colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 7.63 (d, J = 7.5 Hz, 4H, 2-H, 6-H, Ph), 7.43 (t, J = 7.5 Hz, 2H, 4-H, Ph), 7.38 (t, J = 7.5 Hz, 4H, 3-H, 5-H, Ph), 5.73 (br s, 1H, >NH), 5.43-5.32 (m, 4H, -CH=CH-), 5.31-5.19 (m, 4H, -CH=CH-), 3.74 (t, J = 6.5 Hz, 2H, -CH₂-OTBDPS), 3.48 (m as sextet, J = 7.0 Hz, 1H, 10-H), 3.40 (dt, J = 6.5 Hz, J = 6.5 Hz, 2H, -CH₂-NH-), 2.88-2.76 (m, 4H, 7-H, 13-H), 2.16-2.08 (t and dt overlapping, 4H, 2-H, 4-H), 2.04 (dt, J = 7.2 Hz, J = 7.2 Hz, 2H, 16-H), 1.68 (quintet, J = 8.0 Hz, 2H, 3-H), 1.38 -1.24 (m, 6H, 18-H, 19-H, 17-H), 1.07 (s, 9H, -C(CH₃)₃), 1.02 (d, J = 8.5 Hz, 3H, >CH-CH₃), 0.88 (t, J
= 7.0 Hz, 3H, 20-H); Mass spectrum (ESI) m/z (relative intensity) 600 (M⁺+H, 100), 522 (M⁺-Ph, 52). Exact mass (ESI) calculated for C₃₉H₅₈NO₂Si (M⁺+H), 600.4237; found, 600.4238.

(10S, 5Z, 8Z, 11Z, 14Z)-10-Methyl-eicosa-5,8,11,14-tetraenoic acid N-(2-hydroxyethyl)amide (1a). The synthesis was carried out as described for 25, using 30 (10 mg, 0.0166 mmol) and TBAF (0.02 mL, 0.02 mmol, 1M solution in THF) in dry THF (1 mL). The reaction was completed in 1 hour and the crude oil obtained after work up was purified by flash column chromatography on silica gel (57:40:3, ethyl acetate : hexane : MeOH) to afford 1a (5 mg, 83% yield) as a colorless oil. [α]D²⁴.₆ = 99.27º (c = 0.108 g/100 mL in CHCl₃). ¹H NMR (700 MHz, CDCl₃) δ 5.87 (br s, 1H, >NH), 5.43-5.32 (m, 4H, -CH=), 5.30-5.19 (m, 4H, -CH=), 3.73 (t, J = 5.1 Hz, 2H, -CH₂-O-), 3.48 (qdd as sextet, J = 7.2 Hz, 1H, 10-H), 3.42 (dt, J = 5.5 Hz, J = 5.5 Hz, 2H, -CH₂-NH-), 2.87-2.75 (m, 4H, 7-H, 13-H), 2.22 (t, J = 7.6 Hz, 2H, 2-H), 2.12 (dt, J = 7.0 Hz, J = 7.0 Hz, 2H, 4-H), 2.05 (dt, J = 7.4 Hz, J = 7.4 Hz, 2H, 16-H), 1.73 (quintet, J = 7.5 Hz, 2H, 3-H), 1.52 (br s, 1H, OH), 1.38-1.33 (sextet, J = 7.1 Hz, 2H, 17-H), 1.32-1.24 (m, 4H, 18-H, 19-H), 1.02 (d, J = 6.7 Hz, 3H, >CH-CH₃), 0.88 (t, J = 7.1 Hz, 3H, 20-H). ¹³C NMR (175 MHz, CDCl₃) δ 174.17 (>C=O), 134.81 (-CH=), 134.45 (-CH=), 130.53 (-CH=), 129.01 (-CH=), 128.99 (-CH=), 127.69 (-CH=), 126.38 (-CH=), 125.97 (-CH=), 62.71 (-CH₂OH), 42.49 (-NH-CH₂-), 35.95 (C-2), 31.53 (C-18 or C-19), 30.56 (C-10), 29.34 (C-17), 27.23 (C-16), 26.62 (C-4), 25.86 (C-7, C-13), 25.46 (C-3), 22.59 (C-19 or C-18), 21.97 (C₁₀-Me), 14.09 (C-20); Mass spectrum (ESI) m/z (relative intensity) 362 (M⁺+H, 100), 301 (M⁺-NH(CH₂)₂OH, 11). Exact mass (ESI) calculated for C₂₃H₄₀NO₂ (M⁺+H),
362.3059; found, 362.3061. Elemental analysis calculated for C_{23}H_{39}NO_2: C, 76.40; H, 10.87; N, 3.87. Found: C, 76.11; H, 11.17; N, 4.21.

(10S, 5Z, 8Z)-11-[(tert-Butyldiphenylsilyl)oxy]-10-methyl-undeca-5,8-dienoic methyl ester (31). The synthesis was carried out as described for 24 and gave the title compound in 48% yield. Spectroscopic and physical data were identical to those of the enantiomer 24.

(10S, 5Z, 8Z)-11-Hydroxy-10-methyl-undeca-5,8-dienoic methyl ester (32). The synthesis was carried out as described for 25 and gave the title compound in 90% yield. Spectroscopic and physical data were identical to those of the enantiomer 25.

(10S, 5Z, 8Z)-10-Methyl-11-oxo-undeca-5,8-dienoic methyl ester (33). The synthesis was carried out as described for 26 and the product was used in the next step immediately without further purification. Spectroscopic data was identical to that of the enantiomer 26.

(10R, 5Z, 8Z, 11Z, 14Z)-10-Methyl-eicosa-5,8,11,14-tetraenoic methyl ester (2b). The synthesis was carried out as described for 2a and gave the title compound in 40% yield from alcohol 32. Spectroscopic and physical data were identical to those of the enantiomer 2a.

(10R, 5Z, 8Z, 11Z, 14Z)-10-Methyl-eicosa-5,8,11,14-tetraenoic acid (34). The synthesis was carried out as described for 27 and gave the title compound in 86% yield. Spectroscopic data was identical to that of the enantiomer 27.
(10R, 5Z, 8Z, 11Z, 14Z)-10-Methyl-eicosa-5,8,11,14-tetraenoic acid \( N\)-(2-[(\text{tert}-\text{butyldiphenylsilyl}) \text{oxy}]\text{ethyl})\text{amide} \ (35). \) The synthesis was carried out as described for 30 and gave the title compound in 83% yield. Spectroscopic data was identical to that of the enantiomer 30.

(10R, 5Z, 8Z, 11Z, 14Z)-10-Methyl-eicosa-5,8,11,14-tetraenoic acid \( N\)-(2-\text{hydroxyethyl})\text{amide} \ (1b). \) The synthesis was carried out as described for 1a and gave the title compound in 85% yield. Spectroscopic and physical data were identical to those of the enantiomer 1a.
Introduction

Previous efforts in our laboratory aimed at developing novel endocannabinoid templates with potential resistance to hydrolytic and oxidative metabolism, led to (13S)-methyl-anandamide, an endocannabinoid ligand with remarkably high CB-receptor binding affinity (4.8±1.3 nM). In continuation of the SAR studies in this project, we directed our efforts to the design and synthesis of tail-modified covalent probes, that may help determine the amino acid residues and the transmembrane helix(es) involved in binding of these novel analogs.

Figure 3B.1: Structure of 13-(S)-methyl anandamide covalent probes

\[
\text{Polar head group}
\]
\[
\text{cis tetraolefinc chain}
\]
\[
\text{n-pentyl tail}
\]

compound 24. \(Y = \text{N}_3\)
compound 25. \(Y = \text{NCS}\)
Chemistry

**Scheme 3B.1: Retrosynthetic analysis of covalent probes 24 and 25**

Retrosynthetic analysis identified protected methyl ester 20 as the intermediate from which covalent probe analogs 24 and 25 were produced by peptide coupling (*Scheme 3B.1*).

Disconnection of C11=C12 and C14=C15 double bonds in 20 led to three fragments: chiral aldehyde 3 which has the S configuration corresponding to the C13 chiral center of 20 and phosphonium salts 16 and 7.

The (S)-chiral aldehyde 3 was used synthesized as reported in *Chapter 3A*. Newly synthesized phosphonium salt 7 was synthesized from commercially available 6-bromo-hexan-1-ol as shown in *Scheme 3B.2*. 
Scheme 3B.2: Synthesis of phosphonium salt 7

\[
\text{Br} \quad \text{OH} \quad \text{a} \quad \text{Br} \quad \text{OTBDPS} \quad \text{b}
\]

Reagents and conditions: (a) TBDPSCI, imidazole, THF, 0 °C to rt, 1.5 h, 85%; (b) Ph₃P, toluene, 60-63 °C, 5 days, 66%.

The building of the required phosphonium salt fragment 16 was undertaken as illustrated in Scheme 3B.3 that was reported previously.²²⁷ Commercially available 3-butyn-1-ol 8 was converted to its TBDPS protected 9 form in 91% yield, and which was subsequently treated with nBuLi and quenched with paraformaldehyde to give the two carbon homologated alcohol 10 in 68% yield.²²⁷ Conversion of 10 to bromide 11 was carried out by using the PPh₃/CBr₄ method in 79% yield. Copper-assisted cross-coupling of 11 with methyl 5-hexynoate in the presence of CsCO₃ and NaI gave diyne 12 in 75% yield.²⁴¹ Partial hydrogenation of 12 using P-2 nickel catalyst gave its corresponding skipped Z diene 13 in 78% yield. Deprotection of 13 with TBAF at 0 °C led to 14 in 94% yield. The resulting alcohol 14 was converted to bromide 15 in 85% yield. Heating of 15 with PPh₃ in dry CH₃CN for 7 days afforded the required phosphonium salt 16 in 96% yield.²²⁷
Scheme 3B.3: Synthesis of phosphonium salt 16

Reagents and conditions: (a) TBDPSCl, imidazole, THF, 0 °C to r t, 1.5 h, 91%; (b) n- BuLi, THF, 0 °C, 1.5 h, then (CH₂O)ₙ, -50 °C to rt, 1.5 h, 68%; (c) CBr₄, Ph₃P, CH₂Cl₂, 0 °C to r t, 2.5 h, 79%; (d) CH≡C-(CH₂)₃-COOMe, Cs₂CO₃, NaI, CuI, DMF, rt, 2.5 h, 75%; (e) Ni(OAc)₂, NaBH₄, ethylenediamine, H₂, MeOH, r t, 2 h, 78%; (f) TBAF, THF, 0 °C to r t, 1.5 h, 94%; (g) CBr₄, Ph₃P, CH₂Cl₂, -25 °C-0 °C, 1.5 h, 85%; (h) Ph₃P, CH₃CN, 72-75 °C, 8 days, 96%.

The assembly of the synthesized aldehyde 3 with phosphonium salts 16 and 7 into 24 and 25 are shown in Scheme 3B.4.²²⁷ Thus, treatment of 16 with KHMDS and coupling of the resulting ylide with aldehyde 3 at -115 °C produced 17 (63% yield). Desilylation of 17 with TBAF gave alcohol 18 in 85% yield. Dess–Martin periodinane oxidation of 18 led to unstable aldehyde 19,²²⁷ which was used immediately, without purification, in a Wittig reaction with 7, to give protected methyl ester 20 in 43% yield. TBAF deprotection of 20 led to alcohol 21 in 85% yield. Alcohol 21 was directly converted to azide 22 using
diphenyl phosphorazidate and DBU in 71\% yield. Saponification of azide ester 22 with lithium hydroxide in THF/H\textsubscript{2}O led to acid 23, which was coupled with cyclopropylamine to give amide 24 (74\% yield) by using the carbonyldiimidazole activation procedure. Azide probe 24 was converted to the isothiocyanato analog 25 using CS\textsubscript{2} and PPh\textsubscript{3} in 96\% yield.

**Scheme 3B.4**: Synthesis of (13S)-methyl-anandamide tail modified covalent probes

Reagents and conditions: (a) (Me\textsubscript{3}Si)\textsubscript{2}N\textsuperscript{+}K\textsuperscript{-}, THF, -78 °C to -60 °C, 45 min, then 3, -115 °C to -20 °C, 3 h, 63\%; (b) TBAF, THF, 0 °C to r t, 2 h, 85\%; (c) Dess-Martin periodinane, CH\textsubscript{2}Cl\textsubscript{2}, 0 °C to r t, 1.5 h; (d) 7, (Me\textsubscript{3}Si)\textsubscript{2}N\textsuperscript{+}K\textsuperscript{-}, THF, 0 °C, 30 min, then addition of 19, -78 °C, 1 h, 43\% from alcohol 18; (e) TBAF, THF, 0 °C to r t, 2 h, 85\%; (f) DPPA, DBU, DMF, 120 °C, 2 h, 71\%; (g) LiOH, THF/H\textsubscript{2}O, r t, 24 h; (h) carbonyldiimidazole, THF, r t, 2 h, then 24, r t, 2 h, 74\%; (i) CS\textsubscript{2}, PPh\textsubscript{3}, THF, r t, 48 h, 96\%
Results and Discussion

**Table 3B.1**: Binding affinities of C13-Methyl anandamide analogs

<table>
<thead>
<tr>
<th>Compound</th>
<th>CB1 (Kᵢ PMSF) nM</th>
<th>mCB2 (Kᵢ PMSF) nM</th>
<th>hCB2 (Kᵢ PMSF) nM</th>
</tr>
</thead>
<tbody>
<tr>
<td>13(S)-Methyl Anandamide AMG 113</td>
<td>4.8 ± 1.3</td>
<td>137 ± 22</td>
<td>-</td>
</tr>
<tr>
<td>AM 9279</td>
<td>6.3</td>
<td>13.3</td>
<td>8.5</td>
</tr>
<tr>
<td>AM 9280</td>
<td>15.6</td>
<td>47.7</td>
<td>22.1</td>
</tr>
</tbody>
</table>

Covalent probes AM 9279 and AM 9280 bound to both CB1 and CB2 receptors with good low nanomolar binding affinity (**Table 3B.1**). Covalent binding experiments are necessary to confirm if these ligands can covalently label the CB receptors. If these analogs are found to covalently label the CB receptors, amino acid residues and the transmembrane helix(es) involved in binding of these novel analogs can be determined.

Interestingly, compared to the parent analog AM 113 (137 ± 22 nM), covalent probe analogs also bound to the CB2 receptors with low binding affinity. Anandamide analogs with low nanomolar binding to the CB2 receptor are not usual.
**Table 3B.2:** Preliminary cAMP data of C13-Methyl anandamide covalent probes

<table>
<thead>
<tr>
<th>AM #</th>
<th>cAMP (EC&lt;sub&gt;50&lt;/sub&gt; % maximal efficacy) rCB1</th>
<th>cAMP (EC&lt;sub&gt;50&lt;/sub&gt; % maximal efficacy) hCB2</th>
</tr>
</thead>
<tbody>
<tr>
<td>AM 9279</td>
<td><img src="image1" alt="Image" /> 1.9 nM – 48% (agonist)</td>
<td>-</td>
</tr>
<tr>
<td>AM 9280</td>
<td><img src="image2" alt="Image" /> Agonist</td>
<td>Inverse agonist (240%)- No EC&lt;sub&gt;50&lt;/sub&gt;</td>
</tr>
</tbody>
</table>

As seen in *Table 3B.2*, covalent probes were found to be agonists at the CB1 receptor in cAMP assay. AM9280 was found to an inverse agonist. These are preliminary results and compounds are currently being re-tested.

**Experimental Procedure**

6-Bromo-1-(*tert*-butyldiphenylsilyloxy)-hexane (6). To a solution of 6-bromo-hexan-1-ol (5) (5 g, 27.6 mmol) and dry imidazole (4.13 g, 60.7 mmol) in anhydrous THF (55 mL) at 0 °C under an argon atmosphere, was added *tert*-butyldiphenylsilyl chloride (7.9 mL, 30.4 mmol) dropwise. The reaction mixture was stirred for 1.5 hours at 0 °C and then quenched with a saturated aqueous ammonium chloride solution and extracted with diethyl ether. The combined organic extracts were washed with brine, dried (MgSO<sub>4</sub>) and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (5% diethyl ether in hexane) gave 10.2 g (85% yield) of 6.
as a colorless oil.\textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \( \delta \) 7.66 (d, \( J = 7.0 \) Hz, 4H, 2-H, 6-H, Ph), 7.43-7.34 (m, 2H, 4-H, Ph), 3.66 (t, \( J = 6.3 \) Hz, 2H, -CH\textsubscript{2}O-), 3.38 (t, \( J = 6.3 \) Hz, 2H, -CH\textsubscript{2}Br), 1.84 (quintet, \( J = 6.0 \) Hz, 2H, -CH\textsubscript{2}-), 1.55 (quintet, \( J = 6.0 \) Hz, 2H, -CH\textsubscript{2}-), 1.43-1.35 (m, 4H, -CH\textsubscript{2}-), 1.05 (s, 9H, -C(CH\textsubscript{3})\textsubscript{3}); Mass spectrum (ESI) m/z (relative intensity) 421 (M\textsuperscript{+}+H+2, 80), 419 (M\textsuperscript{+}+H, 80), 239 (47), 165 (100), 163 (100). Exact mass (ESI) calculated for C\textsubscript{22}H\textsubscript{32}OBrSi (M\textsuperscript{+}+H), 419.1406; found, 419.1413.

\textbf{[6-\textit{tert}-butyldiphenylsilyloxy]hexyl}triphenylphosphonium bromide (7). A stirred mixture of 6 (5 g, 11.5 mmol) and dried triphenylphosphine (6.0 g, 23.0 mmol) in anhydrous toluene (57 mL) was heated (60-63 °C) for five days under argon. Solvent evaporation and purification by flash column chromatography on silica gel (5-10% methanol in methylene chloride) gave 5.2 g (66% yield) of 7 as a colorless gum. The product was rigorously dried in high vacuo for 6 hours at 50 °C, and used in the next step; \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \( \delta \) 7.86 (m as dd, \( J = 12.5 \) Hz, \( J = 7.5 \) Hz, 6H, 2-H, 6-H, -PPh\textsubscript{3}), 7.77 (m as td, \( J = 7.5 \) Hz, \( J = 1.8 \) Hz, 3H, 4-H, -PPh\textsubscript{3}), 7.69 (m as td, \( J = 7.5 \) Hz, \( J = 4.2 \) Hz, 6H, 3-H, 5-H, -PPh\textsubscript{3}), 7.61(d, \( J = 7.0 \) Hz, 4H, 2-H, 6-H, Ph), 7.42-7.31 (m, 2H, 4-H, Ph), 3.87 (m, 2H, -CH\textsubscript{2}P-), 3.58 (t, \( J = 6.3 \) Hz, 2H, -CH\textsubscript{2}O-), 1.68-1.58 (m, 4H, -CH\textsubscript{2}-), 1.51-1.45 (m, 2H, -CH\textsubscript{2}-), 1.36-1.30 (m, 2H, -CH\textsubscript{2}-), 1.00 (s, 9H, -C(CH\textsubscript{3})\textsubscript{3}); Mass spectrum (ESI) m/z (relative intensity) 602 (M\textsuperscript{+}+H+1-Br, 40) 601 (M\textsuperscript{+}+H-Br, 100). Exact mass (ESI) calculated for C\textsubscript{40}H\textsubscript{46}OSiP (M\textsuperscript{+}+H-Br), 601.3056; found, 601.3052.

\textbf{4-[(\textit{tert}-Butyldiphenylsilyl)oxy]but-1-yne} (9).\textsuperscript{227} The synthesis was carried out as described in reference 227 using 3-butyn-1-ol (8) (5 g, 71.3 mmol), imidazole (10.6 g, 156.8 mmol) and \textit{tert}-butyldiphenylsilyl chloride (21.5 g, 78.3 mmol) and gave 20 g of 9 in 91% yield. \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 500 MHz)\textsuperscript{227}. 262
5-[(tert-Butyldiphenylsilyl)oxy]pent-2-yn-1-ol (10). The synthesis was carried out as described in reference 227 using 9 (18 g, 58.4 mmol), n-BuLi (28.05 mL, 70.13 mmol, 2.5 M solution in hexanes) and (CH₂O)n (10.5 g, 350.6 mmol) and gave 13.4 g of 10 in 68% yield. ¹H NMR (CDCl₃, 500 MHz).

5-(Bromopent-3-ynoxy)-tert-butyl-diphenylsilane (11). The synthesis was carried out as described in reference 227 using 10 (7.34 g, 21.7 mmol) and carbon tetrabromide (7.2 g, 21.7 mmol) and triphenylphosphine (5.7 g, 21.7 mmol) and gave 6.9 g of 11 in 79% yield. ¹H NMR (CDCl₃, 500 MHz).²²⁷

11-[(tert-Butyldiphenylsilyl)oxy]undeca-5,8-diynoic methyl ester (12). The synthesis was carried out as described in reference 227 using Cs₂CO₃ (6.5 g, 19.9 mmol), NaI (2.98 g, 19.9 mmol), CuI (3.8 g, 19.9 mmol), methyl 5-hexynoate (3.01 g, 23.9 mmol) and bromide 11 (8 g, 19.9 mmol) and gave 6.7 g of 12 in 75% yield. ¹H NMR (CDCl₃, 500 MHz).²²⁷

(5Z, 8Z)–11-[(tert-Butyldiphenylsilyl)oxy]undeca-5,8-dienoic methyl ester (13).²²⁷ The synthesis was carried out as described in reference 227 using Ni(OAc)₂ (7.04 g, 28.27 mmol), NaBH₄ (1.26 g, 33.26 mmol), ethylenediamine (2.87 mL), and 12 (7.42 g, 16.6 mmol) and gave 5.86 g of 13 in 78% yield. ¹H NMR (CDCl₃, 500 MHz).²²⁷

(5Z, 8Z)- 11-Hydroxy-undeca-5,8-dienoic methyl ester (14).²²⁷ The synthesis was carried out as described in reference 227 using 17 (5.80 g, 12.9 mmol), tetra-n-butylammonium fluoride (TBAF, 16.9 mL, 16.9 mmol, 1M solution in THF) and gave 2.6 g of 14 in 94% yield. ¹H NMR (CDCl₃, 500 MHz).²²⁷
(5Z, 8Z)-11-Bromo-undeca-5,8-dienoic methyl ester (15). \(^{227}\) The synthesis was carried out as described in reference 227 using 14 (2.59 g, 12.2 mmol), carbon tetrabromide (5.26 g, 15.87 mmol) and triphenylphosphine (4.15 g, 15.87 mmol) and gave 2.85 g of 15 in 85% yield. \(^1\)H NMR (CDCl\(_3\), 500 MHz). \(^{227}\)

(3Z, 6Z)-[10-(methoxycarbonyl)-3,6-decadienyl]triphenylphosphonium bromide (16). \(^{227}\) The synthesis was carried out as described in reference 227 using 15 (1g, 3.63 mmol) and dried triphenylphosphine (1.9 g, 7.26 mmol) and gave 1.3 g of 16 in 96% yield. \(^1\)H NMR (CDCl\(_3\), 500 MHz). \(^{227}\)

(13R, 5Z, 8Z, 11Z)-14-[(tert-Butyldiphenylsilyl)oxy]-13-methyl-tetradeca-5,8,11-trienoic methyl ester (17). \(^{227}\) The synthesis was carried out as described in reference 227 using 16 (1.31 g, 2.44 mmol), potassium bis(trimethylsilyl)amide (2.32 mL mg, 2.32 mmol, 1.0 M in toluene) and aldehyde 3 (400 mg, 1.02 mmol) and gave 0.39 g of 17 in 63% yield. \(^1\)H NMR (CDCl\(_3\), 500 MHz). \(^{227}\)

(13R, 5Z, 8Z, 11Z)-14-hydroxy-13-methyl-tetradeca-5,8,11-trienoic methyl ester (18). \(^{227}\) The synthesis was carried out as described in reference 227 using 17 (5300 mg, 1.05 mmol) and TBAF (1.36 mL, 1.36 mmol, 1M solution in THF) and gave 238 mg of 18 in 85% yield. \(^1\)H NMR (CDCl\(_3\), 500 MHz). \(^{227}\)

(13R, 5Z, 8Z, 11Z)-13-methyl-14-oxo-tetradeca-5,8,11-trienoic methyl ester (19). \(^{227}\) The synthesis was carried out as described in reference 227 using alcohol 25 (100 mg, 0.376 mmol), Dess-Martin Periodane (DMP) (382 mg, 0.902 mmol) and gave sensitive crude product 19 which was used in next step immediately. \(^1\)H NMR (CDCl\(_3\), 500 MHz). \(^{227}\)
(13R, 5Z, 8Z, 11Z)-13-methyl-20-[(tert-Butyldiphenylsilyl)oxy]-eicosa-5,8,11,14-tetraenoic methyl ester (20). To a stirred solution of 7 (1.75 g, 2.57 mmol) in dry THF (9 mL) at 0 °C under an argon atmosphere, was added potassium bis(trimethylsilyl)amide (2.5 mL, 2.5 mmol, 1.0 M solution in THF). The mixture was stirred for 30 min at 0 °C to ensure complete formation of the orange ylide and then it was cooled to -78 °C. A solution of crude aldehyde 19 in dry THF (4 mL) was added dropwise, the reaction mixture was stirred for 60 min at -78 °C and then it was quenched by the addition of saturated aqueous sodium bicarbonate. The mixture was warmed to room temperature extracted with diethyl ether and the combined organic extracts were washed with brine, dried (MgSO₄) and concentrated in vacuo. Purification by flash column chromatography on silica gel (2-8% diethyl ether in hexane) gave 130 mg (43% yield from alcohol 18) of ester 20 as a colorless oil. [α]D²⁶.⁵ = -2227.87° (c = 0.163 g/100 mL in CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 7.66 (d, J = 7.0 Hz, 4H, 2-H, 6-H, Ph), 7.43-7.34 (m, 2H, 4-H, Ph), 5.42-5.31 (m, 4H, 5-H, 6-H, 8-H, 9-H), 5.30-5.20 (m, 4H, 11-H, 12-H, 14-H, 15-H), 3.68-3.63 (t and s overlapping, 5H, 20-H and –OCOCH₃, especially t, J = 6.0 Hz, 20-H and 3.65, s, -OCOCH₃), 3.47 (ddq as sextet, J = 7.5 Hz, 1H, 13-H), 2.88-2.75 (m, 4H, 7-H, 10-H), 2.31(t, J = 7.5 Hz, 2H, 2-H), 2.12-1.99 (dt and bd as m, 4H, 4-H and 16-H), 1.71 (quintet, J = 7.5 Hz, 2H, 3-H), 1.58 (quintet, J = 7.0 Hz, 2H, 17-H), 1.39-1.30 (m, 4H, 18-H, 19-H), 1.04 (s, 9H, -C(CH₃)₃), 1.01 (d, J = 6.5 Hz, 3H, >CH-CH₃); Mass spectrum (ESI) m/z (relative intensity) 610 (M⁺+H+Na, 10), 588 (M⁺+H+1, 47), 587 (M⁺+H, 100). Exact mass (ESI) calculated for C₃₈H₅₅O₃Si (M⁺+H), 587.3920; found, 587.3915.
(13R, 5Z, 8Z, 11Z)-13-methyl-20-Hydroxy-eicosa-5,11,14-tetraenoic methyl ester (21). To a stirred solution of 20 (127 mg, 0.216 mmol) in dry THF (5 mL), under an argon atmosphere at 0 °C, was added TBAF (0.3 mL, 0.3 mmol, 1M solution in THF) dropwise. Stirring was continued for 10 min at 0 °C and for 2.5 hours at room temperature. The reaction mixture was quenched with a saturated aqueous NH₄Cl solution at 0 °C and extracted with AcOEt. The combined organic extracts were washed with brine, dried (MgSO₄) and concentrated under reduced pressure at 37 °C. The crude oil was purified by flash column chromatography on silica gel (35% ethyl acetate in hexane) to afford 21 (64 mg, 85% yield) as a colorless oil. [α]D₂⁵ = 790.53º (c = 0.196 g/100 mL in CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 5.43-5.32 (m, 4H, 5-H, 6-H, 8-H, 9-H), 5.30-5.20 (m, 4H, 11-H, 12-H, 14-H, 15-H), 3.67 (s, 3H, -OCOCH₃), 3.64 (t, J = 6.5 Hz, 2H, 2-H), 3.40 (ddq as sextet, J = 7.5 Hz, 1H, 13-H), 2.88-2.78 (m, 4H, 7-H, 10-H), 2.33 (t, J = 7.5 Hz, 2H, 2-H), 2.15-2.07 (dt and bdt as m, 4H, 4-H and 16-H), 1.71 (quintet, J = 7.5 Hz, 2H, 3-H), 1.58 (quintet, J = 7.0 Hz, 2H, 17-H), 1.44-1.36 (m, 4H, 18-H, 19-H), 1.01 (d, J = 6.5 Hz, 3H, >CH-CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 174.23 (>C=O), 135.11 (-CH=), 134.53 (-CH=), 129.03 (-CH=), 128.96 (-CH=), 128.44 (-CH=), 128.24 (-CH=), 127.98 (-CH=), 125.78 (-CH=), 63.06, 51.63, 35.57, 32.83, 30.62, 29.66, 27.59, 26.66, 25.95, 25.73, 24.88, 22.12; Mass spectrum (ESI) m/z (relative intensity) 371 (33), 350 (M⁺+H+1, 23), 349 (M⁺+H, 100), 331 (M⁺+H–H₂O, 23). Exact mass (ESI) calculated for C₂₂H₃₇O₃ (M⁺+H), 349.2743; found, 349.2742.

(13R, 5Z, 8Z, 11Z)-13-methyl-20-Azido-eicosa-5,8,11,14-tetraenoic methyl ester (22). To a stirred solution of 21 (62 mg, 0.178 mmol) in 5 mL DMF was added DBU (0.1.06 mL, 0.712 mmol) and DPPA (0.15 mL, 0.712 mmol) at 60 °C. The reaction was then
heated to 120 °C and stirred for 2 hours. The reaction mixture was quenched with water and diluted with diethyl ether. The combined organic extracts were washed with brine, dried (MgSO₄) and concentrated under reduced pressure at 33 °C. The crude oil was purified by flash column chromatography on silica gel (10% ethyl acetate in hexane) to afford 22 (47 mg, 71% yield) as a colorless oil. \([\alpha]_D^{25.7} = -4467.63^\circ \ (c = 0.06 \text{ g/100 mL in CHCl}_3)\); \(^1\ce{H} \text{NMR (500 MHz, CDCl}_3\) \(\delta 5.43-5.32 \ (m, 4\text{H, 5-H, 6-H, 8-H, 9-H}), 5.30-5.20 \ (m, 4\text{H, 11-H, 12-H, 14-H, 15-H}), 3.67 \ (s, 3\text{H, -OCOCH}_3), 3.46 \ (ddq as sextet, \(J = 7.5\) Hz, 1\text{H, 13-H}), 3.26 \ (t, \(J = 6.5\) Hz, 2\text{H, 20-H}), 2.88-2.78 \ (m, 4\text{H, 7-H, 10-H}), \ 2.33 \ (t, \(J = 7.5\) Hz, 2\text{H, 2-H}), 2.15-2.07 \ (dt and bdt as m, 4\text{H, 4-H and 16-H}), 1.71 \ (quintet, \(J = 7.5\) Hz, 2\text{H, 3-H}), 1.58 \ (quintet, \(J = 7.0\) Hz, 2\text{H, 17-H}), 1.44-1.36 \ (m, 4\text{H, 18-H, 19-H}), 1.01 \ (d, \(J = 6.5\) Hz, 3\text{H, >CH-CH}_3); \ Mass\ spectrum\ (ESI)\ \text{m/z (relative intensity) 374 (M}^+\text{H, 28), 347 (M}^+\text{H+1-N}_2, \ 24), 346 (M}^+\text{H-N}_2, \ 100). \) Exact mass (ESI) calculated for C\(\text{22H}_{36}\text{N}_3\text{O}_2\ (M}^+\text{H), 374.2808; }\) found, 374.2809.

**\(13\text{S, 5Z, 8Z, 11Z, 14Z}\)-13-methyl-20-Azido-eicosa-5,8,11,14-tetraenoic acid (23).** To a stirred solution of 22 (13 mg, 0.035 mmol) in dry THF (1 mL) at room temperature, under an argon atmosphere, was added 1 M aqueous LiOH solution (0.2 mL). Stirring was continued for 24 h, and then the reaction mixture was acidified with 5% HCl to pH 3, and lipophilic products were extracted with Et₂O. The combined organic extracts were washed with brine and dried (MgSO₄). Solvent evaporation under reduced pressure at 37-39 °C gave pure acid 23 (11 mg, 88% yield) as a colorless oil which was used in the next step without further purification. \([\alpha]_D^{25.4} = -949.38^\circ \ (c = 0.117 \text{ g/100 mL in CHCl}_3)\); \(^1\ce{H} \text{NMR (500 MHz, CDCl}_3\) \(\delta 5.43-5.32 \ (m, 4\text{H, 5-H, 6-H, 8-H, 9-H}), 5.30-5.20 \ (m, 4\text{H, 11-H, 12-H, 14-H, 15-H}), 3.46 \ (ddq as sextet, \(J = 7.5\) Hz, 1\text{H, 13-H}), 3.26 \ (t, \(J = 6.5\) Hz, 2H,
(13S, 5Z, 8Z, 11Z, 14Z)-13-methyl-20-Azido-eicosa-5,8,11,14-tetraenoic acid Cyclopropylamide (24). A mixture of acid 23 (11 mg, 0.031 mmol), and fresh carbonyldiimidazole (14 mg, 0.088 mmol) in dry THF (1 mL) at room temperature under an argon atmosphere, was stirred for 2 hours and then cyclopropylamine (0.03 mL, 0.44 mmol) was added. The reaction mixture was stirred for 2 hours and then diluted with water and ethyl acetate. The organic phase was separated and the aqueous phase extracted with AcOEt. The combined organic layer was washed with brine, dried (MgSO₄) and concentrated in vacuo. The crude product obtained after work up was purified by flash column chromatography on silica gel (59:40:1 ethylacetate: hexane: MeOH), and gave 9 mg (74% yield) of 24 as a colorless oil. [α]D²⁵ = -2490.68° (c = 0.04 g/100 mL in CHCl₃). IR (neat) 3276 (br, OH), 2927, 2093 (s, N₃), 1645, 1541, 1454, 1261, 720 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 5.55 (br s, 1H, -NH), 5.43-5.32 (m, 4H, 5-H, 6-H, 8-H, 9-H), 5.30-5.20 (m, 4H, 11-H, 12-H, 14-H, 15-H), 3.46 (ddq as sextet, J = 7.5 Hz, 1H, 13-H), 3.26 (t, J = 6.5 Hz, 2H, 20-H), 2.88-2.78 (m, 4H, 7-H, 10-H), 2.72-2.66 (m, 1H, -NH-CH₃), 2.14-2.07 (m, 6H, 2-H, 4-H and 16-H), 1.71 (quintet, J = 7.5 Hz, 2H, 3-H), 1.60 (br quintet, J = 7.0 Hz, 2H, 17-H), 1.42-1.34 (m, 4H, 18-H, 19-H), 1.01 (d, J = 6.5 Hz, 3H, >CH-CH₃), 0.79-0.73 (m, 2H, cyclopropyl ring), 0.50-0.45 (m, 2H, cyclopropyl ring); ¹³C
NMR (100 MHz, CDCl$_3$) $\delta$ 174.13 (>C=O), 134.92 (-CH=), 134.60 (-CH=), 129.16 (-CH=), 128.69 (-CH=), 128.30 (-CH=), 128.17 (-CH=), 127.62 (-CH=), 125.68 (-CH=), 51.42, 35.85, 30.49, 29.68, 29.24, 28.78, 27.32, 26.61, 26.41, 25.83, 25.60, 25.42, 22.54, 21.99 (C$_{13}$-Me), 6.61; Mass spectrum (ESI) m/z (relative intensity) 400 (M$^+$+H+1, 27), 399 (M$^+$+H, 100), 372 (M$^+$+H+1-N$_2$, 20), 371 (M$^+$+H-N$_2$, 71). Exact mass (ESI) calculated for C$_{24}$H$_{39}$N$_4$O (M$^+$), 399.3124; found, 399.3122.

(13S, 5Z, 8Z, 11Z, 14Z)-13-methyl-20-Isothiocyanato-eicosa-5,8,11,14-tetraenoic acid Cyclopropylamide (25). To a solution of 24 (15 mg, 0.037 mmol) in anhydrous THF (1 mL) was added triphenyl phsophine (29 mg, 0.111 mmol) and carbon disulfide (26.6 mg, 0.37 mmol) and the reaction mixture was stirred at room temperature for 48 hours. After completion, the reaction mixture was concentrated under pressure and purified by flash column chromatography on silica gel (59:40:1 ethylacetate: hexane: MeOH) and gave 14 mg of 25 as a viscous oil in 96% yield. $[\alpha]_D^{25} = 171.27^\circ$ (c = 0.08 g/100 mL in CHCl$_3$); IR (neat) 3273, 2926, 2091 (s, NCS), 1643, 1536, 1453, 1347, 1021 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 5.55 (br s, 1H, -NH), 5.43-5.32 (m, 4H, 5-H, 6-H, 8-H, 9-H), 5.30-5.20 (m, 4H, 11-H, 12-H, 14-H, 15-H), 3.51 (t, $J$ = 6.5 Hz, 2H, 20-H), 3.46 (ddq as sextet, $J$ = 7.5 Hz, 1H, 13-H), 2.88-2.78 (m, 4H, 7-H, 10-H), 2.72-2.66 (m, 1H, -NH-CH$<$), 2.14-2.07 (m, 6H, 2-H, 4-H and 16-H), 1.71 (quintet, $J$ = 7.5 Hz, 2H, 3-H), 1.60 (br quintet, $J$ = 7.0 Hz, 2H, 17-H), 1.42-1.34 (m, 4H, 18-H, 19-H), 1.01 (d, $J$ = 6.5 Hz, 3H, >CH-CH$_3$), 0.79-0.73 (m, 2H, cyclopropyl ring), 0.50-0.45 (m, 2H, cyclopropyl ring); Mass spectrum (ESI) m/z (relative intensity) 416 (M$^+$+H+1, 28), 415 (M$^+$+H, 100), 358 (8). Exact mass (ESI) calculated for C$_{25}$H$_{39}$N$_2$OS (M$^+$+H), 413.3056; found, 413.3043.
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Appendix 1

$^1$H NMR spectrum of compound 68 in CDCl$_3$ solution
$^{13}$C NMR, COSY, HSQC and NOESY spectra of compound 68 in CDCl$_3$ solutions.
Appendix- 2

$^1$H NMR spectrum of compound 70 in CDCl$_3$ solution
$^{13}$C NMR, COSY, HSQC and HMBC spectra of compound 70 in CDCl$_3$ solutions.