Saturated Cannabinoids: Update on synthesis strategies and biological studies of these emerging cannabinoid analogs.

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ABSTRACT

Natural and non-natural hexahydrocannabinols (HHC) were first described in 1940 by Adam and in late 2021 arose on the drug market in the United States and in some European countries. A background on the discovery, synthesis, and pharmacology studies of hydrogenated and saturated cannabinoids is described. This is harmonized with a summary and comparison of the cannabinoid receptor affinities of various classical, hybrid, and non-classical saturated cannabinoids. A discussion of structure-activity relationships with the four different pharmacophores found in the cannabinoid scaffold is added to this review. According to laboratory studies *in vitro*, and in several animal species *in vivo*, HHC is reported to have broadly similar effects to Δ9-tetrahydrocannabinol (Δ9-THC), the main psychoactive substance in cannabis, as demonstrated both *in vitro* and in several animal species *in vivo*. However, the effects of HHC treatment have not been studied in humans, and thus a biological profile has not been established.

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INTRODUCTION

Cannabis and cannabis substituents have been used in medicine within the United States for centuries, and were first described in the *United States Pharmacopeia* in late 1850 [1]. Due to legal ramifications and political duress, cannabis was dropped from the *United States Pharmacopeia* in the 1940s and labeled a controlled substance in the 1970s. These bureaucratic changes have limited advancements within the field of cannabinoid chemistry [2]. The first cannabinoid was not elucidated until the 1940s, when cannabidiol (CBD) was identified, followed by cannabinol (CBN) [3]. As cannabinoid research becomes accessible again, novel and rare cannabinoids have been elucidated through modern analytical techniques, garnering attention and popularity. However, knowledge about these cannabinoids remains limited to non-existent. Cannabinoid research as a whole has primarily focused on the safety and efficacy of CBD and THC (Tetrahydrocannabinol) for specific ailments and has largely ignored the hundreds of other currently-identified cannabinoids that *Cannabis sativa* biosynthesizes in various concentrations [1-4]. The primary focus of cannabinoid chemistry and the multitude of studies that have been performed are mostly on CBD, and THC evaluating their safety and effects on certain ailments including but not limited to inflammation and anti-proliferative/pro-apoptotic effects within the body [5].

Of the limited studies on cannabinoid derivatives minute amounts of data are produced on saturated cannabinoid derivatives [6,7]. Several studies that have been published focused on hydroxyl derivatives of hydrogenated THC such as 9-Nor-9β-hydroxyhexahydrocannabinol (9-Nor-9β-HHC) or 9-Hydroxyhexahydrocannabinol (9-OH-HHC) or 11-Hydroxyhexahydrocannabinol (11-OH-HHC and 7-OH-HHC), which are identified as metabolites of THC. Commonly confused with HHC (Hexahydrocannabinol) that is in research and consumer markets, due to the nomenclature used, no detailed information is focused on the hydrogenated

derivatives of various cannabinoids such as CBD, THC, THCV (Tetrahydrocannabivarin), and CBDV (Cannabidivarin). As the popularity of cannabinoids skyrockets so does the need for markets to continually update with derivatives that are homologous to THC, CBD, CBDV, and THCV.

Since its discovery in 1940, through catalytic hydrogenation of THC and cannabinoid derivatives, hydrogenated cannabinoids were synthesized, only H_4CBD and HHC were of interest as they were the hydrogenated scaffolds of THC and CBD [8].

The rediscovery of these hydrogenated derivatives is pushing into the medicinal properties that they might share with their parental counterparts. In an earlier study produced by Gallily et al. in 2006 [9], hydrogenated cannabinoid derivatives of CBD and the CBD-DM (Cannabidiol-Dimethylheptyl) scaffolds, which included a mixture of H_4CBD diastereomers, determined that diastereomers of H_4CBD bound to the CB_1 receptor with great affinity, as well the anti-inflammatory capacity of H_4CBD were reported [9]. While minute preliminary studies on the mechanism and the binding affinities of H_4CBD have been produced, no in-depth toxicological profile has been created for H_4CBD and HHC, aside from pre-clinical *in vitro* data that has been published to determine general consumption safety and characterization [10,11].

Against this backdrop, we embark on a comprehensive and critical review, drawing upon meticulously selected published research obtained from esteemed sources such as PubMed, Scopus databases, official international organizations' websites, and others covering from 1940 until 2023. Our intention is to shed light on the present clinical evidence concerning not only hydrogenated derivatives of THC and CBD but also the other captivating, saturated cannabinoids discovered within the *Cannabis Sativa* plant. Additionally, we aim to provide critical insights into the sufficiency of this evidence in supporting their synthesis, characterization, and possible utilization

as medicinal substances. By undertaking this endeavor, we hope to contribute to the broader understanding of saturated cannabinoids and their potential therapeutic applications, while addressing the need for further research in this promising field.

HYDROGENATED TRICYCLIC HEXAHYDROCANNABINOL HOMOLOGS

Since its discovery in 1964, tetrahydrocannabinol (THC) and related analogs such as cannabidiol (CBD), natural and non-natural saturated cannabinoids have caught the attention of research groups all over the world [12-15]. Hexahydrocannbinol (HHC) is a newer cannabinoid to hit the cannabis consumer market, but it is not exactly a new cannabinoid. HHC was discovered in 1944 by the American chemist Roger Adams [8] while explored with the hydrogenation reaction with the THC molecule in marijuana.

Also, (9*R*)-6,6,9-trimethyl-3-pentyl-6a,7,8,9,10,10a-hexahydro-6*H*-benzo[c]chromen-1-ol and other minor oxygenated cannabinoids have been identified as trace components in *Cannabis sativa* plants. They are formed as degenerative byproducts as the THC breaks down. [16] (Figure 1a). In this sense, ElSohly [17] isolated and characterized four hexahydrocannabinols from a high potency *Cannabis sativa L* namely (6a*R*,9*S*,10a*R*)-6,6,9-trimethyl-3-pentyl-6a,7,8,9,10,10a-hexahydro-6*H*-benzo[*c*]chromene-1,9-diol (**2**), (6a*R*,9*R*,10a*R*)-1,9-dihydroxy-6,6,9-trimethyl-3-pentyl-8,9,10,10a-tetrahydro-6*H*-benzo[*c*]chromen-7(6a*H*)-one (**3**), (6a*R*,9*S*,10*S*,10a*R*)-6,6,9-trimethyl-3-pentyl-6a,7,8,9,10,10a-hexahydro-6*H*-benzo[*c*]chromene-1,9,10-triol (**4**), (6a*R*,9*R*,10*S*,10a*R*)-6,6,9-trimethyl-3-pentyl-6a,7,8,9,10,10a-hexahydro-6*H*-benzo[*c*]chromene-1,10-diol (**5**), and (6a*R*,9*S*,10a*S*)-6,6,9-trimethyl-3-pentyl-6a,7,8,9,10,10a-hexahydro-6*H*-benzo[*c*]chromene-1,10a-diol (**6**). (Figure 1b)

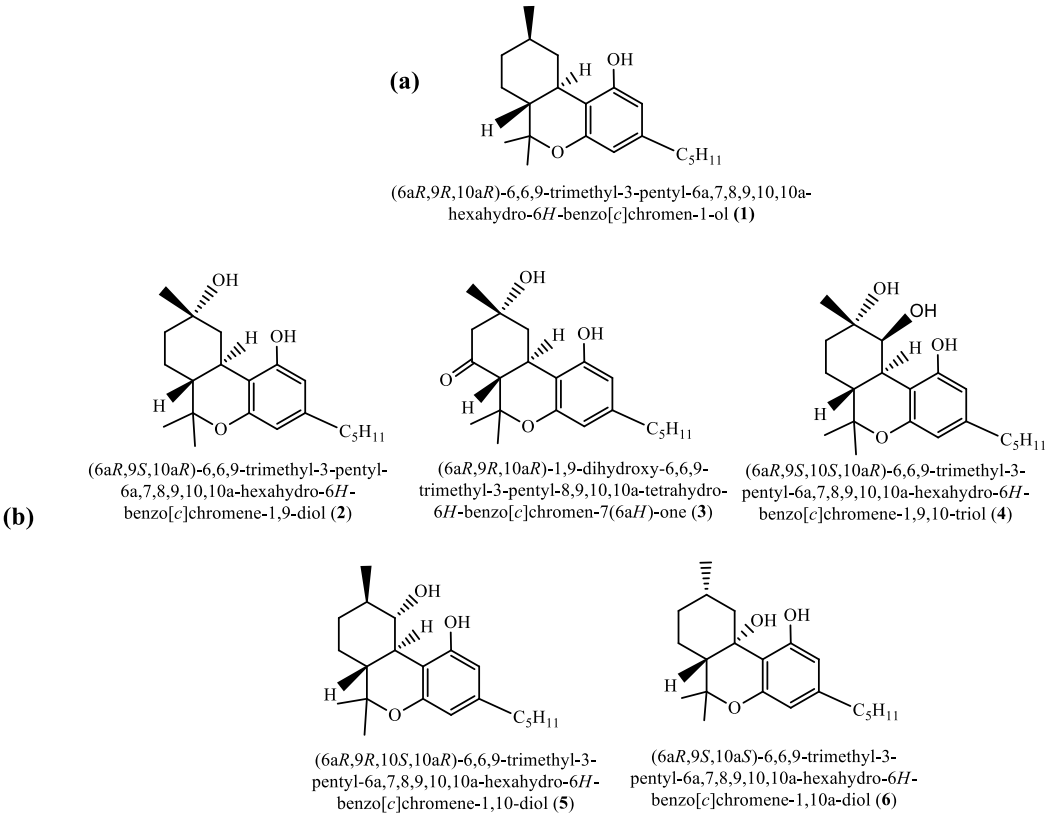
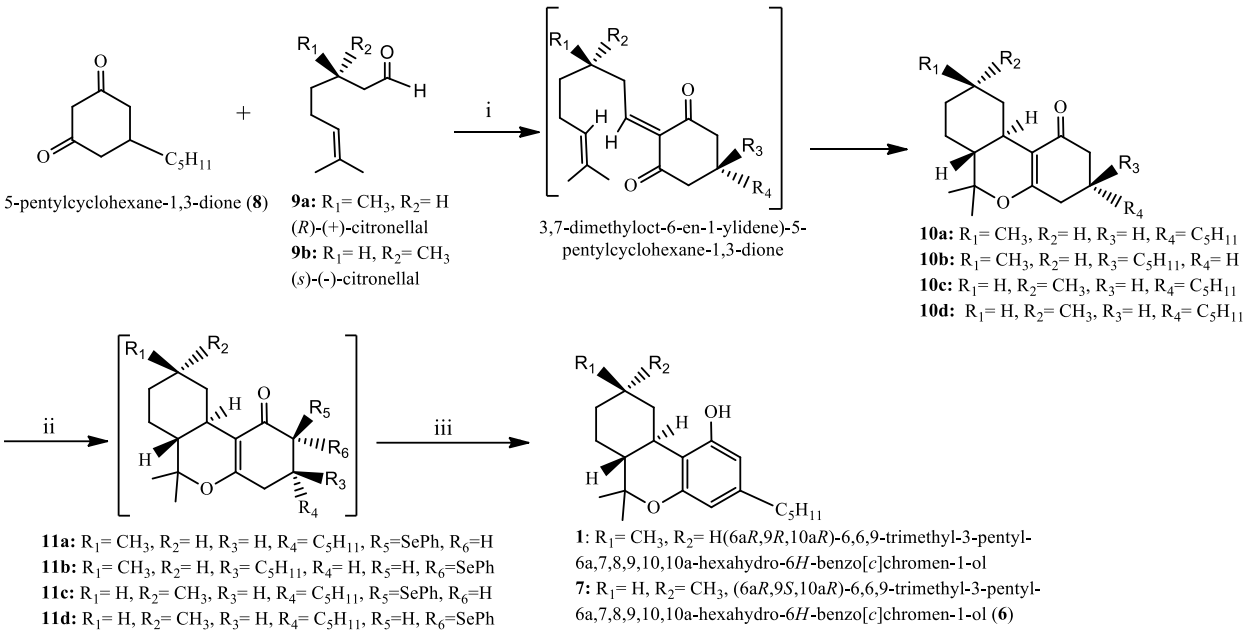


Figure 1: Hexahydrocannabinols isolated from *Cannabis sativa* plants

Synthesis of hexahydrocannabinol and its analogs

Hexahydrocannabinols have been achieved in two different approaches: total synthesis or partial synthesis via hydrogenation of cannabidiol analogues. The first total stereoselective synthesis of natural (6a*R*,9*R*,10a*R*)-6,6,9-trimethyl-3-pentyl-6a,7,8,9,10,10a-hexahydro-6*H*-benzo[*c*]chromen-1-ol (**1**) and its unnatural 6a*R*,9*S*,10a*R*)-6,6,9-trimethyl-3-pentyl-6a,7,8,9,10,10a-hexahydro-6*H*-benzo[*c*]chromen-1-ol (**7**) diastereomer was developed by Tietze [18] starting with 5-pentylcyclohexane-1,3-dione (**8**) and optically pure citronellal (**9a**, **9b**) via a intramolecular Diels-Alder reaction and aldol condensation followed by aromatization and elimination along a two-step reaction. (Scheme 1).



i: 100ºC in dimethylformamide (DMF); **ii**: Lithium *N*,*N* diisopropylamide, benzeneselenenyl chloride; **iii:** 3-chlorobenzoperoxoic acid, -40 ºC to r.t.

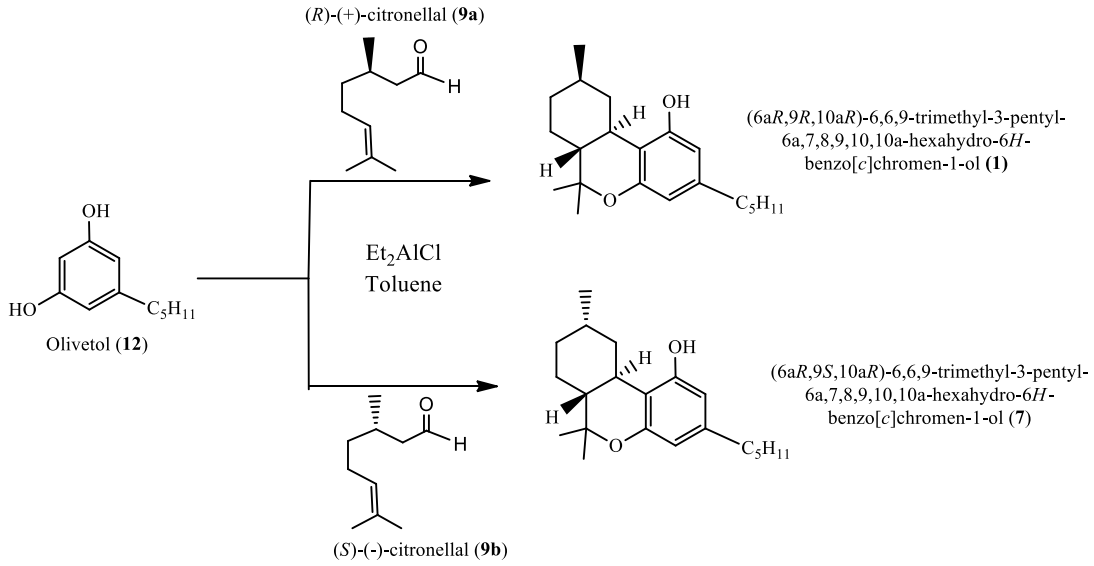
Scheme 1: Total synthesis of (9*R*) hexahydrocannabinol (**1**) and (9*S)* hexahydrocannabinol (**6**) developed by Tietze [18]

The condensation between **8** and **9** generates the adduct 3,7-dimethyloct-6-en-1-ylidene)-5-pentyllcyclohexane-1,3-dione which upon intramolecular cycloaddition affords the substituted 1*H*-benzochromen core (**10a-d**). The chiral center of citronellal *(R*- or *S*- epimers) makes the cycloaddition reaction stereo-controlled. The two epimers are obtained due to the low stereoselectivity of the aldol condensation. However, this does not affect the synthesis of hexahydrocannabinol **1** and **7**, since compounds **10a** and **10b** lose chirality in the subsequent aromatization step.

The aromatization step was carried out using lithium *N*,*N* diisopropylamide to deprotonate the mixture **10a**/**10b** or **10c**/**10d** and benzeneselenenyl chloride to afford compounds **11a**/**11b** or **11c**/**11d**. 3-chlorobenzoperoxoic acid was used for the oxidation reaction to obtain compounds **1**

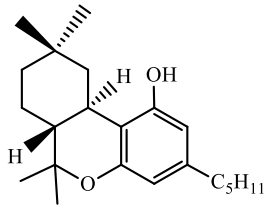
and **7** with 56% and 40% overall yield, respectively. Aromatization and oxidation reactions were achieved in one-pot reaction without isolation of the selenide compounds (**11a-d**).

Other methodology to synthesize 6a*R*,9*R*,10a*R*)-6,6,9-trimethyl-3-pentyl-6a,7,8,9,10,10a-hexahydro-6*H*-benzo[c]chromen-1-ol (**1**) and 6a*R*,9*S*,10a*R*)-6,6,9-trimethyl-3-pentyl-6a,7,8,9,10,10a-hexahydro-6*H*-benzo[c]chromen-1-ol (**7**) was reported by Cornia [19] using diethylaluminium chloride (Et_2AlCl) to mediate the Knoevenagel condensation of olivetol (**12**) with (*R*)-(+)- or (*S*)-(-)-citronellal (**9a, 9b**) (Scheme 3). The reaction was performed with different amounts of Et_2AlCl and the best result was obtained with 0.5 equivalent of Et_2AlCl refluxing in toluene to produce **1a** and **7a** in 57% and 69 % isolated yield respectively, after flash chromatography.

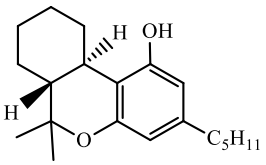


Scheme 2: Total synthesis of (9*R*) hexahydrocannabinol (**1**) and (9*S)* hexahydrocannabinol (**7**) developed by Cornia [19]

Using this procedure Anderson [20] synthesized HHC homologues such as one lacking the C-11 methyl group (11-nor-HHC) and the C-9 geminal dimethyl analogue of HHC (Figure 2).



(6a*R*,10a*R*)-6,6,9,9-tetramethyl-3-pentyl-6a,7,8,9,10,10a-hexahydro-6*H*-benzo[*c*]chromen-1-ol (**13**)



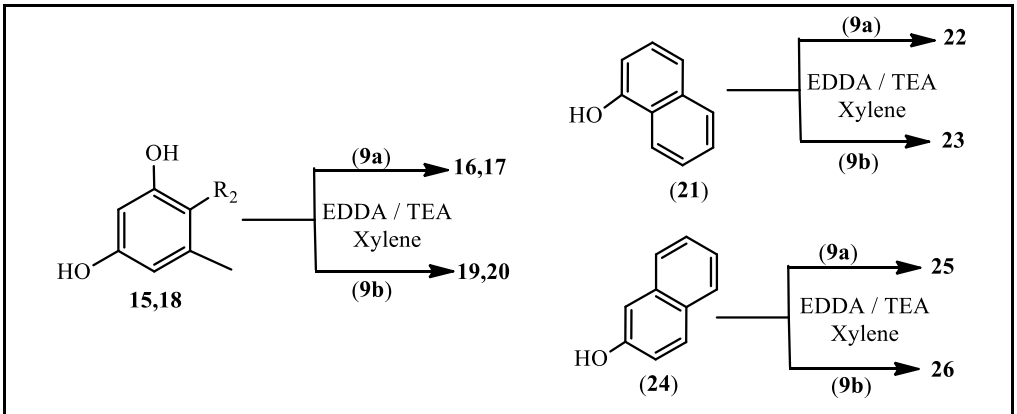
(6a*R*,10a*R*)-6,6-dimethyl-3-pentyl-6a,7,8,9,10,10a-hexahydro-6*H*-benzo[*c*]chromen-1-ol (**14**)

Figure 2: HHC homologues synthesized by Anderson [20]

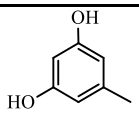
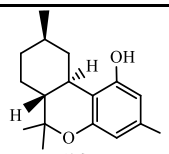
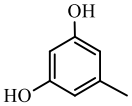
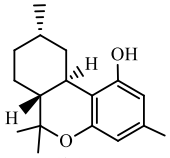
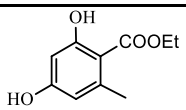
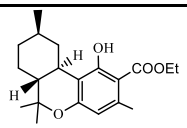
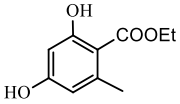
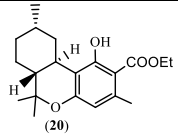
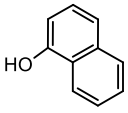
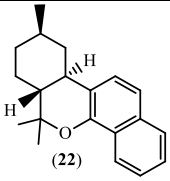
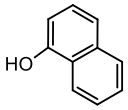
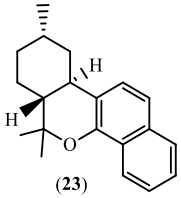
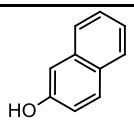
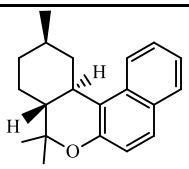
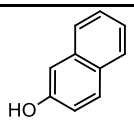
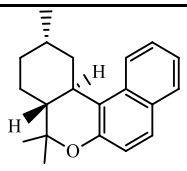
Lee [21] employed the same hetero Diels–Alder approach, for the synthesis (6a*R*,9*R*,10a*R*)-6,6,9-trimethyl-3-pentyl-6a,7,8,9,10,10a-hexahydro-6*H*-benzo[c]chromen-1-ol (**1**) and (6a*R*,9*S*,10a*R*)-6,6,9-trimethyl-3-pentyl-6a,7,8,9,10,10a-hexahydro-6*H*-benzo[c]chromen-1-ol (**7**), but he used ethylenediamine diacetate (EDDA) (20 mol %) as catalyst in presence of triethylamine (TEA) instead of Et_2AlCl. The reaction mixture was refluxed in xylene for 24 h to afford the natural (9*R*)-HHC (**1**) and **(**9*S*)-HHC (**7**) with 72% and 73% yield respectively.

Lee [21] extended the method to synthesize a wide group of hexahydrocannabinol derivatives using several types of resorcinols and naphthols. As seen in table 1, the cycloaddition reactions were accomplished with resorcinols, including ester groups on the benzene ring and with 1- and 2-naphthol.

Table 1: Results of the reactions of resorcinols and naphthols with citronellal[a]

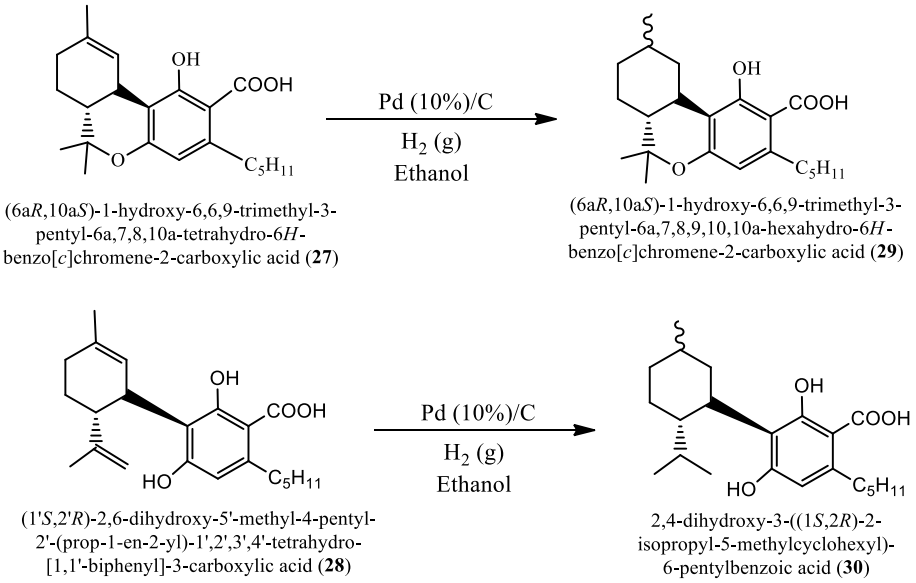


Entry	Starting Material	Citronellal	Product	Yield (%)

1	 (15)	9a	 (16)	68
2	 (15)	9b	 (17)	70
3	 (18)	9a	 (19)	87
4	 (18)	9b	 (20)	86
5	 (21)	9a	 (22)	92
6	 (21)	9b	 (23)	90
7	 (24)	9a	 (25)	72
8	 (24)	9b	 (26)	75

[a] Reaction conditions: starting material (1.0 mmol), citronellal (1.5 mmol), EDDA (20 % mol), TEA (0.2 % mol) in xylene. [21]

The most common partial synthesis of HHC methodology is through the hydrogenation reaction of Δ^9THC or its isomers Δ^8THC and Δ^{10}THC. Scialdone [22] reported the hydrogenation of cannabis oil produced by extraction of the Cannabis sativa. The cannabis extract enriched with (6a*R*,10a*S*)-1-hydroxy-6,6,9-trimethyl-3-pentyl-6a,7,8,10a-tetrahydro-6*H*-benzo[*c*]chromene-2-carboxylic acid (THCA-**27**) or (1'*S*,2'*R*)-2,6-dihydroxy-5'-methyl-4-pentyl-2'-(prop-1-en-2-yl)-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-3-carboxylic acid (CBDA-**28**) was dissolved in absolute ethanol and treated with 10% Pd/C and hydrogen gas at room temperature and atmospheric pressure stirring overnight. The racemic mixture of diastereomers (**29**) and (**30**) was obtained with 88% or 86% of yield, respectively (Scheme 3).



(6a*R*,10a*S*)-1-hydroxy-6,6,9-trimethyl-3-pentyl-6a,7,8,10a-tetrahydro-6*H*-benzo[*c*]chromene-2-carboxylic acid (**27**)

(6a*R*,10a*S*)-1-hydroxy-6,6,9-trimethyl-3-pentyl-6a,7,8,9,10,10a-hexahydro-6*H*-benzo[*c*]chromene-2-carboxylic acid (**29**)

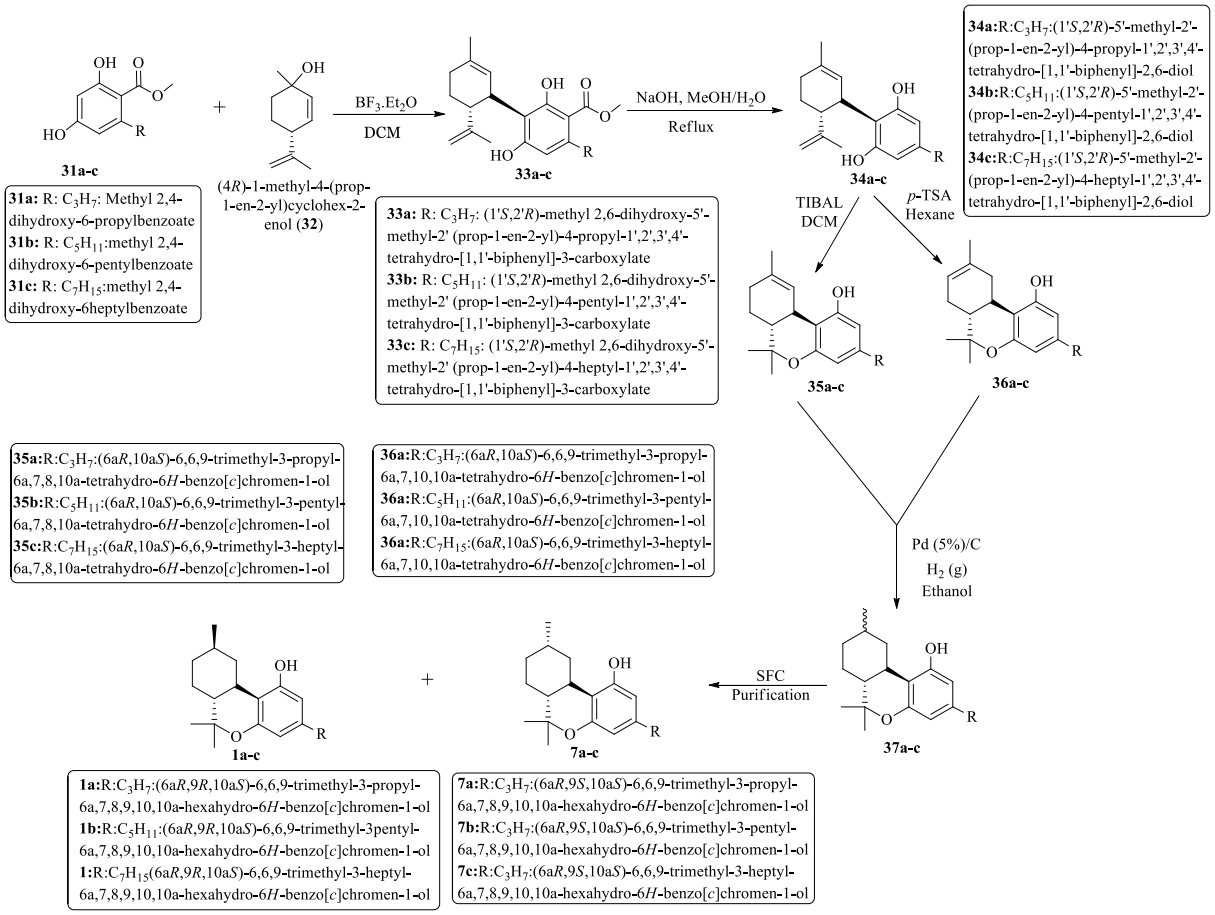
(1'*S*,2'*R*)-2,6-dihydroxy-5'-methyl-4-pentyl-2'-(prop-1-en-2-yl)-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-3-carboxylic acid (**28**)

2,4-dihydroxy-3-((1*S*,2*R*)-2-isopropyl-5-methylcyclohexyl)-6-pentylbenzoic acid (**30**)

Scheme 3: Hydrogenation reaction of HHCA-**27** and CBDA-**28**.

Another example for the synthesis of HHC derivatives was developed by Cruces et al. [10,23] starting with carboxymethyl ester of olivetol analogues. As shown in scheme 4, methyl 2,4-dihydroxy-6-alkylbenzoate analogues (**31a-c**) was coupled with (4*R*)-1-methyl-4-(prop-1-en-2-yl)cyclohex-2-enol (**32**) using boron trifluoride–etherate as catalyst and dichloromethane as solvent to obtain the (1'*S*,2'*R*) -methyl 2,6-dihydroxy-5'-methyl-4-alkyl-2'-(prop-1-en-2-yl)-

1',2',3',4'-tetrahydro-[1,1'-biphenyl]-3-carboxylate derivatives (**33a-c**). It was followed by the hydrolysis reaction with sodium hydroxide in methanol:H_2O to afford (1'*S*,2'*R*)-5'-methyl-4-alkyl-2'-(prop-1-en-2-yl)-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-2,6-diol analogues (**34a-c**). The cyclization reaction was carried out using triisobutylaluminum (TIBAL) as Lewis's acid catalyst to attain Δ^9-THC- **35a-c** or using *p*-Toluenesulfonic acid (*p*-TSA) as protic acid catalyst to afford Δ^8-THC- **36a-c**. Δ^9-THC and Δ^8-THC were hydrogenated using 5 % Pd/C in ethanol to yield 9*S* and 9*R*-(6a*R*,10a*S*)-6,6,9-trimethyl-3-alkyl-6a,7,8,9,10,10a-hexahydro-6*H*-benzo[c]chromen-1-ol isomers in a ratio 3 : 7 (**37a-c**) with 92 % of yield. The pure diastereomers, (6a*R*,9*R*,10a*S*)-6,6,9-trimethyl-3-alkyl-6a,7,8,9,10,10a-hexahydro-6*H*-benzo[c]chromen-1-ol (**1a-c**) (6a*R*,9*S*,10a*S*)-6,6,9-trimethyl-3-alkyl-6a,7,8,9,10,10a-hexahydro-6*H*-benzo[c]chromen-1-ol (**7a-c**) were separated by supercritical fluid chromatography (SFC) using a chiral column. [10] It has been observed that the catalytic hydrogenation of Δ^9-THC using Adam's catalyst affords the (9*S*)-HHC and (9*R*)-HHC isomers in approximate a 1:7 ratio [24].



Scheme 4: Synthetic pathway to obtain 9*R*-HHC-**1a-c** and 9*S*-HHC-**6a-c**

Pathways to obtain natural machaeriols and their synthetic analogs

A novel class of HHC analogs, machaeriols, were isolated from the stem bark of *Machaerium multiflorum* at the beginning of the 21st century [25-27] such as (6a*R*,9*S*,10a*S*)-6,6,9-trimethyl-3-((E)-styryl)-6a,7,8,9,10,10a-hexahydro-6*H*-benzo[c]chromen-1-ol (**38**), (6a*R*,9*S*,10a*S*)-3-((E)-2-hydroxystyryl)-6,6,9-trimethyl-6a,7,8,9,10,10a-hexahydro-6*H*-benzo[c]chromen-1-ol (**39**) (6a*R*,9*S*,10a*S*)-3-(benzofuran-2-yl)-6,6,9-trimethyl-6a,7,8,9,10,10a-hexahydro-6*H*-benzo[c]chromen-1-ol (**42**), and (6a*R*,8*R*,9*R*,10a*S*)-3-(benzofuran-2-yl)-6,6,9-trimethyl-6a,7,8,9,10,10a-hexahydro-6*H*-benzo[c]chromene-1,8-diol (**43**) (Figure 3). However, there are few reports related to the total synthesis of these hydrogenated cannabinoids because the stereo-

controlled construction of the stereocenters of hexahydrodibenzopyran ring depicts a notable synthetic challenge.

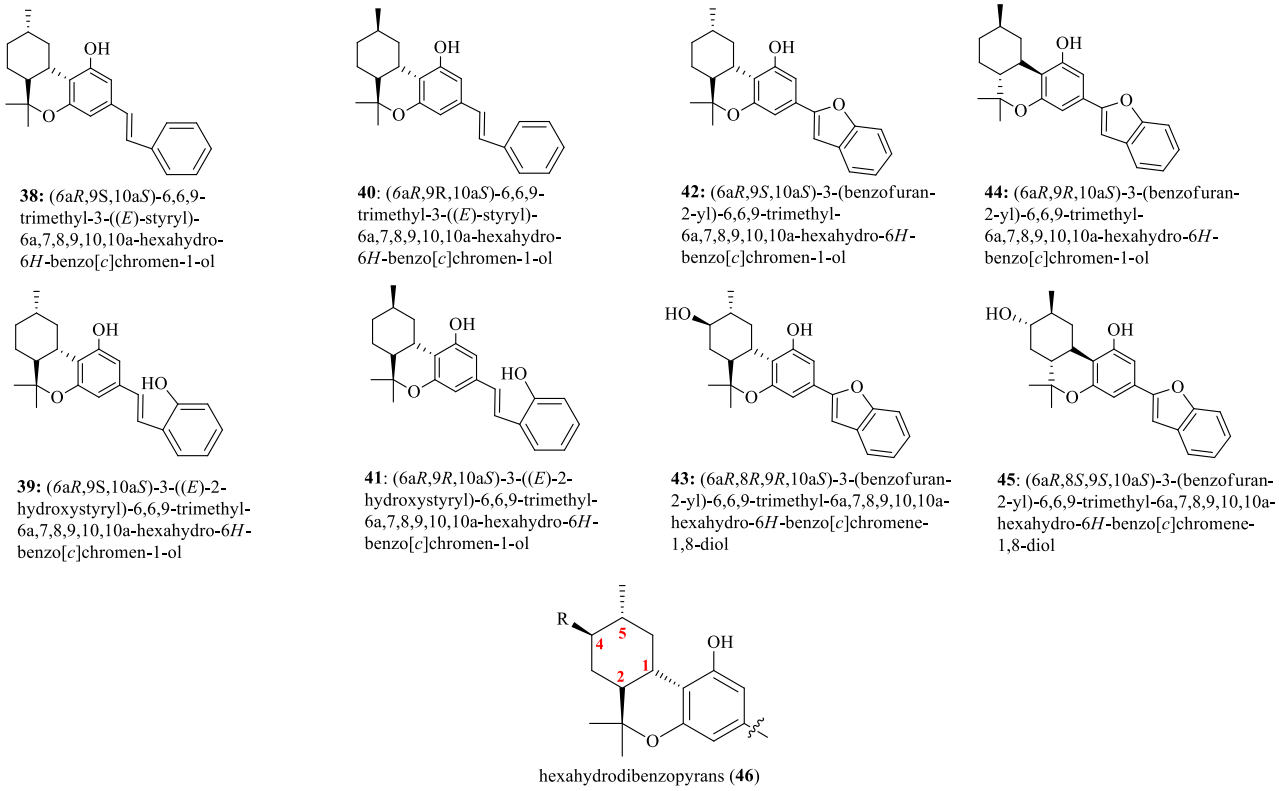
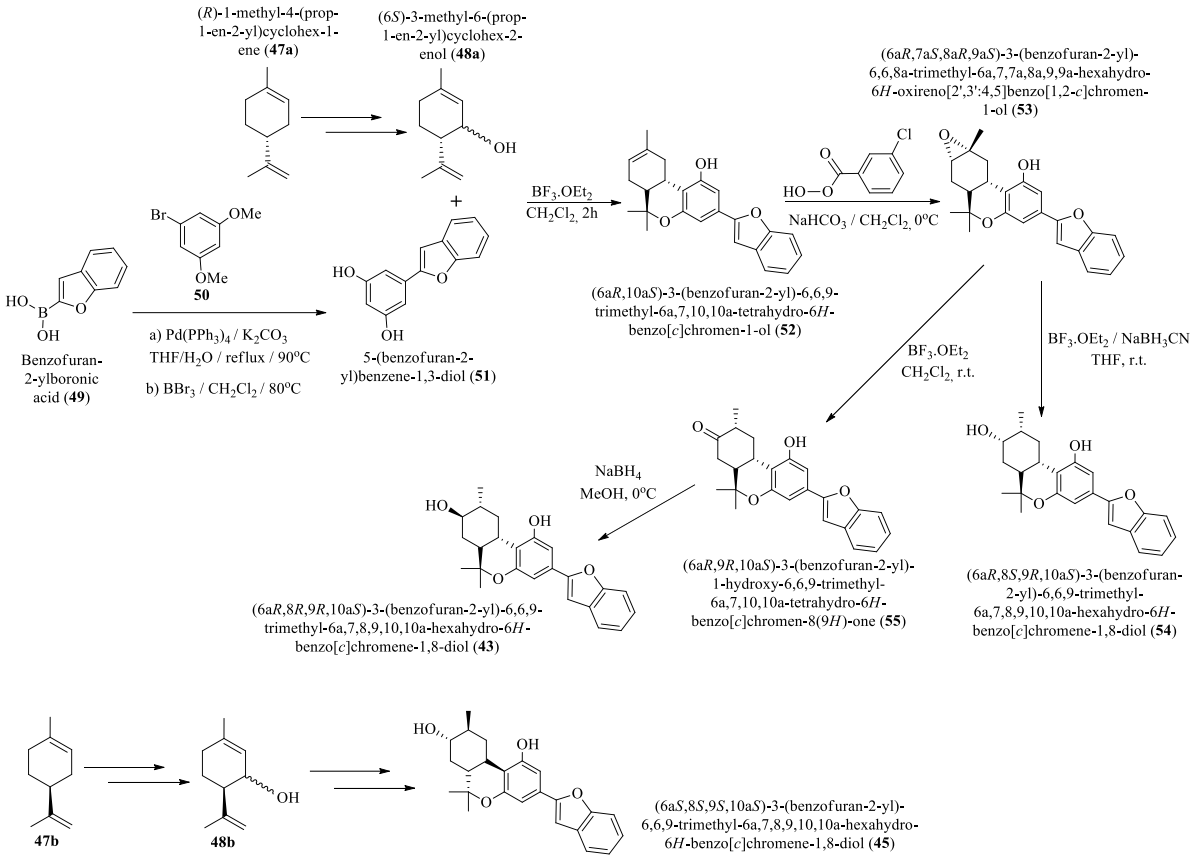


Figure 3: Structures of the natural (+)-machaeriol A−D (**38**, **39**, **42**, **43**), unnatural (-)-machaeriol A−D (**40**, **41**, **44**, **45**), and hexahydrodibenzopyrans (HHDBPs) scaffold (**46**).

The first total synthesis of natural (+)-machaeriol D (**43**) was developed by Pan [28]. The key point in the synthetic route was a highly regio- and sereoselective S_N2' reaction to afford the 5-methyl-2-((prop-1-en-2-yl)cyclohexyl)benzene-1,3-diol scaffold (**46**) with the four stereocenters (C1, C2, C4, C5) present in the final molecule (Figure 3). The main disadvantage of this method is that 18 synthesis steps are required entailing the overall yield of (+)-machaeriol D is lower than 10 %. Dethe [29] improved this procedure by applying an atom economical and protecting group free synthetic strategy with less than 6 operational steps starting with *R*-(+) and *S*-(-)-limonene (**47**). This pathway provides the synthesis of both natural product **43** and its enantiomer **45**. (Scheme 5)

The first step consists in the diastereoselective-coupling reaction between allylic alcohol **45** obtained from *S*-(-)- limonene (**47**) with benzofuran-benzene-diol (**51**) in presence of $BF_3.OEt_2$ followed by isomerization of double bond to generate 90 % isolate yield of *trans*-hexahydrodibenzopyran compound **52**. The high diastereoselectivity showed is due to the bulky isopropenyl group in the allyl alcohol. The second step involved the Prilezhaev epoxidation which was carried out using 3-chlorobenzoperoxoic acid (mCPBA) to afford 74% yield of the epoxide **53**. The reaction was highly stereospecific, and it occurred from the α-face to obtain only one diastereoisomer. Interestingly, the regioselective opening of the epoxide **53** occurs in the presence of the mixture of sodium cyanoborohydride ($NaBH_3CN$) and $BF_3{\cdot}OEt_2$ (1:1) to obtain the epimer of Machaeriol-D (**54**). On the other hand, epoxide **53** undergoes a semipinacol rearrangement catalyzed by $BF_3.OEt_2$ to produce regioselectively the ketone **55** with 82 % of yield. The last step represents the reduction of **55** using sodium borohydride to afford the natural product (+)-machaeriol-D (**43**) in 96% yield.

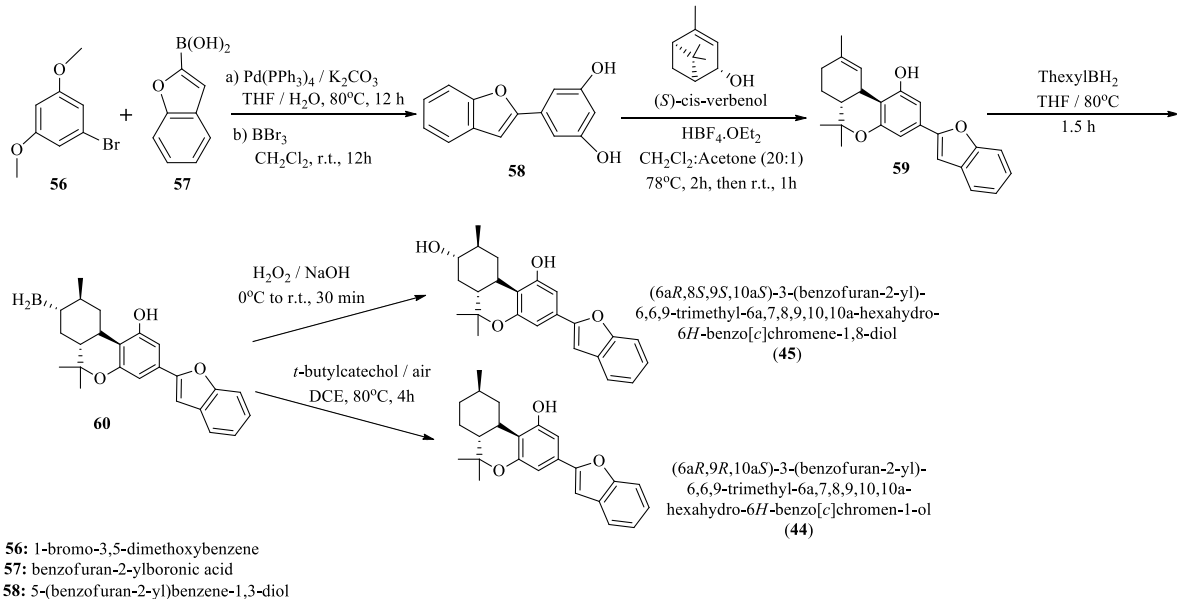


Scheme 5: Pathway to synthesize (+) and (-)-Machaeriol-D-(**43 / 45**) and epimachaeriol-D (**54**)

In similar fashion, the unnatural (-)-machaeriol-D-**45** was synthesized starting from *R*-(+)-limonene (**48b**) (Scheme 5).

On the other hand, Studer [30] reported the synthesis of (−)-Machaeriol B (**44**) and (−)-Machaeriol D (**45**) focusing in the Friedel−Crafts alkylation of 5-(benzofuran-2-yl)benzene-1,3-diol (**58**), which was obtained in 95% yield via Suzuki− Miyaura cross-coupling reaction between **56** and **57**, with (*S*)-cis-verbenol followed by the cyclization that enables the building of the tetrahydrodibenzopyran motif of Δ^8THC. (6a*R*,10a*S*)-3-(benzofuran-2-yl)-6,6,9-trimethyl-6a,7,8,10a-tetrahydro-6*H*-benzo[*c*]chromen-1-ol (**59**) was accomplished with 85 % of yield. Next step was the hydroboration of the double bond in **59**. To achieve a high diastereoselective reaction they used thexylborane followed by oxidation with sodium hydroxide and peroxide to afford

(6a*R*,8*S*,9S,10a*S*)-3-(benzofuran-2-yl)-6,6,9-trimethyl-6a,7,8,9,10,10a-hexahydro-6*H*-benzo[*c*] chromene-1,8-diol (**45**) in 45% overall yield for the last three-steps (cyclization/hydroboration/oxidation) with 97:3 selectivity (measured by GC-FID) (Scheme 6).



Scheme 6: Synthesis of (−)-Machaeriol B (**44**) and (−)-Machaeriol D (**45**) developed by Studer [30]

Also, they synthesized (6a*R*,9*R*,10a*S*)-3-(benzofuran-2-yl)-6,6,9-trimethyl-6a,7,8,9,10,10a-hexahydro-6*H*-benzo[*c*]chromen-1-ol (**44**) starting with hydroboration intermediate **60** applying hydrodeborylation radical chain reaction. In this sense they used the procedure developed by Renaud [31] for the conversion of organoborons to the appropriate alkanes under an air atmosphere by addition of 4-*tert*-butylcatechol (Scheme 6). Compound **44** was isolated in 44% yield over three steps (cyclization/hydroboration/protodeborylation) with 19:1 selectivity.

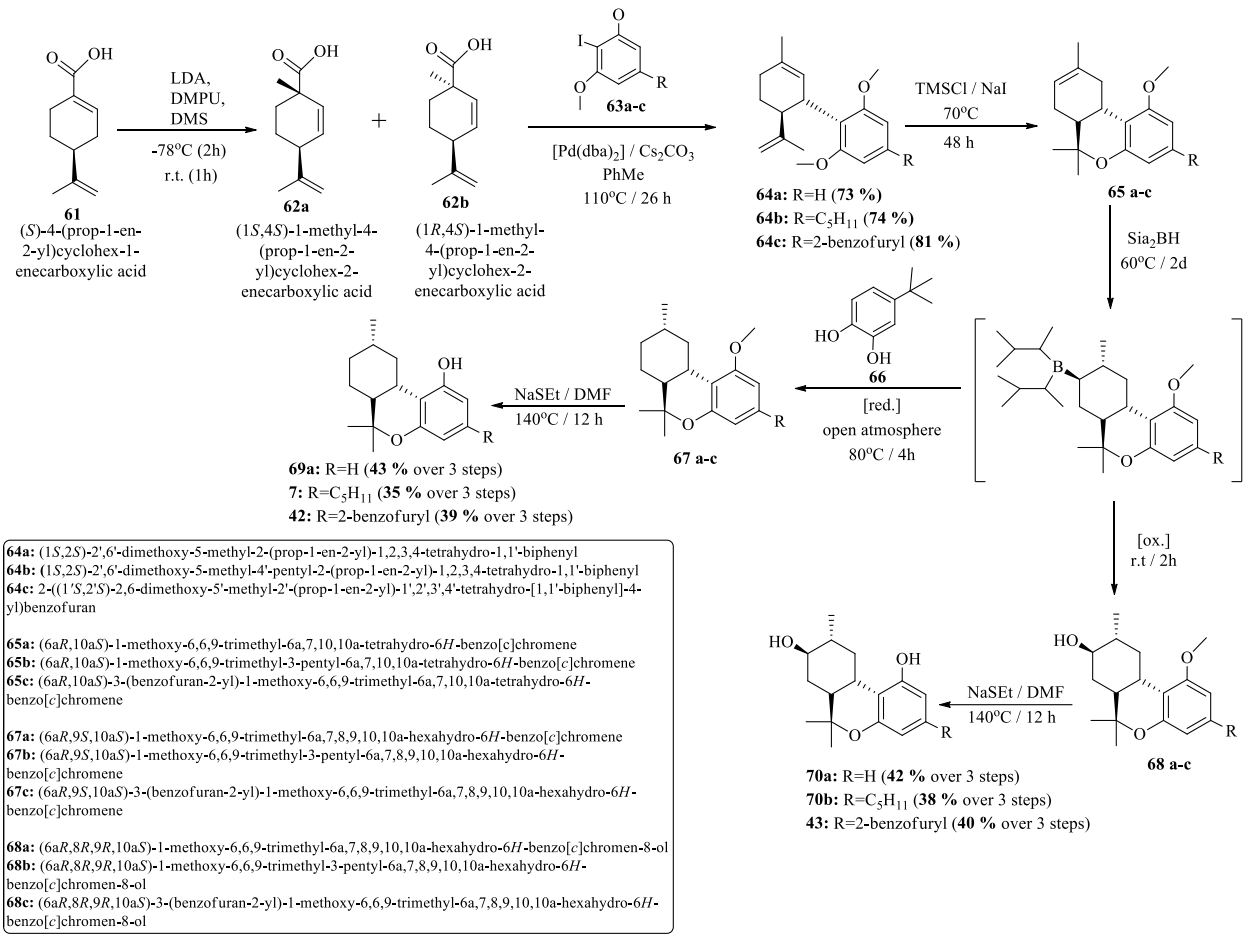
Summarizing, Studer accomplished the synthesis of (−)-machaeriol B (**45**) and D (**44**) in 42% and 43% overall yields over five steps using a Friedel−Crafts coupling reaction and highly

diastereoselective hydroboration followed by either oxidative or reductive way. This route represents the best yield in the fewest steps without protecting groups reported so far for the synthesis of unnatural machaeriol B and D.

Studer [32], also established a five-step route to obtain *S*-HHC (**7**), natural machaeriol B (**42**), D (**43**) and their analogs (6a*R*,9*S*,10a*S*)-6,6,9-trimethyl-6a,7,8,9,10,10a-hexahydro-6*H*-benzo [*c*]chromen-1-ol (**69a**) and (6a*R*,8*R*,9*R*,10a*S*)-6,6,9-trimethyl-6a,7,8,9,10,10a-hexahydro-6*H*-benzo[c]chromene-1,8-diol (**70a**) as shows scheme 7. They began their synthetic approach with the regioselectivity alkylation of commercially available (*S*)-4-(prop-1-en-2-yl)cyclohex-1-enecarboxylic acid (**61**) to obtain (1*S*,4*S*)- 1-methyl-4-(prop-1-en-2-yl)cyclohex-2-enecarboxylic acid **62a** and (1*R*,4*S*)-1-methyl-4-(prop-1-en-2-yl)cyclohex-2-enecarboxylic acid (**62b**) with a 90 % of yield and 1.7:1 diastereoselectivity. To control of the α/g regioselectivity they used lithium *N*,*N* diisopropylamide (LDA) in a THF/DMPU mixture to generate the dienolate from **61** which reacted with dimethyl sulfate (DMS) to yield carboxylic acid **62a,b** with complete α-selectivity. After that, a stereospecific decarboxylative g-arylation was carried out over the mixture of diastereomers (**62a,b**) using bis(dibenzylideneacetone)palladium, cesium carbonate, and 2-iodo-1,3-dimethoxybenzene derivatives (**63a-c**) to generate (1*S*,2*S*)-2',6'-dimethoxy-5-methyl-2-(prop-1-en-2-yl)-1,2,3,4-tetrahydro-1,1'-biphenyl derivatives (**64a-c**) in 73, 74, 81 % yield, respectively as single diastereomers. They demonstrated that diastereomer **62b** does not undergo g-arylation (Scheme 7).

The next step is the formation of Δ^8-tetrahydrodibenzopyran derivatives (**65a-c**) through selective deprotection of one methyl ether followed by cyclization and isomerization in a one-pot reaction using trimethylsilyl chloride (TMSCl) and sodium iodide (NaI). The heterogeneous hydrogenation of **65a-c** compounds in presence of Pt_2O/C afford the mixture of 3:1 *R*-:*S*-diastereomers. To

succeed in this stereoselective issue, they explored the hydroboration using disiamylborane (Sia_2BH) and succeeding radical reduction with 4-*tert*-butylcatechol (**66**) to furnish (6a*R*,9*S*,10a*S*)-1-methoxy-6,6,9-trimethyl-6a,7,8,9,10,10a-hexahydro-6*H*-benzo[*c*]chromene derivatives **67a-c** in acceptable yields and excellent diastereoselectivities (17:1 for **67a**, 19:1 for **67b**, and 22:1 for **67c**). In addition, the hydroboration of **65a-c** using Sia_2BH followed by oxidative reaction in presence of H_2O_2 and NaOH provided the (6a*R*,8*R*,9R,10a*S*)-1-methoxy-6,6,9-trimethyl-6a,7,8,9,10,10a-hexahydro-6*H*-benzo[c]chromen-8-ol (**68a-c**) as single diastereoisomers (d.r. > 99:1) in good yields. The removal of methyl groups, as the last step, was easily attained with ethanethiol sodium salt (NaSEt) in DMF under reflux to obtain the desired products. Therefore, *S*-HHC (**7**), (+)-machaeriol B (**42**) and (+)-machaeriol D (**43**) were synthesized in just five steps in 22%, 18% and 19% overall yield, respectively.



64a: (1*S*,2*S*)-2',6'-dimethoxy-5-methyl-2-(prop-1-en-2-yl)-1,2,3,4-tetrahydro-1,1'-biphenyl
64b: (1*S*,2*S*)-2',6'-dimethoxy-5-methyl-4'-pentyl-2-(prop-1-en-2-yl)-1,2,3,4-tetrahydro-1,1'-biphenyl
64c: 2-((1'*S*,2'*S*)-2,6-dimethoxy-5'-methyl-2'-(prop-1-en-2-yl)-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-4-yl)benzofuran

65a: (6a*R*,10a*S*)-1-methoxy-6,6,9-trimethyl-6a,7,10,10a-tetrahydro-6*H*-benzo[*c*]chromene
65b: (6a*R*,10a*S*)-1-methoxy-6,6,9-trimethyl-3-pentyl-6a,7,10,10a-tetrahydro-6*H*-benzo[*c*]chromene
65c: (6a*R*,10a*S*)-3-(benzofuran-2-yl)-1-methoxy-6,6,9-trimethyl-6a,7,10,10a-tetrahydro-6*H*-benzo[*c*]chromene

67a: (6a*R*,9*S*,10a*S*)-1-methoxy-6,6,9-trimethyl-6a,7,8,9,10,10a-hexahydro-6*H*-benzo[*c*]chromene
67b: (6a*R*,9*S*,10a*S*)-1-methoxy-6,6,9-trimethyl-3-pentyl-6a,7,8,9,10,10a-hexahydro-6*H*-benzo[*c*]chromene
67c: (6a*R*,9*S*,10a*S*)-3-(benzofuran-2-yl)-1-methoxy-6,6,9-trimethyl-6a,7,8,9,10,10a-hexahydro-6*H*-benzo[*c*]chromene

68a: (6a*R*,8*R*,9*R*,10a*S*)-1-methoxy-6,6,9-trimethyl-6a,7,8,9,10,10a-hexahydro-6*H*-benzo[*c*]chromen-8-ol
68b: (6a*R*,8*R*,9*R*,10a*S*)-1-methoxy-6,6,9-trimethyl-3-pentyl-6a,7,8,9,10,10a-hexahydro-6*H*-benzo[*c*]chromen-8-ol
68c: (6a*R*,8*R*,9*R*,10a*S*)-3-(benzofuran-2-yl)-1-methoxy-6,6,9-trimethyl-6a,7,8,9,10,10a-hexahydro-6*H*-benzo[*c*]chromen-8-ol

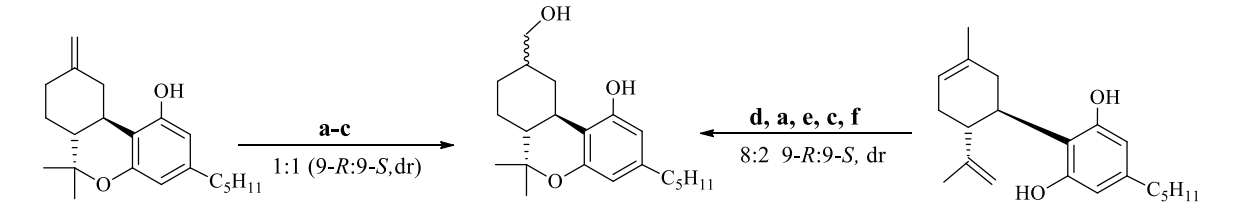
Scheme 7: Synthesis of (6a*R*,9*S*,10a*S*)-6,6,9-trimethyl-6a,7,8,9,10,10a-hexahydro-6*H*-benzo[*c*]chromen-1-ol (**69a**), (6a*R*,8*R*,9*R*,10a*S*)-6,6,9-trimethyl-6a,7,8,9,10,10a-hexahydro-6*H*-benzo[*c*]chromene-1,8-diol (**70a**), (6aR,9S,10aS)-6,6,9-trimethyl-3-pentyl-6a,7,8,9,10,10a-hexahydro-6H-benzo[*c*]chromen-1-ol (**7**), (6a*R*,8*R*,9*R*,10a*S*)-6,6,9-trimethyl-3-pentyl-6a,7,8,9,10,10a-hexahydro-6*H*-benzo[*c*]chromene-1,8-diol (**70b**), (6a*R*,9*S*,10a*S*)-3-(benzofuran-2-yl)-6,6,9-trimethyl-6a,7,8,9,10,10a-hexahydro-6*H*-benzo[*c*]chromen-1-ol (**42**) and (6a*R*,8*R*,9R,10a*S*)-3-(benzofuran-2-yl)-6,6,9-trimethyl-6a,7,8,9,10,10a-hexahydro-6*H*-benzo[*c*]chromene-1,8-diol (**43**) developed by Studer [32].

Partial and total synthesis of 9*R*-11-hydroxyhexahydrocannabinol and its derivatives

9*R*-11-hydroxyhexahydrocannabinol (**71**) was isolated as one of the minor metabolites of Δ^9THC after treating mice (male, Charles River CDl, 23 g) with Δ^9THC (100 mg/kg, i.p.) suspended in Tween 80 and isotonic saline administered at 26 h and 2 h before death by stunning and

decapitation [33]. Also, it was the major metabolite formed by incubation of 9*R*-HHC with hepatic microsomes of rats, guinea pigs and rabbits [34].

There are some reports that have described the partial synthesis 11-hydroxyhexahydrocannabinol as a mixture of diastereomers. The first one was developed by Skinner [28] starting from 6a*S*,10a*R*)-6,6-dimethyl-9-methylene-3-pentyl-6a,7,8,9,10,10a-hexahydro-6H-benzo[*c*]chromen-1-ol (**72**) in three steps with 1:1 (dr, 9*R*:9*S*). The second one was established by Kozela [35] beginning with CBD (**33b**) in five steps with 8:2 (dr, 9*R*:9*S*) (Scheme 8). The overall yields in both synthetic routes are lower than 15%.



(6a*S*,10a*R*)-6,6-dimethyl-9-methylene-3-pentyl-6a,7,8,9,10,10a-hexahydro-6*H*-benzo[*c*]chromen-1-ol (**72**)

(6a*S*,10a*R*)-9-(hydroxymethyl)-6,6-dimethyl-3-pentyl-6a,7,8,9,10,10a-hexahydro-6*H*-benzo[*c*]chromen-1-ol (**71**)

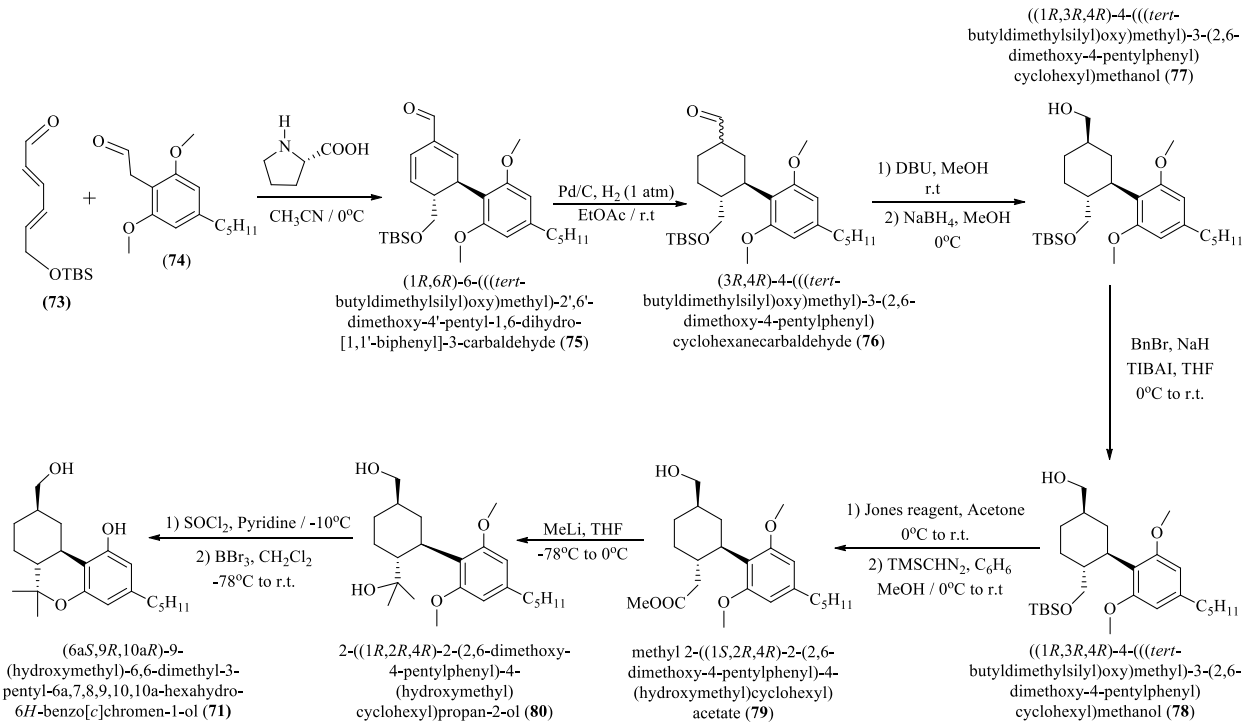
(1'*R*,2'*R*)-5'-methyl-4-pentyl-2'-(prop-1-en-2-yl)-1',2',3',6'-tetrahydro-[1,1'-biphenyl]-2,6-diol (**33b**)

Scheme 8: Partial synthetic approach of (**71**) reported by Skinner [28] and Mechoulam [35]
a: Acetic anhydride, pyridine, r.t. 2h; **b**: BH_3, THF, 0°C, 1h, then $Me_3N^+O^-.2H_2O$, reflux 2h; **c**: NaOH(1M), MeOH, 2h; **d**: *p*-TSA, Hexane, 72h; **e**: SeO_2, ethanol, 24h; **f**: Pd/C, H_2 (1 atm), 24h methanol

The first total synthesis of (**71**) was reported by Appayee [36] applying the inverse-electron-demand Diels–Alder reaction to afford stereoselectively the six-membered ring compound **75** starting with 6-((tert-butyldimethylsilyl)oxy)hexa-2,4-dienal (**73**) and 2-(2,6-dimethoxy-4-pentylphenyl)acetaldehyde and catalyzed by (*S*)-pyrrolidine-2-carboxylic acid. The (1*R*,6*R*)-6-(((tert-butyldimethylsilyl)oxy)methyl)-2',6'-dimethoxy-4'-pentyl-1,6-dihydro-[1,1'-biphenyl]-3-carbaldehyde (**75**) was obtained with 72 % yield and 97 % enantioselectivity. Then, 3-carbaldehyde (**75**) was treated with hydrogen under Pd/C to yield the saturated carbaldehyde (**76**)

as a racemic mixture. Appayee used DBU in MeOH followed by *in situ* reduction of the epimerized product to achieve a good the diastereoselectivity (5:1, dr) of the cyclohexyl methanol (**77**) with 60 % yield after two steps. The conversion of **77** to t 2-((1*R*,2*R*,4*R*)-2-(2,6-dimethoxy-4-pentylphenyl)-4-(hydroxymethyl) cyclohexyl)propan-2-ol (**80**) was accomplished in four steps starting with a benzyl protection of the carbinol, then the direct oxidation of the silyl ethers ether using Jones reagent followed by treatment with trimethylsilyidiazomethan hexane resulted in the cyclohexyl acetate (**79**) 16. Finally, the addition of methyllithium to compound **79** afforded the cyclohexylpropan-2-ol (**80**) with 85 % yield after four steps.

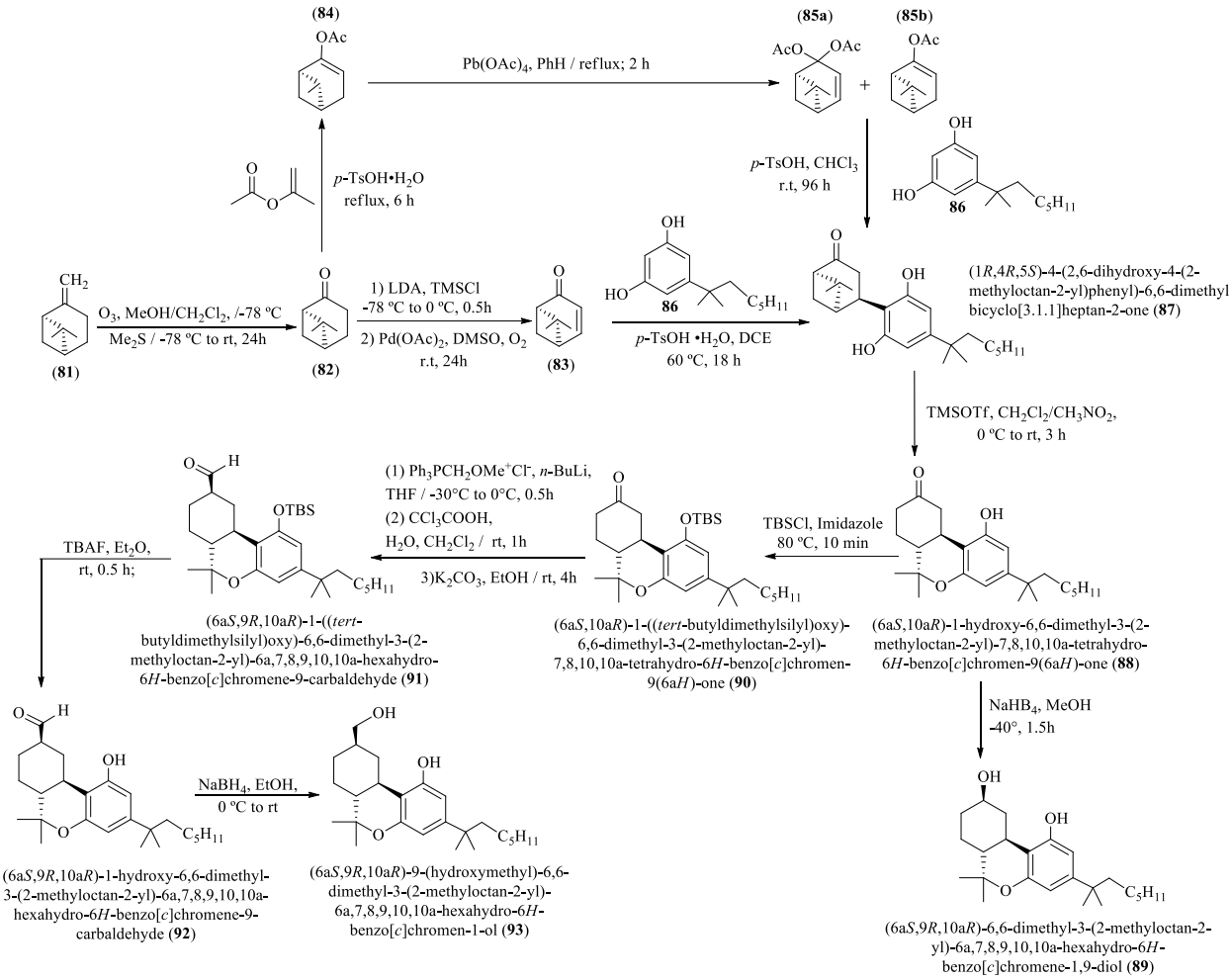
The last step was a challenge due to the presence of free tertiary alcohol group in **80** that triggers multiple dehydrated and rearranged products during the deprotection and cyclization reactions. For this reason, Appayee decided to transform compound **80** into a terminal alkene and treated it with Boron tribromide to obtain 9*R*-11-hydroxyhexahydrocannabinol (**71**) with 24% overall yield (Scheme 9).



Scheme 9: Total synthesis of 9*R*-11-hydroxyhexahydrocannabinol developed by Appayee [36]

C-9 ketocannabinoids: different enantioselective synthetic routes

The first synthesis of a C9-ketocannabinoid related to enantioenriched nabilone (**88**) was first developed by Archer and coworkers at Eli Lilly Company in 1977. [37] (1*R*,4*R*,5*S*)-4-(2,6-dihydroxy-4-(2-methyloctan-2-yl)phenyl)-6,6-dimethyl bicyclo[3.1.1]heptan-2-one (**88**) was produced in four-step synthetic pathway, starting from the inexpensive (1*S*,5*R*)-6,6-dimethyl-2-methylenebicyclo[3.1.1]heptane (**81**). However, the overall yield of Nabilone **88** was lower than 10%. This was assumed to be provoked by the lack of reactivity of (1*R*,5*S*)-6,6-dimethylbicyclo[3.1.1]hept-3-en-2-one (**83**). This led Nikas [38] and later Blaazer [39] and Makriyannis [40.41] to develop an alternative route of synthesis in five steps through the mixture of both terpene acetates **85a** and **85b**. The diacetates (**85**) were synthesized via transesterification of (1*R*,5*R*)-6,6-dimethylbicyclo[3.1.1]heptan-2-one (**82**) with isopropenyl acetate to give (1*R*,5*R*,6*S*)-6-methylbicyclo[3.1.1]hept-2-en-2-yl acetate (**84**) which was then treated with lead tetraacetate in refluxing benzene. Michael addition of resorcinol **86** with the mixture of terpene acetates **85** using *p*-toluenesulfonic acid monohydride as catalyst and heating in DCE produced 83% yield of Michael adduct **87** which cyclized in presence of trimethylsilyl triflate (TMSOTf) to obtain (6a*S*,10a*R*)-1-hydroxy-6,6-dimethyl-3-(2-methyloctan-2-yl)-7,8,10,10a-tetrahydro-6*H*-benzo[*c*]chromen-9(6a*H*)-one (**88)** with 54 % overall yield after five steps. (Scheme 10**)** Reduction of **88** by sodium borohydride furnished (6a*S*,9*R*,10a*R*)-6,6-dimethyl-3-(2-methyloctan-2-yl)-6a,7,8,9,10,10a-hexahydro-6*H*-benzo[*c*]chromene-1,9-diol (**89**).



Scheme 10: Total Synthesis of (-)-nabilone (**88**), canbisol (**89**) the 9*R*- aldehyde nabilone derivative (**92**), and 9*R*-hydroxymethyl nabilone derivative (**93**).

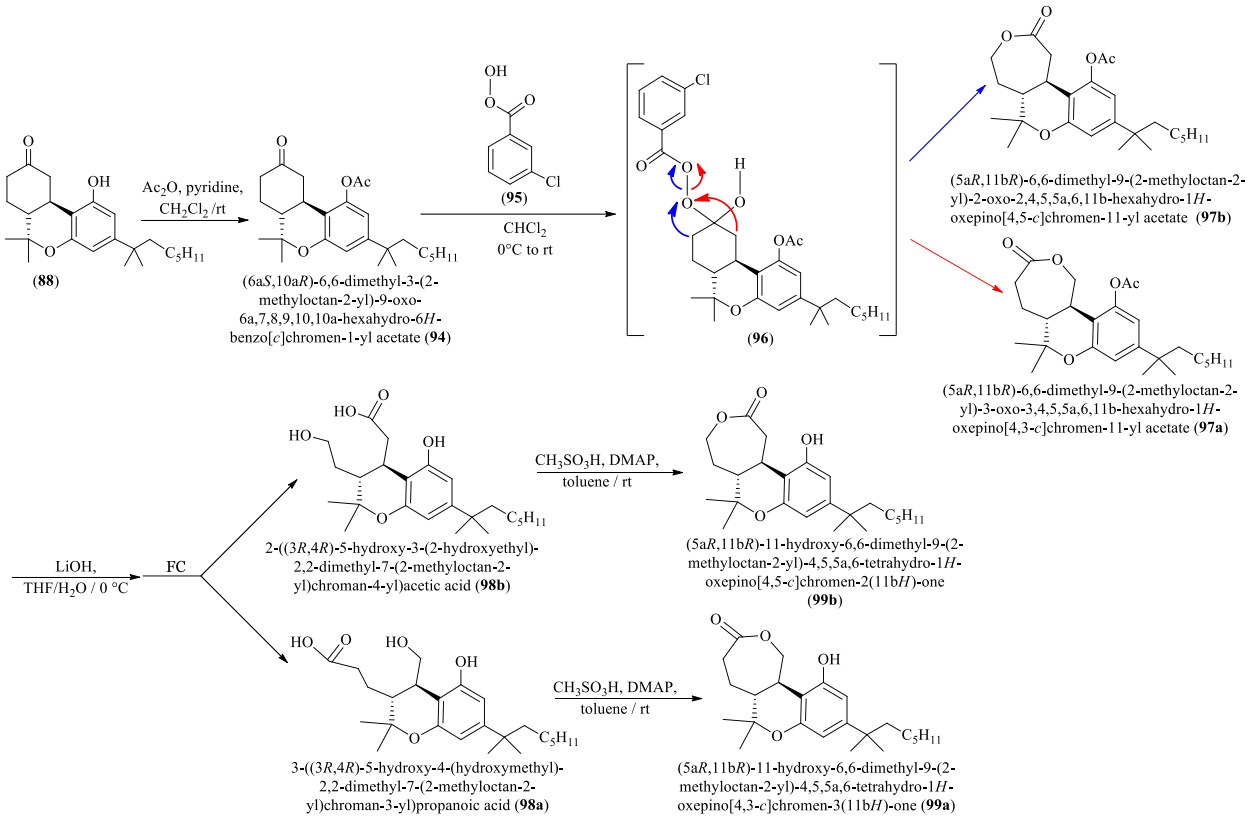
Makriyannis [40] reported the synthesis of (6a*S*,9*R*,10a*R*)-9-(hydroxymethyl)-6,6-dimethyl-3-(2-methyloctan-2-yl)-6a,7,8,9,10,10a-hexahydro-6*H*-benzo[*c*]chromen-1-ol (**93**) from **88** using the Wittig olefination of the (6a*S*,10a*R*)-1-((tert-butyldimethylsilyl)oxy)-6,6-dimethyl-3-(2-methyloctan-2-yl)-7,8,10,10a-tetrahydro-6*H*-benzo[*c*]chromen-9(6a*H*)-one (**90**) to produce an E/Z mixture of methoxymethylene derivatives which were hydrolyzed with trichloroacetic acid to a mixture of diastereomeric C9 aldehydes. Epimerization of this mixture afforded the thermodynamically more stable 9*R*-carbaldehyde **92**. Finally, reduction with sodium borohydride

in ethanol led to (6a*S*,9*R*,10a*R*)-9-(hydroxymethyl)-6,6-dimethyl-3-(2-methyloctan-2-yl)-6a,7,8,9,10,10a-hexahydro-6H-benzo[*c*]chromen-1-ol (**93**) (Scheme 10).

Cannabinoid Lactones modified in the C-Ring

Makriyannis [42] substituted the C-ring in the nabilone structure with a seven-membered lactone. The synthetic pathway started with the acetylation reaction to protect the hydroxyl group in nabilone (**88**) obtaining (6a*S*,10a*R*)-6,6-dimethyl-3-(2-methyloctan-2-yl)-9-oxo-6a,7,8,9,10,10a-hexahydro-6*H*-benzo[*c*]chromen-1-yl acetate (**94**) with 90 % of yield. It was afterward treated with 3-chlorobenzoperoxoic acid (**95**) to furnish a mixture of regioisomeric lactones **97a** and **97b** in 97 % yield after Baeyer−Villiger rearrangement which involves the formation of the tetrahedral intermediate **96**. These regioisomers were not able to separate, so

they were reacted with lithium hydroxide to remove the acetyl group and open the lactone ring to obtain the mixture of corresponding propanoic acids **98a** and **98b** that were separated by flash column chromatography. Finally, the intramolecular cyclization was carried out in each regioisomers in presence of methanesulfonic acid and 4-dimethylaminopyridine to furnish the (5a*R*,11b*R*)-11-hydroxy-6,6-dimethyl-9-(2-methyloctan-2-yl)-4,5,5a,6-tetrahydro-1*H*-oxepino[4,5-*c*]chromen-2(11b*H*)-one (**99b**) and (5a*R*,11b*R*)-11-hydroxy-6,6-dimethyl-9-(2-methyloctan-2-yl)-4,5,5a,6-tetrahydro-1*H*-oxepino[4,3-c]chromen-3(11b*H*)-one (**99a**) with 44-79% overall yield, respectively (Scheme 11).



Scheme 11: Synthesis of (5a*R*,11b*R*)-11-hydroxy-6,6-dimethyl-9-(2-methyloctan-2-yl)-4,5,5a,6-tetrahydro-1*H*-oxepino[4,3-*c*]chromen-3(11b*H*)-one (**99a**) and (5a*R*,11b*R*)-11-hydroxy-6,6-dimethyl-9-(2-methyloctan-2-yl)-4,5,5a,6-tetrahydro-1*H*-oxepino[4,5-*c*]chromen-2(11b*H*)-one (**99b**)

HYDROGENATED BICYCLIC CANNABIDIOL ANALOGS

Cannabidiol (CBD, **34b**) is a naturally occurring compound biosynthesized within the *Cannabis sativa* plant. CBD has gained significant attention in recent years due to its potential therapeutic effects in treating multiple ailments while exhibiting minimal to no psychoactive properties. CBD has been reported to exhibit various effects on the human body. Studies suggest that it possesses anti-inflammatory, analgesic (pain-relieving), anxiolytic (anti-anxiety), and neuroprotective properties [43]. CBD has also shown potential in the treatment of epilepsy, schizophrenia, and

other psychiatric disorders [44]. Additionally, it may have antioxidant and anticancer properties, through studies hypothesizing the mechanisms that CBD might enact on [45].

The mechanisms through which CBD exerts its effects are complex and multifaceted. CBD interacts with several molecular targets in the body, including cannabinoid receptors (CB1 and CB2), serotonin receptors (5-HT1A), and transient receptor potential (TRP) channels [46]. However, CBD does not bind strongly to these receptors, and its effects are believed to be largely mediated through indirect modulation of endogenous neurotransmitter systems. CBD's interaction with the endocannabinoid system (ECS) is of particular importance. Although CBD has low affinity for cannabinoid receptors, it can influence the ECS by inhibiting the enzyme fatty acid amide hydrolase (FAAH), which is responsible for the breakdown of anandamide, an endogenous cannabinoid. By inhibiting FAAH, CBD increases anandamide levels, leading to potential therapeutic effects [47]. Furthermore, CBD has been found to modulate various signaling pathways and molecular targets involved in inflammation, oxidative stress, and neurotransmission. It affects the release and uptake of neurotransmitters such as serotonin, dopamine, and glutamate, contributing to its anxiolytic and antipsychotic properties [48].

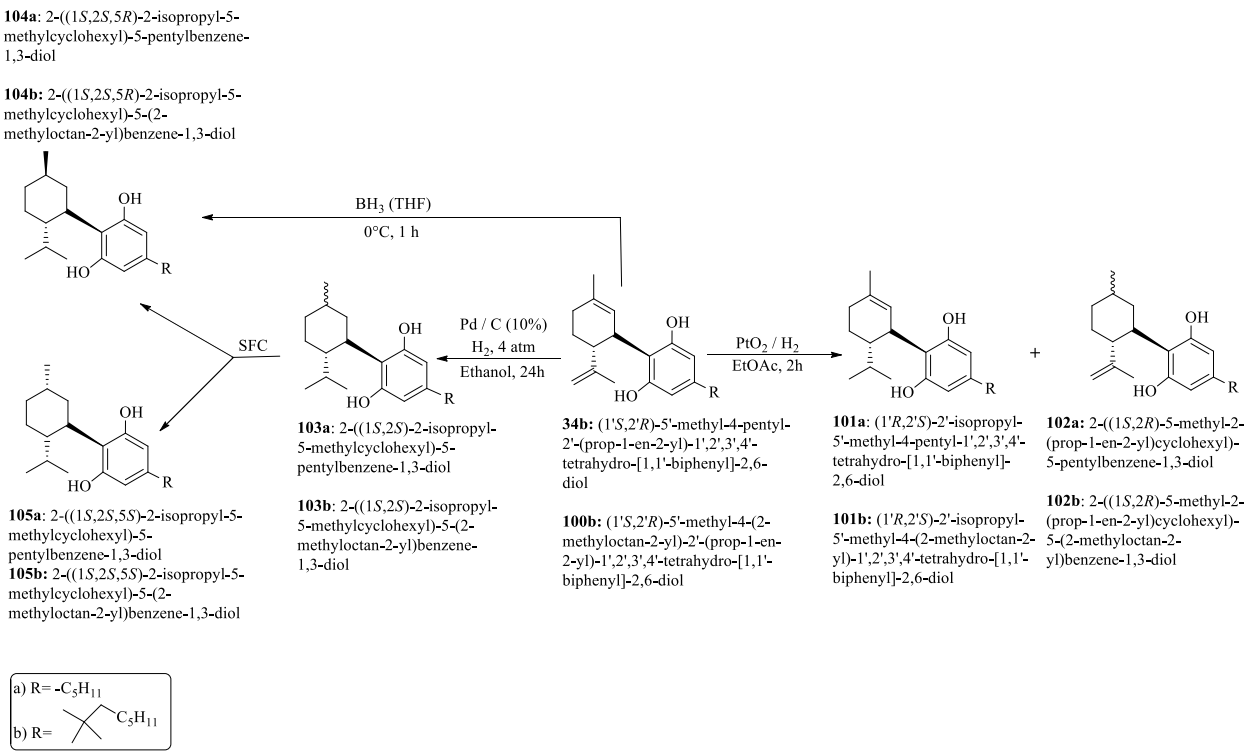
Considering the therapeutic applications of CBD and its low toxicity, there is a marked interest in designing new hydrogenated bicyclic CBD analogs and deciding their pharmacological and clinical effects.

Hydrogenation of CBD and its derivatives

Ben-Shabat [9] reported the partial hydrogenation of CBD (**34b**) and dimethyl-cannabidiol (CBD-DMH, **100**) using Adams Catalyst (PtO_2) to afford a mixture of (1'*R*,2'*S*)-2'-isopropyl-5'-methyl-4-pentyl-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-2,6-diol (**101a**) from CBD or (1'R,2'S)-2'-isopropyl-

5'-methyl-4-(2-methyloctan-2-yl)-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-2,6-diol (**101b**) from CBD-DMH (propen hydrogenated position) and 2-((1*S*,2*R*)-5-methyl-2-(prop-1-en-2-yl)cyclohexyl)-5-pentylbenzene-1,3-diol (**102a**) from CBD and 2-((1*S*,2*R*)-5-methyl-2-(prop-1-en-2-yl)cyclohexyl)-5-(2-methyloctan-2-yl)benzene-1,3-diol (**102b**) from CBD-DMH (C-5' hydrogenated position), being **102** compounds the predominant epimers (86% and 83% respectively). (Scheme 12).

Also, Cruces et al [23,24] described the full hydrogenation of CBD using Pd/C (10 %) and hydrogen under 4 atm of pressure to obtain the racemic mixture of dihydro-CBD (**103a**) (Scheme 12).



Scheme 12: Partial and full hydrogenation of CBD (**34b**) and CBD-DMH (**100b**).

Hydrogenated CBD analogs are relatively obscure compounds. Limited data and experiments have been conducted on the compound. Up until 2023, dihydro-CBD enantiomers (**104a**) and **105a**) were not characterized, until earlier this year when Cruces et al. [10] successfully separated the

pure enantiomers of dihydro-CBD (2-((1'*S*,2'*S*,5'*R*)-2-isopropyl-5-methylcyclohexyl)-5-alkylbenzene-1,3-diol, **104a** and 2-((1'*S*,2'*S*,5'*S*)-2-isopropyl-5-methylcyclohexyl)-5-alkylbenzene-1,3-diol, **105 a**) by Supercritical Fluid Chromatography (SFC) using a chiral column. The stereochemistry of the isomers was characterized using a combination of 1D and 2D NMR techniques and the purity was obtained using HPLC. The (*R*) and (*S*) isomers look similar, there is a remarkable difference in their 3-dimensional structures due to the change in stereochemistry of the cyclohexane/terpene ring. This difference in 3D shapes strongly suggests that one of the isomers could be far more active, interacting with the binding targets with increased affinity and specificity.

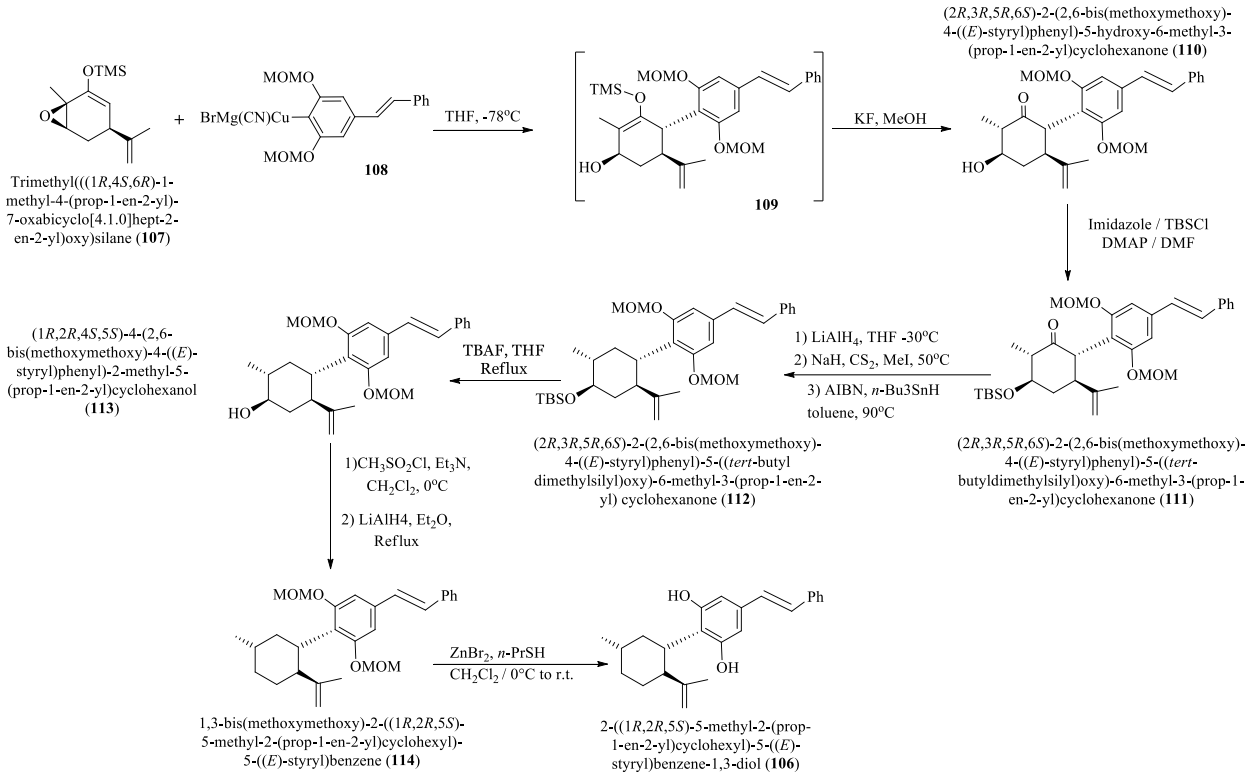
Marson [49] described the enantioselective catalytic hydrogenation of CBD using borane in THF to obtain the *R* enantiomer of dihydro-CBD (2-((1*S*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl)-5-pentylbenzene-1,3-diol, **104a**) with 97 % dr. (Scheme 12**)**.

As reported by Ben-Shabat [9] dihydro-CBD has binding activity within the CB1 region, as compared to the parent scaffold CBD which has primary binding activity within the CB2 receptor. No definitive data that has been produced can provide an explanation of CBD or dihydro-CBD mechanism of action, data does point to the potential activation of CB1/CB2 receptors that induce signaling of multiple pathways such as PKC, PI3K/Akt, and ERK pathways.

Machaeridiols and their synthetic analogs

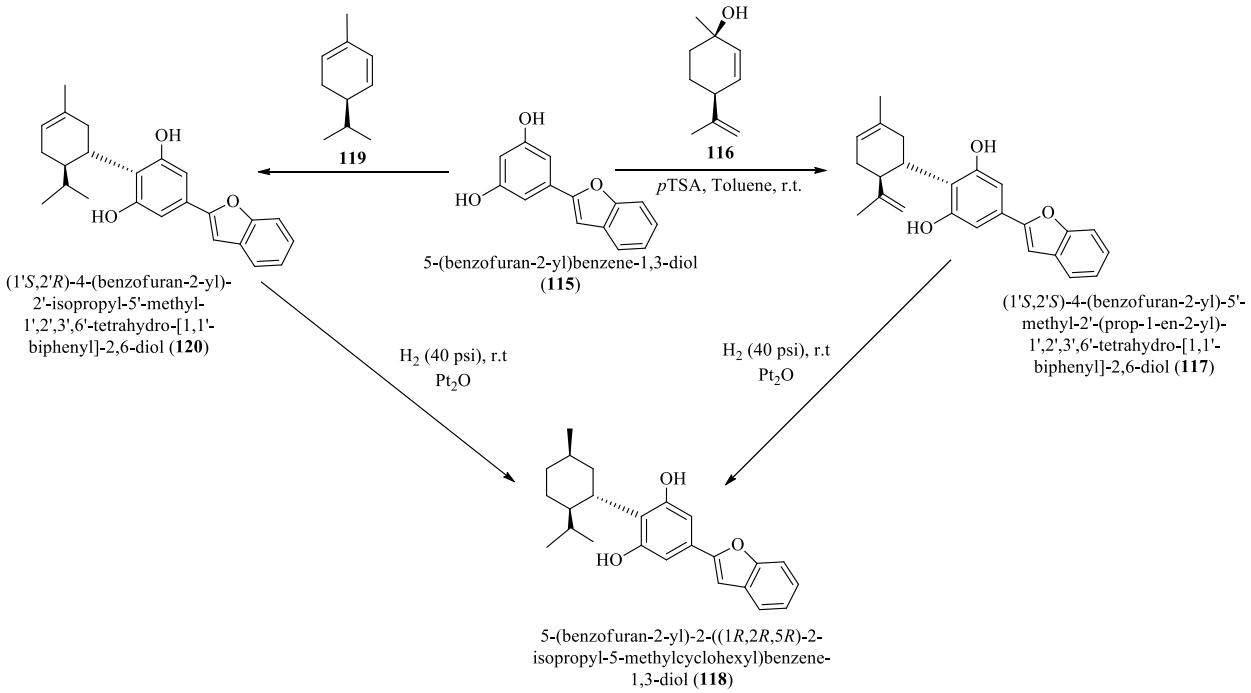
Natural machaeridiol compounds have the skeleton configuration at 1*R* and 2*R* positions opposite to those at 1*S* and 2*S* positions of dihydro-CBD and same as the enantiomer 5*S* position. Also, the macheridiol chemotype is like dihydro-CBD, with then-alkyl moiety replaced by steryl and benzofuranyl forms. Huang [50] introduced the first ten-steps effective route for the synthesis of

(+) Macheridiol A (**106**) using the regio- and stereoselective S_N2'-reaction between trimethyl(((1*R*,4*S*,6*R*)-1-methyl-4-(prop-1-en-2-yl)-7-oxabicyclo[4.1.0]hept-2-en-2-yl)oxy)silane (**107**) and arylcyanocuprates (**108**) to obtain the adduct (**109**) which was hydrolyzed *in sito* to yield (2*R*,3*R*,5*R*,6*S*)-2-(2,6-bis(methoxymethoxy)-4-((*E*)-styryl)phenyl)-5-hydroxy-6-methyl-3-(prop-1-en-2-yl)cyclohexanone (**110**) with the four stereocenters that appear in the Macheridiol core. The second step was the protection of hydroxyl group with tert-butyldimethylsilyl (TBS) to generate compound **111** which underwent the reduction reaction with using lithium aluminum hydride ($LiAlH_4$) followed by xanthation process and reduction via Barton radical deoxygenation to afford compound **112**. For removing the hydroxyl group from hexyl ring, first, it was deprotected and then treated with methanesulfonyl chloride to convert **113** into the corresponding methyl sulfonate derivative and reduce it with $LiAlH_4$ to furnish 1,3-bis(methoxymethoxy)-2-((1*R*,2*R*,5S)-5-methyl-2-(prop-1-en-2-yl)cyclohexyl)-5-((*E*)-styryl)benzene (**114**). Finally, the deprotection of methoxymethyl (MOM) ethers using zinc bromide and propanethiol was carried out to obtain (+) Macheridiol A (**106**) with 50% overall yield (Scheme 13).



Scheme 13: Ten-steps synthetic pathway to obtain (+) Macheridiol A (**106**) developed by Huang [42]

Based on 5-methyl-2-(prop-1-en-2-yl)cyclohexyl)benzene-1,3-diol (Figure 3, **46**) scaffold, Muhammad [51] obtained macheridiol analog (5-(benzofuran-2-yl)-2-((1*S*,2*R*,5*R*)-2-isopropyl-5-methylcyclohexyl)benzene-1,3-diol (**118**)) via coupling reaction between monoterpene units, (1*R*,4*S*)-1-methyl-4-(prop-1-en-2-yl)cyclohex-2-enol (**116**) or (*R*)-5-isopropyl-2-methylcyclohexa-1,3-diene (**119**) with 5-(benzofuran-2-yl)benzene-1,3-diol (**115**) followed by stereoselective reduction using Adam's catalyst. (Scheme 14).



Scheme 14: Synthesis of 5-(benzofuran-2-yl)-2-((1*S*,2*R*,5*R*)-2-isopropyl-5 methylcyclohexyl) benzene-1,3-diol (**118**)

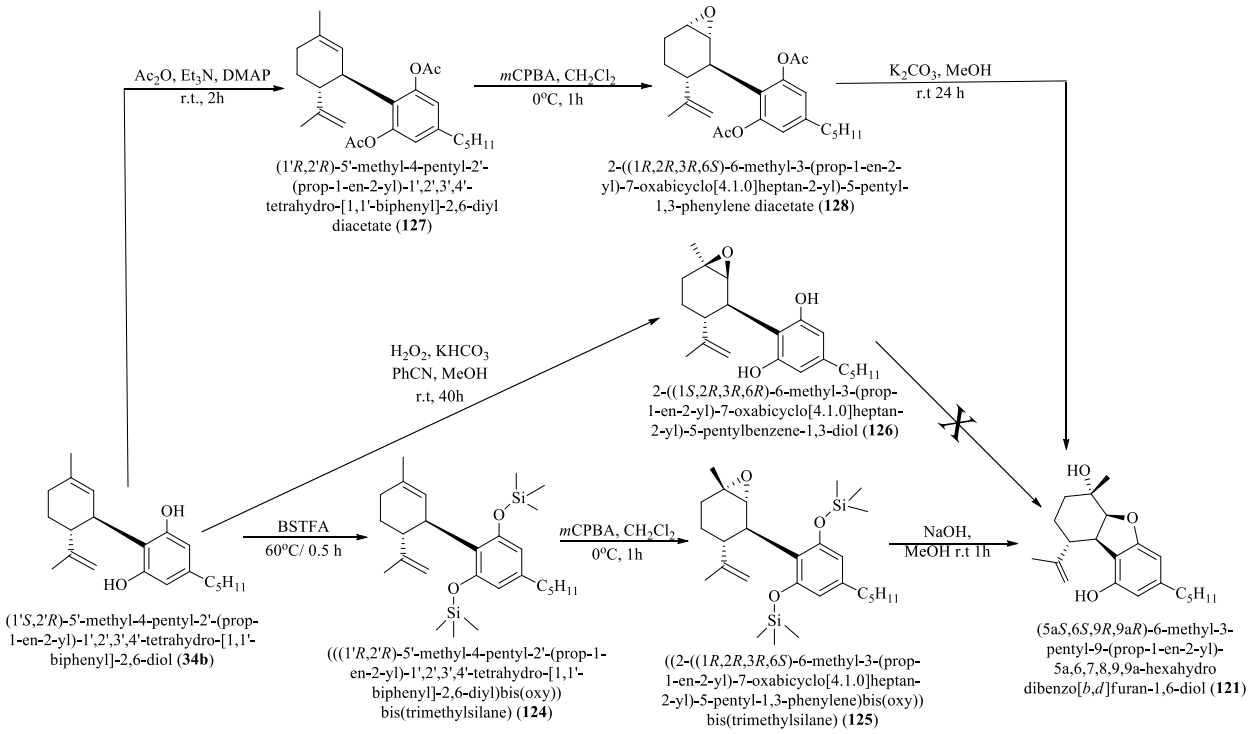
NON-CLASSIC HYDRATED PHYTOCANNABINOIDS AND THEIR SYNTHETIC ANALOGS

Cannabielsoin: a metabolite of cannabidiol

Research into non-classic saturated phytocannabinoids is growing rapidly. For example (5a*S*,6*S*,9*R*,9a*R*)-6-methyl-3-pentyl-9-(prop-1-en-2-yl)-5a,6,7,8,9,9a-hexahydro dibenzo[*b*,*d*]furan-1,6-diol (CBE, **121**) has been reported as a CBD metabolite from plant and mammalian and classified as non-classical cannabinoids for the modification of the ring B (five-ring instead of six-ring) and in the northern aliphatic group in the CBD core. Furthermore, 1-((1*R*,3*S*,3a*S*,8b*R*)-8-hydroxy-6-pentyl-1-(prop-1-en-2-yl)-2,3,3a,8b-tetrahydro-1*H*-cyclopenta [b]benzofuran-3-yl)ethanone (anhydrocannabimovone: ACBM, **122**) and 1-((1*R*,2*R*,3*R*,4*R*)-3-(2,6-dihydroxy-4-pentylphenyl)-2-hydroxy-4-(prop-1-en-2-yl)cyclopentyl)ethanone

(cannabimovone: BM, **123**) have been isolated from a strain of *Cannabis sativa*, but with very low percentages due to limited abundance in the plant and unmanageable purification and isolation processes [52].However, no pharmacological studies of these non-classic hydrogenated cannabinoids have been carried out.

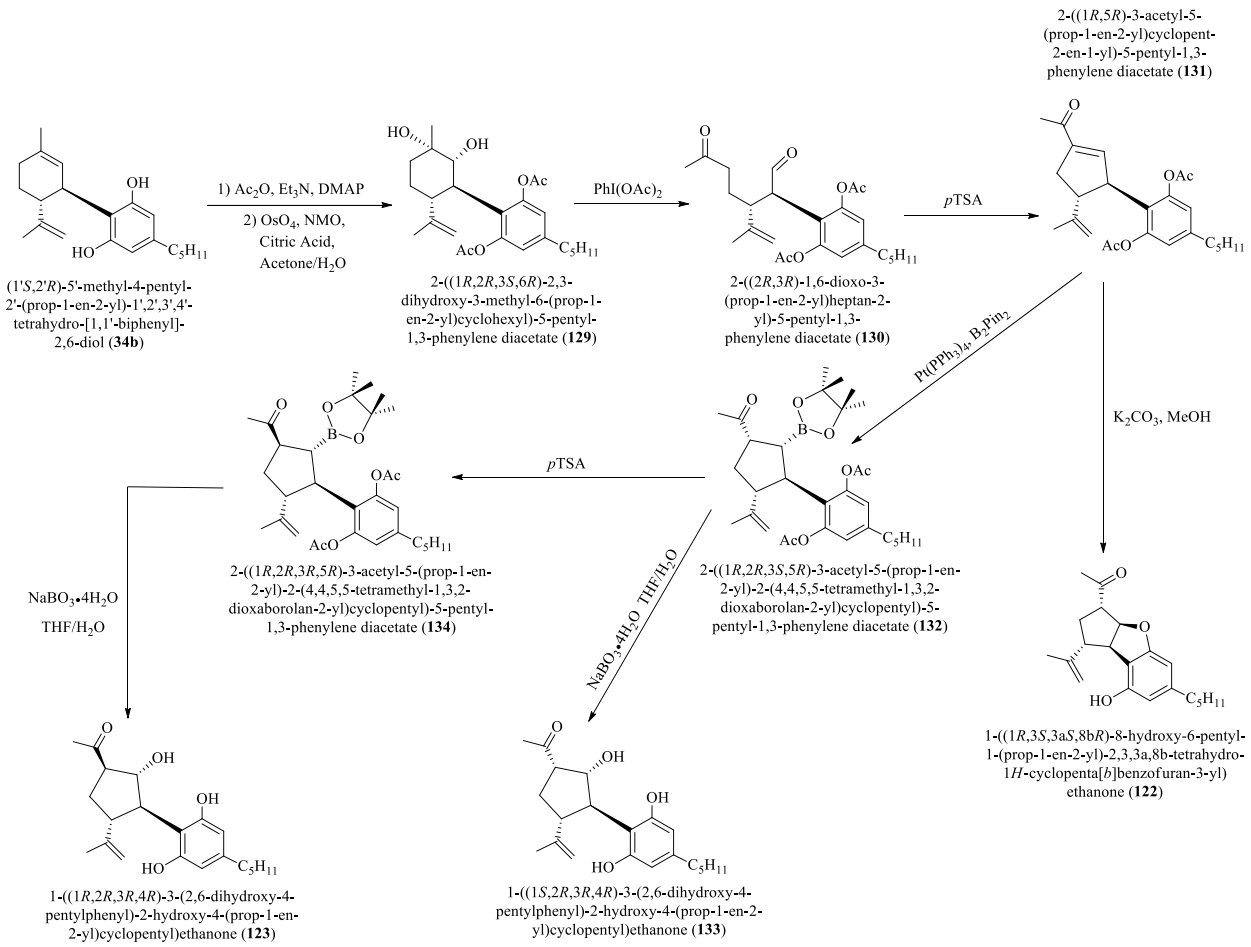
Williamson [53] and later Sarlah [54] developed different ways to synthesize CBE, **121** starting with CBD (**34b**). On the first route, CBD was completely silylated using *N*,*O* bis(trimethylsilyl)trifluoroacetamide (BSTFA) followed by chemoselectively epoxidation to obtain 1*R*,2*R*,3*R*,6S-silyl epoxide (**125**) which was deprotected in presence of sodium hydroxide in methanol to achieve CBE (**121**) in 72% yield (Scheme 15). On the second way, The CBD underwent full acetylation and then chemoselective oxidation to give 1*R*,2*R*,3*R*,6S-acetyl epoxide (**128**). Epoxide **128** was exposed to an excess of potassium carbonate in methanol to deliver CBE (**121**) with 59% yield. Williamson [53] carried out the epoxidation without protecting the CBD, which reversed the major facial selectivity of the epoxidation to obtain the 1*S*,2*R*,3*R*,6*R*-epoxide (**126**) in 43% yield. However, the cyclization of epoxide **126** to generate CBE failed. It is due to a higher energy barrier for equatorial attack of bases on cyclohexane-derived epoxides [55].



Scheme 15: Synthesis of (5a*S*,6*S*,9*R*,9a*R*)-6-methyl-3-pentyl-9-(prop-1-en-2-yl)-5a,6,7,8,9,9a-hexahydro dibenzo[*b*,*d*]furan-1,6-diol (CBE, **121**) via epoxidation.

Cannabimovone, anhydrocannabimovone and their non-natural analogs

Sarlah [54] and Echavarren [56] described a method to obtain *R*-CBM (**123**), its unnatural epimer, *S*-CBM (**133**), and ACBM (**122**) commencing from the full acetylation of CBD as it shows in Scheme 16. Osmium tetroxide (OsO_4) was used as oxidant in the dihydroxylation of cyclohexyl ring on the AcO-CBD to produce the syn-diol **129**, which was subjected to 1,2 diol cleavage using Phenyliodine(III)diacetate ($PhI(OAc)_2$) to afford 2-((2*R*,3*R*)-1,6-dioxo-3-(prop-1-en-2-yl)heptan-2-yl)-5-pentyl-1,3-phenylene diacetate (**130**). After that, aldol condensation in the presence of *p*-toluene sulfonic acid allowed obtaining 2-((1*R*,5*R*)-3-acetyl-5-(prop-1-en-2-yl)cyclopent-2-en-1-yl)-5-pentyl-1,3-phenylene diacetate (**131**). Finally, upon acetyl group removal and intramolecular oxa-Michael reaction, ACBM (**122**) was generated with 2:1 dr and 53 % overall yield Scheme 16.



Scheme 16: Synthetic pathway proposed by Sarlah [54] and Echavarren [56] to obtain the natural products ACBM (**122**) and *R*-CBM (**123**) and the synthetic diastereomer *S*-CBM (**133**)

R- and *S*-CBM (**123** and **133**) epimers were synthesized beginning with **131** via [$Pt(PPh_3)_4$]-catalyzed diboration using bis(pinacolato)diboron (B_2Pin_2) to introduce boryl moiety enantioselectively in its structure and then, undergo the boronate ester **132** to an oxidation with sodium perborate to furnish 1-((1*S*,2*R*,3*R*,4*R*)-3-(2,6-dihydroxy-4-pentylphenyl)-2-hydroxy-4-(prop-1-en-2-yl)cyclopentyl)ethanone (**133**) with 43% overall yield. Boronate ester **132** was epimerized using *p*-toluenesulfonic acid to generate the mixture of diastereoisomers (5:1, dr) which was separated to give 61% yield of 2-((1*R*,2*R*,3*R*,5*R*)-3-acetyl-5-(prop-1-en-2-yl)-2-

(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopentyl)-5-pentyl-1,3-phenylenediacetate (**134**). After boronic ester **134** oxidation, CBM (**123**) was delivered with 39% overall yields on the seven steps synthetic route from commercially available CBD (**34b**) Scheme 16.

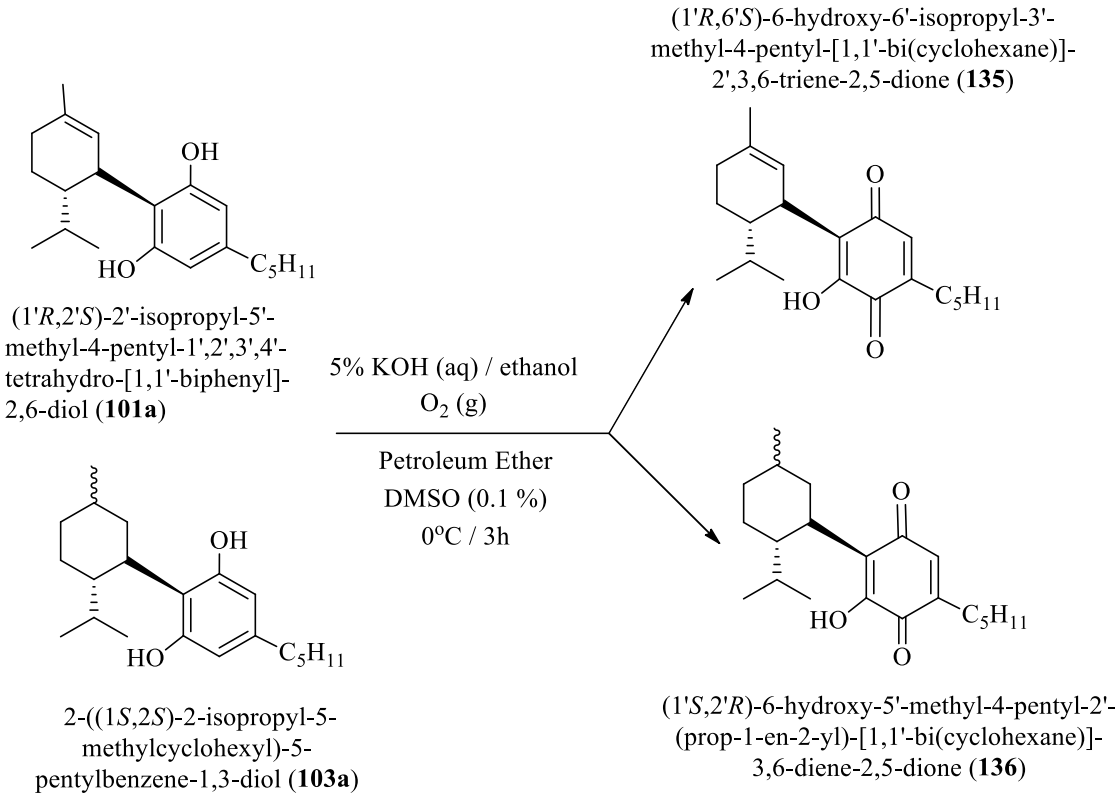
SATURATED QUINONOID CANNABINOID

There are various other saturated cannabinoids that have been explored and studied. Some of which include a variety of quinol compounds. Quinones have various biological activities and several natural and synthetic quinone compounds are currently used as therapeutic drugs. One particular cannabinoid quinone (HU-331: (1'*S*,6'*R*)-6-hydroxy-3'-methyl-4-pentyl-6'-(prop-1-en-2-yl)-[1,1'-bi(cyclohexane)]-2',3,6-triene-2,5-dione), was synthesized in 1968 to address the question of cannabinoids giving a purple color extracted with 5% aqueous KOH in methanol (Beam Test) [57,58]. Much later in the 1990s, HU-331 was studied once again due to the dual potential of its anticancer quinone moiety and non-toxic cannabinoid function. Cannabinoids have distinct pharmacokinetic properties when compared to the known quinoid anticancer drugs. HU-331 was shown to have very high efficacy against human cancer cell lines in-vitro and against in-vivo grafts of human tumors in nude mice [49, 58-60]. Although HU-331 is not saturated, there are several hydrogenated derivates such as: 1'*R*,6'*S*)-6-hydroxy-6'-isopropyl-3'-methyl-4-pentyl-[1,1'-bi(cyclohexane)]-2',3,6-triene-2,5-dione (**135**), (1'*S*,2'*R*)-6-hydroxy-5'-methyl-4-pentyl-2'-(prop-1-en-2-yl)-[1,1'-bi(cyclohexane)]-3,6-diene-2,5-dione (**136**), (6a*R*,10a*S*)-6,6,9-trimethyl-3-pentyl-6a,7,8,9,10,10a-hexahydro-1*H*-benzo[*c*]chromene-1,4(6*H*)-dione (**137**), (6a*R*,10a*S*)-6,6,9-trimethyl-3-pentyl-6a,7,8,9,10,10a-hexahydro-1*H*-benzo[*c*]chromene-1,2(6H)-dione (**138**), (6a*R*,10a*S*)-8-hydroperoxy-6,6-dimethyl-9-methylene-3-pentyl-6a,7,8,9,10,10a-hexahydro-1*H*-

benzo[*c*]chromene-1,4(6*H*)-dione (**139**), and (6a*R*,8*R*,10a*S*)-8-hydroxy-6,6-dimethyl-9-methylene-3-pentyl-6a,7,8,9,10,10a-hexahydro-1*H*-benzo[*c*]chromene-1,4(6*H*)-dione (**140**).

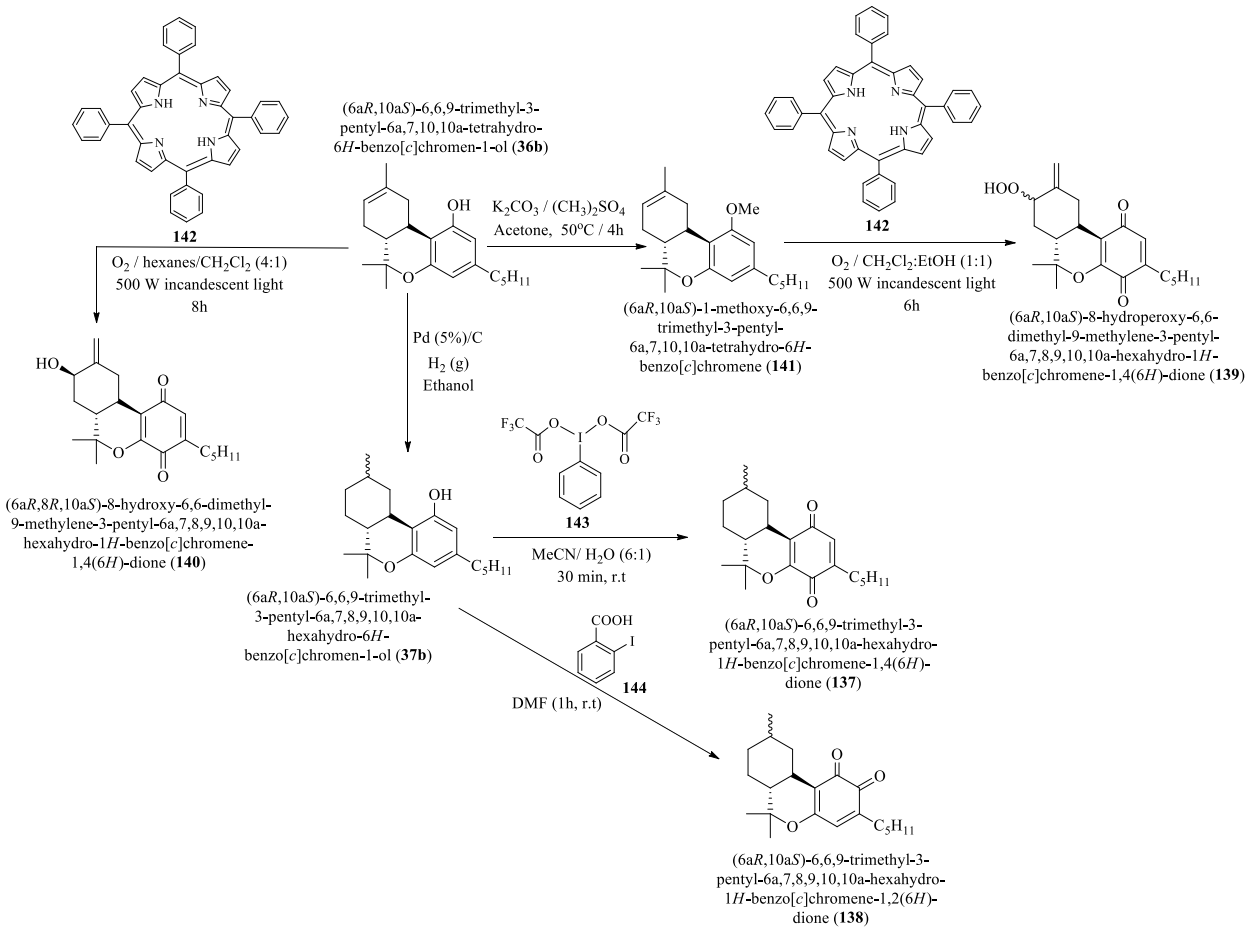
Different oxidation pathways of hydrogenated cannabidiol and tetrahydrocannabinol derivatives

Kogan [61] synthesized (1'*R*,6'*S*)-6-hydroxy-6'-isopropyl-3'-methyl-4-pentyl-[1,1'-bi(cyclohexane)]-2',3,6-triene-2,5-dione (**135**) and (1'*S*,2'*R*)-6-hydroxy-5'-methyl-4-pentyl-2'-(prop-1-en-2-yl)-[1,1'-bi(cyclohexane)]-3,6-diene-2,5-dione (**136**) with around 50 % yield from H_2CBD and H_4CBD, respectively, using aqueous potassium hydroxide (5%) solution in ethanol and bubbling the O_2 into the reaction mixture (Scheme 17).



Scheme 17: Oxidation of H_2-CBD (**101a**) and H_4-CBD (**103a**) to obtain their corresponding quinone derivatives in presence of oxygen.

In 2018 El Sohly's team [62] reported the synthesis of cannabinoid-quinones (**139** and **140**) based on tricyclic HHC. The introduction of the *p*-quinone core was carried out by irradiating with 500 W incandescent light of THC analogs (**141** and **36b**) in presence of 5,10,15,20-tetraphenyl-21*H*,23*H*-porphyrin and O_2. (6a*R*,10a*S*)-8-hydroperoxy-6,6-dimethyl-9-methylene-3-pentyl-6a,7,8,9,10,10a-hexahydro-1*H*-benzo[*c*]chromene-1,4(6*H*)-dione (**139**) and (6a*R*,8*R*,10a*S*)-8-hydroxy-6,6-dimethyl-9-methylene-3-pentyl-6a,7,8,9,10,10a-hexahydro-1*H*-benzo[*c*]chromene-1,4(6*H*)-dione (**140**) were afforded with very low yields, 13.6% and 5.5%, respectively (Scheme 18).



Scheme 18: Different oxidation pathways of HHC derivatives to obtain HHC-quinones

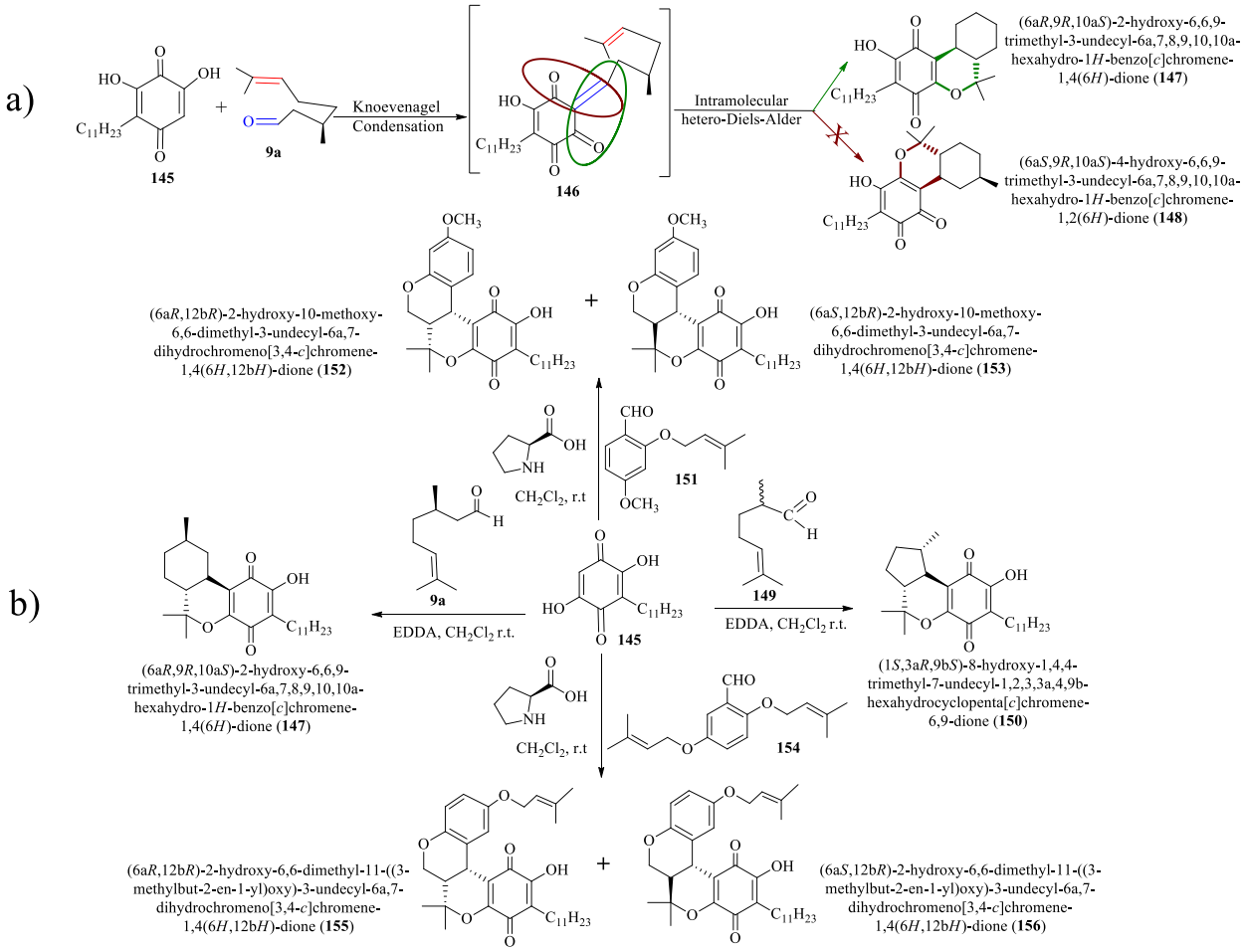
On the other hand, Deng [63] and Morales [64] carried out the oxidation of the HHC racemic mixture (**37b**) in the presence of two different oxidizing agents. When (bis(trifluoroacetoxy)iodo)benzene was used, in an air open-container the *para* (6a*R*,10a*S*)-6,6,9-trimethyl-3-pentyl-6a,7,8,9,10,10a-hexahydro-1*H*-benzo[*c*]chromene-1,4(6*H*)-dione (**137**) was accomplished. However, when using 2-iodobenzoic acid the (6a*R*,10a*S*)-6,6,9-trimethyl-3-pentyl-6a,7,8,9,10,10a-hexahydro-1*H*-benzo[*c*]chromene-1,2(6*H*)-dione (**138**) was afforded.

Applying the domino Knoevenagel intramolecular hetero Diels-Alder reaction to obtain benzoquinone derivatives

Aside from cannabinoid-specific quinones, there are countless other quinone scaffolds that could also be applied to cannabinoid core. Estévez-Braun [65] discusses a series of chromene-benzoquinone derivatives that were synthesized through *one-pot* domino Knoevenagel intramolecular hetero Diels-Alder reaction starting with 2,5-dihydroxy-3-undecylcyclohexa-2,5-diene-1,4-dione (**145**) and unsaturated aldehydes (**9a**, **151** and **154**). 2,5-dihydroxy-3-undecylcyclohexa-2,5-diene-1,4-dione is a natural product isolated as an active ingredient from *Embelia ribes* plant [66].

The coupling reaction between 2,5-dihydroxy-3-undecylcyclohexa-2,5-diene-1,4-dione (**145**) with (*R*)-3,7-dimethyloct-6-enal (**9a**), where the keto group is close to a double bond, drive to the formation of the adduct **146** which suffers *in situ* an intramolecular hetero-Diels−Alder reaction with the dienophile moiety, affording the corresponding chromene-benzoquinone derivatives (**147** and **148**). The polyfunctional adduct **146** has two possible dienes to combine with the dienophile that could lead to *ortho*- or *para*-benzoquinonic derivatives (**147** and **148**), however only was obtained the **147** diastereomer. The high diastereoselectivity through intramolecular hetero

Diels−Alder reaction can be interpreted because the exo-*E*-anti transition state is the only possible can be formed since the endo-*Z*-anti transition state has geometric impediment to be reached. (Scheme 19a).



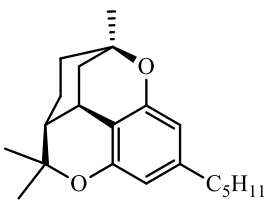
Scheme 19: Reaction between 2,5-dihydroxy-3-undecylcyclohexa-2,5-diene-1,4-dione (**145**) with unsaturated aldehydes to obtain cannabinoid-quinone analogs.

Some cannabinoid-quinone analogs were accomplished using this approach. Knoevenagel condensation was carried in the presence of different organic catalysts such as 1,2-ethanediamine acetate (EDDA) or (*S*)-pyrrolidine-2-carboxylic acid. For the synthesis of (6a*R*,9*R*,10a*S*)-2-hydroxy-6,6,9-trimethyl-3-undecyl-6a,7,8,9,10,10a-hexahydro-1*H*-benzo[c]chromene-1,4(6*H*)-dione (**147**) and (1*S*,3a*R*,9b*S*)-8-hydroxy-1,4,4-trimethyl-7-undecyl-1,2,3,3a,4,9b-

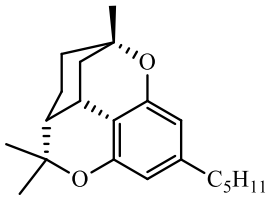
hexahydrocyclopenta[*c*]chromene-6,9-dione (**150**) the best results were obtained using EDDA in dichloromethane. However, when unsaturated aromatic aldehydes (**151** and **154**) were employed to form tetracyclic chromene-benzoquinone derivatives, EDDA gave poor diastereoselective obtaining a racemic mixture of *cis* and *trans* compounds (**152/153** and **155/156**). With the objective of improving the diastereomeric rate, they implemented the condensation in presence of (*S*)-pyrrolidine-2-carboxylic acid, a chiral amino acid and under these conditions the *cis* diastereomer was obtained in higher ratio (**152:153**, 9:1 and **155:156**, 8:1).

BI- TRI- AND TETRA- CYCLIC HYDROGENATED NATURAL CANNABINOID SCAFFOLDS AND

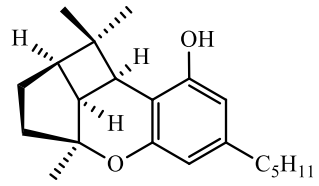
Cannabichromene, (*R*)-2-methyl-2-(4-methylpent-3-en-1-yl)-7-pentyl-2*H*-chromen-5-ol (CBC, **163**), is a minor, chiral, non-psychoactive cannabinoid found in *Cannabis Sativa*. Since first being isolated and identified in 1960s from hashish oil, studies have shown CBC to be a powerful and potent selective CB2 and TRPA1 agonist, leading to its anti-inflammatory activity [67]. CBC is the starting point for obtaining various bi- tri- and tetra- cyclic hydrogenated natural cannabinoid scaffolds such as (6a*R*,9*S*,10a*S*)-6,6,9-trimethyl-3-pentyl-6a,7,8,9,10,10a-hexahydro-6*H*-1,9-epoxybenzo[*c*]chromene (**158**), (1a*R*,1a1*S*,3a*S*,8b*S*)-1,1,3a-trimethyl-6-pentyl-1a,1a1,2,3,3a,8b-hexahydro-1*H*-4-oxabenzo[*f*]cyclobuta[*cd*]inden-8-ol (**159**), (2*R*,5*S*,6*R*)-2-methyl-9-pentyl-5-(prop-1-en-2-yl)-3,4,5,6-tetrahydro-2*H*-2,6-methanobenzo[*b*]oxocin-7-ol (**160**), and (*R*)-2-methyl-2-(4-methylpentyl)-7-pentyl-2*H*-chromen-5-ol (**161**) (Figure 4).



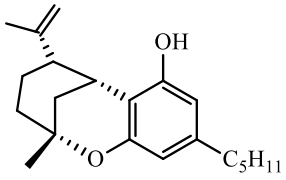
(6a*S*,9*R*,10a*R*)-6,6,9-trimethyl-3-pentyl-6a,7,8,9,10,10a-hexahydro-6*H*-1,9-epoxybenzo[*c*]chromene (**157**)



(6a*R*,9*S*,10a*S*)-6,6,9-trimethyl-3-pentyl-6a,7,8,9,10,10a-hexahydro-6*H*-1,9-epoxybenzo[*c*]chromene (**158**)



(1a*R*,1a^1*S*,3a*S*,8b*S*)-1,1,3a-trimethy pentyl-1a,1a^1,2,3,3a,8b-hexahydro-1 oxabenzo[*f*]cyclobuta[*cd*]inden-8-ol



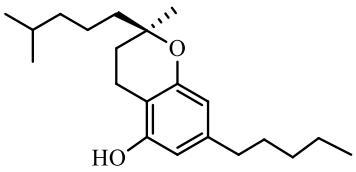


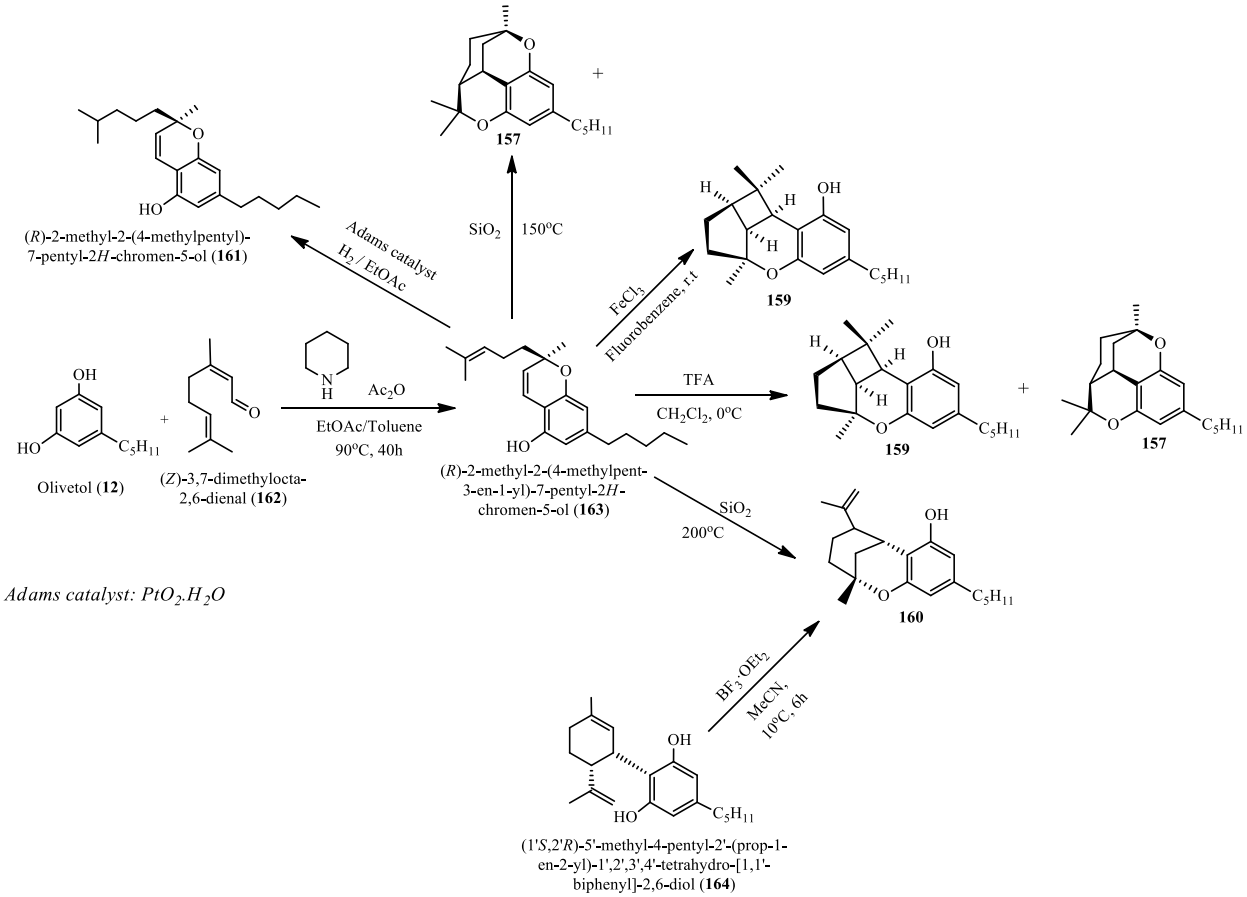
Figure 4: Structures of (-) cannabicitran (**157**) (+)-cannabicitran (**158**), cannabicyclol (**159**), Δ8-*iso*-*cis*-THC (**160**), and tetrahydrocannabichromene (**161**)

CANNABICITRAN

Cannabicitran (CBT, **157/158**) is another naturally found hydrogenated cannabinoid that is saturated and epoxide containing. Recently, Williamson [68] demonstrated that CBT appears as a racemic mixture in *Cannabis sativa* plant after separated both enantiomers: (6a*S*,9*R*,10a*R*)-6,6,9-trimethyl-3-pentyl-6a,7,8,9,10,10a-hexahydro-6*H*-1,9-epoxybenzo[*c*]chromene (**157**) and (6a*R*,9*S*,10a*S*)-6,6,9-trimethyl-3-pentyl-6a,7,8,9,10,10a-hexahydro-6*H*-1,9-epoxybenzo[*c*]chromene (**158**) via preparative HPLC chromatography using a chiral column (Figure 4).

((-)-CBT was synthesized via the [3 + 3] Knoevenagel annulation between olivetol (**12**) and (*Z*)-3,7-dimethylocta-2,6-dienal (**161**) affording (*R*)-7-butyl-2-methyl-2-(4-methylpent-3-en-1-yl)-2*H*-chromen-5-ol (**162**) which suffered an acid-catalyst intramolecular [2 + 2] cyclization in presence of silica gel [69] or trifluoroacetic acid [70, 71] to yield (6a*S*,9*R*,10a*R*)-6,6,9-trimethyl-

3-pentyl-6a,7,8,9,10,10a-hexahydro-6*H*-1,9-epoxybenzo[*c*]chromene (**157**) with 50% or 9%, respectively (Scheme 20).



Scheme 20: Synthetic procedure to obtain (-) cannabicitran (**157**), cannabicyclol (**159**), Δ8-*iso*-*cis*-THC (**160**), and tetrahydrocannabichromene (**161**)

CANNABICYCLOL

Another saturated natural cannabinoid is cannabicyclol (CBL, **159**). CBL's structure had several revisions until finally Marlowe [72] established by X-ray analysis the (1a*R*,1a^1*S*,3a*S*,8b*S*)-1,1,3a-trimethyl-6-pentyl-1a,1a^1,2,3,3a,8b-hexahydro-1*H*-4-oxabenzo[*f*]cyclobuta[cd]inden-8-ol (**159**) as absolute configuration of CBL after treatment it with (*S*)-(+)-ibuprofen (Figure 4).

CBL (**159**) was synthesized by Hsung [73] with 74% of yield from (*R*)-7-butyl-2-methyl-2-(4-methylpent-3-en-1-yl)-2*H*-chromen-5-ol (**162**) via cationic [2π + 2π] cyclization in presence of trifluoracetic acid in dichloromethane at 0°C. CBT (**157**) was formed as a by-product with only 9%. Later, Li [74] developed a pathway to obtain CBL from compound **162** using $FeCl_3$ in fluorobenzene with 79% yield and 0% of CBT (**157**) (Scheme 20).

Δ8-*ISO*-*CIS*-THC

Δ8-*iso*-*cis*-THC (**160**) is obtained with 18% from the protonation of the aliphatic double bond in (*R*)-7-butyl-2-methyl-2-(4-methylpent-3-en-1-yl)-2*H*-chromen-5-ol (**162**) followed by the formation of a benzylic cation, and finally enclosed by the terminal 2-methylbut-2-ene double bond and the loss of a proton [69] (Scheme 20). Also, it can be accomplished starting with (1'*S*,2'*R*)-5'-methyl-4-pentyl-2'-(prop-1-en-2-yl)-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-2,6-diol (**163**) using boron trifluoride etherate as acid-catalyst and acetonitrile as solvent at -10°C via cyclization from Δ5' double bond (Scheme 20).

TETRAHYDROCANNABICHROMENE

Gaoni [70] reported the synthesis of tetrahydrocannabichromene ((*R*)-2-methyl-2-(4-methylpentyl)-7-pentyl-2*H*-chromen-5-ol: **161**) via catalytic hydrogenation of CBC (**163**) using Adams catalyst at atmospheric pressure of hydrogen.

BIOLOGICAL STUDIES OF SATURATED CANNABINOIDS

Although saturated cannabinoids have been known for about 100 years, no absorption, distribution, metabolism, and excretion (ADME) studies have been published in peer-review journals. It is important to consider that HHC has invaded the recreational market in the last two years and its consumption by inhaling, ingesting in the form of edibles, or by taking it sublingually with oils

could trigger psychotropic effects by not knowing the proper dosages and side effects of this product and its analogs.

For this reason, research on the mechanism of action, the interaction in the human organism, and the new biological applications of HHCs and their analogs should be a priority in research projects. In this section of the review, we have compiled all the data on the affinities of saturated cannabinoids for CB1 and CB2 receptors and their relationship with the different functionalities in the HHC scaffold, considering the five distinct regions (terpene moiety, ring B, resorcinol core, lipid tail, and stereocenters) or the four main pharmacophores (alkyl side chain, a phenolic hydroxyl group, a northern aliphatic group, and a southern substituent in the pyran ring) in the HHC structure which are important for cannabimimetic receptor affinities (Figure 5).

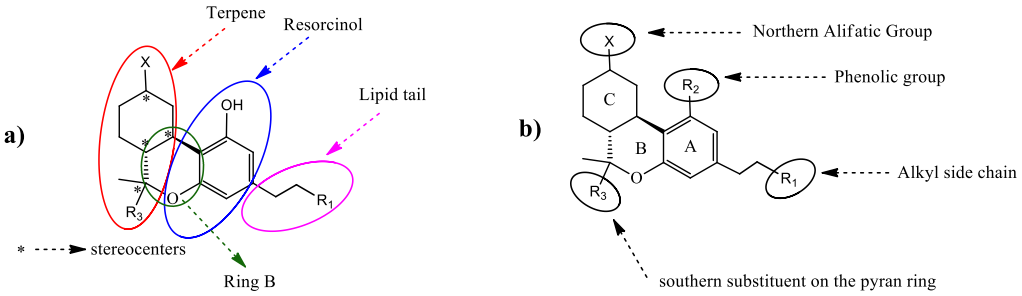


Figure 5: a) HHC scaffold broken down into five distinct regions b) Four major pharmacophores present in the HHC core.

The modification in the terpene moiety determines the role of the ring rigidity and whether the introduction of hydrogen bond donors and acceptors could influence the affinity and selectivity for both CB1 and CB2 receptors. Alteration of the resorcinol ring allows examining the effect of the free hydroxyl group, protected forming ethers, oxidized forming quinones, or removed on the biological activity of hydrogenated cannabinoids. The alkyl chain and stereocenters permit to an evaluation of how geometric constraints and lipophilicity influence binding pockets. Finally, it is

important to determine the difference between bicyclic cannabinoids (CBD analogs, ring B opened) and tricyclic cannabinoids (THC analogs, ring B closed) in receptor affinity.

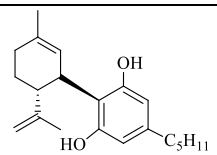
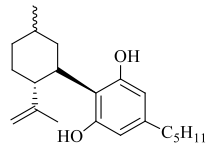
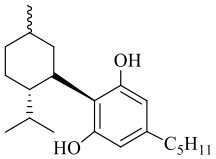
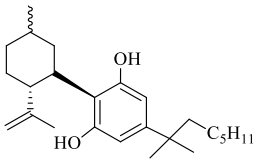
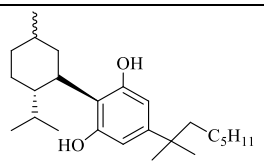
The search to comprehend the molecular basis of the pharmacological effects of cannabinoids led to the identification and characterization of CB receptors. The cannabinoid receptors are membrane-bound receptors that belong to a superfamily of G-protein coupled receptors (GPCRs). To date, two CB receptors, CB1 and CB2, have been isolated, cloned, and expressed. The first cannabinoid receptor (CB1) was discovered when Matsuda cloned and expressed this GPCR from rat brains in 1990 [75] followed by the expression of human CB1 in 1991 by Gerard [76]. In 1993 Munro found, cloned, and expressed a second cannabinoid receptor (CB2) within the preparation of a human promyelocytic leukemia cell line (HL60) [77]

Affinities of hydrogenated cannabinoids for CB1 and CB2 receptors

In contrast to CBD (**34b**), 2-((1*S*,2*S*)-2-isopropyl-5-methylcyclohexyl)-5-pentylbenzene-1,3-diol (**103a**, table 2) and 2-((1*S*,2*S*)-2-isopropyl-5-methylcyclohexyl)-5-(2-methyloctan-2-yl)benzene-1,3-diol (**103b**, table 2) have affinity for the cannabinoid CB1 receptor. It means that by removing the double bond from ring C and from the southern aliphatic chain, the ability to bind to the CB1 receptor increases. Also, by branching the lipophilic chain incorporating two methyl groups, the affinity for the CB1 receptor (comparing compounds **103a** and **103b**) was improved. Ben-Shabat [9] demonstrated that the anti-inflammatory capacity of these compounds owes its origin to the effect on the production of reactive oxygen intermediates (ROIs), nitric oxide (NO), and tumor necrosis factor (TNF). Moreover, Ben-Shabat [9] concluded that the activation of such mediators is not directly through the central cannabinoid receptor CB1 because compound **103b** showed

decreased suppressive effects on ROI, NO, and TNF-R production compared to compound **103a** (Table 2).

Table 2: Affinities (K*i*) of hydrogenated CBD analogs for rCB1 and mCB2

Compound	K*i* (nm)					Function	Reference
	rCB$_1$	**hCB$_1$**	**rCB$_2$**	**mCB$_2$**	**hCB$_2$**		
 **34b**	>10000	-		>10000	-	-	46
 **102a**	>1000	-	-	-	-	-	46, 9
 **103a**	145	-	-	-	-	-	46, 9
 **102b**	124	-	-	-	-	-	46, 9
 **103b**	17	-	-	-	-	-	46, 9

Macheriols and machaeridiols are important types of hexahydrodibenzopyran-cannabinoids. Macheriols are characterized by having a chromane core and an ABC tricyclic system, structurally similar to HHC, and machaeridiols are defined by the open B pyran ring which resembles H$_4$CBD.

The main difference lies in the inversion of stereocenters on the position 6a and 10a for machaeriol or 1 and 2 for machaeridiols. Also, these compounds showed an aralkyl group as a side chain instead of a lipophilic chain as HHC and H_4CBD.

Table 3 reveals that machaeridiols A, B, and C (**106**, **167**, and **168**) show selective binding affinities for CB2 receptors, however machaeriol C and D (**39** and **43**) exhibit affinities for both CB1 and CB2 receptors.

Chittiboyina et al [79] designed a synthetic machaeriol (compound **166**, Table 3) that is CB2 selective agonist which is characterized by a benzothiophene moiety in the side chain. They performed *in-silico* molecular docking experiments to explain the binding affinities of compound **166** into the active sites of CB1 and CB2 receptors protein crystal structures using Maestro, Schrödinger (Figure 6a). This compound showed π−π stacking interactions between hexahydrochromane and benzothiophene cores with the residues Phe170, Phe268, and Trp279 of CB1 receptor. In addition, **166** generated hydrophobic interactions with a series of aquaphobic residues involving Phe108, Phe174, Phe177, Leu193, Val196, Phe200, Ile267, Trp279, Trp356, Leu359, Phe379, Ala380, and Cys386. In a similar fashion compound, **166** exhibited π−π stacking and hydrophobic interactions with CB2 residues. However, the major difference lay in the H-bonding shown between the hydroxyl group of the resorcinol ring and Ser285 (figure 6B, marked with a purple circle), which is an essential residue for CB2 receptor activity.

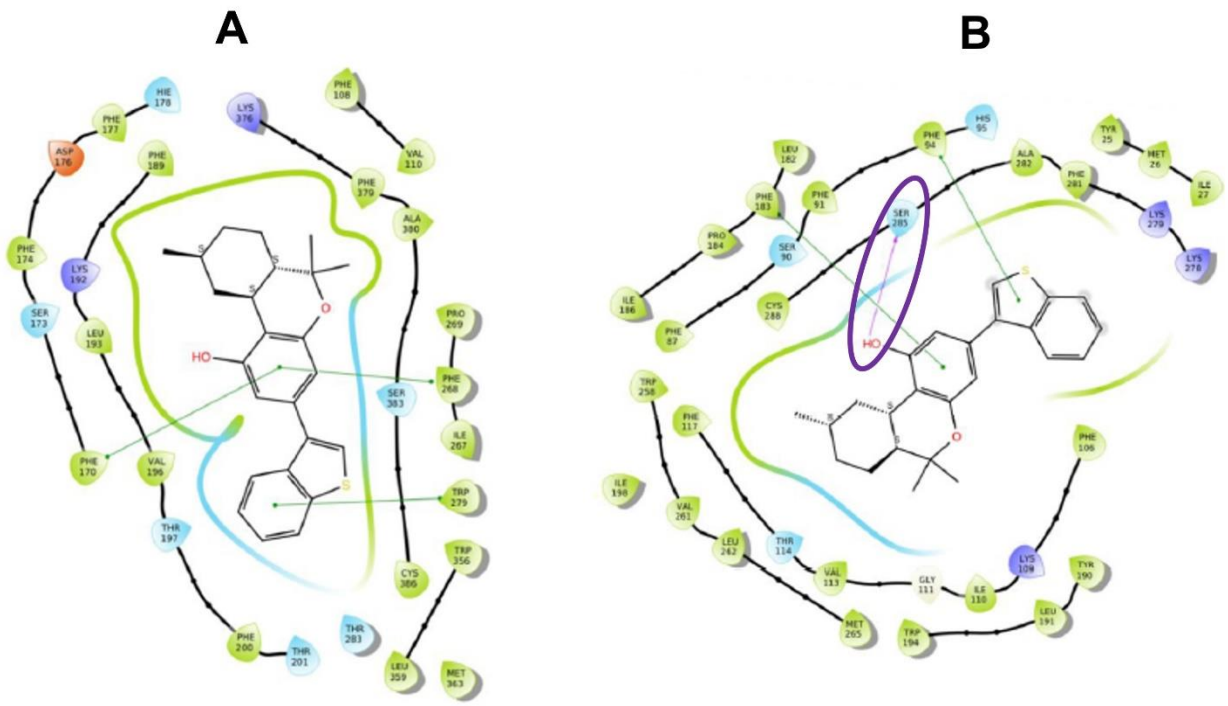
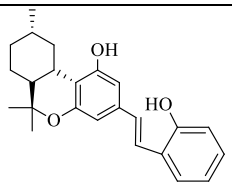
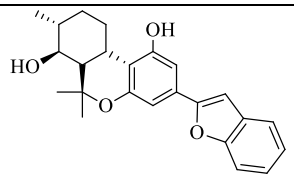
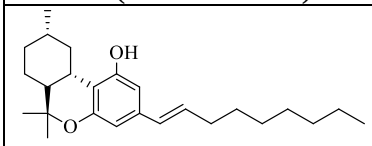
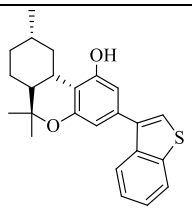
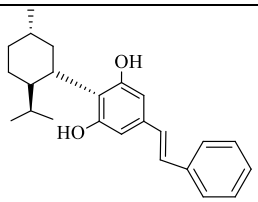
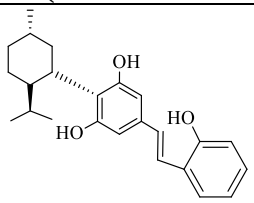
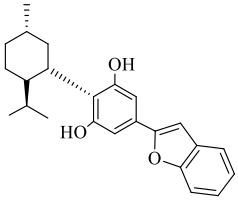


Figure 6: 2D interaction diagrams. **A)** compound **166** against the CB1 receptor **B)** compound **166** against the CB2 receptor [78].

We consider it essential to carry out a more in-depth study of SAR on machaeriol derivatives to achieve novel analogs with better CB2 receptor selectivity, focusing on the side chain and the stereocenters of the HHDBP scaffold (**46**).

Table 3: CB1/CB2 cannabinoid receptor binding affinity for Machaeriol, Machaeridiol, and their homologous

Compound	Ki (μm)					Function	Reference
	rCB$_1$	hCB$_1$	rCB$_2$	mCB$_2$	hCB$_2$		
 **39** (Machaeriol C)	3.27	-	7.76	-	-	-	78

 **43** (Machaeriol D)	1.75	-	1.30	-	-	-	78
 **165**	0.34	-	0.57	-	-	-	79
 **166**	>1000	-	0.040	-	-	CB2 selective agonists	79
 **106** (Machaeridiol A)	>1000	-	1.77	-	-	CB2 selective agonists	78
 **167** (Machaeridiol B)	>1000	-	2.18	-	-	CB2 selective agonists	78
 **168** (Machaeridiol C)	>1000	-	1.11	-	-	CB2 selective agonists -	78

Tables 4, 5, and 8 show how the four main pharmacophores influence the binding affinities of nonclassical and hybrid saturated tricyclic cannabinoids for CB1 and CB2 receptors.

Southern aliphatic hydroxyl chain (SAH)

Modification of SAH generates a family of non-classical cannabinoids that have not been found in the cannabis plant. First, we focus on the effect of the orientation of the SAH group. For this, Makriyannis [82] synthesized compounds **197** and **198** demonstrating that the epimer (6*S*,6a*R*,9*R*,10a*S*)-6-(2-hydroxyethyl)-6-methyl-3-pentyl-6a,7,8,9,10,10a-hexahydro-6*H*-benzo[*c*]chromene-1,9-diol (**197**), which the hydroxyethyl group is in equatorial position, has greater affinity for both receptors CB1 and CB2 resulting in more favorable ligand-receptor interaction (table 4). Second, Makriyannis examined the role of the hydroxyalkyl chain length and bulk in the activity of this scaffold. The binding affinities of compounds **188**, **189**, and **190**, indicate little change in the CB1 and CB2 receptor affinity with increasing chain length. From the receptor binding data that display compounds **186**, **191**, and **190** it can be concluded that the conformation of the side chain is not important for ligand-receptor interaction since the alkyne (**191**), alkene (**186**) analogs exhibit similar receptor affinity to that of the hydroxyalkyl analog (**190**). When incorporating a halogen such as iodine(compound,**199**) the binding affinity for the CB1 and CB2 receptor decreases. From these results, it can be concluded that while the relative configuration 6-axial or 6-equatorial of the SAH appears to be critical, the length and the conformation of the southern hydroxyl chain are of lesser effect in determining the cannabinoid activity. Including a halogen atom is reflected in the loss of affinity for CB1 and CB2 receptors.

Northern aliphatic group (NAG)

Relating NAG we examined the role of the stereochemistry at C-10, the length of the C-10 substituent, and functionality at C-10 in the cannabimimetic activity. The binding affinities data for CB1 and CB2 receptors appear in tables 4, 5, and 8. Table 8, which describes novel hydrogenated adamantyl cannabinoids, shows that all 10β-epimers (equatorial orientation of the C-10-alkyl chain) improve CB1 and CB2 affinities compared to the 9α-epimers. The length of C-

10-alkyl chain does not affect the CB1 and CB2 affinities comparing compounds **218** and **223** in table 8. The iodo-methyl derivative (**220**) sharply decreased CB1/CB2 affinities, revealing poor steroelectronic interactions at CB1 and CB2 residues. Judging by the data of binding affinities of pairs compounds **216** /**223** (table 8) and **93** / **89** (table 4), the functionality on C-10 revealed better CB1/CB2 affinity of CH2OH compared with OH. Judging by the data of binding affinities of pairs compounds 217 /224 (table 8) and 93 / 89 (table 4), C-10 functionality (CH2OH) revealed better CB1/CB2 than the OH group. Contrasting the CB1/CB2 affinity value of compound **93**, table 4 (3.0 / 2.1) and **179**, table 4 (0.6 / 2.65), the introduction of azido group (**179**) increases the affinity for CB1 receptor and remains similar to the affinity for CB1 receptor.

Phenolic Group

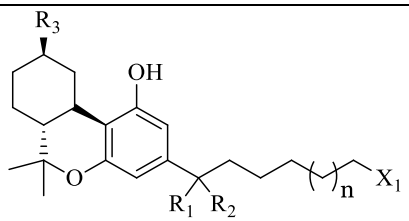
Cannabinoid derivatives in which the hydroxyl group in the resorcinol core was removed or substituted by an alkyl chain to generate an ether group significantly decrease ligand binding to CB1 displaying better selectivity for the CB2 receptor (Comparing compounds **200** and **201**, table 5). Compound **201**, the corresponding methyl ether of **200** exhibits more than 2000-fold CB2-selectivity. Interestingly, affinity to CB2 is only faintly altered by these changes.

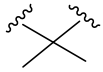
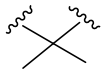
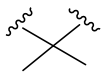
Alkyl side chain

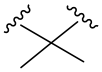
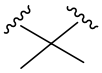
The manipulation of the electronics and conformational flexibility of the lipophilic side chain reveals the complexity and specificity of the cannabinoid-binding pocket as tables 4 and 5 show. Ramification between C-1’ and C-2’ in the side chain as shown in compounds **172/173** and **184/185** leads to increased receptor affinity and selectivity, obtaining a CB1 receptor selective antagonist when it introduces a 4-carbon cycle between C-1’ and C-2’ (compound **193**). Unsaturation at the lipidic chain, no further increase in potency is noted when C-2’ and C-3’ are joined by a double bond, as illustrated in compound **206** (alkene) compared with **207** (unsaturated

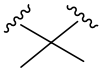
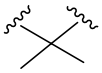
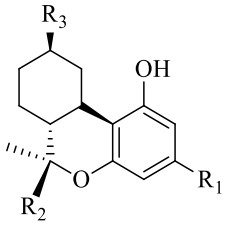
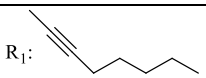
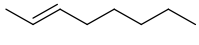
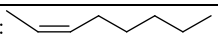
chain) or compound **182** which has a double bond between C-1' and C-2' compared with **184** (alkane). However, in compound **181** which presents a triple bound at C-1' and C-2', the CB2-biding affinity decreases relating to **182** (alkene) and **184** (alkane). The addition of a halogen group and the end of the side chain slightly affects the receptor affinity (compounds **193**, **195**, **196**). Targeted covalent inhibitors (TCIs)represent an interesting development in cannabinoid ligands. Two major types of covalently activated lipidic chains have been employed as TCIs; those upholding electrophilic or photoactivatable functionality. For example, compounds **170**, **174** and **177** which have attached an azide (-N_3, photoactivatable moiety), isothiocyanate (-NCS, electrophilic functional group), or cyano (-NC, electrophilic functional group) functionality respectively, reduce the CB1 and CB2 receptor affinity (table 4).

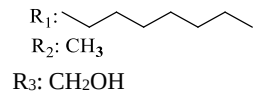
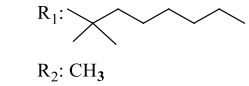
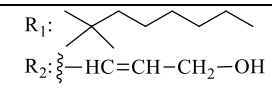
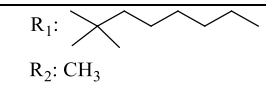
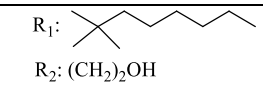
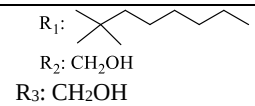
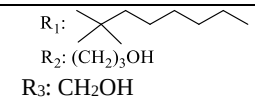
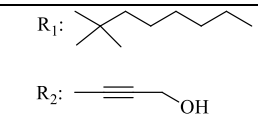
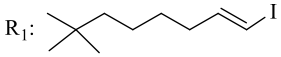
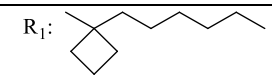
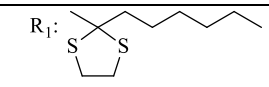
Table 4: Affinities (K*i*) of hybrid / non-classical cannabinoids for rCB1, hCB1, vv, and hCB2.



Compound	Ki (nm)					Function	Reference
	rCB1	**hCB1**	**rCB2**	**mCB2**	**hCB2**		
X_1=H, n=2 R_1 R_2  R_3=CH_2OH **93**	3.0±0.8	-	-	-	2.1±0.6	Agonist	80
X_1=H, n=2 R_1 R_2  R_3=OH **89** (Canbisol)	19.0±0.6				13.1±0.2	-	80
X_1=N_3, n=2 R_1 R_2 	0.41±0.05	-	-	0.8±0.1	1.4±0,06	Agonist	80

R_3=CH_2OH **169**							
X_1=N_3, n=2 R_1 R_2  R_3=CH_2OH **170**	0.40±0.1	-	-	0.8±0.1	0.8±0.1	Agonist	80
X_1=N_3, n=3 R_1 R_2  R_3=CH_2OH **171**	0.5±0.2	-	-	1.6±0.1	1.5±0.3	Agonist	80
X_1=NCS, n=2 R_1 R_2  R_3=CH_2OH **172**	0.39±0.04		-	0.8±0.1	3.15±0.04	Agonist	80
X_1=NCS, n=2 R_1 =R_2=H R_3=CH_2OH **173**	5.65±0.1	9.0±0.4	-		10.50±0.02	Agonist	81
X_1=NCS, n=2 R_1 R_2  R_3=CH_2OH **174**	1.1±0.1	-	-	0.9±0.2	1.3±0.05	Agonist	80
X_1=NCS, n=3 R_1 R_2  R_3=CH_2OH **175**	0.4±0.1	-	-	1.1±0.1	1.0±0.2	Agonist	80
X_1=CN, n=2 R_1 R_2  R_3=CH_2OH **176**	0.4±0.05	-	-	0.8±0.1	0.4±0.2	Agonist	80
X_1=CN, n=2	0.8±0.2	-	-	1.0±0.1	1.4±0.2	Agonist	80

R_1 R_2  R_3=CH_2OH **177**							
X_1=CN, n=3 R_1 R_2  R_3=CH_2OH **178**	0.5±0.1	-	-	0.9±0.1	0.4±0.05	Agonist	80
X_1=N_3, n=2 R_1 R_2  R_3= N_3 **179**	0.60 ±0.2	-	-	-	2.65 ±0.3	Agonist	82
X_1=I, n=2 R_1 R_2  R_3= N_3 **180**	0.67±0.1	-	-	-	0.72±0.1	Agonist	82
							
Compound	**K*i* (nm)**					**Function**	**Reference**
	rCB_1	**hCB_1**	**rCB_2**	**hCB_2**	**mCB_2**		
 R_1: R_2: CH_3 R_3: CH_2OH **181**	-	5.8	-	61.6	-	-	82
 R_1: R_2: CH_3 R_3: CH_2OH **182**	-	1.2	-	5.3	-	-	82
 R_1: R_2: CH_3 R_3: CH_2OH **183**	-	0.8	-	9.5	-	-	82

 **184**	-	1.7	-	14.3	-	-	82
 **185**		0.045		0.061			82
 **186**		0.7		8.6			82
 **187**	-	2.3	-	2.3	-	-	82
 **188**	-	2.8	-	2.3	-	-	82
 **189**	-	2.9	-	2.4	-	-	82
 **190**	-	2.2	-	3.4	-	-	82
 **191**	-	1.21	-	0.3	-	-	82
 **192**	-	0.80	-	0.85	-	-	82
 **193**	-	0.16	-	42.1	-	CB_1 receptor selective antagonist	83
 **194**	-	4.51±0.7	-	13.9±3.4	-	-	41

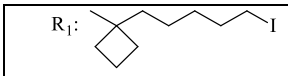
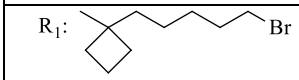
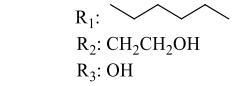
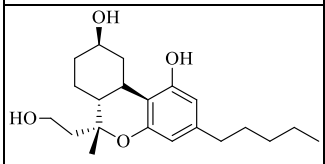
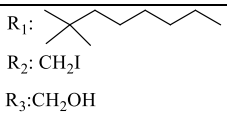
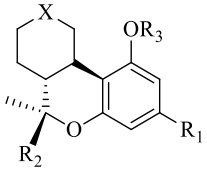
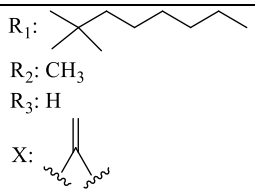
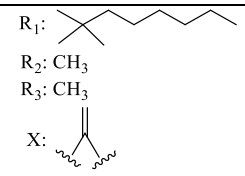
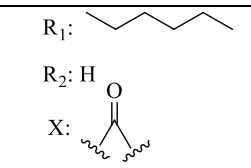
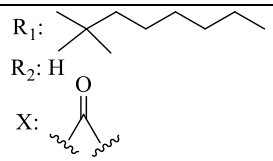
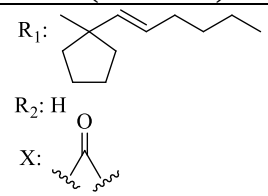
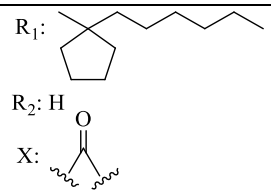
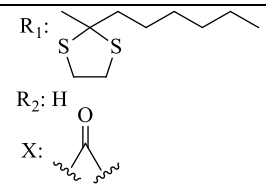
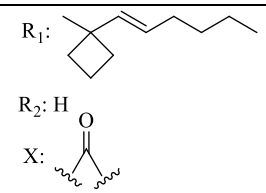
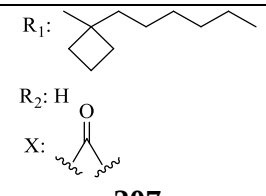
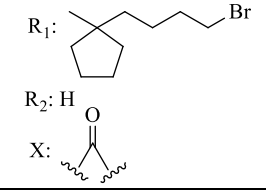
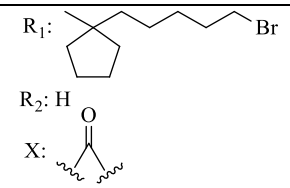
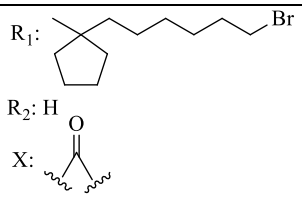
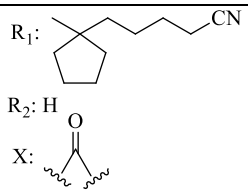
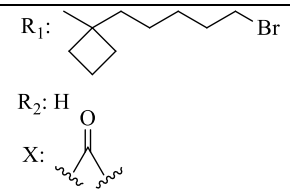
 **195**	-	3.16±0.05	-	4.21±0.93	5.13±1.27	-	41
 **196**	-	1.37±0.35	-	2.76±0.63	1.62±0.45	-	41
 **197**	-	70.5	-	1.99	-	-	82, 85
 **198**	-	1353.9		2476.7	-	-	82, 85
 **199**		40.7		19.7			41

Table 5: Affinities (K*i*) of hybrid / non-classical cannabinoids for hCB1, mCB2, and hCB2.



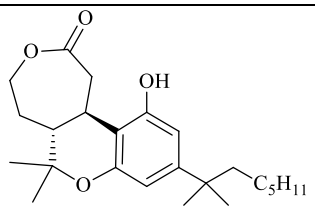
Compound	Ki (nm)					Function	Reference
	rCB1	**hCB1**	**rCB2**	**mCB2**	**hCB2**		
 **200**	-	1.82	-	-	0.58	Agonist Mixed CB_1/CB_2	82
 **201**	-	>20,000	-	-	1.94	CB_2 Selective Agonist	82

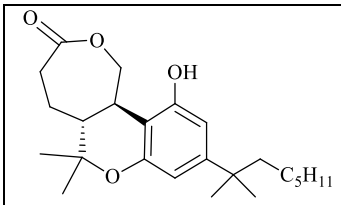
 **202**	-	333.0	-	265	-	-	41
 **88** (Nabilone)	-	2.19	-	1.84		Agonist Mixed CB_1/CB_2	41
 **203**	-	1.23	-	5.25	7.02	-	41
 **204**	-	1.76	-	0.97	3.34	-	41
 **205**	-	6.57	-	42.3	32.6	-	41
 **206**	-	1.13	-	12.0	15.1	-	41
 **207**	-	0.84	-	13.7	11.9	-	41
	-	13.1	-	13.9	-	-	41

208							
 **209**	-	1.03	-	2.59	1.32	-	41
 **210**	-	4.96	-	1.60	3.02	-	41
 **211**	-	3.14		2.78	-	-	41
 **212**	-	2.33		7.56	-	-	41

Incorporating a 7-membered lactone in the ring C of the HHC scaffold generates a selective rCB1 agonist compound (**99a**, table 6). It is interesting that its regioisomer (**99b**) did not display selectivity for rCB1 receptors.

Table 6: Affinities (K*i*) of Cannabinoid Lactones for rCB1, mCB2, and hCB2

Compound	K*i* (nm)					Function	Reference
	rCB$_1$	**hCB$_1$**	**rCB$_2$**	**mCB$_2$**	**hCB$_2$**		
 **99b**	99.0±11	-	-	803.0±87	94.1±13	-	42

 **99a**	4.6±2.8	-	-	792.3±76	54.1±7	Agonist CB_1	42

Cannabinoid-receptor binding affinities presented in table 7 demonstrated that the introduction of the 1,4-quinone moiety (compounds **139** and **140**) led to loss of affinity towards cannabinoid receptors CB1 and CB2.

Table 7: Affinities (K*i*) of Cannabinoid-quinone for rCB1, and mCB2

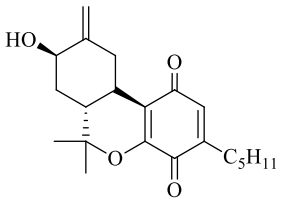
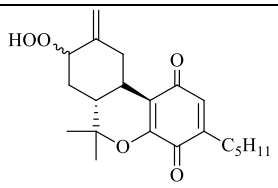
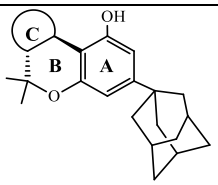
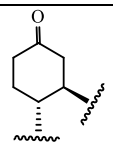
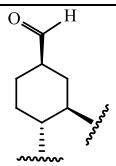
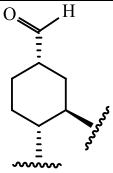
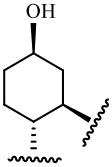
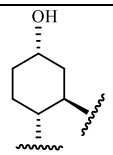
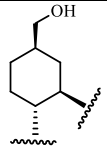
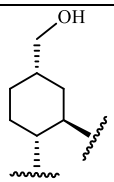
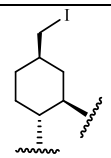
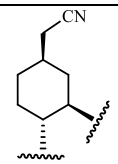
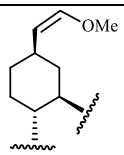
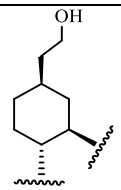
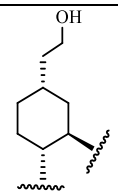
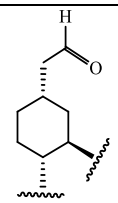
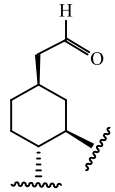
Compound	**Ki (nm)**					**Function**	**Reference**
	rCB_1	**hCB_1**	**rCB_2**	**mCB_2**	**hCB_2**		
 **140**	919.7	-	-	2034.1	-	-	62
 **139**	286.4	-	-	464	-	-	62

Table 8: Affinities (K*i*) of 7-(adamantan-1-yl)-2,2-dimethylchroman-5-ol analogs for rCB1, mCB2, and hCB2

Adamantyl Cannabinoid: 							
Compound	**K*i* (nm)**					**Function**	**Reference**
	rCB_1	**hCB_1**	**rCB_2**	**mCB_2**	**hCB_2**		

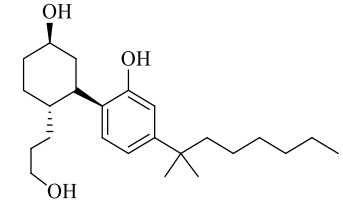
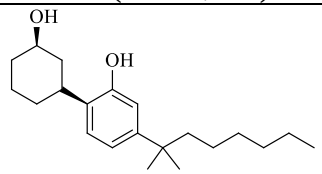
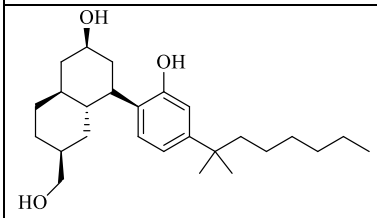
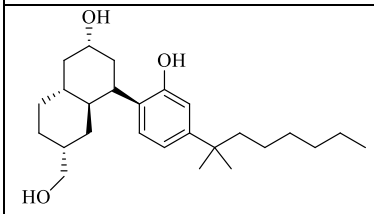
 **213**	175.6	-	-	249.5	338	-	84, 85
 **214**	52.9	-	-	25.7	5.5	Agonist	84, 85
 **215**	480.2	-	-	200.1	90.0	-	84, 85
 **216**	23.9	-	-	39.4	40.5	Agonist	84, 85
 **217**	146.3	-	-	255.0	671.8	-	84, 85
 **218**	4.9	-	-	12.1	11.3	Agonist	84, 85
 **219**	90.1	-	-	95.1	121.2	Agonist	84, 85
 **220**	241.0	-	-	345.0	261.7	-	84, 85

 **221**	48.7	-	-	87.0	100.3	Agonist	84, 85
 **222**	31.0	-	-	90.3	67.2	Agonist	84, 85
 **223**	4.6	-	-	18.4	13.3	Agonist	84, 85
 **224**	40.9	-	-	21	365.3	Agonist	84, 85
 **225**	170.5	-	-	80.1	70.8	Agonist	84, 85
 **226**	13.2	-	-	34.3	11.2	Agonist	84, 85

Nonclassical, bicyclic-hydrogenated cannabinoids are exemplified by the paradigm compound, CP-55,940 (**227**, table 9). This compound acts as a full agonist for both CB1 and CB2 receptors. Compound **228** is obtained by removing the SAH chain from **227** and this leads to the reduction of affinity towards both receptors, CB1 and CB2. Attaching a cyclohexyl group to ring C increases

the receptor binding affinity depending on the stereochemistry of the linkage of this group (Compound **229** and **230**, table 9).

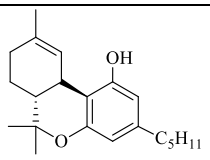
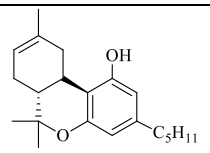
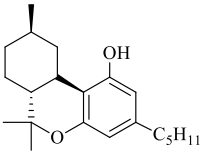
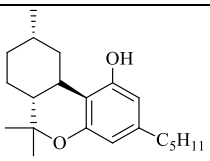
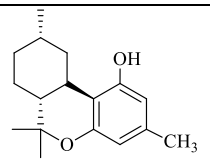
Table 9: Affinities (K*i*) of non-classical cannabinoids for hCB1, and hCB2

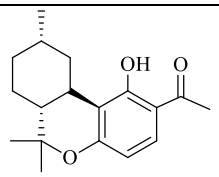
Compound	Ki (nm)					Function	Reference
	rCB$_1$	**hCB$_1$**	**rCB$_2$**	**mCB$_2$**	**hCB$_2$**		
 **227** (CP-55,940)	-	0.58	-	-	0.69	Agonist	86, 87
 **228**	-	61.6	-	-	91.0	-	86, 87
 **229**	-	1.0	-	-	2.4	-	86, 87
 **230**		7079	-	-	7585	-	86, 87

Finally, Aviz-Amador [88] determined via molecular docking experiments *in silico* that HHC (compounds **1** and **7**, table 10), Δ9-THC (**35b**, table 10) and Δ8-THC (**36b**, table 10) exhibit comparable high calculated binding energies to the CB2 receptor, although the binding energy of *S*-HHC epimer (**7**) resulted a little lower. The hydrophobic interactions with the amino acid residues of the receptor protein are crucial and they resulted equal for the three cannabinoids.

However, for the CB1 receptor, *R*-HHC (**1**) and Δ9-THC (**35b**) displayed similar high calculated binding affinities, while Δ8-THC (**36b**) and *S*-HHC (**7**) bound to this receptor with lower affinity. Thapa and co-workers [89-91] demonstrated that compounds **231** and **232** are potent angiogenesis inhibitors. They inhibit endothelial and tumor cell growth and lock the secretion of VEGF in cancer cells. Interestingly these two compounds have poor binding affinities for CB1 and CB2 receptors showing lower binding energy for both receptors.

Table 10: Molecular Docking with D9THC (**35b**), D8THC (**36b**), HHC (**1** and **7**), and HHC analogs (**231** and **232**) binding with CB1 and CB2 receptor.

	Binding energy (Kcal/mol)			
Compound	**CB_1**	**CB_2**	**Interaction type**	**References**
 **35b**	-9.4	-10.4	**CB_1:** Alkyl, π-alkyl, π-σ bond, C-H-bond, van der Waals. **CB_2:** Alkyl, π-alkyl, π-π-T-shaped, π-σ bond	88,92
 **36b**	-6.9	-10.1	**CB_2:** Alkyl, π-alkyl, π-π-T-shaped, π-Donor-H-bond	88
 **1**	-9.1	-10.3	**CB_2:** Alkyl, π-alkyl, π-π-T-shaped, π-σ bond	88
 **7**	-7.2	-9.1	**CB_2:** Alkyl, π-alkyl, π-π-T-shaped, π-π-Stacked	88
 **231**	-6.4	-7.1	-	89-91

 **232**	-5.9	-6.5	-	89-91

PHARMACOLOGICAL AND TOXICOLOGICAL PROPERTIES

Given the emergence of *in vitro* and *in vivo* studies on the use of saturated cannabinoids in the treatment of various diseases, including cancer [93-97], neurological disorders [98-100], diabetes [101, 102], but also the prevalence of consumption of these compounds [24], there is a crucial need to better comprehend their pharmacology and toxicology. In particular, the role of intrinsic efficacy in abuse-related effects, major metabolites, and adverse effects should be the subject of future study. Very limited information is available on the safety of saturated cannabinoids in humans, and serious health damage is highly likely to occur in those who abuse them. In particular, such information will help public health to understand the adverse effect profile that differs from saturated cannabinoids to marijuana [103].

We recently reported the preliminary outcomes of the anticancer properties of HHC analogs in four pancreatic cancer cell lines [104]. Both the (*R*)-HHC and (*R*)-HHC epimers equally reduced the proliferation of cancer cells with IC_{50} values extending from 10.3 to 27.2 μM. These values are similar to the IC_{50} values of the anticancer agents olaparib or veliparib resulting in more efficient compounds for the specific treatment of pancreatic cancer. Optimization led to novel saturated cannabinoids with greater cytotoxicity towards comparable cell lines [105]. Although the IC_{50} values are lower compared to other active antineoplastic compounds on the market the treatment of Pancreatic cancer is still evolving and the need to produce antineoplastics is pertinent. Continued SAR and analogs studies are currently being conducted for our research group to increase bioavailability and increase IC_{50} values from micromolar to nanomolar concentrations

with a set of compounds currently undergoing xerograph and in-vivo experiments, with future results supporting our experimental claims.

The new and rediscovered cannabinoids have no pre-clinical safety profile performed on them and are being consumed. We executed a pre-clinical assessment on the racemic mixture of HHC [11] and H_4CBD [106] to provide a preclinical assessment profile for consumption of these compounds. The analysis of the different cell types revealed varying responses to H_4CBD and HHC. Lung fibroblasts (NHLF) showed a concentration-dependent reduction in cell viability, with maintained concentrations over 24 hours at 6.25-30 μM ensuing in a significant loss of viability. On the contrary, hepatocytes showed a trend of reduced viability at longer exposure times and higher concentrations, but severe cytotoxicity was not observed. This suggests that hepatocytes are less susceptible to the cytotoxic effects of H_4CBD and HHC compared to NHLF. In the hERG assay, H_4CBD and HHC did not inhibit the action potentials within cardiomyocytes, indicating no inhibition of ion channels involved in cardiac function.

These findings provide insight into the cytotoxic effects of H_4CBD and HHC and contribute to establishing research and safety parameters as these compounds continue to gain attention.

SUMMARY AND OUTLOOK

The markets for hydrogenated cannabinoids and related synthetic cannabinoids are rapidly evolving areas with relatively limited information currently available. This review summarizes the discovery, novel synthetic pathways, and pharmacology studies of classical, non-classical, and hybrid hydrogenated cannabinoids discussing the most critical point of view in this area. This is harmonized with a summary and comparison of the cannabinoid receptor affinities of various classical, hybrid, and non-classical saturated cannabinoids. A discussion of structure-activity

relationships with the four different pharmacophores found in the cannabinoid scaffold is added to this review.

Saturated cannabinoid-based therapies like nabilone suffer from undesirable pharmacological properties including poor bioavailability, unpredictable onset/ offset of action, and detoxification. The clear medical need for novel cannabinoid-based medications has encouraged us to pursue this review. We believe the design and development of novel hydrogenated cannabinoids should address the quest for new selective antagonist-based cannabinoids for CB2 receptors with improved drug ability, i.e., improved oral availability, a predictable time course of action, and controllable detoxification. The design of new CB2-selective hydrogenated THC analogs should have little or no affinity for the CB1 receptor, thus eliminating the risk of central CB1-mediated psychotropic effects.

Furthermore, the input of an azido, isothiocyanate, and cyano moiety at diverse tactical positions within these nonclassical-hybrid hydrogenated cannabinoids and the emergence of covalent bonds with different amino acid residues on the CB1 and CB2 receptors allows for a more comprehensive searching of the stereochemical features of the receptor active sites.

The based-cannabinoid research should focus on accomplishing more efficient enantioselective routes to furnish novel synthetic highly enantiopure-saturated nonclassical and hybrid cannabinoids at the disposal of chemists. Many more exclusive ligands can be minded and explored for their pharmacological activity. The accessibility of functionalized bi- and tricyclic cannabinoid skeleton will facilitate the scanning of the CB1 and CB2 receptors. A better comprehension of the receptor binding site may make it possible to project cannabinoids with controlled selectivity and affinity for CB1, CB2, or both cannabinoid receptors to potentially support in the selective handling of the endocannabinoid system.

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