Volume 33 | Number 12 | December 2016 | Pages 1347–1448

# Natural Product Reports

www.rsc.org/npr

ISSN 0265-0568

ROYAL SOCIETY OF CHEMISTRY

REVIEW ARTICLE
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175 YEARS

Natural Product Reports

REVIEW

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Cite this: *Nat. Prod. Rep.*, 2016, **33**, 1357

# Phytocannabinoids: a unified critical inventory

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Covering up to January 2016

*Cannabis sativa* L. is a prolific, but not exclusive, producer of a diverse group of isoprenylated resorcinyl polyketides collectively known as phytocannabinoids. The modular nature of the pathways that merge into the phytocannabinoid chemotype translates in differences in the nature of the resorcinyl side-chain and the degree of oligomerization of the isoprenyl residue, making the definition of phytocannabinoid elusive from a structural standpoint. A biogenetic definition is therefore proposed, splitting the phytocannabinoid chemotype into an alkyl- and a β-aralklyl version, and discussing the relationships between phytocannabinoids from different sources (higher plants, liverworts, fungi). The startling diversity of cannabis phytocannabinoids might be, at least in part, the result of non-enzymatic transformations induced by heat, light, and atmospheric oxygen on a limited set of major constituents (CBG, CBD, $\Delta^9$-THC and CBC and their corresponding acidic versions), whose degradation is detailed to emphasize this possibility. The diversity of metabotropic (cannabinoid receptors), ionotropic (thermos-TRPs), and transcription factors (PPARs) targeted by phytocannabinoids is discussed. The integrated inventory of these compounds and their biological macromolecular end-points highlights the opportunities that phytocannabinoids offer to access desirable drug-like space beyond the one associated to the narcotic target $CB_1$.

Received 13th June 2016

DOI: 10.1039/c6np00074f

www.rsc.org/npr





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## 1. Introduction

Over the past decades, the name "cannabinoid" has become increasingly vague. Originally coined in a phytochemical context to refer to a structurally homogenous class of meroterpenoids typical of cannabis (*Cannabis sativa* L.), the name "cannabinoid" has then been associated to the biological profile of the psychotropic constituent of marijuana ($\Delta^9$-THC), substantially losing its structural meaning and being growingly associated, in accordance with the rules of pharmacological research,[1] to compounds showing affinity to the two GPCR known as cannabinoid receptors ($CB_1$ and $CB_2$), independently from any structural or biogenetic relationship with the cannabis meroterpenoids. To compound semantics even more, $CB_1$ and $CB_2$ are actually $\Delta^9$-THC receptors, since, within the almost 200 known cannabinoids, only $\Delta^9$-THC, its isomer $\Delta^8$-THC, and, to a lower extent, their aromatized derivative CBN (Fig. 1), bind with significant affinity the ligand recognizing site of these receptors.[1] The endogenously produced biological analogues of THC are referred to as endocannabinoids,[1] and it seems

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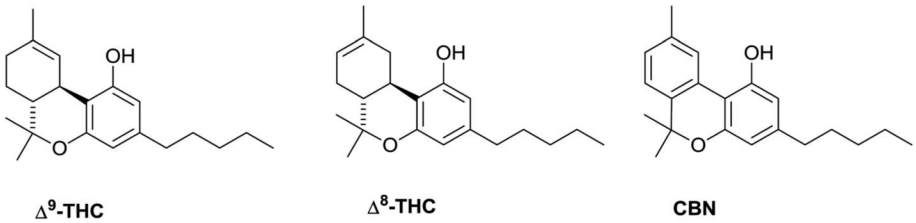



$\Delta^9$-THC $\Delta^8$-THC CBN

Fig. 1 High-affinity phytocannabinoid ligands of cannabinoid receptors.



therefore logical to refer to cannabis meroterpenoids and their analogues of plant origin as phytocannabinoids, emphasizing their botanical origin.

The phytocannabinoid structural motif is biogenetically hybrid, and results from the convergence of the mevalonate and the polyketide pathways. Since both of them are intrinsically modular, variation in terms of polyketide starter and prenyl oligomerization are possible, and indeed Nature has deftly capitalized on this modularity to create chemical diversity that complements the one resulting from the oxidative cyclase phase of isoprenyl diversification. As a result, the name phytocannabinoid is also vague from a structural standpoint. The biogenetic hallmark of phytocannabinoids is a resorcinyl core decorated with *para*-oriented terpenyl and pentyl groups, but compounds with a different degree of isoprenylation (prenyl, sesquiterpenyl) or with a shortened alkyl group (methyl, propyl, or more rarely ethyl and butyl) are also present in *C. sativa*. Phytocannabinoids derived from aliphatic ketide starters are typical of *C. sativa* and are otherwise of limited distribution in Nature, while their analogues derived from an aromatic ketide starter and with a phenetyl-type substituent have a much broader distribution, encompassing not only plants but also liverworts and fungi. Many of these compounds are referred to in the literature as prenylated bibenzyls, a name that hides their relationship with their more famous analogues from cannabis.

To cope with the biogenetic abundance associated with the production of cannabinoids, we propose the classification summarized in Table 1 to address variation of the substituents of the resorcinyl core and of their topological relationships. According to this proposal, "classic" phytocannabinoids are those whose resorcinyl side-chain is derived from a linear aliphatic polyketide starter, while their analogues derived from aromatic starters could be referred to as aralkyl phytocannabinoids. Regarding the relationship between the substituents of the resorcinyl moiety, in most compounds isoprenyl and the resorcinyl side-chain are *para*-related, while analogues where these groups are in an *ortho*-relationship are assigned to the "abnormal" series. Finally, compounds characterized by an elongated or a shortened terpenyl residue should be referred to as sesquicannabinoids when the isoprenyl residue is of the sesquiterpenyl type, and deprenylcannabinoids when the isoprenyl residue is a simple dimethylallyl. Most cannabinoids have so far been isolated as artifacts from their carboxylated forms (pre-cannabinoids or acidic cannabinoids) from plant sources, and are therefore phytocannabinoids, but the generality of the biogenetic origin does not make it unconceivable that compounds of this type could also occur in fungi or bacteria, and some examples of fungal cannabinoids are indeed known. While phytocannabinoids from the abnormal- and the sesquiterpenyl-series occur in cannabis, phytocannabinoids derived from an aromatic ketide starter have never been reported from this plant source.

This review article aims at providing a comprehensive inventory of phytocannabinoids of different botanical origin. Most phytocannabinoids chemotypes were characterized in the 60ties and 70ties,[2–5] but, after a three-decade gap, new structural types have been discovered, as exemplified by sesquicannabinoids[6] and by the isoprenyl esters of pre-cannabinoids.[7] Furthermore, technological advancement, the growth of the natural product community, and the availability of new cannabis breeds are expected to further expand the current inventory of these compounds. Most phytochemical studies on cannabis precede the identification of cannabinoid and TRPs receptors that occurred in the 90ties, and bioactivity was mostly evaluated with the cannabinoid tetrad test in mice, a combination of four different behavioural tests (hypothermia, hypomotility, catalepsy, analgesia) that, although *per se* unspecific, when all four positive were indicative of a $\Delta^9$-THC-type activity.[8] Activities unrelated to the activation of $CB_1$ and the replication of the biological profile of $\Delta^9$-THC were therefore missed.

Various articles have regularly updated the inventory of phytocannabinoids from *C. sativa*,[2–5] but no attempt has so far

Table 1 Major classes of phytocannabinoids *sensu lato*

| Compound class | Ketide starter | Side-chain/isoprenyl topological relationship | Isoprenyl residue |
|---|---|---|---|
| Alkyl phytocannabinoids | Aliphatic | *para* | Terpenyl (C10)-type |
| Aralkyl phytocannabinoids | Aromatic | *para* | Terpenyl (C10)-type |
| Abnormal series | Aliphatic or aromatic | *ortho* | Isoprenyl |
| Sesqui (deprenyl)-series | Aliphatic or aromatic | *ortho* or *para* | Sesquiterpenyl (C15)<br>Deprenyl (C5) |

been done to include in this survey also phytocannabinoids from additional natural sources. Apart from this, we have also tried to outline the basic chemical and biological profile of the various structural types of phytocannabinoids, and to discuss their biogenetic relationships, chemical interconversions, and biomimetic synthesis from terpene derivatives and resorcinols.

The most important phytocannabinoids are commonly referred to using a three-letter acronym system originating from the first investigators in the field, and later updated by ElSohly to include all the major structural types (Fig. 2).[5] Regrettably, there is no single numbering throughout the various classes of phytocannabinoids, and at least five different systems are documented in the literature. As a rule, the reference system is given simple numbers, while positions in the other elements are referred to with primed or doubly primed numbers. There is no agreement, however, on the identification of the reference system. It used to be the terpene moiety in all cases, but it is now growingly considered the aromatic ring in CBG derivatives (but not in CBD). When oxygen bridges are present between the terpenyl and the resorcinyl system, the reference system becomes the corresponding fused heterocycle in accordance with the IUPAC rules, even though this hides relationships between biogenetically corresponding carbons (Fig. 2). Thus, all *p*-menthane-type phytocannabinoids were originally numbered in the same way, using the isoprenoid moiety as a basic system, but, also because of ambiguities in the identification of the starting carbon of the menthane moiety (benzylic carbon *vs.* the methyl-bearing olefin carbon), the terpenoid numbering has now been replaced by the heterocyclic numbering. As a result of this change, $\Delta^9$-tetrahydrocannabinol ($\Delta^9$-THC) and cannabidiol (CBD), although structurally related (Scheme 1), are numbered in a different way (Fig. 2). The terpenoid system is still often used for cannabichromene (CBC) and for cannabicyclol (CBL), both numbered according to CBG, while cannabielsoin (CBE) is numbered according to THC. To avoid confusion, especially when tabulating NMR data, it would be

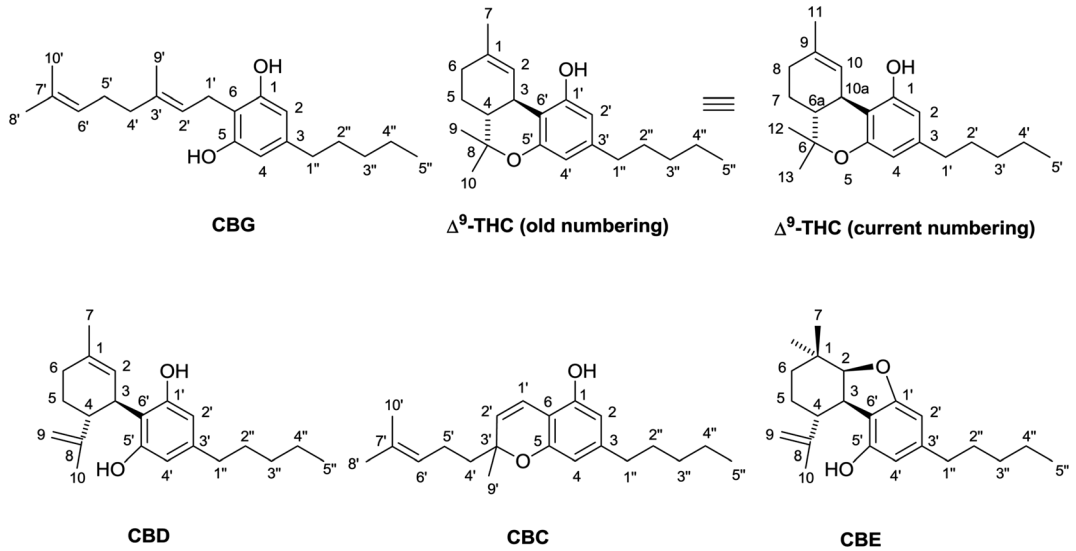
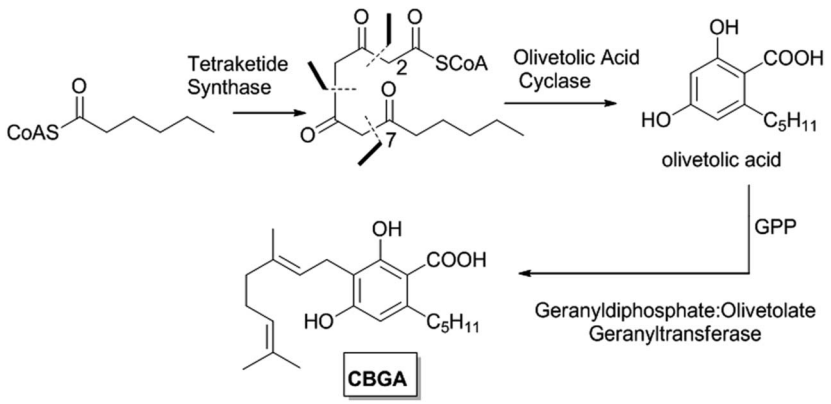



Fig. 2 Phytocannabinoid numbering systems.




Scheme 1 Formation of cannabigerolic acid (CBGA) in *C. sativa*.

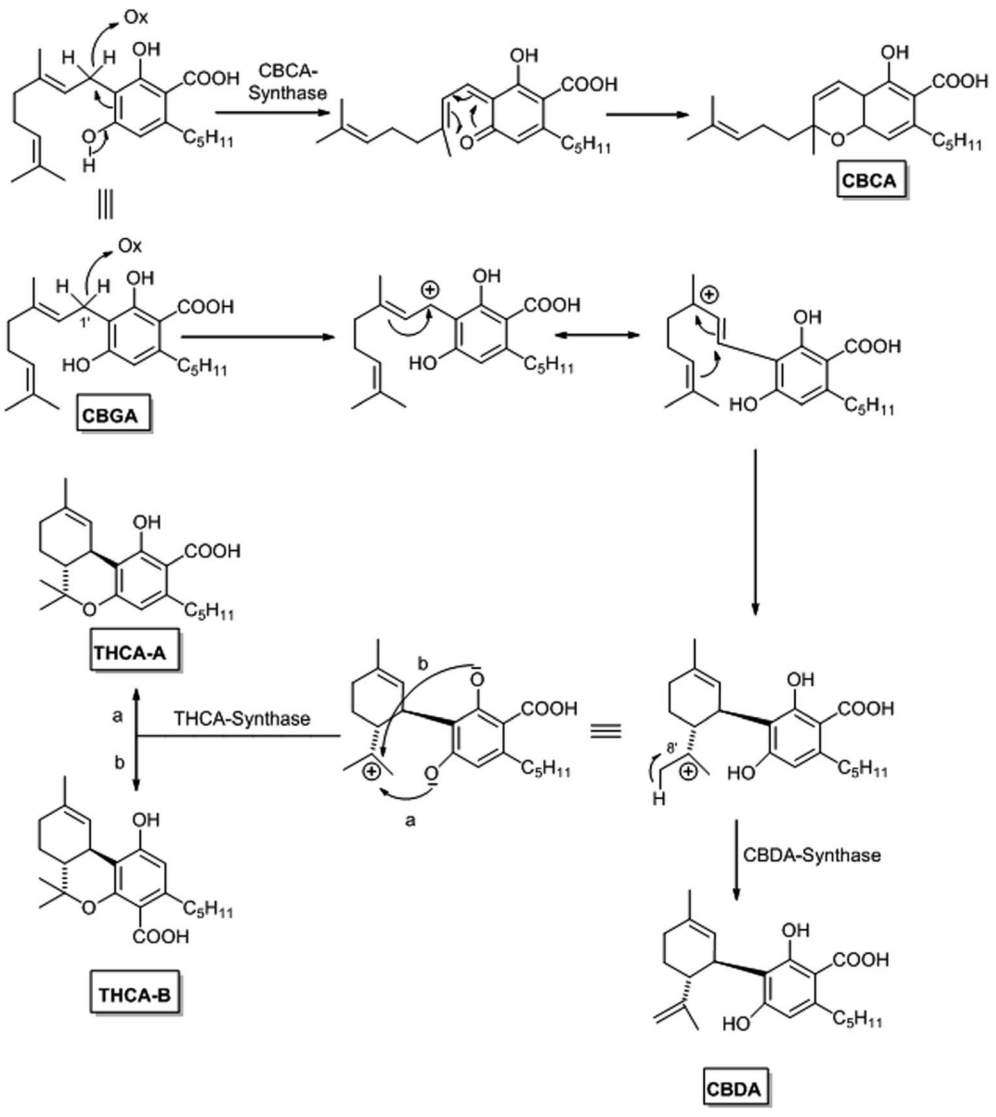
 

practical to have a reference numbering system capable to accommodate all phytocannabinoids having the same type of isoprenyl residue, independently from the closure of oxygenated heterocyclic with the resorcinyl moiety.

## 2. Biogenesis of phytocannabinoids

Neutral phytocannabinoids were long assumed to be genuine natural products, but, while investigating fresh samples of fiber hemp, Schulz and Haffner[9] discovered that their major constituent was not CB, but, rather, its carboxylated version (cannabidiolic acid, CBDA or pre-CBD, Scheme 2), a compound first described by Krejčí and Šantavý in 1955.[10] It is currently assumed that all neutral phytocannabinoids originate from the mostly non-enzymatic decarboxylation of their corresponding carboxylated forms. Consequently, olivetolic acid and not olivetol, was their actual aromatic precursor, and the early biogenetic schemes were elaborated on the basis of the biosynthesis of polyketides, identifying some basic relationships between the small pool of the compounds known at that time. The first step in cannabinoid biosynthesis was correctly considered the condensation of a hexanoylCoA and three activated acetate units to generate the diketo tautomer of olivetolic acid. Farmilo's biogenetic proposal[11] was the first to consider phytocannabinoids in their native carboxylated form, anticipating the existence of THCA before its actual isolation.

Guided by this proposal, the enzymology of phytocannabinoids biosynthesis was substantially clarified. A polyketide origin for the resorcinyl moiety of phytocannabinoids is consistent with the finding that a close relationship exists in *Cannabis* tissues (female flowering tops, leaves, stems and roots) between the levels of hexanoylCoA and the concentrations of the carboxylated form of CBD (pre-CBD, CBDA). A gene encoding a novel type III polyketide synthase (PKS) was cloned from *C. sativa* and named olivetol synthase,[12] but the enzyme actually failed to produce olivetol or olivetolic acid in the




Scheme 2 Biosynthetic origin of the major phytocannabinoids.

absence of a polyketide cyclase enzyme, named olivetolic acid cyclase (OAC) that was cloned from the glandular trichomes of cannabis.[13] This enzyme catalyzes a C-2/C-7 intramolecular aldol condensation, retaining the carboxylic group and forming olivetolic acid. Interestingly, OAC is a dimeric α + β barrel (DABB) protein structurally similar to polyketide cyclases from *Streptomyces* species, indicating evolutionary parallels between polyketide biosynthesis in plants and bacteria.[14]

Regarding the isoprenoid residue, Mechoulam recognized CBG as the precursors of all other types of phytocannabinoids already in 1964,[15] reasoning that this compound has the lowest oxidation level for the isoprenyl moiety. Accordingly, CBG can be formed by the *C*-isoprenylation of olivetolic acid with geranyl diphosphate, and then be converted to CBD, THC and, eventually, CBN. Two years later, the biogenesis of cannabinoids from geranyldiphosphate and olivetolic acid was indeed reported.[16] This biogenetic bluepring was next extended[17] to include the possibility to generate both acidic and neutral cannabinoids, with, however, growing awareness that neutral phytocannabinoids might actually be artifacts formed during harvest and storage of *Cannabis*.[18]

Progress was done in the discovery of the enzymes responsible for the isoprenylation of olivetolic acid, and a specific enzyme, named geranyldiphosphate:olivetolate geranyltransferase, was characterized in young leaves of *C. sativa*.[19] This enzyme catalyzes the first step in cannabinoid formation in hemp, namely the prenylation of olivetolic acid, and accepts geranyldiphosphate (in turn derived from the plastidial 2-methyl-D-erythritol-4-phosphate pathway) as a substrate. In the presence of olivetolic acid (olivetol is not accepted as a substrate), a *ca.* 2 : 1 mixture of cannabigerolic- and cannabinerolic acids is formed. The replacement of geranyldiphosphate with neryldiphosphate changed the ratio to 1 : 1, with rate being only 20% of the one observed with geranyldiphosphate.[19]

The isoprenylation step is next followed by an oxidative cyclase activity that, through the agency of specific enzymes, generates CBCA, CBDA and $\Delta^9$-THCA from CBGA. From a mechanistic standpoint (Scheme 2), the reaction formally involves hydride abstraction from the benzallylic terpenyl carbon. The formation of the resulting cation scrambles the configuration of the adjacent double bond, making it possible the generation of the cyclohexene ring of CBDA and $\Delta^9$-THCA by electrophilic cyclization. Alternatively, the isomerized benzallyl cation can evolve into a quinone methide and generate CBCA by an electrocyclic reaction. The electrophilic cyclization is enzyme-promoted and generates chiral products, while the electrocyclic reaction is probably spontaneous, since CBCA is generated as a racemate.

The electrophilic cyclization step is highly specific in terms of termination. In one version of the process, the C-8 cation (menthane numbering) behaves as a Broensted acid, and is quenched by loss of a proton from C-9 to generate the exocyclic double bond of CBDA (Scheme 2). In the alternative version of the termination, the C-8 menthyl cation behaves as an electrophilic sink for one of the two *ortho*-hydroxyls, generating $\Delta^9$-THCA-A from the hydroxyl *para*- to the carboxylate, and $\Delta^9$-THCA-B from the other phenolic hydroxyl. The oxidative- and the electrophilic cyclase activities are closely associated, and the menthyl cation is not released or leaking from the enzymatic cleft where it is generated, making the two termination process biogenetically orthogonal. This is consistent with the paradoxical observation that, while CBD is easily converted into $\Delta^8$- and $\Delta^9$-THC by acidic treatment under laboratory conditions, CBDA is not converted into THCA in cannabis tissues. CBDA-synthase and THCA-synthase have been cloned from the storage cavity of the glandular trichomes of cannabis,[20,21] and they exclusively produced their corresponding phytocannabinoids. THCA synthase has also been crystallized, and the FAD and substrate-binding sites identified.[22] Apparently, the enzyme selectively produce one of the two isomeric THC acids present in nature, THCA-A.[22] THCA- and CBDA-synthases are similar in terms of mass (both are 74 kDa monomeric proteins), pI, $v_{max}$ and $K_m$ for CBGA, and are 84% identical in their amino-acid sequence.[21,23] Both THCA- and CBDA-synthases show a domain with high homology with the enzyme involved in the oxidative cyclization step of the biosynthesis of berberine, a benzophenantridine alkaloid, in the Californian poppy (*Eschscholtzia californica*). Both processes require molecular oxygen for their activity and form hydrogen peroxide during the oxidative cyclization of the substrate.[24] Also cannabichromenic acid (CBCA) synthase, the enzyme catalyzing the oxidocyclization of CBGA to CBCA has been identified in young leaves of cannabis and next purified and characterized.[25] A summary of the biogenic relationship between the main phytocannabinoids in *Cannabis sativa* L. is reported in Scheme 2.

Genuine oxidative capacity has been detected in cannabis tissues, as shown by the observation that suspension cultures of the plant can convert primary and secondary allylic alcohols into the corresponding carbonyls.[26] It is unclear, however, whether phytocannabinoids are substrates for this activity.

Labelling experiments with $^{14}$C-CBG, and $^{14}$C-olivetolic acid were used to study the production of phytocannabinoids in cannabis roots. These experiments confirmed that C-3 phytocannabinoids derive from an independent biosynthesis and not from the enzymatic shortening of the C-5 side chain by either plant or contaminating fungal tissus.[27] Thus, all the CBGA alkyl-homologs could be used as substrate for the different cannabinoid synthases *in vitro*, although the efficiency of conversion was different within the various homologues.[27] It was also shown that decarboxylation of cannabinoid acids is a continuous process, generating neutral cannabinoids already in the early stages of the plant growth, and next continuing during all the vegetation stage.[27]

There is currently great interest in the expression of the key enzymes involved in the production of phytocannabinoids in fermentable organisms, and in 2015 it was announced that the methylotropic yeast *Pichia pastoris* has been engineered to produce $\Delta^9$-THCA from CBGA.[28] Functional expression of $\Delta^9$-tetrahydrocannabinolic acid synthase (THCAS) was also obtained in baker's yeast (*Saccharomyces cerevisiae*), although an overall lower fermentation yield was obtained.[28]

The genetic of inheritance of the enzymes responsible for the formation of the major cannabinoids is complex, and has been extensively investigated as regards CBDA and THCA synthases. These two enzymes are assumed to be coded for by two

co-dominant alleles, respectively $B_D$ and $B_T$, while a defective form of the allele could be responsible for the accumulation of CBG *via* the production of an inactive or minimally active oxydocyclizing enzyme. The situation is, however, complicated by the presence of a host of THCA- and CBDA-synthase-related pseudogenes that make the inheritance of phytocannabinoids substantially deviating from a simple Mendelian model.[29]

Nature is a biogenetically tinkerer, and prefers to re-use, recycle and re-assemble rather than creating *ex novo* something new. This so called "law of stinginess" is exemplified by the observation that certain isoprenylated ketides replicate, within the framework of compounds derived from an aromatic starter, the features of phytocannabinoids from cannabis (aldol-type derivation of the prenylated aromatic moiety, resorcinyl-type hydroxylation pattern, *C*-monoprenylation), fully qualifying as "phytocannabinoids", as will be discussed in Section 4.2 to highlight the difference between phytocannabinoids and phytocannabinoid-like compounds.

# 3. Naturally occurring phytocannabinoids

## 3.1 Structural diversity

The diversity of natural phytocannabinoids is the result of differences in their three moieties, namely the isoprenyl residue, the resorcinyl core, and the side-chain. These differences are generally orthogonal, that is, biogenetically unrelated. Although impressive, the inventory of alkyl-cannabinoids might have been inflated by the poor oxidative stability of some of the major phytocannabinoids, $\Delta^9$-THC in particular. Furthermore, many investigations were carried out on aged samples of seized marijuana or hashish, and some compounds were only observed as GC peak and tentatively identified by their mass spectrum, without never actually have been isolated.

**3.1.1 The isoprenyl residue.** Apart from its oligomerization degree (prenyl-, terpenyl-, sesquiterpenyl), the isoprenyl moiety of phytocannabinoids can occur in nine basic topological arrangements (Scheme 3), classified according to:

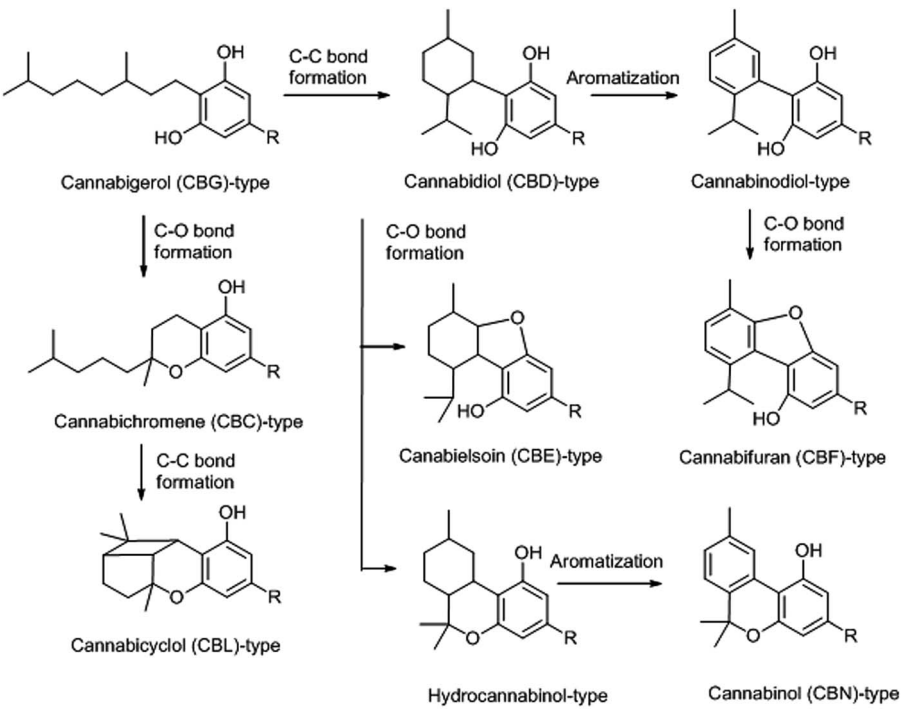
(a) The carbon–carbon connectivity of their isoprenyl moiety, that can be linear (cannabigerol-type compounds), monocyclic (*para*-menthane-type and thymyl-type) or bicyclic (cannabicyclol-type phytocannabinoids)

(b) The closure of oxygen bridges between the isoprenyl and the resorcinyl moieties, that generates cannabichromene (CBC)-type compounds from linear precursors and hydrocannabinol-, cannabielsoin (CBE)- and cannabifuran (CBF)-type compounds from monocyclic precursors.

(c) The aromatization of the *p*-menthyl moiety to a thymyl moiety, that generates cannabinol-type and cannabinodiol-type derivatives from, respectively, THC- and CBD-type precursors.

(d) The closure of additional carbon-bonds, as exemplified by cannabicyclol derivatives.

**3.1.2 The resorcinyl moiety.** The resorcinyl core of native phytocannabinoids is carboxylated, and these compounds are referred to as acidic phytocannabinoids or pre-cannabinoids. In compounds with a single bond between the isoprenyl residue and the aromatic moiety, the two unsubstituted aryl carbons are equivalent. However, when one of the two phenolic oxygens is bound to the isoprenyl residue, the two positions are not identical, and isomeric carboxylated forms have been isolated




Scheme 3 Topological classification of the major skeletal types of phytocannabinoids.

(Fig. 2, type 1 and type 2 pre-cannabinoids). The spectroscopic properties of the two isomeric forms are rather different, since in type 1 pre-cannabinoids the carboxyl group is hydrogen-bonded to the adjacent *ortho*-hydroxyl, while this bond is not possible in their type-2 isomers.[30] This reflects in their carbonyl IR frequencies (*ca.* 1615 $cm^{-1}$ for the hydrogen bonded carboxyl, and *ca.* 1715 $cm^{-1}$ for the non-hydrogen bonded isomeric form) and UV maxima, with the hydrogen-bonded isomers absorbing at a lower frequency ($\lambda_{max}$ *ca.* 250–257 nm) compared to the other type of pre-cannabinoids ($\lambda_{max}$ *ca.* 260–270 nm).[30] Decarboxylation can occur spontaneously in the plant material, and is accelerated by heating at high temperature (>100 °C). The reaction is much faster with intramolecular hydrogen-bonded pre-cannabinoids, despite their higher thermodynamic stability compared to their isomers.[30] The higher thermal stability of type-2 pre-cannabinoids makes it likely that they are absorbed as such from cannabis preparation even from heated products. Nevertheless, virtually nothing is known on the bioactivity of type-2 pre-cannabinoids.

Acidic cannabinoids have been detected in historical samples of *Cannabis* tincture over 100 year old,[31] and these compounds are not decarboxylated under physiological conditions.[32] Up *ca.* 70% decarboxylation has been reported in controlled smoking experiments,[32] but the half-life of acidic phytocannabinoids in plant material at room- or lower temperatures is in the range of hundreds of days.[32] Therefore these compounds are the major form of phytocannabinoids present in edible marijuana. Despite their low volatility, pre-cannabinoids are absorbed from smoked cannabis, and the detection of pre-THC derivatives has even been proposed as a diagnostic test to distinguish the recreational use of marijuana, that contains pre-THC, from positivity due to the assumption of mainstream medications originating from semi-synthetic THC (Marinol®).[32] There is currently great interest for pre-cannabinoids, fostered by the discovery that pre-THC retains activity at both $CB_1$ and $CB_2$, but is not narcotic due to its very poor brain penetration.[33] Pre-cannabinoids can also occur as thermally-stable complex esters with terpenic and sesquiterpenic alcohols, and the pharmacology of these compounds is still unexplored, probably because of the difficulty to purify them from the highly lipophic fractions of cannabis extracts. Methyl esters of pre-cannabinoids were often prepared to facilitate their purification, but hydrolysis by basic treatment to regenerate the native acids has been reported to be unsuccessful.[34] Pre-cannabinoids show strong anti-bacterial activity, similar to the one of their corresponding neutral derivatives.[35] Further structural diversity in the resorcinyl moiety can involve *O*-alkylation, generally with a methyl group, or oxidation to the quinol and hydroquinol level. Cannabinoids from the quinol series are intensively purple-colored in non-acidic conditions, and their easy formation from CBD and CBG is at the basis of the Beam test, a forensic identification method for marijuana.[36] Cannabinoid quinols are unstable toward dimerization and further degradation,[36] and have so far been isolated only in traces from the abnormal series,[37] as their stable acetates from the normal series,[36] or in deoxygenated form.[38] They might also be involved in the mammalian metabolism of phytocannabinoids, but their instability and the lack of reference compounds have combined to leave this issue unsettled.[39] Cannabinoid quinols show interesting bioactivity, and those derived from CBD (HU-313)[40] and CBG (VCE-003)[41] (Fig. 3) are non-adipogenic PPARγ agonists and have been considered for clinical development respectively, as anticancer agent and as neuroprotectory agents.[40–42] These compounds could be stabilized as rapidly re-oxidized aza-Michael adducts without loss of anti-fibrotic activity as in VCE-004-8 (Fig. 3).[43]

The carbon-substitution pattern of the resorcinyl core is generally 1,4, with the isoprenyl and the side-chain *para*-related. Few alkyl phytocannabinoids belong to the so called "abnormal series", where the two carbon substituents are in an *ortho*-relationship (Fig. 2), but these compounds are more common in aralkyl phytocannabinoids. Compounds from the abnormal series derive by a process of prenylation at the carbon in *ortho* or *para* relationship to the resorcinyl hydroxyls, while cannabinoids from the normal series derive from the alkylation of the carbon adjacent to the two resorcinyl hydroxyls (Fig. 4).

**3.1.3 The resorcinyl side-chain.** The ketide substituent of the resorcinyl core can be alkylic or aralkylic. The alkyl residue of the resorcinyl moiety has generally an odd number of carbons, five (olivetoids) or, less frequently three (viridinoids) and one (orcinoids), with the names making reference to their corresponding non-prenylated resorcinyl derivatives (olivetol, divarinol, and orcinol, Fig. 5). Orcinoids are the major phytocannabinoids from *Rhododendron* species, but are otherwise rare in cannabis. Alkyl side chains with an even number of carbons (two or four) are very rare, although compounds of this type have been reported as trace constituents of cannabis. Since hashish is often attack by molds, it was suggested that phytocannabinoids with an even number of carbons might be artifacts derived by fungal ω-oxidation and decarboxylation of their corresponding homologues.[44] However, enzymatic studies provided evidence for the presence of specific ketide synthases

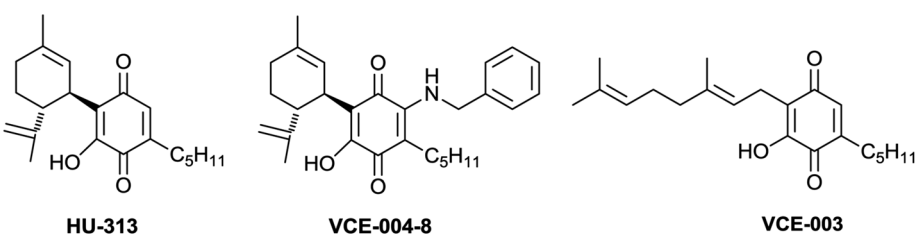



Fig. 3 Bioactive cannabinoid quinols under preclinical/clinical development.

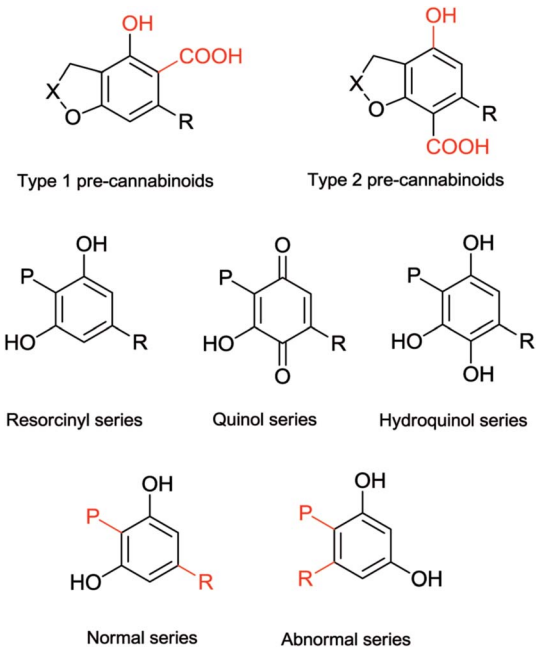



Fig. 4 Diversity of the resorcinyl moiety of cannabinoids (P = prenyl; R = alkyl).

responsible for the generation of these "shortened" alkyl phytocannabinoids.[27] The alkyl residue is a critical element for the phytocannabinoid pharmacophore, and its manipulation can lead to an increased potency compared to the natural compounds.[45]

Aralkyl phytocannabinoids do not occur in *Cannabis*, but have an otherwise broad distribution in plants, both higher (*Helichrysum*, *Amorpha*, *Glycyrrhiza* and other genera) and lower (liverworts from the *Radula* species), with even a single report from a parasitic fungus. The aralkyl residue can be of the phenethyl-, stiryl-, or benzofuranyl type (Fig. 6), and the corresponding compounds have been named bibenzyl-, stilbenyl- and benzofuranyl phytocannabinoids.

# 4. Phytocannabinoids inventory

Depending on the nature of the resorcinyl side-chain, compounds will be sorted out in alkyl- and β-aralkyl phytocannabinoids. Within the two classes, compounds are classified according to the nature of the isoprenyl residue (linear, carbomonocyclic) and the presence of oxygen bridges with the resorcinyl core, making reference to a set of archetypal major chemotypes.

## 4.1 Alkyl phytocannabinoids

**4.1.1 Cannabigerol (CBG)-type compounds.** The structural hallmark of these compounds is the presence of a linear isoprenyl residue, as exemplified by cannabigerol (CBG, **1c**), structurally elucidated in 1964, and also the first natural cannabinoid to be synthesized.[15] The isoprenyl residue of CBG is non-oxygenated, and is therefore at the lower oxidation- and earliest biogenetic state within phytocannabinoids. Although CBG was not identified as a major constituents of *C. sativa* during the first studies on this plant, varieties enriched in this compound have recently been generated by hybridization.[29] Remarkably, a South-African species of everlasting (*Helichrysum umbraculigerum* Less.), is also a major producer of CBG (**1c**) and CBGA (**1d**) (overall *ca.* 0.2% of the aerial parts) as well as of abnormal CBGA (**10a**).[46] Cannabigeroids are one of the most structurally diversified class of phytocannabinoids, with structural changes being associated to the isoprenyl residue (oxidation, double bond isomerization, prenylogation), the resorcinyl core (hydroxylation or oxygenative dehydrogenation), and its substituents (esterification of the C-2 carboxylate with isoprenyl alcohols, acetylation or methylation of one of the two phenolic hydroxyls). The parent compound shows only marginal affinity for $CB_1$, and, based on the SAR of $\Delta^9$-THC that emphasize the relevance of the pyrane B ring for significant binding,[45] all the natural modifications are also expected to be only marginally active on $CB_1$ and $CB_2$. On the other hand, prenylogation increases affinity for $CB_2$,[6] and a systematic evaluation of the

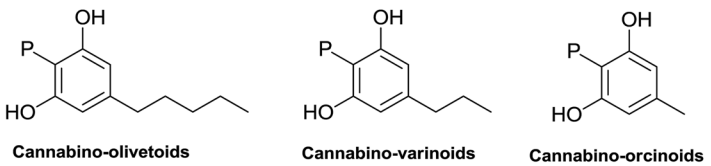



Fig. 5 Major classes of alkyl phytocannabinoids.

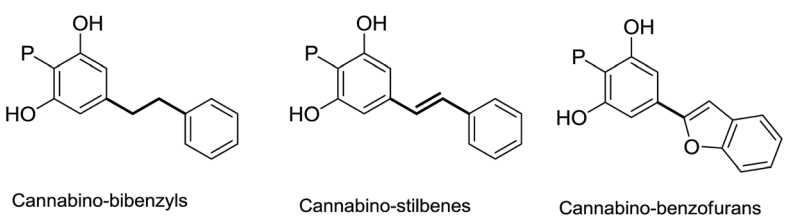



Fig. 6 Major classes of aralkyl phytocannabinoids.

activity on other phytocannabinoids ionotropic- or transcription factor targets should be worth evaluation. Thus, CBG is a powerful antagonist of the menthol receptor TRPM8, a target of relevance for prostate cancer,[47] potently activates α-2 adrenergic receptors, and inhibits with moderate potency $5HT_{1A}$ serotonin receptors.[48] The activation of α-2 receptors inhibits the liberation of catecholamine, and has been associated to sedation, muscle relaxation and analgesia.[49]

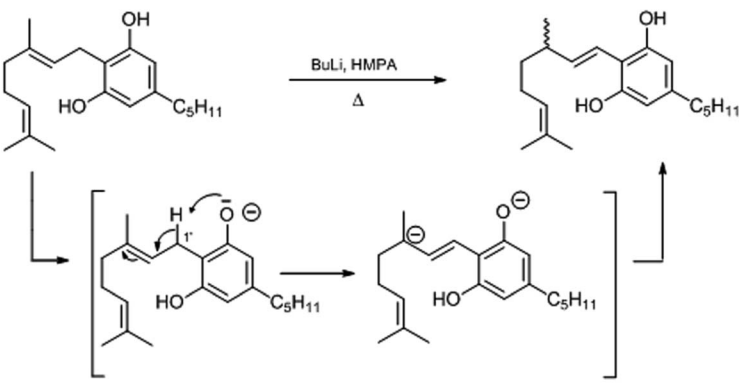
Apart from the parent compounds (CBG and CBGV) and their carboxylic forms, all the other derivatives are minor or trace constituents of cannabis, with the exception of the monomethyl ether of CBG (**1e**), that occurs in significant concentrations in some Asian strain of *Cannabis*.[50] Dihydroxylation of CBG affords chemoselectively the ω-epoxide, identical to the racemic compound (carmagerol, **4**), isolated from the Carmagnola variety of fiber hemp.[51] Also the proximal epoxides were isolated as a racemic mixture, from both the geranyl (CBG) and the neryl (cannabinerolic) series of neutral and acidic cannabinoids.[52] Analogues with an oxidized resorcinyl residue have also been characterized, both in the quinol and the hydroxyhydroquinone form. Quinol cannabinoids are very unstable,[36] and the isolation of **9a** is undoubtedly due to the acetylation of one of the hydroxyl.[53]

It is not clear if the various oxidized versions of cannabigerol are natural products or rather isolation artifacts. The geranylation of olilvetol gives a mixture of CBG and its positional isomer, the so called "abnormal" cannabigerol (**10a**).[15] While abnormal cannabigerol has never been reported from cannabis and only occurs in *H. umbraculigerum*, both its actylated hydroquinol (**10b**) and quinol (**11**) forms have been detected in a high potency $\Delta^9$-THC-strain.[37] The only sesquiterpenyl cannabinoid isolated so far belongs to the cannabigerol series, but it is likely that sesqui-cannabinoids also occur in other structural types biogenetically derived from linear isoprenyl cannabinoids.[6] The deprenyl derivative of *O*-methyl-cannabigerolic acid (amorfrutin 2, 7), a constituent of leguminous plants (see 4.2.1), is one of the few *n*-pentyl-type phytocannabinoids not isolated from cannabis.[54]

CBG is unstable to acids and bases. Mineral acids cyclize the terpenyl moiety,[15] while in strong bases (heating with BuLi in HMPA), the proximal ($\Delta^{2'}$) double bond is isomerized to the phenyl-conjugated *E*-$\Delta^{1'}$-isomer, a reaction mediated by deprotonation at C-1′.[55] Removal of the benzylic proton might involve proton transfer mediated by a phenate ion, since bis-*O*-methyl CBG was stable in these conditions (Scheme 4).[55] Compound **12**,[37] although structurally a chromene, is most likely derived from the intramolecular cyclization of ω-epoxycannabigerol, a compound so far unknown from natural sources, and, as a cyclo-CBG, is therefore included in this group of phytocannabinoids.

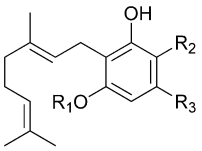
**4.1.2 Cannabichromene (CBC)-type compounds.** In this type of phytocannabinoids, the isoprenyl residue is oxidatively fused to the resorcinyl ring. The parent compound (CBC, **13f**) was independently isolated in 1966 by Mechoulam[62] and Claussen,[63] who assigned the same trivial name to the compound, thus avoiding semantic confusion in the literature. In many varieties of cannabis, the presence of CBC is associated to the one of $\Delta^9$-THC, suggesting an inheritance relationship between the oxidase involved in the generation of CBC and THC from CBG.[29] Conversely, no relationship seems to exist with oxidase involved in the generation of CBD.[29] The concentrations of CBC-type phytocannabinoids has been found higher in the vegetative compared to the reproductive stage of cannabis.[57] CBC is the only major phytocannabinoid that shows a bluish fluorescence under UV light. When thoroughly purified, natural CBC is racemic, and does not show any activity related to activation of $CB_1$.[64] CBC is, however, a potent non-covalent activator of TRPA1.[47]

CBC is the simplest natural phytocannabinoid to obtain by synthesis, being available, apart from CBG by oxidative dehydrogenation, also from the one step condensation of citral and olivetol (see Section 4.1.5 for a discussion on the mechanism of the reaction).[65] CBC is stable, and has been detected in century-old historical samples of cannabis.[31] As with CBG, diversity in the derivatives of CBC is associated to oxidation of the prenyl group and the aromatic ring, with the hydroquinol hydroxylation pattern being stabilized by acetylation. The configurational aspects of hydroxylated cannabichromenes **14** and **16** have not been elucidated. Since natural CBC is racemic, these compounds are most probably a mixture of diastereomers. Remarkably, the orcinol-type cannabichromenes **13b** and **13c** are of fungal and not plant origin, and have been obtained from *Cylindrocarpon olidum* Wollenw., a parasite of the root knot

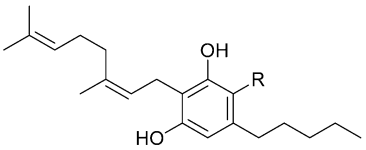



Scheme 4 Isomerization of CBG in basic conditions.

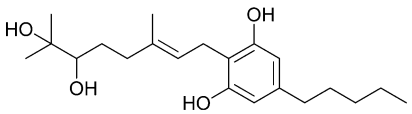
 



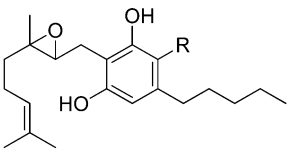

| | | $R_1$ | $R_2$ | $R_3$ | Ref. |
|---|---|---|---|---|---|
| **1a** | Cannabigerovarin (CBGV) | H | H | $C_3H_7$ | [56] |
| **1b** | Cannabigerovarinic acid (CBGVA) | H | COOH | $C_3H_7$ | [57] |
| **1c** | Cannabigerol (CBG) | H | H | $C_5H_{11}$ | [15] |
| **1d** | Cannabigerolic acid (CBGA) | H | COOH | $C_5H_{11}$ | [34] |
| **1e** | *O*-Methylcannabigerol | Me | H | $C_5H_{11}$ | [50] |
| **1f** | Cannabigerolic acid methylether | Me | COOH | $C_5H_{11}$ | [58] |




| | | R | Ref. |
|---|---|---|---|
| **2a** | Cannabinerolic acid | COOH | [59] |
| **2b** | Cannabinerol | H | [60] |



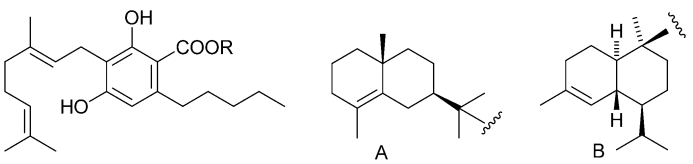

**4** Carmagerol [51]



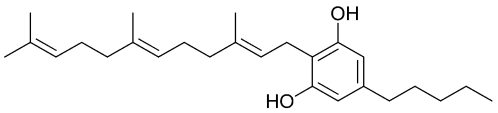

| | | R | Configuration | Ref. |
|---|---|---|---|---|
| **5a** | *rac*-6'-Epoxycannabigerol | H | (2'*S**, 3'*R**) | [52] |
| **5b** | *rac*-6'-Epoxycannabigerolic acid | COOH | (2'*S**, 3'*R**) | [52] |
| **5c** | *rac*-6'-Epoxycannabinerol | H | (2'*R**, 3'*R**) | [52] |
| **5d** | *rac*-6'-Epoxycannabinerolic acid | COOH | (2'*R**, 3'*R**) | [52] |

nematode *Meloidogyne incognita*, a major pest of some cultivated plants,[66] while the sesquicannabinoids confluentin (**13k**) and the anti-HIV agent daurichromenic acid (**13l**) have been isolated from a rhododendron species (*Rhododendron dauricum* L.) with confluentin having also been reported as a constituent of the mushroom from the genus *Albatrellus*.[67] In accordance with the racemic nature of CBC, confluentin (**13j**) was reported as a racemate, while daurichromenic acid (**13k**) as well as several functionalized analogues were isolated in an optically active form.[67] This suggests that racemization *via* an electrocyclic mechanism might be slowed by the presence of a carboxylic group *para* to the chromenic oxygen.

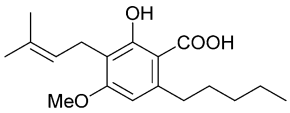
**4.1.3 Cannabidiol (CBD)-type compounds.** CBD (**16e**) was the first genuine phytocannabinoid to be isolated in 1940,[70] but its correct structure elucidation had to wait the advent of NMR spectroscopy, and was only reported more than two decades later, revising the location of the endocyclic double bond (originally reported at C-3, C5-, and C-8 by different authors), and establishing its relative configuration.[71,72] The clarification of the absolute configuration was done by correlation with natural (−)-menthol,[72] although a wrong absolute configuration for this monoterpene was originally assumed.[71] Since CBD is the major phytocannabinoid in fiber hemp, its carboxylated form was also the first pre-cannabinoid to be isolated,[10] and its relationship with CBD was correctly established by the Czech chemist Šantavý. Along with Cahn, Adams and Todd, Šantavý is one of the founding fathers of the chemistry of cannabinoids, but his contributions appeared, mostly in Czech, in scientific



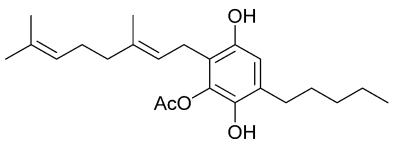

**3a** γ-Eudesmyl cannabigerolate R = A [7]
**3b** γ-Cadinyl cannabigerolate R = B [7]



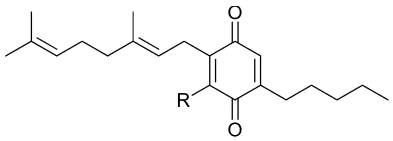

**6** Sesquicannabigerol [6]



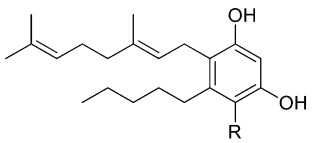

**7** Deprenyl *O*-methyl cannabigerolic acid (= Amorfrutin 2) [54]



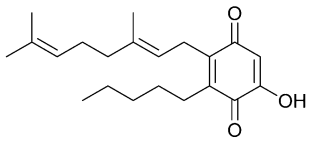

**8** 5-Acetyl-4-hydroxycannabigerol [37]



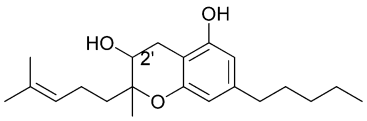

| | R | Ref. |
|---|---|---|
| **9a** Acetylcannabigeroquinol | OAc | [53] |
| **9b** Cannabigeroquinone | H | [61] |




| | R | Ref. |
|---|---|---|
| **10a** Abnormal cannabigerol | H | [46] |
| **10b** Acetyl abnormal hydrocannabigeroquinol | OAc | [37] |




**11** Abnormal cannabigeroquinol [37]




**12** 2'-Hydroxy-1',2'-dihydrocannabichromene (Cyclo-CBG) [37]

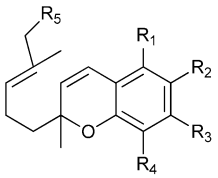
journals of limited distribution outside the Iron Courtain that divided Europe during the cold war, and are still largely overlooked in the phytocannabinoid community. Various modifications[65] of the original synthesis of CBD according to Petrzilka (condensation of *p*-menthadienol and olivetol under mild acidic conditions)[73] have been published. Depending on the strength of the acid, the reaction can stop at the CBD level, or further proceed to a mixture of $\Delta^8$- and $\Delta^9$-THC.[65] During the reaction, abnormal CBD is also formed by a retro Friedel–Craft process, and Razdan carried out a detailed investigation on this remarkable reaction and its subtleties (see also Section 4.1.5).[65]

The isolation of a prenylogue orcinoid analogue of CBD (**17**) was reported from the Alpine rhododendron (*Rododendron ferrugineum* L.).[74] This compound showed only negligible affinity for $CB_1$ and $CB_2$, not unlike CBD.[74] Despite the structural similarity between CBD and $\Delta^9$-THC, the two compounds show a distinct biological profile, and, even though CBD can be electrophilically cyclized to $\Delta^9$-THC by treatment with acids,[65] the two compounds are the result of independent oxidative cyclizations of their common precursor CBGA, and are not interconverted in cannabis tissues.[29] $\Delta^9$-THC and CBD have also quite different oxidative stability. While THC is roughly planar and removal of the benzallylic proton (H-10a) leads to a conjugated radical, the two rings of CBD lie in different planes,[75] and the benzyl radical generated from CBD cannot therefore benefit from conjugation with the aromatic ring. The slow (relatively to the NMR time scale) rotation around the terpenyl–resorcinyl bond is an interesting case of aryl-C($sp^3$) hindered rotation en route to atropisomerism, and is responsible for the temperature-dependence of the NMR spectra of CBD.[75] The impossibility to attain planarity and conjugation due to *E*-strain is also responsible the different behaviour of CBD and $\Delta^9$-THC in bases. While the latter generates the conjugated $\Delta^{10}$ isomer, CBD is isomerized to its further de-conjugated $\Delta^6$-isomer, a compound of unknown bioactivity (Scheme 5).[55]

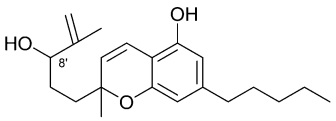
The acid-catalyzed cyclization of CBD to a mixture of narcotic THC isomers might be of relevance for the biological profile of CBD, rationalizing, for instance, the high incidence of somnolence observed in pediatric studies.[76] In simulated gastric fluid (pH = 1), the conversion of CBD, solubilized with sodium dodecyl sulfate, to a mixture of $\Delta^9$ and $\Delta^8$-THC was 98% complete after 2 hours, although the insolubility of CBD might slow down the reaction under physiological conditions.[76] This could also rationalize the observation that CBD is unable to generate significant amounts of $\Delta^9$-THC on smoking marijuana,[77] whose water suspensions are mildly basic (pH *ca.* 8). On the other hand, CBD can do so in the more acidic (pH *ca.* 5.7) tobacco cigarettes when they are spiked with CBD or CBD-containing cannabis oil, a popular practice within cannabis consumers.[3] The pyrolysis of CBD under conditions mimicking smoking gave a complex mixture of products. Apart from small amounts of $\Delta^8$- and $\Delta^9$-THC, the major products identified were cannabielsoin (**39c**) and its C-1 epimer.[78]

Some of the naturally occurring analogues of CBD show interesting structural features, like the presence of an alkyl residue with an even number of carbons (nor-CBD, **16d**) or *O*-alkylation with propyl- and pentyl residues. The isolation of an

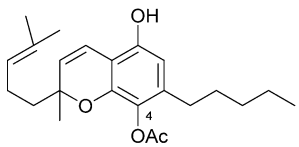
 




| | | $R_1$ | $R_2$ | $R_3$ | $R_4$ | $R_5$ | Ref. |
|---|---|---|---|---|---|---|---|
| **13a** | Cannabiorcichromene | OH | H | $CH_3$ | H | H | [60,67] |
| **13b** | Cannabiorcichromenic acid | OH | COOH | $CH_3$ | H | H | [66] |
| **13c** | Chlorcannabiorcichromenic acid | OH | COOH | $CH_3$ | Cl | H | [66] |
| **13d** | Cannabivarichromene (CBCV) | OH | H | $C_3H_7$ | H | H | [56, 67] |
| **13e** | Cannabichromevarinic acid | OH | COOH | $C_3H_7$ | H | H | [57] |
| **13f** | Cannabichromene (CBC) | OH | H | $C_5H_{11}$ | H | H | [66,68] |
| **13g** | Cannabichromenic acid | OH | COOH | $C_5H_{11}$ | H | H | [69] |
| **13h** | 4-Acetoxycannabichromene | OH | H | $C_5H_{11}$ | OAc | H | [37] |
| **13i** | Anthopogochromenic acid | H | OH | COOH | Me | H | [67] |
| **13j** | Confluentin | OH | H | $CH_3$ | H | Prenyl | [67] |
| **13k** | Daurichromenic acid | OH | COOH | $CH_3$ | H | Prenyl | [67] |

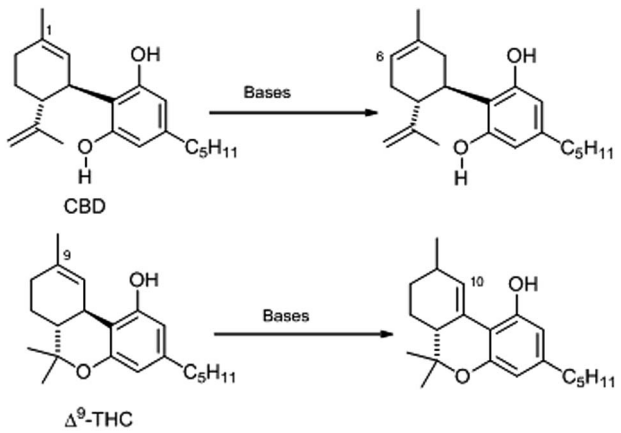



**14** 8'-Hydroxyisocannabichromene [37]




**15** 4-Acetoxycannabichromene [37]

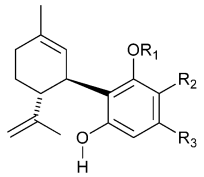
ester of cannabidiolic acid with a dihydroxylated $\Delta^{6a,10a}$-tetrahydrocannabinol derivative (**16j**) has also been reported. This compound was the first complex ester of pre-cannabinoids to be isolated.[79]



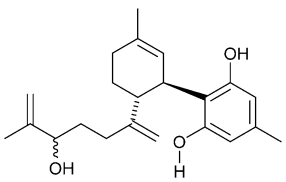

Scheme 5 Base-catalyzed isomerization of CBD and $\Delta^9$-THC.

CBD is an allosteric inhibitor of $CB_1$,[80] and further modulates the activity of $\Delta^9$-THC by interfering with its hepatic allylic hydroxylation, a reaction that generates a metabolite (11-hydroxy $\Delta^9$-THC) with a higher brain penetration and similar potency on $CB_1$.[39] Despite the enormous current interest for the clinical uses of CBD, the first studies for the bioactivity of CBD were actually triggered by its modulating activity on cytochromes and the potential for drug interaction, with the synergizing activity of CBD on the hypnotic effects of barbiturates being already reported in 1942 by Adams himself.[39] CBD seems to have a host of biological targets, including various thermos-TRP channels and the serotonin receptor 5-$HT_{1A}$,[64] and its overall biological profile cannot probably be summarized by the modulation of any single end point of the growing list of CBD biological targets. Currently, the major area of clinical research on CBD is the management of pediatric epilepsy, a use reminiscent of the first report on the medicinal use of *Cannabis* in colonial India by W. B. O'Shaughnessy in 1838.[81]

**4.1.4 Thymyl-type phytocannabinoids (cannabinodiol- and cannabifuran type compounds).** This type of compounds is characterized by aromatization of the menthyl moiety of CBD to give a thymyl group. Cannabinodiol (**18b**) has a checkered history, and its original isolation report most probably actually referred to its oxidatively cyclize analogue cannabifuran (**19a**).[88] Cannabifuran (**19a**) and dehydrocannabifuran (**19b**) were isolated from aged samples of hashish,[89] while cannabioxepane (**20**) was obtained from fiber hemp using a mild isolation protocol.[90] Since CBD is air-stable, its aromatization could be the result of enzymatic activity, and these thymyl-type compounds might therefore be genuine phytochemicals. Also the orcinoid form of cannabinodiol is known,[91] and, just like with many other phytocannabinoids, the syntheses of cannabinodiol predates the actual isolation,

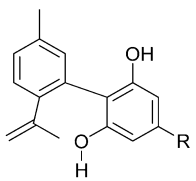



| | $R_1$ | $R_2$ | $R_3$ | Ref. |
|---|---|---|---|---|
| **16a** Cannabidiorcol | H | H | $CH_3$ | [82] |
| **16b** Cannabidivarin | H | H | $C_3H_7$ | [83] |
| **16c** Cannabidivarinic acid | H | COOH | $C_3H_7$ | [57] |
| **16d** *nor*-Cannabidiol | H | H | $C_4H_9$ | [84,85] |
| **16e** Cannabidiol (CBD) | H | H | $C_5H_{11}$ | [70] |
| **16f** *O*-Methylcannabidiol | $CH_3$ | H | $C_5H_{11}$ | [86] |
| **16g** *O*-Propylcannabidiol | $C_3H_7$ | H | $C_5H_{11}$ | [87] |
| **16h** *O*-Pentylcannabidiol | $C_5H_{11}$ | H | $C_5H_{11}$ | [87] |
| **16i** Cannabidiolic acid | H | COOH | $C_5H_{11}$ | [10] |
| **16j** CBDA-THC ester | H | COOA | $C_5H_{11}$ | [79] |

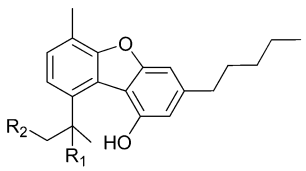



**17** Ferruginene C [74]

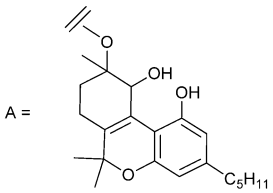
being the major photodegradation product of CBN.[92] Nothing is known on the biological profile of this type of phytocannabinoids.

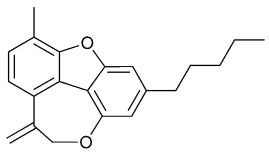



| | R | Ref |
|---|---|---|
| **18a** Cannabinodivarin | $C_3H_7$ | [91] |
| **18b** Cannabinodiol | $C_5H_{11}$ | [91,92] |




| | $R_1$, $R_2$ | Ref. |
|---|---|---|
| **19a** Cannabifuran | H,H | [89] |
| **19b** Dehydrocannabifuran | Δ | [89] |




**20** Cannabioxepane [90]

**4.1.5 Tetrahydrocannabinol-type compounds.** *Cannabis* contains a bouquet of bis-reduced forms of cannabinol, differing for the location of the remaining double bond, the configuration of the stereogenic centers, or both isomeric options. The major constituent, and the flagship constituent of cannabis, is *trans*-$\Delta^9$-THC (**23g**. $\Delta^9$-THC for short), but regio- and stereo-isomers also occur as minor constituents.[93–96,118,121] It is not clear if these compounds are enzymatically produced or if, conversely, they are artifacts originating from the degradation of $\Delta^9$-THC or of CBD.

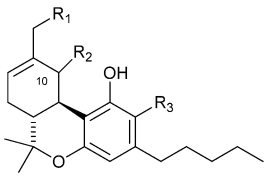
*4.1.5.1. $\Delta^8$-tetrahydrocannabinol ($\Delta^8$-THC)-type compounds.* Compounds of this class might be isolation artifacts resulting from $\Delta^9$-THC by acid- or oxidatively promoted shift of the endocyclic double bond, or from CBD by electrophilic cyclization. The $\Delta^8$ location is thermodynamically more stable than the $\Delta^9$ location, and this drives the isomerization.[65] The major spectroscopic difference between the two isomeric series is the chemical shift of the olefinic proton, that, because of the proximity to the aromatic ring, is more deshielded in the $\Delta^9$-isomer ($\delta$ *ca.* 6.40 in $CDCl_3$) compared to the $\Delta^8$-isomer ($\delta$ *ca.* 5.50 in $CDCl_3$).[93] The electrophilic cyclization of CBD can afford the $\Delta^8$- or the $\Delta^9$-isomer depending on the conditions, with mild acidic conditions favoring the $\Delta^9$-isomer and more forced conditions in terms of acidity and temperature the $\Delta^8$-isomer.[93] $\Delta^8$-THC and $\Delta^9$-THC show a similar profile of activity on cannabinoid receptors, with $\Delta^8$-THC being only slightly less active than $\Delta^9$-THC.[45] It should, however, be interesting to evaluate the profile of the two isomers also in terms of other

targets, like thermo-TRPs and transcription factors of the PPAR family, since this could provide interesting clues to clarify the role of the non-metabotropic targets in the pharmacological profile of $\Delta^9$-THC.

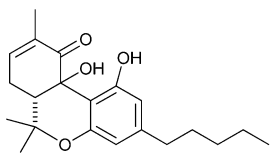
Compounds from the $\Delta^8$ series can be converted into their $\Delta^9$ isomers by addition of hydrochloric acid and base-mediated dehydrohalogenation (Scheme 6).[94] The counter-thermodynamic course of the reaction has been rationalized by assuming that deprotonation occurs intramolecularly *via* a phenate ion, thus favoring deprotonation from C-10 rather than from the other carbons adjacent to C-9.[94] This reaction is of great relevance, since $\Delta^8$-THC is much easier to synthesize than $\Delta^9$-THC (one step from verbenyl olivetol).[95] The isolation of a compound oxygenated at C-11 is interesting, since this is a major route in the human metabolism of $\Delta^9$-THC. In general, compounds from the $\Delta^8$-series are much more stable than their $\Delta^9$-series, and $\Delta^8$-THC has even been detected in a burial tomb dating from the fourth century B.C.[96] Because of the improved stability compared to $\Delta^9$-THC and its easier synthesis, $\Delta^8$-THC proved a better lead structure for phytocannabinoid-inspired probes to explore the biological space around cannabinoid receptors.[45]

location of the double bond turned out to be the only one never considered in all the previous investigations on the elusive narcotic principle of cannabis.[102] As with CBD, Šantavý came independently to the same conclusions, also establishing the absolute configuration of the active narcotic principle by correlation of $\Delta^9$- and $\Delta^8$-THC with CBD.[72] $\Delta^9$-THC belongs to the largest class of phytocannainoids, but the investigation on the phytochemistry of cannabis was long biased on the recreational chemotypes, and future studies on fiber hemp might reveal a different scenario. Diversity within this class of phytocannabinoids is mostly related to oxidation of the *p*-menthene moiety, possibly related to spontaneous degradation of the natural product (see infra), and to the esterification of pre-THC with various isoprenyl alcohols.

$\Delta^9$-THC acts as a partial agonist at both $CB_1$ and $CB_2$,[45] but, unexpectedly, its shorter analogue from the bis-nor type (THCV, **23c**) is instead an antagonist at $CB_1$, an important discovery in the light of the observation that rimonabant and most synthetic inhibitors of $CB_1$ are actually reverse-agonist and not antagonists.[103] The phenolic hydroxyl is critical for the activity, but, surprisingly, branching in the alkyl residue makes it redundant for the interaction with $CB_1$.[104] The native form of $\Delta^9$-THC is



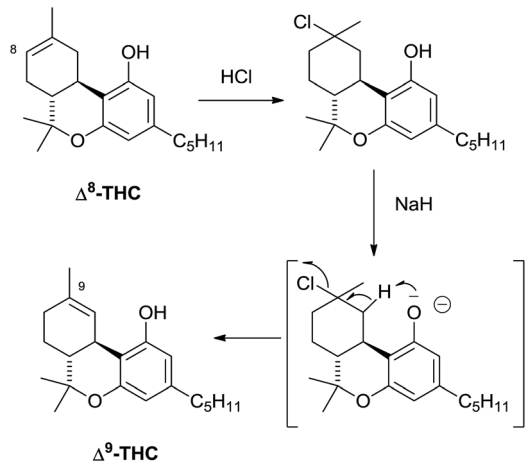

| | | $R_1$ | $R_2$ | $R_3$ | Ref. |
|---|---|---|---|---|---|
| **21a** | *trans*-$\Delta^8$-Tetrahydrocannabinol ($\Delta^8$-THC) | H | H | H | [97] |
| **21b** | *trans*- $\Delta^8$-Tetrahydrocannabinolic acid | H | H | COOH | [98] |
| **21c** | 10α-Hydroxy *trans*- $\Delta^8$-tetrahydrocannabinol | H | α-OH | H | [99] |
| **21d** | 10β-Hydroxy *trans*- $\Delta^8$-tetrahydrocannabinol | H | β-OH | H | [99] |
| **21e** | 11-Acetoxy- $\Delta^8$-tetrahydrocannabinoic acid | OAc | H | COOH | [99] |




**22** 10-Hydroxy-9-oxo-$\Delta^8$-tetrahydrocannabinol [100]

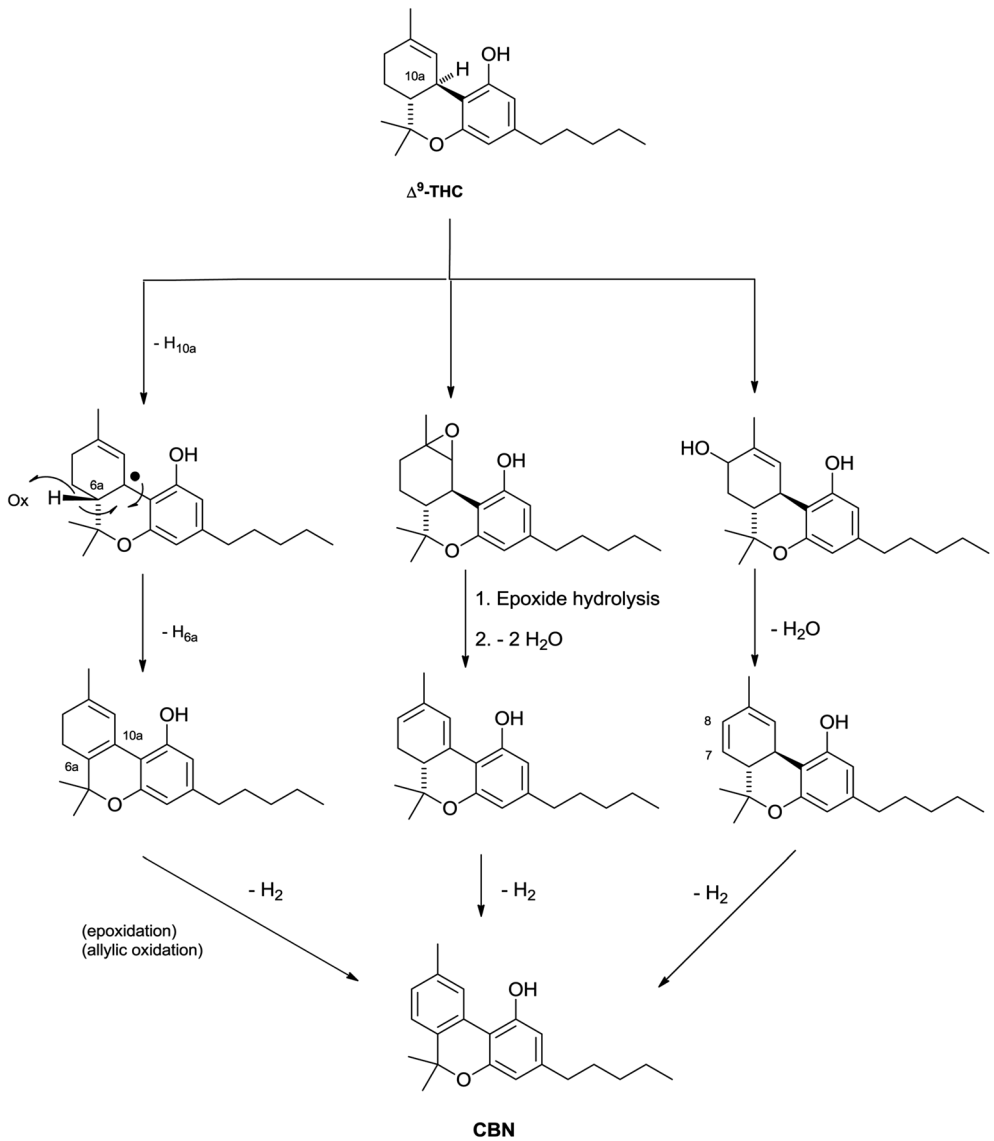
*4.1.5.2. $\Delta^9$-trans-tetrahydrocannabinol ($\Delta^9$-THC)-type compounds.* The early investigations on the phytochemistry of cannabis came to the conclusion that the narcotic constituent of the plant was a reduced form of cannabinol, at that time the only cannabinoid whose structure was known. The nature of this "active" tetrahydrocannabinol, possibly confusingly purified as acetyl derivative already in 1942,[101] remained elusive and confusing until the seminal paper by Gaoni and Mechoulam who in 1964 disclosed its isolation and structure elucidation from a Lebanese sample of hashish.[102] Curiously, the $\Delta^9$-

represented by a mixture of two pre-cannabinoids, THCA-A and THCA-B, very different in terms of physical state (THCA-B was investigated by crystallographic studies, while THCA-A is amorphous), stability toward decarboxylation (THCA-A is decarboxylated at 90 °C, while THCA-B is stable at this temperature), and concentration in plant tissues.[105] The acidic form of $\Delta^9$-THC-A is stabilized toward decarboxylation by esterification with isoprenyl alcohols, and these conjugates occur, as a complex mixture, in narcotic cannabis.[37] The structure of these compounds was only tentatively assessed, and the configuration of the isoprenyl residue should be confirmed by an independent synthesis. $\Delta^9$-THC is unstable as a pure compound, an amorphous gum that easily turns brown, but is more stable in crude form and can be stored in refrigerated methanol solution. The degradation is mainly oxidative, and is triggered by abstraction of the allylic and benzylic hydrogen at C-10a (Scheme 7). The resulting radical undergoes further hydrogen abstraction at C-6a, with formation of a conjugated




Scheme 6 Conversion of $\Delta^8$-THC into $\Delta^9$-THC.

double bond between C-6a and C-10a, en route to aromatization to CBN. Alternative dienes can be generated *via* either epoxidation of the endocyclic double bond, hydrolysis of the epoxide, and twofold dehydration, or *via* allylic oxidation at the C-8 methylene and dehydration. Aromatization of these dienes eventually generates CBN (Scheme 7).[106] At room temperature, the rate of degradation of $\Delta^9$-THC in cannabis has been estimated in *ca.* 5% per month, and 10% for the pure product, but other degradations pathways have been postulated be operative in plant tissues, since the rate of appearance of CBN was significantly lower than the one of disappearance of $\Delta^9$-THC.[106] On the other hand, this discrepancy could be related to the quick formation of intermediates that then converge to CBD at a slower rate. The mechanistic scenario for the aromatization is in accordance with the isolation of some of the intermediate compounds as well as with the detection of radicals by electron spin resonance during the degradation process.[107] There are no




Scheme 7 Possible mechanism for the oxidative degradation of $\Delta^9$-THC to CBN.

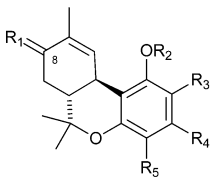
 

recent studies on the degradation of $\Delta^9$-THC, and the development in analytical technology witnessed by the past decades should greatly help the clarification of this important process. Interestingly, a tri-hydrocannabinol (**28**) has been isolated from the pollen of cannabis.[108] This compound could originate by disproportion of a dihydrocannabinol intermediate.

The acidic isomerization of $\Delta^9$-THC generates the thermodynamically more stable $\Delta^8$-isomer, that does not undergo oxidative degradation either in plant material or as a pure product, in accordance with the minor stabilization by resonance of a C-10a radical, that would now only be benzylic and not benzallylic.[109] $\Delta^9$-THC is characterized by an extremely low acute toxicity ($LD_{50}$ > 100 mg $kg^{-1}$ iv in rats), while CBD and other cannabinoids have a measurable toxicity ($LD_{50}$ *ca.* 50 mg $kg^{-1}$ iv in rats for CBD).[104]

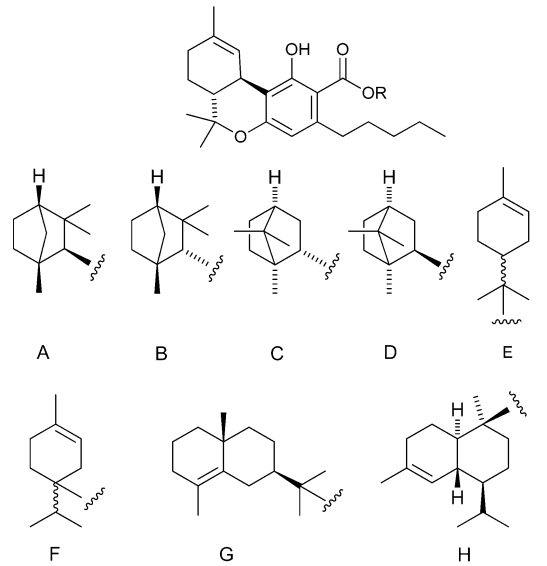
while the generation of the methylene-linked dimer cannabisol (**30**) might be the result of a process similar to the one that forms dicoumarol from 4-hydroxycoumarin.

*4.1.5.3. $\Delta^9$-cis-Tetrahydrocannabinol-type compounds.* The existence of a *cis*-isomer of $\Delta^9$-THC in cannabis has long been known, but the structure of this compound is still unclear, and the confusing history of this compound exemplify the subtleties of cannabinoid chemistry. $\Delta^9$-*cis*-THC is only a trace constituent of narcotic cannabis, but has been reported to occur in fiber hemp in concentrations similar to those of its *trans*-isomer, an important observation waiting, however, confirmation in modern studies.[118] Since the presence of significant amounts of $\Delta^9$-*cis*-THC is associated to the one of large amounts of CBD, it is not unconceivable that $\Delta^9$-*cis*-THC could actually be an artifact, derived by migration of the exocyclic $\Delta^{8(9)}$ double bond of

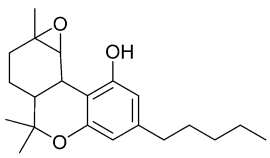



| | | $R_1$ | $R_2$ | $R_3$ | $R_4$ | $R_5$ | Ref. |
|---|---|---|---|---|---|---|---|
| **23a** | $\Delta^9$-*trans*-Tetrahydrocannabiorcol | H,H | H | H | $CH_3$ | H | [82] |
| **23b** | $\Delta^9$-*trans*-Tetrahydrocannabiorcolic acid | H,H | H | COOH | $CH_3$ | H | [84] |
| **23c** | $\Delta^9$-*trans*-Tetrahydrocannabivarin (THCV) | H,H | H | H | $C_3H_7$ | H | [110] |
| **23d** | $\Delta^9$-*trans*-Tetrahydrocannabivarinic acid | H,H | H | COOH | $C_3H_7$ | H | [57,111] |
| **23e** | $\Delta^9$-*trans-nor*-Tetrahydrocannabinol | H,H | H | H | $C_4H_9$ | H | [85] |
| **23f** | $\Delta^9$-*trans-nor*-Tetrahydrocannabinolic acid | H,H | H | COOH | $C_4H_9$ | H | [84] |
| **23g** | $\Delta^9$-*trans*-Tetrahydrocannabinol ($\Delta^9$-THC) | H,H | H | H | $C_5H_{11}$ | H | [102] |
| **23h** | $\Delta^9$-*trans*-Tetrahydrocannabinolic acid A | H,H | H | COOH | $C_5H_{11}$ | H | [18,112] |
| **23i** | $\Delta^9$-*trans*-Tetrahydrocannabinolic acid B | H,H | H | H | $C_5H_{11}$ | COOH | [113] |
| **23j** | 8α-Hydroxy-$\Delta^9$-*trans*-tetrahydrocannabinol | α-OH,H | H | H | $C_5H_{11}$ | H | [99] |
| **23k** | 8β-Hydroxy-$\Delta^9$-*trans*-tetrahydrocannabinol | β-OH,H | H | H | $C_5H_{11}$ | H | [99] |
| **23l** | 8-Oxo- $\Delta^9$-*trans*-tetrahydrocannabinol | =O | H | H | $C_5H_{11}$ | H | [100] |
| **23m** | *O*-Propyl- $\Delta^9$-*trans*-tetrahydrocannabinol | H,H | $C_3H_7$ | H | $C_5H_{11}$ | H | [87] |
| **23n** | *O*-Pentyl- $\Delta^9$-*trans*-tetrahydrocannabinol | H,H | $C_5H_{11}$ | H | $C_5H_{11}$ | H | [87] |
| **23o** | 2-Formyl- $\Delta^9$-*trans*-tetrahydrocannabinol | H,H | H | CHO | $C_5H_{11}$ | H | [100] |

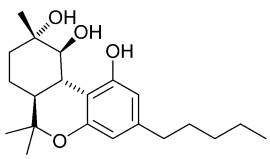
Hydroxylated derivatives of $\Delta^9$-THC have been isolated as a diastereomeric mixture, as expected from a non-enzymatic oxidative process. In some cases, as in **27**, the configuration at the hydroxylated carbons was not assessed, and it is unclear if the isolated compound was a mixture of isomers or, alternatively, configurationally pure.[114] The hydroxylated derivatives of $\Delta^9$-THC have been poorly investigated in terms of bioactivity. Interestingly, microsomal hydroxylation of $\Delta^9$-THC takes place at the allylic methyl (C-11) rather than at the endocyclic allylic methylene (C-8).[45] 11-Hydroxy $\Delta^9$-THC, unknown as a natural product, substantially retains the affinity of the natural product toward $CB_1$ and $CB_2$, but penetrates more easily the brain.[45] Also the epoxide of $\Delta^9$-THC (**25**) has been isolated from cannabis,[99] CBD to a $\Delta^{4(8)}$ position, followed by closure of the pyran ring (Scheme 8). If so, epimerization should be at C-6a (THC numbering), but this reaction has not been clearly observed under laboratory conditions. In accordance with this, treatment with Lewis acids converts racemic $\Delta^9$-*cis*-THC into racemic $\Delta^8$-*trans*-THC, presumably by opening of the oxygen bridge to give a $\Delta^{4,8}$-CBD intermediate, that then re-closes to generate the *trans*-isomer (Scheme 8).[119] However, under these conditions, interconversion from the normal- to the abnormal series has also been observed, showing that also the cleavage of the resorcinyl-menthyl bond *via* a retro-Friedel Craft reaction is, in principle, possible.[119] By using optically active substrates, it was eventually demonstrated that the isomerization takes place *via*



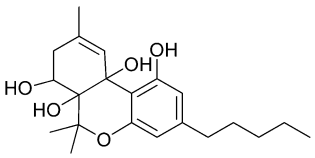

**24a** β-Fenchyl $\Delta^9$-*trans*-Tetrahydrocannabinolate R = A [7]
**24b** α-Fenchyl $\Delta^9$-*trans*-Tetrahydrocannabinolate R = B [7]
**24c** Bornyl $\Delta^9$-*trans*-Tetrahydrocannabinolate R = G [7]
**24d** *epi*-Bornyl $\Delta^9$-*trans*-Tetrahydrocannabinolate R = C [7]
**24e** α-Terpinyl $\Delta^9$-*trans*-Tetrahydrocannabinolate R = E [7]
**24f** 4-Terpinyl $\Delta^9$-*trans*-Tetrahydrocannabinolate R = F [7]
**24g** γ-Eudesmyl $\Delta^9$-*trans*-Tetrahydrocannabinolate R = D [7]
**24h** α-Cadinyl $\Delta^9$-*trans*-Tetrahydrocannabinolate R = H [7]




**25** Tetrahydrocannabinol epoxide [99]



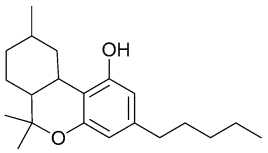

**26** $\Delta^9$-*trans*-Tetrahydrocannabinol glycol (cannabiripsol) [115]



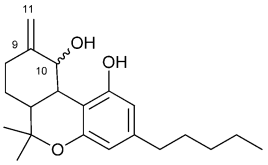

**27** 6a,7,10a-Trihydroxy-$\Delta^9$-tetrahydrocannabinol [116]

cleavage of the pyrane ring, but it is unclear how this relates to the configuration of natural $\Delta^9$-*cis*-THC, if this is, indeed scalemic.[119]

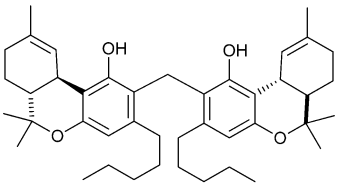
Racemic $\Delta^9$-*cis*-THC can be easily prepared from the condensation of citral and olivetol in acidic medium.[93]




**28** Hexahydrocannabinol [114]




**29** Hydroxy $\Delta^{9,11}$-hexahydrocannabinol [61]



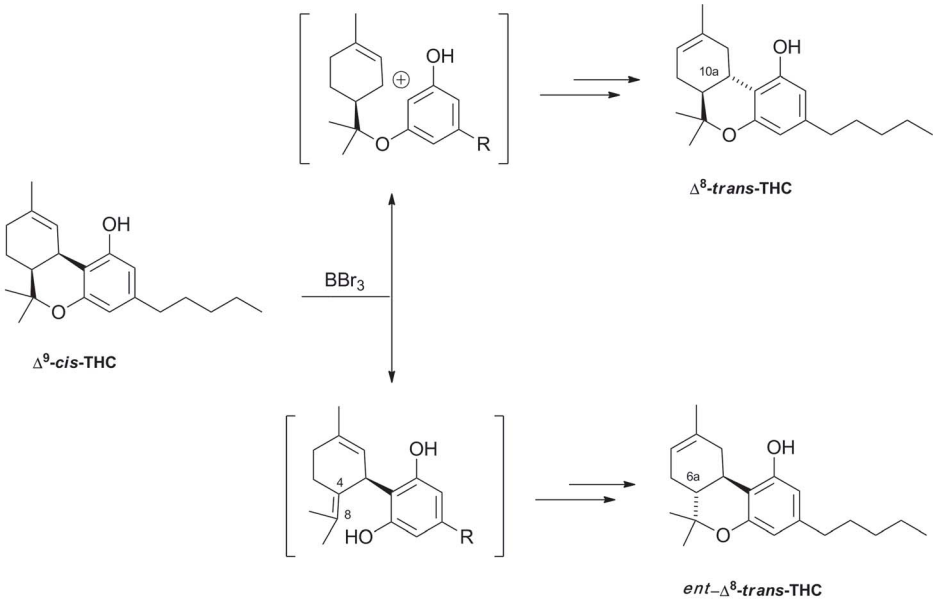

**30** Methylen-bis $\Delta^9$-*trans*-Tetrahydrocannabinol (Cannabisol) [117]

According to the catalysis, the reaction can afford cannabichromene or $\Delta^9$-*cis*-THC. Presumably, the reaction has a concerted course in basic medium, going through a quinone methide intermediate. Conversely, in the presence of protic or Lewis acids, cyclization of the initial 1,2-adduct to a menthyl cation could occur, followed by cyclization to $\Delta^9$-*cis*-THC (Scheme 9). The relative configuration of the final product depends on the nature of the catalyst. While Broensted acids afford essentially the *cis*-isomer, Lewis acids selective for the *trans*-isomer have been developed.[120]

$\Delta^9$-Tetrahydrocannabinols from the *trans* and *cis* series can be distinguished by the chemical shift of the geminal methyls ($\Delta\delta$ 0.25–0.35 in the *trans*-series, and 0.08–0.15 in the *cis*-series) from the signal of the benzylic proton, a broad singlet at around $\delta$ 3.50 ($CDCl_3$) for the *cis*-isomer, and a broad doublet at around $\delta$ 3.20 ($CDCl_3$) for the *trans*-isomer.[55,93] The profile of bioactivity of $\Delta^9$-*cis*-THC has only been investigated for $CB_1$-related activity, with the epimerization causing a general decrease of activity. The recent development of a stereoselective total synthesis of all isomeric forms of $\Delta^9$-tetrahydrocannabinol should make it possible a systematic investigation of the biological translation of the epimerization, as well as a long-awaited evaluation of the configuration of the natural product, if indeed optically active.[121]

Cannabicitran (**32**) might derive from *cis*-THC epoxide by Makovnikov-type protonation of the endocyclic double bond followed by trapping of the tertiary C-9 cation by the free-hydroxyl at C-1. Cannabicitran is an interesting case of "anticipated" natural product, since it was obtained by Crombie[122] from the pyridine-promoted condensation of citral and olivetol, before its actual isolation.[123] In a rare example of fair play within natural product chemists, Crombie acknowledged the




Scheme 8 Possible mechanisms for the isomerization of *cis* to *trans* tetrahydrocannabinols.

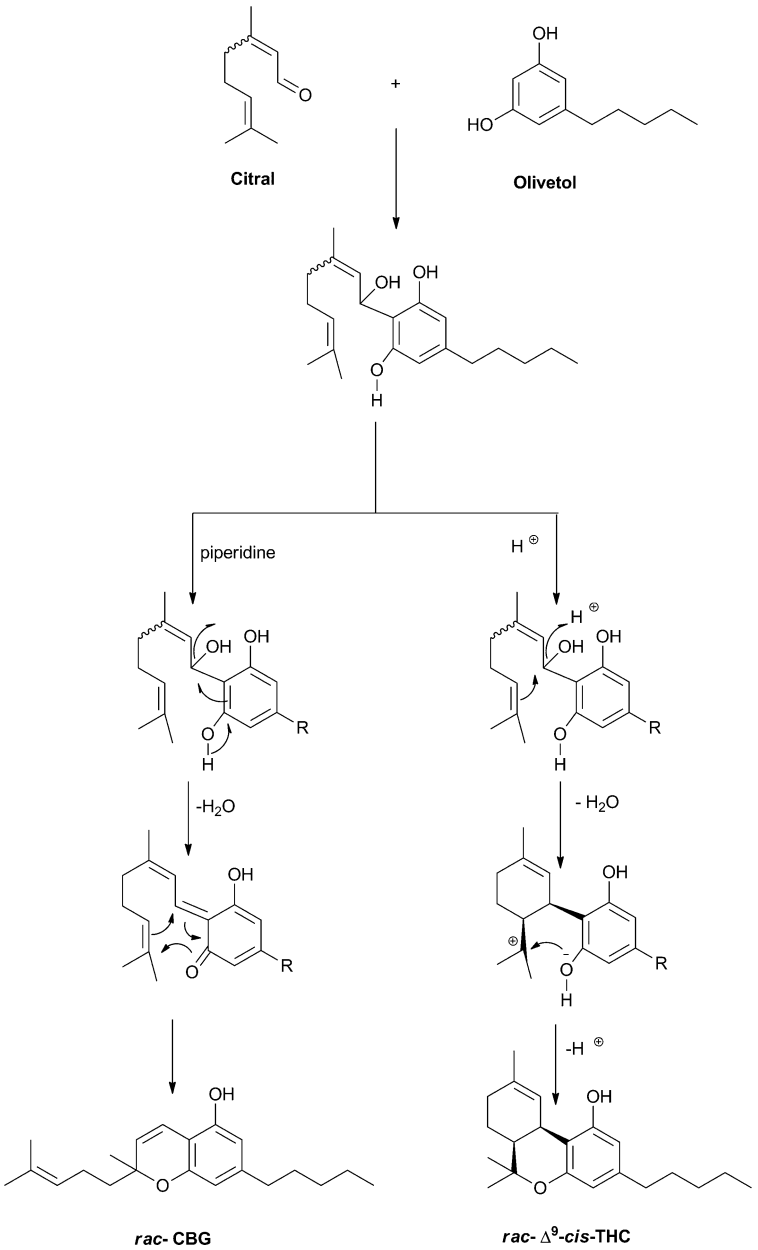
renaming of the compound she had originally named cytrilidene cannabis.

*4.1.5.4. $\Delta^{6a,10a}$ Tetrahydrocannabinol and cannabitriol-type compounds.* Compounds of this type are characterized by conjugation between the double bond on the terpenyl moiety and the resorcinyl residue, and are presumably intermediates in the oxidative aromatizatization of $\Delta^9$-THC, a process triggered by the generation of a C-10a radical (Scheme 7). Although $\Delta^{6a,10a}$-THC is unknown as natural product, an oxygenated analogue (the epoxide **34**) has been isolated from cannabis,[108] and the parent compound was synthesized as a racemate by Adams and Todd during the structure elucidation of cannabinol by the preparation of a series of possible putative structures for the natural product.[124,125] Racemic $\Delta^{6a,10a}$-THC was found active in the dog ataxia assay, and the observation was confirmed by modern studies, that localized cannabinoid activity exclusively in the *S*-enantiomer of the racemate.[126] The activity was lower, but qualitatively similar to the one of $\Delta^9$-THC, and it is therefore surprising that little information exists on compounds of this type, that are stable in ethanol solution and have been detected in historical samples of cannabis tinctures.[84]

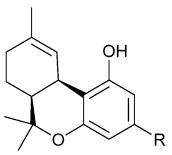
*4.1.5.5. Isotetrahydrocannabinol-type compounds.* Compounds from this class originate from CBD-type phytocannabinoids by protonation of the endocyclic double bond and quenching of the positive charge at C-1 by one of the two symmetrically disposed around C-3 (CBD numbering) phenolic hydroxyl of the resorcinyl moiety. While in THC-type phytocannabinoids the pyrane ring is linearly fused with the aromatic and the terpenyl moieities, in these compounds the junction is bridged. Both the stereochemical details and the biological profile of these compounds are still largely unknown.

**4.1.6. Cannabicyclol (CBL)-type compounds.** Interest in CBL (**38b**), a compound originally named THC-III, was fostered by the wrong assumption of a close structural relationship with THC.[134] After a series of structural revisions, the relative configuration was eventually established by X-ray analysis of the dibromoderivative.[135] CBL can be obtained by irradiation of CBC *via* an intramolecular stereoselective [2 + 2] cycloaddition.[135] This observation, the racemic nature of these phytocannabinoids, and the strict relationship between their concentration in plant material and the one of the corresponding cannabichromenes, strongly suggest that they are artefacts formed during storage of the plant material in the presence of light. Both the normal-(**38b**) and the abnormal (anthopogocyclolic acid, **38f**) version of the acids from the orcinoid series were isolated from a Cinese rhododendron species (*Rhododendron anthopogonoides*). Another rhododendron (*R. dauricum*) afforded the sesqui-cannabinoid rhododaurichromanic acid A (**38g**).[136] Apart from the lack of narcotic properties of CBL,[135] very little is known on the biological profile of these compounds, even though rhododaurichromanic acid A shown potent anti-HIV properties.[136]

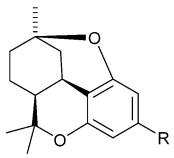
**4.1.7. Cannabielsoin (CBE)-type compounds.** Compounds of this type are named after Elsa Boyanova, who isolated the first members of this class of compounds in the laboratories of Raphael Mechoulam, and who prematurely passed away.[140] These compounds are the result of the formal intramolecular opening of cannabidiol-type epoxides, as evident from the *trans*-relationship of the oxygen functions on the menthyl moiety. The process has been mimicked by epoxidation of the diacetate of CBD. Thus, hydrolysis of the acetate triggered the opening of the oxirane ring by one of the two phenolic *ortho*-hydroxyls, affording a compound identical to the one obtained by decarboxylation of cannabielsoic acid.[141] Cannabielsoic acid A could also be obtained from pre-CBD by oxidation with manganese(IV) dioxide, or, alternatively, by irradiation in an oxygen atmosphere.[30,140] Cannabielsoin-type phytocannabinoids might well be isolation artifacts, but it is remarkable that in all their semi-




Scheme 9 Different course of the condensation of citral and olivetol depending on the conditions (R = *n*-pentyl).



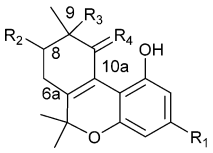
| | | R | Ref. |
|---|---|---|---|
| **31a** | $\Delta^9$-*cis*-Tetrahydrocannabivarin | $C_3H_7$ | [60] |
| **31b** | $\Delta^9$-*cis*-Tetrahydrocannabinol | $C_5H_{11}$ | [118] |



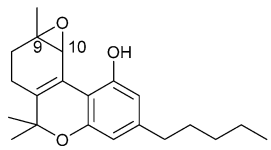
| | | R | Ref. |
|---|---|---|---|
| **32a** | Cannabicitran (citrilidene-cannabis) | $C_5H_{11}$ | [122, 123] |
| **32b** | Cannabiorcicitran | $CH_3$ | [67] |

syntheses from CBD-type compounds, mixtures of compounds unknown as natural products were also obtained.[30,141] Of interest is the occurrence of cannabielsoic acid in two isomeric forms, having the carboxylate located *ortho* or *meta* to the oxygen bridge, a situation reminiscent of the one of pre-THC.[140] Cannabielsoin is a major pyrolytic product of CBD, and is

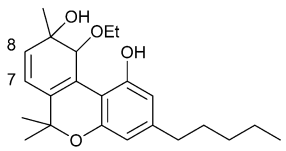
 



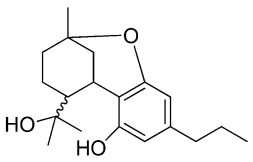

| | $R_1$ | $R_2$ | $R_3$ | $R_4$ | Ref. |
|---|---|---|---|---|---|
| **33a** Bis-*nor* cannabitriol | $C_3H_7$ | H | α-OH | β-OH,α-H | [84] |
| **33b** Bis-*nor*-Cannabitriol isomer | $C_3H_7$ | H | OH | OH, H | [84] |
| **33c** 10-*O*-Ethyl bis-*nor* cannabitriol | $C_3H_7$ | H | α-OH | β-OH,α-H | [84] |
| **33d** Isocannabitriol | $C_5H_{11}$ | OH | OH | H,H | [127] |
| **33e** Cannabitriol | $C_5H_{11}$ | H | α-OH | β-OH,α-H | [128,129] |
| **33f** Cannabitriol isomer | $C_5H_{11}$ | H | OH | OH | [127, 130] |
| **33g** 10-*O*-Ethyl cannabitriol isomer | $C_5H_{11}$ | H | OH | OEt | [130] |
| **33h** 10-Oxo-$\Delta^{6a(10a)}$-tetrahydrocannabinol | $C_5H_{11}$ | H | H | =O | [89] |




**34** 9,10-Anhydrocannabitriol [108]



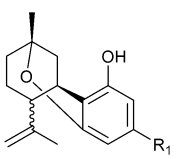

**35** 7,8-Dehydro-10-*O*-ethylcannabitriol [108]




**37** Cannabiglendol [133]

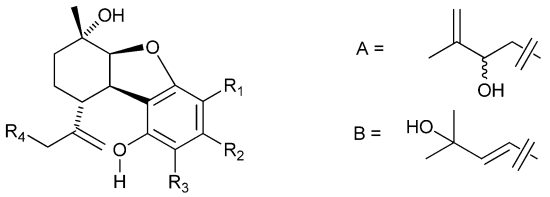
therefore expected to be present in cannabis smoke.[78] It is also a metabolite of CBD in rodents,[142] and in tissue cultures by cannabis and the sugar cane.[143] Nevertheless, and despite interesting clues on the bioactivity of CBD pyrolysates,[78] very little is known on its bioactivity.

Two prenylogues analogues of CBE from the orcinoid series (ferrugienes A and B, **39f** and **39g**) have been isolated from the Alpine rhododendron (*Rhododendron ferrugineum* L.).[74]




| | R | Ref. |
|---|---|---|
| **36a** $\Delta^7$-*cis*-Isotetrahydrocannabivarin | $C_3H_7$ | [131] |
| **36b** $\Delta^7$-*trans*-Isotetrahydrocannabivarin | $C_3H_7$ | [132] |
| **36c** $\Delta^7$-*trans*-Isotetrahydrocannabinol | $C_5H_{11}$ | [132] |

**4.1.8. Cannabinol (CBN)-type compounds.** Cannabinol was the first phytocannabinoid isolated from cannabis. In 1896, by exploiting the crystalline nature of its acetate, Easterfield in Cambridge (UK) managed to obtain cannabinol from the high-boiling fraction of an ethereal extract from an Indian sample of cannabis.[145] Its structure was reported in 1940 by Adams,[70] and cannabinol remained for two decades the only compound of this class to be structurally elucidated. Cannabinol and its derivatives and analogues are considered isolation artifacts, derived from the oxidative aromatization of the corresponding THC-type derivatives, and the isolation of partially aromatized mentadienic derivatives like **41** (7,8-dihydrocannabinol) supports this view. CBN is highly stable toward oxidative degradation, and has been used as a marker for the identification of narcotic cannabis in archeological findings.[146] The aromatization of THC to CBN can be affected by sulfur dehydrogenation at 250 °C.[147] These harsh conditions cause the decarboxylation of pre-cannabinoids, and a milder, but poorly yielding, protocol that uses selenium dioxide and trimethylsilyl polyphosphate has been developed to prepare pre-CBN from pre-THC.[148] The significant overlapping between the diversity of CBN and THC derivatives is in accordance with the view that oxidative aromatization of THC derivatives occurs spontaneously in plant material and in cannabis extracts. Nevertheless, the presence of nor-derivatives of $C_2$- and $C_4$-phytocannabinoids is interesting, and, at least for the $C_2$-cannabinoid nor-cannabivarin (**40b**), unreported in compounds from the THC series, where also hydroxylation at C-7 is unknown. CBN is the only




| | | $R_1$ | $R_2$ | $R_3$ | $R_4$ | Ref. |
|---|---|---|---|---|---|---|
| **39a** | Bisnor-cannabielsoin | H | $C_3H_7$ | H | H | [144] |
| **39b** | Bis-*nor*-Cannabielsoic acid B | COOH | $C_3H_7$ | H | H | [144] |
| **39c** | Cannabielsoin | H | $C_5H_{11}$ | H | H | [142] |
| **39d** | Cannabielsoic acid A | H | $C_5H_{11}$ | COOH | H | [140,30] |
| **39e** | Cannabielsoic acid B | COOH | $C_5H_{11}$ | H | H | [140,30] |
| **39f** | Ferruginene A | H | $CH_3$ | H | A | [74] |
| **39g** | Ferruginene B | H | $CH_3$ | H | B | [74] |

phytocannabinoid existing in all the alkyl versions from methyl to pentyl.

Cannabinol has only weak affinity for $CB_1$ and $CB_2$, *ca.* 10% of the one of THC.[149] nor-Cannabivarin (**40b**), the only phytocannabinoid with an ethyl side chain, and nor-CBN (**4d**) were isolated from an historical bottle of cannabis tincture dating from the first half of the 19th century and prepared from an Indian sample of cannabis resin.[84] The presence of phytocannabinoids with an even number of carbons could be typical of cannabis samples of that origin but, surprisingly, there are no modern studies on the diversity of cannabis in India.

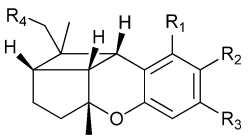
**4.1.9. 8,9-Secomenthyl cannabidiols.** The oxidative cleavage of the endocyclic double bond of $\Delta^9$-THC affords, after trapping of the C-10 aldehyde by the phenolic hydroxyl and dehydration, cannabicoumaronone (Scheme 10).[151] The configurational aspects of these compounds have not been fully clarified. When configuration of a stereocenter was assessed, it was found identical to that of $\Delta^9$-THC (see **3b**, with a *R*-configuration at C-6).[37]

Further oxidative degradation of the furane moiety of cannabicoumaronone leads to cannabichromanones, a class of seco-10 norcannabinoids (Scheme 10). Cannabichromanone itself was isolated from a degraded sample of hashish having as major constituent CBN,[89] and these compounds might well have a non-enzymatic origin.

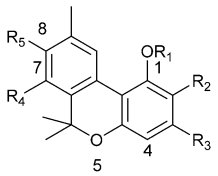
Cannabimovone (**46**) is formally the result of the oxidative fragmentation of the endocyclic bond of CBD followed by intramolecular aldolization (Scheme 11)[153] Interestingly, attempt to mimic this biogenetic relationship with CBD failed to deliver the natural products, affording instead the oxy-Michael adduct of its crotonized version (anhydrocannabimovone, **47**).[153] While cannabimovone showed little affinity for $CB_1$ or $CB_2$, anhydrocannabimovone activated both $CB_1$ and $CB_2$ with a Ki of *ca.* 100 nM.[153] The configuration of the oxygen bridge of anhydrocannabimovone was revised during the total synthesis of cannabimovone.[154]

### 4.2 β-Aralkyl type phytocannabinoids (phytocannabinoid-like compounds, bibenzyl cannabinoids, stiryl cannabinoids)

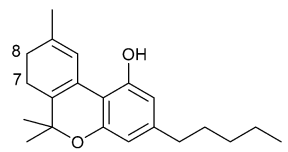
Because of the derivation from an aromatic starter, in these compounds a β-aralkyl residue replaces the alkyl group of cannabis phytocannabinoids, while the connectivity (but not always the configuration) of the isoprenyl moiety closely mimics the one of the cannabis products, overall resulting in similarity



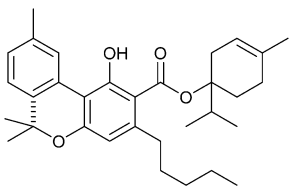

| | | $R_1$ | $R_2$ | $R_3$ | $R_4$ | Ref. |
|---|---|---|---|---|---|---|
| **38a** | Cannabiorcicyclol | OH | H | $CH_3$ | H | [67] |
| **38b** | Cannabiorcicyclolic acid | OH | COOH | $CH_3$ | H | [67] |
| **38c** | Cannabicyclovarin | OH | H | $C_3H_7$ | H | [131,137] |
| **38d** | Cannabicyclol (CBL) | OH | H | $C_5H_{11}$ | H | [134] |
| **38e** | Cannabicyclolic acid | OH | COOH | $C_5H_{11}$ | H | [139] |
| **38f** | Anthopogocyclolic acid | $CH_3$ | COOH | OH | H | [67] |
| **38g** | Rhododaurichromanic acid A | OH | COOH | $CH_3$ | Prenyl | [136] |



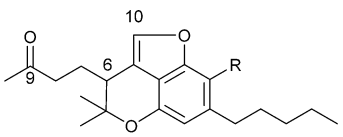

| | | $R_1$ | $R_2$ | $R_3$ | $R_4$ | $R_5$ | Ref. |
|---|---|---|---|---|---|---|---|
| **40a** | Cannabiorcol | H | H | $CH_3$ | H | H | [82] |
| **40b** | nor-Cannabivarin | H | H | $C_2H_5$ | H | H | [84] |
| **40c** | Cannabivarin | H | H | $C_3H_7$ | H | H | [149] |
| **40d** | nor-Cannabinol | H | H | $C_4H_9$ | H | H | [84,85] |
| **40e** | Cannabinol | H | H | $C_5H_{11}$ | H | H | [70, 145] |
| **40f** | Cannabinolic acid | H | COOH | $C_5H_{11}$ | H | H | [34] |
| **40g** | *O*-Methylcannabinol | $CH_3$ | H | $C_5H_{11}$ | H | H | [150] |
| **40h** | *O*-Propylcannabinol | $C_3H_7$ | H | $C_5H_{11}$ | H | H | [87] |
| **40i** | *O*-Penthylcannabinol | $C_5H_{11}$ | H | $C_5H_{11}$ | H | H | [87] |
| **40j** | 7-Hydroxycannabinol | H | H | $C_5H_{11}$ | OH | H | [84] |
| **40k** | 8-Hydroxycannabinol | H | H | $C_5H_{11}$ | H | OH | [37] |
| **40l** | 8-Hydroxycannabinolic acid | H | COOH | $C_5H_{11}$ | H | OH | [37] |




**41** 7,8-Dihydrocannabinol [108]




**42** 4-Terpenyl cannabinolate [7]

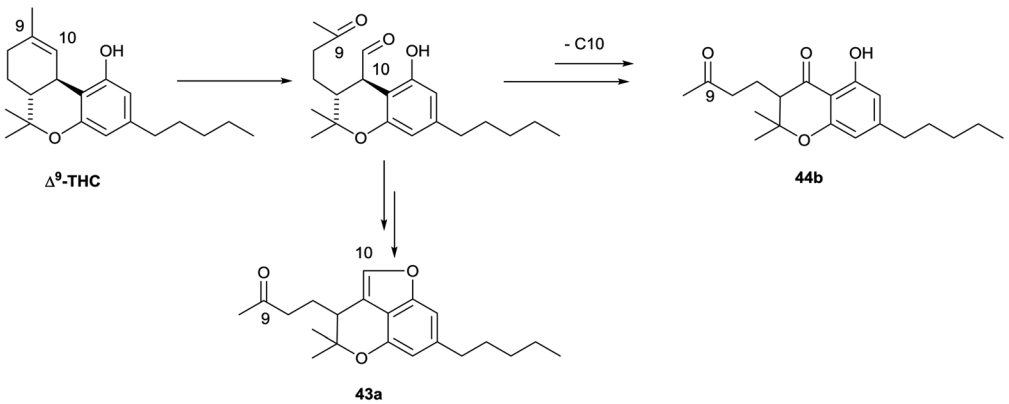



| | R | Ref. |
|---|---|---|
| **43a** Cannabicoumaronone | H | [151] |
| **43b** Cannabicoumarononic acid | COOH | [37] |

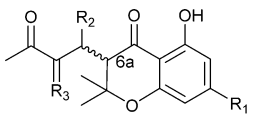
with the major phytocannabinoid chemotypes (CBG, CBC, THC). On the other hand, *O*-methylation of the resorcinyl moiety is rare within alkyl phtytocannabinoids, but is instead common in compounds from the β-aralkyl series, as are oxidative modifications of the isoprenyl residue, especially in compounds from the abnormal series.

**4.2.1 Cannabigerol (CBG) analogues.** Amorfrutins are the best known and investigated β-aralkyl phytocannabinoids of the cannabigerol type.[155,156] Five amorfrutins are known, distinguished by an overlapping and confusing code system of numbers and letters [A (=1), B, 2, 3, C (=4)].[157] With the exception of amorfrutin 2 (7), a pentyl-type cannabinoid, the other amorfrutins are of the phenethyl type and are structurally related to pre-cannabigerol *O*-methyl ether. All amorfrutins share a salicylate core bearing a *para*-methoxy- or hydroxy group, a *meta*-isoprenyl and an *ortho* aralkyl or alkyl substituent. The first member of the class, later named amorfrutin A (=amorfrutin 1, **48d**), was isolated in 1978 by Asakawa from a French collection of the liverwort *Radula complanata* (L.) Dum.,[158] and the following year was also reported by Bohlmann from *Helichrysum umbraculigerum* Less., a South-African species where it co-occurs with CBG.[46] Two years later, amorfrutin A was independently isolated from the seeds of the bastard indigo-bush (*Amorpha fruticosa* L.), a plant native to US, by Mitscher,[159] and from an Australian *Glycyrrhiza* species [*G. acanthocarpa* (Lindl) J. M. Black] by Ghisalberti.[160] Further amorfrutins (**48f**, **48j**, **48l**, **49b**) were obtained from the roots of the Mediterranean species *Glycyrrhiza foetida* Desf.[157] and from the leaves of the American licorice [*G. lepidota* (Nutt) Pursh],[161] while the genus *Radula* has provided a host of analogues.[162] Interestingly, the roots of better known licorices like *G. glabra* L. and *G. uralensis* L. do not contain amorfrutins.[163]

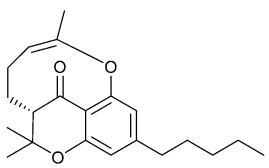
Amorfrutins were originally characterized as anti-bacterial agents,[159] but interest was re-kindled by the discovery that amorfrutin B (**48j**) is a powerful ligand of PPARγ (Ki = 19 nM), showing remarkable insulin-sensitivity activity *in vivo*.[157] The



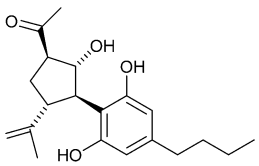

Scheme 10 Oxidative degradation of the endocyclic double bond of $\Delta^9$-THC.



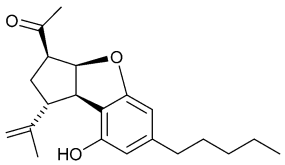
| | $R_1$ | $R_2$ | $R_3$ | Ref. |
|---|---|---|---|---|
| **44a** Bisnor-Cannabichromanone | $C_3H_7$ | H | H,H | [152] |
| **44b** Cannabichromanone | $C_5H_{11}$ | H | H,H | [89] |
| **44c** (6a*R*)-Cannabichromanone B | $C_5H_{11}$ | OH | H,H | [152] |
| **44d** (6a*R*)-Cannabichromanone C | $C_5H_{11}$ | H | =O | [152] |



**45** Cannabichromanone D [152]

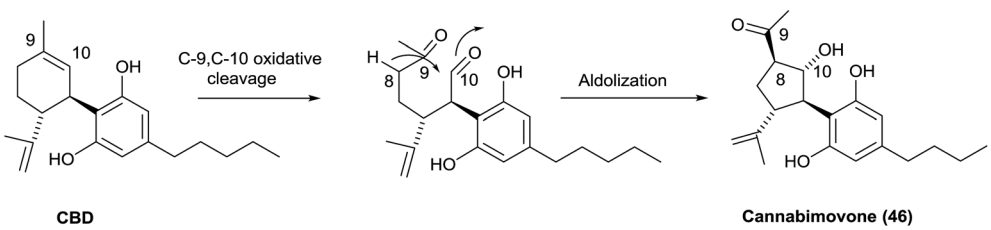


**46** Cannabimovone [153]



**47** Anhydrocannabimovone [153]

interaction of amorfrutins with PPARγ is basically different from the one of glitazones, since a crystallographic analysis has shown that amorfrutins bind PPARγ at the entry side and not at into the pocket of the ligand binding groove of this transcription factor.[164] This finding underlies the observation that the amorfrutin-PPARγ complex associates to a distinct profile of proteins compared to the glitazone-PPARγ complexes, resulting in the selective activation of only of a subset of the genes under PPARγ control. The possibility therefore exists that the modulation of PPARγ by amorfrutins might not be associated to the side-effects typical of glitazones (fluid retention, weight gain, cardiovascular complication, bladder cancer), and animal studies have supported this suggestion.[157] Amorfrutin B (**48j**) is the most powerful compound of the series in terms of PPARγ activation. Its superior activity compared to its demethyl derivative (amorfrutin 4, **48l**) and it deprenyl derivative (amorfrutin A = amorfrutin 1, **48d**) highlights the relevance of *O*-methylation and the oligomerization degree of the isoprenyl residue for superior potency. A second high-affinity target for amorfrutins was identified in the glycolytic enzyme glyceraldehyde 3-phosphate dehydrogenase (GAPDH).[165] Amorfrutins can




Scheme 11 Oxidative degradation of the endocyclic double bond of CBD to cannabimovone (**46**).

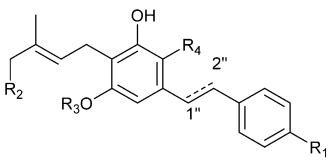
inhibit both its activity and its translocation to the nucleus, a process involved in neuronal death, and hold therefore promise for the management, and possibly also the prevention, of neurodegenerative diseases. Several additional targets have been identified for amorfrutins, including the inhibition of NF-κB activity, the inhibition of iNOS, the corticotropin releasing factor-binding protein, the cysteine protease ATGB4, and the photoreceptor-specific nuclear receptor NR2E3.[155,156] The multifaced profile of end-points makes it possible that amorfrutins could target, apart from diabetes, also a host of other conditions characterized by chronic inflammation, not unlike curcumin. For unclear reasons, amorfrutins and pre-cannabinoids from the phenethyl series are more resistant to decarboxylation compared to the alkyl phytocannabinoids.

Just like amorfrutins, also their analogues were isolated from taxonomically unrelated sources. Thus, the stiryl version of decarboxyamorfrutin C (amporphastilbol, **48g**) was isolated from three leguminous *Amorpha* species (*A. nana* Nutt., *A. fruticosa* L., and *A. canescens* Pursh.),[166] as well as from *H. umbraculigerum*, an asteraceous plant.[46] *H. umbraculigerum* also afforded its phenethyl analogue (**48e**), a compound first isolated from the liverwort *Radula variabilis*.[158] In this context, the phytochemistry of *H. umbraculigerum* is very interesting, since this plant is not only the major natural source of cannabigerol in terms of isolation yield, but also produces its abnormal-, phenethyl- and stiryl-analogues, undoubtedly qualifying as the biogenetically most versatile source of phytocannabinoids known. Interestingly, also amorphastilbol was reported to bind PPARγ (as well as PPARα),[167] but a direct comparison with amorfrutins has not yet been reported.

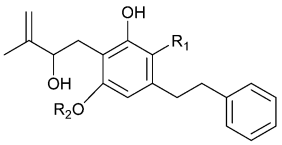
Amorfrutin-type compounds were also isolated from peanut (*Arachis hypogea* L.) seeds infected with an *Aspergillus flavus* fungal strain.[168] Compounds **53a–c** are characterized by a shift of the prenyl double bond in conjugation to the aromatic core, a rare feature in isoprenylated phenolics. These compounds (araphyns, arachidins) act as phytoalexins, helping the plant to resist fungal attack.

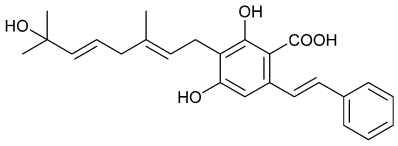
A unique feature of some phytocannabinoids from *H. umbraculigerum* is the esterification of the resorcinyl hydroxyl *para* to the carboxylate group, generally a site of methylation, with branched short-chain carboxylic acids.[46] Within the phytocannabinoids from *H. umbraculigerum*, acylation is a selective feature of compounds from the phenethyl series with a prenyl residue, and was not observed in their stiryl and terpenyl analogues. *O*-Prenylation, along with meta-hydroxylation, has also been reported in a bibenzyl cannabinoid (**55**) from *Glycyrrhiza lepidota*.[161]

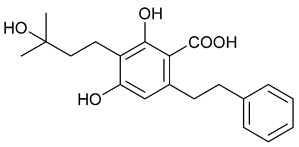
From liverwort of the *Radula* genus, stilbenic phytocannabinoids with an heterocyclized isoprenyl residue have been isolated. Apart from compounds resulting from the acidic cyclization of *o*-hydroxylated prenyl phenols, like compounds **56a**,**b** and **57a**,**b**, also compounds derived from the cyclization of ω-oxygenated precursors have been described.[156] Thus, compounds **57a–c** are formally derived from the intramolecular opening of a terminal epoxide in a $S_N2$ fashion (attack to the least substituted carbon) by the hydroxyl *para* to the carboxylate group. This 7-*endo tet* regiochemistry is unusual in




| | $R_1$ | $R_2$ | $R_3$ | $R_4$ | $\Delta^{1",2"}$ | Ref. |
|---|---|---|---|---|---|---|
| **48a** Demethyldecarboxyamorfrutin A | H | H | H | H | - | [46,169-172, 174] |
| **48b** Demethylamorfrutin A | H | H | H | COOH | - | [169,171,174] |
| **48c** Decarboxyamorfrutin A | H | H | Me | H | - | [160,171,175] |
| **48d** Amorfrutin A (= amorfrutin 1) | H | H | Me | COOH | - | [157,159,160, 171,172] |
| **48e** Heli-Cannabigerol (H-CBG) | H | Prenyl | H | H | - | [46,158,172] |
| **48f** Amorfrutin C (= amorfrutin 4, pre-H-GBC)) | H | Prenyl | H | COOH | - | [46,157] |
| **48g** Amorphastylbol | H | Prenyl | H | H | + | [46,173] |
| **48h** Pre-amorphastylbol | H | Prenyl | H | COOH | + | [46] |
| **48i** Hydroxy Helicannabigenol | OH | Prenyl | H | H | - | [158] |
| **48j** Amorfrutin B | H | Prenyl | Me | COOH | - | [159] |
| **48k** Decarboxyamorfrutin B | H | Prenyl | Me | H | - | [158] |
| **48l** Amorfrutin 4 (=demethylamorfrutin B) | H | Prenyl | H | COOH | - | [157] |
| **48m** Chiricanin A | H | H | H | H | + | [176] |
| **48n** *trans*-Arachidin-2 | OH | H | H | H | + | [168] |



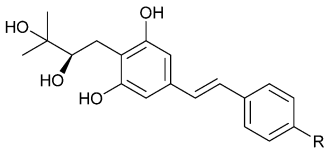




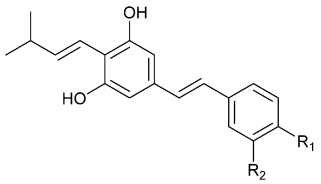
| | | $R_1$ | $R_2$ | Ref. |
|---|---|---|---|---|
| **49a** | Glepidotin C | H | H | [161] |
| **49b** | Amorfrutin 3 | COOH | Me | [156] |

**50** [46]

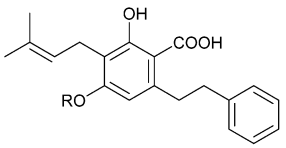
**51** [174]

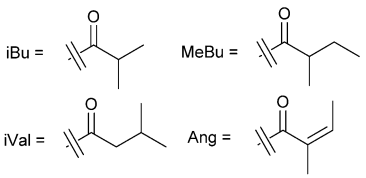


| | R | Ref. |
|---|---|---|
| **52a** Araphyn-3 | OH | [168] |
| **52b** Araphyn-4 | H | [168] |



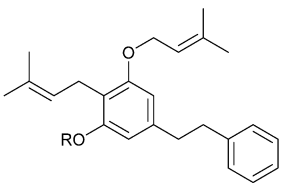
| | $R_1$ | $R_2$ | Ref. |
|---|---|---|---|
| **53a** Araphyn-1 | H | H | [168] |
| **53b** Arachidin-3 | OH | H | [168] |
| **53c** *trans*-Arachidin-1 | OH | OH | [168] |





| | R | Ref. |
|---|---|---|
| **54a** | *i*Bu | [46] |
| **54c** | MeBu | [46] |

| | R | Ref. |
|---|---|---|
| **54b** | *i*Val | [46] |
| **54d** | Ang | [46] |

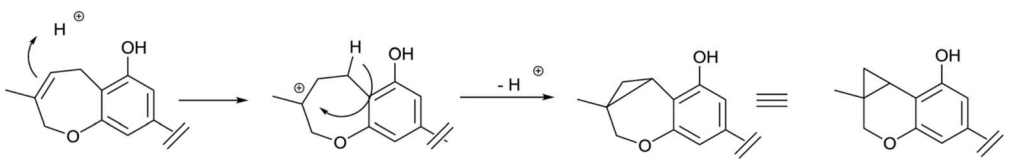


**55** [161]

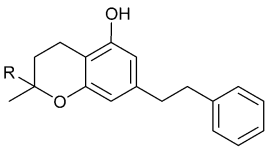
isoprenylated phenolics, but its permitted by the Baldwin rules. A similar regiochemistry of intramolecular cyclization is involved in the generation **58a,c** from their ω-hydroxylated precursors, with compound **58c** being originally assigned the regio-isomeric structure **59**. These compounds are, in turn, the precursor of the unusual cyclopropa-pyranes **60** and **61a,b**, whose generation might involve the protonation of the oxepine double bond and then closure of a cyclopropane ring by loss of one of the benzylic protons (Scheme 12).

The "taxonomy" of a series of chromanes from leguminous plants and liverworts is ambiguous. Biogenetically, they could be considered either as cyclized CBG-type compounds, derived from the cyclization of a prenyl (**56a,b**) or an ω-epoxyprenyl precursor (**62a,b**). Alternatively, as hydrogenated or hydrated CBC analogues. The CBG-type derivation seems more likely, and therefore they are included in this section.

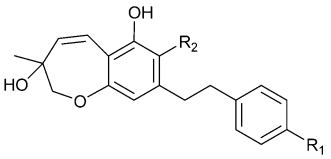
Abnormal phenethyl phytocannabinoids are widespread in liverworts from the genus *Radula*, where, like in *R. variabilis*[177] and *R. kojana*,[178] they can represent the major chemotype of bibenzyls, or even the only type of phytocannabinoids detected, as in *R. voluta*.[179,180] Remarkably, *R. perrottetii* contains abnormal phytocannabinoids from the CBG and CBC series,



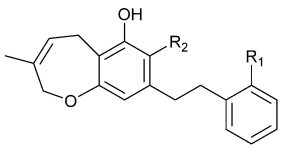
Scheme 12 Possible biogenetic origin of the cyclopropapyranes **60**,**61a,b**.



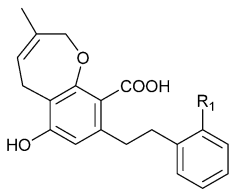
| | R | Ref. |
|---|---|---|
| **56a** | H | [171] |
| **56b** | Prenyl | [171] |



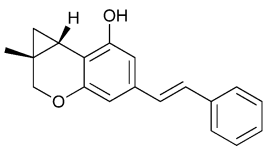
| | $R_1$ | $R_2$ | Ref. |
|---|---|---|---|
| **57a** | H | COOH | [171] |
| **57b** | OH | H | [171] |



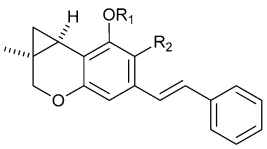
| | $R_1$ | $R_2$ | Ref. |
|---|---|---|---|
| **58a** Radulanin A | H | H | [158, 171] |
| **58b** Radulanin L | OH | H | [171, 172] |
| **58c** Radulanin H | H | COOH | [158, 171] |



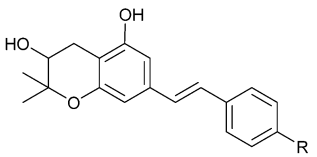
**59** [179]



**60** Radulanin I [175]



| | $R_1$ | $R_2$ | Ref. |
|---|---|---|---|
| **61a** Radulanin J | Me | H | [175] |
| **61b** Radulanin K | H | COOH | [175] |



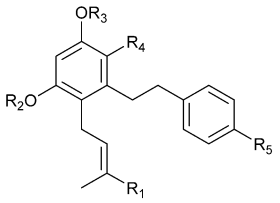
| | $R_2$ | Ref. |
|---|---|---|
| **62a** Chiricanine B | H | [176] |
| **62b** Radulanin K | OH | [176] |

and regular phytocannabinoids from the menthyl-type (THC series).[181] The structural diversity of phenethyl abnormal phytocannabinoids closely parallels the one of their related regular phytocannabinoids (*O*-methylation, prenylation), but also "internal" hydroxylation of the prenyl residue has been reported, as in **64** and **65**. The furan **67** might derive from the degradation of the isopropyl-substituted dihydrobenzofuran derivative **68**, as usual in the biogenesis of furanocoumarins from plants.

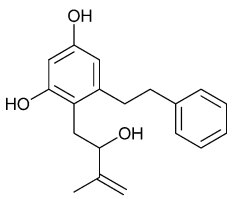
**4.2.2 Cannabichromene (CBC) analogues.** Many β-aralkyl compounds of this group belong to the abnormal series, but the modifications of the isoprenyl core are, otherwise, identical to those documented within alkyl-cannabinoids. As usual, stilbenoid structures prevail within compounds of plant origin, and bibenzyl ones from those of liverwort origin. The geranylated derivatives **72a–d** were isolated from the leaves of phyllanthaceous African tree *Hymenocardia acida* Tul.[184]

**4.2.3 Mentyl cannabinoids (CBD, THC) analogues.** Relatively few compounds of this type from the β-aralkyl series have been reported, and, remarkably, the configuration of at the carbon(s) involved in the junction with the resorcinyl core is different, in terms of absolute or relative configuration, from the one of their analogues from cannabis.[185]

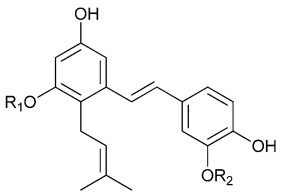
The macheridiol chemotype is similar to the one of CBD, with the β-aralkyl moiety declined in the stiryl (**73a**,**b**) and benzofuranyl (**74**) form. These compounds, as well as the THC analogues from the macheriol chomotype (see infra),[186] were isolated from the stem bark of the Amazonian legumionous liana *Macherium multiflorum* Spruce.[185] The pseudo-enantiomeric configuration at C-3 and C-4 compared to CBD was



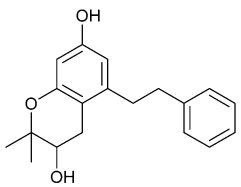

| | $R_1$ | $R_2$ | $R_3$ | $R_4$ | $R_5$ | Δ | Ref. |
|---|---|---|---|---|---|---|---|
| **63a** | H | H | H | H | H | - | [172,175,177-180,182,183] |
| **63b** | H | Me | H | H | H | - | [176,178] |
| **63c** | H | H | Me | H | H | - | [178] |
| **63d** | H | H | H | COOMe | H | - | [175] |
| **63e** | Prenyl | H | H | H | H | - | [172,175,177-180] |
| **63f** | Prenyl | Me | H | H | H | - | [178] |
| **63g** | Prenyl | H | H | COOMe | H | - | [188] |
| **63h** | H | H | H | H | OH | - | [183] |
| **63i** | H | H | H | H | H | + | [183] |
| **63k** | H | Me | H | H | H | + | [176] |



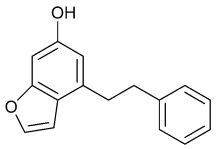

**64** [177,178]



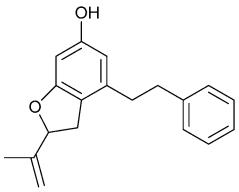

| | $R_1$ | $R_2$ | Ref. |
|---|---|---|---|
| **65a** | H | H | [183] |
| **65b** | H | Me | [183] |
| **65c** | Me | H | [183] |
| **65d** | Me | Me | [183] |




**66** [177]




**67** [174,178]

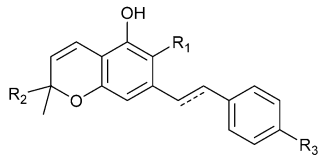



**68** [175,181]

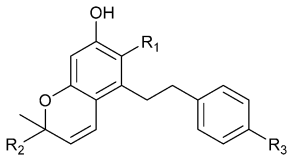
suggested by CD studies. Despite their similarity, the biological profile of machaeridiol is remarkably different, with machaeridiol B (**73b**) being an order of magnitude more potent of machaeridiol C (**74**) as an antimalarial agent.[185]

The occurrence in Nature of the phenethyl analogue of THC was predicted in 1986 by Crombie,[187] an overlooked founder of cannabinoids (and not only this class of compounds) chemistry, based on the occurrence of the phenethyl analogue of CBG, the precursor of THC in cannabis, in lieverworts[158,172] and in higher plants.[46] Two years later, Crombie synthesized the phenethyl version of THC with the aim of investigating its presence in cannabis, but no information on its bioactivity was disclosed.[188] While the phenethyl version of THC is still unknown as a natural product, its *cis* isomer [perrottettinen(e)] was isolated by Asakawa from the Japanese liverworth *Radula perrottetii*[181] and from the New Zeeland liverworth *Radula marginata*,[177] and by Becker from the Costa Rican liverwort *Radula laxiramea*,[174] with the absolute configuration being confirmed by an

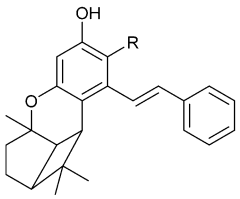
 



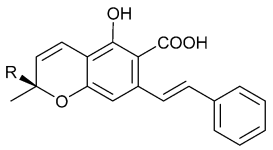
| | $R_1$ | $R_2$ | $R_3$ | Δ | Ref. |
|---|---|---|---|---|---|
| **69a** | H | H | H | - | [172,174,177,178,181] |
| **69b** | COOH | H | H | - | [178] |
| **69c** | H | Prenyl | H | - | [174,180,182] |
| **69d** | H | H | H | + | [168] |
| **69e** | H | H | OH | + | [168] |

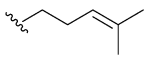
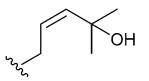
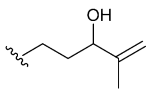
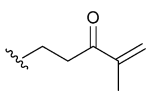


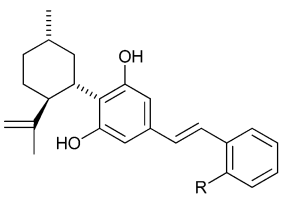
| | $R_1$ | $R_2$ | $R_3$ | Ref. |
|---|---|---|---|---|
| **70a** | H | H | H | [178] |
| **70b** | H | Prenyl | H | [178] |
| **70c** | COOH | Prenyl | H | [178] |
| **70d** | H | H | OH | [179] |



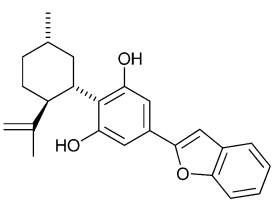
| | R | Ref. |
|---|---|---|
| **71a** | H | [182] |
| **71b** | COOH | [184] |



| | R | Ref. |
|---|---|---|
| **72a** |  | [184] |
| **72b** |  | [184] |
| **72c** |  | [184] |
| **72d** |  | [184] |

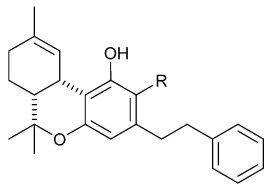


| | | R | Ref. |
|---|---|---|---|
| **73a** | Machaeridiol A | H | [185] |
| **73b** | Machaeridiol B | OH | [185] |

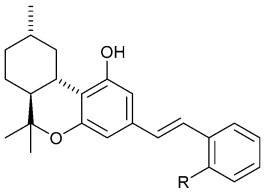


**74** Machaeridiol C [185]

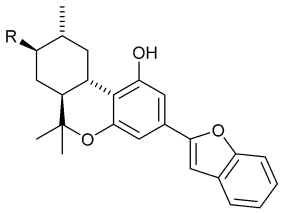
enantioselective synthesis.[189] Since *cis*-THC, a very minor cannabinoid in marijuana but almost equimolar with THC in fiber hemp, is not psychotropic,[85] also perottetinene should not be so. On the other hand, detailed information on the biological profile of the various isomers of THC has never been published, and the biological profile of perrottettinene is unknown, or, at least, it has not been reported in the mainstream literature, despite undocumented claims on its psychotropic properties that circulate on the web.[190] It is remarkable that the enormous efforts of exploration of the biological space around the THC chemotype and the critical role of the C-3 substituent on bioactivity, the "hint" suggested by Nature with the existence of phenethyl versions of the pentyl cannabinoids of *Cannabis* has been so far overlooked. Since cannabinoids have additional



| | R | Ref. |
|---|---|---|
| **75a** Perrottetinen(e) | H | [177,181,187] |
| **75b** Perrottetinenic Acid | COOH | [177] |



| | R | Ref. |
|---|---|---|
| **76a** Machaeriol A | H | [186] |
| **76b** Machaeriol C | OH | [186] |

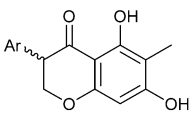


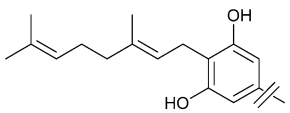
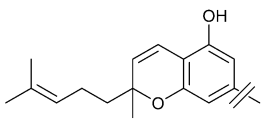
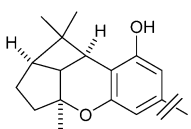
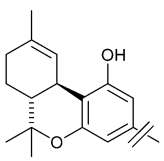
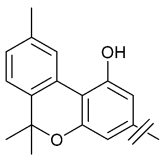
| | R | Ref. |
|---|---|---|
| **77a** Machaeriol B | H | [31] |
| **77b** Machaeriol D | OH | [31] |

targets to the psychotropic $CB_1$ receptor, the exploration around the perrottetinene chemotype seems well worth pursuing.

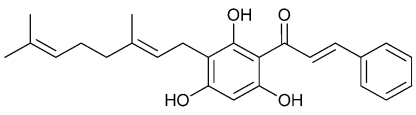
Machaeriols A and B from the Amazonian liana *Machaerium multiflorum* Spruce are analogues of *trans*-dihydroTHC,[186] but show an enantiomeric configuration at the ring junction, as shown by CD studies and enantioselective total syntheses.[191–193] It is not known if machaeriols bind $CB_1$ and are psychotropic.

**4.2.4 Spurious phytocannabinoids.** The enzymatic system involved in the terpenylation of the resorcinyl core of phytocannabinoids and phytocannabinoid-like compounds is not specific, and can be operative also in other classes of phenolics, generating compounds overall similar to phytocannabinoids. However, the *meta*-relationship between the substituents of the

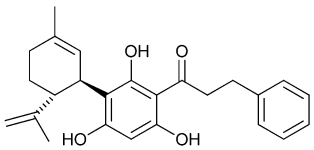


| | Ar | Ref. |
|---|---|---|
| **78a** Desmodianone C |  | [194] |
| **78b** Desmodianone A |  | [194] |
| **78c** Desmodianone D |  | [195] |
| **78d** Desmodianone E |  | [195] |
| **78e** 6-Metiltetrapterol A |  | [195] |

core aromatic ring clearly points to a different biogenetic origin, or, at least, to a different sequency of prenylation *vs.* closure of the polyphenolic aromatic core. Thus, desmodianones (**78a–e**),[194,195] a series of compounds isolated from the South American leguminous species *Desmodium canum* (Gmell) Shintz and Tellung, are basically isoprenylated flavanones with a *meta*-dihydroxylated B-ring, a rare functionalization since, being of shikimate origin, ring B of flavonoids normally bears *ortho*-oxygen groups. Desmodianones could, in principle, be viewed as terpenylated cannabinoids since the structure of this moiety mimics the one of phytocannabinoids (CBG, CBC, CBL, THC, CBN, **78a–e**, respectively), and one of them, the cannabinol analogue **78e**, has also been isolated as a 6-demethylderivative (tetrapterol A) from another leguminous plant (*Sophora tetraptera* J. S. Muell.).[196]

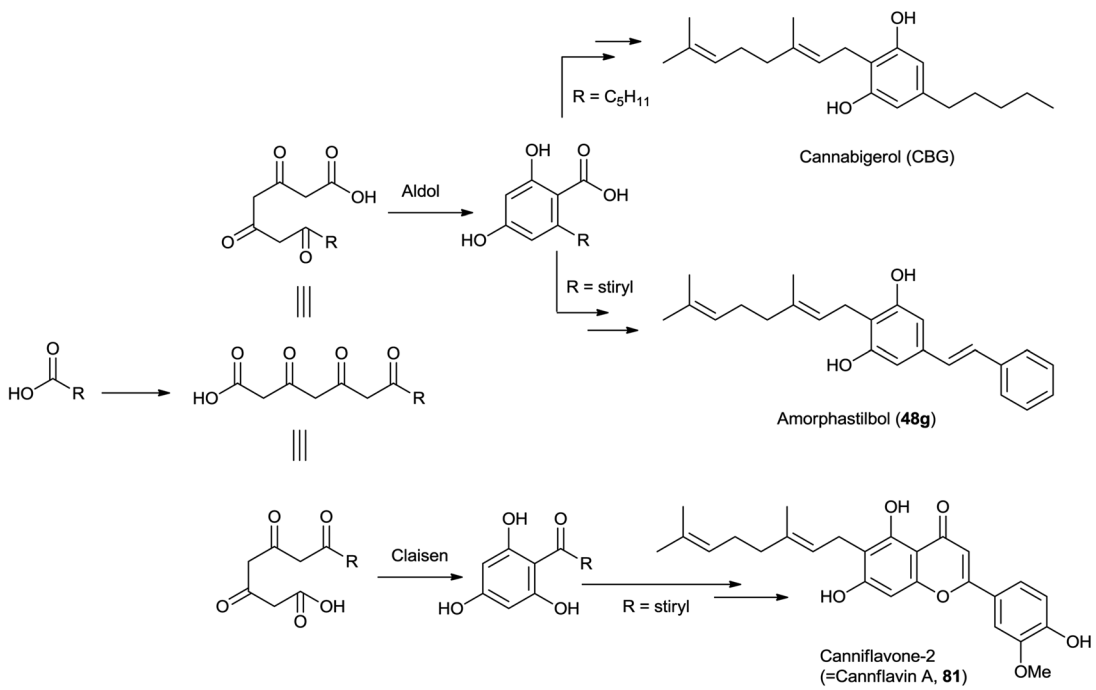


**79** [46]



Linderatin **80** [197]

Similar considerations apply for the large class of isoprenylated acylphloroglucynols like **79** from *H. umbraculigerum*[46] and **80** (linderatin) from a lauraceous *Lindera* species,[197] both isoprenylated flavonoids (chalcone and dihydrochalcone, respectively) rather than phytocannabinoids. There is little reason to consider these compounds phytocannabinoids, since their aromatic core is derived from a Claisen- and not an aldol condensation of a linear ketide, and these compounds should be better considered isoprenylated flavonoids rather than "phloroglucinyl" phytocannabinoid. The two biogenetic processes are exemplified in Scheme 13 by the structure of amorphastilbol (**48g**)[46,173] and canniflavone 2 (= cannflavin A, **81**).[198] For comparison, the analogous process leading to cannabigerol is also reported. Compounds derived from both the aldol (resorcinyl) and the Claisen (phloroglucynyl) series can co-occur taxonomically unrelated plant *C. sativa* and *H. umbraculigerum*, as well as in *Radula* liverworts.[162] Polyprenylated stilbenoids should also not "*a priori*" be considered "phytocannabinoids", because this structural element is not documented within the archetypal compounds of this type from cannabis, nor should prenylated polyphenolic ketides with a hydroxylation profile different from the resorcinol one, or at least that cannot be reconduced to the further oxidation of a resorcinol core to a quinol. Compounds of this type co-occur with phytocannabinoids, *e.g.* demethylamorfrutin A (**48a**),[167,169–172,174] the deoxystilbenoid **82**,[172] and the hydroxylated version of abnormal demethylamorfrutin A (**83**)[178] in *Radula*



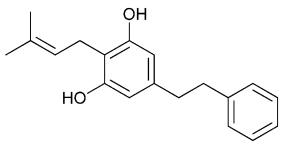

Scheme 13 Biogenetic relationship between resorcinyl (phytocannabinoids) and phloroglucynyl (flavonoids) meroterpenoids.

liverworts, but the biogenetic relationship between the two groups is unclear.

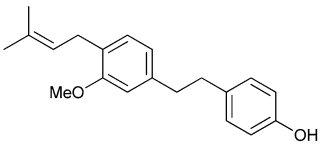
Finally, a compound named "dronabinol alkaloid" (**84**) was reported from *Cassia alata* L., a leguminous medicinal plant.[199] The structure of this compound was only tentatively established and needs confirmation. Even if the proposed structure should be confirmed, there seems to be little reason to consider it as a cannabinoid, since plant aromatic amines are generally of anthranilate origin.

observation in the light of the enormous interest for the pharmacological activity of phytocannabinoids and the messianic await for the development of cannabinoid-based medicines that permeates the media.[200]

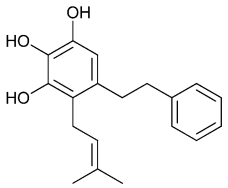
It is tempting to predict that, given the biosynthetic plasticity of *C. sativa*, further types of alkyl phytocannabinoids will be described in the near future from both the natural and the man-induced diversity of cannabis strains. In the wake of the growing interest from amorfrutins, further additions to the



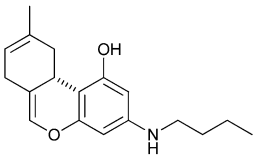

**48a**




**82** [172]




**83** [178]




**84** [199]

## 5. Conclusions

Phytocannabinoids have a limited distribution in Nature, but occur in phylogenetically unrelated sources (higher plants, liverworts, fungi). These compounds are traditionally associated to cannabis, that, with almost 150 alkyl (C-5, C-3, C-1) phytocannabinoids reported, remains their main source of diversity. However, only a few members of the class are accumulated in substantial amounts, namely the ones having the terpenyl residue in the form of a geranyl (CBG-type), a menthyl (CBD-type and THC-type), or a prenylchromanyl (CBC-type) residue. Many of the minor cannabinoids could be auto-oxidation artifacts eventually evolving into aromatized phytocannabinoid of the CBN type, but others might be genuine natural products worth investigating from a bioactivity standpoint.

Apart from the variation of the terpenyl connectivity, structural diversity in phytocannabinoids is also related to the elongation of the isoprenyl moiety from a terpenyl- to a sesquiterpenyl moiety, while shortened analogues (hemiprenyl phytocannabinoids) have only been reported in phytocannabinoids from the aralkyl series. Oxidation of the resorcinyl moiety to a quinol is also documented, but compounds of this type have only been isolated in their acetylated and more stable form. The mammalian metabolism of phytocannabinoids involves allylic oxidation rather than nuclear oxidation to quinoid metabolites, but, due to this instability, these metabolites might have been overlooked. *O*-Methylation was reported in phytocannabinoids obtained from far-East samples of cannabis but it is otherwise rare in alkyl phytocannabinoids, while it is common in compounds from the phenethyl series. Aralkyl cannabinoids have a broader distribution in Nature compared to alkyl cannabinoids, but their accumulation is point-like in terms of producing organisms, with phenethyl substitution prevailing in liverworts and styryl substitution in plant constituents. Most phytocannabinoids still await an evaluation of their biological profile and pharmaceutical potential, a somewhat paradoxical phytocannabinoids inventory should also come from compounds of the aralkyl structural type. By focusing on the remarkable structural diversity of phytocannabinoids and highlighting their largely overlooked wide distribution in plants, we hope to stimulate the exploration of the biological space associated to their natural variation, going beyond the THC structural motif, and paving the way to a full opening of the Pandora's box of their biomedical potential.

## 6. Acknowledgements

We would like to dedicate this article to Prof. Raphael Mechoulam, the Champollion who provided us the Rosetta stone (structure, receptors, endogenous ligands) to decipher the phytocannabinoids enigma, and a remarkable figure of a man. G. A. is grateful to Emerald Health Sciences for financial support to the laboratory.

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