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Synthetic approaches to *cis*-THC, a promising scaffold in medicinal chemistry

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The chemistry of phytocannabinoids has witnessed renewed interest these last decades as a consequence of reduced restrictions, research on the endocannabinoid system and the development of approved therapeutic treatments based on cannabinoids. The medicinal cannabinoid market constitutes a prolific scenario in current medicine. Most studies, however, have focused on only two major components of *Cannabis sativa* L., namely, cannabidiol (CBD, **2**) and (–)-Δ^9-*trans*-tetrahydrocannabinol (Δ^9-*trans*-THC, **6a**), the latter being the main psychoactive compound of this plant. The *cis*-diastereoisomer of Δ^9-*trans*-THC, Δ^9-*cis*-THC, although also present in the same plant, has been less investigated in terms of biological, medicinal and synthetic perspectives. Interestingly, the *cis*-fused tetrahydrobenzo [*c*]chromene motif present in Δ^9-*cis*-THC is embedded in many other natural products which also exhibit interesting biological activities such as anticancer, antifungal, and antiparasitic. This review discloses synthetic approaches that have been established towards the *cis*-fused tetrahydroisochromene system of Δ^9-*cis*-THC.

KEYWORDS

stereoselective synthesis, cannabinoids, THC, isochromenes, hetero-Diels-Alder, bioactive natural products

Introduction

Plants of the genus *Cannabis* have been used by different cultures for millennia (Russo, 2014). Throughout history this plant has been used in religious acts, for recreational purposes, therapeutic uses for the treatment of pain and different disorders and even as a source of fibers for making cloth and cordage (Appendino, 2020). Its history has been as extensive as controversial, generally influenced by social belief around marijuana consumption as well as by all the legal restrictions imposed by different governments on the research and use of this plant and its phytocannabinoid components (Mechoulam, 1986). Investigations during the last century can be divided into three stages: a chemical one, the biochemical era and the current one focused on the commercialization and legal status. The chemical stage mainly dealt with the identification and characterization of the active components of the plant, having a milestone in 1964 with the isolation, structural elucidation and identification of (–)-Δ^9-*trans*-tetrahydrocannabinol [(–)-Δ^9-*trans*-THC, **6a,** Figure 1] as the main psychoactive component of the plant by the group of Mechoulam (Gaoni and Mechoulam, 1964; Mechoulam and Hanuš, 2000). The biochemical era began with the identification of the first cannabinoid receptors leading later to the establishment of what today is known as the endocannabinoid system (ECS),

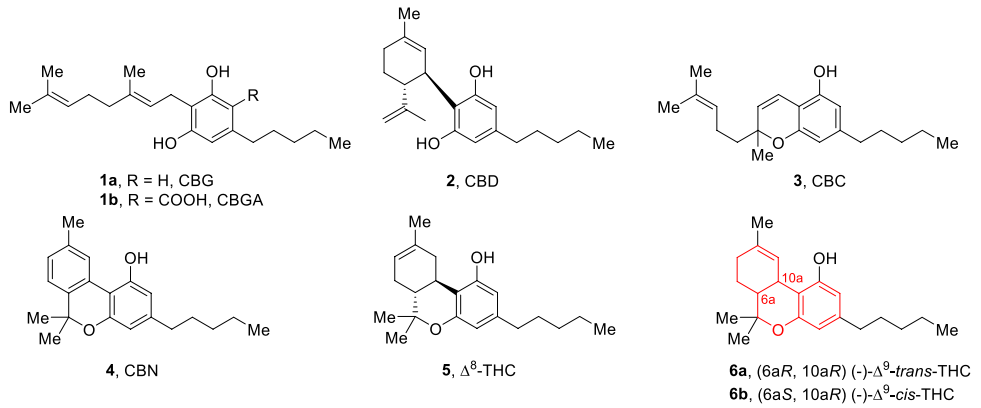


FIGURE 1
Structures of main classes of cannabinoids.

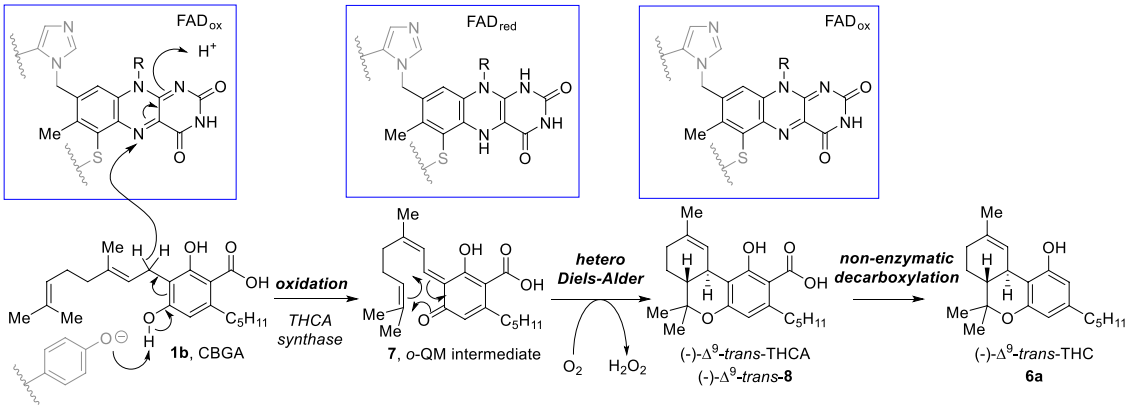
which comprises the cannabinoid receptors, endogenous lipid mediators (endocannabinoids) and the corresponding metabolic enzymes (Mechoulam et al., 2014). The relevance that this system has been shown to possess, particularly on key physiological functions and dysfunctions, has promoted increased interest, a boost in research on cannabinoids and most importantly reduced restrictions opening the way for a commercial era involving the approval of medical treatments based on cannabinoids (Vemuri and Makriyannis, 2015). In this context, a plethora of pharmaceutical products and cosmetics appeared containing cannabidiol (CBD, **2**) or Δ^9-THC (**6a**). Since 1985, FDA has already approved four treatments based on cannabinoids: Marinol® and Syndros®, based on synthetic **6a** as active ingredient, are indicated for the treatment of nausea associated with chemotherapy and anorexia in AIDS patients; Epidiolex®, which contains **2** as active principle, being the first FDA approved treatment to contain a purified extract of the plant and used for the treatment of seizures associated with two severe forms of epilepsy in patients over 2 years of age; and Cesamet®, based on drug nabilone, a synthetic analogue of **6a**, is used to treat nausea and chemotherapy-induced vomit (Khalsa et al., 2022).

Phytocannabinoids are biologically active meroterpenoids of mixed polyketide and terpenoid biosynthetic origin (Degenhardt et al., 2017; Jamieson et al., 2021; Tahir et al., 2021; Purdy et al., 2022). Structurally isoprenylated resorcinols, main classes of cannabinoids include cannabigerol (**1a**, CBG), cannabidiol (**2**, CBD), cannabichromene (**3**, CBC), cannabinol (**4**, CBN), Δ^8-tetrahydrocannabinol (**5**, Δ^8-THC) and Δ^9-tetrahydrocannabinols (**6**, THCs) (Figure 1). To date, more than a hundred cannabinoids have been found to be produced by *Cannabis sativa* L. (Hanuš et al., 2016). Diversification in structure comprises oxidized and cyclized derivatives, analogues with variations in the length of the resorcinyl alkyl chain, and carboxylated versions called acidic cannabinoids which are metabolic precursors in their biosynthesis (*e.g.*, cannabigerolic acid CBGA, **1b**).

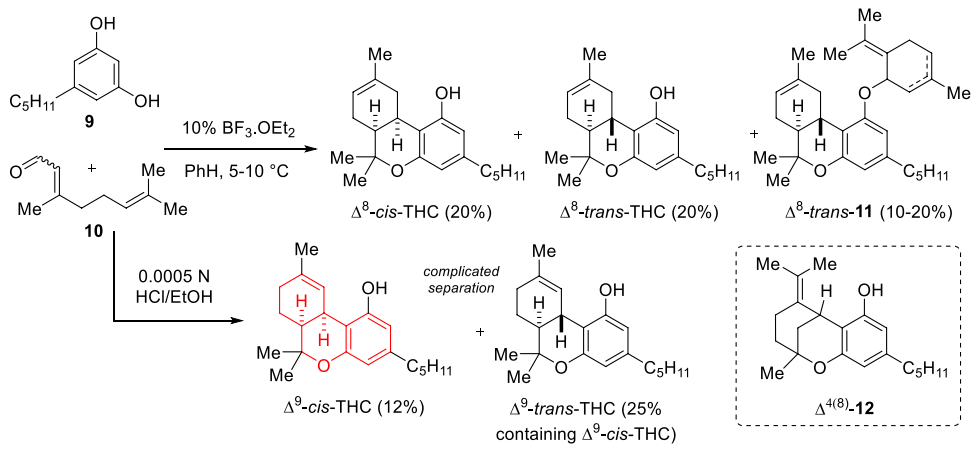
Although literature review reveals that most research studies have focused on only two major components of the plant [namely, CBD (**2**) and (−)-*trans*-Δ^9-tetrahydrocannabinol (Δ^9-*trans*-THC, **6a**)] (Sampson, 2021), over the last two decades there has been an increase in interest in the occurrence, synthesis, and medicinal potential of minor components of the plant, known as "minor cannabinoids" or "rare cannabinoids", probably as a result of reduced restrictions and approvals of cannabinoid-based therapeutic treatments (Walsh et al., 2021; Caprioglio et al., 2022; Maioli et al., 2022; Nguyen et al., 2022). Δ^9-*trans*-THC, (**6a**) the main psychoactive constituent of *Cannabis sativa,* features a tetrahydrobenzo[*c*]chromene motif bearing two stereogenic centers at positions 6a and 10a and thus four stereoisomers can be conceived. Nevertheless, only one of these four compounds is produced in the plant via non-enzymatic decarboxylation of (−)-Δ^9-*trans*-tetrahydrocannabinolic acid [(−)-Δ^9-*trans* THCA, **8**], formed in turn by enzyme tetrahydrocannabinolic acid synthase (THCA synthase) from cannabigerolic acid (**1b**) (Scheme 1). THCA synthase, with the aid of a doubly-covalent attached FAD cofactor (binding residues shown in grey), catalyzes the stereoselective oxidative cyclization of cannabigerolic acid (**1b**) through oxidized *ortho*-quinone intermediate **7**, which undergoes an intramolecular hetero Diels–Alder reaction to deliver (−)-Δ^9-*trans*-tetrahydrocannabinolic acid **8**. While this particular cannabinoid has been assumed as the only relevant isomer since its identification in 1964, the *cis*-stereoisomers of **6a** [(+)- and (−)-Δ^9-*cis*-THC, **6b**] have been both obtained via synthesis as well as identified in *C. Sativa* as minor constituents. The present review discloses the natural occurrence and bioactivity of these minor phytocannabinoids as well as all synthetic approaches that have been established to selectively prepare this medicinally promising enantiomeric pair of natural products.

Synthetic strategies toward Δ^9-*cis*-THC

Shortly after the characterization and identification of (−)-Δ^9-*trans*-THC as the main psychoactive component of *Cannabis*, *cis*-THC as a racemic mixture was first obtained by Taylor and co-workers in 1966 (Scheme 2) (Taylor et al., 1966). The group established a one-pot synthetic strategy based on the acid promoted condensation between olivetol (**9**) and citral (**10**), giving access to Δ^8-*trans*-THC (which at the time had been

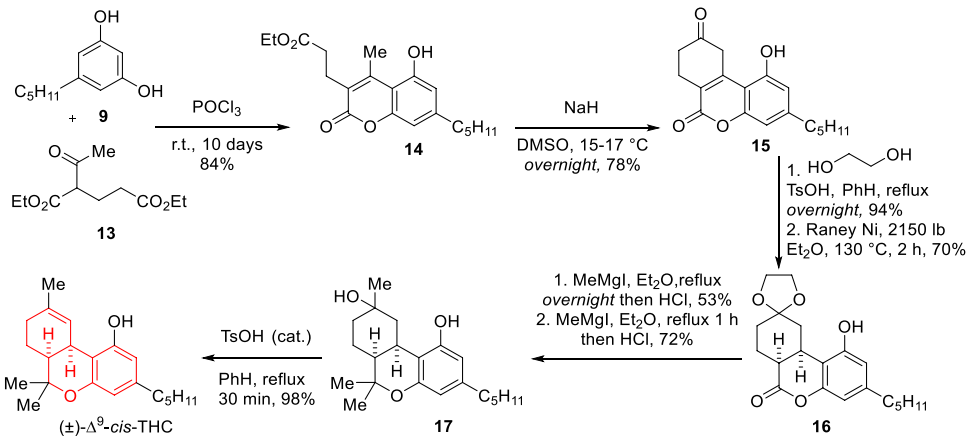


SCHEME 1
Biosynthesis of (–)-Δ^9-*trans*-THC (**6a**) as its acid version (THCA).

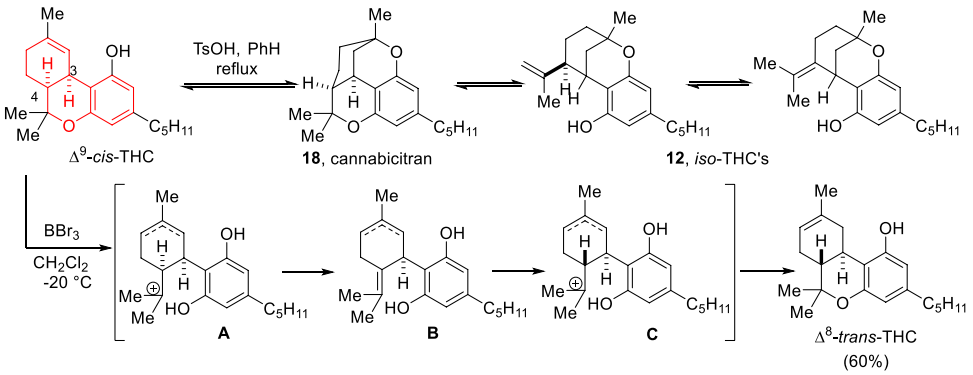


SCHEME 2
First synthesis of (±)-Δ^9-*cis*-THC via condensation between olivetol (**9**) and citral (**10**) (1966).

identified in the plant as another psychoactive constituent) as well as Δ^8-*cis*-THC and Δ^9-*cis*-THC. In particular, treatment of the substrates with BF_3.Et_2O in benzene at 5°C–10°C led to the isolation of Δ^8-*cis*-THC, Δ^8-*trans*-THC and derivative Δ^8-*trans*-**11**, in 20%, 20% and 10%–20% yields, respectively. On the other hand, when the condensation was carried out under milder acid conditions (HCl 0.0005 N) Δ^9-*cis*-THC and Δ^9-*trans*-THC were instead obtained as a mixture hard to separate (12% pure Δ^9-*cis*-THC fraction, *ca* 25% mixture fraction). During this study, acid treatment was also shown to isomerize Δ^9-THC isomers to the corresponding Δ^8-THC products, as well as thermal treatment for the case of Δ^9-*trans*-THC when using vapor phase partition chromatography (280°C) and based on these observations the group proposed that the effects of smoking Cannabis may be due to isomer Δ^8-THC instead of Δ^9-THC (Taylor et al., 1966). The same year, after this report, Gaoni and Mechoulam reevaluated these results and claimed that Δ^9-*cis*-THC does not undergo acid-promoted isomerization toward Δ^8-*cis*-THC and that the structure of the originally proposed product of this transformation (Δ^8-*cis*-THC) should be reassigned to *iso*-THC ($\Delta^{4(8)}$-**12**) (Gaoni and Mechoulam, 1966). The researchers also indicated that Δ^9-*trans*-THC does not undergo thermal isomerization to Δ^8-*trans*-THC and that the isomerization found by Taylor and co-workers on vapor phase chromatography may have been promoted by the nature of the column support used. Mechoulam later demonstrated that both Δ^9-*cis*-THC and Δ^8-*trans*-THC were inert to oxidation conditions that converted Δ^9-*trans*-THC to cannabinol (Mechoulam et al., 1968). This condensation of olivetol (**9**) and citral (**10**) using HCl in EtOH was reinvestigated by Crombie and Ponsford later under reflux conditions for 5 h to afford, after Florisil chromatography, a mixture of Δ^9-*cis*-THC and Δ^9-*trans*-THC in 19% yield (*ca* 5:1 by NMR analysis) (Crombie and Ponsford, 1971). Mechoulam and co-workers also repeated the BF_3.Et_2O promoted direct condensation and found that when the acid was used in low loading (1%) in CH_2Cl_2 for 1 h at room temperature, Δ^9-*trans*-THC was obtained in 20% yield and isomer Δ^9-*cis*-THC in 5% yield (Mechoulam et al., 1972).



SCHEME 3
Synthesis of Δ^9-*cis*-THC by Fahrenholtz and co-workers (1967).



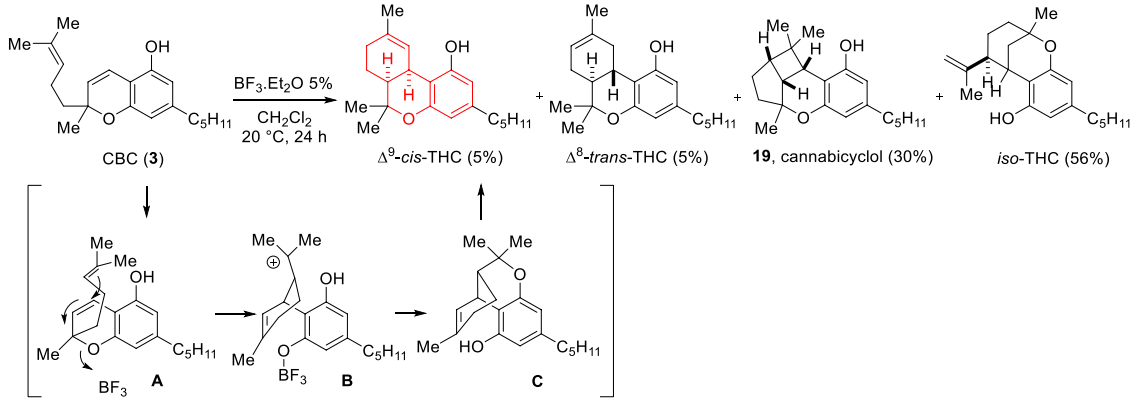
SCHEME 4
Isomerization of Δ^9-*cis*-THC found by Razdan and Zitko (1969).

In 1967, Fahrenholtz and co-workers reported a novel synthetic approach towards many cannabinoids including Δ^9-*cis*-THC, at the time considered an unnatural isomer of THC (Scheme 3) (Fahrenholtz et al., 1967). The synthetic strategy began with a von Pechmann condensation between olivetol (**9**) and diethyl 2-acetylglutarate (**13**) to afford a coumarin intermediate (**14**). Intramolecular condensation was then achieved using NaH in DMSO which led to a ketone intermediate (**15**) which was then protected as a cyclic ketal. Hydrogenation with Raney Ni under vigorous conditions afforded *cis*-lactone **16**, which was treated with MeMgI followed by hydrolysis to afford a ketone intermediate that upon a new sequence of MeMgI treatment followed by hydrolysis yielded alcohol **17**. Acid-catalyzed dehydration of this intermediate produced *cis*-THC in good yield.

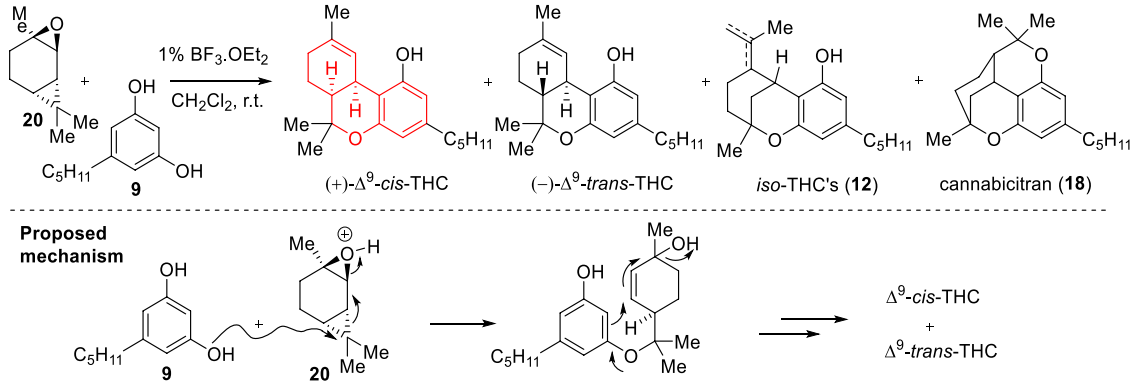
In 1969, Razdan and Zitko reported that through treatment with *p*-toluenesulfonic acid (TsOH) in refluxing benzene, Δ^9-*cis*-THC interconverted with cannabicitran (**18**) and *iso*-THC's (**12**) leading to an equilibrium that favors the *iso*-THC´s (Scheme 4) (Razdan and Zitko, 1969). The acetylation of Δ^9-*cis*-THC was shown to block this process. Cannabicitran (**18**) is established as an intermediate between Δ^9-*cis*-THC and the *iso*-THC's (**12**), a process that cannot take place with the *trans*-THC's since a polycyclic system as cannabicitran cannot be formed with a *trans*-ring fusion. The group also found that BBr_3 isomerizes Δ^9-*cis*-THC to Δ^8-*trans*-THC in 60% yield. The first proposed mechanism involves ionization of the ether linkage followed by epimerization at C-4 via elimination. Almost a decade after this report the group continued to investigate this isomerization making advances on the mechanistic interpretation (Uliss et al., 1978).

Also in 1969, Yagen and Mechoulam reported that on $BF_3.Et_2O$ (5% in dichloromethane) treatment, cannabichromene (CBC, **3**) gives rise to a low yield of Δ^9-*cis*-THC (5%) among other isomers. A mechanism based on the intermediacy of cationic species was proposed to account for the transformation (Scheme 5) (Yagen and Mechoulam, 1969).

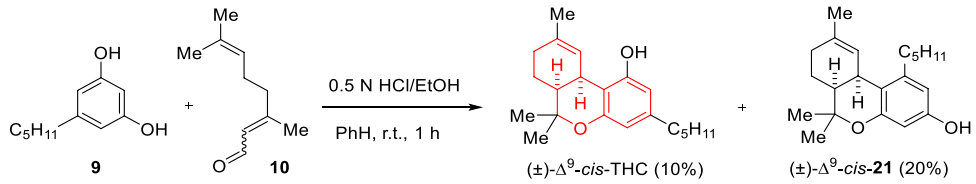
In 1970, Razdan and co-workers reported an asymmetric strategy towards THC-derivatives based on the use of a carene derivative (Scheme 6) (Razdan and Handrick, 1970). During their



SCHEME 5
Acid-promoted isomerization of cannabichromene (**3**) by Yagen and Mechoulam (1969).



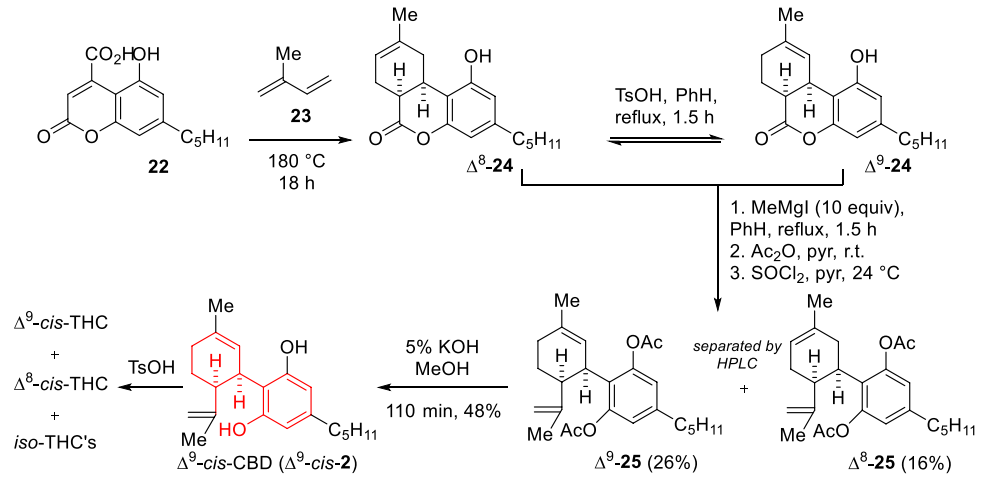
SCHEME 6
Asymmetric synthesis of (+)-Δ^9-*cis*-THC reported by Razdan and Handrick (1970).



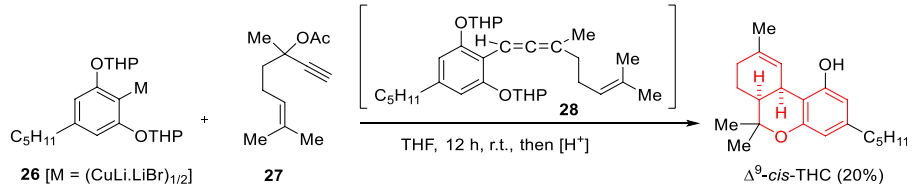
SCHEME 7
Reinvestigation of Taylor's condensation approach by the group of Uliss et al. (1975a).

studies, they found that condensation between (+)-*trans*-2-carene oxide (**20**) and olivetol (**9**) promoted by 1% $BF_3.Et_2O$ in dichloromethane at room temperature or *p*-toluenesulfonic acid in benzene (with a molar ratio of substrates 1.6:1) led to a mixture in which major products were (+)-Δ^9-*cis*-THC and (−)-Δ^9-*trans*-THC (28%).

Taylor's direct condensation between olivetol (**9**) and citral (**10**) was reinvestigated by Razdan and co-workers in 1975 using HCl (0.5 N) in EtOH/benzene for structure-activity relationship studies during their program on THC analogues (Uliss et al., 1975b). The reaction led to the formation of Δ^9-*cis*-THC in 10% yield and regioisomer Δ^9-*cis*-**21** in 20% yield (Scheme 7). The same year the group reported a synthetic strategy to prepare Δ^8-*cis*-THC, an isomer that had not been previously prepared in the THC series (Uliss et al., 1975a). The asymmetric version of this strategy was then realized accomplishing the preparation of (+)-Δ^9-*cis*-THC and (+)-Δ^8-*cis*-THC in 0.7% and 0.06% yields, respectively (Uliss et al., 1977).



SCHEME 8
Synthesis of Δ^9-*cis*-THC from *cis*-CBD (1977).



SCHEME 9
Synthesis of (±)-Δ^9-*cis*-THC reported by Luteijn and Spronck (1979).

Based on a Diels–Alder approach previously developed by Taylor and Strojny (1960), the group of Razdan reported in 1977 an entry to Δ^9-*cis*-THC via prior preparation of *cis*-CBD (Scheme 8) (Handrick et al., 1977). Tandem Diels–Alder reaction/decarboxylation between isoprene (**23**) and 3-carboxy-5-hydroxy-7-pentylcoumarin (**22**) led to lactone **24**, bearing a *cis*-ring fusion, which under acid treatment becomes an equilibrated 1:1 mixture of Δ^8- and Δ^9-olefins. To this mixture, addition of MeMgI leads to a mixture of triols, which upon bis-acetylation and dehydration using thionyl chloride affords Δ^8- and Δ^9-*cis*-CBD diacetates (**25**), separable by HPLC. Basic hydrolysis of Δ^9-**25** provided an entry to Δ^9-*cis*-CBD which upon acid treatment (TsOH) underwent cyclization toward a mixture of Δ^9-*cis*-THC, Δ^8-*cis*-THC and *iso*-THC's in ratio 40:17:43. Remarkably, a recent patent described the use of triisobutylaluminium as efficient Lewis acid for this same cyclization, actually performed on each enantiomer of Δ^9-*cis*-CBD, towards the corresponding Δ^9-*cis*-THC cyclized product (85% yield) (Abdur-Rashid et al., 2020).

In 1979 Luteijn and Spronck reported an alternative synthesis of (±)-Δ^9-*cis*-THC based on the reaction between olivetol bis(tetrahydropyranyl ether)homocuprate (**26**) and dehydrolinalool acetate (**27**) (Scheme 9, overall yield 20%) (Luteijn and Spronck, 1979). The reaction would work via initial S_N2' reaction leading to an allene intermediate (**28**) which upon acid treatment undergoes hydrolysis of the tetrahydropyranyl groups (THP) followed by bicyclization.

In 1984, Rickards' group showed that the use of olivetol di(methoxymethyl)ether as coupling partner of citral (**10**) enables an efficient route to (±)-Δ^9-*cis*-THC (Scheme 10) (Moore et al., 1984). The reaction begins with the alkylation of citral (**10**) with a protected olivetol substrate lithiated at C-2 which yielded the corresponding alcohol product **29** in 79% yield. Reaction of this intermediate with TMSCl in the presence of tetraethylammonium bromide at 0°C, followed by aqueous work-up, led to the formation of (±)-Δ^9-*cis*-THC in 65% yield. The mild conditions are believed to favor the formation of an *ortho*-quinone methyde-type intermediate that undergoes the required intramolecular hetero-Diels Alder reaction towards the product avoiding cationic intermediates. Later, in 2001, Malkov and Kočovský reported that the condensation between olivetol (**9**) and citral (**10**) catalyzed by a Mo(IV) catalyst [$(acac)_2MoCl_2$] affords a mixture of (±)-Δ^9-*cis*-THC and (±)-Δ^9-*trans*-THC in 20% yield and 1:2.2 *cis-trans* ratio (Malkov and Kočovský, 2001).

A major breakthrough in the total synthesis of THC natural products was achieved in 2014, when the group of Carreira established an efficient catalytic asymmetric synthetic strategy to access any stereoisomer of Δ^9-THC (Scheme 11) (Schafroth et al., 2014). This uniform stereodivergent assembly of all stereoisomers of

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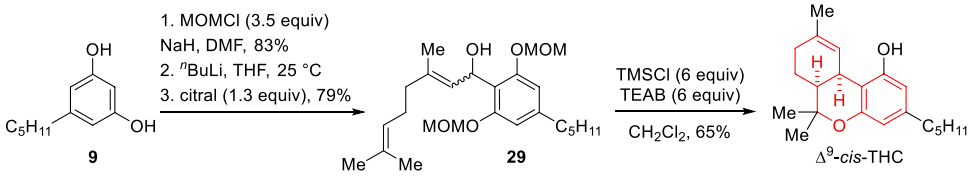
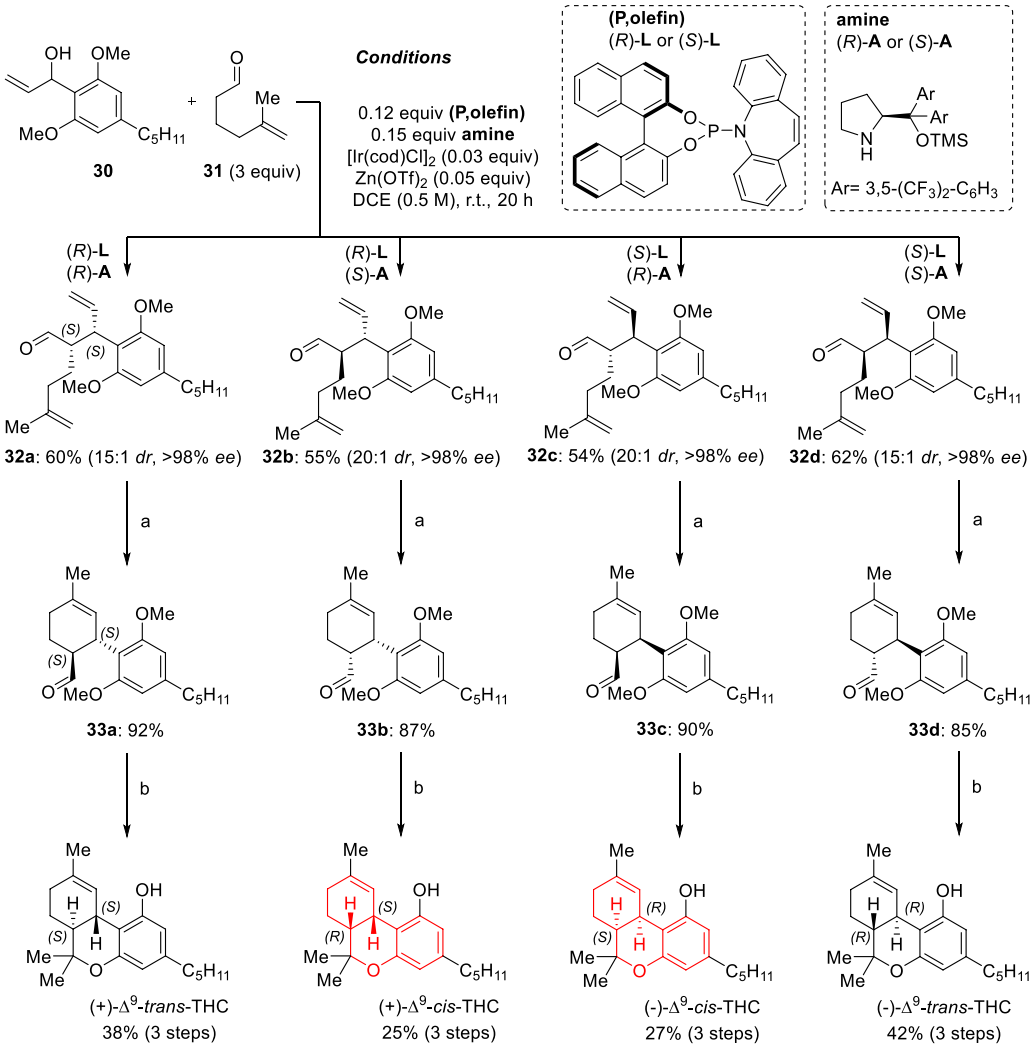


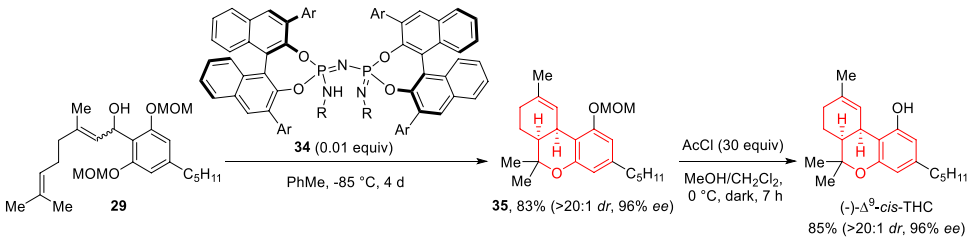
SCHEME 10
Synthesis of Δ^9-*cis*-THC reported by the group of Moore et al. (1984).



Reagents and conditions: a) Grubbs 2nd gen (0.03 equiv), CH_2Cl_2, r.t., 18 h, b) 1. $NaClO_2$ (2.3 equiv), NaH_2PO_4 (2.0 equiv), 2-methyl-2-butene (30 equiv), ^{t}BuOH/H_2O, 25 °C, 2. Me_3SiCHN_2 (1.1 equiv), C_6H_6/MeOH (1:1), 0 °C, 3. MeMgI (10 equiv), Et_2O, 0 °C a 160 °C, 1 atm to 150 mm Hg; then $ZnBr_2$ for work-up, CH_2Cl_2, 25 °C.

SCHEME 11
Catalytic asymmetric synthesis of all Δ^9-THC stereoisomers (2014).

Δ^9-THC was achieved via dual stereodivergent catalysis, applying identical synthetic sequences, under identical reaction conditions and using the same set of substrates though five synthetic steps. The asymmetric approach involves simultaneously using two chiral catalysts, each of which exerts full and independent control over the configuration of one of the stereocenters and the concept was implemented in the α-allylation of 5-methylhex-5-enal (**31**) catalyzed by a chiral Ir/(P,olefin) complex and a chiral amine. In



SCHEME 12
Asymmetric synthesis of (–)-Δ^9-*cis*-THC by Dorsch and Schneider (2023).

the presence of 3 mol% of [{Ir(cod)Cl}$_2$], 12 mol% of (*R*)-**L** or (*S*)-**L**, and 15 mol% of Jørgensen amine (*R*)-**A** or (*S*)-**A**, all possible stereoisomers of γ,δ-unsaturated aldehyde product **32** were obtained in good yields (55%–62%) and excellent selectivity (*dr* 15:1, *er* > 99:1) via activation of both allylic alcohol (**30**) and aldehyde (**31**). Reactions could be performed in Gram scale with similar selectivity and yields. From the aldehyde **32** intermediates, ring-closing metathesis using Grubbs second-generation catalyst first secured cyclohexenecarbaldehydes **33** in 85%–92% yield. Pinnick oxidation of the aldehydes to the corresponding carboxylic acids, followed by treatment with trimethylsilyldiazomethane gave the corresponding methyl esters (60%–66% yield over two steps). The formation of a tertiary alcohol and double methyl ether deprotection was achieved with excess MeMgI at 0°C–160°C at reduced pressure (150 mm Hg). After aqueous work-up and extraction, the organic phase was treated with Lewis acid $ZnBr_2$, which promoted aryl ether formation and thus the formation of each stereoisomer of Δ^9-THC.

More recently, another asymmetric and straightforward approach towards (–)-Δ^9-*cis*-THC, also applicable to many analogues, was reported by Dorsch and Schneider. The group reinvestigated the bicyclization reaction studied by Rickards and found that chiral imidodiphosphorimidates (IDPis, e.g., **34**), as sterically confined Brønsted acid catalysts, allow the cyclization to proceed with high yield and selectivities (Scheme 12) (Dorsch and Schneider, 2023). In particular, cyclization of **29** led to derivative **35** which after MOM-removal using AcCl afforded (–)-Δ^9-*cis*-THC (71% yield from **29**). Some control experiments supported a cationic stepwise mechanism for the organocatalyzed cyclization involving initial carbocycle formation via a Prins-type reaction.

It should be noted that some of the presented strategies, such as Rickards' synthetic sequence, have also been used for the preparation of other natural products bearing the *cis*-fused tetrahydro-6*H*-benzo[*c*]chromene system of Δ^9-*cis*-THC. These natural products can be found in species other than *Cannabis sativa* and include, for instance, perrottetinene from different *Radula* liverwort species (Toyota et al., 1994; Cullmann and Becker, 1999; Park and Lee, 2010), which medicinal potential has attracted considerable attention (Chicca et al., 2018); and epiconicol found in many marine ascidians, which displays considerable antiproliferative activity against different cancer cell lines (Carroll et al., 1993; Garrido et al., 2002; Simon-Levert et al., 2005; Ren et al., 2020). Also, other synthetic strategies have been explored and developed to gain access to this same *cis*-fused structural motif but have not been yet applied to *cis*-THC in particular. A radical cyclization approach was explored by Parker and co-workers to gain access to natural product bisabosqual A (am Ende et al., 2013; am Ende and Parker, 2019). Substituted 1-aryl-1,3-butadienes have been evaluated in Diels–Alder strategies toward *cis*-fused tetrahydrobenzo[*c*]chromenes including epiconicol and some members of palodesangrens family of natural products (Minuti et al., 2015; Tangdenpaisal et al., 2019; Tangdenpaisal et al., 2022). A domino electrocyclic ring-opening/hetero Diels–Alder reaction of 2-prenylated 2*H*-pyrans, originally developed by Chizhova and Anufriev (Chizhova and Anufriev, 2000), has been employed for the synthesis of reduced versions of cannabinoids (Garcia et al., 2009), natural products benzosimuline (Riveira et al., 2016), 7-demethylnaphterpin (Murray et al., 2018), as well as others (Coleman et al., 2019; Murray et al., 2019). Interestingly, a related strategy was developed by Appendino and co-workers using iodine as promoter but to afford aromatized versions of the corresponding tetrahydro-6*H*-benzo[*c*]chromene derivatives (Caprioglio et al., 2019). Based on all the available data, a direct oxidative cyclization method (resembling THCA synthase activity) that converts geranylresorcinols (such as CBG) into *cis*-THC derivatives selectively is also lacking. The only examples involve oxidative cyclization toward chromenes promoted by oxidants such as DDQ, MnO_2 or through Pd-catalyzed procedures (Miyase et al., 1980; Lok et al., 1983; Verotta et al., 2004; Ma et al., 2020). Studies on all the established synthetic strategies in the future will prove whether they can efficiently provide access to *cis*-THC and analogues in order to advance biological studies on these precious molecules.

Natural occurrence and biological activity of *cis*-THC isomers

In 1977, Smith and Kempfert reported for the first time the isolation of Δ^9-*cis*-THC from a natural source (Smith and Kempfert, 1977). Natural Δ^9-*cis*-THC was found as a contaminant during routine analysis of samples of marijuana. An amount of 460 g of dried plant material afforded *ca* 1 mg of the compound which absolute stereochemistry was assigned as (6a*S*,10a*R*) based on circular dichroism studies. The researchers found that this natural product was prominent in samples that had high content of CBD. In general, samples that had CBD:THC ratios of *ca* 16:1 were found to exhibit *trans*:*cis* ratios of THC of about 1:1 to 2:1

(phenotype considered as non-narcotic hemp). Phenotypes having ratios less than 1 showed *trans*-THC:*cis*-THC ratios greater than 10: 1. The total concentration of Δ^9-*cis*-THC in plants having a phenotype ratio greater than *ca* 2 was relatively constant at *ca* 0.04% of the dry plant weight. On the other hand, plants having low amounts or lacking CBD did not exhibit detectable amounts of Δ^9-*cis*-THC. Remarkably, this natural product as well as other *cis*-homologues (different alkyl branched chains) and carboxylated versions were identified more recently in *C. sativa* L. varieties (Basas-Jaumandreu and de las Heras, 2020). In particular, Δ^9-*cis*-THCA (Δ^9-*cis*-tetrahydrocannabinolic acid, Δ^9-*cis*-**8**), found in samples that had not been heated before analysis, would be the biosynthetic precursor of Δ^9-*cis*-THC which would then be formed via non-enzymatic decarboxylation (Tolomeo et al., 2022). As for Δ^9-*cis*-THC, the corresponding carboxylated cannabinoid Δ^9-*cis*-THCA was present in concentrations comparable to or slightly lower than those of the well-known *trans* isomer in CBD-rich or CBG-rich varieties of the plant.

Mechoulam and co-workers were the first to report in1971 on the biological activity of Δ^9-*cis*-THC. The group found that (±)-Δ^9-*cis*-THC was inactive in behavioral tests in adult Rhesus monkeys at doses of 1.5 mg/kg (Edery et al., 1971). Later, in 1975, Razdan's group described racemic Δ^9-*cis*-THC as a mild depressor and reported that it was 20-fold less potent than natural (−)-Δ^9-*trans*-THC in the "popcorn assay", a rarely used mouse model of cannabinoid activity based on the association of ataxia and hyperexcitability to touch (Uliss et al., 1975a). Additionally, in 1984 Razdan and Martin showed that (+)-Δ^9-*cis*-THC, together with (+)-Δ^9-*trans*-THC, were quite less active in behavioral tests in dogs compared to (−)-Δ^9-*trans*-THC (Martin et al., 1981).

In 2021, the groups of Appendino, Carreira and Gertsch published a thorough study on Δ^9-*cis*-THC addressing its natural occurrence, chirality and pharmacological activity (Schafroth et al., 2021). Consistent with the report by Smith and Kempfert, the authors found that in hemp non-narcotic varieties of the plant featuring low content of (−)-Δ^9-*trans*-THC the concentration of Δ^9-*cis*-THC was in the same order of the psychoactive component whereas the concentration of Δ^9-*cis*-THC was below the limits of detection in a sample of medicinal *Cannabis* chemotype with high content of (−)-Δ^9-*trans*-THC. In this same medicinal *Cannabis* sample Δ^9-THC was found with very high enantiomeric purity (*ee* > 99%) and exclusively as the *trans* diastereoisomer. On the contrary, in 34 samples of *Cannabis* varieties in which CBD or CBG was the most prominent phytocannabinoid, Δ^9-THC was found with lower diastereomeric purity. The authors showed that natural Δ^9-*cis*-THC is scalemic (approx. 80–90% enantiomeric purity), the major enantiomer being 6a*S*, 10a*R* [(−)]. Regarding binding affinity to cannabinoid receptors CB_1 and CB_2, (−)-Δ^9-*cis*-THC exhibited binding affinities ten times lower than the ones found for the natural *trans* isomer, whereas (+)-Δ^9-*cis*-THC was found to be inactive. The researchers found that (−)-Δ^9-*cis*-THC mildly inhibits endocannabinoid hydrolytic enzymes similarly to (−)-Δ^9-*trans*-THC. In general, IC_{50} values of these natural tetrahydrocannabinols on endocannabinoid degrading enzymes were higher than the *in vivo* achieved concentrations after *Cannabis* consumption. Possible effects of isomer (−)-Δ^9-*cis*-THC were evaluated *in vivo* and compared with the effects of (−)-Δ^9-*trans*-THC on a series of four tests typically associated with the activation of receptor CB_1 in mice (hypothermia, catalepsy, hypomobility and analgesia). The experiments showed that (−)-Δ^9-*cis*-THC could provoke the complete tetrad in mice with a dose of 50 mg/kg, whereas Δ^9-*trans*-THC exhibited similar potency at lower doses between 6 and 10 mg/kg, according to the different potencies measured *in vitro* for the activation of receptor CB_1. The group proposed that if lower doses of Δ^9-*trans*-THC cause therapeutic beneficial effects with little secondary effects, then less potent (−)-Δ^9-*cis*-THC could retain the therapeutic potential of Δ^9-*trans*-THC without undesired effects. The group also raised the debate on the legal status of all isomers of THC which are currently not distinguished nor discriminated to determine the classification of marijuana samples as narcotics and non-narcotic variants (La Maida et al., 2022).

On the other hand, the same year, first patents appeared on the potential therapeutic use of each enantiomer of Δ^9-*cis*-THC based on animal models of disease (Guy et al., 2021; Guy et al., 2021). Taking into account the natural products featuring the *cis*-fused system that have been shown to display antiproliferative properties against a diverse set of cancer cell lines, future studies should address whether Δ^9-*cis*-THC enantiomers exhibit anticancer potential.

Concluding remarks

Cis-THC, as well as other natural products bearing the *cis*-fused tetrahydrobenzo[*c*]chromene motif, demonstrated an interesting biological activity profile. A review such as this is hoped to enhance both synthetic chemists and medicinal chemists in their pursuit of discovering the biological potential of natural products including Δ^9-*cis*-THC and related systems, leading to more simple, straightforward, and selective synthetic processes as well as greater application possibilities.

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Conflict of interest

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