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Stereoselective Synthetic Strategies to (−)-Cannabidiol

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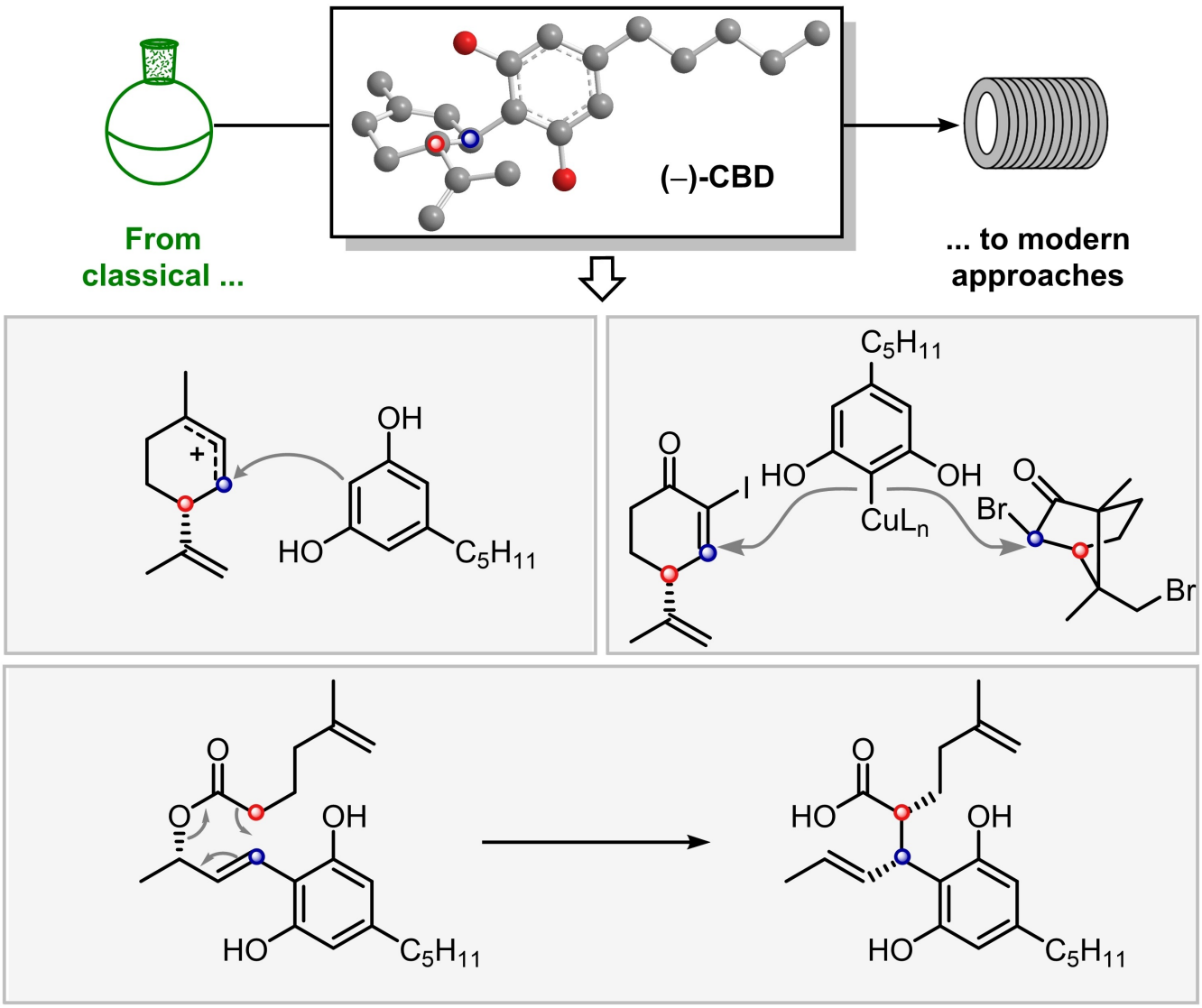

(−)-Cannabidiol (CBD) is a non-psychoactive compound that has already found many medical applications, from the treatment of epilepsy to other neurological disorders. (−)-CBD is usually extracted from *Cannabis Sativa*, but unfortunately, its isolation among many other structurally related cannabinoids can be challenging. This, along with the increased demand for (−)-CBD, prompted chemists to come up with synthetic strategies that could afford this cannabinoid in good yield and high enantiopurity. Herein, we aim to review the fundamental strategies employed in the stereoselective synthesis of (−)-cannabidiol, spanning from classic approaches to automated ones, highlighting the challenges encountered in the total synthesis of this cannabinoid.

1. Introduction

Tetrahydrocannabinol (Δ^9-THC) is the main psychoactive cannabinoid found in *Cannabis Sativa*. (−)-Cannabidiol (known as (−)-CBD) is also extracted from the same plant, and together with Δ^9-THC, accounts for up to 40% of the *Cannabis's* extract (Scheme 1, left).[1] Despite the structural similarity between (−)-CBD and Δ^9-THC, the former is an allosteric negative modulator of cannabinoid receptors.[2] This makes (−)-CBD an appealing pharmaceutical active ingredient without the mind-altering effects of Δ^9-THC. Indeed, (−)-CBD has already shown medical evidence as painkiller, anticonvulsant, antispasmodic, anxiolytic, antinausea, antirheumatoid, and arthritis.[2] Moreover, novel therapeutic uses of (−)-CBD include Alzheimer's, Parkinson's, and severe forms of epilepsy.[3] Not surprisingly, the demand for cannabidiol for health and wellness purposes has dramatically increased in the last decade, fuelled by the rising government approvals of CBD for medical applications.[4] To meet the increasing demand for CBD-infused products on the market, different synthetic routes to cannabidiol have been proposed (including biotechnological approaches).[5] Many strategies, often not stereoselective, start with the use of olivetol, as reported in previous reviews.[4–8] However, a dedicated review on the *stereoselective* synthesis of (−)-cannabidiol that includes modern approaches (e.g. flow chemistry) has not been covered before. In this work, we systematically reviewed the stereoselective synthesis of (−)-cannabidiol focusing on the synthetic approaches employed (and their relative challenges) rather than the starting material used (Scheme 1, right). In particular, based on how the relative *trans*-stereochemical information has been embedded in the desired product, we have classified the synthetic strategies as follows:

1. Friedel-Crafts on olivetol and derivatives.
2. Nucleophilic addition/substitution reactions.
3. Intramolecular Ireland-Claisen rearrangement.

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1.1 Challenges in the total synthesis of (−)-CBD

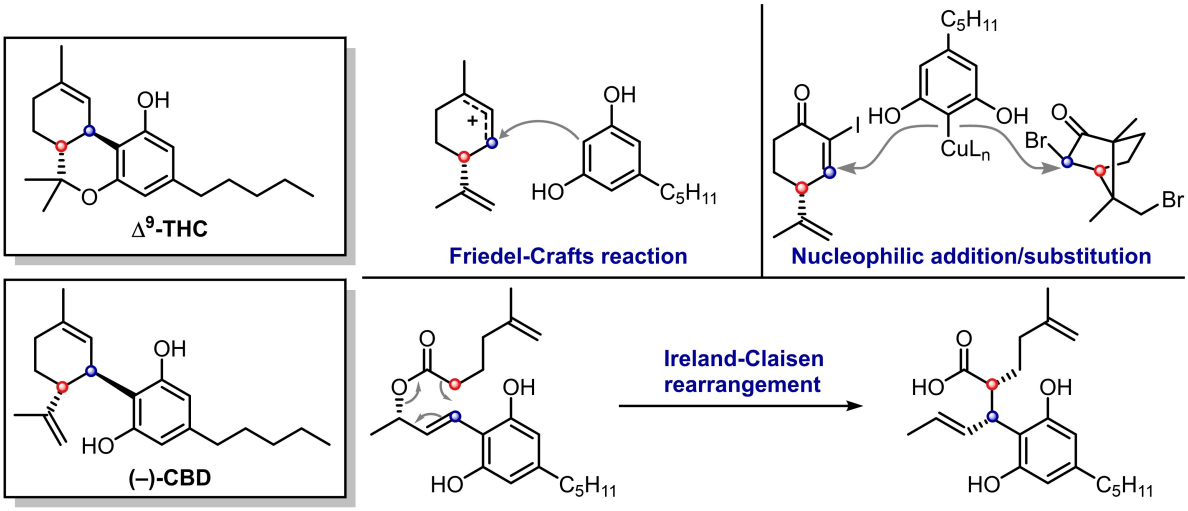
The last century has witnessed spectacular advances in the art of total synthesis, fuelled by the powerful methodology and sophisticated instrumentation available today. Nevertheless, the total synthesis of organic molecules even of medium levels of complexity still presents significant challenges such as time and efficiency.

Moreover, unexpected problems encountered at the late stage of the synthesis (removal of a protecting group or inefficient simple redox steps) may impact the advancement of precious intermediates.[9] As for many other natural products, the total synthesis of (−)-CBD has some pitfalls despite the chemical structure of this cannabinoid is not particularly complex. The most critical challenge is to prevent the cyclisation of (−)-CBD into the psychotic derivative Δ^9-THC, as often observed in the Friedel-Crafts reaction on olivetol or derivatives. In this case, the acidity of the acid catalyst must be tuned to favour the Friedel-Crafts reaction while avoiding further cyclisation. Furthermore, this strategy may generate regioisomers of (−)-CBD which could complicate its isolation. The limitations observed in the Friedel-Crafts reactions have prompted chemists to come up with alternatives, such as nucleophilic addition/substitution and Claisen-Ireland rearrangement strategies. Despite suppressing regioselectivity issues, both strategies may not be suitable for large-scale applications of (−)-CBD since requiring many synthetic steps, including protection and deprotection of the hydroxy groups. The latter deprotection is also challenging since incompatible with acidic conditions that would otherwise promote cyclisation to Δ^9-THC (thus it is usually achieved under harsh basic conditions). Moreover, while in Friedel-Crafts approaches the stereogenic centers are already embedded in the starting chiral pool, many other strategies require asymmetric synthetic steps to control the stereochemistry of the desired product. In the following paragraphs, we have carefully investigated the strategies reported in the total synthesis of (−)-CBD, covering not only the most recent approaches but also underlining the challenges in each strategy.

2. Synthetic Strategies to (−)-Cannabidiol

2.1 Friedel-Crafts reaction on olivetol and derivatives

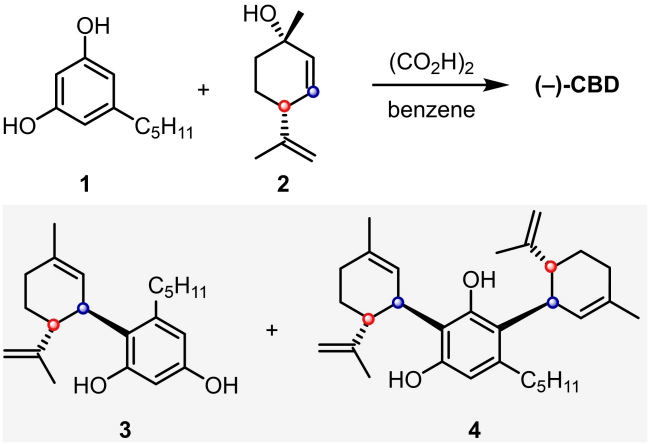
The first method for the stereoselective synthesis of (−)-CBD was described in 1967–1969 by Petrzilka and co-workers[10,11] and it is still now considered a milestone for the development of new synthetic pathways. This approach is based on a



Scheme 1. Δ^9-THC and (−)-CBD (left) and key strategies to create the *trans*-stereochemistry in (−)-CBD (right).

Friedel-Crafts reaction on olivetol (**1**) using oxalic acid as the catalyst and β-terpineol **2** as the chiral electrophile-precursor (Scheme 2).

In this electrophilic aromatic substitution (S_EAr), upon acid-catalysed water-elimination, the allylic carbocation is attached to the less hindered face, yielding the *trans*-configuration observed in the desired product. However, while this one-step synthesis is appealing, it yielded (−)-CBD in only 29% yield due to regioselectivity problems. Indeed, C2-alkylation competed with the desired C4 one, resulting in a predominance of regioisomer **3** and dialkylated product **4**. Moreover, the use of stronger acids (e.g. *p*-toluenesulfonic acid or trifluoroacetic acid) was deleterious for the reaction, inducing cyclization to the more thermodynamically stable Δ^9-THC. Since Petrzilka's pioneering work, implementations of the direct alkylation of olivetol have been reported in the literature. For instance, in 1980 Korte and co-workers isolated (−)-CBD in 41% yield when



Scheme 2. Petrzilka and co-workers' synthesis of (−)-CBD.

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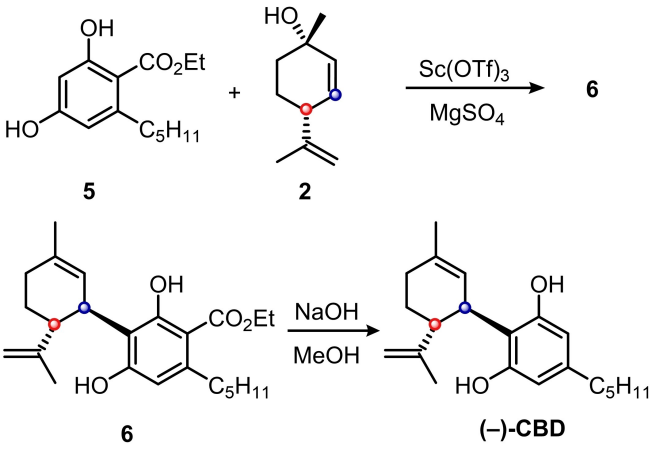
performing the reaction at higher pressure (7–8 kbar), using anhydrous sodium sulfate (Na_2SO_4) as an additive.[12] Another modification of Petrzilka's work was reported by Baek and Mechoulam in 1985.[13] Replacing oxalic acid with BF_3-etherate supported on alumina, (−)-CBD was isolated in 41% as a crystalline product on a 0.8 mmol scale and in 37% on a 100 mmol scale, thus showing how this procedure could potentially be scaled up. Notably, in absence of the alumina layer, the reaction proceeded further, converting (−)-CBD to Δ^9-THC. Indeed, without adsorption of BF_3 on the surface of alumina, this strong Lewis acid could induce cyclisation to the more thermodynamically stable Δ^9-THC.[14]

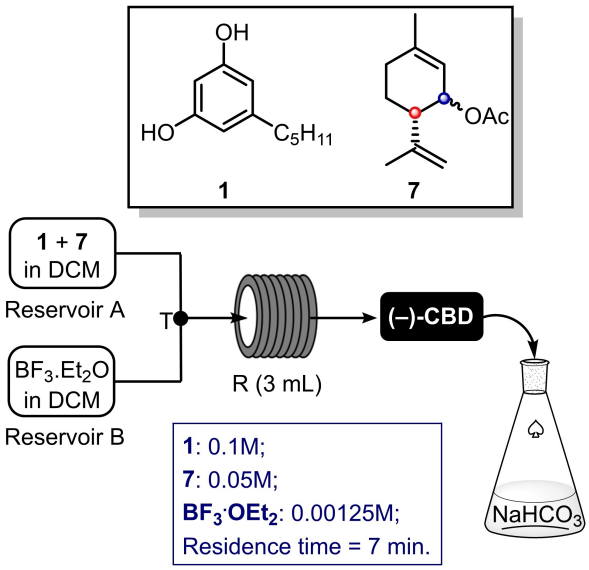
Despite Petrzilka's strategy is still used nowadays, different issues remain. First, $BF_3{\cdot}OEt_2$ supported on alumina is not commercially available and has to be prepared in situ. Secondly, alumina is used in large excess (10:1 ratio compared to the BF_3 catalyst) and it can't be recovered, thus increasing the total waste of this reaction.

For this reason, the use of alternative Lewis acid catalysts has also been investigated. For instance, Pal Singh and co-workers have tested different silver catalysts for the regiospecific coupling between olivetol and **2**.[15] They found that the use of AgOTf gave (−)-CBD in a 40% yield without any cyclisation to Δ^9-THC nor by-product formation. The regiospecificity was attributed to the oxophilic character of Ag^+ which coordinated to the oxygen of **2** promoting a Nucleophilic Substitution Prime Reactions (S_N2') on the allylic alcohol. This concerted mechanism is also responsible for the required *trans*-geometry of the product. $Sc(OTf)_3$ is another example of a Lewis acid employed as a catalyst in the synthesis of cannabinoids, as reported by Burdick and co-workers. In particular, they used $Sc(OTf)_3$ to promote the Friedel-Craft alkylation of the methyl ester of olivetolic acid (**5**), followed then by decarboxylative saponification of intermediate **6** (Scheme 3).[16] Similar multi-step strategies based on Friedel-Crafts reaction of olivetol derivatives have been reported by Dialer and co-workers too.[17]

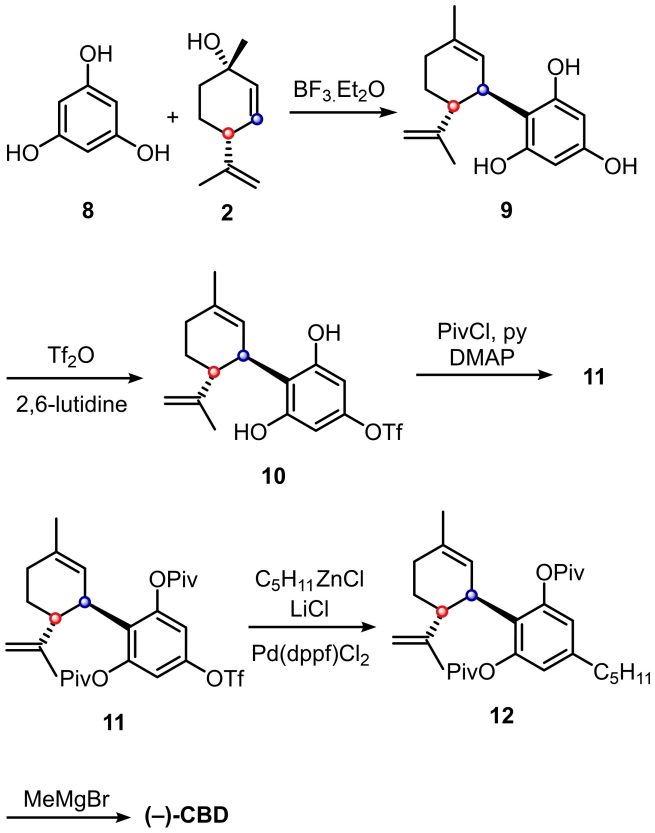
A more modern approach to avoid the use of alumina is based on continuous flow chemical synthesis, as reported by Palmieri and co-workers in 2021.[18] This automated strategy represents the most modern approach to the stereoselective synthesis of (−)-CBD. In their work, the authors used flow equipment constituted of two different reservoirs, as reported in Scheme 4. The first reservoir was filled up with a dichloromethane solution of olivetol (**1**) and acetyl isopiperitenol (**7**), while the second one with a dichloromethane solution of $BF_3{\cdot}Et_2O$. The use of **7** instead of β-terpineol **2** as the carbocation precursor was based on a previous work using unprotected isopiperitenol.[19] With this set-up, (−)-CBD could be isolated in 55% yield, along with a minor amount of regioisomer **3** and dialkylated product **4**. Interestingly, Δ^9-THC was observed only in traces, thus suggesting no cyclisation of (−)-CBD was occurring under these reaction conditions (the outcoming flow needed to be directly quenched with $NaHCO_3$). Indeed, extending the residence time to over 7 minutes, as well as the use of a more concentrated solution of $BF_3{\cdot}Et_2O$, led to the formation of a significant amount of Δ^9-THC. On the other hand, diminishing the residence time, the Friedel-Craft reaction was not complete, leaving 8% of unreacted **7** in the reaction crude. While the one-step alkylation of olivetol offers direct access to (−)-CBD, this method is not suitable for the synthesis of derivatives with different side chains or functional groups. An elegant solution to this problem was proposed in 2020 by Shen, Aisa, and co-workers which replaced olivetol with phloroglucinol (**8**) in the Electrophilic Aromatic Substitution step (Scheme 5).[20] The use of phloroglucinol was also strategic to avoid regioselectivity issues during the S_EAr step, with the only side reaction reported by the authors being the dialkylation of **8**. This could be easily minimized by using phloroglucinol in a 10:1 excess relative to **2**, allowing compound **9** to be isolated in 80% yield (unreacted **8** could be recovered too). To install the pendant pentyl chain in the C4 position, compound **9** underwent a regioselective trifluoroace-



Scheme 3. Burdick and co-workers' synthesis of (−)-CBD.



Scheme 4. Palmieri and co-workers' flow chemical synthesis of (−)-CBD.



Scheme 5. Shen, Aisa, and co-workers' synthesis of (−)-CBD.

tylation using trifluoromethanesulfonic anhydride in the presence of 2,6-lutidine, thus yielding **10** in 78% yield.

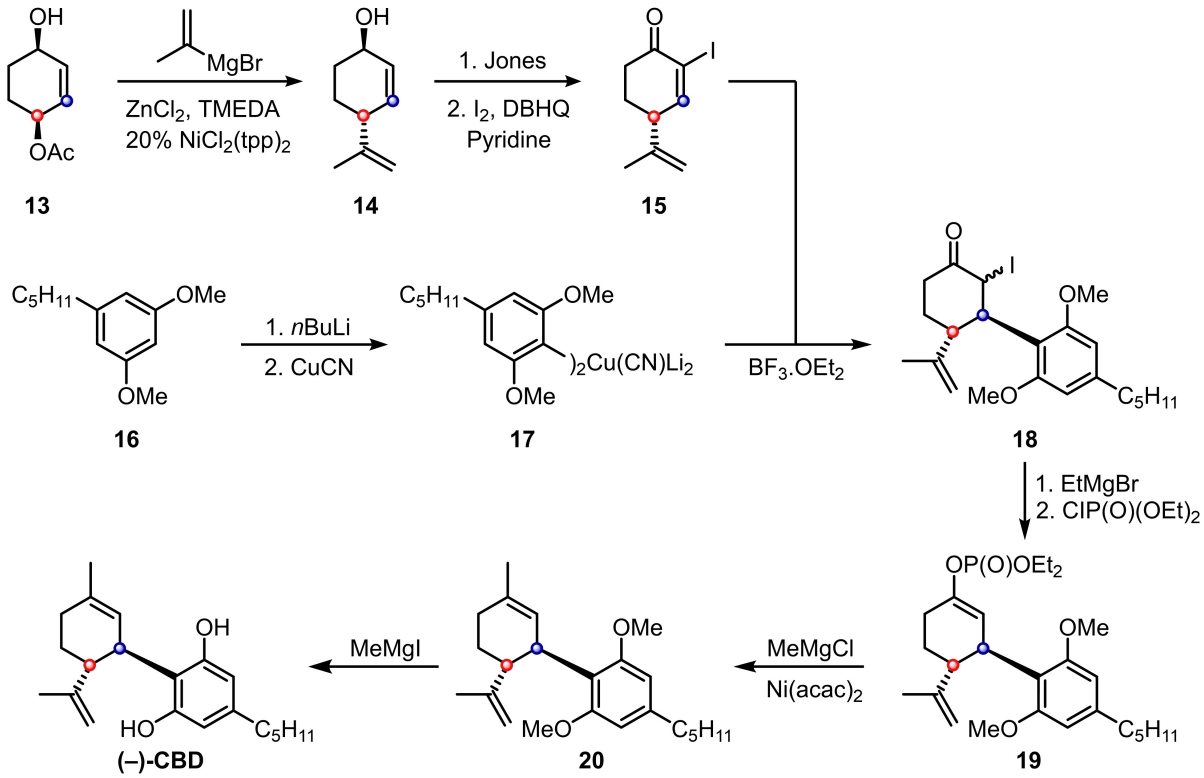
The use of this bulky lutidine is believed to allow the regioselective deprotonation of **9** at the less hindered hydroxy group in position 4. Interestingly, the reaction needed to be performed at −30 °C since higher temperatures favoured the cyclization to the more stable Δ^9-THC scaffold. Direct conversion of **10** to (−)-CBD was attempted via Negishi coupling with a suitable organic zinc reagent. However, this gave the desired product in only 20% yield probably because the deprotonation of the free alcohols was interfering with the catalytic cycle of palladium. This could be solved by protecting the free hydroxy groups of **10** as pivalates. Indeed, the Negishi coupling of **11** with the organozinc reagent yielded compound **12** in 90%, also because the electron-withdrawing pivalate groups may have promoted the oxidative addition of palladium into the aryl triflate. For the final deprotection of **12** the authors avoided acidic conditions to prevent the cyclization into Δ^9-THC. While KOH, NaOMe, and NH_3 afforded (−)-CBD in low yields, using methyl magnesium bromide allowed for the quantitative deprotection, thus furnishing (−)-CBD in an overall 52% yield. It is worth noticing that this multi-step approach yields more (−)-CBD than the traditional direct alkylation of olivetol, allowing also to synthesize other derivatives by choosing a suitable organic zinc reagent.

2.2 Nucleophilic addition/substitution reactions

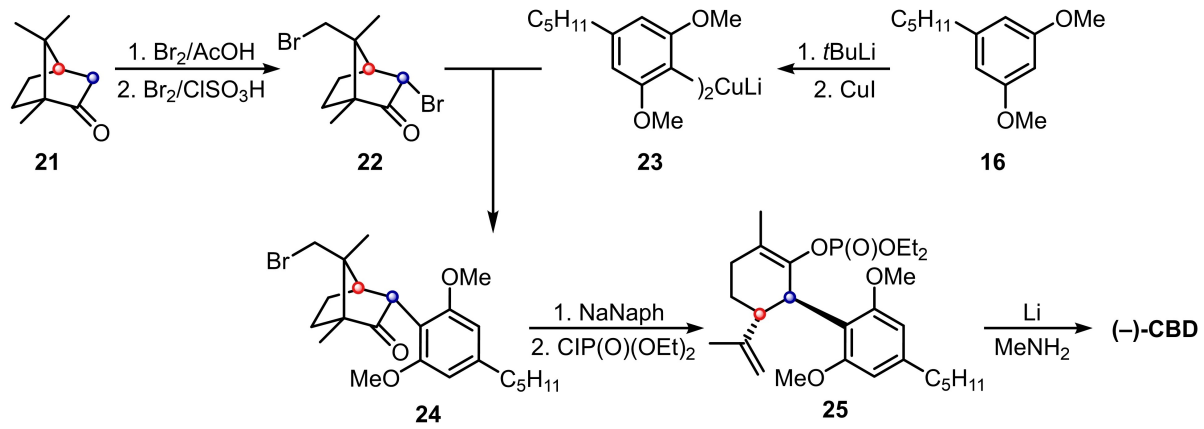
In the Friedel-Crafts reaction on olivetol, the *trans*-configuration of (−)-CBD was constructed by exploiting the shielding of one face of the allylic carbocation by the isopropenyl group. A similar strategy was reported by Kobayashi and co-workers in 2006 but using two different coupling reagents (Scheme 6).[21] In particular, the *trans*-geometry was achieved by the nucleophilic addition of olivetol derivative **17** to Michael acceptor **15**, following a methodology established by the same group some years before.[22] This multi-step synthesis started with 1,4-cyclohexenediol monoacetate **13** as the chiral platform instead of **2**. **13** is not commercially available, but it could be prepared from 1,3-cyclohexadiene via an asymmetric bioenzymatic reaction.[23] Compound **13** was then converted into derivative **14** via a stereo-inverting nickel-catalysed cross-coupling reaction with isopropenylmagnesium bromide, in the presence of $ZnCl_2$ and tetramethylethylenediamine (TMEDA). Compound **14** was oxidized to an α,β unsaturated ketone employing Jones reagent, followed by α-iodination performed with I_2 in the presence of di-*tert*-butylhydroquinone (DBHQ) as electron scavenger, yielding coupling partner **15**. The other partner (**17**) was prepared from bis-methylated olivetol **16**, through regioselective lithiation followed by a reaction with copper cyanide. The nucleophilic addition of olivetol derivative **17** to Michael acceptor **15**, in presence of $BF_3{\cdot}OEt_2$, furnished **18** in a 1:1 ratio diastereomeric ratio. It is worth noticing that, in contrast to the S_EAr of olivetol, this nucleophilic addition cannot generate a regioisomer of **18** since the initial lithiation of **16** is highly regioselective. From compound **18**, elimination of iodide with ethylmagnesium bromide, followed by the quenching of the enolate with ClP(O)(OEt), yielded enol phosphate **19**. A nickel-catalysed Kumada coupling-reaction between **19** and methyl magnesium chloride gave compound **20** whose deprotection yielded in turn (−)-CBD.[24]

The multi-step approach developed by Kobayashi and co-workers has minimal by-products, allowing also to access many (−)-CBD derivatives by changing the coupling partner in the Kumada reaction. However, the reagents employed are more economically demanding compared to Shen and Aisa's method, thus making Kobayashi's strategy not suitable for large-scale applications.

A different methodology to control the *trans*-stereochemistry of (−)-CBD exploits a nucleophilic substitution reaction on 3,9-dibromocamphor (**22**), as reported by Albizati and Vaillancourt in 1992 (Scheme 7).[25] **22**, generated via sequential bromination of camphor **21**, was reacted with aryl cuprate **23** generated from bis-methylated olivetol **16**.[26] It was found that the steric hindrance of the aryl cuprate was crucial to obtain exclusively endo-product **24** (for instance, replacing **23** with PhCuI the corresponding product was isolated as a 4.5:1 endo:exo mixture). Compound **24** has the desired *trans*-configuration, although the isopropenyl group is not revealed yet. Treatment of α-aryl ketone **24** with sodium naphtalenide (NaNaph) induced a fragmentation reaction leading to the corresponding enolate trapped then as vinyl phosphate **25**. The reductive cleavage of **25** with an excess of lithium in



Scheme 6. Kobayashi co-workers' synthesis of (−)-CBD.

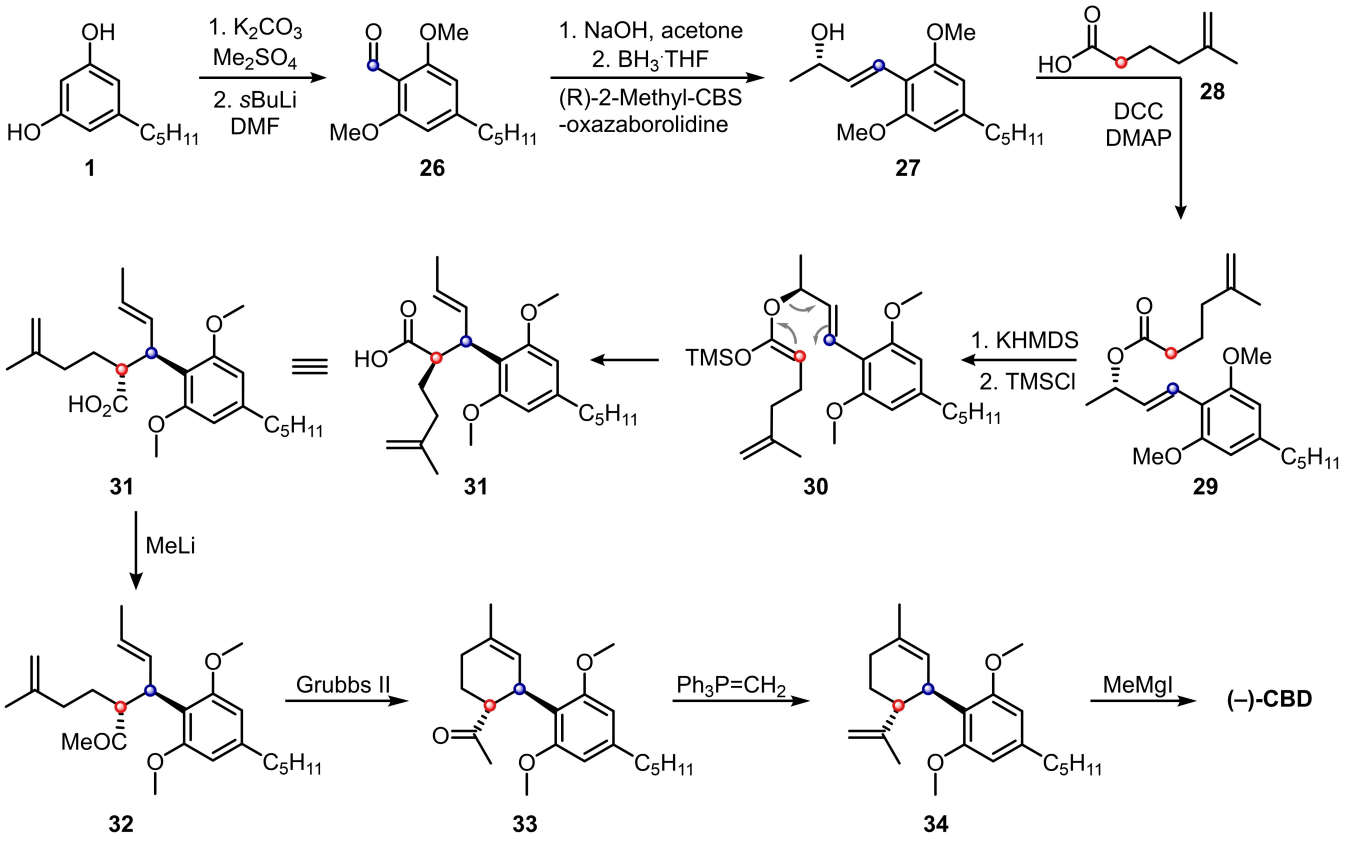


Scheme 7. Albizati and Vaillancourt's synthesis of (−)-CBD.

methylamine resulted also in the deprotection of the hydroxy groups, thus yielding (−)-CBD in 22% overall yield (starting from **22**).

2.3 Intramolecular Ireland-Claisen rearrangements

In the strategies reported so far, the cyclohexanyl moiety of cannabidiol was always embedded in one of the starting materials. A completely different approach to access this motif was reported by Leahy and co-workers in 2018 (Scheme 8).[27] Their synthesis started with the conversion of olivetol **1** into aldehyde **26** through methylation with Me_2SO_4, followed by regioselective lithiation and formylation with dimethylformamide (DMF). Then, **26** underwent aldol condensation with acetone, followed by stereoselective reduction of the corresponding enone with BH_3 in the presence of the chiral Corey-Bakshi-Shibata catalyst. While **27** could be obtained in 94% yield, the stereocontrol was not ideal, as confirmed by an enantiomeric excess not exceeding 77% after recrystallization. However, this was not a problem since the authors showed



Scheme 8. Leahy and co-workers' synthesis of (−)-CBD.

how alcohol **27** could be obtained in high enantiopurity (up to 98% ee) by means of enzymatic kinetic resolution. Acylation of **27** with acid **28** in the presence of *N,N'*-dicyclohexylcarbodiimide (DCC) and 4-(dimethylamino)pyridine (DMAP) afforded allylic ester **29**. Deprotonation with potassium hexamethyldisilazide (KHDMS) followed by treatment with trimethylsilyl chloride (TMSCl) furnished silyl ketene acetal **30**. A [3.3]-sigmatropic rearrangement of **30** (also known as Ireland-Claisen rearrangement) yielded, after work-up, γ,δ-unsaturated acid **31** as a single diastereoisomer. It is worth noting that the diastereoselectivity of the rearrangement determined the relative configuration of **31**, whereas its absolute configuration was dictated by the stereogenic carbon centre of **30**. Then, carboxylic acid **31** was converted into ketone **32** by treatment with an excess of methyllithium, followed by a ring-closing metathesis with a 2nd-generation Grubbs catalyst. In this step, the cyclohexyl moiety was assembled, with **33** containing all the stereogenic information of the desired product. Finally, conversion of the ketone into the isopropenyl group (Wittig reaction on **33**), followed by demethylation of **34** with MeMgI provided (−)-CBD in an overall 13% yield (over 11 steps). This elegant approach was recently applied by our research group in the stereoselective synthesis of (−)-CBD-C_4, an analogue where the *n*-pentyl chain attached to the phenyl ring has been replaced by an *n*-butyl group.[28] Interestingly, in our hands the final deprotection of the hydroxy groups could not be achieved using MeMgI, therefore other deprotection conditions were instead used (specifically, a large excess of sodium ethanethiolate in dry DMF at 140 °C). This highlights how challenging the final deprotection is, knowing that acidic conditions are not viable options since they would induce cyclisation to Δ^9-THC. It has to be noted that despite Ireland-Claised rearrangements are less yielding than other multi-step approaches, the possibility to build the cyclohexenyl ring from scratch could be exploited to access unconventional (−)-CBD derivatives. It is worth mentioning that Diels-Alder reactions have also been used to construct the 6-membered ring of the terpene motif, although the resolution of the racemate is usually a drawback with this approach.[29]

3. Conclusions and future directions

Different strategies have been developed for the stereocontrolled synthesis of (−)-CBD. The shortest one, that is a Friedel-Crafts reaction on olivetol using a suitable chiral terpene precursor, gives (−)-CBD in one step, but it suffers from regioselectivity problems and over-alkylation (usually minimized when performing it in continuous flow or using silver-based Lewis acids). A Friedel-Crafts reaction on phloroglucinol is also a viable route and, despite adding steps to the synthesis, many (−)-CBD derivatives could be obtained *via* this method. Other multi-step syntheses, based on the nucleophilic addition/

substitution of aryl cuprate to chiral terpenoids, allow the control of the *trans*-geometry of (−)-CBD without any significant by-reactions. Finally, an elegant approach to access the relative stereochemistry of (−)-CBD is based on an intramolecular Ireland-Claisen rearrangement, where the terpene motif is then constructed via ring-closing metathesis. In conclusion, while direct methods could be useful to access (−)-CBD, even at a large scale, other multi-steps strategies may be of interest when designing novel derivatives, an important aspect given the popularity of this non-psychoactive cannabinoid.

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Conflict of Interest

There are no conflicts to declare.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Keywords: Cannabidiol · Natural products · Stereoselectivity · Total Synthesis · *trans*-geometry

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