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A Novel and Practical Continuous Flow Chemical Synthesis of Cannabidiol (CBD) and its CBDV and CBDB Analogues

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This article is dedicated to Prof. Franco Cozzi on the occasion of his 70th birthday.

Cannabidiol is one of the main non-psychoactive cannabinoids present in Cannabis sativa and, in the last decade, it is gaining great interest among the scientific community for its pharmaceutical, nutraceutical, and cosmetic applications. Herein, we report the first continuous flow chemical synthesis of cannabidiol (CBD) and its analogues cannabidivarin (CBDV) and cannabidibutol (CBDB). This approach permits to synthesize products in very good yields (55–59%), limiting the formation of psychoactive and illegal cannabinoids such as tetrahydrocannabinol (THC).

Cannabis sativa L. and its derivatives have been used as popular medicines for 5000 years.[1] Epidiolex, a cannabidiol (**CBD**) based medicine developed by GW Pharmaceuticals Inc., has been recently approved by the European Union for the treatment of severe forms of epilepsy associated with Lennox Gastaut and Dravet syndromes.[2] This authorization follows the one granted by the FDA in 2018. The latter is the first approval among more than two hundreds clinical trials currently ongoing on **CBD**, cannabidivarin (**CBDV**) and other cannabinoids. Nowadays, the enormous interest of the pharmaceutical, cosmetic and food supplements industries, as well as the attention of the academical research for these derivatives, resulted in a continuous and growing effort to develop new and ever more efficient syntheses of cannabidiol and its analogues (Figure 1).[3]

CBD, currently the most investigated non-psychoactive cannabinoid, is mainly synthetically pursued by the acid-catalysed terpenylation of olivetol **1a** or olivetolic acid alkyl esters **2** followed by saponification and decarboxylation (Scheme 1). In this context, important results have been obtained using isopiperitenol **3a**, menthadienol **4a**, carene epoxide **5** or their *O*-substituted derivatives, as synthetic

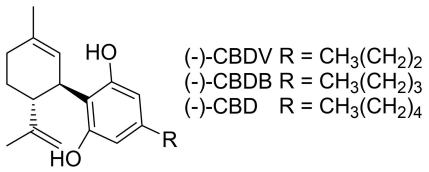
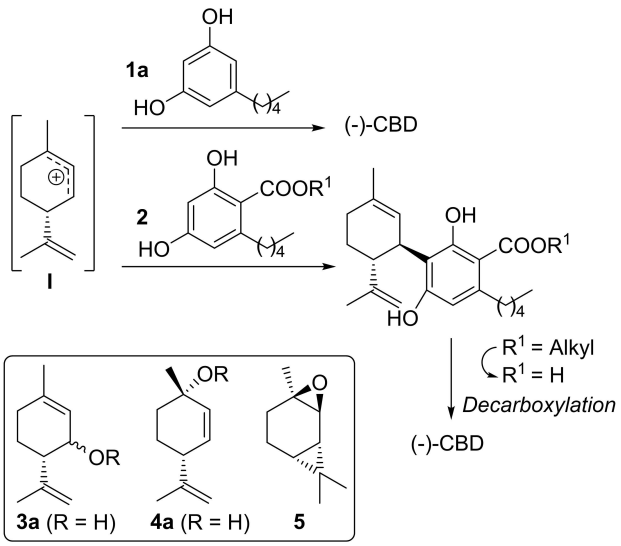


Figure 1. Molecular structure of cannabidivarin (CBDV), cannabidibutol (CBDB) and cannabidiol (CBD).



Scheme 1. Synthesis of CBD *via* terpenylation of olivetol or olivetolic esters.

equivalents of the carbocation **I** under Lewis or Brønsted acid conditions (e.g. $ZnCl_2$, $BF_3 \cdot Et_2O$, *p*-TsOH).[4]

Alternative synthetic approaches involve (i) the reaction of diaryl-lithium cuprates with (+)-3,9-dibromocamphor **6** or α-iodocyclohexenone **7** (Scheme 2, Eq. 1.),[5] and (ii) the derivatization of olivetol with appropriate acyclic structures to give, after a series of synthetic manipulations, the target **CBD** (Scheme 2, Eq. 2).[6] The crucial point of all these methodologies is to minimize the cyclization of **CBD** into the psychoactive tetrahydrocannabinol (Figure 3, **THC**), which is subject to legal restrictions in many countries. Due to this problem and in order to limit its formation, reported methods show important drawbacks concerning yields and scalability.

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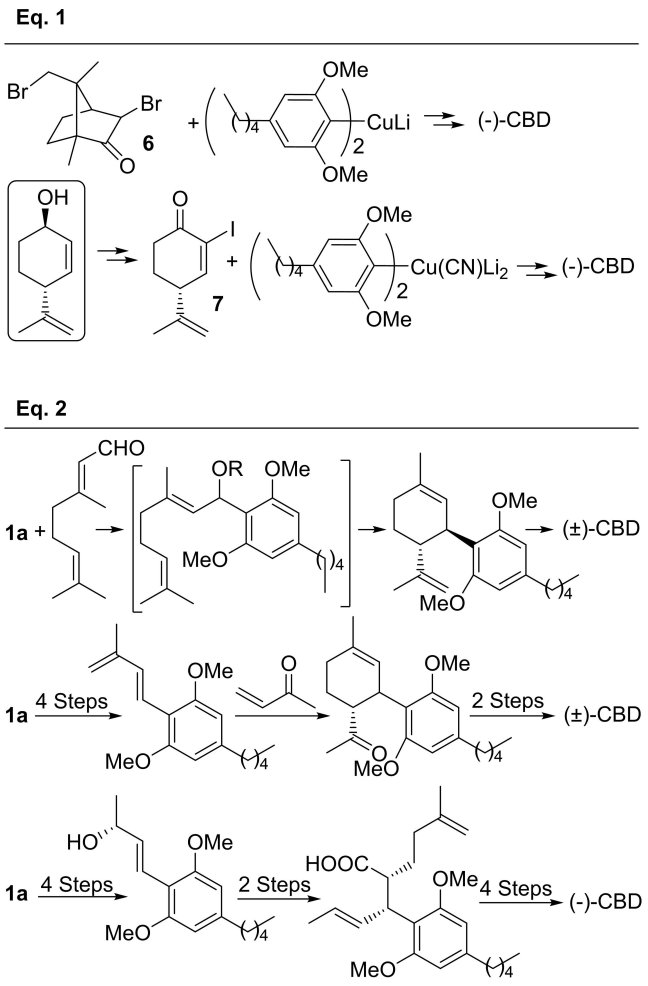

Scheme 2. Alternative synthetic approaches to **CBD**.

Herein, by means of flow chemistry,[7] and following our studies concerning the use of this technology for synthesizing highly functionalized materials,[8] we report an innovative and high yielding continuous approach for producing (−)-**CBD**, strongly reducing its cyclization into **THC**.

With this aim, we implemented a new flow equipment (Figure 2) constituted of two different reservoirs (*A* and *B*), a T-mixing piece (**T**) and a PTFE coil reactor (**R**, 3 mL, i.d. = 0.8 mm, o.d. = 1.58 mm). The reservoir *A* was filled-up with a dichloromethane solution of olivetol **1a** and acetyl isoperitenol **3b** (R=Ac), while the reservoir *B* with a dichloromethane solution of $BF_3 \cdot Et_2O$.

After a series of experiments aimed to profile the process in terms of stoichiometry, reaction temperature and residence time, the best result was recorded at room temperature, starting from a 0.1 M and 0.05 M solutions of **1a** and **3b** respectively (*Reservoir A*), a 0.00125 M solution (2.5 mol% *vs* **3b**) of $BF_3 \cdot Et_2O$ (*Reservoir B*), and with a residence time of 7 minutes (Table 1, *Entry g*). In fact, under these conditions, **(−)-CBD** was isolated in 55% of yield. The main by-products were abnormal cannabidiol and the dialkylated cannabidiol (Figure 3, **8** and **9**) recovered in 19% and 4% of yield respectively. In the end, since **THC** was observed in traces (GC < 0.4%) its isolation was unfeasible.

It is important to point out that an extension of the residence time to over 7 minutes, as well as the use of more concentrate solution of $BF_3 \cdot Et_2O$ led to the formation of significant amount of **THC** (> 5%). On the other hand, a diminishing the residence time, the Friedel–Craft reaction between **1a** and **3b** was not completed and an 8% of unreacted isoperitenol was detected in the reaction crude (Table 1, *Entry i*).

The process was also investigated starting from isopiperitenol **3a**, benzoyl isopiperitenol **3c** (R=Bz) and menthadienol **4a**, however these substrates resulted less efficient than **3b** providing **CBD** in 48%, 16% and 38% of yield respectively.

It is important to point out that, as depicted in Figure 2, in order to prevent the conversion of **CBD** into **THC** it was crucial to directly quench the outcoming flow with a saturated solution of $NaHCO_3$. Furthermore, the use of two equivalents of olivetol **1a** (the excess was recovered after purification) permitted to minimize the formation of the dialkylated cannabidiol.

Successively, with the aim to increase the protocol productivity, we screened the process trend starting from more concentrate solutions of starting materials **1a** and **3b** (Table 2). Under these conditions, the GC analysis of reaction crudes highlighted in all cases a significant increase of the **THC** formation, nevertheless the isolation of **CBD** provided more than satisfactory yields.

Finally, in order to demonstrate the generality of our protocol we explored the synthesis of **CBDV** and **CBDB**, the two most studied analogues of **CBD**.[3b,9] In particular, starting from the olivetol analogues **1b** and **1c** and performing the reaction

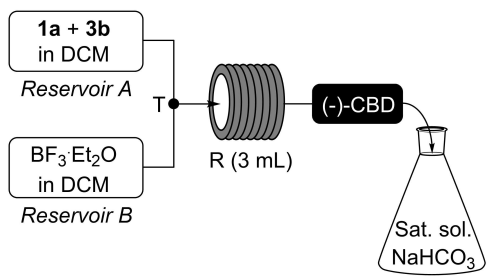

Figure 2. General apparatus for the flow synthesis (−)-**CBD**.

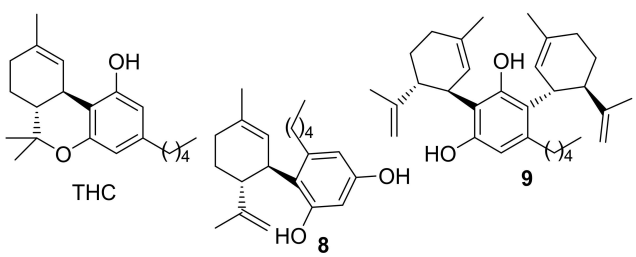

Figure 3. Molecular structures of tetrahydrocannabinol (**THC**), abnormal cannabidiol (**8**) and the dialkylated form of cannabidiol (**9**).

Table 1. Optimization studies

Entry	*Reservoir A* M of **1a** and **3b**	*Reservoir B* [mol%] of $BF_3 \cdot Et_2O$ *vs* **3b**	GC analysis[a] (−)-**CBD**/**8**/**THC**/**9**	Residence time [min]
a	0.05–0.05	20	42.6/22.4/9.6/25.4	8
b	0.075–0.05	20	48.8/22.5/9.5/19.2	8
c	0.1–0.05	20	61.1/22.7/8.9/7.3	8
d	0.1–0.05	10	62.5/22.8/7.6/7.1	8
e	0.1–0.05	5	65.8/22.3/5.2/6.7	8
f	0.1–0.05	2.5	66.0/22.4/5.1/6.5	8
g	0.1–0.05	2.5	70.8/22.6/0.4/6.2	7[b]
i	0.1–0.05	2.5	70.7/22.7/0.2/6.4	6[c]

[a] Percentage normalized considering only peaks of (−)-**CBD**, **8**, **THC** and **9**. [b] 55% Of pure (−)-**CBD** was recovered after flash column chromatography. [c] A 8% of unreacted isoperitenol **3b** was detected in the reaction crude.

Table 2. More concentrated solutions.

M of **1a** and **3b**[a]	GC analysis[b] (−)-**CBD**/**8**/**THC**/**9**	Yield [%][c] of (−)-**CBD**
0.2–0.1	58.3/25.6/8.9/7.2	50
0.5–0.25	53.3/24.7/14.2/7.8	46
1.0–0.5	46.5/26.1/19.8/7.6	41

[a] Reaction conducted with a residence time of 7 minutes and using 2.5% of $BF_3 \cdot Et_2O$. [b] Percentage normalized considering only peaks of (−)-**CBD**, **8**, **THC** and **9**. [c] Yield of the pure isolated product.

under the optimized conditions, **CBDV** and **CBDB** were isolated in 56% and 59% yield respectively (Figure 4). The main by-products for both reactions were the abnormal derivatives **10** and **11**, which were isolated in 30% and 26% of yields.

In conclusion, exploiting the unique features of continuous flow chemical synthesis, we developed a new efficient and simple flow protocol for producing **CBD** in very good yield (55%), in comparison with similar approaches reported in the literature,[10] and limiting its cyclization into the psychoactive tetrahydrocannabinol. Moreover, the process resulted of general applicability since was successfully used for preparing the analogues **CBDV** and **CBDB** in comparable yields (56% and 59%).

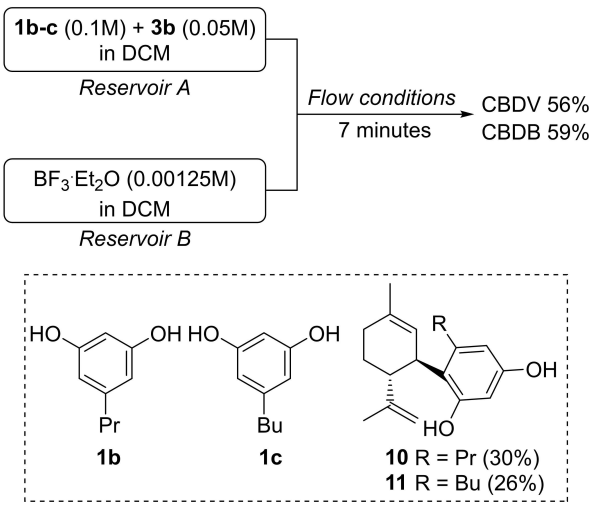

Figure 4. Flow chemical synthesis **CBDV** and **CBDB**.

Experimental Section

General Procedure for the preparation of CBDB, CBV and CBD. The flow equipment was set up according to Figure 2. Acetyl isoperitenol **3b** (2.5 mmol, 0.486 g) and olivetol **1a** [5 mmol, 0.901 g, or its analogues **1b** (0.831 g) and **1c** (0.761 g)] were taken up in dichloromethane (50 mL) and filled into reservoir *A*. $BF_3 \cdot Et_2O$ (0.063 mmol, 7.8 μL) was taken up in dichloromethane (50 mL) and filled into reservoir *B*. The two solutions were simultaneously pumped with a flow rate of 0.214 mL/min for each pump into a T-connector before passing through a 3 mL coil reactor (residence time 7 minutes) and then dropped the outflow into a flask containing 70 mL of a stirring saturated solution of $NaHCO_3$. The two layers were separated, the aqueous one was extracted with DCM (3×40 mL) and the combined collected organic phases were dried over anhydrous Na_2SO_4. After the filtration and solvent evaporation under reduced pressure, the residue was purified by flash column chromatography (hexane:ethyl acetate = 95:5) to give the pure **CBD** in 55% of yield (1.375 mmol, 0.433 g). **CBV** and **CBDB** were isolated in 56% (1.4 mmol, 0.401 g) and 59% (1.475 mmol, 0.443 g) of yield respectively.

Acknowledgements

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Cannabidibutol · Cannabidiol · Cannabidivarin · Flow chemistry · Friedel–Crafts reaction

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