One-flow synthesis of tetrahydrocannabinol and cannabidiol using homo- and heterogeneous Lewis acids

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Abstract

Continuous flow chemistry holds great potential for the production of biologically relevant molecules. Herein, we present an approach for the continuous synthesis of cannabidiol and tetrahydrocannabinol in a one-flow system. The designed route consists of a reaction cascade involving Friedel-Crafts alkylation, subsequent ring opening and cyclisation in up to 45% yield. The reactions were successfully performed using both hetero- and homogeneous Lewis acids in continuous flow and provide yields that are similar to comparable batch processes.

Keywords Cannabinoids · Heterocycles · Flow chemistry · Heterogeneous Lewis acid catalysis

Introduction

An ongoing challenge in organic synthesis is the optimisation of isolated yield in chemical transformations for the production of biologically relevant molecules. A practical approach for reaction optimisation is offered by flow chemistry, which allows efficient and even automated screening for reaction conditions and faster analysis [1–6]. In addition, during the last decade flow chemistry has emerged as a viable approach for the larger scale preparation of fine chemicals and active pharmaceutical ingredients (APIs) [7, 8]. Hence, while batch reactions are still commonly used, flow chemistry is

increasingly applied for safer, scalable and more efficient reactions in academic and industrial settings.

The preparation of APIs in a continuous flow process is desirable as it increases safety, scalability, reproducibility and efficiency. Multistep cascade reactions, which can be carried out in a single flow system (One-Flow) are particularly attractive for the synthesis of pharmaceutically active small molecules [9]. Within the framework of our EU FETOPEN ONE-FLOW project [10], in which cascade one-flow approaches are being developed for the synthesis of APIs, we aimed to implement this strategy for producing cannabinoids.

A class of molecules that are typically prepared in batch are synthetic (phyto-)cannabinoid derivatives. These cannabinol mimetics are derived from naturally occurring molecules that have been isolated from various genera of *Cannabis* [11]. Chemists and biologists have shown great interest in unveiling the function of the endogenous cannabinoid receptors (CB₁ and CB₂) as they play a major role in health and disease [12]. Up till now, a plethora of (ant-)agonists have been identified for both cannabinoid receptors, and are prepared on large scale through batch chemistry [13]. Many of these synthetic routes are experimentally challenging, poorly scalable and afford overall yields up to 40%. Recently, however, Giorgi and co-workers reported the flow synthesis of racemic *ortho*-tetrahydrocannabinols (THC) in flow using multiple heterogeneous catalytic steps (Scheme 1a) [14]. A sequence of citral oxidation with gold nanoparticles, Friedel-Crafts alkylation and a

Highlights

- Development of heterogeneous Lewis acid catalysts for in flow Friedel-Crafts alkylation
- Implementation of homo- and heterogeneous Lewis acids for the preparation of cannabinoids in a one-flow system

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Scheme 1 **a** One-flow synthesis of a diastereomeric mixture of racemic *ortho*- Δ^8 - and Δ^9 -THC using citral (**1**) and olivetol (**2**) by Giorgi et al. **b** Our enantio- and diastereoselective one-flow synthesis of Δ^8 - and Δ^9 -THC

final cyclisation using titanium-doped montmorillonite (Ti/MMT) afforded a variety of THC_s, albeit without stereoselectivity and low regioselectivity.

Alternatively, enantiopure tetrahydrocannabinols can be synthesised using various chiral pool approaches in a limited number of synthetic steps [15–24]. To the best of our knowledge, the application of flow chemistry for the stereoselective synthesis of THC has not yet been reported (Scheme 1b). We herewith report a straightforward one-flow system to efficiently prepare both (–)-*trans*- Δ^8 - and Δ^9 -THCs using homogeneous and heterogeneous Lewis acids.

Results and discussion

Homogeneous flow synthesis of olivetylverbenyl and Δ^8 -THC

Inspired by the chiral pool approach of Mechoulam [16], which we initially used in a batch approach to make THC derivatives, we now set out to use this strategy in a one-flow system to synthesise (–)-*trans*- Δ^8 -THC [25, 26]. Since our group previously investigated such chiral pool approach [27], we were keen to implement the proven batch process into a continuous flow process. In line with our previous batch experiments we initially investigated the flow synthesis of thermodynamically favoured Δ^8 -THC using homogeneous Brønsted catalysts. More specifically, this involved the reaction of (–)-verbenol (**3**) and olivetol (**2**), which in a sequence of Brønsted acid-mediated Friedel-Crafts alkylation, rearrangement and cyclisation in a one-flow reactor afforded (–)-*trans*- Δ^8 -THC (**6**) via the intermediate product olivetylverbenyl (**5**). The setup consisted of syringe pumps, perfluoroalkoxy (PFA) tubing (OD 1/8", ID 1/16" or 1/25"), Super Flangeless fittings, while biphenyl was used as an

internal ^1H -NMR standard to allow reaction monitoring by NMR (see: Supporting information I).

The flow reactions with triflic acid (TfOH) gave promising results affording appreciable amounts of olivetylverbenyl (**5**) and THC product **6**. Unfortunately, the use of TfOH also resulted in the formation of a precipitate, which hampered the flow process (Table 1, entries 1–6). The insoluble precipitate was hypothesised to consist of PEEK polymers formed through degradation of the polymer by TfOH. In contrast, use of the homogeneous Lewis acid $\text{BF}_3\cdot\text{OEt}_2$ did not give precipitation, and showed similar yield. Surprised by the smaller residence time, using $\text{BF}_3\cdot\text{OEt}_2$ we were able to selectively tune the system to afford either more olivetylverbenyl (**5**) or (–)-*trans*- Δ^8 -THC (**6**, entries 7–9 and 14–18, respectively). After more extensive optimisation, we reached yields of up to 47% into olivetylverbenyl (**5**) or 45% into (–)-*trans*- Δ^8 -THC (**6**) (entries 8 and 15, respectively), which is in line with reported maximum yields in batch reactions [17, 28]. A further increase in yield could not be achieved, most likely due to side product formation (in particular olivetyldiverbenyl) and further degradation of (–)-verbenol [16, 29]. Purification of these complex mixtures was conducted using silica gel column chromatography and resulted also in partial recovery of olivetol, indicating that Friedel-Crafts alkylation did not go to completion.

Heterogeneous flow synthesis of CBD, Δ^8 - and Δ^9 -THC

Prompted by the results of homogeneous Lewis acids, we set out to investigate a variety of heterogeneous Lewis acids as well. While homogeneous catalysts are fast and effective on mmol laboratory scale, industry shows more interest in heterogeneous catalysts which generally reach higher turnover numbers and can be more easily recycled [30]. Our attention was drawn to metal-coordinated Amberlyst resins, which can be readily prepared and were shown to be effective in Lewis acid catalysis [31–33]. Six different Lewis acids were selected ($\text{Zn}(\text{OTf})_2$, $\text{Sn}(\text{OTf})_2$, $\text{Cu}(\text{OTf})_2$, $\text{Yb}(\text{OTf})_3$, $\text{Sc}(\text{OTf})_3$ and $\text{In}(\text{OTf})_3$) and immobilised on Amberlyst-15® (Scheme 2). Since $\text{BF}_3\cdot\text{OEt}_2$ appeared very effective under homogeneous reaction conditions, we also included silica-supported boron trifluoride (Silica- BF_3) and polyvinylpyrrolidone-supported boron trifluoride (PVP- BF_3) as heterogeneous catalysts.

The setup consisted of syringe pumps, perfluoroalkoxy (PFA) tubing (OD 1/8", ID 1/16" or 1/25"), Super Flangeless fittings and a Omnifit packed bed reactor (6.6 × 10 mm) (see: Supporting information II). We started the screening with commercially available DOWEX- H^+ and Amberlyst- H^+ in the synthesis of Δ^8 -THC. Only small amounts of olivetylverbenyl (**5**) were observed with DOWEX- H^+ , while Δ^8 -THC was not observed at all (Table 2, entry 1). Inversely, Amberlyst- H^+

Table 1 Homogeneous flow synthesis of olivetolverbenyl (**5**) and (–)-*trans*- Δ^8 -THC (**6**)

entry	Brønsted or Lewis acid (mol%)	t_R (s)	yield ^a (%)	
			olivetolverbenyl (5)	Δ^8 -THC (6)
1	TfOH (0.25)	30	41	9
2		60	26	11
3		240	8	17
4	TfOH (0.50)	30	25	11
5		60	30	17
6		240	6	41
7	BF ₃ ·OEt ₂ (0.10)	30	42	0
8		60	47	0
9		240	41	0
10	BF ₃ ·OEt ₂ (0.25)	30	37	11
11		60	30	15
12		240	7	32
13	BF ₃ ·OEt ₂ (0.50)	30	11	28
14		60	0	38
15		240	0	45
16	BF ₃ ·OEt ₂ (1.00)	30	0	41
17		60	0	41
18		240	0	40

Conditions: A stock solution of olivetol and (–)-verbenol (0.25 M) in DCM and a stock solution of Brønsted or Lewis acid (0.25 M) in DCM were pumped through a PFA reactor (200 μ L) and quenched directly using saturated aqueous NaHCO₃; ^a crude yield based on ¹H-NMR using biphenyl as internal standard

did provide small amounts of (–)-*trans*- Δ^8 -THC (**6**), but interestingly the intermediate product **5** was not observed (entry 2). We hypothesised that DOWEX-H⁺ was not efficient in Friedel-Crafts alkylation and cyclisation and Amberlyst not acidic enough to obtain higher yields of **6**. We then shifted our focus to the Lewis acidic Amberlyst-metal complexes and observed quantitative amounts of Friedel-Crafts product **5**, but no formation of (–)-*trans*- Δ^8 -THC (**6**, entries 3–8). The lack of (–)-*trans*- Δ^8 -THC (**6**) production was attributed to a lower Lewis acid strength compared to conventional BF₃·OEt₂ used for cannabinoid synthesis. In addition, all Amberlyst

resins gave poor dispersion of the reactants because of the resin particle size, which hampered the reproducibility and catalytic activity of the resins (see also: Supporting information II). To increase yields of the low reactive resins we decreased flow rates to 0.01 mL·min^{–1}, but did not obtain the desired tetrahydrocannabinols.

In an attempt to further raise the yields, we changed to the boron trifluoride resins, as the corresponding catalyst is known to be effective in homogeneous flow reactions [33–35]. Interestingly, while pumping the substrate solution through the reactor, a red colour was observed (see: supporting information II). We were delighted to see the formation of small amounts of (–)-*trans*- Δ^8 -THC (**6**) in the crude product, and also observed an increase in yield of **6** by increasing residence time (entries 9 and 10). The PVP-BF₃ resin resulted in a smaller amount of product, and showed faster

Scheme 2 The incorporation of metal triflate Lewis acids on Amberlyst-15®

Table 2 Screening of the heterogeneous catalysts for Δ^8 -THC (**6**) formation

entry	catalyst	yield ^a (%)			
		olivetylverbenyl (5)		Δ^8 -THC (6)	
	$t_R^c \rightarrow$	100 s	1000 s	100 s	1000 s
1	Dowex-H ⁺	17	21	0	0
2	Amberlyst-Zn	31	49	0	0
3	Amberlyst-Sn	43	51	0	0
4	Amberlyst-Cu	29	n.d. ^b	0	0
5	Amberlyst-Yb	31	61	0	0
6	Amberlyst-Sc	36	46	0	0
7	Amberlyst-In	41	55	0	0
8	Amberlyst-H ⁺	0	0	12	14
9	PVP-BF ₃	0	0	28	40
10	Silica-BF ₃	0	0	34	39

Conditions: a stock solution of olivetol and *p*-mentha-2,8-dien-1-ol (0.25 M) in DCM was pumped over a packed bed reactor filled with Lewis acid (approximately 500 mg resin); ^a crude yield based on ¹H-NMR using biphenyl as internal standard; ^b not determined; ^c residence time of 100 and 1000 s corresponds to a flow rate of respectively 0.10 and 0.01 mL·min⁻¹

loss of catalytic activity than the Si-BF₃ resin upon prolonged use (over 15 mL solution) [36–41].

Stimulated by this result, we aimed to prepare the synthetically more challenging cannabidiol (**7**) and (–)-*trans*- Δ^9 -THC (**8**) using Si-BF₃ as well. In batch chemistry, the formation of **8** is hard to optimise, since it readily isomerises to its thermodynamically more stable Δ^8 -isomer **6** [17, 26]. The application of this reaction in a one-flow system, however, allows for more precise control of reaction parameters, and is better suited for optimisation. The flow system yielding Si-BF₃ was applied to *p*-mentha-2,8-dien-1-ol (**4**) and olivetol to successfully afford (–)-*trans*- Δ^9 -THC with minimal amounts of Δ^8 -THC (Table 3) [17].

The flow reactor containing silica-supported boron trifluoride provided a variety of cannabinoid products and was successful in the Friedel-Crafts alkylation and cyclisation reaction. At high flow speeds, thus shorter residence times, mixtures of CBD (**7**) and Δ^9 -THC (**8**) were obtained (entries 1 and 2). In both entries, we did not observe transformation into the thermodynamic Δ^8 -THC isomer (**6**). Both CBD and Δ^9 -THC were isolated in small amounts after silica gel purification. The yield into Δ^9 -THC (**8**) was effectively increased by going to longer residence times, affording up to 40% of yield on NMR and 30% of isolated yield (entry 3). Although there was some isomerisation to the Δ^8 -THC isomer (**6**) visible in the crude NMR spectra, the 30% isolated yield ranks

among the highest yields reported for this one-pot multistep sequence into the Δ^9 -isomer [28]. In addition, this synthetic procedure is also scalable due to the continuous character of the reaction setup. Finally, a further increase in residence time afforded mixtures of CBD (**7**), Δ^9 -THC (**8**) and Δ^8 -THC (**6**) and did not provide any selectivity (entries 4 and 5).

Conclusion

In conclusion, we developed a synthetically versatile flow system to synthesise CBD, Δ^8 - and Δ^9 -THC in up to 45% yield. The studied cascade reaction was effective in homogeneous systems using BF₃OEt₂ or TfOH as the catalyst, but also in a heterogeneous setup using silica-supported boron trifluoride. In the search for heterogeneous solid-supported Lewis acids, we assessed a small variety of Amberlyst-metal complexes to conduct the final chemical transformations of the cascade reaction. The various flow conditions were evaluated using ¹H-NMR and internal standards and seemed to be experimentally feasible for the continuous flow production of cannabinoids. We envision that this hands-on flow system will be highly valuable for organic chemists aiming to prepare enantiopure CBD- and THC-like scaffolds using a chiral pool approach. A follow-up study to investigate the applicability of the system to a wider range of synthetic cannabinoid derivatives is currently ongoing in our laboratories.

Table 3 Heterogeneous flow synthesis of CBD (7) and (–)-*trans*- Δ^9 -THC (8)

entry	t_R (s) ^c	yield ^a (isolated)		
		CBD (7)	Δ^9 -THC (8)	Δ^8 -THC (6)
1	5	20 (12)	20 (8)	0
2	10	26 (12)	20 (14)	0
3	20	10 (7)	40 (30)	7 (n.i.) ^b
4	100	9 (2)	41 (19)	10 (10)
5	200	4 (n.i.) ^b	37 (14)	23 (27)

Conditions: a stock solution of olivetol and *p*-mentha-2,8-dien-1-ol (0.25 M) in DCM was pumped over a packed bed reactor filled with catalyst (500 mg silica-supported boron trifluoride) and quenched directly using saturated aqueous NaHCO₃ solution; ^a crude yield percentage (%) based on ¹H-NMR using biphenyl as internal standard; ^b not isolated; ^c residence time of 5, 10, 20, 100 and 200 s corresponds to flow rates of respectively 2.00, 1.00, 0.50, 0.10 and 0.05 mL·min⁻¹

Experimental section

General information

NMR spectra were recorded on a Bruker Avance III 400 MHz or a Bruker 500 MHz spectrometer and the compounds were assigned using ¹H NMR, ¹³C NMR, ¹¹B NMR, ¹⁹F NMR, COSY, HSQCED and HMBC spectra. Chemical shifts were reported in parts per million (ppm.) relative to reference (CDCl₃: ¹H: 7.26 ppm. and ¹³C 77.16 ppm.; CD₃OD: ¹H: 3.31 ppm. and ¹³C 49.00 ppm.; (CD₃)₂SO: ¹H: 2.50 ppm. and ¹³C 39.52 ppm.) NMR data are presented in the following way: chemical shift, multiplicity (s = singlet, bs = broad singlet, d = doublet, t = triplet, dd = doublet of doublets, ddd = doublet of doublet of doublets, dtd = doublet of triplet of doublets h = heptet, m = multiplet and/or multiple resonances) and coupling constants *J* in Hz. Reactions were monitored using TLC F₂₅₄ (Merck KGaA) using UV absorption detection (254 nm) and by spraying them with cerium ammonium molybdate stain (Hannesian's stain) followed by charring at ca 300 °C. Mass spectra were recorded on a JEOL AccuTOF CS JMS-T100CS (ESI) mass spectrometer. Melting points (m.p.) were determined using a Büchi Melting Point B-545. Automatic flash column chromatography was executed on a Biotage Isolera Spektra One using SNAP or Silicycle cartridges (Biotage, 30–100 µm, 60 Å) 4–50 g. Reactions under protective atmosphere were performed under positive Ar/N₂ flow in flame-dried flasks. Syringe pumps, Chemyx Fusion 100, were obtained from Chemyx. Flow chemistry equipment was obtained from Inacom instruments, Screening Devices and VWR Scientific. Perfluoroalkoxy (PFA) tubing (OD 1/16", ID 1/50"), Super flangeless fittings

(for 1/16"), Low-pressure PEEK T-pieces and crosses (1/4–28 thread, flat bottomed) were used to design homogeneous flow experiments. Heterogeneous experiments used same materials and utilised an adjustable Omnifit® glass reactor (ID 6.6 mm, length 1–50 mm, 006SCC-06-05-AA) (See also: Supporting information III).

Preparation of Amberlyst-metal catalysts

Amberlyst® 15 (hydrogen form, 1.00 g) was added in a polypropylene vessel with frit (25 mL) and mixed with saturated aqueous Na₂SO₄ solution (15 mL). The vessel was closed, mixed for 10 min, filtered using vacuum suction, and washed with saturated aqueous Na₂SO₄ solution (3 × 15 mL). The pH of the filtration was measured, and when the pH >6.0 the Amberlyst-Na was dried in a vacuum oven (50 °C) for 4 h. The obtained Amberlyst-Na was mixed with EtOH (20 mL), the metal triflate (1 mmol/g of resin) was added and the mixture was shaken overnight at r.t. The resin was filtered using vacuum suction, EtOH (20 mL) was added and shaken for 1 h at r.t. The resin was filtered using vacuum suction and finally dried in a vacuum oven (50 °C) for 4 h. to afford the Amberlyst-metal resin.

Preparation of PVP-BF₃

Polyvinylpyrrolidone (PVP, MW 40.000, 1.50 g) was added in a flask and stirred in dry DCM (15 mL). BF₃OEt₂ (2.88 g, 20.2 mmol, 2.50 mL) was dissolved in dry DCM (10 mL) and added to a dripping funnel. The BF₃OEt₂ solution was added dropwise to the PVP solution, and stirred for 1 h at r.t. The stirring bar was removed, and the suspension was filtered and

washed with DCM (2×25 mL) to afford a white powder. The white powder was dried overnight under high vacuum at r.t. to afford PVP-BF₃ resin which was used freshly within two weeks.

Preparation of Si-BF₃

Silica gel 60H (4.11 g, 68.4 mmol) was added in a flask which was evacuated and backfilled thrice with Ar. Dry MeOH (90 mL) was added, and the mixture was stirred to obtain a cloudy suspension. BF₃OEt₂ (58.1 mmol, 7.18 mL, 0.85 equiv) was added dropwise, and the mixture was stirred for 2 h at r.t. The stirring bar was removed, and the solvent carefully evaporated in vacuo to afford a white powder. The white powder was dried overnight under high vacuum at r.t. to afford Si-BF₃ resin which was used freshly within two weeks.

Homogeneous flow synthesis of cannabinoids

Olivetol (1 equiv), (–)-verbenol or *p*-mentha-2,8-dien-1-ol (1 equiv) and biphenyl (0.25 equiv, ¹H-NMR standard) were added in a flask which was evacuated and backfilled thrice with Ar. The reactants were dissolved in dry DCM at r.t. to obtain a 0.25 M reactant solution. Brønsted or Lewis acid (1 equiv) was added in a second flask, and dissolved in dry DCM at r.t. to obtain a 0.25 M catalyst solution. Both solutions were loaded in glass syringes, placed in syringe pumps and connected to a T-piece (PEEK). The PFA tubing reactor was connected to the T-piece and the syringe pumps were set to the according speed. At least ($1.5 \times t_R$) was waited for the system to equilibrate after which obtained samples could be obtained. The reactor outlet was led into a stirred solution of saturated aqueous NaHCO₃. The crude mixture was extracted with DCM, and the organic layers were combined, dried with MgSO₄, concentrated in vacuo and analysed directly. (See also: Supporting information IV).

Heterogeneous flow synthesis of cannabinoids

Olivetol (1 equiv), (–)-verbenol or *p*-mentha-2,8-dien-1-ol (1 equiv) and biphenyl (0.25 equiv, ¹H-NMR standard) were added in a flask which was evacuated and backfilled thrice with Ar. The reactants were dissolved in dry DCM at r.t. to obtain a 0.25 M reactant solution. The heterogeneous catalyst (approx. 150 mg) was added to an Omnifit glass reactor, packed tightly and closed. The reactant solution was loaded in a glass syringe, placed a syringe pump and directly connected to the Omnifit reactor. The pumps were set to the according speed, and the residence time was measured using a stopwatch. The flow speed was adjusted accordingly to obtain the desired residence time. The system was equilibrated for at least ($1.5 \times t_R$) after which samples were obtained. The reactor outlet was led into a stirred solution of saturated aqueous NaHCO₃. The crude mixture was extracted with DCM, and the organic layers were combined, dried with

MgSO₄, concentrated in vacuo and analysed directly. (See also: Supporting information V).

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Data availability The raw data will be accessible on the Radboud University depository.

Compliance with ethical standards

Conflicts of interest/competing interests There are no conflicts of interest.

Code availability Not applicable

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