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Communication

Abnormal Cannabinoids

Biomimetic Cannabinoid Synthesis Revisited: Batch and Flow All-Catalytic Synthesis of (±)-*ortho*-Tetrahydrocannabinols and Analogues from Natural Feedstocks

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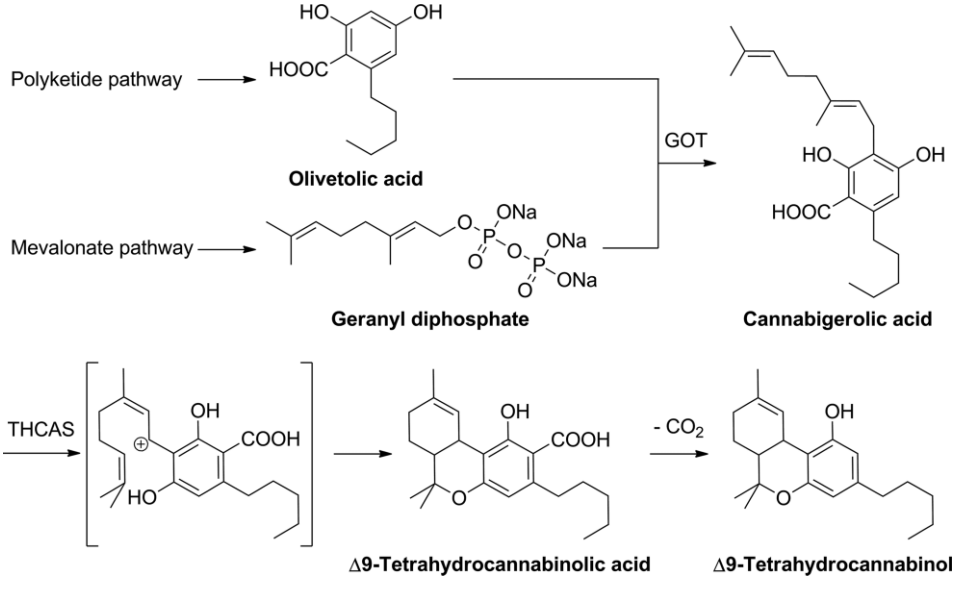
Abstract: Using a combination of Au nanoparticle-catalyzed oxidation under an O_2 atmosphere and a Ti-doped montmorillonite (Ti-MMT)-catalyzed tandem arylation/double cyclization, we developed an original and highly selective method for the synthesis of *ortho*-tetrahydrocannabinol derivatives from simple substrates. The reaction sequence could be performed in two steps in batch mode or in a single operation in continuous-flow reactors. The abnormal regioselectivity was proposed to be the result of the non-innocent role of the MMT support, Ti^{IV} cation coordination, and a Lewis acid-assisted Brønsted acid (LBA) mechanism.

Introduction

In the most recent studies of natural cannabinoid biosynthesis in *Cannabis sativa*, olivetolic acid, arising from a polyketide pathway by the action of an olivetolic acid cyclase (OAC),[1] is combined with geranyl diphosphate (from mevalonate or methylerythritol)[2] to yield cannabigerolic acid.[3] The latter is then oxidized and cyclized by tetrahydrocannabinolic acid (THCA) synthase, an oxidoreductase, to form tetrahydrocannabinolic acid, which upon decarboxylation leads to the formation of tetrahydrocannabinol (THC) (Scheme 1).[4]

The most common natural product with this structure features a double bond connecting carbon atoms 8 and 9 or carbon atoms 9 and 10 (following the dibenzopyran numbering system) and two vicinal asymmetric carbon atoms in either a *trans* or *cis* relative configuration. From a historical perspective, the first reported synthesis of THCs followed a biomimetic route, using olivetol and citral (mixture of neral, *Z*, and geranial, *E*, isomers) as substrates, in which citral offered the required oxidation state. A series of papers described the use of $BF_3{\cdot}OEt_2$,



Scheme 1. Biosynthesis of tetrahydrocannabinol. GOT: geranyl-pyrophosphate-olivetolic acid geranyltransferase; THCAS: tetrahydrocannabinolic acid synthase.

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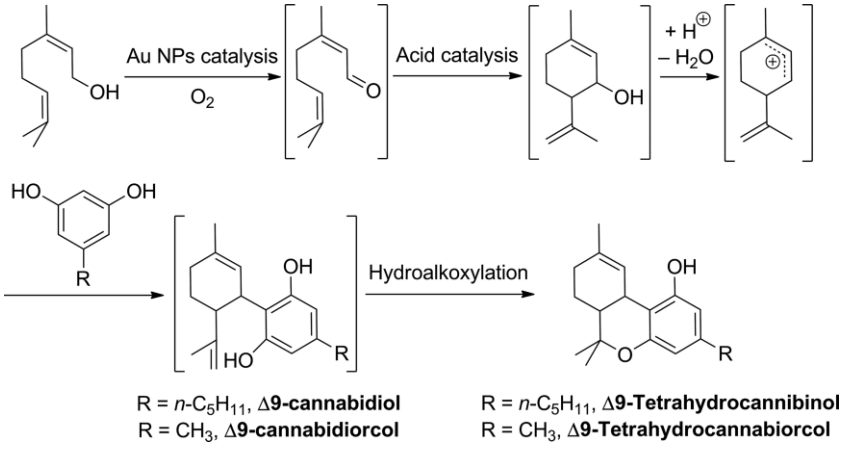


Scheme 2. Synthetic plan for a direct multicatalytic approach to THC derivatives.

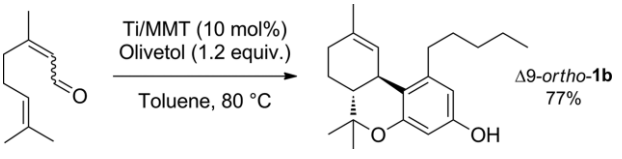
mineral acid,[5] and Mo complexes[6] to assemble these two substrates or the use of pyridine to shift the reactivity towards the formation of isomeric cannabichromene (upon hydroalkoxylation of the C2–C3 double bond of the terpenyl side chain).[7] This low-yielding and moderately selective route was abandoned in favor of a multistep synthesis involving terpenoids such as (–)-verbenol, (+)-chrysanthenol, *para*-mentha-2,8-dien-1-ol, and (+)-carene oxide, which could yield enantioenriched products.[8] Recently, iterative strategies were devised to construct the target molecule by using Diels–Alder cycloaddition as the key step[9] or in an enantioselective fashion by stereodivergent allylation of aliphatic aldehyde[10] or stereospecific decarboxylative arylation.[10] Interestingly, regioisomers featuring inversion on the benzene ring between the alkyl chain and the hydroxy group, that is, *ortho*-THCs, were sometimes described and were considered to be minor secondary products of synthetic reactions.[11] To our best knowledge, there are no reports in the literature describing selective access to these *ortho* products. At the same time, growing interest in natural and synthetic cannabinoids has been observed owing to the various promising biological activities and the need for molecules that are selective for cannabinoid receptor 2 (CB2) over CB1.[12]

We recently became interested in developing multicatalytic reactions triggered by the catalytic oxidation of activated alcohols by Au nanoparticles (NPs).[13] In particular, we devised a bicatalytic one-pot synthesis of substituted chromenes by the assembly of nerol and salicylaldehyde in the presence of K_2CO_3 following an oxidation/oxa-Michael addition/intramolecular aldolization/crotonization sequence.[14] We reasoned that by switching to acid catalysis in the second step instead of base catalysis we could catalyze an intramolecular carbonyl-ene reaction, which, after protonation/dehydration, could potentially lead to an allylic cation that acts as an electrophile and could be further combined with 5-alkylresorcinols such as olivetol to yield THCs (Scheme 2).

Results and Discussion

We screened a series of Lewis and Brønsted acids in a test reaction with citral and orcinol (5-methylresorcinol), thereby focusing on the second step. The acids screened included Lewis acids such as $ZnBr_2$, $Ti(OiPr)_4$, and $TiCl_4$; solid catalysts such as Amberlyst and zeolite; and montmorillonite-doped with metal cations (M-MMT), a type of solid catalyst that we recently used as a Lewis acid in C–O and C–C bond-forming processes.[15] The most interesting results are summarized in Table 1 (see Supporting Information for additional examples). Indeed, conventional Lewis acids delivered mixtures containing Δ9- and Δ8-**1a**, generally in low yields (Table 1, entries 1–4), and *para*-cymene upon intramolecular carbonyl-ene reaction of citral followed by dehydration. However, the use of M-MMT enabled the relatively selective formation of *ortho*-**1a**, which is usually referred to as an "abnormal" derivative in the chemistry of natural cannabinoids.

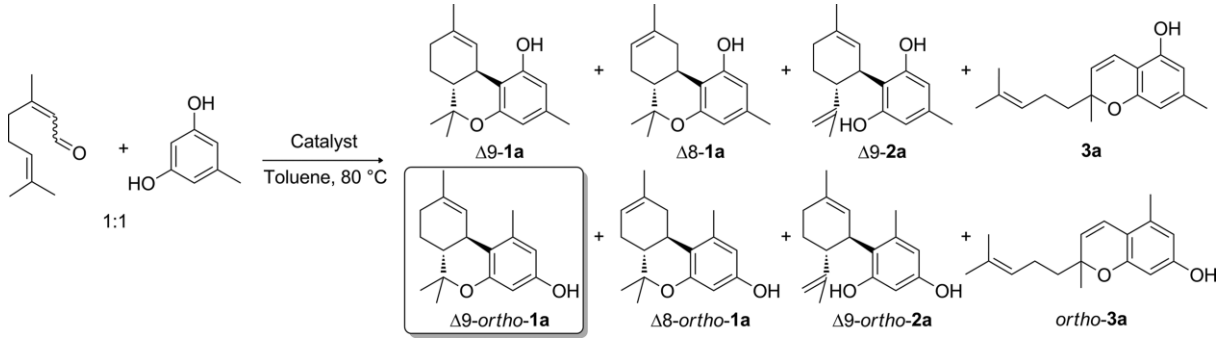
Under the optimized conditions with the use of Ti-MMT as the catalyst (10 mol-%), *ortho*-**1a** was obtained in up to 98 % yield as a 83:17 mixture of the Δ9 and Δ8 isomers (Table 1, entry 13). The *cis*/*trans* ratio was found to be 2:8 in most cases. This result was rather unexpected, as these compounds were typically observed as side products in various syntheses of natural cannabinoids. Under the same reaction conditions but with the use of olivetol instead of orcinol, Δ9-*ortho*-**1b** (Δ9-*ortho*-THC) was obtained in 77 % yield (Scheme 3).



Scheme 3. Formation of the *ortho* analogue of pharmacologically relevant Δ9-THC.

We next focused on the cascade of reactions leading to the formation of the Δ9- and Δ8-*ortho*-products. Given that the formation of small amounts of *para*-cymene was sometimes observed during catalyst screening, we reasoned that the sequence could start with the monomolecular carbonyl-ene reaction of citral leading to isopiperitenol isomers. The latter could lead to *para*-cymene by dehydration and isomerization of the isoprenyl double bond to form a more stable aromatic structure. However, several attempts to observe (by GC–MS) or to

Table 1. Screening of acid catalysts for the reaction of citral (*E*/*Z* = 1:1) with orcinol.[a]

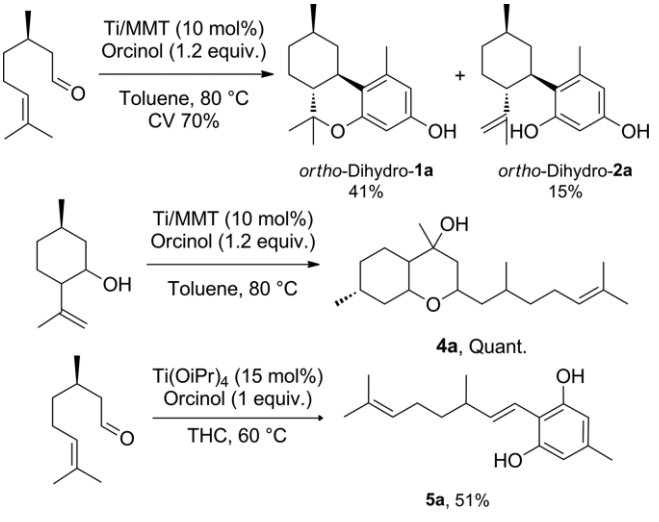


Entry	Catalyst[b]	Time [h]	CV[c] [%]	Yield[c] [%]						
				Δ9-**1a**	Δ9-**2a**	Δ8-**1a**	Δ9-*ortho*-**1a**	Δ9-*ortho*-**2a**	Δ8-*ortho*-**1a**	**3a**/*ortho*-**3a**
1	$ZnBr_2$ (1 equiv.)	8	0	0	0	0	0		0	0
2	$Ti(OiPr)_4$ (15 mol-%)	8	86[d]	10	0	0	0	0	0	31:10
3	BF_3·OEt_2 (10 mol-%)	2	100	38	0	38	0	0	0	12:0
4	$Bi(OTf)_3$ (10 mol-%)	2	100	18	0	36	0	0	21	0
5	TiO_2 (10 mol-%)[e]	8	100[d]	17	0	0	13	5	9	32:5
6	$TiCl_4$ (10 mol-%) Na-MMT (100 mg)	2	100[d]	0	0	0	0	0	0	0
7	zeolite (75 mg)	8	5	0	0	0	0	0	3	2:0
8	Li-MMT (100 mg)	24	11	0	0	0	5	2	0	2:0
9	$TiCl_4$ (10 mol-%)	8	100[d,f]	0	0	0	15	0	6	11:3
10	$TiCl_4$ (10 mol-%) Li-MMT (100 mg)	2	100[d]	0	0	0	8	0	19	0
11	Ge-MMT (10 mol-%)	2	100[d]	0	0	0	6	0	34	0
12	Sn-MMT (10 mol-%)	72	58	0	0	0	19	10	19	5:5
13	Ti-MMT (10 mol-%)	2	100	0	0	0	81[g]	n.d.	17	0

[a] Reaction conditions: citral (1 mmol), orcinol (1 mmol), toluene (2 mL), 80 °C, air, 180 min. [b] For metal-based catalysts, catalyst ratio is related to the metal. [c] Conversion (CV) and selectivity were determined by ^{1}H NMR spectroscopy analysis of the crude product isolated after workup; both *cis* and *trans* diastereomers were formed for **1a** and **2a**, typically in a 2:8 ratio; n.d.: not determined. [d] Paracymene was formed upon the intramolecular carbonyl-ene reaction of citral and dehydration in the reaction medium. [e] Peptized solution. [f] Degradation occurred. [g] Mixture of *trans* and *cis* diastereomers in a 78:22 ratio (see the Supporting Information for full NMR spectroscopy experiments, including the NOE spectrum).

trap the isopiperitenol intermediate were unsuccessful. Considering that the conversion of isopiperitenol into *para*-cymene could be too fast, we turned our attention to (*R*)-citronellal in lieu of citral to prevent conversion into stable benzene structures by isomerization. Indeed, in the presence of Ti-MMT, citronellal was converted into a carbonyl-ene product of citronellal, isopulegol, as the major product. Upon performing the reaction with citronellal and orcinol, under our optimized conditions with Ti-MMT, the reaction followed the expected path and delivered *ortho*-hexahydrocannabiorcol *ortho*-dihydro-**1a** in 41 % yield together with a small amount of corresponding alkylated orcinol *ortho*-dihydro-**2a** from the uncomplete reaction (Scheme 4, top). However, with isopulegol as the starting material and in the presence of orcinol, a different outcome was observed after 2 h with quantitative formation of product **4a**, a class of products not previously observed during our investigations (Scheme 4, middle). This product would be formed by a retro-carbonyl-ene process followed by the formation of the 4-hydroxytetrahydropyrane core by reaction with isopulegol.

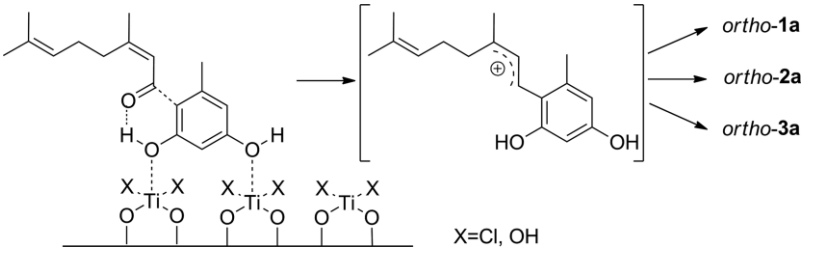
This set of results suggested that an initial carbonyl-ene reaction was not the most critical event in the formation of *ortho*-THC derivatives. To investigate this idea further and to substitute Ti-MMT with a less-efficient catalytic system, citronellal was



Scheme 4. Mechanistic investigations with (*R*)-citronellal and isopulegol.

submitted to the reaction with $Ti(OiPr)_4$ in THF at 60 °C. In this case, styrenyl derivative **5a** was obtained in 51 % yield as the sole product after 2 h (Scheme 4, bottom).

This result suggested an alternative reaction pathway, by which the starting event would be the arylation of the aldehyde



Scheme 5. Putative template effect of Ti-MMT, LBA mode of activation, and subsequent regioselectivity of nucleophilic attack of the arene towards citral in an aldol-Friedel–Crafts-type reaction.

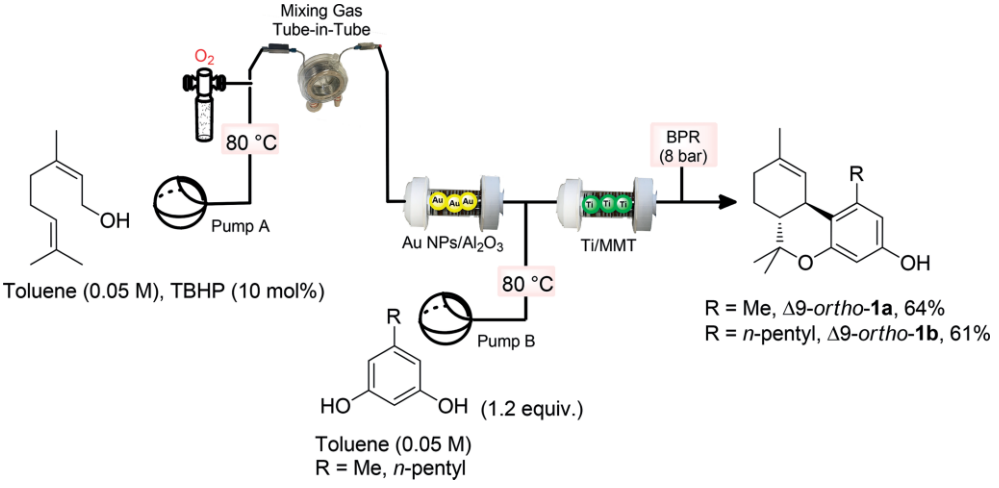


Figure 1. Continuous-flow chemistry setup for the synthesis of *ortho*-THCs. TBHP: *tert*-butyl hydroperoxide, BPR: back-pressure regulator.

function by orcinol, followed by dehydration. Starting from citral, this key intermediate could explain the reactivity observed during screening experiments, including the formation of the corresponding quinone methide intermediate, which is sometimes proposed as an intermediate in the synthesis of THC and its analogues by 6π electrocyclization.[16]

Several attempts to trap a putative quinone methide intermediate by conjugate addition of nucleophiles (*n*PrSH, $BnCH_2SH$, diethyl malonate, allyltrimethylsilane) or by blocking the phenolic group (CH_3COCl, TMSCl, vinyl acetate) were unsuccessful. Attempts to prepare deuterated orcinol in D_2O and in MeOD resulted in the formation of isotopomer mixtures as a result of a high degree of scrambling (mostly on the OH and CH_3 groups).

A series of experiments were then undertaken to gain a better understanding of the regioselectivity of the reaction. First, the role of the hydroxy groups of orcinol was evaluated. Citral was thus treated with modified alkyl resorcinols in the presence of Ti-MMT (10 mol-%) under our optimized conditions. Interestingly, blockage of both hydroxy groups by methylation or acetylation resulted in complete inhibition of the arylation reaction and recovery of unchanged citral. Surprisingly, blockage of a single hydroxy group also completely inhibited the reaction.

On the basis of these observations and taking the regioselectivity in favor of the *ortho* isomers of THC into consideration, we reasoned that Ti-MMT could influence the selectivity through a template effect, by which both hydroxy groups would coordinate to the interlamellar surface, combined with a Lewis acid assisted Brønsted acid process allowed by Ti species. Coordination of the OH groups to Ti^{IV} would indeed result in acidification of the bound hydrogen atom, which would be further transferred to the carbonyl group of citral. Nucleophilic attack of the arene would thus proceed through the most accessible position, that is, the *ortho* position relative to the alkyl substituent (Scheme 5).

Given our interest in the design of multicatalytic chemical processes,[14] we performed a preliminary series of tests to combine the Au NP-catalyzed oxidation of allylic alcohols, such as nerol and geraniol,[13] with the Ti-MMT-catalyzed cyclization described herein in the same reactor. Unfortunately, the catalysts were not compatible under our conditions, and the oxidation step was quenched in the presence of Ti-MMT. We thus moved towards continuous-flow chemistry reactors.

The first stage of the batch→flow transposition was optimization of the Ti-MMT-catalyzed step in flow. At 0.05 M and on a 4 mmol scale, a citral conversion of 100 % and 98 % yield of the cyclized products (Δ9-*ortho*-**1a**, 17 %; Δ8-*ortho*-**1a**, 72 %; and Δ9-*ortho*-**2a**, 9 %) were obtained with a column containing 400 mg of Ti-MMT within a 5 min residence time. With the implementation of a second catalytic column filled with Au NPs/Al_2O_3 (1 g) and using the tube-in-tube technology for efficient O_2 supply, the flow synthesis of *ortho*-THC and analogues was possible from nerol (2.5 mmol scale) and enabled total conversion and the formation of *ortho*-**1a** (Δ8/Δ9 = 1:3.5) and *ortho*-**1b** (Δ8/Δ9 = 1:6) in yields of 81 and 72 % from orcinol and olivetol, respectively (Figure 1).

The change in Δ8/Δ9 selectivity was attributed to a chromatographic effect, as Ti-MMT was charged with only 250 mg in this case. The Δ9/Δ8 isomerization, which is known to be a thermal phenomenon, was observed upon using an 8:2 mixture of Δ9-*ortho*-**1a**/Δ8-*ortho*-**1a** under our reaction conditions over 2 h, leading to a 6:4 mixture.

Conclusions

In conclusion, we found an efficient, selective, and straightforward method to form *ortho*-THC derivatives by combining two catalytic steps. In the future, these structures could serve in the design of novel bioactive molecules for cannabinoid research. Current pharmacological interest in this field focuses on drug candidates with a weak affinity for CB1 and a high affinity for CB2. The former is indeed believed to be involved in the psychoactive characteristics of THC derivatives, whereas the latter is associated with analgesic properties. The phenol hydroxy group was long ago identified as a mandatory structural requirement for the biological activity of THC.[17] Recent structure–activity studies and crystallographic analysis of Δ9-**1a** showed the importance of the phenol group in hydrogen bonding with a serine residue of the CB1 pocket.[18] However, additional studies on CB2 also showed that the absence of this phenol hydroxy group improved CB2/CB1 selectivity.[19] With the efficient production of *ortho*-THC derivatives presented herein, a new subclass of drug candidates with high CB2 selectivity could be envisaged. Moreover, given the current renewed interest in natural cannabinoids, this method for the production of original cannabinoid structures will be useful in the increasing number of pharmacological studies for a broad range of diseases.[12c,12d,12f]

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Keywords: Cannabinoids · Supported catalysts · Flow chemistry · Gold · Nanoparticles

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