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One-step, stereoselective synthesis of octahydrochromanes *via* the Prins reaction and their cannabinoid activities

Shuneize Slater [a], Pradeep B. Lasonkar [a], Saqlain Haider [a], Moneerah J. Alqahtani [b], Amar G. Chittiboyina [a,*], Ikhlas A. Khan [a,b]

[a] National Center for Natural Products Research, School of Pharmacy, The University of Mississippi, University, MS 38677, USA
[b] Division of Pharmacognosy, Department of BioMolecular Sciences, School of Pharmacy, The University of Mississippi, University, MS 38677, USA

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ABSTRACT

Novel, functionalized octahydrochromane derivatives were synthesized in a single step *via* the Prins reaction. Enantiomerically pure (+)-isopulegol was reacted with benzaldehyde to stereoselectively yield the corresponding octahydro-2*H*-chromen-4-ol derivative containing five stereocenters. A total of 10 compounds were synthesized by altering the enantiomer of isopulegol and the substituted benzaldehyde, and the resulting enantiopure octahydrochromanes were screened *in vitro* against the cannabinoid receptor isoforms CB1 and CB2. Compounds containing an olefin at the C4 position [(+)-**3c**, (−)-**3c**, (−)-**7c**, (−)-**9c** and (−)-**11c**] of the octahydrochromane scaffold were found to exhibit reasonable displacement of [^{3}H] CP55,940 from the CB receptors, whereas the corresponding hydroxy analogs [(+)-**3a**, (+)-**3b**, (−)-**3a**, (−)-**3b** and (+)-**5a**] had very little or no effect.

Introduction

The cannabinoid receptors, CB1 and CB2, comprise part of the endocannabinoid system (ECS) along with their endogenous ligands and their related enzymes and transporters. This system is involved in many human diseases and may provide potential targets in drug development.[1] Various research groups have reported that cannabinoid receptors are overexpressed in different cancers and that cannabinoids are able to reduce tumor growth and progression by modulating cancer cell proliferation, tumor angiogenesis, and metastasis.[2,3] CB1 receptors are mainly located in the central nervous system (CNS) with low expression in the periphery, and have been shown to protect the brain and spinal neurons from excitotoxic damage,[4] relieve gastrointestinal (GI) symptoms,[5] and participate in numerous other important functions. CB2 receptors are localized on immune cells and participate in the immunosuppressive and antinociceptive effects of the cannabinoids.[6]

Plant-derived cannabinoids, or phytocannabinoids, have emerged as a major class of compounds with therapeutic potential. Cannabis has been used medicinally for the treatment of neurological disorders such as epilepsy.[7] Cannabidiol **1a** (CBD, Fig. 1), is one of the major non-psychoactive components of *Cannabis sativa* and *Cannabis indica* and has been proposed to possess anticonvulsive, neuroprotective, and anti-inflammatory properties in humans, and thus is protective against epilepsy, anxiety, psychosis, and other CNS disorders.[8]

Cannabidiol **1a** and tetrahydrocannabinol **1b** (THC) are tetrahydrocannabinoids that differ only by the formation of a carbon-oxygen bond in THC to form a pyran ring (Fig. 1). The machaeriols **1c** are another class of compounds that are structurally similar to THC; however, the ring junction stereochemistry is inverted with an additional stereocenter in the A-ring at the C9 position (Fig. 1). Machaeriols are therefore not tetrahydrocannabinoids, but are instead hexahydrocannabinoids. The inversion of stereochemistry at these centers produce different biological properties than those observed with THC. Hexahydrocannabinol analogs, such as LYR-8 **1d** (Fig. 1), are cannabinoid-like compounds with high similarity to the machaeriols which possess little affinity for the CB1 and CB2 receptors, yet directly inhibit the growth of cancer cells, induce apoptosis of cancer cells, and inhibit endothelial cell proliferation and angiogenesis.[9] Recently, Volcho[10] and co-workers reported the highly potent analgesic activity of several octahydro-2*H*-chromen-4-ols derived from isopulegol. The resulting octahydrochromenol product of thiophene-2-carbaldehyde, isopulegol, exhibited analgesic activity in the acetic acid-induced writhing test as well as the hotplate test without any apparent acute toxicity.

Synthetically, these compounds have been prepared using one-step transformations. For example, tetrahydrocannabinoid compounds have been stereoselectively synthesized *via* boron

* Corresponding author.
E-mail address: amar@olemiss.edu (A.G. Chittiboyina).

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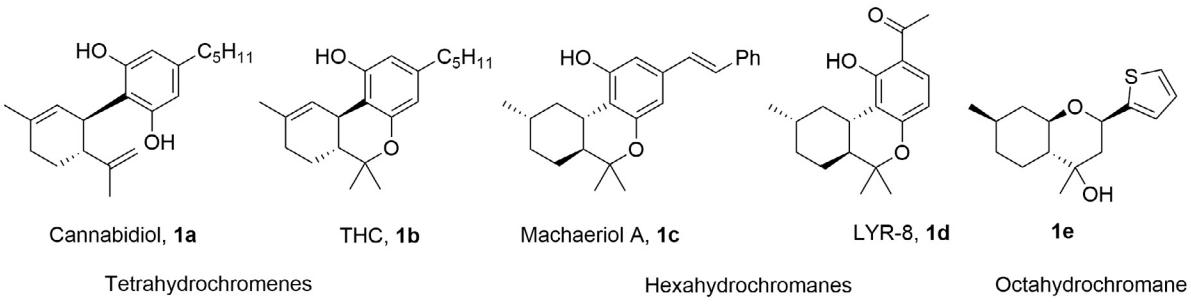
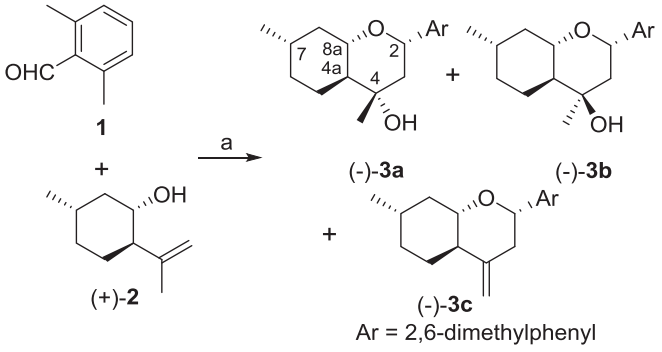


Fig. 1. Selected biologically active compounds based on a chromane scaffold – cannabinoids, machaeriols and octahydrochromanes.

trifluoride catalyzed arylation of a homocuprate,[11] whereas hexahydrochromanes were prepared *via* hetero Diels-Alder cycloaddition.[12] Octahydrochromenols were previously synthesized *via* the Prins reaction of homoallylic alcohols with substituted aryl aldehydes. Lewis acids such as $Sc(OTf)_3$[13] or Montmorillonite K10[14] with and without *p*-TSA[10] were employed to produce octahydrochromanes compounds; however, little information regarding the stereoselectivity and chirality of the homoallylic alcohols was reported.

Keeping in mind the structural similarity between the machaeriols and the octahydrochromanes, herein we report the one-step synthesis of ten novel octahydrochromanes derivatives using a stereoselective Prins cyclization as well as their biological activities against cannabinoid receptors.



Scheme 1. Chiral pool approach for construction of the octahydrochromane scaffold. *Reagents and conditions*: a). $BF_3{\cdot}OEt_2$ (0.05 equiv.), CH_2Cl_2, −40 °C to rt, 6 h, 72%, (**3a**:**3b**:**3c** = 3:1:2).

Results and discussion

Compounds containing a tetrahydropyran moiety are widely used as precursors for the synthesis of biologically active compounds and can be synthesized using the Prins reaction.[15] The acid-catalyzed Prins reaction of pulegols with various aldehydes containing electron-donating and electron-withdrawing substituents is often used for the synthesis of biologically active octahydro-2*H*-chromen-4-ols.[16]

Starting from (+)-isopulegol, (+)-**2**, Prins cyclization with 2,6-dimethylbenzaldehyde (**1**) in the presence of a Lewis acid, resulted in the formation of one major (−)-**3a** and two minor compounds (−)-**3b**,**c** (Scheme 1). Several Lewis acids were screened, including metal triflates, and boron trifluoride diethyl etherate (0.05 equiv.) was found to be superior for this transformation. The stereochemistry of the major compound was determined by 2D-NMR and

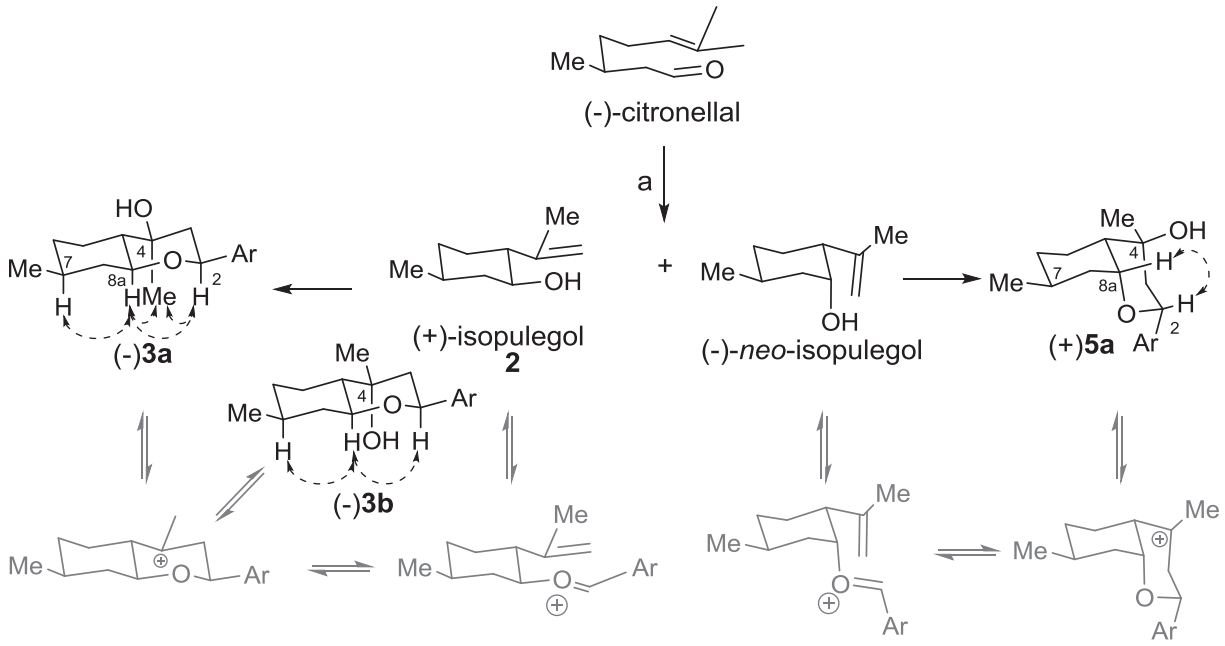


Fig. 2. One-pot ene, Prins reactions of (−)-citronellal with 2,6-dimethylbenzaldehyde and the formation of octahydrochromanes. Key NOE interactions are indicated by dotted arrows. *Reagents and conditions*: a). $BF_3{\cdot}OEt_2$ (0.2 equiv.), CH_2Cl_2, −40 °C to rt, 4.5 h, 48%, (**3a**:**3b**:**5a** = 3.1:1:1.2).

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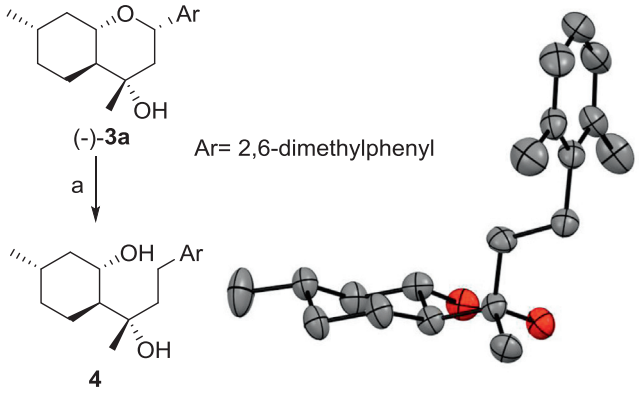
NOESY experiments. Strong NOE correlations were observed between H8a and H7 as well as H8a and H2, suggesting that H8a, H7 and H2 were in the *syn*-configuration. The *syn*-selectivity in the newly formed pyran ring can be envisioned as proceeding *via* formation of an oxonium ion with an aryl group occupying the equatorial position, thus both H8a and H2 are situated in the less hindered axial positions (Fig. 2). The minor compounds (−)-**3b** and (−)-**3c** also exhibited similar correlations, indicating the conserved stereo-preference at the newly created centers. Strong NOE correlations between H8a/H2 and the 4-CH_3 group further confirmed the selectivity as the *S*-configuration for the major compound, chromanol **3a**. Compound (−)-**3c** may either result from the dehydration of **3a**,**b** or be derived from competitive proton elimination of the resulting tertiary carbocation formed after initial cyclization (Fig. 2).

The formation of **4** from (−)-**3a** *via* metal ammonia mediated chemo- and regio-selective hydrogenolysis[17,18] (Scheme 2) further corroborated the observed stereo-preferences in the Prins reaction of benzaldehyde and (+)-isopulegol as (1*S*,3*S*,6*S*,7*S*,9*S*)-octahydro chromanol.[19]

The isopulegols are intramolecular products of the ene reaction of citronellal. In order to assess the feasibility of a one-pot ene, Prins reactions, (−)-citronellal was subjected to the above reaction



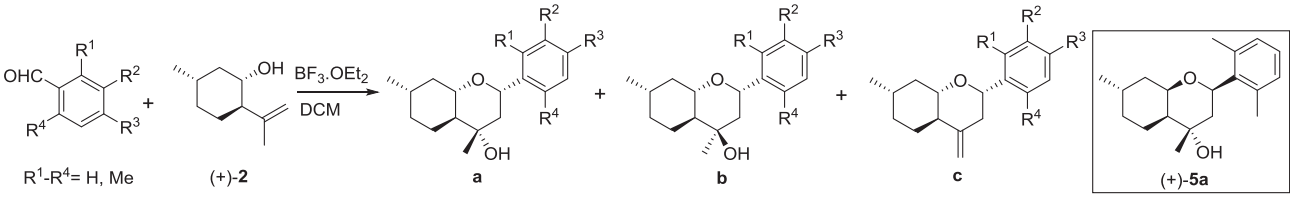
Scheme 2. Confirmation of chirality at the newly created centers. Single crystal X-ray structure of **4** with hydrogens omitted for clarity. *Reagents and conditions*: a). Na/NH_3 (excess), −78 °C, 2 h, 86%.

conditions in the presence of **1**. Three major isolable compounds were formed and their structures were confirmed as (−)-**3a**, (−)-**3b** and (+)-**5a** (Table 1, entry 3). Again, *syn*-selectivity at C8a and C2 was observed for all three compounds, with (−)-**3a** formed as the major component (Fig. 2). The distribution of these compounds are in agreement with reported literature regarding the cyclization of (−)-citronellal to (+)-isopulegol and (−)-neoisopulegol (3:1 ratio).[20] For compound (+)-**5a**, the stereochemistry was determined on the basis of NOESY correlations, wherein H8a and H2 are in the *syn*-configuration and the *S*-configuration at C4 was established on the basis of the lack of NOE correlations between H8a/H2 and the 4-CH_3 group (Fig. 2). The reaction of (−)-**2** with **1**, resulted in the formation of (+)-**3a**–**c** (Table 1, entry 2) while the treatment of (+)-isopulegol with 2,3-, 2,4-dimethyl benzaldehydes, and 2,3,6-trimethyl benzaldehyde with 0.2 equivalents of the Lewis acid for an extended time gave the dehydrated products, octahydrochromanes (−)-**7c**, (−)-**9c** and (−)-**11c**, respectively, as the major compounds (Table 1, entries 4–6). Trimethyl benzaldehyde was prepared from 3,6-dimethyl salicylaldehyde, which was subjected to triflation using *N*-phenyl-bis(trifluoromethanesulfonimide) followed by a Pd(0) catalyzed Suzuki coupling reaction with methyl boronic acid.[21]

All ten compounds were tested for cannabinoid activity with CB1 and/or CB2 receptors.[22] As shown in Table 2, the initial testing of (−)-**3a–c** against CB1 and CB2 receptors showed that octahydrochromane (−)-**3c**, containing an olefin at the C-4 position, was marginally active whereas both chromanols (−)-**3b** and (−)-**3a**, were inactive. Similarly, compound (+)-**5a**, the product of the one-pot ene, Prins reaction of citronellal, was also inactive. Upon switching to the antipode (−)-pulegol (−)-**2**, compound (+)-**3c** was found to possess higher percent displacement of the radio ligand compared to the corresponding C-4 hydroxy analogs (+)-**3b** and (+)-**3a**. The marginally greater activity of these chromenes over chromanols stimulated the synthesis of additional chromene analogs from 2,3-dimethyl (**6**), 2,4-dimethyl (**8**), and 2,3,6-trimethyl benzaldehydes (**10**). No significant difference in CB1 selectivity for 2,3- and 2.6-disubstituted chromenes were observed; however, compound (−)-**9c** with *para*-substitution showed increased % displacement for the CB2 isoform.

Interestingly, compound (−)-**11c**, which is the only compound with 3 methyl groups on the aromatic ring, has high% displacement for CB2 receptors (74.9%) but little affinity towards the CB1 iso-

Table 1
Substrate scope.



Entry	Reactants (ArCHO, monoterpene)		$BF_3{\cdot}OEt_2$			Product yield (%)		
			Equiv.	Temp.	Time			
1	R^1,R^4 = Me; R^2,R^3 = H; 1	(+)-2	0.05	−40 °C to rt	6 h	(−)-3a (36%)	(−)-3b (12%)	(−)-3c (24%)
2	R^1,R^4 = Me; R^2,R^3 = H; 1	(−)-2	0.05	−40 °C to rt	6 h	(+)-3a (34%)	(+)-3b (11%)	(+)-3c (20%)
3	R^1,R^4 = Me; R^2,R^3 = H; 1	(−)-citronellal	0.2	−40 °C to rt	4.5 h	(−)-3a (28%)	(−)-3b (9%)	(+)-5a (11%)
4	R^1,R^2 = Me; R^3,R^4 = H; 6	(+)-2	0.2	0 °C	12 h			(−)-7c (58%)
5	R^1,R^3 = Me; R^2,R^4 = H; 8	(+)-2	0.2	0 °C	12 h			(−)-9c (55%)
6	R^1,R^2,R^4 = Me; R^3 = H; 10	(+)-2	0.2	0 °C	12 h			(−)-11c (62%)

Table 2
CB1 and CB2 percent displacement data for octahydrochromanes and chromenes.

Compound	CB1 Receptor			CB2 Receptor		
	Dp*	Ki (μM) ± SEM	IC_{50} (μM)	Dp*	Ki (μM)±SEM	IC_{50} (μM)
(−)-**3c**	n.a.			49.4		
(−)-**3b**	n.a.			8.1		
(−)-**3a**	n.a.			n.a.		
(+)-**3c**	n.a.			68.5		
(+)-**3b**	28.5			13.8		
(+)-**3a**	n.a.			8.1		
(+)-**5a**	n.a.			n.a.		
(−)-**7c**	18.6			71.9		
(−)-**9c**	59.2			77.6	>1.905 ± 0.38	3.81
(−)-**11c**	16.6			74.9	>0.257 ± 0.07	0.514
CP-55,940		0.001	0.002		0.0018	0.0036

Dp* percent displacement; n.a. not active. Compounds with ≥75% of Dp were assessed for Ki and IC_{50}.

form. Several of these compounds were found to be incompatible with the assay conditions due to their hydrophobicity, in such cases, additional DMSO (0.1–0.2%) was added to the media to overcome solubility and without deleterious effects on the assay protocol and outcome.

Since the tetrahydrocannabinoid cannabidiol and the hexahydrocannabinoid machaeriols are reported to possess anti-cancer activity, selected octahydrochromanes and chromenes were submitted to the NCI's 60-cell line screening program. Unfortunately, none of the compounds inhibited the growth of the examined cancer cells by a reasonable amount in spite of their marginal cannabinoid activities.

Conclusion

In summary, chiral pulegols and various benzaldehydes were utilized in the Prins reaction to produce octahydrochromane compounds. The importance of the stereocenter configurations for biological activity was tested, and it was determined that the stereochemistry is not a factor in the activity of these compounds. However, the number and positions of the substituents on the aromatic ring may play a role in their activity. Determining SAR from this limited set of compounds is premature and is not the focus of the current findings. However, a focused set of compounds with better hydrophilicity will be explored to overcome solubility issues associated with these octahydrochromanes. Importantly, these one-pot reactions may serve as a starting point for new scaffolds with CB1 and/or CB2 selective agonist and antagonist activities which can be explored by varying the homoallylic alcohols and aldehydes used.

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A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.tetlet.2018.01.040.

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