Tetrahedron Letters 59 (2018) 807–810

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

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

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ARTICLE INFO

Article history:
Received 9 November 2017
Revised 5 January 2018
Accepted 16 January 2018
Available online 31 January 2018

Keywords:
Octahydrochromane
Prins cyclization
Enantioselectivity
Cannabinoid receptors

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

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https://doi.org/10.1016/j.tetlet.2018.01.040
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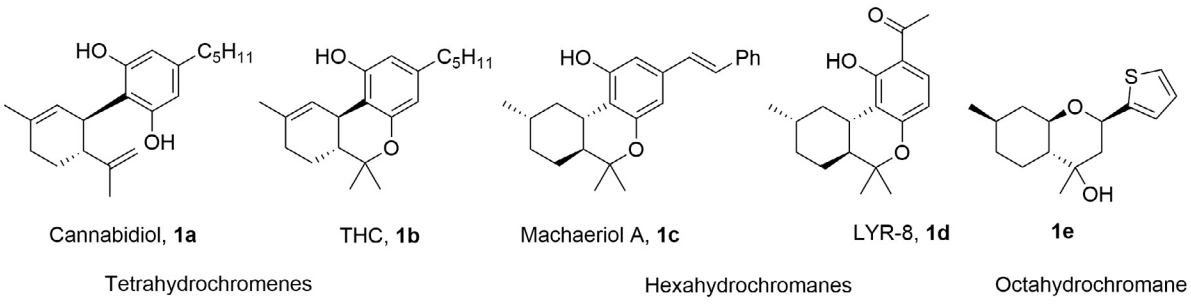
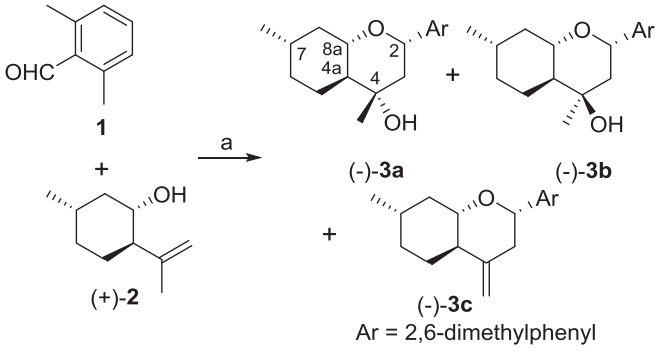


Fig. 1. Selected biologically active compounds based on a chromane scaffold – cannabinoids, machaeriols and octahydrochromanes.

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

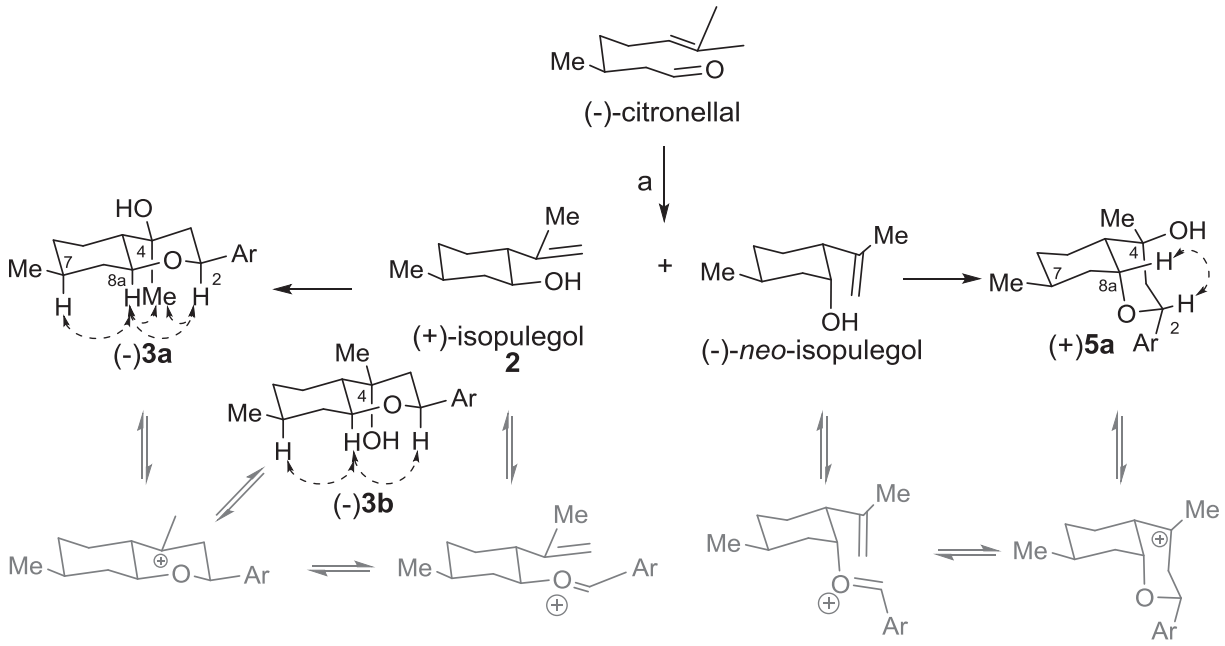


Fig. 2. One-pot ene, Prins reactions of (−)-citronellal with 2,6-dimethylbenzaldehyde and the formation of octahydrochromanes. Key NOE interactions are indicated by dotted arrows. *Reagents and conditions*: a). $BF_3{\cdot}OEt_2$ (0.2 equiv.), CH_2Cl_2, −40 °C to rt, 4.5 h, 48%, (**3a**:**3b**:**5a**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