Organic LETTERS

Letter

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

pubs.acs.org/OrgLett

Short and Protecting-Group-Free Approach to the (−)-Δ^8-THC-Motif: Synthesis of THC-Analogues, (−)-Machaeriol B and (−)-Machaeriol D

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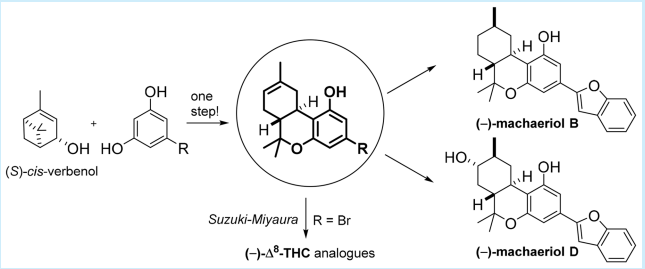
Supporting Information

ABSTRACT: Friedel−Crafts alkylation of resorcinols with (*S*)-*cis*-verbenol and subsequent cyclization allows the construction of the tetrahydrodibenzopyran core of (−)-Δ^8-THC which is also found in other natural products in one step. Using a benzofuryl substituted resorcinol, followed by diastereoselective hydroboration and oxidative or reductive workup, directly provides (−)-machaeriol B and D in 42% and 43% overall yields. Bromoresorcinol as a coupling partner delivers Br−THC that can be applied for late-stage diversification by Suzuki−Miyaura cross-coupling to readily access (−)-Δ^8-THC analogues.



The tetrahydrodibenzopyran motif is found in many natural products such as tetrahydrocannabinols (THC) and machaeriols. (−)-Δ^9-THC and its double bond isomer (−)-Δ^8-THC (Figure 1) are isolated from *Cannabis sativa* L.,[1]

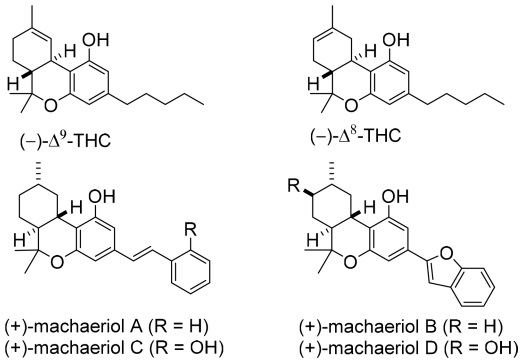


Figure 1. Structures of the natural products (−)-Δ^9-THC, (−)-Δ^8-THC, and (+)-machaeriol A−D.

and they have been used for recreational and therapeutic purposes.[2] THCs interact with cannabinoid receptors CB_1 and CB_2[3,4] which are expressed in the brain/central nervous system (CB_1) and in cells of the immune system (CB_2).[5,6] Since CBs are involved in neurogenesis, metabolism, immune-system activity, and reproduction, they represent key drug targets for the treatment of a number of diseases.[7] Notably, (−)-Δ^9-THC is meanwhile found in the drug market under the name Marinol or Sativex.[8] Importantly, unnatural THC-analogues with the pentyl side chain replaced by other substituents have shown even increased receptor affinity and pharmacological potency.[9]

The structure of (+)-machaeriols A, B, C, D is based on the same THC core motif; however, their side chains and absolute stereochemistry differ. They have been isolated from the bark of *Machaerium multiflorum* spruce (Fabaceae), an Amazonian liana found in Peru.[10,11] (+)-Machaeriol B exhibits potent *in vitro* antimalarial activity against *Plasmodium falciparum* W2 clones and antibacterial properties against methicillin resistant *Staphylococcus aureus*.[11]

To explore the full potential of this interesting structural class with respect to its pharmacology, short and efficient methods enabling the synthesis of natural and unnatural THCs and machaeriol derivatives are demanded. Along these lines, Trost, Zhou, Bräse, Carreira, Leahy, and others have developed elegant syntheses.[12] Some approaches toward (−)-Δ^9-THC and (−)-Δ^8-THC are based on the condensation of resorcinols with natural terpenoids such as (+)-*trans*-2-carenepoxide, (+)-chrysanthenol, (+)-menthadienol, or others.[13] In their pioneering 1967 work, R. Mechoulam, P. Braun, and Y. Gaoni described the reaction of *S*-(*cis*)-verbenol and olivetol, both commercially available, with catalytic $BF_3{\cdot}OEt_2$ to directly deliver (−)-Δ^8-THC in 35% yield (Scheme 1A).[13d] This cascade likely proceeds via regio- and diastereoselective Friedel−Crafts alkylation to give intermediate **A**. Protonation of **A** and subsequent cleavage of the strained four-membered ring in **B** lead to the tertiary cation **C**, that finally cyclizes via C−O bond formation with the phenolic OH-group to give (−)-Δ^8-THC.

Inspired by this straightforward one-step synthesis, we questioned whether this sequence is also applicable to resorcinol derivatives other than olivetol and planned to use that strategy for the construction of the hexahydrodibenzopyran core **2** of (−)-machaeriol B and D (Scheme 1B). Diastereoselective hydroboration of **2** followed by either oxidative or reductive workup, as shown before on the corresponding methyl ether,[14]

Received: March 29, 2018

DOI: 10.1021/acs.orglett.8b01005
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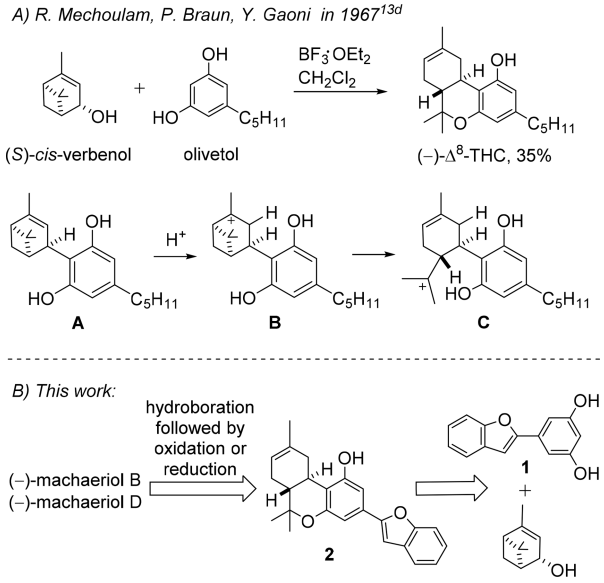
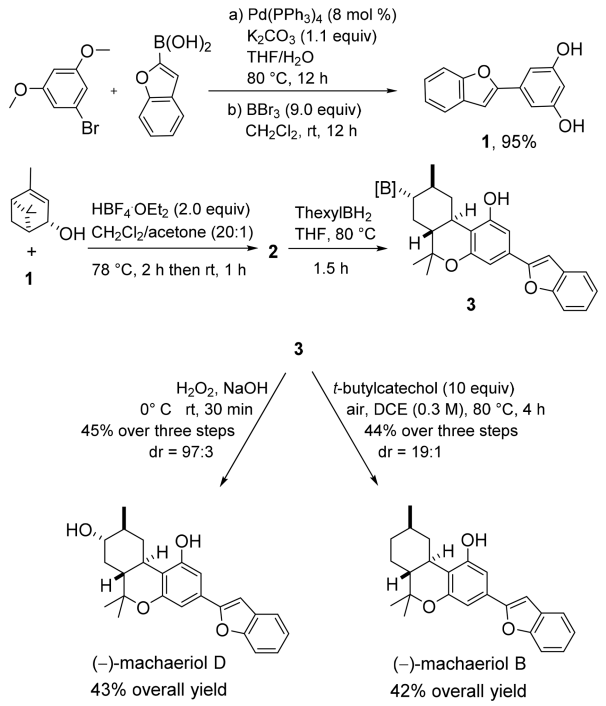
Scheme 1. (A) Friedel–Crafts Alkylation and Subsequent Cyclization of (*S*)-*cis*-Verbenol and Olivetol to (−)-Δ^8-THC;[13d] (B) Retrosynthesis of (−)-Machaeriol B and D



Scheme 2. Synthesis of (−)-Machaeriol B and (−)-Machaeriol D



should directly lead to (−)-machaeriol B and D without the need for any protecting-group strategy.

We commenced our studies by reinvestigating the Friedel–Crafts-type alkylation and subsequent cyclization of (*S*)-*cis*-verbenol and olivetol. Extensive experimentation revealed that the highest yield is achieved in CH_2Cl_2 using 2 equiv of $HBF_4{\cdot}OEt_2$ for 2 h at −78 °C followed by 1 h of stirring at room temperature to give (−)-Δ^8-THC in 54% isolated yield at 1 mmol scale (see Supporting Information (SI)). Note that the NMR yield was significantly higher (69%), and product loss during purification could not be fully prevented.

These optimized reaction conditions were then tested for the synthesis of machaeriols. The required benzofuryl substituted resorcinol **1** was readily obtained in 95% overall yield via Suzuki–Miyaura cross-coupling of 1-bromo-3,5-dimethoxybenzene and benzofuran-2-boronic acid followed by double methyl ether cleavage (Scheme 2). Disappointingly, we initially observed very poor yields for **2**, likely caused by the low solubility of resorcinol **1** in CH_2Cl_2 at −78 °C. This problem was solved by utilizing a solvent mixture (CH_2Cl_2/acetone = 20:1), and the tetrahydrodibenzopyran **2** was formed in 85% yield (determined by GC-FID with mesitylene as an internal standard). To avoid loss of product during purification, as observed upon isolation of (−)-Δ^8-THC (see above), the crude product was directly used for the next step without any further purification.

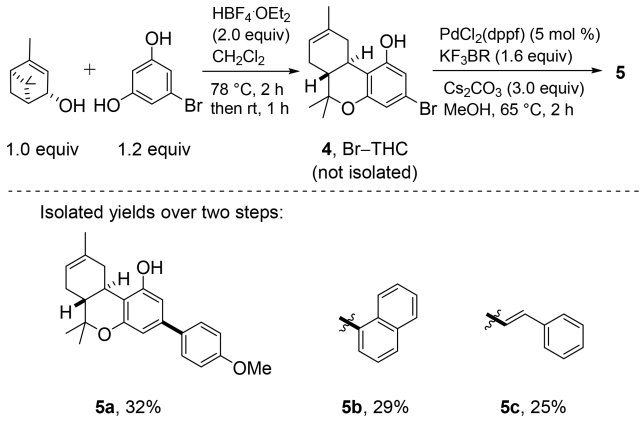
The diastereoselective hydroboration of the double bond in **2** with subsequent oxidation to the corresponding alcohol was studied next. In 1995, J. W. Huffman et al. showed that hydroboration and oxidation of the methyl ether protected Δ^8-THC using $BH_3{\cdot}THF$ provided a 1:1 mixture of the two diastereoisomeric alcohols in 77% yield.[15] Applying Huffman's conditions on the free phenol **2**, we obtained after NaOOH oxidation a 1:1 mixture of both isomers (as measured by GC-FID) in 58% yield over three steps (cyclization/hydroboration/oxidation), demonstrating that the cascade is feasible without protection of the phenolic HO-group. In order to increase selectivity, we switched to bulkier boranes and found that with Sia2BH, which performed well on the O-methyl protected substrate,[14] a high selectivity for, but disappointingly low yield of, (−)-machaeriol D was obtained (12% over three steps). Variation of the steric demand of the hydroboration reagent revealed that thexylborane is best suited in terms of yield and selectivity. Hence, hydroboration of **2** with thexylborane in THF for 1.5 h at 80 °C and oxidation of the corresponding crude alkylborane **3** provided (−)-machaeriol D with an excellent 97:3 selectivity (measured by GC-FID) in 45% overall yield for this three-step sequence (cyclization/hydroboration/oxidation).

Importantly, the crude hydroboration product **3** also serves as an intermediate for the synthesis of (−)-machaeriol B by simple hydrodeborylation. To this end, intermediate **3** was successfully reduced by applying a protocol developed by Renaud et al. for the transformation of alkylboranes to the corresponding alkanes under an air atmosphere by addition of 4-*tert*-butylcatechol[16] to give (−)-machaeriol B in 44% isolated yield over three steps (cyclization/hydroboration/protodeborylation) with 19:1 diastereoselectivity (see SI).

On the basis of the crystal structure of an agonist bound to the human CB_1 receptor, structure activity studies of side chain modified THC derivatives have received much attention recently.[17] For example, Trauner and Carreira described a six-step synthesis of Br-substituted (−)-Δ^9-THC as an intermediate for late-stage diversification through transition-metal catalyzed cross-coupling.[18] Motivated by these reports, we tested 1-bromo-3,5-dihydroxybenzene (1.2 equiv) as a resorcinol coupling partner in the reaction with (*S*)-*cis*-verbenol under our standard protocol ($HBF_4{\cdot}OEt_2$ (2.0 equiv), CH_2Cl_2, −78 °C for 2 h then rt for 1 h) to afford **4**.[19] As for the synthesis of (−)-Δ^8-THC, the tetrahydrodibenzopyran **4** was not further purified and directly used as a crude product in a Pd-catalyzed Suzuki–Miyaura coupling with three different trifluoroborates to give the THC-derivatives **5a**, **5b**, and **5c** in yields ranging from 25–32% over the two steps (Scheme 3). These THC congeners bear different pharmacologically interesting side chains, such as the *trans*-2-

DOI: 10.1021/acs.orglett.8b01005
Org. Lett. XXXX, XXX, XXX–XXX

Scheme 3. One-Step Synthesis of (−)-Δ^8-Br-THC and Subsequent Suzuki−Miyaura Cross-Coupling Provides (−)-Δ^8-THC Derivatives with Different Side Chains



styryl chain of machaeriol A (for **5c**), the bulky and highly active naphthyl group[9] (for **5b**), and a *para*-anisyl substituent (for **5a**).

In summary, we reinvestigated the Friedel−Crafts alkylation and subsequent cyclization of (*S*)-*cis*-verbenol and olivetol and obtained in one step (−)-Δ^8-THC in 54% isolated yield from commercially available starting materials. Using a resorcinol derivative bearing a benzofuryl side chain in place of olivetol, the same cascade was successfully applied to construct the hexahydrodibenzopyran core of (−)-machaeriol B and D. Highly diastereoselective hydroboration with thexylborane followed by either oxidative or reductive workup directly delivers (−)-machaeriol B and D in 42% and 43% overall yields over five steps. To the best of our knowledge, this represents the highest yield reported thus far for the preparation of machaeriol D, and protecting groups are not required. Furthermore, we successfully synthesized in one step (−)-Δ^8-Br-THC **4** as a common intermediate to access three (−)-Δ^8-THC derivatives bearing different side chains via late-stage diversification by Suzuki−Miyaura cross-coupling in a straightforward manner.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01005.

Experimental procedures, characterization data, and ^{1}H and ^{13}C spectra (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank Dr. Felix Klotter (University of Münster) for conducting some experiments on the optimization study and Maren Wissing (University of Münster) for helpful discussions. This work was financially supported by the Deutsche Forschungsgemeinschaft (DFG).

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DOI: 10.1021/acs.orglett.8b01005
Org. Lett. XXXX, XXX, XXX−XXX