Natural Product Synthesis

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Short and Divergent Total Synthesis of (+)-Machaeriol B, (+)-Machaeriol D, (+)-Δ^8-THC, and Analogues[**]

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Abstract: *Short and highly efficient stereoselective syntheses provide machaeriols and cannabinoids in a divergent approach starting from a common precursor, commercially available (S)-perillic acid. Key features of the novel strategy are a stereospecific palladium-catalyzed decarboxylative arylation and a one-pot sequence comprising a stereoselective hydroboration followed by oxidation or reduction of the corresponding intermediary boranes. The divergent approach is convincingly demonstrated by the five-step syntheses of (+)-machaeriol B, (+)-machaeriol D, and related analogues, and the four-step synthesis of (+)-Δ^8-THC and an analogue.*

Since the discovery of the biological and medical importance of (−)-Δ^9-*trans*-tetrahydrocannabinol ((−)-Δ^9-THC, **1**) and its isomer (−)-Δ^8-THC (**2**),[1] the cannabinoid family, which includes phytocannabinoids[2] and endogenous[3] and synthetic cannabinoids,[4] has attracted the attention of scientists worldwide (Figure 1 a). Thus far, more than 60 cannabinoids and related analogues have been identified, and some of them have found applications as psychotomimetic or other drugs.[5] Owing to their great pharmacological potential, considerable efforts have been made towards the synthesis of naturally and structurally related, non-natural cannabinoids (e.g., by the groups of Trost,[6] Zhou,[7] and Bräse[8]). Recently, Carreira et al. presented an elegant approach to the four stereoisomers of Δ^9-THC by using stereodivergent dual catalysis in the key step.[9] Efficient synthetic procedures for members of this important natural product class open the door for further investigations of the pharmacology of natural and—thanks to the synthesis approach—also unnatural isomers.

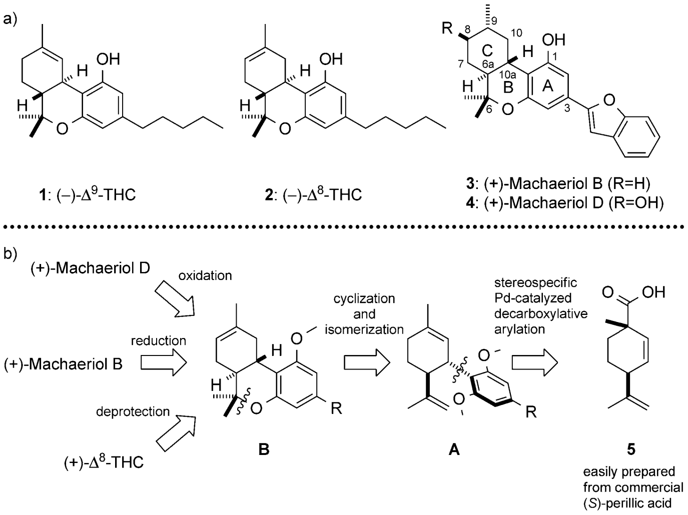

Figure 1. a) Natural cannabinoids and analogues. b) Retrosynthetic analysis.

As a novel class of cannabinoid-related natural products, machaeriols, such as (+)-machaeriol B (**3**) and (+)-machaeriol D (**4**), were isolated from the stem bark of *Machaerium multiflorum* between 2001 and 2003 (Figure 1 a).[10] First investigations revealed that these compounds have potent in vitro antimicrobial activity against methicillin-resistant *S. aureus* and in vitro antimalarial activity against *Plasmodium falciparum* W2 clones. Despite their important biological activities and their promising pharmacological potential, only very few total syntheses of these natural products have been reported thus far.[11] In 2007, Pan et al. accomplished the first total synthesis of (+)-machaeriol D (**4**) using a regio- and stereoselective S_N2' reaction as the key step (longest linear sequence: 18 steps).[11b] Very recently, Dethe and co-workers could reduce the amount of synthetic operations towards **4** to six steps by applying an elegant strategy that also provides access to the unnatural enantiomer.[11f] However, a modular approach allowing for simple and short syntheses of (+)-machaeriol B (**3**) and (+)-machaeriol D (**4**) starting from a common building block has not been disclosed to date.

Herein, we report a divergent strategy for the short synthesis of (+)-machaeriol B (**3**), (+)-machaeriol D (**4**; currently the shortest), and related analogues using a stereospecific palladium-catalyzed decarboxylative arylation and a one-pot stereocontrolled hydroboration, followed by oxidation or reduction of the intermediary borane, as key steps. Moreover, we will show that this modular approach can also be applied to the synthesis of cannabinoid derivatives, such as (+)-Δ^8-THC (*ent*-**2**), starting from the same, readily available (*S*)-perillic acid.

The antimalarial agents (+)-machaeriol B (**3**) and (+)-machaeriol D (**4**) are structurally related to natural THC derivatives, such as **1** and **2**. Although their absolute configurations differ, these compounds feature a tricyclic dibenzopyran motif (ABC ring system) with *trans* connectivity between the pyran skeleton (ring B) and the cyclohexane

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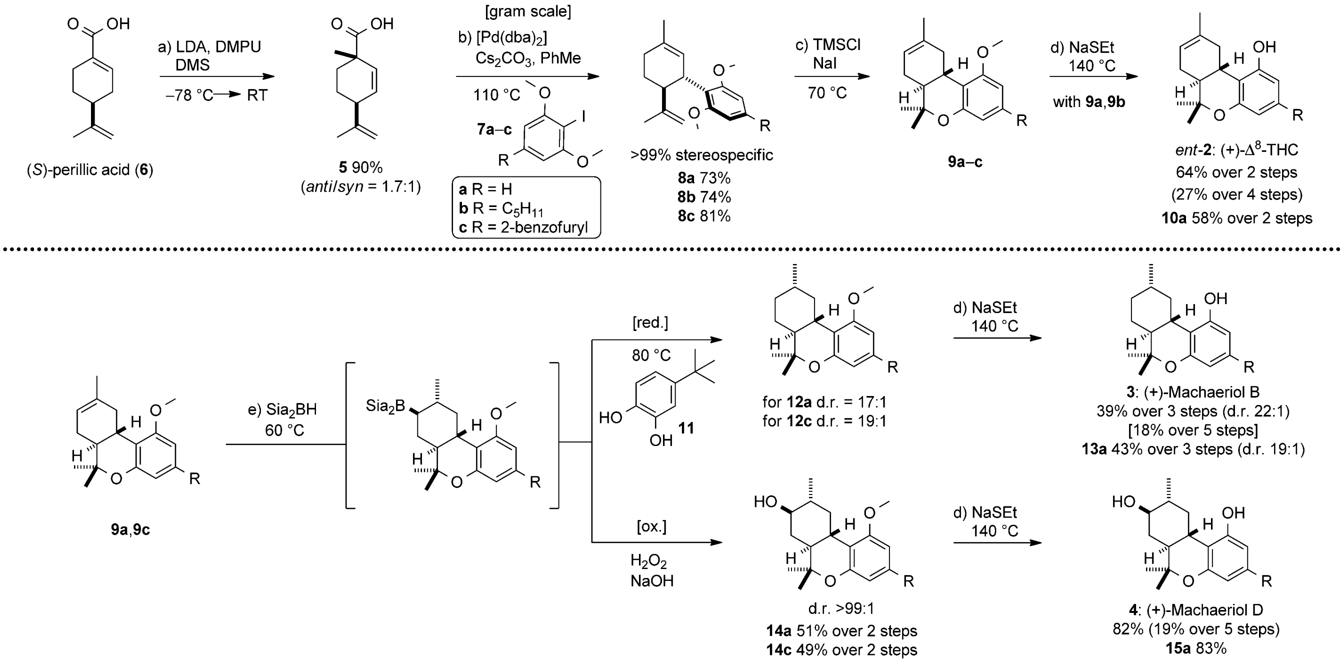
subunit (ring C) at positions C6a and C10a as a common structural unit. However, in contrast to THC derivatives, machaeriols **3** and **4** contain a benzofuran moiety at the C3 position (instead of a pentyl chain) and have a fully saturated cyclohexane core bearing an equatorial methyl group at the C9 position. Compared to the THCs, (+)-machaeriol D (**4**) contains an additional hydroxy-bearing stereogenic center at the C8 position *anti* to the methyl group, rendering its synthesis certainly more challenging.

The structural similarity of all of these compounds motivated us to develop a divergent and short approach that will not only provide access to the natural machaeriols **3** and **4** or related analogues but can also be used for the synthesis of cannabinoids, such as (+)-Δ^8-THC (*ent*-**2**). As one of our key steps, we planned to use a stereospecific palladium-catalyzed decarboxylative γ-arylation[12] for the introduction of various *trans*-configured aryl groups (in ring C) starting from chiral (1*S*,4*S*)-disubstituted cyclohexene-1-carboxylic acid **5** (Figure 1 b). The Δ^9-tetrahydrobiphenyls **A** that are thus obtained should be readily transformed into intermediates of type **B** by a short sequence that includes oxycyclization to install the *trans* pyran core (ring B) and subsequent double-bond isomerization. Δ^8-Tetrahydrodibenzopyrans **B** represent our key intermediates as three divergent transformations of these compounds should lead to all of the targeted compounds. In detail, (+)-machaeriol B (**3**), (+)-machaeriol D (**4**), and related analogues should be accessible from common intermediate **B** (R = 2-benzofuryl) in a one-pot key sequence that is based on a stereocontrolled hydroboration followed by oxidation (for **4**) or reduction (for **3**). On the other hand, simple deprotection of **B** (R = pentyl) will lead to cannabinoids, such as (+)-Δ^8-THC (*ent*-**2**).

Our synthetic studies commenced with the preparation of chiral (1*S*,4*S*)-disubstituted cyclohexene-1-carboxylic acid **5** from commercially available (*S*)-perillic acid (**6**; Scheme 1). Importantly, (*R*)-perillic acid (*ent*-**6**) is also accessible and can be prepared on large scale, which opens the door to the synthesis of both enantiomers of all compounds presented herein.[13] We assumed that the isopropenyl substituent in **6** could be utilized to induce stereoselectivity in the α-methylation. An additional challenge was the control of the α/γ-regioselectivity in the alkylation step. After intensive experimentation, we found that the dienolate generated from **6** upon treatment with LDA in a THF/DMPU[14] mixture reacted with dimethyl sulfate to yield carboxylic acid **5** with excellent yield (90 %, gram scale), complete α-selectivity, and moderate *anti* diastereoselectivity favoring the desired isomer (1.7:1; Scheme 1). The proper choice of base, alkylation reagent, solvent mixture, and reaction temperature turned out to be crucial for successful methylation. All of our attempts to increase the diastereoselectivity by using chiral bases or chiral ligands in combination with sterically demanding organolithium bases were not fruitful. However, as the targeted isomer was formed as the major product, the alkylation was the first step in the synthesis, and we assumed that separation of isomers might not be necessary at this stage, we began to investigate the key step for our synthesis—the stereoselective introduction of aryl groups *trans* to the isopropenyl group.

Recently, we developed a Pd-catalyzed stereospecific decarboxylative coupling of substituted 1,4-cyclohexadiene-



Scheme 1. Total synthesis of machaeriols and cannabinoid analogues. Reagents and conditions: a) LDA (2.5 equiv), −78 °C to RT, 2 h; then DMPU (10 equiv), 15 min, RT; then DMS (1.3 equiv), −78 °C to RT, 1 h; b) $[Pd(dba)_2]$ (10 mol %), Cs_2CO_3 (1.1 equiv), **7 a**–**c** (1.0 equiv), toluene (0.3 M), 110 °C, 26 h; c) TMSCl (1.5 equiv), NaI (2.0 equiv), 70 °C, 24 h; then NaI (0.2 equiv), 70 °C, 24 h; d) NaSEt (10 equiv), DMF, 140 °C, 12 h; e) for hydroboration/reduction: Sia_2BH (4 equiv), 60 °C, 2 d; then **11** (10 equiv), 80 °C, open atmosphere, 4 h; for hydroboration/oxidation: Sia_2BH (2 equiv), 60 °C, 2 d; then H_2O, NaOH, H_2O_2, 2 h, RT.

3-carboxylic acids with aryl iodides leading to 5-arylated 1,3-cyclohexadiene derivatives.[12a,b] Decarboxylative γ-arylation was also successfully applied to the total synthesis of resveratrol-based natural products.[12c] Notably, the carboxylic acids that were used in these successful C(sp^3)–C(sp^2) couplings result, upon decarboxylation, in allylic Pd intermediates that are further stabilized by conjugation either with an additional double bond or an arene. The stability of an anion formed by decarboxylation is known to be an important issue in Pd-catalyzed decarboxylation reactions for the generation of Pd allyl complexes. However, an additional π-stabilizing entity is missing in **5**, and therefore, we expected **5** to be a difficult substrate for decarboxylative γ-arylation.

Pleasingly, when we applied our standard conditions of the stereospecific decarboxylative γ-arylation[12a] to *anti*-**5** using [Pd(dba)$_2$] (10 mol %), Cs$_2$CO$_3$ (1.1 equiv), and iodide **7a**, product **8a** was obtained in 65 % yield with complete stereospecificity. Importantly, upon using the 1.7:1 *anti*/*syn* mixture of **5**, **8a** was obtained in an even slightly better yield (73 %, calculated based on *anti*-**5**), showing that 1) *syn*-**5** does not undergo γ-arylation and, more importantly, that 2) separation of the *anti*/*syn* isomers of **5** is not necessary. This is highly helpful from a practical point of view, in particular for larger-scale preparations of **8a**. Unreacted acid *syn*-**5** can be reisolated after work-up. Therefore, all following experiments were conducted with the isomeric mixture of **5**. With aryl iodides **7b** and **7c** (1.0 equiv), the (3*S*,4*S*)-*trans*-Δ^9-tetrahydrobiphenyls **8b** and **8c** were obtained in good yields as single diastereoisomers (74 % and 81 % based on *anti*-**5**).

We next studied the construction of the *trans*-configured pyran core (ring B) starting from **8a**–**c** through selective deprotection of one methyl ether using trimethylsilyl iodide (TMSI) and subsequent oxycyclization in a one-pot fashion, according to a method of Childers and Pinnick.[15] Unfortunately, upon treatment of **8a** with TMSI, a complex mixture containing various iodinated species was obtained. The quality of the TMSI sample used turned out to be important. As the handling of TMSI is problematic, we envisioned to generate this reagent in situ from trimethylsilyl chloride (TMSCl) and sodium iodide (NaI).[16] After a thorough screen, we found conditions that allowed for the reproducible generation of the *trans*-configured pyran skeleton on larger scale (see Scheme 1). Moreover, under these conditions, Δ^9 to Δ^8 double-bond isomerization also occurred, likely for thermodynamic reasons.[17] The Δ^8-tetrahydrodibenzopyran derivatives **9a**–**c** thus obtained were used for the next steps without any further purification.[18]

With this highly efficient three-step synthesis to intermediates containing the requisite 6,6,6-tricyclic system of machaeriols and cannabinoids in hand, we then investigated the final divergent transformations. Whereas the deprotection of the remaining methoxy group in **9a** and **9b** to form the synthetic cannabinoids (+)-Δ^8-THC (*ent*-**2**, 64 % over 2 steps) and **10a** (58 % over 2 steps) was readily achieved with NaSEt in DMF at elevated temperatures, first attempts towards the synthesis of (+)-machaeriol B (**3**) through a stereocontrolled reduction of the Δ^8-configured double bond in **9a** and **9c** were not rewarding. In particular, hydrogenation of **9a** with heterogeneous catalysts such as Pd/C proceeded with a maximum ratio of 3:1 in favor of the desired stereoisomer, whereas homogenous (non-chiral and chiral) metal catalysts provided the undesired isomer as the major product in all cases. To overcome this stereochemical problem, we tested a method developed by Renaud and co-workers, which is based on a one-pot hydroboration and subsequent radical C–B reduction with 4-*tert*-butylcatechol (**11**).[19] This elegant strategy was used by these authors as the key step for an efficient synthesis of all-*cis*-trimethyldecalin derivatives.[19c] Pleasingly, hydroboration of **9a** and **9c** with disiamylborane (Sia$_2$BH) and subsequent radical reduction with **11** provided hexahydrodibenzopyran derivatives **12a** and **12c** in good yields and very good diastereoselectivities (d.r. 17:1 for **12a** and 19:1 for **12c**). Products **12a** and **12c** were used in the final deprotection step without further purification.[18] Removal of the methyl group afforded (+)-machaeriol B (**3**) and its analogue **13a** in good yield (39 %, d.r. 22:1 for **3** and 43 %, d.r. 19:1 for **13a** over 3 steps). With Sia$_2$BH as a selective hydroboration agent in hand, we focused on the completion of the synthesis of (+)-machaeriol D (**4**). Hydroboration of **9a** and **9c** and oxidative work-up (H$_2$O$_2$, NaOH) provided the secondary alcohols **14a** and **14c** as single diastereoisomers (d.r. > 99:1) in good yields.[20,21] Final deprotection of **14a** and **14c** using NaSEt in DMF at reflux afforded (+)-machaeriol D (**4**) and the related analogue **15a** (d.r. > 99:1) in very good yields (82 % for **4** and 83 % for **15a**; 115 mg of **4** prepared in one sequence).

In summary, we have reported a novel, short, and divergent approach for the stereoselective synthesis of machaeriols and cannabinoid-related compounds from a common precursor. Various aryl groups could be readily installed through stereospecific palladium-catalyzed decarboxylative couplings. Compounds of type **B** were identified as key structural intermediates that provide access to a variety of machaeriols, cannabinoids, and related compounds through efficient follow-up transformations. Therefore, the antimalarial agents (+)-machaeriol B (**3**) and (+)-machaeriol D (**4**) were synthesized in just five steps (thus far the shortest route towards **4**) in 18 % and 19 % overall yield (0.12 g of **4** prepared). Furthermore, (+)-Δ^8-THC was obtained in four steps and 27 % overall yield (0.18 g prepared). Importantly, our modular strategy will enable the large-scale synthesis of further machaeriol and cannabinoid analogues.

Keywords: cannabinoids · decarboxylative couplings · divergent synthesis · natural products · total synthesis

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[17] We assume that the isomerization is thermodynamically favored. Notably, double-bond isomerization occurs before cyclization takes place, as determined by GC-MS analysis.

[18] After purification by column chromatography, target compounds contained tiny amounts of impurities. These side products could be removed during the work-up of the next step.

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[20] Although the hydroboration was not completely selective (> 17:1), we could not identify the minor alcohol isomer after oxidation. Presumably, the minor alkylborane diastereomer is either very slowly or not oxidized under the reaction conditions.

[21] Notably, a similar hydroboration/oxidation sequence of methoxy-protected (−)-Δ^8-THC (**2**) using BH_3 was conducted by Huffman et al. However, the corresponding alcohol was obtained non-selectively as a nearly 1:1 mixture of diastereoisomers; see: J. W. Huffman, W. Kenneth Banner, G. K. Zoorob, H. Howard Joyner, P. H. Reggio, B. R. Martin, D. R. Compton, *Tetrahedron* **1995**, *51*, 1017 – 1032.

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