A Short Total Synthesis for Biologically Interesting (+)- and (–)-Machaeriol A

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Abstract: This paper describes a new and efficient synthetic approach for biologically interesting natural (+)-machaeriol A and its unnatural enantiomer (–)-machaeriol A. The key strategies involve stilbene formation through a Horner–Wadsworth–Emmons reaction and *trans*-hexahydrodibenzopyran formation through a tandem aldol–hetero-Diels–Alder reaction.

Key words: cannabinoid analogues, hetero-Diels–Alder reaction, (+)-machaeriol A, (–)-machaeriol A

Cannabinoids are widely distributed in nature, and have been isolated from Indian hemp, *Cannabis sativa,* which have been used as both a medicine and a psychotomimetic drug since ancient times.[1] These compounds have been shown to have analgetic, antiemetic, psychotropic, and anti-inflammatory properties.[2] They also have potential therapeutic utility for the treatment of asthma and glaucoma.[3] The medical use of cannabinoids as therapeutic agents has been limited by their psychotropic properties.[4] However, the discovery of the two cannabinoid receptors, CB1 and CB2, has ushered in a new era in research into the development of drugs.[5] Currently, Δ^9-tetrahydrocannabinol (Δ^9-THC) and its derivative have been used as a medicine, Marinol® and Cesamet®, for treating patients with chemotherapy-induced nausea and vomiting (CINV), who have failed to respond adequately to conventional antiemetic treatments.[6]

Interestingly, structurally related machaeriols A (**1**), B (**2**), C (**3**), and D (**4**) with cannabinoid analogues were recently isolated from the bark of *Machaerium multiflorum* spruce (Figure 1), which is located in Loreto and Peru.[7]

Machaeriols A (**1**), B (**2**), C (**3**), and D (**4**) have been reported to have potent in vitro antimicrobial activity against *Straphylococcus aureus* (IC_{50}, **1**: 15 μg/mL; **2**: 5.0 μg/mL; **3**: 0.65 μg/mL; **4**: 20 μg/mL) and methicillin-resistant *S. aureus* (IC_{50}, **1**: 10 μg/mL; **2**: 4.5 μg/mL; **3**: 0.7 μg/mL; **4**: 30 μg/mL).[7] They also showed potent in vitro antimalarial activity against *Plasmodium falciparum* W-2 clone (IC_{50}, **1**: 6.0 μg/mL; **2**: 1.2 μg/mL; **3**: 3.0 μg/mL).[7] These important biological activities have led to the development of synthetic approaches. The first synthesis of machaeriol A (**1**) and machaeriol B (**2**) was reported by Avery starting from phloroglucinol through hetero-Diels–Alder cyclization and Suzuki coupling reaction as the key steps in 34% (7 steps) and 32% (7 steps) overall yields, respectively.[8] However, in these synthetic routes, there was no reported data on the specific rotation for the optically pure natural products **1** and **2**. Recently, another total synthesis of (+)-machaeriol A (**1**) was accomplished starting from synthesized enol silyl ether of α,β-epoxycyclohexanone through a S_N2' reaction to aryl cyanocuprate as the key step in overall 26% yield (10 steps).[9] (+)-Machaeriol D (**4**) was also synthesized starting from 4-bromo-2,4-dihydroxybenxzoic acid in 12% overall yield (17 steps).[10] Although a few synthetic approaches to (+)-machaeriol A (**1**), B (**2**), and D (**4**) have been reported, these synthetic routes have many reaction steps and low yield. In particular, the synthesis of enantiomers of these natural products has not been reported.

Recently, we developed a new and useful methodology for preparing a variety of benzopyrans using ethylenediamine diacetate (EDDA)-catalyzed reactions of resorcinols to α,β-unsaturated aldehydes (Scheme 1).[11]

These reactions involve a formal [3+3] cycloaddition through 6π-electrocyclization.[12] This methodology provides a rapid route for the synthesis of benzopyran derivatives with a variety of substituents on the pyranyl ring.[13]

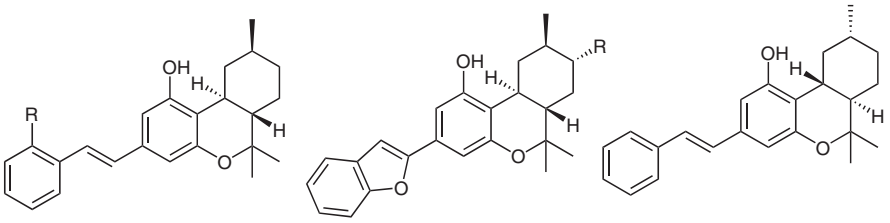

Figure 1 Natural products **1**–**4** isolated from *Machaerium multiflorum* and unnatural enantiomer **5**

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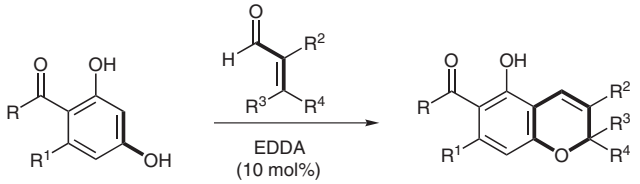


Scheme 1 Benzopyran formation by [3+3] cycloaddition

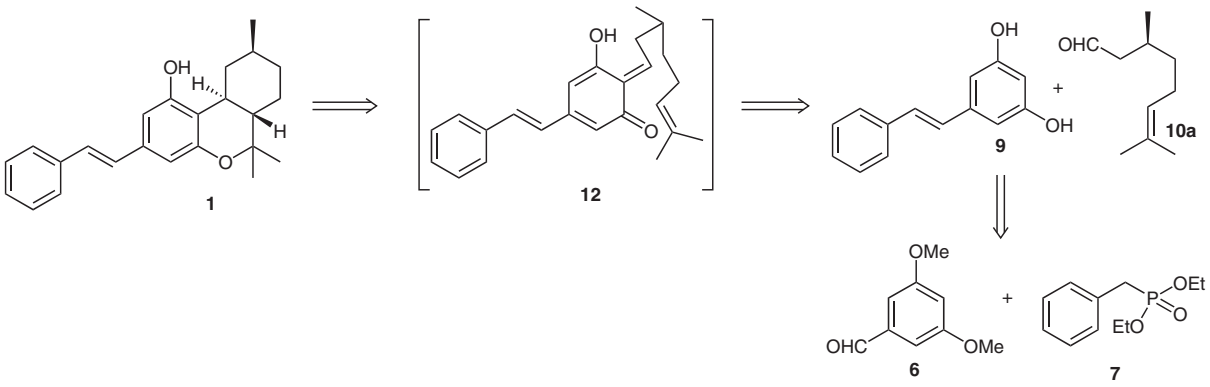
This reaction for the formation of benzopyrans appears to be an ideal method for synthesizing enantiomerically pure molecules with the cannabinoid moiety. As a part of an ongoing study into the synthetic efficacy of this methodology, we report the efficient and concise synthesis of biologically interesting (+)-machaeriol A (**1**) and its unnatural isomer, (–)-machaeriol A (**5**), using hetero-Diels–Alder cycloaddition as a key step.

Scheme 2 shows the retrosynthetic analysis. (+)-Machaeriol A (**1**) can be prepared from reaction of pinosylvin (**9**) and (*S*)-(–)-citronellal (**10a**) through a hetero-Diels–Alder reaction.

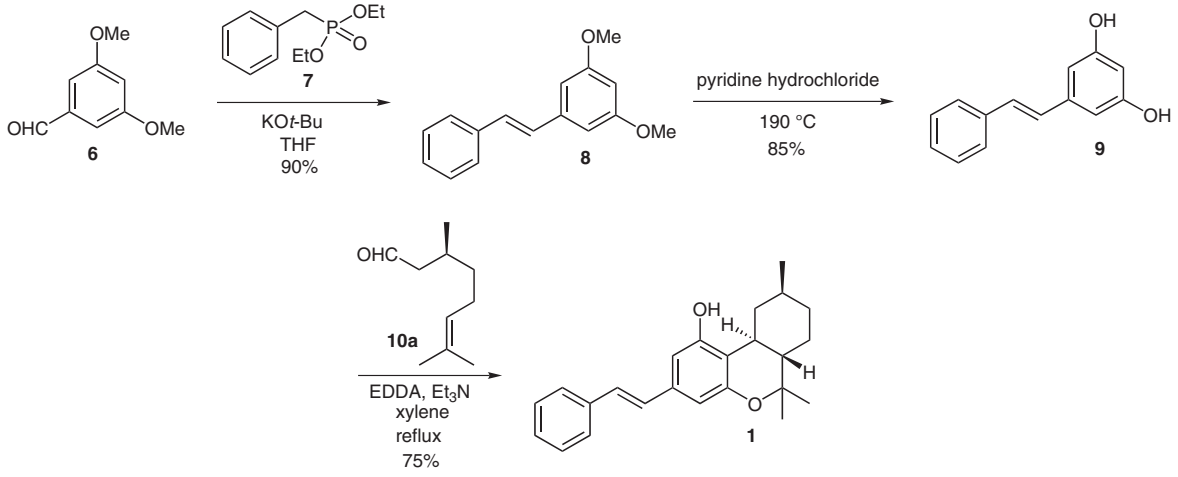
Pinosylvin (**9**) can be generated from a Horner–Wadsworth–Emmons reaction between commercially available diethyl 3,5-dimethoxybenzaldehyde (**6**) and benzylphosphonate (**7**) followed by methyl ether cleavage of the dimethoxy groups.

Scheme 3 shows the efficient and concise synthetic approach to natural (+)-machaeriol A (**1**). First, a reaction of 3,5-dimethoxybenzaldehyde (**6**) and diethyl benzylphosphonate (**7**) in the presence of potassium *tert*-butoxide in THF gave 3,5-dimethoxy-*trans*-stilbene (**8**) in 90% yield.[14] Treatment of compound **8** with pyridine hydrochloride at 190 °C for four hours afforded pinosylvin (**9**, 85%),[14] which was isolated from pine leaf of *Pinus densiflora* and the heartwood of *Pinus sylvestries*.[15] Interestingly, pinosylvin (**9**) with a stilbenoid showed antibacterial, antimicrobial, antifungal, and antioxidant activities.[16] It was also reported to have potent inhibitory effects on tyrosinase and prostaglandin E_2 production in lipopolysaccharide-induced mouse macrophage cells.[17] A reaction of compound **9** with (*S*)-(–)-citronellal (**10a**, $[\alpha]_D$ –15.0, neat) in the presence of ethylenediamine diacetate (20 mol%) and triethylamine (2 mL) as a cocatalyst in refluxing xylene for 24 hours gave (+)-machaeriol A (**1**) in 75% yield.[18] The specific rotation of synthetic material **1** was $[\alpha]_D$ +112.0 (*c* 0.16, MeOH), whereas the reported data is $[\alpha]_D$ +115.4 (*c* 0.39, MeOH).[7b] The spectroscopic data of the synthetic material **1** is in good agreement with those reported data.[7b]

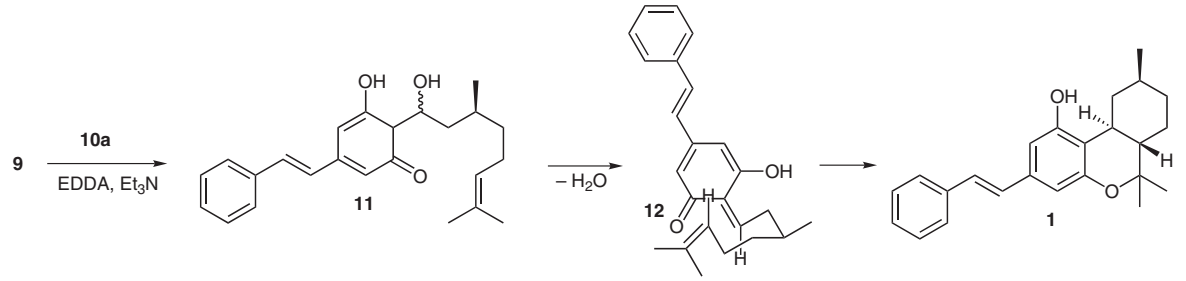
Scheme 4 shows the mechanism for the formation and stereostructure of (+)-machaeriol A (**1**). Aldehyde **10a** was first protonated by EDDA to give a protonated aldehyde,



Scheme 2 Retrosynthetic analysis of natural (+)-machaeriol A (**1**)



Scheme 3 Total synthesis of natural (+)-machaeriol A (**1**)

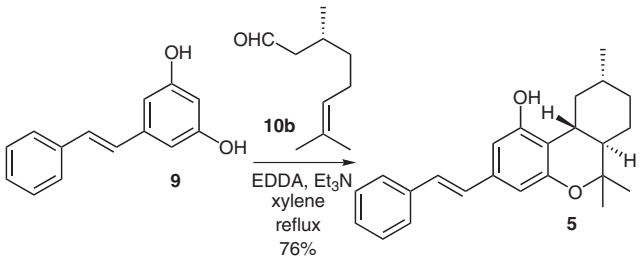


Scheme 4 The mechanism for the formation and stereochemistry of (+)-machaeriol A (**1**)

which was then attacked by pinosylvin (**9**) to yield intermediate **11**.

Such a process for producing aldol-type products by a $Ca(OH)_2$-mediated reaction of resorcinol to enals was already suggested by Shigemasa.[19] The dehydration of compound **11** in the presence of EDDA and Et_3N affords *o*-quinone methide **12**. The stereospecificity of product **1** might be explained by a pseudoequatorial conformation of *o*-quinone methide **12** for the coplanar structure adopted by the methyl group in the chairlike transition state.[20] In the process of the hetero-Diels–Alder reaction of *o*-quinone methide **12**, the *exo* transition state must have been more energetically favorable than the *endo* transition state. This is in good agreement with Marino, who reported the synthesis of hexahydrocannabinol using intramolecular hetero-Diels–Alder cycloaddition of *o*-quinone methide.[21]

Next, the synthesis of unnatural (–)-machaeriol A (**5**) was attempted using pinosylvin (**9**), as shown in Scheme 5.



Scheme 5 Synthesis of unnatural (–)-machaeriol A (**5**)

Treatment of compound **9** with (*R*)-(+)-citronellal (**10b**, $[\alpha]_D$ +12.5, neat) in the presence of ethylenediamine diacetate (20 mol%) and triethylamine (2 mL) in refluxing xylene for 24 hours gave (–)-machaeriol A (**5**) in 76% yield. The specific rotation value of synthetic compound **5** was $[\alpha]_D$ –99.8 (*c* 0.30, MeOH).

In conclusion, a new and concise synthetic route for biologically interesting natural (+)-machaeriol A (**1**) and its enantiomer (–)-machaeriol A (**5**) was developed starting from 3,5-dimethoxybenzaldehyde (**6**) and diethyl benzylphosphonate (**7**). The key strategies involved stilbene formation through a Horner–Wadsworth–Emmons reaction and *trans*-hexahydrodibenzopyran formation through hetero-Diels–Alder cycloaddition. This synthetic route is expected to be widely used in the synthesis of other natural products including cannabinoid analogues.

Acknowledgment

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(18) **Spectral Data for Compound 1**
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.48 (2 H, d, *J* = 7.3 Hz), 7.36 (2 H, dd, *J* = 7.7, 7.3 Hz), 7.27 (1 H, t, *J* = 7.7 Hz), 7.01 (1 H, d, *J* = 16.3 Hz), 6.93 (1 H, d, *J* = 16.3 Hz), 6.63 (1 H, d, *J* = 1.3 Hz), 6.44 (1 H, d, *J* = 1.3 Hz), 3.10 (1 H, br d, *J* = 12.6 Hz), 2.52 (1 H, ddd, *J* = 13.4, 11.1, 2.4 Hz), 1.90–1.87 (2 H, m), 1.68–1.64 (1 H, m), 1.52 (1 H, ddd, *J* = 11.4, 11.1, 2.1 Hz), 1.43 (3 H, s), 1.17–1.12 (2 H, m), 1.12 (3 H, s), 0.98 (3 H, d, *J* = 6.6 Hz), 0.81 (1 H, *J* = 13.4, 12.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.8, 155.6, 137.7, 137.1, 129.0, 128.9, 128.5, 127.9, 126.9, 113.5, 108.8, 106.0, 77.8, 49.5, 39.3, 36.1, 35.9, 33.3, 28.5, 28.1, 23.0, 19.5. IR (neat): 3382, 3026, 2922, 2868, 1615, 1568, 1510, 1451, 1422, 1356, 1265, 1138, 1041, 961, 906, 878, 822, 737, 694 cm^{-1}.

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