

A Cyclotrimerization Route to
Cannabinoids

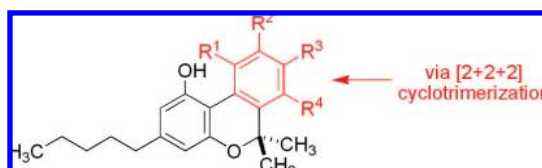
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Received March 13, 2008

ABSTRACT



Three members of the cannabinoid class, cannabinol, cannabinol methyl ether, and cannabinodiol, were synthesized using a microwave-mediated [2 + 2 + 2] cyclotrimerization reaction as the key step. This approach provides a high level of synthetic flexibility allowing for the facile synthesis of cannabinoid analogues.

The natural cannabinoids comprise a group of more than 60 terpenophenolic compounds present in *Cannabis*.¹ Structurally, all phytocannabinoids contain a 5-alkyl (typically a five carbon-chain) resorcinol aromatic ring that is connected at the 2-position to a monoterpene motif. Biosynthetically, this monoterpene unit undergoes cyclization yielding a diverse range of natural products including cannabinol (**1**), cannabinol methyl ether (**2**), cannabinodiol (**3**), Δ^9 -tetrahydrocannabinol (THC, **4**), and cannabichromene (**5**) (Figure 1). Besides the well-known recreational use of the *Cannabis* plant for its psychotropic effects, medicinal applications have been known since the third millennium BC and include antiemetic,² analgesic,^{3,4} and anticonvulsant⁵ properties, among others.^{4,6} Cannabinoids act upon two cellular recep-

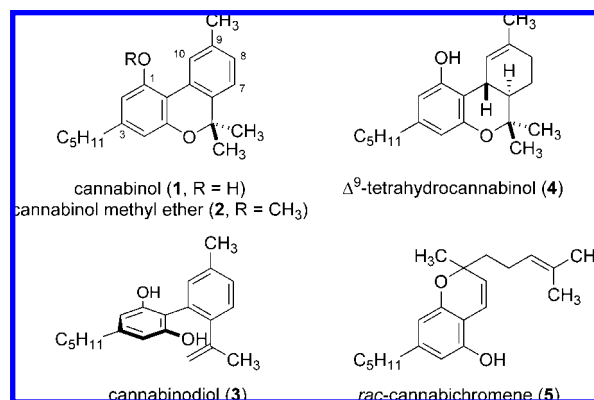


Figure 1. Examples of naturally occurring cannabinoids.

tors, the central cannabinoid receptor, CB₁, found mainly in the brain, and the peripheral cannabinoid receptor, CB₂, found almost exclusively in the immune system.^{7,8} Synthetic cannabinoids which selectively interact with only one recep-

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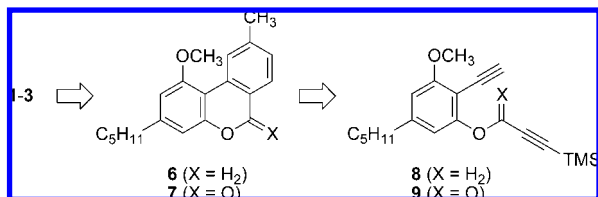
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tor are highly desired,^{9,10} especially since CB₂-selective ligands should limit the side effects associated with CB₁ receptor activation.^{8,11}

Thus far, cannabinol derivatives have primarily been modified at positions C-1, C-3, and C-9.^{10,12} Previous syntheses of cannabinol and its derivatives have relied upon two general strategies: (1) coupling 5-alkyl resorcinols with suitably substituted arenes followed by pyran formation¹³ or (2) generating tetrahydro derivatives first via coupling of 5-alkylresorcinols with appropriate cyclohexene derivatives followed by pyran formation and/or aromatization.^{10,12,14} Accessing broadly substituted C-ring analogues would require more elaborate arene or cyclohexene starting materials. In this paper, we present a flexible synthetic route to the cannabinol core structure based on a [2 + 2 + 2] cyclotrimerization reaction¹⁵ that is amenable to the synthesis of various C-ring analogues from easily accessible alkyne and nitrile precursors.

In order to illustrate the feasibility of a [2 + 2 + 2] cyclotrimerization approach, we synthesized several natural cannabinoids including cannabinol (**1**), cannabinol methyl ether (**2**), and cannabinodiol (**3**). Our synthetic strategy toward **1–3** is depicted in Scheme 1. We envisioned the

Scheme 1. Retrosynthetic Analysis of Cannabinol (**1**), Cannabinol Methyl Ether (**2**), and Cannabinodiol (**3**)

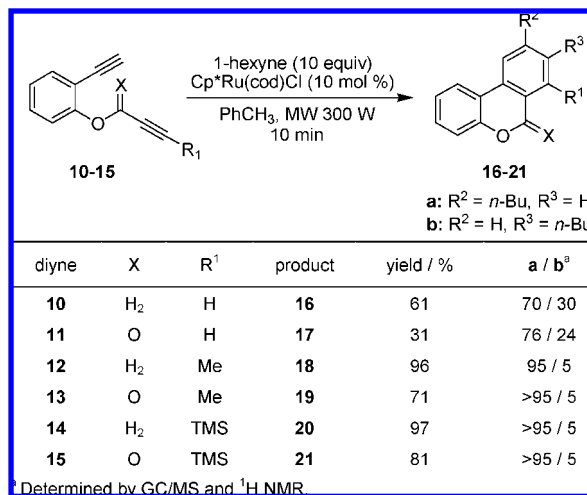


cannabinoids **1–3** being derived from either **6** or **7**. In turn, these tricyclic molecules would be obtained by a regioselective transition-metal-catalyzed [2 + 2 + 2] cyclotrimerization reaction of an appropriately substituted diyne **8** or **9**. These diynes would be readily prepared from commercially

available olivetol. A high level of regioselectivity in the cyclotrimerization step will be induced through a sterically demanding trimethylsilyl (TMS) group which can subsequently be removed in a traceless fashion.

First, the optimal structural features for an efficient and regioselective [2 + 2 + 2] cyclotrimerization reaction toward the cannabinoid core structure were delineated by synthesizing a series of model diynes (**10–15**) that differed in their electronic and steric properties (Scheme 2; see the Supporting

Scheme 2. Investigation of the [2 + 2 + 2] Cyclotrimerization Key Step of the Diynes **10–15**



Information for diyne syntheses). These molecules were subjected to Ru-catalyzed cyclotrimerization reactions (10 mol % of Cp^{*}Ru(cod)Cl¹⁶) with 1-hexyne (10 equiv) under microwave irradiation^{17,18} (toluene, 300 W, 10 min, sealed-vessel). The terminal diyne **10**¹⁹ delivered the cyclotrimerization product **16** in a 61% yield as a 70:30 regioisomeric mixture of pyrans as determined by GC/MS and ¹H NMR analysis. The cyclotrimerization reaction of the ester analogue **11**²⁰ led to an increased regioselectivity in favor of the isomer **17a** over the isomer **17b** (76:24 based on ¹H NMR analysis) with a diminished yield of 31%. This result correlates well with Yamamoto's findings under nonmicrowave irradiation conditions.²⁰ The low yields in case of **10** and **11** are a result of di- and trimerization of the diyne starting material, a problem commonly seen in cyclotrimerization reactions of

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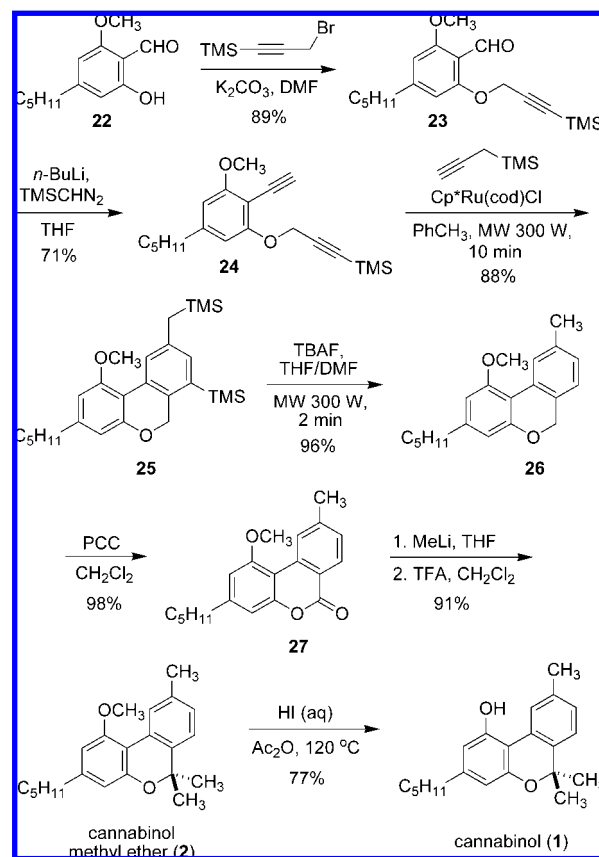
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reactive (terminal) diynes.^{16,21} The introduction of a methyl group ($R^1 = \text{CH}_3$) on one of the triple bonds produced a highly efficient and regioselective cyclotrimerization reaction delivering **18a** (95:5) in 96% yield from the diyne **12**. The corresponding ester derivative **13** was converted in 71% yield into the pyrone **19a** with complete regioselectivity. These results indicated the ability to induce high levels of regioselectivity in the cyclotrimerization reaction toward the tricyclic cannabinoid core. For the synthesis of the natural cannabinoids, a removable regiodirecting group was desired. Toward this goal, the TMS-derivatized diynes **14** and **15** were prepared and investigated in the cyclotrimerization reaction. Continuing with the trend that increased steric bulk leads to a more efficient cyclotrimerization, both diynes **14** and **15** furnished the desired products **20a** (97% yield) and **21a** (81% yield), respectively, both with complete regioselectivity. These trends underscore the necessity to balance reactivity and steric demand in order to achieve highly efficient [2 + 2 + 2] cyclotrimerization reactions. Diynes based on both **14** and **15** are suitable cyclotrimerization precursors for the synthesis of **1–3**, and the ability to replace the TMS group with a hydrogen atom has previously been shown.²²

Our synthesis of **1** commences with the known salicylaldehyde derivative **22**²³ (prepared in three steps from olivetol) which is alkylated with 3-bromo-1-trimethylsilyl-1-propyne to give the propargyl ether **23** (89% yield, Scheme 3). Installation of the second triple bond was accomplished by treatment of **23** with the lithium salt of trimethylsilyldiazomethane²⁴ furnishing the diyne **24** in 71% yield. Attempts to synthesize ester-tethered diynes (as in **9**) via a Corey–Fuchs reaction (and related transformations) or a Sonogashira coupling were unsuccessful or extremely low yielding. As in the case of the model study with the diyne **14**, the compound **24** underwent an efficient and regioselective $\text{Cp}^*\text{Ru}(\text{cod})\text{Cl}$ -catalyzed [2 + 2 + 2] cyclotrimerization reaction with propargyltrimethylsilane under microwave irradiation to deliver the pyran **25** in 88% yield as a single regioisomer. A reaction with propyne under pressurized closed-vessel microwave conditions was not conducted due to its low boiling point. Removal of the aryl- and alkyl-TMS groups was rapidly accomplished by exposure to TBAF under microwave irradiation for 2 min to give the desilylated pyran **26** (96% yield). The next steps involved incorporation of the *gem*-dimethyl substituents at the 6-position of the pyran ring. First, a selective oxidation of the benzylic methylene group with PCC furnished the pyrone **27** in 98% yield.²⁵ Cannabylactones related to **27** have been shown to be selective CB_2 agonists.²⁶ Addition of CH_3Li followed by an

Scheme 3. Total Synthesis of Natural Cannabinol (**1**) and Cannabinol Methyl Ether (**2**)



acid-catalyzed ring closure of the crude diol provided cannabinol methyl ether (**2**), a natural product observed in plant extracts from *Cannabis sativa*,²⁷ in 91% yield over two steps.

Subsequent deprotection of the methylphenol with aqueous HI (77% yield) completed the total synthesis of cannabinol (**1**). The use of BBr_3 in the demethylation reaction delivered **1** with an identical yield.

The developed route to cannabinol was modified to allow for the facile synthesis of the isomeric cannabinoid, cannabinodiol (**3**).²⁸ In this direction, demethylation of the ether **27** with aqueous HI smoothly provided the phenol **28**²⁹ in quantitative yield (Scheme 4). Treatment of **28** with excess MeMgBr furnished a crude triol that was subsequently dehydrated with methanesulfonyl chloride and TEA to deliver the methylstyrene (**29**) in 61% yield over two steps as well as 22% of mesylated cannabinol. Deprotection of the phenolic hydroxy groups with excess MeLi ³⁰ delivered natural cannabinodiol (**3**) in 72% yield.²⁸

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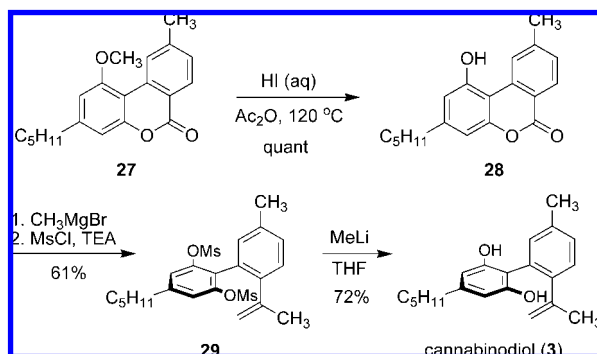
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Scheme 4. Total Synthesis of Cannabinodiol (**3**)



In summary, we have developed a novel route to the cannabinoid framework via a ruthenium-catalyzed microwave-mediated $[2 + 2 + 2]$ cyclotrimerization reaction. Several diyne precursors for the synthesis of the tricyclic core structure were probed to investigate the steric and electronic effects on the $[2 + 2 + 2]$ cyclotrimerization efficiency and

regioselectivity. Three natural products, cannabinol (**1**), cannabinol methyl ether (**2**), and cannabinodiol (**3**), were synthesized to illustrate the flexibility of this approach to the cannabinoid architecture. The developed cyclotrimerization approach enables the rapid introduction of a diverse set of substituents at the 7-, 8-, 9-, and 10-positions (see Figure 1) of the C-ring through the reaction of substituted diynes with a variety of alkynes.^{17,30}

Acknowledgment. This research was supported by the Donors of the American Chemical Society Petroleum Research Fund and the Department of Chemistry at North Carolina State University. We thank CEM Corp. for their support.

Supporting Information Available: General cyclotrimerization protocol, experimental details, and analytical data as well as ^1H NMR spectra for compounds **1–3**, **12–16**, **18–21**, **23–27**, and **29**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL800589E