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A Cyclotrimerization Route to Cannabinoids

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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 anticonvulsant[5] properties, among others.[4,6] Cannabinoids act upon two cellular receptors, the central cannabinoid receptor, CB_1, found mainly in the brain, and the peripheral cannabinoid receptor, CB_2, found almost exclusively in the immune system.[7,8] Synthetic cannabinoids which selectively interact with only one recep-

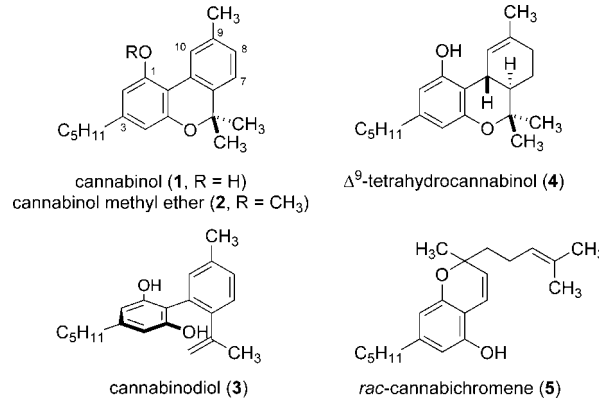

Figure 1. Examples of naturally occurring cannaboids.

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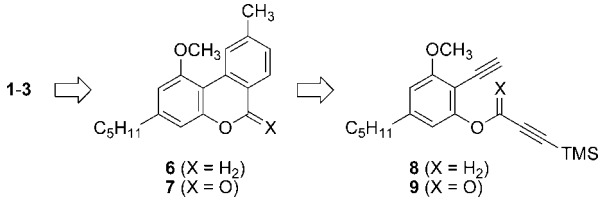
tor are highly desired,[9,10] especially since CB_2-selective ligands should limit the side effects associated with CB_1 receptor activation.[8,11]

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 formation[13] or (2) generating tetrahydro derivatives first via coupling of 5-alkylresorcinols with appropriate cyclohexane 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 reaction[15] 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

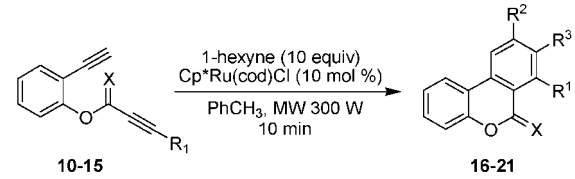
Scheme 1. Retrosynthetic Analysis of Cannabinol (**1**), Cannabinol Methyl Ether (**2**), and Cannabinodiol (**3**)



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**



10-15 **16-21**

a: R^2 = *n*-Bu, R^3 = H
b: R^2 = H, R^3 = *n*-Bu

diyne	X	R^1	product	yield / %	**a** / **b**[a]
10	H_2	H	**16**	61	70 / 30
11	O	H	**17**	31	76 / 24
12	H_2	Me	**18**	96	95 / 5
13	O	Me	**19**	71	>95 / 5
14	H_2	TMS	**20**	97	>95 / 5
15	O	TMS	**21**	81	>95 / 5

[a] Determined by GC/MS and ^{1}H NMR.

Information for diyne syntheses). These molecules were subjected to Ru-catalyzed cyclotrimerization reactions (10 mol % of Cp*Ru(cod)Cl[16]) 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 ^{1}H 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 ^{1}H 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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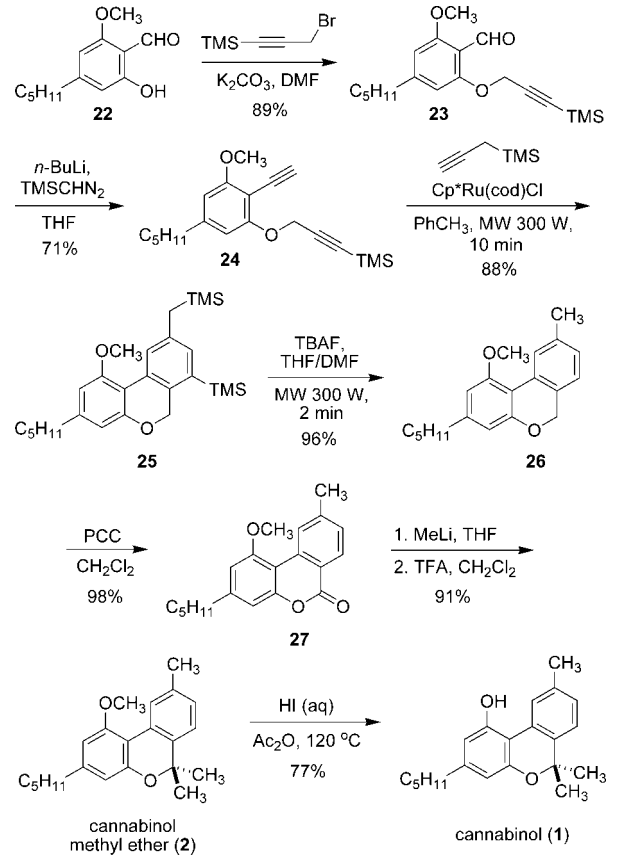
reactive (terminal) diynes.[16,21] The introduction of a methyl group ($R^1 = CH_3$) on one of the triple bonds produced a highly efficient and regioselective cyclotrimerization reaction delivering **18a** (95:5) in 96% yield from the diyne **12**. The corresponding ester derivative **13** was converted 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 trimethylsilyldiazomethane[24] 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 unsuccesful or extremely low yielding. As in the case of the model study with the diyne **14**, the compound **24** underwent an efficient and regioselective Cp*Ru(cod)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] Cannabilactones related to **27** have been shown to be selective CB_2 agonists.[26] Addition of CH_3Li followed by an 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.

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



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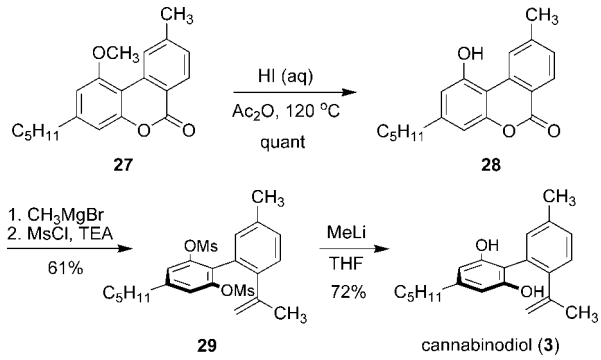
Scheme 4. Total Synthesis of Cannabinodiol (**3**)



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]

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Supporting Information Available: General cyclotrimerization protocol, experimental details, and analytical data as well as ^{1}H 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.

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