

Tricyclic Alkaloid Core Structures Assembled by a Cyclotrimerization—Coupled Intramolecular Nucleophilic Substitution Reaction

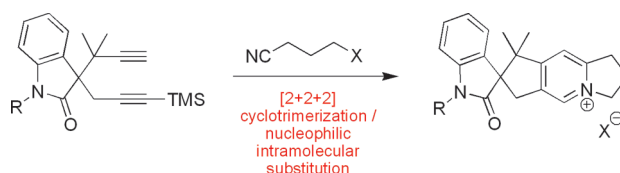
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ABSTRACT



A facile approach to tricyclic alkaloid core structures was developed by sequencing a pyridine-forming [2 + 2 + 2] cyclotrimerization reaction with an intramolecular nucleophilic substitution. This methodology enabled the facile assembly of the spiroindolinone framework of citrinadins A and B, and cyclopiamine B.

Tricyclic alkaloid structures are present in a wide range of natural products, many of which have important biological activity. Figure 1 shows six examples of these types of natural products with the central tricyclic alkaloid core highlighted in red. The citrinadins A (**1**) and B (**2**) are recently isolated marine derived pentacyclic spiroindolinone alkaloids containing a dodecahydrocyclopenta[b]quinolizidine core.^{1,2} They both exhibit important cytotoxic activities against various cancer cell lines with IC₅₀'s in the low micromolar range.^{1,2} No total synthesis of **1** or **2** has been reported to date, but one stereoselective approach to the spirooxindole A,B,C-ring system in seven steps has been accomplished recently.³ Cyclopiamine B (**3**) is another fungal spiroindolinone alkaloid^{4,5} containing six rings including a central tricyclic decahydro-1*H*-cyclopenta[*f*]indolizidine struc-

ture. The biological function of **3** is unknown, and no total synthesis of **3** has been reported.

Other notable natural products containing similar tricyclic alkaloid structures are veraflorizine (**4**), a steroidal cevanine alkaloid⁶ that has also not been synthesized, roserine (**5**), a pyrrolophenanthridinium alkaloid⁷ that has been synthesized once,⁸ and xylopinine (**6**), a protoberberine alkaloid, which is part of a large group of isoquinoline alkaloids that have attracted considerable synthetic interest due to their diverse biological activities.⁹

Building onto our recent applications of microwave-mediated [2 + 2 + 2] cyclotrimerization reactions in the

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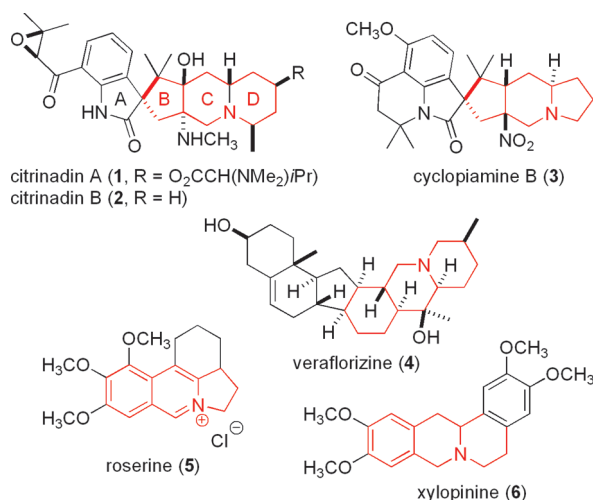


Figure 1. Selected natural products with tricyclic alkaloid core structures shown in red.

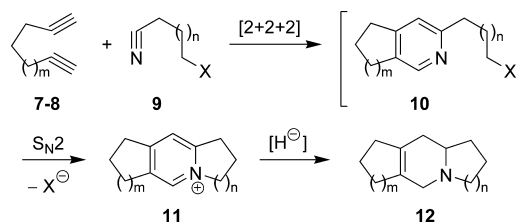
synthesis of alkaloids,^{10,11} we are reporting the sequencing of a cyclotrimerization with an intramolecular pyridinium formation via a nucleophilic substitution to rapidly access a variety of tricyclic alkaloid structures; including the ones present in the natural products shown in Figure 1. Moreover, we are reporting the synthesis of the pentacyclic spiroindolinone core of citrinadin A (1), citrinadin B (2), and cyclopiamine B (3).

The classical [2 + 2 + 2] cyclotrimerization reaction toward pyridines involves the reaction of two alkynes and a nitrile.^{12–14} In order to avoid chemoselectivity issues in the cyclotrimerization step, the two alkynes are often tethered together, leading to the synthesis of fused pyridine rings.^{12–16} These cyclotrimerization reactions are typically conducted under cobalt catalysis.^{12–17} Recently, it was discovered by others^{18–22} and us^{23,24} that microwave irradiation^{25–27} greatly enhances the rates and yields of [2 + 2 + 2] cyclotrimerization reactions. In the case of Co-catalyzed reactions, reaction times are reduced from days to minutes without the necessity of catalyst activation through additives or light irradiation.

We speculated that a [2 + 2 + 2] cyclotrimerization reaction of the commercially available diynes **7** and **8** with

the nitrile **9** tethered to a leaving group X would deliver the intermediate fused pyridine **10** (Scheme 1). A tandem intramolecular S_N2 reaction would directly form the tricyclic pyridinium compounds **11**, which could subsequently be reduced, e.g., with NaBH₄, to give the tricyclic structures **12**. This reaction sequence could provide the alkaloid core structures found in the natural products in Figure 1 in as little as two steps.

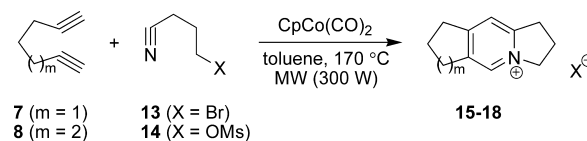
Scheme 1. [2 + 2 + 2] Cyclotrimerization Reaction Coupled with an Intramolecular S_N2 Reaction Enables the Rapid Assembly of Tricyclic Pyridinium Ions **11** and a Subsequent Reduction Delivers the Alkaloid Core Structures **12**^a



^a X = Br, I, OSO₂CH₃; m, n ≥ 1.

The investigation of this approach commenced with commercially available 1,6-heptadiyne (**7**) or 1,7-octadiyne (**8**) by reacting each with either 4-bromobutyronitrile (**13**) or the corresponding cyano mesylate **14**²⁸ to directly produce the tricyclic pyridinium structures **15–18** (Scheme 2). The tricyclic molecules **15–18** were obtained in 22–45% yield (40 min). Increasing the reaction times to 1 h or increasing the amount of the nitrile **13** or **14** to >10 equiv did not afford improved yields.

Scheme 2. Tandem [2 + 2 + 2] Cyclotrimerization–Substitution Reactions Delivering the Pyridinium Compounds **15–18** with Bromide and Mesylate Counterions



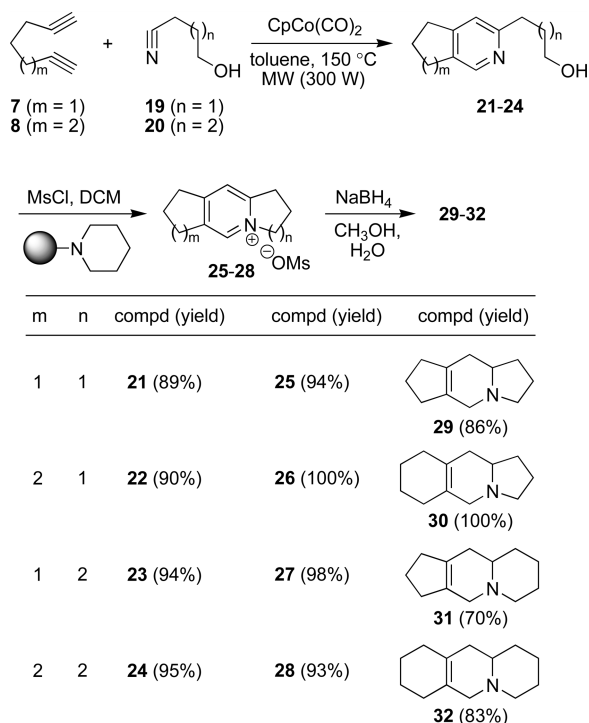
m	X	compd (yield)
1	Br	15 (33%)
2	Br	16 (45%)
1	OMs	17 (22%)
2	OMs	18 (36%)

We suspected that the modest yields for **15–18** were caused by decomposition of the pyridinium salts due to their strong absorption of microwave irradiation based on their ionic nature^{25–27} leading to localized heating in the microwave reactor. Additionally, the intermolecular reaction of the pyridine intermediate **10** with an excess alkyl bromide

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13 or mesylate **14** could potentially lead to a competing side reaction. In order to solve this problem, we employed a two-step cyclotrimerization–substitution process. Here, the diynes **7** and **8** underwent a smooth cyclotrimerization reaction using the $\text{CpCo}(\text{CO})_2$ catalyst in toluene under microwave irradiation (300 W) for 40 min with the known cyano alcohols **19** and **20**.²⁸ This afforded the fused bicyclic pyridine rings **21–24**, bearing an ε -hydroxyalkyl chain (Scheme 3), in

Scheme 3. Two-Step [2 + 2 + 2] Cyclotrimerization–Substitution Reaction Followed by Reduction to the Indolizines and Quinolizines **29–32**

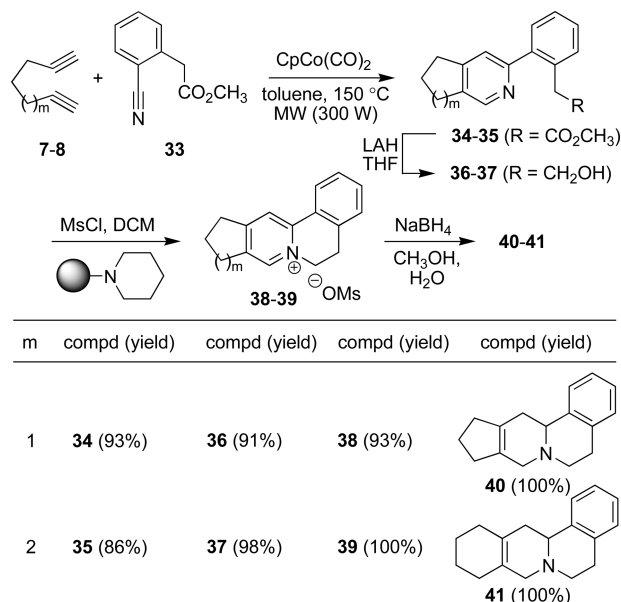


89–95% yield. The hydroxy group was then converted into a mesylate in situ using MsCl and polymer-bound piperidine as the base, thus obviating purification and affording clean products **25–28** in almost quantitative yield. The overall yield for formation of the tricyclic pyridinium compounds **25–28** from the diynes **7–8** was greater than 80%, making this two-step reaction favorable over the tandem one-step reaction depicted in Scheme 2. The reduction of the pyridinium rings was accomplished using NaBH_4 ²⁹ (Scheme 3) to afford the amines **29–32** that display the tricyclic motif found in the natural products **1–6** (Figure 1). The remaining double bond represents a valuable handle for potential further functionalization toward the installation of the substituents present in citrinadin A and B (**1** and **2**), and cyclopiamine B (**3**).

In order to demonstrate the generality of the developed approach, another reaction sequence was performed that would lead to the core structure of xylopinine (**6**). The nitrile **33** was synthesized starting from commercially available 2-iodophenylacetic acid, which was converted to the methyl

ester in 94% yield, followed by a reaction with CuCN ³⁰ delivering the nitrile **33** in 85% yield. The nitrile **33** was reacted in a Co-catalyzed cyclotrimerization reaction with the two diynes **7** and **8** in toluene under microwave irradiation (300 W) for 40 min to give the pyridines **34** and **35** in 93% and 86% yield, respectively (Scheme 4). This

Scheme 4. Three-step Cyclotrimerization–Substitution Reaction to form the Tetracyclic Pyridinium Compounds **38–39** Followed by Reduction to **40–41**



was followed by a LiAlH_4 reduction of the esters **34** and **35** to the alcohols **36** and **37**. The pyridinium formation was conducted under the previously developed cyclization conditions using MsCl and polymer bound piperidine to afford the tricyclic compounds **38** and **39** in near-quantitative yields. Reduction of **38** and **39** with NaBH_4 delivered the tetracyclic molecules **40** and **41** in quantitative yield (Scheme 4).

The developed route shown in Scheme 3 was applied to the synthesis of the core structure of citrinadins A (**1**) and B (**2**) and cyclopiamine B (**3**). The synthesis commenced with the known ester **42** (Scheme 5A).³¹ Reduction of the nitro

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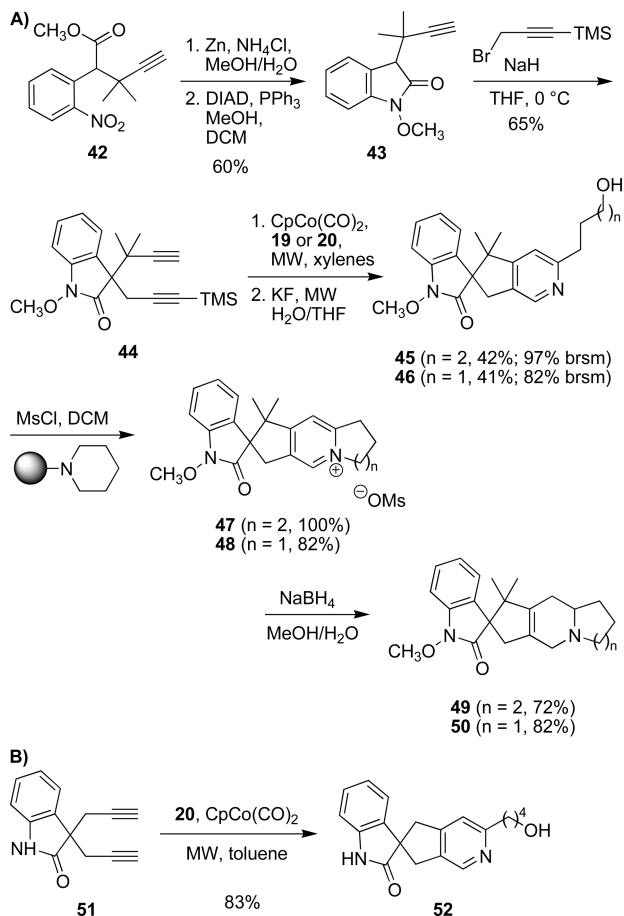
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Scheme 5. (A) Synthesis of Racemic **49** and **50**, the Core Structures of Citrinadin A (**1**) and B (**2**), as Well as Cyclopamine B (**3**).^a (B) Reaction of the Terminal Diyne **51** Produced the Pyridine **52** in Good Yield



^a brsm = based on recovered starting material.

group with zinc and ammonium chloride^{31,32} followed by a Mitsunobu reaction³³ with methanol produced the known methoxy oxindole **43** in 60% yield over both steps. Treatment of **43** with 3-bromo-1-trimethylsilyl-1-propyne and NaH generated the diyne **44** in 65% yield, which set the stage for the [2 + 2 + 2] cyclotrimerization reaction. The cyclotrimerization reaction was accomplished by reacting the diyne **44** with 4-hydroxypentanenitrile (**20**, $n = 2$) for the citrinadin A (**1**) and B (**2**) core and with 4-hydroxybutanenitrile (**19**, $n = 1$) for the cyclopamine B (**3**) core in the presence of

CpCo(CO)_2 under microwave irradiation (300 W, 90 min). This delivered the pyridines **45** and **46** in 42% and 41% yield, respectively. In addition, 57% and 50% of the starting material **44** was recovered, but extending reaction times led to unidentified by-products. Gratifyingly, both compounds were obtained as single regioisomers, since the bulky trimethylsilyl (TMS) group on **44** directs the formation of the desired pyridine regioisomer.^{34–36} However, the sterically demanding TMS group also leads to the moderate cyclotrimerization yields, as previously observed.^{34,37–39} As expected, the cyclotrimerization reaction with the terminal diyne **51** delivered the pyridine **52** in a much higher yield of 83% (Scheme 5B). The majority of the TMS moiety was removed from the cyclotrimerization product of **44** under the cyclotrimerization microwave conditions, and any remaining silyl groups were cleaved by a subsequent treatment with potassium fluoride under microwave irradiation (300 W, 2 min) to give the desired products **45** and **46**. The substitution and reduction sequence following Scheme 3 was then employed by treating the alcohols **45** and **46** with MsCl in the presence of polymer-bound piperidine to produce the pyridinium compounds **47** and **48** in excellent yields. Reduction with NaBH_4 completed the pentacyclic spiroindolinone framework **49** of citrinadin A (**1**) and B (**2**) in 72% yield and the alkaloid core structure **50** of cyclopamine B (**3**) in 82% yield. The overall yield of the assembly of **49** and **50** from the common diyne **44** was 30% and 28%, respectively.

In summary, we developed an expedient route to tricyclic alkaloid core structures by conducting a microwave-mediated [2 + 2 + 2] cyclotrimerization/intramolecular nucleophilic substitution/reduction sequence. This methodology was demonstrated to deliver several tricyclic frameworks in good to excellent yield. These represent the core structures in a variety of natural alkaloids with important biological activities.

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Supporting Information Available: Detailed experimental procedures, analytical data, and copies of NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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