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

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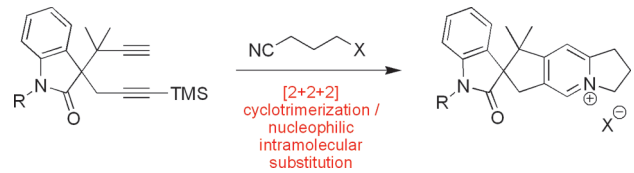
ABSTRACT



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*]quinolizine core.[1,2] They both exhibit important cytotoxic activities against various cancer cell lines with IC_{50}'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*]indolizine structure. 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 alkaloid[6] that has also not been synthesized, roserine (**5**), a pyrrolophenanthridinium alkaloid[7] 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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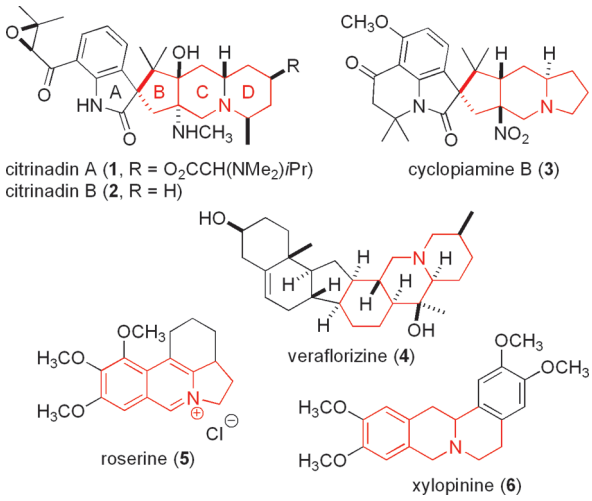


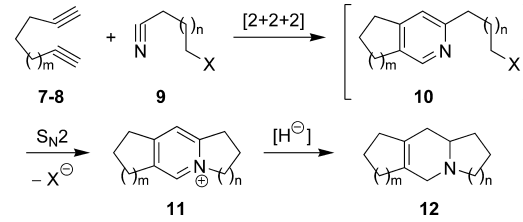
Figure 1. Selected natural products with tricyclic alkaloid core structures shown in red.

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 $NaBH_4$, 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.

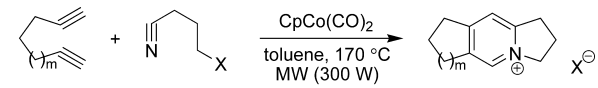
Scheme 1. [2 + 2 + 2] Cyclotrimerization Reaction Coupled with an Intramolecular S_N2 Reaction Enables the Rapid Assembly of Tricyclic Pyridinium Ions **11** and a Subsequent Reduction Delivers the Alkaloid Core Structures **12**[a]



[a] X = Br, I, OSO_2CH_3; *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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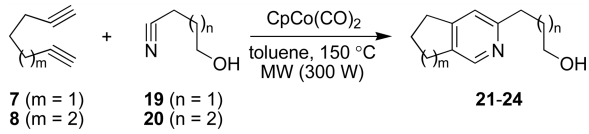
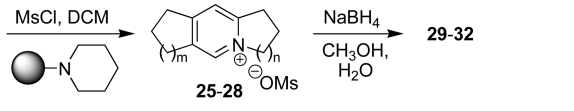
13 or mesylate **14** could potentially lead to a competing side reaction. In order to solve this problem, we employed a two-step cyclotrimerization−substitution process. Here, the diynes **7** and **8** underwent a smooth cyclotrimerization reaction using the $CpCo(CO)_2$ catalyst in toluene under microwave 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**



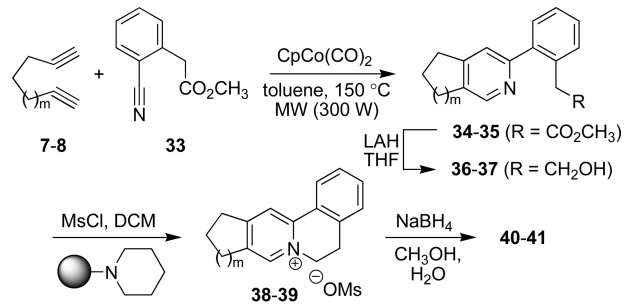


m	n	compd (yield)	compd (yield)	compd (yield)
1	1	**21** (89%)	**25** (94%)	**29** (86%)
2	1	**22** (90%)	**26** (100%)	**30** (100%)
1	2	**23** (94%)	**27** (98%)	**31** (70%)
2	2	**24** (95%)	**28** (93%)	**32** (83%)

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**



m	compd (yield)	compd (yield)	compd (yield)	compd (yield)
1	**34** (93%)	**36** (91%)	**38** (93%)	**40** (100%)
2	**35** (86%)	**37** (98%)	**39** (100%)	**41** (100%)

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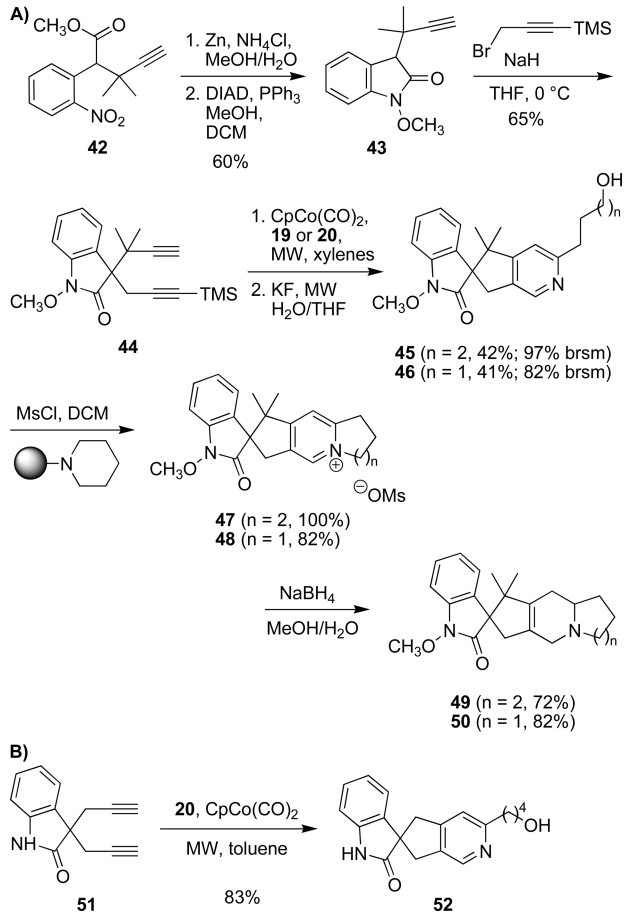
Scheme 5. (A) Synthesis of Racemic **49** and **50**, the Core Structures of Citrinadin A (**1**) and B (**2**), as Well as Cyclopiamine B (**3**).[a] (B) Reaction of the Terminal Diyne **51** Produced the Pyridine **52** in Good Yield



[a] brsm = based on recovered starting material.

group with zinc and ammonium chloride[31,32] followed by a Mitsunobu reaction[33] 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 cyclopiamine 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 cyclopiamine 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 tricylic 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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