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Formal Total Synthesis of Echinopines A and B via Cr(0)-Promoted [6π + 2π] Cycloaddition

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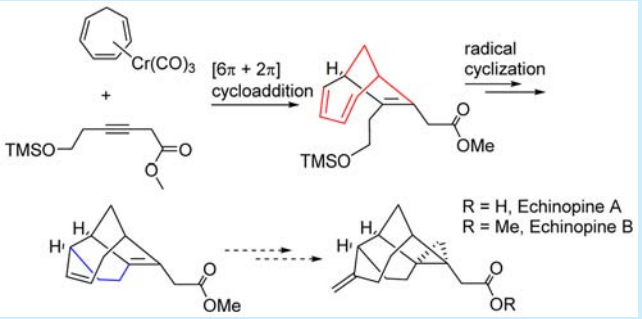
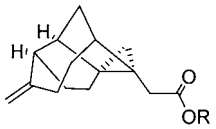
Supporting Information

ABSTRACT: A concise formal synthesis of echinopines A and B is reported. The key [5.5.7] tricyclic intermediate, which has been previously used for the synthesis of echinopine A and B, was assembled using Cr(0)-promoted photochemical [6π + 2π] cycloaddition followed by a radical cyclization step.



The sesquiterpenes echinopines A (**1**) and B (**2**) were recently isolated from the roots of *Echinops spinosus* by Shi and Kiyota.[1] Structures for these novel sesquiterpenoids were unambiguously assigned a unique [3.5.5.7] framework, through detailed spectroscopic studies (Figure 1). It was proposed that



R = H, **Echinopine** A (**1**)
R = Me, **Echinopine** B (**2**)

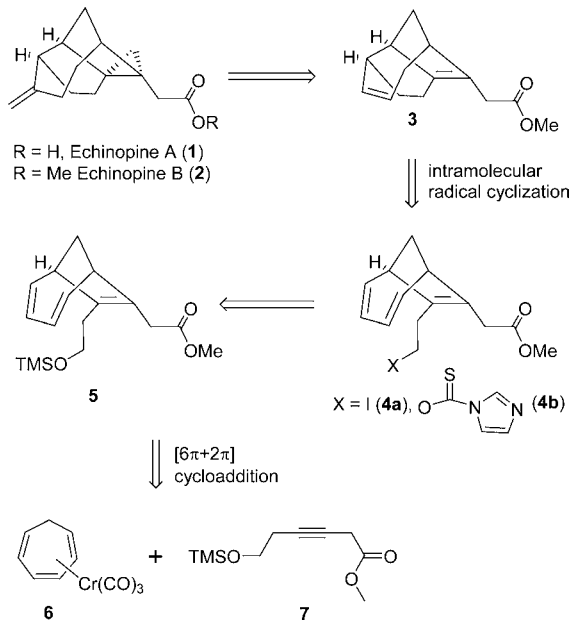
Figure 1. Structures of echinopine A and B.

the echinopines A (**1**) and B (**2**) can be biosynthesized from a guanine type precursor, through a series of rearrangements.[1] The unprecedented tetracyclic structure of these molecules had attracted considerable attention from the synthetic community. In 2009, Mulzer and co-workers reported the first enantioselective total synthesis of **1** and **2** and determined the absolute configurations of these two natural products.[2] Various other groups have also been involved in synthetic studies on **1** and **2**.[3−6] In spite of the successful application of novel methods to this problem, the existing syntheses typically required rather lengthy routes (more than 20 steps). Recently Vanderwal and co-workers achieved a biosynthetically inspired total synthesis of echinopine B via a shorter pathway, although the overall yield was low.[7] Herein, we report a short and efficient formal synthesis of echinopines A and B, using a distinctly different strategy than those previously reported.[3−7]

A major challenge to the successful total synthesis of **1** and **2** is the construction of the bicyclo[4.2.1]nonane core structure. Direct assembly of this unit is not easily addressed by conventional methods as evidenced by the lengthy syntheses described previously. In contrast, it was envisioned that the bicyclo[4.2.1]nonane substructure could be easily built by employing an appropriate Cr(0)-promoted [6π + 2π] cycloaddition reaction (Scheme 1).[8,9]

Furthermore, the total synthesis of **1** and **2** could be seen as deriving from the advanced tricyclic intermediate **3** (Scheme 1). This advanced intermediate could be obtained by an intriguing

Scheme 1. Retrosynthetic Analysis of 1 and 2



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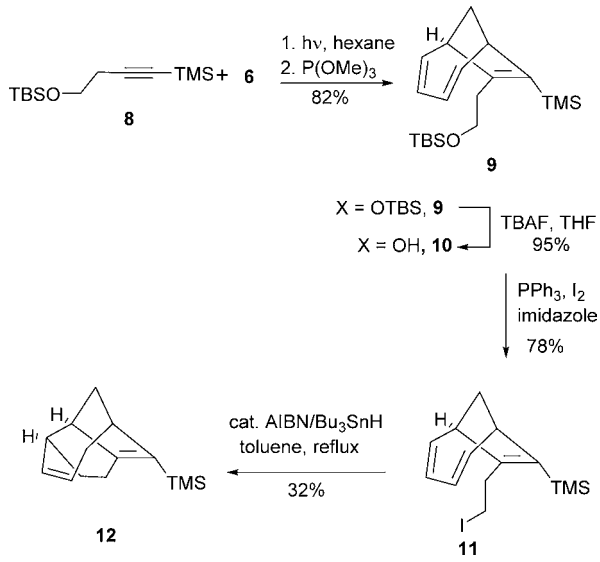
regioselective 5-exo trig intramolecular radical cyclization in compound **4a** or **4b**,[10] which in turn could be accessed from intermediate **5** through simple functional group manipulation.

In turn, the key bicyclo[4.2.1]nonane intermediate **5** could be obtained from the photochemical [6π + 2π] cycloaddition of alkyne **7** and [η^6-1,3,5-cycloheptatriene]tricarbonyl chromium-(0) complex **6**.

Based on extensive experience from our laboratory,[11] the projected photochemical [6π + 2π] cycloaddition between **6** and disubstituted alkynes was plausible without undergoing a multicomponent cycloaddition. However, the lack of precedence for the critical regioselective radical cyclization in a related environment[10] prompted a model study to test the viability of the proposed approach. With this in mind, known trimethylsilyl substituted alkyne **8**[12] was treated with **6** under standard photochemical [6π + 2π] conditions[10] and, after decomplexation with trimethyl phosphite ($P(OMe)_3$), yielded the bicyclo[4.2.1]nonane intermediate **9** in excellent yield (Scheme 2). The silyl-ether compound **9** was subsequently

Scheme 2. Model Study for the Construction of the Tricycle

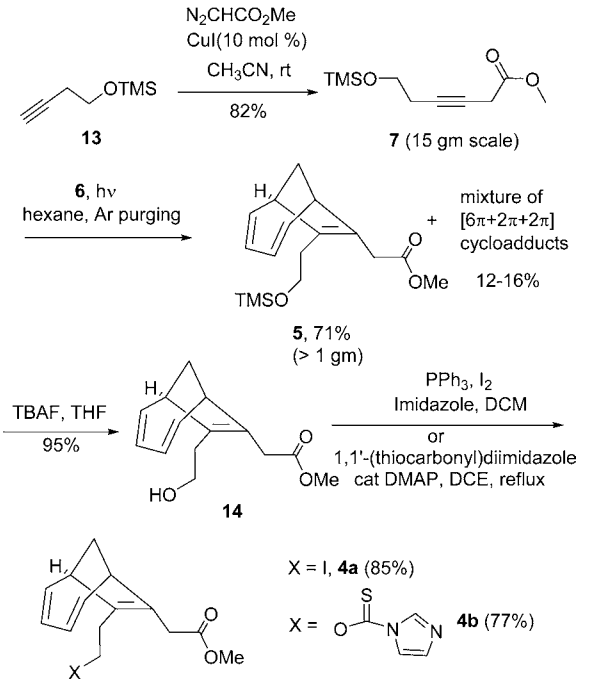


deprotected using tetrabutylammonium fluoride (TBAF) to generate alcohol **10**, which was in turn converted to the corresponding iodo derivative **11** by treatment with PPh_3/I_2. With the desired compound **11** in hand, efforts to effect ring formation employing standard radical cyclization conditions (i.e., reflux with tributyltin hydride (Bu_3SnH) in the presence of catalytic azobis(isobutyronitrile) (AIBN)) were examined.[13]

This afforded the desired [5,5,7] tricyclic core structure **12** with excellent stereo- and regiocontrol, in a modest 32% yield (not optimized) thus providing support for the viability of the intramolecular radical cyclization approach. A visible light induced photoredox radical cyclization procedure failed to produce the desired result.[14]

With the success of the model study, efforts toward the total synthesis of echinopines A (**1**) and B (**2**) were initiated. The requisite substituted alkynoate **7** was easily prepared in multigram quantities, employing the CuI catalyzed C−H insertion method reported by Fu and co-workers (Scheme 3).[15] Following standard reaction conditions for the [6π + 2π] cycloaddition, a dilute hexane solution of **6** (1.0 equiv) and excess alkyne **7** (3 equiv) was irradiated using a Canrad-

Scheme 3. Synthesis of Cyclization Precursors 4a and 4b



Hanovia 450-W medium-pressure mercury vapor lamp under constant Ar purging. After the decomplexation of the resultant cycloadduct, the bicyclo[4.2.1]nonane intermediate **5** was obtained in 71% yield. Unfortunately, the formation of small amounts of undesired [6π + 2π + 2π] tetracyclic cycloadducts could not be avoided under any circumstances and resulted in a reduced 71% yield of the otherwise smooth reaction.[16]

The trimethylsilyl protected primary alcohol **5** was readily deprotected by treatment with TBAF affording the corresponding alcohol **14** in excellent yield. The alcohol **14** was then converted in good yield to the required cyclization precursors **4a** and **4b** with PPh_3/I_2/imidazole and 1,1′-(thiocarbonyl)-diimidazole, respectively.

Having secured a short route to the radical cyclization precursors, our attention turned to the optimization of the key cyclization step. A number of conditions were tested in this context (Table 1). The investigation started with the labile iodo substrate **4a**. The slow addition of a tributyltin hydride/AIBN mixture to the refluxing, diluted toluene solution of **4a** gave a mixture of inseparable products, whereas addition of the tributyltinhydride in one portion gave the desired tricyclic product **3** as a single isolable product in a modest 41% yield. A 1 equiv amount of radical initiator AIBN was found to be optimal in this transformation. Any improvement in yield was not observed after changing the hydride source or the radical initiator. Samarium iodide promoted radical cyclization led to decomposition of the starting material.[17] Finally, it was observed that changing the substrate to the corresponding xanthate **4b** afforded an acceptable 61% yield.[13]

Synthesis of the tricyclic methyl ester derivative **3** constitutes a formal synthesis of echinopines A and B as the conversion of **3** to **1** and **2** can be achieved in five or six steps, respectively, as reported by Magauer, Mulzer, and Tiefenbacher in 2009 (Scheme 4).[2] Thus, we have successfully achieved a formal synthesis of echinopine A and B via a five step (26% overall yield) sequence to the known intermediate **3** starting from the

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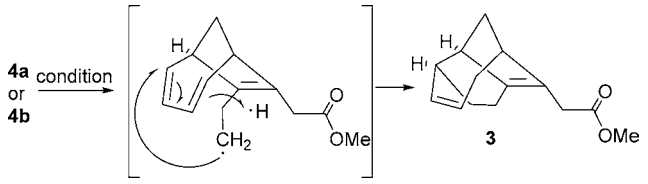
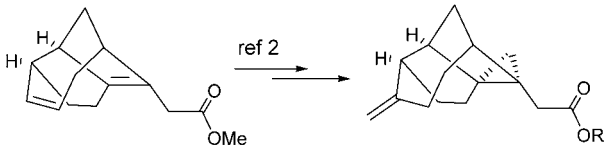
Table 1. Optimization of the Radical Cyclization



entry	substrate	condition	radical initiator	hydride source	time (h)	yield (%)
1	**4a**	A[a]	AIBN (0.1 equiv)	TBTH	2	–[b]
2	**4a**	B[c]	AIBN (0.1 equiv)	TBTH	6	37
3	**4a**	B	AIBN (1 equiv)	TBTH	1.5	41
4	**4a**	B	AIBN/ABCN (1 equiv)	TBTH/TPTH/TTMSS	1–3	28–39
5	**4a**		SmI_2	tBuOH	0.5	–[d]
6	**4b**	A	AIBN (1 equiv)	TBTH	1	–[b]
7	**4b**	B	AIBN (1 equiv)	TBTH	1.5	61

[a]Procedure A: slow addition of TBTH/AIBN mixture to a refluxing dilute toluene solution of **4a**/**4b**, via syringe pump. [b]Complex inseparable mixture. [c]Procedure B: slow addition of TBTH/AIBN mixture to the refluxing dilute toluene solution, via syringe pump. [d]Starting material decomposed.

Scheme 4. Formal Synthesis of Echinopines A and B



commercially available 4-trimethylsiloxy-1-butyne **13** and cycloheptatriene complex **6**.

In summary, an efficient formal synthesis of echinopines A and B has been accomplished using Cr(0)-promoted photoinduced [6π + 2π] cycloaddition as the key step. Use of a novel intramolecular radical cyclization step involving an inactivated cyclic diene to access the tricyclic natural product core has also been reported.

■ ASSOCIATED CONTENT

Supporting Information

All experimental procedures and spectroscopic data of compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01326.

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Notes

The authors declare no competing financial interest.

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