Natural Product Synthesis

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A Synthesis of Echinopine B**

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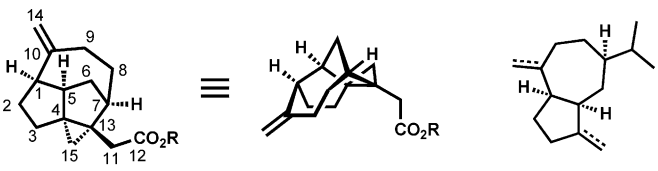
The synthesis of natural products of unprecedented structure can drive innovation in strategy and provide opportunities to test the limits of new methodology; therefore, it remains a worthy venture even when the targets are not yet known to possess important biological activity. In that context, we felt that the synthesis of the structurally unusual echinopines (Scheme 1) was warranted for the opportunity to evaluate metal-catalyzed polycyclizations in complex settings, and to access these natural products and structural analogues for a broader evaluation of their biological properties.



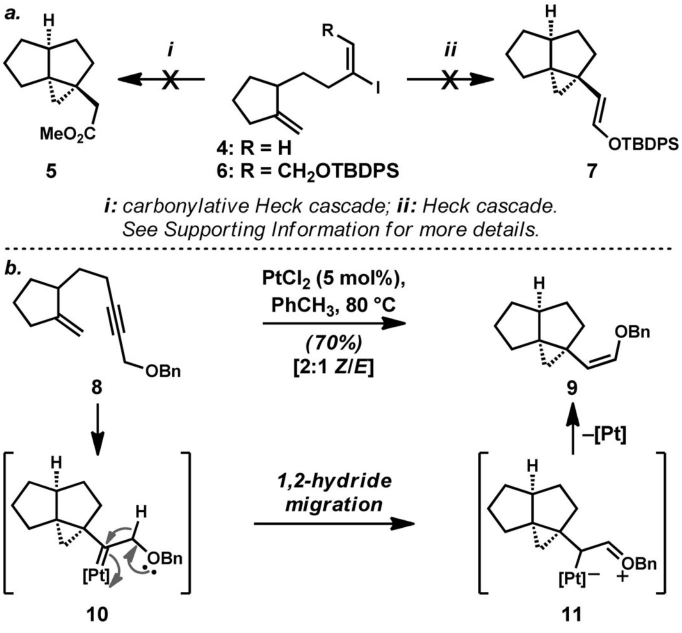
1: R = H: echinopine A
2: R = Me: echinopine B

3: *cis*-guaiane skeleton

Scheme 1. The echinopines and the related guaiane framework.

Echinopines A and B (**1** and **2**) are sesquiterpenes isolated by Kiyota and co-workers from the root of the plant *Echinops spinosus*[1] and they probably originate from biosynthetic modification of the guaiane framework (see **3**). In spite of the lack of reported biological activity, their novel structure inspired several research groups to embark upon and complete syntheses of these compounds. First, in 2009, Magauer, Mulzer, and Tiefenbacher reported a clever enantioselective route beginning from 1,5-cyclooctadiene; this work served to determine the absolute configuration of these natural products.[2] Shortly thereafter in 2010, Nicolaou, Chen, and co-workers in Singapore reported an asymmetric synthesis of these targets.[3] A formal synthesis followed later that year from Chen and co-workers.[4] We felt that a strategy related to the presumed biogenesis of the echinopines might yield a more direct synthesis than these previous routes. We posited that a bioinspired conversion of a suitably functionalized *cis*-fused guaiane-like precursor into the tetracyclic core of the echinopines might take place through a transition-metal catalyzed bicyclization reaction; the cyclopropane acetic acid/ester functional group would then be introduced directly, thus avoiding the multi-step homologation of cyclopropane carboxylate ester intermediates that was employed in previous syntheses. In a third-generation route to the echinopines, Chen and co-workers recently reported the successful execution of a related strategy, providing echinopine B in 25 steps.[5] Herein, we report our synthesis of echinopine B, which proceeds through a concise sequence featuring a one-step conversion of a guaiane-like intermediate to the natural product.

Initially, much effort was put forth to generate the fused tricyclic motif, which consisted of the cyclopropane and two cyclopentane rings, and involved either a carbonylative Heck cascade (**4**→**5**, Scheme 2a) or a Heck bicyclization terminating in β-hydride elimination (**6**→**7**); unfortunately, these approaches were never successful.[6] In late 2009, we were inspired by a $PtCl_2$-catalyzed reaction of alkene-tethered propargylic ethers that was disclosed by Michelet and co-workers.[7] In the simple enyne model system **8** (Scheme 2b),



i: carbonylative Heck cascade; ii: Heck cascade. See Supporting Information for more details.

Scheme 2. a) Attempted Heck cascades to access tricycles relevant to the echinopines. b) Successful enyne cycloisomerization. Bn = benzyl, TBDPS = *tert*-butyldiphenylsilyl.

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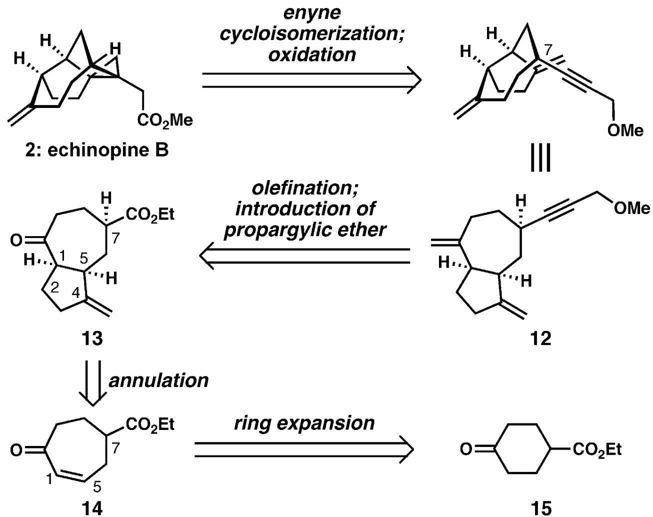
our first reaction under conditions prescribed by Michelet and co-workers efficiently afforded **9**, which contained the key tricyclic architecture of our target molecules. Although reports of coinage-metal-catalyzed enyne cycloisomerization reactions to access fused cyclopropanes were plentiful in the literature,[8,9] Michelet and coworkers' particular advance—using the propargylic ether to induce reaction termination by 1,2-hydride migration—yielded exactly the type of product that we were aiming to access by Heck approaches, and without the need for a complex vinyl halide precursor.

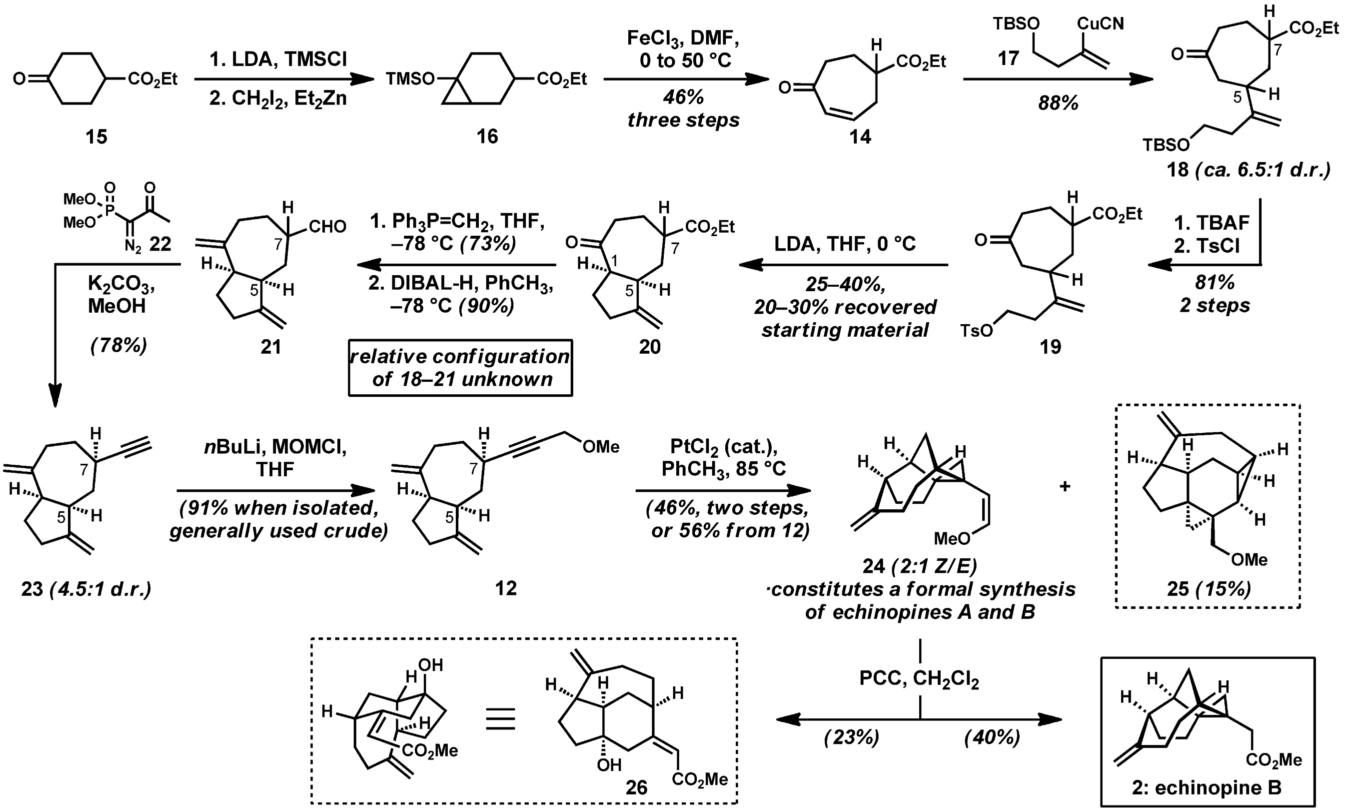
To implement this cycloisomerization reaction in the synthesis of the echinopines, we required a stereocontrolled synthesis of a *cis*-fused guaiane-like bicyclo[5.3.0]decane with a C7 propargylic ether substituent projected into the concavity of the bicycle (**12**, Scheme 3). The propargylic ether should arise from the ester in **13**. The bicyclic structure should be accessible by a Piers-type annulation[10] onto C5 and C1 of δ-substituted cycloheptenone **14**, which would arise from ring expansion of ketoester **15**.

The silyl enol ether of inexpensive ketone **15** underwent a modified Saegusa-type ring expansion[11] via intermediate silyloxycyclopropane **16** to afford cycloheptenone **14** (Scheme 4). We found that the usual two-pot procedure—$FeCl_3$-mediated chlorinative ring expansion followed by elimination of the resulting β-chloroketone—could be performed in a single step: treating **16** with excess $FeCl_3$ in DMF and warming the mixture from 0 to 50 °C gave **14** directly, and in 46 % overall yield from cyclohexanone **15**.



Scheme 3. Pt^{II}-catalyzed ene propargylic ether cycloisomerization approach to the echinopines.

One-step methylenecyclopentane annulations onto cycloheptenone **14** using the bifunctional reagents that Piers and Karunaratna had used successfully on cyclohexenones[10] proved unsuccessful, so a stepwise route was adopted (Scheme 4). After some optimization, treatment of **14** with cuprate **17** reliably gave conjugate adduct **18** as a 6.5:1 mixture of diasteromers in 88 % yield; a single isomer could be isolated from this mixture in 55 % yield, if desired. At this



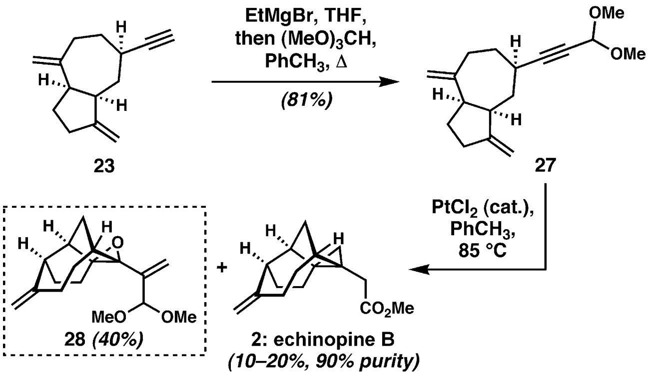
Scheme 4. Synthesis of echinopine B and formal synthesis of echinopine A through ene propargylic ether cycloisomerization. DIBAL-H = diisobutylaluminum hydride, DMF = *N*,*N*-dimethylformamide, LDA = lithium diisopropylamide, MOM = methoxymethyl, PCC = pyridinium chlorochromate, TBAF = tetrabutylammonium fluoride, TBS = *tert*-butyldimethylsilyl, THF = tetrahydrofuran, TMS = trimethylsilyl, Ts = *p*-toluenesulfonyl.

stage, we were unable to determine the relative configuration of the major product, presumably owing to conformational equilibria of the cycloheptanone ring; we note that for a straightforward synthesis, we required annulation onto the same face of the cycloheptenone as the resident C7-ester. In two simple steps, the silyl ether was converted into tosylate ester **19**, which was subjected to base-mediated ring closure to *cis*-bicyclo[5.3.0]decane **20**. Even in this bicyclic setting, the relative stereochemical relationship of the ring junction centers to C7 could not be defined with certainty by NMR spectroscopy. This enolate alkylation reaction was generally not run to complete conversion; rather, we typically isolated the desired product in 25–40% yield and recovered close to 30% of the starting material. In so doing, we avoided problematic C1 epimerization that was observed in the course of longer reaction times. Efforts to improve this reaction using halide and mesylate leaving groups, and with different bases, solvents, and temperatures, never led to a particularly efficient ring closure. Nonetheless, gram quantities of bicycle **20** could be easily obtained through this short route, especially with recycling of recovered **19**.

Wittig reaction of the ketone moiety of **20** followed by ester reduction afforded a single diastereomer of aldehyde **21**. Alkynylation with the Ohira–Bestmann reagent (**22**)[12] led to a 4.5:1 ratio of diastereomeric alkyne products. Subjection of aldehyde **21** to the reaction conditions without phosphonate reagent **22** (K_2CO_3, MeOH, 0°C) led to diastereomeric aldehydes in a 4:1 ratio, the minor component of which was the starting stereoisomer. This control experiment provided circumstantial evidence to support epimerization as the major outcome of the Ohira–Bestmann reaction. Lithiation and methoxymethylation (with MOMCl) of the diastereomeric mixture of alkynes (**23**) led to **12** in high yield.

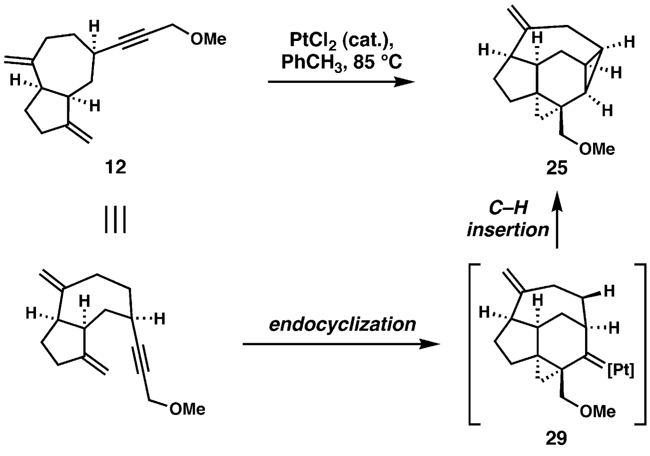
In the initial cycloisomerization experiment, subjection of crude ene-propargylic ether **12** to the conditions prescribed by Michelet and co-workers provided the desired cycloisomerization product **24** as a 2:1 mixture of *Z*/*E* enol-ether isomers (38% yield over two steps from the diastereomeric mixture; the minor diastereomer of the starting material could be observed unchanged in the NMR spectrum of the crude reaction mixture). Successful reaction would only be possible if the C7 configuration were such that the alkyne was projected into the concave face of the *cis*-fused bicyclic ring system; therefore, we hypothesize that the conjugate addition of **17** to **14** generated **18** as predominantly the undesired stereoisomer. The fortuitous epimerization in the course of the alkynylation reaction largely corrected the C7 configuration and enabled the desired cycloisomerization. In later experiments, cycloisomerization was conducted on diastereomerically pure substrate, resulting in a yield of 56% (46% over two steps when **12** is not purified), along with quantities of a cyclopropane-containing side product, which was tentatively assigned as **25**. Although formation of **24** completes a formal synthesis of both echinopines according to the synthesis of Nicolaou, Chen, and co-workers,[3] we opted to generate echinopine B in only one step by enol-ether oxidation as prescribed by Piancatelli et al.[13] Thus, treatment of **24** with PCC provided echinopine B (**2**), along with unexpected side product **26**. The synthesis of echinopine B was complete in only 13 steps.[14]

Although the cycloisomerization reaction smoothly delivered the echinopine architecture from the much simpler guaiane-like bicycle **12**, this sequence required a terminal oxidation step. Furthermore, the efficiency of these last two steps was compromised by the generation of undesired side products **25** and **26**. We considered that cycloisomerization of a substrate at a higher oxidation state might directly generate one of the echinopines while potentially avoiding unwanted reaction pathways. To test this hypothesis, we transformed terminal alkyne **23** directly into dimethyl acetal **27** (Scheme 5). We anticipated the use of a similar Pt^{II}-catalyzed cycloisomerization, because the acetal should confer similar or greater hydride character to the acetal C–H bond. Under the standard reaction conditions that were reported by Michelet and co-workers,[7a] we did indeed observe the formation of echinopine B in moderate yield (up to 20% yield, isolated in about 90% purity), presumably formed via the intermediacy of a hydrolytically unstable ketene acetal. Although ultimately less efficient in terms of overall yield, this process was one step shorter and is, to our knowledge, the first example of the cycloisomerization of an ene-propargylic acetal. From this reaction, yet another major unanticipated side product, the structure of which we have assigned as tetracyclic epoxide **28**, was generated in approximately 40% yield.



Scheme 5. Cycloisomerization of ene-propargylic acetal **27** directly affords echinopine B and unexpected epoxide **28**.

Possible mechanistic pathways for the formation of each of the three unexpected side products, **25**, **26**, and **28**, are shown in Schemes 6, 7, and 8, respectively. In the reports of echinopine syntheses by other research groups,[2–5] there were no mentions of rearrangements of the tetracyclic core; our work demonstrates both the delicate balance of different cycloisomerization reaction manifolds in complex systems and the propensity for the strained echinopine ring system to undergo rearrangement. Only small quantities of each side product were isolated, and their structures were proposed on the basis of extensive NMR experiments coupled with plausible mechanistic hypotheses for the generation of each structure (see below). Our attempts to further validate the proposed structures led us to compare observed and calcu-



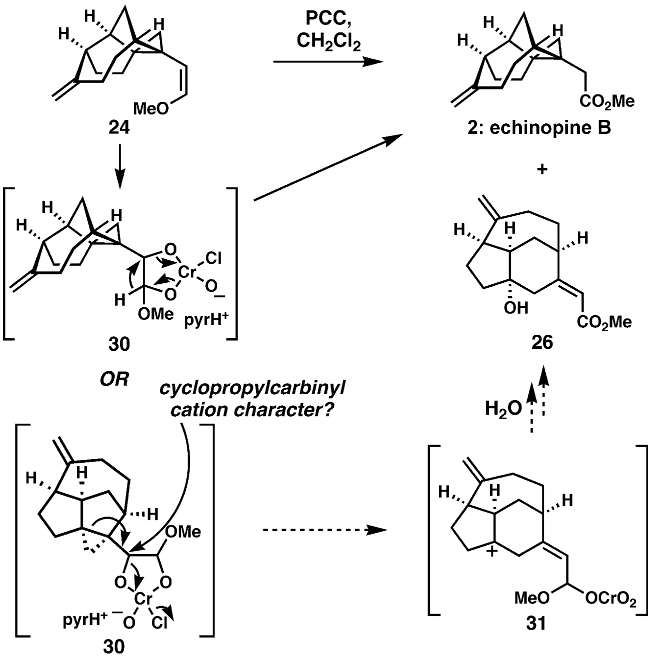
Scheme 6. Plausible mechanism for the formation of **25**.

lated ^{13}C NMR chemical shifts; reasonable matches between experimental and calculated values were observed in each case.[6]

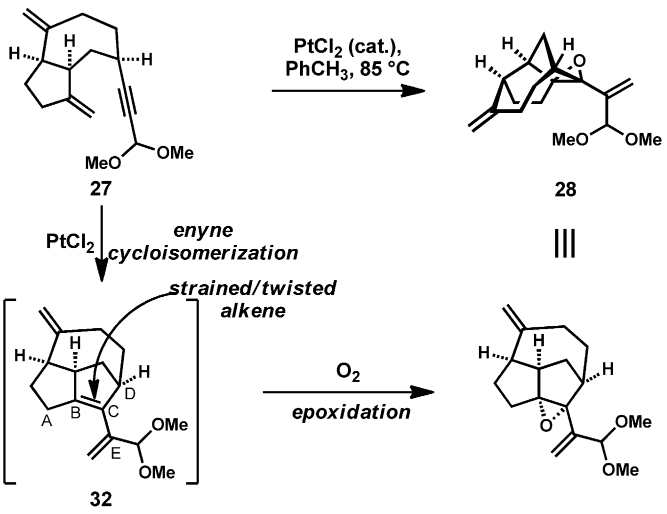
The unexpected product of the cycloisomerization of **12** was assigned as **25** on the basis of NMR spectroscopy and mass spectrometry, as well as a reasonable explanation for its genesis. It is known from the work of Oh and co-workers that, when other pathways for deplatination are not available, the platinum carbenoids that are the immediate products of enyne cycloisomerization can participate in C–H insertion chemistry.[15] They showed that both 5- and 3-membered rings could be formed in this way. To rationalize the formation of **25**, we considered that a regioisomeric (relative to the one that produces **24**) cycloisomerization reaction (a 6-*endo*-type reaction)[16] could give rise to platinum carbenoid **29** (Scheme 6). Assuming that hydride shift and alkyl shift termination pathways are not readily available owing to geometric constraints, insertion into the proximal and well-aligned methylene C–H bond to form cyclopropane **25** seems reasonable. ^{13}C NMR chemical shift predictions for this structure support this hypothesis.[6]

The side product (**26**) of enol-ether oxidation by PCC presumably arises from a mechanism related to that proposed by Cossy et al., who found that PCC oxidation of tricyclic cyclopropylcarbinols often leads to rearrangement with cyclopropane cleavage.[17] The cyclopropylcarbinyl cationic character of the chromate ester intermediates is presumably a key factor in that chemistry. The rearrangement of **24** could proceed along the lines of the pathway shown in Scheme 7, wherein the cyclic chromate ester in **30** imparts enough cyclopropylcarbinyl cationic character to trigger strain-driven cleavage of the cyclopropane. The major disconcerting aspect of this proposal is the presence of the adjacent oxygen atoms that should inductively destabilize any cyclopropylcarbinyl cation character that develops. Nonetheless, the structural assignment of this interesting rearrangement product rests on extensive NMR experimentation and NMR chemical shift predictions.[6]

Epoxide-containing side product **28** also has a logical origin (Scheme 8). There are several well-precedented mechanisms in enyne cycloisomerization chemistry to account for the formation of cyclic dienes of type **32**.[6,9] In this case, the tetrasubstituted alkene is contorted, owing to the complex ring system. For example, calculations indicate dihedral angles for CA-CB-CC-CD of approximately 144°, and for CA-CB-CC-CE of approximately 29°.[6] It is well appreciated that strained alkenes can undergo spontaneous oxidation by molecular oxygen;[18] such a reaction would account for the isolation of **28** which, interestingly, bears the "oxa-echinopine" ring system.



Scheme 7. Plausible mechanism for the rearrangement to form **26**. Pyr = pyridine.



Scheme 8. Plausible mechanism for the generation of epoxide **28**. See the Supporting Information for further mechanistic discussion.

Our current route to echinopine B stands at 13 steps from commercially available materials (12 steps via acetal **27**, but less efficient) and features a Pt^{II}-catalyzed enyne cycloisomerization in a complex setting to generate much of the architecture of this complex target. Our route fares extremely well in comparison to the previously disclosed syntheses that require, at the fewest, 20 steps.[2–5] If the echinopines were to become biologically important, access to enantioenriched cycloheptenone **14** should prove relatively straightforward; also, a resolution in the context of a much shorter synthesis should ultimately prove more efficient than existing, longer, enantioselective routes. Our investigations have also resulted in the generation of three unexpected side products with complex, natural-product-like structures; these unanticipated echinopine analogues, together with the short route for their formation, suggest that a broad array of echinopine-like structures should be readily available from the chemistry we describe. Finally, these fortuitous findings underscore the continued importance of natural product synthesis: we obtained several interesting rearrangement products and uncovered unanticipated reactivity that stems from the implementation of known chemistry in complex settings.

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Keywords: annulation · enyne cycloisomerization · homogeneous catalysis · rearrangement · sesquiterpenes

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