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Total Syntheses of Lyconadins A–C

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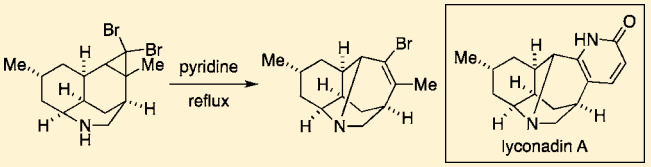
Supporting Information

ABSTRACT: The total synthesis of the *Lycopodium* alkaloid lyconadin A was accomplished and it was applied to the total syntheses of the related congeners, lyconadins B and C. Lyconadin A has attracted attention as a challenging target for total synthesis due to the unprecedented pentacyclic skeleton. Our synthesis of lyconadin A features a facile construction of the highly fused tetracyclic skeleton through a combination of an aza-Prins reaction and an electrocyclic ring opening, followed by formation of a C–N bond. Transformation of the bromoalkene moiety of the tetracycle to a key enone intermediate was extensively investigated, and three methods via sulfide, oxime, or azide intermediates were established. A pyridone ring was constructed from the key enone intermediate to complete the synthesis of lyconadin A. A dihydropyridone ring could also be formed from the same enone intermediate, leading to a synthesis of lyconadin B. Establishment of the conditions for an electrocyclic ring opening without formation of the C–N bond resulted in completion of the total synthesis of lyconadin C.



INTRODUCTION

The *Lycopodium* alkaloids are a group of structurally diverse compounds isolated from the *Lycopodium* species.[1] The complicated structures of the *Lycopodium* alkaloids have provided challenging targets for total synthesis as well as opportunities for development of synthetic methodologies.

Lyconadin A, one of the *Lycopodium* alkaloids, was isolated from *Lycopodium complanatum* in 2001 by Kobayashi et al.[2] Structural elucidation of lyconadin A (**1**, Figure 1) showed an unprecedented pentacyclic skeleton including a 2-pyridone ring, six stereogenic centers, and a tertiary amine at a bridgehead. The first total synthesis of (+)-lyconadin A was accomplished by Beshore and Smith in 2007,[3] featuring use of an intramolecular aldol/conjugate addition cascade and an aminoiodination reaction to construct the core tetracyclic structure. In addition, Smith et al.[4] developed a novel pyridone synthesis during the course of their synthetic studies. Sarpong and co-workers[5] subsequently reported the total syntheses of (±)- and (+)-lyconadin A, in which a unique oxidative C–N bond-forming reaction[6] was used to form the pentacyclic skeleton. In 2011 we also reported our total synthesis of (+)-lyconadin A, which featured a facile construction of the tetracyclic system via a combination of an aza-Prins reaction and an electrocyclic ring opening, and transformation of a bromoalkene moiety to an enone.[7] Herein we discuss the synthesis of (+)-lyconadin A in detail, disclose improvement of the transformation of the bromoalkene moiety, and describe the synthesis of the natural congeners lyconadins B (**2**) and C (**3**).[8]

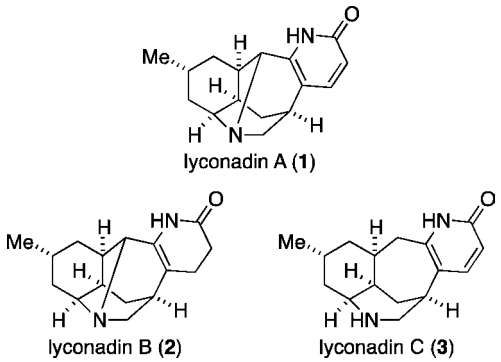


Figure 1. Structure of lyconadins A–C.

RESULTS AND DISCUSSION

Retrosynthesis. Our retrosynthesis of **1** is shown in Scheme 1. Construction of the pyridone moiety in **1** would be based on a procedure developed in our laboratory,[9] which requires enone **4** as a precursor. We envisioned that the carbon framework of **4**, bicyclo[5.4.0]undecane, could be derived from **5** via a ring expansion of the *cis*-decaline system. Both the carbonyl group and the double bond in **5** would form the basis of the unique tertiary amine moiety. Decaline **5** could in turn be prepared by means of a Diels–Alder reaction.

Synthesis of Lyconadin A. The synthesis of lyconadin A began with a Diels–Alder reaction performed according to Overman's conditions (Scheme 2).[10] The known unsaturated ketone **6**[11] was treated with isoprene in the presence of ethylene glycol bis(trimethylsilyl) ether and trimethylsilyl trifluoromethanesulfonate (TMSOTf). The Diels–Alder reac-

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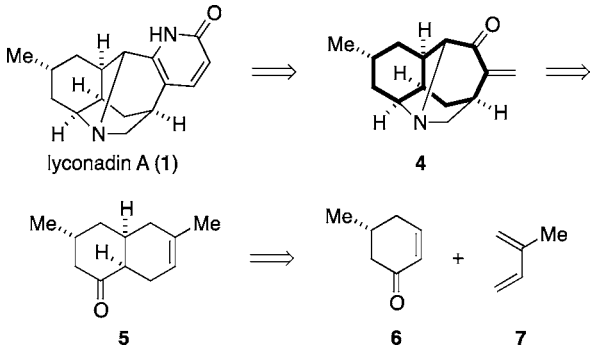
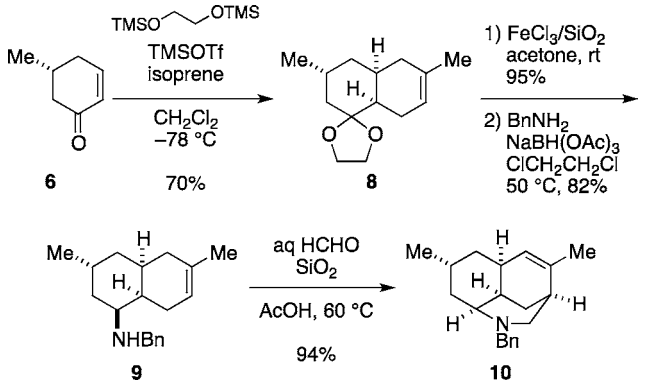
Scheme 1. Retrosynthesis



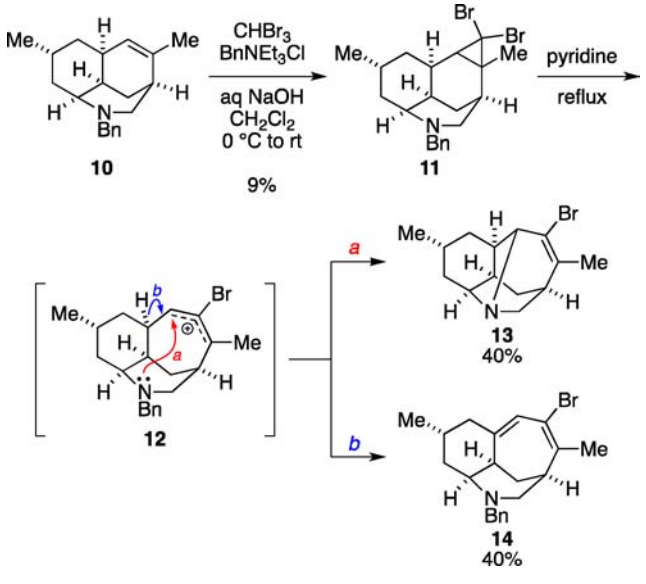
Scheme 2. Diels–Alder Reaction and Aza-Prins Reaction



tion occurred selectively on the opposite side of the methyl group to give **8**. After cleavage of the ethylene ketal under mild conditions,[12] the resulting ketone was subjected to a reductive amination with benzylamine to give secondary amine **9** as the sole isomer. Upon treatment with formalin under acidic conditions, **9** underwent an aza-Prins reaction to produce tricyclic compound **10**.[13]

We next focused on the ring expansion using the double bond. Dibromocyclopropanation of tricyclic compound **10** afforded the desired product **11**, albeit in low yield (Scheme 3).

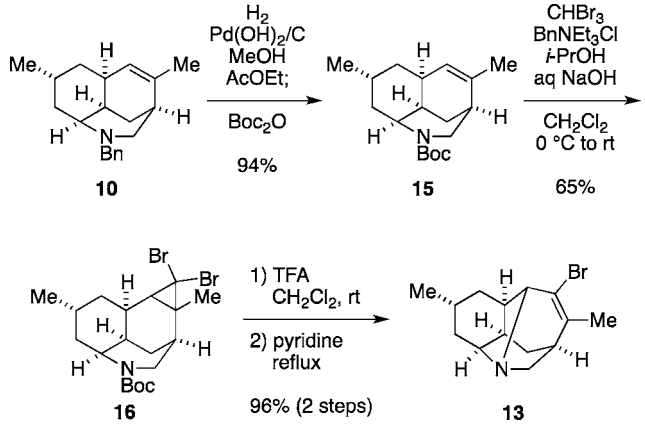
Scheme 3. Attempted Formation of Tetracyclic Core



Upon heating in pyridine, **11** underwent an electrocyclic ring opening to form an allylic carbocation (**12**),[14] which was intercepted by the tertiary amine with loss of the benzyl group to give the desired tetracyclic compound **13** (route a). This reaction, however, was accompanied by formation of undesired diene **14** via deprotonation of the allylic cation (route b). The bulky benzyl group seemed to inhibit approach of the amine to the allylic cation. The sequence was also problematic because of the low yield of the cyclopropanation reaction, which was presumably due to an unwanted reaction of dibromocarbene with the tertiary amine. To solve these problems, we decided to change the benzyl group to another protective group.

Cleavage of the benzyl group by hydrogenolysis followed by addition of Boc_2O afforded Boc-protected compound **15** (Scheme 4).[15] Dibromocyclopropanation of this compound

Scheme 4. Construction of Tetracyclic Skeleton



proceeded in good yield to give **16** as a 5:1 diastereomeric mixture.[16] After cleavage of the Boc group by treatment with trifluoroacetic acid (TFA), the resulting secondary amine was heated in pyridine. As expected, interception of the allylic cation by the amine proceeded smoothly to furnish tetracyclic compound **13** in good yield.

Having established an efficient synthetic route to key compound **13** containing the tetracyclic skeleton, we next focused on transformation of **13** into enone **4**. In our earlier communication,[7] we reported two different routes based on a halogen–lithium exchange of **13** by reaction with *t*-butyllithium in tetrahydrofuran (THF) at −78 °C (Scheme 5). In the first route, treatment of the resulting alkenyllithium with diphenyl disulfide afforded sulfide **17**, which was transformed into enone **4** via a vinylogous Pummerer rearrangement.[17] Oxidation of the sulfide with *m*-chloroperbenzoic acid (*m*CPBA) gave sulfoxide **18** as the sole isomer. Upon treatment with acetic anhydride in the presence of camphorsulfonic acid (CSA), **18** underwent the vinylogous Pummerer rearrangement to furnish **19**. Acidic hydrolysis of **19** in the presence of mercury sulfate afforded enone **4**.

In the second route, treatment of the alkenyllithium derived from **13** with isoamyl nitrite afforded oxime **21** in 37% yield (Scheme 6). This reaction is believed to proceed via formation and isomerization of nitrosoalkene **20**.[18,19] Subsequent hydrolysis of the oxime under acidic conditions afforded the desired enone **4**.

In an effort to improve the efficiency of the transformation, we investigated the use of a variety of electrophiles including peroxides,[20,21] azo compounds,[22] diazo compounds,[23] and

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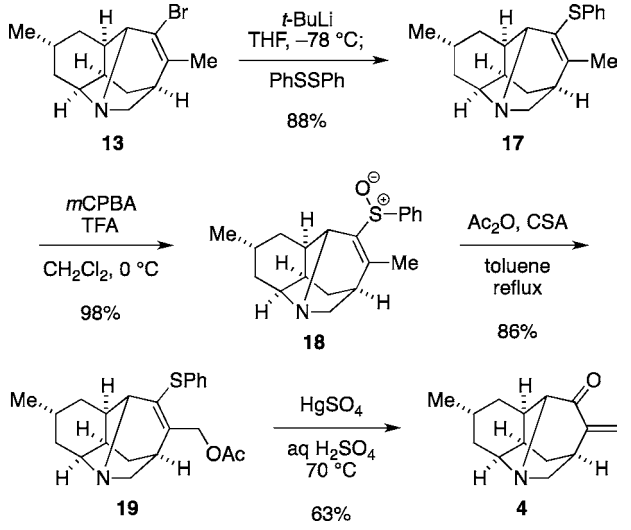
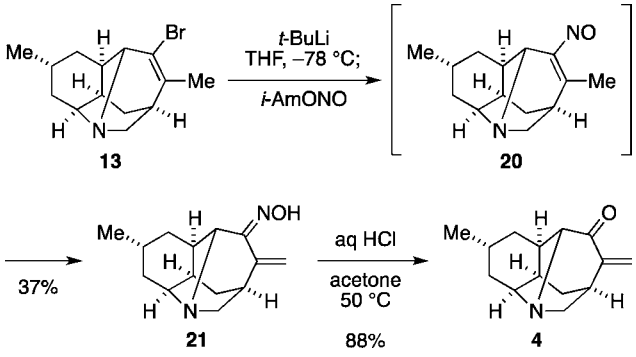
Scheme 5. Transformation into Enone 4 via Vinylogous Pummerer Rearrangement

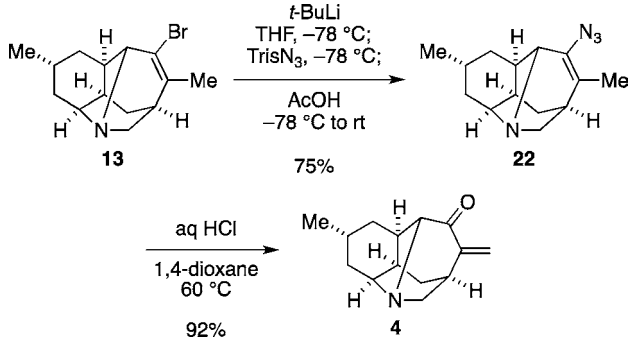


Scheme 6. Transformation into Enone 4 through an Oxime



nitroso compounds.[24,25] After extensive investigation, we found that the reaction of the alkenyllithium with trisyl azide, followed by addition of acetic acid, afforded azide **22** in good yield (Scheme 7).[26] Treatment of **22** with hydrochloric acid in 1,4-

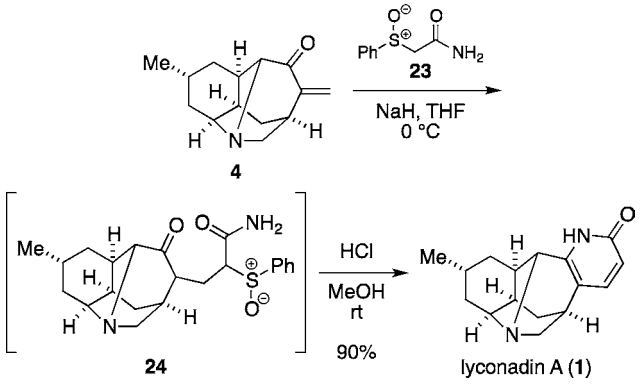
Scheme 7. Transformation into Enone 4 through an Azide



dioxane induced cleavage of the N–N bond with generation of molecular nitrogen to give an α,β-unsaturated imine,[27] which was immediately hydrolyzed in situ to afford enone **4** in 92% yield.

To complete the synthesis, formation of the requisite pyridone ring was conducted according to our procedure with some modifications (Scheme 8).[9] Isolation of the highly polar diastereomeric mixture of adducts **24** caused loss of

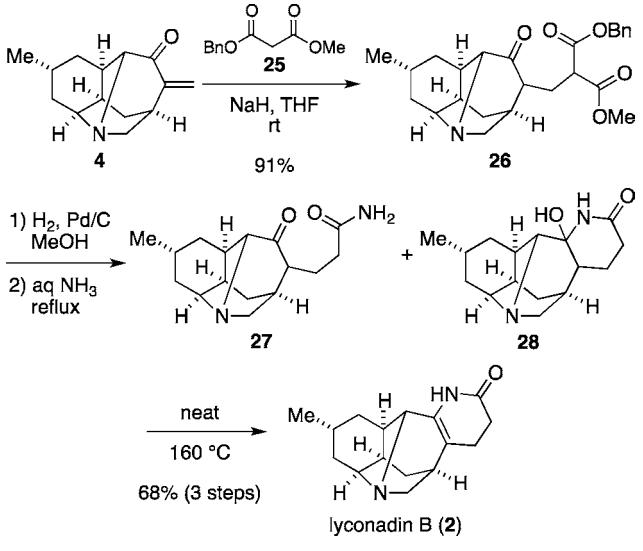
Scheme 8. Completion of Synthesis of Lyconadin A



material. To circumvent this problem, the subsequent cyclization step was performed in a one-pot process. Thus, addition of 2-(phenylsulfinyl)acetamide **23** to the enone in the presence of sodium hydride, followed by treatment with methanolic hydrogen chloride, resulted in construction of the pyridone ring to afford lyconadin A (**1**) in 90% yield.

Synthesis of Lyconadin B. The synthetic route to lyconadin A was next applied to the synthesis of the other lyconadins. By using the key intermediate **4**, lyconadin B (**2**) was prepared without much difficulty. Conjugate addition of an anion of benzyl methyl malonate (**25**) furnished adduct **26** in 91% yield (Scheme 9). Cleavage of the benzyl ester by

Scheme 9. Synthesis of Lyconadin B



hydrogenolysis followed by treatment with aqueous ammonia at reflux gave a mixture of primary amide **27**[28] and hemiaminal **28**. Heating the mixture under an argon atmosphere[29] induced dehydration to furnish lyconadin B (**2**).

Synthesis of Lyconadin C. We next focused on the synthesis of lyconadin C, which lacks one of the C–N bonds in lyconadin A. In our synthesis of lyconadin A, the C–N bond was formed by the intramolecular addition of the secondary amine to an allylic cation generated from electrocyclic ring opening of the dibromocyclopropane. It seemed that introduction of an electron-withdrawing protective group on the secondary amine could easily inhibit the C–N bond formation. Attempted reaction of Boc-protected compound **16**

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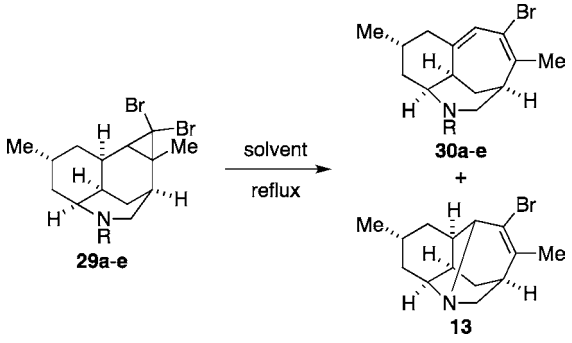
(redefined as **29a** in Table 1) by heating in pyridine, however, resulted in production of a mixture of the desired diene **30a** and

Table 1. Cleavage of Dibromocyclopropane Ring



				yield[a] (%)	
entry	R	substrate	solvent	**30a–e**	**13**
1	Boc	**29a**	pyridine	20	46
2	Ts	**29b**	AcOH	43	51
3	*p*-Ns	**29c**	AcOH	51	42
4	*o*-Ns	**29d**	AcOH	89	trace
5	H	**29e**·HCl	AcOH	62	20
6	H	**29e**·HCl	HCO_2H	74	*b*

[a]Isolated yields. [b]Compound **13** could not be detected.

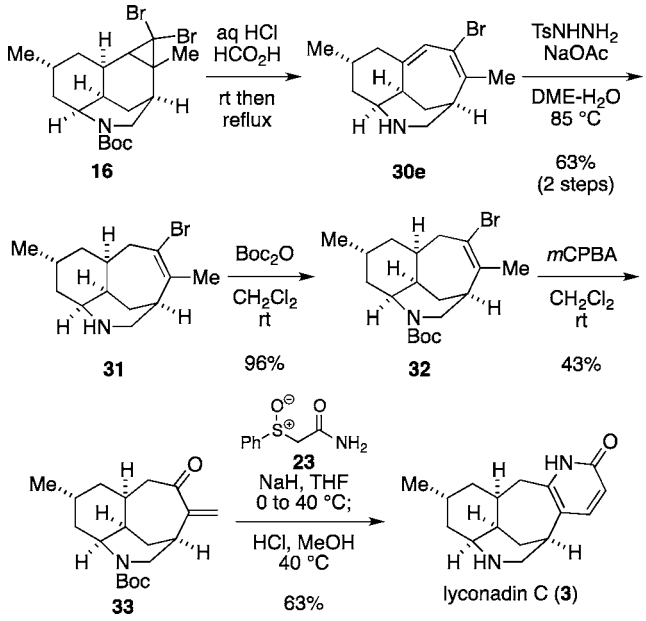
tetracyclic compound **13** (Table 1, entry 1). Since thermal cleavage of the Boc group under the conditions was suspected, we investigated the other substrates that had a sulfonyl group on the nitrogen atom. To our surprise, reaction of Ts- or *p*-Ns-protected compounds (**29b** or **29c**) in refluxing acetic acid also produced the tetracyclic compound **13** (entries 2 and 3). These reactions might involve formation of ammonium intermediates and subsequent cleavage of the sulfonyl groups. Although employing the *o*-Ns group resulted in selective production of **30d** in good yield (entry 4), selective reduction of the double bond (vide infra) in the presence of the nitro group was plagued with difficulties. On the other hand, protection of the nitrogen atom as an ammonium salt proved to be effective for the transformation (entries 5 and 6). Under optimal conditions, heating hydrochloride **29e**·HCl in formic acid selectively produced **30e** in 74% yield.

Having optimized the reaction conditions for cleavage of the dibromocyclopropane intermediate, we turned to completion of the synthesis of lyconadin C (Scheme 10). Compound **16** was treated with hydrochloric acid in formic acid first at room temperature to cleave the Boc group, and the reaction mixture was then heated to reflux to afford **30e**. At this stage, the less hindered C–C double bond was reduced with diimide to give **31** in 63% yield in two steps. After protection of the secondary amine with a Boc group, the product was oxidized with *m*CPBA to furnish enone **33**.[30] Finally, application of our pyridone synthesis afforded lyconadin C (**3**).

CONCLUSION

We have accomplished the total synthesis of lyconadin A and applied it to the synthesis of the related congeners, lyconadins B and C. Our synthesis of lyconadin A features a facile construction of the highly fused tetracyclic skeleton through a combination of an aza-Prins reaction and an electrocyclic ring opening, followed by formation of a C–N bond. Transformation of bromoalkene **13** to enone **4** was extensively

Scheme 10. Synthesis of Lyconadin C



investigated, and three methods via sulfide, oxime, or azide intermediates were established. The synthesis of lyconadin A was completed after construction of a pyridone ring from key intermediate **4**. Construction of a dihydropyridone ring from intermediate **4** led to the synthesis of lyconadin B. Establishment of the conditions for an electrocyclic ring opening without formation of the C–N bond resulted in completion of the total synthesis of lyconadin C.

ASSOCIATED CONTENT

Supporting Information

Additional text with experimental details, characterization data, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(15) When the hydrogenolysis was performed in the presence of Boc_2O, hydrogenation of the double bond also proceeded.

(16) The structure of the major isomer was confirmed by X-ray crystallography.

(17) For a recent review of the Pummerer rearrangement, see (a) Smith, L. H. S.; Coote, S. C.; Sneddon, H. F.; Procter, D. J. *Angew. Chem., Int. Ed.* **2010**, *49*, 5832. For recent applications of the vinylogous Pummerer rearrangement, see (b) Ruano, J. L. G.; Alemán, J.; Aranda, M. T.; Arévalo, M. J.; Padwa, A. *Org. Lett.* **2005**, *7*, 19. (c) Feldman, K. S.; Fodor, M. D. *J. Am. Chem. Soc.* **2008**, *130*, 14964. (d) Shimizu, Y.; Shi, S.-L.; Usuda, H.; Kanai, M.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 1103. (e) Halder, S.; Satyam, A. *Tetrahedron Lett.* **2011**, *52*, 1179.

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(19) The low yield of the reaction can be attributed to in situ formation of an acidic oxime that may have caused protonation of the alkenyllithium.

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(21) Reaction with peroxides did not proceed and gave instead the protonated product.

(22) Reaction with 4-phenyl-1,2,4-triazole-3,5(4*H*)-dione resulted in decomposition of the substrate. While addition to di-*tert*-butyl azodicarboxylate proceeded, further transformation into enone **4** could not be achieved.

(23) Although addition to methyl 2-diazo-2-phenylacetate occurred, the product could not be converted into enone **4**.

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(25) Although a variety of nitroso compounds, including *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide, *N*-nitroso-*N*-methylaniline, and *N*-nitrosodimethylamine, were employed, either no reaction or production of the oxime in low yield occurred.

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(28) Compound **27** was obtained as a mixture of diastereomers. One of the diastereomers is the known compound lyconadin F, which was isolated by Kobayashi and co-workers.[8b]

(29) The presence of oxygen caused autoxidation, giving lyconadin A as the byproduct.

(30) Attempted oxidation of **13** with a variety of oxidants did not give the desired enone **4**. The different behaviors between **13** and **32** under oxidative conditions come from the state of the nitrogen atoms in the compounds.