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Total Syntheses of Lyconadins: Finding Efficiency and Diversity

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Abstract

Lyconadins A–C are important members of the *Lycopodium* alkaloid family with challenging structural features and interesting biological profile. Herein, various synthetic strategies and methods for their preparation are summarized with the focus on constructive bond formation and our efficient and divergent synthesis based on functional group pairing (FGP) strategy.

Keywords

alkaloid; total synthesis; natural product; cyclization; neurodegeneration

Nature has endowed us with an enormous amount of small molecules (small-molecule natural products, SMNPs) with diverse structural skeletons and important functions, some of which have played indispensable roles in discovering life-saving drug molecules¹ and advancing synthetic chemistry in term of both synthetic tactic and strategy.² *Lycopodium* alkaloids are one of the largest families of alkaloid natural products, which are enriched with molecules of potent neurotrophic activities.³ For example, huperzines A (**1**) and B (**2**) are both potent acetylcholine esterase inhibitors and are currently evaluated in clinical application for the treatment of Alzheimer's disease.⁴ Effective therapeutic treatment for neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, multiple sclerosis and Huntington's disease is still very limited. Therefore, natural products with neurotrophic activities are important lead compounds for anti-neurodegenerative drug development.⁵ Lyconadins A–C, members of the *Lycopodium* alkaloid family, were isolated by Kobayashi and co-workers from the club moss *Lycopodium complanatum* but in very low yield.⁶ Both lyconadins A and B have been shown to promote the biosynthesis of nerve growth factors (NGF),⁷ which are essential for maintaining neuronal balances. So far, their mechanisms of action remain unknown. Therefore, further evaluation of these molecules is expected to provide a clear understanding of their biological profile, identify new drug candidates and elucidate critical signaling pathways/cellular targets for neurodegenerative diseases. But their natural scarcity and structural complexity has limited their biomedical development. Therefore, de novo chemical syntheses of these molecules and their analogs become important. Lyconadins A–C share common structural motifs: a 2-pyridone moiety and a polycyclic carbon skeleton. These intriguing molecules haven't escaped the radar of synthetic chemists. Significant efforts have been made toward their chemical synthesis,⁸

culminating in the total syntheses by the Smith (A and B),⁹ Sarpong (A),¹⁰ Fukuyama (A–C),¹¹ Waters (C)¹² groups and our research group (A and C).¹³ Herein, these syntheses were summarized chronologically with the focus on constructive bond formation and our divergent synthesis using functional group pairing (FGP) strategy.¹⁴

The first total synthesis of lyconadins A and B was accomplished by Smith and Beshore in 2007 (Scheme 1). Their synthesis features an α -alkylation to unite two chiral building blocks, **5** and **6**, together to form the C₁₁–C₁₂ bond, an efficient one-pot aldol condensation to form the six-membered carbocycle (cf. **7**→**8**) and an intramolecular conjugate addition to form the C₆–C₇ bond and furnish tricyclic compound **9**, but with undesired stereochemistry at C₁₂. After **9** was converted to amine **10**, aminoiodination with *N*-iodosuccinimide (NIS) built the key C₁₃–N bond and gave the cage-like compound **11**. Compound **11** was then converted to **12** or dihydro-**12** with the requisite carbons for the 2-(dihydro)pyridone synthesis, which was then converted to lyconadins A (**3**) and B (**4**) respectively in one-pot via cyclization of the amide and ketone after decarboxylation.¹⁵

In 2008, Sarpong, Bisai and West accomplished their elegant total synthesis of lyconadin A (Scheme 2). Unlike the Smith synthesis, which built the 2-pyridone moiety at last, the Sarpong synthesis started with bromomethoxypicoline **13**, a masked 2-pyridone. The Stork-Danheiser reaction united **13** and vinylogous ester **14** to form the C₆–C₇ bond. A sequence of cross-metathesis (CM) reaction and Heck reaction converted the Stork-Danheiser product to tricyclic compound **15** with the desired seven-membered ring, which was further elaborated to compound **16** with a carbamate group derived from a Curtius rearrangement. After reductive amination to form the C₁₃–N bond, Sarpong and co-workers developed an elegant and powerful oxidative C–H amination to build the challenging C₆–N bond.¹⁶ The methoxypyridine was then converted to the desired 2-pyridone to complete their total synthesis of lyconadin A.

In 2011, the Fukuyama group completed a concise total synthesis of lyconadin A (Scheme 3A). Their synthetic approach was later adapted to the total synthesis of lyconadins B and C as well. Their synthesis commenced with a Diels-Alder reaction between isoprene and optically active 5-methylcyclohexenone followed by reductive amination to provide *cis*-decaline **18**. Compound **18** then underwent an aza-Prins reaction to give tricyclic compound **19**, which was quickly converted to dibromocyclopropane **20**. The latter, upon heating in refluxing pyridine, was transformed to tetracyclic compound **21** presumably via electrocyclic ring opening of the dibromocyclopropane moiety followed by trapping the resulting allylic cation by the secondary amine. This cascade reaction efficiently expanded the 3,6-fused ring to the desired seven-membered ring and constructed the challenging C₆–N bond. Compound **21** was then converted to enone **22** by several different protocols. The Fukuyama group then developed an efficient 2-pyridone synthesis method¹⁷ by reacting enone **22** with compound **23** to complete the total synthesis of lyconadin A. A similar approach was developed to synthesize lyconadin B as well.

In their lyconadin C synthesis, acidic conditions were developed to convert **20** to tricyclic compound **24** (Scheme 3B). Since the secondary amine was protected as an ammonium salt under acidic conditions, a deprotonation, instead of C₆–N bond formation, took place after

generating the allylic cation from the cyclopropane ring opening to give **24**, which was then converted to lyconadin C using a similar approach developed in their lyconadin A synthesis.

In continuation of their pursuit of *Lycopodium* alkaloid syntheses,¹⁸ the Waters group developed an elegant total synthesis of lyconadin C in 2013 (Scheme 4). Their synthesis also commenced with a Diels-Alder reaction to construct a *cis*-decaline intermediate (cf. **25**), which was converted to tricyclic ketone **26** via a Mannich reaction. After **26** was elaborated to **27**, a rhodium-catalyzed Tiffeneau-Demjanov homologation was developed to expand the six-membered ring to the required seven-membered ring. The resulting ring expansion product was further furnished to **28** via a triflation and a Stille cross coupling. Compound **28** was then converted to lyconadin C (**5**) using an interrupted Curtius rearrangement as the key transformation. In this efficient transformation, the resulting vinyl isocyanate intermediate underwent a 6π -electrocyclization to provide the 2-pyridone system in one-pot.

Our interest in developing natural product based therapeutic treatment for neurodegenerative diseases prompted us to initiate the synthesis of lyconadins in October 2012. We have two synthetic goals in this specific project: (i) achieve total syntheses of these challenging lyconadin natural molecules to quickly provide sufficient materials for biological evaluations; (ii) create a focused small-molecule library based on these privileged structures in order to explore the related chemical space and identify new agents for anti-neurodegenerative development. To accomplish these two goals, we need to find both efficiency and diversity in our synthetic approaches. Inspired by the build-couple-pair (BCP) strategy in diversity-oriented synthesis (DOS) of small molecule libraries,¹⁹ we envisioned a divergent synthesis of lyconadins by using a functional group pairing (FGP) strategy (Scheme 5).²⁰ The central notion of this strategy is to quickly synthesize a pivotal intermediate with the requisite functional groups followed by tuning these functional groups into different pairing modes to build diverse structural skeletons. These skeletons would serve as platforms for the synthesis of the natural products of interest and more importantly a focused small molecule library to allow the investigation of the related chemical space. In the lyconadin case, compound **29** containing the *cis* 6,7-fused carbon bicycle of lyconadins, an amine and a masked enone was designed as our pivotal intermediate, which could be converted to compounds **30**, **31**, and **32** through a formal aza-[4+2] cyclization,^[20] double bond reduction/Mannich reaction, and aza-Michael addition, respectively. These new products would then lead to natural lyconadins as well as a library of unnatural analogs. Obviously, the success of such strategy also requires an efficient and practical approach to prepare the pivotal intermediate (cf. **29**) in large scale.

Our synthesis commenced with conjugate addition of vinylcuprate to enone **33** followed by trapping the resulting enolate with aldehyde **34** to form the C₆-C₇ and C₁₁-C₁₂ bonds. After converting alcohol **35** to triene **36**, ring closing metathesis catalyzed by the Grubbs second-generation catalyst was employed to close the seven-membered ring. Chemo- and stereoselective reduction of **37** provided the *cis* 6,7-fused bicyclic compound **38**. In addition to its quick production from **32**, each step to compound **38** can be conducted in gram scale as well. For the synthesis of lyconadin A, compound **38** was converted to **29** with the challenging cage-like polycyclic system via a reductive amination followed by a formal aza-[4+2] cyclization. In this aza-[4+2] cyclization, C₆-N and C₉-C₁₀ bonds, whose construction

had required multiple steps in the previous synthesis, were formed in one step and formaldehyde served well as a one-carbon stitching unit. Compound **30** was quickly advanced to known enone **22** with a sequence of Lebel olefination²¹ and allylic oxidations. Using the Fukuyama 2-pyridone synthesis protocol, we were able to complete a short total synthesis of lyconadin A.

We then synthesized lyconadin C (**5**) from the same intermediate **38**. A sequence of reductive amination, diimide reduction and removal of the benzyl group converted **38** to **41**. The latter underwent a Mannich reaction to form the tricyclic compound **42**, which was elaborated to lyconadin C (**5**) using a similar approach employed in our lyconadin A (**3**) synthesis.

Retrospectively, protection of the C₄ ketone of **38** as a ketal group turned out to be critical for the success of our lyconadin A synthesis because it allows an in situ release of the ketone or its enol derivative for the formal aza- [4+2] cyclization (Scheme 7, **44**→**45**→**30**). When the enone was released first, an aza-Michael reaction took place to convert **38** to **32**. Efforts to convert **32** to **30** via a Mannich reaction were fruitless presumably due to the structural rigidity of the tricyclic system of **32**. This result rules out the possibility of an aza- Michael-Mannich process for the conversion of **44** to **30**. The possibility still exists for a concerted Diels-Alder cycloaddition or a stepwise Mannich-aza-Michael reaction for this conversion.

In summary, a brief analysis of the total synthesis of lyconadins A-C has been described in this Synfacts article. New strategies and methods have been developed. These syntheses enable further biological evaluations of these neurotrophically active molecules in the context of anti-neurodegeneration.

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Biography

Mingji Dai (left) received his B.S. degree from Peking University in 2002. After two years' research with Professors Zhen Yang and Jiahua Chen in the same university, he went to New York in 2004 and pursued graduate study under the guidance of Professor Samuel J. Danishefsky. After earning his Ph.D. degree in 2009, he took a postdoctoral position in the laboratory of Professor Stuart L. Schreiber at Harvard University and the Broad Institute. In the August of 2012, Mingji began his independent career at the Chemistry Department of Purdue University.

Yang Yang (right) received his B.S. degree from the Huazhong University of Science and Technology, Wuhan, China in 2006. He then went to Shanghai and obtained his Ph.D.

degree at the Shanghai Institute of Organic Chemistry under the guidance of Professor Hongbin Zhai. He is currently a postdoctoral fellow in the group of Professor Mingji Dai at Purdue University.

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Huperzine A (1)

Huperzine B (2)

Lyconadin A (3)

Lyconadin B (4)

Lyconadin C (5)

Figure 1.
Selected *Lycopodium* alkaloids

Figure 2.
Our FGP strategy to natural lyconadins and unnatural analogs

Scheme 1.
The Smith synthesis of lyconadins A and B

Scheme 2.
The Sarpong synthesis of lyconadin A

Scheme 3.
The Fukuyama synthesis of lyconadins A–C

Scheme 6. Synthesis of **32** and investigation of the formal aza-[4+2] cyclization