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Divergent Total Syntheses of Lyconadins A and C

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Abstract

Divergent and concise total syntheses of two lycopodium alkaloids, lyconadins A and C have been developed. The synthesis of lyconadin A with potent neurotrophic activity features an efficient ketal deprotective formal aza-[4+2] cyclization to form the cage-like core structure. A ketal deprotective Mannich reaction was developed to build the tricyclic structure of lyconadin C. Both lyconadins A and C were synthesized from pivotal intermediate **14**. Each step to the synthesis of intermediate **14** was conducted on gram-scale.

Keywords

total synthesis; lycopodium alkaloid; lyconadin; neurodegenerative disease; formal [4+2] cyclization

While advances in therapeutic methods and strategies for the treatment of neurodegenerative diseases have been relatively limited in the past several decades, there is increasingly strong evidence to suggest that naturally-occurring polypeptide neurotrophic factors,^[1] such as nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) may be of significant therapeutic benefit in treating neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease, multiple sclerosis and Huntington's disease.^[2] Unfortunately, these natural neurotrophic factors suffer from poor bioavailability and pharmacokinetics. In addition, direct administration to the brain is usually required.^[3] Recently, small-molecule natural products have been identified to show activity for promoting the production of natural neurotrophic factors or functioning similarly as them for neuron growth and maintenance.^[4] In comparison, small molecules are more likely to cross the blood brain barrier. Their potency, selectivity and pharmacological properties can be readily optimized through structural editing.^[5] They may serve as valuable chemical probes as well.^[6] In this context, we took note of the family of *lycopodium* alkaloids, which are enriched with molecules having neurotrophic activities.^[7] Among them, lyconadins A (**1**) and B (**2**) (Figure 1), isolated by Kobayashi and co-workers, have been shown to enhance the mRNA expression for neurotrophic growth factor biosynthesis in 1321N1 human astrocytoma cells,

In memory of Mr. Qian She who dedicated his whole life to chemistry education.

Supporting information for this article is available on the WWW under <http://www.angewandte.org> or from the author.

suggesting that they may serve as promising lead compounds for anti-neurodegenerative drug discovery.^[8] Structurally, lyconadin C (**3**)^[9] and dihydrolycolucine (**4**)^[10] share common motifs with lyconadins A (**1**) and B (**2**). In addition, lyconadin A has shown modest in vitro anti cancer cell proliferation activity. Their intriguing structural features and important biological activity have motivated many synthetic efforts directed toward their synthesis,^[11] culminating in the elegant total syntheses of the lyconadins by Smith (lyconadins A and B),^[12] Sarpong (lyconadin A),^[13] Fukuyama (lyconadins A, B and C),^[14] and Waters (lyconadin C).^[15] In addition to the total syntheses of these challenging natural molecules, we are particularly interested in creating a focused small-molecule library based on these privileged structures in order to explore the related chemical space and identify new molecules for anti-neurodegenerative agent development. Therefore, we need to develop concise and divergent syntheses^[16] of the lyconadins, which could be adapted for later library production.

As shown in our synthetic plan (Scheme 1), we proposed bicyclic compound **5** (R and X were not specified at the planning stage) as our pivotal intermediate. By pairing the functional groups^[17] in this pivotal intermediate into different reaction modes, we hope to obtain diverse structural skeletons. For example, we proposed to convert intermediate **5** to compounds **6**, **7**, and **8** through a formal aza-[4+2] cyclization,^[18] double bond reduction/Mannich reaction, and aza-Michael addition, respectively. These products would lead not only to the lyconadin natural products of interest, but also various related analogs and a focused library for biological evaluations. In addition to exploring the feasibility of the key functional group pairing reactions, we need to develop an efficient and practical approach to prepare the pivotal intermediate (cf. **5**) in large scale. Herein, we first report efficient and divergent total syntheses of lyconadins A and C.

Our synthesis commenced with commercially available enone **9**. Conjugate addition of vinylcuprate to enone **9** followed by trapping the resulting enolate with aldehyde **10** (synthesized from the corresponding known methyl ester^[19] through DIBAL-H reduction, see supporting information) gave compound **11** in 72% yield as a single diastereomer. Mesylate formation followed by elimination provided trienone **12** in 65% yield. Ring closing metathesis catalyzed by the Grubbs second generation catalyst converted **12** to bicyclic compound **13** with the desired seven-membered ring in 85% yield. Palladium-catalyzed selective 1,4-reduction of compound **13** afforded compound **14** containing the desired 6,7-fused *cis*-ring junction in 74% yield with 10:1 diastereoselectivity.^[20] It is noteworthy that almost no diastereoselectivity was obtained when the 1,4-reduction was performed at the acyclic stage (cf. **12**). A similar result was obtained when L-selectride was used as reducing reagent. The structure of **14** was unambiguously confirmed by X-ray crystallography.^[21] Each step to the synthesis of **14** was conducted on gram-scale.

Reductive amination using a combination of ammonium acetate and sodium cyanoborohydride converted **14** to the corresponding primary amine, which was used directly in the proposed formal aza-[4+2] cyclization step without further purification. We were hoping that an overall tandem formal aza-[4+2] cyclization and ketal deprotection could occur in the same pot to give the desired cage-like ketone **6**. To our delight, upon heating the crude amine in EtOH with HCl and formaldehyde, product **6** was obtained in

68% overall yield from **14**. After experiencing difficulties in converting ketone **6** to the corresponding vinyltriflate or vinyliodide for transition metal catalyzed cross-coupling reactions, we decided to convert the ketone functionality of **6** to an exo-methylene. While the standard Wittig-methylenation as well as the salt-free variations failed, the Lebel modified Wittig procedure gave olefin **15** in 65% yield.^[22] SeO₂-mediated allylic oxidation under acidic condition followed by Dess-Martin oxidation converted **15** to known enone **16**, the Fukuyama-Yokoshima intermediate for the total synthesis of lyconadins A and B. We were able to convert **16** to lyconadin A following a slightly modified Fukuyama-Yokoshima pyridone synthesis protocol.^[14]

Upon completion of the total synthesis of lyconadin A, we began to explore the reduction-Mannich approach to lyconadin C. For purification reasons, benzylamine was used in the reductive amination step and amine **18** was obtained in 87% yield after a diimide reduction^[23] while various catalytic hydrogenation conditions we tried failed to reduce the double bond. Removal of the benzyl group upon Pd/C-catalyzed hydrogenation afforded compound **19** in 92% yield. When **19** was subjected to the condition of HCl and formaldehyde in EtOH at 80 °C, a tandem ketal deprotective Mannich reaction^[24] took place to give the desired tricyclic amine, which was protected as Boc-carbamate **20** immediately. Reduced yield was obtained when a benzylamine or a ketal-deprotected ketone was used under the same Mannich reaction condition. Tricyclic compound **20** was then converted to intermediate **21** smoothly via a sequence of methylenation and allylic oxidation. The latter was furnished to lyconadin C using the slightly modified Fukuyama-Yokoshima pyridone synthesis protocol.^[14]

In addition to the total synthesis, we tried to probe the detailed reaction process of the ketal deprotective formal aza-[4+2] cyclization reaction. In principle, the reaction may go through a concerted aza-Diels-Alder cycloaddition, a stepwise Mannich-aza-Michael process, or an aza-Michael-Mannich process. These processes may take place after the ketal deprotection or in the middle of the ketal deprotection step. We first prepared compound **8** from compound **14** through a reductive amination/ketal deprotection/aza-Michael reaction sequence (Scheme 4). When compound **8** was submitted to the HCl/HCHO reaction condition, the formation of product **6** was not observed. This is presumably due to the structural rigidity of iminium ion **22**, which prohibited the C10 α -carbon from reaching the iminium ion carbon. This result rules out the formation of **6** from an aza-Michael-Mannich process after the ketal deprotection. The possibility still exists for a concerted Diels-Alder cycloaddition or a stepwise Mannich-aza-Michael process. We anticipated that conformer **23b** to be the productive conformer, while it suffers strong 1,3-diaxial interactions. Further experiments will be needed to decipher the reaction mechanism.

In summary, we have developed efficient and divergent total syntheses of lyconadins A and C. The synthesis of lyconadin A features a ketal deprotective formal aza-[4+2] cyclization to form the challenging cage-like core structure and the synthesis of lyconadin C features a ketal deprotective Mannich reaction to construct the tricyclic structure. Both lyconadins A and C were synthesized from common intermediate **14**, which can be prepared in gram-scale shortly from commercially available starting material. This concise and flexible synthetic

route offers opportunities to create focused libraries based on the lyconadins for anti-neurodegenerative agent development.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Structures of lyconadins A–C and dihydrolycolucine

Scheme 1.

Proposed divergent synthesis of natural lyconadins and their unnatural analogs. FGP = Functional Group Pairing.

Scheme 2.

Total synthesis of lyconadin A. Reagents and conditions: a) vinylMgBr (2.2 equiv), CuI (1.1 equiv), **10** (1.1 equiv), THF, -78°C , 72%; b) TEA (3.0 equiv), MsCl (1.5 equiv), DMAP (0.1 equiv), DCM, -78°C to RT; then DBU (3.0 equiv), THF, RT, 65%; c) Grubbs 2nd (0.05 equiv), toluene, 110°C , 85%; d) Pd(PPh₃)₄ (0.03 equiv), Bu₃SnH (2.0 equiv), ZnCl₂ (2.2 equiv), THF, RT, 74% (dr. 10/1); e) NaCNBH₃ (2.0 equiv), NH₄OAc (6.0 equiv), DCE, 50°C ; then HCl (20 equiv), HCHO (10 equiv), EtOH, 80°C , 68%; f) Rh(PPh₃)₃Cl (0.05 equiv), TMSCHN₂ (20 equiv), PPh₃ (6.6 equiv), *i*-PrOH (90 equiv), THF, RT, 64%; g) TFA (5.0 equiv), SeO₂ (3.0 equiv), dioxane, 70°C ; then DMP (3.0 equiv), DCM, RT, 72%; h) NaH, **17**, THF, 0°C ; then 5% HCl in MeOH, 50°C , 70%; MsCl = methanesulfonyl chloride, DMAP = 4-dimethylaminopyridine, TEA = triethylamine, DBU = 1,8-diazabicyclo [5.4.0] undec-7-ene, TMS = trimethylsilyl, DMP = Dess-Martin Periodinane.

Scheme 3.

Total synthesis of lyconadin C. Reagents and conditions: a) NaBH(OAc)₃ (2.0 equiv), BnNH₂ (1.2 equiv), DCE, 50 °C; b) N₂H₄ (6.0 equiv), H₂O₂ (6.0 equiv), EtOH/THF, RT, 87% (two steps from **14**); c) Pd/C, H₂ (1 atm), EtOH, 40 °C, 92%; d) HCl (20 equiv), HCHO (10 equiv), EtOH, 80 °C; then TEA (3.0 equiv), (Boc)₂O (2.0 equiv), MeCN, 46%; e) Rh(PPh₃)₃Cl (0.05 equiv), TMSCHN₂ (20 equiv), PPh₃ (6.6 equiv), *i*-PrOH (90 equiv), THF, RT; f) SeO₂ (0.7 equiv), *t*-BuO₂H (3.0 equiv), DCM, RT; then DMP (3.0 equiv), NaHCO₃ (3.0 equiv), DCM, RT, 64% (two steps from **20**); g) NaH, **17**, THF, 0 °C→40 °C; then 5% HCl in MeOH, 50 °C, 76%.

Scheme 4.

Investigation of the formal aza-[4+2] step. Reagents and conditions: a) NaCNBH₃ (2.0 equiv), NH₄OAc (6.0 equiv), DCE, 50 °C; then HCl (20 equiv), HCHO (10 equiv), EtOH, 80 °C, 68%; b) NaCNBH₃ (2.0 equiv), NH₄OAc (6.0 equiv), DCE, 50 °C; then HCl (20 equiv), EtOH, 80 °C, 53%; c) HCl (20 equiv), HCHO (10 equiv), EtOH, 80 °C.