Natural Products Synthesis

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# Divergent Total Syntheses of Lyconadins A and C**

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*In memory of Qian She*

***Abstract:*** *Divergent and concise total syntheses of two lycopodium alkaloids, lyconadins A and C have been developed. The synthesis of lyconadin A, having potent neurotrophic activity, features an efficient one-pot ketal removal and formal aza-[4+2] cyclization to form the cagelike core structure. A tandem ketal removal/Mannich reaction was developed to build the tricyclic structure of lyconadin C. Both lyconadins A and C were synthesized from a pivotal intermediate.*

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 the 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, and function similarly 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), which were isolated by Kobayashi and co-workers, have been shown to enhance the mRNA expression for neurotrophic growth factor biosynthesis in 1321N1 human astrocytoma cells, thus 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 **1** and **2**. In addition, **1** has shown modest in vitro anticancer activity. Their intriguing structural features and important biological activity have motivated many synthetic efforts toward their synthesis,[11] thus culminating in the elegant total syntheses of the lyconadins by the groups of 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 small-molecule library based on these privileged structures to explore the related chemical space and identify new molecules for the development of anti-neurodegenerative agents. Therefore, we need to develop concise and divergent syntheses[16] of the lyconadins, which could be adapted for later library production.

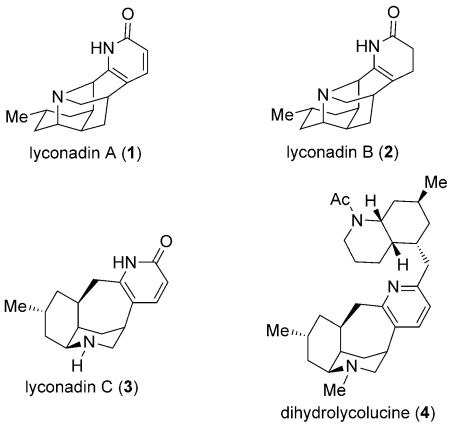


***Figure 1.*** Structures of lyconadins A–C (**1**–**3**) and dihydrolycolucine (**4**).

As shown in our synthetic plan (Scheme 1), we proposed the 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 with different reaction modes, we hoped to obtain diverse structural skeletons. For example, we proposed to convert **5** into the compounds **6**, **7**, and **8** through a formal aza-[4+2] cyclization,[18] double-bond reduction/Mannich reaction, and aza-

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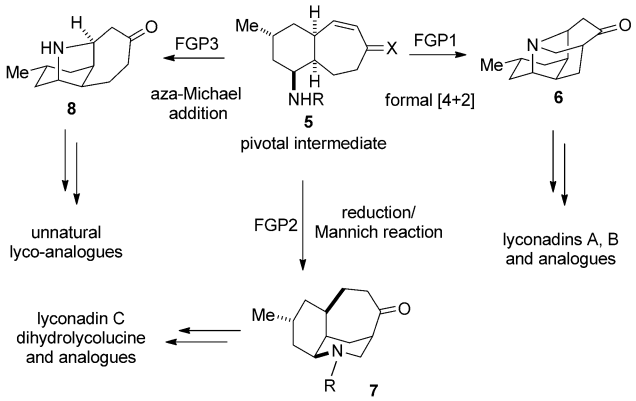
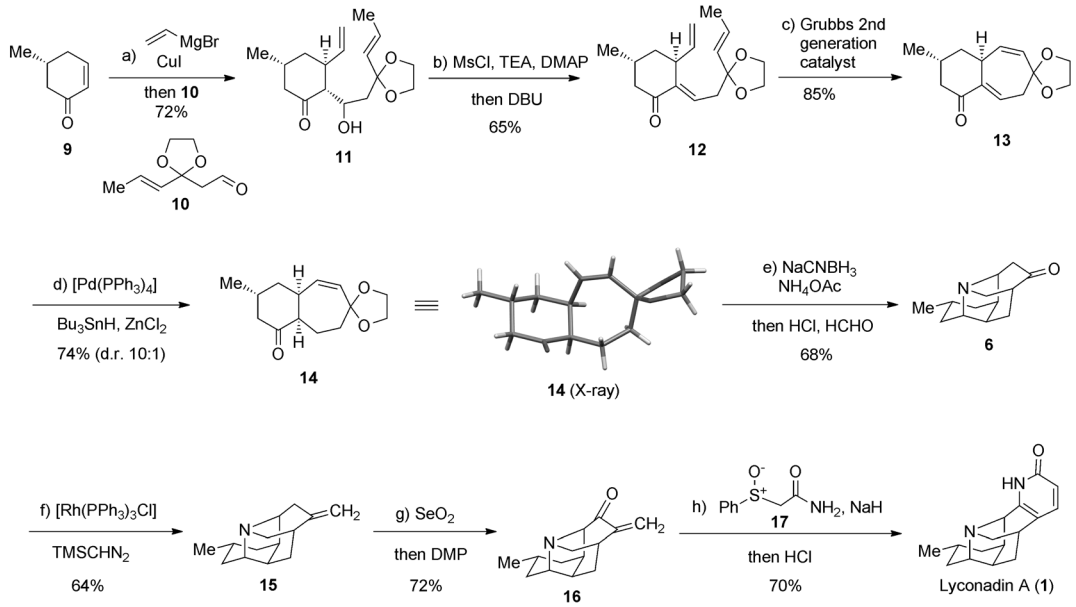



***Scheme 1.*** Proposed divergent synthesis of natural lyconadins and their non-natural analogues. FGP = functional group pairing.

Michael addition, respectively. These products would lead not only to the lyconadin natural products of interest, but also to various related analogues and a library for biological evaluations. In addition to exploring the feasibility of the key functional-group-pairing reactions, we needed to develop an efficient and practical approach to prepare the pivotal intermediate (**5**) on large scale. Herein, we report efficient and divergent total syntheses of lyconadins A (**1**) and C (**3**).

Our synthesis commenced with the commercially available enone **9** (Scheme 2). Conjugate addition of vinylcuprate to **9** and subsequent trapping of the resulting enolate with the aldehyde **10** (synthesized from the corresponding known methyl ester[19] through DIBAL-H reduction; see the Supporting Information) gave the compound **11** in 72% yield as a single diastereomer. Mesylate formation and subsequent elimination provided the trienone **12** in 65% yield. Ring-closing metathesis catalyzed by the Grubbs second-generation catalyst converted **12** into the bicyclic compound **13** with the desired seven-membered ring in 85% yield. Palladium-catalyzed selective 1,4-reduction of **13** afforded the compound **14**, which contains 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 (**12**). A similar result was obtained when L-selectride was used as the 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.

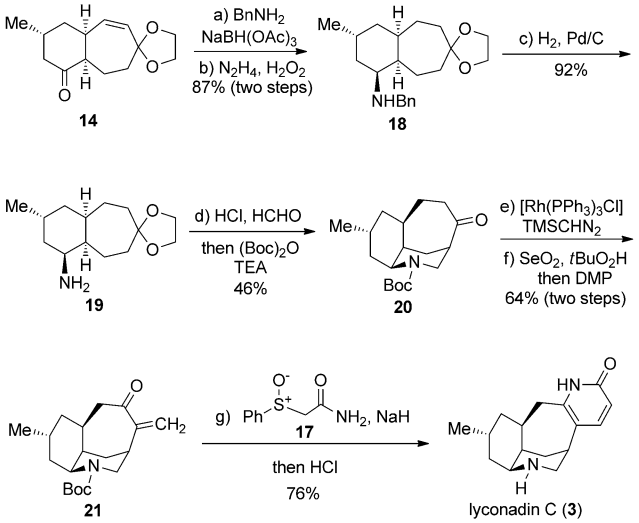
Reductive amination using a combination of ammonium acetate and sodium cyanoborohydride converted **14** into the corresponding primary amine, which was used directly in the proposed formal aza-[4+2] cyclization step without further purification. We were hoping that an overall tandem formal aza-[4+2] cyclization and ketal removal would occur in the same pot to give the desired cagelike ketone **6**. To our delight, upon heating the crude amine in EtOH with HCl and formaldehyde, **6** was obtained in 68% overall yield from **14**. After experiencing difficulties in converting **6** into the corresponding vinyltriflate or vinyliodide for transition metal catalyzed cross-coupling reactions, we decided to convert the ketone functionality of **6** into an *exo* methylene.




***Scheme 2.*** Total synthesis of lyconadin A (**1**). 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), $CH_2Cl_2$, −78 °C→RT; then DBU (3.0 equiv), THF, RT, 65%; c) Grubbs second-generation catalyst (0.05 equiv), toluene, 110 °C, 85%; d) $[Pd(PPh_3)_4]$ (0.03 equiv), $Bu_3SnH$ (2.0 equiv), $ZnCl_2$ (2.2 equiv), THF, RT, 74% (d.r. 10:1); e) $NaCNBH_3$ (2.0 equiv), $NH_4OAc$ (6.0 equiv), DCE, 50 °C; then HCl (20 equiv), HCHO (10 equiv), EtOH, 80 °C, 68%; f) $[Rh(PPh_3)_3Cl]$ (0.05 equiv), $TMSCHN_2$ (20 equiv), $PPh_3$ (6.6 equiv), *i*PrOH (90 equiv), THF, RT, 64%; g) TFA (5.0 equiv), $SeO_2$ (3.0 equiv), 1,4-dioxane, 70 °C; then DMP (3.0 equiv), $CH_2Cl_2$, RT, 72%; h) NaH, **17**, THF, 0 °C; then 5% HCl in MeOH, 50 °C, 70%. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DCE = 1,2-dichloroethane, DMAP = 4-dimethylaminopyridine, DMP = Dess–Martin periodinane, MsCl = methanesulfonyl chloride, TEA = triethylamine, TFA = trifluoroacetic acid, THF = tetrahydrofuran, TMS = trimethylsilyl.

While the standard Wittig methylenation as well as the salt-free variations failed, the Lebel-modified Wittig procedure gave the olefin **15** in 65% yield.[22] $SeO_2$-mediated allylic oxidation under acidic conditions and subsequent Dess–Martin oxidation converted **15** into the known enone **16**, the Fukuyama–Yokoshima intermediate for the total synthesis of lyconadins A and B. We then converted **16** into **1** following the Fukuyama–Yokoshima pyridone synthesis protocol.[14]

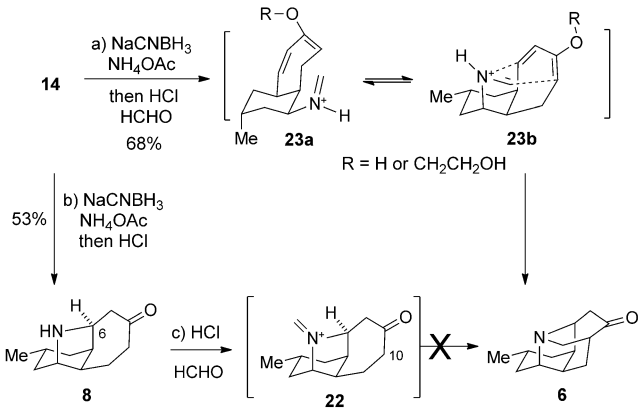
Upon completion of the total synthesis of **1**, we began to explore the reduction/Mannich sequence to **3** (Scheme 3). For purification reasons, benzylamine was used in the reductive amination step and the amine **18** was obtained in 87% yield




***Scheme 3.*** Total synthesis of lyconadin C (**3**). Reagents and conditions: a) $NaBH(OAc)_3$ (2.0 equiv), $BnNH_2$ (1.2 equiv), DCE, 50°C; b) $N_2H_4$ (6.0 equiv), $H_2O_2$ (6.0 equiv), EtOH/THF (1:1), RT, 87% (two steps from **14**); c) Pd/C, $H_2$ (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) $[Rh(PPh_3)_3Cl]$ (0.05 equiv), $TMSCHN_2$ (20 equiv), $PPh_3$ (6.6 equiv), *i*PrOH (90 equiv), THF, RT; f) $SeO_2$ (0.7 equiv), *t*$BuO_2H$ (3.0 equiv), $CH_2Cl_2$, RT; then DMP (3.0 equiv), $NaHCO_3$ (3.0 equiv), $CH_2Cl_2$, RT, 64% (two steps from **20**); g) NaH, **17**, THF, 0°C→40°C; then 5% HCl in MeOH, 50°C, 76%. Boc = *tert*-butoxycarbonyl.

after a diimide reduction,[23] whereas various catalytic hydrogenation conditions we tried failed to reduce the double bond. Removal of the benzyl group upon Pd/C-catalyzed hydrogenation afforded the compound **19** in 92% yield. When **19** was subjected to HCl and formaldehyde in EtOH at 80°C, a tandem ketal removal/Mannich reaction[24] took place to give the desired tricyclic amine, which was immediately protected as the Boc-carbamate **20**. Reduced yield was obtained when a benzylamine or a ketal deprotected ketone was used under the same Mannich reaction conditions. The tricyclic compound **20** was then converted into the intermediate **21** smoothly by a sequence of methylenation and allylic oxidation. The latter was transformed into **3** using the Fukuyama–Yokoshima pyridone protocol.[14]

In addition to the total synthesis, we tried to probe the detailed reaction process of the one-pot ketal removal and 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 removal or during the ketal removal step. We first prepared **8** from **14** through a reductive amination/ketal removal/aza-Michael reaction sequence (Scheme 4). When **8**




***Scheme 4.*** Investigation of the formal aza-[4+2] step. Reagents and conditions: a) $NaCNBH_3$ (2.0 equiv), $NH_4OAc$ (6.0 equiv), DCE, 50°C; then HCl (20 equiv), HCHO (10 equiv), EtOH, 80°C, 68%; b) $NaCNBH_3$ (2.0 equiv), $NH_4OAc$ (6.0 equiv), DCE, 50°C; then HCl (20 equiv), EtOH, 80°C, 53%; c) HCl (20 equiv), HCHO (10 equiv), EtOH, 80°C.

was submitted to the HCl/HCHO reaction conditions, the formation of **6** was not observed, which is presumably due to the structural rigidity of the iminium ion **22**. This result rules out the formation of **6** from an aza-Michael/Mannich process after the ketal removal. The possibility still exists for a concerted Diels–Alder cycloaddition or a stepwise Mannich/aza-Michael process. We anticipate the conformer **23b** to be the productive conformer though it suffers from 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 (**1**) and C (**3**). The synthesis of **1** features a tandem ketal removal and formal aza-[4+2] cyclization to form the challenging cagelike core structure, and the synthesis of **3** features a ketal removal/Mannich reaction to construct the tricyclic structure. Both **1** and **3** were synthesized from a common intermediate (**14**), which can be prepared on gram-scale from commercially available starting materials. This concise and flexible synthetic route offers opportunities to create libraries based on the lyconadins for the development of anti-neurodegenerative agents.

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