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Pyridone Annulation via Tandem Curtius Rearrangement/6π-Electrocyclization: Total Synthesis of (−)-Lyconadin C

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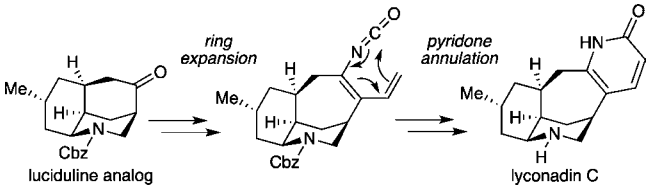
ABSTRACT



A concise, enantioselective total synthesis of the *Lycopodium* alkaloid (−)-lyconadin C was achieved in 12 steps and high overall yield. Key features include construction of a luciduline congener through Mannich-type cyclization and a one-pot, tandem Curtius rearrangement/6π-electrocyclization to fashion the 2-pyridone system of lyconadin C.

The synthetic challenges presented by the *Lycopodium* alkaloids not only serve as inspiration for target-directed total synthesis but also provide the motivation for new advances in synthetic methodology.[1] One area of investigation in our research program in heterocyclic chemistry centers on the synthesis of structurally related *Lycopodium* alkaloids, primarily those which we postulate could be accessible through a common alkaloid precursor. Within this area, we reported an efficient, three-step total synthesis of the tricyclic *Lycopodium* alkaloid luciduline (**1**, Figure 1). In turn, this significantly shorter route than those previously reported[2] enabled us to use luciduline as a synthetic precursor in concise total syntheses of two structurally related *Lycopodium* alkaloids, nankakurines A (**2**) and B (**3**), accomplished through making use of the ketone function in luciduline as a point to install the requisite spiropiperidine.[3] The success of this strategy has prompted us to identify additional *Lycopodium* alkaloids which bear the structural motif present within luciduline.

In 2011, Kobayashi and co-workers disclosed the structural assignments for lyconadin C (**5**), a new member of the lyconadin class of alkaloids obtained from the club moss, *Lycopodium complanatum*.[4] Spectroscopic studies on lyconadin C revealed a tetracyclic ring system containing a 2-pyridone moiety as found in lyconadin A (**4**).[5] While elegant total syntheses of lyconadin A have been reported by Smith,[6] Sarpong,[7] and Fukuyama,[8] to date only one successful synthesis of lyconadin C has been reported by Fukuyama using slight modifications of their previous

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(4) Ishiuchi, K.; Kubota, T.; Ishiyama, H.; Hayashi, S.; Shibata, T.; Kobayashi, J. *Tetrahedron Lett.* **2011**, *52*, 289–292.

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synthesis of lyconadin A.[9] Drawing on the logic employed in our approach to the nankakurines, the common skeletal patterns embedded within lyconadin C and luciduline led us to investigate a synthetic sequence from the luciduline framework to this new alkaloid. In this Letter, we describe a concise and enantioselective total synthesis of lyconadin C that not only passes through a luciduline-like precursor but also features an efficient method for the construction of pyridone-containing heterocycles through a tandem Curtius rearrangement/6π-electrocylization.

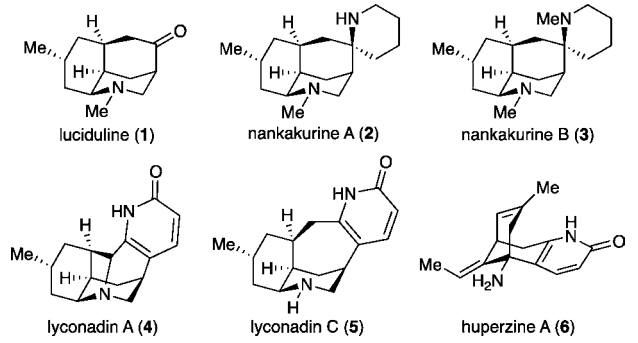
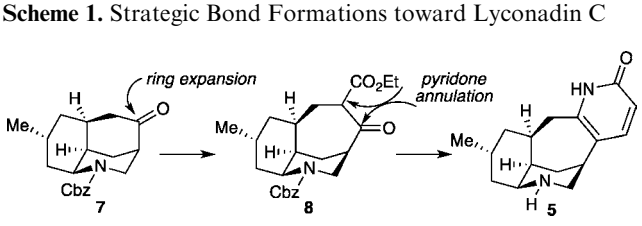


Figure 1. Selected *Lycopodium* alkaloids.

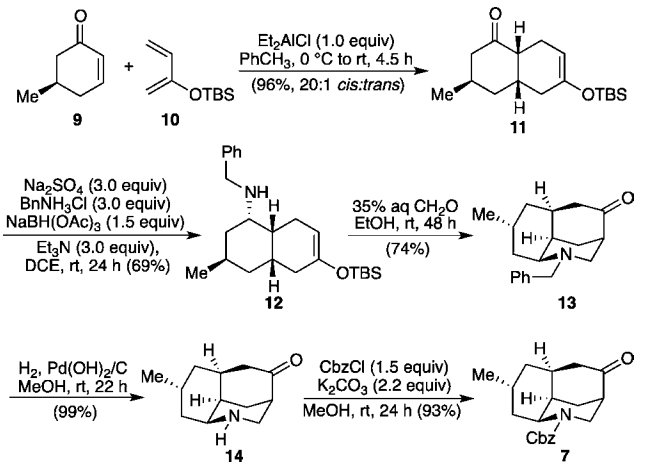
In the early planning stages, we envisioned that the seven-membered ring within lyconadin C could be fashioned through one-carbon ring expansion of a suitable luciduline congener (**7**, Scheme 1). With the ready availability of luciduline or its analogs, we anticipated that such a protocol would provide sufficient quantities of a suitably functionalized cycloheptanone (**8**), which would in turn serve as the foundation on which methods toward pyridone annulation could be investigated.

Scheme 1. Strategic Bond Formations toward Lyconadin C



Our synthesis commenced with a 5-step preparation of Cbz-luciduline analog **7** (Scheme 2), fashioned through a sequence similar to our previous 3-step total synthesis of luciduline (**1**).[3a] Lewis acid mediated Diels–Alder reaction of (*R*)-5-methylcyclohex-2-en-1-one (**9**)[10] and 2-*tert*-butyldimethylsiloxy-1,3-butadiene (**10**)[11] provided *cis*-decalone **11**, now bearing a silyl enol ether function, with minimal amounts of its *trans*-decalone epimer (*cis*/*trans* > 20:1).[12] Conversion of the ketone in **11** to secondary amine **12**, achieved via reductive amination with benzylamine and $NaBH(OAc)_3$,[13] effectively delivered hydride at the desired, convex face of the decalin system (dr > 10:1). Treatment of secondary amine **12** with aqueous formaldehyde at rt cleanly effected Mannich-type ring closure,[14] delivering the benzylamine analog of luciduline (**13**) in 74% yield. Hydrogenolysis of the benzylamine function in **13** and installation of a carbamate group provided Cbz-luciduline (**7**), which could be prepared in gram-scale quantities in high overall yield.

Scheme 2. Synthesis of Luciduline Analog **7**



Having reached the first checkpoint in the synthesis, attention was then given to expansion of the cyclohexanone ring in **7**. While various methods for ring expansions were explored, we identified the rhodium-catalyzed expansion of α-diazoalcohols to be the most effective protocol.[15] Addition of lithiated ethyl diazoacetate onto the ketone function in **7** gave tertiary alcohol **15** (Scheme 3) as a single

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(14) For examples of Mannich-type reactions in the total synthesis of *Lycopodium* alkaloids, see: (a) Heathcock, C. H.; Kleinman, E. F.; Binkly, E. S. *J. Am. Chem. Soc.* **1982**, *104*, 1054–1068. (b) Yang, H.; Carter, R. G.; Zakharov, L. N *J. Am. Chem. Soc.* **2008**, *130*, 9238–9239. (c) Liau, B. B.; Shair, M. D. *J. Am. Chem. Soc.* **2010**, *132*, 9594–9595. (d) Ramharter, J.; Weinstabl, H.; Mulzer, J. *J. Am. Chem. Soc.* **2010**, *132*, 14338–14339. (e) Also see ref 2a.

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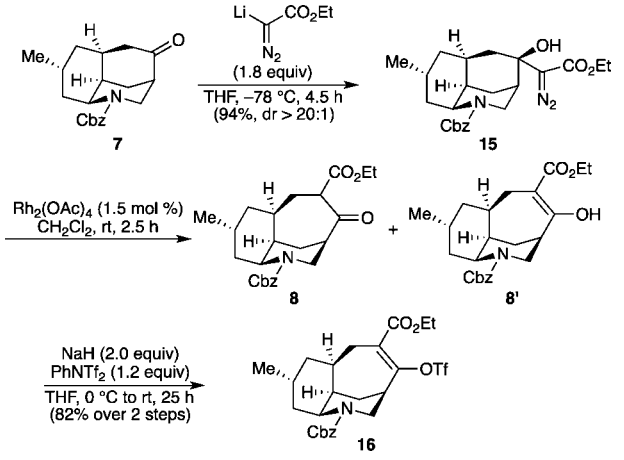
diastereomer in 94% yield. Attempts to effect a direct, one-step Tiffeneau–Demjanov homologation[16] of ketone **7** with ethyl diazoacetate and $BF_3 \cdot OEt_2$ did not give any conversion, while acid-mediated ring expansion[17] of diazoalcohol **15** gave rise to complex mixtures. Ultimately, treatment of diazoalcohol **15** with 1.5 mol % $Rh_2(OAc)_4$ at rt promoted ring expansion within 3 h to yield β-ketoester **8** and its enol tautomer **8′**. With the intention of using the ketone function in **8** and **8′** for subsequent metal-mediated cross-coupling, the crude reaction mixture was directly subjected to enolizing conditions followed by $PhNTf_2$ to afford vinyl triflate **16** in 82% yield over the two steps.

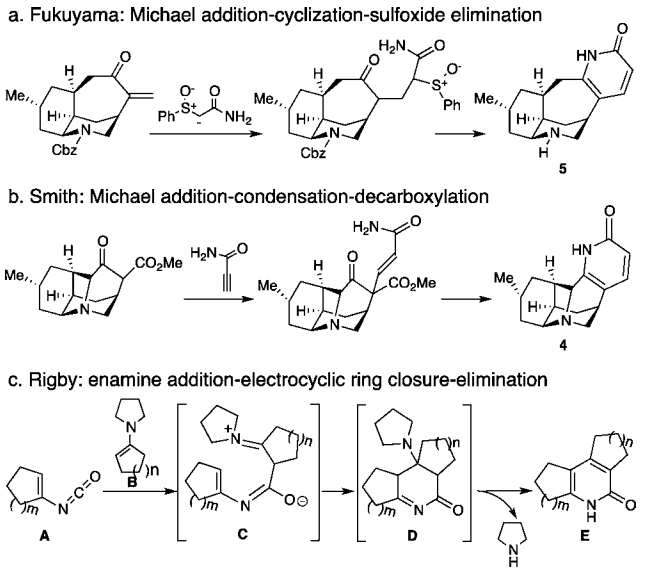
Scheme 3. Ring Expansion of the Luciduline Skeleton and Formation of Vinyl Triflate **16**



We next directed our investigations toward identifying a suitable pyridone ring annulation protocol that would complete the framework of lyconadin C. Previous synthetic efforts toward pyridone-containing *Lycopodium* alkaloids have utilized several tactics for their installation.[18] In the only reported synthesis of lyconadin C to date, Fukuyama and co-workers employed a one-pot Michael addition of 2-(phenylsulfinyl)acetamide followed by cyclization and sulfoxide elimination (Scheme 4a), a strategy also utilized in their total syntheses of lyconadin A (**4**)[8] and huperzine A (**6**).[19] During their pioneering total synthesis of lyconadin A, Smith and co-workers developed an efficient tandem Michael addition–condensation–decarboxylation protocol from β-ketoesters and propionamide (Scheme 4b).[6] In an earlier series of papers, Rigby and co-workers described the use of vinyl isocyanates for the preparation of 2-pyridones through a one-pot, two-step annulation process (Scheme 4c).[20] In their strategy, nucleophilic addition of an enamine (**B**) onto vinyl isocyanate **A** provides a zwitterionic adduct (**C**), which after tautomerization, cyclization, and elimination of pyrrolidine affords the tetrasubstituted pyridone **E**.

While the methods of Smith and Fukuyama proved highly effective in their respective cases, each was unsuitable for our system due to both the type and the location of functionality available in β-ketoester **8** or vinyl triflate **16**. Moreover, the method of Rigby requires either very high temperatures or extended reactions times, and is apparently limited in scope to the formation of pyridones with multiple ring substituents, presumably due to the inherent instability of simple, monosubsituted vinyl enamines. Therefore, it became clear to us that methodology needed to be established that would not only replace the ester function in **8** or **16** with a nitrogen atom but also simultaneously incorporate the additional and necessary functions for subsequent (and ideally, tandem) heterocyclic assembly.

Scheme 4. Previous 2-Pyridone Annulation Tactics in Synthesis



Toward the goal of completing the total synthesis, we wished to investigate a more suitable, intramolecular cyclization strategy to fashion the disubstituted pyridone ring in lyconadin C. We postulated that in order to achieve good reactivity, a system with functional groups in close proximity with favorable π-orbital overlap would be desirable. Cognizant that the requisite pyridone nitrogen in lyconadin C could well be installed through Curtius rearrangement of the corresponding carboxylic acid in ester **16**, we further hypothesized that the intermediate isocyanate species could be more strategically utilized as one component of a projected 6π-electrocyclization, thereby securing the complete pyridone system in a one-pot

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(20) (a) Rigby, J. H.; Balasubramanian, N. *J. Org. Chem.* **1984**, *49*, 4569–4571. (b) Rigby, J. H.; Burkhardt, F. J. *J. Org. Chem.* **1986**, *51*, 1374–1376. (c) Rigby, J. H.; Balasubramanian, N. *J. Org. Chem.* **1989**, *54*, 224–228. (d) Rigby, J. H.; Danca, D. M. *Tetrahedron Lett.* **1997**, *38*, 4969–4972. (e) Rigby, J. H. *Synlett* **2000**, 1–12.

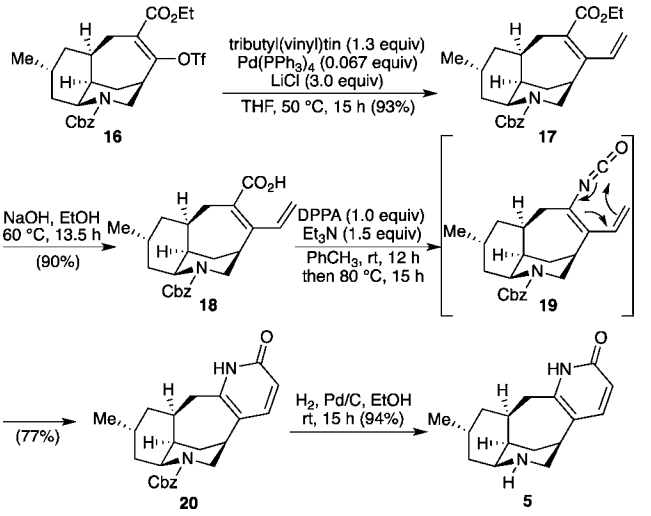
transformation. A conjugated dienyl isocyanate would best serve as the optimal substrate due to the planarity and excellent orbital alignment. This isocyanate would be accessed via a Curtius rearrangement of the corresponding dienyl carboxylic acid. Toward this substrate, Pd-catalyzed Stille cross-coupling[21] of vinyl triflate **16** (Scheme 5) with tributyl(vinyl)tin afforded diene **17** in 93% yield. Saponification of the ester in **17** gave the key isocyanate precursor, carboxylic acid **18**, in 90% yield.

To the best of our knowledge, the 6π-electrocyclization of nonaryl dienyl isocyanates to pyridones under such mild conditions has not been previously reported within the context of alkaloid synthesis. Previously reported electrocyclizations of this type are few and mostly limited in scope to aryl isocyanates, providing pyridones fused to an additional, adjacent aromatic ring.[22] The few other reported examples employing nonaryl isocyanates[23] each require extended reaction times and high temperatures to achieve modest yields.

Treatment of acid **18** with 1 equiv of diphenylphosphoryl azide (DPPA)[24] at rt gave rise to an intermediate acyl azide. Upon heating the reaction mixture to 80 °C, we were gratified to observe that Curtius rearrangement to the corresponding isocyanate was accompanied by spontaneous 6π-electrocyclization, providing pyridone **20** in 77% overall yield. Removal of the Cbz group in **20** delivered lyconadin C. Spectroscopic data, including 2D COSY, HMQC, and HMBC data, for synthetic (−)-lyconadin C as its corresponding TFA salt were in excellent agreement with those of natural (−)-lyconadin C reported by Kobayashi and co-workers.[4]

In summary, an enantioselective and concise total synthesis of (−)-lyconadin C was accomplished in 12 steps and high overall yield. Our synthesis features the short preparation of a luciduline congener through Mannich-type cyclization, followed by ring expansion and tandem Curtius rearrangement/6π-electrocyclization to fashion the pyridone ring. This mild protocol for pyridone formation

Scheme 5. Completion of the Total Synthesis of Lyconadin C



represents a further advancement in the chemistry of vinyl isocyanates, and future applications in total synthesis are anticipated. In addition, our total synthesis of lyconadin C further underscores the synthetic versatility of luciduline and related analogs as intermediates toward more structurally advanced *Lycopodium* alkaloids. We will report our extended investigations on the scope of pyridone annulation, as well as its utility in alkaloid synthesis, in due course, along with further applications of luciduline as a launch point toward additional *Lycopodium* alkaloids.

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Supporting Information Available. Experimental procedures, characterization data, and NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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