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Total Syntheses of (+)-Lyconadin A and (−)-Lyconadin B

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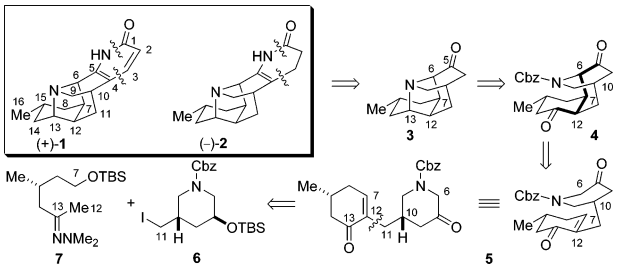
The alkaloids (+)-lyconadin A[1] (**1**) and (−)-lyconadin B[2] (**2**; Scheme 1), isolated by Kobayashi and co-workers from the club moss *Lycopodium complanatum*, respectively, in 2001 and 2006, comprise a new family of *Lycopodium* natural products possessing an unprecedented pentacyclic ring system, with either an α-pyridinone or 3,4-dihydro-α-pyridinone ring fused to a tetracyclic core. Assays against murine lymphoma L1210 and human epidermoid carcinoma KB cells reveal that lyconadin A (**1**) possesses modest in vitro cytotoxicity.[1] The dense stereochemical array, in conjunction with the highly substituted central pyrrolidine ring, renders these alkaloids challenging synthetic targets. While attracting interest in the synthetic community,[3] the lyconadins have not, as yet, succumbed to syntheses. Herein, we disclose the first total syntheses of (+)-lyconadin A (**1**) and (−)-lyconadin B (**2**).

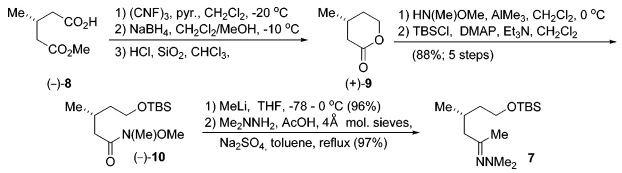
Scheme 1



From the retrosynthetic perspective, late-stage annulation of the α-pyridinone or dihydropyridinone ring onto a tetracyclic ketone (**3**) would permit access to both alkaloids from a common advanced intermediate. Construction of **3**, however, poses a number of synthetic challenges, not the least of which are the four *cis*-fused rings with contiguous stereocenters (C6, 7, 12, and 13). Considerable reduction in molecular complexity could be envisioned by cleavage of the C(13)−N σ-bond to furnish tricycle **4**. Here, one encounters a 7- and two 6-membered rings, in conjunction with a 1,5-diketone (cf. highlighted bonds). We reasoned that **4** could arise via a favorable 7-*endo*-*trig*[4] intramolecular conjugate addition involving enone **5**, which in a single operation would lead (a) to formation of the C(6,7) bond with generation of the requisite stereogenicity at C(6) and C(7), via axial attack *anti* to the methyl group; and (b) upon axial protonation, to the requisite stereocenter at C(12). With this strategy-level reaction in mind, construction of enone **5** would require union of iodide **6** and hydrazone **7**, followed by hydrolysis, oxidation, and generation of the cyclohexenone ring via an intramolecular aldol condensation.

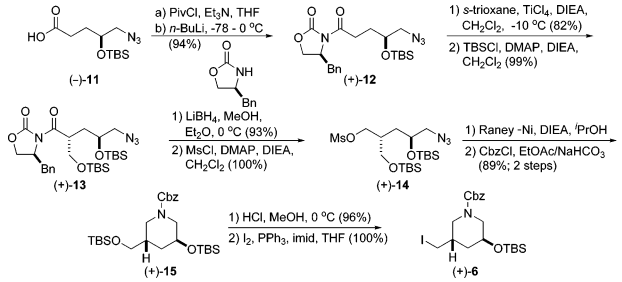
We began with elaboration of the hydrazone **7** (Scheme 2), employing commercially available (−)-methyl (*R*)-3-methylglutarate **8**. Conversion to the acid fluoride, followed by reduction[5] and lactonization, furnished known lactone (+)-**9**.[6] Weinreb amide formation[7] and silyl group protection then led to (−)-**10**. Completion of **7** entailed reaction with methyl lithium followed by hydrazone formation; the overall yield for the seven-step sequence was 82%.

Scheme 2



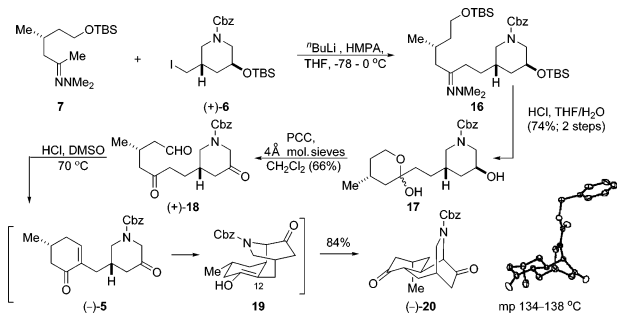
Iodide (+)-**6** was prepared beginning with the known acid (−)-**11**[8] (Scheme 3); conversion to the mixed anhydride and treatment with lithiated L-Phe oxazolidinone furnished (+)-**12**. A titanium enolate aldol reaction with *s*-trioxane[9] followed by silyl group protection then led to (+)-**13**, which upon reductive removal of the chiral auxiliary and mesylation of the resultant alcohol furnished (+)-**14**. Reduction of the azide employing Raney-Ni and, in turn, in situ cyclization and protection of the resultant secondary amine as the benzyloxycarbamate (Cbz) provided the *trans*-3,5-disubstituted piperidine (+)-**15**. Selective removal of the less hindered TBS group via treatment with acid and conversion of the resultant primary alcohol to the iodide completed construction of (+)-**6** in an overall yield of 61% from (−)-**11**.

Scheme 3



Union of (+)-**6** and **7** proceeded efficiently to furnish **16**, employing the lithium anion derived from hydrazone **7** in the presence of HMPA (Scheme 4).[10] The carbonyl and hydroxyl groups

Scheme 4



were next unmasked with aqueous HCl (5%) to provide hemiketal **17** as a mixture of diastereomers; the two-step union−deprotection

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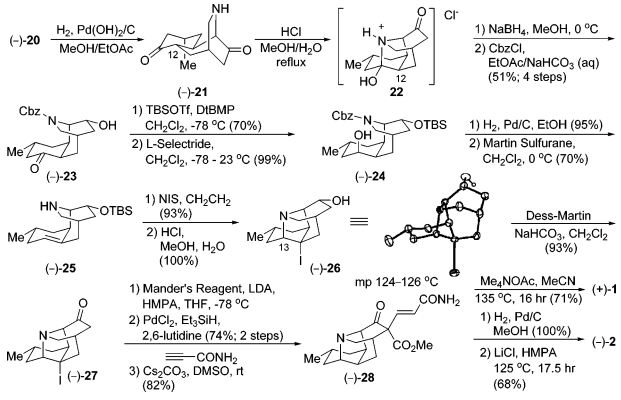
sequence proceeded in 74% yield. Oxidation of both hydroxyls with pyridinium chlorochromate yielded (+)-**18** as a somewhat unstable diketoaldehyde. Initial efforts (i.e., base) to affect the desired intramolecular aldol condensation to furnish enone (−)-**5** led primarily to polymerization, or at best, minor amounts of (−)-**5**. However, treatment of (+)-**18** in DMSO with HCl (25:1 v/v) at 70 °C for 3 h furnished a single crystalline product in 84% yield. X-ray analysis revealed tricyclic ketone (−)-**20**, product of the desired aldol condensation to produce enone (−)-**5** in situ, followed by conjugate addition, presumably of the C(6) enol, *anti* to the cyclohexenone methyl group, thereby securing formation of the critical C(6)−C(10) σ-bond, in conjunction with the requisite stereogenicity at C(7). Although we had envisioned formation of **4** via preferential axial protonation of enol **19**, formation of (−)-**20** can be understood on the basis of thermodynamic stability. Although gratified with construction of (−)-**20**, comprising two new carbon−carbon σ-bonds and two new rings in a single chemical operation, we were now faced with the daunting challenge of correcting the stereogenicity at C(12) in order to install the key C(13)−N bond.

We reasoned that forced epimerization at C(12) might be possible by trapping the desired *cis* C(7)−C(12) epimer as a stable hemiaminal. Toward this end, the Cbz group was removed to provide the free amine (−)-**21** (Scheme 5), which upon heating at reflux in a mixture of water/methanol/HCl (12 N) (17:3:1) induced epimerization at C(12) bringing the nitrogen proximal to the C(13) ketone to furnish hemiaminal salt **22** (^{13}C NMR; hemiaminal carbon δ 97.6 ppm), delivering the desired C(12) stereochemistry. Not surprisingly, however, all attempts to remove the hydroxyl by reduction failed due to the prohibitively high energy of the anti-Bredt iminium ion. Equally unprofitable, all attempts to derivatize the hydroxyl led to cleavage of the C(13)−N σ-bond.

Scheme 5



Undaunted, we chose to exploit the hemiaminal salt to protect the C(13) ketone. Treatment of **22** with $NaBH_4$ led chemo- and stereoselectively to hydroxyketone (−)-**23**, after reprotection of the NH as the Cbz carbamate; the four-step sequence from (−)-**20** proceeded in 51% yield without purification of intermediates.[11] Protection of the hydroxyl group as the TBS ether, followed by L-Selectride reduction, then produced alcohol (−)-**24**. To access the requisite tetracycle, we now faced generation of the C(13)−N bond. To this end, removal of the Cbz group and dehydration exploiting the Martin sulfurane[12] led exclusively to formation of the trisubstituted alkene (−)-**25**. Pleasingly, aminoiodination with *N*-iodosuccinimide (NIS), followed by acid-mediated desilylation, furnished crystalline (−)-**26** in 93% yield for the two steps; X-ray analysis employing the anomalous dispersion technique confirmed assignment of both the relative and absolute stereochemistry.[13] Oxidation with Dess−Martin periodinane then led to (−)-**27** in 93% yield.

Efforts to construct the α-pyridinone ring by direct installation of the requisite C(1)−C(3) carbon chain by alkylation or conjugate addition proved unsuccessful. Activation of the ketone was, however, possible via the Mander[14] protocol to furnish the corresponding β-ketoester. Reductive removal of the iodide[15] followed by Michael addition of propiolamide[16] provided (−)-**28**. With the requisite carbons installed, (+)-lyconadin A (**1**) was generated in 71% yield via a novel one-pot protocol involving decarboxylation, mediated by Me_4NOAc,[17] olefin isomerization, and cyclocondensation. To access (−)-lyconadin B (**2**), an adjustment of oxidation state was required. Hydrogenation of (−)-**28** followed by a similar one-pot protocol, in this case mediated by lithium chloride, furnished (−)-lyconadin B (**2**) in 68% yield. The spectral data (^{1}H and ^{13}C NMR, IR, and chiroptic properties) for synthetic (+)-lyconadin A (**1**) and (−)-lyconadin B (**2**) were in agreement with those recorded for the natural products, confirming their structural and absolute stereochemical assignments.[13]

In summary, a unified synthetic strategy affording (+)-lyconadin A (**1**) and (−)-lyconadin B (**2**), employing a strategy-level intramolecular aldol/conjugate addition cascade, generating two new carbon−carbon σ-bonds, in conjunction with three new stereogenic centers to furnish a complex tricyclic ring system in a single chemical operation, has been achieved.

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Supporting Information Available: Experimental procedures and spectroscopic and analytical data for all new compounds. This material is available free of charge via the internet at http://pubs.acs.org.

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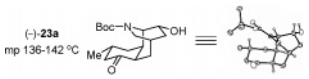
(11) Alternatively, protection of the NH as the Boc carbamate furnished a crystalline hydroxyketone (−)-**23a**; X-ray analysis confirmed the relative stereochemistry.



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