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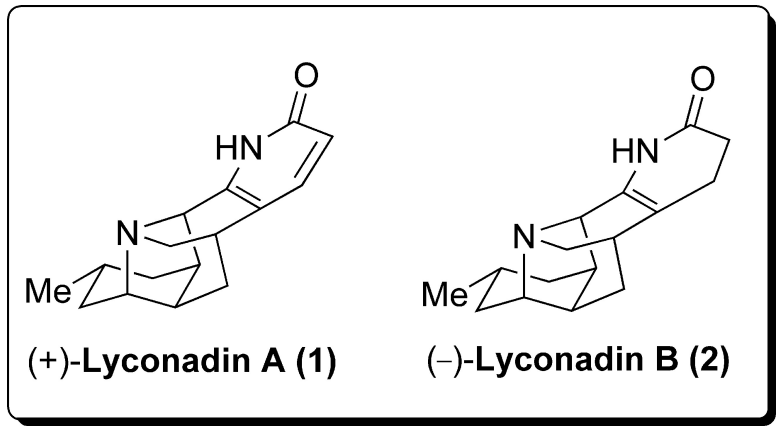

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The Lyconadins: Enantioselective Total Syntheses of (+)-Lyconadin A and (−)-Lyconadin B

Douglas C. Beshore† and Amos B. Smith III*

Department of Chemistry, Laboratory for Research on the Structure of Matter, and Monell Chemical Senses Center, University of Pennsylvania, Philadelphia, Pennsylvania 19104

Received June 27, 2008; E-mail: smithab@sas.upenn.edu

Abstract: A full account of the enantioselective total syntheses of (+)-lyconadin A (**1**) and (−)-lyconadin B (**2**) is presented. Central to this venture was recognition and deployment of a key strategy-level intramolecular aldol/conjugate addition cascade that led, in a single operation, to two new carbon−carbon σ-bonds, three new stereogenic centers, and two new rings, albeit with the incorrect stereogenicity at C(12) for the lyconadins. Correction of the C(12) stereogenicity was achieved via innovative use of a protonated intramolecular aminal. An aminoiodo olefin cyclization, in conjunction with α-pyridinone and 3,4-dihydropyridinone annulation protocols, permitted completion of the syntheses of (+)-lyconadin A (**1**) and (−)-lyconadin B (**2**), respectively.

Introduction

In 2001 and 2006, Kobayashi and co-workers reported the isolation and structural elucidation of (+)-lyconadin A[1] and (−)-lyconadin B,[2] respectively (**1** and **2**, Figure 1), from the methanol extracts of *Lycopodium complanatum*, a new member within this diverse family.[3] Unique to the lyconadins is the unprecedented pentacyclic framework, involving either an α-pyridinone or 3,4-dihydropyridinone ring annulated to a common tetracyclic core, consisting of a central, highly substituted pyrrolidine ring, which in turn is fused to three six-membered rings. From the biomedical perspective, lyconadin A (**1**) possesses modest in vitro cytotoxicity, when assayed against murine lymphoma L1210 and human epidermoid carcinoma KB cells, while both lyconadins A and B (**1** and **2**) induce enhanced mRNA expression for neurotropic growth factor biosynthesis in 1321N1 human astrocytoma cells.[1,2] Despite the intriguing structural features, as well as the pharmacological properties of the lyconadins, only a few reports have been directed toward their syntheses.[4] In 2007, we disclosed the first total syntheses of (+)-lyconadin A (**1**) and (−)-lyconadin B (**2**);[5] the synthesis of lyconadin A in racemic form was subsequently reported by the Sarpong group in early 2008.[6] Presented here is a full account of the evolution and successful execution of the Penn synthetic venture.

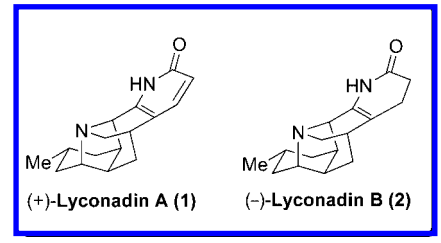


Figure 1. Structures of the alkaloids (+)-lyconadin A (**1**) and (−)-lyconadin B (**2**).

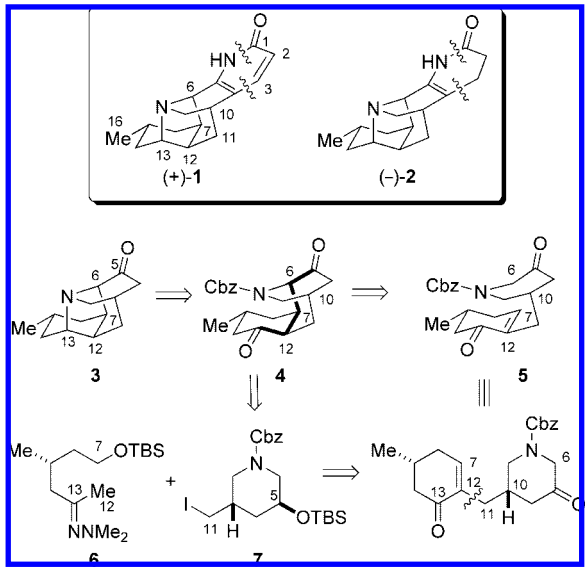
At the outset, we envisioned a late stage divergent approach involving annulation of the requisite α-pyridinone[7] or dihydropyridinone ring onto ketone **3** (Scheme 1), the common tetracyclic core, replete with a number of significant synthetic challenges, including four *cis*-fused rings, punctuated with four contiguous stereocenters [cf. C(6, 7, 12, and 13)]. To reduce this complexity, we envisioned cleavage of the C(13)-*N* σ-bond to furnish tricycle **4**, formally a reductive amination in the synthetic direction, albeit a violation of Bredt's rule.[8] Within **4**, one next encounters a number of intriguing structural elements, including a tricycle consisting of a 7- and two 6-membered rings, a 1,5-diketone (cf. highlighted bonds), an equatorial C(16) methyl group *anti* to the C(6) carbon inscribed within the cyclohexanone framework, and a piperidine ring complete with *cis*-ring fusion at C(6) and C(10). Taken together,

† Present address: Merck Research Laboratories, Department of Medicinal Chemistry, West Point, PA 19486.

(1) (a) Kobayashi, J.; Hirasawa, Y.; Yoshida, N.; Morita, H. *J. Org. Chem.* **2001**, *66*, 5901. (b) Hill, R. A.; Parker, M. C. *Nat. Prod. Rep.* **2001**, *18*, iii–v.
(2) Ishiuchi, K.; Kubota, T.; Hoshino, T.; Obara, Y.; Nakahata, N.; Kobayashi, J. *Bioorg. Med. Chem.* **2006**, *14*, 5995.
(3) For recent reviews of Lycopodium alkaloids, see: (a) Kobayashi, J.; Morita, H. *The Alkaloids: Chemistry and Biology*; Cordell, G. A., Ed.; Elsevier Academic Press: New York, 2005; Vol. 61, p 1. (b) Ma, X.; Gang, D. R. *Nat. Prod. Rep.* **2004**, *21*, 752. (c) Ayer, W. A.; Trifonov, L. S. *Lycopodium Alkaloids*; Academic Press: San Diego, 1994. (d) Ayer, W. A.; Trifonov, L. S. *Alkaloids*; Cordell, G. A., Brossi, A., Ed.; Academic Press: New York, 1994; Vol. 45, p 233. (e) Ayer, W. A. *Nat. Prod. Rep.* **1991**, *8*, 455. (f) MacLean, D. B. *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1985; Vol. 26, p 241.
(4) (a) Tracey, M. R.; Hsung, R. Abstract of Papers, Presented at the 226th National Meeting of the American Chemical Society, New York, September 2003; paper ORGN-721. (b) Crich, D.; Neelamkavil, S. *Org. Lett.* **2002**, *4*, 2573. (c) Castle, S. L. Presented at the 232nd Meeting of the American Chemical Society, San Francisco, CA, September 2006; paper ORGN-064. (d) Grant, S. W.; Zhu, K.; Zhang, Y.; Castle, S. L. *Org. Lett.* **2006**, *8*, 1867.
(5) Beshore, D. C.; Smith, A. B., III. *J. Am. Chem. Soc.* **2007**, *129*, 4148.
(6) Bisai, A.; West, S. P.; Sarpong, R. *J. Am. Chem. Soc.* **2008**, *130*, 7222.
(7) For application: of a one-pot procedure for α-pyridinone ring formation, see: Kozikowski, A. P.; Reddy, E. R.; Miller, C. P. *J. Chem. Soc., Perkin Trans. I* **1990**, 195.
(8) Shea, K. J. *Tetrahedron* **1980**, *36*, 1683.

10.1021/ja804939r CCC: $40.75

Scheme 1. Retrosynthetic Analysis of (+)-Lyconadin A (**1**) and (−)-Lyconadin B (**2**)

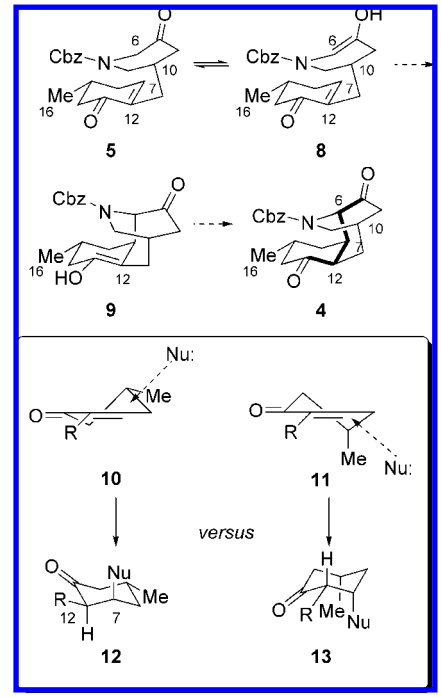


these structural features led us to devise a strategy-level transformation involving intramolecular conjugate addition of the enolate derived from **5** to the α,β-unsaturated ketone to access **4**. According to Baldwin, such a 7-*endo-trig* cyclization should prove favorable.[9]

Since diketone **5** possesses four potentially enolizable centers, three α- and one γ- to the two ketones, careful attention to the various components of the proposed strategy-level tactic would be required.[10] From the stereoelectronic perspective, *only* the C(6) *E*-enol can undergo a favorable intramolecular cyclization (Scheme 2).[9b] Careful choice of the nitrogen protection was also an issue; we selected the electron withdrawing *N*-carboxylbenzyl (Cbz) group to enhance the required enolization. Additionally, the stereogenicity at C(10) suggested formation of a *cis*-fused 7-membered ring; for such a process, two ring conformations would be possible (i.e., **10** and **11**). To minimize $A^{1,3}$ strain, favorable stereoelectronic axial attack should occur from the top face of **10**, in which the methyl group resides in the equatorial position. Conversely, if the ring were to adopt an alternate conformation (i.e., **11**), favorable axial attack could occur from the bottom face. Due to the expected steric repulsion exerted by the axial methyl group on the incoming nucleophile, the latter would presumably be unfavorable. Following this reasoning, reaction via conformation **10** was expected. Protonation of the resulting enol (**9**) at C(12) would then be anticipated to occur axially to provide **4**, possessing the required relative stereogenicity of the three contiguous stereocenters found in the lyconadins. For enone **5**, construction would entail C(11)−C(12) bond formation (Scheme 1), via union of the kinetic enolate[11] of hydrazone **6** with iodide **7**, followed by

(9) (a) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734. (b) Baldwin, J. E.; Lusch, M. J. *Tetrahedron* **1982**, *38*, 2939.
(10) While 7-*endo-trig* conjugate additions are known, their application to the formation of a [5.4.0]undecane-2,7-dione is only precedented from Tokoroyama's studies toward the clerodane diterpenoids: Tokoroyama, T.; Tsukamoto, M.; Iio, H. *Tetrahedron Lett.* **1984**, *25*, 5067.
(11) Stork, G.; Dowd, S. R. *J. Am. Chem. Soc.* **1963**, *85*, 2178.

Scheme 2. Stereochemical Analysis of the Strategic Conjugate Addition

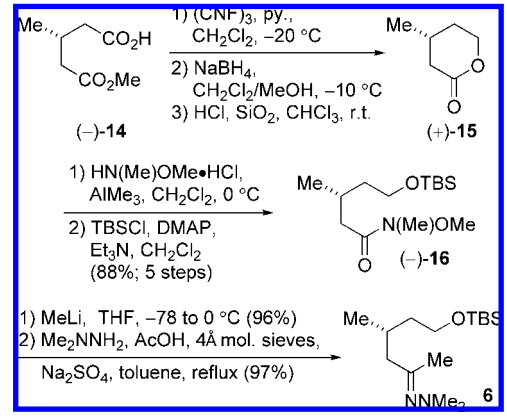


hydrazone hydrolysis, oxidation at C(7), and generation of the cyclohexenone ring via an intramolecular aldol condensation.

Results and Discussion

We began with construction of hydrazone **6** (Scheme 3), employing commercially available methyl (*R*)-3-methylglutarate (−)-**14**. While reduction of the carboxylic acid (−)-**14** is known to proceed with borane,[12] a two-step activation/reduction protocol was found to be more reliable on a larger scale.[13] Under these reaction conditions, partial lactone formation occurred to furnish known lactone (+)-**15**; complete lactonization was achieved upon treatment with acid.[14] Direct installation of the remaining carbon was next envisioned to occur via addition of methyllithium, followed by silylation of the primary hydroxyl group. However, all attempts to silylate the resulting hemiketal

Scheme 3. Construction of Hydrazone **6**

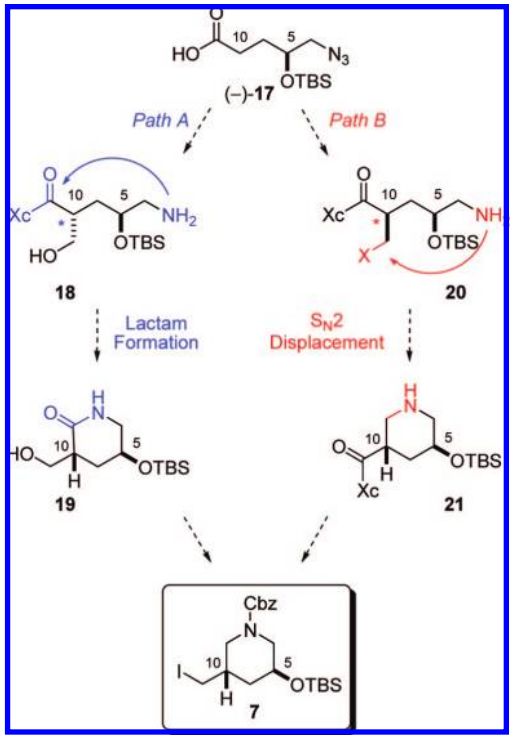


following the addition proved unsuccessful. We therefore turned to a three-step protocol involving a Weinreb amide.[15] Protection of the hydroxyl as the TBS ether, installation of the requisite carbon with methyl lithium, and conversion to the *N,N*-

dimethylhydrazone delivered hydrazone **6** in 82% overall yield for the seven-step sequence.

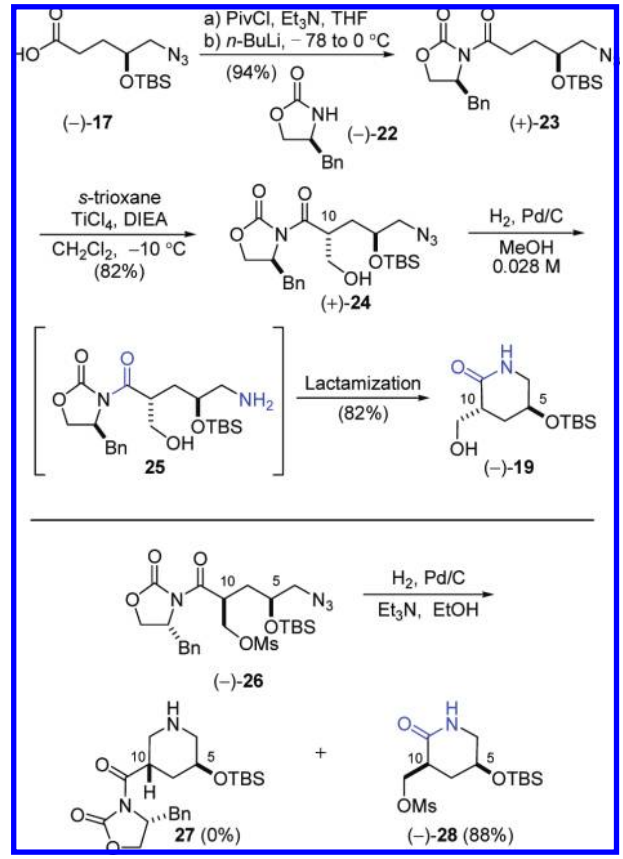
We next turned our attention toward the construction of iodide **7** from known acid[16] (−)-**17** (Scheme 4). Recognizing the pseudo-C_2 symmetry at C(10) in **18** and **20**, either lactam formation via *Path A* (**18** → **19**), or an S_N2 displacement upon interchange of the oxidation states of the acid and primary alcohol via *Path B* (**20** → **21**), could lead to the requisite piperidine.

Scheme 4. Synthetic Strategies to Construct Iodide **7**



We began with *Path A* (Scheme 5). Formation of the mixed anhydride derived from (−)-**17**, followed by treatment with lithiated oxazolidinone (−)-**22**[17] obtained from L-phenylalanine, furnished (+)-**23** in 94% yield. A titanium-mediated aldol reaction with *s*-trioxane then delivered (+)-**24** as a single diastereomer with the requisite stereogenicity at C(10) based on the Evans precedent.[18] Reduction of the azide furnished amine **25**, which underwent spontaneous lactam formation to provide piperidinone (−)-**19** in good yield. Surprisingly, however, all attempts to reduce the lactam to the corresponding secondary amine failed to deliver the piperidine.[19,20] Attempts to exploit the alternative thioamide[21] resulted in either poor conversion and/or erosion of the stereointegrity at C(10), the latter likely due to the formation of the thermodynamically more stable diequitorial thiopiperidinone. We therefore turned to *Path B*. Antipode (−)-**26**[22] was prepared in three steps from oxazolidinone (+)-**22** and acid (−)-**17**. Unfortunately, reduction of the azide led spontaneously to exclusive formation of piperidinone (−)-**28**, rather than the desired piperidine **27**. We reasoned that formation of the desired piperidine could however be achieved if a properly substituted cyclization substrate were employed.

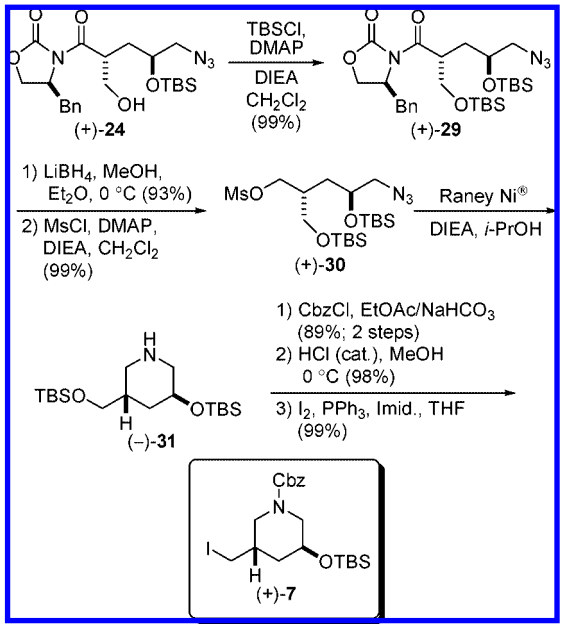
Scheme 5. Synthetic Approaches to Iodide **7**



Toward that end, protection of the primary hydroxyl in (+)-**24** as the TBS ether followed by reductive removal of the oxazolidinone furnished the corresponding primary alcohol, which was subsequently converted to mesylate (+)-**30** (Scheme 6). Hydrogenation of the azide led, as anticipated, to in situ cyclization of the amine to furnish the required piperidine (−)-**31**. Protection of the amino group as the Cbz carbamate, acidic hydrolysis of the primary TBS ether, and conversion of the resulting alcohol to the iodide completed construction of (+)-**7** in 61% overall yield from known acid (−)-**17**. Importantly, this sequence proved both reliable and scalable.

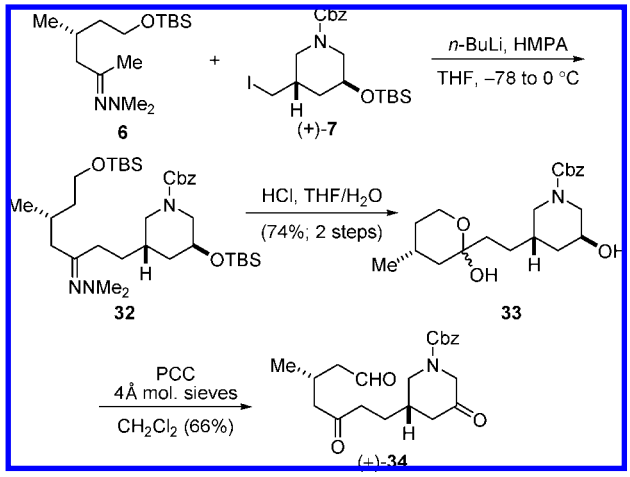
(12) (a) Cid, M. B.; Pattenden, G. *Tetrahedron Lett.* **2000**, *41*, 7373. (b) Alvarez, E.; Cuvigny, T.; Herve du Penhoat, C.; Julia, M. *Tetrahedron* **1988**, *44*, 119.
(13) Kokotos, G.; Noula, C. *J. Org. Chem.* **1996**, *61*, 6994.
(14) Irwin, A. J.; Jones, J. B. *J. Am. Chem. Soc.* **1977**, *99*, 556.
(15) Levin, J. I.; Turos, E.; Weinreb, S. M. *Synth. Commun.* **1982**, *12*, 989.
(16) Kottirsch, G.; Metternich, R.; New Derivatives of Beta-Amino Acids with Anti-Thrombotic Activity. Eur. Patent EP 0 560 730 B1, 1996.
(17) Gage, J. R.; Evans, D. A. *Org. Synth.* **1990**, *68*, 83.
(18) Evans, D. A.; Urpi, F.; Somers, T. C.; Clark, J. S.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1990**, *112*, 8215.
(19) The following conditions were examined: $LiAlH_4$: (a) Meyers, A. I.; Berney, D. *J. Org. Chem.* **1989**, *54*, 4673. Borane: (b) Herdeis, C.; Kaschinshki, C.; Karla, R. *Tetrahedron: Asymmetry* **1996**, *7*, 867. $TiCl_4/NaBH_4$: (c) Umino, N.; Iwakuma, T.; Itoh, N. *Tetrahedron Lett.* **1976**, *10*, 763. (d) Gribble, G. W *Chem. Soc. Rev.* **1998**, *27*, 395. Red-Al: (e) Fréville, S.; Célérier, J. P.; Thuy, V. M.; Lhommet, G. *Tetrahedron: Asymmetry* **1995**, *6*, 2651. AlH_3: (f) Batistini, L.; Zanardi, F.; Rassu, G.; Spanu, P.; Pelosi, G.; Fava, G. G.; Ferrari, M. B.; Casiraghi, G. *Tetrahedron: Asymmetry* **1997**, *8*, 2975.
(20) Masking the hydroxyl as the TBS ether did not improve amide reduction.
(21) Thioamide formation was accomplished utilizing Lawesson's Reagent: Pedersen, B. S.; Scheibye, S.; Nilsson, N. H.; Lawesson, S. O. *Bull. Soc. Chim. Belg.* **1978**, *87*, 223.
(22) See Supporting Information for preparation of (−)-**26**.

Scheme 6. Construction of Iodide (+)-**7**



With the key fragments in hand, union of hydrazone **6** with iodide (+)-**7** was achieved via the Stork[11] metalloimine protocol (Scheme 7). Specifically, the lithium anion[23] derived from hydrazone **6** was treated with iodide (+)-**7** in the presence of HMPA[24] to furnish **32**, the result of exclusive alkylation at the less hindered carbon.[25] Removal of the hydroxyl and carbonyl protective groups with aqueous acid resulted in spontaneous hemiketalization of the ketodiol to furnish **33** as a mixture of diastereomers (ca. 3:1) in 74% overall yield for the two steps. Oxidation of both hydroxyls could not be accomplished under basic conditions (i.e., Parikh-Doering[26] conditions). Rather, mild acidic conditions were required (i.e., Dess-Martin periodinane or pyridinium chlorochromate), suggesting that the pH of the reaction mixture influences the ketone-hemiketal equilibrium. In the end, the less expensive pyridinium chlorochromate proved

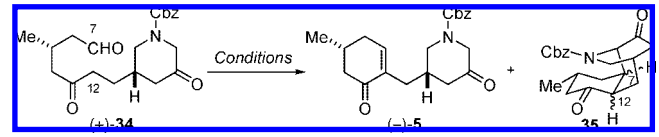
Scheme 7. Fragment Union and Elaboration to Diketoaldehyde (+)-**34**



more scalable (cf. 10 g), furnishing the double oxidation product (+)-**34** in 66% yield.

Diketo aldehyde (+)-**34** proved to be somewhat unstable and difficult to handle. For example, treatment with base (Table 1, entries 1 and 2) led either to decomposition or no reaction. Use of the Stork pyrrolidinium acetate strategy also proved unfruitful (entry 3),[27] resulting in slow decomposition over several hours. Acidic conditions initially appeared no better (entry 4); however, treatment of (+)-**34** in a two-phase system consisting of HCl (12 N aqueous) and chloroform (1:25) at 40 °C for 2 h (entry

Table 1. Conditions Examined and Optimized to Affect Intramolecular Aldol Condensation and Conjugate Addition



entry	conditions	temp (°C)	time (h)	% yield (−)-5[a]	% yield 35[a]
1	NaOMe, MeOH	23	1 min	–	–
2	DBU, THF	23	2	–	–
3	Pyrrolidinium acetate, C_6H_6	105	5	–	–
4	HCl, MeOH	40	18	–	–
5	HCl, $H_2O/CHCl_3$	40	2	24	–
6	HCl (aq.), DMSO	23	1	5[b]	–
7	HCl (aq.), DMSO	40	1	–	5[b]
8	HCl (aq.), DMSO c = 0.02M	50	18	–	43
9	HCl (aq.), DMSO c = 0.01M	70	3	–	54
10	HCl (aq.), DMSO c = 0.005M	70	3	–	84

[a] Isolated yield. [b] Conversion based on ^{1}H NMR analysis of the reaction mixture.

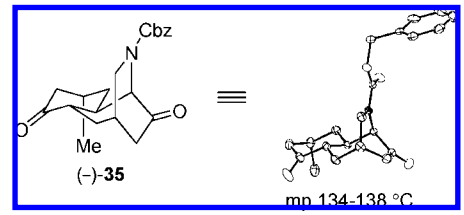
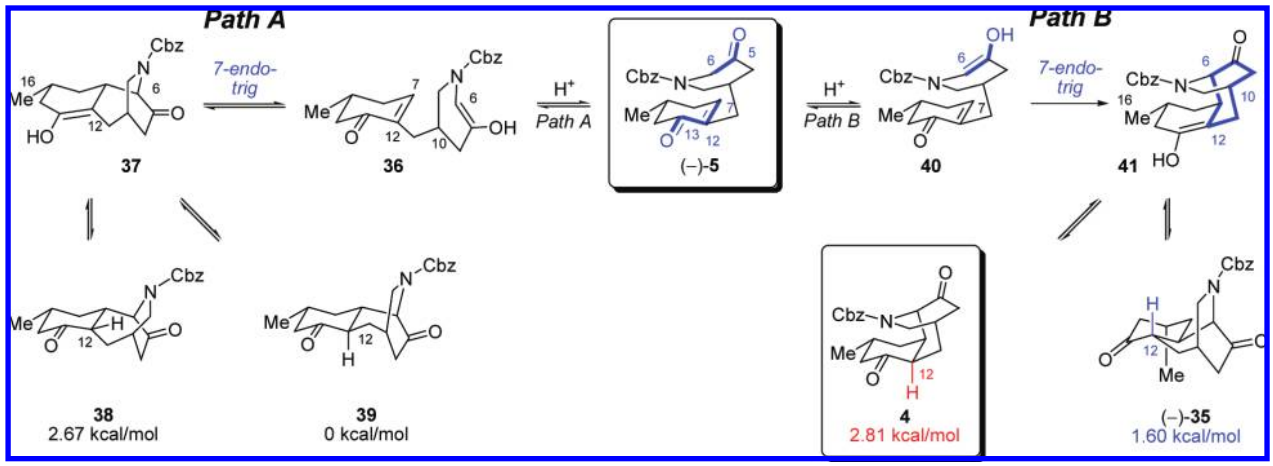


Figure 2. Structure of diketone (−)-**35**.

5) led to enone (−)-**5**, albeit in a modest 24% yield. Attempts to improve the conversion were not fruitful, as competitive polymerization proved persistent. Fortunately, screening solvents and temperature regimes led to more promising results. For example, although treatment of (+)-**34** with hydrochloric acid in dimethyl sulfoxide (entry 6) at ambient temperature for 1 h led to enone (−)-**5** in low yield, at slightly elevated temperatures (40 °C, entry 7) a *new* compound began to appear. Initial ^{1}H NMR analysis suggested the new entity to be the intramolecular conjugate addition product **35** derived from enone (−)-**5**, the next intermediate required in our synthetic sequence! Optimization of this serendipitous result revealed that temperature, time, and acid concentration were critical (Table 1). Best results involved treatment of diketoaldehyde (+)-**34** with aqueous hydrochloric acid in a degassed solution of DMSO (25:1; DMSO:HCl 12 N; v/v) for three hours at 70 °C to provide (−)-**35** as a crystalline solid (mp 134−138 °C; Figure 2); the yield was 84%. Single crystal X-ray analysis revealed that although

(23) Stork, G.; Benaim, J. *J. Am. Chem. Soc.* **1971**, *93*, 5938.
(24) (a) Petersen, J. S.; Tötenberg-Kaulen, S.; Rapoport, H. *J. Org. Chem.* **1984**, *49*, 2948. (b) Panek, J. S.; Beresis, R. T.; Celatka, C. A. *J. Org. Chem.* **1996**, *61*, 6494.
(25) For a comprehensive review see: Whitesell, J. K.; Whitesell, M. A. *Synthesis* **1983**, 517.
(26) Parikh, J. R.; Doering, W. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505.
(27) Stork, G.; Brizzolara, A.; Landesman, H.; Szmuszkovicz, J.; Terrell, R. *J. Am. Chem. Soc.* **1963**, *85*, 207.

Scheme 8. Stereochemical Analysis of the Strategy-Level Conjugate Addition



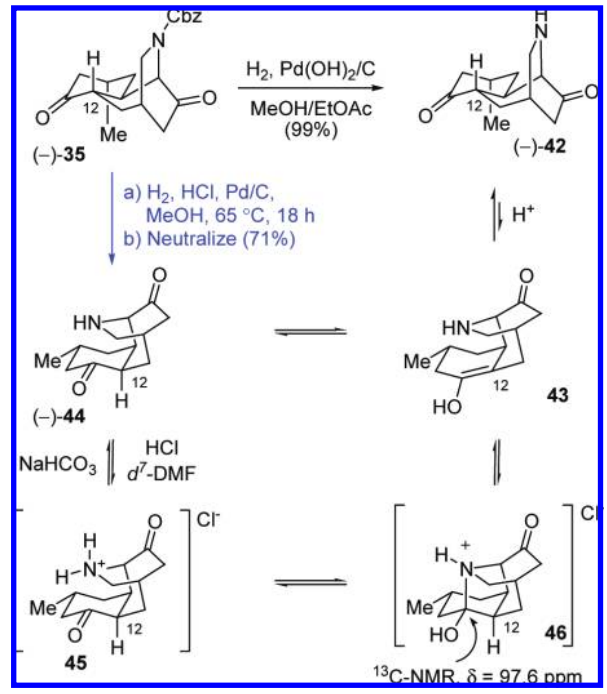
the connectivity was correct, the relative stereochemical outcome at C(12) was not that of the lyconadins. Not withstanding this stereochemical issue, the intramolecular conjugate addition had furnished two new carbon−carbon σ-bonds, two rings, and three contiguous stereocenters in a single operation.

To understand this intriguing observation, as well as to seek a solution to the unfavorable stereochemical outcome, we carefully analyzed the reaction sequence (Scheme 8). The aldol product (−)-**5** has the opportunity to undergo a Baldwin allowed 7-*endo-trig* intramolecular conjugate addition either *syn* or *anti* to the C(16)-methyl group (*Paths A* and *B*). If *Path A* were followed, equatorial attack via the conformation depicted by **36** would result in formation of the C(6)−C(7) bond *cis* to the C(16) methyl group, forming enol **37**, which in turn could undergo protonation either from the top or bottom face to result in **38** or **39**, respectively. Conversely, following *Path B*, axial attack from the top face via what would be a stereoelectronically favorable trajectory would furnish the required stereogenicity at C(6) and C(7), relative to both C(10) and the cyclohexenone C(16) methyl group. Protonation of the resultant enol (**41**) could again occur either from the top or bottom face to furnish **4** or (−)-**35**. In this event, only (−)-**35** was isolated in 84% yield.

Structure calculations employing B3LYP/6−31G** level of theory, performed on the four diastereomers (**4**, **35**, **38**, and **39**) using the Gaussian package,[28] revealed the lowest-energy diastereomer to be **39**, which was not observed. The sole isolated product (−)-**35** proved intermediate in energy, with the congener arising via the stereoelectronically preferred protonation pathway (i.e., **4**) having the highest energy. Taken together, these results suggest that the reaction sequence is not solely under thermodynamic control. Given that the product derived via the stereoelectronically preferred axial protonation (i.e., diastereomer **4**) was not observed, the reaction also cannot be considered to be solely under kinetic control. Rather, the observed product is the result of both kinetic and thermodynamic processes operating at different points along the reaction sequence. Since neither **38** nor **39** were formed during the reaction, we conclude that formation of the C(6)−C(7) σ-bond is irreversible. With P*ath B* the only way forward, the protonation event at C(12) of enol **41** can be understood to occur under thermodynamic control, as **4** is higher in energy than the observed product (−)-**35** ($\Delta\Delta G°_f$ = 1.21 kcal/mol). While we were gratified that the 7-*endo-trig* conjugate addition proceeded efficiently to furnish a single diastereomer, we were now faced with the challenge of correcting the stereogenicity at C(12) to construct the tetracyclic core of the lyconadins.

Recognizing that the relative energy difference between the C(12) epimers [**4** and (−)-**35**] is small, we reasoned that conditions might be found to correct the stereochemical issue. Further analysis suggested the use of protonated hemiaminal **46**, generated by acid-catalyzed epimerization, to trap the desired diastereomer (*vida supra*). With this scenario in mind, removal of the Cbz group in (−)-**35** to reveal the secondary amine **42** (Scheme 9) and treatment with methanolic hydrochloric acid (12N) (10:1; MeOH:HCl; v/v) at reflux for 18 h, followed by concentration and careful neutralization led to (−)-**44** in 71% yield.[29] Pleasingly, this process permits facile epimerization of (−)-**42** to the higher energy epimer (−)-**44**. Support for

Scheme 9. Correction of the Stereogenicity at C(12)

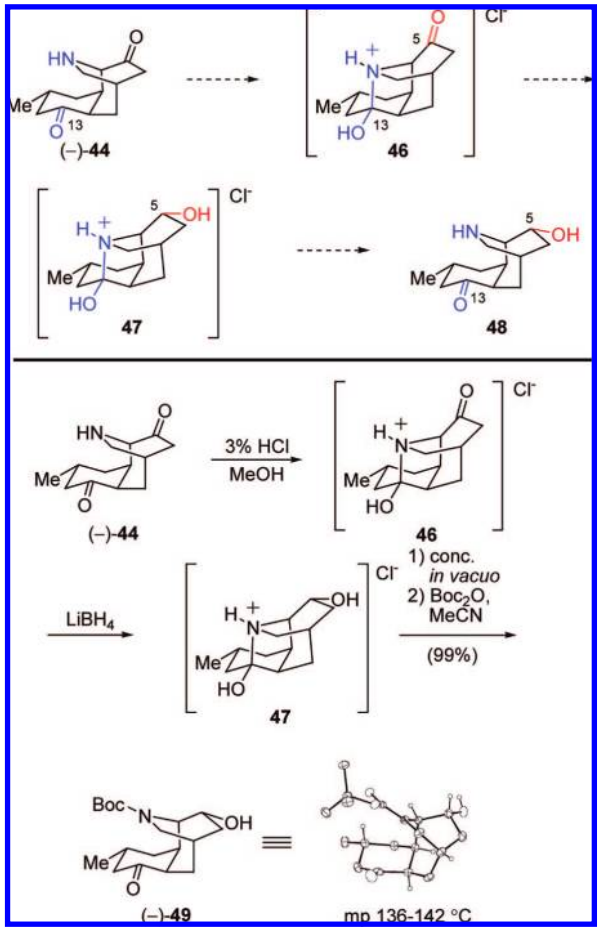


(28) Frisch, M. J. *Gaussian 03*, revision C.01; Gaussian, Inc.: Wallingford, CT, 2004. See Supporting Information for details regarding the described calculations.

intermediacy of the hemiaminal salt was obtained by treatment of (−)-**44** with hydrochloric acid (12N) in d^7-DMF; a new resonance at 97.6 ppm in the ^{13}C NMR, characteristic of a tertiary carbinol salt (cf. **46**), was observed.[30] Upon neutralization with sodium bicarbonate, diketoamine (−)-**44** is regenerated.[31] Given the facile formation of the hemiaminal salt **46**, we reasoned that direct reduction or capture of the hemiaminal might be possible (cf. **3**, Scheme 1). Unfortunately, all efforts to achieve such transformations failed, presumably due to the relative unreactivities of both the sterically congested, nonnucleophilic tertiary alcohol of the aminal and the hindered nitrogen in the corresponding aminoketone. We were therefore forced to revise our strategy. Interconversion of aminoketone (−)-**44** and hemiaminal salt **46** would however play a significant role in our modified tactic to deliver the tetracyclic core for the lyconadins (*vida infra*).

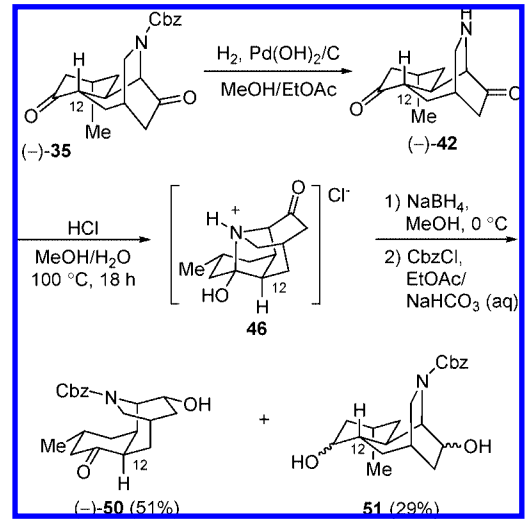
Unable to affect direct formation of the critical *N*-C(13) σ-bond, we explored differentiation of the two carbonyl groups in diketoamine (−)-**44** (Scheme 10), by taking advantage of the hemiaminal salt **46**, to act as an *in situ* mask for the C(13) ketone. Toward this end, treatment of **46** with lithium borohydride led with high selectivity to the equatorial alcohol **47**, which without isolation was protected with *tert*-Boc anhydride (Boc_2O) to furnish the *N*-Boc derivative (−)-**49** as a crystalline solid; single crystal X-ray analysis verified both the structure and relative stereochemistry.

Scheme 10. Hemiaminal Mask for the C(13) Ketone



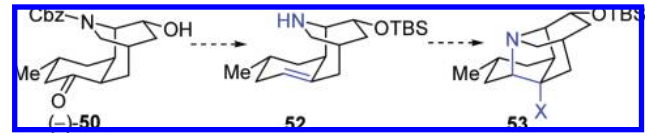
While preparation of (−)-**49** led to invaluable structural information, we anticipated that a more robust nitrogen protecting group (cf. Cbz) would be required to complete the synthetic venture. Thus, in similar fashion, (−)-**35** was converted to (−)-**50** in 51% yield for the four-step sequence (Scheme 11). In this case, a diastereomeric mixture of diols (i.e., **51**; 29% yield) was also formed, the result of incomplete epimerization at C(12) and nonselective reduction of the C(13) and C(5) carbonyl groups. Fortunately, **51** could be recycled via Dess-Martin periodinane[32] oxidation to afford (−)-**35** in 92% yield, thereby permitting efficient material utilization. The overall yield for the four-step sequence was 80%.[33]

Scheme 11. Four-Step Sequence to Correct the C(12) Stereogenicity



Formation of the C(13)-*N* σ-bond (Scheme 12) was the next priority. Recognizing that the C(13) ketone could not be employed directly, we reasoned that if (−)-**50** could be converted to the trisubstituted olefin **52** (Scheme 12), treatment with a suitable electrophile might induce intramolecular cyclization to forge the long-sought σ-bond, and thereby the tetracyclic core of the lyconadins (i.e., **53**).

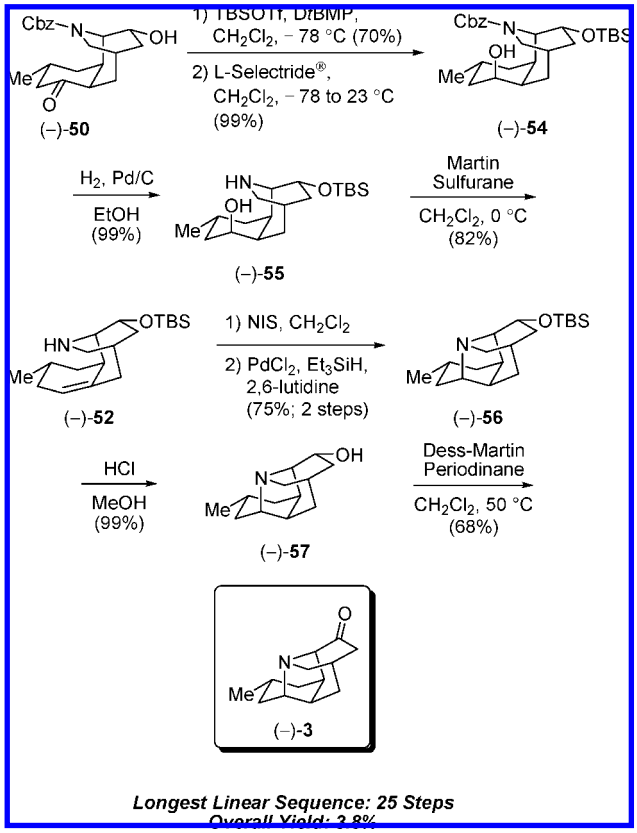
Scheme 12. Synthetic Strategy to Construct the Tetracyclic Core



We began with TBS protection of the secondary hydroxyl[34] (Scheme 13) followed by L-Selectride reduction to provide (−)-

(29) Single crystal X-ray crystallographic analysis unambiguously confirmed the structural identity of compound (−)-**42**. See Supporting Information for details.
(30) Similar ^{13}C-NMR shifts have been observed for hemiaminal salts; see: Hext, N. M.; Hansen, J.; Blake, A. J.; Hibbs, D. E.; Hursthouse, M. B.; Shishkin, O. V.; Mascal, M. *J. Org. Chem.* **1998**, *63*, 6016.
(31) See Supporting Information for details.
(32) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155. (b) Meyer, S. D.; Schreiber, S. L. *J. Org. Chem.* **1994**, *59*, 7549.
(33) Increasing reaction time for the epimerization of (−)-**42** to **46** did not effect the ratio after 18 h (1:3, respectively), suggesting that this represents the equilibrium mixture for the specified conditions.
(34) Protection of the secondary hydroxyl employing standard conditions (i.e., TBSCl, imidazole, DMAP, CH_2Cl_2) afforded a mixture of silylated secondary hydroxyl, the epimeric C(12) protected silylated secondary hydroxyl, as well as the bissilylated secondary hydroxyl C(5) and C(12) enol ether. These reaction byproducts were minimized by employing 2,6-di-*tert*-butyl-4-methylpyridine (DtBMP) as a base.

Scheme 13. Construction of the Tetracyclic Core of the Lyconadins

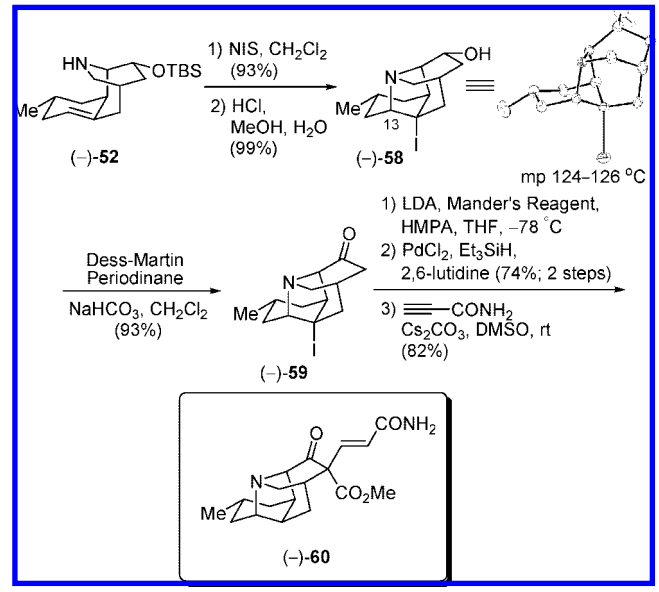


54 with high stereoselectivity (>95:5). Removal of the Cbz group then led to amino alcohol (−)-**55**, which was readily dehydrated with the Martin sulfurane,[35] notably in the presence of the unprotected secondary amine, to generate exclusively trisubstituted olefin (−)-**52** in 82% yield. To construct the tetracyclic core, we initially explored an acid-induced cyclization;[36] however, no reaction was observed. We turned next to *N*-iodosuccinimide (NIS) as a source of iodonium ion.[37] Pleasingly, upon treatment of (−)-**52** with NIS, the requisite 5-*endo* cyclization occurred at ambient temperature to generate **53** (X = I). Reductive removal of the tertiary iodide[38] then furnished (−)-**56** in 75% yield for the two steps. Completion of the tetracyclic core entailed removal of the silyl group to furnish secondary alcohol (−)-**57**, which upon Dess-Martin periodinane oxidation led to (−)-**3**.

At this juncture, we only required installation of the C(1−3) carbon fragment, in conjunction with formation of the α-pyridinone and dihydropyridinone rings to complete the lyconadins. From the outset, we had envisioned use of the one-pot protocol developed by Kozikowski,[39] employing methyl propiolate and ammonia to access (+)-lyconadin A (**1**). Unfortunately, this approach was not successful; only unreacted starting materials were obtained. We turned instead to a report by Mulzer,[40] in which the ketone is first converted to a β-ketoester and then subjected to Michael addition with acrylonitrile. Use of a β-ketoester was expected to enhance reaction with propiolamide.[41] At this point, we had also come to recognize the volatile nature of aminoketone (−)-**3**. Use of the less volatile iodoamine (cf. **53**, X = I), in conjunction with the Mulzer protocol, thus appeared desirable.

Beginning with aminoolefin (−)-**52** (Scheme 14), treatment with *N*-iodosuccinimide to promote olefin cyclization, followed by removal of the silyl group, furnished (−)-**58** as a crystalline solid in 93% for the two steps. Single crystal X-ray diffraction, in conjunction with the anomalous dispersion technique, provided unambiguous assignment of the structure, including confirmation of the absolute stereochemistry.[42] Dess-Martin oxidation then furnished ketone (−)-**59**, *now* a nonvolatile compound that could be readily handled. Installation of the β-ketoester, achieved via the Mander[43] protocol, followed by reductive removal of the iodine and conjugate addition with propiolamide furnished unsaturated amide (−)-**60**, the envisioned common intermediate for both lyconadins.

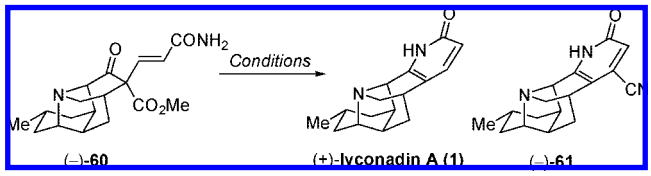
Scheme 14. Preparation of the Penultimate Intermediate for (+)-Lyconadin A (**1**)



Initial attempts to construct the pyridinone ring with sodium hydroxide in DMSO (Table 2, entry 1) led only to polymerization. Milder conditions employing sodium cyanide were therefore investigated (entry 2). Formation of α-pyridinone (−)-**61** occurred, albeit with incorporation of the nitrile group in the ring (20% yield).[44] Use of even less nucleophilic reagents, such as tetramethylammonium acetate[45] (entries 3 and 4),

(35) Arhart, R. J.; Martin, J. C. *J. Am. Chem. Soc.* **1972**, *94*, 5003.
(36) (a) Ruggeri, R. B.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 3714. (b) Heathcock, C. H.; Ruggeri, R. B.; McClure, K. F. *J. Org. Chem.* **1992**, *57*, 2554. (c) Heathcock, C. H.; Kath, J. C.; Ruggeri, R. B. *J. Org. Chem.* **1995**, *60*, 1120.
(37) Diaba, F.; Ricou, E.; Bonjoch, J. *Org. Lett.* **2007**, *9*, 2633.
(38) Boukherroub, R.; Chatgilialoglu, C.; Manuel, G. *Organometallics* **1996**, *15*, 1508.
(39) (a) Kozikowski, A. P.; Ding, Q.; Saxena, A.; Doctor, B. P. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 259. (b) Camps, P.; Muñoz-Torrero, D.; Simon, M. *Synth. Commun.* **2001**, *31*, 3507. (c) Kozikowski, A. P.; Reddy, E. R.; Miller, C. P. *J. Chem. Soc., Perkin Trans I* **1990**, 195.
(40) Högenauer, K.; Baumann, K.; Enz, A.; Mulzer, J. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2627.
(41) Hay, L. A.; Koenig, T. M.; Ginah, F. O.; Copp, J. D.; Mitchell, D. *J. Org. Chem.* **1998**, *63*, 5050.
(42) See Supporting Information for details.
(43) Mander, L. N.; Sethi, S. P. *Tetrahedron Lett.* **1983**, *24*, 5425.
(44) Formation of compound (−)-**61** can be understood as a conjugate addition of cyanide to the unsaturated amide prior to ring closure, followed by ring closure, and then oxidation, thermodynamically driven by aromatization to the α-pyridinone ring. See the following reference for a similar eliminative, aromatization event: Donohue, T. J.; Fishlock, L. P.; Procopiou, P. A. *Org. Lett.* **2008**, *10*, 285.
(45) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1980**, *102*, 4743.

Table 2. Conditions Explored to Affect Formation of (+)-Lyconadin A (**1**)



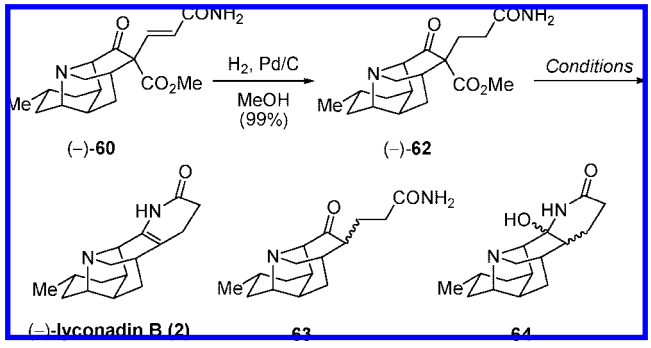
entry	conditions	temp (°C)	time (h)	% yield (+)-**1**[a]
1	NaOH (1 N aq), DMSO	150	1	—
2	NaCN, HMPA	100	2	—[b]
3	Me_4NOAc, HMPA	100	2	44[c]
4	Me_4NOAc, MeCN	135	16	71

[a] Isolated yield. [b] Compound (−)-**61** was isolated in 20% yield. [c] Yield based on recovered starting material.

provided moderate success employing HMPA as solvent; the optimal protocol, however, entailed use of acetonitrile to provide (+)-lyconadin A (**1**) in 71% yield.

For (−)-lyconadin B, we sought formation of the dihydropyridinone ring (Table 3). Hydrogenation of (−)-**60** furnished saturated amide (−)-**62**. However, unlike (+)-lyconadin A (**1**), tetramethylammonium acetate (entry 1) did not lead to the dihydropyridinone, albeit several presumed intermediates (^{1}H NMR), such as **63** and **64**, were encountered that had not been observed during construction of the α-pyridinone ring system. However, all attempts to convert either **63** or **64** to (−)-lyconadin B (**2**) proved unsuccessful.[46] Ultimately, the combination of lithium chloride in HMPA at 125 °C for 17.5 h proved optimal to provide (−)-lyconadin B (**2**) in 68% yield (entry 4).[47]

Table 3. Conditions Examined to Affect Formation of (−)-Lyconadin B (**2**)



entry	conditions	temp (°C)	time (h)	result
1	Me_4NOAc, MeCN	135	15	*only* **63**
2	LiBr, DMA	150	5	**2** + **64**
3	LiBr, DMA	150	15	**2** (26%)[a]
4	LiCl, HMPA	125	17.5	**2** (68%)[a]

[a] Isolated yield.

Pleasingly, the spectral data (^{1}H and ^{13}C NMR, HRMS, IR, chiroptic properties) for synthetic (+)-lyconadin A and (−)-lyconadin B were in complete agreement with those reported for the natural products, confirming the Kobayashi structural and absolute stereochemical assignments.[48] Overall, (+)-lyconadin A (**1**) and (−)-lyconadin B (**2**) were prepared both in 2.2% overall yield, with longest linear sequences of 27 and 28 steps, respectively.

In summary, construction of the lyconadin alkaloids A and B (**1** and **2**) has been achieved. A strategy-level cascade was devised and executed to assemble a common, tricyclic ring system (−)-**35**, during which two new carbon-carbon σ-bonds, three stereogenic centers and two new rings were formed in a single operation, albeit possessing the incorrect stereogenicity at C(12) for the lyconadin skeleton. Isomerization through aegis of an aminal salt corrected this stereochemical issue. Application of a 5-*endo* aminoiodo olefin cyclization then permitted access to the lyconadin tetracyclic core. Final elaboration to the α-pyridinone and 3,4-dihydropyridinone rings was achieved via a three- and four-step reaction sequence, respectively, to complete the total syntheses of (+)-lyconadin A (**1**) and (−)-lyconadin B (**2**).

Experimental Section

Selected experimental procedures for the preparation of (+)-lyconadin A (**1**) and (−)-lyconadin B (**2**) appear below. Full experimental details for all compounds are given in the Supporting Information.

Preparation of Hemiketal 33. Hydrazone **6** (1.12 g, 4.22 mmol, 1.1 equiv) was dissolved in tetrahydrofuran (10 mL) and cooled to −78 °C. *n*-Butyllithium (2.20 mL, 1.7 M in tetrahydrofuran, 3.90 mmol, 1.02 equiv) was added dropwise, and the mixture was stirred for 1 h at −78 °C. Hexamethylphosphoramide (1.0 mL, 10% v/v) was added dropwise, and the mixture was stirred for an additional 15 min at −78 °C, warmed to −60 °C for 15 min, and then cooled to −78 °C. In a separate flask, iodide (+)-**7** (1.88 g, 3.84 mmol) was dissolved in tetrahydrofuran (5 mL), cooled to −78 °C, and added dropwise via syringe to the hydrazone anion. After stirring for 1 h at −78 °C, the dry ice/acetone bath was removed and the reaction mixture was warmed to ambient temperature. After stirring for 30 min at ambient temperature, the reaction mixture was treated with sodium bicarbonate (5 mL, aqueous saturated) and poured into a separatory funnel containing sodium bicarbonate (75 mL, aqueous saturated). The aqueous layer was extracted with ethyl acetate (3 × 100 mL) and the combined organic extracts were dried with sodium sulfate, filtered and concentrated *in vacuo*. The coupling product **32** was used without further purification in the next reaction. High resolution mass spectrum (ES^+) *m/z* 648.4610 [$(M + H)^+$; calculated for $C_{35}H_{66}N_3O_4Si_2$: 648.4592].

The above prepared coupling product **32** was dissolved in tetrahydrofuran (25 mL) and treated with water (10 mL) and hydrochloric acid (2 mL, 12 N aqueous). The mixture was stirred vigorously for 14 h at ambient temperature, poured into water (100 mL), and extracted with ethyl acetate (3 × 100 mL). The combined organic extracts were dried with sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by silica gel gradient chromatography (1:1 to 0:1; hexanes/ethyl acetate), providing the hemiketal **33** (1.07 g, 74% yield over 2 steps) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$; spectrum contains a mixture of ketone and hemiketal diastereomers, which exhibit rotameric signals) δ 7.35−7.27 (5H, m), 5.19−5.05 (2H, br m), 4.06−3.81 (br m), 3.63 (br ddd, *J* = 11.2, 4.5, 1.1 Hz), 3.59 (br t, *J* = 6.3 Hz), 3.44−3.34 (br m), 3.27−3.19 (br m), 3.10 (br dd, *J* = 13.6, 2.0 Hz), 2.91−2.52 (br m), 2.52−2.31 (br m), 2.30−2.08 (br m), 1.99−1.80 (br m), 1.67 (br d, *J* = 11.2 Hz), 1.64−1.55 (br m), 1.52 (br d, *J* = 13.0 Hz), 1.45 (br dd, *J* = 13.4, 7.1 Hz), 1.32 (br tt, *J* = 11.2, 2.8 Hz), 1.14 (br dq, *J* = 12.8, 4.5 Hz), 1.01 (br t, *J*

(46) Conditions examined to convert **63** or **64** to (−)-lyconadin B (**2**) included: Resubjection to reaction conditions. Treatment with acid: (a) Kan, W. M.; Cheng, C.-L.; Chern, C.-Y *Synth. Commun.* **2004**, *34*, 4257. Thermal dehydration: (b) Citterio, A.; Carnevali, E.; Farina, A.; Meille, V.; Alini, S.; Cotarca, L. *Org. Prep. Proced. Int.* **1997**, *29*, 465. Chemical dehydration: (c) Pawlowski, M.; Maurin, J. K.; Leniewshki, A.; Wojtasiewicz, K.; Czarnocki, Z. *Heterocycles* **2005**, *65*, 9.

(47) A rationale for differences in the conditions required for optimal formation of (+)-lyconadin A (**1**) and (−)-lyconadin B (**2**) is not apparent to the authors.

(48) See Supporting Information for details.

= 12.6 Hz), 0.91 (d, J = 6.7 Hz), 0.89 (d, J = 6.3 Hz), 0.86 (d, J = 6.7 Hz) ppm; high resolution mass spectrum (ES^+) m/z 400.2086 [$(M + Na)^+$; calculated for $C_{21}H_{31}NaNO_5$: 400.2100].

Preparation of Diketoaldehyde (+)-34. Hemiketal **33** (10.3 g, 27.3 mmol) was dissolved in dichloromethane (400 mL) and treated with freshly activated 4 Å molecular sieves (20.0 g, 2 weight equiv). To the vigorously stirring mixture was added pyridinium chlorochromate (14.7 g, 68.2 mmol, 2.5 equiv) in several portions over 5 min. After stirring for 1 h, additional pyridinium chlorochromate (14.7 g, 68.2 mmol, 2.5 equiv) was added, the reaction mixture was stirred an additional 1 h and then diluted with diethylether (1 L) and Celite (~60 g). The mixture was stirred vigorously for 1 h and poured directly onto a silica gel column, eluting with diethyl ether (1.5 L), then ethyl acetate, providing aldehyde (+)-**34** (6.76 g, 66%) as a light-green oil: $[\alpha]^{20}_D$ +10.6° (c 1.15, CH_2Cl_2); IR (NaCl plate, neat): 2959 (m), 2930 (m), 2878 (m), 2721 (w), 1700 (s), 1454 (w), 1419 (m), 1367 (w), 1320 (w), 1216 (m), 1117 (m), 971 (w), 914 (w), 762 (w), 734 (w), 699 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$; spectrum contains an ~1:10 mixture of rotamers, * denotes minor rotamer signals) δ 9.72 (br s), *9.63 (br s), 7.40−7.29 (br m), 4.10 (br d, J = 17.5 Hz), 4.04−3.76 (br m), 3.27−3.14 (br m), 2.59 (br d, J = 4.8 Hz), 2.58 (br d, J = 4.1 Hz), 2.55−2.34 (br m), 2.33 (br dd, J = 7.1, 1.5 Hz), 2.30 (br dd, J = 7.1, 1.9 Hz), 2.16 (dd, J = 16.4, 9.7 Hz), 2.09−2.00 (br m), 1.69−1.51 (br m), *1.33 (d, J = 7.1 Hz), 0.98 (d, J = 6.3 Hz) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.6, 204.4, 201.8, 155.3, 136.4, 128.7, 128.4, 128.2, 67.8, 54.2 br, 50.5, 49.3, 47.3 br, 45.0 br, 40.1, 34.0, 26.9, 24.2, 20.5 ppm; high resolution mass spectrum (ES^+) m/z 396.1781 [$(M + Na)^+$; calculated for $C_{21}H_{27}NNaO_5$: 396.1787].

Preparation of Tricycle (−)−35. Aldehyde (+)-**34** (183 mg, 0.490 mmol) was dissolved in dimethylsulfoxide (100 mL) and was sparged under an argon atmosphere. Hydrochloric acid (4 mL) was added, and the vessel was placed into an oil bath preheated to 70 °C for 3 h. The mixture was cooled to ambient temperature, poured into water (300 mL), and extracted with ethyl acetate (3 × 200 mL). The combined organic extracts were dried with sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (1:1; hexanes/ethyl acetate), providing tricycle (−)-**35** (147 mg, 84% yield) as a white solid. X-ray quality crystals were prepared via vapor diffusion from hexanes/dichloromethane; melting point 134−138°: $[\alpha]^{20}_D$ −83.9° (c 2.8, CH_2Cl_2); IR (NaCl plate, thin film, CH_2Cl_2): 2954 (m), 2927 (m), 1702 (s), 1448 (w), 1409 (s), 1346 (m), 1310 (w), 1285 (s), 1233 (m), 1216 (m), 1155 (w), 1110 (m), 1079 (w), 1030 (w), 969 (w), 917 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$; spectrum contains a mixture of rotamers) δ 7.40−7.31 (m), 5.23−5.11 (m), 4.61 (s), 4.47 (s), 3.62 (br t, J = 11.7 Hz), 3.53 (br dd, J = 12.1, 3.9 Hz), 2.68−2.62 (br m), 2.62−2.55 (br m), 2.53−2.34 (br m), 2.26−2.18 (br m), 2.16−2.09 (br m), 2.16 (s), 2.06 (br d, J = 4.5 Hz), 2.03 (s), 2.00 (br dd, J = 11.9, 2.6 Hz), 1.93 (br d, J = 9.3 Hz), 1.81 (br d, J = 12.6 Hz), 1.63 (br d, J = 8.6 Hz), 1.53−1.46 (m), 0.94 (d, J = 7.4 Hz), 0.91 (d, J = 7.1 Hz) ppm; ^{13}C NMR (125 MHz, $CDCl_3$; spectrum contains a mixture of rotamers) δ 211.1, 210.7, 207.8, 207.6, 156.4, 155.8, 136.4, 136.1, 128.7, 128.5, 128.4, 128.2, 67.9, 67.9, 66.1, 65.5, 50.3, 50.3, 47.4, 47.3, 47.3, 47.1, 47.0, 44.0, 43.9, 43.7, 37.5, 30.5, 30.4, 30.3, 26.1, 25.7, 19.5, 19.4 ppm; high resolution mass spectrum (ES^+) m/z 378.1686 [$(M + Na)^+$; calculated for $C_{21}H_{25}NNaO_4$: 378.1681].

Preparation of Alcohol (−)-50. Tricycle (−)-**35** (1.80 g, 5.1 mmol) was dissolved in a 1:1 mixture of methanol/ethyl acetate (500 mL). The solution was sparged under an argon atmosphere and then treated with $Pd(OH)_2/C$ (180 mg, 20% weight Pd). The vigorously stirring mixture was sparged under an atmosphere of hydrogen (1 atm, balloon) and stirred for 90 min. Additional $Pd(OH)_2/C$ (90 mg, 20% weight Pd) was added, and the mixture was sparged under an atmosphere of hydrogen and stirred for an additional 45 min. The reaction mixture was sparged under an atmosphere of argon and filtered through a pad of Celite. The Celite was washed with a 1:1 mixture of methanol/ethyl acetate (500 mL) and concentrated *in vacuo* to provide compound (−)-**42**, which was used without purification in the next reaction. However, purification by silica gradient gel chromatography (99:1 to 94:6; dichloromethane/methanol containing 10% by volume ammonium hydroxide) provided amine (−)-**42**: $[\alpha]^{20}_D$ −163° (c 0.90, CH_2Cl_2); IR (NaCl plate, neat): 3364 (br m), 2953 (m), 2921 (s), 2866 (m), 1708 (s), 1446 (w), 1403 (w), 1380 (w), 1339 (w), 1285 (w), 1232 (w), 1213 (w), 1181 (w), 1113 (w), 1032 (w), 948 (w), 915 (w), 886 (w), 770 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.16 (d, J = 11.2 Hz, 1H), 3.08 (dd, J = 11.3, 4.3 Hz, 1H), 3.04 (s, 1H), 2.73 (dt, J = 12.3, 4.2 Hz, 1H), 2.57 (dd, J = 13.4, 5.9 Hz, 1H), 2.53−2.44 (m, 2H), 2.44−2.40 (m, 2H), 2.21−2.12 (m, 3H), 1.96−1.81 (br m, 1H), 1.87 (dt, J = 12.3, 3.7 Hz, 1H), 1.58 (d, J = 13.4 Hz, 1H), 1.50 (dd, J = 14.9, 12.3 Hz, 1H), 0.95 (d, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.7, 212.6, 66.7, 50.4, 47.4, 44.8, 44.3, 42.6, 37.7, 31.7, 30.7, 27.2, 19.8 ppm; high resolution mass spectrum (CI^+) m/z 221.1411 [$(M^+)^+$; calculated for $C_{13}H_{19}NO_2$: 221.1416].

Amine (−)-**42** was dissolved in an 80:15:5 mixture (1 L) of water:methanol:hydrochloric acid (12 N aqueous) and placed into an oil bath preheated to 100 °C for 18 h. The mixture was cooled to ambient temperature and concentrated *in vacuo* to provide the hemiaminal salt **46**, which was used without purification in the next reaction: ^1H NMR (500 MHz, d^7-DMF) δ 4.20 (ddd, J = 13.0, 3.9, 2.8 Hz, 1H), 3.96 (d, J = 5.6 Hz, 1H), 3.03 (d, J = 11.9 Hz, 1H), 2.69 (dd, J = 14.1, 5.6 Hz, 1H), 2.65−2.60 (m, 2H), 2.47 (dd, J = 10.0, 5.2 Hz, 1H), 2.31−2.23 (m, 1H), 2.12 (s, 1H), 1.89 (br d, J = 13.4 Hz, 1H), 1.76 (d, J = 14.1 Hz, 1H), 1.64 (dd, J = 14.0, 12.1 Hz, 1H), 1.32 (t, J = 11.9 Hz, 1H), 0.96 (d, J = 6.3 Hz, 3H) ppm; ^{13}C NMR (125 MHz, d^7-DMF) δ 204.9, 97.6, 69.5, 47.8, 47.3, 44.5, 43.7, 42.3, 38.2, 29.9, 26.1, 25.1, 21.6 ppm.

Hemiaminal salt **46** was dissolved in methanol (300 mL), cooled to 0 °C and treated with sodium borohydride (600 mg, 15.9 mmol, 3.15 equiv) portionwise over 90 min. Hydrochloric acid (10 mL, 12 N aqueous) was added and the mixture was stirred vigorously for 30 min. The mixture was concentrated *in vacuo* to provide the alcohol as a light yellow foam, which was dissolved in ethyl acetate (100 mL), treated with sodium bicarbonate (50 mL, aqueous saturated) and cooled to 0 °C with vigorous stirring. An ethyl acetate solution (20 mL) of benzyl chloroformate (2.00 mL, 11.5 mmol, 2.27 equiv) was added slowly to the solution over 5 min. The reaction mixture was slowly warmed to ambient temperature over 2 h and then stirred for an additional 14 h. The mixture was poured into water (200 mL) and extracted with ethyl acetate (3 × 250 mL). The combined organic extracts were dried with sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by silica gel gradient chromatography (10:0 to 25:75; hexanes/ethyl acetate), providing alcohol (−)-**50** (919 mg, 51% yield). Upon further elution (25:75 to 0:1; hexanes/ethyl acetate), the diol **51** was obtained (526 mg, 29% yield). The alcohol (−)-**50** was obtained as a white foam: $[\alpha]^{20}_D$ −26.6° (c 0.70, CH_2Cl_2); IR (NaCl plate, thin film, CH_2Cl_2): 3434 (br m), 2927 (m), 2873 (m), 1699 (s), 1452 (m), 1411 (m), 1354 (w), 1312 (m), 1255 (w), 1212 (w), 1114 (m), 1070 (w), 1015 (w), 916 (w), 734 (m), 702 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$; spectrum contains an ~3:1 mixture of rotamers, * denotes minor rotamer signals) δ 7.39−7.28 (m), *5.27−5.22 (br m), 5.14 (br d, J = 12.7 Hz), 5.08 (br d, J = 12.7 Hz), *4.69 (br s), 4.19 (br d, J = 2.6 Hz), *4.05−4.00 (br m), 3.96−3.89 (br m), 3.47 (br d, J = 11.2 Hz), *3.40 (br d, J = 17.1 Hz), *3.19−3.13 (br m), 3.07 (br d, J = 11.5 Hz), 2.97−2.91 (br m), *2.82−2.75 (br m), 2.68−2.59 (br m), 2.56−2.48 (br m), 2.46−2.37 (br m), 2.33 (br dd, J = 14.9, 4.5 Hz), 2.26−2.14 (br m), 1.86 (br dd, J = 14.8, 10.0 Hz), 1.79 (br d, J = 13.8 Hz), *1.75−1.65 (br m), 1.61 (br ddd, J = 13.3, 10.0, 3.5 Hz), 1.54−1.49 (br m), 1.46−1.42 (br m), 0.95 (d, J = 6.7 Hz), *0.86−0.81 (br m) ppm; ^{13}C NMR (125 MHz, $CDCl_3$; spectrum contains an ~3:1 mixture of rotamers, only the major rotamer signals are reported) δ 211.4, 156.5, 136.9, 128.6, 128.0, 127.7, 68.1, 67.4, 58.1, 47.9, 47.7, 46.6, 38.4, 37.4, 34.7, 32.9, 29.2, 22.2 ppm; high resolution

mass spectrum (CI^+) *m/z* 357.1943 [$(M^+)^+$; calculated for $C_{21}H_{27}NO_4$: 357.1940].

Preparation of Alcohol (−)-54. Alcohol (−)-**50** (1.26 g, 3.52 mmol) was dissolved in dichloromethane (70 mL), treated with 2,6-di-*tert*-butyl-4-methylpyridine (1.62 g, 7.91 mmol, 2.25 equiv) and cooled to −78 °C. *tert*-Butyldimethylsilyl trifluoromethanesulfonate (1.01 mL, 4.39 mmol, 1.25 equiv) was added dropwise and the reaction mixture was stirred for 1 h at −78 °C. The reaction mixture was quenched with sodium bicarbonate (5 mL, aqueous saturated) and warmed to ambient temperature. The mixture was poured into water (100 mL) and extracted with dichloromethane (3 × 200 mL), and the combined organic extracts were dried with sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by silica gel gradient chromatography (10:0 to 85:15; hexanes/ethyl acetate), providing the TBS ether (1.17 g, 70% yield) as a colorless oil: $[\alpha]^{20}_D$ −30.1° (*c* 1.65, CH_2Cl_2); IR (NaCl plate, neat): 2951 (s), 2929 (s), 2859 (m), 1701 (s), 1453 (m), 1405 (m), 1351 (w), 1309 (m), 1258 (m), 1213 (w), 1088 (s), 941 (w), 889 (m), 862 (w), 837 (m), 777 (m), 697 (w), 668 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$; spectrum contains a ∼3:1 mixture of rotamers, * denotes minor rotamer signals) δ 7.38−7.29 (m), 5.17 (br d, *J* = 12.3 Hz), 5.08 (br d, *J* = 12.7 Hz), 4.15−4.10 (br m), *4.10−4.05 (br m), 3.94−3.84 (br m), 3.45 (br d, *J* = 11.9 Hz), *3.37 (br d, *J* = 12.3 Hz), *3.16 (br d, *J* = 12.6 Hz), 3.08 (br d, *J* = 11.5 Hz), 2.95−2.89 (m), *2.82−2.75 (br m), *2.66−2.59 (br m), 2.53 (br dd, *J* = 11.0, 5.4 Hz), 2.48−2.37 (br m), 2.33 (br dd, *J* = 14.9, 4.5 Hz), *2.27−2.21 (br m), 2.21−2.11 (br m), *1.94−1.90 (br m), 1.86 (br dd, *J* = 14.5, 9.7 Hz), 1.75−1.64 (br m), 1.60−1.43 (br m), 0.94 (br d, *J* = 6.3 Hz), 0.91−0.87 (br m), 0.80−0.03 (br m) ppm; ^{13}C NMR (125 MHz, $CDCl_3$; spectrum contains a ∼3:1 mixture of rotamers, * denotes minor rotamer signals) δ 211.8, 156.3, 137.1, *128.7, 128.6, *128.3, 128.0, 127.8, 68.4, 67.2, 57.8, *48.5, 47.9, 47.7, 46.9, *46.6, 37.6, 37.3, *35.3, *35.1, *33.8, 33.2, *29.9, 29.5, *29.2, *28.9, 28.5, 25.9, 22.0, *20.9, 18.1, −4.4, *−4.5, −4.6 ppm; high resolution mass spectrum (ES^+) *m/z* 494.2719 [$(M + Na)^+$; calculated for $C_{27}H_{41}NNaO_4Si$: 494.2703].

The above prepared TBS ether (2.50 g, 5.3 mmol) was dissolved in tetrahydrofuran (80 mL) and cooled to −78 °C. L-Selectride (14 mL, 1.0 M in tetrahydrofuran, 2.5 equiv) was added dropwise over 5 min and the reaction mixture stirred for 1 h at −78 °C, warmed to 0 °C and then stirred for an additional 1 h. To the reaction mixture was added additional L-Selectride (5.0 mL, 1.0 M in tetrahydrofuran, 1 equiv) and the mixture stirred for 1 h at 0 °C. The mixture was treated with sodium bicarbonate (10 mL, aqueous saturated), stirred vigorously for 15 min, and then poured into sodium bicarbonate (300 mL, aqueous saturated). The aqueous layer was extracted with ethyl acetate (2 × 300 mL), and the combined organic extracts were dried with sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by silica gel gradient chromatography (10:0 to 1:1; hexanes/ethyl acetate), providing alcohol (−)-**54** (2.50 g, 99% yield) as a colorless oil: $[\alpha]^{20}_D$ −47.6° (*c* 0.30, CH_2Cl_2); IR (NaCl plate, neat): 3388 (br m), 2928 (s), 2861 (m), 1697 (m), 1458 (w), 1415 (m), 1359 (w), 1301 (m), 1255 (w), 1113 (m), 1074 (s), 891 (w), 836 (w), 769 (w), 641 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$; spectrum contains a mixture of rotamers) δ 7.40−7.28 (br m), 5.21−5.10 (m), 4.71−4.47 (br m), 4.45−4.37 (br m), 4.28 (br q, *J* = 6.0 Hz), 4.16 (br q, *J* = 6.0 Hz), 4.14 (br q, *J* = 6.3 Hz), 4.13−4.00 (br m), 3.36−3.23 (br m), 2.70−1.91 (br m), 1.77−1.19 (br m), 1.10−0.84 (br m), 0.08−0.05 (br m) ppm; ^{13}C NMR (125 MHz, $CDCl_3$; spectrum contains a mixture of rotamers) δ 156.6, 156.1, 137.3, 137.2, 128.7, 128.6, 128.1, 128.0, 128.0, 128.0, 127.9, 83.0, 68.3, 68.2, 68.1, 68.0, 67.9, 67.1, 67.1, 67.0, 67.0, 56.1, 55.6, 50.9, 50.5, 37.1, 36.9, 36.5, 35.4, 35.3, 34.7, 34.5, 34.3, 34.2, 34.0, 33.9, 26.1, 26.0, 25.9, 25.5, 19.0, 18.9, 18.8, 18.2, 18.1, 18.0, 15.9, 15.3, 14.7, 9.8, −4.4, −4.4, −4.5, −4.6, −4.7, −4.8 ppm; high resolution mass spectrum (ES^+) *m/z* 496.2854 [$(M + Na)^+$; calculated for $C_{27}H_{43}NNaO_4Si$: 496.2859].

Preparation of Aminoalcohol (−)-55. Alcohol (−)-**54** (731 mg, 1.54 mmol) was dissolved in absolute ethanol (60 mL) and was sparged under an argon atmosphere. Pd/C (200 mg, 5% Pd weight, catalytic) was added and the mixture was sparged under a hydrogen atmosphere (1 atm, balloon). The mixture was stirred vigorously for 90 min and then sparged under an argon atmosphere and filtered through a pad of Celite. The Celite was washed with absolute ethanol (50 mL), and the filtrate was concentrated *in vacuo*. The residue was dissolved in toluene (100 mL) and concentrated *in vacuo* to provide the aminoalcohol (−)-**55** (529 mg, 99% yield) as a white solid, which did not require further purification: $[\alpha]^{20}_D$ −28.8° (*c* 0.25, CH_2Cl_2); IR (NaCl plate, thin film, CH_2Cl_2): 3300 (br m), 3231 (br m), 2953 (s), 2927 (s), 2858 (s), 1541 (w), 1471 (m), 1461 (m), 1388 (m), 1307 (w), 1119 (m), 1093 (s), 1048 (m), 1006 (w), 909 (m), 899 (w), 867 (w), 836 (s), 776 (m), 734 (m), 668 (w), 643 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.98−3.94 (m, 1H), 3.72 (br dd, *J* = 7.6, 4.7 Hz, 1H), 2.95−2.90 (br m, 2H), 2.67−2.64 (br m, 1H), 2.60 (dd, *J* = 9.3, 4.8 Hz, 1H), 2.17−2.11 (m, 2H), 2.08−2.03 (m, 1H), 1.98 (ddd, *J* = 14.3, 9.3, 4.8 Hz, 1H), 1.89−1.82 (m, 2H), 1.77 (br d, *J* = 12.7 Hz, 1H), 1.48−1.42 (m, 2H), 1.27−1.21 (m, 2H), 1.16 (ddd, *J* = 12.7, 10.4, 2.6 Hz, 1H), 0.89−0.88 (m, 12H), 0.05 (s, 3H), 0.04 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$; spectra contains conformational isomers) δ 70.0, 69.9, 59.2, 45.4, 42.9, 41.4, 38.3, 36.2, 36.0, 35.9, 30.4, 29.9, 26.0, 22.9, 22.1, 18.1, −4.3, −4.6 ppm; high resolution mass spectrum (ES^+) *m/z* 340.2656 [$(M + H)^+$; calculated for $C_{19}H_{38}NO_2Si$: 340.2672].

Preparation of Aminoalkene (−)-52. Aminoalcohol (−)-**55** (529 mg, 1.56 mmol) was dissolved in dichloromethane (20 mL) and cooled to 0 °C. In a separate flask, a dichloromethane (10 mL) solution of Martin sulfurane reagent (2.09 g, 3.11 mmol, 2.0 equiv), which was weighed out and stored in a glovebox,[49] was prepared. From this solution, Martin sulfurane reagent (5 mL, 1.0 equiv) was added dropwise to the aminoalcohol. After stirring for 30 min, additional Martin sulfurane reagent (0.5 mL, 0.10 equiv) was added and the mixture stirred for an additional 20 min at 0 °C. The reaction mixture was quenched with sodium carbonate (10 mL, aqueous saturated) and poured into water (100 mL). The aqueous layer was extracted with dichloromethane (2 × 100 mL), and the combined organic extracts were dried with sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by silica gel gradient chromatography (10:0 to 9:1; dichloromethane/methanol containing 10% by volume ammonium hydroxide), providing aminoalkene (−)-**52** (410 mg, 82% yield) as a light-yellow oil: $[\alpha]^{20}_D$ −28.8° (*c* 0.25, CH_2Cl_2); IR (NaCl plate, neat): 3360 (w), 2953 (s), 2926 (s), 2855 (s), 1649 (w), 1538 (w), 1464 (m), 1387 (m), 1253 (m), 1101 (m), 1076 (m), 873 (w), 837 (m), 777 (m), 664 (w), 567 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.59−5.57 (m, 1H), 4.15 (ddd, *J* = 9.3, 6.3, 4.8 Hz, 1H), 2.95−2.82 (m, 2H), 2.80 (dd, *J* = 12.1, 2.0 Hz, 1H), 2.73 (d, *J* = 4.5 Hz, 1H), 2.39 (dd, *J* = 14.5, 6.0 Hz, 1H), 2.37−2.34 (m, 1H), 2.30 (ddd, *J* = 17.3, 8.2, 5.4 Hz, 1H), 2.19 (d, *J* = 17.1 Hz, 1H), 1.96−1.91 (m, 1H), 1.78−1.71 (m, 1H), 1.65−1.59 (m, 1H), 1.57 (dd, *J* = 14.3, 6.5 Hz, 1H), 1.51−1.42 (m, 2H), 0.94 (d, *J* = 6.7 Hz, 3H), 0.90 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.4, 123.2, 68.5, 62.4, 45.9, 44.2, 39.4, 38.0, 35.2, 33.5, 29.9, 26.0, 25.9, 21.1, 18.2, −4.3, −4.5 ppm; high resolution mass spectrum (ES^+) *m/z* 322.2569 [$(M + H)^+$; calculated for $C_{19}H_{36}NOSi$: 322.2566].

Preparation of Alcohol (−)-58. Alkene (−)-**52** (51 mg, 0.16 mmol) was dissolved in dichloromethane (20 mL), and a dichloromethane (5 mL) suspension of *N*-iodosuccinimide (59 mg, 0.16 mmol, 1.01 equiv) was added dropwise over 5 min. After stirring for 20 min, the reaction mixture was treated with a 1:1 mixture (5 mL) of sodium thiosulfate/sodium carbonate (aqueous saturated), stirred vigorously for 10 min, and then poured into water (15 mL) and extracted with dichloromethane (2 × 50 mL). The combined organic extracts were dried with sodium sulfate, filtered, and

(49) Martin sulfurane was handled and stored according to the procedures described herein: Arhart, R. J.; Martin, J. C. *J. Am. Chem. Soc.* **1972**, *94*, 5003.

concentrated *in vacuo*. The residue was purified by silica gel gradient chromatography (100:0 to 96:4; dichloromethane/methanol containing 10% by volume ammonium hydroxide), providing the tetracycle (65 mg, 93% yield) as a light-yellow solid: $[\alpha]^{20}_D$ −2.0° (*c* 0.50, CH_2Cl_2); IR (NaCl plate, thin film, CH_2Cl_2): 2930 (s), 2855 (m), 1458 (m), 1253 (m), 1102 (s), 877 (m), 837 (m), 777 (m), 664 (w), 568 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.20 (dt, J = 8.6, 4.5 Hz, 1H), 3.36 (d, J = 4.5 Hz, 1H), 3.19 (d, J = 13.4 Hz, 1H), 3.13−3.10 (m, 1H), 2.97 (dd, J = 13.8, 5.6 Hz, 1H), 2.78−2.75 (br m, 1H), 2.73 (ddd, J = 13.4, 3.0, 1.9 Hz, 1H), 2.54 (br d, J = 13.4 Hz, 1H), 2.24 (td, J = 13.8, 8.9 Hz, 1H), 1.99−1.89 (m, 2H), 1.86 (br d, J = 13.4 Hz, 1H), 1.84−1.74 (m, 3H), 1.46 (ddd, J = 13.6, 8.4, 1.5 Hz, 1H), 0.96 (d, J = 6.0 Hz, 3H), 0.89 (s, 9H), 0.06 (s, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 75.4, 64.7, 64.1, 56.3, 53.7, 45.0, 42.4, 39.4, 36.6, 32.4, 29.9, 25.9, 23.3, 21.8, 18.2, −4.4, −4.6 ppm; high resolution mass spectrum (ES^+) *m/z* 448.1545 [$(M + H)^+$; calculated for $C_{19}H_{35}INOSi$: 448.1533].

The above prepared tetracycle (20 mg, 0.045 mmol) was dissolved in methanol (5 mL), treated with hydrochloric acid (12 N aqueous, 5 drops from a 9" pipet), and stirred for 18 h at ambient temperature. The reaction mixture was poured into sodium hydroxide (10 mL, 5 N aqueous) and extracted with dichloromethane (2 × 15 mL), and the combined organic extracts were dried with sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by silica gel gradient chromatography (100:0 to 90:10; dichloromethane/methanol containing 10% by volume ammonium hydroxide), providing the alcohol (−)-**58** (15 mg, 99% yield) as an oily solid. X-ray quality crystals were obtained via vapor diffusion from pentane/diethyl ether. Upon slow evaporation of most of the solvent, the mixture was placed into a refrigerator for 24 h and then warmed to ambient temperature; melting point 124−126°: $[\alpha]^{20}_D$ −7.33° (*c* 2.10, CH_2Cl_2); IR (NaCl plate, thin film, CH_2Cl_2): 2925 (s), 2967 (s), 1715 (s), 1454 (m), 1405 (w), 1378 (w), 1346 (w), 1334 (w), 1312 (w), 1281 (w), 1251 (m), 1202 (m), 1161 (m), 1117 (w), 1089 (w), 1068 (m), 1039 (w), 1000 (w), 985 (w), 969 (w), 943 (w), 925 (m), 896 (m), 866 (m), 838 (w), 821 (w), 803 (m), 791 (w), 767 (w), 749 (w), 686 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.19 (dt, J = 8.9, 4.5 Hz, 1H), 3.99 (br s, 1H), 3.38 (d, J = 4.1 Hz, 1H), 3.15 (dd, J = 13.4, 1.5 Hz, 1H), 3.10 (d, J = 1.9 Hz, 1H), 2.97 (dd, J = 13.6, 5.4 Hz, 1H), 2.74−2.69 (m, 2H), 2.54 (br d, J = 13.8 Hz, 1H), 2.32 (td, J = 13.8, 8.8 Hz, 1H), 1.94−1.77 (m, 6H), 1.45 (ddd, J = 13.8, 8.9, 1.5 Hz, 1H), 0.95 (d, J = 5.2 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 75.2, 64.3, 63.8, 60.2, 56.2, 53.7, 44.8, 42.4, 39.2, 35.2, 32.2, 23.4, 21.8 ppm; high resolution mass spectrum (ES^+) *m/z* 334.0679 [$(M + H)^+$; calculated for $C_{13}H_{21}INO$: 334.0668].

Preparation of Iodoketone (−)-59. Alcohol (−)-**58** (30 mg, 0.090 mmol) was dissolved in dichloromethane (7 mL) to which sodium bicarbonate (57 mg, 0.67 mmol, 7.5 eqiuv.) and Dess-Martin periodinane (96 mg, 0.22 mmol, 2.5 equiv) were added and the mixture stirred vigorously for 1 h. The mixture was treated with a 1:1 mixture (3 mL) of sodium carbonate/sodium thiosulfate (aqueous saturated) and stirred for 30 min. The mixture was poured into water (30 mL) and extracted with dichloromethane (3 × 100 mL). The combined organic extracts were dried with sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by silica gel gradient chromatography (100:0 to 96:4; dichloromethane/methanol containing 10% by volume ammonium hydroxide), providing iodoketone (−)-**59** (27 mg, 93% yield) as a white solid: $[\alpha]^{20}_D$ −2.50° (*c* 1.35, CH_2Cl_2); IR (NaCl plate, thin film, CH_2Cl_2): 2925 (s), 2867 (s), 1715 (s), 1454 (m), 1405 (w), 1346 (w), 1334 (w), 1312 (w), 1281 (w), 1251 (m), 1202 (m), 1161 (m), 1099 (w), 1068 (m), 1039 (w), 987 (w), 943 (w), 925 (m), 896 (m), 866 (m), 803 (m), 749 (w), 686 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.67 (m, 1H), 3.29−3.27 (m, 1H), 3.25−3.20 (m, 2H), 3.11 (d, J = 14.1 Hz, 1H), 2.68 (d, J = 14.5 Hz, 1H), 2.57−2.52 (m, 3H), 2.14−2.08 (m, 1H), 1.96−1.74 (m, 5H), 0.96 (d, J = 5.6 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.9, 74.4, 70.6, 58.4, 58.2, 54.1, 52.2, 44.7, 41.1, 38.9, 32.5, 23.4, 21.4 ppm; high resolution mass spectrum (ES^+) *m/z* 332.0509 [$(M + H)^+$; calculated for $C_{13}H_{21}INO$: 332.0511].

Unsaturated Amide (−)-60. Iodoketone (−)-**59** (143 mg, 0.432 mmol) was dissolved in tetrahydrofuran (10 mL) and cooled to −78 °C. Freshly prepared lithium di-*iso*-propylamide[50] (1.4 mL, 0.39 M solution in tetrahydrofuran, 1.3 equiv) was added dropwise, and the solution was stirred for 10 min at −78 °C. Freshly distilled hexamethylphosphoramide (1.0 mL, 10% v/v) was added dropwise over 5 min. The mixture was stirred for an additional 5 min at −78 °C, warmed to −60 °C for 10 min, and then cooled to −78 °C. Methyl cyanoformate (55 μL, 0.691 mmol, 1.6 equiv) was added in one portion, and the reaction mixture was stirred an additional 1 h at −78 °C. The reaction mixture was quenched with sodium bicarbonate (5 mL, aqueous saturated), warmed to ambient temperature, poured into water (50 mL), and extracted with chloroform (3 × 100 mL). The combined organic extracts were dried with sodium sulfate, filtered, and concentrated *in vacuo*. The mixture of β-ketoester diastereomers was used without purification in the next reaction. High resolution mass spectrum (ES^+) *m/z* 390.0573 [$(M + H)^+$; calculated for $C_{15}H_{21}INO_3$: 390.0566].

The above prepared β-ketoester was dissolved in 2,6-lutidine (2.5 mL) and triethylsilane (2.5 mL). The mixture was stirred vigorously and palladium(II)chloride (150 mg, 0.84 mmol, 1.9 equiv) was added in three portions over 90 min. The mixture was stirred an additional 30 min and then carefully treated with sodium bicarbonate (15 mL, aqueous saturated). The mixture was stirred for 30 min, poured into water (20 mL), and extracted with dichloromethane (3 × 100 mL). The combined organic extracts were dried with sodium sulfate, filtered and concentrated *in vacuo*. The residue was dissolved in chloroform (50 mL) and washed twice with hydrochloric acid (20 mL, 1 N aqueous). The pH was adjusted to 8 with solid sodium bicarbonate and extracted with chloroform (3 × 100 mL). The combined organic extracts were dried with sodium sulfate, filtered, and concentrated *in vacuo*. The residue passed through a silica gel plug (100:0 to 96:4; dichloromethane/methanol containing 10% by volume ammonium hydroxide), providing a mixture of desiodo-β-ketoester diastereomers (71 mg, 74% yield). High resolution mass spectrum (ES^+) *m/z* 264.1600 [$(M + H)^+$; calculated for $C_{15}H_{22}NO_3$: 264.1600].

The above prepared desiodo-β-ketoester (9.7 mg, 0.0368 mmol) was dissolved in dimethylsulfoxide (2 mL) and treated with cesium carbonate (120 mg, 0.368 mmol, 10 equiv), followed by the addition of propiolamide (5 mg, 0.0737 mmol, 2 equiv). The mixture was stirred for 24 h at ambient temperature, poured into water (15 mL), and extracted with chloroform (3 × 15 mL). The combined organic extracts were dried with sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by silica gel gradient chromatography (100:0 to 92:8; dichloromethane/methanol containing 10% by volume ammonium hydroxide), providing the unsaturated amide (−)-**60** (10 mg, 82% yield) as a light-yellow solid: $[\alpha]^{20}_D$ −80.3° (*c* 0.12, $CDCl_3$); IR (NaCl plate, thin film, CH_2Cl_2): 3424 (br m), 3363 (br m), 3192 (br m), 2924 (s), 2849 (m), 1740 (s), 1710 (m), 1682 (s), 1455 (m), 1394 (m), 1291 (w), 1268 (w), 1230 (s), 1123 (w), 1070 (m), 1012 (w), 919 (w), 890 (w), 797 (w), 733 (w), 667 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.76 (d, J = 15.6 Hz, 1H), 6.17 (d, J = 15.6 Hz, 1H), 5.90 (br s, 1H), 5.83 (br s, 1H), 3.74 (s, 3H), 3.64 (s, 1H), 3.13 (dd, J = 14.5, 3.7 Hz, 1H), 3.09 (br t, J = 1.9 Hz, 1H), 3.06 (dd, J = 14.3, 1.3 Hz, 1H), 2.75 (d, J = 3.7 Hz, 1H), 2.24 (dd, J = 6.3, 3.7 Hz, 1H), 2.16 (ddd, J = 15.1, 6.5, 3.1 Hz, 1H), 1.87 (br d, J = 13.4 Hz, 1H), 1.81 (br t, J = 3.0 Hz, 1H), 1.79−1.76 (m, 1H), 1.74 (dd, J = 9.5, 5.0 Hz, 1H), 1.70 (br d, J = 15.6 Hz, 1H), 1.05 (t, J = 13.0 Hz, 1H), 1.01

(50) Lithium di-*iso*-propylamide was prepared as follows: Freshly distilled di-*iso*-propylamine (1.4 mL, 10 mmol, 1.1 equiv) was dissolved in tetrahydrofuran (15 mL) and cooled to 0 °C. *n*-Butyl lithium (6.6 mL, 1.37 M solution in tetrahydrofuran) was added dropwise over 5 min, and the mixture was stirred for 1 h at 0 °C. The resulting lithium di-*iso*-propylamide solution (0.39 M) was then used immediately in the reaction.

(ddd, J = 13.4, 11.9, 1.9 Hz, 1H), 0.87 (d, J = 6.3 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.2, 170.2, 166.7, 142.5, 126.5, 74.1, 70.9, 64.3, 55.2, 53.2, 46.3, 44.4, 40.2, 39.1, 35.4, 32.7, 24.9, 21.9 ppm; high resolution mass spectrum (ES^+) m/z 333.1818 [$(M + H)^+$; calculated for $C_{18}H_{25}N_2O_4$: 333.1814].

Preparation of (+)-Lyconadin A (1). Unsaturated amide (−)-**60** (2.8 mg, 0.0084 mmol) was dissolved in anhydrous acetonitrile (1.5 mL) and transferred to a screw cap vial. Tetramethylammonium acetate (11.2 mg, 0.084 mmol, 10 equiv) was added; the vial was sealed and then placed into an oil bath preheated to 135 °C. The reaction mixture was stirred for 16 h, cooled to ambient temperature, and poured into sodium bicarbonate (5 mL, aqueous saturated). The aqueous layer was extracted with dichloromethane (2 × 15 mL) and chloroform (1 × 15 mL). The combined organic extracts were dried with sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by silica gel gradient chromatography (100:0 to 90:10; dichloromethane/methanol containing 10% by volume ammonium hydroxide), providing (+)-lyconadin A (**1**, 1.5 mg, 71% yield) as a light-yellow solid: $[\alpha]^{20}_D$ +33° (*c* 0.13, MeOH); IR (NaCl plate, neat): 3116 (w), 2921 (s), 2855 (m), 1653 (s), 1611 (m), 1559 (w), 1457 (m), 1262 (w), 1192 (w), 1099 (m), 1065 (m), 1024 (w), 946 (w), 797 (w), 678 (m) cm^{-1}; ^{1}H NMR (600 MHz, CD_3OD) δ 7.42 (d, J = 9.0 Hz, 1H), 6.36 (d, J = 8.9 Hz, 1H), 4.27 (s, 1H), 3.60 (m, 1H), 3.59 (m, 1H), 2.93 (d, J = 13.2 Hz, 1H), 2.85 (m, 1H), 2.27 (br d, J = 4.2 Hz, 1H), 2.11 (ddd, J = 14.0, 5.6, 4.0 Hz, 1H), 2.11 (m, 1H), 2.08 (m, 1H), 1.94 (br d, J = 13.3 Hz, 1H), 1.86 (m, 1H), 1.76 (d, J = 13.8 Hz, 1H), 1.19 (t, J = 12.8 Hz, 1H), 1.06 (t, J = 13.0 Hz, 1H), 0.95 (d, J = 6.3 Hz, 3H) ppm; ^{13}C NMR (125 MHz, CD_3OD) δ 165.4, 149.3, 141.8, 126.3, 116.6, 72.6, 64.0, 61.7, 50.8, 48.1, 41.0, 40.5, 34.3, 33.9, 26.2, 22.0 ppm; high resolution mass spectrum (ES^+) m/z 257.1648 [$(M + H)^+$; calculated for $C_{16}H_{21}N_2O$: 257.1654].

Preparation of (−)-Lyconadin B (2). Unsaturated amide (−)-**60** (24 mg, 0.030 mmol) was dissolved in methanol (10 mL), and the solution was sparged under an argon atmosphere. The mixture was treated with Pd/C (5 mg, 10% weight Pd/C), sparged under a hydrogen atmosphere (1 atm, balloon), and then stirred for 3 h. The reaction mixture was sparged under an argon atmosphere and filtered through a pad of Celite. The Celite was washed with methanol (10 mL), and the filtrate was concentrated *in vacuo* to provide the saturated amide (−)-**62** (24 mg, 99% yield), which was used without purification in the next reaction: $[\alpha]^{20}_D$ −61.3° (*c* 0.14, CH_2Cl_2); IR (NaCl plate, neat): 3430 (br m), 3363 (br m), 3203 (br s), 2923 (s), 2849 (m), 1734 (s), 1710 (m), 1669 (s), 1453 (m), 1268 (m), 1227 (m), 1068 (m), 1024 (w), 948 (w), 919 (w), 890 (w), 803 (w) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.60 (br s, 1H), 5.44 (br s, 1H), 3.75 (s, 3H), 3.55 (s, 1H), 3.23 (dd, J = 14.5, 1.9 Hz, 1H), 3.13 (dd, J = 14.3, 3.9 Hz, 1H), 3.10−3.08 (m, 1H), 2.89−2.84 (m, 1H), 2.73 (br d, J = 3.0 Hz, 1H), 2.27−2.16 (m, 2H), 2.10 (ddd, J = 14.9, 6.3, 3.0 Hz, 1H), 2.03−1.98 (m, 1H), 1.96 (dd, J = 6.0, 3.7 Hz, 1H), 1.90−1.85 (m, 1H), 1.79 (br t, J = 3.0 Hz, 1H), 1.76−1.71 (m, 2H), 1.67 (br d, J = 14.9 Hz, 1H), 1.05−0.92 (m, 2H), 0.86 (d, J = 6.3 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.8, 174.6, 172.5, 74.6, 71.1, 60.6, 55.4, 52.6, 45.8, 44.7, 40.4, 39.2, 37.0, 33.8, 33.4, 31.7, 24.9, 22.0 ppm; high resolution mass spectrum (ES^+) m/z 335.1984 [$(M + H)^+$; calculated for $C_{18}H_{27}N_2O_4$: 335.1971].

In a screw-cap vial, the above prepared saturated amide (4.0 mg, 0.012 mmol) was dissolved in freshly distilled hexamethylphosphoramide (2.5 mL). Lithium chloride (5.0 mg, 0.12 mmol, 10 equiv) was added, the vessel was sealed, and the mixture was placed into an oil bath preheated to 125 °C for 17.5 h. The mixture was cooled to ambient temperature and poured into hydrochloric acid (5 mL, 1 N aqueous). The aqueous layer was extracted with chloroform (2 × 15 mL), and the combined organic layers were washed with hydrochloric acid (5 mL, 1 N aqueous). The organic extracts were discarded, and the pH of the combined aqueous layers was carefully adjusted to 12 with sodium carbonate (15 mL, aqueous saturated) and then extracted with chloroform (3 × 15 mL). The combined organic extracts were dried with sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by silica gel gradient chromatography (100:0 to 92:8; dichloromethane/methanol containing 10% by volume ammonium hydroxide), to provide (−)-lyconadin B (**2**; 2.1 mg, 68% yield) as a white solid: $[\alpha]^{20}_D$ −64.0° (*c* 0.025, MeOH); IR (NaCl plate, neat): 3221 (w), 2922 (s), 2849 (m), 1671 (s), 1456 (m), 1373 (m), 1315 (w), 1233 (w), 1175 (w), 1093 (w), 1053 (w), 948 (w), 913 (w), 791 (w), 669 (w) cm^{-1}; ^{1}H NMR (600 MHz, CD_3OD) δ 3.50 (s, 1H), 3.31 (m, 1H), 3.28 (m, 1H), 2.86 (d, J = 12.1 Hz, 1H), 2.52−2.29 (m, 4H), 2.27 (d, J = 4.8 Hz, 1H), 2.13 (m, 1H), 1.96 (m, 1H), 1.95 (s, 1H), 1.95 (m, 1H), 1.85 (d, J = 13.4 Hz, 1H), 1.74 (m, 1H), 1.69 (d, J = 13.3 Hz, 1H), 1.06 (ddd, J = 13.4, 12.4, 2.0 Hz, 1H), 0.95 (t, J = 13.0 Hz, 1H), 0.89 (d, J = 6.5 Hz, 3H) ppm; ^{13}C NMR (125 MHz, CD_3OD) δ 173.3, 135.8, 120.7, 72.6, 63.7, 61.9, 49.9, 48.2, 41.1, 40.9, 34.5, 33.3, 31.5, 26.2, 25.0, 22.1 ppm; high resolution mass spectrum (ES^+) m/z 259.1818 [$(M + H)^+$; calculated for $C_{16}H_{23}N_2O$: 259.1810].

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Supporting Information Available: Experimental procedures, crystallographic information files, complete ref 28, 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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