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Cyclization Approaching to (−)-Lycojapodine A: Synthesis of Two Unnatural Alkaloids

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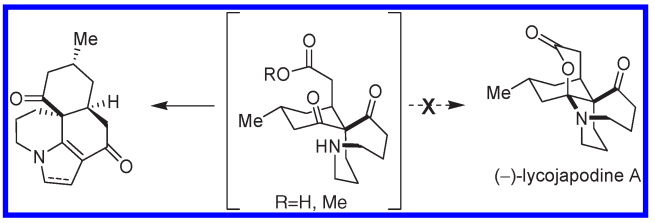


Two unnatural alkaloids were observed for the first time while attempting to initiate a plausibly biomimetic cyclization approaching to (−)-lycojapodine A, one of the newest *Lycopodium* alkaloids.

The *Lycopodium* family of alkaloids has received considerable attention over the years owing to its wide-ranging biological activity and structural complexity.[1] In particular, the intriguing polycyclic system with dense stereochemical array renders these alkaloids challenging synthetic targets.[2] Lycojapodine A,[3] a novel tetracyclic *Lycopodium* alkaloid, was isolated from the club moss *Lycopodium japonium* in early 2009. Its structure and relative stereochemistry were elucidated on the basis of spectroscopic and single-crystal X-ray analysis. To date, no synthesis of this new alkaloid has been reported. Intrigued by its unique architecture of the unprecedented carbinol amine lactone motif and interesting biogenetic links with fawcettimine (Figure 1), we

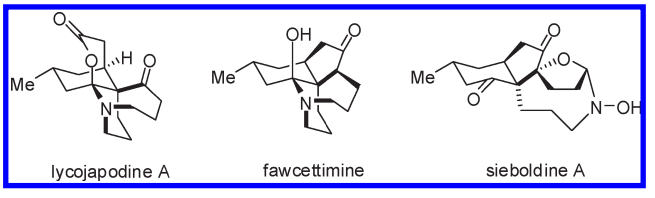
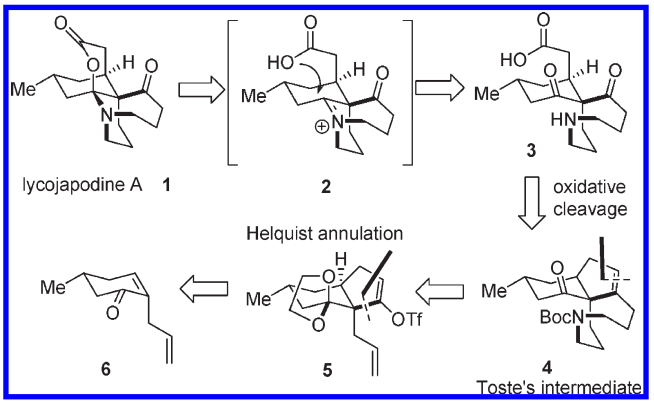


FIGURE 1. Lycojapodine A, fawcettimine, and sieboldine A.

embarked on a program of total synthesis of lycojapodine A. Described in this paper are our attempts to close the final tetracycle in a biomimetic way, which led to a surprising discovery of two novel, unnatural *Lycopodium*-type alkaloids.

SCHEME 1. Retrosynthetic Analysis of Lycojapodine A



Our retrosynthetic analysis of lycojapodine A (**1**) is outlined in Scheme 1. We proposed that the intriguing carbinol amine lactone moiety in target molecule's tetracyclic system could be assembled in a possible biomimetic manner at the final stage from cyclizations of carboxylic acid and imine functionalities through corresponding 6/7/6 tricyclic intermediate **2**. Given the spiro 6/9 bicycle **3**, precursor of tricycle **2**, having two ketone groups, a potential competitive cyclization could emerge. However, fascinated by the beauty of natural connectivity of lycojapodine A, we initially considered that the cyclization drawn in Scheme 1 might be preferred. Next, the 1,5 ketone and carboxylic acid functionalities of bicycle **3** were expected to arise from an oxidative cleavage of the cyclopentenyl ring of 6/5/9 tricycle **4**, which is an intermediate from Toste's recent elegant synthesis of fawcettimine.[4] In order to test the above hypothesis of biomimetic cyclization pathway as soon as we could, how to prepare the tricycle **4** efficiently and rapidly became one of our major concerns. Inspired by Toste's results, we elected to obtain intermediate **4** through our modified route based on Toste's work on fawcettimine. Two of Toste's key features are utilizing a Au(I)-catalyzed alkyne−enol ether cyclization to furnish the cyclopentenyl ring of tricycle **4** as well as employing an intermolecular Suzuki−Miyaura cross-coupling between vinyl iodide and allylic carbamate 9-BBN derivative to introduce amino side chain. In our analysis, the above two processes could be replaced with Helquist annulation[5] and Suzuki−Miyaura cross-coupling with vinyl triflate counterpart, respectively. To our knowledge, Helquist annulation was never used to furnish the backbone of *Lycopodium*

(1) For a recent review of the *Lycopodium* alkaloids, see: Hirasawa, Y.; Kobayashi, J.; Morita, H. *Heterocycles* **2009**, *77*, 679–729.

(2) For selected recent total synthesis of the *Lycopodium* alkaloids, see: (a) Chandra, A.; Pigza, J.; Han, J.-S.; Mutnick, D.; Johnston, J. *J. Am. Chem. Soc.* **2009**, *131*, 3470–3471. (b) Nilsson, B.; Overman, L.; Alaniz, J.; Rohde, J. *J. Am. Chem. Soc.* **2008**, *130*, 11297–11299. (c) Kozak, J.; Dake, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 4221–4223. (d) Bisai, A.; West, S.; Sarpong, R. *J. Am. Chem. Soc.* **2008**, *130*, 7222–7223.

(3) He, J.; Chen, X.-Q.; Li, M.-M.; Zhao, Y.; Xu, G.; Cheng, X.; Peng, L.-Y.; Xie, M.-J.; Zheng, Y.-T.; Wang, Y.-P.; Zhao, Q.-S. *Org. Lett.* **2009**, *11*, 1397–1400.

(4) Linghu, X.; Kennedy-Smith, J. J.; Toste, F. D. *Angew. Chem., Int. Ed.* **2007**, *46*, 7671–7673.

(5) Bal, S. A.; Marfat, A.; Helquist, P. *J. Org. Chem.* **1982**, *47*, 5045–5050.

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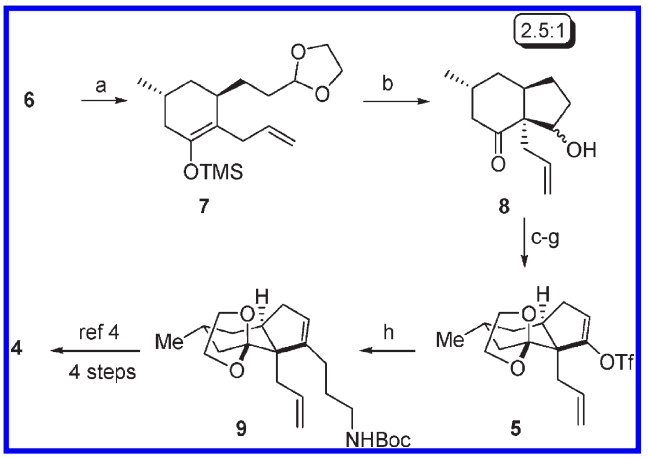
SCHEME 2. Preparation of Tricyclic Azacycle 4[a]

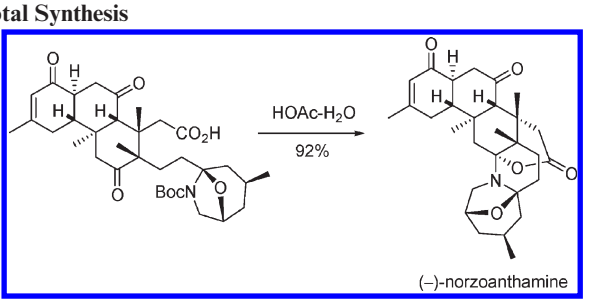


[a]Reagents and conditions: (a) Mg (2.1 equiv), 2-(2-bromoethyl)-1.3-dioxolane (2.0 equiv), THF, 4-DMAP (2.2 equiv), $CuBr \cdot Me_2S$ (0.2 equiv), −78 °C, 1 h, TMSCl (2.2 equiv), then **6**, −78 → − 10 °C, 6 h, Et_3N, 93%; (b) 2 N HCl, THF, rt, 1 h, 50 °C, 1.5 h, 75%; (c) Ac_2O, pyridine, CH_2Cl_2, 4-DMAP, 2 h; (d) ethylene glycol, *p*-TSA (0.2 equiv), benzene, Dean−Stark trap, 1 d; (e) K_2CO_3 (13 equiv), MeOH, rt, 1 d; (f) Dess−Martin (1.3 equiv), CH_2Cl_2, overnight, 52% in four steps; (g) KHMDS (1.6 equiv), $PhNTf_2$ (1.6 equiv), THF, −78 → −30 °C, 1.5 h, $NaHCO_3$, 99%; (h) $H_2C{=}CHCH_2NHBoc$ (1.5 equiv), THF, 9-BBN (2.0 equiv), rt, 4 h; $[Pd(dppf)Cl_2]$ (0.1 equiv), $AsPh_3$ (0.1 equiv), Cs_2CO_3 (1.9 equiv), DMF, 50 °C, 3.5 h, 100%.

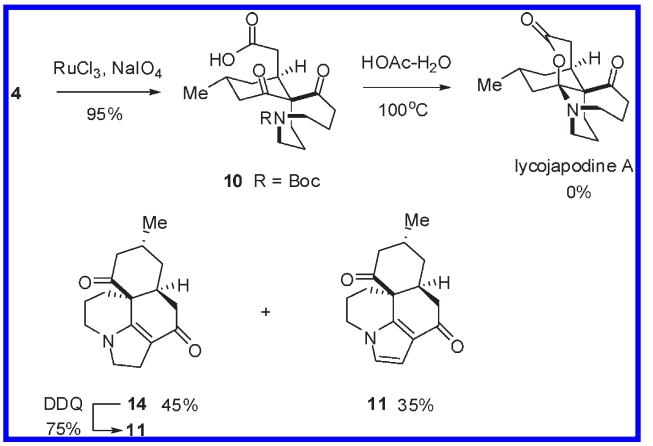
alkaloid. In addition, in contrast to Toste's gold catalysis cyclization, the simple condition of cyclization in Helquist annulation, i.e., heating in 2 N HCl, without noble metal catalysts is also an attractive feature.

Our synthesis started from a known chiral dienone **6** (Scheme 2), whose preparation requires four steps or two steps according to Caine[6] and Toste's procedures, respectively. With dienone **6** in hand, we then tried Helquist annulation and were gratified to find it was very successful. Conjugate addition of the acetal-containing Grignard reagent derived from 2-(2-bromoethyl)-1,3-dioxolane to dienone **6** performed well to provide *trans* silyl enol ether **7** diastereoselectively. This silyl enol ether, upon treatment with 2 N hydrochloric acid, successfully underwent cascade desilylation, acetal hydrolysis, and intramolecular aldol condensation to give a separable 2.5:1 mixture of the aldol products **8** (75%) having correct configuration of quaternary carbon center. The configurations of the resulting hydroxyl groups of **8** were inconsequential (and left unassigned) since they were all subsequently oxidized to a carbonyl moiety. Conversion of **8** → **5** was achieved through a five-step protocol including acetylation, ketalization, deacetylation, oxidation, as well as vinyl triflate formation by using standard conditions (KHMDS, $PhNTf_2$, −78 → −30 °C). Direct protection of carbonyl group in **8** as the cyclic acetal failed, owing to the side reaction of the substrate initiated by a retro-aldol process. It is noteworthy that the above five-step protocol is efficient (exceeds 50% overall yield in five steps) and requires only one single chromatographic purification at the end of the sequence. With the key vinyl triflate **5** in hand, the stage was now set for further elaboration to azatricycle **4**. Intermolecular Suzuki−Miyaura cross-coupling of **5** and allylic carbamate 9-BBN derivative was enlisted according to Toste's conditions. To our delight, the cross-coupling reaction of our vinyl triflate **5** took place quantitatively. Azatricycle **4** was finally synthesized through a four-step reported protocol from compound **9** with our minor modifications (see the Supporting Information).[7]

SCHEME 3. Kobayashi's Key Cyclization in Norzoanthamine Total Synthesis



SCHEME 4. Synthesis of Compounds 11 and 14



With the pivotal intermediate **4** in hand, the next critical task was to employ an oxidative cleavage of cyclopentenyl ring to introduce the keto acid **10** and then to test our hypothesis of biomimetic cyclization to lycojapodine A. In this regard, $RuCl_3/NaIO_4$ conditions turned out to be successful,[8] providing keto acid **10** nearly quantitatively. Prior to our final one-step biomimetic cyclization to (−)-lycojapodine A, we were pleased to find an elegant precedent demonstrated in Kobayashi's recent synthesis of (−)-norzoanthamine,[9] with heating an aqueous acetic acid solution of the substrate at 100 °C, a highly efficient cascade reaction involving cleavage of Boc, condensations of nitrogen atom and keto acid, occurred to provide (−)-norzoanthamine (Scheme 3). Keto acid **10**, upon treatment with the identical conditions reported by Kobayashi with heating for 24 h, led to the formation of two new UV-active substances (Scheme 4). Unfortunately, these compounds were different from lycojapodine A (by TLC comparison) and were eventually characterized as novel tetracyclic alkaloids **11** and **14** (vide infra).

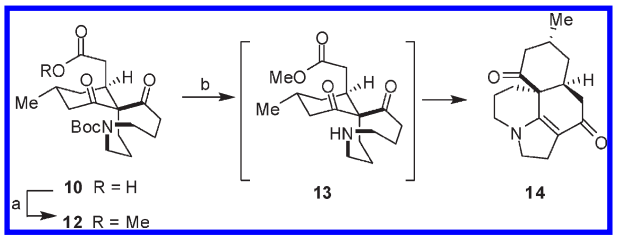
(6) Caine, D.; Procter, K.; Cassell, R. A. *J. Org. Chem.* **1984**, *49*, 2647–2648.

(7) Transformation of **9** to its primary alcohol with original protocol led to poor yield and reproducibility.

(8) Paquette, L. A.; Hu, Y.; Luxenburger, A.; Bishop, R. L. *J. Org. Chem.* **2007**, *72*, 209–222.

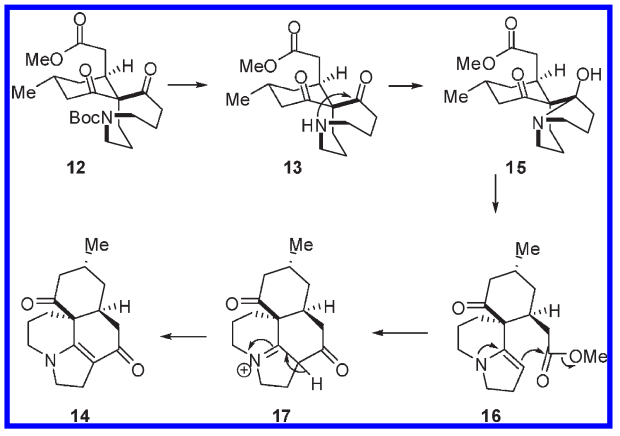
(9) Yamashita, D.; Murata, Y.; Hikage, N.; Takao, K.; Nakazaki, A.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 1404–1406.

SCHEME 5. Synthesis of Compound 14[a]



[a]Reagents and conditions: (a) $TMSCH_2N_2$ (1.6 equiv), CH_2Cl_2, MeOH, rt, 1.5 h, 95%; (b) $ZnBr_2$ (5.0 equiv), CH_2Cl_2 or TFA, CH_2Cl_2, 65%.

SCHEME 6. Possible Mechanism for the Formation of 14



Considering that esters are easier to handle than carboxylic acids, keto acid **10** was then converted into the corresponding methyl ester **12** with trimethylsilyldiazomethane. After removal of the Boc group, a free secondary amine **13** would be expected. Once again, to our surprise, treatment of methyl ester **12** with TFA or $ZnBr_2$ and cleavage of the Boc group accompanied by spontaneous cyclizations occurred to give compound **14** (Scheme 5). In order to clarify the reaction, extensive 1D and 2D NMR analysis for compound **14** was carried out (see the Supporting Information). The ^{13}C NMR spectrum of compound **14** showed the presence of a vinylogous amide moiety (δ 189, 167, 109 ppm). We propose that compound **14** is produced by sequential reactions initiated by cleavage of the Boc and attack of the resulting secondary amine **13** at the ketone functionality inside of the 9-membered azacycle instead of at the expected 6-membered ring (transannular condensation required). Enamine **16** formation was followed by intramolecular nucleophilic substitution to yield tetracyclic imine **17**, which was terminated by β-elimination (Scheme 6). Successful characterization of alkaloid **14** facilitates the structural elucidation of alkaloid **11** (characteristic AB quartet at δ 6.63 and 6.59 ppm for the pyrrole ring appeared in ^1H NMR). Although the detailed mechanism for the formation of **11** under Kobayashi's conditions is unclear, based on the fact that we can also obtain noticeable amount of alkaloid **14** in the reaction of **10** → **11**, we propose that alkaloid **11** may be formed through Polonovski–Potier reaction of *N*-oxide from intermediate **14**,[10] which was formed via a similar pathway depicted in Scheme 6. In addition, the structure of **11** was further verified by the facile oxidation of **14** with DDQ (Scheme 4).

In summary, in this paper, we described our synthetic efforts to lycojapodine A. Unexpected chemoselectivity in a proposed biomimetic 1,3-diketone cyclization was observed and elucidated for the first time. These results may facilitate an understanding of the biosynthesis of this alkaloid and pave the way for further synthetic studies.

(10) We thank one of the reviewers for bringing this to our attention.

Experimental Section

Silyl Enol Ether (7). To a stirred mixture containing 1.02 g (42.5 mmol) of fresh magnesium turnings in 16.5 mL of THF was added a small crystal of iodine and then a solution of 2-(2-bromoethyl)-1,3-dioxolane (8.06 g, 44.5 mmol) in 45 mL of THF over 25 min; a water cooling bath was used to maintain the reaction temperature below 25 °C. The resulting Grignard reagent mixture continued to stir for 1 h at rt before being transferred into a stirred precooled mixture of 4-DMAP (5.54 g, 45.4 mmol) and $CuBr \cdot Me_2S$ (0.856 g, 4.1 mmol) in 30 mL of THF at −78 °C via a cannula. After that, the resulting reaction mixture was stirred at −78 °C for 1 h, and then TMSCl (5.6 mL) and a solution of enone **6** (3.07 g, 20.5 mmol) in 30 mL of THF were added dropwise, respectively, at the same temperature. The reaction was allowed to warm slowly to −10 °C over 6 h and finally quenched by addition of 16.8 mL of triethylamine and diluted with 100 mL of petroleum ether and 50 mL of water. The resulting slurry was filtered through Celite, which was washed with petroleum ether and Et_2O (1:1 mixture). The phases were separated, and the aqueous layer was extracted with ether. The combined organic layers were dried with Na_2SO_4 and concentrated. The crude product was purified with flash column chromatography (petroleum ether/ether 100:1, 1% triethylamine) to provide 6.20 g (93%) as clear oil: $[\alpha]_D$ = +97.4 (c = 0.31, $CHCl_3$); IR (KBr) ν_{max} (cm^{-1}) 2953, 2910, 2878, 1675, 1456, 1410, 1251, 1201, 1142, 1037, 842; ^1H NMR ($CDCl_3$, 500 MHz) δ 5.71 (1H, dt, J = 17.1, 7.9 Hz), 4.94 (2H, m), 4.81 (1H, t, J = 4.6 Hz), 3.96 (2H, t, J = 6.5 Hz), 3.83 (2H, t, J = 6.5 Hz), 3.09 (1H, dd, J = 14.7, 5.4 Hz), 2.50 (1H, dd, J = 14.6, 7.7 Hz), 2.06–2.01 (2H, m), 1.87 (1H, m), 1.74–1.52 (5H, m), 1.27 (1H, m), 1.17 (1H, dt, J = 12.5, 5.5 Hz), 0.93 (3H, d, J = 6.5 Hz), 0.15 (9H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 144.2, 137.2, 116.8, 114.5, 104.8, 64.8, 64.7, 38.6, 35.6, 34.5, 32.6, 32.3, 26.9, 24.8, 21.8, 0.7; HR ESI m/z calcd for $C_{18}H_{33}O_3Si$ $[M + H]^+$ 325.2198, found 325.2196.

Bicyclic Aldol Products (8). To a solution of enol ether **7** (6.20 g, 19.14 mmol) in 130 mL of THF was added 32 mL of 2 N aqueous HCl at rt. The reaction mixture was allowed to stir at rt for 1 h and then was placed in a 50 °C oil bath and stirred for 1.5 h. After being cooled to rt, the reaction mixture was extracted with ether. The combined extracts were washed with saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated, and the crude product was purified with flash column chromatography (petroleum ether/ethyl acetate 20:1→5:1) to provide 2.97 g (75%) of alcohols including the less polar isomer (0.67 g) and more polar one (2.30 g) as slight yellow oil. The spectral data for minor isomer: ^1H NMR ($CDCl_3$, 400 MHz) δ 5.92 (1H, m), 5.10 (1H, d, J = 5.1 Hz), 5.07 (1H, s), 4.23 (1H, d, J = 9.8 Hz), 3.83 (1H, m), 2.49 (1H, dd, J = 13.8, 8.2 Hz), 2.38 (1H, dd, J = 13.8, 6.7 Hz), 2.23–1.97 (5H, m), 1.72–1.51 (5H, m), 1.02 (3H, d, J = 5.9 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 220.5, 133.0, 118.2, 80.7, 57.6, 48.7, 42.0, 39.9, 33.5, 31.0, 28.9, 25.2, 22.3. The spectral data for major isomer: $[\alpha]_D$ = +104.5 (c = 0.76, $CHCl_3$); IR (KBr) ν_{max} (cm^{-1}) 3412, 2940, 2851, 1684, 1459, 1057, 962, 915, 865; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.67 (1H, m), 5.10–5.01 (2H, m), 4.61 (1H, t, J = 2.5 Hz), 2.58 (1H, dd, J = 14.4,

7.3 Hz), 2.38 (2H, m), 1.83 (1H, m), 1.71 (1H, m), 1.61−1.48 (2H, m), 1.33 (1H, m), 1.00 (3H, d, J = 6.3 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 215.0, 134.3, 117.2, 74.9, 61.8, 47.9, 43.7, 36.8, 33.4, 31.8, 29.3, 27.0, 22.3; HR ESI; m/z calcd for $C_{13}H_{20}O_2Na$ $[M + Na]^+$ 231.1360, found 231.1357.

Keto Acid (10). $NaIO_4$ (130 mg, 0.61 mmol) was dissolved with H_2O (0.8 mL) and a 1:1 mixture of CCl_4 and CH_3CN (1.0 mL). To the above stirred solution was added $RuCl_3 \cdot 3H_2O$ (12.6 mg, 0.06 mmol), and the resulting mixture was allowed to stir for 15 min at rt before addition of cyclopentenyl ketone **4** (53 mg, 0.153 mmol) in a 1:1 mixture of CCl_4 and CH_3CN (1.0 mL). The dark reaction was continue to stir for 3 h at rt and diluted with $CHCl_3$ (40 mL) and water (5 mL). The organic layer was separated, washed with $Na_2S_2O_3$ solution and brine, dried, and concentrated. The residue was purified with flash column chromatography ($CHCl_3$/MeOH 20:1) to provide 57 mg of keto acid (95%) as colorless oil: $[\alpha]_D$ = −44.2 (c = 0.16, $CHCl_3$); IR (KBr) ν_{max} (cm^{-1}) 3398, 2962, 2930, 1697, 1413, 1168, 1020, 801; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.36−2.87 (3H, m), 2.70−2.57 (2H, m), 2.43−1.89 (9H, m), 1.80−1.68 (3H, m), 1.46 (9H, s), 1.26−1.23 (3H, m), 1.01 (3H, d, J = 6.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 211.3, 210.8, 177.8, 157.1, 80.1, 79.8, 70.0, 60.4, 49.2, 47.6, 47.0, 46.9, 46.2, 44.7, 37.9, 37.5, 37.2, 36.9, 34.9, 34.8, 33.8, 33.6, 30.5, 29.7, 28.4, 23.3, 21.4, 20.8; HR ESI m/z calcd for $C_{21}H_{33}NO_6Na$ $[M + Na]^+$ 418.2250, found 418.2195.

Tetracyclic Compounds 11 and 14. Keto acid **10** (10.8 mg, 27 μmol) was dissolved in aqueous acetic acid (HOAc/H_2O, v/v = 96:4, 2 mL) and then was placed in a 100 °C oil bath. The resulting deep orange reaction was stirred at 100 °C for 24 h. After the mixture was cooled to rt, the excess acetic acid was removed via vacuum. The residue was diluted with $CHCl_3$, washed with saturated $NaHCO_3$, dried, and concentrated. The crude product was purified with flash column chromatography ($CHCl_3$/MeOH 40:1) to provide 2.4 mg of compound **11** (less polar, 35%) and 3.0 mg of compound **14** (more polar, 45%) as colorless oil. The spectral data for compound **11**: $[\alpha]_D$ = +73.1 (c = 0.24, $CHCl_3$); IR (KBr) ν_{max} (cm^{-1}) 3434, 2931, 1700, 1649, 1517, 1455, 1312, 1230, 756; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.63 (1H, d, J = 3.0 Hz), 6.59 (1H, d, J = 3.0 Hz), 4.09 (1H, dd, J = 12.6, 6.4 Hz), 3.79 (1H, dt, J = 11.9, 6.2 Hz), 2.67−2.28 (7H, m), 2.06−1.80 (3H, m), 1.72−1.64 (2H, m), 1.11 (3H, d, J = 6.1 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 211.4, 191.7, 142.4, 122.9, 118.8, 106.3, 51.9, 45.7, 45.3, 43.7, 42.0, 33.6, 29.8, 29.6, 22.3, 19.0; HR ESI m/z calcd for $C_{16}H_{20}NO_2$ $[M + H]^+$ 258.1494, found 258.1490. The spectral data for alkaloid **14**: $[\alpha]_D$ = −164.1 (c = 0.26, $CHCl_3$); IR (KBr) ν_{max} (cm^{-1}) 3433, 2924, 1708, 1619, 1521, 1451, 1268, 1101, 600; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.77 (1H, dt, J = 10.6, 5.6 Hz), 3.34 (1H, dd, J = 11.8, 5.0 Hz), 3.26 (1H, t, J = 10.9 Hz), 2.87−2.74 (3H, m), 2.58−2.15 (7H, m), 1.92−1.84(2H, m), 1.68−1.48 (3H, m), 1.08 (3H, d, J = 6.1 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 210.0, 188.7, 166.7, 109.3, 54.2, 52.8, 46.5, 45.0, 44.2, 40.0, 33.2, 29.9, 29.8, 23.7, 22.3, 19.2; HR ESI m/z calcd for $C_{16}H_{22}NO_2$ $[M + H]^+$ 260.1650, found 260.1649.

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Supporting Information Available: NMR spectra for all new compounds and experimental procedures and analytical data for compounds **8**, **5**, **9**, **4**, and **12**. This material is available free of charge via the Internet at http://pubs.acs.org