JOC Article
pubs.acs.org/joc

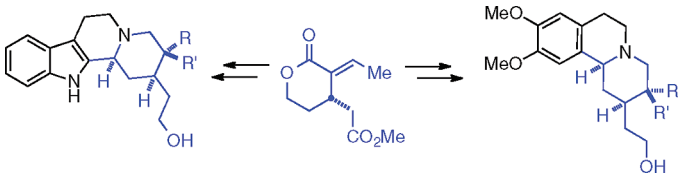
A Divergent Strategy for the Synthesis of Secologanin Derived Natural Products

Brandon J. English[†] and Robert M. Williams*[,†,‡]

[†]*Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523, United States , and* [‡]*University of Colorado Cancer Center, Aurora, Colorado 80045, United States*

rmw@lamar.colostate.edu

Received September 20, 2010



The syntheses of D,L-geissoschizol, D,L-corynantheidol, D,L-dihydrocorynantheol, D,L-protoemetinol, and D,L-3-*epi*-protoemetinol have been accomplished from a single synthetic intermediate.

Introduction

The densely functionalized monoterpene secologanin glucoside (**1**) has been shown to be the common biosynthetic precursor of several structurally diverse classes of natural products.[1] The simple secoiridoids arise from minor modifications to the secologanin core and have been reported to display analgesic,[2] anti-inflammatory,[3] antiarthritic,[4] antiallergenic,[5] antibacterial,[6] and antiviral[7] activities. Strictosidine synthase catalyzes the coupling of secologanin glucoside with tryptamine (**2**) to produce strictosidine (**3**),[8] which is the common precursor of more than 250 structurally diverse naturally occurring alkaloids including important therapeutic agents such as quinine, vinblastine, and reserpine. Additional classes of natural products arise from the coupling of secologanin glucoside with dopamine (**4**) producing the tetrahydroisoquinoline deacetylipecoside (**5**).[9] Modification of **5** gives rise to alkaloids such as the antitumor agent tubulosine[10] and emetine, which displays antiprotozoic[11] activity and may be useful in the treatment of lymphatic leukemia (Scheme 1).[12]

Synthetic access to the secoiridoids and the secologanin alkaloid derivatives has traditionally been pursued on a case-by-case basis by developing novel approaches for a small number of structurally similar synthetic targets. The Cook[13]

*To whom correspondence should be addressed. Phone: +1 970 491 6747. Fax: +1 970 491 3944.

(1) (a) Cordell, G. A. *Lloydia* **1974**, *37* (2), 219. (b) Stöckigt, J.; Zenk, M. H. *J. Chem. Soc., Chem Commun.* **1977**, 646–648. (c) Kutchan, T. M. *Phytochemistry* **1993**, *32*, 493–506.

(2) Beauchamp, G.; Keast, R.; Morel, D.; Liu, J.; Pika, J.; Han, Q.; Lee, C.; Smith, A. B., III; Breslin, P. A. S. *Nature* **2005**, *437*, 45–46.

(3) (a) Ju, H. K.; Moon, T. C.; Lee, E.; Baek, S. H.; An, R. B.; Bae, K.; Son, K. H.; Kim, H. P.; Kang, S. S.; Lee, S. H.; Son, J. K.; Chang, H. W. *Planta Medica* **2003**, *69*, 950–953. (b) Park, K. S.; Chang, I. M. *Planta Medica* **2004**, *70*, 778–779. (c) Benito, P. B.; Lnaza, A. M. D.; Sen, A. M. S.; Galindez, J. S. D.; Matellano, L. F.; Gomez, A. S.; Martinez, M. J. A. *Planta Medica* **2000**, *66*, 324–328. (d) Cimanga, K.; Hermans, N.; Apers, S.; Miert, S. V.; Heuvel, H. V. D.; Claeys, M.; Pieters, L.; Vlietinck, A. *J. Nat. Prod.* **2003**, *66*, 97–102.

(4) (a) Wegener, T. *Z. Phytother.* **1998**, *19*, 284–294. (b) Boje, K.; Lechtenberg, M.; Nahrstedt, A. *Planta Medica* **2003**, *69*, 820–825. (c) Chrubasik, S.; Junck, H.; Breitschwerdt, H; Conradt, C.; Zappe, H. *Eur. J. Anaesthesiol.* **1999**, *16*, 118–129.

(5) Yoshikawa, M.; Ueda, T.; Matsuda, H.; Yamahara, J.; Murakami, N. *Chem. Pharm. Bull.* **1994**, *42*, 1691–1693.

(6) Kumarasamy, Y.; Nahar, L.; Cox, P. J.; Jaspars, M.; Sarker, S. D. *Phytomedicine* **2003**, *10* (4), 344–347.

(7) (a) Bermejo, P.; Abad, M. J.; Diaz, A. M.; Fernandez, L.; Santos, J. D.; Sanches, S.; Villaescusa, L.; Carrasco, L.; Irurzun, A. *Planta Medica* **2002**, *68*, 106–110. (b) Chen, J. L.; Blanc, P.; Stoddart, C. A.; Bogan, M.; Rozhon, E. J.; Parkinson, N.; Ye, Z.; Cooper, R.; Balick, M.; Nanakorn, W.; Kernan, M. R. *J. Nat. Prod.* **1998**, *61*, 1295–1297. (c) Suksmrarn, S.; Wongkrajang, K.; Kirtikara, K.; Suksmrarn, A. *Planta Medica* **2003**, *69*, 877–879.

(8) Treimer, J. F.; Zenk, M. H. *Eur. J. Biochem.* **1979**, *101*, 225–233.

(9) (a) Fujii, T.; Ohba, M. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1983; Vol. 22, pp 1−50. (b) De-Eknamkul, W.; Ounaroon, A.; Tanahashi, T.; Kutchan, T. M.; Zenk, M. H. *Phytochemistry* **1997**, *45* (3), 477–484.

(10) Ma, W. W.; Anderson, J. E.; McKenzie, A. T.; Byrn, S. R.; McLaughlin, J. L.; Hudson., M. S. *J. Nat. Prod.* **1990**, *53*, 1009–1014.

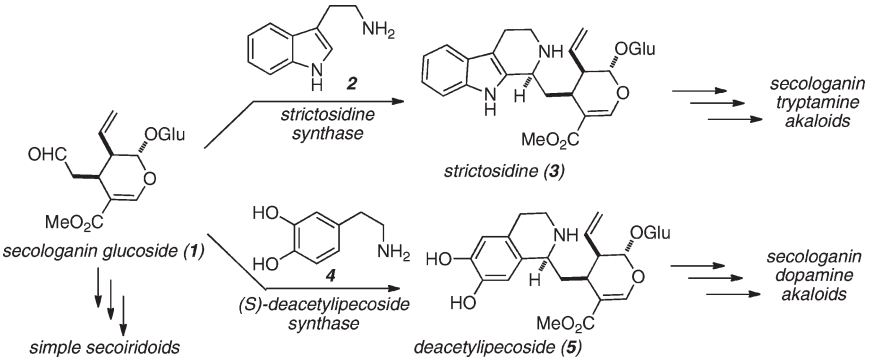
(11) Gonzales-Garza, M. T.; Martlin, S. A.; Mata-Cardena, B. D.; Said-Fernandez, S. *J. Pharm. Pharmacol.* **1993**, *45*, 144.

(12) Liou, Y. F.; Hall, I. H.; Lee, K. H. *J. Pharm. Sci.* **1982**, *71*, 745–749.

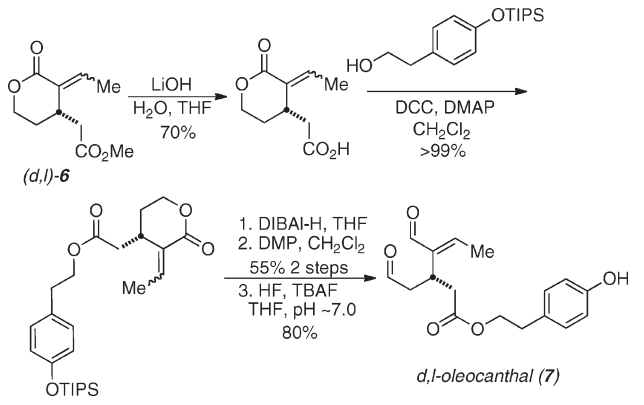
(13) (a) Yu, P.; Wang, T.; Yu, F.; Cook, J. M. *Tetrahedron Lett.* **1997**, *38*, 6819–6822. (b) Wang, T.; Yu, P.; Li, J.; Cook, J. M. *Tetrahedron. Lett.* **1998**, *39*, 8009–8012. (c) Yu, P.; Cook, J. M. *J. Org. Chem.* **1998**, *63* (25), 9160–9161. (d) Li, J.; Yu, P.; Peterson, A.; Weber, R.; Soerens, D.; Grubisha, D.; Bennet, D.; Cook, J. M. *J. Am. Chem. Soc.* **1999**, *121*, 6998. (e) Yu, S.; Berner, M.; Cook, J. M. *J. Am. Chem. Soc.* **2000**, *122*, 7827–7828. (f) Wang, T.; Cook, J. M. *Org. Lett.* **2000**, *2* (14), 2057–2059. (g) Liu, X.; Deschamp, J. R.; Cook, J. M. *Org. Lett.* **2002**, *4*, 3339–3342. (h) Liao, X.; Zhou, H.; Wearing, X. Z.; Ma, J.; Cook, J. M. *Org. Lett.* **2005**, *7*, 3501–3504. (i) Liao, X.; Zhou, H.; Yu, J.; Cook, J. M. *J. Org. Chem.* **2006**, *71*, 8884–8890.

DOI: 10.1021/jo101775n Published on Web 10/22/2010

SCHEME 1. Biosynthesis of Secologanin-Derived Natural Products



SCHEME 2. Previous Conversion of 6 to Oleocanthal (7)



and Martin[14] laboratories have pursued more general synthetic strategies allowing access to a broad selection of secologanin tryptamine alkaloids via a single synthetic strategy. Although highly efficient and productive, these strategies confine their synthetic scope to the tryptamine-derived alkaloids. We have envisioned a more general strategy involving the large-scale synthesis of a functionalized intermediate, which can be rapidly modified to allow access to the simple secoiridoids as well as the tryptamine- and dopamine-derived alkaloids. We recently demonstrated that lactone **6** was a viable intermediate for the synthesis of the simple secoiridoid oleocanthal (**7**) (Scheme 2).[15] Herein we wish to report the use of lactone **6** as a key intermediate in the synthesis of the secologanin tryptamine alkaloids D,L-geissoschizol (**8**), D,L-corynantheidol (**9**), and D,L-dihydrocorynantheol (**10**) as well as the secologanin dopamine alkaloids D,L-3-*epi*-protoemetinol (**11**) and D,L-protoemetinol (**12**) (Figure 1).

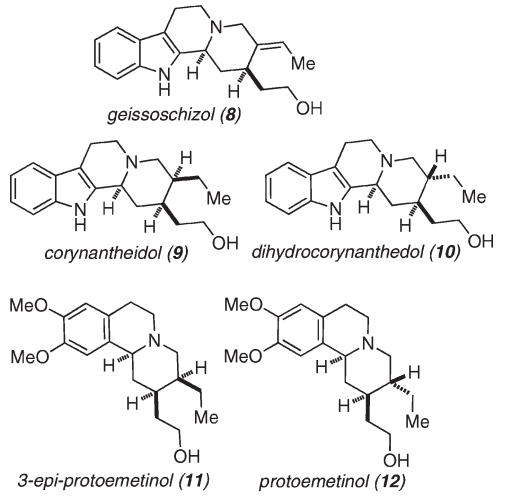


FIGURE 1. Target natural products.

Figure 2 illustrates our retrosynthetic strategy. We planned to form the arylpiperidine rings of the target alkaloids (**13**) via late-stage Bischler−Napieralski cyclization of a hydroxyl-protected lactam (**14**). We predicted that this cyclization would proceed with complete cis-diastereoselectivity based on observations made by Martin and co-workers while working

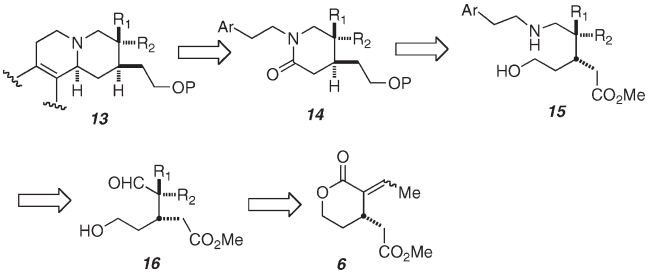


FIGURE 2. Retrosynthetic analysis.

with a similar system.[16] We envisioned the requisite lactam ring of **14** arising from the cyclization of the methyl ester moiety and the secondary amine of a compound of type **15**. This secondary amine would be produced through the reductive amination of an appropriately functionalized aldehyde (**16**) and tryptamine or a dopamine-derived primary amine. The desired oxidation state and relative stereochemistry of the ethyl side chain could be established via selective reduction of the olefin of lactone **6** followed by the reduction of the resulting lactone.

Results and Discussion

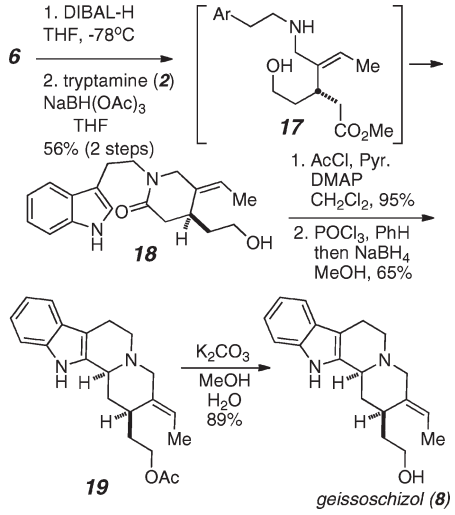
Scheme 3 illustrates our synthesis of D,L-geissoschizol (**8**). Reduction of the lactone carbonyl of **6** followed by reductive amination of the crude aldehyde/lactol mixture both successfully merged the tryptamine and secoiridoid portions of the

(14) (a) Martin, S. F.; Benage, B.; Hunter, J. E. *J. Am. Chem. Soc.* **1988**, *110*, 5925–5927. (b) Martin, S. F.; Benage, B.; Geraci, L. S.; Hunter, J. E.; Mortimore, M. *J. Am. Chem. Soc.* **1991**, *113*, 6161–6171. (c) Martin, S. F.; Chen, K. X.; Eary, C. T. *Org. Lett.* **1999**, *1*, 79–81. (d) Deiters, A.; Chen, K.; Eary, T.; Martin, S. F. *J. Am. Chem. Soc.* **2003**, *125*, 4541–4550.

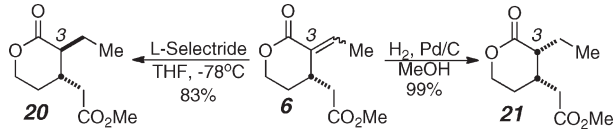
(15) English, B. J.; Williams, R. M. *Tetrahedron Lett.* **2009**, *50* (23), 2713–2715.

(16) Deiters, A.; Pettersson, M.; Martin, S. F. *J. Org. Chem.* **2006**, *71*, 6547–6561.

SCHEME 3. Synthesis of Geissoschizol (8)



SCHEME 4. Selective Reduction of Lactone 6



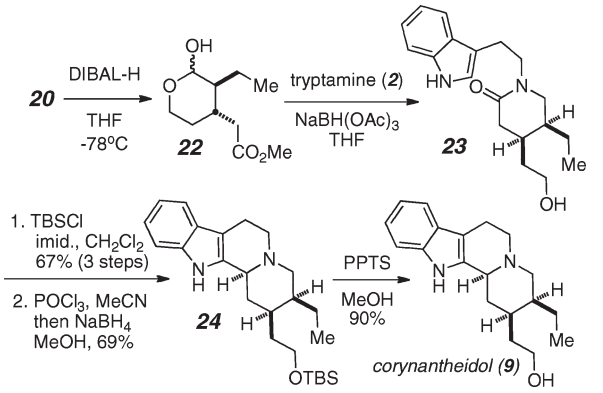
molecule as well as forming the lactam ring of intermediate **18**, presumably via amine **17**, which was not isolated. Protection of the hydroxyl functionality of **18** as the acetate ester followed by Bischler−Napieralski cyclization gave acetate **19** as a single isomer, which was deprotected to yield D,L-geissoschizol (**8**) in good yield.

Next, we turned our attention to the alkaloids bearing reduced ethyl side chains, corynantheidol (**9**) and dihydrocorynantheol (**10**). As part of their 1992 synthesis of these and other related alkaloids, Lounasmaa and co-workers reported the successful hydrogenation of several geissoschizol isomers.[17] Unfortunately, poor diastereoselectivity was observed for these reductions regardless of the geissoschizol isomer or reduction method employed. These observations lead us to pursue a strategy, which introduces the C3 stereogenic centers earlier in the synthesis. We speculated that either of the desired ethyl side chain stereochemistries could be accessed via selective reduction of lactone **6**. As illustrated in Scheme 4, catalytic hydrogenation of the olefin of lactone **6** produces exclusively the cis-isomer of the reduced lactone (**21**). This selectivity is presumably due to the delivery of hydrogen to the least sterically encumbered face of the olefin. Conjugate reduction, conversely, produces exclusively the thermodynamically favored trans-isomer of the reduced lactone (**20**). With the ability to selectively produce lactones **20** and **21** we turned our attention to the completion of some representative natural alkaloid syntheses.

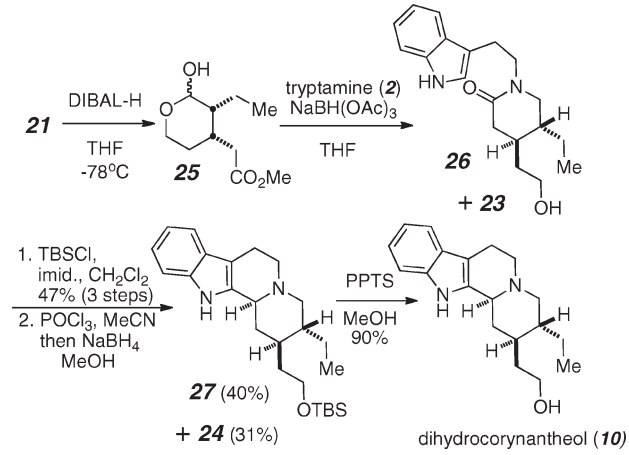
Following a similar protocol to that deployed for our synthesis of geissoschizol, our synthesis of corynantheidol (**9**) (Scheme 5) began with the DIBAL-H reduction of lactone **20** followed by a one-step reductive amination/lactam cyclization to give alcohol **23**. Alcohol protection and Bischler−Napieralski cyclization

(17) Louansmaa, M.; Jokela, R.; Tirkkonen, B.; Miettinen, J.; Halonen, M. *Heterocycles* **1992**, *34* (2), 321–339.

SCHEME 5. Synthesis of Corynantheidol (9)



SCHEME 6. Synthesis of Dihydrocorynantheol (9)

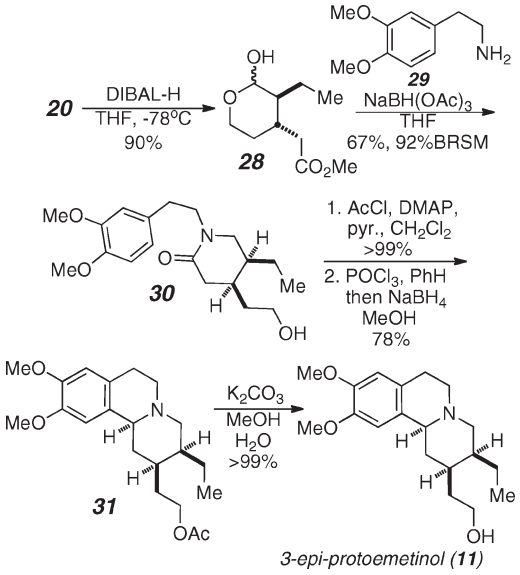


gave tetracycle **24** in good yield and as a single isomer. Removal of the alcohol protecting group with PPTS/MeOH gave D,L-corynantheidol (**9**) in excellent yield.

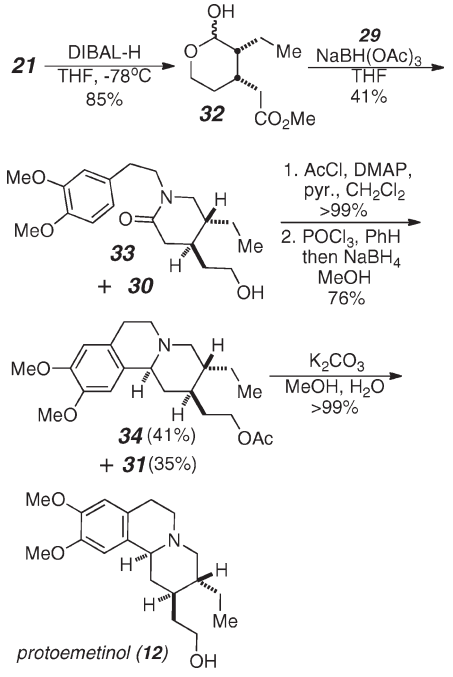
Our attempts to access dihydrocorynantheol (**10**) began via employment of an identical method to that used for its epimer corynantheidol (Scheme 6). Reduction of lactone **6** gave a mixture of lactol isomers (**25**), which was immediately subjected to reductive amination conditions producing the desired lactam (**26**) and its C3 epimer (**23**) as a minor product. Protection of the alcohol and Bischler−Napieralski cyclization of this mixture gave a mixture of two tetracyclic epimers (**24** and **27**) that were readily separated by silica gel flash chromatography. Separate deprotection of **27** and **24** gave D,L-dihydrocorynantheol (**10**) and D,L-corynantheidol (**9**) respectfully.

With control of the secoiridoid portion of the secologanin-derived alkaloids established, we began our investigation of the secoiridoids derived from dopamine. Fortunately very little modification to the procedures developed was necessary for this purpose. Thus, substituting 2-(3,4-dimethoxyphenyl)-ethanamine (**29**) for tryptamine and adjusting Bischler−Napieralski reaction temperature to compensate for a slightly less reactive aromatic nucleophile, the synthesis of D,L-3-*epi*-protoemetinol (**11**) was accomplished by the procedure developed for the synthesis of D,L-corynantheidol (**9**) (Scheme 7) and D,L-protoemetinol (**12**) was synthesized by the procedure developed for the synthesis of D,L-dihydrocorynantheol (**10**) (Scheme 8).

SCHEME 7. Synthesis of 3-*epi*-Protoemetinol (11)



SCHEME 8. Synthesis of Protoemetinol (12)



The syntheses described herein of the tryptamine-derived secologanin alkaloids geissoschizol, corynantheidol, and dihydrocorynantheol and the dopamine-derived secologanin alkaloids protoemetinol and 3-*epi*-protoemetinol taken in context with our previously reported synthesis of oleocanthal demonstrate the potentially broad utility of lactone **6**. The careful manipulation of lactone **6** delivered rapid access to members of, to date, three very distinct classes of secologanin-derived natural products. Current efforts to produce lactone **6** in an enantioselective manner are under investigation.

Experimental Section

Synthesis of (*E*)-1-(2-(1*H*-Indol-3-yl)ethyl)-5-ethylidene-4-(2-hydroxyethyl)piperidin-2-one (18). To a flame-dried 50-mL round-bottomed flask containing 248 mg (1.25 mmol, 1 equiv) of lactone **6** was added 20 mL of dry THF and this solution was cooled to −78 °C. To this solution was dropwise added 1.50 mL (1.2 equiv) of a 1.0 M solution of DIBAl-H in THF and the reaction was allowed to stir for 60 min at this temperature before the dropwise addition of 2 mL of dry MeOH and warming to ambient temperature. To this reaction mixture was added 25 mL of a saturated aqueous solution of Rochelle's salt and the mixture was stirred for 30 min at ambient temperature. This mixture was extracted three times with EtOAc, dried over Na_2SO_4, and concentrated to yield a colorless oil, which was immediately used without purification.

To the above produced residue was added 360 mg (2.25 mmol, 1.5 equiv) of tryptamine, 15 mL of dry THF, and then 954 mg (4.50 mmol, 3 equiv) of $NaBH(OAc)_3$. After being stirred at ambient temperature for 48 h the reaction was added to $NaHCO_{3(sat.)}$ and extracted three times with CH_2Cl_2. Combined organic layers were dried over Na_2SO_4 and concentrated to afford a brown oil that was purified by silica gel chromatography eluting with 5% to 20% MeOH in EtOAc to yield 220 mg (56%, 2 steps) of compound **18** as a white foam.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.00 (br s, 1H), 7.62 (d, J = 7.8 Hz, 1H), 7.33 (d, J = 8.1 Hz, 1H) 7.13 (m, 2H), 6.97 (s, 1H), 5.28 (q, J = 5.7 Hz, 1H), 3.44−3.82 (m, 6H), 3.04 (q, J = 7.5 Hz, 2H), 2.97 (m, 1H), 2.26−2.56 (m, 2H), 1.57 (dd, J = 6.6, 1.5 Hz, 3H), 1.40−1.56 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.7, 136.4, 132.6, 127.4, 122.5, 121.7, 120.8, 119.1, 118.6, 112.3, 111.4, 60.3, 52.5, 47.5, 37.9, 35.2, 29.9, 22.9, 12.8; IR (NaCl, film) 3289, 1620 cm^{-1}; HRMS (+TOF) $[M + H]^+$ 313.1911 calcd for $C_{19}H_{25}N_2O_2$, found 313.1916; R_f 0.18 (5% MeOH in EtOAc).

Synthesis of (*E*)-2-(1-(2-(1*H*-Indol-3-yl)ethyl)-5-ethylidene-2-oxopiperidin-4-yl)ethyl Acetate. To a 10-mL round-bottomed flask containing 65.0 mg (0.208 mmol, 1 equiv) of alcohol **18** dissolved in 1 mL of dry CH_2Cl_2 and 1 mL of dry pyridine was added 30.0 μL (0.416 mmol, 2 equiv) of AcCl followed by a single crystal of DMAP. The reaction was stirred at ambient temperature for 1 h before being added to $NaHCO_{3(sat.)}$, and extracted three times with CH_2Cl_2, dried over Na_2SO_4, and concentrated. The crude residue was purified by silica gel chromatography eluting with 1% to 10% MeOH in CH_2Cl_2 to yield 70 mg (95%) of the desired product as a pale yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.01 (br s, 1H), 7.63 (d, J = 7.8 Hz, 1H), 7.32 (d, J = 8.1 Hz, 1H), 7.15 (t, J = 6.6 Hz, 1H), 7.08 (t, J = 7.2 Hz, 1H), 6.97 (s, 1H), 5.33 (q, J = 6.9 Hz, 1H), 4.01−3.46 (m, 6H), 3.04 (t, J = 7.5 Hz, 2H), 2.97 (m, 1H), 2.50 (dd, J = 17.1, 5.7 Hz, 1H), 2.39 (dd, J = 16.8, 2.1 Hz, 1H), 2.01 (s, 3H), 1.63 (m, 2H), 1.56 (dd, J = 6.9, 1.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 169.2, 136.6, 132.0, 127.6, 122.6, 122.0, 121.8, 119.3, 118.8, 112.6, 111.6, 62.5, 52.6, 47.9, 38.3, 31.3, 30.3, 23.2, 21.2, 12.9; IR (NaCl, film) 1736, 1628 cm^{-1}; HRMS (+TOF) $[M + H]^+$ 355.2016 calcd for $C_{21}H_{27}N_2O_3$, found 355.2014; R_f 0.27 (5% MeOH in CH_2Cl_2).

Synthesis of 2-((2*R*,12b*S*,*E*)-3-Ethylidene-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizin-2-yl)ethyl Acetate (19). To 192 mg (0.542 mmol, 1 equiv) of the above produced acetate dissolved in 5 mL of dry benzene was added 100 μL (1.08 mmol, 2 equiv) of freshly distilled $POCl_3$. The reaction was heated to reflux for 1.5 h before being concentrated under reduced pressure. The resulting residue was taken up in 5 mL of dry MeOH and cooled to 0 °C before 50 mg of $NaBH_4$ was added and the reaction was removed from the ice bath and stirred for 15 min. The reaction was then added to 0.5 M NaOH, extracted three times with CH_2Cl_2, dried over Na_2SO_4, and concentrated. The resulting residue was purified by silica gel chromatography eluting with 5% MeOH in EtOAc to provide 119 mg (65%) of the desired product as a pale yellow foam.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.40 (br s, 1H), 7.45 (d, J = 7.2 Hz, 1H), 7.34 (d, J = 7.2 Hz, 1H), 7.09 (m, 2H), 5.51 (q, J = 6.9 Hz,

1H), 4.24−3.86 (m, 2H), 3.73 (d, J = 10.5 Hz, 1H), 3.04 (m, 3H), 2.64 (m, 3H), 2.08 (s, 3H), 2.05−1.70 (m, 5H), 1.58 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.5, 136.3, 135.5, 135.0, 127.5, 122.1, 121.4, 119.4, 118.2, 111.1, 108.5, 62.9, 60.1, 55.4, 53.0, 35.3, 31.0, 30.7, 21.9, 21.3, 12.9; IR (NaCl, film) 1735 cm^{-1}; HRMS (+TOF) $[M + H]^+$ 339.2073 calcd for $C_{21}H_{27}N_2O_2$, found 339.2072; R_f 0.45 (5% MeOH in EtOAc).

Synthesis of (±)-Geissoshizol (8). To a 10-mL round-bottomed flask containing 50.0 mg (0.148 mmol, 1 equiv) of acetate **19** dissolved in 1 mL of MeOH and 0.5 mL of H_2O was added 245 mg (1.77 mmol, 12 equiv) of K_2CO_3. The reaction was stirred at ambient temperature for 2 h, added to brine, extracted three times with CH_2Cl_2, dried over Na_2SO_4, and concentrated. The resulting oil was purified by silica gel chromatography eluting with 10% MeOH in CH_2Cl_2 to yield 39.0 mg (89%) of the desired product as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (br s, 1H), 7.44 (d, J = 7.6 Hz, 1H), 7.32 (d, J = 7.6 Hz, 1H), 7.15−7.06 (m, 2H), 5.51 (q, J = 6.8 Hz, 1H), 3.67 (m, 3H), 3.25−2.97 (m, 5H), 2.72 (m, 1H), 2.62 (m, 1H), 2.08−1.46 (m, 5H), 1.62 (d, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.4, 136.2, 134.8, 127.5, 121.7, 121.4, 119.5, 118.2, 110.9, 108.6, 61.3, 60.1, 55.3, 52.8, 35.4, 35.2, 31.0, 21.8, 12.9; IR (NaCl, film) 3233, 2851, 2790, 2745 cm^{-1}; HRMS (+TOF) $[M + H]^+$ 297.1961 calcd for $C_{19}H_{25}N_2O$, found 297.1961; R_f 0.14 (5% MeOH in EtOAc). Spectroscopic properties agree in all respects with those previously reported.[13e,18]

Synthesis of Lactone 20. To a 250-mL round-bottomed flask contining 1.10 g (5.55 mmol, 1 equiv) of lactone **6** dissolved in 56 mL of dry THF at −78 °C was added 6.10 mL (1.1 equiv) of a 1.0 M solution of L-Selectride in THF. The reaction was allowed to stir at −78 °C for 60 min and was then added to $NH_4Cl_{(sat.)}$, extracted three times with EtOAc, dried over Na_2SO_4, concentrated, and purified by silica gel chromatography eluting with 2:1 hex./EtOAc to yield 918 mg (83%) of the title compound as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.26 (m, 2H), 3.66 (s, 3H), 2.50 (m, 2H), 2.26 (m, 2H), 2.04 (m, 1H), 1.87 (m, 1H), 1.65 (m, 2H), 0.94 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) major conformer: δ 173.1, 172.2, 67.1, 51.9, 46.6, 38.7, 31.8, 28.4, 22.7, 10.9; IR (NaCl, film) 1732 cm^{-1}; HRMS (+TOF) $[M + H]^+$ 201.1121 calcd for $C_{10}H_{17}O_4$, found 201.1123; R_f 0.52 (1:1 hex./EtOAc)

Synthesis of 1-(2-(1*H*-Indol-3-yl)ethyl)-4-(2-(*tert*-butyldimethylsilyloxy)ethyl)-5-ethylpiperidin-2-one. A 100-mL round-bottomed flask containing 505 mg (2.52 mmol, 1 equiv) of lactone **20** dissolved in 25 mL of dry THF was cooled to −78 °C. To this cooled mixture was slowly added 2.77 mL (2.77 mmol, 1.1 equiv) of a 1.0 M solution of DIBAL-H in THF. The reaction was stirred for 30 min at −78 °C followed by the dropwise addition of 2 mL of MeOH. The reaction was allowed to warm to ambient temperature and was then added to a saturated aqueous solution of NaK tartrate and extracted three tmes with EtOAc. Combined organic layers were dried over Na_2SO_4, concentrated, and purified by silica gel flash chromatography eluting with 1:1 hex./EtOAc to yield 459 mg of an inseparable mixture of the desired lactol mixture (**22**) as a colorless oil.

To a 50-mL round-bottomed flask containing the above prepared lactol mixture dissolved in 23 mL of dry THF was added 546 mg (3.41 mmol, 1.5 equiv) of tryptamine and then 1.44 g (6.81 mmol, 3 equiv) of $NaBH(OAc)_3$. The reaction was allowed to stir at ambient temperature for 48 h before being added to $NaHCO_{3(sat.)}$, extracted three times with EtOAc, dried over Na_2SO_4, and concentrated. The resulting residue containing crude **23** was carried forward without purification.

To the crude alcohol (**23**) prepared above in a 50-mL round-bottomed flask was added 22.7 mL of dry CH_2Cl_2 followed by 411 mg (2.72 mmol, 1.2 equiv) of TBSCl and then 309 mg (4.54 mmol, 2 equiv) of imidazole. The reaction was allowed to stir at ambient temperature for 12 h before being added to brine, extracted into CH_2Cl_2, dried over Na_2SO_4, and concentrated. The resultant residue was purified by silica gel flash chromatography eluting with 1:1 hex./EtOAc to yield 720 mg (67%, 3 steps) of the desired *O*-TBS ether derivative of **23** as a tan foam.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.94 (br s, 1H), 7.66 (d, J = 7.5 Hz, 1H), 7.34 (d, J = 7.5 Hz, 1H), 7.17 (t, J = 7.2 Hz, 1H), 7.10 (t, J = 7.2 Hz, 1H), 6.98 (s, 1H), 3.65 (m, 4H), 3.13 (dd, J = 12.3, 5.1 Hz, 1H), 3.03 (m, 3H), 2.37 (qd, J = 17.7, 6.0 Hz, 2H), 2.07 (m, 1H), 1.68 (m, 1H), 1.54 (m, 1H), 1.14−1.34 (m, 3H), 0.90 (s, 9H), 0.83 (t, J = 7.2 Hz, 3H), 0.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.5, 136.4, 127.4, 122.3, 121.7, 119.0, 118.6, 112.5, 111.4, 60.6, 50.6, 48.3, 38.3, 36.4, 31.5, 31.1, 26.0, 23.0, 20.5, 18.3, 11.8, −5.3; IR (NaCl, film) 3260, 1622 cm^{-1}; HRMS (+TOF) $[M + H]^+$ 429.2932 calcd for $C_{25}H_{41}N_2O_2Si$, found 429.2937; R_f 0.36 (1:1 hex./EtOAc)

Synthesis of Tetracycle 24. To 160 mg (0.373 mmol, 1 equiv) of the above-produced *O*-TBS ether derivative of **23** dissolved in 4 mL of dry MeCN was added 1.21 mL (14.9 mmol, 40 equiv) of dry pyridine followed by 278 μL (2.98 mmol, 8 equiv) of freshly distilled $POCl_3$. The reaction was stirred for 16 h at 40 °C and concentrated under reduced pressure. To the resultant residue was added 4 mL of dry MeOH. This solution was cooled to 0 °C, 142 mg (3.73 mmol, 10 equiv) of $NaBH_4$ was added, and the reaction was stirred at 0 °C for 15 min before being added to $NaHCO_{3(sat.)}$, extracted into CH_2Cl_2, dried over Na_2SO_4, and concentrated. Purification by silica gel flash chromatography eluting with 2:1 hex./EtOAc yielded 107 mg (69%) of the desired product (**24**) as a pale yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (br s, 1H), 7.47 (d, J = 7.2 Hz, 1H), 7.30 (d, J = 7.2 Hz, 1H), 7.11 (m, 2H), 3.72 (t, J = 6.6 Hz, 2H), 3.24 (m, 1H), 3.01 (m, 3H), 2.68 (m, 1H), 2.38 (d, J = 11.4 Hz, 1H), 1.88 (m, 2H), 1.53 (m, 4H), 1.27 (m, 3H), 0.95 (s, 9H), 0.91 (m, 3H), 0.11 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.0, 135.4, 127.6, 121.3, 119.4, 118.2, 110.9, 108.1, 66.7, 61.5, 60.6, 53.5, 39.7, 36.5, 36.4, 32.2, 29.8, 26.2, 18.5, 17.9, 12.8, −5.1; IR (NaCl, film) 2796, 2747 cm^{-1}; HRMS (+TOF) $[M + H]^+$ 413.2951 calcd for $C_{25}H_{41}N_2OSi$, found 413.2948; R_f 0.46 (4:1 hex./EtOAc).

Synthesis of (±)-Corynantheidol (9). To a 25-mL round-bottomed flask containing 40 mg (0.097 mmol, 1 equiv) of tetracycle **24** was added 1 mL of MeOH followed by 49 mg (0.19 mmol, 2 equiv) of PPTS. The reaction was stirred 12 h at ambient temperature, added to 1 N NaOH, extracted twice with CH_2Cl_2, dried over Na_2SO_4, and concentrated. The resulting residue was purified by silica gel flash chromatography eluting with 5% to 20% MeOH in CH_2Cl_2 to yield 26 mg (90%) of corynantheidol (**9**) as a white foam.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 (br s, 1H), 7.45 (d, J = 6.6 Hz, 1H), 7.31 (d, J = 7.2 Hz, 1H), 7.10 (m, 2H), 3.73 (m, 2H), 3.13 (dd, J = 10.8, 0.6 Hz, 1H), 2.99 (m, 3H), 2.66 (m, 1H), 2.54 (m, 1H), 2.32 (d, J = 9.9 Hz, 1H), 1.85 (m, 2H), 1.58−1.48 (m, 5H), 1.26 (m, 2H), 0.91 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.1, 135.4, 127.5, 121.2, 119.3, 118.1, 110.9, 107.9, 60.8, 60.5, 57.9, 53.6, 39.7, 36.4, 36.0, 31.9, 21.8, 17.8, 12.8; IR (NaCl, film) 3412, 3277, 2800, 2749 cm^{-1}; HRMS (+TOF) $[M + H]^+$ 299.2118 calcd for $C_{19}H_{27}N_2O$, found 299.2120; R_f 0.25 (5% MeOH in CH_2Cl_2). Spectroscopic properties agreed in all respects with those previously reported.[13e,17,18]

Synthesis of Lactone 21. To a 100-mL round-bottomed flask containing 1.07 g (5.40 mmol, 1 equiv) of lactone **6** was added 25 mL of dry MeOH then 574 mg of 10% Pd/C. Hydrogen gas

(18) (a) Lounasmaa, M.; Jokela, R. *Heterocycles* **1990**, *31* (7), 1351–1358. (b) Kametani, T.; Kanaya, N.; Honda, T. *Heterocycles* **1981**, *16* (11), 1937–1946. (c) Beard, R. L.; Meyers, A. I. *J. Org. Chem.* **1991**, *56*, 2091–2096. (d) Itoh, T.; Yokoya, M.; Miyauchi, K.; Nagata, K.; Ohsawa, A. *Org. Lett.* **2006**, *8*, 1533. (e) Wenkert, E.; Guo, M.; Pestchanker, M. J.; Shi, Y.-J.; Vankar, Y. D. *J. Org. Chem.* **1989**, *54*, 1166–1174.

was bubbled through this mixture for 5 min and then the reaction was vigorously stirred for 4 h at ambient temperature under balloon pressure of H_2. The reaction was then filtered through a thin pad of Celite, concentrated, and purified by silica gel flash chromatography eluting with 1:1 hex./EtOAc to yield 1.07 g (>99%) of the title compound as a colorless oil. (Note: The trans isomer (**20**) was not detected by ^{1}H NMR, ^{13}C NMR, or TLC.)

^{1}H NMR (300 MHz, $CDCl_3$) (mixture of rotamers) δ 4.26 (m, 2H), 3.63 (s, 1.5H), 3.62 (s, 1.5H), 2.74−2.36 (m, 2H), 2.29−1.99 (m, 3H), 1.89−1.52 (m, 3H), 1.35 (m, 1H), 1.20 (m, 1H), 0.94 (t, J = 7.5 Hz, 1.5H), 0.92 (t, J = 7.2 Hz, 1.5H); ^{13}C NMR (75 MHz, $CDCl_3$) (mixture of rotamers) δ 174.2, 173.4, 172.7, 172.4, 68.6, 67.3, 66.1, 65.6, 52.7, 52.1, 51.9, 46.7, 44.5, 38.9, 38.7, 36.1, 34.3, 33.7, 32.0, 30.3, 29.2, 28.5, 28.0, 27.0, 22.9, 22.8, 20.8, 20.2, 14.0, 12.3, 12.0, 11.1; IR (NaCl, film) 1732 cm^{-1}; HRMS (+TOF) $[M + H]^+$ 201.1121 calcd for $C_{10}H_{17}O_4$, found 201.1126; R_f 0.39 (1:1 hex./EtOAc).

Synthesis of Lactams 26 and 23. To a 100-mL flame-dried round-bottomed flask was added 1.08 g (5.40 mmol, 1 equiv) of lactone **21** dissolved in 25 mL of dry THF. This mixture was cooled to −78 °C before the slow addition of 5.94 mL (5.94 mmol, 1.1 equiv) of a 1.0 M solution of DIBAl-H in THF. The reaction was stirred at −78 °C for 30 min befor the addition of 2 mL of dry MeOH. The reaction was allowed to warm to ambient temperature before being added to a saturated solution of Rochelle's salt, extracted twice into CH_2Cl_2, dried over Na_2SO_4, and concentrated to yield the desired mixture of lactols **21** as a colorless oil, which was immediately used without further purification. (Note: The undesired trans isomer (**20**) was not detected in this crude mixture; however, subjecting this crude mixture to silica gel chromatography did result in the isolation of **20**.)

To a 100-mL round-bottomed flask containing the above produced lactol mixture **21** dissolved in 27 mL of dry THF was added 649 mg (4.05 mmol, 1.5 equiv) of tryptamine followed by 1.72 g (8.10 mmol, 3 equiv) of $NaBH(OAc)_3$. The reaction was allowed to stir at ambient temperature for 24 h before being added to $NaHCO_{3(sat.)}$, extracted twice into CH_2Cl_2, dried over Na_2SO_4, and concentrated to yield a mixture of alcohols as a tan oil, which was used without further purification.

To a 100-mL round-bottomed flask containing the above produced crude mixture of alcohols dissolved in 27 mL of dry CH_2Cl_2 was added 488 mg (3.24 mmol, 1.2 equiv) of TBSCl followed by 368 mg (5.40 mmol, 2 equiv) of imidazole. The reaction was stirred at ambient temperature for 16 h before being added to brine, extracted twice into CH_2Cl_2, dried over Na_2SO_4, and concentrated. The resulting residue was purified by silica gel flash chromatography eluting with 1:1 to 0:1 hex./EtOAc to yield 542 mg (47%, 3 steps) of the desired mixture of isomers as a tan foam.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.78 (br s, 1H), 7.66 (d, J = 7.5 Hz, 1H), 7.35 (d, J = 7.8 Hz, 1H), 7.13 (m, 2H), 6.98 (s, 1H), 3.64 (m, 4H), 3.22−2.86 (m, 4H), 2.28−2.59 (m, 2H), 2.07 (m, 1H), 1.70−1.10 (m, 6H), 0.90 (s, 9H), 0.80 (m, 4H), 0.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0, 169.7, 136.6, 127.7, 122.5, 122.0, 119.3, 118.9, 113.0, 112.9, 111.6, 60.9, 60.6, 51.6, 50.8, 48.5, 48.4, 39.4, 38.5, 36.6, 36.4, 33.1, 31.8, 31.3, 26.2, 23.9, 23.4, 23.2, 20.7, 18.5, 12.1, 11.1; IR (NaCl, film) 3254, 1626 cm^{-1}; HRMS (+TOF) $[M + H]^+$ 429.2932 calcd for $C_{25}H_{41}N_2O_2Si$, found 429.2933; R_f 0.30 (1:1 hex./EtOAc)

Synthesis of Tetracycle 27. To a 100-mL round-bottomed flask containing the above produced crude mixture of alcohols dissolved in 27 mL of dry CH_2Cl_2 was added 488 mg (3.24 mmol, 1.2 equiv) of TBSCl followed by 368 mg (5.40 mmol, 2 equiv) of imidazole. The reaction was stirred at ambient temperature for 16 h before being added to brine, extracted twice into CH_2Cl_2, dried over Na_2SO_4, and concentrated. The resulting residue was purified by silica gel flash chromatography eluting with 1:1 to 0:1 hex./EtOAc to yield 542 mg (47%, 3 steps) of the desired mixture of isomers as a tan foam.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.78 (br s, 1H), 7.66 (d, J = 7.5 Hz, 1H), 7.35 (d, J = 7.8 Hz, 1H), 7.13 (m, 2H), 6.98 (s, 1H), 3.64 (m, 4H), 3.22−2.86 (m, 4H), 2.28−2.59 (m, 2H), 2.07 (m, 1H), 1.70−1.10 (m, 6H), 0.90 (s, 9H), 0.80 (m, 4H), 0.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0, 169.7, 136.6, 127.7, 122.5, 122.0, 119.3, 118.9, 113.0, 112.9, 111.6, 60.9, 60.6, 51.6, 50.8, 48.5, 48.4, 39.4, 38.5, 36.6, 36.4, 33.1, 31.8, 31.3, 26.2, 23.9, 23.4, 23.2, 20.7, 18.5, 12.1, 11.1; IR (NaCl, film) 3254, 1626 cm^{-1}; HRMS (+TOF) $[M + H]^+$ 429.2932 calcd for $C_{25}H_{41}N_2O_2Si$, found 429.2933; R_f 0.30 (1:1 hex./EtOAc)

To a 25-mL round-bottomed flask containing 373 mg (0.870 mmol, 1 equiv) of the above produced mixture of lactams dissolved in 9 mL of dry MeCN was added 1.40 mL (17.4 mmol, 20 equiv) of dry pyridine followed by 406 μL (4.35 mmol, 5 equiv) of $POCl_3$. The reaction was heated to 40 °C for 3 h before being concentrated, taken up in 9 mL of dry MeOH, and cooled to 0 °C. To this solution was added 33 mg of $NaBH_4$ and the reaction was allowed to warm to ambient temperature over 15 min before being added to $NaHCO_{3(sat.)}$, extracted into EtOAc, dried over Na_2SO_4, and concentrated. The crude residue was purified by silica gel flash chromatography eluting with 4:1 to 0:1 hex./EtOAc to yield 142 mg (40%) of the desired trans product **27** as a tan foam along with 113 mg (31%) of the cis product **24** as a tan foam.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (br s, 1H), 7.47 (d, J = 7.2 Hz, 1H), 7.3 (d, J = 7.2 Hz, 1H), 7.11 (m, 2H), 3.73 (m, 2H), 3.13 (m, 3H), 3.00 (m, 1H), 2.72 (m, 1H), 2.59 (td, J = 11.1, 5.4 Hz, 1H), 2.19 (d, J = 11.7 Hz, 1H), 2.10 (t, J = 10.8 Hz, 1H), 1.94 (m, 1H), 1.68 (m, 1H), 1.26−1.51 (m, 4H), 1.16 (m, 1H), 0.932 (s, 12H), 0.10 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.1, 135.1, 127.6, 121.4, 119.5, 118.3, 110.8, 108.3, 61.1, 60.7, 60.0, 53.4, 41.9, 37.3, 35.9, 35.8, 26.1, 23.6, 21.8, 18.5, 11.2, −5.0.; HRMS (+TOF) $[M + H]^+$ 413.2983 calcd for $C_{25}H_{41}N_2O_2Si$, found 413.2985; R_f 0.17 (4:1 hex./EtOAc).

Synthesis of (±)-Dihydrocorynantheol (10). To a 25-mL round-bottomed flask containing 71 mg (0.17 mmol, 1 equiv) of compound **27** was added 1 mL of dry MeOH followed by a spatula tip of PPTS. The reaction was heated at reflux for 3 h, added to 1 N NaOH, extracted twice with CH_2Cl_2, dried over Na_2SO_4, and concentrated. The resultant residue was purified by silica gel flash chromatography eluting with 10% to 20% MeOH in CH_2Cl_2 to yield 46 mg (90%) of the title compound as a white foam.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.04 (br s, 1H), 7.41 (d, J = 7.5 Hz, 1H), 7.29 (d, J = 7.8 Hz, 1H), 7.08 (m, 2H), 3.61 (t, J = 6.0 Hz, 2H), 3.58 (br s, 1H), 3.00 (m, 4H), 2.69 (m, 1H), 2.47 (m, 1H), 2.16 (m, 1H), 1.88 (t, J = 11.4 Hz, 1H), 1.79 (m, 1H), 1.53 (m, 1H), 1.39 (m, 1H), 0.97−1.29 (m, 5H), 0.84 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.4, 134.5, 127.1, 121.3, 119.3, 118.1, 111.3, 107.3, 60.1, 59.9, 53.1, 50.5, 41.3, 37.0, 35.1, 34.9, 23.4, 21.4, 11.0; IR (NaCl, film) 3256, 2813, 2757 cm^{-1}; HRMS (+TOF) $[M + H]^+$ 299.2118 calcd for $C_{19}H_{27}N_2O$, found 299.2116; R_f 0.16 (10% MeOH in CH_2Cl_2). Spectroscopic properties agree in all respects with those previously reported.[17,18]

Synthesis of 1-(3,4-Dimethoxyphenethyl)-5-ethyl-4-(2-hydroxyethyl)piperidin-2-one (30). To a 25-mL round-bottomed flask containing 85 mg (0.42 mmol, 1 equiv) of **20** was added 4.2 mL of dry THF, 114 mg (0.631 mmol, 1.5 equiv) of 2-(3,4-dimethoxyphenyl)ethanamine (**29**), and then 178 mg (0.840 mmol, 2 equiv) of $NaBH(OAc)_3$. The reaction was allowed to stir at ambient temperature for 48 h before being added to $NaHCO_{3(sat.)}$, extracted three times with EtOAc, dried over Na_2SO_4, and concentrated. Purification by silica gel flash chromatography eluting with 5% to 20% MeOH in CH_2Cl_2 produced 95 mg (67%, 92% BRSM) of the desired product as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.69−6.76 (m, 3H), 3.82 (s, 3H), 3.80 (s, 3H) 3.58 (m, 3H), 3.44 (m, 1H), 3.06 (dd, J = 12.0, 4.8 Hz, 1H), 2.93 (dd, J = 12.3, 7.5 Hz, 1H), 2.81 (m, 1H), 2.75 (t, J = 7.5 Hz, 2H), 2.27 (m, 2H), 2.02 (m, 1H), 1.66 (m, 1H), 1.53 (m, 1H), 1.11−1.32 (m, 3H), 0.82 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.4, 148.8, 147.5, 131.5, 120.7, 112.0, 111.2, 60.2, 55.9, 50.6, 49.1, 38.4, 36.3, 33.0, 31.5, 31.4, 20.5, 12.0; IR (NaCl, film) 3406, 1621 cm^{-1}; HRMS (+TOF) $[M + H]^+$ 336.2169 calcd for $C_{19}H_{30}NO_4$, found 336.2174; R_f 0.23 (5% MeOH in CH_2Cl_2).

Synthesis of 2-(1-(3,4-Dimethoxyphenethyl)-5-ethyl-2-oxopiperidin-4-yl)ethyl Acetate. To a 10-mL round-bottomed flask containing 45 mg (0.13 mmol, 1 equiv) of alcohol **30** dissolved in 1 mL of dry CH_2Cl_2 and 1 mL of pyridine was added 19 μL (0.027 mmol, 2 equiv) of AcCl followed by a single crystal of DMAP. The reaction was stirred for 30 min at ambient temperature before being added to $NaHCO_{3(sat.)}$, extracted into CH_2Cl_2, dried over Na_2SO_4, and concentrated. Purification by silica gel flash chromatography eluting with 10% MeOH in CH_2Cl_2 yielded 50 mg (99%) of the desired product as a pale yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.74 (m, 3H), 4.06 (m, 2H), 3.84 (s, 3H), 3.82 (s, 3H), 3.52 (m, 2H), 3.08 (dd, J = 12.3, 4.8 Hz, 1H), 2.96 (dd, J = 12.3, 7.2 Hz, 1H), 2.79 (t, J = 7.8 Hz, 2H), 2.31 (qd, J = 17.4, 6.3 Hz, 2H), 2.02 (s, 3H), 2.00 (m, 1H), 1.67 (m, 2H), 1.26 (m, 3H), 0.84 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 168.9, 149.0, 147.7, 131.7, 120.9, 112.2, 111.4, 62.6, 56.1, 50.7, 49.3, 38.4, 36.4, 33.2, 32.3, 28.1, 21.2, 20.4, 12.1; IR (NaCl, film): 1737, 1640 cm^{-1}; HRMS (+TOF) $[M + H]^+$ 378.2275 calcd for $C_{21}H_{32}NO_5$, found 378.2280.

Synthesis of 2-((2*R*,3*S*,11b*S*)-3-Ethyl-9,10-dimethoxy-2,3,4,6,7,11b-hexahydro-1*H*-pyrido[2,1-*a*]isoquinolin-2-yl)ethyl Acetate (31). To a 25-mL round-bottomed flask containing 190 mg (0.503 mmol, 1 equiv) of 2-(1-(3,4-dimethoxyphenethyl)-5-ethyl-2-oxopiperidin-4-yl)ethyl acetate dissolved in 5 mL of dry benzene was added 94.0 μL (1.06 mmol, 2 equiv) of freshly distilled $POCl_3$. The reaction was heated to reflux for 2 h before being concentrated, taken up in 5 mL of dry MeOH, and cooled to 0 °C. To this stirred solution was carefully added 19 mg (0.50 mmol, 1 equiv) of $NaBH_4$ and the reaction was allowed to warm to ambient temperature for 15 min. The reaction was added to $NaHCO_{3(sat.)}$, extracted three times with CH_2Cl_2, dried over Na_2SO_4, and concentrated. The resulting residue was purified by flash chromatography (10%$_{w/w}$ NEt_3 on silica gel) eluting with 4:1 to 0:1 hex./EtOAc to yield 142 mg (78%) of the desired product as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.66 (s, 1H), 6.55 (s, 1H), 4.16 (t, J = 6.3 Hz, 2H), 3.83 (s, 3H), 3.82 (s, 3H), 3.11−2.94 (m, 3H), 2.82 (dd, J = 10.8, 6 Hz, 1H), 2.55 (dd, J = 15.6, 3.0 Hz, 1H), 2.41 (td, J = 11.7, 3.9 Hz, 1H), 2.25 (dd, J = 11.4, 2.4 Hz, 1H), 2.06 (s, 3H), 1.99 (m, 1H), 1.82 (m, 1H), 1.67 (m, 3H), 1.45 (m, 1H), 1.27 (m, 2H), 0.90 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.5, 147.4, 147.2, 130.7, 127.2, 111.6, 108.0, 63.5, 63.1, 59.1, 56.3, 56.0, 53.2, 39.0, 37.5, 34.0, 32.3, 29.6, 21.3, 17.6, 12.8; IR (NaCl, film) 2802, 2748 (Bohlmann bands), 1737 cm^{-1}; HRMS (+TOF) $[M + H]^+$ 362.2326 calcd for $C_{21}H_{32}NO_4$, found 362.2331.

Synthesis of (±)-3-*epi*-Protoemetinol (11). To a 10-mL round-bottomed flask containing 95.0 mg (0.263 mmol, 1 equiv) of tetracycle **31** was added 2 mL of MeOH, 1 mL of H_2O, and finally 436 mg (3.15 mmol, 12 equiv) of anhydrous K_2CO_3. The reaction was stirred for 2 h at ambient temperature before being added to brine, extracted three times into CH_2Cl_2, dried over Na_2SO_4, and concentrated. The resulting residue was purified by silica gel flash chromatography eluting with 2% to 10% MeOH in CH_2Cl_2 to yield 84 mg (>99%) of the desired product as a white foam.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.67 (s, 1H), 6.56 (s, 1H), 3.83 (s, 3H), 3.82 (s, 3H), 3.71 (t, J = 6.8 Hz, 2H), 3.12−2.94 (m, 3H), 2.82 (dd, J = 10.8, 6.0 Hz, 1H), 2.56 (dd, J = 15.9, 3.0 Hz, 1H), 2.41 (td, J = 11.7, 3.9 Hz, 1H), 2.25 (dd, J = 11.4, 2.4 Hz, 1H), 1.99 (m, 1H), 1.87 (m, 2H), 1.59 (m, 3H), 1.45 (m, 1H), 1.26 (m, 2H), 0.90 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.5, 147.2, 130.9, 127.3, 111.7, 108.2, 63.6, 61.0, 59.3, 56.3, 56.0, 53.3, 39.2, 36.9, 36.6, 34.0, 29.6, 17.7, 12.9; IR (NaCl, film) 3387, 2803, 2749 cm^{-1}(Bohlmann bands); HRMS (+TOF) $[M + H]^+$ 320.2220 calcd for $C_{19}H_{30}NO_3$, found 320.2221; R_f 0.54 (10% MeOH in CH_2Cl_2). All spectral data were in agreement with previous reports.[19]

Synthesis of a Mixture of Alcohols 30 and 33. To a 25-mL flame-dried round-bottomed flask containing 410 mg (2.05 mmol, 1 equiv) of lactone **21** dissolved in 10 mL of dry THF at −78 °C was dropwise added 2.15 mL (2.15 mmol, 1.05 equiv) of a 1.0 M solution of DIBAL-H in THF. The reaction was stirred at −78 °C for 30 min before being added to a saturated solution of Rochelle's salt, extracted three times with CH_2Cl_2, dried over Na_2SO_4, and concentrated to yield 351 mg (84%) of a mixture of lactol isomers, which was used without further purification. To a 50-mL round-bottomed flash containing 290 mg (1.43 mmol, 1 equiv) of the above produced mixture of lactol isomers dissolved in 7 mL of dry THF was added 390 mg (2.15 mmol, 1.5 equiv) of 2-(3,4-dimethoxyphenyl)ethanamine (**29**) dissolved in 7 mL of dry THF. To this mixture was added 909 mg (4.29 mmol, 3 equiv) of $NaBH(OAc)_3$ and the reaction was stirred at ambient temperature for 24 h before being added to $NaHCO_{3(sat.)}$, extracted into CH_2Cl_2, dried over Na_2SO_4, and concentrated. The resulting residue was purified by silica gel chromatography eluting with 5% to 20% MeOH in CH_2Cl_2 to yield 195 mg (41%) of the desired mixture of products.

^{1}H NMR (300 MHz, $CDCl_3$) (mixture of epimers) δ 7 (m, 3H), 3.79 (m, 8H), 3.58 (m, 3H), 3.48 (m, 1H), 3.00 (m, 2H), 2.73 (t, J = 7.5 Hz, 2H, 2.52−2.18 (m, 2H), 1.97 (m, 1H), 1.72−1.51 (m, 2H), 1.19 (m, 3H), 0.77 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) (mixture of epimers) δ 169.9, 169.6 149.0, 147.7, 131.7, 120.9, 120.8, 112.2, 112.0, 111.4, 60.3, 59.8, 56.1, 51.7, 50.8, 49.4, 41.0, 39.6, 38.6, 36.4, 36.0, 35.3, 33.3, 33.2, 31.7, 31.6, 23.8, 20.7, 12.2, 11.2; IR (NaCl, film) 3385, 1621 cm^{-1}; HRMS (+TOF) $[M + H]^+$ 336.2169 calcd for $C_{19}H_{30}NO_4$, found 336.2174; R_f 0.33 (5% MeOH in EtOAc).

Synthesis of 2-((2*R*,3*R*,11b*S*)-3-Ethyl-9,10-dimethoxy-2,3,4,6,7,11b-hexahydro-1*H*-pyrido[2,1-*a*]isoquinolin-2-yl)ethyl Acetate (34). To a 25-mL round-bottomed flask containing 195 mg (0.549 mmol, 1 equiv) of a mixture of alcohols **30** and **33** dissolved in 5 mL of dry CH_2Cl_2 and 1 mL of dry pyridine was added 76 mL (1.10 mmol, 2 equiv) of AcCl followed by a single crystal of DMAP. The reaction was stirred at ambient temperature for 30 min before being added to $NaHCO_{3(sat.)}$, extracted into CH_2Cl_2, dried over Na_2SO_4, and concentrated. The resulting residue was purified by silica gel flash chromatography eluting with 1% to 10% MeOH in CH_2Cl_2 to yield 204 mg (>99%) of the desired mixture of products.

To a 25-mL round-bottomed flask containing 164 mg (0.434 mmol, 1 equiv) of the above produced acetate mixture dissolved in 5 mL of dry benzene was added 81.0 μL (0.869 mmol, 2 equiv) of freshly distilled $POCl_3$. The reaction was heated to reflux for 2 h before being concentrated, taken up in 5 mL of dry MeOH, and cooled to 0 °C. To this stirred solution was carefully added 17 mg (0.43 mmol, 1 equiv) of $NaBH_4$ and the reaction was allowed to warm to ambient temperature for 15 min. The reaction was added to $NaHCO_{3(sat.)}$, extracted three times with CH_2Cl_2, dried over Na_2SO_4, and concentrated. The resulting residue was purified by flash chromatography (10%$_{w/w}$ NEt_3 on silica gel) eluting with 4:1 to 0:1 hex./EtOAc to yield 64 mg (41%) of the desired product (**34**) as a colorless oil as well as 55 mg (35%) of the C3 epimer (**31**).

(19) Nuhant, P.; Raikar, S. B.; Wypych, J.-C.; Delpech, B.; Marazano, C. *J. Org. Chem.* **2009**, *74*, 9413–9421.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.66 (s, 1H), 6.56 (s, 1H), 4.17 (t, J = 6.3 Hz, 2H), 3.85 (s, 3H), 3.83 (s, 3H), 3.03 (m, 4H), 2.61 (dd, J = 15.6, 3.0 Hz, 1H), 2.45 (td, J = 11.4, 3.9 Hz, 1H), 2.31 (m, 1H), 2.05 (s, 3H), 2.00 (m, 2H), 1.66 (m, 1H), 1.42 (m, 3H), 1.27−1.07 (m, 2H), 0.90 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.4, 147.6, 147.3, 130.1, 126.9, 111.6, 108.2, 62.8, 61.6, 56.3, 56.0, 52.7, 41.4, 38.2, 37.4, 31.9, 29.4, 23.7, 21.3, 11.3; IR (NaCl, film) 2802, 2748 (Bohlmann bands), 1737 cm^{-1}; HRMS (+TOF) $[M + Na]^+$ 384.2145 calcd for $C_{21}H_{31}NNaO_4$, found 384.2147.

Synthesis of (±)-Protoemetinol (12). To a 10-mL round-bottomed flask containing 61.0 mg (0.169 mmol, 1 equiv) of acetate **34** was added 1 mL of MeOH, 0.5 mL of H_2O, and finally 280 mg (2.03 mmol, 12 equiv) of anhydrous K_2CO_3. The reaction was stirred for 2 h at ambient temperature before being added to brine, extracted three times into CH_2Cl_2, dried over Na_2SO_4, and concentrated. The resulting residue was purified by silica gel flash chromatography eluting with 2% to 10% MeOH in CH_2Cl_2 to yield 54 mg (>99%) of the desired product as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.66 (s, 1H), 6.55 (s, 1H), 3.82 (s, 3H), 3.81 (s, 3H), 3.72 (m, 2H), 3.14−2.94 (m, 4H), 2.60 (d, J = 16.4 Hz, 1H), 2.46 (td, J = 11.6, 4.0 Hz, 1H), 2.32 (d, J = 13.2 Hz, 1H), 2.01 (m, 1H), 1.90 (m, 1H), 1.63 (m, 1H), 1.41 (m, 3H), 1.23 (m, 2H), 1.09 (m, 1H), 0.89 (t, J = 7.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.5, 147.2, 129.9, 126.7, 111.5, 108.4, 62.8, 61.5, 60.4, 56.2, 55.9, 52.5, 41.2, 37.7, 37.2, 35.9, 29.1, 23.5, 11.2; IR (NaCl, film) 3373, 2801, 2751 cm^{-1} (Bohlmann bands); HRMS (+TOF) $[M + H]^+$ 320.2220 calcd for $C_{19}H_{30}NO_3$, found 320.2224; R_f 0.46 (10% MeOH in CH_2Cl_2). All spectral data were in agreement with previous reports.[19,20]

Acknowledgment. We gratefully acknowledge financial support from the National Institutes of Health (Grant GM068011). Mass spectra were obtained on instruments supported by the National Institutes of Health Shared Instrumentation Grant No. GM49631. We also gratefully acknowledge an Eli Lilly Graduate Fellowship to B.J.E. from Eli Lilly. This paper is dedicated to Professor Raymond L. Funk of Pennsylvania State University on the occasion of his 60th birthday.

Supporting Information Available: Additional experimental details and spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(20) (a) Battersby, A. B.; Kapil, B. S.; Bhakuni, D. S.; Popli, S. P.; Merchant, J. R.; Salgar, S. S. *Tetrahedron Lett*. **1966**, 4965–4971. (b) Chang, J.-K.; Chang, B.-R.; Chuang, Y.-H.; Chang, N.-C. *Tetrahedron* **2008**, *64*, 9685–9688.