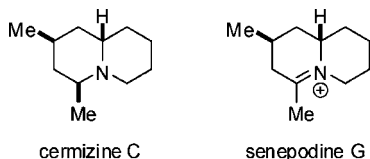# JOC*Note*

Total Synthesis of (−)-Senepodine G and (−)-Cermizine C

Barry B. Snider* and James F. Grabowski

Department of Chemistry, MS 015, Brandeis University, Waltham, Massachusetts 02454-9110

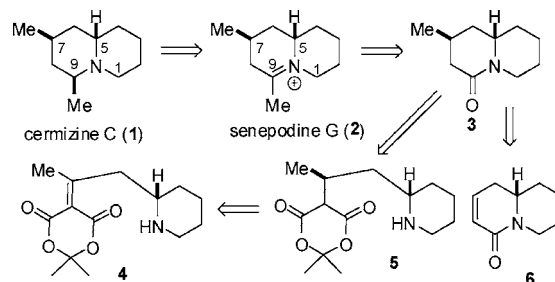*snider@brandeis.edu*

Received October 5, 2006

cermizine C   senepodine G

An efficient, stereospecific synthesis of the alkaloids senepodine G (**2**) and cermizine C (**1**) has been completed using the BF$_3$·Et$_2$O-promoted stereospecific addition of Me$_2$CuLi to α,β-unsaturated lactam **6** to provide lactam **3**, the addition of MeMgBr followed by HCl to convert **3** to senepodine G (**2**) (six steps, 40% overall yield), and the stereospecific NaBH$_4$ reduction of **2** to give cermizine C (**1**) (seven steps, 40% overall yield).

Kobayashi recently reported the isolation of the lycopodium alkaloid cermizine C (**1**) from the club moss *Lycopodium cernuum* and the related alkaloid senepodine G (**2**) from the club moss *Lycopodium chinense* (see Scheme 1).[1-3] The structures were elucidated by 1D and 2D NMR spectroscopic methods. Senepodine G (**2**) is cytotoxic to murine lymphoma L1210 cells with an IC$_{50}$ of 7.8 μg/mL. The absolute configuration of other co-occurring more complex natural products was assigned by modified Mosher's method suggesting that the absolute configurations of **1** and **2** are as drawn.

We set out to synthesize these novel alkaloids as a means of developing chemistry that might be useful for more complex members of these families. We thought that it should be possible to prepare cermizine C (**1**) from senepodine G (**2**) by reduction of the iminium cation with NaBH$_4$. Although similar reductions are known,[2b,4] the stereoselectivity of this reduction is uncertain because steric interactions with the methyl group should direct hydride attack from the bottom face, whereas steric interactions with the right-hand ring should direct hydride attack from the top face. Iminium cation **2** can be prepared by addition of MeMgBr to lactam **3** followed by treatment with HCl. We conceived of two approaches to lactam **3**. We hoped that it might be possible to carry out a directed conjugate reduction of unsaturated Meldrum's acid derivative **4** to give

(1) Morita, H.; Hirasawa, Y.; Shinzato, T.; Kobayashi, J. *Tetrahedron* **2004**, *60*, 7015–7023.

(2) For the isolation of other members of these families, see: (a) Morita, H.; Hirasawa, Y.; Yoshida, N.; Kobayashi, J. *Tetrahedron Lett.* **2001**, *42*, 4199–4201. (b) Hirasawa, Y.; Morita, H.; Kobayashi, J. *Tetrahedron* **2003**, *59*, 3567–3573. (c) Hirasawa, Y.; Morita, H.; Kobayashi, J. *Heterocycles* **2004**, *64*, 515–521.

(3) For a review of lycopodium alkaloids, see: Ma, X.; Gang, D. R. *Nat. Prod. Rep.* **2004**, *21*, 752–772.

(4) Bohlmann, F.; Winterfeldt, E.; Boroschewski, G.; Mayer-Mader, R.; Gatscheff, B. *Chem. Ber.* **1963**, *96*, 1792–1800.

SCHEME 1. Retrosynthesis of Cermizine C (1) and Senepodine G (2)

5, which would cyclize to form lactam **3**. Alternatively, it might be possible to add methylcuprate stereospecifically to unsaturated lactam **6**.

Knoevenagel condensations between a ketone and a β-dicarbonyl compound are typically carried out using an ammonium acetate catalyst. Because (±)-pelletierine (**7**)[5] contains a secondary amine, we treated it with 1 equiv of AcOH to form the acetate salt. Heating this salt with 2.4 equiv of Meldrum's acid in EtOH required 2 days at 60 °C for the complete consumption of the pelletierine. To our surprise, we did not isolate **4**, but rather the β,γ-unsaturated lactam **11** in 68% yield. Equilibration of **11** with K$_2$CO$_3$ in MeOH for 1 day afforded a 3:1 mixture of α,β-unsaturated lactam **13** and β,γ-unsaturated lactam **11**. Treatment of pure **13** with K$_2$CO$_3$ and MeOH afforded the identical 3:1 mixture indicating that equilibrium had been reached. Although α,β-unsaturated carbonyl compounds are usually much more stable than their β,γ-unsaturated isomers, there are examples of both isomers are present at equilibrium.[6] Ban prepared **13** by treatment of *N*-acetylpelletierine with triethyloxonium tetrafluoroborate in CH$_2$Cl$_2$ and then treatment of the resulting intermediate with *t*-BuOK in *t*-BuOH.[7] These conditions presumably led to the same 3:1 equilibrium mixture of **13** and **11** that we observed.

Presumably, the Knoevenagel condensation of **7** and Meldrum's acid occurred to give **4**, which cyclized readily to give the conjugated lactam acid **8**. Equilibration afforded the unconjugated isomer **9**, which decarboxylated to give enol **10**. Kinetic protonation of **10** on the α-carbon formed the β,γ-unsaturated lactam **11**. These reaction conditions, with the amine neutralized as the acetate salt, are mild enough to prevent equilibration to give α,β-unsaturated lactam **13**.

Hydrogenation of either **11** or the 3:1 mixture of **11** and **13** over PtO$_2$ in EtOH at 50 psi of H$_2$ for 6 h as described by Ban afforded a 16:1 mixture of lactams **12** and **3** in 96% yield. Addition of MeMgBr (4 equiv) in THF to **12** at 60 °C for 2.5 h followed by addition of 3 M HCl in MeOH afforded (±)-7-*epi*-senepodine G (**14**) in 100% yield (Scheme 2). A similar reaction at 25 °C gave **14** in 76% yield. Reduction of **14** with NaBH$_4$ in MeOH at 25 °C for 10 min occurred stereospecifically by axial attack from the less-hindered top face to provide (±)-5-*epi*-cermizine C (**15**) in 82% yield.[8] The stereochemistry of

(5) Quick, J.; Oterson, R. *Synthesis* **1976**, 745–746.

(6) (a) Meghani, P.; Joule, J. A. *J. Chem. Soc., Perkins Trans. 1* **1988**, 1–8. (b) Janecki, T.; Bodalski, R.; Wieczorek, M.; Bujacz, G. *Tetrahedron* **1995**, *51*, 1721–1740.

(7) (a) Ban, Y.; Kimura, M.; Oishi, T. *Heterocycles* **1974**, *2*, 323–328. (b) Ban, Y.; Kimura, M.; Oishi, T. *Chem. Pharm. Bull.* **1976**, *24*, 1490–1496.

SCHEME 2. Synthesis of 5-*epi*-Cermizine C (15) and 7-*epi*-Senepodine G (14)

SCHEME 3. Synthesis of Cermizine C (1) and Senepodine G (2)
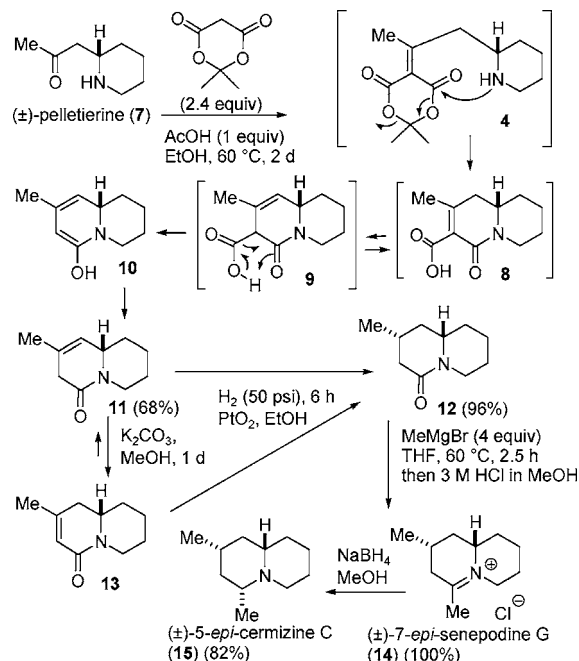
15 was established by NOE studies (see Supporting Information) permitting the assignment of the stereochemistry of the major lactam as **12**, not **3**.

Because we could not isolate **4** and explore the directed conjugate reduction to give **5**, we turned our attention to the alternate route to senepodine G starting with unsaturated lactam **6**. Batey prepared amide alcohol **17** by protection of 2-piperidineethanol (**16**) with TBDMSCl, acylation, and deprotection.[9] We found that reaction of (S)-**16**[10] with 3 equiv of (diethoxyphosphoryl)acetyl chloride[11] and 3.1 equiv of Et(i-Pr)$_2$N in THF afforded the crude ester amide. The ester was selectively hydrolyzed with K$_2$CO$_3$ in EtOH at 60 °C for 4.5 h to provide amide alcohol **17** in 81% yield (see Scheme 3). Dess–Martin oxidation (79% yield) and intramolecular Horner–Wadsworth–Emmons Wittig reaction (80% yield) as described by Batey[9] provided a practical route to optically pure α,β-unsaturated lactam (S)-**6**.

Conjugate addition of Me$_2$CuLi promoted by BF$_3$·Et$_2$O[12] occurred selectively by axial attack from the less-hindered top face to give a > 99:1 mixture of the desired lactam **3** and the epimeric lactam **12** in 80% yield. A similar addition of Me$_2$CuLi promoted by TMSCl[13] gave a 14:1 mixture of **3** and

12 in 77% yield. Addition of MeMgBr (4 equiv) to **3** in THF at 60 °C for 2.5 h followed by addition of 3 M HCl in MeOH afforded a 98% yield of (−)-senepodine G (**2**), with spectral data identical to those reported for the natural product.[1] Lactam **3** was recovered unchanged from treatment with MeMgBr at 25 °C, although the epimeric lactam **12** was converted to **14** in 76% yield under these conditions. Presumably, the methyl group blocks the convex face of **3**. The methyl group of **12** is on the concave face making the top, convex face less hindered so that addition of MeMgBr occurs under milder conditions.

Reduction of **2** with NaBH$_4$ in MeOH at 25 °C for 10 min provided (−)-cermizine C (**1**), which was isolated as its hydrochloride salt in 82% yield.[8] The spectral data for cermizine hydrochloride (**1**) are identical to those reported for the natural product,[1] which was isolated in minute amounts (2.2 mg) and not indicated to be the protonated form. Hydride addition to **2** took place stereospecifically by axial attack from the bottom face. Apparently the directing effect of the methyl group is greater than that of the right-hand ring (see Figure 1).
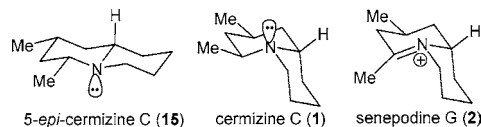
FIGURE 1. Stable conformations of 5-*epi*-cermizine C (**15**), cermizine C (**1**), and senepodine G (**2**).

Neutralization of the hydrochloride salt of **1** gave the free amine, which is not stable in air. On the other hand, the free base of 5-*epi*-cermizine C (**15**) is stable in air. The stable conformation of 5-*epi*-cermizine C (**15**) is a *trans*-quinolizidine, as indicated by a Bohlmann band at 2783 cm^{-1}, while the most stable conformation of cermizine C (**1**) was shown to be a *cis*-quinolizidine by Kobayashi (see Figure 1).[1] *cis*-Quinolizidines have been reported to react with air to give N-oxides more

(8) In 1935, Ochiai reported the addition of MeMgI to **12** or its diastereomer, followed by high-pressure hydrogenation to give **14** or a diastereomer: Ochiai, E.; Tsuda, K.; Yokoyama, J. *Chem. Ber.* **1935**, *68*, 2291−2298. For a related conversion of a lactam to a methyl quinolizidine with MeMgBr and NaBH$_3$CN, see: Comins, D. L.; Zheng, Z.; Goehring, R. R. *Org. Lett.* **2002**, *4*, 1611−1613.
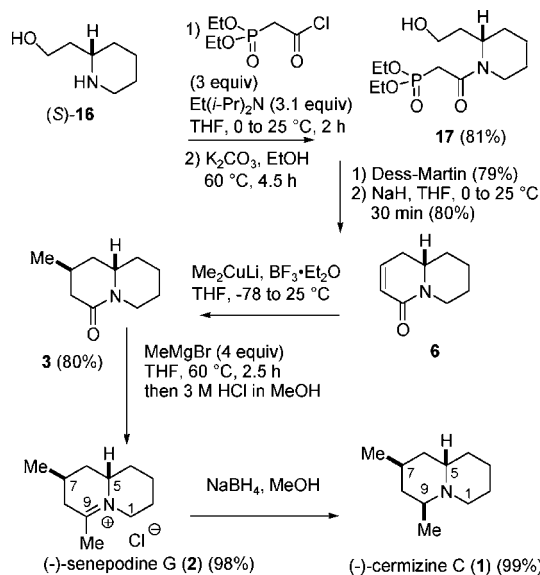
(9) (a) Grzyb, J. A.; Batey, R. A. *Tetrahedron Lett.* **2003**, *44*, 7485−7488. (b) Grzyb, J. A.; Shen, M.; Yoshina-Ishii, C.; Chi, W.; Brown, R. S.; Batey, R. A. *Tetrahedron* **2005**, *61*, 7153−7175.

(10) (a) Toy, M. S.; Price, C. C. *J. Am. Chem. Soc.* **1960**, *82*, 2613−2616. (b) Beyerman, H. C.; Van Den Bosch, S.; Breuker, J. H.; Maat, L. *Recl. Trav. Chim. Pays-Bas* **1971**, *90*, 755−764. (c) Craig, J. C.; Lee, S.-Y. C.; Pereira, W. E., Jr.; Beyerman, H. C.; Maat, L. *Tetrahedron* **1978**, *34*, 501−504.

(11) Teichert, A.; Jantos, K.; Harms, K.; Studer, A. *Org. Lett.* **2004**, *6*, 3477−3480.

(12) (a) Yamamoto, Y.; Yamamoto, S.; Yatagai, H.; Ishihara, Y.; Maruyama, K. *J. Org. Chem.* **1982**, *47*, 119−126. (b) Smith, A. B., III; Jerris, P. J. *J. Am. Chem. Soc.* **1981**, *103*, 194−195.

(13) (a) Matsuzawa, S.; Horiguchi, Y.; Nakamura, E.; Kuwajima, I. *Tetrahedron* **1989**, *45*, 349−362. (b) Nakamura, E.; Yamanaka, M.; Mori, S. *J. Am. Chem. Soc.* **2000**, *122*, 1826−1827. (c) Alexakis, A.; Berlan, J.; Besace, Y. *Tetrahedron Lett.* **1986**, *27*, 1047−1050.

readily than *trans*-quinolizidines.[14] Quinolizidines are also known to readily scavenge carbon dioxide from the air to form bicarbonate salts.[15]

The optical rotation of synthetic senepodine G (**2**), [α]$_D$ −77, has the same sign as that of natural senepodine G, [α]$_D$ −35,[1] suggesting that the natural product has the absolute configuration shown. The difference in magnitude may result from errors resulting from the small amount (1 mg) of the natural product available. The optical rotation of synthetic cermizine C (**1**), [α]$_D$ −2, has the opposite sign as that of natural cermizine C, [α]$_D$ +4.[1] However, Kobayashi indicated that the [α]$_D$ value of cermizine C is not reliable due to the small amount of sample and the small value of the optical rotation. It is most likely that cermizine C has the same absolute configuration as senepodine G, although this need not be the case because they were isolated from different *Lycopodium* species. Because of the low value, the [α]$_D$ of cermizine C is not very useful. We have therefore provided the CD spectra of synthetic senepodine G (**2**) and cermizine C (**1**) from 200 to 400 nm in the Supporting Information. These data may be more useful for comparison purposes.

In conclusion, we have developed an efficient, stereospecific synthesis of the alkaloids senepodine G (**2**) and cermizine C (**1**) using the BF$_3$·Et$_2$O-promoted stereospecific addition of Me$_2$-CuLi to α,β-unsaturated lactam **6** to give lactam **3**, the addition of MeMgBr followed by HCl to convert **3** to senepodine G (**2**) (six steps, 40% overall yield), and the stereospecific NaBH$_4$ reduction of **2** to give cermizine C (**1**) (seven steps, 40% overall yield).

Experimental Section

3,6,7,8,9,9a-Hexahydro-2-methyl-(4*H*)-quinolizin-4-one (11). Meldrum's acid (778 mg, 5.40 mmol) and AcOH (0.26 mL, 4.5 mmol) were added in succession to a solution of pelletierine (**7**)[5] (636 mg, 4.50 mmol) in EtOH (5 mL), and the resulting clear solution was heated to 60 °C and stirred for 1 day. The yellow solution was allowed to cool; an aliquot was concentrated under reduced pressure, and the ¹H NMR spectrum indicated that there was a 3:1 mixture of **11** and **7** and that no Meldrum's acid remained. Meldrum's acid (778 mg, 5.40 mmol) was added to the yellow solution, and the resulting solution was heated to 60 °C and stirred for 1 day. The EtOH was removed under reduced pressure, and the resulting yellowish liquid was diluted with EtOAc (30 mL). The resulting solution was washed with a saturated Na$_2$CO$_3$ solution (6 mL), dried over MgSO$_4$, and concentrated under reduced pressure to give 638 mg of a yellowish liquid. Flash chromatography on silica gel (EtOAc) yielded 503 mg (68%) of **11**: ¹H NMR 5.30 (br s, 1), 4.85 (ddd, 1, *J* = 12.5, 2.4, 2.4), 3.75 (br d, 1, *J* = 11.0), 2.86 (br d, 1, *J* = 20.8), 2.83 (br d, 1, *J* = 20.8), 2.46 (ddd, 1, *J* = 12.8, 12.5, 2.5), 1.92−1.78 (m, 3), 1.70 (s, 3), 1.58−1.35 (m, 2), 1.23 (dddd, 1, *J* = 12.2, 12.2, 11.0, 3.7); ¹³C NMR 166.0, 128.9, 120.1, 58.2, 42.1, 36.3, 34.3, 25.3, 24.7, 21.8; IR (neat) 1644; HRMS (ES) calcd for C$_{10}$H$_{16}$NO (MH$^+$) 166.1232, found 166.1228.

(2*S**,5*R*)-2-Octahydro-2-methyl-(4*H*)-quinolizin-4-one (12). PtO$_2$ (8 mg, 0.03 mmol) was added to a solution of **11** (440 mg, 2.66 mmol) in EtOH (4 mL), and the resulting suspension was shaken under 50 psi of H$_2$ for 6 h. The catalyst was removed by filtration through Celite, and the resulting solution was concentrated under reduced pressure to give 425 mg (96%) of a 16:1 mixture of **12** and **3** as a clear liquid.

The spectral data for **12** were determined from the mixture: ¹H NMR 4.76 (br d, 1, *J* = 13.8), 3.17 (dddd, 1, *J* = 11.0, 11.0, 6.7, 2.5), 2.45 (ddd, 1, *J* = 16.4, 3.4, 3.4), 2.39 (br dd, 1, *J* = 13.8, 12.8), 1.98−1.66 (m, 6), 1.46−1.30 (m, 2), 1.26−1.10 (m, 2), 0.97 (d, 3, *J* = 6.1); ¹³C NMR 169.4, 56.6, 41.8, 41.1, 39.5, 34.5, 26.4, 25.3, 24.2, 21.2; IR (neat) 1643. The spectral data match those previously reported for **12**.[7]

1,6,7,8,9,9a-Hexahydro-2-methyl-(4*H*)-quinolizin-4-one (13). K$_2$CO$_3$ (293 mg, 2.12 mmol) was added to a solution of **11** (35 mg, 0.21 mmol) in MeOH (2 mL), and the resulting suspension was stirred at 25 °C for 22 h. The suspension was filtered through Celite and MgSO$_4$, and the resulting solution was concentrated under reduced pressure to give 35 mg of a 3:1 mixture of **13** and **11**. Flash chromatography on silica gel (EtOAc) yielded 3 mg of **13**, followed by 29 mg of a 3:1 mixture of **13** and **11**, and 1 mg of **11**.

Data for **13**: ¹H NMR 5.69 (s, 1), 4.48 (br d, 1, *J* = 13.0), 3.42−3.35 (m, 1), 2.50 (br dd, 1, *J* = 13.0, 12.6), 2.37 (dd, 1, *J* = 17.4, 6.1), 2.15 (br dd, 1, *J* = 17.4, 9.8), 1.90−1.65 (m, 3), 1.86 (s, 3), 1.55−1.35 (m, 3); ¹³C NMR 166.3, 149.0, 120.0, 54.6, 42.7, 36.3, 33.4, 24.8, 23.9, 22.7; IR (neat) 1674, 1612. The spectral data match those previously reported.[7]

K$_2$CO$_3$ (8 mg, 0.06 mmol) was added to a solution of **13** (1 mg, 0.006 mmol) in MeOH (1 mL), and the resulting suspension was stirred at 25 °C for 22 h. The suspension was filtered through Celite and MgSO$_4$, and the resulting solution was concentrated under reduced pressure to give 1 mg of a 3:1 mixture of **13** and **11**.

7-*epi*-Senepodine G Chloride (14). A 1.4 M solution of MeMgBr in 3:1 toluene/THF (0.84 mL, 1.2 mmol) was added dropwise to a solution of **12** (49 mg, 0.29 mmol) in dry THF (4 mL), and the resulting solution was stirred at 60 °C for 2.5 h. The solution was allowed to cool. MeOH (5 mL) was added, and the resulting solution was concentrated under reduced pressure. HCl (3 M) in MeOH (2 mL) was added, and the resulting solution was concentrated under reduced pressure. Flash chromatography on silica gel (70:29:1 CH$_2$Cl$_2$/MeOH/3 M HCl in MeOH) yielded 59 mg (100%) of **14** as a clear wax: ¹H NMR (CD$_3$OD) 4.51 (br d, 1, *J* = 12.5), 3.95−3.80 (m, 1), 3.43 (br dd, 1, *J* = 12.5, 12.2), 2.94 (br d, 1, *J* = 20.8), 2.58−2.40 (m, 1), 2.47 (s, 3), 2.20−2.10 (m, 2), 2.06−1.68 (m, 5), 1.57 (dddd, 1, *J* = 12.2, 12.2, 12.2, 4.3), 1.36 (ddd, 1, *J* = 12.4, 12.4, 12.4), 1.04 (d, 3, *J* = 6.7); ¹³C NMR (CD$_3$OD) 188.8, 64.3, 54.6, 44.1, 38.5, 34.9, 26.1, 24.6, 24.1, 23.6, 20.4; HRMS (EI) calcd for C$_{11}$H$_{20}$N (M$^+$) 166.1596, found 166.1599.

5-*epi*-Cermizine C (15). NaBH$_4$ (4 mg, 0.104 mmol) was added to a solution of **14** (19 mg, 0.094 mmol) in MeOH (4 mL), and the resulting suspension was stirred at 25 °C for 10 min. AcOH (∼2 drops) was then added, and the resulting solution was concentrated under reduced pressure. The residue was diluted with a 3:1 H$_2$O/saturated Na$_2$CO$_3$ solution (4 mL), and the resulting aqueous solution was extracted with EtOAc (3 × 10 mL). The combined extracts were dried over MgSO$_4$ and concentrated under reduced pressure to give 13 mg (82%) of **15** as a clear oil: ¹H NMR (CD$_3$OD) 3.35−3.27 (m, 1), 2.20−2.10 (m, 1), 2.02−1.92 (m, 1), 1.84 (br dd, 1, *J* = 11.9, 11.9), 1.76−1.50 (m, 6), 1.40−1.25 (m, 2), 1.14−0.88 (m, 3), 1.12 (d, 3, *J* = 6.1), 0.90 (d, 3, *J* = 6.1); ¹³C NMR (CD$_3$OD) 64.4, 62.1, 52.5, 43.9, 42.6, 33.8, 31.4, 26.4, 24.9, 22.1, 19.8; IR (neat) 2926, 2783; HRMS (ES) calcd for C$_{11}$H$_{22}$N (MH$^+$) 168.1752, found 168.1752. TFA (excess) was added to a solution of **5** in CD$_3$OD: ¹H NMR (CD$_3$OD) 3.79 (br d, 1, *J* = 12.5, H$_{1eq}$), 3.21−3.10 (m, 1, H$_9$), 3.06 (br dd, 1, *J* = 11.3, 11.3, H$_5$), 2.74 (ddd, 1, *J* = 12.8, 12.5, 2.5, H$_{1ax}$), 2.15−1.65 (m, 7, contains H$_7$), 1.62−1.48 (m, 2), 1.40−1.24 (m, 2), 1.37 (d, 3, *J* = 6.7), 0.98 (d, 3, *J* = 6.1).

(Diethoxyphosphoryl)acetyl Chloride. (Diethoxyphosphoryl)-acetic acid (3.001 g, 15.3 mmol) was added dropwise to thionyl chloride (3 mL), and the resulting solution was stirred at 25 °C

(14) Nizamkhodzhaeva, A. N.; Ishbaev, A. I.; Aslanov, Kh. A.; Mukhamedzhanov, S. Z. *Chem. Abstr.* **1978**, *88*, 121499v.

(15) Moynehan, T. M.; Schofield, K.; Jones, R. A. Y.; Katritzky, A. R. *J. Chem. Soc.* **1962**, 2637−2658.

for 1.75 h and concentrated under reduced pressure (<20 °C) to give (diethoxyphosphoryl)acetyl chloride which was used without further purification. The spectral data matched those previously reported.[11]

Diethyl{2-[(2S)-2-(2-hydroxyethyl)piperidin-1-yl]-2-oxoethyl}-phosphonate (17). A solution of (diethoxyphosphoryl)acetyl chloride (3.283 g, 15.3 mmol) in dry THF (6 mL) was added dropwise to a solution of (S)-2-piperdineethanol[10b] (659 mg, 5.10 mmol) in dry THF at 0 °C. (The detailed procedure for the resolution of 2-piperidineethanol is provided in the Supporting Information.) EtN(i-Pr)$_2$ (2.8 mL, 16 mmol) was added dropwise to the yellow suspension, and the resulting dark orange suspension was stirred at 0 °C for 1 h. The suspension was allowed to warm to 25 °C and was stirred for an additional 1 h. H$_2$O (50 mL) was added to the suspension, and the aqueous solution was extracted with EtOAc (4 × 120 mL). The combined extracts were dried over MgSO$_4$ and concentrated under reduced pressure to yield 3 g of the crude ester amide as a yellowish liquid, which was used without purification.

K$_2$CO$_3$ (3.524 g, 25.5 mmol) was added to a solution of crude ester amide (3 g) in dry EtOH (40 mL), and the resulting suspension was heated to 60 °C and stirred for 4.5 h. The suspension was allowed to cool, and excess EtOH was removed under reduced pressure. The residue was diluted in EtOAc (100 mL), and the suspension was filtered through Celite. The resulting solution was concentrated under reduced pressure to give 3 g of a dark yellow oil. Flash chromatography on silica gel (39:1 to 23:2 CH$_2$Cl$_2$/MeOH) yielded 1.264 g (81% from (S)-2-piperdineethanol) of **17** as a light yellow oil: $[\alpha]^{23}_D$ −29 (c 1.0, CHCl$_3$); IR (neat) 3424, 2941, 1624, 1450, 1248; HRMS (ES) calcd for C$_{13}$H$_{27}$NO$_5$P (MH$^+$) 308.1627, found 308.1638; the ^{1}H NMR and ^{13}C NMR spectra indicated a complex mixture of amide rotamers that match those previously reported[9] and are available in the Supporting Information.

Diethyl {2-Oxo-2-[(2S)-2-(2-oxoethyl)piperidin-1-yl]ethyl} Phosphonate. Dess−Martin reagent (840 mg, 1.98 mmol) was added to a solution of **17** (484 mg, 1.58 mmol) in dry CH$_2$Cl$_2$ (15 mL), and the resulting suspension was stirred for 15 h at 25 °C. The suspension was filtered through Celite and K$_2$CO$_3$, and the resulting solution was concentrated under reduced pressure to give 1.314 g of a white solid. Flash chromatography on silica gel (49:1 EtOAc/Et$_3$N) yielded 383 mg (79%) of the aldehyde as a clear oil: $[\alpha]^{23}_D$ −22 (c 1.0, CHCl$_3$); the spectral data match those previously reported.[9]

(2S)-1,6,7,8,9,9a-Hexahydro-(4H)-quinolizin-4-one (6). NaH (60% dispersion in oil, 43 mg, 1.1 mmol) was added to a solution of the above aldehyde (312 mg, 1.02 mmol) in dry THF (20 mL) at 0 °C, and the resulting suspension was allowed to warm to 25 °C over 30 min. The orange solution was diluted with H$_2$O (20 mL) and CH$_2$Cl$_2$, and the organic and aqueous layers were separated. The aqueous layer was extracted with EtOAc (3 × 80 mL), and the combined organic extracts were dried over MgSO$_4$. The resulting solution was concentrated under reduced pressure to give 180 mg of a clear oil. Flash chromatography on silica gel (49:1 CH$_2$Cl$_2$/MeOH) afforded 124 mg (80%) of **6** as a clear oil: $[\alpha]^{23}_D$ +47 (c 1.0, CHCl$_3$); the spectral data match those previously reported.[9]

(2S,5S)-2-Octahydro-2-methyl-(4H)-quinolizin-4-one (3). MeLi (1.6 M) in Et$_2$O (4.0 mL, 6.4 mmol) was added dropwise to a suspension of CuI (625 mg, 3.28 mmol) in dry THF (20 mL) at 0 °C, and the resulting solution was stirred at 0 °C for 30 min. The solution was cooled to −78 °C, and BF$_3$·OEt$_2$ (0.41 mL, 3.2 mmol) was added dropwise. The resulting solution was stirred at −78 °C for 5 min. A solution of **6** (242 mg, 1.60 mmol) in dry THF (10 mL) was added dropwise, and the resulting solution was allowed to warm to 25 °C over 20 min. Saturated NH$_4$Cl solution (40 mL) was added, and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 100 mL), and the combined extracts

were dried over MgSO$_4$. The resulting solution was concentrated under reduced pressure to give 456 mg of a yellow amorphous solid. Flash chromatography on silica gel (49:1 to 23:1 CH$_2$Cl$_2$/MeOH) gave 215 mg (80%) of **3** as an oil: $[\alpha]^{23}_D$ −21 (c 1.0, CHCl$_3$); ^{1}H NMR 4.76 (dddd, 1, J = 13.1, 4.0, 2.0, 2.0), 3.37−3.29 (m, 1), 2.46 (br d, 1, J = 16.5), 2.41 (ddd, 1, J = 13.1, 12.8, 3.0), 2.11−2.00 (m, 1), 1.97 (dd, 1, J = 16.5, 9.2), 1.92−1.84 (m, 1), 1.72−1.32 (m, 7), 0.98 (d, 3, J = 6.1); ^{13}C NMR 168.5, 55.5, 43.0, 40.6, 36.8, 33.6, 25.4, 25.0, 24.4, 20.4; IR (neat) 1639; HRMS (EI) calcd for C$_{10}$H$_{17}$NO (M$^+$) 167.1310, found 167.1313.

Alternatively, TMSCl was used to promote the conjugate addition according to the following procedure: 1.6 M MeLi in Et$_2$O (0.35 mL, 0.56 mmol) was added dropwise to a suspension of CuI (56 mg, 0.29 mmol) in dry THF (3 mL) at 0 °C, and the resulting solution was stirred at 0 °C for 30 min. The solution was cooled to −78 °C, and a solution of **6** (21 mg, 0.14 mmol) and TMSCl (0.035 mL, 0.28 mmol) in dry THF (2 mL) was added dropwise. The resulting solution was allowed to warm to 25 °C over 1 h. Saturated NH$_4$Cl solution (5 mL) was added, and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 10 mL), and the combined extracts were dried over Na$_2$SO$_4$. The resulting solution was concentrated under reduced pressure to give 30 mg of a yellow amorphous solid. Flash chromatography on silica gel (49:1 to 24:1 CH$_2$Cl$_2$/MeOH) gave 18 mg (77%) of a 14:1 mixture of **3** and **12** as an oil.

Senepodine G Chloride (2). MeMgBr (1.4 M) in 3:1 toluene/THF (0.36 mL, 0.50 mmol) was added dropwise to **3** (21 mg, 0.13 mmol) in dry THF (4 mL), and the resulting solution was heated to 60 °C for 2.5 h. The solution was allowed to cool. MeOH (5 mL) was added, and the resulting solution was concentrated under reduced pressure. HCl (3 M) in MeOH (2 mL) was added, and the resulting solution was concentrated under reduced pressure. Flash chromatography on silica gel (70:29:1 CH$_2$Cl$_2$/MeOH/3 M HCl in MeOH) yielded 25 mg (98%) of **2** as a clear wax: $[\alpha]^{23}_D$ −77 (c 1.0, MeOH), lit.[1] $[\alpha]^{26}_D$ −35 (c 0.3, MeOH); ^{1}H NMR (CD$_3$OD) 4.51 (br d, 1, J = 12.8), 4.25−3.93 (m, 1), 3.55 (br dd, 1, J = 12.8, 12.8), 3.01 (dd, 1, J = 20.7, 4.3), 2.55−2.42 (m, 1), 2.46 (s, 3), 2.10−1.72 (m, 9), 1.05 (d, 3, J = 6.7); ^{13}C NMR (CD$_3$OD) 186.9, 64.8, 56.1, 43.9, 35.5, 34.7, 27.6, 24.7, 23.9, 21.9, 20.5; HRMS (EI) calcd for C$_{11}$H$_{20}$N (M$^+$) 166.1596, found 166.1599. The spectral data match those reported for the natural product.[1]

Cermizine C Hydrochloride (1). NaBH$_4$ (5 mg, 0.1 mmol) was added to a solution of **2** (25 mg, 0.12 mmol) in MeOH (4 mL), and the resulting suspension was stirred at 25 °C for 10 min. HCl (3 M) in MeOH (1 mL) was added, and the resulting solution was concentrated under reduced pressure. The residue was diluted with 3:1 CH$_2$Cl$_2$/MeOH (10 mL), and the resulting suspension was filtered to remove inorganic solids, dried over Na$_2$SO$_4$, and concentrated under reduced pressure to give 25 mg (99%) of **1** as a clear wax: $[\alpha]^{23}_D$ −2 (c 0.4, MeOH), lit.[1] $[\alpha]^{25}_D$ +4 (c 0.8, MeOH); ^{1}H NMR (CD$_3$OD) 3.90−3.80 (m, 1), 3.68−3.55 (m, 2), 3.08 (ddd, 1, J = 13.4, 13.4, 3.0), 2.17 (dddd, 1, J = 13.4, 13.4, 13.4, 4.3), 2.06−1.54 (m, 9), 1.38−1.20 (m, 1), 1.33 (d, 3, J = 6.1), 0.95 (d, 3, J = 6.7); ^{13}C NMR (CD$_3$OD) 61.3, 51.2, 49.9, 41.7, 38.3, 25.4, 24.6, 23.8, 21.6, 18.4, 17.7; HRMS (EI) calcd for C$_{11}$H$_{21}$N (M$^+$) 167.1673, found 167.1674. The spectral data match those reported for the natural product.[1]

Supporting Information Available: General procedures, details of NOE experiments on **15**, and copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

JO062067W