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

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Abstract

An efficient, stereospecific synthesis of the alkaloids senepodine G (**2**) and cermizine C (**1**) has been completed using the $\text{BF}_3 \cdot \text{Et}_2\text{O}$ promoted stereospecific addition of Me_2CuLi to α,β -unsaturated lactam **6** to provide lactam **3**, the addition of MeMgBr followed by HCl to convert **3** to senepodine G (**2**) (6 steps, 40% overall yield) and the stereospecific NaBH_4 reduction of **2** to give cermizine C (**1**) (7 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).^{1,2,3} 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 $\mu\text{g/mL}$. The absolute configuration of other co-occurring more complex natural products were 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 **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. Since ($\pm$)-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_2CO_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** 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 isomer, there are examples of unsaturated amides in which significant amounts of both isomers are present at equilibrium.⁶ Ban prepared **13** by treatment of *N*-acetyl pelletierine with triethyloxonium tetrafluoroborate in CH_2Cl_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 PtO₂ in EtOH at 50 psi H₂ 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 ($\pm$)-7-*epi*-senepodine G (**14**) in 100% yield. A similar reaction at 25 °C gave **14** in 76% yield. Reduction of **14** with NaBH₄ in MeOH at 25 °C for 10 min occurred stereospecifically by axial attack from the less hindered top face to provide ($\pm$)-5-*epi*-cermizine C (**15**) in 82% yield.⁸ The stereochemistry of **15** was established by NOE studies (see supporting material) permitting the assignment of the stereochemistry of the major lactam as **12**, not **3**.

Since 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 chloride¹¹ and 3.1 equiv of Et(*i*-Pr)₂N in THF afforded the crude ester amide. The ester was selectively hydrolyzed with K₂CO₃ 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 Batey⁹ provided a practical route to optically pure α,β -unsaturated lactam (*S*)-**6**.

Conjugate addition of Me₂CuLi promoted by BF₃·Et₂O¹² 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 Me₂CuLi promoted by TMSCl¹³ 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 NaBH₄ 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).

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 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**), $[\alpha]_D -77$, has the same sign as that of natural senepodine G, $[\alpha]_D -35$,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**), $[\alpha]_D -2$, has the opposite sign as that of natural cermizine C, $[\alpha]_D +4$.¹ However, Kobayashi indicated that the $[\alpha]_D$ value of cermizine C is not reliable due to the small amount of sample and 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 since they were isolated from different *Lycopodium* species. Because of the low value, the $[\alpha]_D$ of cermizine C is not very useful. We have therefore provided the CD spectra of synthetic senepodine G (**2**) and cermizine C (**1**) from 200–400 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 $\text{BF}_3 \cdot \text{Et}_2\text{O}$ promoted stereospecific addition of Me_2CuLi to α,β -unsaturated lactam **6** to give lactam **3**, the addition of MeMgBr followed by HCl to convert **3** to senepodine G (**2**) (6 steps, 40% overall yield) and the stereospecific NaBH_4 reduction of **2** to give cermizine C (**1**) (7 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 d. 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 d. 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_2CO_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, $J = 12.2, 12.2, 11.0, 3.7$); ^{13}C 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 $\text{C}_{10}\text{H}_{16}\text{NO}$ (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, $J = 6.1$); ^{13}C 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-(4H)-quinolizin-4-one (13)

K₂CO₃ (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 MgSO₄ 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

K₂CO₃ (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 MgSO₄ 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. 3 M HCl in MeOH (2 mL) was added and the resulting solution was concentrated under reduced pressure. Flash chromatography on silica gel (70:29:1 CH₂Cl₂/MeOH/3 M HCl in MeOH) yielded 59 mg (100%) of **14** as a clear wax: ¹H NMR (CD₃OD) 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 (CD₃OD) 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 C₁₁H₂₀N (M⁺) 166.1596, found 166.1599.

5-*epi*-Cermizine C (15)

NaBH₄ (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 H₂O/saturated Na₂CO₃ solution (4 mL) and the resulting aqueous solution was extracted with EtOAc (3 × 10 mL). The combined extracts were dried over MgSO₄ and concentrated under reduced pressure to give 13 mg (82%) of **15** as a clear oil: ¹H NMR (CD₃OD) 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 (CD₃OD) 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 C₁₁H₂₂N (MH⁺) 168.1752, found 168.1752. TFA (excess) was added to a solution of **5** in CD₃OD: ¹H NMR (CD₃OD) 3.79 (br d, 1, *J* = 12.5, H_{1eq}), 3.21-3.10 (m, 1, H₉), 3.06 (br dd, 1, *J* = 11.3, 11.3, H₅), 2.74 (ddd, 1, *J* = 12.8, 12.5, 2.5, H_{1ax}), 2.15-1.65 (m, 7, contains H₇), 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 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-piperidineethanol^{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. H₂O (50 mL) was added to the suspension and the aqueous solution was extracted with EtOAc (4 × 120 mL). The combined extracts were dried over MgSO₄ and concentrated under reduced pressure to 3 g of the crude ester amide as a yellowish liquid, which was used without purification.

K₂CO₃ (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 CH₂Cl₂/MeOH) yielded 1.264 g (81% from (*S*)-2-piperidineethanol) of **17** as a light yellow oil: [α]_D²³ -29 (*c* 1.0, CHCl₃); IR (neat) 3424, 2941, 1624, 1450, 1248; HRMS (ES) calcd for C₁₃H₂₇NO₅P (MH⁺) 308.1627, found 308.1638; the ¹H NMR and ¹³C NMR spectra indicated a complex mixture of amide rotamers that match those previously reported⁹ 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 CH₂Cl₂ (15 mL) and the resulting suspension was stirred for 15 h at 25 °C. The suspension was filtered through Celite and K₂CO₃ and the resulting solution was concentrated under reduced pressure to 1.314 g of a white solid. Flash chromatography on silica gel (49:1 EtOAc/Et₃N) yielded 383 mg (79%) of the aldehyde as a clear oil: [α]_D²³ -22 (*c* 1.0, CHCl₃); 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 H₂O (20 mL) and CH₂Cl₂ 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 MgSO₄. The resulting solution was concentrated under reduced pressure to give 180 mg of a clear oil. Flash chromatography on silica gel (49:1 CH₂Cl₂/MeOH) afforded 124 mg (80%) of **6** as a clear oil: [α]_D²³ +47 (*c* 1.0, CHCl₃); the spectral data match those previously reported.⁹

(2S,5S)-2-Octahydro-2-methyl-(4H)-quinolizin-4-one (3)

1.6 M MeLi in Et₂O (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 BF₃·OEt₂ (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 NH₄Cl 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 MgSO₄. 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 CH₂Cl₂/MeOH) gave 215 mg (80%) of **3** as an oil: [α]_D²³ -21 (*c* 1.0, CHCl₃); ¹H

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 $\text{C}_{10}\text{H}_{17}\text{NO}$ (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_2O (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_4Cl 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_2SO_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 $\text{CH}_2\text{Cl}_2/\text{MeOH}$) gave 18 mg (77%) of a 14:1 mixture of **3** and **12** as an oil.

Senepodine G Chloride (**2**)

1.4 M MeMgBr 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. 3 M HCl in MeOH (2 mL) was added and the resulting solution was concentrated under reduced pressure. Flash chromatography on silica gel (70:29:1 $\text{CH}_2\text{Cl}_2/\text{MeOH}/3$ M HCl in MeOH) yielded 25 mg (98%) of **2** as a clear wax: $[\alpha]^{23}_{\text{D}} -77$ (c 1.0, MeOH), lit.¹ $[\alpha]^{26}_{\text{D}} -35$ (c 0.3, MeOH); ^1H NMR (CD_3OD) 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_3OD) 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 $\text{C}_{11}\text{H}_{20}\text{N}$ (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. 3 M HCl in MeOH (1 mL) was added and the resulting solution was concentrated under reduced pressure. The residue was diluted with 3:1 $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (10 mL) and resulting suspension was filtered to remove inorganic solids, dried over Na_2SO_4 and concentrated under reduced pressure to give 25 mg (99%) of **1** as a clear wax: $[\alpha]^{23}_{\text{D}} -2$ (c 0.4, MeOH), lit.¹ $[\alpha]^{25}_{\text{D}} +4$ (c 0.8, MeOH); ^1H NMR (CD_3OD) 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_3OD) 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 $\text{C}_{11}\text{H}_{21}\text{N}$ (M^+) 167.1673, found 167.1674. The spectral data match those reported for the natural product.¹

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References and Notes

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Figure 1.
Stable conformations of 5-*epi*-cermizine C (**15**), cermizine C (**1**) and senepodine G (**2**).

SCHEME 1.

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

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**)