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Enantioselective synthesis of (*S*)-1,6,7,8,9,9a-hexahydroquinolizin-4-one. Formal synthesis of the lycopodium alkaloids senepodine G and cermizine C

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ABSTRACT

The synthesis of the title compound, a key intermediate in the synthesis of some lycopodium and lupin alkaloids, is reported. From a stereochemical standpoint the key steps are the stereoselective cyclocondensation of ketodiester **1** with (*R*)-phenylglycinol and the stereocontrolled reduction, with retention of configuration, of the oxazolidine ring in the resulting oxazolopiperidone lactam **2**.

1. Introduction

Senepodine G and cermizine C are two quinolizidine alkaloids, which were isolated in 2004 from the club moss *Lycopodium chinense* and *Lycopodium cernuum*, respectively (Fig. 1).[1] Senepodine G exhibits cytotoxicity against murine lymphoma L120 cells. Last year a stereospecific total synthesis of these alkaloids was reported, thus confirming the proposed structures.[2]

A key intermediate of the synthesis was unsaturated lactam **7**, which was prepared in enantiopure form from (*S*)-2-piperidinethanol. A stereoselective conjugate addition of Me_2CuLi in the presence of $BF_3{\cdot}Et_2O$ was used to introduce the C-2 methyl substituent with the required configuration, whereas a MeMgBr addition followed by HCl was used to install the C-4 methyl group. The synthesis of cermizine C required a subsequent stereoselective $NaBH_4$ reduction step.

In the racemic series, unsaturated lactam **7** has also been used as a key intermediate in the total synthesis of the lupin alkaloids, leontiformine and leontiformidine.[3]

In the context of our studies on the enantioselective synthesis of piperidine-containing natural products from phenylglycinol-derived oxazolopiperidone lactams,[4] we herein report a convenient synthesis of enantiopure unsaturated hexahydroquinolizin-4-one **7**.

The key step is the stereoselective cyclocondensation of the achiral ketodiester **1**, which already incorporates the nine carbon atoms present in the target lactam **7**, and (*R*)-phenylglycinol, which acts as a chiral and latent form of ammonia. In this step, a stereocenter at the nitrogen α-position is generated and the resulting enantiopure oxazolopiperidone lactam incorporates a butyrate chain that allows the construction of the quinolizidone ring.

The synthetic sequence is outlined in Scheme 1.

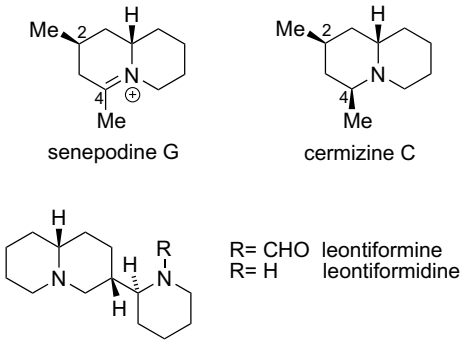

Figure 1. Quinolizidine alkaloids synthesized from unsaturated lactam **7**.

2. Results and discussion

Treatment of a toluene solution of ketodiester **1**[5] with (*R*)-phenylglycinol in the presence of a catalytic amount of AcOH in a Dean–Stark apparatus gave a mixture (87% overall yield) of bicyclic lactam **2** and its C-8a epimer (8a-*epi*-**2**), which were easily separated by column chromatography. The major isomer **2** was isolated in 73% yield.

Next, $LiAlH_4$ reduction of **2** brought about both the reduction of the lactam and ester carbonyl groups and the reductive opening of the oxazolidine ring, which took place with complete retention of configuration,[6] to give piperidine diol **3** in 68% yield.[7]

Hydrogenation of **3** in the presence of $(Boc)_2O$ using $Pd(OH)_2$ as the catalyst afforded the protected piperidine alcohol derivative **4** in 83% yield, which was then oxidized (86% yield) with PDC in DMF to give acid **5**. A somewhat less satisfactory route to **5** was the Dess–Martin oxidation of alcohol **4** (78%) followed by $NaClO_2$ oxidation of the resulting aldehyde (85%). Deprotection of **5** with TMSCl followed by heating of the resulting amino acid in refluxing xylene gave enantiopure quinolizidin-4-one **6** in 72% yield.[8]

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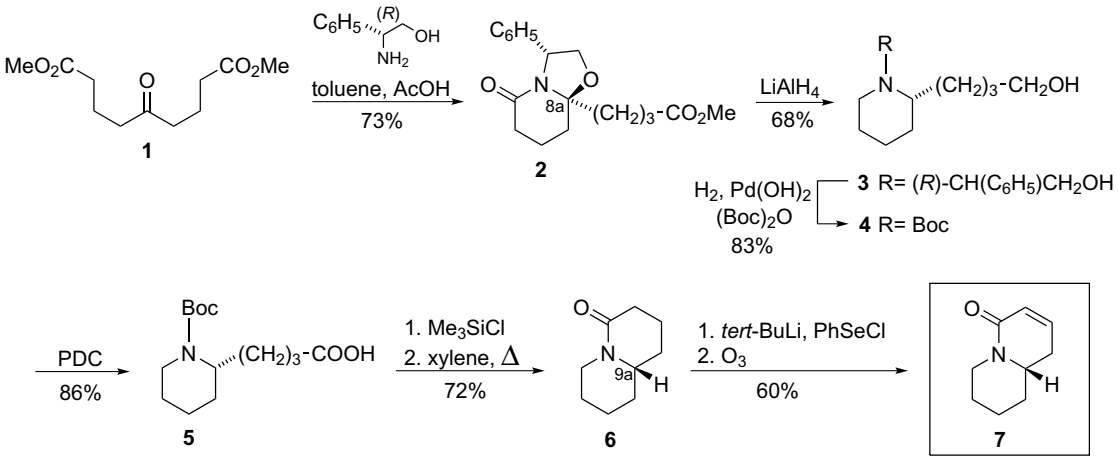

Scheme 1. Enantioselective synthesis of unsaturated lactam **7**.

Finally, bicyclic lactam **6** was converted to the target unsaturated lactam **7** by treatment with *tert*-BuLi and PhSeCl, followed by ozonolysis of the resulting mixture of seleno derivatives.[9]

The above preparation of the partially reduced quinolizin-4-one **7**, a key intermediate in the synthesis of quinolizidine alkaloids, illustrates further the potential of phenylglycinol-derived oxazolopiperidone lactams[10] for the enantioselective synthesis of piperidine-containing natural products.

3. Experimental

All non-aqueous reactions were performed under an inert atmosphere. Drying of the organic extracts during the workup of reactions was performed over anhydrous Na_2SO_4 or $MgSO_4$. Evaporation of solvents was accomplished with a rotatory evaporator. Thin-layer chromatography was carried out on SiO_2 (Silica Gel 60 F_{254}), and the spots were located by UV or 1% aqueous $KMNO_4$. Chromatography refers to flash column chromatography and was carried out on SiO_2 (Silica Gel 60, SDS, 35–70 μ). Melting points were determined in a capillary tube and are uncorrected. Unless otherwise indicated, NMR spectra were recorded in $CDCl_3$ at 200 or 300 MHz (^{1}H) and 50.3 or 75.4 MHz (^{13}C). The chemical shifts are reported as δ values, in parts per million (ppm) relative to TMS (0 ppm) or relative to residual chloroform (7.26 ppm, 77.0 ppm) as an internal standard. IR spectra were recorded on a Nicolet 205 FT-IR spectrophotometer with samples prepared as thin films on NaCl salt plates, and only noteworthy absorptions are listed. Optical rotations were measured on a Perkin–Elmer 241 polarimeter using a 1 dm cell with a total volume of 1 mL. THF was distilled from sodium/benzophenone. Anhydrous solvents for reactions were distilled at atmospheric pressure prior to use and dried using standard procedures. Microanalyses were performed by the Centre d'Investigació i Desenvolupament (CSIC), Barcelona. High-resolution mass spectra (HRMS) were performed by the Unidade de Espectrometria de Masas, Santiago de Compostela and Unitat d'Espectrometria de Masses (SCT), Barcelona.

3.1. Methyl (3*R*,8a*R*)-5-oxo-3-phenyl-2,3,5,6,7,8-hexahydrooxazolo[3,2-*a*]piperidine-8a-butyrate 2

(*R*)-Phenylglycinol (4.6 g, 33.4 mmol) was added to a solution of ketodiester **1** (6.4 g, 27.8 mmol) and AcOH (2.4 mL, 41.7 mol) in toluene (240 mL). The mixture was heated at reflux for 7 h with azeotropic elimination of water produced by a Dean–Stark apparatus. The resulting mixture was cooled and concentrated to give an oil. Flash chromatography (1:1 hexane–EtOAc to EtOAc) afforded lactam **2** (6.5 g, 73%) and 8a-*epi*-**2** (1.2 g, 14%). Compound **2** (higher R_f): IR (NaCl) 1735, 1650 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.41–1.99 (m, 8H), 2.24–2.70 (m, 4H), 3.60 (s, 3H, CH_3), 3.86 (dd, J = 8.8, 8.0 Hz, 1H, H-3), 4.50 (t, J = 8.8 Hz, 1H, H-2), 5.36 (t, J = 8.0 Hz, 1H, H-2), 7.15–7.38 (m, 5H, H-Ar); ^{13}C NMR ($CDCl_3$, 50,3 MHz) δ 16.7 (CH_2), 19.4 (CH_2), 30.7 (CH_2), 30.8 (CH_2), 33.3 (CH_2), 33.8 (CH_2), 51.5 (CH_3), 58.5 (CH), 69.4 (CH_2), 95.6 (C), 125.4 (CH-*o*), 127.1 (CH-*p*), 128.5 (CH-*m*), 139.8 (C-*i*), 169.7 (CO), 173.4 (CO); $[\alpha]_D^{22} = -94.2$ (*c* 1.0, MeOH); Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.30; N, 4.41. Found: C, 68.07; H, 7.28; N, 4.33. Compound 8a-*epi*-**2** (lower R_f): IR (NaCl) 1733, 1650 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.61–2.00 (m, 8H), 2.22–2.45 (m, 4H), 3.70 (s, 3H, CH_3), 3.92 (dd, J = 9.3, 1.8 Hz, 1H, H-3), 4.40 (dd, J = 9.3, 7.2 Hz, 1H, H-2), 4.94 (dd, J = 7.2, 1.8 Hz, 1H, H-2), 7.26–7.30 (m, 5H, H-Ar); ^{13}C NMR ($CDCl_3$, 75,4 MHz) δ 16.8 (CH_2), 19.3 (CH_2), 29.8 (CH_2), 30.1 (CH_2), 33.2 (CH_2), 33.5 (CH_2), 51.5 (CH_3), 58.9 (CH), 71.2 (CH_2), 94.8 (C), 126.1 (CH-*o*), 127.2 (CH-*p*), 128.4 (CH-*m*), 141.5 (C-*i*), 167.2 (CO), 173.4 (CO); $[\alpha]_D^{22} = -50.6$ (*c* 1.2, MeOH); Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.30; N, 4.41. Found: C, 67.90; H, 7.29; N, 4.31.

3.2. (*S*)-1-[(*R*)-1-Phenyl-2-hydroxyethyl]piperidine-2-butanol 3

At first $LiAlH_4$ (239 mg, 6.3 mmol) was slowly added to a cooled solution (0 °C) of lactam **2** (200 mg, 0.63 mmol) in anhydrous THF (10 mL), and the mixture was stirred at rt for 1 h. The reaction mixture was quenched with water, and the resulting mixture was extracted with EtOAc. The organic extracts were dried and concentrated, and the resulting residue was chromatographed (EtOAc to 98:2 EtOAc–MeOH) to give alcohol **3** (119 mg, 68%) as an oil: IR (NaCl) 3383 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.05–1.84 (m, 13H), 2.37–2.45 (m, 1H), 2.85–2.91 (m, 1H), 3.59 (dd, J = 10.5, 5.7 Hz, 1H), 3.68 (t, J = 6.3 Hz, 2H), 3.98 (t, J = 10.5 Hz, 1H), 4.29 (dd, J = 10.5, 5.7 Hz, 1H), 7.17–7.34 (m, 5H, H-Ar); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 20.5 (CH_2), 24.1 (CH_2), 26.4 (CH_2), 31.4 (CH_2), 32.2 (CH_2), 33.2 (CH_2), 45.5 (CH_2), 57.2 (CH), 59.5 (CH_2), 60.5 (CH), 62.7 (CH_2), 127.6 (CH-*o*), 128.1 (CH-*p*), 128.8 (CH-*m*), 135.9 (C-*i*); $[\alpha]_D^{22} - 84.7$ (*c* 0.9, MeOH); HMRS calcd for $C_{17}H_{27}NO_2$ ($M+H^+$): 278.2120, found: 278.2115.

3.3. (*S*)-1-(*tert*-Butoxycarbonyl)piperidine-2-butanol 4

A solution of alcohol **3** (2.4 g, 8.7 mmol) and di-*tert*-butyl dicarbonate (3.8 g, 17.6 mmol) in EtOAc (300 mL) containing 40% $Pd(OH)_2$/C (960 mg) was stirred under hydrogen at rt for 24 h. The catalyst was removed by filtration through a Celite pad, and

the filtrate was concentrated to give a residue, which was chromatographed (8:2 to 1:1 hexane–EtOAc) to afford alcohol **4** (1.9 g, 83%): IR (NaCl) 3442, 1692 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.36–1.87 (m, 20H), 2.80–2.88 (m, 2H), 3.70 (t, J = 6.6 Hz, 2H), 4.04 (d, J = 12.9 Hz, 1H), 4.30 (s, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 18.8 (CH_2), 22.3 (CH_2), 25.5 (CH_2), 28.2 (CH_2), 28.3 ($3CH_3$), 29.2 (CH_2), 32.4 (CH_2), 38.6 (CH_2N), 50.1 (CHN), 62.3 (CH_2OH), 78.9 (C), 155.1 (CO); $[\alpha]_D^{22} = -32.6$ (c 1.0, MeOH); Anal. Calcd for $C_{14}H_{27}NO_3$: C, 65.33; H, 10.57; N, 5.44. Found: C, 65.08; H, 10.59; N, 5.38.

3.4. (*S*)-1-(*tert*-Butoxycarbonyl)piperidine-2-butanoic acid 5

3.4.1. Method A

PDC (23.2 g, 61.6 mmol) was added to a solution of alcohol **4** (2.6 g, 10.3 mmol) in anhydrous DMF (80 mL), and the mixture was stirred at rt for 24 h. The reaction mixture was quenched with water, and the resulting mixture was extracted with Et_2O. The organic extracts were dried and concentrated to give acid **5** (2.4 g, 86%) as an oil: IR (NaCl) 1689 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.26–1.80 (m, 18H), 2.36–2.42 (m, 2H), 2.73 (t, J = 12.5 Hz, 2H), 3.97 (d, J = 12.5 Hz, 1H), 4.22 (s, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 19.0 (CH_2), 21.4 (CH_2), 25.6 (CH_2), 28.5 (CH_2), 28.5 ($3CH_3$), 29.0 (CH_2), 33.7 (CH_2N), 38.7 (CH_2CO), 49.9 (CHN), 79.3 (C), 155.2 (CO), 178.7 (COOH); $[\alpha]_D^{22} = -40.8$ (c 1.0, MeOH); Anal. Calcd for $C_{14}H_{25}NO_4$: C, 61.97; H, 9.29; N, 5.16. Found: C, 61.54; H, 9.22; N, 4.92.

3.4.2. Method B

Dess–Martin reagent (850 mg, 2 mmol) was added to a solution of alcohol **4** (360 mg, 1.4 mmol) in anhydrous CH_2Cl_2 (6 mL), and the mixture was stirred at rt for 3 h. Then Et_2O (12 mL), 1 M aqueous $Na_2S_2O_4$ (2 mL), and saturated aqueous $NaHCO_3$ (2 mL) were added, and the resulting mixture was stirred for 45 min. The aqueous layer was extracted with Et_2O, and the combined organic extracts were washed with brine, dried, and concentrated. The resulting residue was chromatographed (7:3 hexane–EtOAc) to give crude (*S*)-1-(*tert*-butoxycarbonyl)piperidine-2-butanal (280 mg, 85%) as an oil: IR (NaCl) 1687 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.42–1.89 (m, 18H), 2.52–2.59 (m, 2H), 2.80 (t, J = 12 Hz, 2H), 4.04 (d, J = 12 Hz, 1H), 4.30 (s, 1H), 9.83 (s, 1H); ^{13}C NMR ($CDCl_3$, 75,4 MHz) δ 18.6 (CH_2), 18.8 (CH_2), 25.4 (CH_2), 28.3 (CH_2), 28.3 ($3CH_3$), 28.8 (CH_2), 38.5 (CH_2N), 43.3 (CH_2CO), 49.7 (CHN), 78.9 (C), 154.8 (CO), 202.0 (CHO); $[\alpha]_D^{22} = -17.7$ (c 1.0, MeOH).

A solution of the above aldehyde (1.3 g, 5 mmol) in CH_3CN (52 mL), *tert*-BuOH (155 mL), and 2-methyl-2-butene (3 mL) was stirred rapidly as it was cooled (0 °C). A solution of $NaClO_2$ (3.5 g, 39 mmol) and NaH_2PO_4 (552 mg, 4 mmol) in H_2O (60 mL) was added dropwise over a period of 10 min at 0 °C, and the mixture was then partitioned between EtOAc (300 mL) and brine (90 mL). The organic layer was washed with 1 M $Na_2S_2O_4$ (2 × 100 mL), dried, and concentrated. The resulting residue was chromatographed (1:1 hexane–EtOAc) to give acid **5** (1.1 g, 85%).

3.5. (*S*)-1,2,3,6,7,8,9,9a-Octahydroquinolizin-4-one 6

TMSCl (505 μL, 4 mmol) was added to a solution of acid **5** (537 mg, 2 mmol) in CH_3CN (12 mL) containing NaI (600 mg, 4 mmol). The mixture was stirred at rt for 1 h, filtered, and concentrated to give the crude amino acid (800 mg), which was used without further purification in the next step.

A solution of the above-mentioned amino acid in xylene (100 mL) was heated at reflux for 24 h with azeotropic elimination of water produced by a Dean–Stark apparatus. The resulting mixture was concentrated, and the residue was taken up in EtOAc and washed with brine. The combined organic extracts were dried and concentrated to give quinolizidin-4-one **6** (220 mg, 72%): IR (NaCl) 1637 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.27–1.86 (m, 9H), 1.90–2.05 (m, 1H), 2.32–2.44 (m, 3H), 3.10–3.30 (m, 1H), 4.75–4.82 (m, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 19.2 (CH_2), 24.5 (CH_2), 25.3 (CH_2), 30.5 (CH_2), 33.0 (CH_2), 34.0 (CH_2), 42.4 (CH_2), 56.8 (CH), 169.3 (CNO); $[\alpha]_D^{22} = -3.7$ (c 1.0, $CHCl_3$).

3.6. (*S*)-1,6,7,8,9,9a-Hexahydroquinolizin-4-one 7

At first *tert*-BuLi (0.4 mL of a 1.7 M solution in hexane, 0.7 mmol) was slowly added at −78 °C to a solution of **6** (70 mg, 0.45 mmol) in THF (5 mL), and the mixture was stirred for 20 min. Then, a solution of PhSeCl (95 mg, 0.5 mmol) in THF (2 mL) was slowly added, and the mixture was stirred at −78 °C for 2 h. Saturated aqueous NH_4Cl was added, and the resulting mixture was extracted with EtOAc. The combined organic extracts were dried and concentrated. The residue was chromatographed (7:3 hexane–EtOAc) affording the two C-3 epimers of (9a*S*)-3-(phenylselanyl)-1,2,3,6,7,8,9,9a-octahydroquinolizin-4-one. Higher R_f (45 mg, 33%): IR (NaCl) 1624 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.29–1.55 (m, 4H), 1.61–1.70 (m, 2H), 1.82–1.91 (m, 2H), 2.04–2.24 (m, 2H), 2.41 (td, J = 13.0, 3.0 Hz, 1H), 3.23–3.32 (m, 1H), 4.04 (dd, J = 5.0, 3.0 Hz, 1H), 4.72–4.79 (m, 1H), 7.27–7.29 (m, 3H, H-Ar), 7.65–7.68 (m, 2H, H-Ar); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 24.5 (CH_2), 25.3 (CH_2), 26.6 (CH_2), 28.2 (CH_2), 33.7 (CH_2), 43.5 (CH_2), 43.6 (CH), 56.9 (CH), 127.8 (CH-Ar), 128.9 (CH-Ar), 129.2 (C-*i*), 135.1 (CH-Ar), 167.8 (CNO). Lower R_f (51 mg, 37%): IR (NaCl) 1636 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.08–1.21 (m, 1H), 1.25–1.50 (m, 2H), 1.65–2.15 (m, 7H), 2.39 (td, J = 13.0, 3.0 Hz, 1H), 3.15–3.25 (m, 1H), 3.99 (t, J = 4.0 Hz, 1H), 4.69–4.76 (m, 1H), 7.27–7.30 (m, 3H, H-Ar), 7.68–7.71 (m, 2H, H-Ar); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 24.1 (CH_2), 25.1 (CH_2), 26.8 (CH_2), 27.2 (CH_2), 34.1 (CH_2), 42.6 (CH_2), 43.5 (CH), 56.9 (CH), 127.9 (CH-Ar), 128.9 (CH-Ar), 129.4 (C-*i*), 135.0 (CH-Ar), 168.3 (CNO).

A stream of ozone gas was bubbled through a cooled (−78 °C) solution of the above-mentioned mixture of selenides (220 mg, 0.71 mmol) in anhydrous CH_2Cl_2 (25 mL) until it turned pale blue. The solution was purged with O_2, and the temperature was slowly raised to 25 °C. After 30 min of stirring, the mixture was washed with brine, and the organic solution was dried and concentrated. The residue was chromatographed (7:3 hexane–EtOAc) to give **7** (92 mg, 85%) as an oil: IR (NaCl) 1668, 1614 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.38–1.55 (m, 3H), 1.72–1.85 (m, 3H), 2.14–2.25 (m, 1H), 2.46–2.58 (m, 2H), 3.39–3.48 (m, 1H), 4.62 (dd, J = 11.4, 1.8 Hz, 1H), 5.86–5.91 (m, 1H), 6.43–6.50 (m, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 23.8 (CH_2), 24.7 (CH_2), 30.9 (CH_2), 33.3 (CH_2), 42.9 (CH_2), 54.6 (CH), 124.5 (CH), 137.9 (CH), 165.3 (CNO); $[\alpha]_D^{22} = +45.1$ (c 1.0, $CHCl_3$). {lit.[2] $[\alpha]_D^{22} = +47.0$ (c 1.0, $CHCl_3$)}.

Acknowledgments

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