A Synthesis of Senecionine, a Representative of Hepatotoxic, Macrocyclic Pyrrolizidine Alkaloids of Retronecine Type

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Synopsis. Described is a synthesis of (−)-senecionine, the best-known hepatotoxic, 12-membered pyrrolizidine alkaloid of retronecine type. Integerrinecic acid lactone methyl ester was converted into protected senecic acid, which was regioselectively coupled with (+)-retronecine, achieving the first synthesis of (−)-senecionine.

Macrocyclic pyrrolizidine alkaloids are attractive synthetic targets owing to interesting biological activities such as marked hepatotoxicity and carcinogenicity as well as intriguing chemical structures characterized by the macrocyclic diester moiety.[1] The final crucial step in the total synthesis of these alkaloids is regioselective coupling of a pyrrolizidine diol (necine) such as retronecine (**5**) with a diacid (necic acid), constructing the characteristic macrocyclic diester moiety. Overcoming this synthetic hurdle, several research groups including us have recently achieved the total synthesis of macrocyclic pyrrolizidine alkaloids such as (−)-integerrimine (**3**).[2] Herein we wish to disclose a synthesis of (−)-senecionine (**1**), the best-known hepatotoxic pyrrolizidine alkaloid isolated from *Senecio* plants as a poisonous principle of livestock poisoning by these plants.[1]

The synthesis of (−)-senecionine (**1**) required optically active protected senecic acid (**6**) and (+)-retronecine (**5**), the latter being synthesized enantioselectively in the course of our previous synthesis of (−)-integerrimine (**3**).[2a] Our efforts were therefore concentrated on the preparation of **6** and the regioselective coupling of that with **5**. The preparation of **6** started with the known (*E*)-lactone **8** employed in our synthesis of (−)-integerrimine (**3**).[2a] Thus, photosensitized isomerization of **8** using benzophenone as a sensitizer afforded desired (*Z*)-lactone **9** in 35% yield along with recovered **8** (48%). Basic hydrolysis of **9** followed by esterification of the resulting diacid with CH_2N_2 gave the corresponding dimethyl ester, which upon treatment with dimethyl sulfoxide and acetic anhydride afforded methylthiomethyl (MTM) ether **7** in 70% overall yield. Basic hydrolysis of **7** provided desired **6** in 97% yield, which was converted into cyclic anhydride **10** with dicyclohexylcarbodiimide. The reaction of **10** with stannoxane **11**[2a] derived from (+)-retronecine (**5**) proceeded regioselectively to give desired seco acid **12** in 91% yield (Chart 1). The crucial lactonization of **12** suffered from the easy isomerization of the (*Z*)-ethylidene group into (*E*)-ethylidene one during lactonization. In fact, lactonization of **12** under Yamaguchi's conditions[3] resulted in the exclusive formation of integerrimine MTM ether (**4**)[2a] and none of desired senecionine MTM ether (**2**) could be obtained. In contrast, lactonization of **12** under Keck's conditions[4] proceeded satisfactorily to some extent to provide desired **2** along with isomer **4** (Table 1). The mixture of **2** and **4** could be separated easily by HPLC. Finally, deprotection of **2** with Ph_3CBF_4[2a] furnished (−)-senecionine (**1**) in 81% yield. Spectral and physical properties of synthetic (−)-**1** were identical with those of natural **1** in all respects.

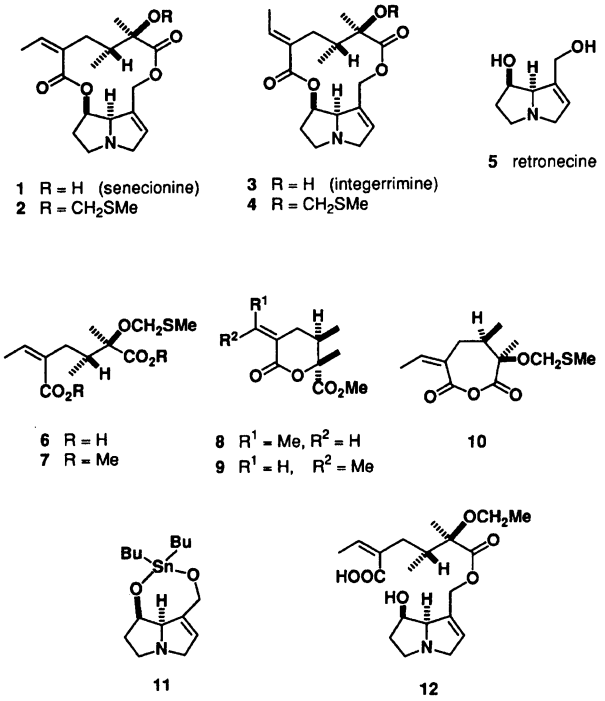

Chart 1.

In summary, the first synthesis of the natural enantiomer of senecionine (**1**) has been achieved although the lactonization step was somewhat unsatisfactory in efficiency.

Experimental

Optical rotations were measured on a JASCO DIP-181 polarimeter. IR spectra were taken on a JASCO IR-810 spectrophotometer. ^{1}H NMR spectra were recorded on either JEOL JNM EX-270 (270 MHz) or JEOL JNM-C675 (270 MHz) spectrometer in $CDCl_3$: Chemical shifts (δ) are reported in ppm downfield from internal tetramethylsilane, and coupling constants in Hz. Low-resolution (EIMS and FABMS) and high-resolution mass spectra (HRFABMS) were measured on a JEOL JMS-LG2000 instrument. Fuji-Davison silica gel BW-820MH was used for column chro-

Table 1. Lactonization of Seco Acid **12** by Keck's Method[a)]

Entry	Reagent (equiv)	Time	Yield[b)] %	**2** : **4**[c)]
1	DCC (2), CSA (2), DMAP (1.2)	6 d	57	2 : 3
2	DCC (2), CSA (2), DMAP (5)	14 h	66	1 : 2
3	DCC (2), CSA (2), DMAP (5)	4 h	49	4 : 5
4	DCC (2), CSA (2), DMAP (2.2)	4 h	47	1 : 1
5	DCC (2), CSA (2), DMAP (1.2)	2 d	27	4 : 1
6	DCC (2), CSA (2), Py (5)	14 h	10	2 : 1

a) All reactions were performed at room temperature in $CHCl_3$. b) Isolated yield of the mixture of **2** and **4**. c) Determined by ^1H NMR spectral analysis of the mixture.

matography. Merck precoated silica gel 60 F_{254} plates, 0.25 mm thickness were used for analytical thin-layer chromatography (TLC). Dichloromethane (CH_2Cl_2) and pyridine were distilled from calcium hydride (CaH_2) under nitrogen. Dimethyl sulfoxide was distilled from CaH_2 under reduced pressure. Benzene and toluene were distilled from sodium (Na) under nitrogen. Tetrahydrofuran (THF) was distilled from sodium-benzophenone ketyl. Methanol (MeOH) was distilled from $Mg(OMe)_2$ under nitrogen. Chloroform ($CHCl_3$) was distilled from phosphorus pentaoxide.

Senecic Acid Lactone Methyl Ester (9). A solution of **8**[2a)] (54.3 mg, 0.256 mmol) in degassed benzene (5.5 ml) containing benzophenone (46.6 mg, 0.256 mmol) was placed in a 20-ml Pyrex flask and stirred under nitrogen. The flask was irradiated with an Eikosha 300-W high-pressure mercury lamp at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure. The oily residue was purified by column chromatography on silica gel [6 g, benzene→benzene–EtOAc (40/1→30/1)], affording **9** (19.0 mg, 35%) as a colorless oil and recovered **8** (26.1 mg, 48%). **9:** $[\alpha]_D^{24.5}$ +74.6° (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 1745 (shoulder), 1735 (shoulder), 1730, 1635, 1275 cm^{-1}; ^1H NMR (270 MHz) δ=1.03 (3 H, d, *J*=7.1 Hz), 1.53 (3 H, s), 2.16 (3 H, ddd, *J*=1.3, 2.3, 7.3 Hz), 2.25 (1 H, dddq, *J*=1.3, 5.0, 15.5, 1.3 Hz), 2.38 (1 H, ddq, *J*=5.0, 5.0, 7.1 Hz), 2.56 (1 H, dddq, *J*=2.3, 5.0, 15.5, 2.3 Hz), 3.77 (3 H, s), 6.12 (1 H, ddq, *J*=1.3, 2.1, 7.3 Hz); EIMS *m/z* (rel intensity) 212 (M^+; 33), 153 (100), 135 (19), 125 (26), 114 (26), 110 (13), 81 (49), 78 (35), 55 (37). HRFABMS. Found: *m/z* 213.1141. Calcd for $C_{11}H_{17}O_4$: M+H, 213.1127.

***O*-(Methylthio)methylsenecic Acid Dimethyl Ester (7).** A stirred mixture of **9** (10.1 mg, 0.048 mmol) and saturated aqueous $Ba(OH)_2$ solution (1.6 ml) under nitrogen was heated under reflux for 1 h. After cooling, the reaction mixture was acidified to pH 2 with 1 M HCl (1 M=1 mol dm^{-3}), saturated with NaCl, and extracted with ether (4×8 ml). The combined extracts were dried and concentrated under reduced pressure to give a diacid, which was converted into the dimethyl ester by treatment with CH_2N_2. The crude dimethyl ester was dissolved in a mixture of dimethyl sulfoxide (1 ml) and acetic anhydride (1 ml) under nitrogen. The mixture was stirred at 40 °C for 24 h and concentrated in vacuo. The oily residue was purified by column chromatography on silica gel [2 g, benzene→benzene–EtOAc (30/1)], affording **7** (10.1 mg, 70% overall) as a colorless oil: $[\alpha]_D^{27.0}$ +30.8° (*c* 0.54, $CHCl_3$); IR ($CHCl_3$) 1730, 1710, 1260, 1120 cm^{-1}; ^1H NMR (270 MHz) δ=0.82 (3 H, d, *J*=6.6 Hz), 1.40 (3 H, s), 1.93 (1 H, dd, *J*=10.6, 12.9 Hz), 1.96 (3 H, dd, *J*=1.0, 6.9 Hz), 1.94—2.11 (1 H, m), 2.22 (3 H, s), 2.60 (1 H, br d, *J*=12.9 Hz), 3.72 (3 H, s), 3.74 (3 H, s), 4.54 (1 H, d, *J*=10.9 Hz), 4.68 (1 H, d, *J*=10.9 Hz), 6.00 (1H, q, *J*=6.6 Hz); EIMS *m/z* (rel intensity) 304 (M^+; 4), 286 (9), 272 (4), 257 (7), 245 (32), 227 (45), 195 (100), 135 (53), 61 (88). HRFABMS. Found: *m/z* 327.1262. Calcd for $C_{14}H_{24}O_5SNa$: M+Na, 327.1242.

***O*-(Methylthio)methylsenecic Acid (6).** To a solution of **7** (15.8 mg, 0.052 mmol) in 1 M KOH in degassed MeOH (0.52 ml, 0.52 mmol) under nitrogen was added degassed H_2O (1.7 ml), and the mixture was heated under reflux for 2.5 h. After cooling, the mixture was acidified to pH 2 with 1 M HCl, saturated with NaCl, and extracted with EtOAc (4×8 ml). The combined extracts were dried and concentrated under reduced pressure. The oily residue was purified by column chromatography on silica gel [0.5 g, $CHCl_3$→$CHCl_3$–MeOH–AcOH (300/20/1)], affording **6** (13.9 mg, 97% overall) as a colorless oil: $[\alpha]_D^{27.0}$ +38.5° (*c* 0.49, $CHCl_3$); IR ($CHCl_3$) 3600—2800, 1680, 1560, 1275, 1150 cm^{-1}; ^1H NMR (270 MHz) δ=0.92 (3 H, d, *J*=6.9 Hz), 1.48 (3 H, s), 1.85—2.00 (1 H, m), 2.03 (3 H, d, *J*=7.3 Hz), 2.09—2.20 (1 H, m), 2.23 (3 H, s) 2.68 (1 H, br d, *J*=12.2 Hz), 4.57 (1 H, d, *J*=10.6 Hz), 4.73 (1 H, d, *J*=10.6 Hz), 6.19 (1 H, q, *J*=7.3 Hz); EIMS *m/z* (rel intensity) 276 (M^+; 3), 258 (6), 231 (8), 153 (68), 61 (100). HRFABMS. Found: *m/z* 277.1084. Calcd for $C_{12}H_{21}O_5S$: M+H, 277.1100.

***O*- (Methylthio)methylsenecic Anhydride (10).** To a solution of **6** (13.9 mg, 0.050 mmol) in CH_2Cl_2 (0.7 ml) under nitrogen was added a solution of dicyclohexylcarbodiimide (DCC) (10.3 mg, 0.050 mmol) in CH_2Cl_2 (0.3 ml). The mixture was stirred at room temperature for 2.5 h and concentrated under reduced pressure. The residue was suspended in benzene (2 ml), and insoluble materials were removed by filtration through a cotton plug. The filtrate and washings were combined and concentrated under reduced pressure to give crude **10** (14.4 mg) as a colorless solid: IR ($CHCl_3$) 1785, 1745, 1640, 1140, 1110, 960 cm^{-1}; ^1H NMR (270 MHz) δ=1.03 (3 H, d, *J*=6.9 Hz), 1.57 (3 H, s), 2.04 (1 H, m), 2.06 (1 H, m), 2.18 (3 H, s), 2.19 (3 H, dd, *J*=1.7, 7.3 Hz), 2.73 (1 H, br dd, *J*=6.4, 14.9 Hz), 4.43 (1 H, d, *J*=11.2 Hz), 4.52 (1 H, d, *J*=11.2 Hz), 6.30 (1 H, q, *J*=7.3 Hz); EIMS *m/z* (rel intensity) 258 (M^+; 7), 183 (60), 164 (33), 153 (100), 61 (90). This material was sufficiently pure and used for the next reaction without further

purification.

Seco Acid (12). A mixture of (+)-retronecine (**5**)[2a] (25.2 mg, 0.161 mmol) and Bu_2SnO (46.4 mg, 0.186 mmol) in benzene (13 ml) under nitrogen was heated under reflux for 23 h with continuous removal of water using a Dean–Stark water separator. After cooling, the reaction mixture was concentrated under reduced pressure to leave crude retronecine stannoxane **11** as a white solid, which was suspended in toluene (2 ml) under nitrogen. To the cooled (0 °C), stirred suspension of **11** was added dropwise a solution of **10** (14.4 mg) in toluene (2 ml). The mixture was stirred at 0 °C for 30 min and then at room temperature for 30 min and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel [8 g, $CHCl_3$–MeOH (5/4)], affording **12** (18.9 mg, 91% from **6**) as a colorless amorphous solid: $[\alpha]_D^{26.0}$ +29.3° (*c* 0.91, $CHCl_3$); IR ($CHCl_3$) 3600—3000, 1735, 1240, 1110 cm^{-1}; ^1H NMR (270 MHz) δ=0.90 (3 H, d, *J*=6.8 Hz), 1.44 (3 H, s), 1.86 (1 H, d, *J*=7.3 Hz), 1.94 (3 H, d, *J*=13.2 Hz), 1.95—2.12 (1 H, m), 2.23 (3 H, s), 2.12—2.26 (1 H, m), 2.55 (1 H, br d, *J*=13.2 Hz), 2.98 (1 H, ddd, *J*=6.8, 10.2, 10.2 Hz), 3.58 (1 H, br d, *J*=15.0 Hz), 3.73—3.81 (1 H, m), 4.32 (1 H, br d, *J*=15.0 Hz), 4.53 (1 H, d, *J*=10.7 Hz), 4.64—4.73 (1 H, m), 4.72 (1 H, d, *J*=10.7 Hz), 4.76 (1 H, d, *J*=2.9 Hz), 4.83 (1 H, d, *J*=2.9 Hz), 5.59 (1 H, q, *J*=7.3 Hz), 5.76 (1 H, br s); FABMS *m/z* (rel intensity) 436 [$(M+Na)^+$; 21], 414 [$(M+H)^+$; 100], 366 (5), 336 (4), 308 (4), 238 (15), 138 (31). HRFABMS. Found: *m/z* 414.1985. Calcd for $C_{20}H_{32}NO_6S$: M+H, 414.1951.

Lactonization of Seco Acid (12) By Keck's Method (Table 1).[4] **(a) (Entry 1).** To a mixture of **12** (9.7 mg, 0.024 mmol), DMAP (3.4 mg, 0.028 mmol), and (±)-10-camphorsulfonic acid (CSA) (10.9 mg, 0.047 mmol) in $CHCl_3$ (2.1 ml) under nitrogen was added a solution of DCC (9.7 mg, 0.047 mmol) in $CHCl_3$ (0.3 ml). The reaction mixture was stirred at room temperature for 6 d, and then saturated $NaHCO_3$ solution was added. The aqueous mixture was made basic to pH 10 with 1 M K_2CO_3, saturated with NaCl, and extracted with $CHCl_3$ (4×8 ml). The combined extracts were dried and concentrated under reduced pressure. The oily residue was purified by column chromatography on silica gel [4 g, $CHCl_3$–MeOH (40/1→20/1)→$CHCl_3$–MeOH–H_2O (10/8/1)], affording a 2:3 mixture[5] of senecionie MTM ether (**2**) and integerrimine MTM ether (**4**) (5.3 mg, 57% overall) as a colorless oil.

(b) (Entry 2). Lactonization of **12** (6.8 mg, 0.017 mmol) with 2 equiv of DCC, 2 equiv of CSA, and 5 equiv of DMAP (room temperature, 14 h) was performed as described before to afford a 1:2 mixture[5] of **2** and **4** (4.3 mg, 66%).

(c) (Entry 3). Lactonization of **12** (5.8 mg, 0.014 mmol) with 2 equiv of DCC, 2 equiv of CSA, and 5 equiv of DMAP (room temperature, 4 h) was performed as described before to afford a 4:5 mixture[5] of **2** and **4** (2.7 mg, 49%).

(d) (Entry 4). Lactonization of **12** (5.5 mg, 0.013 mmol) with 2 equiv of DCC, 2 equiv of CSA, and 2.2 equiv of DMAP (room temperature, 4 h) was performed as described before to give a 1:1 mixture[5] of **2** and **4** (2.5 mg, 47%).

(e) (Entry 5). Lactonization of **12** (5.0 mg, 0.012 mmol) with 2 equiv of DCC, 2 equiv of CSA, and 1.2 equiv of DMAP (room temperature, 2 d) was performed as described before to give a 4:1 mixture[5] of **2** and **4** (1.3 mg, 27%).

Separation of the Mixture of Senecionine MTM Ether (2) and Integerrimine MTM Ether (4). The mixture of **2** and **4** could be separated by HPLC [Develosil ODS-HG-5 (250×10 mm ID), solvent 0.02 M $AcONH_4$–CH_3CN (50/50); flow rate 6 ml min^{-1}; detection UV 220 nm] to give pure **4** (t_R 8.2 min) and **2** (t_R 10.0 min). **2:** A colorless oil; $[\alpha]_D^{21.0}$ +34.8° (*c* 0.44, $CHCl_3$); IR ($CHCl_3$) 1735, 1710, 1445, 1230, 1165, 1105 cm^{-1}; ^1H NMR (270 MHz) δ=0.91 (3 H, d, *J*=6.6 Hz), 1.45 (3 H, s), 1.66 (1 H, ddq, *J*=1.0, 10.9, 6.6 Hz), 1.83 (3 H, dd, *J*=1.7, 6.9 Hz), 1.85—1.98 (1 H, m), 2.06—2.22 (1 H, m), 2.24 (3 H, s), 2.35 (1 H, m), 2.39 (1 H, br dd, *J*=5.6, 14.2 Hz), 2.55 (1 H, ddd, *J*=5.6, 9.2, 12.2 Hz), 3.28 (1 H, br dd, *J*=9.2, 9.2 Hz), 3.38 (1 H, ddd, *J*=1.7, 5.0 15.5 Hz), 3.95 (1 H, d, *J*=15.5 Hz), 3.96 (1 H, d, *J*=11.9 Hz), 4.28 (1 H, m), 4.61 (1 H, d, *J*=10.6 Hz), 4.96 (1 H, d, *J*=10.6 Hz), 5.00 (1 H, dd, *J*=4.0, 4.0 Hz), 5.43 (1 H, d, *J*=11.9 Hz), 5.72 (1 H, dq, *J*=1.3, 6.9 Hz), 6.19 (1 H, br d, *J*=1.7 Hz); FABMS *m/z* (rel intensity) 418 [$(M+Na)^+$; 8], 396 [$(M+H)^+$; 100], 348 (10), 334 (6), 318 (7), 290 (11), 166 (18), 149 (52), 136 (30), 120 (54). HRFABMS. Found: *m/z* 396.1871. Calcd for $C_{20}H_{30}NO_5S$: M+H, 396.1845. **4:** A colorless oil: $[\alpha]_D^{30.0}$ +56.2° (*c* 0.14, $CHCl_3$) [Lit,[2a] $[\alpha]_D^{24.0}$ +51.2° (*c* 0.52, $CHCl_3$)]. HRFABMS. Found: *m/z* 396.1872. Calcd for $C_{20}H_{30}NO_5S$: M+H, 396.1845.

(−)-Senecionine (1). To a stirred solution of **2** (8.1 mg, 0.21 mmol) in CH_2Cl_2 (0.7 ml) under nitrogen was added a solution of triphenylcarbenium tetrafluoroborate (10.5 mg, 0.032 mmol) in CH_2Cl_2 (0.4 ml). The reaction mixture was stirred at room temperature for 6.5 h, and saturated $NaHCO_3$ solution (1.0 ml) was added. The aqueous mixture was made basic to pH 10 with 1 M K_2CO_3, saturated with NaCl, and extracted with $CHCl_3$ (4×6 ml). The combined extracts were washed with saturated NaCl solution, dried, and concentrated under reduced pressure. Oily residue was purified by column chromatography on silica gel [2 g, $CHCl_3$–MeOH (30/1→15/1)], providing **1** (5.6 mg, 81%) as colorless crystals: Mp 236—238 °C (EtOH); $[\alpha]_D^{30.0}$ −55.1° (*c* 0.06, $CHCl_3$) [Lit,[6] mp 232 °C (EtOH); $[\alpha]_D$ −54.6° (*c* 1.63, $CHCl_3$)]; IR ($CHCl_3$) 3540, 1715, 1450, 1230, 1165 cm^{-1}; ^1H NMR (270 MHz) δ=0.92 (3 H, d, *J*=6.3 Hz), 1.33 (3 H, s), 1.68 (1 H, dq, *J*=10.6, 6.3 Hz), 1.76 (1 H, dd, *J*=10.6, 12.4 Hz), 1.84 (3 H, dd, *J*=1.7, 6.9 Hz), 2.06—2.20 (2 H, m), 2.38 (1 H, dd, *J*=5.9, 13.5 Hz), 2.55 (1 H, ddd, *J*=5.9, 8.6, 12.5 Hz), 3.13 (1 H, br s), 3.26 (1 H, dd, *J*=8.6, 8.6 Hz), 3.40 (1 H, ddd, *J*=1.3, 5.9, 15.6 Hz), 3.94 (1 H, br d, *J*=15.6 Hz), 4.05 (1 H, d, *J*=11.5 Hz), 4.27 (1 H, br s), 5.02 (1 H, dd, *J*=3.3, 3.3 Hz), 5.50 (1 H, d, *J*=11.5 Hz), 5.72 (1 H, dq, *J*=1.3, 6.9 Hz), 6.19 (1 H, d, *J*=1.7 Hz); FABMS *m/z* (rel intensity) 358 [$(M+Na)^+$; 9], 336 [$(M+H)^+$; 100], 307 (2), 154 (13), 136 (18), 118 (33). HRFABMS. Found: *m/z* 336.1827. Calcd for $C_{18}H_{26}NO_5$: M+H, 336.1811.

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