

Enantioselective Synthesis of the Macrocyclic Pyrrolizidine Alkaloid Yamataimine

Haruki NIWA,^{*,#} Kazuto KUNITANI, Tomohiro NAGOYA, and Kiyoyuki YAMADA*

Department of Chemistry, Faculty of Science, Nagoya University, Chikusa, Nagoya 464

(Received June 24, 1994)

Described is a short-step synthesis of optically active yamataimine, a 12-membered pyrrolizidine alkaloid of retronecine type. Methyl (1*S*,5*R*)-5-methyl-2-oxocyclopentanecarboxylate derived from (*R*)-(+)-pulegone was converted into the necic acid component required for the synthesis of yamataimine, in a nine-step sequence. Regioselective coupling of (+)-retronecine with the necic acid component via tin-mediated regioselective acylation followed by macrolactonization led to the first synthesis of (+)-yamataimine.

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 (**4**) with a diacid (necic acid), constructing the characteristic macrocyclic diester moiety (Chart 1). Overcoming this synthetic hurdle, several research groups including us have recently achieved the total synthesis of macrocyclic pyrrolizidine alkaloids such as integerrimine (**2**) and senecionine (**3**).²⁾ As part of our continuing research in this field, herein we wish to disclose the first synthesis of the natural enantiomer of yamataimine (**1**),³⁾ a 12-membered macrocyclic pyrrolizidine alkaloid of retronecine type.

Results and Discussion

Yamataimine (**1**) was isolated by Furuya and Hikichi from *Cacalia yatabei* Maxim. (Compositae, yamataimingasa in Japanese).³⁾ The structure of **1** including absolute stereochemistry was determined by chemical and spectral means coupled with X-ray crystallo-

graphic analysis. The C-2 position of the necic acid part in yamataimine (**1**) has the *S* configuration, while the corresponding stereocenter in most of 12-membered pyrrolizidine alkaloids has the *R* configuration as shown in structures **2** and **3**.

The present synthesis of (+)-yamataimine (**1**) required optically active protected necic acid **5** and (+)-retronecine (**4**), the latter being synthesized enantioselectively in the course of our previous synthesis of (–)-integerrimine (**2**).^{2a)} Our efforts were therefore concentrated on the preparation of **5** followed by regioselective coupling with **4**, where we intended to utilize the tin-mediated regioselective acylation method developed by us.^{2a)} As the starting material for the preparation of **5**, we chose methyl (1*S*,5*R*)-5-methyl-2-oxocyclopentanecarboxylate (**7**) readily accessible from (*R*)-(+)-pulegone (**6**).⁴⁾ Keto ester **7** was alkylated with methyl iodide and K₂CO₃⁵⁾ to give desired keto ester **8a** in 59% yield along with stereoisomer **8b** in 19% yield (Scheme 1). The stereochemistry of **8a** and **8b** was unambiguously verified by NOE experiments (Fig. 1). Baeyer–Villiger oxidation of **8a** gave desired lactone **9a** (40%) and undesired **9b** (40%) in a ratio of 1:1. As reported by Narasaka,⁶⁾ Baeyer–Villiger oxidation of the diastereomer **8b** (racemic) proceeded regioselectively to give desired **9a'** and undesired **9b'** (both racemic) in a ratio of 6:1 (Scheme 2). No regioselectivity in Baeyer–Villiger oxidation of **8a** may be attributed to the formation of an intramolecular hydrogen bond between the hydroxyl group and the ester carbonyl one in intermediate **A** (Fig. 2). This intramolecular hydrogen bond may decrease the electron density at C-1, retarding migration of the quaternary center (C-1). Introduction of the (*E*)-ethylidene group into the position α to the lactone carbonyl group in **9a** was effected by the conventional three-step sequence⁷⁾ (i; LDA, then CH₃CHO. ii; Ac₂O–Et₃N–DMAP. iii; DBU), providing **10** in 77% overall yield. Catalytic hydrogenation of **10** proceeded in high degree of asymmetric induction to yield the desired lactone **11** as the sole product in 98% yield. The stereochemistry of the ethyl group in **11** was proved by NOE experiments (Fig. 3). Methanolysis of **11** with K₂CO₃–MeOH followed by treatment with dimethyl sulfoxide and acetic anhydride afforded a 2:1 mixture of desired (methylthio)methyl (MTM)

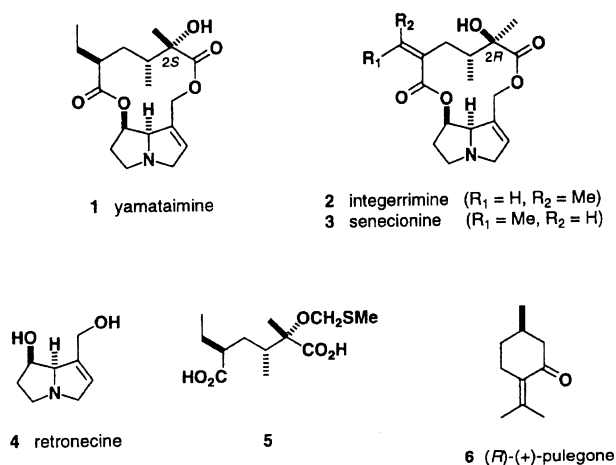
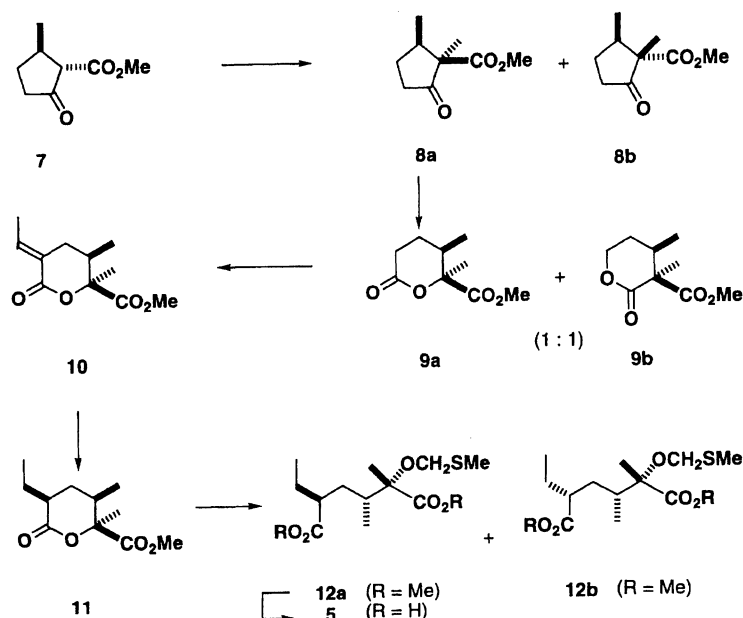


Chart 1.

#Present address: Department of Applied Physics and Chemistry, the University of Electro-Communications, Chofu, Tokyo 182.



Scheme 1.

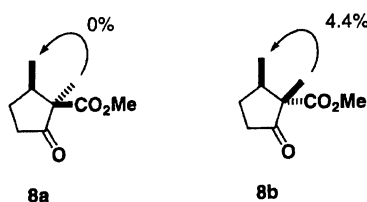
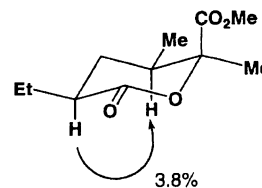
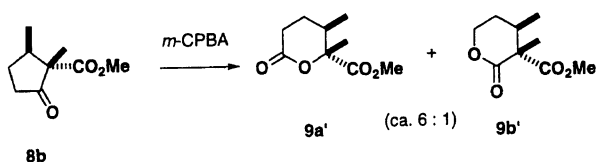


Fig. 1. NOE Experiments of 8a and 8b.



11

Fig. 3. NOE Experiments of 11.



Scheme 2.

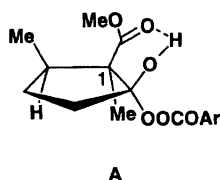


Fig. 2. Intermediate A in Baeyer-Villiger Oxidation of 8a.

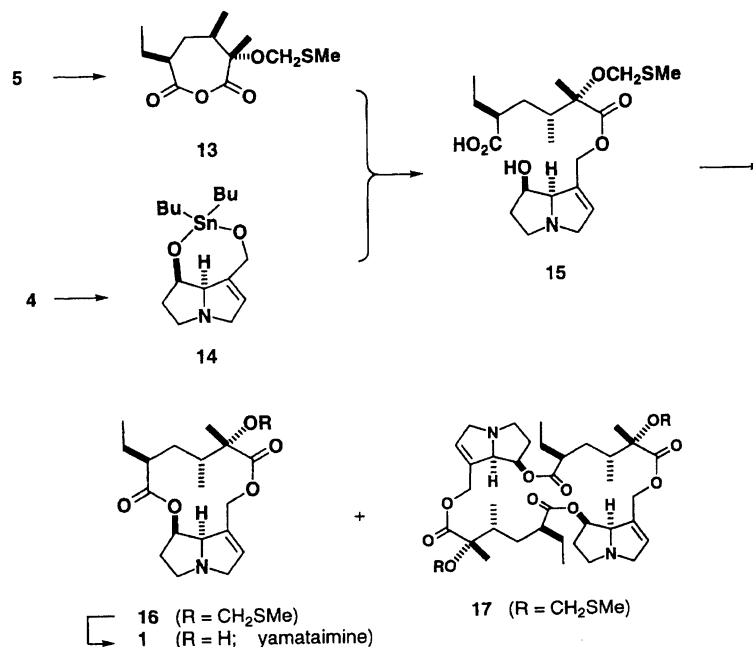
ether **12a** and diastereomer **12b** in 99% combined yield. Epimerization of the ethyl group occurred during basic methanolysis of **11**. Pure **12a** could be obtained by HPLC separation. Although unequivocal evidence for the stereochemical assignment of **12a** and **12b** could not be obtained at this stage, we assumed the major product to be as depicted in formula **12a**. This stereochemical assignment was confirmed by the successful synthesis of (+)-yamataimine (**1**) using the major product **12a**. Basic hydrolysis of **12a** provided the desired diacid **5** in 91% yield.

The optically active protected necic acid **5** was in

hand. The stage was now set for regioselective construction of the 12-membered diester from (+)-retronecine (**4**) and **5**. Thus, **5** was converted into cyclic anhydride **13** with dicyclohexylcarbodiimide (Scheme 3). The reaction of **13** with tin alkoxide **14**²⁾ derived from (+)-retronecine (**4**) proceeded in highly regioselective manner to give desired seco acid **15** as the sole product in 81% yield. Of four possible monoesters, the only desired monoester **15** was formed in this acylation. The crucial lactonization of **15** suffered from low chemical yield of **16**. In fact, lactonization of **15** under Keck's conditions⁸⁾ provided desired **16** in 16% yield. The prolonged reaction resulted in the formation of dimer **17** (10%) in addition to **16** (13%). Lactonization of **15** under Yamaguchi's conditions⁹⁾ gave similar results with slight epimerization of the ethyl group. Finally, deprotection of **16** with Ph_3CBF_4 ^{2,10)} provided (+)-yamataimine (**1**) in 64% yield. Spectral and physical properties of synthetic (+)-yamataimine (**1**) were identical with those of natural **1** in all respects.

Conclusion

The first synthesis of the natural enantiomer of yamataimine (**1**) has been achieved, although the yield of the lactonization step was unsatisfactory.



Scheme 3.

Experimental

Optical rotations were measured on a JASCO DIP-181 polarimeter. IR spectra were taken on a JASCO IR-810 spectrophotometer. ^1H 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, CIMS, and FABMS) and high-resolution mass spectra (HREIMS and HRFABMS) were measured on a JEOL JMS-LG2000 instrument. Fuji-Davison silica gel BW-820MH was used for column chromatography. Merck precoated silica gel 60 F₂₅₄ plates, 0.25 mm thickness were used for analytical thin-layer chromatography (TLC). Acetone was distilled from anhydrous K_2CO_3 under nitrogen. 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 Na-benzophenone ketyl. Methanol (MeOH) was distilled from $\text{Mg}(\text{OMe})_2$ under nitrogen. Chloroform (CHCl_3) was distilled from phosphorus pentoxide. Unless otherwise stated, organic solutions obtained by extractive workup were washed with saturated aqueous NaCl solution, dried over anhydrous Na_2SO_4 , and concentrated under reduced pressure by a rotary evaporator.

Methyl (1*S*,5*R*)-5-Methyl-2-oxocyclopentanecarboxylate (7).⁴⁾ To a cooled (-4 — -5 °C), mechanically stirred mixture of (*R*)-(+)-pulegone (**6**) (4.8 g, 32.1 mmol) and NaHCO_3 (829 mg, 9.9 mmol) in ether (33 ml) under nitrogen was added dropwise Br_2 (2.0 ml, 39 mmol) over a 40-min period. The mixture was filtered through a column of anhydrous Na_2SO_4 and the filtrate and washings were added to an ice-cooled solution of NaOMe in MeOH [prepared from Na (1.64 g, 71.5 mmol) and MeOH (23 ml)] under nitrogen. The reaction mixture was heated under reflux for 2.5 h with stirring. After cooling, 5% aqueous HCl solution was

added and the aqueous mixture was extracted with ether (3×16 ml). The combined extracts were washed, dried, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel [140 g, hexane–benzene–ether (74/40/1 $\rightarrow$ 40/40/1 v/v) $\rightarrow$ benzene–ether (40/1) $\rightarrow$ ether], affording a 1:1 mixture (determined by ^1H NMR) of (1*R*,5*R*)- and (1*S*,5*R*)-2-isopropylidene-5-methylcyclopentanecarboxylic acid methyl esters (4.54 g, 77%) as a colorless oil. Ozonolysis of this material (4.35 g, 23.6 mmol) was performed in MeOH (20 ml) at -78 °C followed by reductive workup with dimethyl sulfide (1 ml). Purification of the crude product by column chromatography on silica gel [70 g, hexane–ether (2/1)] afforded **7** (2.37 g, 63%) as a colorless oil: $[\alpha]_D$ not measured; IR (CHCl_3) 1760, 1730, 1440, 1225, 1130 cm^{-1} ; ^1H NMR (270 MHz) δ = 1.19 (3H, d, J = 6.3 Hz), 1.40–1.56 (1H, m), 2.15–2.50 (3H, m), 2.78 (1H, d, J = 11.2 Hz), 3.76 (3H, s); EIMS m/z (rel intensity) 156 (M^+ ; 46), 141 (27), 128 (58), 125 (42), 109 (47), 101 (83). HREIMS. Found: m/z 156.0785. Calcd for $\text{C}_8\text{H}_{12}\text{O}_3$: M, 156.0786. The ^1H NMR spectral analysis indicated that this material contained a small amount (ca. 17%) of the cis isomer of **7**.

Methyl (1*R*,5*R*)-1,5-Dimethyl-2-oxopentanecarboxylate (8a). To a vigorously stirred suspension of anhydrous K_2CO_3 (4.42 g, 32.0 mmol) in acetone (11 ml) under nitrogen were added a solution of **7** (1.24 g, 7.95 mmol) in acetone (9 ml) and CH_3I [1 ml, 16 mmol; passed through a column of alumina (E. Merck Art. 1077, activity I) just prior to use]. The mixture was vigorously stirred for 11 h at room temperature and filtered through a pad of Celite®. The filtration residue was washed thoroughly with acetone. The filtrate and washings were combined and concentrated under reduced pressure. Water was added to the oily residue and the aqueous mixture was extracted with ether (4×10 ml). The extracts were combined, washed, dried, and concentrated under reduced pressure. The oily residue was purified by column chromatography on silica gel [65 g, hexane–benzene–ether (50/50/1 $\rightarrow$ 10/10/1)], affording desired **8a**

(796 mg, 59%) and diastereomer **8b** (228 mg, 19%) as a colorless oil, respectively.

8a: $[\alpha]_D^{28} +82.1^\circ$ (*c* 1.02, CHCl₃); IR (CHCl₃) 1750, 1730, 1240 cm⁻¹; ¹H NMR (270 MHz) δ =1.05 (3H, d, *J*=6.3 Hz), 1.27 (3H, s), 1.77–1.86 (1H, m), 2.00–2.11 (2H, m), 2.26 (1H, ddd, *J*=8.6, 10.9, 19.1 Hz), 2.59 (1H, ddd, *J*=1.3, 8.6, 19.1 Hz), 3.67 (3H, s); EIMS *m/z* (rel intensity) 170 (*M*⁺; 72), 142 (100), 139 (27), 127 (42), 115 (55), 111 (53), 83 (94). HREIMS. Found: *m/z* 170.0970. Calcd for C₉H₁₄O₃: *M*, 170.0943.

8b: $[\alpha]_D^{28} +42.9^\circ$ (*c* 1.26, CHCl₃); IR (CHCl₃) 1750, 1730, 1265 cm⁻¹; ¹H NMR (270 MHz) δ =1.02 (3H, d, *J*=6.9 Hz), 1.15 (3H, s), 1.53 (1H, dddd, *J*=9.7, 9.7, 10.9, 12.5 Hz), 2.05–2.20 (1H, m), 2.35–2.45 (2H, m), 2.68–2.80 (1H, m), 3.71 (3H, s); EIMS *m/z* (rel intensity) 170 (*M*⁺; 22), 155 (2), 142 (92), 139 (35), 127 (33), 115 (53). HREIMS. Found: *m/z* 170.0969. Calcd for C₉H₁₄O₃: *M*, 170.0943.

(4*R*,5*S*)-5-Methoxycarbonyl-4-methyl-5-hexanolide (9a). A stirred mixture of **8a** (277 mg, 1.63 mmol), Li₂CO₃ (11.9 mg, 0.16 mmol), and *m*-chloroperbenzoic acid (*m*-CPBA) (80% purity, 461 mg, 2.14 mmol) in CH₂Cl₂ (4 ml) was heated under reflux. After 3 d, a solution of *m*-CPBA (80% purity, 452 mg, 2.10 mmol) in CH₂Cl₂ was added. The mixture was heated under reflux with stirring for an additional 1 d. After cooling, the excess reagent was destroyed with dimethyl sulfide (0.5 ml). Saturated aqueous NaHCO₃ solution (5 ml) was added and the aqueous mixture was extracted with CH₂Cl₂ (3×10 ml). The combined extracts were washed, dried, and concentrated under reduced pressure. The oily residue was purified by column chromatography on silica gel [15 g, benzene–EtOAc (40/1 → 10/1)], affording desired **9a** (121 mg, 40%) as a colorless oil along with isomer **9b** (120 mg, 40%) and recovered **8a** (57 mg, 20%).

9a: $[\alpha]_D^{10.5} +41.0^\circ$ (*c* 0.67, CHCl₃); IR (CHCl₃) 1735, 1270, 1125, 1110 cm⁻¹; ¹H NMR (270 MHz) δ =1.07 (3H, d, *J*=6.9 Hz), 1.50–1.66 (1H, m), 1.64 (3H, s), 1.81 (1H, dddd, *J*=2.3, 4.0, 7.9, 17.8 Hz), 1.90–2.03 (1H, m), 2.55 (1H, ddd, *J*=7.9, 10.6, 18.5 Hz), 2.72 (1H, ddd, *J*=2.3, 7.3, 18.5 Hz), 3.79 (3H, s); CIMS *m/z* (rel intensity) 187 [(*M*+H)⁺; 24], 169 (3), 155 (3), 141 (2), 127 (100), 109 (3), 99 (49). HREIMS. Found: *m/z* 127.0774. Calcd for C₇H₁₁O₂: *M*–CO₂Me, 127.0759.

9b: $[\alpha]_D^{21.5} +34.7^\circ$ (*c* 0.85, CHCl₃); IR (CHCl₃) 1745, 1720, 1135 cm⁻¹; ¹H NMR (270 MHz) δ =1.03 (3H, d, *J*=6.9 Hz), 1.57 (3H, s), 1.67–1.76 (1H, m), 1.90–2.00 (1H, m), 2.04–2.20 (1H, m), 3.75 (3H, s), 4.35 (1H, ddd, *J*=3.6, 11.2, 11.2 Hz), 4.58 (1H, ddd, *J*=2.6, 2.6, 11.2 Hz); CIMS *m/z* (rel intensity) 187 [(*M*+H)⁺; 11], 155 (11), 142 (8), 127 (100). HREIMS. Found: *m/z* 127.0763. Calcd for C₇H₁₁O₂: *M*–CO₂Me, 127.0759.

(4*R*,5*S*)-2-[(*E*)-Ethylidene]-5-methoxycarbonyl-4-methyl-5-hexanolide (10). To a cooled (–78 °C) solution of diisopropylamine (0.50 ml, 3.57 mmol) in THF (10.0 ml) under nitrogen was added 1.5*M* BuLi (1 *M*=1 moldm⁻³) in hexane (2.13 ml, 3.30 mmol). The mixture was warmed to 0 °C, stirred for 10 min, and cooled to –78 °C. To the solution of LDA in THF was added dropwise a solution of **9a** (395 mg, 2.12 mmol) in THF (5 ml), and the mixture was stirred at –78 °C for 1 h. To the enolate solution was added hexamethylphosphoric triamide (1.5 ml, 8.63 mmol). After the mixture was stirred for 10 min, freshly dis-

tilled acetaldehyde (0.6 ml, 10.7 mmol) was added, and the reaction mixture was stirred at –78 °C for 10 min and then at –40 °C for 3 h. The reaction was quenched by addition of saturated aqueous NH₄Cl solution (5 ml) and the aqueous mixture was extracted with EtOAc (3×10 ml). The combined extracts were dried and concentrated under reduced pressure. The crude product was dissolved in CH₂Cl₂ (15 ml). To the solution were added Ac₂O (0.8 ml), triethylamine (1.2 ml), and 4-dimethylaminopyridine (DMAP) (16 mg). After the mixture was stirred at room temperature for 14 h, 1,8-diazabicyclo[5.4.0]undec-7-ene (0.7 ml, 5.1 mmol) was added. The reaction mixture was stirred at room temperature for 2 d, and 1 *M* HCl (10 ml) was added. The aqueous mixture was extracted with ether (3×10 ml). The combined extracts were washed, dried, and concentrated under reduced pressure. The oily residue was purified by column chromatography on silica gel [20 g, hexane–ether (2/1 → 1/1)], affording **10** (345 mg, 77% overall) as a colorless oil: $[\alpha]_D^{27} +17.1^\circ$ (*c* 0.85, MeOH); IR (CHCl₃) 1740, 1715, 1640, 1125 cm⁻¹; ¹H NMR (270 MHz) δ =1.14 (3H, d, *J*=6.9 Hz), 1.64 (3H, s), 1.78 (3H, ddd, *J*=1.0, 1.7, 7.3 Hz), 1.93–2.17 (2H, m), 2.54–2.61 (1H, m), 3.76 (3H, s), 7.17 (1H, ddq, *J*=2.0, 2.6, 7.3 Hz); EIMS *m/z* (rel intensity) 212 (*M*⁺; 29), 194 (5), 180 (7), 162 (4), 153 (100). HREIMS. Found: *m/z* 212.1064. Calcd for C₁₁H₁₆O₄: *M*, 212.1049.

(2*S*,4*R*,5*S*)-2-Ethyl-5-methoxycarbonyl-4-methyl-5-hexanolide (11). A mixture of **10** (340 mg, 1.60 mmol) and 10% Pd/C (17.4 mg) in EtOAc (10 ml) under hydrogen was vigorously stirred at room temperature for 16 h. The reaction mixture was filtered through a pad of Celite®. The filtration residue was washed thoroughly with EtOAc. The combined filtrate and washings were concentrated under reduced pressure. The oily residue was purified by column chromatography on silica gel [6 g, hexane–ether (2/1)], providing **11** (334 mg, 98%) as a colorless oil: $[\alpha]_D^{25} +76.0^\circ$ (*c* 0.59, MeOH); IR (CHCl₃) 1740, 1225, 1205, 1120 cm⁻¹; ¹H NMR (270 MHz) δ =0.96 (3H, t, *J*=7.6 Hz), 1.05 (3H, d, *J*=6.9 Hz), 1.22–1.50 (1H, m), 1.61 (3H, s), 1.53–1.73 (1H, m), 1.90 (1H, ddd, *J*=3.6, 7.3, 13.9 Hz), 1.91–2.10 (2H, m), 2.44 (1H, dddd, *J*=4.0, 4.3, 7.3, 15.2 Hz), 3.76 (3H, s); EIMS *m/z* (rel intensity) 186 [(*M*–C₂H₄)⁺; 6], 155 (100), 127 (73), 114 (9). HREIMS. Found: *m/z* 186.0911. Calcd for C₉H₁₄O₄: *M*–C₂H₄, 186.0892.

Dimethyl (2*S*,3*R*,5*S*)-5-Ethyl-2,3-dimethyl-2-[(methylthio)methoxy]hexanedioate (12a). A mixture of **11** (80.8 mg, 0.378 mmol) and anhydrous K₂CO₃ (58.4 mg, 0.423 mmol) in MeOH (5 ml) under nitrogen was stirred at room temperature for 13 h. Amberlite® IRC-50 (H form, 878 mg) was added and the mixture was stirred for an additional 1 h at room temperature. The mixture was filtered through a cotton plug and the resin was washed thoroughly with MeOH. The filtrate and washings were combined and concentrated under reduced pressure. The crude product was dissolved in dimethyl sulfoxide (2 ml) under nitrogen and Ac₂O (2 ml) was added. 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 [3 g, hexane–ether (10/1)], providing a 2:1 mixture of **12a** and **12b** (116 mg, 99%) as a colorless oil. This mixture could be separated by HPLC [Develosil® ODS-10 (250×20 mm ID); solvent CH₃CN–H₂O (54/45); flow rate 8 ml min⁻¹; detection UV 215 nm, recycled 4 times] to give

desired **12a** (t_R 316 min, 71 mg) and diastereomer **12b** (t_R 307 min, 25 mg) as a colorless oil, respectively.

12a: $[\alpha]_D^{27} +14.8^\circ$ (c 0.59, MeOH); IR (CHCl₃) 1730, 1225, 1200, 1120 cm⁻¹; ¹H NMR (270 MHz) δ =0.89 (3H, t, J =7.3 Hz), 0.95 (3H, d, J =6.6 Hz), 1.16 (1H, ddd, J =3.3, 10.9, 13.5 Hz), 1.36 (3H, s), 1.41—1.85 (4H, m), 2.20 (3H, s), 2.32—2.42 (1H, m), 3.67 (3H, s), 3.73 (3H, s), 4.53 (1H, d, J =10.8 Hz), 4.59 (1H, d, J =10.8 Hz); EIMS m/z (rel intensity) 306 (M^+ ; 4), 275 (8), 259 (21), 247 (35), 230 (74), 197 (95), 169 (100), 155 (34), 137 (42), 109 (45). HREIMS. Found: m/z 275.1328. Calcd for C₁₃H₂₃O₄S: M -OMe, 275.1317.

12b: $[\alpha]_D^{27} +9.5^\circ$ (c 0.92, MeOH); IR (CHCl₃) 1730, 1480, 1210, 1035 cm⁻¹; ¹H NMR (270 MHz) δ =0.89 (3H, t, J =7.8 Hz), 0.95 (3H, d, J =6.8 Hz), 1.36 (3H, s), 1.30—1.60 (4H, m), 1.97 (1H, qdd, J =6.8, 3.2, 16.5 Hz), 2.19 (3H, s), 2.30 (1H, dddd, J =5.3, 5.6, 8.3, 8.3 Hz), 3.67 (3H, s), 3.72 (3H, s), 4.52 (1H, d, J =10.8 Hz), 4.57 (1H, d, J =10.8 Hz); EIMS m/z (rel intensity) 306 (M^+ ; 1), 275 (16), 247 (42), 230 (99), 197 (100), 169 (92), 155 (42), 137 (50), 109 (59). HREIMS. Found: m/z 275.1346. Calcd for C₁₃H₂₃O₄S: M -OMe, 275.1317.

(2S,3R,5S)-5-Ethyl-2,3-dimethyl-2-[(methylthio)methoxy]hexanedioic Acid (5). To a solution of **12a** (38.7 mg, 0.126 mmol) in THF (1 ml) under nitrogen were added H₂O (4 ml) and 5 M aqueous LiOH solution (0.25 ml) and the mixture was stirred at room temperature for 2 d. The progress of the reaction was monitored by TLC. After none of **12a** could be detected by TLC (ca. 2 d), the mixture was heated under reflux for an additional 1 h, cooled to room temperature, diluted with 10% aqueous citric acid solution (5 ml), and extracted with EtOAc (3×5 ml). The combined extracts were dried and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel [4 g, hexane-EtOAc (1/1)], providing **5** (32 mg, 91%) as colorless needles: Mp 90—91 °C (hexane-ether); $[\alpha]_D^{20} -9.7^\circ$ (c 0.81, MeOH); IR (CHCl₃) 3600—2200, 1710, 1460, 1380, 1225, 1045 cm⁻¹; ¹H NMR (270 MHz) δ =0.98 (3H, t, J =7.3 Hz), 1.06 (3H, d, J =6.6 Hz), 1.16—1.32 (1H, m), 1.40 (3H, s), 1.40—1.60 (1H, m), 1.60—1.86 (2H, m), 1.90—2.06 (1H, m), 2.24 (3H, s), 2.32—2.46 (1H, m), 4.58 (1H, d, J =10.6 Hz), 4.64 (1H, d, J =10.6 Hz); EIMS m/z (rel intensity) 278 (M^+ ; 5), 233 (8), 213 (30), 202 (22), 184 (18), 173 (4), 155 (84), 137 (14), 127 (22), 109 (18). Found: C, 51.66; H, 7.73%. Calcd for C₁₂H₂₂O₅S: C, 51.78; H, 7.97%.

(2S,3R,5S)-5-Ethyl-2,3-dimethyl-2-[(methylthio)methoxy]hexanedioic Anhydride (13). To a solution of **5** (32.0 mg, 0.115 mmol) in CH₂Cl₂ (1 ml) under nitrogen was added dicyclohexylcarbodiimide (DCC) (27.4 mg, 0.133 mmol). The mixture was stirred at room temperature for 2 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 **13** (32 mg) as a colorless oil: IR (CHCl₃) 1795, 1750, 1475, 1040 cm⁻¹; ¹H NMR (270 MHz) δ =0.98 (3H, t, J =7.6 Hz), 0.98 (3H, d, J =6.9 Hz), 1.20—1.45 (1H, m), 1.54 (3H, s), 1.60—2.00 (4H, m), 2.00—2.14 (1H, m), 2.19 (3H, s), 4.45 (1H, d, J =11.2 Hz), 4.53 (1H, d, J =11.2 Hz); EIMS m/z (rel intensity) 260 (M^+ ; 47), 242 (8), 232 (11), 218 (3), 213 (7), 184 (31), 156 (100), 138 (26), 127 (95), 101 (54). This material was sufficiently pure and

used for the next reaction without further purification.

Seco Acid (15). A mixture of (+)-retronecine (**4**)^{2a} (17.9 mg, 0.115 mmol) and Bu₂SnO (31.6 mg, 0.127 mmol) in benzene (5 ml) under nitrogen was heated under reflux for 24 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 tin alkoxide **14** as a white solid, which was suspended in toluene (1 ml) under nitrogen. To the cooled (0 °C), stirred suspension of **14** was added dropwise a solution of **13** (14.4 mg) in toluene (2 ml). The mixture was stirred at 0 °C for 30 min and then at room temperature for 16 h and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel [3 g, CHCl₃-MeOH (5/1 → 1/1 → 1/5)], affording **15** (35.6 mg, 81% from **5**) as a colorless amorphous solid: $[\alpha]_D^{27.0} +2.4^\circ$ (c 0.99, MeOH); IR (CHCl₃) 3600—3000, 1730, 1380, 1250, 1120, 1000 cm⁻¹; ¹H NMR (270 MHz) δ =0.80 (3H, t, J =7.3 Hz), 0.89 (3H, d, J =6.6 Hz), 0.85—1.03 (4H, m), 1.23 (3H, s), 1.16—1.54 (2H, m), 2.07 (3H, s), 1.80—2.20 (2H, m), 2.87 (1H, ddd, J =6.6, 10.2, 10.6 Hz), 3.46 (1H, d, J =15.2 Hz), 3.60 (1H, ddd, J =0.3, 0.3, 6.6 Hz), 4.17 (1H, d, J =15.2 Hz), 4.45 (2H, m), 4.48 (1H, br s), 4.62 (1H, br s), 4.60—4.68 (1H, m), 4.76 (1H, d, J =13.9 Hz), 5.76 (1H, br s); FABMS (matrix: 3-nitrobenzyl alcohol) m/z (rel intensity) 438 [(M +Na)⁺; 2], 416 [(M +H)⁺; 100]. HRFABMS. Found: m/z 416.2076. Calcd for C₂₀H₃₄NO₆S: M +H, 416.2107.

Yamataimine MTM Ether (16) and Dimer 17. To a mixture of DCC (654 mg, 3.17 mmol), 4-dimethylamino-pyridine (DMAP) (1.12 g, 9.18 mmol), and (±)-10-camphorsulfonic acid (CSA) (833 mg, 3.59 mmol) in CHCl₃ (50 ml) under nitrogen was added a solution of **15** (150 mg, 0.36 mmol) in CHCl₃ (100 ml) over a 4-d period at room temperature. After being stirred for an additional 1 d, the mixture was concentrated under reduced pressure to a volume of 50 ml and washed with 1 M aqueous Na₂CO₃ solution (10 ml). The aqueous layer was extracted with CHCl₃ (3×10 ml). The organic layers were combined, washed, dried, and concentrated. The residue was purified by repeated column chromatography on silica gel [10 g, benzene-MeOH (10/1)], affording yamataimine MTM ether (**16**) (22.3 mg, 16%) as colorless needles.

16: Mp 141.5—143 °C (hexane-ethanol); $[\alpha]_D^{25} +64.8^\circ$ (c 0.50, MeOH); IR (CHCl₃) 1725, 1600, 1440, 1380, 1205, 1100 cm⁻¹; ¹H NMR (270 MHz) δ =0.88 (3H, t, J =7.6 Hz), 1.00 (3H, d, J =6.6 Hz), 1.01—1.09 (1H, m), 1.29 (3H, s), 1.22—1.49 (2H, m), 1.81—1.98 (2H, m), 1.99—2.28 (2H, m), 2.16 (3H, s), 2.29—2.49 (2H, m), 3.28 (1H, br d, J =17.5 Hz), 3.25—3.38 (1H, m), 3.97 (1H, br d, J =17.5 Hz), 3.99 (1H, d, J =11.3 Hz), 4.22 (1H, m), 4.44 (1H, d, J =9.9 Hz), 4.58 (1H, d, J =9.9 Hz), 5.04 (1H, br dd, J =3.0, 3.3 Hz), 5.48 (1H, d, J =11.3 Hz), 6.14 (1H, br s); EIMS m/z (rel intensity) 397 (M^+ ; 13), 350 (14), 336 (4), 321 (12), 292 (100), 136 (61), 120 (83). Found: C, 60.17; H, 7.58; N, 3.70%. Calcd for C₂₀H₃₁NO₅S: C, 60.43; H, 7.86; N, 3.52%. Lactonization of **15** (26.5 mg, 0.064 mmol) with DCC (143 mg, 0.69 mmol), DMAP (201 mg, 1.65 mmol), and CSA (153 mg, 0.66 mmol) in CHCl₃ (30 ml) was performed at room temperature for 7 d to give **16** (3.2 mg, 13%) along with dimer **17** (2.6 mg, 10%).

17: $[\alpha]_D$ not measured; IR (CHCl₃) 1725, 1600, 1460, 1440 cm⁻¹; ¹H NMR (270 MHz) δ =0.85 (6H, t, J =7.4 Hz),

0.95 (6H, d, $J=6.8$ Hz), 1.12 (2H, ddd, $J=3.1, 11.1, 14.2$ Hz), 1.32 (6H, s), 1.20–1.70 (8H, m), 1.88–2.04 (2H, m), 2.06–2.15 (2H, m), 2.17 (6H, s), 2.24–2.36 (2H, m), 2.64 (2H, dd, $J=9.6, 18.1$ Hz), 3.27–3.41 (4H, m), 3.93 (2H, br d, $J=14.0$ Hz), 4.33 (2H, br s), 4.48 (2H, d, $J=10.6$ Hz), 4.57 (2H, d, $J=10.6$ Hz), 4.60 (2H, d, $J=13.6$ Hz), 4.88 (2H, d, $J=13.6$ Hz), 5.33 (2H, dd, $J=0.7, 3.5$ Hz), 5.76 (2H, br s); FABMS (matrix: 3-nitrobenzyl alcohol) m/z (rel intensity) 795 [(M+H)⁺; 36]. HRFABMS. Found: m/z 795.3893. Calcd for C₄₀H₆₃N₂O₁₀S₂: M+H, 795.3925.

(+)-Yamataimine (1). To a stirred solution of **16** (18.4 mg, 0.046 mmol) in CH₂Cl₂ (1.5 ml) under nitrogen was added a solution of triphenylcarbenium tetrafluoroborate (35.7 mg, 0.11 mmol) in one portion. The reaction mixture was stirred at room temperature for 16 h. The reaction was quenched by addition of 1 M aqueous K₂CO₃ solution (5 ml) and the aqueous mixture was extracted with CHCl₃ (3×10 ml). The combined extracts were washed, dried, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel [3 g, benzene–MeOH (10/1)], providing **1** (9.9 mg, 64%) as colorless needles: Mp 178.5–180 °C (hexane–EtOH); $[\alpha]_D^{24} +59.3^\circ$ (c 0.14, EtOH) [Lit,³⁾ mp 181–182 °C (petroleum ether–acetone); $[\alpha]_D^{18} +63.6^\circ$ (EtOH); IR (CHCl₃) 3580, 1725, 1650, 1460, 1445, 1270, 1240, 1200, 1140, 1120, 1065 cm⁻¹; ¹H NMR (270 MHz) $\delta=0.88$ (3H, t, $J=7.5$ Hz), 1.02 (3H, d, $J=6.6$ Hz), 1.00–1.14 (1H, m), 1.21 (3H, s), 1.19–1.70 (4H, m), 2.00–2.58 (5H, m), 3.32–3.43 (2H, m), 4.04 (1H, br d, $J=15.5$ Hz), 4.12 (1H, d, $J=11.9$ Hz), 4.30 (1H, br s), 5.03 (1H, dd, $J=3.0, 3.0$ Hz), 5.35 (1H, d, $J=11.9$ Hz), 6.15 (1H, br s); EIMS m/z (rel intensity) 337 (M⁺; 25), 309 (1), 293 (9), 278 (3), 250 (6), 222 (26), 209 (8), 138 (53), 136 (55), 119 (100), 106 (16). HREIMS. Found: m/z 337.1910. Calcd for C₁₈H₂₇NO₅: M, 337.1889.

We thank Professor Tsutomu Furuya, Kitasato Uni-

versity for providing us with authentic yamataimine and the spectral data. Financial support from the Ministry of Education, Science and Culture [a Grant-in-Aid for Scientific Research No. 05680499] is gratefully acknowledged.

References

- 1) A. R. Mattocks, "Chemistry and Toxicology of Pyrrolizidine Alkaloids," Academic Press, London (1986), Chaps. 1, 3, 7, and 11.
- 2) a) H. Niwa, Y. Miyachi, O. Okamoto, Y. Uosaki, A. Kuroda, H. Ishiwata, and K. Yamada, *Tetrahedron*, **48**, 393 (1992); b) H. Niwa, T. Ogawa, O. Okamoto, and K. Yamada, *Tetrahedron*, **48**, 10531 (1992), and references cited therein; c) H. Niwa, T. Sakata, and K. Yamada, *Bull. Chem. Soc. Jpn.*, **67**, 1990 (1994).
- 3) M. Hikichi and T. Furuya, *Tetrahedron Lett.*, **1978**, 767.
- 4) J. N. Marx and L. R. Norman, *J. Org. Chem.*, **40**, 1602 (1975).
- 5) A. Barco, S. Benetti, and G. P. Pollini, *Synthesis*, **1973**, 316.
- 6) K. Narasaka, T. Sakakura, T. Uchimarui, D. Guédin-Vuong, *J. Am. Chem. Soc.*, **106**, 2954 (1984).
- 7) J. D. White, J. C. Amedio, Jr., S. Gut, S. Ohira, and L. R. Jayasinghe, *J. Org. Chem.*, **57**, 2270 (1992).
- 8) E. P. Boden and G. E. Keck, *J. Org. Chem.*, **50**, 2394 (1985).
- 9) J. Inanaga, K. Hirata, H. Saeki, T. Katsuki, and M. Yamaguchi, *Bull. Chem. Soc. Jpn.*, **52**, 1989 (1979).
- 10) H. Niwa and Y. Miyachi, *Bull. Chem. Soc. Jpn.*, **64**, 716 (1991).