An Improved Synthesis of (±)-Otonecine and a Synthesis of a 12-Membered Otonecine Diester

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Synopsis. (±)-4-Methyl-1-phenylthio-8-oxa-4-azabicyclo[5.2.1]decane-9,10-dione was efficiently converted into (±)-otonecine, which was regioselectively coupled with (*E*)-2-ethylidenehexanedioic acid to give a 12-membered otonecine diester.

Macrocyclic pyrrolizidine alkaloids containing otonecine (**1**) or retronecine (**2**) as the necine base portion are known to exhibit remarkable hepatotoxicity and, in certain cases, carcinogenicity and antitumor activity.[1] Characteristic structures coupled with diverse biological activities have made these alkaloids attractive synthetic targets. Although numerous results on the synthesis of retronecine-containing pyrrolizidine alkaloids have been published,[2,3] only limited progress has so far been achieved on the synthesis of pyrrolizidine alkaloids of otonecine type.[4] Herein we wish to disclose an improved synthesis of (±)-otonecine (**1**) and a synthesis of racemic 12-membered otonecine diester **3** as a prelude to the total synthesis of macrocyclic pyrrolizidine alkaloids of otonecine type.

Previously, we reported the first synthesis of (±)-otonecine (**1**),[4] in which the selective reduction of the lactone group in bicyclic selenide **4** suffered from the problem of low chemical yield (17%) owing to the presence of the C–Se bond liable to be cleaved reductively. We anticipated that this disadvantage might be overcome by replacing phenylseleno group into a reductive cleavage-resistant phenylthio group as shown in bicyclic sulfide **5** (Chart 1). Thus, our efforts towards improving the synthesis of (±)-**1** started from the known methiodide **6**.[4] Treatment of **6** with NaH in tetrahydrofuran (THF) followed by reaction with *S*-phenyl benzenethiosulfonate afforded the desired bicyclic sulfide **5** in 84% yield. The crucial reduction of **5** with diisobutylaluminum hydride in THF in the presence of a Lewis acid dimethylaluminum chloride proceeded successfully and subsequent acetylation of the crude product provided desired diacetate **7** in 82% yield. Oxidation of **7** was effected with *m*-chloroperbenzoic acid in CH_2Cl_2 to give the corresponding sulfoxide, which upon heating in refluxing toluene provided (±)-otonecine diacetate (**8**) in 46% overall yield. Methanolysis of **8** gave (±)-**1** in 94% yield. The present synthesis furnished (±)-**1** in 30% overall yield from **6**, while our previous synthesis[4] could never provide more than a 6% overall yield of (±)-**1** from **6**.

For the regioselective synthesis of 12-membered otonecine diester **3** from (±)-**1** and diacid **9**, we utilized the method recently reported by White.[5] Thus, diacid **9** prepared from ethyl hydrogen adipate in a five-step sequence was converted into cyclic anhydride **11**, which upon treatment with 2,2,2-trifluoroethanol in pyridine furnished monoester **10** in 72% overall yield. The reaciton of (±)-**1** with **10** under Keck's conditions[6] proceeded regioselectively to furnish 7-*O*-acylated otonecine monoester **12** in 49% yield. Of two hydroxyl groups in (±)-**1**, the secondary one was selectively acylated in the reaction. This abnormal reactivity of **1** in the acylation reaction may be due to an intramolecular hydrogen bond between the secondary hydroxyl group and the ketone strongly polarizing by a transannular interaction with the amino group. As a result, the nucleophilicity of the secondary hydroxyl group in **1** may increase more than that of the primary one. The final step was lactonization of **12**, which was effected with Bu_3SnOMe in refluxing toluene[5] to give **3** in 46% yield.

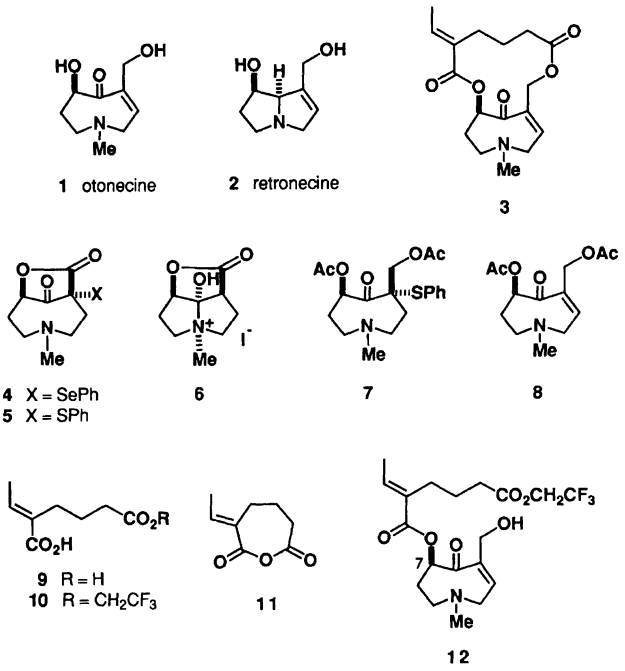

Chart 1.

In summary, the improved synthesis of (±)-otonecine (**1**) and the synthesis of 12-membered otonecine diester **3** were achieved.

Experimental

Melting points are uncorrected. 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: 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, HRCIMS, and HRFABMS) were measured on a JEOL JMS-LG2000 instrument. Fuji-Davison silica gel BW-820MH and Merck aluminum oxide 90 (activity II-III, Art. 1097) (alumina) were used for column chromatography. Merck precoated silica gel 60 F_{254} plates, 0.25 mm thickness were used for analytical thin-layer chromatography (TLC) and for preparative TLC. Dichloromethane (CH_2Cl_2), pyridine, and diisopropylamine were distilled from calcium hydride (CaH_2) under nitrogen. 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.

(R^*, R^*)-4-Methyl-1-phenylthio-4-aza-8-oxabicyclo[5.2.1.]decane-9,10-dione (5). To a suspension of NaH (22.8 mg of 60% dispersion in mineral oil, 0.569 mmol) in THF (0.7 ml) under nitrogen was added powdered **6**[4] (31.2 mg, 0.096 mmol) in one portion. The mixture was stirred at room temperature for 10 min, and a solution of (*S*)-phenyl benzenethiosulfonate (36.2 mg, 0.145 mmol) in THF (0.7 ml) was added. The mixture was stirred at room temperature for 30 min, and the reaction was quenched by addition of saturated NH_4Cl solution (0.5 ml). The mixture was diluted with saturated $NaHCO_3$ solution (1 ml), saturated with NaCl, and extracted with EtOAc (5×4.5 ml). The combined extracts were washed, dried, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel [1.5 g, $CHCl_3$–MeOH (10/1)→MeOH], affording **5** (24.5 mg, 84%) as colorless needles: Mp 154—155 °C (hexane–benzene); IR ($CHCl_3$) 1765, 1670, 1115, 1055 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ=2.01 (3H, s), 2.19 (1H, ddd, J=3.6, 3.6, 14.5 Hz), 2.38—2.84 (6H, m), 2.91, (1H, dd, J=4.9, 12.5 Hz), 3.70 (1H, dd, J=1.8, 3.6 Hz), 7.26—7.40 (3H, m), 7.59—7.63 (2H, m); EIMS m/z (rel intensity) 291 (M^+; 15), 182 (100), 139 (2), 109 (6), 83 (4), 65 (4). Found: C, 61.70; H, 5.81; N, 4.73%. Calcd for $C_{15}H_{17}NO_3S$: C, 61.83; H, 5.88; N, 4.81%.

(4R^*,6S^*)-1-Methyl-6-acetoxy-4-acetoxymethyl-4-(phenylthio)azacyclooctan-5-one (7). To a stirred solution of **5** (38.7 mg, 0.133 mmol) in toluene (1.5 ml) under argon was added 0.54 M dimethylaluminum chloride (1 M=1 mol dm^{-3}) in toluene (0.32 ml, 0.173 mmol) at room temperature. The mixture was stirred at room temperature for 30 min and then cooled to −78 °C. To the cooled mixture was added 1 M diisobutylaluminum hydride in hexane (0.53 ml, 0.53 mmol). The mixture was allowed to warm to 0 °C and stirred at 0 °C for 20 min and then at room temperature for an additional 3.5 h. The reaction was quenched by addition of EtOAc (1 ml). The mixture was stirred for 15 min and concentrated under reduced pressure. The residue was suspended in pyridine (1 ml) under nitrogen, and acetic anhydride (0.5 ml) was added. The mixture was vigorously stirred at room temperature for 1 d and filtered through a pad of Celite. The combined filtrate and washings were concentrated under reduced pressure. The residue was purified by column chromatography on alumina [6 g, $CHCl_3$→EtOAc], providing **7** (41.2 mg, 82%) as colorless needles: Mp 106.5—107.5 °C (hexane–benzene); IR ($CHCl_3$) 1735, 1685, 1375, 1240, 1045 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ=2.14 (3H, s), 2.17 (3H, s), 2.22 (3H, s), 2.03—2.28 (4H, m), 2.24—2.67 (4H, m), 3.94 (1H, d, J=13.1 Hz), 4.25 (1H, d, J=13.1 Hz), 5.91 (1H, dd, J=4.3, 9.2 Hz), 7.26—7.45 (5H, m); EIMS m/z (rel intensity) 379 (M^+; 21), 320 (17), 270 (15), 222 (72), 162 (100), 129 (50), 58 (24). Found: C, 60.01; H, 6.64; N, 3.72%. Calcd for $C_{19}H_{25}NO_5S$: C, 60.14; H, 6.64; N, 3.69%.

(±)-Otonecine Diacetate (8). To a cooled (−30 °C), stirred solution of **7** (7.6 mg, 0.022 mmol) in CH_2Cl_2 (1 ml) was added *m*-chloroperbenzoic acid (4.8 mg, 0.023 mmol). The mixture was stirred at −30 °C for 1.5 h, and the reaction was quenched by addition of dimethyl sulfide (0.1 ml). The mixture was concentrated under reduced pressure. The residue was dissolved in saturated $NaHCO_3$ solution (0.5 ml). The aqueous mixture was saturated with NaCl and extracted with EtOAc (4×5 ml). The combined extracts were concentrated under reduced pressure to give the crude sulfoxide, which was dissolved in toluene (1.5 ml). The mixture was heated under reflux for 1 h under nitrogen. After cooling, the mixture was concentrated under reduced pressure. The oily residue was purified by column chromatography on alumina [1 g, benzene→$CHCl_3$→acetone], affording **8** (2.5 mg, 46%) as a colorless amorphous solid: IR ($CHCl_3$) 1740, 1640, 1375, 1245 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ=1.95 (1H, ddd, J=3.1, 3.1, 15.6 Hz), 2.09 (3H, s), 2.18 (3H, s), 2.28 (3H, s), 2.31—2.39 (1H, m), 2.73 (1H, d, J=3.0 Hz), 2.77 (1H, d, J=2.0 Hz), 3.15 (1H, br d, J=7.8 Hz), 3.26 (1H, br d, J=7.8 Hz), 4.63 (1H, br dd, J=1.0, 12.5 Hz), 4.71 (1H, dddd, J=1.7, 1.7, 1.7, 12.5 Hz), 5.28 (1H, dd, J=3.3, 3.3 Hz), 5.82 (1H, br s); EIMS m/z (rel intensity) 269 (M^+; 28), 227 (38), 210 (100). HREIMS. Found: m/z 269.1288. Calcd for $C_{13}H_{19}NO_5$: M, 269.1263.

(±)-Otonecine (1). To a solution of **8** (15.5 mg, 0.058 mmol) in MeOH (1.3 ml) under nitrogen was added 0.43 M NaOMe in MeOH (0.74 ml, 0.32 mmol). The mixture was stirred at room temperature for 1 h, and Amberlite IRC-50 (H form, 1 g) was added. The mixture was stirred at room temperature for 30 min and filtered through a cotton plug. The resin was thoroughly washed with MeOH and then eluted with saturated NH_3 in MeOH (ca. 100 ml). Concentration of the eluent provided (±)-**1** (10 mg, 94%) as a colorless oil: IR ($CHCl_3$) 3400, 1568, 1382, 1054 cm^{-1}; ^1H NMR (270 MHz, CD_3OD) δ=1.98 (1H, dddd, J=2.0, 2.0, 5.8, 12.8 Hz), 2.05—2.24 (1H, m), 2.33 (3H, s), 2.84—2.99 (1H, m), 3.08 (1H, dddd, J=2.0, 2.0, 5.8, 12.0 Hz), 3.55 (2H, br d, J=2.0 Hz), 3.92 (1H, br dd, J=2.6, 2.6 Hz), 4.07 (1H, dddd, J=1.7, 1.7, 1.7, 14.2 Hz), 4.17 (1H, br dd, J=1.7, 14.2 Hz), 5.71 (1H, m); EIMS m/z (rel intensity) 185 (M^+; 88), 168 (50), 128 (100), 126 (77), 110 (21). HREIMS. Found: m/z 185.1061. Calcd for $C_9H_{15}NO_3$: M, 185.1052. Spectral properties of synthetic (±)-**1** were identical with those of natural **1** in all respects.

(*E*)-2-Ethylidenehexanedioic Acid (9). Compound **9** was prepared from ethyl hydrogen adipate in a five-step sequence [(i) LDA; CH_3CHO, THF; (ii) CH_2N_2; (iii) CH_3SO_2Cl, Py; (iv) DBU, benzene; (v) KOH, MeOH]: Mp 127.0—128.5 °C (EtOH); IR (KBr) 3400—2800, 1710, 1700, 1650, 1420, 1410, 1300, 1280, 1240 cm^{-1}; ^1H NMR (270 MHz, acetone-d_6) δ=1.67 (2H, br tt, J=7.4, 7.4 Hz),

1.78 (3H, d, J=7.1 Hz), 2.26 (2H, t, J=7.4 Hz), 2.33 (2H, br t, J=7.4 Hz), 6.86 (1H, q, J=7.1 Hz); CIMS m/z (rel intensity) 173 (M^++H; 17), 155 (100), 154 (54), 127 (31), 126 (40), 112 (22). HRCIMS. Found: m/z 173.0840. Calcd for $C_8H_{13}O_4$: M+H, 173.0814.

6-(2,2,2-Trifluoroethyl) Hydrogen (*E*)-2-Ethylidenehexanedioate (10). Compound **10** was prepared from **9** through **11** in a two-step sequence [(i) DCC, CH_2Cl_2; (ii) CF_3CH_2OH, Py]: Mp 35.5—37.0 °C (pentane); IR ($CHCl_3$) 1755, 1690, 1645, 1410, 1170 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ=1.75—1.87 (2H, m), 1.85 (3H, d, J=7.3 Hz), 2.38 (2H, t, J=7.3 Hz), 2.45 (2H, t, J=7.3 Hz), 4.47 (1H, q, J=8.6 Hz), 7.11 (1H, q, J=7.3 Hz); EIMS m/z (rel intensity) 254 (M^+; 4), 236 (76), 217 (19), 208 (94), 194 (98), 180 (20). Found: C, 47.30; H, 4.93%. Calcd for $C_{10}H_{13}O_4F_3$: C, 47.25; H, 5.15%.

7-*O*-[(*E*)-2-Ethylidene-5-(2,2,2-trifluoroethoxycarbonyl)pentanoyl]otonecine (12). To a stirred solution of (±)-**1** (11.2 mg, 0.061 mmol) in $CHCl_3$ (0.9 ml) under nitrogen were added a solution of **10** (15.4 mg, 0.061 mmol) in $CHCl_3$ (0.9 ml), 4-dimethylaminopyridine (DMAP) (37.0 mg, 0.303 mmol), and (±)-10-camphorsulfonic acid (CSA) (28.1 mg, 0.121 mmol). To the mixture was added a solution of DCC (25.0 mg, 0.121 mmol) in $CHCl_3$ (0.9 ml), and the mixture was stirred at room temperature for 1.5 h. The mixture was directly subjected to purification by column chromatography on silica gel [4 g, $CHCl_3$→$CHCl_3$–MeOH (50/1→5/1)→$CHCl_3$–MeOH–concd NH_3 aq (50/10/1)→MeOH–concd NH_3 aq (20/1)], providing an 8:1 mixture[7] of salt (±)-**12**·CSA and DMAP (20.6 mg) as a colorless amorphous solid. This material was dissolved in saturated $NaHCO_3$ solution (1 ml), and the aqueous solution was saturated with NaCl and extracted with $CHCl_3$ (8 ml×4). The combined extracts were washed, dried, and concentrated under reduced pressure, affording an 8:1 mixture[7,8] of free **12** and DMAP (13.1 mg; calculated yield of **12**, 49%). As free **12** was unstable and liable to undergo solvolysis in a hydroxylic solvent such as MeOH, free **12** was liberated from the salt just prior to use, and the mixture of free **12** and DMAP was used for the next reaction without further purification. Spectral data of **12:** IR ($CHCl_3$) 3600—3200, 1755, 1710, 1650, 1170 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ=1.84 (3H, d, J=6.9 Hz), 1.79—1.90 (2H, m), 2.06 (1H, dddd, J=3.3, 3.3, 3.3, 14.5 Hz), 2.26 (3H, s), 2.30—2.46 (1H, m), 2.41 (2H, t, J=7.9 Hz), 2.46 (2H, t, J=7.3 Hz), 2.70—2.88 (2H, m), 3.23 (2H, m), 4.15 (1H, br dd, J=1.7, 12.9 Hz), 4.29 (1H, br dd, J=1.3, 12.9 Hz), 4.47 (2H, q, J=8.6 Hz), 5.27 (1H, dd, J=3.3, 3.3 Hz), 5.73 (1H, br s), 7.00 (1H, q, J=6.9 Hz); FABMS m/z (rel intensity) 422 [$(M+H)^+$; 16], 307 (9), 154 (100), 137 (54), 109 (25). HRFABMS. Found: m/z 422.1768. Calcd for $C_{19}H_{27}NO_6F_3$: M+H, 422.1791.

12-Membered Otonecine Diester (3). To a solution of a 1:1 mixture[7,8] of free **12** and DMAP (3.7 mg; the calculated content of **12**, 2.7 mg, 6.8 μmol) in toluene (1.5 ml) under nitrogen was added 8.7 μM Bu_3SnOMe in toluene (0.1 ml, 0.87 μmol). The mixture was heated under reflux for 22 h. After cooling, the mixture was concentrated under reduced pressure. The residue was dissolved in 0.01 M HCl (0.5 ml). The mixture was washed with EtOAc (4×0.5ml), made basic to pH 9 with K_2CO_3, saturated with NaCl, and extracted with $CHCl_3$ (1 ml×4). The combined extracts were dried and concentrated under reduced pressure. The oily residue was purified by preparative TLC on silica gel [200×100×0.25 mm, $CHCl_3$–MeOH–concd NH_3 aq (50/10/1)], affording **3** (1.0 mg, 46%) as a colorless amorphous solid: IR ($CHCl_3$) 1720, 1710, 1260, 1170 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ=1.54—1.76 (1H, m), 1.82 (3H, d, J=6.9 Hz), 1.85—1.96 (1H, m), 2.05—2.16 (1H, m), 2.16 (3H, s), 2.26—2.54 (5H, m), 2.74—2.91 (2H, m), 3.23 (1H, br ddd, J=2.0, 2.0, 18.8 Hz), 3.36 (1H, br d, J=18.8 Hz), 4.40 (1H, d, J=11.2 Hz), 5.08 (1H, d, J=11.2 Hz), 5.22 (1H, dd, J=3.3, 5.9 Hz), 6.02 (1H, br s), 6.87 (1H, q, J=6.9 Hz); EIMS m/z (rel intensity) 321 (M^+; 100), 293 (14), 266 (7), 249 (14), 182 (5), 167 (10), 155 (14), 128 (32), 110 (35). HRFABMS. Found: m/z 322.1669. Calcd for $C_{17}H_{24}NO_5$: M+H, 322.1655.

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7) The ratio was determined by ^1H NMR spectral analysis of the mixture.

8) The ratio of **12** and DMAP widely varied from batch to batch (1:1—8:1).