A Tin-Mediated One-Step Synthesis of (+)-Dicrotaline, an 11-Membered Dilactonic Pyrrolizidine Alkaloid

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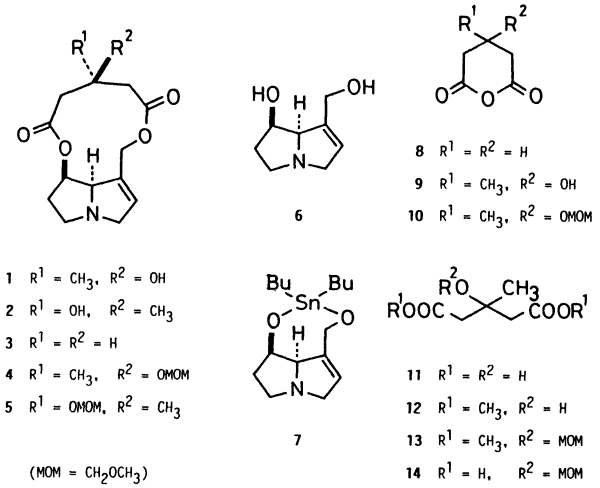
Synopsis. A new synthesis of (+)-dicrotaline (**1**), an 11-membered dilactonic pyrrolizidine alkaloid of retronecine (**6**) type has been achieved in one step by utilizing a tin-mediated lactonization process.

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 presence of a large-ring dilactone.[1] The final crucial step in the total synthesis of these alkaloids is the formation of the large-ring dilactone from a pyrrolizidine diol ["necine," the most commonly (+)-retronecine (**6**)] and a diacid ("necic acid"). Overcoming this synthetic hurdle, some of the macrocyclic pyrrolizidine alkaloids have been synthesized recently by several research groups including us.[2,4a] Herein we wish to disclose a new, single-step synthesis of (+)-dicrotaline (**1**),[2b] an 11-membered dilactonic pyrrolizidine alkaloid of retronecine (**6**) type by virtue of a tin-mediated lactonization reaction.[3]

Shanzer et al. have reported the novel synthesis of macrocyclic tetralactones by the reaction of various cyclic anhydrides with stannoxanes derived from diols and dibutyltin oxide (Bu_2SnO).[3a] We envisioned that this tinmediated "template-driven" macrocyclization process would be applicable to the construction of macrocyclic pyrrolizidine dilactones. In fact, treatment of the stannoxane intermediate **7**[4a] prepared from **6**[4b] and Bu_2SnO, with glutaric anhydride (**8**) in refluxing xylene provided in one step an 11-membered dilactone **3**[5] in 32% yield. We therefore applied this tin-mediated dilactone formation process to the synthesis of **1**. Thus, dicrotalic anhydride (**9**)[2b,6] prepared from dicrotalic acid (3-hydroxy-3-methylglutaric acid) (**11**)[6] was treated with **7** in refluxing xylene to give **1**[2b] and the diastereomer **2**[2b] in 10 and 12% yields, respectively. Spectral (^{1}H NMR, IR, and mass spectra) and chiroptical properties of synthetic **1** were identical with those of natural **1**. Although **1** could be synthesized in one step, the diastereoselectivity and the chemical yield were unsatisfactory, which may be explained by the presence of the free hydroxyl group in the anhydride **9**. Therefore, we next examined the lactonization using the protected cyclic anhydride **10** and **7**. The anhydride **10** was prepared from the the dimethyl ester **12**[6] as follows: (i) conversion of **12** into the methoxymethyl (MOM) ether **13**;[7] (ii) hydrolysis of **13** into the diacid **14**; (iii) conversion of **14** into **10**. Treatment of **10** with **7** under the conditions described above, however, provided a 1 : 1 mixture of the dilactones **4** and **5** in 19% yield. No improvement on the diastereoselectivity and the chemical yield in the dilactone formation could be achieved even employing **10**.

In summary, a one-step synthesis of (+)-dicrotaline (**1**) has been achieved by using the tin-mediated lactonization process although there has been a limitation in view of the diastereoselectivity and the chemical yield.



Experimental

Melting points are uncorrected. Infrared (IR) spectra were obtained on a JASCO Model IR-810 spectrophotometer. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a JEOL JNM-C675 (270 MHz) or a JEOL 90QE (90 MHz) spectrometer in $CDCl_3$ using tetramethylsilane (TMS) as an internal standard. Chemical shifts were expressed in parts per million (ppm) downfield from TMS (δ=0.0) and coupling constants in Hz. Optical rotations were measured on a JASCO DIP-181 polarimeter. The low- (CIMS and EIMS) and high-resolution (HRCIMS and HREIMS) mass spectra were recorded on a JEOL JMS-LG2000 instrument. Fuji-Davison silica gel BW-820-MH was used for column chromatography. Merck precoated silica gel 60 F_{254} plates, 0.25 mm thickness, were used for analytical and preparative thin-layer chromatography (TLC). Xylene and benzene were distilled from Na under nitrogen. Dichloromethane was distilled from CaH_2 under nitrogen. Tetrahydrofuran (THF) was distilled from Na-benzophenone ketyl under nitrogen. Chloroform was distilled from phosphorus pentoxide (P_2O_5).

17,18,19,20-Tetranorcrotalanan-11,15-dione (3). A mixture of **6**[4b] (25.9 mg, 0.167 mmol) and Bu_2SnO (49.9 mg, 0.200 mmol) in benzene (5 ml) was heated under reflux for 23 h with continuous removal of water by use of Molecular Sieves 4A (ca. 1 g). After cooling, the mixture was concentrated under reduced pressure to leave **7** as a pale yellow oil, which was suspended in xylene (3 ml). To the stirred suspension cooled at −25 °C was added a solution of **8** (21.0 mg, 0.184 mmol) in xylene (2 ml). The mixture was gradually warmed to room temperature for 3 h with stirring and then heated under reflux for 18 h. After cooling, the reaction mixture was concentrated under reduced pressure. Purifica-

tion of the residual oil by column chromatography on silica gel (2.5 g) with acetone–MeOH (1/0→5/1 volume ratio) afforded 13.5 mg (32% from **6**) of **3** as a colorless oil; $[\alpha]_D^{13}$ +37.8° (*c* 1.28, $CHCl_3$); lit,[5] $[\alpha]_D^{13}$ +39.0° (*c* 1.0, $CHCl_3$). The chiroptical and spectral (IR, ^1H NMR, and MS) properties of synthetic **3** were identical with those reported for **3**.[5]

(+)-Dicrotaline (1) and (+)-Epidicrotaline (2). The stannoxane **7** prepared from 20.2 mg (0.130 mmol) of **6** and 37.0 mg (0.150 mmol) of Bu_2SnO as described above was suspended in xylene (4.3 ml). To the stirred suspension was added **9**[2b,6] (19.3 mg. 0.134 mmol) at room temperature. The mixture was heated under reflux for 19 h. After cooling, the reaction mixture was concentrated under reduced pressure. Separation and purification of the residual oil with column chromatography on silica gel (3 g) with $CHCl_3$–MeOH (4/1→0/1 volume ratio) gave a mixture of **1** and **2** (11.6 mg) along with the unreacted **6** (16 mg, 79%). Further separation of the mixture of **1** and **2** by preparative TLC on silica gel with $CHCl_3$–MeOH–28% NH_3 aq (70/10/1 volume ratio) provided 3.8 mg (10% from **6**) of **1** as a colorless oil[8] and 4.2 mg (12% from **6**) of **2** as a colorless oil, respectively. **1**: $[\alpha]_D^{22}$ +11° (*c* 0.38, $CHCl_3$); lit,[2b] $[\alpha]_D^{18}$ +8.1° (*c* 1.18, $CHCl_3$). The hydrochloride of **1**: mp 198—200 °C decomp (EtOH); lit, mp 200 °C decomp (EtOH),[9] mp 211—212 °C decomp (EtOH).[2b] **2**: $[\alpha]_D^{22}$ +44° (*c* 0.32, $CHCl_3$); lit,[2b] $[\alpha]_D^{18}$ +43.3° (*c* 0.72, $CHCl_3$). Spectral (IR, ^1H NMR, and MS) properties of synthetic **1** and **2** were identical with those of natural **1** and those reported to synthetic **2**, respectively.[2b]

Dimethyl 3-(Methoxymethoxy)-3-methylglutarate (13). Dimethyl 3-hydroxy-3-methylglutarate (**12**) was prepared from **11** by the reported procedure.[6] To a solution of **12** (93.2 mg, 0.491 mmol) in $CHCl_3$ (3 ml) was added dimethoxymethane (methylal) (3 ml) and P_2O_5 (1.5 g).[7] The mixture was vigorously stirred at room temperature for 30 min. The reaction mixture was poured into a precooled, saturated aqueous $NaHCO_3$ solution (3 ml) and extracted with ether (3×8 ml). The extracts were combined, dried, and concentrated. Purification of the residual oil by column chromatography on silica gel (2 g) with hexane–EtOAc (6/1 volume ratio) gave 87.2 mg (76%) of **13** as a pale yellow oil; IR ($CHCl_3$) 1740, 1440, 1230, 1150, 1035 cm^{-1}; ^1H NMR (90 MHz) δ=1.49 (3H, s), 2.84 (4H, s), 3.35 (3H, s), 3.68 (6H, s), 4.76 (2H, s); CIMS (200 eV) *m/z* (rel intensity) 235 (M^++1; 100), 205 (40), 204 (95), 203 (51), 201 (57), 174 (92), 173 (40), 161 (46), 147 (96), 142 (90), 117 (65), 113 (40). HRCIMS. Found: *m/z* 235.1176. Cacld for $C_{10}H_{19}O_6$: M+H, 235.1181.

3-(Methoxymethoxy)-3-methylglutaric Acid (14). To a solution of **13** (47.6 mg, 0.203 mmol) in THF (2 ml) was added 0.5 M LiOH (2 ml) (1 M=1 mol dm^{-3}). The mixture was vigorously stirred at 40 °C for 24 h. The reaction mixture was neutralized by the addition of Amberlite CG-50 (acid form, 0.5 g). After being stirred for 10 min, the mixture was filtered through a column packed with Amberlite CG-50 (0.5 g). The column was washed thoroughly with MeOH. The filtrate and the column washings were combined and concentrated under reduced pressure. Purification of the residual oil by column chromatography on silica gel (4 g) with hexane–EtOAc–AcOH (15/15/1 volume ratio) gave 30.1 mg (76%) of **14** as a colorless oil; IR ($CHCl_3$) 3700—2400 (broad), 1720, 1025 cm^{-1}; ^1H NMR (90 MHz) δ=1.51 (3H, s), 2.89 (4H, s), 3.38 (3H, s), 4.80 (2H, s); CIMS (200 eV) *m/z* (rel intensity) 207 (M^++1; 3), 175 (100), 159 (40), 155 (37), 145 (84), 141 (65), 128 (20), 103 (37), 85 (21). HRCIMS. Found: *m/z* 207.0863. Calcd for $C_8H_{15}O_6$: M+H, 207.0868.

3-(Methoxymethoxy)-3-methylglutaric Anhydride (10). To a solution of **14** (46.2 mg, 0.224 mmol) in CH_2Cl_2 (1 ml) was added a solution of dicyclohexylcarbodiimide (46.2 mg, 0.224 mmol) in CH_2Cl_2 (1 ml) under nitrogen. The mixture was stirred at room temperature for 45 min and concentrated under reduced pressure. The residue was diluted with anhydrous acetone (5 ml) and insoluble materials were removed by filtration through a cotton plug. The filtrate was concentrated to leave 42.6 mg of crude **10** as a colorless oil; IR ($CHCl_3$) 1820, 1770, 1065, 1030 cm^{-1}; ^1H NMR (270 MHz) δ=1.44 (3H, s), 2.62 (2H, d, *J*=16.5), 3.16 (2H, d, *J*=16.5), 3.33 (3H, s), 4.72 (2H, s); CIMS (200 eV) *m/z* (rel intensity) 189 (M^++1; 22), 159 (100), 141 (87), 127 (55), 115 (33), 99 (38), 85 (37). HRCIMS. Found: *m/z* 189.0744. Calcd for $C_8H_{13}O_5$: M+H, 189.0763. The crude **10** was used for the next reaction without further purification.

13-(Methoxymethoxy)-17,19,20-trinorcrotalanan-11,15-diones (4 and 5). The stannoxane **7** prepared from 12.0 mg (0.0774 mmol) of **6** and 22.4 mg (0.0914 mmol) of Bu_2SnO as described before was suspended in xylene (3 ml). To the stirred suspension cooled at 0 °C was added a solution of **10** (16.0 mg, 0.0851 mmol) in xylene (1.0 ml). The mixture was stirred at 0 °C for 30 min and then at room temperature for 2 h. To the reaction mixture was added an another solution of **10** (5.8 mg, 0.030 mmol) in xylene (0.36 ml). After being stirred at 35 °C for additional 7 h, the mixture was heated under reflux for 36 h. After cooling, the reaction mixture was concentrated under reduced pressure. Separation of the residual oil by column chromatography on silica gel (2 g) with acetone→MeOH afforded 4.9 mg (19%) of a 1:1 mixture of **4** and **5** as a colorless oil. **4** and **5**: IR ($CHCl_3$) 1740, 1260, 1150, 1030 cm^{-1}; ^1H NMR (270 MHz) δ=1.57 (1.5H, s), 1.61 (1.5H, s), 2.2—2.3 (2H, complex pattern), 2.4—2.9 (5H, complex pattern), 3.43 (1.5H, s), 3.45 (1.5H, s), 3.5—3.6 (2H, complex pattern), 4.0—4.2 (2H, complex pattern), 4.56 (1H, m), 4.81 (2H, m), 5.22 (0.5H, m), 5.28 (0.5H, m), 5.32 (0.5H, d, *J*=12.9), 5.37 (0.5H, d, *J*=12.5), 5.92 (0.5H, br s), 5.95 (0.5H, br s); EIMS (70 eV) *m/z* (rel intensity) 325 (M^+; 45), 310 (7), 294 (26), 280 (6), 265 (53), 242 (28), 220 (23), 138 (51), 137 (71), 136 (86), 121 (74), 120 (75), 95 (78), 94 (100), 93 (63), 80 (55). HREIMS. Found: *m/z* 325.1535. Calcd for $C_{16}H_{23}O_6N$: M, 325.1526.

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