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Total Synthesis of Optically Active Monocrotaline, a Carcinogenic Pyrrolizidine Alkaloid Possessing an Eleven-Membered Retronecine Dilactone

Haruki Niwa,* Takeshi Ogawa, Osamu Okamoto, and Kiyoyuki Yamada*

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

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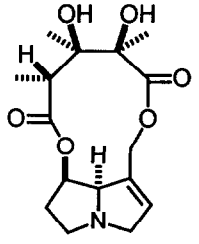
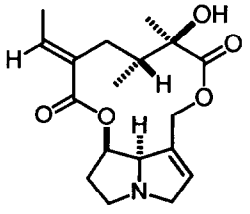
Abstract *— A total synthesis of the natural enantiomer of monocrotaline (1), a representative of carcinogenic pyrrolizidine alkaloids having an 11-membered retronecine dilactone was achieved through regioselective coupling of (+)-retronecine (3) and the optically active protected necic acid 8, the latter being prepared enantioselectively from the meso-diester 11.*

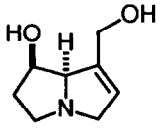
More than 200 pyrrolizidine alkaloids have been found in various plant species belonging to Compositae, Leguminosae, and Boraginaceae families.[1] Of those, the pyrrolizidine alkaloids having retronecine (**3**) or otonecine (**4**) as the necine base portion are known to exhibit marked hepatotoxicicty and, in certain cases, antitumor activity and carcinogenicity.[2] In particular, the greatest toxicity is shown by the retronecine- or otonecine-based macrocyclic dilactones. Monocrotaline (**1**) and integerrimine (**2**) are representatives of 11- and 12-membered retronecine dilactones, respectively.[2] The unique biological activities coupled with characteristic chemical structures have made macrocyclic pyrrolizidine alkaloids attractive synthetic targets. During the past three decades, the results of a number of synthetic studies on pyrrolizidine alkaloids have been published. However, most of the synthetic studies have been directed towards the necine portions, and only a few 11-membered[3] and 12-membered[4] alkaloids have so far been synthesized. Herein we disclose a full account of the stereo- and regiocontrolled total synthesis of the natural enantiomer of monocrotaline (**1**).[5]



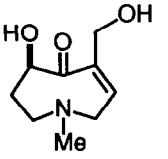
1 monocrotaline



2 integerrimine



3 retronecine

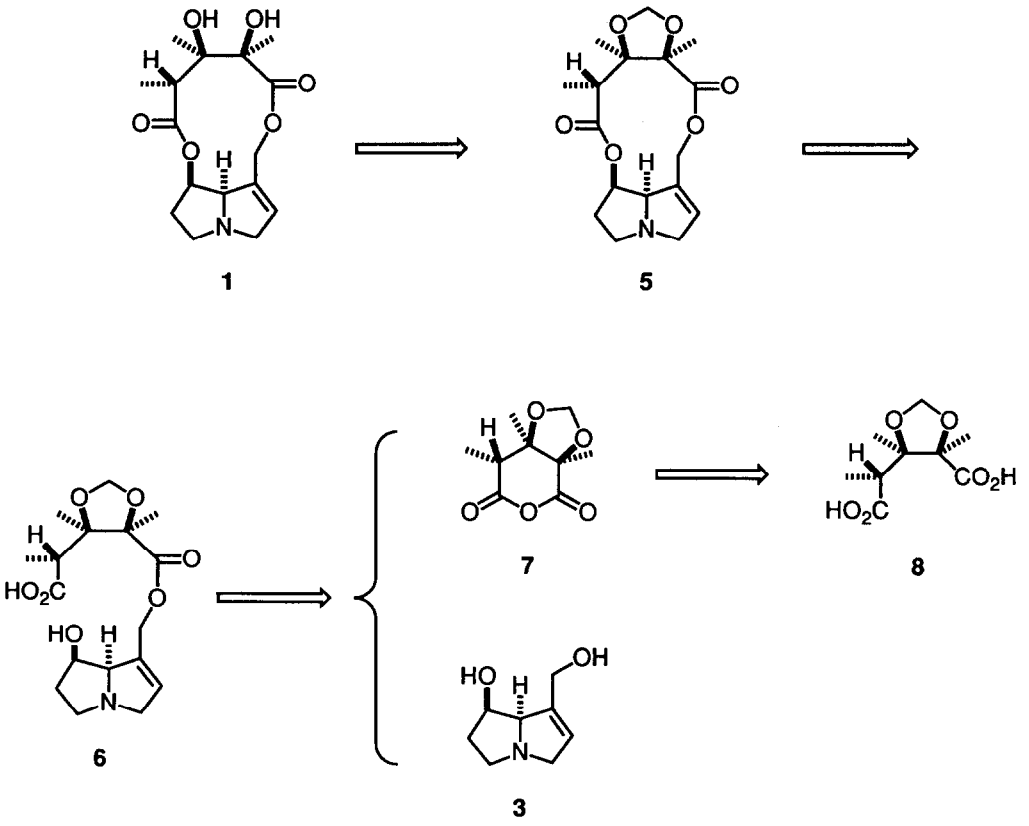


4 otonecine

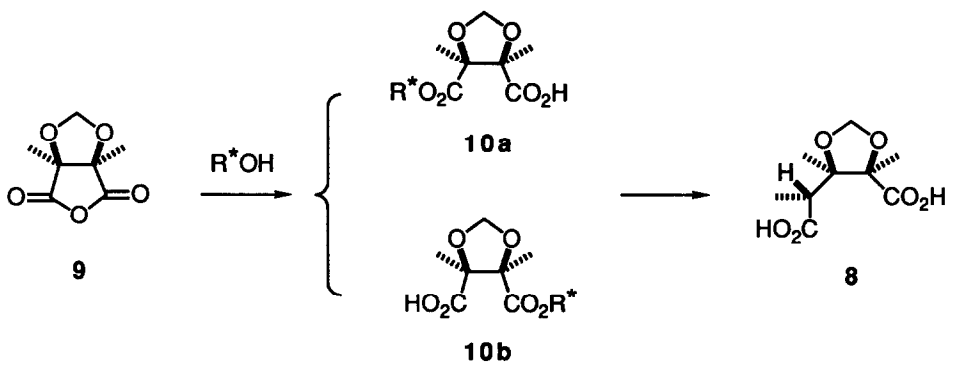
Monocrotaline (**1**) found in various species of *Crotalaria* plants (Leguminosae) is the best-known carcinogenic alkaloid. Plants containing monocrotaline (**1**) are often used for certain medicinal herbs and foodstuffs. There has been concern that chronic intake of monocrotaline (**1**) may lead to human cancer. Monocrotaline (**1**) is also considered to be a poisonous principle of livestock poisoning by *Crotalaria* plants.[2] The structure of monocrotaline (**1**) including the absolute stereochemistry was determined on the basis of extensive chemical and spectral studies coupled with the X-ray crystallographic analysis.[6] The first synthesis of monocrotaline (**1**) was achieved by Vedejs and co-workers in 1987.[3d]

The crucial step in the synthesis of monocrotaline (**1**) was considered to be regioselective construction of the characteristic 11-membered dilactone moiety. For the solution of this synthetic problem, we intended to utilize the lactonization method employed in our recent synthesis of (–)-integerrimine (**2**).[4c] Scheme **1** shows our plan for the synthesis of monocrotaline (**1**), where the penultimate step is lactonization of a seco acid **6**. We anticipated that the seco acid **6** would be assembled regioselectively by virtue of the tin-mediated acylation[4c] of (+)-retronecine (**3**) with the cyclic anhydride **7** derived from the optically active protected necic acid **8**. We had already achieved the enantioselective synthesis of (+)-retronecine (**3**) in the course of the total synthesis of

Scheme 1



Scheme 2



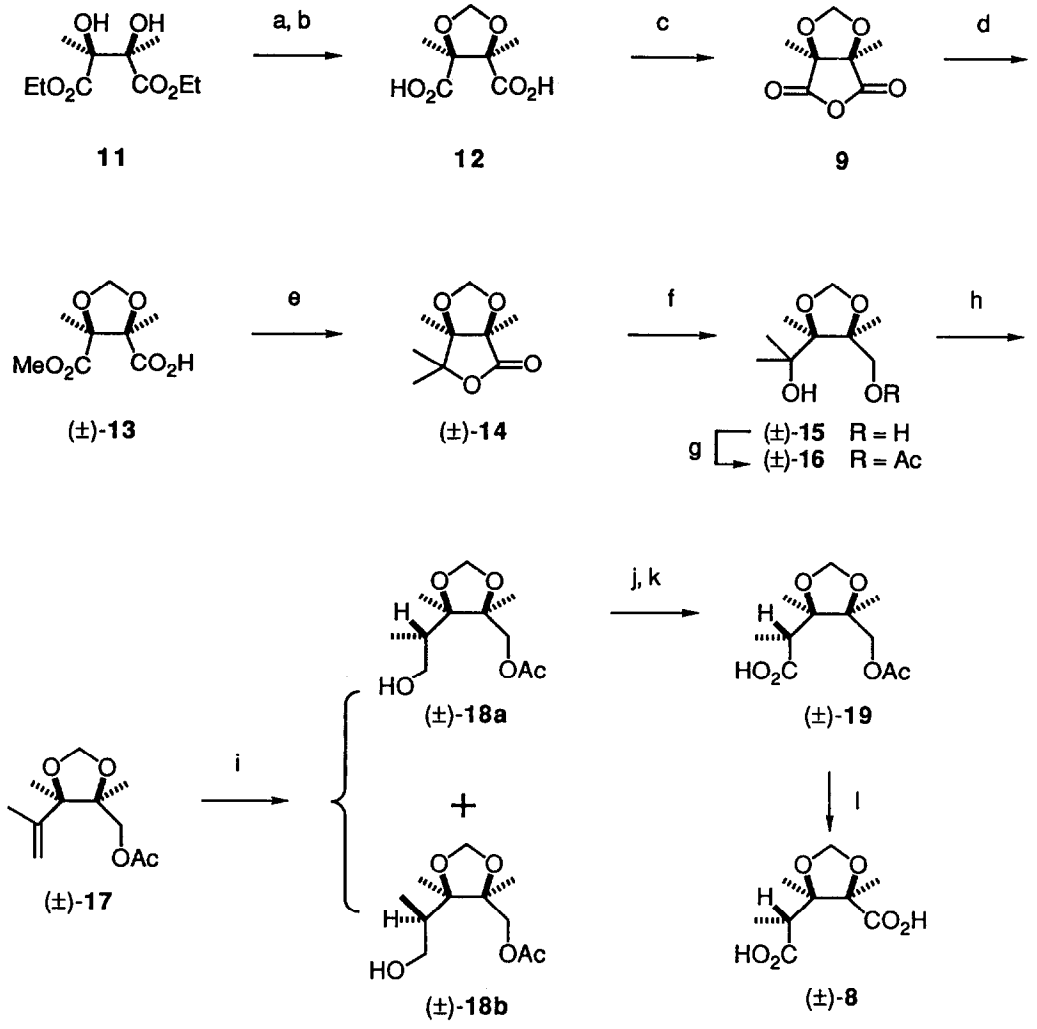
(–)-integerrimine (**2**).[4c] Therefore, our efforts were concentrated on the synthesis of the protected necic acid **8** in the optically active form.[7]

Scheme **2** shows our basic strategy for the synthesis of the protected necic acid **8** in the optically active form. Retrosynthetic analysis of **8** implied a chiral monoester **10a** (or **10b**), accessible by regioselective ring opening of the *meso*-anhydride **9** with an appropriate chiral alcohol (R*OH in Scheme **2**), to be a suitable synthetic intermediate. The quaternary stereocenters in **10a** (or **10b**) corresponded to those of **8**. Elaboration of **8** from **10a** (or **10b**) required stereocontrolled construction of an additional stereocenter bearing the secondary methyl group. As the starting material, we chose the readily available *meso*-diester **11**.[8]

Protection of the *meso*-diester **11** followed by alkaline hydrolysis provided the *meso*-diacid **12** in 83% overall yield, which was transformed quantitatively into the cyclic *meso*-anhydride **9** (Scheme **3**). In order to find an efficient route to optically active **8**, we first examined the synthesis of racemic **8** from **9**. Thus methanolysis of **9** quantitatively afforded the racemic monoester (±)-**13**, which upon Grignard reaction with MeMgI provided the racemic lactone (±)-**14** in 70% yield. Reduction of (±)-**14** with $LiAlH_4$ gave the racemic diol (±)-**15**, selective acetylation of which yielded the racemic monoacetate (±)-**16** in 94% overall yield. Dehydration of (±)-**16** with $POCl_3$–pyridine gave the racemic olefin (±)-**17** in 91% yield, which was then subjected to stereoselective hydroboration. Thus, reaction of (±)-**17** with borane-THF complex in THF followed by oxidation with alkaline H_2O_2 provided the desired racemic alcohol (±)-**18a** (70%) as the major product along with the isomeric alcohol (±)-**18b** (7%).[9] The hydroboration of (±)-**17** proceeded with high degree of asymmetric induction; (±)-**18a** and (±)-**18b** were obtained in a ratio of 10:1. The stereochemical outcome of this hydroboration reaction may be explained by application of Houk's transition state model (Scheme **4**):[10] In the hydroboration of (±)-**17**, the transition state **A** leading to (±)-**18a** may be more favorable than the sterically more crowded transition state **B** leading to (±)-**18b**. Swern oxidation[11] of (±)-**18a** followed by $KMnO_4$ oxidation[12] of the resulting aldehyde provided the racemic monoacid (±)-**19** in 78% overall yield. Final oxidation of (±)-**19** with Na_2RuO_4[13] in aqueous NaOH afforded the racemic protected necic acid (±)-**8** in 98% yield, whose spectral properties were identical with those of authentic **8**[3d] derived from natural monocrotaline (**1**).

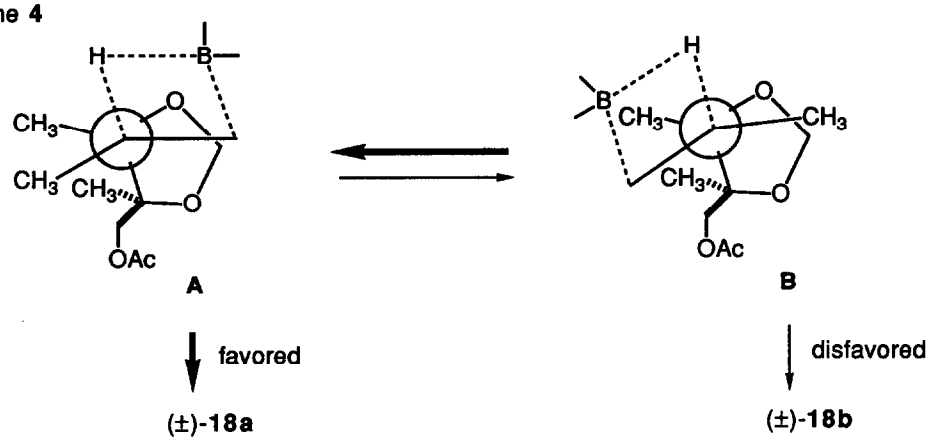
As we could develop the efficient route to (±)-**8**, we proceeded with the synthesis of optically active **8**, which started with regioselective ring opening of the *meso*-anhydride **9** with (*S*)-1-phenylethyl alcohol

Scheme **3**



(a) $MeOCH_2OMe$, P_2O_5, $CHCl_3$, 50 °C, 85%; (b) LiOH, H_2O–THF, 50 °C, 98%; (c) Ac_2O, CH_2Cl_2, reflux, 100%; (d) MeOH, 100%; (e) MeMgI, ether, 0 °C, then 1 M HCl, 70%; (f) $LiAlH_4$, ether, 94%; (g) Ac_2O, pyridine, 100%; (h) $POCl_3$, pyridine, 90 °C, 91%; (i) BH_3•THF, THF, then 30% H_2O_2–NaOH, 70% (±)-**18a** and 7% (±)-**18b**; (j) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C, then Et_3N, –78 °C; (k) $KMnO_4$, pH 7 phosphate buffer, *t*-BuOH, 78% from (±)-**18a**; (l) Na_2RuO_4, 1 M NaOH, 98%.

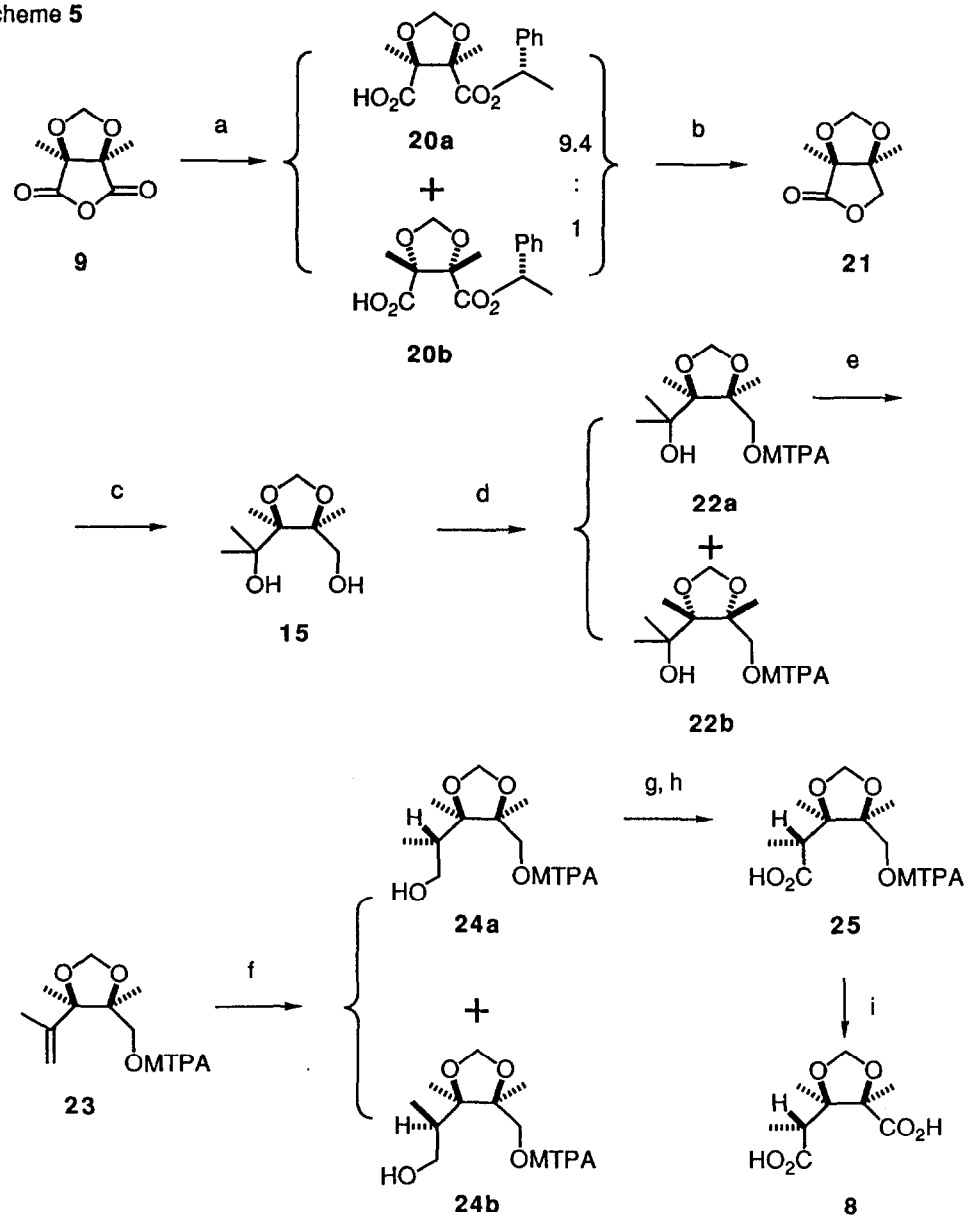
Scheme 4



(Scheme 5).[14] Thus, reaction of the anhydride **9** with (*S*)-1-phenylethyl alcohol in the presence of 4-(dimethylamino)pyridine and triethylamine in toluene at –78 °C provided an inseparable 9.4:1 mixture of the diastereomeric acids **20a** and **20b** in 83% yield.[15] Reduction of the inseparable mixture of **20a** and **20b** with $LiBHEt_3$ in THF and subsequent lactonization gave the optically active lactone **21**[16] in 89% yield. At this stage the chiral auxiliary, (*S*)-1-phenylethyl alcohol was recovered in 78% yield. Grignard reaction of **21** with MeMgI in ether–THF yielded the optically active diol **15**[16] in 86% yield. For obtaining the optically pure material and protecting the primary hydroxyl group, the optically active diol **15** was subjected to selective acylation with the acyl chloride prepared from (*R*)-α-methoxy-α-(trifluoromethyl)-phenylacetic acid (MTPA),[17] to provide the diastereomerically pure MTPA esters **22a** and **22b** in 88% and 9% yields, respectively, after chromatographic separation. Dehydration of **22a** with $POCl_3$ afforded the olefin **23** (83%), which was subjected to hydroboration followed by alkaline H_2O_2 oxidation to give the desired alcohol **24a** and the isomer **24b** in 81% and 5% yields, respectively, after chromatographic separation. High degree of asymmetric induction was observed again in the hydroboration of **23** as it was in the case of **17**. In this case, the ratio of **24a** and **24b** was 16:1. The conversion of **24a** into optically active **8** was achieved by a three-step sequence: (1) Swern oxidation[11] of **24a** into the corresponding aldehyde: (2) $KMnO_4$ oxidation[12] of the aldehyde into the carboxylic acid **25** (86% from **24a**) (3) Na_2RuO_4 oxidation[13] of **25** into optically active **8** (86%). Spectral and physical properties of synthetic **8** were identical with those of authentic **8** derived from natural monocrotaline (**1**)[3d] in all respects.

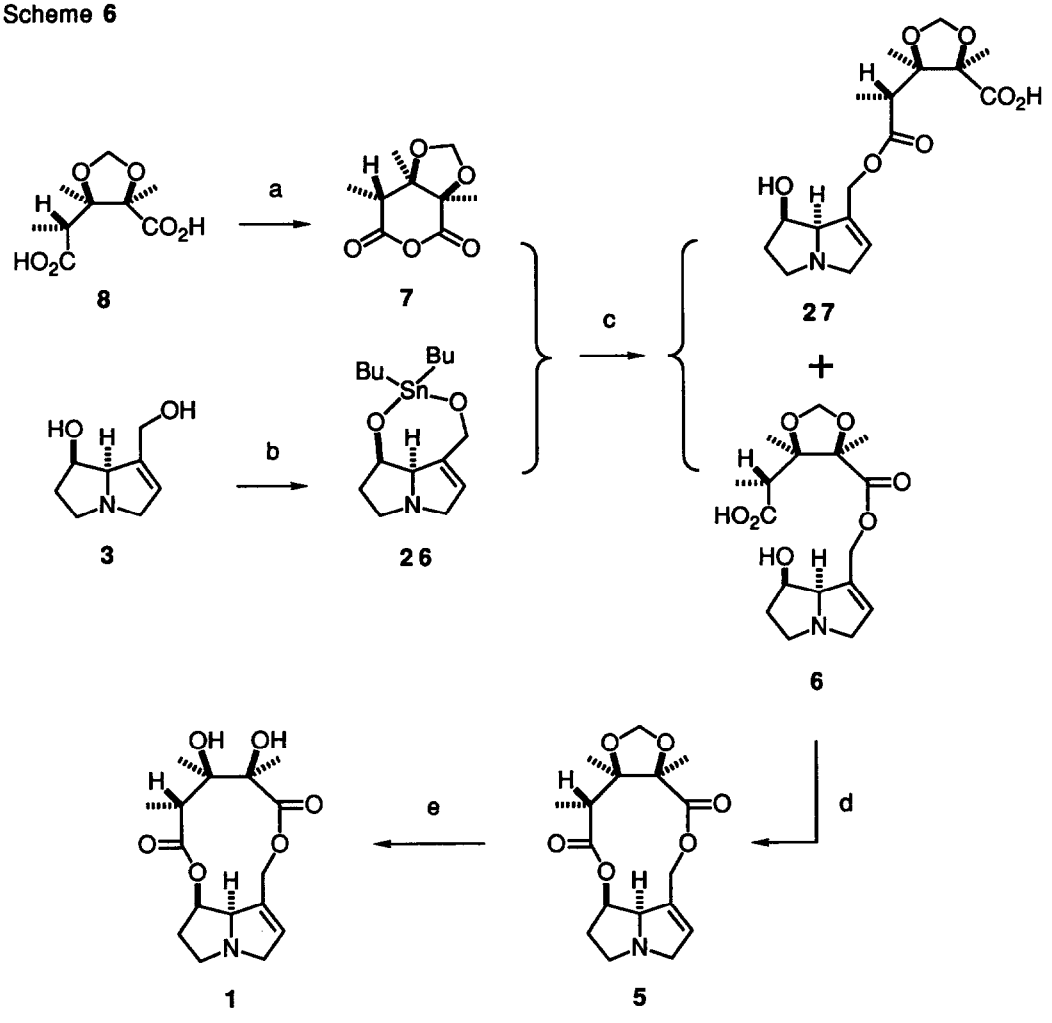
The optically active protected necic acid **8** was now in hand. At this point all that remained to complete a synthesis of optically active monocrotaline (**1**) was regioselective construction of the unsymmetrical 11-membered dilactone moiety and the removal of the protecting group. For the regioselective construction of the 11-membered dilactone, we intended to utilize the reaction of the cyclic anhydride **7** with the cyclic stannoxane **26** (Scheme 6). Thus, the protected necic acid **8** was converted into the cyclic anhydride **7** by treatment with acetic anhydride, while (+)-retronecine (**3**)[4c,18] was converted into the cyclic stannoxane **26** as described before.[4c] Reaction of **7** with **26** in toluene at –40 °C provided a 3:1 mixture of monoesters **6** and **27** in 82% yield from **8**. Pure **6** was obtained by either recrystallization or HPLC separation of the mixture. Of four possible monoesters, the desired monoester **6** was formed predominantly in this reaction. Preferential formation of **6** resulting from the ring opening of the cyclic anhydride **7** by the attack of the primary alkoxide

Scheme **5**



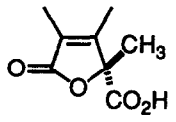
(a) (*S*)-1-phenylethyl alcohol, DMAP, Et_3N, toluene, –78 °C, 83%; (b) $LiBHEt_3$, THF, 0 °C, then 1 M HCl, 89%; (c) MeMgI, ether–THF, reflux, 86%; (d) (*S*)-α-methoxy-α-(trifluoromethyl)-phenylacetyl chloride, DMAP, toluene, 88% **22a** and 9% **22b**; (e) $POCl_3$, pyridine, 85 °C, 83%; (f) BH_3•THF, THF, 0 °C, then 30% H_2O_2–NaOH, 81% **24a** and 5% **24b**; (g) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C, then Et_3N, –78 °C; (h) $KMnO_4$, pH 7 phosphate buffer, *t*-BuOH, 86% from **24a**; (i) Na_2RuO_4, 1 M NaOH, 86%.

Scheme 6



(a) Ac_2O, CH_2Cl_2, reflux; (b) Bu_2SnO, benzene, reflux; (c) toluene, –40 ° C to room temp., 60% **6** and 22% **27** from **8**; (d) DCC, DMAP, DMAP•HCl, $CHCl_3$, 64%; (e) $Ph_3C•BF_4$, CH_2Cl_2, then 1 M HCl, 86%.

group in **26** at the more highly substituted carbonyl group in **7** may be explained by the nucleophilic approach trajectory analysis[19] and the electronic effect of an α-alkoxy substituent. Direct reaction of **3** and **7** was inferior to the tin-mediated esterification: The chemical yield was decreased owing to substantial formation of the lactone **28** from **7** and the decreased regioselectivity for the acylation was observed. Now the stage was set for elaboration of the 11-membered dilactone moeity. Lactonization of **6** into **5** under the conditions of Corey,[20a] Gerlach,[20b] or Mukaiyama[20c] was failed. On the other hand, lactonization of **6** by the original procedure reported by Yamaguchi[21] suffered from low chemical yield (37% **5**) and the concomitant formation of the epimer **29** (7%). Although lactonization under Yamaguchi's conditions *in the absence of* Et_3N prevented



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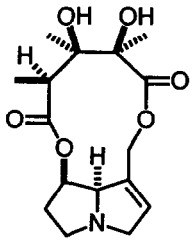

29

the formation of the epimer **29**, the conditions still suffered from low chemical yield (37% **5**). A much better result for the lactonization of **6** was obtained by utilizing Keck's method.[22] Thus, treatment of **6** with DCC–DMAP in the presence of DMAP·HCl with $CHCl_3$ as solvent afforded **5** in 64% yield. No epimerization of the secondary methyl group was observed in this lactonization. Finally, deprotection of **5** with $Ph_3C{\cdot}BF_4$[23] provided (–)-monocrotaline (**1**) in 86% yield. Spectral and physical properties of synthetic monocrotaline (**1**) [mp 187–190 °C (decomp.) (EtOH), $[\alpha]_D^{12}$ –55.0° (*c* 0.16, $CHCl_3$)] were identical with those of natural **1** [mp 189–194 °C (decomp.) (EtOH); $[\alpha]_D^{12}$ –59.3° (*c* 0.60, $CHCl_3$)] in all respects.

In conclusion, we have achieved the total synthesis of monocrotaline (**1**), a representative of 11-membered dilactonic alkaloids of retronecine type, in the optically active form.

Experimental

Melting points are uncorrected. IR spectra were taken on a JASCO IR-810 spectrophotometer. ^1H NMR spectra were recorded on either JEOL FX-90QE (90 MHz) or JEOL JNM-C675 (270 MHz) spectrometer: Chemical shifts (δ) are reported in ppm downfield from internal tetramethylsilane in $CDCl_3$ or DSS in D_2O, and coupling constants in Hz. Low-resolution (EIMS, CIMS, DCIMS, and FABMS) and high-resolution mass spectra (HREIMS, HRCIMS, and HRFABMS) were measured 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 thin layer chromatography (TLC) and Merck silica gel PF_{254} for preparative TLC. Ether and tetrahydrofuran (THF) were distilled from sodium–benzophenone ketyl under nitrogen. Dichloromethane (CH_2Cl_2), pyridine, and triethylamine (Et_3N) were distilled from calcium hydride (CaH_2) under nitrogen. Dimethyl sulfoxide was distilled from CaH_2 under reduced pressure. Toluene, and benzene were distilled from sodium under nitrogen. Methanol (MeOH) was distilled from $Mg(OMe)_2$ under nitrogen. Chloroform ($CHCl_3$) was distilled from P_2O_5 under nitrogen. Unless otherwise stated, the organic solutions obtained by extractive workup were washed with saturated aqueous NaCl solution, dried over anhydrous sodium sulfate (Na_2SO_4) and concentrated under reduced pressure by a rotary evaporator.

***meso*-2,3-Dimethyl-2,3-methylenedioxysuccinic Acid (12).** To a solution of *meso*-2,3-dimethyl-2,3-dihydroxysuccinic acid diethyl ester (**11**)[8] (56.6 mg, 0.241 mmol) in $CHCl_3$ (2 ml) were added P_2O_5 (300 mg) and dimethoxymethane (0.32 ml). The mixture was vigorously stirred at 50 °C for 1.5 h. The reaction mixture was decanted and the supernatant solution was transferred into a separatory funnel. The supernatant organic solution was washed with saturated $NaHCO_3$ solution (1 ml). The residue remained in the reaction flask was dissolved in saturated $NaHCO_3$ solution (5 ml), and the aqueous mixture was extracted with ether (4 x 5 ml). The supernatant organic solution and the ethereal extracts were combined, dried, and concentrated under reduced pressure, yielding an oily residue. Purification by column chromatography on silica gel (5 g)

with 60:1→5:1 benzene–ether provided *meso*-2,3-dimethyl-2,3-methylenedioxysuccinic acid diethyl ester (50 mg, 85%) as a pale yellow oil: IR ($CHCl_3$) 1745, 1290, 1140, 1020, and 1005 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.29 (6 H, t, J = 7.1 Hz), 1.53 (6 H, s), 4.19 (4 H, q, J = 7.1 Hz), 5.16 (1 H, d, J = 1.2 Hz), and 5.31 (1 H, d, J = 1.2 Hz); CIMS *m/z* (relative intensity) 247 [$(M+H)^+$, 60], 201 (18), 173 (100), and 55 (30) [HRCIMS. Found: 247.1185. $C_{11}H_{19}O_6$ [$(M+H)^+$] requires: 247.1181]. To a solution of *meso*-2,3-dimethyl-2,3-methylenedioxysuccinic acid diethyl ester (1.86 g, 7.56 mmol) in THF (20 ml) was added 10% aqueous LiOH solution (18 ml). After being stirred vigorously at 50 °C for 7 h, the reaction mixture was cooled to room temperature, and concentrated to ca. 15 ml under reduced pressure. The mixture was cooled to 0 °C, and adjusted to pH 1 with conc. HCl. The resulting aqueous mixture was extracted with EtOAc (3 x 15 ml). The combined extracts were washed, dried, and concentrated to leave crude crystals of **12** (1.40 g, 98%). This material was sufficiently pure by TLC and ^1H NMR spectral analyses, and used for the next reaction without further purification. The analytical sample was obtained by recrystallization from hexane–EtOAc. **12**: mp 126–127 °C (hexane–EtOAc); IR (KBr) 3400–2400 (broad), 1750, 1735, 1675, 1145, 1110, and 990 cm^{-1}; ^1H NMR (270 MHz, CD_3COCD_3) δ 1.46 (6 H, s), 5.13 (1 H, d, J = 1.3), and 5.23 (1 H, d, J = 1.3 Hz); CIMS *m/z* (relative intensity) 191 [$(M+H)^+$, 5], 190 (M^+, 4), 185 (46), 146 (76), 127 (85), 115 (31), 101 (100), 100 (80), and 87 (65). Anal. Calcd for $C_7H_{10}O_6$: C, 44.22; H, 5.30. Found: C, 44.25; H, 5.35.

***meso*-2,3-Dimethyl-2,3-methylenedioxysuccinic Anhydride (9).** A mixture of **12** (97.0 mg, 0.511 mmol) and acetic anhydride (0.48 ml, 5.1 mmol) in CH_2Cl_2 (5 ml) under nitrogen was heated under reflux for 5 h, cooled to room temperature, and then concentrated under reduced pressure. The residue was azeotroped with benzene (3 x 1 ml) to give pure, moisture-sensitive **9** (88.6 mg, quantitative) as colorless crystals: mp 76.5–78.0 °C (hexane–benzene); IR ($CHCl_3$) 1875, 1800, 1120, 1105, 1065, 1010, and 950 cm^{-1}; ^1H NMR (270 MHz, toluene-d_8) δ 1.08 (6 H, s), 4.21 (1 H, d, J = 1.3 Hz), and 4.68 (1 H, d, J = 1.3 Hz); CIMS *m/z* (relative intensity) 173 [$(M+H)^+$, 2], 145 (100), 127 (11), 115 (32), 102 (65), 101 (75), 100 (94), 99 (55), and 87 (54) [HRCIMS. Found: 145.0484. $C_6H_9O_4$ [$(M+H-CO)^+$] requires: 145.0501].

1-Methyl Hydrogen (2*S,3*R**)-2,3-Dimethyl-2,3-methylenedioxysuccinate [(±)-13].** A solution of **9** (1.27 g, 7.38 mmol) in MeOH (10 ml) under nitrogen was stirred at room temperature for 1.5 h, and then concentrated under reduced pressure. Purification of the residual oil by column chromatography on silica gel (20 g) with 150:10:1.6 benzene–dioxane–acetic acid provided (±)-**13** (1.50 g, quantitative) as a colorless oil: IR ($CHCl_3$) 3600–2500 (broad), 1745, 1285, 1140, and 1155 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.55 (6 H, s), 3.75 (3 H, s), 5.18 (1 H, d, J = 1.0 Hz), and 5.32 (1 H, d, J = 1.0 Hz); CIMS *m/z* (relative intensity) 205 [$(M+H)^+$, 91], 159 (100), 145 (82), 131 (24), 127 (30), and 101 (22) [HREIMS. Found: 205.0741. $C_8H_{13}O_6$ [$(M+H)^+$] requires: 205.0712].

(2*R,3*S**)-2,3,4-Trimethyl-2,3-methylenedioxy-4-pentanolide [(±)-14].** To a mixture of Mg (56.8 mg, 2.34 mmol) in ether (2 ml) under nitrogen was introduced dropwise MeI (0.14 ml, 2.34 mmol). The mixture was stirred at room temperature for 1 h, and cooled to 0 °C. To the ice-cooled ethereal solution of MeMgI was added dropwise a solution of (±)-**13** (53.3 mg, 0.261 mmol) in ether (2.0 ml), and the reaction mixture was vigorously stirred at 0 °C for 1 h. The reaction was quenched by the addition of ice-cooled, saturated NH_4Cl solution (1 ml). The mixture was acidified with 1 M HCl (2 ml), stirred for 10 min at room temperature, and then extracted with ether (5 x 5 ml). The extracts were combined, washed, dried, and concentrated under reduced pressure. The oily residue was purified by column chromatography on silica gel (1 g) with 10:1→1:1 hexane–ether to give (±)-**14** (33.8 mg, 70%) as colorless crystals; mp 141–142 °C (hexane–ether); IR ($CHCl_3$) 1775, 1160, 1095, and 960 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.26 (3 H, s), 1.37 (3 H, s), 1.50 (3 H, s), 1.55 (3 H, s), 4.87 (1 H, s), and 5.12 (1 H, s); CIMS *m/z* (relative intensity) 187 [$(M+H)^+$,

100], 159 (9), 143 (5), 129 (18), 112 (20), 101 (19), and 99 (19) [HRCIMS. Found: 187.0940. $C_9H_{15}O_4$ [(M+H)$^+$] requires: 187.0970]. Anal. Calcd for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 57.61; H, 7.54.

(2*S,3*R**)-2,3,4-Trimethyl-2,3-methylenedioxy-1,4-pentanediol [(±)-15].** To a solution of (±)-**14** (50.0 mg, 0.269 mmol) in ether (1 ml) under nitrogen was added $LiAlH_4$ (51 mg, 1.3 mmol). The reaction mixture was stirred at room temperature for 2 h, and then cooled to 0 °C. To the cooled reaction mixture was added powdered NaF (600 mg), and the mixture was stirred for ca. 10 min. To the vigorously stirred mixture was added dropwise 5% H_2O in THF (5 ml). The mixture was stirred at room temperature for 30 min, and filtered through a pad of Celite. The filter cake was washed thoroughly with 5% H_2O in THF. The filtrate and washings were combined and concentrated under reduced pressure. The oily residue was purified by column chromatography on silica gel (1 g) with 1:3 hexane–ether, affording (±)-**15** (48.0 mg, 94%) as colorless crystals: mp 106–107 °C (ether–hexane); IR ($CHCl_3$) 3575, 3475, 1100, and 955 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.22 (3 H, s), 1.35 (3 H, s), 1.39 (6 H, s), 2.90 (1 H, br s, OH), 3.55 (1 H, br, OH), 3.47 (1 H, d, J = 12.0 Hz), 3.78 (1 H, d, J = 12.0 Hz), 4.98 (1 H, d, J = 1.0 Hz), and 5.08 (1 H, d, J = 1.0 Hz); CIMS *m/z* (relative intensity) 191 [(M+H)$^+$, 14], 173 (95), 159 (7), 143 (55), 127 (36), 101 (25), 99 (26), 87 (100), and 85 (125). Anal. Calcd for $C_9H_{18}O_4$: C, 56.82; H, 9.54. Found: C, 56.59; H, 9.59.

(3*R,4*S**)-5-Acetoxy-2,3,4-trimethyl-3,4-methylenedioxy-2-pentanol [(±)-16].** A mixture of (±)-**15** (206 mg, 1.08 mmol), pyridine (1 ml), and acetic anhydride (1 ml) was stirred at room temperature for 3 h and concentrated under reduced pressure. The residue was azeotroped with toluene (3 x 2 ml) to give pure (±)-**16** (266 mg, quantitative) as colorless crystals: mp 51.5–52.5 °C (hexane); IR ($CHCl_3$) 3575, 1740, 1245, 1140, 1120, 1105, and 960 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.22 (3 H, s), 1.26 (3 H, s), 1.33 (3 H, s), 1.36 (3 H, s), 2.09 (3 H, s), 2.50 (1 H, br s, OH), 4.11 (1 H, d, J = 12.1 Hz), 4.61 (1 H, d, J = 12.1 Hz), 5.00 (1 H, d, J = 1.1 Hz), and 5.09 (1 H, d, J = 1.1 Hz); CIMS *m/z* (relative intensity) 233 [(M+H)$^+$, 3], 232 (5), 216 (10), 215 (50), 185 (25), 174 (12), 173 (20), 157 (9), 143 (70), 127 (53), 99 (53), and 87 (100). Anal. Calcd for $C_{11}H_{20}O_5$: C, 56.88; H, 8.68. Found: C, 56.51; H, 8.79.

(3*R,4*S**)-5-Acetoxy-2,3,4-trimethyl-3,4-methylenedioxy-1-pentene [(±)-17].** To a solution of (±)-**16** (150 mg, 0.646 mmol) in pyridine (5 ml) under nitrogen was added $POCl_3$ (0.12 ml, 1.29 mmol) and the mixture was heated at 90 °C for 8 h. After the reaction mixture was cooled to 0 °C, ice (1 g) was added, and the mixture was extracted with ether (4 x 5 ml). The combined extracts were washed, dried, and concentrated under reduced pressure to give an oily residue. Purification by column chromatography on silica gel (2 g) with 2:1 hexane–ether gave (±)-**17** (126 mg, 91%) as a colorless oil: IR ($CHCl_3$) 1740, 1645, 1255, 1135, and 1105 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.31 (3 H, s), 1.37 (3 H, s), 1.80 (3 H, m), 2.08 (3 H, s), 3.79 (1 H, d, J = 11.5 Hz), 4.11 (1 H, d, J = 11.5 Hz), 4.92 (1 H, m), 5.08 (1 H, d, J = 1.0 Hz), 5.11 (1 H, d, J = 1.0 Hz), and 5.22 (1 H, m); CIMS *m/z* (relative intensity) 215 [(M+H)$^+$, 45], 185 (43), 173 (5), 155 (5), 141 (20), 125 (67), 117 (23), 11 (42), 101 (56), 100 (84), 98 (100), 95 (33), and 83 (58) [HRCIMS. Found: 215.1304. $C_{11}H_{19}O_4$ [(M+H)$^+$] requires: 215.1284].

(2*S,3*R**,4*S**)-5-Acetoxy-2,3,4-trimethyl-3,4-methylenedioxy-1-pentanol [(±)-18a].** To a solution of (±)-**17** (17.0 mg, 0.0794 mmol) in THF (0.2 ml) under nitrogen was added a 1.0 M solution of BH_3·THF in THF (0.125 ml, 0.125 mmol), and the mixture was stirred at room temperature for 2 h. To the reaction mixture were added 3 M NaOH (0.01 ml) and 30% H_2O_2 (0.013 ml), and the mixture was stirred at room temperature for an additional 2 h. The reaction mixture was diluted with water (1 ml), and the aqueous mixture was extracted with ether (4 x 5 ml). The extracts were combined, washed, dried, and concentrated to leave an oily residue. Purification by column chromatography on silica gel (1 g) with 1:1 hexane–ether

provided (±)-**18a** (11.5 mg, 63%) as a colorless oil, together with a 1:1 mixture[15] of (±)-**18a** and (±)-**18b** (2.7 mg, 14%) as a colorless oil. (±)-**18a**: IR ($CHCl_3$) 3625, 3500, 1740, 1245, and 1110 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.12 (3 H, d, J = 6.9 Hz), 1.12 (3 H, s), 1.34 (3 H, s), 2.05 (1 H, m), 2.12 (3 H, s), 3.44 (1 H, dd, J = 7.4, 10.6 Hz), 3.70 (1 H, dd, J = 5.3, 10.6 Hz), 4.15 (1 H, d, J = 11.2 Hz), 4.27 (1 H, d, J = 11.2 Hz), 4.98 (1 H, d, J = 1.2 Hz), and 5.00 (1 H, d, J = 1.2 Hz); CIMS *m/z* (relative intensity) 233 [$(M+H)^+$, 80], 215 (47), 203 (65), 186 (60), 173 (46), 159 (45), 155 (86), 143 (86), and 125 (100) [HRCIMS. Found: 233.1401. $C_{11}H_{21}O_5$ [$(M+H)^+$] requires: 233.1389]. The ^1H NMR spectral data (270 MHz, $CDCl_3$) for the minor (±)-**18b**: δ 0.89 (3 H, d, J = 7.3 Hz), 1.17 (3 H, s), 1.33 (3 H, s), 2.05 (1 H, m), 2.11 (3 H, s), 3.44 (1 H, dd, J = 5.0, 11.0 Hz), 3.86 (1 H, dd, J = 8.6, 11.0 Hz), 4.02 (1 H, d, J = 11.2 Hz), 4.30 (1 H, d, J = 11.2 Hz), 5.01 (1 H, d, J = 1.1 Hz), and 5.04 (1 H, d, J = 1.1 Hz).

(2*R,3*R**,4*S**)-5-Acetoxy-2,3,4-trimethyl-3,4-methylenedioxypentanoic Acid [(±)-19].** To a cooled (–78 °C), stirred solution of oxalyl chloride (0.035 ml, 0.401 mmol) in CH_2Cl_2 (0.6 ml) under nitrogen was added dropwise a solution of dimethyl sulfoxide (0.056 ml, 0.786 mmol) in CH_2Cl_2 (0.3 ml). The mixture was stirred for 2 min, and then a solution of (±)-**18a** (60.8 mg, 0.262 mmol) in CH_2Cl_2 (0.6 ml) was added dropwise. After the mixture was stirred for 15 min at –78 °C, Et_3N (0.18 ml, 1.31 mmol) was added. The reaction mixture was stirred at –78 °C for an additional 1 h. The reaction was quenched with 1 M pH 7 phosphate buffer (0.5 ml) with simultaneous removal of the cooling bath. The mixture was extracted with CH_2Cl_2 (3 x 3 ml). The organic layers were combined, dried, and concentrated. The oily residue was taken up in ether (ca. 5 ml), and insoluble materials were removed by filtration through a cotton plug. The filtration residue was washed thoroughly with ether. The filtrate and washings were combined and concentrated to give the crude aldehyde (60 mg) as a colorless oil. This labile aldehyde was immediately used for the next reaction without further purification. To a solution of the crude aldehyde (60 mg) in *t*-BuOH (1.6 ml) were added 1 M pH 7 phosphate buffer (1.3 ml) and 1 M $KMnO_4$ solution (1.6 ml, 1.6 mmol), and the reaction mixture was stirred for 2 min. The reaction was quenched with saturated $NaHSO_3$ solution (0.1 ml). The mixture was diluted with 6 M HCl (0.5 ml), and was saturated with NaCl. The resulting aqueous mixture was extracted with EtOAc (4 x 6 ml). The extracts were combined, washed, dried, and concentrated to leave an oily residue, which was purified by column chromatography on silica gel (5 g) with ether to give (±)-**19** (50.3 mg, 78% overall from (±)-**18a**) as colorless crystals: mp 76–77 °C (hexane–ether); IR ($CHCl_3$) 3600–2400 (broad), 1735, 1710, 1240, 1105, and 1045 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.32 (3 H, s), 1.34 (3 H, s), 1.41 (3 H, d, J = 7.1 Hz), 2.08 (3 H, s), 2.85 (1 H, q, J = 7.1 Hz), 4.13 (1 H, d, J = 11.2 Hz), 4.28 (1 H, d, J = 11.2 Hz), 4.98 (1 H, d, J = 1.3 Hz), and 4.99 (1 H, d, J = 1.3 Hz); CIMS *m/z* (relative intensity) 186 [$(M-AcOH)^+$, 67], 156 (55), 129 (69), 100 (100), and 83 (79). Anal. Calcd for $C_{11}H_{18}O_6$: C, 53.65; H, 7.37. Found: C, 53.48; H, 7.43.

(2*R,3*R**,4*R**)-2,3,4-Trimethyl-2,3-methylenedioxypentanedioic Acid [(±)-8].** To a solution of (±)-**19** (19.3 mg, 0.0785 mmol) in 1 M NaOH (1 ml) was added a 0.66 M solution of Na_2RuO_4 in 1 M NaOH (3.6 ml, 0.24 mmol), and the reaction mixture was stirred at room temperature for 1 h. The reaction was quenched by the addition of *i*-PrOH (0.5 ml), and the mixture was filtered through a pad of Celite. The filter cake was washed with 1 M NaOH (1 ml). The filtrate and washings were combined, cooled to 0–5 °C in an ice-bath, acidified to pH 1 with 6 M HCl, and saturated with NaCl. The resulting aqueous mixture was extracted with EtOAc (5 x 4 ml). The extracts were combined, washed, dried, and concentrated to leave a colorless solid. Purification by column chromatography on silica gel (1 g) with ether afforded (±)-**8** (16.7 mg, 98%) as colorless crystals: mp 148–150 °C (benzene–EtOAc); IR ($CHCl_3$) 3400–2400 (broad), 1730, 1385, 1290, and 1130 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.37 (3 H, d, J = 7.4 Hz), 1.50 (3 H, s), 1.53 (3 H, s), 3.13 (1 H, q, J = 7.4 Hz), 5.07 (1 H, d, J = 0.8 Hz), and 5.12 (1 H, d, J = 0.8 Hz); DCIMS *m/z* (relative

intensity) 219 [$(M+H)^+$, 8], 201 (20), 173 (10), 145 (13), 125 (10), and 100 (8). Anal. Calcd for $C_9H_{14}O_6$: C, 49.54; H, 6.47. Found: C, 49.52; H, 6.43.

1-[(*S*)-1'-Phenylethyl] Hydrogen (2*R*,3*S*)-2,3-Dimethyl-2,3-methylenedioxysuccinate (20a) and 1-[(*S*)-1'-Phenylethyl] Hydrogen (2*S*,3*R*)-2,3-Dimethyl-2,3-methylenedioxysuccinate (20b). To a cooled (–78 °C), stirred mixture of *meso*-**9** (200 mg, 1.16 mmol), 4-(dimethylamino)pyridine (28.3 mg, 0.232 mmol), and Et_3N (0.195 ml, 1.41 mmol) in toluene (2.3 ml) under nitrogen was added (*S*)-1-phenylethyl alcohol (0.17 ml, 1.42 mmol). After the reaction mixture was stirred at –78 °C for 66 h, saturated $NaHCO_3$ solution (3 ml) and water (3 ml) were added with simultaneous removal of the cooling bath. The mixture was stirred for ca. 10 min and washed with ether (3 x 10 ml). The aqueous layer was acidified to pH 1 with conc. HCl (1 ml), and was saturated with NaCl. The resulting aqueous mixture was extracted with ether (4 x 15 ml). The extracts were combined, washed , dried, and concentrated to leave an oily residue. Purification by column chromatography on silica gel (20 g) with 1:10 ether–benzene containing 1% AcOH, affording an inseparable 9.4:1 mixture[15] of **20a** and **20b** (283 mg, 83%) as a colorless oil: $[\alpha]_D^{28}$ –90.5° (*c* 1.18, $CHCl_3$); IR ($CHCl_3$) 3600–2400, 1740, 1280, and 1140 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$, the signals for the major product **20a** are shown) δ 1.54 (3 H, s), 1.55 (3 H, d, *J* = 6.6 Hz), 1.56 (3 H, s), 5.16 (1 H, d, *J* = 1.2 Hz), 5.29 (1 H, d, *J* = 1.2 Hz), 5.90 (1 H, q, *J* = 6.6 Hz), and 7.3–7.4 (5 H, complex pattern); EIMS *m/z* (relative intensity) 294 (M^+, 6), 249 (2), 189 (3), and 145 (100) [HREIMS. Found: 294.1128. $C_{15}H_{18}O_6$ (M^+) requires: 294.1103].

(2*S*,3*S*)-2,3-Dimethyl-2,3-methylenedioxy-4-butanolide (21). To a cooled (0 °C), stirred solution of the 9.4:1 mixture of **20a** and **20b** (114 mg, 0.388 mmol) in THF (3.9 ml) was added dropwise a 1 M solution of $LiBHEt_3$ in THF (2.0 ml, 2.0 mmol), and the reaction mixture was stirred at 0 °C for 1.2 h. To the reaction mixture were added dropwise water (0.5 ml) and 1 M HCl (4 ml), and the mixture was stirred at room temperature for an additional 40 min. After being saturated with NaCl, the mixture was extracted with ether (3 x 15 ml). The extracts were combined, dried, and concentrated. The oily residue was purified by column chromatography on silica gel (20 g) with 2:1 hexane–EtOAc, affording **21** (54.8 mg, 89%; calculated optical purity based on the ratio of **20a** and **20b**, 81% ee) as a colorless oil, with recovery of (*S*)-1-phenylethyl alcohol (36.6 mg, 78%). **21**: $[\alpha]_D^{28}$ +78.3 ° (*c* 1.19, $CHCl_3$); IR ($CHCl_3$) 1790, 1120, 1100, 1080, and 1020 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.35 (3 H, s), 1.48 (3 H, s), 4.15 (1 H, d, *J* = 10.6 Hz), 4.48 (1 H, d, *J* = 10.6 Hz), 4.94 (1 H, s), and 5.13 (1 H, s); EIMS *m/z* (relative intensity) 158 (M^+, 55), 114 (4), 100 (94), 99 (77), and 84 (100) [HREIMS. Found: 158.0579. $C_7H_{10}O_4$ (M^+) requires: 158.0579].

(2*S*,3*R*)-2,3,4-Trimethyl-2,3-methylenedioxy-1,4-pentanediol (15). To a mixture of Mg (544 mg, 22.4 mmol) in ether (20 ml) under nitrogen was introducd dropwise MeI (1.25 ml, 20.1 mmol). The mixture was stirred at room temperature for 1 h. To the ice-cooled ethereal solution of MeMgI was added dropwise a solution of **21** (55.6 mg, 0.353 mmol) in THF (20 ml), and the reaction mixture was heated under reflux for 51 h. After the reaction mixture was cooled to room temperature, saturated NH_4Cl solution (10 ml) was added dropwise. The mixture was stirred for 10 min and extracted with ether (3 x 50 ml). The extracts were combined, washed, dried, and concentrated under reduced pressure. The oily residue was purified by column chromatography on silica gel (5 g) with 1:3→1:1 ether–hexane to give **15** (57.5 mg; 86%, calculated optical purity based on the ratio of **20a** and **20b**, 81% ee) as colorless crystals; mp 96.5–101.5 °C (hexane–ether); $[\alpha]_D^{28}$ –44.1 ° (*c* 0.898, $CHCl_3$). Anal. Calcd for $C_9H_{18}O_4$: C, 56.82; H, 9.54. Found: C, 56.81; H, 9.37.

(2'*R*,3*R*,4*S*)-5-[2'-Methoxy-2'-(trifluoromethyl)phenylacetoxy]-2,3,4-trimethyl-3,4-methylenedioxy-2-pentanol (22a) and (2'*R*,3*S*,4*R*)-5-[2'-Methoxy-2'-(trifluoromethyl)phenylacetoxy]-2,3,4-trimethyl-3,4-methylenedioxy-2-pentanol (22b). A mixture of (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid [(+)-MTPA] (125 mg, 0.534 mmol) and oxalyl chloride (0.2 ml, 2.4 mmol) was heated under reflux for 1 h. After cooling, the reaction mixture was concentrated under reduced pressure to give the crude acid chloride of (+)-MTPA. The crude acid chloride was azeotroped with toluene (3 x 2 ml) and used for the next reaction without further purification. To an ice-cooled, stirred solution of the acid chloride in toluene (1 ml) under nitrogen were added 4-(dimethylamino)pyridine (70 mg, 0.576 mmol) and a solution of **15** (30.4 mg, 0.160 mmol) in toluene (1 ml). The ice-bath was removed, and the reaction mixture was stirred at room temperature for 2 h. The mixture was recooled to 0 °C and washed with successively with 1 M HCl (1 ml) and saturated $NaHCO_3$ solution (1 ml). The organic layer was dried and concentrated to give an oily residue. Purification by column chromatography on silica gel (1 g) with 3:1 hexane–ether gave a 9.4:1 mixture[15] of **22a** and **22b** (64.0 mg, 98%) as a colorless oil. Separation of the mixture by HPLC [Develosil ODS 10/20 (250 mm x 20 mm ID), 50% EtOH, flow rate 5.5 ml/min, detection UV 256 nm] provided pure **22a** (56.9 mg, 88%) and **22b** (5.5 mg) (9%) as a colorless oil, respectively. **22a:** $[\alpha]_D^{17}$ +22.1° (*c* 0.97, $CHCl_3$); IR ($CHCl_3$) 3560, 1750, 1270, 1170, 1120, and 1100 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.21 (3 H, s), 1.23 (3 H, s), 1.33 (3 H, s), 1.35 (3 H, s), 2.48 (1 H, br, OH), 3.61 (3 H, q, *J* = 1.3 Hz), 4.08 (1 H, d, *J* = 12.2 Hz), 5.01 (1 H, d, *J* = 1.2 Hz), 5.10 (1 H, d, *J* = 1.2 Hz), 5.11 (1 H, d, *J* = 12.2 Hz), 7.39 (3 H, complex pattern), and 7.59 (2 H, complex pattern); CIMS *m/z* (relative intensity) 407 [$(M+H)^+$, 1], 389 (29), 359 (5), 259 (6), 173 (100), 143 (39), 99 (89), and 87 (45) [HRCIMS. Found: 407.1654. $C_{19}H_{26}O_6F_3$ [$(M+H)^+$] requires: 407.1682]. **22b:** $[\alpha]_D^{20}$ +50.9° (*c* 0.96, $CHCl_3$); IR ($CHCl_3$) 3560, 1750, 1270, 1175, 1120, and 1100 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.20 (3 H, s), 1.24 (3 H, s), 1.27 (3 H, s), 1.33 (3 H, s), 2.45 (1 H, br, OH), 3.56 (3 H, q, *J* = 1.3 Hz), 4.12 (1 H, d, *J* = 12.2 Hz), 5.00 (1 H, d, *J* = 1.0 Hz), 5.12 (1 H, d, *J* = 12.2 Hz), 5.15 (1 H, d, *J* = 1.0 Hz), 7.39 (3 H, complex pattern), and 7.55 (2 H, complex pattern); EIMS *m/z* (relative intensity) 406 (M^+, 3), 347 (10), 318 (10), 259 (4), 189 (100), 159 (25), 114 (48), and 101 (86) [HREIMS. Found: 406.1604. $C_{19}H_{25}O_6F_3$ (M^+) requires: 406.1603].

(2'*R*,3*R*,4*S*)-5-[2'-Methoxy-2'-(trifluoromethyl)phenylacetoxy]-2,3,4-trimethyl-3,4-methylenedioxy-1-pentene (23). To a solution of **22a** (112 mg, 0.276 mmol) in pyridine (1 ml) under nitrogen was added $POCl_3$ (0.05 ml, 0.55 mmol), and the mixture was heated at 85 °C for 17 h. The reaction mixture was cooled to 0 °C, and ice (1 g) was added. The mixture was stirred for ca. 10 min, and acidified to pH 1 with conc. HCl. The resulting aqueous mixture was extracted with ether (4 x 5 ml). The combined extracts were washed, dried, and concentrated to leave an oily residue. Purification by column chromatography on silica gel (5 g) with 1:1 hexane–ether yielded **23** (88.6 mg, 83%) as colorless crystals: mp 57.0–59.0 °C (pentane); $[\alpha]_D^{19}$ +2.90° (*c* 0.99, $CHCl_3$); IR ($CHCl_3$) 1750, 1640, 1270, 1170, 1120, and 1105 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.29 (3 H, s), 1.35 (3 H, s), 1.68 (3 H, m), 3.60 (3 H, q, *J* = 1.3 Hz), 3.75 (1 H, d, *J* = 11.5 Hz), 4.57 (1 H, d, *J* = 11.5 Hz), 4.84 (1 H, m), 5.08 (1 H, d, *J* = 1.0 Hz), 5.12 (1 H, d, *J* = 1.0 Hz), 5.22 (1 H, m), 7.40 (3 H, complex pattern), 7.56 (2 H, complex pattern); CIMS *m/z* (relative intensity) 389 [$(M+H)^+$, 100], 359 (29), 189 (29), 156 (28), 155 (50), 125 (95), and 99 (98). Anal. Calcd for $C_{19}H_{23}O_5F_3$: C, 58.76; H, 5.97. Found: C, 58.76; H, 5.96.

(2'*R*,2*S*,3*R*,4*S*)-5-[2'-Methoxy-2'-(trifluoromethyl)phenylacetoxy]-2,3,4-trimethyl-3,4-methylenedioxy-1-pentanol (24a) and (2'*R*,2*R*,3*R*,4*S*)-5-[2'-Methoxy-2'-(trifluoromethyl)phenylacetoxy]-2,3,4-trimethyl-3,4-methylenedioxy-1-pentanol (24b). To an ice-cooled, stirred solution of **23** (26.4 mg, 0.068 mmol) in THF (0.2 ml) under nitrogen was added a 1.0

M solution of BH_3·THF in THF (0.1 ml, 0.1 mmol). After the reaction mixture was stirred at 0 °C for 20 h, 3 M NaOH (0.01 ml) and 30% H_2O_2 (0.013 ml) were added. The mixture was stirred at room temperature for 3 h, diluted with water (1 ml), and saturated with NaCl. The resulting aqueous mixture was extracted with EtOAc (4 x 5 ml). The extracts were combined, washed, dried, and concentrated to leave an oily residue. Purification by column chromatography on silica gel (1 g) with 6:1→1:1 hexane–ether provided the desired **24a** (22.3 mg, 81%) as colorless crystals, together with the stereoisomer **24b** (3.2 mg, 5%) as a colorless oil. **24a**: mp 71.0–72.5 °C (hexane–ether); $[\alpha]_D^{16}$ +34.1° (*c* 0.58, $CHCl_3$); IR ($CHCl_3$) 3625, 3575, 1755, 1270, 1175, 1120, and 1105 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.99 (3 H, d, *J* = 6.6 Hz), 1.08 (3 H, s), 1.36 (3 H, s), 1.81 (1 H, m), 3.22 (1 H, dd, *J* = 6.8, 11.1 Hz), 3.50 (1 H, dd, *J* = 6.3, 11.1 Hz), 3.61 (3 H, q, *J* = 1.3 Hz), 4.18 (1 H, d, *J* = 11.2 Hz), 4.60 (1 H, d, *J* = 11.2 Hz), 4.96 (1 H, d, *J* = 1.0 Hz), 4.98 (1 H, d, *J* = 1.0 Hz), 7.42 (3 H, complex pattern), and 7.55 (2 H, complex pattern) ; CIMS *m/z* (relative intensity) 407 [$(M+H)^+$, 92], 389 (7), 359 (36), 347 (14), 329 (5), 173 (73), 155 (100), 143 (42), and 125 (25). Anal. Calcd for $C_{19}H_{25}O_6F_3$: C, 56.15; H, 6.20. Found: C, 56.12; H, 6.27. **24b**: $[\alpha]_D^{13}$ +31.1° (*c* 0.46, $CHCl_3$); IR ($CHCl_3$) 3540, 1755, 1270, 1170, 1110, and 1100 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.71 (3 H, d, *J* = 7.3 Hz), 1.15 (3 H, s), 1.32 (3 H, s), 1.92 (1 H, m), 3.35 (1 H, dd, *J* = 4.5, 11.3 Hz), 3.61 (3 H, q, *J* = 1.3 Hz), 3.81 (1 H, dd, *J* = 8.6, 11.3 Hz), 4.03 (1 H, d, *J* = 11.2 Hz), 4.69 (1 H, d, *J* = 11.2 Hz), 5.00 (1 H, d, *J* = 1.0 Hz), 5.03 (1 H, d, *J* = 1.0 Hz), 7.42 (3 H, complex pattern), and 7.55 (2 H, complex pattern) ; CIMS *m/z* (relative intensity) 407 [$(M+H)^+$, 65], 389 (25), 359 (67), 347 (20), 329 (12), 173 (100), 155 (44), 143 (65), and 125 (25) [HRCIMS. Found: 407.1659. $C_{19}H_{26}O_6F_3$ [$(M+H)^+$] requires: 407.1682].

(2'*R*,2*R*,3*R*,4*S*)-5-[2'-Methoxy-2'-(trifluoromethyl)phenylacetoxy]-2,3,4-trimethyl-3,4-methylenedioxypentanoic Acid (25). To a cooled (–78 °C), stirred solution of oxalyl chloride (0.006 ml, 0.07 mmol) in CH_2Cl_2 (0.1 ml) under nitrogen was added dropwise a solution of dimethyl sulfoxide (0.01 ml, 0.15 mmol) in CH_2Cl_2 (0.05 ml). The mixture was stirred for 2 min, and a solution of **24a** (16.5 mg, 0.0406 mmol) in CH_2Cl_2 (0.4 ml) was added dropwise. After the mixture was stirred for 2 min at –78 °C, Et_3N (0.028 ml, 0.20 mmol) was added. The reaction mixture was stirred at –78 °C for an additional 1 h. The reaction was quenched by addition of 1 M pH 7 phosphate buffer (0.6 ml) with simultaneous removal of the cooling bath. The aqueous mixture was extracted with CH_2Cl_2 (5 x 3 ml). The organic layers were combined, dried, and concentrated. The oily residue was taken up in ether (ca. 5 ml), and insoluble materials were removed by filtration through a cotton plug. The filtration residue was washed thoroughly with ether. The filtrate and washings were combined and concentrated to give the crude aldehyde (21 mg) as a colorless oil. This labile aldehyde was immediately used for the next reaction without further purification. To a solution of the crude aldehyde (21 mg) in *t*-BuOH (0.24 ml) were added 1 M pH 7 phosphate buffer (0.2 ml) and 1 M $KMnO_4$ solution (0.24 ml, 0.24 mmol), and the reaction mixture was stirred for 5 min. The reaction mixture was cooled to 0–5 °C with an ice-bath, and saturated $NaHSO_3$ solution (0.2 ml) was added. The mixture was stirred for ca. 10 min, diluted with 6 M HCl (0.2 ml), and saturated with NaCl. The resulting aqueous mixture was extracted with EtOAc (5 x 4 ml). The extracts were combined, washed, dried, and concentrated to leave a colorless solid. Purification by column chromatography on silica gel (1 g) with 6:1→1:1 hexane–ether provided **25** (14.7 mg, 86% overall from **24a**) as colorless crystals: mp 116–118 °C (hexane–ether); $[\alpha]_D^{18}$ +11.0° (*c* 0.59, $CHCl_3$); IR ($CHCl_3$) 3400–2500 (broad), 1745, 1710, 1270, 1170, 1110, and 1100 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.28 (3 H, s), 1.29 (3 H, s), 1.37 (3 H, d, *J* = 7.0 Hz), 2.77 (1 H, q, *J* = 7.0 Hz), 3.59 (3 H, q, *J* = 1.3 Hz), 4.18 (1 H, d, *J* = 11.2 Hz), 4.87 (1 H, d, *J* = 11.2 Hz), 4.97 (1 H, d, *J* = 1.0 Hz), 4.99 (1 H, d, *J* = 1.0 Hz), 7.40 (3 H, complex pattern), and 7.56 (2 H, complex pattern); CIMS *m/z* (relative intensity) 421 [$(M+H)^+$, 5], 416 (6), 373 (6), 329 (8), 259 (15), 203 (12), 189 (30), 187 (100), 175 (25), and 173 (35). Anal. Calcd for $C_{19}H_{23}O_7F_3$: C, 54.29; H, 5.51. Found: C, 54.24; H, 5.52.

(2*R*,3*R*,4*R*)-2,3,4-Trimethyl-2,3-methylenedioxypentanedioic Acid (8). A solution of **25** (25.1 mg, 0.0598 mmol) in 1 M NaOH (0.5 ml) was stirred at room temperature for 1 h. To the solution was added a 0.66 M solution of Na_2RuO_4 in 1 M NaOH (2.7 ml, 0.18 mmol), and the reaction mixture was stirred at room temperature for 30 min. The reaction was quenched by addition of *i*-PrOH (0.2 ml), and the mixture was filtered through a pad of Celite. The filter cake was washed with 1 M NaOH (1 ml). The filtrate and washings were combined, cooled to 0–5 °C in an ice-bath, and acidified to pH 1 with 6 M HCl. The aqueous mixture was washed with hexane (4 x 10 ml), saturated with NaCl, and then extracted with EtOAc (4 x 10 ml). The extracts were combined, washed, dried, and concentrated to leave a colorless solid. Purification by column chromatography on silica gel (1 g) with ether afforded **8** (11.2 mg, 86%) as colorless crystals: mp 127–129 °C (benzene); $[\alpha]_D^{17}$ +41.7° (*c* 0.57, $CHCl_3$) [authentic sample:[3d] mp 127–131 °C (benzene), $[\alpha]_D^{16}$ +41.7° (*c* 0.57, $CHCl_3$)]. Anal. Calcd for $C_9H_{14}O_6$: C, 49.54; H, 6.47. Found: C, 49.47; H, 6.51.

(2*R*,3*R*,4*R*)-2,3,4-Trimethyl-2,3-methylenedioxypentanedioic Anhydride (7). To a solution of **8** (88.8 mg, 0.407 mmol) in CH_2Cl_2 (3 ml) under nitrogen was added acetic anhydride (0.27 ml). The reaction mixture was heated under reflux for 3.5 h, cooled to room temperature, and concentrated under reduced pressure. The residue was azeotroped with benzene (3 x 2 ml), affording **7** (81.7 mg, quantitative) as colorless crystals. This material was sufficiently pure and used for the next reaction without further purification. The analytical sample was obtained by recrystallization from ether. **7**: mp 88–89.5 °C (ether); $[\alpha]_D^{11}$ –22.0° (*c* 0.30, $CHCl_3$); IR ($CHCl_3$) 1825, 1775, 1115, 1030, and 1010 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.31 (3 H, s), 1.33 (3 H, d, *J* = 7.1 Hz), 1.60 (3 H, s), 3.04 (1 H, q, *J* = 7.1 Hz), 5.00 (1 H, s), and 5.11 (1 H, s); EIMS *m/z* (relative intensity) 200 (M^+, 3), 185 (2), 171 (1), 142 (4), 126 (10), 100 (100), 99 (35), and 83 (37). Anal. Calcd for $C_9H_{12}O_5$: C, 54.00; H, 6.04. Found: C, 53.83; H, 6.07.

Seco Acid 6. A mixture of (+)-retronecine (**3**) (285 mg, 1.14 mmol) and Bu_2SnO (285 mg, 1.14 mmol) in benzene (37 ml) under nitrogen was heated under reflux for 24 h with continuous removal of water by using Molecular Sieves 4A. After being cooled to room temperature, the reaction mixture was concentrated under reduced pressure, yielding the crude retronecine stannoxane **26** as an amorphous solid. Crude **26** was suspended in toluene (12 ml) under nitrogen. To the cooled (–78 °C), stirred toluene suspension of **26** was added a solution of **7** (198 mg, 0.990 mmol) in toluene (3 ml). The reaction mixture was brought to –40 °C and kept at this temperature for 2 h with continuous stirring. Then the reaction mixture was allowed to warm to room temperature, and directly subjected to purification by column chromatography on silica gel (20 g) with 5:4:1 $CHCl_3$–MeOH–H_2O to give a 3:1 mixture of the desired **6** and and the regioisomer **27** (287 mg, 82%) as an amorphous solid. This mixture was separated by HPLC [Develosil ODS-10 (250 x 20 mm ID), 15:85 MeOH–0.02 M NH_4OAc, flow rate 8 ml/min; detection UV 215 nm], providing pure **6** (210 mg, 60%) as colorless powder, and **27** (77 mg, 22%) as colorless powder. **6**: 126–131 °C (ethanol–H_2O); $[\alpha]_D^{12}$ –46.3° (*c* 0.16, H_2O); IR (KBr) 3600–2600 (broad), 1725, 1590, 1130, 1110, and 1100 cm^{-1}; ^1H NMR (270 MHz, D_2O) δ 1.22 (3 H, d, *J* = 7.4 Hz), 1.44 (3 H, s), 1.54 (3 H, s), 2.2–2.3 (2 H, m), 2.45 (1 H, q, *J* = 7.4 Hz), 3.33 (1 H, m), 3.9–4.0 (2 H, m), 4.48 (1 H, d, *J* = 15.9 Hz), 4.71 (1 H, d, *J* = 12.9 Hz), 4.99 (1 H, d, *J* = 12.9 Hz), 5.11 (1 H, s), 5.18 (1 H, s), and 5.96 (1 H, br s); FABMS *m/z* (relative intensity) 356 [$(M+H)^+$, 100] [HRFABMS. Found: 356.1703. $C_{17}H_{26}NO_7$ [$(M+H)^+$] requires: 356.1709]. **27**: $[\alpha]_D^{28}$ –20.3° (*c* 0.947, H_2O); IR (KBr) 3600–2600 (broad), 1745, 1610, 1150, 1115, and 1090 cm^{-1}; ^1H NMR (270 MHz, D_2O) δ 1.26 (3 H, d, *J* = 6.9 Hz), 1.39 (3 H, s), 1.43 (3 H, s), 2.2–2.3 (2 H, m), 2.95 (1 H, q, *J* = 6.9 Hz), 3.31 (1 H, m), 3.9–4.0 (2 H, m), 4.46 (1 H, d, *J* = 16.3 Hz), 5.02 (1 H, s), 5.10 (1 H, s), and 5.94 (1 H, br s); FABMS *m/z* (relative intensity) 356 [$(M+H)^+$, 100] [HRFABMS. Found: 356.1689. $C_{17}H_{26}NO_7$ [$(M+H)^+$] requires: 356.1709].

Monocrotaline Methylene Acetal (5). (A) Lactonization by Yamaguchi's Method. To a stirred solution of **6** (17.0 mg, 0.0479 mmol) in THF (0.5 ml) under nitrogen was added Et_3N (0.013 ml, 0.096 mmol). Subsequently a solution of 2,4,6-trichlorobenzoyl chloride (23 mg, 0.096 mmol) in THF (0.5 ml) was added and the reaction mixture was stirred at room temperature for 3.5 h and diluted with toluene (3 ml). The mixture was added dropwise over a 1-h period to a refluxing toluene (10 ml) solution containing 4-(dimethylamino)pyridine (35.1 mg, 0.287 mmol) under nitrogen, and the mixture was heated under reflux for an additional 10 min. After being cooled to room temperature, the reaction mixture was concentrated to leave an oily residue, which was purified by preparative TLC on silica gel (70:10:1 $CHCl_3$–MeOH–conc. NH_3), affording a mixture of hydrochlorides of **5** and **29**. Free **5** and **29** were obtained by dissolving the salts in $CHCl_3$ (2 ml) and by washing the $CHCl_3$ solution with saturated $NaHCO_3$ solution (0.5 ml). Concentration of the $CHCl_3$ solution afforded a mixture of free **5** and **29** (10.5 mg) as a colorless oil. Separation of the mixture by HPLC [Develosil OD-10/20 (250 x 20 mm ID), 30:70 CH_3CN–0.04 M NH_4OAc, flow rate 8 ml/min, detection UV 217 nm] provided pure **5** (5.9 mg, 37%) as colorless crystals, along with the stereoisomer **29** (1.1 mg, 7%) as a colorless oil. **5**: mp 175–178 °C (decomp.) (MeOH); $[\alpha]_D^{14}$ +19.6° (*c* 0.28, $CHCl_3$) [authentic sample:[3d] mp 177–179 °C (decomp.) (MeOH), $[\alpha]_D^{27}$ +20.3° (*c* 0.55, $CHCl_3$)]; IR ($CHCl_3$) 1740, 1190, 1130, and 1115 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.29 (3 H, d, *J* = 7.2 Hz), 1.42 (3 H, s), 1.47 (3 H, s), 2.0–2.1 (2 H, m), 2.58 (1 H, m), 2.63 (1 H, q, *J* = 7.2 Hz), 3.30 (1 H, ddd, *J* = 2.1, 6.9, 9.1 Hz), 3.43 (1 H, dd, *J* = 5.1, 15.9 Hz), 3.91 (1 H, dd, *J* = 2.6, 15.9 Hz), 4.33 (1 H, d, *J* = 12.0 Hz), 4.35 (1 H. m), 5.09 (1 H, d, *J* = 1.5 Hz), 5.24 (1 H, d, *J* = 1.5 Hz), 5.30 (1 H, ddd, *J* = 2.0, 4.3, 4.3 Hz), 5.36 (1 H, d, *J* = 12.0 Hz), and 6.01 (1 H, br s); CIMS *m/z* (relative intensity) 338 [$(M+H)^+$, 100], 293 (6), 214 (5), 201 (6), 173 (29), and 120 (45). Anal. Calcd for $C_{17}H_{23}NO_6$: C, 60.52; H, 6.87; N, 4.15. Found: C, 60.24; H, 6.83; N, 4.16. **29**: $[\alpha]_D^{14}$ +13.6° (*c* 0.14, $CHCl_3$); IR ($CHCl_3$) 1735, 1255, 1130, and 1105 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.12 (3 H, d, *J* = 7.4 Hz), 1.49 (3 H, s), 1.59 (3 H, s), 2.0–2.2 (2 H, m), 2.66 (1 H, m), 2.93 (1 H, q, *J* = 7.4 Hz), 3.4–3.5 (2 H, m), 4.06 (1 H, d, *J* =16.5 Hz), 4.43 (1 H, d, *J* = 12.2 Hz), 4.57 (1 H. m), 5.08 (1 H, d, *J* = 1.5 Hz), 5.28 (1 H, d, *J* = 1.5 Hz), 5.32 (1 H, m), 5.32 (1 H, d, *J* = 12.2 Hz), and 6.04 (1 H, br s); CIMS *m/z* (relative intensity) 338 [$(M+H)^+$, 37], 250 (5), 136 (9), and 120 (100) [HRCIMS. Found: 338.1616. $C_{17}H_{24}NO_6$ [$(M+H)^+$] requires: 338.1604].

(B) Lactonization by Keck's Method. To a mixture of **6** (11.7 mg, 0.033 mmol), 4-(dimethylamino)pyridine (13.0 mg, 0.107 mmol), and 4-(dimethylamino)pyridine hydrochloride (11.2 mg, 0.074 mmol) in $CHCl_3$ (1.2 ml) under nitrogen was added dicyclohexylcarbodiimide (14.9 mg, 0.0723 mmol). The reaction mixture was stirred for 85 h, and directly subjected to separation by column chromatography on silica gel (5 g) with 40:1→20:1→5:1 $CHCl_3$–MeOH, yielding **5** (7.1 mg, 64%).

(–)-Monocrotaline (1). To a solution of **5** (10.1 mg, 0.0298 mmol) in CH_2Cl_2 (1 ml) under nitrogen was added triphenylcarbenium tetrafluoroborate ($Ph_3C{\cdot}BF_4$) (24 mg, 0.073 mmol), and the reaction mixture was heated under reflux for 48 h. After cooling, the reaction mixture was extracted with 1 M HCl (3 ml). The aqueous layer was washed with CH_2Cl_2 (2 x 2 ml), allowed to stand at room temperature for 17.5 h, and made basic (pH 9) with saturated $NaHCO_3$ solution. The resulting mixture was saturated with NaCl, and extracted with EtOAc (4 x 8 ml). The combined extracts were washed, dried, and concentrated. The residual oil was purified by column chromatography on silica gel (1 g) with 100:5:1 $CHCl_3$–MeOH–conc. NH_3, providing (–)-**1** (8.4 mg, 86%) as colorless crystals: mp 187–190 °C (decomp.) (EtOH) ; $[\alpha]_D^{12}$ –55.0° (*c* 0.16, $CHCl_3$) [lit.[6a] mp 197–198 °C (decomp.) (EtOH); $[\alpha]_D$ –54.7° (*c* 5.05, $CHCl_3$)] [natural **1**: mp 189-194 °C (decomp.) (EtOH); $[\alpha]_D^{12}$ –59.3° (*c* 0.60, $CHCl_3$)]; IR ($CHCl_3$) 3540, 1735, 1190, and 1110 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.22 (3 H, d, *J* = 7.0 Hz), 1.35 (3 H, s), 1.44 (3 H, s), 2.1–2.2 (2 H, m), 2.63 (1 H, m), 2.80 (1 H, q, *J* = 7.0 Hz), 3.31 (1 H, m), 3.51 (1 H, dd, *J* = 4.0, 16.6 Hz), 3.98(1 H, d, *J* = 16.6 Hz), 4.49 (1 H, m), 4.69 (1 H, d, *J* = 12.0 Hz), 4.91 (1 H, d, *J* = 12.0 Hz), 5.08 (1 H, m), and 6.05 (1 H, br s); CIMS *m/z*

(relative intensity) 326 [$(M+H)^+$, 100], 325 (M^+, 15), 324 (29), 308 (21), 283 (6), 264 (19), 236 (18), 151 (12), 138 (35), and 120 (96) [HRCIMS. Found: 326.1590. $C_{16}H_{24}NO_6$ [$(M+H)^+$] requires: 326.1604].

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REFERENCES AND NOTES

1. (a) Smith, L. W.; Culvenor, C. C. J. *J. Nat. Prod.* **1981**, *44*, 129–152. (b) Robins, D. J. *Fortschr. Chem. Org. Naturst.* **1982**, *41*, 115–203. (c) Robins, D. J. *Nat. Prod. Rep.* **1984**, *1*, 235–243; **1985**, *2*, 213–220; **1986**, *3*, 297–305; **1987**, *4*, 577–590; **1989**, *6*, 221–230; **1989**, *6*, 577–589; **1990**, *7*, 377–386; **1991**, *8*, 213–221; **1992**, *9*, 313–321.

2. Mattocks, A. R. *Chemistry and Toxicology of Pyrrolizidine Alkaloids*; Academic Press: London, 1986.

3. (a) (+)-Dicrotaline: Devlin, J. A.; Robins, D. J. *J. Chem. Soc., Chem. Commun.* **1981**, 1272–1274; Brown, K.; Devlin, J. A.; Robins, D. J. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1819–1824. (b) (+)-Dicrotaline: Niwa, H.; Okamoto, O.; Ishiwata, H.; Kuroda, A.; Uosaki, Y.; Yamada, K. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 3017–3019. (c) (±)-Fulvine and (±)-crispatine: Vedejs, E.; Larsen, S. D. *J. Am. Chem. Soc.* **1984**, *106*, 3030–3032. (d) (–)-Monocrotaline (**1**): Vedejs, E.; Ahmad, S.; Larsen, S. D.; Westwood, S. *J. Org. Chem.* **1987**, *52*, 3937–3938.

4. (a) (±)-Integerrimine (**2**): Narasaka, K.; Sakakura, T.; Uchimaru, T.; Morimoto, K.; Mukaiyama, T. *Chem. Lett.* **1982**, 455–458: Narasaka, K.; Sakakura, T.; Uchimaru, T.; Güedin-Vuong, D. *J. Am. Chem. Soc.* **1984**, *106*, 2954–2961. (b) (–)-Integerrimine (**2**) and (+)-usaramine: White, J. D.; Ohira, S. *J. Org. Chem.* **1986**, *51*, 5492–5494: White, J. D.; Amedio, J. C., Jr.; Gut, S.; Jayasinghe, L. *J. Org. Chem.* **1989**, *54*, 4268–4270: White, J. D.; Amedio, J. C., Jr.; Gut, S.; Ohira, S.; Jayasinghe, L. R. *J. Org. Chem.* **1992**, *57*, 2270–2284. (c) (–)-Integerrimine (**2**): Niwa, H.; Miyachi, Y.; Uosaki, Y.; Yamada, K. *Tetrahedron Lett.* **1986**, *27*, 4601–4604: Niwa, H.; Miyachi, Y.; Okamoto, O.; Uosaki, Y.; Yamada, K. *Tetrahedron Lett.* **1986**, *27*, 4605–4609: Niwa, H.; Miyachi, Y.; Uosaki, Y.; Kuroda, A.; Ishiwata, H.; Yamada, K. *Tetrahedron Lett.* **1986**, *27*, 4609–4610: Niwa, H.; Miyachi, Y.; Okamoto, O.; Uosaki, Y.; Kuroda, A.; Ishiwata, H.; Yamada, K. *Tetrahedron* **1992**, *48*, 393–412.

5. Preliminary communication: Niwa, H.; Okamoto, O.; Yamada, K. *Tetrahedron Lett.* **1988**, *29*, 5139–5142.

6. (a) Adams, R.; Rogers, E. F. *J. Am. Chem. Soc.* **1939**, *61*, 2815–2824. (b) Adams, R.; Shafer, P. R.; Braun, B. H. *J. Am. Chem. Soc.* **1952**, *74*, 5612–5615. (c) Robins, D. J.; Crout, D. H. G. *J. Chem. Soc. (C)*, **1969**, 1386–1391. (d) Robins, D. J.; Crout, D. H. G. *J. Chem. Soc. (C)*, **1970**, 1334–1336. (e) Matsumoto, T.; Takahashi, M.; Kashihara, Y. *Bull. Chem. Soc. Jpn.*, **1979**, *52*, 3329–3336. (f) Stoeckli-Evans, H. *Acta Crystallogr., Sect. B.* **1979**, *35*, 231–234.

7. Concurrent with our work, Vedejs and co-workers reported the synthesis of racemic **8** in the different approach and derivation of optically active **8** from natural monocrotaline (**1**); see Ref. 3d.

8. Tatsumi, S.; Izumi, Y.; Imaida, M.; Fukuda, Y.; Akabori, S. *Bull. Chem. Soc. Jpn.* **1966**, *39*, 602–604.

9. The relative stereochemistry of the secondary methyl groups in **18a** and **18b** was assigned as shown by the successive conversion of the former isomer **18a** into the desired (±)-**8**.

10. Houk, K. N.; Rondan, N. G.; Wu, Y.-D.; Metz, J. T.; Paddon-Row, M. N. *Tetrahedron* **1984**, *40*, 2257–2274.

11. Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480-2482. Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651–1660.

12. Abiko, A.; Roberts, J. C.; Takemasa, T.; Masamune, S. *Tetrahedron Lett.* **1986**, *27*, 4537–4540.

13. Lee, D. G.; Hall, D. T.; Cleland, J. H. *Can. J. Chem.* **1972**, *50*, 3741–3743.

14. The similar regioselective ring opening reaction of a *meso*-anhydride with (*R*)-1-phenylethyl alcohol was reported: Rosen, T.; Heathcock, C. H. *J. Am. Chem. Soc.* **1985**, *107*, 3731–3733. The related studies: Theisen, P. D.; Heathcock, C. H. *J. Org. Chem.* **1988**, *53*, 2374–2378: Suda, Y.; Yago, S.; Shiro, M.; Taguchi, T. *Chem. Lett.* **1992**, 389–392: Ohtani, M.; Matsuura, T.; Watanabe, F.; Narisada, M. *J. Org. Chem.* **1991**, *56*, 2122–2127: Ohtani, M.; Matsuura, T.; Watanabe, F.; Narisada, M. *J. Org. Chem.* **1991**, *56*, 4120–4123.

15. The ratio was determined by the ^{1}H NMR spectral analysis of the mixture.

16. This material is not optically pure, the optical purity of which is calculated to be 81% ee on the basis of the ratio of the diastereomers **20a** and **20b**. The structural formula of the major enantiomer is depicted for this material.

17. Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543–2549.

18. Niwa, H.; Okamoto, O.; Miyachi, Y.; Uosaki, Y.; Yamada, K. *J. Org. Chem.* **1987**, *52*, 2941–2943.

19. Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 738–741. Kayser, M. M.; Morand, P. *Tetrahedron Lett.* **1979**, 695–698 and references cited therein.

20. (a) Corey, E. J.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1974**, *96*, 5614–5616. (b) Gerlach, H.; Thalmann, A. *Helv. Chim. Acta* **1974**, *57*, 2661–2663. (c) Mukaiyama, T.; Usui, M.; Saigo, K. *Chem. Lett.* **1976**, 49–50.

21. Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989–1993.

22. Boden, E. P.; Keck, G. E. *J. Org. Chem.* **1985**, *50*, 2394–2395.

23. Barton, D. H. R.; Magnus, P. D.; Smith, G.; Streckert, G.; Zurr, D. *J. Chem. Soc., Perkin Trans. 1* **1972**, 542–552.