Stereoselective Synthesis of (−)-Trachelanthic Acid and (+)-Viridifloric Acid, Necic Acid Components of Pyrrolizidine Alkaloids from a Common Intermediate

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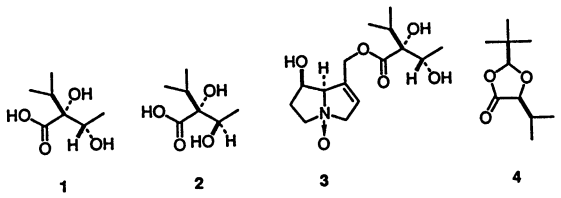
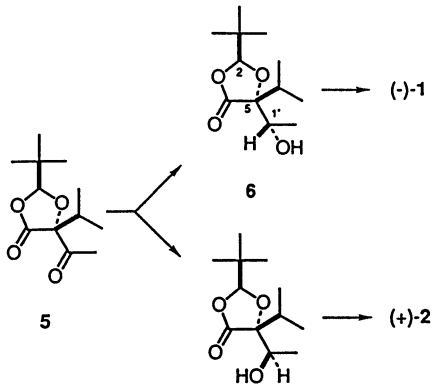
Synopsis. Diastereoselective reduction of a side-chain keto group in (2*S*,5*R*)-5-acetyl-2-(*t*-butyl)-5-isopropyl-1,3-dioxolan-4-one (**5**) with (*i*-Bu)$_2$AlH in ether afforded (1′*S*,2*S*,5*R*)-2-(*t*-butyl)-5-(1′-hydroxyethyl)-5-isopropyl-1,3-dioxolan-4-one (**6**), while reduction of **5** with LiBH(*s*-Bu)$_3$ in ether gave the (1′*R*)-isomer **7** predominantly. (−)-Trachelanthic acid (**1**) and (+)-viridifloric acid (**2**) were synthesized upon hydrolysis of **6** and **7**, respectively.

2-Substituted 2,3-dihydroxybutanoic acids are known to be necic acid components of certain pyrrolizidine alkaloids.[1] In particular, (2*R*,3*S*)-2,3-dihydroxy-2-isopropylbutanoic acid [(−)-trachelanthic acid (**1**)] is the necic acid component of an antitumor pyrrolizidine alkaloid, indicine *N*-oxide (**3**).[1] Described herein is the enantioselective synthesis of (−)-trachelanthic acid (**1**)[2] and the diastereomer, (+)-viridifloric acid (**2**)[3] by utilizing the diastereoselective ketone reduction of (2*S*,5*R*)-5-acetyl-2-(*t*-butyl)-5-isopropyl-1,3-dioxolan-4-one (**5**) (Scheme 1).

The optically pure ketone **5** was prepared by Collins oxidation of a diastereomeric mixture of **6** and **7**, which was obtained by aldol reaction of acetaldehyde with the lithium enolate generated from (2*S*,5*S*)-2-(*t*-butyl)-5-isopropyl-1,3-dioxolan-4-one **4**.[4,5] The side-chain keto group in **5** was reduced with various metal hydrides and the results are summarized in Table 1.





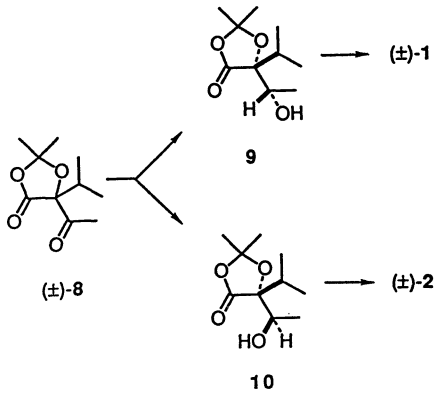
Scheme 1.

Glass et al. reported the synthesis of (±)-**1** and (±)-**2** by utilizing the diastereoselective reduction of a similar ketone (±)-**8** with KBH(*s*-Bu)$_3$ in tetrahydrofuran (THF) (**9**:**10**=100:0) and with Zn(BH$_4$)$_2$ in ether (**9**:**10**=1:7) as illustrated in Scheme 2.[6] In our cases, however, the reduction of **5** with Zn(BH$_4$)$_2$ in ether gives a 1:2 mixture of **6** and **7** (entry 1). Moreover, no diastereoselectivity is observed in the reduction of **5** with KBH(*s*-Bu)$_3$ in THF (entry 2). Diastereoselectivity in the reduction with KBH(*s*-Bu)$_3$ depends on reaction solvent and the formation of **7** increases with decreasing solvent polarity (compare entries 2—4). On the other hand, solvent effect is somewhat complicated in the reduction of **5** with LiBH(*s*-Bu)$_3$. Thus the reduction of **5** with LiBH(*s*-Bu)$_3$ in THF gives **6** as the major product (entry 5), while the reverse selectiv-

Table 1. Diastereoselective Reduction of **5**[a]

Entry	Reducing reagent	Solvent	Time h	Yield[b] % **6**+**7**	Product ratio[c] **6** : **7**
1	Zn(BH$_4$)$_2$	Ether	5	30	1 : 2
2	KBH(*s*-Bu)$_3$	THF	4	86	1 : 1
3		Ether	3	65	1 : 6
4		Toluene	3	83	1 :11
5	LiBH(*s*-Bu)$_3$	THF	2	80	3 : 1
6		Ether	2	67	1 :16
7		Toluene	2	60	1 : 4
8	LiBH(*s*-Bu)$_3$ -ZnCl$_2$	THF	3	91	6 : 1
9		Ether	1	79	4.5: 1
10	(*i*-Bu)$_2$AlH	Ether	3	65	12 : 1

a) All reactions were performed at −78 °C. b) Isolated yield of the mixture. c) Determined by ^{1}H NMR spectral analysis of the mixture.



Scheme 2.

ity leading to **7** is observed on reduction in ether (entry 6, **6**:**7**=1:16) and in toluene (entry 7, **6**:**7**=1:4). Interestingly **6** is obtained as the major product in the LiBH(*s*-Bu)$_3$ reduction of **5** in the presence of $ZnCl_2$ in ether and in THF as well (entry 8, 9). The marked selectivity leading to **6** is observed in the reduction of **5** with (*i*-Bu)$_2$AlH in ether (entry 10, **6**:**7**=12:1).[7]

The diastereomeric mixture of **6** and **7** could be separated easily by HPLC. Finally, acidic hydrolysis of **6** and **7** provided (−)-trachelanthic acid (**1**) (82%) and (+)-viridifloric acid (**2**) (80%), respectively. Spectral and chiroptical properties of synthetic **1** and **2** were identical with those of natural **1** and **2**.

In summary, (−)-trachelanthic acid (**1**) and (+)-viridifloric acid (**2**) were synthesized enantioselectively by utilizing the diastereoselective reduction of **5** with (*i*-Bu)$_2$AlH in ether and LiBH(*s*-Bu)$_3$ in ether, respectively.

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) spectrometer in $CDCl_3$ using tetramethylsilane (TMS) as an internal standard. Chemical shifts are 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 high-resolution (HRCIMS) mass spectra were recorded on a JEOL JMS-LG2000 instrument using methane as the reagent gas. 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). High-performance liquid chromatography (HPLC) was performed with a JASCO TRIROTAR-II instrument equipped with a UV detector (JASCO UVIDEC-II) set at 215 nm. Toluene was distilled from Na under nitrogen. Tetrahydrofuran (THF) and ether were distilled from Na-benzophenone ketyl under nitrogen. Diisopropylamine, dichloromethane (CH_2Cl_2), and pyridine (Py) were distilled from CaH_2 under nitrogen. Acetaldehyde was distilled just prior to use under nitrogen. Unless otherwise stated, organic solutions obtained extractive workup were washed with saturated brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure by a rotary evaporator.

(2*S*,5*R*)-5-Acetyl-2-(*t*-butyl)-5-isopropyl-1,3-dioxolan-4-one (5). To a solution of diisopropylamine (0.23 ml, 1.6 mmol) in THF (7 ml) cooled to −78 °C under nitrogen was added dropwise a 1.7 M solution of butyllithium in hexane (0.92 ml, 1.5 mmol) (1 M=1 mol dm^{-3}). The solution was stirred at −78 °C for 30 min and cooled to −100 °C with a liquid N_2–THF bath. To the cooled solution was added dropwise a solution of (2*S*,5*S*)-2-(*t*-butyl)-5-isopropyl-1,3-dioxolan-4-one (**4**)[4,5] (190 mg, 1.02 mmol) in THF (0.76 ml). After the mixture was stirred for 1 h at −100 °C, acetaldehyde (0.13 ml, 2.3 mmol) was added to the mixture. The reaction mixture was allowed to warm to room temperature with stirring. After 1 h, a saturated NH_4Cl solution (2 ml) and a saturated NaCl solution (2 ml) were added and the mixture was extracted with ether (4×20 ml). The extracts were combined, dried, and concentrated. The residual oil was purified by repeated column chromatography first on silica gel (50 g) with CH_2Cl_2 and then on silica gel (30 g) with hexane–ether (5/1 volume ratio) to give a 6:1 mixture[8] of **6** and **7** (134 mg, 59%) as a colorless oil.

To a solution of $CrO_3 \cdot 2Py$ (1.01 g, 3.88 mmol) in CH_2Cl_2 (10 ml) was added a solution of the mixture of **6** and **7** (90.4 mg, 0.393 mmol) in CH_2Cl_2 (2 ml) at room temperature. After stirring for 40 min, the reaction mixture was diluted with ether (50 ml). The mixture was passed through a column of Florisil and the column was washed thoroughly with ether. The organic layers were combined and concentrated. The residual oil was purified by column chromatography on silica gel (5 g, CH_2Cl_2) to give **5** (87.7 mg, 98%) as a colorless oil: $[\alpha]_D^{14}$ +103° (*c* 0.885, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 270 MHz) δ=0.95, (3H, d, *J*=6.9 Hz), 1.03 (9H, s), 1.03 (3H, d, *J*=6.9 Hz), 2.31 (3H, s), 2.63 (1H, qq, *J*=6.9, 6.9 Hz), and 5.15 (1H, s); IR ($CHCl_3$) 1790, 1735, 1235, 1185, and 1135 cm^{-1}; CIMS *m/z* (rel intensity) 229 [(M+H)$^+$, 15], 201 (17), 186 (89), 115 (54), and 87 (100). HRCIMS. Found: *m/z* 229.1425. Calcd for $C_{12}H_{21}O_4$: M+H, 229.1440.

(*i*-Bu)$_2$AlH Reduction of 5. To a solution of **5** (124 mg, 0.544 mmol) in ether (13 ml) cooled to −78 °C under nitrogen was added dropwise a 1 M solution of (*i*-Bu)$_2$AlH in hexane (0.82 ml, 0.82 mmol). The reaction mixture was stirred at −78 °C for 3 h and the reaction was quenched by the addition of a saturated potassium sodium tartrate solution (5 ml). The mixture was allowed to warm to room temperature with stirring. After 20 min, the mixture was extracted with ether (3×20 ml). The extracts were combined, washed, dried, and concentrated. The residual oil was purified by column chromatography on silica gel (7g, CH_2Cl_2) to give a 12:1 mixture[8] of **6** and **7** (76.6 mg, 65%) as a colorless oil.

LiBH(*s*-Bu)$_3$ Reduction of 5. To a solution of **5** (14 mg, 0.061 mmol) in ether (1.2 ml) was added dropwise a 1 M solution of LiBH(*s*-Bu)$_3$ in THF (0.12 ml, 0.12 mmol) at −78 °C. The mixture was stirred at −78 °C for 2 h and the reaction was quenched by the addition of water (0.5 ml). The mixture was allowed to warm to room temperature with stirring. After 30 min, a 30% H_2O_2 solution (0.5 ml) was added to the mixture and the stirring was continued for additional 45 min. The mixture was saturated with NaCl and extracted with ether (3×5 ml). The extracts were combined, washed with a saturated $Na_2S_2O_3$ solution (2 ml) and a saturated NaCl solution (2 ml), dried, and concentrated to leave a white solid. Purification of the solid by column chromatography on silica gel (2 g, CH_2Cl_2) gave a 1:16 mixture[8] of **6** and **7** (9.4 mg, 67%) as colorless crystals. Similarly, reduction of **5** with LiBH(*s*-Bu)$_3$ were performed in THF (**6**:**7**=3:1, 80%) and in toluene (**6**:**7**=1:4, 60%) at −78 °C.[8]

LiBH(*s*-Bu)$_3$–$ZnCl_2$ Reduction of 5. To a solution of **5** (13 mg, 0.0510 mmol) in THF (1.2 ml) was added anhydrous $ZnCl_2$ (58 mg, 0.41 mmol) at 0 °C under nitrogen. The mixture was stirred for 1 h at 0 °C and then cooled to −78 °C.

To the cooled solution was added dropwise a 1 M solution of LiBH(*s*-Bu)$_3$ in THF (0.12 ml, 0.12 mmol). The reaction mixture was stirred at −78 °C for 3 h and the reaction was quenched by the addition of water (0.5 ml). The mixture was allowed to warm to room temperature with stirring. After 10 min, a 30% H_2O_2 solution (0.5 ml) was added and the stirring was continued for additional 50 min. The mixture was saturated with NaCl and extracted with ether (4×5 ml). The extracts were combined, washed with saturated $Na_2S_2O_3$ solutions (2×2 ml) and a saturated $NaHCO_3$ solution (2 ml), dried, and concentrated. The residual oil was purified by column chromatography on silica gel (2 g, CH_2Cl_2) to give a 6 : 1 mixture[8] of **6** and **7** (11.9 mg, 91%) as a colorless oil. Similarly, reduction of **5** with LiBH(*s*-Bu)$_3$-$ZnCl_2$ in ether at −78 °C gave a 4.5 : 1 mixture[8] of **6** and **7** (79%).

KBH(*s*-Bu)$_3$ Reduction of 5. To a solution of **5** (6.9 mg, 0.030 mmol) in toluene (0.6 ml) cooled to −78 °C under nitrogen was added dropwise a 1 M KBH(*s*-Bu)$_3$ solution in THF (0.06 ml, 0.06 mmol). The reaction mixture was stirred at −78 °C for 3 h and the reaction was quenched by the addition of water (0.5 ml). The mixture was allowed to warm to room temperature with stirring. After 30 min, a 30% H_2O_2 solution (0.5 ml) was added and the stirring was continued for additional 2 h. The mixture was saturated with NaCl and extracted with ether (4×2 ml). The extracts were combined, washed with saturated $Na_2S_2O_3$ solutions (2×2 ml) and a saturated NaCl solution (2 ml), dried, and concentrated. Purification of the residual oil by preparative TLC (CH_2Cl_2) gave a 1 : 11 mixture[8] of **6** and **7** (5.8 mg, 83%) as colorless crystals. Similarly, reduction of **5** with KBH(*s*-Bu)$_3$ were performed in ether (**6** : **7**=1 : 6, 65%) and in THF (**6** : **7**=1 : 1, 86%) at −78 °C.[8]

Zn(BH$_4$)$_2$ Reduction of 5. To a 0.052 M solution of Zn(BH$_4$)$_2$ in ether[6] (3 ml, 0.16 mmol) cooled to −78 °C under nitrogen was added a solution of **5** (11 mg, 0.0482 mmol) in ether (0.5 ml). The reaction mixture was stirred at −78 °C for 5 h and the reaction was quenched by the addition of saturated NH_4Cl solution (1 ml). The mixture was extracted with ether (4×5 ml). The extracts were combined, washed, dried, and concentrated. Purification of the residual oil by preparative TLC (CH_2Cl_2) gave a 1 : 2 mixture[8] of **6** and **7** (7.8 mg, 30%) as a colorless oil.

Separation of the Mixture of 6 and 7. The mixture of **6** and **7** was able to be separated by HPLC [Develosil ODS-10 (250×20 mm ID); solvent MeOH-H_2O (75/25); flow rate 8 ml min^{-1}; detection UV 215 nm; recycled twice] to give pure **6** (t_R 54 min) and **7** (t_R 50 min). **6**: Colorless oil; $[\alpha]_D^{16}$ +2.2° (*c* 0.98, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 270 MHz) δ=1.00 (9H, s), 1.06 (3H, d, *J*=6.9 Hz), 1.06 (3H, d, *J*=6.9 Hz), 1.33 (3H, d, *J*=6.6 Hz), 1.96 (1H, d, *J*=5.6 Hz), 2.09 (1H, qq, *J*=6.9, 6.9 Hz), 4.31 (1H, dq, *J*=5.6, 6.6 Hz), and 5.42 (1H, s); IR ($CHCl_3$) 3625, 3450, 1780, and 1165 cm^{-1}; CIMS *m/z* (rel intensity) 231 [$(M+H)^+$, 15], 186 (49), 173 (10), 145 (11), and 87 (100). HRCIMS. Found: *m/z* 231.1587. Calcd for $C_{12}H_{23}O_4$: M+H, 231.1596. **7**: Mp 108—109 °C (pentane); $[\alpha]_D^{14}$ −39.0° (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 270 MHz) δ=0.98 (3H, d, *J*=6.9 Hz), 0.98 (3H, d, *J*=6.9 Hz), 1.00 (9H, s), 1.39 (3H, d, *J*=6.6 Hz), 1.64 (1H, d, *J*=5.6 Hz) , 2.12 (1H, qq, *J*=6.9, 6.9 Hz) , 4.23 (1H, dq, *J*=5.6, 6.6 Hz), and 5.55 (1H, s); IR ($CHCl_3$) 3600, 3450, 1780, 1170, and 1100 cm^{-1}; CIMS *m/z* (rel intensity) 231 [$(M+H)^+$, 11], 186 (66), 173 (15), 145 (12), and 87 (100). HRCIMS. Found: *m/z* 231.1581. Calcd for $C_{12}H_{23}O_4$: M+H, 231.1596.

(−)-Trachelanthic Acid (1) and (+)-Viridifloric Acid (2). A mixture of **6** (66.5 mg, 0.289 mmol) and 1 M HCl (7 ml) was heated under reflux for 3 h. After cooling, the reaction mixture was concentrated in vacuo. Purification of the residual oil by column chromatography on silica gel [5 g, $CHCl_3$-MeOH (10/1)] gave (−)-**1** (38.6 mg, 82%): Mp 88.5—89.5 °C (benzene-hexane); $[\alpha]_D^{14}$ −4.5° (*c* 1.0, EtOH) [Lit,[2a] mp 89.5—90 °C (benzene-hexane); $[\alpha]_D^{25}$ −4.8° (*c* 0.51, EtOH)]. Similarly, acidic hydrolysis of **7** (31.4 mg) and subsequent purification provided (+)-**2** (17.6 mg, 80%): Mp 117—118 °C (ether-hexane); $[\alpha]_D^{14}$ +1.9° (*c* 0.73, H_2O) [Lit,[3] mp 117—119 °C (ether-petroleum ether); $[\alpha]_D^{25}$ +1.8° (*c* 2.73, H_2O)].

References

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7) Reduction of **5** with (*i*-Bu)$_2$AlH in hexane gave also a 12 : 1 mixture of **6** and **7**, however the yield was poor owing to over-reduction of the lactone moieties.

8) The ratio of **6** and **7** was determined by ^{1}H NMR spectral analysis of the mixture.