Synthesis of (S)-(+)-Methyl β,γ -Dihydroxy- α -methylenebutyrate and (S)-(-)-Tulipalin B[†]

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The synthesis of (S)-(+)-methyl β,γ -dihydroxy- α -methylenebutyrate and (S)-(-)-tulipalin B, antibacterial substances isolated from *Spiraea thunbergii* Sieb. has been accomplished starting from isopropylidene-D-glyceraldehyde.

In connection with our synthetic studies of α,β -unsaturated lactones, we have been interested in the synthesis of optically active unsaturated carbonyl compounds having a variety of biological activities. In 1975, K. Ohkuma and his co-workers isolated two antibacterial substances from *Spiraea thunbergii* Sieb.,^{1,2)} one of which was identified with tulipalin B (**2**),^{5~7)} the cyclized aglycone of tuliposide B. The latter is known as a bactericidal glucosyl ester in tulip.^{5,6)} The structure of another component of *S. thunbergii* was assigned to be methyl β,γ -dihydroxy- α -methylenebutyrate (**1**). The absolute stereochemistry of (+)-**1** and (-)-**2** was shown to be (S)⁸⁾ by the identity of the crystalline (+)- β,γ -dihydroxy- α -methylenebutyric acid derived from components of *S. thunbergii* with that obtained from tuliposide B having the (S) configuration.^{6,9)} The synthesis of these compounds has been reported only in racemic form.^{3,4,10)}

In this paper, we wish to describe the first synthesis of (S)-(+)-methyl β,γ -dihydroxy- α -methylenebutyrate and (S)-(-)-tulipalin B starting from isopropylidene-D-glyceraldehyde (**3**) which is easily accessible from D-mannitol.^{11,12)} Oxidation of **3** with alkaline permanganate gave the potassium salt **4**¹³⁾ ($[\alpha]_D^{25} + 30.1^\circ$) in good yield. Then, this was treated with oxalyl chloride followed by diazomethane.

Decomposition of the crude diazomethylketone **6** thus obtained was effected by heating with benzoic acid in dry dioxane in the presence of copper powder. Chromatographic purification afforded the crystalline keto benzoate **7** ($[\alpha]_D^{25} + 79.0^\circ$) in 69% yield. The Wittig olefination of **7** was conducted by use of methyltriphenylphosphonium iodide and *n*-butyl lithium in tetrahydrofuran to give the olefinic alcohol **9** ($[\alpha]_D^{25} + 40.7^\circ$) in 65% yield. Employment of ether in place of tetrahydrofuran resulted in the formation of the olefinic benzoate **8** (19%) ($[\alpha]_D^{25} + 36.7^\circ$) along with **9** (24%). The Corey's procedure¹⁴⁾ using dimsyl sodium in dimethylsulfoxide afforded **9** only in low yield. The olefinic benzoate **8** was readily hydrolyzed to **9** with aq. alkaline solution. Then, this alcohol was submitted to oxidation with active manganese dioxide followed by silver oxide. The pure olefinic carboxylic acid **11** ($[\alpha]_D^{24} + 47.3^\circ$) was obtained in good yield after chromatography. Transformation of **11** into natural tulipalin B (**2**) was effected by acid hydrolysis. The lactonic substance thus obtained was identical with tulipalin B prepared in racemic form by selenium dioxide oxidation¹⁰⁾ of α -methylene- γ -butyrolactone in the IR and NMR spectra, and chromatographic behaviors. The optical rotation of the synthetic material ($[\alpha]_D^{24} - 88^\circ$) was almost the same as that recorded for natural tulipalin B ($[\alpha]_D^{20} - 82^\circ$).⁶⁾ Accordingly, it was confirmed by the unambiguous synthesis described abo-

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usual manner to give the crude diazomethylketone **6** (IR $\nu_{\text{max}}^{\text{film}}$ cm^{-1} : 2120, 1630). Then, this ketone was heated with benzoic acid (7.6 g) in dry dioxane (140 ml) in the presence of Cu powder (*ca.* 100 mg) until effervescent evolution of N_2 ceased and at reflux temperature for additional 15 min. The reaction mixture was poured into ice-water, neutralized with aq. NaHCO_3 and filtered. The filtrate was extracted with CHCl_3 . Evaporation gave a highly viscous oil which on column chromatography (SiO_2) afforded (+)-**7** (7.5 g), mp 67~69°C. Recrystallization from Et_2O gave an analytically pure material, mp 71~72°C. $[\alpha]_{\text{D}}^{25} + 79.0^\circ$ ($c=1.18$, CHCl_3). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 1750, 1723. NMR (CDCl_3) δ : 1.38 (3 H, s), 1.52 (3 H, s), 4.18 (2 H, d, $J=6$ Hz), 4.58 (1 H, t, $J=6$ Hz), 5.17 (2 H, s), 7.4 (3 H, m), 8.0 (2 H, m). Anal. Found: C, 63.63; H, 6.21. Calcd. for $\text{C}_{14}\text{H}_{16}\text{O}_5$: C, 63.62; H, 6.10%.

(±)-Keto benzoate **7** was obtained from (±)-**5** according to the procedure like that described above. mp 56~57°C (Et_2O -hexane). The IR spectra (CHCl_3) and NMR spectra (CDCl_3) of (±)- and (+)-**7** were identical each other.

The Wittig reaction of (+)-**7**.

a) To the ylide prepared from $\text{Ph}_3\text{P}^+\text{CH}_3\text{I}^-$ (6.06 g), BuLi/hexane (1.7 M, 8.8 ml) and THF (50 ml) was added dropwise a solution of (+)-**7** (1.32 g) in THF (15 ml) at $-10 \sim -15^\circ$. After stirring at room temperature for 24 hr, the reaction mixture was poured into cold aq. AcOH. The organic layer was separated and the aq. layer was extracted with AcOEt. The usual work-up gave a crude product which on column chromatography (SiO_2) afforded the pure (+)-olefinic alcohol **9** (515 mg). $[\alpha]_{\text{D}}^{24} + 40.7^\circ$ ($c=1.13$, CHCl_3). IR $\nu_{\text{max}}^{\text{film}}$ cm^{-1} : 3400, 1655. NMR (CCl_4) δ : 1.32 (3 H, s), 1.38 (3 H, s), 2.04 (1 H, br), 3.58 (1 H, t, $J=8$ Hz), 4.03 (1 H, t, $J=8$ Hz), 4.05 (2 H, s), 4.55 (1 H, t, $J=8$ Hz), 5.10 (2 H, split s). MS *m/e*: 159 ($\text{M}^+ + 1$, 24%), 143 ($\text{M}^+ - \text{CH}_3$, 43), 128 ($\text{M}^+ - \text{CH}_3 \times 2$, 6), 110 ($\text{M}^+ - \text{C}_3\text{H}_5\text{O}$, 13), 83 (100).

(±)-Olefinic alcohol **9** was prepared from (±)-**7** by the method like that described above.

b) The ylide solution was prepared from $\text{Ph}_3\text{P}^+\text{CH}_3\text{I}^-$ (11.3 g), BuLi/hexane (1.4 M, 16.7 ml) and Et_2O (200 ml). To this mixture was added dropwise a solution of (+)-**7** (4.40 g) in THF (15 ml) at $-5 \sim 0^\circ$. After stirring at room temperature overnight, the reaction was quenched with aq. AcOH. The work-up in the usual way afforded a mixture of products, from which (+)-olefinic benzoate **8** (1.06 g) was isolated along with (+)-**9** (0.50 g) after column chromatography (SiO_2). The physical properties of (+)-**8** are as follows. $[\alpha]_{\text{D}}^{24} + 36.7^\circ$ ($c=1.09$, CHCl_3). IR $\nu_{\text{max}}^{\text{film}}$ cm^{-1} : 1730, 1660. NMR (CCl_4) δ : 1.33 (3 H,

s), 1.38 (3 H, s), 3.67 (1 H, t, $J=8$ Hz), 4.05 (1 H, t, $J=8$ Hz), 4.53 (1 H, t, $J=8$ Hz), 4.72 (2 H, s), 5.20 (1 H, bs), 5.27 (1 H, bs), 7.3 (3 H, m), 7.9 (2 H, m). Anal. Found: C, 68.67; H, 7.03. Calcd. for $\text{C}_{15}\text{H}_{18}\text{O}_4$: C, 68.68; H, 6.92%.

(+)-Olefinic benzoate **8** (0.995 g) was hydrolyzed with 10% NaOH (7.6 ml) in aq. EtOH. The usual work-up gave (+)-**9** (0.576 g) after passing through a short column (SiO_2).

The Wittig reaction of (±)-**7** under the conditions described in b) gave the similar results.

(+)-Olefinic acid **11**. A suspension of (+)-**9** (515 mg) and active MnO_2 (8.4 g) in CH_2Cl_2 (40 ml) was shaken at room temperature. After 35 hr, the inorganic materials were filtered off through celite 545 and thoroughly washed with CH_2Cl_2 . The combined filtrates were evaporated to give the crude olefinic aldehyde **10** (IR $\nu_{\text{max}}^{\text{film}}$ cm^{-1} : 2810, 2680, 1680, 1622) which was used in the next step without further purification. To a suspension of Ag_2O prepared from AgNO_3 (1.15 g) and NaOH (0.54 g) in H_2O (16 ml) was added the above crude (+)-**10** under ice-cooling, and the mixture was stirred at room temperature for 1 hr. Filtration followed by acidification of the filtrate with sat. aq. oxalic acid furnished, after extraction with AcOEt, an oil which on passing through a short column of SiO_2 gave (+)-**11** (412 mg). $[\alpha]_{\text{D}}^{24} + 47.3^\circ$ ($c=1.12$, CHCl_3). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3000~2500, 1700, 1620. NMR (CDCl_3) δ : 1.43 (3 H, s), 1.45 (3 H, s), 3.64 (1 H, dd, $J=8$ and 7 Hz), 4.36 (1 H, dd, $J=8$ and 7 Hz), 4.88 (1 H, tt, $J=7$ and 2 Hz), 6.16 (1 H, t, $J=2$ Hz), 6.24 (1 H, t, $J=2$ Hz), 8.62 (1 H, br). Anal. Found: C, 56.01; N, 7.22. Calcd. for $\text{C}_9\text{H}_{12}\text{O}_4$: C, 55.80; H, 7.03%.

(±)-Acid **11** was prepared from (±)-**9** according to the manner similar to that described above. Mp 61-62°C.

(+)-Olefinic ester **12**. The Na salt was prepared from (+)-**11** (312 mg) and NaH (140 mg, 50% in mineral oil) in HMPA (7 ml) by stirring at room temperature. After 45 min, MeI (1.03 g) was added in one portion and the mixture was stirred at room temperature for 40 hr. The reaction mixture was poured into dil. AcOH, neutralized with NaHCO_3 and extracted with Et_2O . The usual work-up gave a crude ester which was purified by column chromatography on SiO_2 . The desired (+)-**12** weighed 217 mg. $[\alpha]_{\text{D}}^{24} + 44.0^\circ$ ($c=1.18$, CHCl_3). IR $\nu_{\text{max}}^{\text{film}}$ cm^{-1} : 1720, 1630. NMR (CCl_4) δ : 1.38 (6 H, s), 3.56 (1 H, dd, $J=8$ and 7 Hz), 3.76 (3 H, s), 4.32 (1 H, dd, $J=8$ and 7 Hz), 4.76 (1 H, tt, $J=7$ and 2 Hz), 6.00 (1 H, t, $J=2$ Hz), 6.20 (1 H, t, $J=2$ Hz). MS *m/e*: 171 ($\text{M}^+ - \text{CH}_3$, 70%), 156 ($\text{M}^+ - \text{CH}_2\text{O}$ or $\text{M}^+ - \text{CH}_3 \times 2$, 13), 97 (100).

(±)-Ester **12** was obtained from (±)-**11** by the

procedure like that described above.

(+)-Methyl β , γ -dihydroxy- α -methylenebutyrate (1). Ninety-one milligrams of (+)-12 was dissolved in 80% aq. AcOH (0.2 ml) and heated at 80° for 1.5 hr. Evaporation *in vacuo* left an oil which was passed through a short column of Florisil. Elution with Et₂O gave a small amount of the starting (+)-12 and the desired (+)-1 (47 mg). $[\alpha]_D^{24} + 15^\circ$ ($c = 0.94$, MeOH) [lit.,²⁾ $[\alpha]_D^{24} + 22.1^\circ$ ($c = 1$, MeOH)]. IR $\nu_{\text{max}}^{\text{film}}$ cm⁻¹: 3400, 1720, 1635. NMR (CDCl₃) δ : 2.48 (1 H, br), 3.18 (1 H, br), 3.56 (1 H, dd, $J = 11$ and 7 Hz), 3.76 (3 H, s), 3.80 (1 H, dd, $J = 11$ and 3 Hz), 4.60 (1 H, m), 5.98 (1 H, splitted s), 6.36 (1 H, s). MS m/e : 147 ($M^+ + 1$, 100%), 129 ($M^+ + 1 - \text{H}_2\text{O}$, 56), 116 ($M^+ - \text{CH}_2\text{O}$, 8), 115 ($M^+ - \text{CH}_2\text{OH}$, 18).

($\pm$)-Dihydroxy ester 1 was obtained from ($\pm$)-12 by the method described above.

(-)-Tulipalin B (2).

a) From (+)-11. Fifty-four milligrams of (+)-11 was heated under reflux with 1 N HCl (2 ml) for 1 hr. The product was isolated with Et₂O in the usual manner. Column chromatography (SiO₂) of the crude sample using Et₂O-MeOH as eluent gave a pure sample of (-)-2, $[\alpha]_D^{24} - 88^\circ$ ($c = 0.85$, CHCl₃) [lit.,⁶⁾ $[\alpha]_D^{20} - 82^\circ$ ($c = 1.0$, CHCl₃)]. IR $\nu_{\text{max}}^{\text{film}}$ cm⁻¹: 3420, 1760, 1670. NMR (CDCl₃) δ : 3.20 (1 H, br), 4.12 (1 H, dd, $J = 4$ and 10 Hz), 4.47 (1 H, dd, $J = 6$ and 10 Hz), 4.92 (1 H, m), 5.98 (1 H, d, $J = 2$ Hz), 6.37 (1 H, d, $J = 2$ Hz).

b) From (+)-1. Fifty milligrams of (+)-1 was treated with 5% aq. NaOH (2 ml) at room temperature overnight followed by acidification with dil. HCl. The usual work-up, after chromatography on SiO₂ gave (-)-2.

($\pm$)-Tulipalin B (2).

a) From (+)-11. The reaction was carried out according to the above method a).

b) From α -methylene- γ -butyrolactone. This compound was prepared according to the Hutchinson's procedure.¹⁰⁾ Thus, a mixture of α -methylene- γ -butyrolactone (3.30 g) and SeO₂ (4.0 g) in dioxane (440 ml) was refluxed for 2 hr. Filtration through celite

545 followed by evaporation gave a mixture of products, from which ($\pm$)-2 (1.45 g) was isolated after column chromatography (SiO₂).

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