Note

Stereochemistry of (–)-Vertinolide

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Vertinolide (**1**) is a new derivative of tetronic acid, isolated from *Verticillium intertextum* by Trifonov *et al.*,¹⁾ and its chemical structure has been determined by X-ray analysis.²⁾ But its stereochemistry has remained obscure. This paper describes the synthesis of (+)-tetrahydrovertinolide (**2**) from (S)-(–)- γ -valerolactone- γ -carboxylic acid (**3**) and the determination of the absolute configuration of natural (–)-vertinolide (**1**). Our synthetic strategy of **2** consists of the construction of a tetronic acid skeleton **6** from γ -valerolactone- γ -carboxylic acid, protection of the phenolic hydroxyl group, construction of the side chain by a Grignard reaction and regeneration of the hydroxyl group.³⁾

(S)-(–)- γ -Valerolactone- γ -carboxylic acid (**3**) ($[\alpha]_D -16.0^\circ$ ($c=1.0$, H_2O)) was converted with $SOCl_2$ in benzene to its acid chloride (**4**) in an 80% yield, ($[\alpha]_D -7.7^\circ$ ($c=1.35$, $CHCl_3$), $+19.4^\circ$ ($c=1.0$, benzene)). The ketoester **5** was synthesized by the reaction of **4** and methyl propionate with lithium diisopropylamide in ether at $-78^\circ C$ in a 79% yield, ($[\alpha]_D +8.36^\circ$ ($c=2.75$, $CHCl_3$), IR $\nu_{max} cm^{-1}$: 1790, 1740, 1735, 1640). Hydrolysis of the ketoester **5** with 5% aqueous NaOH solution followed by acidification with dil. HCl solution easily gave **6** in a 79% yield, mp $123 \sim 124^\circ C$, $[\alpha]_D +5.2^\circ$ ($c=1.73$, EtOH); Anal. Found: C, 53.83; H, 6.20. Calcd. for $C_9H_{12}O_5$: C, 54.0; H, 6.20%; IR $\nu_{max} cm^{-1}$: 1720, 1670 ~ 1630; 1H -NMR δ : 1.41 (3H, s), 1.64 (3H, s), 2.07 (4H, m); ^{13}C -NMR (DMSO- d_6) (δ in ppm from proton noise decoupled spectra; multiplicity from off-resonance spectra) δ : 183.9 (s), 174.1 (s), 173.6 (s), 95.5 (s), 81.9 (s), 31.9 (t), 28.6 (t), 23.3 (q), 6.3 (q). The carboxylic acid **6** was methylated with methanol-

sulfuric acid to give **7**, $[\alpha]_D +16.9^\circ$ ($c=1.3$, acetone); 1H -NMR ($CDCl_3$) δ : 3.68 (OCH_3). The ester **7** was converted with $NaH-ClCH_2OCH_3$ to the methoxymethyl derivative **8** in a 75% yield, $[\alpha]_D +7.9^\circ$ ($c=1.26$, $CHCl_3$); MS m/z 258 (M^+ , 12%); 1H -NMR ($CDCl_3$) δ : 3.66 (3H, s), 5.28 (2H, s). The ester **8** was reduced with sodium borohydride in methanol to give **9**, $[\alpha]_D +10.3^\circ$ ($c=0.87$, $CHCl_3$). The oxidation of **9** with pyridinium chlorochromate-sodium acetate gave the aldehyde **10**, $[\alpha]_D +10.3^\circ$ ($c=1.07$, $CHCl_3$); 1H -NMR ($CDCl_3$) δ : 9.63 (CHO). The aldehyde **10** was reacted with *n*-pentylmagnesium bromide in ether to give the hydroxy-lactone **11** as an epimeric mixture. The mixed alcohol **11** was oxidized with pyridinium chlorochromate-sodium acetate to the ketone **12**, $[\alpha]_D +4.5^\circ$ ($c=0.9$, $CHCl_3$); MS m/z : 298 (M^+ , 23%). The methoxymethyl group of **12** was removed with sulfuric acid-acetic acid to give the desired tetrahydrovertinolide ((S)-**2**, mp $61 \sim 62^\circ C$). The spectral data were as follows: $[\alpha]_D +16.8^\circ$ ($c=4.5$, $CHCl_3$); ORD ($c=0.1$, $CHCl_3$) $[\alpha]^{22} (nm)$: -195° (341); 0° (328); $+380^\circ$ (300); IR $\nu_{max}^{KBr} cm^{-1}$: 1740, 1715 ~ 1685, 1670 ~ 1640; UV $\lambda_{max}^{MeOH} nm (\epsilon)$: 228 (12000, acidic); MS m/z : 258 (M^+ , 1%), 230, 225, 199; 1H -NMR ($CDCl_3$) δ : 0.88 (3H, s), 1.28 (2H, m), 1.2 ~ 1.4 (4H, m), 1.4 ~ 1.6 (2H, m), 1.49 (3H, s), 1.70 (3H, s), 2.09 (2H, t), 2.41 (2H, t); ^{13}C -NMR (acetone- d_6) δ : 209.3, 177.3, 174.2, 96.2, 82.5, 42.9, 36.8, 32.0, 31.1, 24.0, 23.6, 23.1, 14.2, 6.3; ^{13}C -NMR ($CDCl_3$) δ : 211.3, 177.7, 176.0, 96.2, 83.2, 41.9, 36.4, 31.3, 30.1, 23.7, 23.5, 23.1, 13.9, 5.9. These data were in good accord with those of tetrahydrovertinolide (**2**) derived from natural vertinolide.²⁾ The chemical structure of (S)-**2** was further confirmed by methylation with diazomethane as in the case of the natural one. Two methylated products **13** and **14** were produced and separated by preparative TLC.⁴⁾ The spectral data of the less polar product **13** were as follows: $[\alpha]_D +8.6^\circ$ ($c=0.75$, $CHCl_3$); IR $\nu_{max}^{film} cm^{-1}$: 1760, 1725, 1670; 1H -NMR ($CDCl_3$) δ : 0.88 (3H, t), 1.26 (2H, br.s), 1.40 (3H, s), 1.4 ~ 1.5 (4H, m), 2.00 (3H, s), 2.00 (2H, m), 2.37 (4H, m), 4.10 (3H, s); MS m/z : 269 ($M^+ +1$, 2.7%), 268 (M^+ , 4), 253 (2), 240 (1.6), 225 (4), 198 (40). These spectral data were consistent with the structure of **13**. The spectral data of the more polar product **14** were as follows: $[\alpha]_D -26.0^\circ$ ($c=0.25$, $CHCl_3$) IR $\nu_{max}^{film} cm^{-1}$: 1710 ~ 1685, 1590; 1H -

NMR (CDCl_3) δ : 0.88 (3H, t), 1.43 (3H, s), 1.4~1.5 (4H, m), 1.54 (3H, s), 1.26 (2H, br.s), 2.10 (2H, m), 2.38 (4H, m), 4.01 (3H, s); ^{13}C -NMR (CDCl_3) δ : 209.5, 200.2, 179.4, 91.8, 87.6, 55.9, 42.8, 36.3, 31.4, 30.1, 23.5, 22.4, 22.2, 13.4, 4.0; MS m/z : 269 ($\text{M}^+ + 1$, 5.8%), 268 (M^+ , 24), 250 (8), 235 (2), 240 (2), 225 (10). These spectral data were identical with those of **14** derived from natural vertinolide.²⁾

A comparison of the specific rotation of synthesized (*S*)-**2** ($[\alpha]_{\text{D}} + 16.8^\circ$) with that of natural one ($[\alpha]_{\text{D}} + 19.2^\circ$) ($c = 0.05$, CHCl_3) showed that natural (–)-vertinolide had an (*S*)-configuration at the chiral center. Further synthetic work on vertinolide via **6** is now in progress.

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