

SYNTHESIS OF (-)-VERTINOLIDE

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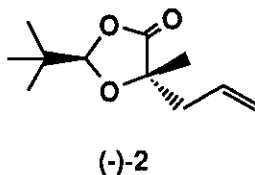
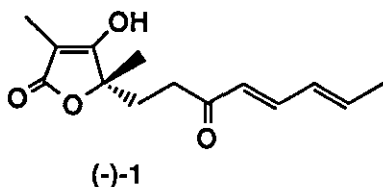
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Abstract - (-)-Vertinolide, a β -tetronic acid derivative isolated from *Verticillium intertextum* as one of the mycotoxins, was synthesized starting from (*R*)-lactic acid as the chiral source using Seebach's chiral self-reproduction method.

(-)-Vertinolide (**1**) is a β -tetronic acid derivative isolated from a culture broth of *Verticillium intertextum* as one of the mycotoxins.¹ Its chemical structure was determined by X-ray crystallographic analysis in 1982.² Three total syntheses have since confirmed the original assignment and unambiguously established the 5-(*S*) absolute configuration.³

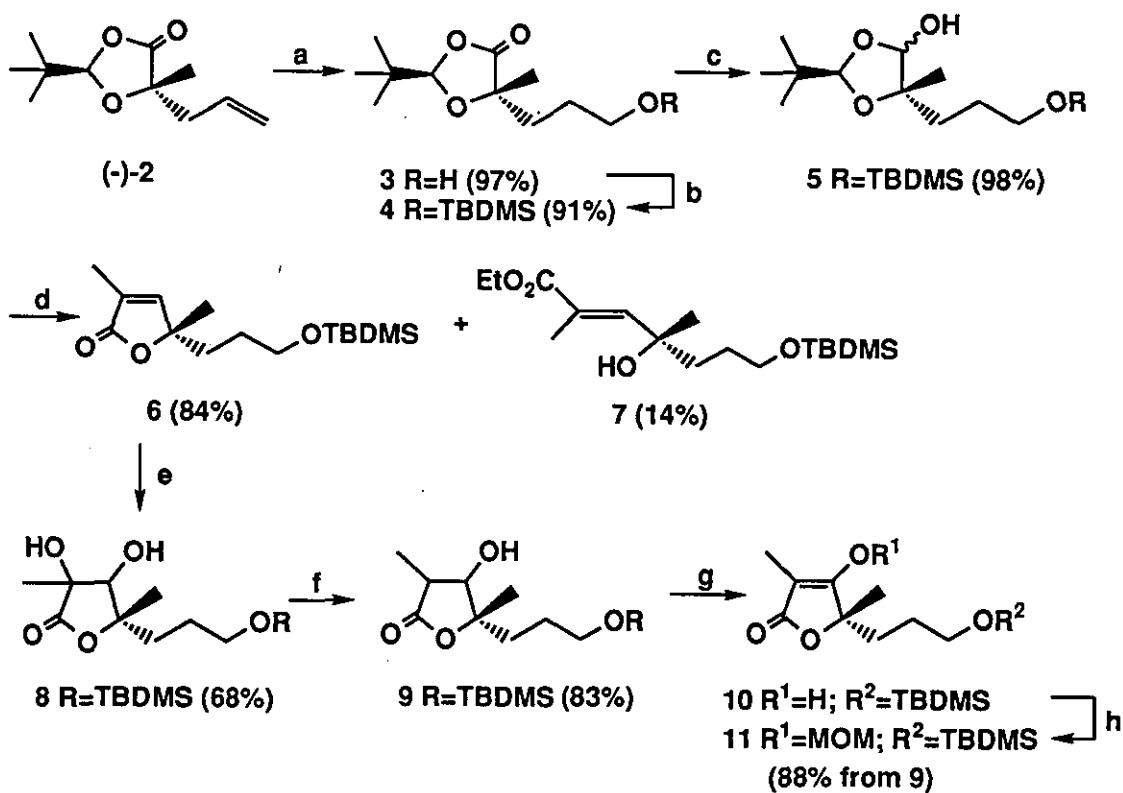
In the course of our chiral synthetic studies on biologically active natural products, which have a chiral quaternary carbon atom substituted by one oxygen, we have reported the synthesis of (-)-malyngolide and (-)-frontalin starting from D-lactose and (+)-ipomeamarone from (*S*)-lactic acid as chiral sources, respectively.⁴ (-)-Vertinolide (**1**) has a chiral quaternary carbon atom that is substituted by one oxygen atom. Therefore, we investigated the method for the synthesis of (-)-**1** as our next synthetic target.

In our synthetic work on (-)-**1**, the dioxolanone derivative ((-)-**2**) was chosen as a starting chiral synthon. Because (-)-**2** possesses the proper chiral center required for (-)-**1**. The synthon ((-)-**2**) had been synthesized by us^{4d} using Seebach's chiral self-reproduction method,⁵ involving the stereoselective allylation of (2*R*,5*R*)-(-)-2-*t*-butyl-5-methyl-1,3-dioxolan-4-one, prepared by the condensation of (*R*)-lactic acid with 2,2-dimethylpropanal.



Hydroboration of (-)-**2** with 9-borabicyclo[3.3.1]nonane (9-BBN) and subsequent H₂O₂ oxidation gave the alcohol (**3**) in 97% yield,⁶ of which hydroxyl group was protected as *t*-butyldimethylsilyl (TBDMS) ether to form **4**⁷ in 91% yield. For the construction of the butenolide ring, first of all, **4** was reduced with diisobutylaluminum hydride (DIBAL-H) to give the hemiacetal (**5**) in 98% yield.^{4d} Wittig-Horner reaction of **5** with triethyl 2-phosphonopropionate in the presence of NaH in THF furnished the desired

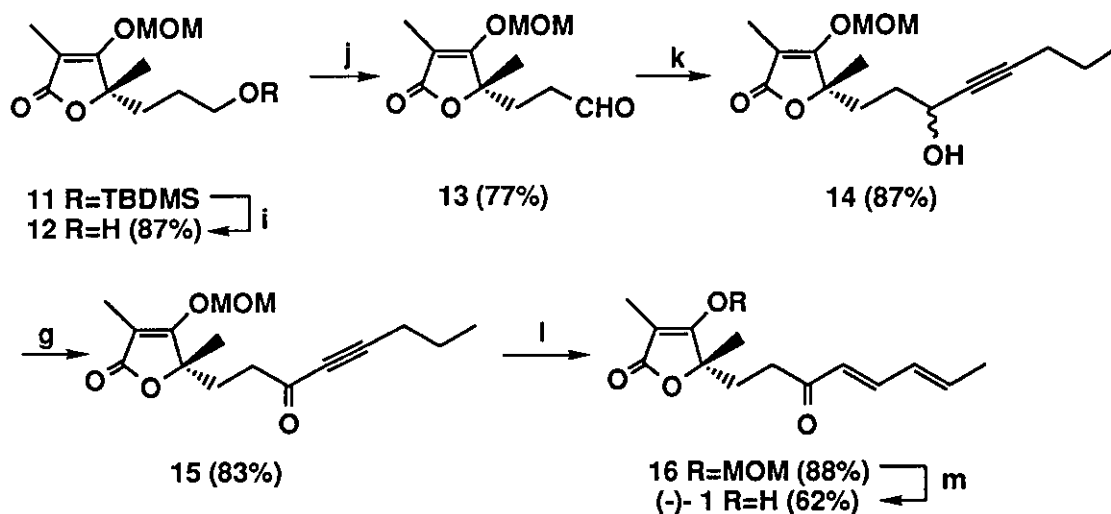
butenolide (6) and (*E*)-conjugated ester (7) in 84 and 14% yields, respectively. Conversion of the butenolide ring of 6 to the β -hydroxybutenolide ring (β -tetrone acid skeleton) was achieved by three step reaction. Thus, dihydroxylation of 6 was performed by $\text{RuCl}_3\text{-NaIO}_4$ oxidation⁸ to form 8 in 68% yield. Reductive dehydroxylation at the α -position of 8 was best carried out by employing freshly prepared SmI_2 (Sm metal and CH_2I_2) in the presence of hexamethylphosphoric triamide (HMPA) in $\text{THF-H}_2\text{O}$ ⁹ to give 9 in 83% yield. The alcohol (9) was subsequently oxidized with $\text{DMSO-(CF}_3\text{CO)}_2\text{O-Et}_3\text{N}$ to furnish 10, of which hydroxyl group was protected as the methoxymethyl (MOM) ether and purified to give 11 in 88% yield from 9.



Scheme 1. Reagents and conditions: a) 0.5M 9-BBN in THF soln. room temperature, 3 h.; 31% H_2O_2 -3M NaOH aq. room temperature, 4 h. b) TBDMSCl, imidazole in CH_2Cl_2 , room temperature, 4 h. c) 1.5M DIBAL-H in toluene soln. -78°C , 20 min. d) triethyl 2-phosphonopropionate, NaH in THF, room temperature, 3 h. e) $\text{RuCl}_3\text{-NaIO}_4$ in $\text{H}_2\text{O-AcOEt-MeCN}$, 15 min. f) Sm, CH_2I_2 , HMPA in $\text{THF-H}_2\text{O}$, 0°C , 2 h. g) $\text{DMSO-(CF}_3\text{CO)}_2\text{O}$ in CH_2Cl_2 , -78°C , 30 min.; Et_3N , -78°C , 1 h. h) MOMCl, NaH in THF-HMPA (10:1), room temperature, 6.5 h.

As the construction of the protected β -tetrone acid moiety was accomplished, modification of the side chain of 11 was examined next. After removal of the TBDMS protecting group of 11 with tetrabutylammonium fluoride (TBAF) (87%), PCC-AcONa oxidation of the alcohol (12) gave the aldehyde (13) in 77% yield. Treatment of 13 with 1-pentyne and $n\text{-BuLi}$ ¹⁰ at low temperature yielded the alcohol (14) in 87% yield, which was oxidized with $\text{DMSO-(CF}_3\text{CO)}_2\text{O-Et}_3\text{N}$ to give the ynone (15) in 83% yield. When the

isomerization of the ynone (**15**) to the known dienone (**16**)^{3b} was first tried with $\text{Ph}_3\text{P-Pd}(\text{OAc})_2$ in toluene at 100 °C,^{3c} 11 the isolated product in 71% yield was not **16**, but a 2,5-disubstituted furan derivative. On the contrary, refluxing the toluene solution of **15** and Ph_3P (20 mol %)¹² in the absence of $\text{Pd}(\text{OAc})_2$ gave the desired dienone (**16**) in 88% yield. Finally, removal of the MOM protecting group^{3b} furnished (-)-vertinolide (**1**) in 62% yield; mp 145–149 °C, $[\alpha]_{\text{D}}^{24}$ -23.11 ($c=0.52$, CHCl_3); lit.,² mp 149.2–152.3 °C; $[\alpha]_{\text{D}}^{20}$ -25.0 ($c=0.05$, CHCl_3); lit.,^{3a} mp 146–149 °C; $[\alpha]_{\text{D}}$ -22 ($c=0.054$, CHCl_3); lit.,^{3b} mp 149–151 °C; $[\alpha]_{\text{D}}$ -25.0 ($c=0.65$, CHCl_3); lit.,^{3c} mp 146–149 °C; $[\alpha]_{\text{D}}^{20}$ -23 ($c=0.1$, CHCl_3). The ir, ¹H-nmr, and ms spectral data¹³ of the synthetic (-)-**1** are identical to those of the reported one.³



Scheme 2. Reagents and conditions: i) 1.0M TBAF in THF soln. in THF, 0 °C, 2.5 h. j) PCC-MS-AcONa in CH_2Cl_2 , room temperature, 1 h. k) 1-pentyne, 1.6M *n*-BuLi in hexane soln. in THF, -20 °C, 3 h. l) Ph_3P in toluene, reflux, 8.5 h. m) 5% HCl in MeOH, room temperature, 10 h.

ACKNOWLEDGMENTS

We thank Dr. Didier Desmaele of Universite de Paris for supplying ir, nmr, and ms spectra of the synthetic (-)-vertinolide. We are also grateful to the Pharmaceutical Research and Technology Institute of Kinki University for financial support.

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13. Ir (CHCl₃): 3600~2400, 1740, 1690 (sh), 1670 (sh), 1660, 1630, 1590, 1300, 1100, 1060, 990, 950, 900 cm⁻¹. ^1H -nmr (CDCl₃) δ : 1.49 (3H, s, CH₃C), 1.70 (3H, s, CH₃C=), 1.89 (3H, d, $J=6.0$ Hz, CH₃CH=), 2.05~2.26 (2H, m, CH₂CH₂CO), 2.48, 2.68 (total 2H, each ddd, $J=16.5, 8.5, 6.0$ Hz, CH₂CH₂CO), 6.05 (1H, d, $J=15.5$ Hz, COCH=CH), 6.10~6.38 (2H, m, CH=CHCH₃), 7.19 (1H, dd, $J=15.5, 10.0$ Hz, COCH=CH). HRms (m/z): Calcd for C₁₄H₁₈O₄ (M⁺): 250.1205. Found: 250.1221.

Received, 30th August, 1996