SYNTHESIS OF (-)-VERTINOLIDE

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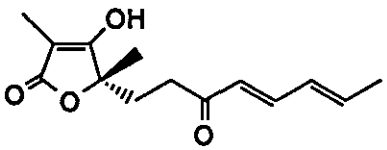
Abstract - (-)-Vertinolide, a β-tetronic acid derivative isolated from *Verticillium intertextum* as one of the mycotoxins, was synthesized starting from (*R*)-lactic acid as the chiral source using Seebach's chiral self-reproduction method.

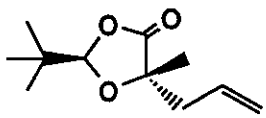
(-)-Vertinolide (**1**) is a β-tetronic acid derivative isolated from a culture broth of *Verticillium intertextum* as one of the mycotoxins.[1] Its chemical structure was determined by X-ray crystallographic analysis in 1982.[2] Three total syntheses have since confirmed the original assignment and 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.



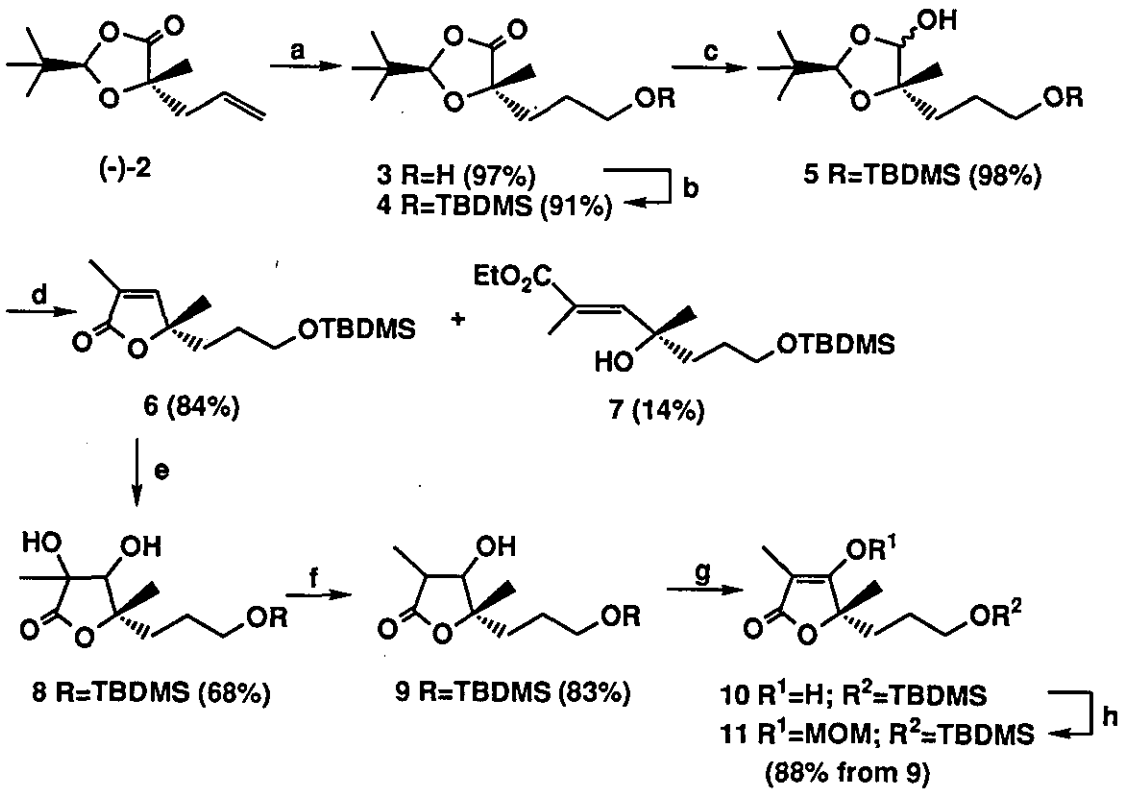
(-)-1



(-)-2

Hydroboration of (-)-**2** with 9-borabicyclo[3.3.1]nonane (9-BBN) and subsequent H_2O_2 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

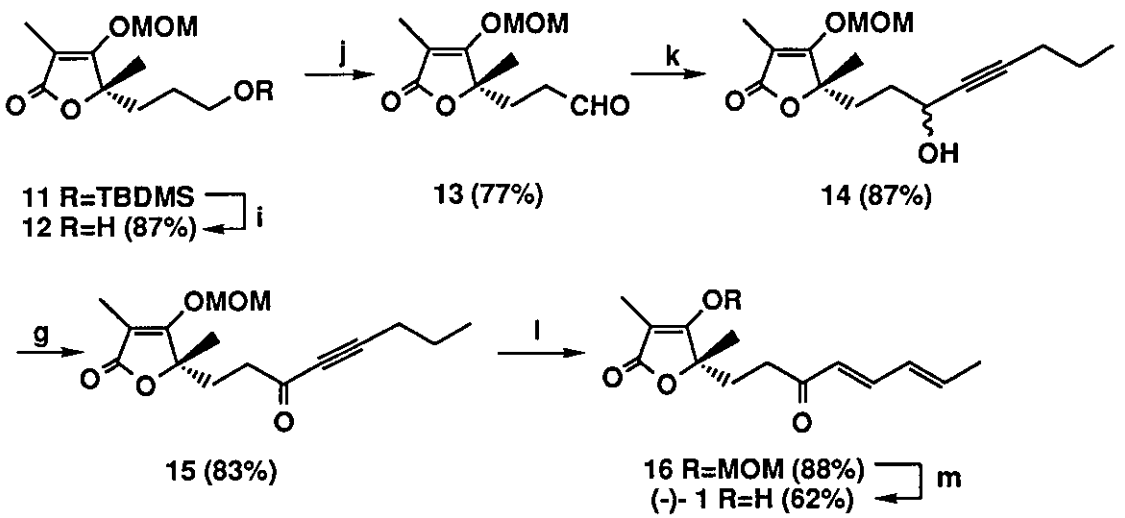
butenolide (**6**) and (*E*)-conjugated ester (**7**) in 84 and 14% yields, respectively. Conversion of the butenolide ring of **6** to the β-hydroxybutenolide ring (β-tetronic acid skeleton) was achieved by three step reaction. Thus, dihydroxylation of **6** was performed by $RuCl_3$-$NaIO_4$ oxidation[8] 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 THF-H_2O[9] to give **9** in 83% yield. The alcohol (**9**) was subsequently oxidized with DMSO-$(CF_3CO)_2O$-Et_3N 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) $RuCl_3$-$NaIO_4$ in H_2O-AcOEt-MeCN, 15 min. f) Sm, CH_2I_2, HMPA in THF-H_2O, 0 °C, 2 h. g) DMSO-$(CF_3CO)_2O$ 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-tetronic 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*-BuLi[10] at low temperature yielded the alcohol (**14**) in 87% yield, which was oxidized with DMSO-$(CF_3CO)_2O$-Et_3N 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 Ph_3P-$Pd(OAc)_2$ 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 $Pd(OAc)_2$ 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, $[\alpha]_D^{24}$ -23.11 (*c*=0.52, $CHCl_3$); lit.,[2] mp 149.2~152.3 °C; $[\alpha]_D^{20}$ -25.0 (*c*=0.05, $CHCl_3$); lit.,[3a] mp 146~149 °C; $[\alpha]_D$ -22 (*c*=0.054 $CHCl_3$); lit.,[3b] mp 149~151 °C; $[\alpha]_D$ -25.0 (*c*=0.65, $CHCl_3$); lit.,[3c] mp 146~149 °C; $[\alpha]_D^{20}$ -23 (*c*=0.1, $CHCl_3$). The ir, ^{1}H-nmr, and ms spectral data[13] 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.

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13. Ir ($CHCl_3$): 3600~2400, 1740, 1690 (sh), 1670 (sh), 1660, 1630, 1590, 1300, 1100, 1060, 990, 950, 900 cm^{-1}. ^{1}H-nmr ($CDCl_3$) δ: 1.49 (3H, s, CH_3C), 1.70 (3H, s, CH_3C=), 1.89 (3H, d, *J*=6.0 Hz, $C\underline{H}_3CH$=), 2.05~2.26 (2H, m, $C\underline{H}_2CH_2CO$), 2.48, 2.68 (total 2H, each ddd, *J*=16.5, 8.5, 6.0 Hz, $CH_2C\underline{H}_2CO$), 6.05 (1H, d, *J*=15.5 Hz, $COC\underline{H}$=CH), 6.10~6.38 (2H, m, $C\underline{H}$=$C\underline{H}CH_3$), 7.19 (1H, dd, *J*=15.5, 10.0 Hz, COCH=$C\underline{H}$). HRms (*m/z*): Calcd for $C_{14}H_{18}O_4$ (M^+): 250.1205. Found: 250.1221.

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