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Stereoselective Synthesis of C_3-C_9 Segment of Soraphen A

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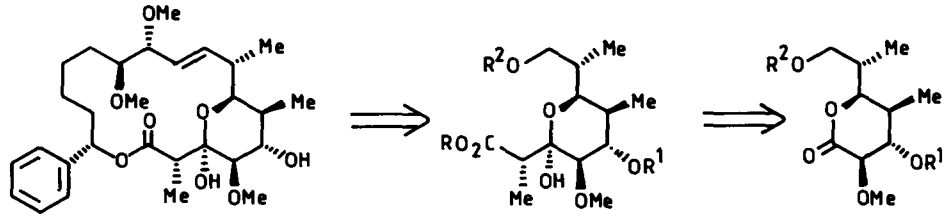
Abstract : A synthetic route to optically pure lactone moiety comprising C_3-C_9 segment of Soraphen A is described.

Soraphen A **1**, isolated from myxobacterium Sorangium cellulosum, exhibits powerful broad spectrum fungicidal activity against several pathogenic plant fungi[1a]. The chemical degradation of **1** unequivocally elucidated its structure[1b]. The Japp-Klingemann retroaldol and ozonolysis reactions of soraphen A provided an useful C_3-C_9 degraded product **3** which was used in the addition reaction of ester enolate by Sinnes et al[2a] to complete the semi-synthesis of a model southern part (C_1-C_9) **2** of soraphen A. Prompted by these recent reports[2], we wish to communicate our own findings on first stereoselective synthesis of a lactone derivative encompassing C_3-C_9 segment **14** of soraphen A.

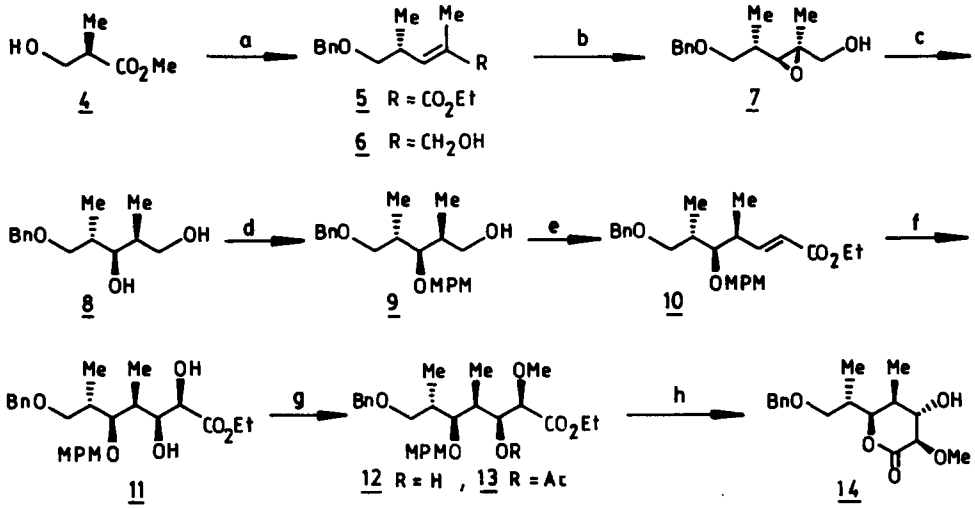


1 **2** **3**

The synthesis was initiated with commercially available (R)-methyl 3-hydroxy-2-methylpropionate **4** which was converted into the unsaturated ester **5** by a rational approach described in scheme. Reduction of **5** with DIBAL-H gave the allylic alcohol **6** which on Sharpless asymmetric epoxidation with (+)-DIPT provided **7** with 95% diastereomeric excess (HPLC)[3]. Reductive ring opening of **7** with Red-Al followed by periodate oxidation to remove 1,2-diol, produced almost exclusively the 1,3-diol **8**[4]. Protection-deprotection sequence carried out with **8** produced the alcohol **9** which was transformed into (E)-unsaturated ester **10** by successive Swern oxidation and Wittig reaction with PPh_3=$CHCO_2Et$. Compound **10** was subjected to Sharpless asymmetric dihydroxylation[5] in presence of AD-mix-α to give **11** and its diastereomer in a 92:8 ratio (HPLC). At this stage selective methylation at C-2 was sought. We observed that MeI-Ag_2O combination in CH_2Cl_2 gave the satisfying results to obtain **12**. In order to substantiate structural assignment, **12** was converted into the monoacetate derivative **13**. In the ^{1}H-NMR spectrum of **13**, the expected downfield shift of resonances (5.3 ppm) due to H-3 was noted indicating the presence of the acetate group at C-3 and methoxyl group at C-2. Subsequently **12** was treated with DDQ-CH_2Cl_2 and HCl-MeOH to provide the requisite lactone **14** whose ^{1}H-NMR spectrum showed striking similarity with reported data for the degraded products of **1**[2a]. The spectral

data of **14** - ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 1.00 (d, 6H, J=6.0 Hz), 2.02 (m, 2H), 2.34 (bs, 1H, OH), 3.50 (m, 2H), 3.60 (s, 3H), 3.62 (dd, 1H, J=9.0, 1.0 Hz), 3.76 (d, 1H, J=6.0 Hz), 4.38 (dd, 1H, J=10.0, 2.0 Hz), 4.42 (s, 2H), 7.3 (m, 5H); IR: 1754 (C=O), 3430 (OH) cm^{-1}; MS: m/z 308 (M^+), proved the assigned structure.

Scheme



a) i) ref. 6; ii) Ph_3P=C(Me)CO_2Et, CH_2Cl_2, RT, 18 h, 70%; iii) DIBAL-H, CH_2Cl_2, -78°-0°, 2 h, 90%; b) (+)-DIPT, Ti(OiPr)$_4$, TBHP 4A Molecular sieves, CH_2Cl_2, -20°, 16 h, 73%; c) Red-Al, THF, -10°-RT, 48 h, 74%; d) i) TBS-Cl, Imid., DMF, RT, 18 h, 70%; ii) KH, THF, MPM-Br, RT, 18 h, 89%; iii) 1M Bu_4NF, THF, RT, 3 h, 83%; e) i) $(COCl)_2$, DMSO, Et_3N, -78°, 1 h; ii) PPh_3=CHCO_2Et, RT, 18 h, overall 70%; f) AD-mix α, 1:1-tBuOH-H_2O, $CH_3SO_2NH_2$, 0°, 20 h, 85%; g) Moist Ag_2O, MeI, CH_2Cl_2, RT, 18 h, 80%; h) i) DDQ, CH_2Cl_2, 4A Molecular sieves; ii) HCl, MeOH, RT, 4 h, over all 80%.

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