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Concise Total Synthesis of (+)-Goniofufurone and Goniobutenolides A and B

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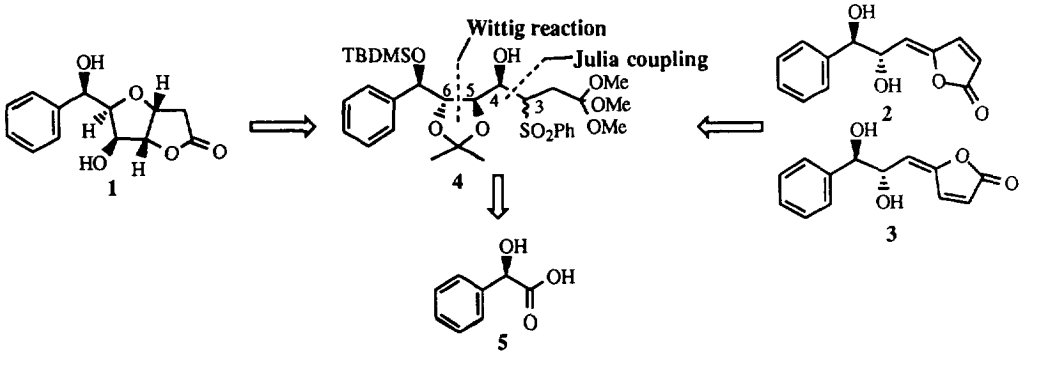
Abstract : Cytotoxic styryl lactones, (+)-goniofufurone and goniobutenolides A and B have been prepared in optically and diastereomerically pure form from (R)-(-)-mandelic acid *via* the β-hydroxy sulfone **4** as a common intermediate. Copyright © 1996 Elsevier Science Ltd

A group of bioactive styryl lactones has been recently isolated from the ethanol extract of the stem bark of *Goniothalamus giganteus* Hook. f. & Thomas (Annonaceae) from Thailand[1a-c]. Among them, (+)-goniofufurone **1**[1a] and goniobutenolides A **2** and B **3**[1c] were shown to possess significant cytotoxic activities toward several human tumor cell lines. The relative and absolute stereochemistries of compoud **1-3** were established throught combined NMR[1a,c] and synthetic studies[2a-b,3a]. Their unique and intriguing structures have attracted considerable attention and several papers describing their synthesis have been published[2,3].

As part of a program directed toward total synthesis of styryl lactones[4], we described herein a short and efficient route to compounds **1-3** from commercial D-mandelic acid **5**.

In our retrosynthetic analysis of **1-3**, because of their structural similarities, we envisioned that these compounds could be available from a common advanced intermediate the C7 orthoester **4** *via* differential functional group manipulations (Scheme 1). Compound **4** itself can be traced retrosynthetically to mandelic acid **5** by disassembly C3-C4 and C5-C6 bonds.

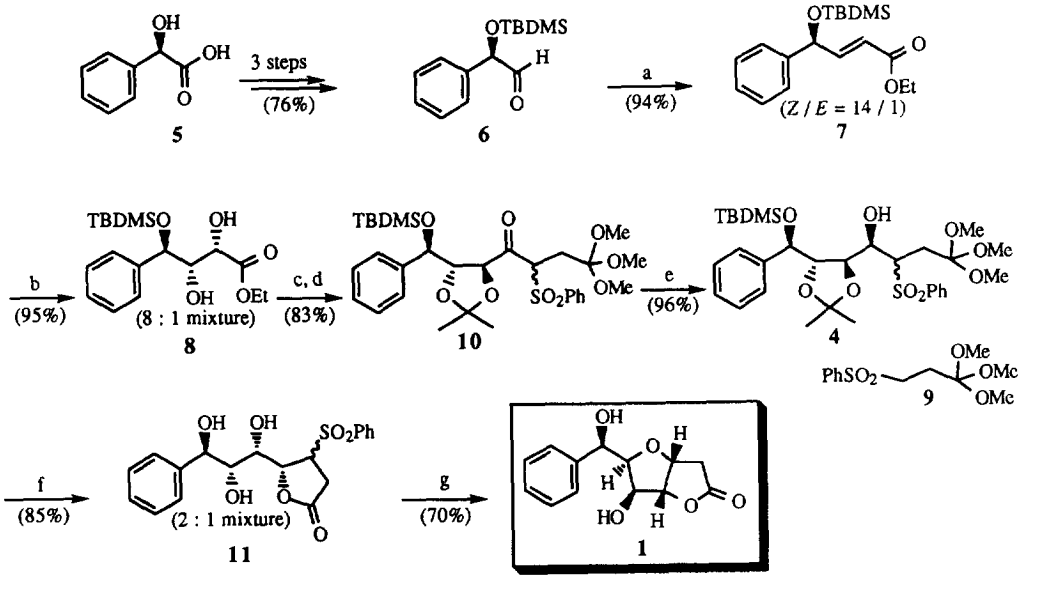


Scheme 1

The starting point of our synthesis of compounds **1-3** was the known enantiopure β-*t*-butyldimethylsilyoxy aldehyde **6**[5] prepared from (R)-mandelic acid in 76% overall yield by sequential acid-catalysed esterification, O-silylation and reduction of the ester function with diisobutylaluminium hydride (Scheme 2). Wittig condensation between ethoxycarbonylmethylenetriphenylphosphorane and aldehyde **6** in refluxing toluene occurred with high degree of selectivity to afford the (*E*)-α,β-unsaturated ester **7** in 88% yield along with the (*Z*)-isomer (6%) easily separable by chromatography. Dihydroxylation of (*E*)-alkene **7** in the presence of a catalytic amount of OsO_4 and an excess of N-methylmorpholine N-oxyde in water-acetone (4:1)[7] gave diastereoselectively the desired triol **8**[6] in 84% yield after chromatographic separation of the 89:11 mixture of the two diastereomers. The assignment of the relative configuration (2,3-*syn*, 3,4-*anti*)[8] of diol **8** was based on literature results on osmylation of similarly constituted compounds[9,10].

At this stage of the synthesis, our plan called for the installation of the α,β-unsaturated-γ-butyrolactone unit. To this end, the 1,2-*syn* diol of **8** was protected as its acetonide and the resulting compound, treated with an excess of the lithium salt of methyl 3-phenylsulfonyl orthopropionate **9**[11], afforded the β-keto sulfone **10** in 83% overall yield as an equal and unseparable mixture of diastereomers.

Among the tasks remaining for the synthesis of styryl lactone **1** was the introduction of C4 stereogenic center through reduction of the C4 keto group of **10**. Gratifyingly, reduction of an ethereal solution of β-keto sulfone **10** with lithium aluminium hydride was completely diastereoselective[12] at -78°C to give epimeric sulfones **4**. We have no explanation yet for this surprisingly high stereoselective reduction, unaffected by the configuration of the stereogenic center bearing the phenylsulfonyl group[13].

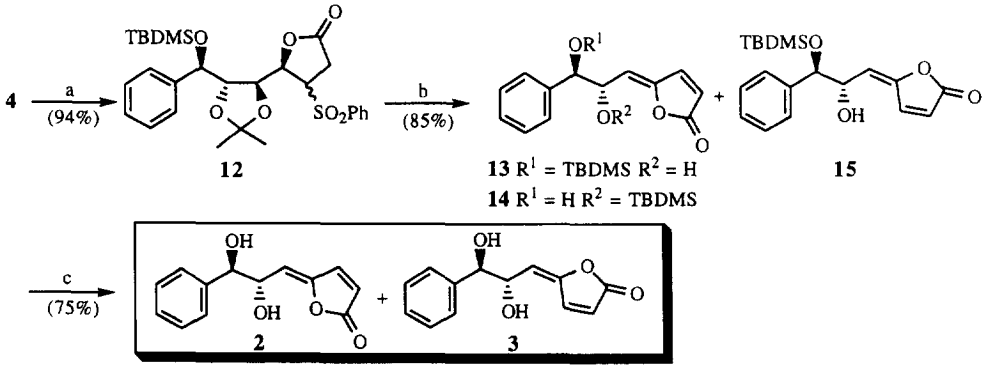


Scheme 2

Reagents and conditions : (a) $Ph_3P{=}CH\text{-}CO_2Et$, toluene, 110°C, 30 min; (b) cat. OsO_4, NMO, acetone-H_2O (4-1), RT, 5h ; (c) 2-methoxypropene, 10-camphorsulfonic acid, CH_2Cl_2, RT, 10 min; (d) methyl 3-phenylsulfonyl orthopropionate **9** (3 equiv), n-BuLi, THF, -78°C, 30 min then add 2,3-acetonide **8**, -78°C to RT; (e) $LiAlH_4$, Et_2O, -78°C, 2 h ; (f) THF-AcOH-1N HCl (1:1:1), reflux, 3h; (g) DBU (3 equiv), CH_2Cl_2, 0°C, 50min.

The completion of the synthesis of (+)-goniofufurone **1** only required a few functional group manipulations. Complete removal of the silyl and acetal protecting groups of **4** as well as orthoester hydrolysis and lactone formation was effected in AcOH-1N HCl-THF (1:1:1) at 65°C[14] to provide the triol lactone **11** as a 1:2 mixture of diastereomers in 85% yield. Treatment of **11** with 3 equiv 1,8-diazabicyclo[5,4,0]undecen-7-ene (DBU) in CH_2Cl_2 induced elimination of $PhSO_2H$ and concomitant cyclisation *via* intramolecular Michael reaction to give (+)-goniofufurone **1** in 70% yield as plates mp 147-149°C, $[\alpha]_D^{20}$ + 10 (*c* 0.6, EtOH) [lit.[1a] mp 152-154°C, $[\alpha]_D^{22}$ + 9 (*c* 0.5, EtOH)]. Synthetic goniofufurone **1** exhibited spectral data (^1H and ^{13}C NMR, IR) identical to those reported for the natural material[1a].

Next, we turned our attention to the synthesis of goniobutenolides A and B (**2**,**3**) from **4** (Scheme 3). Treatment of the orthoester sulfone **4** with a catalytic amount of anhydrous 10-camphorsulfonic acid in boiling toluene effected smooth γ-butyrolactone formation to give **12** in 94% yield as a 1:2 mixture of diastereomers. Gratifyingly, DBU-induced elimination of sulfenic acid was accompanied by a spontaneous β-elimination with acetone formation to give a mixture of three compounds **13-15** (2.2 : 0.6 : 1 ratio) in 85% yield. The product corresponding to the 1,2-*t*-butyldimethylsilyl group migration[15] of **15** was not detected. The position of *t*-butyldimethylsilyl group and the configuration of C5-C6 double bond of **13-15** were established by ^1H NMR spectroscopy. Finally, treatment of the mixture of isomers **13-15** with acetic acid in THF-H_2O cleanly removed the TBDMS protecting group to afford a 3:1 mixture of goniobutenolides A and B (75% yield). Chromatographic separation of **2** and **3** (cyclohexane-tBuOMe, 1:7)[3c] first afforded pure goniobutenolide B[16] **3** as a white solid, mp 142-144°C, $[\alpha]_D^{20}$ -107 (*c* 0.3, $CHCl_3$) [lit.[3c] mp 143-146°C, $[\alpha]_D^{20}$ -106.8 (*c* 0.25, $CHCl_3$)], followed by goniobutenolide A **2** obtained as an oil, $[\alpha]_D^{20}$ +183 (*c* 0.3, $CHCl_3$) [lit. $[\alpha]_D^{27}$ +192 (*c* 0.25, $CHCl_3$)[3c], $[\alpha]_D^{27}$ +87 (*c* 0.25, $CHCl_3$)[2n,3b]].



Scheme 3

Reagents and conditions : (a) cat. 10-camphorsulfonic acid, toluene, reflux, 1h 30; (b) DBU (3 equiv), CH_2Cl_2, 0°C, 1h; (c) AcOH-THF-H_2O (3:1:1), 60°C, 14h.

In conclusion, we have developed a new and convergent route to (+)-goniofufurone and goniobutenolides A and B from (R)-2-*t*-butyldimethylsilyloxy-2-phenylacetaldehyde **6** respectively in 7 and 8 steps in about 45%

overall yield. Furthermore, β-hydroxy sulfone **4** available in 5 steps and 75% overall yield from **6** may be a valuable starting material for preparation of other styryl lactones. Studies along this line are currently underway.

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