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Total Synthesis of Antitumor Agents, (+)-Goniopypyrone and (+)-7-*epi*-Goniofufurone

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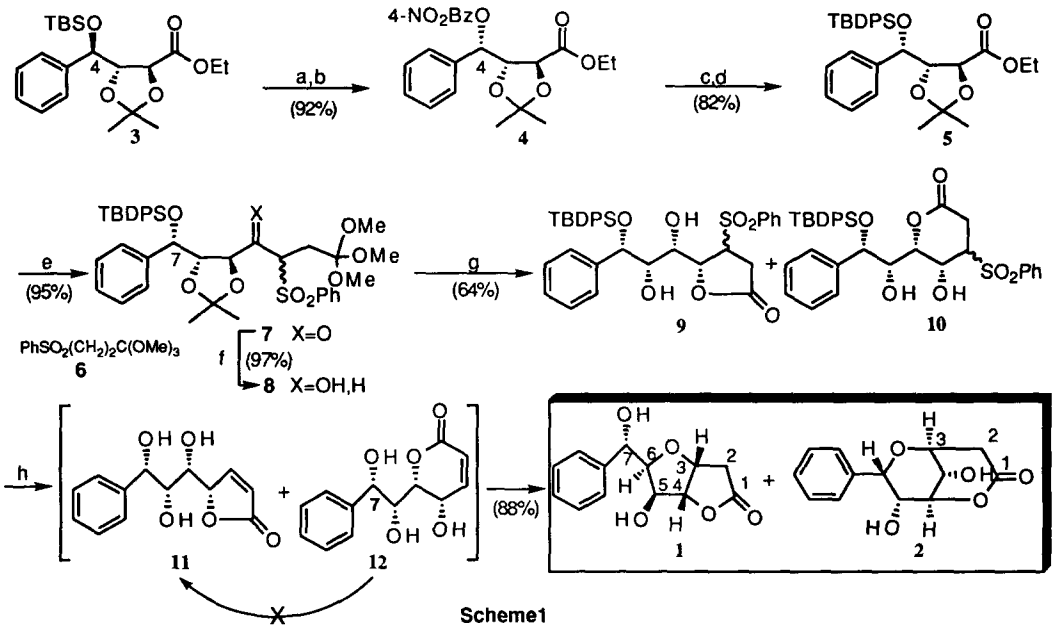
Abstract : Synthesis of enantiopure (+)-7-*epi*-goniofufurone **1** and (+)-goniopypyrone **2** has been achieved from C-4 carbon chain chiron **3**, readily available from (*R*)-mandelic acid.

Several bioactive styryllactones have been isolated from the ethanol extract of the stem bark of *Goniothalamus giganteus* Hook. f. & Thomas (Annonaceae) growing in Thailand.[1a-c]Among them (+)-7-*epi*-goniofufurone **1** and (+)-goniopypyrone **2** were found to possess cytotoxic activities toward human tumor cell lines.[2] The exciting combination of their unique structural features and potent biological activities has attracted considerable synthetic attention and several different approaches of **1**[3] and **2**[4], mainly from carbohydrates, have appeared in the literature.

As part of our program directed toward the synthesis of styryllactones, we recently described the asymmetric synthesis of (+)-goniodiol [5a-c], (+)-goniofufurone[6] and (+)-goniobutenolides A and B.[6] Herein, we report a short synthesis of **1** and **2** from the enantiopure **3**, which has been previously used in our laboratory in the synthesis of several other styryllactones.[6]

The first stage of the synthesis of **1** and **2**, inversion of the C-4 stereogenic center of the ester **3**, available on a multigram scale from (*R*)-mandelic acid in 6 steps (61 % yield)[5c,6], was effected by first O-desilylation with Et3N.3HF[7] followed by Mitsunobu reaction in the presence of 4-nitrobenzoic acid[8] to provide without any racemization the diester **4** in 92 % yield (Scheme 1). Then, sequential saponification of the C-4 ester of **4** and protection of the resulting alcohol as a *t*- butyldiphenylsilyl ether gave **5** in 82 % yield. The next task of the synthesis, introduction of the C-1-C-3 fragment of **1** and **2**, was realized by using the homoenolate equivalent **6**.[5a,b, 6] Thus, exposure of the ester **5** to an excess of the lithium salt of **6** afforded the ß-ketosulfone **7** that treated with $LiAlH_4$, at low temperature yielded desired epimeric sulfones **8** in 97 % yield. As already observed by us [6] on C-7 epimeric **7**, $LiAlH_4$ reduction occurred with complete 1, 2-*syn* selectivity. The stage was now set up for the lactonization reaction. To this end, heating an aqueous acetic solution of compound **8** effected cleavage of the acetonide group, orthoester hydrolysis and lactone formation to give a 2:1 mixture of isomeric lactones **9** and **10**[9] (64 % yield). Finally, treatment of the mixture of **9** and **10** with NBu4F at room temperature induced removal of TBDPS protecting group, $PhSO_2H$ elimination and intramolecular Michael addition to afford, after chromatographic separation, pure (+)-goniopypyrone **2** (29 % yield) and(+)-7-*epi* -goniofufurone **1** (59 % yield).[10]

It is noteworthy that in contrast with its corresponding C-7 epimer, the α-pyrone **12**, did not isomerize to **11**[11], a precursor of **1**, which dismisses the hypothesis of Shing *et al.*[3] that 7-*epi* -goniotriol **12** was one of the possible biogenetic precursor of 7-*epi* -goniofufurone **1**.



Scheme1

Reagents and conditions : (a) $Et_3N.3HF$, CH_3CN, RT, 6 days ; (b) DEAD, PPh_3, 4-NO_2PhCO_2H, THF, 0°C to RT, 2h ; (c) K_2CO_3, EtOH-CH_2Cl_2 (3:1), RT, 90 min ; (d) *t*-$BuPh_2SiCl$, imidazole, DMF, RT, 4 days ; (e) **6** (2.5 equiv), *n*-BuLi, THF, -78°C, 30 min then add **5**, -78°C to RT ; (f) $LiAlH_4$, Et_2O, -78°C, 90 min ; (g) 80% AcOH, reflux, 7h, (h) NBu_4F, RT, 1h.

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