A Synthesis of Goniofufurone

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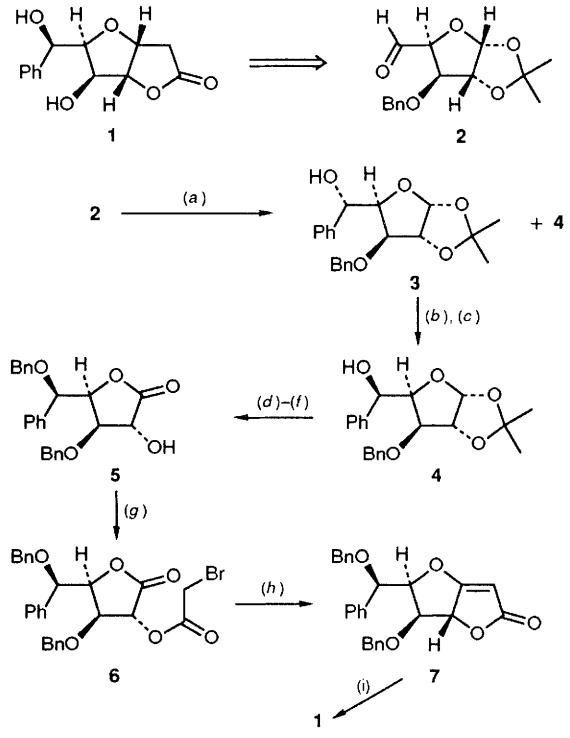
The total synthesis of natural (+)-goniofufurone from D-glucose is reported.

Goniofufurone, a novel styryl lactone isolated from the stem bark of *Goniothalamus gigantius*, and shown to be cytotoxic to human tumour cells,[1] has attracted recent synthetic attention;[2,3] indeed the total synthesis of its enantiomer[3] has confirmed the absolute configuration of goniofufurone as **1**. We report herein the synthesis of **1** from D-glucose which in the furanose form has the same stereochemistry in the tetrahydrofuran ring as that found in goniofufurone; analysis of **1** indicates that the aldehyde **2** is a suitable starting material for the synthesis. The key step of the synthesis involves the Wittig cyclisation of a stabilised phosphorane with a butyrolactone.[4]



Scheme 1 *Reagents and conditions*: (*a*) PhMgBr, Et_2O, reflux (78%), **3**:**4**; 14:1; (*b*) pyridinium chlorochromate (PCC), CH_2Cl_2; (*c*) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, −78 °C (67%), **3**:**4**; 1:8; (*d*) BnBr, tetrahydrofuran (THF), NaH (87%); (*e*) CF_3CO_2H–H_2O (7:3) (85%); (*f*) Br_2–$BaCO_3$, dioxane, H_2O (54%); (*g*) $BrCOCH_2Br$, pyridine, Et_2O (87%); (*h*) PPh_3, MeCN, then 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), reflux, 30 min (88%); (*i*) H_2, 10% Pd on C (58%) (Bn = $PhCH_2$)

Inch has reported[5] that the addition of ethereal phenylmagnesium bromide to **2** (prepared in four steps from glucose, 53% overall yield[6]) gave a 78% yield of two alcohols **3** and **4** in a ratio of 14:1 ratio, respectively, the minor product **4** possessing the correct stereochemistry for goniofufurone. The reaction proceeds under chelation control and efforts to change the ratio in favour of **4** were unsuccessful (although use of phenyllithium in diethyl ether gave **3**:**4** in 2:1 ratio and 60% yield). However, oxidation of a 14:1 mixture followed by rereduction led to a separable (flash chromatography) 1:8 mixture in 69% overall yield.

Protection of the C(5) hydroxy group in **4** as a benzyl ether was followed by removal of the acetonide protecting group and bromine oxidation of the resulting hemiacetal to give an α-hydroxy butyrolactone **5**. Bromoacetylation of **5** proceeded smoothly to give **6** in 87% yield; *in situ* formation of a phosphonium salt followed by base-mediated Wittig cyclisation gave the bicyclic tetronic ester **7** in 88% yield. Catalytic hydrogenation of **7** effected removal of both the C(3)–C(4) double bond and the two benzyl protecting groups to give goniofufurone **1** in 58% yield as plates (from EtOAc–hexane), m.p. 151–152 °C, $[\alpha]_D^{24}$ + 8.5 (*c* 0.8, EtOH) {lit.[1] $[\alpha]_D$ + 9.0 (*c* 0.5, EtOH)}.

This synthesis represents a rapid entry (13 steps from D-glucose) to systems of this type and should enable easy access to structural analogues of goniofufurone.

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† *Note added in proof*: A synthesis of (+)-goniofufurone has recently been reported by Shing *et al.*[7]