Total Synthesis of Antitumour Agent (+)-Goniofufurone

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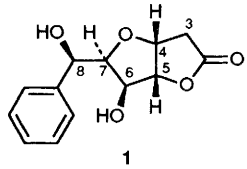
The absolute configuration of the natural goniofufurone is confirmed as **1** by a short and stereoselective synthesis in eight steps from D-*glycero*-D-*gulo*-heptono-γ-lactone with an overall yield of 12.7%.

Goniofufurone, a novel lactone isolated from the stem bark of *Goniothalamus giganteus* Hook. f., Thomas (Annonaceae), has been shown to be cytotoxic to human tumour cells.[1] Recently, the absolute configuration **1** was assigned to goniofufurone by us on the basis of an unambiguous synthesis of its enantiomer from D-*glycero*-D-*gulo*-heptono-γ-lactone (D-glucoheptonic-γ-lactone).[2] This paper now describes, from the same starting material, the first total synthesis of **1** which is identical to the natural goniofufurone, thereby confirming its absolute configuration.

The route to goniofufurone **1** is illustrated in Scheme 1. Commercially available D-*glycero*-D-*gulo*-heptono-γ-lactone **2** (D-glucoheptonic-γ-lactone) was transformed into the known diacetonide **3**[2,3] from which the terminal isopropylidene group was selectively hydrolysed to give the triol **4**, m.p. 160–161 °C; $[\alpha]_D^{20}$ − 77 (*c* 0.6, EtOH).† Glycol cleavage oxidation[4] of **4** with sodium periodate followed by reaction of phenylmagnesium bromide with the liberated aldehyde in diethyl ether gave a mixture of **5** and its 6-epimer in a ratio of *ca.* 3:2. Separation of the mixture by flash chromatography



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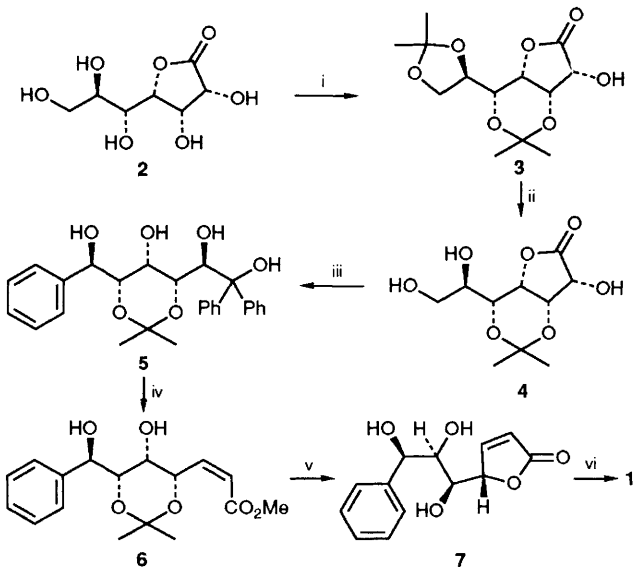
† All new compounds gave satisfactory analytical and spectral data.



Scheme 1 *Reagents and conditions*: i, acetone, anhydrous $ZnCl_2$, H_3PO_4, room temp., 1 day (66%); ii, 75% aq. AcOH, room temp., 1 day (88%); iii, $NaIO_4$, MeOH, H_2O, room temp., 1 h (100%); then PhMgBr, Et_2O, room temp., 4 h (40%); iv, $NaIO_4$, MeOH, room temp., 4 h (95%); then $Ph_3P{=}CHCO_2Me$, MeOH, room temp., 2 h (90%); v, 75% aq. AcOH, room temp., 1 day (85%); vi, THF, cat. DBU, room temp., 1 day (75%)

afforded the tetraol **5** in a yield of 40%, m.p. 200–202 °C, $[\alpha]_D^{20}$ + 126 (*c* 0.5, EtOAc). Another glycol cleavage oxidation[4] of the vicinal diol moiety in **5** followed by immediate Wittig alkenation in methanol furnished stereoselectively[5] the (*Z*)-alkene **6** (*Z*:*E* ratio 6:1), m.p. 134–135 °C; $[\alpha]_D^{20}$ + 64 (*c* 1.0, EtOH). Acid hydrolysis of the acetone group in **6** proceeded with concomitant lactonisation, giving the γ-lactone **7**, m.p. 110–111 °C; $[\alpha]_D^{20}$ − 73 (*c* 0.6, EtOH). The intramolecular Michael addition reaction[2] of **7**, induced by a catalytic amount of 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) in tetrahydrofuran (THF), gave the target molecule **1** as transparent prisms, m.p. 152–154 °C; $[\alpha]_D^{20}$ + 8.6 (*c* 0.5 in EtOH). The spectroscopic data of the synthetic goniofufurone **1** are in accord with those reported[1] and since the natural goniofufurone had m.p. 152–154 °C and $[\alpha]_D^{22}$ + 9 (*c* 0.5 in EtOH), the absolute configuration **1** for the natural material is confirmed.

We thank the Hong Kong UPGC and the Ho Tim & Ho Yin Research Grant for financial support.

Received, 16th March 1992; Com. 2/013781

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