

Total Synthesis of Antitumour Agent (+)-Goniofufurone

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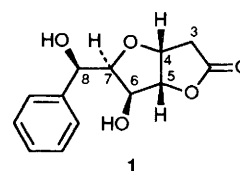
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The absolute configuration of the natural goniofufurone is confirmed as **1** by a short and stereoselective synthesis in eight steps from *D-glycero-D-gulo*-heptono- γ -lactone with an overall yield of 12.7%.

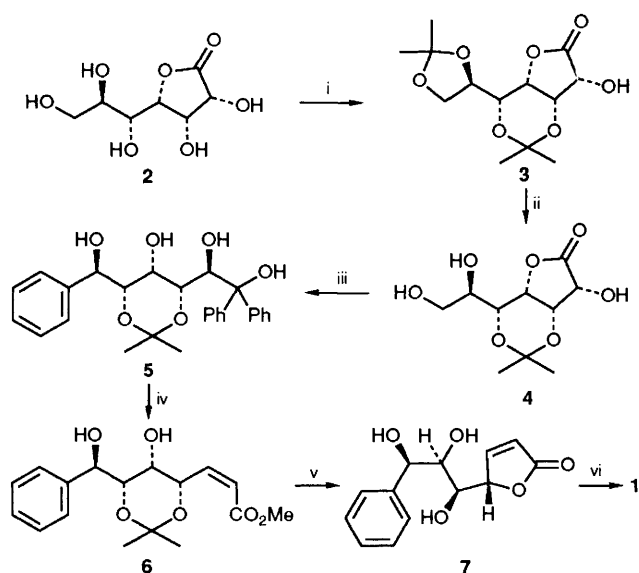
Goniofufurone, a novel lactone isolated from the stem bark of *Goniothalamus giganteus* Hook. f., Thomas (Annonaceae), has been shown to be cytotoxic to human tumour cells.¹ Recently, the absolute configuration **1** was assigned to goniofufurone by us on the basis of an unambiguous synthesis of its 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 oxidation⁴ 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



[†] 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 $\text{Ph}_3\text{P}=\text{CHCO}_2\text{Me}$, 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, $[\alpha]_{\text{D}}^{20} + 126$ (c 0.5, EtOAc). Another glycol cleavage oxidation⁴ of the vicinal diol moiety in **5** followed by

immediate Wittig alkenation in methanol furnished stereoselectively⁵ the (*Z*)-alkene **6** (*Z*:*E* ratio 6:1), m.p. 134–135 °C; $[\alpha]_{\text{D}}^{20} + 64$ (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; $[\alpha]_{\text{D}}^{20} - 73$ (c 0.6, EtOH). The intramolecular Michael addition reaction² 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; $[\alpha]_{\text{D}}^{20} + 8.6$ (c 0.5 in EtOH). The spectroscopic data of the synthetic goniofufurone **1** are in accord with those reported¹ and since the natural goniofufurone had m.p. 152–154 °C and $[\alpha]_{\text{D}}^{22} + 9$ (c 0.5 in EtOH), the absolute configuration **1** for the natural material is confirmed.

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References

- X. P. Fang, J. E. Anderson, P. E. Fanwick and J. L. McLaughlin, *J. Chem. Soc., Perkin Trans. 1*, 1990, 1655.
- T. K. M. Shing and H.-C. Tsui, *J. Chem. Soc., Chem. Commun.*, 1992, 432.
- T. K. M. Shing, Z.-H. Zhou, H.-C. Tsui and T. C. W. Mak, *J. Chem. Soc., Perkin Trans. 1*, 1992, 887.
- For a recent review, see T. K. M. Shing, in *Comprehensive Organic Synthesis*, ed. B. M. Trost and I. Fleming, Pergamon Press, Oxford, 1991, vol. 7, p. 703.
- J. M. J. Tronchet and B. Gentile, *Helv. Chim. Acta*, 1979, **62**, 2091.