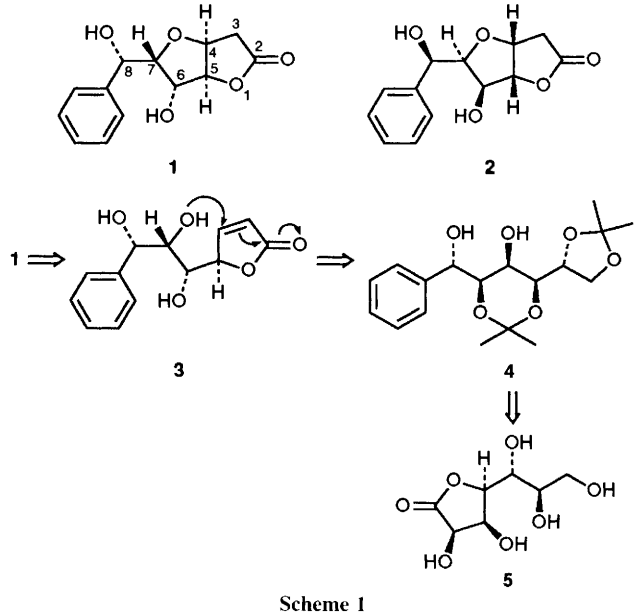
Goniofufurone: Synthesis and Absolute Configuration

Tony K. M. Shing* and Hon-chung Tsui

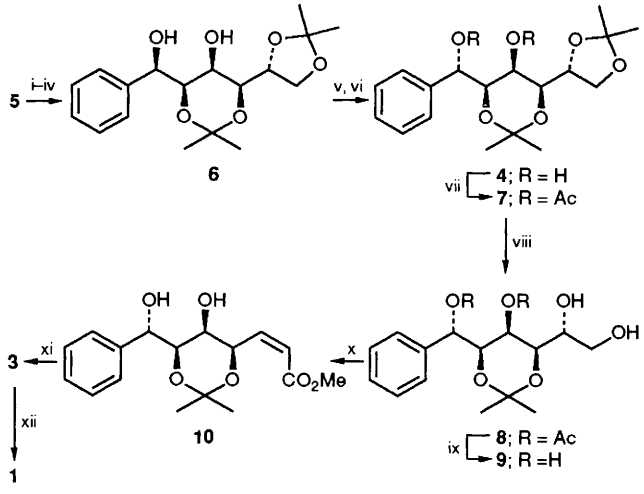
Department of Chemistry, The Chinese University of Hong Kong, Shatin, Hong Kong

The absolute configuration of natural goniofufurone is shown to be **2** by an unambiguous synthesis of its enantiomer **1** from D-*glycero*-D-*gulo*-heptono-γ-lactone involving an intramolecular Michael reaction as the key step.

Recently, a novel styryl-lactone goniofufurone has been isolated from the ethanolic extracts of the stem bark of *Goniothalamus giganteus* Hook. f., Thomas (Annonaceae) and shown to be cytotoxic to human tumour cells.[1] The structure of goniofufurone, which represents a new natural skeleton, was revealed by X-ray crystallography to be **1** or its enantiomer **2**.[1] We now report, starting from affordable and abundant D-*glycero*-D-*gulo*-heptono-γ-lactone, an unambiguous synthesis of **1** which is identical to the natural goniofufurone except for the sign of the optical rotation, thereby enabling the assignment of the absolute configuration **2** to the natural material.



Scheme 1



Scheme 2 *Reagents and conditions*: i, acetone, anhydrous $ZnCl_2$, H_3PO_4, room temp., 1 day (66%); ii, $NaBH_4$, MeOH, 0 °C to room temp., 12 h (98%); iii, $NaIO_4$, MeOH, H_2O, room temp., 3 h (100%); iv, PhMgBr, THF, 0 °C (74%), **6**:**4** = 8:1; v, pyridinium chlorochromate, CH_2Cl_2, 4 Å molecular sieve, room temp., 3 h (61%); vi, $CeCl_3·7H_2O$, $NaBH_4$, MeOH, −78 °C (70%), **6**:**4** = 1:19; vii, $(MeCO)_2O$(Ac_2O), pyridine, cat. *N*,*N*-dimethylaminopyridine, CH_2Cl_2, room temp., 1 day (80%); viii, 50% aq. AcOH, room temp., 15 h (81%); ix, MeOH, cat. NaOMe, room temp., 2 h (93%); x, $NaIO_4$, MeOH, H_2O, room temp., 30 min; then $Ph_3P{=}CHCO_2Me$, MeOH, room temp., 2 h (92%, from **9**); xi, 80% aq. AcOH, room temp., 2 days (83%); xii, 0.05% (v/v) DBU in THF, room temp., 1 day (71%)

Retrosynthetic analysis of **1** shows that the [3.3.0] bicyclic ring system of the molecule can be assembled *via* an intramolecular Michael protocol[2] of the γ-lactone **3** (Scheme 1). We envisaged that the formation of the five-membered furanoid ring in **1** should be the most facile process and the resulting [3.3.0] bicycle should then be *cis*-fused; in this way, the desired stereochemistry at C-4 would be controlled by the preexisting chirality at C-5 of the α,β-unsaturated lactone **3**. Further disconnection of **3** indicates that it can be derived from the known styryl-alcohol **4**[3] *via* sequential selective hydrolysis, glycol cleavage reaction and Wittig reaction. The alcohol **4** is then readily accessible from D-*glycero*-D-*gulo*-heptono-γ-lactone **5**.[3]

The route to goniofufurone is illustrated in Scheme 2. Our previous work has shown that the lactone **5** can be readily converted into the styryl-alcohol **6**, and into its 6-epimer **4** in an overall yield of 21%.[3] Acetylation of **4** gave the diacetate **7** from which the terminal acetonide was selectively hydrolysed to the diol **8**, $[\alpha]_D^{24}$ + 19 (*c* 1.0, EtOAc).† Deacetylation of **8** with a catalytic amount of NaOMe in methanol led to the tetraol **9**, m.p. 170–172 °C; $[\alpha]_D^{23}$ + 6.0 (*c* 0.5, EtOH).‡ Glycol cleavage oxidation[4] of the vicinal diol in **9** followed by immediate Wittig alkenation in methanol, afforded stereoselectively[5] the *Z*-alkene **10** (*Z*:*E* ratio 7:1), m.p. 135–136 °C; $[\alpha]_D^{24}$ −65 (*c* 0.9, EtOH). Acid removal of the acetone group in **10** occurred with concomitant lactonisation, providing the γ-lactone **3**, m.p. 109–111 °C; $[\alpha]_D^{22}$ +72 (*c* 0.9, EtOH). The intramolecular Michael addition reaction of **3**, induced by a catalytic amount of 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) in tetrahydrofuran (THF), gratifyingly proceeded as planned to give the target molecule **1** as white plates, m.p. 152–154 °C; $[\alpha]_D^{24}$ −8.5 (*c* 0.8, EtOH). The spectroscopic data of the synthetic goniofufurone **1** are identical to those reported,[1] and since the reported $[\alpha]_D$ value of goniofufurone is +9.0 (*c* 0.5, EtOH),[1] the absolute configuration of natural goniofufurone must be **2**.

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† All new compounds gave satisfactory analytical and spectral data.

‡ Selective hydrolysis of **4** to give **9** directly was unsuccessful.