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FIRST TOTAL SYNTHESIS OF POTENT ANTITUMOUR AGENT (+)-GONIOPYPYRONE

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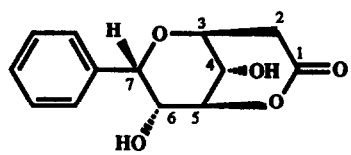
Abstract—The structure and absolute stereochemistry of the natural goniopypyrone is confirmed as 1 by a short and stereoselective synthesis in nine steps from D-*glycero*-D-*gulo*-heptono-γ-lactone with an overall yield of 9.7 %.

Recently, four styryl-lactones, (+)-goniopypyrone, (+)-goniofufurone, (+)-goniotriol and (+)-8-acetylgoniotriol, which are cytotoxic to human tumour cells,[1,2] have been isolated from the ethanolic extracts of the stem bark of *Goniothalamus giganteus* Hook. f., Thomas (Annonaceae).[1,2] Amongst these lactones, (+)-goniopypyrone is the most bioactive, exhibiting nonselective ED_{50} values of *ca.* 6.7×10^{-1} $\mu g ml^{-1}$ in several human tumour cell lines;[1] its novel skeleton is also most intriguing and presents a formidable synthetic challenge. The structure and relative configuration of (+)-goniopypyrone has been determined by X-ray crystallography to be **1** or its enantiomer.[1] As part of our long-term programme in the fabrication of heavily oxygenated lactones as potential antitumour agents from sugars, we recently described the total syntheses of (+)-goniofufurone[3] and of (-)-goniotriol and (-)-8-acetylgoniotriol[4] from commercially available D-*glycero*-D-*gulo*-heptono-γ-lactone (D-glucoheptonic-γ-lactone). This paper now discloses, from the same starting material, the first total synthesis of **1** which is identical to the natural goniopypyrone, thereby confirming its constitution and absolute configuration.



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The construction of goniopypyrone **1** is depicted in Scheme 1. Our previous work has shown that D-*glycero*-D-*gulo*-heptono-γ-lactone **2** could be converted into the triol **3** in two steps with an overall yield of 58%.[3,5] Glycol cleavage oxidation[6] of **3** with sodium metaperiodate followed by reaction of the liberated aldehyde with phenylmagnesium bromide in tetrahydrofuran (THF) gave a mixture of **4** and its 6-epimer in a ratio of *ca.* 2.5 : 1.[5,7] Separation of the mixture by flash chromatography afforded the tetraol **4** in a yield of 37%, m.p. 167—168 °C, $[\alpha]_D^{20}$ + 174° (*c* 0.5, EtOAc).[8] A second glycol cleavage oxidation[6] of the vicinal diol moiety in **4** followed by immediate Wittig alkenation in anhydrous methanol furnished stereoselectively[9,10] the *Z*-alkene **5** (> 95% *Z*), m.p. 110—111 °C; $[\alpha]_D^{20}$ - 128° (*c* 0.8, EtOAc). The *Z*-alkene **5** was induced to lactonise by a catalytic amount of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in boiling THF, providing the pyrone **6**, m.p. 207—208 °C, sinters at 192°C; $[\alpha]_D^{20}$ - 77.4° (*c* 1.0, EtOH). Acid hydrolysis of the

acetone group in **6** furnished the triol **7**, m.p. 133—134 °C; $[\alpha]_D^{20}$ + 53.4° (*c* 0.6, EtOH). The intramolecular Michael type ring closure[3,5] of **7**, involving the 7-OH and mediated by a catalytic amount of DBU in THF, gave the target pyran **1** as long needles, m.p. 180—182 °C; $[\alpha]_D^{20}$ + 55.5° (*c* 0.6, EtOH). Participation of the 6-OH of **7** in the intramolecular Michael reaction to form the corresponding furanoid ring was reasoned to be unfavourable, attributable to severe steric interaction between the lactone ring and the benzyl moiety. The spectroscopic data of the synthetic **1** are in accord with those reported[1] and since the reported $[\alpha]_D^{22}$ value of goniopypyrone (m.p. 182—184 °C) is + 54° (*c* 0.4, EtOH),[1] the structure and absolute stereochemistry of natural goniopypyrone is confirmed as **1**.

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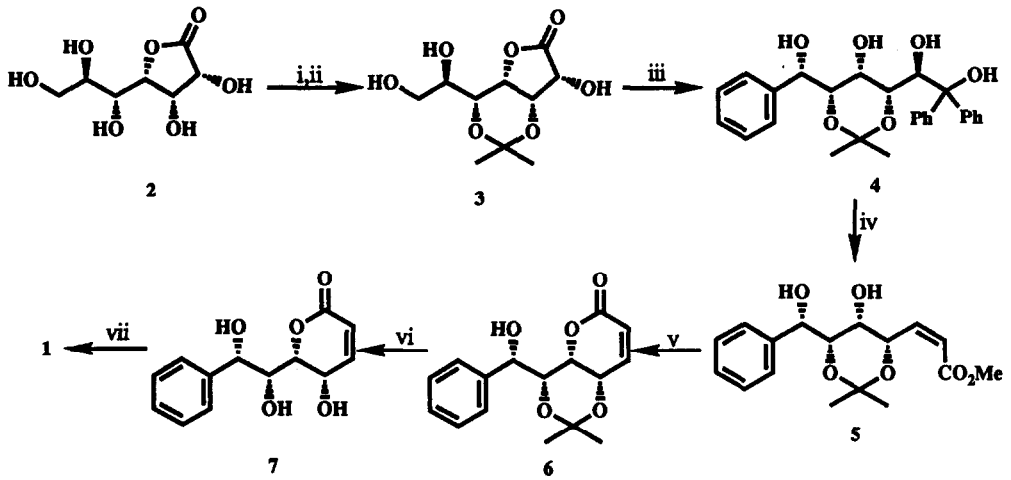

Scheme 1 *Reagents and conditions*: i, acetone, $ZnCl_2$, cat. H_3PO_4 (66%); ii, 75% aq. AcOH, room temp., 1 day (88%); iii, $NaIO_4$, MeOH, H_2O, then PhMgBr, THF, 0 °C (37%); iv, $NaIO_4$, MeOH, H_2O, then $Ph_3P{=}CHCO_2Me$, anhydrous MeOH, room temp. (86%); v, cat. DBU, THF, reflux (78%); vi, 75% aq AcOH, 70-80 °C (90%); vii, cat. DBU, THF, room temp. (75%).

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7 The ratio was *ca* 2 : 3 when diethyl ether was used as solvent.[3]
8 All new compounds gave satisfactory analytical and spectral data.
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