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GONIOTRIOL AND 8-ACETYLGONIOTRIOL: SYNTHESES AND ABSOLUTE CONFIGURATIONS

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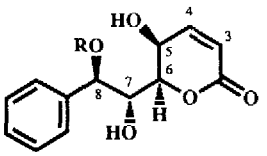
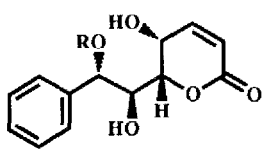
Abstract—The absolute configurations of natural goniotriol and 8-acetylgoniotriol are shown to be **1** and **2** respectively by unambiguous syntheses of their enantiomers **3** and **4** from D-*glycero*-D-*gulo*-heptono-γ-lactone.

Goniotriol was isolated from the leaves and twigs of *Goniothalamus sesquipedalis* Wall (Annonacea)[1] and from the stem bark of *Goniothalamus giganteus* Hook. f., Thomas (Annonaceae)[2] whereas 8-acetylgoniotriol has recently been extracted from the latter species.[3] Both compounds were shown to be cytotoxic to human tumour cells.[2,3] Based on NMR spectral studies[3,4] and *X*-ray crystallographic analysis,[2] the structures of goniotriol and 8-acetylgoniotriol were determined to be **1** and **2** respectively or their enantiomers **3** and **4.** We have a long-term programme in the syntheses of heavily oxygenated lactones as potential antitumour agents from carbohydrates and recently described the enantiospecific synthesis of a related cytotoxic styryl-lactone, (+)-altholactone, from D-gulonolactone.[5] We also reported a synthesis of the (6*R*,7*S*)-diastereoisomer of the antitumour antibiotic asperlin from D-glucose.[6] Now, this paper describes, starting from commercially available D-*glycero*-D-*gulo*-heptono-γ-lactone, unambiguous syntheses of **3** and **4** which are identical to the natural goniotriol and 8-acetylgoniotriol respectively except for the signs of the optical rotation, thereby enabling the assignments of the absolute configurations **1** and **2** to the respective natural materials.



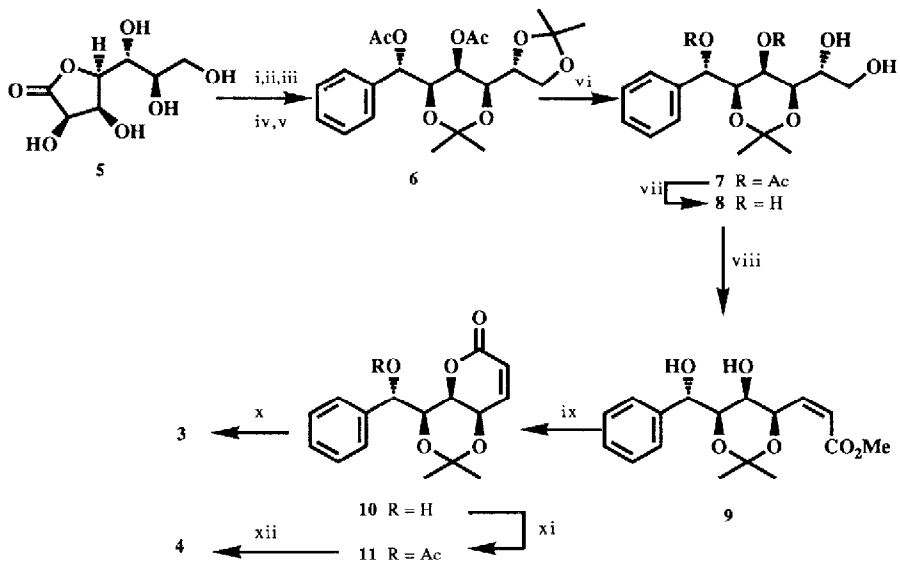
(**1**) R = H
(**2**) R = Ac



(**3**) R = H
(**4**) R = Ac

The route to goniotriol **3** and 8-acetylgoniotriol **4** is illustrated in Scheme 1. Our previous work has shown that the D-*glycero*-D-*gulo*-heptono-γ-lactone **5** can be readily transformed into the styryl-diacetate **6** in an overall yield of 23%.[7] The terminal isopropylidene group in **6** was selectively hydrolysed to the diol **7**, $[\alpha]_D^{24}$ + 19° (*c* 1.0, EtOAc).[8] Deacetylation of **7** with a catalytic amount of NaOMe in methanol gave the tetraol **8**, m.p. 170—172 °C; $[\alpha]_D^{24}$ + 6.0° (*c* 0.5, EtOH). Glycol cleavage oxidation[9] of **8** with periodate followed by immediate Wittig olefination in methanol afforded stereoselectively the *Z*-alkene **9** (*Z*:*E* ratio 7:1), m.p. 135—136 °C; $[\alpha]_D^{24}$ - 65° (c 0.9, EtOH). Lactonisation of *Z*-alkene **9**, induced by a catalytic amount of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in boiling tetrahydrofuran (THF), furnished the styrylpyrone **10**, m.p. 191—192 °C; $[\alpha]_D^{20}$ - 130° (*c* 1.0, MeOH). Acid hydrolysis of the acetone group in **10** gave the target molecule **3** as prism crystals, m.p. 170—171 °C; $[\alpha]_D^{20}$ - 119° (*c* 1.1, MeOH). The spectroscopic data of the synthetic goniotriol **3** are in accord with those reported,[1,2] and since the reported $[\alpha]_D$ value of goniotriol (m.p. 170 °C) is + 121° (MeOH),[2] the absolute configuration of natural goniotriol must be **1**.

On the other hand, acetylation of the 2-pyrone **10** gave the monoacetate **11** in a yield of 90%, m.p. 190—191 °C; $[\alpha]_D^{20}$ - 13° (*c* 0.6, EtOH). Acid removal of the acetal in **11** led to the other target molecular **4** as a white solid, m.p. 158—159 °C; $[\alpha]_D^{20}$ - 30° (*c* 0.9, EtOH). The spectroscopic data of the synthetic 8-acetylgoniotriol **4** are also identical to those reported,[3] but the reported m.p. had 158—159 °C and $[\alpha]_D$ value had + 30° (*c* 0.4, EtOH).[3] The absolute configuration of natural 8-acetylgoniotriol must be **2**.



Scheme 1 *Reagents and conditions*: i, acetone, anhydrous $ZnCl_2$, H_3PO_4, room temp., 1 day (66%); ii, $NaBH_4$, MeOH, room temp., 12 h (98%); iii, $NaIO_4$, MeOH, H_2O, room temp., 3 h (100%); iv, PhLi, THF, 0 °C (45%); v, Ac_2O, pyridine, cat. *N,N*-dimethylaminopyridine, CH_2Cl_2, room temp., 1 day (80%) vi, aq. AcOH, room temp., 12 h (81%); vii, MeOH, cat. NaOMe, room temp., 2 h (93%); viii, $NaIO_4$, MeOH, H_2O, room temp., 30 min., then Ph_3P=CHCOOMe, MeOH, room temp., 2 h (92%); ix, DBU, THF, reflux, 12 h (83%); x, 75% aq. AcOH, 70-80°C, 4 h (90%); xi, Ac_2O, pyridine, room temp., 12 h (90%); xii, 75% aq. AcOH, 70-80°C, 4 h (88%).

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References and Notes

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