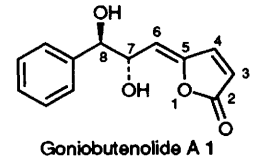
Goniobutenolides A and B: Serendipitous Syntheses, Relative and Absolute Configuration

Tony K. M. Shing,* Vincent W.-F. Tai and Hon-Chung Tsui

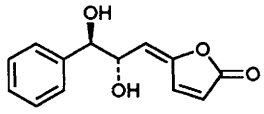
Department of Chemistry, The Chinese University of Hong Kong, Shatin, Hong Kong

The relative and absolute stereochemistries of natural goniobutenolides A and B are established as **1** and **2** respectively by short syntheses of them and their 8-epimers.

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 several styryllactones which were isolated from the ethanolic extracts of the stem bark of *Goniothalamus giganteus* Hook. f., Thomas (Annonaceae).[1,2] All these styryllactones, (+)-goniofufurone,[3] (−)-goniotriol,[3f,4] (−)-8-acetylgoniotriol[3f,4] and (+)-goniopypyrone[3f,5] have been successfully synthesised firstly by us and then by others. During our synthetic studies towards the configurational analogues of goniotriol, we discovered by chance the construction of two new styryllactones goniobutenolides A and B which had recently been isolated also from the bark of *G. giganteus* (Annonaceae) and shown to possess marginal cytotoxicity against human tumour cell lines.[6] Their gross structures were determined by spectroscopic techniques which suggested the presence of a *threo*-diol moiety, but their absolute configurations were not assigned.[6] This paper now discloses the first total syntheses of goniobutenolides A and B as well as their 8-epimers, thereby reassigning the relative configuration of the diol moiety as *erythro* and establishing their absolute stereochemistries as **1** and **2**, respectively.



Goniobutenolide A 1



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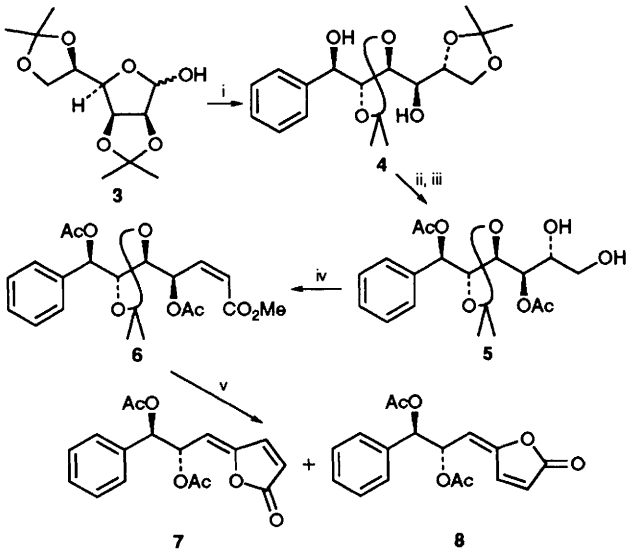


Scheme 1 *Reagents and conditions*: i, PhMgBr, THF, reflux (52%); ii, Ac_2O, pyridine, CH_2Cl_2, room temp. (96%); iii, 50% aq. AcOH, room temp. (91%); iv, $NaIO_4$, MeOH, room temp. then $Ph_3P{=}CHCO_2Me$, room temp. (overall 47%); v, 80% aq. AcOH, reflux, then Ac_2O, NEt_3, CH_2Cl_2, room temp. (combined overall 53%), **7**:**8** = *ca.* 2:1

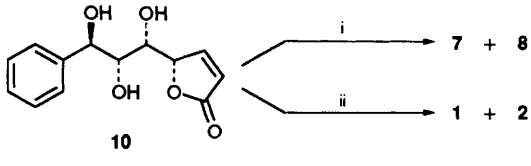
The serendipitous syntheses of the acetyl derivatives of goniobutenolides A and B are shown in Scheme 1. Reaction of the readily available diacetone-D-mannose **3**[7] with phenylmagnesium bromide in THF gave the benzyl alcohol **4**,† mp 103–104 °C; $[\alpha]_D^{24}$ −28 (*c* 0.6, $CHCl_3$) and its epimer in a ratio of *ca.* 4:3.‡ Acetylation of **4** followed by selective hydrolysis of the terminal acetonide gave the diol **5**, mp 106–107 °C; $[\alpha]_D^{25}$ + 11 (*c* 1.3, $CHCl_3$). Glycol cleavage oxidation[9] of the vicinal diol moiety in **5** followed by immediate Wittig alkenation afforded the *Z*-alkene **6** (*Z*:*E* ratio *ca.* 1:1 as determined by ^1H NMR spectral analysis), $[\alpha]_D^{25}$ −9 (*c* 0.7, $CHCl_3$). Hydrolysis of the remaining acetonide blocking group in **6** with aqueous acetic acid followed by acetylation [acetic anhydride (Ac_2O)–triethylamine–CH_2Cl_2] furnished a mixture of two diacetates, assigned as **7**, $[\alpha]_D^{24}$ +75 (*c* 1.7, $CHCl_3$) and **8**, $[\alpha]_D^{24}$ −63 (*c* 0.7, $CHCl_3$). The spectral data of **7** and **8** were in accord with those of diacetylgoniobutenolide A[6] and diacetylgoniobutenolide B,[6] respectively. It was speculated that acidic removal of the acetonide group in **6** was accompanied by acetyl migration and lactonisation which, upon the acetylation conditions, underwent elimination at C-5,6 to yield **7** and **8**. This speculation was proved correct by transforming the known trihydroxy-butenolide **10**[3a] into the identical compounds **7** and **8** under the same acetylation conditions in a combined yield of 99% (Scheme 2).

At this stage, the syntheses of goniobutenolides A and B were obvious and should be completed simply by deacetylation. However, attempts to remove the esters from **7** and **8** *via* alkaline or acid hydrolysis proved detrimental and no desired products were isolable. Fortunately, the syntheses of **1** and **2** were finally realized from **10** by the fact that trifluoroacetyl ester could be easily hydrolysed under mild conditions.[10] Thus trifluoroacetylation [trifluoroacetic anhydride (TFAA)–triethylamine–CH_2Cl_2] of **10** followed by *in situ* methanolysis to remove the esters gave **1** and **2** in an overall yield of 79% (Scheme 2).

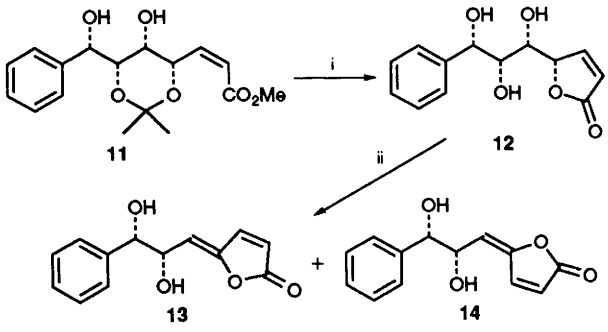
Both synthetic **1** and **2** displayed spectroscopic data (^1H and ^{13}C NMR) in accord with those of the natural compounds. However, their physical constants show discrepancies.

	Goniobutenolide A		Goniobutenolide B	
	mp/°C	$[\alpha]_D$	mp/°C	$[\alpha]_D$
Synthetic	Yellow oil	+187	148–149	−112
Natural	Yellow oil	+82	Yellow oil	−36.5

In addition, the relative stereochemistry of the diol moiety in natural **1** and in **2** was previously assigned[6] as *threo*, but that in the synthetic compounds was *erythro*. These discrepancies



Scheme 2 *Reagents and conditions*: i, Ac_2O, NEt_3, CH_2Cl_2, room temp. (combined 99%), **7**:**8** = *ca.* 2:1; ii, TFAA, NEt_3, CH_2Cl_2, room temp., then MeOH (combined overall 79%), **1**:**2** = *ca.* 1:3



Scheme 3 *Reagents and conditions*: i, 75% aq. AcOH, 80 °C (74%); ii, TFAA, NEt_3, CH_2Cl_2, 0 °C → room temp., then MeOH, room temp. (65%), **13**:**14** = *ca.* 1:2.4

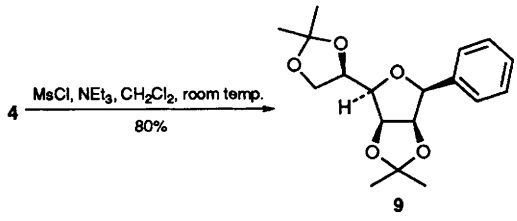
prompted us to synthesise the corresponding *threo*-diastereoisomers for comparison. Thus acidic deacetonation of the known *Z*-enoate **11**[5a] occurred with spontaneous lactonisation to give the trihydroxybutenolide **12**, mp 143–145 °C (MeOH); $[\alpha]_D^{21}$ −85 (*c* 0.3, MeOH) (Scheme 3). Trifluoroacetylation of **12** followed by *in situ* methanolysis provided the *threo*-diastereoisomers **13**, mp 94–96 °C; $[\alpha]_D^{21}$ +144 (*c* 0.3, $CHCl_3$), and **14**, mp 117–119 °C; $[\alpha]_D^{21}$ −196 (*c* 0.3, $CHCl_3$), in 65% yield. Their ^{1}H NMR spectra§ were different from those reported[6] for (+)-goniobutenolide A and (−)-goniobutenolide B. Compound **13** showed the diagnostic 8-H resonated at δ 4.71 ($J_{8,7}$ 6.3 Hz) and 7-H at δ 4.87 ($J_{7,8}$ 6.3, $J_{7,6}$ 8.3 Hz) whereas the 8-H and 7-H of (+)-goniobutenolide A[6] resonated at δ 4.94 ($J_{8,7}$ 4.3 Hz) and δ 4.98 ($J_{7,8}$ 4.3, $J_{7,6}$ 8.4 Hz), respectively. Compound **14** showed the diagnostic 8-H resonated at δ 4.62 ($J_{8,7}$ 7.8 Hz) and 7-H at δ 4.55 ($J_{7,8}$ 7.8, $J_{7,6}$ 7.3 Hz) whereas the corresponding protons of (−)-goniobutenolide B[6] resonated at δ 4.87 ($J_{8,7}$ 4.5 Hz) and δ 4.63 ($J_{7,8}$ 4.5, $J_{7,6}$ 7.9 Hz), respectively. Therefore, the relative and absolute stereochemistries of the natural (+)-goniobutenolide A and (−)-goniobutenolide B must be **1** and **2**, respectively, and our synthetic materials had higher purity which led to discrepancies between the physical constants of the synthetic and of the natural materials.

We thank the Hong Kong UPGC for financial support.

Received, 4th March 1994; Com. 4/01317D

Footnotes

† The stereochemistry of the newly formed alcohol in **4** was confirmed by conversion into the known[8] phenyl *C*-glycoside **9**. (Ms = $MeSO_2$).



‡ All new compounds gave satisfactory analytical and spectral data.

§ ^{1}H NMR (400 MHz, $CDCl_3$) data for compounds **13** and **14**: for **13**, δ 2.64 (1 H, d, *J* 3.9 Hz, OH), 2.72 (1 H, d, *J* 4.4 Hz, OH), 4.71 (1 H, dd, $J_{8,7}$ 6.3, $J_{8,OH}$ 4.4 Hz, 8-H), 4.87 (1 H, ddd, $J_{7,6}$ 8.3, $J_{7,OH}$ 3.9 Hz, 7-H), 5.33 (1 H, d, 6-H), 6.17 (1 H, d, $J_{3,4}$ 5.4 Hz, 3-H), 7.28–7.40 (6H, m, Ph and 4-H); for **14**, δ 2.59 (1 H, t, *J* 2.9, OH), 2.94 (1 H, t, *J* 2.4, OH), 4.55 (1 H, ddd, $J_{7,8}$ 7.8, $J_{7,6}$ 7.3, $J_{7,OH}$ 2.4 Hz, 7-H), 4.62 (1 H, dd, $J_{8,OH}$ 2.9 Hz, 8-H), 5.57 (1 H, dd, $J_{6,3}$ 1.5 Hz, 6-H), 6.12 (1 H, dd, $J_{3,4}$ 5.4 Hz, 3-H), 7.29–7.38 (5 H, m, Ph), 7.53 (1 H, d, 4-H).

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