Enantiospecific Syntheses of (+)- and (−)-Altholactone (Goniothalenol)

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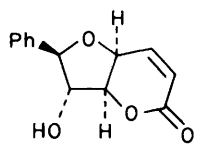
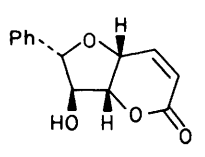
(+)-Altholactone (**1**) and its enantiomer (**2**) have been synthesised from D-gulonolactone and D-mannose, respectively, with stereocontrolled reduction ($Et_3SiH/BF_3{\cdot}Et_2O$) of the lactols (**4**) and (**10**) as a key step.

Altholactone has been isolated from an unidentified Polyathea species[1] and from the stem bark of *Goniothalamus Giganteus* (Annonaceae);[2] it has been demonstrated to be active against P388 leukemia *in vivo* and cytotoxic to brine shrimp *in vitro*.[2] *X*-Ray crystallography has enabled the assignment of structure (**1**) or its enantiomer (**2**).[2] Very recently the absolute configuration (**1**) was assigned on the basis of a total synthesis[3] from D-glucose; this prompted us to disclose our independent synthetic endeavour. We now describe short and enantiospecific syntheses of (+)- and (−)-altholactone from D-gulonolactone and D-mannose, respectively, thereby confirming the absolute configuration (**1**) for the natural material.

The route to (+)-altholactone (**1**) is shown in Scheme 1. Commercially available D-gulonolactone (**3**) was converted into the corresponding diacetonide, which reacted with phenyl-lithium to give the lactol (**4**),† m.p. 103—105 °C; $[\alpha]_D^{20}$ −54.5° (*c* 1.4 in $CHCl_3$). Stereocontrolled reduction of (**4**) with Et_3SiH mediated by $BF_3{\cdot}Et_2O$[4] proceeded smoothly with concomitant partial deacetonation, furnishing exclusively the α-D-*C*-phenyl derivative (**5**), $[\alpha]_D^{20}$ −45.0° (*c* 0.3 in $CHCl_3$). Presumably, the approach of the hydride to the less hindered α-face of the incipient carbocation secured the desired stereochemistry of the phenyl moiety (Figure 1). Oxidation of the diol (**5**) with periodate, followed by immediate Wittig olefination, afforded stereoselectively[5] the *Z*-olefin (**6**) (*Z* : *E* ratio 6 : 1), $[\alpha]_D^{20}$ + 55.0° (*c* 0.4 in $CHCl_3$). Deacetonation of (**6**) occurred with spontaneous lactonisation, giving the 7-*epi*-altholactone (**7**),‡ m.p. 121—123 °C; $[\alpha]_D^{22}$ + 23.5° (*c* 0.4 in EtOH). The Walden inversion of the free hydroxy group in (**7**), a transformation which would complete the synthesis of altholactone, proved difficult. After considerable experimentation, nucleophilic displacement of the trifluoromethanesulphonate derived from (**7**) with caesium propionate[6] was successful and the ester (**8**) was isolated; m.p. 174—175 °C; $[\alpha]_D^{20}$ + 139.0° (*c* 0.7 in $CHCl_3$). The ester



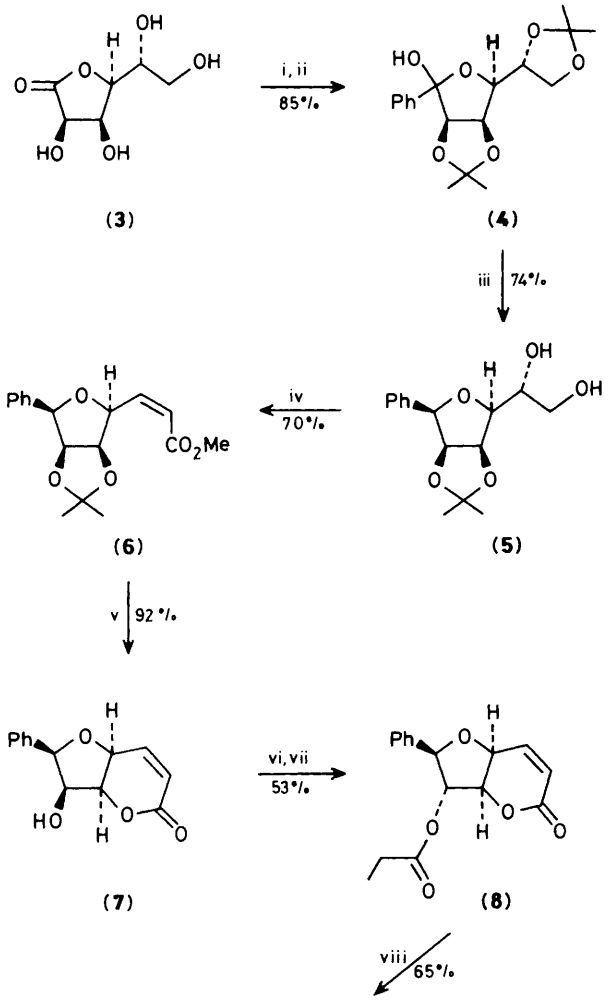
(**1**)



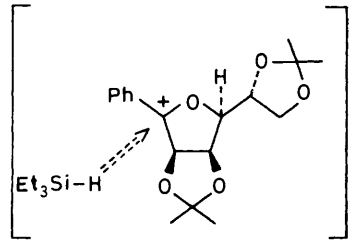
(**2**)

† All new compounds gave satisfactory analytical and spectral data.

‡ The antitumour activities of these new 2-pyrones will be reported later.

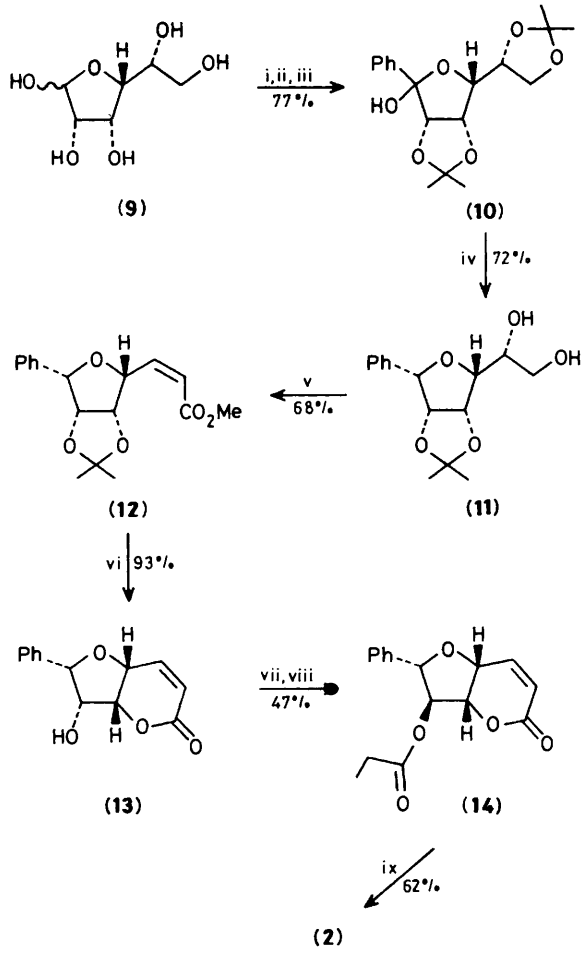


Scheme 1. *Reagents:* i, Me_2CO, H_2SO_4; ii, PhLi, tetrahydrofuran (THF), −78 °C; iii, Et_3SiH, $BF_3{\cdot}Et_2O$, MeCN, −20 °C; iv, $NaIO_4$, aq. MeOH; then $Ph_3P{=}CHCO_2Me$; v, aq. CF_3CO_2H (aq. TFA); vi, $(CF_3SO_2)_2O$, CH_2Cl_2, pyridine, −10 °C; vii, $EtCO_2Cs$, $HCONMe_2$; viii, aq. NaOH; then TFA.



(8) was then saponified to yield (+)-altholactone (1), $[\alpha]_D^{20}$ + 185.2° (*c* 0.2 in EtOH).

On the other hand, (−)-altholactone (2) was synthesised from D-mannose (9) as shown in Scheme 2. Thus acetonation of (9) followed by oxidation and subsequent reaction with phenyl-lithium gave the lactol (10), m.p. 111—112 °C; $[\alpha]_D^{22}$ + 49.0° (*c* 1.3 in $CHCl_3$), which was reduced to the β-D-*C*-phenyl derivative (11), m.p. 104—106 °C; [α] + 62.0° (*c* 1.6 in $CHCl_3$). The diol (11) was then transformed into the *Z*-olefin (12) [enantiomeric with (6)], $[\alpha]_D^{20}$ − 57.5° (*c* 1.0 in CH_2Cl_2), and into the lactone (13),‡ m.p. 121—122 °C; $[\alpha]_D^{20}$ − 24.1° (*c* 1.0 in EtOH). Esterification of (13) followed by



Scheme 2. *Reagents:* i, Me_2CO, H_2SO_4; ii, pyridinium chlorochromate, 3 Å molecular sieves, CH_2Cl_2; iii, PhLi, THF, −78 °C; iv, Et_3SiH, $BF_3{\cdot}Et_2O$, MeCN, −20 °C; v, $NaIO_4$, aq. MeOH; then $Ph_3P{=}CHCO_2Me$; vi, aq. TFA; vii $(CF_3SO_2)_2O$, CH_2Cl_2, pyridine, −10 °C; viii, $EtCO_2Cs$, $HCONMe_2$; ix, aq. NaOH; then TFA.

nucleophilic substitution afforded the ester (14), m.p. 174—176°C; $[\alpha]_D^{23}$ − 127° (*c* 0.8 in $CHCl_3$), which was saponified to yield the enantiomeric altholactone (2),‡ $[\alpha]_D^{22}$ − 180.5° (*c* 0.2 in EtOH).

The spectroscopic data (i.r., mass, and ^1H n.m.r.) of both synthetic (1) and (2) are identical with those reported,[2] and since the reported $[\alpha]_D$ values of altholactone are + 188.0° (EtOH)[1] and + 184.7° (EtOH),[2] the absolute configuration of natural altholactone must be (1).

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