Stereoselective Synthesis of (±)-Ancistrofuran: Stereoselective Reduction of a γ-Hydroxyketone

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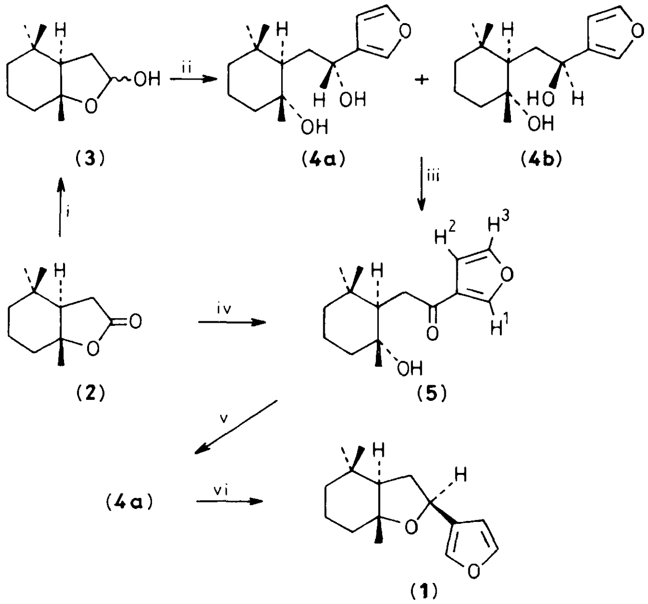
A remarkably stereoselective reduction of a γ-hydroxyketone with two equiv. of lithium triethylborohydride has been observed and this effect has been suggested to originate from 'chelation control'; the reaction has been utilised in a short stereoselective synthesis of ancistrofuran.

The major soldiers of the West African termite, *Ancistrotermes cavithorax*, produce a defensive secretion which consists predominantly of ancistrofuran (**1**).[1] Although two syntheses of this compound have been reported[2,3] neither route was stereoselective and both involved difficult separations of undesired isomers. We now report an efficient and stereoselective synthesis of ancistrofuran, together with a remarkably stereoselective reduction of a γ-hydroxyketone.

The starting material was the lactone (**2**) which is readily available *via* the mercury(II) ion initiated cyclisation of homogeranic acid.[3] Reduction of the lactone (**2**) with di-isobutylaluminium hydride yielded the hemiacetal (**3**)[3] in 60% yield; subsequent reaction with two equiv. of 3-lithiofuran yielded a 1 : 1 mixture of two diastereoisomeric diols [(**4a**) and (**4b**)]. This mixture of diols was not normally separated but oxidised with MnO_2 in CH_2Cl_2 to yield the ketone (**5**)† in 90% yield.

The ketone (**5**) is also available in 60% yield in one step from the reaction of lactone (**2**) with one equiv. of 3-lithiofuran. The ketone (**5**), a white crystalline solid m.p. 77—78 °C (Et_2O), exists predominantly in the γ-hydroxyketone form there being no evidence of lactol formation, ν_{max} (CCl_4), 3300 br.s, 1670s cm^{-1}; ^1H n.m.r. δ 8.05 (1H, m, H^1‡), 7.2 (1H, m, H^3‡), 6.73 (1H, m, H^2‡), 2.8 (2H, m, CH_2CO–), 1.07 (1H, m, –CH–), 1.1—1.8 (6H, m, 3 × CH_2), 1.1 (3H, s, –CH_3), 0.82 (6H, s, gem 2 × CH_3).



Scheme 1. *Reagents and conditions*: i, $AlBu^i_2H$, toluene, −78 °C; ii, 3-lithiofuran (2 equiv.), tetrahydrofuran (THF), −78 °C; iii, MnO_2, CH_2Cl_2, 12 h; iv, 3-lithiofuran (1 equiv.), THF, −78 °C; v, $LiBHEt_3$ (2 equiv.), THF, −78 °C; vi, p-$MeC_6H_4SO_2Cl$ (1 equiv.), pyridine (2 equiv.), CH_2Cl_2, room temp., 48 h.

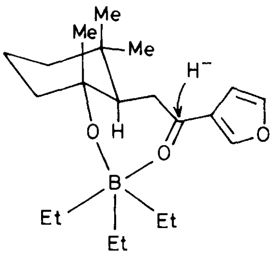
Reduction of ketone (**5**) with $LiAlH_4$, $ZnBH_4$, and $NaBH_4$ all yielded mixtures of the diols (**4a**) and (**4b**) (Table 1). However, reduction with two equiv. of lithium triethylborohydride in tetrahydrofuran proceeded in a highly stereoselective manner to yield the required diol (**4a**) as the only product in 88% yield as a white crystalline solid m.p. 85—87 °C (Et_2O). Treatment of the diol with one equiv. of toluene-*p*-sulphonyl chloride and two equiv. of pyridine in methylene chloride gave a quantitative yield of ancistrofuran§ (**1**) (Scheme 1) *via* esterification of the secondary alcohol and S_N2 displacement by the tertiary alcohol.

It is proposed that the basis of this remarkably high degree of stereoselectivity in the reduction is due to initial reaction of the reducing agent with the tertiary alcohol and subsequent chelation to the carbonyl to yield the cyclic structure (**6**). Attack of hydride from a second equiv. of the reducing agent can now only occur from the least hindered β-face. Stereoselective reduction of α-hydroxyketones[4] and β-hydroxyketones[5] have been reported and Kishi *et al.* have developed conditions for the reduction of some γ- and δ-epoxy ketones.[6] This appears to be the first example of stereoselective reduction of a γ-hydroxyketone. The use of 'chelation

Table 1. Reduction of γ-hydroxyketone (**5**).

Reducing Agent	(**4a**)[a]	(**4b**)[a]	Yield (%)[b]
$LiAlH_4$	40	60	80
$NaBH_4$	50	50	84
$ZnBH_4$	60	40	66
$LiBEt_3H$	100	0	88

[a] Ratio of products measured by g.l.c. (3 m × 3 mm), 5% OV101 at 190 °C. [b] Refers to isolated yield.



(**6**)

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† All new compounds gave satisfactory elemental microanalyses and/or accurate mass measurements.

‡ Furanoid protons, designated on structure (**5**).

§ Identical with the authentic sample.

control' in the reaction of Grignards[7] and cuprates with carbonyl compounds[8] is well documented and the present work represents a further example of stereocontrol in reactions of acyclic systems.

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