The Stereoselective Introduction of a Hydroxy Group into the 2,8-Dioxabicyclo[3.2.1]octan-3-one System[1]

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The silyl lactone enol ether (**2**) provides a means for the stereospecific introduction of a hydroxy group at the 4-position of the 2,8-dioxabicyclo[3.2.1]octan-3-one system; the hydroxy group can also be inverted by treatment with base.

The 7-oxabicyclo[2.2.1]heptanyl system has been employed as an agent to control stereochemistry in a number of syntheses including routes to daunosamine,[2] both ribose and nucleotide analogues,[3–5] methyl shikimate,[6] and cantharidin,[7] but no method has been reported for the stereoselective introduction of a hydroxy group at the 4-position of a 2,8-dioxabicyclo[3.2.1]octan-3-one system. The introduction of a hydroxy group has been achieved through oxidative degradation;[5] this stereospecific introduction of a hydroxy group is, however, paramount to the use of an oxygen-bridged bicyclic system as a carbohydrate synthon.

With the ubiquitous use of chiral templates and auxiliaries in present synthetic methodology, a general method for the synthesis of any hexose derivative[8] would be extremely useful. We envisaged that the 7-oxabicyclo[2.2.1]heptanyl system, which is available from a stereochemically controlled Diels–Alder reaction,[9,10] could be used in this regard; this has led to the total synthesis of mannose.[1] To fulfil these requirements, a method was required for the introduction of a hydroxy group at the 4-position† of the 2,8-dioxabicyclo[3.2.1]octanyl lactone (**1**) in a stereospecific manner. The lactone (**1**) was readily available by the route outlined in Scheme 1.[9]

Reaction of the lactone (**1**) with lithium di-isopropylamide (LDA) under the standard conditions followed by chlorotrimethylsilane gave the enol ether (**2**) in excellent yield. Treatment of this ether (2) with *m*-chloroperbenzoic acid (MCPBA) gave the α-hydroxylactone (**3**) specifically.[5,11,12]

While trying to open the lactone (**3**), we found that the 4-hydroxy group could be susceptible to epimerization. This was put to use for inversion at this centre by deprotonation with 2 equiv. of LDA followed by aqueous work-up. This presumably occurs through enolate dianion formation and reprotonation from the least sterically congested top face. The

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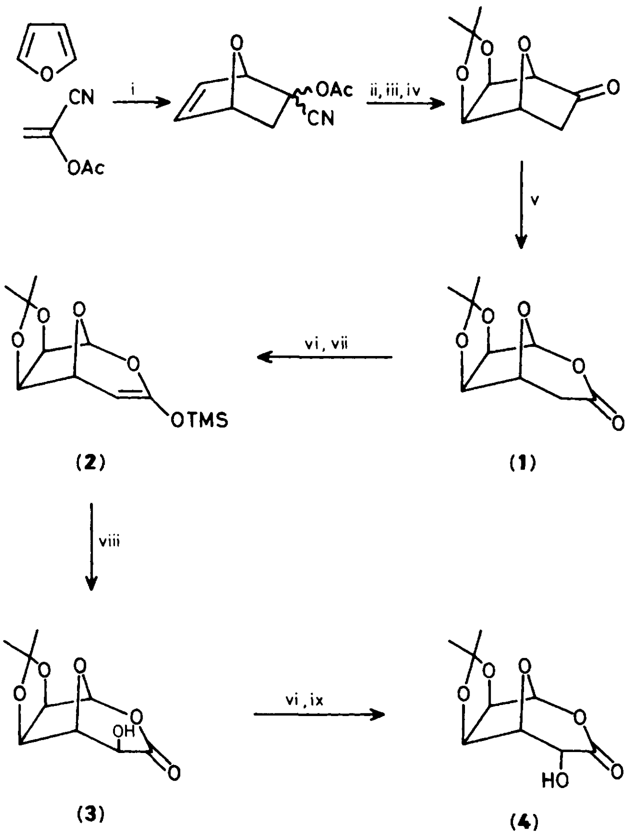
† The bicyclic numbering system has been used.



Scheme 1. *Reagents and conditions*: i, ZnI$_2$; ii, OsO$_4$, H$_2$O$_2$; iii, (MeO)$_2$CMe$_2$, *p*-MeC$_6$H$_4$SO$_3$H; iv, KOH; v, MCPBA, CH$_2$Cl$_2$; vi, LDA, tetrahydrofuran, −78 °C; vii, Me$_3$SiCl; viii, MCPBA; ix, NH$_4$Cl, H$_2$O.

conversion is not quantitative but can be improved upon by repetition of the deprotonation–protonation procedure. The reaction is slow as the base has to deprotonate the lactone from the most hindered face. Hence, the reiterative process is required to maximize yield and minimize side reactions. Alternative methods for the inversion of hindered alcohols have been advocated.[13]

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