The First Example of a Robinson Annulation on a Carbohydrate Derivative

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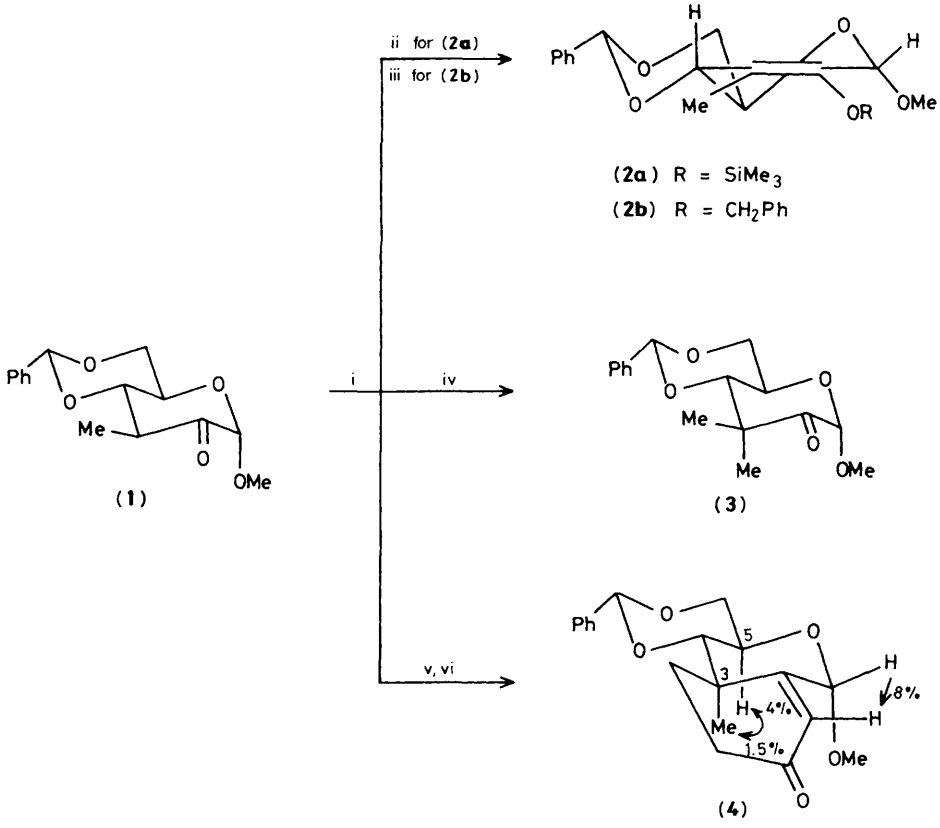
The stereocontrolled synthesis of a tricyclic carbohydrate derivative using the Robinson annulation on methyl 4,6-*O*-benzylidene-3-deoxy-3-*C*-methyl-α-D-arabino-hexapyranoside-2-ulose is reported.

As part of a synthetic programme in our laboratory a need arose for a complex chiral cyclohexenone. In view of the success of carbohydrates in various synthetic ventures,[1] we thought that they would also provide the answer to this problem. Our plan was to carry out a Robinson annulation on an appropriate carbohydrate derivative. Although enolates



Scheme 1. *Reagents:* i, *N*-lithio-2,2,6,6-tetramethylpiperidine, Et_2O, 0.5 h, 0 °C; ii, Me_3SiCl (3 equiv.); iii, $-Et_2O$, + tetrahydrofuran (THF), $PhCH_2Br$ (7 equiv.), hexamethylphosphoramide (HMPA) (0.5 equiv.); iv, $-Et_2O$, + THF, MeI (7 equiv.), HMPA (0.5 equiv.); v, 3-trimethylsilyl-3-buten-2-one, 0 °C, 2 h; vi, 4% aqueous KOH (0.35 equiv.), MeOH, 80 °C, 6 h.

derived from sugar precursors[2] have been reported we know of no example of a Robinson annulation in this series of compounds.

Our initial work was directed at forming the enolate of the known glucose derived ketone (**1**).[3] Deprotonation with lithium di-isopropylamide led to reduction of the carbonyl group giving a mixture of axial and equatorial alcohols (ratio 1:4).[4] Extensive studies revealed that ketone (**1**) was cleanly deprotonated with *N*-lithio-2,2,6,6-tetramethylpiperidine to give an enolate which reacted at oxygen with Me_3SiCl and $PhCH_2Br$ to give (**2a**)† (76%) and (**2b**)‡ (54%) respectively (Scheme 1). Alkylation with methyl iodide occurs on carbon leading to ketone (**3**)‡ (66%). After several unproductive attempts to react the enolate of (**1**) with methyl vinyl ketone, the use of 3-trimethylsilylbutenone[5] was successful; it underwent reaction with the enolate in diethyl ether at 0 °C. The initial product could be isolated and gave spectra consistent with Michael addition followed by O-cyclisation onto the ring carbonyl group. Treatment of the initial product with 4% KOH–MeOH gave (**4**)‡ as an oil in 40% yield from (**1**). {$[\alpha]_D$ −38° (*c* 3.3, $CHCl_3$); $\nu_{max.}$ 1685 cm^{-1}; ^1H n.m.r. (300 MHz) δ 1.48 (3H, s); 1.87 (1H, dt, *J* 5.0, 14.02 Hz); 2.25 (1H, ddd, *J* 13.45, 4.98, 2.56 Hz); 2.43 (1H, dddd, *J* 17.56, 4.98, 2.57, 0.82 Hz); 2.55 (1H, ddd, *J* 17.54, 14.61, 5.01 Hz); 3.38—3.41 (1H, d) overlapping 3.41 (3H, s); 3.71 (1H, t, *J* 10.15 Hz), 4.19 (1H, dt, *J* 5.15, 9.75 Hz); 4.34 (1H, dd, *J* 10.25, 5.16 Hz); 4.89 (1H, s); 5.54 (1H, s); 5.86 (1H, s); 7.32—7.51 (5H, m). 4% Nuclear Overhauser enhancement (n.O.e.) between δ 1.48 and 4.19; 2% n.O.e. between δ 1.48 and 2.55; 1.5% n.O.e. between δ 1.48 and 2.25, and 1.5% n.O.e. between δ 4.19 and 1.48}. The stereochemistry of (**4**) rests on the n.O.e. evidence and in particular on the enhancement between the axial methyl group at δ 1.48 and the axial proton 5-H δ 4.19 (dt). This evidence leads us to the unexpected structure (**4**), which is the result of an initial reaction of the enone on the β-face of the enolate derived from ketone (**1**); attack on the α-face is possibly being hindered by the OLi and OMe groups. Subsequent cyclisation and elimination then yields the product (**4**) where the new bond at C-3 is equatorial.

To the best of our knowledge this is the first example of a Robinson annulation on a sugar derivative; this reaction should be useful to us in a natural product synthesis.

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† Satisfactory spectroscopic data was obtained for this compound.

‡ Satisfactory spectroscopic and microanalytical data was obtained for this compound.

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