The First Example of a Robinson Annulation on a Carbohydrate Derivative

Roger V. Bonnert and Paul R. Jenkins*

Department of Chemistry, Leicester University, Leicester LE1 7RH, U.K.

The stereocontrolled synthesis of a tricyclic carbohydrate derivative using the Robinson annulation on methyl 4,6-O-benzylidene-3-deoxy-3-C-methyl- α -p-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, Me₃SiCl (3 equiv.); iii, $-Et_2O$, + tetrahydrofuran (THF), PhCH₂Br (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 precursors² 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 Me₃SiCl and PhCH₂Br 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-trimethylsilylbutenone⁵ 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). {[α]_D -38° (c 3.3, CHCl₃); v_{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%

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

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.

We acknowledge the financial support of the S.E.R.C.

Received, 29th August 1986; Com. 1240

References

- 1 S. Hanessian, 'Total Synthesis of Natural Products: The "Chiron" Approach,' Pergamon Press, Oxford, 1983.
- 2 A. Klemer and H. Wilbers, *Liebigs, Ann. Chem.*, 1985, 2328; A. Klemer and H. Beerman, J. Carbohydr. Chem., 1983, 3, 457; A. Klemer and H. Thiemeyer, *Liebigs, Ann. Chem.*, 1984, 1094; A. Klemer and H. Stegt, J. Carbohydr. Chem., 1985, 4, 205.
- 3 D. R. Hicks and B. Fraser-Reid, Synthesis, 1974, 203; J. R. Pougny and P. Sinay, J. Chem. Res. (M), 1982, 0183.
- 4 C. Kowalski, X. Creary, A. J. Rollin, and M. L. Burke, J. Org. Chem., 1978, 43, 2601.
- 5 R. K. Boeckman, Jr., D. M. Blum, B. Ganem, and W. Halvey, Org. Synth., 1978, 58, 152; G. Stork and B. Ganem, J. Am. Chem. Soc., 1973, 95, 6152,; R. K. Boeckman, Jr., ibid., p. 6867.

[†] Satisfactory spectroscopic data was obtained for this compound.