The Synthesis and X-Ray Crystal Structure of a Cyclopentaannulated Sugar; the First Example of an Intramolecular Aldol Cyclopentaannulation in Carbohydrate Chemistry

Andrew J. Wood, Paul R. Jenkins,* John Fawcett and David R. Russell

Department of Chemistry, Leicester University, Leicester, UK LE1 7RH

A 1,4-dicarbonyl compound **5** has been constructed by a sequence involving opening of a protected glucose epoxide with allyl magnesium chloride, alkylation and Wacker oxidation; the 1,4-dicarbonyl compound readily undergoes cyclisation under basic conditions to produce a cyclopentaannulated sugar derivative **6**, whose structure was confirmed by X-ray crystallography.

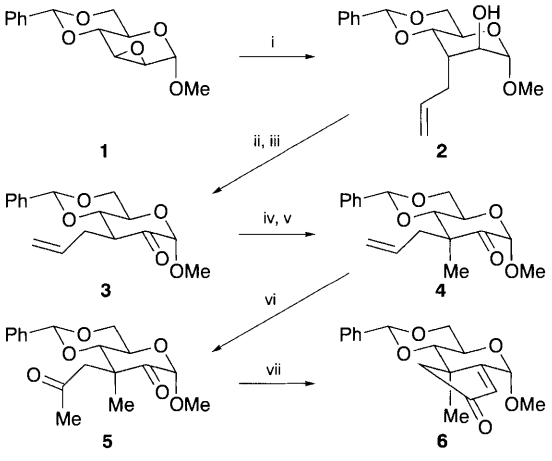
Strategies for the conversion of carbohydrates into carbocycles are of two types; the first involves the cyclisation of an open chain sugar derivative so that most, if not all the carbons of the sugar are incorporated into the carbocyclic ring, while in the second the carbocycle is formed onto the sugar ring which is then modified or removed.[1] We have published[2] an example of the latter strategy, in which we take advantage of the chirality of the cyclic carbohydrate to form a carbocycle by a Robinson annulation and then fragment the sugar so that only two of the sugar carbon atoms end up in the carbocyclic product. This method may be useful in the synthesis of natural products which consist of annulated carbohydrates or where a highly functionalised enantiomerically pure cyclohexane is required. We are at present using this strategy in a synthetic approach to taxoids.[2]

In seeking to extend the concept of carbohydrate annulation using an intramolecular aldol cyclisation, we were stimulated by the number of monoterpenoid natural products of the iridoid class which have the cyclopentan-(c)-pyran structure.[3] Here we report a successful procedure for the cyclopentaannulation of a glucose derivative which may have applications in the synthesis of iridoids.

Our new results are summarised in Scheme 1.† The epoxide **1**[4] was opened with allyl magnesium chloride[5] to produce an alcohol which was oxidised to the corresponding ketone by the Swern procedure and epimerised to the ketone **3**.[6] Deprotonation and reaction with methyl iodide was carried out in a similar way to our previous work[2] to produce the ketone **4**. Wacker oxidation[7] of the olefin **4** proceeded well to yield the 1,4-diketone **5** which was readily cyclised to the enone **6**.[8] The structure of **6** was confirmed by X-ray crystallography as shown in Fig. 1.‡

A range of other structures were prepared to test the scope and limitations of the cyclopentaannulation strategy. The structure **7** was prepared by Wacker oxidation of the olefin **3** and ketones **8** and **9** were prepared from the α-epoxide by an analogous route to that shown in Scheme 1. Treatment of diketone **7** with potassium hydroxide in refluxing ethanol gave decomposition as did reaction with methanol and *p*-toluene sulfonic acid, however starting material was obtained with sodium hydride and potassium *tert*-butoxide in toluene although traces of benzaldehyde were also observed indicating a small amount of fragmentation of the benzylidene group. Treatment of diketone **8** with sodium hydroxide in refluxing methanol gave no cyclisation but a product was isolated which we tentatively assign to the fragmentation of the sugar ring with the benzylidene group still present. Decomposition was observed when **8** was reacted with lithium hexamethyldisilazane at room temperature. Three different cyclisation conditions were used on diketone **9**, potassium *tert*-butoxide in toluene, sodium carbonate in methanol and sodium methoxide in methanol and in all cases starting material was isolated with a trace of benzaldehyde. One possible explanation of this is that deprotonation takes place α to the ring carbonyl groups in **7**, **8** and **9** instead of at the end of the side chain which is required for cyclisation.

In conclusion we have developed a route for the cyclopentaannulation of a glucose derivative which may prove useful in the synthesis of iridoids, and will also provide a synthesis of chiral cyclopentanoid compounds when the sugar rings in the product **9** are removed by fragmentation.



Scheme 1 *Reagents and conditions*: i, CH_2CHCH_2MgCl, THF, 85%; ii, DMSO, $(CF_3CO)_2O$, 1 h, −78 °C, Et_3N; iii, Et_3N, DMF, 36 h, 79%; iv, *N*-lithio-2,2,6,6-tetramethylpiperidine, Et_2O, 0.5 h, 0 °C; v, MeI (7 equiv.) 60%; vi, $PdCl_2$, $CuCl_2$, O_2, DMF, 0.5 h, 80%; vii, Bu^{t}OK, toluene, 0.5 h, 90%

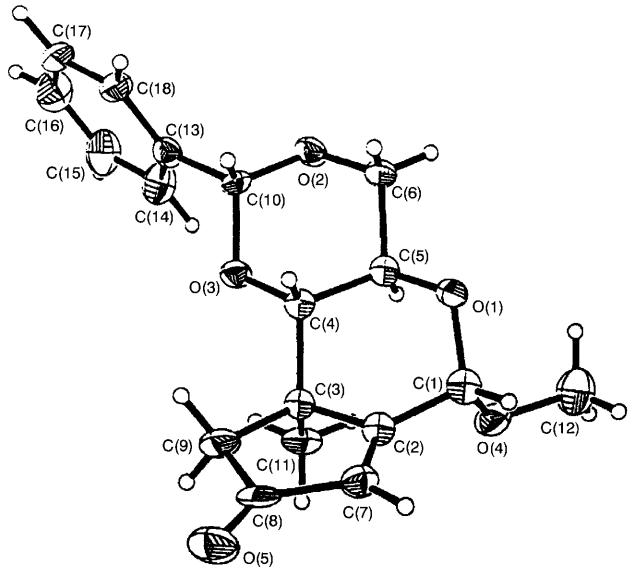
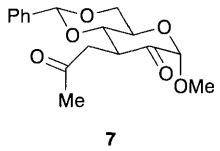


Fig. 1 The X-Ray crystal structure of the cyclopentenone **6** with 30% thermal ellipsoids



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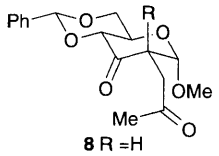

8 R = H
9 R = Me

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Footnotes

† Compounds **2–6** were fully characterised by spectroscopic data and microanalysis.

‡ *Crystal data* for **6**: $C_{18}H_{20}O_5$, M = 316.34, orthorhombic, space group $P2_12_12_1$, a = 8.343(1), b = 8.915(1), c = 22.506(3) Å, V = 1673.9(4) Å^3, Z = 4, D_c = 1.225 Mg m^{-3}, $F(000)$ = 672, S = 1.072, Mo-Kα radiation (λ = 0.71069 Å), μ = 0.091 mm^{-1} (no abs. correction), T = 293 K. Siemens P4 diffractometer, ω-scan, $2\theta_{max}$ = 44.0°; 1695 reflections measured, 1535 independent reflections (R_{int} = 0.037). The structure was solved by direct methods (program SHELXTL-pc; G. M. Sheldrick, release 4.2, Siemens Analytical X-ray Instruments Inc, Madison, WI, 1991) and refined by full-matrix least-squares on F^2 (program SHELX 93; G. M. Sheldrick, Universität Göttingen, 1993) with 171 variables. H atoms are in calculated positions and were treated as riding atoms. Refinement of anisotropic displacement parameters was limited by the ratio of observed data to variables, consequently C(1)–C(5) inclusive were refined as isotropic atoms. $R1$ = 0.0596 for 1059 observed [$I > 2\sigma(I)$], $wR2$ = 0.1469 for all independent reflections residual electron density.

Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Information for Authors, Issue No. 1.

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