Annelated Pyranosides: Some Cyclohexano- and Cyclopentano-sugars

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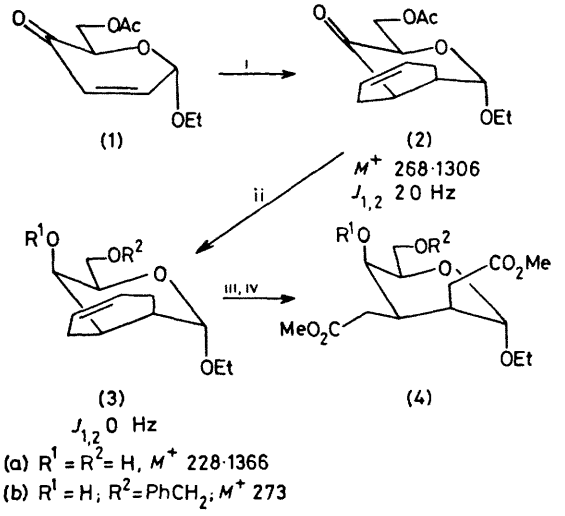
Summary The carbohydrate α-enone (**1**) condenses with butadiene in the presence of an excess of aluminium chloride to give the *lyxo* adduct (**2**), exclusively, reduction of which is also stereospecific, a method has been developed to convert the product into the cyclopentano-furanoside (**7**)

IN connection with our studies on the use of carbohydrate derivatives as chiral templates in organic synthesis,[1] we have been interested in the preparation of annelated pyranosides as potential precursors of chiral, functionalised cycloalkyl residues. Previously,[2] we had developed stereospecific routes to cyclopropano-pyranosides, and the synthetic utility of these has recently been demonstrated by an enantiospecific synthesis of (+)- and (−)-forms of chrysanthemum dicarboxylic acid from the same starting material.[3] Cyclobutano-pyranosides have also been prepared in our laboratory,[4] but the preponderance of five- and six-membered rings amongst natural products prompted us to investigate routes to cyclopentano- and cyclohexano-sugars.



SCHEME 1. Reaction conditions: i, butadiene, $AlCl_3$, CH_2Cl_2, −78 °C (yield 80—90%); ii, $LiAlH_4$ (yield 80%); iii, RuO_4; iv, CH_2N_2.

Ready access to cyclohexano-pyranosides appeared to be *via* Diels–Alder reactions of carbohydrate α-enones, and because of its ease of preparation,[5] compound (**1**) was chosen for initial investigation. We had been encouraged by the work of Jones[6a] and Hutchinson[6b] on the use of 2-hydroxy-5-oxo-5,6-dihydro-2*H*-pyran, a hemiacetal analogue of (**1**), as a dienophile. However application of the high-temperature procedure[6] to the reaction of (**1**) with butadiene led to extensive decomposition.

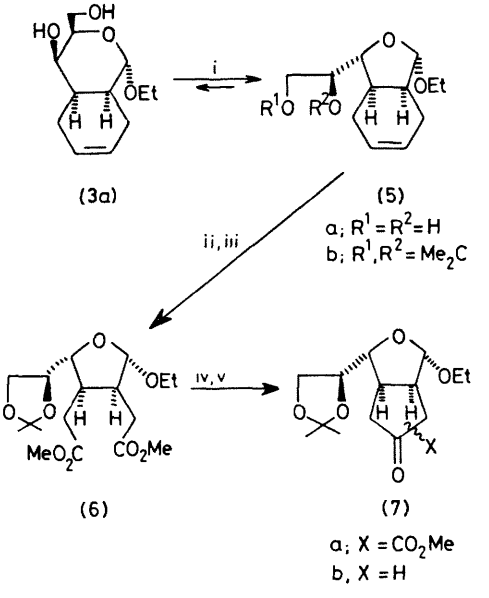
The use of Lewis acid catalysts for enhancing the reactivity of dienophiles is well known,[7] although their application to substrates as highly oxygenated as (**1**) was without precedent. After extensive experimentation, a procedure was developed† employing a generous excess of aluminium chloride which afforded an 80—90% yield of a single adduct (**2**).‡ (Interestingly boron trifluoride–diethyl ether and tin (IV) chloride were ineffective.) Our procedure, which may be operated on a preparative scale, is in contrast with the recently described high-pressure (*ca.* 150,000 lb in^{-2}) approach of Jurczak and Tkacz, which requires specialised apparatus.[8]

Reduction of (**2**) with $LiAlH_4$ gave (**3a**)‡ as the exclusive product. The stereochemistry of the Diels–Alder addition was suggested by the apparent coupling constants (220 MHz) for (**2**) and (**3**) shown in Scheme 1. According to our previous studies,[9] these values are indicative of axial substitution at C-2.

Because of the highly hindered nature of the C-4 hydroxy group, selective reaction at the primary group is readily carried out at room temperature even with benzyl chloride. A wide variety of protected samples of (**3**) is therefore obtainable.

To prepare the cyclopentano-sugars we tried Jung's method[10] for converting alkenes into cyclopentanones but we failed to adapt this for the annelation of a variety of hex-2-enopyranosides. We therefore attempted to contract the cycloalkyl ring of (**3**) following the well established procedure,[11] but all attempts at Dieckmann cyclisation of (**4**) failed, and treatment of various samples of (**3**) with $Tl^{III}NO_3$[12] led to extensive decomposition.

We reasoned that these failures were due, in part, to the severe 1,3-interaction between the C-2 and C-4 substituents of (**3**) and models indicated that our prospects would be much better if the sugar ring of (**3**) were furanoid instead of pyranoid. Accordingly the diol (**3a**) was



SCHEME 2. Reaction conditions: i, 1% EtOH–HCl; ii, RuO_4; iii, CH_2N_2 (yield 50—60%); iv, Bu^{t}OK, PhH, 23 °C (yield 75%); v, NaCl, Me_2SO (yield 85%).

† A solution of the enone (**1**) (10 g) in dry methylene chloride (100 ml) was cooled to −78 °C and butadiene (60 ml) was added. Aluminium chloride (9 g) was then added with stirring, and the temperature was raised to −40 °C. After 2·5 h the mixture was poured into ice-cold aqueous sodium hydrogen carbonate and compound (**2**) (9·8 g; 78% yield) was then recovered after customary processing followed by silica gel column chromatography.

‡ All new compounds gave satisfactory mass spectral analysis as well as supporting spectroscopic (i.r. and 220 MHz n.m.r.) data.

dissolved in 1% EtOH–HCl and followed to constant optical rotation at room temperature (*ca.* 5 h). The product which consisted of (**5a**) (*ca.* 95% by $NaIO_4$ analysis) could be converted directly into the acetonide (**5b**)‡ [*m/e* 254 (M^+); 239 (M^+-15)], which was then converted into the diester (**6**)‡ [*m/e* 331 (M^+-15)]. This diester (**6**) cyclised smoothly (Bu^{t}OK, PhH, 23 °C, 5 h) to give (**7a**)‡ [*m/e* 299 (M^+-15)]; the stereo- and regio-chemistry of the conversion are currently being examined. In any event, ready decarboxylation was effected using the Krapcho procedure[13] giving the cyclopentanofuranoside (**7b**)‡ (M^+, obs. 256·1272; calc. 256·1311) in 70% yield.

We thank the National Research Council of Canada, Bristol Laboratories (Syracuse), and Merck, Sharp, and Dohme (Rahway) for financial support. We thank Dr. A. Grey of the Canadian 220 MHz N.M.R. Centre for the 220 MHz spectra.

(*Received, 14th September* 1979; *Com.* 990.)

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