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Polycyclic scaffolds from fructose

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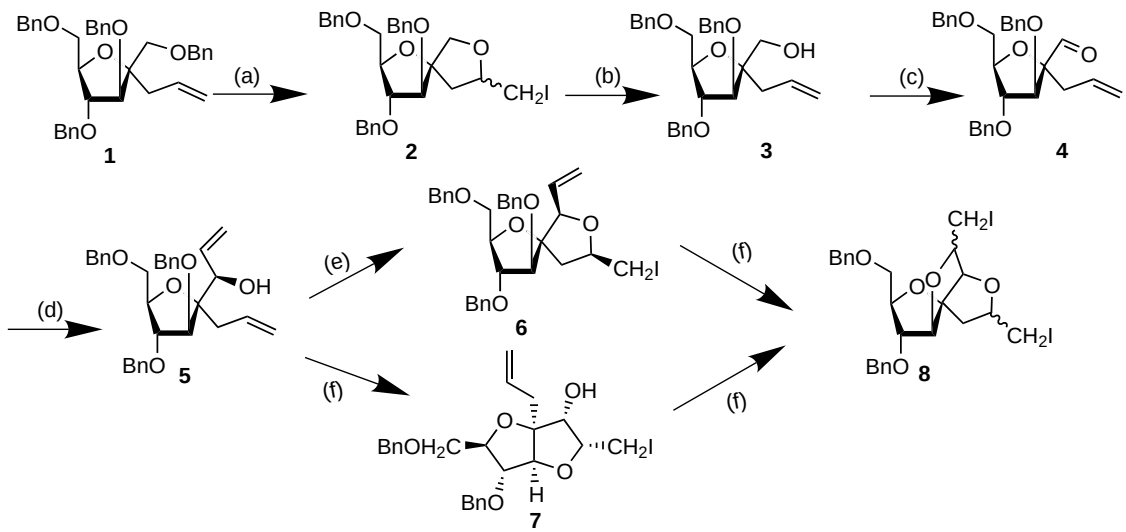
Abstract—Iodocyclisation of polybenzylated allyl α-*C*-fructofuranoside **1** afforded the bicyclic iodoether **2** through debenzylation at C-1; treatment of **2** with zinc and acetic acid restored the allylic group with concomitant deprotection of the hydroxyl group at C-1, which was oxidised to the corresponding aldehyde **4**. Reaction of **4** with vinylmagnesium bromide afforded diene **5**, whose double bonds were reacted regioselectively in order to obtain, upon iodocyclisation under different experimental conditions, bicycles **6** or **7**, or tricycle **8**.

Carbohydrates are of great interest, due to their unique characteristics as polyfunctional molecules which are enantiomerically pure and conformationally rigid. These features make this class of compounds particularly attractive as scaffolds for combinatorial chemistry,[1] and for the design of novel peptidomimetics. For example, carbohydrates have been used as a rigid backbone on which aminoacidic side chains were introduced,[2] or as mimics of peptide loops, such as β-turns, which induce conformational rigidity once included into bioactive peptides.[3]

In this context, we are interested in the synthesis of carbohydrate-derived scaffolds with enhanced conformational rigidity compared to the parent monosaccharide. One possible way to reduce the molecular flexibility is the introduction of a second, and possibly a third ring on the sugar backbone. Towards this aim,



Scheme 1. (a) I_2, dry THF; (b) Zn, AcOH, Et_2O/EtOH 1/1; (c) DMSO/Ac_2O 2/1; (d) vinylmagnesium bromide, dry THF, 0°C; (e) I_2, dry THF; (f) I_2, dry DCM.

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we developed a procedure that allows bi- and tricyclic compounds to be obtained starting from fructose, one of the most abundant natural sugars, which does present interesting features: it possesses two 'arms' on the furanosidic ring, the C-1 and C-6 hydroxymethylene groups, and offers the possibility of inserting an additional appendage at the anomeric centre. These arms can be exploited in the formation of the second and the third ring, and in further functionalisations.

Methyl fructofuranoside was benzylated according to the classical method (NaH, BnBr, DMF, quantitative yield), and an allylic appendage was then introduced at the anomeric position by treatment with allyltrimethylsilane in the presence of boron trifluoride etherate as Lewis acid catalyst[4] (57% yield). The spatial relationship between the double bond and the oxygen at C-1 in the polybenzylated allyl α-*C*-fructoside **1** is such that a 5-*exo* cyclisation/debenzylation can occur upon treatment with I_2 (1.2 equiv.) in THF (Scheme 1). This reaction afforded the spiro-compound **2** (as a mixture of diastereomers) in 98% yield. Treatment of compound **2** with zinc in acetic acid gave derivative **3**, having the C-1 hydroxyl group selectively deprotected and the double bond re-established (80% yield). This selective deprotection was exploited for the introduction of a second double bond which, upon treatment with iodine, gave raise to a further cyclisation.

In more detail (Scheme 1), oxidation of alcohol **3** (DMSO–Ac_2O, 83% yield) afforded the corresponding aldehyde **4**, which reacted stereoselectively with vinylmagnesium bromide (2 equiv., THF) giving the (*R*) allylic alcohol **5** in 75% yield and 98% d.e. (determined by HPLC). The high stereoselectivity of this reaction can be ascribed to the formation of a Cram-chelated intermediate where the magnesium ion coordinates the carbonyl group and the furanosidic oxygen, as depicted in Fig. 1. Attack of the nucleophile is allowed only on the *re* face of the carbonyl group of this intermediate, the benzyloxy group at C-3 preventing the attack on the *si* face.

Compound **5** can be transformed into two different bicyclic structures. If the double bond of the α-allylic substituent is activated by I_2 (1 equiv.) in THF as solvent, a 5-*exo* cyclisation occurs with the unprotected OH derived from the Grignard reaction, affording bicyclic compound **6** (89% yield based on both diastereoisomers, in a 6:1 ratio in favour of isomer **6**, as determined by ^{1}H NMR). When the iodocyclisation is performed with 1 equiv. of iodine in dichloromethane, then the benzyloxy group at C-3 is involved in a 5-*exo* cyclisation with the β-allylic substituent, affording the bicyclic compound **7** (70% yield based on both diastereoisomers, in a 6:1 ratio in favour of isomer **7**, as determined by ^{1}H NMR). It is worth noting that different rigid bicyclic structures can be obtained just by switching the reaction medium. Both these bicyclic compounds **6** and **7** can undergo further iodocyclisation in dichloromethane, affording the tricyclic compound **8** as a mixture of diastereomers (66% yield). The full characterisation of compounds **6** and **7** was performed by ^{1}H NMR and COSY experiments on a 400 MHz spectrometer (Bruker Avance). The absolute configurations of the new stereocentres were determined by NMR NOESY experiments, using *mixing time* values optimised for these bicyclic structures; the analysis of NOE cross peak correlations also allowed the acquirement of fundamental information about the whole conformational arrangement of the bicyclic scaffolds to be acquired. In compound **6** the fructose furan oxygen points upward and the oxygen of the second ring points downwards. In compound **7**, the fructofuranose ring is essentially planar, while in the second ring the furanosidic oxygen is orientated below the plane.

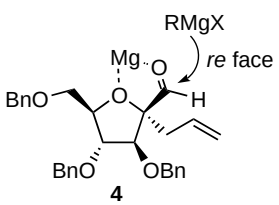

Figure 1.

The formation of the third cycle confirmed the (*R*) stereochemistry of the stereocentre formed at C-1 in the Grignard reaction since only in this diastereomer is the double bond properly orientated for the cyclisation with the benzyloxy group at C-3. The stepwise introduction of two electrophilic functional groups (the iodides), and the presence of two differentiable benzyloxy groups (a primary and a secondary) make this tricyclic scaffold extremely flexible for further elaborations.

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