Towards conformationally-locked difluorosugar analogues: an unexpected sense of dihydroxylation†

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Received (in Cambridge, UK) 31st October 2003, Accepted 3rd December 2003
First published as an Advance Article on the web 5th January 2004

Difluorinated cyclooctenones, synthesised using RCM, can be used as templates for stereoselective oxidative transformations to products that undergo transannular reactions to afford conformationally-locked analogues of 2-deoxy-2,2-difluorosugars with different stereochemical relationships between the C-2 and C-3 hydroxyl groups.

Various tactics exist for the modulation of the reactivity of glycosic bonds, and much knowledge can be gained from the activity. Kirby and co-workers1 used conformationally locked bicyclic acetal 1 to reveal the effect of n-π* orbital interactions during the progression of 1 to the putative oxacarbenium intermediate 2 on the hydrolysis pathway. The stereoelectronic barrier imposed by the bicyclic architecture deactivates 1 by a factor of 1013 relative to 3 which is similarly substituted (Scheme 1).

Purely electronic effects are also important. For example, Withers3 has demonstrated that 2,2-difluoro sugars with very good leaving groups undergo reaction with glycosidases to label an active site nucleophile (an aspartate) with the sugar residue. The stability of the acylal 5 (Scheme 2) is such that a proteolytic digest can be used to prepare degradation fragments suitable for MS–MS sequencing of the glycosidase. Though many glycosidases are encoded on the human genome, the functions of relatively few are understood, so substrates that can be used to reveal structure, and potentially function, are invaluable.

We have an ongoing interest in the synthesis and chemistry of fluorinated sugar analogues4 and we read about the cyclooctanolic analogues of monosaccharides described by Vasella,5 Sinaj,6b Mehta6c and van Boom6d with interest. Having prepared difluorinated cyclooctenones 6a–6c rapidly using metallated difluoroeno derivatives and RCM chemistry,5 we decided to explore their use as model precursors to cycitol and hexose analogues to establish that the cyclooctenones were suitable templates for stereoselective oxidation reactions, and show that transannular reactions would lead to the formation of base-stable bicyclic hemiacetals.

Exposure of 6b to dihydroxylation conditions resulted in a smooth reaction and the formation of a single product (81%) with a sharp 19F NMR spectrum at ambient temperature (the 19F NMR spectrum of 6b is broad) (Scheme 3). Protection as the acetonide (100%), crystallisation and X-ray diffraction analysis revealed that 11b had been formed. We confirmed the presence of 9b after dihydroxylation, by HMBC, finding a clear cross-peak between H-5 and hemiacetal carbon C-1 (δC, 153.4). The equatorial location of the hydroxyl group at C-2 was revealed by the large 1Jrel,H coupling constant (24.1 Hz) with H-3.

The sense of stereoselection in the reaction of 7b is interesting. The crystal structure of 6b reveals that the two available alkene faces are very different; on steric grounds, trans,cis,triol 8b would be the expected product (attack from the more open and convex upper face), but the osmium reagent has attacked from the more crowded concave face. Coordination of the osmium tetroxide to the ketonic carbonyl oxygen and delivery of the reagent to the lower face of the alkene (Fig. 1) must be invoked to explain this outcome,6 which is in marked contrast to the sense of attack expected for a molecule with such a distinct topology.6

![Scheme 1](image1)

Scheme 1 Relative rates for spontaneous hydrolysis: 1, krel 1013; 2, krel (1.0).

![Scheme 2](image2)

Scheme 2 Reaction leading to the inhibition of α-galactosidase (i) from Pseudomonas chlororaphis.

† Electronic supplementary information (ESI) available: ROESY spectrum of 6b at 223 K. See http://www.rsc.org/suppdata/cc/b3/b313813e/
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Fig. 1 Dihydroxylation of racemic cis-diastereoisomer 6b occurs from the less accessible surface of the alkene.
Dihydroxylation of 6c, which exists as a 1 : 1.5 mixture of conformers, afforded a 4 : 1 mixture of diastereoisomers (88% combined yield). The major diastereoisomer was assigned as 10c; it fails to form an acetonide and the $\Delta_{3,4}$ coupling constant is much smaller (11.3 Hz), whereas the minor diastereoisomer was like 9b.

These products arise from an oppose sense of stereoselection in which the upper face carbamoyloxy group may be involved in the delivery of the reagent. The explicit assumption made here is that 6b reacts through the major solution conformer rather than through some especially reactive minor species. We are grateful to a referee for recommending the inclusion of this statement.

Scheme 4 Reagents and conditions: i, 50% NaOH, Bu$_3$NHSO$_4$, Bu$_3$N, allyl bromide, 72 hours, rt, 100%.

Similar, the low temperature ROESY spectrum of 6b contained a clear cross peak between H-3 and H-8 and one of the H-6 methylene protons. Conformational searching using the MMFF94 force field in MacSpartan Pro$^6$ revealed only 3 types of ring conformer. Of these, only the one corresponding to the crystal structure located those three protons within 3 Å. The ketonic carbonyl group is associated with the crowded lower face of the alkene and the angle made between the allylic C–O bond and the alkyl group is such that the conventional model for stereoelectronic control of allylic alcohol dihydroxylation cannot be used to explain the outcome of the reaction.$^7$ The explicit assumption made here is that 6b reacts through the major solution conformer rather than through some especially reactive minor species. We are grateful to a referee for recommending the inclusion of this statement.

Notes and references

$^\dagger$ Crystal data for 11b mp 162–163 °C: $\text{C}_9\text{H}_7\text{F}_2\text{F}_2\text{NO}_5\text{C}_2\text{H}_5$ $M = 393.4$; monoclinic, $a = 14.0963(11), b = 12.8611(10), c = 11.1642(9)$ Å; $\alpha = 90°, \beta = 104.3220(9), \gamma = 90°$; $D = 1.9611(3)$ Å; $T = 150(2)$ K, space group $P2_1/c$, $Z = 4$, $\mu_{MoK\alpha} = 0.111$ mm$^{-1}$, 13865 reflections measured, 3452 unique ($R_{int} = 0.034$) which were used in all calculations: $R_1 = 0.0369$, $wR_2 = 0.0834$. The final $wR(F^2)$ was 0.0887 (all data). CCDC 223552. See http://www.rsc.org/suppdata/cc/b3/31381s1 for crystallographic data in .cif or other electronic format.

$^\ddagger$ It is possible that the solution conformation is very different to that revealed by the X-ray structure$^6$ but we are confident that they are very similar.