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

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Diffuorinated 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 glycosidic bonds, and much knowledge can be gained from the activity of glycosidases, and much knowledge can be gained from the activity of glycosidases. Kirby and co-workers have 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 10^3 relative to 3 which is similarly substituted (Scheme 1).

Purified electronic effects are also important. For example, Withers has demonstrated that 2,2-difluoroglycosides 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 used as templates for stereoselective oxidative transformations, 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 of 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-3 and hemiacetal carbon C-1 (3C, δ). The equatorial location of the hydroxyl group at C-2 was revealed by the large 1JHF 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 7b 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,

Dihydroxylation of racemic cis-distereoisomer 6b occurs from the less accessible surface of the alkalene.

† 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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Scheme 1 Relative rates for spontaneous hydrolysis: 1, krel 10–13; 3, krel (1.0).

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

Scheme 3 Reagents and conditions: i, 2% OsO4, NMO, t-BuOH/acetonate/ water, 0 °C, 48 hours; ii, acetone, Cs2SO4, TEOH, rt, 16 hours. (DEC = CONEi)

Fig. 1 Dihydroxylation of racemic cis-distereoisomer 6b occurs from the less accessible surface of the alkalene.
Dihydroxylation of 6c, which exists as a 1:1.5 mixture of conformers, afforded a 4.5:1 mixture of diastereoisomers (88% combined yield). The major diastereoisomer was assigned as conformers, afforded a 4.5:1 mixture of diastereoisomers (88% monoclinic, wR = 0.0843. The final R = 0.0369, wR2 = 0.0843. The final wR(F2) = 0.0887 (all data). CCDC 223552. See http://www.rcsb.org/pdb/suppdb/cif/6b/cif for crystallographic data in .cif or other electronic format. § Crystal data for 11b mp 162–163 °C: C11H22F2NO6. M = 393.4; monoclinic, α = 14.0963(11), β = 12.8611(10), γ = 11.1642(9) Å; α = 90, β = 104.3220(1), γ = 90°; U = 1961.13(3) Å3; T = 150(2) K, space group P21/c, Z = 4, µMo-Kα = 0.111 mm−1, 13865 reflections measured, 3452 unique (Rint = 0.0344) which were used in all calculations; R1 = 0.0369, wR2 = 0.0843. The final wR(F2) was 0.0887 (all data). CCDC 223552. See http://www.rcsb.org/pdb/suppdb/cif/6b/cif for crystallographic data in .cif or other electronic format. ¶ It is possible that the solution conformation is very different to that revealed by the X-ray structure but we are confident that they are very similar. The low temperature ROESY spectrum of 6b contained a clear cross peak between H-3, H-8 and one of the H-6 methylene protons. Conformational searching using the MMFF94 force field in MacSpartan Pro revealed only 3 types of ring conformer. Of these, the only 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 alkynyl group is such that the conventional model for stereoelectronic control of allylic alcohol dihydroxylation cannot be used to explain the outcome of the reaction.9 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

8 MacSpa rtan Pro, Wavefunction Ltd., Irvine, CA.