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

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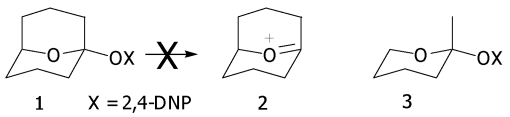
Received (in Cambridge, UK) 31st October 2003, Accepted 3rd December 2003
First published as an Advance Article on the web 5th January 2004

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.

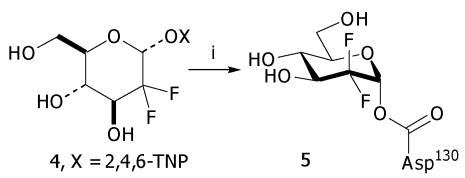
Various tactics exist for the modulation of the reactivity of glycosidic bonds, and much knowledge can be gained from the activity. Kirby and co-workers[1] used conformationally locked bicyclic acetal **1** to reveal the effect of n–σ* orbital interactions during the progression of **1** to the putative oxacarbenium intermediate **2** on the hydrolysis pathway. The stereoelectronic barrier imposed by the bicyclic architecture deactivates **1** by a factor of 10^{13} relative to **3** which is similarly substituted (Scheme 1).

Purely electronic effects are also important. For example, Withers[2] 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 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 analogues[3] and we read about the cyclooctanic analogues of monosaccharides described by Vasella,[4a] Sinaÿ,[4b] Mehta[4c] and van Boom[4d] with interest. Having prepared difluorinated cyclooctenones **6a–6c** rapidly using metallated difluoroenol derivatives and RCM chemistry,[5] we decided to explore their use as model precursors to cyclitol 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.



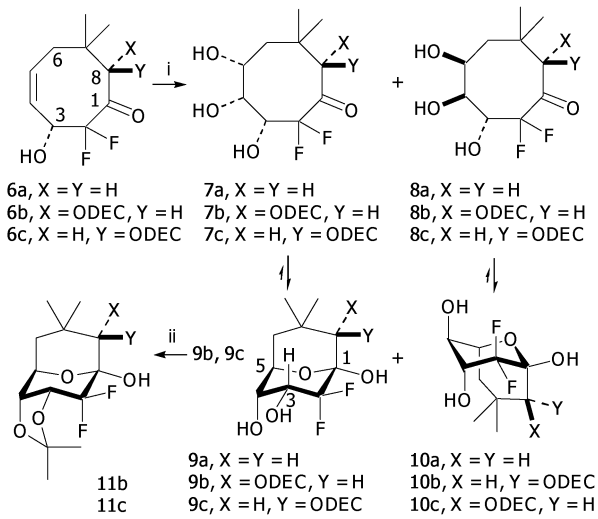
Scheme 1 Relative rates for spontaneous hydrolysis: **1**, k_{rel} 10^{-13}; **3**, k_{rel} (1.0).



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

Exposure of **6b** to dihydroxylation conditions resulted in a smooth reaction and the formation of a single product (81%) with a sharp ^{19}F NMR spectrum at ambient temperature (the ^{19}F 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 ($^3J_{C-H}$). The equatorial location of the hydroxyl group at C-2 was revealed by the large $^3J_{H-F}$ 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.¶



Scheme 3 *Reagents and conditions*: i, 2% OsO_4, NMO, *t*-BuOH/acetone/water, 0 °C, 48 hours; ii, acetone, $CuSO_4$, TsOH, rt, 16 hours. (DEC = $CONEt_2$)

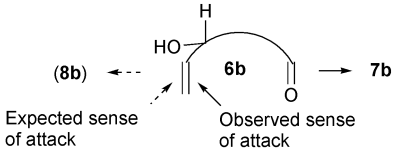


Fig. 1 Dihydroxylation of racemic *cis*-diastereoisomer **6b** occurs from the less accessible surface of the alkene.

† 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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DOI: 10.1039/b313813e

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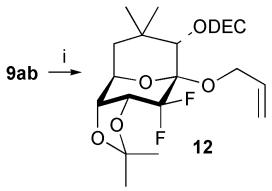

Scheme 4 *Reagents and conditions*: i, 50% NaOH, Bu_4NHSO_4, Bu_4NI, allyl bromide, 72 hours, rt, 100%.

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 **10c**; it fails to form an acetonide and the $^3J_{H-F}$ coupling constant is much smaller (11.3 Hz), whereas the minor diastereoisomer was like **9b**. These products arise from an *opposite* sense of stereoselection in which the upper face carbamoyloxy group may be involved in the delivery of the reagent.[7]

Exposure of **6a** to the osmium reagent produced a 1 : 1 mixture of hemiacetals from **7a** and **8a**; VT NMR shows that **6a** is the most flexible of the three cyclooctenones ($\Delta G^{\ddagger}$ = 11.9 ± 0.2 kcal mol^{-1} *versus* $\Delta G^{\ddagger}$ = 15.1 ± 0.2 kcal mol^{-1} for **6c**, at 223 K). As delivery from an exocyclic group cannot be involved, we propose that ketone-carbonyl group delivery to the more crowded face competes with open-face attack upon a conformer in which the carbonyl group is not available to direct attack. Extensive molecular modelling will be required to support these ideas.

Derivatisation of the hemiacetal hydroxyl group under basic conditions could be complicated by retro-aldol with the expulsion of a difluoroenolate and decomposition under basic conditions. However, we were able to convert **11b** to allyl ether **12**‖ quantitatively under PTC conditions (Scheme 4), confirming that the hemiacetals are stable in basic media.

Understanding the sense of stereoselection in these systems presents a challenge; nevertheless, it is clear that we can prepare sugar-like and stable hemiacetals with considerable potential for further derivatisation, from our cyclooctenones.

We thank the Universities of Birmingham and Leicester, the EPSRC (Project grant GR/K84882) and GSK (studentship to SP) and the University of Leicester and Universities UK (studentship and ORS Award respectively to EU).

Notes and references

§ Crystal data for **11b** mp 162–163 °C: $C_{18}H_{29}F_2NO_6$; M = 393.4; monoclinic, a = 14.0963(11), b = 12.8611(10), c = 11.1642(9) Å; α = 90, β = 104.3220(1), γ = 90°; U = 1961.1(3) Å^3; T = 150(2) K, space group $P2_1/c$, Z = 4, μ(Mo-K$_\alpha$) 0.111 mm^{-1}, 13865 reflections measured, 3452 unique (R_{int} = 0.0344) which were used in all calculations: R_1 = 0.0369, wR_2 = 0.0843. The final $wR(F^2)$ was 0.0887 (all data). CCDC 223552. See http://www.rsc.org/suppdata/cc/b3/b313813e/ 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[6] 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[8] 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 alkenyl 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.

‖ Selected data for **12**; R_f (15% ethyl acetate in light petroleum) 0.27; mp 106–107 °C; (Found C, 58.09; H, 7.73; N, 3.17. $C_{21}H_{33}F_2NO_6$ requires: C, 58.19; H, 7.67; N, 3.23%); ν_{max} (solid)/cm^{-1} 2969m (C–H), 2938m (C–H), 2887m (C–H), 1687s (C=O), 1650m (C=C); δ_H (300 MHz, $CDCl_3$); 5.83 (1H, ddt, J 17.3, 10.5, 5.1, C*H*=CH$_2$), 5.22 (1H, dq, J 17.3, 1.8, =C*H*$_a$H$_b$), 5.01 (1H, dq, J 10.5,1.8, =CH$_a$*H*$_b$), 4.75 (1H, d, $^4J_{H-F}$ 1.2, H-8), 4.61 (1H, ddd, $^3J_{H-F}$ 12.3, 10.5, J 5.4, H-3), 4.53 (1H, br. dd, J 11.5, 4.2, H-5), 4.42 (1H, ddq, ^2J 13.2, J 5.0, ^4J, $^5J_{H-F}$ 1.8, =CHC*H*$_a$H$_b$), 4.33 (1H, ddq, ^2J 13.2, J 5.0, ^4J, $^5J_{H-F}$ 1.8, =CHCH$_a$*H*$_b$), 4.02–3.99 (1H, m, H-4), 3.42–3.12 (4H, m, –NC*H*$_2$), 2.11 (1H, dd, ^2J 14.3, J 11.5, H-6$_{eq}$), 1.50 (3H, s, –CH$_3$), 1.30–1.22 (4H, env., –CH$_3$ and H-6$_{ax}$), 1.17 (3H, s, –CH$_3$), 1.08–1.04 (6H, m, –NCH$_2$C*H*$_3$), 0.88 (3H, s, –CH$_3$); δ_C (75 MHz, $CDCl_3$) 154.0, 134.1, 115.9 (dd, $^1J_{C-F}$ 262.0, 257.3), 115.2, 109.9, 95.0 (dd, $^2J_{C-F}$ 26.3, 19.1), 79.2 (d, $^3J_{C-F}$ 6.8), 73.0 (dd, $^2J_{C-F}$ 23.5, 19.8), 74.0, 66.5, 64.3, 41.2, 40.3, 38.3, 33.7, 28.9, 25.8, 25.7, 22.9, 14.2, 13.4; δ_F (282 MHz, $CDCl_3$) −117.2 (1F, dd, ^2J 246.3, $^3J_{F-H}$ 10.5), −119.5 (1F, dd, ^2J 246.3, $^3J_{F-H}$ 12.3). *Nota bene* the size of the H–F coupling constants. Conversion of triol **9b** to acetal **11b** causes dramatic changes to the $^3J_{H-F}$ values, presumably because formation of the additional ring junction constrains the dihedral angles between H-3 and the CF_2 centre.

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