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Unexpectedly Selective Formation and Reactions of Epoxycyclooctenones under Microwave-Mediated Conditions

John Fawcett, Gerry A. Griffith, Jonathan M. Percy,* and Emi Uneyama

Department of Chemistry, University of Leicester, University Road, Leicester LE1 7RH, United Kingdom

jmp29@le.ac.uk

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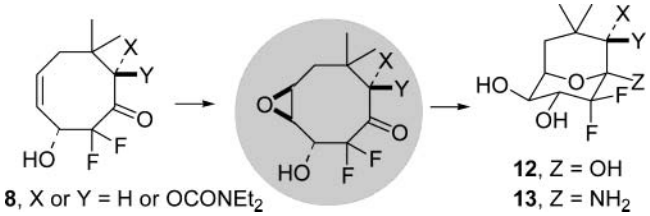
ABSTRACT

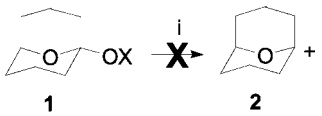


Topologically mobile difluorinated cyclooctenones undergo rapid, high-yielding, and completely stereoselective epoxidations with methyl(trifluoromethyl)dioxirane. The epoxides resist conventional hydrolysis but react smoothly in basic media under microwave irradiation to afford unique hemiacetals and hemiaminals in good yield.

Kirby and co-workers[1] used conformationally locked bicyclic acetals such as **1** to reveal the importance of n−σ* orbital interactions during progression 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 similarly substituted but flexible congeners (Scheme 1).

Scheme 1. Kirby's Stereoelectronically Deactivated Acetal[a]



[a] Conditions: (i) H_2O, Δ.

These seminal results suggest a general method for the design of sugar analogues which are conformationally committed and in which the "glycosidic" bond is unusually stable and is certainly immune to the action of glycosidases and glycosyl transferases. Van Boom,[2] Sinaÿ,[3] Vasella,[4] and more recently, Kirby and co-workers[5] have synthesized analogues **3**−**6** of saccharides which present unusual conformations (Figure 1).

Withers and co-workers[6] have demonstrated the considerable value of 2,2-difluorosugar analogues for glycosidase active-site labeling while Davies and Withers[7] have shown that even a single fluorine atom at C-2 modifies the reactivity of even reactive intermediates on glycosylation pathways so that they can exist for long enough for X-ray structures to be obtained in contact with the enzyme. It occurred to us that species of general type **7** which combine both electronic

* To whom correspondence should be addressed. Fax: +44 116 252 3789. Tel: +44 116 252 2140.

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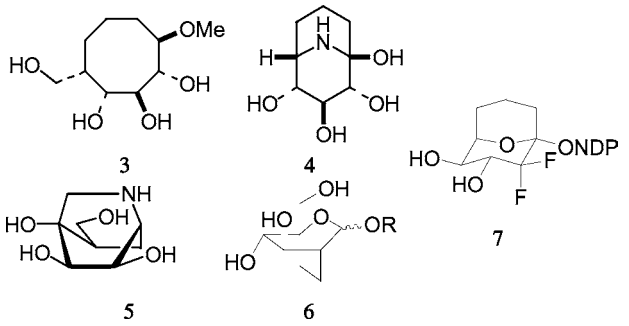


Figure 1. Conformationally restricted analogues of saccharides.

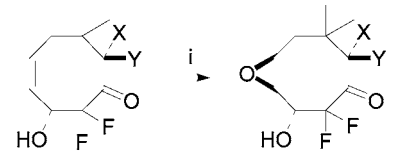
and stereoelectronic attenuation of glycosidic reactivity could therefore be interesting synthetic targets.

Recently, we described[8] routes to model difluorinated cyclooctenones **8a**−**c** based on metalated enol acetal/[2,3]-Wittig[9] or metalated enol carbamate/aldol sequences;[10] both culminated in effective RCM reactions.

We also carried out dihydroxylation reactions and found significant differences between the three model compounds.[11]

Epoxidation reactions were attempted using the excellent method for *in situ* generation of methyl trifluoromethyldioxirane described by Yang.[12] All three model substrates reacted to 100% conversion to deliver crystalline epoxides **9a**−**c** in high yield and as single (racemic) diastereoisomers (Scheme 2) in contrast to the outcomes of the dihydroxylation reactions.

Scheme 2. Epoxidation Reactions of Cyclooctenones[a]



8a, X = Y = H
8b, X = ODEC, Y = H
8c, X = H, Y = ODEC
(DEC = $CONEt_2$)

9a, X = Y = H, 82%
9b, X = ODEC, Y = H, 98%
9c, X = H, Y = ODEC, 90%

[a] Reagents and conditions: (i) F_3CCOCH_3, Oxone, Na_2EDTA, $MeCN/H_2O$, 4 °C.

The epoxides were characterized by X-ray crystallographic analysis in each case.[13] The sense of epoxidation stereoselectivity is interesting. Henbest oxidation (with *m*-CPBA) of cyclooct-2*Z*-en-1-ol delivers the *trans*-epoxy alcohol. This textbook example[14] is rationalized on the basis of the unusual topology of the cyclooctene ring which results in the ability of the "lower face" hydroxyl group to deliver the peracid to the "upper" face of the alkene through the familiar hydrogen bonded mechanism. Intermolecular hydrogen bonding has also been implicated in dioxirane oxidations,[15] especially in nonpolar media. The Yang epoxidation occurs in aqueous acetonitrile so we would be surprised if intermolecular hydrogen bonding was important. Conformational searching (MMFF94 in MacSpartan Pro)[16] revealed a family of conformers.

Duplicate conformers were removed and the geometries were optimized for all typical conformers (AM1//RHF 6-31G*). The three calculated lowest energy conformer types, reoptimized at the RHF 6-31G**, are shown for **8a** (Figure 2).

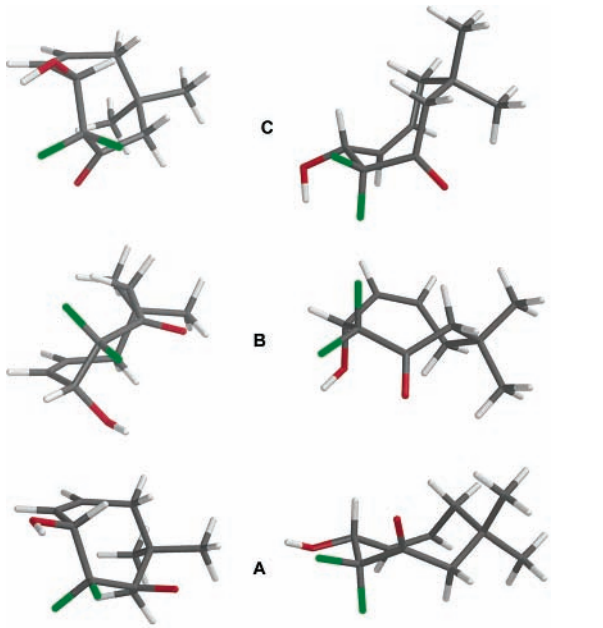


Figure 2. Calculated lowest energy conformers of **8a**; only **A** and **C** are admissable on the basis of the observed $^3J_{H-F}$ coupling constants.

Of the three types, only **A** and **C** are consistent with the observed $^3J_{H-F}$ coupling constants measured in the VT ^{19}F NMR spectrum at 223 K (ca. 26 and 20 Hz), respectively. Conformer **B** features the adjacent methine proton bisecting the F−C−F angle, an arrangement unlikely to give rise to coupling constants greater than or equal to 20 Hz. Dioxirane attack from the least hindered face of **A** or **C** or hydrogen-bonded delivery results in the observed outcome, though the

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(16) MacSpartan Pro, Wavefunction, Inc.

H−C−C−O dihedral angles in **A** and **C** are very different to the angle (130°) proposed by Adam and co-workers[17] to rationalize examples of acyclic stereocontrol (Table 1).

Table 1. Dihedral Angles for the Three Conformers **A**−**C**

conformer	relative energy (kcal mol^{-1})	H−C−C−F dihedral (deg)	H−C−C−O dihedral (deg)
A	(0.00)	174.5	−16.4
B	0.53	60.7	129.8
C	1.64	163.9	−33.6

Indeed, it is very difficult to see how the dioxirane can get close enough to the alkene within a hydrogen-bonded complex. Conformer **B** has a better H−C−C−O dihedral angle (129.8°) but cannot play a part in the reaction because both topological control *and* delivery would afford the *cis*-product unambiguously.

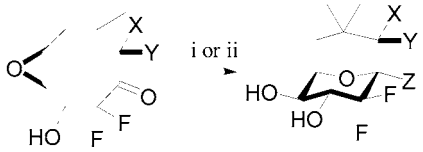
The epoxides proved remarkably resistant to hydrolysis under a range of conventional conditions in the presence of Brønsted and water-stable Lewis acids.

We anticipated that each epoxide would be protonated and then undergo solvolysis with relief of strain to release a hydroxyl group which would "reach" transannularly for the ketonic carbonyl group, with further relief of strain.

Even the presence of HFIP in the reaction medium[18] had no effect upon the rate of disappearance of starting material; in all cases, we were able to recover the epoxides unchanged after long reaction times.

Starting materials were consumed only when we exposed basic aqueous solutions of **9a**−**c** to coherent microwave irradiation (CEM Discover). Rapid reactions led to the formation of **10a**−**c** (concentrated ammonia solution) and **11a**−**c** (aqueous *N*-methylimidazole) (Scheme 3).

Scheme 3. Microwave-Mediated Epoxide Solvolysis Reactions[a]



9a, X = Y = H
9b, X = ODEC, Y = H
9c, X = H, Y = ODEC

(DEC = $CONEt_2$)

10a, X = Y = H, Z = NH_2, 60%
10b, X = ODEC, Y = H, Z = NH_2, 70%
10c, X = H, Y = ODEC, Z = NH_2, 78%
11a, X = Y = H, Z = OH, 71%
11b, X = ODEC, Y = H, Z = OH, 75%
11c, X = H, Y = ODEC, Z = OH, 72%

[a] Reagents and conditions: (i) NH_3 (aq) or (ii) 10% *N*-methylimidazole (aq), both 30W μW, 100 °C, 10 min.

X-ray structures were obtained for representative educts **10c** and **11a** (Figure 3).

The formation of **10a**−**c** arises from attack of ammonia on the ketonic carbonyl group, followed by transannular ring opening of the epoxide; however, the highly selective outcome was most unexpected. Ring-flipping of the cyclooctenone is likely to be very active under the microwave conditions, and ammonia is a small nucleophile, so it seems unlikely that any selectivity is expressed in the formation of the first hemiaminal. Thermodynamically, the formation of a new C−O bond is more favorable than the formation of a C−N bond, but this type of preference would only exert (thermodynamic) control over the outcome of a reversible reaction; it is very hard to see how the transannular reaction with strain-relieving opening of an epoxide could be reversible. Instead, we believe that the key species in the reaction is **12**, the conjugate base of the hemiaminal formed by "open-face" attack of the nucleophile on the cyclooctenone (Scheme 4). This species is presumably formed reversibly; diastereoisomer **13** cannot present a nucleophilic alkoxide on the closed face where approach along the back projection of the epoxide C−O bond can occur. Instead, the reaction channels through **12** which allows a stereoelectronically favorable

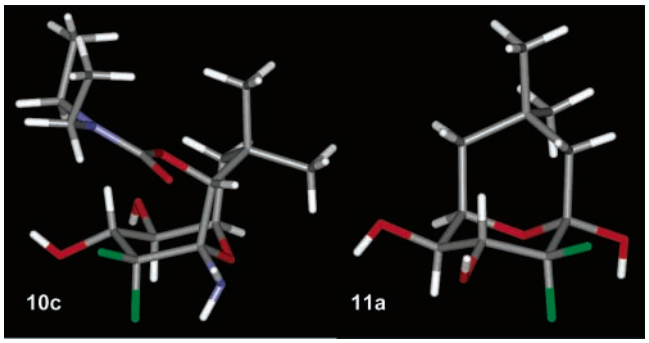
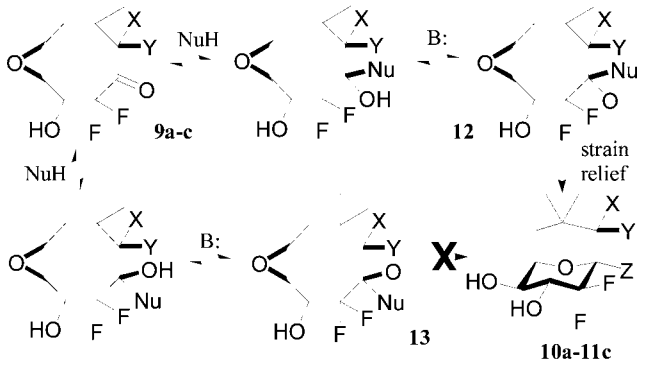


Figure 3. X-ray structures for **10c** and **11a**.

Scheme 4. Proposed Mechanism for Microwave-Mediated Transannular Epoxide Solvolytic Ring Opening



NuH = H_2O or NH_3; B: = NH_3 or *N*-methylimidazole

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approach by the nucleophile. A neutral amino group appears not to be sufficiently nucleophilic to trigger epoxide opening or **13** (Nu = NH_2) would be capable of progressing to an azabicyclic product. Other nitrogen nucleophiles failed to trigger the reaction; we were unable to consume starting material when **9a**−**c** was microwaved in the presence of sodium azide or aqueous imidazole.

However, **9a**−**c** reacted with an aqueous solution (10%) of *N*-methylimidazole to afford **11a**−**c** in good yield, presumably (given the stereochemical outcome) via initial general base catalyzed attack of water upon the ketonic carbonyl group. Attempts to reproduce the result in aqueous sodium hydroxide solution with microwave irradiation led to much poorer conversion of starting material. Strain-relieving retroaldol ring opening to release a difluoroenolate, leading to decomposition, is a significant possible side reaction under stronger base conditions, once the alkoxide is formed under the higher pH conditions.[10]

Current work seeks to establish useful subsequent reactions of **10** and **11**, to discover conditions under which a wider set of nucleophiles can be added to the ketonic carbonyl group.

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Supporting Information Available: Experimental procedures, characterization, and crystal structure data (CIF) for **9b**, **10c**, and **11a** and calculation procedures, conformers, energies, and Cartesian coordinates for **8a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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