# Stereoselective Intramolecular Oxime Olefin Cycloadditions Involving Carbohydrate Derived Precursors

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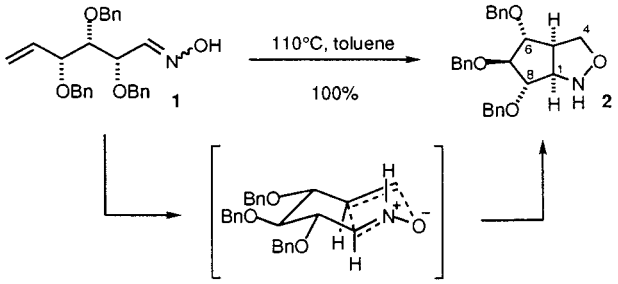
**Abstract:** Intramolecular oxime olefin cycloaddition reactions of carbohydrate derived precursors can be used to prepare highly functionalised 3-oxa-2-azabicyclo[3.3.0]hexanes with good to excellent levels of stereocontrol.

In 1970, the first example of an intramolecular oxime olefin cycloaddition (IOOC) reaction was reported by Oppolzer and Keller.[1] Further examples of IOOC reactions have been reported by the groups of Wildman,[2] Grigg,[3] Heathcock,[4] Hassner,[5] among others.[6] As part of a programme directed towards the synthesis of novel glycosidase inhibitors, we wished to determine whether IOOC reactions of carbohydrate derived precursors could be used to construct highly functionalised 3-oxa-2-azabicyclo[3.3.0]hexanes.[7] Furthermore, while some of the previous work indicated that good levels of stereocontrol can be accomplished in relatively simple IOOC reactions, it was unclear at the outset of our studies whether good, predictable levels of stereocontrol could be accomplished in more complex systems. In this letter, we describe a series of stereoselective IOOC reactions using carbohydrate derived precursors and provide some insight into the factors which control the stereochemical outcome of these reactions.

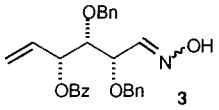
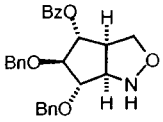
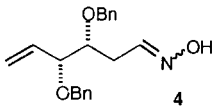
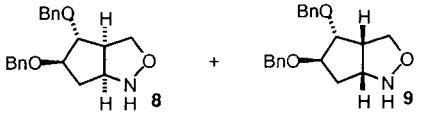
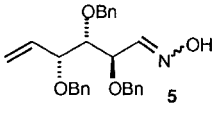
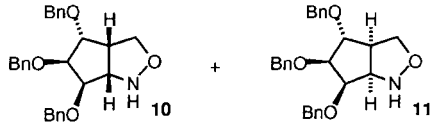
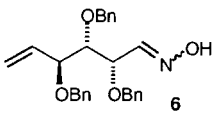
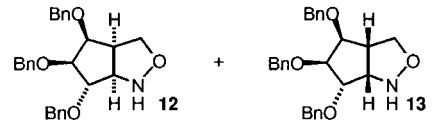
Our initial studies were conducted with oxime **1**, which was prepared in 6 steps from methyl α-D-glucopyranoside using a Vasella fragmentation as the key step.[7a,b] To our delight, thermolysis of this oxime in refluxing toluene for 15 hours produced bicycle **2** in quantitative yield as essentially a single stereoisomer as judged by NMR spectroscopy (Scheme 1).[8,9] Similar results were obtained using either pure (*E*)-**1** or a mixture of (*E*)-**1** and (*Z*)-**1**. The *cis* ring junction and relative stereochemical relationships within bicycle **2** were established using selective nOe difference measurements.[9] To account for the observed stereochemical outcome of this reaction, we suggest that after initial 1,2-prototropic shift, the cycloaddition proceeds with the oxime and olefin components in *exo* orientations and the benzyl ethers orientated in *pseudo* equatorial positions about the forming 5-membered ring.




**Scheme 1**

To test the generality of this reaction, and to probe the remarkable stereospecificity of this cycloaddition, we have undertaken several other related reactions using other oxime precursors (see Table 1). Oximes **3**-**6**, derived from D-glucose, D-glucal, D-mannose and D-galactose respectively, all undergo intramolecular oxime olefin cycloadditions in good yields. Benzoate protected oxime **3** yielded cycloadduct **7** as the sole product (Table 1, Entry 1). In the other cases, two stereoisomeric cycloadducts were produced in varying proportions depending on the precise structure of the oxime substrate (Table 1, Entries 2-4). With the exception of 2-deoxyglucose series (Table 1, Entry 2), the stereochemistry of the products was elucidated using nOe difference measurements.

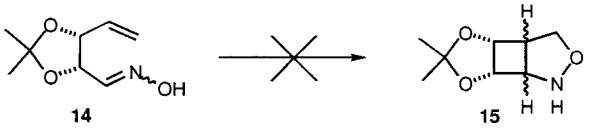
**Table 1**

| Entry | Oxime Precursor | Cycloaddition Product(s) | Yield | Diastereomeric Ratio¶ |
|---|---|---|---|---|
| 1 |  **3** |  **7** | 74% | n/a |
| 2 |  **4** |  **8** + **9** | 70% | 2 : 1§ |
| 3 |  **5** |  **10** + **11** | 84% | 4 : 1 (**10**:**11**) |
| 4 |  **6** |  **12** + **13** | 83% | 6 : 1 (**12**:**13**) |

All cycloadditon reactions were performed in refluxing toluene (15-60 h) and monitored by tlc. ¶Diastereomeric ratios were determined by $^1$H NMR analysis, (Entries 1 & 2) or by separation of the diastereomeric adducts by column chromatography (Entries 3 & 4). § Stereochemistry of major adduct could not be determined

From these results, it would appear that the stereogenic centre adjacent to the oxime carbon atom on the linking tether exerts the greatest influence on the stereochemical outcome of these reactions. In major cycloadducts **2**, **7**, **10** and **12**, this ether substituent is positioned in an *exo* orientation relative to the bicyclic ring. Further evidence in support of the importance of this substituent is provided by the observation that low stereoselectivity is observed in the reaction of oxime **4** which only possesses a methylene group next to the oxime carbon atom. These findings parallel observations made concerning intramolecular nitrone olefin cycloadditions.[10]

Preliminary attempts to use this chemistry for the construction of functionalised cyclobutanes has proven unsuccessful. Thermolysis of oxime **14** (prepared in 5 steps from D-ribose) in refluxing toluene, failed to produce cyclobutane **15** and only unreacted oxime was returned in high yield. Attempts to facilitate the cycloaddition by the use of higher boiling solvents (xylene or 1,2-dichlorobenzene) were unsuccessful.




**Scheme 2**

In summary, we have demonstrated that intramolecular oxime olefin cycloaddition reactions of carbohydrate derived precursors can be used to prepare highly functionalised 3-oxa-2-azabicyclo[3.3.0]hexanes with good to excellent levels of stereocontrol. We believe that this chemistry will provide an expedient entry into a variety of highly functionalised cyclopentanoids,[7a] and work to exploit these findings are ongoing.

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**References and Notes**

(1) Oppolzer, W.; Keller, K. *Tetrahedron Lett.*, **1970**, 1117.

(2) Slabaugh, M.R.; Wildman, W.C. *J. Org. Chem.*, **1971**, *36*, 3202.

(3) (a) Grigg, R.; Thianpantangul, S. *J. Chem. Soc., Perkin Trans. 1*, **1984**, 653; (b) Grigg, R.; Markandu, J.; Perrior, T.; Surendrakumar, S.; Warnock, W.J. *Tetrahedron Lett.*, **1990**, *31*, 559; (c) Grigg, R.; Heaney, F.; Markandu, J.; Surendrakumar, S.; Thornton-Pett, M.; Warnock, W.J. *Tetrahedron*, **1991**, *47*, 4007.

(4) Norman, M.H.; Heathcock, C.H. *J. Org. Chem.*, **1987**, *52*, 226.

(5) (a) Padwa, A.; Chiacchio, U.; Dean, D.C.; Schoffstall, A.M.; Hassner, A.; Murthy, K.S.K. *Tetrahedron Lett.*, **1988**, *29*, 4169; (b) Hassner, A.; Maurya, R.; Mesko, E. *Tetrahedron Lett.*, **1988**, *29*, 5313; (c) Hassner, A.; Maurya, R. *Tetrahedron Lett.*, **1989**, *30*, 2289; (d) Hassner, A.; Maurya, R. *Tetrahedron Lett.*, **1989**, *30*, 5803; (e) Hassner, A.; Maurya, R.; Padwa, A.; Bullock, W.H. *J. Org. Chem.*, **1991**, *56*, 2775; (f) Hassner, A.; Maurya, R.; Padwa, A.; Bullock, W.H. *J. Org. Chem.*, **1991**, *56*, 2775; (g) Hassner, A.; Maurya, R.; Friedman, O.; Gottlieb, H.E.; Padwa, A.; Austin, D. ; *J. Org. Chem.*, **1993**, *58*, 4539.

(6) (a) Arnone, A.; Cavicchioli, M.; Donadelli, A.; Resnati, G. *Tetrahedron: Asymmetry*, **1994**, *5*, 1019; (b) Baskaran, S.; Aurich, H.G., *Synlett*, **1998**, 277.

(7) Intramolecular nitrone cycloadditions of carbohydrate derived precursors have been described, see (a) Bernet, B.; Vasella, A.; *Helv. Chim. Acta*, **1979**, *62*, 1990; (b) Bernet, B.; Vasella, A.; *Helv. Chim. Acta*, **1979**, *62*, 2400; (c) Ferrier, R.J.; Furneaux, R.H.; Prasit, P.; Tyler, P.C.; Brown, K.L.; Gainsford, G.J.; Diehl, J.W. ; *J. Chem. Soc., Perkin Trans. 1*, **1983**, 1621.

(8) All new compounds have been fully characterised using standard spectroscopic and analytical techniques.

(9) ***Typical procedure:*** A stirred solution of oxime **1** (87 mg, 0.20 mmol) in dry toluene (3 ml) under nitrogen was heated at reflux overnight. On cooling, the solvent was removed *in vacuo* to give **2** as a white solid (87 mg, 100%); m.p. 108°C (recrystallised from ether/hexane); $[\alpha]_D$ -3° (*c* 0.93, $CHCl_3$); Found: C 75.16; H 6.72; N 3.22% Calc. for $C_{27}H_{29}NO_4$: C 75.15; H 6.77; N 3.24%; Observed ($M^+$): 431.2103; $C_{27}H_{29}NO_4$ requires 431.2097; $\nu_{max}$ (KBr) 3206, 3028, 2874, 1497, 1453, 1360, 1117, 1094, 1069, 1029 $cm^{-1}$; $\delta_H$ (400 MHz, $C_6D_6$) 2.49 (1H, m, H-5), 2.87 (1H, m, H-4), 3.35 (1H, dd, 10.0, 6.5 Hz, H-1), 3.65 (1H, d, 8.5 Hz, H-4), 3.70 (1H, t, 8.0 Hz, H-6), 4.00 (1H, dd, 8.0, 6.5 Hz, H-8), 4.07 (1H, t, 8.0 Hz, H-7), 4.47 (1H, d, 12.0 Hz, PhCH), 4.52 (1H, bs, NH), 4.59 (1H, d, 12.0 Hz, PhCH), 4.76 (1H, d, 12.0 Hz, PhCH), 4.88 (1H, d, 12.0 Hz, PhCH), 4.90 (1H, d, 12.0 Hz, PhCH), 4.99 (1H, d, 12.0 Hz, PhCH), 7.12-7.46 (15H, m, Ph); $\delta_C$ (100 MHz, $C_6D_6$) 49.8 (C-5), 66.5 (C-1), 71.9 ($CH_2$), 72.1 ($CH_2$), 72.4 ($CH_2$), 75.4 (C-4), 85.3 (C-6), 86.1 (C-7 & C-8), 127.3 (CH), 127.4 (CH), 127.55 (CH), 127.63 (CH), 127.68 (CH), 127.74 (CH), 128.24 (CH), 128.27 (CH), 128.33 (CH), 138.9 (C), 139.1 (C), 139.3 (C). Selected nOe data: irradiation of H-1 enhances H-5 (9.6%), H-7 (2.8%), H-8 (2.0%) and NH (5.0%); irradiation of H-5 enhances H-1 (9.4%) and H-4 (3.1%).

(10) For a discussion and leading reference, see reference 6a.