Novel Routes to the Kainates: Stereoselectivity in Addition Reactions to Pyrrole [1,2*c*]-oxazol-3-one

A. J. Murray, P. J. Parsons,* E. S. Greenwood, E. M. E. Viseux

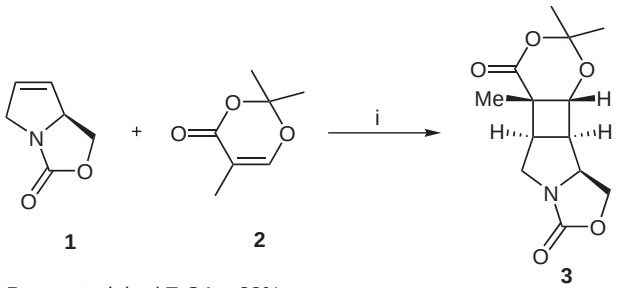
Department of Chemistry, University of Sussex, Falmer, Brighton, East Sussex, BN1 9QJ, UK
E-mail: P.J.Parsons@sussex.ac.uk

Received 20 February 2004

Abstract: This paper describes the addition of a range of electrophiles to **1**. An unusual and unpredicted stereochemistry of addition has been observed in line with our original photochemical observations.

Key words: electrophilic attack, photochemical addition, kainates, oxazolidinone, *ab initio* calculations, molecular modelling

We have been involved in the synthesis of kainic acid and the family of excitatory amino acids.[1] We recently reported that the photochemical addition of the oxazolidine **1** to the enone **2** resulted in the formation of the cyclobutane **3** with unexpected stereochemical outcome (Scheme 1).

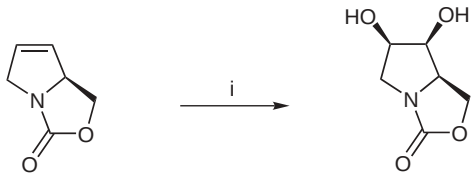


1 **2** **3**

Reagents: i. hν / EtOAc, 38%.

Scheme 1

A recent paper by Pyne and co-workers has described the dihydroxylation of alkene **1** in which they also observed the unexpected diol **4** (Scheme 2).[2]



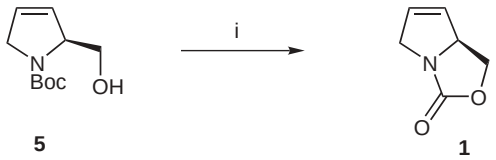
1 **4**

Reagents: i. OsO_4 (cat.), NMO, $(CH_3)_2CO/H_2O$, 7 h, 83%.

Scheme 2

We have also observed this apparent reversal of selectivity in hydroxylation reactions[3] and we now wish to report on our other findings in this area together with molecular modelling studies for the facial selectivity observed.

The oxazolidine **1**[4] was synthesised from the alcohol **5** (Scheme 3).[5]



5 **1**

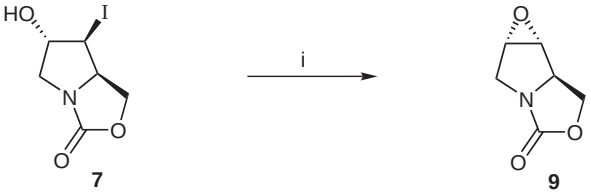
Reagents: i. Et_2NSF_3, CH_2Cl_2, 75%.

Scheme 3

The enantiomerically pure oxazolidine **1** was reacted with a series of electrophilic reagents and other activated reagents to give products with unexpected stereochemistry (Table 1).

Of note, the approach of electrophiles on alkene **1** in all entries is directed on the *endo* face. The observed regiochemistry and diastereoselectivity of the nucleophilic attack of hydroxide or chloride nucleophiles on the activated iodonium and episulfonium ionic intermediates in entries 4 and 5 suggest that the reaction proceeds under steric control, with delivery made on the least hindered carbon.

Treatment of the iodohydrin **7** with base gave the enantiomerically pure epoxide **9** (Scheme 4).



7 **9**

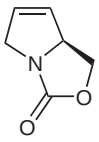
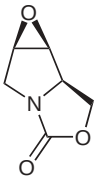
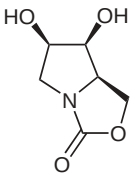
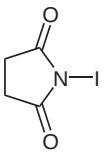
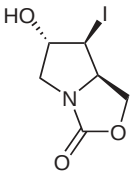
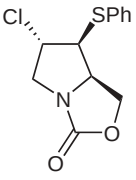
Reagents: i. KOH, EtOAc, 45%.

Scheme 4

Hadjiarapoglou previously reported on the stereoselectivity of the epoxidation of alkenes by DMDO. It was proposed that hydrogen bonding between the dioxirane and the substrate (Figure 1) accounted for the observed facial selectivity.[7] However, stabilisation of the transition state

SYNLETT 2004, No. 9, pp 1589–1591
Advanced online publication: 29.06.2004
DOI: 10.1055/s-2004-829076; Art ID: D04504ST

Table 1 Reaction of **1** with a Series of Electrophilic Reagents

Entry	Starting material	Reagent	Product	Yield
1	 **1**	*m*-CPBA		33%
2	**1**	DMDO[6]	**6**	80%
3	**1**	OsO_4	 **4**	83%
4	**1**		 **7**	60%
5	**1**	PhSCl	 **8**	65%

could not account for the facial discrimination observed on our system, as this would lead to an approach of the β-face leading to epoxide **9**. Pyne discordantly invokes a stereoelectronic shielding of pseudo-axial protons H5β and H7α, favouring the *endo* selectivity.[2]

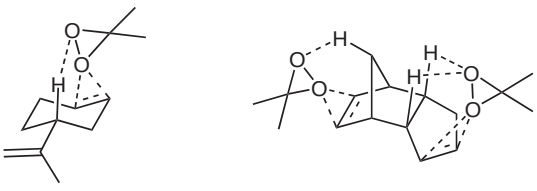


Figure 1 Hadjiarapoglou's proposed transition state for the epoxidation of cyclic alkenes

A quantitative theoretical characterisation of the origin of the complete diastereoselection of both the electrophilic dihydroxylation and the electrophilic epoxidation of the alkene **1** was accomplished by locating the most stable conformer by molecular mechanics conformational searching and *ab initio* studies at the 6-31G* level. Figure 2 shows plots of the preferred conformation (as calculated with MM+ set) and molecular orbitals of the most stable conformer using the 6-31G* polarisation basis set. Of note, the model predicts that the lone pair of electrons of the nitrogen atom in the oxazolidinone ring is out of conjugation with the carbonyl functionality. Indeed, the observed IR stretch frequency of the C=O bond is at the higher end (1751 cm^{-1}) for an *N*-alkyl substituted oxazolidinone. The HOMO reveals an unsymmetrical π bond with a higher electronic density on the *endo* face of the bicyclic system, partially accounting for the exceptional *endo* diastereoselectivity of the electrophilic attack of DMDO and osmium tetroxide observed on our system. Though Furstoss observed *endo* approach of the π-system on the lactone analogue **10** (Figure 3),[8] only partial selectivity was observed. This electrophilic attack of the cyclopentene cannot be rationalised from hyperconjugative electron release from an axial hydrogen atom (the Cieplak effect),[9] as there is no activation by a neighbouring carbonyl group. Once again, the stabilising effect by hydrogen bonding postulated by Hadjiarapoglou does not explain the observed *endo* selectivity in the case of the lactone analogue.

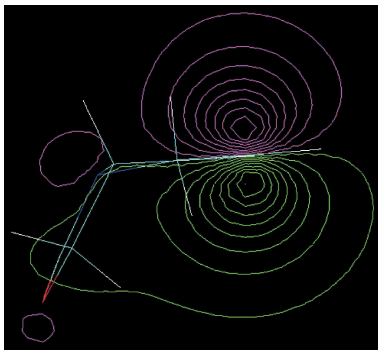
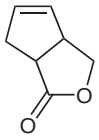


Figure 2 6-31G* representation of the HOMO of oxazolidinone **1**



10

Figure 3

Interestingly, it was noticed when modelling the lactone analogue that the pseudoaxial protons exert a different shielding effect on the convex face of the alkene to the one in our oxazolidinone. Indeed, the replacement of a nitrogen atom by a carbon atom has a tremendous impact on the conformation of the bicyclic system. The access to the concave face of the lactone is therefore much more restricted, due to a more folded butterfly shape. These observations could account for the lower facial selectivity of the epoxidation of the lactone (Figure 4).

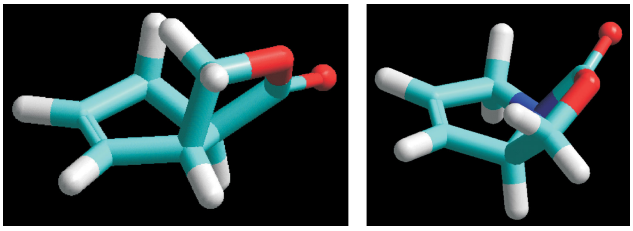
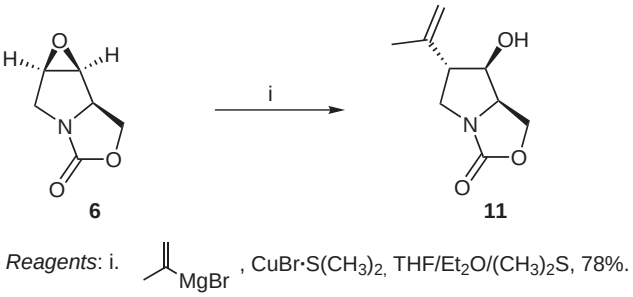


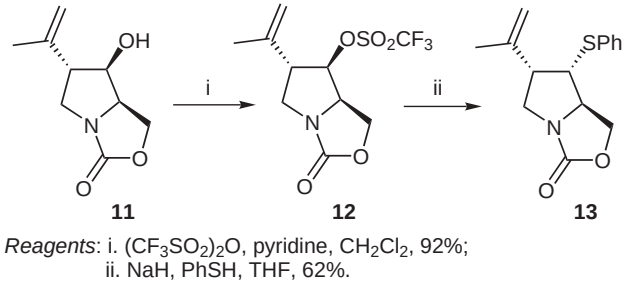
Figure 4 MM+ representations of the lactone analogue **10** (left) and oxazolidinone **1** (right)

With the epoxide **6** in hand, we next studied the addition of nucleophiles to it in order to prepare kainate analogues. Addition of isopropenylmagnesium bromide to **6** in the presence of cuprous bromide dimethyl sulfide complex gave the alcohol **11** as the major product (Scheme 5).[10]



Scheme 5

The chemistry shown in Scheme 5 is very pleasing as it allows a facile entry into the kainate ring system. The alcohol **11** was converted into its triflate ester **12**. Displacement of the triflate group in **12** with thiophenol in the presence of base gave the oxazolidinone **13** (Scheme 6).



Scheme 6

Application of the chemistry described in Scheme 6 to the total synthesis of kainic acid and its analogues will be reported in the near future.

Acknowledgement

We thank the EPSRC, the Royal Commission for the Exhibition of 1851 and Tocris Cookson Ltd for grants. We wish to thank Dr. A. G. Avent and Dr. A. K. Sada for performing NMR and mass spectroscopy experiments. We thank Dr. C. Penkett for very useful discussions.

References

(1) Greenwood, E. S.; Parsons, P. J. *Tetrahedron* **2003**, *18*, 3307.
(2) Davis, A. S.; Gates, N. J.; Lindsay, K. B.; Tang, M.; Pyne, S. G. *Synlett* **2004**, 49.
(3) Murray, A. *Third Year Report*; University of Sussex: UK, **2002**.
(4) Greenwood, E. S. *D. Phil Thesis*; University of Sussex: UK, **2001**.
(5) (a) Schumacher, K. K.; Jiang, J.; Joullie, M. M. *Tetrahedron: Asymmetry* **1998**, *9*, 47. (b) Abraham, D. J.; Mokotoff, M.; Sheh, L.; Simmons, J. C. *J. Med. Chem.* **1983**, *26*, 549. (c) Zhao, H.; Thurkauf, A. *Synlett* **1999**, 1280.
(6) **Typical Experimental Procedure**:[11]
(5*R*,6*S*,7*R*)-1-aza-3-oxa-6,7-epoxybicyclo[3,3,*0*]-octan-2-one (6).
To a stirred solution of oxazolidinone **1** (4.00 g, 32 mmol) in dimethoxymethane (130 mL) and MeCN (260 mL) were added tetrabutylammonium hydrogen sulfate (0.43 g, 1.28 mmol), acetone (71 mL, 960 mmol) and K_2CO_3 (0.1 M in water, 64 mL). A solution of EDTA (4×10^{-4} M in water, 341 mL) acidified with enough HOAc to dissolve the insoluble solid was added to oxone® (78.7 g, 992 mmol). The resulting solution and a solution of K_2CO_3 (87.2 g, 631.5 mmol) in water (341 mL) were concomitantly added to the initial solution of oxazoline **1** over 5 h. The reaction mixture was then extracted with EtOAc (3×100 mL) and washed with brine (100 mL) and water (100 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The resulting oil was purified by flash column chromatography (60% EtOAc–petroleum ether) to give epoxide **6** as a white crystalline solid (3.60 g, 80%); mp (uncorrected) 60–63 °C; $[\alpha]^{23}_D$ –8.6 (*c* = 1.91, $CHCl_3$). IR (film): 3059, 2922, 1748 (s), 1410 (s), 1199, 1075 (s) cm^{-1}. ^1H NMR (500 MHz, C_6D_6): δ = 3.95 (dd, *J* = 8.7, 3.6 Hz, 1 H), 3.87 (apparent t, *J* = 8.7 Hz, 1 H), 3.80 (d, *J* = 13.2 Hz, 1 H), 3.08 (dd, *J* = 8.7, 3.6 Hz, 1 H), 2.97 (d, *J* = 2.8 Hz, 1 H), 2.91 (d, *J* = 2.8 Hz, 1 H), 2.50 (d, *J* = 13.2 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.2, 64.5, 58.4, 55.7, 55.5, 48.9. HRMS: *m*/*z* [M^+] calcd for $C_6H_7NO_3$: 141.0426; found: 141.0420.
(7) Asouti, A.; Hadjiarapoglou, L. P. *Synlett* **2001**, 1847.
(8) Andrau, L.; Lebreton, J.; Viazzo, P.; Alphand, V.; Furstoss, R. *Tetrahedron Lett.* **1997**, *38*, 825.
(9) (a) Cieplak, A. S. *J. Am. Chem. Soc.* **1981**, *103*, 4540. (b) Katagiri, N.; Ito, Y.; Kitano, K.; Toyota, A.; Kaneko, C. *Chem. Pharm. Bull.* **1994**, *42*, 2653. (c) Mahmodian, M.; Baines, B. S.; Dawson, M. J.; Lawrence, G. C. *Enzyme Microb. Technol.* **1992**, *14*, 911.
(10) The addition of 2-propenylmagnesium bromide in the presence of Cu(I) gave a 6:1 mixture of regioisomers in favour of desired alcohol **10** as determined by high field NMR (500 MHz).
(11) Modification of the procedure described in: Shi, Y.; Whang, Z.; Froha, M. *J. Org. Chem.* **1998**, *63*, 6425.