Tetrahedron Letters,Vol.30,No.11,pp 1309-1310,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

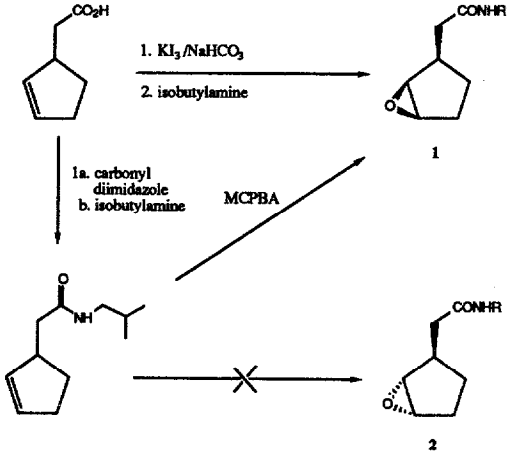
CARBONYL DIRECTED EPOXIDATION IN γ,δ-UNSATURATED ACID DERIVATIVES

Fariborz Mohamadi* and Michael M. Spees
Lilly Research Laboratories
Eli Lilly and Company
Indianapolis, Indiana 46285

Abstract: The epoxidation of cyclopent-2-ene and cyclohex-2-ene acetic acid derivatives with MCPBA provided predominately the syn epoxide.

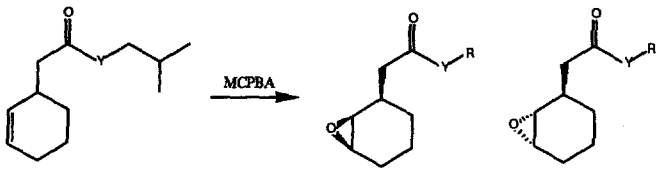
As part of a program directed towards the discovery and development of novel protease inhibitors,[1] our laboratory examined the synthesis of vicinal aminoalcohols derived from the hydrogenation of ß-azidoalcohols obtained from the ammonium azide mediated opening of epoxides. In an attempt to synthesize both diastereomeric epoxides we discovered a stereochemical anomaly that we report in this paper.[2] Epoxidation of the isobutyl cyclopent-2-ene acetamide with *m*-chloro-perbenzoic acid (MCPBA) provided predominately (>20:1 by NMR) a single diastereomeric epoxide (1). The stereochemistry of the epoxidation was confirmed by the iodolactonization of the cyclopent-2-ene acetic acid followed by aminolysis of the lactone in isobutylamine to provide the intermediate iodohydrin which undergoes dehydroiodination to form epoxide 1 in 70% overall yield.

We found it suprising that the allylic substituent did not force the MCPBA epoxidation to form diastereomeric epoxide 2. If a hydrogen bond is formed between the amide and the peracid, it would explain the stereochemical outcome of the epoxidation. To test this hypothesis, the isosteric ester analog of the amide (isobutyl cyclopent-2-ene acetate) was reacted with MCBPA and we found the ester also directs the epoxidation.[3] The lower stereoselectivity is consistent with a decrease in the basicity of the oxygen of an ester with respect to the corresponding amide.

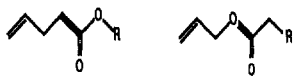


To elucidate the conformational influence of the cyclopentene ring in this process the epoxidation of the isobutylamide and isobutyl ester of cyclohex-2-ene acetic acid was carried out. As illustrated in Scheme I we discovered both the amide and the ester (although to a lesser extent) deliver MCPBA to the syn face of the carbocyclic alkene.[4]

SCHEME I



In methylene chloride the assumed hydrogen bond formed between MCPBA and the oxygen of the alkene seems to override any steric hindrance that would favor formation of the anti diastereomer.[5] Although the ring size of the transition state for the carbonyl directed epoxidation of γ,δ-unsaturated cyclic acid derivatives is the same as that of the allylic alcohol and amine derivatives, it is surprising that replacement of a bond with 3-fold for a bond of 2-fold barrier of rotation (bond highlighted below) has little consequence on the stereochemical outcome of this reaction.



---

[1] For examples of protease inhibitors with acylated vicinal aminoalcohols used as transition-state analogs for the hydrated amide of the peptide bond being hydrolyzed see: "Peptides Structure and Function, Proceedings of the Ninth American Peptide Symposium", Deber, C.M.; Hruby, V.J. and Kopple, K.D.; Pierce Chemical Co. (1985) p 729-782. Kokubu, T. *et. al.*; *Hypertension* 8 11 **1986**. Thaisrivongs, S. *et. al.*; *J. Med. Chem.* 29 2080, 2088 **1986**. Luly, J.R. *et. al.*; *J. Med. Chem.* 31 532 **1988**. Kempf, D.J. *et. al.*; *J. Med. Chem.* 30 1978 **1987**.

[2] For examples of allylic alcohol ester directed epoxidations see: Henbest, H.B. and Wilson , R.A.L.; *J. Chem. Soc.* 1958 **1957**. McKittrick, B.A. and Ganem, B.G.; *Tetrahedron Lett.* 26 4895 **1985**. For examples of allylic amine derivative directed epoxidations see: reference 1. Roush, W.R.; Smith, J.A. and Brown, R.J.; *J. Org. Chem.* 51 50 **1986**. Hauser, F.M. *et. al.*; *J. Org. Chem.* 52 5127 **1987**.

[3] By NMR we see about a 3:1 ratio of products, the major component of which after hydrolysis and carbonyl diimidazole mediated coupling with isobutylamine forms **1**.

[4] As in the cyclopent-2-ene acetic acid case, the stereochemical outcome of the epoxidation was verified by an iodolactonization followed by aminolysis and dehydroiodination of the resulting iodohydrin.

[5] A typical experimental procedure for the epoxidation is as follows: The alkene (5.1 mmole) is dissolved in 20 mL of CH_2Cl_2. At 0° C, 55% MCPBA (5.5 mmole) is added and the reaction warmed to room temperature for 20 minutes. The reaction is partitioned between 1 N NaOH and CH_2Cl_2 and the aqueous layer is extracted 2X with CH_2Cl_2. The combined organic layer is dried (Na_2SO_4), filtered, concentrated and purified by flash chromatography. The reactions proceed in good yield (>80% yield) and all epoxides have been characterized by ^{13}C-NMR, ^{1}H-NMR, IR and MS.

(Received in USA 13 December 1988)