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Diastereoselective Epoxidation of Dipeptide Olefins

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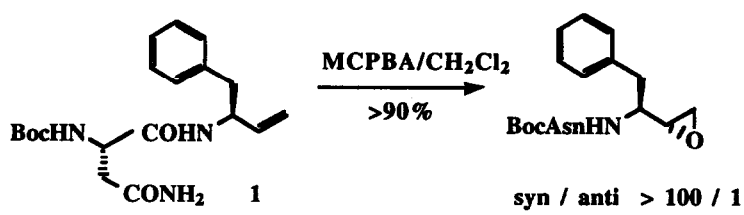
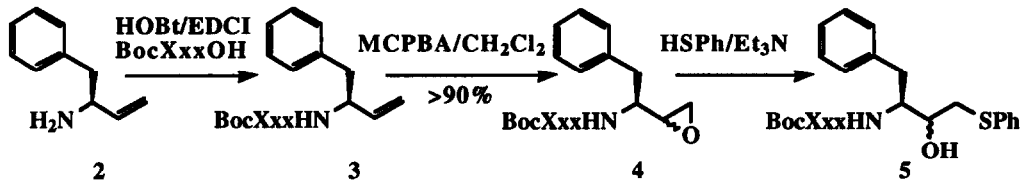
Abstract: *m*-Chloroperbenzoic acid (MCPBA) epoxidation of dipeptide olefins proceeds in high syn diastereoselectivity (38:1-300:1). This is partially caused by conformational constraints introduced by the side chain that orients the allylic NH in a favorable position for hydrogen bonding to MCPBA. The possibility of an additional hydrogen bond between the N-terminal NH and MCPBA is excluded.

The excellent diastereoselectivity obtained by epoxidation of acyclic allylic alcohols has made 2,3-epoxy alcohols a common unit for synthesis of optically active compounds[1]. Aminoalkyl epoxides are also important synthetic intermediates that are generally synthesized by *meta*-chloroperbenzoic acid (MCPBA) oxidation of an allylic amide[2,3]. The directive effect of the allylic NH on the stereochemistry of the epoxidation of allylic amides has been extensively investigated[2] in the cyclic case, where a hydrogen bond between an oxygen of MCPBA and the allylic NH is thought to direct the epoxidation syn to the amino group. Stereoselective epoxidation of acyclic allylic amides[3] however, shows diastereoisomeric ratios between 3:1 and 20:1 for mono substituted olefins depending on the protecting group on the allylic nitrogen, with the Boc and phenylurea groups more selective than the trichloroacetoamido and benzamido groups. When an additional substituent is present on the olefin, the selectivity varies considerably depending on the electronic and steric properties of the substituent.
In the course of our studies of inhibitors of HIV protease, we found that epoxidation of dipeptide olefin **1** proceeded in high stereoselectivity[4]. In order to evaluate the generality of this reaction, we have characterized the role of the N-terminal amino acid side chain in controlling the selectivity of the epoxidation.

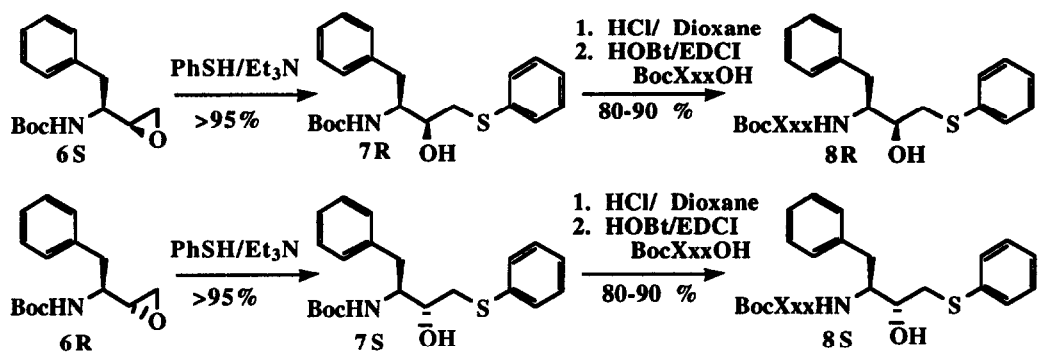


Amino olefin **2** was synthesized from BocPhe-OH by reduction to the aldehyde BocPhe-H followed by Peterson olefination[5]. Coupling of the crude amine to the appropriate amino acid using HOBt/EDCI or

iso-butylchloroformate gave a series of dipeptides **3** in 40-60 % overall yields. After epoxidation[6] the products **4** were immediately reacted with thiophenol/Et_3N[7] to give alcohols **5**[8].



To determine the stereochemistry and the diastereoisomeric ratios of **5**, the known epoxides **6R** and **6S** were prepared[9]. Each diastereoisomer was reacted with thiophenol/Et_3N to afford alcohols **7S** and **7R**, which were converted to dipeptides **8R** and **8S** by HOBt/EDCI coupling with the appropriate amino acid[10].



Alcohols **5** were found to be identical to stereoisomer **8S** by ^1H-, ^{13}C-NMR, t.l.c. and HPLC, thus confirming the syn epoxidation of olefins **3**.

The effect of substrate side chain structure on diastereoisomeric ratios of the crude alcohols **5a-e** was determined by HPLC (Table I). Replacement of Asn with Leu (**5a**) did not affect the diastereoselectivity of the epoxidation, which was increased somewhat by introduction of Ala (**5c**) and decreased by Phe (**5b**). The importance of the N-terminal amide for the observed selectivity was evaluated with the N-MeAla derivative **5e**. HPLC analysis of the crude mixture of alcohols showed only a slight decrease in diastereoselectivity, thus excluding the possibility of an additional contribution from the N-terminal NH group. To determine the importance of the allylic NH group, the N-methyl analog **11** was synthesized by methylation of olefin **9** with $(MeO)_3BF_4$ followed by BOP-Cl mediated coupling with BocAlaOH. This olefin was considerably less reactive then the unsubstituted analog **5c** and no epoxide could be isolated[11].

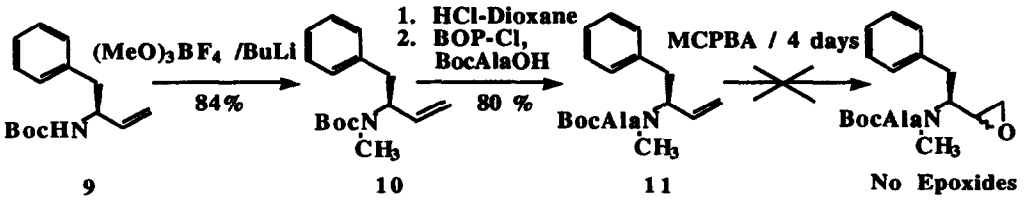
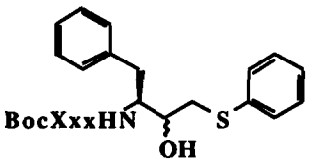


Table I. Diastereoisomeric ratios of alcohols 5a-e.



Entry	Xxx	HPLC conditions[a]	t_R (S, R)	Ratio (S : R)[b]
5a	Leu	30% MTBE[c] in Cyclohexane sat. with H_2O	12.9, 15.6	100 : 1
5b	Phe	0.5% *iso*Propanol in CH_2Cl_2 sat with H_2O	14.7, 19.1	67 : 1
5c	Ala	5-10 % MTBE in CH_2Cl_2 sat. with H_2O	24.0, 25.8	300 : 1
5d	Gly	9 % MTBE in CH_2Cl_2 sat. with H_2O	18.1, 20.9	38 : 1
5e	MeAla	40% MTBE in Cyclohexane sat. with H_2O	8.8, 10.7	190 : 1

[a]Isocratic except for entry 5c were a gradient was used. Flow 1ml/min. Column Zorbax Silica 4.6mmx25cm.[b] All ratios were determined as an average of three determinations. Error: +/- 5%, except for entry 5c where for partial overlap an error of +/- 15% was estimated. [c]MTBE: *tert*-butyl methyl ether.

The primary role of the allylic NH in the epoxidation is confirmed by the lack of reactivity of **11**. The results of Table I establish that the high syn selectivity originally found for the Asn derivative **1** was not determined by an interaction between the Asn side chain and MCPBA. The side chain is however clearly important as shown by the one order of magnitude loss in selectivity shown by the Gly analog **5d** compared to the Ala analog **5c**, but the diastereoselectivity is only slightly diminished by increasing the steric size of the side chain. These results imply that conformational restrictions imposed by the presence of the side chain are partially responsible for enhancing selectivity, probably by orienting the NH optimally for hydrogen bonding to MCPBA. Most importantly, synthesis of peptide epoxides with high diastereoselectivity appears to be general for a variety of dipeptidyl olefins. This procedure should provide a useful approach to chiral amino alcohols. The role of the N-terminal carbonyl group and the optimization of the electronic properties of the allylic NH for determining selectivity are under investigation.

Acknowledgements
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6. **Typical procedure:** A solution of the olefin in CH_2Cl_2 (0.02mmol/ml) was cooled at 0°C and MCPBA was added (2 eq.). The ice bath was removed and the solution stirred at room temp. for 36hours. The reaction mixture was then diluted with CH_2Cl_2, washed with 0°C Na_2SO_3 (10%), $NaHCO_3$ (sat.)x3, H_2O and Brine, dried over Na_2SO_4 and concentrated to afford the crude epoxide. By ^{1}H-NMR the yields were estimated >90%.
7. Thiophenol was chosen for its high reactivity towards epoxides and the increase in UV absorbance of the products thus improving the sensitivity of the detection of very small amounts of diastereoisomeric alcohols.
8. **Typical procedure:** the crude mixture from the epoxidation was dissolved in MeOH (0.04mmol/ml) and Et_3N was added (1eq), followed by PhSH (4 eq). The solution was refluxed for 3hours, the solvent evaporated and the mixture directly analyzed by HPLC. An analytical sample was purified by silica gel chromatography to afford the pure alcohol. All compounds synthesized were characterized by ^{1}H- and ^{13}C-NMR (DEPT analysis)and HR-Mass.
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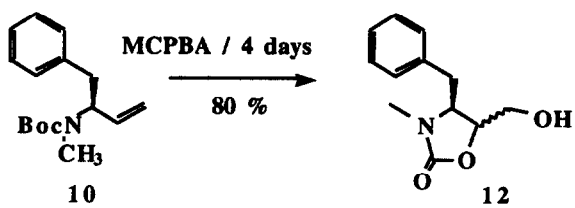
10. All compounds synthesized were characterized by ^{1}H- and ^{13}C-NMR (DEPT analysis) and HR-Mass.
11. Characterization of the products is under current investigation. The epoxidation of olefin **10** was also attempted and a 1:1 mixture of oxazolidones **12** was isolated.



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