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Stereoselective Synthesis of Protected Amino alkyl Epoxides.

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Abstract: The mechanism of epoxidation of chiral allyl amines has been investigated. The intrinsic stereoselectivity for epoxidation is shown to be approximately 5:1 and is independent of the nitrogen substituent. However, the nature of the N-protecting group influences the stability of the undesired epoxide to the acidic media, with the minor diastereomer undergoing preferential decomposition. Conditions are reported for the highly stereoselective synthesis of epoxide **9R**, an important building block in the synthesis of several enzyme inhibitors.

meta-Chloroperbenzoic acid (MCPBA) peroxidation of allylic amines has been shown to give syn epoxides preferentially in ratios varying from 3:1 to 200:1 (Table I).[1-8] In the course of synthesizing a series of HIV protease inhibitors, we found that epoxidation of the BocAsn derivative **6** and several other dipeptide olefins (**7-8**) proceeded with very high stereoselectivity.[6,7] Similar results have been reported recently by Albech and Persky.[8]

Table I.

n	R	R'	R/S	Ref.
1	CH_2OAc	Boc	7.5 : 1	3
2	COOMe	Cbz	4 : 1	4
3	$CH_2CH(CH_3)_2$	Boc	15 : 1	5
4	$CH_2CH(CH_3)_2$	Phthaloyl	4 : 1	5
5	$CH_2CH(CH_3)_2$	Tosyl	3 : 1	5
6	Benzyl	Boc	13 : 1	5
7	Benzyl	BocAsn	>100:1	6
8	Benzyl	BocMeAla	190 :1	7

The unusually high apparent diastereoselectivity evident in the latter examples has not been satisfactorily rationalized. It could be caused by an exceptionally favorable transition state for epoxidation (as described in Ref. 8), or it could be caused by preferential decomposition of the minor diastereomer, as suggested by the work of W.R. Roush et al.[9] who observed formation of an oxazolidine from a benzoyl protected epoxide.

In order to test if decomposition of epoxide **9S** might alter the observed stereoselectivity, the epoxidation of olefin **6** to **9R** and **9S** (Scheme 1) was monitored by HPLC (Figure 1) at three different MCPBA concentrations (2, 4, 8eq) and two temperatures (22 and 40°C). With short reaction times and low concentrations of MCPBA, the initial diastereoisomeric ratio obtained was approximately 5:1. The ratio increases with longer reaction times and larger amounts of MCPBA (Figure 1A) as the minor diastereomer decomposes. A new product **10** was isolated from the reaction mixture by chloroform extraction of the combined aqueous phases (**10** was not isolated when ethyl acetate was used[8]). The trans (threo) stereochemistry of **10** was confirmed[10] by ^{1}H-NMR[11] (J_{4-5} = 5.7Hz) *versus* oxazolidinone **11**, prepared from pure epoxide **9R**, which has cis (erythro) stereochemistry (J_{4-5} = 8.3Hz).[12]

Scheme 1.

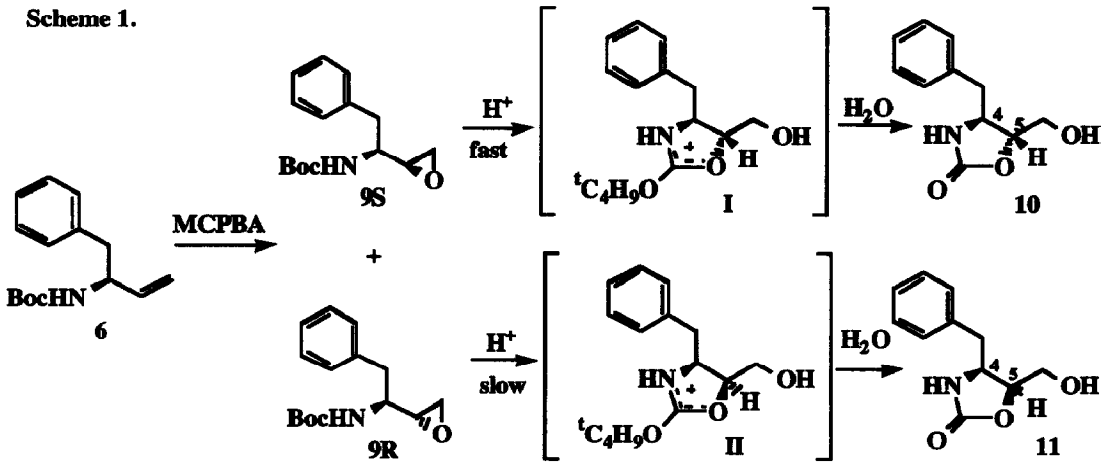
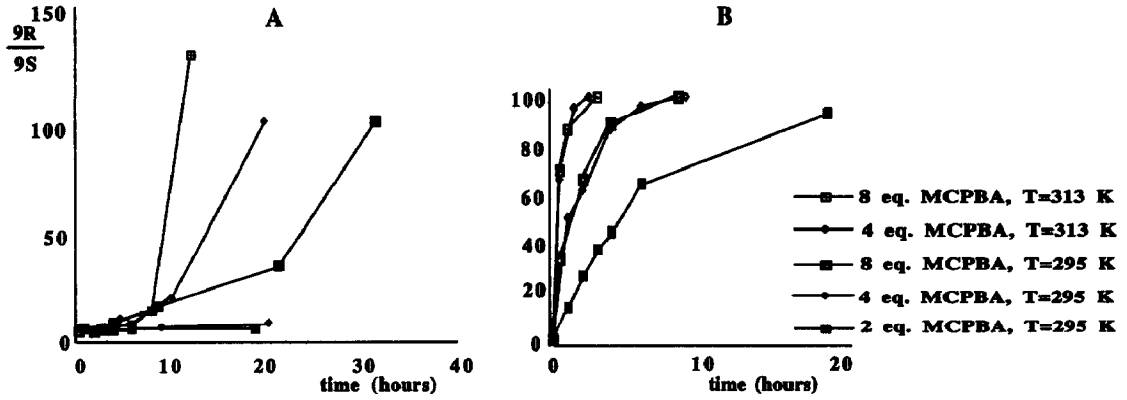


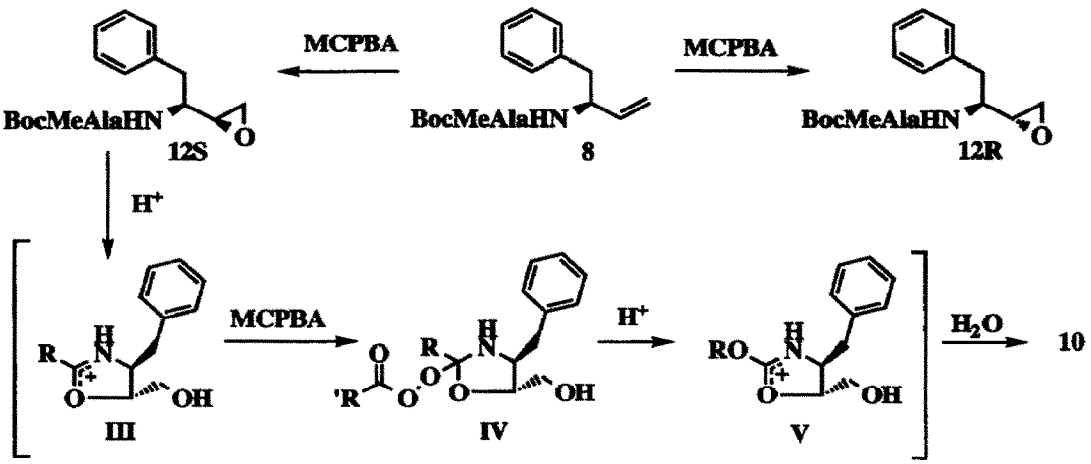
Figure 1. (A) Diastereomeric ratios (**9R/9S**) and (B) conversion of olefin **6** (%) determined by HPLC[a].



[a]Gradient, 2% *iso*-Propanol/Heptane-20% *iso*-Propanol/Heptane. Flow 2ml/min. Column Zorbax Silica 4.6mmx25cm. t*R*: **9(R)** 4.5min; **9(S)** 5.7min; **10** 15.3min; **11** 15.7min

Epoxidation of allyl amine **8** (Table I) also gave unusually high ratios of epoxide **12R** to **12S** due to further reaction of the minor diastereomer.[7] Surprisingly, oxazolidinone **10** (Scheme 2) also was extracted from the combined aqueous phases. Based on recovery of **10**, the calculated stereoselectivity is 4:1, similar to the ratios obtained in entries 2 and 5 (Table I). By refluxing **12R** in MCPBA, oxazolidinone **11**[12] was also synthesized. Oxazolidinones **10** and **11** may be formed by a Baeyer-Villiger-like rearrangement of intermediate oxazolidine[13] **III**, followed by hydrolysis of iminoether **V**.

Scheme 2



Our results show that the stereoselectivity of allylic amine epoxidation is approximately 5:1 for a variety of nitrogen substituents. The nature of the N-protecting group influences the rate by which diastereomeric epoxides react further to give oxazolidinones **10** and **11**. By judicious choice of conditions (Figure 1B), the desired epoxide **9R** can be obtained in good yield by reaction of the olefin in refluxing dichloromethane in the presence of an excess of peracid.

The well known epoxide **9R**[14] has been used widely in the synthesis of several enzyme inhibitors[15] Since the separation of epoxide diastereomers is difficult,[14] the conditions reported here[16] will allow the synthesis of this important building block in very high diastereoisomeric purity.

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References and Notes

1. Pettersson, H.; Gogoll, A.; Bäckvall, Jan-E. *J. Org. Chem.* **1992**, *57*, 6025.
2. Hauser, F. M.; Ellenberger, S. R.; Glusker, J. P.; Smart, C. J.; Carrel, H. L. *J. Org. Chem.* **1986**, *51*, 50.

3. Ohfune, Y.; Kurokawa, N. *Tetrahedron Lett.* **1984**, *25*, 1587.
4. Shaw, K. J.; Luly, J. R.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 4515.
5. Luly, J. R.; Dellaria, J. F.; Plattner, J. J.; Soderquist, J. L.; Yi, N. *J. Org. Chem.* **1987**, *52*, 1487.
6. Rich, D. H.; Sun, C. Q.; Vara Prasad, J.V.N.; Pathiasseril, A.; Toth, M. V.; Marshall, G. R.; Clare, M.; Mueller, R. A.; Houseman, K. *J. Med. Chem.* **1991**, *34*, 1222-5.
7. Romeo, S.; Rich, D. H. *Tetrahedron Lett.* **1993**, *34*, 7187-7190.
8. Albeck, A; Persky, R; *J. Org. Chem.* **1994**, *59*, 653-657.
9. Roush, W. R.; Straub, J. A.; Brown, R. J. *J. Org. Chem.* **1987**, *52*, 5127.
10. Rich, D. H.; Sun, E. T. O.; Ulm, E. *J. Med. Chem.* **1980**, *23*, 27-33.
11. **(4S,5R)-4-benzyl-5-hydroxymethyloxazolidin-2-one (10)** IR($CHCl_3$)1760 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 2.88 (m, 2H), 3.46 (dd, 1H, J_1=12.7Hz,J_2=4.3Hz), 3.73 (dd, 1H, J_1= 12.7Hz, J_2= 3Hz), 4.01 (m, 1H, irradiation at 2.88∂ caused to collapse into a doublet $J_{4,5}$= 5.7Hz), 4.36 (m, 1H), 5.65 (s, 1H), 7.15-7.35 (m, 5H); ^{13}C-NMR ($CDCl_3$): 41.50 (CH_2), 54.88 (CH), 62.67 (CH_2), 81.97 (CH), 127.32 (CH), 129.03 (CH), 129.10 (CH), 135.73 (C), 158.69 (C); exact mass calcd for $C_{11}H_{14}NO_3$ (M+1) 208.0974, found (HRMS-EI) 208.0915.
12. **(4S,5S)-4-benzyl-5-hydroxymethyloxazolidin-2-one (11)** The epoxide **9R** or **12R** was dissolved in dichloromethane and MCPBA was added (2-8eq, based on commercially 50% MCPBA, Fluka), the solution was then refluxed for 60 hours. After cooling, the suspension was diluted with chloroform, washed with Na_2SO_3 (sat., 0 °C, x2), $NaHCO_3$ (sat., x3), H_2O and brine, dried (Na_2SO_4) and concentrated. After silica gel chromatography (96/4 dichloromethane/*iso*propanol) **11** was isolated (34% yield), and a considerable amount (approx. 50% w/w) of a more polar complex mixture was also formed. IR ($CHCl_3$ + 10%MeOH) 1750cm^{-1}; ^{1}H-NMR ($CDCl_3$ +10% CD_3OD) 2.82 (dd, 1H, J_1= 13.3Hz, J_2=10.7Hz), 3.00 (dd, 1H, J_1= 13.7Hz, J_2=4.1Hz), 3.90 (m, 2H), 4.20 (m, 1H), 4.74 (m, 1H, irradiation at 3.90∂ caused to collapse into a doublet $J_{4,5}$= 8.3Hz), 7.19-7.37 (m, 5H); ^{13}C-NMR ($CDCl_3$ +10% CD_3OD): 35.82 (CH_2), 55.86 (CH), 59.91 (CH_2), 79.56 (CH), 127.01 (CH), 128.79 (CH), 128.89 (CH), 137.13 (C), 159.31 (C); exact mass calcd for $C_{11}H_{14}NO_3$ (M+1) 208.0974, found (HRMS-EI) 208.0986.
13. Aue, H.D.; Thomas, D. *J. Org. Chem.* **1974**, *39*, 3855-3862.
14. Evans, B.E.; Rittle, K.E.; Homnick, C.F.; Springer, J.P.; Hirshfield, J.; Veber, D.F. *J. Org. Chem.* **1985**, *50*, 4615.
15. 1992 references for **9R**: Rich, D. H.; Vara Prasad, J. V. N.; Sun, C. Q.; Green, J.; Mueller, R.; Houseman, K.; MacKenzie, D.; Malkovsky, M. *J. Med. Chem.* **1992** *35*, 1685-1701. Thompson, W. J.; Fitzgerald, P. M.; Holloway, M. K.; Emini, E. A.; Darke, P. L.; McKeever, B. M.; Schleif, W. A.; Quintero, J. C.; Zugay, J. A.; Tucker, T. J.; et al.*J. Med. Chem.* **1992** *35*, 1685-701. Kempf, D. J.; Sowin, T. J.; Doherty, E. M.; Hannic, S. M.; Codavoci, L.; Henry, R. F.; Green, B. E.; Spanton, S. G.; Norbeck, D. W. *J. Org. Chem.* **1992**, *57*, 5692-5700. Ashton,W. T.; Cantone, C. L.; Tolman, R. L.; Greenlee, W. J.; Lynch, R. J.; Schorn, T. W.; Strouse, J. F.; Siegl, P. K. S. *J. Med. Chem.* **1992**, *35*, 2772-2781. Askin, D.; Wallace, M. A.; Vacca, J. P.; Reamer, R. A.; Volante, R. P.; Shinkai, I. *J. Org. Chem.* **1992**, *57*, 2771-2773.
16. **(2R,3S)-3-[N-(*tert*Butoxycarbonyl)amino]-1,2-epoxy-4-phenylbutane (9R)**
To a solution of olefin **6** in dichloromethane (50-100 mM) was added MCPBA (4eq.) (8eq. based on commercially 50% MCPBA, Fluka). The mixture was refluxed for 20 hours. After cooling, the suspension was diluted with ether, washed with Na_2SO_3 (sat., 0 °C, x2), $NaHCO_3$ (sat., x3), H_2O and brine, dried (Na_2SO_4) and concentrated. After silica gel chromatography (85-Hexane / 15-MTBE / 1-*iso*Propanol) the pure epoxide was isolated (yield >65%). The diasteroisomeric purity (>100:1) was determined by HPLC (2%*iso*Propanol/Heptane, flow 2ml/min.) t_R**9S** 4.5min; t_R**9R** 5.7min; ^{1}H-NMR and ^{13}C-NMR are in agreement with the literature.[14]
Oxazolidinones **10** and **11** were obtained in a 2:1 ratio (^{1}H-NMR) by extracting the combined aqueous phases with $CHCl_3$ (x6). Silica gel chromatography (95 Dichloromethane/ 5 *iso*Propanol) afforded oxazolidinones **10** and **11**. (combined 27% yield) [(**11**):9 %; (**10**): 18%]. Based on the combined material the overall yield of the reaction was >92% and the stereoselectivity was 4 : 1.

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