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Stereoselective Synthesis of an *Erythro N*-protected α-Amino Epoxide Derivative

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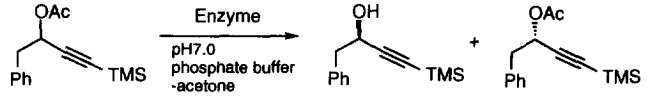
Abstract: *Erythro* α-amino epoxide, an important intermediate for synthesis of protease inhibitors, was synthesized from propargylic alcohol in a highly enantio- and diastereoselective manner.

α-Amino epoxide derivatives are key compounds for the synthesis of protease inhibitors, HIV-PR inhibitors,[1] Renin inhibitors,[2] Cystein protease inhibitors.[3]

While *threo* α-amino epoxides are stereoselctively obtained directly by epoxidation of allylic amines,[4] a variety of approaches towards the synthesis of *erythro* α-amino epoxides has been recently investigated.[5] However, racemization is a serious problem in the case of synthesis from amino acids or their derivatives.[6] In this paper we report synthesis of an *erythro N*-protected amino epoxide from propargylic alcohol in a highly stereoselective manner using lipase kinetic resolution and stereoselective epoxidation. This procedure is free from the racemization problem because amino acid derivatives are not used.

Our synthetic route is shown in Scheme 1. Kinetic resolution of propargylic alcohol **1** was achieved by asymmetric hydrolysis[7] of acetate **2** using Lipase PS in pH 7.0 phosphate buffer including 10% acetone to give the desired **1-(R)** (>99%ee), $[\alpha]^{D}_{20}$ +7.2° (*c*=1.00, CH_3Cl). The results of kinetic resolution by several lipases are summarized in Table 1. Propargylic alcohol **1-(R)** was converted to *cis* olefin **3a** by hydrogenation in the presence of Lindlar catalyst and quinoline in MeOH for 14h. Epoxidation of *cis* olefin **3a** using *m*-CPBA in dichloromethane at room temperature proceeded highly stereoselectively to afford *threo* epoxide **4**. (>99%de)[9] The high selectivities resulted from the effect of 1,3-strain due to *cis*-TMS substitution.[10] In the case of monosubstituted olefin **3b**, selectivity of epoxidation under the same conditions was low(59:41). This comparison showed the *cis*-TMS substitution was very effective for stereoselective epoxidation. To remove the

Table 1 Kinetic resolution of propargylic alcohol using Lipase



2 **1-(R)** **2-(S)**

Entry	Enzyme	Time	1-(R)Yield (%)[a]	ee (%)[b]
1	Lipase PS	24	18	> 99
2		144	62	> 99
3		312	90	> 99
4	Lipase AY	96	88	96
5	Lipase AK	96	76	94
6	Pancreatin F	96	46	4

[a] Isolated yield.
[b] Determined by HPLC analysis. (column: DAICEL CHIRALCEL OJ-B, solvent: MeOH/H_2O=2/1)

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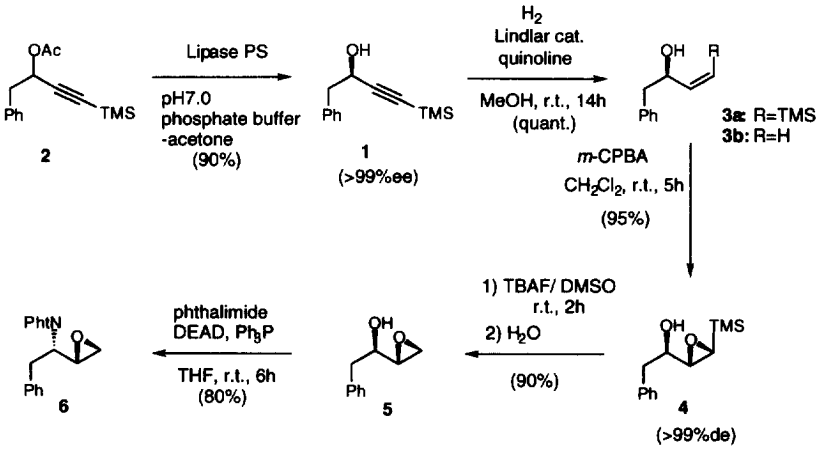

Scheme 1

TMS group, epoxide **4** was treated with tetrabuthylammonium fluoride in dimethylsulfoxide at room temperature and the reaction mixture was quenched with water and extracted with ether.[10, 11] *N*-substitution was accomplished using the Mitsunobu reagent (DEAD, Ph_3P) and phthalimide in tetrahydrofuran at r. t. for 6h to afford *erythro* α-amino epoxide **6**.[12] Conversion to Saquinavir (Ro31-8959) from amino epoxide **6** was already achieved by the Roche group.[13]

As described above, we have succeeded in developing a synthetic route to an *erythro N*-protected amino epoxide in a highly stereoselective manner using lipase kinetic resolution and stereoselective epoxidation. This synthetic route allows the synthesis of important building blocks for protease inhibitors. Furthermore, enantiomer of **6** can be synthesized by this procedure.

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References and Notes

1. Review: Thaisrivongs, S. *Ann. Rep. Med. Chem.*, **1994**, *29*, 133.
2. Luly, J. R.; Plattner, J. J.; Stein, H.; Yi, N.; Soderquist, J. L.; Marcotte, P. A.; Kleinert, H. D.; Perum, T. J. *Biochem. Biophys. Res. Comm.*, **1987**, *143*, 44.
3. Albeck, A.; Fluss, S.; Persky, R. *J. Am. Chem. Soc.*, **1996**, *118*, 3591.
4. a) Luly, J. R.; Dellaria, J. F.; Plattner, J. J.; Soderquist, J. L.; Yi, N. *J. Org. Chem.*, **1987**, *52*, 1487. b) Albeck, A.; Persky, R. *J. Org. Chem.*, **1994**, *59*, 653. c) Romeo, S.; Rich, D. H. *Tetrahedron Lett.*, **1994**, *35*, 4939.
5. a) Evans, B. E.; Rittle, K. E.; Homnick, C. F.; Springer, J. P.; Hirshfield, J.; Veber, D. F. *J. Org. Chem.*, **1985**, *50*, 4615. b) Reetz, M. T.; Binder, J. *Tetrahedron Lett.*, **1989**, *30*, 5425. c) Pegorier, L.; Petit, Y.; Larcheveque, M. *J. Chem. Soc., Chem. Commun.*, **1994**, 633. d) Albeck, A.; Persky, R. *Tetrahedron*, **1994**, *50*, 6333. e) Green, B. E.; Chen, X.; Norbek, D. W.; Kempf, D. J. *Synlett*,, **1995**, 613. f) Heinsoo, A.; Raidaru, G.; Linask, K.; Jarv, J.; Zetterstrom, M.; Langel, U. *Tetrahedron: Asymmetry*, **1995**, 2245. g) Beaulieu, P. L.; Wernic, D.; Duceppe, J.-S.; Guindon, Y. *Tetrahedron Lett.*, **1995**, *6*, 3317. h) Rotella, D. P. *Tetrahedron Lett.*, **1995**, *36*, 5453. i) Ng, J. S.; Przybyla, C, A.; Lui, C.; Yen, J. C.; Muellner, F. W.; Weyker, C. L.; *Tetrahedron*, **1995**, *51*, 6397. j) Branalt, J.; Kvarnstrom, I.; Classon, B.; Samuelsson, B.; Nillroth, U.; Danielson, U. H.; Karlen, A.; Hallberg, A. *Tetrahedron Lett.*, **1997**, *38*, 3483.
6. Stanfield, C. F.,; Parker, J. E.,; Kanellis, P. *J. Org. Chem.*, **1981**, *46*, 4797.
7. In this case, kinetic resolution by lipase-catalyzed esterification of racemic alcohol **1** did not give good results.[8]
8. Allevi, P.; Ciuffreda, P; Anastasia, M. *Tetrahedron: Asymmetry*, **1997**, 8, 93.
9. Diastereoselective ratios were determined by NMR analysis.
10. a) Tomioka, H.; Suzuki, T.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.*, **1982**, *23*, 3387. b) Kurihara, M; Ishii, K.; Kasahara, Y.; Kameda, M; Pathak, A. K.; Miyata, N *Chem. Lett.*, **1997**, 1015.
11. Chan, T. H.; Lau, P. W. K.; Li, M. P. *Tetrahedron Lett.*, **1976**, *31*, 2667.
12. Spectral analyses of **6** were in agreement with those previous reported.[13]
13. Parkes, K. E. B.; Bushnell, D. J.; Crackett, P. H.; Dunsdon, S. J.; Freeman, A. C.; Gunn, M. P.; Hopkins, R. A.; Lambert, R. W.; Martin, J. A.; Merrett, J. H.; Redshaw, S.; Spurden, W. C.; Thomas, G. J. *J. Org. Chem.*, **1994**, *59*, 3656.