

SELECTIVITY IN EPOXIDATION:  
ACYCLIC DIASTEREO- AND ENANTIO-SELECTION  
WITH PEROXIDE MEDIATED BY TITANIUM(IV) AND WITH PERACID<sup>1</sup>

Minoru Isobe\*, Masato Kitamura, Shigeru Mio and Toshio Goto  
Laboratory of Organic Chemistry, Faculty of Agriculture, Nagoya University,  
Chikusa, Nagoya 464, JAPAN

Summary : *New diastereoselective epoxidation on the olefin 1 with TBHP mediated by Ti(IV) is described to give the epoxide 2 which has reverse orientation of the one, 3, with MCPBA. Ti-mediation was ineffective on the olefin 4, on which MCPBA worked in high selectivity. Example of kinetic resolution is also described on 1b under Katsuki-Sharpless condition.*

The diastereoselectivity or intramolecular asymmetric induction in epoxidation of alkoxyolefins such as 1c and 4e has been studied by Kishi and his collaborators<sup>2</sup> with MCPBA or VOacac-TBHP (tert-butylhydroperoxide).<sup>3</sup> The stereochemistry of the epoxides with MCPBA and VOacac-TBHP were both elucidated to be 3 (*anti*).<sup>2</sup> However, no selective condition has been available to obtain the reversely oriented epoxide as 2 (*syn*), the required stereoisomer for the synthesis of our target maytansine.<sup>1,4</sup> We have surmounted the current problem by finding a new acyclic diastereoselection in titanium(IV)-mediated epoxidation with TBHP. The striking *syn*-selectivity in reverse manner to the known *anti*-configuration [eq. 1] prompted us to report herein our results together with a respect to the limitation [eq. 2]. We also describe an example of kinetic resolution [eq. 3] of the racemic 1b under Katsuki-Sharpless condition<sup>5</sup> for enantioselection of the intermediate 1b for maytansine.

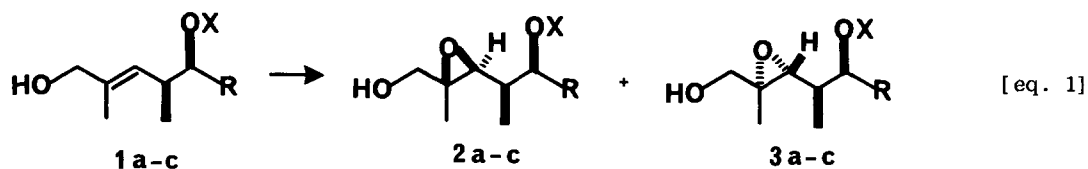
A typical experiment for Ti(IV)-mediated epoxidation follows. To a solution of the olefin 1a (77 mg) in dry CH<sub>2</sub>Cl<sub>2</sub> (2 ml) was added titanium(IV) isopropoxide (0.15 ml) at -20°C with stirring. After 5 min, anhydrous 3M TBHP solution in CH<sub>2</sub>Cl<sub>2</sub> (0.35 ml) was added and the mixture was stirred for additional 2.5 hr at this temperature under nitrogen atmosphere to afford, after work-up,<sup>5</sup> 64 mg of the largely *syn*-epoxide 2a in 90% yield. Epoxidation of 1a with 1.2 eq. MCPBA was achieved in dry CH<sub>2</sub>Cl<sub>2</sub> at -20°C for 10 min to afford largely the *anti*-epoxide<sup>6</sup> 3a in quantitative

yield. Vanadium catalyzed epoxidation<sup>3</sup> with 3 eq. TBHP was done at room temperature in dry  $\text{CH}_2\text{Cl}_2$ . The olefin 1b was also epoxidized with TBHP-Ti(IV) isopropoxide and with MCPBA. The ratios of the product epoxides are depicted in the table.<sup>7</sup> Similar alkoxy-olefins 4a-d, when treated with MCPBA and TBHP-Ti(IV) isopropoxide, on the contrary, afforded both *anti*-epoxides as major products [eq. 2].

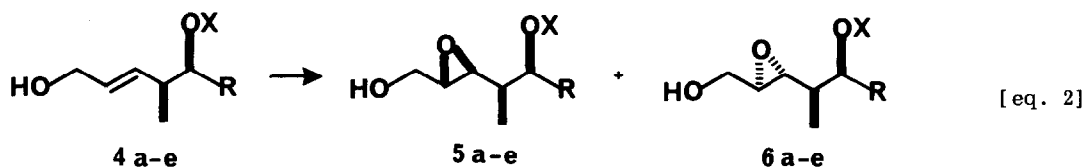
Coordination of MCPBA with the hydroxyl and etherial moieties of the substrates as 1 might rationalize the selectivity of epoxidation to occur from the chelating face<sup>2</sup> via pseudo-intramolecular process affording a single diastereoisomer. On the other hand, the oxidation with TBHP-Ti(IV) proceeds on the other face. This may be due to shielding of the chelating face by complex-formation of Ti cation bonded with the oxygen atoms; and, thus, the oxidation agent should eventually attack from the less hindered site in intermolecular manner. Significance of the olefinic methyl group in 1 is shown in the Ti(IV)-mediated epoxidation upon comparison with the case in 4, particularly is evident by comparison with 1a and 4d. An almost exclusive *anti*-epoxides (6b,c,d) were obtained with MCPBA on 4b,c,d which have bulkier groups than 4a,e.<sup>2</sup> In case of the olefin 4 lacking the methyl group, the selectivity was also affected by the existence of the one more asymmetric carbon in 4a,b,c,d compared to 4e; the high selectivity with MCPBA which would rapidly react in the flexible conformation from the chelation face; the low selectivity with Ti(IV)-TBHP which would react even from the chelation face.

Taking account for the reaction velocities, we found our *diastereoselective* [TBHP-Ti(IV) isopropoxide] reaction to be even faster than *enantioselective* [TBHP-Ti(IV) isopropoxide and (+)-L-DET(diethyl tartrate)] reaction under the Katsuki-Sharpless condition.<sup>5,9</sup> The racemic olefin 1b was treated in dry  $\text{CH}_2\text{Cl}_2$  with TBHP and Ti(IV) isopropoxide both in the presence and absence of (+)-L-DET at  $-20^\circ\text{C}$  for 12 hrs, and the products were analyzed as the (+)-MTPA ( $\alpha$ -methoxy- $\alpha$ -trifluoromethylphenylacetic) ester as shown in eq. 3. Although no starting material was left in case of "without DET", a significant amount (ca. 15%) of the starting olefin was recovered from the reaction mixture "with DET". The left olefin was found to be optically pure (9, >95% purity).<sup>10</sup> When the reaction "with DET" was interrupted in 5 hrs, the olefin 9 was obtained in 45% yield of the theoretical amount. In these cases we found no *anti*-epoxide 3b as detectable product. The current kinetic resolution process is of practical interest in the resolution of each of the enantiomeric olefins.

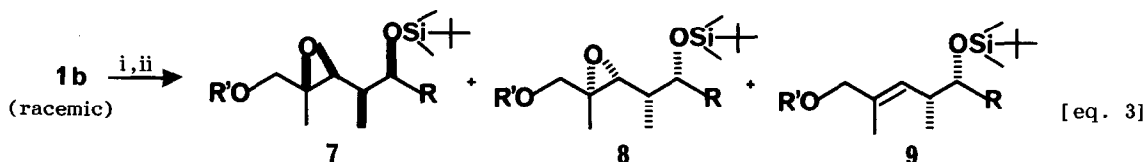
We have recently succeeded in the total synthesis of ( $\pm$ )-maytansinol,<sup>1,4</sup> the epoxide of which was introduced diastereoselectively into an acyclic olefin under the currently found condition with



	X	R	ratios 2 : 3		
			TBHP-Ti(IV)	TBHP-VOacac	MCPBA
<b>1a</b>	SiMe <sub>2</sub> Bu <sup>t</sup>	(CH <sub>2</sub> ) <sub>3</sub> CH <sub>2</sub> OSiMe <sub>2</sub> Bu <sup>t</sup>	10 : 1	3 : 2	1 : >25
<b>1b</b>	SiMe <sub>2</sub> Bu <sup>t</sup>	CH <sub>2</sub> C(OMe) <sub>2</sub> CH(OMe)- CH <sub>2</sub> OAc	> 25 : 1	-	1 : >25
<b>1c<sup>2</sup></b>	CH <sub>2</sub> Ph	H	-	4 : 3 <sup>2</sup>	1 : >25 <sup>2</sup>



	X	R	ratios 2 : 3		
			TBHP-Ti(IV)	TBHP-VOacac	MCPBA
<b>4a</b>	CH <sub>2</sub> O(CH <sub>2</sub> ) <sub>2</sub> OCH <sub>3</sub>	CH <sub>2</sub> CH <sub>2</sub> Ph	1 : 1.8	-	1 : 4
<b>4b</b>	SiMe <sub>2</sub> Bu <sup>t</sup>	CH <sub>2</sub> CH <sub>2</sub> Ph	1 : 2.3	2 : 5	1 : >25
<b>4c</b>	SiMePh <sub>2</sub>	CH <sub>2</sub> CH <sub>2</sub> Ph	1 : 1.6	-	1 : >25
<b>4d</b>	SiMe <sub>2</sub> Bu <sup>t</sup>	(CH <sub>2</sub> ) <sub>3</sub> CH <sub>2</sub> OSiMe <sub>2</sub> Bu <sup>t</sup>	1 : 4.0	-	1 : >25
<b>4e<sup>2</sup></b>	CH <sub>2</sub> Ph	H	-	-	2 : 3 <sup>2</sup>



R' = (+)-MTPA

i) TBHP/Ti(O-iPr)<sub>4</sub>/(+)-L-DET /  
-20°C/above period: ii) MTPACl

12 hr 7 : 8 : 9 = 3 : 2 : 1

5 hr 7 : 8 : 9 = 2 : 1 : 1

TBHP-Ti(IV). The detail of the total synthesis will be described shortly.

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#### REFERENCES AND NOTES

1. These results were presented in part in the 28th IUPAC Congress, Vancouver, British Columbia, Canada, August 16-21 (1981). For our previous papers, see a) M. Isobe, M. Kitamura, T. Goto; *Tetrahedron Lett.*, **22**, 239 (1981); b) M. Isobe, Y. Ichikawa, M. Kitamura, T. Goto; *Chemistry Lett.*, 457 (1981).
2. a) M.R. Johnson, T. Nakata, Y. Kishi; *Tetrahedron Lett.*, 4343 (1979); b) M.R. Johnson, Y. Kishi; *Tetrahedron Lett.*, 4347 (1979).
3. a) B.E. Rossiter, T.R. Verhoeven, K.B. Sharpless; *Tetrahedron Lett.*, 4733 (1979); b) E. D. Mihelich; *Tetrahedron Lett.*, 4729 (1979); c) R.B. Dehnel, G.H. Whitham; *J. Chem. Soc. Perkin I*, 953 (1979); d) T. Itoh, K. Jitsukawa, K. Kaneda, S. Teranishi; *J. Am. Chem. Soc.*, **101**, 159 (1979).
4. For the structure, see a) S.M. Kupchan, Y. Komoda, W.A. Court, G.J. Thomas, R.M. Smith, A. Karim, C.J. Gilmore, R.C. Haltiwanger, R.F. Bryan; *J. Am. Chem. Soc.*, **94**, 1354 (1972); for syntheses, see b) A.I. Meyers, P.J. Reider, A.L. Campbell; *J. Am. Chem. Soc.*, **102**, 6597 (1980); c) E.J. Corey, L.O. Weigel, A.R. Chamberlin, H. Cho, D.H. Jua; *J. Am. Chem. Soc.*, **102**, 6613 (1980).
5. a) T. Katsuki, K.B. Sharpless; *J. Am. Chem. Soc.*, **102**, 5974 (1980); b) B.E. Rossiter, T. Katsuki, K.B. Sharpless; *J. Am. Chem. Soc.*, **103**, 464 (1981).
6. The stereochemistry of the epoxide with MCPBA in a similar system is also assigned to be *anti*: unpublished results and private communication of Professor G. Stork (1980).
7. The ratios were counted from the epoxidic protons in pmr spectra:  $\frac{2b}{3b}$  [3.00ppm(J= 9Hz)/2.97(J= 10)]. For the epoxides 2a and 3a, were analyzed the protons on the corresponding benzoates: benzoates of  $\frac{2a}{3a}$  [2.94(J= 9.1)/2.89(J= 9.6)]. As for the (+)-MTPA-esters of 2a [major, 2.82(J= 9)/minor, 2.87(J= 8.5)].
8. The ratios were determined from the methyl signals:  $\frac{5a}{6a}$  [0.94ppm(J= 7.0)/1.01(J= 7.0)]. The de-silylated diol of  $\frac{5b}{6b}$  [0.96(J= 7.2)/1.00(J= 7.2)]. Also  $\frac{5c}{6c}$  [0.98(J= 6.5)/1.04 (J= 6.5)].
9. A.I. Meyers has recently prepared the optically active olefin (+)-1c, which was further introduced into chiral epoxide (-)-2c "with DET" under Katsuki-Sharpless's condition.<sup>5</sup> We thank Professor Meyers for sending us the preprint: A.I. Meyers, J.P. Hudspeth; *Tetrahedron Lett.*, **22**, 3925 (1981).
10. 9 was smoothly converted into 8 in 2.5 hr by treatment with TBHP-Ti(IV) without DET. The structures are temporally assigned as the major epoxide 7 to have *S*-configuration.<sup>5a</sup>

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