Pergamon

*Tetrahedron Letters*, Vol. 38, No. 3, pp. 433-436, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(96)02318-0

# Specific Asymmetric Mono-epoxidation of *Meso* 2,3-*syn*-*bis*-Allylic Alcohols Having a Bicyclo[2.2.1]heptane Framework

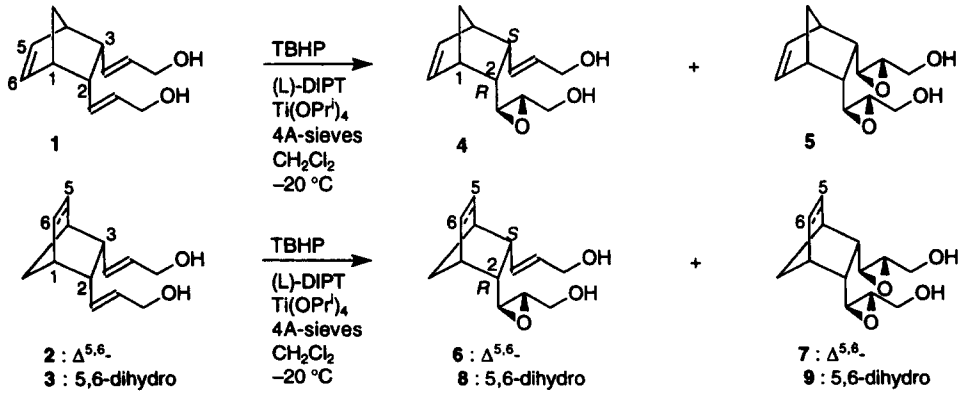
**Takahiko Taniguchi and Kunio Ogasawara***

*Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980-77, Japan*
Fax +81-22-217-6845; E-mail c21799@cctu.cc.tohoku.ac.jp

**Abstract:** The Katsuki-Sharpless asymmetric epoxidation reaction of *meso syn*-2,3-*bis*-*endo*- and *exo*-allyl alcohols on a bicyclo[2.2.1]heptane framework took place regio- and stereo-selectively in a unilateral way to give the corresponding mono-epoxidation products as the major product.


When two allylic alcohols are contained in a symmetric molecule, the Katsuki-Sharpless asymmetric epoxidation (AE reaction)[1] takes place in a twofold way to give a $C_2$ symmetric chiral *bis*-epoxide.[2] We now have found an interesting exception where the reaction terminated at the single oxidation stage to give regio- and stereo-selectively a single mono-epoxide when a *meso syn*-*bis*-allylic alcohol having a bicyclo[2.2.1]heptane framework was used as substrate.

Thus, AE reaction[3] of the *endo*-*bis*-allylic alcohol[4] **1** with 2 equiv. (=4 mol equiv.) of *tert*-butyl hydroperoxide (TBHP) in the presence of a catalytic amount of diisopropyl (*L*)-tartrate (*L*-DIPT) (0.24 equiv.=0.48 mol equiv.) and titanium(IV) isopropoxide (0.2 equiv.=0.4 mol equiv.) gave stereoselectively the mono-epoxide **4** and the di-epoxide **5** in yields of 39 and 12% (3.4:1) after 168 h. When **1** was oxidized under non-catalytic conditions using 1.5 equiv. of TBHP in the presence of a small excess of *L*-DIPT (1.2 equiv.) and titanium(IV) isopropoxide (1.1 equiv.), the reaction proceeded at a faster rate and terminated after 30 h to give a mixture consisting of the mono-epoxide **4** and the di-epoxide **5** in a ratio of 7.3:1 in 54% total yield.

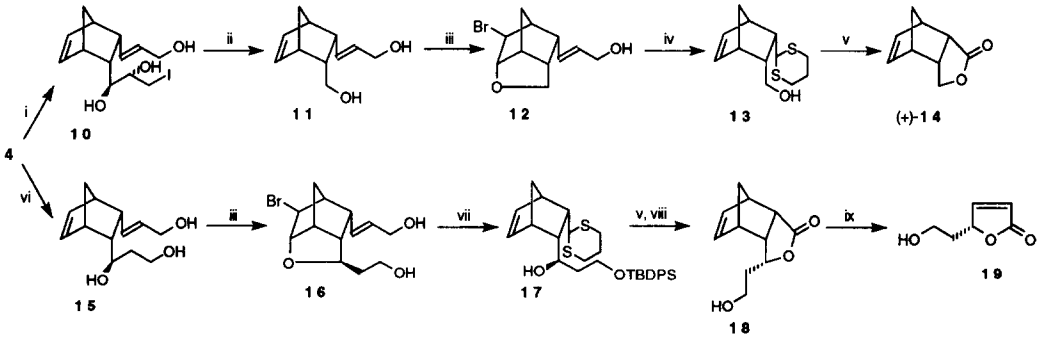



**Scheme 1**

Surprisingly, when the reaction was carried out with 3 equiv. of TBHP in the presence of two molar excess of both *L*-DIPT (2.4 equiv.) and titanium(IV) isopropoxide (2.2 equiv.), the mono-epoxide **4**, $[\alpha]_D^{29}$ +1.3 (*c* 1.0, $CHCl_3$), was obtained as the major product in 63% yield accompanied by 6% yield of the di-epoxide **5**, $[\alpha]_D^{30}$ −19.2 (*c* 0.4, $CHCl_3$), after 8 h. Optical purity of the mono-epoxide **4** was estimated to be 89% ee which was determined in the later stage. Even in the presence of a large excess (>4 equiv.) of each of the reagents, the mono-epoxide **4** was still the major product which was generated in 50% yield accompanied by 6% of the di-epoxide **5**. In all cases, none of other products besides the mono-epoxide **4** and the diepoxide **5** could be isolated. When the mono-epoxide **4** after isolation was subjected to the epoxidation conditions using an excess amount of the reagents (~4.5 equiv.), the same di-epoxide **5**, $[\alpha]_D^{28}$ −18.8 (*c* 0.6, $CHCl_3$), was obtained in 35% yield as the single oxidation product accompanied by the unreacted **4** in 43% recovery after 48 h. This indicated that the second epoxidation occurred in the same facial selectivity as that of the first epoxidation but at a much slower rate.

Quite similarly, the diastereomeric *meso exo-bis*-allylic alcohol **2**[5] and its 5,6-dihydro-congener **3**[5] furnished the corresponding mono-epoxide **6**, $[\alpha]_D^{29}$ −25.0 (*c* 0.9, $CHCl_3$), and **8**, $[\alpha]_D^{29}$ −20.1 (*c* 0.5, $CHCl_3$), as the major products, respectively, accompanied by the corresponding di-epoxides **7**, $[\alpha]_D^{30}$ +8.9 (*c* 0.4, $CHCl_3$), and **9**, $[\alpha]_D^{30}$ +10.8 (*c* 0.3, $CHCl_3$), as the minor products under the same oxidation conditions without formation of any detectable amount of other products. Thus, the highest mono- and di-epoxide ratios of the reaction after separation of the products were 8.8:1 in total yield of 53% for **2** and 9.1:1 in total yield of 57% for **3** when the oxidation was carried out using 3 equiv. of TBHP in the presence of 2.4 equiv. of L-DIPT and 2.2 equiv. of titanium(IV) isopropoxide, respectively. Optical purities of the products were estimated to be 98% ee which was determined in the later stage (**Scheme 1**).

In order to determine the stereochemistry and the absolute configuration of the oxidation products, the mono-epoxide **4** was treated with lithium iodide[6] to give the 1,2-glycol **10**, $[\alpha]_D^{30}$ +3.5 (*c* 2.8, $CHCl_3$), *via* spontaneous Payne rearrangement and nucleophilic addition. On oxidative cleavage of the glycol bond, followed by borohydride reduction in the same flask, **10** furnished the diol **11**, $[\alpha]_D^{31}$ +38.4 (*c* 1.2, $CHCl_3$), which was exposed to *N*-bromosuccinimide (NBS) to yield the single bromo-ether **12**, $[\alpha]_D^{30}$ +20.3 (*c* 1.7, $CHCl_3$), by regioselective bromo-etherification. **12** was then transformed into the dithiane **13**, $[\alpha]_D^{29}$ +86.6 (*c* 0.5, $CHCl_3$), by sequential olefin cleavage, thio-ketalization, and reductive bromo-ether cleavage. At this




**Scheme 2**

*Reagents and conditions*: i, LiI, 1,2-dimethoxyethane, 70 °C, 52%; ii, $NaIO_4$, $CH_2Cl_2$-$H_2O$ (4:1), then $NaBH_4$, 79%; iii, NBS, $CH_2Cl_2$, 87% for **12** and 96% for **16**; iv, (a) $OsO_4$ (cat.), *N*-methylmorphorine *N*-oxide (NMO), acetone-$H_2O$ (1:1), (b) $NaIO_4$, $CH_2Cl_2$-$H_2O$ (4:1), (c) 1,3-propanedithiol, $BF_3$·$OEt_2$, (d) Zn, AcOH-EtOH (1:10), 70 °C, 46% overall; v, (a) MeI, $NaHCO_3$, MeCN-$H_2O$ (8:1), (b) pyridinium dichromate (PDC), $CH_2Cl_2$, 68% overall; vi, Red-Al, THF, 83%; vii, (a) $OsO_4$ (cat.), NMO, acetone-$H_2O$ (1:1), (b) $NaIO_4$, $CH_2Cl_2$-$H_2O$ (4:1), (c) 1,3-propanedithiol, $BF_3$·$OEt_2$, (d) *tert*-butyldiphenyl (TBDPS) chloride, 4-*N*,*N*-dimethylaminopyridine (DMAP), (e) Zn, AcOH-EtOH (1:10), 70 °C, 45% overall; viii, $Bu_4NF$, THF, 37% from **17**, diphenyl ether, 260 °C, 84%.

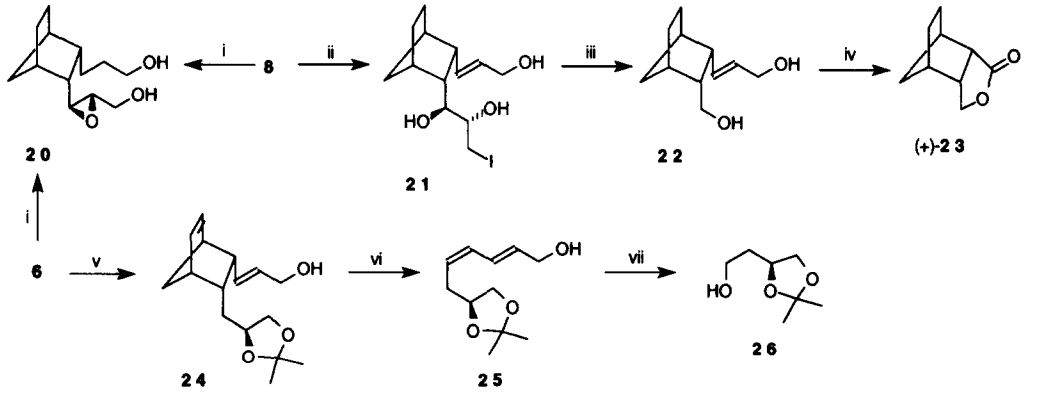
point, the optical purity was determined to be 89% ee by $^1$H NMR of the MTPA esters[7] of **13**. Finally, **13** was hydrolyzed and oxidized to give the known lactone[8] (+)-**14**, mp 121-123 °C, $[\alpha]_D^{25}$ +99.1 (*c* 0.3, $CHCl_3$) [lit.[8]: $[\alpha]_D^{25}$ +143 (*c* 5.2, $CHCl_3$)]. Formation of the (+)-lactone **14** determined unambiguously that the epoxidation took place selectively at the allylic alcohol group on the pro-*R* C2-center of **1** though the facial selectivity was still uncertain at this stage.

On the other hand, to determine the facial selectivity of the epoxidation, **4** was treated with sodium bis(2-methoxyethoxy)aluminum hydride[9] (Red-Al) to give the 1,3-glycol **15**. Reaction of **15** with NBS gave the single bromo-ether **16**, mp 87-89 °C, $[\alpha]_D^{26}$ +38.0 (*c* 1.0, $CHCl_3$), regioselectively. After protection of the primary hydroxy group, **16** was transformed into the dithiane **17**, $[\alpha]_D^{23}$ +32.6 (*c* 1.6, $CHCl_3$), by sequential olefin cleavage, thio-ketalization, and the reductive bromo-ether cleavage. On hydrolysis, followed by oxidation and desilylation, **17** gave the tricyclic γ-lactone **18**, $[\alpha]_D^{27}$ +147.0 (*c* 1.12, $CHCl_3$), which gave the known butenolide[10] **19**, $[\alpha]_D^{26}$ –45.8 (*c* 0.6, $CHCl_3$) {lit.[10]: $[\alpha]_D^{21}$ –46.4 (*c* 0.62, $CHCl_3$)}, on thermolysis in diphenyl ether. This clarified unambiguously the stereochemistry of the epoxy bond of **4** as *S*:*S*-configuration. The stereochemical outcome was in accordance with that expected by the empirical rule[1] (**Scheme 2**).

Thus, it has been concluded that the mono-epoxidation of the *meso endo-bis*-allyl alcohol **1** occurred at the allylic double bond on the pro-*R* C2-center from the outside of the molecule (the C1-C2 face) as well as that the di-epoxidation occurred from the outside face of the allylic double bond on the pro-*R* C2-center and from the inside face (the C2-C3 face) of the allylic double bond on the pro-*S* C3-center.

To determine the stereochemistry and the absolute configuration of the diastereomeric mono-epoxide **6** and its 5,6-dihydro congener **8**, both of the compounds were hydrogenated under catalytic conditions. Both compounds gave the same perhydro-epoxide **20**, $[\alpha]_D^{28}$ –5.1 (*c* 1.0, $CHCl_3$) from **6** and $[\alpha]_D^{25}$ –4.9 (*c* 0.8, $CHCl_3$), from **8**, indicating that the 5,6-double bond did not affect the stereochemistry and optical yield of the AE reaction. Having established the stereochemical relationship between **6** and **8**, **8** was transformed into the known bicyclic lactone (+)-**23**,[7] $[\alpha]_D^{30}$ +71.3 (*c* 0.5, $CHCl_3$) {lit.[7]: $[\alpha]_D^{25}$ +89.8 (*c* 0.6, $CHCl_3$)}, *via* the triol **21**, $[\alpha]_D^{30}$ –5.4 (*c* 3.0, $CHCl_3$), and the diol **22**, $[\alpha]_D^{28}$ –33.4 (*c* 1.0, $CHCl_3$)}, by sequential Payne rearrangement, glycol cleavage, reduction, double bond cleavage, and oxidation. This clarified that the epoxidation of **2** as well as of **3** took place at the allylic group on the pro-*R* C2-center. Optical purities of the products were estimated to be 98% ee by $^1$H NMR analysis of the *bis*-MTPA esters[8] of the diol **22**.

To determine the facial selectivity, the epoxide **6**, on the other hand, was treated with diisobutylaluminum




**Scheme 3**

*Reagents and conditions*: i, $H_2$, 10% Pd-C, AcOEt, 62% from **6** and 72% from **8**; ii, LiI, 1,2-dimethoxyethane, 70 °C, 51%; iii, $NaIO_4$, $CH_2Cl_2$-$H_2O$ (4:1), then $NaBH_4$, 87%; iv, (a) $OsO_4$ (cat.), NMO, acetone-$H_2O$ (1:1), (b) $NaIO_4$, $CH_2Cl_2$-$H_2O$ (4:1), (c) PDC, $CH_2Cl_2$, 60% overall; v, DIBAL, $CH_2Cl_2$, 68%; vi, (a) 2,2-dimethoxypropane, pyridinium *p*-toluenesulfonate (cat.), acetone, reflux, (b) diphenyl ether, 260 °C, 87% overall; vii, $O_3$, $CH_2Cl_2$-MeOH (1:1), then $NaBH_4$, 59%.

hydride (DIBAL)[11] to give selectively the 1,2-glycol which was transformed into the acetonide **24**, $[\alpha]_D^{28}$ −57.2 (*c* 0.5, $CHCl_3$). Thermolysis of **24** in diphenyl ether gave the dienol **25**, $[\alpha]_D^{28}$ −19.7 (*c* 0.3, $CHCl_3$), which, on sequential ozonolysis and reduction in the same flask, furnished the known primary alcohol[12] (+)-**26**, $[\alpha]_D^{28}$ +4.2 (*c* 0.3, EtOH) {lit.[12] for (−)-**26**: $[\alpha]_D^{20.5}$ −3.7 (*c* 3.6, EtOH)}. This determined unambiguously the stereochemistry of the epoxy bonds of **6** and **8** as *S*:*S*-configuration, respectively.

Thus, it was concluded that the epoxidation of **2** as well as of its 5,6-dihydro congener **3** occurred at the allylic double bond on the pro-*R* C2-center from the outside face (the C1-C2 face) of the molecule by following the empirical rule.[1] Moreover, since both di-epoxides **7** and **9** possessed optical rotations, the second epoxidation occurred from the inside face (the C2-C3 face); otherwise, they should afford the *meso* products (**Scheme 3**).

The mono-epoxidation was found to be specific to the substrates having a *meso syn-bis*-allylic alcohol functionality on the bicyclo[2.2.1]heptane framework. Namely, the diastereomeric racemic *anti*-2,3-*bis*-allyl alcohol gave an inseparable mixture of two *bis*-epoxides (ca. 1:1) in 97% yield without formation of any mono-epoxidation product in the presence of each 2.2 equiv. of TBHP, *L*-DIPT, and titanium(IV) isopropoxide. Moreover, the specific mono-epoxidation observed seemed not merely to be due to the steric factor as the mono-benzyl ether of **1** gave a mixture of two diastereomeric mono-epoxides in 93% yield with complete consumption of the starting material under the same conditions.

Taking into account these observations, it may be presumed that the complexation occurred first with each of the two allylic hydroxy groups in the substrates to generate the *bis*-complexed intermediate under the conditions. However, the epoxidation occurred only from the outside face of the complex molecule owing to the steric interaction between the two complexes in the molecule which prevents the epoxidation from the more congested inside face (**Fig. 1**).

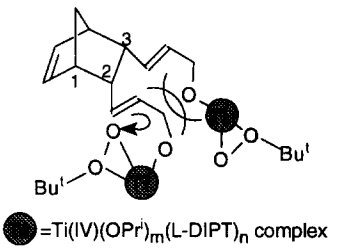



**Fig. 1**

## REFERENCES AND NOTES


1. For a pertinent review, see: Johnson, R. A.; Sharpless, K. B. *Comprehensive Organic Synthesis* Vol. 7 (Ed.: B. M. Trost), Pergamon: Oxford, 1991; pp. 389-422.
2. Hoye, T. R.; Suhadolnik, J. C. *J. Am. Chem. Soc.* **1985**, *107*, 5312-5313; Hoye, T. R.; Suhadolnik, J. C. *Tetrahedron* **1986**, *42*, 2855-2862.
3. Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765-5780.
4. Compound **3** was prepared from the Diels-Alder adduct of cyclopentadiene and diethyl maleate employing standard transformations involving the Horner-Emmons reaction.
5. Oda, H.; Kobayashi, T.; Kosugi, M.; Migita, T. *Tetrahedron* **1995**, *51*, 695-702.
6. Bonini, C.; Federici, C.; Rossi, L.; Righi, G. *J. Org. Chem.* **1995**, *60*, 4803-4812.
7. Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512-519.
8. Lok, K. P.; Jakovac, I. J.; Jones, J. B. *J. Am. Chem. Soc.* **1985**, *107*, 2521-2526.
9. Finan, J. M.; Kishi, Y. *Tetrahedron Lett.* **1982**, *23*, 2719-2722.
10. Suemune, H.; Hizuka, M.; Kamashita, T.; Sakai, K. *Chem. Pharm. Bull.* **1989**, *37*, 1379-1381.
11. Ma, P.; Martin, V. S.; Masamune, S.; Sharpless, K. B.; Viti, S. M. *J. Org. Chem.* **1982**, *47*, 1378-1380.
12. Mori, K.; Takigawa, T.; Matsuo, T. *Tetrahedron* **1979**, *35*, 933-940.


(*Received in Japan* 1 *November* 1996; *revised* 18 *November* 1996; *accepted* 22 *November* 1996)