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# A Total Synthesis of 6,7-Dihydroeponemycin and Determination of Stereochemistry of the Epoxide Ring

**Hideaki Hoshi, Takeshi Ohnuma, Shimpei Aburaki, Masataka Konishi & Toshikazu Oki**

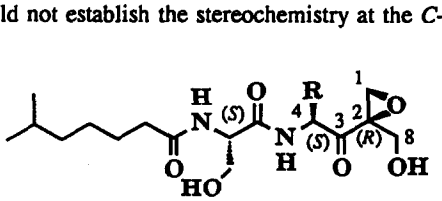
Bristol-Myers Squibb Research Institute, 2-9-3 Shimo-meguro, Meguro-ku, Tokyo 153, Japan

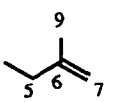
**Abstract:** A total synthesis of 6,7-dihydroeponemycin 2 was achieved via the epoxide intermediate 8a. Unresolved absolute configuration of the epoxide ring in 2 and eponemycin 1 was determined to be 2*R* by application of the asymmetric Sharpless epoxidation of 9.

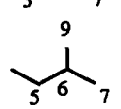
Eponemycin 1[1] was isolated from the fermentation broth of *Streptomyces hygroscopicus* No. P247-71. It shows strong *in vitro* cytotoxicity against various tumor cells and selective *in vivo* antitumor activity against B-16 melanoma in mice. Recently, T. Oikawa et al., reported that 1 is a powerful angiogenesis inhibitor to both proliferation and migration of endothelial cells[2].

The structural studies clarified a unique structure of eponemycin, which consisted of isooctanoic acid, L-serine and an epoxyketone unit. The absolute configuration at the *C*-2 had, however, not been determined. 6,7-Dihydroeponemycin 2, obtained by catalytic hydrogenation of 1, showed strong antitumor activity comparable to 1, whereas the epoxide-opened derivative was found inactive[1]. We recently reported a related antitumor antibiotic epoxomicin which also has an epoxyketone unit but no olefinic bond side chain[3]. Thus, the epoxyketone was considered to be a key structural unit but the olefinic bond was not for the activity of this class of antibiotics.

A total synthesis of 1 was recently achieved by U. Schmidt *et al.*,[4] who constructed the epoxide by the Sharpless or hydrogen peroxide oxidation to a 3-ketoallyl alcohol at the last step of the synthesis and thus it could not establish the stereochemistry at the *C*-2.



R:  **Eponemycin 1**

R:  **6,7-Dihydroeponemycin 2**

In this communication, we describe a total synthesis of **2** and elucidation of the absolute configuration of the epoxide ring using the asymmetric Sharpless epoxidation to a 3-alkoxyallylic alcohol.

Starting material **4** was prepared from 2-bromo-2-propen-1-ol[5] in 70.5 % yield by successive treating with *n*-BuLi and *p*-methoxybenzyl chloride. Lithiation of **4** with *n*-BuLi at -105°C, followed by coupling *in situ* with *N*-Z-(*S*)-leucinal **3**[6] gave an inseparable epimeric mixture of allyl alcohol **5**. Reaction of **5** with (+)-MTPA-Cl, followed by separation of the products with a silica gel column gave isomers **6a** (62 %) and **6b** (27 %)[7]. Treatment of **6a** with NaOMe in MeOH gave **5a** (50 %) along with oxazolidinone derivative **7a** (22 %), while a similar reaction of **6b** exclusively afforded **7b** (78 %). Comparison[8] of the chemical shifts and coupling constants of ring protons in **7a** (*cis*) and **7b** (*trans*)[9] indicated that the *C*-3 stereochemistries of **6a** and **6b** were 3*R* and 3*S*, respectively. The Sharpless epoxidations[10] of **5a** using L-(+)-DIPT and D-(-)-DIPT unexpectedly resulted in isolation of epoxide **8a** as the major product with 58 and 38 % yields, respectively. Although the production of a small amount of *C*-2 epimeric epoxide was observed (**8b**, < 3 %), the Sharpless oxidations seemed not to proceed stereoselectively in this case.

Therefore, the Sharpless epoxidation using the primary alcohol[11] as the recognition site was investigated for elucidation of the *C*-2 stereochemistry. Treatment of **6a** with DDQ[12] followed by the Sharpless epoxidation of the resulting **9** with D-(-)-DIPT and L-(+)-DIPT afforded the epoxides **10a** and **10b**[13], respectively, with high stereoselectivity. This indicated the absolute configurations of *C*-2 of **10a** and **10b** to be 2*R* and 2*S*, respectively based on the Sharpless rule. Meanwhile, the epoxide **8a** was sequentially treated with (+)-MTPA-Cl and DDQ to afford exclusively **10a**, which was identical with the compound derived from **9** by HPLC, IR, and $[\alpha]_D$. Thus, the absolute configuration of the epoxide ring in **8a** was determined to be 2*R*.

Sequential transformations of **8a** by hydrogenolysis, *N*-acylation with *O*-acetyl-*N*-isooctanoyl-L-serine, the Swern oxidation of the secondary alcohol, mild alkaline cleavage of the acetyl group and final deprotection of the PMB group with DDQ afforded (2*R*)-6,7-dihydroeponemycin, which was identical with **2** in all respects.

In conclusion, a total synthesis of (2*R*)-6,7-dihydroeponemycin **2** was performed via the (2*R*)-epoxide intermediate **8a** and hence the *C*-2 stereochemistry of eponemycin has been established as 2*R*.

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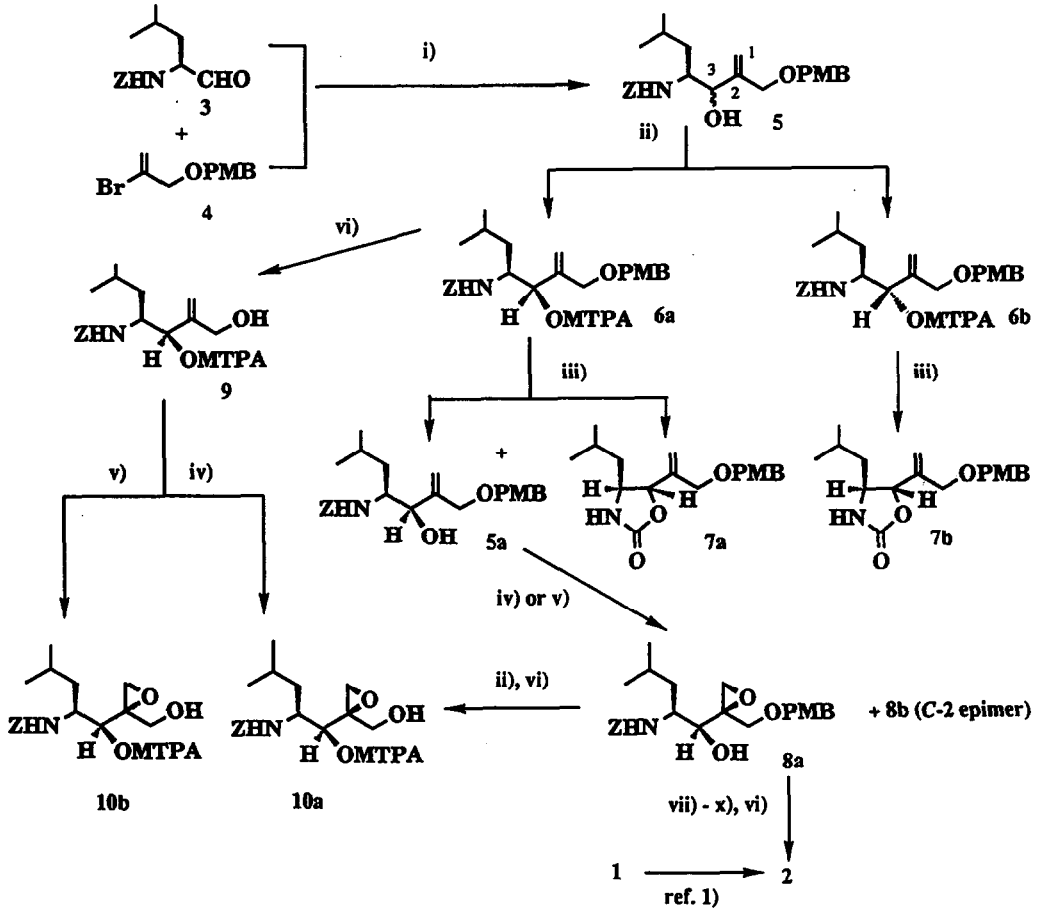


Z : benzyloxycarbonyl, PMB: *p*-methoxybenzyl, MTPA: α-methoxy-α-(trifluoromethyl)phenylacetyl

Reagents and conditions

i) **4**, *n*-BuLi 1.6M hexane, THF, -105°C, 0.5h; **3**, -100 ~ -105°C, 0.5h, 26 %; ii) (+)-MTPA-Cl, DMAP, $CH_2Cl_2$, r.t., 20h, **6a** (62 %), **6b** (27 %); iii) NaOMe (6 eq.), MeOH, r.t., 4h, **5a** (50 %), **7a** (22 %), **7b** (78 %); iv) Ti(*i*-PrO)$_4$, D-(-)-DIPT, t-BuOOH, $CH_2Cl_2$, -15°C, 48h, **8a** (38 %), **10a** (68 %); v) Ti(*i*-PrO)$_4$, L-(+)-DIPT, t-BuOOH, $CH_2Cl_2$, -15°C, 48h, **8a** (58 %), **10b** (50 %); vi) DDQ (1.5 eq.), $CH_2Cl_2$-$H_2O$, r.t., 16h, **9** (90 %), **10a** (86 %), **2** (75 %); vii) $H_2$-Pd/C, EtOAc, r.t., 10 min. ; viii) *O*-acetyl-*N*-isooctanoyl-L-serine, *N*-hydroxysuccinimide, DCC, EtOAc, r.t., 1h, 42 %; ix) DMSO-$(COCl)_2$-TEA, $CH_2Cl_2$, -60°C, 1h, 57 %; x) $K_2CO_3$ (2eq.), 80 % MeOH-$H_2O$, r.t., 15 min., 88 %

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7. 400 MHz-$^1$H NMR ($CDCl_3$): **6a** $\delta$ 3.85 and 3.92 (1H each, d, J=12.4 Hz, 8-H), 4.10 (1H, m, 4-H), 5.14 and 5.28 (1H each, s, vinyl-H), 5.55 (1H, d, J=3.8 Hz, 3-H). **6b**: $\delta$ 3.99 and 4.18 (1H each, d, J=12.4 Hz, H-8), 4.08 (1H, m, 4-H), 5.03 and 5.14 (1H each, s, vinyl-H), 5.58 (1H, d, J=2.1 Hz, 3-H).

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9. The 4-H and 5-H signals in the 400 MHz-$^1$H NMR ($CDCl_3$) spectra of **7a** and **7b** are as follows. **7a**(*cis*): $\delta$ 3.83(ddd, J=11.1, 7.7 and 3.9Hz, 4-H), 5.18(d, J=7.7Hz, 5-H), **7b**(*trans*): $\delta$ 3.77 (ddd, J=9.0, 6.0 and 4.7 Hz, 4-H), 4.65 (d, J=6.0 Hz, 5-H).

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12. Oikawa, Y.; Tanaka, T.; Horita, K.; Yoshioka, T.; Yonemitsu, O., *Tetrahedron Lett.* **1984**, 25, 5393 - 5396.

13. 400 MHz-$^1$H NMR ($CDCl_3$) : **10a** : $\delta$ 2.71 and 2.74 (1H each, d, J=4.7 Hz, 1-H), 3.54 and 3.89 (1H each, d, J=12.4 Hz ,8-H), 4.17 (1H, m, 4-H), 5.31 (1H, d, J=4.7Hz, 3H), **10b** : $\delta$ 2.62 and 2.70 (1H each, d, J=4.7 Hz, 1-H), 3.59 and 3.88 (1H each, d, J=12.4 Hz, 8-H), 4.18 (1H, m, 4-H), 5.00 (1H, d, J=6.4 Hz, 3-H).


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