The Synthesis of Eponemycin[1]

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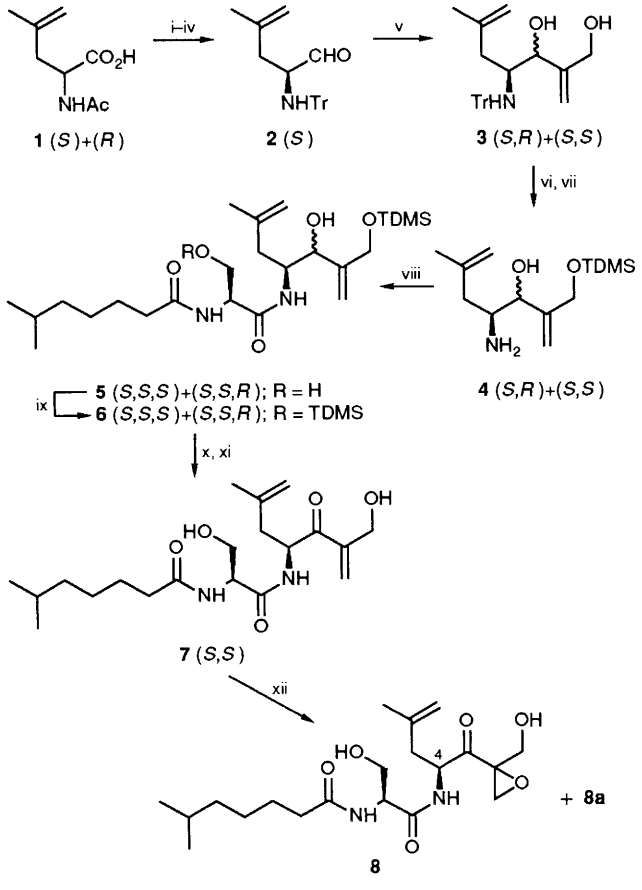
Eponemycin, a highly potent specific *in vivo* antitumour antibiotic against B16 melanoma, which was previously isolated from culture filtrates of *Streptomyces hygroscopicus* No. P247-71, is synthesized.

In 1989 eponemycin **8** was isolated for the first time from culture filtrates of *Strepotomyces hygroscopicus* No. P247-71 and its structure determined by degradation experiments and NMR spectroscopic analysis.[2] The configuration at the epoxide ring, however, was not elucidated. This antibiotic substance exhibits a specific activity towards B16 melanoma cells.

Similar to the strongly cytostatic cyclotetra-peptides of the chlamydocin group—chlamydocin[3] and WF-3161[4]—possessing an (*S,S*)-2-amino-8-oxo-9,10-epoxydecanoic acid unit in the ring and the antitumour active antibiotic agents of the manumycin group[5] as well as LL-C10037α,[6] the epoxy ketone group of eponemycin is also the most sensitive group. The epoxy rings of oxiranyl ketones are very rapidly opened by nucleophiles and such substances are thus powerful alkylating agents.



Abbreviations: Ac = acetyl; TDMS = *tert*-butyldimethylsilyl; Tr = trityl

Scheme 1 *Reagents and conditions*: i, 25% ammonia, H_2O, acylase I, pH 7–7.2, 33 °C, 24 h; ii, $LiAlH_4$, tetrahydrofuran (THF), 0 °C to reflux, 2 h, 41% (i + ii); iii, Tr–Cl, triethylamine (TEA), CH_2Cl_2, 20 °C, 2 h, 85%; iv, $(COCl)_2$, dimethyl sulfoxide (DMSO), CH_2Cl_2, −80 °C, 30 min., TEA, −80 to 20 °C, quant.; v, 2-bromo-3-hydroxypropene, *tert*-butyllithium 1.6 mol dm^{-3} pentane, diethyl ether, −80 to 0 °C, 4 h, −80 °C, **2**, 1 h, 0 °C, 2 h, H_2O, 84%; vi, TDMS–Cl, imidazole, dimethylformamide (DMF), 20 °C, 24 h, 94%; vii, acetic acid, 20 h; viii, (*S*)-*N*-(6-methylheptanoyl) serine, diphenylphosphorylazide (DPPA), TEA, DMF, −4 °C, 24 h, 72%; ix, TDMS–Cl (1.2 equiv.), imidazole, DMF, 50 °C, 24 h, 82%; x, $(COCl)_2$, DMSO, CH_2Cl_2, −80 °C, 30 min., ethyldiisopropylamine, −80 to 20 °C, quant.; xi, 50% HF in H_2O, MeCN, 20 °C, 2 h, 86%; xii, $KHCO_3$, H_2O_2, benzonitrile, methanol, 4 °C, 15 h, 40% **8** + 40% 4-epi-**8a** + 5% **8a**

For the construction of the 'eastern' half of the molecule, we have prepared (*S*)-γ-didehydroleucine by enzymatic acyl cleavage of the racemic *N*-acetyl derivative **1**. Subsequent reduction to the amino alcohol, protection of nitrogen by a trityl group and oxidation furnished the aldehyde **2**, which was then converted into the allylic diol **3** by treatment with the dilithium derivative $LiO–CH_2–C(Li)=CH_2$.[7†] The primary hydroxy group was selectively protected and the trityl group removed to give **4** which was coupled with (*S*)-*N*-(6-methylheptanoyl) serine to yield the amide **5**.

Initially, we had intended to construct the extremely sensitive and electrophilic epoxy ketone unit in the last step by oxidation of a secondary epoxy alcohol, as in our synthesis of the antibiotics chlamydocin[3] and WF3161.[4] However, preliminary experiments with the diol **9** revealed that a Sharpless oxidation was not possible since a six-membered ring titanium alcoholate was apparently formed irreversibly. Since the masking of a secondary hydroxy group and the deprotection of a primary hydroxy group in **5** appeared to be rather laborious, we have also protected the second hydroxy group to produce **6** and then oxidized the product to the corresponding vinyl ketone. Subsequent removal of both protecting groups gave the substrate **7** for epoxidation. The oxidation of such electron-poor allyl alcohols under the conditions of the Sharpless reaction has not been reported previously in the literature.

The reaction with **7** did indeed proceed in a rather complicated manner. Uniform reaction products were not obtained either with D(−)- or with L(+)-diethyl tartrate. The enantioselective reaction is apparently perturbed by the two stereogenic centres, and the reaction rate is decreased by the presence of the carbonyl group at the double bond. However, both enantiomers **8** and **8a**‡ could be separated by HPLC. The isomer with the lower retention time was identical in all

† Attempts to obtain the lithium compound from 2-bromoallyl alcohol benzyl ether by halogen lithium exchange were unsuccessful. We were not able to induce the dilithium derivative to react with the corresponding (*Z*)-aminoaldehyde.

‡ *Spectroscopic data* for **8a**: ^1H NMR (250 MHz, $CDCl_3$): 7.13 (d, *J* 6.7 Hz, 1H), 6.62 (d, *J* 7.2 Hz, 1H), 4.89 (s, 1H), 4.82 (s, 1H), 4.61 (ddd, *J* 10.3, 6.6 and 3.9 Hz, 1H), 4.46 (ddd, *J* 7.3, 4.4 and 3.3 Hz, 1H), 4.20 (dd, *J* 12.6 and 4.9 Hz, 1H), 4.04 (d, *J* 11.4 Hz, 1H), 3.74 (dd, *J* 12.6 and 5.6 Hz, 1H), 3.59 (m, 1H), 3.40 (br, 1H), 3.35 (d, *J* 4.9 Hz, 1H), 3.12 (d, *J* 4.9 Hz, 1H), 2.58 (dd, *J* 14.0 and 10.4 Hz, 1H), 2.43 (br, 1H), 2.27 (t, *J* 7.8 Hz, 2H), 2.07 (dd, *J* 14.0 and 3.6 Hz, 1H), 1.77 (s, 3H), 1.69–1.43 (m, 3H), 1.39–1.27 (m, 2H), 1.22–1.10 (m, 2H) and 0.86 (d, *J* 6.6 Hz, 6H). ^{13}C NMR (63 MHz; $CDCl_3$): 207.1, 174.4, 171.3, 140.2, 115.0, 62.8, 62.4, 61.5, 53.7, 50.9, 49.5, 38.6, 38.5, 36.5, 27.8, 27.0, 25.8, 22.6 and 21.6.

respects with the natural product. Hence, the result of the Sharpless reaction does not allow any conclusions to be drawn about the stereochemistry at the epoxide ring.

The strong double induction by the two stereogenic centres prompted us to investigate the nucleophilic epoxidation in the absence of an optically active catalyst. The reaction with hydrogen peroxide, potassium hydrogen carbonate and benzonitrile gave rise to eponemycin and the (4*R*)-epimer of **8a** (1 : 1 ratio) which could, however, be separated by preparative HPLC. With potassium hydrogen carbonate eponemycin slowly epimerises to give a 1 : 1 mixture of **8** and 4-epi-**8**.

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