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Absolute Stereochemistry of Vicenistatin, A Novel 20-Membered Macrocyclic Lactam Antitumor Antibiotic

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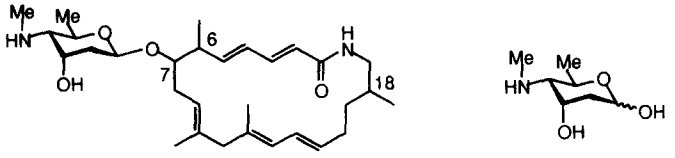
Abstract

The absolute stereochemistry of the aglycon part of an antitumor antibiotic vicenistatin (**1**) was determined by a synthetic approach. Two relevant components degradatively derived from natural **1** were compared with the corresponding synthetic standards prepared from known compounds by stereochemically defined chemistry. The absolute configuration of **1** turned out to be 6*S*,7*S*,18*S*.

Keywords: macrolactam; antitumor antibiotic; absolute stereochemistry;

Vicenistatin (**1**), an antitumor antibiotic isolated from *Streptomyces* sp. HC-34, is interesting because of its novel structure including a 20-membered macrocyclic lactam and an aminosugar (vicenisamine: **2**) [1]. A major characteristic feature is its significant inhibitory activity especially against HL-60 (human leukemia) and COLO205 (human colon carcinoma) *in vitro* and Co-3 (human colon carcinoma) *in vivo*. The structure shown in Fig.1 was determined mainly by extensive NMR spectral analysis [1]. While the absolute structure of **2** was elucidated, the absolute stereochemistry of the macrolactam aglycon has yet to be determined [1]. This intriguing novel structure prompted us to explore the chemical features essential to its biological activities.



Vicenistatin (**1**) Vicenisamine (**2**)

Fig. 1

First to be done along this line was to elucidate the remaining absolute stereochemistry of the three asymmetric centers of the aglycon. For the unambiguous assignment of the absolute stereochemistry, we took advantage of the chemical synthesis of relevant partial structures in a

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stereochemically defined manner. Degradation of vicenistatin (**1**) was undertaken first, which was carried out by ozonolysis and acidic hydrolysis to obtain two fragments (triol **3** and aminoalcohol **4**) containing the C6-C7 asymmetric unit and the C18 chiral center, respectively. The resulting triol **3** was converted to the corresponding benzoate **5** and Mosher's ester **6** derived with (*R*)-(+)-MTPA (methoxytrifluoromethylphenylacetic acid). The aminoalcohol **4** was also transformed to **7** with (*R*)-(+)-MTPA (Fig. 2).[1]

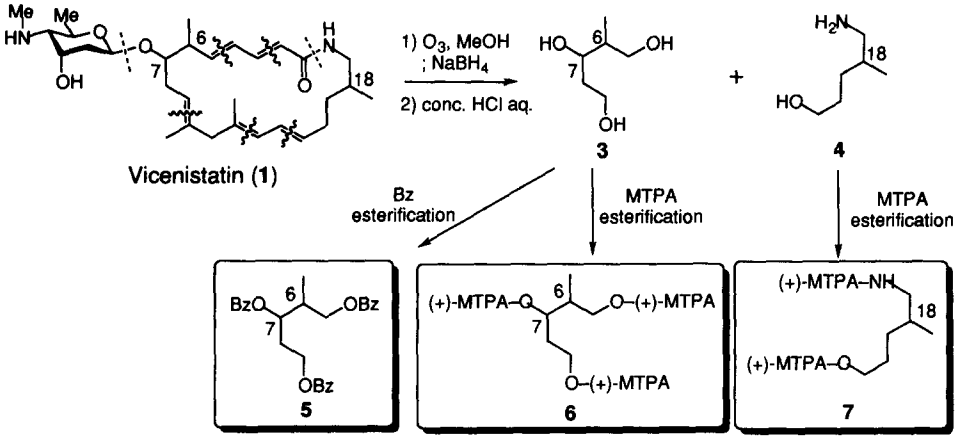


Fig. 2

Next was the synthesis of the authentic samples. Prediction of the relative stereochemistry seemed to be difficult by spatial remoteness between the two asymmetric units (C6/C7 and C18), which would necessitate laborious synthesis of every stereoisomers. To reduce the number of the necessary standards, computational conformational analysis of the aglycon and comparison of the NMR coupling constants between the predicted conformations and those of experimental were carried out prior to the synthesis.

Molecular mechanics calculations were performed for all eight possible diastereomers of the aglycon using the combination of CONFLEX-MM2 [2]. The ^{1}H-^{1}H coupling constants between C6-H, C7-H and C8-H$_2$ of all possible diastereomers were estimated by population analysis of the major stable conformers, followed by application of the Karplus-Altona equation [3]. Among the diastereomers, two structures, (6*S*,7*S*,18*R*)-**1** and (6*R*,7*R*,18*S*)-**1**, turned out to be closely similar to the natural **1**.

Both enantiomers of amioalcohol **4** were synthesized from (*R*)- and (*S*)-citronellol **8**, and the aminoalcohols were derivatized to the corresponding diastereomeric Mosher's esters as shown in Fig. 3. Two stereochemically defined standards (**10** and **11**[2]) and Mosher's ester (**7**) derived from natural **1** were compared by ^{1}H-NMR spectroscopy, and simple inspection allowed assignment of C18 to be *S* (Fig. 4).

1. Degradation and derivatization of vicenistatin: Ozone gas was bubbled into a solution of vicenistatin in MeOH at –50°C for 2h. After reductive treatment by $NaBH_4$, conc. HCl was added and refluxed for 1h. Then the reaction mixture was evaporated and the residue was derivatized with (+)-MTPA chloride or benzoyl chloride, respectively, in pyridine.

2. Compound **11**: ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.31-7.61 (m, 10 H, Ar), 6.78-6.97 (m, 1 H, NH), 4.32 (dt, 1 H, *J* = 6.6, 10.7 Hz, one of 15H), 4.24 (dt, 1 H, *J* = 6.5 Hz, 10.7 Hz, one of 15H), 3.59 (s, 3 H, OCH_3), 3.39 (s, 3 H, OCH_3), 3.26 (ddd, 1 H, *J* = 6.3, 6.3, 13.1 Hz, one of 19-H), 3.08 (ddd, 1 H, *J* = 6.6, 6.6, 13.1 Hz, one of 19-H), 1.58-1.87 (m, 3 H, 16, 18-H), 1.06-1.42 (m, 2 H, 17-H), 0.87 (d, 3 H, *J* = 6.8 Hz, 18-CH_3); Anal. Calcd for $C_{26}H_{29}O_5NF_6$: C 56.83, H 5.32, N 2.55. Found: C 57.10, H 5.55, N 2.65.

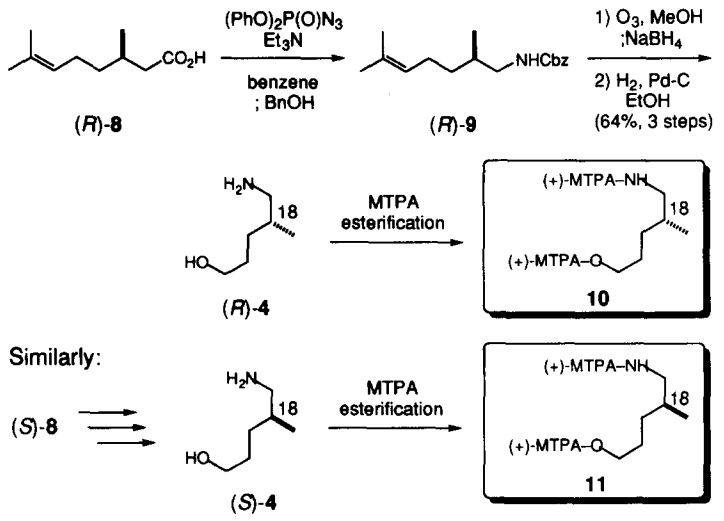


Fig. 3

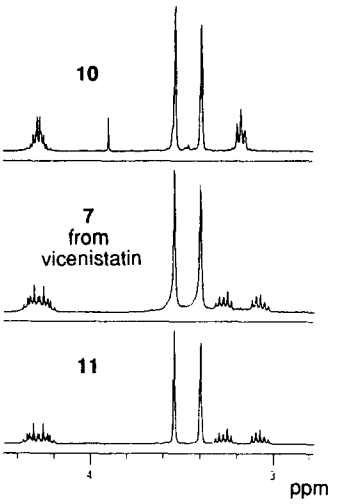


Fig. 4: ^{1}H-NMR Spectra of C_{15}-C_{19}

The remaining C6-C7 portion was expected to be 6*R*,7*R* as discussed above, and the triol **3** was synthesized from methyl (*S*)-3-hydroxy-2-methylpropionate *via* a known alcohol **12** {$[\alpha]_D^{18}$ –8.6° (*c* = 1.47, $CHCl_3$); Lit.: $[\alpha]_D$ –8.3° (*c* = 1.6, $CHCl_3$)} (7 steps) (Fig. 5) [4,5,6]. The ^{1}H-NMR spectrum of the naturally derived tribenzoate **5** was identical with that of the synthetic specimen (6*R*,7*R*)-**14**[3], but not with that of a minor by-product, (6*R*,7*S*)-**14**, which arose in the course of Sharpless' epoxidation. This result confirmed the relative stereochemistry of C6-C7. As to the absolute stereochemistry, the ^{1}H-NMR spectrum of the synthetic (6*R*,7*R*)-tri-(*R*)-MTPA ester **15** was quite different from that of the naturally derived Mosher's ester **6** with (*R*)-(+)-MTPA, but rather showed complete agreement with that of **16**[4] esterified with (*S*)-(–)-MTPA (Fig. 6). Consequently, the absolute stereochemistry of C6-C7 was proved to be enantiomeric to the synthetic (6*R*,7*R*)-**3**. In conclusion, the absolute configuration of the macrolactam aglycon was unequivocally determined to be 6*S*,7*S*,18*S* as shown in Fig. 7.

Although our attempt to predict the relative stereochemistry of the conformationally rather restricted aglycon was unsuccessful, this was probably because computation was done without considering the solvent effects. Actually, vicenistatin **1** is insoluble in less polar solvents and the NMR data were collected mostly by using pyridine-d_5, which could have significant effects on the actual conformation of **1**.

3. Compound (6*R*,7*R*)-**14**: ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.93-8.07 (m, 6 H, *o*-Ar), 7.47-7.59 (m, 3 H, *p*-Ar), 7.28-7.47 (m, 6 H, *m*-Ar), 5.65 (dt, 1 H, *J* = 4.2, 8.8 Hz, 7-H), 4.50 (dt, *J* = 5.8, 11.2 Hz, one of 9-H), 4.32-4.44 (m, 1 H, one of 9-H), 4.37 (dd, 1 H, *J* = 11.1, 5.9 Hz, one of 5-H), 4.28 (dd, 1 H, *J* = 7.1, 11.1 Hz, one of 5-H), 2.15-2.50 (m, 3 H, 6, 8-H), 1.21 (d, 3 H, *J* = 6.8 Hz, 6-CH_3); ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 171.9, 166.4, 165.9, 162.3, 134.5, 133.7, 133.1, 132.9, 130.5, 130.1, 129.9, 129.9, 129.8, 129.6, 129.5, 129.5, 129.2, 128.8, 128.4, 128.4, 128.3, 128.3, 71.6, 66.1, 61.6, 36.5, 30.9, 11.8; MS *m/z* (relative intensity) 446 (1.3, M^+), 324 (36), 283 (55), 219 (59), 203 (57), 161 (44), 106 (100), 105 (38), 97 (47), 68 (50), 51 (34).

4. Compound **16**: ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.31-7.54 (m, 15 H, Ar), 5.13 (ddd, 1 H, *J* = 3.4, 4.6, 8.1 Hz, 7-H), 4.30 (ddd, *J* = 5.1, 6.1, 11.2 Hz, one of 9-H), 4.00-4.16 (m, 1 H, one of 9-H), 4.06 (dd, 1 H, *J* = 6.7, 11.1 Hz, one of 5-H), 3.94 (dd, 1 H, *J* = 6.5, 11.1 Hz, one of 5-H), 3.51 (br d, 3 H, *J* = 0.96 Hz, OCH_3), 3.50 (br d, 3 H, *J* = 0.96 Hz, OCH_3), 3.49 (br d, 3 H, *J* = 0.96 Hz, OCH_3), 1.93-2.16 (m, 3 H, 6, 8-H), 0.82 (d, 3 H, *J* = 6.8 Hz, 6-CH_3); MS *m/z* (relative intensity) 782 (0.83, M^+), 549 (94), 315 (53), 189 (95), 105 (38), 81 (100).

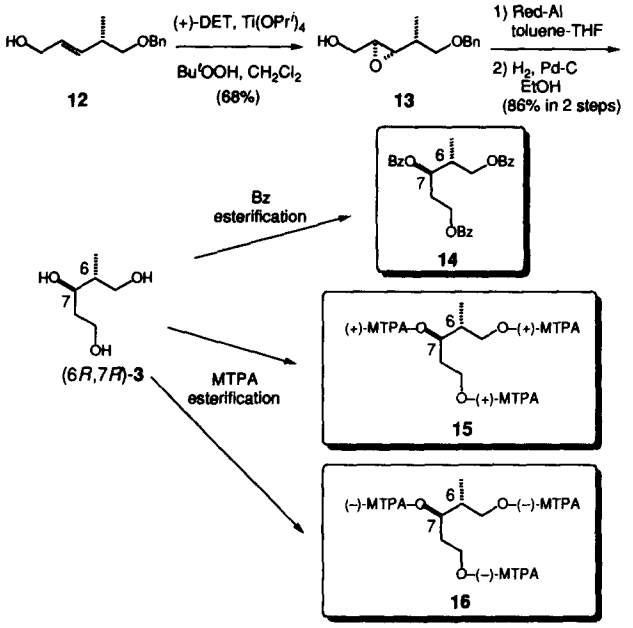


Fig. 5

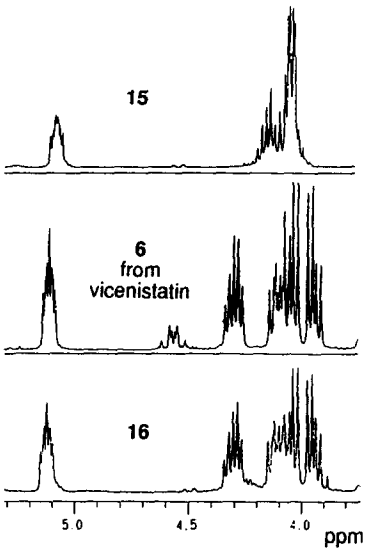
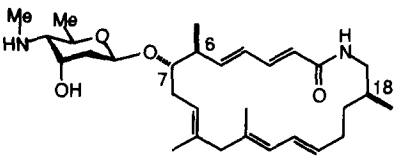


Fig. 6: ^{1}H-NMR Spectra of C_5-C_9



Vicenistatin (**1**)

Fig. 7 : Absolute Stereochemistry of Vicenistatin

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References

[1] Shindo K, Kamishohara M, Odagawa A, Matsuoka M, Kawai H. J. Antibiot. 1993;46:1076-1081.
[2] Goto H, Osawa E. J. Am. Chem. Soc. 1989;111:8950-8951.
[3] Haasnoot CAG, de Leeuw FAAM, Altona C. Tetrahedron 1980;36:2783-2792.
[4] Ireland RE, Thaisrivongs S, Dussault PH. J. Am. Chem. Soc. 1988;110:5768-5779.
[5] Nagaoka H, Kishi Y. Tetrahedron 1981;37:3873-3888.
[6] Meyers AI, Hudspeth JP. Tetrahedron Lett. 1981;22:3925-3928.