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SYNTHESIS OF A BICYCLIC HEXAPEPTIDE AS A PLAUSIBLE ACTIVE CENTER IN VANCOMYCIN

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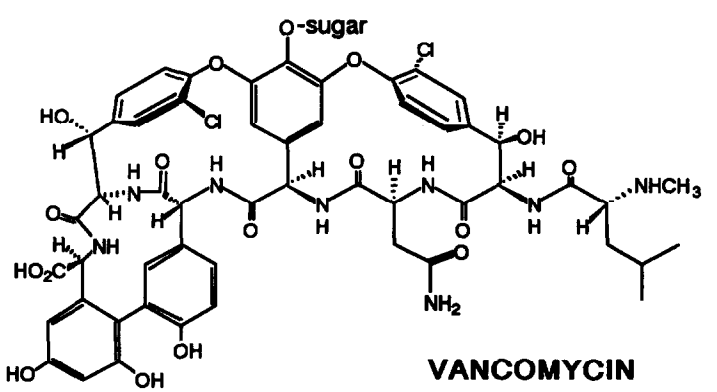
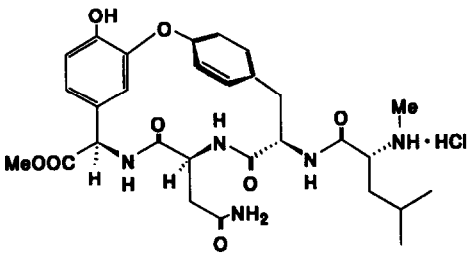
Summary: A bicyclic hexapeptide included in vancomycin has been synthesized using TTN oxidation method. This synthetic compound has the two macrocyclic peptide moieties, one of which is regarded as an active center in vancomycin which forms a binding pocket for the carboxylate region of the terminal D-Ala-D-alanine.

Both vancomycin[1] and ristocetin,[2] which belong to a large group of glycopeptide antibiotics, are quite attractive from view points of physiological activity, molecular recognition and natural products synthesis. Recently, synthetic studies on vancomycin and related antibiotics have been carried out by Still,[3] Hamilton,[4] Pearson[5] and others. As discussed in the previous paper,[6] we have two different methods to construct a macrocyclic diaryl ether: one is the oxidative phenolic coupling methodology developed by us,[7] and the remaining one is the Ullmann coupling methodology.[8] Of them, our method is quite simple and must be superior to the latter in the case of vancomycin and ristocetin having *p*-hydroxyphenylglycin moieties, whose epimerization takes place at the α-position quite easily. Thus, we synthesized two macrocyclic oligopeptides (1 and 2), one of which is regarded as a plausible active center in vancomycin.[6] Quite recently, synthetic study on vancomycin has also been carried out by Evans et al.[9] following our synthetic method, although some modification is formed. We describe herein a successful synthesis of a bicyclic hexapeptide (3), which is expected to bind to N-acetyl-D-Ala-D-alanine selectively as compared with the simple tetrapeptide (1).

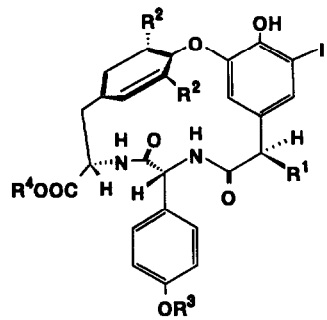
According to essentially the same procedure as described in the previous paper,[6] the tripeptide (4)[10] was treated with TTN (3 equiv.) in THF-MeOH (19:1) (0 °C, 2.3 h) directly to give a macrocyclic diphenyl ether (5), in



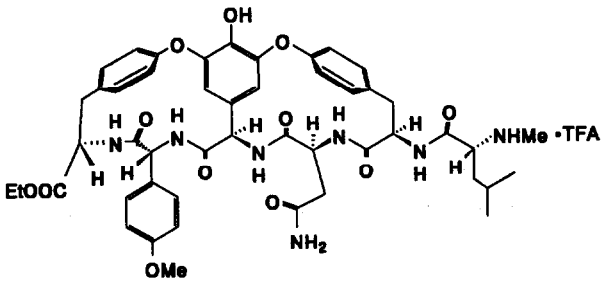
VANCOMYCIN



1



2 R^1 = NHZ, R^2 = Cl, R^3 = Bn, R^4 = Me
5 R^1 = NHZ, R^2 = Br, R^3 = R^4 = Me
6 R^1 = NH_2·HBr, R^2 = Br, R^3 = Me, R^4 = Et



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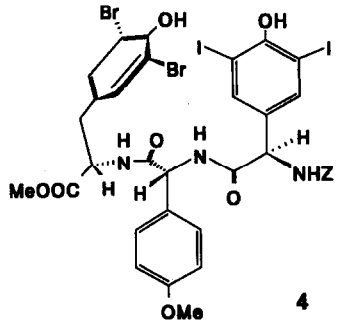

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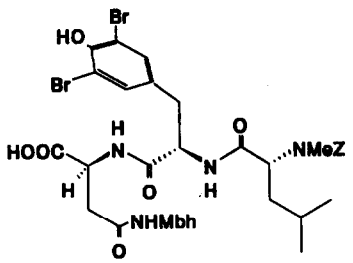

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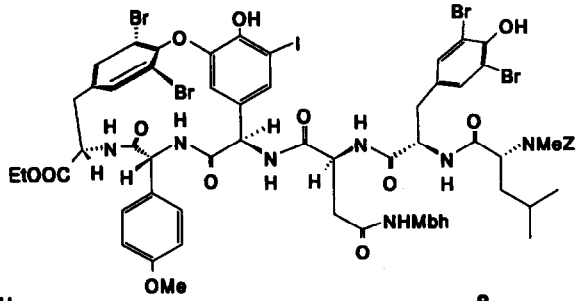
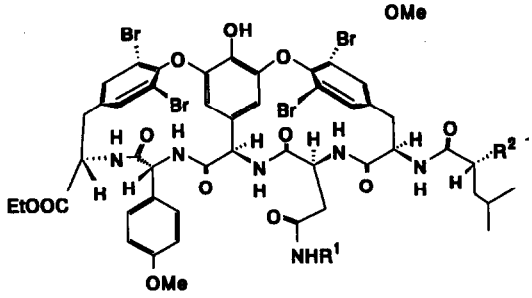


8



9 R^1 = Mbh, R^2 = NMeZ
10 R^1 = H, R^2 = NHMe·HBr

43% yield, which was deprotected in a usual manner (30% HBr/AcOH/anisole, room temp.)and then directly heated with EtOH to give the corresponding ethyl ester (6)[11,12] in almost quantitative yield. The compound (6) so far obtained was connected to a tripeptide (7)[10] in a usual manner [DCC (1 eqiv.), HOBt (1 equiv.), NMM (1 equiv.)/DMF; 0 °C → room temp., 10 h] to give a monocyclic hexapeptide (8),[11] in 82% yield. Then, 8 was further subjected to TTN oxidation[13] in MeOH (-10 °C, 8 h) followed by zinc reduction in AcOH (-10 °C → room temp., 3 h) to afford a bicyclic hexapeptide (9), in 34.7% yield, which was characterized as the corresponding amine (10).[11,14] Finally, the hexapeptide (9) was readily converted into the desired target oligopeptide (3)[11] in two steps [1) H_2/Pd-black/MeOH (room temp., 18 h); 2) 30% TFA in CH_2Cl_2/anisole (room temp., 1 h)]. In addition to some molecular recognition experiments, synthetic study on vancomycin is further in progress.

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10. These two tripeptides (4 and 7) were easily synthesized in a usual manner and gave satisfactory spectral data consistent with the assigned structures.
11. The spectral data for the new compounds are in accord with the structures assigned, and only selected data are cited: 3: $C_{48}H_{55}N_7O_{12}$ [m/z 936.49 (M^++H)]; $[\alpha]_D^{24}$ -15.34° (c 0.14, MeOH); IR (film) 3300, 2950, 1740, 1650 and 1510 cm^{-1}; δ (CD_3OD) 0.91 (3H, d, J= 6.6 Hz), 0.94 (3H, d, J= 6.6 Hz), 1.22 (3H, t, J= 7.1 Hz),

2.36 (3H, s), 2.43 (1H, dd, J= 4.4, 15.1 Hz), 2.55 (1H, dd, J= 10, 15.1 Hz), 2.77 (1H, t, J= 13.4 Hz), 2.94 (1H, t, J= 10.1 Hz), 3.03 (1H, dd, J= 5.1, 13.4 Hz), 3.11 (1H, dd, J= 4.4, 10.1 Hz), 3.72 (3H, s), 4.17 (2H, q, J= 7.1 Hz), 4.38 (1H, dd, J= 4.4, 10 Hz), 4.48 (1H, dd, J= 4.9, 11.7 Hz), 4.98 (1H, dd, J= 5.1, 13.4 Hz), 5.35 (1H, s), 5.49 (1H, s), 5.68 (1H, d, J= 2.4 Hz), 5.70 (1H, d, J= 2.4 Hz), 6.74 (1H, dd, J= 2.4, 8.5 Hz), 6.84 (2H, d, J= 8.8 Hz, overlapped with 1H signal), 7.11 (1H, dd, J= 2, 8.3 Hz), 7.16 (1H, dd, J= 2.4, 8.5 Hz), 7.21 (1H, dd, J= 2.4, 8.5 Hz), 7.30 (2H, d, J= 8.8 Hz, overlapped with 1H signal), and 7.40 (2H, complex). **5**: $C_{35}H_{30}N_3O_9Br_2I$ [m/z 923.86 (M^++H)]; IR (nujol) 3350, 1730, 1660, and 1510 cm^{-1}; δ (CD_3OD) 2.67 (1H, t, J= 13.5 Hz), 3.70 (6H, s), 5.37 (1H, s), 5.90 (1H, d, J= 3 Hz), 6.73 (2H, d, J= 9 Hz), 7.45 (2H, t, J= 3 Hz), and 7.73 (1H, d, J= 3 Hz). **6**: $C_{28}H_{26}N_3O_7Br_2I$ [m/z 803.87 (M^++H)]; $[\alpha]_D^{23}$ +66.1° (c 1.06, MeOH); IR (film) 3325, 2925, 1740, 1660 and 1510 cm^{-1}; δ (CD_3OD) 1.17 (3H, t, J= 7.1 Hz), 2.70 (1H, broad t, J= 7.1 Hz), 3.75 (3H, s), 4.15 (2H, q, J= 7.1 Hz), 5.07 (1H, broad dd, J= 5.1, 7.1 Hz), 5.26 (1H, s), 5.92 (1H, d, J= 2.1 Hz), 6.84 (2H, d, J= 9 Hz), 7.31 (2H, d, J= 9 Hz), 7.41 (1H, d, J= 2.1 Hz), 7.47 (1H, d, J= 2.1 Hz), and 7.77 (1H, d, J= 2.1 Hz). **7**: $C_{43}H_{48}N_4O_{10}Br_2$ [m/z 941.28 (M^++H)]; $[\alpha]_D^{24}$ +25.6° (c 1.0, $CHCl_3$); IR (film) 3325, 2950, 1650, and 1510 cm^{-1}; δ (CD_3OD) 2.67 (3H, s), 3.69 (6H, s), 5.13 (1H, broad s), 6.09 (1H, broad t, J= 3.9 Hz), 7.81 (4H, d, J= 9 Hz), 8.13 (4H, d, J= 9 Hz), 8.29 (2H, s), and 8.32 (5H, s).**8**: $C_{71}H_{72}N_7O_{16}Br_4I$ [m/z 1726.21 (M^++H)]; $[\alpha]_D^{24}$ -2.28° (c 1.0, MeOH); IR (film) 3350, 2975, 1740, 1660, and 1510 cm^{-1}; δ (CD_3OD) 3.70 (3H, s), 7.03 (2H, d, J= 8.3 Hz), 7.09 (2H, d, J= 8.3 Hz), and 7.46 (2H, s). **9**: $C_{71}H_{71}N_7O_{16}Br_4{\cdot}Na$ [m/z 1620.36 (M^++Na)]. **10**: $[\alpha]_D^{25}$ +17.6° (c 0.11, MeOH); IR (film) 3300, 2950, 1740, 1660, and 1510 cm^{-1}; δ (CD_3OD) 0.91 (3H, d, J= 6.6 Hz), 0.95 (3H, d, J= 6.6 Hz), 1.20 (3H, t, J= 7.1 Hz), 2.37 (3H, s, overlapped with 1H signal), 2.52 (1H, dd, J= 9.5, 14.9 Hz), 2.73 (1H, t, J= 13.2 Hz), 2.86 (1H, t, J= 12.2 Hz), 3.10 (1H, dd, J= 2.5, 13.2 Hz), 3.73 (3H, s), 4.15 (2H, q, J= 7.1 Hz), 4.40 (1H, dd, J= 4.4, 9.5 Hz), 5.49 (1H, s), 5.56 (1H, s), 5.63 (1H, d, J= 1.9 Hz), 5.71 (1H, d, J= 1.9 Hz), 6.84 (2H, d, J= 8.8 Hz), 7.29 (2H, d, J= 8.8 Hz), 7.41 (1H, d, J= 1.9 Hz), 7.56 (1H, d, J= 1.9 Hz), 7.68 (1H, d, J= 1.9 Hz), and 7.78 (1H, d, J= 1.9 Hz).

12. The ethyl ester (**6**) is easier than the corresponding methyl one in handling.
13. Interestingly, the macrocyclic diphenyl ether (**5**) was directly produced by TTN oxidation of **4**, whereas TTN oxidation of the substrate (**8**) afforded the methoxy dienone which was then subjected to zinc reduction to give the bicyclic hexapeptide (**9**). These remarkable differences have not yet been explained well.
14. This compound (**10**) was readily produced from **9** by using 30% HBr in AcOH containing anisole (30 eqiv.).

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