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SYNTHETIC STUDY ON VANCOMYCIN: SYNTHESIS OF A MACROCYCLIC TETRAPEPTIDE AS A PLAUSIBLE ACTIVE CENTER IN VANCOMYCIN

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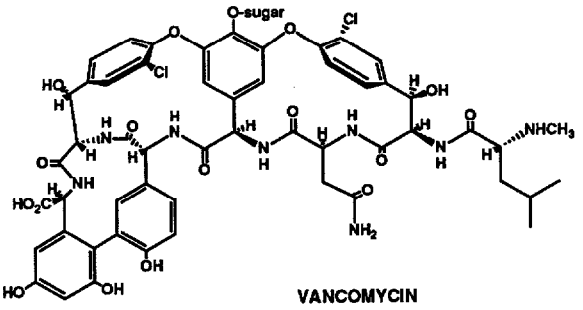
Summary: Two macrocyclic peptides included in vancomycin have been synthesized using TTN oxidation method. Of them, the macrocyclic tetrapeptide is regarded as an important moiety of vancomycin which forms a binding pocket for the carboxylate region of the terminal D-Ala-D-alanine.

Vancomycin, a glycopeptide antibiotic produced by Streptomyces orientalis,[1,2] is 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 other groups. We describe herein the syntheses of two macrocyclic peptides (**1** and **2**), one of which is considered to be an important moiety of vancomycin forming a binding pocket for the carboxylate region of the terminal D-Ala-D-alanine.[6] As demonstrated by total syntheses of OF 4949-III and K-13, the synthesis of isodityrosine was carried out by two different methods: one is the oxidative phenolic coupling methodology developed by us,[7,8] and the other one is the Ullmann coupling methodology.[5,9] The coupling yield in the former is not necessarily satisfied. Clearly, however, our synthetic method is quite simple and seems to be more effective for vancomycin synthesis rather than the latter. First of all, the macrocyclic tetrapeptide (**1**), which is expected to bind to N-acyl-D-Ala-D-alanine, has been synthesized starting from 3,5-dichloro-D-tyrosine methyl ester, as follows.

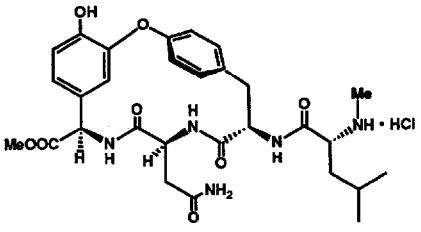
This methyl ester was connected to N-benzyloxycarbonyl-N-methyl-D-leucine using DCC (1.2 equiv) - 1-hydroxybenzotriazole (1 equiv) - N-methylmorpholine (1 equiv) in DMF - THF (0 °C - room temp., 14 h) and then treated with 2N aq.NaOH in MeOH (room temp., 30 min) to afford a dipeptide (**3**),[10] in 88% overall yield. According to the same procedure as described above, **3** was converted into the corresponding tripeptide (**4**),[10] in good yield, which was further reacted with 3,5-diiodo-4-hydroxy-D-phenylglycine methyl ester using DCC (1.2 equiv) - 1-hydroxybenzotriazole (1.1 equiv) in DMF (0 °C - room temp., 13 h) to afford a desired tetrapeptide (**5**)[10] in 73% yield.

In the next step, the substrate (**5**) was subjected to the oxidative phenolic coupling reaction using TTN (1 equiv) in THF - MeOH (16 : 1) (0 °C - room temp., 12 h) to give rise to a desired macrocyclic diphenyl ether (**6**),[10] in 21% yield, which was characterized as the corresponding amide (**7**)[11] quantitatively produced on deprotection using 20% TFA in CH_2Cl_2

containing anisole (room temp., 15.5 h). In this case, it should be noted that the macrocyclic diphenyl ether (**6**) was directly formed from **5** without epimerization at the phenylglycine moiety (see Scheme 1), in contrast to the K-13 synthesis,[8] wherein TTN



VANCOMYCIN



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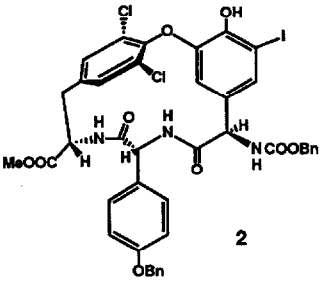

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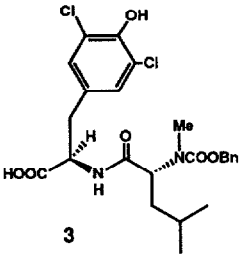

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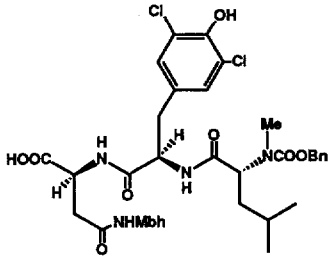

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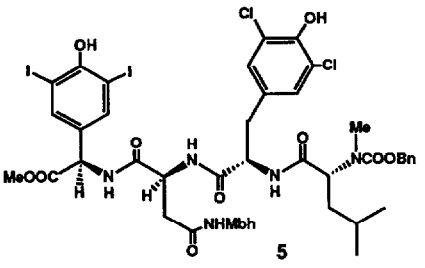

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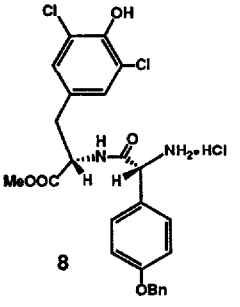

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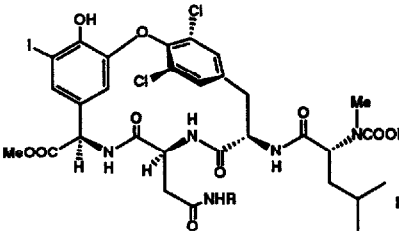
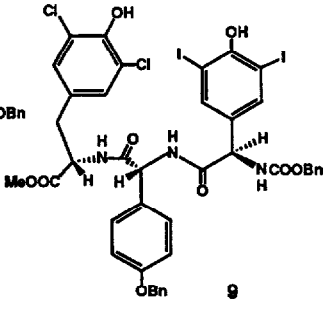


6 R = Mbh
7 R = H



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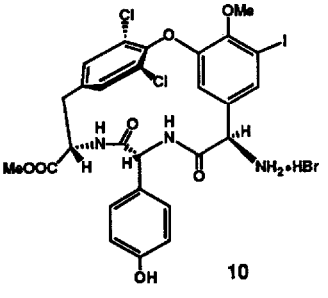

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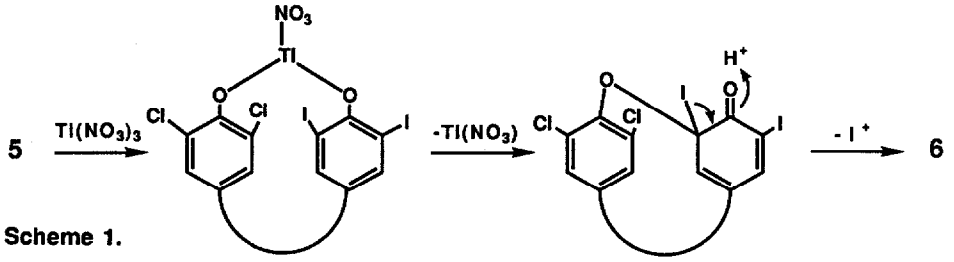

Scheme 1.

oxidation of the substrate afforded the methoxy dienone which was then subjected to zinc reduction to give the corresponding macrocyclic diphenyl ether.[12] The compound (**6**) so far obtained was further converted to the target compound (**1**)[11] in 5 steps [1) anisole/30% HBr/AcOH (room temp., 1 h), then dil.$NaHCO_3$; 2) $(Boc)_2O$/MeOH (room temp., 4.5 h); 3) H_2/Pd-C/NaOAc/MeOH (room temp., 4 days); 4) 4N HCl/dioxane (room temp., 1.5 h); 5) dil.$NaHCO_3$; 91% overall yield]. The macrocyclic diphenyl ether (**1**) will be used for the binding experiments with N-acyl-D-Ala-D-alanine. Furthermore, the compound (**6**) is regarded as an important synthetic intermediate for vancomycin and related antibiotics. The tripeptide (**2**) included in vancomycin molecule was also synthesized, as follows.

3,5-Dichloro-L-tyrosine methyl ester was connected to N-t-butoxycarbonyl-4-benzyloxy-L-phenylglycine in usual way [DCC (1.2 equiv) - 1-hydroxybenzotriazol (1 equiv) - N-methylmorpholine (1 equiv) in DMF (0 °C - room temp., overnight)] and then treated with 2N HCl in dioxane (room temp., 4.5 h) to afford a dipeptide (**8**),[10] in 80% overall yield, which was reacted with N-benzyloxycarbonyl-3,5-diiodo-4-methoxymethoxy-D-phenylglycine under the similar conditions and then hydrolyzed with 0.5N HCl in MeOH (room temp., 1.5 h) to give a tripeptide (**9**),[10] in 80% overall yield. This tripeptide was subjected to oxidative phenolic coupling reaction using TTN (3 equiv) in EtOAc - THF - MeOH (15 : 5 : 1) (0 - 4 °C, 2 h) to afford the corresponding macrocyclic compound (**2**),[11] in 35 - 40% yield, which was characterized as the methyl ester (**10**)[11] derived from **2** in 2 steps [1) CH_2N_2/MeOH (room temp., 1 h) (100%); 2) 30% HBr in AcOH containing anisole (room temp., 8.5 h) (50%)]. The compound (**2**) so far obtained will be utilized for vancomycin synthesis. Further synthetic studies on vancomycin and ristocetin are in progress.

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References

1. M. H. McCormick, W. M. Stark, G. E. Pittenger, R. C. Pittenger, and J. M. McGuire, Antibiot. Annu, **1955/1956**, 606.
2. G. M. Sheldrick, P. G. Jones, O. Kennard, D. H. Williams, and G. A. Smith, Nature

(London), **271**, 223 (1978); M. P. Williamson and D. H. Williams, J. Am. Chem. Soc., **103**, 6580 (1981); C. M. Harris, H. Kopecka, and T. M. Harris, J. Am. Chem. Soc., **105**, 6915 (1983).

3. D. W. Hobbs and W. C. Still, Tetrahedron Lett., **28**, 2805 (1987).
4. M. J. Mann, N. Pant, and A. D. Hamilton, J. Chem. Soc., Chem. Commun., **1986**, 158; N. Pant and A. D. Hamilton, J. Am. Chem. Soc, **110**, 2002 (1988).
5. A. J. Pearson, P. R. Bruhn, F. Gouzoules, and S. Lee, J. Chem. Soc., Chem. Commun., **1989**, 659.
6. M. P. Williamson, D. H. Williams, and S. J. Hammond, Tetrahedron, **40**, 569 (1984); J. P. Waltho, J. Cavanagh, and D. H. Williams, J. Chem. Soc., Chem. Commun., **1988**, 707.
7. H. Noda, M. Niwa, and S. Yamamura, Tetrahedron Lett., **22**, 3247 (1981); S. Nishiyama, K. Nakamura, Y. Suzuki, and S. Yamamura, ibid., **27**, 4481 (1986); S. Nishiyama, Y. Suzuki, and S. Yamamura, ibid., **29**, 559 (1988).
8. S. Nishiyama, Y. Suzuki, and S. Yamamura, Tetrahedron Lett., **30**, 379 (1989).
9. U. Schmidt, D. Weller, A. Holder, and A. Lieberknecht, Tetrahedron Lett., **29**, 3227 (1988); D. A. Evans and J. A. Ellman, J. Am. Chem. Soc., **111**, 1063 (1989); D. Boger and D. Yohannes, Tetrahedron Lett., **30**, 2053 (1989) and J. Org. Chem., **54**, 2498 (1989).
10. All new compounds described herein 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: **1** as an amorphous powder: $C_{29}H_{37}N_5O_8$ [m/z 584(M^++1)]; $[\alpha]_D^{23}$ -16° (c 0.05, MeOH); IR (film) 3250, 1740, 1670, 1630, 1590, 1540, 1510 cm^{-1}; ^1H NMR (CD_3OD): δ 0.98(3H, d, J = 6.4 Hz), 1.02(3H, d, J = 6.4 Hz), 1.52(1H, m), 1.64(1H, m), 1.72(1H, m), 2.60(1H, dd, J = 8.3, 11 Hz), 2.94(1H, t, J = 11 Hz), 3.20(1H, dd, J = 5.8, 11 Hz), 3.81(3H, s), 4.63 - 4.72(2H, complex), 5.50(1H, s), 6.10(1H, d, J = 1.5 Hz), 6.83(1H, dd, J = 1.5, 8.3 Hz), 6.87(1H, d, J = 8.3 Hz), 7.01(1H, dd, J = 2.9, 7.8 Hz), 7.05(1H, dd, J = 2.9, 7.8 Hz), 7.21(1H, dd, J = 2.9, 7.8 Hz), 7.48(1H, dd, J = 2.9, 7.8 Hz). **7** as an amorphous powder: $C_{37}H_{40}N_5O_{10}Cl_2I$ [m/z 912(M^++1)]; $[\alpha]_D^{23}$ -13.3° (c 0.53, $CHCl_3$); IR (film) 3300, 1750, 1670, 1500 cm^{-1}; ^1H NMR (CD_3OD): δ 0.92 - 1.01(6H, complex), 1.52(1H, m), 1.66(1H, m), 1.78(1H, m), 2.47(1H, m), 2.87(1H, m), 2.97(3H, s), 2.97(1H, overlapped with N-Me singlet), 3.35(1H, overlapped with the solvent signal), 3.84(3H, s), 4.77(1H, br.s), 4.91(2H, overlapped with the solvent signal), 5.22(2H, s), 5.49(1H, s), 5.98(1H, d, J = 2.0 Hz), 7.27(1H, br.s), 7.33 - 7.44 (6H, complex), 7.57 (1H, br.s). **10** as an amorphous powder: $[\alpha]_D^{24}$ -102° (c 1.00, MeOH); IR (film) 3250, 3050, 2950, 1750, 1670, 1560, 1520 cm^{-1}; ^1H NMR (CD_3OD): δ 2.94(1H, dd, J = 7.3, 14.7 Hz), 3.73(1H, dd, J = 3.9, 14.7 Hz), 3.85(3H, s), 4.07(3H, s), 4.25(1H, dd, J = 3.9, 7.3 Hz), 4.43(1H, s), 4.63(1H, d, J = 7.8 Hz), 5.75(1H, s), 5.90(1H, d, J = 2.0 Hz), 6.82 (2H, d, J = 8.8 Hz), 7.21(2H, d, J = 8.8 Hz), 7.33(1H, d, J = 2.0 Hz), 7.50(1H, d, J = 2.0 Hz), 7.83(1H, d, J = 2.0 Hz).
12. These remarkable differences have not yet been explained well.

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