Journal of Inclusion Phenomena **5** (1987), 109–111.

SYNTHETIC ANALOGS OF PEPTIDE-BINDING ANTIBIOTICS

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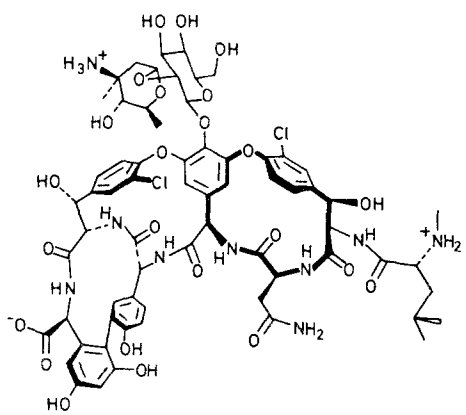
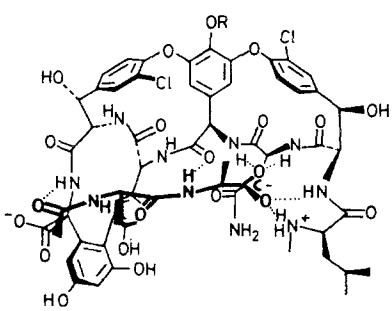
The vancomycin family of antibiotics offers an attractive target in synthetic host-guest chemistry. Vancomycin (1) has been shown by ^1H nmr to form discreet complexes with the -D-Ala-D-Ala fragment found in bacterial cell walls. The structure of the active complex (2) involves six hydrogen bonds between the antibiotic and dipeptide substrate. The complexation is strongly substrate- and stereoselective due to the concave nature of the cavity formed by the biphenyl and triphenyl diether components. Our interest lies in designing synthetic analogs of vancomycin both as novel receptors for peptide carboxylate substrates and as potentially interesting antibiotics.

In simplifying the complex structure of (1) we are eliminating all features that do not play a direct role in binding (e.g. carbohydrate and benzylic hydroxyl groups). We are also, in our early models, focusing on the right hand portion of (1) which forms, in (2), five of the six hydrogen bonds to the substrate.

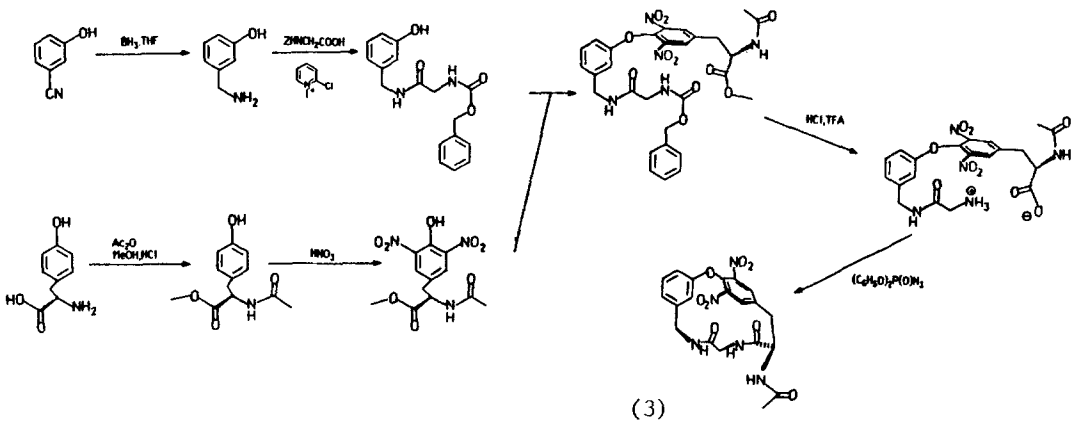


(1)



(2)

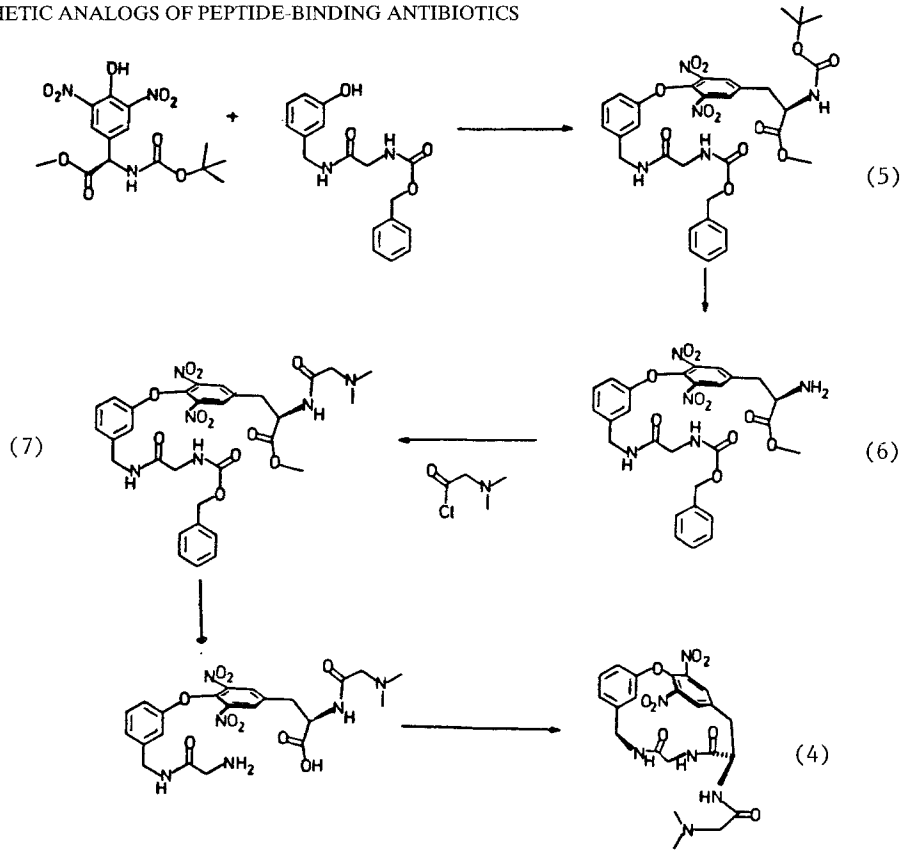
Our first synthetic analog (3) contains the three amide bonds involved in H-bonding to the carboxylate terminus as well as the key diphenyl ether functionality. The synthesis of (3) shown in scheme 1, involves a multistep sequence from 3-cyanophenol and D-(or L-) dinitrotyrosine. The ^{1}H nmr of (3) shows the 2-H proton resonance of the benzylamine ring to be shifted upfield



(3)

to 5.85 ppm. This is very similar to the resonance of the equivalent proton in vancomycin which occurs at 5.65 ppm and is due to the cyclic peptide constraining the 2-H proton to lie under the adjacent benzene ring. Despite the spectroscopic, and thus probable conformational, similarity between (3) and the right hand ring in (1) no complexation between (3) and carboxylate substrates was detected. This is most probably due to the absence, in (3), of the key N-terminal ammonium group of vancomycin which has been shown to play, via electrostatic interactions, an important role in carboxylate binding.

Our second model compound (4) incorporates the N-terminal ammonium group as a dimethylglycine residue. Inspection of CPK models suggested that the addition of a methyl group to the N-terminus would not hinder the approach of a substrate or the formation of the complex. However the use of a tertiary amine considerably simplifies the synthetic strategy to (4). This is shown is scheme 2 and involves preliminary protection of dinitrotyrosine as its



t-butoxycarbonyl derivative (5) followed by diphenyl ether formation and deprotection to amine (6). Addition of dimethylglycine acid chloride to (6) formed the tripeptide (7) which could be deprotected and cyclized, as with (3), to form analog (4). Preliminary studies of the interaction of the hydrochloride salt of (4) with carboxylate substrates indicate ^{1}H nmr behavior very similar to that of vancomycin, particularly involving loss of a single amide resonance and formation of a new resonance at 11.9 ppm. Further details of this study as well as the synthesis of (3) and (4) were presented in Lancaster.

References

1. M.P. Williamson and D.H. Williams, J. Am. Chem. Soc. 1981, 103, 6580. M.P. Williamson, D.H. Williams, and S.J. Hammond, Tetrahedron, 1984, 40, 569.