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SYNTHESIS OF PHENOLICALLY LINKED CYCLIC PEPTIDES

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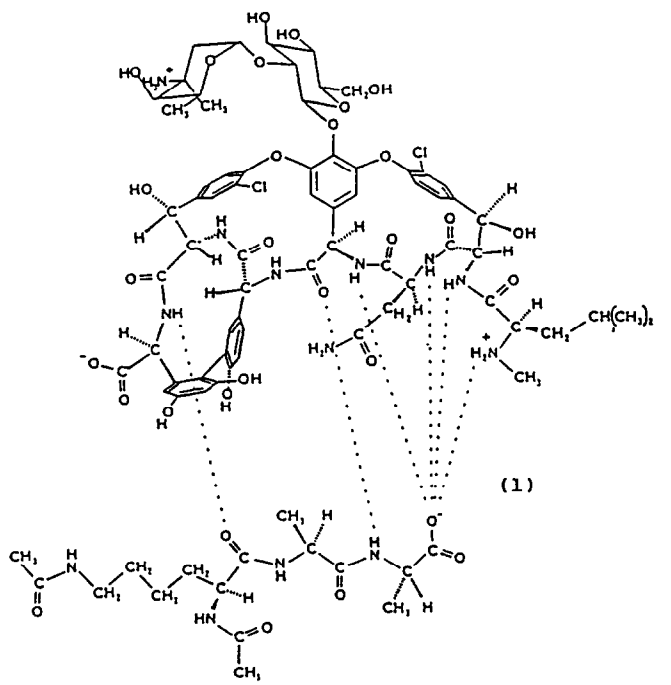
Abstract: Cyclization of a diaryl ether containing an α, ω-amino acid residue leads to cyclic peptides which resemble the vancomycin binding pocket.

The glycopeptide antibiotics, exemplified by vancomycin, are believed to act by complexation with the carboxyl terminal of a pentapeptide unit which usually forms cross links in the bacterial cell wall[1]. This complexation has been shown *in vitro* initially by the UV experiments of Perkins[2] and, more recently, by the elegant NMR studies of Williams[3]. From this work, the hydrogen bonds involved in binding have been mapped as shown in the diagram (1). Our work with iodonium salts[4] has provided a synthesis of functionalised diaryl ethers. Their conversion to cyclic peptides which mimic the carboxylate binding pocket involving the first four amino acids of the core heptapeptide in vancomycin[5] is the subject of this note.



(1)

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In order to simplify our approach, and negate the problems of enantio-specific amino acid synthesis, we chose to synthesise structures lacking the carboxyl terminus, e.g. (8). Thus the aldehyde (2)[4] was converted to the azido acid (5) as described in Scheme 1. Conversion of the acid to the hydroxy succinimido ester was achieved with DCC and N-hydroxy-succinimide. Hydrogenation of the latter, in the presence of just over one equivalent of trifluoroacetic acid, gave the activated ester amine trifluoroacetate (7) which, on heating with pyridine[6] in dilute solution (2mM), gave none of the desired product. The amino acid (6) could be produced by hydrogenation of the azide, (5), but attempted cyclization using DCC and DMAP[7] was unsuccessful. Treatment of the amino acid (6) in dilute DMF solution with triethylamine and diphenylphosphoryl azide[9] gave the desired cyclic peptide (8), along with the cyclodimer (9) and polymeric material. Conversion to the cyclic monomer was a low yielding process (9%) but the molecule's characteristic ^{1}H-NMR (*vide infra*) made identification straightforward. The ^{1}H-NMR of the cyclodimer shows the expected resonances for Boc and MeO, but the resolution is too poor for complete assignment. The evidence for its structure rests with the FAB - mass spectrum which shows ions at 961 ($\underline{M}Na^+$) and 939 ($\underline{M}H^+$), along with fragments showing loss of one and two Boc groups.

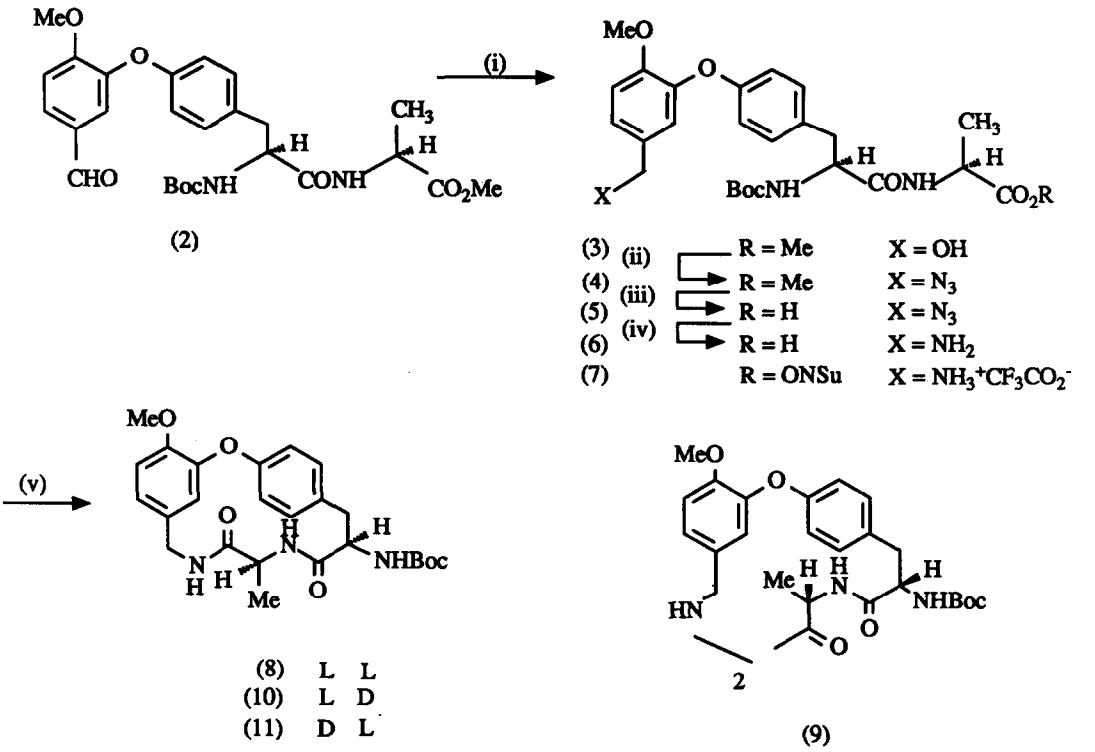
Yields in the cyclization of peptides are very variable, with substantial differences arising in the formation of different amide bonds, even within the same molecule[9]. With this in mind, we set about making the requisite precursor for formation of the alternative amide (Scheme 2). Thus the aldehyde (12) was converted via the alcohol (13) and azide (14) to the amino ester (15) which was then coupled with Z-alanine to give the protected precursor (16). Saponification of the ester gave the acid (17) which was hydrogenated to amino acid (18). Cyclization of (18), as before, gave the cyclic monomer (8), but still in low yield (9.5%).

The structure of (8) was assigned by examination of the ^{1}H-NMR[10] which shows the characteristic high field aromatic proton 3b as a narrow doublet (J = 2.0Hz) at δ5.91, found in vancomycin[11] at δ5.65, and in Hamilton's synthetic peptide[5] at δ5.84. The protons in the methylene groups, z_1 and x_3, appear as well separated signals with a $\Delta\delta$ of 1.6ppm in the latter case. This, taken with the fact that the aromatic tyrosine protons appear as individual multiplets, implies a rigid conformation with the phenyl groups nearly orthogonal; proton 3b, is thus in the shielding region of the tyrosine aromatic ring. Irradiation at 3b produced n.O.e.s. in the alanine methine x_2 as well as the tyrosine protons 1e and 1c, confirming the cyclic nature of the molecule.

The diastereomer with D-tyrosine and L-alanine (10) and its optical isomer with L-tyrosine and D-alanine (11) were both synthesised as described in Scheme 1 without significant changes in yield.

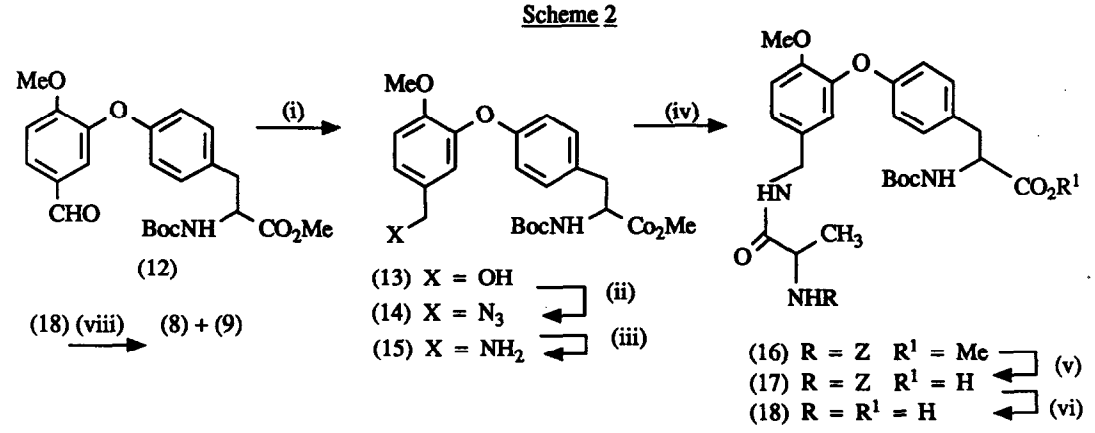
While none of these derivatives showed the characteristic change in uv on mixing with N-acetyl D-alanyl-D-alanine that is observed with vancomycin[2], (10) did show a small amount of antibacterial activity *in vitro*. It is interesting to note that (10) contains the same stereochemistry as vancomycin and that the enantiomer (11) did not show this activity.

Scheme 1



(i) $NaBH_4$, MeOH, 0°, RT, 30 min, 86%; (ii) PPh_3, $^iPrO_2CN{=}NCO_2{}^iPr$,HN_3 in $PhCH_3$, THF, RT, 15 min, 95%; (iii) NaOH (1.2 eq), aq MeOH, 2-3h, RT, 80%; (iv) 10% Pd/C,H_2, THF/H_2O (1:1), RT, 90 min; (v) $(PhO)_2PON_3$, Et_3N, 2.5mM, DMF, addition at 0°C, (30 min), 3 days, -5°C.

Scheme 2



(i) $NaBH_4$ (1 equiv), MeOH, RT, 30 min, 83%; (ii) PPh_3, $iPrO_2CN{=}NCO_2iPr$,HN_3 in $PhCH_3$, THF, RT, 15 min, 80%; (iii) 10% Pd/C (cat), H_2,THF/H_2O 1:1,90 min, quant; (iv) Et_3N, Z-Ala-OH, HOBT, DCC, THF/DMF, RT, overnight 58%; (v) NaOH (aq, 1.3), MeOH, RT, 3h, 35%; (vi) H_2, 10% Pd/C (cat), THF/H_2O; (vii) Et_3N, $(PhO)_2PON_3$,THF/H_2O, 9% (8) and 36% (9).

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10. N.m.r. nomenclature is that used by Williams;
Compound (8) δ_H ($CDCl_3$); 1.33 (3H, d, *J*, 6.7Hz, z_2), 1.45 (9H, s, $(CH_3)_3C$), 2.77 (1H, d, *J* 12.2 and 12.2Hz, z_1), 3.20 (1H, dd, *J* 12.2 and 5.2Hz, z_1), 3.70 (1H, dd, *J* 15.8 and 3.5Hz, x_3), 3.95 (3H, s, OCH_3), 4.10 (1H, m, x_2), 4.27 (1H, bm, x_1), 4.94 (1H, dd, *J* 15.8 and 9.5Hz, x_3), 5.32 (1H, d, *J* 8.8Hz, w_1), 5.85 (1H, bm, w_3), 5.91 (1H, d, *J* 2.0Hz, 3b), 6.37 (1H, d, *J* 7.2Hz, w_2), 6.70 (1H, dd, *J* 8.1 and 2.0Hz, 3f), 6.84 (1H, m + 1H, d, *J* 8.1Hz, 3e), 7.07 (1H, m), 7.37 (1H, m).

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