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SYNTHESIS OF ANALOGUES OF THE BIPHENOMYCIN ANTIBIOTICS

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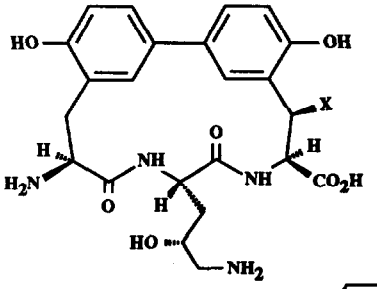
SUMMARY:

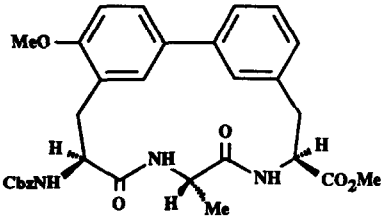
The oxidative coupling of L-tyrosine derivatives with vanadium oxyhalides has given dityrosine intermediates which were cyclized to give analogues of the biphenomycin antibiotics.

The biphenomycin antibiotics (1) are natural products produced by *Streptomyces griseorubiginosus*. Their isolation and characterization was first described by workers at Fujisawa[1] and their stereochemistry was fully defined by a later nmr study[2]. Our interest in these compounds was prompted by their spectrum of antibacterial activity which includes activity against some resistant Gram positive bacteria[3].

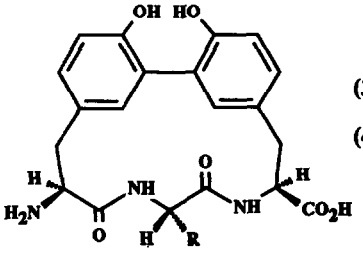
In any synthetic approach to the biphenomycins a suitable method is required for the formation of the biphenyl bond and this method should be compatible with the functionality found in protected amino acids. The Pd(0) catalysed coupling of an aryl boronic acid with an aryl bromide has been used successfully[4] in the synthesis of the analogue (2). Our work has examined the possibility of using an oxidative method for coupling two tyrosine residues and this led to the preparation of the analogues (3) and (4).



(1) X = H, OH



(2)

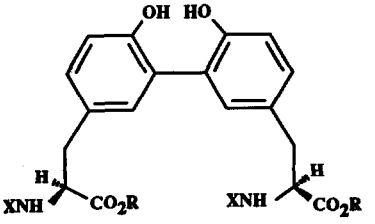


(3) R = Me

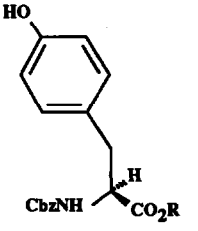
(4) R = $CH_2CH_2CH_2NH_2$

The oxidation of tyrosine or a derivative with hydrogen peroxide in the presence of horse-radish peroxidase has been described[5,6] although the yields of the resulting dityrosine compounds (5) and (6) were generally low (ca 10%) for these oxidative coupling reactions.

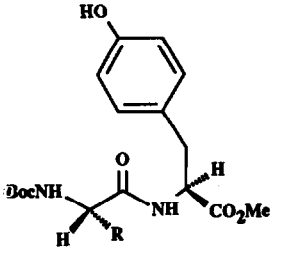
It seemed possible that alternative reagents might give an improved method for preparing dityrosine derivatives. The protected tyrosine (7) was therefore treated with $FeCl_3$ and with $K_3Fe(CN)_6$ but without success. Attention was then turned to vanadium oxytrifluoride and vanadium oxytrichloride which have been used by other authors for phenolic oxidation[7,8]. Compound (7) was therefore treated with VOF_3 (1eq.) (CH_2Cl_2/TFA/TFAA/-20°C,0.5h) and the dityrosine derivative (8) was obtained in 40% yield. The ^1H and ^{13}C nmr spectra of this compound[9] were consistent with those of similarly substituted biphenyls[6,10]. A similar reaction of (7) with $VOCl_3$ (1.3eq.) gave a 20% yield of (8). These yields compare favourably with



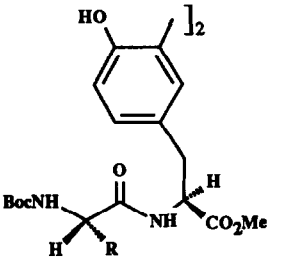
(5) X = H R = H
(6) X = CHO R = Me
(8) X = Cbz R = Me
(9) X = Cbz R = NP



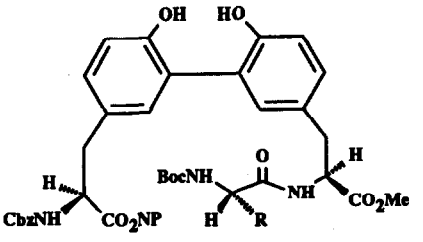
(7) R = Me
(10) R = NP



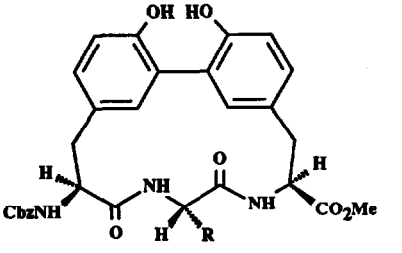
(11a,b)



(12a,b)



(13a,b)



(14a,b)

Cbz = benzyloxycarbonyl
NP = *p*-nitrophenyl
Boc = tert-butyloxycarbonyl

a: R = Me
b: R = $CH_2CH_2CH_2NHCbz$

the earlier reports[5,6], particularly when allowance is made for recovered starting material (up to 40%).

When a derivative of *o*-tyrosine was treated in a similar way there was no apparent reaction. The relative inertness of *o*-substituted phenols to oxidation by vanadium reagents has been remarked on before [8].

The possibility of using vanadium oxytrifluoride to bring about an intramolecular reaction was also examined. Thus the tripeptide Cbz-L-Tyr-L-Ala-L-Tyr-OMe was treated with VOF_3 in dilute solution but none of the desired cyclic product **(14a)** could be identified in the complex reaction mixture.

The application of this method to mixtures of tyrosine derivatives was examined next in the hope that it would provide an expedient synthesis of biphenomycin analogues. The dipeptides **(11a,b)** were available in near quantitative yields by conventional peptide coupling of L-tyrosine methyl ester with N-Boc-L-alanine and with α-N-Boc-δ-N-Cbz-L-ornithine (DCC/HOBT/DMF/THF). Each of the peptides **(11a,b)** was mixed with N-Cbz-L-tyrosine *p*-nitrophenyl ester **(10)** and added to a stirred solution of vanadium oxytrichloride (1.3eq) in dry THF (-60° to 0°C, 2 h). After a work-up procedure with aqueous citric acid, chromatography on silica gel was used to separate the main components of the reaction mixture. Recovery of unreacted starting materials was appreciable in each case (ca.50%) and the optical purity of these compounds was not changed by the reaction conditions. The dityrosine derivative **(9)** was obtained in yields of ca. 9% but the dimeric products **(12a,b)** were not identified in these reactions. However, the desired products **(13a,b)** were isolated although in low yield (7 and 5% respectively).

Removal of the Boc protecting group from the intermediates **(13a,b)** (TFA/CH_2Cl_2/RT, quantitative) was followed by a cyclization reaction which was carried out in dilute solution (0.005 Molar) (pyridine (20eq.)/HOBT(cat)/DMF, 100°C) with a syringe pump being used for the addition of the precursor over a period of 2 to 5 hours. The cyclic products **(14a,b)**[9] were the only products isolated from these reactions (yields 49% and 40% respectively). Saponification (0.1N $NaOH/H_2O$/MeOH/RT, quantitative) and hydrogenolysis (H_2/ 10% Pd-C/H_2O/dioxan, 85%) gave the desired biphenomycin analogues **(3)** and **(4)**. The nmr spectra of these compounds clearly differentiated each proton of the two tyrosine moieties present in the molecule.[9]

Neither of the derivatives **(3)** and **(4)** displayed appreciable antibacterial activity. At present, little is known about the mechanism of action of the biphenomycins[2] but it would appear from these results, particularly that of compound **(4)**, that the position of the hydroxyl groups in the molecule is significant.

ACKNOWLEDGEMENT:

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9. All compounds gave satisfactory spectroscopic data. Full data on selected compounds is given below:

Compound (3) $[\alpha]_D^{25}$ -24° (c 0.1 H_2O); λ_{max} H_2O 285nm (5,300); υ_{max}(KBr) 1653, 1620-1540 cm^{-1}; δ (400MHz D_2O) 1.37 (3H,d,J=7Hz), 2.20 (1H,dd,J=14,10.5Hz), 2.80 (1H,d,J=14Hz), 3.06 (1H,dd, J=15.2, 4.2Hz), 3.32 (1H,dd,J=15.2,3Hz), 4.10 (1H,d,J=10.5Hz), 4.40 (1H,dd,J=4.2,3Hz), 4.90 (1H,q,J=7Hz), 6.76 (1H,d,J=2.1), 6.79 (1H,d,J=8.2Hz), 6.86 (1H,d,J=2Hz), 6.90 (1H,d,J=8.2Hz), 7.08 (1H,dd,J=8.2,2Hz), 7.12 (1H,dd,J=8.2,2.1Hz); FAB MS MH^+414 MNa^+436.

Compound (4) isolated as dihydrochloride, $[\alpha]_D^{24}$ -10.8° (c 0.15 H_2O); λ_{max} H_2O 284nm (5,300); υ_{max}(KBr) 1720w,1660 cm^{-1}; δ (400MHz D_2O) 1.7-1.95 (4H,m), 2.90 (1H,dd,J=14.6,10.8Hz), 2.95-3.10 (2H,m), 3.18 (1H,dd,J=15.2,4.6Hz), 3.22 (1H,dd,J=14.6,ca.1Hz), 3.39 (1H,dd,J=15.2,3.2Hz), 4.44 (1H, dd,J=4.6,3.2Hz), 4.56 (1H,dd,J=10.8,ca.1Hz), 4.68 (1H,dd,J=ca.7,ca.7Hz), 6.76 (1H,d,J=2.2Hz), 6.93 (1H,d,J=8.3Hz), 6.96 (1H,d,J=8.2Hz), 7.02 (1H,d,J=2.2Hz), 7.16 (1H,dd,J=8.2,2.2Hz), 7.27 (1H,dd, J=8.3,2.2Hz); FAB HRMS Found MH^+457.2072 Calc for $C_{23}H_{29}N_4O_6$ 457.2087.

Compound (8) $[\alpha]_D^{28}$ +18.6° (c 0.3 $CHCl_3$); λ_{max} EtOH 245 (9,400) 291nm (7,000); ν_{max}($CHCl_3$) 3430, 3100-3500,1740(shoulder),1720cm^{-1}; δ (400 MHz $CDCl_3$) 2.85 (1H, dd, J= 13.5, 7.5Hz), 3.15 (1H,dd, J=13.5,4.5Hz), 3.73 (3H,s), 4.62-4.70 (1H,br), 5.00 (2H,AB), 5.31 (1H,br d,J=8Hz), 6.10 (1H br,exch. D_2O), 6.89 (1H,d,J=8.2Hz), 7.00 (1H,dd,J=8.2,1.8Hz), 7.04 (1Hd,J=1.8Hz), 7.2-7.35 (5H,m); ^{13}C nmr δ(100Mhz $CDCl_3$) *inter alia* 38.2 (t,CH_2), 55.1 (d,CH), 117.0 (d,C5), 123.5 (s,C3), 128.1 (s,C1), 130.9 (d,C2 or C6), 131.7 (d,C6 or C2), 152.8 (s,C4); FAB MS MH^+656.

Compound (14a) mp.280-283°C (acetone); $[\alpha]_D^{24}$+39.4° (c 1.1 MeOH); λ_{max} MeOH 290nm (6,600); υ_{max}(KBr) 1720,1700,1654 cm^{-1}; δ (400MHz d_6DMSO) 1.21 (3H,d,J=7Hz), 2.86 (1H,dd,J=15,10.8Hz), 2.88 (1H,dd,J=14.5,3Hz), 2.97 (1H,dd,J=14.5,6.3Hz), 3.02 (1H,dd,J=15,1.5Hz), 3.70 (3H,s), 4.38 (1H,ddd,J=6.5,6.3,3Hz), 4.56 (1H,ddd,J=10.8,9.1,1.5Hz), 4.66 (1H,dq,J=8.7,7Hz), 5.07 (2H,AB), 6.30 (1H, brd, J=6.5Hz), 6.68 (1H,d,J=2Hz), 6.72 (1H,d,J=8.1Hz), 6.76 (1H,d,J=8.1Hz), 6.80 (1H,dd,J=8.1,2Hz), 6.98 (1H,d,J=2Hz), 7.00 (1H,dd,J=8.1,2Hz), 7.30-7.40 (5H,m), 8.57 (1H,d,J=8.7Hz), 8.87 (1H,d,J=9.1Hz), 9.15 (2H,br); FAB MS MH^+562; Found C,64.04, H5.45, N,7.43% Calc for $C_{30}H_{31}N_3O_8$ C,64.16, H,5.56, N,7.48%.
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