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Studies Directed Towards the Total Synthesis of Vancomycin : Formation of Biphenyl Ether by Macrocyclisation

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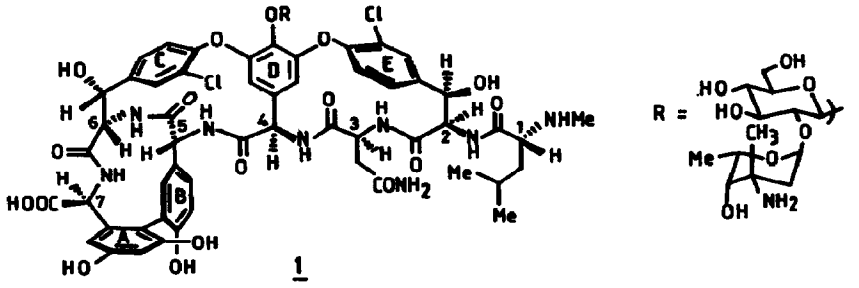
Abstract : A simple methodology for the construction of D-O-E diphenyl ether 16-membered ring system present in Vancomycin by intramolecular dispacement of fluorine by phenoxide reaction is described.

Vancomycin (1)[1], the widely recognized member of a family of clinically effective glycopeptide antibiotics[2], forms six hydrogen bonds with C-terminal D-Ala-D-Ala of the peptidoglycan precursors[2] and disrupting the bacterial cell wall biosynthesis. In addition, non-bonded interactions between the alanine methyl groups and hydrophobic region of the antibiotic may account for its strong substrate and stereospecificity[2,3]. Five of the six hydrogen bonds are found near the right hand ring of the antibiotic, and they form a binding pocket for the carboxylate region of the terminal D-Alanine.



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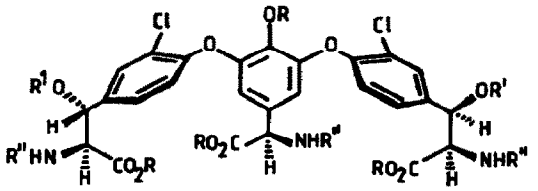
The complex functionalities present in these antibiotics, specially the inherent difficulty associated with the preparation of the dipeptide binding pocket composed of the D-O-E (2) and C-O-D fragments both 16-membered rings, have made the total synthesis of this molecule a difficult rask.

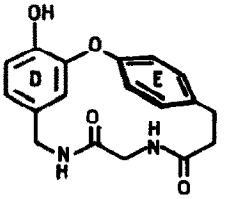
Macrolactamisation to construct model D-O-E and C-O-D rings, as reported by Hamilton et al[4a] and Crimmin et al[4b] resulted in less than 10% yield. However, the same strategy followed by Williams et al[5a] and Pearson et al[5b] failed to provide any cyclized product. Other notable approaches for the construction of D-O-E and C-O-D rings include Thallium (III) promoted intramolecular oxidative coupling developed originally by Yamamura et al[6a] and later adopted by Evans et al[6b]. The drastic conditions for some of these approaches are not compatible with the sensitive functionalities present in the parent molecule and, also the yields from

these methods are only moderate. Thus, the development of a mild approach to construct the D-O-E and C-O-D rings of Vancomycin, in high yields is, still, very much warranted to achieve the total synthesis of Vancomycin.



(R = R' = R'' = H)

Vancomycinic acid 3



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After successful synthesis of different fragments and important functionalities present in Vancomycin and related glycopeptide antibiotics, like biphenyl AB segment[7], β -hydroxy-α-amino acids[8], and Vancomycinic acid (3)[9] having the biaryl ether linkage, the most notable structural moiety present in these antibiotics, we focussed attention on the challenging task of final ring closure reactions.

Several attempts to construct the D-O-E ring by macrocyclisation through the amide bond closure[10] failed, leaving the diaryl ether linkage as the only site of choice to carry out the desired ring closure. Similar approach was attempted by Boger et al[11] employing Ullmann reaction to achieve this goal in moderate yield but adopting drastic conditions.

Herein, we report a successful application of our earlier reported method[12] based on "Ortho-Nitro-promoted" Ullmann ether synthesis to construct a model D-O-E ring[13]. The salient feature, in the present work, is the slight modification of this method[12], by the replacement of bromo with fluoro in the ortho-nitro aryl halide component which facilitated, the coupling reaction under extremely mild condition with dramatic improvement in the yield.

Our synthesis started with the commercially available 3-fluoro-4-nitro toluene, which was converted to the aldehyde **4** by chromium trioxide oxidation in acetic anhydride and sulfuric acid followed by treatment with ethanol and aq. H_2SO_4. This was then converted to amine **5** using ammonium acetate and sodium cyanoborohydride in dry methanol.

Acid **8** was prepared starting from the conversion of p-hydroxyphenyl propionic acid to amide **7** by coupling with glycine benzyl ester using N,N-dicyclohexyl carbodiimide (DCCI) and 1-hydroxy benzotriazole (HOBT) in DMF. Hydrogenation of **7**, followed by coupling of the acid **8** with amine **5** by active ester method using HOBT, DCC in DMF at room temperature for 12 h furnished linear dipeptide **9**.

The final intramolecular macrocyclisation was carried out with NaH, $CuBr.Me_2S$ complex in pyridine (0.002 M) for 18 h at room temperature to obtain the cyclic compound **10** in 71% yield. In our subsequent experiment, it was found that the intramolecular macrocyclisation

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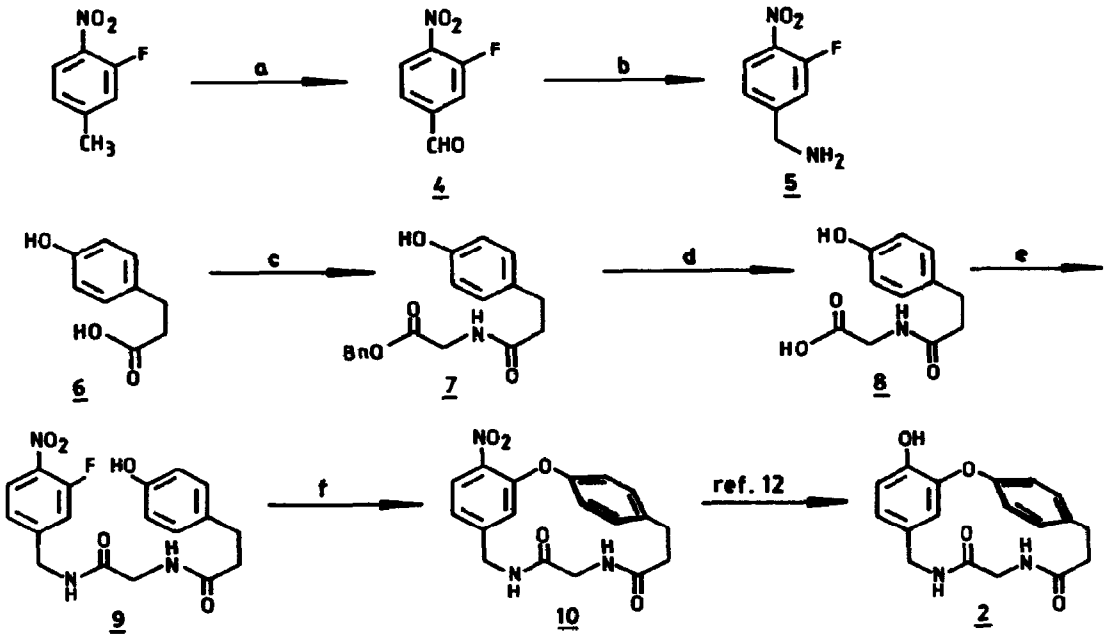

a) (i) CrO_3 (2.7 eq), Ac_2O, H_2SO_4 (4.0 eq), 0°C, 3 h; (ii) EtOH, H_2O (1:1), H_2SO_4, 1 h, 55%; b) $AcONH_4$ (10.0 eq), $NaBH_3CN$ (1.0 eq), Mol. Sieves, MeOH, 24 h, 61%; c) (i) DCC (1.5 eq), HOBT (1.0 eq), DMF, 0°C, 0.5 h; (ii) $BnOOC-CH_2-NH_2$, DMF, rt, 12 h, 87%; d) Pd-C/H_2, EtOAc, 2 h, 92%; e) (i) DCC (1.5 eq), HOBT (1.0 eq), DMF, 0°C, 0.5 h; (ii) 5 in DMF, rt, 12 h, 82%; f) NaH (1.0 eq), Pyridine (0.002 M), rt, 18 h.

proceeds equally well in the absence of $CuBr.Me_2S$ complex, thereby demonstrating that, this reaction is proceeding by a simple displacement of activated fluorine by phenoxide anion. The facile conversion of nitro to hydroxy function has been demonstrated in our earlier work[12].

In conclusion, a nitro group in the ortho position of the aryl fluoride component serves as an excellent promoter for intramolecular 16-membered biphenyl ether formation under extremely mild conditions. Presently, work on the extension of this method for the synthesis of Vancomycin D-O-E and C-O-D rings is under progress.

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