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Synthetic Studies Towards Glycopeptide Antibiotics : Synthesis of the 16-membered Cyclic Tripeptide (DOEG Ring) System of Teicoplanin

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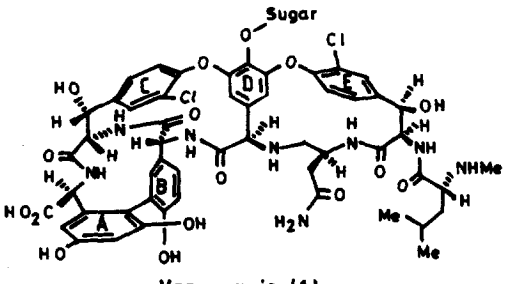
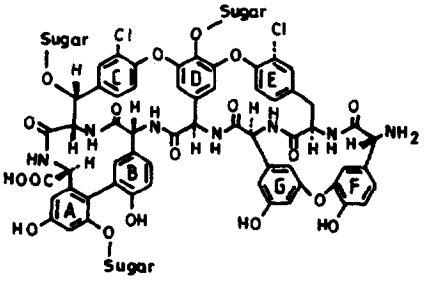
Abstract : The synthesis of the 16-membered cyclic DOEG ring system of teicoplanin, which forms the binding pocket for the carboxylate region of terminal D-Ala-D-Ala of the bacterial cell wall via macroetherification of linear tripeptide **20** is described. Copyright © 1996 Published by Elsevier Science Ltd

In our efforts to achieve the synthesis of vancomycin, the most sought after member of the vancomycin-teicoplanin family of glycopeptide antibiotics (or dalbaheptides), we have reported the first synthesis of vancomycinic acid[1] (CDE moiety) and actinoidic acid (AB segment)[2]. Our attempts to construct DOE or COD rings through macrolactamization of corresponding linear tripeptides failed to provide any cyclisation product. This was also confirmed by various other groups[3]. The bio-mimetic approach adopted by Yamamura[4] and Evans[5] for the construction of DOE and COD models of vancomycin by thallium (III) nitrate intramolecular oxidative coupling seems to be the most logical to achieve the synthesis of **1**. However, their methodology where both ortho positions of the phenoxide units are substituted by halogen atoms is not suitable for vancomycin or teicoplanin synthesis because of the inherent difficulty in selective removal of one chlorine atom from each of the aryl amino acids of the bicyclo C-O-D-O-E biaryl ether segment. Hence we resorted to an alternative approach of macrocyclisation by using the aromatic nucleophilic substitution reaction (S_NAr) for the synthesis of the 17-membered K-13[6] and the 16-membered model ring[7] system of dalbapeptides.



Vancomycin (1)

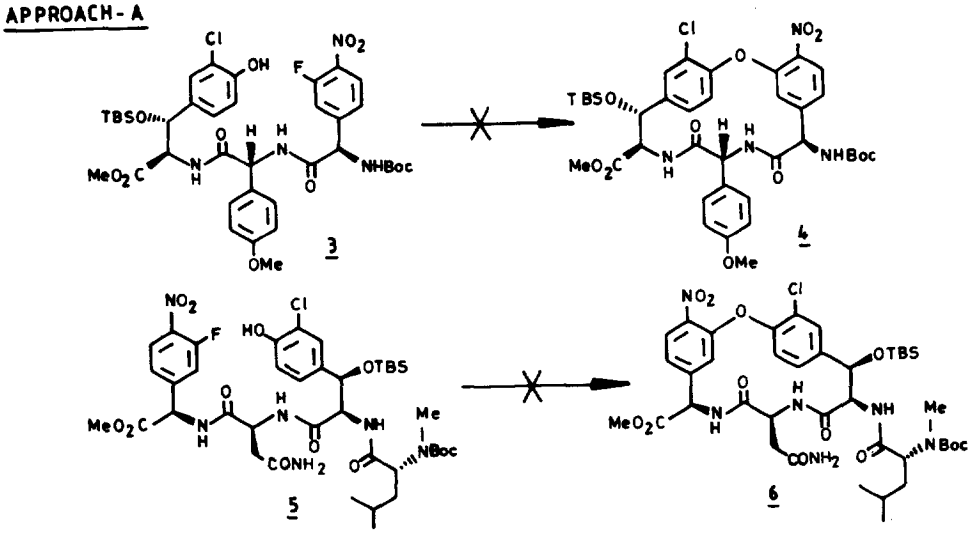


Teicoplanin (2)

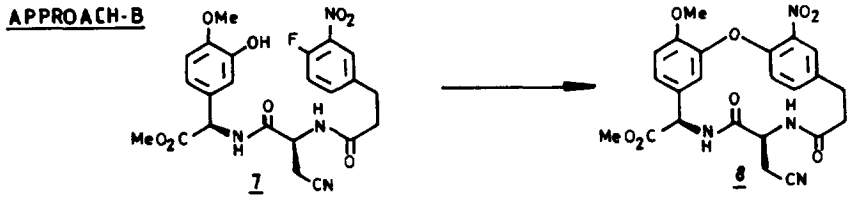
In principle, two strategies could be examined for the S_NAr approach to construct the actual 16-membered COD or DOE biaryl ether systems of vancomycin or teicoplanin. In the first instance, one can plan the displacement of the fluoride atom adjacent to the nitro group in ring D with the phenoxide of the chloro-tyrosine residue (ring C or E) (approach A). Alternatively, this could be effected by displacing the fluoride atom present in the nitrotyrosine

residue (ring C or E) with the phenoxide anion of the centrally located D ring (approach B).

However, our efforts to construct the COD ring (4) or DOE ring (6) of vancomycin from the corresponding tripeptide residue (3) or the tetrapeptide residue (5), representing approach A, failed under various conditions tried by us. In both these cases the reaction provided



recovered starting materials while by extending the reaction period, undesirable decomposition of starting material was observed. This is attributed to hydrolysis of the susceptible nitrofluorophenyl glycine peptide bond under the conditions employed. The presence of the p-nitro group on phenylglycine seems to be the main source of the problem. Having failed to build the 16-membered macrocycle by approach A, we resorted[8] to approach B and successfully completed the core segment of teicoplanin.

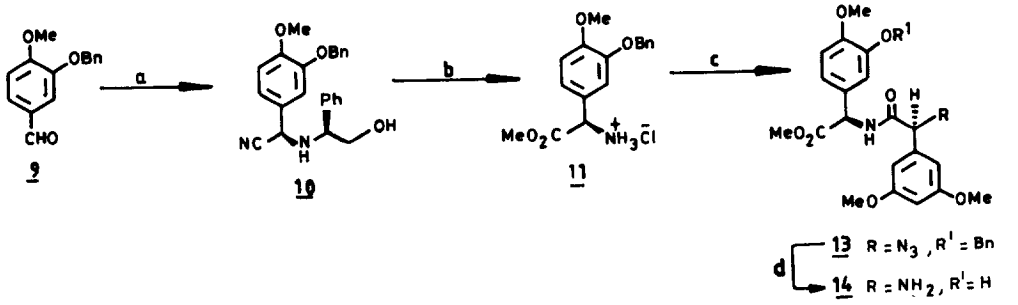


The tripeptide (7) in which the nitro and fluoro substitutions were present on the phenylpropionic acid group was cyclised under optimal conditions [K_2CO_3, DMF (0.01M), r.t. 10h] to the required product 8 in 45% yield. This successful modification was then extended to complete the core synthesis of DOEG ring system of teicoplanin.

Accordingly, the benzyl protected isovanillin derivative 9 on treatment with (S)-phenylglycinol in chloroform followed by sequential addition of methanol and TMSCN at 0°C gave a mixture of diastereomers 10 (85:15)[9]. The major diastereomer was seperated by flash chromatography. The nitrile was converted into the methyl ester by treatment with ethereal HCl

in dry methanol. The chiral auxiliary appendage was removed by oxidative cleavage using lead tetraacetate (LTA) followed by treatment with dilute HCl to give the hydrochloride salt **11**. The compound **11** was neutralised and then coupled with (S)-α-azido-3,5-dimethoxyphenylacetic acid (**12**)[10] using DCC and HOBT in DMF to provide **13** in 90% yield, which on hydrogenation afforded the amine **14** (Scheme 1).

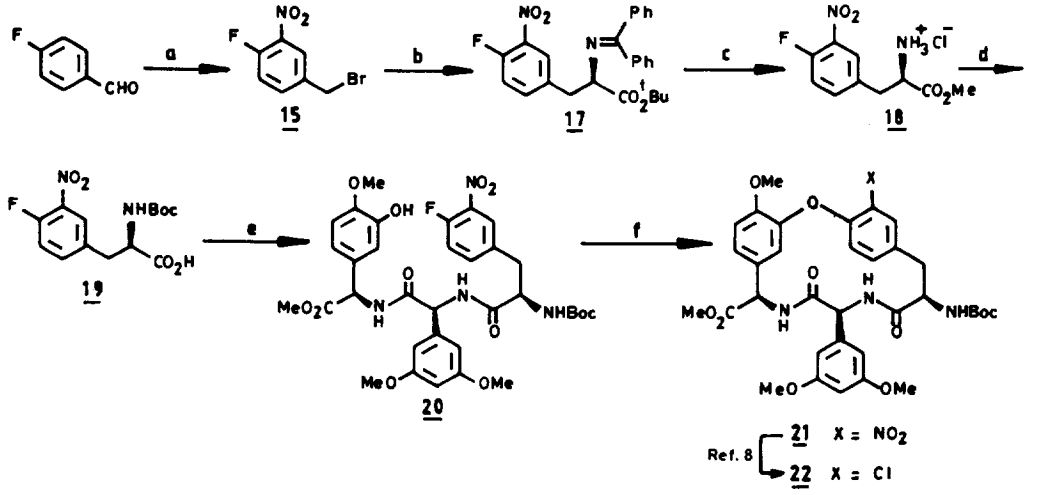
Scheme 1



Reagents : a) i) (S)-phenylglycinol, $CHCl_3$; ii) MeOH, TMSCN; b) i) methanolic HCl, 0°C-r.t.; ii) LTA, CH_2Cl_2-MeOH (3:1); c) (S)-α-azido-3,5-dimethoxyphenylacetic acid (12), DCC, HOBT, DMF; d) H_2, Pd/C, MeOH.

(R)-4-Fluoro-3-nitrophenylalanine (**19**) was prepared from 4-fluorobenzaldehyde. The derived bromo-derivative **15** was subjected to asymmetric phase transfer catalysed alkylation of prochiral glycine Schiff's base **16** using the chiral phase transfer catalyst, N-benzylcinchoninium bromide, to afford the alkylated product **17** in 80% yield (Scheme 2). The one pot conver-

Scheme 2



Reagents : a) i) fuming HNO_3, H_2SO_4, 0°C; ii) $NaBH_4$, MeOH; iii) PBr_3, ether; b) i) $(Ph)_2C{=}NCH_2CO_2{}^tBu$ (16), N-benzylcinchoninium bromide, 50% aq. NaOH; c) i) methanolic HCl; ii) $SOCl_2$, MeOH; d) i) $(BOC)_2O$, $NaHCO_3$, THF; ii) K_2CO_3, MeOH-H_2O (5:1); e) 14, EDCI, HOBT, DMF; f) K_2CO_3 (3.0 eq.), DMF (0.01M), 18 h.

sion of **17** to **18** occurred concomitantly by treatment with methanolic HCl followed by addition of thionyl chloride.

The stereochemical outcome of this reaction was based on well established precedent[11] and the enantiomeric purity of the product **18** was found to be 85% as measured by ^{1}H NMR analysis of the Mosher amide. Compound **18** was protected as NHBoc derivative and the methyl ester was hydrolysed with K_2CO_3 in methanol followed by coupling with dipeptide **13** employing EDCI and HOBT as promoters in DMF to afford the tripeptide **20** in 80% yield. When **20** was subjected to cyclization conditions [K_2CO_3, DMF (0.01M), 40°, 18h] the 16-membered macrocycle DOEG ring system (**21**) was obtained in 42% yield as a mixture of atropisomers. The structure of **21** was substantiated by ^{1}H NMR, IR and FAB Mass spectral analysis.

In conclusion, an efficient route to the construction of the 16-membered DOEG ring of teicoplanin is described for the first time. The chemistry developed herein will play a crucial role in the total synthesis of these glycopeptide antibiotics.

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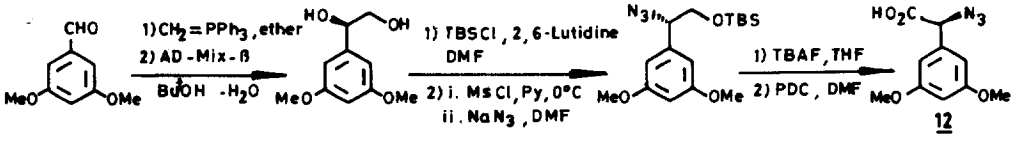

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