Synthesis of a model bicyclic C-O-D-O-E ring of vancomycin by a one-pot, double S_NAr based macrocyclization

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Double cyclization of linear pentapeptide 3 by treatment with CsF in DMF at −5 °C gives a model bicyclic CODOE ring 2 of vancomycin in a one-pot fashion.

The glycopeptide antibiotics of the vancomycin **1** (Fig. 1) family are clinically important for the treatment of infections due to methicillin-resistant *Staphylococcus aureus* and other gram positive organisms.[1] After more than 35 years of clinical use, resistance to the drug has been recently detected[2] and led to renewed interests in this field. Both structural modifications of antibiotics[3] and the syntheses of designed non-natural products[4] have appeared addressing the vancomycin resistance phenomena.

The complex structure of vancomycin makes it a challenging synthetic target.[5] Until now, the thallium trinitrate promoted oxidative phenolic coupling method developed by Yamamura[6] and Evans[7] is among the most efficient. Nevertheless, the problem of stereoselective introduction of only one substituent (Cl or other transformable group) into the aromatic C and E rings had not yet been addressed at the outset of our work and is probably one of the most difficult synthetic obstacles.

Our own contribution in this field is the discovery of an efficient macrocyclization using intramolecular nucleophilic aromatic substitution (S_NAr) for biaryl ether formation.[8] Based on this technique, we report herein our preliminary results on the efficient synthesis of model bicyclic CODOE ring **2** of vancomycin with the aim of controlling the atropdiastereoselectivity in the cyclization step. The characteristic feature of this synthesis is the double S_NAr reaction of the linear pentapeptide **3** leading, in one step, to the desired bicyclic system.

The (*R*)-*N*-Boc-4-methoxy-3,5-diisopropyloxy phenyl glycine **8** has been previously prepared in this laboratory *via* asymmetric Strecker reaction.[9] However the enantiomeric excess was only 80%. A more efficient synthesis was thus developed (Scheme 2). A conventional five-step sequence starting from the known aldehyde **4**[9] gave the one-carbon homologated acid **5** which was transformed into the imide **6** in 85% yield. Electrophilic azidation of **6** under Evans conditions[10] afforded a diastereoisomerically pure compound **7** (71%) which was converted into the desired amino acid **8** *via* a two step sequence.†

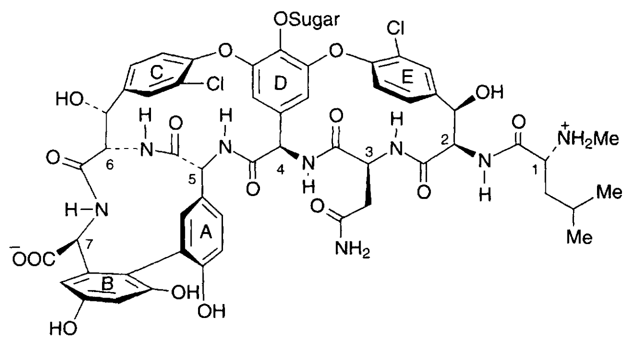
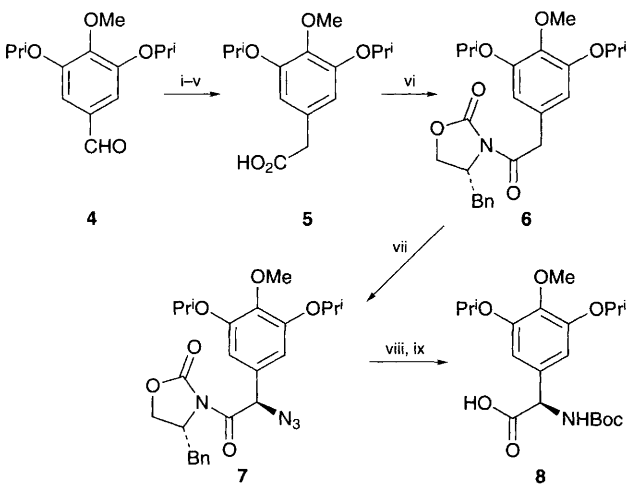
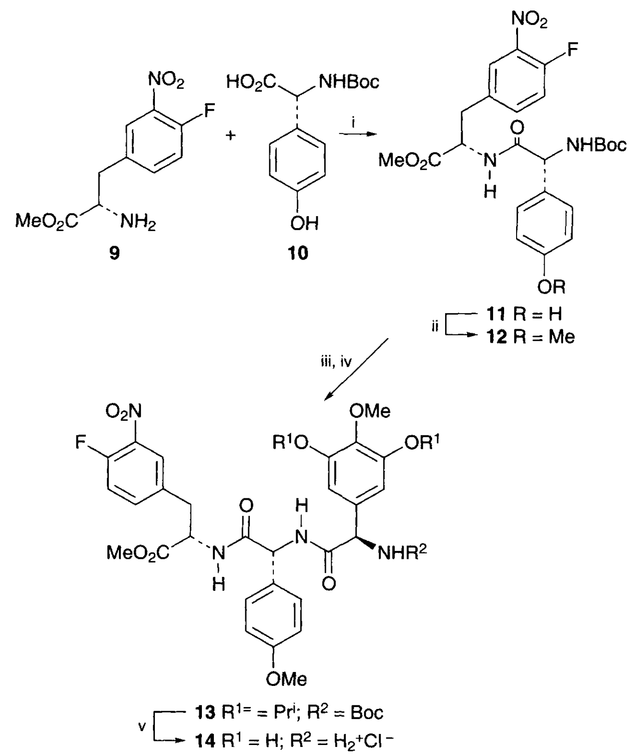


Fig. 1 Vancomycin **1**



Scheme 1 *Reagents and conditions*: i, $NaBH_4$, EtOH, 92%; ii, PBr_3, toluene, 90%; iii, NaCN, Me_2SO, 97%; iv, K_2CO_3, H_2O_2, Me_2SO, 94%; v, KOH, ethyleneglycol, 88%; vi, Me_3CCOCl, Et_3N, THF, then lithium salt of (*R*)-4-phenylmethyl-2-oxazolidinone, 85%; vii, KHDMS, $TrisylN_3$, THF, then Me_2SO, NaI, NaOAc, 71%; viii, 10% Pd/C, Boc_2O, EtOAC, 85%; ix, LiOH, THF–H_2O, 90%



Scheme 2 *Reagents and conditions*: i, EDC, HOBt, CH_2Cl_2, 92%; ii, CsF, MeI, DMF, 83%; iii, TFA–CH_2Cl_2, anisole; iv, EDC, HOBt, CH_2Cl_2, Et_3N, **8**; v, BCl_3, CH_2Cl_2, then MeOH, 100%

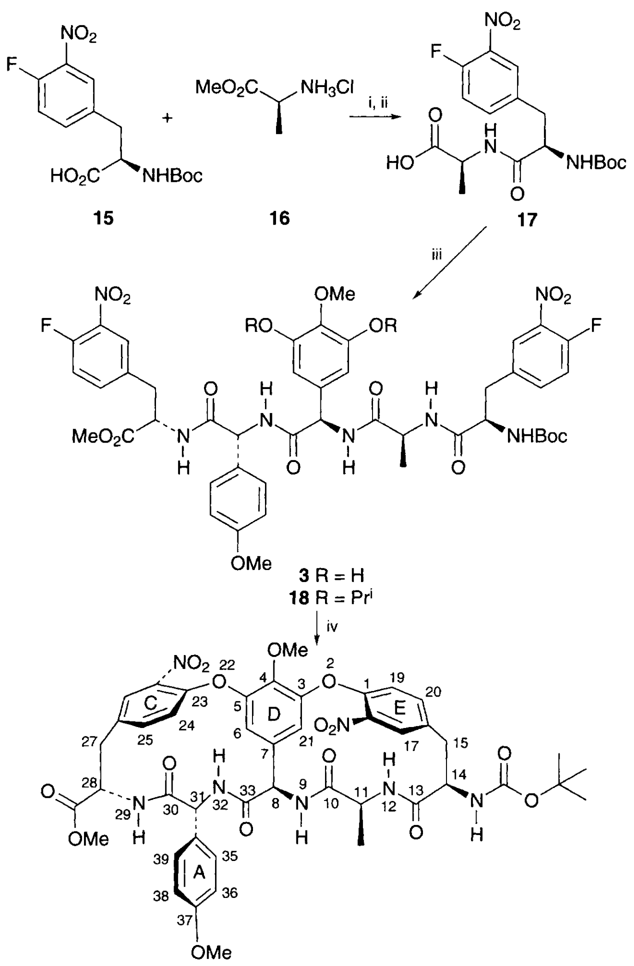
Coupling of (*S*)-methyl-4-fluoro-3-nitrophenyl alanate **9**, prepared by alkylation of Schollköpf's bislactim ether,[11,4] with *N*-Boc-(*R*)-4-hydroxyphenyl glycine **10** (EDC, HOBt) gave, after methylation (MeI, CsF, DMF), dipeptide **12** in 83% yield. Under these methylation conditions, neither racemization nor the formation of 14-membered macrocycle‡ have been detected. Removal of the Boc group under mild acidic conditions followed by coupling with amino acid **8** provided the tripeptide **13** which was deprotected (BCl_3) to give the corresponding hydrochloride salt of aminophenol **14** in quantitative yield.

Elongation of **14** to pentapeptide **3** was accomplished as shown in Scheme 3. Coupling of known *N*-Boc-(*R*)-3-nitro-4-fluorophenyl alanine with methyl (*S*)-alanate followed by hydrolysis provided the dipeptide **17**. [3 + 2]Segment coupling between the tripeptide **14** and the dipeptide **17** gave the pentapeptide **3** (65%). This reaction is noteworthy in that the two phenolic functions do not need to be protected and no trace of *O*-acylated compound was isolated.

Cyclization of **3** was first attempted at room temperature, by means of different bases (K_2CO_3, CsF) in different solvents (DMF, Me_2SO) with or without additive (18-crown-6). In every case, reaction mixtures containing at least four cyclized compounds were obtained and this result was tentatively attributed to the presence of two newly created axial chiral centres leading to the four atropisomers.§ When the cyclization was run at −5 °C using dry CsF as a promoter in DMF, one major product **2** was formed and was isolated in 60% yield. The cyclized structure of **2** was evidenced by the presence of characteristic upfield shielded protons H-6 and H-21 (δ 5.59 and 6.03, respectively). In order to verify if any racemization had occurred during the cyclization, pentapeptide **18** was prepared from **13** following the same synthetic scheme. When **18** was submitted to the above mentioned cyclization conditions for 4 days, a diastereoisomerically pure **18** was recovered quantitatively. This control experiment clearly showed that little, if any, racemization occurred under the cyclization conditions.

The assignment of ^1H NMR spectra of **2** was carried out by COSY, NOESY experiments performed in CD_3CN and in $[^2H_6]Me_2SO$ solution at 60 °C because of the better resolution observed. It is important to note that there was no atropisomerisation at this temperature as the spectra recorded before and after heating (15 h) were identical. The stereochemistry of amide bonds (all *trans* configuration) as well as two axial chiral centres were determined as shown in Scheme 3 according to the NOE studies. Representive NOE cross peaks of **2** were as follows: NH32/H35, H6 H8; NH29/H31; H17/H15; H40/27′, NH9/21, Me; H25/H28, H27; H20/H15′; H19/H21; H24/H6, H14/H20.

We thank Mr J.-F. Gallard for 2D NMR experiments.



Scheme 3 *Reagents and conditions*: i, EDC, HOBt, Et_3N, CH_2Cl_2, 99%; ii, K_2CO_3, MeOH, H_2O, 98%; iii, EDC, HOBt, **14**, Et_3N, CH_2Cl_2, 65%; iv, CsF, DMF, −5 °C, 60%

Footnotes

† All new compounds described herein gave spectral data consistent with the assigned structures.

‡ A 14 membered macrocycle was formed when compound **11** was treated with CsF in DMF at room temperature. Obviously, in the presence of MeI, intermolecular methylation proceeded much faster than the intramolecular S_NAr reaction.

§ All of the four isolated compounds show the characteristics peaks of upfield shifted protons H-6 and H-21 indicating the bicyclic structure.

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