Total Syntheses of Vancomycin**

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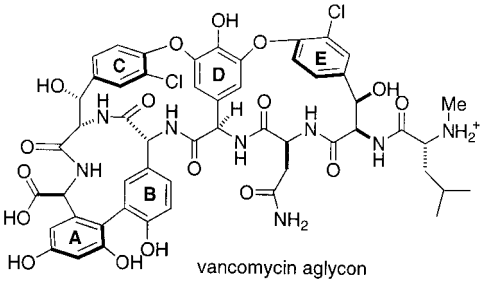
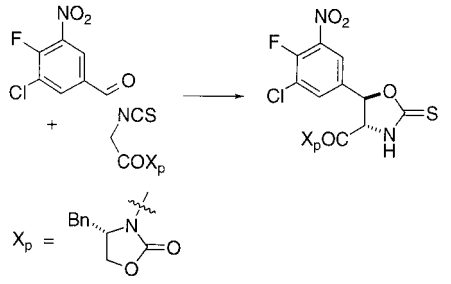
Five consecutive papers in this journal recently described two syntheses of the vancomycin aglycon. D. A. Evans and coworkers developed one route at Harvard University,[1, 2] while the other stemmed from K. C. Nicolaou's group at the Scripps Research Institute in La Jolla, California.[3–5] The syntheses represent an amalgamation of synthetic methodologies in schemes that took some of the most skillful bench chemists in academia years to execute. The comparisons and contrasts in the two appoaches used are discussed herein.



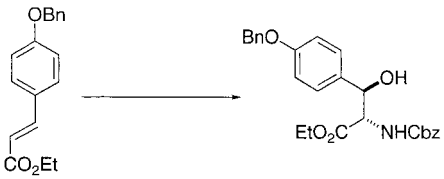
vancomycin aglycon

Stereoselective syntheses of several unnatural amino acids were required to initiate this work. Evans' group used asymmetric reactions of chiral enolates to generate these starting materials [Eq. (1); Bn = benzyl]. In this particular example, an isothiocyanate functionality traps the alcohol of an aldol product giving a thiooxazolidinone that provides O- and N-protection in subsequent steps.



(1)

Nicolaou's group initiated their project to prepare vancomycin after many routes to the requisite amino acids had been published. They could have made their building blocks by repeating and/or modifying published procedures, but instead chose to develop new approaches or rely on those of colleagues at the Scripps Institute. One such example features Sharpless' aminohydroxylation methodology [Eq. (2); Cbz = carbobenzoxy = benzyloxycarbonyl].[6]



(2)

A major obstacle to synthesis of the vancomycin aglycon has been construction of the fused macrocyclic ring systems with generation of the correct atropisomers. The two groups overcame this in different ways (Schemes 1 and 2, respectively). Evans' group began by forming the macrocycle encapsulating the **AB** biaryl functionality; for this they used an oxidative coupling developed almost ten years ago.[7] A S_NAr reaction was then used to form the biaryl ether linkage between rings **C** and **D**, thus for the formation of the **C**-*O*-**D** ring.[8] This cyclization reaction also set one of the amide bonds in the **AB** ring into its required *cis*-orientation.

Scheme 2 indicates that, unlike the Evans' approach, the Nicolaou group constructed the **C**-*O*-**D** ring *before* the **AB** system. They used their copper-mediated coupling methodology, involving a triazine ligating group, to form the ether linkage in the first macrocyclization. Unfortunately, this step gave no significant selectivity with respect to the atropisomer formed, hence separation of diastereomeric products was necessary. The precursor to the **AB** ring contained an amino acid with a preformed (Suzuki) **AB** biaryl fragment. Cyclization to form the **AB** ring system was accomplished by a macrolactamization reaction.

Another significant difference in the two syntheses relates to the C-terminus of the **ABC**-*O*-**D** entity, that is at the amino acid precursor fragment attached to aryl ring **A**. The chiral center of this substituent is stereochemically delicate; it epimerized if the C-terminus was an ester, for instance. The Evans group found that the corresponding *N*-methylamide imparted resistance to epimerization at this center making it resilient to subsequent steps in the synthesis, while the Nicolaou group avoided the problem by using a corresponding O-protected alcohol. These strategies necessitated some interesting functional group manipulations towards the end of the synthesis (see below).

Our interpretation of the two synthetic strategies is that the nature of the C-terminus, and the order of construction of the **AB** and **C**-*O*-**D** rings, is relatively unimportant, but the latter factor did have significant indirect consequences. Specifically, the Evans group was able to achieve atropisomeric stereoselectivity in their **C**-*O*-**D** ring construction process and this might not have possible if the **AB** ring was not already in place.

Development of a stereoselective **C**-*O*-**D** macrocyclization reaction came about by evaluating a flawed approach to give the **C**-*O*-**D** ring, formulating a hypothesis concerning factors governing the stereoselectivity of that process, then adjusting the overall synthetic strategy to accommodate its intrinsic

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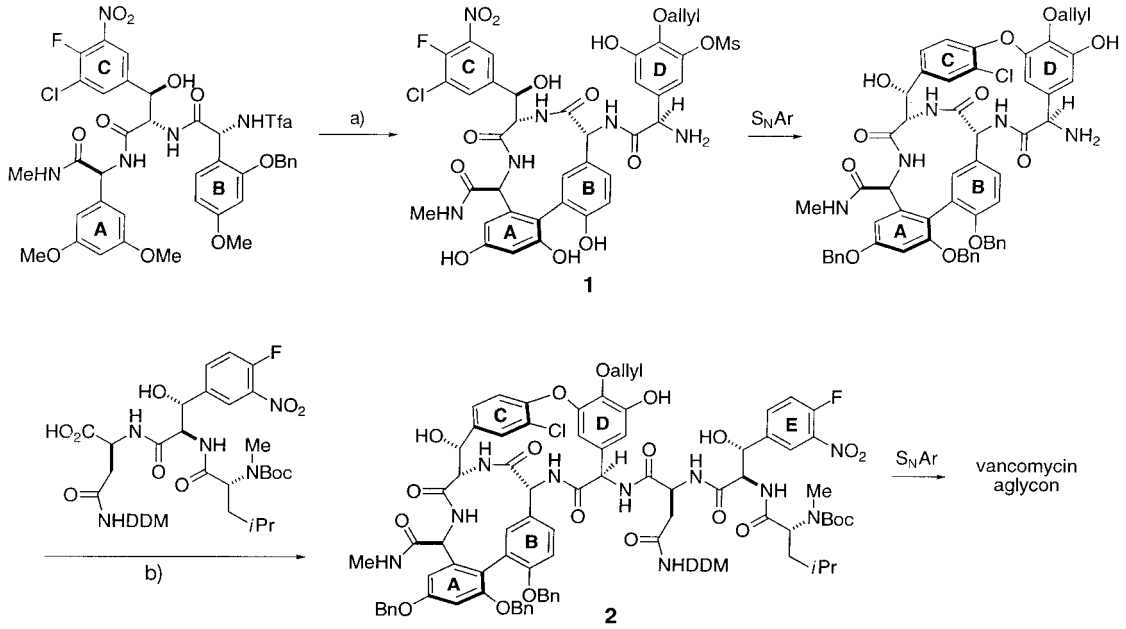
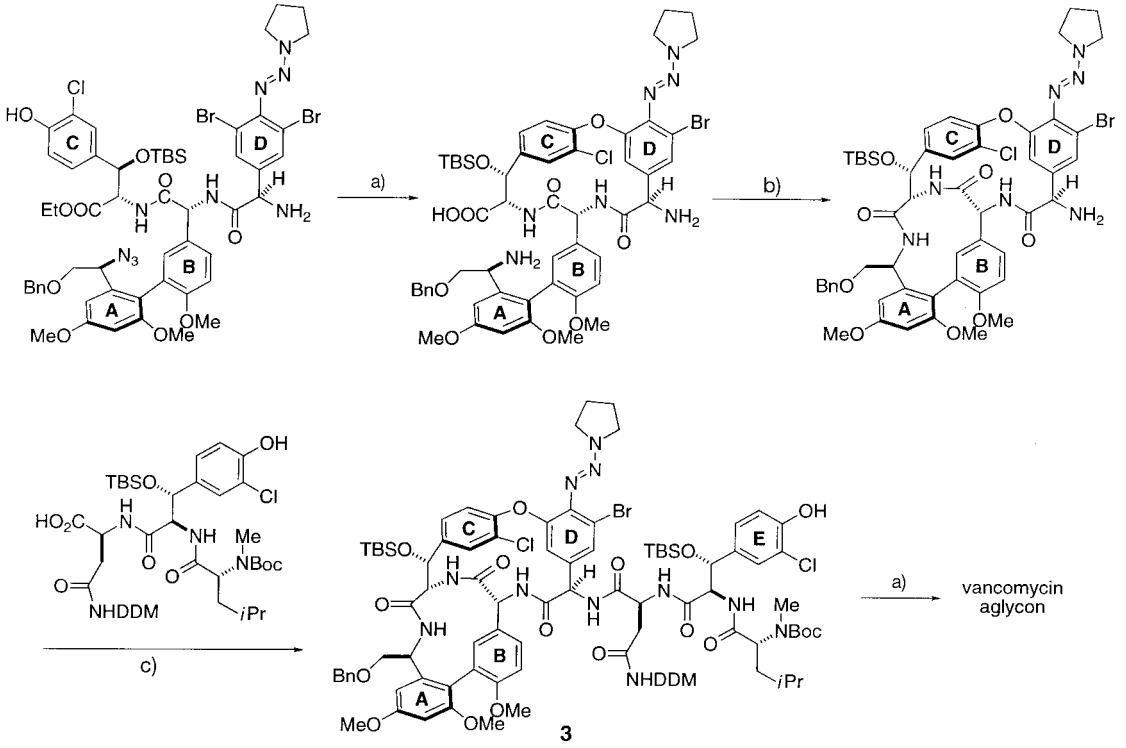


Scheme 1. Synthesis of the vancomycin aglycon according to Evans et al.: a) oxidative biaryl coupling. b) Coupling with a preformed tripeptide. Tfa = Trifluoroacetyl; DDM = 4,4′-dimethyloxydiphenylmethyl; Boc = *tert*-butoxycarbonyl.



Scheme 2. Synthesis of the vancomycin aglycon according to Nicolaou et al.: a) copper-mediated coupling. b) Macrolactamization. c) Coupling with a preformed tripeptide. TBS = *tert*-butyldimethylsilyl.

stereochemical bias. Thus Evans' group originally focussed their efforts on an analogue of compound **1** (Scheme 1) without a chlorine atom on ring **C**. Their intent was to replace the **C**-ring nitro group by a chlorine atom. However, a 7:1 atropisomeric selectivity in the undesired sense was achieved under several sets of reaction conditions. Consequently, they accepted the fact that the nitro group was somehow forced into that orientation during the cyclization, and added the chlorine substituent shown in compound **1**. Their new, and ultimately successful, plan was to substitute the nitro group with a hydrogen after it had served to facilitate the S_NAr process with the desired atropisomeric selectivity. In this way the **C**-*O*-**D** structure was formed with a 5:1 bias in favor of the isomer required for the new approach. The macrocyclization process was also accelerated by the chlorine substituents (reaction time 1.5 h versus 66 h previously) since it increased

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the electrophilicity of the neighboring fluorine substitutents. In fact, the aryl fluoride was so reactive that the steps leading to formation of compound **1** had to be designed very carefully to avoid premature S_NAr reactions.

Both groups wisely elected to couple their **ABC**-*O*-**D** ring intermediates with preformed protected-tripepetides, thus making the synthesis more convergent. As a result, the East and West US-Coast teams entered the end-game with similar intermediates, that is compounds **2** and **3**, respectively.

Only the Evans' team could construct the **D**-*O*-**E** ring with selectivity for the desired atropisomer. Their S_NAr macrocyclization approach gave a 5:1 ratio of diastereoisomers, whereas in Nicolaou's group a rather disappointing 1:3 selectivity was obtained. The Nicolaou group was able to recycle the undesired isomer by exploiting observations made by Boger and co-workers.[9, 10] Thus the undesired atropisomer was heated to 140 °C in DMSO for 4 h; this gave a thermodynamic 1:1 mixture of **D**-*O*-**E** ring isomers which was separated to give the desired one. However this discovery must have been a small conciliation for the sour stereochemical twist of fate that afflicted them in this final macrocyclization.

Having formed the **ABC**-*O*-**D**-*O*-**E** skeleton, both groups were left with the task of functional group manipulations and deprotection steps to form the final product. These seem routine to describe but can be tortuously difficult in practice. Nicolaou's group formed the desired C-terminal acid by a deprotection/oxidation operation on their masked alcohol. Conversion of an N-methyl amide to the corresponding group in the Evans synthesis seems harder, but was in fact accomplished in 68% yield by nitrosation and subsequent treatment with basic peroxide. This transformation was possible since that particular amide functionality is the least hindered of the eight present in this aglycon precursor.

Nicolaou's group approach to the **C**-*O*-**D**-*O*-**E** framework required that they convert a triazine to a phenolic hydroxy group on ring **D**. This was accomplished in several steps. The triazine was reduced to an amine, and diazotized in the presence of KI to give the corresponding aryl iodide. Unfortunately, 40% of the diazonium compound was reduced ($ArNH_2 \rightarrow ArH$ instead of $ArNH_2 \rightarrow ArI$), and the problem of converting the remaining aryl iodide into a phenol remained. In a very bold step, this iodide was treated with excess MeMgBr and *i*PrMgBr and the resulting Grignard species was then quenched with trimethylborate to give the aryl boronate. Finally, the phenol was formed by oxidation with basic peroxide.

The Nicolaou group entered this area relatively recently, hence it is truly remarkable that they were able to develop a synthesis of the vancomycin aglycon so quickly. However, their route stumbles over the sections that involve atropisomeric selectivity or removal of the triazine. Evans' group synthesis addresses or avoids these problems. It is a more polished effort that took many years and high levels of financial and human resources to develop.

After this contribution was submitted, the Nicolaou group reported the successful transformation of the vancomycin aglycon into vancomycin itself.[11] Their procedure featured three protection steps, that is silylation of all six hydroxyl groups, formation of a methyl ester at the C-terminus, and N-terminal protection with a benzyloxycarbonyl group. The central phenolic-OH was then unmasked, and sequentially coupled with two monosaccharide units. Finally, deprotection gave the desired product.

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