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Synthesis of a model 22-membered AB-C-O-D ring of vancomycin containing biaryl and biaryl ether linkages

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Abstract

Synthesis of a 22-membered macrocycle with an *endo* aryl–aryl ether linkage and a biaryl bond related to the AB-C-O-D ring of vancomycin is described.

Vancomycin **1** (Scheme 1), an eminent example of the glycopeptide antibiotics,[1] has found extensive clinical use over the last 40 years and is the drug of last resort for the treatment of infections due to methicillin-resistant *Staphylococcus aureus* and other gram positive organisms in patients allergic to β-lactam antibiotics.[2] The recent emergence of vancomycin-resistant enterococci (VRE) has further emphasized the importance of this field since an efficient therapeutic alternative has yet to be found.[3]

The complex molecular architecture of this class of natural products, their intriguing mode of action, together with their important antibiotic activity have intrigued synthetic chemists for decades.[4] Intensive research has brought about three landmark total syntheses of the vancomycin aglycon.[5–7] Having developed syntheses of a bicyclic C-O-D-O-E model of vancomycin[8] as well as of the tricyclic C-O-D-O-E-F-O-G ring of teicoplanin[9] based on an efficient cycloetherification methodology,[10] we turned our attention to the synthesis of the macrocycle with a biaryl linkage. Intramolecular oxidative coupling,[11] nickel catalyzed intramolecular aryl–aryl coupling[12] and macrolactamization[13] have previously been developed for the construction of the 12-membered AB ring of vancomycin. Our strategy, fundamentally different from the previous studies, is outlined in Scheme 1. Instead of synthesizing the individual AB and C-O-D rings sequentially, our plan calls for the construction of the 22-membered AB-C-O-D macrocycle **3** followed by a transannular cycloamidation leading to the bicyclic compound **2** in one operation. We report in this letter our preliminary results concerning the synthesis of the AB-C-O-D macrocycle **3**.

The synthesis of cyclization precursor is summarized in Scheme 2. The biaryl oxazoline **5**,[14] obtained as a mixture of two atropisomers,[15] was first transformed to the corresponding biaryl aldehyde **6**. This was realized in three consecutive steps without isolation of any intermediate. Thus, selective *N*-methylation (MeI, Me_2CO) of oxazoline, reduction of the transient oxazolinium (L-Selectride®) and hydrolysis

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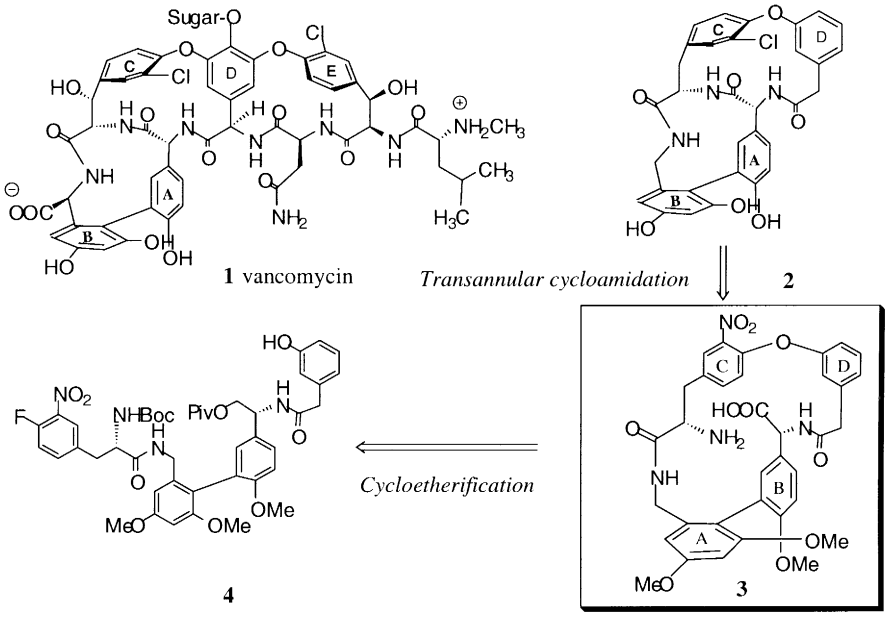
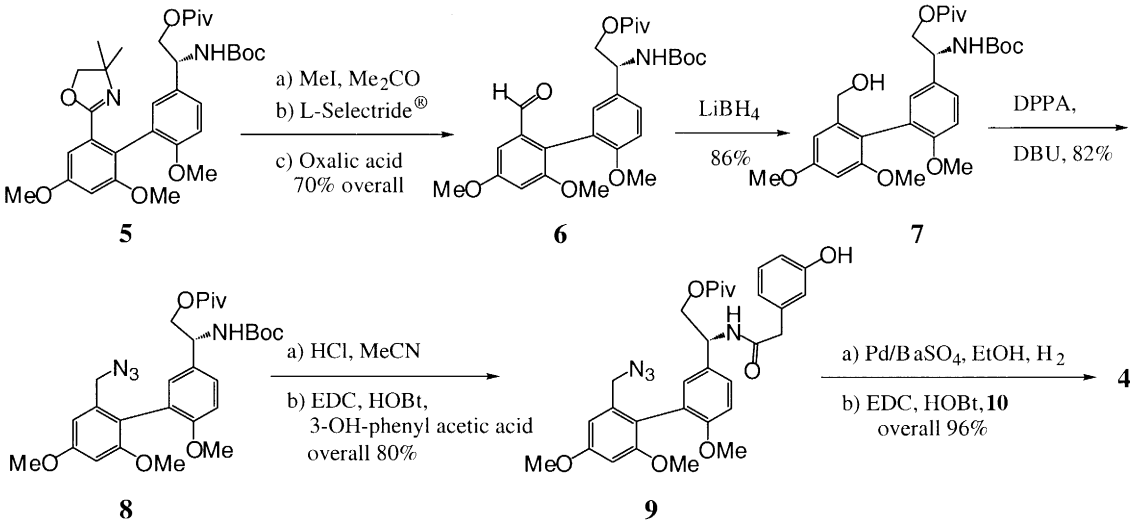


Scheme 1.

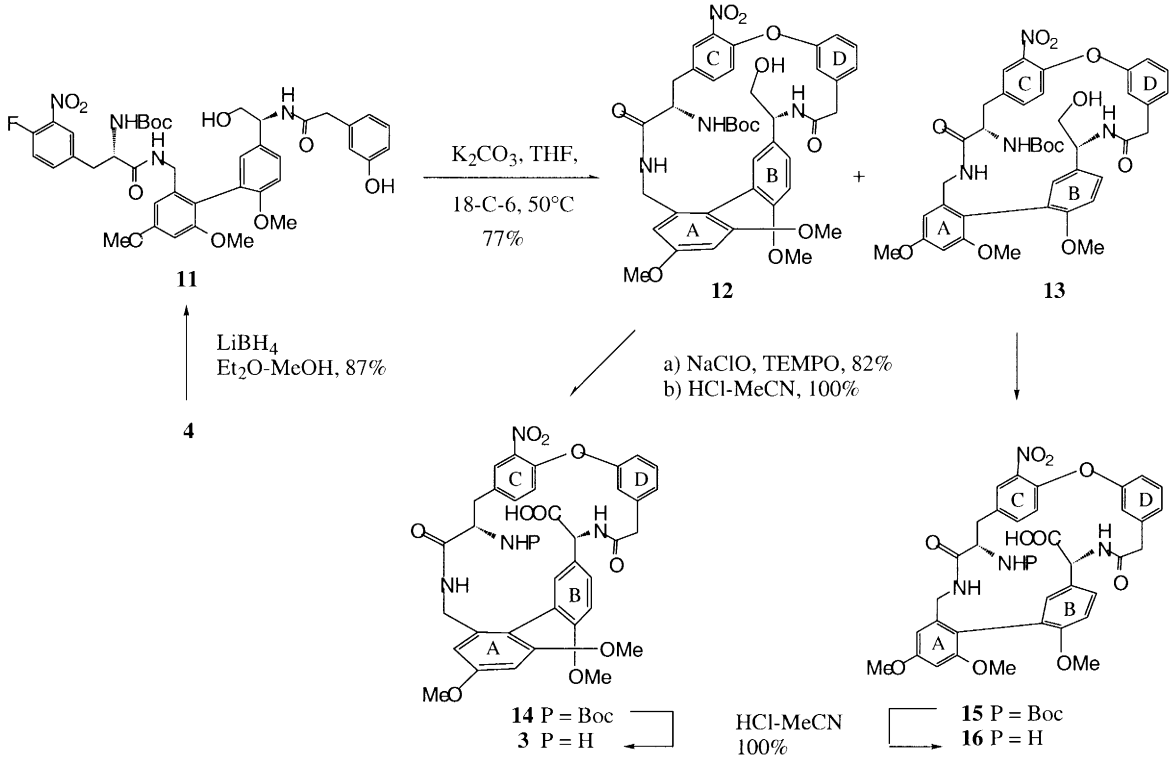
(oxalic acid) of the so-produced oxazolidine gave the aldehyde **6** in 70% overall yield. Reduction of the aldehyde **6** to alcohol **7** ($LiBH_4$) followed by reaction with DPPA in the presence of DBU gave the azide **8**.[16] This latter reaction, specific for the benzylic alcohol, worked nicely provided that the reaction was performed at a relatively high concentration (0.6 M) in toluene. Removal of the *N*-Boc function in the azide **8** (HCl, MeCN) followed by coupling with 3-hydroxyphenylacetic acid (EDC, HOBt) afforded the amide **9** in 80% overall yield. Hydrogenolysis of **9** in the presence of Lindlar's catalyst in ethanol gave the corresponding benzylamine which was coupled with L-*N*-Boc-4-fluoro-3-nitrophenyl alanine (**10**)[17] to give the compound **4** as an inseparable mixture of atropoisomers.



Scheme 2.

Using various cycloetherification conditions, compounds **4** failed to give the desired 22-membered

macrocycles. Since the failure could result from the steric hindrance caused by the bulky pivaloyl residue, this protecting group was removed under reductive conditions ($LiBH_4$, Et_2O–MeOH). After surveying several reaction conditions, it appeared that heating a solution of **11** in THF (0.01 M) in the presence of K_2CO_3 and crown ether 18-C-6 at 50°C afforded the desired AB-C-O-D ring as a two separable atropostereomers **12** and **13** in 77% yield (Scheme 3). It has to be noted that the 22-membered macrocycle is quite flexible and that no planar chirality was created around the biaryl ether linkage upon cyclization.

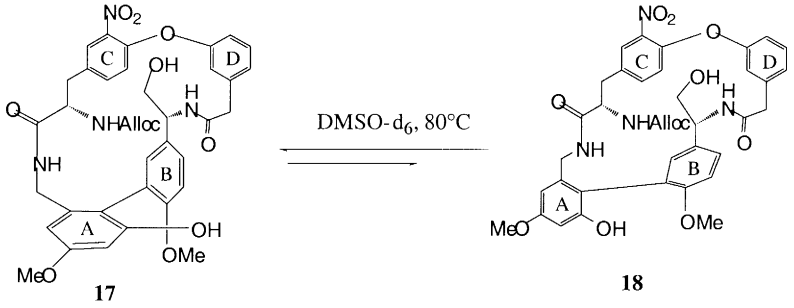


Scheme 3.

Problems were encountered in the attempted oxidation of the primary alcohol to a carboxylic acid. After screening of various oxidation methods, the oxoammonium salt mediated oxidation using a couple TEMPO–NaOCl was selected for further optimization.[18] Chlorination of the electron-rich aromatic ring (ring A) was found to be the major side reaction. However, when the reaction temperature was carefully maintained between −5°C and 0°C, the desired acid **14** was obtained in good yield. Removal of *N*-Boc residue under mild acidic conditions (HCl in MeCN) gave **3** in quantitative yield. Compound **13** was converted into **16** in a similar fashion.

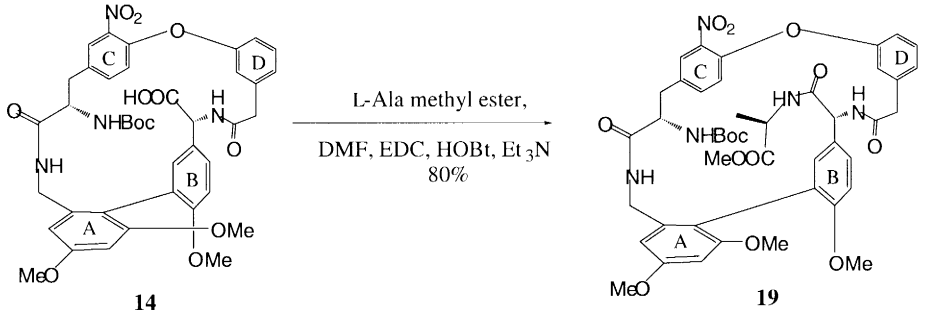
In order to determine the axial chirality of compounds **12** and **13**, the *N*-Alloc derivatives **17** and **18** with a free hydroxy group on the A ring were prepared and their thermal equilibration was examined (Scheme 4). Assuming that the most stable atropoisomer has the natural configuration as observed earlier by Evans,[11] the atropisomerism of **17** and **18**, and hence of **12** and **13**,[19] was tentatively assigned as shown. Due to the conformational flexibility of **17** and **18**, we were unable to determine their axial chirality from NOE studies.

Preliminary studies on the transannular cycloamidation of compounds **3** and **16** did not give the expected bicyclic compounds; decomposition of the starting macrocycle was instead observed. In a control experiment, we have successfully coupled **14** with L-alanine methyl ester to give compound



Scheme 4.

19 in 80% yield (Scheme 5). This result was encouraging and warrants a more detailed survey of cycloamidation conditions.



Scheme 5.

Acknowledgements

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19. The synthesis of compound **17** will be reported in a full paper. Chemical correlation between compounds **12** and **17**, **13** and **18** have been performed. Unpublished results.