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Synthesis of Four Atropdiastereoisomers of C-O-D-O-E Ring of Vancomycin by Sequential Cycloetherifications

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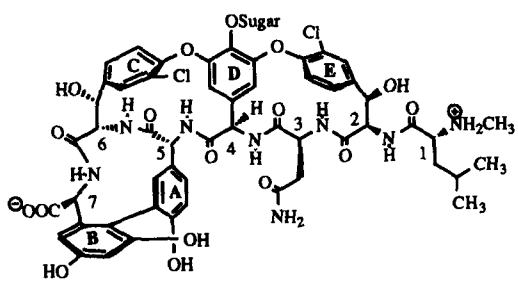
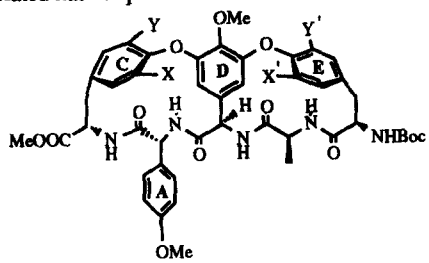
Abstract: All four atropdiastereoisomers of model bicyclic C-O-D-O-E ring of vancomycin have been synthesized by way of sequential S_NAr based macrocyclization.

Vancomycin (1)[1] is a prominent representative of the clinically important family of glycopeptide antibiotics. For more than 35 years, it has been a drug of choice and in fact, the drug of last-resort for treatment of serious infections due to methicillin-resistant *Staphylococcus aureus* and other gram-positive microorganisms. The potent activity of this family of antibiotics has been attributed to its high affinity with the bacterial cell wall terminal D-Ala-D-Ala.[2] The structurally challenging and clinical significance of this family of natural products have spurred multidisciplinary interest over the last decades.[3] Since the first synthesis of a model 16-membered C-O-D ring by Hamilton's group in 1986,[4] important progress,[5] including the synthesis of model bicyclic C-O-D-O-E subunit of vancomycin,[6] has been made towards the long awaited total synthesis of this complex molecule and related natural products.



Vancomycin 1



2a X = Y' = NO_2, Y = X' = H
2b X = X' = NO_2, Y = Y' = H
2c X = X' = H, Y = Y' = NO_2
2d X =Y' = H, Y = X' = NO_2

Figure 1

Our own interest in this field has led to the discovery of an efficient cyclo-etherification method hingered upon an intramolecular S_NAr reaction.[7,8] Formation of biaryl ether bond with concomitant ring closure characterizes this cyclization methodology.[9] Besides the mild conditions and high yield, another unique and important feature of this reaction is that it offers a possibility to address the

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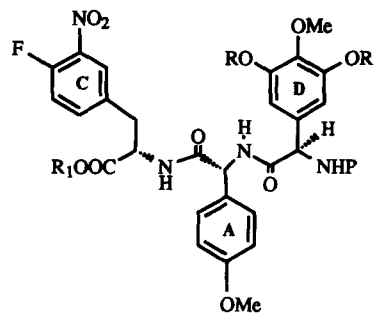
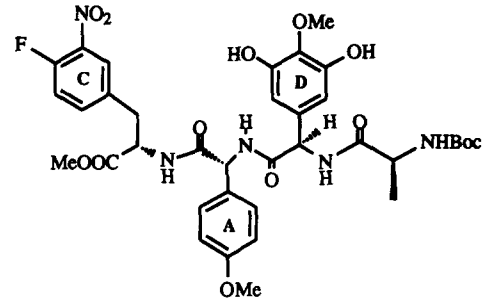
atropdiastereoselection of the macrocyclization, one of the most subtle synthetic challenges presented in vancomycin. We have reported in a preceeding communication[10] an exceptionally concise synthesis of model C-O-D-O-E ring of vancomycin using a one pot double S_NAr based macrocyclization strategy and thus highlighted the power of our approach. Although a fair atropisomer selectivity was achieved under carefully controlled conditions (**2d** was isolated in 50-60% yield from the one-pot bis-cyclization), it was difficult to obtain other atropisomers in pure form under various cyclization conditions. The purpose of present letter is to describe the synthesis of all four atropisomers **2a-2d** by sequential S_NAr based macro-cycloetherification.



3 R = i-Pr, R_1 = Me, P = Boc
4a R = P = H, R_1 = Me
4b R = P = R_1 = H



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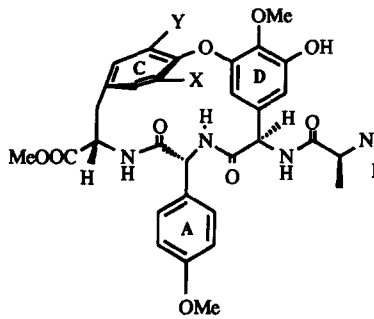
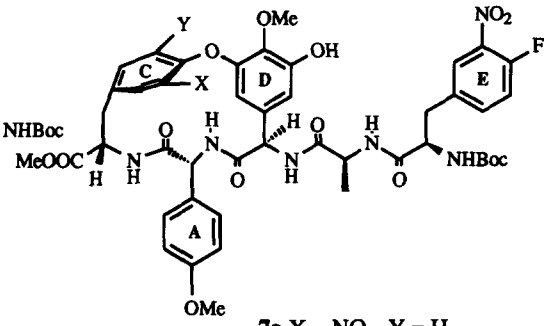
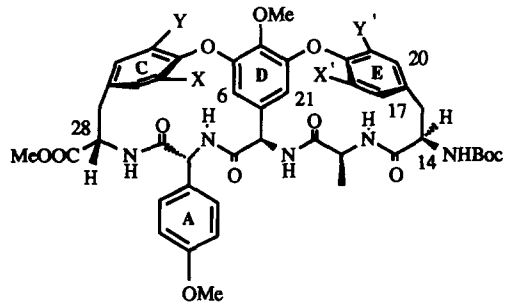


6a X = NO_2, Y = H
6b X = H, Y = NO_2



7a X = NO_2, Y = H
7b X = H, Y = NO_2

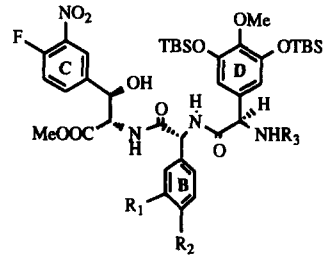


2a X = Y' = NO_2, Y = X' = H
2b X = X' = NO_2, Y = Y' = H
2c X = X' = H, Y = Y' = NO2
2d X =Y' = H, Y = X' = NO_2

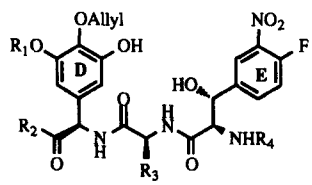
Figure 2

Treatment of tripeptide **3**, prepared as described previously,[10] with BCl_3[11] in CH_2Cl_2 at 0°C for 6h followed by slow addition of anhydrous methanol gave the chloride salt of amino ester **4a** in quantitative yield (NMR measurement). It is appropriate to point out the importance of the work-up procedure (MeOH) as it not only transformed the BCl_3 into the volatile trimethyl borate, but also determined in large part the reproducibility of the results. In fact, the methyl ester of C-terminal carboxyl group may be partially converted into the corresponding acyl chloride in the course of the reaction.[12] Re-esterification[13] occurred, however, after addition of MeOH to afford the observed compound **4a**.[14] When the reaction was quenched by addition of water, a mixture of **4a** and fully deprotected product **4b** was obtained. Coupling of crude amino ester **4a** with L-*N*-Boc alanine (EDC, HOBt) gave the tetrapeptide **5** in 60% overall yield. Macrocyclization proceeded smoothly at 0°C using CsF as base in DMF affording two atropisomers **6a** (M configuration,[15] natural) and **6b** (P configuration, non-natural) in a 3/7 ratio in 75% yield. We noted that the atropdiastereoselectivity of this reaction was temperature dependent. Thus, when the cyclization was performed at room temperature, the ratio of **6a** to **6b** became 2/3 with a net increase of product **6a**. As thermal equilibrium between **6a** and **6b** did not take place at room temperature, the product distribution under these two sets of conditions reflected their kinetic preference. No epimerization occurred when the reaction was run below 60°C in agreement with our previous observations. The stereochemical assignments of **6a** and **6b** are based on NOESY experiments. For compound **6a**, a NOE was observed between $H_{ortho\ to\ nitro}$ and H-28 , characteristic and diagnostic of M configuration, while for **6b**, a NOE was observed between $H_{para\ to\ nitro}$ and H-28 indicative of P configuration.

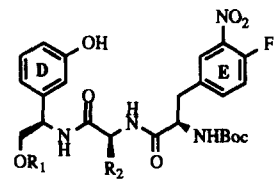
A similar degree of atropdiastereoselection has been observed in the cyclization of compounds **8a**,[7g] **8b**[8a] and **9a**,[8a] **9b**.[8d] Noting the significant structural difference of these compounds in the peripherial of peptide chain in terms of functionality and substitution pattern, we suspect that other control elements may be required in order to achieve higher atropdiastereoselection. In this respect, excellent atropdiastereoselection observed in the related bis-cyclization studies[10] and in the cyclization of **10a**, **10b**, **10c**[7f, 16] are remarkable and should provide a basis for understanding the intrinsic atropdiastereoselectivity of cyclization.



8a $R_1 = R_2 = H$, R_3 = Troc
8b R_1 = Br, R_2 = OMe, R_3 = Boc



9a $R_1 = H$, $R_2 = O^tBu$, $R_3 = CH_2CN$, R_4 = Boc
9b R_1 = Me, R_2 = NHMe, R_3 = $CH_2CONHDdm$,
R_4 = D-*N*-Boc-*N*-methyl Leu



10a $R_1 = H$, R_2 = Me
10b R_1 = Me, R_2 = Me
10c $R_1 = H$, R_2 =
3-isopropyloxyphenyl

Figure 3

Mild deprotection of the *N*-Boc function of **6a** (HCl-MeCN) followed by coupling with D-*N*-Boc-4-fluoro-3-nitrophenyl alanine (DPPA, Et_3N) gave pentapeptide **7a** in 50% overall yield. Macrocyclization of **7a** under the same conditions (CsF, DMF, room temperature) gave the bicyclic compounds **2a** and **2b**[17] in a 3/1 ratio in 50% yield. Once again, the stereochemical assignment of **2a** and **2b** was based on NOESY

experiments using H-14 as a reference peak. Compound **2a** has the correct atropisomerism related to vancomycin. The same synthetic scheme applied to **6b** afforded the other two atropisomers **2c** and **2d** in a 1/2 ratio in 50% yield. Compound **2d** was identical in all respects with that prepared previously *via* one-pot double cyclization strategy.[10]

In conclusion, we reported herein the successful synthesis of all four atropisomers of model bicyclic C-O-D-O-E ring of vancomycin. Efforts at understanding and hence controlling the atropdiastereoselection of cyclization, as well as examining atropdiastereoselectivity in the projected transformation of nitro function to chlorine atom are in progress and will be reported in due course.

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14) A control experiment has shown that deprotection of 3,5-diisopropyloxy-4-methoxyphenyl acetic acid with BCl_3 followed by addition of MeOH gave methyl 3,5-dihydroxy-4-methoxyphenyl acetate quantitatively.
15) The configuration (P or M) of the atropisomer was determined by viewing the atropisomer as helix. "For this designation, only the ligands of highest priority in front and in the back of the framework are considered. If the turn from the priority front ligand to the priority rear ligand is clockwise, the configuration is P, if counterclockwise it is M". See: Eliel, E. L.; Willen, S. H. *"Stereochemistry of Organic Compounds"* John Wiley & Sons Inc., **1994**, Chapter 14.
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17) All new compounds gave spectra data consistent with the assigned structures.

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