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Development of New Stereodiverse Diaminocyclitols as Inhibitors of Influenza Virus Neuraminidase

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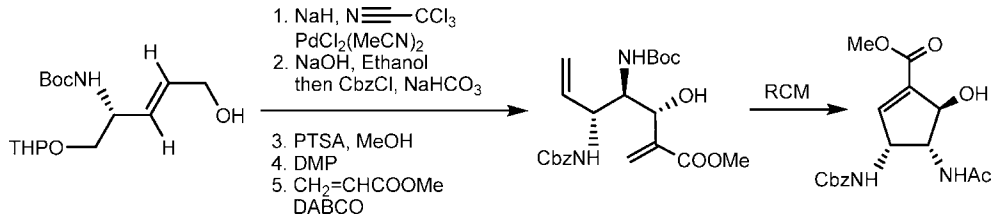
ABSTRACT



A concise and modular approach to synthesize a new type of cyclopentene-based diaminocyclitol library from D-serine and L-serine has been developed, and key steps in this synthesis are an aza-Claisen rearrangement, a ring-closing metathesis, and a Baylis−Hillman reaction. The developed chemistry may offer a unique way to investigate the neuraminidase (NA) mutation by systematically mapping the changes within its binding sites.

The outbreak of 2009 H1N1 influenza A virus that is believed to have originated in Mexico is rapidly spreading across the globe.[1] This virus is spreading from person-to-person, probably in much the same way that regular seasonal influenza viruses spread. Thus, influenza is one of the most deadly viruses known to humans.[2]

Current prevention and treatment of influenza rely on vaccines and antiviral drugs. However, development of new vaccines that are effective against the newly emerged influenza virus will have many difficulties, and the efficacy of the vaccines is difficult to test thoroughly because of low incidences of human infection at an early stage. It may be too late to use it in control of an influenza pandemic if the vaccine is not effective when administered to humans. Therefore, the development of small molecular based antiviral drugs is even more important in the event that new

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highly virulent strains can lead to global pandemics resulting in millions of deaths.[3]

Currently, oseltamivir (Tamiflu) and zanamivir (Relenza) are influenza neuraminidase (NA) inhibitors[4] that are highly effective to all strains of influenza viruses. However, the recent emergence of oseltamivir (**A** in Figure 1) resistant

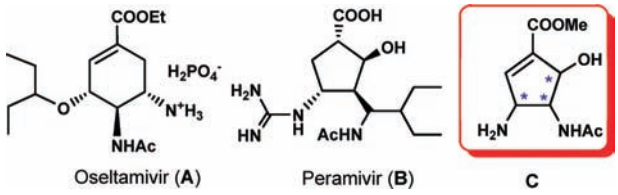

Figure 1. Structures of antiviral drugs.

influenza virus variants[5] underscores an urgent need for studying neuraminidase mutation.[6] Given the significant sequence variations across strains and the unpredictable mutations by gene reassortment and random mutations,[7] the understanding of inhibitor−neuraminidase interactions at the molecular level represents the main goal of the current research.[8] Herein we report our effort for the development of a concise strategy for the modular synthesis of diverse diaminocyclitols; the developed chemistry offers an alternative approach to the existing strategies for NA mutation and identification of NA inhibitors in response to emerging drug-resistant influenza viruses.

The scaffold selection of our NA inhibitors was based on the structures of oseltamivir (**A**) and peramivir (**B**).[9] Because all the existing NA inhibitors have a carboxylate group and an acetyl-amino group at the opposite ends of the ring system,[10] we therefore selected **C** as our synthetic target in consideration of its potential as a scaffold for diversity-oriented synthesis of its library. To this end, we carried out a preliminary computational analysis (see Supporting Information for details). Since scaffold **C** has three chiral centers, we wished that our developed chemistry could allow us to stereoselectively synthesize its corresponding eight stereoisomers.

Synthetically, we would like to explore the RCM reaction as a key step to construct the framework of **C** because of its operational simplicity, high chemoselectivity, and remarkable tolerance for functional group substitution,[11] and this synthetic strategy has been successfully demonstrated by Yao and co-workers[12] in the syntheses of six-membered-ring based diaminocyclitols.

Our synthesis started with the syntheses of diamines **3** and **4** from **1**, which can be easily made from L-serine[13] (Scheme 1).

Synthetically, alcohol **1** was first oxidized by CrO_3−pyridine to its aldehyde, which then reacted with methyl 2-(dimethoxyphosphoryl) acetate to afford an ester, followed by DIBAl-H/BF_3•Et_2O reduction to afford allylic alcohol **2** in overall 58% yield in three steps. To make diamines **3**, alcohol **2** was reacted with 2,2,2-trichloroacetonitrile in the presence of NaH to form an allyl trichloroacetimidate, which underwent Pd-catalyzed aza-Claisen rearrangement[14] to diastereoselectively afford an *anti*-diamine in 65% yield, which was then subjected to a hydrolysis to remove its trichloroacetyl group, followed by protection with a Cbz group and removal of THP with PTSA/MeOH to give compound **3** in 61% yield. Mechanistically, this aza-Claisen rearrangement might proceed through a formation of a Pd complex, which also might trigger the rearrangement as illustrated in Scheme 1.

To make *syn*-diamine,[15] we applied a thermal aza-Claisen rearrangement[16] to obtain compound **4**. To this end, alcohol **2** was first reacted with trichloroacetonitrile in the presence of NaH; the formed adduct then refluxed in *o*-xylene to afford diamines as a pair of diastereoisomers (1/1 ratio), which without purification were subjected to hydrolysis, followed by Cbz protection and removal of THP with PTSA/MeOH to give *anti*-diamine **3** and *syn*-diamine **4** (1/1 ratio) in a combined yield of 48% in four steps.

The stereochemistries of **3** and **4** were determined by converting them into their corresponding imdazolidine-2-

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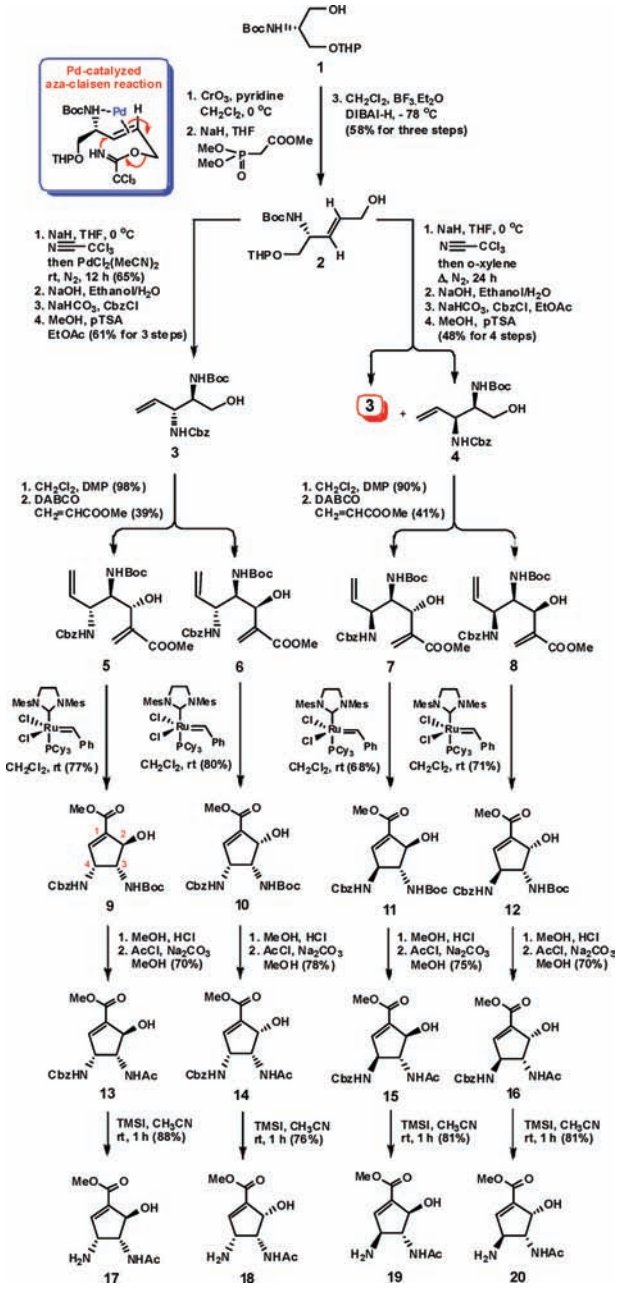
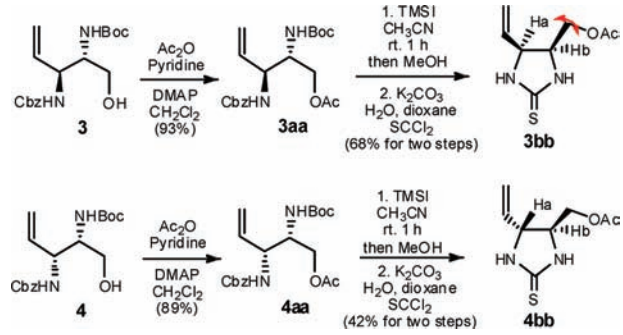
Scheme 1. Syntheses of Diaminocyclitols **9**−**20**



thiones **3bb** and **4bb** by the chemistries illustrated in Scheme 2. Accordingly, the free hydroxyl groups in **3** and **4** were protected as their acetate **3aa** and **4aa**, which were then treated with TMSI in CH_3CN at room temperature to remove their protecting groups Boc and Cbz, followed by reaction with thiophosgene in the presence of base to give their corresponding **3bb** and **4bb**, respectively. 2D NMR (NOESY) studies showed that the correlation between Ha and Hb was observed in **3bb**, indicating their *cis*-relationship between Ha and Hb of **3bb**. On the other hand, no correlation between Ha and Hb in **4bb** was observed, indicating their *trans*-relationship between Ha and Hb of **4bb** (see Supporting Information for details).

Scheme 2. Syntheses of Compounds **3bb** and **4bb**



With this general aza-Claisen rearrangement protocol to access *anti*- and *syn*-diamines **3** and **4** in hand, we next pursued their transformation to the corresponding dienes **5**, **6**, **7**, and **8** through a sequential oxidation and a Baylis−Hillman reaction.[17] In this maneuver, **3** was first oxidized to its aldehyde in 98% yield, and the formed aldehyde then underwent Baylis−Hillman reaction to give almost equal amounts of compounds **5** and **6** in a combined yield of 39%. Both compounds were separated by a silica gel chromatography. To circumvent the issue of this low yield, we profiled the reaction conditions according to the reported procedure,[18] but no improvement was observed. Since the starting material is stable under the reaction conditions, we can recycle it by chromatography. Following the same approach, dienes **7** and **8** were made from *cis*-diamine **4** in a combined yield of 35% and separated by a silica gel chromatography.

With those dienes, we then started to investigate their cyclization. An initial attempt was made by treatment of substrate **5** with both first and second generation Grubbs catalysts. Quite interestingly, the present system consisting of methyl acrylate exhibited a remarkable reactivity toward the second generation of Grubbs catalyst, enabling the catalytic cyclization of **5** in CH_2Cl_2 to afford the desired product **9** in 77% yield at room temperature.

To profile the reaction scope, compounds **6**, **7**, and **8** were subjected to the same conditions mentioned above, and the desired products **10**, **11**, and **12** were also obtained in good yields. However, no reaction proceeded when first generation Grubbs catalyst was utilized, and only starting materials were recovered. The relative stereochemistry of compounds **9**, **10**, **11**, and **12** was determined by ^{1}H NMR and NOE experiments (see Supporting Information for details).

Having succeeded in the formation of **9**, **10**, **11**, and **12**, we then turned our attention to test the functional group interconversion. Selective removal of the Boc group in the presence of a Cbz group from substrates **9**, **10**, **11**, and **12** was achieved in high yields using HCl/MeOH. An initial attempt to carry out their acylation with organic bases (such

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as Et_3N and pyridine) and acetic anhydride or acyl chloride in anhydrous solvents (such as THF, CH_2Cl_2, and DMF) did not result in the formation of the desired product, but instead, the starting materials were converted to unidentified products. Since the results could be attributed to the free hydroxyl group at the allylic position of substrates, which could compete with acylation under anhydrous conditions, and the formed products might cause decomposition, we therefore performed the reaction using MeOH as a solvent. As a result, the desired amides **13**, **14**, **15**, and **16** were obtained in good yields in the presence of Na_2CO_3 as a base with AcCl as an acylating agent.[19]

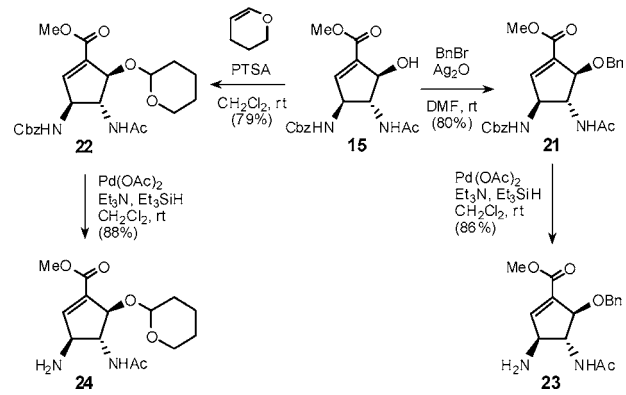
Since the C-4 position is uniformly occupied by basic groups such as an amine or guanidine in all known inhibitors,[20] we therefore explored the reaction conditions to remove the Cbz group in compounds **13**, **14**, **15**, and **16**. Fortunately, TMSI was found to be an effective agent to remove the Cbz, and the desired products **17**, **18**, **19**, and **20** were obtained in good yields.

Thus, we developed a concise and modular synthetic approach to synthesize four diaminocyclitols **17**−**20** from L-serine, and the developed chemistry was successfully applied to constructing their enantiomers from D-serine. The details for their syntheses are provided in the Supporting Information.

Given diaminocyclitols **17**−**20** as potential scaffolds to probe NA mutation, we then chose **15** as a model to convert it to the oseltamivir-type molecules. To this end, **15** was first reacted with 3,4-dihydro-2*H*-pyran in the presence of PTSA to give **22** in 79% yield, followed by reaction with Et_3SiH in the presence of $Pd(OAc)_2$ and Et_3N[21] to afford the corresponding amine **24** in 86% yield. In addition, **15** could also undergo sequential benzylation and hydrogenation to give product **24** in high yields (Scheme 3).

In summary, we have developed an efficient and concise method for diversity-oriented synthesis of a new type of diaminocyclitols. The synthetic protocol embodies aza-Claisen rearrangement, ring-closing metathesis, and Baylis−Hillman reactions and is accomplished in a modular manner.

Scheme 3. Synthesis of Diaminocyclitols **23** and **24**



The large synthetic opportunity offered by this work could be realized by the facile syntheses of all the valuable chiral compounds with the relative and absolute stereochemistry around scaffold **C**. Therefore, we can anticipate that our program for synthesis of stereodiverse diaminocyclitols may find application in synthesis of useful probes for the study of viral mutation and in the development of small molecules as therapeutic agents against influenza virus variants.

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Supporting Information Available: Experimental procedure and NMR and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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