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Atropselective Macrocyclization of Diaryl Ether Ring Systems: Application to the Synthesis of Vancomycin Model Systems

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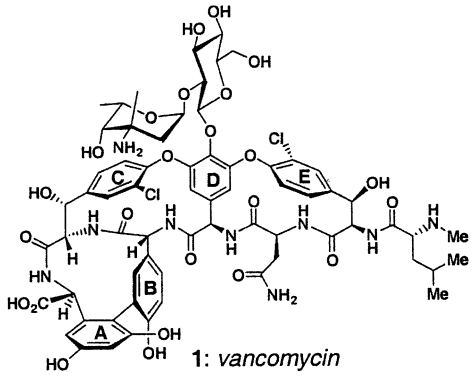
Abstract: Vancomycin is the last line of defense available in the clinic for treating multidrug-resistant bacterial infections. Vancomycin contains two 16-membered diaryl ether macrocycles, each of which contains a stereogenic axis across the diaryl ether linkage. Since an effective total synthesis of vancomycin requires that these stereogenic axes be formed in a stereoselective manner, we have developed an atropselective variation of the triazene mediated diaryl ether forming reaction. This variation introduced an energetic penalty into the transition state of the undesired atropisomer. This reaction is used to synthesize the C−O−D diaryl ether macrocycle found in vancomycin with high diastereoselectivity (de > 90%), providing the naturally occurring atropisomeric configuration.

Introduction

The total synthesis of vancomycin (**1**, Figure 1)[1] has been of considerable interest to the chemical community over the past few years. This is due to its unique and extraordinarily challenging molecular architecture, as well as its critical role as the last clinical antibiotic effective for treatment of multidrug-resistant bacterial infections. While three groups, including ours,[2−4] have completed the total synthesis of the vancomycin aglycon, only one has succeeded in achieving control (5:1) over the atropisomeric outcome of the diaryl ether forming macrocyclization reactions.[3] A method that can be applied generally to the vancomycin macrocyclizations with enhanced atropselectivity is highly desirable.



1: *vancomycin*

Figure 1. Structure of vancomycin (**1**).

To exemplify this problem, we refer to the diaryl ether macrocyclizations of our total synthesis of vancomycin.[2] The cyclization of the first vancomycin ring system (C−O−D ring system) proceeded with no selectivity, affording a ca. 1:1 mixture of atropisomers. The macrocyclization of the second ring system (D−O−E ring system) occurred in our advanced model system with complete stereoselectivity for the unnatural atropisomeric configuration. In our total synthesis of vancomycin the second ring system was formed with the unnatural atropisomeric configuration favored by a ratio of 3:1 to the natural configuration.[2]

A temporary solution to the atropisomer problem was based on work originally carried out in the Boger laboratories.[5] Thermal equilibration of the atropisomers provided a 1:1 mixture of natural and unnatural configurations. Chromatographic separation of this mixture provided the necessary quantities of the isomer possessing the natural atropisomeric configuration.

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While this approach was successfully employed in our[2] and the Boger[4] syntheses of the vancomycin aglycon, a more effective and intellectually pleasing solution was deemed worthy of pursuit.

Below we present the design and development of a diastereoselective macrocyclization forming one or the other atropisomer of the diaryl ether ring systems. This approach allowed for the synthesis of a single atropisomer of the vancomycin type C−O−D diaryl ether ring system. It is also one of the first examples of the stereoselective synthesis of nonbiaryl stereogenic axes.[6−8]

Experimental Design

From the outset of our investigations toward the development of the traizine-based diaryl ether forming macrocyclization,[9] we considered the possibility of designing an atropselective version of the reaction. Three potential mechanisms were identified by which atropselectivity could be designed into this process. The first approach would involve the temporary use of bulky substituents on the C and E aromatic rings to direct the chlorines into the correct orientation through unfavorable steric interactions. The second method relied on the potential use of stereogenic centers in the triazine moiety to influence the atropisomeric outcome of the reaction. The last hypothesis required the possible development of an asymmetric copper ligand to influence the atropselectivity.

Of these three methods, the first approach was viewed as the most attractive solution to the problem at hand. Furthermore, the required system would be the easiest to design and had a high likelihood of success. In addition, this strategy would be independent from the method of macrocyclization. Thus, it would, conceivably, be applicable to other macrocyclization conditions employed in the synthesis of vancomycin systems such as the popular nitro group activated nucleophilic aromatic substitution.[1,10]

The steric hindrance approach was to rely on the β-hydroxy groups found on the tyrosine residues in vancomycin to provide a handle for inducing atropselectivity. By placing a bulky auxiliary group in the ortho position on the tyrosine moiety, an unfavorable steric interaction with the protected benzylic alcohol would be induced, creating an energetic penalty that would funnel the reaction down the lower energy pathway, forming a single atropisomeric product (Figure 2).

In selecting an appropriate substituent to influence the stereogenic outcome of the reaction, we searched for one that was synthetically tractable and compatible with our triazene mediated diaryl ether forming reaction, and, therefore, a protected phenolic group was identified as a suitable candidate. The required amino acid derivatives could be generated from readily available starting materials employing the aldol reaction. Furthermore, on the basis of work by the Evans group,[11,12] it seemed likely that the auxiliary bearing phenolic group could be successfully removed. Last, the added electron density from the auxiliary oxygen substituent was expected to improve the efficiency of our diaryl ether formation by increasing the nucleophilicity of the phenolic moiety. The fact that the C−O−D ring system of vancomycin cyclizes with no atropselectivity[2f] made it an ideal model system to test this hypothesis.

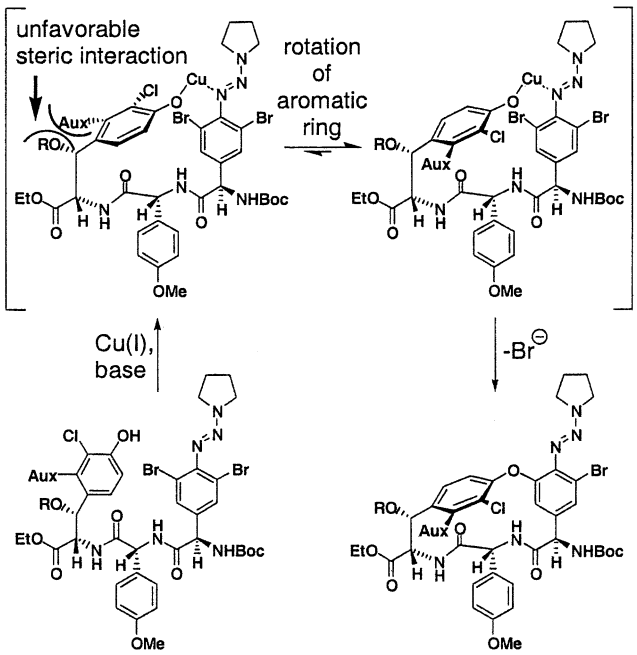

Figure 2. Design of an atropselective macrocyclization for a vancomycin C−O−D ring system. The bulky auxiliary group on the aromatic ring is expected to generate an unfavorable steric interaction with the β-hydroxy group on the tyrosine residue. This should favor one atropisomeric transition state over the other.

On the basis of the above considerations, we identified the modified C−O−D systems **3** and **5** as our targets (Scheme 1). According to our mechanism, the cyclization of compound **2** was expected to provide **3a** as the major product. To further probe the level of control through this design, it was decided to employ diastereomer **4**, which possessed the opposite stereochemistry at the β-hydroxy group of the tyrosine residue, as well. Following similar reasoning, this system was expected to show preference for the atropisomer of opposite configuration, **5b**.

Results

Computer Simulations. Before undertaking any experimental verification of our hypothesis, we performed a preliminary test by conducting computer simulations. The C−O−D ring systems **3a** and **3b**, as well as the β-hydroxy group epimers **5a** and **5b**, were computationally modeled in order to identify the lowest energy conformation for each compound. Molecular dynamics followed by minimization was performed using Discover 3.0 with the CVFF[13] and CFF91[14] force fields. The results were similar. Compound **3a** was significantly more stable than compound **3b** (−7.3 kcal/mol CVFF; −5.6 kcal/mol CFF91). Compound **5b**, however, was found to be only slightly more

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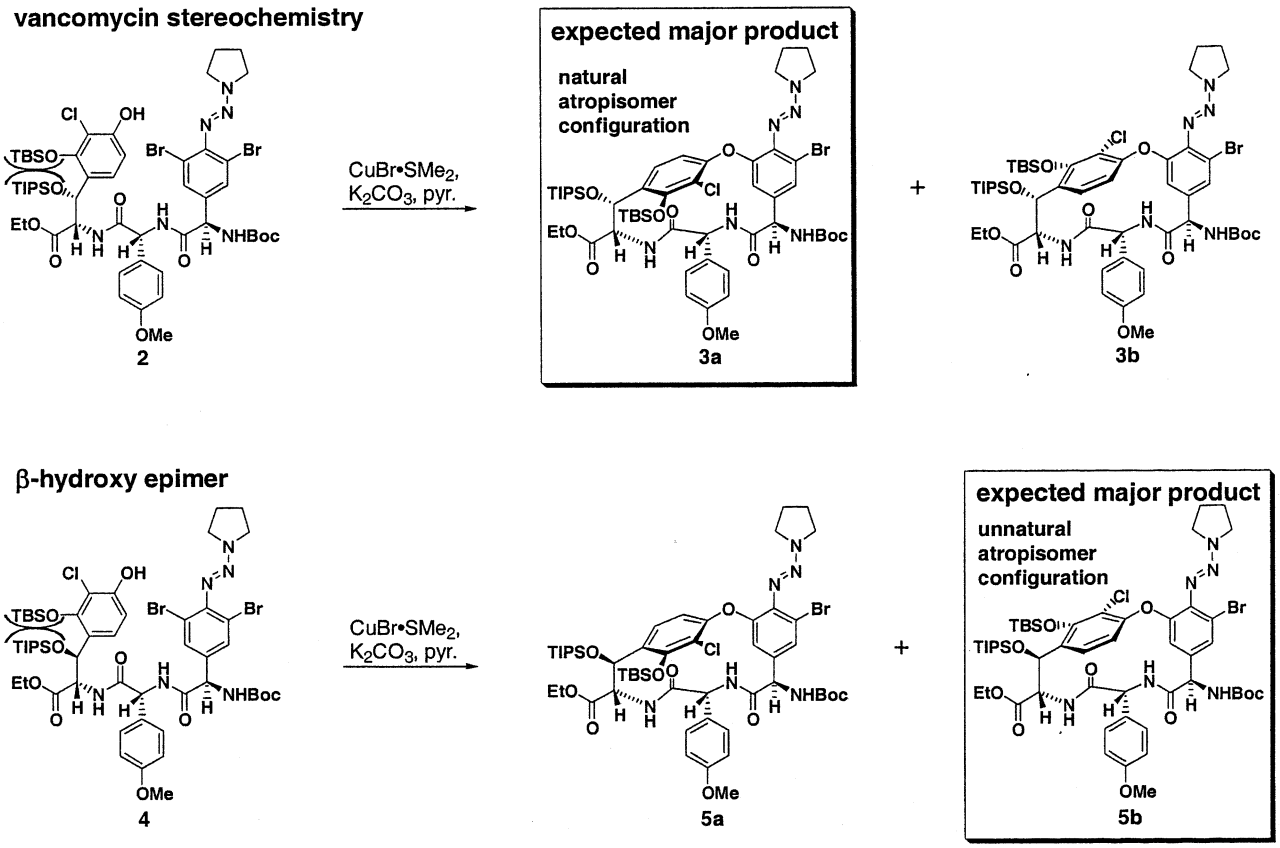
Scheme 1. Designed Substrates To Test the Bulky Substituent Hypothesis for Atropselective Macrocyclization



stable than its atropisomer **5a** (−2.5 kcal/mol CVFF; −0.4 kcal/mol CFF91).

On the basis of these calculations, we expected to see dramatic atropselectivity from the cyclization of compound **2**. The C−O−D model **3a**, with the chlorine in the natural configuration relative to vancomycin, was expected to predominate in a calculated ratio of greater than 1000:1 to that of C−O−D model **3b** (ratio of **3a**:**3b** ca. 33 000:1, CVFF; ca. 2900:1, CFF91). On the other hand, the cyclization of precursor **4** was expected to provide only moderate atropselectivity for compound **5b** (ratio of **5b**:**5a** ca. 35:1, CVFF; ca. 2:1, CFF91).

While these data confirmed that the proposed approach could select for either atropisomeric configuration, the disparity between the degrees of atropselectivity was, at first, surprising. Subsequent analysis of the unfavorable atropisomers **3b** and **5a** revealed, however, that the large difference in selectivity was likely due to the low energetic penalty imposed in compound **5a** (see Figure 3). Thus, while compound **3b** is highly unfavorable due to the enforced eclipsing of the phenolic TBS and benzylic OTIPS groups, compound **5a** can adopt a staggered conformation, thereby reducing the unfavorable steric interaction.

Atropselective Synthesis of C−O−D Ring Systems. From the required building blocks **6**−**9** (Figure 4), compounds **8** and **9** were already in hand from our previous studies.[2] Intermediates **6** and **7** (both racemic) were synthesized via aldol-based chemistry as outlined in Scheme 2.

Thus, 2,4-dihydroxybenzaldehyde (**10**) was selectively chlorinated at the 3-position (NaOCl, NaOH, H_2O, 55% yield),[15]

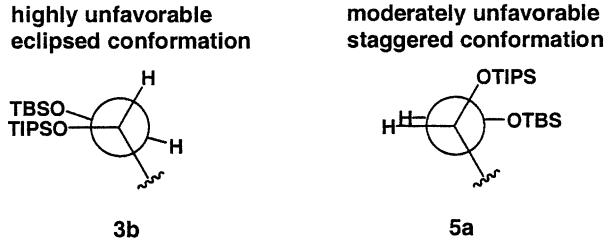


Figure 3. Newman projections point to the likely cause of the low atropselectivity predicted by molecular modeling calculations for the cyclization of compound **4**. These projections depict the orientation across the bond connecting the β-carbon to the aromatic ring. Compound **3b** adopts the highly unfavorable eclipsing orientation, while compound **5a** can adopt the more stable staggered conformation.

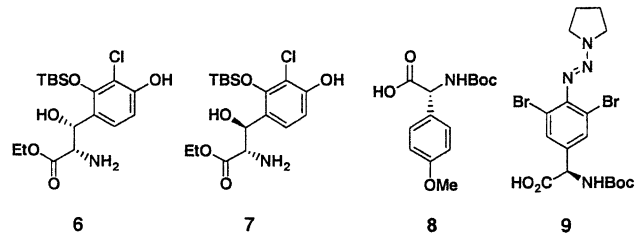


Figure 4. Key building blocks (**6**−**9**) required for the atropselective synthesis of the C−O−D ring systems.

providing the monochloro derivative **11**. The fully protected benzaldehyde **13** was obtained by selective protection of the more acidic phenolic group of **11**, furnishing benzyl ether **12**

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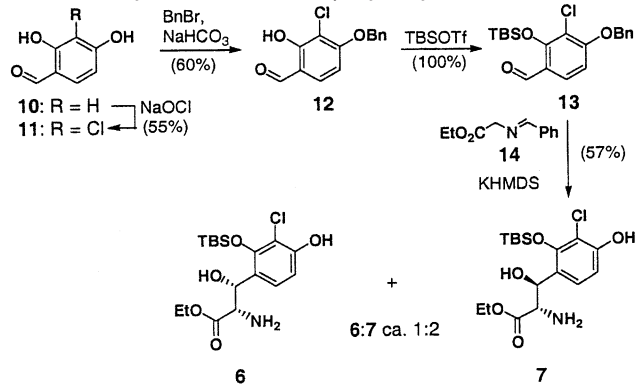
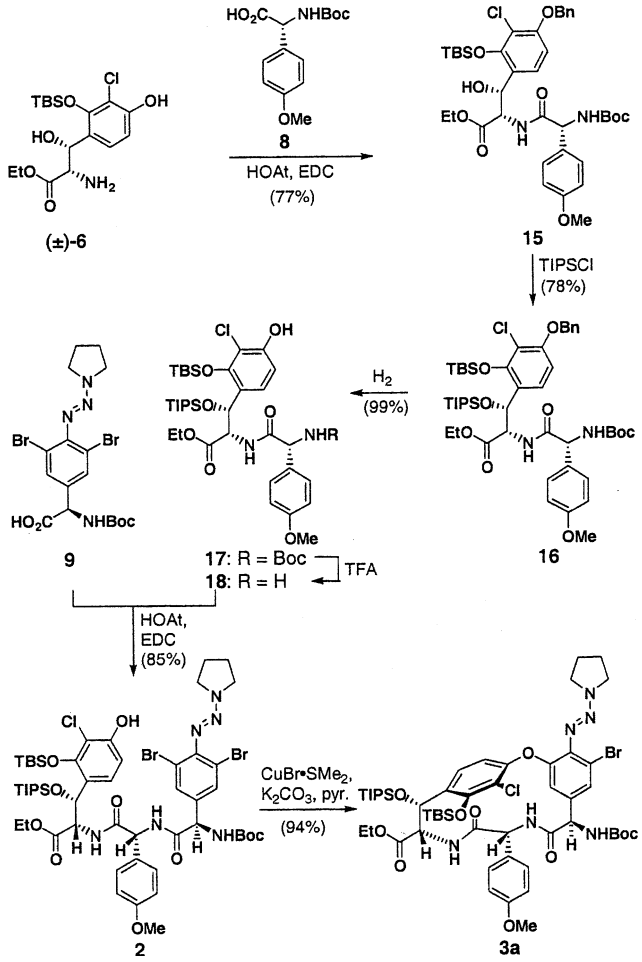
Scheme 2. Synthesis of Racemic β-Hydroxy Amino Acids **6** and **7**



Scheme 3. Atropselective Synthesis of the C−O−D Ring System **3a**



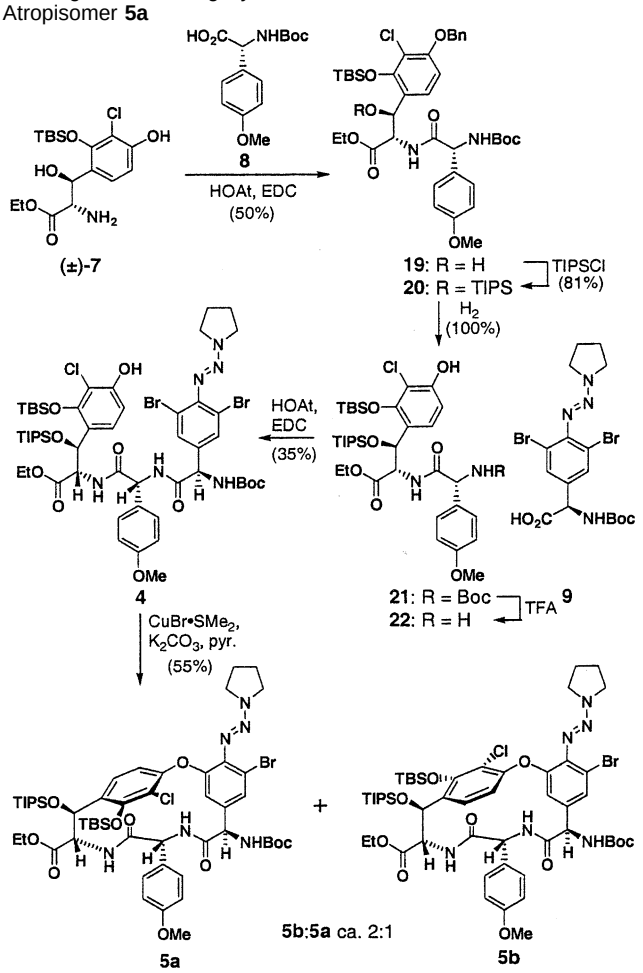
(BnBr, $NaHCO_3$, KI catalyst, 60% yield),[16] followed by treatment with TBSOTf and Et_3N (100% yield). Benzaldehyde **13** was condensed with iminoglycinate **14**[17] under the influence of KHMDS to provide a 1:2 mixture of racemic β-hydroxy tyrosines **6** and **7** in a combined yield of 57%.[18] The two diastereoisomers **6** and **7** were chromatographically separated and employed separately.

Scheme 3 depicts the coupling of β-hydroxy tyrosine derivative (±)-**6** with carboxylic acid **8**[2] (HOAt, EDC) to furnish the dipeptide **15** together with its diastereomer in a combined yield of 77%. Chromatographic purification of **15** followed by protection of the benzylic hydroxy group gave bis-silyl ether **16** (TIPSCl, imid., 78% yield). Hydrogenolysis of the benzyl ether from **16** (H_2, $Pd(OH)_2$/C, 99% yield) and subsequent removal of the Boc group formed phenolic amine **18** via intermediate **17**, which was immediately coupled with triazene carboxylic acid **9**[2] (HOAt−EDC), affording the cyclization precursor **2** in 85% overall yield from **16**.

Ring closure of the latter compound (**2**) under the standard cyclization conditions ($CuBr\cdot SMe_2$, K_2CO_3, pyr.) furnished compound **3a** in 94% yield as a single atropisomer as determined by ^1H NMR spectroscopic analysis. The stereochemistry of atropisomer **3a** was confirmed by NOE studies (see Figure 5). This result is consistent with the predictions of the computer simulation studies described above.

To test the atropselectivity in the macrocyclization of the epimeric β-hydroxy tyrosine series, the required precursor **4** was assembled as shown in Scheme 4. Thus, racemic **7** was coupled with carboxylic acid **8** in the presence of HOAt−EDC, leading to peptide **19** together with its diastereomer in 50% combined yield. Protection of the hydroxyl group as a TIPS ether (TIPSCl, imid., 81% yield) gave a mixture of diastereomeric products (ca. 1:1) from which the desired isomer (**20**) was chromato-

Scheme 4. Atropselective Macrocyclization of Precursor **4** Forming C−O−D Ring System **5b** in a ca. 2:1 Ratio with Its Atropisomer **5a**



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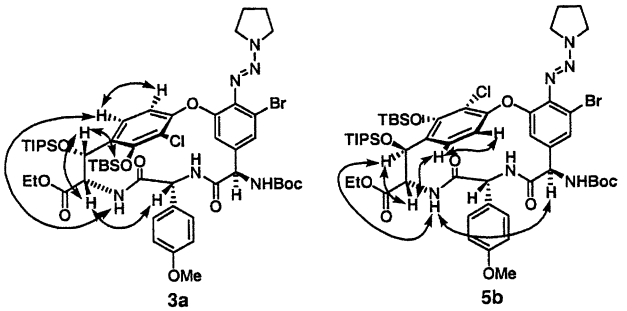

Figure 5. Observed NOEs confirming the stereochemistry of atropisomer **3a** and **5b**. The $^1H-^1H$ NOEs were determined via COSY and ROESY experiments performed in CD_3COCD_3 using a 600 MHz NMR instrument.

graphically separated. Hydrogenolysis of the benzyl ether, followed by Boc removal and coupling with the triazene carboxylic acid **9**, led to precursor **4** via amine **22** (35% overall yield from **20**). Treatment of precursor **4** under the standard cyclization conditions ($CuBr\cdot SMe_2$, K_2CO_3, pyr.) provided compounds **5a** and **5b** in a combined yield of 55% (**5a**:**5b**, ca. 1:2). The stereochemical assignment of compound **5b** was confirmed by NOE studies (see Figure 5).

Conclusion

Through strategic placement of a bulky substituent on the aromatic ring of the tyrosine residue, we were able to enforce an atropselective macrocyclization reaction leading to a single atropisomer of a cyclopeptide diaryl ether related to the C−O−D ring system of vancomycin. The design of this highly atropselective macrocyclization relied on prohibiting interactions between the bulky auxiliary group and the TIPS protecting group of the β-hydroxy moiety of the tyrosine system for the unwanted atropisomer. A similar approach using the opposite stereochemistry of the β-hydroxy moiety of the tyrosine derivative led to the undesired atropisomer as the major product, providing credence to the bulky substituent hypothesis. Interestingly, these designs were based on computational modeling studies which predicted the outcome of these ring closures to a high degree of accuracy. This method could potentially be applied to the atropselective synthesis of vancomycin and other substances exhibiting such atropisomers.

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Supporting Information Available: Experimental procedures and compound characterization (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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