Brønsted acid-promoted azide–olefin [3 + 2] cycloadditions for the preparation of contiguous aminopolyols: The importance of disiloxane ring size to a diastereoselective, bidirectional approach to zwittermicin A

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Abstract
We report the first study of substrate-controlled diastereoselection in a double [3 + 2] dipolar cycloaddition of benzyl azide with α,β-unsaturated imides. Using a strong Brønsted acid (triflic acid) to activate the electron deficient imide π-bond, high diastereoselection was observed provided that a 1,1,3,3-tetraisopropoxydisiloxanylidene group (TIPDS) is used to restrict the conformation of the central 1,3-anti diol. This development provides a basis for a stereocontrolled approach to the aminopolyol core of (−)-zwittermicin A using a bidirectional synthesis strategy.

Introduction
Structural motifs such as 1,2-aminoalcohol, 1,2- and 1,3-diol are very prevalent features in natural products, especially polyketides. The structures of some of these, such as sorbistin A1 [1] or zwittermicin A [2], contain mostly aminopolyol moieties. Aminoalcohol and diol motifs are often constructed via alkene functionalization such as aminohydroxylation [3] and dihydroxylation [4] reactions, or by methods that forge the carbon–carbon bond such as the glycolate Mannich reaction [5]. Recently, we developed a Brønsted acid-promoted azide–olefin reaction as an alternative to metal catalyzed aminohydroxylation reactions [6-8]. Triflic acid-promoted reaction of an alkyl azide with an α,β-unsaturated imide delivers a formal anti-aminohydroxylation product. We wondered whether azide–olefin functionalization could be used to prepare the complex aminopolyol...
Scheme 1: Retrosynthetic analysis outlining the stereocontrolled construction of the aminopolyol core of (−)-zwittermicin A using an azide–olefin double cycloaddition.
maintain its two alkene substituents in a \textit{pseudo}-equatorial arrangement. We reasoned that expansion of the ring from six to eight members through the formation of a disiloxanylidene derivative might better achieve this goal by providing greater flexibility around the oxygen-substituted edge (Scheme 2).

The 8-membered ring methyl carbamate 8 incorporating a tetraisopropoxydisiloxanylidene group \cite{24,25} (TIPDS) was prepared. Not only did bis(imide) 8 provide the bis(triazoline) with high diastereoselection (Table 1, entry 5), it favored the desired \textit{anti,anti} 13a (30\% yield). Introduction of the isopropyl carbamate in bis(imide) 9 led to a significant increase in the yield of the 2,3-\textit{anti}-bis(triazoline) 14 (79\%) without loss of diastereoselection (Table 1, entry 6).

Due to the flexibility of the disiloxane ring we were unable to determine reliably the relative stereochemistry of 13 or 14 by NOE. However, bis(triazolines) 10a and 14a could be converted to the corresponding bis(oxazolidine diones) by treatment with

### Table 1: Substrate-controlled double \([3 + 2]\) cycloaddition.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alkene</th>
<th>PG</th>
<th>R</th>
<th>Conditions(^a)</th>
<th>Product</th>
<th>a:b:c(^b)</th>
<th>Yield (%)(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>Me</td>
<td>A</td>
<td>10</td>
<td>1:2:1</td>
<td>72</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>Me</td>
<td>B</td>
<td>10</td>
<td>1:2.5:5.4</td>
<td>67</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>i-Pr</td>
<td>B</td>
<td>11</td>
<td>1:9:9</td>
<td>54</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>7</td>
<td>i-Pr</td>
<td>B</td>
<td>12</td>
<td>ND(^d)</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>8</td>
<td>Me</td>
<td>B</td>
<td>13</td>
<td>18:1:1</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>9</td>
<td>i-Pr</td>
<td>B</td>
<td>14</td>
<td>18:1:1</td>
<td>79</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)Conditions A: Bn\(_3\) (excess), microwave 100 °C, 1 h; Conditions B: TfOH (5 equiv), Bn\(_3\) (10 equiv) MeCN [0.2 M], -20 °C, 18 h. \(^b\)Ratio of products was measured using the \(^1\)H NMR of the crude reaction mixture. \(^c\)Combined isolated yield. \(^d\)ND = not determined due to signal overlap in \(^1\)H NMR.
triflic acid at room temperature (Scheme 3). The silyl protecting groups were removed with HF·pyridine in THF, and 15 and 16 converted to the same 1,3-diol 17 (Scheme 3).

Conclusion
In summary, this first study of the substrate-controlled diastereoselective addition of benzyl azide to an unsaturated bis(imide) has demonstrated that high diastereoselection is possible using an anti-1,3-diol scaffold. However, it is important to protect this diol as an 8-membered dialkoxydisiloxane instead of a more traditional 6-membered dialkoxysilane. The anti,anti-selectivity observed in this transformation provides a foundation for the straightforward preparation of the aminopolyol backbone of (−)-zwittermicin A using a bidirectional chain functionalization strategy.

Supporting Information
Supporting Information File 1
Experimental procedures, ¹H and ¹³C NMR spectra.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-6-138-S1.pdf]

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References
26. Caution should always be exercised when azides are heated or treated with strong acid, but we have never observed an uncontrolled reaction or off-gas during our studies.

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