

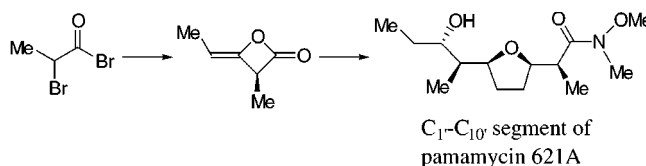
Catalytic, Asymmetric Synthesis of the  
C<sub>1</sub>–C<sub>10</sub> Segment of Pamamycin 621AMichael A. Calter<sup>\*,†</sup> and F. Christopher Bi

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## ABSTRACT



This paper describes a catalytic, asymmetric approach to the C<sub>1</sub>–C<sub>10</sub> segment of pamamycin 621A. We synthesize this segment in a convergent manner, with each of the coupling partners ultimately deriving from enantiomerically enriched methylketene dimer.

The pamamycins, a family of closely homologous macrocycles, exhibit antibacterial and antifungal activity. The supply of pamamycins from natural sources is limited, and these molecules occur as a complex, hard-to-separate mixture of the homologues (Figure 1).<sup>1</sup>

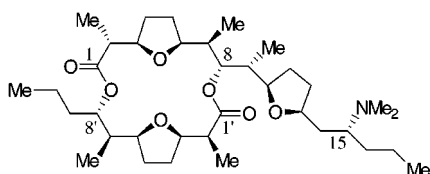
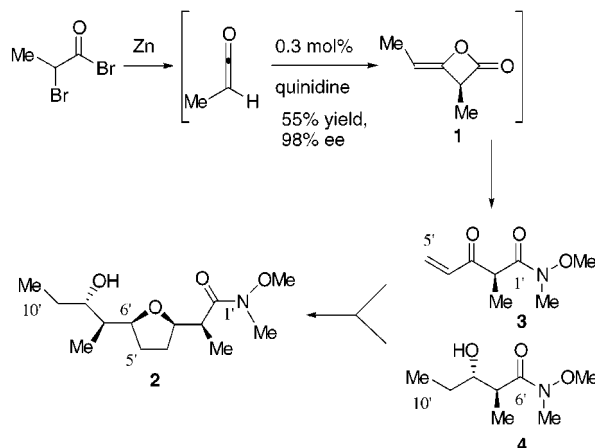


Figure 1. Pamamycin 621A.

Although the antibiotic activity of the pamamycins has made them popular targets for total synthesis, no groups have synthesized any member of the pamamycin family.<sup>2</sup> Furthermore, the length and the reliance on auxiliary-controlled

reactions of the current approaches to the pamamycins make them unattractive for producing the amounts of compounds necessary for clinical testing. We have developed an alternate synthesis to a portion of pamamycin 621A that requires relatively few steps and employs methylketene dimer **1**, available from asymmetric catalysis, as the ultimate source of all the chiral centers in the target (Scheme 1).<sup>3</sup> Additionally, this synthesis promises to be flexible enough to assemble both the C<sub>1</sub>–C<sub>8</sub> and C<sub>1</sub>–C<sub>8</sub> fragments by the same basic method.

## Scheme 1



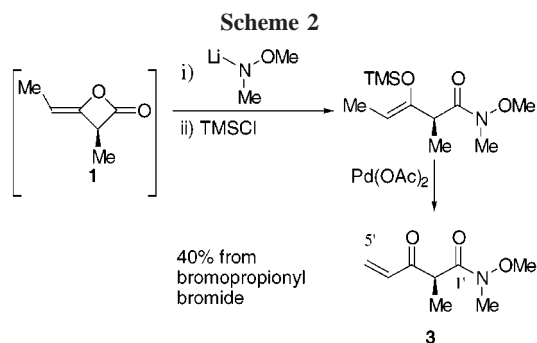
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(1) Kondo, S.; Yasui, K.; Natsume, M.; Katayama, M.; Marumo, S. *J. Antibiot.* **1991**, 32, 3087–3090.

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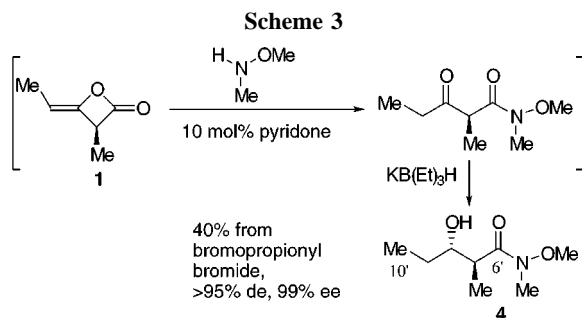
We chose to demonstrate our method by synthesizing **2**, which corresponds to the C<sub>1'</sub>–C<sub>10'</sub> segment of pamamycin 621A. Although **2** does not contain C<sub>11'</sub> and therefore does not comprise a complete synthon for the bottom half of pamamycin, a minor modification of the sequence should afford the complete bottom half synthon. Our route to **2** passes through  $\alpha,\beta$ -unsaturated ketone **3** and  $\beta$ -hydroxyamide **4**. Both of these intermediates are available in a very rapid and convenient manner from bromopropionyl bromide.

The preparation of **3** began with the addition of the lithium amide derived from *N,O*-dimethylhydroxylamine (produced by the reaction of the amine with *n*-butyllithium) to methylketene dimer **1**, followed by in situ trapping of the resulting lithium enolate to afford a trimethylsilyl enol ether (Scheme 2). The instability of this compound caused us to use it

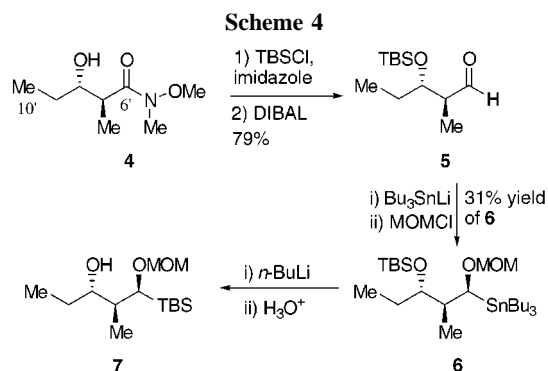


without purification in the subsequent oxidation step. The optimal conditions we found for the oxidation of the silyl ether were the use of a stoichiometric amount of Pd(II), to give **3** in 40% overall yield from bromopropionyl bromide.<sup>4</sup> The low overall yield of **3** and the use of stoichiometric palladium were obvious drawbacks to this route, and we are exploring alternate conditions for the oxidation. Also note that a potential route to the homologous equivalent of **4** necessary for the synthesis of the complete C<sub>1'</sub>–C<sub>11'</sub> segment could start with **3** and proceed via conjugate addition of a methyl anion equivalent followed by ketone reduction.

Our route to **4** started with opening **1** with *N,O*-dimethylhydroxylamine itself to yield a  $\beta$ -ketoamide (Scheme 3).<sup>5</sup> This  $\beta$ -ketoamide was reduced in situ with KB(Et)<sub>3</sub>H to yield *anti*- $\beta$ -hydroxyamide **4** with high diastereo- and enantioselectivity.<sup>6</sup>

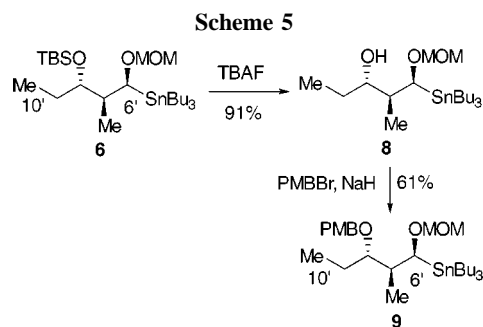


To couple the two portions of the segment, we decided to convert C<sub>6'</sub> of **4** into a nucleophilic center in preparation for addition to the electrophilic C<sub>5'</sub> of **3**. To accomplish this switch, we first protected the C<sub>8'</sub>-hydroxyl and then reduced the Weinreb amide to form aldehyde **5** (Scheme 4).<sup>7</sup> Addition



of tributylstannyl lithium to **5**, followed by protection, gave a 3:1 mixture of  $\alpha$ -alkoxystannanes in low yield.<sup>8</sup> The major diastereomer is that predicted by the Felkin–Anh model.<sup>9,10</sup> However, this reaction appeared to be under partial thermodynamic control, as variation of the reaction time resulted in a variation of the diastereomeric ratio of the products.<sup>11</sup> We had intended to use the major diastereomer, **6**, as a precursor for a cuprate reagent to add to **3**. However, attempted transmetalation of **6** resulted in complete transfer of the TBS group from oxygen to carbon.

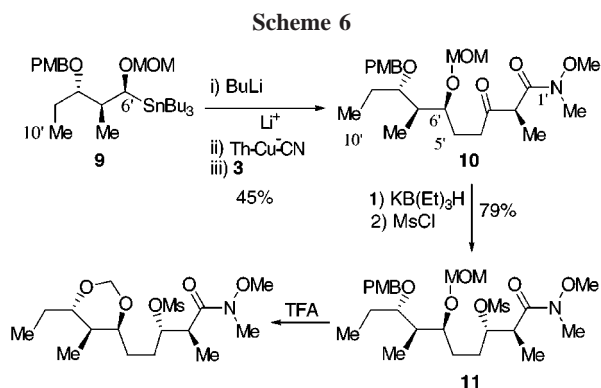
To preclude the possibility of silyl migration, we converted the C<sub>8'</sub>-hydroxyl protecting group from silyl ether to PMB ether (Scheme 5). Synthesis of **9** using this method afforded



higher overall yields than an alternative method involving installation of the PMB protecting group prior to stannate addition.

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We coupled **3** and **9** by first transmetallating **9** to a form a mixed, higher order cuprate and then adding the cuprate to **3** to yield **10** (Scheme 6).<sup>12</sup> Reduction of **10** under



conditions selective for the *anti* alcohol,<sup>5</sup> followed by mesylation, yielded **11**. At this point, it was necessary to remove the MOM ether from the C<sub>6</sub>-hydroxyl. However, this deprotection was hampered by the unexpected lability of the PMB group on the C<sub>8</sub>-hydroxyl. For example, treatment of **11** with TFA resulted in initial loss of the PMB group, followed by formal formation.

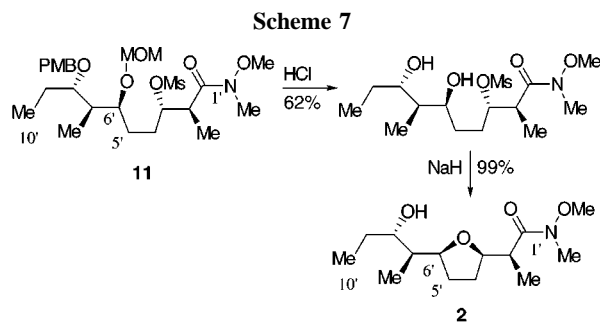
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(10) The stereochemistry of the addition products was proven by <sup>1</sup>H NMR analysis of the formals formed from **8** and its diastereomer by treatment with TFA.

(11) For evidence of thermodynamic control in stannate addition, see: Sawyer, J. S.; Macdonald, T. L.; McGarvey, G. J. *J. Am. Chem. Soc.* **1984**, 106, 3376–3377.

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However, treatment of **11** with HCl in MeOH cleanly removed both the PMB and MOM groups (Scheme 7).<sup>13</sup>



Cyclization of the resulting diol with NaH was highly selective for the desired five-membered ring, affording the desired C<sub>1</sub>–C<sub>10</sub> segment, **2**, in excellent yield.<sup>14</sup>

In summary, we have developed a convergent, catalytic, asymmetric approach to the C<sub>1</sub>–C<sub>10</sub> segment of pamamycin 621A. Furthermore, this method should also be amenable to the synthesis of the C<sub>1</sub>–C<sub>9</sub> segment of the pamamycins. For example, use of the enantiomer of **1**, combined with *syn* selective reduction following coupling, should yield the diastereomer necessary for the synthesis of the C<sub>1</sub>–C<sub>9</sub> segment of pamamycin 621A.

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