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Catalytic, Asymmetric Synthesis of the $C_{1'}$–$C_{10'}$ Segment of Pamamycin 621A

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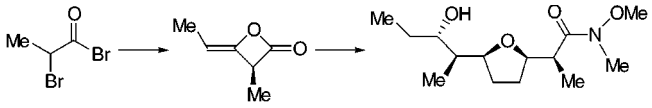
ABSTRACT



$C_{1'}$-$C_{10'}$ segment of pamamycin 621A

This paper describes a catalytic, asymmetric approach to the $C_{1'}$–$C_{10'}$ 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).[1]

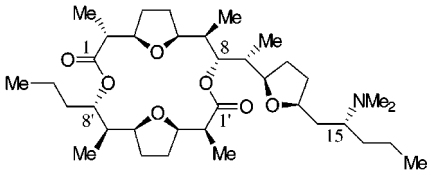
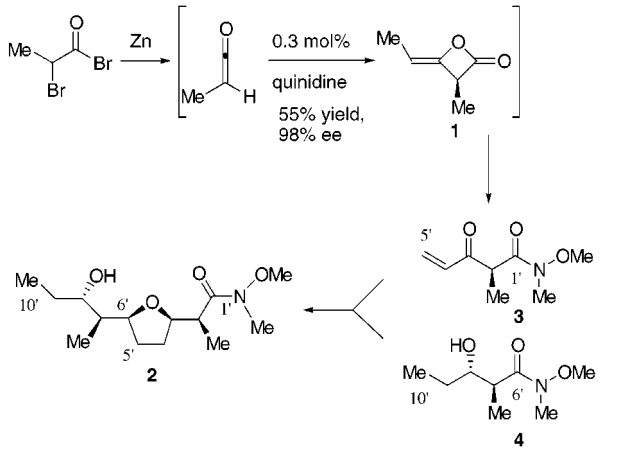


Figure 1. Pamamycin 621A.

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.[2] 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).[3] Additionally, this synthesis promises to be flexible enough to assemble both the $C_{1'}$–$C_{8'}$ and C_1–C_8 fragments by the same basic method.

Scheme 1



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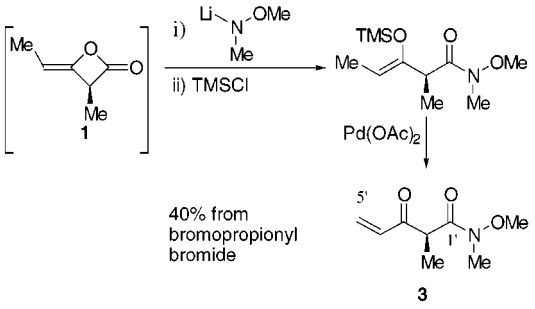
We chose to demonstrate our method by synthesizing **2**, which corresponds to the $C_{1'}-C_{10'}$ segment of pamamycin 621A. Although **2** does not contain $C_{11'}$ and therefore does not comprise a complete synthon for the bottom half of pamamycin, a minor modification of the sequence should afford the complete bottom half synthon. Our route to **2** passes through α,β-unsaturated ketone **3** and β-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

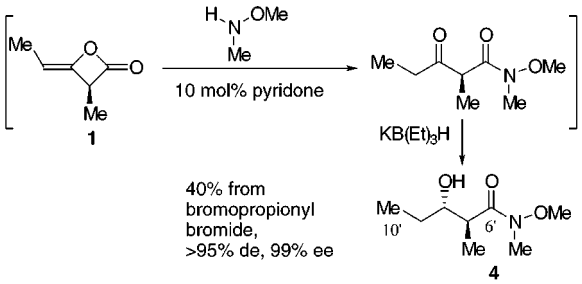
Scheme 2



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.[4] 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 $C_{1'}-C_{11'}$ segment could start with **3** and proceed via conjugate addition of a methyl anion equivalent followed by ketone reduction.

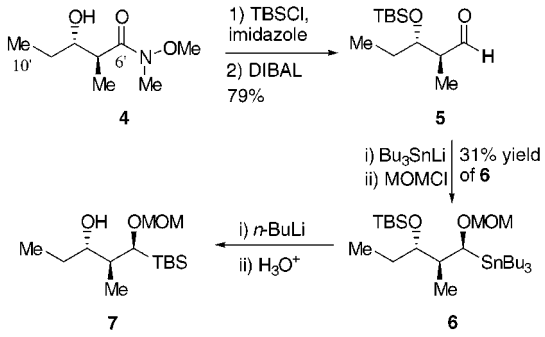
Our route to **4** started with opening **1** with *N*,*O*-dimethylhydroxylamine itself to yield a β-ketoamide (Scheme 3).[5] This β-ketoamide was reduced in situ with $KB(Et)_3H$ to yield *anti*-β-hydroxyamide **4** with high diastereo- and enantioselectivity.[6]

Scheme 3



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

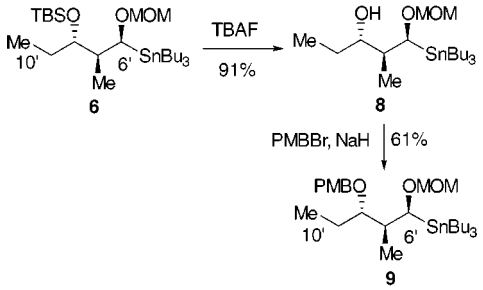
Scheme 4



of tributylstannyllithium to **5**, followed by protection, gave a 3:1 mixture of α-alkoxystannanes in low yield.[8] The major diastereomer is that predicted by the Felkin−Anh model.[9,10] 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.[11] 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 $C_{8'}$-hydroxyl protecting group from silyl ether to PMB ether (Scheme 5). Synthesis of **9** using this method afforded

Scheme 5



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

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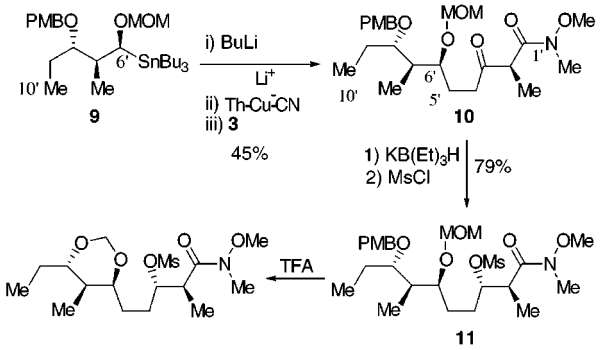
We coupled **3** and **9** by first transmetallating **9** to a form a mixed, higher order cuprate and then adding the cuprate to **3** to yield **10** (Scheme 6).[12] Reduction of **10** under

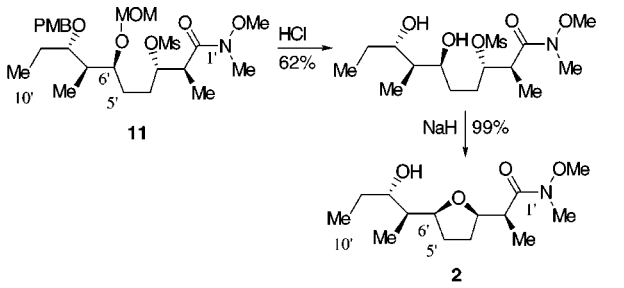
Scheme 6



conditions selective for the *anti* alcohol,[5] followed by mesylation, yielded **11**. At this point, it was necessary to remove the MOM ether from the $C_{6'}$-hydroxyl. However, this deprotection was hampered by the unexpected lability of the PMB group on the $C_{8'}$-hydroxyl. For example, treatment of **11** with TFA resulted in initial loss of the PMB group, followed by formal formation.

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

Scheme 7



Cyclization of the resulting diol with NaH was highly selective for the desired five-membered ring, affording the desired $C_{1'}-C_{10'}$ segment, **2**, in excellent yield.[14]

In summary, we have developed a convergent, catalytic, asymmetric approach to the $C_{1'}-C_{10'}$ segment of pamamycin 621A. Furthermore, this method should also be amenable to the synthesis of the C_1-C_9 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_1-C_9 segment of pamamycin 621A.

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