# An Aldol Approach to the Total Synthesis of Pamamycin 621 A

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#### ABSTRACT



Pamamycin 621A was synthesized through a convergent route, with the THF rings constructed from Evans aldols in the presence of the chiral auxiliaries without suffering racemization or elimination. The basic amino group was introduced at a late stage through reduction of an azido group with *n*-Bu<sub>3</sub>SnH, which also demonstrates for the first time the great potential of this largely forgotten reduction protocol in synthesis of multifunctional substrates.

Pamamycin 621A (1) is one of the 19 macrodiolide homologues generated by various Streptomyces species.<sup>1</sup> Because of their interesting structures and bioactivities (such as autoregulatory, anionophoric, antifungal, antibacterial activity), pamamycins have received remarkable attention from the synthetic community since the late 1990s and consequently promoted the appearance of many elegant syntheses.<sup>2</sup> However, most studies were directed toward 607, the simplest member in the family. Among the remainder, only 621A and 635B (Figure 1) have been synthesized to date.<sup>2g</sup>

A prominent structural feature present in all pamamycins is the occurrence of three 2,5-*cis*-disubstituted-THF rings incorporated into the "hidden" polyketide chains. Recently, en route to a total synthesis of nonactin (4) we developed an effective means<sup>3</sup> for construction of similar rings from syn-aldols generated by Evans/Crimmins aldolization<sup>4</sup> without suffering from the otherwise readily occurring side

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Figure 1. Pamamycins 621A (1), 607 (2), 635B (3), and nonactin (4).

reactions such as  $\alpha$ -racemization and  $\beta$ -elimination caused by the aldol carbonyl group. The ester carbonyl carbons in the end product thus could be maintained at the same oxidation level throughout the whole sequence without need for recourse to otherwise unavoidable operations such as protection, reduction, and reoxidation at these carbons. Here, in this communication, we wish to further demonstrate the potential of this protocol (with modification/extension) through a novel and efficient synthesis of **1**.

Our retrosynthetic analysis is outlined in Figure 2. The dilactone framework of **1** was first disconnected into a "larger



Figure 2. Major fragments involved in this work.

fragment" **5** and a "smaller fragment" **6**. The hydroxyacid **5** was then further disconnected into two major subunits, alkyne **7** and aldehyde **8**. The synthesis of **7** is depicted in Scheme 1. Starting from **9**, now a readily accessible<sup>5</sup> chiral building block, through TBS/MOM protections, removal of the acetonide, oxidative cleavage of the vicinal diol and Corey–Fuchs<sup>6</sup> reaction, alkyne **7** was obtained in 75% overall yield (from **9**).



The fragment 8 was built up from the known enal  $13^7$  via the route shown in Scheme 2. The C-6/C-7 and C-8/C-9



stereogenic centers were introduced with excellent control of the absolute configurations via two Evans/Crimmins aldolizations.

The aldolization leading to **18** was best realized with (–)-sparteine<sup>4d</sup> as the base (94% yield, dr >95:5). Use of TMEDA under the otherwise identical conditions led to much lower yields and diastereoselectivity. TMS protection<sup>8</sup> and reductive cleavage of the chiral auxiliary led to aldehyde **8** (not very stable), which was directly treated with lithiated **7** to afford a readily separable 2:3 mixture of **19a** and **19b** (Scheme 3).

With the stereochemistry on C-10 secured by redox transformation of **19a** to **19b**, we set out to transform **19b**<sup>9</sup> into **21** through desilylation, diol protection, and deprotection/oxidation at the C-3. The C-2/C-3 stereogenic centers were then generated by reaction with **12**. Removal of the TBS group in **22** was achieved with HF<sup>•</sup>py. The C–C double/triple bonds were saturated by hydrogenation in the presence of Et<sub>3</sub>N,<sup>10</sup> which

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<sup>(8)</sup> Without the TMS protection, the two C-10 epimers (**19a** and **19b** without the TMS group on C-8 OH) were inseparable on silica gel.

<sup>(9) (</sup>a) Essentially no reaction occurred if using Zn or Mg salt of **7**. The asymmetric protocol of Carreira (see, (b) Frantz, D. E.; Fassler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 1806–1807) also failed to yield any products here. (c) The relative configurations of **19a/b** were established through NOEs of their C-8 OH/C-10 OH acetonides.

<sup>(10)</sup> For a literature precedent using a primary amine for such a purpose, see: Czech, B. P.; Barsch, R. A. J. Org. Chem. **1984**, 49, 4076–4078.



made it possible to remain an intact BnO– and consequently the C-6 OH required in the later THF-ring formation.

Mesyaltion leading to **24** was uneventful. Subsequent removal of the acetonide group with TFA/MeOH–CH<sub>2</sub>Cl<sub>2</sub> (1:1) did not give the expected diol but a mono-THF species formed through alkylation of the C-10 OH by the C-13 mesylate!<sup>11</sup> Exposure of this crude product to H<sub>2</sub>/Pd–C/THF followed by heating in 2,6-lutidine at 120 °C afforded the desired **25a** in 93% yield. Alternatively, **25a** could also be obtained by treatment of **24** with H<sub>2</sub>/Pd–C (excess)/MeOH/rt for 2 h followed by heating in 2,6-lutidine, though the yield was slightly lower (86%). In the presence of CSA after prolonged reaction, the hydrogenation alone could lead directly to diol **25b** in 68% yield.<sup>12</sup> Cleavage of the chiral auxiliary in **25a** with LiOH/H<sub>2</sub>O<sub>2</sub><sup>13</sup> completed the whole synthesis of **5**.

Synthesis of 6 began with an Evans/Crimmins aldolization between aldehyde  $26^{14}$  and acyloxazolidinone 12 (Scheme 4).



The resulting **27** was transformed into the corresponding Weinreb amide and ketone sequentially by reaction with AlMe<sub>3</sub>/MeNH(OMe)·HCl and *n*-PrMgBr, respectively. The C-8' stereogenic center was then introduced by a  $Me_4NBH(OAc)_3^{15}$  reduction. Removal of the TBS group and acetonization of the diol provided alcohol **29**, which on oxidation yielded the aldehyde required for the next aldol reaction.

The MgCl<sub>2</sub>/TMSCl<sup>16</sup>-mediated anti aldolization leading to **27** was first attempted under the literature conditions without success. However, when the amounts of MgCl<sub>2</sub>/Et<sub>3</sub>N were increased from the literature recommended 0.1/2.0 equiv to 1.0/2.5 equiv, respectively, the desired **30** could be isolated in 56% yield (from **29**).<sup>17</sup> Addition of NaSbF<sub>6</sub><sup>16</sup> in this case did not lead to any improvements but substantially lower yield and diastereoselectivity.

The alcohol **30** was converted into **31** over three steps of reactions: hydrogenation of the C–C double bond, mesylation of the C-3' OH, and removal of the acetonide. Treatment of **31** under the previously<sup>3</sup> established 2,6-lutidine/120 °C conditions led to **6** in 90% yield (dr 10:1 before separation). Use of an even bulkier base, 2,6-di-*tert*-butylpyridine, to replace 2,6-lutidine resulted in slightly better yield but worse diastereoselectivity (dr 5:1). Better diastereoselectivity (dr

(11) We are not aware of similar precedents in the literature; such an etherification usually occurs only under basic conditions.

(12) We are not aware of any literature precedents.

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(17) We are not aware of any precedents of application of this protocol to complex enals with an eliminable ethereal group at the allylic position.

95:5) could be obtained in neat pyridine at 110 °C, but the yield of isolated **6** was only 62%.

The coupling between **5** and **6** (Scheme 5) under the Yamaguchi<sup>18</sup> conditions occurred smoothly despite the



significantly increased steric crowding around the C-8' OH caused by the extra C-7' methyl group (compared with its counterpart in Kang's<sup>2e</sup> synthesis<sup>19</sup>). Subsequent treatment with LiOH/H<sub>2</sub>O<sub>2</sub> yielded **32**. The dilactone ring was then closed in 66% yield using another Yamaguchi esterification. Notably, at this step heating to 110 °C proved to be necessary, as lower temperatures led to poor yields or even complete failure.

The MOM group was hydrolyzed with 10% HBr. The resulting alcohol was treated with Ph<sub>3</sub>P/DEAD/(PhO)<sub>2</sub>-

 $P(O)N_3^{20}$  to afford azide **33**. Further conversion of the azido functionality into  $-NMe_2$  was troublesome. The literature<sup>2e</sup> conditions (e.g., H<sub>2</sub>/Pd-C/HCHO/ HCO<sub>2</sub>H) led repeatedly to complex mixtures. Ph<sub>3</sub>P or SnCl<sub>2</sub> reduction followed by treatment with NaBH<sub>3</sub>CN/HCHO/AcOH also resulted in mixtures. Finally, we were pleased to find that treatment of **33** with *n*-Bu<sub>3</sub>SnH<sup>21</sup> in refluxing toluene (in the absence of any added radical initiators) could afford the desired intermediate primary amine cleanly, which on further exposure to NaBH<sub>3</sub>CN/HCHO/AcOH led to end product<sup>22</sup> **1** in 92% yield.

In conclusion, an effective enantioselective total synthesis of pamamycin 621A was achieved. The characteristic THF's motifs were constructed from aldols in the presence of chiral auxiliaries with configuration inversions at the positions  $\beta$  to carbonyl groups. Elaboration of the C-1 and C-1' was thus greatly simplified. The basic nitrogen functionality was introduced at a rather late stage, which greatly facilitated isolation and characterization of the enantiopure intermediates. A number of interesting phenomena were observed, including the unexpected THF-ring closures under acidic conditions. Finally, an *n*-Bu<sub>3</sub>SnH reduction of azide to amine was achieved for the first time in multifunctional/sensitive substrates. Such a mild protocol may find broad applications in total synthesis of other natural products.

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Supporting Information Available: Selected experiments, physical and spectroscopic data listing, <sup>1</sup>H as well as <sup>13</sup>C NMR spectra for 25a, 25b, 5, 6, "5 + 6", 30′, 30″, 31, 32, 32′, 32″, 33, and 1. This material is available free of charge via the Internet at http://pubs.acs.org.

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<sup>(18)</sup> For Yamaguchi esterification, see: Yamaguchi, M.; Innaga, J.; Hirata, K.; Saeki, H.; Katsuki, T. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989–1993.

<sup>(19)</sup> In other routes involving similar coupling, the C-8 OH was all masked as either a TBS ether or an acetate (ref 2a,g,f).

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<sup>(22)</sup> Stirring of the CDCl<sub>3</sub> with  $K_2CO_3$  before use made it easier to obtain a "normal-looking" <sup>1</sup>H NMR spectrum. Otherwise, the spectrum of 1 might be different from run to run, with the *N*-methyl groups appearing at different chemical shifts as the most prominent phenomenon. Another very interesting phenomenon observed with 1 is that in CH<sub>2</sub>Cl<sub>2</sub> its [ $\alpha$ ] is of opposite sign to that in CHCl<sub>3</sub>!