

An Aldol Approach to the Total Synthesis of Pamamycin 621 A

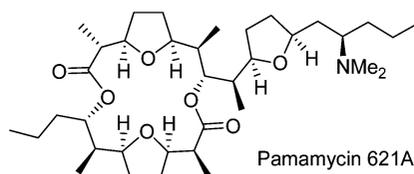
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ABSTRACT



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*-Bu₃SnH, 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.¹ 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.² 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.^{2g}

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 means³ for construction of similar rings from

syn-aldols generated by Evans/Crimmins aldolization⁴ without suffering from the otherwise readily occurring side

(1) (a) McCann, P. A.; Pogell, B. M. *J. Antibiot.* **1979**, *32*, 673–678. (b) Kondo, S.; Yasui, K.; Natsume, M.; Katayama, M.; Marumo, S. *J. Antibiot.* **1988**, *41*, 1196–1204. (c) Natsume, M.; Kondo, S.; Marumo, S. *J. Chem. Soc., Chem. Commun.* **1989**, 1911–1913. (d) Natsume, M.; Yasui, K.; Kondo, S.; Marumo, S. *Tetrahedron Lett.* **1991**, *32*, 3087–3090. (e) Natsume, M.; Tazawa, J.; Yagi, K.; Abe, H.; Kondo, S.; Marumo, S. *J. Antibiot.* **1995**, *48*, 1159–1164. (f) Natsume, M.; Honda, A.; Oshima, Y.; Abe, H.; Kondo, S.; Tanaka, F.; Marumo, S. *Biosci. Biotechnol. Biochem.* **1995**, *59*, 1766–1768. For a recent review, see: (g) Metz, P. *Top. Curr. Chem.* **2005**, *244*, 215–249.

(2) For total syntheses, see: (a) Gernay, O.; Kumar, N.; Thomas, E. J. *Tetrahedron Lett.* **2001**, *42*, 4969–4974. (b) Lee, E.; Jeong, E. J.; Kang, E. J.; Sung, L. T.; Hong, S. K. *J. Am. Chem. Soc.* **2001**, *123*, 10131–10132. (c) Jeong, E. J.; Kang, E. J.; Sung, L. T.; Hong, S. K.; Lee, E. J. *Am. Chem. Soc.* **2002**, *124*, 14655–14662. (d) Wang, Y.; Bernsmann, H.; Gruner, M.; Metz, P. *Tetrahedron Lett.* **2001**, *42*, 7801–7804. (e) Kang, S. H.; Jeong, J. W.; Hwang, Y. S.; Lee, S. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 1392–1395. (f) Lanners, S.; Norouzi-Arasi, H.; Salom-Roig, X. J.; Hanquet, G. *Angew. Chem., Int. Ed.* **2007**, *46*, 7086–7089. (g) Fischer, P.; Segovia, A. B. G.; Gruner, M.; Metz, P. *Angew. Chem., Int. Ed.* **2005**, *44*, 6231–6234. For fragment syntheses, see: (h) Walkup, R. D.; Park, G. *Tetrahedron Lett.* **1988**, *29*, 5505–5508. (i) Walkup, R. D.; Kim, S. W.; Wagdy, S. D. *J. Org. Chem.* **1993**, *58*, 6486–6490. (j) Walkup, R. D.; Kim, S. W. *J. Org. Chem.* **1994**, *59*, 3433–3441. (k) Walkup, R. D.; Kim, Y. S. *Tetrahedron Lett.* **1995**, *36*, 3091–3094. (l) Mavropoulos, I.; Perlmutter, P. *Tetrahedron Lett.* **1996**, *37*, 3751–3754. (m) Arista, L.; Gruttadauria, M.; Thomas, E. J. *Synlett* **1997**, 627–628. (n) Mandville, G.; Girard, C.; Bloch, R. *Tetrahedron: Asymmetry* **1997**, *8*, 3665–3673. (o) Mandville, G.; Bloch, R. *Eur. J. Org. Chem.* **1999**, 2303–2307. (p) Solladie, G.; Salom-Roig, X. J.; Hanquet, G. *Tetrahedron Lett.* **2000**, *41*, 551–554. (q) Bernsmann, H.; Hungerhoff, B.; Fechner, R.; Frohlich, R.; Metz, P. *Tetrahedron Lett.* **2000**, *41*, 1721–1724. (r) Calter, M. A.; Bi, F. C. *Org. Lett.* **2000**, *2*, 1529–1531. (s) Solladie, G.; Salom-Roig, X. J.; Hanquet, G. *Tetrahedron Lett.* **2000**, *41*, 2737–2740. (t) Bernsmann, H.; Frohlich, R.; Metz, P. *Tetrahedron Lett.* **2000**, *41*, 4347–4351. (u) Bernsmann, H.; Gruner, M.; Metz, P. *Tetrahedron Lett.* **2000**, *41*, 7629–7633. (v) Bernsmann, H.; Gruner, M.; Frolich, R.; Metz, P. *Tetrahedron Lett.* **2001**, *42*, 5377–5380. (w) Miura, A.; Takigawa, S.-y.; Furuya, Y.; Yokoo, Y.; Kuwahara, S.; Kiyota, H. *Eur. J. Org. Chem.* **2008**, 4955–4962.

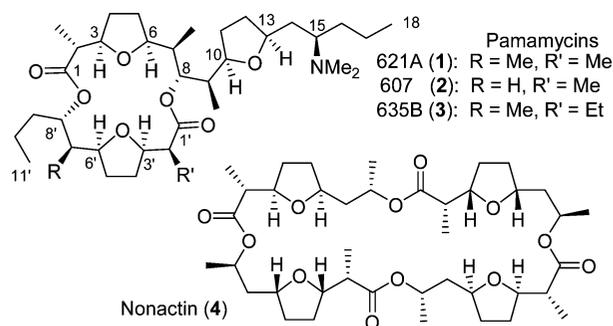


Figure 1. Pamamycins 621A (1), 607 (2), 635B (3), and nonactin (4).

reactions such as α -racemization and β -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

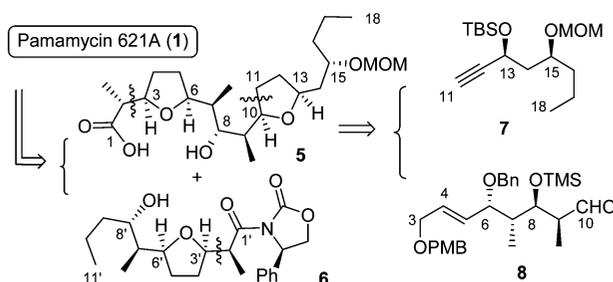


Figure 2. Major fragments involved in this work.

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 accessible⁵ chiral building block, through TBS/MOM protections, removal of the acetonide, oxidative cleavage of the vicinal diol and Corey–Fuchs⁶ reaction, alkyne **7** was obtained in 75% overall yield (from **9**).

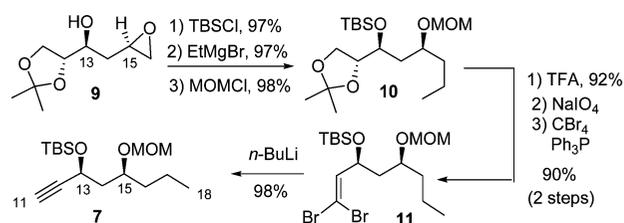
(3) Wu, Y.-K.; Sun, Y.-P. *Org. Lett.* **2006**, *8*, 2831–2834.

(4) (a) Evans, D. A.; Bartoli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127–2129. (b) Evans, D. A.; Rieger, D. L.; Bilodeau, M. T.; Urpi, F. *J. Am. Chem. Soc.* **1991**, *113*, 1047–1049. (c) Crimmins, M. T.; King, B. W.; Tabet, E. A. *J. Am. Chem. Soc.* **1997**, *119*, 7883–7884. (d) Crimmins, M. T.; Chaudhary, K. *Org. Lett.* **2000**, *2*, 775–777. (e) Crimmins, M. T.; King, B. W.; Tabet, E. A.; Chaudhary, K. *J. Org. Chem.* **2001**, *66*, 894–902.

(5) (a) Mulzer, J.; Pietschman, C.; Schollhorn, B.; Buschmann, J.; Luger, P. *Liebigs Ann. Chem.* **1995**, 1433–1439. For a practical access to multi-ten grams of **9**, see: (b) Wu, J.-Z.; Gao, J.; Ren, G.-B.; Zhen, Z.-B.; Zhang, Y.-H.; Wu, Y.-K. *Tetrahedron* **2009**, *65*, 289–299.

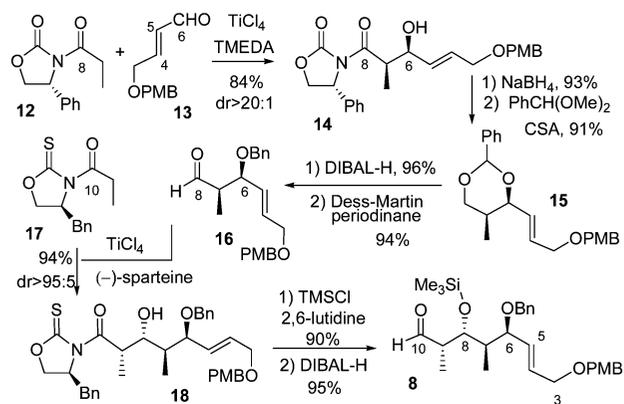
(6) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 3769–3772.

Scheme 1



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

Scheme 2



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^{4d} as the base (94% yield, dr>95:5). Use of TMEDA under the otherwise identical conditions led to much lower yields and diastereoselectivity. TMS protection⁸ 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**⁹ 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·py. The C–C double/triple bonds were saturated by hydrogenation in the presence of Et₃N,¹⁰ which

(7) Marshall, J. A.; Schaaf, G.; Nolting, A. *Org. Lett.* **2005**, *7*, 5331–5333.

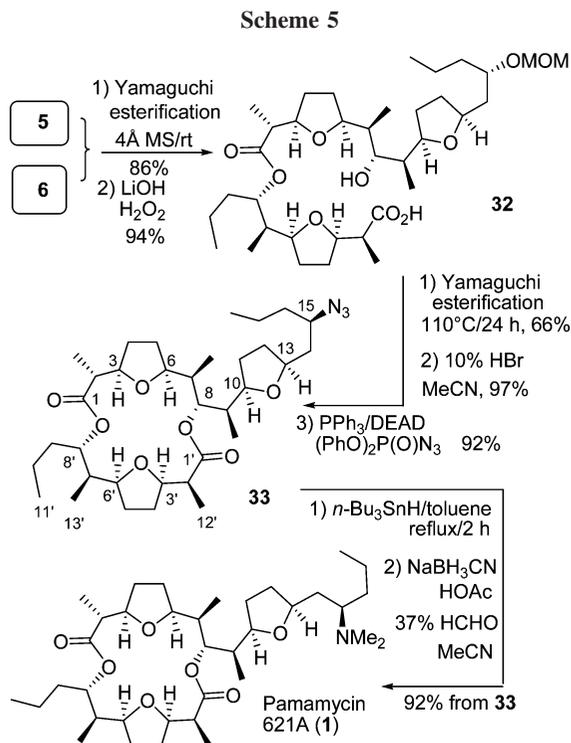
(8) Without the TMS protection, the two C-10 epimers (**19a** and **19b** without the TMS group on C-8 OH) were inseparable on silica gel.

(9) (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.

(10) 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.

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 Yamaguchi¹⁸ 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^{2e} synthesis¹⁹). Subsequent treatment with LiOH/H₂O₂ 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 Ph₃P/DEAD/(PhO)₂-

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

(19) 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).

P(O)N₃²⁰ to afford azide **33**. Further conversion of the azido functionality into –NMe₂ was troublesome. The literature^{2e} conditions (e.g., H₂/Pd–C/HCHO/HCO₂H) led repeatedly to complex mixtures. Ph₃P or SnCl₂ reduction followed by treatment with NaBH₃CN/HCHO/AcOH also resulted in mixtures. Finally, we were pleased to find that treatment of **33** with *n*-Bu₃SnH²¹ in refluxing toluene (in the absence of any added radical initiators) could afford the desired intermediate primary amine cleanly, which on further exposure to NaBH₃CN/HCHO/AcOH led to end product²² **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 β 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*-Bu₃SnH 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, ¹H as well as ¹³C 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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(20) Lal, B.; Pramanik, E. N.; Manhas, M. S.; Bose, A. K. *Tetrahedron Lett.* **1977**, 1977–1980.

(21) Redlich, H.; Roy, W. *Liebigs. Ann. Chem.* **1981**, 1215–1222.

(22) Stirring of the CDCl₃ with K₂CO₃ before use made it easier to obtain a “normal-looking” ¹H 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 CH₂Cl₂ its [α] is of opposite sign to that in CHCl₃!