Total syntheses of amythiamicins A, B and C†‡

K. C. Nicolaou,*[abc] Dattatraya H. Dethe[a] and David Y.-K. Chen*[a]

Received (in Cambridge, UK) 25th March 2008, Accepted 11th April 2008
First published as an Advance Article on the web 8th May 2008
DOI: 10.1039/b805069b

Total syntheses of the thiopeptide antibiotics amythiamicins A, B and C are reported.

Isolated from a strain of *Amycolatopsis* sp. MI481-42F4, amythiamicins A, B and C[1] (**1**–**3**, Fig. 1) are members of the trisubstituted pyridine subclass of the thiopeptide family of antibiotics.[2] In addition to their impressive antibiotic properties against Gram-positive bacteria, including MRSA,[1a] these substances also exhibit activity against *Plasmodium falciparum*, the causative parasite responsible for malarial infections.[3] The antiparasitic properties of these thiopeptides are believed to be exerted through inhibition of protein synthesis by binding to elongation factor EF-Tu. This mechanism of action is similar to that exhibited by GE2270A but with a different binding site.[3] In view of their novel molecular architectures and mechanism of action, amythiamicins A, B and C (**1**–**3**) were deemed worthy synthetic targets.[4] In this communication we report expedient total syntheses of all three natural products **1**–**3** through application of our recently developed synthetic technologies[5] for the construction of thiopeptide antibiotics.

Our synthetic strategy towards the amythiamicins features application of the powerful hetero-Diels–Alder dimerization process,[5] followed by oxidative aromatization to assemble the trisubstituted pyridine core of the molecule. A subsequent regioselective macrocyclization engaging the C1 carboxylic acid terminus was envisaged for the construction of the 29-membered macrolactam ring of the amythiamicins while at the same time activating the C1′ terminus of the growing molecule so as to facilitate side chain attachment, thereby enabling a "one-pot", tandem bis-amidation process.[5d,6]

The synthesis of the required thiazolidine **9** and its dimerization to trisubstituted pyridine **12** is summarized in Scheme 1. Thus, coupling of α-bromo ketone **4**[5d] with thioamide **5**[7] in the presence of TFAA and pyridine gave bis-thiazole **6** in 78% yield. Reduction of the ethyl ester group within **6** (DIBAL-H) (85% yield) followed by condensation with amino thiol TFA salt **8**[5b] afforded thiazolidine **9** in 80% yield (*ca.* 7 : 3 mixture of diastereomers) for the two steps. Exposure of thiazolidine **9** to the previously established reagent mix (Ag_2CO_3, DBU, $BnNH_2$, py) under the optimized reaction conditions (−12 °C, 1 h)[5d] smoothly delivered dehydropiperidine **11** in 51% yield as a *ca.* 1 : 1 mixture of diastereoisomers through the intermediacy of heterodiene **10**. Finally, oxidative aromatization (DBU, EtOAc) with concomitant extrusion of ammonia gave trithiazolyl pyridine **12** in 36% yield.

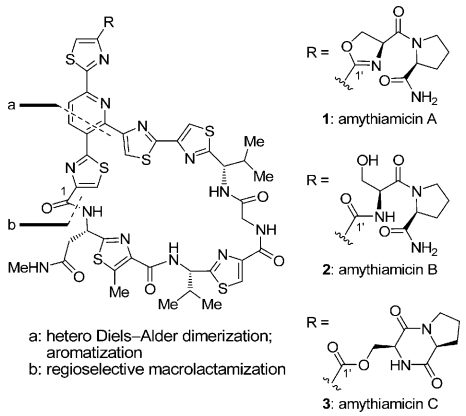
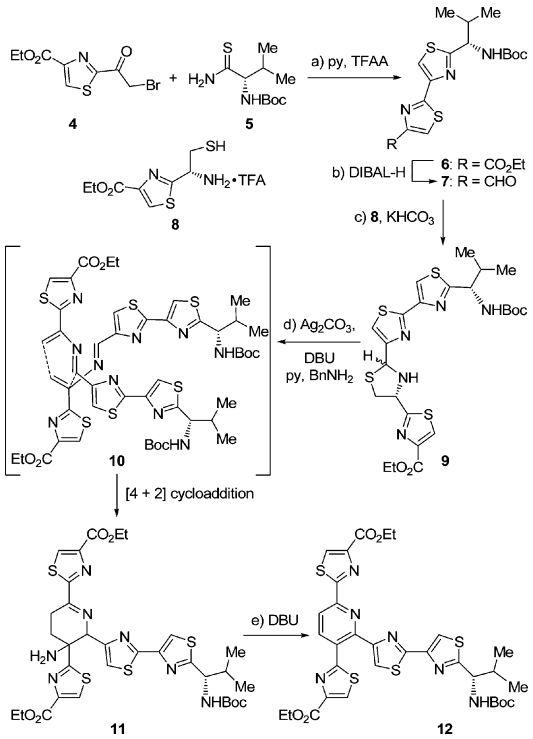


Fig. 1 Molecular structures and retrosynthetic analysis of amythiamicins A (**1**), B (**2**) and C (**3**). (a) Hetero-Diels–Alder dimerization; (b) regioselective macrolactamization.

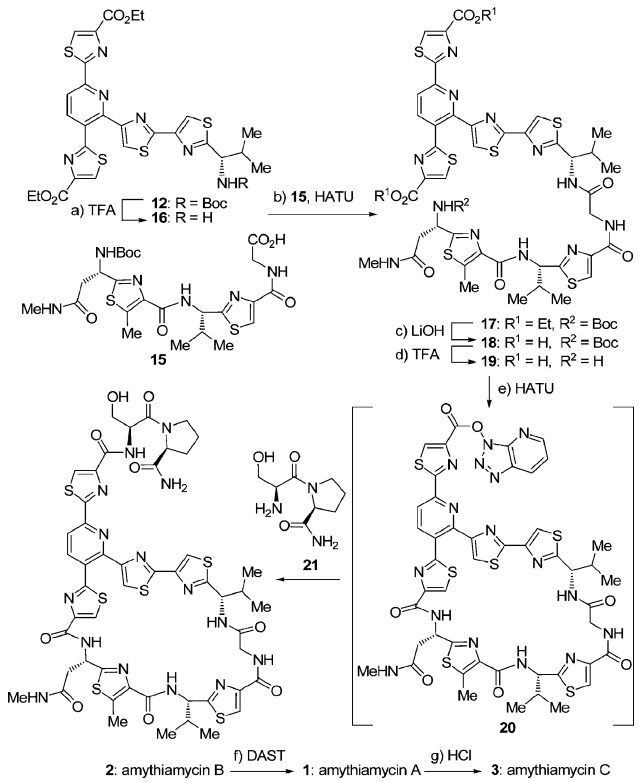
The other major fragment required for the total synthesis of the amythiamicin molecule, tripeptide carboxylic acid **15**, was prepared by the coupling of carboxylic acid **13**[5d] with glycine methyl ester (HATU, iPr$_2$NEt), followed by saponification (LiOH) as shown in Scheme 2 (54% overall yield).

The union of trithiazolyl pyridine **12** and tripeptide carboxylic acid **15** and further elaboration to amythiamicins A (**1**), B (**2**) and C (**3**) are shown in Scheme 3. Thus, removal of the Boc group from **12** (TFA) followed by coupling of the resulting amine (**16**) with carboxylic acid **15** (HATU, iPr$_2$NEt) afforded hexathiazole pyridine **17** in 60% yield for the two steps from **12**. Exposure of di-ester **17** to excess LiOH in aqueous DME followed by treatment with TFA furnished amino di-acid **19** *via* Boc di-acid **18**, setting the stage for the anticipated "one-pot" sequential intramolecular/intermolecular bis-amidation. In the event, and under previously established conditions,[5d,6] subjecting **19** to excess HATU and iPr$_2$NEt under high dilution conditions (0.001 M in CH_2Cl_2–DMF 4 : 1) induced regioselective macrolactamization, affording the presumed activated macrolactam intermediate **20**, which was treated, without isolation, with the HCl salt of prolinamide–serine conjugate (**21**),[8] delivering amythiamicin B (**2**) in 25% yield over the three steps from

[a] *Chemical Synthesis Laboratory@Biopolis, Institute of Chemical and Engineering Sciences (ICES), Agency for Science, Technology and Research (A*STAR), 11 Biopolis Way, The Helios Block, #03-08 Singapore 138667. E-mail: david_chen@ices.a-star.edu.sg*
[b] *Department of Chemistry and The Skaggs Institute for Chemical Biology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037, USA. E-mail: kcn@scripps.edu*
[c] *Department of Chemistry and Biochemistry, University of California, San Diego, 9500 Gilman Drive, La Jolla, California 92093, USA*
† Dedicated to Andrew B. Holmes on the occasion of his 65th birthday.
‡ Electronic supplementary information (ESI) available: Experimental details and NMR spectra. See DOI: 10.1039/b805069b



Scheme 1 Synthesis of trithiazolyl pyridine **12**. Reagents and conditions: (a) **4** (1.5 equiv.), 4 Å MS, DMF, 0 → 25 °C, 18 h; then TFAA (1.5 equiv.), pyridine (3.0 equiv.), CH_2Cl_2, 0 °C, 3 h, 78%; (b) DIBAL-H (1.0 M in toluene, 2.0 equiv.), toluene, −78 °C, 3 h, 85%; (c) **8**·TFA (1.2 equiv.), $KHCO_3$ (10.0 equiv.), MeOH–H_2O (3.75 : 1), 25 °C, 16 h, 80% (*ca.* 3 : 1 mixture of diastereoisomers); (d) Ag_2CO_3 (1.0 equiv.), $BnNH_2$ (2.0 equiv.), DBU (0.25 equiv.), pyridine, −12 °C, 1 h; then H_2O–EtOAc (1 : 1), 25 °C, 1 h, 51% (*ca.* 1 : 1 mixture of diastereoisomers); (e) DBU (5.0 equiv.), EtOAc, reflux, 5 h, 36%. DMF = *N*,*N*′-dimethylformamide; TFA = trifluoroacetic acid; TFAA = trifluoroacetic anhydride; DIBAL-H = diisobutylaluminium hydride; Bn = benzyl; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

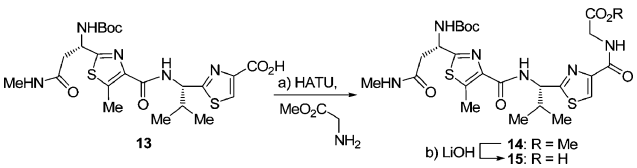


Scheme 3 Total syntheses of amythiamicins A (**1**), B (**2**) and C (**3**). Reagents and conditions: (a) TFA–CH_2Cl_2 (1 : 4), 25 °C, 2 h; (b) **15** (1.2 equiv.), HATU (1.5 equiv.), iPr_2NEt (5.0 equiv.), CH_2Cl_2, 25 °C, 16 h, 60% for two steps from **12**; (c) LiOH (10.0 equiv.), DME–H_2O (4 : 1), 5 h; (d) TFA–CH_2Cl_2 (1 : 4), 25 °C, 2 h; (e) HATU (5.0 equiv.), iPr_2NEt (10.0 equiv.), CH_2Cl_2–DMF (4 : 1) (0.001 M), 0 °C, 3 h; then **21** (5.0 equiv.), 0 → 25 °C, 24 h, 25% for the three steps; (f) DAST (1.5 equiv.), CH_2Cl_2, −25 °C, 1 h, 70%; (g) aq. HCl, 110 °C, 1 h, 60%. DAST = *N*,*N*′-diethylaminosulfur trifluoride.

di-ester **17**. Exposure of **2** to DAST converted its hydroxy amide moiety to the corresponding thiazoline unit, thus furnishing amythiamicin A (**1**) in 70% yield. The latter was then transformed to amythiamicin C (**3**) through the action of aq. HCl by a literature procedure.[1c] Synthetic **1**–**3** exhibited identical physical properties (^1H and ^{13}C NMR, mass spectra for **1** and **2**; ^1H NMR spectra for **3**) to those reported for the corresponding natural products.[1c]

Notable for their brevity and convergency, the described total syntheses allow facile entries to these antibiotics (**1**–**3**) and their analogs, and provide yet another demonstration of the hetero-Diels–Alder dimerization approach to this type of structural motif.

We thank Ms Doris Tan (ICES) for high resolution mass spectrometric (HRMS) assistance. Financial support for this work was provided by A*STAR, Singapore.



Scheme 2 Preparation of tripeptide carboxylic acid fragment **15**. Reagents and conditions: (a) glycine methyl ester (1.2 equiv.), HATU (1.2 equiv.), iPr_2NEt (5.0 equiv.), CH_2Cl_2, 25 °C, 12 h, 60%; (b) LiOH (5.0 equiv.), DME–H_2O (4 : 1), 25 °C, 2 h, 90%. HATU = *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate; DME = ethylene glycol dimethyl ether.

Notes and references

1 (*a*) K. Shimanaka, N. Kinoshita, H. Iinuma, M. Hamada and T. Takeuchi, *J. Antibiot*., 1994, **47**, 668–674; (*b*) K. Shimanaka, Y. Takahashi, H. Iinuma, H. Naganawa and T. Takeuchi, *J. Antibiot*., 1994, **47**, 1145–1152; (*c*) K. Shimanaka, Y. Takahashi, H. Iinuma, H. Naganawa and T. Takeuchi, *J. Antibiot*., 1994, **47**, 1153–1159.

2 (*a*) M. C. Bagley, J. W. Dale, E. A. Merritt and X. Xiong, *Chem. Rev*., 2005, **105**, 685–714; (*b*) R. A. Hughes and C. J. Moody, *Angew. Chem., Int. Ed*., 2007, **46**, 7930–7954.

3 B. Clough, K. Rangachari, M. Strath, P. R. Preiser and R. J. M. Wilson, *Protist*, 1999, **150**, 189–195.

4 For total synthesis of amythiamicin D, see: (*a*) R. A. Hughes, S. P. Thompson, L. Alcaraz and C. J. Moody, *J. Am. Chem. Soc*., 2005, **127**, 15644–15651; (*b*) R. A. Hughes, S. P. Thompson, L. Alcaraz and C. J. Moody, *Chem. Commun*., 2004, 946–948.

5 (*a*) K. C. Nicolaou, M. Zak, B. S. Safina, A. A. Estrada, S. H. Lee and M. Nevalainen, *J. Am. Chem. Soc*., 2005, **127**, 11176–11183; (*b*)

K. C. Nicolaou, B. S. Safina, M. Zak, S. H. Lee, M. Nevalainen, M. Bella, A. A. Estrada, C. Funke, F. J. Zecri and S. Bulat, *J. Am. Chem. Soc*., 2005, **127**, 11159–11175; (*c*) K. C. Nicolaou, B. Zou, D.-H. Dethe, D. B. Li and D. Y.-K. Chen, *Angew. Chem., Int. Ed*., 2006 **45**, 7786–7792; (*d*) K. C. Nicolaou, D.-H. Dethe, G. Y. C. Leung, B. Zou and D. Y.-K. Chen, *Chem. Asian J*., 2008, **3** 413–429.

6 T. Mori, S. Higashibayashi, T. Goto, M. Kohno, Y. Satouchi, K. Shinko, K. Suzuki, S. Suzuki, H. Tohmiya, K. Hashimoto and M. Nakata, *Tetrahedron Lett*., 2007, **48**, 1331–1335.

7 Prepared in two steps from Boc-L-valine: (i) DCC, *N*-hydroxysuccinimide, NH_4OH; (ii) Lawesson's reagent.

8 O. Delgado, H. M. Müller and T. Bach, *Chem.–Eur. J*., 2008, **14**, 2322–2339.

