Total syntheses of amythiamicins A, B and C†‡

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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.

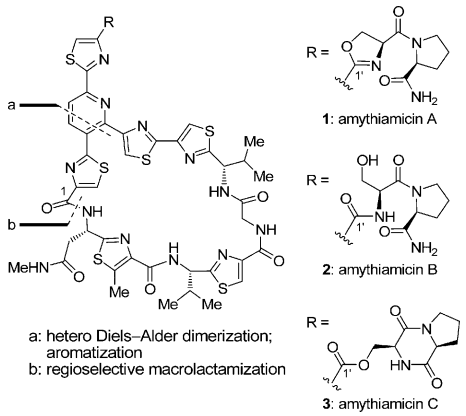

Fig. 1 Molecular structures and retrosynthetic analysis of amythiamicins A (**1**), B (**2**) and C (**3**). (a) Hetero-Diels–Alder dimerization; (b) regioselective macrolactamization.

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

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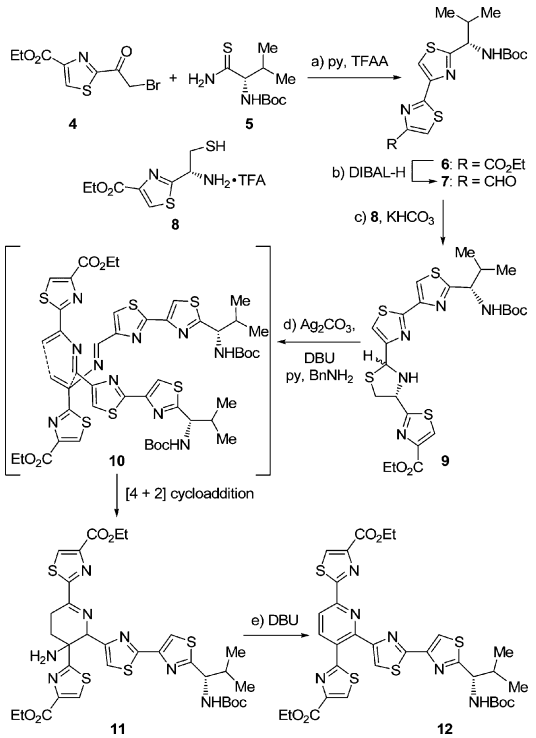
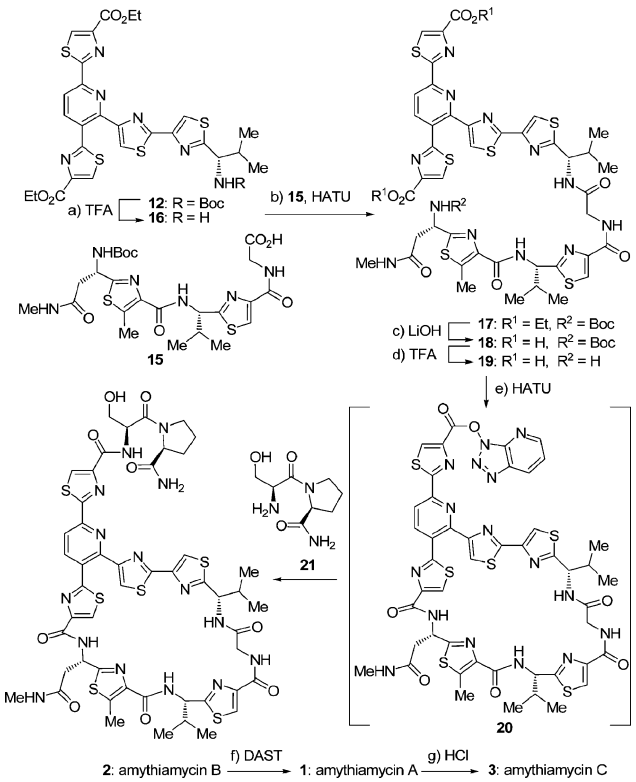


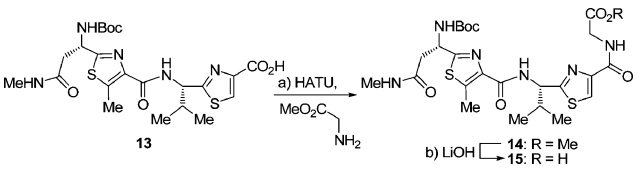
Scheme 1 Synthesis of trithiazolyl pyridine **12**. Reagents and conditions: (a) **4** (1.5 equiv.), 4 Å MS, DMF, 0 → 25 °C, 18 h; then TFAA (1.5 equiv.), pyridine (3.0 equiv.), CH_2Cl_2, 0 °C, 3 h, 78%; (b) DIBAL-H (1.0 M in toluene, 2.0 equiv.), toluene, −78 °C, 3 h, 85%; (c) **8**·TFA (1.2 equiv.), $KHCO_3$ (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.



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.

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