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First synthesis of an amythiamicin pyridine cluster†

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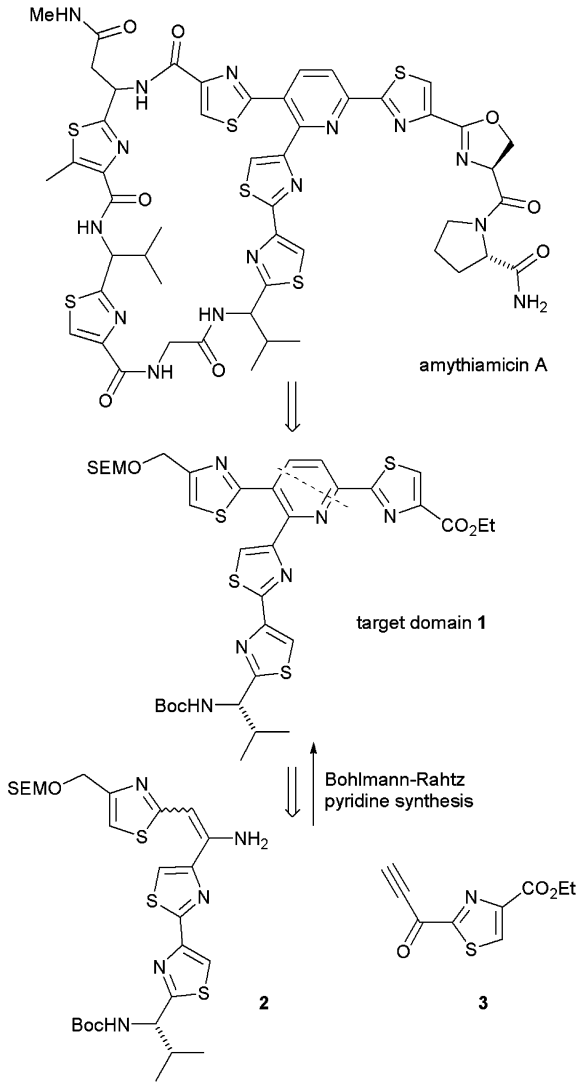
The pyridine-containing central domain of the amythiamicin group of thiopeptide antibiotics is prepared in protected form in 9 steps, 93% *ee* and 18% overall yield from (*S*)-2-[1-(*tert*-butoxycarbonylamino)-2-methylpropyl]thiazole-4-carboxylic acid by Michael addition–cyclodehydration of a 2-(2-thiazolyl)enamine and 1-(2-thiazolyl)propynone.

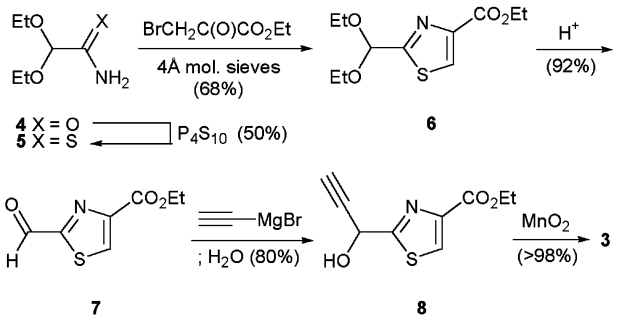
The amythiamicins[1] are members of the thiopeptide class of antibiotics, a family of sulfur-containing highly modified cyclic peptides isolated for their effectiveness against methicillin resistant *Staphylococcus aureus* (MRSA).[2] Structurally, amythiamicin A is a macrocyclic thiopeptide that contains a heterocyclic ensemble of heavily modified amino acids centred about a polythiazolylpyridine core. Although no route to amythiamicin A has appeared in the literature, the synthesis of other thiopeptide antibiotics and their heterocyclic components has attracted considerable international interest, resulting in the total synthesis of micrococcin P1[3] and promothiocin A.[4] At this time the configuration of three of the five stereogenic centres present in amythiamicin is not known but, as a working hypothesis, it was assumed that they were derived from the more common L-amino acids based on degradation studies on the structurally related antibiotic GE2270A (MDL 62,879).[5]



Scheme 1 Synthetic approach to the central amythiamicin domain **1**.

As part of our interest in the discovery of new heteroannulation methods for the synthesis of pyridines,[6,7] we set out to establish a rapid route to the heterocyclic core of the amythiamicins by Michael addition–cyclodehydration of enamine **2** and alkynone **3** that would proceed with total control of regiochemistry and generate the pyridine heterocycle in the correct oxidation state (Scheme 1). Central to our strategy was the need to minimise subsequent manipulation following the heteroannulation reaction, facilitated by the use of 1-(2-thiazolyl)propynone **3**, anticipated to be highly reactive and to require an unusual Bohlmann–Rahtz procedure in order for efficient cyclization to the target pyridine **1**. Although a simpler 1-(2-thiazolyl)propynone has been used before in a Bohlmann–Rahtz reaction with an enamine this required a five-fold excess of reagent, limiting its use as a method to access pyridines substituted at C-6.[4] We sought to validate a more efficient and rapid route to these pyridines and, in so doing, facilitate the synthesis of the amythiamicin central heterocyclic domain with suitable functionality for elaboration of the natural product.

The first component, 1-(2-thiazolyl)propyn-1-one **3**, was prepared in five steps (Scheme 2) from 2,2-diethoxyacetamide (**4**) by thionation with phosphorus pentasulfide, Hantzsch thiazole synthe-



Scheme 2 Synthesis of 1-(2-thiazolyl)propyn-1-one **3**.

Table 1 Methods for the synthesis of model pyridine **10**

Entry	Substrate	Conditions	Yield[a] (%)
1	**9**	Neat, 150 °C, 4 h	80
2	**3**	Toluene–$ZnBr_2$, reflux, 2 h	30
3	**3**	Toluene–AcOH, 50 °C, 2 h	35
4	**8**	Toluene–AcOH, MnO_2, 50 °C, 5 h	33
5	**9**	Toluene–AcOH, 50 °C, 1.5 h	> 98

[a] Isolated yield after purification on silica.

† Electronic supplementary information (ESI) available: experimental details. See http://www.rsc.org/suppdata/cc/b3/b310944e/

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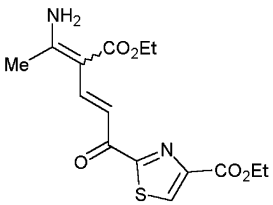
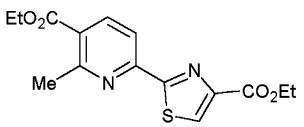
sis with ethyl bromopyruvate in ethanol in the presence of 4 Å molecular sieves, followed by acid catalysed acetal deprotection to give aldehyde **7** that could be stored at room temperature. Addition of ethynylmagnesium bromide in THF with aqueous work up and subsequent oxidation of propargylic alcohol **8** with manganese(IV) oxide gave propynone **3**. As anticipated, this substrate proved unstable at room temperature and so was generated from aldehyde **7** as required. In order to establish new heteroannulation conditions suitable for this substrate, propynone **3** was reacted with ethyl β-aminocrotonate by a variety of different methods (Table 1) to give model pyridine **10** substituted at C-6 in accordance with the target amythiamicin domain. When dienone **9**, generated by Michael addition in ethanol at 50 °C, was heated to 150 °C (entry 1) cyclodehydration to pyridine **10** was incomplete and so alternative conditions were sought. Acid catalysed one-step procedures failed to give satisfactory yields (entries 2, 3), as did tandem oxidation–heteroannulation[8] of propargylic alcohol **8** (entry 4) and so we investigated a new cyclodehydration method, hitherto reported only as an aside in the development of one-step acid-catalysed Bohlmann–Rahtz procedures.[6] Dienone **9**, generated by Michael addition in ethanol, was stirred at 50 °C in toluene–acetic acid to give pyridine **10** in > 98% yield (entry 5).



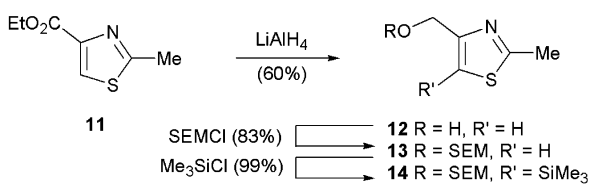
dienone intermediate **9**



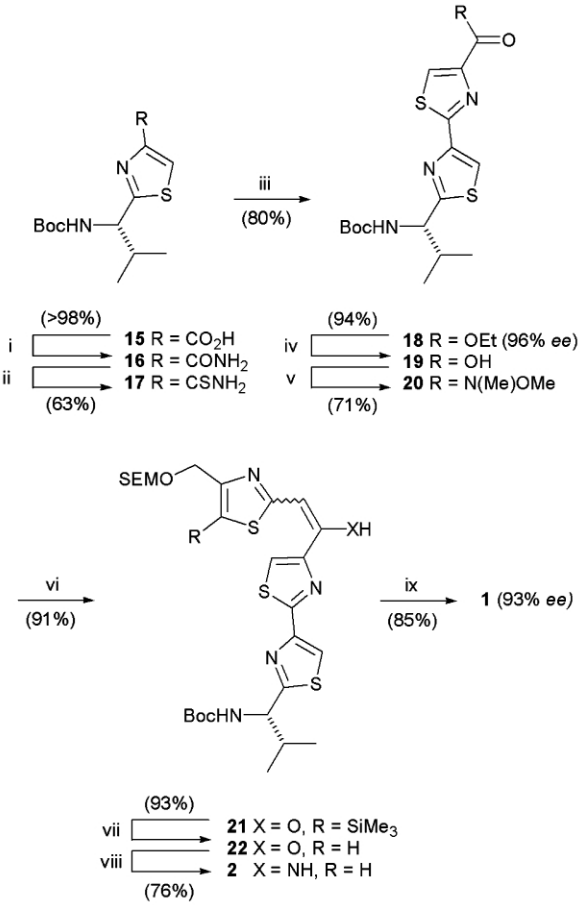
model pyridine **10**

With successful conditions established in a model system for rapid introduction of the C-6 substituent, efforts were directed towards establishing the group at C-3 with similar rapidity. Hantzsch thiazole **11** was reduced with lithium aluminium hydride to give alcohol **12**, which was protected as 2-(trimethylsilyl)-ethoxy-methyl (SEM) ether **13** (Scheme 3). Directed 5-lithiation with *n*-butyllithium and reaction with chlorotrimethylsilane provided thiazole **14** as a protected pyridine C-3 building block for the synthesis of amythiamicin.

N-Protected L-valine was transformed to valine-derived thiazole **15** by the modified Hantzsch procedure of Meyers,[9] followed by hydrolysis. Reaction with ethyl chloroformate under basic conditions, aminolysis of the mixed anhydride with aqueous ammonia and thionation of amide **16** using Lawesson's reagent (LR) gave thioamide **17** (Scheme 4). Hantzsch thiazole synthesis with ethyl bromopyruvate under basic conditions followed by hydroxythiazoline dehydration, using a mixture of trifluoroacetic anhydride and 2,6-lutidine, gave chiral bis-thiazole **18** in 96% *ee* [HPLC on Chiralpak AD]. Hydrolysis with lithium hydroxide, formation of Weinreb amide **20** and reaction with the lithio-derivative of 2-methylthiazole **14** gave Claisen condensation product **21**. Protodesilylation using tetrabutylammonium fluoride in THF followed by microwave irradiation of thiazole **22** and ammonium acetate in toluene at 120 °C provided enamine **2** for submission to the key Bohlmann–Rahtz reaction. Utilizing conditions successful for the synthesis of model pyridine **10**, Michael addition of enamine **2** and propynone **3** in ethanol followed by acetic acid-catalysed cyclodehydration at 70 °C, gave the amythiamicin heterocyclic



Scheme 3 Synthesis of thiazole building block **14**.



Scheme 4 *Reagents and conditions*: (i) EtO_2CCl, THF, Et_3N then aq. NH_3; (ii) LR; (iii) $NaHCO_3$, ethyl bromopyruvate then trifluoroacetic anhydride, 2,6-lutidine; (iv) LiOH, H_2O, MeOH; (v) EtO_2CCl, THF, Et_3N then HN(Me)OMe·HCl; (vi) **14**, *n*-BuLi; H_2O; (vii) TBAF, THF, RT, 1 h; (viii) NH_4OAc, μwave, 120 °C (100 W), PhMe, 30 min; (ix) **3**, EtOH, 60 °C; toluene–AcOH, 70 °C.

domain **1** with total regiocontrol in 85% yield and 93% *ee*. This work represents the first synthesis of this heterocyclic cluster, in protected form, generated in only 9 steps and 18% overall yield from **15**, and constitutes a rapid route to the amythiamicin antibiotic family.

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