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Thiopeptide Antibiotics

From Amino Acids to Heteroaromatics—Thiopeptide Antibiotics, Nature's Heterocyclic Peptides**

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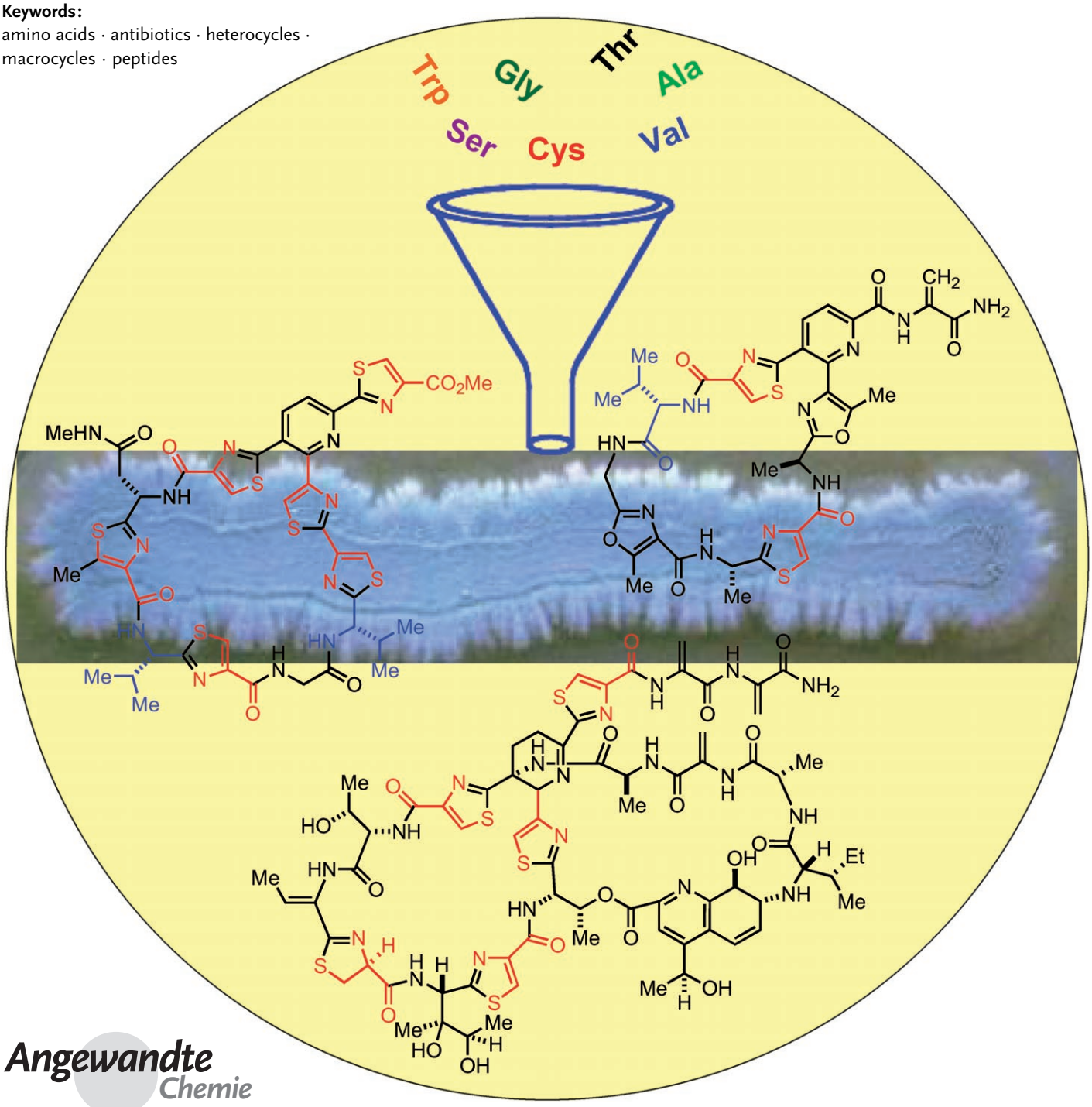
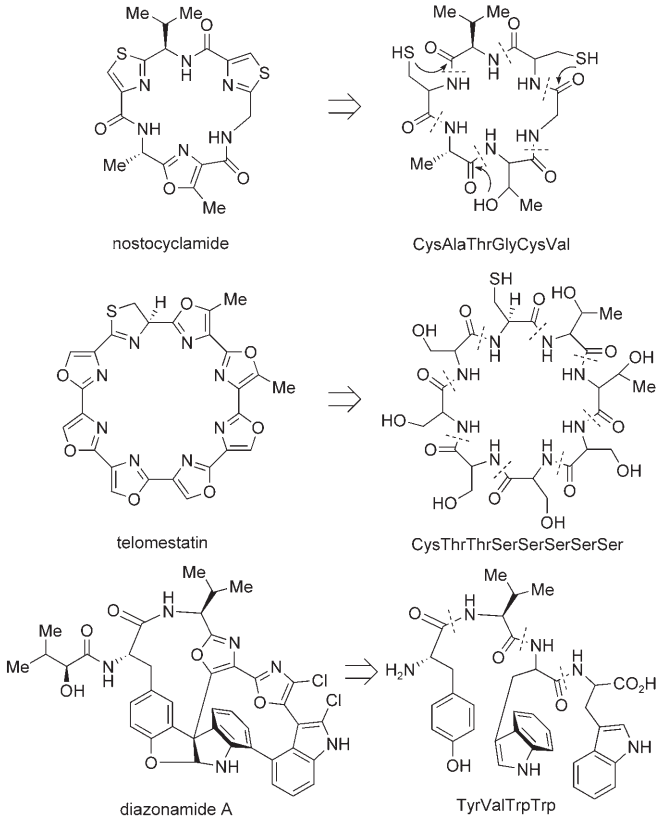


Amino acids, the building blocks of proteins, also serve as precursors to a wide range of other naturally occurring substances including alkaloids, antibiotics, and, the subject of this Review, heterocyclic peptides. Simple α-amino acids are converted into complex arrays of heteroaromatic rings that display interesting and potent biological activity. The thiopeptide antibiotics, with their complex molecular architectures, are wonderful examples. In this Review we show how organic chemists have developed innovative methods for the synthesis of the heterocyclic ring systems, including routes inspired by the likely biosynthetic processes, and successfully assembled such building blocks into the final target molecule by application of orthogonal protecting groups and coupling methodologies.

From the Contents

1. Introduction

Although the term "heterocyclic peptide" is used in several ways in the literature, we use it to define a group of natural products that are peptidic in origin, that is, derived from α-amino acids, but consist largely of heteroaromatic rings, often in a macrocyclic array. The most important heteroaromatic rings are thiazoles, oxazoles, indoles, and pyridines, and they occasionally occur as their di- or tetrahydro derivatives. Three examples are nostocyclamide, telomestatin, and diazonamide A. Although the details of the biosynthetic pathways have not been worked out in every case, their amino acid origins are clear. Thus, nostocyclamide[1–5] likely derives in nature from a hexapeptide as a result of heterocyclizations of cysteine and threonine side chains in the CysAlaThrGlyCysVal sequence, followed by oxidative aromatization. Likewise, the potent telomerase inhibitor telomestatin[6,7] is almost certainly derived from a CysThrThrSerSerSerSerSer octapeptide. The amino acid origins of other heteroaromatic natural products are perhaps less clear. A more recent example is diazonamide A,[8–11] for which the putative biosynthetic precursor is the TyrValTrpTrp tetrapeptide,[12,13] which has to undergo a series of oxidation, cyclodehydration, and chlorination reactions to give the natural product. Although we have indicated the likely amino acid precursors to nostocyclamide, telomestatin, and diazonamide A as hexa-, octa-, and tetrapeptides, respectively, there is no implication that the biosynthetic pathway involves formation of all the peptide bonds before the various heterocyclization steps occur.



The heterocyclic peptides that form the topic of this article are the thiopeptide antibiotics. This is a class of sulfur-rich, highly modified, cyclic peptides characterized by common structural features such as thiazole and, in some cases, oxazole rings, dehydroamino acids, and a heteroaromatic core consisting of a tri- or tetrasubstituted pyridine ring all in a macrocyclic array. The five-membered heterocycles derive from amino acids by the aforementioned cyclization of serine, threonine, or cysteine side chains, followed by aromatization, although the exact details of this process are far from clear. The assembly of the component amino acids into an appropriate peptide may occur by a ribosomal process

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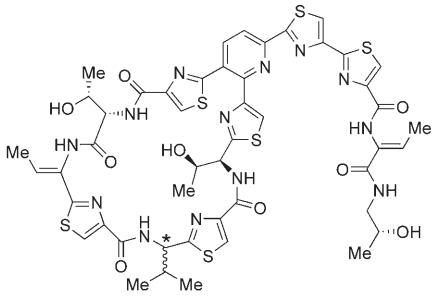
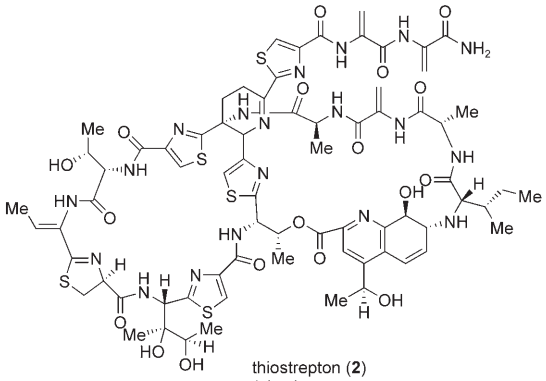
[**] The Frontispiece shows a picture of *Streptomyces azureus*, the organism that produces thiostrepton (from: *Appl. Environ. Microbiol.* **1990**, *56*, 575–577).

or by nonribosomal peptide synthesis (NRPS).[14–16] Thereafter, either the linear peptide is modified by a series of cyclodehydration and oxidation enzymes, or the heterocyclizations are effected during the growth of the peptide chain by multienzyme complexes. Both processes are known to operate in the biosynthesis of other oxazole- and thiazole-containing natural products,[17] but it is likely that the thiopeptide antibiotics are assembled by some variant of the NRPS machinery.

The thiopeptide (or thiostrepton) family of natural products comprises about 80 compounds, many of which—such as the micrococcins (for example, micrococcin P1 (**1**))



micrococcin P1
1a Bycroft-Gowland structure *R configuration
1b Bagley structure *S configuration



thiostrepton (**2**)
(also known as
thiostrepton A)

and thiostrepton (**2**)—have been known for over 50 years, although in many cases, the structures have only been fully elucidated more recently. Even now some structural uncertainties remain, no more so than in the case of micrococcin itself, the first thiopeptide to be isolated in 1948, and one of the first to attract the attention of synthetic organic chemists. The structure of a substance known as micrococcin P was first investigated by Walker and co-workers,[18–22] but following the discovery that micrococcin P was actually a mixture of two compounds, micrococcins P1 and P2, it was Bycroft and Gowland who assigned micrococcin P1 as structure **1a**.[23] (The proposal outlined in Ref. [23] for the biosynthesis of the pyridine ring formed the inspiration for our synthesis of amythiamicin D a quarter of a century later.[24])

Initially, synthesis served to confuse rather than clarify the structure of micrococcin P1, since the first reported study described a compound that is epimeric with the Bycroft–Gowland structure **1a** in the isoalaninol side chain.[25,26] Thereafter, the landmark synthesis of **1a** by Ciufolini and Shen,[27] in combination with their NMR studies,[28] showed that the Bycroft–Gowland structure **1a** for micrococcin P1 has the correct connectivity but contains a stereochemical misassignment. Bagley and Merritt subsequently proposed this misassignment to be at the valine-derived thiazole center.[29] Hence, it is most likely that micrococcin P1 has the structure **1b**, but the issue awaits resolution by total synthesis.

Most of the thiopeptide antibiotics inhibit protein synthesis in bacteria, and possess common modes of action: They act by binding to the complex formed between 23S rRNA and ribosomal protein L11, thereby inhibiting the action of GTP-dependent elongation factors.[30,31] Other thiopeptides such as GE2270A act directly on the elongation factor proteins, thereby inhibiting their action.[32,33] The biological properties of the thiopeptide antibiotics have recently been covered in an excellent review that also focuses on their isolation and structural characterization.[34] Despite the fascinating biological activity of the thiopeptide antibiotics, relatively few synthetic studies have been carried out to date, and only six members of this series of natural products (thiostrepton (**2**), promothiocin A (**3**), amythiamicin D (**4**), GE2270A (**5**), GE2270T, siomycin A (**9**)) have succumbed to total synthesis to date. However, the syntheses of various fragments of other thiopeptides have been reported. Compounds **3**–**9** are some of the compounds that have attracted the attention of synthetic chemists. Our aim herein is to complement the recent

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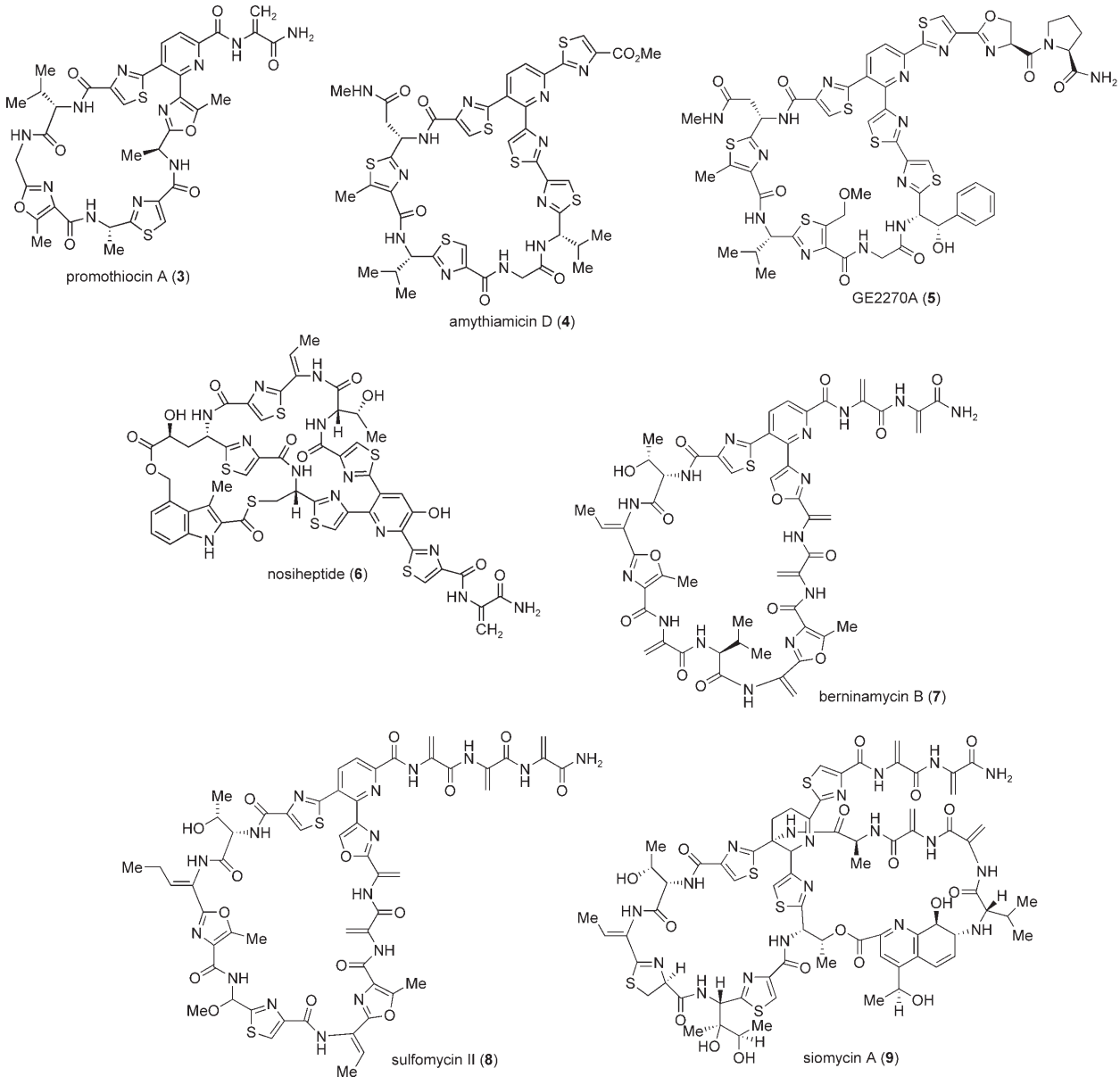
Rachael Hughes grew up in Hertfordshire, and obtained her first degree at the University of Bristol in 1997. She remained in Bristol to undertake PhD research with Christine Willis, before carrying out postdoctoral research with Chris Moody at the University of Exeter in 2001. During her time in Exeter, she was instrumental in completing the first total synthesis of the heterocyclic peptide amythiamicin D. Subsquently, she was appointed to a postdoctoral position in the University of Oslo working with Tore Hansen.



review,[34] and highlight the synthetic challenges posed by these natural products.

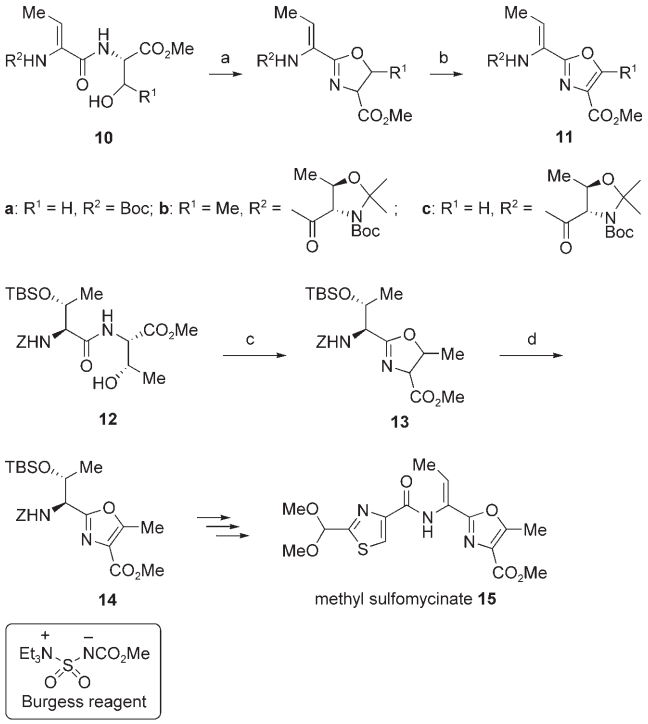
2. Building Blocks of Thiopeptide Antibiotics

Although the retrosynthetic analysis of thiopeptide antibiotics by fragmenting the molecule at the various amide bonds to reveal the heterocyclic building blocks is straightforward, the synthesis of thiopeptide antibiotics presents a twofold problem. On the one hand, there is the construction of the individual building blocks, with appropriate orthogonal protecting groups and, secondly, there is the subsequent coupling reactions of the various fragments. From a synthetic chemist's point of view, this is not without challenges, and is reflected in the fact that despite considerable synthetic effort on various thiopeptide fragment structures, very few total syntheses have been reported. Rather than present a comprehensive review of the synthesis of such fragment structures (oxazoles, thiazoles, etc.), we offer a personal selection of the synthetic methods that have been used to synthesize thiopeptides, unashamedly highlighting work from our own laboratory.

2.1. Oxazoles

The synthesis of oxazole-containing natural products has been the subject of considerable interest over the last two decades, and a number of routes to the ring system, often based on classical strategies, have been reported.[35,36] One of the most common strategies involves the heterocyclization of serine or threonine side chains onto an amide carbonyl group to give an oxazoline that is subsequently oxidized to the

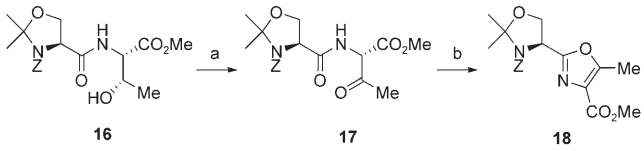
oxazole, thereby mimicking the most likely biogenesis of the heteroaromatic ring.[17,34] A number of reagents have been employed to effect the cyclodehydration step,[37] for example, DAST, Deoxo-Fluor, Burgess reagent, $SOCl_2$ followed by AgOTf, or Mitsunobu conditions. Likewise, the oxidation step can be achieved in a number of ways using reagents such as MnO_2, NiO_2, $BrCCl_3$/DBU, $CuBr_2$/DBU. Specific examples of such methodology are shown in Scheme 1. Thus, the serine



Scheme 1. Synthesis of oxazole fragments of the berninamycins, A10255G, and sulfomycins. Reagents and conditions: a) for **10a**, Ph_3P, DEAD, THF (61%); for **10b**, Burgess reagent, THF (77%); for **10c**, Ph_3P, DEAD, THF, then MnO_2, benzene (21% over 2 steps); b) MnO_2, benzene (**11a**, 42%; **11b**, 48%); c) Deoxo-Fluor, CH_2Cl_2 (65%); d) $BrCCl_3$, DBU, CH_2Cl_2 (52%).

derivative **10a** was cyclodehydrated under Mitsunobu conditions to an oxazoline and subsequently oxidized using manganese(IV) oxide in modest yield to oxazole **11a**, a fragment of berninamycin.[38] A second component of berninamycin, oxazole **11b**, and the closely related oxazole **11c**, a fragment of antibiotic A10255G, were prepared in a similar manner (Scheme 1).[38,39] Methyl sulfomycinate **15**, a degradation product of the sulfomycin thiopeptide antibiotics, was prepared from oxazole **14**, which was obtained from serine derivative **12** by cyclodehydration and oxidation of the resulting oxazoline **13** (Scheme 1).[40]

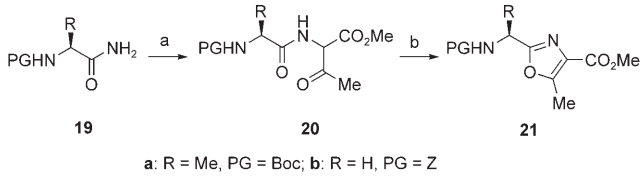
An alternative strategy towards the synthesis of the oxazole fragments of the thiopeptides essentially reverses the order of the above steps and carries out an oxidation step before the cyclodehydration (Scheme 2).[41] Threonine derivative **16** is oxidized to the β-ketoamide **17** with Jones' reagent (the Dess–Martin periodinane is a commonly used alternative) and cyclodehydration to the oxazole **18**, a fragment of



Scheme 2. Synthesis of an oxazole fragment of the berninamycins. Reagents and conditions: a) Jones' reagent, acetone; b) Ph_3P, I_2, Et_3N, $CHCl_3$ (86% over 2 steps).

berninamycin, was achieved by using the Wipf protocol (Ph_3P, I_2, Et_3N).[42]

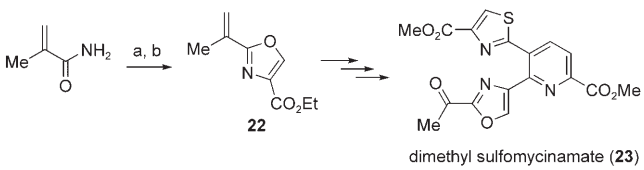
Our alternative to the previous strategy involved formation of intermediate β-ketoamides **20** by a chemoselective N-H insertion reaction of the rhodium carbene derived from methyl diazoacetoacetate into an *N*-protected amino acid carboxamide **19**. The reaction is general and was used in the synthesis of both oxazole fragments (**21a**,**b**) of promothiocin A (Scheme 3).[43,44] β-Ketoamides are also intermediates



Scheme 3. Synthesis of the oxazole fragments of promothiocin A. Reagents and conditions: a) methyl diazoacetoacetate, $Rh_2(OAc)_4$, $CHCl_3$ (**20a**, 80%; **20b**, 71%); b) Ph_3P, I_2, Et_3N, CH_2Cl_2 (**21a**, 70%; **21b**, 56%).

in the Robinson–Gabriel oxazole synthesis, and hence a number of methods for their cyclodehydration have been devised, although we tend to favor the previously mentioned Wipf protocol (Ph_3P, I_2, Et_3N).[42] In the Robinson–Gabriel method the intermediate β-ketoamide is formed by acylation of an α-amino carbonyl derivative, and hence our N-H insertion methodology is complementary in that it forms what eventually becomes the oxazole 3–4 C–N bond.

Finally, an oxazole precursor **22** to dimethyl sulfomycinamate (**23**) was obtained by reaction of 2-methylacrylamide with ethyl bromopyruvate (Scheme 4).[45] This reaction is

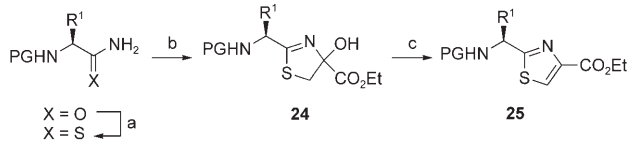


Scheme 4. Synthesis of an oxazole fragment of dimethyl sulfomycinamate. Reagents and conditions: a) EtO_2CCOCH_2Br, $NaHCO_3$, THF (80%); b) TFAA, 2,6-lutidine, THF (94%).

analogous to the Hantzsch thiazole synthesis, a process sometimes referred to as the Blümlein–Lewy cyclization.

2.2. Thiazoles

When it comes to the synthesis of the heteroaromatic thiazole building blocks of the thiopeptide antibiotics, the Hantzsch reaction is preeminent. Discovered by Arthur Rudolf Hantzsch (1857–1935) in 1889 during his time at the ETH in Zürich, in its original form the reaction simply involves heating a thioamide with an α-halocarbonyl compound. However, when these conditions are used on thioamides derived from α-amino acids, partial racemization of the stereocenter results. Investigations by Holzapfel and coworkers,[46] and also by Aguilar and Meyers,[47] resulted in the development of the so-called modified Hantzsch reaction. These experimental conditions (Scheme 5) give the desired

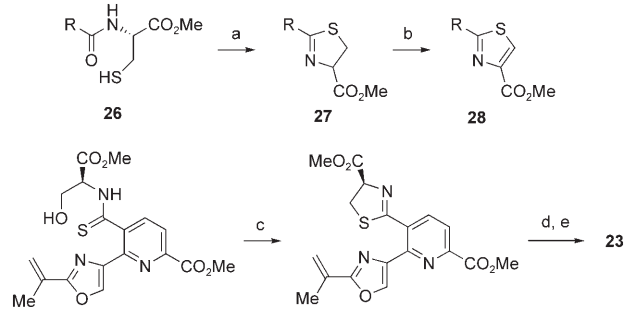


Scheme 5. The modified Hantzsch thiazole synthesis. Reagents and conditions: a) Lawesson's reagent; b) EtO_2CCOCH_2Br, $KHCO_3$, DME, −15 °C; c) TFAA, 2,6-lutidine, DME, −15 °C. R^1 = Me, *i*Pr, *i*Bu, Bn.

thiazole amino acids **25** as single isomers, presumably by preventing racemization of the starting thioamide or the intermediate 4-hydroxythiazoline **24**.

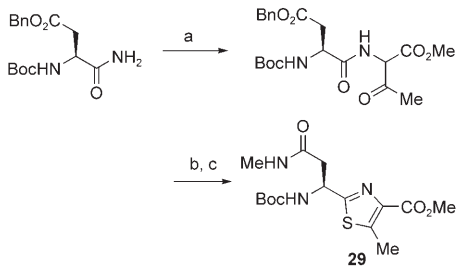
Unsurprisingly, the Hantzsch reaction has found wide use in the synthesis of thiopeptide thiazole fragments. Examples include the thiazole building blocks of promothiocin A (**3**),[44] amythiamicin D (**4**),[24] GE2270A (**5**),[48–50] nosiheptide (**6**),[51,52] A10255G,[39] thiocilline,[53] and cyclothiazomycin.[54]

By analogy with the use of serine derivatives in the synthesis of oxazolines, and hence oxazoles, the biomimetic cyclodehydration of the corresponding cysteine derivatives **26** would be expected to give thiazolines **27** and hence thiazoles **28**. This is indeed the case, and the strategy has found use in the synthesis of thiazole-containing natural products (Scheme 6, top).[36] However, an alternative thiazoline-based strategy has found greater favor in the synthesis of thiopeptide fragments. This approach involves the cyclization of a serine derivative onto a thioamide (Scheme 6, bottom), and, for example, has been used in the synthesis of the aforementioned dimethyl sulfomycinamate (**23**).[45]



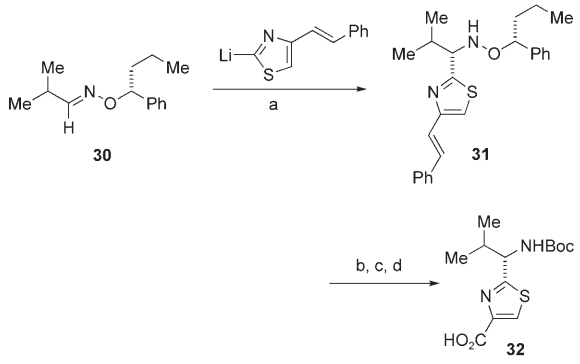
Scheme 6. Synthesis of thiazole fragments of thiopeptide antibiotics. Reagents and conditions: a) H^+; b) MnO_2 or NiO_2; c) Burgess reagent, THF, 70 °C (87%); d) MnO_2, CH_2Cl_2, microwave, 100 °C (79%); e) OsO_4, $NaIO_4$, MeCN, H_2O, dioxane (80%).

We decided to adapt our rhodium carbene methodology for the synthesis of thiazoles. Thus, chemoselective N-H insertion into an amino acid carboxamide was followed by reaction of the resulting β-ketoamide with Lawesson's reagent to give the thiazole directly.[55] This protocol proved highly effective and was successfully used in the synthesis of the aspartate-derived thiazole fragment **29** of amythiamicin D (**4**) and GE2270A (**5**, Scheme 7).[24]



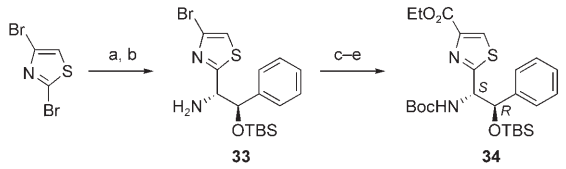
Scheme 7. Synthesis of the aspartate-derived fragment of amythiamicin D and GE2270A. Reagents and conditions: a) methyl diazoacetoacetate, $[Rh_2(OCOC_7H_{15})_4]$, CH_2Cl_2 (74%); b) Lawesson's reagent, THF, reflux (65%); c) 1. Pd/C, H_2, MeOH (80%); 2. EtO_2CCl, Et_3N, CH_2Cl_2, then $MeNH_2$, THF, 0 °C (73%).

In a completely different approach to thiazole-containing amino acids, we have also exploited the versatile chiral oxime ether methodology developed extensively in our laboratory over the last decade.[56] Addition of 2-lithio-4-styrylthiazole to the chiral oxime ether **30** of isobutyraldehyde proceeded in good yield with excellent stereocontrol to give the hydroxylamine **31**. Subsequent reductive cleavage of the N–O bond, protection of the resulting amine with a Boc group, and oxidative cleavage of the alkene gave the thiazole **32**, a common fragment of thiopeptide antibiotics such as amythiamicin D (**4**) and GE2270A (**5**, Scheme 8).[57]



Scheme 8. Synthesis of a thiazole fragment of amythiamicin D and GE2270A. Reagents and conditions: a) $BF_3{\cdot}OEt_2$, toluene, −78 °C (79%, >95% *de*); b) $[Mo(CO)_6]$, MeCN, then Boc_2O (71%); c) O_3, CH_2Cl_2, −78 °C, then Me_2S (76%); d) $NaClO_2$, MeCN, aq H_2O_2, NaH_2PO_4 buffer (92%).

In yet another approach, Bach and co-workers have elegantly exploited the differential reactivity of 2,4-dibromothiazole in a synthesis of the phenylserine-derived thiazole fragment of antibiotic GE2270A.[58] The methodology is illustrated by the synthesis of the *threo*-thiazole **34** (the natural product is believed to possess an *erythro* configuration; the synthesis of the *erythro* isomer is also reported). Regioselective metalation of 2,4-dibromothiazole followed by quenching with (*R*)-*O*-TBS-mandelonitrile and reduction with sodium borohydride gave the *threo*-thiazole **33** (d.r. 79/21). After protection of the free amino group, a second metalation reaction quenched with CO_2 gave, after esterification, thiazole **34** (Scheme 9).[58]



Scheme 9. Synthesis of the phenylserine-derived thiazole (*threo* isomer) of GE2270A: the natural product has *S,S-erythro* stereochemistry (see Section 3.6). Reagents and conditions: a) *i*PrMgBr, THF, then (*R*)-*O*-TBS-mandelonitrile; b) $NaBH_4$, EtOH (73% over 2 steps, 58% *de*); c) Boc_2O, CH_2Cl_2 (94%); d) *t*BuLi, Et_2O, −78°C, then solid CO_2; e) EtI, K_2CO_3, DMF (47% over 2 steps).

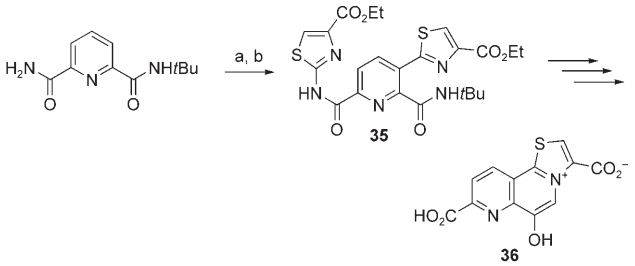
2.3. Pyridines

Tri- or tetrasubstituted pyridines, or occasionally their di- or tetrahydro derivatives, are found in all known thiopeptide antibiotics, and many methods have therefore been investigated for their synthesis. The strategies employed can be divided into two groups: 1) modification of an existing pyridine ring and 2) synthesis of the pyridine ring from acyclic precursors.

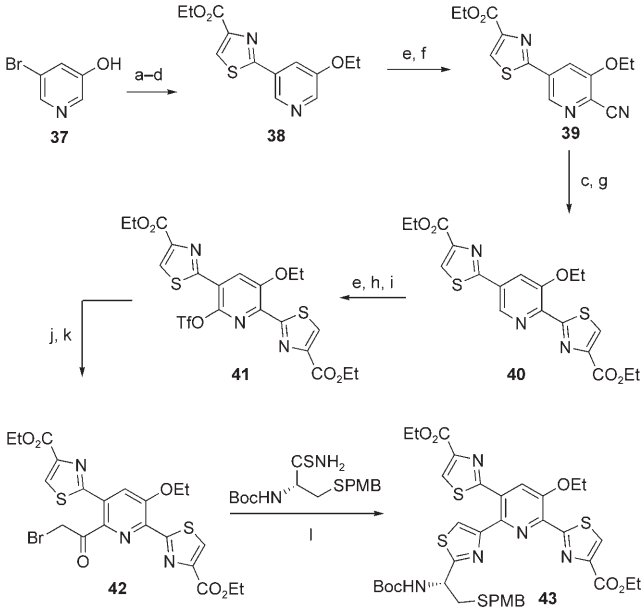
2.3.1. Modification of an Existing Pyridine Ring

Initial methods for the synthesis of the heterocyclic cores of the thiopeptide antibiotics focused on the stepwise addition of thiazole or oxazole groups onto suitably functionalized pyridine precursors. Hence in early work, Kelly and co-workers demonstrated in the synthesis of berninamycinic acid **36** that heteroatom-facilitated lithiation at the C-3 position of the pyridine ring and quenching with $MeOCH_2N{=}C{=}S$ gave a protected thioamide. This could subsequently be converted into thiazole **35** under classical Hantzsch conditions, and hence afford berninamycinic acid (**36**, Scheme 10).[59]

Shin and co-workers have published the results of extensive research relating to the synthesis of the central pyridine cores of many different thiopeptide antibiotics, for example A10255,[60] berninamycin,[61] cyclothiazomycin,[54,62,63] GE2270A,[49,64,65] micrococcin P,[66] nosiheptide,[67,68] and thiocilline I.[69] There are a number of common strategies applied in these syntheses as illustrated in the routes to the substituted pyridines of nosiheptide (**6**, Scheme 11) and GE2270A (**5**, Scheme 12). The tetrasubsti-

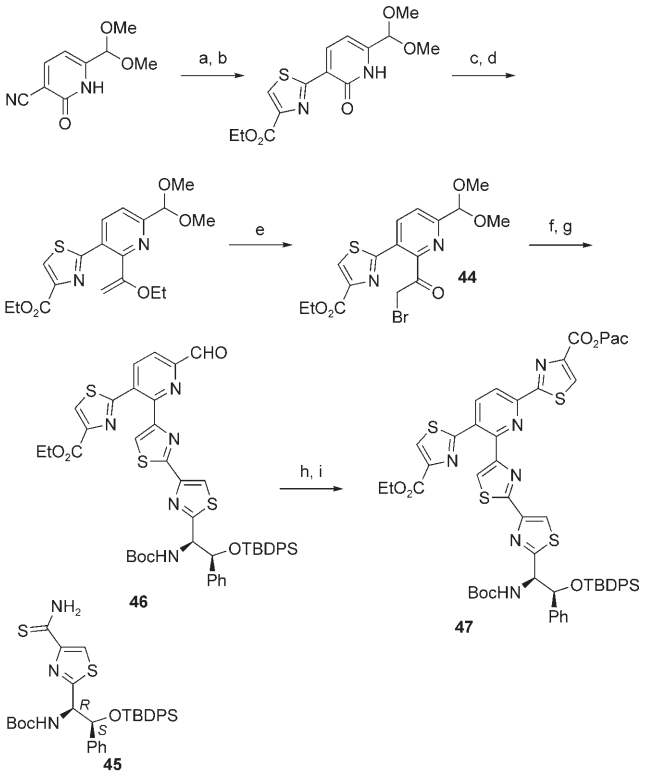


Scheme 10. Synthesis of berninamycinic acid. Reagents and conditions: a) *n*BuLi, THF, 0°C, then $MeOCH_2N{=}C{=}S$ (67%); b) EtO_2CCOCH_2Br, MeCN, reflux (94%).



Scheme 11. Preparation of the protected tetrasubstituted pyridine core of nosiheptide. Reagents and conditions: a) CuCN, DMF, reflux (85%); b) Et_2SO_4, K_2CO_3, DMF, reflux (80%); c) H_2S, pyridine, Et_3N (100%); d) EtO_2CCOCH_2Br, EtOH (81%); e) *m*CPBA, CH_2Cl_2 (100%); f) TMSCN, Et_3N, MeCN, reflux (83%); g) EtO_2CCOCH_2Br, K_2CO_3, THF, 0°C then TFAA, pyridine, THF, 0°C (95%); h) Ac_2O, 100°C (97%); i) Tf_2O, iPr_2NEt, DMAP, CH_2Cl_2 (75%); j) $H_2C{=}C(OEt)SnBu_3$, $Pd(OAc)_2$, dppp, Et_3N, DMF, 60→70°C (85%); k) NBS, THF, H_2O, 0°C (85%); l) EtOH (39%).

tuted pyridine unit **43** of **6** was built up in a stepwise fashion from 5-bromo-3-hydroxypyridine (**37**). A common tactic is to use a nitrile/thioamide/thiazole sequence to introduce the 2-thiazolyl substituents, and this method is indeed used twice (**37**→**38**, **39**→**40**) in the synthesis of nosiheptide fragment **43**. Another strategy applied here is the Reissert method for activation of the 2- and 6-positions of the pyridine ring. Oxidation of the pyridine nitrogen atom with *m*CPBA, followed by treatment with either trimethylsilyl cyanide or acetic anhydride, allows formation of 2-cyanopyridines or 2-pyridones. This four-step procedure involves formation of triflate **41**, a Stille cross-coupling, followed by reaction with NBS to give bromoketone **42**, and lastly a Hantzsch reaction to give the desired thiazole moiety in pyridine **43**.[67,68] However, to use this pyridine in a total synthesis of nosihep-

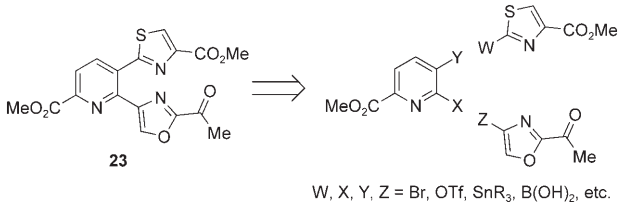


Scheme 12. Synthesis of the protected trisubstituted pyridine core of GE2270A. Reagents and conditions: a) H_2S, DMAP, Et_3N, pyridine (90%); b) EtO_2CCOCH_2Br, $KHCO_3$, THF then TFAA, pyridine, THF (53%); c) Tf_2O, DMAP, pyridine (93%); d) ethyl vinyl ether, Et_3N, dppp, $Pd(OAc)_2$, toluene, reflux (73%); e) NBS, THF, H_2O; f) **45**, $KHCO_3$, DME then TFAA, pyridine, 0°C (63% over 2 steps); g) aq HCl (2 M), THF; h) TFA·H_2N-Cys-OPac, Et_3N, toluene; i) MnO_2, toluene (41% over 3 steps).

tide, one would have to differentiate the two ethyl ester groups, and effect the required orthogonal deprotection.

In the synthesis of the trisubstituted pyridine fragment **47** of GE2270A,[49,64,65] both nitrile/thioamide/thiazole and 2-pyridone to 4-thiazolyl sequences were employed successfully starting from 3-cyano-6-dimethoxymethyl-2-pyridone. The bisthiazole unit was installed by treating the 2-bromoacetylpyridine **44** with the thiazole-4-thiocarboxamide **45**, prepared from a *threo*-phenylserine derivative. The reason for the choice of this particular configuration of phenylserine as a building block is unclear, and was unfortunate in light of subsequent evidence (see Schemes 9 and 16) that the natural product is (*S*,*S*)-*erythro* configured. The final 2-thiazolyl group was attached by using the Shioiri method, whereby the dimethoxyacetal was unmasked to give aldehyde **46**. Subsequent treatment of **46** with the Pac ester of cysteine, followed by oxidation of the intermediate thiazoline with manganese dioxide gave **47**. In the last of the trio of publications on GE2270A by Shin and co-workers,[65] the elaboration of a pyridine core into the complete GE2270A (**5**) macrocycle is described (without spectroscopic data), leaving only the closure of the oxazoline in the side chain and one desilylation. These steps are yet to be reported, although if successful, would of course result in a *threo* isomer that would be epimeric with the natural product at one center.

Although the above approaches successfully deliver appropriately substituted pyridine units, they do involve the stepwise construction of the five-membered heterocycles. A more convergent approach would involve transition-metal-catalyzed cross-coupling reactions between the pyridine ring and the other heterocycles. For example, disconnection across the biaryl bonds divides a 2,3,6-trisubstituted pyridine ring into three parts, each possessing a similar degree of complexity, as outlined for dimethyl sulfomycinamate in Scheme 13.

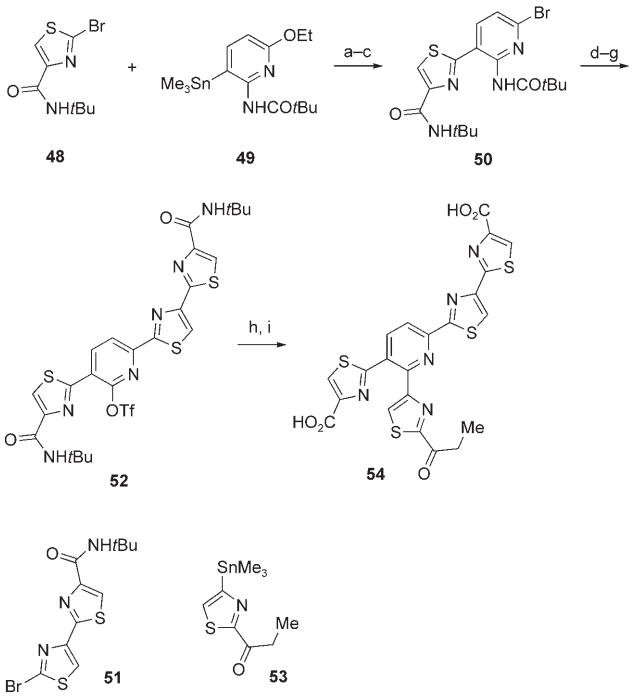


Scheme 13. Retrosynthetic analysis of dimethyl sulfomycinamate.

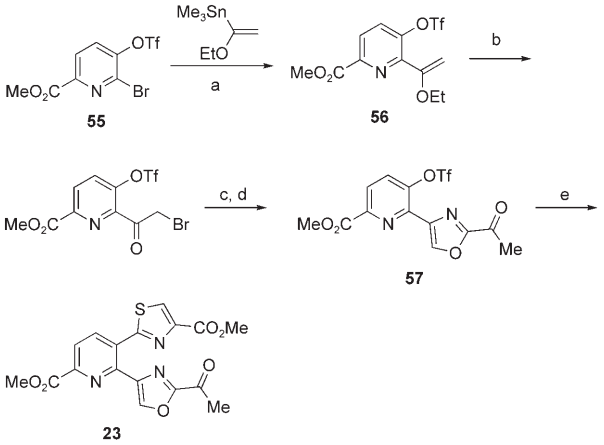
This methodology was first demonstrated in the thiopeptide arena by Kelly et al. in the synthesis of micrococcinic acid (**54**),[70] where all three pyridine–thiazole bonds were formed by palladium-catalyzed heterobiaryl coupling reactions. Coupling of 2-bromothiazole **48** with 3-trimethylstannylpyridine **49** forms the first pyridine–thiazole bond, which is subsequently modified to give bromopyridine **50**. The second pyridine–thiazole bond was produced by treating a 1:1 mixture of **50** and **51** in the presence of Sn_2Me_6 and $[PdCl_2(PPh_3)_2]$. The intermediate stannane is immediately consumed to give the cross-coupled product, which is converted into pyridine triflate **52**. The final pyridine–thiazole bond is produced by coupling to 4-trimethylstannylthiazole (**53**), and hydrolysis gives micrococinnic acid (**54**, Scheme 14).

Kelly and Lang have extended this methodology to the synthesis of dimethyl sulfomycinamate (**23**, Scheme 15).[71] The doubly activated pyridine derivative **55** acts as the starting point for the introduction of an oxazole at the 2-position and a thiazole at the 3-position of the pyridine ring. Direct incorporation of an oxazole moiety at the 2-position proved problematic, because of the inability to prepare a suitably functionalized oxazole triflate. Instead, a four-step procedure was developed to introduce this functionality. Coupling between the pyridine derivative **55** and $H_2C{=}C(OEt)SnBu_3$ gave **56** with complete regioselectivity. Reaction with NBS, followed by methacrylamide in a Hantzsch–Blümlein–Lewy oxazole synthesis and oxidative cleavage of the double bond gave the pyridine–oxazole fragment **57**. Coupling of pyridine triflate **57** and methyl 2-bromothiazole-4-carboxylate, by in situ formation of a stannane, gave **23**.

The most concise route to date to a thiopeptide pyridine core by using palladium catalyzed cross-coupling methodology has been synthesis of the degradation product **62** of GE2270A (**5**) by Heckmann and Bach.[72] Starting from 2,3,6-tribromopyridine, this four-step synthesis employs three

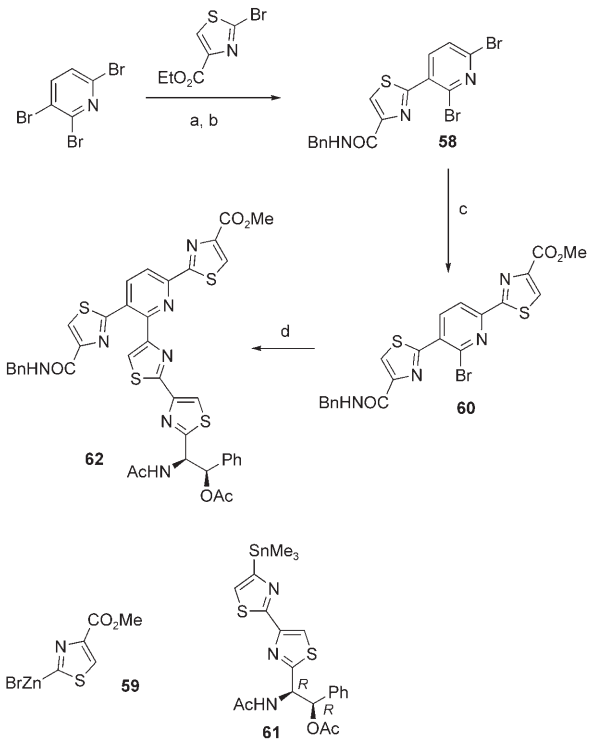


Scheme 14. Synthesis of micrococcinic acid. Reagents and conditions: a) $[PdCl_2(PPh_3)_2]$, toluene, sealed tube, 95 °C (55 %); b) Me_3SiI, $CHCl_3$ (72 %); c) $POBr_3$, benzene, 55 °C (88 %); d) **51**, Sn_2Me_6, $[PdCl_2(PPh_3)_2]$, dioxane, 90 °C (49 %); e) H_2SO_4, MeOH, reflux (66 %); f) aq HNO_2, 0 °C (97 %); g) Tf_2O, pyridine (58 %); h) **53**, $[Pd(PPh_3)_4]$, LiCl, dioxane, reflux (89 %); i) H_3O^+ (80 %).



Scheme 15. Synthesis of dimethyl sulfomycinamate. Reagents and conditions: a) $[PdCl_2(PPh_3)_2]$, dioxane, 100 °C (97 %); b) NBS, THF, H_2O (95 %); c) $H_2C{=}C(Me)CONH_2$, THF sealed tube, 100 °C (65 %); d) OsO_4, $NaIO_4$, dioxane, H_2O (85 %); e) methyl 2-bromothiazole-4-carboxylate, Sn_2Bu_6, $[Pd(PPh_3)_4]$, $[PdCl_2(PPh_3)_2]$, LiCl, dioxane, 100 °C (35 %).

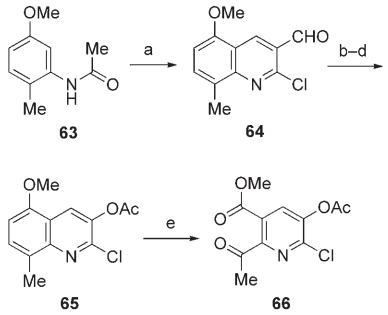
consecutive C–C bond-formation reactions (Scheme 16). The first bromine–lithium exchange proceeded with complete regioselectivity at C-3 to give the 3-lithiopyridine. Transmetalation with zinc chloride, then Negishi cross-coupling with ethyl 2-bromothiazole-4-carboxylate gave pyridine derivative **58**. The next Negishi cross-coupling reaction



Scheme 16. Synthesis of the heterocyclic core of *ent*-GE2270A. Reagents and conditions: a) BuLi, $ZnCl_2$, THF, then ethyl 2-bromothiazole-4-carboxylate, $[PdCl_2(PPh_3)_2]$ (81 %); b) $BnNH_2$, DiBALH, THF, CH_2Cl_2 (86 %); c) **59**, $[PdCl_2(PPh_3)_2]$, THF, DMA (78 %); d) **61**, $[Pd(PPh_3)_4]$, dioxane, 80 °C (61 %).

between **58** and the thiazole zinc derivative **59** gave the desired 3,6-disubstituted pyridine derivative **60**, with 6.5:1 regioselectivity over the corresponding 2,3-disubstituted isomer. Finally, **60** underwent a Stille cross-coupling reaction with the (*R*,*R*)-*erythro*-bisthiazolestannane **61** to give the pyridine core **62**. By comparison of optical rotation values, it transpired that the synthetic **62** was enantiomeric with the material obtained by degradation of the natural product, and hence Heckmann and Bach were able to assign, for the first time, the stereochemistry of the phenylserine residue in the natural product as *S*,*S*-*erythro*.

Finally, in a completely different approach, we have recently investigated the possibility of using a readily accessible quinoline as the pyridine precursor (Scheme 17).[73] Thus, treatment of the simple acetanilide **63** with phosphoryl chloride in DMF results in a double Vilsmeier reaction to give the quinoline **64**. Baeyer–Villiger reaction followed by hydrolysis and reprotection of the hydroxy group as its acetate gave the 2,3,5,8-tetrasubstituted quinoline **65**. The benzene ring is then oxidatively cleaved by ozonolysis to reveal the 2,3,5,6-tetrasubstituted pyridine derivative **66**, adorned with suitable functionality for further elaboration (C-5 ester to thioamide and hence thiazole; C-6 acetyl group to bromoacetyl and hence thiazole; C-2 chloro group to thiazole by palladium-catalyzed cross-coupling) into the nosiheptide pyridine fragment. Further studies along these lines are in progress.



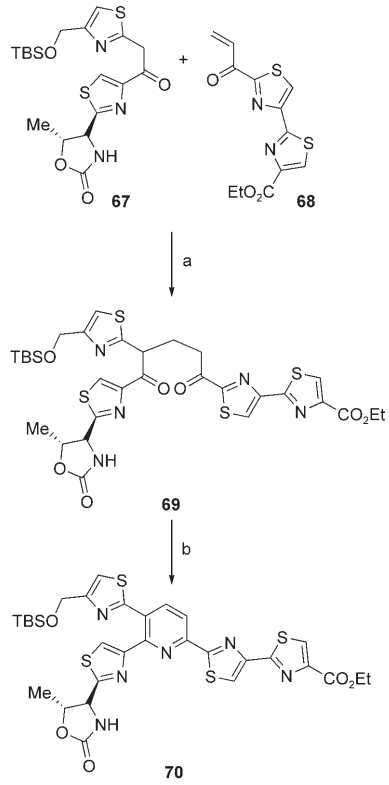
Scheme 17. Synthesis of a 2,3,5,6-tetrasubstituted pyridine from a quinoline precursor. Reagents and conditions: a) $POCl_3$, DMF, 0 °C, then 120 °C (79 %); b) $MeCO_3H$, $CHCl_3$; c) $KHCO_3$, aq MeOH (46 % over 2 steps); d) Ac_2O, K_2CO_3, DMF, 50 °C (93 %); e) O_3, CH_2Cl_2, −20 °C, then Me_2S, −20 °C (45 %).

2.3.2. *Synthesis of the Pyridine Ring*

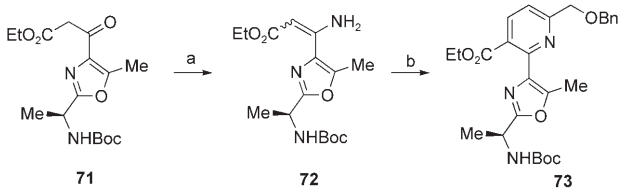
In this section we consider the de novo synthesis of the pyridine cores of heterocyclic peptides. The syntheses vary in the complexity of the groups attached to the acyclic precursors, and we include examples where the pyridine products contain only simple functionality, although we focus on fully substituted thiopeptide core structures.

A decade ago at the outset of our own work on the synthesis of 2,3,6-trisubstituted pyridine derivatives related to thiopeptide antibiotics, all the published approaches relied on the stepwise modifications of existing pyridine rings (see Section 2.3.1). However, during the course of our early work, Ciufolini and Shen published a concise and convergent synthesis of the complete heterocyclic core **70** of the micrococcins.[74] The pyridine ring, complete with its three thiazole groups was obtained through the union of fragments **67** and **68**, the thiazole groups in which were all generated by Hantzsch thioamide reactions. Michael addition of the enolate of ketone **67** to the enone **68** initially proved troublesome, but use of a heterogeneous base (lithium carbonate) yielded the desired 1,5-diketone **69** in almost quantitative yield. Conversion of the diketone **69** into a pyridine ring was effected by treatment with ethanolic ammonium acetate followed by oxidation of the intermediate dihydropyridine with DDQ to give the micrococcin core structure **70** (Scheme 18).

In parallel, we had been exploring an alternative route to substituted pyridines based on the reaction of an ynone with an enamine.[75] This route to pyridines was first reported by Bohlmann and Rahtz 50 years ago,[76] but had found little use at the time. Although this reaction is clearly related to the well-known reaction of enones with enamines (the Hantzsch dihydropyridine synthesis), the use of ynones advantageously delivers the aromatic ring directly, thereby obviating the need for an additional oxidation (aromatization) step. In our synthesis of promothiocin A, the required enamine **72** was prepared from the oxazole **21a** (R = Me, PG = Boc, Scheme 3) by homologation to the β-ketoester **71** followed by reaction with ammonium acetate. The key pyridine-forming step was conducted by allowing the initial conjugate addition of the enamine **72** to 1-benzyloxy-3-butyn-2-one to proceed at 50 °C followed by removal of the solvent and heating the residue to about 140 °C to effect cyclization. This resulted in a good yield of the desired pyridine **73** (Scheme 19), thereby paving the way for the first total synthesis of promothiocin A (**3**, see Section 3.2 for details).[44,77]

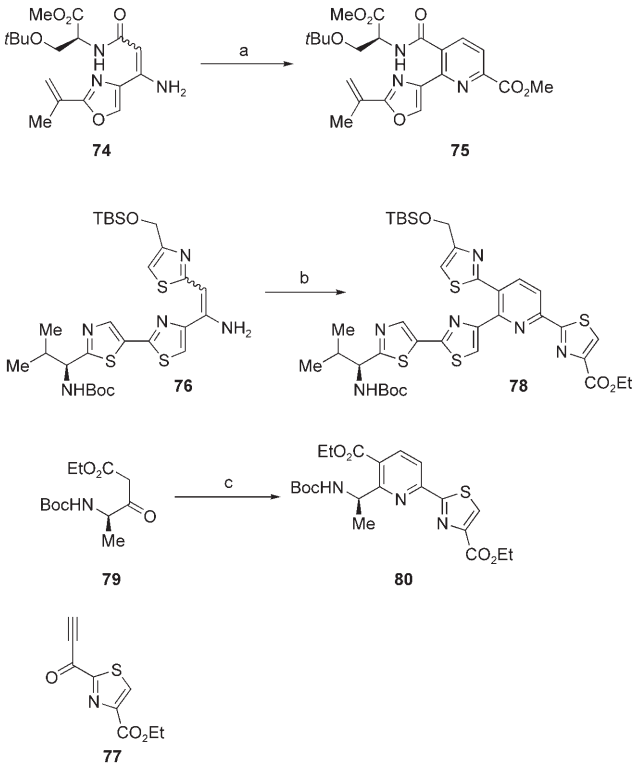


Scheme 18. Synthesis of the pyridine-thiazole core of the micrococcins. Reagents and conditions: a) cat. Li_2CO_3, EtOAc (99 %); b) NH_4OAc, EtOH, then DDQ, $CHCl_3$ (98 %).

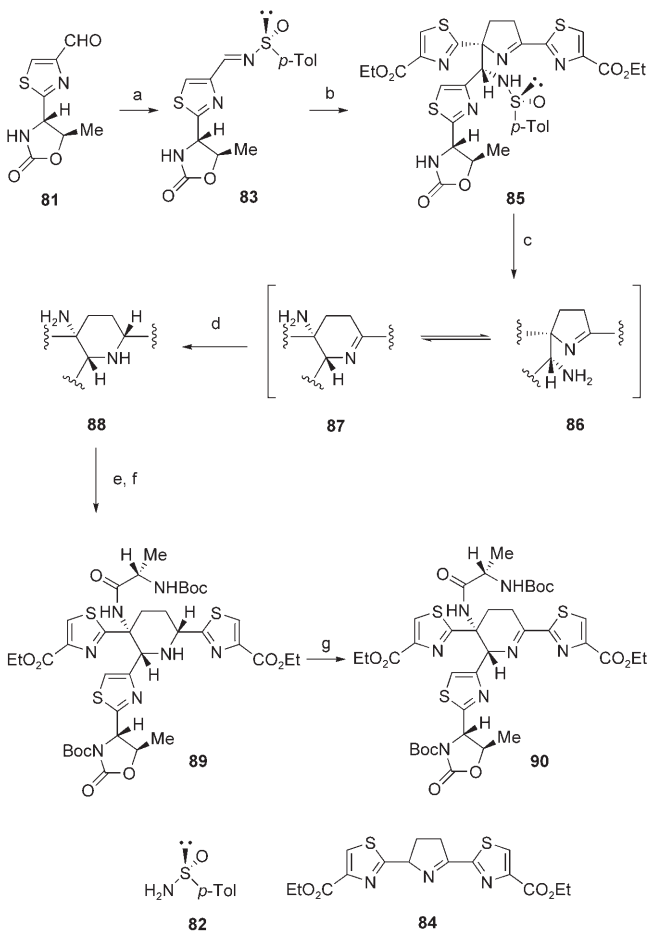


Scheme 19. Synthesis of the pyridine precursor to promothiocin A by the Bohlmann–Rahtz method. Reagents and conditions: a) NH_4OAc, AcOH, benzene (85 %); b) $HC{\equiv}CCOCH_2OBn$, heat (83 %).

Following our successful demonstration that the Bohlmann–Rahtz method could be used for the synthesis of relatively complex pyridine derivatives, Bagley and co-workers embarked on a more detailed study of the reaction, and developed a range of modified conditions, including a one-pot three-component (ynone, 1,3-dicarbonyl, ammonium acetate) coupling reaction.[78] They were then able to use these reactions in the synthesis of the pyridine domains of other thiopeptides (Scheme 20). Thus, the pyridine precursor **75** to



Scheme 20. Routes to the pyridine domains of dimethyl sulfomycinamate, amythiamicin, and cyclothiazomycin. Reagents and conditions: a) $Me_3SiC{\equiv}CCOCO_2Me$, MeOH, RT (93%); b) **77**, EtOH, 60°C, then toluene-AcOH, 70°C (85%); c) NH_4OAc, EtOH, RT, then **77** followed by NIS, 0°C (55%).

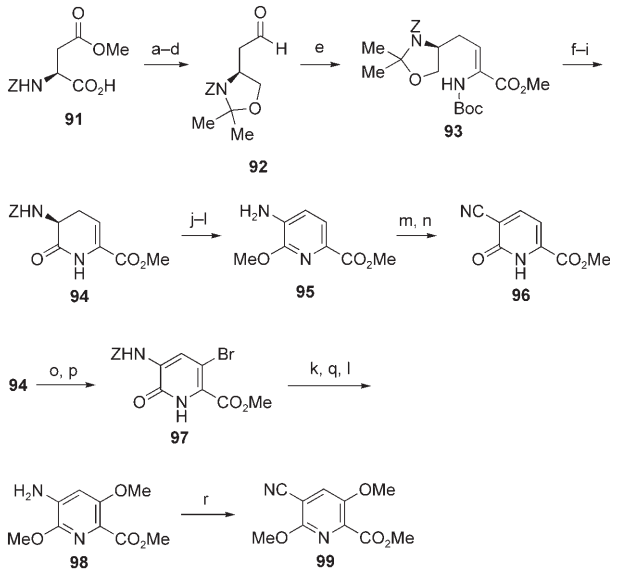


Scheme 21. Synthesis of the tetrasubstituted dehydropiperidine core of the thiostrepton family. Reagents and conditions: a) **82**, $LiClO_4$, Et_3N (8 equiv), THF; b) **84**, Et_3N (from previous step), THF, −25°C (71% over 2 steps); c) TFA, EtOH; d) $NaBH_3CN$, AcOH, EtOH (52% over 2 steps); e) Boc_2O, DMAP, Et_3N, THF, 0°C (84%); f) (*S*)-Boc-Ala-OH, CIP, HOAt, iPr_2NEt, CH_2Cl_2 (93%); g) *t*BuOCl, THF, −78°C, then cat. DMAP, Et_3N (95%).

dimethyl sulfomycinamate (**23**) was obtained in excellent yield from enamine **74**,[79] although the synthesis was subsequently repeated under the one-pot conditions.[45,78] In a similar manner, the pyridine core **78** of the amythiamicins, fully adorned with the requisite thiazole groups, was assembled from enamine **76** and ynone **77** in good yield,[80a] and a similar method was used to access the pyridine domain of micrococcin P1.[80b] Ynone **77** was also successfully employed in the preparation of the pyridine domain **80** of cyclothiazomycin. The reaction was carried out directly from the β-ketoester **79** by using the aforementioned one-pot protocol and gave the pyridine **80** in modest yield.[81]

Hashimoto and co-workers have described the enantioselective synthesis of the tetrasubstituted dehydropiperidine **90** of the thiostrepton family of antibiotics.[82] In this notable synthesis (Scheme 21), a coupling reaction between an azomethine ylide derived from **84** and the chiral sulfinimine **83**, prepared from threonine by way of the thiazole-4-carboxaldehyde **81** and used directly, gives the five-membered imine derivative **85**. Desulfinylation with TFA in ethanol generates an equilibrium mixture of the five-membered imine **86** and the six-membered imine **87**. Steric hindrance around the imine function in **86** results in **87** being stereoselectively reduced with $NaBH_3CN$. Subsequent protection of the oxazolidinone NH group in **88** with Boc_2O, followed by condensation of the free amino group with Boc-Ala-OH gave piperidine **89**. Dehydrogenation of **89** with *t*BuOCl and triethylamine gave the target tetrasubstituted dehydropiperidine core **90** of the thiostrepton family of antibiotics.

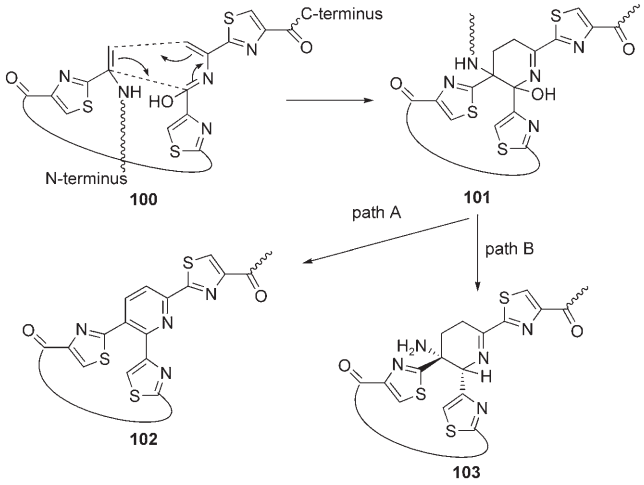
Shin and co-workers have developed a lengthy synthesis of 2,3,6-tri- and 2,3,5,6-tetrasubstituted pyridine derivatives starting from aspartic acid in the pursuit of usefully substituted heterocyclic precursors for the micrococcins and nosiheptide.[83] Protection of (*S*)-aspartic acid as its *N*-Z methyl ester **91** was followed by stepwise elaboration to the aldehyde **92**, which was subjected to a Horner–Wadsworth–Emmons reaction with $(EtO)_2POCH(NHBoc)CO_2Me$ to give the dehydroamino acid **93** (Scheme 22). Cleavage of the isopropylidene group, a two-stage oxidation and TFA-mediated removal of the Boc group then provided the dihydropyridone **94** (in 48% over the four steps), which subsequently served as a precursor to both tri- and tetrasubstituted pyridines. Further oxidation with MnO_2 followed by O methylation and deprotection of the nitrogen atom gave the 3-aminopyridine **95**. The key step is now the introduction of a carbon substituent at C-3 and this was achieved by diazotization, conversion into the iodide under classical Sandmeyer



Scheme 22. Synthesis of tri- and tetrasubstituted pyridines. Reagents and conditions: a) DCC, HOBt, THF, then $NaBH_4$ (86%); b) *p*-TsOH, 2,2-dimethoxypropane, acetone (87%); c) $NaBH_4$, $CaCl_2$, EtOH (91%); d) SO_3, pyridine, DMSO, Et_3N, $CHCl_3$; e) $(EtO)_2POCH(NHBoc)CO_2Me$, DBU, $CHCl_3$ (91% over 2 steps); f) 4% TFA in $CHCl_3$ (87%); g) SO_3, pyridine, DMSO, Et_3N, $CHCl_3$ (61%); h) Jones reagent, acetone (90%); i) TFA (100%); j) MnO_2, $CHCl_3$ (80%); k) MeI, Ag_2CO_3, $CHCl_3$ (87%); l) 10% Pd/C, H_2, MeOH (99%); m) 1. $NaNO_2$, 3 M HCl, THF; 2. CuI; 3. CuI, $[Pd(PPh_3)_4]$, KCN, MeCN (40% over 3 steps); n) BBr_3, CH_2Cl_2 (84%); o) 1. NBS, $CHCl_3$; 2. Et_3N (98%); p) $CuBr_2$, DBU, HMTA (84%); q) NaOMe, CuI, DMF (62%); r) $NaNO_2$, HCl, THF, then CuCN, $CuSO_4$, H_2O (31%).

conditions, followed by a Cu^I- and Pd^0-catalyzed reaction with KCN. Cleavage of the methyl ether gave pyridone **96**, suitable for further elaboration, presumably by way of the corresponding triflate at C-2 and conventional manipulation of the nitrile at C-3 and ester substituents at C-6 into thiazole rings, although this has not been reported as yet. In parallel, dihydropyridone **94** was brominated and oxidized to pyridone **97** (Scheme 22). Copper-catalyzed displacement of the bromide gave **98**, and a subsequent similar series of transformations involving the 3-amino group gave the tetrasubstituted pyridine **99** in modest yield. Further elaboration of **99** to a useful precursor to nosiheptide is awaited.

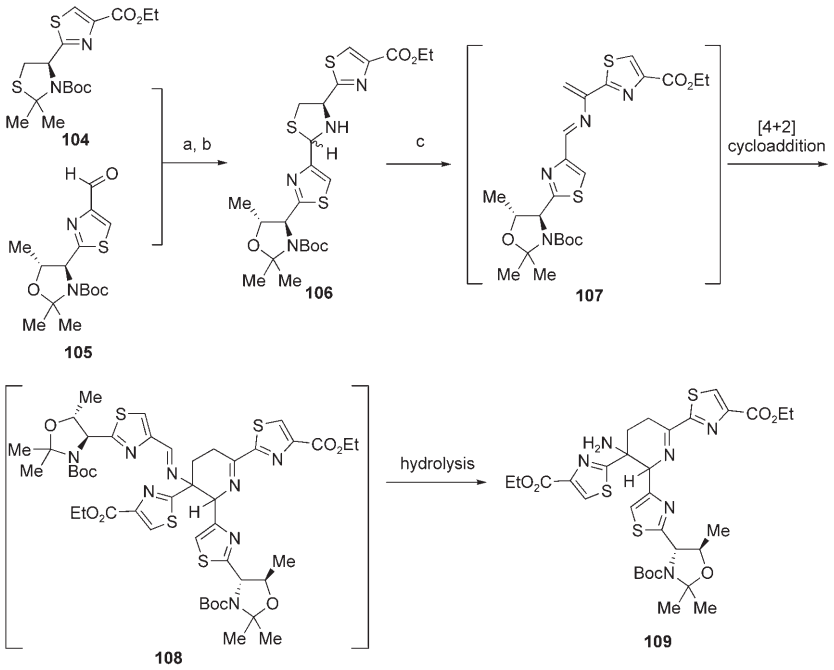
One of the more interesting approaches to the central pyridine rings of the thiopeptide antibiotics to emerge is that based on the proposed biosynthesis. In 1978 Bycroft and Gowland not only reported the structure of micrococcin P1,[23] but also suggested that its pyridine ring, as well the tetrahydropyridine ring in thiostrepton, could be biogenetically derived from the "interaction of two dehydroalanine units", themselves derived by dehydration of two serine residues in the peptide precursor. This fascinating proposal was subsequently supported by isotope labeling experiments by Floss and co-workers,[84,85] who also interpreted the Bycroft–Gowland proposal as a cycloaddition reaction, although not necessarily concerted. Such an intramolecular aza-Diels–Alder reaction would involve a 2-azadiene derivative **100** (the enol form of an amide bond) and would lead to the hydroxytetrahydropyridine **101**. Subsequent aromatization by dehydration and loss of the -NHCOR unit would give the pyridine core **102** of the micrococcins (Scheme 23, path A). Alternatively, dehydration and 1,4-reduction would lead to the tetrahydropyridine **103** of thiostrepton (Scheme 23, path B).



Scheme 23. Hypothesis for the biosynthesis of the pyridine (path A) and tetrahydropyridine (path B) cores of the thiopeptide antibiotics.

Inspired by this elegant proposal, in 2001 we set out to demonstrate its validity. However, unbeknown to us, Nicolaou et al. had also been stimulated by the Bycroft–Gowland–Floss hypothesis, and since his work was submitted two months before our own, we give it due precedence, although the two approaches are distinctly different. The strategy of Nicolaou et al. involved generating a 2-azadiene whose dimerization through a hetero-Diels–Alder reaction would lead to a tetrahydropyridine suitable for further elaboration into thiostrepton.[86,87] To implement this strategy, two thiazole building blocks **104** and **105** were constructed by standard methods from cysteine and threonine, respectively. Union of these fragments gave thiazolidine **106**, the precursor to the desired 2-azadiene (Scheme 24). Treatment of the thiazolidine **106** with silver carbonate and DBU, conditions originally developed by Öhler and Schmidt,[88] revealed that the formed 2-azadiene **107** underwent spontaneous Diels–Alder dimerization to give the tetrahydropyridine **108**. Hydrolysis removed the superfluous thiazole and gave the sought after tetrahydropyridine **109** as a mixture of diastereomers, along with the recyclable thiazole-4-carboxaldehyde **105**.[86,87] Subsequently, it was discovered that addition of an amine nucleophile (benzylamine) at the outset facilitated the release of the desired amine **109** from the intermediate imine **108**, and prevented deleterious side reactions.

Our own biosynthesis-inspired Diels–Alder route to pyridines was somewhat different since we sought to replicate the serine-derived diene–dienophile combination revealed in the Bycroft–Gowland–Floss hypothesis. Thus, the dienes chosen for study were 1-alkoxy-2-azadienes that mimic the proposed dehydroalanine dipeptide diene by fixing it in the

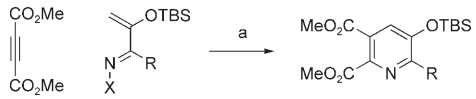


Scheme 24. Synthesis of the tetrahydropyridine domain of thiostrepton. Reagents and conditions: a) TFA, CH_2Cl_2 (1:1), 0 °C, then EtOH, H_2O (1:1), 25 °C; b) $KHCO_3$, EtOH, H_2O (1:1), 0→25 °C (90% over 2 steps from **104**); c) Ag_2CO_3, DBU, $BnNH_2$, −12 °C, then H_2O, EtOAc (1:1), −12→25 °C (60% plus 68% recovered **105**).

reduction of the oxime of 2-acetylthiazoles. The critical Diels–Alder reaction was carried out by heating **112** and **113** in toluene under microwave irradiation, and gave the desired pyridine **114**, albeit in modest yield, suitably functionalized for subsequent conversion into the natural product (see Section 3.3).

In parallel work directed towards the 2,3,5,6-tetrasubstituted pyridine core of nosiheptide, where the presence of the hydroxy group at C-3 poses an additional challenge, we have also explored the Diels–Alder reaction of 1-azadienes.[91] A series of oxime- or hydrazone-based 3-siloxy-1-azabutadienes underwent hetero-Diels–Alder reactions with electron-deficient alkynes to give 3-siloxypyridines (Scheme 26). Although the yields are modest, the starting Diels–Alder components are readily available and the reaction provides a very rapid entry into 2,3,5,6-tetrasubstituted pyridines bearing oxygen substituents at C-3. Recently, this approach has been extended to the synthesis of the complete nosiheptide pyridine core.[92]

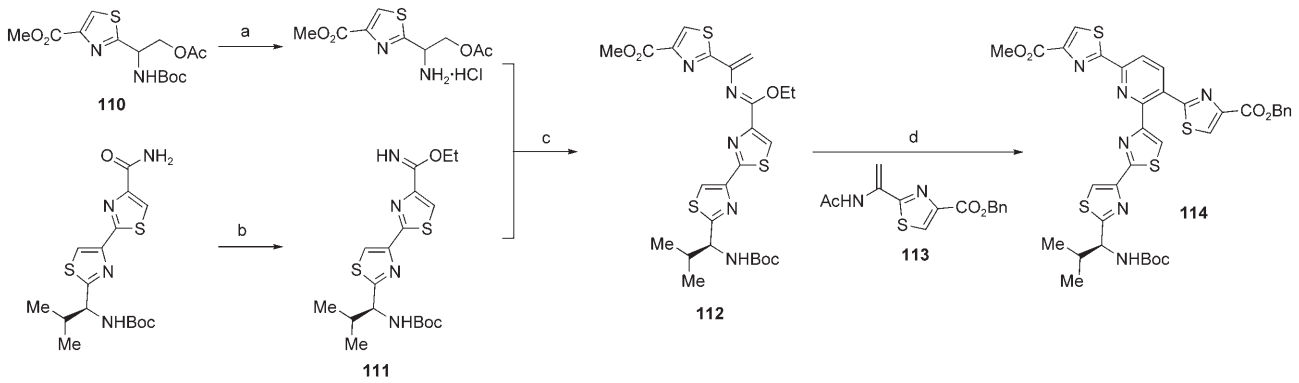
required enol form, whilst the dienophiles were *N*-acetyldehydroalanine derivatives, where the NHAc group mimicks the N-terminus peptide chain (see Scheme 23). After a number of preliminary studies to establish the viability of such an approach,[89] we were able to employ a "biomimetic" aza-Diels–Alder reaction in the synthesis of the 2,3,6-thiazolyl-substituted pyridine core **114** of the amythiamicins (Scheme 25).[24,90] Thus, deprotection of the serine-derived thiazole **110**, and merger of the resulting amine with the valine-derived bisthiazole imidate **111** gave, after elimination of the acetoxy group, the 2-azadiene **112**. Although dienophile **113** could also be derived from serine by elimination of acetate from a thiazole analogous to **110**, it proved more convenient to access such dehydroalanine derivatives by



Scheme 26. Hetero-Diels–Alder reaction of 3-siloxy-1-azabutadienes (R = Me or CO_2Me; X = OTBS or NMe_2). Reagents and conditions: a) toluene, microwave, 110–180 °C (24–56%).

2.4. Indoles

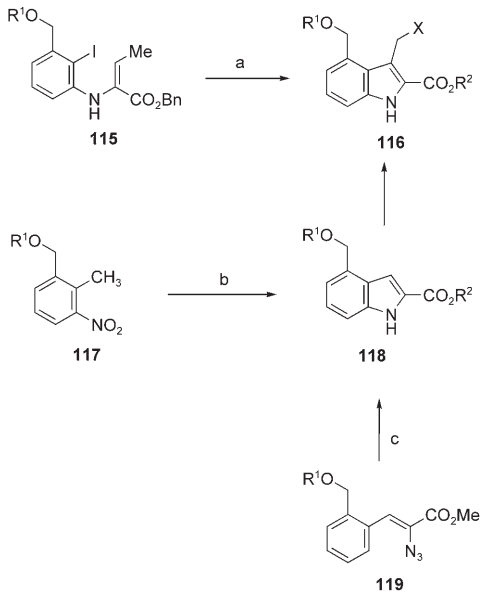
The presence of indole rings in the thiopeptide antibiotics is confined to the nosiheptide group of compounds, which comprises nosiheptide (**6**) itself, glycothiohexide, S54832A-1,



Scheme 25. Synthesis of the pyridine core of the amythiamicins. Reagents and conditions: a) 4 M HCl in dioxane; b) $Et_3O^+PF_6^-$, CH_2Cl_2 (100%); c) CH_2Cl_2, then DBU, $CHCl_3$ (63% over 3 steps from **110**); d) toluene, microwave, 120 °C (33%).

and the more recently discovered nocathiacins.[34] The indole ring is incorporated into the heterocyclic peptide macrocycle by way of ester (or thioester) links to the carboxylate group at C-2 and the hydroxymethyl group at C-4. The indole 3-position either bears a methyl group as in nosiheptide (**6**) or a second hydroxymethyl group that is also incorporated into the macrocyclic ring. In nosiheptide, it has been suggested that the 2,3,4-trisubsituted indole ring is biosynthesized from tryptophan by rearrangement to 3-methylindole-2-carboxylic acid (with loss of formaldehyde and ammonia) followed by a separate methylation at C-4.[84] Interestingly, the nocathiacins and S54832A-1 contain the relatively rare *N*-hydroxyindole fragment. In the main, synthetic efforts have focused on 2,3,4-trisubstituted indoles represented by the general structure **116** (X = H or O-PG).

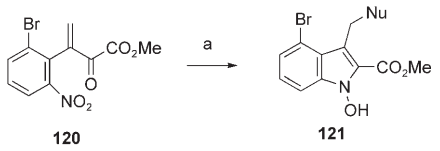
Synthetic routes to the nosiheptide indole **116** (X = H) have been developed based on an intramolecular Heck reaction of an iodoaniline derivative **115**,[93a] or a classical Reissert synthesis of nitrotoluene **117** to give a 4-substituted indole-2-carboxylate **118**. Following hydrolysis to the corresponding carboxylic acid (**118**, R^2 = H), the 3-position was methylated (Scheme 27).[93b] We used the thermolysis of



Scheme 27. Routes to indole fragments of nosiheptide and glycothiohexide. Reagents and conditions: a) Heck reaction; b) Reissert reaction; c) azide thermolysis.

readily available azidocinnamates **119** to access the same 2,4-disubstituted indole **118**, followed by introduction of the C-3 substituent by formylation. Subsequent reduction of the aldehyde gave both 3-methyl and 3-hydroxymethyl compounds, depending on the conditions.[94]

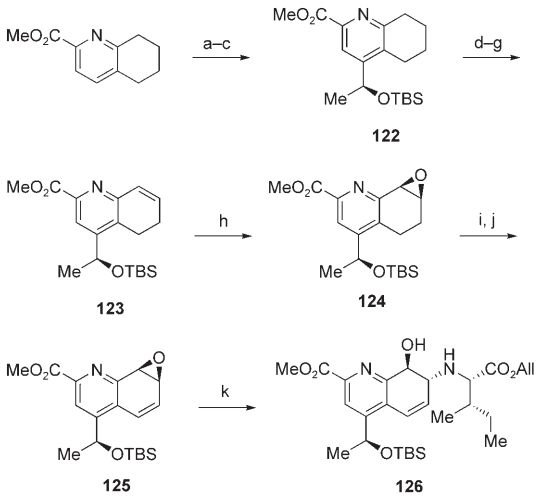
A new synthesis of *N*-hydroxyindoles **121** by reduction of the nitro compounds **120** has recently been reported as part of model studies towards the nocathiacins (Scheme 28).[95]



Scheme 28. Synthesis of *N*-hydroxyindoles related to the nocathiacins. Reagents and conditions: a) $SnCl_2$, DME, NuH (18–75%).

2.5. 7,8-Dihydroquinolines

The 7,8-dihydroquinoline ring is a feature of thiostrepton (**2**) and the more recently isolated thiopeptin and siomycin series of antibiotics.[34] It is biosynthesized from tryptophan and the proposed mechanism involves initial methylation at C-2, followed by ring expansion.[85] The common structural element features a 8-hydroxy-4-(hydroxyethyl)-7,8-dihydroquinoline-2-carboxylate attached to a valine or isoleucine residue at C-7. The synthesis of such a quinoline has been addressed by two research groups, both electing to use ring opening of a chiral epoxide formed by Jacobson-style asymmetric epoxidation as the key step (Scheme 29).[87,96–98]



Scheme 29. Synthesis of the dihydroquinoline fragment of thiostrepton. Reagents and conditions: a) MeCHO, H_2O_2, $FeSO_4$, TFA (99%); b) modified CBS reduction (95%, 90% *ee*); c) TBSOTf, Et_3N, CH_2Cl_2 (95%); d) *m*CPBA, CH_2Cl_2; e) TFAA, CH_2Cl_2; f) aq K_2CO_3 (55% over 3 steps); g) Burgess reagent, THF, benzene (60%); h) asymmetric epoxidation (82%; 74% *de*); i) NBS, AIBN, CCl_4 (44%); j) DBU, THF (96%); k) (*S*)-H-Ile-OAll, $LiClO_4$, MeCN (69%).

Since both strategies are essentially the same, only the route developed by Nicolaou et al. is shown in Scheme 29. Starting from methyl 5,6,7,8-tetrahydroquinoline-2-carboxylate, introduction of an acetyl group at C-4 by nucleophilic addition of an acetyl radical species is followed by asymmetric reduction of the ketone and protection of the resulting alcohol to give **122**. Oxygenation at C-8 by way of a Boekelheide rearrangement followed by dehydration gave **123**, the substrate for

asymmetric epoxidation. Diastereoselective epoxidation using NaOCl in the presence of a Katsuki Mn-salen catalyst gave the major epoxide **124**, which was then subjected to radical bromination and elimination to give **125**. Finally, opening of the epoxide with isoleucine allyl ester in the presence of lithium perchlorate gave the desired quinoline **126** (Scheme 29), a compound that served as a key intermediate in the landmark synthesis of thiostrepton by Nicolaou et al. (see Section 3.4). The Hashimoto–Nakata route differs mainly in the timing of the steps, the 4-acetyl group being reduced after the epoxidation step, and delivered a dihydroquinoline suitable for incorporation into their synthesis of siomycin A (see Section 3.5).

3. Total Synthesis of Thiopeptide Antibiotics

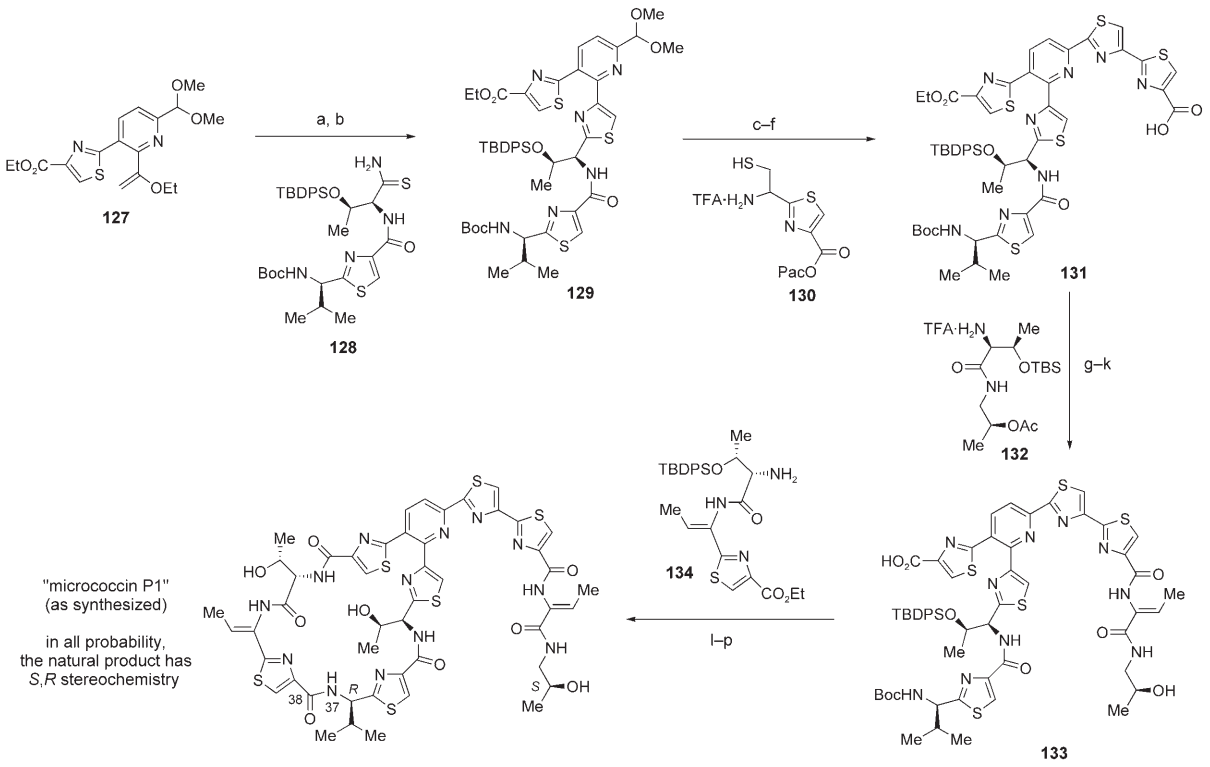
Despite the fact that some of the thiopeptide antibiotics have been known for 50 years or more, there was a complete lack of progress towards their total synthesis until the late 1990s. Only six members of this family of natural products have fallen to unambiguous synthesis to date: promothiocin A, amythiamicin D, thiostrepton, GE2270A, GE2270T, and siomycin A. However, there has been some progress towards others, such as nosiheptide. The synthesis of micrococcin has been reported three times, although none of the final molecules actually coincide with the natural product.

3.1. Micrococcin

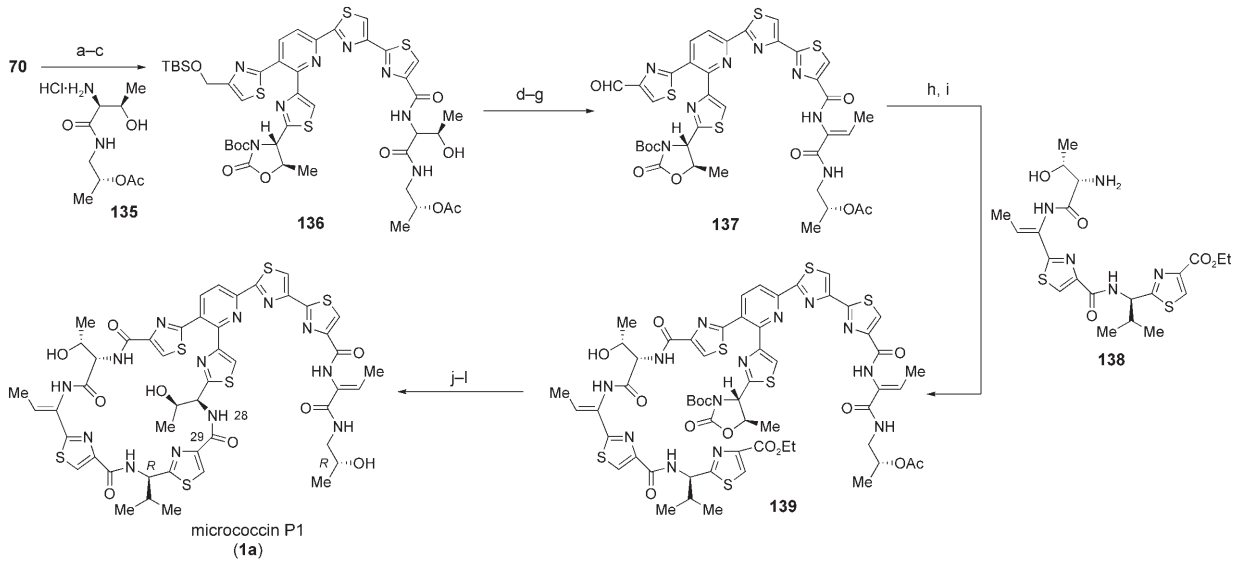
In accord with its status as the first thiopeptide to be isolated in 1948, micrococcin was also the first to be "synthesized", although we use the word advisedly. In 1997, Shin et al. reported the synthesis of a natural product described as micrococcin P,[99] a substance whose structure had been worked on extensively by Walker and co-workers at the National Institute for Medical Research in London.[18–22] This choice of molecule for synthesis was somewhat surprising since micrococcin P had clearly been shown to be a mixture of two components, designated micrococcin P1 and micrococcin P2, some 20 years earlier.[23] Hence, one has to conclude that this work by Shin et al., subsequently reported in a full paper,[100] does not describe the synthesis of any known natural product. A few months later, the Shin research group reported the first synthesis of micrococcin P1.[25] In this report, and the subsequent article,[26] the synthesis of the overall Bycroft–Gowland structure **1a** is described, although the researchers inexplicably chose to prepare a molecule that was epimeric with **1a** in the isoalaninol side chain. Again this is very surprising since the *R* stereochemistry of this center was not in doubt, having been established unambiguously in the original work by Walker et al.,[19,22] and therefore the structure of the synthesized molecule does not correspond to the thiopeptide, although the authors clearly believed that they had obtained the natural product itself.

Nevertheless, in view of Shin's substantial contributions to the thiopeptide arena, we do include the "synthesis" of micrococcin P1 (Scheme 30). The synthesis was designed to effect macrocyclization at the 37–38 amide bond and proceeded from the pyridine **127**, prepared as described in Scheme 12. Pyridine **127** was converted into the bromoacetyl derivative for a Hantzsch reaction with the thioamide **128**, which was prepared by coupling an (*R*)-valine-derived thiazole with protected threoninamide followed by conversion into the thioamide. The resulting coupled product **129** was deprotected and the resulting pyridine carboxaldehyde condensed with the cysteine-derived thiazole **130** to give, after oxidation of the thiazoline with MnO_2 and selective hydrolysis of the Pac ester, the 2,3,6-tristhiazolylpyridine **131**. Coupling of the carboxylate to threonine derivative **132** was achieved using the BOP reagent, and this was followed by selective cleavage of the TBS ether, standard dehydration of the threonine residue to give the dehydropeptide derivative, and hydrolysis of the ester and acetate groups to give advanced intermediate **133**. The final fragment **134** was introduced by coupling to the thiazole-4-carboxylate, sequential deprotection of the C and N termini and macrocyclization, again by using the BOP protocol. Finally, removal of the two silyl ethers delivered "micrococcin P1", epimeric with Bycroft–Gowland structure **1a** in the isoalaninol side chain. As it later transpired, the product of this synthesis is also epimeric with the likely structure of the natural product at the valine-derived thiazole center, so it appears that the Shin research group have been thwarted in their attempts to complete a total synthesis of a thiopeptide natural product by choice of epimeric configurations of their starting materials.

It was the 1999 synthesis by Ciufolini and Shen that finally laid to rest the Bycroft–Gowland structure **1a** for micrococcin P1.[27] Building on their elegant earlier work that provided the pyridine domain **70** (Scheme 18), Ciufolini and Shen elected to effect the key macrocyclization at the 28–29 amide bond. Thus, the ethyl ester in pyridine core **70** was hydrolyzed, an additional Boc-protecting group installed on the oxazolidinone, and the free acid coupled with the threonine derivative **135** to give **136** in excellent yield over the three steps (Scheme 31). After deprotection of the silyl ether, the resulting 4-hydroxymethylthiazole underwent chemoselective oxidation to the thiazole-4-carboxaldehyde, before the dehydroamino acid residue was installed by dehydration of the threonine side chain. Pinnick oxidation of the thiazole aldehyde **137** then provided a carboxylic acid coupling partner for the threonine tripeptide **138**, which was duly accomplished using BOPCl. The final steps were achieved by deprotection of both the N and C termini of **139** and macrocyclization using DPPA to afford the target structure **1a** in an impressive 5.7% overall yield over the longest linear sequence of 23 steps. Unfortunately, as already alluded to, this synthesis of a micrococcin also failed to produce a molecule that was identical to natural micrococcin P1, prompting the aforementioned reexamination of the Bycroft–Gowland structure **1a** (see Section 1)[28,29] and its reformulation as **1b**. We await the final chapter in the micrococcin story when the structure is at last confirmed by total synthesis.



Scheme 30. Synthesis of "micrococcin P1". Reagents and conditions: a) NBS, aq THF; b) **128**, $KHCO_3$, DMF, 0 °C, then TFAA, pyridine (69% from **127**); c) 2 M HCl, THF; d) **130**, toluene; e) MnO_2, toluene (28% from **129**); f) 1 M LiOH, THF (100%); g) **132**, BOP, iPr_2NEt, DMF (89%); h) 70% AcOH, THF (64%); i) MsCl, Et_3N, CH_2Cl_2, 0 °C; j) DBU, CH_2Cl_2 (97% over 2 steps); k) 1 M LiOH, THF (72%); l) **134**, BOP, iPr_2NEt, DMF (91%); m) 1 M LiOH, THF; n) TFA, CH_2Cl_2; o) BOP, iPr_2NEt, DMF; p) TBAF, THF (13% over 4 steps from **133**).



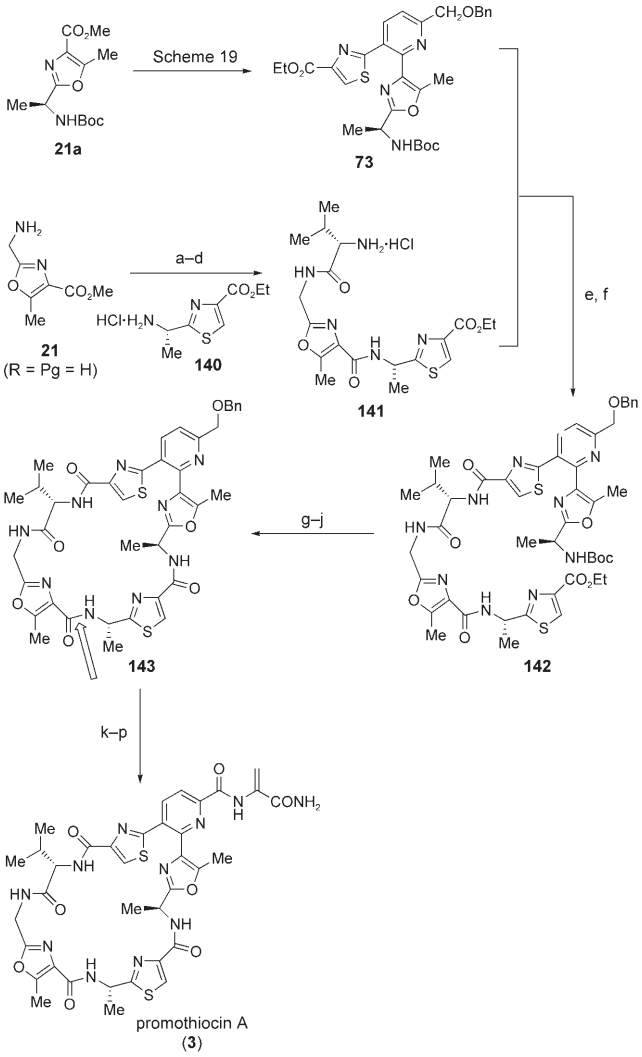
Scheme 31. Synthesis of structure **1a** of micrococcin P1. Reagents and conditions: a) LiOH, aq THF; b) Boc_2O, DMAP, Et_3N, CH_2Cl_2; c) **135**, BOPCl, Et_3N, MeCN (84% over 3 steps); d) TBAF, THF; e) MnO_2, EtOAc; f) MsCl, Et_3N, CH_2Cl_2; g) DBU, $CHCl_3$ (68% over 4 steps); h) $NaClO_2$, 2-methylbutene, NaH_2PO_4, aq THF; i) **138**, BOPCl, Et_3N, MeCN (76% over 2 steps); j) LiOH, aq THF; k) HCl, dioxane; l) DPPA, Et_3N, DMF (65% over 3 steps).

3.2. Promothiocin A

We achieved the first undisputed chemical synthesis of a naturally occurring thiopeptide antibiotic, that of promothiocin A (**3**), in mid-1998.[77] At the outset, the stereochemistry of the natural product was not known, and therefore we assumed that the three stereocenters were derived from *S* amino acids, a somewhat dangerous assumption in view of the foregoing

discussion on the stereochemical confusion that is rife in the thiopeptide arena. The starting points for the synthesis were two oxazoles **21a** and **b** obtained by our rhodium carbene route (Scheme 3). Thus, oxazole **21a** (R = Me, PG = Boc) was elaborated into pyridine **73** by using the Bohlmann–Rahtz chemistry discussed earlier (Scheme 19). The choice of a protected primary alcohol at the pyridine 6-position, rather than the more obvious ester functionality, was dictated by a desire to avoid possible issues with selective (orthogonal) deprotection of one ester group in the presence of other(s). In parallel, oxazole **21b** (R = H, PG = Z) was deprotected by hydrogenolysis and the resulting amine was coupled with *N*-Boc-valine, activated by using mixed anhydride methodology. Hydrolysis of the oxazole ethyl ester, a second isobutyl chloroformate activation, and coupling to the (*S*)-alanine-derived thiazole **140**, prepared by the modified Hantzsch reaction (Scheme 5), gave the valine-oxazole-thiazole tripeptide **141** (Scheme 32), after acidic cleavage of the Boc protecting group. The scene was now set for coupling with the pyridine fragment **73**, and this was set in motion by hydrolysis of the ethyl ester in **73**, and another mixed anhydride coupling to **141** to give the linear heterocyclic peptide **142** in good yield.

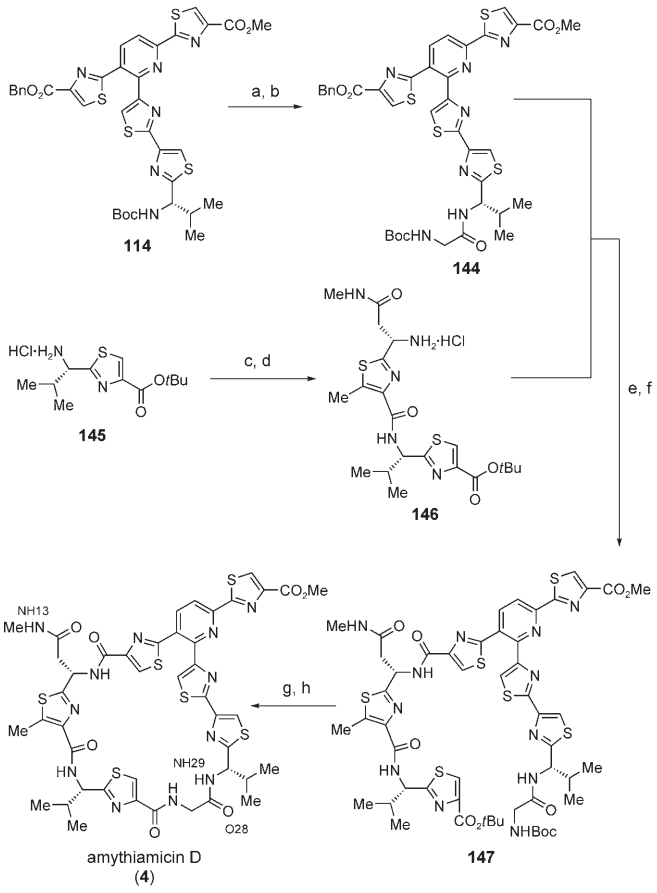
Although there are many methods to effect macrolactamization as already seen, we favored the Schmidt protocol,[101] since we had recently used it successfully in a synthesis of nostocyclamide.[2,3] Hence the C-terminal ethyl ester in **142** was saponified, and converted into the corresponding pentafluorophenyl ester in the presence of the water-soluble carbodiimide reagent EDCI. The pentafluorophenyl ester was not purified, but was treated with HCl in dioxane to effect cleavage of the N-terminal Boc group. Work up and treatment with triethylamine resulted in the desired lactamization to give macrocycle **143**. In a second synthesis of the macrocycle **143**, we effected an alternative cyclization step by forming the arrowed amide bond between the oxazole and thiazole residues (Scheme 32). At this stage our choice of the benzyloxymethyl group as a carboxyl precursor returned to haunt us. The final steps proved far from trivial, requiring six separate operations to convert CH_2OBn into CO_2H and install the dehydroalaninamide side chain (Scheme 32). Gratifyingly, the final product possessed identical spectroscopic properties to those reported for the natural product, thereby completing the first definitive total synthesis of a thiopeptide, promothiocin A (**3**), and establishing the stereochemistry of the natural product.



Scheme 32. The synthesis of promothiocin A. (The arrow in structure **143** indicates the alternative site for macrocyclization.) Reagents and conditions: a) (*S*)-Boc-Val-OH, *i*BuO_2CCl, NMM, THF (87%); b) LiOH, aq THF (93%); c) *i*BuO_2CCl, NMM, THF, **140** (84%); d) AcCl, EtOH (100%); e) LiOH, aq THF (94%); f) *i*BuO_2CCl, NMM, THF, **141** (69%); g) LiOH, aq THF (97%); h) C_6F_5OH, EDCI, CH_2Cl_2 (ca. 100%); i) HCl, dioxane; j) Et_3N, $CHCl_3$ (55% over 2 steps); k) $BCl_3{\cdot}Me_2S$, CH_2Cl_2 (39%); l) IBX, DMSO (81%); m) $NaClO_2$, 2-methylbutene, KH_2PO_4, aq *t*BuOH (70%); n) (*S*)-H-Ser(OTBS)-NH_2, EDCI, CH_2Cl_2 (50%); o) TBAF, THF (57%); p) MsCl, Et_3N, CH_2Cl_2, then more Et_3N (59%).

3.3. Amythiamicin D

The second thiopeptide antibiotic to succumb to synthesis (again by us) was amythiamicin D (**4**).[24,90] The amythiamicins are among the most biologically active of the thiopeptides, reportedly exhibiting activity not only against MRSA,[102] but also against *Plasmodium falciparum*, the malaria parasite.[103] At the time we embarked upon the synthesis, we were again faced with a situation where the configuration of the three chiral centers was unknown. Therefore, we again assumed that they derived from *S* amino acids, although on this occasion we were encouraged in this assumption by the structure of the closely related natural product GE2270A (**5**), where more detailed structural information existed.[48] The cornerstone of our synthetic strategy was the use of a biosynthesis-inspired hetero-Diels–Alder reaction to construct the pyridine core of the antibiotic (Schemes 23 and 25). Thus the Diels–Alder product, pyridine **114**, was elaborated by addition of the glycine residue to give the complete right-side fragment **144** in excellent yield (Scheme 33). Concurrently, the valine-derived thiazole **145**, obtained as usual by a modified Hantzsch reaction, was coupled to the carboxylic acid formed by hydrolysis of thiazole **29**, prepared by using our rhodium carbene method-



Scheme 33. Synthesis of amythiamicin D. Reagents and conditions: a) TFA, $CHCl_3$; b) Boc-Gly-OH, PyBOP, iPr_2NEt, CH_2Cl_2 (95% over 2 steps); c) carboxylic acid derived by hydrolysis of **29**, EDCI, HOBt, DMF, 0°C (48%); d) HCl, dioxane (88%); e) H_2, Pd black, MeOH; f) **146**, PyBOP, iPr_2NEt, DMF (60% over 2 steps); g) TFA, $CHCl_3$; h) DPPA, iPr_2NEt, DMF, 0°C (73% over 2 steps).

ology (Scheme 7). This approach resulted in the formation of the bisthiazole peptide **146** after unblocking of the N terminus by careful removal of the *N*-Boc group in the presence of the *tert*-butyl ester. The deprotection of benzyl ester **144** in preparation for coupling to amine **146** proved surprisingly problematic and could only be achieved by hydrogenolysis over palladium black. With the acid in hand, the coupling reaction proceeded smoothly to give the cyclization precursor **147**. Simultaneous removal of the N- and C-terminal protecting groups, followed by a high-yielding DPPA-mediated macrolactamization completed the synthesis.

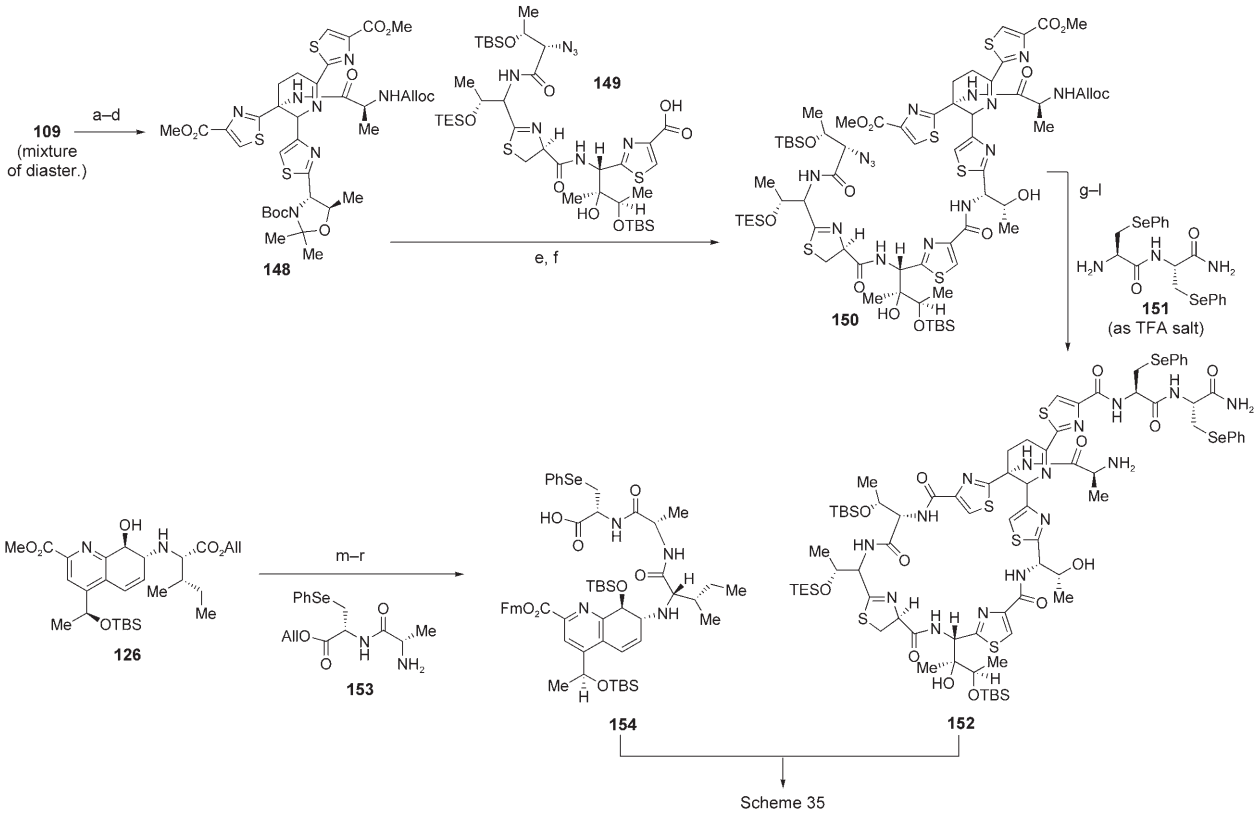
Our synthetic amythiamicin D (**4**) had properties consistent with those described for the natural product, thereby suggesting that our initial assumption about the configuration of the chiral centers was correct. Subsequent correspondence with the scientists who isolated the antibiotic[104] revealed that unpublished X-ray crystallographic data substantiated the all-*S* stereochemistry, thereby providing final confirmation that we had completed the first synthesis of the natural thiopeptide amythiamicin D.

However, there was one final twist in the tale. Although our synthetic material appeared to be absolutely identical to the natural product, one signal in the ^1H NMR spectrum, assigned to NH29, showed significant concentration dependence. This prompted a more detailed NMR study[105] that not only revealed the presence of a single transannular hydrogen bond involving NH13 and O28, but also evidence for self-association of the thiopeptide in solution. These features are perhaps not surprising: with molecular weights of over 1000 Da, and arrays of rings linked by peptide bonds, the thiopeptides can be regarded as a microcosm of the protein world.[106]

3.4. Thiostrepton

The synthesis of thiostrepton (**2**), first isolated in 1954, by Nicolaou et al. represents a landmark not only in the field of heterocyclic peptides, but also in the wider field of complex molecule synthesis.[87,107–109] The strategy is convergent, and whilst relying on standard peptide technology to form amide bonds, it also deviates from convention, for example, in its use of the azido group as a masked amine to obviate potentially difficult deprotection steps.[110–113] The synthesis starts with the tetrahydropyridine core **109**. Although this key building block was readily obtained through the elegant Diels–Alder dimerization outlined in Scheme 24, its subsequent elaboration was far from trivial, and it proved essential to capture the free amino group before it initiated unwanted side reactions. This was achieved by employing the small reactive electrophile azidoalanine acid chloride, which reliably acylated the free amino group of **109**. Subsequent transesterification followed by reduction of the azido group with tin(II) chloride gave a diastereomeric mixture of amines that were separable by chromatography. It was established that the less polar isomer had the correct stereochemistry by its conversion into a known compound obtained by degradation of the natural product. Finally, the pure amine was protected as its allyl carbamate **148** (Scheme 34). Cleavage of the oxazolidine unit in TFA was followed by coupling of the resulting free amino group with the thiazole-4-carboxylate of the building block **149** (again with its terminal amino group masked as an azide) to give cyclization precursor **150**. This first coupling of two major fragments of thiostrepton was promoted by HATU, HOAt, and Hünig's base, a combination of reagents that also features in subsequent amide bond forming reactions. In the event, a totally regioselective hydrolysis of one of the thiazole methyl esters proved overly optimistic, and the best conditions delivered a 2:1 mixture of monoacids. Closure of the macrocycle, following reduction of the azide group, only occurred from one of the monoacids and gave the desired macrolactam, although this was not firmly established until much later in the synthesis. Hydrolysis of the remaining methyl ester followed by HATU/HOAt/iPr_2NEt-mediated coupling with the bis(phenylseleno) dipeptide **151**, and removal of the Alloc protecting group gave macrocycle **152**.

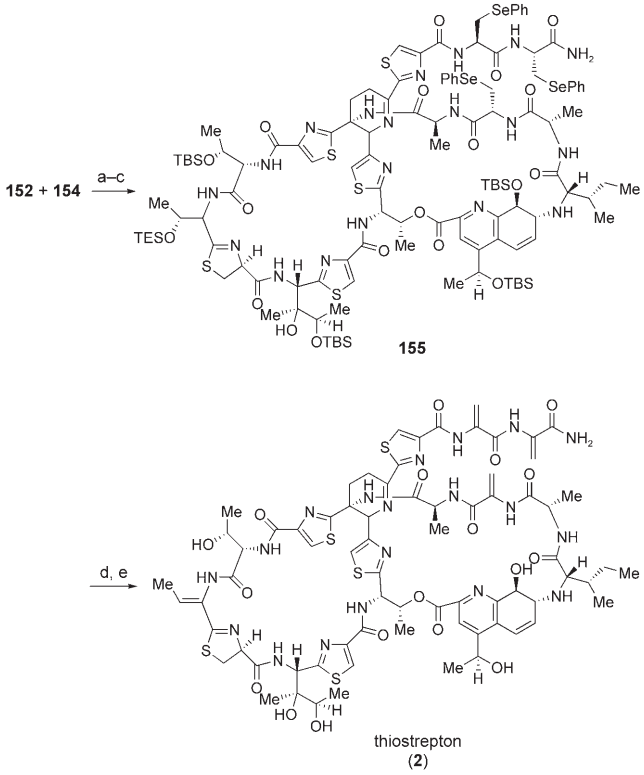
Dihydroquinoline **126** (Scheme 29) was readied for attachment to the macrocycle **152** in a six-step sequence (Scheme 34). After protection of the 8-hydroxy group as its TBS ether, the methyl ester was hydrolyzed and the more labile 9-fluorenylmethyl ester was installed using a Yamagu-



Scheme 34. Synthesis of key building blocks towards thiostrepton. Reagents and conditions: a) (*S*)-$MeCHN_3COCl$, Et_3N, THF (70%); b) nBu_2SnO, MeOH (80%); c) $SnCl_2$, aq MeOH (44% + 38% diastereomer); d) AllocCl, iPr_2NEt, DMAP, THF (92%); e) TFA, CH_2Cl_2; f) **149**, HATU, HOAt, iPr_2NEt, DMF (73% over 2 steps); g) Me_3SnOH, $(ClCH_2)_2$ (52% includes other monoacid); h) Me_3P, aq THF; i) HATU, HOAt, iPr_2NEt, DMF (32% over 2 steps from mixture of monoacids); j) Me_3SnOH, $(ClCH_2)_2$ (100%); k) **151**, HATU, HOAt, iPr_2NEt, DMF (85%); l) $[PdCl_2(PPh_3)_2]$, nBu_3SnH, CH_2Cl_2 (86%); m) TBSOTf, iPr_2NEt, THF (94%); n) NaOH, aq MeOH, THF (89%); o) ArCOCl, Et_3N, DMAP, toluene, FmOH (64%); p) $[PdCl_2(PPh_3)_2]$, nBu_3SnH, CH_2Cl_2 (100%); q) **153**, HATU, HOAt, iPr_2NEt, DMF (85%); r) $[PdCl_2(PPh_3)_2]$, nBu_3SnH, CH_2Cl_2 (100%). Ar = 2,4,6-trichlorophenyl.

chi esterification. Deprotection of the allyl ester, HATU/HOAt coupling to the dipeptide **153**, and final deprotection of the new allyl ester gave acid **154** (Scheme 34).

The endgame was initiated by the union of fragments **152** and **154** again by using the HATU/HOAt protocol, followed by cleavage of the Fm ester with diethylamine and Yamaguchi macrolactonization to furnish the complete framework **155** of thiostrepton. Treatment with *tert*-butyl hydroperoxide effected oxidative elimination of all three phenylseleno groups to reveal the three sensitive dehydroalanine residues. Finally, treatment with HF·pyridine not only removed all five silicon protecting groups but fortuitously also effected elimination of the TES-bearing oxygen atom to give the natural product thiostrepton (**2**, Scheme 35).



Scheme 35. Completion of the synthesis of thiostrepton. Reagents and conditions: a) HATU, HOAt, iPr_2NEt, DMF (68%); b) Et_2NH, CH_2Cl_2 (87%); c) ArCOCl, Et_3N, DMAP, toluene (42%); d) *t*BuOOH, CH_2Cl_2 (68%); e) HF·pyridine, THF (52%). Ar = 2,4,6-tri-chlorophenyl.

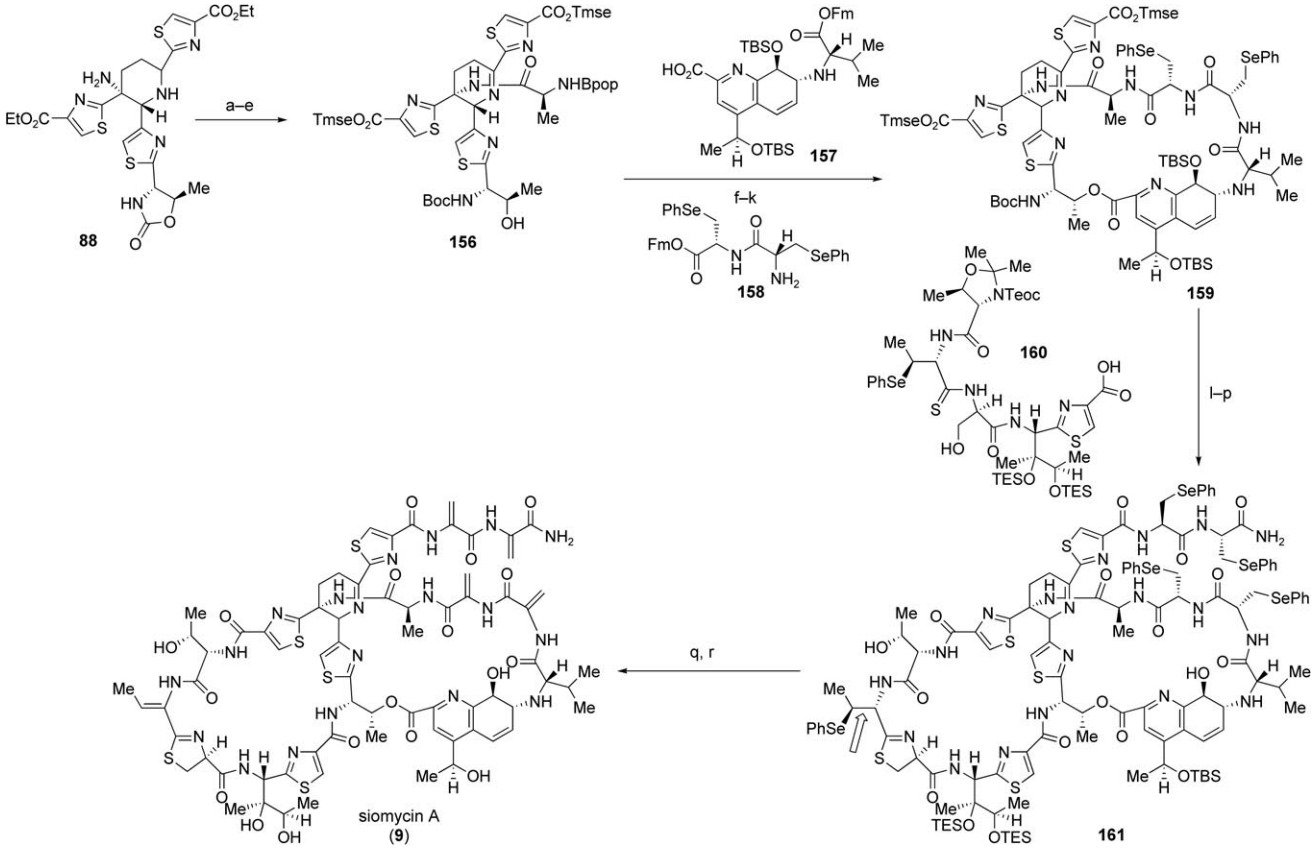
3.5. Siomycin A

Another thiopeptide that has recently been synthesized is siomycin A (**9**).[114] This thiopeptide is very closely related to thiostrepton, only differing in the dehydroalanine-valine fragment attached to the 7-position of the dihydroquinoline instead of an alanine-isoleucine residue. The overall strategy used by Hashimoto, Nakata, and co-workers is similar to the route used by Nicolaou et al. to thiostrepton in terms of the disconnections of the major building blocks, although they elected to form the right-side dihydroquinoline-containing macrocycle first. The route relies on earlier studies by the research group,[82,97,98,115,116] including their approach to the tetrahydropyridine (Scheme 21) and dihydroquinoline (Scheme 29) units discussed earlier. The starting point was the aminopiperidine **88** (Scheme 21), which was transesterified to provide the more labile Tmse esters on the two thiazole groups, and the oxazolidinone NH group *N*-protected. Coupling to alanine, *N*-protected with the unusual Bpop carbamate, ensued using the CIP reagent favored by the research group, and this was followed by selective removal of the oxazolidinone and dehydrogenation to the tetrahydropyridine **156** (Scheme 36).

The valine-substituted dihydroquinoline **157**, prepared in a similar manner to its isoleucine analogue (see Scheme 29), was incorporated, the Fm ester was deprotected, and the resulting carboxylic acid coupled to the next fragment **158**, again using the CIP coupling reagent. Sequential removal of Bpop and Fm protecting groups using magnesium perchlorate and diethylamine, respectively, gave an amino acid that was cyclized using HATU to give macrocycle **159**.

Thereafter, removal of the Boc group, accompanied by desilylation of the dihydroquinoline 8-hydroxy group, was followed by incorporation of pentapeptide **160**,[116] in which the hydroxymethylthioamide serves as the precursor to the thiazoline ring. Formation of the thiazoline by treatment with DAST was followed by removal of Teoc, acetonide, and Tmse protecting groups using zinc chloride, side-chain elongation with the dipeptide **151**, and macrocyclization to give **161**. However, just as in the route used by Nicolaou et al., it was not clear until the end of the synthesis which thiazole carboxylic acid coupled to which partner, and an equal amount of a regioisomeric cyclization-elongation product was indeed obtained.

The conversion of **161** into the natural product was achieved in two simple operations: 1) treatment with HF·pyridine to strip off the three silyl groups was actually accom-

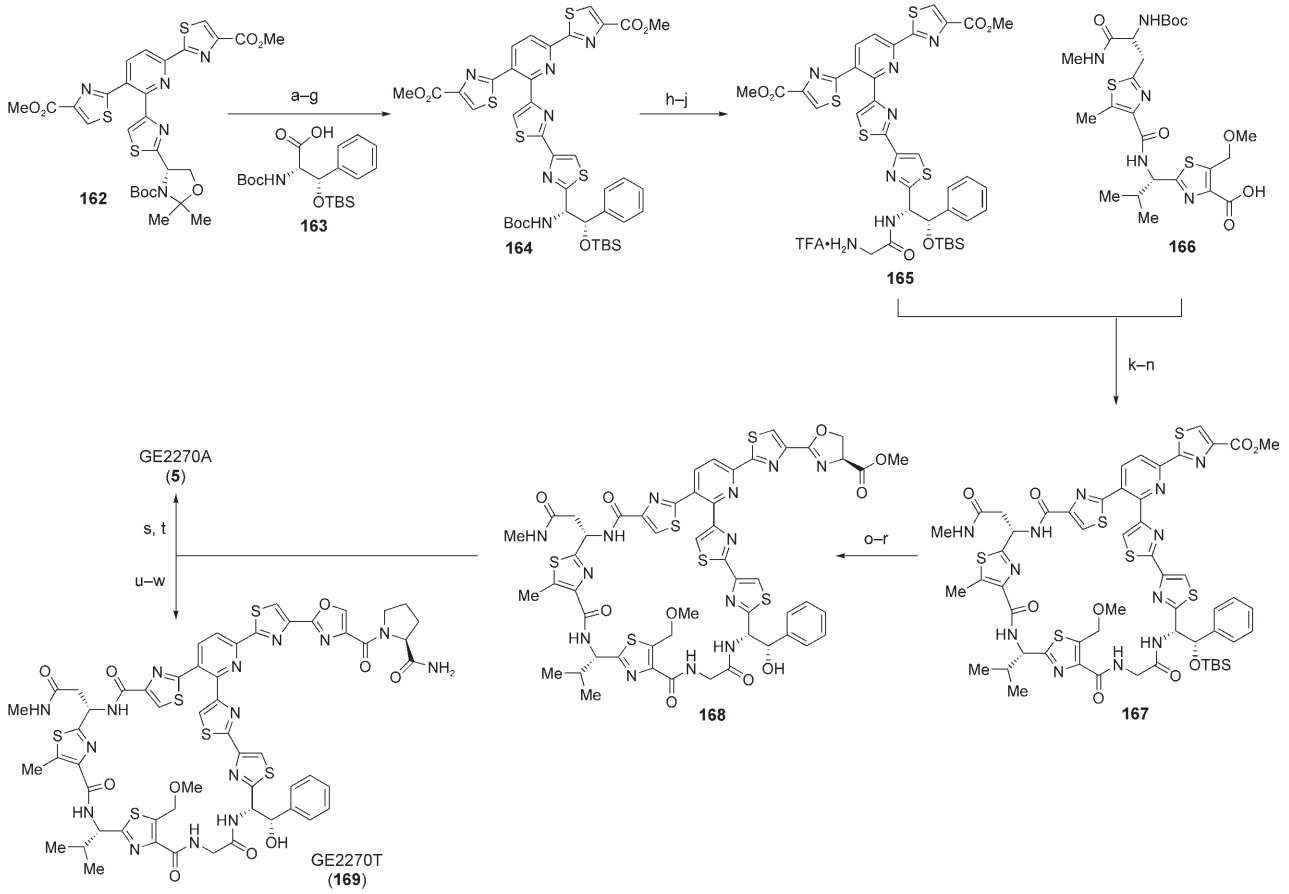


Scheme 36. Synthesis of siomycin A. (The arrow indicates the site of dehydroselenation in step q.) Reagents and conditions: a) $Me_3SiCH_2CH_2OH$, $(iPrO)_4Ti$, 100 °C; b) Boc_2O, DMAP, Et_3N, THF (66% over 2 steps); c) (*S*)-Bpop-Ala-OH, CIP, HOAt, iPr_2NEt, CH_2Cl_2 (83%); d) Cs_2CO_3, $Me_3SiCH_2CH_2OH$; e) *t*BuOCl, THF, −78 °C, then DMAP, Et_3N (61% over 2 steps); f) **157**, CIP, DMAP, iPr_2NEt, CH_2Cl_2 (67%); g) Et_2NH, CH_2Cl_2; h) **158**, CIP, HOAt, iPr_2NEt, CH_2Cl_2 (94% over 2 steps); i) $Mg(ClO_4)_2$, MeCN; j) Et_2NH, CH_2Cl_2 (67% over 2 steps); k) HATU, NMM, CH_2Cl_2 (79%); l) HCl, dioxane; m) **160**, HATU, iPr_2NEt, CH_2Cl_2 (60% over 2 steps); n) DAST, CH_2Cl_2, −78 °C (87%); o) $ZnCl_2$, Et_2O, $MeNO_2$; p) **151**, HATU, iPr_2NEt, DMF, CH_2Cl_2; q) HF·pyridine, THF; r) *t*BuOOH, CH_2Cl_2 (7% over 4 steps).

panied by dehydroselenation at the indicated residue to give the thermodynamically more stable *Z* alkene, and 2) a final oxidative elimination of the four remaining selenides gave the natural product siomycin A. Interestingly, the final two steps could not be reversed, as in the synthesis of thiostrepton by Nicolaou et al., since siomycin A was unstable to the HF·pyridine conditions and slowly degraded to siomycin B by loss of the double dehydroalanine side chain from the uppermost thiazole unit in Scheme 36. However, like the Nicolaou route to give thiostrepton, the preparation of siomycin A is a major achievement in the field of complex natural product synthesis.

3.6. GE2270A and GE2270T

The latest thiopeptides to succumb to synthesis are two members of the GE2270 series, GE2270A (**5**), and its dehydro derivative GE2270T (**169**), in which the side-chain oxazoline is replaced by the corresponding oxazole. The first synthesis of GE2270A was reported by the Nicolaou research group,[117] who used the hetero-Diels–Alder dimerization strategy employed in the aforementioned synthesis of thiostrepton (see Scheme 24), followed by aromatization of the initial tetrahydropyridine. This approach delivered the 2,3,6-thiazolyl-substituted pyridine **162**, which was deprotected, coupled to the phenylserine derivative **163**, and elaborated by a standard five-step sequence to the tetrathiazole **164** (Scheme 37). Following incorporation of the glycine residue, the pyridine domain **165** was coupled to the bisthiazole **166** to yield the macrocyclization precursor. Next, treatment with one equivalent of Me_3SnOH resulted in cleavage of both the thiazole-4-carboxylate groups, installed at the 3- and 6-positions of the pyridine ring, to give a 1:1 mixture of monocarboxylic acids. Following separation, the correct regioisomer (with the thiazole-4-carboxylic acid at C-3 of the pyridine ring) was cyclized to give the desired macrocycle **167** in modest yield. Interestingly, the compound with a free thiazole acid attached at C-6 of the pyridine ring did not undergo cyclization, so subsequent macrocyclizations could be carried out on the mixture of acids. With the macrocyclic core **167** in hand, it remained only to elaborate the side chain. Thus, cleavage of the remaining thiazole methyl ester, was



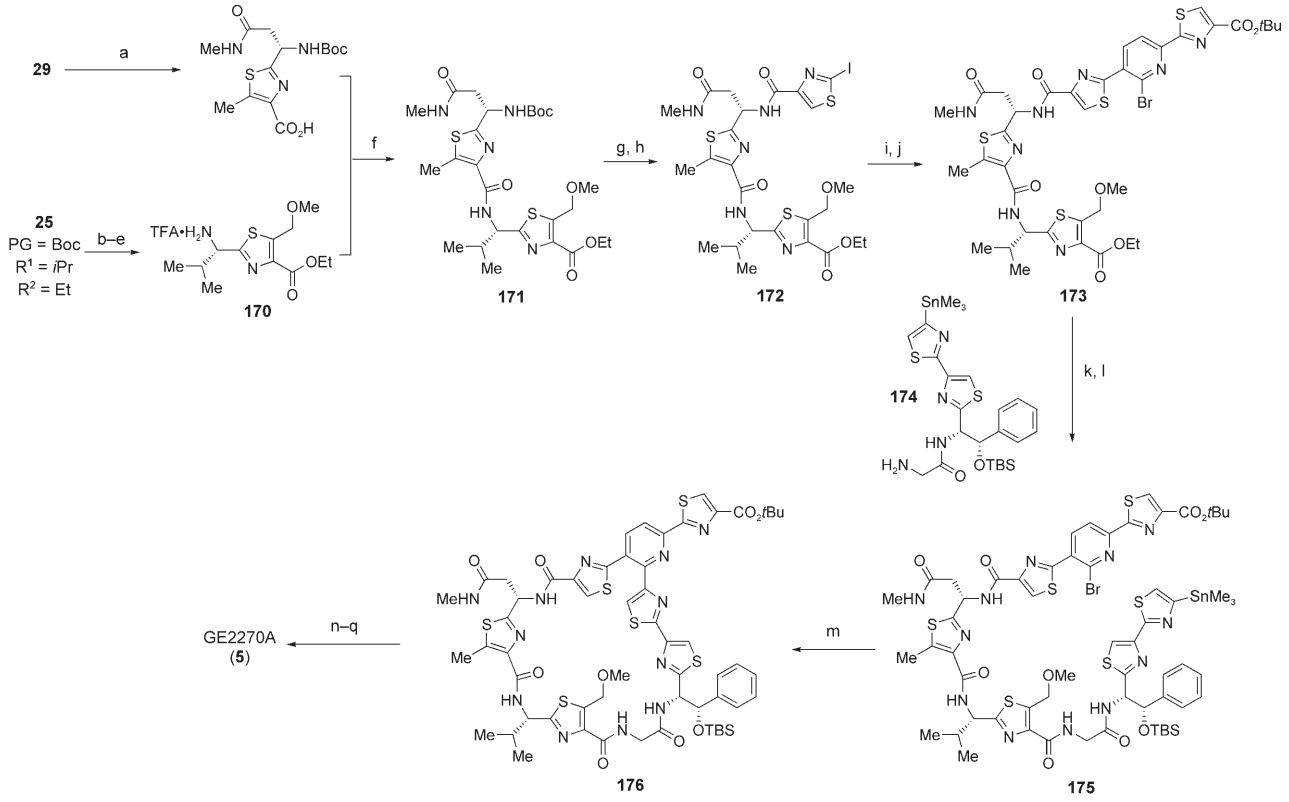
Scheme 37. Synthesis of GE2270A and GE2270T. Reagents and conditions: a) aq TFA; b) **163**, HATU, *i*Pr_2NEt, CH_2Cl_2 (85% over 2 steps); c) TBSCl, imidazole, DMF (82%); d) Lawesson's reagent, benzene, reflux (80%); e) HF·pyridine, THF (92%); f) DAST, CH_2Cl_2, −78°C; g) $BrCCl_3$, DBU, CH_2Cl_2, 0°C (69% over 2 steps); h) TFA, CH_2Cl_2; i) Boc-Gly-OH, HATU, *i*Pr_2NEt, CH_2Cl_2 (90% over 2 steps; j) TFA, CH_2Cl_2; k) HATU, *i*Pr_2NEt, CH_2Cl_2 (66% over 2 steps); l) Me_3SnOH, 1,2-dichloroethane, 60°C (20% plus 20% regioisomer); m) TFA, CH_2Cl_2; n) FDPP, DMF, CH_2Cl_2 (20% over 2 steps); o) Me_3SnOH, 1,2-dichloroethane, 80°C; p) (*S*)-H-Ser-OMe, HATU, *i*Pr_2NEt, CH_2Cl_2 (55% over 2 steps); q) DAST, CH_2Cl_2, −25°C (85%); r) TBAF, THF (80%); s) Me_3SnOH, 1,2-dichloroethane, 80°C; t) (*S*)-H-Pro-NH_2, HATU, *i*Pr_2NEt, CH_2Cl_2 (60% over 2 steps); u) $BrCCl_3$, DBU, CH_2Cl_2, 0°C; v) Me_3SnOH, 1,2-dichloroethane, 80°C; w) (*S*)-H-Pro-NH_2, HATU, *i*Pr_2NEt, CH_2Cl_2 (40% over 3 steps).

followed by coupling to serine methyl ester, closure to the oxazoline ring, and removal of the TBS group to provide **168**. Cleavage of the methyl ester, followed by coupling to prolinamide gave the thiopeptide GE2270A (**5**, Scheme 37). Alternatively, oxazoline **168** was dehydrogenated to the corresponding oxazole by treatment with $BrCCl_3$ and DBU, and this was followed by ester cleavage and coupling to prolinamide to deliver GE2270T (**169**).[117]

Shortly after the completion of the synthesis of GE2270A by Nicolaou et al., Bach and co-workers published their own route to the antibiotic.[118] At the heart of the strategy is the stepwise metalation and palladium-catalyzed cross-coupling of a 2,3,6-trihalopyridine developed earlier by the research group (see Scheme 16). The synthesis started from the thiazoles **25** (PG = Boc, $R^1 = i$Pr, R^2 = Et), obtained by a Hantzsch reaction (Scheme 5), and **29**. The N-protecting group in thiazole **25** was switched to trityl, thereby allowing lithiation at C-5 without concomitant racemization, and introduction of the methoxymethyl group. Thereafter, coupling of thiazole **170** with the acid derived by hydrolysis of ester **29** gave the bisthiazole **171**, which was subsequently deprotected and coupled with 2-iodothiazole-4-carboxylic acid to provide the coupling partner **172**. The first Negishi coupling was carried out between iodide **172** with the zinc reagent derived from 2,6-dibromo-3-iodopyridine, and this was followed by a second Negishi reaction with 4-*tert*-butoxycarbonyl-2-thiazolylzinc bromide that occurred, as expected, selectively at the 6-position of the pyridine ring, and gave the advanced intermediate **173** (Scheme 38). Hydrolysis of the ethyl ester, and coupling to the bisthiazole **174**, prepared from 2,4-dibromothiazole (see Scheme 9), gave **175**, thereby setting the stage for macrocyclization by a daring intramolecular Stille coupling reaction. Pleasingly, this key step proceeded in 75% yield to give macrocycle **176**, and is the first example in the thiopeptide arena of a cyclization being conducted by a method other than amide bond formation. The final steps of the synthesis involved cleavage of the *tert*-butyl ester, introduction of the complete Ser-Pro dipeptide, closure of the oxazoline ring, and final deprotection of the silyl ether to give the natural product GE2270A (**5**, Scheme 38).[118]

4. Concluding Remarks

Heterocyclic peptides, such as the thiopeptide antibiotics, comprise a complex group of naturally occurring macrocyclic compounds. The structures derive in nature from α-amino acids that undergo a series of modifications and heterocyclizations to form cyclic motifs of heteroaromatic rings. The



Scheme 38. Synthesis of GE2270A. Reagents and conditions: a) LiOH, MeOH, 0°C; b) TFA, CH_2Cl_2; c) TrCl, Et_3N, DME (98% over 2 steps); d) LDA, THF, −78°C, then ICH_2OMe (74%); e) TFA, CH_2Cl_2 (ca. 100%); f) EDCI, HOBt, DMF, −10°C→25°C (92% over 2 steps from **29**); g) AcCl, EtOH, 0°C; h) 2-iodothiazole-4-carboxylic acid, EDCI, HOBt, DMF, −10°C→25°C (99% over 2 steps); i) 2,6-dibromo-3-pyridylzinc iodide, $[Pd_2(dba)_3]$, tri(2-furyl)phosphane, THF, DMA, 45°C (87%); j) 4-tert-butoxycarbonyl-2-thiazolylzinc bromide, $[PdCl_2(PPh_3)_2]$, DMA, 45°C (48%); k) LiOH, *tert*-BuOH, THF; l) **174**, DPPA, iPr_2NEt, DMF (87% over 2 steps); m) $[Pd(PPh_3)_4]$, toluene, 85°C (75%); n) TFA, CH_2Cl_2; o) H-Ser-Pro-NH_2, TOTU, iPr_2NEt, DMF (65% over 2 steps); p) DAST, CH_2Cl_2, −78°C; q) TBAF, THF (55% over 2 steps).

resulting natural products often elicit potent antibacterial effects, and this, in combination with their intriguing, multifaceted structures, has served to allure the synthetic chemist.

As we hope to have demonstrated herein, organic chemists have risen to the challenge posed by these remarkable molecules, and whilst not forsaking classical approaches such as the Hantzsch thiazole synthesis, have come up with a raft of innovative routes to the heterocyclic building blocks, including ones inspired by the biosynthetic routes favored by nature. However, developing elegant routes to the building blocks of complex natural products is long way from completing a total synthesis, and the fact that only six thiopeptide antibiotics have succumbed to synthesis is testament of the challenges that they pose. The assembly of building blocks into the final target molecule requires intelligent application of orthogonal protecting groups (and mild methods for their removal) and coupling methodologies, as well as the ability to deal with reactive functionality such as dehydroalanines. We hope that heterocyclic peptides will continue to provide ample opportunity for innovation and invention in organic synthesis, and stimulate organic chemists for years to come.

Abbreviations

Ac	acetyl
AIBN	azobisisobutyronitrile
All	allyl
Alloc	allyloxycarbonyl
Bn	benzyl
Boc	*tert*-butoxycarbonyl
BOP	(benzotriazol-1-yloxy)tris(dimethylamino)-phosphonium hexafluorophosphate
BOPCl	bis(2-oxo-3-oxazolidinyl)phosphinic chloride
Bpop	[1-methyl-1-(4-biphenylyl)]ethoxycarbonyl
CBS	Corey–Bakshi–Shibata reduction
CIP	2-chloro-1,3-dimethylimidazolidium hexafluorophosphate
DAST	diethylaminosulfur trifluoride
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
Deoxo-Fluor	bis(2-methoxyethyl)aminosulfur trifluoride
DiBALH	diisobutylaluminum hydride
DMA	dimethylacetamide
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DPPA	diphenylphosphoryl azide
dppp	1,3-bis(diphenylphosphanyl)propane
EDCI	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
FDPP	pentafluorophenyl diphenylphosphinate
Fm	9-fluorenylmethyl
GTP	guanosine triphosphate
HATU	*O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate
HMTA	hexamethylenetetramine
HOAt	1-hydroxy-7-aza-benzotriazole
HOBt	1-hydroxybenzotriazole
IBX	*o*-iodoxybenzoic acid
LDA	lithium diisopropylamide
*m*CPBA	3-chloroperbenzoic acid
MRSA	methicillin-resistant *Staphyllococcus aureus*
Ms	methanesulfonyl
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
NMM	*N*-methylmorpholine
Nu	nucleophile
Pac	phenacyl
PG	protecting group
PMB	4-methoxybenzyl
p-Tol	4-tolyl
PyBOP	(benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate
salen	*N*,*N*′-bis(salicylidene)ethylenediamine
TBAF	tetra-*n*-butylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
Teoc	2-(trimethylsilyl)ethoxycarbonyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
TMSCN	trimethylsilyl cyanide
Tmse	2-trimethysilylethyl
TOTU	*O*-[(ethoxycarbonyl)cyanomethyleneamino]-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate
Tr	trityl
Ts	4-toluenesulfonyl
Z	benzyloxycarbonyl

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