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Total Synthesis of Thiopeptide Antibiotics GE2270A, GE2270T, and GE2270C1

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Dedicated to Professor Teruaki Mukaiyama on the occasion of his 80th birthday

Abstract: The total syntheses of the thiopeptide antibiotics GE2270A (**7**), GE2270T (**8**), and GE2270C1 (**9**) are described. The original synthetic strategies employed utilized the hetero-Diels–Alder reaction to construct the pyridine core of the target molecules and relied on a macrolactamization process to construct the macrocycle. The hetero-Diels–Alder-based strategy finally evolved allows the introduction of all four thiazole units attached to the pyridine ring and a one-pot sequence for macrocyclization and side-chain extension, culminating in highly convergent and expedient syntheses of these molecules as exemplified by a 24-step synthesis of GE2270C1 (**9**).

Keywords: antibiotics · Diels–Alder reaction · macrocyclization · natural products · total synthesis

Introduction

The outbreak and rampage of infectious diseases continue to pose serious threats to the span and quality of human lives all around the world.[1] Particularly menacing are the increasing occurrences of difficult-to-treat infections due to drug-resistant bacteria. New antibiotics to treat these conditions are, therefore, critically needed. In this context, and owing to their powerful antibacterial properties, thiopeptide antibiotics have received considerable attention.[2] Since the isolation of micrococcin (**1**; probable structure shown in Scheme 1) in 1948,[3a] several other members of this class of natural products, including thiostrepton (**2**),[3b–d] amythiamicin D (**3**),[3e] promothiocin A (**4**),[3f] nocathiacin 1 (**5**),[3g] and Sch 40832 (**6**)[3h] (all shown in Scheme 1) have been reported. The novel structures and important biological activities of these molecules have not escaped the attention of synthetic chemists, who have already achieved elegant total syntheses of some of them.[4]

In 1991, a collection of pyridine-containing thiopeptide antibiotics isolated from the fermentation broth of *Planobispora rosea* ATCC53773 was reported (Scheme 2).[5a] After a detailed spectroscopic analysis, a global structure of the GE2270 factors, as these compounds were named, was put forward[5b] and later revised through extensive degradation studies.[5c,d] Furthermore, the relative and absolute stereochemistry of their hydroxy phenylalanine domain was unambiguously determined by Heckmann and Bach.[5e] Among the 10 structurally related GE2270 factors, GE2270T (with an oxazole-containing side chain) was identified as the most potent against a selected number of bacterial strains, including methicillin- and vancomycin-resistant strains.[6] These antibiotics were found to inhibit bacterial protein synthesis in both Gram-positive and Gram-negative bacteria by acting specifically on the GTP-bound form of Ef-Tu, the elongation factor required for the binding of aminoacyl-tRNA to the ri-

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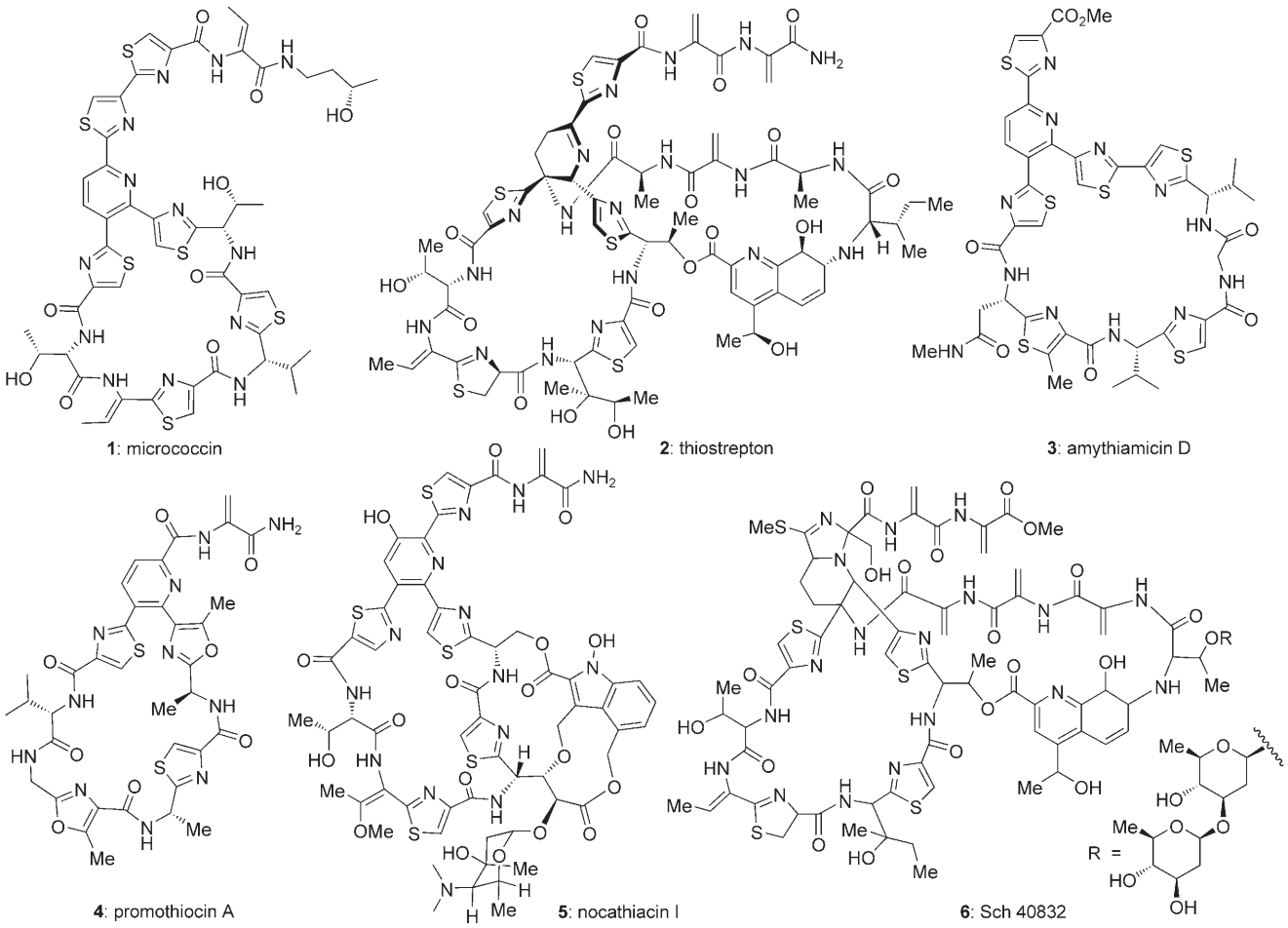


Scheme 1. Representative members of the thiopeptide class of antibiotics.

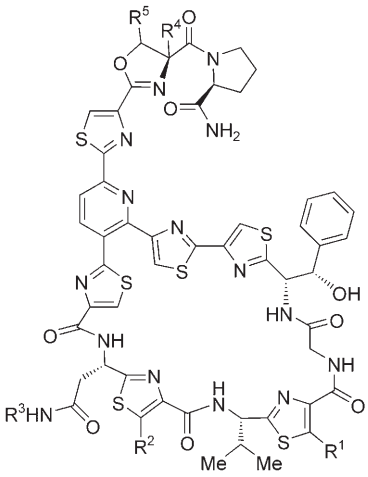
bosomal A site.[7] As this function in eukaryotes is performed by elongation factor EF-1α, this inhibitory mechanism is selective for prokaryotic protein biosynthesis.

Herein, we describe in detail our synthetic studies that culminated in the total synthesis of three members of the GE2270 thiopeptide family (Scheme 2),[8] namely, GE2270A (**7**), GE2270T (**8**), and GE2270C1 (**9**), through strategies that feature applications of complex hetero-Diels–Alder dimerization technologies and regioselective macrocyclizations.

Results and Discussion

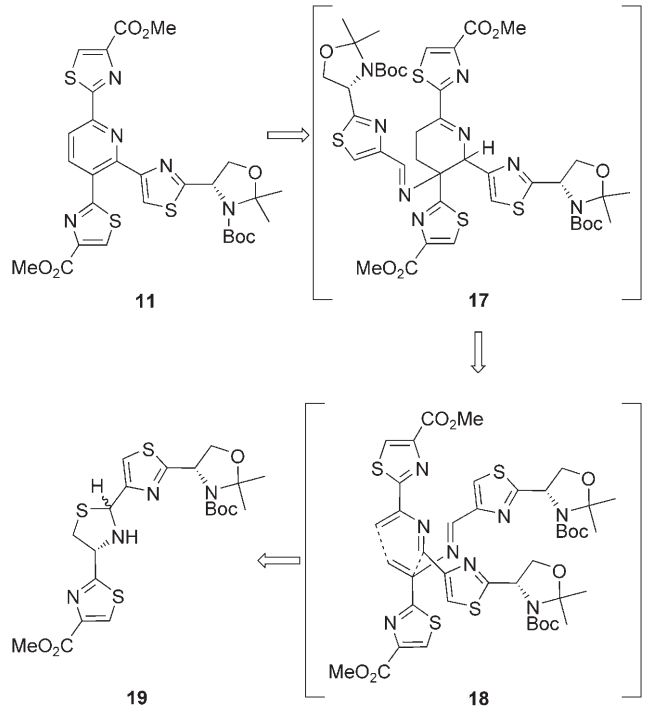
Retrosynthetic Analysis

The modularity of the GE2270 antibiotics (Scheme 2) presents the opportunity for a convergent strategy for their construction and a flexible entry to rationally designed analogues for studies of structure–activity relationships (SARs). As illustrated in Scheme 3, the retrosynthetic disassembly of GE2270A (**7**), GE2270T (**8**), and GE2270C1 (**9**) involves the ruptures of an oxazoline (for GE2270A (**7**) and GE2270C1 (**9**)) or oxazole (for GE2270T (**8**)), a thiazole, and five amide bonds (①–⑤) to lead to building blocks **10**–**16**. The construction of the seven azoles/azolines residing within the target molecules was envisaged through the application of a Gabriel–Robinson[9]-type cyclodehydration of the corresponding thioamide or amide precursors to cast the six thiazoles (upon oxidation of the intermediate thiazoline) and the oxazole (upon oxidation of the intermediate oxazoline)/oxazoline moieties, respectively. The amply demonstrated power of the Diels–Alder reaction in casting six-membered carbo- or heterocyclic systems has had a profound impact on chemical synthesis and the way synthetic chemists think about their science.[10] The application of the hetero-Diels–Alder reaction, in particular, has been useful in the total synthesis of a number of thiopeptide antibiotics, including thiostrepton (**2**).[4c–e] Inspired by biosynthetic considerations,[11] this retrosynthetic analysis as applied to the GE2270 class of antibiotics is shown in Scheme 4, in which the originally derived pyridine fragment **11** (Scheme 3) was traced back to thiazolidinone **19** via heterodiene **18** and its Diels–Alder homodimer **17**. Thus, the central elements of the designed synthetic strategy for the projected total synthesis of the targeted members of the GE2270 family of compounds (**7**–**9**) became the hetero-Diels–Alder dimeriza-

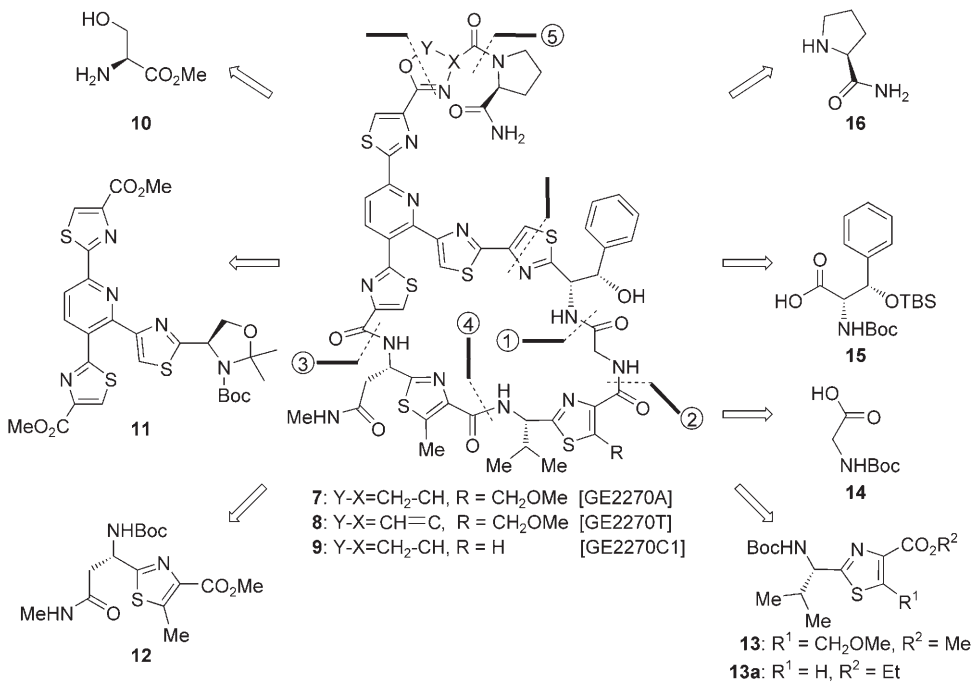


GE2270A(**7**)	: R^1 = CH_2OMe	; R^2 = CH_3	; R^3 = CH_3	; R^4,R^5 = H
GE2270B1	: R^1 = CH_2OMe	; R^2 = CH_3	; R^3 = H	; R^4,R^5 = H
GE2270B2	: R^1 = CH_3	; R^2 = CH_3	; R^3 = CH_3	; R^4,R^5 = H
GE2270C1(**9**)	: R^1 = H	; R^2 = CH_3	; R^3 = CH_3	; R^4,R^5 = H
GE2270C2a	: R^1 = CH_2OMe	; R^2 = CH_2OH	; R^3 = CH_3	; R^4,R^5 = H
GE2270C2b	: R^1 = CH_2OMe	; R^2 = H	; R^3 = CH_3	; R^4,R^5 = H
GE2270D1	: R^1 = H	; R^2 = CH_3	; R^3 = H	; R^4,R^5 = H
GE2270D2	: R^1 = CH_2OH	; R^2 = CH_3	; R^3 = CH_3	; R^4,R^5 = H
GE2270E	: R^1 = CH_2OH	; R^2 = CH_3	; R^3 = H	; R^4,R^5 = H
GE2270T(**8**)	: R^1 = CH_2OMe	; R^2 = CH_3	; R^3 = CH_3	; R^4,R^5 = C=C

Scheme 2. Structures of the GE2270 family of antibiotics.



Scheme 4. Retrosynthetic analysis of trithiazole pyridine fragment **11** through the hetero-Diels–Alder reaction.

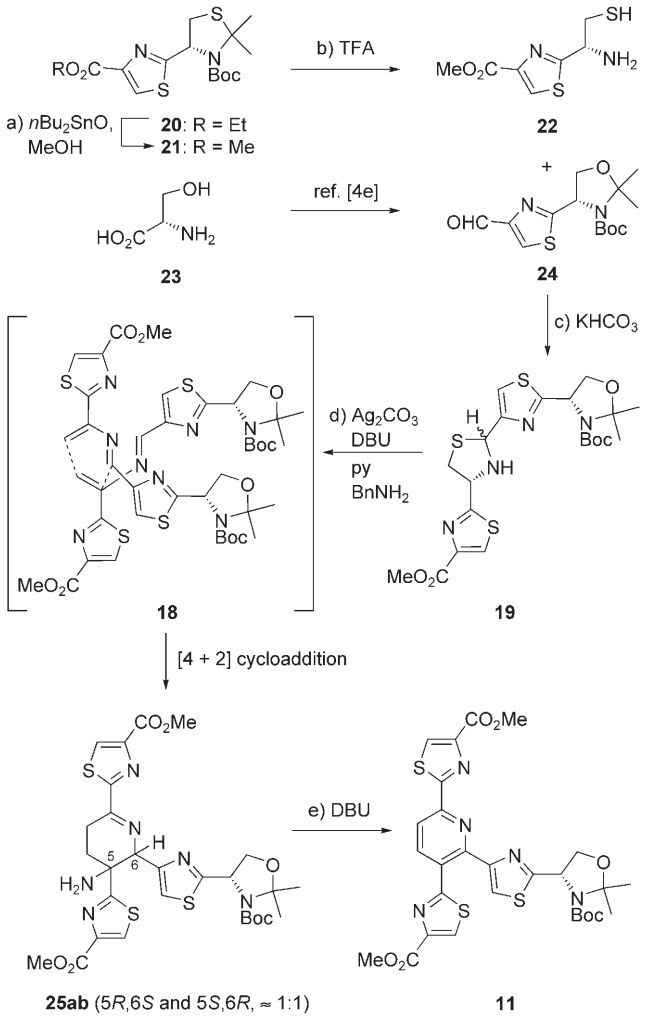


Scheme 3. Retrosynthetic analysis of antibiotics GE2270A (**7**), GE2270T (**8**), and GE2270C1 (**9**), leading to key fragments **10**–**16**.

tion to construct the thiazolyl pyridine domain (Scheme 4) and the search for the most suitable site for the macrocyclization reaction to form the macrocycle of the molecule (Scheme 3). Each of the four amide bonds embedded within the 29-membered macrocycle, designated as ①, ②, ③, and ④, could be constructed either intermolecularly as part of the fragment assembly or intramolecularly as part of the macrocyclization process. As a result of this analysis, therefore, the preparation of trithiazolyl pyridine **11**, trisubstituted thiazole **13**, and hydroxyphenyl alanine **15** became our first synthetic objectives.

Construction of Thiazolyl Pyridine Fragment 11

Scheme 5 summarizes the synthesis of the desired thiazolyl pyridine fragment **11**, starting with the known thiazole ethyl ester derivative **20**.[4e] Thus, transesterification of **20** with nBu$_2$SnO[12] in MeOH resulted in the formation of methyl ester **21** (84% yield), which was subjected to the action of TFA to afford amino thiol **22**. Condensation ($KHCO_3$) of the latter compound with aldehyde **24**, derived from L-serine



Scheme 5. Synthesis of trithiazole pyridine system **11**. Reagents and conditions: a) nBu_2SnO (1.5 equiv), MeOH, reflux, 6 h, 84%; b) TFA/CH_2Cl_2 (1:1), 25 °C, 4 h; then MeOH/H_2O (1:1), 25 °C, concentration in vacuo; c) **22**·TFA (1.0 equiv), **24** (1.0 equiv), $KHCO_3$ (3.0 equiv), MeOH/H_2O (1:1), 25 °C, 16 h, 85% over two steps (≈3:1 mixture of diastereomers); d) Ag_2CO_3 (1.1 equiv), $BnNH_2$ (1.3 equiv), DBU (0.25 equiv), pyridine, −12 °C, 1 h; then H_2O/EtOAc (1:1), 25 °C, 1 h, 64%; e) DBU (5.0 equiv), EtOAc, reflux, 5 h, 50%. Bn = benzyl, Boc = *tert*-butoxycarbonyl, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, py = pyridine, TFA = trifluoroacetic acid.

(**23**) by adaptation of a literature procedure,[4e] then led to thiazolidine **19** in 85% overall yield (≈3:1 mixture of diastereomers). Treatment of **19** with Ag_2CO_3 in the presence of an optimized mixture[4e] of DBU/$BnNH_2$ (1:4) in pyridine at −12 °C led to the generation of the transient heterodiene **18**, which underwent spontaneous dimerization through the anticipated Diels–Alder reaction to furnish dehydropiperidine system **25ab** as an inconsequential mixture of diastereomers (5*R*,6*S* and 5*S*,6*R*) in 64% yield.[13] The completion of the pyridine core required the extrusion of ammonia and oxidative aromatization, a process that was accomplished by heating **25ab** at reflux with excess DBU in EtOAc (50% yield).

Construction of Thiazole Fragments 13 and 39

The construction of thiazoles **13** and **39** was carried out as shown in Scheme 6. Thus, for thiazole **13**, Boc-glycine methyl ester (**26**) was treated with LDA followed by addition of acid chloride **27** to afford ketone **28** in 59% yield. $LiBH_4$ reduction of the latter compound followed by exposure of the resulting alcohol derivative **29** to TFA furnished amino alcohol **30**. The latter compound was coupled with Boc-L-valine under the influence of HATU[14] to afford dipeptide **31**, silylation (TBSCl, imidazole) of which resulted in the formation of compound **32** in 55% overall yield over the four steps. In preparation for the ring closure to form the required thiazole moiety, amide **32** was treated with the Lawesson reagent,[15] which led, after desilylation (TBAF), to hydroxy thioamide **34** via **33** (61% overall yield over the two steps). The temporary masking of the hydroxy group was found to be essential for the success of the sulfurization reaction. Cyclization of **34** in the presence of DAST[16] proceeded smoothly to afford thiazoline **35**, whose conversion into thiazole **13** was accomplished through the action of $BrCCl_3$ and DBU[17] (84% overall yield over the two steps). Intermediates **29**–**35** were inconsequential mixtures of diastereomers (≈1:1) that converged into a single product in the final aromatization step.

The rather lengthy synthetic sequence described above for the preparation of thiazole **13** prompted us to develop an alternative and more efficient approach to this ring system based on the carbene insertion chemistry pioneered by Moody and co-workers[18] (Scheme 6B). Thus, upon slow addition of a solution of diazocarbonyl compound **37** in chloroform (prepared in two steps from ethyl 4-chloroacetoacetate) to a solution of Boc-L-valinamide (**36**) and $Rh(OAc)_2$ (cat.) in chloroform at reflux, smooth formation of β-ketoamide **38** was observed in 54% yield (≈1:1 mixture of diastereomers). The latter compound was converted into the corresponding thioamide by the action of the Lawesson reagent, an operation that was followed by cyclodehydration in situ to deliver conveniently the trisubstituted thiazole **39** in 58% yield.

Synthesis of Hydroxy Phenylalanine Derivative 15

The synthesis of phenylalanine derivative **15** was initially accomplished through an adaptation of a literature procedure[19] (Scheme 7A). Thus, L-serine-derived hydroxy carbamate **40** was converted into its TBS ether **41** (TBSCl, imidazole, 85% yield), from which the Cbz group was removed (H_2, 10% Pd/C) and replaced with a Boc group (Boc_2O, 90% overall yield) to afford intermediate **42**. The orthoester group of the latter compound was then cleaved by sequential treatment with PPTS and LiOH to afford the desired hydroxy phenylalanine derivative **15** in 95% overall yield.

A more expedient and scalable sequence to hydroxy phenylalanine derivative **15** was then developed, starting with ethyl cinnamate (**43**) and employing a Sharpless asymmetric dihydroxylation[20] reaction (Scheme 7B). Treatment of **43**

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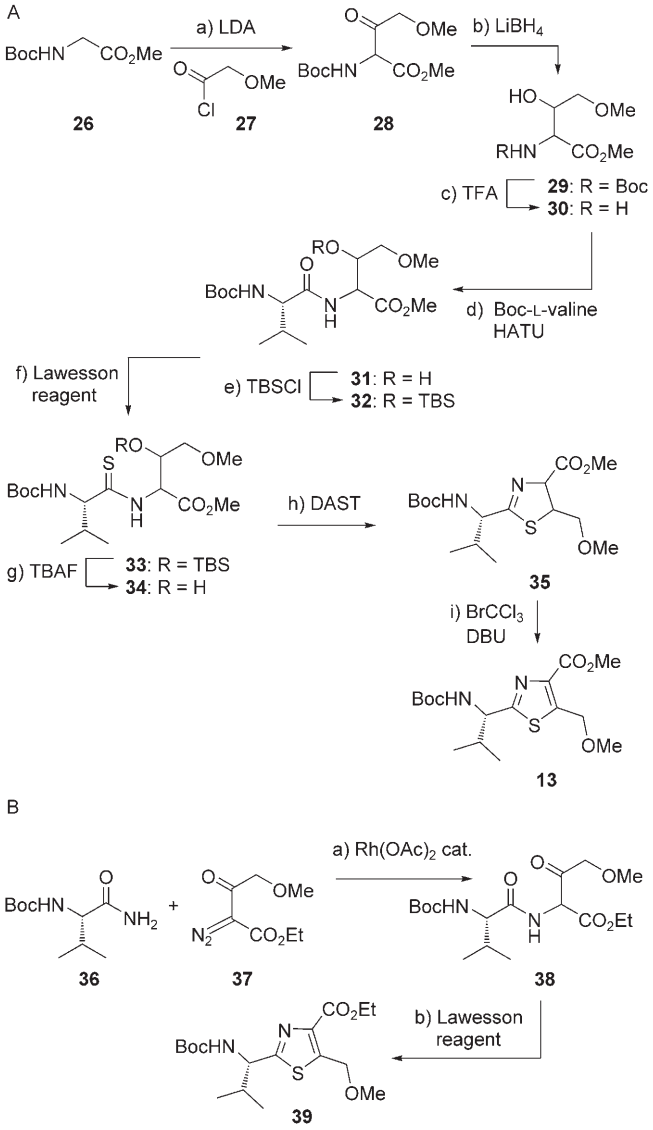
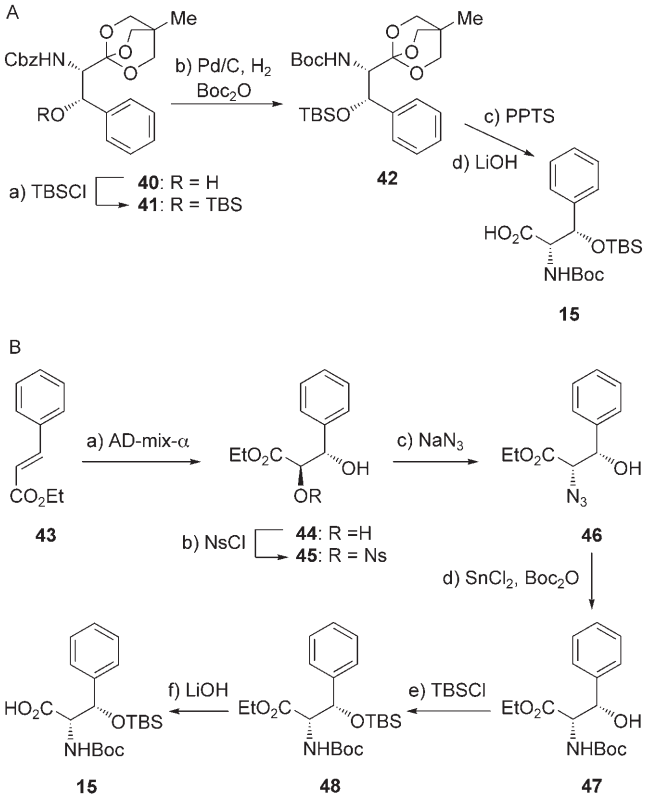


Scheme 6. Synthesis of trisubstituted thiazole fragments **13** and **39**. Reagents and conditions: A: a) LDA (2.5 equiv), methoxyacetyl chloride (1.2 equiv), THF, −78→25 °C, 16 h, 59 %; b) $LiBH_4$ (1.0 equiv), THF/CH_2Cl_2/MeOH (4:2:1), −78 °C, 5 min; c) TFA/CH_2Cl_2 (1:4), 0 °C, 1 h; d) Boc-L-valine (1.1 equiv), HATU (1.5 equiv), iPr_2NEt (3.0 equiv), CH_2Cl_2, 0→25 °C, 3 h, 71 % over three steps (≈1:1 mixture of diastereomers); e) TBSCl (1.3 equiv), imidazole (1.6 equiv), DMF, 25 °C, 16 h, 77 % (≈1:1 mixture of diastereomers); f) Lawesson reagent (1.5 equiv), THF, reflux, 16 h, 66 % (≈1:1 mixture of diastereomers); g) TBAF (1.0 M in THF, 1.5 equiv), THF, 25 °C, 5 h, 93 % (≈1:1 mixture of diastereomers); h) DAST (1.2 equiv), CH_2Cl_2, −78 °C, 30 min; i) $BrCCl_3$ (1.1 equiv), DBU (2.2 equiv), CH_2Cl_2, 0 °C, 1 h, 84 % over two steps. B: a) $Rh(OAc)_2$ (0.02 equiv), **37** (1.4 equiv), $CHCl_3$, reflux, 24 h, 54 % (≈1:1 mixture of diastereomers); b) Lawesson reagent (2.0 equiv), THF, reflux, 16 h, 58 %. DAST = *N,N*-diethylaminosulfur trifluoride, DMF = *N,N*-dimethylformamide, HATU = *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate, LDA = lithium diisopropylamide, TBAF = tetra-*n*-butylammonium fluoride, TBS = *tert*-butyldimethylsilyl.

with AD-mix-α gave diol **44** in 87 % yield and with >99 % *ee*. Nosylation (NsCl, Et_3N, 84 % yield) of the latter compound followed by treatment with NaN_3 furnished hydroxy azide **46** in 76 % yield via nosylate **45**. $SnCl_2$-mediated



Scheme 7. Two alternative syntheses of amino acid derivative **15**. Reagents and conditions: A: a) TBSCl (2.6 equiv), imidazole (3.9 equiv), DMF, 25 °C, 16 h, 85 %; b) Pd/C (10 % *w/w*, 0.03 equiv), Boc_2O (1.5 equiv), MeOH, H_2 (balloon), 25 °C, 6 h, 90 %; c) PPTS (0.1 equiv), DME/H_2O (5:1), 25 °C, 30 min; d) LiOH·H_2O (1.6 equiv), DME/H_2O (1:1), 25 °C, 72 h, 95 % over two steps. B: a) AD-mix-α (1.4 g mmol^{-1}), $MeSO_2NH_2$ (1.0 equiv), *t*BuOH/H_2O (1:1), 0→25 °C, 16 h, 87 % (>99 % *ee*); b) NsCl (1.0 equiv), Et_3N (1.5 equiv), CH_2Cl_2, 0 °C, 6 h, 84 %; c) NaN_3 (6.0 equiv), DMF, 42 °C, 48 h, 76 %; d) $SnCl_2$·$2H_2O$ (5.0 equiv), H_2O/dioxane (4:1), 0→25 °C, 5 h; then Boc_2O (1.5 equiv), 0→25 °C, 18 h, 97 %; e) TBSCl (2.0 equiv), imidazole (3.0 equiv), DMF, 25 °C, 18 h, 90 %; f) LiOH (1.4 equiv), DME/H_2O (1:1), 25 °C, 72 h, 97 %. AD = asymmetric dihydroxylation, Cbz = benzyloxycarbonyl, DME = 1,2-dimethoxyethane, Ns = *para*-nitrobenzenesulfonyl, PPTS = pyridinium *para*-toluenesulfonate.

reduction of the azide group in **46** followed by trapping of the resulting amine in situ with Boc_2O furnished hydroxy Boc derivative **47** in 97 % overall yield. Finally, silylation of **47** (TBSCl, imidazole, 90 % yield) followed by ester hydrolysis (LiOH, 97 % yield) gave the targeted phenylalanine derivative **15**.

Fragment Assembly and Macrolactamization Studies

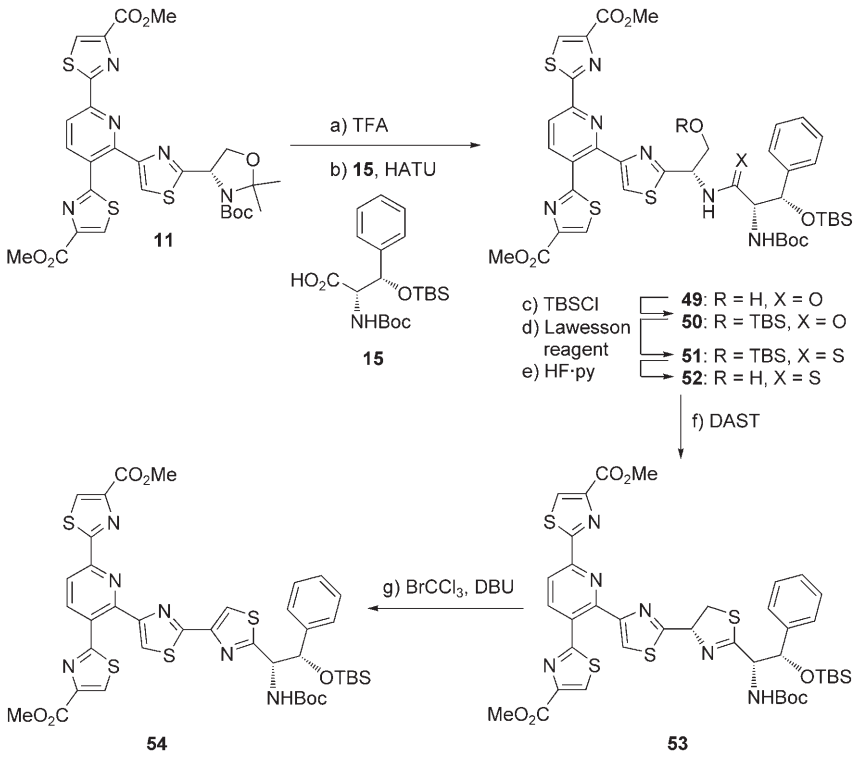
With all the required fragments in hand, our next objectives were their assembly and the investigation of the various options for macrolactam formation. To this end, we first elaborated trithiazolyl pyridine fragment **11** to the more advanced intermediate **49** through attachment of the phenylalanine fragment **15** (Scheme 8). Thus, removal of the Boc and acetonide groups from **11** through the action of TFA followed by peptide coupling of the resulting amino alcohol with car-

boxylic acid **15** in the presence of HATU and iPr$_2$NEt led to amide **49** (85% yield over the two steps). The conversion of **49** into the required hydroxy thioamide **52** was then carried out by a three-step procedure (1) TBSCl, imidazole, 82% yield; 2) Lawesson reagent, 80% yield; 3) HF·py, 92% yield) via the intermediates **50** and **51**. The fourth thiazole unit was then forged onto the growing molecule by treatment of **52** with DAST to form the intermediate thiazoline **53**, which was oxidized ($BrCCl_3$, DBU) to the desired fragment **54** in 69% overall yield.

In preparation for the intended macrolactamization study, dipeptides **58** and **60** and tripeptide **62** were prepared from building blocks **12**[21] and **13** (Scheme 9). Thus, HATU-mediated peptide coupling of carboxylic acid **55** (obtained from methyl ester **12** by LiOH hydrolysis) with amine **56** (obtained from Boc carbamate **13** by exposure to TFA) proceeded smoothly to afford bis-thiazole **57** in 80% yield. The conversion of **57** into the allyl Boc derivative **59** required saponification (LiOH) followed by reaction of the resulting carboxylic acid **58** with $KHCO_3$ and allyl bromide (70% overall yield). The tripeptide **61** was then accessed from **58** through coupling with glycine allyl ester in the presence of HATU and iPr$_2$NEt in 87% yield.

Macrocyclization at site ① (Scheme 3) was the first option to be examined (Scheme 10). The first challenge faced in this approach was the differentiation of the two methyl ester termini within the advanced intermediate **54** that were to serve as handles to extend the chains of the molecule. Given their similarities, the best that could be achieved with these groups was partial hydrolysis with Me_3SnOH[22] to afford a mixture (≈1:1, inseparable) of monoacids **66** and **67** (71% combined yield) together with the recovered starting material **54** (25%). Coupling of **66**+**67** with tripeptide amine **62** (prepared by TFA-mediated Boc removal from **61**; Scheme 9) was performed under HATU/iPr$_2$NEt conditions to furnish a mixture of peptides **68** and **69** (≈1:1) in 60% yield. With all the essential elements of the GE2270A (**7**)/GE2270T (**8**) skeleton, these precursors were then subjected as a mixture to the removal of first the allyl group from the carboxylate end ([Pd(PPh$_3$)$_4$] cat.) and then the Boc group from the amine terminal (TFA) to afford the two *seco*-amino acids required for the macrolactamization reaction. The expectation was that perhaps the *seco*-amino acid corresponding to the naturally occurring macrolactam would cyclize in preference to the other, thereby leading to the selectivity and separation that we were seeking. Much to our disappointment, however, neither of the two amino acid peptide regioisomers closed upon exposure to FDPP[23] and iPr$_2$NEt under conditions of high dilution (CH_2Cl_2/DMF = 4:1, 0.0003 M) to form the expected macrolactams **70** and **71**. We can only speculate that the bulky TBS group close to the amine group prevented the two ends from coming together in a productive way.

We next proceeded to investigate the feasibility of macrolactam formation by ring closure at site ② (Scheme 3), as shown in Scheme 11. In preparation for this ring closure, intermediate **54** was further extended at its amine terminus by first removing its Boc group (TFA) to reveal the free amine **72**, and then coupling with Boc-glycine under the HATU/iPr$_2$NEt conditions to give diester **73** in 90% overall yield over the two steps. In a similar manner to the controlled hydrolysis performed on diester **54** described above (Scheme 10), Me_3SnOH-induced saponification of **73** afforded an inseparable mixture of monoacids **74** and **75** (≈1:1) in 45% combined yield, plus 50% recovered starting material. Final extension of the growing assemblies **74**+**75** required attachment at the bis-thiazole subunit, a task that was readily accomplished by a HATU/



Scheme 8. Synthesis of tetrathiazole pyridine subunit **54**. Reagents and conditions: a) TFA/H_2O (3:1), 25 °C, 1 h; b) **15** (1.1 equiv), HATU (1.3 equiv), iPr$_2$NEt (3.0 equiv), CH_2Cl_2, 25 °C, 3 h, 85% over two steps; c) TBSCl (2.0 equiv), imidazole (3.0 equiv), DMF, 25 °C, 16 h, 82%; d) Lawesson reagent (1.5 equiv), benzene, reflux, 16 h, 80%; e) HF·pyridine (10.0 equiv), pyridine/THF (1:8), 25 °C, 2 h, 92%; f) DAST (1.4 equiv), CH_2Cl_2, −78 °C, 30 min; g) $BrCCl_3$ (1.4 equiv), DBU (2.7 equiv), CH_2Cl_2, 0 °C, 1 h, 69% over two steps.

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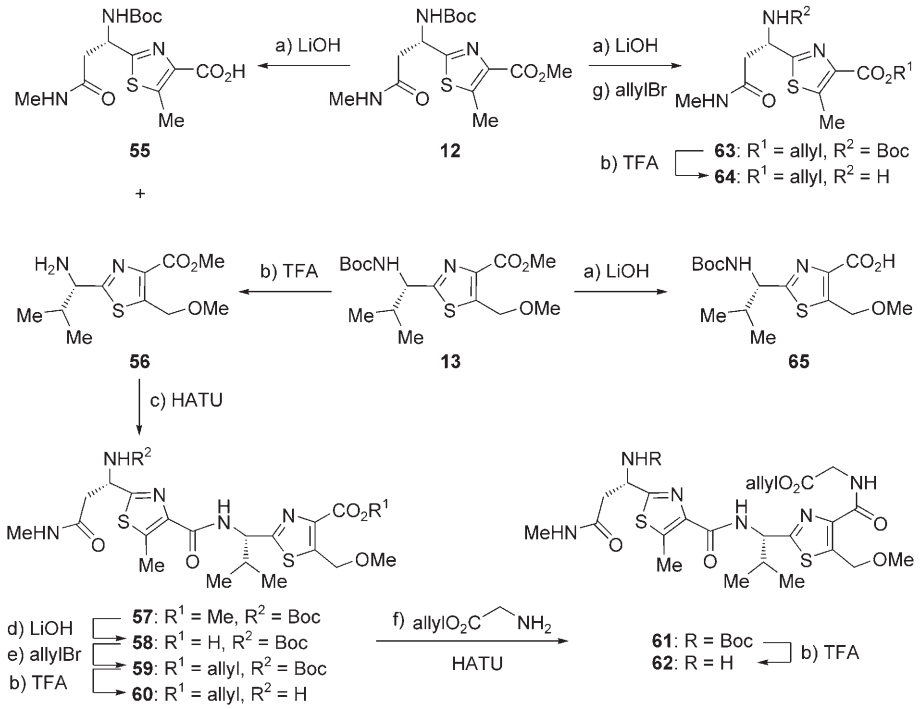


Scheme 9. Syntheses of thiazoles **64** and **65** and bis-thiazole fragments **58**, **60**, and **62**. Reagents and conditions: a) LiOH (3.5 equiv), MeOH/H_2O (4:1), 25 °C, 3 h; b) TFA/CH_2Cl_2 (1:4), 25 °C, 2 h; c) HATU (1.2 equiv), iPr$_2$NEt (2.0 equiv), CH_2Cl_2, 25 °C, 16 h, 80% over two steps from **55**; d) LiOH (3.5 equiv), MeOH/H_2O (6:1), 25 °C, 16 h; e) allyl bromide (2.0 equiv), $KHCO_3$ (3.0 equiv), DMF, 25 °C, 3 h, 70% over two steps; f) glycine allyl ester (1.1 equiv), HATU (1.5 equiv), iPr$_2$NEt (5.7 equiv), CH_2Cl_2, 25 °C, 12 h, 87%; g) allyl bromide (2.0 equiv), $KHCO_3$ (3.0 equiv), DMF, 25 °C, 3 h, 75% over two steps from **12**.

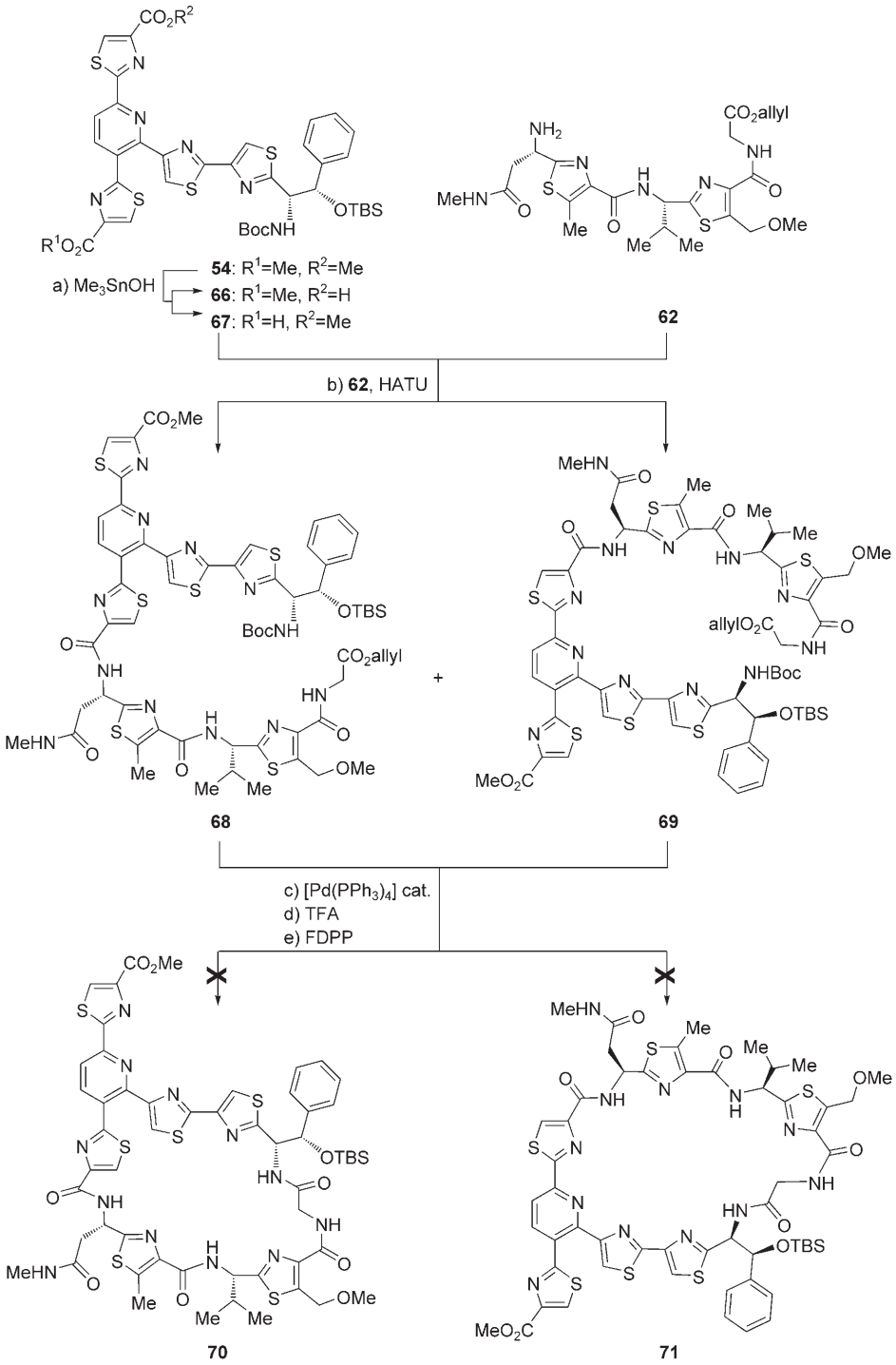
iPr$_2$NEt-facilitated coupling with amino bis-thiazole **60** (obtained from derivative **59** by TFA-induced Boc cleavage; Scheme 9) to afford a mixture of tetrapeptides **76** and **77** in 70% combined yield. At this juncture and just like before, we opted to proceed with the mixture to the macrolactamization stage in the hope that preferential cyclization would occur, in which case we expected to isolate the desired macrocycle for the final drive toward the targeted natural products. Gratifyingly, sequential deprotection of the carboxylic acid ([Pd(PPh$_3$)$_4$] cat.) and amine (TFA) groups followed by exposure of the resulting mixture of amino acid chains to FDPP and iPr$_2$NEt in CH_2Cl_2/DMF (4:1, 0.0003 M) furnished a single macrocycle **70** in 25% yield over the three steps from **76**+**77**. The observed similarities of the ^{1}H NMR spectrum of synthetic **70** with that of the degradatively derived material[5d] lacking the TBS group suggested that we, indeed, had arrived at the correct regioisomeric lactam through the above reaction, which apparently left behind the undesired amino acid (whose final fate was not determined). The fact that we obtained the desired compound was confirmed by desilylation of **70** to **78** (TBAF, 78% yield), whose ^{1}H NMR spectral data were consistent with those reported for the degradation product, and thence by its conversion into the natural products GE2270 A (**7**) and GE2270T (**8**), as will be discussed below.

Continuing our macrocyclization studies, we then turned our attention to the ring closure at site ③ (Scheme 3), as illustrated in Scheme 12. Thus, dipeptide **73** was deprotected (TFA) to afford the amine **79**, which was coupled with bis-thiazole carboxylic acid **58** (derived from methyl ester **57**; Scheme 9) in the presence of HATU and iPr$_2$NEt to furnish methyl ester Boc advanced intermediate **80** in 66% overall yield over the two steps. The partial hydrolysis of the latter compound with Me$_3$SnOH gave, as before, the two regioisomeric carboxylic acids **81** and **82** as a mixture (≈1:1, 40% yield, plus 50% recovered starting material), which, after chromatographic separation (silica, EtOAc/MeOH = 1:1) from the remaining starting material, was treated with TFA to liberate the amine group. The resulting mixture of amino acids was then subjected to high-dilution macrolactamization under the usual conditions (FDPP, iPr$_2$NEt, CH_2Cl_2/DMF = 4:1, 0.0003 M). Again, we were pleased to observe the formation of a single macrolactam **70**, albeit in lower yield (20% from **81**+**82**) but identical to the one obtained from cyclization at site ② as described above (Scheme 11).

The macrocyclization studies were concluded with ring closure at site ④ (Scheme 3), as summarized in Scheme 13. Thus, coupling of amine **79** (Scheme 12) with carboxylic acid **65** (derived from thiazole **13**; Scheme 9) under the HATU conditions gave, in 70% overall yield, dipeptide **83**, which was partially saponified (Me$_3$SnOH) to afford a mixture of monoacids **84** and **85** (56% yield) together with 23% recovered starting material. Coupling of **84**+**85** with thiazole amine **64** (derived from thiazole **12**; Scheme 9) in the presence of HATU resulted in the formation of regioisomeric peptides **86** and **87** in 68% combined yield. This mixture **86**+**87** was then subjected to the macrocyclization conditions (FDPP, iPr$_2$NEt, CH_2Cl_2/DMF = 4:1, 0.0003 M) after deprotection of the carboxylic and amine termini (1) [Pd(PPh$_3$)$_4$] cat.; 2) TFA) to afford macrolactam **70** (15% yield) as a single isomer, which, again, proved identical to the previously obtained macrocycle.

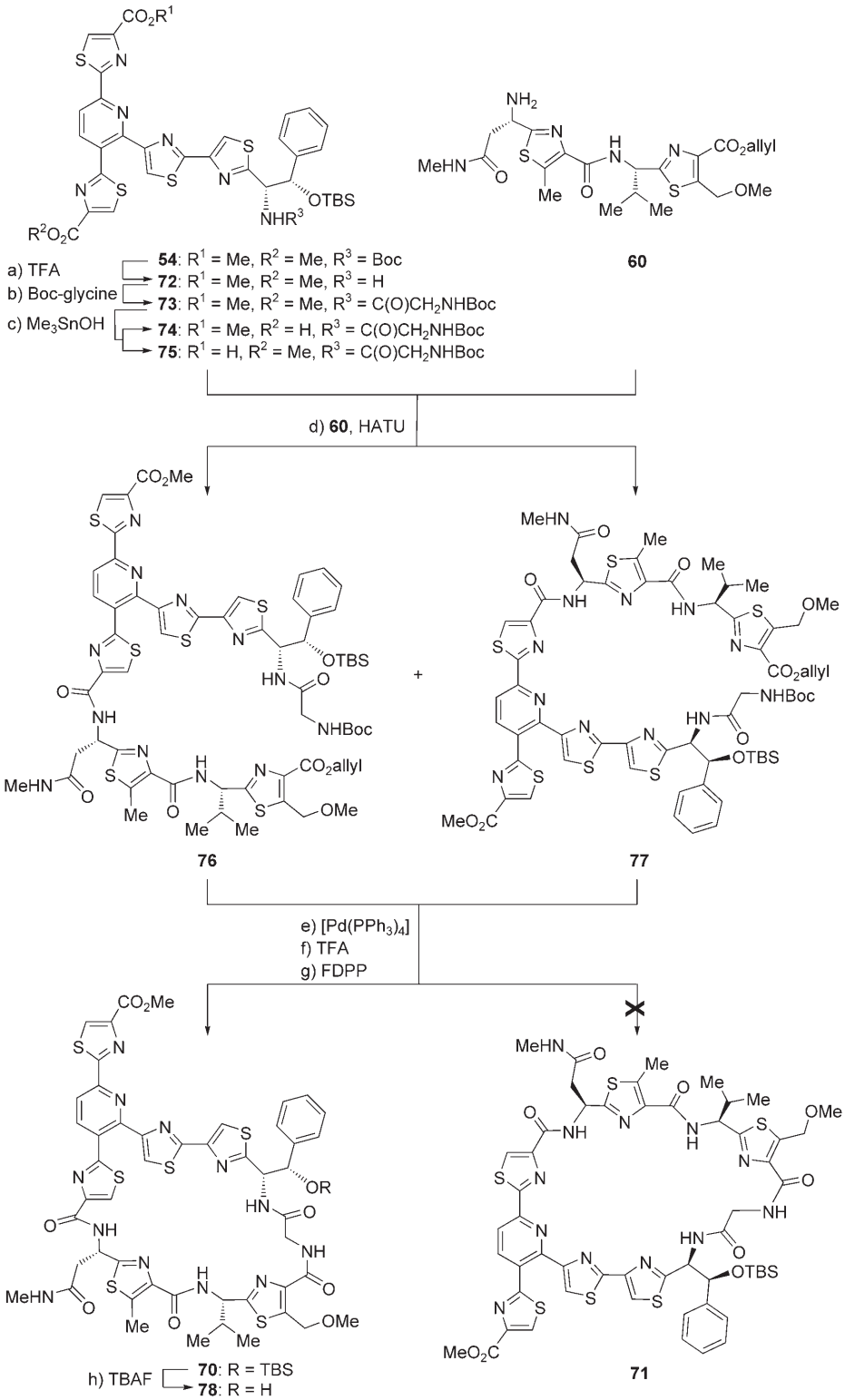
Completion of the Total Synthesis of GE2270A and GE2270T

The successful construction of macrocyclic compound **70** set the stage for the total synthesis of both GE2270A (**7**) and

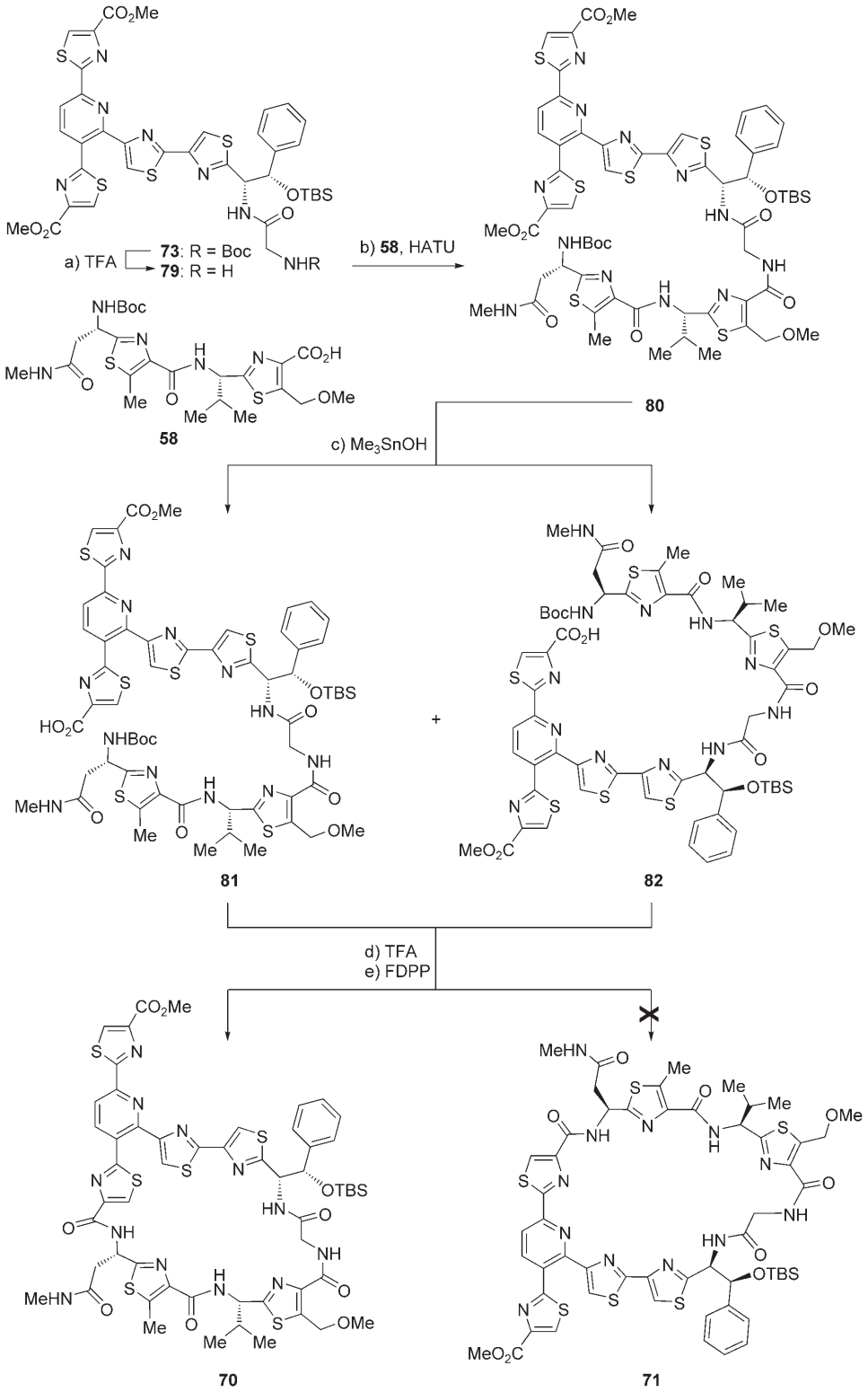


Scheme 10. Attempted construction of macrocycle **70** (ring-closure mode ①, Scheme 3). Reagents and conditions: a) Me_3SnOH (1.0 equiv), 1,2-dichloroethane, 60 °C, 16 h, **66**+**67** (71%) plus **54** (25%); b) **62** (1.1 equiv), HATU (3.6 equiv), iPr_2NEt (10.0 equiv), CH_2Cl_2, 25 °C, 16 h, 60%; c) $[Pd(PPh_3)_4]$ (0.2 equiv), NMA (2.0 equiv), THF, 25 °C, 1 h; d) TFA/CH_2Cl_2 (1:4), 25 °C, 1 h; e) FDPP (5.0 equiv), iPr_2NEt (10.0 equiv), CH_2Cl_2/DMF (4:1) (0.0003 M), 25 °C, 24 h. FDPP = pentafluorophenyl diphenylphosphinate, NMA = *N*-methylaniline.

GE2270T (**8**). Scheme 14 depicts the chemistry that led successfully to these targets through common intermediate **90**. Thus, saponification of the methyl ester group in **70** with Me_3SnOH gave the corresponding carboxylic acid, which was coupled with L-serine methyl ester under the influence of HATU and iPr_2NEt to afford peptide **88** in 70% overall yield over the two steps. Ring closure to the required oxazoline intermediate was then accomplished by reaction of **88** with DAST, a process that proceeded smoothly to furnish **89** in 80% yield. Exposure of the latter compound to TBAF



Scheme 11. Construction of macrocycle **70** (ring-closure mode ②, Scheme 3). Reagents and conditions: a) TFA/CH_2Cl_2 (1:4), 25 °C, 1 h; b) Boc-glycine (1.4 equiv), HATU (1.3 equiv), *i*Pr_2NEt (3.0 equiv), CH_2Cl_2, 25 °C, 24 h, 90 % over two steps; c) Me_3SnOH (1.0 equiv), 1,2-dichloroethane, 60 °C, 16 h, **74**+**75** (45 %) plus **73** (50 %); d) **60** (1.5 equiv), HATU (2.0 equiv), *i*Pr_2NEt (3.0 equiv), CH_2Cl_2, 25 °C, 16 h, 70 %; e) [$Pd(PPh_3)_4$] (0.2 equiv), NMA (2.0 equiv), THF, 25 °C, 1 h; f) TFA/CH_2Cl_2 (1:4), 25 °C, 1 h; g) FDPP (5.0 equiv), *i*Pr_2NEt (10.0 equiv), CH_2Cl_2/DMF (4:1) (0.0003 M), 25 °C, 24 h, 25 % over three steps; h) TBAF (1.0 M in THF, 1.3 equiv), THF, 25 °C, 2 h, 78 %.



Scheme 12. Construction of macrocycle **70** (ring-closure mode ③, Scheme 3). Reagents and conditions: a) TFA/CH_2Cl_2 (1:4), 25 °C, 1 h; b) **58** (1.3 equiv), HATU (2.0 equiv), *i*Pr_2NEt (3.0 equiv), CH_2Cl_2, 25 °C, 24 h, 66% over two steps; c) Me_3SnOH (1.0 equiv), 1,2-dichloroethane, 60 °C, 16 h, **81**+**82** (40%) plus **80** (50%); d) TFA/CH_2Cl_2 (1:4), 25 °C, 1 h; e) FDPP (2.5 equiv), *i*Pr_2NEt (5.0 equiv), DMF/CH_2Cl_2 (1:4) (0.0003 M), 25 °C, 24 h, 20% over two steps.

gave, through desilylation, hydroxy compound **90** in 80% yield. For the synthesis of GE2270A (**7**), the latter intermediate was subjected to saponification (Me_3SnOH) and coupling with L-prolinamide (**16**) in the presence of HATU and *i*Pr_2NEt to lead to synthetic GE2270A (**7**). Synthetic **7** exhibited identical physical properties (^{1}H and ^{13}C NMR

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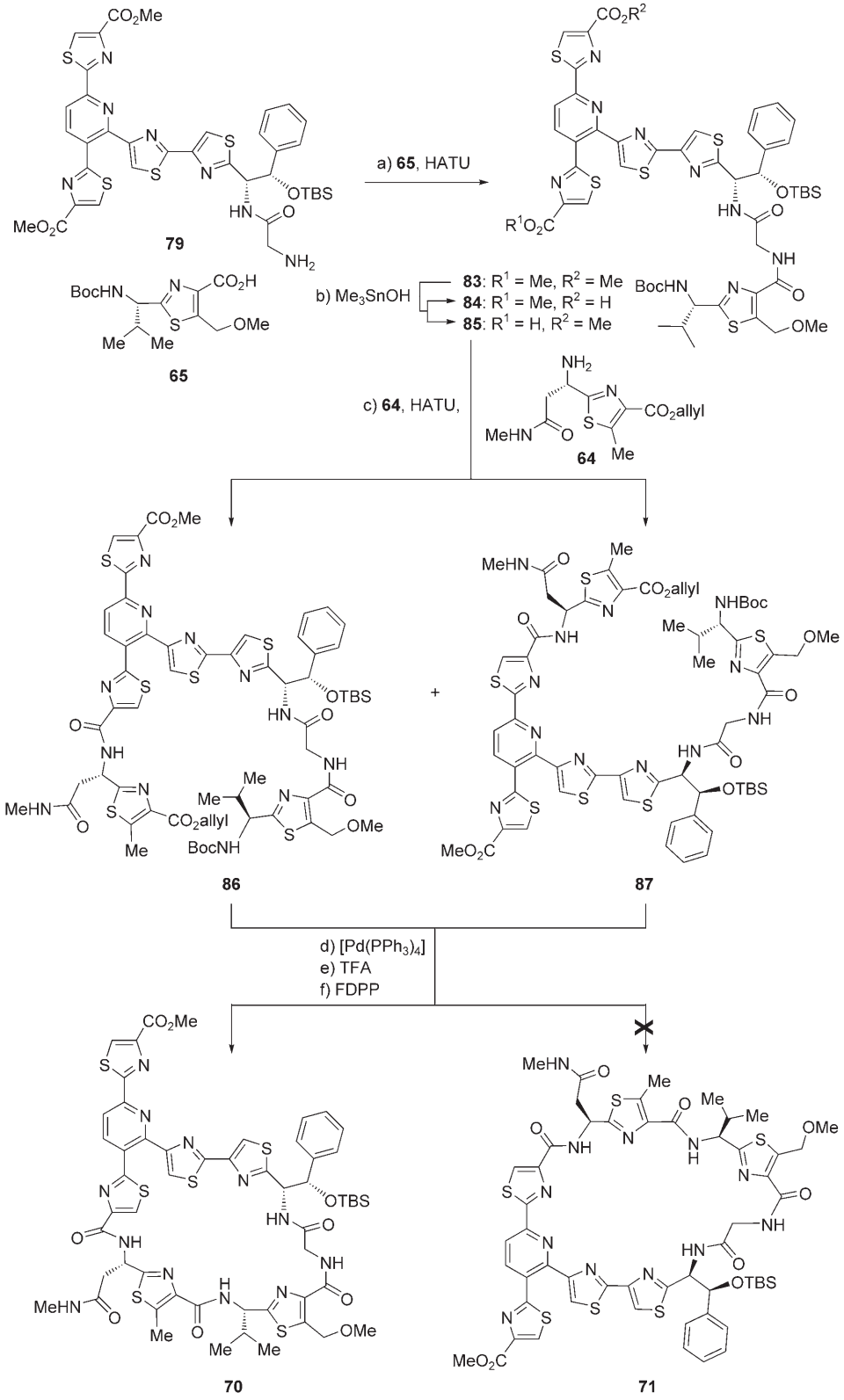
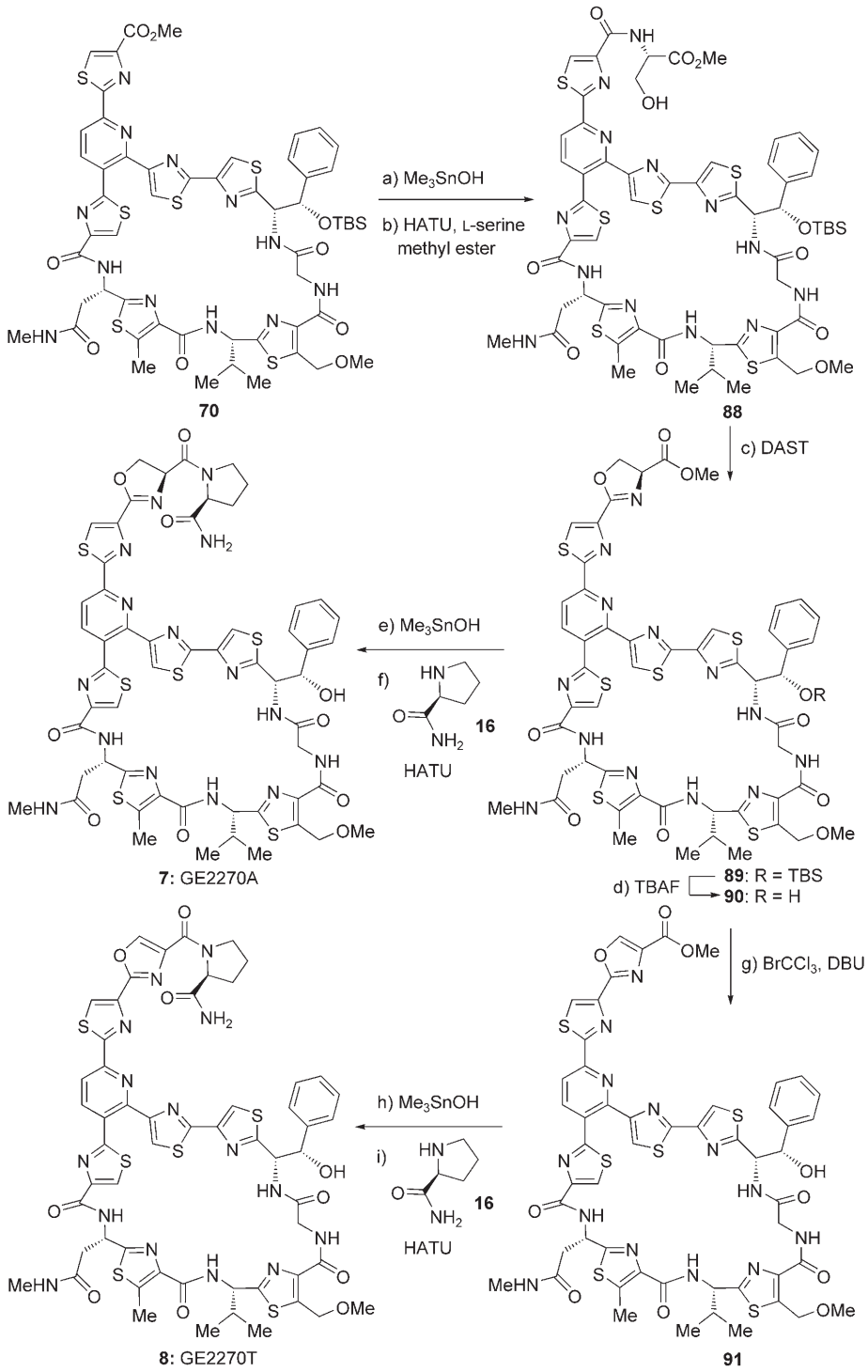


Scheme 13. Construction of macrocycle **70** (ring-closure mode ④, Scheme 3). Reagents and conditions: a) **65** (1.6 equiv), HATU (3.0 equiv), *i*Pr_2NEt (6.3 equiv), CH_2Cl_2, 25 °C, 16 h, 70 % over two steps from **73**; b) Me_3SnOH (1.0 equiv), 1,2-dichloroethane, 60 °C, 16 h, **84**+**85** (56 %) plus **83** (23 %); c) **64** (2.3 equiv), HATU (4.0 equiv), *i*Pr_2NEt (8.5 equiv), CH_2Cl_2, 25 °C, 16 h, 68 %; d) [$Pd(PPh_3)_4$] (0.2 equiv), NMA (2.0 equiv), THF, 25 °C, 1 h; e) TFA/CH_2Cl_2 (1:4), 25 °C, 1 h; f) FDPP (5.0 equiv), *i*Pr_2NEt (10.0 equiv), CH_2Cl_2/DMF (4:1) (0.0003 M), 25 °C, 24 h, 15 % over three steps.



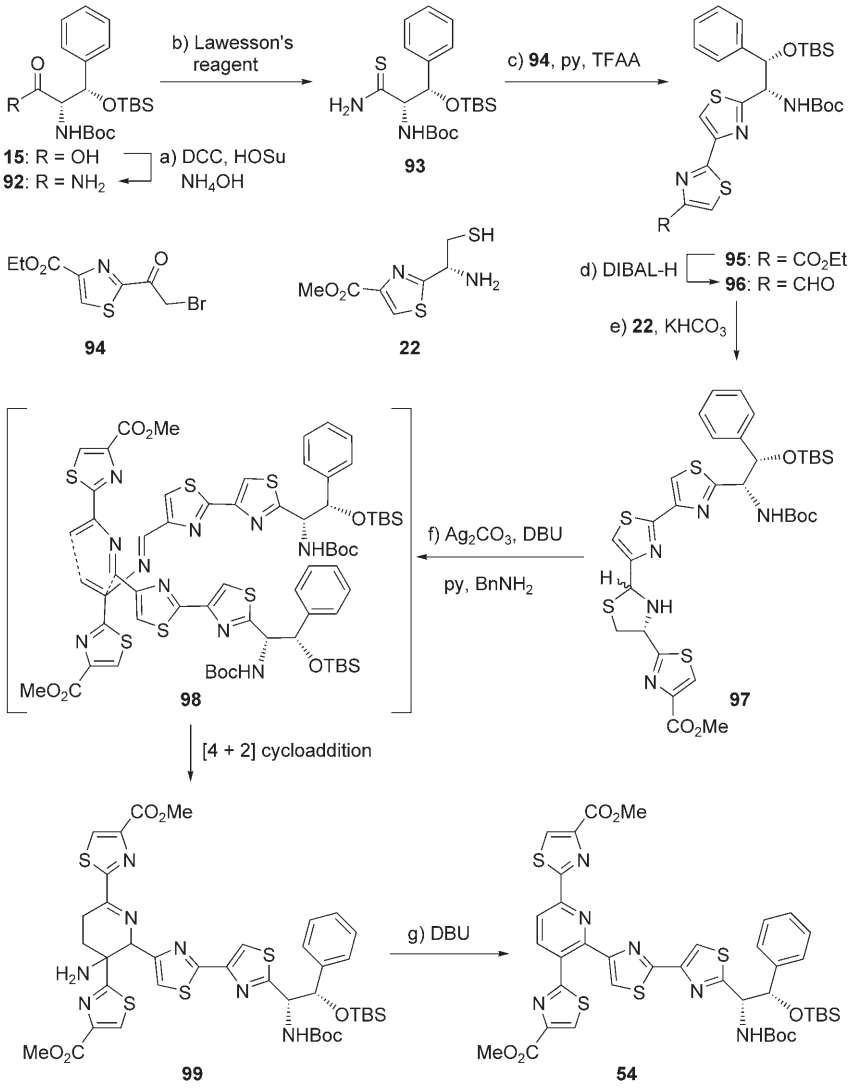
Scheme 14. Completion of the total syntheses of GE2270 A (**7**) and GE2270T (**8**). Reagents and conditions: a) Me_3SnOH (10.0 equiv), 1,2-dichloroethane, 60 °C, 16 h; b) L-serine methyl ester (1.1 equiv), HATU (1.5 equiv), iPr_2NEt (3.0 equiv), CH_2Cl_2, 25 °C, 16 h, 70% over two steps; c) DAST (1.5 equiv), CH_2Cl_2, −25 °C, 1 h, 80%; d) TBAF (1.0 M in THF, 1.2 equiv), THF, 25 °C, 3 h, 80%; e) Me_3SnOH (10.0 equiv), 1,2-dichloroethane, 60 °C, 16 h; f) **16** (1.1 equiv), HATU (1.2 equiv), iPr_2NEt (2.0 equiv), CH_2Cl_2, 25 °C, 16 h, 60% over two steps; g) $BrCCl_3$ (1.5 equiv), DBU (3.0 equiv), CH_2Cl_2, 0 °C, 2 h, 80%; h) Me_3SnOH (10.0 equiv), 1,2-dichloroethane, 60 °C, 5 h; i) **16** (1.1 equiv), HATU (1.2 equiv), iPr_2NEt (1.5 equiv), CH_2Cl_2, 25 °C, 16 h, 63% over two steps.

spectroscopic and MS data) to those reported for the natural product.[5b,d] The total synthesis of GE2270T (**8**) from **90** required initial aromatization of the oxazoline to the oxazole moiety ($BrCCl_3$/DBU, 80%) to afford **91**, followed by subsequent attachment of the L-prolinamide unit (**16**; HATU, iPr_2NEt) after liberation of the carboxy group through the

action of Me_3SnOH (63% yield over the two steps). The spectral data of synthetic GE2270T (**8**) were in agreement with its structure and with those reported for the natural substance.[5c] After completion of this work, a more convergent approach to GE2270A (**7**), which involves a coupling procedure to attach the required L-serine-L-prolinamide dipeptide unit that avoids diketopiperazine formation, was reported by Bach and co-workers.[4h] Their elegant total synthesis of GE2270A (**7**) also features a conceptually different strategy for the construction of the macrocycle of this structure.

Second-Generation Synthesis of Tetrathiazolyl Pyridine 54 and Total Synthesis of GE2270C1 (9)

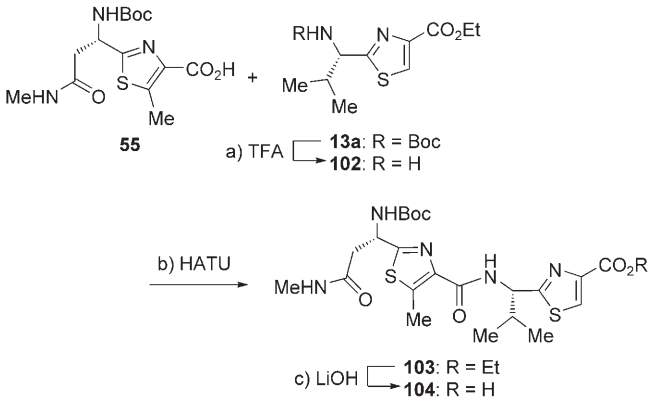
Although the synthetic strategy described above allowed the total synthesis of GE2270A (**7**) and GE2270T (**8**) and opened the way to the construction of other members, natural or designed, of the GE family, it left room for improvement. Of particular interest to us was the possibility of moving the hetero-Diels–Alder reaction downstream in the hope of shortening the sequence for the construction of the tetrathiazole pyridine core fragment **54** by several steps. Specifically, a strategy involving introduction of the hydroxy phenylalanine subunit into the hetero-Diels–Alder precursor would result in a more convergent approach, provided the [4+2] dimerization step could be performed on such an ela-



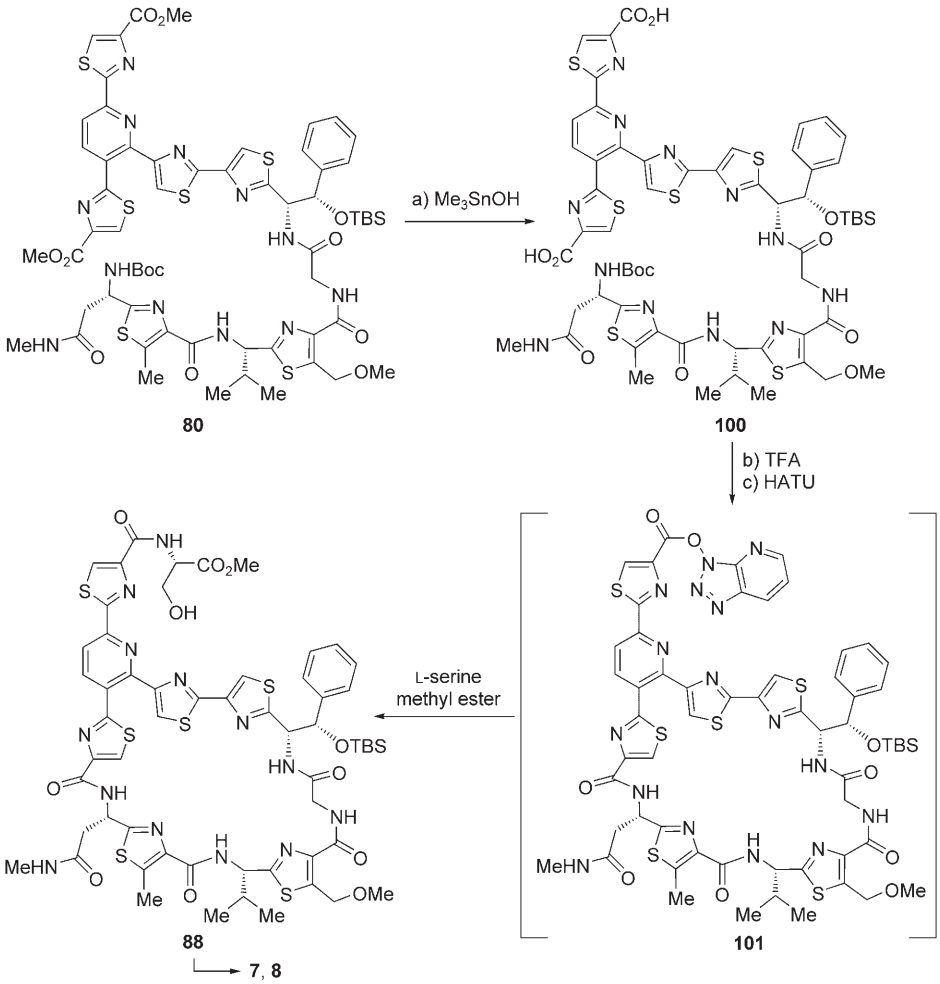
Scheme 15. Second-generation synthesis of tetrathiazole pyridine fragment **54**. Reagents and conditions: a) DCC (1.2 equiv), HOSu (1.2 equiv), THF, 25 °C, 16 h; then NH_4OH (25% aq.), EtOAc, 0 °C, 3 h; b) Lawesson reagent (0.7 equiv), DME, 25 °C, 12 h, 98% over two steps; c) **92** (1.4 equiv), 4-Å molecular sieves, DMF, 0→25 °C, 18 h; then TFAA (1.5 equiv), pyridine (3.0 equiv), CH_2Cl_2, 0 °C, 3 h, 82%; d) DIBAL-H (1.0 M in toluene, 2.4 equiv), toluene, −78 °C, 4 h, 71%; e) **22**·TFA (1.2 equiv), $KHCO_3$ (7.2 equiv), MeOH/H_2O (3.75:1), 25 °C, 16 h, 78%; f) Ag_2CO_3 (1.1 equiv), $BnNH_2$ (2.0 equiv), DBU (0.25 equiv), pyridine, −12 °C, 3 h; then H_2O/EtOAc (1:1), 25 °C, 2 h, 56% (≈1:1 mixture of diastereomers); e) DBU (6.0 equiv), EtOAc, reflux, 5 h, 33%. DCC = dicyclohexylcarbodiimide, DIBAL-H = diisobutylaluminum hydride, HOSu = *N*-hydroxysuccinimide, TFAA = trifluoroacetic anhydride.

borated system. Indeed, this proposal was validated in the laboratory (Scheme 15). Thus, conversion of phenylalanine derivative **15** into its amide **92** (DCC, HOSu, NH_4OH) followed by treatment of the latter compound with the Lawesson reagent led to thioamide **93** in 98% yield over the two steps. Condensation of the latter compound with α-bromoketone **94** (prepared by bromination of ethyl 2-acetylthiazole-4-carboxylate[4d] under Br_2/AcOH conditions) in the presence of trifluoroacetic anhydride and pyridine gave the expected bis-thiazole **95** in 82% yield, whose reduction with DIBAL-H furnished aldehyde **96** (71% yield). Reaction of **96** with amino thiol **22** (Scheme 5) in the presence of $KHCO_3$ afforded the coveted thiazolidine **97** in 78% yield.

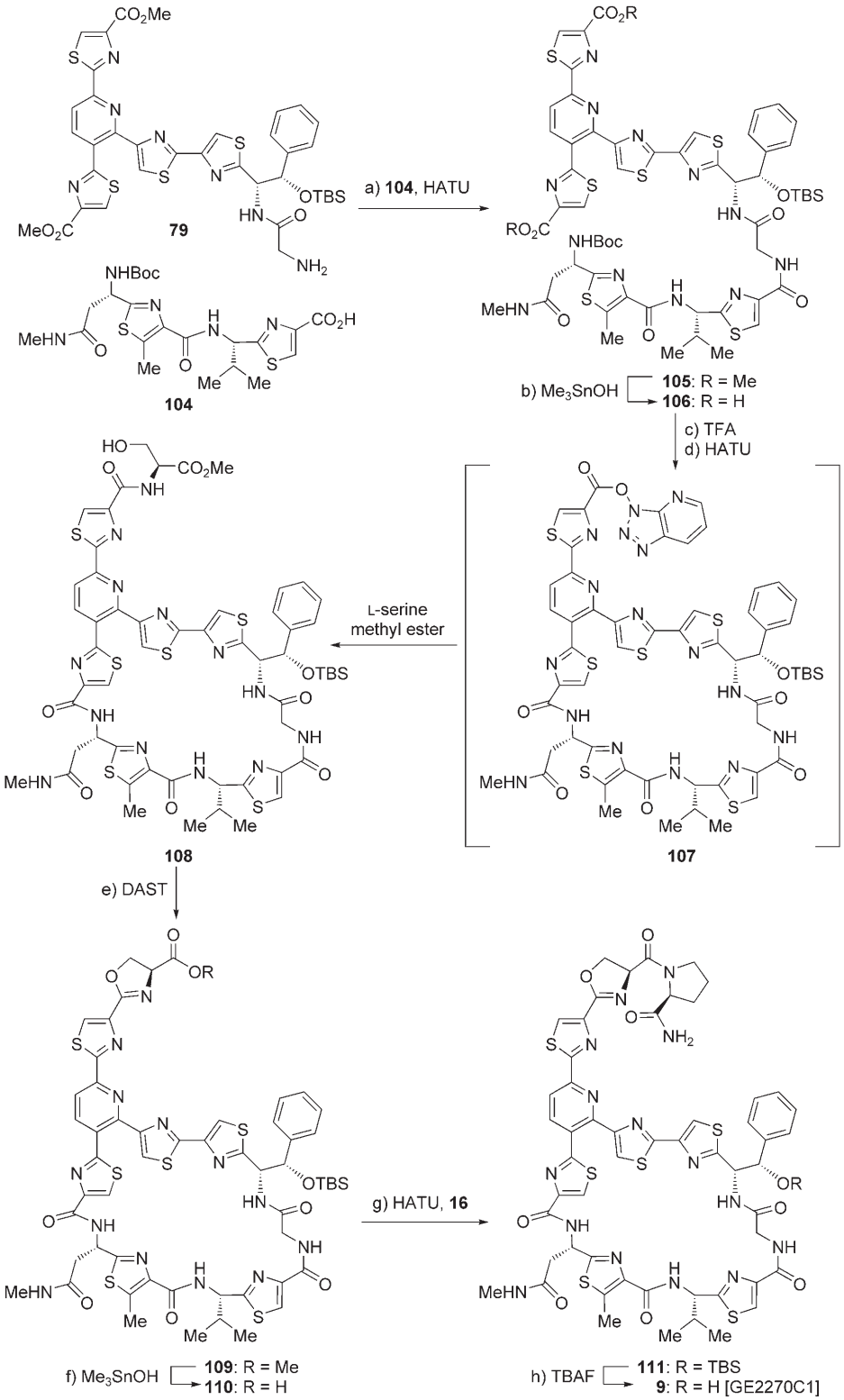
Pleasantly, precursor **97** entered into the desired Diels–Alder/dimerization cascade upon exposure to the established conditions (Ag_2CO_3, DBU, $BnNH_2$, py), thus furnishing the desired dehydropiperidine system **99** (56% yield, ≈1:1 inconsequential mixture of diastereomers) through the intermediacy of heterodiene **98**. Apparently, the increase in molecular complexity had little, if any, effect on the efficiency of this process, an observation that speaks well for its future applications in other situations. Finally, deamination/aromatization of dehydropiperidine **99** was effected with DBU in ethyl acetate at reflux to complete the construction



Scheme 17. Synthesis of bis-thiazole subunit **104**. Reagents and conditions: a) TFA/CH_2Cl_2 (1:4), 25 °C, 2 h; b) **55** (1.0 equiv), **102** (1.1 equiv), HATU (1.2 equiv), *i*Pr_2NEt (2.0 equiv), CH_2Cl_2, 25 °C, 16 h, 76% over two steps; c) LiOH (2.0 equiv), MeOH/H_2O (2:1), 25 °C, 4 h.



Scheme 16. Synthesis of compound **88** by utilizing tandem peptide-bond formation. Reagents and conditions: a) Me_3SnOH (20.0 equiv), 1,2-dichloroethane, 60 °C, 36 h; b) TFA/CH_2Cl_2 (1:4), 25 °C, 1 h; c) HATU (5.0 equiv), *i*Pr_2NEt (10.0 equiv), CH_2Cl_2/DMF (4:1) (0.0003 M), 25 °C, 18 h; then L-serine methyl ester (10.0 equiv), 25 °C, 24 h, 33% over three steps. For the conversion of **88** into **7** and **8**, see Scheme 14.



Scheme 18. Total synthesis of GE2270C1 (**9**). Reagents and conditions: a) **104** (1.2 equiv), HATU (1.5 equiv), *i*Pr_2NEt (3.0 equiv), CH_2Cl_2, 25 °C, 24 h, 73 % over two steps from **73**; b) Me_3SnOH (20.0 equiv), 1,2-dichloroethane, 60 °C, 36 h; c) TFA/CH_2Cl_2 (1:4), 25 °C, 2 h; d) HATU (5.0 equiv), *i*Pr_2NEt (10.0 equiv), CH_2Cl_2/DMF (4:1) (0.0003 M), 25 °C, 18 h; then L-serine methyl ester (10.0 equiv), 25 °C, 24 h, 35 % over three steps; e) DAST (1.5 equiv), CH_2Cl_2, −25 °C, 1 h, 74 %; f) Me_3SnOH (10.0 equiv), 1,2-dichloroethane, 60 °C, 16 h; g) **16** (1.4 equiv), HATU (1.2 equiv), *i*Pr_2NEt (2.0 equiv), CH_2Cl_2, 25 °C, 16 h, 60 % over two steps; h) TBAF (1.0 M in THF, 1.2 equiv), THF, 25 °C, 6 h, 69 %.

of tetrathiazole pyridine **54** (33% yield). This second-generation synthesis of **54** involves 13 linear steps from ethyl cinnamate as opposed to the original sequence, which required 20 steps from L-serine.

A further improvement of the synthesis beyond the hetero-Diels–Alder reaction segment of the route was sought and realized. Specifically, we considered a new tactic for the macrolactamization step, which was now to be attempted with the corresponding amino dicarboxylic acid with subsequent in situ extension of the remaining carboxylate chain. As shown in Scheme 16, this new strategy was first implemented in the preparation of compound **88**, a key intermediate in the total synthesis of GE2270A (**7**) and GE2270T (**8**). Thus, upon complete saponification of bis-methyl ester **80** (Me_3SnOH, **100**), the amino bis-acid resulting from removal of the Boc group (TFA) from Boc-protected bis-acid **100** was treated with 5.0 equivalents of HATU in the presence of iPr$_2$NEt in CH_2Cl_2/DMF (4:1) under conditions of high dilution (0.0003 M) at 25 °C. The reaction was allowed to proceed for 18 h to complete the macrolactamization, thus presumably furnishing activated macrolactam **101**. At this stage, L-serine methyl ester was added, and the reaction was allowed to proceed for another 24 h. We were delighted to isolate, at the end of this period, macrolactam **88** (33% overall yield from **80**) containing the desired L-serine residue. This one-pot process proved more expedient and efficient than that originally used for the total synthesis of GE2270A (**7**) and GE2270T (**8**).

This new technology was also implemented in the total synthesis of GE2270C1 (**9**). For this purpose, bis-thiazole carboxylic acid **104** was required, and it was synthesized from fragments **55** and **13a**[24] (Scheme 17). Thus, Boc cleavage (TFA) from **13a** followed by coupling of the resulting amine (**102**) with acid **55** under the influence of HATU and iPr$_2$NEt furnished peptide **103** (76% overall yield), which upon exposure to LiOH led to **104** (90% yield).

As shown in Scheme 18, peptide coupling of amine **79** with carboxylic acid **104** in the presence of HATU and iPr$_2$NEt led to bis-ester **105** (73% yield), which was taken through an analogous sequence to the one described in Scheme 16 for the preparation of **88**, thus leading to macrolactam **108**, via bis-acid **106** and activated macrolactam **107**, in 35% yield over the three steps from bis-methyl ester **105**. The conversion of intermediate **108** into the final product **9** followed a sequence in which, in contrast to that described for GE2270A (**7**) and GE2270T (**8**), the unmasking of the TBS-protected benzylic alcohol was reserved for the final step: 1) DAST, **109**; 2) Me_3SnOH, **110**; 3) **16**, HATU, iPr$_2$NEt, **111**; 4) TBAF, **9**, 31% overall yield; Scheme 18. The total synthesis of GE2270C1 (**9**) by these improved strategies, namely, complex hetero-Diels–Alder dimerization (preparation of compound **54**; Scheme 15) and tandem peptide formation (Scheme 18), was thus accomplished in 24 linear steps from ethyl cinnamate. The spectroscopic data (^{1}H and ^{13}C NMR, MS) of the synthetic material are in perfect accordance with those reported for the natural product.[5c]

Conclusions

The described total syntheses of the antibiotics GE2270A (**7**), GE2270T (**8**), and GE2270C1 (**9**) feature cascade sequences based on the hetero-Diels–Alder reaction and macrolactam-forming processes. Furthermore, macrocyclic ring closure at site ③ permitted a short cut to the final target by allowing concomitant introduction of a side-chain appendage into the structure. The synthetic technologies and strategies reported herein may facilitate the generation of novel analogues of these potent antibiotics for studies of chemical biology[25] and may find further applications in medicinal and heterocyclic chemistry.

Acknowledgements

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