Thiopeptide Antibiotics

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Total Synthesis of Antibiotics GE2270A and GE2270T**

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Among the thiopeptide antibiotics, GE2270A (**1**) and GE2270T (**2**, Scheme 1) occupy a commanding position, not only because of their novel molecular architectures but also as a result of their potent activities against Gram positive bacteria.[1] These thiazolyl peptide antibiotics isolated from *Planobispora rosea* ATCC53773 exert their selective anti-

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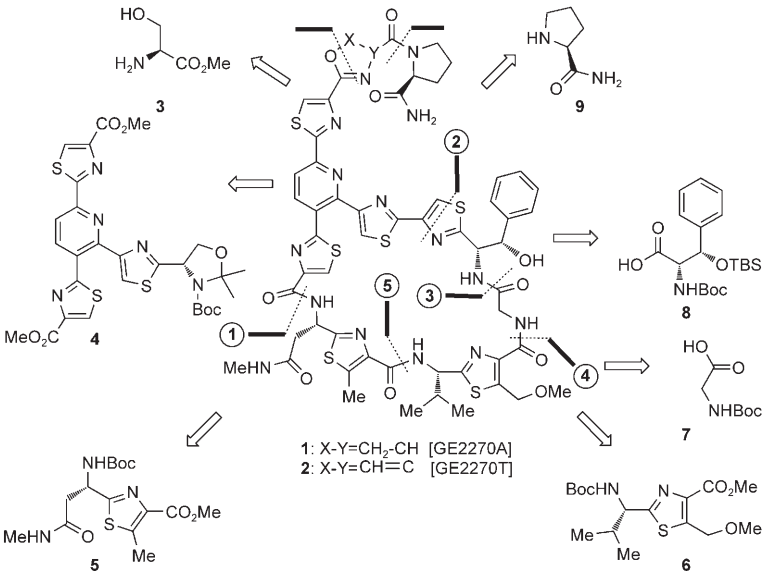
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

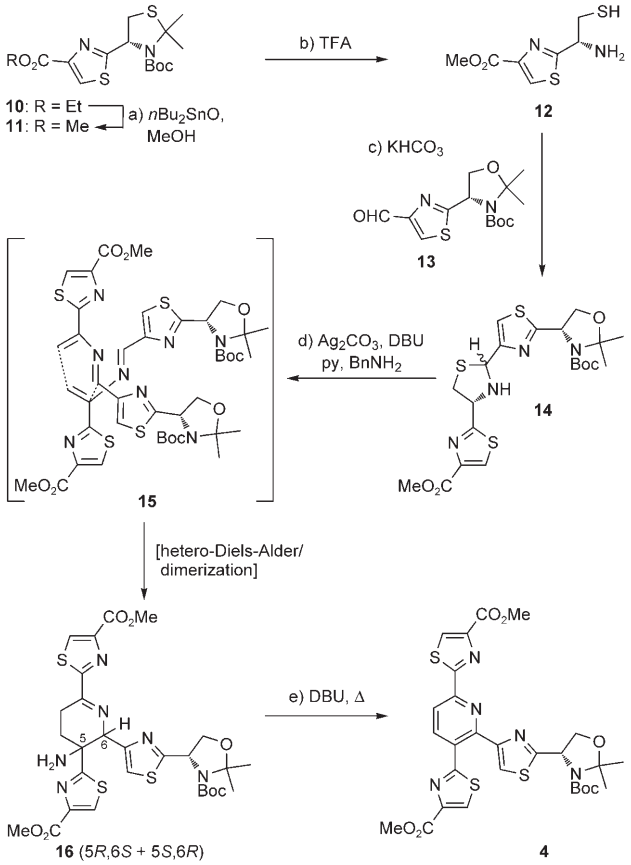


Scheme 1. Retrosynthetic analysis of antibiotics GE2270A (**1**) and GE2270T (**2**) leading to key fragments **3**–**9**. Boc = *tert*-butyloxycarbonyl, TBS = *tert*-butyldimethylsilyl.

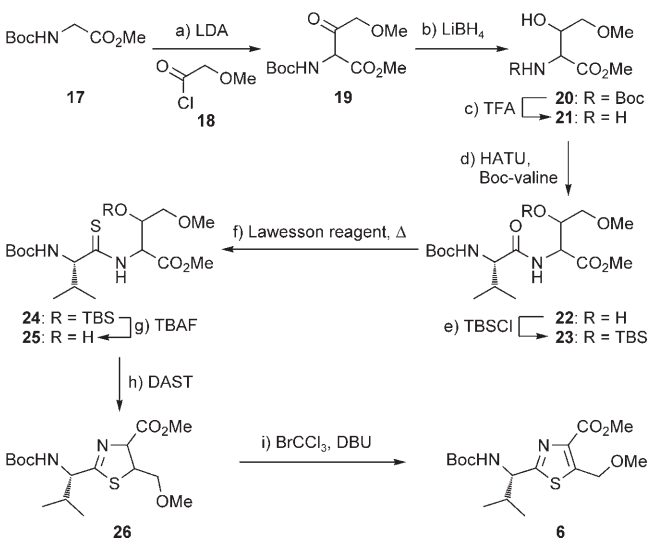
bacterial properties through inhibition of the bacterial elongation factor Tu, but not the eukaryote elongation factor-1 alpha.[2] The complete structure of GE2270A (**1**) has been fully established through the notable efforts of Tavecchia and co-workers,[3] and of Heckmann and Bach.[4] Furthermore, synthetic studies toward the GE2270 factors were also reported by the research groups of Bach[4,5] and Shin.[6] Herein, we report the total synthesis of GE2270A (**1**) and GE2270T (**2**) through a convergent strategy that features a hetero-Diels–Alder/dimerization process[7] to construct the trithiazolyl pyridine core of the molecule.

Inspection of the structures of GE2270A (**1**) and GE2270T (**2**) reveals, in addition to the 29-membered macrocycle, the presence of one pyridine, one phenyl, one proline, and six thiazole rings, as well as one oxazoline system in the case of **1**, or one oxazole moiety in the case of **2**. A convergent strategy towards **2** that would provide the oxazoline intermediate en route should additionally provide access to **1**, and therefore was preferred. Furthermore, the introduction of the proline-containing tail in the final stages of the synthesis would allow a convenient entry into a range of designed analogues of these naturally occurring antibiotics for structure–activity-relationship (SAR) studies.[2b] Scheme 1 shows the seven key building blocks **3**–**9** required for such a strategy, as derived from the indicated retrosynthetic analysis. The assembly of **3**–**9** into the final structures **1** and **2** would demand the construction of the remaining three rings, namely one thiazole, one oxazoline- or oxazole-ring system, and the macrocycle. The latter ring could, in principle, be conveniently closed at any of the five indicated sites through amide bond formation (①–⑤, Scheme 1).

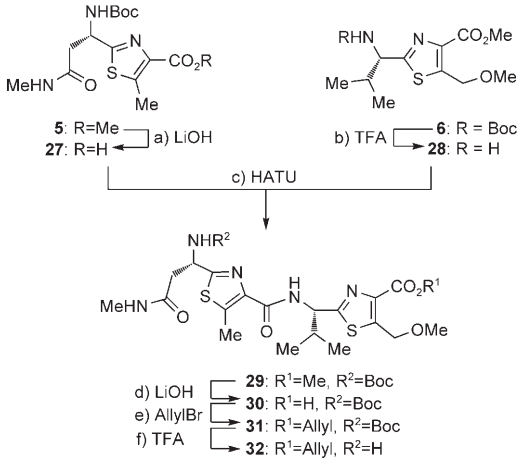
Scheme 2 summarizes the construction of the pyridine core **4**, which is the central scaffold equipped with suitable functionalities for extension in three directions as required for the target molecules. Thus, the thiazole derivative **10**, which had been previously synthesized,[7a] was converted into its methyl ester **11** (84% yield) by simple ester exchange.[8] Removal of the Boc-acetonide protecting group from methyl ester thiazole derivative **11** with TFA provided the amino thiol **12**. Engagement of **12** with aldehyde **13** (prepared by adaptation of a literature procedure)[7a] proceeded smoothly in the presence of $KHCO_3$ to afford thiazolidine **14** (82% yield for the two steps), an intermediate that served admirably as a precursor to heterodiene **15** (Ag_2CO_3, DBU, pyridine, $BnNH_2$).[7a] The latter species **15** proved quite fleeting and furnished under the reaction conditions, and after hydrolysis, the intended [4+2]-cycloaddition/dimerization product, the amino dehydropiperidine fragment **16** in 60% yield as a 1:1 mixture of *trans* diastereoisomers.[7a] Finally, heating a solution of **16** with DBU in EtOAc to reflux gave the desired trisubstituted pyridine core **4** in 50% yield through aromatization, which involved expulsion of ammonia and dehydrogenation.



Scheme 2. Synthesis of trithiazole-substituted pyridine **4**. Reagents and conditions: a) nBu_2SnO, 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) **12**·TFA (1.0 equiv), **13** (1.0 equiv), $KHCO_3$ (3.0 equiv), MeOH/H_2O (1:1), 25 °C, 16 h, 82% for the two steps; d) Ag_2CO_3 (1.1 equiv), $BnNH_2$ (1.0 equiv), DBU (0.25 equiv), py, −15 °C, 1 h; then H_2O/EtOAc (1:1), 1 h, 60%; e) DBU (5.0 equiv), EtOAc, reflux, 5 h, 50%. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, py = pyridine, TFA = trifluoroacetic acid.



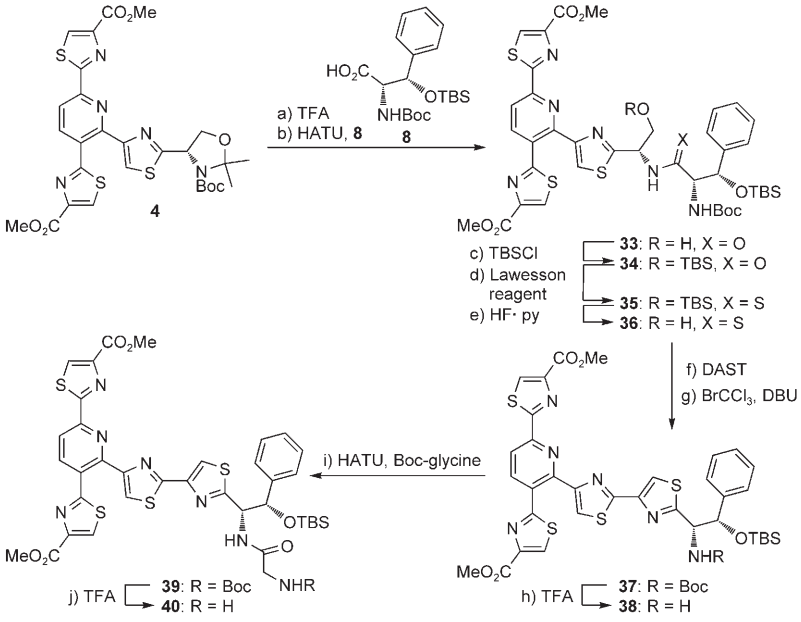
Scheme 3. Synthesis of trisubstituted thiazole **6**. Reagents and conditions: a) LDA (2.5 equiv), methoxyacetyl chloride (1.2 equiv), THF, −78 to 25 °C, 16 h, 59%; b) $LiBH_4$ (1.0 equiv), THF/CH_2Cl_2/MeOH (4:2:1), −78 °C, 5 min; c) TFA/CH_2Cl_2 (1:4), 0 °C, 1 h; d) Boc-valine (1.1 equiv), HATU (1.5 equiv), *i*Pr_2NEt (3.0 equiv), CH_2Cl_2, 25 °C, 3 h, 71% for the three steps; e) TBSCl (1.1 equiv), imidazole (1.5 equiv), DMF, 20 °C, 16 h, 77%; f) Lawesson reagent (1.5 equiv), THF, reflux, 16 h, 66%; g) TBAF (1.1 equiv), THF, 5 h, 93%; h) DAST (1.5 equiv), CH_2Cl_2, −78 °C, 1 h; i) $BrCCl_3$ (1.1 equiv), DBU (2.2 equiv), CH_2Cl_2, 0 °C, 1 h, 84% for the two steps. DAST = *N*,*N*′-diethylaminosulfur trifluoride, HATU = *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate, LDA = lithium diisopropylamide, TBAF = tetrabutylammonium fluoride.



Scheme 4. Synthesis of bisthiazole subunits **30** and **32**. Reagents and conditions: a) LiOH (3.5 equiv), MeOH, 25 °C, 16 h; b) TFA/CH_2Cl_2 (1:4), 25 °C, 1 h; c) HATU (1.1 equiv), *i*Pr_2NEt (2.0 equiv), CH_2Cl_2, 25 °C, 3 h, 80% for the two steps from **5**; d) LiOH (3.5 equiv), MeOH, 25 °C, 16 h; e) $KHCO_3$ (3.0 equiv), allyl bromide (2.0 equiv), DMF, 25 °C, 3 h, 70% for the two steps; f) TFA/CH_2Cl_2 (1:4), 25 °C, 1 h, 90%.

Scheme 3 summarizes the synthesis of the thiazole derivative **6** from the Boc-glycine methyl ester **17**. Thus, C-acylation of **17** with methoxyacetyl chloride (**18**) as facilitated by LDA at −78 °C produced the Boc derivative **19** (59% yield). Sequential exposure of **19** to $LiBH_4$ and TFA reduced the ketone moiety and liberated the amine, which provided amino alcohol **21** via intermediate **20**. Reaction of **21** with Boc-valine in the presence of HATU and *i*Pr_2NEt afforded the hydroxy dipeptide **22** in 71% yield over the three steps. Protection of the hydroxy group of **22** as a TBS ether furnished derivative **23** (77% yield). Exposure of **23** to Lawesson reagent in refluxing THF led to thioamide **24** in 66% yield. Removal of the TBS group gave **25** (93% yield) and subsequent treatment first with DAST,[9] and then with $BrCCl_3$ and DBU,[10] furnished the thiazole intermediate **6**, through the intermediacy of compound **26**, in 84% overall yield for the two steps.

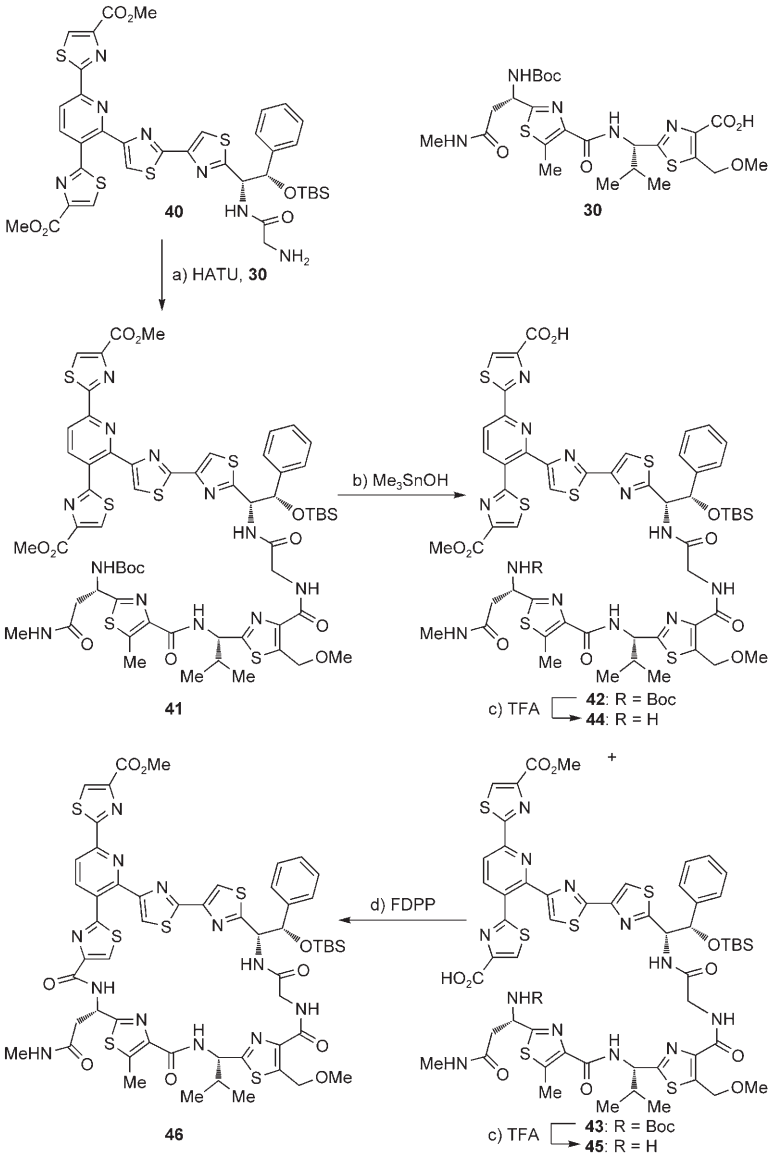
With all seven required fragments **3**–**9** now available, their assembly into the target molecules **1** and **2** became our next task. From all the possible strategies, we chose first to pursue the one involving macrocycle construction by forming amide bond ① (Scheme 1). To this end, the carboxylic acid **27** (generated by saponification of methyl ester **5**,[11] Scheme 4) was coupled with amine **28** (generated by removal of the Boc group from **6**) under the influence of HATU and *i*Pr_2NEt to afford peptide **29** in 80% overall yield from **5**



Scheme 5. Synthesis of tetrathiazole **40**. Reagents and conditions: a) TFA/H_2O (3:1), 25 °C, 1 h; b) **8** (1.1 equiv), HATU (1.2 equiv), *i*Pr_2NEt (3.0 equiv), CH_2Cl_2, 25 °C, 3 h, 85% for the two steps from **4**; 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·py (10 equiv), pyridine/THF (1:8), 25 °C, 2 h, 92%; f) DAST (1.5 equiv), CH_2Cl_2, −78 °C, 1 h; g) $BrCCl_3$ (1.5 equiv), DBU (3.0 equiv), CH_2Cl_2, 0 °C, 1 h, 69% for the two steps from **36**; h) TFA/CH_2Cl_2 (1:4), 25 °C, 1 h; i) Boc-glycine (1.1 equiv), HATU (1.2 equiv), *i*Pr_2NEt (3.0 equiv), CH_2Cl_2, 25 °C, 24 h, 90% for the two steps; j) TFA/CH_2Cl_2 (1:4), 25 °C, 1 h.

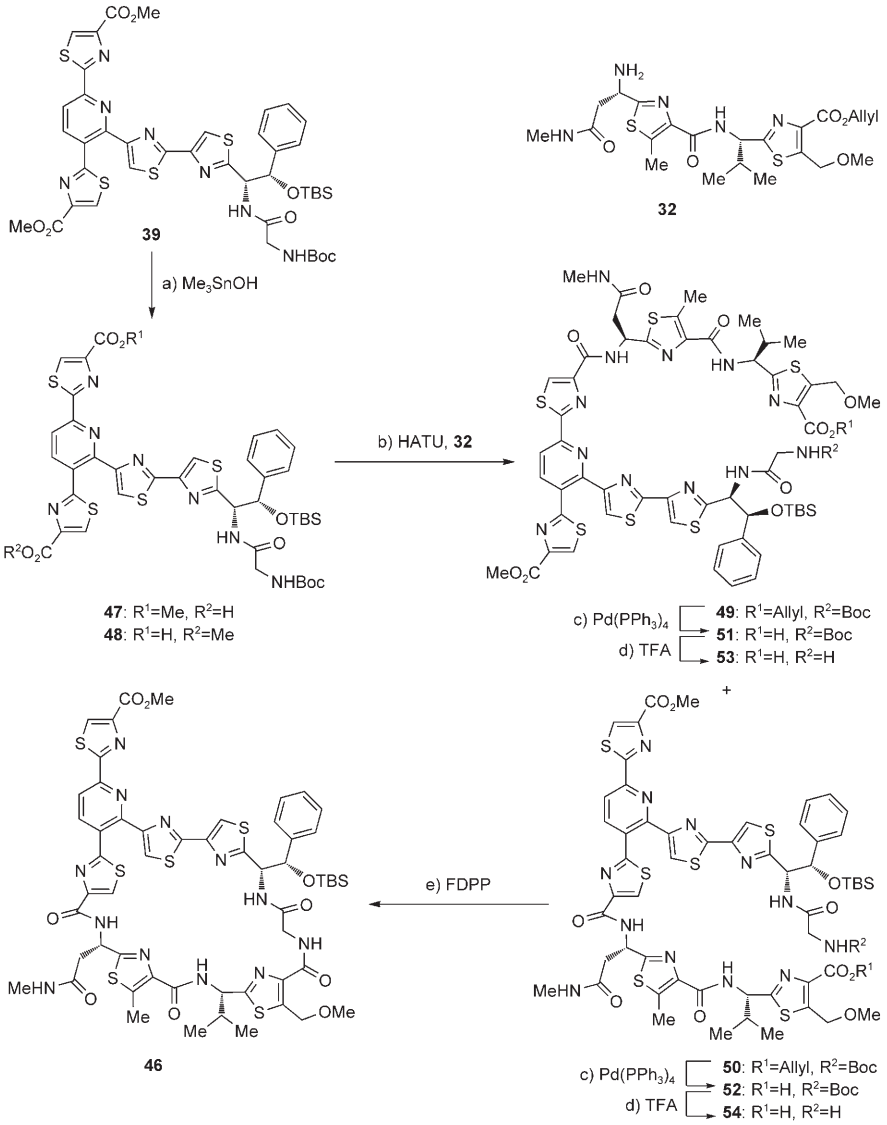
(Scheme 4). Basic hydrolysis of the methyl ester of compound **29** then led to carboxylic acid **30**. Next to be targeted was the hexacyclic system **40**, whose construction from the pyridine core structure **4** is summarized in Scheme 5. Thus, **4** was exposed to acidic conditions (TFA/H_2O) which led to the collapse of the Boc-acetonide protecting group, thereby generating the corresponding amino alcohol. This amino alcohol was then coupled with the carboxylic acid derivative **8** (prepared through a modification of a literature procedure)[12] in the presence of HATU and iPr$_2$NEt to afford the hydroxy dipeptide **33** in 85% yield over the two steps. In preparation for the construction of the fourth thiazole system required in the growing fragment, compound **33** was sequentially converted into the TBS-ether derivative **34** (TBSC1, 82% yield), thioamide **35** (Lawesson reagent, 80% yield), and hydroxy thioamide **36** (HF·py, 92% yield). Conversion of **36** into tetrathiazole **37** was carried out by sequential exposure to DAST[9] and $BrCCl_3$/DBU[10] in 69% overall yield. The Boc group was then cleaved off this intermediate (TFA/CH_2Cl_2), which allowed its elongation to the glycine derivative **40** through a sequence that involved liberation of the amine to afford **38** (TFA), coupling with the Boc-glycine (HATU/iPr$_2$NEt) to give **39** (90% overall yield) and cleavage of the newly introduced Boc group (TFA).

The resulting amine **40** was coupled with the dithiazole-containing carboxylic acid **30** (Scheme 6) through the action of HATU and iPr$_2$NEt to afford peptide **41** (66% overall yield from **39**), which was further elaborated to the macrocycle **46** as indicated in Scheme 6. Thus, treatment of diester **41** with 1.0 equiv of Me_3SnOH[13] resulted in the formation of the two monoacids **42** and **43** in 40% combined yield and in around a 1:1 ratio (90% based on recovered starting material). Chromatographic separation of the two regioisomers gave the pure carboxylic acids **42** and **43**, each of which was separately subjected to Boc removal (TFA) and macrocyclization conditions. While the amino acid **45** derived from the less polar isomer **43** ($R_f = 0.58$, silica gel, EtOAc/MeOH 1:1) underwent smooth ring closure (verified by LC-MS analysis) to furnish macrocycle **46**, the regioisomeric amino acid **44**, derived from the more polar isomer **42** ($R_f = 0.47$, silica gel, EtOAc/MeOH 1:1), failed to cyclize. In light of these observations, subsequent cyclizations were carried out with the mixture of amino acids **44** and **45** (FDPP/iPr$_2$NEt, CH_2Cl_2/DMF 4:1, 0.0003 M), a practice that proved more convenient and efficient, and which led to the isolation of macrocycle **46** in 20% overall yield from **42**/**43**.



Scheme 6. Construction of macrocycle **46** (ring closure ①, Scheme 1). Reagents and conditions: a) **30** (1.1 equiv), HATU (1.5 equiv), iPr$_2$NEt (3.0 equiv), CH_2Cl_2, 25 °C, 24 h, 66% for the two steps from **39**; b) Me_3SnOH (1.0 equiv), 1,2-dichloroethane, 60 °C, 16 h, **42**: 20% and **43**: 20% (90% based on recovered starting material); c) TFA/CH_2Cl_2 (1:4), 25 °C, 1 h; d) FDPP (5.0 equiv), DMF/CH_2Cl_2 (1:4), 0.0003 M, 24 h, 20% for the two steps. FDPP = pentafluorophenyl diphenylphosphinate.

The identical macrocycle **46** was obtained through a modified route in which the macrocycle was formed by ring closure ④ (see Scheme 1) as shown in Scheme 7. Thus, compound **39** was hydrolyzed with Me_3SnOH[13] to afford a mixture of inseparable monocarboxylic acids **47** and **48** (ca. 1:1 ratio, 45% along with 50% recovered starting material). Acids **47** and **48** were then coupled with amine **32**, which was obtained from **30** by allylation ($KHCO_3$/allyl bromide, 70% from **29** via intermediate **31**) and TFA-induced removal of the Boc group (90%, Scheme 4), in the presence of HATU and

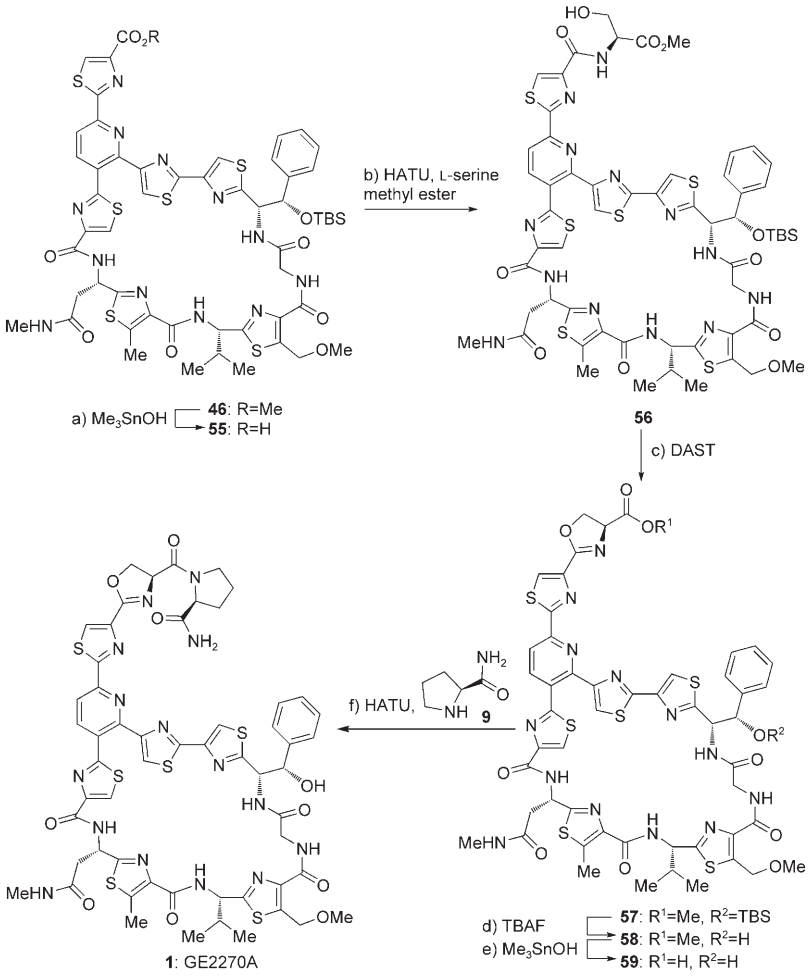


Scheme 7. Alternative construction of macrocycle **46** (ring closure ④, Scheme 1). Reagents and conditions: a) Me_3SnOH (1.0 equiv), 1,2-dichloroethane, 60 °C, 20 h, **47**/**48** (ca. 1:1 ratio) 45% (90% based on 50% recovered starting material); b) **32** (1.1 equiv), HATU (1.5 equiv), iPr_2NEt (3.0 equiv), CH_2Cl_2, 25 °C, 16 h, 70%; c) $[Pd(PPh_3)_4]$ (20 mol%), 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 equiv), CH_2Cl_2/DMF (1:4, 0.30 mM), 25 °C, 24 h, 30% for the three steps. NMA = *N*-methylaniline.

iPr_2NEt, to afford the coupling products **49** and **50**. The mixture of **49**/**50** was converted into cyclization precursors **53** and **54** by deallylation with $[Pd(PPh_3)_4]$ and Boc removal (TFA). Exposure of the mixture of **53** and **54** to the macrolactamization conditions (FDPP/iPr_2NEt, CH_2Cl_2/DMF 4:1, 0.0003 M) again furnished only one macrocycle **46** (30% overall yield from **49**/**50** for the three steps), which was proven from chromatographic and spectroscopic data to be identical to the one obtained from **43** or **42**/**43**, as described earlier (Scheme 6). Again, the formation of a single regioisomer **46** in this cyclization reaction points to a unique structural feature of these systems. The structural identity of the formed macrocycle and the precise reasons for its preference in these reactions were not known at this stage. While the tentatively assigned structure **46** was later proven by its eventual conversion to the natural products **1** and **2** (described below), the rationale for its formation in preference to its regioisomer remains to be elucidated.

Macrolactamizations were also performed at sites ③ and ⑤ (see Scheme 1) using amino acid precursors prepared by modifications of the chemistry described above.[14] Interestingly, while ring closure at site ⑤ proceeded smoothly and again furnished the same macrocycle **46** (15% overall yield for the last three steps involving deprotection of the amino acid and formation of the peptide bond) as from the ring closures at ① and ④, macrolactamization at site ③ was not feasible because of the reluctance of fragments longer than glycine to couple with the amino group of that site.

The final stages of the total synthesis of GE2270A (**1**) are shown in Scheme 8. Thus, the methyl ester of advanced

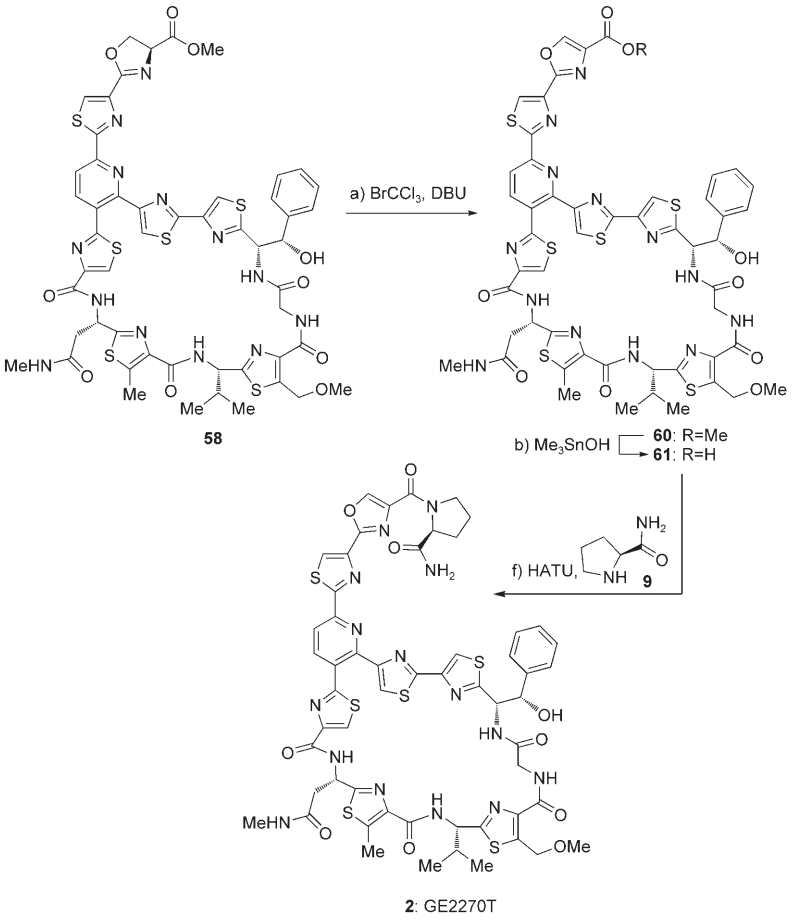


Scheme 8. Completion of the total synthesis of GE2270A (**1**). Reagents and conditions: a) Me_3SnOH (10 equiv), 1,2-dichloroethane, 80 °C, 5 h; b) L-serine methyl ester (1.1 equiv), HATU (1.5 equiv), iPr_2NEt (3.0 equiv), CH_2Cl_2, 25 °C, 16 h, 55% for the two steps; c) DAST (1.5 equiv), CH_2Cl_2, −25 °C, 1 h, 85%; d) TBAF (1.2 equiv), THF, 25 °C, 80%; e) Me_3SnOH (10 equiv), 1,2-dichloroethane, 80 °C, 1 h; f) L-proline amide (1.1 equiv), HATU (1.2 equiv), iPr_2NEt (2.0 equiv), CH_2Cl_2, 25 °C, 3 h, 60% for the two steps.

macrocycle **46** was hydrolyzed with Me_3SnOH,[13,15] affording carboxylic acid **55**. The convergent strategy for the introduction of the required dipeptide fragment (L-serine-L-prolin-amide) was unsuccessful. A stepwise approach was adopted whereby attachment of the L-serine moiety was carried out first, thereby yielding hydroxy methyl ester **56** in 55% overall yield for the two steps. Generation of the desired oxazoline moiety was then carried out by exposing hydroxy amide **56** to DAST[9] in CH_2Cl_2 at −25 °C to furnish ester silyl ether **57** in 85% yield. Sequential treatment of the latter compound with TBAF followed by Me_3SnOH[13,15] led, through the intermediacy of hydroxy methyl ester **58** (80% yield), to hydroxy carboxylic acid **59**, which was set for the final coupling. Indeed, reaction of **59** with L-proline amide **9** in the presence of HATU and iPr_2NEt furnished GE2270A (**1**) in 60% overall yield from **58**. Synthetic **1** exhibited identical physical properties (in ^1H and ^{13}C NMR spectra, and MS) to those reported[1c] for the naturally occurring substance. Although no specific optical rotation has been reported for GE2270A (**1**), we assumed that **1** and its congeners were derived in nature from natural amino acids, as previously suggested by degradation studies.[3]

Advanced intermediate oxazoline **58** encountered along the way to **1** was also converted into GE2270T (**2**) as shown in Scheme 9. Thus, exposure of oxazoline **58** to the action of $BrCCl_3$ and DBU[10] gave oxazole methyl ester **60**. Hydrolysis of **60** to give carboxylic acid **61** was smoothly accomplished by Me_3SnOH.[13,15] Finally, coupling of **61** with L-proline amide **9**, facilitated by HATU and iPr_2NEt as described above, furnished GE2270T (**2**) in 40% overall yield from **58** (three steps). The physical properties of synthetic **2** were in accordance with its assigned structure and the literature data.[1c]

The chemistry described herein demonstrates the applicability of the [4+2]-cycloaddition/dimerization cascade involving heterodienes[7] in complex molecule construction, and the exquisite regioselective preferences of the ring-closing reactions in thiopeptide-like substrates. Furthermore, the high convergency associated with this route renders this strategy particularly suited for analogue synthesis and SAR



Scheme 9. Completion of the total synthesis of GE2270T (**2**). Reagents and conditions: a) $BrCCl_3$ (1.5 equiv), DBU (3.0 equiv), CH_2Cl_2, 0 to 25 °C, 16 h; b) Me_3SnOH (10 equiv), 1,2-dichloroethane, 80 °C, 6 h; c) L-proline amide (1.1 equiv), HATU (1.2 equiv), iPr_2NEt (1.5 equiv), CH_2Cl_2, 25 °C, 5 h, 40% for the three steps.

studies, especially at the proline–oxazole tail end[2b] of the molecule, with an advanced intermediate serving as a common precursor to a wide variety of designed molecules as potential new antibacterial agents.

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