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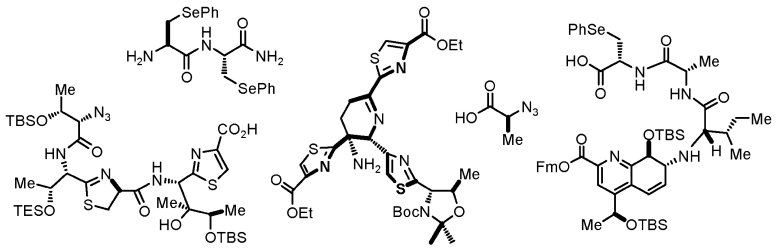

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Total Synthesis of Thiostrepton. Retrosynthetic Analysis and Construction of Key Building Blocks

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Abstract: The first phase of the total synthesis of thiostrepton (**1**), a highly complex thiopeptide antibiotic, is described. After a brief introduction to the target molecule and its structural motifs, it is shown that retrosynthetic analysis of thiostrepton reveals compounds **23**, **24**, **26**, **28**, and **29** as potential key building blocks for the projected total synthesis. Concise and stereoselective constructions of all these intermediates are then described. The synthesis of the dehydropiperidine core **28** was based on a biosynthetically inspired aza-Diels−Alder dimerization of an appropriate azadiene system, an approach that was initially plagued with several problems which were, however, resolved satisfactorily by systematic investigations. The quinaldic acid fragment **24** and the thiazoline−thiazole segment **26** were synthesized by a series of reactions that included asymmetric and other stereoselective processes. The dehydroalanine tail precursor **23** and the alanine equivalent **29** were also prepared from the appropriate amino acids. Finally, a method was developed for the direct coupling of the labile dehydropiperidine key building block **28** to the more advanced and stable peptide intermediate **27** through capture with the highly reactive alanine equivalent **67** under conditions that avoided the initially encountered destructive ring contraction process.

Introduction

The thiopeptide antibiotics are a growing class of naturally occurring substances with novel molecular architectures and powerful antibacterial properties. Their mode of action almost invariably involves inhibition of protein biosynthesis in bacteria. Known also as thiazolyl peptides, these antibiotics share a number of structural motifs, including several heterocycles (e.g. a dehydropiperidine, a pyridine, oxazoles, thiazoles, indoles), at least one macrocycle, and dehydroamino acid residues. Figure 1 displays a number of representative examples from this class of compounds, whose chemistry, biology, and use in medicine have been recently reviewed.[1]

Among members of the thiopeptide family of antibiotics, thiostrepton (**1**) occupies a special place not only due to its historical position and imposing structure, but also because of its biology and medicinal value. First isolated in 1954 from *Streptomyces azureus*, it was subsequently found in fermentation extracts of *Streptomyces hawaiiensis* and *Streptomyces laurentii*.[2]

Recognized as the flagship of the thiopeptide class of antibiotics, **1** is used in animal health care as a topical antibiotic,[3] its use in humans being limited by its low solubility and bioavailability which lead to development of drug resistance by the proliferating bacteria. The antibiotic properties of **1** against Gram-positive bacteria have been traced to its binding to the 23S region of ribosomal RNA and protein L11, an occurrence that inhibits the GTPase-dependent activities of the 50S ribosomal subunit.[4] In addition to its antimicrobial activity, **1** exhibits significant activity against *Plasmodium falciparum*,[5] the parasite responsible for the majority of human malaria, and selective cytotoxicity against certain cancer cells.[6] Furthermore, a recent report attributed to **1**, and its thiopeptide sibling siomycin, potent immunosuppressive properties.[7]

Studies aimed at elucidation of the biosynthetic origins of **1** shined considerable light on the way nature assembles this

(1) Bagley, M. C.; Dale, J. W.; Merritt, E. A.; Xiong, X. *Chem. Rev.* **2005**, *105*, 685−714.

(2) Isolation: (a) Pagano, J. F.; Weinstein, M. J.; Stout, H. A.; Donovick, R. *Antibiot. Ann.* **1955**−**1956**, 554−559. (b) Vandeputte, J.; Dutcher, J. D. *Antibiot. Ann.* **1955**−**1956**, 560−561. (c) Steinberg, B. A.; Jambor, W. P.; Suydam, L. O. *Antibiot. Ann.* **1955**−**1956**, 562−565. Structure determination: (d) Bond, C. S.; Shaw, M. P.; Alphey, M. S.; Hunter, W. N. *Acta Crystallogr.* **2001**, *D57*, 755−758. (e) Anderson, B.; Hodgkin, D. C.; Viswamitra, M. A. *Nature* **1970**, *225*, 233−235. (f) Hensens, O. D.; Albers-Schönberg, G. *J. Antibiot.* **1983**, *36*, 799−813. (g) Hensens, O. D.; Albers-Schönberg, G. *J. Antibiot.* **1983**, *36*, 814−831. (h) Hensens, O. D.; Albers-Schönberg, G. *J. Antibiot.* **1983**, *36*, 732−845.

(3) Dennis, S. M.; Nagaraja, T. G.; Dayton, A. D. *Res. Vet. Sci.* **1986**, *41*, 251−256.

(4) Xing, Y.; Draper, D. E. *Biochemistry* **1996**, *35*, 1581−1588.

(5) (a) McConkey, G. A.; Rogers, M. J.; McCutchan, T. F. *J. Biol. Chem.* **1997**, *272*, 2046−2049. (b) Hardman, J. G.; Limbird, L. E.; Molinoff, P. B.; Ruddon, R. W. A.; Gilman, G. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 9th ed.; The McGraw-Hill Co.: New York, 1996; pp 965−985.

(6) Jonghee, K. PCT Int. Appl. WO 2002066046, 2002.

(7) Ueno, M.; Furukawa, S.; Abe, F.; Ushioda, M.; Fujine, K.; Johki, S.; Hatori, H.; Ueda, J. *J. Antibiot.* **2004**, *57*, 590−596.

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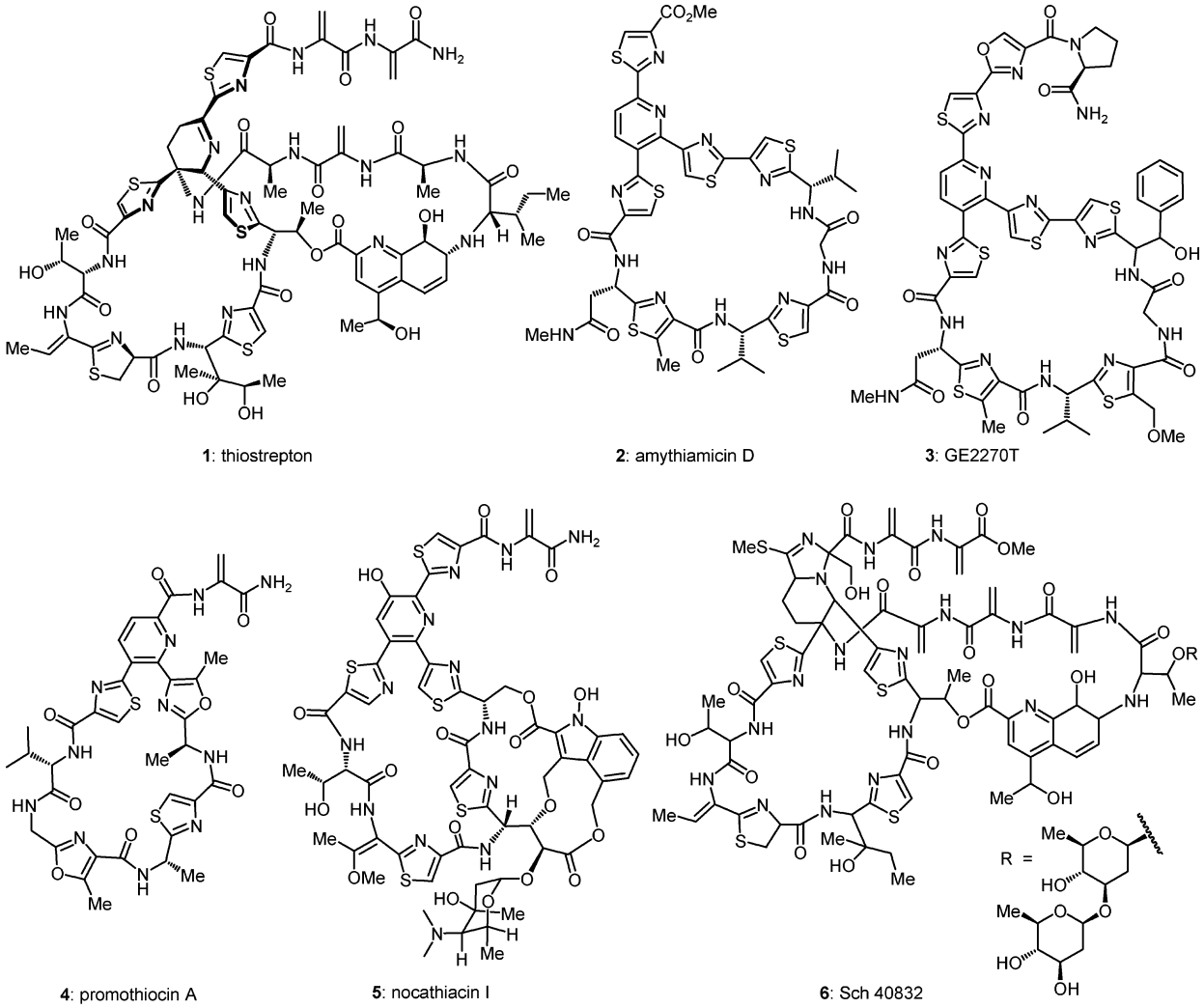


Figure 1. Molecular structure of thiostrepton (**1**) and other selected members of the thiopeptide class of antibiotics.

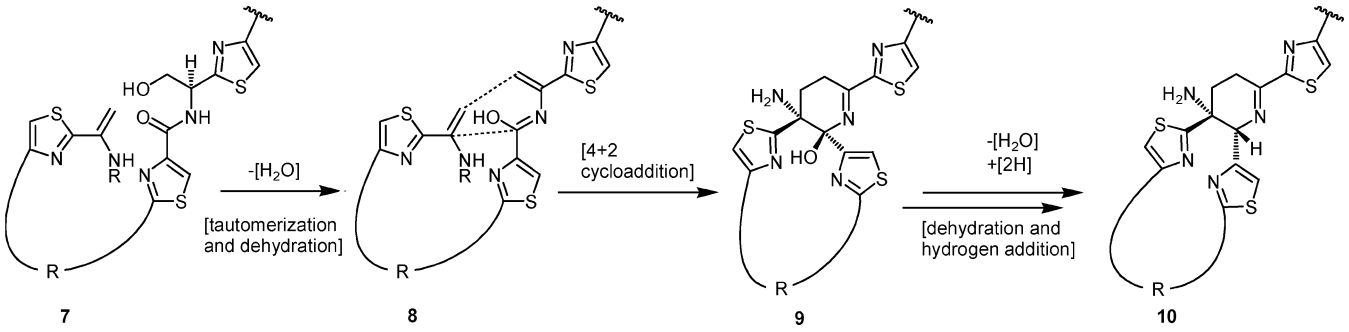


Figure 2. Biogenetic origins of thiostrepton's dehydropiperidine core.

natural product from readily available building blocks.[8] Thus, feeding experiments using isotopically labeled precursors including cysteine, isoleucine, methionine, serine, threonine, and tryptophan to nurture *S. azureus* ATCC 14921 or *S. laurentii* ATCC 31255 demonstrated the amino acid origin of all structural motifs of the molecule. Most intriguingly, these studies pointed to the Diels−Alder origin of the dehydropiperidine nucleus, as shown in Figure 2. Equally fascinating was the pathway suggested for the biogenesis of the quinaldic acid residue, which apparently begins with tryptophan and involves methylation and oxidation followed by imine ring rupture and expansion, epoxidation, and epoxide opening (see Figure 3).

Thiostrepton's unique molecular structure is both stunningly complex and highly sensitive. As shown in Figure 4, at its heart lies a dehydropiperidine core serving as a lynchpin on which stand the bis-dehydroalanine tail and the molecule's two macrocyclic domains, the 26-membered thiazoline-containing ring and the 27-membered quinaldic acid-containing system. This acid- and base-sensitive molecule includes within its structure 10 rings, 17 stereogenic centers, 11 peptide bonds, an imine functionality, a secondary amine group, and several sites

(8) (a) Mocek, U.; Zeng, Z.; O'Hagan, D.; Zhou, P.; Fan, L.-D. G.; Beale, J. M.; Floss, H. G. *J. Am. Chem. Soc.* **1993**, *115*, 7992−8001. (b) Priestley, N. D.; Smith, T. M.; Shipley, P. R.; Floss, H. G. *Bioorg. Med. Chem.* **1996**, *4*, 1135−1147.

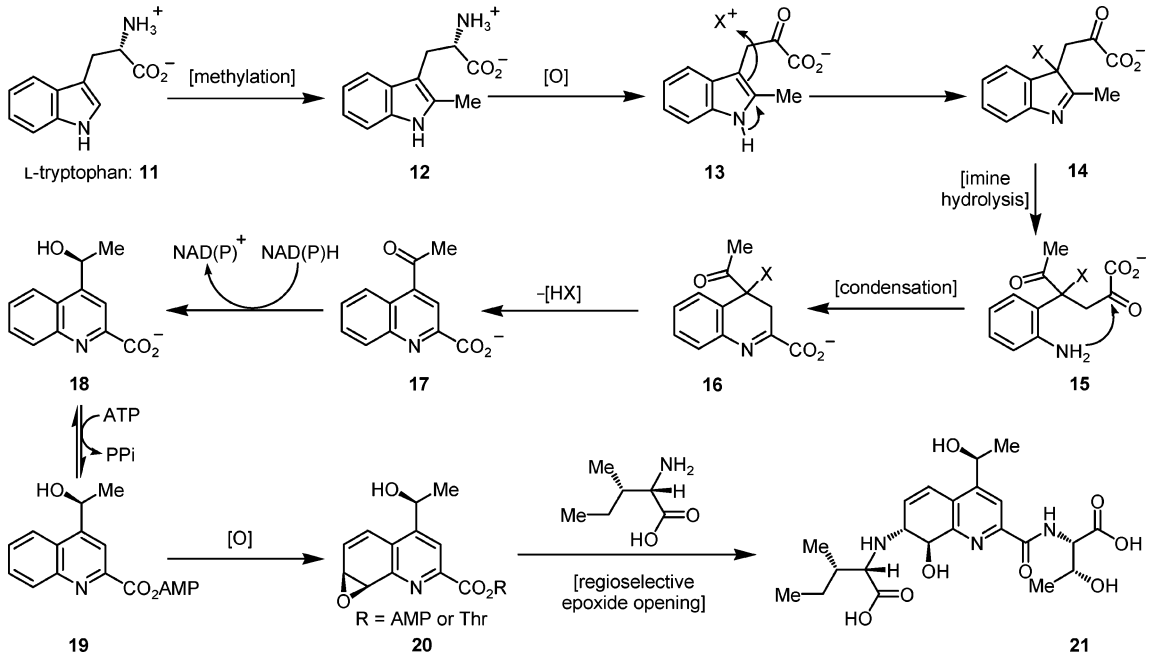


Figure 3. Biogenetic origins of thiostrepton's quinaldic acid domain.

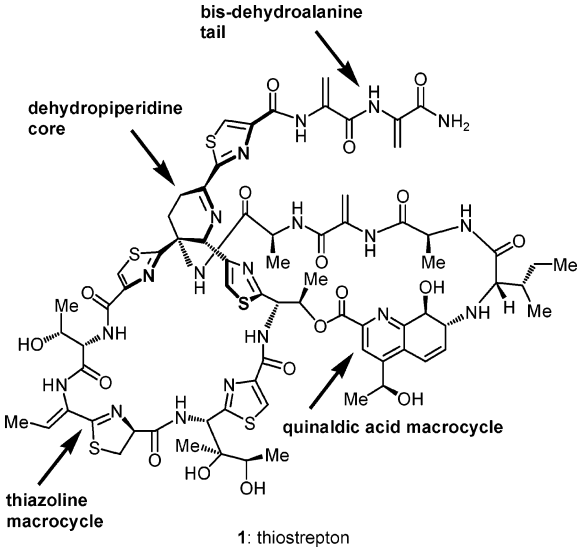


Figure 4. Special structural motifs of **1**.

of unsaturation. It is the impressive totality and puzzling connectivity of these features that make the total synthesis of **1** a most demanding and daunting task.[9] In this and the following article,[10] we describe the details of the endeavor that led to the accomplishment of this task.

Results and Discussion

1. Retrosynthetic Analysis. Given the above-described structural motifs of **1**, and recognizing its four sensitive and challenging sites (see Figure 4), we chose the retrosynthetic blueprint shown in Figure 5 as one most worthy of pursuit. Thus, because of the labile nature of the dehydroalanine moieties, it was decided to protect all three of them as phenylselenium derivatives, masking devices that could unleash the required olefinic bonds at the end of the synthesis upon simple (and innocuous) oxidation/syn elimination. Equally important at this early stage was deemed the protection of all four secondary hydroxyl groups of **1** by *tert*-butyldimethylsilyl (TBS) ether formation. The sterically encumbered tertiary hydroxyl group was left unprotected, for it was not expected to cause any problems along the synthetic path. Another strategic decision was made at this stage, namely the introduction of a triethylsilyl (TES)-protected hydroxyl group at a position β to the thiazoline ring with the anticipation that this group may give rise, at the right moment, to the desired *Z*-double bond in conjugation to the thiazoline ring. These retrosynthetic manipulations led us from **1** to the advanced intermediate **22**, whose conversion to the target molecule (**1**) should require only two operational steps. Rupture of the two amide bonds and one ester bond indicated on structure **22** then led to the detachment of the masked bis-dehydroalanine tail and disassembly of the quinaldic acid-containing 27-membered ring of the molecule, leading, upon suitable protections, to the key building blocks **23** and **24** and

(9) Synthetic studies from these laboratories: (a) Nicolaou, K. C.; Zak, M.; Safina, B. S.; Lee, S. H.; Estrada, A. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 5092−5097. (b) Nicolaou, K. C.; Safina, B. S.; Zak, M.; Estrada, A. A.; Lee, S. H. *Angew. Chem., Int. Ed.* **2004**, *43*, 5087−5092. (c) Nicolaou, K. C.; Nevalainen, M.; Zak, M.; Bulat, S.; Bella, M.; Safina, B. S. *Angew. Chem., Int. Ed.* **2003**, *42*, 3418−3424. (d) Nicolaou, K. C.; Nevalainen, M.; Safina, B. S.; Zak, M.; Bulat, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 1941−1945. (e) Nicolaou, K. C.; Safina, B. S.; Funke, C.; Zak, M.; Zécri, F. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 1937−1940. Synthetic studies from other laboratories: (f) Higashibayashi, S.; Kohno, M.; Goto, T.; Suzuki, K.; Mori, T.; Hashimoto, K.; Nakata, M. *Tetrahedron Lett.* **2004**, *45*, 3707−3712. (g) Higashibayashi, S.; Hashimoto, K.; Nakata, M. *Tetrahedron Lett.* **2002**, *43*, 105−110. For the total syntheses of simpler members of the thiopeptide class of antibiotics, see: (h) Hughes, R. A.; Thompson, S. P.; Alcaraz, L.; Moody, C. J. *Chem. Commun.* **2004**, 946−948. (i) Higashibayashi, S.; Mori, T.; Shinko, K.; Hashimoto, K.; Nakata, M. *Heterocycles* **2002**, *57*, 111−122. (j) Bagley, M. C.; Bashford, K. E.; Hesketh, C. L.; Moody, C. J. *J. Am. Chem. Soc.* **2000**, *122*, 3301−3313. (k) Ciufolini, M. A.; Shen, Y.-C. *Org. Lett.* **1999**, *1*, 1843−1846. (l) Okumura, K.; Nakamura, Y.; Shin, C.-G. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 1561−1569. (m) Okumura, K.; Saito, H.; Shin, C.-G.; Yoshimura, J.; Umemura, K. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 1863−1870. (n) Okumura, K.; Ito, A.; Yoshioka, D.; Shin, C.-G. *Heterocycles* **1998**, *48*, 1319−1324. (o) Moody, C. J.; Bagley, M. C. *Chem. Commun.* **1998**, 2049−2050. (p) Shin, C.-G.; Okumura, K.; Shigekuni, M.; Nakamura, Y. *Chem. Lett.* **1998**, 139−140. (q) Ciufolini, M. A.; Shen, Y. C. *J. Org. Chem.* **1997**, *62*, 3804−3805. (r) Okumura, K.; Shigekuni, M.; Nakamura, Y.; Shin, C.-G. *Chem. Lett.* **1996**, 1025−1026. (s) Nakamura, Y.; Shin, C.-G.; Umemura, K.; Yoshimura, J. *Chem. Lett.* **1992**, 1005−1008. (t) Kelly T. R.; Jagoe, C. T.; Gu, Z. *Tetrahedron Lett.* **1991**, *32*, 4263−4266.

(10) Nicolaou, K. C.; Zak, M.; Safina, B. S.; Estrada, A. A.; Lee, S. H.; Nevalainen, M. *J. Am. Chem. Soc.* **2005**, *127*, http://dx.doi.org/10.1021/ja052934z.

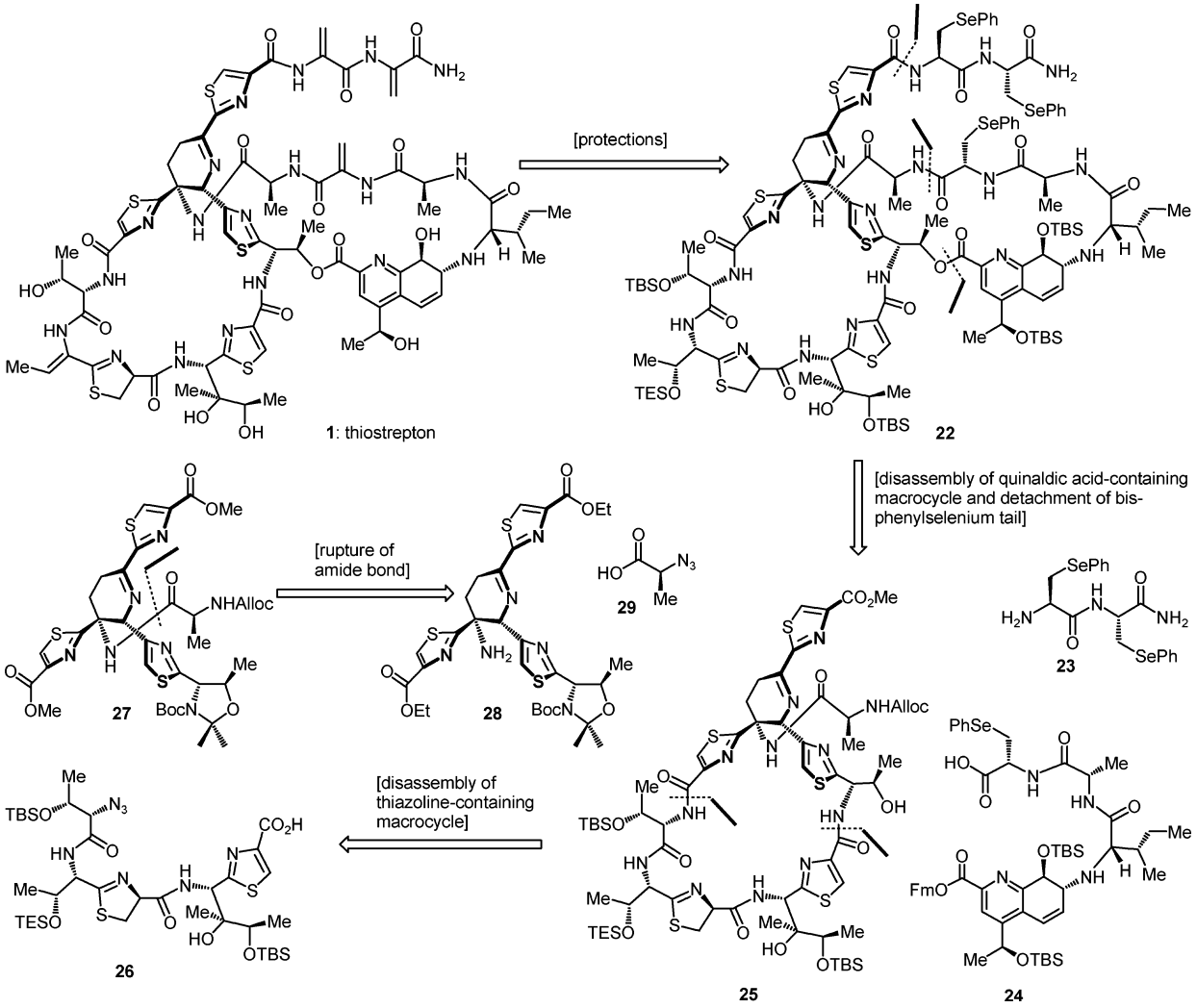


Figure 5. Retrosynthetic analysis of **1** and definition of key building blocks **23**, **24**, **26**, **28**, and **29**. TES, triethylsilyl; Boc, *tert*-butoxycarbonyl; TBS, *tert*-butyldimethylsilyl; Fm, 9-fluorenylmethyl; Alloc, allyloxycarbonyl.

the advanced intermediate **25**. The latter substrate (**25**) was then retrosynthetically doubly cut further at the indicated amide bonds to unravel the key intermediates **26** (appropriately modified to an azide moiety representing the required amino group) and **27** (appropriately protected as shown). Finally, excision of the alanine residue by rupturing the indicated amide bond on structure **27** traced the origins of this intermediate to the key building blocks dehydropiperidine **28** and the alanine equivalent **29**. The exchange of methyl for ethyl esters in the last retrosynthetic transform reflects only the ready access to the ethyl ester variant of one of the starting materials, as shown in Figure 6, in which the final and most daring retrosynthetic step is revealed.

Inspired by the biomimetic proposal regarding the origin of the dehydropiperidine domain of thiostrepton,[8] we decided to incorporate an aza-Diels−Alder dimerization strategy in our plans for the laboratory construction of this core structure. Figure 6 outlines, in retrosynthetic format, this proposal. Thus, scission of the key building block **28** through a retro-Diels−Alder reaction/dimerization as indicated led to the monomeric unit **30**, an azadiene system that was expected to arise, by H_2S abstraction, from thiazolidine **31**. The latter compound (**31**) was then easily traced to its components, aldehyde **32** and amino thiol derivative **33**. These starting materials were, in turn, traceable to cysteine and threonine, as will become apparent in the following section. In addition to the biosynthetic considerations, supporting this hypothetical plan was a previous report[11] involving generation and dimerization of a relevant azadiene system, although these results, shown in Figure 7, by no means assured the desired outcome in our present situation. Nevertheless, the aesthetic appeal and potential practical benefits of the approach were enough to override any doubts we may have had at the outset, and, therefore, we embarked on the daring adventure with optimism.

2. Construction of Building Blocks. Having decided upon the road map toward **1** as charted by the retrosynthetic analysis depicted in Figures 5 and 6, we embarked on the construction of the so-defined key building blocks required for the total synthesis. Mindful of the previous report[11] alluded to above regarding the dimerization of azadiene **34** (Figure 7) to dehydropiperidine system **35**, whose existence proved only transient on the way to enamine **36** and subsequently to aza-Mannich product **37** and enamine **38**, we entered this venture with considerable trepidation, but confident that we could alter

(11) (a) Wulff, G.; Klinken, H. T. *Tetrahedron* **1992**, *48*, 5985−5990. (b) Wulff, G.; Lindner, H. G.; Böhnke, H.; Steigel, A.; Klinken, H. T. *Liebigs Ann. Chem.* **1989**, 527−531. (c) Wulff, G.; Böhnke, H. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 90−92.

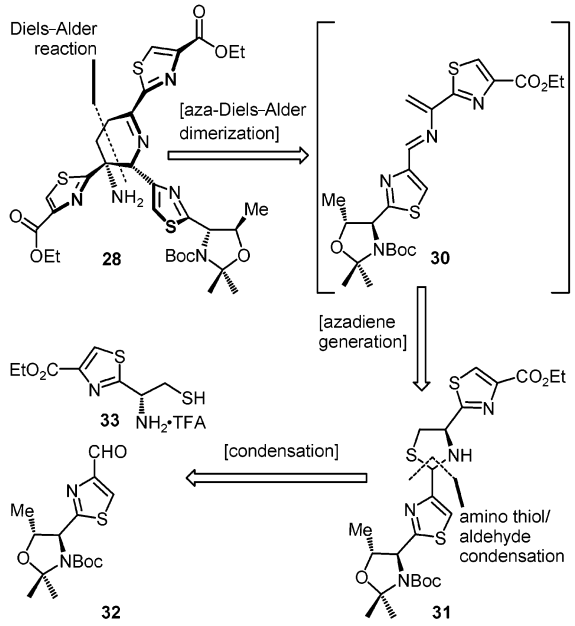


Figure 6. Retrosynthetic analysis of dehydropiperidine core **28** via a biomimetically inspired aza-Diels−Alder reaction and definition of amino thiol **33** and aldehyde **32** as starting materials.

the outcome to fit our purposes. Scheme 1 summarizes the syntheses of amino thiol TFA salt **33** (for abbreviations of all reagents and protecting groups used herein, see the legends in the schemes) and aldehyde **32** from the known L-cysteine and L-threonine derivatives **39**[9l,m] and **43**,[12] respectively, and their condensation to afford the desired thiazolidine **31** (+**31′**). Thus, L-cysteine derivative **39** was transformed to thioamide **41** through amide **40** by first coupling with *N*-hydroxysuccinimide (HOSu) as facilitated by DCC, followed by reaction with aqueous ammonia (**39**→**40**, 65% yield) and exposure to Lawesson's reagent (**40**→**41**, 85% yield). The latter thioamide (**41**) was then engaged with ethyl bromopyruvate ($BrCH_2COCO_2Et$) under basic conditions ($KHCO_3$) in a reaction followed by TFAA-assisted dehydration in the presence of pyridine (Hantzsch reaction)[13] to afford, in 90% yield, thiazole **42**. Exposure of this thiazole (**42**) to TFA cleaved both its *N*-Boc and acetonide groups, producing the TFA salt (**33**) of the desired amino thiol. The synthesis of aldehyde **32** commenced with L-threonine derivative **43**, which was first converted to amide **44** ($ClCO_2Et$, Et_3N; then NH_4OH, 78% yield) and then to thioamide **45** (Lawesson's reagent, 83% yield). The conversion of thioamide **45** to thiazole **46** proceeded along similar lines as for the transformation of **41** to **42** described above ($BrCH_2COCO_2Et$, $NaHCO_3$; then TFAA, py) in 83% yield. Subsequent reduction of thiazole ester **46** with DIBAL-H in toluene at −78 °C resulted in the formation of the required aldehyde **32** in 87% yield. Finally, condensation of the two fragments, amino thiol TFA salt **33** and aldehyde **32**, in aqueous EtOH in the presence of $KHCO_3$ produced thiazolidine **31** (+**31′**) as a 1:1 mixture of two diastereomers in 90% combined yield over two steps from **42**.

With thiazolidine **31** (+**31′**) in hand, we then proceeded to explore its much anticipated conversion to azadiene **30** and the outcome of the Diels−Alder dimerization of this intermediate,

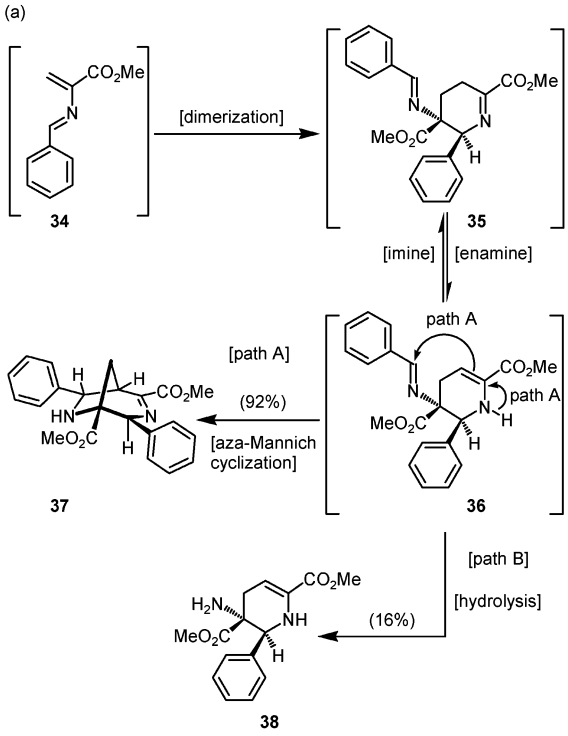


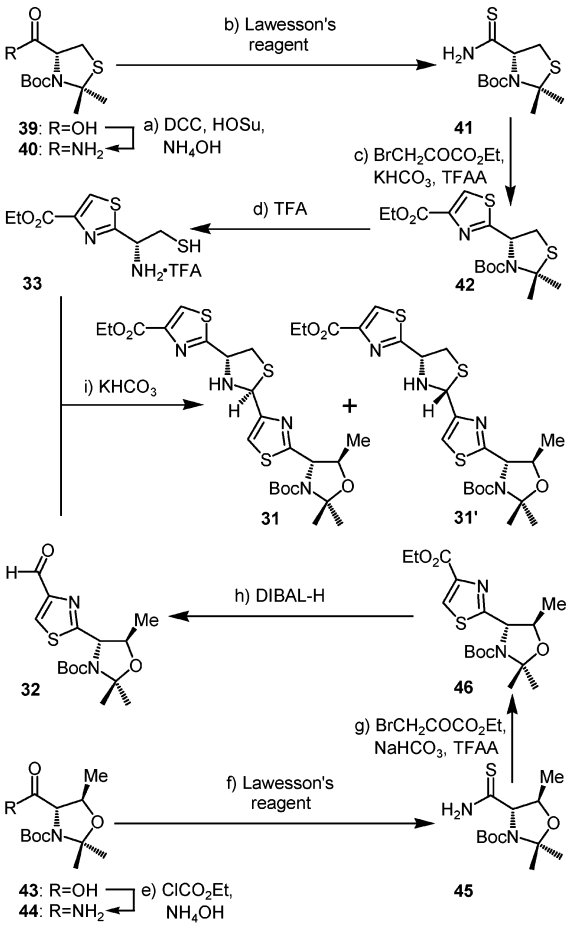
Figure 7. (a) Precedent[11] for the proposed biomimetically inspired aza-Diels−Alder dimerization reaction to construct the dehydropiperine core (**28**) of thiostrepton. (b) Comparison of product **38** from the literature-known reaction[11] and the desired dehydropiperidine core (**28**) of **1**.

which was expected to be only a transient species (Scheme 2). Indeed, upon exposure of thiazolidine **31** (+**31′**) to Ag_2CO_3 and DBU in pyridine at −12 °C, the fleeting azadiene **30** was apparently generated and dimerized according to the expected Diels−Alder mode to afford, upon workup, three products: bridged polycyclic imine system **49** (+**49′**) (63% yield, ca. 1:1 mixture of 5*R*,6*S* and 5*S*,6*R* diastereomers), dehydropiperidine **28** (+**28′**) (22% yield, ca. 1:1 mixture of 5*R*,6*S* and 5*S*,6*R* diastereomers), and aldehyde **32** (20% yield). While the structures of the dimeric products were evident from their NMR spectra, their stereochemical assignments required X-ray crystallographic analysis, a fortunate forthcoming event (vide infra).

These initial observations were delightful in that, unlike the previous results of such reactions mentioned above,[11] the stereochemistry of the thiazole substituents on the dehydropiperidine ring was trans (see Figure 7), as desired for **1**, but obviously unsatisfactory with regard to the ratio of the products. The major dimeric compound **49** (+**49′**) was apparently the result of an initial imine-to-enamine rearrangement (path B) within the Diels−Alder adduct **47** (+**47′**), followed by a stereoselective aza-Mannich cyclization as shown on the result-

(12) Kemp, D. S.; Carey, R. I. *J. Org. Chem.* **1989**, *54*, 3640−3646.
(13) (a) Kelly, R. C.; Ebhard, I.; Wicniensky, N. *J. Org. Chem.* **1986**, *51*, 4590−4594. (b) Holzapfel, C.; Pettit, G. J. *J. Org. Chem.* **1985**, *50*, 2323−2327.

Scheme 1. Synthesis of Thiazolidine **31** (+**31′**)[a]



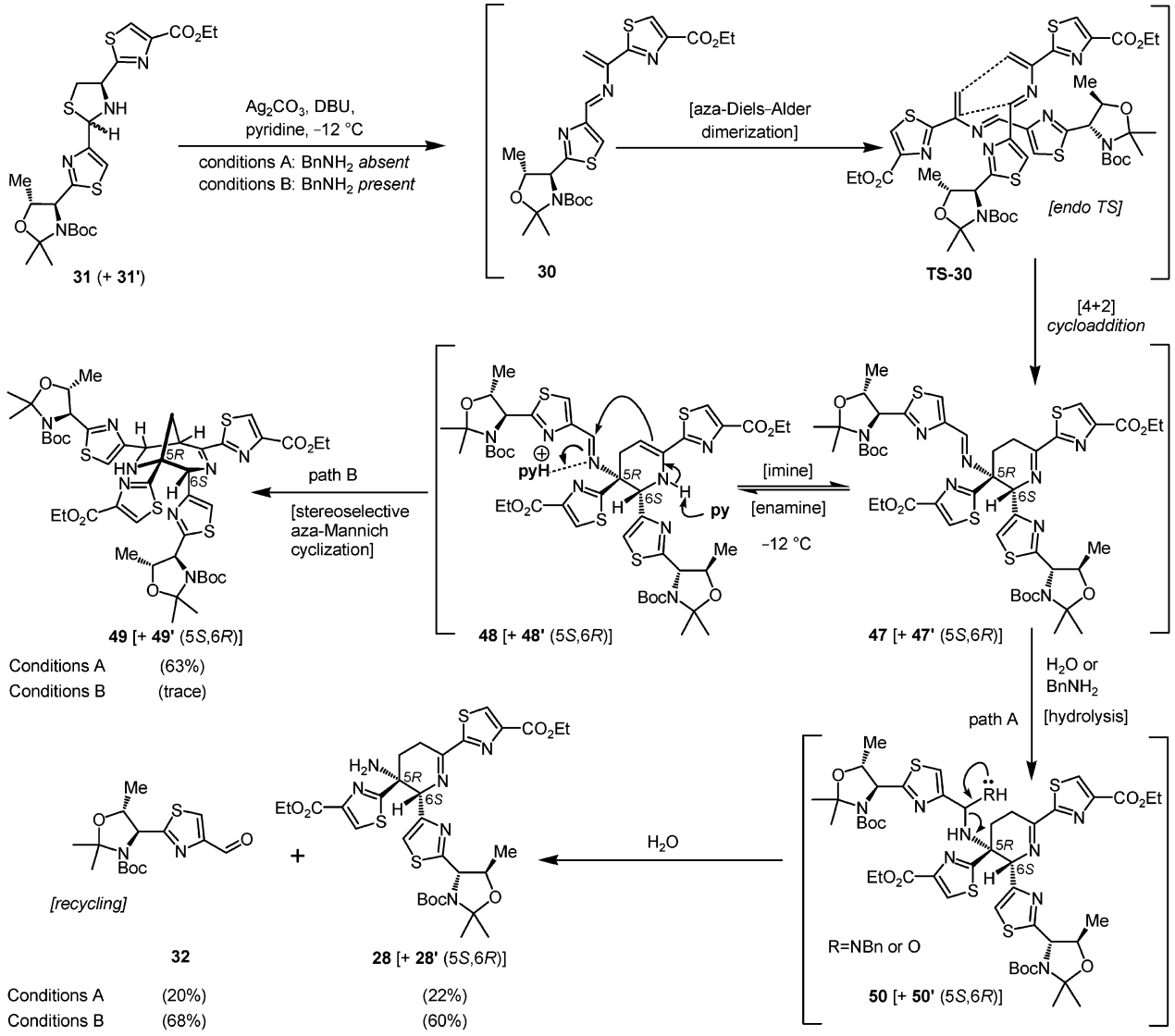
[a] Reagents and conditions: (a) DCC (1.2 equiv), HOSu (1.2 equiv), THF, 25 °C, 3 h; then 28% NH_4OH_{aq}, EtOAc, 0 °C, 30 min, 65%; (b) Lawesson's reagent (0.5 equiv), DME, 25 °C, 12 h, 85%; (c) $BrCH_2COCO_2Et$ (3.1 equiv), $KHCO_3$ (8.4 equiv), DME, 0 °C, 5 min; then 25 °C, 24 h; then TFAA (1.5 equiv), py (3.0 equiv), 0 °C, 2 h, 90%; (d) TFA:CH_2Cl_2 (1:1), 0 °C, 4 h; then EtOH:H_2O (1:1), 25 °C, concentration in vacuo; (e) $ClCO_2Et$ (1.1 equiv), Et_3N (1.1 equiv), THF, 0 °C, 2.5 h; then 28% NH_4OH_{aq}, 0 °C, 2 h; then 25 °C, 16 h, 78%; (f) Lawesson's reagent (0.6 equiv), benzene, 80 °C, 1 h, 83%; (g) $BrCH_2COCO_2Et$ (3.0 equiv), $NaHCO_3$ (8.0 equiv), DME, 25 °C, 24 h; then TFAA (4.0 equiv), py (9.0 equiv), DME, 0 °C, 2 h, 83%; (h) DIBAL-H (2.4 equiv), PhMe, −78 °C, 2 h, 87%; (i) **32** (1.0 equiv), **33** (1.0 equiv), $KHCO_3$ (3.0 equiv), EtOH:H_2O (1:1), 0−25 °C, 16 h, 90% (over two steps from **42**). Abbreviations: DCC, 1,3-dicyclohexylcarbodiimide; DME, ethylene glycol dimethyl ether; HOSu, *N*-hydroxysuccinimide; TFA, trifluoroacetic acid; TFAA, trifluoroacetic anhydride; py, pyridine; *p*-TsOH, *p*-toluenesulfonic acid; DIBAL-H, diisobutylaluminum hydride.

ing structure **48** (+**48′**) in Scheme 2. In an effort to suppress the formation of this undesired product (rare as it was) and increase the yield of the desired dehydropiperidine compound **28** (+**28′**), which is the result of hydrolysis of the initially formed Diels−Alder product **47** (+**47′**), we added benzylamine to the reaction mixture right from the outset. The expectation was that, as previously demonstrated,[11a] the thiazole aldehyde component of the imine **47** (+**47′**) would rapidly engage the added benzylamine and release the desired primary amine **28** (+**28′**) prior to the damaging aza-Mannich rearrangement. Indeed, this turned out to be the case, for when benzylamine (1.2 equiv) was added to the initial reaction mixture (conditions B), the yield of the dehydropiperidine fragment **28** (+**28′**) increased to 60% at the expense of the aza-Mannich rearrangement product **49** (+**49′**), which was now obtained only in trace amounts. Furthermore, the thiazole aldehyde **32** was isolated in 68% yield and could be recycled through incorporation into the starting thiazolidine **31** (+**31′**).

At this juncture, a method was sought to determine the stereochemistry of the two diastereomers obtained from the Diels−Alder dimerization of azadiene **30** (Scheme 2). Since the two pairs of compounds received at the end of this cascade [i.e. the dehydropiperidine **28** (+**28′**) and the aza-Mannich cyclization products **49** (+**49′**)] were interrelated, assignment of the structure to one of the four compounds would reveal the structures of all. The task was not trivial, however, due to the remoteness of the starting stereocenters from the newly generated ones (i.e. separated by the full length of the thiazole ring). Thus, compound **49** and its diastereomer **49′** (chromatographically inseparable mixture) were chosen for further manipulation in the hope for a critical clue. Pleasantly, reduction of the aza-Mannich mixture of products **49** + **49′** with $NaCNBH_3$ in EtOH in the presence of AcOH proceeded to afford exclusively and stereoselectively two diastereomeric diamines, **51** and **51′**, which were separable by silica gel column chromatography (Scheme 3). Much to our pleasant surprise, the less polar of these isomers (**51**) crystallized beautifully (EtOAc), and X-ray crystallographic analysis of one of these crystals (see ORTEP drawing, Figure 8) revealed its absolute stereochemistry and, by extension, that of all other compounds in the series. Before being able to advance dehydropiperidine **28** (+**28′**) (chromatographically inseparable ca. 1:1 mixture of 5*R*,6*S* and 5*S*,6*R* diastereomers) toward **1**, it was first necessary to complete the deceptively standard task of capping its labile primary amine.

Despite the fact that our dehydropiperidine fragment **28** (+**28′**) was an inseparable mixture of 5*R*,6*S* and 5*S*,6*R* diastereomers, we proceeded to the next stage, which called for establishment of the required peptide chain onto the primary amino group of the molecule. To this end, **28** (+**28′**) was reacted with *N*-Alloc-L-alanine derivative **52** in the presence of HOAt and EDC in the hope of obtaining amide **53** (+**53′**). Indeed, not only was an amide formed under these conditions, but luckily, the two expected diastereomers (84% combined yield, ca. 1:1 ratio) were now chromatographically separable and, therefore, obtained in pure form. Furthermore, removal of the *N*-Boc-acetonide protecting device (TFA, 100%) from the more polar isomer resulted in the formation of an amino alcohol whose 1:1 L-tartaric acid salt crystallized upon standing in EtOAc for a prolonged period of time (Figure 9). X-ray crystallographic analysis of this crystalline compound (**58**) led to a surprise, in that it revealed (see ORTEP drawing, Figure 9) the presence of a dehydropyrrolidine ring instead of the assumed dehydropiperidine core with which we started (see structures **57** and **57′**, Scheme 4, and **58**, Figure 9). A mechanistic explanation for this ring contraction is shown in Scheme 4. Thus, intramolecular attack of the primary amine within **28** (+**28′**) onto the imine (upon activation of the latter under the reaction conditions) could lead to the bicyclic core shown in structure **54** (+**54′**), which may reverse back to the starting material or proceed further to form the amino dehydropyrrolidine **55** (+**55′**), the overall process representing a ring contraction. The five-membered imine compound **55** (+**55′**) then couples to the activated alanine derivative **56** to form the observed amide product **57** (+**57′**).

Scheme 2. Hetero-Diels–Alder Dimerization Reaction: Tuning of Reaction Conditions To Produce Dehydropiperidine Core **28** (+**28′**) or Aza-Mannich Adduct **49** (+**49′**) as the Major Product of the Reaction[a]



[a] Reagents and conditions: (a) conditions A involved Ag_2CO_3 (1.0 equiv), DBU (0.25 equiv, 0.047 M pyridine solution), −12 °C, 1 h, then H_2O:EtOAc (1:1), −12 to 25 °C, 1 h, **49** (+**49′**), 63%; **28** (+**28′**) 22%; **32**, 20%; (b) conditions B involved Ag_2CO_3 (1.0 equiv), DBU (0.25 equiv, 0.047 M pyridine solution), $BnNH_2$ (1.2 equiv), −12 °C, 45 min, then H_2O:EtOAc (1:1), −12 to 25 °C, 1 h, **49** (+**49′**), trace; **28** (+**28′**), 60%; **32**, 68%. Abbreviations: $BnNH_2$, benzylamine; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene.

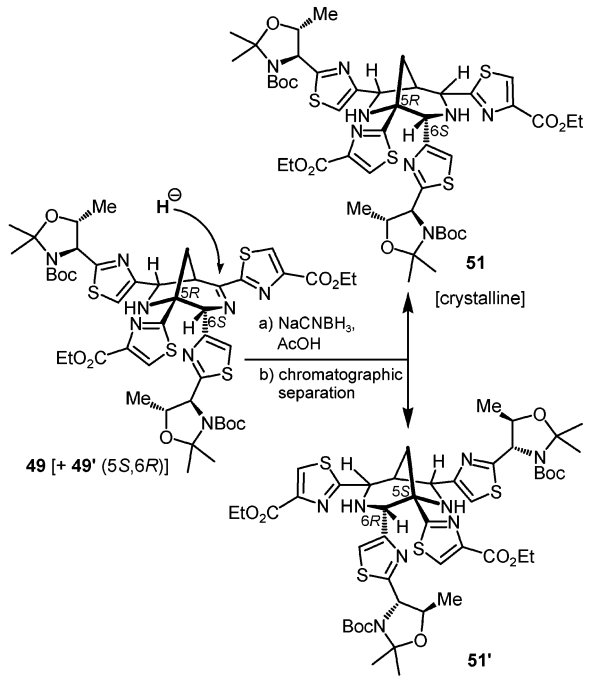
Faced with this new hurdle of the imine core contraction, we set out to investigate conditions that would avoid it during the crucial amide bond formation, capping the labile primary amine within dehydropiperidine structure **28** (+**28′**). Our first foray envisioned a reduction–oxidation sequence[9g] as a safe expedition to the desired L-alanine coupled product **27** (+**27′**), as shown in Scheme 5. Thus, dehydropiperidine **28** (+**28′**) was stereoselectively[14] reduced with $NaCNBH_3$ in the presence of AcOH, leading to piperidine intermediate **59** (+**59′**) in 63% yield. The latter compound [**59** (+**59′**)] entered into selective (reacting only with its primary amino group) coupling with *N*-Alloc-L-Ala (**52**) as facilitated by HATU, HOAt, and *i*-Pr_2-NEt to produce peptides **60** (+**60′**) in 88% yield, whose ethyl ester groups were conveniently exchanged to methyl esters by the action of *n*-Bu_2SnO in MeOH at 70 °C (95% yield).[15] Finally, the targeted imino peptides **27** (+**27′**) were generated from their secondary amine counterparts by oxidation with *t*-BuOCl at −78 °C, a reaction that proceeded, in 69% yield, to afford the chromatographically separable products **27** (+**27′**). Despite its success, however, this sequence failed to satisfy our need for large amounts of the desired dehydropiperidine peptide due to nonreproducibility on a large scale and its rather roundabout nature. We, therefore, embarked on a systematic search for a direct approach to capturing the desired six-membered imino amine with a suitably reactive L-alanine equivalent.

As part of our search, a variety of electrophiles were explored as partners in the coupling reaction of dehydropiperidine fragment **28** (+**28′**) under appropriate conditions. The results listed in Table 1 encapsulate the essence of our observations, which was that relatively large and less reactive electrophiles lead to complete rearrangement of the dehydropiperidines to the undesired five-membered ring compounds (entries 1 and

(14) The configuration of the newly formed stereocenter (i.e. *C*2) was assigned by NOE studies of a peptide-coupled derivative (see ref 9d).

(15) Baumhof, P.; Mazitschek, R.; Giannis, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 3672–3674.

Scheme 3. Reduction of Imino Amine **49** (+**49′**) to Crystalline Diamine **51** and Its Diastereomer **51′** [a]



[a] Reagents and conditions: (a) $NaCNBH_3$ (2.0 equiv), AcOH:EtOH (1:1), 25 °C, 2 h; (b) column chromatography, silica gel, CH_2Cl_2:EtOAc, 1:1, **51** (5*R*,6*S*) 40%, **51′** (5*S*,6*R*) 37%.

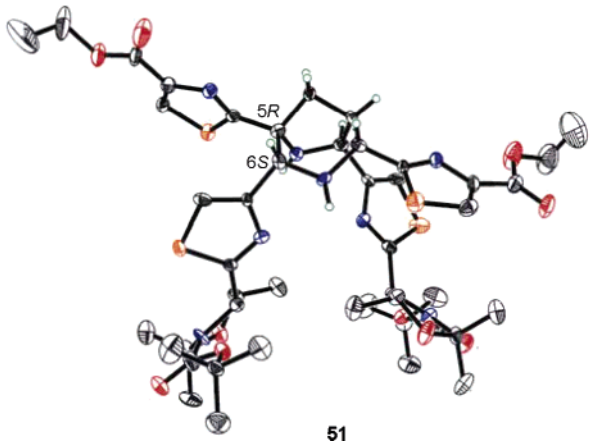


Figure 8. X-ray crystallographic ORTEP drawing of analysis-derived diamine **51** (5*R*,6*S*).

2), whereas smaller and more potent electrophiles react with retention of the desired six-membered ring core structure (entries 5 and 6). Somewhere between lay the medium-sized electrophiles, which give mixtures of the two types of products, as seen in entries 3 and 4. These conclusions were not arrived at randomly, but rather through a logical sequence of experiments.

It should first be noted that, similar to the results of entry 1, Table 1 (and Scheme 4), reaction of dehydropiperidine core **28** (+**28′**) with *N*-Alloc and other carbamate-protected L-alanine substrates (i.e. Boc, Fmoc derivatives), in the presence of a variety of standard coupling reagents (i.e. HATU, TBTU, PyBOP, CIP), led to exclusive formation of the undesired five-membered imino peptide **II** (+**II′**). Frustrated by the inability to capture the six-membered imine with an alanine derivative, we then attempted to rescue it with other electrophiles in an effort to gain a better understanding of the imine contraction

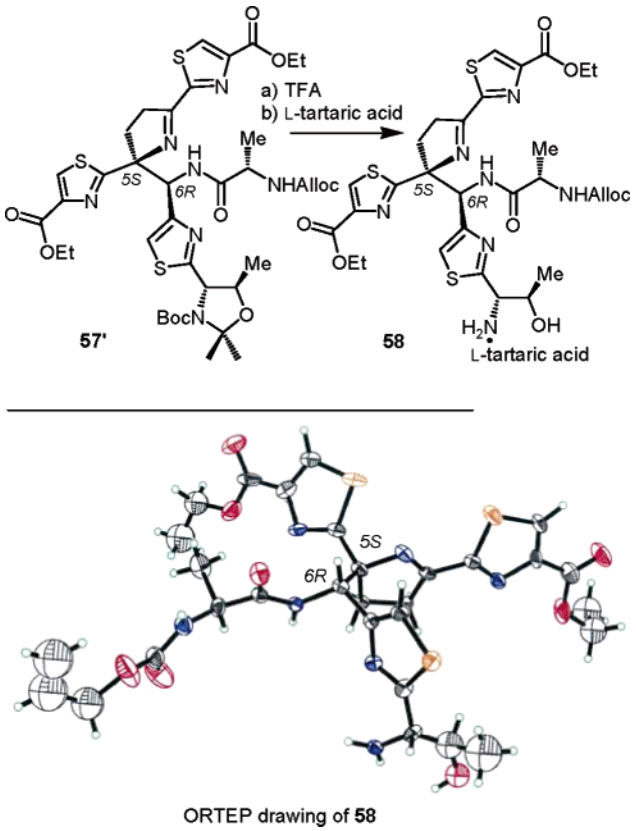
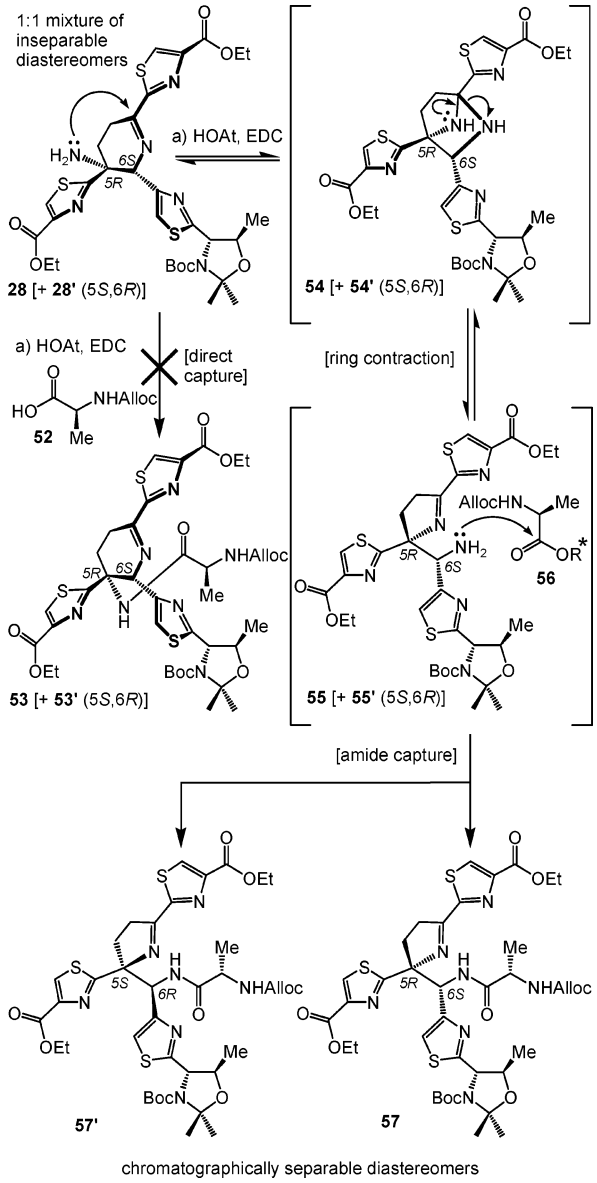


Figure 9. Conversion of L-alanine-coupled dehydropyrrolidine **57′** to amino alcohol **58** and ORTEP drawing of **58** (5*S*,6*R*) obtained by X-ray crystallographic analysis of its 1:1 salt with L-tartaric acid (L-tartaric acid not shown). Reagents and conditions: (a) TFA:CH_2Cl_2 (1:1), 0−25 °C, 2 h, 100%; (b) L-tartaric acid (1.0 equiv), EtOAc.

process. After much experimentation, the first promising coupling results were obtained during an attempt to engage the free amine of dehydropiperidine core **28** (+**28′**) with allyl chloroformate **64** in the presence of 4-DMAP and *i*-Pr_2NEt in CH_2Cl_2 (entry 3, Table 1). This reaction, which was presumed to proceed via the allyl 4-*N*,*N*-dimethylpyridinium carbonate adduct (see Table 1, entry 3), produced a mixture of six- and five-membered *N*-Alloc-coupled imines (84% combined yield), with the desired six-membered dehydropiperidine **65** (+**65′**) predominating in a ca. 3:1 ratio. In an effort to improve the selectivity of this reaction for the six-membered imine, the coupling was attempted with allyl carbonate−HOAt reagent **62**[16] in acetonitrile (entry 2, Table 1). In this case, the selectivity for the desired six-membered ring product was completely eroded, leading exclusively, and in 87% yield, to the undesired five-membered *N*-Alloc derivative **63** (+**63′**). The coupling reaction was then carried out with allyl chloroformate (**64**) and *i*-Pr_2-NEt in CH_2Cl_2 (or THF) in the *absence* of 4-DMAP (entry 5, Table 1), this time resulting in the exclusive formation of the desired six-membered *N*-Alloc amide **65** (+**65′**) in 83% yield. These coupling reactions (i.e. those depicted in entries 2, 3, and 5, Table 1) gave two important clues as to how to secure the capture of the desired six-membered imine with an alanine derivative. It was reasoned that chloride-containing electrophiles were favoring capture of the six-membered imine, as did conducting the reaction in less polar solvents such as CH_2Cl_2

(16) Hayakawa, Y.; Wakabayshi, S.; Kato, H.; Noyori, R. *J. Am. Chem. Soc.* **1990**, *112*, 1691−1696.

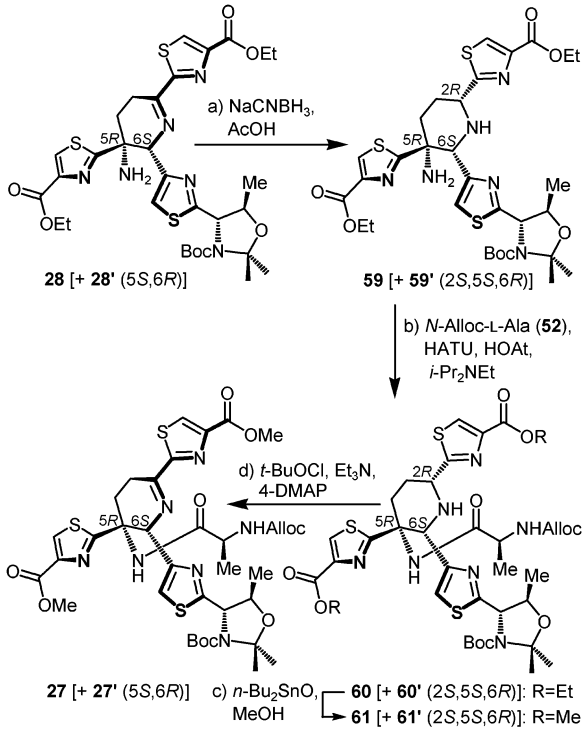
Scheme 4. Unexpected Six- to Five-Membered Imine Ring Contraction during Attempted Coupling of *N*-Alloc-L-Ala (**52**) with Dehydropiperidine Core **28** (+**28′**)[a]



[a] Reagents and conditions: (a) i. *N*-Alloc-L-Ala-OH (**52**) (1.2 equiv), HOAt (1.3 equiv), EDC (1.3 equiv), DMF, 0−25 °C, 24 h, 84% combined yield; ii. separation of diastereomers (silica gel, Et_2O:toluene, 6:4−8:2). Abbreviations: HOAt, 1-hydroxy-7-azabenzotriazole; EDC, 1-ethyl-(3-dimethylaminopropyl)carbodiimide hydrochloride; DMF, *N*,*N*-dimethylformamide; R*, activating group.

or THF. Using this intelligence information as a guide, dehydropiperidine core **28** (+**28′**) was exposed to *N*-Alloc alanine acid chloride **66** and *i*-Pr_2NEt in THF (entry 4, Table 1), providing a mixture of six- and five-membered *N*-Alloc alanine-coupled imines (76% combined yield) in which the undesired five-membered dehydropyrrolidine **57** (+**57′**) was predominating (ca. 2:1 ratio). With these results in hand, and mindful of the smaller size of allyl chloroformate (**64**) as compared to that of *N*-Alloc alanine acid chloride **66**, we set out to explore the reactivity of a smaller alanine equivalent that could, potentially, mirror more closely the six-membered imine coupling preference of allyl chloroformate. Indeed, when dehydropiperidine core **28** (+**28′**) was combined with azido alanine acid chloride **67** [prepared by (i) copper(II)-catalyzed

Scheme 5. Reduction−Oxidation Route to Dehydropiperidine Peptide Fragment **27** (+**27′**)[a]



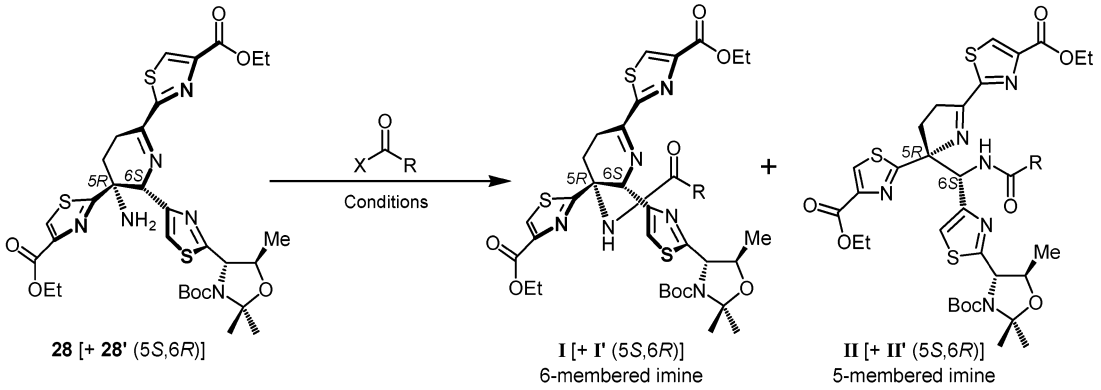
[a] Reagents and conditions: (a) $NaCNBH_3$ (2.0 equiv), EtOH:AcOH (4:1), 0 °C, 1 h, 63%; (b) *N*-Alloc-L-Ala-OH (**52**) (5.0 equiv), HOAt (5.0 equiv), HATU (5.0 equiv), *i*-Pr_2NEt (10.0 equiv), DMF, 0−25 °C, 48 h, 88%; (c) *n*-Bu_2SnO (3.0 equiv), MeOH, 70 °C, 6 h, 95%; (d) *t*-BuOCl (2.0 equiv), THF, −78 °C, 20 min; then 4-DMAP (0.2 equiv), Et_3N (5.0 equiv), −78 to 25 °C, 80 min, 38% (**27**) +31% (**27′**). Abbreviations: HATU, *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate; 4-DMAP, 4-dimethylaminopyridine.

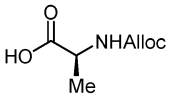
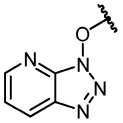
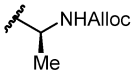
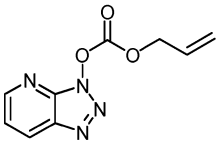
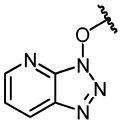
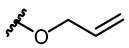
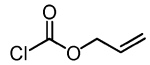
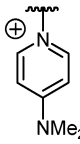
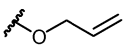
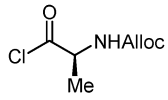
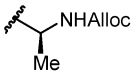
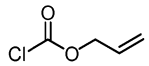
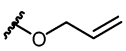
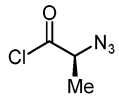
diazo-transfer reaction of L-alanine[17] and (ii) exposure of the resulting *N*-azido-L-alanine derivative to oxalyl chloride] in the presence of Et_3N in THF, exclusive formation of the coveted six-membered alanine coupled imine product **68** (+**68′**) was observed, in 70% yield. Thus, success was finally achieved in securing direct and exclusive access to the desired dehydropiperidine peptide **68**, albeit still as a 1:1 mixture with its 5*S*,6*R*-diastereomer **68′**. Separation of **68** from its undesired sibling, **68′**, and definitive identification as the desired isomer (5*R*,6*S*) were still lingering problems, however.

Figure 10 outlines a postulated mechanistic rationale for the dependence of the coupling reaction on electrophile size and reactivity. When the dehydropiperidine core **28** (+**28′**) is depicted in its (presumed) preferred half-chair conformation, it becomes apparent that its free amine is rather sterically encumbered. Not only is it attached to a quaternary center, but it is also shielded by the two thiazole rings that surround it. A large electrophile (e.g. activated *N*-Alloc-L-ala **56**) is apparently unable to link with the free amine directly (path A), thus allowing the six-membered imine core **28** (+**28′**) to undergo contraction to its five-membered counterpart (path B), and thereby producing the coupled five-membered imine dehydropyrrolidine **II** (+**II′**). Conversely, a small and more aggressive electrophile is capable of approaching close enough to the free

(17) (a) Nyffeler, P. T.; Liang, C.-H.; Koeller, K. M.; Wong, C.-H. *J. Am. Chem. Soc.* **2002**, *124*, 10773−10778. (b) Alper, P. B.; Hung, S.-C.; Wong, C.-H. *Tetrahedron Lett.* **1996**, *37*, 6029−6032.

Table 1. Selective Capture of the Five- or Six-Membered Imine: Electrophile Effects



Entry	Electrophile Conditions	X	R	Product(s) [Ratio **I** (+ **I'**) : **II** (+ **II'**)]	Yield (%)	Comments
1	 **51**, (1.2 equiv) EDC (1.3 equiv), HOAt (1.2 equiv), DMF, 24 h, 25 °C			**57** (+ **57'**) [0 : 100]	84	- large electrophile - exclusive 5-membered imine formation
2	 **62**, (1.5 equiv) CH_3CN, 4 h, 25 °C			**63** (+ **63'**) [0 : 100]	87	- large electrophile - exclusive 5-membered imine formation
3	 **64**, (5.0 equiv) *i*-Pr_2NEt (10 equiv), 4-DMAP (0.2 equiv), CH_2Cl_2, 25 °C, 2 h			**65** (+ **65'**) : **63** (+ **63'**) [75 : 25]	84	- medium-sized electrophile - mixture of 5- and 6-membered imines
4	 **66**, (1.1 equiv) *i*-Pr_2NEt (3.0 equiv), THF, 0 °C, 2 h			**53** (+ **53'**) : **57** (+ **57'**) [33 : 67]	76	- medium-sized electrophile - mixture of 5- and 6-membered imines
5	 **64**, (5.0 equiv) *i*-Pr_2NEt (10 equiv), CH_2Cl_2, or THF, 25 °C, 2 h			**65** (+ **65'**) [100 : 0]	83	- small electrophile - exclusive 6-membered imine formation
6	 **67**, (2.4 equiv) Et_3N (8.0 equiv), THF, 0 °C, 1 h			**68** (+ **68'**) [100 : 0]	70	- small electrophile - exclusive 6-membered imine formation

amine of the dehydropiperidine core **28** (+**28′**) (path A) so as to allow the desired amide bond formation, producing the desired six-membered dehydropiperidine system **I** (+**I′**).

With the coupling of dehydropiperidine core **28** (+**28′**) and L-ala equivalent **67** reliably affording the intact dehydropiperidine peptide **68** (+**68′**), as shown in Scheme 6, the latter compound was subjected to transesterification conditions (*n*-Bu_2SnO, MeOH, 75 °C),[15] furnishing the bis-methyl ester mixture of diastereomeric compounds **69** (+**69′**) in 80% yield. Reduction of this mixture with $SnCl_2 \cdot 2H_2O$ then produced the

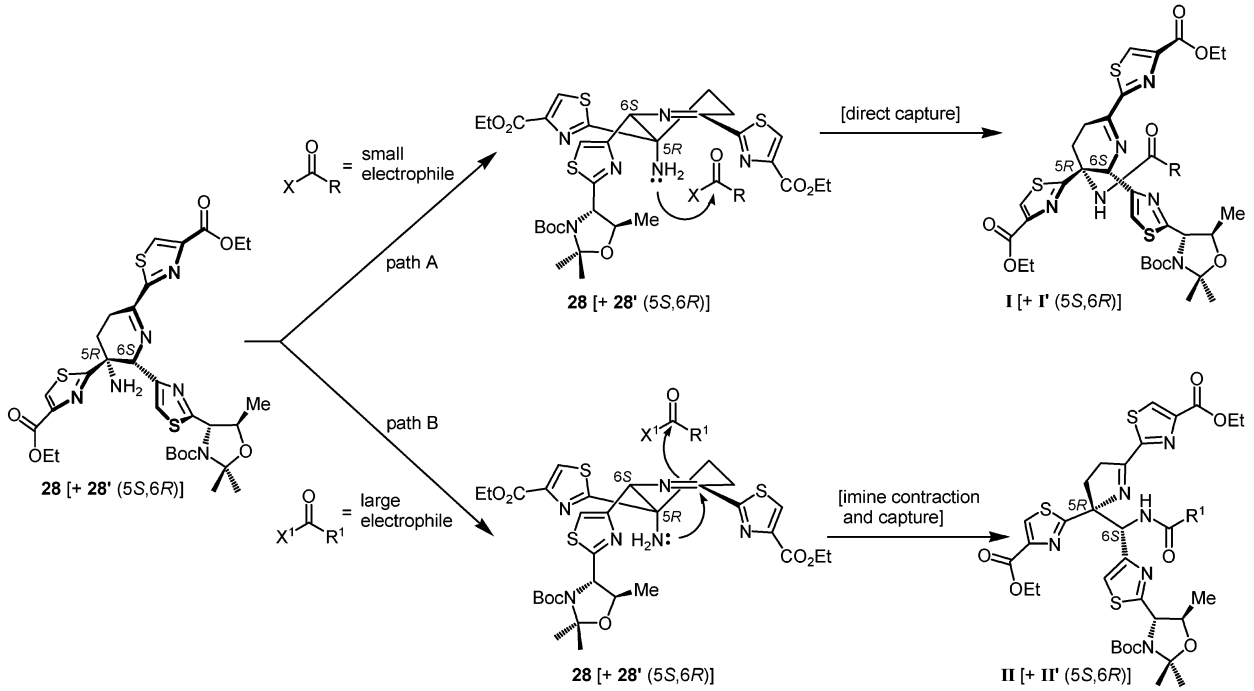
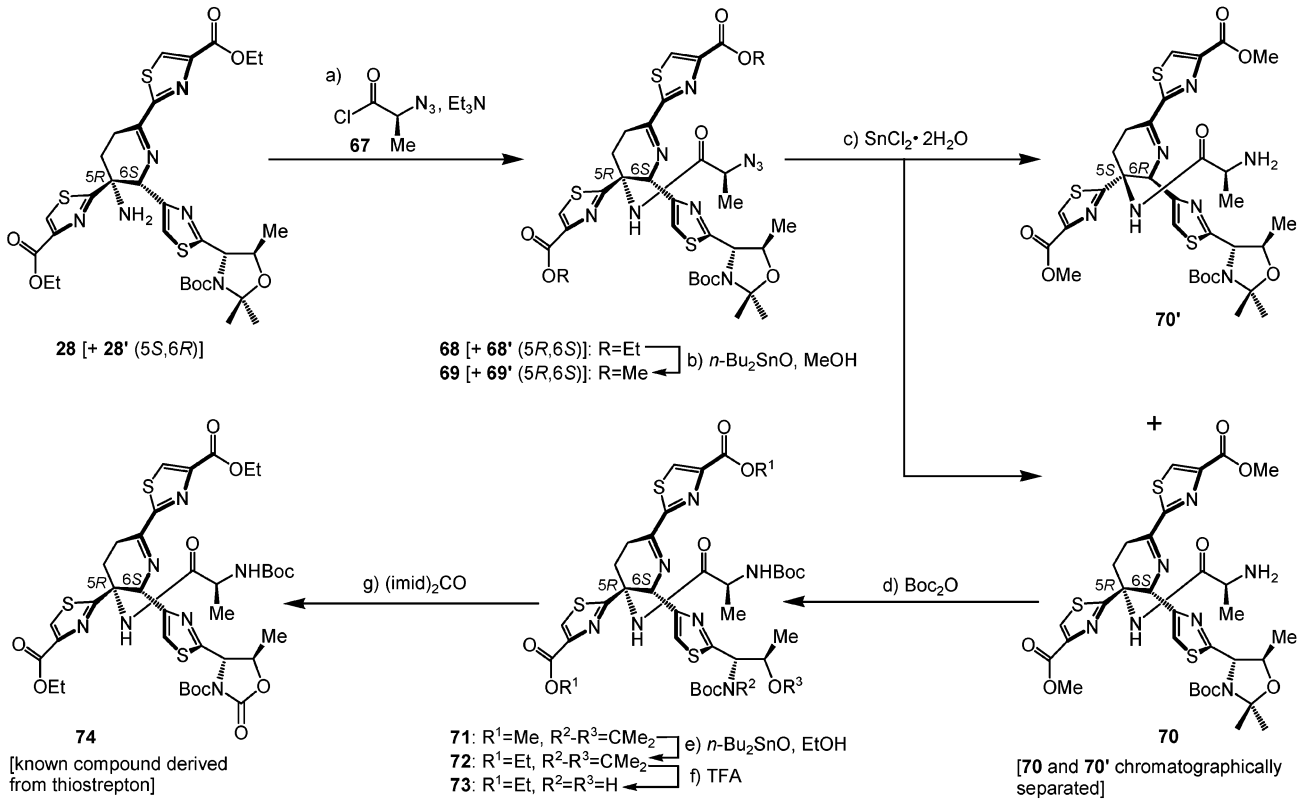


Figure 10. Proposed mechanistic rationale for the imine contraction within **28** (+**28′**).

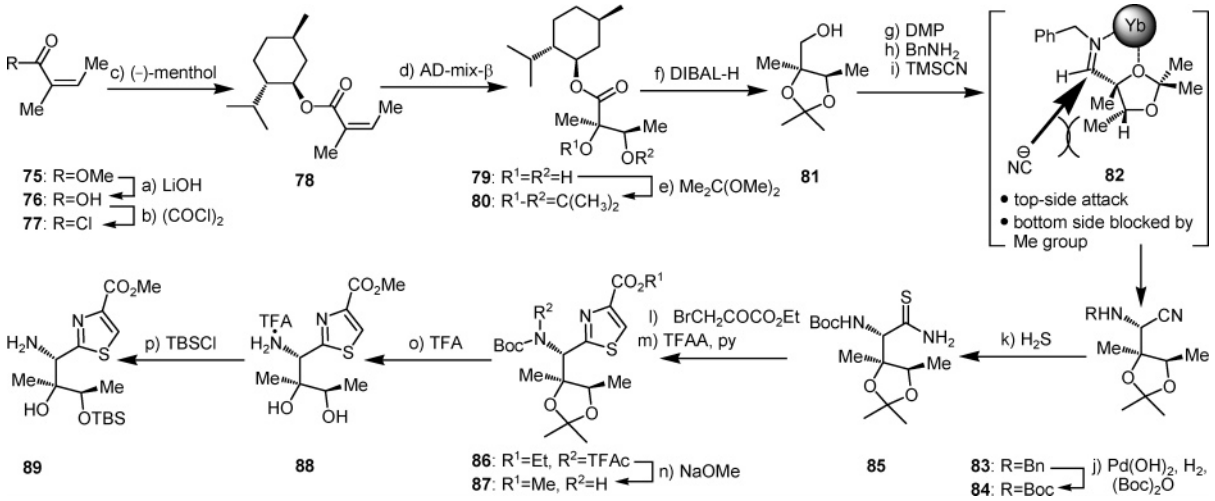
Scheme 6. Separation of Dehydropiperidine Diastereomers **70** and **70′** and Elucidation of Their *C*5/*C*6 Stereochemistry by Conversion to Known Thiostrepton-Derived Compound **74**[a]



[a] Reagents and conditions: (a) **67** (2.4 equiv), Et_3N (8.0 equiv), THF, 0 °C, 1 h, 70%; (b) *n*-Bu_2SnO (3.0 equiv), MeOH, 75 °C, 7.5 h, 80%; (c) i. $SnCl_2 \cdot 2H_2O$ (3.0 equiv), MeOH, H_2O, 25 °C, 2 h; ii. silica gel, CH_2Cl_2:MeOH 98:2−96:4, **70** (5*R*,6*S*) 44%, **70′** (5*S*,6*R*) 38%; (d) Boc_2O (5.0 equiv), *i*-Pr_2NEt (10.0 equiv), 4-DMAP (0.1 equiv), THF, 25 °C, 1 h, 61%; (e) *n*-Bu_2SnO (5.0 equiv), EtOH, 65 °C, 5 h, 79%; (f) TFA:MeOH (1:1), 0 °C, 1 h, 54% (+40% recovered **72**); (g) $(imid)_2CO$ (3.0 equiv), 4-DMAP (4.0 equiv), DMF, 25 °C, 48 h, 81%. Boc_2O, di-*tert*-butyl dicarbonate.

corresponding amines which, much to our delight, exhibited sufficiently different chromatographic mobilities on silica gel so as to allow their separation into pure samples, **70** (5*R*,6*S*, 44% yield) and **70′** (5*S*,6*R*, 38% yield). The stereochemical identities of the two isomers were determined by conversion of the less polar diastereomer (**70**, silica gel, CH_2Cl_2:MeOH 96:4, $R_f = 0.34$) to the known compound **74** (Scheme 6) derived from a thiostrepton degradation product.[9g] The sequence from **70** to

Scheme 7. Synthesis of Thiazole Fragment **89**[a]



[a] Reagents and conditions: (a) LiOH (1.1 equiv), MeOH:H_2O (1:1), reflux, 4 h, 90%; (b) KOH (1.0 equiv), $(COCl)_2$ (5.0 equiv), Et_2O, DMF (cat.), 0 °C, 4 h; (c) (−)-menthol (0.7 equiv), Et_2O, 25 °C, 48 h, 70% (two steps); (d) AD-mix-β (1.5 equiv), $MeSO_2NH_2$ (1.0 equiv), *t*-BuOH:H_2O (1:1), 0 °C, 24 h, 90%, 90:10 dr; (e) $Me_2C(OMe)_2$ (22 equiv), *p*-TsOH (0.05 equiv), 25 °C, 1 h, 100%; (f) DIBAL-H (2.2 equiv), CH_2Cl_2, −78 °C, 2 h, 90%; (g) DMP (1.1 equiv), $NaHCO_3$ (2.0 equiv), CH_2Cl_2, 0 °C, 1 h; then 25 °C, 4 h; (h) $BnNH_2$ (2.2 equiv), $Yb(OTf)_3$ (0.2 equiv), 4 Å MS, CH_2Cl_2, 25 °C, 3 h; (i) TMSCN (2.5 equiv), CH_2Cl_2, 25 °C, 2 h, 90% (three steps), >95:5 dr; (j) $(Boc)_2O$ (1.1 equiv), EtOAc, 20% $Pd(OH)_2$ (0.2 equiv), H_2, 25 °C, 8 h, 75%; (k) H_2S, Et_3N:EtOH:py (1.7:1.7:1), sealed tube, 25 °C, 24 h, 91%; (l) $BrCH_2COCO_2Et$ (3.0 equiv), $KHCO_3$ (8.0 equiv), DME, 0 °C, 4 h; then 25 °C, 16 h; (m) TFAA (4.0 equiv), py (8.0 equiv), 0 °C, 2 h; then 25 °C, 1 h, 82% (two steps); (n) NaOMe (3.2 equiv), MeOH, 0 °C, 5 h, 91%; (o) TFA:CH_2Cl_2:MeOH (1.1:1.0:0.1), 0 °C, 1 h; then 25 °C, 2 h; (p) TBSCl (2.2 equiv), Et_3N (3.3 equiv), CH_2Cl_2, 0 °C, 3 h, 87% (over two steps). Abbreviations: DMP, Dess−Martin periodinane; TMSCN, trimethylsilyl cyanide; *p*-TsOH, *p*-toluenesulfonic acid; TBSCl, *tert*-butyldimethylsilyl chloride; TFAc, trifluoroacetyl.

74 proceeded smoothly as follows. *N*-Boc protection (Boc_2O, *i*-Pr_2NEt, 4-DMAP) of the newly generated amine in **70** furnished derivative **71** in 61% yield. Exposure of this derivative to *n*-Bu_2SnO in EtOH at 65 °C[15] caused transesterification of both ester groups, furnishing bis-ethyl ester **72** (79% yield), whose *N*-Boc-acetonide structural motif was broken down to afford the corresponding *N*-Boc hydroxy compound **73** by stirring in TFA:MeOH at 0 °C (54% yield, plus 40% recovered starting material **72**). Finally, exposure of compound **73** to carbonyl diimidazole and 4-DMAP led to the targeted carbamate derivative **74** (81% yield), whose spectral data were in complete agreement with those reported[9g] for the naturally derived substance, thus confirming the 5*R*,6*S* stereochemistry for intermediate **70** and, therefore, its relatives.

Having solved all the problems associated with the dehydropiperidine core fragment and secured an expedient route to the key building block **70**, we then turned our attention to the other required fragments for our synthesis. We will first describe the assembly of the thiazoline−thiazole fragment **26** (see Scheme 9), beginning with the stereoselective construction of the thiazole subunit **89**, as shown in Scheme 7. Thus, commercially available angelic acid methyl ester (**75**) was first hydrolyzed with LiOH in MeOH:H_2O (1:1) to afford angelic acid[18] (**76**, 90% yield), which was then converted to its acid chloride (**77**, oxalyl chloride) and whose reaction with (−)-menthol furnished angelic acid menthyl ester **78** (70% over two steps). Exposure of the latter compound (**78**) to Sharpless asymmetric dihydroxylation conditions (AD-mix-β, $MeSO_2NH_2$) provided diol **79** in 90% yield and ca. 90:10 diastereomeric ratio.[19] This 1,2-diol (**79**) was then converted to the corresponding acetonide (2,2-dimethoxypropane, *p*-TsOH cat., 100% yield), at which point the minor stereoisomer was removed by silica gel chromatography to afford isomerically pure compound **80**. This compound was then treated with DIBAL-H, conditions which cleaved the chiral auxiliary group and generated the required primary alcohol (**81**, 90% yield), setting the stage for the pending three-step, one-pot sequence to install the final stereogenic center of the targeted thiazole unit. Thus, alcohol **81** was first oxidized with DMP to afford the corresponding aldehyde, which was condensed with benzylamine in the presence of 4 Å molecular sieves to give benzylimine **82**, whose substrate-controlled asymmetric Strecker-type reaction with TMSCN in the presence of catalytic amounts of $Yb(OTf)_3$ (Scheme 7) resulted in the formation of nitrile **83** in 90% overall yield and >95:5 diastereoselectivity. The high stereoselectivity observed in this process can be rationalized by the rendition of **82** in Scheme 7. Hydrogenolysis of the benzyl group within nitrile **83** in the presence of Boc_2O produced *N*-Boc derivative **84** (75% yield), which was then reacted with excess H_2S and Et_3N in a sealed tube to afford thioamide **85** in 91% yield. Hantzsch reaction (ethyl bromopyruvate, $KHCO_3$) of the latter intermediate (**85**), followed by dehydration of the incipient hydroxythiazoline with TFAA and pyridine, led to thiazole trifluoroacetate **86** in 82% overall yield. Exposure of the latter compound (**86**) to NaOMe in MeOH served both to cleave the superfluous trifluoroacetate group and to transesterify the ethyl ester, furnishing methyl ester **87** in 91% yield. Finally, upon TFA-induced removal of both the *N*-Boc and acetonide from **87** to afford amino diol **88**, the secondary hydroxyl group so generated was selectively blocked with TBS over the tertiary hydroxyl moiety, forming the desired thiazole intermediate **89** in 87% overall yield. That this intermediate possessed the correct stereochemistry as shown was proven beyond doubt by an X-ray crystallographic analysis (see ORTEP drawing, Figure 11) of the related *N*-Boc ethyl ester derivative **90**, prepared from compound **86** upon reaction with NaOEt in EtOH (90% yield) and crystallization from EtOAc.

(18) Buckles, R. E.; Mock, G. V. *J. Org. Chem.* **1950**, *15*, 680−684.
(19) (a) Torres-Valencia, J. M.; Cerda-García-Rojas, C. M.; Joseph-Nathan, P. *Tetrahedron: Asymmetry* **1998**, *9*, 757−764. (b) Miyashita, M.; Shiina, I.; Miyoshi, S.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 1516−1527.

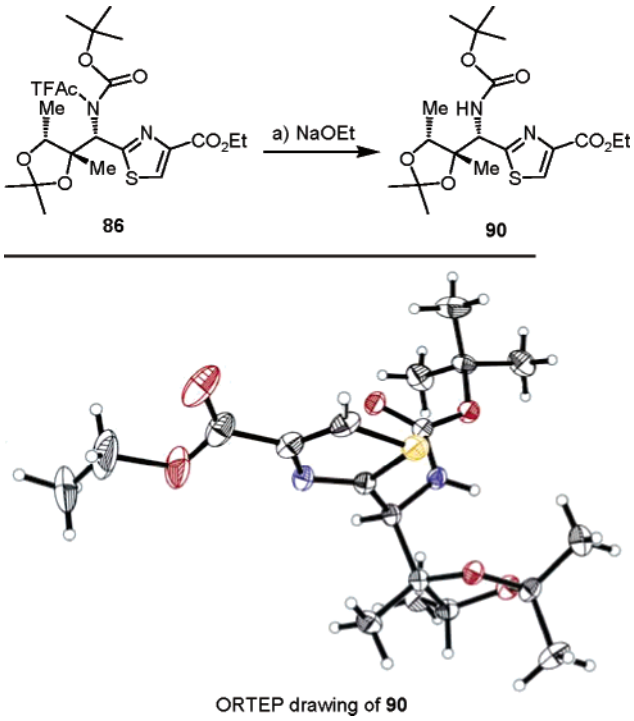
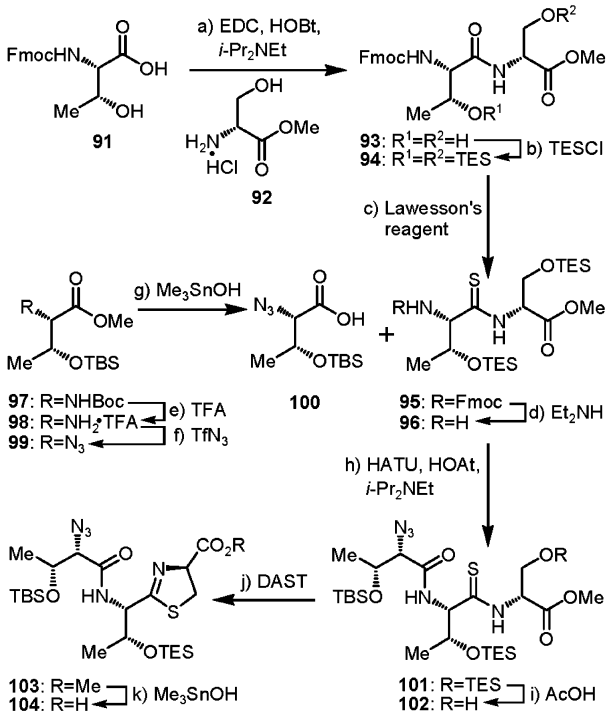


Figure 11. Synthesis of thiazole amino diol derivative **90** and proof of relative stereochemistry by X-ray crystallographic analysis. Reagents and conditions: (a) NaOEt (1.0 equiv), EtOH, 0 °C, 1 h, 90%. TFAc, trifluoroacetyl.

The second required fragment for the thiazoline−thiazole domain, thiazoline subunit **104**, was synthesized as shown in Scheme 8. *N*-Fmoc-L-threonine **91** was coupled with D-serine methyl ester hydrochloride **92** in the presence of HOBt, EDC, and *i*-Pr_2NEt to furnish dipeptide **93** in 93% yield. Protection of the free hydroxyls of the latter compound (**93**) as TES ethers (TESCl, imid., 81% yield) was followed by exposure of the resulting amide derivative **94** to Lawesson's reagent in refluxing benzene, affording, selectively, thioamide **95** (83% yield). Removal of the *N*-Fmoc group (Et_2NH, 83% yield) from this intermediate then revealed free amine **96**. In parallel, L-threonine derivative **97**[20] was converted to the free amine **98** by the action of TFA, and then to azide **99**, via a copper-catalyzed ($CuSO_4 \cdot 5H_2O$) diazo-transfer reaction with TfN_3,[17] in 84% overall yield for the two steps. The resulting azido ester **99** (the azide group serving as a masking device for the eventually required amino group) was then saponified, in quantitative yield, to its carboxylic acid counterpart **100** by the mild action of Me_3SnOH, conditions that did not cause any epimerization at the azide group-bearing center. The two readily available building blocks **96** and **100** were then coupled together through the action of HATU, HOAt, and *i*-Pr_2NEt, furnishing tripeptide **101** (78% yield), from which the primary alcohol-bound TES group was selectively removed by exposure to AcOH:THF:H_2O (10:3.3:1) at ambient temperature (60% yield, plus 17% recovered starting material **101**). Activation of the resulting hydroxy thioamide **102** with diethylaminosulfur trifluoride (DAST) in CH_2Cl_2 at −78 °C led to thiazoline **103** in 88% yield, which was then treated with Me_3SnOH in 1,2-dichloroethane at 80 °C to afford, in quantitative yield, carboxylic acid **104**, impressively suffering no significant epimerization at any

(20) Muir, J. C.; Pattenden, G.; Thomas, R. M. *Synthesis* **1998**, 613−618.

Scheme 8. Synthesis of Thiazoline Fragment **104**[a]



[a] Reagents and conditions: (a) D-Ser-OMe•HCl (1.0 equiv), *i*-Pr_2NEt (2.0 equiv), HOBt (1.2 equiv), EDC (1.2 equiv), CH_2Cl_2, 0 °C, 1 h; then 25 °C, 2 h, 93%; (b) TESCl (2.2 equiv), imidazole (3.0 equiv), DMF, 0 °C, 30 min; then 25 °C, 12 h, 81%; (c) Lawesson's reagent (0.55 equiv), benzene, reflux, 3 h, 83%; (d) Et_2NH (6.5 equiv), DMF, 0 °C, 30 min; then 25 °C, 30 min, 83%; (e) TFA:CH_2Cl_2 (1:1), 0 °C, 1.5 h; (f) TfN_3 (3.0 equiv), Et_3N (4.0 equiv), $CuSO_4 \cdot 5H_2O$ (0.05 equiv), MeOH:H_2O:CH_2Cl_2 (3.3:1:1), 25 °C, 1.5 h, 84% (two steps); (g) Me_3SnOH (3.0 equiv), 1,2-DCE, 80 °C, 3 h, 100%; (h) HATU (1.1 equiv), HOAt (1.1 equiv), *i*-Pr_2NEt (2.0 equiv), DMF, −20 °C, 20 min; then 0 °C, 20 min, 78%; (i) THF:AcOH:H_2O (10:3.3:1), 25 °C, 18 h, 60% (+17% recovered **101**); (j) DAST (1.2 equiv), CH_2Cl_2, −78 °C, 30 min, 88%; (k) Me_3SnOH (3.0 equiv), 1,2-dichloroethane, 80 °C, 1.5 h, 100%. Abbreviations: HOBt, 1-hydroxybenzotriazole hydrate; TESCl, triethylsilyl chloride; DAST, diethylaminosulfur trifluoride; TfN_3, trifluoromethanesulfonyl azide; AcOH, acetic acid; Fmoc, fluorenylmethoxycarbonyl; TES, triethylsilyl.

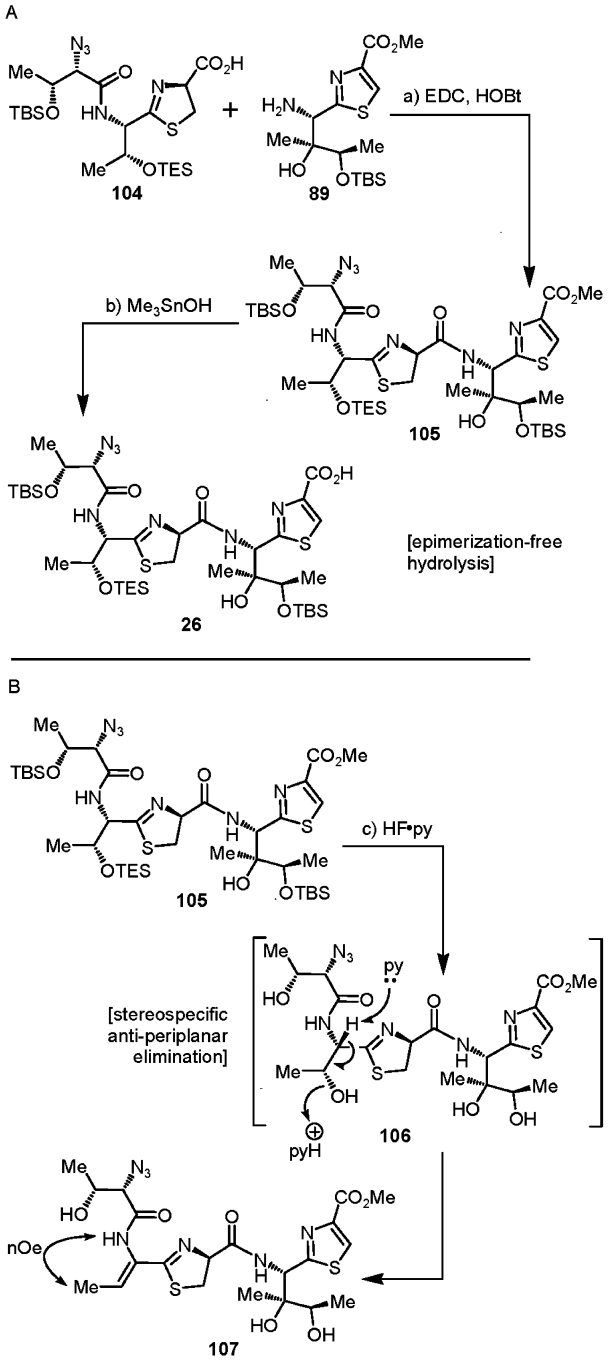
of its vulnerable centers. The mildness and selectivity of this Me_3SnOH-based method for hydrolyzing esters is indeed remarkable, for thiazoline **103** is highly sensitive and prone to epimerization at no less than three of its stereogenic sites. The scope and generality of this method have been investigated and reported elsewhere.[21]

Scheme 9A depicts the coupling of thiazole amine **89** with carboxylic acid **104**, which proceeded smoothly under the influence of HOBt and EDC to afford, in 73% yield, the thiazoline−thiazole-coupled product **105**. The methyl ester group of the latter compound (**105**) was then gently, and quantitatively, hydrolyzed with Me_3SnOH[21] to the corresponding carboxylic acid, leading to the key building block **26**.

Furthermore, and in order to ensure the feasibility of the anticipated desilylation of its protected hydroxyl groups, fragment **105** was treated with HF•py in THF at ambient temperature (Scheme 9B). Much to our delight, not only did all three silyl

(21) (a) Nicolaou, K. C.; Estrada, A. A.; Zak, M.; Lee, S. H.; Safina, B. S. *Angew. Chem., Int. Ed.* **2005**, *44*, 1378−1382. (b) Furlan, R. L. E.; Mata, E. G.; Mascaretti, O. A. *J. Chem. Soc., Perkin Trans. 1* **1998**, 355−358. (c) Furlan, R. L. E.; Mata, E. G.; Mascaretti, O. A.; Pena, C.; Coba, M. P. *Tetrahedron* **1998**, *54*, 13023−13034. (d) Furlan, R. L. E.; Mascaretti, O. A. *Aldrichim. Acta* **1997**, *30*, 55−69. (e) Furlan, R. L. E.; Mata, E. G.; Mascaretti, O. A. *Tetrahedron Lett.* **1996**, *37*, 5229−5232.

Scheme 9. (A) Synthesis of Thiazoline−Thiazole Subunit **26**; (B) Determination of Configuration of Thiazoline Olefin **107**[a]

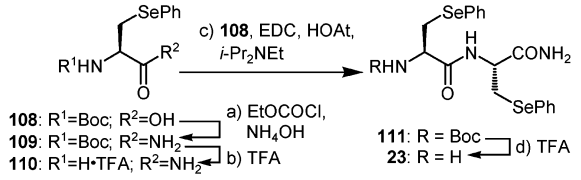


[a] Reagents and conditions: (a) EDC (1.1 equiv), HOBt (1.1 equiv), DMF, 0 °C, 1 h, 73%; (b) Me_3SnOH (6.0 equiv), 1,2-dichloroethane, 4 h, 80 °C, 100%; (c) HF•py (excess), THF, 0−25 °C, 18 h, 78%.

groups of **105** come off in a nondestructive manner, but also the expulsion of the TES group was accompanied by elimination, resulting in the formation of the *Z*-trisubstituted olefin **107**. The *Z*-geometry of the olefinic bond within **107** was established by the observation of an NOE between the protons on its vinylic methyl group and the nearby NH proton (as indicated on the structure in Scheme 9B).

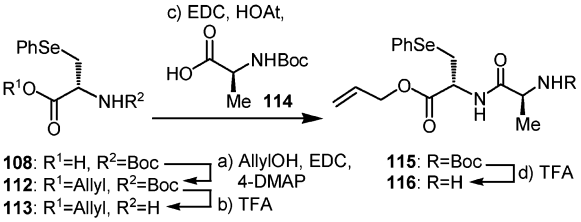
The synthesis of the dehydropiperidine tail equivalent, bis-phenylselenyl dipeptide **23**, was carried out as summarized in Scheme 10. Thus, the phenylselenoalanine derivative **108**[22] was activated by mixed anhydride formation (EtOCOCl) and, thence,

Scheme 10. Synthesis of the Bis-phenylselenium Tail Fragment **23**[a]



[a] Reagents and conditions: (a) ethyl chloroformate (1.1 equiv), *i*-Pr_2NEt (1.1 equiv), THF, 0−25 °C, 1.5 h; then 28% NH_4OH_{aq}, 0−25 °C, 13.5 h, 89%; (b) TFA:CH_2Cl_2 (1:1), 0−25 °C, 1 h; (c) **108** (1.2 equiv), HOAt (1.1 equiv), EDC (1.1 equiv), *i*-Pr_2NEt (1.5 equiv), DMF, 0 °C, 25 min; then 25 °C, 5 h, 82% (two steps); (d) TFA:CH_2Cl_2 (1:1), 0−25 °C, 1.5 h, 100%. Ph, phenyl.

Scheme 11. Construction of Phenylselenyl Dipeptide **116**[a]



[a] Reagents and conditions: (a) AllylOH (2.0 equiv), EDC (1.1 equiv), 4-DMAP (0.1 equiv), CH_2Cl_2, 0 °C, 5 min; then 25 °C, 3 h, 70%; (b) TFA:CH_2Cl_2 (1:1), 25 °C, 2 h; (c) *N*-Boc-L-Ala-OH (**114**) (1.1 equiv), HOAt (1.1 equiv), EDC (1.1 equiv), DMF, 25 °C, 2 h, 60% (two steps); (d) TFA:CH_2Cl_2 (1:1), 25 °C, 30 min. AllylOH, allyl alcohol.

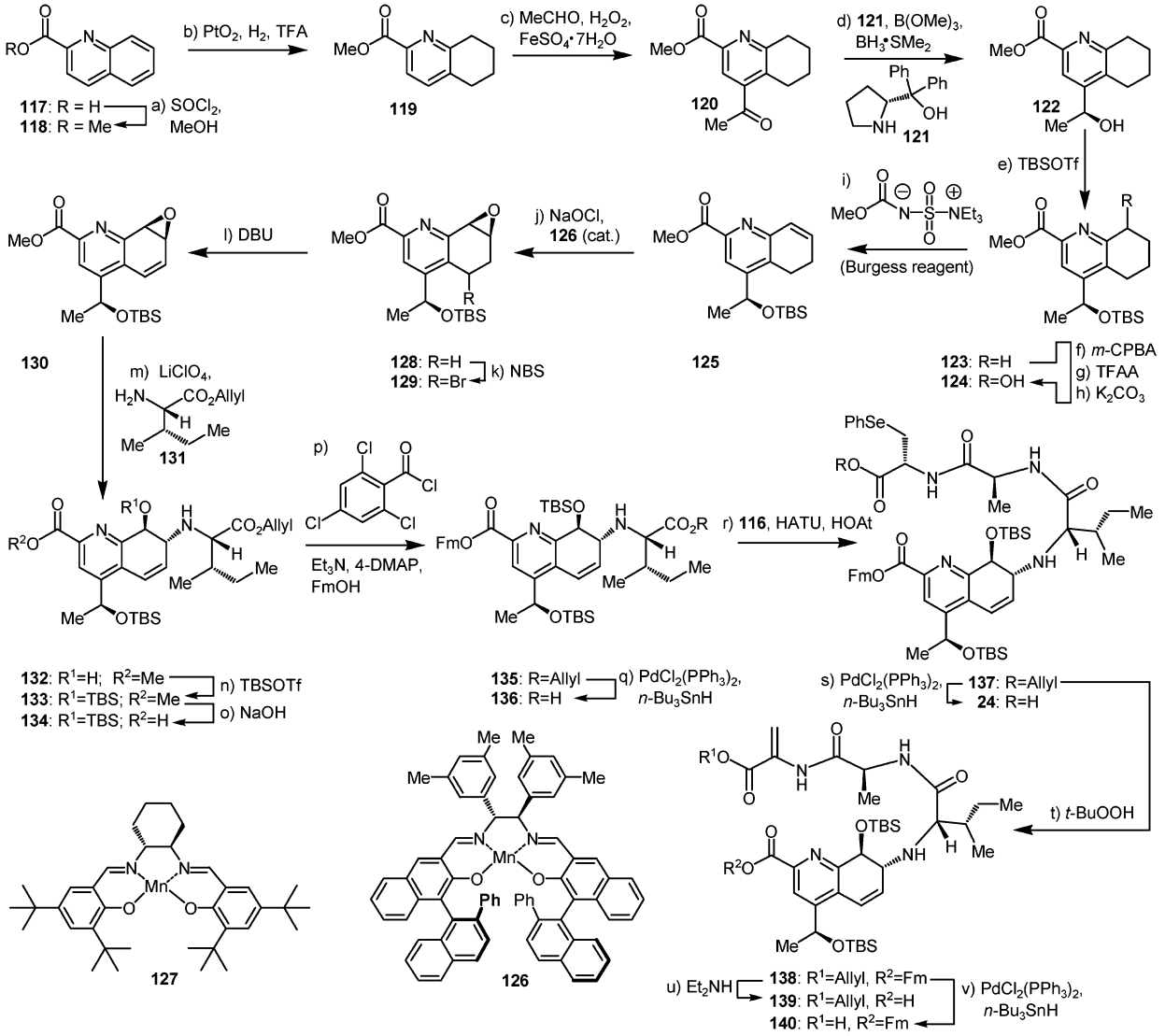
converted to its primary amide counterpart **109** (89% yield) by exposure to NH_4OH before removal of its *N*-Boc protecting group with TFA to afford amine **110**. The latter compound (**110**) was then coupled with acid **108** under the influence of HOAt, EDC, and *i*-Pr_2NEt to furnish dipeptide **111** (82% yield for two steps), from which the *N*-Boc group was cleaved by treatment with TFA in CH_2Cl_2 (1:1), an operation that yielded the desired building block **23** in quantitative yield.

The phenylselenyl dipeptide **116** required for incorporation into the quinaldic acid domain of thiostrepton was synthesized as shown in Scheme 11. Thus, carboxylic acid **108**[22] was converted to its allyl ester derivative (**112**, allyl alcohol, EDC, 4-DMAP, 70% yield), from which the *N*-Boc was cleaved (TFA) to reveal primary amine **113**. The required coupling of the latter compound (**113**) with *N*-Boc-L-alanine **114** was then successfully accomplished by the action of HOAt and EDC, leading to dipeptide **115** in 60% yield over two steps. Finally, the *N*-Boc group was dismantled from **115** with TFA, furnishing the desired amine **116**.

The synthesis of the quinaldic acid fragment **24** began with quinoline-2-carboxylic acid **117**, and proceeded as shown in Scheme 12. Thus, the methyl ester **118** was produced in 99% yield from **117** by reaction with $SOCl_2$ in MeOH, and was selectively reduced to pyridine system **119**, in 60% yield, by the action of H_2 (55 psi) in the presence of PtO_2 and TFA.[23] In the subsequent step, an acetyl radical ($^{\bullet}COCH_3$), generated from acetaldehyde, $FeSO_4{\cdot}7H_2O$, and H_2O_2,[24] was attached to the position para to the protonated (TFA) pyridine nitrogen atom of **119**, leading in 99% yield to methyl ketone **120**. Asymmetric

(22) Okeley, N. M.; Zhu, Y.; van der Donk, W. A. *Org. Lett.* **2000**, *2*, 3603−3606.
(23) Vierhapper, F. W.; Eliel, E. L. *J. Org. Chem.* **1975**, *40*, 2729−2734.
(24) Priestley, N. G.; Smith, T. M.; Shipley, P. R.; Floss, H. G. *Bioorg. Med. Chem.* **1996**, *4*, 1135−1147.

Scheme 12. Synthesis of Quinaldic Acid Fragment **24** and Deprotected Compounds **138**, **139**, and **140**[a]



[a] Reagents and conditions: (a) $SOCl_2$ (3.0 equiv), MeOH, 60 °C, 6 h, 99%; (b) PtO_2, H_2, TFA (excess), 25 °C, 5 h, 60%; (c) MeCHO (85 equiv), H_2O_2 (10.2 equiv), $FeSO_4 \cdot 7H_2O$ (0.13 equiv), TFA (1.2 equiv), 0 °C, 2 h, 99%; (d) **121** (0.04 equiv), $B(OMe)_3$ (0.12 equiv), $BH_3 \cdot SMe_2$ (1.9 equiv), THF, 0 °C, 30 min, 95%, 90% ee; (e) TBSOTf (1.1 equiv), Et_3N (3.3 equiv), CH_2Cl_2, 0−25 °C, 3 h, 95%; (f) *m*-CPBA (2.5 equiv), CH_2Cl_2, 0−25 °C, 12 h; (g) TFAA (2.5 equiv), CH_2Cl_2, 0−25 °C, 14 h; (h) K_2CO_3 (2 M aqueous solution):CH_2Cl_2 (3:1), 25 °C, 6 h, 75% (three steps); (i) Burgess reagent (1.2 equiv), THF, 25 °C, 20 min, concentrated in vacuo; then benzene, reflux, 1 h, 60%; (j) **126** (0.01 equiv), 4-Ph-py-*N*-oxide (0.1 equiv), NaOCl [0.79 M solution in phosphate buffer adjusted to pH 11.5 with NaOH (2 M aqueous solution)]:CH_2Cl_2 (1:1)], 25 °C, 1 h, 82%, 87:13 dr; (k) NBS (1.1 equiv), AIBN (0.1 equiv), CCl_4, 80 °C, 30 min, 44% (+29% recovered starting material **128**); (l) DBU (1.1 equiv), THF, 25 °C, 2 h, 96%; (m) H-L-Ile-OAllyl **131** (3.0 equiv), $LiClO_4$ (5.0 equiv), MeCN, 60 °C, 22 h, 69%; (n) TBSOTf (3.0 equiv), *i*-Pr_2NEt (5.0 equiv), THF, 0−25 °C, 3 h, 94%; (o) NaOH (3.2 equiv), H_2O:MeOH:THF (1:1:1.2), 0 °C, 30 min; then 25 °C, 5 h, 89%; (p) 2,4,6-trichlorobenzoyl chloride (2.0 equiv), Et_3N (6.0 equiv), toluene, 25 °C, 4 h; then FmOH (3.0 equiv), 4-DMAP (0.1 equiv), 25 °C, 14 h, 64%; (q) $PdCl_2(PPh_3)_2$ (0.1 equiv), *n*-Bu_3SnH (1.1 equiv), CH_2Cl_2, 0 °C, 1 h, 100%; (r) **116** (1.5 equiv), HATU (1.1 equiv), HOAt (1.1 equiv), DMF, 25−40 °C, 1 h, sonication; then 25 °C, 2 h, 85%; (s) $PdCl_2(PPh_3)_2$ (0.1 equiv), *n*-Bu_3SnH (25 equiv), CH_2Cl_2, −45 °C, 5 min; then 0 °C, 30 min, 100%; (t) *t*-BuOOH (5−6 M in decane):CH_2Cl_2 (0.9:1), 0 °C, 5 min; then 25 °C, 2 h, 82%; (u) Et_2NH:CH_2Cl_2 (1:10), 0 °C, 5 min; then 25 °C, 3 h, 60%; (v) $PdCl_2(PPh_3)_2$ (0.1 equiv), *n*-Bu_3SnH (50 equiv), CH_2Cl_2, 0 °C, 5 min; then 25 °C, 30 min, 100%. Abbreviations: TBSOTf, *tert*-butyldimethylsilyl trifluoromethanesulfonate; *m*-CPBA, *m*-chloroperoxybenzoic acid; AIBN, 2,2′-azabisisobutyronitrile; NBS, *N*-bromosuccinimide; FmOH, 9-fluorenemethanol; Fm, 9-fluorenylmethyl.

reduction of this ketone by a modified CBS procedure,[25] employing chiral ligand **121**, $B(OMe)_3$, and BH_3, afforded enantiomerically enriched (90% ee) secondary alcohol **122** in 95% yield, which was then protected as a TBS ether (TBSOTf, Et_3N, 95% yield), leading to derivative **123**. The latter compound (**123**) was then converted to its hydroxylated derivative **124** by a three-step Boekelheide-type sequence[26] involving (a) *N*-oxidation with *m*-CPBA, (b) trifluoroacetylation of the resulting *N*-oxide with TFAA, and (c) K_2CO_3-induced trifluoroacetate migration and hydrolysis. The newly installed hydroxyl group in **124** was then eliminated in a dehydration process effected by Burgess reagent,[27] furnishing olefinic compound **125** (60% yield), which was subsequently utilized in an asymmetric epoxidation reaction mediated by the Katsuki catalyst **126**[28] to produce epoxide **128** in 82% yield and ca. 87:13 diastereomeric

(25) (a) For a pertinent review in this area, see: Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986−2012. (b) Masui, M.; Shioiri, T. *Synlett* **1997**, 273−274.

(26) Fontenas, C.; Bejan, E.; Haddou, H. A.; Galavoine, G. A. *Synth. Commun.* **1995**, *25*, 629−633.

(27) Burgess, E. M.; Penton, H. R.; Taylor, E. A. *J. Org. Chem.* **1973**, *38*, 26−31.

ratio. It is noteworthy that attempted asymmetric epoxidation of olefin **125** with the commercially available Jacobsen−Katsuki catalyst **127**[29] led to low epoxide yields and poor diastereoselectivity in a reaction that was accompanied by significant aromatization to the quinoline ring system. NBS-induced bromination of epoxide **128** in the presence of AIBN (cat.) allowed the formation of bromide **129** (diastereomeric mixture, 44% combined yield, plus 29% recovered starting material **128**), exposure of which to DBU at ambient temperature led to allylic epoxide **130** in 96% yield. Epoxide **130** was then opened regioselectively and, as expected, stereospecifically[30] by the amino group of L-isoleucine allyl ester **131** in the presence of $LiClO_4$ in acetonitrile at 60 °C to afford amino alcohol **132** in 69% yield. Treatment of this substance (**132**) with TBSOTf in the presence of *i*-Pr_2NEt then furnished bis-TBS derivative **133** in 94% yield. The methyl ester of **133** was then selectively hydrolyzed by the action of NaOH in H_2O:MeOH:THF (1:1:1.2), leading to carboxylic acid **134** in 89% yield. The 9-fluorenylmethyl (Fm) group was then installed onto the newly generated carboxyl moiety through a Yamaguchi-type[31] esterification reaction (2,4,6-trichlorobenzoyl chloride, Et_3N; then FmOH, 4-DMAP, 64% yield), leading to diester **135**, from which the allyl group was cleaved using the *n*-$Bu_3SnH-PdCl_2(PPh_3)_2$ (cat.) method[32] to give carboxylic acid **136** in quantitative yield. Finally, coupling of carboxylic acid **136** with dipeptide **116**, as facilitated by HATU and HOAt, led to conjugate **137** in 85% yield. The allyl ester of **137** was then selectively cleaved employing the *n*-$Bu_3SnH-PdCl_2(PPh_3)_2$ (cat.) protocol,[32] furnishing the targeted quinaldic acid key building block **24** in quantitative yield.

Attempted selective deprotection of the Fm-protected carboxyl end of **137** under basic conditions (e.g. Et_2NH) led to partial elimination of its phenylseleno group, resulting in a mixture of products. However, treatment of this compound (**137**) with excess *t*-BuOOH effected selective selenium oxidation and spontaneous elimination of the resulting selenoxide to afford dehydroalanine derivative **138** in 82% yield. The Fm group could then be removed from the latter intermediate (**138**) by the action of Et_2NH, generating carboxylic acid **139** in 60% yield. Alternatively, the same diester derivative **138** could be converted to the regioisomeric carboxylic acid **140** by the action of *n*-Bu_3SnH in the presence of catalytic amounts of $PdCl_2(PPh_3)_2$ in quantitative yield. These results proved useful to us as we contemplated how to proceed over the treacherous ground that surely would lie ahead.

Conclusion

Described herein is the chemistry that provided the foundation for the eventual total synthesis of thiostrepton (**1**). Thus, efficient synthetic routes to all required key building blocks (**23**, **24**, **26**, **28**, and **29**) are detailed. Of particular interest was the evolution of the synthetic scheme toward the dehydropiperidine core of the molecule. Thus, inspired by the proposed biosynthesis of **1**, the described campaign to synthesize the dehydropiperidine core **28** began with a hetero-Diels−Alder dimerization reaction of azadiene system **30**, but was met immediately with a problem: the formed adduct suffered rapid aza-Mannich rearrangement to a bridged bicyclic system (**49** + **49′**). This problem was solved by adding benzylamine to the reaction mixture, which caused imine exchange, liberating the free amine before the destructive rearrangement, and led predominantly to the desired dehydropiperidine product **28** (+**28′**). This product (**28**, 5*R*,6*S*) was, however, formed as an inseparable 1:1 mixture with its diastereomer (**28′**, 5*S*,6*R*). The trans relationship of the two thiazoles on the imine ring was proven by NMR spectroscopy and X-ray crystallographic analysis of a derivative (**51**) of the aza-Mannich rearrangement product, but the relative stereochemistry between the core centers and those across from the thiazole ring could not be defined within each isomer due to the lack of single compounds at this stage. In an effort to grow the peptide chain upon the primary amino group, and in the hope that the new derivatives would be chromatographically separable, the Diels−Alder mixture of products (**28** + **28′**) was then coupled with *N*-Alloc alanine. Indeed, not only were the two formed diastereomers **57** and **57′** separable by silica gel chromatography, but also a derivative of one of them crystallized with one molecule of L-tataric acid. The X-ray crystallographic analysis of this salt (**58**), while solving the relative stereochemistry problem, revealed another: a rearrangement of the amino-imine from the desired six-membered ring to a dead-end, five-membered amino-imine system. This newly arisen obstacle was overcome upon a systematic exploration of a series of alanine equivalents and coupling conditions, eventually leading to a coupling procedure that suffered no rearrangement and which furnished the desired alanine-bound dehydropiperidine core (**70**) of thiostrepton. The problem of determining the relative stereochemistry within this core, however, resurfaced since no crystalline derivatives were in sight. This thorny problem was solved by converting one of the coupled products (**70**) to a degradation product (**74**) obtained from natural thiostrepton. It is worth noting that, besides overcoming the initial hurdles toward the dehydropiperidine core of thiostrepton, these investigations provided a wealth of novel skeleta for molecular diversity construction relevant to chemical biology and medicinal chemistry studies.

With the successful completion of the extendable dehydropiperidine core and the remaining fragments also at hand, we were then poised for the next phase of the campaign: the assembly of the synthesized key building blocks and elaboration of the resulting advanced intermediates to thiostrepton. These endeavors, accompanied as they were with their own complications, are described in the following article.[10]

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(28) (a) Ito, K.; Yoshitake, M.; Katsuki, T. *Tetrahedron* **1996**, *52*, 3905−3920. (b) Sasaki, H.; Irie, R.; Hamada, T.; Suzuki, K.; Katsuki, T. *Tetrahedron* **1994**, *50*, 11827−11838. (c) For a pertinent review in this area, see: Katsuki, T. *Curr. Org. Chem.* **2001**, *5*, 663−678.

(29) (a) Jacobsen, E.; Zhang, W.; Muci, A. R.; Ecker, J. R.; Deng, L. *J. Am. Chem. Soc.* **1991**, *113*, 7063−7064. (b) Irie, R.; Noda, K.; Ito, Y.; Matsumoto, N.; Katsuki, T. *Tetrahedron Lett.* **1990**, *31*, 7345−7348.

(30) (a) Boyd, D. R.; Davies, R. J. H.; Hamilton, L.; McCullough, J. J.; Malone, J. F.; Porter, H. P.; Smith, A. *J. Org. Chem.* **1994**, *59*, 984−990. (b) Bushman, D. R.; Sayer, J. M.; Boyd, D. R.; Jerina, D. M. *J. Am. Chem. Soc.* **1989**, *111*, 2688−2691.

(31) (a) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989−1993. (b) Nicolaou, K. C.; Patron, A. P.; Ajito, K.; Richter, P. K.; Khatuya, H.; Bertinato, P.; Miller, R. A.; Tomaszewski, M. J. *Chem. Eur. J.* **1996**, *2*, 847−868.

(32) (a) de la Torre, B. G.; Torres, J. L.; Bardají, E.; Clapés, P.; Xaus, N.; Jorba, X.; Calvet, S.; Albericio, F.; Valencia, G. *J. Chem. Soc., Chem. Commun.* **1990**, 965−967. (b) For a review on the use and removal of allylic protecting groups, see: Guibé, F. *Tetrahedron* **1998**, *54*, 2967−3042.

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Supporting Information Available: Experimental procedures and compound characterization (PDF, CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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