Natural Products Synthesis

Total Synthesis of Thiostrepton, Part 1: Construction of the Dehydropiperidine/ Thiazoline-Containing Macrocycle**

K. C. Nicolaou, Brian S. Safina, Mark Zak, Anthony A. Estrada, and Sang Hyup Lee*

In memory of Murray Goodman

Thiostrepton (**1**), a powerful antibiotic isolated from *Streptomyces azureus* ATCC 14921, *Streptomyces hawaiiensis* ATCC 12236, and *Streptomyces laurentii* ATCC 31255,[1] exhibits a remarkable biological profile and an imposing molecular architecture. Recognized as the flagship member of the growing class of thiopeptide antibiotics, this naturally occurring substance is extensively used in animal health care.[2] In addition, thiostrepton (**1**) exhibits impressive antimalarial activity and is effective against *Plasmodium falciparum*, the parasite responsible for the majority of human malaria.[3] Furthermore, selective cytotoxicity against cancer cells has been recently attributed to preparations that contain thiostrepton (**1**).[4] The antibiotic activity of **1** against Gram-positive bacteria has been traced to its binding to the 23*S*

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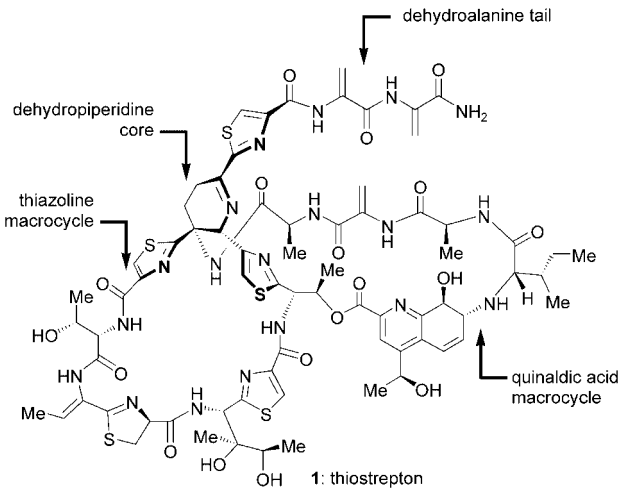
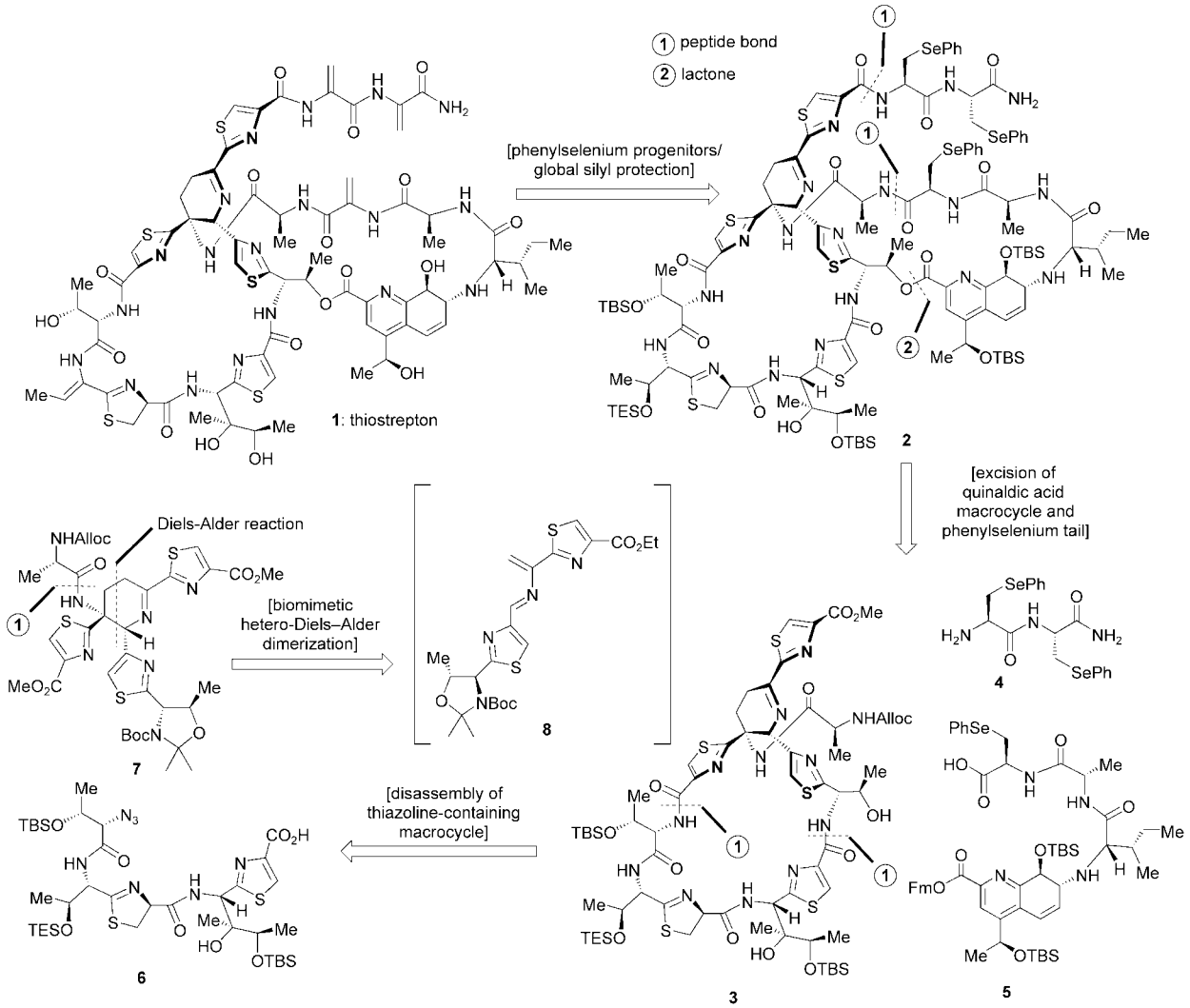
[**] We thank Dr. D. H. Huang and Dr. G. Siuzdak for NMR spectroscopic and mass spectrometric assistance, respectively. Financial support for this work was provided by grants from the National Institutes of Health (USA) and the Skaggs Institute for Chemical Biology, and fellowships from the National Institutes of Health (USA) (to A.A.E.) and The Skaggs Institute for Research (to M.Z.).

 DOI: 10.1002/ange.200461340



region of ribosomal RNA and protein L11, an event that blocks the GTPase-dependent activities of the 50*S* ribosomal subunit.[5] The molecular architecture of **1** is both stunningly complex and highly sensitive. At its heart lies a dehydropiperidine core which serves as a lynchpin holding the bisdehydroalanine tail and the two macrocyclic domains, the 26-membered thiazoline-containing ring and the 27-membered quinaldic acid ring system. This acid- and base-sensitive structure contains 10 rings, 11 peptide bonds, an imine functionality, a secondary amine, numerous sites of unsaturation, and 17 stereogenic centers, all of which make the task of its total synthesis all the more daunting, as already recognized by several potential suitors.[6] Herein and in the following Communication in this issue[7] we report the total synthesis of thiostrepton (**1**) in its naturally occurring form by a highly convergent strategy.

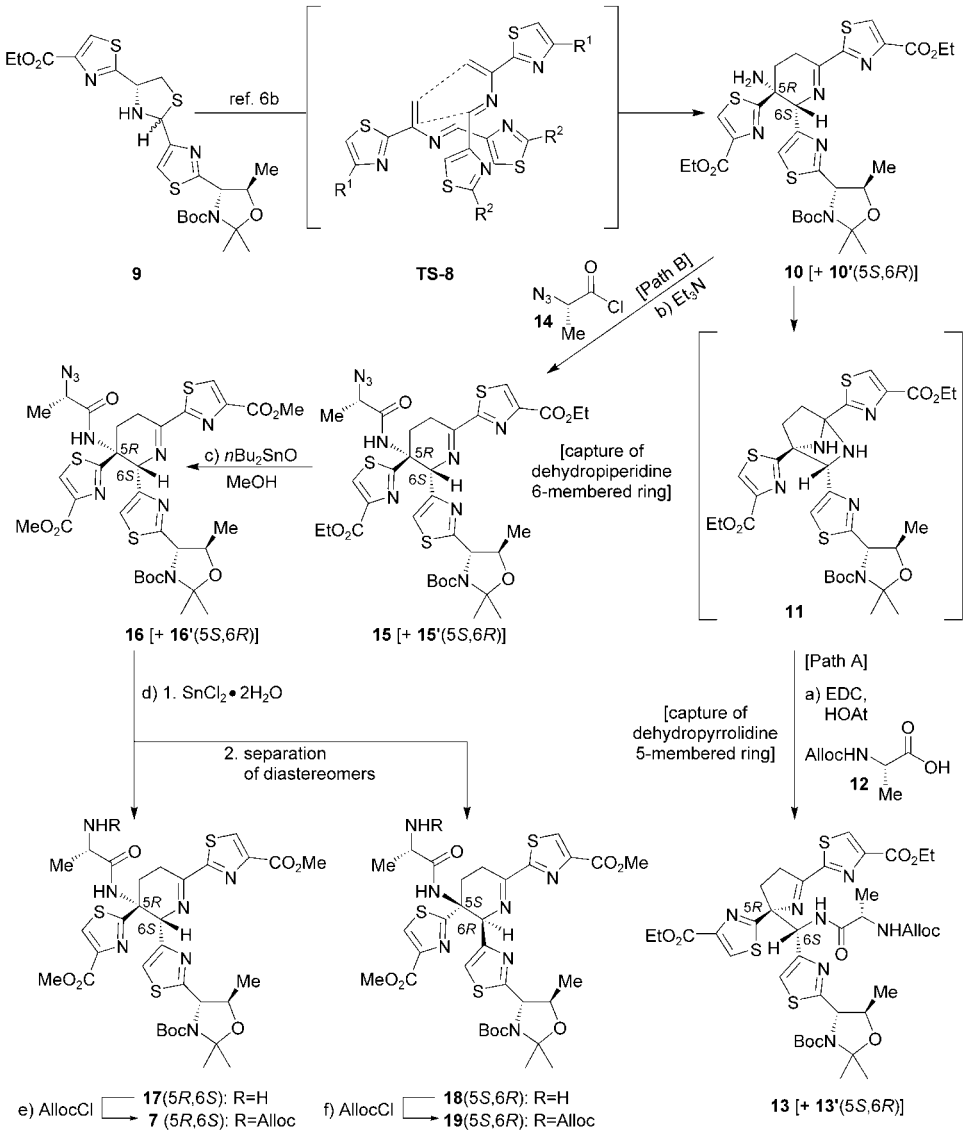
After several aborted attempts to synthesize **1**, we finally settled on the general strategy depicted retrosynthetically in Scheme 1. Because of the sensitive nature of the three dehydroalanine units of **1**, it was decided to protect them as phenylseleno surrogate groups; the equally sensitive *Z* double bond conjugated to the thiazoline moiety was also masked as a TES-protected hydroxy group, thereby leading (with further protection) to advanced intermediate **2** as a potential progenitor to **1**. It was anticipated that these delicate



Scheme 1. Retrosynthetic analysis of thiostrepton (**1**). Alloc = allyloxy carbonyl; Boc = *tert*-butoxycarbonyl; TBS = *tert*-butyl dimethylsilyl; TES = triethylsilyl; FM = 9-fluorenylmethyl.

functionalities would be released, the latter in its proper geometrical form, under suitably mild conditions at the end of the synthesis to generate the desired target without risking its feared destruction. The retrosynthetic transformation of **2** led to macrocycle **3**, truncated by the excision of the bisphenylselenium derivative **4** and the quinaldic acid intermediate **5**. Retrosynthetic cleavage of macrocycle **3** at the two indicated peptide bonds (note the flexibility of macrolactamization site) led to azido thiazoline derivative **6** and dehydropiperidine core **7** (Scheme 1). Finally, disassembly of **7** through a hetero-Diels–Alder-type dimerization led to heterodiene **8**, which was previously demonstrated in our laboratories[6b] to be a fleeting but viable precursor to the desired dehydropiperidine scaffold in a manner not so dissimilar to that proposed to be preferred by nature.[8]

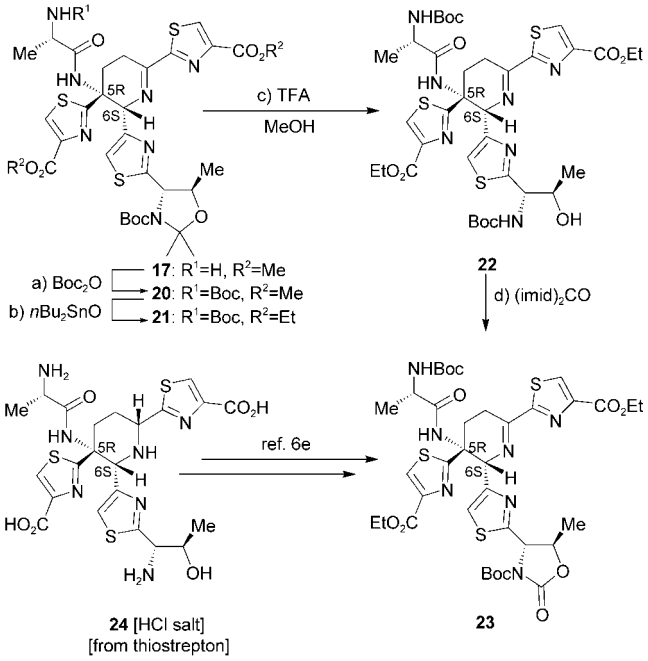
The first task was to prepare the dehydropiperidine building block **7**, an objective that turned out to be a considerable challenge, despite our early success in securing the free primary amine of the dehydropiperidine core **10**.[6b] Scheme 2 outlines the chemical steps by which subtarget **7** was reached. Thus, as previously reported,[6b] treatment of thiazolidine **9** with silver carbonate in the presence of DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) and benzylamine generated fleeting azadiene **8**, whose spontaneous hetero-Diels–Alder dimerization (see **TS-8**) afforded, upon aminolysis, the dehydropiperidine core primary amine **10** as a 1:1 mixture with its chromatographically inseparable 5*S*,6*R* diastereomer **10′**.[6b] Capturing the free amino group of these dehydropiperidine intermediates as amides with carboxy-activated alanine derivatives proved to be a thorny synthetic problem, as these substrates were susceptible to an apparent imine contraction facilitated by the neighboring amine function (see **11**, Scheme 2). The failed attempts to couple **10** (+ **10′**) with alanine derivatives under several conditions are exemplified by the reaction of *N*-Alloc alanine (**12**) in the presence of EDC–HOAt which led to the five-membered ring imine **13** (+ **13′**), presumably via the indicated aminal **11** (path A), as previously reported.[6c] It was only after extensive experimentation that precise conditions were found to capture the six-membered imine in its tracks by engaging its amino group before it had a chance to instigate the troublesome imine contraction. These conditions involved the use of the smaller, more-reactive electrophile **14**, the acyl chloride of the azide equivalent of alanine.[9] Thus, treatment of the dehydropiperidine amine **10** (+ **10′**) with excess **14** and triethylamine in THF at 0 °C for 12 h (path B) produced, exclusively and in 68% yield, amide **15** (+ **15′**) in which the six-membered imine ring was intact. The diastereomeric alanine-coupled dehydropiperidine derivatives continued to behave as inseparable mixtures until their ethyl esters were exchanged for the methyl esters (nBu$_2$SnO, MeOH, 76% yield, **16** (+ **16′**)) and the azide groups were reduced to primary amines ($SnCl_2 \cdot 2H_2O$, 79% total yield **17** (+ **18**)), at which stage they were separated by silica-gel flash-column chromatography. The individual primary amines were



Scheme 2. Construction of dehydropiperidine core **7**. Reagents and conditions: a) **12** (2.0 equiv), EDC (1.2 equiv), HOAt (1.3 equiv), DMF, 25 °C, 12 h, 84%; b) **14** (2.0 equiv), Et_3N (4.0 equiv), THF, 0 °C, 12 h, 68%; c) nBu$_2$SnO (2.0 equiv), MeOH, 75 °C, 6 h, 76%; d) 1. $SnCl_2 \cdot 2H_2O$ (3.0 equiv), MeOH, H_2O, 25 °C, 2 h; 2. silica gel, 100% EtOAc; then 5% MeOH/EtOAc, (5*R*,6*S*)-**17** 44%, (5*S*,6*R*)-**18** 35%; e) AllocCl (5.0 equiv), iPr$_2$EtN (10.0 equiv), 4-DMAP (0.1 equiv), THF, 25 °C, 92%; f) AllocCl (5.0 equiv), iPr$_2$EtN (10.0 equiv), 4-DMAP (0.1 equiv), THF, 25 °C, 89%. **TS-8**, $R^1 = CO_2Et$, R^2 = Boc acetonide threonine side chain. EDC = 1-ethyl-(3-dimethylaminopropyl)carbodiimide hydrochloride; HOAt = 1-hydroxy-7-azabenzotriazole; DMF = *N*,*N*-dimethylformamide; 4-DMAP = 4-(dimethylamino)pyridine.

then protected as their *N*-Alloc derivatives **7** (Table 1) and **19** (AllocCl, iPr_2NEt, 4-DMAP (cat.), 92% yield **7**, 89% yield **19**).

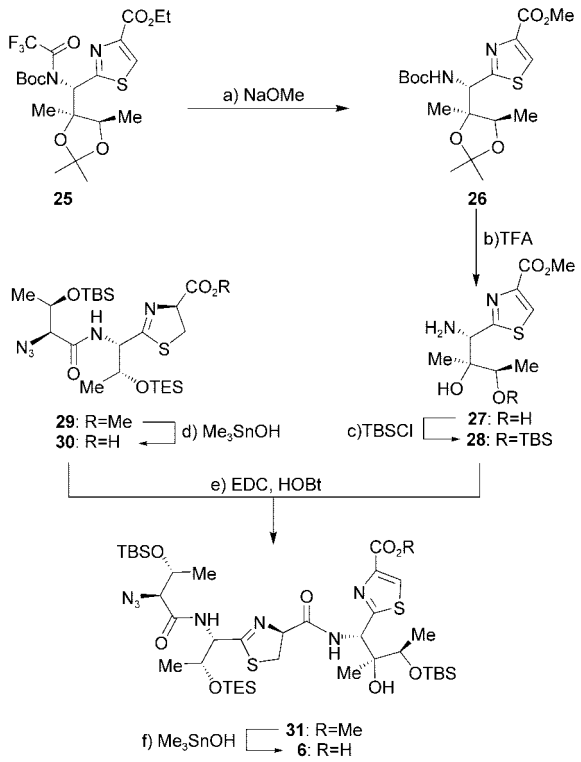
To distinguish between the 5*R*,6*S* and 5*S*,6*R* diastereomeric amines **17** and **18**, respectively, it was necessary to convert one of them into the known degradation product **23**[6e] for spectroscopic comparison (Scheme 3). Thus, the less polar of the two diastereomers (which turned out to be **17**) was converted into compound **23** by the route shown in Scheme 3.



Scheme 3. Determination of C5, C6 stereochemistry of dehydropiperidine **17**. Reagents and conditions: a) Boc_2O (5.0 equiv), iPr_2EtN (10.0 equiv), 4-DMAP (0.1 equiv), THF, 25 °C, 1 h, 61%; b) nBu_2SnO (2.0 equiv), EtOH, 65 °C, 5 h, 79%; c) TFA, MeOH, 0 °C, 30 min, 54% plus 40% recovered starting material; d) $(imid)_2CO$ (3.0 equiv), 4-DMAP (0.1 equiv), DMF, 25 °C, 24 h, 81%. Boc = *tert*-butoxycarbonyl; imid = imidazole; TFA = trifluoroacetic acid.

The ^1H and ^{13}C NMR spectra of synthetic **23** were identical to those previously reported[6e] for the 5*R*,6*S* diastereomer, thereby confirming the correct stereochemistry for our less-polar synthetic intermediate **17**. With this stereochemical ambiguity clarified, we turned our attention to the required thiazoline building block **6**.

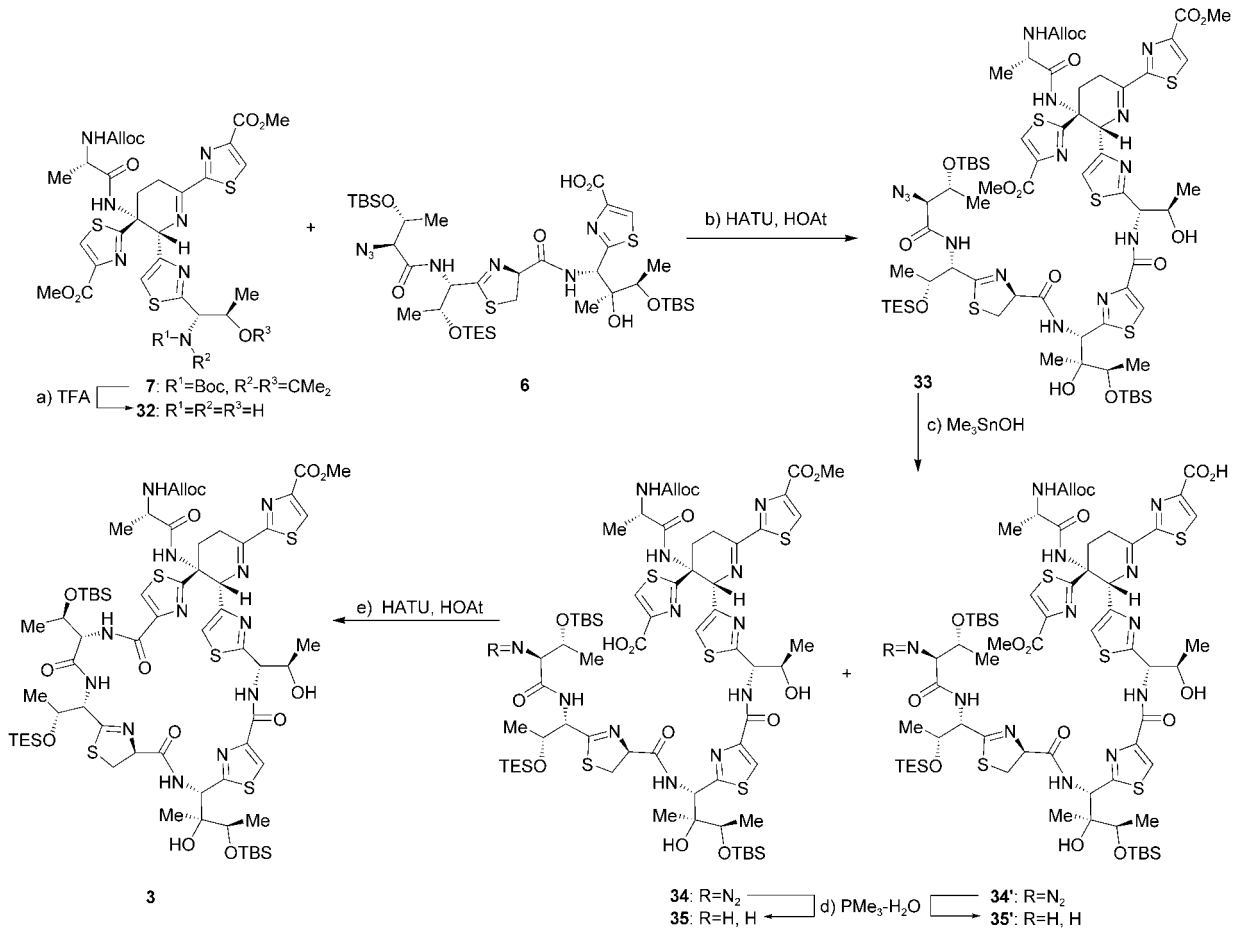
Scheme 4 summarizes the construction of the thiazoline–thiazole-containing fragment **6** from the previously synthesized building blocks, thiazole **25**[6c] and thiazoline **29**.[6c] In our attempts to liberate the carboxylic acid group within thiazoline **29** we faced the expected epimerization and elimination problems, both of which were solved through a remarkably mild and efficient protocol in which trimethyltin hydroxide was used. Thus, exposure of methyl ester **29** to Me_3SnOH[10] in 1,2-dichloroethane at 80 °C led to carboxylic acid **30** in quantitative yield. In parallel, protected thiazole derivative **25** was converted into its amino methyl ester derivative **28** by: a) ester exchange and concomitant cleavage



Scheme 4. Construction of thiazoline–thiazole subunit **6**. Reagents and conditions: a) NaOMe (3.2 equiv), MeOH, 0 °C, 4 h, 91%; b) TFA/CH_2Cl_2/MeOH (1.1:1:0.1), 0 °C, 1 h, 99%; c) TBSCl (2.2 equiv), Et_3N (3.3 equiv), CH_2Cl_2, 0 °C, 3 h, 87%; d) Me_3SnOH (3.0 equiv), 1,2-dichloroethane, 80 °C, 1 h, 100%; e) EDC (1.2 equiv), HOBt (1.2 equiv), DMF, 0 °C, 1.5 h, 73%; f) Me_3SnOH (3.0 equiv), 1,2-dichloroethane, 80 °C, 1 h, 100%. HOBt = hydroxybenzotriazole.

of the *N*-trifluoroacetate (to give **26** in 91% yield), b) cleavage of the *N*-Boc and acetonide protecting groups (to afford **27** in 99% yield), and finally c) protection of the more reactive secondary alcohol as a TBS ether to provide **28** in 87% yield. The two fragments **28** and **30** were then coupled through the action of EDC–HOBt to furnish dipeptide **31** (Table 1) in 73% yield. The methyl ester of **31** was hydrolyzed under mild conditions to afford the target carboxylic acid **6** in quantitative yield and without epimerization or elimination around the sensitive thiazoline site.

The elaboration of the two advanced building blocks **7** and **6** into the thiazoline-containing macrocycle **3** is outlined in Scheme 5. Thus, in preparation for coupling with the thiazoline containing carboxylic acid **6**, the dehydropiperidine derivative **7** was subjected to the action of TFA in CH_2Cl_2 at 0 °C to furnish amino alcohol **32** in good yield. The union of the latter compound with **6** was facilitated by HATU–HOAt and led to coupled product **33** in 73% overall yield from **7**. The mild action of Me_3SnOH in 1,2-dichloroethane at 50 °C resulted in the formation of monoacids **34** and **34′** (54% total yield) together with considerable amounts of the corresponding diacid (28% yield) and starting diester (14%). (Both the diacid and starting diester could be recovered and recycled—the diacid after methylation with EDC–MeOH.) Finally, the mixture of azido compounds **34** and **34′** was reduced with PMe_3–H_2O[9] to afford the corresponding mixture of primary



Scheme 5. Construction of advanced thiazoline-containing macrocycle **3**. Reagents and conditions: a) TFA/CH_2Cl_2 (1:1), 0 °C, 2 h; b) **6** (1.0 equiv), HATU (1.2 equiv), HOAt (1.2 equiv), iPr$_2$NEt (3.0 equiv), DMF, 0 °C, 30 min, 73% (two steps); c) Me_3SnOH (8.0 equiv), 1,2-dichloroethane, 50 °C, 5 h, 54% (28% diacid, 14% recovered starting material); d) Me_3P (6.0 equiv), THF/H_2O (10:1), 0 °C, 1 h; e) HATU (5.0 equiv), HOAt (5.0 equiv), iPr$_2$NEt (6.0 equiv), DMF (2.0 mM), 65 h, 32% (from mixture of monoacids **34** and **34'**). HATU = *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate.

Table 1: Selected physical properties for compounds **31**, **7**, and **3**.

31: R_f = 0.32 (silica gel, EtOAc/hexanes 1:3); $[\alpha]_D^{32} = -22.9$ ($CHCl_3$, c = 1.0); IR (film): $\tilde{\nu}_{max}$ = 3392, 2959, 2881, 2115, 1725, 1680,1497, 1247, 1103, 836, 775 cm^{-1}; ^{1}H NMR (600 MHz, CD_3OD): δ = 8.37 (s, 1 H), 5.45 (s, 1 H), 5.01 (dt, J = 9.7, 1.3 Hz, 1 H), 4.7 (m, 1 H), 4.48 (dq, J = 6.6, 3.0 Hz, 1 H), 4.36 (dq, J = 6.1, 2.2 Hz, 1 Hz, 1 H), 4.03 (q, J = 6.1 Hz, 1 H), 3.93 (d, J = 4.0 Hz, 1 H), 3.91 (s, 3 H), 3.62 (dd, J = 11.4, 1.7 Hz, 1 H), 3.38 (dd, J = 11.4, 1.7 Hz, 1 H), 1.35 (d, J = 6.2 Hz, 3 H), 1.27 (d, J = 6.2 Hz, 3 H), 1.23 (d, J = 6.2 Hz, 3 H), 1.01 (s, 3 H), 0.99 (t, J = 14.5 Hz, 9 H), 0.95 (s, 9 H), 0.90 (s, 9 H), 0.64 (dq, J = 7.9, 2.6 Hz, 6 H), 0.12 (s, 6 H), 0.09 (s, 3 H). 0.08 ppm (s, 3 H); ^{13}C NMR (150 MHz, CD_3OD): δ = 175.8, 173.5, 127.8, 170.9, 163.3, 146.5, 130.0, 79.3, 76.3, 71.4, 71.1, 70.3, 70.3, 59.7, 57.9, 52.8, 36.8, 26.6, 26.4, 21.6, 21.5, 18.9, 18.9, 18.3, 17.9 ppm; HRMS (ESI-TOF): calcd for $C_{39}H_{73}N_7O_8S_2Si_3H^+$ [M+H$^+$]: 916.4342; found: 916.4343

7: R_f = 0.43 (silica gel, EtOAc/hexanes 8:2); $[\alpha]_D^{32} = +14.2$ (solvent $CHCl_3$, c = 1.0); IR (film) $\tilde{\nu}_{max}$ = 3318, 3096, 2966, 2919, 1719, 1701, 1502, 1478, 1367, 1237, 1214, 1132, 1096, 991, 773 cm^{-1}; ^{1}H NMR (500 MHz, CD_3CN, 66 °C): δ = 8.27 (s, 1 H), 8.04 (s, 1 H), 7.13 (s, 1 H), 5.84–5.75 (m, 1 H), 5.68 (br s, 1 H), 5.35 (br s, 1 H), 5.20 (dq, J = 17.3, 1.8 Hz, 1 H), 5.11 (dq, J = 11.6, 1.8 Hz, 1 H), 4.75 (d, J = 5.8 Hz, 1 H), 4.30 (dd, J = 13.2, 6.3 Hz, 1 H), 4.24–4.17 (br, 1 H), 4.02 (dt, J = 20.6, 7.0 Hz, 1 H), 3.90 (s, 3 H), 3.85 (s, 3 H), 3.41 (ddd, J = 13.9, 7.0, 2.2 Hz, 1 H), 3.14 (ddt, J = 19.8, 6.3, 2.2 Hz, 1 H), 2.97–2.86 (m, 1 H), 2.72–2.63 (m, 1 H), 1.64 (s, 3 H), 1.59 (s, 3 H), 1.39 (d, J = 6.3 Hz, 3 H), 1.33, (br, 9 H), 1.31 ppm (d, J = 6.9 Hz, 3 H); ^{13}C NMR (125 MHz, CD_3CN, 66 °C): δ = 176.7, 174.3, 173.9, 170.7, 164.7, 162.7, 157.0, 153.5, 148.8, 147.8, 134.4, 131.9, 129.1, 120.3, 96.1, 81.8, 78.7, 67.7, 67.2, 66.5, 61.1, 53.4, 52.9, 52.8, 28.9, 28.4, 26.0, 19.1, 18.5 ppm; HRMS (ESI-TOF): calcd for $C_{36}H_{45}N_7O_{10}S_3H^+$ [M+H$^+$]: 832.2463; found: 832.2459

3: R_f = 0.37 (silica gel, EtOAc/hexanes 7:3); $[\alpha]_D^{32} = +16.9$ ($CHCl_3$, c = 1.0); IR (film) $\tilde{\nu}_{max}$ = 3394, 2927, 1670, 1528, 1483, 1256, 1101 cm^{-1}; ^{1}H NMR (500 MHz, CD_3CN, 66 °C): δ = 8.30 (s, 1 H), 8.16 (s, 1 H), 7.87 (br d, J = 10.0 Hz, 1 H), 7.77 (br d, J = 8.4 Hz, 1 H), 7.37 (s, 2 H), 5.95–5.90 (br, 1 H), 5.80–5.71 (m, 1 H), 5.57 (d, J = 8.8 Hz, 1 H), 5.37–5.33 (m, 1 H), 5.27–5.22 (m, 1 H), 5.18 (dq, J = 17.3, 1.5 Hz, 1 H), 5.08 (dq, J = 10.7, 1.5 Hz, 1 H), 4.98 (dt, J = 9.2, 1.9 Hz, 1 H), 4.83 (br d, J = 8.8 Hz, 1 H), 4.73–4.69 (br, 1 H), 4.64–4.59 (br, 1 H), 4.30–4.23 (br, 3 H), 4.10 (q, J = 6.3 Hz, 1 H), 3.95 (quint, J = 7.0 Hz, 1 H), 3.64 (dd, J = 13.2, 7.4 Hz, 1 H), 3.57 (d, J = 9.2 Hz, 2 H), 3.24 (br d, J = 16.5 Hz, 1 H), 2.92–2.83 (m, 1 H), 2.49–2.42 (m, 1 H), 1.32 (d, J = 6.2 Hz, 3 H), 1.24 (d, J = 6.3 Hz, 3 H), 1.23 (d, J = 7.0 Hz, 3 H), 1.21 (d, J = 6.6 Hz, 3 H), 1.10 (d, J = 6.3 Hz, 3 H), 1.05 (s, 3 H), 0.98 (s, 9 H), 0.96 (t, J = 8.1 Hz, 9 H), 0.95 (s, 9 H), 0.64 (q, J = 7.7 Hz, 6 H), 0.20 (s, 3 H), 0.19 (s, 3 H), 0.12 (s, 3 H), 0.09 (s, 3 H); HRMS (ESI-TOF): calcd for $C_{65}H_{100}N_{12}O_{14}S_5Si_3H^+$ [M+H$^+$]: 1517.5466; found: 1517.5432

amines **35** and **35′**, which upon ring closure in the presence of HATU–HOAt–*i*Pr_2NEt gave the desired macrocycle **3** in 32% overall yield from mono acids **34** and **34′** as the only identifiable cyclic product. The formation of only one macrolactam in this reaction is remarkable, and was noted with a measure of considerable trepidation, as the product, in principle, could have had the wrong connectivity (i.e. that arising from **35′**). Only the eventual conversion of **3** (Table 1) into thiostrepton (**1**) could confirm its proper structure, a wish that came true as we describe in the following Communication in this issue.[7]

Received: July 16, 2004
Published Online: September 3, 2004

Keywords: antibiotics · azadienes · cycloaddition · natural products · total synthesis

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