Natural Product Analogues

Synthetic Studies on Thiostrepton: Construction of Thiostrepton Analogues with the Thiazoline-Containing Macrocycle**

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Thiostrepton (**1**, Scheme 1)[1] is a highly complex thiopeptide antibiotic endowed with an unusual molecular architecture and a mode of action that involves RNA binding. As part of our program directed towards the total synthesis of this unique natural product, we have already reported synthetic approaches to both its dehydropiperidine domain[2] and its segment corresponding to the quinaldic acid macrocycle.[3] Herein we disclose further advances that pave the way for an eventual total synthesis of **1** and its analogues by addressing the remaining challenges posed by the imposing and sensitive structure of the molecule. Specifically, we describe: 1) the construction of the thiazoline **7** and thiazole **8** fragments, 2) the synthesis of the dehydropyrrolidine isomer **4** of the dehydropiperidine domain and its 5*S*,6*S* diastereoisomer **4′**, and 3) the assembly of these fragments into thiostrepton analogues **2** and **3**, which lack only the quinaldic acid macrocycle and differ from thiostrepton (**1**) at the imine-containing ring core (Scheme 1).

We begin with our previously reported[2] biomimetically inspired aza-Diels–Alder dimerization, which delivered the dehydropiperidine domain **9** (5*R*,6*R*-diastereoisomer, Scheme 2) as a 1:1 mixture with its 5*S*,6*S*-diastereoisomer **9′** (not shown). In solution, these dehydropiperidine compounds (**9** and **9′**) rearrange into their dehydropyrrolidine counterparts **4** and **4′**, respectively, reaching an equilibrium via aminal **10** and **10′**.[4] The six-membered ring imine **9** (and **9′**) can be selectively reduced with $NaCNBH_3$ under acidic conditions over its five-membered counterpart (**4** and **4′**), presumably due to less steric hindrance around the C=N bond, to render diamine **11** (and **11′**), as we already reported.[2] However, under standard amide bond-forming conditions (EDC, HOAt) with alloc-L-Ala-OH (**5**, Scheme 1), the five-membered ring imine **4** (and **4′**) is selectively captured, leading to compound **13** (and **13′**), obtained as a mixture of 5*R*,6*R*- and 5*S*,6*S*-diastereoisomers, which were chromatographically separated (72% combined yield). On the other hand, diamine **11** (and **11′**) can also be coupled with alloc-L-Ala-OH (**5**) (HOAt, HATU, $EtNiPr_2$) predominantly at the primary amine site (2:1 ratio of regioisomers) yielding, upon oxidation with *t*BuOCl and base-induced elimination of HCl from the resulting chloroamine, the dehydropiperidine peptide **12** (and **12′**) in 21% overall yield (from **9** and **9′**). While attempting to optimize this route to **12** (and **12′**), we opted to construct analogues **2** and **3** utilizing the more available dehydropyrrolidine intermediates **13** and **13′** with the dual aim of scouting the ground for the total synthesis of thiostrepton (**1**) and to produce novel thiostrepton analogues for biological evaluation.

With ample quantities of the central core **13** and its 5*S*,6*S* diastereoisomer (**13′**) in hand, we proceeded to construct the remaining key building blocks **6**–**8** (Scheme 1). Scheme 3 outlines the synthesis of the thiazole amino acid equivalent **8**, starting from angelic acid methyl ester (**14**). Thus, sequential conversion of commercially available **14** into its acid **15** (90% yield), acid chloride **16**, and (−)-menthyl ester **17** (70% over two steps) allowed a diastereoselective dihydroxylation with AD-mix-β and $MeSO_2NH_2$, leading to diol **18**[5] (90% yield, d.r. 90:10). The latter compound, **18**, was further protected as acetonide **19** (100% yield) and then reduced with DIBAL-H (90%) to alcohol **20**. In a remarkable one-pot sequence, alcohol **20** was oxidized with DMP; the aldehyde obtained in this manner was engaged in situ with benzylamine in the presence of $Yb(OTf)_3$[6] and molecular sieves (4 Å), and the resulting imine was treated with trimethylsilyl cyanide[7] to furnish Strecker addition product **21** in 90% overall yield. To our delight, not only did this sequence produce virtually a single stereoisomer (d.r. > 95:5 according to ^1H NMR spec-

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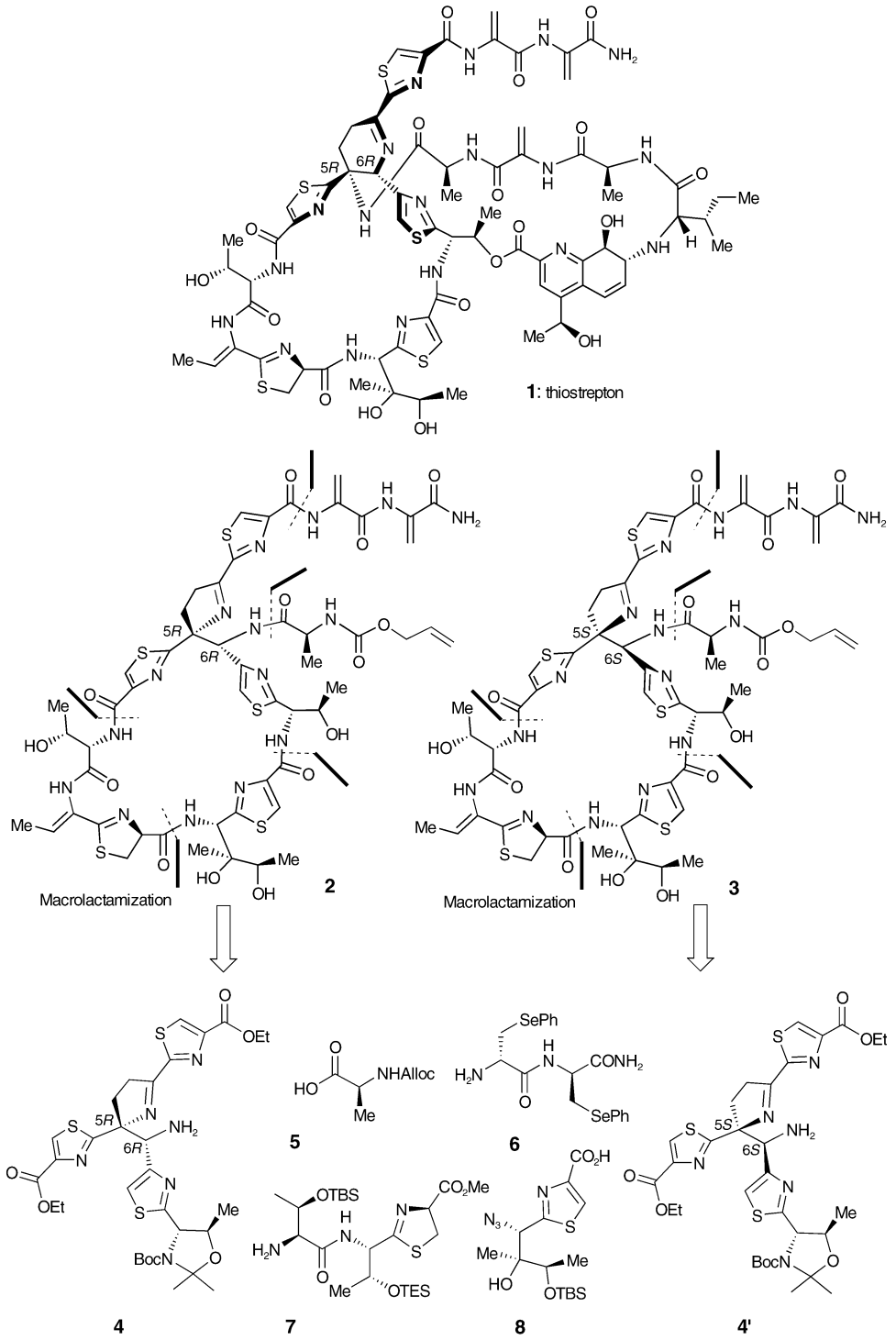
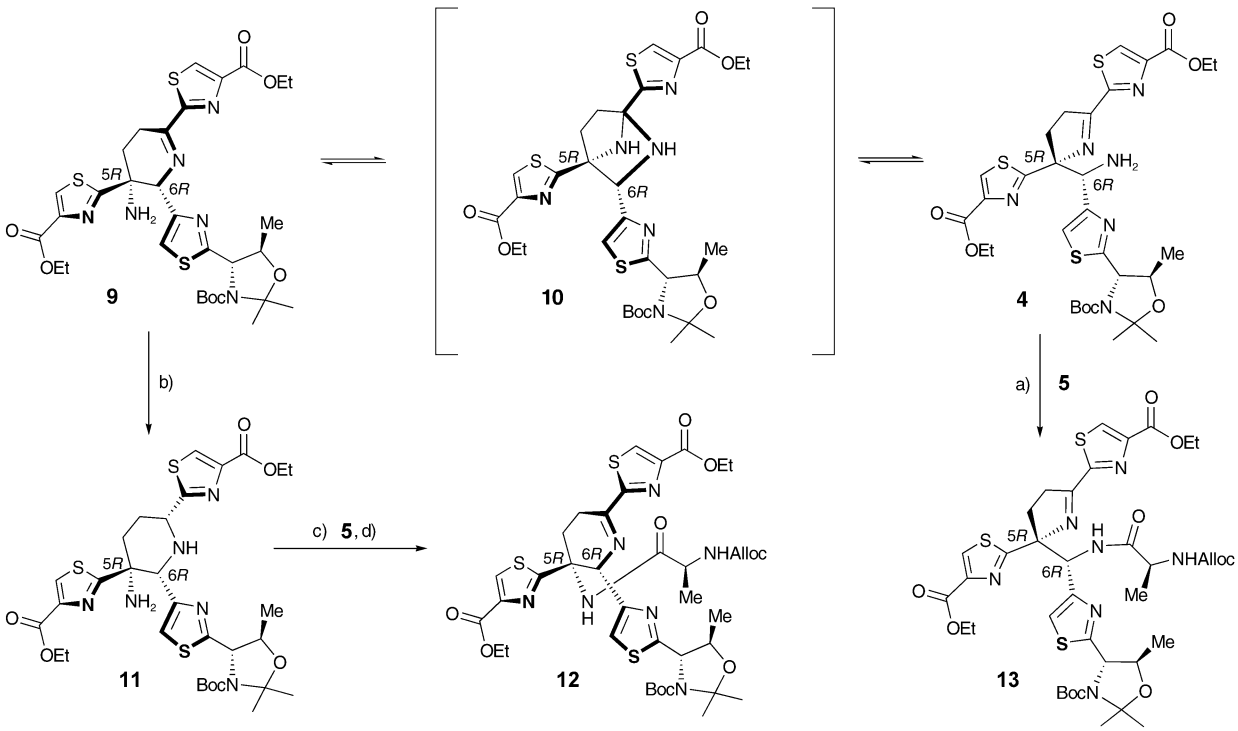


Scheme 1. Structures of thiostrepton (**1**) and analogues **2** and **3**, and retrosynthetic analysis of the latter two compounds to building blocks **4**–**8** and **4′**. Alloc = allyloxycarbonyl; Boc = *tert*-butoxycarbonyl; TBS = *tert*-butyldimethylsilyl; TES = triethylsilyl.

troscopic analysis), but, also, the obtained material possessed the correct stereochemistry, as proven by X-ray crystallographic analysis of a subsequent intermediate (i.e. **25**, see ORTEP drawing, Scheme 3). Hydrogenolysis of the benzyl group of **21** in the presence of $(Boc)_2O$ led to Boc derivative **22** in 75% yield. Treatment of **22** with H_2S in the presence of Et_3N in a sealed tube afforded thioamide **23** (90%), which was then treated with ethyl bromopyruvate under standard Hantzsch conditions[8] to afford thiazole **24** in 82% yield. For reasons of protecting-group compatibility in subsequent steps, we moved to modify the diol and amine functionalities within the latter substrate by first removing the groups guarding



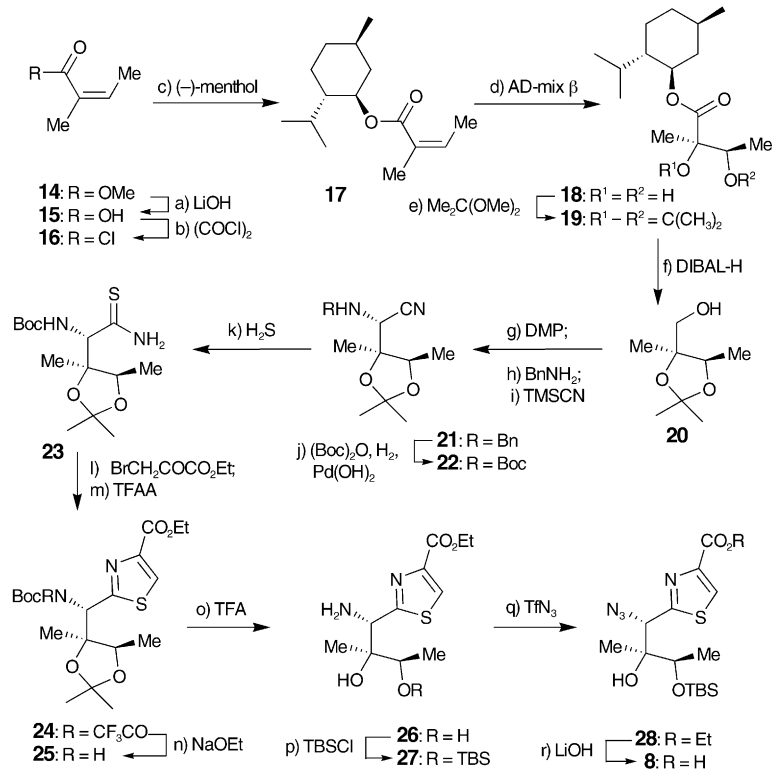
Scheme 2. Construction of dehydropiperidine and dehydropyrrolidine systems **12** and **13**. Reagents and conditions: a) 1) Alloc-L-Ala-OH (**5**) (1.2 equiv), HOAt (1.3 equiv), EDC (1.3 equiv), DMF, 25 °C, 12 h; 2) separation of diastereomers (silica gel, Et_2O/toluene (60–80%), then EtOAc/hexane(90%)), 72% combined yield; b) $NaCNBH_3$ (2.0 equiv), AcOH/EtOH (1:4), 0 °C, 1 h, 50%; c) Alloc-L-Ala-OH (**5**) (1.1 equiv), HOAt (1.1 equiv), HATU (1.1 equiv), $EtNiPr_2$ (3.0 equiv), DMF, 25 °C, 2 h, 60%; d) *t*BuOCl (1.2 equiv), THF, −78 °C, 0.5 h, 4-DMAP (0.2 equiv), Et_3N (2.0 equiv), 25 °C, 10 min, 70%. HATU = *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate; EDC = 1-ethyl-(3-dimethylaminopropyl)carbodiimide hydrochloride; DMF = *N*,*N*-dimethylformamide; 4-DMAP = 4-dimethylaminopyridine; HOAt = 1-hydroxy-7-azabenzotriazole. Compounds **4**, **9**–**13** are accompanied (ca. 1:1) by their 5*S*,6*S* diastereoisomers (**4**′, **9**′–**13**′, respectively, structures not shown).

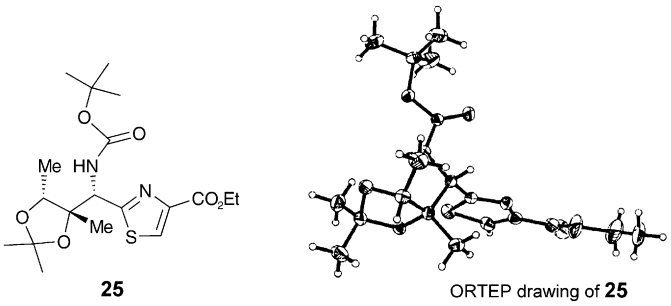
them and then remasking them in a different way. Thus, **24** was exposed to NaOEt in ethanol, furnishing the crystalline derivative **25** by removal of the trifluoroacetate group in quantitative yield. The latter compound (**25**) was then treated with TFA to furnish amino diol **26**, which was selectively converted into monosilyl ether **27** by reaction with TBSCl in the presence of Et_3N (81% yield over two steps). Finally, conversion of the amine within **27** into the corresponding azide (**28**) through the diazo-transfer procedure,[9] followed by basic hydrolysis of the ethyl ester, afforded the targeted building block **8** in 78% overall yield.

The synthesis of thiazoline moiety **7**, a structural element unique to thiostrepton—the other peptide antibiotics of the same family contain a thiazole instead—was carried out as summarized in Scheme 4 (p. 3422). Coupling of commercially available Fmoc-threonine (**29**) with D-serine methyl ester under standard conditions (EDC, HOBt, Et_3N) gave dipeptide **30** in 70% yield. Silylation of both hydroxy groups of **30** (81% yield), followed by thiocarbonylation with Lawesson's reagent, gave thioamide **32** (79% yield) via bis-TES-derivative **31**. The next requisite amino acid equivalent, compound **37**, was prepared from TBS-protected Boc-L-threonine methyl ester (**34**)[10] by first removing the Boc group with TFA, and then converting the corresponding primary amine of **35** into an azide functionality through the above-mentioned diazo-transfer procedure to provide **36** (72% over two steps). Hydrolysis of the ester provided acid **37** (93% yield), which was then coupled under standard conditions (HATU, HOAt, Et_3N) with amine **33** generated from its Fmoc derivative **32** through the action of Et_2NH to afford tripeptide surrogate **38** (75% from **32**). The primary TES group of **38** was selectively cleaved with THF/AcOH/H_2O (3:1:1) at 25 °C to furnish alcohol **39**, which upon exposure to DAST[11] led smoothly to the expected thiazoline **40** (90% yield). The final step required to complete the synthesis of **7** was the Staudinger reaction[12] of the azide to form the amino group, a transformation smoothly effected with trimethylphosphane and water (92% yield).

Scheme 5 (p. 3422) depicts the synthesis of the dipeptide equivalent to the top side chain of thiostrepton, bisseleno dipeptide **6**. This intermediate was synthesized from known L-serine derivative **41**[13] by first generating the amino selenoamide **43** (via **42**) and then coupling the two (**41** and **43**) under the influence of EDC and HOBt (58% over two steps), followed by removal of the remaining Boc group with TFA (95% yield).

The assembly of the targeted thiostrepton analogue **2** from the five-membered ring imine core **13** and the described





Scheme 3. Synthesis of thiazole amino acid equivalent **8**. Reagents and conditions: a) LiOH (0.7 equiv), $MeOH/H_2O$ (1:1), reflux, 4 h, 90%; b) KOH (1.0 equiv), $(COCl)_2$ (5.0 equiv), Et_2O, DMF (cat.), 2 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 d.r.; e) $Me_2C(OMe)_2$ (22.0 equiv), TsOH (0.05 equiv), 25 °C, 1 h, 100%; f) DIBAL-H (2.0 equiv), CH_2Cl_2, −78 °C, 2 h, 90%; g) DMP (1.1 equiv), $NaHCO_3$ (2.0 equiv), CH_2Cl_2, 25 °C, 3 h; h) $BnNH_2$ (1.2 equiv), $Yb(OTf)_3$ (0.2 equiv), molecular sieves (4 Å), CH_2Cl_2, 25 °C, 2 h; i) TMSCN (2.5 equiv), CH_2Cl_2, 25 °C, 3 h, 90% (three steps), >95:5 d.r.; j) $(Boc)_2O$ (1.1 equiv), EtOAc, 20% Pd/$Pd(OH)_2$ (0.2 equiv), H_2, 25 °C, 12 h, 75%; k) H_2S, Et_3N/EtOH/pyridine (1.7:1.7:1), sealed tube, 25 °C, 12 h, 90%; l) $BrCH_2COCO_2Et$ (3.0 equiv), $NaHCO_3$ (8.0 equiv), DME, 25 °C, 24 h, 82%; m) TFAA (4.0 equiv), pyridine (9.0 equiv), 0 °C, 1 h, 82% (two steps); n) NaOEt (1.0 equiv), EtOH, 0 °C, 1 h, 100%; o) TFA/EtOH/CH_2Cl_2 (1:1:1), 0–25 °C, 4 h; p) TBSCl (2.2 equiv), Et_3N (3.0 equiv), CH_2Cl_2, 0–25 °C, 12 h, 81% (two steps); q) TfN_3 (3.0 equiv), Et_3N (3.0 equiv), $CuSO_4$ (0.05 equiv), MeOH/H_2O/CH_2Cl_2 (3.3:1:1), 25 °C, 12 h, 82%; r) LiOH (3.0 equiv), THF/H_2O (1:1), 0 °C, 2 h, 95%. DMP = Dess–Martin periodinane; DIBAL-H = diisobutylaluminum hydride; TMS = trimethylsilyl; DME = ethylene glycol dimethyl ether; TFAA = trifluoroacetic anhydride; TFA = trifluoroacetic acid; Ts = *p*-toluenesulfonyl; Tf = trifluoromethanesulfonyl.

building blocks **6**–**8** proceeded as shown in Scheme 6 (p. 3423). Thus, the less polar isomer **13** (5*R*,6*R*) was treated with TFA/CH_2Cl_2 (1:1) to afford amino alcohol **45** while its more polar diastereoisomer **13′** (5*S*,6*S*, not shown) led, under the same conditions, to the corresponding amino alcohol **45′** (5*S*,6*S*, see Figure 1). Crystallization experiments with these diastereoisomers provided a crystalline derivative of the more polar compound (**45′**) with L-tartaric acid, whose X-ray crystallographic analysis revealed its absolute configuration (see ORTEP drawing, Figure 1), and, by extension, that of diastereoisomer **45**. Amino alcohol **45** was then coupled with thiazole amino diol **8** in the presence of HATU and HOAt to afford peptide **46** (65% yield over two steps, Scheme 6). The next problematic issue in the sequence was the differentiation between the two ethyl esters within compound **46**. As a result of the conjugation of one of the thiazole moieties with the imine functionality of **46**, we expected the ester on that thiazole to be more electron-deficient, and, therefore, more prone to hydrolysis. Gratifyingly, we found that, indeed, treatment of the latter compound, **46**, with 1 equivalent of lithium hydroxide in a 3:1:1 mixture of THF/EtOH/H_2O generated, regioselectively, a single carboxylic acid in 52% yield (plus 28% recovered starting material). More significantly,

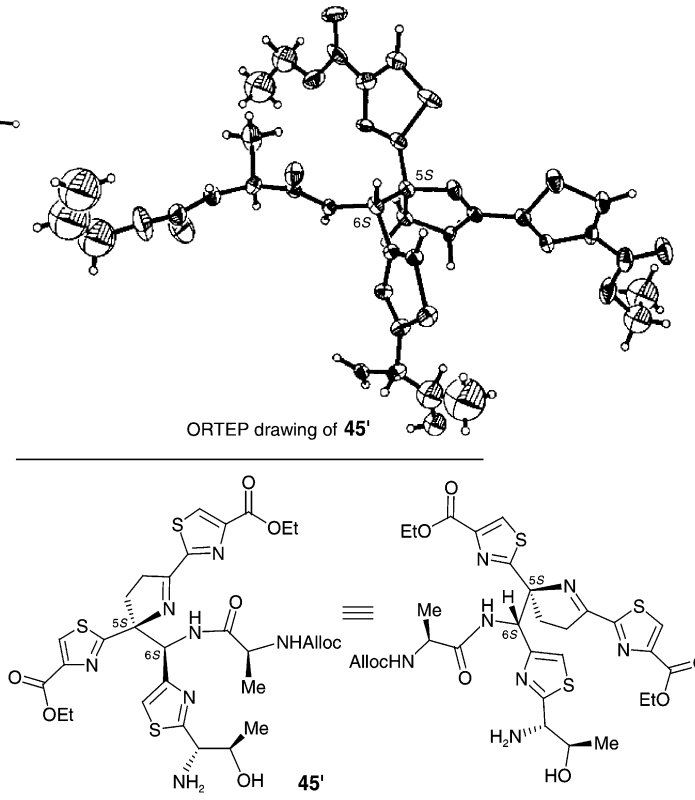
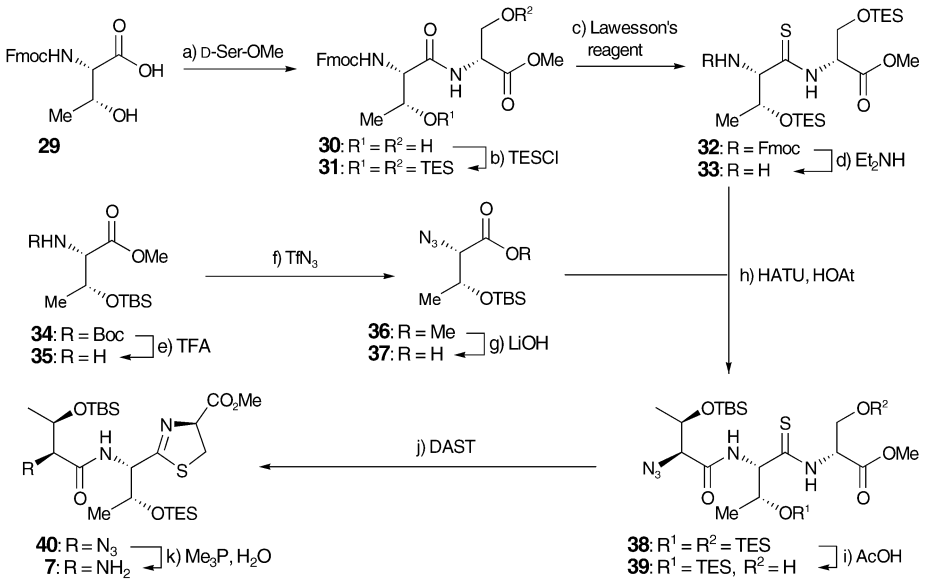
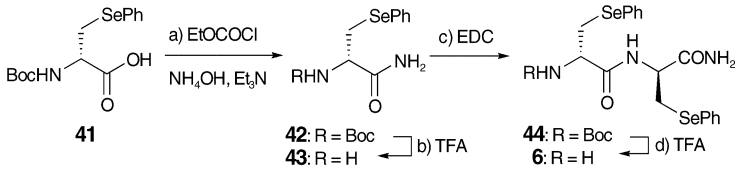


Figure 1. ORTEP drawing of **45′** (4*S*,5*S*) obtained by X-ray crystallographic analysis of its 1:1 salt with L-tartaric acid (L-tartaric acid not shown).



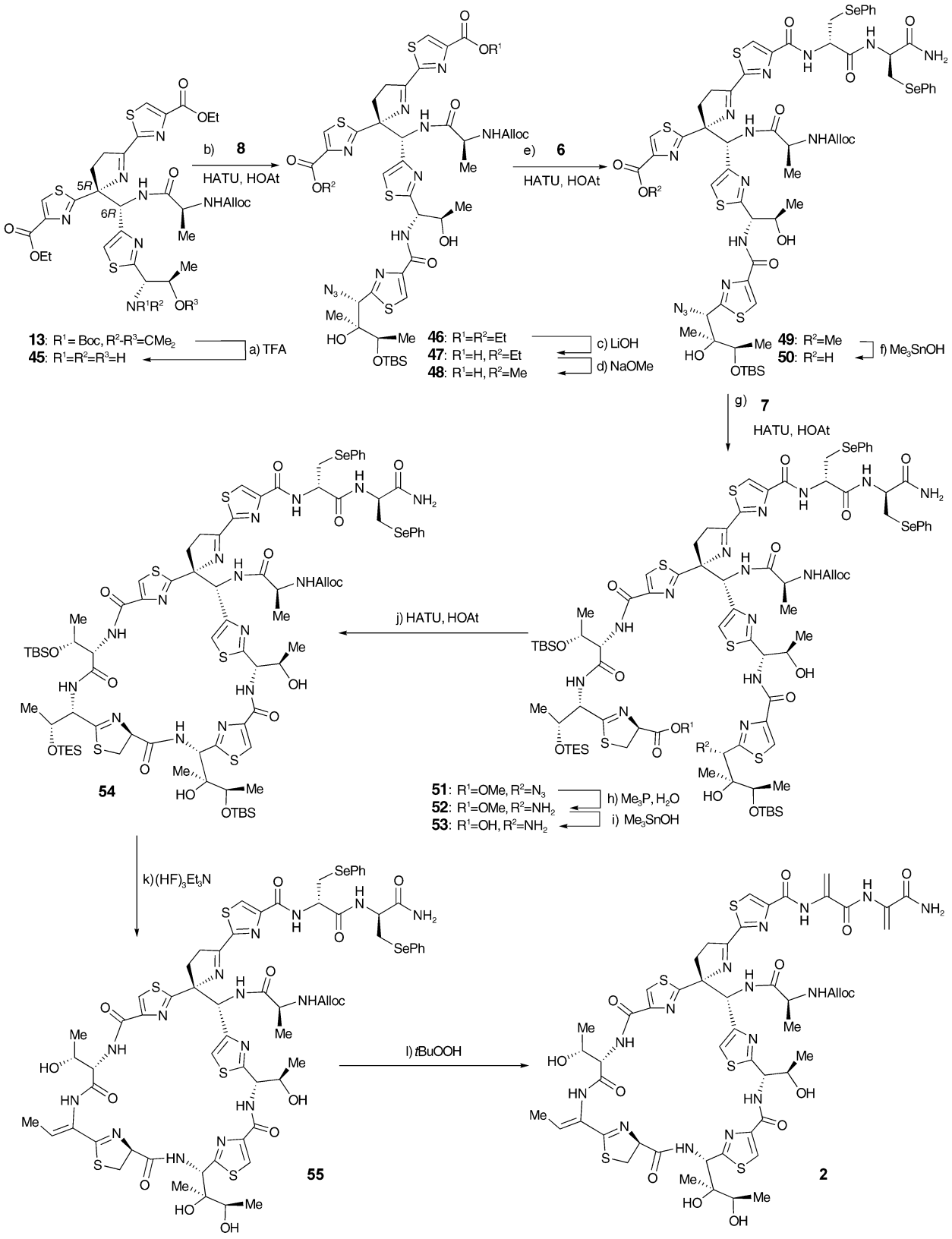
Scheme 4. Synthesis of thiazoline moiety **7**. Reagents and conditions: a) D-Ser-OMe·HCl (1.0 equiv), Et_3N (3.0 equiv), HOBt (1.2 equiv), EDC (1.2 equiv), CH_2Cl_2, 25 °C, 2 h, 70%; b) TESCl (2.2 equiv), imidazole (3.0 equiv), CH_2Cl_2, 25 °C, 12 h, 81%; c) Lawesson's reagent (0.55 equiv), benzene, reflux, 2 h, 79%; d) Et_2NH (6.5 equiv), DMF, 25 °C; e) TFA/CH_2Cl_2 (1:1), 25 °C, 2 h; f) TfN_3 (3.0 equiv), Et_3N (3.0 equiv), $CuSO_4$ (0.05 equiv), MeOH/H_2O/CH_2Cl_2 (3.3:1:1), 25 °C, 14 h, 72% (two steps); g) LiOH (1.0 equiv), THF/H_2O (1:1), 0 °C, 3 h, 93%; h) HATU (1.1 equiv), HOAt (1.1 equiv), Et_3N (2.0 equiv), DMF, 25 °C, 12 h, 75% (two steps from 32); i) THF/AcOH/H_2O (3:1:1), 25 °C, 12 h, 75% (based on 35% recovered **38**); j) DAST (1.2 equiv), CH_2Cl_2, −78 °C, 20 min, 90%; k) Me_3P (3.0 equiv), THF/H_2O (20:1), 0 °C, 1 h, 92%. HOBt = 1-hydroxybenzotriazole hydrate; DAST = diethylaminosulfur trifluoride; Fmoc = fluorenylmethoxycarbonyl.



Scheme 5. Synthesis of side-chain precursor **6**. Reagents and conditions: a) ethyl chloroformate (1.05 equiv), NH_4OH (30 equiv), $EtNiPr_2$ (1.05 equiv), THF, 0–25 °C, 1 h, 89%; b) TFA/CH_2Cl_2 (1:1), 0 °C, 1 h; c) **41**, HOBt (1.1 equiv), EDC (1.1 equiv), $EtNiPr_2$ (1.5 equiv), DMF, 25 °C, 5 h, 58% (two steps); d) TFA, CH_2Cl_2 (1:1), 0 °C, 1 h, 95%.

extensive NMR studies revealed that carboxylic acid **47** was, in fact, the product of this hydrolysis reaction. The remaining ethyl ester of compound **47** was then transesterified to a methyl ester (MeONa/MeOH, 90% yield), and the carboxylic acid function of resulting **48** was coupled to side-chain precursor **6** (HATU, HOAt) to afford tetrapeptide **49** in 83% yield. The inserted transesterification step was necessary to avoid subsequent complications that arose when attempts were made to hydrolyze the more robust ethyl ester, leading to elimination of the rather labile PhSe residues and side reactions thereof. In contrast, the methyl ester of **49** could be cleaved with trimethyltin hydroxide in refluxing dichloroethane (85% yield), conditions which avoided the loss of the selenium moieties otherwise observed in the presence of other reagents, that is, lithium hydroxide. The resulting acid **50** was then coupled to thiazoline segment **7** at 0 °C (HATU, HOAt) to afford product **51** in 75% yield. The obligatory low-temperature conditions employed in this coupling reaction were necessary to avoid premature elimination of the OTES group, which would lead to the conjugated thiazoline system (see structure **2**). Subsequent Staudinger reduction of the azide group within **51** (Me_3P, H_2O), followed by Me_3SnOH-induced methyl ester hydrolysis, led to amino acid **53** via amino ester **52**. Remarkably, the stereochemical integrity of the sensitive thiazoline moiety was preserved in the hydrolysis,[14] suggesting that this Me_3SnOH-mediated non-acidolytic and non-nucleophilic hydrolysis[15] could be a general mild method for the benign cleavage of esters within labile substrates. The key macrolactamization of amino acid **53** was smoothly effected by exposure to HATU and HOAt (0.3 mM concentration), leading to macrolactam **54** in 51% overall yield from **51**. Critically, exposure of **54** to $3\,HF{\cdot}Et_3N$ in THF at room temperature resulted in the cleavage of the two TBS groups, with concomitant base-promoted antiperiplanar elimination of the OTES moiety, furnishing the desired conjugated thiazoline system **55**.[16] Finally, the choice of the PhSe groups as potential progenitors of the olefinic bonds of the top side chain of the targeted molecule paid dividends in that treatment of the bisseleno derivative **55** with *t*BuOOH at ambient temperature resulted in the smooth formation of the five-membered imine analogue **2** of thiostrepton (**1**), lacking only the macrocycle that contains the quinaldic acid group. It should be stressed that the introduction of the last two double bonds into thiostrepton-like structures was proven to be a real challenge owing to the unusual sensitivity of the resulting dehydroamino acids.[17] Thiostrepton analogue **3** (Scheme 1) was synthesized from **4′** via **45′** by an analogous route to that described for **2**, and in similar yields (see Table 1).

Preliminary biological screening[18] with **2** and **3** indicated the lack of any significant antibacterial activity as compared to **1**, suggesting, perhaps, the importance of both the six-membered ring imine and the quinaldic acid motifs of thiostrepton for the recognition of its biological targets.



Scheme 6. Synthesis of the thiazoline macrocyclic system **2**. Reagents and conditions: a) TFA/CH_2Cl_2 (1:1), 25 °C, 2 h; b) **8** (1.0 equiv), $EtNiPr_2$ (3.0 equiv), HOAt (1.1 equiv), HATU (1.1 equiv), DMF, 25 °C, 12 h, 65% (two steps); c) LiOH (1.0 equiv), $THF/EtOH/H_2O$ (3:1:1), 0 °C, 1.5 h, 52% (28% recovered **46**); d) NaOMe (2.0 equiv), MeOH, 0 °C, 1 h, 90%; e) **6** (1.1 equiv), HOAt (1.2 equiv), HATU (1.2 equiv), DMF, 25 °C, 5 h, 83%; f) Me_3SnOH (13.0 equiv), 1,2-dichloroethane, reflux, 4 h, 85%; g) **7** (1.1 equiv), HOAt (1.2 equiv), HATU (1.2 equiv), DMF, 0 °C, 15 min, 75%; h) Me_3P (3.0 equiv), THF/H_2O (20:1), 0 °C, 30 min; i) Me_3SnOH (10.0 equiv), reflux, 1 h; j) HOAt (4.0 equiv), HATU (4.0 equiv), DMF (0.3 mM), 25 °C, 12 h, 51% (three steps); k) $(HF)_3{\cdot}Et_3N$ (30.0 equiv), THF, 25 °C, 48 h, 50%; l) *t*BuOOH (5 M in decane, 20.0 equiv), CH_2Cl_2, 25 °C, 3 h, 60%.

Table 1: Selected data for compounds **2** and **3**.

2: $R_f = 0.32$ (silica gel, CH_2Cl_2/MeOH, 9:1); $[\alpha]_D^{20} = -104.7$ ($c = 0.20$, MeOH); IR (film): $\tilde{\nu}_{max} = 3350, 2927, 2857, 1653, 1512, 1482, 1089, 1059\ cm^{-1}$; ^1H NMR (600 MHz, CD_3OD, 45 °C): $\delta = 8.52$ (s, 1 H), 8.19 (s, 1 H), 8.08 (s, 1 H), 7.44 (s, 1 H), 6.63 (q, $J = 7.0$ Hz, 1 H), 6.47, (d, $J = 1.5$ Hz, 1 H), 6.21 (d, $J = 1.0$ Hz, 1 H), 5.98 (br s, 1 H), 5.85 (br s, 1 H), 5.70 (d, $J = 1.5$ Hz, 1 H), 5.69 (d, $J = 1.0$ Hz, 1 H), 5.51 (s, 1 H), 5.24 (br d, $J = 17.0$ Hz, 1 H), 5.19 (t, $J = 9.2$ Hz, 1 H), 5.13 (br d, $J = 11.0$ Hz, 1 H), 5.09 (d, $J = 4.0$ Hz, 1 H), 4.47–4.41 (m, 3 H), 4.19–4.15 (m, 1 H), 4.13 (q, $J = 7.0$ Hz, 1 H), 3.81 (br d, $J = 10.6$ Hz, 1 H), 3.70 (dd, $J = 9.7$, 1.8 Hz, 1 H), 3.48 (dd, $J = 8.8$, 2.6 Hz, 1 H), 2.85 (quintet, $J = 7.4$ Hz, 1 H), 2.62 (dt, $J = 8.3$, 3.0 Hz, 1 H), 1.82 (d, $J = 7.0$ Hz, 3 H), 1.32 (d, $J = 6.6$ Hz, 3 H), 1.25 (d, $J = 7.5$ Hz, 3 H), 1.24 (s, 3 H), 1.21 (d, $J = 6.6$ Hz, 3 H), 1.05 ppm (d, $J = 6.1$ Hz, 3 H); ^{13}C NMR (125 MHz, CD_3OD, 45 °C): $\delta = 175.4, 173.8, 171.8, 171.5, 169.9, 168.3, 164.6, 164.2, 163.9, 163.4, 161.2, 153.5, 152.2, 150.7, 149.6, 136.4, 136.1, 136.0, 134.4, 130.9, 125.6, 119.3, 117.9, 107.2, 106.1, 102.5, 88.0, 80.14, 76.9, 71.3, 71.0, 69.8, 69.5, 66.9, 59.4, 58.1, 57.5, 37.5, 36.9, 33.7, 30.8, 30.4, 20.9, 19.8, 19.4, 17.5, 14.5$ ppm; HRMS (MALDI): calcd for $C_{52}H_{61}N_{15}O_{14}S_5$ [M+H$^+$]: 1280.3199; found: 1280.3184

3: $R_f = 0.32$ (silica gel, CH_2Cl_2/MeOH, 9:1); $[\alpha]_D^{20} = +98.5$ ($c = 0.55$, MeOH); IR (film): $\tilde{\nu}_{max} = 3375, 2913, 2853, 1658, 1643, 1449, 1249, 1061, 733\ cm^{-1}$; ^1H NMR (600 MHz, CD_3OD, 45 °C): $\delta = 8.51$ (s, 1 H), 8.21 (s, 1 H), 8.12 (s, 1 H), 7.34 (br s, 1 H), 6.61 (q, $J = 7.0$ Hz, 1 H), 6.49, (d, $J = 1.5$ Hz, 1 H), 6.20 (d, $J = 1.5$ Hz, 1 H), 5.86–5.78 (br s, 2 H), 5.71–5.69 (m, 2 H), 5.54 (br s, 1 H), 5.23–5.19 (m, 3 H), 5.09 (b, 1 H). 4.48–4.42 (m, 3 H), 4.38–4.32 (m, 3 H), 4.19–4.16 (m, 1 H), 3.90 (q, $J = 6.6$ Hz, 1 H), 3.65 (t, $J = 10.7$ Hz, 1 H), 3.45 (dd, $J = 8.8$, 2.2 Hz, 1 H), 3.21–3.18 (m, 1 H), 2.59 (dt, $J = 8.3$, 3.1 Hz, 1 H), 1.80 (d, $J = 7.0$ Hz, 3 H), 1.39 (s, 3 H), 1.33–1.31 (m, 6 H), 1.24–1.22 ppm (m, 6 H); ^{13}C NMR (150 MHz, CD_3OD, 45 °C): $\delta = 175.3, 174.8, 174.0, 173.6, 172.0, 171.7, 170.9, 168.3, 164.6, 164.2, 163.7, 161.2, 152.2, 150.6, 149.9, 136.6, 136.4, 136.2, 130.8, 130.2, 119.1, 117.9, 107.3, 106.0, 87.8, 80.1, 76.8, 70.7, 69.8, 69.2, 66.8, 60.2, 59.1, 58.1, 58.0, 37.2, 37.0, 26.4, 20.7, 20.6, 19.5, 18.7, 17.6, 14.6$ ppm; HRMS (MALDI): calcd for $C_{52}H_{61}N_{15}O_{14}S_5$ [M+H$^+$]: 1280.3199; found: 1280.3197

Within the described chemistry may lie clues for both the successful total synthesis of thiostrepton (**1**) and the design of bioactive analogues of this intriguing natural product.

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