Natural Products Synthesis

Total Synthesis of Thiostrepton, Part 2: Construction of the Quinaldic Acid Macrocycle and Final Stages of the Synthesis**

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

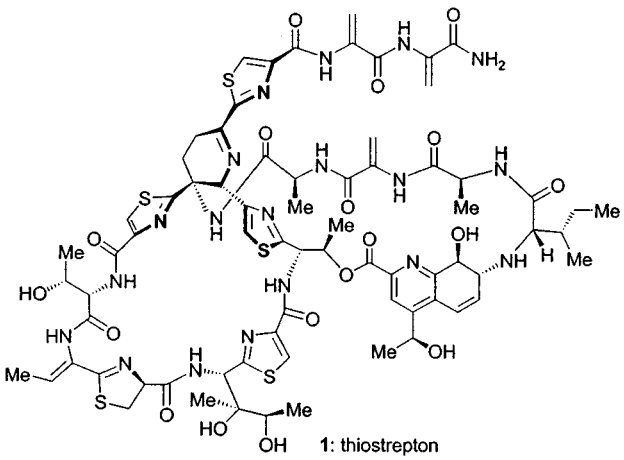
In the preceding Communication in this issue[1] we described the construction of the thiazoline-containing macrocycle **2** as an advanced intermediate toward the total synthesis of thiostrepton (**1**). Herein we report the construction of suitable dipeptide (**8**, Scheme 1) and quinaldic acid (**22**, Scheme 2) fragments, their union with **2**, and the final stages of the total synthesis of **1**.

Scheme 1 outlines the synthesis of the required dipeptide derivative **8** from **3**, a known phenylseleno-substituted derivative of alanine.[2] Thus, **3** was converted into allyl ester **4**, which was treated with TFA to effect its conversion into the amino derivative **5**. Coupling of amine **5** with Boc-L-alanine

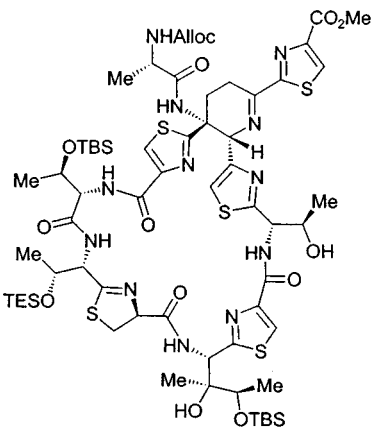
[*] Prof. Dr. K. C. Nicolaou, M. Zak, B. S. Safina, Dr. S. H. Lee, A. A. Estrada
Department of Chemistry and The Skaggs Institute for Chemical Biology
The Scripps Research Institute
10550 North Torrey Pines Road, La Jolla, California 92037 (USA)
Fax: (+1) 858-784-2469
and
Department of Chemistry and Biochemistry
University of California, San Diego
9500 Gilman Drive, La Jolla, California 92093 (USA)
E-mail: kcn@scripps.edu

[**] 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.).

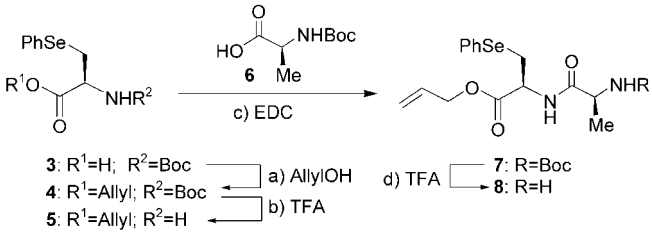
  DOI: 10.1002/ange.200461341



1: thiostrepton



2: thiazoline-containing macrocycle

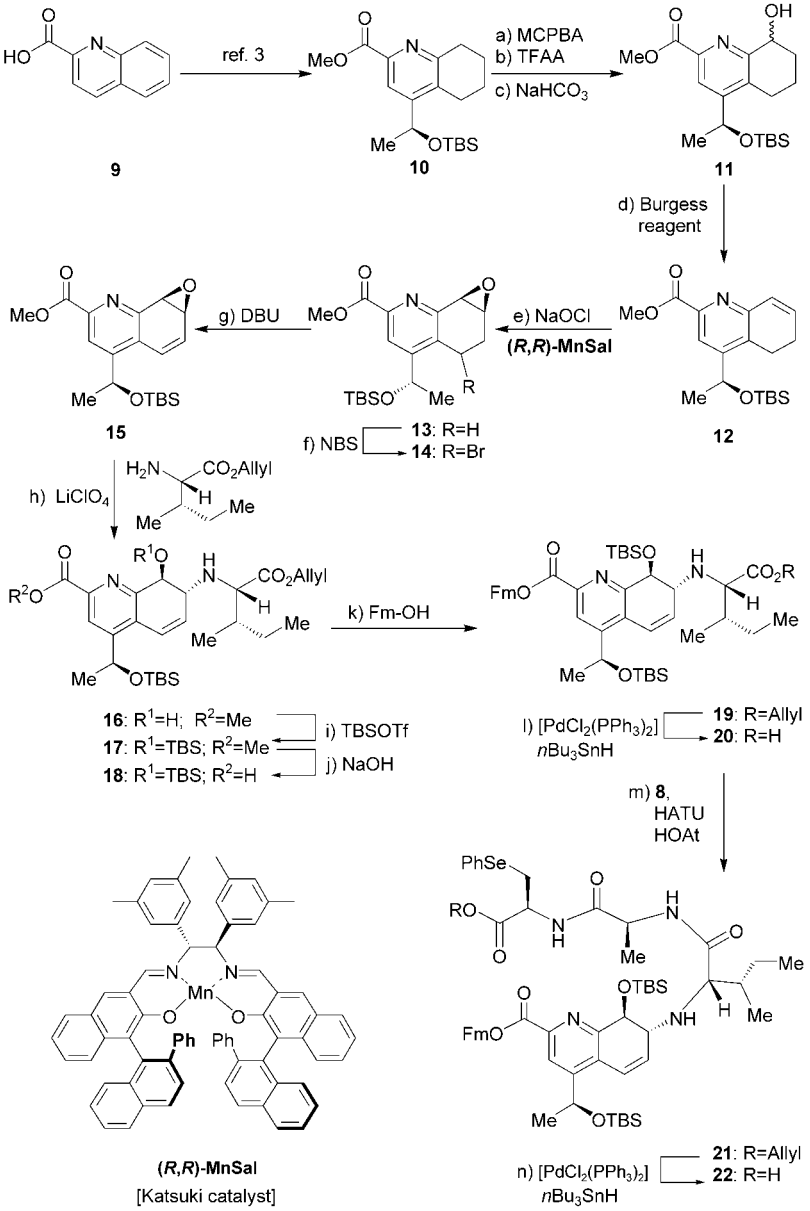


Scheme 1. Construction of dipeptide **8**. Reagents and conditions: a) AllylOH (2.0 equiv), EDC (1.1 equiv), 4-DMAP (0.1 equiv), CH_2Cl_2, 25 °C, 3 h, 70%; b) TFA/CH_2Cl_2 (1:1), 0 °C, 1 h; c) Boc-L-Ala-OH (1.1 equiv), HOAt (1.1 equiv), EDC (1.1 equiv), DMF, 25 °C, 2 h, 60% (two steps); d) TFA/CH_2Cl_2 (1:1), 0 °C, 30 min, 99%. EDC = 1-ethyl-(3-dimethylaminopropyl)carbodiimide hydrochloride, 4-DMAP = 4-dimethylamino pyridine; TFA = trifluoroacetic acid; Boc = *tert*-butoxycarbonyl; HOAt = 1-hydroxy-7-azabenzotriazole; DMF = *N*,*N*-dimethylformamide.

(**6**) proceeded under the influence of EDC–HOAt to afford dipeptide **7** (60% overall yield from **4**), whose TFA-mediated deprotection liberated primary amine **8**, ready for coupling with the appropriate quinaldic acid moiety.

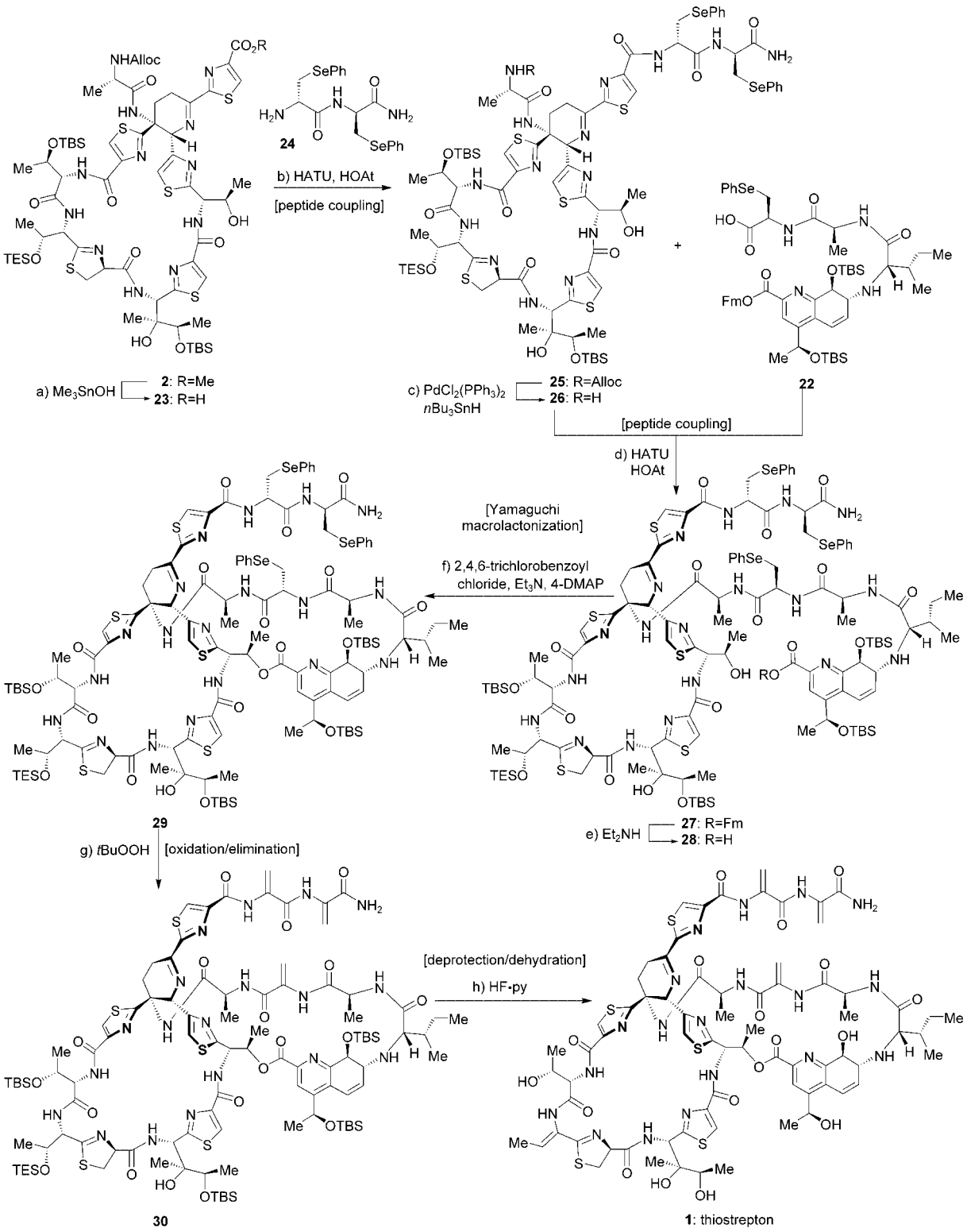
Scheme 2 delineates the synthesis of the entire quinaldic acid chain **22** which commenced from 2-quinoline carboxylic acid (**9**) and proceeded through asymmetric epoxidation of olefin **12** and sequential attachment to the resulting epoxide of an isoleucine residue and of dipeptide **8**. Thus, **9** was converted in five steps and good overall yield as previously described[3] into functionalized methyl ester **10**. The latter compound was then oxygenated to afford **11** in 65% overall yield through a Boekelheide-type sequence[4] involving a) MCPBA-mediated *N*-oxide formation; b) TFAA-induced acylation of the generated *N*-oxide; and c) $NaHCO_3$-facilitated rearrangement–hydrolysis of the resulting trifluoroacetate. Alcohol **11** was then dehydrated by treatment with Burgess reagent to afford olefin **12** in 68% yield. The product **12** served well as the precursor to the desired compound **13** in a diastereoselective epoxidation reaction brought about by NaOCl in the presence of the Katsuki manganese–salen catalyst **(*R*,*R*)-MnSal** and 4-phenyl-pyridine *N*-oxide.[5] Under these conditions, epoxide **13** was obtained as a mixture of diastereomers with the desired one predominating in ≈87:13 ratio and 82% combined yield. Chromatographic separation of **13** followed by radical bromination led to a mixture of diastereomeric bromides **14** (40% yield plus 26% recovered starting material) which were eliminated by exposure to DBU to afford epoxyolefin **15** in 96% yield. The epoxide moiety within **15** was then regio- and stereoselectively opened by the free amine of L-isoleucine allyl ester in the presence of lithium perchlorate to afford aminoalcohol **16** in 69% yield. Presumably, the observed regioselectivity in this reaction is due to coordination of the lithium ion with the quinaldic acid nitrogen atom which simultaneously activates the epoxide moiety and deactivates the benzylic site through destabilization of the incipient carbocation at that position.[6] The hydroxy group of **16** was then protected as a TBS ether by treatment with TBSOTf in the presence of iPr$_2$NEt to furnish bis(silyl ether) **17** (96% yield), whose methyl ester was selectively hydrolyzed by exposure to NaOH to afford carboxylic acid **18** (89% yield). This maneuver was necessary to install a protecting group on the pyridine-bound carboxy group suitable for the subsequent and rather delicate elaboration of the growing chain of the molecule. As such a moiety, the fluorenylmethyl (Fm) group was then introduced at this position by esterification with FmOH and through the Yamaguchi[7] protocol, leading to ester **19** in 64% yield. The allyl ester group was then removed from the isoleucine residue by palladium-catalyzed reductive cleavage,[8] which gave rise to the corresponding carboxylic acid **20** in good yield. Coupling of **20** with dipeptide **8** (Scheme 1) under established conditions generated quinaldic acid derivative **21** (Table 1) in 66% yield from **19**. Finally, treatment of **21** with [$PdCl_2(PPh_3)_2$]–nBu$_3$SnH liberated the targeted carboxylic acid **22** in 87% yield, ready for incorporation into the growing frame of **1**.

The completion of the total synthesis of thiostrepton (**1**) is depicted in Scheme 3. Advanced thiazoline macrocycle **2**[1] was treated with Me_3SnOH[9] in 1,2-dichloroethane at 65 °C to liberate carboxylic acid **23**, which was coupled with the bisphenylselenium tail derivative **24** (prepared as previously described)[10] under the influence of HATU–HOAt to afford intermediate **25** (Table 1) in 83% overall yield from **2**. Exposure of **25** to [$PdCl_2(PPh_3)_2$]–nBu$_3$SnH[8] cleaved its Alloc group and furnished primary amine **26** in 86% yield in preparation for the incorporation of **22**. Indeed, coupling of amino compound **26** with carboxylic acid **22** was effected once again with HATU–HOAt, leading to polypeptide **27** (Table 1) in 64% yield. It was now time to consider the final macro-



Scheme 2. Synthesis of quinaldic acid subunit **22**. Reagents and conditions: a) MCPBA (1.0 equiv), CH_2Cl_2, 25 °C, 12 h; b) TFAA (3.0 equiv), CH_2Cl_2, 25 °C, 12 h; c) $NaHCO_3$ (2 M), CH_2Cl_2, 8 h, 65% (three steps); d) Burgess reagent (1.2 equiv), THF/benzene (1:1), reflux, 3.5 h, 68%; e) **(*R*,*R*)-MnSal** (0.01 equiv), 4-Ph-py-*N*-oxide (0.1 equiv), NaOCl (0.79 M), phosphate buffer adjusted to pH 11.5 with NaOH (2.0 M), CH_2Cl_2, 25 °C, 1 h, 82%, ≈87:13 ratio of products; f) NBS (1.1 equiv), AIBN (0.1 equiv), CCl_4, 80 °C, 40 min, 40% (and 26% recovered starting material); g) DBU (1.1 equiv), THF, 25 °C, 2 h, 96%; h) H-L-Ile-OAllyl (3.0 equiv), $LiClO_4$ (5.0 equiv), MeCN, 60 °C, 22 h, 69%; i) TBSOTf (3.0 equiv), *i*Pr_2NEt (5.0 equiv), THF, 25 °C, 3 h, 96%; j) NaOH, MeOH, THF, 25 °C, 6 h, 89%; k) 2,4,6-trichlorobenzoyl chloride (2.0 equiv), Et_3N (6.0 equiv), toluene, 25 °C, 12 h; then FmOH (3.0 equiv), 4-DMAP (0.1 equiv), 25 °C, 12 h, 64%; l) $[PdCl_2(PPh_3)_2]$ (0.1 equiv), *n*Bu_3SnH (1.1 equiv), CH_2Cl_2, 0 °C, 1 h; m) **8** (1.1 equiv), HATU (1.1 equiv), HOAt (1.1 equiv), DMF, 25 °C, 3 h, 66% (two steps); n) $[PdCl_2(PPh_3)_2]$, (0.1 equiv), *n*Bu_3SnH (1.1 equiv), CH_2Cl_2, 0 °C, 30 min, 87%. MCPBA = *m*-chloroperoxybenzoic acid; TFAA = trifluoroacetic anhydride; NBS = *N*-bromosuccinimide; AIBN = 2,2′-azabisisobutyronitrile; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; TBS = *tert*-butyldimethylsilyl; OTf = trifluoromethanesulfonate; Fm = 9-fluorenylmethyl; HATU = *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate.

cyclization to the thiostrepton skeleton from this long-sought precursor. To this end, the Fm group was ejected from **27** by exposure to Et_2NH, and the resulting hydroxy acid **28** (87% yield) was subjected to macrolactonization under the Yamaguchi[7] conditions to afford polycycle **29** (42% yield). All that now remained before reaching the coveted target, thiostrepton (**1**), was the unmasking of all its functionalities. First, all three phenylseleno groups within **29** were expelled by *t*BuOOH-mediated oxidation, followed by spontaneous *syn* elimination of the resulting selenoxides, to furnish **30** (68% yield) with all three dehydroalanine subunits in place. Finally, the TES and four TBS groups were removed by exposure to excess HF·py in THF at ambient temperature, conditions which also caused the desired elimination of the oxygen



Scheme 3. Completion of the total synthesis of thiostrepton (**1**). Reagents and conditions: a) Me_3SnOH (10.0 equiv), 1,2-dichloroethane, 65 °C, 2.5 h; b) **24** (2.0 equiv), HATU (1.2 equiv), HOAt (1.2 equiv), iPr_2NEt (3.0 equiv), DMF, 0 °C, 2 h, 83 % (two steps); c) $[PdCl_2(PPh_3)_2]$ (0.1 equiv), nBu_3SnH (50.0 equiv), 0 °C, 1 h, 86 %; d) **22** (1.1 equiv), HATU (1.1 equiv), HOAt (1.1 equiv), iPr_2NEt (3.0 equiv), DMF, 0 °C, 1.5 h, 64 %; e) Et_2NH/CH_2Cl_2 (1:6.5), 25 °C, 2.5 h, 87 %; f) 1. 2,4,6-trichlorobenzoyl chloride (30 equiv), Et_3N (40 equiv), concentrated in toluene, 25 °C, 24 h; 2. 4-DMAP (30 equiv), toluene (0.5 mM), 24 h, 25 °C, 42 %; g) *t*BuOOH (6.0 M in decane)/CH_2Cl_2 (1:10), 25 °C, 3 h, 68 %; h) HF·py/THF (1:5), 25 °C, 24 h, 52 %. Alloc = allyloxycarbonyl; TBS = *tert*-butyldimethylsilyl; TES = triethylsilyl.

Table 1: Selected physical properties for compounds **21**, **25**, **27**, and **1**.

21: $R_f = 0.3$ (silica gel, EtOAc/hexanes 1:5); $[\alpha]_D^{32} = +44$ ($CHCl_3$, $c = 0.045$); IR (film): $\tilde{\nu}_{max} = 3302, 2954, 2857, 1739, 1647, 1517, 1458, 1249, 1211, 1124, 1090\ cm^{-1}$; ^1H NMR (600 MHz, CD_3CN, 70 °C): $\delta = 8.10$ (s, 1H), 7.85–7.75 (m, 4H), 7.54–7.52 (m, 2H), 7.44–7.41 (m, 2H), 7.39–7.34 (m, 2H), 7.28–7.26 (m, 4H), 6.99 (br d, $J = 3.0$ Hz, 1H), 6.89 (d, $J = 10.0$ Hz, 1H), 6.40 (dd, $J = 10.1$, 5.3 Hz, 1H), 5.89–5.82 (m, 1H), 5.29–5.18 (m, 4H), 4.80 (d, $J = 3.5$ Hz, 1H), 4.75–4.63 (m, 4H), 4.51–4.48 (m, 1H), 4.46–4.40 (m, 2H), 4.35–4.32 (quint, $J = 7.3$, 7.0 Hz, 1H), 3.49–3.46 (m, 1H), 3.35–3.23 (m, 4H), 3.07 (d, $J = 5.3$ Hz, 1H), 1.70–1.60 (br s, 1H), 1.38 (d, $J = 6.6$ Hz, 3H),1.30 (d, $J = 7.0$ Hz, 3H), 0.94 (t, $J = 5.1$ Hz, 3H), 0.90 (s, 9H), 0.86 (d, $J = 7.1$ Hz, 1H), 0.14 (s, 3H), 0.10 (s, 3H), −0.015 (s, 3H), −0.098 ppm (s, 3H); ^{13}C NMR (150 MHz, CD_3CN, 70 °C): $\delta = 174.8, 173.5, 171.3, 166.5, 157.5, 152.6, 147.3, 145.5, 145.5, 144.4, 143.7, 142.7, 134.6, 134.5, 134.5, 133.8, 133.5, 130.8, 130.6, 129.2, 128.8, 128.6, 128.3, 126.8, 126.6, 123.3, 123.1, 121.4, 119.0, 76.1, 68.2, 68.1, 67.0, 65.7, 65.6, 58.8, 54.2, 50.0, 48.5, 39.9, 30.3, 29.1, 27.8, 26.7, 26.6, 26.5, 19.5, 19.3, 19.2, 19.2, 19.1, 18.9, 16.7, 14.2, 12.2, −3.5, −3.8, −4.0, −4.2$ ppm; HRMS (ESI-TOF): calcd for $C_{59}H_{80}N_4O_8SeSi_2$ [M+Na^+]: 1131.4572; found: 1131.4598.

25: $R_f = 0.40$ (silica gel, 7% MeOH/CH_2Cl_2); ^1H NMR (600 MHz, CD_3CN, 70 °C): $\delta = 8.16$ (s, 1H), 8.03 (d, $J = 7.0$ Hz, 1H), 7.90 (d, $J = 9.2$ Hz, 1H), 7.80–7.57 (m, 2H), 7.56–7.52 (m, 1H), 7.50–7.49 (m, 2H), 7.39 (s, 1H), 7.28–7.27 (m, 4H), 7.24–7.23 (m, 3H), 5.93 (br s, 1H), 5.79–5.75 (m, 1H), 5.58 (d, $J = 9.2$ Hz, 1H), 5.39–5.38 (m, 1H), 5.24 (br s, 1H), 5.20 (dd, $J = 17.1$, 1.3 Hz, 1H), 5.09 (dd, $J = 10.6$, 1.1 Hz, 1H), 5.00 (dt, $J = 9.2$, 1.4 Hz, 1H), 4.86–4.84 (m, 1H), 4.72–4.65 (m, 2H), 4.6 (br s, 1H), 4.52–4.48 (m, 2H), 4.32–4.25 (m, 4H), 4.12 (q, $J = 6.1$, 2.4 Hz, 1H), 4.00 (quint, $J = 6.6$, 2.5 Hz, 1H), 3.69–3.64 (m, 1H), 3.58 (d, $J = 9.2$ Hz, 2H), 3.44–3.19 (m, 6H), 2.89 (br s, 1H), 2.46 (br s, 1H), 1.33 (d, $J = 6.1$ Hz, 3H), 1.25 (d, $J = 4.0$ Hz, 3H), 1.24 (d, $J = 3.0$ Hz, 3H), 1.22 (d, $J = 6.6$ Hz, 3H), 1.10 (d, $J = 6.1$ Hz, 3H), 0.98 (s, 9H), 0.97–0.94 (m, 9H), 0.95 (s, 9H), 0.66 (q, $J = 7.9$ Hz, 6H), 0.20 (s, 3H), 0.19 (s, 3H), 0.12 (s, 3H), 0.09 ppm (s, 3H); HRMS (ESI-TOF): calcd for $C_{82}H_{117}N_{15}O_{15}S_5Se_2Si_3$ [M+Na^+]: 1978.4987; found: 1978.4973.

27: $R_f = 0.55$ (silica gel, 7% MeOH/CH_2Cl_2); ^1H NMR (600 MHz, CD_3CN, 70 °C): $\delta = 8.15$ (s, 1H), 8.09 (s, 1H), 8.02 (d, $J = 7.9$ Hz, 1H), 7.87 (d, $J = 8.3$ Hz, 1H), 7.84–7.82 (m, 2H), 7.76 (d, $J = 7.9$ Hz, 1H), 7.73 (d, $J = 7.0$ Hz, 1H), 7.57–7.56 (m, 2H), 7.50–7.48 (m, 2H), 7.46 (br s, 1H), 7.41–7.38 (m, 2H), 7.32 (t, $J = 7.4$ Hz, 2H), 7.26–7.15 (m, 9H), 7.14 (d, $J = 4.0$ Hz, 1H), 6.87 (s, 1H), 6.86 (d, $J = 10.1$ Hz, 1H), 6.36 (dd, $J = 10.1$ Hz, 1H), 5.56 (d, $J = 9.7$ Hz, 1H), 5.37 (s, 1H), 5.25–5.23 (m, 2H), 4.97 (m, 1H), 4.84–4.82 (m, 1H), 4.77 (d, $J = 3.5$ Hz, 1H), 4.72–4.60 (m, 5H), 4.52–4.49 (m, 2H), 4.41 (t, $J = 6.0$ Hz, 1H), 4.38–4.31 (m, 2H), 4.28–4.24 (m, 2H), 4.19 (t, $J = 8.2$ Hz, 1H), 4.10–4.05 (m, 2H), 3.63–3.55 (m, 4H), 3.48–3.45 (m, 1H), 3.44–3.32 (m, 4H), 3.30–3.10 (m, 2H), 2.96–2.86 (m, 1H), 2.45 (br s, 1H), 1.35 (d, $J = 7.0$ Hz, 3H), 1.32 (d, $J = 6.1$ Hz, 3H), 1.24–1.21 (m, 9H), 1.16–1.15 (d, $J = 6.1$ Hz, 3H), 1.09 (d, $J = 6.1$ Hz, 3H), 1.03 (s, 3H), 0.97–0.90 (m, 27H), 0.88 (s, 9H), 0.82 (d, $J = 6.6$ Hz, 3H), 0.75 (s, 9H), 0.66 (q, $J = 8.3$ Hz, 6H), 0.17 (s, 3H), 0.16 (s, 3H), 0.11 (s, 3H), 0.10 (s, 3H), 0.09 (s, 3H), 0.08 (s, 3H), −0.03 (s, 3H), −0.11 ppm (s, 3H); HRMS (ESI-TOF): calcd for $C_{134}H_{187}N_{19}O_{20}S_5Se_3Si_5$ [M+H^+]: 2922.9217; found: 2922.9215.

1 (thiostrepton, synthetic and natural): ^1H NMR (600 MHz, [D_8]THF, thiostrepton is more soluble and stable in this solvent than in $CDCl_3$; for proton numbering and abbreviations, see: ref. 11): $\delta = 10.03$ (s, 1H; CONH), 9.69 (s, 1H; CONH), 9.30 (s, 1H; CONH), 8.65 (s, 1H; CONH), 8.39 (s, 1H; Ar-H), 8.31 (br s, 1H; OH or NH), 8.29 (s, 1H; Ar-H), 8.20 (s, 1H; Ar-H), 8.03 (br s, 1H; CONH), 7.62 (d, $J = 5.6$ Hz, 1H; CONH), 7.58 (d, $J = 10.3$ Hz, 1H; CONH), 7.54 (br s, 1H; Thstn 3-OH), 7.53 (s, 1H; Ar-H), 7.48 (br s, 1H; OH or NH), 7.42 (d, $J = 7.7$ Hz, 1H; CONH), 7.32 (s, 1H; Ar-H), 7.07 (d, $J = 7.7$ Hz, 1H; Q 8-OH), 6.99 (br s, 1H; OH or NH), 6.92 (d, $J = 9.7$ Hz; Q 5-H), 6.75 (d, $J = 2.0$ Hz, 1H; Deala-H), 6.58 (d, $J = 7.5$ Hz, 1H; CONH), 6.56 (s, 1H; Deala-H), 6.45 (q, $J = 6.1$ Hz, 1H; Thr(2) 3-H), 6.32 (dd, $J = 9.7$, 5.6 Hz; Q 6-H), 6.13 (q, $J = 7.1$ Hz, 1H; But 3-H), 5.89 (d, $J = 9.8$ Hz, 1H; Thr(2) 2-H), 5.84 (d, $J = 9.2$ Hz, 1H; Thstn 2-H), 5.77 (s, 1H; Deala-H), 5.55 (s, 1H; Deala-H), 5.49 (s, 1H; OH or NH), 5.47–5.46 (m, 1H, Pip 6-Hβ), 5.30 (q, $J = 6.1$ Hz, 1H; Q 11-H), 5.20 (s, 1H; Deala-H), 5.04 (dd, $J = 8.7$, 4.1 Hz, 1H; Cys 4-Hβ), 4.84 (t, $J = 7.7$ Hz, 1H; Ala(2) 2-H), 4.73 (d, $J = 7.1$ Hz, 1H; Q 8-H), 4.35 (dd, $J = 7.9$, 3.5 Hz, 1H; Thr(1) 2-H), 4.29 (d, $J = 4.6$ Hz, 1H; Q 7-Hβ), 4.20–4.15 (m, 2H; Pip 4-Hα, Thstn 4-OH), 3.90 (quint, $J = 6.5$ Hz, 1H; Ala(1) 2-H), 3.85 (quint, $J = 5.7$ Hz, 1H; Thstn 4-H), 3.24 (t, $J = 12.3$ Hz, 1H; Cys 5-Hα), 3.00–2.93 (m, 2H; Ile 2-H, Pip 3-Hα), 2.39–2.35 (m, 1H; Pip 4-Hβ), 1.60 (d, $J = 7.2$ Hz, 3H; CH_3), 1.33 (d, $J = 3.5$ Hz, 3H; CH_3), 1.32 (d, $J = 3.1$ Hz, 3H; CH_3), 1.27 (d, $J = 6.6$ Hz, 3H; CH_3), 1.16 (s, 3H; CH_3), 1.14 (s, 3H; CH_3), 1.06 (d, $J = 6.1$ Hz, 3H; CH_3), 0.96 (t, $J = 7.0$ Hz, 3H; CH_3), 0.88 ppm (d, $J = 6.6$ Hz, 3H; CH_3).

marked with the TES group to form the required thiazoline-conjugated double bond in its proper *Z* geometry, leading directly to thiostrepton (**1**). Synthetic **1** exhibited identical physical properties (R_f, HPLC, optical rotation, ^1H NMR, mixed ^1H NMR, ^{13}C NMR, and MS) to an authentic sample of **1** (Table 1).[11]

The chemistry described herein and in the preceding Communication in this issue[1] constitutes a highly convergent and stereoselective synthesis of the most complex member of the thiopeptide class of antibiotics, thiostrepton (**1**). With the impressive range of biological effects exhibited by members of this proliferating family of natural products, these studies may facilitate chemical biology and drug-discovery efforts in diverse areas of current interest.

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

Keywords: antibiotics · natural products · peptide coupling · protecting groups · total synthesis

[1] K. C. Nicolaou, B. S. Safina, M. Zak, A. A. Estrada, S. H. Lee, *Angew. Chem.* **2004**, *116*, 5197–5202; *Angew. Chem. Int. Ed.* **2004**, *43*, 5087–5092; see preceding Communication in this issue.
[2] N. M. Okeley, Y. Zhu, W. A. van der Donk, *Org. Lett.* **2000**, *2*, 3603 – 3606.
[3] K. C. Nicolaou, B. S. Safina, C. Funke, M. Zak, F. J. Zécri, *Angew. Chem.* **2002**, *114*, 2017 – 2020; *Angew. Chem. Int. Ed.* **2002**, *41*, 1937 – 1940.
[4] C. Fontenas, E. Bejan, H. A. Haddou, G. A. Galavoine, *Synth. Commun.* **1995**, *25*, 629 – 633.
[5] a) K. Ito, M. Yoshitake, T. Katsuki, *Tetrahedron* **1996**, *52*, 3905 – 3920; b) H. Sasaki, R. Irie, T. Hamada, K. Suzuki, T. Katsuki, *Tetrahedron* **1994**, *50*, 11827 – 11838; c) for a pertinent review in this area, see: T. Katsuki, *Curr. Org. Chem.* **2001**, *5*, 663 – 678.
[6] a) D. R. Boyd, R. J. H. Davies, L. Hamilton, J. J. McCullough, J. F. Malone, H. P. Porter, A. Smith, *J. Org. Chem.* **1994**, *59*, 984 – 990; b) D. R. Bushman, J. M. Sayer, D. R. Boyd, D. M. Jerina, *J. Am. Chem. Soc.* **1989**, *111*, 2688 – 2691.
[7] a) J. Inanaga, K. Hirata, H. Saeki, T. Katsuki, M. Yamaguchi, *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989 – 1993; b) K. C. Nicolaou, A. P. Patron, K. Ajito, P. K. Richter, H. Khatuya, P. Bertinato, R. A. Miller, M. J. Tomaszewski, *Chem. Eur. J.* **1996**, *2*, 847 – 868.

[8] B. G. de la Torre, J. L. Torres, E. Bardají, P. Clapés, N. Xaus, X. Jorba, S. Calvet, F. Albericio, G. Valencia, *J. Chem. Soc. Chem. Commun.* **1990**, 965 – 967.
[9] R. L. E. Furlan, E. G. Mata, O. A. Mascaretti, *J. Chem. Soc. Perkin Trans. 1* **1998**, 355 – 358.
[10] K. C. Nicolaou, M. Nevalainen, M. Zak, S. Bulat, M. Bella, B. S. Safina, *Angew. Chem.* **2003**, *115*, 3540 – 3546; *Angew. Chem. Int. Ed.* **2003**, *42*, 3418 – 3424.
[11] a) O. D. Hensens, G. Albers-Schönberg *J. Antiobiot.* **1983**, *36*, 799 – 813; b) O. D. Hensens, G. Albers-Schönberg, *J. Antibiot.* **1983**, *36*, 814 – 831; c) O. D. Hensens, G. Albers-Schönberg, *J. Antibiot.* **1983**, *36*, 832 – 845.

