Pergamon

Tetrahedron Letters 43 (2002) 105–110

TETRAHEDRON LETTERS

Synthetic studies on the thiostrepton family of peptide antibiotics: synthesis of the tetrasubstituted dehydropiperidine and piperidine cores

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Received 12 October 2001; revised 29 October 2001; accepted 2 November 2001

Abstract—The tetrasubstituted dehydropiperidine and piperidine cores of the thiostrepton family of peptide antibiotics were synthesized which featured the coupling between the azomethine ylide and the enantiopure sulfinimine, and the subsequent stereoselective reduction of the six-membered imine.

In 1955, thiostrepton was isolated from the culture broth of *Streptomyces azureus* by the Squibb group.[1] Its structure was elucidated by chemical degradation studies,[2] X-ray crystallographic analysis,[3] and NMR studies.[4] Other structurally related antibiotics, the siomycins,[5] the thiopeptins,[6] and Sch 18640,[7] were also isolated. The characteristic structure of this thiostrepton family of peptide antibiotics is the bicyclic structure containing a tetrasubstituted dehydropiperidine and/or piperidine moiety, a tetrasubstituted dihydroquinoline moiety, four thiazole moieties, a thiazoline moiety, dehydroamino acid moieties, and a dihydroxyisoleucine moiety (Fig. 1). Because of these complex structural features, synthetic studies on the thiostrepton family of antibiotics have scarcely been attempted.[8] Most efforts have focused on the syntheses of the much simpler thiopeptide antibiotics.[9,10] These antibiotics show high activities against Gram-positive bacteria and mycobacteria.[1,5,6a,b] In this letter, we describe the enantioselective synthesis of the tetrasubstituted dehydropiperidine and piperidine cores, **1** and **2**, of the thiostrepton family of antibiotics.

The retrosynthetic analysis is shown in Scheme 1. The tetrasubstituted dehydropiperidine core **1** would be derived from the tetrasubstituted piperidine core **2** by dehydrogenation.[11] The precursor **3** of **2** would be obtained from the six-membered imine derivative **4** by stereoselective reduction. It is likely that the six-membered imine derivative **4** exists in the equilibrium mixture of the five-membered imine derivative **6a** via the intermediate **5a**. We anticipated that the six-membered imine **4** in this equilibrium mixture would be preferentially reduced due to steric hindrance around the imine function in the five-membered imine **6a**. It is expected that this stereoselective reduction would be realized by considering the stereoelectronic effect shown in Scheme 1. In order to synthesize the equilibrium mixture of **4**–**6a**, we selected the coupling reaction between the azomethine ylide derived from **7** and the chiral sulfinimine **8** or **9**, followed by desulfinylation. This coupling reaction may proceed via the 1,3-dipolar cycloaddition[12] (giving **5b**) or the 1,2-addition reaction (giving **6b**). There is a precedent for the 1,3-dipolar cycloaddition between the azomethine ylides derived from the *N*-benzylidene α-aminoesters and the chiral sulfinimines.[13,14] The stereochemical outcome described in the literature[13a] matches our demand when sulfinimine **8** is used. On the other hand, when this reaction proceeds via the 1,2-addition reaction, it is possible to control the C6 stereochemistry in **6b** by employing sulfinimine **8** or its epimer **9**;[15] however, the C5 stereochemistry in **6b** is unpredictable.

One of the key segments, 2,5-dithiazolyl-1,2-dehydropyrrolidine **7**,[16] was prepared from the known pyrrolidine dicarboxylic acid derivatives (Schemes 2 and 3).[17] *cis*-1-Boc-2,5-dicarbethoxypyrrolidine **10**[17] (Scheme 2) was hydrolyzed to the acid, which was converted into the

Keywords: thiostrepton; piperidines; sulfinimines; stereoselective reduction.

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0040-4039/02/$ - see front matter
PII: S0040-4039(01)02090-1

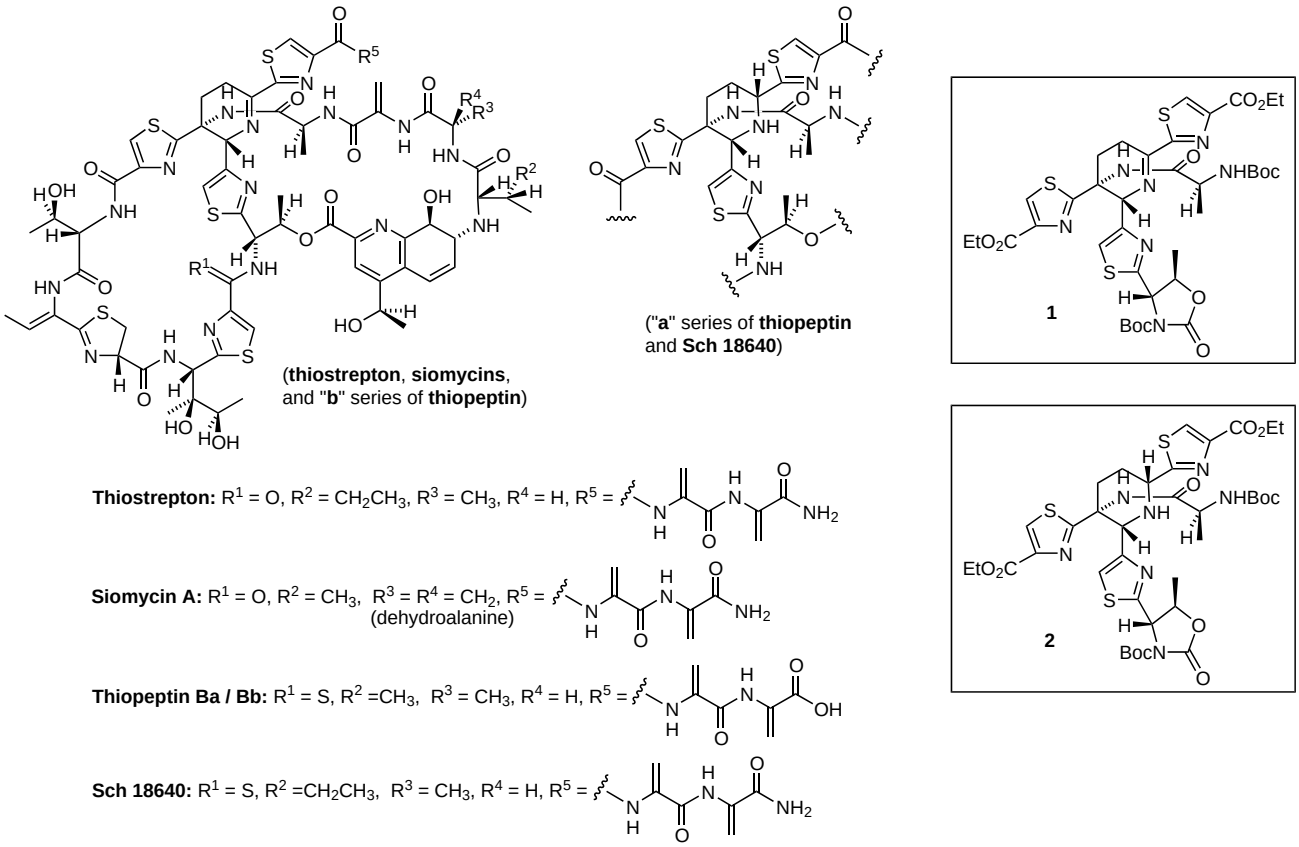
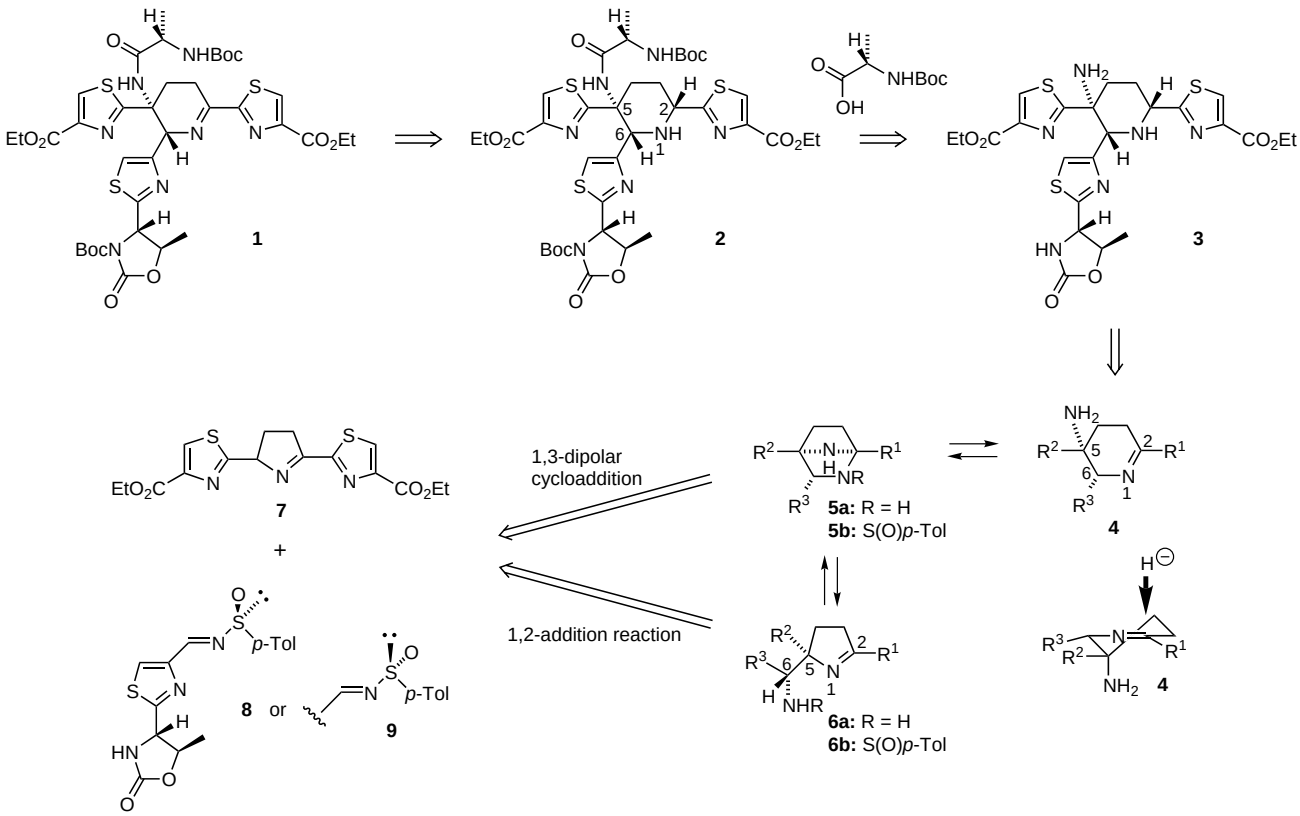
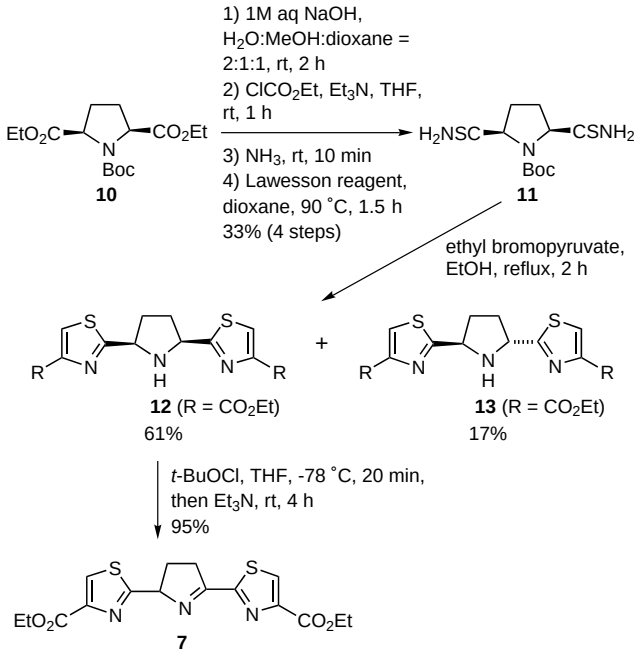


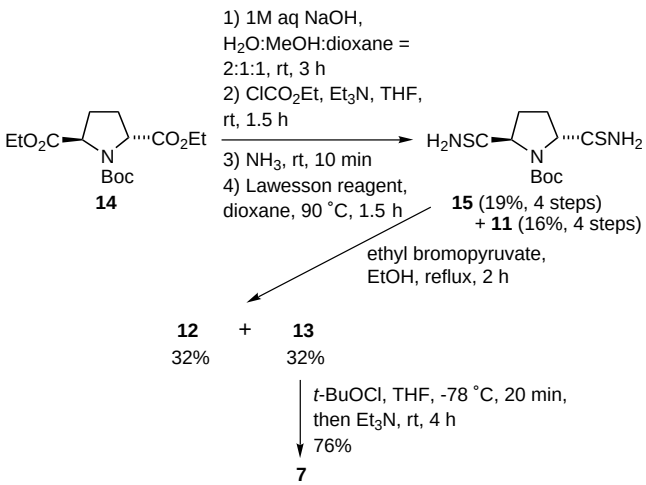
Figure 1.



Scheme 1.



Scheme 2.



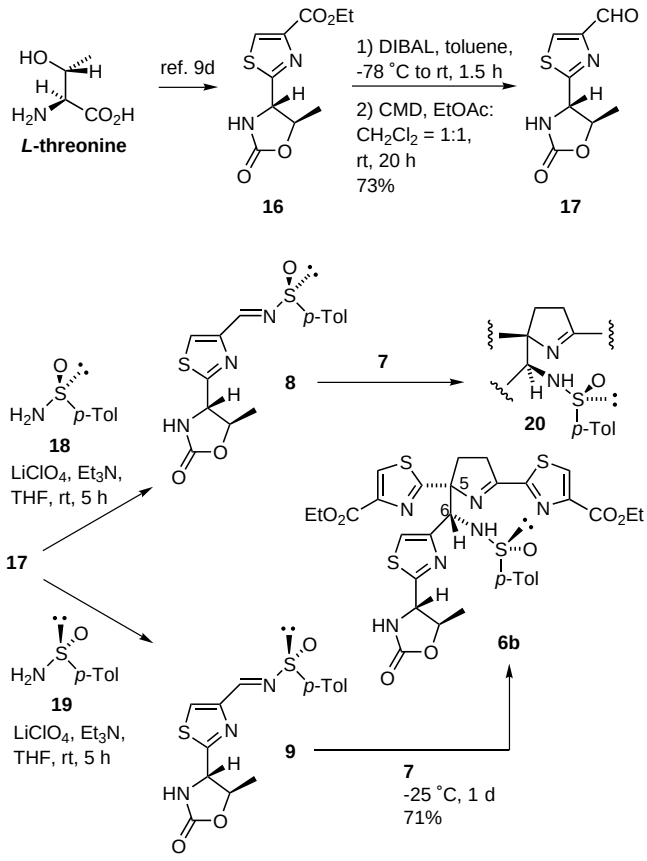
Scheme 3.

mixed anhydride; and into this solution, gaseous NH_3 was introduced. The resulting amide was treated with Lawesson reagent,[18] giving thioamide **11** in 33% overall yield. Treatment of **11** with ethyl bromopyruvate[9d] in EtOH afforded **12** and its *trans*-isomer **13** in 61 and 17% yields, respectively. Treatment of **12** with *t*-BuOCl[19] in THF followed by triethylamine provided **7** in 95% yield. In addition, *trans*-1-Boc-2,5-dicarbethoxypyrrolidine **14**[17] (Scheme 3) was also transformed to **7** by the same procedure as described in the *cis*-series. From thioamide **15**, obtained from **14** in 19% yield together with the 16% yield of the *cis*-isomer **11**, a comparable yield (each 32%) of **12** and **13** was obtained and then **13** was converted into **7** in 76% yield.

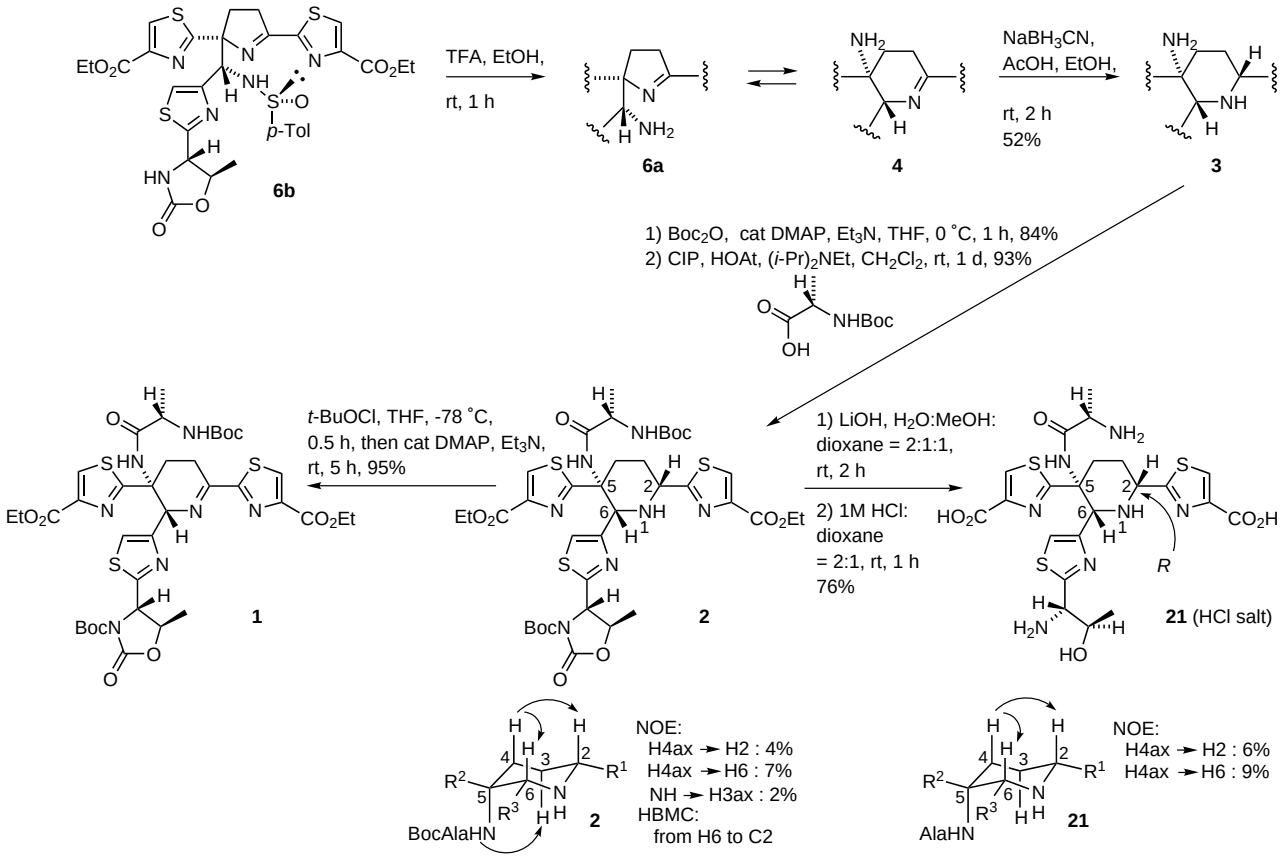
Synthesis of another key segment, the chiral sulfinimine **8** or **9**, and its connection with **7** began with the known **16**,[9d] which was prepared from L-threonine (Scheme 4).

DIBAL reduction of **16** followed by oxidation with chemical manganese dioxide (CMD)[20] afforded aldehyde **17** in 73% yield. Condensation of **17** (1 equiv.) in THF with the Davis sulfinamide[21] **18** (1 equiv.) or **19** (1 equiv.) in the presence of $LiClO_4$ (8 equiv.) and Et_3N (8 equiv.) provided sulfinimine **8** or **9**, respectively.[22] Each solution of these sulfinimines was directly used in the subsequent coupling. First, based on the results described in the literature,[13a] dehydropyrrolidine **7** and sulfinimine **8** were selected for the coupling partners. However, this coupling proceeded via the 1,2-addition reaction (not the 1,3-dipolar cycloaddition); furthermore, the following transformation of the coupling product **20** led to the diastereomer of **21** (vide infra) having the opposite configurations at the C2, C5, and C6 positions.[23] Therefore, sulfinimine **9** was next chosen as the coupling partner. To the above-mentioned solution was added **7** at −25°C. After 1 day, the addition product **6b** and its diastereomer[24] were obtained in 71 and 17% yields, respectively. The ^1H NMR signal of NHSO (δ 5.79, $J=8.7$ Hz) in **6b** supported the five-membered imine structure; however, the C5 and C6 configurations could not be determined at this stage.

With the addition product **6b** in hand, we turned our attention to the final stage (Scheme 5). After desulfinylation of **6b** with TFA in EtOH, the obtained mixture of **4**–**6a** was subjected to reduction with $NaBH_3CN$ in AcOH/EtOH to afford piperidine **3** in 52% yield as the sole reduction product. Subsequent protection of the oxazoline amine in **3** with Boc_2O followed by condensa-



Scheme 4.



Scheme 5.

tion with Boc-Ala-OH using 2-chloro-1,3-dimethylimidazolidium hexafluorophosphate (CIP)[25] and 1-hydroxy-7-azabenzotriazole (HOAt) afforded piperidine **2**[26] in 78% yield. The HMBC spectrum of **2** (from H6 to C2) supported the piperidine skeleton and the NOE experiments of **2** supported the relative configurations of the piperidine ring. The absolute structure of **2** was confirmed by its transformation to **21**, which was a degradation product from natural thiopeptin B_a.[27,28] Finally, dehydrogenation of **2** with *t*-BuOCl[19] and triethylamine gave dehydropiperidine **1**[29] in 95% yield.

In summary, we have synthesized, for the first time, the tetrasubstituted dehydropiperidine and piperidine cores, **1** and **2**, of the thiostrepton family of antibiotics via the coupling reaction of the azomethine ylide derived from **7** and the chiral sulfinimine **9**, followed by stereoselective reduction of the six-membered imine function. We believe that the synthetic route described herein is a convergent and unique one. Synthetic studies of other portions in the thiostrepton family of antibiotics are now in progress.

Acknowledgements

This research was supported by a Grant-in Aid for Scientific Research on Priority Areas (A) 'Exploitation of Multi-Element Cyclic Molecules' from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

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26. Compound **2**: $[\alpha]_D^{30}$ +20.9 (*c* 1.00, MeOH); IR ($CHCl_3$): 1820, 1795, 1720, 1500, 1370, 1325, 1100, 1070, and 1045 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 8.54 (1H, br s), 8.12 (1H, s), 7.84 (1H, s), 6.89 (1H, s), 5.45 (1H, d, $J=6.0$ Hz), 5.17 (1H, d, $J=2.7$ Hz), 5.03 (1H, dq, $J=2.7$ and 6.3 Hz), 4.59 (1H, s), 4.46 (1H, dd, $J=2.7$ and 10.1 Hz), 4.41 (2H, q, $J=7.2$ Hz), 4.40 (2H, q, $J=7.2$ Hz), 4.16 (1H, dq, $J=6.0$ and 6.6 Hz), 3.51 (1H, ddd, $J=3.0$, 3.0, and 14.1 Hz), 2.72 (1H, ddd, $J=3.6$, 14.1, and 14.1 Hz), 2.24 (1H, dddd, $J=2.7$, 3.0, 3.6, and 18.0 Hz), 2.01 (1H, dddd, $J=3.0$, 10.1, 14.1, and 18.0 Hz), 1.61 (3H, d, $J=6.3$ Hz), 1.46 (9H, s), 1.45 (3H, d, $J=6.6$ Hz), 1.39 (6H, t, $J=7.2$ Hz), 1.30 (9H, s). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 174.9, 173.3, 173.0, 167.4, 161.4, 161.3, 155.3, 152.8, 151.3, 148.8, 146.8, 127.3, 127.1, 119.7, 85.4, 79.7, 75.8, 64.9, 61.5, 61.4, 61.3, 61.2, 58.0, 51.4, 30.7, 28.2,

28.1, 27.8, 27.4, 20.4, 18.7, 14.3. HRMS (FAB$^+$) calcd for $C_{37}H_{50}N_7O_{11}S_3$ (M+H)$^+$: 864.2731. Found: 864.2726.

27. According to Ref. 6f, the authors have isolated two degradation products, **IIA** and **IIB**, from thiopeptin B_a as the piperidine residue. Compound **IIA**, the epimer of compound **IIB** at the C2 position in the piperidine ring, was formed from **IIB** as an artifact under their degradation conditions. Therefore, compound **IIB** was the intact piperidine residue. Unfortunately, they could not analyze the coupling constant $J_{2,3}$ of compound **IIB** because the C2 proton signal overlapped with the C6 proton signal at the 100 MHz NMR spectrometer (see Ref. 28). Instead, judging from the coupling constant ($J_{2,3}=3.5$ and 12.0 Hz) in the ^{1}H NMR spectrum of compound **IIA** together with X-ray analysis of thiostrepton,[3] they proposed that compound **IIA** was **21** and hence the C2 configuration of the piperidine ring in natural thiopeptin B_a was *S*. On the other hand, according to Ref. 4f, the authors proposed the C2 configuration of the piperidine ring in thiopeptin B_a to be *R* judging from the coupling constant ($J_{2,3}=3.5$ and 10.0 Hz) in the ^{1}H NMR spectrum of thiopeptin A_{1a} (thiopeptin A_{1a} is methyl ester of thiopeptin B_a at the terminal position in R^5 depicted in Fig. 1). These two arguments conflicted. Therefore, we did NOE experiments for both **2** and synthetic **21** that are shown in Scheme 5 and unambiguously determined the C2, C5, and C6 relative configurations. Additionally, the absolute configuration of the piperidine ring in synthetic **21** was confirmed by comparison of its optical rotation with that of the compound **IIB** described in Refs. 6f and 28. Compound **21**: $[\alpha]_D^{30}$ +45.6 (*c* 1.02, 1 M HCl) [lit.[6f,28] $[\alpha]_D^{26}$ +44.7 (*c* 1.02, 1 M HCl)]. UV (1 M HCl) λ_{max} 239 nm (ε 19500) [lit.[6f,28] UV (1 M HCl) λ_{max} 240 nm (ε 16900)]. IR (KBr): 1685, 1580, and 1380 cm^{-1} [lit.[6f,28] IR (KBr): 1690, 1580, 1480, and 1370 cm^{-1}]. ^{1}H NMR (D_2O, 300 MHz): δ 8.64 (1H, s), 8.49 (1H, s), 7.59 (1H, s), 5.45 (1H, s), 5.37 (1H, br d, $J=16.5$ Hz), 4.94 (1H, d, $J=6.9$ Hz), 4.50 (1H, q, $J=6.9$ Hz),), 4.38 (1H, dq, $J=6.6$ and 6.9 Hz), 3.44 (1H, br d, $J=14.7$ Hz), 2.94 (1H, br dd, $J=12.6$ and 14.7 Hz), 2.79 (1H, br d, $J=12.6$ Hz), 2.47 (1H, br ddd, 12.6, 12.6, and 16.5 Hz), 1.77 (3H, d, $J=6.9$ Hz), 1.32 (3H, d, $J=6.6$ Hz) [lit.[28] ^{1}H NMR (D_2O, 100 MHz): δ 8.61 (1H, s), 8.46 (1H, s), 7.59 (1H, s), 5.48 (1H, s), 5.40 (1H), 5.0–4.7 (1H), 4.52 (1H, q, $J=8$ Hz), 4.40 (1H, dq, $J=6.5$ and 6.5 Hz), 3.6–3.3 (1H), 3.2–2.2 (3H), 1.77 (3H, d, $J=8$ Hz), 1.30 (3H, d, $J=6.5$ Hz)]. ^{13}C NMR (D_2O, 75 MHz): δ 172.3, 171.5, 166.4, 166.2 165.2, 164.9, 147.5, 147.2, 146.2, 132.5, 132.1, 126.5, 68.9, 62.6, 62.2, 58.4, 58.3, 51.3, 32.1, 26.3, 20.1, 18.1 [lit.[28] ^{13}C NMR (D_2O, 25 MHz): δ 172.3, 171.4, 166.4, 165.8 165.2, 164.8, 147.4, 147.1, 146.0, 132.6, 132.1, 126.6, 68.9, 62.6, 62.2, 58.4, 58.4, 51.4, 32.2, 26.2, 20.2, 18.2].

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29. Compound **1**: $[\alpha]_D^{30}$ +23.3 (*c* 1.00, $CHCl_3$). IR ($CHCl_3$): 1820, 1720, 1500, 1370, 1330, 1160, 1100, 1070, and 1045 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.43 (1H, br s), 8.19 (1H, s), 7.91 (1H, s), 7.00 (1H, s), 5.43 (1H, br s), 5.30–5.12 (3H, m), 4.51–4.34 (4H, m), 3.99 (1H, dq, $J=5.7$ and 7.2 Hz), 3.63 (1H, ddd, $J=0.0$, 5.4 and 13.8 Hz), 3.46–3.31 (1H, m), 3.12–2.92 (1H, m), 2.80 (1H, ddd, $J=6.0$, 13.2, and 13.8 Hz), 1.61 (3H, d, $J=6.3$ Hz), 1.50 (9H, s), 1.47–1.35 (6H, m), 1.35 (3H, d, $J=7.2$ Hz), 1.21 (9H, s). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 175.2, 173.7, 168.9, 167.6, 163.6, 161.2, 161.1, 155.2, 153.2, 150.5, 148.6, 147.9, 147.0, 130.0, 127.3, 120.0, 85.2, 79.6, 74.9, 66.7, 61.6, 61.4, 61.3, 59.8, 51.9, 27.9, 27.8, 26.9, 24.5, 20.5, 17.9, 14.2, 14.2. HRMS (FAB$^+$) calcd for $C_{37}H_{48}N_7O_{11}S_3$ (M+H)$^+$: 862.2574. Found: 862.2573.