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Tetrahedron Letters
Tetrahedron Letters 45 (2004) 3707–3712

Synthetic studies on thiostrepton family of peptide antibiotics: synthesis of the pentapeptide segment containing dihydroxyisoleucine, thiazoline and dehydroamino acid

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Received 1 March 2004; revised 13 March 2004; accepted 17 March 2004

Abstract—The dihydroxyisoleucine-, thiazoline- and dehydroamino acid-containing pentapeptide of the thiostrepton family of peptide antibiotics was synthesized, which featured the β-lactone opening by phenylselenylation, the vinylzinc addition to the chiral sulfinimine, the Wipf oxazoline–thiazoline conversion method and the oxidative *syn*-elimination of the phenylseleno group.

We have recently reported the synthesis of the dehydropiperidine[1] and dihydroquinoline[2] segments (**1** and **2**, respectively) of the thiostrepton family of peptide antibiotics (Fig. 1).[3,4] In this letter, we report the synthesis of the pentapeptide segment **3** containing the dihydroxyisoleucine, thiazoline and dehydroamino acid portions.[5] We also report the synthesis of carboxylic acid **4** and amine **5**; both of which will serve as intermediates for the total synthesis of the thiostrepton family of peptide antibiotics.

In general, the thiazolines are sensitive to epimerization;[6] therefore, it is necessary to construct the thiazoline portion of **3** in the later stage of its synthesis. Moreover, even if the fully protected pentapeptide **3** is synthesized, it is predicted that we will have difficulty in liberating the free carboxylic acid or the free amine from **3** without the thiazoline epimerization. Therefore, we planned to synthesize the more suitable intermediates, carboxylic acid **4** and amine **5**; both of which would be derived from the synthetic precursor of **3**. The phenylseleno group in **4** and **5**, as the masked precursor to the labile dehydroamino acid portion, is another advantage of these compounds.

The retrosynthetic analysis is illustrated in Scheme 1. The thiazoline portion of pentapeptide **3** would be constructed from β-hydroxyamide **7** through β-hydroxythioamide **6** via the Wipf oxazoline–thiazoline conversion method.[6d–f] The *Z*-dehydroamino acid portion of **3** would be obtained by the oxidative *syn*-elimination of the phenylseleno group.[7] The more suitable intermediates, **4** and **5**, would be derived from **6** by standard methods. β-Hydroxyamide **7** is divided into carboxylic acid **8** and the dihydroxyisoleucine derivative **9**. Tripeptide **8** would be obtained from three amino acids **10**–**12** by consecutive condensations as well as the phenylselenylation of the β-lactone part. The β-lactone function would act as not only the protecting group of the carboxylic acid group for condensation but also the activating group of the hydroxy group for phenylselenylation. Two amino acids, **10** and **11**, could be obtained from L-threonine (**13**). The dihydroxyisoleucine derivative **9** would be obtained from the trisubstituted olefin **14** by the stereoselective dihydroxylation. The chiral olefin **14** would be obtained from the chiral sulfinimine **15** by the diastereoselective addition of an organometallic reagent.[8] Enantiomerically pure sulfinimines are versatile intermediates for the asymmetric syntheses of the amine derivatives and a variety of nucleophiles add to chiral sulfinimines in a highly diastereoselective manner.[8] If this reaction mainly affords the adduct having the undesired configuration, all we have to do is use the enantiomer of **15**. Sulfinimine **15** could be easily obtained from the known thiazole aldehyde **16**[9] and the

Keywords: Thiostrepton; Thiazolines; Thioamides; Sulfinimines; Dihydroxyisoleucine.
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0040-4039/$ - see front matter © 2004 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2004.03.099

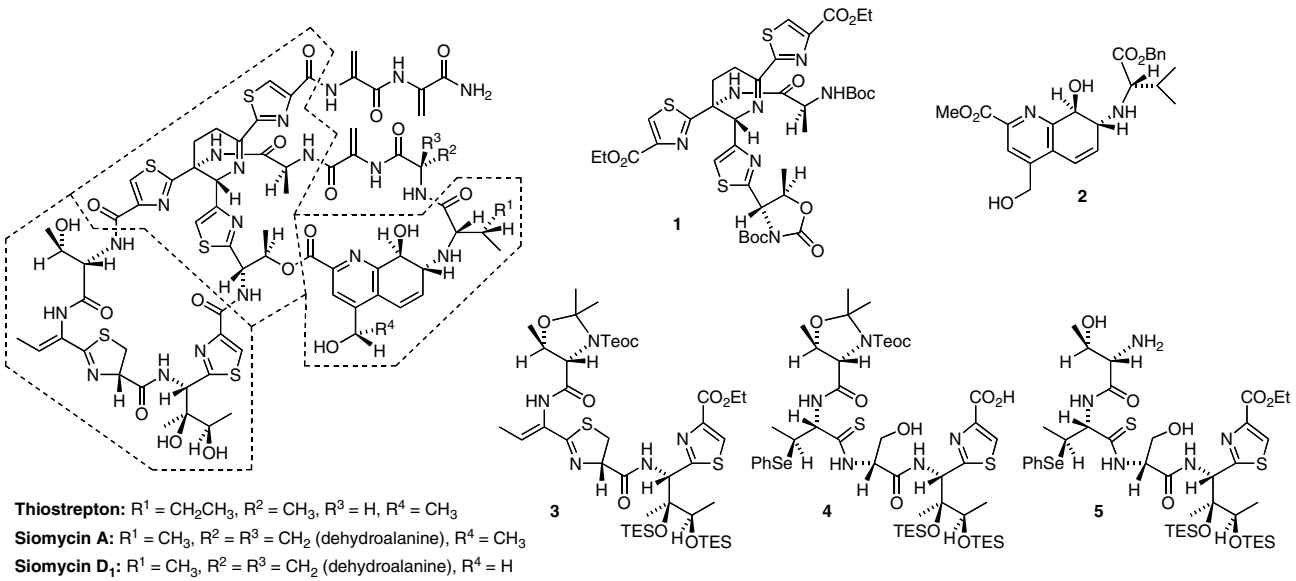
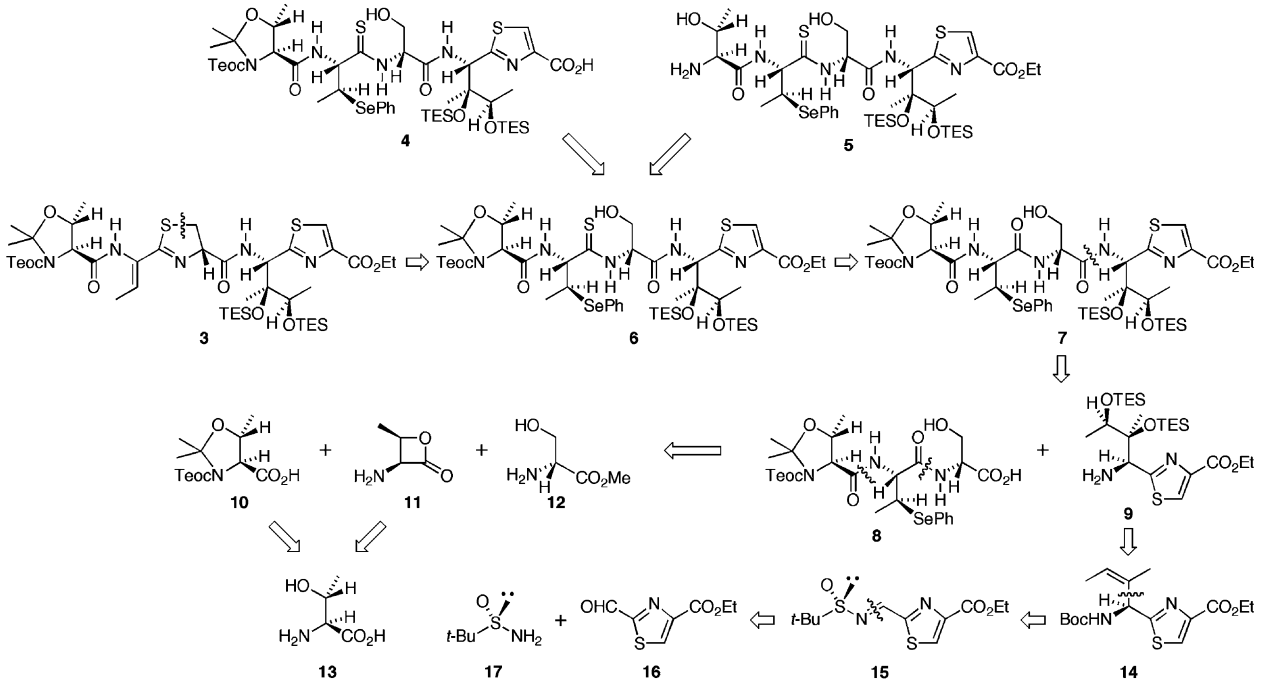


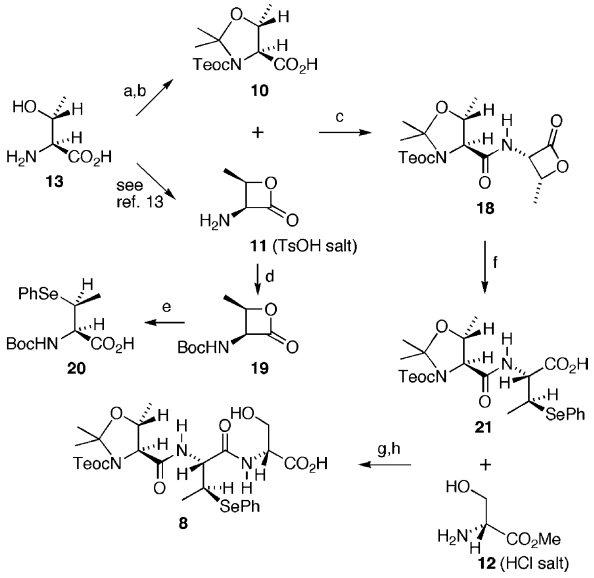
Figure 1.



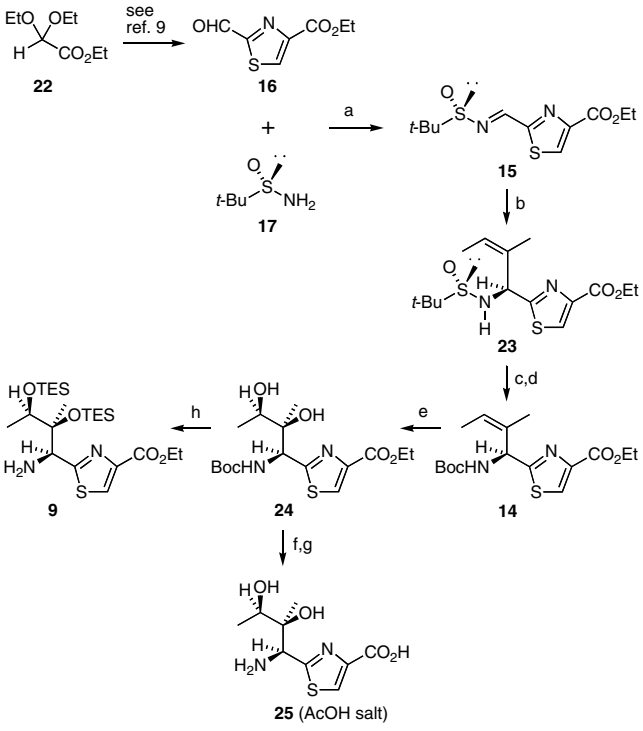
Scheme 1. Retrosynthetic analysis of **3**–**5**.

Ellman chiral sulfinamide **17**[10] using the Cs_2CO_3-mediated sulfinimine synthesis recently developed by our group.[11]

Tripeptide **8** was synthesized as follows (Scheme 2). L-Threonine (**13**) was treated with 2-(trimethylsilyl)ethyl 4-nitrophenyl carbonate[12] and triethylamine followed by acetonization to afford **10** quantitatively. β-lactone **11** (TsOH salt) was prepared from **13** by the Vederas method.[13] Coupling of **10** (1.0 equiv) with **11** (1.1 equiv) was realized with PyBOP[14] and *i*-Pr_2NEt in CH_2Cl_2 to give **18** in 66% yield from **10**. The crucial step for the synthesis of **8** was the β-lactone opening by phenylselenylation. Phenylselenylation was tested using **19** (derived from **11**) as the model compound. First, Shirahama's conditions[7a] (PhSeNa)[15] were applied to **19**, resulting in failure probably because attack of nucleophiles at the β-position of the threonine β-lactone is disfavored in contrast to the facile ring openings at the methylene of the serine-derived β-lactones.[13] There are other methods available for the nucleophilic phenylselenylation reactions: $PhSeSiMe_3 + KF$,[16] $PhSeSiMe_3 + ZnI_2$,[17] both of which had been used for the lactone-opening reactions, and $PhSeSiMe_3$ and/or PhSeH used for opening of the



Scheme 2. Synthesis of tripeptide **8**. Reagents and conditions: (a) TeocOPh(*p*-NO_2) (1.1 equiv), Et_3N (3.0 equiv), dioxane–H_2O (1:1), rt, 20 h; (b) acetone dimethylacetal (3.0 equiv), *p*-TsOH (0.1 equiv), acetone, rt, 6 h, quantitative yield (two steps); (c) **10** (1.0 equiv), **11** (1.1 equiv), PyBop (1.2 equiv), *i*-Pr_2NEt (2.4 equiv), CH_2Cl_2, rt, 2.5 h, 66% from **10**; (d) Boc_2O (2.0 equiv), *i*-Pr_2NEt (1.2 equiv), THF, rt, 16 h, 77%; (e) PhSeH (1.5 equiv), DMF, 80 °C, 2 h, quantitative yield; (f) PhSeH (1.5 equiv), DMF, 80 °C, 2 h, 94%; (g) **21** (1.0 equiv), **12** (1.1 equiv), DMTMM (1.1 equiv), NMM (1.1 equiv), MeOH, rt, 6 h, 82% from **21**; (h) 1 M aq NaOH (1.5 equiv), MeOH–dioxane–H_2O (1:1:1), rt, 1 h. Teoc = 2-(trimethylsilyl)ethoxycarbonyl, PyBop = benzotriazolyloxy-tris(pyrrolidino)-phosphonium hexafluorophosphate, Boc = *t*-butoxycarbonyl, DMTMM = 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride, NMM = *N*-methylmorpholine.



Scheme 3. Synthesis of the dihydroxyisoleucine derivative **9**. Reagents and conditions: (a) **16** (1.0 equiv), **17** (1.0 equiv), Cs_2CO_3 (1.0 equiv), CH_2Cl_2, rt, 2 h, quantitative yield; (b) (*Z*)-2-bromo-2-butene (5.0 equiv), 1.62 M *t*-BuLi (10 equiv) in ether, THF, −78 °C, 5 min, then 1 M $ZnCl_2$ (5.0 equiv) in ether, 0 °C, 15 min, then **15** (1.0 equiv) in THF, −78 to −40 °C, 6 h, 87%; (c) 10 wt% HCl–MeOH, rt, 0.5 h; (d) Boc_2O (1.2 equiv), Et_3N (1.2 equiv), dioxane, rt, 2 h, 83% (two steps); (e) OsO_4 (0.1 equiv), NMO (3.0 equiv), DABCO (0.2 equiv), *t*-BuOH–H_2O (85:15), rt, 12 h, 56%; (f) 1 M aq NaOH (1.5 equiv), EtOH–dioxane (2:1), rt, 0.5 h; (g) 3 M HCl–EtOAc, then DOWEX 50W, pyridine–acetic acid buffer (pH 3.1), 65% (two steps); (h) TESOTf (4.0 equiv), 2,6-lutidine (6.0 equiv), CH_2Cl_2, rt, 1 h, 92%. NMO = *N*-methylmorpholine *N*-oxide, DABCO = 1,4-diazabicyclo[2.2.2]octane, TES = triethylsilyl, Tf = trifluoromethanesulfonyl.

oxazoline and oxazine rings.[18] Among them, the PhSeH method[18] was the best choice in view of the easy experimental procedures (PhSeH, DMF, 80 °C, 2 h), quantitatively giving **20**.[19] To the best of our knowledge, this is the first example of the opening reaction of β-substituted β-lactones using PhSeH. β-Lactone **18** was then subjected to the same conditions to afford the desired **21** in 94% yield. Condensation of **21** (1.0 equiv) with **12** (HCl salt, 1.1 equiv) using DMTMM[20] and NMM in MeOH afforded tripeptide (82% yield). Hydrolysis of this tripeptide with aqueous NaOH gave the desired tripeptide **8**, which was used for the next step without purification.

The synthesis of the dihydroxyisoleucine derivative **9** started with the known thiazole aldehyde **16**,[9] which was prepared from ethyl diethoxyacetate (**22**) (Scheme 3). Condensation of **16** (1.0 equiv) with the Ellman chiral sulfinamide **17**[10] (1.0 equiv) in CH_2Cl_2 using our recently developed method with Cs_2CO_3 (1.0 equiv) as an amine-activating and dehydrating reagent[11] quantitatively produced **15**. The first crucial step in the synthesis of **9** was the regioselective and diastereoselective addition of the organometallic reagent to the sulfinimine group of **15** in the presence of the ethoxycarbonyl group. To the vinyllithium reagent prepared from (*Z*)-2-bromo-2-butene (1.1 equiv) and *t*-BuLi (2.2 equiv) in THF or Et_2O was added at −78 °C a solution of **15** (1.0 equiv) in THF or Et_2O, resulting in the decomposition of **15**. In contrast, transmetallation of the above vinyllithium reagent (in THF) to the vinylzinc reagent by the addition of ethereal $ZnCl_2$ (1.1 equiv) was realized at 0 °C; to this was added **15** (1.0 equiv) in THF at −78 °C. The mixture was stirred at −40 °C for 6 h, affording the desired adduct **23** in ca. 20% yield. Fortunately, using excess amounts of the vinylzinc reagent (5.0 equiv) afforded **23** in 87% yield as the sole adduct.[21] The stereochemistry of **23** was confirmed in the later stage (vide infra). To the best of our knowledge, this is the first example of the addition of the vinylzinc reagent to the chiral sulfinimine.[22] The next crucial step was the dihydroxylation of the trisubstituted double bond in order to construct the dihydroxyisoleucine portion. We expected that the Hauser's sulfoxide-mediated intramolecular dihydroxylation of olefins[23] was applicable to allylic sulfinamides; however, only the oxidation of the sulfinamide to the sulfonamide occurred. Therefore, the sulfinamide **23** was transformed into carbamate **14** in 83% yield. Dihydroxylation of **14** was conducted under the variety of conditions including the Sharpless asymmetric dihydroxylation;[24] the best result was obtained using OsO_4

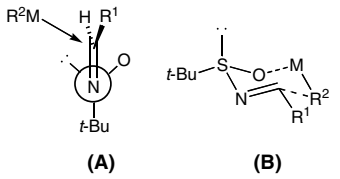


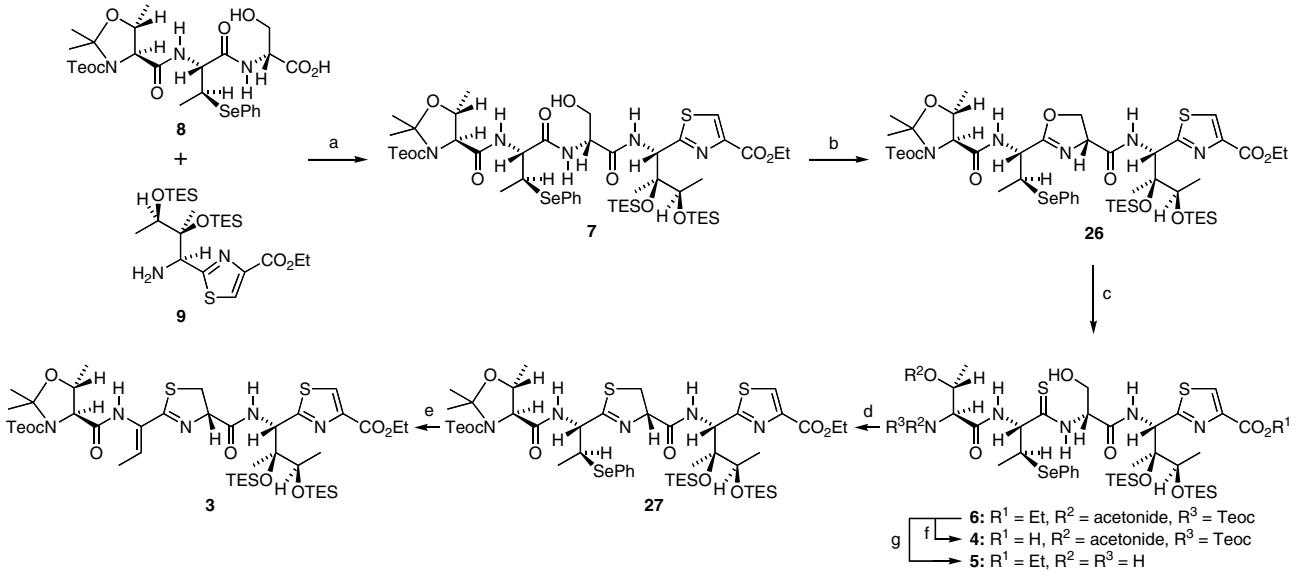
Figure 2. Transition-state model.

(0.1 equiv), NMO (3 equiv) and DABCO (0.2 equiv)[25] in 85:15 *t*-BuOH–H_2O at rt for 12 h, affording a 84% yield of a 2:1 mixture of **24** and its diastereoisomer, from which the desired **24** was easily separated by silica-gel column chromatography. The structure determination of **24** (and hence **23**) was realized by its transformation into the naturally derived degradation product, thiostreptine (**25**),[26–28] and comparing the optical rotation and ^{1}H NMR spectrum. Disilylation of **24** with TESOTf and 2,6-lutidine afforded, concomitant with cleavage of the Boc group,[29] **9** in 92% yield.

The high selectivity of the addition of the vinylzinc reagent to sulfinimine **15** might be rationalized by the open transition-state model **A**[8,22b,30] shown in Figure 2, where the addition occurs from the *Si* face of the imine. On the basis of the Davis statement,[22b] we speculate that the existence of heteroatoms in the thiazole ester disrupts and prevents forming of the chelated transition state (**B** in Fig. 2, *Re* face attack). On the other hand, the selectivity of the dihydroxylation of **14**, albeit it was only 2:1, might be explained by considering that the carbamate group serves to deliver the oxidant to the desired face of the double bond.[31]

Condensation of carboxylic acid **8** (1.1 equiv) with the dihydroxyisoleucine derivative **9** (1.0 equiv) was conducted with CIP,[32] HOAt and *i*-Pr_2NEt in CH_2Cl_2 to give pentapeptide **7** in 83% yield from **9**. Now the crucial Wipf oxazoline–thiazoline conversion method was realized as follows.[6,33] Treatment of **7** with DAST[34] gave oxazoline **26** in 85% yield, which was subjected to H_2S in MeOH–Et_3N (1:1) to afford thioamide **6** in 90% yield. Thioamide **6** was again treated with DAST[34] to give thiazoline **27**, which was subsequently treated with TBHP in TFE–CH_2Cl_2 (1:1) to afford the desired pentapeptide **3** in 57% yield from **6**. The structure of **3** was confirmed by its ^{1}H and ^{13}C NMR spectra, including H–H COSY, HMQC and HMBC. At this stage, we tried hydrolysis of the ethyl ester of **3** under a variety of conditions (e.g., aqueous NaOH in EtOH–dioxane (2:1), aqueous $Ba(OH)_2$ in MeOH,[35] Me_3SiOK in THF[36]); however, but not unexpectedly, the complete epimerization occurred.[37] Furthermore, treatment of **3** with trimethyltin hydroxide, which could be used for hydrolysis of methyl phenylacetate,[38] afforded carboxylic acid contaminated with ca. 20% of the epimerization product.[37] On the other hand, deprotection of the Teoc group of **3** with $ZnCl_2$[39] in nitromethane at 50 °C resulted in an ca. 20% epimerization.[37] Therefore, we considered that carboxylic acid **4** and amine **5** would be the more suitable intermediates for elaboration of the pentapeptide portion usable for the total synthesis of the thiostrepton family of peptide antibiotics. To this end, thioamide **6** was treated with aqueous NaOH in EtOH–dioxane (2:1) to afford carboxylic acid **4** quantitatively. Moreover, treatment of thioamide **6** with $ZnCl_2$[39] in nitromethane afforded amine **5** in 58% yield (Scheme 4).

In summary, we have synthesized the pentapeptide segment **3** of the thiostrepton family of peptide antibiotics and the more suitable synthetic intermediates, carboxylic acid **4** and amine **5**. The key reactions were the



Scheme 4. Synthesis of pentapeptides **3**–**5**. Reagents and conditions: (a) **8** (1.1 equiv), **9** (1.0 equiv), CIP (1.2 equiv), HOAt (1.2 equiv), *i*-Pr_2NEt (2.4 equiv), CH_2Cl_2, rt, 0.5 h, 83% from **9**; (b) DAST (1.5 equiv), CH_2Cl_2, −78 °C, 5 min, 85%; (c) H_2S, MeOH–Et_3N (1:1), rt, 6 h, 90%; (d) DAST (1.5 equiv), CH_2Cl_2, −78 °C, 5 min; (e) TBHP (10 equiv), TFE–CH_2Cl_2 (1:1), rt, 2 h, 57% from **6**; (f) 1 M aq NaOH (3.0 equiv), EtOH–dioxane (2:1), rt, 5 h, quantitative yield; (g) $ZnCl_2$ (15 equiv), nitromethane, rt, 15 h, 58%. CIP = 2-chloro-1,3-dimethylimidazolidium hexafluorophosphate, HOAt = 1-hydroxy-7-azabenzotriazole, DAST = diethylaminosulfur trifluoride, TBHP = *t*-butylhydroperoxide, TFE = 2,2,2-trifluoroethanol.

β-lactone opening by phenylselenylation, the vinylzinc addition to the chiral sulfinimine, the Wipf oxazoline–thiazoline conversion method and the oxidative *syn*-elimination of the phenylseleno group. Synthetic studies of the thiostrepton family of peptide antibiotics using segments **1**, **2** and **4** (or **5**) 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. $[\alpha]_D^{28} - 2.8$ (*c* 1.00, 1 M AcOH) [lit.[27a] $[\alpha]_D^{25} - 4$ (*c* 1, 1 M AcOH), lit.[27b] $[\alpha]_D^{20} - 2.8$ (*c* 1, AcOH), lit.[27c] $[\alpha]_D^{25} -$ 4.4 (*c* 1, 1 M AcOH)].
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28. We prepared the enantiomer of **25** starting from the enantiomer of sulfinamide **17**. Optical rotation of the enantiomer of **25** was +4.4 (*c* 1.00, 1 M AcOH, 28 °C). We also prepared the diastereomer of **25** starting from the minor diastereomer of **24**. Its ^1H NMR spectrum was different from that of **25**.
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