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Total synthesis of siomycin A

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Dedicated to Professor Yoshito Kishi on the occasion of his forthcoming 70th birthday

Abstract—We have succeeded in the total synthesis of siomycin A, a representative compound of the thiostrepton family of peptide antibiotics, featuring the one-pot cyclization–elongation of our strategic intermediates and the late-stage formations of the thiazoline and dehydroamino acid moieties.

Siomycin A was isolated in 1961 from the culture broth of *Streptomyces sioyaensis* by the Shionogi group[1] and is a representative of the thiostrepton family of peptide antibiotics (Fig. 1).[2] The structure of siomycin A was elucidated by chemical degradation studies[3] and NMR spectral studies[4] by comparison with those of thiostrepton. Other structurally-related antibiotics, the thiopeptins, Sch 18640, and Sch 40832, were also isolated.[2] The characteristic structure of this family is the bicyclic skeleton containing dehydropiperidine, dihydroquinoline, four thiazoles, thiazoline, dehydroamino acids, and dihydroxyisoleucine. Fascinated by their stunningly complex structural features, we[5] and the Nicolaou group[6] have aimed to synthesize these antibiotics. Recently, Nicolaou and his co-workers have succeeded in the fascinating total synthesis of thiostrepton.[7] Other efforts have focused on the syntheses of the structurally simpler thiopeptide antibiotics: for example, the micrococcins,[8] promothiocin A,[9] amythiamicin D,[10]

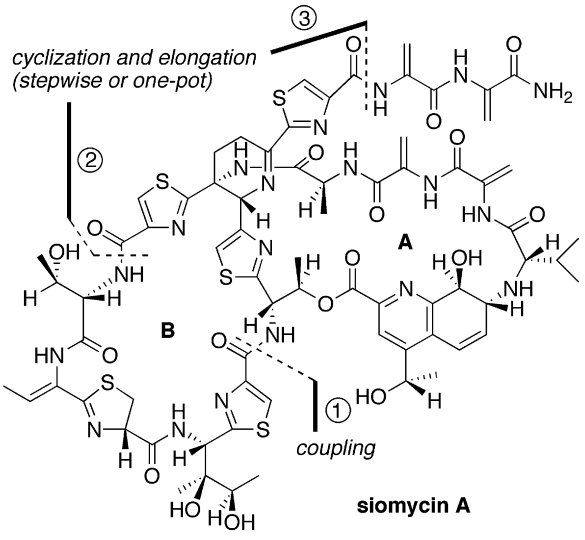

Figure 1. Structure of siomycin A.

GE2270A,[11] and GE2270T.[11] We now report the total synthesis of siomycin A by the coupling (① in Fig. 1) of our strategic intermediates, the cyclic core portion **1**[5e] (A-ring, Fig. 1 and Scheme 1) and the pentapeptide portion **2**[5c] (Scheme 1), followed by cyclization (② in Fig. 1, B-ring) of the resulting coupling product and elongation (③ in Fig. 1) of the side chain **3** (Scheme 2) onto the cyclization product.[12] We anticipated that this

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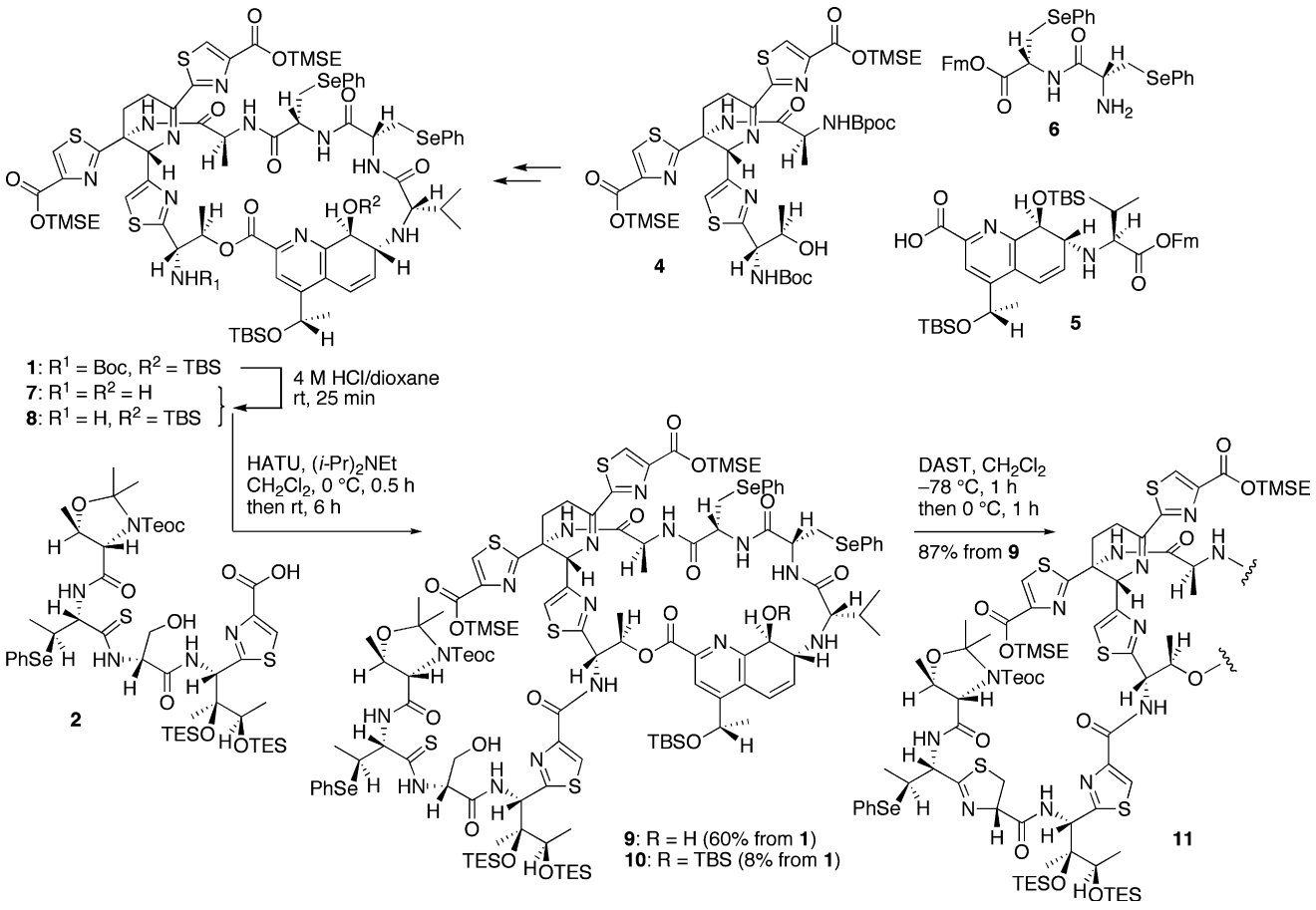


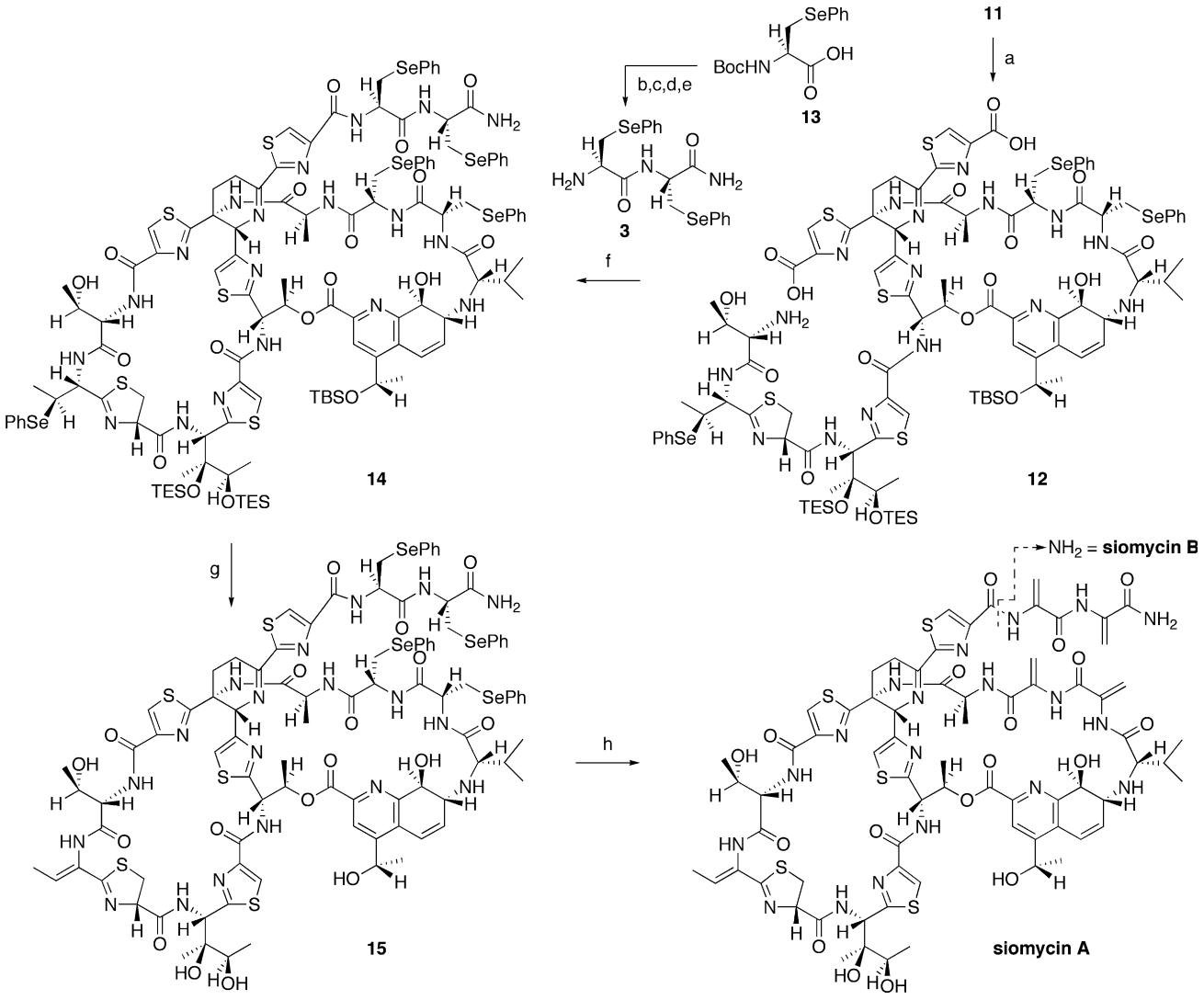
Scheme 1. Synthesis of the intermediate **11**. Boc = *tert*-butoxycarbonyl, Bpoc = 1-methyl-1-(4-biphenyl)ethoxycarbonyl, Fm = 9-fluorenylmethyl, TBS = *tert*-butyldimethylsilyl, TMSE = 2-(trimethylsilyl)ethyl, HATU = *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate, TES = triethylsilyl, Teoc = 2-(trimethylsilyl)ethoxycarbonyl, DAST = (diethylamino)sulfur trifluoride.

cyclization–elongation step would be realized in the stepwise manner after the selective deprotection of one of the two TMSE esters, or more conveniently, in the one-pot operation via the regioselective cyclization–elongation of the dicarboxylic acid secured by the simultaneous deprotection of the two TMSE esters. Other challenging tasks included the well-timed constructions of the easily racemizing thiazoline ring and the fastidious dehydroamino acids including four dehydroalanines and the trisubstituted (*Z*)-olefin next to the thiazoline ring.

We have already reported the synthesis of the siomycin cyclic core portion **1**[5e] by the coupling of the dehydropiperidine segment **4**,[5a,e] the dihydroquinoline segment **5**,[5b,d] and the masked dehydroalanine (i.e., β-phenylselenoalanine) segment **6**[5e] (Scheme 1). For the coupling partner of **1**, we selected **2**[5c] which has the hydroxymethylthioamide function as the precursor of the thiazoline ring (Scheme 1). The Boc group in **1** was first deprotected with 4 M HCl/dioxane to afford **7** along with a small amount of **8**. This crude mixture was coupled with **2** (1.0 equiv) using HATU[13] (1.0 equiv) and $(i\text{-Pr})_2$NEt (5.0 equiv) in CH_2Cl_2, giving **9** and its TBS ether **10** in 60% and 8% yields, respectively.

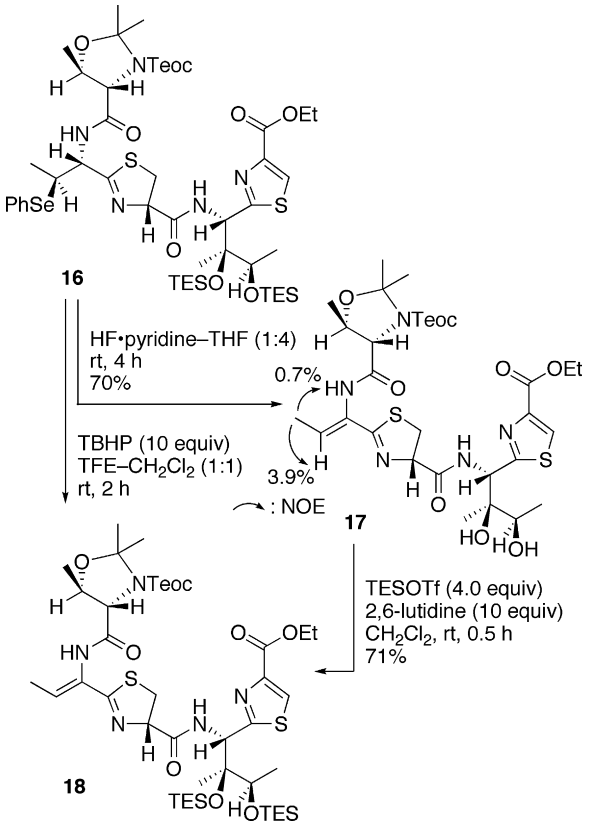
We first attempted selectively deprotecting one of the two TMSE esters in **9**. It was anticipated that $ZnCl_2$, which had been used as a deprotection reagent of the Teoc group,[14] would be suitable for the deprotection of the TMSE ester, and additionally, the simultaneous deprotection of the Teoc and acetonide groups would occur. However, under the restricted conditions ($ZnCl_2$ (100 equiv)/ether, nitromethane, rt, 24 h), we could not realize this requirement; the dicarboxylic acid and a mixture of the monocarboxylic acids were nonselectively obtained, although the Teoc and acetonide groups were smoothly cleaved.[5c]

We then turned our attention to the regioselective cyclization–elongation of the dicarboxylic acid. Prior to this, **9** was first treated with DAST[5c,15] (1.6 equiv) in CH_2Cl_2 to give thiazoline **11** in 87% yield (Scheme 1). Deprotection of the three kinds of protecting groups (Teoc, acetonide, and TMSE) in **11** was cleanly realized with $ZnCl_2$[14] (100 equiv)/ether in nitromethane (rt, 48 h), giving the cyclization–elongation precursor **12** (Scheme 2). The side chain **3**[7c] was prepared from the known β-phenylselenoalanine **13**[5e,7c] by the following four-step sequence: (1) amidation, (2) deprotection of the Boc group, (3) condensation of another **13**, and (4) deprotection of the Boc group. The one-pot operation was carried out under the conditions including, as the cyclization step, EDC–HOAt–$(i\text{-Pr})_2$NEt–DMF (EDC = (1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydro-



Scheme 2. Completion of the total synthesis of siomycin A. Reagents and conditions: (a) 1 M $ZnCl_2$/ether, $MeNO_2$, rt, 48 h; (b) $ClCO_2Et$, Et_3N, THF, −15 °C, 10 min, then 28% NH_4OH, −15 °C to rt, 2 h; (c) TFA–CH_2Cl_2 (1:1), rt, 1.5 h; (d) **13**, CIP, HOAt, (*i*-Pr)$_2$NEt, DMF, rt, 2 h; (e) TFA–CH_2Cl_2 (1:1), rt, 2 h, 68% (4 steps); (f) HATU, (*i*-Pr)$_2$NEt, DMF–CH_2Cl_2 (1:4), 0 °C, 3 h, then **3**, rt, 24 h; (g) HF·pyridine–THF (1:4), rt, 20 h; (h) 4 M TBHP/CH_2Cl_2, TFE–CH_2Cl_2 (1:5), rt, 1 h, 7% from **11**. TFA = trifluoroacetic acid, CIP = 2-chloro-1,3-dimethylimidazolidium hexafluorophosphate, HOAt = 1-hydroxy-7-azabenzotriazole, TBHP = *tert*-butyl hydroperoxide, TFE = 2,2,2-trifluoroethanol.

chloride) and HATU[13]–(*i*-Pr)$_2$NEt–solvent (e.g., DMF, THF, dioxane, DMF–CH_2Cl_2 (1:4), DMF–CH_3CN (1:4)), followed by the subsequent elongation with **3**. Among them, the best conditions were HATU (5.0 equiv) and (*i*-Pr)$_2$NEt (5.0 equiv) in DMF–CH_2Cl_2 (1:4, 1 mM for **12**) at 0 °C for 3 h followed by the addition of **3** (5.0 equiv, rt, 24 h), affording the crude products including **14** after removing the excess **3** by Sephadex LH-20 ($CHCl_3$). Although the structure of **14** could not be confirmed at this stage, we proceeded to the two-step transformation into siomycin A. These crude products were treated with HF·pyridine–THF (1:4)[7d] to afford the crude products including **15**, which were finally subjected to the oxidative elimination (4 M TBHP/CH_2Cl_2, TFE–CH_2Cl_2 (1:5), rt, 1 h),[5c,e,6c,7b,d] giving siomycin A in 7% yield from **11**. The synthetic siomycin A was identical with the natural siomycin A based on the ^{1}H NMR, ^{13}C NMR, IR, and MS spectra, TLC, and optical rotation (see Supplementary data). It is noteworthy that the final two-step operation could not be reversed, in contrast to Nicolaou's thiostrepton synthesis,[7b,d] because it was found that siomycin A gradually changed into siomycin B,[16] which is the side chain degradation product of siomycin A, under the HF·pyridine–THF (1:4) conditions (rt, during 24 h). In addition, when the model pentapeptide **16**[5c] was subjected to the HF·pyridine–THF (1:4) conditions (rt, 4 h), the *Z*-olefin **17** was obtained in 70% yield as the sole product (Scheme 3). The stereochemistry of **17** was confirmed by NOE analysis of the ^{1}H NMR spectrum, and additionally, by the transformation (TESOTf, 2,6-lutidine) into **18** which was identical to the sample[5c] derived from **16** by *syn* elimination using TBHP. These facts mean that the dehydroselenation next to the thiazoline C2-position affords the thermodynamically stable *Z*-olefin and account for the *Z*-selectivity from **14** to **15**. Unfortunately, during the cyclization–elongation step, an almost equal amount of the product was obtained whose struc-



Scheme 3. Dehydroselenation of the model pentapeptide **16**. Tf = trifluoromethanesulfonyl.

ture was tentatively assigned, after HF·pyridine and TBHP treatment and subsequent separation from siomycin A, to the regioisomeric cyclization–elongation product based on the ^{1}H NMR and MS spectra (see Supplementary data).

In summary, we have succeeded in the total synthesis of siomycin A, a representative compound of the thiostrepton family of peptide antibiotics, by the coupling of the three intermediates, **1**, **2**, and **3**. The drawback in the cyclization–elongation step will be improved once the dehydropiperidine segment having the differentiated protecting groups instead of the bis-TMSE ester in **4** is secured, which is now in progress in our laboratories.

Acknowledgments

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Supplementary data

Spectral data of natural and synthetic siomycin A and the regioisomeric cyclization–elongation product. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.12.121.

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