Convenient Synthesis of the Main Tridehydropentapeptide Skeleton for a Macrocyclic Antibiotic, Sulfomycin I

Tetsuya Kayano, Yasuchika Yonezawa, and Chung-gi Shin*
Laboratory of Organic Chemistry, Faculty of Engineering, Kanagawa University, Kanagawa-ku, Yokohama 221-8686

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A convenient synthesis of the main tridehydropentapeptide skeleton [Fragment B–C derivative] of a thiostrepton-type macrocyclic antibiotic, sulfomycin I, was first achieved.

An antibiotic sulfomycin I (**1**),[1] isolated from the culture of *Streptomyces viridchromogenes* MCRL-0368, has a unique macrocyclic structure. The natural **1** features two substructures, the main tridehydropentapeptide segment (**2**) called Fragment B–C and the central heterocyclic skeleton (**3**) called Fragment A, the former of which includes characteristic structures, a dehydrotripeptide skeleton [**4**, Fragment B] and a didehydro-dipeptide skeleton [**5**, Fragment C], as shown in Figure 1. So far, however, the geometry of the 3-hydroxy-1-butenyl group and the configuration of the chiral center of the 2-[(1-amino-1-methoxy)methyl]thiazole-4-carbonyl moiety in Fragment B have not yet been identified.

Recently, we have already reported briefly a novel synthesis of the 2,3,6-trisubstituted pyridine segment **3**,[2] which is the common structure of similar antibiotics, such as berninamycin A, B,[3] and A10225 G, J.[4] The interesting structure and bioactivity of **1** attracted our attention and prompted us to investigate its total synthesis and structure-bioactivity relation-ship. Here, we wish to report a convenient synthesis of the *N*,*O*-protected **2** [(**P**)-**2**] from the two building blocks, the *N*,*O*-protected dehydrotripeptide **19** as the precursor of **4** [*C*-component] and the *O*-protected dipeptide **29** as the precursor of **5** [*N*-component]. The final coupling of the *C*-component with the *N*-component and then synchronous dehydration of the two OH groups of the formed dehydro-pentapeptide **30** was first achieved to give the desired (**P**)-**2**.

First of all, to synthesize the left-half segment of **4**, coupling of phosphorylglycine-OMe (**6**) with *N*-Boc-*N*,*O*-Ip-L-Thr-OH (**7**) (Ip = isopropylidene) using DCC and *N*-hydroxybenzotriazole (HOBt) gave the corresponding dipeptide **8**. Subsequently, Hornor–Emmons reaction of **8** with (*S*)-2-[(*O*-TPS)hydroxy]-propanal[5] by using DBU afforded the expected Δ^2-dehydrodipeptide,[6] *N*-Boc-*N*,*O*-Ip-L-Thr-(*Z*,*S*)-ΔApe(TPS)-OMe (**9**) (TPS = *t*-butyldiphenylsilyl, ΔApe = 2-amino-4-hydroxy-2-pentenoic acid), the ester of which was hydrolyzed with 1 M LiOH to give the hydrolyzate **10**. The configuration of the ΔApe residue [δ 4.57 (γ-H), 6.48 (=CH–)] was confirmed to be (*Z*)-geometry.[7] Secondly, coupling of **10** with H-L-Thr-OMe by using BOP[8] and $(i\text{-Pr})_2$NEt, followed by oxidation of the formed tripeptide **11** with Jones reagent gave the oxidized Δ^2-dehydrotripeptide **12**. Oxazolation[9] of **12** with PPh_3 and I_2 in the presence of Et_3N gave the corresponding 5-methyloxazole-4-carboxylate **13**, the ester of which was hydrolyzed with 1 M LiOH to give the expected hydrolyzate **14**, as shown in Scheme 1.

Thirdly, coupling of **14** with ethyl 2-(1-amino-2-hydroxyethyl)thiazole-4-carboxylate (**15**)[10] by the BOP method gave the corresponding dehydrotripeptide **16**. Conversion[11] of the CH_2OH group of **16** to AcO group using $Pb(OAc)_4$, followed by methoxylation[11] of the formed α-acetoxy derivative **17** with Et_3N in MeOH gave the expected Fragment B derivative **18**[12] as a mixture of the diastreomeric isomers in a 1:1 ratio. Finally, ester hydrolysis of **18** with 1 M LiOH gave the hydrolyzate **19**, as shown in Scheme 2.

On the other hand, to synthesize the precursor of Fragment C **29**, at first, *N*-Cbz-*N*,*O*-Ip-L-Thr-OH (**20**) (Cbz = benzyloxycarbonyl) was coupled with H-L-Thr-OMe by using DCC to give the dipeptide **21**, the hydroxy group of which was dehydrated with methanesulfonyl chloride (MsCl) in the presence of Et_3N and with DBU gave the expected (*Z*)-Δ^2-dehydrodipeptide **22**.[13] Subsequent bromination[7] of **22** with NBS, followed by oxazolation of the formed β-bromo derivative **23** with Cs_2CO_3 gave the protected 5-methyloxazole-4-carboxylate **24**.[14] Secondly, ester hydrolysis of **24** with 1 M LiOH gave the corresponding hydrolyzate **25**, which was coupled with H-L-Thr(TPS)-OMe by using diphenyl phosphorazidate (DPPA) and Et_3N to give the corresponding dipeptide **26**. Thirdly, consecutive deprotections of the Ip group with trifluoroacetic acid (TFA) giving *O*-deprotected dipeptide **27**, similarly the TPS group with 1 M tetrabuty-

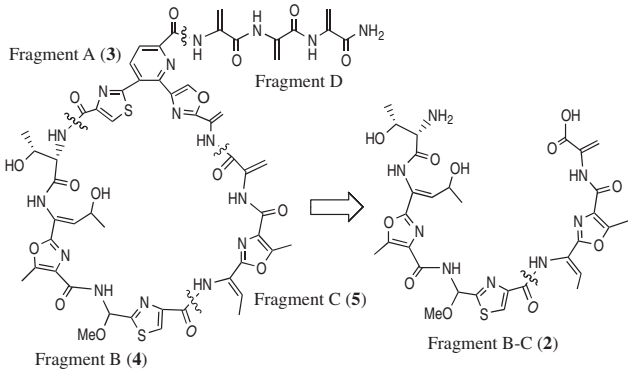
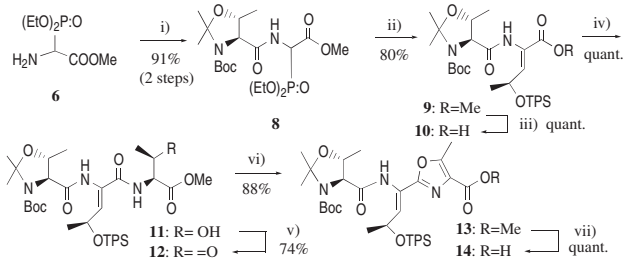
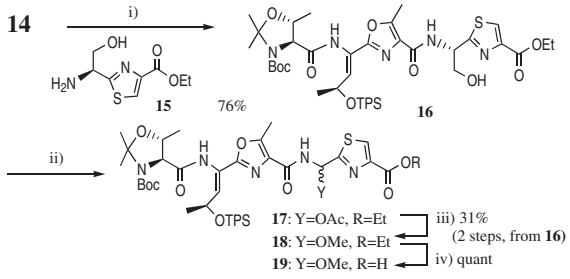


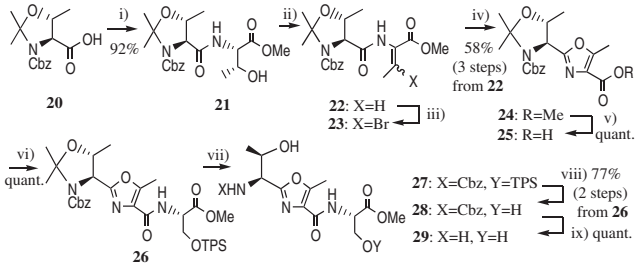
Figure 1. Sulfomycin I (**1**).



Scheme 1. Reagents and conditions: i) **7**, DCC, HOBt/DMF, ii) DBU, CH_3-CH(OTPS)CHO/THF, iii) 1 M LiOH/dioxane:H_2O, iv) BOP, $(i\text{-Pr})_2$NEt, H-L-Thr-OMe/DMF, v) 2.67 M Jones reagent/acetone, vi) I_2, PPh_3, $Et_3N/CHCl_3$, vii) 1 M LiOH/dioxane:H_2O.



Scheme 2. Reagents and conditions: i) BOP, $(i\text{-Pr})_2$NEt/DMF, ii) $Pb(OAc)_4$/EtOAc, iii) Et_3N/MeOH, iv) 1 M LiOH/dioxane:H_2O.



Scheme 3. Reagents and conditions: i) DCC, HOBt, H-L-Thr-OMe/DMF, ii) a) MsCl, $Et_3N/CHCl_3$, b) $DBU/CHCl_3$, iii) a) NBS/THF, b) Et_3N/THF, iv) Cs_2CO_3/dioxane, v) 1 M LiOH/dioxane:H_2O, vi) DPPA, Et_3N, H-L-Ser-(OTPS)OMe/DMF, vii) TFA/$CHCl_3$, viii) 1 M TBAF/THF, ix) 10%Pd-C, H_2/MeOH.

lammonium fluoride (TBAF) to the *O*,*O*-free derivative **28** and then the Cbz group with 10% Pd–C/H_2 gave the precursor of the right-half dipeptide **29** of **2**, as shown in Scheme 3. Without isolation, the obtained **29** was used intact for the next reaction.

Finally, fragment condensation between **19** and **29** by the BOP method was tried successfully to give the *N*,*O*-protected dehydropentapeptide **30**, the two hydroxy groups of which were then dehydrated simultaneously, similarly to the case of **22**, to give the expected (2*Z*,4*Z*)-$\Delta^{2,4,5}$-tridehydropentapeptide (**P**)-**2**[6,15] [70% yield. MALDI–TOFMS Found: m/z 1217.94 $(M + Ag)^+$. Calcd for $C_{55}H_{68}N_8O_{13}SSi$ 1217.19 $(M + Ag)^+$] as the precursor of Fragment B–C, as shown in Scheme 4.

The structure of all new products thus obtained were confirmed by the ^{1}H NMR spectral data and the satisfactory results of the elemental analyses. In particular, from the ^{1}H NMR spectrum of **2**, the new appearance of the chemical shifts of two protons of the vinyl group at $\delta = 5.78$ (s) and $\delta = 6.39$–6.45 (m) and that of the olefinic proton of the 2-propenyl group at $\delta = 6.58$–6.60 (m) supports the formation of Fragment B–C (**P**)-**2**.

In conclusion, it is important that the synthesis of the main Fragment B–C skeleton of **1** was readily achieved by fragment condensation between Fragment B and C. Consequently, the final macrocyclization position in the total synthesis of **1** could be definitely specified.

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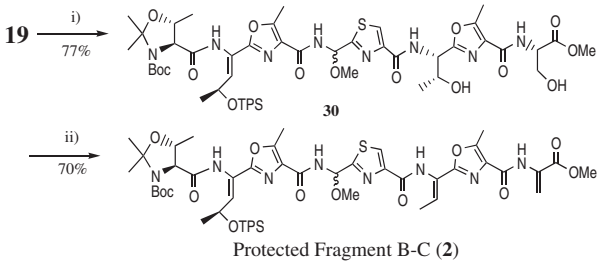

Scheme 4. Reagents and conditions: i) **29**, BOP, $(i\text{-Pr})_2$NEt/DMF ii) a) MsCl, $Et_3N/CHCl_3$, b) $DBU/CHCl_3$.

References and Notes

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6 In this paper, the symbols Δ^2, $\Delta^{2,3}$, and $\Delta^{2,4,5}$ indicate the position number of double bond of α-dehydroamino acid (ΔAA) and ΔAA-derived oxazole residues from *N*-terminus in sequence.
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12 **18**: Colorless syrup. Diastereomer (1:1). $[\alpha]_D^{26}$ $-64.7°$ (*c* 0.94, $CHCl_3$). ^{1}H NMR (DMSO-d_6) δ 1.02 (s, 9H, TPS's *t*-Bu), 1.16–1.19 (m, 3H, CH_3CH(OTPS)), 1.25–1.27 (m, 3H, CH_3CH$_2$), 1.28–1.32 (m, 12H, Boc's *t*-Bu, Thr's CH_3), 1.41, 1.48 (each s, 6H, Ip's $CH_3 \times 2$), 2.59 (s, 3H, oxazole's CH_3), 3.48 (s, 3H, OCH_3), 3.80–3.84 (m, 1H, Thr's β-H), 3.89–3.90 (m, 1H, Thr's α-H), 4.27–4.32 (m, 2H, CH$_2$CH$_3$), 4.93 (m, 1H, CH$_3$C*H*(O-TPS)), 6.38–6.42 (m, 2H, olefin's H, NHC*H*OCH$_3$), 7.33–7.44 and 7.59–7.63 (each m, 10H, TPS's Ph $\times$ 2), 8.21 (br s, 1H, N*H*CHOCH$_3$), 9.11 (br s, 1H, NH), 8.49 (s, 1H, thiazole's ring-H), 9.11 (br s, 1H, NH). MALDI–TOFMS Found: m/z 998.48 $(M + Ag)^+$. Calcd for $C_{45}H_{59}N_5O_{10}SSi$: 997.99 $(M + Ag)^+$.
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15 (**P**)-**2**: Colorless syrup. Diastereomer (1:1). $[\alpha]_D^{26}$ $-11.9°$ (*c* 0.36, $CHCl_3$). ^{1}H NMR (DMSO-d_6) δ 1.01 (s, 9H, TPS's *t*-Bu), 1.13–1.17 (m, 3H, Thr's CH_3), 1.21–1.24 (m, 3H, CH_3CH-(OTPS)), 1.30 (s, 9H, Boc's *t*-Bu), 1.39 and 1.47 (each s, 6H, Ip's $CH_3 \times 2$), 1.75–1.79 (m, 3H, CH_3CH=C), 2.54, 2.55, 2.57, and 2.58 (each s, 6H, oxazole's ring $CH_3 \times 2$), 3.49, 3.50 (each s, 3H, OCH_3), 3.73–3.77 (m, 4H, Thr's β-H, $COOCH_3$), 3.88 (br s, 1H, Thr's α-H), 4.89 (m, 1H, CH$_3$C*H*(OTPS)), 5.78 (CH*H*=C), 6.39–6.45 (m, 3H, olefin's H, NHC*H*, C*H*H=C), 6.58–6.60 (m, 1H, CH$_3$C*H*=C), 7.33–7.38 and 7.57–7.62 (each m, 10H, TPS's Ph $\times$ 2), 8.41–8.47 (m, 2H, thiazole's ring-H, N*H*CH), 9.15, 9.26, and 9.60 (each br s, 3H, NH).

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