

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

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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 dihydro-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, Horner–Emmons reaction of **8** with (*S*)-2-[(*O*-TPS)hydroxy]propanal⁵ by using DBU afforded the expected Δ^2 -dehydro-

dipeptide,⁶ *N*-Boc-*N,O*-Ip-L-Thr-(*Z,S*)- Δ Ape(TPS)-OMe (**9**) (TPS = *t*-butyldiphenylsilyl, Δ Ape = 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 Δ Ape 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 BOP⁸ and (*i*-Pr)₂NEt, followed by oxidation of the formed tripeptide **11** with Jones reagent gave the oxidized Δ^2 -dehydrotripeptide **12**. Oxazolation⁹ of **12** with PPh₃ and I₂ in the presence of Et₃N 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-hydroxy-ethyl)thiazole-4-carboxylate (**15**)¹⁰ by the BOP method gave the corresponding dehydrotripeptide **16**. Conversion¹¹ of the CH₂OH group of **16** to AcO group using Pb(OAc)₄, followed by methoxylation¹¹ of the formed α -acetoxy derivative **17** with Et₃N in MeOH gave the expected Fragment B derivative **18**¹² as a mixture of the diastereomeric 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 Et₃N and with DBU gave the expected (*Z*)- Δ^2 -dehydrotripeptide **22**.¹³ Subsequent bromination⁷ of **22** with NBS, followed by oxazolation of the formed β -bromo derivative **23** with Cs₂CO₃ 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 Et₃N 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 tetrabutyl-

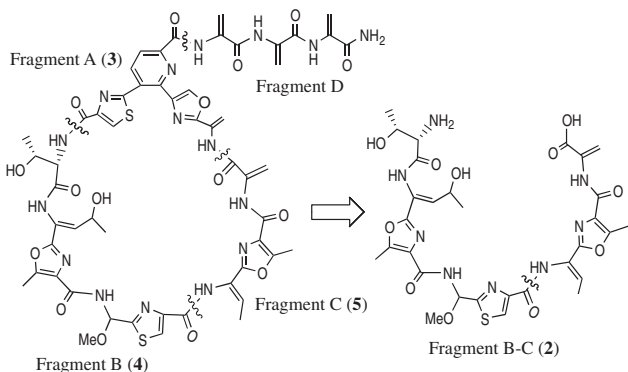
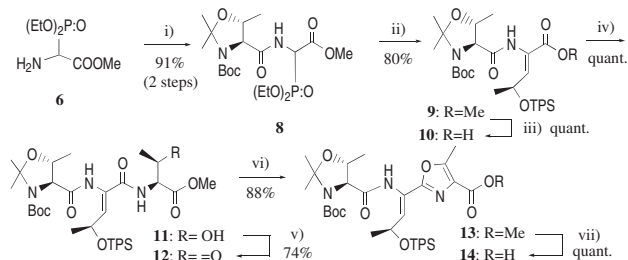
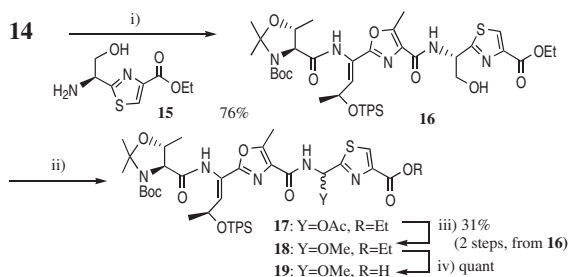


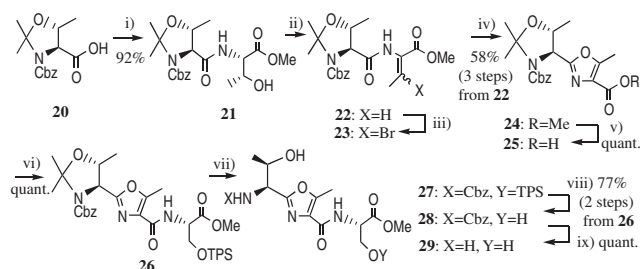
Figure 1. Sulfomycin I (**1**).



Scheme 1. Reagents and conditions: i) **7**, DCC, HOBt/DMF, ii) DBU, CH₃-CH(OTPS)CHO/THF, iii) 1 M LiOH/dioxane:H₂O, iv) BOP, (*i*-Pr)₂NEt, H-L-Thr-OMe/DMF, v) Jones reagent/acetone, vi) I₂, PPh₃, Et₃N/CHCl₃, vii) 1 M LiOH/dioxane:H₂O.



Scheme 2. Reagents and conditions: i) BOP, $(i\text{-Pr})_2\text{NEt}/\text{DMF}$, ii) $\text{Pb}(\text{OAc})_4/\text{EtOAc}$, iii) $\text{Et}_3\text{N}/\text{MeOH}$, iv) $1\text{ M LiOH}/\text{dioxane}:\text{H}_2\text{O}$.



Scheme 3. Reagents and conditions: i) DCC, HOBt, $\text{H-L-Thr-OMe}/\text{DMF}$, ii) a) MsCl , $\text{Et}_3\text{N}/\text{CHCl}_3$, b) DBU/CHCl_3 , iii) a) NBS/THF , b) $\text{Et}_3\text{N}/\text{THF}$, iv) $\text{Cs}_2\text{CO}_3/\text{dioxane}$, v) $1\text{ M LiOH}/\text{dioxane}:\text{H}_2\text{O}$, vi) DPPA , Et_3N , $\text{H-L-Ser-(OTPS)OMe}/\text{DMF}$, vii) TFA/CHCl_3 , viii) $1\text{ M TBAF}/\text{THF}$, ix) $10\%\text{Pd-C}$, H_2/MeOH .

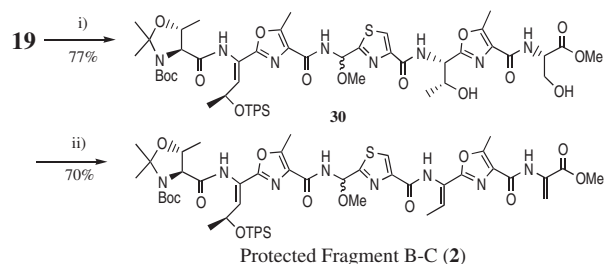
lammonium fluoride (TBAF) to the O,O -free derivative **28** and then the Cbz group with $10\%\text{ Pd-C}/\text{H}_2$ gave the precursor of the right-half dipeptide **29** of **2**, as shown in Scheme 3. Without isolation, the obtained **29** was used intact for the next reaction.

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 $(2Z,4Z)\text{-}\Delta^{2,4,5}\text{-tridehydropentapeptide (P)-2}^{6,15}$ [70% yield. MALDI-TOFMS Found: m/z 1217.94 ($\text{M} + \text{Ag}$) $^+$. Calcd for $\text{C}_{55}\text{H}_{68}\text{N}_8\text{O}_{13}\text{SSi}$ 1217.19 ($\text{M} + \text{Ag}$) $^+$] as the precursor of Fragment B-C, as shown in Scheme 4.

The structure of all new products thus obtained were confirmed by the ^1H NMR spectral data and the satisfactory results of the elemental analyses. In particular, from the ^1H NMR spectrum of **2**, the new appearance of the chemical shifts of two protons of the vinyl group at $\delta = 5.78$ (s) and $\delta = 6.39\text{--}6.45$ (m) and that of the olefinic proton of the 2-propenyl group at $\delta = 6.58\text{--}6.60$ (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, $(i\text{-Pr})_2\text{NEt}/\text{DMF}$ ii) a) MsCl , $\text{Et}_3\text{N}/\text{CHCl}_3$, b) DBU/CHCl_3 .

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- 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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- 18**: Colorless syrup. Diastereomer (1:1). $[\alpha]_{\text{D}}^{26} -64.7^\circ$ (c 0.94, CHCl_3). ^1H NMR ($\text{DMSO}-d_6$) δ 1.02 (s, 9H, TPS's *t*-Bu), 1.16–1.19 (m, 3H, $\text{CH}_3\text{CH}(\text{OTPS})$), 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 $\text{CH}_3 \times 2$), 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_2CH_3), 4.93 (m, 1H, $\text{CH}_3\text{CH}(\text{O-TPS})$), 6.38–6.42 (m, 2H, olefin's H, NHCHOCH_3), 7.33–7.44 and 7.59–7.63 (each m, 10H, TPS's Ph $\times 2$), 8.21 (br s, 1H, NHCHOCH_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 ($\text{M} + \text{Ag}$) $^+$. Calcd for $\text{C}_{45}\text{H}_{59}\text{N}_5\text{O}_{10}\text{SSi}$: 997.99 ($\text{M} + \text{Ag}$) $^+$.
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- (P)-2**: Colorless syrup. Diastereomer (1:1). $[\alpha]_{\text{D}}^{26} -11.9^\circ$ (c 0.36, CHCl_3). ^1H NMR ($\text{DMSO}-d_6$) 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, $\text{CH}_3\text{CH}(\text{OTPS})$), 1.30 (s, 9H, Boc's *t*-Bu), 1.39 and 1.47 (each s, 6H, Ip's $\text{CH}_3 \times 2$), 1.75–1.79 (m, 3H, $\text{CH}_3\text{CH}=\text{C}$), 2.54, 2.55, 2.57, and 2.58 (each s, 6H, oxazole's ring $\text{CH}_3 \times 2$), 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, $\text{CH}_3\text{CH}(\text{OTPS})$), 5.78 ($\text{CHH}=\text{C}$), 6.39–6.45 (m, 3H, olefin's H, $\text{NHCH}(\text{CHH}=\text{C})$), 6.58–6.60 (m, 1H, $\text{CH}_3\text{CH}=\text{C}$), 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, NHCH), 9.15, 9.26, and 9.60 (each br s, 3H, NH).