Convenient Synthesis of the Main Dehydrohexapeptide Skeleton Constituting a Macrocyclic Antibiotic, Berninamycin A

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The first convenient synthesis of the main dehydrohexapeptide segment of a macrocyclic antibiotic, berninamycin A, containing a 3-hydroxy-L-valine residue and having three vinyl groups and a 1-propenyl group, was accomplished.

The antibiotic berninamycin A (**1**),[1,2] isolated from the culture of *Streptomyces bernensis*, is a unique macrocyclic peptide constructed of polyoxazolylthiazole dehydropeptide, as shown in Figure 1. The peptide **1** features a main dehydrohexapeptide skeleton **2** consisted of two substructures, -ΔAla-L-HyVal-2-(1-amino-1-ethenyl)-5-methyloxazole-4-carbonyl-ΔAla- (**3**, Fragment C) (ΔAla = dehydroalanine. HyVal = 3-hydroxy-L-valine) and -L-Thr-[(*Z*)-1-amino-1-propenyl]-5-methyloxazole-4-carbonyl- (**4**, Fragment B).[3]

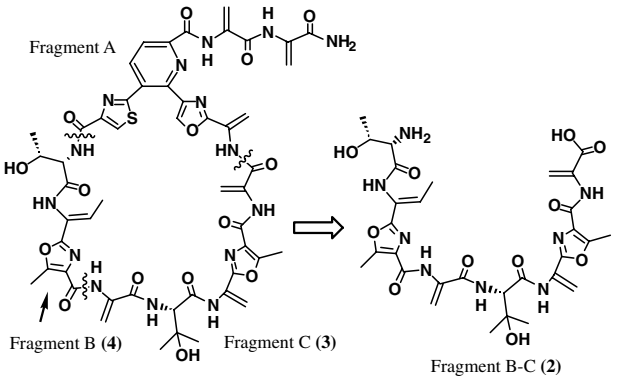


Figure 1. Berninamycin A (1).

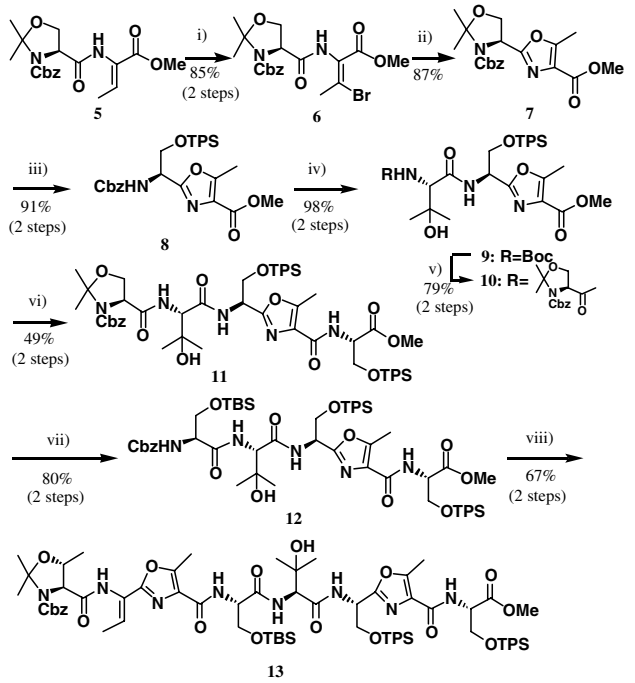
Recently, we have reported briefly novel syntheses of the central pyridine skeleton (Fragment A),[4,5] L- and D-HyVal,[6] and the main dehydrohexapeptide of berninamycin B,[7] the first of which is the common structure of similar antibiotics, A10255G and J.[8] The attractive structure as well as the bioactivity of **1** prompted us to study the total synthesis and the structure-bioactivity relationship.

Herein, we wish to report a convenient synthesis of the protected **2** [(**P**)-**2**] by fragment condensation of the precursors of **3** with **4** and then by simultaneous selective β-elimination of the three primary alcohols of the obtained hexapeptide **18**.

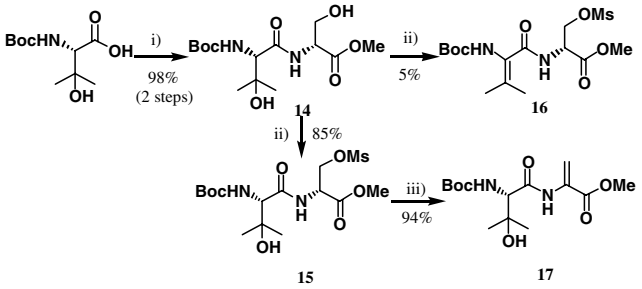
Similarly to the case of berninamycin B,[7] attempts to couple dehydrotetrapeptide containing a HyVal residue at the C-terminus with an amine (*N*-) component dipeptide and, alternatively, a carboxyl (*C*-) component dehydrotripeptide with tripeptide containing HyVal at the N-terminus were both found to be entirely unsuccessful. Therefore, the *N*-component tetrapeptide containing the HyVal residue at the second position from the N-terminus in sequence was synthesized and then subjected to the coupling with the protected **4**. First, the starting *N*, *O*-isopropylidene (Isop)-*N*-Cbz-5-methyloxazole-4-carboxylate **7** (Cbz = benzyloxycarbonyl) was synthesized by oxazolation of the protected Ser-ΔAbu(β-Br)-OMe **6**,[9] derived from *N*, *O*-Isop-*N*-Cbz-L-Ser-ΔAbu-OMe **5** (Abu = 2-amino-2-butenoic acid) and *N*-bromosuccinimide (NBS), with Cs_2CO_3.[10] Subsequently, *N*, *O*-deprotection of the Isop group of **7** with trifluoroacetic acid (TFA) and then protection of the hydroxy group with *tert*-butyldiphenylsilyl chloride (TPS-Cl) in the presence of imidazole gave methyl 2-[1-(Cbz)amino-2-(*O*-TPS)]ethyl-5-methyloxazole-4-carboxylate (**8**).[11] *N*-Deprotection of the Cbz group of **8** with 10% Pd/C, followed by coupling with *tert*-butoxycarbonyl (Boc)-L-HyVal-OH by using BOP[12] and $(i\text{-Pr})_2$NEt gave the corresponding dipeptide **9**. The Boc group of **9** was also deprotected with TFA and then further coupled with *N*, *O*-Isop-*N*-Cbz-Ser-OH by the mixed anhydride method using pivaloyl chloride (Piv-Cl) and Et_3N to give the protected Ser-L-HyVal-5-methyloxazole derivative **10**. Next, ester hydrolysis of **10** with 1 M LiOH, followed by stepwise elongation with H-L-Ser(TPS)-OMe by the BOP method gave the corresponding tetrapeptide **11**, the Isop group of which was deprotected by using TFA and then the formed primary alcohol was in situ protected with *tert*-butyldimethylsilyl chloride (TBS-Cl) to give *O*-TBS-tetrapeptide **12**. Lastly, after deprotecting the Cbz group of **12** with 10% Pd/C, fragment condensation with **4** by the BOP method proceeded smoothly to give the protected dehydrohexapeptide **13**[13] as the precursor of **2** in 67% yield in two steps from **11**, as shown in Scheme 1. As a result, it was suggested that the final intramolecular cyclization position in the total synthesis of **1** could be definitely specified. This fact is very important and different from the case of berninamycin B.

Furthermore, to examine whether the selective β-elimination of only the primary alcohol of **13** occurs or not, the substrate Boc-HyVal-Ser(TPS)-OMe was independently prepared by coupling of Boc-HyVal-OH with H-Ser(TPS)-OMe. After deprotecting the TPS group with 1 M TBAF (tetrabutylammonium fluoride), β-elimination of only the primary alcohol of the formed **14** was attempted by combinations of various concentrations of methanesulfonyl chloride (Ms-Cl) and Et_3N. As a result, in the case using Ms-Cl (1.2 equiv) and Et_3N (1.5 equiv) at −20 °C, only the primary alcohol was selectively protected with Ms group to give the corresponding mesyloxy derivative **15**, accompanied with a small amount of dehydrovalyldipeptide **16**. Subsequently, the *O*-Ms group of **15** was β-eliminated with DBU to give the expected dipeptide **17**,[14] as shown in Scheme 2.

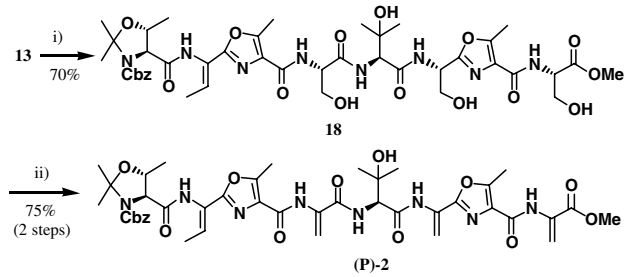
Finally, similarly to the case of **17**, deprotection of three *O*-protecting groups of **13** with 1 M TBAF, followed by β-elimination of the formed dehydrohexapeptide **18** with Ms-Cl and Et_3N and then DBU in one-pot gave the expected (**P**)-**2**[15] in 75% yield in two steps, as shown in Scheme 3.



Scheme 1. Reagent and conditions: i) a) NBS/THF, b) Et_3N/THF, ii) Cs_2CO_3/dioxane, iii) a) TFA/$CHCl_3$, b) TPSCl, imidazole/DMF, iv) a) 10%Pd-C, H_2/MeOH, b) BOP, $(i\text{-Pr})_2$NEt, Boc-HyVal-OH/DMF, v) a) TFA/$CHCl_3$, b) PivCl, Et_3N, MS4A, Cbz-Isop-Ser-OH/DMF, vi) a) 1 M LiOH/MeOH, b) BOP, $(i\text{-Pr})_2$NEt, H-Ser(TPS)-OMe/DMF vii) a) TFA/$CHCl_3$, b) TBSCl, imidazole/DMF, viii) a) 10%Pd-C, H_2/MeOH, b) BOP, $(i\text{-Pr})_2$NEt, Fragment B/DMF.



Scheme 2. Reagent and conditions: i) a) BOP, $(i\text{-Pr})_2$NEt, H-Ser(TPS)-OMe/DMF, b) 1 M TBAF/THF, ii) MsCl, Et_3N/$CHCl_3$, iii) DBU/$CHCl_3$.



Scheme 3. Reagent and conditions: i) 1 M TBAF/THF, ii) a) MsCl, Et_3N/$CHCl_3$, b) DBU/$CHCl_3$.

The structures 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 appearances of the chemical shifts of six protons of the three vinyl group at $\delta = 5.42, 5.67, 5.87, 6.24, 6.54,$ and 6.64 and that of the olefinic proton of the propenyl group at $\delta = 6.45$–6.60 supports the formation of Fragment B-C derivative [(**P**)-**2**] of the natural **1**.

In conclusion, it is noteworthy that a convenient synthesis of the main dehydrohexapeptide was achieved by the selective β-elimination of many primary alcohols and the final cyclization position in the total synthesis of **1** could be definitely specified.

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12 BOP: Benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate.
13 **13**: Colorless amorphous material. $[\alpha]_D^{24}$ +6.9° (*c* 0.67, MeOH). ^{1}H NMR ($CDCl_3$) $\delta = 0.00$ (s, 6H, TBS's $CH_3 \times 2$), 0.80, 0.88, 0.93 (each s, 27H, TPS's $Bu^t \times 2$, TBS's *t*-Bu), 1.11, 1.22 (each s, HyVal's $CH_3 \times 2$), 1.41 (d, 3H, Thr's CH_3, $J = 6.0$ Hz), 1.50–1.60 (m, 9H, Isop's $CH_3 \times 2$, propenyl's CH_3), 2.45, 2.50 (each s, 6H, oxazole's $CH_3 \times 2$), 3.66 (s, 3H, OMe), 3.84–4.06 (m, 7H, Ser's α-H × 3, Ser's β-H × 3, Thr's α-H), 4.20–4.25 (m, 1H, Thr's β-H), 4.37 (d, 1H, HyVal α-H, $J = 8.5$ Hz), 4.51 (q, 1H, Ser's α-H, $J = 4.0$ Hz), 4.75 (q, 1H, Ser's α-H, $J = 8.5$ Hz), 5.04 (s, 2H, Cbz's CH_2), 5.09 (q, 1H, Ser's α-H, $J = 8.5$ Hz), 6.42 (br s, 1H, propenyl's H), 7.11–7.52 (m, 20H, TPS's Ph × 2, Cbz's Ph, NH × 5). Found: C, 63.36; H, 6.96; N, 7.49%. Calcd for $C_{80}H_{106}N_8O_{16}Si_3$: C, 63.21; H, 7.03; N, 7.37%.
14 **17**: Colorless crystals. Mp 71–73 °C. ^{1}H NMR ($CDCl_3$) $\delta = 1.22$, 1.35 (each s, 6H, HyVal's $CH_3 \times 2$), 1.44 (s, 9H, Boc's Bu^t), 3.85 (s, 3H, OMe), 4.17 (m, 1H, HyVal's CH), 5.60 (br d, 1H, NH), 5.95, 6.60 (each s, 2H, vinyl's H × 2), 8.79 (br s, 1H, NH).
15 (**P**)-**2**: Colorless syrup. ^{1}H NMR ($CDCl_3$) $\delta = 1.21$, 1.37 (each s, 6H, HyVal's $CH_3 \times 2$), 1.48 (d, 3H, Thr's CH_3, $J = 6.0$ Hz), 1.51–1.79 (m, 6H, Isop's $CH_3 \times 2$), 1.67 (s, 3H, propenyl's CH_3), 2.63, 2.94 (each s, 3H, oxazole's $CH_3 \times 2$), 3.83 (s, 3H, OCH_3), 3.96 (d, 1H, Thr's α-H, $J = 8.0$ Hz), 4.27–4.33 (m, 1H, Thr's β-H), 4.63 (br d, 1H, HyVal's α-H, $J = 7.5$ Hz), 5.09–5.12 (m, 2H, Cbz's CH_2), 5.42, 5.67, 5.87, 6.24, 6.54, 6.64 (each s, 6H, vinyl's H × 6), 6.45–6.60 (m, 1H, propenyl's H), 7.08 (d, 1H, NH, $J = 8.5$ Hz), 7.16–7.27 (m, 6H, Cbz's Ph, NH), 9.25 (br s, 1H, NH), 9.31, 9.62 (each s, 2H, NH × 2). Found: C, 57.89; H, 5.76; N, 13.05%. Calcd for $C_{42}H_{50}N_8O_{13}$: C, 57.66; H, 5.76; N, 12.81%.