Useful Synthesis of the Main Dehydrohexapeptide Segment of a Macrocyclic Antibiotic, Berninamycin B

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The useful synthesis of tetradehydrohexapeptide segment **2**, which is the main skeleton of a macrocyclic antibiotic, berninamycin B, was first achieved. The skeleton **2** is constructed, in turn, of 2-[(*Z*)-1-amino-1-propenyl]-5-methyl-oxazole-4-carboxylic acid, α-dehydroalanine (ΔAla), L-Val, 2-[1-amino-1-ethenyl]-5-methyloxazole-4-carboxylic acid residues, besides L-Thr and ΔAla at the N- and C-termini, respectively.

Antibiotic berninamycin B (**1**),[1,2] isolated from the culture of *Streptomyces bernensis*, is a unique macrocyclic polyoxazole dehydropeptide. The natural product (**1**) features two interesting substructures, the main dehydrohexapeptide segment **2** called the Fragment B-C and the central heterocyclic skeleton **3** called the Fragment A, the former of which contains three vinyl and one 1-propenyl functional groups, as shown in Figure 1.

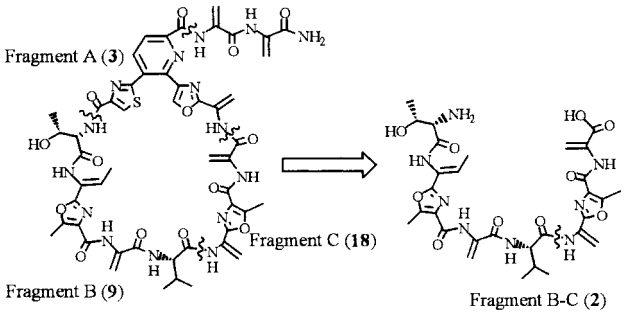
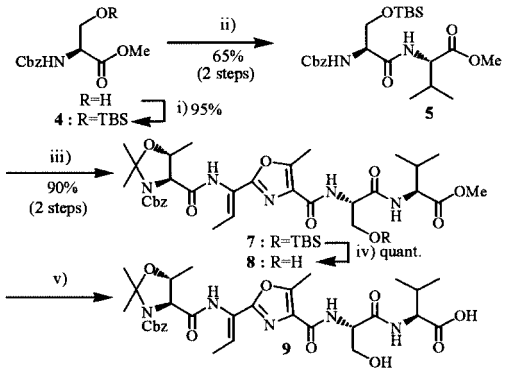


Figure 1. Berninamycin B (**1**).

Recently, we have reported briefly on the novel syntheses of partial Fragment B[3] and pyridine skeleton (**3**),[4] the latter of which is the common structure of similar antibiotics A10255 G and J.[5] The attractive structure as well as the bioactivity of **1** prompted us to study the total synthesis and the structure–bioactivity relationship.

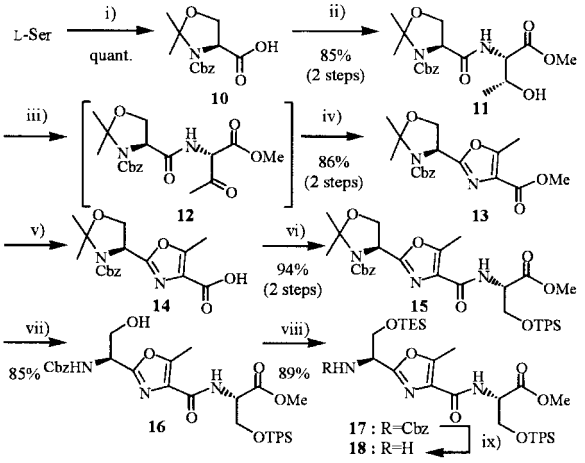
Herein, we wish to report convenient synthesis of **2** from the two building blocks, the *N*,*O*-protected dehydrotetrapeptide **9** [carboxy (*C*-) component] and the *N*,*O*-protected dipeptide **18** [amine (*N*-) component]. Furthermore, final fragment condensation between the *C*- and *N*-components and then stepwise β-elimination of the three OH groups of the Ser residue were first achieved to give the desired *N*,*O*-protected tetradehydrohexapeptide **2** [(**P**)-**2**].

At first, to synthesize **9**, *N*-benzyloxycarbonyl(Cbz)-Ser-OMe was protected with *t*-butyldimethylsilyl chloride (TBSCl) to give the corresponding Ser(TBS) derivative **4**. Ester hydrolysis with 1 M LiOH in dioxane, followed by coupling with L-Val-OMe gave Cbz-Ser(TBS)-L-Val-OMe (**5**) in two steps. Subsequently, after deprotecting the Cbz group of **5** with 10% Pd-C, fragment condensation with 2-{*N*-Cbz-*N*,*O*-isopropylidene(Ip)-L-Thr-[(*Z*)-1-amino-1-propenyl]}-5-methyloxazole-4-caboxylic acid (**6**) [3] as the *C*-component by using BOP[6] as a condensing agent and $(i\text{-Pr})_2$NEt gave the corresponding dehydrotetrapeptide methyl ester **7** containing Ser(TBS) residue. Deprotection of TBS group with 1 M tetrabutylammonium fluoride (TBAF) gave the expected 2-{*N*-Cbz-*N*,*O*-Ip-L-Thr-[(*Z*)-1-amino-1-propenyl]}-5-methyloxazole-4-carbonyl-L-Ser-L-Val-OMe (**8**).[7] Ester hydrolysis of **8** with 1 M LiOH gave the corresponding Fragment B derivative **9**, which was immediately subjected to the later condensation, without purification, as shown in Scheme 1.



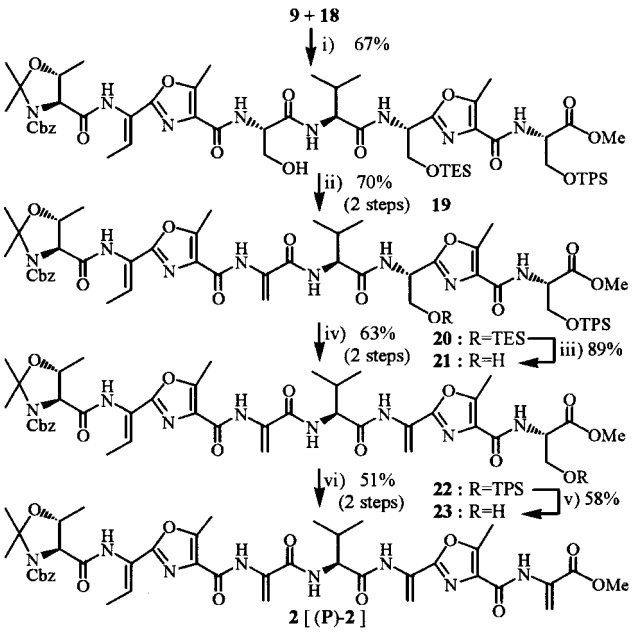
Scheme 1. Reagents and conditions : i) TBSCl, imidazole, DMF, 0 °C, 1 h, rt,1 h, ii) (a) 1 M LiOH, H_2O-dioxane, 0 °C, 1 h, rt, 3 h, (b) DCC, HOBt, DMF, H-Val-OMe, 0 °C, 1 h, rt, 6 h, iii) (a) 10% Pd-C, H_2, MeOH, rt, 3 h, (b) **6**, BOP, $(i\text{-Pr})_2$NEt, 0 °C, 1 h, rt, 6 h, iv) 1 M TBAF, THF, rt, 1 h, v) 1 M LiOH, H_2O-dioxane, 0 °C, 1 h, rt, 3 h

On the other hand, to synthesize the precursor of Fragment C derivative **18**, coupling of *N*-Cbz-*N*,*O*-Ip-L-Ser-OH (**10**), derived from L-Ser for 4 steps, with L-Thr(TBS)-OMe by using DCC and HOBt, followed by deprotection of the TBS group with 1 M TBAF gave the corresponding Ser-Thr-OMe (**11**). Intramolecular cyclization of **11** by the oxidations with Jones reagent and then with PPh_3 and I_2 proceeded to give the corresponding 5-methyloxazole-4-carboxylate **13** via unstable α-acetyldipeptide intermediate **12**. Subsequently, firstly, ester hydrolysis of **13** with 1 M LiOH, followed by elongation of the obtained carboxylic acid **14** with H-Ser(TPS)-OMe (TPS = *t*-butyldiphenylsilyl) by using diphenylphosphoryl azide (DPPA) in the presence of Et_3N gave the corresponding 5-methyloxazole-4-carbonyl-Ser(TPS)-OMe **15**. Secondarily, selective cleavage of the Ip group of **15** with trifluoroacetic acid (TFA) gave 2-(1-amino-2-hydroxy)ethyl-5-methyloxazole derivative **16**, the OH group of which was protected with triethylsilyl chloride (TESCl) to give 2-[1-*N*-(Cbz)amino-2-*O*-(TES)hydroxy]ethyl-5-methyloxazole derivative **17**.[8] Finally, hydrogenolysis of Cbz group of **17** gave the expected *N*-deprotected dipeptide **18** as the precursor of the *N*-component of **2**, as shown in Scheme 2.



Scheme 2. Reagents and conditions : i) (a) CbzCl, $NaHCO_3$, Et_2O-H_2O, 0 °C, 2 h, rt, 4 h, (b) CH_3I, $KHCO_3$, DMF, 0 °C, 1 h, rt, 6 h, (c) DMP, TosOH, acetone, rt, 12 h, (d) 1 M LiOH, H_2O-dioxane, 0 °C, 1 h, rt, 3 h, ii) (a) H-Thr(TBS)-OMe, DCC, HOBt, DMF, 0 °C, 1 h, rt, 6 h, (b) TBAF, THF, rt, 6 h, iii) Jones reagent, acetone, 0 °C, 1 h, rt, 2 h, iv) I_2, PPh_3, Et_3N, $CHCl_3$, 0 °C, 30 min, v) 1 M LiOH, MeOH, vi) H-Ser(TPS)-OMe, DPPA, Et_3N, DMF, 0 °C, 1 h, rt, 6 h, vii) TFA, $CHCl_3$, 0 °C, 30 min, rt, 1 h, viii) TESCl, imidazole, CH_2Cl_2, 0 °C, 1 h, rt, 1 h, ix) 10% Pd-C, H_2, EtOH, rt, 1 h

Furthermore, coupling of **9** with **18** by the BOP method gave the expected *O*-TES protected dehydrohexapeptide **19**, which was then subjected to the simultaneous β-elimination of the three hydroxy groups. At present, however, the satisfactory results have not been obtained yet. Therefore, the stepwise elimination was tried successfully to give the expected **2** as follows.



Scheme 3. Reagents and conditions : i) BOP, $(i\text{-Pr})_2NEt$, CH_2Cl_2, 0 °C, 1 h, rt, 12 h, ii) (a) MsCl, Et_3N, $CHCl_3$, 0 °C, 30 min, (b) DBU, $CHCl_3$, 0 °C, 30 min, (iii) 70% AcOH, THF, rt, 30 min, iv) (a) MsCl, Et_3N, $CHCl_3$, 0 °C, 30 min, (b) DBU, $CHCl_3$, 0 °C, 30 min, v) TBAF, THF, 0 °C, 1 h, rt, 3 h, vi) (a) MsCl, Et_3N, $CHCl_3$, 0 °C, 30 min, (b) DBU, $CHCl_3$, 0 °C, 30 min

The central Ser residue was converted to α-dehydroalanine (ΔAla) by successive mesylation with MsCl and β-elimination with DBU to give didehydrohexapeptide **20** by the method reported earlier.[9] After selective deprotection of the TES group with 70% AcOH, the OH group of the formed **21** was further mesylated and then β-eliminated to give the corresponding tridehydrohexapeptide **22**. Finally, similarly to the case of **21**, deprotection of TPS group of **22** with TBAF gave tridehydrohexapeptide **23**, followed by β-elimination gave the expected main skeletal tetradehydrohexapeptide **2**,[10] as shown in Scheme 3.

The structures of all the 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 chemical shifts of six protons of the three vinyl group at δ = 5.45, 5.77, 5.95, 6.45, 6.56 and 6.69 ppm and that of olefinic proton of the propenyl group at δ = 6.56 ppm were found to be very similar to those of the natural berninamycin B (**1**).

In conclusion, a convenient synthesis of the main tetradehydrohexapeptide segment **2** of **1** was first accomplished. By using this result, further investigation on the total synthesis of **1** is currently under way in our laboratory.

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References and Notes

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6 BOP: Benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate.
7 **8**: Colorless syrup. $[\alpha]_D^{27}$ +4.45° (*c* 1.03, MeOH). ^1H NMR($CDCl_3$) δ = 0.88, 0.90(each d, 6H, Val's $CH_3 \times 2$, *J* = 8.5, 9.0 Hz), 1.51(d, 3H, Thr's CH_3, *J* = 6.0 Hz), 1.56–1.85(m, 9H, Ip and propenyl's CH_3), 2.18(m, 1H, Val's β-H), 2.60(s, 3H, oxazole's CH_3), 3.47(s, 3H, OCH_3), 4.05(d, 1H, Thr's α-H, *J* = 6.0 Hz), 4.14(m, 1H, Ser's α-H), 4.35(m, 1H, Thr's β-H), 4.50(d, 1H, Val's α-H, *J* = 8.5 Hz), 4.60(m, 1H, Ser's α-H), 5.13(m, 2H, Cbz's CH_2), 6.50(br s, 1H, propenyl's H), 7.19–7.27(m, 6H, Cbz's Ph and NH), 7.48(br s, 1H, NH), 7.78(br d, 1H, NH, *J* = 6.0 Hz).
8 **17**: Colorless syrup. $[\alpha]_D^{27}$ –21.6° (*c* 1.10, MeOH). ^1H NMR δ = 0.58(q, 6H, TES's CH_2, *J* = 8.0 Hz), 0.89(t, 9H, TES's CH_3, *J* = 8.0 Hz), 1.04(s, 9H, TPS's *t*-Bu), 3.60(s, 3H, oxazole's CH_3), 3.76(s, 3H, OCH_3), 4.01(m, 2H, Ser's β-H), 4.04(m, 1H, Ser's α-H), 4.79(m, 2H, Ser's β-H), 4.99(m, 1H, Ser's α-H), 5.15(ABq, 2H, Cbz's CH_2, *J* = 12.3 Hz), 5.63(br s, 1H, NH), 7.31–7.62(m, 15H, Cbz's Ph and TPS's Ph × 2), 7.73(m, 1H, NH, *J* = 6.0 Hz).
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10 **2**: Colorless amorphous material. $[\alpha]_D^{26}$ –21.7° (*c* 0.94, $CHCl_3$).^1H NMR δ = 1.06, 1.09(each d, 6H, Val's $CH_3 \times 2$, *J* = 6.5, 7.0 Hz), 1.52(d, 3H, Thr's CH_3, *J* = 6.0 Hz), 1.60–1.75(m, 9H, Ip and propenyl's CH_3), 2.30(m, 1H, Val's β-H), 2.61, 2.70(each s, 6H, oxazole's $CH_3 \times 2$), 3.88(s, 3H, OCH_3), 4.02(d, 1H, Thr's α-H, *J* = 7.5 Hz), 4.37(m, 1H, Thr's β-H), 4.54, 4.55(each d, 1H, Val's α-H, *J* = 6.5, 7.5 Hz), 5.15(m, 2H, Cbz's CH_2), 5.45, 5.77, 5.95, 6.45, 6.56, 6.69(each s, 6H, vinyl's H), 6.56(br s, 1H, propenyl's H), 6.89(m, 1H, NH), 7.05–7.47(br s, 6H, Cbz's Ph and NH), 8.18(s, 1H, NH), 9.15(s, 1H, NH), 9.29(br s, 1H, NH).