SYNTHESES AND ACTIVITIES OF SOME BACTOBOLIN DERIVATIVES

YOSHIO NISHIMURA, SHINICHI KONDO and TOMIO TAKEUCHI

Institute of Microbial Chemistry,
3-14-23 Kamiosaki, Shinagawa-ku, Tokyo 141, Japan

(Received for publication October 31, 1991)

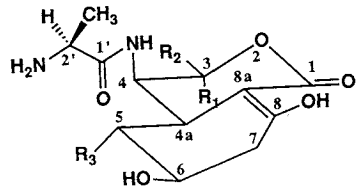
Some derivatives of bactobolin were prepared from bactobolin by dehydration or substitution reactions through tris(dimethylamino)alkoxyphosphonium salt formation. A derivative with low toxicity, 6-deoxybactobolin, showed moderate activity against Gram-positive and Gram-negative bacteria including methicillin-resistant *Staphylococcus aureus*.

Bactobolin (**1**) having strong antimicrobial and antitumor activities was isolated from culture filtrates of *Pseudomonas* sp. BMG13-A7 and the absolute structure was determined (Fig. 1).[1] It is structurally related to actinobolin (**2**) produced by *Streptomyces griseoviridis* var. *atrofaciens*.[2,3] These antibiotics differ considerably in their biological activity including toxicity, **1** being more potent than **2**.[4] Their structural novelties and biological activities have stimulated interest in the total synthesis[5~10] and in the chemical modification of the amino acid moiety.[11] Furthermore, **1** demonstrated a suppressing effect on antibody production[12] as well as prophylactic and therapeutic effect on autoimmune encephalomyelitis.[13] On the other hand, 5-deoxybactobolin (**3**),[14] a minor product of *Pseudomonas*, showed relatively low toxicity, about one fifth of the level of **1**. These facts prompted us to modify the C-5 and C-6 positions of the skeleton and led to 6-ene-bactobolin (**6**), 6-deoxybactobolin (**7**), 4a,6-diene-bactobolin (**9**) and 6-β-imidazoyl-6-deoxybactobolin (**11**).

Synthesis

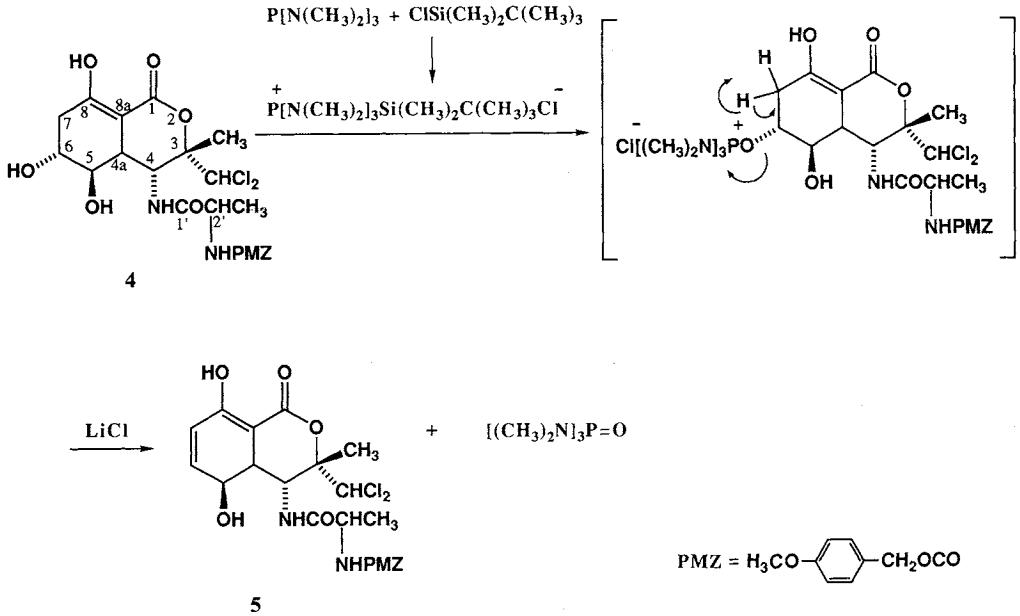
The amino group of **1** was first protected with *p*-methoxybenzyloxycarbonyl group[15] to give **4** in 90% yield. Elimination of the 6-hydroxyl group of **4** proved troublesome until we discovered that the new dehydration process (Scheme 1) by tris(dimethylamino)alkoxyphosphonium salt[16] formation *in situ* followed by treatment with lithium chloride at 70°C in *N*,*N*-dimethylformamide (DMF) gave 6-ene compound **5** in 70% yield. The 6-H and 7-H at δ 6.02 (d, $J=10$ Hz) and 6.60 (d, $J=10$ Hz), respectively, in ^{1}H NMR spectrum are clearly indicative of 6,7-double bond. On the other hand, the similar dehydration process was carried out at 110°C to give straightforwardly aromatized compound **8** in 70% yield. Removal of the protecting group of **5** with trifluoroacetic acid resulted in **6** (73% yield). Reduction of **5** with palladium on carbon furnished 6-deoxy compound **7** in 75% yield. The ^{1}H NMR spectrum of **7** shows protons at 1.85 (dt, $J=11$ and 7 Hz, 6-H_{ax}) and 2.14 (m, 6-H_{eq}), indicative of deoxygenation at C-6. The similar deprotection of **8** yielded **9** in 81% yield. These reaction sequences

Fig. 1. The structures of bactobolin congeners.



Bactobolin (**1**): $R_1=CH_3$, $R_2=CHCl_2$, $R_3=OH$
Actinobolin (**2**): $R_1=H$, $R_2=CH_3$, $R_3=OH$
5-Deoxybactobolin (**3**): $R_1=CH_3$, $R_2=CHCl_2$, $R_3=H$

Scheme 1. The possible mechanism of dehydration through tris(dimethylamino)alkoxyphosphonium salt.



are shown in Scheme 2.

Next, we turned our attention to the replacement of the 6-hydroxyl group with a basic substituent utilizing tris(dimethylamino)alkoxyphosphonium salt. Thus treatment of tris(dimethylamino)alkoxyphosphonium chloride of **5** with imidazole in DMF gave 6-β-imidazoyl compound **10**, which was converted upon hydrogenolysis into **11** in 35% yield (Scheme 2).

Biological Activities

All derivatives **6**, **7**, **9** and **11** showed less acute intravenous toxicity in mice (tolerated at a dose of 50 mg/kg) than **1** (LD_{50} 6.25~12.5 mg/kg). However, the antimicrobial activity (Table 1) and cytotoxicity against mouse P388 leukemia cells and its multidrug-resistant subline, P388/ADR (Table 2), were also decreased. Among them, **7** showed moderate activity against *Staphylococcus aureus* FDA 209P and *E. coli* NIHJ (Table 1) as well as methicillin-resistant *Staphylococcus aureus* (Table 3). The antimicrobial activity of **7** was superior to that of **2** as shown in Table 3.

Experimental

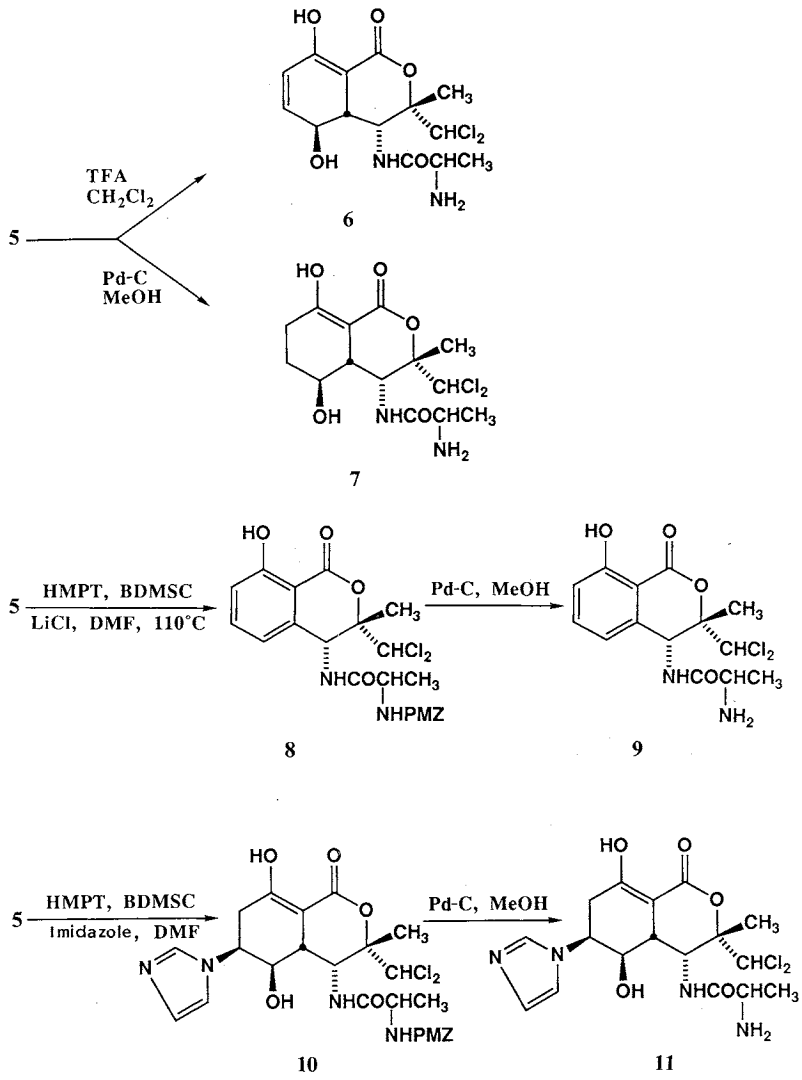
General Methods

Melting points were determined with a Yanagimoto apparatus and were uncorrected. IR spectra were determined on a Hitachi Model 260-10 spectrophotometers. Optical rotations were measured with a Perkin-Elmer Model 241 polarimeter. ^{1}H NMR spectra were recorded with Jeol GX-400 and JNM-EX270 spectrometers. Chemical shifts are expressed in δ values (ppm) with tetramethylsilane as an internal standard. The mass spectra were taken by a Jeol SX102.

2′-*N*-(*p*-Methoxybenzyloxycarbonyl)bactobolin (**4**)

To a solution of bactobolin (**1**) (100 mg) in DMF (2 ml) were added *p*-methoxybenzyl-4,6-dimethylpyrimidyl-2-thiol carbonate (102.8 mg) and *N*,*N*-diisopropylethylamine (0.27 ml), and the mixture was stirred at room temperature for 3 hours. Evaporation of the solvent gave an oil which was dissolved

Scheme 2. Reaction sequences.



HMPT = $P[N(CH_3)_2]_3$, BDMSC = $ClSi(CH_3)_2C(CH_3)_3$

Table 1. Antimicrobial activity of bactobolin (**1**) and its derivatives by broth dilution method.

Test organism	MIC μg/ml				
	1	**6**	**7**	**9**	**11**
Staphylococcus aureus FDA 209P	<0.20	6.25	3.13	100	12.5
Escherichia coli NIHJ	<0.20	3.13	1.56	50	25.0

MICs were determined by 2-fold broth dilution method at 37°C for 17 hours in nutrient medium (*S. aureus*) or 0.5% peptone medium (*E. coli*).

in chloroform. The solution was washed with water, dried over $MgSO_4$ and filtered. Evaporation of the solvent gave an oil which was subjected to preparative thin-layer chromatography on silica gel developed with a mixture of chloroform - methanol (15 : 1) to give a colorless solid of **4** (128 mg, 90%). The solid was

Table 2. Cytotoxicity of bactobolin (**1**) and its derivatives.

Compound	IC_{50} (μg/ml)	
	P388	P388/ADR
1	0.044	0.064
6	2.1	1.9
7	1.7	2.7
9	>10	>10
11	1.1	8.9

Mouse P388 leukemia cells and the multidrug-resistant subline P388/ADR were incubated with each sample for 72 hours in RPMI-1640 medium supplemented with 10% fetal calf serum and 10 μM 2-hydroxyethyldisulfide. The rate of survival cells was measured by MTT assay and IC_{50} value was calculated.

Table 3. Antibacterial activities of bactobolin (**1**) and its derivatives against methicillin-resistant *Staphylococcus aureus*.

Compound	MIC (μg/ml)			
	Range	50%	90%	209P[a]
1	≤0.20~0.39	0.39	0.39	0.39
2	12.5~25	12.5	12.5	12.5
6	12.5~25	25	25	12.5
7	6.25~12.5	6.25	12.5	6.25

MICs were determined by 2-fold agar dilution method at 37°C for 18 hours using Bacto Mueller Hinton Medium (Difco) according to the method of Japan Society of Chemotherapy. Fifty strains of methicillin-resistant *S. aureus* isolated from a hospital in Osaka in 1986~1990 (purchased from Takeda Analytical Research Laboratories Ltd.) were used.

[a] 209P: *S. aureus* FDA 209P.

crystallized from chloroform to give a colorless crystal of **4**: MP 143~144°C; $[\alpha]_D^{24}$ −15.9° (*c* 1.04, MeOH); IR (KBr) cm^{-1} 3400, 3300, 3010, 2940, 2910, 2840, 1700 (sh), 1615 (sh), 1520, 1460, 1390, 1340, 1320, 1300, 1240, 1175, 1150, 1120, 1070, 1030, 925; ^1H NMR ($CDCl_3$, 400 MHz, 40°C) δ 1.30 (3H, d, *J*=7 Hz, 2′-CH_3), 1.60 (3H, s, 3-CH_3), 2.50 (1H, dd with a small coupling, *J*=9 and 19 Hz, 7-H_{ax}), 2.81 (1H, br d with small couplings, *J*=10 Hz, 4a-H), 2.97 (1H, dd, *J*=7 and 19 Hz, 7-H_{eq}), 3.02 (1H, br s, 6-OH), 3.17 (dt, *J*=3 and 10 Hz, 5-H), 3.81 (3H, s, OCH_3), 3.96 (1H, dt, *J*=7 and 9 Hz, 6-H), 4.20 (1H, quintet, *J*=7 Hz, 2′-H), 4.44 (1H, d, *J*=3 Hz, 5-OH), 4.73 (1H, dd, *J*=4 and 10 Hz, 4-H), 5.0 and 5.07 (2H, ABq, *J*=12 Hz, $-CH_2-$), 5.06 (1H, d, *J*=7 Hz, 2′-NH), 6.06 (1H, s, $-CHCl_2$), 7.78 (1H, d, *J*=10 Hz, 4-NH), 7.89 (2H, d with small couplings, *J*=9 Hz, aromatic protons), 7.27 (2H, d with small couplings, *J*=9 Hz, aromatic protons) and 12.88 (1H, s, 8-OH); MS (FAB, positive) *m/z* 547 $(M+H)^+$, 410, 136, 122, 107.

6-Ene-2′-*N*-(*p*-methoxybenzyloxycarbonyl)bactobolin (**5**)

To a solution of **4** (100 mg) in DMF (1 ml) were added hexamethylphosphoric triamide (HMPT) (0.07 ml) and *tert*-butyldimethylsilyl chloride (55.1 mg) at 0°C, and the mixture was stirred at room temperature for 4 hours. To the resulting tris(dimethylamino)alkoxyphosphonium salt was added lithium chloride (69 mg), and then the mixture was stirred at 70°C overnight. Evaporation of the solvent gave an viscous solid which was taken into chloroform. Evaporation of the chloroform solution gave an oil which was subjected to preparative thin-layer chromatography on silica gel to give an oil of **5** (68 mg, 70%): $[\alpha]_D^{24}$ +94.5° (*c* 0.66, MeOH); IR ($CHCl_3$) cm^{-1} 3430, 3000, 2950, 2840, 1710, 1675, 1615, 1575, 1515, 1470, 1460, 1390, 1370, 1340, 1305, 1250, 1210 (sh), 1185, 1170, 1130, 1095, 1070, 1040; ^1N NMR ($CDCl_3$, 400 MHz) δ 1.39 (3H, d, *J*=7 Hz, 2′-CH_3), 1.63 (3H, s, 3-CH_3), 3.18 (1H, dd, *J*=4 and 15 Hz, 4a-H), 4.15~4.35 (3H, m, 5-H, 2′-H and 5-OH), 4.72 (1H, dd, *J*=4 and 9.8 Hz, 4-H), 4.99 and 5.05 (2H, ABq, $-CH_2-$), 5.14 (1H, br d, *J*=7 Hz, 2′-NH), 6.02 (1H, d, *J*=10 Hz, 6-H), 6.13 (1H, s, $-CHCl_2$), 6.59 (1H, d, *J*=10 Hz, 7-H), 6.88 (2H, d, aromatic protons), 7.06 (1H, d, *J*=9.8 Hz, 4-NH) and 7.27 (2H, d, aromatic protons); MS (FAB, positive) *m/z* 529 $(M+H)^+$, 341, 136, 121, 107, 89.

6-Ene-bactobolin (**6**)

To a solution of **5** (20 mg) in anhydrous dichloromethane (0.4 ml) was added trifluoroacetic acid (0.03 ml) at 0°C, and the mixture was stirred at room temperature overnight. Evaporation of the solvent gave an oil which was dissolved in chloroform. The solution was washed with water, dried over $MgSO_4$ and filtered. Evaporation of the filtrate gave an oil which was subjected to preparative thin-layer chromatography on silica gel developed with chloroform-methanol (7:1) to give an amorphous solid of **6** (10 mg, 73%): MP >200°C (dec); $[\alpha]_D^{24}$ +159° (*c* 0.44, MeOH); IR (KBr) cm^{-1} 3425, 3000, 2880, 1650, 1630 (sh), 1530 (sh), 1430 (sh), 1390, 1370, 1345, 1260, 1155 (sh), 1130, 1090, 1070, 1020 (sh), 1000,

980, 930; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.39 (3H, d, J=7 Hz, 2'-CH_3), 1.64 (3H, s, 3-CH_3), 3.21 (1H, dd, J=4.5 and 14.5 Hz, 4a-H), 3.61 (1H, q, J=7 Hz, 2'-H), 4.17 (1H, dt, J=2.4 and 14.5 Hz, 5-H), 4.65 (1H, dd, J=4.5 and 9.5 Hz, 4-H), 5.92 (1H, s, $-CHCl_2$), 6.01 (1H, dd, J=3 and 10 Hz, 6-H), 6.59 (1H, dd, J=2 and 10 Hz, 7-H) and 8.03 (1H, d, J=9.5 Hz, -NHCO-); MS (FAB, positive) m/z 365 $(M+H)^+$, 341, 136, 120, 107, 89.

6-Deoxybactobolin (**7**)

The solution of **5** (18 mg) in methanol (10 ml) was stirred under an atmosphere of hydrogen gas in the presence of 10% palladium on carbon at room temperature for 3 hours. After filtration, the residue was washed with methanol. The filtrate and washings were combined and evaporated. The colorless amorphous solid of **7** (9.4 mg, 75%) was obtained: MP 131~133°C; $[\alpha]_D^{24}$ −24.8° (c 0.07, H_2O); IR (KBr) cm^{-1} 3425, 2980, 2940, 2880, 1650, 1540 (sh), 1460 (sh), 1400, 1330 (sh), 1245, 1210 (sh), 1170 (sh), 1120, 1070, 980, 960, 925 (sh), 900; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.4 (3H, d, J=7 Hz, 2'-CH_3), 1.72 (3H, s, 3-CH_3), 1.84 (1H, dt with a small coupling, J=7 and 12 Hz, 6-H_{ax}), 2.14 (1H, m, 6-H_{eq}), 2.55 (1H, ddd, J=2, 7 and 12 Hz, 7-H_{ax}), 2.59 (1H, dt, J=1.5 and 7 Hz, 7-H_{eq}), 2.83 (1H, d with small couplings, J=9 Hz, 4a-H), 3.26 (1H, ddd, J=4, 9 and 12 Hz, 5-H), 3.60 (1H, q, J=7 Hz, 2'-H), 4.69 (1H, dd, J=3.5 and 9.8 Hz, 4-H), 5.90 (1H, s, $-CHCl_2$) and 7.96 (1H, d, J=9.8 Hz, -NHCO-); MS (FAB, positive) m/z 367 $(M+H)^+$, 341, 136, 121, 107, 89.

4a,6-Diene-2'-*N*-(*p*-methoxybenzyloxycarbonyl)bactobolin (**8**)

To a solution of **4** (100 mg) in dry DMF (1 ml) were added HMPT (0.07 ml) and *tert*-butyldimethylsilyl chloride (56 mg) at 0°C, and the mixture was stirred at room temperature for 3 hours. To the resulting tris(dimethylamino)alkoxyphosphonium salt was added lithium chloride (16 mg), and the mixture was stirred at 110°C overnight. Evaporation of the solvent gave an oil which was dissolved in chloroform. The chloroform solution was washed with water, dried over $MgSO_4$ and filtered. Evaporation of the filtrate gave an oil. The oil was subjected to preparative thin-layer chromatography on silica gel developed with chloroform - methanol (30 : 1) and gave a pale brown oil of **8** (70 mg, 75%): $[\alpha]_D^{24}$ −101° (c 1.52, MeOH); IR ($CHCl_3$) cm^{-1} 3430, 3300, 3010, 2970, 2950, 2840, 1690, 1620, 1590, 1520, 1470, 1390, 1355, 1320, 1310, 1245, 1220 (sh), 1180, 1170, 1110, 1075, 1040, 950, 940, 910; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.28 (3H, d, J=7 Hz, 2'-CH_3), 1.60 (3H, s, 3-CH_3), 3.80 (3H, s, $-OCH_3$), 4.13 (1H, q, J=7 Hz, 2'-H), 5.00 (2H, br s, $-CH_2-$), 5.25 (1H, br d, J=7 Hz, 2'-NH), 5.58 (1H, d, J=10 Hz, 4-H), 6.20 (1H, s, $-CHCl_2$), 6.86 (2H, d with small couplings, J=8 Hz, aromatic protons), 7.02 (2H, br d, J=8 Hz, aromatic protons (?)), 7.20~7.35 (3H, m, 5-H (?), 7-H (?) and 4-NH (?)), 7.47~7.60 (1H, m, 6-H (?)) and 10.59 (1H, br s, 8-OH); MS (FAB, positive) m/z 511 $(M+H)^+$, 443, 341, 136, 121, 107, 89, 77.

4a,6-Diene-bactobolin (**9**)

The solution of **8** (22 mg) in methanol (9 ml) was stirred under an atmosphere of hydrogen gas in the presence of 10% palladium on carbon at room temperature for 3 hours. After removal of catalysts, evaporation of the solvent gave a colorless foam of **9** (12.2 mg, 81%): $[\alpha]_D^{24}$ −20.7° (c 0.47, MeOH); IR (KBr) cm^{-1} 3400, 3300 (sh), 3000, 1690, 1620, 1590, 1510 (sh), 1470, 1390, 1350, 1310, 1240, 1210, 1165, 1110, 1075, 1060, 1030, 955, 935; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.36 (3H, d, J=7 Hz, 2'-CH_3), 1.66 (3H, s, 3-CH_3), 3.49 (1H, q, J=7 Hz, 2'-H), 5.56 (1H, d, J=10.5 Hz, 4-H), 6.04 (1H, s, $-CHCl_2$), 7.53 (1H, dd, J=7.5 and 8 Hz, 6-H), 7.01 (1H, dd, J=1 and 8 Hz, 5-H (?)), 7.05 (1H, d, J=7.5 Hz, 7-H (?)) and 8.05 (1H, d, J=10.5 Hz, 4-NH); MS (FAB, positive) m/z 347 $(M+H)^+$, 307, 136, 107.

6-Deoxy-6-β-imidazoyl-2'-*N*-(*p*-methoxybenzyloxycarbonyl)bactobolin (**10**)

To a solution of **5** (200 mg) in dry DMF (2 ml) were added HMPT (0.14 ml), *tert*-butyldimethylsilyl chloride (110 mg) and imidazole (50 mg), and the mixture was stirred at room temperature overnight. Another portion of imidazole (50 mg) was added to the mixture, and then the mixture was further stirred at room temperature overnight. Evaporation of the solvent gave an oil which was dissolved in chloroform. The chloroform solution was washed with water, dried over $MgSO_4$ and filtered. Evaporation of the filtrate gave an oil. The oil was subjected to preparative thin-layer chromatography on silica gel developed with chloroform - methanol (15 : 1) to give a pale red solid of **10** (109 mg, 50%): MP 134~135°C; $[\alpha]_D^{24}$ +36°

(*c* 0.27, MeOH); IR (KBr) cm^{-1} 3400, 3020, 1710, 1660, 1610, 1540, 1520, 1460, 1400, 1330, 1305, 1250, 1180, 1160, 1140, 1115, 1090, 1070, 1040, 1030, 970, 910; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.41 (3H, d, $J=7$ Hz, 2'-CH_3), 1.58 (3H, s, 3-CH_3), 2.48 (1H, d with small couplings, $J=10$ Hz, 4a-H), 2.94 (1H, d, $J=20$ Hz, 7-H), 3.22 (1H, br d with small couplings, $J=20$ Hz, 7-H), 3.67 (1H, d with small couplings, $J=10$ Hz, 5-H), 3.81 (3H, s, $-OCH_3$), 4.18 (1H, q, $J=7$ Hz, 2'-H), 4.60 (1H, dd, $J=3.8$ and 10 Hz, 4-H), 4.76 (1H, br s with small couplings, 6-H), 4.95 and 5.06 (2H, ABq, $J=12$ Hz, $-CH_2-$), 5.05 (1H, d, $J=7$ Hz, 2'-NH), 5.98 (1H, s, $-CHCl_2$), 6.84 (1H, d, $J=10$ Hz, 4-NH), 6.90 (2H, d with small couplings, $J=7$ Hz, aromatic protons), 6.98, 7.10 and 7.60 (1H, each s, imidazoyl protons), 7.28 (2H, d with small couplings, $J=7$ Hz, aromatic protons) and 13.2 (1H, br s, 8-OH); MS (FAB, positive) *m/z* 597 $(M+H)^+$, 341, 136, 121, 107, 89, 77.

6-Deoxy-6-β-imidazoylbactobolin (**11**)

The solution of **10** (30 mg) in methanol was stirred under an atmosphere of hydrogen gas in the presence of 5% palladium on carbon at room temperature for 6 hours. After removal of catalysts, evaporation of the solvent gave a colorless amorphous solid of **11** (13 mg, 60%): MP >200°C (dec); $[\alpha]_D^{24}$ +88° (*c* 0.14, MeOH); IR (KBr) cm^{-1} 3440, 1650, 1560, 1480 (sh), 1440, 1400, 1330, 1280, 1240, 1170, 1130, 1090, 1020, 980, 920; ^1H NMR (CD_3OD, 270 MHz, 40°C) δ 1.54 (3H, d, $J=6.9$ Hz, 2'-CH_3), 1.59 (3H, s, 3-CH_3), 2.56 (1H, br d, $J=9.9$ Hz, 4a-H), 2.95 (1H, d, $J=20$ Hz, 7-H), 3.69 (1H, dd, $J=3.3$ and 9.9 Hz, 5-H), 4.07 (1H, q, $J=6.9$ Hz, 2'-H), 4.83 (1H, d, $J=4$ Hz, 4-H), 4.88 (1H, m, 6-H), 6.15 (1H, s, $-CHCl_2$), 7.25, 7.30 and 8.15 (1H, each s, imidazole); MS (FAB, positive) *m/z* 433 $(M+H)^+$, 341, 329, 136, 120, 107, 89.

Acknowledgment

The authors are grateful to members of Pharmaceutical Research Center, Meiji Seika Kaisha, Ltd. for the large scale preparation of bactobolin and for the evaluation of cytotoxicity. We also express to sincerely thank Dr. MASA HAMADA for determination of antimicrobial activities, and Mr. SHINYA NACHI for his technical assistance.

References

1) KONDO, S.; Y. HORIUCHI, M. HAMADA, T. TAKEUCHI & H. UMEZAWA: A new antitumor antibiotic, bactobolin, produced by *Pseudomonas*. J. Antibiotics 32: 1069~1071, 1979
2) HASKELL, T. H. & Q. R. BARTZ: Actinobolin, a new broad-spectrum antibiotic. Isolation and characterization. Antibiot. Ann. 1958-1959: 505~509, 1959
3) ANTOSZ, F. J.; D. B. NELSON, D. L. HERALD, Jr. & M. E. MUNK: The structure and chemistry of actinobolin. J. Am. Chem. Soc. 92: 4933~4942, 1970
4) HORI, M.; K. SUZUKAKE, C. ISHIKAWA, H. ASAKURA & H. UMEZAWA: Biochemical studies on bactobolin in relation to actinobolin. J. Antibiotics 34: 465~468, 1981
5) YOSHIOKA, M.; H. NAKAI & M. OHNO: Stereocontrolled total synthesis of (+)-actinobolin by an intramolecular Diels-Alder reaction of a chiral *Z* diene derived from L-threonine. J. Am. Chem. Soc. 106: 1133~1135, 1984
6) ASKIN, D.; C. ANGST & S. DANISHEFSKY: A total synthesis of N-acetylactinobolamine. J. Org. Chem. 50: 5005~5007, 1985
7) KOZIKOWSKI, A. P.; T. R. NIEDUZAK, T. KONOIKE & J. P. SPRINGER: π-Facial selection in intermolecular Diels-Alder reactions: total syntheses of (+)-actinobolin and (+)-5,6,10-*triepi*-actinobolin. J. Am. Chem. Soc. 109: 5167~5175, 1987
8) GARIGIPATI, R. S.; D. M. TSCHAEN & S. M. WEINREB: Total synthesis of (+)-actinobolin. J. Am. Chem. Soc. 107: 7790~7792, 1985
9) RAHMAN, M. A. & B. FRASER-REID: Actinobolin via the anomeric effect. J. Am. Chem. Soc. 107: 5576~5578, 1985
10) GARIGIPATI, R. S. & S. M. WEINREB: Stereoselective total synthesis of the antitumor antibiotic (−)-bactobolin. J. Org. Chem. 53: 4143~4145, 1988
11) MUNAKATA, T.: Bactobolins, antitumor antibiotics from *Pseudomonas*. II. Synthesis and biological activities of related compounds. Yakugaku Zasshi 101: 138~147, 1981
12) ISHIZUKA, M.; S. FUKASAWA, T. MASUDA, J. SATO, N. KANBAYASHI, T. TAKEUCHI & H. UMEZAWA: Antitumor effect of bactobolin and its influence on mouse immune system and hematopoietic cells. J. Antibiotics 33: 1054~1062, 1980
13) TABIRA, T.; Y. DA-LIN, T. YAMAMURA & T. AOYAGI: Prophylactic and therapeutic effect of bactobolin on

autoimmune encephalomyelitis. Proc. Jpn. Acad. 63, Ser. B.: 127~130, 1987

14) MUNAKATA, T.; J. SAKAI, H. MATSUKI & K. ISAGAI: Bactobolins, antitumor antibiotics from *Pseudomonas*. I. Structures and antimicrobial activities. Yakugaku Zasshi 101: 132~137, 1981

15) NAGASAWA, T.; K. KUROIWA, K. NARITA & Y. ISOWA: New agents for *t*-butyloxycarbonylation and *p*-methoxybenzyloxycarbonylation of amino acids. Bull. Chem. Soc. Jpn. 46: 1269~1272, 1973

16) CASTRO, B.; Y. CHAPLEUR, B. GROSS & C. SELVE: Sels d'alkyloxyphosphonium III—Activation sélectivé de l'hydroxyle primaire du méthyl, α-D-glucopyrannoside. Tetrahedron Lett. 1972: 5001~5004, 1972