CHEMICAL MODIFICATION OF FORTIMICINS: PREPARATION OF 4-N-SUBSTITUTED FORTIMICIN B

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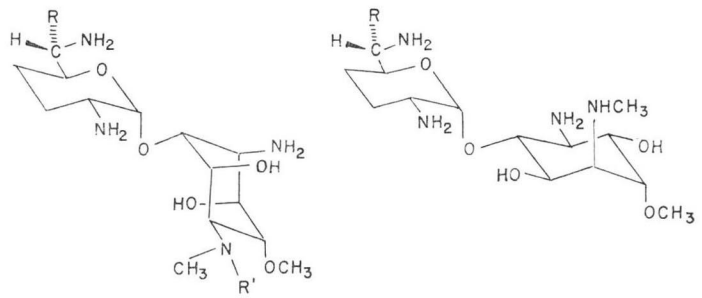
(Received for publication January 11, 1979)

Among the new aminoglycoside antibiotic family of fortimicins, components A, C and D have higher activity compared to their 4-N-deacylated components B and KE. Synthesis and antibacterial activities of 4-N-acyl- and 4-N-alkyl-fortimicin B derivatives are described. 4-N-Acylfortimicin B's, which are relatively unstable in alkaline conditions, were converted to stable 4-N-alkyl derivatives with diborane. The activity is greatly affected by the 4-N-substituents, and the presence of hydrophilic group(s) is necessary to confer activity on the derivatives. 4-N-(2-Aminoethyl)-, 4-N-(4-amino-2-hydroxybutyl)- and 4-N-(2-hydroxy-4-methylaminobutyl)-fortimicin B are the most potent compounds among them.

Fortimicins are new aminoglycoside antibiotics produced by *Micromonospora* sp.,[1,2] and the structures of fortimicin A(**1**), B(**2**), C(**3**), D(**4**) and KE(**5**) (Fig. 1) have been determined.[3,4] High activities of fortimicins A, C and D compared to their 4-N-deacylated components, *i.e.*, fortimicin B and KE, suggested the preparation of 4-N-substituted fortimicin B and KE. However, 4-N-acyl derivatives of fortimicin B and KE are relatively unstable in alkaline conditions.[1~4] It was necessary, therefore, to prepare more stable 4-N-alkyl derivatives, and because of their stability a wider variety of alkyl residues could be considered as 4-N-substituents than acyl. In this paper, preparation of a series of 4-N-alkylfortimicin B's from 4-N-acyl derivatives, and their antibacterial activities are reported.

Fig. 1. Structures of fortimicins.



1 R = CH_3, R' = $COCH_2NH_2$ **2** R = CH_3
3 R = CH_3, R' = $COCH_2NHCONH_2$ **5** R = H
4 R = H, R' = $COCH_2NH_2$

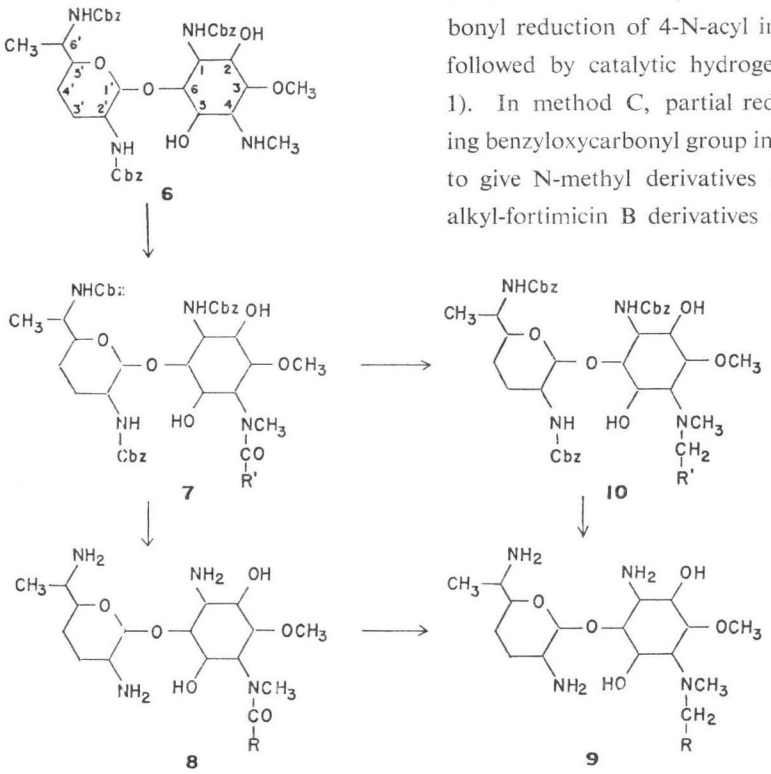
Preparation of 4-N-Acylfortimicin B

4-N-Acyl derivatives of fortimicin B (**8**) were prepared from 1,2′,6′-tri-N-benzyloxycarbonyl-fortimicin B (**6**) *via* intermediate (**7**) (Scheme 1) according to the method of the Abbott group.[5] Several new 4-N-acyl-fortimicin B derivatives (**8**) are presented in Table 1.

Preparation of 4-N-Alkylfortimicin B

Diborane reduction of 4-N-acylfortimicin B (**8**) free base gave 4-N-alkylfortimicin B (**9**) (method A). Lithium aluminum hydride reduction of **8** also gave **9** in relatively low yield. Some 4-N-acyl derivatives are too unstable to afford their free bases. In these cases **9** was obtained by diborane reduction of trifluoroacetate of **8** (method B) or by selective amide carbonyl reduction of 4-N-acyl intermediate (**7**) with diborane followed by catalytic hydrogenolysis (method C) (Scheme 1). In method C, partial reduction of the amino protecting benzyloxycarbonyl group in the acyl residue had occurred to give N-methyl derivatives (**9f**, **9m** and **9p**). The 4-N-alkyl-fortimicin B derivatives (**9**) prepared are presented in Table 1.

Scheme 1. Preparation of 4-N-substituted fortimicin B.



The structures of 4-N-substituted fortimicin B derivatives were confirmed by mass, PMR, CMR spectra and elemental analyses. For example, PMR and CMR parameters of 4-N-(2-aminoethyl)fortimicin B (**9e**) are presented in Tables 2 and 3, respectively. It is noteworthy that the coupling constants of fortamine protons in **9e** free base are apparently different from those of fortimicin A[4], suggesting the conformation of **9e** differs from fortimicin A in the free base form. Within each of the two series of compounds described by formulae **8** and **9**, changes in the nature of the R group had little effect on the cyclitol ring proton coupling constants.

Antibacterial Activities of Fortimicin B Derivatives

Minimum inhibitory concentrations (MIC's) of fortimicin B derivatives prepared in this study are presented in Tables 4 and 5. MIC measurement was carried out according to the two-fold agar dilution method using a medium of pH 8.0[1] (Table 4) or the Japanese Minimum Requirements for Antibiotic Preparations using a medium of pH 7.2 (Table 5).

The activity was greatly affected by the 4-N-substituent. Derivatives substituted by simple aliphatic residue (**8a**$\sim$**8c** and **9a**$\sim$**9d**) have almost no activity, but introduction of hydrophilic group(s) (OH, NH_2, $NHCONH_2$) to the 4-N-side chain produced significant biopotency. In a series of ω-aminoalkyl substituted derivatives (**9e**$\sim$**9i**), elongation of the chain length tends to decrease activity, although 4-aminobutyl derivative (**9h**) is more potent than 3-aminopropyl derivative (**9g**). This phenomenon is

Table 1. 4-N-Substituted fortimicin B derivatives (**8** and **9**).

Compound	R	Method	Rf[a]	Analyses[b]	$[\alpha]_D$[c]
8a	$-CH_2CH_3$		0.46	B	+136.8° [f]
8b	$-(CH_2)_2CH_3$		0.48	B	+131.0° [f]
8c	$-(CH_2)_3CH_3$		0.49	B	+116.3° [f]
8d	$-CH_2OH$		0.46	A	+89.3° [d]
8e	$-(CH_2)_3NH_2$		0.44	A	+81.8° [d]
8f	$-(CH_2)_4NH_2$		0.47	B	+89.5° [d]
8g	$-(CH_2)_5NH_2$		0.42	A	+74.9° [d]
9a	$-CH_3$	A	0.60	B	
9b	$-CH_2CH_3$	A	0.66	B	
9c	$-(CH_2)_2CH_3$	A	0.71	B	
9d	$-(CH_2)_3CH_3$	A	0.72	B	
9e	$-CH_2NH_2$	A, C	0.41	A	+77.8° [f]
9f	$-CH_2NHCH_3$	C	0.43	B	+68.0° [f]
9g	$-(CH_2)_2NH_2$	A	0.43	A	+71.9° [f]
9h	$-(CH_2)_3NH_2$	A	0.43	A	+72.8° [d]
9i	$-(CH_2)_4NH_2$	A	0.47	B	+67.3° [d]
9j	$-CH_2OH$	A	0.46	B	+77.4° [d]
9k	$-CH_2NH(CH_2)_2NH_2$	A	0.36	A	+69.0° [d]
9l	$-CH(OH)(CH_2)_2NH_2$ (*S*)	B, C	0.27	A	+78.6° [d]
9m	$-CH(OH)(CH_2)_2NHCH_3$ (*S*)	C	0.34	A	+77.5° [d]
9n	$-CH(OH)(CH_2)_2NH_2$ (*RS*)	C	0.27	A	+92.5° [e]
9o	$-CH(OH)CH_2NH_2$ (*S*)	C	0.35	A	+86.5° [d],[g]
9p	$-CH(OH)CH_2NHCH_3$ (*S*)	C	0.40	A	+74.5° [d],[g]
9q	$-CH(OH)(CH_2)_3NH_2$ (*S*)	C	0.34	A	+75.5° [e],[g]

[a] TLC on silica gel, solvent; *i*-PrOH - $CHCl_3$ - 28%NH_4OH (2: 1: 1).

[b] A: Deviation of C, H, N analytical values of the sulfate from the calculated values fell within a ±0.4% error. B: Elemental analysis was not performed, but the structure was supported by mass and PMR spectra.

[c] measured as sulfate in water (*c* 1.0) except for **8f** as hydrochloride.

[d] measured at 23°C, [e] 24°C, [f] 25°C.

[g] *c* 0.2.

Table 2. PMR parameters of 4-N-(2-aminoethyl)fortimicin B (**9e**)[a,b].

	Chemical shifts[c]				
	Free base	Hydrochloride		Free base[d]	Hydrochloride
H-1′	4.92	5.39	H-1	3.16	~3.9
H-2′	~2.4	~3.5	H-2	4.06	~4.7
CH_2-3′,4′	1.2~1.9	1.5~2.1	H-3	3.85	4.41
H-5′	~3.5	~3.9	H-4	3.09	3.99
H-6′	2.76	3.40	H-5	4.16	4.87
CH_3-6′	1.02	1.36	H-6	3.74	4.28
			OCH_3	3.40	3.55
			NCH_3	2.38	3.16
			$NCH_2CH_2NH_2$	2.70	

(to be continued)

Table 2 (continued)

Coupling constants					
	Free base	Hydrochloride		Free base[d]	Hydrochloride
$J_{1',2'}$	3.8	3.8	$J_{1,2}$	5.5	
$J_{5',6'}$	6.6	7.0	$J_{2,3}$	3.0	3.8
			$J_{3,4}$	8.0	11
			$J_{4,5}$	3.8	2
			$J_{5,6}$	5.5	3.8
			$J_{1,6}$	5.5	~3

a) measured in D_2O.
b) Analyses were performed with the aid of spin-decoupling experiments, and each resonance was correlated to carbon resonance (*cf.* Table 3).
c) reported in ppm downfield from internal DSS.
d) Analysis in the aminocyclitol portion was supported by simulation.

Table 3. CMR parameters of 4-N-(2-aminoethyl)-fortimicin B (**9e**)[a,b,c].

	Free base	Hydrochloride	β-shift
C-1′	100.6	96.8	3.5
C-2′	50.5	51.8	
C-3′	27.0	21.6	5.4
C-4′	27.3	26.3	
C-5′	75.1	70.9	4.2
C-6′	50.3	49.4	
CH_3-6′	18.6	15.4	3.2
C-1	54.9	53.2	
C-2	71.8	65.7	6.1
C-3	76.9	71.5	5.4
C-4	60.7	63.2	
C-5	71.3	67.6	3.7
C-6	80.6	76.0	4.6
OCH_3	57.5	56.9	
NCH_3	40.6	40.3	
4-N-$CH_2CH_2NH_2$	39.2	35.4	3.8
4-N-$CH_2CH_2NH_2$	58.0	52.8	5.2

a) measured in D_2O, dioxane (67.4 ppm) as an internal standard.
b) reported in ppm downfield from TMS.
c) Assignment of resonances and their correlation to proton resonances were performed with off-resonance and single proton decoupling experiments (*cf.* Table 2).

the same as the ω-aminoacyl derivatives[5] **8e** and **8g**, (compound **8f** is decomposed under assay conditions). The ω-amino-2-hydroxyalkyl derivatives (**9l**~**9q**) are more potent than ω-aminoalkyl derivatives of the same chain length, and the most potent compounds are 4-amino-2-hydroxybutyl derivatives (**9l**, **9m** and **9n**). Elongation or shortening of the chain length showed marked decrease in activity. Such chain length dependency of the activity seems stricter than ω-amino-2-hydroxy-acyl[6] or -alkyl[7] derivatives of kanamycin A. Among the compounds prepared in this study, **9e**, **9l**, **9m** and **9n** have the most potent activity, although those antibacterial spectra are almost the same as that of fortimicin A.

Experimental

Mass spectra were obtained on a JEOL JMS-01SG-2 spectrometer at 30 eV. PMR and CMR spectra were measured on a JEOL PS-100 or a JEOL PFT-100A spectrometer in the CW and FT mode in D_2O solution. Chemical shifts of PMR are reported in ppm downfield from internal DSS. Chemical shifts of CMR were measured from internal dioxane (67.4 ppm) and are reported in ppm downfield from TMS. IR spectra were obtained on a Shimazu IR-27G spectrometer. Elemental analyses were performed on a Yanagimoto CHN Corder MT-1. Optical rotations were measured with a Perkin-Elmer model 141 polarimeter. Reported pD values are uncorrected pH meter readings of deuterated solution.

Table 4. Antibacterial spectra of 4-N-substituted fortimicin B (Minimum inhibitory concentration, mcg/ml, pH 8.0).

Test organisms*	SA	BS	EC	PV	SS	ST	KP
1	0.04	0.04	0.16	0.32	0.63	0.16	0.16
2	12.5	12.5	25	25	50	12.5	50
3	0.16	0.32	0.08	0.63	1.25	0.32	0.63
8a	12.5	50	50	200	>200	50	>200
8b	6.25	12.5	6.25	100	50	12.5	25
8c	100	25	>100	>200	>200	>200	>200
8d	1.25	5	1.25	2.5	5	1.25	5
8e	0.32	0.16	1.25	1.25	2.5	0.63	2.5
8g	>20	>20	>20	>20	>20	>20	>20
9a	1.56	3.13	3.13	6.25	6.25	3.13	50
9b	3.13	12.5	6.25	12.5	12.5	6.25	100
9c	12.5	25	25	100	25	12.5	>200
9d	25	200	100	>200	100	100	>200
9e	0.16	0.16	0.32	0.63	1.25	0.32	0.63
9f	0.04	0.32	0.16	1.25	5	1.25	5
9g	1.25	2.5	5	10	20	1.25	80
9h	0.32	0.32	1.25	2.5	2.5	1.25	5
9i	1.25	0.63	5	10	5	2.5	20
9j	1.25	>80	5	10	10	1.25	40
9k	0.63	1.25	1.25	5	5	1.25	5
9l	0.04	0.04	0.16	0.32	1.25	0.16	0.32
9m	0.04	0.04	0.08	0.32	0.63	0.08	0.32
9n	0.08	0.04	0.16	0.32	0.63	0.16	0.63
9o	0.16	0.32	2.5	1.25	2.5	0.63	2.5
9p	0.16	0.63	2.5	2.5	2.5	0.63	5
9q	0.32	0.32	1.25	2.5	5	1.25	10

* SA: *Staphylococcus aureus* KY4279 ATCC6538P, BS: *Bacillus subtilis* KY4273, EC: *Escherichia coli* KY4271 ATCC26, PV: *Proteus vulgaris* KY4277 ATCC6897, SS: *Shigella sonnei* KY4281 ATCC9290, ST: *Salmonella typhosa* KY4278 ATCC9992, KP: *Klebsiella pneumoniae* KY4275 ATCC10031.

While 4-N-acylfortimicin B derivatives (**8**) were prepared by the method of the Abbott group[5], 4-N-alkyl derivatives (**9**) were prepared by three methods (methods A, B and C). For each method used there is given a representative procedure which is shown below.

4-N-Hydantoylfortimicin B (fortimicin C) (**3**)

To an ice-cooled, stirred solution of hydantoic acid 71 mg (0.6 mmol) and 1-hydroxybenzotriazole 81 mg (0.6 mmol) in dimethylformamide 5 ml was added dicyclohexylcarbodiimide 124 mg (0.6 mmol), and stirred for 1 hour under ice-cooling. To the reaction mixture was added 1,2′,6′-tri-N-benzyloxycarbonylfortimicin B[5] 375 mg (0.5 mmol), and the solution was stirred for 18 hours at room temperature. To the reaction mixture were added 0.2 N hydrochloric acid in methanol (prepared by diluting 2 ml of conc. hydrochloric acid to 120 ml with methanol) 15 ml and 10% palladium on carbon *ca* 50 mg. Hydrogen gas was bubbled through the reaction mixture for 16 hours at room temperature. The catalyst was removed by filtration and methanol was evaporated under reduced pressure. To the residue was added water 50 ml, insoluble material was removed by filtration and the filtrate was adjusted to pH 6 with 1 N sodium hydroxide. The resulting solution was chromatographed on a column of

Table 5. Antibacterial spectra of 4-N-substituted fortimicin B (Minimum inhibitory concentration, mcg/ml, pH 7.2).

Test organisms	Inactivating enzyme	1	3	8d	9e	9l	9m	9n
S. aureus FDA 209P		0.78	3.12	3.12	0.78	0.4	0.78	0.4
S. aureus Smith		0.78	6.25	3.12	0.78	0.4	0.4	0.4
E. coli NIHJC-2		3.12	12.5	12.5	3.12	3.12	1.56	3.12
E. coli 3100		6.25	12.5	12.5	6.25	12.5	12.5	12.5
S. enteritidis G-14		6.25	25	25	25	3.12	3.12	6.25
S. sonnei ATCC9290		6.25	25	25	6.25	3.12	6.25	6.25
P. aeruginosa BMH# 1		12.5	100	50	12.5	6.25	12.5	12.5
E. coli 76-2	ANT(2″)	3.12	12.5	6.25	3.12	6.25	6.25	3.12
E. coli 57R/W677	ANT(2″)	12.5	25	25	12.5	12.5	12.5	12.5
E. coli R12 Z-388	ANT (2″)	12.5	6.25	25	6.25	12.5	6.25	12.5
E. coli R17 Z-343	AAC(6′)	1.56	3.12	6.25	0.78	3.12	3.12	1.56
E. coli R18 KY8321	ANT(2″)	3.12	6.25	6.25	3.12	6.25	12.5	6.25
E. coli R19 KY8348	AAC(3)-I	>100	>100	>100	>100	>100	>100	>100
E. coli R20 KY8349	APH(3′)-I	3.12	12.5	12.5	3.12	1.25	1.25	3.12
P. aeruginosa UCLA4184		25	50	100	12.5	25	50	25
P. aeruginosa R4 KY8511	AAC(3)-I	>100	>100	>100	>100	>100	>100	>100
P. aeruginosa R5 KY8512	APH(3′)-I, II	12.5	50	50	12.5	6.25	12.5	12.5
P. aeruginosa R9 KY8516	AAC(6′)	50	>100	100	25	25	50	50
Providencia sp. 164	AAC(2′)-II	25	100	100	12.5	25	25	25
S. marcescens 1065	AAC(6′)	6.25	50	50	6.25	6.25	6.25	6.25
K. pneumoniae 3020 Y-60	ANT(2″)	12.5	100	>100	50	12.5	12.5	25

Amberlite CG-50 (NH_4^+) 10 ml, eluting with 0.15 N ammonium hydroxide. Fractions containing the product were combined and evaporated under reduced pressure to give **3** 135 mg (62%), which was identical with fortimicin C[4] obtained by fermentation in all respects.

4-N-(2-Aminoethyl)fortimicin B (**9e**): Method A

Fortimicin A 200 mg (0.49 mmol) was suspended in tetrahydrofuran 10 ml and to the mixture was added 1 M solution of diborane in tetrahydrofuran 10 ml. The reaction mixture was stirred for 2 hours at room temperature. After excess diborane was decomposed by adding a small amount of water, the reaction mixture was evaporated to dryness. To the residue was added 80% hydrazine solution 20 ml, and the solution was refluxed for 2 hours. After evaporation of the solvent under reduced pressure, the residue was dissolved in water 10 ml, and the solution was adjusted to pH 6 with 1 N hydrochloric acid. The resulting solution was chromatographed on a column of Amberlite CG-50 (NH_4^+) 10 ml, eluting with 0.5 N ammonium hydroxide. Fractions containing the product were combined and evaporated under reduced pressure to give **9e** 146 mg (76%). MS (*m/e*): 392 $(M+H)^+$, 341, 282, 278, 250, 143, 126. PMR and CMR parameters are presented in Tables 2 and 3, respectively.

Aqueous solution of **9e** was adjusted to pH 2 with 5 N sulfuric acid and was added to 10 fold volume of ethanol. The resulting precipitate was collected, washed with ethanol and dried to give sulfate.

Anal. Calcd. for $C_{17}H_{37}N_5O_5 \cdot 2.5H_2SO_4 \cdot C_2H_5OH \cdot H_2O$: C 32.56, H 7.21, N 9.99.
Found: C 32.55, H 7.19, N 9.93.

$[\alpha]_D^{25}$ +77.8° (*c* 1.0, water).

4-N-[(*S*)-4-Amino-2-hydroxybutyl] fortimicin B (**9l**): Method B

To a solution of 1,2′,6′-tri-N-benzyloxycarbonyl-4-N-[(*S*)-4-benzyloxycarbonylamino-2-hydroxybutyryl] fortimicin B[5] (**7**, R′=CH(OH)$(CH_2)_2$NHCbz) 350 mg (0.36 mmol) in methanol 10 ml were added trifluoroacetic acid 0.2 ml and 10% palladium on carbon *ca* 50 mg. Hydrogen gas was

bubbled through the solution for 16 hours at room temperature. The catalyst was removed by filtration and the filtrate was evaporated to dryness to give trifluoroacetate of 4-N-[(*S*)-4-amino-2-hydroxybutyryl]fortimicin B[5] (**8**, $R'=CH(OH)(CH_2)_2NH_2$). To the trifluoroacetate were added tetrahydrofuran 10 ml and 1 M diborane solution in tetrahydrofuran 5 ml and the reaction mixture was stirred for 2.5 hours at room temperature. After excess diborane was decomposed by adding a small portion of water, the reaction mixture was evaporated to dryness. The residue was treated by hydrazine and chromatographed on a column of Amberlite CG-50 (NH_4^+) as above to give **9l*** 85 mg (54%). MS (*m/e*): 436 $(M+H)^+$, 294, 219, 143, 126. PMR (D_2O, pD=10.7): 1.05 (3H, d, J=6.6 Hz, CH_3-6′), 1.2~1.9 (6H, m, CH_2-3′,4′,3″), 2.44 (3H, s, NCH_3), 3.43 (3H, s, OCH_3), 4.96 (1H, d, J=3.7 Hz, H-1′). CMR (D_2O, pD=12.5): 18.7 (CH_3-6′), 27.0 (C-3′), 27.3 (C-4′), 37.9 (C-3″), 38.3 (C-4″), 40.5 (NCH_3), 50.4 (C-6′), 50.5 (C-2′), 54.9 (C-1), 57.4 (OCH_3), 61.5 (C-4), 62.0 (C-1″), 67.4 (C-2″), 70.8 (C-5), 71.7 (C-2), 75.1 (C-5′), 76.7 (C-3), 80.6 (C-6), 100.6 (C-1′).

4-N-[(*S*)-4-Amino-2-hydroxybutyl]fortimicin B (**9l**) and 4-N-[(*S*)-2-Hydroxy-4-methylaminobutyl]-fortimicin B (**9m**): Method C

To a solution of 1,2′,6′-tri-N-benzyloxycarbonyl-4-N-[(*S*)-4-benzyloxycarbonylamino-2-hydroxybutyryl]fortimicin B (**7**, $R'=CH(OH)(CH_2)_2NHCbz$) 606 mg (0.62 mmol) in tetrahydrofuran 10 ml was added 1 M diborane solution in tetrahydrofuran 10 ml, and the solution was stirred for 2 hours at room temperature. After excess diborane was decomposed by adding a small amount of water, the reaction mixture was evaporated to dryness. The residue was dissolved in 0.2 N hydrochloric acid in methanol 20 ml, and stirred for 18 hours at room temperature. The solution was evaporated under reduced pressure. Then the residue was dissolved in the mixture of ethylacetate 20 ml and 5% sodium hydrogen carbonate 10 ml. The organic layer was washed with water, dried over sodium sulfate and solvent was evaporated. The resulting residue was chromatographed on a column of silica gel 25 g. Elution with chloroform - methanol (95: 5) gave 1,2′,6′-tri-N-benzyloxycarbonyl-4-N-[(*S*)-4-benzyloxycarbonylamino-2-hydroxybutyl]fortimicin B (**10**, $R'=CH(OH)(CH_2)_2NHCbz$) 231 mg. Catalytic hydrogenolysis of this compound, followed by chromatography using Amberlite CG-50 (NH_4^+), afforded **9l** 61 mg (25%), which was identical with the preparation obtained as above in method B. Further elution of the silica column with chloroform - methanol (4: 1) gave 1,2′,6′-tri-N-benzyloxycarbonyl-4-N-[(*S*)-2-hydroxy-4-methylaminobutyl]fortimicin B (**10**, $R'=CH(OH)(CH_2)_2NHCH_3$) 191 mg. Catalytic hydrogenolysis of this compound, followed by chromatography using Amberlite CG-50 (NH_4^+), gave **9m**** 79 mg (29%). MS (*m/e*): 450 $(M+H)^+$, 336, 308, 143, 126. PMR (D_2O, pD=10.8): 1.03 (3H, d, J=6.6 Hz, CH_3-6′), 1.2~1.9 (6H, m, CH_2-3′,4′,3″), 2.39 (3H, s, NCH_3-4″), 2.43 (3H, s, NCH_3-4), 3.43 (3H, s, OCH_3), 4.96 (1H, d, J=3.7 Hz, H-1′). CMR (D_2O, pD=11.9): 18.6 (CH_3-6′), 27.1 (C-3′), 27.3 (C-4′), 34.4 (C-3″), 35.4 (NCH_3-4″), 40.4 (NCH_3-4), 48.0 (C-4″), 50.3 (C-6′), 50.5 (C-2′), 54.9 (C-1), 57.3 (OCH_3), 61.5 (C-4), 61.8 (C-1″), 68.0 (C-2″), 70.8 (C-5), 71.7 (C-2), 75.2 (C-5′), 76.5 (C-3), 80.5 (C-6), 100.6 (C-1′).

Acknowledgements

We are indebted to Messrs. K. KITAURA and S. SATO of Pharmaceutical Research Laboratory, Kyowa Hakko Kogyo Co., for the antibacterial data. We acknowledge the collaboration of Dr. J. B. MCALPINE and his associates of Abbott Laboratories, U.S.A.

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* The 4-N-substituent of **9l** was numbered as follows: 4-N-$\overset{1''}{C}H_2\overset{2''}{C}H(OH)\overset{3''}{C}H_2\overset{4''}{C}H_2NH_2$.

** The 4-N-substituent of **9m** was numbered as follows: 4-N-$\overset{1''}{C}H_2\overset{2''}{C}H(OH)\overset{3''}{C}H_2\overset{4''}{C}H_2NHCH_3$.

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