DEACETYLATION EFFECT OF *N,N*-DIMETHYLVANCOSAMINE IN SAPTOMYCINS D AND E

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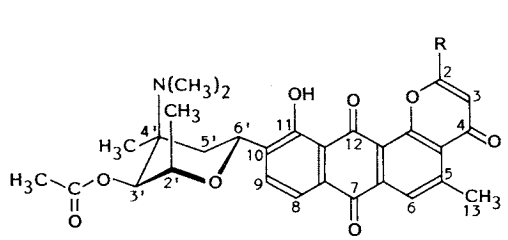
We previously reported two novel pluramycin-group antibiotics, saptomycins D and E, isolated from the fermentation broth of *Streptomyces* sp. HP530[1]. These compounds are effective against murine Meth A fibrosarcoma. Saptomycins D and E are deangolosaminyl pluramycin-group antibiotics, having the sugar *N,N*-dimethylvancosamine at the C-10 position as in ankinomycin[2] (Fig. 1). Pluramycin A[3], neopluramycin[4], kidamycin[5], hedamycin[6], PD121222[7], epoxykidamycin[8] and rubiflavins[9] possess another sugar, angolosamine, at C-8. The structures of pluramycin-group compounds were investigated in detail by several groups. The structure of kidamycin was determined on the basis of the X-ray analysis of triacetylmethoxykidamycin bis(methylammonium iodide) by FURUKAWA *et al.*[10,11]. As a result of this analysis, the absolute configurations of the two sugars were determined to be 2*R*,3*S*,4*R*,6*R* in angolosamine at C-8, and 2*S*,3*S*,4*S*,6*R* in *N,N*-dimethylvancosamine at C-10. The conformations of these sugars in the crystals were also determined and found to be a chair form in angolosamine and a boat form in *N,N*-dimethylvancosamine. SÉQUIN and FURUKAWA reported that the conformations of the sugars in kidamycin and hedamycin were the same in solution as in the crystals of triacetylmethoxykidamycin bis(methylammonium iodide). They suggested that *N,N*-dimethylvancosamine altered its conformation by acetylation of its 3-OH group, too[6]. These antibiotics, however, possessed two similar aminosugars, angolosamine and *N,N*-dimethylvancosamine, which gave complex spectra in ^{1}H NMR. The conformational change in *N,N*-dimethylvancosamine with acetylation at the 3-OH was not confirmed.

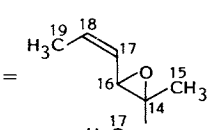
In this paper, we report the determination of the conformation of 3-acetyl-*N,N*-dimethylvancosamine in saptomycins D and E, in solution compared with their deacetyl derivatives, and the influence of acetylation at 3-OH on the biological properties.

Saptomycins D and E differed only in substituents at C-2 (Fig. 1). The aminosugar at C-10 was *N,N*-dimethylvancosamine acetylated at 3-OH in both compounds. This substituent was found in pluramycin A and neopluramycin, but most of other related compounds, kidamycin, hedamycin, rubiflavins, PD121222 and ankinomycin, had the sugar with a free 3-OH group. This acetyl group affected the conformation of *N,N*-dimethylvancosamine, and this alteration was expected to induce changes in the role of their biological activities. Saptomycins D and E were deacetylated quantita-

Fig. 1. Structures of saptomycin D (**1a**), E (**2a**) and their deacetyl derivatives (**1b** and **2b**).



Saptomycin D (**1a**) R=



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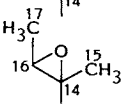
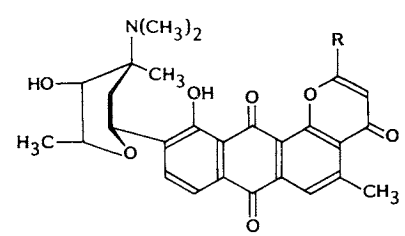
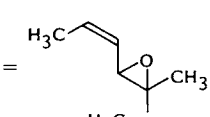




Deacetylsaptomycin D (**2a**) R=



Deacetylsaptomycin E (**2b**) R=

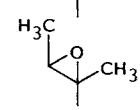
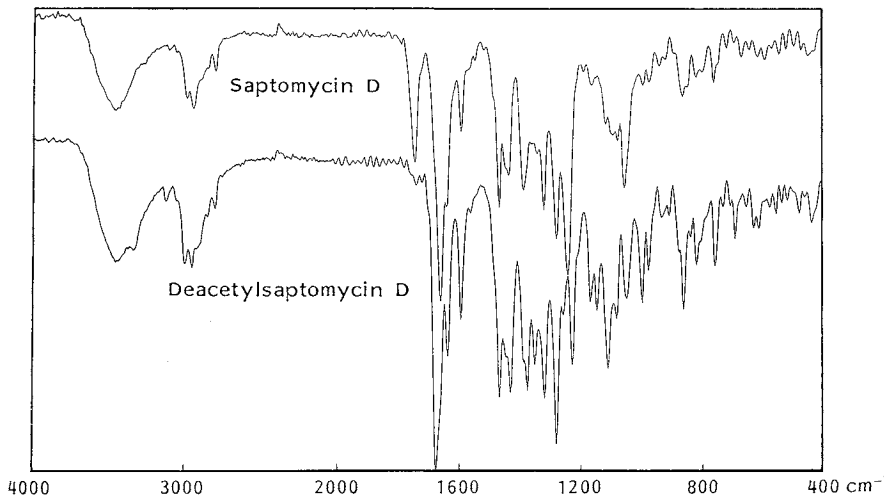


Fig. 2. IR spectra of saptomycin D (**1a**) and deacetylsaptomycin D (**2a**).



tively when saptomycins D and E were stirred in CH_3OH at room temperature for 48 hours.

Deacetylsaptomycin D had the molecular formula of $C_{33}H_{35}NO_8$ as determined by FAB-MS (*m/z* 574, $(M+H)^+$) and high resolution FAB-MS (*m/z* 574.2408 calcd for $C_{33}H_{36}NO_8$: 574.2441) spectra. The IR spectrum showed the disappearance of a strong absorption band at 1745 cm^{-1} from the acetyl carboxyl group of saptomycin D (Fig. 2). ^1H NMR and ^{13}C NMR data on deacetylsaptomycin D (Fig. 3 and Table 1) indicated that the removal of only the acetyl substituent cannot cause drastic changes in the chemical shift of the sugar with deacetylation.

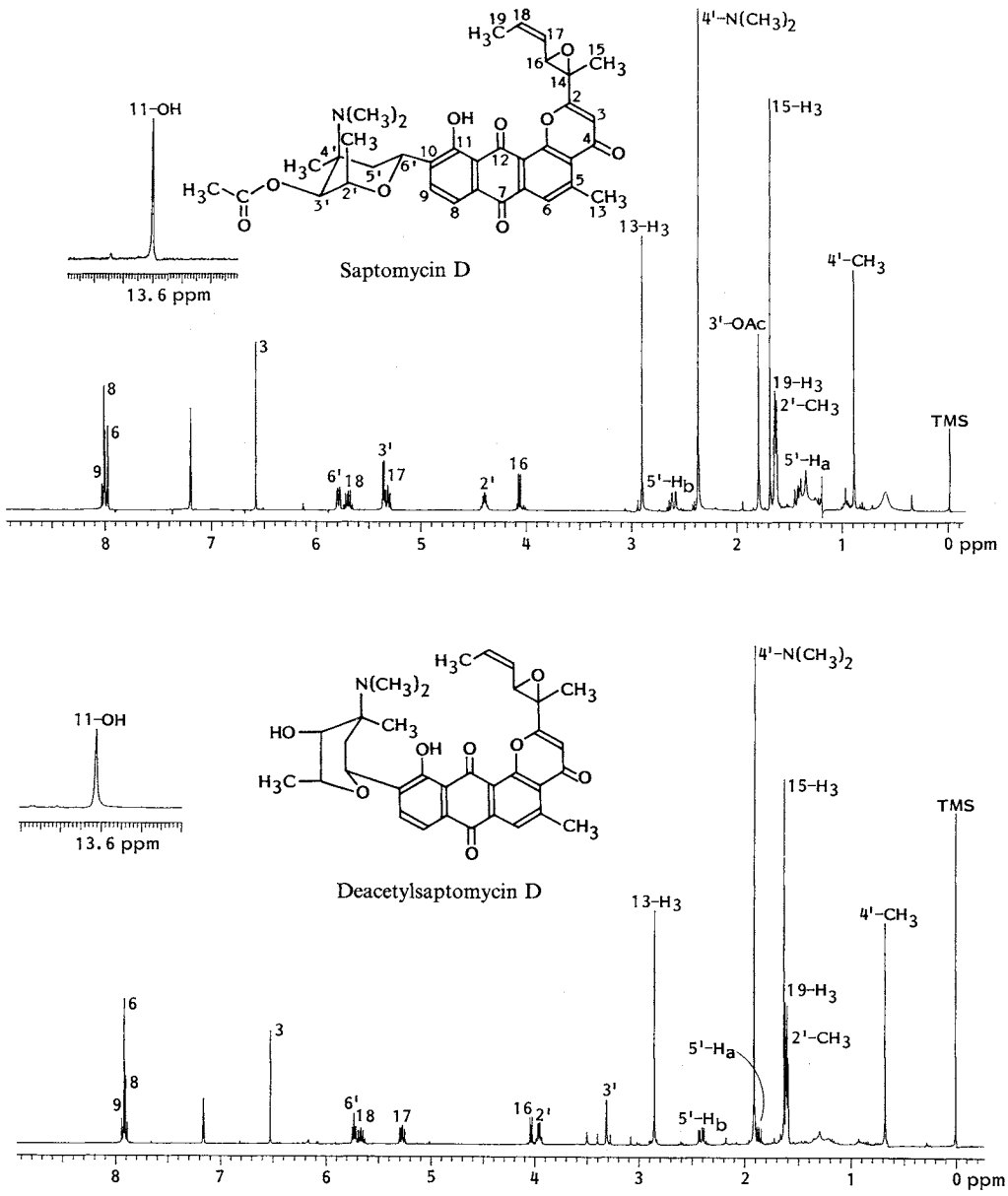
(a) The chemical shifts of some protons of the sugar moiety showed an upfield shift: 2′-H (0.44 ppm), 3′-H (2.05 ppm), 5′-H_b (0.19 ppm), 6′-H (0.06 ppm), 2′-CH_3 (0.02 ppm), 4′-CH_3 (0.21 ppm) and 4′-$N(CH_3)_2$ (0.46 ppm), while that of 5′-H_a showed a downfield shift of 0.45 ppm.

(b) C-2′ (−1.8 ppm), C-3′ (−5.7 ppm), C-5′ (−5.9 ppm), C-6′ (+3.2 ppm), 2′-CH_3 (+2.7 ppm), 4′-CH_3 (−0.5 ppm) and 4′-$N(CH_3)_2$ (−2.7 ppm) changed their chemical shifts in the ^{13}C NMR data with deacetylation.

SÉQUIN and FURUKAWA *et al.* reported that the acetylation of kidamycin and isokidamycin, the only configurational isomers at the linkage of a *N,N*-dimethylvancosamine substituent, produced different acetylation shifts of *N,N*-dimethylvancosamine in ^1H NMR and ^{13}C NMR spectra[5,6]. The acetylation shifts of kidamycin were as large as the deacetylational shifts of saptomycin D, while isokidamycin showed small shifts due to acetylation. The value of the acetylation shifts of kidamycin and those of deacetylation of saptomycin D were almost opposite: the acetylation shifts of kidamycin to kidamycin triacetate; 2′-H (+0.25 ppm), 3′-H (+1.85 ppm), 6′-H (−0.02 ppm), 2′-CH_3 (−0.08 ppm), 4′-CH_3 (+0.22 ppm) and 4′-$N(CH_3)_2$ (+0.04 ppm) in ^1H NMR data; C-2′ (+3.0 ppm), C-3′ (+4.9 ppm), C-4′ (+0.5 ppm), C-5′ (+8.4 ppm), C-6′ (−4.7 ppm), 2′-CH_3 (−2.9 ppm), 4′-CH_3 (+1.5 ppm) and 4′-$N(CH_3)_2$ (+2.3 ppm) in ^{13}C NMR (SÉQUIN *et al.* have reported reversed assignments for two carbons at C-3′ and C-6′, confirmed by the ^{13}C-^1H HETCOR experiment). As a result of the analyses, the 3′-acetyl substituent induced conformational changes in saptomycin D and its similar compounds, but the configurational isomer at the sugar linkage, isokidamycin, did not have its conformation influenced by the 3′-acetyl substituent.

The determination of the conformations of the *N,N*-dimethylvancosamine moiety was based on NOESY experiments and the value of ^1H-^1H coupling constant in ^1H NMR data. The summary of these experiments is shown in Fig. 4. The sugar of saptomycin D had a chair conformation. The proton at C-6 (5.79 ppm) exhibited an ABX system with two vicinal protons at C-5 (1.42 ppm and 2.60 ppm). The coupling constants of $J_{5'\text{-}H_a/6'\text{-}H}$ = 10.1 Hz and $J_{5'\text{-}H_b/6'\text{-}H}$ = 3.1 Hz meaned the relation between 6′-H and 5′-H_a to be *axial-axial* and 6′-H and 5′-H_b to be *axial-equatorial*. 2′-H and 3′-H had a vicinal coupling constant of $J_{2'\text{-}H/3'\text{-}H}$ = 5.2 Hz.

Fig. 3. ^{1}H NMR spectra of saptomycin D (**1a**) and deacetylsaptomycin D (**2a**) (C_6D_6, 400 MHz).



This behavior of the ^{1}H-^{1}H coupling pattern on the *N*,*N*-dimethylvancosamine moiety of saptomycin D was very similar to that of altromycins[1,2]. Further, the NOESY experiment supported the conformational similarity of the common sugar moiety between saptomycin D and altromycins. 1,3,5-Triaxial cross peaks between 2'-CH_3, 4'-$N(CH_3)_2$ and 6'-H and a 1,3-diaxial cross peak between 5'-H_a and 3'-H were observed in this NOESY experiment. On the other hand, deacetylsaptomycin D had a boat-like conformation as reported for kidamycin[5], hedamycin[6] and ankinomycin[2]. The values of the coupling constants between 5'-H_a, 5'-H_b and 6'-H ($J_{5'\text{-}H_a/6'\text{-}H}$ = 7.3 Hz, $J_{5'\text{-}H_b/6'\text{-}H}$ = 6.1 Hz and $J_{5'\text{-}H_a/5'\text{-}H_b}$ = 13.7 Hz) suggested a boat-like conformation rather than a chair, and analysis of vicinally coupled protons at C-2' and C-3' ($J_{2'\text{-}H/3'\text{-}H}$ = 2.8 Hz) supported this suggestion. Nuclear overhauser effects were observed with 2'-H and 3'-H, 2'-CH_3 and 6'-H, 5'-H_a and 6'-H,

Table 1. ^{13}C NMR chemical shifts[a] of saptomycin D (**1a**), E (**1b**) and their deacetyl derivatives (**2a** and **2b**).

Carbon	Chemical shifts (δ) in ppm			
	1a	**2a**	**1b**	**2b**
C-2	167.1 s	167.1 s	167.8 s	167.9 s
C-3	109.9 d	109.9 d	109.5 d	109.4 d
C-4	178.4 s	178.3 s	178.3 s	178.3 s
C-4a	126.6 s	126.6 s	126.7 s	126.7 s
C-5	149.7 s	149.6 s	149.8 s	149.7 s
C-6	125.8 d	125.7 d	125.9 d	125.8 d
C-6a	136.2 s	136.2 s	136.2 s	136.2 s
C-7	181.3 s	181.3 s	181.3 s	181.3 s
C-7a	131.1 s	131.1 s	131.1 s	131.1 s
C-8	119.4 d	119.2 d	119.4 d	119.2 d
C-9	133.6 d	133.4 d	133.6 d	133.3 d
C-10	140.7 s	141.5 s	140.7 s	141.5 s
C-11	159.4 s	159.7 s	159.4 s	159.7 s
C-11a	116.3 s	116.5 s	116.3 s	116.5 s
C-12	188.0 s	187.9 s	188.1 s	187.9 s
C-12a	119.9 s	119.9 s	119.9 s	119.2 s
C-12b	156.3 s	156.4 s	156.3 s	156.3 s
C-13	24.0 q	24.0 q	24.0 q	24.0 q
C-14	59.1 s	59.0 s	57.4 s	57.4 s
C-15	14.4 q	14.4 q	13.6 q	13.6 q
C-16	61.6 d	61.5 d	61.7 d	61.8 d
C-17	124.1 d	124.0 d	13.8 q	13.7 q
C-18	133.4 d	133.3 d	—	—
C-19	13.7 q	13.7 q	—	—
C-2′	70.8 d	69.0 d	70.8 d	69.0 d
C-3′	76.9 d	71.2 d	76.9 d	71.2 d
C-4′	58.0 s	58.0 s	58.0 s	58.0 s
C-5′	43.0 t	37.1 t	43.0 t	37.0 t
C-6′	64.1 d	67.3 d	64.1 d	67.4 d
2′-CH_3	14.7 q	17.4 q	14.7 q	17.4 q
4′-CH_3	13.8 q	13.3 q	13.8 q	13.3 q
4′-$N(CH_3)_2$	39.7 q	37.0 q	39.7 q	37.0 q
3′-OCO–	169.7 s	—	169.6 s	—
3′-OCO–CH_3	20.7 q	—	20.6 q	—

[a] δ from TMS in C_6D_6, 100 MHz.

5′-H_b and 6′-H and 3′-H and 4′-CH_3 in the NOESY spectrum of deacetylsaptomycin D. The stereochemistry satisfying the preceding requirements was in accord with a flexible twist conformation such as the boat-type as in the case of ankinomycin *et al.* As a result of this investigation, we concluded that the conformation of the *N,N*-dimethylvancosamine moiety of saptomycin D was the chair form, which was altered upon deacetylation to a boat-like form, although the configuration was not changed.

Deacetylsaptomycin E (as $C_{31}H_{33}NO_8$) was derived under the same conditions as in the case of deacetylsaptomycin D. This deacetyl derivative showed a change of its aminosugar into a boat-like form; hence deacetylsaptomycins D and E were the same structure except for side chains at C-2 (Fig. 1).

As shown in Table 2, saptomycins D and E and deacetylsaptomycins D and E strongly inhibited cell growth of murine Meth A fibrosarcoma *in vitro*. The IC_{50} values of this experiment suggested that the deacetylation C-3′ enhanced the cytocidal activity against Meth A approximately 2-fold, and a 1,2-epoxy-1-methyl-propyl substituent at C-2 as in saptomycin E showed stronger activity *in vitro* than a 1,2-epoxy-1-methyl-3-(*Z*)-pentenyl substit-

Table 2. Cytotoxicity against Meth A fibrosarcoma cell line of saptomycin D (**1a**), E (**1b**) and their deacetyl derivatives (**2a** and **2b**).

Compound	IC_{50} (μg/ml)
1a	123.9
2a	52.5
1b	46.8
2b	27.7

120 hours culture in RPMI1640 10% FBS, MTT assay, IC_{50} value was calculated with Probit's method.

Fig. 4. Summary of ^1H-^1H coupling constants and NOESY data of *N,N*-dimethylvancosamine.

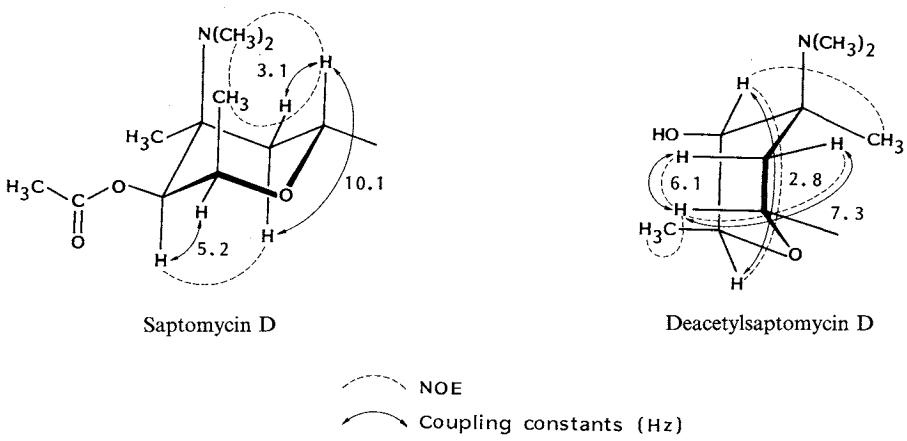


Table 3. Antitumor activities of saptomycin D (**1a**), E (**1b**) and their deacetyl derivatives (**2a** and **2b**) against Meth A fibrosarcoma in mice.

Dose (mg/kg/day)	Antitumor activity T/C (%)			
	1a	**2a**	**1b**	**2b**
5.0	—	—	>192	—
2.5	—	—	>196	83
1.25	—	—	127	>187
0.625	—	—	104	183
0.5	>215	185	—	—
0.3125	—	—	—	107
0.25	192	123	—	—
0.125	123	108	—	—
0.0625	108	92	—	—

Six mice (CDF_1, female) were inoculated ip with 1×10^6 Meth A cells on day 0. Each sample dissolved in CH_3OH-PBS(−) (1:9) was administered ip on days 1~4. The increase in life span was indicated as T/C (%).

uent as in saptomycin D. These compounds were effective against Meth A *in vivo* as shown in Table 3. The result of this experiment led to an interesting observation. The influences of the deacetylation and the difference in the side chain at C-2 showed an opposite tendency. The antitumor activity of saptomycin D was the highest of all the test compounds. Furthermore, the side chain as in saptomycin D showed greater effect against Meth A *in vivo* than that of saptomycin E. The LD_{50} values (ip) of saptomycin D and deacetylsaptomycin D were 45 mg/kg and 40 mg/kg, respectively; therefore, deacetylation at C-3′ showed no effect on the LD_{50} value of saptomycin D.

Experimental

General

NMR spectra were recorded on a Varian VXR400 spectrometer using TMS as an internal standard. FAB-MS and HRFAB-MS were taken on a JEOL JMS-SX102 spectrometer. IR spectra were measured on a Hitachi 270-30 spectrometer. Optical rotations were measured on a Horiba SEPA-200 spectrometer and UV spectra were recorded on a Hitachi 200-20 spectrometer.

Saptomycin D (1a)

The reported procedure[1] gave saptomycin D of yellowish red powder: $[\alpha]_D^{20}$ +152° (*c* 0.1, $CHCl_3$); UV λ_{max}^{MeOH} nm (ε) 246 (51,600), 265 (sh 29,000), 418 (9,800); FAB-MS *m/z* 616 $(M+H)^+$; HRFAB-MS *m/z* 616.2556 ($(M+H)^+$, calcd for $C_{35}H_{38}NO_9$: 616.2546); IR spectrum shown as Fig. 2; ^1H NMR (C_6D_6, 400 MHz) δ 13.60 (1H, s, 11-OH), 8.02 (1H, d, *J*=7.9 Hz, 9-H), 7.99 (1H, d, *J*=7.9 Hz, 8-H), 7.98 (1H, s, 6-H), 6.58 (1H, s, 3-H), 5.79 (1H, dd, *J*=3.1 and 10.1 Hz, 6′-H), 5.70 (1H, ddq, *J*=1.2, 7.1 and 11.2 Hz, 18-H), 5.36 (1H, d, *J*=5.2 Hz, 3′-H), 5.32 (1H, ddq, *J*=1.8, 7.6 and 11.2 Hz, 17-H), 4.40 (1H, dq, *J*=5.2 and 6.8 Hz, 2′-H), 4.06 (1H, dd, *J*=1.2 and 7.6 Hz, 16-H), 2.90 (3H, s, 13-H_3), 2.60 (1H, dd, *J*=3.1 and 14.0 Hz, 5′-H_b), 2.37 (6H, s, 4′-$N(CH_3)_2$), 1.80 (3H, s, 3′-OAc), 1.68 (3H, s, 15-H_3), 1.63 (3H, d, *J*=6.8 Hz, 2′-CH_3), 1.63 (3H, dd, *J*=1.8 and 7.1 Hz, 19-H_3), 1.42 (1H, dd, *J*=10.1 and 14.0 Hz, 5′-H_a), 0.89 (3H, s, 4′-CH_3); ^{13}C NMR data shown as Table 1.

Saptomycin E (1b)

The reported procedure[1] gave saptomycin E of yellow powder: $[\alpha]_D^{20}$ +147° (*c* 0.1, $CHCl_3$); UV λ_{max}^{MeOH} nm (ε) 244 (47,200), 265 (sh 28,000), 425 (10,800); FAB-MS *m/z* 590 $(M+H)^+$; HRFAB-MS *m/z* 590.2398 ($(M+H)^+$, calcd for $C_{33}H_{36}NO_9$: 590.2390); IR ν_{max} (KBr) cm^{-1} 1740, 1665, 1642, 1590; ^1H NMR (C_6D_6, 400 MHz) δ 13.73 (1H, s, 11-OH), 7.98 (1H, d, *J*=7.9 Hz, 9-H), 7.97 (1H, s, 6-H), 7.95 (1H, d, *J*=7.9 Hz, 8-H), 6.47 (1H, s, 3-H), 5.74 (1H, dd, *J*=2.5 and 10.0 Hz, 6′-H), 5.30 (1H, d, *J*=5.1 Hz, 3′-H), 4.34 (1H, dq, *J*=5.1 and 6.6 Hz, 2′-H), 2.99 (1H, q, *J*=5.4 Hz, 16-H), 2.86 (3H, s, 13-H_3), 2.58 (1H, dd, *J*=2.5 and 14.0 Hz, 5′-H_b), 2.32 (6H, s, 4′-$N(CH_3)_2$), 1.76 (3H, s, 3′-OAc), 1.58 (3H, d, *J*=6.6 Hz, 2′-CH_3), 1.56 (3H, s, 15-H_3), 1.40 (1H, dd, *J*=10.0 and 14.0 Hz, 5′-H_a), 0.99 (3H, d, *J*=5.4 Hz, 17-H_3), 0.84 (3H, s, 4′-CH_3); ^{13}C NMR data shown as Table 1.

Deacetylsaptomycin D (2a)

14.3 mg of saptomycin D was dissolved in 28 ml of methanol and stirred at room temperature for 48 hours. The resulting methanol solution was concentrated *in vacuo*. The yellowish red powder obtained almost quantitatively was purified by a silica gel preparative TLC plate (Silica gel 60, F_{254s}, No. 13794, Merck) developed by the solvent system of chloroform-methanol (9:1). 12.3 mg of deacetylsaptomycin D was yielded as yellowish red powder: $[\alpha]_D^{20}$ +271° (*c* 0.1, $CHCl_3$); UV λ_{max}^{MeOH} nm (ε) 240 (46,500), 263 (sh 28,800), 415 (9,700); FAB-MS *m/z* 574 $(M+H)^+$; HRFAB-MS *m/z* 574.2408 ($(M+H)^+$, calcd for $C_{33}H_{36}NO_8$: 574.2441); IR spectrum shown as Fig. 2; ^1H NMR (C_6D_6, 400 MHz) δ 13.61 (1H, s, 11-OH), 7.93 (1H, d, *J*=8.0 Hz, 9-H), 7.92 (1H, s, 6-H), 7.90 (1H,

d, J=8.0 Hz, 8-H), 6.52 (1H, s, 3-H), 5.73 (1H, dd, J=6.1 and 7.3 Hz, 6'-H), 5.66 (1H, ddq, J=11.1, 7.1 and 1.2 Hz, 18-H), 5.27 (1H, ddq, J=7.5, 11.1 and 1.8 Hz, 17-H), 4.03 (1H, dd, J=7.5 and 1.2 Hz, 16-H), 3.96 (1H, dq, J=2.8 and 6.5 Hz, 2'-H), 3.31 (1H, d, J=2.8 Hz, 3'-H), 2.85 (3H, s, 13-H_3), 2.41 (1H, dd, J=13.7 and 6.1 Hz, 5'-H_b), 1.91 (6H, s, 4'-N(CH_3)$_2$), 1.87 (1H, dd, J=13.7 and 7.3 Hz, 5'-H_a), 1.63 (3H, s, 15-H_3), 1.61 (3H, d, J=6.5 Hz, 2'-CH_3), 1.60 (3H, dd, J=7.1 and 1.8 Hz, 19-H_3), 0.68 (3H, s, 4'-CH_3); ^{13}C NMR data shown as Table 1.

Deacetylsaptomycin E (**2b**)

8.0 mg of saptomycin E was dissolved in 16 ml of methanol and stirred at room temperature for 48 hours. The resulting methanol solution was concentrated *in vacuo*. The yellow powder obtained almost quantitatively was purified by a silica gel preparative TLC plate (Silica gel 60, F_{254s}, No. 13794, Merck) developed by the solvent system of chloroform-methanol (9:1). 5.5 mg of deacetylsaptomycin E was yielded as yellow powder: $[\alpha]_D^{20}$ +159° (c 0.1, $CHCl_3$); UV λ_{max}^{MeOH} nm (ε) 245 (54,100), 266 (sh 32,000), 415 (11,000); FAB-MS m/z 548 $(M+H)^+$; HRFAB-MS m/z 548.2311 ($(M+H)^+$, calcd for $C_{31}H_{34}NO_8$: 548.2285); IR ν_{max} (KBr) cm^{-1} 3580, 1678, 1648, 1605; ^{1}H NMR (C_6D_6, 400 MHz) δ 13.73 (1H, s, 11-OH), 7.94 (1H, d, J=8.0 Hz, 9-H), 7.93 (1H, s, 6-H), 7.90 (1H, d, J=8.0 Hz, 8-H), 6.48 (1H, s, 3-H), 5.74 (1H, dd, J=6.3 and 7.3 Hz, 6'-H), 3.95 (1H, dq, J=6.5 and 2.8 Hz, 2'-H), 3.31 (1H, d, J=2.8 Hz, 3'-H), 2.96 (1H, q, J=5.4 Hz, 16-H), 2.86 (3H, s, 13-H_3), 2.43 (1H, dd, J=6.3 and 13.7 Hz, 5'-H_b), 1.90 (6H, s, 4'-N(CH_3)$_2$), 1.90 (1H, dd, J=7.3 and 13.7 Hz, 5'-H_a), 1.61 (3H, d, J=6.5 Hz, 2'-CH_3), 1.56 (3H, s, 15-H_3), 0.98 (3H, d, J=5.4 Hz, 17-H_3), 0.67 (3H, s, 4'-CH_3); ^{13}C NMR data shown as Table 1.

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