CHEMICAL MODIFICATION OF ANTHRACYCLINE ANTIBIOTICS. III

4'''-AMINO, 4'''-ALKYLAMINO AND 4'''-AMIDE DERIVATIVES OF ACLACINOMYCIN A

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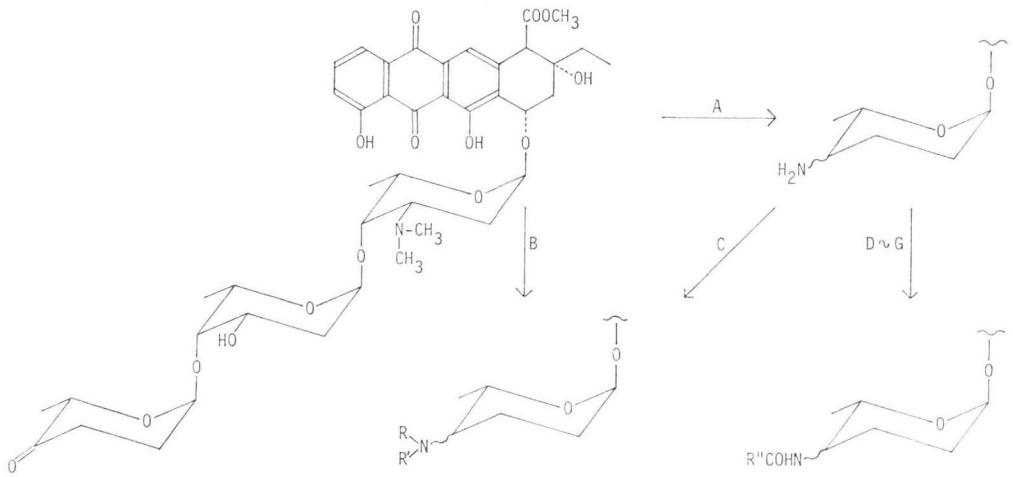
(4'''*R*)- and (4'''*S*)-4'''-Deoxo-4'''-aminoaclacinomycin A were derived by the reductive amination of aclacinomycin A, and further modified to 4'''-alkylamino and 4'''-amide derivatives by reductive *N*-alkylation and acylation.

In the course of the study on chemical modification of anthracycline antibiotics, it was found that the reductive amination of the C–4''' carbonyl function of aclacinomycin A (**1**)[1,2] afforded (4'''*R*)-4'''-deoxo-4'''-aminoaclacinomycin A (**2**) and (4'''*S*)-4'''-deoxo-4'''-aminoaclacinomycin A (**3**). Since these derivatives displayed remarkable inhibitory effects on DNA and RNA syntheses of cultured leukemia L1210 cells, further chemical modification of these compounds were expected to lead to more potent antitumor agents. The present paper describes the syntheses of 4'''-aminoaclacinomycin A, 4'''-alkylamino and 4'''-amide derivatives.

Reductive amination[3] of the C–4''' carbonyl function of aclacinomycin A (**1**) was successfully achieved by use of ammonium acetate - sodium cyanoborohydride ($NaBH_3CN$). Treatment of **1** with the above reagents in methanol at room temperature for several hours gave an epimeric mixture of 4'''-amino derivatives which were separated by silica gel column chromatography to afford **2** and **3** in 46 and 11% yields. The elemental analysis of both compounds indicated that two nitrogen atoms existed in each molecule. The by-products in this reaction system were MA144 M1 and N1[2] which were stereoisomers of the C–4''' hydroxyl group formed by reduction of the C–4''' carbonyl group of **1**.

Configuration of the C–4''' position of **2** and **3** was determined by the following manner. Treatment of **2** with methanolic hydrogen chloride gave readily an anomeric mixture (α-anomer=major product) of disaccharides and aklavin[4]. The ^{1}H-NMR spectrum of α-anomer (**4**) showed an overlapped broad singlet of two anomeric protons at δ 4.75 having a half height width (W_H) of *ca.* 6 Hz. This supports that the each anomeric proton is in an equatorial orientation. Spin decoupling of the doublet at δ 1.14 caused the multiplet at δ 3.86 to a singlet with W_H=3 Hz, therefore the signal at δ 1.14 and 3.86 are attributed to the C–5 methyl and C–5 H of 2-deoxy-L-fucose[5] moiety, respectively. The multiplet at δ 3.66 was changed into a doublet (J=10 Hz) by the irradiation of the doublet at δ 1.17, moreover the signals at δ 3.66 and 2.45 were coupled with each other. From these results, the signals at δ 1.17, 2.45 and 3.66 were assigned to the C–5' methyl, C–4' H and C–5' H of the aminosugar moiety, respectively. A characteristic large coupling constant value ($J_{4',5'}$=10 Hz) suggests the *trans*-diaxial conformation between the C–4' H and C–5' H. Thus, the C–4''' position of **2** was confirmed to be *R*-configuration. On the other hand, the main component of disaccharides obtained by methanolysis of **3** is an α-anomer (**5**) which is characterized by the equatorial orientation of two anomeric protons

Scheme 1.



A: $AcONH_4$ - $NaBH_3CN$, B: primary amine - $NaBH_3CN$, C: carbonyl compound - $NaBH_3CN$, D: acid anhydride, E: β-propiolactone, F: mixed acid anhydride, G: carboxylic acid - DCC.

with each W_H=*ca.* 6 Hz. The value of $J_{4',5'}$=3 Hz in **5** indicates that the configuration of the C–4′ H is equatorial. This evidence supports that the C–4‴ position of **3** is in *S*-configuration.

4‴-Alkylamino derivatives of **1** were synthesized by the methods as shown in Scheme 1. Reductive amination[3] of the C–4‴ carbonyl group of **1** with primary alkylamines in the presence of $NaBH_3CN$ afforded corresponding 4‴-alkylamino derivatives in 16∼43% yields. The reaction was carried out by use of $NaBH_3CN$ (3 molar excess) and amines (10 molar excess) in methanol. The C–4‴ configuration of the resulting compounds was determined by ^{1}H-NMR analysis of each sugar residue obtained by methanolysis or by comparison with the corresponding compound prepared by the following alternate method.

Reductive *N*-alkylation[3] of **2** and **3** was performed by use of $NaBH_3CN$ (3∼6 molar excess) and carbonyl compounds (10∼15 molar excess) in methanol or aqueous methanol to afford 4‴-monoalkylamino or 4‴-dialkylamino derivatives in 21∼70% yields. By using acetone, cyclohexanone, benzaldehyde and 3-pyridylaldehyde as carbonyl compounds in this reaction, **2** was converted into the corresponding 4‴-monoalkylamino derivatives. While, paraformaldehyde as a carbonyl compound afforded selectively 4‴-dimethylamino derivatives of **2** or **3**. In addition, *N*-alkylation of **2** with glutalaldehyde gave 4‴-piperidino derivative.

N-Acylation of **2** and **3** was performed by acid anhydride, mixed acid anhydride, β-propiolactone[8] and carboxylic acid - dicyclohexyl-carbodiimide (DCC). For example, acetylation of **2** with acetic anhydride in methanol gave (4‴*R*)-4‴-deoxo-4‴-acetamideaclacinomycin A (**16**). Similarly, **3** gave (4‴*S*)-4‴-deoxo-4‴-acetamideaclacinomycin A (**17**). In the ^{13}C-NMR spectra of **16** and **17**, the resonances of each 4‴-carbon atom bearing the acetamide group were observed at δ 49.7 and 46.9, respectively.

The structure of the resulting compounds were confirmed by ^{1}H- and ^{13}C-NMR, IR and UV spectrometries and elemental analysis. Physical data and yields of each derivative are summarized in Table 1. The detailed evaluation of their antitumor activity will be reported elsewhere.

Table 1. Pysical data and yields of aclacinomycin A derivatives.

Compound	4‴-Substituent (configuration)	mp. (°C)	$[\alpha]_D^{22}$*	Vis.* ($E_{1cm}^{1\%}$)	Method	Yield (%)**
2	NH_2 (*R*)	147~150	+31	435(148)	A	46
3	NH_2 (*S*)	146~149	+30	435(147)	A	11
6	$NHCH_3$ (*R*)	145~149	+86	432(133)	B	36
7	$NHCH_3$ (*S*)	147~150	+72	432(125)	B	16
8	$N(CH_3)_2$ (*R*)	143~147	+78	432(135)	C	70
9	$N(CH_3)_2$ (*S*)	149~153	+68	432(147)	C	42
10	$NCH(CH_3)_2$ (*R*)	147~151	+90	433(140)	C	40
11	NH-⟨H⟩ (*R*)	144~147	+72	432(131)	C B	64 17
12	$NHCH_2CH_2OH$ (*R*)	141~143	+69	432(138)	B	43
13	$NHCH_2$-⟨⟩ (*R*)	132~135	+70	432(134)	C B	46 20
14	$NHCH_2$-⟨=N⟩ (*R*)	124~128	+60	433(135)	C	21
15	N⟨⟩ (*R*)	154~157	+27	435(143)	C	21
16	$NHCOCH_3$ (*R*)	168~171	+31	435(133)	D	82
17	$NHCOCH_3$ (*S*)	166~169	+27	435(133)	D	78
18	$NHCOCH(CH_3)_2$ (*R*)	158~162	+30	435(153)	D	88
19	$NHCOCH(CH_3)_2$ (*S*)	157~161	+29	435(144)	D	77
20	$NHCOCH_2CH_2OH$ (*R*)	154~157	+31	435(143)	E	59
21	$NHCOCH_2CH_2OH$ (*S*)	147~150	+30	435(138)	E	48
22	$NHCOCH_2N(CH_3)_2$ (*R*)	142~144	+26	435(142)	F	71
23	$NHCOCH_2N(CH_3)_2$ (*S*)	142~145	+26	435(132)	F	56
24	$NHCOCH_2CH_2COOH$ (*R*)	154~157	+30	435(138)	D	70
25	$NHCOCH_2CH_2COOH$ (*S*)	155~158	+20	435(142)	D	64
26	NHCO-⟨H⟩ (*R*)	164~166	+38	435(146)	G	67
27	NHCO-⟨⟩ (*R*)	157~161	+25	435(146)	D	76
28	NHCO-⟨⟩ (*S*)	154~156	+30	435(147)	D	67

* Compounds **8**~**14**: in MeOH, other compounds: in $CHCl_3$.
** Isolated yield.

Experimental

Melting point, IR (KBr) and UV-Vis. spectra, optical rotation and ^1H- and ^{13}C-NMR ($CDCl_3$) spectra were measured by the same methods as described in the previous paper[7].

(4‴*R*)-4‴-Deoxo-4‴-aminoaclacinomycin A (**2**) and (4‴*S*)-4‴-deoxo-4‴-aminoaclacinomycin A (**3**)

A mixture of **1** (2.0 g), $AcONH_4$ (2.0 g) and $NaBH_3CN$ (460 mg) in MeOH (150 ml) was stirred at room temperature for 2 hours, then poured into cold 0.5% aqueous AcOH (400 ml), and washed with $CHCl_3$ (100 ml×2). The aqueous layer was adjusted pH at 8 with $NaHCO_3$ and reextracted with $CHCl_3$ (200 ml×3). After dried (Na_2SO_4) and evaporated the $CHCl_3$ layer, the resulting brownish yellow powder (1.38 g) was subjected to silica gel column (Silica Gel 60, 70~230 mesh, E. Merck), and fractionated with a mixture of $CHCl_3$ - MeOH (10 : 1 v/v) to obtain **2** (576 mg): IR 1735, 1675, 1625 cm^{-1}; ^1H-NMR δ 0.85~1.40 (12H, m, $4CH_3$), 2.16 (6H, s, $N(CH_3)_2$), 3.67 (3H, s, OCH_3), 4.08 (1H, s,

C-10H), 4.80 (1H, bs, C-1‴ H), 5.02 (1H, bs, C-1″ H), 5.25 (1H, bs, C-7 H), 5.49 (1H, bs, C-1′ H), 7.10 ~7.90 (4H, m, aromatic H); *Anal.* calcd. for $C_{42}H_{56}N_2O_{14}\cdot H_2O$: C 60.70, H 7.03, N 3.37; found: C 60.68, H 6.90, N 3.38. The elution with a mixture of $CHCl_3$ - MeOH (5: 1) afforded **3** (112 mg): IR 1735, 1670, 1620 cm^{-1}; ^{1}H-NMR δ 4.80 (1H, bs, C-1‴ H), 5.04 (1H, bs, C-1″ H), 5.26 (1H, bs, C-7 H), 5.49 (1H, bs, C-1′ H); *Anal.* calcd. for $C_{42}H_{56}N_2O_{14}\cdot\frac{1}{2}H_2O$: C 61.37, H 6.99, N 3.41; found: C 61.18, H 7.08, N 3.45.

Methyl 2,6-dideoxy-4-*O*-[(2*R*,5*R*,6*S*)-5-amino-6-methyltetrahydropyran-2-yl]-α-L-lyxo-hexopyranoside (**4**)

To a solution of **2** (100 mg) in dry MeOH (8.5 ml) was added 1.43 ml of 0.6 N methanolic HCl. After stirring for 2.5 hours at 24°C, the mixture was diluted with $CHCl_3$ (50 ml), and then extracted with water (25 ml). The acidic aqueous layer was washed several times with $CHCl_3$, neutralized to pH 8 with $NaHCO_3$ and extracted with $CHCl_3$ (30 ml×5). After dried (Na_2SO_4) and evaporated the extract, the resulting syrup was chromatographed on silica gel using a mixture of $CHCl_3$ - MeOH (5 : 1) to afford **4** (23.4 mg) as a syrup: $[\alpha]_D^{22}$ −16.6° (*c* 0.58, $CHCl_3$); ^{1}H-NMR δ 1.14 (3H, d, C-5 CH_3), 1.17 (3H, d, C-5′ CH_3), 1.5~2.0 (6H, m, C-2, C-2′ & C-3 H_2), 2.45 (1H, m, C-4′ H), 3.25 (3H, s, C-1 OCH_3), 3.50 (1H, bs, C-4 H), 3.66 (1H, m, C-5′ H), 3.86 (2H, m, C-3 & C-5 H), 4.75 (2H, bd, C-1 & C-1′ H).

Methyl 2,6-dideoxy-4-*O*-[(2*R*,5*S*,6*S*)-5-amino-6-methyltetrahydropyran-2-yl]-α-L-lyxo-hexopyranoside (**5**)

Prepared from **3** (77 mg) by the same procedure described for **4**, as a syrup (yield 12.0 mg): $[\alpha]_D^{22}$ −7.5° (*c* 0.55, $CHCl_3$); ^{1}H-NMR δ 1.80 (3H, d, C-5 H), 1.16 (3H, m, C-2, C-2′ & C-3′ H_2), 2.78 (1H, bs, C-4′ H), 3.25 (3H, s, C-1 OCH_3), 3.49 (1H, bs, C-4 H), 3.7~4.0 (2H, m, C-3 & C-5 H), 4.18 (1H, m, C-5′ H), 4.75 (2H, bs, C-1 & C-1′ H).

(4‴*R*)-4‴-Deoxo-4‴-methylaminoaclacinomycin A (**6**) and (4‴*S*)-4‴-deoxo-4‴-methylaminoaclacinomycin A (**7**)

To a solution of **1** (200 mg) and methylamine·HCl (166 mg) in MeOH (5 ml) was added 46 mg of $NaBH_3CN$. After stirring at room temperature for 1.5 hours, the reaction mixture was worked up by the same procedure described for **2** and **3**, and the resulting products were then purified by PLC (preparative layer chromatography: Silica Gel 60 F_{254}, E. Merck; $CHCl_3$ - benzene - MeOH, 6: 1: 2) to afford **6** (58 mg): ^{1}H-NMR δ 2.51 (3H, s, NHCH_3); *Anal.* calcd. for $C_{43}H_{58}N_2O_{14}\cdot\frac{3}{2}H_2O$: C 60.48, H 7.20, N 3.28; found: C 60.56, H 7.07, N 3.22, and **7** (26.6 mg): ^{1}H-NMR δ 2.50 (3H, s, NHCH_3); *Anal.* calcd. for $C_{43}H_{58}N_2O_{14}$: C 62.46, H 7.20, N 3.28; found: C 62.04, H 7.07, N 3.22.

(4‴*R*)-4‴-Deoxo-4‴-dimethylaminoaclacinomycin A (**8**)

To a solution of **2** (100 mg) and paraformaldehyde (46 mg, 80% purity) in 50% aqueous MeOH (10 ml) were added 14 μl of AcOH and 39 mg of $NaBH_3CN$. The mixture was stirred at room temperature for 1.5 hours, diluted with $CHCl_3$ (20 ml), and then washed with 0.1% aqueous $NaHCO_3$ (50 ml) and 5% aqueous NaCl. After dried (Na_2SO_4) and evaporated the $CHCl_3$ layer, the resulting residue was chromatographed on silica gel column using a mixture of $CHCl_3$ - MeOH (10: 1) to yield **8** (72 mg): ^{1}H-NMR δ 2.18 (6H, s, $N(CH_3)_2$), 2.25 (6H, s, $N(CH_3)_2$); *Anal.* calcd. for $C_{44}H_{60}N_2O_{14}$: C 62.84, H 7.19, N 3.33; found: C 62.40, H 6.98, N 3.39.

(4‴*S*)-4‴-Deoxo-4‴-dimethylaminoaclacinomycin A (**9**)

By the same procedure as described above **3** (50 mg) was converted into **9** (30.2 mg); ^{1}H-NMR δ 2.17 (6H, s, $N(CH_3)_2$), 2.23 (6H, s, $N(CH_3)_2$); *Anal.* calcd. for $C_{44}H_{60}N_2O_{14}$: C 62.84, H 7.19, N 3.33; found: C 62.71, H 7.08, N 3.41.

(4‴*R*)-4‴-Deoxo-4‴-isopropylaminoaclacinomycin A (**10**)

Compound **2** (50 mg) was treated overnight with Me_2CO (34 μl) in the presence of 0.5 N methanolic HCl (0.21 ml) and $NaBH_3CN$ (19 mg) in MeOH (3 ml). The resulting product was purified by PLC ($CHCl_3$ - MeOH, 4 : 1) to yield **10** (21 mg): ^{1}H-NMR δ 0.95~1.35 (18H, m, $6CH_3$), 2.90 (1H, m, NHC$H(CH_3)_2$); *Anal.* calcd. for $C_{45}H_{62}N_2O_{14}\cdot\frac{3}{2}H_2O$: C 61.28, H 7.42, N 3.18; found: C 61.43, H 7.08, N 2.96.

(4‴*R*)-4‴-Deoxo-4‴-cyclohexylaminoaclacinomycin A (**11**)

$NaBH_3CN$ (39 mg) was added to a solution of **2** (100 mg) and cyclohexanone (0.127 ml) in MeOH (5 ml) which contained 15 μl of AcOH. After 3 hours, the mixture was worked up, and the resulting material was chromatographed on silica gel column ($CHCl_3$ - MeOH, 30 : 1) to afford **11** (70 mg): ^{1}H-NMR δ 1.35~2.05 (18H, m, $9CH_2$); *Anal.* calcd. for $C_{48}H_{66}N_2O_{14}$: C 64.41, H 7.43, N 3.13; found: C 64.14, H 7.65, N 3.16.

(4‴*R*)-4‴-Deoxo-4‴-(2-hydroxyethylamino)aclacinomycin A (**12**)

Prepared from **1** (300 mg) and 2-aminoethanol (0.16 ml) by the same procedure as described for **6** and **7**, (yield 129 mg): ^{1}H-NMR δ 2.7 (2H, m, $NHCH_2CH_2OH$), 3.58 (2H, t, $NHCH_2CH_2OH$); *Anal.* calcd. for $C_{44}H_{60}N_2O_{15}\cdot\frac{3}{2}H_2O$: C 59.79, H 7.18, N 3.17; found: C 59.85, H 6.96, N 2.77.

(4‴*R*)-4‴-Deoxo-4‴-benzylaminoaclacinomycin A (**13**)

Obtained from **2** (100 mg) and benzaldehyde (0.13 ml) by the same procedure as described for **11**, (yield 51 mg): ^{1}H-NMR δ 3.78 (2H, d, $NHCH_2C_6H_5$), 7.15~7.85 (9H, aromatic H); *Anal.* calcd. for $C_{49}H_{62}N_2O_{14}$: C 65.17, H 6.92, N 3.10; found: C 64.60, H 6.65, N 2.69.

(4‴*R*)-4‴-Deoxo-4‴-(3-picorylamino)aclacinomycin A (**14**)

Prepared from **2** (200 mg) and 3-pyridinealdehyde (0.13 ml) by the same procedure as described for **11**, (yield 23.8 mg): ^{1}H-NMR δ 3.82 (2H, d, $NHCH_2$Py), 7.10~8.55 (8H, m, aromatic H); *Anal.* calcd. for $C_{48}H_{61}N_3O_{14}\cdot\frac{3}{2}H_2O$: C 61.92, H 6.93, N 4.51; found: C 61.84, H 6.56, N 4.71.

(4‴*R*)-4‴-Deoxo-4‴-piperidinoaclacinomycin A (**15**)

Prepared from **2** (150 mg) and 50% aqueous glutalaldehyde (0.37 ml) by the same procedure as described for **8**, (yield 34.8 mg): ^{1}H-NMR δ 2.2~2.6 (6H, m, C-8 H_2 & $N\langle^{CH_2}_{CH_2}$); *Anal.* calcd. for $C_{47}H_{64}N_2O_{14}\cdot\frac{1}{2}H_2O$: C 63.43, H 7.36, N 3.15; found: C 63.22, H 7.34, N 3.19.

(4‴*R*)-4‴-Deoxo-4‴-acetamideaclacinomycin A (**16**)

Compound **2** (50 mg) was treated with acetic anhydride (65 μl) in dry MeOH (5 ml) at 25°C for 5 minutes. The mixture was diluted with $CHCl_3$ (30 ml) and washed with 1% aqueous $NaHCO_3$ and water. After dried (Na_2SO_4) and evaporated the organic layer, the residue was chromatographed on silica gel column ($CHCl_3$ - MeOH, 30 : 1) to afford **16** (43 mg): ^{1}H-NMR δ 2.00 (3H, s, $COCH_3$), 5.52 (2H, bd, C-1′ H, N*H*CO); *Anal.* calcd. for $C_{44}H_{58}N_2O_{15}$: C 61.81, H 6.84, N 3.28; found: C 62.15, H 6.71, N 3.66.

(4‴*R*)-4‴-Deoxo-4‴-isobutyrylaminoaclacinomycin A (**18**)

Prepared from **2** (50 mg) and isobutyric anhydride (97 μl) by the same procedure described above, (yield 48 mg): ^{1}H-NMR δ 0.95~1.35 (18H, m, $6CH_3$), 5.52 (1H, d, N*H*CO); *Anal.* calcd. for $C_{46}H_{62}N_2O_{15}\cdot\frac{1}{2}H_2O$: C 61.94, H 7.12, N 3.14; found: C 61.86, H 7.20, N 3.21.

(4‴*R*)-4‴-Deoxo-4‴-(2-hydroxypropionylamino)aclacinomycin A (**20**)

A mixture of **2** (50 mg) and β-propiolactone (20 μl) in dry CH_2Cl_2 (2 ml) was allowed to stand at room temperature for 3 days. The reaction mixture was worked up and the resulting material was purified by PLC ($CHCl_3$ - MeOH, 5 : 1) to afford **20** (32 mg): ^{1}H-NMR δ 2.43 (2H, t, $COCH_2CH_2OH$), 3.90 (2H, t, $COCH_2CH_2OH$), 6.24 (1H, bd, N*H*CO); *Anal.* calcd. for $C_{45}H_{60}N_2O_{16}\cdot\frac{3}{2}H_2O$: C 59.27, H 6.91, N 3.07; found: C 59.27, H 6.65, N 3.20.

(4‴*R*)-4‴-Deoxo-4‴-dimethylaminoglycylaminoaclacinomycin A (**22**)

To a stirring solution of dimethylglycin·HCl (43 mg) and triethylamine (85 μl) in dry CH_2Cl_2 (5 ml) was added 39 μl of isobutylchloroformate at −20°C. After 5 minutes, **2** (50 mg) dissolved in CH_2Cl_2 (1 ml) was added and the mixture was stirred for 20 minutes at −5°C. The mixture was worked up and the crude product was purified by PLC ($CHCl_3$ - benzene - MeOH, 6 : 2 : 1) to yield **22** (39 mg): ^{1}H-NMR δ 2.32 (6H, s, $COCH_2N(CH_3)_2$), 2.98 (2H, s, $COCH_2N(CH_3)_2$), 7.18 (1H, d, N*H*CO); *Anal.* calcd. for $C_{46}H_{63}N_3O_{15}\cdot\frac{3}{2}H_2O$: C 59.73, H 7.19, N 4.54; found: C 59.63, H 6.91, N 4.49.

(4‴*R*)-4‴-Deoxo-4‴-(3-carboxypropionylamino)aclacinomycin A (**24**)

A methanol (3 ml) solution of **2** (50 mg) and succinic anhydride (9.2 mg) was stirred at room

temperature for 1 hour. The mixture was diluted with $CHCl_3$ (30 ml), and washed with pH 6.5 acetate buffer. After dried (Na_2SO_4) and evaporated the organic layer, the resulting residue (49 mg) was purified by PLC ($CHCl_3$ - benzene - MeOH, 6 : 2 : 1) to yield **24** (39 mg): ^{1}H-NMR δ 2.5 ($COCH_2CH_2$-COOH & others), 6.75 (1H, bd, N*H*CO).

(4‴*R*)-4‴-Deoxo-4‴cyclohexanoylaminoaclacinomycin A (**26**)

A mixture of **2** (50 mg), cyclohexanecarboxylic acid (10 mg) and dicyclohexylcarbodiimide (16 mg) in dry CH_2Cl_2 (5 ml) was stirred at room temperature for 6 hours. The solid was filtered off and the filtrate was diluted with $CHCl_3$ (30 ml), washed with 1% aqueous $NaHCO_3$ and water, and evaporated to dryness. The resulting residue was chromatographed on silica gel column to afford **26** (38 mg): ^{1}H-NMR δ 1.0~2.1 (32H, m, $4CH_3$ & $10CH_2$), 5.42 (1H, bd, N*H*CO); *Anal.* calcd. for $C_{49}H_{66}N_2O_{15}$: C 63.76, H 7.21, N 3.03; found: C 63.54, H 7.08, N 3.14.

(4‴*R*)-4‴-Deoxo-4‴-benzoylaminoaclacinomycin A (**27**)

Compound **2** (50 mg) was treated with benzoic anhydride (42 mg) in dry MeOH (3 ml) at room temperature for 30 minutes to afford **27** (43 mg): ^{1}H-NMR δ 6.10 (1H, bd, N*H*CO), 7.15~7.85 (9H, m, aromatic H); *Anal.* calcd. for $C_{49}H_{60}N_2O_{15}\cdot H_2O$: C 62.95, H 6.68, N 3.00; found: C 62.71, H 6.50, N 2.96.

Other amide derivatives (**17**, **19**, **21**, **23**, **25** and **28**) were obtained by the corresponding procedures from **3** as a starting material, respectively.

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