CHEMICAL MODIFICATION OF ERYTHROMYCINS VII.[1] MOLECULAR REARRANGEMENT OBSERVED DURING CHEMICAL MODIFICATION STUDY OF THE DESOSAMINE UNIT OF ERYTHROMYCINS

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Abstract —— The reaction of 2'-O-methanesulfonylerythromycin A derivatives (**2**) with a variety of nucleophilic reagents gave 2'-dimethylamino-3'-substituted derivatives (**3**). The reaction took place with neighboring group-participated nucleophilic substitution involving migration of participating 3'-dimethylamino group. This migration was also observed in the case of N-oxide of the dimethylamino group.

Erythromycin A (**1a**),[2] a naturally occurring macrolide antibiotic, is clinically useful against infections of Gram-positive bacteria and *Mycoplasma pneumoniae*. It is composed of a polyfunctionalized 14-membered lactone ring substituted with the desosamine and cladinose sugar units. A great number of derivatives of **1a** have been synthesized and the structure-activity relationship has been well documented.[3] The presence of vicinal dimethylamino and hydroxyl groups in the desosamine moiety is said to be essential for the antibacterial activity.

Keeping this in mind, we have planned the preparation of a series of erythromycins having a different substituent at the 2'-position of the desosamine unit in order to obtain further insight about the structure-activity relationship. The synthetic strategy of our choice for this purpose is nucleophilic substitution of 2'-O-methanesulfonyl derivatives. During this synthetic study we have found neighboring group-participated nucleophilic substitution involving migration of participating dimethylamino group and also observed migration of N-oxide of dimethylamino group through the nucleophilic substitution.

Attempted replacements of 2'-O-methanesulfonyloxy group by a series of nucleophiles unexpectedly afforded the rearranged products, 2'-dimethylamino-3'-substituted derivatives in good yields, because of the neighboring participation of the adjacent dimethylamino group (Table 1). Only the use of lithium chloride as the nucleophile gave the expected 2'-chloro derivative (**4**).

Such neighboring participation has been observed for α-DL-arabinohexopyranoside where attempted replacement of the tosyloxy group by nucleophiles afforded the rearranged products due to the neighboring participation of the dimethylamino group.[4]

The reaction of **1a** and 6-O-methylerythromycin A (**1c**) with methanesulfonyl chloride, performed in the presence of triethylamine in acetone solution, afforded the corresponding 2',4"-di-O-methanesulfonylerythromycin A derivatives (**2a**) and (**2c**), respectively. 4"-O-Formylerythromycin A (**1b**)[5] and 4"-O-formyl-6-O-methyl-erythromycin A (**1d**) prepared from **1a** and **1c** were also allowed to react with methanesulfonyl chloride in a similar manner as above using dichloromethane instead of acetone giving 2'-O-methanesulfonyl derivatives (**2b**) and (**2d**), respectively.

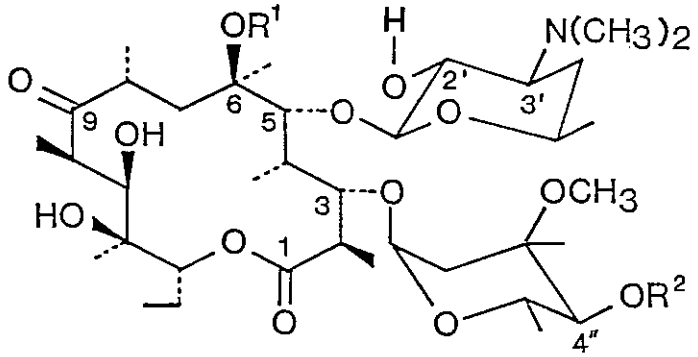
Treatment of the compound **2d** in N,N-dimethylformamide (DMF) at 60 °C with sodium formate as a nucleophile afforded the rearranged diformate (**3a**), which on hydrolysis with aqueous sodium hydrogencarbonate in methanol solution gave 3'-hydroxyl derivative (**3b**) in 51.8% overall yield.

In a similar manner, **2c** was allowed to react with dimethylamine to give **3i** in 55.3% yield. Reaction of **2b** and **2d** with sodium azide in methanol at 50-60 °C provided the 3'-azido derivatives **3f** and **3d**, respectively.

Furthermore, **2a-d** readily gave the corresponding 3'-substituted derivatives on treatment with a variety of oxygen, nitrogen and sulfur nucleophiles, thus establishing the generality of the present reaction. The results are shown in Table 1.

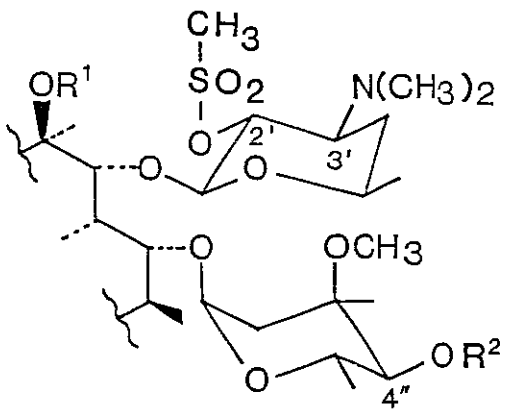
The structure of the products (**3a-r**) has been confirmed by nmr spectroscopy including the proton-proton and proton-carbon shift correlation 2D nmr technique (Table 2).

The ^{13}C nmr chemical shifts assignment for the amino sugar moiety of the representative compounds is shown in Table 3.



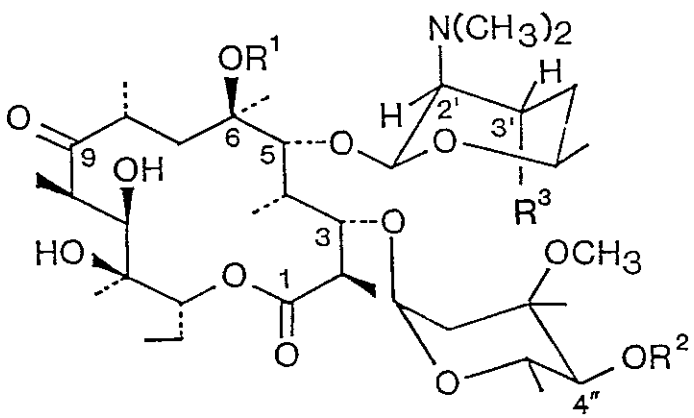
	R^1	R^2
1a :	H	H
1b :	H	CHO
1c :	CH_3	H
1d :	CH_3	CHO

CH_3SO_2Cl / $(C_2H_5)_3N$



	R^1	R^2
2a :	H	SO_2CH_3
2b :	H	CHO
2c :	CH_3	SO_2CH_3
2d :	CH_3	CHO

Nucleophile

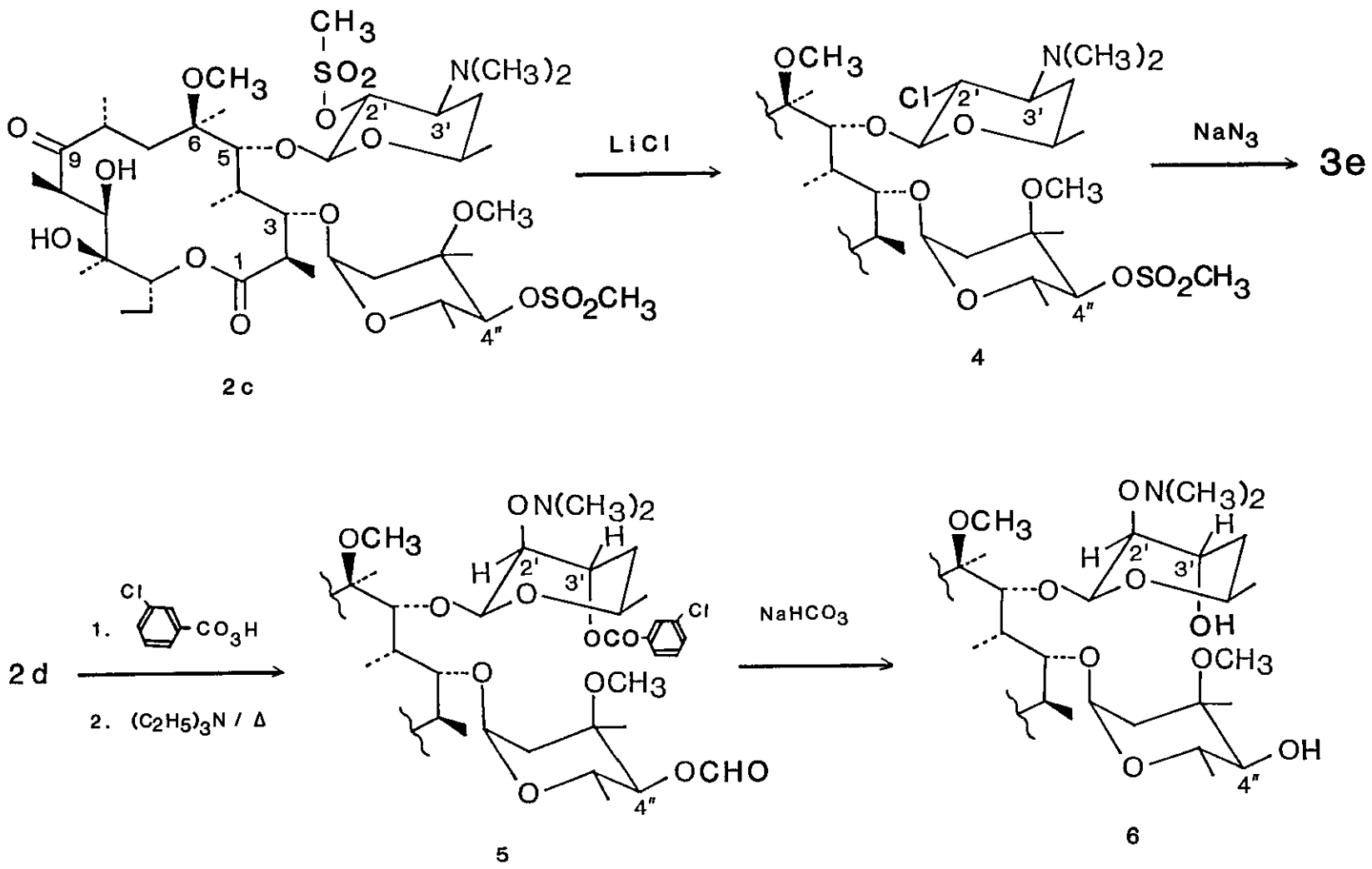


3 a – r

In the ^{1}H nmr spectra of the compound **3**, the resonances of the anomeric proton of desosamine (1'-H) were observed at 4.90-5.07 ppm with downfield and those of NMe_2 were at 2.51-2.64 ppm with distinguishable upfield shifts as compared with those for **1** and **2** (1'-H: 4.41-4.44 ppm, NMe_2: 2.28-2.29 ppm). In addition, the coupling constants of $J_{1'-2'}$ and $J_{2'-3'}$ for **3** were determined to be 2.1-2.5 and 2.5-3.1 Hz as compared to those for **1** and **2** (7.2-7.3 and 10.2-10.3 Hz), respectively, which may be explained by the change of the bond interaction between 1'-H and 2'-H from axial-axial in **1** and **2** to axial-equatorial in **3**. The ^{13}C nmr spectra of **3** revealed the upfield shifts at C-2' and C-5' and the downfield at C-3', C-4' and NMe_2 as compared with those of **1** and **2** (Table 3).
In conclusion, the presented results indicated that the dimethylamino group at C-3' in **2** was rearranged to C-2', yieldling the 3'-substituted compound **3**.

On the other hand, the compound **2c** was heated under reflux with lithium chloride in acetonitrile to yield the 2'-chloro derivative (**4**). The values of $J_{1'-2'}$ and $J_{2'-3'}$, in **4** (7.5 and 11.1 Hz) were comparable with those in **1c** (7.2 and 10.2 Hz), indicating that the nucleophilic replacement proceeded without the rearrangement of dimethylamino group to afford **4**. When **4** was heated under reflux with sodium azide in methanol, the rearrangement of dimethylamino group took place accompanying the nucleophilic reaction to give **3e**.

Based on these findings, the mechanism of the nucleophilic substitution could be reasonably explained by the following pathway. The intramolecular reaction between 2'-O-methanesulfonyl and 3'-dimethylamino groups occurs in the beginning to yield 2'3'-aziridinium intermediate, which was detectable by TLC, but could not be isolated because of its instability. The nucleophilic substitution takes place through the aziridinium intermediate with trans-diaxial ring-opening to yield the 2'-dimethylamino-3'-substituted derivative.
On the other hand, lithium chloride gave the original diequatorial ring-opening derivative **4**, because owing to a chelating ability of lithium cation upon the oxygen atom at C-1', chloride anion tends, therefore, to attack the neighbouring 2'-carbon atom.


2c
LiCl
4
NaN3
3e
2d
1. Cl CO3H
2. (C2H5)3N / Δ
5
NaHCO3
6

It is particularly noteworthy that the neighboring group participation was observed for N-oxide of the dimethylamino group. Namely, treatment of **2d** with 3-chloroperoxybenzoic acid in acetone gave the corresponding N-oxide, which could not be isolated due to the instability of the compound. After addition of triethylamine and DMF, the mixture was heated at 60 °C to afford the 3'-(3-chlorobenzoyloxy) derivative (**5**). The 3-chlorobenzoic acid generated in the cause of the oxidation, could be acting as the nucleophile in the presence of the base. Hydrolysis of **5** with sodium hydrogencarbonate in methanol gave (**6**). The structure of **6** has been confirmed by 2D nmr spectra as (2'S, 3'R)-3'-dedimethylamino-2'-dehydroxy-2'-dimethylaminoxy-3'-hydroxy-6-O-methylerythromycin A.

With regard to the structure-activity relationship, the compounds **3** and **4** are almost losing their antibacterial activity, indicating that the naturally occurring vicinal structure of dimethylamino and hydroxyl groups in the amino sugar unit is necessary to exhibit the activity.

EXPERIMENTAL

Melting points were taken using a Yanaco micro melting point apparatus and are uncorrected. Fast atom bombardment mass spectra (FAB-Ms) were recorded on a JEOL JMX-SX 102 mass spectrometer. Nmr spectra were recorded on Varian XL-200 or JEOL JNM-GX 400 spectrometer. Column chromatography was performed by the use of silica gel 60 (70-230 mesh, E. Merck).

4"-O-Formyl-6-O-methylerythromycin A (**1d**) Formic acid (40 ml) was mixed with acetic anhydride (80 ml) at 50 °C. After 10 min, the mixture was cooled to 0 °C and then added dropwise to a solution of 6-O-methylerythromycin A (**1c**; 40 g, 54 mmol) and dry pyridine (80 ml) in CH_2Cl_2 (800 ml). After stirring at room temperature for 5 h, the reaction mixture was washed with sat. aq. $NaHCO_3$ solution and water. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to leave a foam.

Crystallization from CH_2Cl_2-EtOAc gave 2',4"-di-O-formyl-6-O-methylerythromycin A as colorless crystals, yield 34.1 g (79.3%), mp 259-261°C (dec). FAB-Ms: m/z 804 (M^++H). ^{1}H Nmr ($CDCl_3$) δ : 2.29 (6H, s, 3'-NMe_2), 3.02 (3H, s, 6-OMe), 3.35 (3H, s, 3"-OMe), 8.17 (1H, s, 2'-OCHO), 8.22 (1H, s, 4"-OCHO).

The material (6.56 g, 8.2 mmol) prepared above was dissolved in MeOH (220 ml) and the solution was stirred at 17°C for 2.5 h. The resulting solution was diluted with water and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by column chromatograhy using acetone and then crystallized from CH_2Cl_2-diisopropyl ether to give **1d** as colorless crystals, yield 4.2 g (66.3%), mp 231-232°C. FAB-Ms: m/z 776 (M^++H). ^{1}H Nmr ($CDCl_3$) δ : 2.28 (6H, s, 3'-NMe_2), 3.04 (3H, s, 6-OMe), 3.34 (3H, s, 3"-OMe), 8.22 (1H, s, 4"-OCHO).

2',4"-Di-O-methanesulfonylerythromycin A (**2a**) To a mixture of erythromycin A (**1a**, 7.34 g, 10 mmol) and Et_3N (4.04 g, 40 mmol) in dry acetone (150 ml), $MeSO_2Cl$ (3.56 g, 30 mmol) was added dropwise with stirring at 3-7°C. After the addition the reaction mixture was stirred at 0-3°C for 30 min and then at room temperature for 2 h. The most of solvent was evaporated *in vacuo* and the residue was poured into a mixture of EtOAc (300 ml) and 5% aq. $NaHCO_3$ solution (300 ml) with stirring. The organic layer was washed with 5% aq. $NaHCO_3$ solution and water and then dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by column chromatography using EtOAc/hexane (2:1) giving **2a** as a colorless foam, yield 6.74 g (75.7 %), mp.144-147°C (dec). FAB-Ms: m/z 890 (M^++H). ^{1}H Nmr (acetone-d_6) δ : 2.88 (6H, s, 3'-NMe_2), 3.12 (3H, s, 4"-OSO_2Me), 3.16 (3H, s, 2'-OSO_2Me), 3.33 (3H, s, 3"-OMe).

In a similar manner as above, 2',4"-di-O-methanesulfonyl-6-O-methylerythromycin A (**2c**) was obtained from **1c**. Crystallization from EtOAc-hexane gave colorless crystals in 41.7%, mp 163-164°C. FAB-Ms: m/z 904 (M^++H). ^{1}H Nmr ($CDCl_3$) δ : 2.30 (6H, s, 3'-NMe_2), 3.01 (3H, s, 6-OMe), 3.09 (3H, s, 4"-OSO_2Me), 3.20 (3H, s, 2'-OSO_2Me), 3.33 (3H, s, 3"-OMe), 4.62 (1H, d, J=7.3 Hz, 1'-H).

4"-O-Formyl-2'-O-methanesulfonylerythromycin A (**2b**) A solution of $MeSO_2Cl$ (2.3 g, 20 mmol) in CH_2Cl_2 (20 ml) was added to a stirred solution of **1b** (7.62 g, 10 mmol) and Et_3N (3.03 g, 30 mmol) in CH_2Cl_2 (80 ml) at 0-5°C. The reaction mixture was stirred at 0-3°C for 1 h and at room temperature for 2 h. The resulting mixture was diluted with CH_2Cl_2 and washed with 5% aq. $NaHCO_3$ solution and water. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to leave a form. Chromatographic purification using silica gel with EtOAc/hexane (2:1) gave **2b** as a colorless foam, yield 6.55 g (78.0%), mp 150-152°C (dec). FAB-Ms: m/z 840 (M^++H). ^{1}H Nmr (acetone-d_6) δ : 2.29 (6H, s, 3'-NMe_2), 3.16 (3H, s, 2'-OSO_2Me), 3.32 (3H, s, 3"-OMe), 8.23 (1H, s, 4"-OCHO).

In a similar reaction, 4"-O-formyl-6-O-methylerythromycin A (**1d**) gave 4"-O-formyl-2'-O-methanesulfonyl-6-O-methylerythromycin A (**2d**) as colorless crystals from EtOAc-hexane in 18.7% yield, mp 174-176°C (dec). FAB-Ms: m/z 854 (M^++H). ^{1}H Nmr ($CDCl_3$) δ : 1.36 (3H, s, 6-Me), 2.28 (6H, 3'-NMe_2), 3.02 (3H, s, 6-OMe), 3.20 (3H, s, 2'-OSO_2Me), 3.35 (3H, s, 3"-OMe), 4.78 (1H, d, J=7.2 Hz, 1'-H), 8.22 (1H, s, 4"-OCHO).

(2'S,3'R)-3'-Dedimethylamino-2'-dehydroxy-2'-dimethylamino-3'-substituted erythromycin A derivatives (**3a-r**) The following procedures were typical to the methods used to prepare the 3'-substituted derivatives.

Method A: (2'S,3'R)-3'-Dedimethylamino-2'-dehydroxy-2'-dimethylamino-3'-hydroxy-6-O-methylerythromycin A (**3b**) A stirred mixture of **2d** (0.8 g, 0.9 mmol) and sodium formate (0.8 g, 11.8 mmol) in DMF (10 ml) was heated at 60°C for 3 h. The reaction mixture was poured into water and extracted with EtOAc. The organic layer was washed with water, dried over $MgSO_4$ and concentrated *in vacuo* to give a solid. Crystallization from CH_2Cl_2-petroleum ether afforded **3a** as colorless crystals, yield 0.55 g (73.0%), mp 199-201°C (Table 1).
Compound **3a** (0.3 g, 0.40 mmol) was treated with a mixture of 5% aq. $NaHCO_3$ solution-MeOH (20 ml, 1:1 v/v) and CH_2Cl_2 (10 ml) at room temperature for 1 day.

After evaporation of the MeOH, the reaction mixture was extracted with EtOAc. The organic layer was washed with water, dried over $MgSO_4$ and concentrated *in vacuo* to leave a colorless foam. Crystallization from EtOAc-petroleum ether gave **3b** as colorless crystals, yield 0.21 g (51.8% from **2d**), mp 208-210.5°C (dec), (Table 1). Similarly, the compounds **3c**, **3g-i**, **3k-o**, **3q** and **3r** were prepared by the reaction of **2** with the corresponding nucleophile (Table 1).

Method B: (2'S,3'R)-3'-Azido-3'-dedimethylamino-2'-dehydroxy-2'-dimethylamino-erythromycin A (**3f**) A mixture of **2b** (2.0 g, 2.4 mmol) and NaN_3 (2.0 g, 30.8 mmol) in MeOH (100 ml) was stirred at 60°C for 2 h. Most of the solvent was distilled *in vacuo* and the residue was dissolved in EtOAc. The organic layer was washed with water and dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by column chromatography using EtOAc/hexane (2:1) and then crystallized from $CHCl_3$-Et_2O to afford **3f** as colorless crystals, yield 1.2 g (66.7%), mp 153.5-155°C, (Table 1).
The compounds **3d**, **3e**, **3j** and **3p** were prepared in a similar procedure described above (Table 1).

(2'R,3'S)-2'-Chloro-2'-dehydroxy-4"-O-methanesulfonyl-6-O-methylerythromycin A (**4**) A mixture of **2c** (0.5 g, 0.55 mmol) and LiCl (1 g, 2.3 mmol) in MeCN (10 ml) was heated under reflux for 6 h. The reaction mixture was poured into brine and extracted with EtOAc. The organic layer was washed with water, dried over $MgSO_4$ and concentrated *in vacuo* to leave a solid. Crystallization from EtOH gave pure **4** as crystals, yield 0.235 g (50.3%), mp 211-212°C (dec). FEB-Ms: m/z 844 (M^++H). ^{1}H Nmr ($CDCl_3$) δ : 1.37 (3H, s, 6-Me), 2.34 (6H, s, 3'-NMe_2), 3.02 (3H, s, 6-OMe), 3.08 (3H, s, 4"-OSO_2Me), 3.34 (3H, s, 3"-OMe), 3.49 (1H, dd, J=10.5 and 7.2 Hz, 2'-H), 3.68 (1H, m, 5'-H), 4.63 (1H, d, J=7.2 Hz, 1'-H).

Reaction of 2'-chloro compound **4** with sodium azide A mixture of **4** (0.15 g, 0.18 mmol) and NaN_3 (0.25 g, 4 mmol) in MeOH (20 ml) was heated under reflux for 5 h. After evaporation of the solvent, the residue was dissolved in EtOAc and the organic layer was washed with water. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to leave a solid. Crystallization from MeOH gave **3e** as

colorless crystals, yield 0.03 g (19.6%). Physicochemical properties of this compound were identical to those prepared from **2c** and NaN_3 according to the Method B.

(2'S,3'R)-3'-Dedimethylamino-2'-dehydroxy-2'-dimethylaminoxy-3'-hydroxy-6-O-methylerythromycin A (**6**) A mixture of **2d** (0.85 g, 1 mmol) and 3-chloroperoxybenzoic acid (0.346 g, 2 mmol) in acetone (15 ml) was stirred at room temperature for 25 min. To this mixture, Et_3N (1 ml, 7 mmol) and DMF (15 ml) were added and the resulting mixture was heated at 50-60 °C for 1.5 h. The reaction mixture was diluted with EtOAc (150 ml) and washed with brine, aq. $NaHCO_3$ solution, and brine, successively. The organic layer was dried over $MgSO_4$ and evaporated *in vacuo* to leave a solid. Crystallization from EtOAc-petroleum ether gave (2'S,3'R)-3'-(3-chlorobenzoyloxy)-3'-dedimethylamino-2'-dehydroxy-2'-dimethylaminoxy-4"-O-formyl-6-O-methylerythromycin A (**5**) as colorless needles, yield 0.732 g (78.7%), mp 124-127 °C. FAB-Ms: m/z 930 (M^++H). ^{1}H Nmr ($CDCl_3$) δ : 1.47 (3H, s, 6-Me), 2.70 (6H, s, 2'-NMe_2), 2.89 (3H, s, 3"-OMe), 3.04 (3H, 6-OMe), 3.88 (1H, dd, J=1.7 and 3.0 Hz, 2'-H), 3.93 (1H, m, 5'-H), 4.84 (1H, d, J=1.8 Hz, 1'-H), 5.47 (1H, m, 3'-H), 7.38, 7.56, 8.05, 8.06 (4H, Ar-H), 8.18 (1H, s, 4"-OCHO).

A mixture of **5** (0.5 g, 0.5 mmol) and $NaHCO_3$ (0.2 g, 2.5 mmol) in MeOH (20 ml) was heated under reflux for 3 h. After evaporation of the solvent, the residue was extracted with EtOAc and the organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to leave a foam. Crystallization from EtOAc gave **6** as colorless crystals, yield, 0.274 g (68.7%), mp 225-226 °C. FAB-Ms: m/z 764 (M^++H). ^{1}H Nmr ($CDCl_3$) δ : 1.45 (3H, s, 6-Me), 2.30 (1H, d, J=1.3 Hz, 3'-OH), 2.64 (6H, s, 2'-$ONMe_2$), 3.03 (3H, s, 6-OMe), 3.31 (3H, s, 3"-OMe), 3.67 (1H, dd, J=3.6 and 1.5 Hz, 2'-H), 3.86 (1H, m, 5'-H), 4.26 (1H, m, 3'-H), 4.86 (1H, d, J=1.5 Hz, 1'-H).

Table 1. (2'S,3'R)-3'-Dedimethylamino-2'-dehydroxy-2'-dimethylamino-3'-substituted erythromycin A derivatives 3a-r

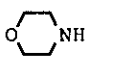
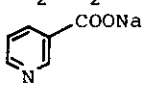
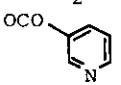
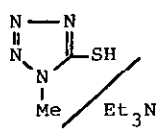
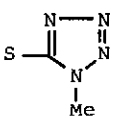
Nucleophile	Product (3)	R^1	R^2	R^3	Method	Yield (%)	mp (°C)
HCOONa	a	Me	CHO	OCHO	A	73.0	199-201
HCOONa	b	Me	H	OH	A	51.8	208-210.5
HCOONa	c	H	H	OH	A	61.9	146-148
NaN_3	d	Me	H	N_3	B	64.1	218-220
NaN_3	e	Me	SO_2Me	N_3	B	38.3	216-216.5 (dec)
NaN_3	f	H	H	N_3	B	66.7	153.5-155
NaN_3	g	H	SO_2Me	N_3	A	71.4	115-117
NH_3	h	H	H	NH_3	A	84.8	132-135
Me_2NH	i	Me	SO_2Me	NMe_2	A	55.3	206-207 (dec)
$PhCH_2NH_2$	j	Me	SO_2Me	$NHCH_2Ph$	B	61.6	203-205 (dec)
	k	H	H		A	69.7	134-136
Me_2NCH_2COONa	l	H	SO_2Me	$OCOCH_2NMe_2$	A	73.0	130-132
	m	H	CHO		A	87.4	133-135
$Me_2NCSSNa$	n	H	CHO	$SCSNMe_2$	A	69.8	143-147
EtOCSSK	o	H	CHO	SCSOEt	A	80.5	113-115
MeOH	p	Me	SO_2Me	OMe	B	36.6	161-162 (dec)
	q	H	CHO		A	85.4	130-132
NaF	r	Me	SO_2Me	F	A	41.1	199-200

Table 2. FAB-Ms and ^{1}H Nmr Data of Erythromycin Derivatives 3a-r

Compd	Molecular Formula	FAB-Ms m/z	^{1}H nmr ($CDCl_3$/TMS) δ J (Hz)
3a	$C_{40}H_{69}NO_{15}$ (803.99)	804	1.45(3H,s,6-Me), 2.56(6H,s,2'-NMe_2), 2.70(1H,d,J=2.1 and 2.5,2'-H), 3.06(3H, s,6-OMe), 3.29(3H,s,3"-OMe), 3.97(1H,m,5'-H), 4.92(1H,d,J=2.1,1'-H), 5.36 (1H,m,3'-H), 8.12(1H,s,3'-OCHO), 8.19(1H,s,4"-OCHO)
3b	$C_{38}H_{67}NO_{13}$ (747.97)	748	1.46(3H,s,6-Me), 2.64(6H,s,2'-NMe_2), 2.77(1H,dd,J=2.2 and 2.7,2'-H), 3.05 (3H,s,6-OMe), 3.30(3H,s,3'-OMe), 3.98(1H,m,5'-H), 4.31(1H,ddd,J=2.5,2.7 and 3.0,3'-H), 5.07(1H,d,J=2.2,1'-H)
3c	$C_{37}H_{67}NO_{13}$ (733.95)	734	1.51(3H,s,6-Me), 2.51(6H,s,2'-NMe_2), 3.29(3H,s,3"-OMe), 5.01(1H,d,J=2.2, 1'-H)
3d	$C_{38}H_{68}N_4O_{12}$ (772.99)	773	1.45(3H,s,6-Me), 2.53(6H,s,2'-NMe_2), 2.55(1H,dd,J=2.2 and 3.1,2'-H), 3.04 (3H,s,6-OMe), 3.34(3H,s,3"-OMe), 4.01(1H,m,3'-H), 4.90(1H,d,J=2.2,1'-H)
3e	$C_{39}H_{70}N_4O_{14}S$ (851.08)	851	1.44(3H,s,6-Me), 2.51(6H,s,2'-NMe_2), 3.04(3H,s,6-OMe), 3.06(3H,s,4"-OSO_2Me), 3.35(3H,s,3"-OMe), 3.90(1H,m,5'-H), 4.02(1H,m,3'-H), 4.91(1H,d,J=2.2,1'-H)
3f	$C_{37}H_{66}N_4O_{12}$ (858.96)	859	1.50(3H,s,6-Me), 2.53(6H,s,2'-NMe_2), 3.33(3H,s,3"-OMe), 3.80(1H,m,5'-H), 4.90(1H,d,J=2.1,1'-H)
3g	$C_{38}H_{68}N_4O_{14}S$ (837.05)	837	1.50(3H,s,6-Me), 2.57(6H,s,2'-NMe_2), 3.08(3H,4"-OSO_2Me), 3.35(3H,s,3"-OMe), 4.91(1H,d,J=2.2,1'-H)
3h	$C_{37}H_{68}N_2O_{12}$ (732.96)	733	1.53(3H,s,6-Me), 2.59(6H,s,2'-NMe_2), 3.28(3H,s,3'-OMe), 3.55(1H,m,3'-H), 4.02(1H,m,5'-H), 5.07(1H,d,J=2.2,1'-H)

(continued)

3i	$C_{41}H_{76}N_2O_{14}S$ (853.13)	853	1.44(3H,s,6-Me), 2.23(6H,s,3'-NMe_2), 2.52(6H,s,2'-NMe_2), 3.04(3H,s,6-OMe), 3.05 (3H,s,4"-OSO_2Me), 3.31(3H,s,3"-OMe), 3.88(1H,m,5'-H), 5.00(1H,d,J=2.2,1'-H)
3j	$C_{46}H_{78}N_2O_{14}S$ (915.15)	915	1.45(3H,s,6-Me), 2.53(6H,s,2'-NMe_2), 2.98(3H,s,4"-OSO_2Me), 3.04(3H,s,6-OMe), 3.15(3H,s,3"-OMe), 3.76 and 3.86(2H,ABq,J=13,NCH_2Ph), 4.83(1H,d,J=2.2,1'-H), 7.16-7.44(5H,Ar-H)
3k	$C_{41}H_{74}N_2O_{13}$ (803.05)	803	1.51(3H,s,6-Me), 2.56(6H,s,2'-NMe_2), 3.30(3H,s,3"-OMe), 4.95(1H,d,J=2.1,1'-H)
3l	$C_{42}H_{76}N_2O_{16}S$ (897.14)	897	1.55(3H,s,6-Me), 2.41(6H,s,$COCH_2NMe_2$), 2.57(6H,s,2'-NMe_2), 3.08(3H,s, 4"-OSO_2Me), 3.34(3H,s,3"-OMe), 4.85(1H,d,J=2.5,1'-H)
3m	$C_{44}H_{70}N_2O_{15}$ (867.05)	867	1.55(3H,s,6-Me), 2.67(6H,s,2'-NMe_2), 2.89(3H,s,3"-OMe), 5.00(1H,d,J=2.2,1'-H), 7.38,8.26,8.77,9.28(4H,Ar-H), 8.18(1H,s,4"-OCHO)
3n	$C_{41}H_{72}N_2O_{13}S_2$ (865.17)	865	1.54(3H,s,6-Me), 2.63(6H,s,2'-NMe_2), 3.29(3H,s,3"-OMe), 3.30,3.56(6H,$CSNMe_2$), 4.83(1H,d,J=2.5,1'-H), 8.20(1H,s,4"-OCHO)
3o	$C_{41}H_{71}NO_{14}S_2$ (866.15)	866	1.33(3H,t,J=7.3,$CH_2\underline{CH}_3$), 1.50(3H,s,6-Me), 2.60(6H,s,2'-NMe_2), 2.47(2H,q,J=7.3, $\underline{CH}_2CH_3$), 3.32(3H,s,3"-OMe), 5.00(1H,d,J=2.5,1'-H), 8.19(1H,s,4"-OCHO)
3p	$C_{40}H_{73}NO_{15}S$ (840.03)	840	1.41(3H,s,6-Me), 2.82(6H,s,3'-OMe), 3.06(6H,s,2'-NMe_2), 3.10(3H,s,6-OMe), 3.28 3H,s,4"-OSO_2Me), 3.42(3H,s,3"-OMe), 4.91(1H,m,3'-H), 5.13(1H,d,J=2.2,1'-H)
3q	$C_{40}H_{67}N_5O_{13}S$ (860.06)	860	1.53(3H,s,6-Me), 2.62(6H,s,2'-NMe_2), 3.24(3H,s,N-Me), 3.69(3H,s,3"-OMe), 4.98 (1H,d,J=2.5,1'-H), 8.20(1H,s,4"-OCHO)
3r	$C_{39}H_{70}FNO_{14}S$ (828.05)	828	1.43(3H,s,6-Me), 2.54(6H,s,2'-NMe_2), 3.05(3H,s,6-OMe), 3.06(3H,s,4"-OSO_2Me), 3.28(3H,s,3"-OMe), 4.92(1H,d,J=2.2,1'-H)

Table 3. Comparison of ^{13}C Nmr Chemical Shift for Amino Sugar Moiety of Erythromycin Derivatives

Compd	^{13}C Nmr ($CDCl_3$/TMS) δ							
	C-1'	C-2'	C-3'	C-4'	C-5'	5'-CH_3	$N(CH_3)_2$	3'-CHO
1a	103.2	70.9	65.4	28.6	68.8	21.3	40.2	
1c	102.9	71.0	65.6	28.6	68.8	21.5	40.3	
2c	99.2	80.9	63.6	29.6	67.5	21.5	40.2	
2d	99.3	80.9	63.4	29.6	67.5	21.2	40.2	160.3
3a	100.7	61.2	71.0	33.8	66.8	21.2	44.7	160.3
3b	100.3	64.4	68.3	36.0	66.6	21.5	45.1	
3d	100.4	61.6	60.1	32.7	67.0	21.4	44.9	
3f	100.3	61.6	60.2	32.7	66.9	21.5	44.9	
4	101.4	62.0	65.5	31.4	67.9	21.9	40.1	
6	98.6	78.9	65.8	34.9	67.4	21.4	48.4	

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