SYNTHETIC STUDIES OF ERYTHROMYCIN DERIVATIVES

SYNTHESES AND ANTIMICROBIAL ACTIVITIES OF 3″-*EPI*-ERYTHROMYCIN A AND (9*S*)-11-DEHYDROXY-9-DEOXO-9-HYDROXY-11-OXOERYTHROMYCIN A

MASAYA NAKATA,* TETSURO TAMAI, YUKIKO MIURA,
MITSUHIRO KINOSHITA and KUNIAKI TATSUTA

Department of Applied Chemistry, Faculty of Science and Technology, Keio University,
3-14-1 Hiyoshi, Kohoku-ku, Yokohama 223, Japan

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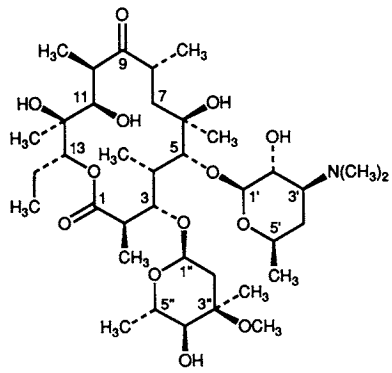
Two new derivatives, 3″-*epi*-erythromycin A (**2**) and (9*S*)-11-dehydroxy-9-deoxo-9-hydroxy-11-oxoerythromycin A (**3**), have been synthesized by using glycosylation with glycal (Ferrier rearrangement), bromomethoxylation and bis(tributyltin) oxide-bromine oxidation as the key steps. Their antimicrobial activities were compared with those of erythromycin A (**1**).

Erythromycin A (**1**) is one of the most important members of macrolide antibiotics.[1] A number of erythromycin A derivatives have been prepared in an attempt to improve biological activities.[1,2] However, little attention has been directed to the modification of the rather inaccessible C-3″ position of the cladinose moiety. An example has been reported by HAUSKE and co-workers.[3] They synthesized 4″-deoxy-3″,4″-dihydrofuranylerythromycin A derivatives by using diazo phosphonate mediated intramolecular cyclization. During the course of the total synthetic studies of erythromycin A (**1**),[4~8] we found that 3″-*epi*-erythromycin A (**2**) could be obtained *via* bromomethoxylation of **7**, which possesses the 2″,3″-unsaturated sugar at the C-3 position. We also found that the C-11 hydroxyl group of the 9,11-diol system, which had been considered to be inert to the oxidation conditions,[6~9] could be oxidized to the carbonyl group. Although the 11-oxoerythromycin A derivatives have been prepared by Abbott Laboratories[10,11] and were isolated in the fermentation broth of *Saccharopolyspora* sp. L53-18 by Toyo Jozo Group,[12~16] all these compounds are 9,12-cyclic ether derivatives. We succeeded the first synthesis of (9*S*)-11-dehydroxy-9-deoxo-9-hydroxy-11-oxoerythromycin A (**3**) by using bis(tributyltin) oxide-bromine oxidation of the 9,11-diol function as a key step.

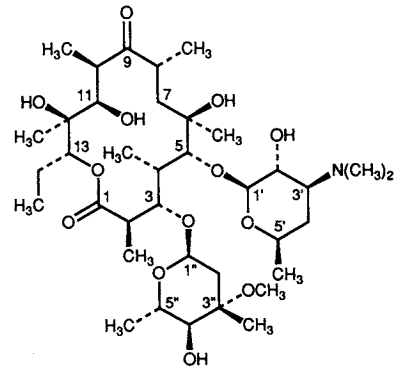
We now report not only the syntheses of 3″-*epi*-erythromycin A (**2**) and (9*S*)-11-dehydroxy-9-deoxo-9-hydroxy-11-oxoerythromycin A (**3**), but also their antimicrobial activities.

Chemistry

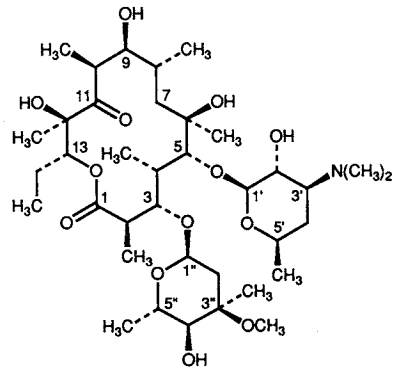
The 2′-hydroxyl group of (9*S*)-9-deoxo-5-*O*-(β-D-desosaminyl)-9-hydroxy-erythronolide A (**4**), which was derived from natural erythromycin A (**1**),[17] was protected (80% yield) with a methoxycarbonyl group by treatment with methyl chloroformate. Subsequent acetonation of the 9,11-dihydroxyl groups, using 2-methoxypropene and pyridinium *p*-toluenesulfonate (PPTS) in CH_2Cl_2, afforded the 9,11-acetonide **5** in 84% yield. This compound had been also prepared from (9*S*)-9-deoxo-9-hydroxyerythronolide A during the course of the total synthetic studies of erythromycin A (**1**).[8] Glycosylation of **5** with the glycal **6**,[8] which was prepared[18] from naturally derived methyl L-cladinoside[19,20] (see Experimental), in the presence of (±)-10-camphorsulfonic acid (CSA) and molecular sieves 4A powder (MS 4AP) in CH_2Cl_2 was succeeded[18,21,22] with the concomitant demethanolization (Ferrier rearrangement),[23] to give the



Erythromycin A (**1**)

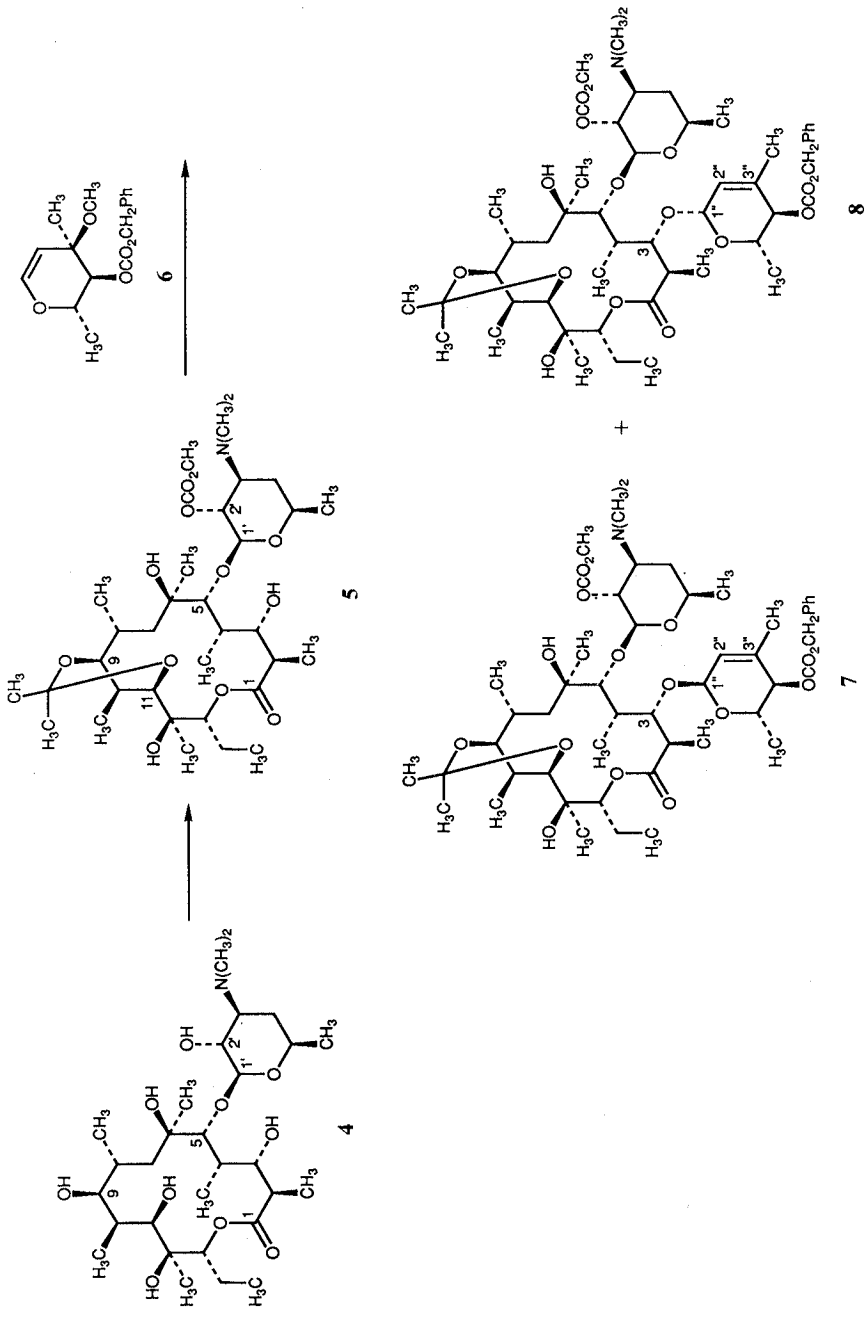


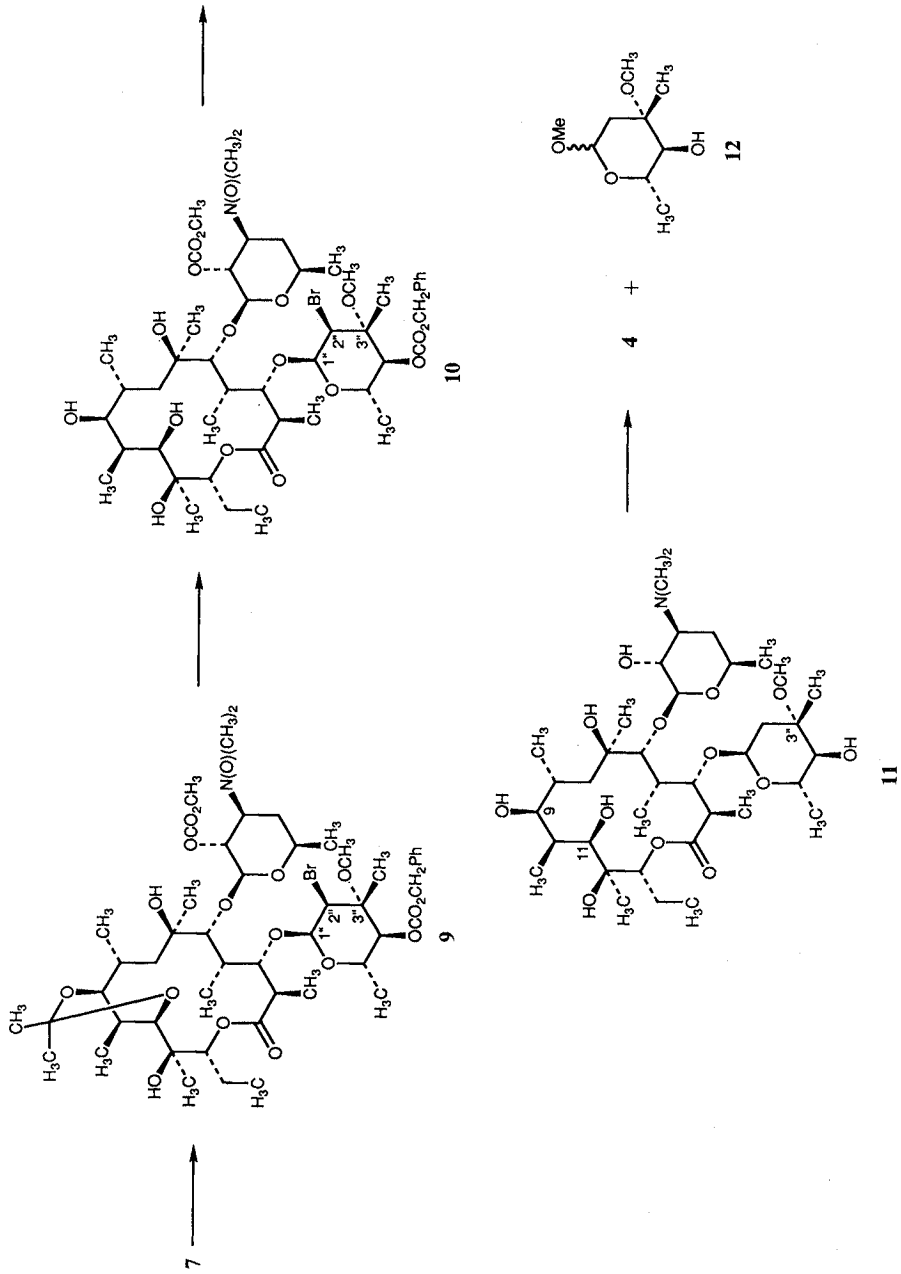
3″-*epi*-Erythromycin A (**2**)



(9*S*)-11-Dehydroxy-9-deoxo-9-hydroxy-11-oxoerythromycin A (**3**)

2″,3″-olefin **7** and **8** in 43% and 8% yields, respectively. The anomeric (C-1″) configuration of each product could not be determined at this stage, because of the very small ($J_{1'',2''} = \sim 0$ Hz) coupling constant of each product, but was confirmed in the later stage (*vide infra*). Treatment of the major product **7** with 3-chloroperoxybenzoic acid (MCPBA) in $CHCl_3$ gave the *N*-oxide, which was subjected to bromomethoxylation with *N*-bromosuccinimide (NBS) in MeOH to afford the bromide **9** in 46% yield and as-yet-unidentified byproducts. Neither the regio- nor the stereoisomers of **9** were isolated in this reaction. Acid treatment (50 (v/v) % aqueous acetic acid) of **9** gave the 9,11-diol **10** in 96% yield. At this stage, the C-1″ configuration of **7** and **8** and the C-1″, C-2″ and C-3″ configurations of **9** and **10** were determined as follows. In the ^{1}H NMR spectra, the anomeric (C-1″) protons of **9** and **10** appeared as narrow doublets ($J_{1'',2''} = 2.6$ Hz for **9**, $J_{1'',2''} = 3.2$ Hz for **10**) excluding the axial-axial relationship between H-1″ and H-2″. Debromination and reduction of the *N*-oxide of **10** with tributyltin hydride (TBTH) and 2,2′-azobis(2-methylpropionitrile) (AIBN) followed by deprotection of the 2′- and 4″-hydroxyl protecting groups gave **11**. The ^{1}H NMR spectrum and TLC mobilities of this sample were not identical with those of the authentic (9*S*)-9-deoxo-9-hydroxyerythromycin A.[17] Furthermore, hydrolysis of **11** with 1% HCl-MeOH gave **4** and **12** in quantitative yields. The ^{1}H NMR spectrum and TLC mobilities of **4** were identical with those of the naturally derived **4**,[17] while the sugar moiety **12** was not identical with the




7
9
10
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4 +
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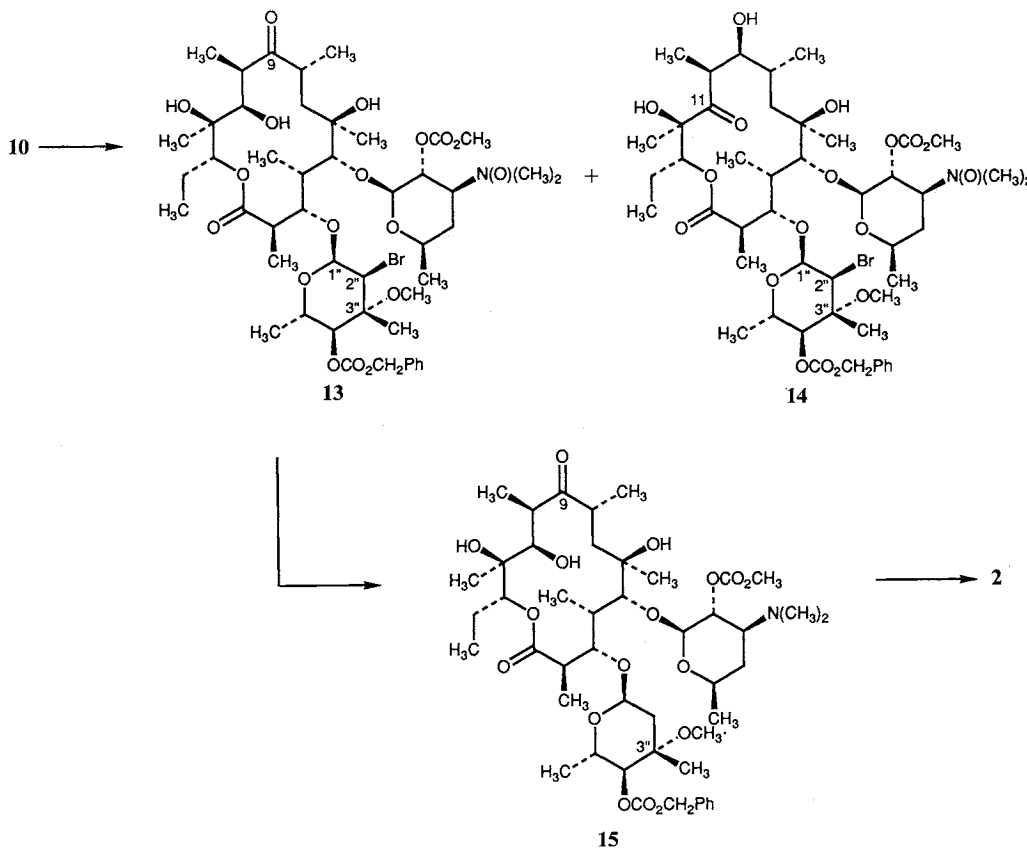
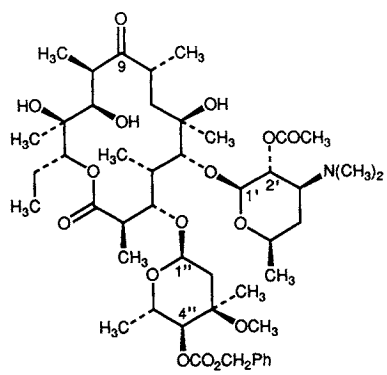


naturally derived methyl L-cladinoside[19,20] on TLC and the ^{1}H NMR spectrum of **12** clearly showed that it was methyl 3-*epi*-L-cladinoside. These observations and the *trans*-fashioned behavior of bromomethoxylation on olefin with NBS in MeOH confirmed the structures of **9** and **10** (hence **7** and **8**) as depicted.

With the compound having the 3″-*epi*-cladinose moiety in hand, our next concern was the oxidation of the hydroxyl group in the aglycone and the transformation to 3″-*epi*-erythromycin A (**2**). Among the investigated oxidation conditions, the bis(tributyltin) oxide-bromine oxidation[24~26] gave the satisfactory result. Treatment of **10** with these reagents in CH_2Cl_2 afforded the 9-oxo compound **13** and the 11-oxo compound **14** in 54% and 27% yields, respectively. This oxidation procedure has already been used in the total synthesis of erythromycin A (**1**).[8] Treatment of **13** with TBTH and AIBN afforded **15** in 64% yield. Finally, demethoxycarbonylation of **15** with warm MeOH followed by debenzyloxycarbonylation by hydrogenolysis afforded 3″-*epi*-erythromycin A (**2**) in 80% yield. The C-9 chemical shift (222.3 ppm) in the ^{13}C NMR spectrum of **15** was similar to that (221.9 ppm) of erythromycin A (**1**).[27] On the other hand, the C-11 chemical shift (215.6 ppm) of **14** was similar to that (216.4 ppm) of **3** (*vide infra*).

Following these results, it was anticipated that (9*S*)-11-dehydroxy-9-deoxo-9-hydroxy-11-oxoerythromycin A (**3**) might be available by bis(tributyltin) oxide-bromine oxidation of the 9,11-diol function in the aglycone bearing the suitably protected sugar moieties. To this end, 2′-*O*-acetyl-4″-*O*-(benzyloxycarbonyl)erythromycin A (**16**), derived from erythromycin A (**1**) by the literature procedure,[11] was



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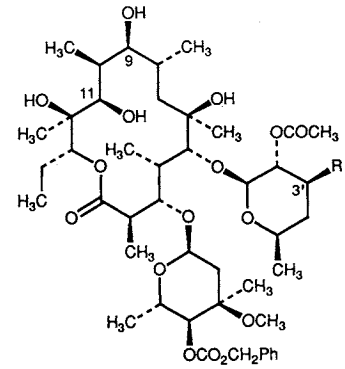
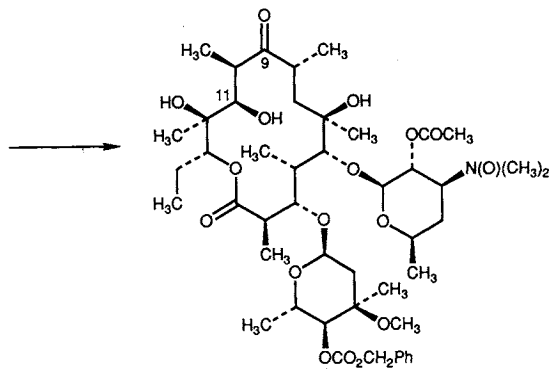


17 R=N(CH$_3$)$_2$
18 R=N(O)(CH$_3$)$_2$



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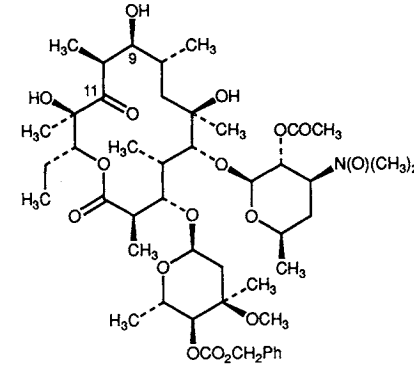

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3

Table 1. Antibacterial activities of **1**, **2** and **3** (MIC, μg/ml).

Organisms	1	2	3
Staphylococcus aureus FDA 209P	<0.78	<0.78	0.78
S. aureus Smith	<0.78	<0.78	1.56
S. aureus MS 9610	>100	>100	>100
S. aureus No. 5	>100	>100	>100
S. aureus No. 17	<0.78	<0.78	1.56
Micrococcus luteus PC I1001	0.78	1.56	0.78
Bacillus subtilis NRRL B-558	<0.78	<0.78	0.39
Corynebacterium bovis 1810	<0.78	<0.78	0.39
Escherichia coli NIHJ	6.25	25	>100
E. coli K-12	50	100	>100
E. coli ML 1629	100	>100	>100
Klebsiella pneumoniae PCI 602	6.25	25	50
Shigella dysenteriae JS 11910	1.56	3.12	12.5
Salmonella enteritidis 1891	3.12	3.12	12.5
S. typhi T-63	50	>100	>100
Proteus vulgaris OX 19	50	100	>100
Serratia marcescens	50	>100	>100
Pseudomonas aeruginosa A3	50	>50	100

Medium: Mueller-Hinton agar (Difco), 37°C.

reduced with $NaBH_4$ to afford **17** (77% yield), which was treated with MCPBA to give **18** in 96% yield. When **18** was subjected to bis(tributyltin) oxide-bromine, the regioisomeric oxo compounds **19** and **20** were formed in 57% and 13% yields, respectively. The 9-oxo compound **19** was identical with the authentic sample derived from **16** by MCPBA oxidation by comparison with ^1H NMR spectrum and Rf-values on TLC. The 11-oxo compound **20** was then transformed to (9*S*)-11-dehydroxy-9-deoxo-9-hydroxy-11-oxoerythromycin A (**3**) by selective reduction and deprotection in 83% yield. The structure of **3** was elucidated by its reduction with $NaBH_4$ in MeOH to the authentic (9*S*)-9-deoxo-9-hydroxyerythromycin A.[17]

Biological Results

The minimal inhibitory concentrations (MIC) of **1**, **2** and **3** were determined against laboratorial strains by standard agar dilution methods and are shown in Table 1. Although two new derivatives **2** and **3** retained antibacterial activity, none of these showed significant improvement against all bacteria. Nevertheless, 11-oxo compound **3** is the first example among the intact 14-membered macrolide antibiotics and hence we believe that this could become a useful new lead compound in the modification studies of macrolide antibiotics.

Experimental

Melting points were determined on a micro hot-stage Yanaco MP-S3 and were uncorrected. Optical rotations were measured on a JASCO DIP-360 photoelectric polarimeter in $CHCl_3$ unless otherwise noted. IR spectra were recorded on a BIO RAD DIGILAB FTS-65 spectrometer and NMR spectra were on either a JEOL GSX270 or a JEOL GSX400 spectrometer in $CDCl_3$ using TMS as internal standard unless otherwise noted. Silica-gel TLC and column chromatography were performed on Merck TLC $60F_{254}$ and Merck Kieselgel 60, respectively. Air- and/or moisture-sensitive reactions were carried out under an atmosphere of argon with oven-dried glassware. In general, organic solvents were purified and dried by the appropriate procedure, and evaporation and concentration were carried out under reduced pressure below 30°C, unless otherwise noted.

(9*S*)-9-Deoxo-9-hydroxy-9,11-*O*-isopropylidene-5-*O*-(2-*O*-methoxycarbonyl-β-D-desosaminyl)-erythronolide A (**5**)

To a vigorously stirred mixture of **4**[17] (13.1 g, 22.7 mmol) and $NaHCO_3$ (7.63 g, 90.8 mmol) in CH_2Cl_2 (454 ml) and water (153 ml) was added at room temperature methyl chloroformate (3.49 ml, 45.2 mmol). After 16.5 hours at room temperature, the organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (3 × 300 ml). The combined organic layers were washed with saturated aqueous NaCl, dried and concentrated. The residue was chromatographed on silica gel (800 g) with 1:1 hexane-acetone to afford colorless crystals (11.5 g, 80%). To a stirred solution of this sample (7.47 g, 11.7 mmol) and 2-methoxypropene (6.75 ml, 70.5 mmol) in dry CH_2Cl_2 (74.7 ml) was added at 0°C PPTS (3.84 g, 15.3 mmol). After 12 hours at room temperature, the reaction mixture was poured into cold saturated aqueous $NaHCO_3$ and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were washed with saturated aqueous NaCl, dried and concentrated. The residue was chromatographed on silica gel (480 g) with 1:1 $CHCl_3$-acetone to afford **5** (6.69 g, 84%) as colorless crystals: Rf=0.27 (1:1 $CHCl_3$-acetone); mp 164~166°C (colorless flakes from 1:1 acetone-hexane): $[\alpha]_D^{31}$ +1.0° (*c* 1.14); IR ($CHCl_3$) 1726 and 1750 cm^{-1}; ^1H NMR (400 MHz) δ=0.83 (3H, t, *J*=7.0 Hz, 3 × H-15), 0.92, 0.95, 1.16, 1.21 and 1.26 (each 3H, each d, *J*=~7.0 Hz, 5 × Me), 1.20 and 1.25 (each 3H, each s, 6- and 12-Me), 1.46 and 1.47 (each 3H, each s, CMe_2), 2.28 (6H, s, NMe_2), 2.60 (1H, s, OH), 2.66 (1H, dq, *J*=6.5 Hz and 7.0 Hz, H-2), 2.76 (1H, m, H-3'), 3.45~3.66 (5H, m, H-3, 5, 5', 9 and 11), 3.78 (3H, s, OMe), 4.55~4.65 (2H, m, H-1' and 2'), 5.13 (1H, dd, *J*=1.0 Hz and 11.0 Hz, H-13) and 5.28 (1H, s, OH). Found: C 60.11, H 8.94, N 1.99%. Calcd for $C_{34}H_{61}NO_{12}$: C 60.42, H 9.10, N 2.07%.

4-*O*-Benzyloxycarbonyl-L-cladinal (**6**)

To a stirred solution of methyl L-cladinoside[19,20] (10.1 g, 53.1 mmol) and 4-dimethylaminopyridine (25.9 g, 212 mmol) in dry CH_2Cl_2 (101 ml) was added at 0°C benzyl chloroformate (30.3 ml, 212 mmol). After 20 hours at room temperature, EtOH (12 ml) was added and the mixture was poured into cold water (160 ml). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2×100 ml). The combined organic layers were washed with saturated aqueous NaCl, dried and concentrated. The residue was dissolved in 0.8 M HCl in 50% aqueous acetonitrile (520 ml) and the mixture was warmed at 50°C for 18 hours. After being cooled to 0°C, the reaction mixture was neutralized with solid $NaHCO_3$. The mixture was extracted with CH_2Cl_2 (3×150 ml) and the extracts were dried and concentrated. The residue was chromatographed on silica gel (600 g) with 2:1 hexane-ethyl acetate to afford 4-*O*-benzyloxycarbonyl-L-cladinose (15.1 g, 92%) as a colorless syrup: Rf=~0.4 (2:1 hexane-ethyl acetate); $[\alpha]_D^{30}$ −32.1° (*c* 0.73, MeOH); IR ($CHCl_3$) 1747 cm^{-1}; ^1H NMR (270 MHz, $\alpha:\beta=1:2.5$) for $\alpha:\delta=1.20$ (3H, d, $J=6.6$ Hz, 5-Me), 1.24 (3H, s, 3-Me), 1.76 (1H, dd, $J_{1,2ax}=4.0$ Hz and $J_{gem}=14.4$ Hz, H-2ax), 2.12 (1H, dd, $J_{1,2eq}=1.2$ Hz and $J_{gem}=14.4$ Hz, H-2eq), 3.41 (3H, s, 3-OMe), 4.26 (1H, dq, $J_{4,5}=10.0$ Hz, $J_{5,Me}=6.6$ Hz, H-5), 4.47 (1H, d, $J_{4,5}=10.0$ Hz, H-4), 5.07 (1H, ddd, $J_{1,2ax}=4.0$ Hz, $J_{1,2eq}=1.2$ Hz and $J_{1,OH}=11.0$ Hz, H-1), 5.19 and 5.23 (each 1H, ABq, $J_{gem}=12.0$ Hz, OCH_2Ph), 5.47 (1H, d, $J_{1,OH}=11.0$ Hz, OH) and 7.30~7.40 (5H, m, Ph). For $\beta:\delta=1.17$ (3H, d, $J=6.6$ Hz, 5-Me), 1.18 (3H, s, 3-Me), 1.44 (1H, dd, $J_{1,2ax}=9.4$ Hz and $J_{gem}=14.0$ Hz, H-2ax), 2.30 (1H, dd, $J_{1,2eq}=2.0$ Hz and $J_{gem}=14.0$ Hz, H-2eq), 3.20 (1H, d, $J=6.4$ Hz, OH), 3.27 (3H, s, 3-OMe), 4.07 (1H, dq, $J_{4,5}=9.4$ Hz, $J_{5,Me}=6.6$ Hz, H-5), 4.44 (1H, d, $J_{4,5}=9.4$ Hz, H-4), 5.05 (1H, ddd, $J_{1,2ax}=9.4$ Hz, $J_{1,2eq}=2.0$ Hz and $J_{1,OH}=6.4$ Hz, H-1), 5.18 and 5.21 (each 1H, ABq, $J_{gem}=12.0$ Hz, OCH_2Ph) and 7.30~7.40 (5H, m, Ph). Found: C 61.73, H 6.86%. Calcd for $C_{16}H_{22}O_6$: C 61.92, H 7.14%. To a stirred solution of this sample (15.1 g, 48.7 mmol) in dry CH_2Cl_2 (151 ml) were added at 0°C triethylamine (30.5 ml, 219 mmol) and *p*-toluenesulfonic chloride (13.9 g, 72.9 mmol). After 37 hours at room temperature, EtOH (8.4 ml) was added and the mixture was poured into cold water (200 ml). The mixture was extracted with ethyl acetate (3×200 ml) and the extracts were washed with saturated aqueous NaCl, dried and concentrated. The residue was chromatographed on silica gel (700 g) with 8:1 hexane-ethyl acetate to afford **6** (12.7 g, 89%) as a colorless syrup: Rf=0.75 (2:1 hexane-ethyl acetate); $[\alpha]_D^{26}$ −161° (*c* 1.53); IR ($CHCl_3$) 1640 and 1744 cm^{-1}; ^1H NMR (270 MHz) $\delta=1.23$ (3H, s, 3-Me), 1.25 (3H, d, $J=7.5$ Hz, 5-Me), 3.27 (3H, s, 3-OMe), 4.29 (1H, dq, $J_{4,5}=11.1$ Hz and $J_{5,Me}=7.5$ Hz, H-5), 4.66 (1H, d, $J_{4,5}=11.1$ Hz, H-4), 4.71 (1H, d, $J_{1,2}=6.3$ Hz, H-2), 5.18 and 5.22 (each 1H, ABq, $J_{gem}=12.0$ Hz, OCH_2Ph), 6.37 (1H, d, $J_{1,2}=6.3$ Hz, H-1) and 7.30~7.40 (5H, m, Ph).

(9*S*)-3-*O*-(4-*O*-Benzyloxycarbonyl-2,3,6-trideoxy-3-*C*-methyl-α-L-*threo*-2-enohexopyranosyl)-9-deoxo-9-hydroxy-9,11-*O*-isopropyridene-5-*O*-(2-*O*-methoxycarbonyl-β-D-desosaminyl)erythronolide A (**7**) and Its 3-*O*-β-Isomer **8**

To a vigorously stirred suspension of **5** (102 mg, 0.151 mmol), **6** (221 mg, 0.756 mmol) and MS 4AP (490 mg) in dry CH_2Cl_2 (0.76 ml) was added at room temperature CSA (210 mg, 0.904 mmol). After 25 minutes at room temperature, the reaction mixture was filtered with Celite into ethyl acetate containing triethylamine (0.12 ml) and the filter cake was washed with ethyl acetate. The combined filtrate and washings were concentrated and the residue was chromatographed on silica gel (63 g) with 1:2 hexane-ethyl acetate to afford **7** (60.8 mg, 43%) and **8** (11.3 mg, 8%) as colorless crystals.

7: Rf=0.44 (1:2 hexane-ethyl acetate); mp 185~186°C (colorless needles from 1:3 ethyl acetate-hexane); $[\alpha]_D^{29}$ −4.3° (*c* 0.70); IR (KBr) 1745 and 1750 cm^{-1}; ^1H NMR (400 MHz) $\delta=0.84$ (3H, t, $J=7.5$ Hz, 3×H-15), 0.89, 0.97, 1.08, 1.15, 1.22 and 1.29 (each 3H, each d, $J=7.2$, 7.2, 6.0, 6.7, 7.2 and 6.4 Hz, 6×Me), 1.15 and 1.25 (each 3H, each s, 6- and 12-Me), 1.43 and 1.45 (each 3H, each s, CMe_2), 1.72 (3H, br s, 3″-Me), 1.40~2.30 (9H, m), 2.23 (6H, s, NMe_2), 2.59 (1H, s, OH), 2.71 (1H, m, H-3′), 2.85 (1H, dq, $J_{2,3}=8.8$ Hz and $J_{2,Me}=7.2$ Hz, H-2), 3.45~3.55 (3H, m, H-5 or 11, H-5′ and H-9), 3.59 (1H, d, $J=5.4$ Hz, H-5 or 11), 3.76 (3H, s, OMe), 3.92 (1H, dq, $J_{4'',5''}=7.5$ Hz and $J_{5'',Me}=6.4$ Hz, H-5″), 4.04 (1H, dd, $J_{2,3}=8.8$ Hz and $J_{3,4}=1.6$ Hz, H-3), 4.49~4.56 (2H, m, H-1′ and 2′), 4.65 (1H, br, OH), 4.91 (1H, d, $J_{4'',5''}=7.5$ Hz, H-4″), 5.04 (1H, dd, $J=2.4$ Hz and 10.9 Hz, H-13), 5.17 and 5.21 (each 1H, ABq, $J_{gem}=12.0$ Hz, OCH_2Ph), 5.25 (1H, br s, H-1″), 5.65 (1H, br s, H-2″) and 7.36 (5H, s like, Ph). Found: C 63.01, H 8.03, N 1.48%. Calcd for $C_{49}H_{77}NO_{16}$: C 62.87, H 8.29, N 1.50%.

8: Rf=0.28 (1:2 hexane-ethyl acetate); mp 98~99°C (colorless powders from 1:4 acetone-hexane);

$[\alpha]_D^{29}$ −3.1° (*c* 0.68); IR (KBr) 1738 and 1754 cm^{-1}; ^1H NMR (400 MHz) δ=0.83 (3H, t, J=7.5 Hz, 3×H-15), 0.93 and 0.96 (each 3H, each d, each J=7.5 Hz, 2×Me), 1.15~1.30 (18H, m, 6×Me), 1.45~2.35 (9H, m), 1.47 and 1.50 (each 3H, each s, CMe_2), 1.69 (3H, br s, 3″-Me), 2.29 (6H, s, NMe_2), 2.57 (1H, s, OH), 2.68~2.80 (2H, m, H-2 and 3′), 3.41 (1H, m, H-5′), 3.52 (1H, d, J=1.8 Hz, H-5 or 11), 3.54 (1H, dd, $J_{8,9}=J_{9,10}$=3.0 Hz, H-9), 3.65 (1H, dq, $J_{4'',5''}$=8.0 Hz and $J_{5'',Me}$=6.4 Hz, H-5″), 3.72 (1H, d, J=4.5 Hz, H-5 or 11), 3.77 (3H, s, OMe), 3.97 (1H, d, $J_{2,3}$=10.4 Hz and $J_{3,4}$=0 Hz, H-3), 4.42 (1H, d, $J_{1',2'}$=7.2 Hz, H-1′), 4.54 (1H, dd, $J_{1',2'}$=7.2 Hz and $J_{2',3'}$=10.4 Hz, H-2′), 5.04 (1H, d, $J_{4'',5''}$=8.0 Hz, H-4″), 5.10 (1H, dd, J=2.4 Hz and 11.0 Hz, H-13), 5.20 (2H, s, OCH_2Ph), 5.23 (1H, br s, H-1″), 5.28 (1H, s, OH), 5.65 (1H, br s, H-2″) and 7.38 (5H, s like, Ph). Found: C 63.20, H 8.09, N 1.34%. Calcd for $C_{49}H_{77}NO_{16}$: C 62.87, H 8.29, N 1.50%.

(9*S*,2″*S*)-4″-*O*-Benzyloxycarbonyl-2″-bromo-9-deoxo-9-hydroxy-9,11-*O*-isopropylidene-2′-*O*-methoxycarbonyl-3″-*epi*-erythromycin A *N*-Oxide (**9**)

To a stirred solution of **7** (1.93 g, 2.06 mmol) in dry $CHCl_3$ (39 ml) was added at 0°C MCPBA (533 mg, 3.09 mmol). After 5 minutes at 0°C, the reaction mixture was poured into saturated aqueous $NaHCO_3$ and the organic layer was separated. The aqueous layer was extracted with $CHCl_3$ and the combined organic layers were washed with saturated aqueous NaCl, dried and concentrated. The residue (1.96 g, 2.06 mmol) was dissolved in dry MeOH (21 ml) and to this was added NBS (1.83 g, 10.3 mmol) and the mixture was stirred at room temperature for 40 hours. The reaction mixture was poured into saturated aqueous $NaHCO_3$ and extracted with $CHCl_3$. The extracts were washed with saturated aqueous NaCl, dried and concentrated. The residue was chromatographed on silica gel (438 g) with 3 : 2 ethyl acetate - MeOH to afford **9** (1.01 g, 46%) as colorless foams: Rf=0.31 (3 : 2 ethyl acetate - MeOH); mp 112~113°C (colorless flakes from 1 : 10 $CHCl_3$ - hexane); $[\alpha]_D^{29}$ −31.0° (*c* 0.46); IR (KBr) 1757 cm^{-1}; ^1H NMR (400 MHz) δ=0.83 (3H, t, J=7.4 Hz, 3×H-15), 0.92, 0.94, 1.05, 1.16, 1.30 and 1.42 (each 3H, each d, J=7.7, 7.7, 6.0, 6.0, 7.0 and 6.4 Hz, 6×Me), 1.15, 1.21, 1.46, 1.47 and 1.48 (each 3H, each s, CMe_2, 3″-, 6- and 12-Me), 2.45~2.55 (1H, m, H-4′eq), 2.59 (1H, s, OH), 2.92 (1H, dq, $J_{2,3}$=9.4 Hz and $J_{2,Me}$=6.4 Hz, H-2), 3.17 and 3.30 (each 3H, each s, NMe_2), 3.27 (3H, s, 3″-OMe), 3.48~3.55 and 3.60~3.85 (2H and 3H, each m, H-3′, 5, 5′, 9 and 11), 3.80 (3H, s, COOMe), 3.96 (1H, d, $J_{2,3}$=9.4 Hz and $J_{3,4}$=0 Hz, H-3), 4.05~4.15 (1H, m, H-5″), 4.11 (1H, d, $J_{1'',2''}$=2.6 Hz, H-2″), 4.59 (1H, d, $J_{4'',5''}$=4.6 Hz, H-4″), 4.82 (1H, dd, $J_{1',2'}$=7.2 Hz and $J_{2',3'}$=10.1 Hz, H-2′), 4.91 (1H, d, $J_{1',2'}$=7.2 Hz, H-1′), 4.92 (1H, br s, OH), 5.07 (1H, dd, J=2.4 Hz and 11.0 Hz, H-13), 5.15 (1H, d, $J_{1'',2''}$=2.6 Hz, H-1″), 5.13 and 5.19 (each 1H, ABq, J_{gem}=11.5 Hz, OCH_2Ph) and 7.37 (5H, s like, Ph). Found: C 56.15, H 7.32, N 1.29%. Calcd for $C_{50}H_{80}BrNO_{18}$: C 56.49, H 7.58, N 1.32%.

(9*S*,2″*S*)-4″-*O*-Benzyloxycarbonyl-2″-bromo-9-deoxo-9-hydroxy-2′-*O*-methoxycarbonyl-3″-*epi*-erythromycin A *N*-Oxide (**10**)

A mixture of **9** (665 mg, 0.626 mmol) and 50 (v/v) % aqueous acetic acid (33 ml) was warmed at 50°C for 18 hours. The mixture was concentrated and the residue was chromatographed on silica gel (96 g) with 10 : 1 $CHCl_3$ - MeOH to afford **10** (614 mg, 96%) as colorless crystals: Rf=0.21 (10 : 1 $CHCl_3$ - MeOH); mp 123~125°C (not recrystallized); $[\alpha]_D^{28}$ −32.1° (*c* 0.53); IR (KBr) 1758 cm^{-1}; ^1H NMR (400 MHz) δ=0.89 (3H, t, J=7.4 Hz, 3×H-15), 0.95, 1.06, 1.07, 1.19, 1.34 and 1.38 (each 3H, each d, J=7.4, 6.4, 6.2, 6.9, 6.9 and 6.4 Hz, 6×Me), 1.09, 1.20 and 1.48 (each 3H, each s, 3″-, 6- and 12-Me), 2.62 (1H, br s, OH), 2.74 (1H, m, H-4′eq), 2.92 (1H, dq, $J_{2,3}=J_{2,Me}$=7.4 Hz, H-2), 3.07 and 3.22 (each 3H, each s, NMe_2), 3.29 (3H, s, 3″-OMe), 3.37 (1H, br), 3.50 (1H, m, H-3′), 3.70 (1H, br), 3.79 (3H, s, COOMe), 3.75~3.90 (2H, m), 4.06 (1H, dq, $J_{4'',5''}=J_{5'',Me}$=6.2 Hz, H-5″), 4.12 (1H, d, $J_{2,3}$=8.0 Hz and $J_{3,4}$=0 Hz, H-3), 4.17 (1H, d, $J_{1'',2''}$=3.2 Hz, H-2″), 4.15~4.55 (3H, br, 3×OH), 4.62 (1H, d, $J_{4'',5''}$=6.2 Hz, H-4″), 4.75 (1H, dd, J=1.6 Hz and 10.9 Hz, H-13), 4.82~4.90 (2H, m, H-1′ and 2′), 5.13 and 5.22 (each 1H, ABq, J_{gem}=11.7 Hz, OCH_2Ph), 5.25 (1H, d, $J_{1'',2''}$=3.2 Hz, H-1″) and 7.36 (5H, s like, Ph). Found: C 55.49, H 7.50, N 1.30%. Calcd for $C_{47}H_{76}BrNO_{18}$: C 55.18, H 7.49, N 1.37%.

Degradation of **10**

To a stirred solution of **10** (11.0 mg, 0.0108 mmol) in dry benzene (0.11 ml) were added at room temperature TBTH (0.029 ml, 0.108 mmol) and 0.1 M solution of AIBN in dry benzene (0.043 ml,

0.0043 mmol). After 19 hours at 50°C, the reaction mixture was concentrated and the residue was chromatographed on silica gel (2 g) with 3:1 hexane-acetone to afford (9*S*)-4″-*O*-benzyloxycarbonyl-9-deoxo-9-hydroxy-2′-*O*-methoxycarbonyl-3″-*epi*-erythromycin A (8.3 mg, 83%) as colorless crystals: Rf=0.67 (1:1 hexane-acetone); ^{1}H NMR (400 MHz) δ=0.89 (3H, t, J=8.0 Hz, 3×H-15), 0.89, 1.00, 1.18, 1.20, 1.22 and 1.49 (each 3H, each d, J=7.2, 6.2, 7.5, 7.2, 6.4 and 6.6 Hz, 6×Me), 1.08, 1.08 and 1.22 (6H and 3H, each s, 3×Me), 2.18 (6H, s, NMe_2), 2.63 (1H, br s, OH), 2.70~2.80 (2H, m, H-2 and 3′), 3.10~3.20 (1H, m), 3.21 (3H, s, 3″-OMe), 3.52 (1H, br), 3.63 (1H, m), 3.75 (3H, s, COOMe), 3.94 (1H, br), 4.00~4.20 (4H, m), 4.55~4.63 (2H, m), 4.80 (1H, d like, J=~9.8 Hz), 4.85 (1H, d, J=7.8 Hz), 5.07 (1H, dd, J=1.9 Hz and 8.6 Hz, H-13), 5.14 (2H, br s, OCH_2Ph) and 7.30~7.40 (5H, m, Ph). A mixture of this sample (3.7 mg, 0.0040 mmol), Pd-black and MeOH was hydrogenolysed under an 1 atm of hydrogen for 5 minutes. The catalyst was filtered and washed with MeOH. The combined filtrate and washings were heated at 55°C for 17 hours. After concentration, the residue was chromatographed on silica gel (0.5 g) with 1:1 $CHCl_3$-MeOH to afford **11** (2.8 mg, 95%) as colorless crystals: Rf=0.29 (1:1 CH_2Cl_2-MeOH); ^{1}H NMR (400 MHz) δ=0.90 (3H, t, J=7.2 Hz, 3×H-15), 1.09, 1.14, 1.19, 1.21, 1.24 and 1.40 (each 3H, each d, J=7.0, 6.7, 7.2, 7.2, 6.2 and 6.6 Hz, 6×Me), 1.09, 1.24 and 1.33 (each 3H, each s, 3″-, 6- and 12-Me), 2.37 (6H, br s, NMe_2), 2.60~2.75 (2H, m, H-3′ and OH), 2.83 (1H, dq, $J_{2,3}=J_{2,Me}$=7.2 Hz, H-2), 3.22 (3H, s, 3″-OMe), 3.25 (1H, br), 3.31 (1H, d, $J_{4'',5''}$=6.2 Hz, H-4″), 3.37 (1H, dd, $J_{1',2'}$=7.7 Hz and $J_{2',3'}$=9.8 Hz, H-2′), 3.60 (1H, br s), 3.63 (1H, m, H-5′), 3.93 (1H, d, J=3.5 Hz), 4.01 (1H, dq, $J_{4'',5''}$=6.2 Hz and $J_{5'',Me}$=6.2 Hz, H-5″), 4.08 (1H, br d, $J_{2,3}$=8.0 Hz and $J_{3,4}$=0 Hz, H-3), 4.15~4.30 (1H, m), 4.36 (1H, d, J=1.9 Hz), 4.49 (1H, d, $J_{1',2'}$=7.7 Hz, H-1′), 4.78 (1H, dd, J=1.6 Hz and 10.2 Hz, H-13), 4.86 (1H, br, OH) and 5.01 (1H, dd, $J_{1'',2''ax}=J_{1'',2''eq}$=4.0 Hz, H-1″). This sample was not identical with naturally derived (9*S*)-9-deoxo-9-hydroxyerythromycin A.[17] This sample (4.8 mg, 0.0065 mmol) was dissolved in 1% HCl-MeOH (0.5 ml) and stood at room temperature for 2 days. The reaction mixture was neutralized with solid $NaHCO_3$ and concentrated. The residue was chromatographed on silica gel (1 g) with 1:1 hexane-ethyl acetate and then 1:1 CH_2Cl_2-MeOH to afford **12** (1.2 mg, 100%) as a colorless syrup and **4** (3.8 mg, 100%) as colorless crystals.

12: Rf=0.32 (for α) and 0.24 (for β) (2:1 hexane-ethyl acetate); ^{1}H NMR (400 MHz, $\alpha:\beta$=1.5:1) for α: δ=1.31 (3H, d, J=6.4 Hz, 5-Me), 1.34 (3H, s, 3-Me), 1.77 (1H, dd, $J_{1,2ax}$=4.8 Hz and J_{gem}=12.8 Hz, H-2ax), 2.07 (1H, dd, $J_{1,2eq}$<1.0 Hz and J_{gem}=12.8 Hz, H-2eq), 3.22 and 3.32 (each 3H, each s, 2×OMe), 3.67 (1H, dq, $J_{4,5}$=9.6 Hz and $J_{5,Me}$=6.4 Hz, H-5) and 4.75 (1H, br d, $J_{1,2ax}$=4.8 Hz and $J_{1,2eq}$<1.0 Hz, H-1), for β: δ=1.25 (3H, s, 3-Me), 1.34 (3H, d, J=6.1 Hz, 5-Me), 1.64 (1H, dd, $J_{1,2ax}$=9.8 Hz and J_{gem}=12.0 Hz, H-2ax), 2.05 (1H, dd, $J_{1,2eq}$=1.8 Hz and J_{gem}=12.0 Hz, H-2eq), 3.23 and 3.49 (each 3H, each s, 2×OMe), 3.43 (1H, dq, $J_{4,5}$=9.4 Hz and $J_{5,Me}$=6.1 Hz, H-5) and 4.42 (1H, dd, $J_{1,2ax}$=9.8 Hz and $J_{1,2eq}$=1.8 Hz, H-1). This sample of **12** was not identical with methyl L-cladinoside.[19,20]

(2″*S*)-4″-*O*-Benzyloxycarbonyl-2″-bromo-2′-*O*-methoxycarbonyl-3″-*epi*-erythromycin A *N*-Oxide (**13**) and (9*S*,2″*S*)-4″-*O*-Benzyloxycarbonyl-2″-bromo-11-dehydroxy-9-deoxo-9-hydroxy-2′-*O*-methoxycarbonyl-11-oxo-3″-*epi*-erythromycin A *N*-Oxide (**14**)

To a stirred solution of **10** (367 mg, 0.359 mmol) in dry CH_2Cl_2 (9.5 ml) were added at room temperature bis(tributyltin) oxide (0.238 ml, 0.467 mmol) and 1 M solution of bromine in dry CH_2Cl_2 (0.467 ml, 0.467 mmol). After 6.5 hours at room temperature, the reaction mixture was poured into acetonitrile and the solution was thoroughly washed with hexane. The acetonitrile layer was concentrated and the residue was chromatographed on silica gel (110 g) with 12:1 $CHCl_3$-MeOH to afford **13** (199 mg, 54%) as colorless crystals and **14** (101 mg, 27%) as a colorless glass.

13: Rf=0.52 (10:1 $CHCl_3$-MeOH); mp 119~122°C (colorless needles from 1:8 acetonitrile-ether); $[\alpha]_D^{27}$ −50.7° (*c* 0.56); IR (KBr) 1758 cm^{-1}; ^{1}H NMR (400 MHz) δ=0.84 (3H, t, J=7.2 Hz, 3×H-15), 0.93, 1.03, 1.14, 1.17, 1.27 and 1.39 (each 3H, each d, J=7.7, 6.4, 6.6, 6.4, 6.9 and 6.9 Hz, 6×Me), 1.14, 1.36 and 1.47 (each 3H, each s, 3×Me), 2.58~2.70 (2H, m), 2.89 (1H, dq, $J_{2,3}$=10.1 Hz and $J_{2,Me}$=6.9 Hz, H-2), 3.07 and 3.19 (each 3H, each s, NMe_2), 3.13 (1H, br s), 3.27 (3H, s, 3″-OMe), 3.50 (1H, m), 3.75 (1H, d, J=10.1 Hz), 3.83 (3H, s, COOMe), 3.93 (1H, br s), 4.08 (1H, dq, $J_{4'',5''}$=3.8 Hz and $J_{5'',Me}$=6.9 Hz, H-5″), 4.09 (1H, d, $J_{1'',2''}$=2.7 Hz, H-2″), 4.55 (1H, d, $J_{4'',5''}$=3.8 Hz, H-4″), 4.80~4.87 (2H, m, H-1′ and 2′), 5.07 (1H, d, $J_{1'',2''}$=2.7 Hz, H-1″), 5.08 (1H, dd, J=1.9 Hz and 11.2 Hz, H-13), 5.13 and 5.18 (each 1H, ABq, J_{gem}=11.5 Hz, OCH_2Ph) and 7.36 (5H, s like, Ph). Found: C 54.86, H 6.94, N 1.45%. Calcd

for $C_{47}H_{74}BrNO_{18}$: C 55.29, H 7.31, N 1.37%.

14: Rf=0.38 (10:1 $CHCl_3$-MeOH); $[\alpha]_D^{29}$ −21.8° (*c* 1.40); IR (KBr) 1758 cm^{-1}; ^1H NMR (400 MHz) δ=0.85 (3H, t, *J*=7.4 Hz, 3×H-15), 0.93 (3H, d, *J*=7.0 Hz, 4-Me), 1.17 (3H, d, *J*=7.0 Hz, Me), 1.19 (3H, d, *J*=7.0 Hz, Me), 1.20 (3H, s, Me), 1.22 (3H, d, *J*=7.0 Hz, Me), 1.29 (3H, d, *J*=7.0 Hz, 3×H-6″), 1.38 (3H, d, *J*=7.0 Hz, 2-Me), 1.47 and 1.48 (each 3H, each s, 2×Me), 1.62 (1H, m, H-4′ax), 1.70~1.90 (2H, m, 2×H-14), 1.95 (1H, m, H-4), 2.30 (1H, br), 2.49 (1H, br dq, *J*=~0 Hz and 7 Hz), 2.61 (1H, dq, $J_{2,3}$=7.2 Hz and $J_{2,Me}$=7.0 Hz, H-2), 2.72 (1H, m, H-4′eq), 3.08 and 3.22 (each 3H, each s, NMe_2), 3.28 (3H, s, 3″-OMe), 3.39 (1H, br s, OH), 3.50 (1H, m, H-3′), 3.64 (1H, d, $J_{4,5}$=6.4 Hz, H-5), 3.67 (1H, m, H-5′), 3.81 (3H, s, COOMe), 4.03 (1H, dq, $J_{4'',5''}$=8.2 Hz and $J_{5'',Me}$=7.0 Hz, H-5″), 4.17 (1H, d, $J_{1'',2''}$=3.2 Hz, H-2″), 4.33 (1H, dd, $J_{2,3}$=7.2 Hz and $J_{3,4}$=1.6 Hz, H-3), 4.69 (1H, d, $J_{4'',5''}$=8.2 Hz, H-4″), 4.72 (1H, d, $J_{1',2'}$=6.4 Hz, H-1′), 4.88 (1H, dd, $J_{1',2'}$=6.4 Hz and $J_{2',3'}$=9.8 Hz, H-2′), 4.95 (1H, dd, *J*=3.4 Hz and 9.4 Hz, H-13), 5.19 (1H, d, $J_{1'',2''}$=3.2 Hz, H-1″), 5.17 and 5.22 (each 1H, ABq, J_{gem}=12.0 Hz, OCH_2Ph) and 7.37 (5H, s like, Ph); ^{13}C NMR (67 MHz, $CDCl_3$=77.0) δ=10.0, 10.4, 10.9, 15.9, 17.5, 18.1, 18.3, 20.8, 22.7, 24.0, 25.6, 33.6, 38.0, 38.3, 42.7, 47.7, 48.1, 49.7, 52.1, 54.5, 55.4, 61.5, 67.5, 68.2, 70.1, 74.6, 75.9, 76.0, 76.7, 77.2, 79.0, 80.6, 82.5, 83.0, 96.1, 97.2, 99.6, 107.0, 128.4, 128.7, 128.8, 135.0, 154.6, 176.7 and 215.6.

4″-*O*-Benzyloxycarbonyl-2′-*O*-methoxycarbonyl-3″-*epi*-erythromycin A (**15**)

To a solution of **13** (130 mg, 0.127 mmol) in dry benzene (2.6 ml) were added TBTH (0.342 ml, 1.27 mmol) and AIBN (4.2 mg, 0.026 mmol). After 23 hours at 40°C, TBTH (0.342 ml, 1.27 mmol) and AIBN (4.2 mg, 0.026 mmol) were added and the new mixture was stirred at 80°C for 18 hours. After being cooled to ambient temperature, the mixture was concentrated. The residue was chromatographed on silica gel (120 g) with 3:1 hexane-ethyl acetate (0.8 liter), 1:1 hexane-ethyl acetate (2.6 liters) and finally 4:1 $CHCl_3$-acetone to afford **15** (75.4 mg, 64%) as a colorless glass: Rf=0.37 (3:1 $CHCl_3$-acetone); IR (KBr) 1754 cm^{-1}; ^1H NMR (270 MHz) δ=0.83 (3H, t, *J*=7.8 Hz, 3×H-15), 0.90, 1.02, 1.14, 1.16, 1.18 and 1.36 (each 3H, each d, *J*=7.6, 6.3, 7.0, 7.0, 7.0 and 7.0 Hz, 6×Me), 1.15, 1.24 and 1.37 (each 3H, each s, 3×Me), 2.18 (6H, s, NMe_2), 2.55~2.75 (2H, m, H-3′ and 8), 2.82 (1H, dq, $J_{2,3}$=10.0 Hz and $J_{2,Me}$=7.0 Hz, H-2), 3.08 (1H, dq, $J_{9,10}$=~1.0 Hz and $J_{10,Me}$=7.0 Hz, H-10), 3.12 (1H, br s, OH), 3.21 (3H, s, 3″-OMe), 3.50 (1H, m, H-5′), 3.69 (1H, d, $J_{2,3}$=10.0 Hz and $J_{3,4}$=0 Hz, H-3), 3.78 (3H, s, COOMe), 3.76~3.80 (2H, m, H-5 and 11), 3.90 (1H, br s, OH), 4.02 (1H, dq, $J_{4'',5''}$=4.0 Hz and $J_{5'',Me}$=7.0 Hz, H-5″), 4.48 (1H, dd, $J_{1',2'}$=8.0 Hz and $J_{2',3'}$=10.0 Hz, H-2′), 4.54 (1H, d, $J_{4'',5''}$=4.0 Hz, H-4″), 4.56 (1H, d, $J_{1',2'}$=8.0 Hz, H-1′), 4.96 (1H, dd, $J_{1'',2''ax}$=7.6 Hz and $J_{1'',2''eq}$=2.4 Hz, H-1″), 5.08 (1H, dd, *J*=2.0 Hz and 11.0 Hz, H-13), 5.14 (2H, s, OCH_2Ph) and 7.35 (5H, s like, Ph); ^{13}C NMR (100 MHz, $CDCl_3$=77.0) δ=8.5, 10.6, 12.0, 15.6, 16.2, 17.6, 18.0, 20.3, 20.9, 21.2, 26.9, 29.7, 37.8, 40.6, 44.4, 45.3, 49.0, 54.6, 63.2, 67.9, 69.3, 70.0, 71.4, 74.5, 75.0, 82.8, 83.2, 95.1, 100.1, 128.5, 128.7, 135.0, 155.0, 155.3, 175.2 and 222.3.

3″-*epi*-Erythromycin A (**2**)

A solution of **15** (54.4 mg, 0.0587 mmol) in MeOH (2.5 ml) was warmed at 50°C for 21 hours. After concentration, the residue was dissolved in ethyl acetate (1.0 ml) and Pd-black in ethyl acetate was added. This was hydrogenolysed under an 1 atm of hydrogen for 0.5 minutes. The catalyst was filtered and washed with ethyl acetate. The combined filtrate and washings were concentrated and the residue was chromatographed on silica gel (5 g) with 5:1 $CHCl_3$-MeOH to afford **2** (34.5 mg, 80%) as colorless crystals: Rf=0.38 (2:1 $CHCl_3$-MeOH); mp 138~140°C (colorless needles from 1:1 ethyl acetate-hexane); $[\alpha]_D^{29}$ −43.6° (*c* 0.39); IR (KBr) 1717 cm^{-1}; ^1H NMR (400 MHz, $CHCl_3$=7.26) δ=0.84 (3H, t, *J*=7.8 Hz, 3×H-15), 1.10 (3H, d, *J*=7.0 Hz, 4-Me), 1.13 (3H, s, Me), 1.14 (3H, d, *J*=7.0 Hz, 10-Me), 1.16 (3H, d, *J*=7.0 Hz, 8-Me), 1.17 (3H, d, *J*=7.0 Hz, 2-Me), 1.23 (3H, d, *J*=6.0 Hz, 5′-Me), 1.33 (3H, d, *J*=6.0 Hz, 5″-Me), 1.36 (3H, s, Me), 1.48 (3H, s, Me), 1.48 (1H, m, H-14), 1.79 (1H, dd, $J_{1'',2''ax}$=4.2 Hz and J_{gem}=13.0 Hz, H-2″ax), 1.85~2.05 (3H, m, 2×H-7 and H-14), 2.08 (1H, dd, $J_{1'',2''eq}$=2.6 Hz and J_{gem}=13.0 Hz, H-2″eq), 2.33 (6H, s, NMe_2), 2.55 (1H, m, H-3′), 2.68 (1H, m, H-8), 2.84 (1H, dq, $J_{2,3}$=9.0 Hz and $J_{2,Me}$=7.0 Hz, H-2), 3.08 (1H, q, $J_{10,11}$=~0 Hz and $J_{10,Me}$=7.0 Hz, H-10), 3.09 (1H, br, OH), 3.21 (3H, s, OMe), 3.24 (1H, dd, $J_{1',2'}$=7.8 Hz and $J_{2',3'}$=10.0 Hz, H-2′), 3.29 (1H, d, $J_{4'',5''}$=8.0 Hz, H-4″), 3.53 (1H, m, H-5′), 3.63 (1H, d, $J_{4,5}$=7.4 Hz, H-5), 3.81 (1H, s, $J_{10,11}$=~0 Hz, H-11), 3.84 (1H, dq, $J_{4'',5''}$=8.0 Hz and $J_{5'',Me}$=6.0 Hz, H-5″), 3.92 (1H, br, OH), 4.00 (1H, d, $J_{2,3}$=9.0 Hz and $J_{3,4}$=0 Hz,

H-3), 4.36 (1H, d, $J_{1',2'}=7.8$ Hz, H-1'), 4.98 (1H, dd, $J_{1'',2''ax}=4.2$ Hz and $J_{1'',2''eq}=2.6$ Hz, H-1'') and 5.03 (1H, dd, $J=2.0$ Hz and 11.2 Hz, H-13). Found: C 60.12, H 8.91, N 1.99%. Calcd for $C_{37}H_{67}NO_{13}$: C 60.55, H 9.20, N 1.91%.

(9*S*)-2'-*O*-Acetyl-4''-*O*-benzyloxycarbonyl-9-deoxo-9-hydroxyerythromycin A (**17**)

To a stirred solution of **16**[11] (518 mg, 0.569 mmol) in 2-propanol (10 ml) was added at room temperature $NaBH_4$ (32.3 mg, 0.854 mmol). After 2 hours at room temperature, the reaction mixture was neutralised with solid CO_2 and the insoluble materials were filtered and washed with 2-propanol. The combined filtrate and washings were concentrated and the residue was chromatographed on silica gel (60 g) with 40:1 $CHCl_3$-MeOH to afford **17** (402 mg, 77%) as colorless crystals: Rf=0.41 (20:1 $CHCl_3$-MeOH); mp 90°C (not recrystallized); $[\alpha]_D^{26}$ −44.3° (*c* 0.70); IR (KBr) 1744 cm^{-1}; ^1H NMR (270 MHz) $\delta=0.89$ (3H, t, $J=7.8$ Hz, 3×H-15), 0.94, 1.08 and 1.12 (each 3H, each d, $J=7.8$, 6.2 and 7.0 Hz, 3×Me), 1.10, 1.17 and 1.21 (each 3H, each s, 3''-, 6- and 12-Me), 1.15~1.225 (9H, m, 3×Me), 1.66 (1H, dd, $J_{1'',2''ax}=4.4$ Hz and $J_{gem}=15.0$ Hz, H-2''ax), 2.03 (3H, s, OAc), 2.26 (6H, s, NMe_2), 2.43 (1H, d, $J_{1'',2''eq}=\sim0$ Hz and $J_{gem}=15.0$ Hz, H-2''eq), 2.68 (1H, s, OH), 2.65~2.85 (2H, m, H-2 and 3'), 3.34 (3H, s, OMe), 3.30~3.40 and 3.45~3.65 (each 1H, each br, 2×OH), 3.64 (1H, d, $J_{4,5}=5.8$ Hz, H-5), 3.73 (1H, br t, H-9), 3.76 (1H, m, H-5'), 3.94 (1H br, OH), 4.04 (1H, dd, $J_{2,3}=4.6$ Hz and $J_{3,4}=2.0$ Hz, H-3), 4.10 (1H, d, $J_{10,11}=2.0$ Hz, H-11), 4.28 (1H, dq, $J_{4'',5''}=9.8$ Hz and $J_{5'',Me}=6.2$ Hz, H-5''), 4.48 (1H, d, $J_{4'',5''}=9.8$ Hz, H-4''), 4.75~4.83 (2H, m, H-1' and 2'), 4.87 (1H, dd, $J=3.0$ Hz and 9.6 Hz, H-13), 5.10 (1H, d, $J_{1'',2''ax}=4.4$ Hz and $J_{1'',2''eq}=\sim0$ Hz, H-1''), 5.13 and 5.23 (each 1H, ABq, $J_{gem}=12.2$ Hz, OCH_2Ph) and 7.35 (5H, s like, Ph). Found: C 61.73, H 8.34, N 1.51%. Calcd for $C_{47}H_{77}NO_{16}$: C 61.89, H 8.51, N 1.54%.

(9*S*)-2'-*O*-Acetyl-4''-*O*-benzyloxycarbonyl-9-deoxo-9-hydroxyerythromycin A *N*-Oxide (**18**)

To a stirred solution of **17** (1.21 g, 1.33 mmol) in dry CH_2Cl_2 (12 ml) was added at 0°C MCPBA (342 mg, 1.98 mmol). After 0.5 hour at room temperature, the reaction mixture was poured into saturated aqueous $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted with $CHCl_3$. The combined organic layers were washed with saturated aqueous NaCl, dried and concentrated. The residue was chromatographed on silica gel (60 g) with 8:1 $CHCl_3$-MeOH to afford **18** (1.18 g, 96%) as colorless foams: Rf=0.42 (5:1 $CHCl_3$-MeOH); mp 117~118°C (not recrystalized); $[\alpha]_D^{24}$ −53.6° (*c* 0.43); IR (KBr) 1752 cm^{-1}; ^1H NMR (270 MHz) $\delta=0.89$ (3H, t, $J=7.2$ Hz, 3×H-15), 0.92 (3H, d, $J=7.2$ Hz, Me), 1.05~1.25 (24H, m, 8×Me), 1.65 (1H, dd, $J_{1'',2''ax}=4.4$ Hz and $J_{gem}=15.6$ Hz, H-2''ax), 2.11 (3H, s, OAc), 2.40 (1H, d, $J_{1'',2''eq}=\sim0$ Hz and $J_{gem}=15.6$ Hz, H-2''eq), 2.70~2.85 (2H, m, H-2 and 4'eq), 2.77 (1H, br s, OH), 3.07 and 3.25 (each 3H, each s, NMe_2), 3.33 (4H, s, OMe contaminated with 1H), 3.58 (1H, m, H-3'), 3.65~3.75 (2H, m), 3.80~4.10 (2H, br, 2×OH), 3.96 (1H, m, H-5'), 4.03 (1H, d, $J_{2,3}=4.0$ Hz and $J_{3,4}=\sim0$ Hz, H-3), 4.10~4.30 (1H, br, OH), 4.19 (1H, dq, $J_{4'',5''}=9.0$ Hz and $J_{5'',Me}=6.2$ Hz, H-5''), 4.46 (1H, d, H-4'', $J_{4'',5''}=9.0$ Hz, H-4''), 4.85~4.93 (2H, m, H-1' and 2'), 5.09 (1H, dd, $J=3.0$ Hz and 6.8 Hz, H-13), 5.125 (1H, d, $J_{1'',2''ax}=4.4$ Hz and $J_{1'',2''eq}=\sim0$ Hz, H-1''), 5.12 and 5.23 (each 1H, ABq, $J_{gem}=12.0$ Hz, OCH_2Ph) and 7.35 (5H, s like, Ph). Found: C 60.54, H 7.83, N 1.36%. Calcd for $C_{47}H_{77}NO_{17}$: C 60.82, H 8.36, N 1.51%.

2'-*O*-Acetyl-4''-*O*-benzyloxycarbonylerythromycin A *N*-Oxide (**19**) and (9*S*)-2'-*O*-Acetyl-4''-*O*-benzyloxycarbonyl-11-dehydroxy-9-deoxo-9-hydroxy-11-oxoerythromycin A *N*-Oxide (**20**)

To a stirred solution of **18** (435 mg, 0.469 mmol) in dry CH_2Cl_2 (4.4 ml) were added at 0°C bis(tributyltin) oxide (0.310 ml, 0.608 mmol) and 2 M solution of bromine in dry CH_2Cl_2 (0.304 ml, 0.608 mmol). The same amounts of the reagents were added at an 1 hour interval (total 3.04 mmol each). The reaction mixture was concentrated and the residue was dissolved in acetonitrile. The organic layer was thoroughly washed with hexane and the acetonitrile layer was concentrated and the residue was chromatographed on silica gel (50 g) with 8:1 $CHCl_3$-MeOH to afford **19** (247 mg, 57%) and **20** (56.4 mg, 13%) as colorless crystals.

19: Rf=0.42 (8:1 $CHCl_3$-MeOH); ^1H NMR (270 MHz) $\delta=0.84$ (3H, t, $J=7.2$ Hz, 3×H-15), 0.93 (3H, d, $J=7.6$ Hz, Me), 1.075~1.225 (21H, m, 7×Me), 1.39 (3H, s, Me), 1.78 (1H, br s, OH), 2.12 (3H, s, OAc), 2.38 (1H, d, $J_{1'',2''eq}=0$ Hz and $J_{gem}=15.0$ Hz, H-2''eq), 2.60~2.75 (1H, m, H-8), 2.75~2.95 (2H, m, H-2 and 4'eq), 3.14 (1H, s, OH), 3.05 (4H, s, NMe contaminated with 1H), 3.24 (3H, s, NMe), 3.32

(3H, s, OMe), 3.48 (1H, d, $J_{4,5}=6.6$ Hz, H-5), 3.45~3.55 (1H, m, H-3'), 3.77 (1H, br s, H-11), 3.80~3.90 (1H, m, H-5'), 3.92 (1H, d, $J_{2,3}=9.8$ Hz and $J_{3,4}=0$ Hz, H-3), 3.97 (1H, s, OH), 4.22 (1H, dq, $J_{4'',5''}=9.8$ Hz and $J_{5'',Me}=6.0$ Hz, H-5''), 4.43 (1H, d, $J_{4'',5''}=9.8$ Hz, H-4''), 4.72 (1H, d, $J_{1',2'}=7.4$ Hz, H-1'), 4.97 (1H, d, $J_{1'',2''ax}=5.0$ Hz and $J_{1'',2''eq}=0$ Hz, H-1''), 5.00~5.10 (2H, m, H-2' and 13), 5.12 and 5.23 (each 1H, ABq, $J_{gem}=12.0$ Hz, OCH_2Ph) and 7.35 (5H, s like, Ph). This sample of **19** was identical with the one derived from **16** by MCPBA oxidation.

20: Rf=0.29 (8:1 $CHCl_3$-MeOH); mp 116~118°C (not recrystallized); $[\alpha]_D^{24}$ −6.3° (*c* 0.51); IR (KBr) 1754 cm^{-1}; ^1H NMR (270 MHz) $\delta=0.89$ (3H, t, $J=7.2$ Hz, 3×H-15), 0.97 (3H, d, $J=7.0$ Hz, Me), 1.10~1.30 (21H, m, 7×Me), 1.49 (3H, s, Me), 2.13 (3H, s, OAc), 2.23 (1H, br s, OH), 2.85~2.95 (1H, m, H-4'eq), 3.09 and 3.26 (each 3H, each s, NMe_2), 3.31 (3H, s, OMe), 3.36 (1H, s), 3.55~3.65 (1H, m, H-3'), 3.70 (1H, d, $J=5.0$ Hz), 3.80~3.90 (1H, m, H-5'), 4.25~4.35 (1H, m, H-5''), 4.47 (1H, d, $J_{4'',5''}=10.0$ Hz, H-4''), 4.74~4.83 (2H, m), 5.05~5.20 (2H, m, H-2' and 13), 5.14 and 5.23 (each 1H, ABq, $J_{gem}=12.0$ Hz, OCH_2Ph) and 7.35 (5H, s like, Ph).

(9*S*)-11-Dehydroxy-9-deoxo-9-hydroxy-11-oxoerythromycin A (**3**)

A mixture of **20** (12.5 mg, 0.0135 mmol), 20% $Pd(OH)_2$ on carbon (6.3 mg) and MeOH (1 ml) was stirred at room temperature under 1 atm of H_2 for 17 minutes. The catalyst was filtered and washed with MeOH. The combined filtrate and washings were concentrated and the residue was dissolved in MeOH (0.5 ml) and warmed at 50°C for 12 hours. After concentration, the residue was chromatographed on silica gel (2 g) with 13:2 $CHCl_3$-MeOH to afford **3** (8.2 mg, 83%) as colorless crystals: Rf=0.41 (5:1 $CHCl_3$-MeOH); mp 140~142°C (colorless powder from 1:2 $CHCl_3$-hexane); $[\alpha]_D^{27}$ −2.9° (*c* 0.92); IR (KBr) 1733 and 1757 cm^{-1}; ^1H NMR (270 MHz) $\delta=0.85$ (3H, t, $J=7.4$ Hz, 3×H-15), 1.07 (3H, d, $J=6.8$ Hz, Me), 1.15~1.30 (21H, m, 7×Me), 1.45 (3H, s, Me), 2.10 (1H, br s, OH), 2.35 (6H, s, NMe_2), 2.65 (1H, m, H-3'), 3.02 (2H, dd, $J_{4'',5''}=J_{4'',OH}=9.2$ Hz, H-4'' contaminated with 1H), 3.26 (3H, s, OMe), 3.42 (1H, dd, $J=7.6$ Hz and 9.4 Hz), 3.49 (1H, d, $J=2.4$ Hz), 3.62 (1H, m, H-5'), 4.09~4.19 (2H, m), 4.14 (1H, s, OH), 4.38 (1H, d, $J_{1',2'}=7.8$ Hz, H-1'), 4.48 (1H, s, OH), 4.76 (1H, d, $J_{1'',2''ax}=5.0$ Hz and $J_{1'',2''eq}=0$ Hz, H-1'') and 5.10 (1H, dd, $J=4.0$ Hz and 9.0 Hz, H-13); ^{13}C NMR (100 MHz, $CDCl_3=77.0$) $\delta=10.0$, 10.68, 10.71, 16.5, 17.4, 17.6, 21.1, 21.4, 22.8, 24.2, 25.1, 29.9, 34.9, 37.9, 40.5, 42.1, 42.8, 47.4, 49.1, 49.4, 64.2, 66.4, 69.5, 70.5, 72.5, 79.4, 81.3, 83.0, 91.4, 99.0, 106.6, 106.7, 176.8 and 216.4. Found: C 60.31, H 8.60, N 1.85%. Calcd for $C_{37}H_{67}NO_{13}$: C 60.55, H 9.20, N 1.91%.

Reduction of **3**

To a stirred solution of **3** (3.0 mg, 0.0041 mmol) in MeOH (0.1 ml) was added at 0°C $NaBH_4$ (1.0 mg, 0.026 mmol). After 12 hours at room temperature, the reaction mixture was neutralized with Amberlite CG-50 and the insoluble materials were filtered and washed with MeOH. The combined filtrate and washings were concentrated and the residue was chromatographed on silica gel (1 g) with 2:1 $CHCl_3$-MeOH to afford (9*S*)-9-deoxo-9-hydroxyerythromycin A[17] (1.5 mg, 50%). The ^1H NMR spectrum and the TLC mobilities of this sample were identical with those of the authentic sample.[17]

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References

1) Omura, S. (*Ed.*): Macrolide Antibiotics. Chemistry, Biology, and Practice. Academic Press, 1984
2) Kirst, H. A.: Structural modification of macrolide antibiotics. *In* Recent Progress in the Chemical Synthesis of Antibiotics. *Eds.*, G. Lukacs & M. Ohno, pp. 39~63, Springer-Verlag, 1990
3) Hauske, J. R.; M. Guadliana & K. Desai: Neutral sugar modifications of macrolide antibiotics. Diazo phosphonate mediated intramolecular cyclizations. J. Org. Chem. 47: 5019~5021, 1982
4) Kinoshita, M.; N. Ohsawa & S. Gomi: A chiral synthesis of 3,5,7-tri-*O*-benzyl-1,4,6-trideoxy-4,6-di-*C*-methyl-

keto-L-*ido*-2-heptulose, a synthetic segment of the C-1～C-6 portion of erythronolide A. Carbohydr. Res. 109: 5～23, 1982

5) KINOSHITA, M.; M. ARAI, K. TOMOOKA & M. NAKATA: Synthetic studies of erythromycins. II. Enantiospecific synthesis of a C-10-C-13 segment of erythronolide A from D-ribose. Tetrahedron Lett. 27: 1811～1814, 1986
6) KINOSHITA, M.; M. ARAI, N. OHSAWA & M. NAKATA: Synthetic studies of erythromycins. III. Total synthesis of erythronolide A through (9*S*)-9-dihydroerythronolide A. Tetrahedron Lett. 27: 1815～1818, 1986
7) NAKATA, M.; M. ARAI, K. TOMOOKA, N. OHSAWA & M. KINOSHITA: Total synthesis of erythronolide A. Bull. Chem. Soc. Jpn. 62: 2618～2635, 1989
8) TOSHIMA, K.; S. MUKAIYAMA, T. YOSHIDA, T. TAMAI & K. TATSUTA: Application of efficient glycosylation of 2,6-anhydro-2-thio sugar to the total synthesis of erythromycin A. Tetrahedron Lett. 32: 6155～6158, 1991
9) COREY, E. J. & L. S. MELVIN, Jr.: Selective chromic acid oxidation of alcohols in the erythromycin series in consequence of conformational immobility. Tetrahedron Lett. 1975: 929～932, 1975
10) FREIBERG, L. A.; C. M. EDWARDS, D. J. BACINO, L. L. KLEIN, R. STEPHENS, S. SPANTON & K. KIM: Synthesis of (9*S*,11*S*)-9-deoxo-12-deoxy-9,12-epoxyerythromycin A (A-63483) and related compounds, a new class of acid stable macrolide antibiotics. Program and Abstracts of the 29th Intersci. Conf. on Antimicrob. Agents Chemother., No. 1028, p. 276, Houston, Sept. 17～20, 1989
11) FREIBERG, L. A.; L. L. KLEIN, C. M. YEUNG, C. M. EDWARDS & D. J. BACINO (Abbott Laboratories): Preparation and antibiotic activity of erythromycin derivatives. PCT Int. Appl. 90 11288 Oct. 4, 1990
12) YAGINUMA, S.; A. MORISHITA, K. ISHIZAWA, S. MUROFUSHI, M. HAYASHI & N. MUTOH: Sporeamicin A, a new macrolide antibiotic. I. Taxonomy, fermentation, isolation and characterization. J. Antibiotics 45: 599～606, 1992
13) MORISHITA, A.; K. ISHIZAWA, N. MUTOH, T. YAMAMOTO, M. HAYASHI & S. YAGINUMA: Sporeamicin A, a new macrolide antibiotic. II. Structure determination. J. Antibiotics 45: 607～612, 1992
14) MORISHITA, A.; N. MUTOH, K. ISHIZAWA, T. SUZUKI, S. YOKOIYAMA & S. YAGINUMA: Sporeamicin A, a new macrolide antibiotic. III. Biological properties. J. Antibiotics 45: 613～617, 1992
15) MORISHITA, A.; S. MUROFUSHI, K. ISHIZAWA, N. MUTOH & S. YAGINUMA: Isolation and characterization of sporeamicin B. J. Antibiotics 45: 809～812, 1992
16) MORISHITA, A.; S. MUROFUSHI, K. ISHIZAWA, N. MUTOH & S. YAGINUMA: Isolation and characterization of sporeamicin C. J. Antibiotics 45: 1011～1015, 1992
17) SIGAL, M. V., Jr.; P. F. WILEY, K. GERZON, E. H. FLYNN, U. C. QUARCK & O. WEAVER: Erythromycin. VI. Degradation studies. J. Am. Chem. Soc. 78: 388～395, 1956
18) TATSUTA, K.; Y. KOBAYASHI, H. GUNJI & H. MASUDA: Synthesis of oleandomycin through the intact aglycone, oleandolide. Tetrahedron Lett. 29: 3975～3978, 1988
19) FLYNN, E. H.; M. V. SIGAL, Jr., P. F. WILEY & K. GERZON: Erythromycin. I. Properties and degradation studies. J. Am. Chem. Soc. 76: 3121～3131, 1954
20) TOSHIMA, K.; T. YOSHIDA, S. MUKAIYAMA & K. TATSUTA: *De novo* highly stereocontrolled synthesis of 2,6-dideoxy sugars by use of 2,6-anhydro-2-thio sugars. Carbohydr. Res. 222: 173～188, 1991
21) WAKAMATSU, T.; H. NAKAMURA, E. NAKA & Y. BAN: Synthetic studies on antibiotic macrodiolide: synthesis of the A-segment of elaiophylin. Tetrahedron Lett. 27: 3895～3898, 1986
22) TOSHIMA, K.; K. TATSUTA & M. KINOSHITA: Total synthesis of elaiophylin (azalomycin B). Bull. Chem. Soc. Jpn. 61: 2369～2381, 1988
23) FERRIER, R. J. & N. PRASAD: Unsaturated carbohydrates. Part IX. Synthesis of 2,3-dideoxy-α-D-*erythro*-hex-2-enopyranosides from tri-*O*-acetyl-D-glucal. J. Chem. Soc. (C) 1969: 570～575, 1969
24) SAIGO, K.; A. MORIKAWA & T. MUKAIYAMA: A new method for the oxidation of alcohol to carbonyl compound. Chem. Lett. 1975: 145～146, 1975
25) SAIGO, K.; A. MORIKAWA & T. MUKAIYAMA: A facile method for the oxidation of alcohols. Bull. Chem. Soc. Jpn. 49: 1656～1658, 1976
26) UENO, Y. & M. OKAWARA: Oxidation using distannoxane I. Selective oxidation of alcohols. Tetrahedron Lett. 1976: 4597～4600, 1976
27) EVERETT, J. R. & J. W. TYLER: An analysis of the ^{1}H and ^{13}C N.m.r. spectra of erythromycin A using two-dimensional methods. J. Chem. Soc. Perkin Trans. I. 1985: 2599～2603, 1985