CHEMICAL MODIFICATION OF ERYTHROMYCINS. IX.[1)]

SELECTIVE METHYLATION AT THE C-6 HYDROXYL GROUP OF ERYTHROMYCIN A OXIME DERIVATIVES AND PREPARATION OF CLARITHROMYCIN

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Although erythromycin A contains five hydroxyl groups, regioselective methylation at the C-6 hydroxyl group was achieved to the extent of 90% when a 9-*O*-substituted erythromycin A 9-oxime was employed as substrate.

The methylation and its selectivity are dependent on an *O*-protecting group at the 9-oxime, solvent, base, and methylating reagent. In particular, the use of a polar aprotic solvent is indispensable for the methylation. Among the 9-oxime derivatives, 2'-*O*,3'-*N*-bis(benzyloxycarbonyl)-*N*-demethylerythromycin A 9-[*O*-(2-chlorobenzyl)oxime] was the most important intermediate for the synthesis of clarithromycin (6-*O*-methylerythromycin A).

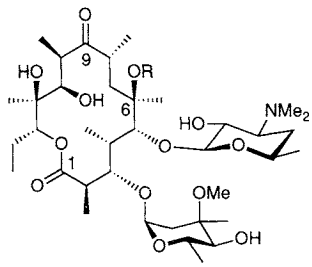
Erythromycin A (**1**) is one of the most important macrolide antibiotics for treating respiratory, cutaneous, and genital infections.[2,3)] It is extremely unstable to acid and undergoes dehydration *in vivo* to an inactive 6,9 : 9,12-spiroketal, anhydroerythromycin A (**2**), when administered orally.

Clarithromycin (6-*O*-methylerythromycin A) (**3**) also has strong antibacterial activity but is more stable to acid than **1** due to the presence of the C-6 methoxy group.[4,5)] Accordingly, **3** exhibits higher concentrations in the lung and plasma than **1**, when administered orally to animals.[6)]

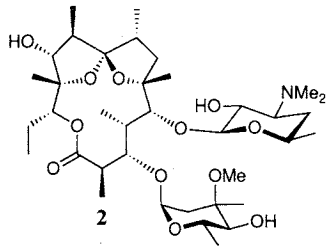
Since **1** has five hydroxyl groups, it is difficult to alkylate the C-6 hydroxyl group selectively. In the preceding paper,[7)] we reported the synthesis of **3** *via* 2'-*O*,3'-*N*-bis(benzyloxycarbonyl)-*N*-demethylerythromycin A (**4**). In spite of many attempts to methylate **4** under a variety of reaction conditions, methylation occurs at the secondary C-11 hydroxyl rather than the *tertiary* C-6 hydroxyl group. Under optimum conditions the desired 6-*O*-methyl derivative (**5**) was obtained in 39% yield (94% pure by HPLC analysis), which was contaminated with the 6,11-di-*O*-methyl and 6,12-di-*O*-methyl derivatives (**6** and **7**). The 11-*O*-methylated compound (**8**) was formed in 42% yield. If the 11 position was protected as the *O*-methoxyethoxymethyl, *O*-trimethylsilyl† or the 11,12-cyclic carbonate derivative,[8)] the corresponding 9-*O*-methyl derivatives were obtained exclusively as the 6,9-hemiacetals.

2'-*O*,3'-*N*-Bis(benzyloxycarbonyl)-*N*-demethylerythromycin B (**9**), which lacks the hydroxyl group in the 12 position can be methylated to give the 6-*O*-methyl derivative in 87% yield.[9)] This suggested that the conformation of the aglycone ring of erythromycin derivatives may influence the selectivity of methylation. We therefore investigate other derivatives with conformation of the aglycone ring different than that of **1**. We have found that 9-oxime derivatives of **4**, namely 2'-*O*,3'-*N*-bis(benzyloxycarbonyl)-*N*-demethylerythromycin A 9-oxime (**10**) and its *O*-substituted oxime derivatives react with methyl iodide

† Our unpublished results.



1 Erythromycin A (R=H)
3 Clarithromycin (R=Me)



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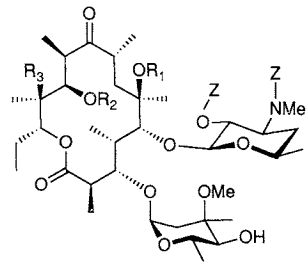


4 $R_1=R_2=H$, $R_3=OH$
5 $R_1=Me$, $R_2=H$, $R_3=OH$
6 $R_1=R_2=Me$, $R_3=OH$
7 $R_1=Me$, $R_2=H$, $R_3=OMe$
8 $R_1=H$, $R_2=Me$, $R_3=OH$
9 $R_1=R_2=R_3=H$
($Z=COOCH_2Ph$)

and sodium hydride to give the corresponding 6-*O*-methyl derivatives in high yield.[10]

Results and Discussion

Oximation of **4** with hydroxylamine hydrochloride and sodium acetate in methanol gave the oxime **10** in 75% yield. Oxime **10** was treated with methyl iodide and potassium hydroxide to afford 2'-*O*,3'-*N*-bis(benzyloxycarbonyl)-*N*-demethyl-6-*O*-methylerythromycin A 9-(*O*-methyloxime) (**17a**) in 78% yield, accompanied by the simultaneous reaction of the oxime hydroxyl group with the alkylating reagent. With regard to the synthesis of **3**, this oxime group should be protected with an appropriate group, which is readily removed since regeneration of the ketone from the *O*-methyloxime functionality is generally difficult under mild condition.[11,12] We first applied benzyloxycarbonyl, acetyl or trimethylsilyl groups as protecting groups for the oxime, but these were too unstable during methylation under alkaline conditions. However, when the oxime group of **10** was protected with a benzyl group, methylation proceeded smoothly to afford the 6-*O*-methyl derivative (**20a**) in 76% yield.

Oximation of erythromycin derivatives provided predominantly the *E*-oxime, which was isolated as crystals, while the *Z*-oxime was very unstable and easily convertible to the *E*-oxime in chloroform solution or by heating.[13] Unless otherwise noted, all synthetic operations were carried out on the stable *E*-oxime.

Studies on the Selectivity of Methylation

The selectivity of C-6 methylation was studied using several 9-oxime protecting groups as well as various solvents, bases and methylating reagents. The results of these are briefly discussed below. Methyl, allyl, trityl, benzyl and 2-chlorobenzyl groups were all used as protecting groups for the oxime. These were prepared by treatment of **10** with the corresponding halides. Each 1 g of *O*-substituted oximes (**12**~**16**) was then reacted with methyl iodide (1.3 equiv) and a base (1.1 equiv) in a solvent (20 ml) under ice-cooling for 1.5 hours. The ratios of methylated products **17**~**21** (**a**~**d**) were assessed by HPLC. As shown in Table 1, greater than 90% selectivity was achieved for C-6 methylation (based on recovered starting

Scheme 1. Preparation of 2′-*O*,3′-*N*-bis(benzyloxycarbonyl)-*N*-demethylerythromycin A 9-[*O*-(substituted)-oxime] (**17**~**21**).

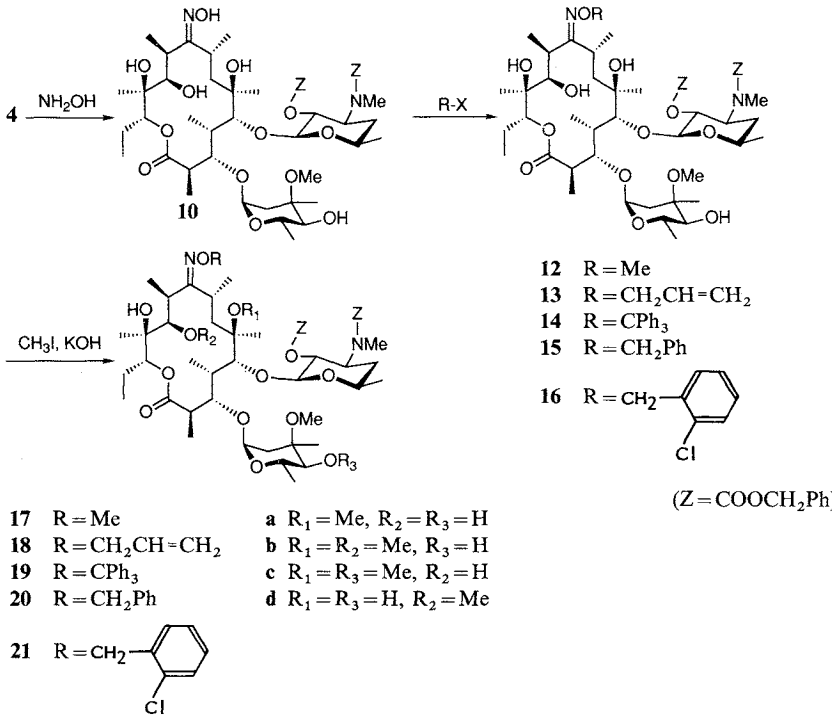


Table 1. Effect of oxime protecting groups on the selectivity of methylation of 2′-*O*,3′-*N*-bis(benzyloxycarbonyl)-*N*-demethylerythromycin A 9-oxime derivatives.

12~**16** $\xrightarrow[\text{DMSO-THF (1 : 1)}]{\text{CH}_3\text{I (1.3 equiv)}, \text{KOH (1.1 equiv)}}$ **17**~**21** (**a**~**d**)

Products	Ratios of methylated products (%)[a]					Isolated yield of 6-OMe (%)
	6-OH s.m.[b]	6-OMe **a**	6,11-di-OMe **b**	6,4″-di-OMe **c**	11-OMe **d**	
17	9.1	79.9	6.7	1.6	0.9	80[c]
18	8.6	84.5	5.2	1.5	1.4	98
19	18.2	78.4	0.4	0.9	1.4	59
20	7.1	84.1	5.6	1.2	1.6	76
21	4.6	86.2	4.0	1.3	1.2	86

[a] Area % by HPLC analysis.
[b] Unreacted starting material.
[c] Foam.

material). Although the trityl group (**14**→**19a**) was the best of all, the rate of methylation was slow. The 2-chlorobenzyl group (**16**→**21a**) gave relatively small amounts of over-methylated products (**21b, c**) and 11-*O*-methyl derivative (**21d**), but the reaction was faster than in the other cases. The bulkier the protecting group, the greater the reaction selectivity observed.

Thus, the order of selectivities was found to be trityl > 2-chlorobenzyl > benzyl = allyl > methyl. We

Table 2. Effect of solvents on the selectivity of methylation of 2'-*O*,3'-*N*-bis(benzyloxycarbonyl)-*N*-demethylerythromycin A 9-[*O*-(2-chlorobenzyl)oxime] **16**.

Products	Ratios of methylated products **21** (%)[a]				
	6-OH s.m.[b]	6-OMe **a**	6,11-di-OMe **b**	6,4''-di-OMe **c**	11-OMe **d**
DMSO	14.2	63.7	16.9	1.5	2.2
DMSO-THF (1:2)	4.4	84.0	4.8	3.2	0.8
DMSO-THF (1:1)	4.6	86.2	4.0	1.3	1.2
DMSO-THF (1:1)[c]	9.5	78.3	4.6	1.6	3.2
DMF	5.8	80.5	6.7	1.4	3.4
DMF-THF (1:1)	18.4	64.1	4.6	6.2	2.2
NMP[d]	18.3	71.6	3.6	0.8	3.2
THF	94.1	—	—	—	—
Dioxane	95.8	—	—	—	—
Toluene	96.2	—	—	—	—

[a] Area % by HPLC analysis.
[b] Unreacted starting material **16**.
[c] Using $(CH_3)_2SO_4$ instead of CH_3I.
[d] 1-Methyl-2-pyrrolidinone.

used 2-chlorobenzyl group for all the following studies.

The effect of reaction solvent is shown in Table 2. This is an important factor in regulating both the reactivity and selectivity. Methylation was not observed in tetrahydrofuran (THF), dioxane or toluene, but proceeded smoothly in polar aprotic solvent such as dimethyl sulfoxide (DMSO) or *N*,*N*-dimethylformamide (DMF).

The reactivity and selectivity of methylation were greatly enhanced by the use of a 1:1 mixture of DMSO and THF. In a mixture of DMF and THF, both the reactivity and selectivity were decreased compared with a mixture of DMSO and THF, giving a greater ratio of the 6,4''-di-*O*-methyl derivative (**21c**). Using 1-methyl-2-pyrrolidinone, **21c** was formed in a relatively small amount.

Among the common methylating reagents, methyl iodide gave the desired product **21a** in 86.2%, compared with dimethyl sulfate, which afforded 78.3%. The latter reagent tends to afford more of the 11-*O*-methyl derivative than the former.

The optimum conditions, within a series, are therefore a 1:1 mixture of DMSO and THF and methyl iodide as the alkylating reagent.

We also studied the effect of the base on the reaction and examined a number of strong and weak bases (Table 3). Potassium hydride and potassium hydroxide were superior to their sodium analogues both in reactivity and selectivity. No reaction was observed with lithium hydroxide due to its weak basicity. Potassium *tert*-butoxide and *n*-butyl lithium gave inferior results.

With regard to quaternary ammonium compounds, Triton B could be used, but tetrabutylammonium acetate did not give the product. Potassium carbonate salt was also inactive. The utility of the bases' cations followed the order $K^+ > Na^+ >$ quaternary ammonium $> Li^+$. Potassium hydroxide is a suitable base for methylation with regard to selectivity and ease of handling.

The isolation of the unstable minor isomer of 9-oxime ((*Z*)-**10**) was effected by column chromatography. Without further purification, (*Z*)-**10** was treated with 2-chlorobenzyl chloride to afford (*Z*)-2'-*O*,3'-*N*-bis(benzyloxycarbonyl)-*N*-demethylerythromycin A 9-[*O*-(2-chlorobenzyl)oxime] ((*Z*)-**16**), which could be purified by crystallization and subjected to methylation.

Table 3. Effect of bases on the selectivity of methylation of 2'-*O*,3'-*N*-bis(benzyloxycarbonyl)-*N*-demethylerythromycin A 9-[*O*-(2-chlorobenzyl)oxime] **16**[a].

Products	Ratios of methylated products **21** (%)[b]				
	6-OH s.m.[c]	6-OMe **a**	6,11-di-OMe **b**	6,4″-di-OMe **c**	11-OMe **d**
KH	2.2	88.6	4.9	1.5	0.9
KOH	4.6	86.2	4.0	1.3	1.2
tert-BuOK	21.5	67.3	2.5	3.3	0.9
K_2CO_3	96.3	—	—	—	—
NaH	6.2	78.9	8.8	2.1	1.1
NaOH	6.0	78.8	9.1	2.7	1.2
n-BuLi	66.1	23.5	1.9	0.3	1.0
LiOH	95.6	—	—	—	—
Triton B	16.1	65.4	9.2	4.6	1.5
TBAA[d]	96.3	—	—	—	—

[a] Using CH_3I in DMSO-THF (1:1).
[b] Area % by HPLC analysis.
[c] Unreacted starting material **16**.
[d] Tetrabutylammonium acetate.

The oxime configuration was determined by NMR using ^1H and ^{13}C chemical shifts.

As shown in Table 4, NMR spectra of the major oximes (**11** and **16**) showed that the signal attributed to 8-H revealed characteristic downfield shift and C-8 was subjected to significant upfield shift. Both displacements can be attributed to a *trans* *O*-substituted group of the oxime moiety and establishes that the major oxime is the *E*-isomer, and the minor one is the *Z*-oxime. These results also agree with those reported on erythromycin A 9-oxime.[14]

Table 4. NMR of (*E*)- and (*Z*)-erythromycin 9-oxime derivatives.

	11	(*Z*)-**11**	**16**	(*Z*)-**16**
8-H	3.77	2.89	3.75	2.87
10-H	2.66	2.84	2.63	2.82
8-C*H*$_3$	1.00	1.13	1.00	1.14
10-C*H*$_3$	1.13	1.26	1.13	1.26
C-8	26.8	35.4	26.7	35.5
C-10	33.1	34.4	33.1	34.4
8-*C*H$_3$	18.6	20.0	18.5	20.0
10-*C*H$_3$	14.6	11.3	14.6	11.3

Recorded on a JEOL JNM-GX400 spectrometer with ^1H NMR at 400 MHz and ^{13}C NMR at 100 MHz in $CDCl_3$.

^{13}C NMR chemical shifts of the aglycone of clarithromycin and its related compounds are shown in Table 5.

Certain protons and carbons of compounds having benzyloxycarbonyl group showed two splitted chemical shifts in $CDCl_3$. However, when each of **16** and (*Z*)-**16** was dissolved in DMSO-d_6 and taken ^1H and ^{13}C NMR at 60°C, two splitted signals appeared at ambient temperature turned out to be single one. The changes in chemical shifts may result in part from a mixture of the spectroscopic rotamers (Table 6).

Comparative methylations of **16** and (*Z*)-**16** were examined and the result are shown in Fig. 1 indicating no noticeable differences in terms of reactivity and selectively.

The Regioselectivity of *O*-Methylation

It is considered that the regioselectivity of erythromycin derivatives depends upon the equilibrium between hydroxyl form and its dissociated alkoxide form under basic conditions. We then examined them by MNDO and PM 3 methods in MOPAC 5.0 semiempirical molecular orbital program package[15] using 2'-*O*-trimethylsilylerythromycin A (**22**) and its 9-(*O*-allyl)oxime (**23**).

The calculation showed that in the 9-keto compound (**22**), the alkoxide form at the C-11 and the

Table 5. ^{13}C NMR chemical shifts of the aglycone carbons of clarithromycin and its related compounds.[a]

Carbon	**1**[b]	**4**	**10**	**11**	(*Z*)-**11**	**16**	(*Z*)-**16**	**21a**	(*Z*)-**21a**	**3**[b]
1	175.8	175.6, 175.7	175.3, 175.4	175.3	175.7	175.2, 175.2	175.6, 175.7	175.4, 175.4	175.6, 175.7	175.9
2	44.8	44.9	44.6	44.7	44.6	44.6	44.4	45.0	45.1, 45.2	45.1
3	79.9	79.5	79.7	80.0	79.3	79.4, 79.5	78.7	7.9	77.9, 78.0	78.5
4	39.3	38.9, 39.1	38.5, 38.6	39.1	40.3	38.7, 38.8	39.9, 40.0	38.5, 38.6	38.8, 38.9	39.3
5	83.5	83.7, 84.0	83.6, 83.8	83.2	83.4	83.6	83.4, 83.5	80.2, 80.3	80.2, 80.3	80.8
6	74.8	74.8	75.1	75.2	75.4	75.0	75.2	78.5	78.6, 78.7	78.5
7	38.4	37.9	37.3, 37.4	37.8	38.0	37.3	37.8	36.9	35.9, 36.3	39.4
8	45.0	44.7	25.3	26.8	35.4	26.7	35.6	26.5	35.5	45.3
9	221.6	221.1	171.7	172.7	169.3	172.4	169.0	170.9	169.5	221.1
10	37.9	38.2, 38.3	32.7	33.1	34.4	33.1	34.4	33.1	34.7	37.7
11	68.7	68.8	70.9	70.4	70.5	70.4	70.6	70.0	70.2	69.1
12	74.7	74.7	74.4	74.2	75.3	74.2	75.2	74.0	74.7	74.3
13	76.8	76.9	77.1	76.9	76.9	76.9	74.9	76.8	76.7	76.7
14	21.1	21.3	21.1	21.1	21.4	21.2	21.7	21.3	21.4, 21.5	21.1
2-Me	16.0	15.9	16.2	16.1	15.3	16.0	15.0	16.0	15.9	16.0
4-Me	9.2	8.8	8.9	9.2	9.2	8.7	8.7	8.7	8.5, 8.6	9.1
6-Me	26.8	26.9	27.0	26.9	26.4	26.8	26.1	20.0	19.7	19.8
8-Me	18.3	18.3	18.5	18.6	20.0	18.5	20.0	18.6	19.7	18.0
10-Me	12.0	12.1	14.4	14.6	11.3	14.6	11.3	15.3	11.4	12.3
12-Me	16.2	16.4	16.5	16.3	17.0	16.4	17.0	16.3	16.9	16.0
14-Me	10.7	10.7	10.6	10.7	10.8	10.7	10.8	10.6	10.6	10.6
6-OMe								50.6	49.5	50.7

[a] 50 MHz chemical shifts (ppm) $CDCl_3$.
[b] Data from ref 13.

Table 6. NMR of **16** and (*Z*)-**16** at different temperatures.

	16		(*Z*)-**16**	
	Ambient temperature	60°C	Ambient temperature	60°C
3′-NCH_3	2.72 and 2.73	2.73	2.72 and 2.74	2.75
3″-OCH_3	2.92 and 3.26	3.17	2.93 and 3.24	3.16
C-1′	98.6 and 98.9	98.9	98.7 and 98.9	99.0
C-1″	94.9 and 95.1	95.3	94.8 and 95.0	95.2
$PhCH_2OCONCH_3$	155.3 and 155.5	155.5	155.3 and 155.5	155.5

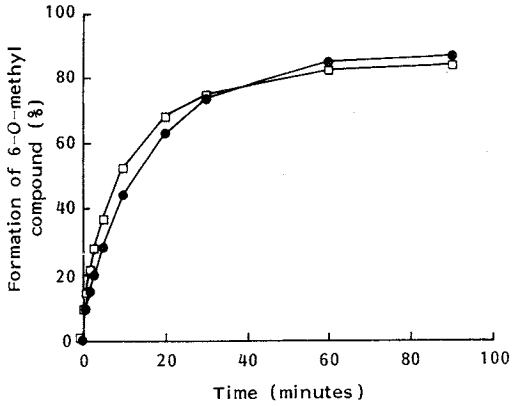
Recorded on a JEOL JNM-GX400 spectrometer with ^1H NMR at 400 MHz and ^{13}C NMR at 100 MHz in DMSO-d_6.

hydroxyl form at the C-6 is more stable by *ca.* 9 kcal/mol than the alkoxide form at the C-6 and the hydroxyl form at the C-11, whereas in the 9-oxime compound (**23**), the alkoxide form at the C-6 is more stable by *ca.* 8 kcal/mol than that at the C-11. Therefore, in the 9-oxime structure methylation occurs at the C-6 hydroxyl nearly exclusively.†

† The results will be reported and discussed elsewhere.

Fig. 1. Comparison of methylation between (*E*)- and (*Z*)-2′-*O*,3′-*N*-bis(benzyloxycarbonyl)-*N*-demethylerythromycin A 9-[*O*-(2-chlorobenzyl)oxime] **16** and (*Z*)-**16**.

□ **21a**, ● (*Z*)-**21a**.

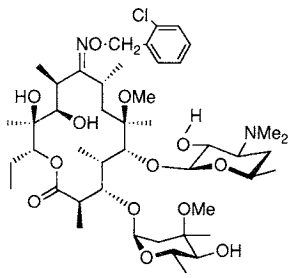


Synthesis of Clarithromycin

Optimal conditions were established for the protective group, solvent, base, and methylating reagent. Using the 2-chlorobenzyl group as the protecting group for the 9-oxime, we attempted the synthesis of **3** as follows.

The 9-oxime **10** was allowed to react with 2-chlorobenzyl chloride in DMF to afford the 9-[*O*-(2-chlorobenzyl)oxime] derivative (**16**) in nearly quantitative yield. Compound **16** was also prepared by treatment of erythromycin A 9-oxime with 2-chlorobenzyl chloride, followed by protection with benzyloxycarbonyl chloride.

Methylation of **16** with methyl iodide and potassium hydroxide in a mixture of DMSO and



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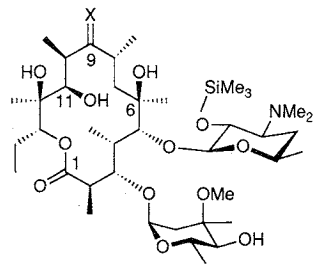
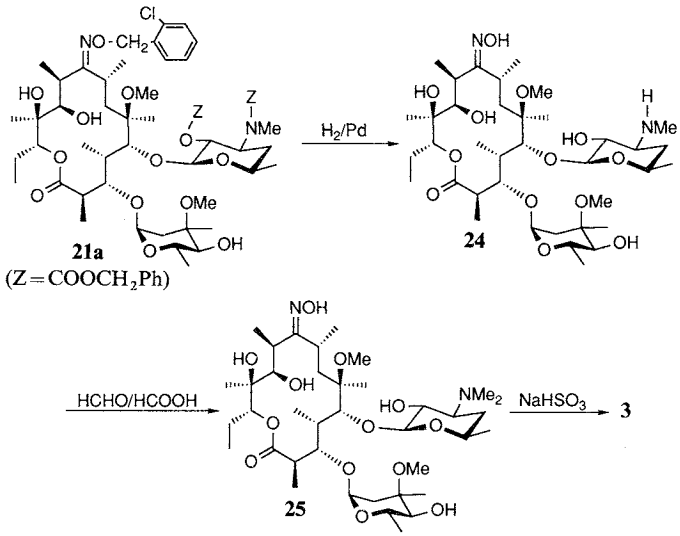


22 X=O
23 X=NOCH$_2$CH=CH$_2$

Scheme 2. Preparation of clarithromycin.



THF (1:1) afforded the 6-*O*-methyl derivative (**21a**), which could be purified by crystallization from isopropanol to provide pure **21a** in 86% yield. Removal of both the benzyloxycarbonyl and 2-chlorobenzyl groups of **21a** by catalytic hydrogenation furnished 6-*O*-methyl-*N*-demethylerythromycin A 9-oxime (**24**) in 90% yield. Compound **24** underwent reductive *N*-methylation in ethanol with formaldehyde in the presence of formic acid under mild reflux to afford 6-*O*-methylerythromycin A 9-oxime (**25**) in 94% yield from **21a**. Finally, treatment of the oxime derivative **25** with sodium bisulfite in refluxing aqueous ethanol gave **3**, which was crystallized from ethanol to afford pure **3**. It was also prepared directly from **24** by reductive *N*-methylation and successive deoximation in one pot without isolation of the oxime **25** (72%).

The present synthesis efficiently provides clarithromycin **3** in 45~48% overall yield from **4**.

Experimental

MP's were determined on a Yanagimoto micro-melting points apparatus and are uncorrected. IR spectra were measured on a JASCO DS-701G IR spectrometer. ^{1}H NMR and ^{13}C NMR were recorded on a Varian XL-200 spectrometer operating at 200 and 50 MHz for ^{1}H and ^{13}C NMR, respectively. Mass spectra were recorded on a JEOL JMS-SX102 mass spectrometer.

Silica gel (Wakogel C-200) was used for column chromatography. TLC was performed on silica gel $60F_{254}$ plates (E. Merck). HPLC was carried out on a 4.6×250 mm column of TSK Gel OD-120 A with 85:15 CH_3CN-H_2O at a flow rate of 1 ml/minute at 40°C. Reaction was monitored at 220 nm.

2'-*O*,3'-*N*-Bis(benzyloxycarbonyl)-*N*-demethylerythromycin A 9-Oxime (**10**)

A mixture of 2'-*O*,3'-*N*-bis(benzyloxycarbonyl)-*N*-demethylerythromycin A (**4**) (250 g, 0.25 mol), anhydrous sodium acetate (124.6 g, 1.5 mol) and hydroxylamine hydrochloride (87.93 g, 1.25 mol) in methanol (1,000 ml) was stirred at room temperature for 6 days and then refluxed for 30 minutes. The reaction mixture was concentrated *in vacuo* to about a half volume and poured into water (300 ml). The resulting crystals were filtered, triturated with successive, water, saturated $NaHCO_3$, and water, and then filtered. Crystallization from CH_2Cl_2-*n*-hexane gave 189.96 g (75%) of **10**: MP 152~154°C; IR (KBr) cm^{-1} 3600~3200, 1760, 1735, 1700; ^{1}H NMR ($CDCl_3$) δ 2.82 and 2.86 (3H, NCH_3), 3.02 and 3.38 (3H, 3''-OCH_3), 5.00~5.22 (4H, $COOCH_2$×2), 7.14~7.48 (10H, aromatic H), 8.14~8.44 (1H, br s, =NOH); ^{13}C NMR ($CDCl_3$) δ 28.8 and 28.9 (NCH_3), 49.5 (3''-OCH_3), 67.2 and 67.5 ($NCOOCH_2$), 69.4 and 69.7 ($OCOOCH_2$), 171.1 (C-9), 175.3 and 175.4 (C-1); FD-MS *m/z* 1,003 (M^++1).

Anal Calcd for $C_{52}H_{78}N_2O_{17}$: C 62.26, H 7.84, N 2.79.
Found: C 62.50, H 7.61, N 2.67.

Methylation of Compound **10**

To a stirred solution of **10** (1.0 g, 1.0 mmol) in anhydrous DMSO-THF (1:1, 12 ml) were added CH_3I (35 mg, 2.5 mmol) and 85% KOH powder (14 mg, 2.0 mmol) under ice-cooling. The reaction mixture was stirred at room temperature for 2 hours. Triethylamine (2 ml, 14 mmol) was added and the mixture was extracted with EtOAc. The organic layer was washed with saturated brine and dried ($MgSO_4$). The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (EtOAc-*n*-hexane, 1:1) to afford 0.8 g (78%) of 2'-*O*,3'-*N*-bis(benzyloxycarbonyl)-6-*O*-methyl-*N*-demethylerythromycin A 9-(*O*-methyloxime) (**17a**) as a colorless foam: IR (KBr) cm^{-1} 3500~3350, 1750, 1735, 1700; ^{1}H NMR ($CDCl_3$) δ 2.85 and 2.99 (3H, NCH_3), 3.00 and 3.38 (3H, 3''-OCH_3), 3.05 (3H, s, 6-OCH_3); 3.79 (3H, s, =$NOCH_3$), 5.1~5.3 (4H, $COOCH_2$×2), 7.2~7.4 (10H, aromatic H); ^{13}C NMR ($CDCl_3$) δ 50.5 (6-OCH_3), 63.4 (=$NOCH_3$).

Anal Calcd for $C_{54}H_{82}N_2O_{17}$: C 62.89, H 8.02, N 2.72.
Found: C 62.48, H 7.93, N 2.65.

Erythromycin A 9-[*O*-(2-Chlorobenzyl)oxime] (**11**)

A mixture of erythromicin A 9-oxime (1.498 g, 2.0 mmol), 2-chlorobenzyl chloride (354 mg, 2.2 mmol)

and 85% KOH powder (165 mg, 2.5 mmol) in DMF (100 ml) was stirred at room temperature for 5 hours. The reaction mixture was poured into ice-water (500 ml) and extracted with EtOAc. The extract was washed with saturated brine and dried ($MgSO_4$). The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (EtOAc) and then crystallized from *n*-hexane to afford 1.562 g (89%) of **11**: MP 114~117°C. ^{13}C NMR (see Table 5).

The Other Isomer of **11** ((*Z*)-**11**)

Compound (*Z*)-**11** was prepared from (*Z*)-erythromycin 9-oxime and 2-chlorobenzyl chloride as described for the preparation of **11**. MP 111~114°C; ^{13}C NMR (see Table 5).

2'-*O*,3'-Bis(benzyloxycarbonyl)-*N*-demethylerythromycin A 9-[*O*-(2-Chlorobenzyl)oxime] (**16**)

Method A

To an ice-cooled solution of **10** (170 g, 0.17 mol) and 2-chlorobenzyl chloride (30.02 g, 0.19 mol) in DMF (680 ml), was added 85% KOH powder (12.3 g, 0.19 mol) with stirring. The resulting mixture was stirred for 3 hours under ice-cooling. The mixture was poured into water. The precipitate was filtered, triturated with successive, water and 15% aqueous ethanol (3 : 1) and filtrated. There was obtained 189.74 g (99%) of **16**, which was crystallized from EtOAc-*n*-hexane: MP 111~113°C; IR (KBr) cm^{-1} 3500~3200, 1748, 1735, 1700; ^1H NMR ($CDCl_3$) δ 2.80 and 2.84 (3H, NCH_3), 3.00 and 3.37 (3H, 3''-OCH_3), 5.15 (2H, s, =$NOCH_2$), 5.00~5.24 (4H, $COOCH_2 \times 2$), 7.20~7.52 (14H, aromatic H); FD-MS *m/z* 1,127 ($M^+ + 1$).

Anal Calcd for $C_{59}H_{83}ClN_2O_{17}$: C 62.84, H 7.42, N 2.48.
Found: C 62.41, H 7.41, N 2.45.

Method B

To a mixture of **11** (5 g, 5.7 mmol) and $NaHCO_3$ (5.77 g) in dioxane (8.5 ml) was added dropwise benzyloxycarbonyl chloride (8.14 ml, 10 equiv) with stirring at 55~56°C. The mixture was stirred at 65°C for 1 hour, cooled and then diluted with CH_2Cl_2. The resulting mixture was filtered and the filtrate was diluted with *n*-hexane to afford **16** (5.92 g, 92%). Physico-chemical properties of this compound agree with those of the one obtained by method A.

The Other Isomer of **16** [(*Z*)-**16**]

Crude **10** (113 g) was chromatographed over silica gel (MeOH-$CHCl_3$, 0~5 : 100, gradient elution). The fractions (Rf 0.5 by TLC developed by EtOAc-*n*-hexane, 2 : 1) gave the major **10** (92.5 g). Subsequently, the fractions (Rf 0.3) were collected and concentrated to dryness *in vacuo* to afford (*Z*)-**10** (5.1 g), which was contaminated by a small amount of **10**. The *Z*-isomer could not be obtained in pure form because of isomerization during chromatography and work-up. An ice-cooled solution of (*Z*)-**10** (5.1 g, 5.08 mmol) and 2-chlorobenzyl chloride (1.25 g, 7.76 mmol) in DMF (40 ml) was treated with 85% KOH powder (0.51 g, 7.73 mmol). The reaction mixture was stirred for 2 hours. The resulting solution was diluted with saturated brine (100 ml) and extracted with EtOAc (100 ml). The organic layer was washed with saturated brine (4 × 100 ml) and dried ($MgSO_4$). The solvent was removed *in vacuo* and the residue was purified by column chromatography (EtOAc-*n*-hexane, 1 : 2~1 : 1). The first fractions gave **16** (1.51 g, 26%) and the second (*Z*)-**16** (3.39 g, 59%). (*Z*)-**16** was crystallized from *n*-hexane-ether to afford colorless crystals: MP 145~147°C; IR (KBr) cm^{-1} 3422, 2947, 1748, 1708; ^1H NMR ($CDCl_3$) δ 2.81 and 2.85 (3H, NCH_3), 3.01 and 3.38 (3H, 3''-OCH_3), 5.02~5.21 (6H, $COOCH_2 \times 2$ and =$NOCH_2$), 7.22~7.41 (14H, aromatic H); FAB-MS *m/z* 1.127 (MH^+).

Anal Calcd for $C_{59}H_{83}ClN_2O_{17}$: C 62.84, H 7.42, N 2.48.
Found: C 62.52, H 7.43, N 2.24.

2'-*O*,3'-*N*-Bis(benzyloxycarbonyl)-*N*-demethylerythromycin A 9-(*O*-Methyloxime) (**12**)

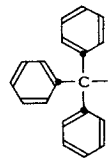
To a solution of **10** (2.0 g, 2.0 mmol) in acetone (100 ml) were added CH_3I (426 mg, 6.0 mmol) and 85% KOH powder (290 mg, 2.2 mmol) at room temperature and the reaction mixture was stirred for 2.5 hours. The solvent was evaporated *in vacuo* and the residue was crystallized from ether-*n*-hexane to give

colorless crystals of **12** (1.92 g, 95%): MP 118~121°C; IR (KBr) cm^{-1} 3426, 2947, 1751, 1708, 1627; ^1H NMR ($CDCl_3$) δ 2.81 and 2.85 (3H, NCH_3), 3.00 and 3.38 (3H, 3″-OCH_3), 3.82 (3H, s, =$NOCH_3$), 5.00~5.16 (4H, $COOCH_2 \times 2$), 7.20~7.37 (10H, aromatic H); ^{13}C NMR ($CDCl_3$) δ 28.9 (NCH_3), 49.0 and 49.6 (3″-OCH_3), 61.8 (=$NOCH_3$), 67.2 and 67.5 ($NCOOCH_2$), 69.4 and 69.7 ($OCOOCH_2$); FAB-MS *m/z* 1,017 (MH^+).

2′-*O*,3′-*N*-Bis(benzyloxycarbonyl)-*N*-demethylerythromycin A 9-(*O*-Allyloxime) (**13**)

Compound **13** was prepared from **10** (3 g, 3 mmol) by the same procedure as **16** (Method A). There was obtained 1.9 g (60%) of **12**: IR (KBr) cm^{-1} 3436, 2974, 1751, 1704, 1631; ^1H NMR ($CDCl_3$) δ 2.81 and 2.85 (3H, NCH_3), 3.00 and 3.38 (3H, 3″-OCH_3), 4.50~4.53, 5.12~5.21 and 5.80~5.99 (5H, $CH_2CH=CH_2$), 5.01~5.20 (4H, $COOCH_2 \times 2$), 7.05~7.40 (10H, aromatic H); ^{13}C NMR ($CDCl_3$) δ 28.9 (NCH_3), 49.5 and 49.8 (3″-OCH_3), 67.1 and 67.9 ($NCOOCH_2$), 69.4 and 69.7 ($OCOOCH_2$) 74.8 ($OCH_2CH=CH_2$), 118.1 ($OCH_2CH=CH_2$), 133.8 ($OCH_2CH=CH_2$); FAB-MS *m/z* 1,043 (MH^+).

2′-*O*,3′-*N*-Bis(benzyloxycarbonyl)-*N*-demethylerythromycin A 9-(*O*-Trityloxime) (**14**)

A solution of **10** (1.0 g, 1 mmol), trityl chloride (1.0 g, 3 mmol) and triethylamine (1 ml, 7 mmol) in DMF (2 ml) was stirred at 80~100°C for 5 hours. The resulting mixture was poured into water (300 ml) and extracted with CH_2Cl_2. The organic layer was washed with saturated brine and dried ($MgSO_4$). After removal of the solvent, the crude product was purified by column chromatography (EtOAc-*n*-hexane, 1:2) to afford **14** (0.8 g, 65%): MP 126~128°C; IR (KBr) cm^{-1} 3467, 2974, 1752, 1737, 1704; ^1H NMR ($CDCl_3$) δ 2.81 and 2.85 (3H, NCH_3), 2.98 and 3.38 (3H, 3″-OCH_3), 4.98~5.16 (4H, $COOCH_2 \times 2$), 7.2~7.4 (25H, aromatic H); ^{13}C NMR ($CDCl_3$) δ 28.9 (NCH_3), 49.0 and 49.5 (3″-OCH_3), 67.2 and 67.5 ($NCOOCH_2$), 69.4 and 69.7 ($OCOOCH_2$), 144.2 []; FAB-MS *m/z* 1,245 (MH^+).

2′-*O*,3′-*N*-Bis(benzyloxycarbonyl)-*N*-demethylerythromycin A 9-(*O*-Benzyloxime) (**15**)

Compound **15** was prepared from **10** (20.06 g, 20 mmol) using 60% NaH (120 mg, 30 mmol) instead of KOH by the same procedure as **16** (Method A). The crude product was purified by silica gel column chromatography (Art. 7734, E. Merck, EtOAc-*n*-hexane, 1:2~1:1) to afford **15** (17.9 g, 82%), which was crystallized from EtOAc-petroleum ether: MP 105~107°C; IR (KBr) cm^{-1} 3400, 1750, 1735, 1700; ^1H NMR ($CDCl_3$) δ 2.79 and 2.84 (3H, NCH_3), 2.99 and 3.37 (3H, 3″-OCH_3), 5.00~5.20 (6H, $COOCH_2 \times 2$ and =$NOCH_2$), 7.20~7.50 (15H, aromatic H); ^{13}C NMR ($CDCl_3$) δ 28.9 (NCH_3), 49.0 and 49.5 (3″-OCH_3), 67.1 and 67.4 ($NCOOCH_2$), 69.4 and 69.7 ($OCOOCH_2$), 76.1 (=$NOCH_2$), 172.1 (C-9), 175.0 and 175.1 (C-1).

Anal Calcd for $C_{59}H_{84}N_2O_{17}$: C 64.82, H 7.74, N 2.56.
Found: C 64.41, H 7.56, N 2.64.

2′-*O*,3′-*N*-Bis(benzyloxycarbonyl)-6-*O*-methyl-*N*-demethylerythromycin A 9-[*O*-(2-Chlorobenzyl)-oxime] (**21a**)

To a stirred solution of **16** (140 g, 0.124 mol) and CH_3I (10.05 ml, 0.161 mol) in anhydrous DMSO-THF (1:1, 560 ml) was added 85% KOH powder (9.83 g, 0.149 mol) under ice-cooling. After stirring at 5°C for 2 hours, the reaction was quenched with triethylamine (28 ml, 0.387 mol) and stirring was continued for a further 2 hours. The resulting mixture was poured into a two-phase mixture of EtOAc-saturated brine (1,800 ml/900 ml). The organic layer was washed successively with saturated brine, 1 N HCl (saturated with NaCl), saturated brine, saturated $NaHCO_3$, and then saturated brine. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo* to afford crude product. Crystallization from isopropanol gave colorless crystals of **21a** (120.9 g, 86%): MP 191~193°C; IR (KBr) cm^{-1} 3600~3200, 1752, 1732, 1690; ^1H NMR ($CDCl_3$) δ 2.82 and 2.86 (3H, NCH_3), 2.98 (3H, s, 6-OCH_3), 3.01 and 3.40 (3H, 3″-OCH_3), 5.0~5.22 (4H, $COOCH_2 \times 2$), 5.42 and 5.48 (2H, ABq, $J=12$ Hz, =$NOCH_2$), 7.18~7.52 (14H, aromatic H); FD-MS *m/z* 1,141 ($M^+ + 1$).

Anal Calcd for $C_{60}H_{85}ClN_2O_{17}$: C 63.12, H 7.50, N 2.45.
Found: C 63.10, H 7.39, N 2.52.

The Other Isomer of **21a** ((*Z*)-**21a**)

(*Z*)-**16** (1.128 g, 1.0 mmol), CH_3I (0.1 ml, 1.6 mmol) and 85% KOH powder (86 mg, 1.3 mmol) were treated in anhydrous DMSO-THF (1:1, 14 ml) according to the same procedure as **21a** to afford (*Z*)-**21a** (0.68 g, 60%). Crystallization from EtOAc-*n*-hexane gave colorless crystals (0.56 g): MP 172~175°C; IR (KBr) cm^{-1} 3403, 2977, 1755, 1737, 1692; ^1H NMR ($CDCl_3$) δ 2.81 and 2.85 (3H, NCH_3), 2.97 (3H, s, 6-OCH_3), 3.00 and 3.38 (3H, 3″-OCH_3), 5.01~5.19 (6H, $COOCH_2 \times 2$ and $=NOCH_2$), 7.20~7.44 (14H, aromatic H); FAB-MS *m/z* 1,141 (MH^+).

Anal Calcd for $C_{60}H_{85}ClN_2O_{17}$: C 63.12, H 7.50, N 2.45.
Found: C 63.31, H 7.57, N 2.32.

Related Methylation Products of **21a**

The isopropanol mother liquor obtained by the recrystallization of **21a** described above was evaporated to dryness *in vacuo*. The residue was chromatographed over silica gel (CH_2Cl_2-EtOAc, 197:2~100:3~9:1) and three fractions were obtained. From the first fraction there was obtained 2′-*O*,3′-*N*-bis(benzyloxycarbonyl)-6,4″-di-*O*-methyl-*N*-demethylerythromycin A 9-[*O*-(2-chlorobenzyl)oxime] (**21c**) as a foam: IR (KBr) cm^{-1} 3436, 2975, 2831, 1751, 1735, 1707, 1456, 1406, 1382, 1338; ^1H NMR ($CDCl_3$) δ 2.80 and 2.84 (3H, NCH_3), 2.97 and 3.37 (3H, 3″-OCH_3) 2.98 and 2.99 (3H, 6-OCH_3), 3.49 and 3.50 (3H, 4″-OCH_3), 7.16~7.46 (14H, aromatic H); ^{13}C NMR ($CDCl_3$) δ 28.6 (NCH_3), 49.2 and 49.5 (3″-OCH_3), 50.7 (6-OCH_3), 72.7 ($=NOCH_2$), 89.0 (C-4″), 167.8 (C-9), 175.5 and 175.6 (C-1); FAB-MS *m/z* 1,155 (MH^+).

The second fraction was concentrated and the residue was crystallized from isopropanol-CH_2Cl_2 to afford a solid which was a mixture of **21a** and 2′-*O*,3′-*N*-bis(benzyloxycarbonyl)-6,11-di-*O*-methyl-*N*-demethylerythromycin A 9-[*O*-(2-chlorobenzyl)oxime] (**21b**) as a foam. Analytical data of **21b**:† IR (KBr) cm^{-1} 3461, 2977, 1754, 1731, 1698, 1457, 1381, 1338; ^1H NMR ($CDCl_3$) δ 2.81 and 2.86 (3H, NCH_3), 2.98 and 3.40 (3H, 3″-OCH_3) 3.02 and 3.03 (3H, 6-OCH_3), 3.60 (3H, s, 11-OCH_3), 7.16~7.46 (14H, aromatic H); ^{13}C NMR ($CDCl_3$) δ 28.7 (NCH_3), 49.0 and 49.5 (3″-OCH_3), 50.2 (6-OCH_3), 62.1 (11-OCH_3), 72.3 ($=NOCH_2$), 167.8 (C-9), 175.5 and 175.6 (C-1); FAB-MS *m/z* 1,155 (MH^+).

The third fraction was concentrated and the residue was recrystallized from a mixture of EtOAc and CH_2Cl_2 7 times to give a solid which was identical with **16** by instrumental analyses.

The mother liquors obtained by each crystallization were collected and evaporated to dryness. The residue was purified by column chromatography (CH_2Cl_2-EtOAc, 20:1) to afford 2′-*O*,3′-*N*-bis(benzyloxycarbonyl)-11-*O*-methyl-*N*-demethylerythromycin A 9-[*O*-(2-chlorobenzyl)oxime] (**21d**) as a foam: IR (KBr) cm^{-1} 3469, 2975, 2938, 1752, 1734, 1704, 1456, 1381, 1334, 1293; ^1H NMR ($CDCl_3$) δ 2.81 and 2.86 (3H, NCH_3), 2.97 and 3.40 (3H, 11-OCH_3), 7.17 and 7.46 (14H, aromatic H); ^{13}C NMR ($CDCl_3$) δ 28.8 (NCH_3), 48.9 and 49.5 (3″-OCH_3), 72.3 ($=NOCH_2$), 176.1 (C-1); FAB-MS *m/z* 1,141 (MH^+).

2′-*O*,3′-*N*-Bis(benzyloxycarbonyl)-6-*O*-methyl-*N*-demethylerythromycin A 9-(*O*-Methyloxime) (**17a**)

Compound **17a** was prepared from **12** (1.02 g, 1.0 mmol) by the same procedure as **21a**. There was obtained 0.82 g (80%) of **17a** as a foam, which was identical with that obtained from the methylation of **10**.

2′-*O*,3′-*N*-Bis(benzyloxycarbonyl)-6-*O*-methyl-*N*-demethylerythromycin A 9-(*O*-Allyloxime) (**18a**)

Compound **18a** was prepared from **13** (1 g, 1 mmol) by the same procedure as in the following selectivity of methylation from compound **12**~**16**. There was obtained 1 g (98%) of **18a**. The reaction was carried out with the intention of the selectivity of methylation and **18a** was not further characterized.

2′-*O*,3′-*N*-Bis(benzyloxycarbonyl)-6-*O*-methyl-*N*-demethylerythromycin A 9-(*O*-Trityloxime) (**19a**)

Compound **19a** was prepared from **14** (450 mg, 0.36 mmol) by the same procedure as **21a**. There was

† The reference standard sample was prepared as follows. The oximation of 2′-*O*,3′-*N*-bis(benzyloxycarbonyl)-6,11-di-*O*-methyl-*N*-demethylerythromycin A[5] with hydroxylamine hydrochloride in the presence of sodium acetate followed by treating 2-chlorobenzyl chloride and potassium hydroxide in DMF gave the desired **21b**.

obtained the crude **19a**, which was purified by column chromatography (CH_2Cl_2) to give pure **19a** (270 mg, 59%) as colorless foam: IR (KBr) cm^{-1} 3436, 2975, 1752, 1735, 1707; ^1H NMR ($CDCl_3$) δ 2.81 and 2.86 (3H, NCH_3), 2.98 and 3.39 (3H, 3″-OCH_3), 2.99 and 3.00 (3H, 6-OCH_3), 5.10~5.19 (4H, $COOCH_2$), 7.20~7.40 (25H, aromatic H); FAB-MS *m/z* 1,259 (MH^+).

2′-*O*,3′-*N*-Bis(benzyloxycarbonyl)-6-*O*-methyl-*N*-demethylerythromycin A 9-(*O*-Benzyloxime) (**20a**)

Compound **20a** was prepared from **15** (1.09 g, 1 mmol) by the same procedure as **21a**. Working-up following column chromatography (EtOAc-*n*-hexane, 1:1), there was obtained 830 mg (76%) of **20a**, which was crystallized from Et_2O-petroleum ether to afford colorless crystals: MP 154.5~156°C; IR (KBr) cm^{-1} 3400, 1750, 1735, 1700; ^1H NMR ($CDCl_3$) δ 2.80 and 2.84 (3H, NCH_3), 2.98 (3H, s, 6-OCH_3), 3.03 and 3.38 (3H, 3″-OCH_3), 4.96~5.24 (6H, $COOCH_2 \times 2$ and $=NOCH_2$), 7.20~7.50 (15H, aromatic H); ^{13}C NMR ($CDCl_3$) δ 28.8 (NCH_3), 49.0 and 49.5 (3″-OCH_3), 67.1 and 67.4 ($NCOOCH_2$), 69.4 and 69.7 ($OCOOCH_2$), 75.8 ($=NOCH_2$), 170.3 (C-9), 175.4 and 175.5 (C-1).

Anal Calcd for $C_{60}H_{86}N_2O_{17}$: C 65.08, H 7.83, N 2.53.
Found: C 64.76, H 7.83, N 2.53.

Selectivity of Methylation for Compounds **12~16**

Each 1 g of oxime derivative **12~16** was allowed to react with CH_3I (1.3 equiv mol) and 85% KOH powder (1.1 equiv mol) in a mixture of DMSO-THF (1:1, 10 ml) and the reaction mixture was stirred under ice-cooling for 1.5 hours. Fifty percent aqueous dimethylamine solution (0.5 ml) was added to the resulting mixture and stirring was continued at room temperature for a further 0.5 hour. The reaction mixture was extracted with EtOAc and the organic layer was washed with saturated brine and dried ($MgSO_4$). After evaporation of the solvent *in vacuo* the residual foam was subjected to HPLC analysis. The ratios of each methylated product **12~16** (**a~d**) were calculated from the Rf value of the corresponding peak in analogy with **21a~d**.

Comparison of Methylation Between Two Isomers **16** and (*Z*)-**16**

Methylation was carried out using each 1 g of **16** and (*Z*)-**16** as described for the preparation of **21a**. Samples (0.1 ml of the reaction mixture) were collected after 1, 2, 3, 5, 10, 20, 30, 60 and 90 minutes and poured into a mixture of EtOAc (1 ml), water (1 ml) and 50% aqueous dimethylamine solution (1 drop) with occasional shaking. The organic layer was concentrated to dryness *in vacuo* and the residue was subjected to HPLC analysis. The retention time of **16**, **21a**, (*Z*)-**16** and (*Z*)-**21a** is 16.4, 25.2, 13.5 and 22.6 minutes, respectively.

6-*O*-Methyl-*N*-demethylerythromycin A 9-Oxime (**24**)

A mixture of compound **21a** (80 g, 0.07 mol), palladium black (8 g) and acetic acid (20 ml) in methanol-water (560 ml/20 ml) was stirred under atmospheric pressure of hydrogen at room temperature for 7 hours. The catalyst was removed by filtration and washed with methanol (200 ml). The filtrate and washing were combined and diluted with water (1,000 ml). The pH of the resulting mixture was adjusted to about 10.3 with 1 N NaOH. After stirring for a further 2 hours, the precipitated solid was filtered, triturated with water, and filtered to provide the crude product (52.6 g). It was dissolved in a minimum amount of ethanol and allowed to stand overnight at 5°C to give colorless crystals of **24** (47.09 g, 90%): MP 247~249°C; IR (KBr) cm^{-1} 3600~3200, 1727, 1710; ^1H NMR ($CDCl_3$) δ 2.41 (3H, s, NCH_3), 3.10 (3H, s, 6-OCH_3), 3.32 (3H, s, 3″-OCH_3), 8.4~8.8 (1H, br s, =NOH); ^{13}C NMR ($CDCl_3$) δ 33.2 (NCH_3), 49.5 (3″-OCH_3), 51.2 (6-OCH_3), 170.8 (C-9), 175.5 (C-1); SIMS-MS *m/z* 749 (MH^+).

Anal Calcd for $C_{37}H_{68}N_2O_{13}$: C 59.34, H 9.15, N 4.74.
Found: C 59.35, H 8.87, N 4.78.

6-*O*-Methylerythromycin A 9-Oxime (**25**)

A mixture of **24** (7.49 g, 10 mmol), HCOOH (0.92 g, 20 mmol) and 35% aqueous HCHO (5.14 ml, 62 mmol) in methanol (100 ml) was heated under reflux for 5 hours. The mixture was evaporated *in vacuo* and added into water (100 ml). The pH of the mixture was adjusted to 9.5~10.5 and then it was extracted with CH_2Cl_2. The organic layer was washed with saturated brine, dried ($MgSO_4$) and evaporated *in vacuo*.

The residue was crystallized from ethanol-petroleum ether to give **25** (6.82 g, 94%): MP 169~171°C (it solidifies at 180~185°C and remelts at 248~251°C); IR (KBr) cm^{-1} 3400, 1730, 1625; ^1H NMR ($CDCl_3$) δ 2.29 (6H, s, $N(CH_3)_2$), 3.11 (3H, s, 6-OCH_3), 3.33 (3H, s, 3″-OCH_3); ^{13}C NMR ($CDCl_3$) δ 40.24 ($N(CH_3)_2$), 49.5 (3″-OCH_3), 51.2 (6-OCH_3), 170.1 (C-9), 175.7 (C-1); SIMS-MS *m/z* 763 (MH^+).

Anal Calcd for $C_{38}H_{70}N_2O_{13}$: C 59.82, H 9.25, N 3.67.
Found: C 59.83, H 8.85, N 3.58.

Clarithromycin (3)

Method A

A mixture of **25** (7.63 g, 10 mmol) and $NaHSO_3$ (4.16 g, 40 mmol) in ethanol-water (32 ml/48 ml) was gently heated under reflux for 6 hours. The reaction mixture was cooled to room temperature and poured into water (80 ml). The pH of the mixture was adjusted to 10~10.3 with 1 N NaOH. The resulting crystalline precipitates were filtered, triturated with water and then filtered. Crystallization from ethanol gave 5.09 g (68%) of **3** as colorless orthorhombic needles: MP 223~225°C (ref. 6, 222~225°C).

Anal Calcd for $C_{38}H_{69}NO_{13}$: C 61.02, H 9.30, N 1.87.
Found: C 61.08, H 9.06, N 2.05.

Method B

A mixture of compound **24** (5.0 g, 6.68 mmol), 35% aqueous HCHO (2.3 ml, 26.7 mmol) and 99% HCOOH (0.5 ml, 13.2 mmol) in ethanol (25 ml) was heated under reflux for 2 hours. To this solution was added $NaHSO_3$ (4.86 g, 46.8 mmol) and water (25 ml). The mixture was heated under reflux for a further 2 hours and then diluted with water (150 ml). To this mixture was added dropwise 2 N NaOH (*ca.* 20 ml) with stirring until a pH about 10.5 was reached. The resulting mixture was allowed to stand for 3 hours at room temperature with occasional stirring. The precipitated crystals were filtered, triturated with water and filtered. Two recrystallizations from ethanol afforded 3.59 g (72%) of **3** as orthorhombic needles.

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