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# Synthetic studies of erythromycin derivatives: 6-*O*-methylation of (9*S*)-12,21-anhydro-9-dihydroerythromycin A derivatives

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Dedicated to Professor K. C. Nicolaou on the occasion of his being awarded the Tetrahedron Prize in 2003

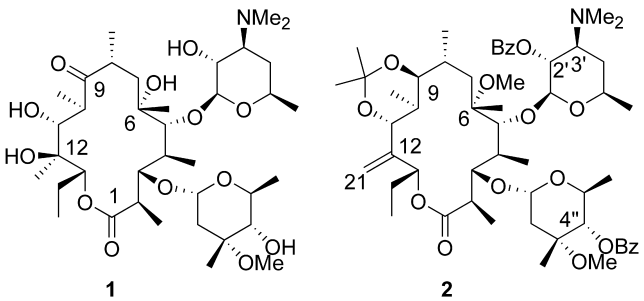
**Abstract**—Synthetic studies on methylation of erythromycin derivatives were conducted. Methylation of **6** resulted in the formation of the C-3′ quaternary ammonium salts with a rate faster than 6-*O*-methylation. In dipolar aprotic solvent and under strong base conditions, 6-*O*-methylation, C-3′ quaternary ammonium salts formation and 2-*C*-methylation proceeded simultaneously to yield a mixture of three different products **7**, **8** and **9**. The quaternary ammonium salts were converted back to the corresponding tertiary amines **2**, **10** and starting material **6** by employing sodium 4-pyridinethiolate as a *N*-demethylation reagent. The 6-*O*-methylation was eventually achieved in a good yield when a carbobenzyloxy (Cbz) group was utilized to protect the *C*-3′-dimethylamino group of **4**. In this report, we will discuss the details of different reaction courses in the methylation of (9*S*)-12, 21-anhydro-9-dihydroerythromycin A derivatives.


## 1. Introduction

Erythromycin A (**1**) is the best known of the medicinally important macrolide antibiotics. However, **1** is unstable under acidic conditions. The reason for this instability is the reversible attack of C-6 hydroxyl group on the C-9 ketone.[1,2] Simultaneously, the resulting hemiketal intermediate is directly converted to the antibacterially inactive 6,9,9,12-spiroketal.[2] To reduce the acid sensitivity of **1**, much attention has been focused on the modification of C-9 ketone moiety.[2,3] Accordingly, these strategies include the conversion of the C-9 ketone to amines[4] and to oximes.[5] Ring expansion procedures making use of the ketone functional group has also been reported.[6] Other approaches to secure acid stable erythromycin derivatives involve the replacement of the C-8 α-acidic hydrogen atom with inert substituents[7,8] as well as the alkylation of the C-6 hydroxyl group.[9]

Since (9*S*)-9-dihydroerythromycin A possesses weak antibacterial activity,[2] only few attention has been placed on the preparation of 9-dihydroerythromycin A derivatives[10,11] in the recent two decades. Another interesting modification on erythromycin is regiospecific olefin formation on C-12,21 positions.[12]

We have undertaken a research program with the aim to synthesize 9-dihydroerythromycin A derivatives. Herein, we report our synthetic studies on the preparation of erythromycin derivative **2** whose structural features are the C-9 hydroxyl group, C-6 methoxyl group and C-12, C-21-alkene.




**1** **2**

## 2. Result and discussion

### 2.1. The synthesis of compound 2 via quaternary ammonium salts

At the outset, we designed a route as shown in the Scheme 1 to synthesize (9*S*)-9,11-*O*-isopropylidene-6-*O*-methyl-2′,4″-*O*-bis(benzoyl)-12,21-anhydro-9-dihydroerythromycin A (**2**),

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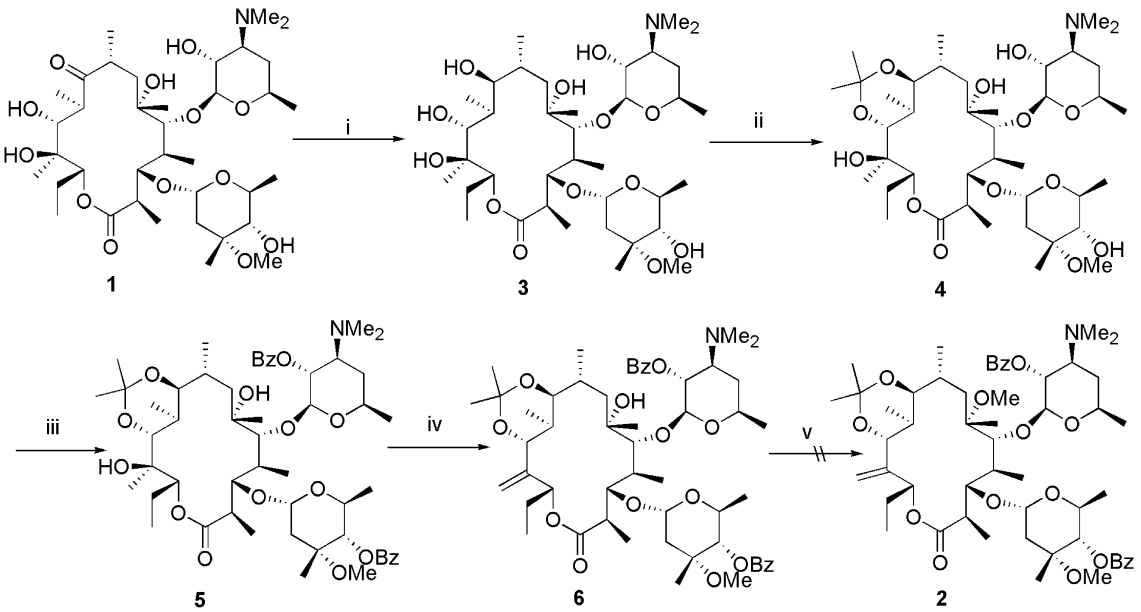



**Scheme 1.** *Reagents and conditions*: (i) $NaBH_4$, ethanol, 79%; (ii) 2,2-dimethoxypropane, PPTS, $CH_2Cl_2$, 89%; (iii) benzoic anhydride, DMAP, $Et_3N$, EtOAc, 84%; (iv) $SOCl_2$, $Et_3N$, EtOAc, 0°C, 77%; (v) $CH_3I$, NaH, DMSO–THF.

starting from erythromycin A (**1**). The C-9 ketone was first reduced to a hydroxyl group, affording (9*S*)-9-dihydroerythromycin A (**3**). Subsequent acetonide formation of 9,11-dihydroxyl groups of **3** yielded compound **4**. The C-2′ and C-4″ hydroxyl groups were protected to give dibenzoyl ester **5**. The C-12 hydroxyl group was allowed to undergo a dehydration step to form a C-12, C-21 double bond[12] as depicted in compound **6**.

The presence of C-12, C-21 double bond in **6** may provide a conformation that may alter the *p*Ka of C-6-hydroxyl group. Consequently, we found it difficult to obtain a 6-*O*-methylation product in a usual manner. Many attempts to methylate **6** under a variety of reaction conditions including change of solvents, bases and methylating reagents have been unfruitful. Finally, we found that solvents have played an important role in regulating the reactivity of **6**. Only in dipolar aprotic solvents such as *N*,*N*-dimethyl formamide (DMF), dimethylsulfoxide (DMSO), hexamethylphosphoramide (HMPA) could we obtain some 6-*O*-methylation products accompanied with the C-3′ quaternary ammonium salts. In solvents such as THF, 1,4-dioxane, toluene, no reaction could be observed. DMSO–THF, on the other hand, mainly led to the formation of quaternary ammonium salts.

The effect of bases on the reaction results was also studied. Potassium hydroxide, Hünig's base (diisopropylethylamine) were both found to give no reaction, and sodium hydride in DMF was found to result in 6-*O*-methylation products.

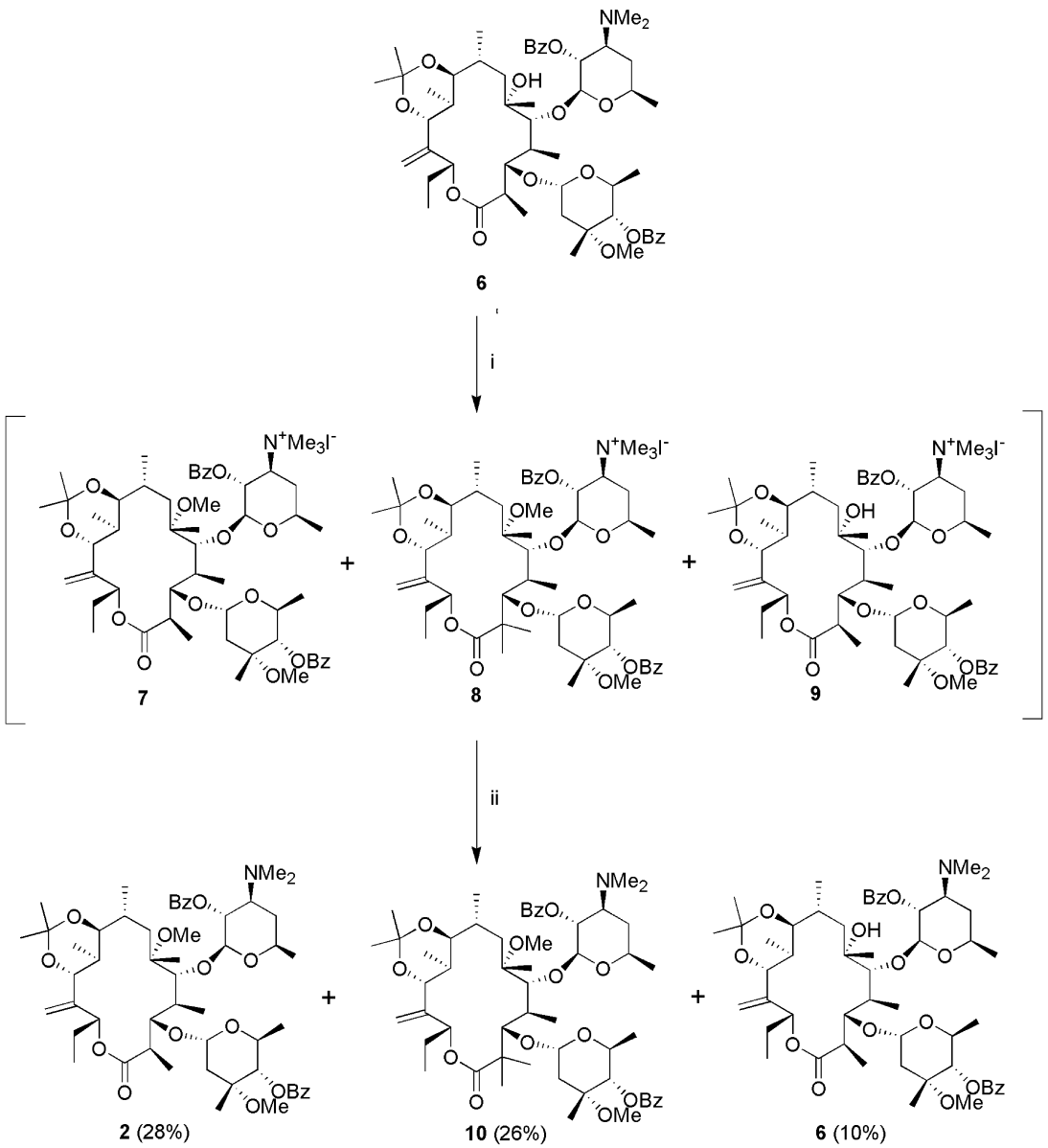
Among the common methylating reagents, methyl iodide displayed a better activity towards 6-*O*-methylation than that observed for dimethyl sulfate. Thus, using sodium hydride as base, methyl iodide in DMF afforded 6-*O*-methylation product together with the C-3′ quaternary ammonium salts as depicted in Scheme 2. Methylation at C-2 was also observed under this condition.

In order to prepare **2** from the quaternary ammonium salts, *N*-demethylation was attempted using thiophenoxide anion[13] in toluene. This condition gave only Hoffmann elimination products along with some unidentified side products. Employing ethanolamine[14] as the *N*-demethylation reagent for quaternary ammonium salts, we obtained compounds with not only the C-3′ demethylation but also the deprotection of the C-2′ and C-4″ benzoyl groups.

Eventually the *N*-demethylation was achieved with sodium 4-pyridinethiolate after many tests in our laboratory. The structure of 4-pyridinethiol is similar to that of thiophenol, but 4-pyridinethiol does not give the unbearable smell of thiophenol. Moreover, 4-pyridinethiolate is a ambident anion and shows many activities.[15] Based on this reason, we tested sodium 4-pyridinethiolate as a *N*-demethylation reagent, and satisfied result was obtained. As a result, the 6-*O*-methylation product **2**, the 6-*O*-methylation and 2-*C*-methylation product **10** and the starting material **6** were isolated as shown in Scheme 2.

The above results indicate that the rate of methylation for different functional groups in compound **6** is in an order of C-3′ tertiary amine > C-6 hydroxy group > C-2 carbon. Although in practice, it is difficult to differentiate C-6 hydroxy methylation from the C-2 process.

Watanabe reported that the formation of quaternary ammonium salts could be retarded by protection of 2′,4″-hydroxyl groups with trimethylsilyl ethers.[16] Similarly, we protected the 2′,4″-hydroxyl groups of **3** as trimethylsilyl ethers, affording **11** (Scheme 3). Dehydration of the C-12 hydroxyl group in **11** furnished the C-12, C-21 double bond in **12** as shown in Scheme 3. Nevertheless, methylation of the C-6 hydroxyl group with methyl iodide and sodium hydride in DMF also yielded the quaternary ammonium salts plus some de-trimethylsilyl products. The desired compound **13** could not be obtained from **12**.



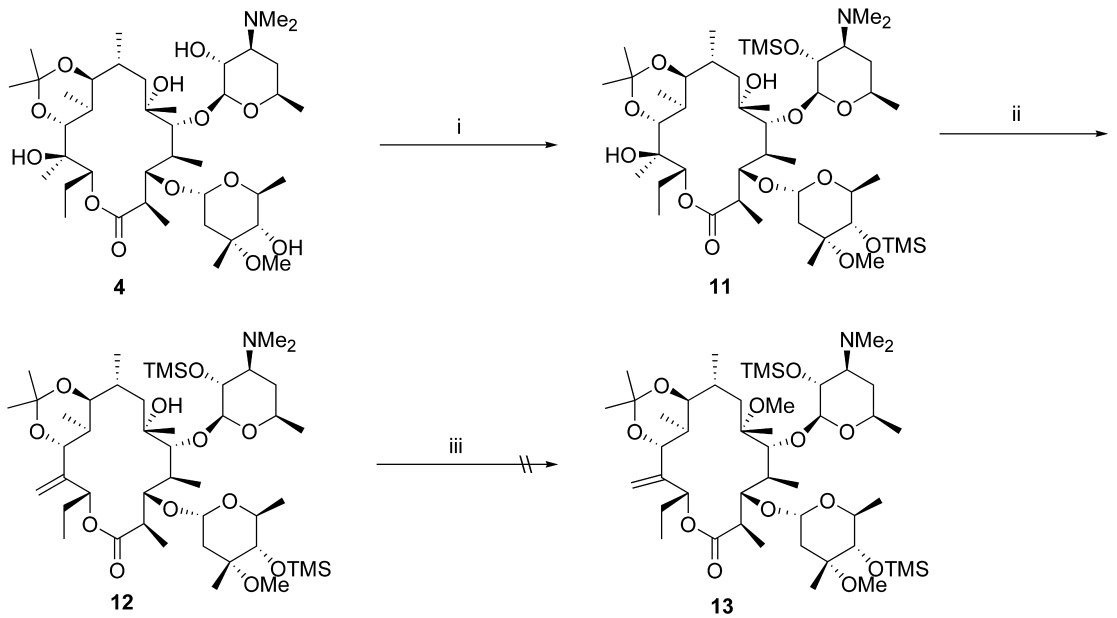

**Scheme 2.** *Reagents and conditions*: (i) $CH_3I$, NaH, DMF, rt 24 h, 61%; (ii) (a) AgCl; (b) 4-pyridinethiol, NaH, $CH_3CN$, reflux, 24 h.

### 2.2. Preparation of 2 via C-3′ amino protection with carbobenzyloxy group (Cbz)

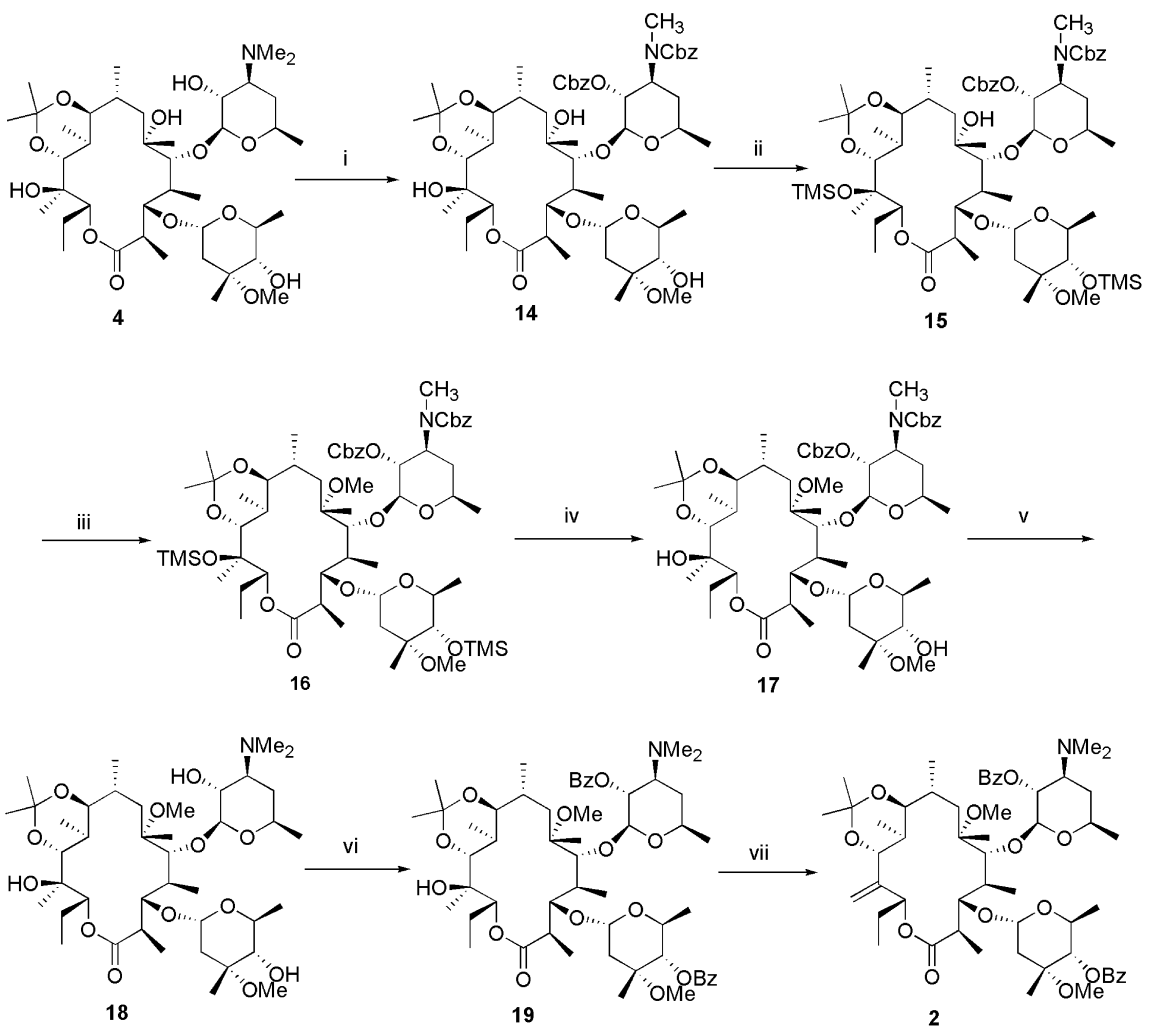
In order to prepare the 6-*O*-methylation products as well as to avoid the formation of quaternary ammonium salts, the C-3′ amino group of **4** was protected by utilizing a carbobenzyloxy group (Cbz)[17] as shown in Scheme 4. In this case, we observed different reactivities for the C-6, C-12, and C-4″ hydroxyl groups of compound **14**. As it turned out, the most reactive one is the 4″-hydroxyl group. The second reactive position is the C-12 hydroxy group, while the C-6 hydroxyl group is the least reactive. In this manner, the C-12 and C-4″ hydroxyl groups were preferentially protected as trimethylsilyl ethers **15**. Sodium hydride and methyl iodide in DMF straightforwardly furnished the 6-*O*-methylation product **16** in 84% yield. In sharp contrast to substrate **6**, methylation of **15** under the same conditions did not give any C-2 methylated product. Deprotection of the trimethylsilyl group using *N*-tetrabutylammonium fluoride,[18] and conversion of *N*,*N*-methylbenzyloxycarbonylamino group to *N*,*N*-dimethylamino group by a literature method[19] afforded compound **18** in 83% yield. Treatment of **18** with benzoic anhydride furnished **19**. Compound **19** was successfully dehydrated to form **2** in 88% yield. The overall yield of **2** from **4** is 17%.

Another 6-*O*-methylation strategy to prepare **2** is to employ the C-3′ amino protected version of compound **6** (Scheme 5). However, after the C-3′ amino group of **6** was protected with Cbz group, the methylation of the resulting **20** afforded not only the desired mono-methylation product **21**, but also the di-methylation product **22** as a result of both 6-OH and 2-*C*-methylation. Deprotection of the Cbz groups with $PdCl_2$ and triethylsilane,[20] followed by formation of 3′-*N*,*N*-dimethyl group yielded compounds **2** and **10**, respectively. The structures of **2** and **10** were further confirmed by X-ray single crystal diffraction analysis (Figs. 1 and 2).

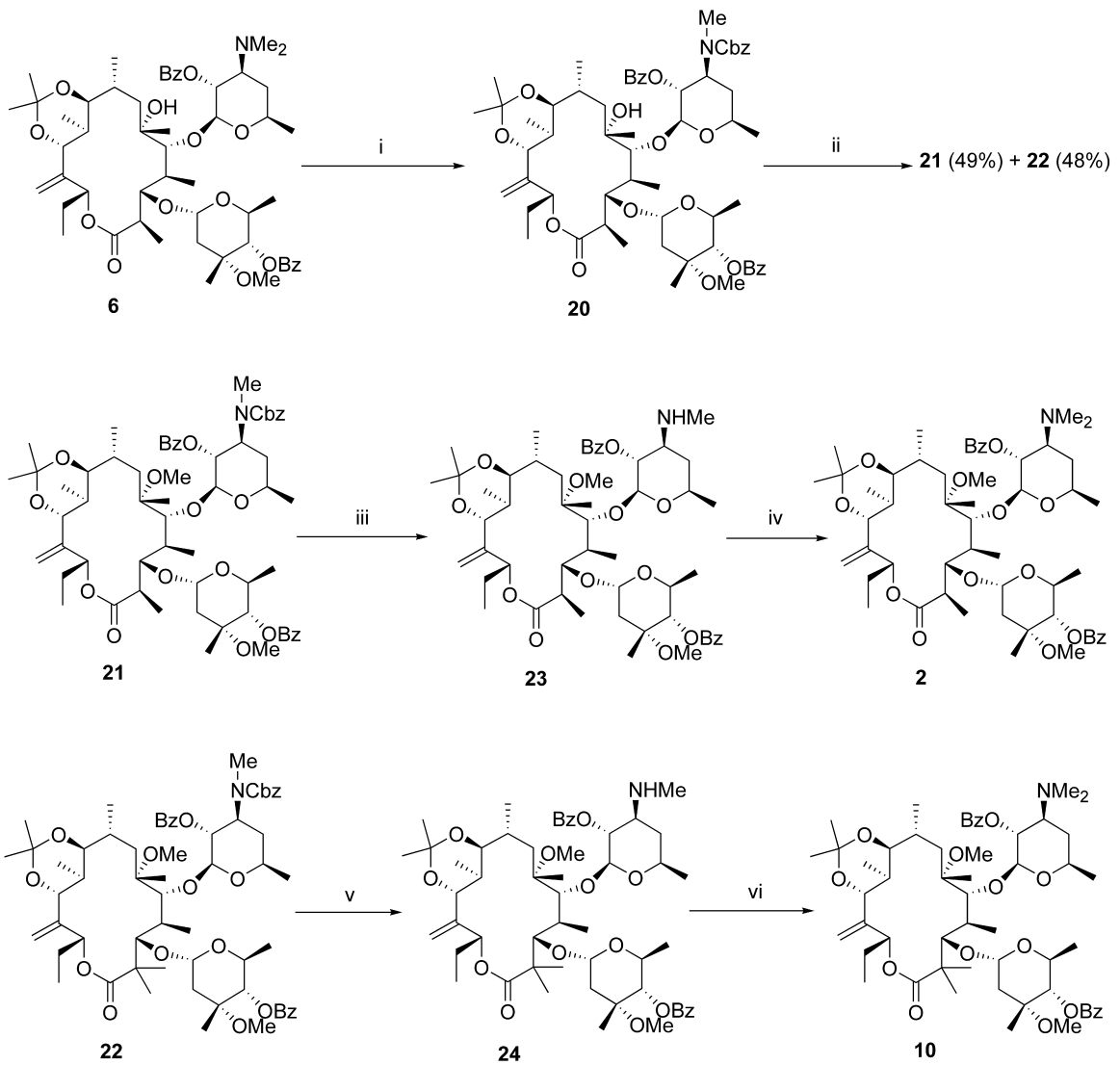
As shown in Schemes 2 and 5, the C-6 hydroxyl group and C-2 carbon have almost the same reactivities toward




**Scheme 3.** *Reagents and conditions*: (i) $(CH_3)_3SiCl$, imidazole, DMAP, EtOAc, 90%; (ii) $SOCl_2$, $Et_3N$, EtOAc, 0°C, 91.5%; (iii) $CH_3I$, NaH, DMF.




**Scheme 4.** *Reagents and conditions*: (i) benzyl chloroformate, $NaHCO_3$, 1,4-dioxane, 60–65°C, 83%; (ii) $(CH_3)_3SiCl$, imidazole, DMF, 56%; (iii) $CH_3I$, DMF, NaH, 84%; (iv) *n*-$Bu_4NF$, THF, 66%; (v) (a) $H_2$, 10% Pd–C, acetic acid, $CH_3OH$, $H_2O$; (b) HCHO, HCOOH, $CH_3OH$, reflux, 5 h, 83%; (vi) benzoic anhydride, DMAP, $Et_3N$, EtOAc, 90%; (vii) $SOCl_2$, $Et_3N$, EtOAc, 88%.




**Scheme 5.** *Reagents and conditions*: (i) benzyl chloroformate, $NaHCO_3$, 1,4-dioxane, 60–65°C, 87%; (ii) $CH_3I$, NaH, DMF; (iii) $Et_3SiH$, $Et_3N$, $PdCl_2$, $CH_2Cl_2$, reflux, reacted yield (R.Y.) 91%; (iv) HCHO, HCOOH, $CH_3OH$, reflux, 68%; (v) $Et_3SiH$, $Et_3N$, $PdCl_2$, $CH_2Cl_2$, reflux, R.Y. 95%; (vi) HCHO, HCOOH, $CH_3OH$, reflux, 81%.

methylation in derivatives containing the C-12, C-21 double bond. In a polar aprotic solvent and under strong base conditions, these positions could be methylated by methyl iodide nearly simultaneously to form both C-6-*O*-methylation and 2-*C*-methylation products.

## 3. Conclusion

We have successfully synthesized (9*S*)-9,11-*O*-isopropylidene-6-*O*-methyl-2′,4″-*O*-bis(benzoyl)-12,21-anhydro-9-dihydroerythromycin A (**2**) via both quaternary ammonium salts as intermediate and C-3′ amino group Cbz-protected procedure. When the C-9 ketone of erythromycin A (**1**) was reduced to a hydroxyl group, 6-*O*-methylation of its derivatives led to the formation of C-3′ quaternary ammonium salts. A new *N*-demethylation method of quaternary ammonium salts was developed by way of employing sodium 4-pyridinethiolate as an *N*-demethylation reagent. Exclusive 6-*O*-methylation was eventually achieved in a good yield when a carbobenzyloxy (Cbz) group was utilized to protect the C-3′-dimethylamino group of **4**. However, in (9*S*)-9-dihydroerythromycin derivatives with the presence of the C-12, C-21 double bond, the C-6 hydroxyl group and C-2 carbon have almost the same reactivities toward methylation. The methylation products obtained were the 6-*O*-methylation product, as well as the 6-*O*-methylation and the 2-*C*-methylation product. The difference observed may be due to the conformation difference of the macrocycles between the two series.

## 4. Experimental

### 4.1. General information

All reagents and solvents were reagent grade. Further purification and drying by standard methods were employed when necessary. Erythromycin A and its derivatives were pre-dried azeotropically from benzene. THF was distilled from sodium benzophenone ketyl. $CH_2Cl_2$ and EtOAc were distilled from $CaH_2$. DMF, DMSO and HMPA were

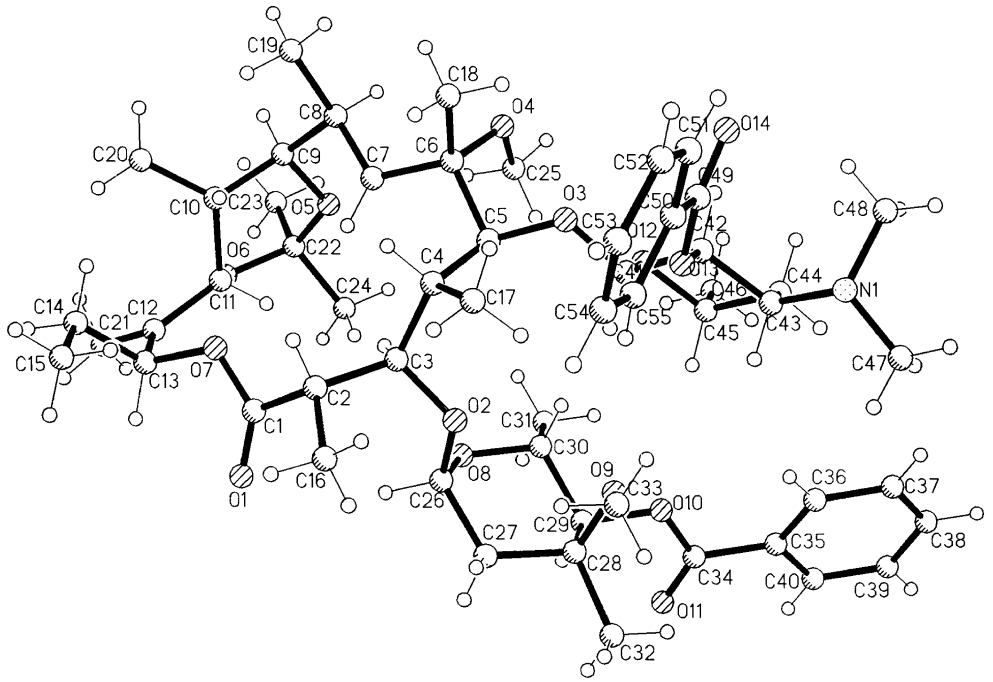



**Figure 1.** Crystal structure of compound **2**.

redistilled and stored in screw-cap vials with molecular sieve (4A). All organic solvents were evaporated under reduced pressure with a rotary evaporator. The plates used for thin-layer chromatography (TLC) were E. Merck silica gel $60F_{254}$ (0.1 mm thickness) precoated on aluminum plates, and they were visualized under both long (365 nm) and short (254 nm) UV light. Compounds on TLC plates were visualized with a spray of 5% dodoca-molybdophosphoric acid in ethanol and with subsequent heating. Column chromatography was performed using E. Merck silica gel (230–400 mesh).

Melting points were measured using Electrothermal IA9100 digital melting point apparatus and were uncorrected. IR spectra were measured on a Nicolet 420 FT-IR spectrometer. NMR spectra were recorded on a Bruker DPX-300 spectrometer (300.13 MHz for $^1$H and 75.47 MHz for $^{13}$C). All NMR measurements were carried out at 300 K in deuterated chloroform solution unless otherwise stated. Chemical shifts are reported as parts per million (ppm) in $\delta$ unit in the scale relative to the resonance of $CDCl_3$ (7.26 ppm in the $^1$H, 77.00 ppm for the central line of the triplet in the $^{13}$C modes, respectively). Coupling constants

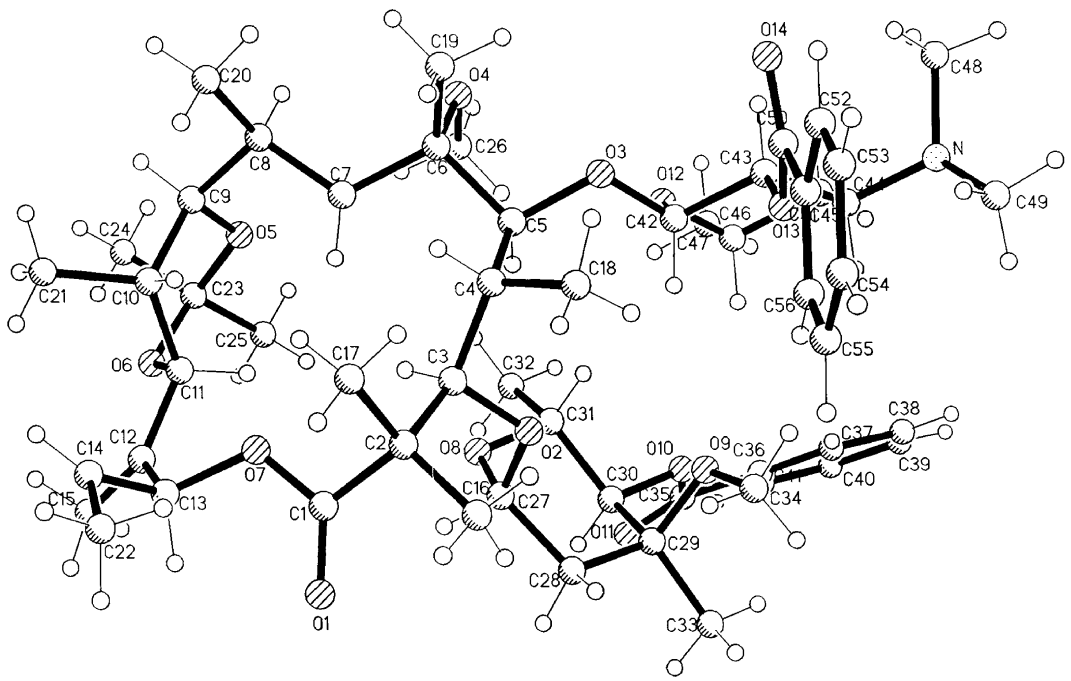



**Figure 2.** Crystal structure of compound **10**.

(*J*) are reported in Hz. Splitting patterns are described by using the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. $^1$H NMR data is reported in this order: chemical shift; multiplicity; coupling constant(s), number of proton. Mass spectra (ERMS and HRMS) were obtained with a Thermofinnigan MAT95XL spectrometer or API 2000 LC/MS/MS system. Relevant data were tabulated as *m/z*. Elemental analyses were performed at Shanghai Institute of Organic Chemistry, the Chinese Academy of Sciences, China.

**4.1.1. (9*S*)-9-Dihydroerythromycin A (3).** To a solution of $NaBH_4$ (23 g, 0.6 mol) in absolute EtOH (200 mL) at 0°C under $N_2$ was added dropwise for 40 min a solution of erythromycin A (**1**) (75 g, 0.1 mol) in absolute EtOH (200 mL). The ice bath was then removed and the reaction mixture was stirred at rt for 18 h. After that, $CO_2$ was bubbled through for 1 h and the reaction mixture became very thick. Triethanolamine (25 mL) was added and the resulting mixture was stirred for another 5 h. Removal of solvent in vacuo resulted in a syrup. To this was added EtOAc (500 mL) and 5% aq. $KH_2PO_4$ (500 mL). The organic layer was separated and the aqueous layer was thoroughly extracted with EtOAc (500 mL) and $CHCl_3$ (2×500 mL). The organic extracts were combined, dried over $Na_2SO_4$ and filtered. The filtrate was concentrated in vacuo to give a white foam, which was purified on a silica gel column (500 g, hexanes–acetone 1:1 with 1% $Et_3N$) to give **3** (58 g, 79%). Recrystallization from isopropyl alcohol–water yielded colorless crystals, mp 132–134°C, lit.,[21] mp 133–135°C; IR (KBr) cm$^{-1}$ 3412 (m), 3234 (w), 1731 (m), 1167 (s); $^1$H NMR ($CDCl_3$)[22] $\delta$ 0.88 (t, *J*=7.5 Hz, 3H), 1.07, 1.09, 1.16, 1.19, 1.33 (each d, *J*=6.9, 7.5, 7.2, 6.6, 6.3 Hz, each 3H, 5×Me), 1.11, 1.22, 1.24, 1.26 (each s, 4×Me), 1.40–1.70 (m, 4H), 1.8–2.0 (m, 4H), 2.1–2.2 (m, 2H), 2.33 (s, 1H), 2.40 (br s, 6H, $NMe_2$), 2.6–2.8 (m, 3H), 2.88 (s, 1H, OH), 3.05 (t, *J*=9 Hz, 1H), 3.31 (s, 3H, 3″-OMe), 3.36 (m, 2H), 3.65 (m, 1H), 3.70 (d, *J*=5.4 Hz, 1H), 3.73 (s, 1H), 3.75 (m, 1H), 4.0–4.1 (m, 2H), 4.36 (s, 1H, OH), 4.55 (m, 2H), 4.63 (s, 1H, OH), 4.90 (dd, *J*=9.9, 2.7 Hz, 1H), 4.96 (d, *J*=3.9 Hz, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ 9.5, 11.1, 15.0, 15.1, 16.6, 18.1, 20.1, 21.1, 21.5, 21.7, 25.2, 29.7, 30.9, 34.2, 34.9, 37.1, 40.5, 41.6, 45.8, 49.9, 65.1, 66.4, 69.1, 70.7, 70.8, 72.7, 74.4, 75.0, 77.6, 77.8, 79.4, 83.1, 85.0, 96.5, 103.2; MS *m/z* 736 ($MH^+$).

**4.1.2. (9*S*)-9,11-*O*-Isopropylidene-9-dihydroerythromycin A (4).** To a solution of **3** (2.7 g, 3.7 mmol) in dry $CH_2Cl_2$ (20 mL) was added 2,2-dimethoxypropane (100 mL, 81 mmol) and pyridinium *p*-toluenesulfonic acid (PPTS) (2.7 g, 11 mmol). The mixture was stirred at rt under $N_2$ for 40 h. Then $Et_3N$ (3 mL) was added and the reaction mixture was concentrated in vacuo. The residue was re-dissolved in $CHCl_3$ (50 mL), and washed successively with 5% aq. $KH_2PO_4$ (50 mL), 1N $NH_3{\cdot}H_2O$ (50 mL) and brine (50 mL). The solution was dried over $Na_2SO_4$ and concentrated in vacuo. The residue was purified on a silica gel column (100 g, hexanes–acetone 3:1 to 1:1 with 1% $Et_3N$) to give a light yellow foam **4** (2.1 g, 89% based on 0.44 g recovered **3**), mp 105–106°C; IR (KBr) cm$^{-1}$ 3430 (m), 1734 (s), 1378 (s), 1165 (s); $^1$H NMR ($CDCl_3$)[22] $\delta$ 0.83 (t, *J*=7.5 Hz, 3H), 0.97 (d, *J*=7.8 Hz, 3H), 1.08 (d, *J*=7.5 Hz, 3H), 1.15 (s, 3H), 1.19 (d, *J*=9 Hz, 3H), 1.21 (d, *J*=4.2 Hz, 3H), 1.24 (s, 6H), 1.30 (s, 3H), 1.31 (d, *J*=4.5 Hz, 3H), 1.40 (s, 6H, $CMe_2$), 1.45–1.75 (m, 3H), 1.85–2.10 (m, 4H), 2.15–2.35 (m, 4H), 2.44 (br s, 6H, $NMe_2$), 2.57 (s, 1H, OH), 2.67 (m, 1H), 2.90 (m, 1H), 3.04 (m, 2H), 3.19 (m, 1H), 3.31 (s, 3H, 3″-OMe), 3.36 (s, 1H, OH), 3.5 (m, 3H), 3.62 (d, *J*=6.9 Hz, 1H), 4.01 (m, 1H), 4.16 (d, *J*=9 Hz, 1H), 4.49 (d, *J*=7.2 Hz, 1H), 4.74 (s, 1H, OH), 4.97 (d, *J*=4.2 Hz, 1H), 5.05 (dd, *J*=10.8, 2.4 Hz, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ 7.6, 8.9, 15.3, 15.5, 15.9, 18.0, 19.0, 20.4, 20.8, 20.9 21.1, 23.6, 25.7, 27.6, 28.4, 29.4, 32.4, 34.6, 40.0, 44.4, 48.9, 65.0, 68.2, 68.9, 70.6, 72.3, 73.9, 75.7, 77.6, 79.2, 79.9, 83.4, 95.5, 101.2, 102.3; MS *m/z* 776.9 ($MH^+$).

**4.1.3. (9*S*)-9,11-*O*-Isopropylidene-2′,4″-*O*-bis(benzoyl)-9-dihydro erythromycin A (5).** To a solution of **4** (6.5 g, 8.4 mmol) in anhydrous EtOAc (50 mL) at 0°C was added sequentially 4-dimethylaminopyridine (DMAP) (4.1 g, 33.5 mmol), $Et_3N$ (4.7 ml, 33.5 mmol) and benzoic anhydride (7.6 g, 33.5 mmol). The reaction was warmed to rt and stirred under $N_2$ for 20 h. The reaction was quenched by adding cold sat. aq. $NaHCO_3$ solution (30 mL) and the organic layer was separated. The aqueous layer was extracted with $CH_2Cl_2$ (30 mL). The combined organic layer was washed with brine (50 mL). The solution was dried over $Na_2SO_4$ and concentrated in vacuo. The residue was purified on a silica gel column (200 g, 8:1 hexanes–acetone with 1% $Et_3N$) to give **5** (6.91 g, 84%) as a white foam, mp 131–133°C; IR (KBr) cm$^{-1}$ 3419 (w), 1725 (s), 1268 (s), 710 (m); $^1$H NMR ($CDCl_3$) $\delta$ 0.70 (d, *J*=7.2 Hz, 3H), 0.79 (t, *J*=7.5 Hz, 3H), 0.93 (d, *J*=5.7 Hz, 3H), 0.96 (d, *J*=7.5 Hz, 3H), 1.01 (s, 3H), 1.12 (d, *J*=6.6 Hz, 3H), 1.18 (d, *J*=6.9 Hz, 3H), 1.21 (s, 3H), 1.23 (s, 3H), 1.39 (s, 3H), 1.41 (s, 6H, $CMe_2$), 1.5–1.9 (m, 9H), 2.17 (m, 1H), 2.38 (br s, 6H, $NMe_2$), 2.56 (s, 1H, OH), 2.75 (t, *J*=7.2 Hz, 1H), 3.11 (m, 2H), 3.43 (m, 2H), 3.54 (s, 3H, 3″-OMe), 3.9 (m, 1H), 4.07 (d, *J*=8.1 Hz, 1H), 4.48 (m, 1H), 4.54 (m, 2H), 4.95 (m, 3H), 5.13 (d, *J*=4.8 Hz, 2H), 7.44 (m, 4H), 7.57 (m, 2H), 8.02 (d, *J*=8.1 Hz, 4H); $^{13}$C NMR ($CDCl_3$) $\delta$ 10.0, 11.2, 16.2, 16.3, 16.8, 18.6, 21.7, 21.9, 24.6, 28.6, 30.7, 32.1, 33.5, 35.2, 41.2, 41.5, 45.2, 46.5, 50.1, 64.0, 64.3, 68.2, 69.9, 73.1, 73.7, 74.1, 74.3, 76.8, 79.4, 79.6, 80.8, 84.5, 96.0, 100.5, 102, 2, 128.7, 128.9, 130.2, 130.6, 131.5, 133.1, 133.9, 166.0, 166.7, 176.0; MS *m/z* 985 ($MH^+$). Anal. calcd for $C_{54}H_{81}NO_{15}$: C, 65.90; H, 8.30; N, 1.42. Found: C, 65.62; H, 8.41; N, 1.41.

**4.1.4. (9*S*)-9,11-*O*-Isopropylidene-2′,4″-*O*-bis(benzoyl)-12,21-anhydro-9-dihydroerythromycin A (6).** To a solution of **5** (8 g, 8.13 mmol) in dry EtOAc (80 mL) was added $Et_3N$ (4.6 mL, 32.5 mmol) at 0°C under $N_2$. Then $SOCl_2$ (0.66 mL, 8.94 mmol) was added dropwise quickly. The reaction mixture was kept at 0°C for 1.5 h after which TLC showed very little starting material left. Then cold sat. aq. $NaHCO_3$ solution (50 mL) was added to quench the reaction and the organic layer was separated. The aqueous layer was extracted with EtOAc (50 mL). The combined organic layer was washed with brine (50 mL), dried over $Na_2SO_4$ and concentrated in vacuo. The crude material was purified on a silica gel column (200 g, 3:2 hexanes–EtOAc with 1% $Et_3N$) to afford **6** (6.2 g, 77.3%), mp 188–190°C; IR (KBr) cm$^{-1}$ 3528 (w), 1726 (s), 1268 (s), 710 (m); $^1$H NMR ($CDCl_3$) $\delta$ 0.66 (d, *J*=6.9 Hz, 3H), 0.82 (m, 6H), 0.90

(d, $J$=5.7 Hz, 3H), 1.01 (d, $J$=6.6 Hz, 3H), 1.05 (d, $J$=7.2 Hz, 3H), 1.17 (m, 9H), 1.27 (s, 3H), 1.32 (s, 3H), 1.5–1.9 (m, 8H), 2.0–2.3 (m, 2H), 2.33 (s, 6H, $-NMe_2$), 2.45 (m, 2H), 3.07 (m, 1H), 3.15 (s, 1H), 3.29 (m, 1H), 3.51 (m, 1H), 3.55 (s, 3H, 3″-$OCH_3$), 3.78 (s, 1H, –OH), 3.94 (m, 1H), 4.22 (s, 1H), 4.46 (m, 1H), 4.66 (d, $J$=4.5 Hz, 1H), 4.89 (d, $J$=9.6 Hz, 1H), 4.99 (s, 1H), 5.03 (d, $J$=7.5 Hz, 1H), 5.19 (d, $J$=10.2 Hz, 1H), 5.24 (s, 1H), 5.46 (t, $J$=7.5 Hz, 1H), 7.41 (m, 4H), 7.53 (m, 2H), 7.98 (m, 4H); $^{13}$C NMR ($CDCl_3$) $\delta$ 8.6, 10.6, 12.0, 14.0, 15.2, 17.4, 17.8, 20.8, 21.1, 21.2, 23.7, 24.2, 27.9, 29.2, 31.8, 32.7, 33.2, 34.9, 37.5, 40.7, 42.9, 44.0, 49.2, 63.3, 63.6, 68.0, 68.2, 71.9, 73.2, 73.9, 76.3, 79.2, 80.3, 85.2, 94.8, 99.5, 100.4, 112.6, 128.2, 129.4, 129.7, 130.5, 132.5, 133.2, 144.1, 165.3, 165.9, 175.8; MS $m/z$ 967 ($MH^+$), 989 (M+Na). Anal. calcd for $C_{54}H_{79}NO_{14}$: C, 67.13; H, 8.24; N, 1.45. Found: C, 66.68; H, 8.31; N, 1.38.

**4.1.5. (9*S*)-*N*-Demethyl-2′-*O*-3′-*N*-bis(carbobenzyloxy)-9,11-*O*-isopropylidene-9-dihydroerythromycin A (14).** A suspension of **4** (2.1 g, 2.7 mmol) in dry 1,4-dioxane (6 mL) with $NaHCO_3$ (2.7 g, 32 mmol) was heated to approximately 60°C, and benzyl chloroformate (3.8 mL, 27 mmol) was added dropwise. The resulting mixture was stirred and heated at 65°C for 3 h. It was then cooled, diluted with $CH_2Cl_2$ (50 mL), and filtered through sintered glass funnel. To the filtrate was added sat. aq. $NaHCO_3$ solution (40 mL). The organic layer was separated, washed with brine (40 mL), dried over $Na_2SO_4$ and concentrated in vacuo. The thick oil was chromatographed on a silica gel column (200 g, hexanes–EtOAc 5:2 with 1% $Et_3N$ and hexanes–acetone 5:2 with 1% $Et_3N$) to give **14** (2.3 g, 83%), mp 97–99°C; IR (KBr) $cm^{-1}$ 3421 (m), 1750 (s), 1735 (s), 1259 (s); $^1$H NMR ($CDCl_3$) $\delta$ 0.82 (m, 6H), 0.94 (d, $J$=7.2 Hz, 3H), 1.1–1.3 (m, 24H), 1.40, 1.42 (s, 6H, $CMe_2$), 1.5–1.8 (m, 5H), 1.90 (m, 3H), 2.1–2.4 (m, 3H), 2.30 (s, 1H, OH), 2.80, 2.83 (2s, 3H, NMe), 3.00 (m, 1H), 3.01, 3.37 (2s, 3H, 3″-$OCH_3$), 3.48 (s, 1H, OH), 3.5–3.7 (m, 3H), 3.95 (m, 1H), 4.1 (m, 1H), 4.52 (s, 1H, OH), 4.65 (m, 1.5H), 4.77 (m, 0.5H), 5.0–5.1 (m, 6H), 7.30 (m, 10H); $^{13}$C NMR ($CDCl_3$) $\delta$ 8.5, 10.3, 13.9, 15.4, 15.6, 16.0, 18.0, 18.8, 20.6, 21.0, 21.3, 23.7, 25.8, 27.7, 29.9, 32.5, 35.0, 35.2, 35.9, 36.3, 40.7, 44.4, 49.2, 49.7, 60.0, 64.5, 65.1, 65.3, 66.7 67.1, 67.5, 69.0, 69.2, 72.5, 73.2, 73.4, 74.7, 75.9, 77.6, 78.5, 79.9, 83.9, 84.1, 95.3, 99.3, 101.3, 126.5, 126.8, 127.2, 127.5, 127.7, 127.9, 128.0, 128.2, 135.0, 135.1, 136.2, 136.4, 154.2, 154.3, 155.8, 156.2, 175.0, 175.1; MS $m/z$ 1054 ($MH^+$); HRMS (FAB) calcd for $C_{55}H_{83}NO_{17}Na$ (M+Na): 1052.5559. Found: 1052.5579.

**4.1.6. (9*S*)-*N*-Demethyl–2′-*O*-3′-*N*-bis(carbobenzyloxy)-9,11-*O*-isopropylidene-12,4″-*O*-bis(trimethylsilyl)-9-dihydroerythromycin A (15).** To a solution of **14** (0.9 g, 0.9 mmol) and imidazole (0.36 g, 5.2 mmol) in DMF (5 mL) was added $(CH_3)_3SiCl$ (0.45 mL, 3.5 mmol). The resulting mixture was stirred at rt for 20 h. Then $Et_3N$ (1 mL) was added and the mixture was stirred for an additional 30 min. To this mixture were added EtOAc (20 mL) and sat. aq. $NaHCO_3$ (15 mL). The organic layer was separated, washed with brine (15 mL), dried over $MgSO_4$ and evaporated. The residue was chromatographed on a silica gel column (200 g, hexanes–acetone 10:1 with 3% $Et_3N$) to give **15** (0.57 g, 56%) and side products including mono-TMS-protected and tri-TMS-protected products (The side products could be re-used by completely deprotection of TMS groups to form material **14**), mp 116–117°C; IR (KBr) $cm^{-1}$ 3510 (w), 3421 (w), 1751 (s), 1736 (s), 1707 (s), 1253 (s); $^1$H NMR ($CDCl_3$) $\delta$ 0.13 (m, 18H, $SiMe_3$), 0.85 (m, 6H), 0.96 (d, $J$=7.2 Hz, 3H), 1.02 (s, 2H), 1.08–1.25 (m, 20H), 1.32 (s, 1H), 1.38, 1.48 (2s, 6H, $CMe_2$), 1.5–1.9 (m, 7H), 2.10–2.35 (m, 3H), 2.8 (m, 1H), 2.81, 2.85 (2s, 3H, –NMe), 3.01, 3.38 (2s, 3H, 3″-OMe), 3.15 (m, 1H), 3.43 (m, 2H), 3.45 (m, 1H), 3.95 (s, br, 1H, OH), 4.05–4.20 (m, 2H), 4.38 (s, br, 1H, OH), 4.76 (m, 1H), 4.94 (m, 2H), 5.07–5.15 (m, 5H), 7.20–7.35 (m, 10H); $^{13}$C NMR ($CDCl_3$) $\delta$ 0.9, 3.1, 8.9, 10.6, 15.0, 16.8, 18.4, 18.9, 19.0, 19.3, 21.4, 21.5, 22.2, 22.4, 24.4, 24.8, 30.2, 33.0, 35.0, 35.4, 35.5, 35.9, 36.4, 41.2, 44.4, 49.0, 49.4, 65.0, 66.9, 67.3, 69.2, 69.4, 70.0, 73.3, 73.4, 75.3, 78.3, 80.3, 80.5, 84.1, 84.3, 95.3, 98.7, 100.9, 127.5, 127.7, 127.8, 127.9, 129.0, 128.2, 128.3, 128.35, 128.4, 135.4, 135.5, 136.7, 136.8, 154.6, 156.3, 156.5, 175.8; MS $m/z$ 1196 (M+Na). Anal. calcd for $C_{61}H_{99}NO_{17}Si_2$: C, 62.37; H, 8.50; N, 1.19. Found: C, 62.30; H, 8.54; N, 1.29.

**4.1.7. (9*S*)-6-*O*-Methyl-*N*-demethyl–2′-*O*-3′-*N*-bis(carbobenzyloxy)-9,11-*O*-isopropylidene-12,4″-*O*-bis(trimethylsilyl)-9-dihydroerythromycin A (16).** To a solution of **15** (1.1 g, 0.9 mmol) in DMF (10 mL) were added $CH_3I$ (0.3 ml, 4.8 mmol) and NaH (0.12 g, 3.0 mmol). The mixture was stirred at rt for 12 h. The reaction was then quenched by adding $Et_3N$ (0.5 mL). To this mixture were added EtOAc (60 mL) and sat. aq. $NaHCO_3$ (40 mL). The organic layer was separated and was washed with brine (40 mL), dried over $MgSO_4$ and chromatographed on a silica gel column (200 g, hexanes–acetone 10:1 with 3% $Et_3N$) to give **16** (0.9 g, 84%), mp 115–116°C; IR (KBr) $cm^{-1}$ 1751 (s), 1735 (s), 1706 (s), 1251 (s); $^1$H NMR ($CDCl_3$) $\delta$ 0.10 (2s, 18H, 2×$SiMe_3$), 0.86 (m, 6H), 0.99 (m, 9H), 1.10 (m, 14H), 1.28 (m, 6H), 1.36 (s, 4H), 1.4–1.8 (m, 5H), 1.90 (s, 1H), 2.10 (m, 1H), 2.2–2.4 (m, 2H), 2.48 (m, 1H), 2.78, 2.82 (2s, 3H, NMe), 2.93, 3.39 (2s, 3H, 3″-OMe), 3.05 (t, $J$=7.2 Hz, 1H), 3.28 (s, 1H), 3.31, 3.33 (2s, 3H, 6-OMe), 3.68 (s, 1H), 3.80 (m, 1H), 4.11 (m, 3H), 4.60 (m, 1H), 4.86 (m, 2H), 4.90–5.10 (m, 5H), 7.20–7.35 (m, 10H); $^{13}$C NMR ($CDCl_3$) $\delta$ 0.9, 2.4, 9.5, 11.6, 17.0, 17.4, 19.7, 19.8, 20.0, 21.4, 22.4, 24.2, 27.6, 28.3, 31.4, 32.2, 35.1, 35.3, 35.6, 36.1, 36.6, 44.7, 48.7, 49.3, 64.9, 66.7, 66.9, 67.3, 69.1, 69.4, 73.1, 73.3, 75.0, 75.2, 79.6, 80.4, 80.8, 80.9, 94.8, 98.7, 100.5, 127.3, 127.7, 127.8, 128.0, 128.1, 128.2, 128.3, 128.35, 128.4, 135.4, 135.5, 135.56, 154.5, 154.6, 156.3, 156.6, 176.2; MS $m/z$ 1189 ($MH^+$), 1211 (M+Na). Anal. calcd for $C_{62}H_{101}NO_{17}Si_2$: C, 62.65; H, 8.56; N, 1.18. Found: C, 62.63; H, 8.63; N, 1.20.

**4.1.8. (9*S*)-6-*O*-Methyl-*N*-demethyl-2′-*O*-3′-*N*-bis(carbobenzyloxy)-9,11-*O*-isopropylidene-9-dihydroerythromycin A (17).** To a solution of **16** (0.9 g, 0.8 mmol) in THF (5 mL) was added a 1 M THF solution of *n*-$Bu_4NF$ (1.5 mL, 1.5 mmol). The mixture was stirred at rt for 6 h, and quenched by addition of EtOAc (20 mL) and sat. aq. $NaHCO_3$ (10 mL). The organic layer was separated, washed with brine (10 mL), dried over $MgSO_4$ and evaporated. The residue was purified on silica gel column (100 g, hexanes–acetone 5:1 with 1% $Et_3N$) to give **17** (0.52 g, 66%), mp 105–107°C; IR (KBr) $cm^{-1}$ 3552 (w), 1751 (s), 1734 (s),

1702 (s), 1255 (s); $^1$H NMR ($CDCl_3$) $\delta$ 0.86 (m, 6H), 0.99 (d, $J$=6.9 Hz, 3H), 1.10–1.25 (m, 22H), 1.32 (d, $J$=4.5 Hz, 3H), 1.40 (s, 3H), 1.4–1.7 (m, 5H), 1.7–2.0 (m, 3H), 2.1 (m, 2H), 2.2 (m, 1H), 2.35 (m, 1H), 2.60 (m, 1H), 2.71 (s, 1H), 2.78, 2.82 (2s, 3H, NMe), 2.91, 3.43 (2s, 3H, 3″-OMe), 3.03 (m, 1H), 3.31, 3.32 (2s, 3H, 6-OMe), 3.38 (s, 1H), 3.7–3.8 (m, 1H), 3.80 (m, 1H), 3.95 (m, 2H), 4.35 (m, 0.5H), 4.55 (m, 0.5H), 4.74–4.89 (m, 3H), 5.00–5.15 (m, 4H), 5.20 (m, 1H), 7.22–7.32 (m, 10H); $^{13}$C NMR ($CDCl_3$) $\delta$ 8.9, 11.0, 13.9, 14.0, 16.3, 16.6, 17.0, 17.1, 18.6, 20.5, 20.7, 21.6, 21.7, 22.6, 24.2, 25.2, 26.8, 28.2, 28.4, 29.0, 30.2, 31.5, 32.1, 33.5, 34.5, 34.6, 35.5, 36.0, 43.8, 45.1, 48.7, 49.5, 50.2, 65.1, 65.3, 67.0, 69.3, 69.5, 70.0, 72.9, 73.9, 75.0, 77.7, 78.0, 78.3, 79.3, 80.2, 94.3, 94.4, 99.2, 100.9, 127.4, 127.8, 128.0, 128.1, 128.2, 128.3, 128.35, 128.4, 128.5, 135.2, 135.4, 136.4, 136.7, 154.4, 154.5, 156.1, 156.6, 176.8; MS $m/z$ 1067 (M+Na), 1083 (M+K). Anal. calcd for $C_{56}H_{85}NO_{17}$: C, 64.41; H, 8.20; N, 1.34. Found: C, 64.07; H, 8.02; N, 1.33.

**4.1.9. (9*S*)-9,11-*O*-Isopropylidene-6-*O*-methyl-9-dihydroerythromycin A (18).** A mixture of **17** (0.49 g, 0.47 mmol), 10% Pd–C (55 mg) and $CH_3COOH$ (0.2 mL) in $CH_3OH/H_2O$ (5.6 mL/0.2 mL) was stirred under atmospheric pressure of hydrogen at rt for 20 h. The catalyst was removed by filtration and the filtered cake was washed with $CH_3OH$ (2 mL). The combined filtrate was diluted with water (10 mL). The pH of the resulting mixture was adjusted to about 10 with 1N NaOH. The precipitated solids were filtered and dried in vacuo to give a white solid intermediate (0.32 g, 88%).

A mixture of the intermediate (0.28 g, 0.36 mmol) prepared above, HCOOH (33 mg, 0.72 mmol) and 35% aqueous HCHO (0.19 mL, 2.30 mmol) in $CH_3OH$ (10 mL) was heated under reflux for 5 h. The mixture was evaporated in vacuo and was added into water (10 mL). The pH of the mixture was adjusted to 9.5–10.5 and then it was extracted with $CH_2Cl_2$ (3×20 mL). The organic layer was washed with brine (30 mL), dried over $MgSO_4$ and evaporated in vacuo. The residue was purified on a silica gel column (50 g, hexanes–acetone 1:1 with 1% $Et_3N$) to give **18** (0.27 g, 94%; two steps 83%), mp 113–115°C; IR (KBr) cm$^{-1}$ 3447 (m), 1733 (s), 1168 (s); $^1$H NMR ($CDCl_3$) $\delta$ 0.85 (t, $J$=7.2 Hz, 3H), 0.98 (d, $J$=6.9 Hz, 3H), 1.09 (m, 6H), 1.15 (s, 3H), 1.22 (m, 12H), 1.28 (s, 3H), 1.35, 1.40 (2s, 6H, $CMe_2$), 1.45–1.80 (m, 3H), 1.85 (m, 3H), 2.15 (m, 3H), 2.32 (s, 6H, $NMe_2$), 2.36 (s, 1H), 2.40 (s, 1H), 2.55 (m, 1H), 2.62 (s, 1H), 2.74 (m, 2H), 3.0 (m, 2H), 3.31 (s, 3H, 6-OMe), 3.33 (s, 3H, 3″-OMe), 3.35 (s, 2H), 3.50 (s, 1H), 3.55 (m, 1H), 3.84 (d, $J$=6.2 Hz, 1H), 4.00 (m, 2H), 4.57 (d, $J$=7.2 Hz, 1H), 4.90 (dd, $J$=10.2, 2.7 Hz, 1H), 5.15 (d, $J$=4.5 Hz, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ 9.5, 11.0, 11.5, 14.5, 16.3, 16.7, 17.9, 18.6, 20.8, 21.3, 21.7, 21.8, 24.4, 28.1, 28.4, 30.4, 30.9, 32.7, 33.3, 34.7, 40.3, 43.3, 45.3, 49.3, 50.2, 65.3, 65.7, 70.3, 70.9, 72.9, 74.0, 77.7, 77.8, 78.0, 78.3, 79.2, 80.5, 94.9, 100.9, 102.1, 176.6; MS $m/z$ 791 (MH$^+$); HRMS (FAB) calcd for $C_{41}H_{76}NO_{13}$ (MH$^+$): 790.5311. Found: 790.5317.

**4.1.10. (9*S*)-9,11-*O*-Isopropylidene-6-*O*-methyl-2′,4″-*O*-bis(benzoyl)-9-dihydroerythromycin A (19).** To a solution of **18** (0.20 g, 0.25 mmol) in dry EtOAc (5 mL) was added sequentially DMAP (0.12 g, 1 mmol), $Et_3N$ (0.14 mL, 1 mmol), and benzoic anhydride (0.23 g, 1 mmol) at 0°C under $N_2$. The reaction was warmed to rt and stirred for 20 h. The sat. aq. $NaHCO_3$ (10 mL) and EtOAc (20 mL) were added to quenched the reaction. The organic layer was separated, washed with brine (10 mL), dried over $Na_2SO_4$ and evaporated under reduced pressure. The residue was purified on a silica gel column (100 g, hexanes–acetone 5:1 with 1% $Et_3N$) to give **19** (0.19 g, 90%) and a mono-protected product (0.04 g), mp 125–126°C; IR (KBr) cm$^{-1}$ 1727 (s), 1268 (s), 711 (m); $^1$H NMR ($CDCl_3$) $\delta$ 0.66 (d, $J$=7.2 Hz, 3H), 0.80 (t, $J$=7.2 Hz, 3H), 0.93 (d, $J$=6.0 Hz, 6H), 1.03 (s, 3H), 1.04 (d, $J$=6.9 Hz, 3H), 1.11–1.17 (m, 14H), 1.30, 1.36 (2s, 6H, $CMe_2$), 1.4–1.9 (m, 7H), 2.05 (m, 1H), 2.29 (s, 6H, $NMe_2$), 2.29–2.51 (m, 2H), 2.70 (s, 1H), 3.0 (m, 1H), 3.27 (s, 3H, 6-OMe), 3.31 (s, 1H), 3.32 (s, 1H), 3.55 (s, 3H, 3″-OMe), 3.77 (d, $J$=5.4 Hz, 1H), 3.93 (s, 1H), 4.00 (m, 1H), 4.45 (m, 1H), 4.84 (dd, $J$=7.8, 2.7 Hz, 1H), 4.91 (d, $J$=9.9 Hz, 1H), 5.01 (d, $J$=7.5 Hz, 1H), 5.20–5.30 (m, 2H), 7.35–7.55 (m, 6H), 7.95–8.0 (m, 4H); $^{13}$C NMR ($CDCl_3$) $\delta$ 9.5, 10.8, 14.3, 16.2, 16.4, 17.3, 18.2, 20.4, 21.0, 21.3, 21.6, 24.2, 28.0, 30.1, 30.7, 31.7, 32.4, 33.2, 34.9, 40.8, 43.4, 45.1, 49.3, 50.2, 63.1, 63.5, 67.3, 69.5, 72.4, 73.1, 73.8, 77.6, 78.0, 79.1, 79.2, 80.2, 94.6, 99.6, 100.7, 128.0, 128.2, 129.5, 129.8, 130.8, 132.4, 133.2, 165.2, 166.2, 176.6; MS $m/z$ 998 (MH$^+$); HRMS (FAB) calcd for $C_{55}H_{84}NO_{15}$ (MH$^+$): 998.5835. Found: 998.5859.

**4.1.11. (9*S*)-9,11-*O*-Isopropylidene-6-*O*-methyl-2′,4″-*O*-bis(benzoyl)-12,21-anhydro-9-dihydroerythromycin A (2).** To a solution of **19** (0.10 g, 0.10 mmol) in dry EtOAc (5 mL) was added $Et_3N$ (0.06 mL, 0.40 mmol), then $SOCl_2$ (0.008 mL, 0.11 mmol) at 0°C under $N_2$. The reaction temperature was kept at 0°C for 1 h. Then the reaction was quenched by adding sat. aq. $NaHCO_3$ (5 mL) and the organic layer was separated. The aqueous layer was extracted with EtOAc (10 mL). The organic layer was washed with brine (10 mL). The solution was dried over $MgSO_4$ and concentrated in vacuo. The crude material was purified on a silica gel column (20 g, hexanes–EtOAc 3:2 with 1% $Et_3N$) to give **2** (86 mg, 88%), crystallization from acetone–*n*-hexane yielded colorless crystals, mp 129–130°C; IR (KBr) cm$^{-1}$ 1727 (s), 1268 (s), 711 (m); $^1$H NMR ($CDCl_3$) $\delta$ 0.72 (d, $J$=7.2 Hz, 3H), 0.81 (m, 6H), 0.95 (d, $J$=5.7 Hz, 3H), 0.99 (d, $J$=6.9 Hz, 3H), 1.11–1.27 (m, 14H), 1.35, 1.40 (2s, 6H, $CMe_2$), 1.4–1.8 (m, 6H), 1.90 (m, 1H), 2.12 (m, 2H), 2.32 (s, 6H, $NMe_2$), 2.50 (m, 2H), 3.00 (m, 1H), 3.29 (s, 3H, 6-OMe), 3.57 (s, 3H, 3″-OMe), 3.76 (d, $J$=5.7 Hz, 1H), 3.95 (m, 1H), 4.10 (m, 2H), 4.27 (s, 1H), 4.51 (m, 1H), 4.77 (s, 1H), 4.91 (d, $J$=9.9 Hz, 1H), 4.98 (d, $J$=7.5 Hz, 1H), 5.07 (s, 1H), 5.30 (m, 2H), 7.38–7.98 (m, 6H), 8.00 (m, 4H); $^{13}$C NMR ($CDCl_3$) $\delta$ 10.0, 10.6, 15.5, 18.5, 20.2, 21.0 21.3, 23.9, 27.5, 31.5, 31.7, 33.1, 35.1, 40.9, 44.1, 49.4, 63.3, 63.8, 67.6, 72.3, 73.1, 76.7, 79.0, 79.4, 79.5, 94.9, 100.1, 100.4, 113.1, 128.1, 128.3, 129.6, 129.9, 130.9, 132.4, 133.3, 143.4, 165.2, 166.2, 175.9; MS $m/z$ 980 (MH$^+$); HRMS (FAB) calcd for $C_{55}H_{82}NO_{14}$ (MH$^+$): 980.5730. Found: 980.5720. Anal. calcd for $C_{55}H_{81}NO_{14}$: C, 67.39; H, 8.33; N, 1.43. Found: C, 66.95, H; 8.35; N, 1.35.

**4.1.12. (9*S*)-9,11-*O*-Isopropylidene-2′,4″-*O*-bis(trimethylsilyl)-9-dihydroerythromycin A (11).** To a solution

of **4** (5.0 g, 6.5 mmol) in dry EtOAc (60 mL) was added imidazole (2.0 g, 29.4 mmol) and DMAP (15 mg, cat.). Then $(CH_3)_3SiCl$ (2.5 mL, 19.3 mmol) was added quickly. The mixture was stirred at rt for 2 h. Then $Et_3N$ (3 mL) was added and the mixture was stirred for an additional 30 min. To this mixture were added EtOAc (50 mL) and sat. aq. $NaHCO_3$ (40 mL). The organic layer was separated, washed with brine (40 mL), dried over $MgSO_4$ and evaporated in vacuo. The residue was chromatographed on a silica gel column (200 g, hexanes–acetone 10:1 with 3% $Et_3N$) to give **11** (5.3 g, 90%), mp 66–68°C; IR (KBr) $cm^{-1}$ 3430 (m), 1734 (s), 1166 (s); $^1H$ NMR ($CDCl_3$) $\delta$ 0.06 (s, 9H), 0.10 (s, 9H), 0.81 (t, $J$=7.2 Hz, 3H), 0.93 (d, $J$=7.2 Hz, 3H), 1.03 (d, $J$=7.2 Hz, 3H), 1.10–1.30 (m, 23H), 1.37, 1.40 (2s, 6H, $CMe_2$), 1.40–1.55 (m, 2H), 1.60–1.95 (m, 6H), 2.20 (br s, 6H, $NMe_2$), 2.32 (d, $J$=15 Hz, 1H), 2.59 (m, 2H), 2.75 (t, $J$=7.2 Hz, 1H), 3.15 (m, 2H), 3.27 (s, 3H, 3″-OMe), 3.45 (m, 1H), 3.50 (d, $J$=1.8 Hz, 1H), 3.55 (d, $J$=7.5 Hz, 1H), 3.68 (m, 1H), 4.18 (m, 1H), 4.25 (d, $J$=6.9 Hz, 1H), 4.46 (s, 1H, OH), 4.49 (d, $J$=7.2 Hz, 1H), 4.94 (m, 1H), 4.97 (s, 1H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 0.8, 1.0, 9.7, 10.6, 15.5, 16.2, 16.4, 18.7, 19.1, 21.0, 21.2, 21.7, 22.2, 24.1, 26.8, 27.7, 29.6, 29.9, 32.9, 34.6, 40.9, 41.2, 44.9, 49.5, 65.0, 67.5, 69.2, 73.2, 73.3, 73.6, 73.9, 76.2, 78.9, 80.2, 80.7, 82.2, 95.9, 101.6, 102.1, 176.2; MS $m/z$ 921 ($MH^+$). Anal. calcd for $C_{46}H_{89}NO_{13}Si_2$: C, 60.03; H, 9.75; N, 1.52. Found: C, 59.75; H, 9.79; N, 1.48.

**4.1.13. (9*S*)-9,11-*O*-Isopropylidene-2′,4″-*O*-bis(trimethylsilyl)-12,21-anhydro-9-dihydroerythromycin A (12).** To a solution of **11** (3.7 g, 4.0 mmol) in dry EtOAc (40 mL) at 0°C was added $Et_3N$ (2.3 mL, 16 mmol). Then $SOCl_2$ (0.32 mL, 4.4 mmol) was added quickly via syringe. The mixture was stirred at 0°C for 1.5 h. To the reaction mixture was added sat. aq. $NaHCO_3$ (40 mL) and the organic layer was separated. The aqueous layer was extracted with EtOAc (2×20 mL). The organic extracts were combined and washed with brine (30 mL), dried over $MgSO_4$ and concentrated in vacuo. The crude material was purified on a silica gel column (200 g, hexanes–acetone 10:1 with 3% $Et_3N$) to give **12** (3.30 g, 91.5%), mp 64–66°C; IR (KBr) $cm^{-1}$ 3503 (w), 1734 (s), 1249 (s); $^1H$ NMR ($CDCl_3$) $\delta$ 0.07 (s, 9H), 0.09 (s, 9H), 0.87 (m, 6H), 1.06 (m, 6H), 1.13 (s, 3H), 1.15–1.25 (m, 15H), 1.35, 1.39 (2s, 6H, $CMe_2$), 1.4–2.0 (6H), 2.06 (d, $J$=12.9 Hz, 1H), 2.21 (br s, 6H, $NMe_2$), 2.29 (s, 1H), 2.35 (s, 1H), 2.57 (m, 2H), 3.11 (d, $J$=9.3 Hz, 1H), 3.26 (m, 1H), 3.29 (s, 3H, 3″-OMe), 3.32 (m, 1H), 3.53 (d, $J$=6.3 Hz, 1H), 3.74 (m, 1H), 4.19 (m, 1H), 4.20 (s, 1H, OH), 4.31 (d, $J$=8.7 Hz, 1H), 4.58 (d, $J$=6.3 Hz, 1H), 4.60 (d, $J$=7.2 Hz, 1H), 5.0 (s, 1H), 5.24 (s, 1H), 5.48 (t, $J$=6.9 Hz, 1H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 0.5, 0.9, 10.2, 10.6, 12.8, 15.3, 17.8, 18.9, 21.1, 22.3, 22.4, 23.9, 27.3, 29.0, 29.2, 33.0, 33.5, 35.2, 38.2, 40.9, 44.0, 44.4, 49.1, 65.2, 65.3, 67.8, 68.4, 72.7, 73.7, 74.2, 76.1, 78.6, 79.5, 80.5, 84.4, 95.2, 100.6, 101.9, 112.6, 144.3, 176.1; MS $m/z$ 903 ($MH^+$), 925 (M+Na). Anal. calcd for $C_{46}H_{87}NO_{12}Si_2$: C, 61.23; H, 9.72; N, 1.55. Found: C, 61.83; H, 9.93; N, 1.50.

**4.1.14. (9*S*)-*N*-Demethyl-*N*-carbobenzyloxy-9,11-*O*-isopropylidene-2′,4″-*O*-bis(benzoyl)-12,21-anhydro-9-dihydroerythromycin A (20).** Compound **6** (4.0 g, 4.1 mmol) was dissolved in dry 1,4-dioxane (10 mL) containing $NaHCO_3$ (4.8 g, 57.1 mmol). The mixture was heated to about 60°C. Benzyl chloroformate (5.6 mL, 40 mmol) was added to the reaction mixture dropwise. After the completion of the addition, the temperature was raised to 65°C and the mixture was stirred for 3 h. The reaction mixture was then allowed to cool to rt, and diluted with $CH_2Cl_2$ (50 mL). Then the mixture was filtered, and the filtered cake was washed with $CH_2Cl_2$. To the filtrate sat. aq. $NaHCO_3$ (40 mL) was added. The organic layer was separated, washed with brine (40 mL), dried over $Na_2SO_4$ and concentrated in vacuo. The thick oil was chromatographed over silica gel twice (150 g, hexanes–EtOAc 5:2 and 1% $Et_3N$) to give the product **20** (3.9 g, 87%) as white foam, mp 132–134 °C; IR (KBr) $cm^{-1}$ 3528 (w), 1727 (s), 1706 (m), 1266 (s), 712 (m); $^1H$ NMR ($CDCl_3$) $\delta$ 0.63 (m, 3H), 0.85 (m, 6H), 1.03 (m, 8H), 1.11–1.23 (m, 12H), 1.28, 1.34 (2s, 6H, $CMe_2$), 1.50–1.80 (m, 6H), 1.90 (s, 1H), 2.05 (m, 1H), 2.3 (m, 2H), 2.48 (m, 2H), 2.81, 2.86 (2s, 3H, NMe), 3.14, 3.62 (2s, 3H, 3″-OMe), 3.30 (d, $J$=3.9 Hz, 1H), 3.5 (m, 1H), 4.0 (m, 1H), 4.23 (m, 2H), 4.45 (m, 1H), 4.65 (m, 1H), 4.9 (m, 2H), 5.0 (d, 2H), 5.1 (m, 1H), 5.2 (m, 2H), 5.45 (m, 1H), 7.08–7.26 (m, 5H), 7.38 (m, 4H), 7.52 (m, 2H), 7.98 (m, 4H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 9.2, 10.6, 11.9, 14.0, 15.2, 17.4, 1.9, 20.4, 20.6, 20.8, 21.0, 21.2, 21.4, 23.7, 28.0, 28.2, 29.2, 32.7, 33.3, 34.7, 34.9, 35.9, 36.3, 37.4, 42.8, 44.1, 48.7, 49.3, 60.1, 63.6, 66.8, 67.6, 67.7, 67.8, 68.0, 71.0, 73.1, 73.9, 76.1, 78.7, 79.1, 85.3, 85.4, 94.7, 94.9, 99.0, 100.5, 112.7, 127.1, 127.6, 128.1, 128.3, 128.4, 129.2, 129.3, 129.5, 129.7, 129.8, 129.9, 132.8, 132.9, 133.0, 133.2, 136.2, 136.4, 144.0, 155.9, 156.6, 165.0, 165.3, 165.9, 166.1, 170.8, 175.8; MS $m/z$ 1108 (M+Na). Anal. calcd for $C_{61}H_{83}NO_{16}$: C, 67.44; H, 7.70; N, 1.29. Found: C, 67.07; H, 7.74; N, 1.39.

**4.1.15. (9*S*)-*N*-Demethyl-*N*-carbobenzyloxy-6-*O*-methyl-9,11-*O*-isopropylidene-2′,4″-*O*-bis(benzoyl)-12,21-anhydro-9-dihydroerythromycin A (21) and (9*S*)-2-methyl-*N*-demethyl-*N*-carbobenzyloxy-6-*O*-methyl-9,11-*O*-isopropylidene-2′,4″-*O*-bis(benzoyl)-12,21-anhydro-9-dihydroerythromycin A (22).** To a solution of **20** (2.0 g, 1.84 mmol) in DMF (8 mL) were added $CH_3I$ (0.6 ml, 9.6 mmol) and NaH (0.22 g, 5.5 mmol). The mixture was stirred at rt for 20 h, and was then quenched by $Et_3N$ (1 mL). To this mixture were added EtOAc (40 mL) and sat. aq. $NaHCO_3$ (30 mL). The organic layer was separated and was washed with brine (30 mL), dried over $MgSO_4$ and chromatographed on silica gel column (200 g, hexanes–EtOAc 5:2 with 0.5% $Et_3N$) to give **21** (1.01 g, 49%) and **22** (1.0 g, 48%).

The data of **21**, mp 127–129°C; IR (KBr) $cm^{-1}$ 3528 (w), 1726 (s), 1706 (s), 1266 (s), 712 (m); $^1H$ NMR ($CDCl_3$) $\delta$ 0.68 (m, 3H), 0.86 (m, 3H), 0.9–1.05 (m, 6H), 1.05–1.30 (m, 18H), 1.36 (s, 5H), 1.4–1.8 (m, 7H), 1.90 (m, 1H), 2.1–2.6 (m, 3H), 2.81, 2.86 (2s, 3H, NMe), 3.14, 3.66 (2s, 3H, 3″-OMe), 3.29, 3.31 (2s, 3H, 6-OMe), 3.57 (s, 1H), 3.8 (m, 1H), 4.2 (m, 1H), 4.5 (m, 2H), 4.7 (m, 1H), 4.8–4.95 (m, 4H), 5.0–5.2 (m, 2H), 5.30 (m, 2H), 5.5 (m, 1H), 7.0–7.3 (m, 5H), 7.40 (m, 4H), 7.53 (m, 2H), 8.0 (m, 4H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 9.8, 10.2, 10.7, 14.2, 15.5, 18.0, 18.3, 18.5, 20.1, 20.6, 20.9, 21.3, 21.5, 23.9, 27.7, 28.3, 31.5, 33.1, 34.8, 35.1, 35.8, 43.8, 44.2, 48.8, 49.5, 63.3, 63.7, 67.1, 67.2, 67.5, 69.2, 71.0, 71.3, 73.0, 78.9, 79.1, 79.4, 94.8, 99.5,

100.6, 113.0, 127.1, 127.1, 127.3, 127.6, 127.6, 128.0, 128.2, 128.3, 128.4, 129.4, 129.6, 130.1, 132.7, 132.8, 133.2, 136.4, 143.5, 156.0, 156.7, 165.3, 166.3, 175.8; MS *m/z* 1122 (M+Na); HRMS (FAB) calcd for $C_{62}H_{85}NO_{16}Na$ (M+Na): 1122.5761. Found: 1122.5798.

The data of **22**, mp 135–137°C; IR (KBr) $cm^{-1}$ 1724 (s), 1264 (s), 711 (m); $^1H$ NMR ($CDCl_3$) $\delta$ 0.70–0.90 (m, 6H), 0.90–1.05 (m, 7H), 1.16 (m, 14H), 1.26 (s, 3H). 1.27 (s, 3H), 1.38 (s, 6H, $CMe_2$), 1.4–1.8 (m, 5H), 2.15 (m, 1H), 2.30 (m, 2H), 2.45 (m, 1H), 2.80, 2.85 (2s, 3H, NMe), 3.14, 3.65 (2s, 3H, 3″-OMe), 3.33, 3.35 (2s, 3H, 6-OMe), 3.40 (s, 1H), 3.65–3.85 (m, 1H), 4.25 (m, 1H), 4.3–4.6 (m, 3H), 4.8–5.0 (m, 4H), 5.0–5.2 (m, 2H), 5.34 (m, 2H), 5.55 (m, 1H), 7.0–7.3 (m, 5H), 7.41 (m, 4H), 7.54 (m, 2H), 8.00 (m, 4H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 10.1, 11.0, 15.7, 18.3, 18.9, 19.5, 20.6, 20.9, 21.2, 21.4, 23.8, 26.0, 27.7, 28.0, 28.2, 31.3, 32.8, 34.4, 35.1, 35.4, 35.7, 36.1, 37.0, 46.1, 48.7, 48.8, 49.5, 63.5, 63.6, 66.7, 66.8, 67.2, 67.3, 67.5, 68.9, 70.9, 71.3, 72.9, 79.0, 79.3, 79.5, 80.2, 93.7, 99.7, 100.3, 113.1, 127.1, 127.6, 128.1, 128.3, 129.4, 129.5, 129.6, 129.8, 129.9, 130.0, 132.7, 132.8, 133.2, 133.3, 136.4, 142.1, 156.0, 156.7, 165.1, 166.3, 178.2; MS *m/z* 1137 (M+Na); HRMS (FAB) calcd for $C_{63}H_{88}NO_{16}(MH^+)$: 1136.5917. Found: 1136.5941. Anal. calcd for $C_{63}H_{87}NO_{16}$: C, 67.90; H, 7.87; N, 1.26. Found: C, 66.61; H, 7.86; N, 1.21.

**4.1.16. (9*S*)-*N*-Demethyl-6-*O*-methyl-9,11-*O*-isopropylidene-2′,4″-*O*-bis(benzoyl)-12,21-anhydro-9-dihydroerythromycin A (23).** A suspension of **21** (1.30 g, 1.18 mmol), triethylsilane (0.75 mL, 4.72 mmol), $Et_3N$ (0.12 mL, 0.83 mmol), and $PdCl_2$ (63 mg, 0.35 mmol) in $CH_2Cl_2$ (10 mL) was refluxed for 21 h. The reaction mixture was cooled to rt, then EtOAc (40 mL) was added. The mixture was filtered. To the filtrate was added sat. aq. $NH_4Cl$ solution (30 mL). The organic layer was separated and washed with brine (30 mL), dried over $MgSO_4$. After concentration, the residue was purified on a silica gel column (100 g, hexanes–acetone 5:2 with 1% $Et_3N$) to give **23** (0.53 g, 45%, reacted yield 91%), mp 98–100°C; IR (KBr) $cm^{-1}$ 3505 (w), 1722 (s), 1263 (s), 712 (m); $^1H$ NMR ($CDCl_3$) $\delta$ 0.73 (m, 3H), 0.75–0.9 (m, 6H), 0.9–1.05 (m, 9H), 1.05–1.22 (m, 13H), 1.28 (s, 3H), 1.35 (s, 3H), 1.42 (s, 3H), 1.5–1.8 (m, 5H), 1.8–2.0 (m, 3H), 2.36 (s, 1H), 2.41 (s, 3H, NMe), 3.0–3.1 (m, 1H), 3.30 (s, 3H, 6-OMe), 3.55 (s, 3H, 3″-OMe), 3.7–3.8 (m, 1H), 4.0–4.1 (m, 1H), 4.26 (s, 1H), 4.40–4.77 (m, 2H), 4.85–5.0 (m, 2H), 5.0–5.2 (m, 1H), 5.2–5.4 (m, 1.5H), 5.55 (m, 0.5H), 7.4–7.5 (m, 4H), 7.5–7.6 (m, 2H), 8.0–8.1 (m, 4H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 10.1, 10.7, 11.6, 15.5, 18.5, 20.2, 20.5, 20.6, 21.0, 21.3, 23.7, 23.9, 26.9, 27.6, 28.4, 31.5, 32.3, 32.6, 33.2, 35.1, 36.6, 37.9, 38.0, 39.8, 44.2, 46.2, 49.5, 63.4, 63.7, 67.6, 68.5, 68.7, 69.4, 73.1, 74.0, 74.9, 78.8, 79.1, 79.3, 79.6, 94.9, 99.6, 100.4, 113.2, 128.2, 128.3, 129.6, 129.9, 130.3, 132.8, 133.0, 133.3, 142.9, 143.4, 165.5, 166.2, 175.9; MS *m/z* 966 ($MH^+$); HRMS (FAB) calcd for $C_{54}H_{80}NO_{14}$ ($MH^+$): 966.5573. Found: 966.5591.

**4.1.17. Preparation of 2 from 23.** To a solution of **23** (0.53 g, 0.54 mmol) in $CH_3OH$ (10 mL) was added HCHO (0.32 mL, 3.85 mmol) and HCOOH (38 mg, 0.83 mmol). The mixture was refluxed for 6 h. The solvent was evaporated to dryness in vacuo. The residue was added EtOAc (25 mL) and sat. aq. $NaHCO_3$ (25 mL). The organic layer was separated and washed with brine (20 mL). Then the solution was dried over $Na_2SO_4$, concentrated in vacuo. The crude product was purified on a silica gel column (100 g, hexanes–acetone 5:2 with 1% $Et_3N$) to give **2** (0.36 g, 68%): the spectroscopic data were identical to an authentic sample prepared previously.

**4.1.18. (9*S*)-2-Methyl-*N*-demethyl-6-*O*-methyl-9,11-*O*-isopropylidene-2′,4″-*O*-bis(benzoyl)-12,21-anhydro-9-dihydroerythromycin A (24).** To a solution of **22** (0.96 g, 0.86 mmol) in dry $CH_2Cl_2$ (10 mL) was added triethylsilane (0.56 mL, 3.48 mmol), $Et_3N$ (0.085 mL, 0.61 mmol), $PdCl_2$ (46 mg, 0.26 mmol). The mixture was stirred and refluxed for 7 h under $N_2$. After the mixture was cooled to rt, EtOAc (40 mL) was added. The mixture was filtered. A solution of sat. aq. $NH_4Cl$ (30 mL) was added to the filtrate. The organic layer was separated and washed with brine (30 mL), dried over $MgSO_4$, concentrated in vacuo. The crude product was purified on a silica gel column (150 g, hexanes–acetone 5:2 with 1% $Et_3N$) to give **24** (0.39 g, 95% based on recovered starting material (0.50 g)), mp 130–132°C; IR (KBr) $cm^{-1}$ 3520 (w), 1724 (s), 1266 (s), 711 (m); $^1H$ NMR ($CDCl_3$) $\delta$ 0.7–0.9 (m, 9H), 0.9–1.1 (m, 9H), 1.1–1.3 (m, 18H), 1.37 (s, 3H), 1.4–1.6 (m, 2H), 1.6–1.75 (m, 3H), 1.85–2.05 (m, 3H), 2.1–2.2 (m, 1H), 2.39 (s, 3H, NMe), 2.4–2.5 (m, 1H), 3.0–3.1 (m, 1H), 3.35 (s, 3H, 6-OMe), 3.55 (s, 3H, 3″-OMe), 3.79 (d, *J*=6.3 Hz, 1H), 4.0–4.15 (m, 1H), 4.31 (s, 1H), 4.46 (s, 1H), 4.47–4.56 (m, 1H), 4.58 (d, *J*=4.5 Hz, 1H), 4.91 (d, *J*=9.6 Hz, 1H), 4.96 (s, 1H), 5.02 (d, *J*=7.5 Hz, 1H), 5.28 (d, *J*=7.8 Hz, 1H), 5.34 (s, 1H), 5.55 (m, 1H), 7.41–7.46 (m, 4H), 7.55–7.58 (m, 2H), 7.98–8.04 (m, 4H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 10.2, 11.3, 15.7, 18.1, 18.9, 19.6, 20.7, 20.9, 21.2, 23.8, 26.0, 27.6, 28.0, 31.3, 32.1, 32.9, 34.5, 35.7, 37.0, 37.7, 46.3, 48.9, 49.5, 63.5, 69.0, 71.3, 73.0, 74.6, 76.7, 77.8, 79.0, 79.6, 79.9, 80.3, 93.8, 99.8, 100.4, 113.1, 128.2, 128.3, 129.6, 129.6, 129.8, 130.2, 132.8, 133.3, 142.2, 165.3, 166.2, 178.2; MS *m/z* 980 ($MH^+$); HRMS (FAB) calcd for $C_{55}H_{82}NO_{14}$ ($MH^+$): 980.5730. Found: 980.5747.

**4.1.19. (9*S*)-2-Methyl-6-*O*-methyl-9,11-*O*-isopropylidene-2′,4″-*O*-bis(benzoyl)-12,21-anhydro-9-dihydroerythromycin A (10).** To a solution of **24** (0.39 g, 0.40 mmol) in $CH_3OH$ (10 mL) was added HCHO (0.23 mL, 2.80 mmol) and HCOOH (27 mg, 0.60 mmol). The mixture was refluxed for 1 h. The solvent was evaporated to dryness in vacuo. The residue was added EtOAc (30 mL) and sat. aq. $NaHCO_3$ (20 mL). The organic layer was separated and washed with brine (20 mL). Then the solution was dried over $Na_2SO_4$, and concentrated in vacuo. The crude product was purified on a silica gel column (50 g, hexanes–acetone 5:2 with 1% $Et_3N$) to give **10** (0.32 g, 81%), crystallization from acetone–*n*-hexane yielded colorless crystals, mp 245–248°C; IR (KBr) $cm^{-1}$ 1725 (s), 1267 (s), 711 (m); $^1H$ NMR ($CDCl_3$) $\delta$ 0.75–0.90 (m, 9H), 0.90–1.05 (m, 8H), 1.1–1.2 (m, 13H), 1.27 (s, 3H), 1.38 (s, 3H), 1.41 (s, 3H), 1.45–1.6 (m, 2H), 1.6–1.8 (m, 2H), 1.9–2.1 (m, 1H), 2.1–2.2 (m, 1H), 2.32 (s, 6H, $NMe_2$), 2.4–2.55 (m, 2H), 2.95–3.05 (m, 1H), 3.35 (s, 3H, 6-OMe), 3.38–3.40 (m, 1H), 3.58 (s, 3H, 3″-OMe), 3.79 (d, *J*=6.6 Hz, 1H), 3.95–4.05 (m, 1H), 4.31 (s, 1H), 4.47 (s, 1H), 4.47–4.56 (m, 1H), 4.58 (d, *J*=4.5 Hz, 1H), 4.92 (d,

$J$=9.6 Hz, 1H), 4.96 (s, 1H), 5.01 (d, $J$=7.5 Hz, 1H), 5.32–5.36 (m, 2H), 5.55 (m, 1H), 7.39–7.45 (m, 4H), 7.47–7.58 (m, 2H), 7.99–8.02 (m, 4H); $^{13}$C NMR ($CDCl_3$) $\delta$ 10.1, 11.2, 15.7, 18.0, 18.9, 19.6, 20.6, 21.0, 21.2, 23.8, 26.0, 27.6, 28.0, 31.3, 31.5, 32.8, 34.5, 35.4, 37.0, 40.8, 46.3, 48.8, 49.5, 63.5, 63.9, 67.6, 68.9, 72.3, 73.0, 76.7, 77.8, 78.9, 79.0, 79.6, 80.3, 93.7, 100.0, 100.3, 113.1, 128.1, 128.3, 129.5, 129.8, 130.8, 132.4, 133.2, 142.2, 165.1, 166.1, 178.2; MS $m/z$ 994 ($MH^+$); HRMS (FAB) calcd for $C_{56}H_{84}NO_{14}(MH^+)$: 994.5886. Found: 994.5917. Anal. calcd for $C_{56}H_{83}NO_{14}$:C, 67.65; H, 8.41; N, 1.41. Found: C, 67.51; H, 8.48; N, 1.32.

**4.1.20. Preparation of compound 2 and 10 via (9*S*)-3′-*N*-trimethyl-9,11-*O*-isopropylidene-6-*O*-methyl-2′,4″-*O*-bis(benzoyl)-12,21-anhydro-9-dihydroerythromycin A quaternary ammonium salt.** To a solution of **6** (2.0 g, 3.1 mmol) in dry DMF (10 mL) cooled in an ice-bath was added $CH_3I$ (0.65 mL, 10.50 mmol). Then NaH (0.25 g, 6.30 mmol) was added. The ice-bath was removed. Then the mixture was stirred at rt for 20 h. The reaction was quenched by $Et_3N$ (1.5 mL). After stirring for another 1 h, the mixture was poured into $H_2O$ (100 mL). White precipitate was formed. The mixture was filtered by sintered glass filter, washed with water. The solid was re-dissolved in $CH_2Cl_2$ (30 mL), and washed with brine (20 mL). The solution was dried over $Na_2SO_4$ and concentrated in vacuo. A light yellowish solid (2.1 g, 61%) was obtained as a mixture of quaternary ammonium iodide salts (**7**, **8**, **9**).

To a solution of the quaternary ammonium iodide salt (2.1 g, 1.9 mmol) prepared above in $CH_3OH$ (100 mL) was added freshly prepared AgCl[13] (2.0 g, 13.9 mmol) (prepared by reacting $AgNO_3$ with NaCl solution, filtered, washed with $H_2O$, dried in vacuo under dark). The mixture was stirred at rt for 5 h. The AgCl–AgI precipitate was filtered, and the methanolic filtrate was evaporated to dryness under vacuo. The iodide anion of the quaternary ammonium salt was exchanged for chloride. The quaternary ammonium iodide salts (**7**, **8**, **9**) were transfer into their corresponding chloride salts (**7′**, **8′**, **9′**) (1.85 g, 95%).

To a solution of 4-pyridinethiol (0.54 g, 4.40 mmol) in dry acetonitrile (100 mL) at 0°C was added NaH (0.18 g, 4.40 mmol). Then the mixture was stirred at rt for 1 h. To this mixture a solution of quaternary ammonium chloride salts (**7′**, **8′**, **9′**) (1.5 g, 1.5 mmol) in dry acetonitrile (100 mL) was added via syringe. The mixture was then heated to reflux under $N_2$ for 36 h. The solvent was evaporated to dryness. The residue was re-dissolved in EtOAc (100 mL), washed with sat. aq. $NaHCO_3$ (50 mL), and brine (50 mL), dried over $MgSO_4$ and evaporated. The residue was chromatographed on a silica gel column (200 g, hexanes–ethyl acetate 5:2 with 1% $Et_3N$) to give **2** (0.4 g, 28%) and **10** (0.38 g, 26%): the spectroscopic data of **2** and **10** were identical to those of authentic samples prepared previously.

### 4.2. X-Ray single crystal structure analyses of compound 2

The structure of **2** was determined by X-ray crystallography with a crystal that measured 0.72×0.45×0.40 mm. Diffraction measurements were made on a Bruker SMART CCD diffractometer with graphite monochromated Mo Kα radiation. Preliminary indications of the unit cell based on randomly selected reflections revealed orthorhombic symmetry with the following lattice parameters: $a$=15.9378(10) Å, $b$=17.3582(11) Å, $c$=20.2866(12) Å, with $\alpha=\beta=\gamma=90.0°$. The space group was $P2_12_12_1$, $Z$=4 with one molecule of composition $C_{55}H_{80}NO_{14}$. The calculated density was 1.159 g/cm$^3$. There were 38332 reflections collected with $\theta$ ranging from 1.54 to 28.12°, of those reflections 13606 with $I>2\sigma(I)$ were observed. The structure was solved by SHELXS-97. The crystal structure of **2** has been deposited at the Cambridge Crystallography Data Centre (CCDC 196617).

### 4.3. X-Ray single crystal structure analyses of compound 10

The structure of **10** was determined by X-ray crystallography with a crystal that measured 0.75×0.34×0.24 mm. Diffraction measurements were made on a Bruker SMART CCD diffractometer with graphite monochromated Mo Kα radiation. Preliminary indications of the unit cell based on randomly selected reflections revealed orthorhombic symmetry with the following lattice parameters: $a$=11.0189(6) Å, $b$=20.8812(11) Å, $c$=24.7103(14) Å, with $\alpha=\beta=\gamma=90.0°$. The space group was $P2_12_12_1$, $Z$=4 with one molecule of composition $C_{56}H_{82}NO_{14}$. The calculated density was 1.160 g/cm$^3$. There were 38944 reflections collected with $\theta$ ranging from 1.28 to 28.07°, of those reflections 13791 with $I>2\sigma(I)$ were observed. The structure was solved by SHELXS-97. The crystal structure of **10** has been deposited at the Cambridge Crystallography Data Centre (CCDC 196618).

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