Synthesis of 9-Deoxo-4″-deoxy-6,9-epoxyerythromycin Derivatives: Novel and Acid-Stable Motilides

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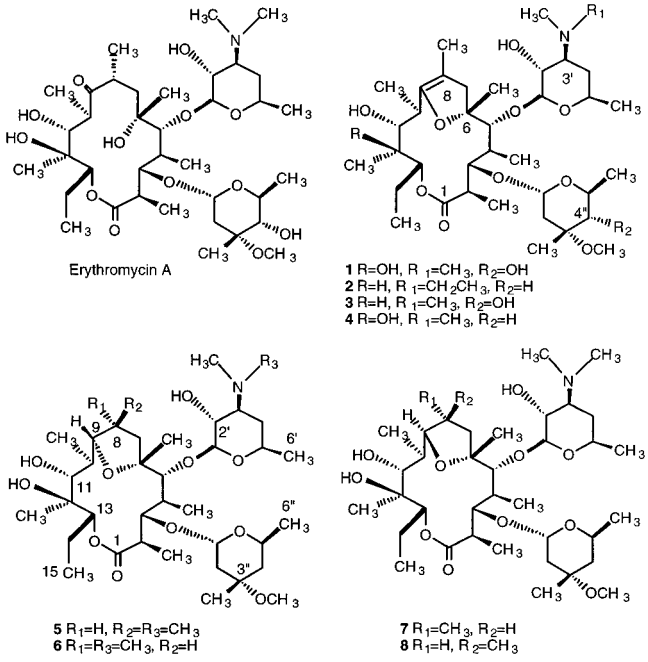
In our quest toward the discovery of highly potent and acid-stable motilides, novel 4″-deoxy derivatives of 9-deoxo-6,9-epoxyerythromycin were designed, synthesized, and evaluated for their gastrointestinal prokinetic activities. These compounds, in their 9*R* configuration, were more potent than their 6,9-enol ether homologues in inducing well-coordinated smooth muscle contractions in an in vitro rabbit duodenal assay: e.g., (9*R*),(8*S*)-9-deoxo-4″-deoxy-3′-*N*-desmethyl-3′-*N*-ethyl-6,9-epoxyerythromycin A (**10**) and (9*R*),(8*S*)-9-deoxo-4″-deoxy-3′-*N*-desmethyl-3′-*N*-ethanol-6,9-epoxyerythromycin A (**15**) had a pED_{50} of 8.54 and 8.11 compared to a pED_{50} of 7.22 for compound **2** (ABT-229). Reduction of the 6,9-enol ether, which was aimed at improving the acid stability, afforded the most stable motilides to date with $t_{1/2}$ of 5.5 h for **10** and **15**. Compounds **10** and **15** bind specifically to rabbit antral smooth muscle motilin receptors with pIC_{50} values of 8.52 and 8.70.

Introduction

Macrolides such as **1**, derived from erythromycin, lack antibacterial activity but produce well-coordinated contractions of the gastrointestinal tract.[1,2] These compounds mimic the action of the endogenous prokinetic peptide hormone motilin[3−6] and thus are designated motilides.[7] For example, compound **2** (ABT-229), an orally efficacious congener of **1**, is currently in phase IIB clinical trials[8−11] for the treatment of diabetic gastroparesis and gastroesophageal reflux disease. Structure−activity studies of this class of compounds show that the enol ether moiety is of considerable importance for potency,[2,7,12,13] since macrolides, such as clarithromycin and roxithromycin, in which the formation of an enol ether is impossible due to structural features, showed reduced smooth muscle-stimulating activity.[14] However this also leads to compounds with low acid stability and, consequently, reduced oral efficacy. The conformation of the macrolactone[15] at C-9 to C-12 is also critical for prokinetic potency (Chart 1). For example, the conformation of erythromycin B-6,9-hemiketal (**3**), as determined by NMR, is superimposable on the X-ray crystal structure of **1** (Chart 1). On the other hand, conformation of the 12-epi congener of **3** differs considerably in the same region as previously shown.[15] It is noteworthy that compound **3** has demonstrated good gastrointestinal motility activities (pED_{50} of 6.88), while its 12-epi congener is weaker (pED_{50} of 5.60).[15] Furthermore, deoxygenation of the neutral sugar (cladinose) at the 4″-position has also been shown[12,16] to increase prokinetic potency.

The aim of the current study was to design and synthesize highly potent motilides which would also

Chart 1



demonstrate good acid stability. The direct approach to greater acid stability was to reduce the 8,9-double bond and to provide 9-deoxo-6,9-epoxy (hereinafter simply called 6,9-epoxy) derivatives, with 4″-deoxy congeners maintaining pharmacological activity. Reduction of this 8,9-double bond would lead to four possible 6,9-epoxy diastereomers: **5** and **6** with 9*R* configuration as well as **7** and **8** with 9*S* configuration. In this paper, we present modeling studies that led to the prediction of relative prokinetic potencies of the four possible diastereomers, based on their energy-minimized conformation. We also describe the preparation and evaluation of three of the four possible diastereo-

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‡ It is with regret that we announce the loss of our friend and colleague, Mr. Albert Petersen.

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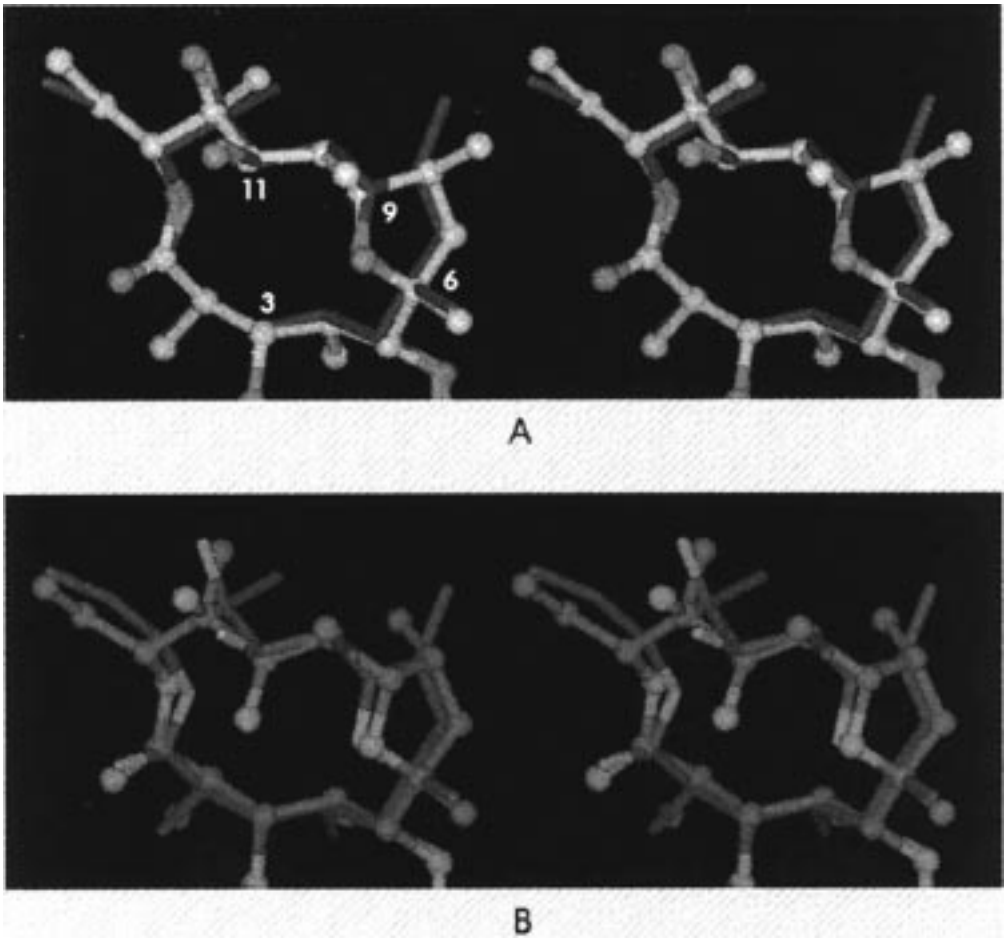


Figure 1. Comparison between compounds **5** or **7** and the corresponding 8,9-unsaturated compound. The macrolide ring of compound **5** (ball-and-stick model in yellow) is almost identical to that of the unsaturated compound (stick model in green) (panel A), while the positions of the C-11 and C-12 hydroxy groups of compound **7** (ball-and-stick model in cyan) are significantly different from those of the unsaturated compound (stick model in green) (panel B). All the oxygen atoms are in red. Cladinose and desosamine rings are not shown for clarity.

mers and report the synthesis and evaluation of new highly potent and acid-stable motilides.

Molecular Modeling

We have shown in a previous study that the X-ray crystal structures of **1** and **4** are essentially identical to the modeled minimum-energy conformation obtained by molecular mechanics method.[17] The 8,9-double bond in **4** was saturated to give the starting compounds **5**−**8**, which were then modeled from the X-ray structure of **4**. The final structures were obtained from the energy minimization by Insight II (Version 95.0) using DISCOVER CVFF force field and atomic charges. Conjugate gradients algorithm was used for the minimization with the maximum derivative set to be 0.001 for the convergence criterion. A comparison of the modeled structures shows that the conformations of all four compounds are in general very similar to that of **4**. However a close examination of these structures revealed that the positions of the C-12 and especially C-11 hydroxy groups of **7** and **8** are quite different from those of **5** and **6**. Figure 1 shows a comparison between **5** and **7** superimposed over enol ether **4**. In addition, the conformation of compound **8** is significantly different in the area around the C-8 methyl group. The distance between the C-8 methyl of compound **6** and the C-8 methyl of **4** is somewhat closer than the corresponding distance between compounds **5** and **4**. The activities of **5** and **6** are similar but very different from that of **7**. Thus, the major difference between the ability of compounds **5**−**8** to mimic **4** is at positions C-11 and C-12, and the position of the C-8 methyl group is much less important.

In summary, the conformations of compounds **5** and **6** are similar to the conformation of 8,9-unsaturated compound **4** followed by compound **8** and then **7**. The observed contractile activity in vitro of these compounds (Table 2) agreed with the conformational similarity and indicated that the positions of the C-11 and C-12 hydroxy, especially the C-11 hydroxy group, played the most important role for the difference in the contractile activity.

Chemistry

Preparation of 4″-deoxyerythromycin A 6,9-hemiketal (**4**) has been previously reported.[12] To access the 8*S* and 8*R* congeners, 4″-deoxyerythromycin A 6,9-hemiketal (**4**) was treated under hydrogen pressure[18] (4 atm) in a mixture of glacial acetic acid and 2 equiv of difluoroacetic acid over Adams' catalyst (PtO_2) to give in 70% yield a mixture of 5:1:1 of motilides **5**, **6**, and **7**. No trace of diastereomer **8** was observed in the reaction mixture. This reaction was also accompanied by the formation of rearranged side products (~20%) in which the deoxy-

Table 1. Determination of the Configuration of the Isomers

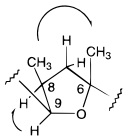
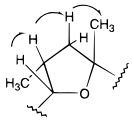
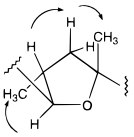
compound	NOE
5 8*S*,9*R*	
7 8*R*,9*S*	
6 8*R*,9*R*	

Table 2. In Vitro Prokinetic Activities of 4″-Deoxy-6,9-epoxy Analogues

compound	pED_{50}
2	7.22
5	7.93
6	7.80
7	5.45
9	7.64
10	8.54
11	4.71
12	6.67
13	7.75
14	4.00
15	8.11
16	6.43
17	5.71

cladinose was cleaved. The desired components were separated by HPLC. Compound **8**, which thus far has been synthetically elusive, remains a subject for further investigation in our laboratories. Configuration of the three 6,9-epoxy epimers was determined via analysis of their COSY and ROESY spectra. Thus, as shown in Table 1 for compound **5**, H-8 and H-9 showed an NOE to each other, while the C-8 methyl group showed an NOE to the C-6 methyl indicating that the C-8 methyl group has the *S* configuration. This compound has shown the same structural and conformational characteristics as the compound resulting from hydrogenation of **1** previously described by Abbott investigators[18] including one member of our research team.

H-8 and H-9 of **7** showed an NOE to each other; H-8 showed an NOE to one of the protons (δ 1.85) of C-7, which in turn showed an NOE to the C-6 methyl, suggesting 8*R*,9*S* configuration for **7**. As for the third isomer **6**, H-9 and the C-8 methyl showed an NOE to each other. H-8 showed an NOE to one of the protons (δ 1.81) on C-7, which in turn showed an NOE to the C-6 methyl, establishing the configuration 8*R*,9*R* for **6**. To the best of our knowledge these is the first description of this two new diastereomers resulting from hydrogenation of the 6,9-enol ether. Compound **5** was selected for further derivatization on the basis of its superior in vitro prokinetic activity (Table 2) and availability for further modification of the 3′-amino group. Thus **5** was N-demethylated using conditions described by Freiberg.[19] This latter process afforded 4″-deoxy-3′-*N*-desmethyl-9-deoxo-6,9-epoxyerythromycin A (**9**) (Scheme 1). Reaction of **9** with the corresponding alkyl halide and *N*,*N*-diisopropylethylamine in hot acetonitrile (70 °C) gave *N*-desmethyl-*N*-substituted derivatives[7] (Scheme 1).

The aforementioned route quickly provided compounds for studying the effects of the reduction of the 6,9-enol ether as well as a limited assessment of effects of 3′-amino modifications on the contractile activity of the 4″-deoxy-6,9-epoxyerythromycin congener.

Biological Activity

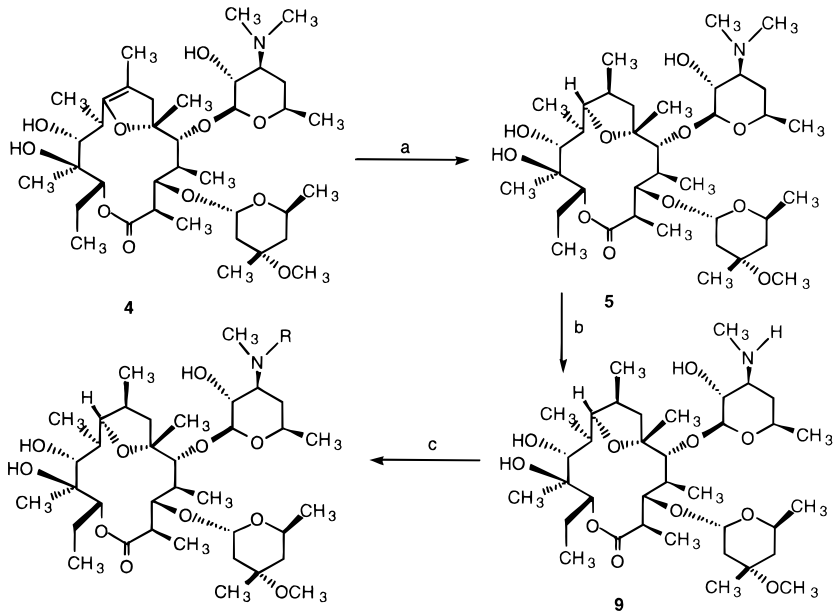
Prokinetic activity was studied in vitro by measuring smooth muscle contractility from rabbit duodenum isolated tissue. Longitudinal smooth muscle of the duodenum of New Zealand white rabbits (male) was bluntly separated from circular smooth muscle in a balanced electrolyte solution at pH 7.40. Isolated muscle (25 mg) was mounted in a tissue bath and attached to force transducers for measurement of contractile activity. A dose−response curve was generated with the test compound, and results are expressed (n = 3) as fractional activity relative to the response observed in the presence of 10^{-6} M methacholine (Sigma). From the dose−response profile, a pED_{50} (−log concentration yielding half-maximal contraction) was calculated as a comparative parameter for evaluating contraction induction potency.

Motilin Receptor Binding. Rabbits were sacrificed and the stomach was removed to ice-cold buffer. The lower half of the stomach was isolated, rinsed with saline, and opened along the lesser curvature. The antrum (easily recognized because of the thickness of its muscular layer) was separated, finely minced, and homogenized with 15 volumes of cold buffer (mM: Tris-HCl, 50; sucrose, 250; KCl, 50; $MgCl_2$, pH 7.4) with standard inhibitors (mM: iodoacetate, 1.0; pepstatin, 0.001; phenylmethanesulfonyl fluoride, 0.1; trypsin inhibitor type 1−5, 0.1 g/L; bacitracin, 0.25 g/L; Sigma). A Tekmar tissumizer mixer was used for homogenization. The homogenate was centrifuged at 2000*g* for 20 min, washed once with buffer, and resuspended in 0.9% NaCl to yield the crude membrane preparation. Protein was determined by commercial assay method (Bio-Rad).

Binding of motilin was performed on a 100-μL volume of crude membranes (0.5−1.0 mg of protein) in 200 μL of buffer A (mM: Tris-HCl, 50; $MgCl_2$, 10; BSA, 1.5%, pH 8.0) with 50 μL (50 pM final concentration) of [^{125}I]-nleu^{13}-porcine-motilin (Amersham) for 60 min at 30 °C as described by Bormans.[20] Reaction was stopped by dilution with cold buffer, and bound motilin was separated by centrifugation (4500*g*, 45 min). Pellets were counted in a γ-counter, with all data corrected for nonspecific binding. All assays were performed in quadruplicate or greater multiples. Displacement assays of bound motilin with macrolides were performed by adding increasing macrolide concentrations (in buffer A) to the incubation medium for 60 min. Results are consistent with a single class of motilin receptor; no other receptor class was distinguishable or studied. Data are expressed as the concentration of macrolide reducing specific motilin binding to 50%. This concentration is referred to as the IC_{50} and the −log as the pIC_{50}.

Acid Stability. Selected test compounds were prepared as 0.2 mg/mL solutions in ethanol; 0.5 mL of the

Scheme 1[a]



[a] (a) $AcOH/CHF_2CO_2H/PtO_2$; (b) $I_2/NaOAc/CH_3OH/h\nu$; (c) alkyl halide/$NC_2H_5[(CH_3)_2CH]_2/CH_3CN$.

stock solution was mixed with 4.5 mL of a preheated (37 °C) pH 3.0 phosphate buffer (50 mM). The mixture was incubated at 37 °C, and aliquots of 0.4 mL were taken at selected times to 8 h, for analysis by HPLC (see Experimental Section). The fraction of compound remaining was plotted with reference to the initial peak area, and acid stability rate constants and disappearance half-lives were calculated.

Results and Discussion

Reduction of the 6,9-enol ether in **4** did not lead to loss of biological activity but in fact led to an increase in in vitro potency in the case of compounds with the 9*R* configuration; e.g., motilides **5** and **6** showed pED_{50} values of 7.93 and 7.80, respectively, compared to 7.22 for **2**.

However a noticeable loss in contractile activity was observed for motilide **7** with 9*S* configuration. It is noteworthy to point out the profound effect of 4″-deoxygenation on in vitro potency of compounds with 9*R* configuration, when compared to 9-dihydro-6,9-epoxyerythromycin A with 8*R*,9*R* configuration and an in vitro pED_{50} of 6.00 (Abbott generated value) and as compared to 9-dihydro-4″-deoxy-6,9-epoxyerythromycin A (**7**) with pED_{50} of 7.80.[18] As in the case of the motilides reported by both Sunazuka et al.[21] and Koga et al.[22] modification of the 3′-amine also influenced activity in the 6,9-epoxy series. In this case, however, the secondary amine **9** was as potent as the *N*,*N*-dimethyl homologue **5**. In a series of *N*-alkyl-*N*-methyl derivatives, the *N*-ethyl-*N*-methyl derivative **10** was the most potent (Table 2). Further extension of the alkyl carbon chain or introduction of an arylalkyl decreased, or led to loss of, activity. Substitution by an isopropyl group did not show the same increase of potency in vitro as was demonstrated by Tsuzuki.[7] Unexpectedly the replacement of the methyl group in **5** by an alkanol group led to compound **15** with very high in vitro potency (pED_{50} of 8.11). The derivatives containing a fluoroalkyl or a saturated alkylamino and alkylcyano group did not lead to any increase of potency over their parent, compound **9**. Therefore, it is difficult to predict the effect of N-substituents in the 4″-deoxy-6,9-epoxy series, based on the results of these studies.

Table 3. Antibacterial Activities of **5**, **10**, and **15** (Mean MICs in μg/mL)

organism (no. of strains)	**5**	**10**	**15**
S. aureus (5)	>100	>100	>100
Streptococcus sp. (4)	>100	>100	>100
E. coli (5)	>100	>100	>100

The next objective was to demonstrate that the selected compounds bind specifically to rabbit antral smooth muscle motilin receptors, since this binding has been correlated closely with rabbit duodenal and human antral smooth muscle contractility as shown for **2** (ABT-229) and other motilides.[23] Compounds **5**, **10**, and **15** were studied for their displacement of bound [^{125}I]-motilin from tissue prepared from isolated rabbit antral smooth muscle. The study shows that the compounds specifically bind to motilin receptors and displace bound motilin with pIC_{50} values of 8.84, 8.52, and 8.70. This compares favorably with 8.12 for **2** (ABT-229).

The in vitro antibacterial activity of the selected compounds was also evaluated against a panel of Gram-positive and Gram-negative organisms. As shown in Table 3, the compounds are devoid of activity against erythromycin-susceptible organisms such as *Strepto-*

coccus pneumoniae and *Streptococcus pyogenes* as well as against erythromycin-resistant species such as *Escherichia coli*.

We also studied the acid stability of the above compound at pH 3.0. At pH 3.0, **2** is rapidly degraded with a $t_{1/2} = 0.15$ h. The $t_{1/2}$ for **5**, **10**, and **15** under these conditions is 5.5 h, illustrating that 6,9-epoxyerythromycin A derivatives are significantly more acid-stable motilides. The goal of improved acid stability has therefore been attained by removal of the double bond in the enol ether system.

Conclusion

9-Deoxo-4″-deoxy-6,9-epoxyerythromycin A derivatives with 9*R* configuration represent a novel class of motilides with superior in vitro potency as compared to ABT-229. The compounds demonstrated significantly improved acid stability. These properties qualify this series for further evaluation as potential backup drug candidates to ABT-229 (**2**) for the treatment of gastrointestinal motility disorders.

Experimental Section

NMR spectra were recorded on a GE QE500 spectrometer at 500 MHz for ^{1}H NMR with chemical shifts in ppm downfield from an internal TMS standard. D_2O was added to remove exchangeable protons from the ^{1}H NMR spectra. Coupling constants are in Hz. The desorption chemical ionization (DCI/NH_3) and fast atom bombardment (FAB) mass spectra were measured on a Finnigan SSQ700 instrument and a Finningan MAT 95 instrument, respectively. Melting points were determined on a Mel Temp II instrument and are uncorrected. Optical rotations were measured at the sodium D line with a Perkin-Elmer 241 polarimeter at 25 °C. All solvents were either distilled or of analytical reagent quality. All reactions were carried out under an inert atmosphere of dry nitrogen using oven-dried or flame-dried glassware. The progress of all reactions was monitored by TLC on E. Merck precoated silica gel (0.2-mm layer) plates containing a fluorescent indicator. Detection was first by UV (254 nm) and then by charring with a solution of ammonium molybdate tetrahydrate (12.5 g) and cerium sulfate tetrahydrate (5.0 g) in 10% aqueous sulfuric acid (500 mL). Flash chromatography was performed using silica gel (230−400 mesh, Merck). To determine the extent of hydrogenation reaction and to purify the product, a Rainin HPLC system with a Rheodyne injector (500-μL or 2.0-mL loop), an ABI UV/VIS (205 nm), and a Shimadzu RID-6A (1×10^{-6}RIU) detector were used. YMC ODS-A columns (250 × 4.6 mm, 250 × 20 mm preparative) were used. The mobile phases consisted of phosphate buffer (0.05 M NaH_2PO_4, pH 6.0:CH_3CN:MeOH, 50:10:40) at a flow rate of 1.2 mL/min (analytical) and phosphate buffer (0.05 M NaH_2PO_4, pH 6.9: CH_3CN:MeOH, 42:5:48) at a flow rate of 3 mL/min (semi-preparative). All elemental analyses were within ±0.4% of the calculated values. Erythromycin A was available from the Chemical and Agricultural Products Division of Abbott Laboratories.

(9*R*),(8*S*)-9-Deoxo-4″-deoxy-6,9-epoxyerythromycin A (5). To a mixture of **4** (0.4 g, 0.55 mmol) in glacial acetic acid (24 mL) were added PtO_2 (0.4 g) and difluoroacetic acid (0.1 mL, 1.1 mmol). The reaction mixture was shaken under 4 atm of H_2 at room temperature in a Parr apparatus. The reaction mixture was monitored by HPLC and was complete after 3 h. The reaction was quenched by the addition of ammonium acetate (0.3 g), and after 15 min the mixture was filtered. After concentration in vacuo, the residue was dissolved in CH_2Cl_2 (150 mL) and washed three times with 8% $NaHCO_3$ (3 × 100 mL). The organic phase was dried over sodium sulfate (4.0 g) and the solvent removed to give crude product. The major products **5** (0.2 g, 50%; HPLC %/t_R 100/22.2), **6** (0.04 g, 10%; 99/23.0), and **7** (0.04 g, 10%; 97/23.2) were isolated by HPLC.

Product **5**: mp 129−131 °C; $[\alpha]_D$ −63.2 (*c* 0.75, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.90 (t, $J = 7.5$, 3H, H-15), 0.98 (d, $J = 7.5$, 3H, 10-CH_3), 1.09 (d, $J = 7.5$, 3H, 4-CH_3), 1.13 (d, $J = 5$, 3H, 8-CH_3), 1.13 (s, 3H, 12-CH_3), 1.14 (s, 3H, 3″-CH_3), 1.17 (d, $J = 5$, 3H, H-6′), 1.18 (d, $J = 7.5$, 3H, 2-CH_3), 1.21 (m, 1H, H-4′a), 1.21 (d, $J = 5$, 3H, H-6″), 1.34 (m, 1H, H-4″a), 1.43 (m, 1H, H-2″a), 1.48 (s, 3H, 6-CH_3), 1.49 (m, 1H, H-14a), 1.51 (m, 1H, H-7a), 1.63 (m, 1H, H-4″b), 1.67 (m, 1H, H-4′b), 1.90 (m, 1H, H-4), 1.96 (m, 1H, H-14b), 2.16 (m, 1H, H-10), 2.27 (m, 1H, H-2″b), 2.29 (s, 6H, $N(CH_3)_2$), 2.29 (m, 1H, H-8), 2.31 (m, 1H, H-7b), 2.49 (m, 1H, H-3′), 2.73 (m, 1H, H-2), 3.19 (dd, $J = 10$, 7.5, 1H, H-2′), 3.23 (d, $J = 10$, 1H, H-11), 3.28 (s, 3H, OCH_3), 3.61 (m, 1H, H-5′), 3.67 (d, $J = 5$, 1H, H-9), 3.80 (d, $J = 7.5$, 1H, H-5), 4.21 (t, $J = 5$, 1H, H-3), 4.41 (m, 1H, H-5″), 4.43 (d, $J = 7.5$, 1H, H-1′), 4.82 (dd, $J = 10$, 2, 1H, H-13), 5.32 (d, $J = 5$, 1H, H-1″); MS *m/e* 702 ($M + H^+$). Anal. ($C_{37}H_{67}NO_{11}$) C, H, N.

Compound 6: mp 120−121 °C; $[\alpha]_D$ −55.0 (*c* 0.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.89 (d, $J = 6$, 3H, 10-CH_3), 0.90 (t, $J = 7$, 3H, H-15), 0.94 (d, $J = 6$, 3H, 8-CH_3), 1.10 (d, $J = 7.5$, 3H, 4-CH_3), 1.14 (s, 3H, 3″-CH_3), 1.15 (d, $J = 6$, 3H, H-6′), 1.16 (s, 3H, 12-CH_3), 1.17 (d, $J = 7.5$, 3H, 2-CH_3), 1.18 (d, $J = 6$, 3H, H-6″), 1.20 (m, 1H, H-4′a), 1.32 (m, 1H, H-4″a), 1.32 (s, 3H, 6-CH_3), 1.42 (m, 1H, H-2″a), 1.49 (m, 1H, H-14a), 1.61 (m, 1H, H-4″b), 1.63 (m, 1H, H-7a), 1.66 (m, 1H, H-4′b), 1.81 (m, 1H, H-7b), 1.85 (m, 1H, H-4), 1.95 (m, 1H, H-14b), 2.07 (m, 1H, H-8), 2.12 (m, 1H, H-10), 2.27 (m, 1H, H-2″b), 2.29 (s, 6H, $N(CH_3)_2$), 2.49 (m, 1H, H-3′), 2.71 (m, 1H, H-2), 3.18 (m, 1H, H-2′), 3.19 (m, 1H, H-9), 3.28 (s, 3H, OCH_3), 3.35 (d, $J = 7.5$, 1H, H-11), 3.61 (m, 1H, H-5′), 3.79 (d, $J = 7.5$, 1H, H-5), 4.15 (t, $J = 3$, 1H, H-3), 4.39 (m, 1H, H-5″), 4.46 (d, $J = 7.5$, 1H, H-1′), 4.81 (dd, $J = 10$, 3, 1H, H-13), 5.33 (d, $J = 4.5$, 1H, H-1″); MS *m/e* 702 ($M + H^+$). Anal. ($C_{37}H_{67}NO_{11}\cdot 0.25H_2O$) C, H, N.

Compound 7: mp 140 °C; $[\alpha]_D$ −40.2 (*c* 0.34, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.94 (d, $J = 7.5$, 3H, 10-CH_3), 0.94 (t, $J = 7.5$, 3H, H-15), 1.00 (d, $J = 7.5$, 3H, 8-CH_3), 1.05 (d, $J = 7.5$, 3H, 4-CH_3), 1.13 (s, 6H, 3″-CH_3, 12-CH_3), 1.18 (d, $J = 7.5$, 3H, H-6″), 1.18 (m, 1H, H-4′a), 1.19 (d, $J = 7.5$, 3H, H-6′), 1.20 (d, $J = 7.5$, 3H, 2-CH_3), 1.32 (m, 1H, H-4″a), 1.35 (s, 3H, 6-CH_3), 1.43 (m, 2H, H-2″a, H-7a), 1.49 (m, 1H, H-14a), 1.64 (m, 1H, H-4″b), 1.85 (m, 1H, H-7b), 1.90 (m, 1H, H-14b), 1.91 (m, 1H, H-10), 1.97 (m, 1H, H-4′b), 1.99 (m, 1H, H-4), 2.22 (m, 1H, H-2″b), 2.30 (s, 6H, $N(CH_3)_2$), 2.54 (m, 1H, H-8), 2.61 (m, 1H, H-3′), 2.70 (m, 1H, H-2), 3.21 (m, 1H, H-2′), 3.27 (s, 3H, OCH_3), 3.67 (m, 1H, H-5′), 3.78 (d, $J = 7.5$, 1H, H-5), 3.80 (s, 1H, H-9), 3.87 (s, 1H, H-11), 4.11 (t, $J = 3$, 1H, H-3), 4.33 (m, 1H, H-5″), 4.48 (d, $J = 7.5$, 1H, H-1′), 4.80 (dd, $J = 12$, 2.5, 1H, H-13), 5.25 (d, $J = 5$, 1H, H-1″); MS *m/e* 702 ($M + H^+$). Anal. ($C_{37}H_{67}NO_{11}$) C, H, N.

(9*R*),(8*S*)-9-Deoxo-4″-deoxy-3′-*N*-desmethyl-6,9-epoxyerythromycin A (9). $NaOAc\cdot 3H_2O$ (2.0 g, 14.69 mmol) and I_2 (0.75 g, 2.97 mmol) were added sequentially to a methanolic (100 mL) solution of **5** (1.9 g, 2.71 mmol). The mixture was exposed to a flood lamp (200 W) and stirred for 3 h. Saturated aqueous $Na_2S_2O_7$ (8 mL) was added, and the mixture was diluted with CH_2Cl_2 (300 mL). The solution was washed with 8% $NaHCO_3$ (3 × 200 mL), 10% Na_2CO_3 (200 mL), and H_2O (3 × 250 mL). The organic phase was dried (Na_2SO_4, 15.0 g) and evaporated in vacuo and the residue purified by flash chromatography using $CHCl_3$:CH_3OH:NH_4OH, 90:10:1, to yield 1.4 g (75%) of solid **9**: mp 134−136 °C; $[\alpha]_D$ 41.0 (*c* 0.58, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.88 (t, $J = 7$, 3H), 0.95 (d, $J = 7$, 3H), 1.04 (d, $J = 7$, 3H), 1.12 (d, $J = 7$, 3H), 1.12 (s, 3H), 1.13 (s, 3H), 1.16 (d, $J = 7$, 3H), 1.17 (d, $J = 7$), 1.18 (d, $J = 7$, 3H), 1.21 (m, 1H), 1.32 (m, 1H), 1.43 (s, 3H), 1.44 (m, 2H), 1.47 (m, 1H), 1.62 (m, 1H), 1.89 (m, 1H), 1.95 (m, 2H), 2.09 (m, 1H), 2.24 (m, 1H), 2.25 (m, 1H), 2.29 (m, 1H), 2.44 (s, 6H), 2.60 (m, 1H), 2.70 (m, 1H), 3.14 (dd, $J = 9$, 6, 1H), 3.24 (m, 1H), 3.26 (s, 3H), 3.66 (m, 1H), 3.67 (m, 1H), 3.82 (d, $J = 7$, 1H), 4.23 (t, $J = 3$, 1H), 4.38 (d, $J = 7$, 1H), 4.40 (m, 1H), 4.74 (dd, $J = 10$, 3, 1H), 5.27 (d, $J = 5$, 1H); MS (FAB) 688 ($M + H^+$). Anal. ($C_{36}H_{65}NO_{11}$) C, H, N.

General Procedure for the Preparation of 3′-*N*-Desmethyl-3′-*N*-substituted Derivatives. To an anhydrous

CH_3CN (10 mL) solution of **9** (0.1 g, 0.14 mmol) were added 10 equiv of the appropriate halide and 10 equiv of *N*,*N*-diisopropylethylamine. The reaction mixture was stirred at 80 °C (6−8 h). The solution was then diluted with CH_2Cl_2 (50 mL) and washed with 8% $NaHCO_3$ (2 × 25 mL) and H_2O (25 mL). The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure, and the residue was chromatographed (CH_3Cl_3:CH_3OH:NH_4OH, 95:5:0.5) to afford the desired products. By using this procedure, the following compounds were prepared.

(9*R*),(8*S*)-9-Deoxo-4″-deoxy-3′-*N*-desmethyl-3′-*N*-ethyl-6,9-epoxyerythromycin A (10). Compound **9** (0.1 g, 0.14 mmol), iodoethane (0.12 mL, 1.4 mmol), and *N*,*N*-diisopropylethylamine (0.25 mL, 1.4 mmol) gave **10** as a solid (89%): mp 129−131 °C; $[\alpha]_D$ 46.2 (*c* 0.78, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.89 (t, *J* = 7, 3H), 0.98 (d, *J* = 7, 3H), 1.06 (m, 3H), 1.09 (d, *J* = 7, 3H), 1.12 (d, *J* = 7, 3H), 1.13 (s, 3H), 1.14 (s, 3H), 1.16 (d, *J* = 7, 3H), 1.17 (d, *J* = 7, 3H), 1.20 (m, 1H), 1.21 (d, *J* = 7, 3H), 1.35 (m, 1H), 1.40 (m, 1H), 1.45 (s, 3H), 1.49 (m, 1H), 1.50 (m, 1H), 1.60 (m, 1H), 1.64 (m, 1H), 1.90 (m, 1H), 1.95 (m, 1H), 2.15 (m, 1H), 2.22 (s, 3H), 2.28 (m, 1H), 2.29 (m, 1H), 2.30 (m, 1H), 2.35 (m, 1H), 2.52 (m, 1H), 2.60 (m, 1H), 2.72 (m, 1H), 3.20 (dd, *J* = 10, 6, 1H), 3.27 (s, 3H), 3.30 (m, 1H), 3.59 (m, 1H), 3.70 (d, *J* = 6, 1H), 3.77 (d, *J* = 7.5, 1H), 4.19 (t, *J* = 3, 1H), 4.37 (m, 1H), 4.45 (d, *J* = 7.5, 1H), 4.80 (dd, *J* = 12, 3, 1H), 5.26 (d, *J* = 4.5, 1H); MS *m*/*e* 716 (M + H$^+$). Anal. ($C_{38}H_{69}NO_{11}$·0.5H_2O) C, H, N.

(9*R*),(8*S*)-9-Deoxo-4″-deoxy-3′-*N*-desmethyl-3′-*N*-butyl-6,9-epoxyerythromycin A (11). 1-Iodobutane (0.17 mL, 1.4 mmol) and *N*,*N*-diisopropylethylamine (0.26 mL, 1.4 mmol) were added to a solution of **9** in CH_3CN to give **11** in 93% yield: mp 140 °C; $[\alpha]_D$ 43.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.87 (t, *J* = 7.5, 3H), 0.89 (t, *J* = 7.5, 3H), 0.90 (m, 2H), 0.90 (d, *J* = 7.5, 3H), 0.97 (d, *J* = 7.5, 3H), 1.09 (m, 2H), 1.10 (d, *J* = 7.5, 3H), 1.12 (s, 3H), 1.13 (s, 3H), 1.15 (d, *J* = 7, 3H), 1.18 (d, *J* = 7.5, 3H), 1.20 (m, 1H), 1.21 (d, *J* = 7, 3H), 1.31 (m, 1H), 1.39 (m, 1H), 1.44 (s, 3H), 1.48 (m, 1H), 1.49 (m, 1H), 1.59 (m, 1H), 1.63 (m, 1H), 1.87 (m, 1H), 1.92 (m, 1H), 2.15 (m, 1H), 2.21 (s, 3H), 2.24 (m, 1H), 2.27 (m, 1H), 2.30 (m, 1H), 2.31 (m, 1H), 2.50 (m, 1H), 2.55 (m, 1H), 2.74 (m, 1H), 3.18 (dd, *J* = 10, 7, 1H), 3.24 (m, 1H), 3.27 (s, 3H), 3.55 (m, 1H), 3.61 (m, 1H), 3.73 (d, *J* = 7.5, 1H), 4.17 (t, *J* = 3, 1H), 4.40 (m, 1H), 4.43 (d, *J* = 7.5, 1H), 4.80 (dd, *J* = 10.5, 3, 1H), 5.29 (d, *J* = 4.5, 1H); MS (FAB) 744 (M + H$^+$). Anal. ($C_{40}H_{73}NO_{11}$·0.25H_2O) C, H, N.

(9*R*),(8*S*)-9-Deoxo-4″-deoxy-3′-*N*-desmethyl-3′-*N*-fluoroethyl-6,9-epoxyerythromycin A (12). Compound **9** (0.1 g), 1-bromo-2-fluoroethane (0.11 mL, 1.4 mmol), and *N*,*N*-diisopropylethylamine (0.27 mL, 1.4 mmol) gave 85 mg of **12** (80%): mp 137−139 °C; $[\alpha]_D$ 29.0 (*c* 1.10, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.87 (t, *J* = 7.5, 3H), 0.97 (d, *J* = 7.5, 3H), 1.08 (d, *J* = 7.5, 3H), 1.11 (d, *J* = 7.5, 3H), 1.12 (s, 3H), 1.13 (s, 3H), 1.15 (m, 2H), 1.17 (d, *J* = 7.5, 3H), 1.18 (d, *J* = 7.5, 3H), 1.19 (d, *J* = 7.5, 3H), 1.20 (m, 1H), 1.31 (m, 1H), 1.38 (m, 1H), 1.47 (s, 3H), 1.49 (m, 2H), 1.60 (m, 1H), 1.65 (m, 1H), 1.88 (m, 2H), 2.15 (m, 1H), 2.30 (m, 1H), 2.31 (m, 2H), 2.33 (s, 3H), 2.51 (m, 2H), 2.63 (m, 1H), 2.71 (m, 1H), 3.20 (m, 1H), 3.27 (s, 3H), 3.30 (d, *J* = 9, 1H), 3.60 (m, 1H), 3.66 (m, 1H), 3.74 (d, *J* = 7.5, 1H), 4.18 (t, *J* = 3, 1H), 4.40 (m, 1H), 4.42 (d, *J* = 7.5, 1H), 4.81 (dd, *J* = 12, 3, 1H), 5.30 (d, *J* = 4, 1H); MS *m*/*e* 734 (M + H$^+$). Anal. ($C_{38}H_{68}FNO_{11}$) C, H, F, N.

(9*R*),(8*S*)-9-Deoxo-4″-deoxy-3′-*N*-desmethyl-3′-*N*-isopropyl-6,9-epoxyerythromycin A (13). *N*,*N*-Diisopropylethylamine (0.27 mL, 1.4 mmol), 2-iodopropane (0.14 mL, 1.4 mmol), and **9** gave **13** as a solid (69%): mp 131 °C; $[\alpha]_D$ 52.0 (*c* 0.40, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.88 (t, *J* = 7.5, 3H), 0.94 (d, *J* = 7.5, 3H), 0.99 (d, *J* = 7.5, 3H), 1.03 (d, *J* = 7, 3H), 1.04 (d, *J* = 7, 3H), 1.13 (d, *J* = 7.5, 3H), 1.14 (s, 3H), 1.15 (s, 3H), 1.17 (s, 3H), 1.19 (d, *J* = 7.5, 3H), 1.20 (d, *J* = 7.5, 3H), 1.22 (m, 1H), 1.33 (m, 1H), 1.40 (m, 1H), 1.48 (s, 3H), 1.50 (m, 1H), 1.52 (m, 1H), 1.65 (m, 1H), 1.70 (m, 1H), 1.90 (m, 2H), 2.14 (m, 1H), 2.22 (s, 3H), 2.25 (m, 1H), 2.28 (m, 1H), 2.30 (m, 1H), 2.40 (m, 1H), 2.45 (m, 1H), 2.71 (m, 1H), 3.14 (dd, *J* = 10, 7, 1H), 3.23 (d, *J* = 9, 1H), 3.30 (s, 3H), 3.50 (m, 1H), 3.62 (d, *J* = 5.5, 1H), 3.80 (d, *J* = 7, 1H), 4.18 (t, *J* = 3, 1H), 4.39 (m, 1H), 4.35 (d, *J* = 7, 1H), 4.82 (dd, *J* = 10, 3, 1H), 5.29 (d, *J* = 4.5, 1H); MS *m*/*e* 730 (M + H$^+$). Anal. ($C_{39}H_{71}NO_{11}$) C, H, N.

(9*R*),(8*S*)-9-Deoxo-4″-deoxy-3′-*N*-desmethyl-3′-*N*-benzyl-6,9-epoxyerythromycin A (14). Using derivative **9**, benzyl bromide (0.17 mL), and *N*,*N*-diisopropylethylamine (0.27 mL) gave compound **14** in 75% yield: mp 152−155 °C; $[\alpha]_D$ 32.4 (*c* 0.60, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.92 (t, *J* = 7, 3H), 0.97 (d, *J* = 7, 3H), 1.00 (d, *J* = 7, 3H), 1.10 (d, *J* = 7, 3H), 1.12 (s, 3H), 1.13 (s, 3H), 1.15 (d, *J* = 5.5, 3H), 1.18 (d, *J* = 7, 3H), 1.19 (m, 1H), 1.20 (d, *J* = 5.5, 3H), 1.31 (m, 1H), 1.39 (m, 1H), 1.45 (s, 3H), 1.50 (m, 1H), 1.53 (m, 1H), 1.59 (m, 1H), 1.66 (m, 1H), 1.88 (m, 1H), 1.95 (m, 1H), 2.10 (m, 1H), 2.25 (s, 3H), 2.27 (m, 1H), 2.29 (m, 1H), 2.34 (m, 1H), 2.45 (m, 1H), 2.68 (m, 1H), 3.20 (dd, *J* = 10, 7.5, 1H), 3.25 (s, 3H), 3.27 (d, *J* = 9, 1H), 3.60 (m, 1H), 3.66 (d, *J* = 5, 1H), 3.75 (m, 1H), 4.19 (t, *J* = 3, 1H), 4.39 (m, 1H), 4.45 (d, *J* = 7, 1H), 4.90 (dd, *J* = 11, 3, 1H), 5.30 (m, 3H), 7.31 (m, 5H); MS *m*/*e* 778 (M + H$^+$). Anal. ($C_{43}H_{71}NO_{11}$·0.5H_2O) C, H, N.

(9*R*),(8*S*)-9-Deoxo-4″-deoxy-3′-*N*-desmethyl-3′-*N*-ethanol-6,9-epoxyerythromycin A (15). Motilide **9** (0.075 g, 0.11 mmol), 2-iodoethanol (0.09 mL, 1.1 mmol), and *N*,*N*-diisopropylethylamine (0.19 mL, 1.1 mmol) led to **15** in 89% yield: mp 118−121 °C; $[\alpha]_D$ 29.9 (*c* 0.65, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.88 (t, *J* = 7.5, 3H), 0.95 (d, *J* = 7, 3H), 0.97 (d, *J* = 7, 3H), 1.05 (d, *J* = 7.5, 3H), 1.13 (s, 3H), 1.15 (s, 3H), 1.16 (d, *J* = 7, 3H), 1.17 (d, *J* = 7.5, 3H), 1.19 (d, *J* = 6.5, 3H), 1.20 (m, 1H), 1.30 (m, 1H), 1.39 (m, 1H), 1.44 (s, 3H), 1.46 (m, 1H), 1.55 (m, 1H), 1.60 (m, 1H), 1.63 (m, 1H), 1.88 (m, 1H), 1.92 (m, 1H), 2.15 (m, 1H), 2.26 (m, 1H), 2.29 (m, 1H), 2.33 (m, 1H), 2.36 (s, 3H), 2.45 (m, 1H), 2.60 (m, 1H), 2.77 (m, 1H), 2.80 (m, 1H), 3.23 (m, 1H), 3.25 (s, 3H), 3.30 (d, *J* = 8.5, 1H), 3.60 (m, 4H), 3.78 (d, *J* = 7.5, 1H), 4.16 (t, *J* = 3, 1H), 4.35 (m, 1H), 4.44 (d, *J* = 8, 1H), 4.83 (dd, *J* = 10.5, 3, 1H), 5.30 (d, *J* = 4.5, 1H); MS *m*/*e* 732 (M + H$^+$). Anal. ($C_{38}H_{69}NO_{12}$) C, H, N.

(9*R*),(8*S*)-9-Deoxo-4″-deoxy-3′-*N*-desmethyl-3′-*N*-ethylamino-6,9-epoxyerythromycin A (16). Using **9** (0.1 g, 0.14 mmol), 2-bromoethylamine hydrobromide (0.44 g, 2.1 mmol), and *N*,*N*-diisopropylethylamine (0.5 mL, 2.8 mmol) gave product **16** in 20% yield: mp 161 °C; $[\alpha]_D$ 19.6 (*c* 0.70, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.89 (t, *J* = 7, 3H), 0.93 (d, *J* = 7, 3H), 0.99 (d, *J* = 7.5, 3H), 1.04 (d, *J* = 7, 3H), 1.07 (s, 3H), 1.09 (s, 3H), 1.12 (d, *J* = 7, 3H), 1.14 (d, *J* = 7.5, 3H), 1.16 (d, *J* = 7, 3H), 1.20 (m, 1H), 1.25 (m, 1H), 1.35 (m, 1H), 1.43 (s, 3H), 1.45 (m, 1H), 1.49 (m, 1H), 1.55 (m, 1H), 1.80 (m, 1H), 1.88 (m, 1H), 2.15 (m, 2H), 2.25 (m, 2H), 2.31 (s, 3H), 2.32 (m, 2H), 2.33 (m, 2H), 2.50 (m, 1H), 2.60 (m, 1H), 3.21 (dd, *J* = 10, 7, 1H), 3.25 (s, 3H), 3.26 (m, 1H), 3.55 (m, 1H), 3.61 (d, *J* = 6, 1H), 3.72 (d, *J* = 7, 1H), 4.19 (t, *J* = 3, 1H), 4.43 (m, 1H), 4.46 (d, *J* = 7, 1H), 4.85 (dd, *J* = 10.5, 3, 1H), 5.31 (d, *J* = 4.5, 1H); MS (FAB) 731 (M + H$^+$). Anal. ($C_{38}H_{70}N_2O_{11}$·0.5H_2O) C, H, N.

(9*R*),(8*S*)-9-Deoxo-4″-deoxy-3′-*N*-desmethyl-3′-*N*-acetonitrilo-6,9-epoxyerythromycin A (17). Bromoacetonitrile (0.1 mL), *N*,*N*-diisopropylethylamine (0.26 mL), and derivative **9** gave compound **17** in 65% yield: mp 138 °C; $[\alpha]_D$ 69.9 (*c* 1.50, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.88 (t, *J* = 7.5, 3H), 0.93 (d, *J* = 7.5, 3H), 0.97 (d, *J* = 7.5, 3H), 1.05 (d, *J* = 7.5, 3H), 1.10 (s, 3H), 1.12 (s, 3H), 1.17 (d, *J* = 7, 3H), 1.18 (d, *J* = 7.5, 3H), 1.20 (d, *J* = 7, 3H), 1.22 (m, 1H), 1.30 (m, 1H), 1.40 (m, 1H), 1.44 (s, 3H), 1.47 (m, 1H), 1.49 (m, 1H), 1.60 (m, 1H), 1.64 (m, 1H), 1.85 (m, 1H), 1.92 (m, 1H), 2.15 (m, 1H), 2.22 (m, 1H), 2.25 (m, 1H), 2.30 (m, 1H), 2.47 (s, 3H), 2.65 (m, 1H), 2.72 (m, 1H), 3.23 (m, 2H), 3.25 (s, 3H), 3.42 (m, 1H), 3.65 (m, 3H), 3.76 (d, *J* = 7.5, 1H), 4.17 (t, *J* = 3, 1H), 4.34 (m, 1H), 4.44 (d, *J* = 7, 1H), 4.80 (d, *J* = 10.5, 3, 1H), 5.29 (d, *J* = 5, 1H); MS *m*/*e* 727 (M + H$^+$). Anal. ($C_{38}H_{66}N_2O_{11}$) C, H, N.

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