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Novel Antibacterial Macrolides: Synthesis of 15-Membered Diolides

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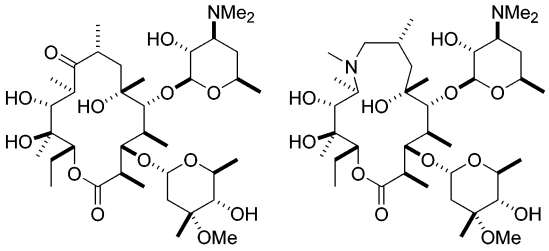
Novel 15-membered macrolides possessing the dilactone skeleton, diolides **13a** and **13b**, have been synthesized in our research program aimed at finding new antibacterial macrolides. Key strategic elements of the approach include the ring-expanding reaction of 13-membered dilactones, prepared from erythromycin A (Ery-A), to 15-membered dilactones via intramolecular translactonization. The absolute configuration at the regenerated C-8 position of the new diolides was determined by chemical transformation, leading to the corresponding lactam analogues, whose stereochemistry is known in the literature. For further confirmation, X-ray analysis was performed. The X-ray structure determination of **13a** revealed a backbone conformation similar to that of Ery-A. Novel 15-membered diolide **13a** and the 11,12-diol **18** exhibited antibacterial activities comparable to that of Ery-A.

Introduction

The erythromycin family consists of an important antibiotics known for some 50 years. Erythromycin A (Ery-A, **1**) has provided effective and, above all, safe antibiotic therapy for much of that time. However, it undergoes decomposition within the acidic medium of the stomach, which results in poor oral bioavailability and undesired gastrointestinal side effects.[1] In the past decade, a number of new semisynthetic erythromycin derivatives have been synthesized by structural modifications. They addressed the above shortcomings and offered better biological and pharmacodynamic properties than the parent Ery-A.[2,3]



Erythromycin A (Ery-A, **1**) Azithromycin (**2**)

Structural modification of Ery-A is still considered to be one of the most effective approaches for producing macrolide antibiotics having novel characteristics. The chemistry performed on Ery-A in the past can be divided into two main categories: (1) modification of peripheral substituents on the macrolide nucleus and (2) transformation affecting the aglycon scaffold, which is expected to lead to significant biological improvements. From a synthetic point of view, the latter approach is considered to be more challenging[4] but often results in decrease or loss of antibacterial potency. Only a limited number of such approaches were successful, exemplified by the azalides (e.g., azithromycin, **2**).[5] In the course of our exploratory investigation on macrolides, we were attracted to this latter approach and set out to find a route to a new nucleus. This led us to try modifications of the framework of erythromycin derivatives. Our efforts led to the establishment of a synthetic route to a novel 15-membered diolide. Here we report the synthesis of new diolides that demonstrate antibacterial activities comparable to that of Ery-A.

Results and Discussion

Plannning. Our strategy for synthesizing the 15-membered diolide **5** was planned to involve a ring-

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(1) Kurath, P.; Jones, P. H.; Egan, R. S.; Perun, T. J. *Experientia* **1971**, *27*, 362.

(2) For recent reviews, see: (a) Chu, D. T. W. *Med. Res. Rev.* **1999**, *19*, 497−520. (b) Bryskier, A. *Expert Opin. Invest. Drugs* **1999**, *8*, 1171−1194. (c) Bryskier, A. *Expert Opin. Invest. Drugs* **1997**, *6*, 1697−1709. (d) Chu, D. T. W. *Expert Opin. Invest. Drugs* **1995**, *4*, 65−94. (e) Wu, Y. J. *Curr. Pharm. Design.* **2000**, *6*, 181−223. (f) Wu, Y. J.; Su, W. G. *Curr. Med. Chem.* **2001**, *8*, 1727−1758.

(3) Morimoto, S.; Takahashi, Y.; Adachi, T.; Nagate, T.; Watanabe, Y.; Omura, S. *J. Antibiot.* **1990**, *43*, 286.

(4) For example, see: (a) 11-membered analogues: Kirst, H. A.; Wind, J. A.; Paschal. J. W. *J. Org. Chem.* **1987**, *52*, 4359. (b) 12-Membered analogues: Kibwage, I. O.; Busson, R.; Janssen, G.; Hoogmartens, J.; Vanderhaeghe H.; Brache J. *J. Org. Chem.* **1987**, *52*, 990. (c) 13-Membered analogues: Burnell-Curty, C.; Faghih, R.; Pagano, T.; Henry, R. F.; Lartey, P. A. *J. Org. Chem.* **1996**, *61*, 5153. (d) 14-Membered azalide: Jones, A. B. *J. Org. Chem.* **1992**, *57*, 4361.

(5) Bright, G. M.; Nagel, A. A.; Bordner, J.; Desai, K. A.; Dibrino, J. N.; Nowakowska, J.; Vincent, L.; Watrous, R. W.; Sciavolino, F. C.; English. A. R.; Retsema, J. A.; Anderson. M. R.; Brennan, L. A.; Borovoy, R. J.; Cimochowaski, C. R.; Faiella, J. A.; Girard, D.; Herbert, C.; Manousos, M.; Mason, R. *J. Antibiot.* **1988**, *41*, 1029.

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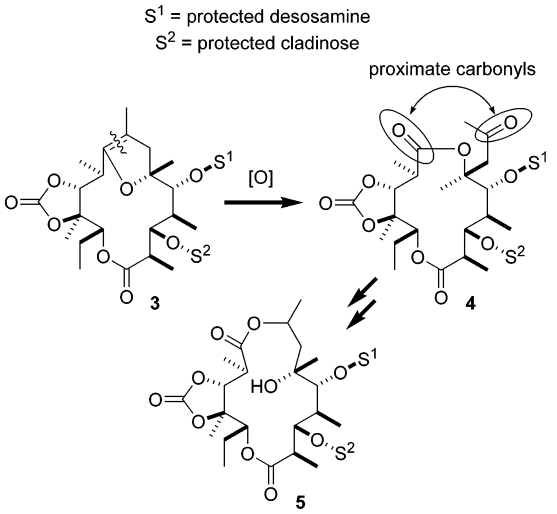
SCHEME 1

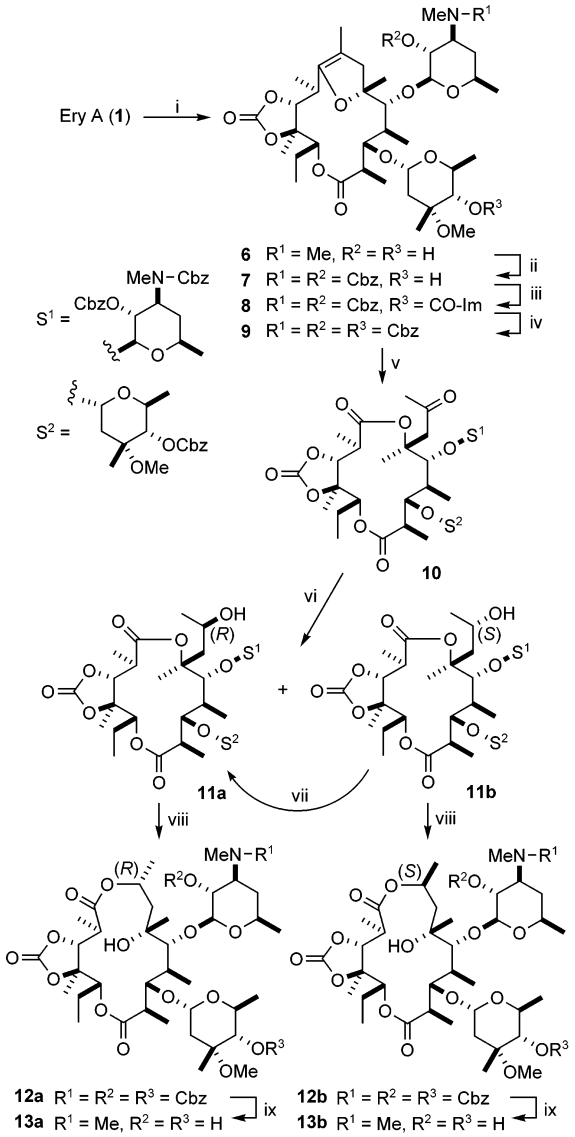


expanding reaction via intramoleular transesterification of the 13-membered diolide **4** (Scheme 1). The 13-membered diolide **4** was expected to be obtained via oxidative cleavage at the double bond of the enol ether **3**, which was readily available from Ery-A. From inspection of the space-filling model of **4**, we perceived that the two carbonyl groups in the backbone and in the pendant chain were relatively proximate, and functionalization of the pendant carbonyl and the subsequent reconstruction of the larger ring system would be a promising route. Thus we decided to employ the diolide **4** as a retethered ring system for effective reannealing of the full macrolide. Reduction of the pendant carbonyl to the hydroxy group would realize a synthetic route to the 15-membered diolide **5**. Protection of the sugar moieties was carried out using Cbz groups.

Construction of a 15-Membered Skeleton. Scheme 2 summarizes the synthetic route to the 15-membered diolides. The starting enol ether **6**, which is readily available from **1** according to literature,[6] was protected with Cbz groups at the 3′-amino group and the 2′-hydroxy group of the desosaminyl moiety, accompanied by demethylation at the 3′-amino group.[7] Since protection of the 4″-hydroxy group of the cladinosyl moiety using Cbz-Cl and DMAP did not give a satisfactory result, an alternative method was required. Functionalization of the 4″-position as the imidazole carbamate **8**, followed by treatment with BnOH/NaH was found effective for affording the 2′,3′,4″-tris(Cbz) derivative **9** in high yield.[8]

With the fully protected enol ether derivative **9** in hand, oxidative cleavage of the double bond was investigated. Pyridinium chlorochromate (PCC) on Celite introduced by Chandrasekaran et al.[9] for the selective

SCHEME 2



[a] Key: (i) ref. 6; (ii) Cbz-Cl, $NaHCO_3$, 1,4-dioxane, quant.; (iii) Im_2CO, K_2CO_3, THF; (iv) BnOH, NaH, THF, 80%; (v) PCC, Celite^R, 1,2-dichloroethane, 42%; (vi) BH_3, THF, **11a** 64%, **11b** 29%; (vii) 1) MsCl, Et_3N, CH_2Cl_2, 2) THF, H_2O, 73%; (viii) NaH, THF, **12a** 98%, **12b** 90%; (ix) 1) H_2, $Pd(OH)_2$/C, acetate buffer, EtOH 2) HCHO, **13a** 94%, **13b** 89%.

cleavage of enol ether double bonds furnished the desired 13-membered diolide **10** having an acetonyl side chain in acceptable yield.

The keto group in the acetonyl side chain was quantitatively reduced with an excess (10 equiv) of BH_3–THF complex to yield the corresponding alcohols **11a** and **11b** as a 2:1 mixture of stereoisomers. Each isomer was separable by silica gel column chromatography (**11a**, 64%; **11b**, 29%). The $NaBH_4$ (10 equiv) reduction was very sluggish and was not examined in detail. On the other hand, conversion of the alcohol **11b** to **11a** was investigated. The mesylation of **11b**, followed by treatment with aqueous THF, gave **11a** in good yield. This displacement is likely to have proceeded via the S_N2 mechanism, because **11a** was transformed to **11b** and **12b** by the same procedure.

(6) Murphy, H. W.; Stephens, V. C.; Conine, J. W. USA Patent 3417077 (1968). (b) Slawinski, W.; Bojarska-Dahlig, H.; Glabski, T.; Dziegielewska, I.; Biedrzycki, M.; Naperty, S. *Rec. J. R. Nether. Chem. Soc.* **1975**, *94*, 236. (c) Hauske. J. R.; Kostek. G. *J. Org. Chem.* **1982**, *47*, 1595.

(7) Flynn, E. H.; Murphy, H. W.; McMahon, R. E. *J. Am. Chem. Soc.* **1955**, *77*, 3104−3105.

(8) Yasukata, T.; Narukawa, Y. Unpublished results from these laboratories. This method for Cbz-protection of the cladinosyl moiety of erythromycin derivatives was originally invented.

(9) Baskaran, S.; Islam, I.; Raghavan, S.; Chandrasekaran, S. *Chem. Lett.* **1987**, 1175. (b) Kraft, P.; Tochtermann, W. *Liebigs Ann. Chem.* **1995**, *8*, 1409.

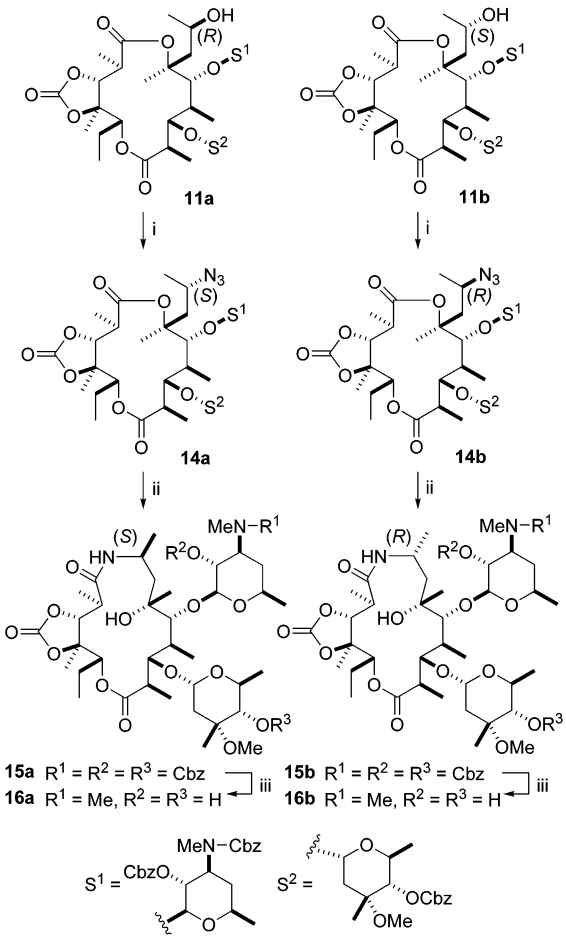
The next stage, the key transesterification, went as expected. Treatment of **11a** and **11b** with NaH successfully afforded the 15-membered diolides **12a** and **12b**, respectively, in excellent yield. Each 15-membered diolide was deprotected and *N*-methylated to give **13a** and **13b** in high yield.

Determination of the Absolute Configuration at C-8. Next, we tried to determine the absolute configuration at the C-8 position of the new diolides **13a** and **13b**. To this end, we transformed **11a** and **11b** to the lactam derivatives corresponding to **13a** and **13b**. The Merck group reported that 8a-azahomoerythromycin was obtained via Beckmann rearrangement of erythromycin-9(*Z*)-oxime.[10] Since the (*R*)-stereochemistry at the C-8 position was retained under the Beckmann rearrangement conditions, the transformation to the lactam derivatives and comparison with the stereochemically authentic sample obtained from Merck's 8-(*R*)-8a-azahomoerythromycin should enable us to determine the absolute configuration. Also, this transformation would demonstrate the extension of our synthetic method to the preparation of lactam analogues. Thus, alcohol **11a** and **11b** were converted to the 8a-azahomoerythromycin derivatives in three steps (Scheme 3). **11a** and **11b** were converted to the azides **14a** and **14b** via Mitsunobu reaction with inversion of the stereochemistry. Staudinger reduction of **14a** and **14b** spontaneously gave rise to ring expansion via lactam formation to produce the desired **15a** and **15b**, which were deprotected and *N*-methylated to give **16a** and **16b**, respectively.

The ^{1}H NMR of the 11,12-carbonate derived from the authentic 8-(*R*)-8a-azahomoerythromycin was consistent with that of **16b**, and not of **16a**. Since **11a** and **16b** have the same (*R*)-stereochemistry, taking account of the inversion at the Mitsunobu reaction, we concluded that the absolute configuration at the C-8 position of **13a** is *R*, which is the same as that of Ery-A. Consequently, **13b** has the (*S*)-configuration. Furthermore, X-ray structure determination of **13a** and **13b** was successfully performed, which confirmed their stereochemistry.[11] The superimposition of **13a** and **13b** with Ery-A (**1**) is shown in Figure 1. The stereochemistry and backbone conformation of **13a** were similar to those of Ery-A (**1**) (Figure 1a). Contrarily, the superimposition of **13b** indicated very poor fit. The backbone conformation of **13b** deviated from that of Ery-A(**1**), so the 6-hydroxy and 9-carbonyl groups were directed toward the outside of the macrolide nucleus (Figure 1b).

Synthesis of 11,12-Diol 18. To investigate the conformational effect of the 11,12-cyclic carbonate moiety on the antibacterial activities, we synthesized 11,12-diol **18**. To this end, we planned to convert the 11,12-cyclic carbonate **12a** into 11,12-diol **17** (Scheme 4). Initial attempts for removing the cyclic carbonate group under hydrolytic conditions (K_2CO_3/MeOH−H_2O, or NaOH/THF−H_2O) were unsuccessful and resulted in competitive decomposition of the diolide frame as well as hydrolysis of Cbz groups in the sugar moieties.[12] To

SCHEME 3



[a] Key: (i) HN_3, DEAD, PPh_3, THF, **14a** 87%, **14b** 42%; (ii) Ph_3P, H_2O, THF, **15a** 52%, **15b** 88%; (iii) 1) H_2, $Pd(OH)_2$/C, acetate buffer, EtOH, 2) HCHO, **16a** 96%, **16b** 57%.

suppress the detrimental side reaction, we turned our efforts to the use of carbon nucleophiles. In our independent studies, we found that treatment of the 13-membered diolide **10** with MeMgBr in THF (0 °C, 1 h) afforded the 11-OAc, 12-OH derivative **19**, which was deprotected and *N*-methylated to give **20** (Scheme 5). Thus, we expected that the use of a Grignard reagent would be effective for removing the 11,12-cyclic carbonate group. However, treatment of **12a** with MeMgBr gave complex mixtures of products without **17** (Table 1, entry 1). Then, we assumed that the use of a bifunctional Grignard reagent with two nucleophilic sites would be more effective, since the second nucleophilic attack should occur intramolecularly. As expected, treatment of **12a** with Normant reagent[13] successfully gave **17** in 34% yield (Table 1, entry 2). Furthermore, a bis-Grignard reagent,[14] which was prepared from dibromobutane, was much more effective, to give **17** in 65% yield (Table 1,

(10) Wilkening, R. R.; Ratcliffe, R. W.; Doss, G. A.; Bartizal, K. F.; Graham, A. C.; Herbert, C. M. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 1287. (b) Wilkening, R. R.; Ratcliffe, R. W.; Doss, G. A.; Mosley, R. T.; Ball, R. G. *Tetrahedron*, **1997**, *53*, 16923.

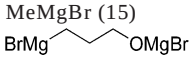
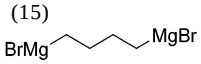
(11) X-ray crystal structures and crystal data for **13a** and **13b** are reported in the Supporting Information.

(12) For basic hydrolysis of 11,12-cyclic carbonate of erythromycin analogues, see: (a) Faghih, R.; Burnell-Curty, C.; Lartey, P. A.; Peterson, A.; Klein, L. L.; Bennani, Y. L.; Nellans, H. N. *Eur. J. Med. Chem.* **1999**, 34 (3), 261. (b) Hunt, E.; Tyler, J. W. *J. Chem. Soc., Perkin. Trans. 2.* **1990**, 2157.

(13) Cahiez, G.; Alexakis, A.; Normant, J. F. *Tetrahedron Lett.* **1978,** 3013.

(14) Cannon, K. C.; Know, G. R. In *Handbook of Grignard Reagents*; Silverman, G. S.; Rakita. P. E., Ed.; Marcel Dekker: New York, 1996; pp 497−526.

TABLE 1. Removal of 11,12-Cyclic Carbonate

entry[a]	nucleophile (equiv)	temp (°C)	time	yield (%) of **17**
1	MeMgBr (15)	−78 → 0	5 h	complex mixture
2	 (15)	−78 → 0	6 h	34
3	 (5)	−78	2 h, 50 min	65

[a] All reactions were performed in THF.

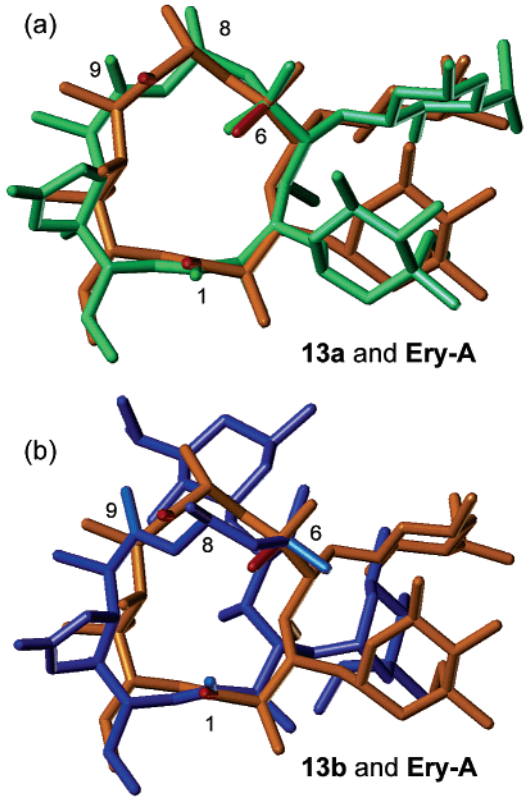
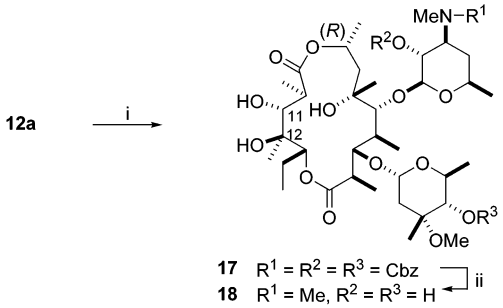


FIGURE 1. Superimposition of crystal structures: (a) **13a** (green) and Ery-A (**1**, yellow) and (b) **13b** (blue) and Ery-A (**1**, yellow).

SCHEME 4

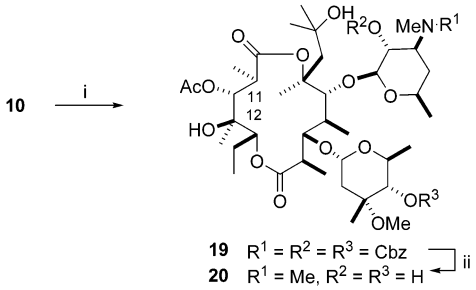


[a] Key: (i) See Table 1; (ii) 1) H_2, $Pd(OH)_2$/C, acetate buffer, EtOH 2) HCHO, 97%.

entry 2). It is noteworthy that chemoselective removal of 11,12-cyclic carbonate was performed with the Cbz groups intact. Finally, **17** was deprotected and *N*-methylated to give **18** in 97% yield (Scheme 4).

Antibacterial Activity. The in vitro antibacterial activities[15] of the 15-membered diolides and the corresponding lactam analogues against a panel of both Gram-positive and Gram-negative organisms are presented with that of Ery-A (**1**) as a reference compound in Table 2. The compounds having a natural 8-(*R*) configuration (**13a, 16b**, and **18**) had antibacterial activities comparable to that of Ery-A (**1**), and contrarily, **13b** and **16a**, which had the unnatural 8-(*S*) configuration, had almost no antibacterial activities. The 11,12-diol **18** showed the most potent antibacterial activities among these 15-membered macrolides.

SCHEME 5



[a] Key: (i) MeMgBr, THF, 51%; (ii) 1) H_2, $Pd(OH)_2$/C, acetate buffer, EtOH 2) HCHO, 92%.

TABLE 2. In Vitro Antibacterial Activity[15] (MIC, μg/mL) of Various Products

strain[a]	Ery-A (**1**)	**13a**	**13b**	**16a**	**16b**	**18**
S.a. JC-1	0.2	3.13	>100	>100	3.13	0.78
S.p. SR16675	1.56	1.56	>100	25	6.25	3.13
H.i. 88652	3.13	6.25	100	50	3.13	3.13

[a] *S.a.* = *Staphylococcus aureus*; *S.p.* = *Streptococcus pneumoniae*; *H.i.* = *Haemophilus influenzae*.

Conclusion

In conclusion, we established a novel synthetic route to the 15-membered diolides **13a** and **13b** and determined their stereochemistry. The antibacterial activities of the diolides, **13a**, **13b,** and **18** and their corresponding lactams **16a** and **16b** were evaluated, which revealed that the natural 8-(*R*)-**13a**, 8-(*R*)-**16b**, and 8-(*R*)-**18** have much more potent activities than the unnatural 8-(*S*)-**13b** and 8-(*S*)-**16a**. The structure−activity relationship of their related compounds will be reported elsewhere.

Experimental Section

8,9-Anhydro-2′-*O*,3′-*N*-bis(benzyloxycarbonyl)-3′-*N*-demethylerythromycin A 6,9-Hemiketal Cyclic 11,12-Car-

(15) MICs (minimum inhibitory concentrations) were determined by NCCLS (National Committee for Clinical Laboratory Standards) recommended microbroth dilution methods using cation-adjusted Mueller Hinton broth (Difco Laboratories, Detroit, MI).

bonate (7). A slurry of **6**[6] (40.0 g, 54.0 mmol) and $NaHCO_3$ (68.0 g, 0.81 mol) in 1,4-dioxane (70 mL) was heated to 71 °C. Cbz-Cl (92.1 g, 0.54 mol) was dropwise added to the mixture, the temperature of which was maintained at 70−75 °C during the addition. After being stirred at the same temperature for 1 h, the reaction mixture was cooled to room temperature and then treated with Et_3N (1.5 mL, 10.8 mmol) and stirred for another hour. The insoluble salt was filtered off and washed with a 1:1 mixture of $CHCl_3$ and *n*-hexane (400 mL). The filtrate was concentrated and the remaining benzyl alcohol was removed by distillation at 70 °C under reduced pressure. The resultant residue was purified by column chromatography on silica gel (*n*-hexane:EtOAc = 2:1) to give 54.3 g (quant) of **7** as a colorless foam: IR ($CHCl_3$) ν_{max} 3550, 2968, 2930, 1796, 1742, 1692, 1453, 1381, 1329 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.38, 3.02 (two s, 3H), 2.85, 2.81 (two s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.6, 156.6, 156.2, 154.7, 154.6, 153.2, 147.7, 136.7, 136.6, 135.5, 135.3, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.7, 104.9, 100.5, 95.1, 95.0, 87.4, 87.2, 85.1, 82.5, 79.9, 79.7, 78.1, 76.1, 76.0, 75.7, 74.9, 74.8, 73.0, 69.7, 69.5, 68.3, 67.5, 67.19, 65.6 (2C), 54.8, 49.7, 49.1, 43.7, 43.1, 41.7, 36.4, 35.9, 34.6, 31.9, 28.7, 25.4, 22.3, 21.6, 20.8, 18.3, 15.7, 13.5, 12.8, 12.2, 10.6, 8.2; MS (FAB) *m/z* 995 (M^+), 412, 260, 170, 91; HRFABMS calcd for $C_{53}H_{73}NNaO_{17}$ (M^+ + Na) *m/z* 1018.4777, found *m/z* 1018.4766.

8,9-Anhydro-3′-*N*-demethyl-2′-*O*,3′-*N*,4″-*O*-tris(benzyloxycarbonyl)erythromycin A 6,9-Hemiketal Cyclic 11,-12-Carbonate (9). To a solution of **7** (54.3 g, 54.5 mmol) in THF (540 mL) were added K_2CO_3 (14.9 g, 0.108 mol) and 1,1′-carbonyldiimidazole (13.1 g, 81.0 mmol), and the mixture was stirred at room temperature for 1 h. Next, K_2CO_3 (8.96 g, 64.8 mmol) and 1,1′-carbonyldiimidazole (8.76 g, 54.0 mmol) were added to the mixture, which was stirred for another hour. After filtration, the filtrate was evaporated and worked up in EtOAc to give 60.6 g of crude **8**. To a solution of the crude **8** in THF (500 mL) were added benzyl alcohol (11.2 mL, 0.108 mol) and NaH (60% in oil, 2.81 g, 70.3 mmol) at room temperature. The reaction mixture was stirred for 1 h at the same temperature and quenched with ice-cold 10% aqueous H_3PO_4 (500 mL). The resultant mixture was worked up in EtOAc and the crude product was purified by column chromatography on silica gel (*n*-hexane:EtOAc = 5:1 and 3:1) to give 48.7 g (80%) of **9** as a colorless foam. IR ($CHCl_3$) ν_{max} 2970, 2932, 1796, 1740, 1692, 1452, 1382, 1334 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.36, 2.94 (two s, 3H), 2.83, 2.79 (two s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.6, 156.6, 156.2, 155.6, 154.7, 154.6, 153.2, 147.6, 136.7, 136.5, 135.5, 135.2, 128−127, 104.8 (2C), 100.0, 95.1, 95.0, 87.1, 85.1, 82.7, 82.5, 79.6, 76.2, 76.1, 75.7, 75.1, 75.0, 72.7, 69.8, 69.7, 69.6, 69.4, 67.6, 67.5, 67.1, 63.0, 54.8, 49.5, 49.0, 43.4, 42.9, 41.5, 36.4, 35.9, 34.8, 31.9, 28.7, 25.5, 22.3, 20.9, 17.8, 15.7, 13.4, 12.7, 12.2, 10.6, 8.1; MS (FAB) *m/z* 1129(M^+), 412, 293, 261, 260, 170, 91; HRFABMS calcd for $C_{61}H_{79}NNaO_{19}$ (M^+ + Na) *m/z* 1152.5144, found *m/z* 1152.5148.

3′-*N*-Demethyl-6-deoxy-6,9-epoxy-7,8-nor-6-(2-oxopropyl)-2′-*O*,3′-*N*,4″-*O*-tris(benzyloxycarbonyl)erythromycin A Cyclic 11,12-Carbonate (10). To a suspension of PCC (98%, 47.8 g, 0.217 mol) and Celite (57 g) in 1,2-dichloroethane (350 mL) was dropwise added a solution of **9** (24.4 g, 21.6 mmol) in 1,2-dichloroethane (200 mL) at room temperature and the mixture was stirred at 50−55 °C for 8 h. The mixture was filtered through a pad of Celite and purified by column chromatography on silica gel (*n*-hexane:EtOAc = 2:1). The combined pure fractions were crystallized from methanol to give 10.6 g (42%) of **10** as white crystals: mp 170−171 °C (MeOH); IR ($CHCl_3$) ν_{max} 2972, 2936, 1804, 1737, 1695, 1453, 1383, 1332 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.37, 2.96 (two s, 3H), 2.84, 2.79 (two s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.0, 176.4, 171.7, 156.7, 156.2, 155.5, 154.7, 154.6, 152.6, 136.8, 136.4, 135.3, 135.3, 135.2, 128.6, 128.5, 128.4, 128.2, 128.1, 128.0, 127.9, 127.6, 98.9, 95.2, 95.1, 86.7, 86.6, 85.6, 82.4, 81.6, 80.0, 75.0, 74.8, 72.7, 72.6, 69.9, 69.8, 69.6, 67.6, 67.1, 63.0, 54.6, 49.3, 48.7, 46.8, 46.7, 43.8, 42.8, 42.1, 36.3, 35.8, 34.7, 34.6, 31.7, 31.6, 24.9, 22.4, 21.1, 21.0, 17.9, 17.8, 15.8, 12.9, 11.7, 10.6, 8.2; MS (FAB) *m/z* 1184 (M^+ + Na), 170, 91; HRFABMS calcd for $C_{61}H_{79}NNaO_{21}$ (M^+ + Na) *m/z* 1184.5042, found *m/z* 1184.5040.

3′-*N*-Demethyl-6-deoxy-6,9-epoxy-6-[(*R*)-2-hydroxypropyl]-7,8-nor-2′-*O*,3′-*N*,4″-*O*-tris(benzyloxycarbonyl)-erythromycin A Cyclic 11,12-Carbonate (11a) and 3′-*N*-Demethyl-6-deoxy-6,9-epoxy-6-[(*S*)-2-hydroxypropyl]-7,8-nor-2′-*O*,3′-*N*,4″-*O*-tris(benzyloxycarbonyl)erythromycin A Cyclic 11,12-Carbonate (11b). To a solution of **10** (19.0 g, 16.4 mmol) in THF (190 mL) was dropwise added BH_3–THF complex (1.0 M solution in THF, 164 mL) at ice-bath temperature over 35 min. The mixture was stirred at the same temperature for 1.5 h and diluted with EtOAc (500 mL). Under cooling with an ice-bath, 5% aqueous $NaHCO_3$ was added dropwise and the mixture was stirred at the ice-bath temperature for 1 h. After usual workup, the resultant residue was purified by column chromatography on silica gel (*n*-hexane:EtOAc = 3:2) to afford 12.2 g (64%) of the more polar (*R*)-isomer **11a** and 5.45 g (29%) of the less polar (*S*)-isomer **11b**, respectively, as white crystals.

Compound **11a**: mp 201−203 °C (*n*-hexane, EtOAc); IR ($CHCl_3$) ν_{max} 3500, 2972, 2936, 1805, 1740, 1693, 1453, 1383, 1332 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.38, 2.87 (two s, 3H), 2.83, 2.78 (two s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.0, 171.9, 156.7, 156.3, 155.5, 154.9, 154.8, 152.5, 136.7, 136.5, 135.2, 135.1, 128.6, 128.5, 128.3, 128.2, 128.1, 128.0, 127.9, 127.6, 98.9, 95.3, 95.2, 89.9, 85.2, 82.3, 81.6, 80.7, 75.2, 75.0, 74.7, 74.6, 72.7, 72.6, 69.9, 69.8, 69.7, 67.6, 67.2, 64.3, 63.1, 54.3, 49.3, 48.7, 44.1, 43.3, 43.2, 42.9, 42.8, 36.3, 35.8, 34.7, 34.5, 28.5, 24.8, 22.9, 22.3, 21.1, 21.0, 17.8, 16.0, 13.3, 11.7, 10.5, 8.6; MS (FAB) *m/z* 1186 (M^+ + Na), 91; HRFABMS calcd for $C_{61}H_{81}NNaO_{21}$ (M^+ + Na) *m/z* 1186.5199, found *m/z* 1186.5206.

Compound **11b**: mp 133−134 °C (*n*-hexane, EtOAc); IR ($CHCl_3$) ν_{max} 3528, 2972, 2934, 1805, 1740, 1693, 1453, 1383, 1333 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.39, 2.86 (two s, 3H), 2.81, 2.76 (two s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.0, 171.4, 156.7, 156.2, 155.5, 154.9, 152.5, 136.7, 136.4, 135.2, 135.1, 135.0, 128.7, 128.6, 128.5, 128.4, 128.2, 128.1, 128.0, 127.9, 127.6, 99.4, 95.6, 95.5, 89.9, 85.2, 82.3, 81.7, 80.9, 75.0, 74.9, 74.1, 72.7, 72.6, 70.2, 69.9, 70.2, 70.0, 69.9, 67.7, 67.6, 67.2, 63.8, 63.2, 54.4, 49.3, 48.7, 44.5, 42.7, 42.6, 36.2, 35.7, 34.6, 34.5, 28.5, 25.1, 22.3, 22.1, 21.1, 20.9, 17.9, 17.8, 16.3, 13.0, 11.7, 10.5, 8.1; MS (FAB) *m/z* 1186 (M^+ + Na), 91; HRFABMS calcd for $C_{61}H_{81}NNaO_{21}$ (M^+ + Na) *m/z* 1186.5199, found *m/z* 1186.5197.

Conversion of Alcohol 11b to 11a by Inversion of C-8 Stereochemistry. To a cooled solution of **11b** (2.00 g, 1.72 mmol) in CH_2Cl_2 (20 mL) were added Et_3N (2.4 mL, 17.2 mmol) and MsCl (1.3 mL, 17.2 mmol) at −40 to −30 °C. The reaction mixture was stirred at the same temperature for 2 h and worked up in EtOAc. The resultant mesylated product (2.48 g) was dissolved in a 4:1 mixture (100 mL) of THF and water and heated at 75 °C for 2.5 h. After the mesylated product had disappeared from the TLC, the reaction mixture was concentrated and worked up in EtOAc. The crude product was purified by column chromatography on silica gel (*n*-hexane:EtOAc = 3:2) to give 1.46 g (73%) of **11a** as a colorless foam.

8-(*R*)-3′-*N*-Demethyl-8a-oxa-2′-*O*,3′-*N*,4″-*O*-tris(benzyloxycarbonyl)-8a-homoerythromycin A Cyclic 11,12-Carbonate (12a). To a solution of **11a** (12.2 g, 10.5 mmol) in THF (120 mL) was added portionwise NaH (60% in oil; 629 mg, 15.7 mmol), and the mixture was stirred for 50 min at room temperature. The reaction was quenched with 10% HCl (4.8 mL) and diluted with water. The mixture was then worked up in EtOAc. The crude product was purified by column chromatography on silica gel (*n*-hexane:EtOAc = 3:1 and 2:1) to give 11.9 g (98%) of **12a** as a colorless foam. IR ($CHCl_3$) ν_{max} 3520, 2972, 2934, 1802, 1738, 1692, 1454, 1382, 1333 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.38, 2.98 (two s, 3H), 2.83, 2.80 (two s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.2, 176.1, 172.0, 156.6, 156.3, 155.5, 154.8, 154.7, 152.8, 136.8, 136.6, 135.5,

135.3, 135.2, 98.9, 98.8, 95.1, 85.5, 82.6, 82.3, 82.2, 81.5, 76.2, 76.1, 75.2, 75.0, 74.0, 72.7, 72.6, 69.8, 69.7, 69.6, 69.4, 67.8, 67.5, 67.1, 63.2, 54.7, 49.4, 48.9, 44.5, 41.8, 40.6, 40.5, 36.3, 35.8, 35.0, 34.9, 28.9, 25.5, 22.9, 22.1, 21.2, 21.1, 20.8, 17.7, 15.5, 15.0, 12.8, 10.5, 8.9; MS (FAB) *m/z* 1186 ($M^+ + Na$), 170, 91; HRFABMS calcd for $C_{61}H_{81}NNaO_{21}$ ($M^+ + Na$) *m/z* 1186.5199, found *m/z* 1186.5195.

8-(*R*)-8a-Oxa-8a-homoerythromycin A Cyclic 11,12-Carbonate (13a). A solution of **12a** (2.00 g, 1.72 mmol) in 0.5 M acetate buffer (pH 4.5, 36 mL) and EtOH (180 mL) was stirred at room temperature for 1.5 h under H_2 atmosphere in the presence of 20% $Pd(OH)_2$/C (400 mg). Next, 37% HCHO (13 mL) was added to the reaction mixture and the stirring was continued for another hour under the same conditions. The mixture was filtered and concentrated. After being diluted with water, the mixture was basified with 5% aqueous $NaHCO_3$ and then worked up in EtOAc. The resultant residue was crystallized from acetone and water to yield 1.25 g (94%) of **13a** as white crystals: mp 207−208 °C (H_2O, acetone); IR ($CHCl_3$) ν_{max} 3430, 2970, 2932, 1801, 1732, 1456, 1378, 1318 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 5.29 (sextet, 1H, J = 5.8 Hz), 5.02 (dd, 1H, J = 9.3 Hz, 3.3 Hz), 4.89 (d, 1H, J = 4.2 Hz), 4.82 (d, 1H, J = 7.2 Hz), 4.48 (d, 1H, J = 7.8 Hz), 4.31 (t, 1H, J = 4.2 Hz), 4.04 (dq, 1H, J = 9.0 Hz, 6.0 Hz), 3.68 (d, 1H, J = 6.0 Hz), 3.56 (ddq, 1H, J = 10.8 Hz, 1.4 Hz, 6.0 Hz), 3.31 (s, 3H), 3.26 (dd, 1H, J = 10.5 Hz, 7.5 Hz), 3.04 (d, 1H, J = 9.0 Hz), 2.71 (quintet, 1H, J = 6.6 Hz), 2.67 (qd, 1H, J = 6.9 Hz, 4.5 Hz), 2.50 (ddd, 1H, J = 12.0 Hz, 10.2 Hz, 3.6 Hz), 2.35 (d, 1H, J = 15.0 Hz), 2.29 (s, 6H), 1.88 (m, 1H), 1.81 (m, 1H), 1.77 (dd, 1H, J = 14.7 Hz, 5.7 Hz), 1.72−1.66 (m, 3H), 1.65 (m, 1H), 1.59 (dd, 1H, J = 15.0 Hz, 4.8 Hz), 1.42 (s, 3H), 1.36 (d, 3H, J = 6.6 Hz), 1.32 (d, 3H, J = 7.2 Hz), 1.30 (s, 3H), 1.29 (d, 3H, J = 6.6 Hz), 1.25−1.23 (two d and s, 9H), 1.10 (d, 3H, J = 7.2 Hz), 0.93 (t, 3H, J = 7.5 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 175.6, 171.9, 152.9, 103.7, 96.3, 85.8, 84.1, 81.9, 78.2, 77.7, 77.0, 73.9, 72.8, 70.6, 69.8, 69.5, 65.9, 65.2, 49.4, 45.3, 42.4, 41.7, 40.4, 40.3, 35.0, 28.7, 26.1, 22.8, 22.0, 21.5, 21.2, 18.0, 15.9, 14.3, 13.0, 10.5, 10.0; MS (FAB) *m/z* 776 ($M^+ + H$), 618, 158; HRFABMS calcd for $C_{38}H_{66}NO_{15}$ ($M^+ + H$) *m/z* 776.4433, found *m/z* 776.4434. Anal. Calcd for $C_{38}H_{65}NO_{15}\cdot 1.3H_2O$: C, 57.10; H, 8.52; N, 1.75. Found: C, 57.11; H, 8.42; N, 1.84.

8-*epi*-(*S*)-3′-*N*-Demethyl-8a-oxa-2′-*O*,3′-*N*,4″-*O*-tris(benzyloxycarbonyl)-8a-homoerythromycin A Cyclic 11,12-Carbonate (12b). Compound **12b** was prepared from **11b** in 90% yield as a colorless foam by the same procedure as **12a**. IR ($CHCl_3$) ν_{max} 3500, 2974, 2934, 1802, 1736, 1693, 1454, 1382, 1332 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.34, 3.02 (two s, 3H), 2.81, 2.78 (two s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.0, 170.2, 156.6, 156.1, 155.4, 154.4, 154.3, 152.9, 136.7, 136.6, 135.2, 135.1, 128.6, 128.5, 128.1, 128.0, 127.9, 127.8, 127.6, 99.8, 96.4, 85.5, 84.2, 83.9, 82.3, 82.1, 78.1, 75.0, 74.0, 72.5, 70.5, 69.9, 69.8, 69.6, 68.4, 67.4, 67.1, 63.4, 54.9, 49.4, 49.0, 45.2, 45.0, 44.8, 42.0, 40.8, 36.3, 35.8, 35.2, 35.1, 29.0, 22.5, 21.2, 20.9, 20.8, 17.5, 17.4, 15.5, 14.2, 14.1, 14.0, 12.5, 12.4, 10.6, 9.2, 9.1; MS (FAB) *m/z* 1186 ($M^+ + Na$), 412, 293, 261, 260, 170, 91; HRFABMS calcd for $C_{61}H_{81}NNaO_{21}$ ($M^+ + Na$) *m/z* 1186.5199, found *m/z* 1186.5227.

8-*epi*-(*S*)-8a-Oxa-8a-homoerythromycin A Cyclic 11,-12-Carbonate (13b). Compound **13b** was prepared from **12b** in 89% yield as white crystals by the same procedure as **13a**: mp 149−151 °C (H_2O, acetone); IR ($CHCl_3$) ν_{max} 3540, 3434, 2968, 2930, 1798, 1731, 1455, 1374, 1360 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 5.52 (s, 1H), 5.07 (dd, 1H, J = 10.8 Hz, 1.8 Hz), 5.00 (qd, 1H, J = 6.0 Hz, 8.4 Hz), 4.83 (d, 1H, J = 3.6 Hz), 4.71 (d, 1H, J = 9.0 Hz), 4.25 (d, 1H, J = 7.2 Hz), 4.08 (dq, 1H, J = 9.6 Hz, 6.0 Hz), 3.89 (s, 1H), 3.45 (m, 1H), 3.32 (bs,1H), 3.28 (d, 1H, J = 9.6 Hz), 3.25 (s, 3H), 3.10−3.00 (m, 3H), 2.79 (dq, 1H, J = 9.6 Hz, J = 6.6 Hz), 2.41 (ddd, 1H), 2.34 (d, 1H, J = 9.6 Hz), 2.32 (bs, 1H), 2.25 (s, 6H), 2.20 (dd, 1H, J = 15.0 Hz, 8.4 Hz), 2.10 (m, 1H), 1.88 (m, 1H), 1.65−1.55 (m, 3H), 1.47 (d, 1H, J = 15.0 Hz), 1.47 (s, 3H), 1.40 (s, 3H), 1.34 (d, 3H, J = 6.6 Hz), 1.27 (d, 3H, J = 6.6 Hz), 1.28−1.18 (four d and s, 15H), 1.18 (partially hidden-dd, 1H), 0.90 (t, 3H, J = 7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.77, 170.33, 153.72, 104.82, 98.99, 84.59, 84.18, 84.04, 83.11, 77.59, 77.38, 75.02, 72.58, 70.39, 69.62, 69.47, 65.91 (two carbon signals crossed over each other), 49.23, 45.43, 44.77, 41.06, 40.23, 39.84, 35.82, 30.82, 28.19, 22.33, 21.42, 21.37, 21.20, 17.37, 16.30, 13.22, 11.37, 10.01, 8.81; MS (FAB) *m/z* 776 ($M^+ + H$), 618, 158; HRFABMS calcd for $C_{38}H_{66}NO_{15}$ ($M^+ + H$) *m/z* 776.4433, found *m/z* 776.4430. Anal. Calcd for $C_{38}H_{65}NO_{15}\cdot 0.5H_2O$: C, 58.15; H, 8.48; N, 1.78. Found: C, 58.19; H, 8.44; N, 1.98.

3′-*N*-Demethyl-6-deoxy-6,9-epoxy-6-[(*S*)-2-azidopropyl]-7,8-nor-2′-*O*,3′-*N*,4″-*O*-tris(benzyloxycarbonyl)erythromycin A Cyclic 11,12-Carbonate (14a). To a solution of **11a** (500 mg, 0.43 mmol) in THF (7.5 mL) was added triphenylphosphine (564 mg, 2.15 mmol), hydrogen azide (1.7 M solution in toluene, 2.5 mL, 4.25 mmol), and DEAD (0.34 mL, 2.16 mmol) successively under ice-cooling. The mixture was stirred for 40 min at ice-bath temperature. The reaction was quenched with water and the mixture was worked up in EtOAc. The crude product was purified by column chromatography on silica gel (*n*-hexane:EtOAc = 2:1) to give 445 mg (87%) of **14a** as a colorless foam: IR ($CHCl_3$) ν_{max} 2972, 2936, 2100, 1805, 1740, 1692, 1453, 1383, 1333 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.39, 2.86 (two s, 3H), 2.83, 2.79 (two s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.2, 171.5, 156.7, 156.3, 155.5, 154.7, 154.6, 152.6, 136.8, 136.5, 135.4, 135.3, 135.2, 128.7, 128.6, 128.5, 128.4, 128.2, 128.1, 128.0, 127.9, 127.8, 127.6, 98.9, 98.6, 95.2, 95.1, 88.5, 85.3, 82.4, 81.6, 80.6, 75.1, 75.0, 72.7, 72.6, 69.9, 69.8, 69.5, 67.6, 67.1, 63.1, 54.6, 54.1, 49.3, 48.7, 43.8, 42.9, 42.7, 40.0, 36.3, 35.8, 34.7, 34.5, 28.6, 23.0, 22.4, 21.1, 21.0, 20.8, 17.8, 15.6, 13.2, 11.8, 10.5; MS (FAB) *m/z* 1211 ($M^+ + Na$), 412, 261, 170, 91; HRFABMS calcd for $C_{61}H_{80}N_4NaO_{20}$ ($M^+ + Na$) *m/z* 1211.5263, found *m/z* 1211.5255.

3′-*N*-Demethyl-6-deoxy-6,9-epoxy-6-[(*R*)-2-azidopropyl]-7,8-nor-2′-*O*,3′-*N*,4″-*O*-tris(benzyloxycarbonyl)erythromycin A Cyclic 11,12-Carbonate (14b). Compound **14b** was prepared from **11b** in 42% yield as a colorless foam by the same procedure as **14a**. IR ($CHCl_3$) ν_{max} 2972, 2936, 2102, 1804, 1741, 1692, 1452, 1384, 1333 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.38, 2.88 (two s, 3H), 2.82, 2.78 (two s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.7, 171.2, 156.4, 155.9, 155.2, 154.5, 154.4, 152.3, 150.4, 136.5, 136.3, 135.1, 135.0, 134.9, 128.4, 128.3, 128.1, 127.9, 127.8, 127.7, 127.6, 98.5, 95.0, 94.9, 88.1, 88.0, 85.1, 82.2, 81.5, 80.4, 75.2, 75.0, 74.9, 72.6, 72.5, 70.8, 69.8, 69.7, 69.4, 67.4, 67.3, 67.0, 64.2, 63.0, 54.3, 54.1, 49.2, 48.5, 43.5, 43.4, 42.8, 42.6, 39.0, 36.2, 35.7, 34.6, 34.5, 32.2, 32.0, 28.4, 26.2, 22.4, 22.0, 21.9, 21.6, 21.1, 21.0, 20.9, 17.7, 17.6, 15.7, 15.6, 14.1, 13.4, 11.6, 10.4, 8.4; MS (FAB) *m/z* 1211 ($M^+ + Na$), 412, 293, 261, 260, 170, 91; HRFABMS calcd for $C_{61}H_{80}N_4NaO_{20}$ ($M^+ + Na$) *m/z* 1211.5263, found *m/z* 1211.5261.

8-*epi*-(*S*)-8a-Aza-3′-*N*-demethyl-2′-*O*,3′-*N*,4″-*O*-tris(benzyloxycarbonyl)-8a-homoerythromycin A Cyclic 11,12-Carbonate (15a). To a solution of **14a** (250 mg, 0.21 mmol) in THF (7.5 mL) was added triphenylphosphine (442 mg, 1.69 mmol), and the mixture was stirred for 1 h at room temperature. Next, water (0.24 mL) was added to the mixture, which was heated at 60 °C for 3 h. After being cooled, the reaction mixture was diluted with water and worked up in EtOAc. The crude product was purified by column chromatography on silica gel (*n*-hexane:EtOAc = 1:1) to give 128 mg (52%) of **15a** as a colorless foam: IR ($CHCl_3$) ν_{max} 3500, 2972, 2934, 1799, 1737, 1691, 1508, 1453, 1382, 1334 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.36, 2.98 (two s, 3H), 2.83, 2.79 (two s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.2, 170.9, 156.6, 156.2, 155.5, 154.7, 154.6, 152.9, 136.8, 136.6, 135.4, 135.3, 135.2, 128.7, 128.6, 128.5, 128.4, 128.2, 128.1, 128.0, 127.9, 127,8, 127.6, 99.2, 95.1, 95.0, 86.8, 83.9, 82.6, 82.2, 75.1, 75.0, 74.8, 72.6, 69.9, 69.8, 69.6, 68.0, 67.5, 67.1, 63.2, 54.6, 49.4, 49.0, 44.7, 44.2, 43.4, 42.5, 42.4, 41.1, 36.3, 35.8, 35.0, 34.9, 28.8, 22.4, 21.1, 21.0, 20.9, 17.6, 15.4, 14.9, 13.5, 10.5, 8.9; MS (FAB) *m/z* 1163 ($M^+ + H$), 412, 170, 91; HRFABMS calcd for $C_{61}H_{82}N_2O_{20}$ ($M^+ + H$) *m/z* 1185.5359, found *m/z* 1185.5360.

8-(*R*)-8a-Aza-3′-*N*-demethyl-2′-*O*,3′-*N*,4″-*O*-tris(benzyloxycarbonyl)-8a-homoerythromycin A Cyclic 11,12-Carbonate (15b). Compound **15b** was prepared from **14b** in 88% yield as a colorless foam by the same procedure as **15a**. IR ($CHCl_3$) ν_{max} 3420, 2970, 2934, 1797, 1740, 1691, 1510, 1453, 1382, 1333 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.40, 2.98 (two s, 3H), 2.83, 2.80 (two s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.0, 171.0, 156.6, 156.3, 155.5, 154.8, 154.7, 152.9, 136.8, 136.6, 135.5, 135.4, 135.3, 128.7, 128.6, 128.5, 128.4, 128.1, 127.9, 127.8, 127.7, 127.6, 98.5, 95.0, 94.9, 86.0, 85.3, 84.7, 82.7, 81.7, 75.4, 75.1, 74.1, 72.7, 69.8, 69.7, 69.6, 69.5, 69.4, 67.5, 67.4, 67.1, 63.1, 54.7, 49.3, 48.8, 44.4, 44.1, 42.9, 42.3, 42.1, 36.3, 35.8, 35.0, 28.9, 25.0, 22.8, 22.6, 21.3, 20.8, 17.7, 17.6, 16.2, 16.1, 14.5, 10.1, 8.9, 8.8; MS (FAB) *m/z* 1185 (M^+ + Na), 170, 91; HRFABMS calcd for $C_{61}H_{82}N_2O_{20}$ (M^+ + H) *m/z* 1185.5359, found *m/z* 1185.5359.

8-*epi*-(*S*)-8a-Aza-8a-homoerythromycin A Cyclic 11,12-Carbonate (16a). Compound **16a** was prepared from **15a** in 96% yield as white powder by the same procedure as **13a**: IR ($CHCl_3$) ν_{max} 3418, 2970, 2932, 1798, 1731, 1656, 1523, 1456, 1376 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.98 (bs, 1H), 4.96 (dd, 1H, J = 9.6 Hz, 3.3 Hz), 4.83 (d, 1H, J = 4.5 Hz), 4.44−4.30 (m, 3H), 4.06 (dq, 1H, J = 9.6 Hz, 6.0 Hz), 4.0 (m, 1H), 3.54 (m, 1H), 3.40 (d, 1H, J = 5.1 Hz), 3.33 (m, 1H), 3.28 (s, 3H), 3.02 (d, 1H, J = 9.0 Hz), 2.81 (m, 1H), 2.67 (dq, 1H, J = 6.9 Hz, 5.4 Hz), 2.57 (m, 1H), 2.32 (s, 6H), 2.30 (m, 1H), 2.10−1.45 (m, 11H), 1.61 (s, 3H), 1.40−1.20 (m, 21H), 1.13 (d, 3H, J = 7.2 Hz), 0.93 (t, 3H, J = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.2, 170.3, 152.7, 104.5, 96.5, 86.6, 84.8, 82.9, 77.9, 75.9, 72.7, 70.8, 69.9, 66.0, 64.8, 49.4, 44.6, 44.2, 43.6, 42.0, 41.7, 40.5, 35.0, 29.4, 26.2, 22.5, 22.2, 21.5, 21.2, 18.0, 5.7, 14.6, 13.8, 10.5, 10.5; MS (FAB) *m/z* 775 (M^+ + H), 617, 158; HRFABMS calcd for $C_{38}H_{67}N_2O_{14}$ (M^+ + H) *m/z* 775.4592, found *m/z* 775.4589.

8-(*R*)-8a-Aza-8a-homoerythromycin A Cyclic 11,12-Carbonate (16b). Compound **16b** was prepared from **15b** in 57% yield as white crystals by the same procedure as **13a**: IR ($CHCl_3$) ν_{max} 3420, 2968, 2932, 1796, 1736, 1670, 1509, 1456, 1379 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.58 (d, 1H, J = 5.6 Hz), 5.22 (dd, 1H, J = 9.3 Hz, 3.6 Hz), 4.97 (1H, d, J = 3.9 Hz), 4.66 (d, 1H, J = 9.0 Hz), 4.53 (d, 1H, J = 7.2 Hz), 4.39 (dd, 1H, 5.7 Hz, 2.7 Hz), 4.20 (m, 1H), 4.11 (bm, 1H), 4.06 (dq, 1H, J = 9.0 Hz, 6.0 Hz), 3.81 (bs, 1H), 3.77(d, 1H, J = 5.4 Hz), 3.59 (m, 1H), 3.31 (s, 3H), 3.30 (d, 1H, J = 7.2 Hz), 3.06 (t, 3H, J = 9.6 Hz), 2.71−2.44 (m, 3H), 2.34 (s, 6H), 2.40−2.30 (d × 2, 2H), 1.90−1.55 (m, 7H), 1.40−1.20 (m, 21H), 1.07 (d, 3H, J = 7.2 Hz), 0.91 (t, 3H, J = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.5, 171.0, 153.1, 103.8, 96.6, 86.5, 85.4, 84.2, 78.9, 74.0, 72.9, 70.7, 69.3, 66.1, 65.1, 49.4, 45.6, 44.6, 42.2, 41.7, 40.4, 35.1, 29.1, 25.9, 22.6, 22.3, 21.6, 21.2, 17.9, 16.7, 16.3, 14.9, 10.2, 9.9; MS (FAB) *m/z* 775 (M^+ + H), 617, 158; HRFABMS calcd for $C_{38}H_{67}N_2O_{14}$ (M^+ + H) *m/z* 775.4592, found *m/z* 775.4587.

8-(*R*)-3′-*N*-Demethyl-8a-oxa-2′-*O*,3′-*N*,4″-*O*-tris(benzyloxycarbonyl)-8a-homoerythromycin A (17). Compound **12a** (100 mg, 0.086 mmol) was dissolved with THF (1 mL) and cooled to −78 °C under N_2 atmosphere. To this solution was added slowly a THF solution of bis-Grignard reagent (0.44 M, 975 μL), prepared from dibromobutane and magnesium, and the mixture stirred at −78 °C for 2 h and 50 min. After consumption of **12a** was confirmed by TLC, 10% HCl and EtOAc were added into the reaction mixture, and the mixture stirred at 0 °C for 20 min. The mixture was worked up in EtOAc to yield a crude product. Purification by silica gel chromatography (*n*-hexane:EtOAc = 1:1) afforded 64 mg (65%)-of **17** as a colorless foam. IR ($CHCl_3$) ν_{max} 3538, 3470, 2970, 2930, 1737, 1693, 1453, 1381, 1333 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.37, 2.95 (two s, 3H), 2.83, 2.79 (two s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.6, 178.5, 175.0, 156.6, 156.3, 155.6, 155.6, 154.7, 154.7, 136.8, 136.6, 135.6, 135.5, 135.5, 135.2, 128.7, 128.6, 128.5, 128.3, 128.2, 128.0, 99.6, 94.9, 94.9, 82.8, 82.6, 75.7, 75.2, 75.0, 72.5, 70.2, 69.8, 69.7, 69.6, 69.4, 67.4, 67.2, 67.1, 65.2, 62.9, 54.6, 49.5, 44.9, 41.7, 41.2, 39.3, 36.5, 36.0, 34.9, 27.5, 22.4, 21.9, 21.0, 17.9, 17.8, 16.6, 14.9, 11.3, 9.6, 8.6, 8.5; MS (FAB) *m/z* 1160 (M^+ + Na); HRFABMS calcd for $C_{60}H_{83}NNaO_{20}$ (M^+ + Na) *m/z* 1160.5406, found *m/z* 1160.5431.

8-(*R*)-8a-Oxa-8a-homoerythromycin A (18). Compound **18** was prepared from **17** in 97% yield as a white powder by the same procedure as **13a**: IR ν_{max} ($CHCl_3$) 3532, 3438, 2968, 2932, 1718, 1454, 1378, 1325 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.27 (m, 1H), 4.91 (d, 1H, J = 4.5 Hz), 4.80 (dd, 1H, J = 9.8 Hz, 2.6 Hz), 4.42 (d, 1H, J = 7.2 Hz), 4.27 (dd, 1H, J = 6.6 Hz, 3 Hz), 4.02 (m, 1H), 3.85 (bs, 1H), 3.51 (d, 1H, J = 7.5 Hz), 3.49 (m, 1H), 3.33 (s, 3H), 3.23 (dd, 1H, J = 9.9 Hz, 7.2 Hz), 3.04 (d, 1H, J = 9.0 Hz), 2.82−2.66 (m, 2H), 2.49 (m, 1H), 2.35 (d, 1H, J = 12 Hz), 2.33 (s, 6H), 2.0−1.8 (m, 3H), 1.7−1.5 (m, 5H), 1.42 (s, 3H), 1.30 (d, 3H, J = 6.3 Hz), 1.24−1.20 (four d and s, 15H), 1.15 (s, 3H), 1.08 (d, 3H, J = 7.5 Hz), 0.91 (t, 3H, J = 7.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.6, 174.9, 103.3, 95.2, 83.3, 76.7, 75.7, 74.9, 72.8, 70.9, 70.3, 69.0, 67.3, 65.6, 65.5, 49.5, 45.5, 42.2, 41.2, 40.4, 40.1, 34.7, 28.8, 27.6, 22.4, 21.9, 21.6, 21.4, 18.3, 16.7, 15.0, 11.3, 9.5, 9.3; MS (FAB) *m/z* 750 (M + H); HRFABMS calcd for $C_{37}H_{68}NO_{14}$ (M^+ + H) *m/z* 750.4640, found *m/z* 750.4637.

3′-*N*-Demethyl-6-deoxy-6,9-epoxy-6-(2-hydroxy-2-methylpropyl)-7,8-nor-2′-*O*,3′-*N*,4″-*O*-tris(benzyloxycarbonyl)-11-*O*-acetylerythromycin A (19). Compound **10** (500 mg, 0.43 mmol) was dissolved in THF (5 mL) and cooled to −78 °C under N_2 atmosphere. To this solution was added slowly MeMgBr (0.92 M in THF), and the mixture stirred at 0 °C for 1 h. After consumption of **10** was confirmed by TLC, 10% aqueous H_3PO_4, 10% aqueous HCl and EtOAc were added into the reaction mixture. The mixture was worked up in EtOAc to yield a crude product. Purification by silica gel chromatography (*n*-hexane:EtOAc = 1:1) afforded 260 mg (51%) of **19** as a colorless foam: IR ($CHCl_3$) ν_{max} 3015, 2978, 1741, 1696, 1456, 1383, 1262 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.28, 2.89 (two s, 3H), 2.83, 2.80 (two s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.1, 176.1, 175.2, 169.5, 156.6, 156.3, 155.5, 154.8, 136.8, 136.5, 135.4, 135.3, 135.2, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 98.2, 94.1, 93.9, 89.6, 82.5, 80.4, 80.1, 75.7, 75.0, 72.8, 70.8, 69.7, 67.5, 67.1, 62.9, 54.5, 49.1, 48.5, 44.8, 42.9, 42.7, 42.2, 36.4, 35.8, 32.1, 31.4, 28.7, 24.6, 23.4, 21.4, 21.3, 21.0, 20.7, 15.8, 11.5, 11.2, 9.3; MS (FAB) *m/z* 1216 (M^+ + Na); HRFABMS calcd for $C_{63}H_{87}NNa\ O_{21}$ (M^+ + Na) *m/z* 1216.5668, found *m/z* 1216.5685.

6-Deoxy-6,9-epoxy-6-(2-hydroxy-2-methylpropyl)-7,8-nor-11-*O*-acetylerythromycin A (20). Compound **20** was prepared from **19** in 92% yield as a colorless foam by the same procedure as **13a**: IR ν_{max} ($CHCl_3$) 3471, 3015, 2978, 1732, 1602, 1456, 1382 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.30 (d, 1H, J = 10.5 Hz), 4.85 (dd, 1H, J = 10.8 Hz, 2.4 Hz), 4.66−4.59 (m, 2H), 4.30 (d, 1H, J = 5.7 Hz), 4.28 (bs, 1H), 3.97 (m, 1H), 3.60 (m, 1H), 3.34 (s, 3H), 3.20 (dd, 1H, J = 10.5 Hz, 7.2 Hz), 3.10 (m, 2H), 2.66 (qd, 1H, J = 7.2 Hz, 1.8 Hz), 2.46 (m, 1H), 2.4−2.2 (m, 2H), 2.29 (s, 6H), 2.10 (s, 3H), 1.88 (s, 3H), 1.78 (qd, J = 7.5 Hz, 2.4 Hz), 1.73−1.50 (m, 4H), 1.40−1.30 (m, 9H), 1.28−1.12 (m, 16H), 0.88 (t, 3H, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.7, 174.6, 169.1, 101.5, 94.0, 89.6, 80.4, 79.6, 77.9, 75.6, 75.4, 73.1, 70.7, 70.1, 68.8, 65.5, 65.3, 49.2, 46.0, 43.2, 42.9, 42.3, 40.3, 34.5, 32.2, 31.2, 28.6, 24.0, 23.2, 21.7, 21.3, 20.7, 17.5, 15.7, 11.4, 11.3, 9.80; MS (FAB) *m/z* 806 (M^+ + H); HRFABMS calcd for $C_{40}H_{72}NO_{15}$ (M^+ + H) *m/z* 806.4902, found *m/z* 806.4901.

Supporting Information Available: Photocopies of ^1H and ^{13}C NMR spectra for **7**, **9**, **10**, **11a**, **11b**, **12a**, **12b**, **14a**, **14b**, **15a**, **15b**, **16a**, **16b**, **17**, **18**, **19**, **20**, which were not analyzed, and crystal data and ORTEP for **13a** and **13b**. This material is available free of charge via the Internet at http://pubs.org.

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