g, 0.37 mmol), was dissolved in anhydrous methylene chloride (1.0 mL) and was added via a syringe to the solution of diol **39a**, which was held at −25 °C. The reaction mixture was permitted to stir for 2.5 h and was diluted with $CHCl_3$ (50 mL). This solution was extracted with an aqueous solution of Na_2CO_3 (20 mL, 10% (w/w)) and water (2 × 20 mL). The organic layer was dried ($MgSO_4$) and the solvent was removed under reduced pressure to provide a light yellow oil. The crude product was analyzed by gas chromatography and GC–mass spectroscopy. The analysis indicated that the product was a mixture of four dienes and four unsaturated alcohols. Retention times: dienes (MW = 186), 9.75, 9.99, 10.56, and 10.86 min; unsaturated alcohols (MW = 204), 16.03, 17.72, 18.22, and 18.51 min (GC column, 5% phenylmethylsilicone; carrier gas, He, at 18 psi; flow rate, 50 mL/min; initial oven temperature, 130 °C; hold initial oven temperature, 2 min; final oven temperature, 200 °C; oven temperature rate, 0.5 °C/min).

Acknowledgment. We thank the National Science Foundation and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this work. The technical assistance of Mr. Keith Krumnow, Mr. Frank Laib, and Mr. Noel Wittaker is also gratefully acknowledged. Financial support for the initial phases of this work was provided by the Graduate School (UWM). NMR spectrometers (250 and 500 MHz) were purchased by grants from the NSF and NIH (BRSG) instrument programs, respectively. Helpful discussions with Mr. Greg Kubiak, Dr. Steve Bertz, and Dr. Gary Molander are also acknowledged.

Supplementary Material Available: Chemical shifts and coupling constants for **26a** and **26b** (2 pages). Ordering information is given on any current masthead page.

Modification of Macrolide Antibiotics. Synthesis of 11-Deoxy-11-(carboxyamino)-6-*O*-methylerythromycin A 11,12-(Cyclic esters) via an Intramolecular Michael Reaction of *O*-Carbamates with an α,β-Unsaturated Ketone[1]

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The synthesis of 11-deoxy-11-(carboxyamino)-6-*O*-methylerythromycin A 11,12-(cyclic esters) **13** was accomplished in five steps from 6-*O*-methylerythromycin A in 40% overall yield. The process featured a mild and stereoselective intramolecular Michael addition of C-12 *O*-carbamates to an α,β-unsaturated ketone. The Michael reaction required base catalysis and the rate of addition was fastest in polar solvents such as 10% aqueous acetonitrile or dimethylformamide. Reaction of the key intermediate acyl imidazole **11a** with primary amines produced in one operation the cyclic 11,12-carbamates. The stereochemistry of the product carbamates was determined by minimum energy calculations, two-dimensional NMR spectroscopic techniques, and ^{13}C NMR correlations.

Erythromycin A (**1**) commands a premier position in the market place as a safe and effective antibiotic for the treatment of gram-positive pathogens.[2] In particular, erythromycin A is the drug of choice for the treatment of Legionnaires' disease, an infection produced by *Legionella pneumophila*. However, one major limitation to erythromycin A therapy is its short in vivo half-life in humans (2 h).[3] Erythromycin A undergoes in vivo dehydration to anhydroerythromycin A, an inactive C-6/C-12 spiroketal metabolite.[4] Methods for inhibiting spirocyclization by ketone modification include (1) C-9 oxime;[5] (2) C-9 amino;[6] and (3) C-9 ketone replacement with ring expansion.[7] Two erythromycin A derivatives have been developed which stabilize the macrolide from spiroketalization while maintaining the C-9 carbonyl.

The first compound, 6-*O*-methylerythromycin A (**2**), prevents the formation of the spiroketal by blocking the C-6 hydroxyl group.[8] This antibiotic has shown excellent pharmacokinetic parameters and is undergoing clinical evaluation. Another approach to stabilizing the macrolide toward acid is masking the C-12 hydroxyl group. Erythromycin A 11,12-carbonate (**3**) fulfills this requirement.[9] The carbonate exhibits increased in vivo potency with a fourfold increase in in vivo half-life.[10] However, a major disadvantage of the carbonate is its liver toxicity. Both 6-*O*-methylerythromycin A 11,12-carbonate and erythromycin A 11,12-carbonate (**3**) were fivefold more hepatotoxic than erythromycin A (**1**) in the in vitro rat liver hepatotoxicity screen.[11] In connection with our efforts

(1) Dedicated to the memory of F.Q.B.
(2) For a comprehensive review of macrolide antibiotics, see: Omura, S.; Tanaka, H. *Macrolide Antibiotics, Chemistry, Biology, and Practice*; Omura, S., Ed.; Academic Press: New York, 1984.
(3) Welling, P. G.; Craig, W. A. *J. Pharm. Sci.* **1978**, *67*, 1057.
(4) Kurath, P.; Jones, P. H.; Egan, R. S.; Perun, T. J. *Experientia* **1971**, *27*, 362.
(5) Djokic, S.; Tamburasev, Z. *Tetrahedron Lett.* **1966**, 1645. Chantot, J. F.; Bryskier, A.; Gasc, J. C. *J. Antibiot.* **1986**, 660.
(6) Egan, R. S.; Freiberg, L. A.; Washburn, W. H. *J. Org. Chem.* **1974**, *39*, 2492.
(7) Djokic, S.; Kobrehel, G.; Lazarevski, G.; Lopotar, N.; Tamburasev, Z.; Kamenar, B.; Nagl, A.; Vickovic, I. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1881.
(8) 6-*O*-Methylerythromycin A (TE-031) is an in-licensed drug from the Taisho Pharmaceutical Co., Ltd., Tokyo, Japan: Watanabe, Y.; Morimoto, S.; Omura, S. U.S. Pat. 4 331 803, 1982.
(9) Neszmelyi, A.; Bojanska-Dahlig, H. *J. Antibiotic.* **1978**, *31*, 487.
(10) Mannisot, P. T.; Vuorela, A.; Mantyla, R.; Hanhijarvi, H.; Rauramaa, V. *Int. Congr. of Chemother.* **1983**, *5*, 107/5.
(11) Kingsley, E.; Gray, P.; Tolman, K. G.; Tweedale, R. *J. Clin. Pharmacol.* **1983**, *23*, 178.

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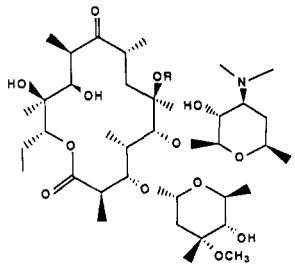
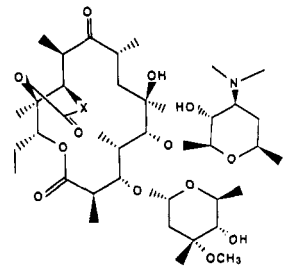


1, R = H erythromycin A

2, R = CH_3 6-*O*-methylerythromycin A

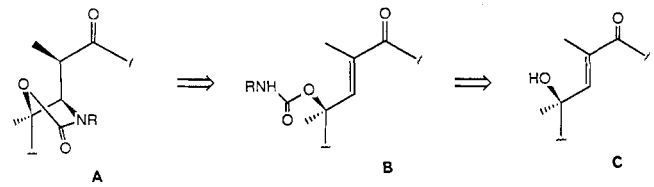


3, X = O erythromycin A 11,12-carbonate

4, X = NR 11-deoxy-11-(carboxyamino)erythromycin A 11,12-(cyclic ester)

to develop acid-stable erythromycin A analogues, we envisioned a new and novel series of compounds based on the cyclic carbamate structure (**4**). Furthermore, we hoped that these new derivatives would maintain the increased potency but be devoid of the liver toxicity. This paper will describe a new and general methodology for the synthesis of 11-deoxy-11-(carboxyamino)erythromycin A 11,12-(cyclic esters) useful for structure–activity evaluation in the antiinfective area.

The key step in our strategy involves the intramolecular Michael reaction B → A. Thus, allylic alcohol C, available



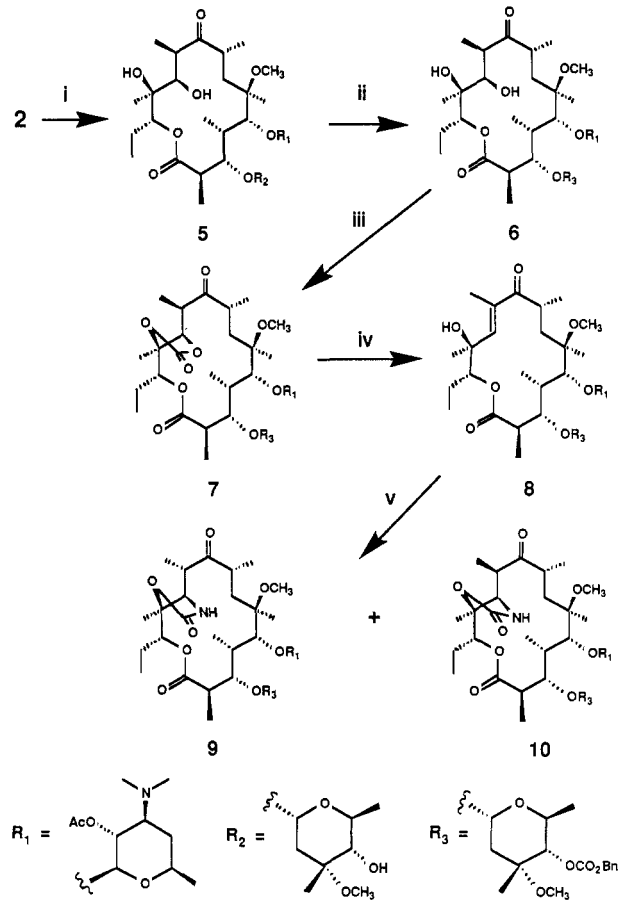
A B C

from erythromycin A, undergoes acylation to B producing the C-12 *O*-carbamate. Intramolecular Michael reaction gives rise to the cyclic C-11/C-12 carbamate. It should be noted that the stereochemistry at C-11 is dictated by the conformation of the α,β-unsaturated ketone and the appended C-12 *O*-carbamate in B. Another stereochemical concern is the protonation at C-10 after Michael addition. α protonation affords natural configuration while β attack generates a C-10 epimer. Hirama and co-workers have described an intramolecular Michael addition of *O*-carbamates to α,β-unsaturated esters.[12] They found a high degree of stereoselectivity in forming cyclic carbamates. 6-*O*-Methyl erythromycin A (**2**) was used to evaluate our synthetic plan. The C-6 methoxy group inhibits the formation of C-6/C-9 hemiacetal epimers, thereby confining the macrolide to its keto form. This restriction greatly simplifies the spectroscopic analysis of the product carbamates.

Results and Discussion

6-*O*-Methylerythromycin A reacted with acetic anhydride–triethylamine in dichloromethane forming the C-2′ acetate **5** in 73% yield (Scheme I). The neighboring dimethylamino group at C-3′ was thought to increase the reactivity of the C-2′ hydroxyl group over C-4″ and C-11 due to hydrogen bonding. Protection of the cladinose sugar was accomplished by acylation with benzyl chloroformate–DMAP at −20 °C. The protection sequence afforded diol **6** in 64% overall yield from **2**. Introduction of the C-10/C-11 double bond was accomplished in a two-step process. First, diol **6** was converted into the carbonate **7** ($NaN(TMS)_2$, carbonyldiimidazole, −35 °C to

Scheme I[a]



[a] Reagents and conditions: (i) Ac_2O, Et_3N; (ii) CbzCl, DMAP −20 °C; (iii) $NaN(TMS)_2$, −35 °C, carbonyldiimidazole, room temperature, 15 min; (iv) DBU, reflux; (v) chlorosulfonyl isocyanate, room temperature.

room temperature) and then β-elimination of the carbonate **7** (DBU, benzene reflux) afforded the unsaturated ketone **8** in 66% yield from **6**.[13] Enone **8** was allowed to react with chlorosulfonyl isocyanate in dichloromethane at room temperature. Two cyclic C-11/C-12 carbamates **9** and **10** were isolated in 4% and 6% yield, respectively, as the only identifiable products. The reaction produced significant amounts of unidentifiable polar byproducts, presumably formed from degradation of the starting material or product by the corrosive chlorosulfonyl isocyanate.[14] Inspection of the 300-MHz ^{1}proton and 500-MHz carbon NMR spectra of both **9** and **10** revealed three significant differences. First, the ^{1}H NMR signals for the methoxy groups in **9** and **10** appeared at 3.09 and 2.92 ppm, respectively. The C-6 methoxy protons for **7** are 2.97 ppm. The unusual high field absorption for the methyl ethers is explained by its close proximity to the C-9 carbonyl shielding zone.[15] Second, the coupling constants ($J_{C_{10}-C_{11}}$) in **9** and **10** were 1 and 0 Hz, respectively, while the carbonate **7** has a 0 Hz coupling for its C-11 methine. Finally, the carbon resonance for C-10 in **9** was 14.1 ppm lower field than the corresponding resonance for the C-10 carbon of **7**. The epimeric carbamate **10** had a value of 37.3 ppm for the C-10 carbon, differing by only −0.5 ppm (Table I).

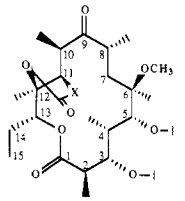
(12) Hirama, M.; Shigemoto, T.; Yamazaki, Y.; Ito, S. *J. Am. Chem. Soc.* **1985**, *107*, 1797.

(13) A similar strategy has been used for the synthesis of the 10,11-unsaturated ketone of erythromycin A, see: Hauske, J. R.; Kostek, G. *J. Org. Chem.* **1982**, *47*, 1595.

(14) Graf, R. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 172.

(15) Single-crystal X-ray structure of **2** shows the C-6 methoxy group 3.43 Å above the C-9 ketone, Stephen Spanton unpublished results.

Table I. ^{13}C NMR Chemical Shift Assignments ($CDCl_3$) for the Macrolide Ring Carbons of the Cyclic Carbonate 7 and Cyclic Carbamate Epimers 9 and 10



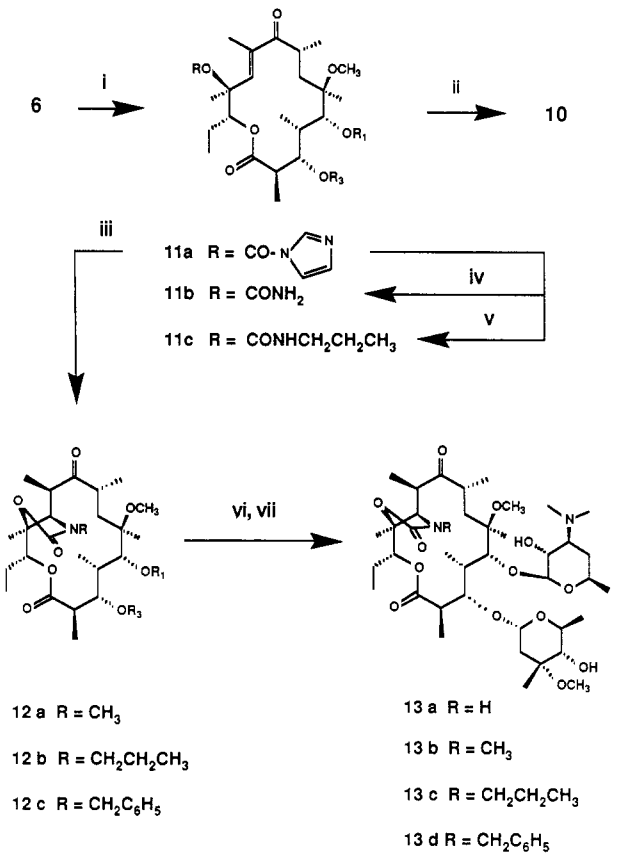
position	7	9	Δ ppm[a]	10	Δ ppm[a]
1	176.3	179.2	(+2.9)	176.3	(0)
2	45.2	45.7	(+0.5)	45.1	(−0.1)
2-CH_3	15.5	14.9	(−0.6)	15.6	(+0.1)
3	77.0	76.7	(−0.3)	77.0	(0)
4	39.6	42.5	(+2.9)	39.4	(−0.2)
4-CH_3	8.9	8.9	(0)	8.8	(−0.1)
5	79.4	77.4	(−2.0)	79.5	(+0.1)
6	78.6	*b*		78.3	(−0.3)
6-CH_3	20.0	22.1	(+2.1)	19.6	(−0.4)
7	38.7	42.9	(+4.9)	38.8	(+0.1)
8	44.4	41.1	(−3.9)	45.0	(+0.6)
8-CH_3	18.1	19.1	(+1.0)	18.0	(−0.1)
9	212.8	214.7	(+1.9)	218.1	(+5.3)
10	37.8	51.9	(+14.1)	37.3	(−0.5)
10-CH_3	12.7	10.4	(−2.3)	13.6	(+0.9)
11	80.7	58.4	(−22.3)	57.7	(−23.0)
12	84.9	*b*		83.8	(−1.1)
12-CH_3	13.2	16.3	(+4.1)	13.6	(+0.4)
13	75.4	77.0	(+1.6)	75.6	(+0.2)
14	22.0	21.5	(−0.5)	21.9	(−0.1)
15	10.3	10.6	(+0.3)	10.3	(0)
6-OCH_3	50.2	51.1	(+0.9)	50.0	(−0.2)

[a] Numbers in parentheses indicate chemical shift differences in parts per million from carbonate 7. [b] No observation.

Though we were gratified to obtain the cyclic carbamate, the yield from enone 8 was unacceptable. This obstacle was alleviated when a two-step procedure was achieved. Reaction of **6** with 1.2 equiv of $NaN(TMS)_2$ at −35 °C followed by addition of 4 equiv of carbonyldiimidazole and stirring at room temperature for 18 h furnished the acyl imidazole **11a** in 82% isolated yield. The intermediate carbonate **7** that was formed undergoes eliminations forming the alkoxide of 8 which was trapped with excess carbonyldiimidazole. Reaction of **11a** with gaseous ammonia in acetonitrile at −40 °C produced the C-12 *O*-carbamate **11b**, which on treatment with potassium *tert*-butoxide in THF between −5 and 5 °C afforded the Michael addition product in 64% yield. This procedure produced *only one* stereoisomer which was identical (^1H and ^{13}C NMR, HPLC) in all respects with the cyclic carbamate **10** obtained by the reaction of chlorosulfonyl isocyanate and enone 8. Furthermore, reaction of **11a** with methylamine, propylamine, and benzylamine in 10% aqueous acetonitrile afforded the cyclic carbamates **12a–c** directly, without isolation of the C-12 *O*-carbamate intermediate (Scheme II). Again, only one stereoisomer was obtained in each example as judged by HPLC and NMR spectroscopy. The protecting groups were removed (methanol, 4 days, room temperature then H_2 Pd/C) and the 11-deoxy-11-(carboxyamino)-6-*O*-methylerythromycin A 11,12-(cyclic esters) **13a–d** were obtained. The mild reaction conditions needed to effect cyclization of the C-12 *O*-carbamates, especially the N-substituted examples, prompted us to explore the Michael reaction further.

The uncyclized *O*-carbamate **11b** was dissolved into either methanol, 10% aqueous acetonitrile, dimethylformamide, tetrahydrofuran, or dichloromethane at room temperature. HPLC analysis of each solvent system did

Scheme II[a]



[a] Reagents and conditions: (i) $NaN(TMS)_2$, −40 °C, carbonyldiimidazole, room temperature, 18 h; (ii) *t*-BuOK; (iii) RNH_2 aqueous CH_3CN, room temperatue; (iv) NH_3; (v) propylamine; (vi) methanol, room temperature; (vii) H_2, Pd/C.

not reveal any cyclization. However, when **11b** was stirred in THF at 0 °C and treated with sodium bis(trimethylsilyl)amide, sodium hydride, and potassium *tert*-butoxide, the cyclic carbamate **10** was formed. These results are consistent with the base-catalyzed mechanism of the Michael reaction. Next we studied the relative rate of the formation of the *N*-propyl cyclic 11,12-carbamate **12b** in different solvents. The relative rate of the reaction of **11a** with 5 equiv of propylamine at room temperature, as judged by HPLC, was ordered as follows: 10% aqueous acetonitrile ≃ dimethylformamide > acetonitrile > dichloromethane > tetrahydrofuran. When the cyclization was performed in tetrahydrofuran at 0 °C with the uncyclized propylcarbamate **11c** as substrate and 1.2 equiv of base for 1 h, the cyclization was complete with potassium *tert*-butoxide, sodium bis(trimethylsilyl)amide, and sodium hydride. Weaker bases such as 1,8-diazabicyclo[5.4.0]undec-7-ene and tetramethylguanidine in tetrahydrofuran at room temperature for 1 h afforded 75% and 10% yield of cyclized product **12b**. Triethylamine and propylamine as base catalysts produced no cyclization under these reaction conditions. Again, the cyclization of substituted *O*-carbamates was facilitated by bases and the reaction rate was enhanced with polar solvents. These observations suggested charge development in the transition state and the nucleophilic species is probably the imidate form of the carbamate.

Stereochemistry and Conformation

The stereochemical outcome at C-11 in the C-11/C-12 carbamate ring forming reaction is dictated by the lowest energy conformation of the 10,11-unsaturated ketone and

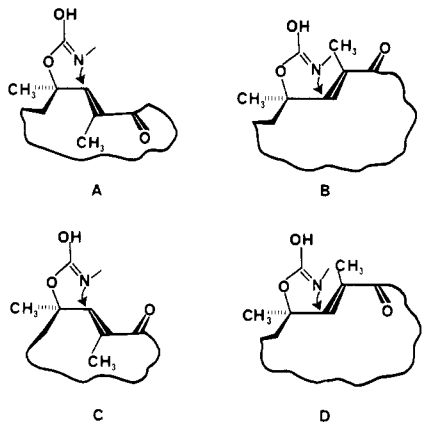


Figure 1. Four low energy conformations of the unsaturated ketone **11b** with calculated energies of (A) 58.8, (B) 52.3, (C) 56.6, and (D) 53.7 kcal/mol.

the C-12 appended *O*-carbamate. Conformers of the 10,11-unsaturated ketone were generated by selecting the 290 lowest energy conformations of erythromycin A by using the program RINGSEEK.[16] Forty-eight of these structures had conformational energy less than 10 kcal/mol above the minimum energy. These conformations were transformed into the 10,11-unsaturated ketone by deleting the C-10 proton and C-11 hydroxyl and the resulting geometries were minimized by MM2 calculations. from the 48 enone conformers, there exists 16 unique examples whose MM2 energy is within 5 kcal/mol from the minimum. these 16 are arranged into four categories (Figure 1). The lowest energy conformer in category B has a steric energy of 52.3 kcal/mol, while the lowest energy conformers in categories D, C, and A have steric energies of 53.7, 56.6, and 58.8 kcal/mol, respectively. Therefore, B is predicted to be the lowest energy conformer and attack by the *O*-carbamate produced the natural configuration at C-11.

The stereochemistry at C-10 was established by NMR spectroscopy. The ^1H and ^{13}C NMR spectra of **9** and **10** were unambiguously assigned through the use of two-dimensional homonuclear and heteronuclear correlation techniques. Outside of the expected changes in the chemical shifts at C-11, the ^1H and ^{13}C NMR spectra of **10** were virtually identical with those of the carbonate **7**. The extreme similarity between the ^{13}C NMR spectra of **7** and **10** (Table I) indicated that they have the same stereochemistry at C-10 and C-11 and the same conformation of the erythronolide ring. The chemical shift differences between **7** and **9** vary significantly, especially at C-10. The vicinal coupling constant between the protons on C-10 and C-11 was the same for **7** and **10** ($J \cong 0$ Hz). This pattern of similar chemical shifts and coupling constants was also observed for **12a**, **12b**, and **12c**. Therefore, by comparison to carbonate **7**, the intramolecular Michael reaction yielded the natural configuration at C-10 and C-11. At present, single-crystal X-ray analysis is being performed to unequivocally determine the absolute stereochemistry of the 11,12-cyclic carbamates.

Conclusion

We have developed an efficient and general route to 11-deoxy-11-carboxyamino)-6-*O*-methylerythromycin A 11,12-(cyclic esters). This approach featured a mild and stereoselective intramolecular Michael addition of *O*-carbamates to an α,β-unsaturated ketone. The Michael addition was the fastest when using strong bases in polar solvents. The reaction accommodated a variety of substituents on the nitrogen atom, thereby making the process useful for derivatization. It was also demonstrated that the cyclic carbamates **10** and **12** possess the natural configuration of erythromycin at C-10 and C-11. We are currently applying this methodology to the erythromycin A series (C-6, OH) and developing a structure–activity relationship of these novel macrolides.

Experimental Section

General. Melting points are uncorrected. Proton and carbon-13 NMR spectra were recorded on a General Electric Model QE 300 (300 MHz) or GN 500 (500 MHz) or Nicolet NT-360 (360 MHz) spectrometer. Mass spectral data were collected on a Kratos MS-50 spectrometer using fast atom bombardment techniques (FAB).

Silica gel chromatographic purifications were performed on either Woelm 32–63 μm silica gel supplied by Universal Scientific of Atlanta, GA, or Matrex silica chromatography medium 35–75 μm silica gel manufactured by Amicron Corporation of Danvers, MA. Compounds were eluted from the column according to the procedure of Still[17] or with gravity flow and with the solvent indicated. Fractions of 2 to 20 mL were taken with an automatic fraction collector and analyzed by thin-layer chromatography (TLC) on Merck glass plates precoated with 0.25 mm of GF-254 silica gel. Thin-layer chromatographs were developed by using 2–5% methanol in ethyl acetate for compounds **5–12** and 90:8:2 chloroform/methanol/concentrated ammonium hydroxide for compounds **3a–d**. Only one compound was detected when visualized with 1% ceric sulfate–2.5% ammonium molybate in 10% sulfuric acid solution. Some compounds after purification retained solvent as judged by NMR. Consequently, elemental analyses for those compounds had lower carbon percentages. Analytical high pressure liquid chromatography (HPLC) was conducted on a C-18 μ-Bondapak column (2 mm × 30 cm). The HPLC solvent was prepared by combining 650 mL of acetonitrile, 300 mL of water, 50 mL of methanol, 13.5 g of sodium acetate trihydrate, and 0.6 mL of glacial acetic acid. The eluent flow was monitored by a Waters Lamda-Max Model 481 spectrophotometer. Reagent grade solvents were filtered through a 45-μm Teflon-brand Millipore filter before use. Tetrahydrofuran (THF) was purified by distillation from sodium benzophenone ketyl. Acetonitrile, dichloromethane, and dimethylformamide (DMF) were distilled from calcium hydride and stored over 4-Å molecular sieves. 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) was distilled from potassium hydroxide. All other solvents were reagent grade. Sodium bis(trimethylsilyl)amide in tetrahydrofuran was obtained from the Aldrich Chemical Co. and titrated before use in THF using the yellow dianion of diphenylacetic acid as an end point indicator.

2′-*O*-Acetyl-6-*O*-methylerythromycin A (5). A solution of 6-*O*-methylerythromycin A (**2**) (100.4 g, 0.13 mol) and triethylamine (16.29 g, 0.16 mol) in 500 mL of dichloromethane was cooled in an ice–water bath. Acetic anhydride (27.4 g, 0.27 mol) was added to the solution, the bath was removed, and the reaction mixture was stirred for 5.5 h. A 500-mL solution of 0.5 M NaH_2PO_4 was added and the aqueous layer was separated. The aqueous phase was extracted (3 × 100 mL) with chloroform. The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give 94.8 g of crude product which was recrystallized from acetonitrile, affording 80.9 g (73%) of acetate **5**: mp 251–254 °C; $[\alpha]^{25}_D$ −234.4° (*c* 0.39, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 4.76 (dd, 1 H, J = 7.5 and 10.5 Hz, CHOAc), 3.37 (s, 3 H, C-3″ OCH_3), 3.02 (s, 3 H, C-6 OCH_3), 2.27 (s, 6 H, $N(CH_3)_2$), 2.06 (s, 3 H, $OCOCH_3$), 1.13 (s, 3 H, C-12 CH_3); ^{13}C NMR ($CDCl_3$) δ 221.09 (C-9), 175.6 (C-1), 169.9 ($OCOCH_3$), 71.8 (C-2′); MS, m/e $(M + H)^+$ 790.4964 (calcd for $C_{40}H_{72}NO_{14}$, 790.4952). Anal. Calcd for $C_{40}H_{72}NO_{14}$: C, 60.75; H, 9.11; N, 1.77. Found: C, 60.65; H, 8.93; N, 1.76.

2′-*O*-Acetyl-4″-*O*-(benzyloxycarbonyl)-6-*O*-methylerythromycin A (6). A solution of acetate **5** (80.13 g, 101.4 mmol)

(16) RINGSEEK is a computer program developed by the Computer Assisted Molecular Design department of Abbott Laboratories.

(17) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

and (dimethylamino)pyridine (DMAP) (49.55 g, 405.6 mmol) in 600 mL of dichloromethane was cooled to −40 °C with overhead stirring. Benzyl chloroformate (60.55 g, 354.9 mmol) was added at a rate to maintain the reaction temperature below −40 °C. After 1 h at −40 °C, the yellow slurry was warmed to −20 °C and kept at that temperature for 24 h. TLC (5% methanol in ethyl acetate) showed incomplete reaction. The reaction mixture was cooled again to −35 °C and 10 g (81.9 mmol) of DMAP and 11.8 g (67.4 mmol) of benzyl chloroformate were added. The reaction mixture was warmed to −20 °C and stirred for 48 h, and 300 mL of a 3% solution of sodium bicarbonate was added. The layers were separated and the organic layer was washed with water (3 × 150 mL) and dried ($MgSO_4$). The solvents were concentrated under reduced pressure and the residue was recrystallized from acetonitrile to give 81.72 g (87%) of the benzyl carbonate **6** as a white solid: mp 192–194 °C; $[\alpha]^{25}_D$ −216.2° (*c* 0.50, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.36 (s, 5 H, C_6H_5), 5.26 (d, 1 H, *J* = 12 Hz, $OCOCH_2Ph$), 5.13 (d, 1 H, *J* = 12 Hz, $OCOCH_2C_6H_5$), 4.48 (d, 1 H, *J* = 9.8 Hz, $CHOCO_2Bn$), 2.04 (s, 3 H, $OCOCH_3$), 1.12 ns, 3 H, C-12 CH_3); MS, *m/e* (relative intensity) 924 (M^+, 6), 200 (100). Anal. Calcd for $C_{48}H_{77}NO_{16}$: C, 62.38; H, 8.39; N, 1.51. Found: C, 62.23; H, 8.33; N, 1.44.

2′-*O*-Acetyl-4″-*O*-(benzyloxycarbonyl)-6-*O*-methylerythromycin A 11,12-Carbonate (7). A solution of 0.51 g (0.55 mmol) of diol **6** in 10 mL of THF at −35 °C was treated with 0.7 mL (0.6 mmol) of a 0.84 M sodium bis(trimethylsilyl)amide in THF. After 10 min, a solution of 0.33 g (2.0 mmol) of carbonyldiimidazole in 5 mL of THF was added. The reaction was warmed to room temperature and kept at that temperature for 15 min. The solution was cooled again to 0–5 °C (ice–water bath) and 0.5 M NaH_2PO_4 solution was added. The aqueous layer was extracted twice with ethyl acetate. The combined organic layers were dried ($MgSO_4$) and concentrated to a yellow oil. The residue was purified by flash chromatography using (1:1:.01) acetonitrile/CH_2Cl_2/concentrated ammonium hydroxide as eluent, affording 370 mg (70%) of carbonate **7**: mp 248–250 °C; IR ($CDCl_3$) 1800 (cyclic carbonate C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.35 (s, 5 H, C_6H_5), 5.25 (d, 1 H, *J* = 12 Hz, OCO_2CH_2Ph), 5.13 (d, 1 H, *J* = 12 Hz, OCO_2CH_2Ph), 4.60 (s, 1 H, C-11 CH), 3.33 (s, 3 H, C-3″ OCH_3), 2.97 (s, 3 H, C-6 OCH_3), 2.43 (m, 1 H, C-10 CH), 1.48 (s, 3 H, C-12 CH_3), 1.14 (d, 3 H, *J* = 7 Hz, C-10 CH_3); ^{13}C NMR ($CDCl_3$) 154.0 (C-11/C-12 carbonate C=O). Anal. Calcd for $C_{49}H_{75}NO_{17}$: C, 61.94; H, 7.95; N, 1.47. Found: C, 61.60; H, 8.21; N, 1.40.

2′-*O*-Acetyl-4″-*O*-(benzyloxycarbonyl)-10,11-didehydro-6-*O*-methylerythromycin A (8). A solution of carbonate **7** (2.67 g, 2.80 mmol) and DBU (5.0 mL) in 100 mL of benzene was heated at reflux temperature for 22 h, cooled to room temperature, and poured into a 0.5 M NaH_2PO_4 solution. The aqueous layer was extracted twice with ethyl acetate. The organic extracts were dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography using 10% methanol in dichloromethane to yield 2.54 g (94%) of **8** as a white solid: mp 103–107 °C; $[\alpha]^{25}_D$ −148.2° (*c* 0.41, $CHCl_3$); UV max (95% C_2H_5OH) 234 nm (ε 8915), 208 (12 286), 194 (2608); IR ($CDCl_3$) 1670 (unsaturated ketone C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.36 (s, 5 H, C_6H_5), 6.50 (s, 1 H, CH=CCO), 3.14 (s, 3 H, C-6 OCH_3), 2.02 (s, 3 H, $OCOCH_3$), 2.01 (s, 3 H, C-10 CH_3), 1.41 (s, 3 H, C-12 CH_3); ^{13}C NMR ($CDCl_3$) 207.5 (C-9), 175.3 (C-1), 169.8 ($OCOCH_3$), 155.4 (OCO_2Bn), 141.2 (C-11), 135.1 (C-10). Anal. Calcd for $C_{48}H_{75}NO_{15}$: C, 63.63; H, 8.35; N, 1.54. Found: C, 63.20; H, 8.65; N, 1.38.

Reaction of Chlorosulfonyl Isocyanate with Enone 8. To a solution of 3.44 g (3.8 mmol) of enone **8** in 100 mL of dry dichloromethane cooled in an ice–salt bath was added 733 mg (5.2 mmol) of chlorosulfonyl isocyanate. The reaction mixture was warmed to room temperature over 4 h. Another 733 mg (5.2 mmol) of chlorosulfonyl isocyanate was added and the reaction stirred an additional 1.5 h. A 0.5 M solution of NaH_2PO_4 was added to the cooled reaction mixture (0 °C). The organic layer was separated, washed with saturated sodium bicarbonate, dried ($MgSO_4$), and concentrated. The crude residue was purified by gravity silica gel chromatography using 5% methanol in chloroform as eluent. The first cyclic carbamate **9** was isolated in 4% yield (150 mg) as a yellow gum: ^1H NMR ($CDCl_3$) δ 7.36 (s, 5 H, C_6H_5), 5.95 (br s, 1 H, OCONH), 5.25 (d, 1 H, *J* = 12 Hz, $OCO_2CH_2C_6H_5$), 5.12 (d, 1 H, *J* = 12 Hz, $OCO_2CH_2C_6H_5$), 3.40 (br d, 1 H, *J* = 1 Hz C-11 CHN), 3.34 (s, 3 H, C-3″ OCH_3), 3.09 (s, 3H, C-6 OCH_3), 2.25 (s, 6H, $N(CH_3)_2$), 2.04 (s, 3H, $OCOCH_3$); MS, *m/e* (relative intensity) 949 (M^+, 71), 859 (23), 815 (11), 200 (100), 158 (28), 116 (25).

Carbamate **10** was eluted second and was obtained as a white solid: yield, 230 mg (6%); $[\alpha]^{25}_D$ −161.1° (*c* 0.22, $CHCl_3$); IR (CCl_4) 3200–3600 (carbamate NH); ^1H NMR ($CDCl_3$) δ 7.36 (s, 5 H, C_6H_5), 5.80 (s, 1 H, NH), 5.27 (d, 1 H, *J* = 12 Hz, $OCO_2CH_2C_6H_5$), 5.13 (d, 1 H, *J* = 12 Hz, $OCO_2CH_2C_6H_5$), 3.68 (s, 1 H, C-11 CHN), 3.33 (s, 3 H, C-3″ OCH_3), 2.92 (s, 3 H, C-6 OCH_3), 2.86 (m, 1 H, C-10 CH), 2.25 (s, 6 H, $N(CH_3)_2$), 2.05 (s, 3 H, $OCOCH_3$), 1.41 (s, 3 H, C-12 CH_3), 1.13 (d, 3 H, *J* = 7 Hz, C-10 CH_3). Anal. Calcd for $C_{49}H_{76}N_2O_{16}$: C, 61.95; H, 8.07; N, 2.95. Found: C, 61.56; H, 8.21; N, 2.62.

Acyl Imidazole 11a. To a solution of 5.36 g (5.79 mmol) of diol **6** in 50 mL of tetrahydrofuran cooled to −40 °C in a dry ice–acetone bath was added 6.95 mL (6.95 mmol) of 1 M sodium bis(trimethylsilyl)amide in tetrahydrofuran. After 2.5 h, 3.75 g (23.04 mmol) of carbonyldiimidazole in 55 mL of a 2:3 DMF/THF solution was added. The bath was removed and the reaction mixture stirred for 18 h. A solution of 0.5 M NaH_2PO_4 was added. The product was isolated by extraction of the reaction mixture with chloroform. Drying of the extracts with $MgSO_4$ and concentration gave the acyl imidazole. The crude product was purified by flash chromatography using 10% methanol in ethyl acetate. Evaporation of the solvent fractions afforded 4.76 g (82%) of acyl imidazole **11a**: mp 145–148 °C; $[\alpha]^{25}_D$ −163.4° (*c* 0.45, $CHCl_3$); UV max (95% C_2H_5OH) 230 nm (ε 13 437), 208 (17 634), 194 (3133); IR (KBr) 1675 (unsaturated carbonyl C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.08 (s, 1 H, imidazole), 7.37 (s, 6 H, C_6H_5, imidazole), 7.07 (s, 1 H, imidazole), 6.65 (br s, 1 H, CH=CCO), 5.82 (dd, 1 H, *J* = 3 and 10.5 Hz, C-13 CH), 5.26 (d, 1 H, *J* = 12 Hz, $OCO_2CH_2C_6H_5$), 5.14 (d, 1 H, *J* = 12 Hz, $OCO_2CH_3C_6H_5$), 3.34 (s, 3 H, C-3″ OCH_3), 3.13 (s, 3 H, C-6 OCH_3), 2.24 (s, 6 H, N-$(CH_3)_2$), 2.03 (s, 3 H, $OCOCH_3$), 1.85 (s, 3 H, C-10 CH_3); ^{13}C NMR ($CDCl_3$) 204.5 (C-9), 174.3 (C-1), 169.8 ($OCOCH_3$), 155.4 (OCO_2Bn), 145.7 (OCO imidazole) 138.6, 137.7, 136.9, 135.0, 130.7, 128.51, 128.49, 128.0, 117.03 (aromatic, C-10 and C-11). Anal. Calcd for $C_{52}N_{77}N_3O_{16}$: C, 62.45; H, 7.76; N, 4.20. Found: C, 62.26; H, 7.77; N, 3.93.

Cyclic Carbamate 11b. To a solution of 7.94 g (7.94 mmol) of acyl imidazole **11a** in 225 mL of acetonitrile at −40 °C was added 150 mL of ammonia. After stirring at −40 °C for 2.5 h, nitrogen gas was bubbled through the solution for 3 h to remove excess ammonia. The reaction mixture was concentrated under reduced pressure to give 7.12 g (90%) of a white amorphous solid. A 390-mg sample was purified by flash chromatography using 10% 2-propanol in ethyl acetate. A 350-mg sample of carbamate **11b** was obtained: mp 130–133 °C; $[\alpha]^{25}_D$ −125.1° (*c* 0.45, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.35 (s 5 H, C_6H_5), 6.64 (br s, 1 H, CH=CCO), 5.80 (dd, 1 H, *J* = 3 and 10.5 Hz, C-13 CH), 5.25 (d, 1 H, *J* = 12 Hz, $OCO_2CH_2C_6H_5$), 5.13 (d, 1 H, *J* = 12 Hz, $OCO_2CH_2C_6H_5$), 3.33 (s, 3 H, C-3″ OCH_3), 3.20 (s, 3 H, C-6 OCH_3), 2.23 (s, 6 H, N-$(CH_3)_2$), 2.00 (s, 3 H, $OCOCH_3$), 1.92 (s, 3 H, C-10 CH_3), 1.57 (s, 3 H, C-12 CH_3); ^{13}C NMR 206.0 (unsaturated ketone C-9), 174.4 (C-1), 169.7 ($OCOCH_3$), 155.5 ($OCO_2CH_2C_6H_5$), 154.2 ($OCONH_2$). Anal. Calcd for $C_{49}H_{76}N_2O_{16}$: C, 61.95; H, 8.07; N, 2.95. Found: C, 62.16; H, 8.14; N, 2.77.

Cyclic Carbamate 11c. To a solution of 620 mg (0.62 mmol) of acyl imidazole **11a** in 8.2 mL of dichloromethane at room temperature was added 110 mg (1.86 mmol) of propylamine. After being stirred for 1.5 h, the reaction mixture was concentrated and the residue was purified by flash chromatography using 10% methanol in ethyl acetate. The propyl carbamate was obtained as a tan solid: yield 540 mg (88%); mp 90–95 °C; $[\alpha]^{25}_D$ −136.9° (*c* 0.08, $CHCl_3$); ^1H NMR δ 7.35 (s, 5 H, C_6H_5), 6.68 (br s, 1 H, CH=CCO), 5.80 (dd, 1 H, *J* = 3 and 10.5 Hz, C-13 CH), 5.24 (d, 1 H, *J* = 12 Hz, $OCO_2CH_2C_6H_5$), 5.13 (d, 1 H, *J* = 12 Hz, $OCO_2CH_2C_6H_5$), 3.32 (s, 3 H, C-3″ OCH_3), 3.19 (s, 3 H, C-6 OCH_3), 2.23 (s, 6 H, $N(CH_3)_2$), 1.99 (s, 3 H, $OCOCH_3$), 1.88 (s, 3 H, C-10 CH_3), 1.54 (s, 3 H, C-12 CH_3); MS, *m/e* $(M + H)^+$ 991.5732 (calcd for $C_{52}H_{83}N_2O_{16}$ 991.5742).

2′-*O*-Acetyl-11-deoxy-11-(carboxyamino)-4″-*O*-(benzyloxycarbonyl)-6-*O*-methylerythromycin A 11,12-(Cyclic ester) (10). A solution of crude cyclic carbamate **11b** (7.82 g, 7.67 mmol) in 225 mL of THF was stirred and cooled to −5 °C. Potassium

tert-butoxide (1.0 g, 8.44 mmol) was added and the reaction mixture stirred for 30 min at 0 to 5 °C (ice–water bath). A solution of 250 mL of 0.5 M NaH_2PO_4 was added and the mixture extracted with two 100-mL portions of ethyl acetate. The combined extracts were dried ($MgSO_4$) and concentrated to give 6.83 g of a white solid. Purification of the crude Michael adduct by flash chromatography using 5% methanol in ethyl acetate gave 4.66 g (64%) of the cyclic carbamate: mp 261–263 °C dec; the ^1H NMR, ^{13}C NMR, MS, and TLC R_f value of the product are the same as diastereomer **10** produced from **8** and chlorosulfonyl isocyanate.

General Procedure for the Synthesis of N-Substituted Cyclic Carbamates. 2′-*O*-Acetyl-11-deoxy-11-(carboxymethylamino)-4″-*O*-(benzyloxycarbonyl)-6-*O*-methylerythromycin A 11,12-(Cyclic ester) (12a). To a solution of 255 mg (0.25 mmol) of acyl imidazole **11a** in 0.34 mL of 10% aqueous acetonitrile was added 0.11 mL (38.8 mg, (1.25 mmol) of 40% aqueous methylamine at 35 °C. After 2.5 h 15 mL of dichloromethane was added to the reaction mixture. The combined organic solvents were washed three times with 15 mL of 0.5 M NaH_2PO_4 solution, dried ($MgSO_4$), and concentrated to give a white amorphous solid. The product was purified by using 10% methanol in ethyl acetate by flash chromatography, affording 202 mg (84%) of the cyclic methylcarbamate (**12a**): mp 269–271 °C dec; $[\alpha]^{25}_D$ −165.2° (*c* 0.11 $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.36 (s, 5 H, C_6H_5), 5.26 (d, 1 H, J = 12 Hz, $OCO_2CH_2C_6H_5$), 5.13 (d, 1 H, J = 12 Hz, $OCO_2CH_2C_6H_5$), 3.53 (s, 1 H, C-11 CH), 3.33 (s, 3 H, C-3″ OCH_3), 3.08 (s, 3 H, $OCONCH_3$), 2.98 (s, 3 H, C-6 OCH_3), 2.25 (s, 6 H, $N(CH_3)_2$), 2.05 (s, 3 H, $OCOCH_3$), 1.39 (s, 3 H, C-12 CH_3); ^{13}C NMR ($CDCl_3$) 215.8 (C-9), 176.4 (C-1), 169.9 ($OCOCH_3$), 157.8 ($OCONCH_3$), 155.4 ($OCO_2CH_2C_6H_5$); MS, *m/e* $(M + H)^+$ 963.5415 (calcd for $C_{50}H_{79}N_2O_{16}$, 963.5429). Anal. Calcd for $C_{50}H_{79}N_2O_{16}$: C, 62.35; H, 8.76; N, 2.91. Found: C, 60.83; H, 8.11; N, 2.47.

2′-*O*-Acetyl-11-deoxy-11-(carboxypropylamino)-4″-*O*-(benzyloxycarbonyl)-6-*O*-methylerythromycin A 11,12-(cyclic ester) (12b) was prepared as above by using 255 mg (0.25 mmol) of acyl imidazole **11a**, 74 mg (0.1 mL, 1.25 mmol) of propylamine, and 0.34 mL of 10% aqueous acetonitrile. After 3.5 h, the product was isolated by flash chromatography using 5% methanol in ethyl acetate: yield 226 mg (91%); mp 208–211 °C dec; $[\alpha]^{25}_D$ −180.3° (*c* 0.06, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.36 (s, 5 H, C_6H_5), 5.26 (d, 1 H, J = 12 Hz, $OCO_2CH_2C_6H_5$), 5.13 (d, 1 H, J = 12 Hz, $OCO_2CH_2C_6H_5$), 3.62 (s, 1 H, C-11 CH), 3.34 (s, 3 H, C-3″ OCH_3), 3.00 (s, 3 H, C-6 OCH_3), 2.25 (s, 6 H, $N(CH_3)_2$), 2.05 (s, 3 H, $OCOCH_3$), 1.40 (s, 3 H, C-12 CH_3); ^{13}C NMR ($CDCl_3$) 216.0 (C-9), 176.1 (C-1), 169.9 ($OCOCH_3$), 157.4 (OCON), 155.5 ($OCO_2CH_2C_6H_5$). Anal. Calcd for $C_{52}H_{82}N_2O_{16}$: C, 62.96; H, 8.27; N, 2.82. Found: C, 62.81; H, 8.45; N, 2.80.

2′-*O*-Acetyl-11-deoxy-11-(carboxybenzylamino)-4″-*O*-(benzyloxycarbonyl)-6-*O*-methylerythromycin A 11,12-(cyclic ester) (12c) was prepared above by using 225 mg (0.25 mmol) of acyl imidazole **11a**, 137 mg (0.14 mL, 1.25 mmol) of benzylamine, and 0.34 mL 10% aqueous acetonitrile, reaction time 4.5 h. Flash chromatography on silica (5% methanol in ethyl acetate) gave 219 mg (84%) of the benzylcarbamate **12c**: mp 225–228 °C; $[\alpha]^{25}_D$ −178.3° (*c* 0.07, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.47–7.18 (m, 10 H, two C_6H_5), 5.25 (d, 1 H, J = 12 Hz, $OCO_2CH_2C_6H_5$), 5.12 nd, 1 H, J = 12 Hz, $OCO_2CH_2C_6H_5$), 3.57 (s, 1 H, C-11 CH), 3.32 (s, 3 H, C-3″ OCH_3), 3.12 (q, 1 H, J = 3.3 Hz, C-10 CH), 2.43 (s, 3 H, C-6 OCH_3), 2.24 (s, 6 H, $N(CH_3)_2$), 2.03 (s, 3 H, $OCOCH_3$), 1.44 (s, 3 H, C-12 CH_3); ^{13}C NMR ($CDCl_3$) 216.0 C-9), 175.2 (C-1), 169.9 ($OCOCH_3$), 157.7 (OCON), 155.4 ($OCO_2CH_2C_6H_5$). Anal. Calcd for $C_{56}H_{82}N_2O_{16}$: C, 64.72; H, 7.95; N, 2.70. Found: C, 65.03; H, 7.95; N, 2.56.

General Procedure for the Removal of the 2′-*O*-Acetyl and 4″-*O*-Benzyloxycarbonyl Protecting Groups. 11-Deoxy-11-(carboxyamino)-6-*O*-methylerythromycin A 11,12-(Cyclic ester) (13a). A solution of 1.2 g (1.26 mmol) of cyclic carbamate **10** in 100 mL of methanol was stirred at room temperature for 4 days. The solvent was removed under reduced pressure. The deacylated product was redissolved in 10 mL of methanol and submitted to hydrogenolysis conditions; 1.0 g of Pd/C at 4 atm for 2 h. The catalyst was filtered through a 45-μm Teflon-brand Millipore filter. The methanol was removed under high vacuum and the product purified by flash chromatography using (95:4:1) chloroform/methanol/concentrated ammonium hydroxide. The cyclic carbamate **13a** was obtained in 85% yield (830 mg) over the two steps: mp 161–163 °C dec; $[\alpha]^{25}_D$ −137.2° (*c* 0.08, $CHCl_3$); IR (KBr) 3700–3120 (br, OH), 1770 (ester C=O), 1740 (cyclic carbamate C=O), 1700 (ketone C=O); ^1H NMR ($CDCl_3$) δ 5.80 (s, 1 H, NH), 5.30 (dd, 1 H, J = 3 and 10.5 Hz, C-13 CH), 4.91 (d, 1 H, J = 4.5 Hz, C-1″ CH), 4.44 (d, 1 H, J = 7.5 Hz, C-1′ CH), 3.68 (s, 1 H, C-11 CH), 3.34 (s, 3 H, C-3″ OCH_3), 2.94 (s, 3 H, C-6 OCH_3), 2.38 (s, 6 H, $N(CH_3)_2$), 1.43 (s, 3 H, C-12 CH_3); ^{13}C NMR ($CDCl_3$) 218.1 (C-9), 176.7 (C-1), 158.3 (OCONH); MS, *m/e* $(M + H)^+$ 773.4789 (calcd for $C_{39}H_{69}N_2O_{13}$, 773.4799). Anal. Calcd for $C_{39}H_{69}N_2O_{13}$: C, 60.60; H, 8.87; N, 3.62. Found: C, 57.24; H, 8.30; N, 3.05.

11-Deoxy-11-(carboxymethylamino)-6-*O*-methylerythromycin A 11,12-(cyclic ester) (13b) was prepared as above by using 135 mg (0.14 mmol) of carbamate cyclic **12a**, 20 mL of methanol, 118 mg Pd/C, and 20 mL of methanol. The product was isolated by flash chromatography: yield 80 mg (73%); mp 258–261 °C dec; $[\alpha]^{25}_D$ −170.1° (*c* 0.005, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 4.96 (dd, 1 H, J = 3 and 10.5 Hz, C-13 CH), 4.91 (d, 1 H, J = 4.5 Hz, C-1″ CH), 4.44 (d, 1 H, J = 7.5 Hz, C-1′ CH), 3.55 ns, 1 H, C-11 CH), 3.33 (s, 3 H, C-3″ OCH_3), 3.10 (s, 3 H, $OCONCH_3$), 3.02 (s, 3 H, C-6 OCH_3), 2.32 (s, 6 H, $N(CH_3)_2$), 1.41 (s, 3 H, C-12 CH_3); ^{13}C NMR ($CDCl_3$) 215.7 (C-9), 176.7 (C-1), 157.7 ($OCONCH_3$); MS, *m/e* $(M + H)^+$ 787.4937 (calcd for $C_{40}H_{71}N_2O_{13}$, 787.4956). Anal. Calcd for $C_{40}H_{71}N_2O_{13}$: C, 61.05; H, 8.97; N, 3.56. Found: C, 58.88; H, 9.09; N, 3.39.

11-Deoxy-11-(carboxypropylamino)-6-*O*-methylerythromycin A 11,12-(cyclic ester) (13c) was prepared as by using 540 mg (0.54 mmol) of cyclic carbamate **12b**, 25 mL of methanol, 440 mg Pd/C, and 50 mL of methanol. Chromatography gave 270 mg (60%) of cyclic carbamate **13c**: mp 231–234 °C dec; $[\alpha]^{25}_D$ −177.8° (*c* 0.16, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 4.98 (dd, 1 H, J = 3 and 10.5 Hz, C-13 CH), 4.89 (d, 1 H, J = 4.5 Hz, C-1″ CH), 4.44 (d, 1 H, J = 7.5 Hz, C-1′ CH), 3.63 (s, 1 H, C-11 CH), 2.38 (s, 6 H, $N(CH_3)_2$), 1.38 (s, 3 H, C-12 CH_3); ^{13}C NMR ($CDCl_3$) 215.9 (C-9), 176.4 (C-1), 157.3 ($OCONC_3H_7$); MS, *m/e* $(M + H)^+$ 815.5260 (calcd for $C_{42}H_{75}N_2O_{13}$, 815.5269). Anal. Calcd for $C_{42}H_{75}N_2O_{13}$: C, 61.89; H, 9.15; N, 3.44. Found: C, 60.28; H, 9.06; N, 3.19.

11-Deoxy-11-(carboxybenzylamino)-6-*O*-methylerythromycin A 11,12-(cyclic ester) (13d) was prepared as above by using 500 mg (0.48 mmol) of cyclic carbamate **12c**, 25 mL of methanol, 480 mg Pd/C, and 50 mL of methanol. Chromatography afforded 380 mg (71%) of cyclic carbamate **13d**: mp 252–255 °C dec; $[\alpha]^{25}_D$ −187.1° (*c* 0.19, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 5.00 (d, 1 H, J = 3 and 10.5 Hz, C-13 CH), 4.89 (d, 2 H, J = 6 H, $C_6H_5CH_2N$), 3.59 (s, 1 H, C-11 CH), 3.31 (s, 3 H, C-3″ OCH_3), 2.47 (s, 3 H, C-6 OCH_3), 2.27 (s, 6 H, $N(CH_3)_2$), 1.40 (s, 3 H, C-12 CH_3); ^{13}C NMR ($CDCl_3$) 215.9 (C-9), 175.4 (C-1), 157.7 ($OCONCH_2C_6H_5$); MS, *m/e* $(M + H)^+$ 863.5272 (calcd for $C_{46}H_{75}N_2O_{13}$, 863.5269). Anal. Calcd for $C_{46}H_{75}N_2O_{13}$: C, 64.01; H, 8.64; N, 3.25. Found: C, 62.48; H, 8.61; N, 3.03.

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Registry No. **2**, 81103-11-9; **5**, 103461-66-1; **6**, 113777-91-6; **7**, 113792-83-9; **8**, 113777-92-7; **9**, 113777-93-8; **10**, 113830-15-2; **10** (deacylated), 113778-00-0; **11a**, 113777-94-9; **11b**, 113777-95-0; **11c**, 113777-96-1; **12a**, 113777-97-2; **12b**, 113777-98-3; **12c**, 113777-99-4; **13a**, 113778-01-1; **13b**, 113778-02-2; **13c**, 113778-03-3; **13d**, 113792-84-0; $ClSO_2NCO$, 1189-71-5; $PrNH_2$, 107-10-8.