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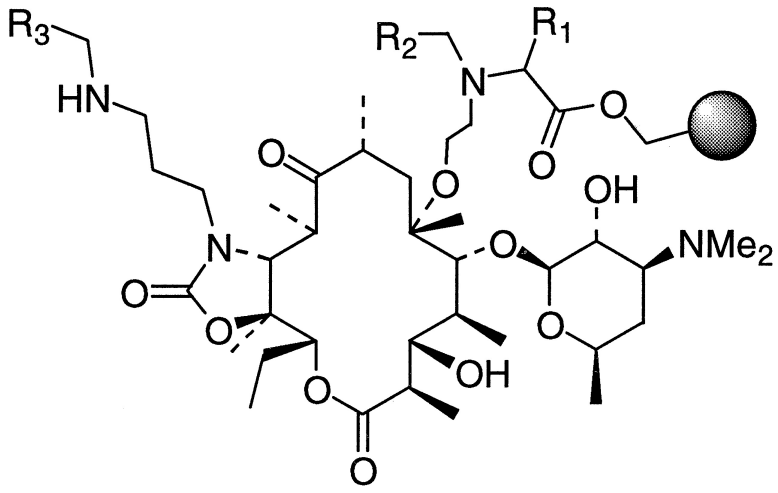

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Solid-Phase Synthesis of Macrolide Analogues

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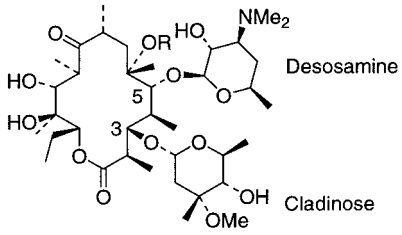
The synthesis of a solid-phase macrolide library is described. The library introduces three sites of diversity to a suitable macrolide scaffold via reductive aminations.

As a part of a lead discovery program at Abbott Labs, we have developed an efficient synthesis of a solid-phase macrolide combinatorial library. To our knowledge, this is the first example of a library that employs the macrolide core as a template for combinatorial synthesis.

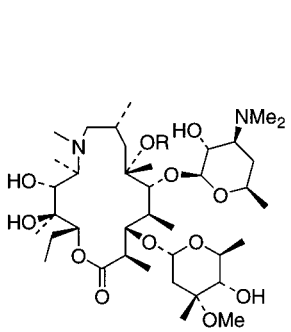
Macrolides are a class of antibiotic compounds that contain a large lactone (macro-olide) ring of 12 to 16 atoms and several sugars linked to the lactone ring. Macrolides have been extensively used, over the past 40 years, for the treatment of upper and lower respiratory tract infections and are considered to be very well tolerated and safe. Among them, erythromycin A (Ery-A), **1**, is the oldest and most widely used, especially against Gram-positive bacteria and *Mycoplasma pneumoniae*.



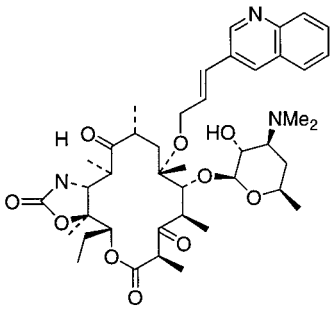
1 R = H Erythromycin A

2 R = Me Clarithromycin

Erythromycin A was first isolated[1] in 1952 from *Streptomyces erythreus*, and its structure[2] and absolute stereochemistry[3] were elucidated a few years later. It consists of a 14-membered lactone ring (erythronolide) and two sugars, cladinose and desosamine, glycosidically attached to C-3 and C-5 of the erythronolide ring, respectively. Although erythromycin A is an extremely important antibiotic with high efficacy and low toxicity, its structure has been heavily modified in search of derivatives with broad spectrum activity and bioavailability. Erythromycin A is unstable under the acidic conditions of the stomach, rendering degradation products that are inactive and cause gastrointestinal discomfort. Structural modifications of the erythromycin structure resulted in acid stable derivatives clarithromycin (Biaxin) **2** and azithromycin (Zithromax) **3**.[4] These compounds showed better bioavailability, tissue penetration (distribution), and potency, and they are the most commercially successful second-generation erythromycin analogues. A third-generation of macrolide antibiotics with increased activity against macrolide resistant organisms is currently under development.[5] Abbott's clinical candidate ABT-773[6] **4** exemplifies this class of compounds (ketolides) that are 11,12-carbamate Ery-A derivatives with a ketone at C-3 instead of the cladinose sugar. ABT-773 showed increased activity against inducible and constitutive resistant strains and *Haemophilus influenzae*.



3 Azithromycin



4 ABT-773

While yet a fourth generation of powerful antibacterial candidates is emerging, macrolides have been also considered for other uses such as in the areas of gastroenterology, rheumatology, cardiology, and cancer.[7] Thus, we envisioned a large macrolide combinatorial library that could be used for general screening.

Confronted with a molecule of such complexity, there were many factors involved in the selection of an appropriate core. The core had to be accessible from easily available starting materials, tolerant to reaction conditions on solid phase and to monomer diversity, stable to cleavage conditions, and able to accommodate at least three sites of diversity. Additionally, we wanted to limit the strong antibacterial activity inherited with the macrolide structure by designing a core that is expected to have marginal antibacterial potency.

We have decided to use aldehyde **5** (Figure 1) as an appropriate core that would fulfill the above-mentioned criteria. The core can be obtained in seven steps from 6-*O*-allyl-erythromycin A,[9] an intermediate in the synthesis of ABT-773, and is accessible in large quantities. Since most of the synthetic efforts in the area have been focused on modifications of the main macrolide ring and/or the sugars, we decided to introduce our diversity at remote sites that

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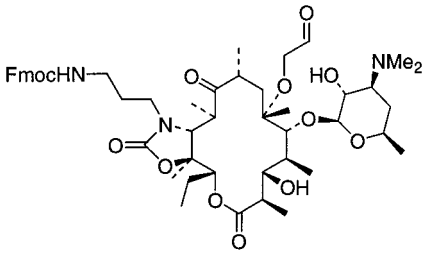


5

Figure 1.

would cover a wider area in space. We have also eliminated the cladinose sugar as it would be too unstable under cleavage conditions. Finally, to limit the antibacterial activity of our library, the 3-OH group was chosen instead of the 3-ketone.[8]

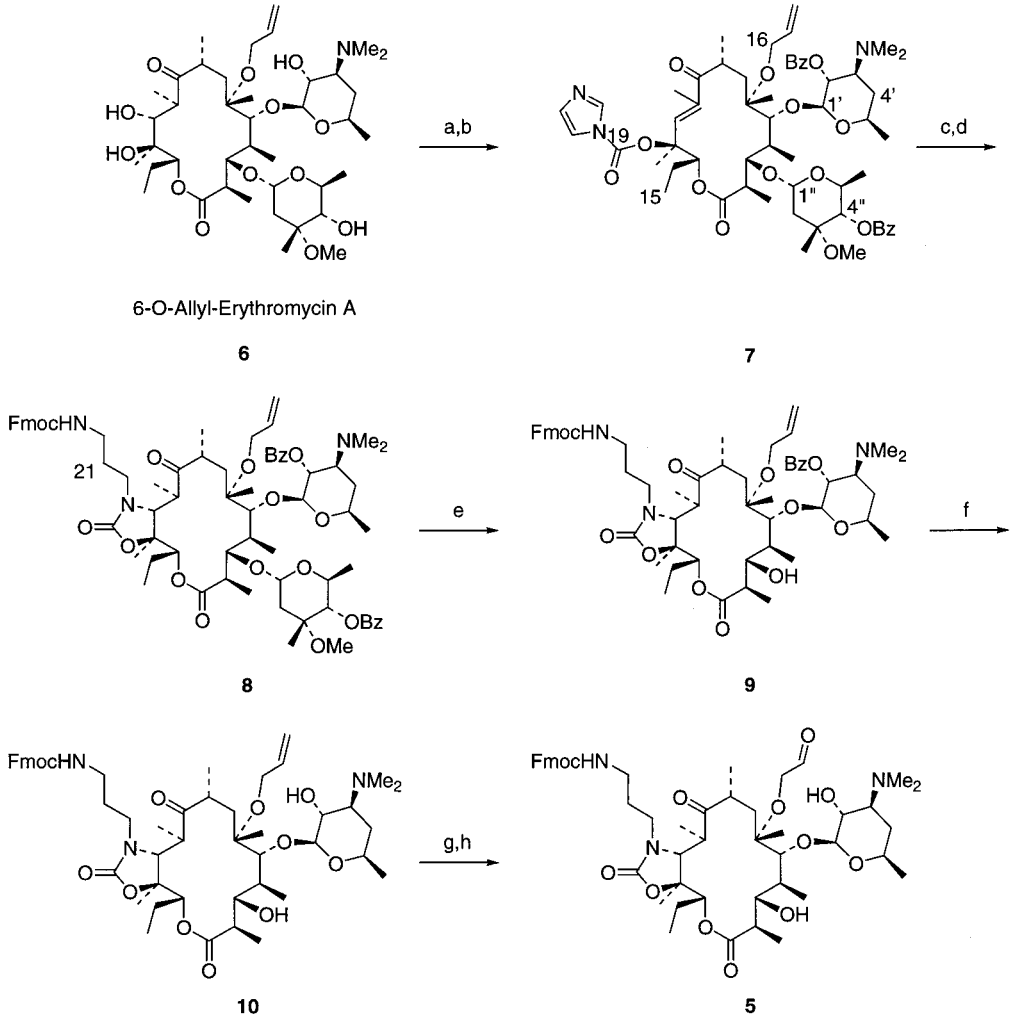
Results and Discussion

The core synthesis (Scheme 1) started with 6-*O*-allyl-erythromycin A (**6**) prepared in three steps from erythromycin A.[9] Benzoylation of **6** proceeded only on the sugar hydroxy groups, leaving the 11-OH and 12-OH free. Subsequent reaction with carbonyldiimidazole and sodium hexamethyldisilazide resulted in elimination of 11-OH and formation of the 12-*O*-acylimidazolide **7**. Heating of **7** with excess 1,3-diaminopropane, followed by Fmoc protection of the free amino group, yielded cyclic carbamate **8**. Finally, hydrolysis of the cladinose sugar with a 1:1 mixture of 1 N aqueous HCl/MeOH at 55 °C gave des-cladinose compound **9** in 55% overall yield starting from **6**. The formation of 10,11-cyclic carbamates of erythromycin A has been reported before to proceed with retention of the configuration at C-10.[10,11] We have observed similar results based on ^{1}H NMR chemical shifts and NOE experiments.

To complete the core synthesis, the 2′-OH group was deprotected and the resulting carbamate **10** was subjected to ozonolysis. Ozonolysis cleaved the allylic double bond as expected, but it also oxidized the amino group of desosamine to the corresponding *N*-oxide. Treatment with triphenylphosphine reduced the *N*-oxide back to the amine, and the desired aldehyde **5** was isolated as a stable solid that can be stored at −20 °C for months without significant decomposition.

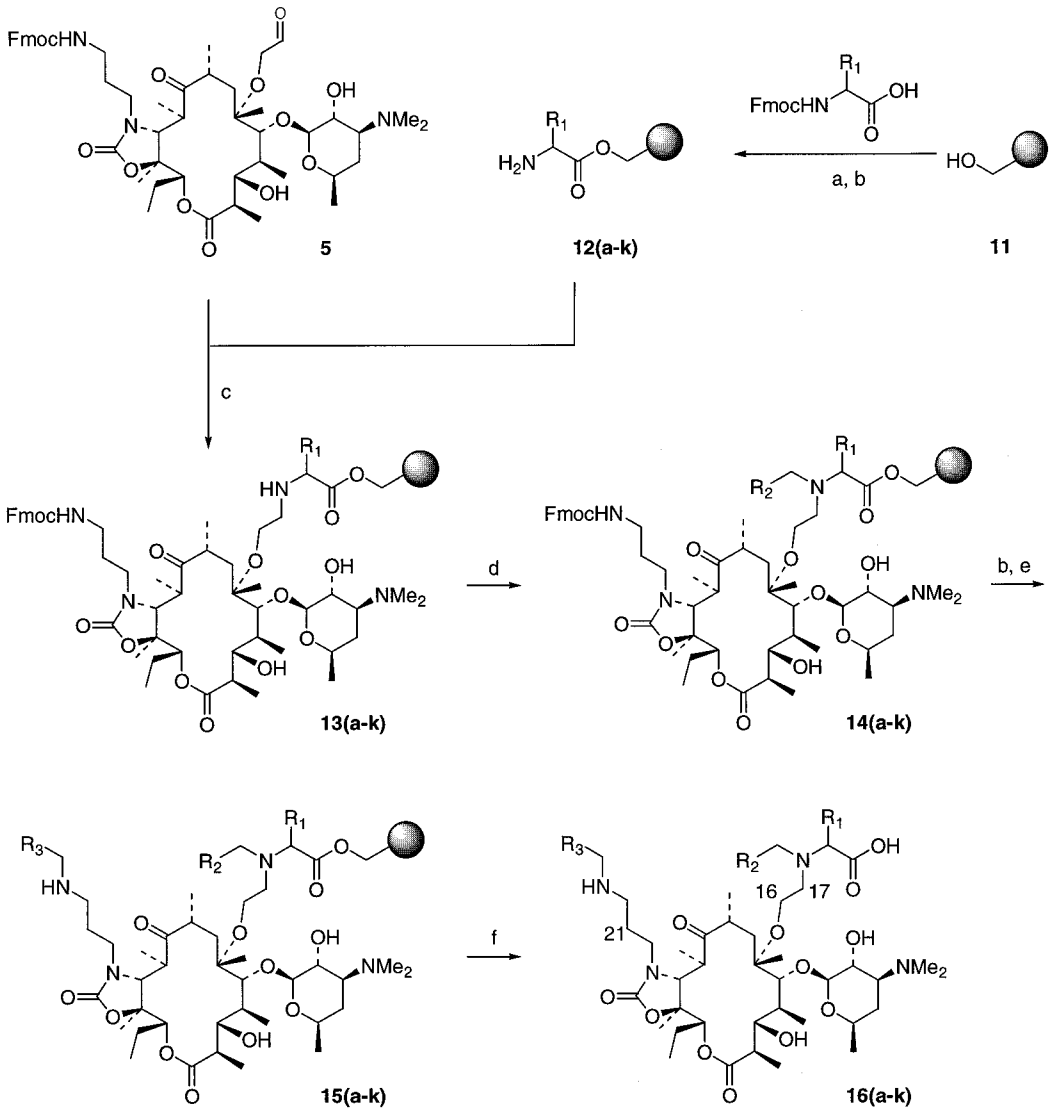
For the library synthesis we used aminonomethylpolystyrene resin containing a fluorine tag[12] and an extended

Scheme 1[a]



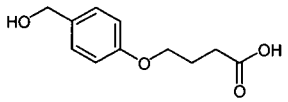
[a] Reagents and conditions: (a) Bz_2O, Et_3N, DMAP, CH_2Cl_2; (b) CDI, $NaN(TMS)_2$, THF/DMF; (c) 1,3-diaminopropane, MeCN, 70 °C; (d) Fmoc-Cl, py, CH_2Cl_2; (e) 1 N aqueous HCl/EtOH, 1:1 ratio, 55 °C; (f) MeOH, 55 °C; (g) O_3, CH_2Cl_2, −78 °C, Me_2S, −78 °C to 0 °C; (h) PPh_3, THF, 70 °C.

Scheme 2[a]



[a] Reagents and conditions: (a) DIC, DMAP, CH_2Cl_2/THF; (b) 20% piperidine/DMF, two times; (c) 10% AcOH/DMF, wash, $NaCNBH_3$, 10% AcOH/DMF; (d) R_2CHO, 10% AcOH/DMF, $NaCNBH_3$; (e) R_3CHO, 10% AcOH/DMF, wash, $NaCNBH_3$, 10% AcOH/DMF; (f) 90% TFA/CH_2Cl_2.

modified Wang type linker (structure shown below) prepared

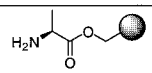
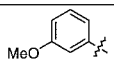
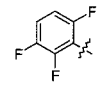
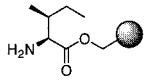
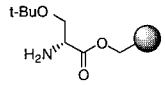
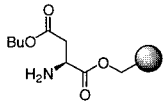
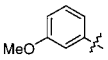
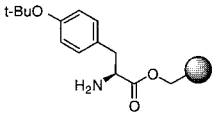
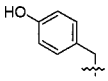
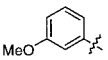
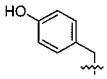
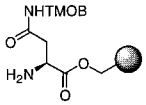


from methyl-4-bromobutyrate and 4-hydroxybenzyl alcohol upon treatment with Cs_2CO_3 and subsequent ester hydrolysis with LiOH. The resulting resin **11** (Scheme 2) was treated twice with an Fmoc-protected amino acid to introduce the first site of diversity in order to obtain sufficient loading. The Fmoc group was then removed, and the macrolide core **5** was loaded on the resin via a reductive alkylation of the free amine **12**. The resulting secondary amine **13** was reacted with aldehydes as the second diversity site. It was found[13] that only aliphatic aldehydes with a methylene or an aliphatic cyclic group next to the carbonyl could react in satisfactory yields with any amino acid. Aromatic aldehydes afforded low yields with unhindered amino acids and did not react at all with bulky ones. The third site of diversity was again introduced via a reductive alkylation of the tethered primary amine with an aromatic aldehyde. Aliphatic aldehydes also work, but the products are accompanied by bis-addition byproducts. The final product **15** was cleaved from the resin using 95% TFA/CH_2Cl_2. The cleaved products **16** were isolated as TFA salts after high-throughput HPLC purification using 0.1% aqueous TFA/MeCN gradient. Table 1 summarizes representative examples of the above synthetic sequence.

It should be noted that the above methodology was developed for the production of a large mix and split combinatorial library of about 70 000 members. The Fmoc groups were very important in assisting with quantitation experiments to determine loading after each step of the synthesis. Reaction completion was determined by ninhydrin tests on the mixtures.

With the exception of proline and tryptophan, all other commercially available Fmoc-protected amino acids have been evaluated, and most of them, upon loading to the resin and deprotection of the Fmoc group, readily participated in

Table 1. Solid-Phase Synthesis of Macrolide Analogues

Resin	Structure	Loading (mmol/g)[a]	Cleaved Compound	R1	R2	R3	# of TFA salts	Purity[b]	Yield[c]
12a		0.54	**16a**				4	57 %	9 %
12b	”	0.54	**16b**				4	54 %	17 %
12c		0.59	**16c**				4	90 %	15 %
12d	”	0.59	**16d**				4	61 %	19 %
12e		0.6	**16e**				5	90 %	9 %
12f		0.48	**16f**				4	100 %	23 %
12g	”	0.48	**16g**				4	90 %	18 %
12h		0.58	**16h**				4	100 %	21 %
12i	”	0.58	**16I**				4	100 %	19 %
12j		0.32	**16j**				6	100 %	33 %
12k	”	0.32	**16k**				6	100 %	31 %

[a] Loadings are based on Fmoc quantitation tests of the resin-loaded Fmoc-protected amino acids. [b] Purity of crude compounds cleaved of the resin are based on analytical HPLC with ELSD detection. [c] Overall yield starting from resin **12** after HT-HPLC purification. Yields were determined based on Fmoc loadings of resins **12**.

the reductive amination of the macrolide core. Functional groups on the amino acids were protected with TFA cleavable protecting groups. Serine, threonine, and tyrosine were protected with the *tert*-butyl group; asparagine and glutamine were protected with the TMOB (trimethoxybenzyl) group, aspartic acid with the *n*-butyl group, histidine with the DNP (dinitrophenyl) group. However, we were not successful in deprotecting *tert*-butyl cysteine with TFA.

For the second reductive alkylation, most commercially available aliphatic aldehydes have been evaluated. The diversity on this site was somewhat limited due to steric hindrance. Any α-hydroxylated, α-branched (with the exception of simple cyclic rings), or conjugated acetylenic aldehydes did not participate in the reaction. Most conjugated or unconjugated double bonds were reduced at variable rates. Aromatic aldehydes reacted sluggishly or not at all depending on the bulkiness of the amino acid group. However, when the aromatic ring was moved one or more carbons away from the carbonyl group, the reaction proceeded well. Similarly, hydroxy groups on positions other than α to the carbonyl were well tolerated.

The third site was populated by reductive alkylations with aromatic aldehydes. The reaction tolerated a variety of substituted aromatic and also heterocyclic aldehydes, including furfurals, thiophene-carboxaldehydes, and helicin (a carbohydrate-substituted aromatic aldehyde). The only notable exception was pyrroles, although indoles provided the desired product.

Experimental Section

All reactions were performed in dried flasks under N_2. Anhydrous dichloromethane, THF, and DMF were purchased from Aldrich. The solid-phase reactions were carried in glass peptide tubes pretreated with Sigmacote. All ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker 500 MHz and 400 MHz instruments.

For peak assignment numbers, see Schemes 1 and 2. The following system was used for the branches. AA (amino acid) refers to the amino acid R1, starting with the acid carbon as number 1. AL (aliphatic aldehyde) refers to branch R2, starting the numbering from the carbon attached to the amine. AR (aromatic aldehyde) refers to branch R3, starting the numbering from the carbon attached to the amine.

Fmoc Quantitation. Resin loading was determined by exact weighting of 2−5 mg of resin, treating it with 0.4 mL of piperidine and 0.4 mL of CH_2Cl_2 for 10 min, then bringing

the volume up to 10 mL with CH_2Cl_2, and measuring the UV absorption at 301 nm. The loading was calculated based on the following equation:

$$\text{loading (mmol/g of resin)} = (A_{301\text{nm}} \times 10\ \text{mL})/(7800 \times \text{grams of resin})$$

Ninhydrin Test. A total of 2−5 mg of resin was subsequently treated with 75 μL of monitor 1 (purchased from Perkin-Elmer, 76 w/w phenol/ethanol), 100 μL of monitor 2 (0.0002 M potassium cyanide/pyridine), and 0.75 μL of monitor 3 (0.28 M ninhydrin/pyridine). The mixture was heated at 100 °C for 5 min. Dark blue beads and solution indicate the presence of a primary amine (positive test).

2′,4″-Di-*O*-benzoyl-6-*O*-allyl-erythromycin A. 6-*O*-Allyl-erythromycin A **6** (10 g,12.9 mmol) was dissolved in CH_2Cl_2 (100 mL) and treated with benzoylanhydride (8.1 g, 32.3 mmol), triethylamine (3.6 mL, 25.8 mmol), and DMAP (1.6 g, 12.9 mmol). The mixture was allowed to stir for 2 days and then the solvent was removed. The crude mixture was redissolved in a small amount of CH_2Cl_2, loaded to a column (silica gel), and eluted with 50% ethyl acetate/hexanes to give a white foamy solid. MS (ESI): *m*/*z* 982 [M + 1]. ^{1}H NMR ($CDCl_3$): δ (ppm) 8.03 (m, 2H, H-8″, Bz), 8.03 (m, 2H, H-8′, Bz), 7.60 (m, 1H, H-10″, Bz), 7.57 (m, 1H, H-10′, Bz), 7.46 (m, 2H, H-9″, Bz), 7.45 (m, 2H, H-9′, Bz), 5.88 (m, 1H, H-17), 5.14 (dd, J = 17.2 Hz, J = 1.5 Hz, 1H, H-18b), 5.10 (m, 1H, H-18a), 5.08 (m, 1H, H-13), 5.07 (m, 1H, H-2′), 5.03 (m, 1H, H-1″), 4.99 (d, J = 7.6 Hz, 1H, H-1′), 4.94 (d, J = 9.5 Hz, 1H, H-4″), 4.48 (m, 1H, H-5″), 3.94 (dd, J = 11.4 Hz, J = 5.4 Hz, 1H, H-16b), 3.92 (m, 1H, H-5′), 3.83 (dd, J = 11 Hz, J = 7.4 Hz, 1H, H-16a), 3.73 (m, 1H, H-5), 3.71 (m, 1H, H-3), 3.62 (bs, 1H, H-11), 3.57 (brs, 1H, 11-OH), 3.55 (s, 3H, 3″-OMe), 3.08 (brs, 1H, 12-OH), 2.99 (m, 1H, H-10), 2.96 (m, 1H, H-3′), 2.85 (m, 1H, H-2), 2.59 (m, 1H, H-8), 2.49 (d, J = 15 Hz, 1H, H-2″b), 2.33 (s, 6H, 3′-NMe), 1.90 (m, 1H, H-4), 1.88 (m, 1H, H-14b), 1.76 (dd, J = 15.4 Hz, J = 5.1 Hz, 1H, H-2″a), 1.72 (m, 1H, H-4′b), 1.70 (m, 1H, H-7b), 1.53 (d, J = 13.9 Hz, 1H, H-7a), 1.41 (s, 3H, 6-Me), 1.39 (m, 1H, H-14a), 1.36 (m, 1H, H-4′a), 1.23 (s, 3H, 3″-Me), 1.21 (m, 3H, 5″-Me), 1.21 (m, 3H, 2-Me), 1.13 (d, J = 7.0 Hz, 3H, 8-Me), 1.09 (d, J = 6.9 Hz, 3H, 10-Me), 1.03 (s, 3H, 12-Me), 0.93 (d, J = 5.9 Hz, 3H, 5′-Me), 0.80 (t, J = 7.4 Hz, H-15), 0.76 (d, J = 7.7 Hz, 3H, 4-Me). ^{13}C NMR ($CDCl_3$): δ (ppm) 219.9 (C-9), 174.9 (C-1), 166.1 (C-6″, Bz), 165.5 (C-6′, Bz), 135.8 (C-17), 133.3 (C-10″, Bz), 132.6 (C-10′, Bz), 130.9 (C-7′, Bz), 129.9 (C-7″, Bz), 129.6 (C-8′, Bz), 129.6 (C-8″, Bz), 128.4 (C-9″, Bz), 128.2 (C-9′, Bz), 116.8 (C-18), 99.8 (C-1′), 96.1 (C-1″), 80.0 (C-5), 79.2 (C-6), 78.8 (C-4″), 78.5 (C-3), 76.3 (C-13), 74.4 (C-12), 73.0 (C-3″), 72.6 (C-2′), 68.5 (C-11), 67.4 (C-5′), 65.7 (C-16), 63.87 (C-5″), 63.7 (C-3′), 49.5 (3″-OMe), 45.4 (C-8), 44.4 (C-2), 40.9 (3′-NMe), 37.9 (C-4), 37.7 (C-7), 37.5 (C-10), 35.4 (C-2″), 31.7 (C-4′), 21.3 (5′-Me), 21.2 (C-14), 21.1 (6-Me), 18.5 (5″-Me), 18.4 (8-Me), 16.3 (12-Me), 16.0 (2-Me), 12.3 (10-Me), 10.5 (C-15), 9.4 (4-Me).

12-*O*-Acyl-Imidazolide 7. 2′,4″-Di-*O*-benzoyl-6-*O*-allyl-erythromycin from above was dissolved in a 2:1 mixture of THF/DMF (130 mL), and CDI (8.4 g, 51.7 mmol) was added at once into the solution. Sodium hexamethyldisilazide (1 M in THF, 18.1 mL, 18.1 mmol) was then added slowly. The reaction mixture became viscous, and TLC showed almost immediate disappearance of starting material and formation of the intermediate cyclic 10,11-*O*-carbonate (R_f = 0.5, 50% acetone/hexanes). Upon stirring for 24 h, TLC showed formation of the desired product (R_f = 0.3, 50% acetone/hexanes). The reaction was quenched with water and extracted three times with ethyl acetate. The organic layer was washed with brine and dried over Na_2SO_4. The solution was condensed, loaded on a column, and eluted with plain ethyl acetate to yield a pale yellow-white glassy solid.

2′,4″-Di-*O*-benzoyl-11-deoxy-11-(3-aminopropanylamino)-11,12-carbamate-6-*O*-allyl-erythromycin A. Imidazolide **7** was dissolved in MeCN (70 mL) and added to a solution of 1,3 diaminopropane (21.6 mL, 258.4 mmol) in MeCN (180 mL). The mixture was heated at 70 °C for 1 h, and the excess diamine and the solvent were removed by heating at 70 °C under vacuum for 5 h with occasional redissolving in CH_2Cl_2 to release diamine trapped in the glassy solid. The resulting solid was further pumped overnight at room temperature to remove traces of diamine, and it was then subjected to the next reaction.

2′,4″-Di-*O*-benzoyl-11-deoxy-11-(3-*N*-Fmoc-aminopropanylamino)-11,12-carbamate-6-*O*-allyl-erythromycin A (8). The amine obtained in the previous step was dissolved in CH_2Cl_2 (250 mL), and to that were added, in two portions, pyridine (4.2 mL, 51.6 mmol) and Fmoc-Cl (6.6 g, 25.8 mmol). After 1 h, the crude mixture was loaded on a column and eluted with plain ethyl acetate to give a white solid, which was used for the following step.

2′-*O*-Benzoyl-11-deoxy-11-(3-*N*-Fmoc-aminopropanylamino)-11,12-carbamate-6-*O*-allyl-3-hydroxy-erythronolide A (9). The Fmoc-protected amine **8** was dissolved in EtOH (125 mL), and the resulting solution was treated with 1 N aqueous HCl (125 mL) for 9 h at 55 °C. The reaction mixture was poured into saturated aqueous $NaHCO_3$ until the pH was greater than 8, and the product was extracted with CH_2Cl_2 and purified by column chromatography with plain ethyl acetate as the eluent to obtain a white solid (7.3 g, 55% overall yield for five steps). MS (ESI): *m*/*z* 1024 [M + 1]. ^{1}H NMR ($CDCl_3$): δ (ppm) 8.07 (m, 2H, H-8′, Bz), 7.75 (d, J = 7.5 Hz, 2H, H-30, Fmoc), 7.63 (m, 2H, H-27, Fmoc), 7.57 (m, 2H, H-10′, Bz), 7.45 (m, 2H, H-9′, Bz), 7.38 (m, 2H, H-29, Fmoc), 7.30 (m, 2H, H-28, Fmoc), 5.75 (m, 1H, H-17), 5.62 (brt, 1H, 22-NH), 5.15 (d, J = 17.2 Hz, 1H, H-18b), 5.04 (m, 1H, H-18a), 5.03 (m, 1H, H-2′), 4.98 (m, 1H, H-13), 4.78 (d, J = 7.5 Hz, 1H, H-1′), 4.36 (m, 1H, H-24b, Fmoc), 4.33 (m, 1H, H-24a, Fmoc), 4.21 (m, 1H, H-25, Fmoc), 3.82 (m, 1H, H-16b), 3.79 (m, 1H, H-5), 3.76 (m, 1H, H-16a), 3.60 (m, 2H, H-20), 3.56 (m, 1H, H-5′), 3.56 (bs, 1H, H-11), 3.41 (m, 1H, H-3), 3.35 (m, 1H, H-22b), 3.11 (m, 1H, H-22a), 3.01 (m, 1H, H-10), 2.89 (m, 1H, H-3′), 2.62 (m, 1H, H-8), 2.61 (m, 1H, H-2), 2.28 (s, 6H, 3′-NMe), 2.12 (d, J = 6.2 Hz, 1H, 3-OH), 1.91 (m, 1H, H-4), 1.89 (m, 1H, H-14b), 1.83 (m, 1H, H-21b), 1.79 (m, 1H, H-4′b), 1.77 (m, 1H, H-21a), 1.63 (m, 1H, H-7b), 1.47 (m, 1H, H-14a), 1.42 (m, 1H, H-4′a), 1.40 (m, 1H, H-7a), 1.31 (s, 3H, 6-Me), 1.30 (s, 3H, 12-Me), 1.26

(d, $J = 6.6$ Hz, 3H, 5′-Me), 1.20 (d, $J = 6.6$ Hz, 3H, 2-Me), 1.10 (d, $J = 7.1$ Hz, 3H, 8-Me), 1.02 (d, $J = 6.7$ Hz, 3H, 10-Me), 0.79 (t, $J = 7.4$ Hz, H-15), 0.76 (d, $J = 7.5$ Hz, 3H, 4-Me). ^{13}C NMR ($CDCl_3$): δ (ppm) 215.6 (C-9), 175.1 (C-1), 165.4 (C-6′, Bz), 157.7 (C-19), 156.4 (C-23, Fmoc), 144.1 (C-26, Fmoc), 141.3 (C-31, Fmoc), 136.1 (C-17), 132.7 (C-10′, Bz), 130.6 (C-7′, Bz), 129.7 (C-8′, Bz), 128.2 (C-9′, Bz), 127.5 (C-29, Fmoc), 127.0 (C-28, Fmoc),125.2 (C-27, Fmoc), 119.8 (C-30, Fmoc), 116.1 (C-18), 99.9 (C-1′), 83.0 (C-12), 80.2 (C-5), 79.6 (C-6), 77.2 (C-3), 76.2 (C-13), 72.1 (C-2′), 69.0 (C-5′), 66.6 (C-24, Fmoc), 64.6 (C-16), 63.4 (C-3′), 60.9 (C-11), 47.3 (C-25, Fmoc), 45.5 (C-8), 44.0 (C-2), 40.8 (3′-NMe), 40.7 (C-20), 39.1 (C-10), 38 (C-22), 37.8 (C-7), 36.0 (C-4), 31.8 (C-4′), 27.3 (C-21), 22.1 (C-14), 21.1 (5′-Me), 20.3 (6-Me), 19.1 (8-Me), 15.1 (2-Me), 14.2 (10-Me), 14.1 (12-Me), 10.2 (C-15), 7.9 (4-Me).

11-Deoxy-11-(3-*N*-Fmoc-aminopropanylamino)-11,12-carbamate-6-*O*-allyl-3-hydroxy-erythronolide A (10). A solution of erythronolide **9** (5.3 g, 5.2 mmol) in MeOH (200 mL) was heated at 55 °C for 23 h at which point the solvent was evaporated and the crude mixture was subjected to column chromatography with 75% acetone/hexanes, to remove the methyl benzoate byproduct, and then 75% acetone/hexanes plus 0.5% Et_3N to elute the product as a white foamy solid (4.4 g, 92% yield). MS (ESI): *m*/*z* 920 [M + 1]. ^{1}H NMR ($CDCl_3$): δ (ppm) 7.76 (d, $J = 7.5$ Hz, 2H, H-30, Fmoc), 7.64 (m, 2H, H-27, Fmoc), 7.39 (m, 2H, H-29, Fmoc), 7.31 (m, 2H, H-28, Fmoc), 5.79 (m, 1H, H-17), 5.60 (brt, 1H, 22-NH), 5.18 (m, 1H, H-18b), 5.06 (dd, $J = 10.5$ Hz, $J = 1.5$ Hz, 1H, H-18a), 5.02 (m, 1H, H-13), 4.43 (d, $J = 7.5$ Hz, 1H, H-1′), 4.35 (m, 2H, H-24, Fmoc), 4.22 (t, $J = 7.3$ Hz, 1H, H-25, Fmoc), 3.84 (m, 2H, H-16), 3.82 (m, 1H, H-11), 3.80 (m, 1H, H-5), 3.65 (m, 1H, H-3), 3.60 (m, 1H, H-20b), 3.50 (m, 1H, H-5′), 3.39 (m, 1H, H-20a), 3.36 (m, 1H, H-22b), 3.22 (dd, $J = 10.3$, $J = 7.3$ Hz, 1H, H-2′), 3.13 (m, 1H, H-22a), 3.04 (m, 1H, H-10), 2.75 (m, 1H, H-8), 2.74 (m, 1H, H-2), 2.45 (m, 1H, H-3′), 2.25 (s, 6H, 3′-NMe), 2.18 (s, 1H, 3-OH), 1.95 (m, 1H, H-4), 1.95 (m, 1H, H-14b), 1.80 (m, 2H, H-21), 1.77 (m, 1H, H-7b), 1.65 (m, 1H, H-4′b), 1.58 (m, 1H, H-14a), 1.57 (m, 1H, H-7a), 1.46 (s, 3H, 12-Me), 1.30 (d, $J = 6.6$ Hz, 3H, 2-Me), 1.28 (s, 3H, 6-Me), 1.23 (d, 3H, 5′-Me), 1.23 (m, 1H, H-4′a), 1.17 (d, 3H, 8-Me), 1.16 (d, 3H, 4-Me), 1.07 (d, $J = 6.6$ Hz, 3H, 10-Me), 0.87 (t, $J = 8.3$ Hz, H-15). ^{13}C NMR ($CDCl_3$): δ (ppm) 215.1 (C-9), 176.0 (C-1), 157.5 (C-19), 156.4 (C-23, Fmoc), 144.1 (C-26, Fmoc), 141.2 (C-31, Fmoc), 135.7 (C-17), 127.5 (C-29, Fmoc), 127.0 (C-28, Fmoc), 125.2 (C-27, Fmoc), 119.8 (C-30, Fmoc), 115.8 (C-18), 106.6 (C-1′), 88.6 (C-5), 82.9 (C-12), 80.0 (C-6), 78.2 (C-3), 76.6 (C-13), 70.6 (C-2′), 70.1 (C-5′), 66.7 (C-24, Fmoc), 63.7 (C-16), 65.6 (C-3′), 61.0 (C-11), 47.3 (C-25, Fmoc), 44.6 (C-2), 44.1 (C-8), 40.4 (C-20), 40.2 (3′-NMe), 40.2 (C-10), 37.9 (C-22), 37.8 (C-7), 36.8 (C-4), 28.0 (C-4′), 27.2 (C-21), 22.1 (C-14), 21.2 (5′-Me), 20.0 (6-Me), 18.1 (8-Me), 15.4 (2-Me), 14.1 (12-Me),13.0 (10-Me), 10.3 (C-15), 8.1 (4-Me).

11-Deoxy-11-(3-*N*-Fmoc-aminopropanylamino)-11,12-carbamate-6-*O*-carboxymethyl-3-hydroxy-erythronolide A (5). Erythronolide **10** (4.2 g, 4.6 mmol) in CH_2Cl_2 (100 mL) was placed in a three-neck round-bottom flask and cooled at −78 °C under a flow of N_2. Ozone was then bubbled through the solution until a blue color persisted (approximately 40 min). The ozone flow was stopped and replaced with a N_2 flow at −78 °C until the blue color disappeared. Dimethylsulfite (1.4 mL, 19.1 mmol) was then added slowly at −78 °C ,and the reaction mixture was allowed to warm to 0 °C over 1 h at which point the solvent was removed and the resulting yellow solid was dissolved in THF (100 mL) and treated with triphenyl phosphine (3.8 g, 14.4 mmol). The mixture was heated under N_2 at 70 °C for 4 h, and then it was allowed to cool. The solvent was evaporated to give a brown-white crude solid, which was purified by column chromatography (first 75% acetone/hexanes, then 75% acetone/hexanes plus 0.5% Et_3N) to obtain a slightly yellowish white solid (2.7 g, 64% yield). MS (ESI): *m*/*z* 922 [M + 1]. ^{1}H NMR ($CDCl_3$): δ (ppm) 9.64 (s, 1H, H-17), 7.76 (d, $J = 7.3$ Hz, 2H, H-30, Fmoc), 7.65 (m, 2H, H-27, Fmoc), 7.39 (m, 2H, H-29, Fmoc), 7.32 (m, 2H, H-28, Fmoc), 5.57 (brt, 1H, 22-NH), 4.99 (m, 1H, H-13), 4.46 (d, $J = 6.9$ Hz, 1H, H-1′), 4.36 (m, 2H, H-24, Fmoc), 4.24 (t, $J = 7.1$ Hz, 1H, H-25, Fmoc), 3.87 (m, 2H, H-16), 3.80 (m, 1H, H-11), 3.78 (m, 1H, H-5), 3.63 (m, 1H, H-20b), 3.58 (m, 1H, H-3), 3.48 (m, 1H, H-5′), 3.42 (m, 1H, H-20a), 3.33 (m, 1H, H-22b), 3.23 (dd, $J = 10.0$, $J = 7.3$ Hz, 1H, H-2′), 3.15 (m, 1H, H-22a), 3.08 (m, 1H, H-10), 2.78 (m, 1H, H-8), 2.73 (m, 1H, H-2), 2.52 (m, 1H, H-3′), 2.29 (s, 6H, 3′-NMe), 2.16 (s, 1H, 3-OH), 1.95 (m, 1H, H-14b), 1.94 (m, 1H, H-4), 1.84 (m, 1H, H-7b), 1.74 (m, 2H, H-21), 1.68 (m, 1H, H-4′b), 1.61 (m, 1H, H-7a), 1.58 (m, 1H, H-14a), 1.46 (s, 3H, 12-Me), 1.35 (s, 3H, 6-Me), 1.28 (d, $J = 6.6$ Hz, 3H, 2-Me), 1.23 (m, 1H, H-4′a), 1.20 (d, 3H, 5′-Me), 1.19 (d, 3H, 8-Me), 1.15 (d, 3H, 4-Me), 1.08 (d, $J = 6.8$ Hz, 3H, 10-Me), 0.87 (t, $J = 7.1$ Hz, H-15). ^{13}C NMR ($CDCl_3$): δ (ppm) 215.4 (C-9), 201.5 (C-17), 176.2 (C-1), 157.3 (C-19), 156.4 (C-23, Fmoc), 144.1 (C-26, Fmoc), 141.2 (C-31, Fmoc), 127.5 (C-29, Fmoc), 127.0 (C-28, Fmoc), 125.2 (C-27, Fmoc), 119.8 (C-30, Fmoc), 106.2 (C-1′), 87.6 (C-5), 82.8 (C-12), 81.0 (C-6), 78.0 (C-3), 76.9 (C-13), 70.5 (C-2′), 70.0 (C-5′), 68.8 (C-16), 66.7 (C-24, Fmoc), 65.6 (C-3′), 60.9 (C-11), 47.3 (C-25, Fmoc), 44.6 (C-2), 44.3 (C-8), 40.4 (C-20), 40.2 (3′-NMe), 40.2 (C-10), 37.9 (C-22), 37.8 (C-7), 37.0 (C-4), 28.2 (C-4′), 27.2 (C-21), 22.0 (C-14), 21.2 (5′-Me), 20.0 (6-Me), 18.0 (8-Me), 15.4 (2-Me), 14.2 (12-Me),13.1 (10-Me), 10.2 (C-15), 8.1 (4-Me).

Synthesis of Resin 12c. In a peptide tube, resin **11** (1.2 g, 0.8 mmol), suspended in CH_2Cl_2 (6 mL), was treated with a solution of Fmoc-L-isoleucine (865 mg, 2.4 mmol) in THF (4 mL), followed by addition of DIC (0.4 mL, 2.5 mmol) and DMAP (30 mg, 0.25 mmol). After the tubes were rotated for 6 h, the liquids were drained and the resin was washed twice with CH_2Cl_2 and DMF. New portions of reagents were added to the resin, and the tube was rotated overnight. The resin was washed two times each with DMF, MeOH, CH_2Cl_2, 1:1 DMF/CH_2Cl_2, 1:1 MeOH/CH_2Cl_2, and CH_2Cl_2 and dried in a vacuum desiccator. Loading was determined by Fmoc quantitation experiments to be 0.59 mmol/g (95% yield).

Resin-Bound 11-Deoxy-11-(3-*N*-Fmoc-aminopropanylamino)-11,12-carbamate-6-*O*-(*N*-L-isoleucine)ethyl-3-hydroxy-erythronolide A (13c). In a peptide tube, resin **12c** (1.2 g, 0.7 mmol) suspended in 20% piperidine/DMF (12 mL) was rotated for 0.5 h. The liquids were drained, and the reaction was repeated one more time with fresh portions of reagents. The resin was then washed two times each with DMF, MeOH, CH_2Cl_2, 1:1 DMF/CH_2Cl_2, 1:1 MeOH/CH_2Cl_2, and CH_2Cl_2 and dried in a vacuum desiccator. The ninhydrin test was positive.

In a peptide tube, the resin was rotated with the macrolide aldehyde **5** (640 mg, 0.7 mmol) in 10% AcOH/DMF (10 mL) for 2 h at which point the liquids were drained and the reaction was repeated one more time with fresh portions of reagents. The resin was washed three times with DMF (10 mL each) and suspended again in 10% AcOH/DMF (10 mL). $NaCNBH_4$ (400 mg, excess) was added, and the tube was left open until bubbling subsided. The mixture was then rotated overnight, and the resin was washed two times each with DMF, MeOH, CH_2Cl_2, 1:1 DMF/CH_2Cl_2, 1:1 MeOH/CH_2Cl_2, and CH_2Cl_2 and dried in a vacuum desiccator. The ninhydrin test was negative. Loading was 0.3 mmol/g (79% yield).

A small amount of the resin was subjected to TFA cleavage with 90% TFA/CH_2Cl_2 (1 mL) for 1 h to yield a white foamy solid. MS (ESI): *m*/*z* 1037 [M + 1]. ^{1}H NMR ($CDCl_3$): δ (ppm) 7.78 (d, J = 7.3 Hz, 2H, H-30, Fmoc), 7.66 (m, 2H, H-27, Fmoc), 7.38 (m, 2H, H-29, Fmoc), 7.30 (m, 2H, H-28, Fmoc), 5.04 (brs, 1H, H-13), 4.65 (d, J = 7.4 Hz, 1H, H-1′), 4.35−4.29 (m, 2H, H-24, Fmoc), 4.24 (m, 1H, H-25, Fmoc), 3.87 (d, J = 2.3 Hz, 1H, H-5), 3.72 (m, 1H, H-20b), 3.71 (m, 1H, H-16b), 3.63 (m, 1H, H-5′), 3.59 (m, 1H, H-11), 3.58 (m, 1H, H-20a), 3.56 (m, 1H, H-16a), 3.49 (d, J = 3.4 Hz, 1H, H-2AA), 3.41 (dd, J = 10.5, J = 7.1 Hz, 1H, H-2′), 3.34 (m, 1H, H-10), 3.33 (m, 1H, H-3′), 3.30 (m, 1H, H-3), 3.23 (m, 2H, H-22), 3.08 (m, 1H, H-17b), 3.02 (m, 1H, H-17a), 2.71 (dd, J = 10.3 Hz, J = 6.6 Hz, 1H, H-2), 2.80 (s, 6H, 3′-NMe), 2.57 (m, 1H, H-8), 2.02 (m, 1H, H-4′b), 1.97 (m, 1H, H-7b), 1.96 (m, 1H, H-3AA), 1.87 (m, 1H, H-14b), 1.86 (m, 1H, H-4), 1.74 (m, 2H, H-21), 1.68 (m, 1H, H-4bAA), 1.62 (m, 1H, H-14a), 1.54 (m, 1H, H-7a), 1.49 (m, 1H, H-4′a), 1.48 (s, 3H, 12-Me), 1.37 (m, 1H, H-4aAA), 1.35 (s, 3H, 6-Me), 1.27 (d, J = 6.2 Hz, 3H, 5′-Me), 1.18 (d, 3H, 2-Me), 1.17 (d, 3H, 8-Me), 1.10 (d, J = 7.6 Hz, 3H, 4-Me), 1.02 (d, J = 1.1 Hz, 3H, 10-Me), 1.01 (d, J = 6.7 Hz, 3H, H-3-MeAA), 0.91 (t, J = 7.2 Hz, 3H, H-4-MeAA), 0.86 (t, J = 7.4 Hz, H-15). ^{13}C NMR ($CDCl_3$): δ (ppm) 219.4 (C-9), 177.7 (C-1), 172 (C-1AA), 159.5 (C-19), 159.0 (C-23, Fmoc), 145.5 (C-26, Fmoc), 142.6 (C-31, Fmoc), 128.8 (C-29, Fmoc), 128.2 (C-28, Fmoc), 126.3 (C-27, Fmoc), 120.9 (C-30, Fmoc), 102.4 (C-1′), 85.0 (C-12), 81.7 (C-5), 81.0 (C-6), 78.1 (C-13), 77.4 (C-3), 70.7 (C-2′), 69.4 (C-5′), 68.7 (C-2AA), 68.1 (C-24, Fmoc), 67.0 (C-3′), 63.1 (C-11), 59.1 (C-16), 48.7 (C-25, Fmoc), 48.0 (C-17), 47.0 (C-8), 45.7 (C-2), 42.5 (C-20), 40.8 (C-10), 40.1 (3′-NMe), 39.7 (C-22), 39.1 (C-7), 38.5 (C-4), 37.6 (C-3AA), 31.8 (C-4′), 29.3 (C-4AA), 27.5 (C-21), 23.1 (C-14), 21.3 (5′-Me), 20.9 (6-Me), 19.5 (8-Me), 16.09 (2-Me), 15.4 (3-MeAA), 14.8 (12-Me),14.7 (10-Me), 12.5 (4-MeAA), 10.6 (C-15), 9.2 (4-Me).

Resin-Bound 11-Deoxy-11-(3-*N*-Fmoc-aminopropanylamino)-11,12-carbamate-6-*O*-(*N*,*N*-*n*-butyl,L-isoleucine)-ethyl-3-hydroxy-erythronolide A (14c). In a peptide tube, resin **13c** (33 mg, 0.01 mmol) was suspended in 10% AcOH/DMF (0.5 mL) and treated with *n*-buraldehyde (20 μL, 0.2 mmol) for 2 h at which point $NaCNBH_4$ (30 mg, excess) was added, and the tube was rotated overnight. The resin was washed two times each with DMF, MeOH, CH_2Cl_2, 1:1 DMF/CH_2Cl_2, 1:1 MeOH/CH_2Cl_2, and CH_2Cl_2 and dried in a vacuum desiccator. A small amount of resin was subjected to TFA cleavage with 90% TFA/CH_2Cl_2 (1 mL) for 1 h to yield a white foamy solid. MS (ESI): *m*/*z* 1093 [M + 1]. ^{1}H NMR ($CDCl_3$): δ (ppm) 7.78 (d, J = 7.5 Hz, 2H, H-30, Fmoc), 7.66 (d, J = 7.1 Hz, 2H, H-27, Fmoc), 7.37 (m, 2H, H-29, Fmoc), 7.29 (m, 2H, H-28, Fmoc), 5.05 (brd, J = 10.6 Hz, 1H, H-13), 4.65 (d, J = 7.2 Hz, 1H, H-1′), 4.40 (dd, J = 10.3 Hz, J = 7.2 Hz, 1H, H-24b, Fmoc), 4.30 (dd, J = 10.3 Hz, J = 7.5 Hz, 1H, H-24a, Fmoc), 4.23 (m, 1H, H-25, Fmoc), 3.90 (d, J = 2.4 Hz, 1H, H-5), 3.75 (m, 1H, H-20b), 3.64 (m, 1H, H-5′), 3.57 (m, 1H, H-11), 3.55 (m, 1H, H-20a), 3.52 (m, 2H, H-16), 3.43 (dd, J = 10.6, J = 7.1 Hz, 1H, H-2′), 3.35 (m, 1H, H-3′), 3.33 (m, 1H, H-10), 3.32 (m, 1H, H-3), 3.31 (m, 1H, H-2AA), 3.22 (m, 2H, H-22), 2.96 (m, 2H, H-17), 2.9 (m, 2H, H-1AL), 2.81 (s, 6H, 3′-NMe), 2.73 (m, 1H, H-2), 2.56 (m, 1H, H-8), 2.02 (m, 1H, H-4′b), 1.95 (m, 1H, H-7b), 1.91 (m, 1H, H-4), 1.90 (m, 1H, H-3AA), 1.85 (m, 1H, H-14b), 1.74 (m, 2H, H-21), 1.74 (m, 1H, H-4bAA), 1.69 (m, 1H, H-2bAL), 1.61 (m, 1H, H-14a), 1.60 (m, 1H, H-2aAL), 1.54 (m, 1H, H-7a), 1.50 (s, 3H, 12-Me), 1.49 (m, 1H, H-4′a), 1.36 (s, 3H, 6-Me), 1.31 (m, 1H, H-4aAA), 1.30 (m, 2H, H-3AL), 1.27 (d, J = 6.1 Hz, 3H, 5′-Me), 1.22 (d, J = 6.5 Hz, 3H, 2-Me), 1.16 (d, J = 7.2 Hz, 3H, 8-Me), 1.11 (d, J = 7.5 Hz, 3H, 4-Me), 1.01 (d, J = 6.8 Hz, 3H, 10-Me), 0.99 (d, J = 6.8 Hz, 3H, H-3-MeAA), 0.94 (t, J = 7.2 Hz, 3H, H-4-MeAA), 0.87 (t, J = 7.1 Hz, H-15), 0.86 (t, J = 7.1 Hz, 1H, 3-MeAL). ^{13}C NMR ($CDCl_3$): δ (ppm) 218.5 (C-9), 177.7 (C-1), 173.5 (C-1AA), 159.6 (C-19), 158.8 (C-23, Fmoc), 145.4 (C-26, Fmoc), 142.6 (C-31, Fmoc), 128.8 (C-29, Fmoc), 128.2 (C-28, Fmoc), 126.3 (C-27, Fmoc), 120.9 (C-30, Fmoc), 102.4 (C-1′), 85.1 (C-12), 81.4 (C-5), 81.1 (C-6), 78.0 (C-13), 77.7 (C-3), 73.1 (C-2AA), 70.6 (C-2′), 69.3 (C-5′), 68.1 (C-24, Fmoc), 67.0 (C-3′), 63.5 (C-11), 59.9 (C-16), 53.8 (C-1AL), 49.9 (C-17), 49.1 (C-25, Fmoc), 47.1 (C-8), 45.7 (C-2), 42.9 (C-20), 40.5 (C-10), 40.2 (3′-NMe), 39.8 (C-22), 39.2 (C-7), 38.5 (C-4), 34.5 (C-3AA), 31.9 (C-4′), 28.8 (C-2AL), 28.1 (C-4AA), 22.7 (C-14), 21.3 (5′-Me), 21.2 (C-3AL), 21.1 (6-Me), 19.8 (8-Me), 16.01 (2-Me), 15.7 (3-MeAA), 15.0 (12-Me),14.9 (10-Me), 14.2 (3-MeAL), 12.2 (4-MeAA), 10.6 (C-15), 9.4 (4-Me).

Resin-Bound 11-Deoxy-11-(3-*N*-benzyl-aminopropanylamino)-11,12-carbamate-6-*O*-(*N*,*N*-*n*-butyl,L-isoleucine)-ethyl-3-hydroxy-erythronolide A (15c). In a peptide tube, resin **14c** (0.01 mmol) was treated with 20% piperidine/DMF (0.5 mL) and rotated for 0.5 h. The liquids were drained, and the reaction was repeated one more time with fresh portions of reagents. The resin was then washed two times

Table 2. ^{1}H NMR Data (δ ppm) in CD_3OD for Compounds **16a**−**k**

position	**16a**	**16b**	**16c**	**16d**	**16e**	**16f**	**16g**	**16h**	**16i**	**16j**	**16k**
2	2.76 (m, 1H)	2.76 (m, 1H)	2.76 (m, 1H)	2.76 (m, 1H)	2.75 (m, 1H)	2.74 (m, 1H)	2.77 (m, 1H)	2.75 (m, 1H)	2.76 (m, 1H)	2.75 (m, 1H)	2.76 (m, 1H)
2-Me	1.24 (d, *J* = 6.5 Hz, 3H)	1.23 (d, *J* = 6.5 Hz, 3H)	1.24 (d, *J* = 6.6 Hz, 3H)	1.24 (d, *J* = 6.9 Hz, 3H)	1.25 (d, *J* = 6.6 Hz, 3H)	1.23 (d, *J* = 6.5 Hz, 3H)	1.24 (d, *J* = 6.6 Hz, 3H)	1.23 (d, *J* = 6.6 Hz, 3H)	1.23 (d, *J* = 6.5 Hz, 3H)	1.23 (d, *J* = 6.6 Hz, 3H)	1.23 (d, *J* = 6.6 Hz, 3H)
3	3.26 (m, 1H)	3.28 (m, 1H)	3.26 (m, 1H)	3.34 (m, 1H)	3.27 (m, 1H)	3.28 (m, 1H)	3.31 (m, 1H)	3.26 (m, 1H)	3.29 (m, 1H)	3.27 (m, 1H)	3.35 (m, 1H)
4	1.88 (m, 1H)	1.87 (m, 1H)	1.87 (m, 1H)	1.93 (m, 1H)	1.86 (m, 1H)	1.87 (m, 1H)	1.92 (m, 1H)	1.88 (m, 1H)	1.91 (m, 1H)	1.87 (m, 1H)	1.90 (m, 1H)
4-Me	1.12 (d, *J* = 7.3 Hz, 3H)	1.11 (d, *J* = 7.3 Hz, 3H)	1.12 (d, *J* = 7.3 Hz, 3H)	1.12 (d, *J* = 7.3 Hz, 3H)	1.12 (d, *J* = 7.6 Hz, 3H)	1.11 (d, *J* = 7.7 Hz, 3H)	1.12 (d, *J* = 7.7 Hz, 3H)	1.12 (d, *J* = 7.7 Hz, 3H)	1.12 (d, *J* = 7.7 Hz, 3H)	1.12 (d, *J* = 7.7 Hz, 3H)	1.13 (d, *J* = 7.3 Hz, 3H)
5	3.90 (d, *J* = 3.3 Hz, 1H)	3.90 (d, *J* = 3.3 Hz, 1H)	3.91 (d, *J* = 2.6 Hz, 1H)	3.91 (d, *J* = 2.6 Hz, 1H)	3.90 (d, *J* = 2.9 Hz, 1H)	3.89 (d, *J* = 3.0 Hz, 1H)	3.89 (d, *J* = 3.0 Hz, 1H)	3.89 (d, *J* = 2.9 Hz, 1H)	3.87 (d, *J* = 2.9 Hz, 1H)	3.90 (d, *J* = 2.9 Hz, 1H)	3.89 (d, *J* = 2.6 Hz, 1H)
6-Me	1.41 (s, 3H)	1.39 (s, 3H)	1.40 (s, 3H)	1.37 (s, 3H)	1.41 (s, 3H)	1.39 (s, 3H)	1.37 (s, 3H)	1.38 (s, 3H)	1.36 (s, 3H)	1.39 (s, 3H)	1.38 (s, 3H)
7a	1.99 (m, 1H)	1.97 (m, 1H)	1.99 (m, 1H)	1.97 (m, 1H)	2.00 (m, 1H)	1.97 (m, 1H)	1.96 (m, 1H)	1.99 (m, 1H)	1.97 (m, 1H)	1.98 (m, 1H)	1.99 (m, 1H)
7b	1.57 (m, 1H)	1.56 (m, 1H)	1.60 (m, 1H)	1.59 (m, 1H)	1.57 (m, 1H)	1.57 (m, 1H)	1.57 (m, 1H)	1.58 (m, 1H)	1.58 (m, 1H)	1.58 (m, 1H)	1.59 (m, 1H)
8	2.61 (m, 1H)	2.60 (m, 1H)	2.57 (m, 1H)	2.58 (m, 1H)	2.62 (m, 1H)	2.60 (m, 1H)	2.59 (m, 1H)	2.63 (m, 1H)	2.63 (m, 1H)	2.61 (m, 1H)	2.60 (m, 1H)
8-Me	1.20 (d, *J* = 7.3 Hz, 3H)	1.20 (d, *J* = 7.3 Hz, 3H)	1.20 (d, *J* = 7.3 Hz, 3H)	1.18 (d, *J* = 7.3 Hz, 3H)	1.20 (d, *J* = 6.9 Hz, 3H)	1.19 (d, *J* = 7.3 Hz, 3H)	1.18 (d, *J* = 7.3 Hz, 3H)	1.21 (d, *J* = 7.3 Hz, 3H)	1.21 (d, *J* = 6.9 Hz, 3H)	1.20 (d, *J* = 7.3 Hz, 3H)	1.20 (d, *J* = 7.3 Hz, 3H)
10	3.36 (m, 1H)	3.36 (m, 1H)	3.36 (m, 1H)	3.33 (m, 1H)	3.37 (m, 1H)	3.35 (m, 1H)	3.34 (m, 1H)	3.36 (m, 1H)	3.35 (m, 1H)	3.37 (m, 1H)	3.39 (m, 1H)
10-Me	1.04 (d, *J* = 6.9 Hz, 3H)	1.03 (d, *J* = 6.9 Hz, 3H)	1.06 (d, *J* = 6.9 Hz, 3H)	1.07 (d, *J* = 6.9 Hz, 3H)	1.05 (d, *J* = 6.6 Hz, 3H)	1.03 (d, *J* = 7.0 Hz, 3H)	1.04 (d, *J* = 7.0 Hz, 3H)	1.05 (d, *J* = 6.6 Hz, 3H)	1.05 (d, *J* = 6.9 Hz, 3H)	1.03 (d, *J* = 7.0 Hz, 3H)	1.05 (d, *J* = 6.9 Hz, 3H)
11	3.50 (m, 1H)	3.50 (m, 1H)	3.48 (m, 1H)	3.47 (m, 1H)	3.50 (m, 1H)	3.50 (m, 1H)	3.55 (m, 1H)	3.53 (m, 1H)	3.56 (m, 1H)	3.51 (m, 1H)	3.53 (m, 1H)
12-Me	1.50 (s, 3H)	1.50 (s, 3H)	1.50 (s, 3H)	1.51 (s, 3H)	1.50 (s, 3H)	1.49 (s, 3H)	1.50 (s, 3H)	1.50 (s, 3H)	1.51 (s, 3H)	1.50 (s, 3H)	1.51 (s, 3H)
13	4.94 (dd, *J* = 11.0 Hz, *J* = 2.6 Hz, 1H)	4.93 (dd, *J* = 11.0 Hz, *J* = 2.6 Hz, 1H)	4.96 (dd, *J* = 10.8 Hz, *J* = 2.3 Hz, 1H)	4.99 (dd, *J* = 11.0 Hz, *J* = 2.6 Hz, 1H)	4.96 (dd, *J* = 10.8 Hz, *J* = 2.3 Hz, 1H)	4.94 (dd, *J* = 11.0 Hz, *J* = 2.5 Hz, 1H)	4.97 (dd, *J* = 11.0 Hz, *J* = 2.6 Hz, 1H)	4.95 (dd, *J* = 11.0 Hz, *J* = 2.6 Hz, 1H)	4.97 (dd, *J* = 11.0 Hz, *J* = 2.6 Hz, 1H)	4.95 (dd, *J* = 11.0 Hz, *J* = 2.6 Hz, 1H)	4.98 (dd, *J* = 10.8 Hz, *J* = 2.5 Hz, 1H)
14a	1.84 (m, 1H)	1.83 (m, 1H)	1.84 (m, 1H)	1.84 (m, 1H)	1.83 (m, 1H)	1.82 (m, 1H)	1.83 (m, 1H)	1.83 (m, 1H)	1.84 (m, 1H)	1.83 (m, 1H)	1.85 (m, 1H)
14b	1.63 (m, 1H)	1.64 (m, 1H)	1.63 (m. 1H)	1.63 (m. 1H)	1.64 (m, 1H)	1.63 (m, 1H)	1.64 (m, 1H)	1.63 (m, 1H)	1.64 (m, 1H)	1.63 (m, 1H)	1.64 (m. 1H)
15	0.84 (t, *J* = 7.5 Hz, 3H)	0.85 (t, *J* = 7.5 Hz, 3H)	0.84 (t, *J* = 7.3 Hz, 3H)	0.86 (t, *J* = 7.5 Hz, 3H)	0.86 (t, *J* = 7.2 Hz, 3H)	0.83 (t, *J* = 7.3 Hz, 3H)	0.86 (t, *J* = 7.3 Hz, 3H)	0.84 (t, *J* = 7.3 Hz, 3H)	0.87 (t, *J* = 7.3 Hz, 3H)	0.84 (t, *J* = 7.3 Hz, 3H)	0.86 (t, *J* = 7.3 Hz, 3H)
1′	4.66 (d, *J* = 7.0 Hz, 1H)	4.64 (d, *J* = 7.0 Hz, 1H)	4.66 (d, *J* = 7.0 Hz, 1H)	4.68 (d, *J* = 6.9 Hz, 1H)	4.64 (d, *J* = 6.9 Hz, 1H)	4.65 (d, *J* = 7.0 Hz, 1H)	4.67 (d, *J* = 7.0 Hz, 1H)	4.64 (d, *J* = 7.0 Hz, 1H)	4.65 (d, *J* = 6.9 Hz, 1H)	4.66 (d, *J* = 6.9 Hz, 1H)	4.66 (d, *J* = 6.9 Hz, 1H)
2′	3.44 (m, 1H)	3.43 (m, 1H)	3.44 (m, 1H)	3.44 (m, 1H)	3.44 (m, 1H)	3.43 (m, 1H)	3.44 (m, 1H)	3.44 (m, 1H)	3.44 (m, 1H)	3.44 (m, 1H)	3.44 (m, 1H)
3′	3.39 (m, 1H)	3.38 (m, 1H)	3.39 (m, 1H)	3.38 (m, 1H)	3.40 (m, 1H)	3.39 (m, 1H)	3.39 (m, 1H)	3.40 (m, 1H)	3.39 (m, 1H)	3.39 (m, 1H)	3.39 (m, 1H)
4′a	2.03 (m, 1H)	2.02 (m, 1H)	2.03 (m, 1H)	2.03 (m, 1H)	2.03 (m, 1H)	2.02 (m, 1H)	2.03 (m, 1H)	2.03 (m, 1H)	2.03 (m, 1H)	2.03 (m, 1H)	2.04 (m, 1H)
4′b	1.52 (m, 1H)	1.51 (m, 1H)	1.52 (m, 1H)	1.52 (m, 1H)	1.52 (m, 1H)	1.50 (m, 1H)	1.52 (m, 1H)	1.51 (m, 1H)	1.52 (m, 1H)	1.52 (m, 1H)	1.53 (m, 1H)
5′	3.67 (m, 1H)	3.65 (m, 1H)	3.66 (m, 1H)	3.67 (m, 1H)	3.65 (m, 1H)	3.65 (m, 1H)	3.67 (m, 1H)	3.65 (m, 1H)	3.67 (m, 1H)	3.67 (m, 1H)	3.67 (m, 1H)
5′-Me	1.30 (d, *J* = 5.8 Hz, 3H)	1.29 (d, *J* = 5.8 Hz, 3H)	1.29 (d, *J* = 5.9 Hz, 3H)	1.30 (d, *J* = 6.2 Hz, 3H)	1.29 (d, *J* = 6.3 Hz, 3H)	1.29 (d, *J* = 5.8 Hz, 3H)	1.31 (d, *J* = 5.9 Hz, 3H)	1.28 (d, *J* = 5.9 Hz, 3H)	1.31 (d, *J* = 6.3 Hz, 3H)	1.30 (d, *J* = 6.3 Hz, 3H)	1.31 (d, *J* = 5.9 Hz, 3H)
16a	3.73 (m, 1H)	3.74 (m, 1H)	3.72 (m, 1H)	3.47 (m, 2H)	3.75 (m, 1H)	3.70 (m, 1H)	3.51 (m, 1H)	3.64 (m, 2H)	3.51 (m, 1H)	3.73 (m, 1H)	3.67 (m, 1H)
16b	3.68 (m, 1H)	3.62 (m, 1H)	3.64 (m, 1H)		3.64 (m, 1H)	3.62 (m, 1H)	3.43 (m, 1H)		3.41 (m, 1H)	3.60 (m, 1H)	3.52 (m, 1H)
17a	3.23 (m, 1H)	3.23 (m, 1H)	3.27 (m, 1H)	2.98 (m, 1H)	3.42 (m, 1H)	3.17 (m, 1H)	2.95 (m, 1H)	3.21 (m, 2H)	3.03 (m, 1H)	3.28 (m, 1H)	3.26 (m, 1H)
17b	3.07 (m, 1H)	3.12 (m, 1H)	3.10 (m, 1H)	2.75 (m, 1H)	3.24 (m, 1H)	3.05 (m, 1H)	2.89 (m, 1H)		2.96 (m, 1H)	3.20 (m, 1H)	3.22 (m, 1H)
20a	3.80 (m, 1H)	3.81 (m, 1H)	3.80 (m, 1H)	3.81 (m, 1H)	3.78 (m, 1H)	3.81 (m, 1H)	3.80 (m, 1H)	3.81 (m, 1H)	3.80 (m, 1H)	3.81 (m, 1H)	3.86 (m, 1H)
20b	3.53 (m, 1H)	3.54 (m, 1H)	3.50 (m, 1H)	3.55 (m, 1H)	3.51 (m, 1H)	3.51 (m, 1H)	3.53 (m, 1H)	3.53 (m, 1H)	3.56 (m, 1H)	3.52 (m, 1H)	3.57 (m, 1H)
21a	2.29 (m, 1H)	2.25 (m, 1H)	2.37 (m, 1H)	2.42 (m, 1H)	2.28 (m, 1H)	2.27 (m, 1H)	2.28 (m, 1H)	2.309 (m, 1H)	2.29 (m, 1H)	2.27 (m, 1H)	2.33 (m, 1H)
21b	2.08 (m, 1H)	2.10 (m, 1H)	2.19 (m, 1H)	2.30 (m, 1H)	2.16 (m, 1H)	2.10 (m, 1H)	2.21 (m, 1H)	2.12 (m, 1H)	2.17 (m, 1H)	2.11 (m, 1H)	2.22 (m, 1H)
22	3.18 (m, 1H)	3.23 (m, 1H)	3.21 (m, 1H)	3.34 (m, 1H)	3.23 (m, 1H)	3.17 (m, 1H)	3.26 (m, 1H)	3.16 (m, 1H)	3.24 (m, 1H)	3.17 (m, 1H)	3.33 (m, 1H)
AA-2	4.00 (m, 1H)	4.04 (m, 1H)	3.78 (m, 1H)	3.29 (m, 1H)	4.14 (m, 1H)	4.37 (m, 1H)	4.10 (dd, *J* = 8.3 Hz, *J* = 6.0 Hz, 1H)	4.11 (t, *J* = 6.9 Hz, 1H)	3.91 (m, 1H)	4.43 (dd, *J* = 8.8 Hz, *J* = 5.1 Hz, 1H)	4.35 (dd, *J* = 10.5 Hz, *J* = 4.5 Hz, 1H)

Table 2 (Continued)

position	**16a**	**16b**	**16c**	**16d**	**16e**	**16f**	**16g**	**16h**	**16i**	**16j**	**16k**
AA-3	1.58 (m, 3H)	1.58 (m, 3H)	2.05 (m, 1H)	1.88 (m, 1H)	1.65 (m, 2H)	3.08 (m, 1H)	2.95 (m, 1H)	3.32 (m, 1H)	3.24 (m, 1H)	3.10 (m, 1H)	3.07 (m 1H)
						2.96 (m, 1H)	2.77 (m, 1H)	3.17 (m, 1H)	2.98 (m, 1H)	2.95 (m, 1H)	2.94 (m, 1H)
AA-3-Me			1.07 (m, 3H)	0.98 (m, 3H)							
AA-4a			1.69 (m, 1H)	1.27 (m, 2H)							
AA-4b			1.45 (m, 1H)								
AA-5			1.03 (t, *J* = 7.7 Hz, 3H)	0.96 (t, *J* = 7.7 Hz, 3H)				7.22 (d, *J* = Hz, 2H)	7.16 (d, *J* = Hz, 2H)		
AA-6								6.77 (d, *J* = Hz, 2H)	6.74 (d, *J* = Hz, 2H)		
AA-9											
AL-1a	3.22 (m, 2H)	3.11 (m, 2H)	3.15 (m, 2H)	2.65 (m, 1H)	3.38 (m, 1H)	3.28 (m, 1H)	2.95 (m, 1H)	3.20 (m, 1H)	2.90 (m, 1H)	3.41 (m, 1H)	3.35 (m, 1H)
AL-1b				2.76 (m, 1H)	3.26 (m, 1H)	3.17 (m, 1H)	2.73 (m, 1H)	3.14 (m, 1H)	2.71 (m, 1H)	3.28 (m, 1H)	3.06 (m, 1H)
AL-2a	1.73 (m, 2H)	1.77 (m, 1H)	1.82 (m, 1H)	1.62 (m, 1H)	1.85 (m, 1H)	1.72 (m, 2H)	2.89 (m, 1H)	1.73 (m, 2H)	1.56 (m, 1H)	1.74 (m, 2H)	1.76 (m, 1H)
AL-2b			1.66 (m, 1H)								
AL-3a	1.43 (m, 2H)	1.83 (m, 1H)	1.44 (m, 2H)	1.93/1.75 (m, 1H)	1.84 (m, 1H)	1.40 (m, 2H)	1.86/1.76 (m, 1H)	1.30 (m, 2H)	1.72/1.57 (m, 1H)	1.43 (m, 2H)	1.90/1.76 (m, 1H)
AL-3b		1.08 (m, 1H)		0.99 (m, 1H)	1.08 (m, 1H)		0.96 (m, 1H)		0.96/0.85 (m, 1H)		1.02 (m, 1H)
AL-4a	1.01 (t, *J* = 7.4 Hz, 3H)	1.79 (m, 1H)	1.01 (m, 3H)	1.75 (m, 1H)	1.79 (m, 1H)	0.98 (t, *J* = 7.3 Hz, 3H)	1.76 (m, 1H)	0.92 (t, *J* = 7.5 Hz, 3H)	1.74/1.67 (m, 1H)	1.00 (t, *J* = 7.3 Hz, 3H)	1.76 (m, 1H)
AL-4b		1.35 (m, 1H)		1.32 (m, 1H)	1.36 (m, 1H)		1.31 (m, 1H)		1.31/1.23 (m, 1H)		1.31 (m, 1H)
AL-5a		1.71 (m, 1H)		1.69 (m, 1H)	1.72 (m, 1H)		1.71 (m, 1H)		1.67 (m, 1H)		1.71 (m, 1H)
AL-5b		1.23 (m, 1H)		1.24 (m, 1H)	1.24 (m, 1H)		1.24 (m, 1H)		1.23 (m, 1H)		1.23 (m, 1H)
AR-1a	4.26 (d, *J* = 13.2 Hz, 1H)	4.41 (m, 2H)	4.26 (d, *J* = 13.2 Hz, 1H)	4.62 (d, *J* = 13.2 Hz, 1H)	4.40 (m, 2H)	4.24 (d, *J* = 12.8 Hz, 1H)	4.42 (m, 2H)	4.22 (d, *J* = 13.2 Hz, 1H)	4.40 (m, 2H)	4.28 (d, *J* = 13.2 Hz, 1H)	4.60 (m, 2H)
AR-1b	4.20 (d, *J* = 12.8 Hz, 1H)		4.26 (d, *J* = 13.2 Hz, 1H)	4.56 (d, *J* = 13.2 Hz, 1H)		4.20 (d, *J* = 12.8 Hz, 1H)		4.16 (d, *J* = 12.8 Hz, 1H)		4.23 (d, *J* = 13.2 Hz, 1H)	
AR-2											
AR-3	7.33 (m, 1H)					7.33 (m, 1H)		7.33 (m, 1H)		7.51 (m, 2H)	
AR-4			7.51 (m, 2H)	8.30 (m, 1H)						7.43 (m, 2H)	8.27 (m, 1H)
AR-4-MeO	3.81 (s, 3H)					3.81 (s, 3H)		3.81 (s, 3H)			
AR-5	6.98 (m, 1H)	7.47 (m, 1H)	7.43 (m, 3H)	7.76 (m, 1H)	7.47 (m, 1H)	6.97 (m, 1H)	7.48 (m, 1H)	6.97 (m, 1H)	7.47 (m, 1H)	7.43 (m, 1H)	7.74 (m, 1H)
AR-6	7.09 (m, 1H)	7.12 (m, 1H)		7.79 (m, 1H)	7.13 (m, 1H)	7.09 (m, 1H)	7.14 (m, 1H)	7.08 (m, 1H)	7.12 (m, 1H)		7.81 (m, 1H)
AR-7	7.05 (m, 1H)			7.84 (m, 1H)		7.05 (m, 1H)		7.03 (m, 1H)			7.81 (m, 1H)
3′-NMe-1	2.88 (s, 3H)	2.87 (s, 3H)	2.88 (s, 3H)	2.88 (s, 3H)	2.88 (s, 3H)	2.87 (s, 3H)	2.89 (s, 3H)	2.88 (s, 3H)	2.88 (s, 3H)	2.88 (s, 3H)	2.88 (s, 3H)
3′-NMe-2	2.80 (s, 3H)	2.79 (s, 3H)	2.80 (s, 3H)	2.80 (s, 3H)	2.80 (s, 3H)	2.79 (s, 3H)	2.80 (s, 3H)	2.80 (s, 3H)	2.80 (s, 3H)	2.80 (s, 3H)	2.80 (s, 3H)

Table 3. ^{13}C NMR Data (δ ppm) in CD_3OD for Compounds **16a**−**k**

position	**16a**	**16b**	**16c**	**16d**	**16e**	**16f**	**16g**	**16h**	**16i**	**16j**	**16k**
1	177.8	177.8	177.8	177.4	177.5	177.7	177.5	177.8	177.5	177.8	177.8
2	45.7	45.7	45.7	45.7	45.5	45.7	45.7	45.7	45.7	45.7	45.8
2-Me	16.0	16.0	16.0	16.0	15.6	16.0	16.0	16.0	16.0	16.0	16.0
3	77.6	77.2	77.7	77.7	77.2	77.4	77.6	77.4	77.5	77.4	77.6
4	38.6	38.6	38.6	38.2	38.4	38.5	38.3	38.5	38.4	38.5	38.5
4-Me	9.1	9.2	9.1	9.1	8.8	9.1	9.2	9.2	9.2	9.2	9.2
5	80.9	80.7	81.0	80.7	80.3	81.0	81.3	80.8	81.1	80.8	81.0
6	81.7	81.7	81.6	81.4	81.3	81.5	80.9	81.6	81.1	81.6	81.4
6-Me	20.8	20.9	20.9	20.9	20.7	20.9	20.9	20.9	21.1	20.9	20.9
7	39.2	39.2	39.2	39.3	39.1	39.2	39.4	39.2	39.3	39.1	39.2
8	47.1	47.1	47.2	47.3	46.6	47.1	47.2	47.1	47.1	47.1	47.2
8-Me	19.6	19.7	19.6	19.6	19.3	19.6	19.7	19.6	19.6	19.7	19.7
9	219.1	219.2	219.1	218.8	219.0	219.2	219.1	219.2	219.0	219.5	219.7
10	40.5	40.5	40.3	40.2	40.2	40.5	40.3	40.5	40.4	40.5	40.5
10-Me	15.0	14.9	15.1	15.1	14.9	14.9	15.0	15.0	14.9	15.0	15.1
11	64.0	63.8	64.9	64.4	64.0	64.0	63.9	64.2	64.0	64.1	64.1
12	85.2	85.2	85.4	85.6	84.9	85.3	85.4	85.3	85.4	85.2	85.3
12-Me	14.8	14.8	14.7	14.6	14.5	14.8	14.7	14.8	14.7	14.8	14.8
13	78.2	78.2	78.2	77.8	77.9	78.1	77.7	78.2	77.9	78.2	78.2
14	23.1	23.1	23.1	23.2	22.8	23.1	23.1	23.1	23.2	23.1	23.1
15	10.6	10.5	10.5	10.6	10.2	10.6	10.6	10.6	10.6	10.6	10.6
1′	102.3	102.3	102.3	102.1	101.9	102.2	102.2	102.3	102.3	102.2	102.2
2′	70.3	70.3	70.4	70.4	70.0	70.4	70.3	70.3	70.3	70.3	70.3
3′	67.0	67.0	67.1	67.1	66.7	67.1	67.0	67.0	68.7	67.0	67.0
4′	31.2	31.2	31.3	31.2	30.8	31.3	31.2	31.2	31.2	31.2	31.2
5′	69.4	69.4	69.3	69.3	69.0	69.3	69.3	69.3	69.3	69.4	69.4
5′-Me	21.2	21.1	21.1	21.2	20.8	21.1	21.2	21.1	21.1	21.1	21.2
16	59.1	59.1	58.8	61.8	58.8	59.7	61.3	59.2	60.7	59.4	60.1
17	52.4	53.4	51.3	51.9	52.2	53.2	53.2	52.5	52.8	52.3	53.3
19	159.5	159.6	159.8	160.0	159.3	159.6	159.8	159.6	159.8	159.6	159.6
20	43.4	43.1	44.1	43.8	43.0	43.3	43.2	43.6	43.3	43.3	43.3
21	25.8	25.8	26.0	25.9	25.5	25.8	25.9	25.8	25.8	25.8	25.8
22	46.5	46.8	46.5	47.5	46.4	46.4	46.9	46.5	47.0	46.4	47.4
AA-1	173.1	173.0	170.9	174.3	169.8	172.8	173.2	172.1	173.6	171.1	171.3
AA-2	64.1	64.2	72.2	71.6	67.9	63.7	63.6	69.0	68.7	32.5	32.5
AA-3	12.0	12.8	34.5	35.1	17.08	33.1	34.5	34.4	34.8	175.2	176.3
AA-3-Me			15.2	16.2							
AA-4			28.7	27.7			175.1	127.0	128.9		
AA-5			12.2	11.5				131.4	131.3		
AA-6								116.7	116.4		
AA-9								158.0	157.6		
AL-1	53.5	60.5	52.4	61.2	61.6	54.8	61.3	54.4	61.3	54.9	61.5
AL-2	27.4	35.6	26.8	36.8	35.0	28.7	42.2	27.6	36.3	28.6	35.8
AL-3	21.0	32.0	20.9	32.7	31.6	21.0	32.2	20.9	32.1	21.0	31.8
		32.0		32.6			32.2		32.1		31.7
AL-4	13.9	26.6	14.0	27.1	26.5	14.0	26.9	13.9	26.8	14.0	26.8
		26.6		27.0			27.0		26.8		26.6
AL-5		26.9		27.5	26.8		27.4		27.3		27.1
AL-6											
AR-1	52.2	39.5	52.3	50.1	38.9	52.2	39.6	52.2	39.4	52.3	65.0
AR-2	134.3	116.8	132.7	127.9	117.5	134.1	110.7	134.1	110.9	132.8	128.1
AR-3	131.3	150.7	130.2	150.1	151.4	131.3	150.7	131.3	158.4	131.0	150.2
AR-4	161.6	148.4	131.0	127.0	149.2	161.7	147.4	161.6	148.4	130.5	126.9
AR-4-MeO	55.8					55.9		55.8			
AR-5	115.9	120.5	130.5	132.6	120.5	116.1	120.7	115.9	120.6	130.2	132.4
AR-6	116.4	112.8		135.8	112.7	116.3	112.9	116.4	112.9		135.8
AR-7	122.9	162.7		135.0	157.9	122.9	162.7	122.9	162.5		134.9
3′-NMe-1	42.3	42.3	42.2	42.3	41.9	42.2	42.3	42.2	42.2	42.2	42.2
3′-NMe-2	37.4	37.4	37.6	37.5	37.1	37.5	37.4	37.4	37.4	37.4	37.4

each with DMF, MeOH, CH_2Cl_2, 1:1 DMF/CH_2Cl_2, 1:1 MeOH/CH_2Cl_2, and CH_2Cl_2 and dried in a vacuum desiccator. The ninhydrin test was positive.

Subsequently, in a peptide tube, the resin was rotated with benzaldehyde (20 μL, 0.2 mmol) in 10% AcOH/DMF (0.5 mL) for 2 h at which point the liquids were drained, and the reaction was repeated one more time with fresh portions of reagents. The resin was washed three times with DMF (10 mL each) and suspended again in 10% AcOH/DMF (0.5 mL). $NaCNBH_4$ (30 mg, excess) was added, and the tube was rotated overnight. The resin was washed two times each with DMF, MeOH, CH_2Cl_2, 1:1 DMF/CH_2Cl_2, 1:1 MeOH/CH_2Cl_2, and CH_2Cl_2 and dried in a vacuum desiccator. The ninhydrin test was negative.

11-Deoxy-11-(3-*N*-benzyl-aminopropanylamino)-11,12-carbamate-6-*O*-(*N*,*N*-*n*-butyl,L-isoleucine)ethyl-3-hydroxy-

Table 4. Elemental Analysis for Compounds **16a**−**k**

compd	elemental analysis calculated for	found
16a	$C_{58}H_{88}F_{12}N_4O_{21}$: C, 49.57; H, 6.31; F, 16.22; N, 3.99; O, 23.91.	C, 49.23; H, 6.23, N, 4.16
16b	$C_{60}H_{87}F_{15}N_4O_{20}$: C, 49.05; H, 5.97; F, 19.40; N, 3.81; O, 21.78	C, 48.16; H, 5.87; F, 18.01; N, 3.64
16c	$C_{60}H_{92}F_{12}N_4O_{20}$: C, 50.84; H, 6.54; F, 16.08; N, 3.95; O, 22.58	C, 50.56; H, 6.81; N, 4.19
16d	$C_{63}H_{95}F_{12}N_5O_{22}$: C, 50.36; H, 6.37; F, 15.17; N, 4.66; O, 23.43	C, 49.88; H, 6.57; N, 4.85
16e	$C_{60}H_{87}F_{15}N_4O_{21}$: C, 46.56; H, 5.55; F, 21.38; N, 3.50; O, 23	C, 45.96; H, 5.52; N, 2.94
16f	$C_{59}H_{88}F_{12}N_4O_{23}$: C, 48.89; H, 6.12; F, 15.73; N, 3.87; O, 25.39	C, 48.62; H, 6.06; N, 3.42
16g	$C_{61}H_{87}F_{15}N_4O_{22}$: C, 48.41; H, 5.79; F, 18.83; N, 3.70; O, 23.26	C, 48.62; H, 5.86; F, 16.49; N, 3.39
16h	$C_{64}H_{92}F_{12}N_4O_{22}$: C, 51.33; H, 6.19; F, 15.23; N, 3.74; O, 23.51	C, 51.22; H, 6.12; N, 3.34
16i	$C_{66}H_{91}F_{15}N_4O_{21}$: C, 50.77; H, 5.87; F, 18.25; N, 3.59; O, 21.52	C, 50.72; H, 5.79; F, 16.05; N, 3.23
16j	$C_{62}H_{89}F_{18}N_5O_{25}$: C, 45.23; H, 5.45; F, 20.77; N, 4.25; O, 24.30	C, 45.88; H, 5.59; N, 3.97
16k	$C_{65}H_{92}F_{18}N_6O_{27}$: C, 45.09; H, 5.36; F, 19.75; N, 4.85; O, 24.95	C, 45.41; H, 5.32; N, 4.65

erythronolide A (16c). In a vial, resin **15c** (0.01 mmol) was rotated with 90% TFA/CH_2Cl_2 (1 mL) for 1 h. The liquids were evaporated, and the cleaved product was taken up in MeOH and filtered. Evaporation of the solvent gave a crude product, which was further purified by high-throughput HPLC (MeCN/NH_4OAc−buffer) to give 3.3 mg of product (34% overall yield from **13c**, 26% yield from starting resin **11**). MS (ESI): *m*/*z* 961 [M + 1]. ^{1}H NMR ($CDCl_3$): δ (ppm) 7.54 (m, 2H, H-4AR), 7.40 (m, 3H, H-3AR, H-5AR), 5.00 (dd, J = 10.6 Hz, J = 2.6 Hz, 1H, H-13), 4.68 (d, J = 7.0 Hz, 1H, H-1′), 4.28 (d, J = 13.2 Hz, 1H, H-1bAR), 4.17 (d, J = 12.8 Hz, 1H, H-1aAR), 3.91 (d, J = 2.6 Hz, 1H, H-5), 3.79 (m, 1H, H-20b), 3.65 (m, 1H, H-5′), 3.59 (m, 1H, H-11), 3.46 (m, 1H, H-20a), 3.40 (dd, J = 10.6, J = 7.3 Hz, 1H, H-2′), 3.38 (m, 1H, H-16b), 3.34 (m, 1H, H-16a), 3.33 (m, 1H, H-3), 3.31 (m, 1H, H-10), 3.25 (m, 1H, H-3′) 3.11 (m, 2H, H-22), 2.91 (m, 1H, H-17b), 2.92 (m, 1H, H-2AA), 2.83 (m, 1H, H-1bAL), 2.76 (s, 6H, 3′-NMe), 2.73 (m, 1H, H-2), 2.71 (m, 1H, H-1aAL), 2.58 (m, 1H, H-8), 2.54 (m, 1H, H-17a), 2.33 (m, 1H, H-21b), 2.09 (m, 1H, H-21a), 1.99 (m, 1H, H-4′b), 1.96 (m, 1H, H-4), 1.95 (m, 1H, H-7b), 1.83 (m, 1H, H-14b), 1.78 (m, 1H, H-4bAA), 1.73 (m, 1H, H-3AA), 1.60 (m, 1H, H-14a), 1.56 (m, 1H, H-7a), 1.53 (m, 2H, H-2AL), 1.50 (s, 3H, 12-Me), 1.48 (m, 1H, H-4′a), 1.38 (m, 2H, H-3AL), 1.35 (s, 3H, 6-Me), 1.30 (d, J = 6.2 Hz, 3H, 5′-Me), 1.23 (d, J = 6.5 Hz, 3H, 2-Me), 1.16 (d, J = 7.4 Hz, 3H, 8-Me), 1.14 (m, 1H, H-4aAA), 1.11 (d, J = 7.4 Hz, 3H, 4-Me), 1.02 (d, 3H, 10-Me), 0.96 (t, J = 7.3 Hz, 1H, 3-MeAL), 0.94 (m, 3H, H-3-MeAA), 0.92 (t, J = 7.7 Hz, 3H, H-4-MeAA), 0.83 (t, J = 7.3 Hz, H-15). ^{13}C NMR ($CDCl_3$): δ (ppm) 218.2 (C-9), 178.1 (C-1AA), 176.9 (C-1), 133.4 (C-2AR), 131.0 (C-4AR), 130.2 (C-5AR), 130.0 (C-3AR), 102.3 (C-1′), 85.2 (C-12), 81.4 (C-5), 80.4 (C-6), 77.9 (C-3), 77.5 (C-13), 73.2 (C-2AA), 70.8 (C-2′), 69.4 (C-5′), 66.9 (C-3′), 64.0 (C-11), 62.9 (C-16), 53.0 (C-1AL), 52.1 (C-1AR), 52.0 (C-17), 47.1 (C-8), 46.3 (C-22), 45.7 (C-2), 43.8 (C-20), 40.2 (C-10), 40.1 (3′-NMe), 39.4 (C-7), 38.1 (C-4), 35.0 (C-3AA), 31.6 (C-4′), 31.1 (C-2AL), 27.2 (C-4AA), 25.9 (C-21), 23.4 (C-14), 21.4 (C-3AL), 21.2 (5′-Me), 21.0 (6-Me), 19.7 (8-Me), 16.5 (3-MeAA), 15.9 (2-Me), 15.0 (10-Me), 14.8 (12-Me), 14.5 (3-MeAL), 11.5 (4-MeAA), 10.6 (C-15), 9.2 (4-Me).

Compounds **16a**−**k** were prepared following the same procedure described above for the synthesis of **16c**. ^{1}H NMR and ^{13}C NMR data for these compounds are summarized in Tables 2 and 3. Elemental analysis data for compounds **16a**−**k** are presented in Table 4.

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References and Notes

(1) McGuire, J. M.; Bunch, R. L.; Anderson, R. C.; Boaz, H. E.; Flynn, E. H.; Powell, H. M.; Smith, J. W. "Ilotycin," A new antibiotic. *Antibiot. Chemother.* **1952**, *2*, 281−283.

(2) Wiley: P. F.; Gerzon, K.; Flynn, E. H.; Sigal, M. V. Jr.; Weaver, O.; Quarck, U. C.; Chauvette, R. R.; Monahan, R. Erythromycin. X. Structure of Erythromycin. *J. Am. Chem. Soc*. **1957**, *79*, 6062−6077.

(3) Harris, D. R.; McGeachin, S. G.; Mills, H. H. The Structure and Stereochemistry of Erythromycin A. *Tetrahedron Lett*. **1965**, *11*, 679−685.

(4) Latrey, P. A.; Perun, T. J. Synthetic Modifications of the Erythromycin A Macrolactone: Effects on Biological Activity. In *Studies in Natural Products Chemistry*; Rahman, A., Ed.; Elsevier Science Publishers B. V: Amsterdam, 1993; Vol. 13, pp 155−185.

(5) Chu, D. T. W.; Recent Progress in Novel Macrolides, Quinolones and 2-Pyridones to Overcome Bacterial Resistance. *Med. Res. Rev.* **1999**, *19*, 497−520.

(6) Or, Y. S.; Clark, R. F.; Wang, S.; Chu, D. T. W.; Nilius, A. M.; Flamm, R. K.; Mitten, M.; Ewing, P.; Alder, J.; Ma, Z. Design, Synthesis, and Antimicrobial Activity of 6-O-Substituted Ketolides Active against Resistant Respiratory Track Pathogens. *J. Med. Chem*. **2000**, *43*, 1045−1049.

(7) Bryskier, A.; Agouridas, C.; Chantot. J. F. New medical targets for macrolides. *Exp. Opin. Invest. Drugs* **1994**, *3*, 405−410.

(8) 3-Keto analogues are known to exhibit better antibacterial profiles than 3-OH analogues.

(9) For experimental details, see ref 6.

(10) Baker, W. R.; Clark, J. D.; Stephens, R. L.; Kim, K. H. Modifications of macrolide antibiotics. Synthesis of 11-deoxy-11-(carboxyamino)-6-*O*-methylerythromycin A 11,12-(cyclic esters) via intramolecular Michael reaction of *O*-carbamates with an α,β-unsaturated ketone. *J. Org. Chem*. **1988**, *53*, 2340−2345.

(11) Griesgraber, G.; Or, Y. S.; Chu, D. T. W.; Nilius, A. M.; Johnson, P. M.; Flamm, R. K.; Henry, R. F.; Plattner, J. J. 3-Keto-11,12-carbazate Derivatives of 6-*O*-Methylerythromycin A. Synthesis and In Vitro Activity. *J. Antibiot.* **1996**, *49*, 465−477.

(12) Hochlowski, J. E.; Whittern, D. N.; Sowin, T. J. Encoding of Combinatorial Chemistry Libraries by Fluorine-19 NMR. *J. Comb. Chem*. **1999**, *1*, 291−293.

(13) Searle, X.; Sowin, T. J. Unpublished results.

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