Anhydrolide Macrolides. 2. Synthesis and Antibacterial Activity of 2,3-Anhydro-6-*O*-methyl 11,12-Carbazate Erythromycin A Analogues

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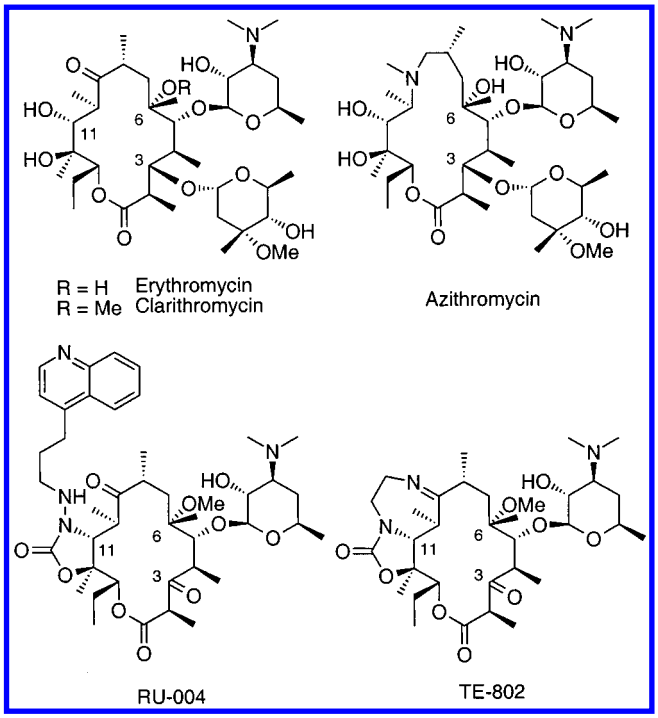
A series of 3-descladinosyl-2,3-anhydro-6-*O*-methylerythromycin A 11,12-cyclic carbazate analogues was prepared and evaluated for antibacterial activity. These 2,3-anhydro macrolides were found to be potent antibacterial agents in vitro against macrolide-susceptible organisms including *Staphylococcus aureus* 6538P, *Streptococcus pyogenes* EES61, and *Streptococcus pneumoniae* ATCC6303. These compounds were also very active against some organisms that show macrolide resistance (*S. aureus* A5177, *S. pyogenes* PIU2584, and *S. pneumoniae* 5649). The compounds generally showed poor activity against organisms with constitutive MLS resistance. Selected compounds were evaluated in vivo in mouse protection studies. Although most of the compounds tested in vivo showed poor efficacy, two compounds, **38** and **57**, were more active than clarithromycin against *S. pneumoniae* ATCC6303.

Introduction

Macrolide antibiotics, like erythromycin (Chart 1), have been extensively used in the treatment of bacterial infections for over 40 years. They are generally effective in the treatment of upper and lower respiratory tract infections, and because of their safety, they are often prescribed for children. Erythromycin however is quickly degraded under the acidic conditions found in the stomach to give inactive byproducts resulting in low bioavailability. Cleavage of the acid-labile cladinose moiety at C-3 is a common problem. Other degradation pathways which lead to inactive compounds often involve interaction of the hydroxyl groups at C-6 and C-12 with the carbonyl at C-9.[1] In addition to the loss of antibacterial activity, some of these degradation products have been shown to cause intestinal peristalsis resulting in the gastrointestinal discomfort often associated with taking this drug.[2]

Recently, semisynthetic erythromycin derivatives have been prepared which overcome some of the acid instability problems.[3] Clarithromycin, the 6-*O*-methyl derivative of erythromycin,[4] has the C-6 hydroxyl blocked which prohibits it from interacting with the C-9 carbonyl. In azithromycin, the C-9 carbonyl has been removed via a Beckmann rearrangement/ring expansion of erythromycin 9-oxime.[5,6] In addition to maintaining potent activity against erythromycin-sensitive organisms, these second-generation macrolides also show increased activity against *Legionella*, *Branhamella* spp., and *Chlamydia* and *Pasteurella mutocida*. Azithromycin also has therapeutic utility against *Haemophilus influenzae*, and clarithromycin exhibits good activity against *Helicobactor pylori* and has been approved in a combination regiment for the treatment of peptic ulcer disease.

Chart 1



Unfortunately, like erythromycin, both clarithromycin and azithromycin are ineffective against organisms that show macrolide−lincosamide−streptogramin B (MLS) cross-resistance. Organisms with this type of resistance are able to selectively dimethylate an adenine residue in their ribosomal RNA. This methylation occurs in the MLS binding region and thus confers resistance to macrolide, lincosamide, and streptogramin B antibiotics. Other forms of resistance include the presence of esterases which cleave the lactone ring and macrolide efflux mechanisms. Organisms with macrolide resistance are becoming more prevalent, especially in hos-

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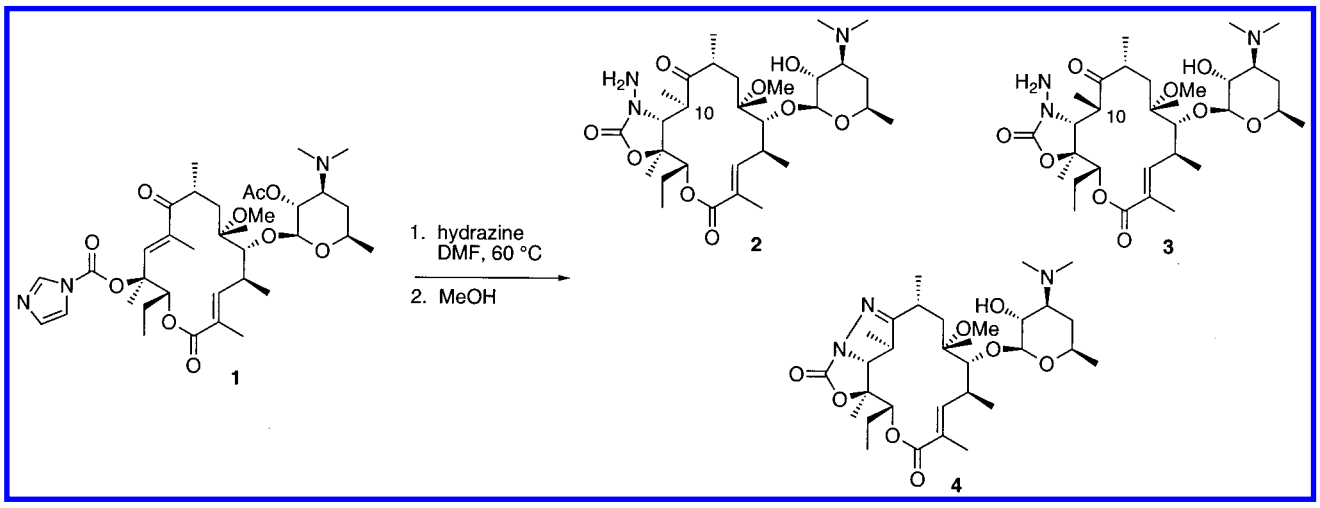
Scheme 1



pital settings. Recently, over 20% of the clinically isolated pneumoncocci in France were found to be resistant to macrolides, and in Japan 18−20% were resistant.[7] The incidence of macrolide resistance in staphylococci in clinical isolates from South Africa over a period from May 1992 to July 1992 was found to be about 70%.[8] Because of the increase in macrolide-resistant bacteria, much effort has gone into developing new macrolides with better activity against these organisms.

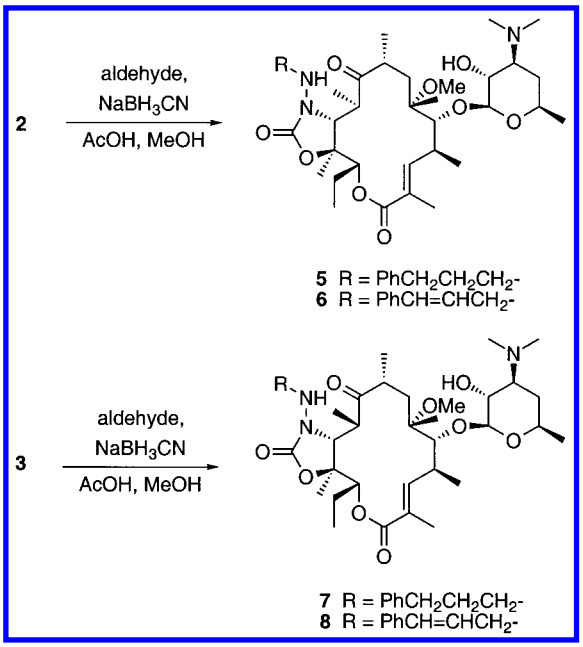
Recently, a series of 3-ketoclarithromycin derivatives was developed. In this series, the cladinose sugar has been removed and the resulting alcohol at the C-3 position was oxidized to a ketone. In addition to maintaining good activity against erythromycin-susceptible organisms, these "ketolides", which include RU-004[9,10] and TE-802,[11] also show activity against strains that have inducible MLS resistance. This 3-keto modification also disproved the long-held belief that the cladinose sugar was essential for antibacterial activity. With this knowledge, we undertook a search for new macrolide derivatives with novel modifications in this region of the molecule.

In the companion paper, we describe a series of clarithromycin derivatives that have been dehydrated at the 2,3-positions.[12] These compounds were further modified by forming cyclic carbamates at the 11,12-positions. While these compounds had increased activity against MLS-resistant organisms, the broad-spectrum activity was only moderate. On the basis of previous structure−activity relationship (SAR) studies, we felt that replacing the carbamate with a cyclic carbazate at the 11,12-positions would give compounds with better activity.[10,13] Herein, we describe the synthesis and antibacterial activity of these anhydrolide carbazates.

Chemistry

The key acylimidazolide intermediate **1** was prepared following the procedure described in the companion paper.[12] To prepare the parent carbazate, compound **1** was treated with hydrazine in dimethylformamide, followed by methanolysis of the 2′-acetate, to give the mixture of products shown in Scheme 1. Chromatographic separation of the mixture gave us the desired

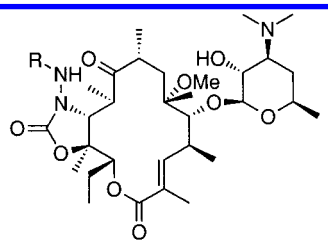
Scheme 2



carbazate **2** (39%) along with the epimeric 10(*S*)-carbazate **3** (49%). We also obtained a small amount of the pyrazoline **4** (6%) whose unique structure was determined by X-ray crystallography. The terminal amino group of carbazates **2** and **3** is set for further modification. From previous studies of 11,12-carbamate derivatives of clarithromycin[14] and our experience in the 3-keto carbazate series,[13] we felt that the most promising substituents on the carbazate nitrogen would consist of an aromatic ring attached by an alkyl chain.

Reductive alkylation of **2** with hydrocinnamaldehyde and cinnamaldehyde, in the presence of $NaBH_3CN$ and acetic acid, gave the desired compounds **5** and **6**, respectively (Scheme 2). The epimeric 10(*S*)-carbazate **3** also underwent successful alkylation to give compounds **7** and **8**. The overall antibacterial activity of the compounds with the natural 10(*R*) stereochemistry was better than that of the 10(*S*) compounds (vide infra), which is generally the case for macrolide derivatives of this type.[12,13] Because of this, we placed our emphasis on preparing compounds in the 10(*R*) series (Chart 2). Compounds **9**−**28** and **30**−**52** were prepared by reduc-

Chart 2



9	R = $PhCH_2$-	**34**	R = 4-NO_2-$PhCH_2$-
10	R = $Ph(CH_2)_2$-	**35**	R = 2-NO_2-$Ph(CH_2)_3$-
11	R = 1-naphthyl-CH=$CHCH_2$-	**36**	R = 3-NO_2-$Ph(CH_2)_3$-
12	R = 4-Cl-$PhCH_2$-	**37**	R = 4-NO_2-$Ph(CH_2)_3$-
13	R = 2-Cl-$Ph(CH_2)_3$-	**38**	R = 4-NO_2-PhCH=$CHCH_2$-
14	R = 3-Cl-$Ph(CH_2)_3$-	**39**	R = 5-NO_2-2-furanyl-CH=$CHCH_2$-
15	R = 4-Cl-$Ph(CH_2)_3$-	**40**	R = 2-OH-5-NO_2-$PhCH_2$-
16	R = 2,4-Cl-$Ph(CH_2)_3$-	**41**	R = 4-Me_2N-$PhCH_2$-
17	R = 4-F-$Ph(CH_2)_3$-	**42**	R = 4-Me_2N-naphthyl-CH_2-
18	R = 4-F_3C-$PhCH_2$-	**43**	R = 4-AcN-$PhCH_2$-
19	R = 4-MeO-$PhCH_2$-	**44**	R = 4-AcN-$Ph(CH_2)_3$-
20	R = 4-MeO-$Ph(CH_2)_3$-	**45**	R = 2-pyridyl-CH_2-
21	R = 4-PhO-$PhCH_2$-$_2$-	**46**	R = 3-pyridyl-CH_2-
22	R = 4-MeS-$PhCH_2$-	**47**	R = 4-pyridyl-CH_2-
23	R = 4-cyano-$PhCH_2$-	**48**	R = 4-quinolyl-$(CH_2)_3$-
24	R = 2-OH-$PhCH_2$-	**49**	R = 3-indolyl-CH_2-
25	R = 3-OH-$PhCH_2$-	**50**	R = 4-Ph-imidazolyl-$(CH_2)_3$-
26	R = 4-OH-$PhCH_2$-	**51**	R = 2-benzotriazolyl-$(CH_2)_3$-
27	R = 2,5-OH-$PhCH_2$-	**52**	R = 1-benzotriazolyl-$(CH_2)_3$-
28	R = 3,4-OH-$PhCH_2$-	**53**	R = 4-NH_2-$PhCH_2$-
29	R = 2-$HOCH_2$-$PhCH_2$-	**54**	R = 2-NH_2-$Ph(CH_2)_3$-
30	R = 2-OH-$Ph(CH_2)_3$-	**55**	R = 3-NH_2-$Ph(CH_2)_3$-
31	R = 3-OH-$Ph(CH_2)_3$-	**56**	R = 4-NH_2-$Ph(CH_2)_3$-
32	R = 4-OH-$Ph(CH_2)_3$-	**57**	R = 4-NH_2-PhCH=$CHCH_2$-
33	R = 2-OH-naphthyl-CH_2-	**58**	R = 4-AcN-PhCH=$CHCH_2$-

tive alkylation of **2** with the corresponding aldehydes. Compound **29** was prepared by reductive alkylation with terephthalaldehyde (benzene-1,4-dicarboxaldehyde); however, the second formyl group of the starting aldehyde undergoes reduction during the reaction to give the hydroxymethyl compound. The amino compounds **53**−**57** were prepared by reducing the corresponding nitro compounds **34**−**38** using Zn in the presence of HCl. Compound **58** was prepared by selective N-acetylation of **57** with acetyl chloride.

We were also able to perform some modifications on pyrazoline **4** (Scheme 3). The imine at C-9 was selectively reduced with $NaBH_3CN$ to give the tetrahydropyrazole **59**. This in turn was subjected to reductive alkylation to give phenylpropyl-substituted compound **60**.

Results and Discussion

All of the compounds were tested in vitro against a number of Gram-positive strains including *Staphylococcus aureus*, *Streptococcus pyogenes*, and *Streptococcus pneumoniae*. Table 1 shows the antibacterial activity against erythromycin-susceptible organisms (*S. aureus* 6538P, *S. pyogenes* EES61, and *S. pneumoniae* ATCC6303) and a number of erythromycin-resistant strains. The resistant strains can be broken down into different categories. Some of the organisms tested have MLS cross-resistance. *S. aureus* A5177 has inducible MLS resistance, while *S. aureus* A-5278, *S. pyogenes* 930, and *S. pneumoniae* 5979 have a constitutive form of MLS resistance. *S. pyogenes* PIU2584 and *S. pneumoniae* 5649 are also resistant to erythromycin, but unlike the organisms with MLS resistance, these organisms are susceptible to clindamycin and are probably resistant due to a macrolide efflux mechanism. We also tested against a strain of ampicillin-resistant *Haemophilus influenzae* to monitor activity against this Gram-negative organism.

The parent carbazate with the natural stereochemistry at C-10, compound **2**, has moderate antibacterial activity against the erythromycin-susceptible organisms but is less active than erythromycin itself. However, compound **2** has slightly better activity than erythromycin against *S. aureus* A5177, the strain with inducible MLS resistance, and much better activity against resistant *S. pyogenes* PIU2584 and *S. pneumoniae* 5649. No antibacterial activity was seen against the constitutively resistant strains. The compound with the 10-epi stereochemistry (**3**) showed a significant decrease in activity against all strains tested.

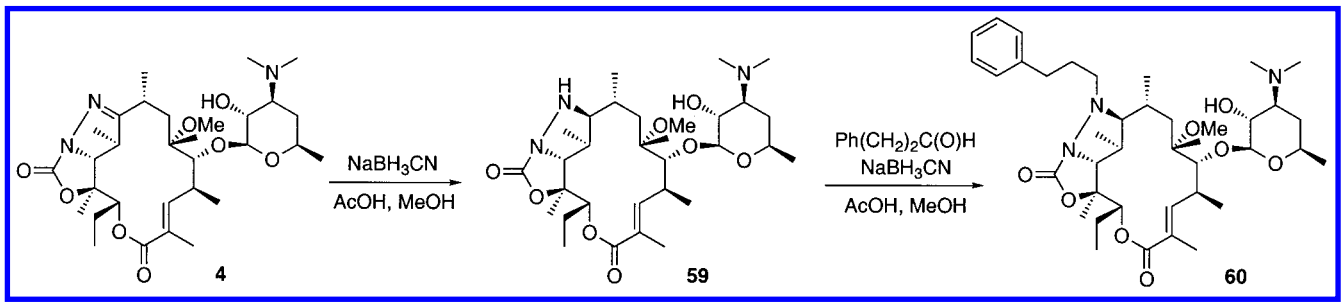
The alkylated carbazates generally showed much better activity than the parent compounds **2** and **3**. Compounds **5** and **6**, substituted with hydrocinnamyl and cinnamyl, respectively, showed erythromycin-like activity against susceptible strains and very good activity against the resistant *S. aureus* A5177, *S. pyogenes* PIU2584, and *S. pneumoniae* 5649. The activity against the constitutively resistant organisms, while still poor, was better than that of erythromycin itself. The alkylated compounds with the 10(*S*) stereochemistry, **7** and **8**, showed better activity than the parent carbazate **3**, but the overall activity is significantly lower compared to the activity of the analogous compounds with 10(*R*) stereochemistry. However, the alkylated derivatives with 10(*S*) stereochemistry did show a slight improvement against the constitutively resistant organisms.

The remaining carbazates (**9**−**58**) all have the natural C-10(*R*) stereochemistry. The compounds generally maintained good activity against the erythromycin-susceptible organisms and against the resistant *S. aureus* A5177, *S. pyogenes* PIU2584, and *S. pneumoniae* 5649. The best compounds against these organisms have the hydroxy- and nitro-substituted aromatic rings (**24**−**26**, **29**−**33**, **34**−**40**). While most of the compounds tested were still inactive against the constitutively resistant organisms, a few, especially the compounds with the unsubstituted and halogenated aromatic rings (**10**−**16**, **21**), started to show some activity against these organisms. There were even a few compounds identified (**24**, **39**, **48**, **57**) with increased activity against *H. influenzae*.

The pyrazoline **4** had no antibacterial activity in our screen. This was somewhat surprising considering the similarity in structure to TE-802.[11] The strain of the fused pyrazoline and carbamate rings, perhaps, forces the rest of the macrolide into a conformation unfavorable for ribosomal binding. The reduced compound **59** and the alkylated compound **60** were also very poor antibacterial agents.

The 2,3-anhydro 11,12-carbazates have in vitro activity similar to that of the 3-keto analogues that we had previously prepared.[13] Both classes retain activity against erythromycin-susceptible strains and show increased activity against the resistant *S. aureus* A5177, *S. pyogenes* PIU2584, and *S. pneumoniae* 5649. Due to its activity against MLS-resistant organisms, RU-004

Scheme 3



has been the most publicized member of the 3-keto macrolides.[9,10] This compound, which contains a 4-quinolylpropyl side chain attached to the 11,12-carbazate, was prepared at Roussel-Uclaf by the group that had done the initial research efforts in the 3-keto class of clarithromycin derivatives. When we compare the in vitro activity of RU-004 with its 2,3-anhydro counterpart, compound **48**, we see that RU-004 is slightly more active against most of the strains tested. Where RU-004 is clearly superior to **48** is against the constitutively resistant organisms *S. pyogenes* 930 (RU-004 MIC = 2 μg/mL vs **48** MIC > 64 μg/mL) and *S. pneumoniae* 5979 (RU-004 MIC = 8 μg/mL vs **48** MIC > 64 μg/mL). RU-004 is rather unique in its increased in vitro activity against these organisms because the majority of compounds in both the 3-keto and 2,3-anhydro classes lack this ability. However, RU-004 still lacks activity against the constitutively resistant *S. aurues* A-5278.

Compounds **2**, **5**, **15**, **32**, **38**, **43**, **48**, and **57** were evaluated for in vivo activity against the macrolide-susceptible strains *S. aureus* NCTC10649M and *S. pnuemoniae* ATCC6303 in mouse protection studies following protocols described previously.[15] Compounds **2**, **5**, **15**, **32**, **43**, and **48** were all at least 2-fold less active than the standard, clarithromycin, against both organisms (data not shown). However, the compounds with the 4-nitro (**38**)- and 4-amino (**57**)-substituted cinnamyl side chains, while still 2-fold less active than clarithromycin against *S. aureus* NCTC10649M, were much better than clarithromycin against *S. pneumoniae* ATCC6303 (Table 2). Compound **38** was approximately 2-fold more active and compound **57** was approximately 3-fold more active than clarithromycin against this strain.

Conclusion

In summary, a series of N-alkylated derivatives of 2,3-anhydro-11-hydrazo-6-*O*-methylerythromycin 11,12-cyclic carbazates was prepared and evaluated for in vitro antibacterial activity. These compounds were generally better than or equal to erythromycin in potency when tested against macrolide-susceptible organisms. More importantly, these compounds had increased activity against the erythromycin-resistant strains *S. aureus* A5177, *S. pyogenes* PIU2584, and *S. pneumoniae* 5649. It appears that like the 3-ketolides, these 2,3-anhydro derivatives also do not induce MLS resistance. These compounds, however, were not very active against organisms with constitutive MLS resistance. The encouraging in vivo data of compounds **38** and **57** warrant further investigation. We are currently evaluating more compounds from this class in vivo, and the results will be reported in due time.

Experimental Section

All solvents and reagents were reagent grade unless otherwise noted. Elemental analyses were obtained from Robertson Laboratories, Madison, NJ. Chromatographic purifications were carried out using flash chromatography (60 mesh silica gel, 0.04−0.063 mm; E. Merck). ^{1}H and ^{13}C NMR spectra were taken in $CDCl_3$ at 300 or 500 MHz, and chemical shifts are reported in ppm relative to $CHCl_3$ assigned at 7.26 and 77.0 ppm, respectively. Proton assignments were determined from ^{1}H−^{1}H COSY experiments and can be found in the Supporting Information. All final compounds, unless otherwise noted, were analyzed by ^{1}H NMR, ^{13}C NMR, MS, and elemental analysis and in general had a chemical purity of >95% as determined by ^{1}H NMR. 3-(2-Chlorophenyl)propanal, 3-(3-chlorophenyl)propanal, 3-(4-chlorophenyl)propanal, 3-(2,4-dichlorophenyl)propanal, 3-(2-hydroxyphenyl)propanal, 3-(3-hydroxyphenyl)propanal, 3-(4-hydroxyphenyl)propanal, 3-(4-methoxyphenyl)propanal, 3-(2-nitrophenyl)propanal, 3-(3-nitrophenyl)propanal, 3-(4-nitrophenyl)propanal, and 3-(4-acetamidophenyl)propanal were prepared by the Pd-mediated coupling of the corresponding aryl iodides with allyl alcohol.[16] The preparation of 3-(1-benzotriazolyl)propanal, 3-(2-benzotriazolyl)propanal, 3-(4-phenylimidazolyl)propanal, and 3-(4-quinolyl)propanal is described below. All other reagents were purchased from Aldrich Chemical Co. and used without further purification.

For in vitro studies, the minimum inhibitory concentrations were determined by standard agar dilution methods.[17]

2,3-Anhydro-5-*O*-desosaminyl-11-hydrazo-6-*O*-methylerythronolide A, 11,12-Carbamate (2). A solution of the 12-*O*-acylimidazolyl compound **1** (4.00 g, 5.81 mmol) dissolved in 20 mL of DMF was treated with hydrazine (0.45 mL, 14.4 mmol, 2.5 equiv). After stirring for 30 min, the reaction mixture was diluted with CH_2Cl_2 (200 mL) and washed with 5% KH_2PO_4 solution and H_2O (3×). The organic portion was dried with Na_2SO_4 and concentrated under reduced pressure to give a white foam. This was dissolved in 50 mL of MeOH, and the reaction mixture was left standing overnight. The MeOH was then removed under reduced pressure. Chromatography (SiO_2, 10% MeOH/*tert*-butyl methyl ether with 1% NH_4OH) separated the 10(*S*)-epimer **3** (1.73 g) from the 10(*R*)-epimer **2** and the dihydropyrazole **4**. A second chromatography (5−10% MeOH/CH_2Cl_2 with 0.2% NH_4OH) separated the 10(*R*)-epimer **2** (1.38 g) and the dihydropyrazole **4** (0.22 g). Compound **2**: CI MS *m*/*z* 612 $(M + H)^+$; ^{13}C NMR ($CDCl_3$) δ 216.9, 169.6, 155.9, 146.6, 122.9, 104.7, 83.2, 81.7, 78.9, 77.9, 70.2, 69.5, 65.7, 63.1, 48.8, 44.4, 40.3, 40.1, 37.0, 28.3, 21.7, 21.0, 19.9, 17.7, 16.9, 14.0, 12.6, 10.5. Anal. ($C_{31}H_{53}N_3O_9$) C, H, N.

10-*epi*-2,3-Anhydro-5-*O*-desosaminyl-11-hydrazo-6-*O*-methylerythronolide A, 11,12-carbamate (3): CI MS *m*/*z* 612 $(M + H)^+$; ^{13}C NMR ($CDCl_3$) δ 215.1, 171.9, 157.3, 144.5, 124.1, 105.2, 83.9, 83.8, 78.6, 78.3, 70.4, 69.5, 65.6, 63.7, 50.4, 45.6, 42.6, 41.0, 40.2, 36.8, 28.3, 21.2, 21.2, 21.0, 19.9, 17.4, 16.9, 11.7, 10.4, 10.4. Anal. ($C_{31}H_{53}N_3O_9$) C, H, N.

2,3-Anhydro-9-deoxo-5-*O*-desosaminyl-11-hydrazo-6-*O*-methylerythronolide A, 9-imine 11,12-carbamate (4): CI

Table 1. In Vitro Activity of 2,3-Anhydro-6-*O*-methyl 11,12-Carbazate Erythromycin Analogues

	MIC (μg/mL)									
	S. aureus			*S. pyogenes*			*S. pneumoniae*			*H. flu*
entry	6538P[a]	A5177[b]	A-5278[c]	EES61[a]	PIU2584[d]	930[c]	ATCC6303[a]	5649[d]	5979[c]	DILL
Ery A	0.2	3.1	>100	0.03	32	>128	0.06	16	>128	4
2	1.56	1.56	>100	0.25	1	>64	0.25	1	>64	32
3	50	50	>100	8	32	>128	8	16	>128	>128
4	>100	>100	>100	>128	>128	>128	>128	>128	>128	>128
5	0.1	0.1	50	0.06	1	32	0.125	2	64	16
6	0.02	0.1	100	0.06	0.5	32	0.03	1	32	8
7	12.5		25	2	8	8	2	8	16	>128
8	12.5	6.2	50	4	8	16	1	4	16	>64
9	0.39	0.2	>100	0.03	1	>64	0.06	1	>64	8
10	0.78	0.78	>100	0.25	2	64	0.25	2	>64	>64
11	0.39	0.39	25	0.125	1	8	0.125	1	16	16
12	0.2	0.2	100	0.03	1	32	0.06	1	32	16
13	0.2	0.2	50	0.03	1	16	0.125	1	32	16
14	0.39	0.39	50	0.25	1	16	0.25	2	32	32
15	0.1	0.05	25	0.125	1	16	0.03	1	16	16
16	0.39	0.39	25	0.06	1	8	0.125	2	8	16
17	0.39	0.2	50	0.03	1	64	0.06	1	64	16
18	0.78	0.78	100	0.06	2	16	0.06	2	16	16
19	0.2	0.2	>100	0.03	1	>64	0.125	2	>64	8
20	0.39	0.39	>100	0.03	1	64	0.06	2	>64	16
21	1.56	1.56	25	0.25	2	8	0.25	2	16	>64
22	0.39		>100	0.03	1	64	0.03	0.5	64	8
23	0.05	0.02	>100	0.015	0.5	128	0.03	0.5	>128	4
24	0.2	0.2	>100	0.03	0.5	>64	0.06	2	>64	2
25	0.2	0.1	>100	0.03	0.5	>128	0.03	1	>128	4
26	0.2	0.2	>100	0.03	1	>128	0.03	1	>128	4
27	3.1	3.1	>100	0.25	4	128	0.25	2	128	32
28	0.78	0.78	>100	1	16	>128	1	2	>128	32
29	0.2	0.2	>100	0.03	0.5	>128	0.03	1	>128	4
30	0.2	0.2	>100	0.03	2	>128	0.03	2	>128	16
31	0.1	0.1	>100	0.06	1	128	0.03	0.5	>128	4
32	0.2	0.1	>100	0.004	0.25	>64	0.004	1	>64	4
33	0.2		100	0.06	0.5	32	0.03	0.25	32	8
34	0.05	0.05	>100	0.03	1	128	0.03	1	>128	8
35	0.1	0.01	>100	0.03	0.5	64	0.03	1	128	8
36	0.2	0.2	>100	0.004	0.25	64	0.004	0.25	128	8
37	0.1	0.1	>100	0.03	1	64	0.03	1	64	8
38	0.2	0.2	100	0.06	1	32	0.03	1	64	8
39	0.02	0.01	>100	0.004	0.25	64	0.03	0.5	>128	2
40	0.1		>100	0.015	0.25	>128	0.03	0.25	>128	4
41	0.2	0.2	>100	0.125	1	128	0.125	1	>128	16
42	3.1	3.1	100	0.25	2	16	0.5	2	32	16
43	0.78	0.78	>100	0.03	2	>64	0.125	1	>64	4
44	0.39	0.39	>100	0.06	2	>128	0.06	2	>128	8
45	0.39	0.39	>100	0.06	1	>128	0.06	1	>128	8
46	0.39	0.39	>100	0.03	1	>64	0.06	1	>64	8
47	0.39	0.2	>100	0.03	0.5	>128	0.03	1	>128	8
48	0.2	0.1	>100	0.004	0.5	>64	0.004	1	>64	2
49	0.39	0.39	>100	0.06	0.5	>64	0.125	1	>64	8
50	0.2		>100	0.03	1	128	0.03	0.5	>128	8
51	0.2	0.2	>100	0.004	1	128	0.004	0.5	>128	8
52	0.2	0.1	>100	0.03	1	>128	0.03	1	>128	4
53	0.78	0.78	>100	0.06	1	>128	0.25	1	>128	16
54	0.39	0.39	>100	0.06	1	128	0.03		>128	16
55	0.2	0.2	>100	0.03	1	>128	0.03		>128	4
56	0.39		>100	0.03	1	>128	0.03	1	>128	4
57	0.2	0.2	>100	0.03	1	>128	0.03	1	>128	2
58	0.2	0.2	>100	0.06	1	>64	0.03	1	>64	4
59	>100	>100	>100	>128	>128	>128	>128	>128	>128	>128
60	100	50	100	16	64	64	16	64	64	>64
RU-004	0.1	0.05	>100	0.008	0.25	2	0.004	0.5	8	1

[a] *S. aureus* 6538P, *S. pyogenes* EES61, and *S. pneumoniae* ATCC6303: erythromycin-susceptible. [b] *S. aureus* A5177: inducible MLS resistance. [c] *S. aureus* A-5278, *S. pyogenes* 930, and *S. pneumoniae* 5979: constitutive MLS resistance. [d] *S. pyogenes* PIU2584 and *S. pneumoniae* 5649: erythromycin-resistant, clindamycin-susceptible.

MS *m/z* 594 $(M + H)^+$; ^{13}C NMR ($CDCl_3$) δ 171.3, 166.9, 156.4, 145.1, 124.3, 105.1, 86.6, 84.6, 80.1, 79.5, 73.7, 70.8, 69.4, 65.9, 50.4, 44.8, 40.3, 40.0, 38.1, 30.8, 28.6, 26.2, 25.7, 21.8, 21.4, 19.7, 18.0, 17.9, 12.0, 12.0. Anal. ($C_{31}H_{51}N_3O_8$) C, H, N.

Gereral Procedure for the Preparation of Alkylated Carbazates 5−52. 2,3-Anhydro-5-*O*-desosaminyl-11-[(3-phenylpropyl)hydrazo]-6-*O*-methylerythronolide A, 11,-12-Carbamate (5). A solution of **2** (263 mg, 0.430 mmol) dissolved in 5 mL of MeOH was treated with hydrocinnamaldehyde (280 μL, 2.13 mmol, 5 equiv) and AcOH (122 μL, 2.13 mmol, 5 equiv). The reaction mixture was stirred under N_2 and monitored by TLC. After the starting material had been consumed, $NaBH_3CN$ (200 mg) was added and additional acetic acid was added dropwise until bromocresol green

Table 2. In Vivo Efficacy of Compounds **38** and **57**[a,b]

	S. aureus NCTC10649M		*S. pneumoniae* ATCC6303	
entry	MIC (μg/mL)	ED_{50}	MIC (μg/mL)	ED_{50}
38	0.2	50.1 (31.7−79.2)	0.004	16.8 (9.1−31.0)
57	0.2	39.9 (25.6−62.3)	0.03	9.9 (6.7−14.7)
clarithromycin[c]	0.39	22.4−24.8 (13.3−37.9)	0.03	27.2−34.6 (20.2−52.7)

[a] Values are ED_{50} reported in mg/kg/day (95% confidence interval). [b] Mice were intraperitoneally infected with 1000 × LD_{50} for *S. aureus* and 100 × LD_{50} for *S. pneumoniae*. Macrolides were administered orally at 1 and 5 h pi. [c] Values for clarithromycin represent the range for two trials.

indicator had turned from blue to yellow. After stirring for 3 h, the reaction mixture was added to saturated $NaHCO_3$ solution and extracted into CH_2Cl_2. The organic portion was washed with H_2O and brine, dried over Na_2SO_4, and concentrated under reduced pressure. Chromatography (5% MeOH/CH_2Cl_2 containing 0.1% concentrated NH_4OH) gave the product as a white solid (159 mg, 51% yield): CI MS *m/z* 730 $(M + H)^+$; ^{13}C NMR ($CDCl_3$) δ 217.2, 169.1, 155.8, 145.9, 142.1, 128.4, 128.1, 125.5, 123.9, 104.8, 83.1, 81.5, 78.9, 77.8, 70.2, 69.6, 65.7, 57.9, 49.0, 48.0, 44.3, 40.7, 40.1, 40.0, 37.2, 33.2, 29.5, 28.1, 21.8, 21.1, 20.4, 18.2, 17.0, 14.7, 14.5, 13.0, 10.6. Anal. ($C_{40}H_{63}N_3O_9$) C, H, N.

2,3-Anhydro-5-*O*-desosaminyl-11-[(3-phenyl-2-propenyl)hydrazo]-6-*O*-methylerythronolide A, 11,12-Carbamate (6). The title compound was prepared from **2** and cinnamaldehyde. Chromatography (4% MeOH/CH_2Cl_2 containing 0.2% concentrated NH_4OH) gave the product as a white foam (27% yield): CI MS *m/z* 728 $(M + H)^+$; ^{13}C NMR ($CDCl_3$) δ 217.5, 169.4, 156.0, 146.2, 136.9, 134.0, 128.4, 127.4, 126.7, 125.8, 123.8, 105.0, 83.3, 81.8, 79.0, 78.6, 70.3, 69.8, 65.8, 57.8, 51.0, 49.5, 44.4, 40.8, 40.2, 40.1, 37.4, 28.2, 21.8, 21.2, 20.5, 18.4, 17.1, 14.8, 14.8, 13.1, 10.4. Anal. ($C_{40}H_{61}N_3O_9$) C, H, N.

10-*epi*-2,3-Anhydro-5-*O*-desosaminyl-11-[(3-phenylpropyl)hydrazo]-6-*O*-methylerythronolide A, 11,12-Carbamate (7). The title compound was prepared from **3** and hydrocinnamaldehyde. Chromatography (5% MeOH/CH_2Cl_2 containing 0.2% concentrated NH_4OH) gave the product as a white foam (47% yield): CI MS *m/z* 730 $(M + H)^+$; ^{13}C NMR ($CDCl_3$) δ 214.9, 171.7, 156.5, 144.4, 141.7, 128.3, 128.2, 125.9, 124.3, 105.1, 83.9, 83.8, 78.6, 78.0, 70.4, 69.6, 65.6, 62.7, 50.1, 49.7, 46.0, 42.1, 41.0, 40.2, 36.8, 33.3, 29.5, 28.3, 21.4, 21.2, 20.9, 19.8, 17.5, 16.9, 11.8, 10.5, 10.4. Anal. ($C_{40}H_{63}N_3O_9$) C, H, N.

10-*epi*-2,3-Anhydro-5-*O*-desosaminyl-11-[(3-phenyl-2-propenyl)hydrazo]-6-*O*-methylerythronolide A, 11,12-Carbamate (8). The title compound was prepared from **3** and cinnamaldehyde. Chromatography (5% MeOH/CH_2Cl_2 containing 0.2% concentrated NH_4OH) gave the product as a white foam (35% yield): CI MS *m/z* 728 $(M + H)^+$; ^{13}C NMR ($CDCl_3$) δ 215.0, 171.9, 156.7, 144.5, 136.8, 134.0, 128.5, 127.7, 126.5, 124.5, 124.3, 105.3, 84.2, 84.0, 78.7, 78.2, 70.5, 69.6, 65.8, 62.6, 52.3, 50.3, 46.1, 42.4, 41.1, 40.3, 37.0, 28.5, 21.5, 21.3, 20.9, 19.9, 17.5, 17.0, 11.9, 10.5, 10.4. Anal. ($C_{40}H_{61}N_3O_9$) C, H, N.

2,3-Anhydro-5-*O*-desosaminyl-11-[(phenylmethyl)hydrazo]-6-*O*-methylerythronolide A, 11,12-Carbamate (9). The title compound was prepared from **2** and benzaldehyde. Chromatography (5% MeOH/CH_2Cl_2 with 0.1% NH_4OH) gave the compound as a white powder (57% yield): CI MS *m/z* 702 $(M + H)^+$; ^{13}C NMR ($CDCl_3$) δ 217.2, 169.3, 155.6, 146.0, 136.7, 129.2, 128.2, 127.4, 124.2, 104.9, 83.4, 81.6, 79.2, 77.3, 70.4, 69.8, 65.8, 58.6, 52.6, 49.6, 44.3, 41.1, 40.2, 40.1, 37.4, 28.3, 21.9, 21.2, 20.8, 18.4, 17.2, 14.9, 14.4, 13.1, 10.7. Anal. ($C_{38}H_{59}N_3O_9$) C, H, N.

2,3-Anhydro-5-*O*-desosaminyl-11-[(2-phenylethyl)hydrazo]-6-*O*-methylerythronolide A, 11,12-Carbamate (10). The title compound was prepared from **2** and phenylacetaldehyde. Chromatography (4% MeOH/CH_2Cl_2 with 0.1% NH_4OH) gave the compound as a white powder (37% yield): CI MS *m/z* 716 $(M + H)^+$; ^{13}C NMR ($CDCl_3$) δ 217.1, 169.2, 155.9, 146.1, 139.4, 128.7, 128.2, 125.9, 123.8, 104.8, 83.2, 81.6, 78.9, 77.8, 70.2, 69.6, 65.7, 58.4, 50.1, 49.1, 44.2, 40.8, 40.1, 40.0, 37.2, 34.4, 28.1, 21.8, 21.1, 20.4, 18.2, 17.0, 14.7, 14.4, 13.0, 10.7. Anal. ($C_{39}H_{61}N_3O_9$) C, H, N.

2,3-Anhydro-5-*O*-desosaminyl-11-[(3-(1-naphthyl)-2-propenyl)hydrazo]-6-*O*-methylerythronolide A, 11,12-Carbamate (11). The title compound was prepared from **2** and 3-(1-naphthyl)-2-propenal. Chromatography (5% MeOH/CH_2Cl_2 with 0.1% NH_4OH) gave the compound as a white solid (81% yield): CI MS *m/z* 778 $(M + H)^+$; ^{13}C NMR ($CDCl_3$) δ 217.1, 169.3, 155.9, 146.3, 134.6, 133.4, 131.1, 130.6, 129.0, 128.1, 127.5, 125.7, 125.6, 125.4, 124.1, 123.7, 104.8, 83.3, 81.8, 79.0, 78.0, 70.2, 69.6, 65.7, 57.8, 51.1, 49.4, 44.2, 40.7, 40.1, 39.9, 37.3, 28.1, 21.5, 21.1, 20.4, 18.2, 17.0, 14.6, 12.9, 10.1. Anal. ($C_{44}H_{63}N_3O_9$) C, H, N.

2,3-Anhydro-5-*O*-desosaminyl-11-[((4-chlorophenyl)methyl)hydrazo]-6-*O*-methylerythronolide A, 11,12-Carbamate (12). The title compound was prepared from **2** and 4-chlorobenzaldehyde. Chromatography (3% MeOH/CH_2Cl_2 with 0.1% NH_4OH) gave the compound as a white solid (47% yield): CI MS *m/z* 736 $(M + H)^+$; ^{13}C NMR ($CDCl_3$) δ 217.5, 169.4, 155.5, 146.2, 135.3, 133.2, 130.7, 128.4, 124.0, 104.9, 83.2, 81.6, 79.2, 78.2, 70.3, 69.8, 65.8, 58.2, 51.8, 49.5, 44.4, 40.9, 40.2, 40.1, 37.4, 28.2, 21.8, 21.2, 20.7, 18.4, 17.1, 14.8, 14.6, 13.1, 10.7. Anal. ($C_{38}H_{58}ClN_3O_9$) C, H, N.

2,3-Anhydro-5-*O*-desosaminyl-11-[(3-(2-chlorophenyl)propyl)hydrazo]-6-*O*-methylerythronolide A, 11,12-Carbamate (13). The title compound was prepared from **2** and 3-(2-chlorophenyl)propanal. Chromatography (3% MeOH/CH_2Cl_2 with 0.1% NH_4OH) gave the compound as a white foam (27% yield): CI MS *m/z* 764 $(M + H)^+$; ^{13}C NMR ($CDCl_3$) δ 217.3, 169.3, 155.9, 146.1, 139.8, 133.9, 130.7, 129.3, 127.2, 126.8, 124.0, 104.9, 83.3, 81.7, 79.1, 77.9, 70.4, 69.8, 65.9, 58.1, 49.2, 48.1, 44.4, 40.9, 40.3, 40.2, 37.4, 31.1, 28.4, 27.9, 21.9, 21.2, 20.5, 18.4, 14.8, 14.6, 13.1, 10.7. Anal. ($C_{40}H_{62}ClN_3O_9$) C, H, N.

2,3-Anhydro-5-*O*-desosaminyl-11-[(3-(3-chlorophenyl)propyl)hydrazo]-6-*O*-methylerythronolide A, 11,12-Carbamate (14). The title compound was prepared from **2** and 3-(3-chlorophenyl)propanal. Chromatography (3% MeOH/CH_2Cl_2 with 0.1% NH_4OH) gave the compound as a white foam (50% yield): CI MS *m/z* 764 $(M + H)^+$; ^{13}C NMR ($CDCl_3$) δ 217.3, 169.3, 155.9, 146.0, 144.3, 134.0, 129.5, 128.6, 126.8, 125.8, 124.1, 104.9, 83.2, 81.7, 79.1, 77.9, 70.4, 69.8, 65.9, 58.0, 49.2, 47.9, 44.4, 40.8, 40.2, 37.4, 33.0, 29.4, 28.3, 21.9, 21.2, 20.5, 18.3, 17.1, 14.8, 14.6, 13.1, 10.7. Anal. ($C_{40}H_{62}ClN_3O_9$) C, H, N.

2,3-Anhydro-5-*O*-desosaminyl-11-[(3-(4-chlorophenyl)propyl)hydrazo]-6-*O*-methylerythronolide A, 11,12-Carbamate (15). The title compound was prepared from **2** and 3-(4-chlorophenyl)propanal. Chromatography (10% MeOH/*tert*-butyl methyl ether with 1% NH_4OH) gave the compound as a white foam (57% yield): CI MS *m/z* 764 $(M + H)^+$; ^{13}C NMR ($CDCl_3$) δ 217.3, 169.2, 155.8, 145.9, 140.5, 131.2, 129.8, 128.2, 124.0, 104.8, 83.0, 81.6, 78.9, 77.7, 70.2, 69.6, 65.7, 57.9, 49.0, 47.8, 44.4, 40.6, 40.1, 40.1, 37.2, 32.5, 32.5, 29.4, 28.2, 21.8, 21.1, 20.4, 18.2, 17.0, 14.7, 14.5, 13.0, 10.7. Anal. ($C_{40}H_{62}ClN_3O_9$) C, H, N.

2,3-Anhydro-5-*O*-desosaminyl-11-[(3-(2,4-dichlorophenyl)propyl)hydrazo]-6-*O*-methylerythronolide A, 11,12-Carbamate (16). The title compound was prepared from **2** and 3-(2,4-dichlorophenyl)propanal. Chromatography (5−10% MeOH/*tert*-butyl methyl ether with 1% NH_4OH) gave the compound as a white foam (36% yield): CI MS *m/z* 799 $(M + H)^+$; ^{13}C NMR ($CDCl_3$) δ 216.9, 168.8, 155.5, 145.6, 137.9, 134.1, 131.8, 131.2, 128.6, 126.6, 123.7, 104.4, 82.8, 81.2, 78.6, 77.4, 69.9, 69.3, 65.5, 57.6, 48.8, 44.0, 40.4, 39.8, 39.7, 36.9,

28.1, 21.5, 20.8, 20.1, 17.9, 16.7, 14.4, 14.2, 12.7, 10.3. Anal. ($C_{40}H_{61}Cl_2N_3O_9$) C, H, N.

2,3-Anhydro-5-*O*-desosaminyl-11-[(3-(4-fluorophenyl)-propyl)hydrazo]-6-*O*-methylerythronolide A, 11,12-Carbamate (17). The title compound was prepared from **2** and 3-(4-fluorophenyl)propanal. Chromatography (3% MeOH/CH_2Cl_2 with 0.1% NH_4OH) gave the compound as a white solid (61% yield): CI MS *m/z* 748 $(M + H)^+$; ^{13}C NMR ($CDCl_3$) δ 217.3, 169.3, 161.3, 155.9, 146.0, 137.7, 129.8, 124.1, 114.9, 104.9, 83.2, 81.6, 79.1, 77.9, 70.4, 69.8, 65.8, 58.1, 49.1, 47.9, 44.7, 40.8, 40.2, 40.1, 37.4, 32.5, 29.7, 28.2, 21.9, 21.2, 20.5, 18.3, 17.1, 14.8, 14.6, 13.1, 10.7. Anal. ($C_{40}H_{62}FN_3O_9$) C, H, N.

2,3-Anhydro-5-*O*-desosaminyl-11-[((4-(trifluoromethyl)-phenyl)methyl)hydrazo]-6-*O*-methylerythronolide A, 11,-12-Carbamate (18). The title compound was prepared from **2** and 4-(trifluoromethyl)benzaldehyde. Chromatography (5% MeOH/CH_2Cl_2 with 0.1% NH_4OH) gave the compound as a fluffy white solid (42% yield): CI MS *m/z* 770 $(M + H)^+$; ^{13}C NMR ($CDCl_3$) δ 217.5, 169.4, 155.5, 146.2, 140.9, 129.5, 125.2, 124.1, 104.9, 83.3, 81.7, 79.3, 78.2, 70.4, 69.8, 65.8, 58.3, 52.1, 49.6, 44.4, 41.0, 40.2, 40.1, 37.4, 28.3, 21.8, 21.2, 20.7, 18.4, 17.2, 14.8, 14.5, 13.1, 10.6. Anal. ($C_{39}H_{58}F_3N_3O_9$) C, H, N.

2,3-Anhydro-5-*O*-desosaminyl-11-[((4-methoxyphenyl)-methyl)hydrazo]-6-*O*-methylerythronolide A, 11,12-Carbamate (19). The title compound was prepared from **2** and 4-methoxybenzaldehyde. Chromatography (3% MeOH/CH_2Cl_2 with 0.1% NH_4OH) gave the compound as a white powder (32% yield): CI MS *m/z* 732 $(M + H)^+$; ^{13}C NMR ($CDCl_3$) δ 217.2, 169.4, 159.0, 155.6, 146.0, 130.5, 128.9, 124.2, 113.7, 104.9, 83.4, 81.6, 79.2, 78.3, 70.4, 69.8, 65.8, 58.5, 55.2, 51.9, 49.6, 44.3, 41.1, 40.2, 40.1, 37.4, 28.3, 21.9, 21.2, 20.8, 18.4, 17.2, 14.9, 14.4, 13.1, 10.7. Anal. ($C_{39}H_{61}N_3O_{10}$) C, H, N.

2,3-Anhydro-5-*O*-desosaminyl-11-[(3-(4-methoxyphenyl)-propyl)hydrazo]-6-*O*-methylerythronolide A, 11,12-Carbamate (20). The title compound was prepared from **2** and 3-(4-methoxyphenyl)propanal. Chromatography (10% MeOH/*tert*-butyl methyl ether with 1% NH_4OH) gave the compound as a white foam (62% yield): CI MS *m/z* 760 $(M + H)^+$; ^{13}C NMR ($CDCl_3$) δ 217.3, 169.2, 157.7, 155.9, 146.0, 134.3, 129.4, 124.0, 113.7, 104.8, 83.2, 81.6, 79.0, 77.9, 70.3, 69.7, 65.8, 58.0, 55.2, 49.1, 48.1, 44.4, 40.8, 40.2, 40.1, 37.3, 32.4, 29.8, 28.3, 21.9, 21.2, 20.5, 18.3, 17.1, 14.8, 14.6, 13.1, 10.7. Anal. ($C_{41}H_{65}N_3O_{10}$) C, H, N.

2,3-Anhydro-5-*O*-desosaminyl-11-[((4-phenoxyphenyl)-methyl)hydrazo]-6-*O*-methylerythronolide A, 11,12-Carbamate (21). The title compound was prepared from **2** and 4-(phenoxyphenyl)benzaldehyde. Chromatography (5% MeOH/CH_2Cl_2 with 0.1% NH_4OH) gave the compound as a white foam (73% yield): CI MS *m/z* 794 $(M + H)^+$; ^{13}C NMR ($CDCl_3$) δ 217.3, 169.3, 157.3, 156.4, 155.5, 146.0, 131.5, 130.7, 129.5, 124.0, 122.9, 118.7, 118.6, 104.8, 83.2, 81.5, 79.1, 78.1, 70.2, 69.6, 65.7, 58.3, 51.8, 49.5, 44.3, 40.9, 40.1, 40.0, 37.3, 28.1, 21.8, 21.1, 20.6, 18.3, 17.0, 14.8, 14.4, 13.0, 10.6. Anal. ($C_{44}H_{63}N_3O_{10}$) C, H, N.

2,3-Anhydro-5-*O*-desosaminyl-11-[((4-(methylthio)phenyl)methyl)hydrazo]-6-*O*-methylerythronolide A, 11,12-Carbamate (22). The title compound was prepared from **2** and 4-(methylthio)benzaldehyde. Chromatography (5% MeOH/CH_2Cl_2 with 0.1% NH_4OH) gave the compound as a white foam (43% yield): CI MS *m/z* 748 $(M + H)^+$; ^{13}C NMR ($CDCl_3$) δ 217.3, 169.3, 155.5, 146.0, 137.3, 133.7, 129.7, 126.6, 124.1, 104.8, 83.3, 81.6, 79.1, 78.2, 70.3, 69.7, 65.8, 58.4, 52.0, 49.5, 44.3, 41.0, 40.2, 40.0, 37.4, 28.3, 31.9, 21.2, 20.7, 18.4, 17.1, 16.0, 14.9, 14.5, 13.1, 10.6. Anal. ($C_{39}H_{61}N_3O_9S$) C, H, N.

2,3-Anhydro-5-*O*-desosaminyl-11-[((4-cyanophenyl)-methyl)hydrazo]-6-*O*-methylerythronolide A, 11,12-Carbamate (23). The title compound was prepared from **2** and 4-cyanobenzaldehyde. Chromatography (5% MeOH/CH_2Cl_2 with 0.1% NH_4OH) gave the compound as a white foam (42% yield): CI MS *m/z* 727 $(M + H)^+$; ^{13}C NMR ($CDCl_3$) δ 217.6, 169.5, 155.5, 146.3, 142.5, 132.0, 129.9, 124.1, 118.9, 111.3, 104.9, 83.3, 81.7, 79.3, 78.1, 70.4, 69.8, 65.9, 58.1, 52.2, 49.5, 44.5, 40.9, 40.2, 40.0, 37.4, 28.3, 21.7, 21.3, 20.6, 18.4, 17.2, 14.8, 14.5, 13.0, 10.6. Anal. ($C_{39}H_{58}N_4O_9$) C, H, N.

2,3-Anhydro-5-*O*-desosaminyl-11-[((2-hydroxyphenyl)-methyl)hydrazo]-6-*O*-methylerythronolide A, 11,12-Carbamate (24). The title compound was prepared from **2** and 2-hydroxybenzaldehyde. Chromatography (5% MeOH/CH_2Cl_2 with 0.2% NH_4OH) gave the compound as a white foam (55% yield): CI MS *m/z* 718 $(M + H)^+$; ^{13}C NMR ($CDCl_3$) δ 217.7, 169.3, 157.7, 155.6, 146.4, 129.5, 129.4, 123.5, 121.2, 119.4, 117.2, 104.9, 83.1, 82.3, 79.0, 78.1, 70.3, 69.7, 65.8, 58.5, 51.5, 49.5, 44.5, 40.5, 40.2, 37.3, 28.3, 21.8, 21.2, 20.3, 18.2, 17.0, 14.7, 14.7, 13.0, 10.6. Anal. ($C_{38}H_{59}N_3O_{10}$) C, H, N.

2,3-Anhydro-5-*O*-desosaminyl-11-[((3-hydroxyphenyl)-methyl)hydrazo]-6-*O*-methylerythronolide A, 11,12-Carbamate (25). The title compound was prepared from **2** and 3-hydroxybenzaldehyde. Chromatography (5% MeOH/CH_2Cl_2 with 0.1% NH_4OH) gave the compound as a white foam (56% yield): CI MS *m/z* 718 $(M + H)^+$; ^{13}C NMR ($CDCl_3$) δ 217.3, 169.6, 155.9, 155.8, 146.3, 137.8, 129.9, 124.1, 121.6, 116.9, 114.9, 104.9, 83.1, 81.5, 79.2, 78.9, 70.4, 69.8, 65.8, 58.4, 52.1, 49.7, 44.5, 40.9, 40.2, 40.2, 37.4, 28.3, 22.1, 21.2, 20.7, 18.5, 17.1, 15.0, 14.6, 13.1, 10.7. Anal. ($C_{38}H_{59}N_3O_{10}$) C, H, N.

2,3-Anhydro-5-*O*-desosaminyl-11-[((4-hydroxyphenyl)-methyl)hydrazo]-6-*O*-methylerythronolide A, 11,12-Carbamate (26). The title compound was prepared from **2** and 4-hydroxybenzaldehyde. Chromatography (5% MeOH/CH_2Cl_2 with 0.2% NH_4OH) gave the compound as a white foam (38% yield): CI MS *m/z* 718 $(M + H)^+$; ^{13}C NMR ($CDCl_3$) δ 217.4, 169.5, 155, 155.6, 146.1, 130.7, 128.3, 124.0, 115.2, 104.7, 83.2, 81.8, 79.1, 78.3, 70.3, 69.6, 65.8, 58.4, 52.0, 49.6, 44.3, 41.0, 40.3, 40.3, 37.3, 28.5, 21.9, 21.2, 20.7, 18.4, 17.1, 14.9, 14.5, 13.1, 10.7. Anal. ($C_{38}H_{59}N_3O_{10}$) C, H, N.

2,3-Anhydro-5-*O*-desosaminyl-11-[((2,5-dihydroxyphenyl)methyl)hydrazo]-6-*O*-methylerythronolide A, 11,12-Carbamate (27). The title compound was prepared from **2** and 2,5-dihydroxybenzaldehyde. Chromatography (5% MeOH/CH_2Cl_2 with 0.1% NH_4OH) gave the compound as a white foam (23% yield): CI MS *m/z* 734 $(M + H)^+$; ^{13}C NMR ($CDCl_3$) δ 217.3, 169.6, 155.9, 155.8, 146.3, 137.8, 129.9, 124.1,121.6, 116.9, 114.9, 104.9, 83.1, 81.5, 79.2, 78.9, 70.4, 69.8, 65.8, 58.4, 52.1, 49.7, 44.5, 40.9, 40.2, 40.2, 37.4, 28.3, 22.1, 21.2, 20.7, 18.5, 17.1, 15.0, 14.6, 13.1, 10.7. Anal. ($C_{38}H_{59}N_3O_{11}$) C, H, N.

2,3-Anhydro-5-*O*-desosaminyl-11-[((3,4-dihydroxyphenyl)methyl)hydrazo]-6-*O*-methylerythronolide A, 11,12-Carbamate (28). The title compound was prepared from **2** and 3,4-dihydroxybenzaldehyde. Chromatography (10% MeOH/CH_2Cl_2 with 0.2% NH_4OH) gave the compound as a white foam (56% yield): CI MS *m/z* 734 $(M + H)^+$; ^{13}C NMR ($CDCl_3$) δ 217.4, 169.5, 156.1, 146.4, 144.4, 143.3, 128.2, 124.0, 122.0, 117.0, 115.3, 104.8, 83.0, 81.8, 79.1, 78.6, 70.4, 69.7, 65.7, 58.5, 51.9, 49.7, 44.4, 40.8, 40.2, 37.4, 28.4, 22.0, 21.2, 20.7, 18.4, 17.1, 15.0, 14.7, 13.1, 10.7. Anal. ($C_{38}H_{59}N_3O_{11}$) C, H, N.

2,3-Anhydro-5-*O*-desosaminyl-11-[((4-(hydroxymethyl)-phenyl)methyl)hydrazo]-6-*O*-methylerythronolide A, 11,-12-Carbamate (29). The title compound was prepared from **2** and terephthaldicarboxaldehyde. Chromatography (4% MeOH/CH_2Cl_2 with 1% NH_4OH) gave the compound as a white foam (54% yield): CI MS *m/z* 732 $(M + H)^+$; ^{13}C NMR ($CDCl_3$) δ 217.3, 169.3, 155.5, 146.0, 140.2, 136.2, 129.5, 127.0, 124.1, 104.8, 83.3, 81.6, 79.1, 78.3, 70.3, 69.7, 65.7, 65.3, 58.8, 52.2, 49.5, 44.3, 41.0, 40.2, 40.1, 37.4, 28.3, 21.9, 21.2, 20.7, 18.4, 17.1, 14.9, 14.5, 13.1, 10.7. Anal. ($C_{39}H_{61}N_3O_{10}$) C, H, N.

2,3-Anhydro-5-*O*-desosaminyl-11-[(3-(2-hydroxyphenyl)-propyl)hydrazo]-6-*O*-methylerythronolide A, 11,12-Carbamate (30). The title compound was prepared from **2** and 3-(2-hydroxyphenyl)propanal. Chromatography (5% MeOH/CH_2Cl_2 with 0.1% NH_4OH) gave the compound as a white foam (54% yield): CI MS *m/z* 746 $(M + H)^+$; ^{13}C NMR ($CDCl_3$) δ 217.2, 169.4, 156.2, 155.3, 146.3, 130.3, 127.4, 127.2, 123.9, 120.1, 116.9, 104.9, 83.1, 82.0, 79.0, 77.9, 70.3, 69.7, 65.8, 57.4, 49.3, 45.7, 44.6, 40.5, 40.2, 40.1, 37.4, 28.3, 27.8, 26.3, 21.9, 21.2, 20.4, 18.4, 17.1, 14.8, 14.7, 13.1, 10.8. Anal. ($C_{40}H_{63}N_3O_{10}$) C, H, N.

2,3-Anhydro-5-*O*-desosaminyl-11-[(3-(3-hydroxyphenyl)-propyl)hydrazo]-6-*O*-methylerythronolide A, 11,12-Carbamate (31). The title compound was prepared from **2** and 3-(3-hydroxyphenyl)propanal. Chromatography (5% MeOH/CH_2Cl_2 with 0.1% NH_4OH) gave the compound as a white foam (40% yield): CI MS *m/z* 746 $(M + H)^+$; ^{13}C NMR ($CDCl_3$) δ 217.4, 170.1, 156.2, 156.0, 146.5, 143.2, 129.4, 123.8, 120.8, 115.4, 113.1, 104.8, 83.1, 81.3, 78.9, 78.5, 70.4, 69.7, 65.8, 58.3, 49.0, 48.0, 44.4, 40.7, 40.2, 40.2, 37.3, 33.0, 28.5, 28.4, 22.0, 21.2, 20.4, 18.3, 17.0, 14.9, 14.6, 13.1, 10.9. Anal. ($C_{40}H_{63}N_3O_{10}$) C, H, N.

2,3-Anhydro-5-*O*-desosaminyl-11-[(3-(4-hydroxyphenyl)-propyl)hydrazo]-6-*O*-methylerythronolide A, 11,12-Carbamate (32). The title compound was prepared from **2** and 3-(4-hydroxyphenyl)propanal. Chromatography (5% MeOH/CH_2Cl_2 with 0.2% NH_4OH) gave the compound as a white foam (57% yield): CI MS *m/z* 746 $(M + H)^+$; ^{13}C NMR ($CDCl_3$) δ 217.4, 169.3, 156.0, 154.0, 146.2, 133.8, 129.4, 124.0, 115.2, 104.8, 83.1, 79.0, 77.9, 70.4, 69.8, 65.7, 58.0, 49.2, 48.1, 44.4, 40.2, 40.1, 37.3, 32.4, 29.8, 28.3, 21.9, 21.2, 20.5, 18.3, 17.1, 14.8, 14.6, 13.1, 10.7. Anal. ($C_{40}H_{63}N_3O_{10}$) C, H, N.

2,3-Anhydro-5-*O*-desosaminyl-11-[((2-hydroxynaphth-yl)methyl)hydrazo]-6-*O*-methylerythronolide A, 11,12-Carbamate (33). The title compound was prepared from **2** and 2-hydroxy-1-naphthaldehyde. Chromatography (5% MeOH/CH_2Cl_2 with 0.1% NH_4OH) gave the compound as a white foam (38% yield): CI MS *m/z* 768 $(M + H)^+$; ^{13}C NMR ($CDCl_3$) δ 217.7, 169.3, 156.3, 155.8, 146.4, 132.9, 129.7, 128.7, 128.5, 126.3, 123.7, 122.5, 121.9, 119.5, 112.0, 104.8, 83.5, 82.7, 79.1, 78.0, 70.3, 69.7, 65.7, 60.3, 49.4, 4.8, 44.5, 44.3, 40.7, 40.3, 40.2, 37.3, 29.1, 28.2, 21.9, 21.2, 20.4, 18.2, 17.1, 14.8, 14.5, 13.1, 10.6. Anal. ($C_{42}H_{61}N_3O_{10}$) C, H, N.

2,3-Anhydro-5-*O*-desosaminyl-11-[((4-nitrophenyl)-methyl)hydrazo]-6-*O*-methylerythronolide A, 11,12-Carbamate (34). The title compound was prepared from **2** and 4-nitrobenzaldehyde. Chromatography (5% MeOH/CH_2Cl_2 with 0.1% NH_4OH) gave the compound as a white powder (61% yield): CI MS *m/z* 747 $(M + H)^+$; ^{13}C NMR ($CDCl_3$) δ 217.7, 169.5, 155.5, 147.5, 146.4, 144.6, 130.0, 124.0, 123.4, 104.9, 83.2, 81.7, 79.2, 78.0, 70.3, 69.8, 65.8, 58.0, 51.9, 49.6, 44.5, 40.8, 40.2, 40.0, 37.4, 28.3, 21.7, 21.2, 20.6, 18.4, 17.1, 14.7, 14.6, 13.1, 10.7. Anal. ($C_{38}H_{58}N_4O_{11}$) C, H, N.

2,3-Anhydro-5-*O*-desosaminyl-11-[(3-(2-nitrophenyl)-propyl)hydrazo]-6-*O*-methylerythronolide A, 11,12-Carbamate (35). The title compound was prepared from **2** and 3-(2-nitrophenyl)propanal. Chromatography (10% MeOH/CH_2Cl_2 with 1% NH_4OH) gave the compound as a white foam (84% yield): CI MS *m/z* 775 $(M + H)^+$; ^{13}C NMR ($CDCl_3$) δ 217.4, 169.2, 155.9, 149.1, 146.2, 137.3, 133.0, 132.5, 126.9, 124.5, 123.9, 104.9, 83.3, 81.7, 79.0, 77.8, 70.3, 69.7, 65.8, 57.9, 49.3, 47.9, 44.5, 40.7, 40.3, 40.2, 37.4, 30.4, 28.9, 28.4, 21.9, 21.2, 20.5, 18.3, 17.1, 14.8, 14.7, 13.1, 10.7. Anal. ($C_{40}H_{62}N_4O_{11}$) C, H, N.

2,3-Anhydro-5-*O*-desosaminyl-11-[(3-(3-nitrophenyl)-propyl)hydrazo]-6-*O*-methylerythronolide A, 11,12-Carbamate (36). The title compound was prepared from **2** and 3-(3-nitrophenyl)propanal. Chromatography (10% MeOH/*tert*-butyl methyl ether with 1% NH_4OH) gave the compound as a white foam (92% yield): CI MS *m/z* 775 $(M + H)^+$; ^{13}C NMR ($CDCl_3$) δ 217.4, 169.3, 156.0, 146.1, 144.3, 135.0, 129.2, 124.1, 123.3, 121.0, 104.9, 83.3, 81.7, 79.1, 77.8, 70.4, 69.7, 65.9, 58.0, 49.2, 47.8, 44.5, 40.8, 40.3, 40.1, 37.4, 32.9, 29.4, 28.4, 21.9, 21.2, 20.5, 18.4, 17.2, 14.7, 14.6, 13.1, 10.7. Anal. ($C_{40}H_{62}N_4O_{11}$) C, H, N.

2,3-Anhydro-5-*O*-desosaminyl-11-[(3-(4-nitrophenyl)-propyl)hydrazo]-6-*O*-methylerythronolide A, 11,12-Carbamate (37). The title compound was prepared from **2** and 3-(4-nitrophenyl)propanal. Chromatography (5−10% MeOH/CH_2Cl_2 with 0.1% NH_4OH) gave the compound as a white foam (77% yield): CI MS *m/z* 775 $(M + H)^+$; ^{13}C NMR ($CDCl_3$) δ 217.5, 169.2, 155.9, 150.2, 146.2, 146.0, 129.3, 124.0, 123.5, 104.8, 83.0, 81.7, 79.0, 77.7, 70.3, 69.7, 65.7, 57.8, 49.0, 47.6, 44.5, 40.6, 40.1, 40.1, 37.3, 33.1, 29.2, 28.2, 21.8, 21.1, 20.4, 18.2, 17.0, 14.6, 14.5, 13.0, 10.7. Anal. ($C_{40}H_{62}N_4O_{11}$) C, H, N.

2,3-Anhydro-5-*O*-desosaminyl-11-[(3-(4-nitrophenyl)-2-propenyl)hydrazo]-6-*O*-methylerythronolide A, 11,12-Carbamate (38). The title compound was prepared from **2** and 4-nitrocinnamaldehyde. Chromatography (4% MeOH/CH_2Cl_2 with 0.1% NH_4OH) gave the compound as a white foam (48% yield): CI MS *m/z* 773 $(M + H)^+$; ^{13}C NMR ($CDCl_3$) δ 217.6, 169.5, 156.0, 146.8, 146.3, 143.4, 131.8, 131.3, 127.2, 123.8, 123.8, 104.9, 83.2, 81.8, 79.1, 78.3, 70.3, 69.7, 65.7, 57.5, 50.8, 49.5, 44.4, 40.6, 40.2, 40.0, 37.4, 28.2, 21.7, 21.2, 20.5, 18.3, 17.1, 14.7, 14.7, 13.0, 10.5. Anal. ($C_{40}H_{60}N_4O_{11}$) C, H, N.

2,3-Anhydro-5-*O*-desosaminyl-11-[(3-(2-(5-nitrofuranyl))-2-propenyl)hydrazo]-6-*O*-methylerythronolide A, 11,12-Carbamate (39). The title compound was prepared from **2** and 5-nitro-2-furanacrolein. Chromatography (4% MeOH/CH_2Cl_2 with 0.1% NH_4OH) gave the compound as a yellow solid (67% yield): CI MS *m/z* 763 $(M + H)^+$; ^{13}C NMR ($CDCl_3$) δ 217.6, 169.5, 155.8, 155.2, 151.4, 146.3, 132.9, 124.0, 120.1, 113.6, 110.1, 104.7, 83.3, 81.9, 79.1, 78.1, 70.2, 69.5, 65.8, 58.0, 50.3, 49.5, 44.4, 40.7, 40.2, 40.0, 37.3, 28.7, 21.7, 21.2, 20.5, 18.3, 17.2, 14.7, 14.6, 13.1, 10.7. Anal. ($C_{38}H_{58}N_4O_{12}$) C, H, N.

2,3-Anhydro-5-*O*-desosaminyl-11-[((2-hydroxy-5-nitro-phenyl)methyl)hydrazo]-6-*O*-methylerythronolide A, 11,-12-Carbamate (40). The title compound was prepared from **2** and 2-nitro-5-hydroxybenzaldehyde. Chromatography (5−10% MeOH/CH_2Cl_2 with 0.1% NH_4OH) gave the compound as a white foam (42% yield): CI MS *m/z* 763 $(M + H)^+$; ^{13}C NMR ($CDCl_3$) δ 218.3, 169.3, 164.1, 155.8, 146.7, 140.3, 125.9, 125.4, 123.5, 121.4, 117.5, 104.9, 83.1, 82.8, 79.1, 77.6, 70.3, 69.7, 65.7, 58.6, 51.5, 49.6, 44.4, 40.5, 40.2, 40.2, 37.3, 28.3, 21.7, 21.2, 20.3, 18.1, 17.0, 14.6, 14.5, 13.0, 10.5. Anal. ($C_{38}H_{58}N_4O_{12}$) C, H, N.

2,3-Anhydro-5-*O*-desosaminyl-11-[((4-(dimethylamino)-phenyl)methyl)hydrazo]-6-*O*-methylerythronolide A, 11,-12-Carbamate (41). The title compound was prepared from **2** and 4-(dimethylamino)benzaldehyde. Chromatography (4% MeOH/CH_2Cl_2 with 0.1% NH_4OH) gave the compound as a white powder (64% yield): CI MS *m/z* 745 $(M + H)^+$; ^{13}C NMR ($CDCl_3$) δ 217.0, 169.3, 155.6, 150.1, 145.9, 130.2, 124.6, 124.2, 112.6, 104.8, 83.4, 81.6, 79.2, 78.4, 70.4, 69.7, 65.9, 58.7, 52.0, 49.6, 44.1, 40.7, 40.5, 40.3, 40.1, 37.4, 28.4, 22.0, 21.2, 20.8, 18.5, 17.2, 15.0, 14.4, 13.1, 10.7. Anal. ($C_{40}H_{64}N_4O_9$) C, H, N.

2,3-Anhydro-5-*O*-desosaminyl-11-[((4-(dimethylamino)-naphthyl)methyl)hydrazo]-6-*O*-methylerythronolide A, 11,12-Carbamate (42). The title compound was prepared from **2** and 4-(dimethylamino)-1-naphthaldehyde. Chromatography (5−10% MeOH/CH_2Cl_2 with 0.1% NH_4OH) gave the compound as a white foam (20% yield): CI MS *m/z* 795 $(M + H)^+$; ^{13}C NMR ($CDCl_3$) δ 217.0, 169.4, 155.6, 151.1, 146.0, 133.7, 129.1, 127.4, 127.1, 126.2, 125.1, 124.9, 124.3, 113.2, 104.8, 83.5, 81.8, 79.2, 78.3, 70.4, 69.7, 65.9, 59.3, 50.6, 49.6, 45.2, 44.1, 41.3, 40.2, 40.1, 37.4, 28.4, 22.0, 21.2, 20.8, 18.5, 17.2, 15.0, 14.4, 13.1, 10.7. Anal. ($C_{44}H_{66}N_4O_9$) C, H, N.

2,3-Anhydro-5-*O*-desosaminyl-11-[((4-(acetylamino)-phenyl)methyl)hydrazo]-6-*O*-methylerythronolide A, 11,-12-Carbamate (43). The title compound was prepared from **2** and 4-acetamidobenzaldehyde. Chromatography (5% MeOH/CH_2Cl_2 with 0.2% NH_4OH) gave the compound as a white powder (44% yield): CI MS *m/z* 759 $(M + H)^+$; ^{13}C NMR ($CDCl_3$) δ 217.3, 169.3, 168.3, 155.6, 146.1, 137.3, 133.5, 129.9, 124.0, 119.7, 104.9, 83.2, 81.7, 79.1, 78.1, 70.3, 69.7, 65.8, 58.4, 52.1, 49.6, 44.3, 41.0, 40.2, 40.1, 37.4, 28.3, 24.6, 21.9, 21.2, 20.7, 18.4, 17.1, 14.9, 14.6, 13.1, 10.7. Anal. ($C_{40}H_{62}N_4O_{10}$) C, H, N.

2,3-Anhydro-5-*O*-desosaminyl-11-[(3-(4-(acetylamino)-phenyl)propyl)hydrazo]-6-*O*-methylerythronolide A, 11,-12-Carbamate (44). The title compound was prepared from **2** and 3-(4-acetamidophenyl)propanal. Chromatography (5% MeOH/CH_2Cl_2 with 0.2% NH_4OH) gave the compound as a white solid (18% yield): CI MS *m/z* 787 $(M + H)^+$; ^{13}C NMR

($CDCl_3$) δ 217.2, 169.3, 155.9, 146.1, 138.2, 135.7, 128.9, 124.0, 120.0, 104.9, 83.3, 81.7, 79.1, 77.9, 70.4, 69.7, 65.9, 58.1, 49.2, 48.1, 44.4, 40.8, 40.2, 40.1, 37.4, 32.7, 29.6, 28.4, 24.5, 21.9, 21.2, 20.5, 18.3, 17.1, 14.8, 14.5, 13.1, 10.7. Anal. ($C_{42}H_{66}N_4O_{10}$) C, H, N.

2,3-Anhydro-5-*O*-desosaminyl-11-[(2-pyridylmethyl)-hydrazo]-6-*O*-methylerythronolide A, 11,12-Carbamate (45). The title compound was prepared from **2** and 2-pyridinecarboxaldehyde. Chromatography (5% MeOH/CH_2Cl_2 with 0.1% NH_4OH) gave the compound as a white solid (41% yield): CI MS *m*/*z* 703 $(M + H)^+$; ^{13}C NMR ($CDCl_3$) δ 217.3, 168.9, 157.2, 155.6, 149.0, 145.6, 136.2, 124.0, 122.9, 122.0, 104.7, 83.1, 81.7, 78.8, 78.0, 70.3, 69.6, 65.7, 58.5, 54.0, 49.5, 44.4, 40.8, 40.2, 40.2, 37.2, 28.3, 21.9, 21.1, 20.5, 18.3, 17.0, 14.8, 14.5, 13.1, 10.7. Anal. ($C_{37}H_{58}N_4O_9 \cdot {}^1/_2H_2O$) C, H, N.

2,3-Anhydro-5-*O*-desosaminyl-11-[(3-pyridylmethyl)-hydrazo]-6-*O*-methylerythronolide A, 11,12-Carbamate (46). The title compound was prepared from **2** and 3-pyridinecarboxaldehyde. Chromatography (5−10% MeOH/CH_2Cl_2 with 0.1% NH_4OH) gave the compound as a white solid (56% yield): CI MS *m*/*z* 703 $(M + H)^+$; ^{13}C NMR ($CDCl_3$) δ 217.5, 169.3, 155.4, 150.3, 148.8, 146.2, 136.9, 132.3, 124.0, 123.2, 104.8, 83.1, 81.7, 79.1, 77.9, 70.2, 69.7, 65.7, 58.3, 50.0, 49.5, 44.3, 40.8, 40.2, 40.0, 37.3, 28.2, 21.7, 21.1, 20.6, 18.3, 17.1, 14.7, 14.4, 13.0, 10.6. Anal. ($C_{37}H_{58}N_4O_9$) C, H, N.

2,3-Anhydro-5-*O*-desosaminyl-11-[(4-pyridylmethyl)-hydrazo]-6-*O*-methylerythronolide A, 11,12-Carbamate (47). The title compound was prepared from **2** and 4-pyridinecarboxaldehyde. Chromatography (5% MeOH/CH_2Cl_2 with 0.1% NH_4OH) gave the compound as a white solid (44% yield): CI MS *m*/*z* 703 $(M + H)^+$; ^{13}C NMR ($CDCl_3$) δ 217.6, 169.5, 155.5, 149.8, 146.3, 145.9, 124.1, 123.9, 105.0, 83.3, 81.8, 79.3, 78.1, 70.4, 69.8, 65.9, 58.2, 51.5, 49.6, 44.5, 40.9, 40.3, 40.1, 37.5, 28.3, 21.8, 21.3, 20.7, 18.4, 17.2, 14.8, 14.5, 13.1, 10.6. Anal. ($C_{37}H_{58}N_4O_9$) C, H, N.

Ethyl 3-(4-Quinolyl)propenoate. A suspension of LiCl (972 mg, 22.9 mmol, 1.2 equiv) in 60 mL of anhydrous CH_3CN was treated with triethyl phosphonoacetate (4.55 mL, 22.9 mmol, 1.2 equiv) and DBU (3.05 mL, 20.4 mmol, 1.07). The mixture was stirred under nitrogen until everything was in solution. Quinoline-4-carboxyaldehyde (3.00 g, 19.1 mmol, 1.00 mmol) was then added, and the reaction mixture was stirred for 6 h. The reaction was quenched by addition of 5% KH_2PO_4 solution and then extracted into ether. The organic portion was washed with water and brine, dried over $MgSO_4$, and concentrated under reduced pressure. Chromatography (*t*-BuOMe) gave 4.21 g of the desired compound as a yellow oil (97% yield): ^1H NMR ($CDCl_3$) δ 8.95 (d, 1H), 8.43 (d, 1H), 8.16 (m, 1H), 7.78 (m, 1H), 7.64 (m, 1H), 7.54 (d, 1H), 6.65 (d, 1H), 4.34 (q, 2H), 1.39 (t, 3H).

Ethyl 3-(4-Quinolyl)propionate. Ethyl 3-(4-quinolyl)-propenoate (2.60 g) was dissolved in 20 mL of methanol, and the reaction vessel was flushed with nitrogen. Pd/C (10%) (50 mg) was added, and the vessel was then flushed with H_2. The reaction mixture was then stirred rapidly under 1 atm of H_2 pressure for 17 h. The mixture was filtered through a Celite pad, and the filtrate was concentrated under reduced pressure. Chromatography (50% ethyl acetate/hexane) gave 1.51 g of the desired compound as a colorless oil (58% yield): ^1H NMR ($CDCl_3$) δ 8.82 (d, 1H), 8.13 (d, 1H), 8.05 (m, 1H), 7.72 (m, 1H), 7.58 (m, 1H), 7.27 (d, 1H), 4.16 (q, 2H), 3.43 (t, 2H), 2.79 (t, 2H), 1.25 (t, 3H).

3-(4-Quinolyl)propanal. Ethyl 3-(4-quinolyl)propionate (1.51 g, 6.59 mmol, 1.0 equiv) was dissolved in 60 mL of dry toluene, and the solution was cooled to −78 °C under nitrogen. DIBAL-H (13.2 mL, 13.2 mmol, 2.0 equiv) was added dropwise over 10 min; the reaction mixture was then allowed to stir for an additional 2 h. The reaction was then quenched with a solution containing water (0.25 mL) and acetic acid (1 mL) dissolved in 3 mL of ether. The mixture was allowed to warm to room temperature and then filtered. The filtrate was concentrated under reduced pressure. Chromatography (75−100% ethyl acetate/hexane) gave 0.79 g of the desired compound as a light-yellow oil (65% yield): ^1H NMR ($CDCl_3$) δ 9.90 (s, 1H), 8.82 (d, 1H), 8.14 (d, 1H), 8.00 (m, 1H), 7.73 (m, 1H), 7.59 (m, 1H), 7.26 (d, 1H), 3.44 (t, 2H), 2.97 (m, 2H).

2,3-Anhydro-5-*O*-desosaminyl-11-[(3-(4-quinolyl)propyl)-hydrazo]-6-*O*-methylerythronolide A, 11,12-Carbamate (48). The title compound was prepared from **2** and 3-(4-quinolyl)propanal. Chromatography (10% MeOH/*tert*-butyl methyl ether with 1% NH_4OH) gave the compound as an off-white foam (53% yield): CI MS *m*/*z* 781 $(M + H)^+$; ^{13}C NMR ($CDCl_3$) δ 217.4, 169.3, 156.0, 150.1, 148.4, 148.1, 146.0, 129.9, 129.0, 127.6, 126.3, 124.1, 123.9, 121.1, 104.7, 83.2, 81.7, 79.0, 77.8, 70.3, 69.5, 65.8, 57.9, 49.1, 48.1, 44.5, 40.8, 40.2, 40.1, 37.3, 29.5, 28.2, 28.2, 21.9, 21.2, 21.2, 20.4, 18.3, 17.2, 14.7, 14.6, 13.1, 10.7. Anal. ($C_{43}H_{64}N_4O_9$) C, H, N.

2,3-Anhydro-5-*O*-desosaminyl-11-[(3-indolylmethyl)hydrazo]-6-*O*-methylerythronolide A, 11,12-Carbamate (49). The title compound was prepared from **2** and indole-3-carboxaldehyde. Chromatography (5% MeOH/CH_2Cl_2 with 0.2% NH_4OH) gave the compound as a colorless solid (60% yield): CI MS *m*/*z* 741 $(M + H)^+$; ^{13}C NMR ($CDCl_3$) δ 217.0, 169.4, 155.7, 146.1, 136.3, 127.4, 124.4, 123.5, 121.9, 119.6, 119.5, 111.7, 110.9, 104.8, 83.6, 81.7, 79.2, 78.2, 70.4, 69.8, 65.8, 59.0, 49.5, 44.1, 44.0, 41.3, 40.2, 40.0, 37.4, 28.3, 21.9, 21.2, 20.9, 18.4, 17.2, 14.9, 14.3, 13.0, 10.7. Anal. ($C_{40}H_{60}N_4O_9$) C, H, N.

2-(2-(4-Phenylimidazolyl)ethyl)-1,3-dioxolane. 4-Phenylimidazole (2.01 g, 14.0 mmol, 1.0 equiv) was added to a suspension of NaH (1.17 g, 29.3 mmol, 2.1 equiv) in DMF (25 mL) at 0 °C under nitrogen. 2-(2-Bromoethyl)-1,3-dioxolane (1.80 mL, 15.3 mmol, 1.1 equiv) was added dropwise, and the reaction mixture was warmed to room temperature. After stirring for 28 h, the reaction mixture was partitioned between Et_2O and brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. Chromatography (5% MeOH/CH_2Cl_2) gave 2.15 g of the desired product as an oil (63% yield): CI MS *m*/*z* 245 $(M + H)^+$; ^1H NMR ($CDCl_3$) δ 7.76 (m, 2H), 7.53 (m, 1H), 7.36 (m, 2H), 7.27−7.19 (m, 2H), 4.87 (t, 1H), 4.12 (t, 2H), 3.98 (m, 2H), 3.86 (m, 2H), 2.19 (m, 2H).

3-(4-Phenylimidazolyl)propanal. 2-(2-(4-Phenylimidazolyl)ethyl)-1,3-dioxolane (1.96 g) was dissolved in 25 mL of acetone and treated with 20 mL of 2 N HCl. The reaction mixture was heated to 50 °C. After 24 h, 1 mL of concentrated HCl was added, and the heating was continued for 3 days. After cooling, the reaction mixture was neutralized with 1 N NaOH and extracted into 200 mL of CH_2Cl_2. The organic layer was separated, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to give 300 mg of the desired product as a white solid: CI MS *m*/*z* 201 $(M + H)^+$; ^1H NMR ($CDCl_3$) δ 9.81 (s, 1H), 7.75 (m, 2H), 7.53 (m, 1H), 7.36 (m, 2H), 7.27−7.19 (m, 2H), 4.28 (t, 2H), 2.99 (t, 2H).

2,3-Anhydro-5-*O*-desosaminyl-11-[(3-(4-phenylimidazolyl)propyl)hydrazo]-6-*O*-methylerythronolide A, 11,-12-Carbamate (50). The title compound was prepared from **2** and 3-(4-phenylimidazolyl)propanal. Chromatography (5% MeOH/CH_2Cl_2 with 0.1% NH_4OH) gave the compound as a colorless solid (74% yield): CI MS *m*/*z* 796 $(M + H)^+$; ^{13}C NMR ($CDCl_3$) δ 217.5, 169.3, 156.0, 146.3, 142.0, 137.5, 134.4, 128.4, 126.4, 124.7, 123.8, 115.1, 104.9, 83.1, 81.8, 78.9, 77.5, 70.2, 69.7, 65.7, 57.6, 49.1, 44.8, 44.4, 44.3, 40.5, 40.1, 40.0, 37.3, 29.1, 28.2, 21.7, 21.1, 20.3, 18.2, 17.0, 14.6, 14.6, 13.0, 10.7. Anal. ($C_{43}H_{65}N_5O_9$) C, H, N.

2-(2-(1-Benzotriazolyl)ethyl)-1,3-dioxolane and 2-(2-(2-Benzotriazolyl)ethyl)-1,3-dioxolane. Benzotriazole (2.02 g, 17.0 mmol, 1.0 equiv) was added to a suspension of NaH (1.35 g, 33.8 mmol, 2.0 equiv) in DMF (25 mL) at 0 °C under nitrogen. 2-(2-Bromoethyl)-1,3-dioxolane (2.00 mL, 17.0 mmol, 1.0 equiv) was added dropwise, and the reaction mixture was warmed to room temperature. After stirring for 3 h, the reaction mixture was partitioned between Et_2O and brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. Chromatography (25% EtOAc/hexanes) gave 550 mg of 2-(2-(2-benzotriazolyl)ethyl)-1,3-dioxolane as an oil (15% yield): CI MS *m*/*z* 220 $(M + H)^+$; ^1H NMR ($CDCl_3$) δ 7.85 (m, 2H), 7.37 (m, 2H), 5.00 (t, 1H), 4.88 (t, 2H), 3.99

(m, 2H), 3.86 (m, 2H), 2.51 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 144.4, 126.2, 118.0, 101.8, 65.2, 51.7, 33.9. The column was then eluted with 50% EtOAc/hexanes to give 630 mg of 2-(2-(1-benzotriazolyl)ethyl)-1,3-dioxolane as an oil (17% yield): CI MS *m/z* 220 $(M + H)^+$; ^{1}H NMR ($CDCl_3$) δ 8.07 (m, 1H), 7.60 (m, 1H), 7.50 (m, 1H), 7.38 (m, 1H), 4.94 (t, 1H), 4.81 (t, 2H), 4.00 (m, 2H), 3.87 (m, 2H), 2.41 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 146.0, 133.0, 127.2, 123.8, 120.0, 109.3, 101.6, 65.1, 43.1, 33.6.

3-(2-Benzotriazolyl)propanal. 2-(2-(2-Benzotriazolyl)-ethyl)-1,3-dioxolane (550 mg) was dissolved in 25 mL of acetone and treated with 10 mL of 2 N HCl. The reaction mixture was heated to 50 °C for 2 days. After cooling, the reaction mixture was diluted with 50 mL of CH_2Cl_2. The organic layer was separated, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to give 300 mg of the desired product as a white solid: CI MS *m/z* 176 $(M + H)^+$; ^{1}H NMR ($CDCl_3$) δ 9.92 (t, 1H), 7.90 (m, 2H), 7.39 (m, 2H), 5.08 (t, 2H), 3.34 (m, 2H).

3-(1-Benzotriazolyl)propanal. 2-(2-(1-Benzotriazolyl)-ethyl)-1,3-dioxolane (630 mg) was dissolved in 25 mL of acetone and treated with 10 mL of 2 N HCl. The reaction mixture was heated to 50 °C for 2 days. After cooling, the reaction mixture was diluted with 50 mL of CH_2Cl_2. The organic layer was separated, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to give 350 mg of the desired product as a white solid: CI MS *m/z* 176 $(M + H)^+$; ^{1}H NMR ($CDCl_3$) δ 9.88 (s, 1H), 8.06 (m, 1H), 7.64 (m, 1H), 7.53 (m, 1H), 7.39 (m, 1H), 4.92 (t, 2H), 3.34 (t, 2H).

2,3-Anhydro-5-*O*-desosaminyl-11-[(3-(2-benzotriazolyl-)propyl)hydrazo]-6-*O*-methylerythronolide A, 11,12-Carbamate (51). The title compound was prepared from **2** and 3-(2-benzotriazolyl)propanal. Chromatography (5−10% MeOH/*tert*-butyl methyl ether with 1% NH_4OH) gave the compound as a colorless solid (90% yield): CI MS *m/z* 771 $(M + H)^+$; ^{13}C NMR ($CDCl_3$) δ 217.2, 169.2, 156.0, 146.1, 144.4, 125.9, 125.0, 124.1, 118.0, 104.8, 83.2, 81.7, 79.1, 77.8, 70.3, 69.7, 65.9, 58.2, 54.2, 49.2, 45.7, 44.4, 40.8, 40.3, 40.1, 37.3, 28.6, 28.3, 21.9, 21.2, 20.5, 18.3, 17.2, 14.8, 14.5, 13.1, 10.7. Anal. ($C_{40}H_{62}N_6O_9$) C, H; N: calcd, 10.90; found, 10.30.

2,3-Anhydro-5-*O*-desosaminyl-11-[(3-(1-benzotriazolyl-)propyl)hydrazo]-6-*O*-methylerythronolide A, 11,12-Carbamate (52). The title compound was prepared from **2** and 3-(1-benzotriazolyl)propanal. Chromatography (3−5% MeOH/*tert*-butyl methyl ether with 1% NH_4OH) gave the compound as a colorless solid (76% yield): CI MS *m/z* 771 $(M + H)^+$; ^{13}C NMR ($CDCl_3$) δ 217.4, 169.2, 156.2, 146.3, 145.2, 133.5, 127.1, 123.9, 123.7, 119.6, 110.2, 104.9, 83.2, 81.8, 79.1, 77.6, 70.3, 69.7, 65.9, 57.7, 49.3, 45.6, 45.4, 44.5, 40.6, 40.2, 40.1, 37.4, 28.4, 28.1, 21.8, 21.2, 20.4, 18.3, 17.1, 14.7, 14.6, 13.0, 10.7. Anal. ($C_{40}H_{62}N_6O_9$) C, H, N.

Gereral Procedure for the Preparation of Compounds 53−57. 2,3-Anhydro-5-*O*-desosaminyl-11-[(3-(4-aminophenyl)methyl)hydrazo]-6-*O*-methylerythronolide A, 11,12-Carbamate (53). Acetyl chloride (300 μL, 4.2 mmol) was added to 5 mL of MeOH, and the mixture was stirred for 15 min. Compound **34** (144 mg, 0.193 mmol), dissolved in 10 mL of MeOH, was then added to the solution followed by Zn dust (380 mg, 5.8 mmol). After the mixture stirred for 12 h, a saturated solution of K_2CO_3 was added (1 mL). EtOAc (25 mL) was then added, and the organic portion was decanted from the solids. The organic portion was washed with H_2O and brine, dried over Na_2SO_4, and concentrated under reduced pressure. Chromatography (5% MeOH/CH_2Cl_2 with 0.1% NH_4OH) gave the compound (85 mg) as a white powder (62% yield): CI MS *m/z* 717 $(M + H)^+$; ^{13}C NMR ($CDCl_3$) δ 217.2, 169.3, 155.6, 145.9, 145.7, 130.4, 126.7, 124.1, 115.0, 104.8, 83.3, 81.5, 79.1, 78.3, 70.3, 69.7, 65.8, 58.5, 52.0, 49.6, 44.2, 41.1, 40.2, 40.1, 37.6, 28.3, 21.9, 21.2, 20.7, 18.4, 17.1, 14.9, 14.5, 13.1, 10.7. Anal. ($C_{38}H_{60}N_4O_9$) C, H, N.

2,3-Anhydro-5-*O*-desosaminyl-11-[(3-(2-aminophenyl)-propyl)hydrazo]-6-*O*-methylerythronolide A, 11,12-Carbamate (54). The title compound was prepared by reducing compound **35** following the procedure that was used to prepare compound **53**. Chromatography (5% MeOH/CH_2Cl_2 with 0.1% NH_4OH) gave the compound as a white foam (71% yield): CI MS *m/z* 745 $(M + H)^+$; ^{13}C NMR ($CDCl_3$) δ 217.3, 169.1, 155.9, 146.1, 145.0, 129.7, 126.7, 126.1, 123.8, 117.9, 115.3, 104.8, 83.0, 81.6, 78.9, 77.6, 70.2, 69.6, 65.7, 57.5, 49.1, 47.5, 44.4, 40.5, 40.1, 40.0, 37.2, 28.4, 28.2, 27.7, 21.7, 21.1, 20.3, 18.2, 17.0, 14.6, 14.6, 13.0, 10.6. Anal. ($C_{40}H_{64}N_4O_9$) C, H, N.

2,3-Anhydro-5-*O*-desosaminyl-11-[(3-(3-aminophenyl)-propyl)hydrazo]-6-*O*-methylerythronolide A, 11,12-Carbamate (55). The title compound was prepared by reducing compound **36** following the procedure that was used to prepare compound **53**. Chromatography (10% MeOH/CH_2Cl_2 with 0.1% NH_4OH) gave the compound as a white foam (49% yield): CI MS *m/z* 745 $(M + H)^+$; ^{13}C NMR ($CDCl_3$) δ 217.2, 169.5, 155.8, 146.4, 146.0, 143.3, 129.1, 124.0, 118.9, 115.5, 112.6, 104.8, 83.3, 81.6, 79.0, 78.0, 70.3, 69.7, 65.9, 58.1, 49.2, 48.1, 4.4, 40.9, 40.3, 40.1, 37.3, 33.3, 29.3, 28.4, 21.9, 21.2, 20.5, 18.3, 17.1, 14.8, 14.6, 13.1, 10.7. Anal. ($C_{40}H_{64}N_4O_9$) C, H, N.

2,3-Anhydro-5-*O*-desosaminyl-11-[(3-(4-aminophenyl)-propyl)hydrazo]-6-*O*-methylerythronolide A, 11,12-Carbamate (56). The title compound was prepared by reducing compound **37** following the procedure that was used to prepare compound **53**. Chromatography (3−5% MeOH/CH_2Cl_2 with 0.1% NH_4OH) gave the compound as a white foam (26% yield): CI MS *m/z* 745 $(M + H)^+$; ^{13}C NMR ($CDCl_3$) δ 217.2, 169.1, 155.7, 145.9, 144.0, 132.1, 129.1, 123.9, 115.1, 104.8, 83.1, 81.5, 78.9, 77.8, 70.2, 69.6, 65.7, 57.9, 49.0, 48.0, 44.3, 40.7, 40.1, 40.0, 37.2, 32.3, 29.7, 28.2, 21.8, 21.1, 20.4, 18.2, 17.0, 14.7, 14.5, 13.0, 10.6. Anal. ($C_{40}H_{64}N_4O_9$) C, H, N.

2,3-Anhydro-5-*O*-desosaminyl-11-[(3-(4-aminophenyl)-2-propenyl)hydrazo]-6-*O*-methylerythronolide A, 11,12-Carbamate (57). The title compound was prepared by reducing compound **38** following the procedure that was used to prepare compound **53**. Chromatography (5% MeOH/CH_2Cl_2 with 0.2% NH_4OH) gave the compound as a white powder (58% yield): CI MS *m/z* 743 $(M + H)^+$; ^{13}C NMR ($CDCl_3$) δ 217.3, 169.4, 156.1, 146.1, 145.8, 133.9, 127.9, 123.9, 122.0, 115.0, 104.9, 83.4, 81.7, 79.1, 78.6, 70.4, 69.7, 65.9, 58.0, 51.2, 49.5, 44.3, 40.9, 40.3, 40.0, 37.4, 28.5, 21.8, 21.2, 20.6, 18.4, 17.2, 14.8, 14.7, 13.0, 10.4. Anal. ($C_{40}H_{62}N_4O_9$) C, H, N.

2,3-Anhydro-5-*O*-desosaminyl-11-[(3-(4-(acetylamino)-phenyl)-2-propenyl)hydrazo]-6-*O*-methylerythronolide A, 11,12-Carbamate (58). A solution of compound **57** (120 mg, 0.162 mmol) in 3 mL of dry CH_2Cl_2 was cooled to 0 °C. Acetyl chloride (12 μL, 0.17 mmol, 1.05 equiv) was added, and the mixture was stirred for 3 h. The reaction was then quenched with saturated $NaHCO_3$ solution and extracted into CH_2Cl_2. The organic portion was washed with H_2O and brine, dried over Na_2SO_4, and concentrated under reduced pressure. Chromatography (7−10% MeOH/CH_2Cl_2 with 0.1% NH_4OH) gave the compound (103 mg) as a white solid (81% yield): CI MS *m/z* 785 $(M + H)^+$; ^{13}C NMR ($CDCl_3$) δ 217.5, 169.4, 168.4, 156.2, 146.2, 137.5, 133.4, 132.8, 127.2, 124.8, 123.8, 119.6, 104.9, 83.3, 81.9, 79.0, 78.5, 70.3, 69.7, 65.8, 57.8, 51.1, 49.6, 44.4, 40.7, 40.2, 40.1, 37.4, 28.3, 24.6, 21.8, 21.2, 20.5, 18.4, 17.1, 14.8, 14.8, 13.0, 10.5. Anal. ($C_{42}H_{64}N_4O_{10}$) C, H, N.

9-Amino-2,3-anhydro-9-deoxo-5-*O*-desosaminyl-11-hydrazo-6-*O*-methylerythronolide A, 11,12-Carbamate (59). A solution of **4** (318 mg, 0.536 mmol) dissolved in 10 mL of MeOH and 1 mL of AcOH was treated with $NaBH_3CN$ (300 mg). After the mixture stirred for 24 h, another 200-mg portion of $NaBH_3CN$ and 0.5 mL of AcOH were added. After stirring for 3 days, the reaction mixture was added to saturated $NaHCO_3$ solution and extracted into CH_2Cl_2. The organic portion was washed with H_2O and brine, dried over Na_2SO_4, and concentrated under reduced pressure to give the product as a white solid (297 mg, 93% yield): CI MS *m/z* 596 $(M + H)^+$; ^{13}C NMR ($CDCl_3$) δ 168.9, 158.9, 143.1, 125.9, 104.2, 83.3, 82.6, 79.2, 78.8, 78.0, 76.7, 70.4, 69.5, 65.8, 50.3, 40.3, 37.6, 37.2, 35.3, 33.3, 28.6, 26.8, 25.4, 21.1, 21.1, 20.4, 19.8, 18.1, 12.4, 12.2. Anal. ($C_{31}H_{53}N_3O_8$) C, H, N.

2,3-Anhydro-9-deoxo-5-*O*-desosaminyl-11-hydrazo-9-((3-phenylpropyl)amino)-6-*O*-methylerythronolide A, 11,-12-Carbamate (60). A solution of **59** (88 mg, 0.148 mmol) dissolved in 5 mL of MeOH was treated with hydrocinnama-

ldehyde (100 μL, 0.760 mmol, 5 equiv) and $NaBH_3CN$ (55 mg, 0.859 mmol, 6 equiv). Acetic acid was added dropwise until bromocresol green indicator had turned from blue to yellow. After stirring for 15 h, the reaction mixture was added to saturated $NaHCO_3$ solution and extracted into CH_2Cl_2. The organic portion was washed with H_2O and brine, dried over Na_2SO_4, and concentrated under reduced pressure. Chromatography (5−10% MeOH/CH_2Cl_2 containing 0.2% concentrated NH_4OH) gave the product as a white solid (45 mg, 43% yield): CI MS *m/z* 714 $(M + H)^+$; ^{13}C NMR ($CDCl_3$) δ 169.2, 159.0, 143.2, 142.2, 128.5, 128.3, 125.8, 125.7, 104.9, 85.4, 82.7, 82.6, 79.5, 78.7, 72.8, 70.4, 69.5, 65.8, 58.7, 50.2, 40.3, 37.6, 37.5, 36.0, 33.1, 33.0, 30.1, 28.7, 26.8, 25.1, 21.8, 21.1, 20.8, 20.0, 17.9, 12.5, 12.0. Anal. ($C_{40}H_{63}N_3O_8 \cdot {}^1/_2H_2O$) C, H, N.

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Supporting Information Available: ^1H NMR chemical shifts and peak assignments for compounds **2**−**60** (8 pages). Ordering information is given on any current masthead page.

References

(1) Kurath, P.; Jones, P. H.; Egan, R. S.; Perun, T. J. Acid Degradation of Erythromycin A and Erythromycin B. *Experientia* **1971**, *27*, 362.

(2) Itoh, Z.; Nakaya, K.; Suzuki, H.; Aria, H.; Wakabayashi, K. Erythromycin mimics Exogenous Motilin in Gastrointestinal Contractile Activity in the Dog. *Am. J. Physiol.* **1984**, *247*, G688−G694.

(3) (a) Zuckerman, J. M.; Kaye, K. M. The Newer Macrolides. Azithromycin and Clarithromycin. *Infect. Dis. Clin. North Am.* **1995**, *9* (3), 731−745. (b) Chu, D. T. W. Recent Developments in 14- and 15-Membered Macrolides. *Exp. Opin. Invest. Drugs* **1995**, *4* (2), 65−94. (c) Bahal, N.; Nahata, M. C. The New Macrolide Antibiotics: Azithromycin, Clarithromycin, Dirithromycin, and Roxithromycin. *Ann. Pharmacother.* **1992**, *26* (1), 46−55.

(4) Morimoto, S.; Takahashi, Y.; Adachi, T.; Nagate, T.; Wantanabe, Y.; Omura, S. Chemical Modifications of Erythromycins II. Synthesis and Antibacterial Activity of *O*-Alkyl Derivatives of Erythromycin A. *J. Antibiot.* **1990**, *43*, 286−305.

(5) Djokic, S.; Kobrehel, G.; Lazarevski, G. Erythromycin Series XII. Antibacterial In Vitro Evaluation of 10-Dihydro-10-Deoxo-11-Azaerythromycin A. *J. Antibiot.* **1987**, *40*, 1006−1015.

(6) Bright, G. M.; Nagel, A. A.; Bordner, J.; Desai, K. A.; Dibrino, J. N.; Nowakowska, J.; Vincent, L.; Waltrous, R. M.; Sciavolino, F. C.; English, A. R.; Retsema, J. A.; Anderson, M. A.; Brennan, L. A.; Borovoy, R. J.; Cimochowski, C. R.; Faiella, J. A.; Girard, A. E.; Girard, D.; Herbert, C.; Manousos, M.; Mason, R. Synthesis, In Vitro and In Vivo Activity of Novel 9-Deoxo-9a-Aza-9a-Homoerythromycin A Derivatives; A New Class of Macrolide Antibiotics. *J. Antibiot.* **1988**, *41*, 1029−1047.

(7) Yoshida, R.; Kaku, M.; Kohno, S.; Ishida, K.; Mizukane, R.; Takemura, H.; Tanaka, H.; Usui, T.; Tomona, K.; Koga, H.; Hara, K. Trends in Antimicrobial Resistance of *Streptococcus pnuemoniae* in Japan. *Antimicrob. Agents Chemother.* **1995**, *39*, 1196−1198.

(8) Gardee, Y.; Kirby, R. The Incidence of Induible Macrolide-Lincosamide-Streptogramin B Resistance in Methicillin-Resistant Staphylococci in Clinical Isolates From the Eastern Cape Area of South Africa. *Lett. Appl. Microbiol.* **1993**, *17*, 264−268.

(9) (a) Agouridas, C.; Bonnefoy, A.; Chantot, J. F.; Le Martret, O.; Denis, A. (Roussel-Uclaf) EP596802-A1, May 11, 1994. (b) Le Martret, O.; Agouridas, C.; Bonnefoy, A.; Chantot, J. F.; Denis, A. (Roussel-Uclaf) FR2697524-A1, May 6, 1994.

(10) Agouridas, C.; Benedetti, Y.; Chantot, J. F.; Denis, A.; Le Martret, O. (Roussel-Uclaf) EP676409-A1, Oct. 11, 1995. Also see: Agouridas, C.; Benedetti, Y.; Denis, A.; Le Martret, O.; Chantot, J. F. 35th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, CA, Sept. 17−20, 1995; Abstr. No. F157.

(11) Asaka, T.; Kashimura, M.; Misawa, Y.; Ono, T.; Suzuki, K.; Yoshida, H.; Yoshida, T.; Akashi, T.; Yokoo, C.; Nagate, T.; Morimoto, S. A New Macrolide Antibiotic, TE-802; Synthesis and Biological Properties. 35th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, CA, Sept. 17−20, 1995; Abstr. No. F176.

(12) Elliott, R. L.; Pireh, D.; Griesgraber, G.; Nilius, A. M.; Ewing, P. J.; Bui, M.-H.; Raney, P. M.; Flamm, R. K.; Kim, K.; Henry, R. F.; Chu, D. T. W.; Plattner, J. J.; Or, Y. S. Anhydrolide Macrolides. 1. Synthesis and Antibacterial Activity of 2,3-Anhydro-6-*O*-methyl 11,12-Carbamate Erythromycin A Analogues. *J. Med. Chem.* **1998**, *41*, 1651−1659.

(13) 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*, 465−77.

(14) (a) Baker, W. R.; Clark, J.; 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 an Intramolecular Michael Reaction of *O*-Carbamates with an α,β-Unsaturated Ketone. *J. Org. Chem.* **1988**, *53*, 2340−2345. (b) Fernandes, P. B.; Baker, W. R.; Frieberg, L. A.; Hardy, D. J.; McDonald, E. J. New Macrolides Active against *Streptococcus pyogenes* with Inducible or Constitutive Type of Macrolide-Lincosamide-Streptogramin B Resistance. *Antimicrob. Agents Chemother.* **1989**, *33*, 78−81.

(15) Hardy, D. J.; Swanson, R. N.; Shipkowitz, N. L.; Frieberg, L. A.; Lartey, P. A.; Clement, J. J. In Vitro Activity and In Vivo Efficacy of a New Series of 9-Deoxo-12-Deoxy-9,12-Epoxyerthromycin A Derivatives. *Antimicrob. Agents Chemother.* **1991**, *35*, 922−928.

(16) Jeffery, T. Palladium-catalysed Vinylation of Organic Halides under Solid−Liquid Phase Transfer Conditions. *J. Chem. Soc., Chem. Commun.* **1984**, 1287−1289.

(17) *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically*; National Committee for Clinical Laboratory Standards: Villanova, PA, 1985: M7-A, Vol. 5, No. 22.

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