3-Keto-11,12-carbazate Derivatives of 6-*O*-Methylerythromycin A

Synthesis and *In Vitro* Activity

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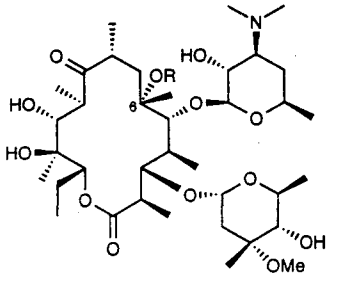
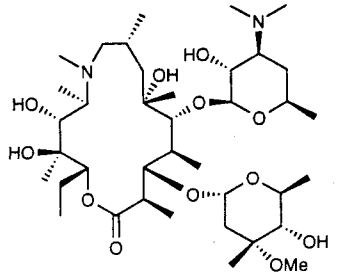
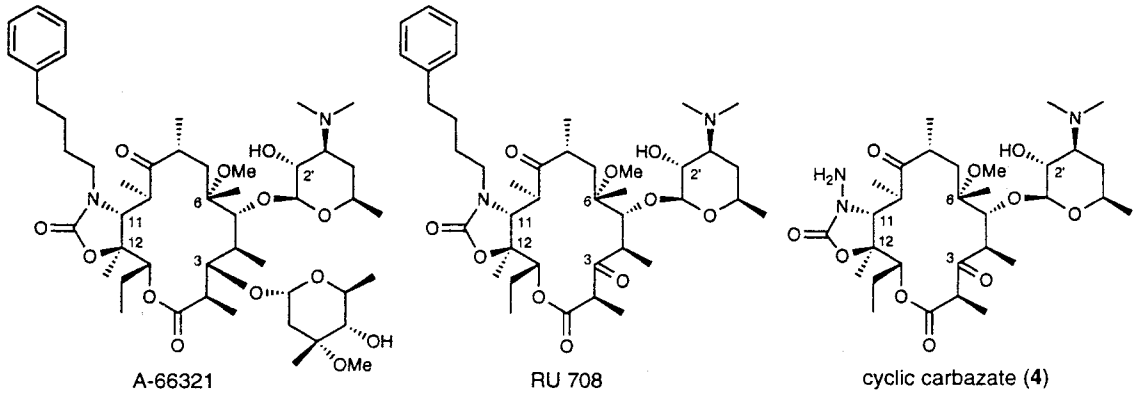
The 11,12-cyclic carbazate of 3-keto-6-*O*-methylerythromycin A (**4**) was prepared. This compound shows *in vitro* antibacterial activity comparable to erythromycin A (**1**) against erythromycin-susceptible organisms and increased activity against some erythromycin-resistant organisms. Using **4** as a lead, a series of analogues was prepared by acylation or alkylation of the carbazate nitrogen. Several of the *N*-alkylated derivatives showed dramatically improved antibacterial activity against both susceptible and resistant organisms as compared to erythromycin A.

Macrolide antibiotics are usually safe and effective agents for the treatment of upper and lower respiratory tract infections. Erythromycin A (**1**), a 14-membered macrolide, continues to be the most widely used of the orally administered macrolide antibiotics. However, under the acidic conditions found in the stomach, erythromycin is quickly degraded to inactive by-products resulting in low bioavailability[1]. These acid degradation products have also been shown to enhance the stimulation of intestinal peristalsis resulting in the gastrointestinal discomfort often associated with taking erythromycin[2]. For this reason, an intensive search for agents with increased acid stability was conducted in the past decade. The results of these efforts yielded several semi-synthetic derivatives of erythromycin which overcame some of the previous drawbacks while maintaining a good overall spectrum of antibacterial activity[3]. The two most successful of these second generation macrolide antibiotics are the 6-*O*-methyl derivative of erythromycin, clarithromycin (**2**)[4], and the 15-membered azalide, azithromycin (**3**), which is formed by a Beckmann rearrangement of erythromycin 9-oxime[5,6]. Both of these compounds have increased acid stability resulting in better bioavailability and pharmacokinetics. In addition to maintaining antibacterial activity against erythromycin susceptible organisms, these macrolides also showed improved activity against *Legionella*, *Chlamydia* and *Campylobacter* spp., and in the case of azithromycin, improved activity against *Haemophilus influenzae*. Both clarithromycin (Biaxin) and azithromycin (Zithromax) are currently enjoying commercial success as front line agents in the treatment of respiratory tract infections.

Unfortunately, like erythromycin and other 14-membered macrolides, both clarithromycin and azithromycin have poor efficacy against macrolide-resistant bacteria. Because organisms with the inducible or the constitutive type of cross-resistance to macrolide, lincosamide, and streptogramin B (MLS) antibiotics are prevalent, increased effort has gone into developing a third generation of macrolide antibiotics to address this







problem. It has been shown that modifications can be made to erythromycin to give compounds that are more effective against macrolide-resistant organisms[7]. Some of the more promising compounds demonstrating increased activity against MLS resistant organisms are the 11,12-cyclic carbamate derivatives of clarithromycin that were prepared at Abbott Laboratories[8]. One of the best compounds, A-66321, showed increased *in vitro* activity against a constitutively resistant strain of *Streptococcus pyogenes*[9]. In recent work reported by Roussel Uclaf, the cladinose sugar of clarithromycin was removed by acid catalyzed hydrolysis and the resulting hydroxyl group was oxidized to give a ketone functionality at C-3. This compound, referred to as a ketolide, was further modified to produce derivatives that showed erythromycin-like activity against susceptible organisms and improved activity against several resistant organisms that had either the inducible or constitutive type of MLS resistance[10,11]. This discovery also disproved a long held belief that the cladinose sugar was essential for antibacterial activity. One of the Roussel compounds that showed very encouraging overall activity, RU 708, is the ketolide version of A-66321.

Using these leads as a starting point, we decided to prepare a compound having an amino group directly attached to the carbamate nitrogen, thus generating a novel carbazate derivative of the ketolide (**4**). We expected that such a compound would also demonstrate improved activity against resistant organisms. In addition, the amino group would provide a useful handle to which we could attach a wide variety of substituents in an effort to optimize activity. Recently, it was revealed that researchers at Roussel Uclaf had also been working on compounds of this type[12,13]. Herein, we wish to report a detailed account of our research efforts in this area. The synthesis and antibacterial activities of **4** and several *N*-substituted derivatives are described below.

Chemistry

Our synthetic strategy, which paralleled that used to form the 11,12-cyclic carbamates[8], involved reacting the 12-*O*-acyl imidazolide **5** with hydrazine to afford the intermediate carbazate **5a** which could undergo an intramolecular Michael addition to the enone (Scheme 1). A key concern was whether the intermediate **5a** would close to form the desired 5-membered ring, or if cyclization would occur to form a 6-membered ring. When we reacted imidazolide **5**, which was prepared in a manner similar to that found in the patent literature[10], with hydrazine (2 equiv) in DMF at room temperature, the starting material was quickly consumed. The isolated product (**6**) was treated with MeOH to remove the 2′-*O*-benzoyl protecting group to give a compound (**7**) which crystallized from EtOAc. The X-ray crystal structure for **7** showed that the 5-membered ring had been formed (Fig. 1). However, to our surprise, compound **7** had 10-(*S*) stereochemistry, which is epimeric to natural erythromycin.

In order to generate the carbazate with the natural 10-(*R*) stereochemistry, we treated **5** with a large excess of hydrazine (10 equiv) in DMF at 60°C for 6 hours to afford a mixture that contained predominately the 2′-*O*-benzoyl protected compound **8**. This mixture was treated with MeOH at 60°C to remove the 2′-*O*-benzoate and the product was crystallized from EtOAc. X-ray analysis showed that the resulting compound (**4**) was the carbazate with natural stereochemistry at C-10 (Fig. 2).

Therefore, we were able to control the resulting stereochemistry at C-10 by choosing the appropriate reaction conditions. Apparently, the initial cyclization of the intermediate carbazate **5a** proceeds rapidly to give the kinetic product with unnatural 10-(*S*) stereochemistry, but when the reaction is heated in the presence of excess hydrazine, a thermodynamic equilibrium is reached which greatly favors the 10-(*R*) carbazate.

Scheme 1.

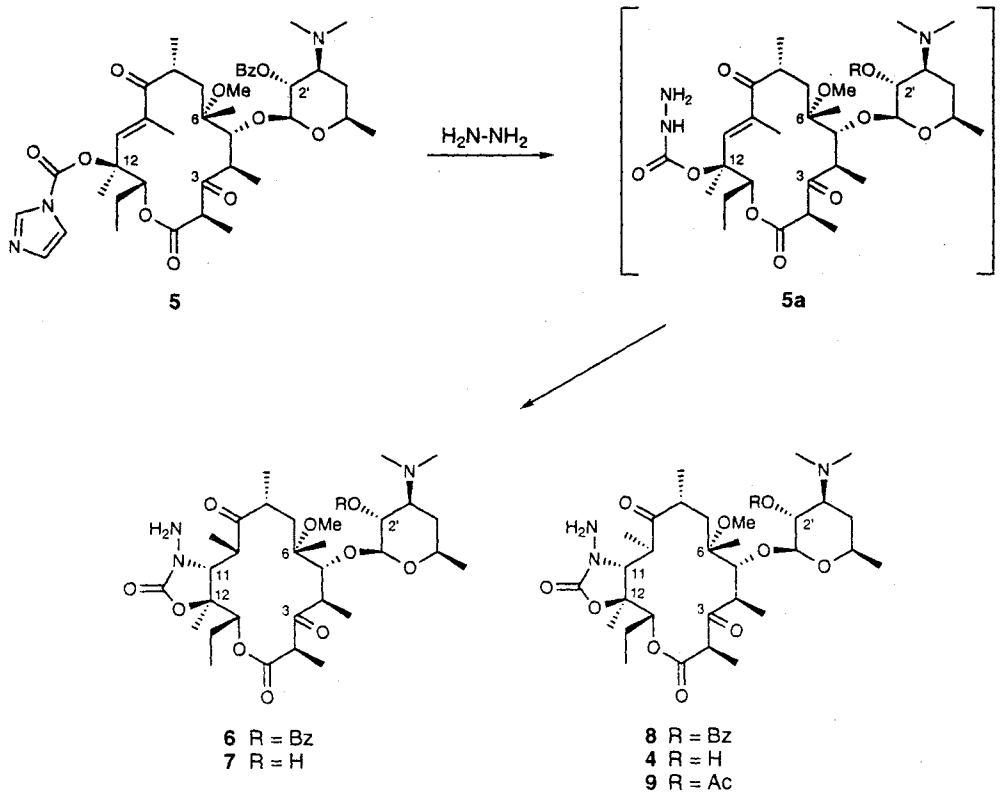
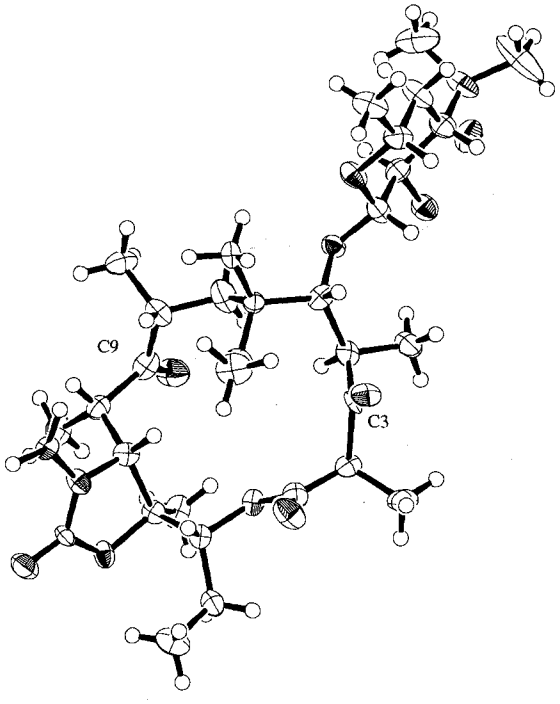


Fig. 1. Structure of 10-epi carbazate **7**.

Fig. 2. Structure of carbazate **4**.



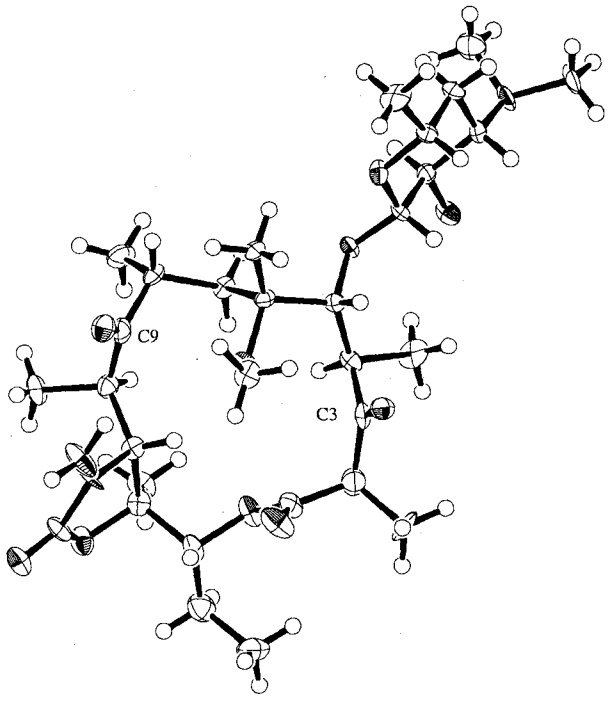
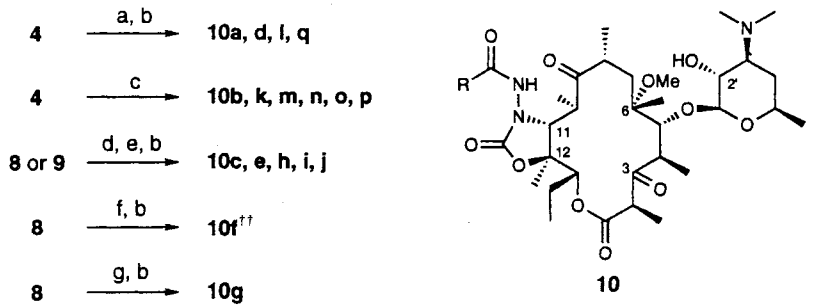


Table 1. MIC values for carbazate **4** and the 10-*epi*-carbazate **7**.

	Compound	MIC (μg/ml)						
		Staphylococcus aureus			*Streptococcus pyogenes*			*E. coli*
		6538P	A5177	A-5278	EES61	2548	930	JUHL
1	Erythromycin	0.2	3.1	>100	0.02	6.2	>100	100
4	10-(*R*)-carbazate	0.2	0.2	>100	0.2	0.39	>100	100
7	10-(*S*)-carbazate	6.2	6.2	>100	1.56	6.2	>100	—

S. aureus 6538P and *S. pyogenes* EES61: erythromycin susceptible.
S. aureus A5177: inducible MLS resistance.
S. pyogenes 2548: erythromycin resistant, clindamycin susceptible.
S. aureus A-5278 and *S. pyogenes* 930: constitutive MLS resistance.

Scheme 2.



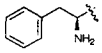
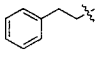
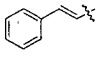
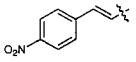
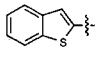
a) $(RCO)_2O$ or RCOCl (excess), DMAP, CH_2Cl_2; b) MeOH; c) RCOCl (1.1 equv.), CH_2Cl_2; d) RCO_2H, EDCI·HCl, DMAP, Et_3N, CH_2Cl_2; e) TFA, CH_2Cl_2 (if necessary); f) CH_3SO_2Cl, Et_3N, CH_2Cl_2; g) TMSNCO, toluene, 80°C. †† Compound **10f** is a sulfonamide, where the amide carbonyl is replaced by a sulfonyl group.

In addition to the crystal structures, we could also differentiate between the 10-(*R*) and 10-(*S*) epimers by ^1H NMR analysis. The compound with the natural (*R*) stereochemistry shows a signal for the C-11 methine proton that appears to be a singlet (3.61 ppm, $J_{10-11}=0$ Hz), while the spectrum for the compound with the unnatural (*S*) stereochemistry revealed a doublet for the C-11 proton (3.48 ppm, $J_{10-11}=1\sim2$ Hz). The observation that the ^1H NMR spectra of 11,12-cyclic carbamate derivatives of clarithromycin reveal a singlet for compounds with 10-(*R*) stereochemistry and a doublet for compounds with 10-(*S*) stereochemistry has been observed previously[5] and appears to be quite general. This should provide a reliable method for determining the stereochemistry at C-10 for compounds of this type.

When carbazates **4** and **7** were tested *in vitro*, we found that **4**, the compound with the natural stereochemistry at C-10, had much better antibacterial activity than **7** (Table 1). In fact, carbazate **4** had activity comparable to erythromycin against susceptible organisms and better activity against some of the erythromycin-resistant strains. This promising activity encouraged us to explore the SAR of *N*-substituted derivatives of **4**.

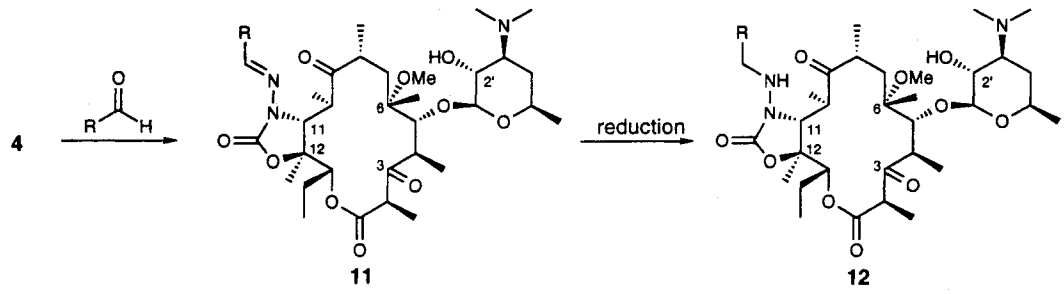
The first series of compounds that we pursued were *N*-acyl derivatives of **4** (Scheme 2). Initial attempts to form the *N*-acetylated derivative **10a** by reacting carbazate **4** with acetic anhydride (1.1 equiv) gave almost exclusively the 2′-*O*-acetylated compound **9**. In order to prepare **10a**, we reacted **4** with an excess of acetic anhydride (5 equiv) to give the bis acetylated product which was then deprotected at 2′ by reacting with MeOH. This same strategy was also used to prepare **10d**, **10l**, **10q**. In contrast to the reaction with acetic anhydride, we found that reaction of **4** with a slight excess of an acid chloride (1.1 equiv) gave almost exclusive acylation at the carbazate nitrogen. Compounds **10b**, **10k**, **10m**~**10p** were prepared from the unprotected carbazate **4** in this manner. Another method for preparing *N*-acylated derivatives involved coupling either of the 2′-*O*-protected carbazates (**8** or **9**) with carboxylic acids (or appropriately protected amino acids) utilizing a carbodiimide (1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI·HCl)) mediated reaction catalyzed by dimethylaminopyridine (DMAP). The acylated

Table 2. MIC values for acylated carbazates **10**.

Entry	R=	MIC (μg/ml)						
		Staphylococcus aureus			*Streptococcus pyogenes*			*E. coli*
		6538P	A5177	A-5278	EES61	2548	930	JUHL
10a	CH_3–	0.78	—	>100	—	3.1	>100	25
10b	$CH_3CH_2CH_2CH_2$–	0.78	0.78	>100	0.05	0.39	>100	—
10c	$CH_3OCH_2CH_2OCH_2$–	1.56	1.56	>100	0.05	3.1	>100	>100
10d	$CH_3OC(O)CH_2$–	1.56	—	>100	—	3.1	>100	50
10e	$(EtO)_2P(O)CH_2$–	1.56	3.1	>100	0.05	3.1	>100	—
10f	CH_3SO_2–	3.1	3.1	>100	0.01	0.39	>100	50
10g	H_2N–	3.1	6.2	>100	—	12.5	>100	100
10h	H_2NCH_2–	1.56	1.56	>100	0.05	6.2	>100	100
10i	$(CH_3)_2NCH_2$–	0.2	0.2	>100	0.02	—	>100	25
10j		0.78	—	>100	—	1.56	>100	50
10k		1.56	—	>100	—	3.1	>100	100
10l		1.56	0.78	>100	1.56	1.56	>100	50
10m		0.78	0.78	>100	0.39	0.39	>100	50
10n		0.78	0.78	>100	0.05	0.39	>100	>100
10o		0.39	0.39	>100	0.1	0.39	>100	>100
10p		0.2	0.2	>100	—	0.2	>100	50
10q		0.39	0.39	>100	—	0.39	100	>100
4	10-(*R*)-carbazate	0.2	0.2	>100	0.2	0.39	>100	100
1	Erythromycin	0.2	3.1	>100	0.02	6.2	>100	100

S. aureus 6538P and *S. pyogenes* EES61: erythromycin susceptible.
S. aureus A5177: inducible MLS resistance.
S. pyogenes 2548: erythromycin resistant, clindamycin susceptible.
S. aureus A-5278 and *S. pyogenes* 930: constitutive MLS resistance.

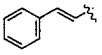
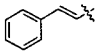
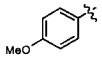
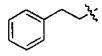
Scheme 3.



products were then appropriately deprotected to give compounds **10c**, **10e**, **10h**~**10j**. We also reacted **8** with methanesulfonyl chloride to give sulfonamide **10f** after deprotection. In addition, **8** was reacted with trimethylsilyl isocyanate, followed by deprotection, to synthesize **10g**. Thus, we found that most standard amide bond forming reactions could be employed to give a wide variety of *N*-acylated carbazates.

A second series of *N*-alkylated carbazates was prepared using a two-step reductive alkylation procedure (Scheme 3). Carbazate **4** could be directly condensed with an aldehyde to give the intermediate imine **11**, although substituted benzaldehydes required an acid catalyst to facilitate the reaction. The initial method to reduce the imine double bond by catalytic hydrogenation (Pd on carbon), used to prepare **12a**, proved to be very sluggish at 1 atm of H_2 pressure. We subsequently found that reduction with sodium cyanoborohydride ($NaBH_3CN$)

Table 3. MIC values for imine derivatives **11** and *N*-alkylated carbazates **12**.

Entry	R=	MIC (μg/ml)						
		Staphylococcus aureus			*Streptococcus pyogenes*			*E. coli*
		6538P	A5177	A-5278	EES61	2548	930	JUHL
11a		0.78	0.78	>100	0.02	0.39	>100	50
11b		1.56	1.56	>100	0.05	1.56	>100	>100
12a		0.2	0.1	>100	0.01	0.39	>100	>100
12b		0.2	0.2	>100	0.05	0.39	12.5	100
12c		0.39	0.2	>100	0.01	—	>100	50
12d		0.02	0.02	>100	0.01	0.1	>100	100
12e		0.02	0.02	>100	0.02	0.1	>100	>100
12f		0.39	0.2	>100	0.01	0.1	50	>100
12g		0.01	0.01	>100	≤0.005	0.1	25	12.5
RU 708		0.39	0.2	100	0.02	0.39	50	100
4	10-(*R*)-carbazate	0.2	0.2	>100	0.2	0.39	>100	100
1	Erythromycin	0.2	3.1	>100	0.02	6.2	>100	100

S. aureus 6538P and *S. pyogenes* EES61: erythromycin susceptible.
S. aureus A5177: inducible MLS resistance.
S. pyogenes 2548: erythromycin resistant, clindamycin susceptible.
S. aureus A-5278 and *S. pyogenes* 930: constitutive MLS resistance.

in the presence of AcOH was more facile, and the *N*-alkylated carbazates **12b**~**12g** were prepared using this procedure.

In Vitro Antibacterial Activity

The 3-keto carbazates were tested *in vitro* against both erythromycin-susceptible and erythromycin-resistant organisms using standard agar dilution methods. *Staphylococcus aureus* 6538P and *Streptococcus pyogenes* EES61 are erythromycin susceptible organisms. *Staphylococcus aureus* A5177 has inducible MLS resistance and *Staphylococcus aureus* A-5278 and *Streptococcus pyogenes* 930 both have constitutive MLS resistance. *Streptococcus pyogenes* 2548 is also erythromycin resistant, but as opposed to MLS resistant organisms, this strain is susceptible to clindamycin. We also routinely tested against *Escherichia coli* JUHL to monitor activity against Gram-negative organisms.

The first series of compounds tested (Table 2) were the acylated carbazates **10**. Most of these compounds maintain reasonable activity against erythromycin susceptible strains and against the resistant *S. aureus* A5177 and *S. pyogenes* 2548 compared to erythromycin, but no significant activity is seen against the constitutively resistant or Gram-negative organisms. The derivatives with the alkyl side chains (**10a**, **10b**) and the alicyclic side chains containing hetero atoms (**10c**~**10h**) are generally not as active as the parent carbazate **4**, although the compound prepared from dimethyl glycine (**10i**) does have activity comparable to **4**. In general, the derivatives with an aromatic substituent (**10j**~**10q**) have better activity, however these compounds still do not show increased activity compared to the parent carbazate **4**.

The second series of compounds, the imines **11** and particularly the *N*-alkylated compounds **12**, show more encouraging activity (Table 3). Generally, the *N*-alkylated derivatives (**12a**, **12b**) have better activity than the corresponding imines (**11a**, **11b**). The best compounds are the 4-substituted benzyl derivatives (**12d**, **12e**) and the phenylpropyl derivative (**12g**). In addition to being effective against the erythromycin susceptible organisms, these compounds are 150~300 times more active than erythromycin against the inducibly resistant *S. aureus* A5177 and 60 times more active against *S. pyogenes* 2548. The best compound, **12g**, also shows increased, though not outstanding, activity against the constitutively

Table 4. ^{1}H NMR chemical shifts for selected compounds.

Position	4	7	10a	10i	10n	10o	10p	11a	12a	12g
2	3.84	3.87	3.83	3.83	3.83	3.84	3.84	3.85	3.88	3.86
2-CH_3	1.37	1.42	1.35	1.35	1.37	1.38	1.37	1.35	1.38	1.37
4	3.06	3.10	3.07	3.10	3.05	3.06	3.05	3.18	3.10	3.08
4-CH_3	1.30	1.30	1.30	1.31	1.30	1.31	1.30	1.33	1.33	1.32
5	4.24	4.19	4.26	4.26	4.25	4.22	4.22	4.25	4.31	4.29
6-CH_3	1.34	1.32	1.30	1.30	1.27	1.26	1.25	1.41	1.40	1.35
6-OCH_3	2.67	2.83	2.57	2.57	2.51	2.49	2.48	2.89	2.83	2.65
7	1.84	2.29	1.83	1.80	1.81	1.82	1.83	1.77	1.84	1.81
	1.63	1.46	1.66	1.70	1.66	1.69	1.67	1.64	1.68	1.64
8	2.67	2.77	2.62	2.62	2.59	2.63	2.62	3.01	2.76	2.67
8-CH_3	1.17	1.05	1.17	1.16	1.16	1.20	1.20	1.18	1.19	1.18
10	3.10	3.53	3.07	3.08	3.07	3.10	3.10	3.09	3.21	3.16
10-CH_3	1.08	1.17	1.16	1.18	1.15	1.22	1.22	1.12	1.07	1.07
11	3.61	3.48	3.68	3.73	3.69	3.78	3.76	4.65	3.86	3.74
12-CH_3	1.45	1.67	1.52	1.53	1.52	1.55	1.55	1.60	1.47	1.47
13	5.02	4.95	5.83	5.88	5.83	5.94	5.89	5.14	4.95	5.04
14	1.94	1.84	2.02	2.02	2.02	2.05	2.04	2.02	1.82	1.96
	1.55	1.61	1.56	1.55	1.56	1.59	1.59	1.64	1.48	1.57
15	0.85	0.87	0.95	0.95	0.96	0.99	0.98	0.93	0.79	0.96
1′	4.30	4.29	4.34	4.34	4.33	4.32	4.31	4.30	4.30	4.29
2′	3.18	3.18	3.17	3.18	3.16	3.16	3.16	3.18	3.20	3.17
3′	2.45	2.46	2.47	2.47	2.45	2.46	2.44	2.45	2.48	2.45
4′	1.67	1.66	1.69	1.68	1.67	1.67	1.66	1.67	1.69	1.66
	1.23	1.21	1.22	1.22	1.21	1.22	1.19	1.24	1.24	1.22
5′	3.55	3.53	3.57	3.57	3.56	3.55	3.54	3.54	3.56	3.55
6′	1.24	1.23	1.25	1.24	1.23	1.22	1.19	1.23	1.26	1.25
-$N(CH_3)_2$	2.27	2.27	2.27	2.27	2.26	2.27	2.25	2.26	2.29	2.27
-NH_2	4.42	3.85	—	—	—	—	—	—	—	—
-NH-	—	—	8.28	9.24	8.32	8.53	8.69	—	5.56	5.32

All spectra were taken in $CDCl_3$ at 500 MHz and chemical shifts are reported in ppm relative to TMS. Individual proton assignments were determined from ^{1}H-^{1}H COSY experiments.

resistant *S. pyogenes* 930 and the Gram-negative *E. coli* JUHL. Comparison of **12g** to the analogous phenylbutyl substituted carbamate, RU 708[10], reveals that the carbazate is more active against all of the organisms tested, except for the constitutively resistant *S. aureus* A-5278. Hence, for this example, it appears that the additional nitrogen in the carbazate gives a significant increase in overall antibacterial activity†††.

Experimental

^{1}H NMR spectra were taken at 500 MHz in $CDCl_3$ and chemical shifts are reported in ppm relative to TMS as an internal standard. Assignments for individual protons were made based on ^{1}H-^{1}H COSY experiments. These assignments are listed for selected compounds in Table 4. ^{13}C NMR were taken in $CDCl_3$ and chemical shifts are reported in ppm relative to $CDCl_3$ (77.0 ppm). Elemental analyses were obtained from Robertson Laboratories, Madison, New Jersey. Compounds were purified by flash chromatography on E. Merck silica gel 60 (230~400 mesh), eluting with the indicated solvent system.

2′-*O*-Benzoyl-11-deoxy-5-*O*-desosaminyl-10-*epi*-11-hydrazo-6-*O*-methyl-3-oxoerythronolide A, 11,12-Carbamate (6) and 11-Deoxy-5-*O*-desosaminyl-10-*epi*-11-hydrazo-6-*O*-methyl-3-oxoerythronolide A, 11,12-Carbamate (7)

Hydrazine (265 μl, 8.38 mmol) was added to a solution of imidazolide **5** (3.23 g, 4.21 mmol) in 12 ml of dimethyl formamide. The reaction mixture was stirred at room temperature for 20 minutes and then partitioned between EtOAc (75 ml) and H_2O (50 ml). The layers were separated and the aqueous portion was extracted with two additional portions of EtOAc (50 ml). The combined organic layers were then washed with H_2O and brine, dried (Na_2SO_4) and concentrated under reduced pressure. Purification by flash chromatography (SiO_2, EtOAc-hexanes-NH_4OH (66:33:1)) gave **6** (1.92 g, 2.63 mmol, 62%) as a white foam. A portion of the white foam (183 mg, 0.250 mmol) was dissolved in MeOH (15 ml) and stirred at room temperature overnight. The

††† After we had prepared our series of *N*-substituted carbazate derivatives, Roussel Uclaf revealed a similar series of compounds[12,13]. In fact, RU 004, which has a 3-(4-quinolyl)propyl group attached to the carbazate nitrogen, was featured at the 35th Interscience Conference on Antimicrobial Agents Chemotherapy, Abstr. No. F157~F175, San Francisco, Sept. 17~20, 1995.

reaction mixture was concentrated under reduced pressure and purified by flash chromatography (SiO_2, CH_2Cl_2 - MeOH - NH_4OH (95 : 5 : 0.2)) to give **7** (110 mg, 0.175 mmol, 70%) as a white foam. Crystals of **7** were grown from EtOAc for X-ray analysis: **6**: CI-MS *m/z* 732 $(M+H)^+$; ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.6, 205.5, 170.5, 165.2, 157.4, 132.8, 130.3, 129.7, 128.3, 101.9, 83.0, 78.0, 77.8, 72.0, 69.1, 63.5, 50.9, 50.4, 48.6, 45.7, 41.9, 41.2, 40.8, 31.5, 21.4, 21.2, 21.0, 19.4, 17.6, 16.5, 14.4, 10.6, 10.4. **7**: mp 225~227°C; CI-MS *m/z* 628 $(M+H)^+$; ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.4, 205.5, 170.5, 157.5, 104.2, 83.1, 78.9, 78.2, 77.8, 70.3, 69.5, 65.7, 63.5, 50.9, 50.7, 48.8, 45.8, 41.9, 41.2, 40.3, 28.4, 21.6, 21.2, 21.0, 19.5, 17.7, 16.5, 14.6, 10.6, 10.4. *Anal* Calcd for $C_{31}H_{53}N_3O_{10}$: C 59.57, H 8.57, N 6.45. Found: C 59.22, H 8.61, N 6.64.

2′-*O*-Benzoyl-11-deoxy-5-*O*-desosaminyl-11-hydrazo-6-*O*-methyl-3-oxoerythronolide A, 11,12-Carbamate (**8**) and 11-Deoxy-5-*O*-desosaminyl-11-hydrazo-6-*O*-methyl-3-oxoerythronolide A, 11,12-Carbamate (**4**)

Hydrazine (4 ml, 0.13 mol) was added to a solution of imidazolide **5** (7.4 g, 9.6 mmol) in 30 ml of DMF. The reaction mixture was heated to 55°C under an atmosphere of nitrogen for 6 hours. The reaction mixture was then cooled followed by the addition of EtOAc (200 ml) and satd NH_4Cl soln (200 ml). The layers were separated and the aqueous portion was extracted with two additional portions of EtOAc (200 ml). The combined organic layers were then washed with H_2O and brine, dried (Na_2SO_4) and concentrated under reduced pressure. The resulting white foam contained mostly the 2′-*O*-benzoate **8**. The white foam was dissolved in MeOH (200 ml) and heated to 60°C overnight. The reaction mixture was cooled and concentrated under reduced pressure. Purification by flash chromatography (SiO_2, CH_2Cl_2 - MeOH - NH_4OH (95 : 4 : 1)) gave **4** (4.1 g, 6.5 mmol, 68%) as a white foam. Crystals of **4** were grown from EtOAc for X-ray analysis: **8**: CI-MS *m/z* 732 $(M+H)^+$; ^{13}C NMR (75 MHz, $CDCl_3$) δ 217.3, 204.1, 169.6, 165.2, 156.1, 132.8, 130.4, 129.7, 128.3, 101.5, 80.8, 78.1, 77.8, 77.0, 72.0, 69.3, 63.6, 62.9, 51.0, 49.2, 46.9, 44.7, 40.7, 39.4, 39.2, 31.4, 22.0, 21.0, 19.6, 18.0, 15.4, 14.2, 13.9, 13.8, 10.3. **4**: mp 219~220°C; CI-MS *m/z* 628 $(M+H)^+$; ^{13}C NMR (75 MHz, $CDCl_3$) δ 217.3, 203.9, 169.6, 156.1, 103.8, 80.8, 79.0, 78.0, 76.8, 70.3, 69.5, 65.8, 62.8, 51.1, 49.3, 47.5, 44.6, 40.2, 39.5, 39.4, 28.2, 22.0, 21.1, 19.6, 18.0, 15.7, 14.2, 13.9, 13.7, 10.3. *Anal* Calcd for $C_{31}H_{53}N_3O_{10}$: C 59.31, H 8.51, N 6.69. Found: C 59.22, H 8.61, N 6.64.

2′-*O*-Acetyl-11-deoxy-5-*O*-desosaminyl-11-hydrazo-6-*O*-methyl-3-oxoerythronolide A, 11,12-Carbamate (**9**)

A solution of carbazate **4** (2.00 g, 3.19 mmol, 1.0 equiv) in CH_2Cl_2 (30 ml) was treated with acetic anhydride (305 μl, 3.23 mmol, 1.0 equiv) at 0°C under nitrogen. After stirring for 1 hour, the reaction was warmed to room temperature and stirred an additional 2 hours. The reaction was quenched by addition of satd $NaHCO_3$ soln and extracted into CH_2Cl_2. The organic portion was washed with H_2O and brine, dried (Na_2SO_4) and concentrated under reduced pressure. Purification by flash chromatography (SiO_2, CH_2Cl_2 - MeOH - NH_4OH (96 : 4 : 0.2)) gave **9** (1.35 g, 2.02 mmol, 62%) as a white powder: CI-MS *m/z* 670 $(M+H)^+$; ^{13}C NMR (75 MHz, $CDCl_3$) δ 217.3, 204.0, 169.7, 169.6, 156.1, 101.3, 80.8, 78.1, 77.8, 77.1, 71.5, 69.2, 63.4, 62.9, 51.1, 49.3, 46.9, 44.7, 40.6, 39.4, 39.2, 30.5, 22.1, 21.4, 21.0, 19.6, 18.1, 15.4, 14.1, 14.0, 13.9, 10.3. *Anal* Calcd for $C_{33}H_{55}N_3O_{11}$: C 59.18, H 8.28, N 6.27. Found: C 59.36, H 8.36, N 6.33.

11-Deoxy-5-*O*-desosaminyl-11-acetylhydrazo-6-*O*-methyl-3-oxoerythronolide A, 11,12-Carbamate (**10a**)

A solution of carbazate **4** (190 mg, 0.303 mmol, 1.0 equiv) in CH_2Cl_2 (5 ml) was treated with acetic anhydride (143 μl, 1.51 mmol, 5.0 equiv) and dimethylamino pyridine (74 mg, 0.60 mmol, 2.0 equiv). After stirring under nitrogen for 18 hours, the reaction was quenched by addition of satd $NaHCO_3$ soln and extracted into CH_2Cl_2. The organic portion was washed with H_2O and brine, dried (Na_2SO_4) and concentrated under reduced pressure. Purification by flash chromatography (SiO_2, CH_2Cl_2 - MeOH (93 : 7)) gave a white powder (113 mg) which was the *N*-acetylated compound protected as the 2′-*O*-acetate. The white solid was dissolved in MeOH (10 ml) and heated to 60°C for 6 hours to remove the 2′-*O*-acetate. The reaction mixture was cooled and concentrated under reduced pressure. Purification by flash chromatography (SiO_2, CH_2Cl_2 - MeOH - NH_4OH (93 : 7 : 0.1)) gave **10a** (82 mg, 0.123 mmol, 40%) as a white powder: CI-MS *m/z* 670 $(M+H)^+$; ^{13}C NMR (75 MHz, $CDCl_3$) δ 218.3, 204.9, 168.7, 168.4, 154.6, 103.4, 82.7, 77.8, 77.7, 77.3, 70.3, 69.5, 65.9, 61.9, 51.1, 48.9, 47.0, 45.1, 40.2, 39.6, 38.9, 28.3, 22.2, 21.2, 20.5, 19.5, 18.2, 15.2, 14.7, 14.3, 13.9, 10.4. *Anal* Calcd for $C_{33}H_{55}N_3O_{11}$: C 59.18, H 8.28, N 6.27. Found: C 59.53, H 8.55, N 5.93.

11-Deoxy-5-*O*-desosaminyl-11-(1-oxopentyl)hydrazo-6-*O*-methyl-3-oxoerythronolide A, 11,12-Carbamate (**10b**)

A solution of **4** (135 mg, 0.215 mmol, 1.0 equiv) in CH_2Cl_2 (2 ml) was treated with valeryl chloride (28 μl, 0.236 mmol, 1.1 equiv). After stirring under nitrogen for 15 hours, the reaction was quenched by addition of satd $NaHCO_3$ soln and extracted into CH_2Cl_2. The organic portion was washed with H_2O and brine, dried (Na_2SO_4) and concentrated under reduced pressure. Purification by flash chromatography (SiO_2, CH_2Cl_2 - MeOH - NH_4OH (95 : 5 : 0.2)) gave **10b** (102 mg, 0.143 mmol, 67%) as a white powder after concentrating from Et_2O - hexanes: CI-MS *m/z* 712 $(M+H)^+$; ^{13}C NMR (75 MHz, $CDCl_3$) δ 218.2, 204.9, 171.3, 168.7, 154.5, 103.4, 82.6, 77.8, 77.7, 77.3, 70.3, 69.6, 65.9, 61.9, 51.1, 49.1, 47.0, 45.1, 40.2, 39.6, 39.0, 28.3, 26.9, 22.3, 22.2, 21.2, 19.5, 18.2, 15.2, 14.7, 14.3, 14.0, 13.7, 10.4. *Anal* Calcd for $C_{36}H_{61}N_3O_{11}$: C 60.74, H 8.64, N 5.90. Found:

C 61.02, H 8.89, N 5.66.

11-Deoxy-5-*O*-desosaminyl-11-((methoxyethoxy)-acetyl)hydrazo-6-*O*-methyl-3-oxoerythronolide A, 11,12-Carbamate (**10c**)

2'-*O*-acetyl carbazate **9** (250 mg, 0.373 mmol, 1.0 equiv), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI·HCl) (268 mg, 1.40 mmol, 3.8 equiv) and dimethylaminopyridine (DMAP) (96 mg, 0.79 mmol, 2.1 equiv) were dissolved in 5 ml of CH_2Cl_2 and stirred under nitrogen. Methoxyethoxyacetic acid (180 μl, 1.59 mmol, 4.2 equiv) and Et_3N (265 μl, 1.90 mmol, 5.1 equiv) were then added to the reaction and stirring was continued overnight. The reaction was quenched by addition of 5% aq KH_2PO_4 soln and extracted into CH_2Cl_2 (30 ml). The organic portion was washed with 5% KH_2PO_4 soln (2×), H_2O and brine, dried over Na_2SO_4 and concentrated under reduced pressure. Purification by flash chromatography (SiO_2, CH_2Cl_2-MeOH-NH_4OH (96:4:0.1)) gave 204 mg of white powder. This was dissolved in MeOH (10 ml) to remove the 2'-*O*-acetate. After stirring overnight, the reaction was concentrated under reduced pressure. The resulting material was passed through a small plug of SiO_2, eluting with 5% MeOH-CH_2Cl_2, and concentrated to give **10c** (146 mg, 53%) as a white solid: CI-MS *m/z* 744 $(M+H)^+$; ^{13}C NMR (75 MHz, $CDCl_3$) δ 216.8, 204.7, 168.7, 167.9, 154.3, 103.5, 82.9, 78.0, 77.8, 77.2, 71.6, 71.2, 70.3, 70.1, 69.5, 65.8, 62.0, 58.9, 51.0, 48.9, 47.2, 44.8, 40.1, 39.5, 38.6, 28.2, 22.1, 21.1, 19.4, 18.0, 15.5, 14.4, 14.2, 13.8, 10.4. *Anal* Calcd for $C_{36}H_{61}N_3O_{13}$: C 58.13, H 8.27, N 5.65. Found: C 58.22, H 8.44, N 5.42.

11-Deoxy-5-*O*-desosaminyl-11-((methoxycarbonyl)-acetyl)hydrazo-6-*O*-methyl-3-oxoerythronolide A, 11,12-Carbamate (**10d**)

A solution of carbazate **8** (304 mg, 0.416 mmol, 1.0 equiv) in CH_2Cl_2 (5 ml) was treated with methyl malonyl chloride (89 μl, 0.83 mmol, 2.0 equiv). After stirring under nitrogen for 3 hours, the reaction was quenched by addition of satd $NaHCO_3$ soln and extracted into CH_2Cl_2 (30 ml). The organic portion was washed with H_2O and brine, dried (Na_2SO_4) and concentrated under reduced pressure. Purification by flash chromatography (SiO_2, CH_2Cl_2-MeOH-NH_4OH (96:4:0.1)) gave 320 mg of a white solid. This white solid was dissolved in MeOH (10 ml) and heated to 45°C for 18 hours. The reaction mixture was cooled and concentrated under reduced pressure. Purification by flash chromatography (SiO_2, CH_2Cl_2-MeOH-NH_4OH (93:7:0.1)) gave **10d** (213 mg, 0.293 mmol, 70%) as a white solid: CI-MS *m/z* 728 $(M+H)^+$; ^{13}C NMR (75 MHz, $CDCl_3$) δ 217.2, 204.5, 168.6, 167.6, 162.8, 154.0, 103.3, 82.7, 77.7, 77.7, 77.0, 70.1, 69.3, 65.7, 61.8, 52.4, 50.9, 48.8, 46.9, 44.7, 40.0, 39.4, 38.5, 28.0, 21.9, 20.9, 19.3, 17.9, 15.2, 14.4, 14.1, 13.7, 10.2. *Anal* Calcd for $C_{35}H_{57}N_3O_{13}$: C 57.76, H 7.89, N 5.77. Found: C 57.52, H 8.02, N 5.39.

11-Deoxy-5-*O*-desosaminyl-11-((diethylphosphono)-acetyl)hydrazo-6-*O*-methyl-3-oxoerythronolide A, 11,12-Carbamate (**10e**)

This compound was prepared from **8** and diethyl phosphonoactetic acid in a manner similar to that described for the preparation of **10c**. Purification by flash chromatography (SiO_2, CH_2Cl_2-MeOH-NH_4OH (95:5:0.2)) gave **10e** (53% yield) as a white solid: CI-MS *m/z* 806 $(M+H)^+$; ^{13}C NMR (75 MHz, $CDCl_3$) δ 217.1, 204.8, 168.8, 162.4 (d, $J=5$ Hz), 154.0, 103.5, 82.8, 78.1, 77.8, 77.3, 70.3, 69.5, 65.9, 63.6 (d, $J=6$ Hz), 62.8 (d, $J=6$ Hz), 61.9, 51.1, 49.1, 47.1, 44.7, 40.2, 39.6, 38.8, 33.8 (d, $J=133$ Hz), 28.3, 22.2, 21.2, 19.5, 18.1, 16.4 (d, $J=6$ Hz), 16.3, (d, $J=6$ Hz)15.4, 14.6, 14.3, 14.0, 10.4. *Anal* Calcd for $C_{37}H_{64}N_3O_{14}P$: C 55.14, H 8.00, N 5.21, P 3.84. Found: C 54.96, H 8.30, N 5.28, P 3.75.

11-Deoxy-5-*O*-desosaminyl-11-(methanesulfonyl)hydrazo-6-*O*-methyl-3-oxoerythronolide A, 11,12-Carbamate (**10f**)

A solution of 2'-*O*-benzoyl carbazate **8** (148 mg, 0.202 mmol, 1.0 equiv) in CH_2Cl_2 (2 ml) was treated with methanesulfonyl chloride (20 μl, 0.26 mmol, 1.3 equiv) and Et_3N (72 μl, 0.52 mmol, 2.6 equiv). After stirring under nitrogen for 20 hours, the reaction was quenched by addition of satd $NaHCO_3$ soln and extracted into CH_2Cl_2 (30 ml). The organic portion was washed with H_2O and brine, dried (Na_2SO_4) and concentrated under reduced pressure. Purification by flash chromatography (SiO_2, hexanes-acetone (6:4)) gave 131 mg of a white solid. The white solid was dissolved in MeOH (10 ml). After stirring for 2 days, the reaction was concentrated under reduced pressure. Purification by flash chromatography (SiO_2, CH_2Cl_2-MeOH (9:1)) gave **10f** (67 mg, 0.095 mmol, 47%) as a white powder: CI-MS *m/z* 706 $(M+H)^+$; ^{13}C NMR (75 MHz, $CDCl_3$) δ 219.3, 204.3, 168.3, 154.4, 103.5, 82.3, 78.1, 77.6, 77.0, 70.3, 69.5, 66.0, 62.9, 51.0, 50.3, 46.9, 44.6, 42.9, 40.2, 39.9, 28.4, 22.5, 21.2, 19.6, 18.3, 15.1, 14.8, 14.6, 14.3, 10.3. *Anal* Calcd for $C_{32}H_{55}N_3O_{12}S$: C 54.45, H 7.85, N 5.95. Found: C 54.19, H 8.00, N 5.87.

11-Deoxy-5-*O*-desosaminyl-11-(aminocarbonyl)hydrazo-6-*O*-methyl-3-oxoerythronolide A, 11,12-Carbamate (**10g**)

A solution of 2'-*O*-benzoyl carbazate **8** (192 mg, 0.263 mmol, 1.0 equiv) in toluene (3 ml) was treated with trimethylsilyl isocyanate (350 μl, 2.59 mmol, 10 equiv) and was heated to 80°C. After stirring for 2 days, the reaction was cooled and concentrated under reduced pressure. Purification by flash chromatography (SiO_2, *m/z* 713 $(M+H)^+$; ^{13}C NMR (75 MHz, $CDCl_3$) δ 216.8, 204.9, 168.7, 168.6, 154.5, 103.4, 83.0, 77.8, 77.7, 77.5, 70.3, 69.5, 65.9, 62.2, 62.1, 51.1, 49.2, 46.8, 46.3, 45.0, 40.2, 39.4, 38.6, 28.3, 22.3, 21.1, 19.5, 18.3, 15.0, 14.6, 14.3, 14.0, 10.4. *Anal* Calcd for $C_{35}H_{60}N_4O_{11}$: C 58.97, H 8.48, N 7.86. Found: C 59.19, H 8.49, N 7.86.

11-Deoxy-5-*O*-desosaminyl-11-(phenylalanyl)hydrazo-6-*O*-methyl-3-oxoerythronolide A, 11,12-Carbamate (**10j**)

This compound was prepared from **8** and *N*-Boc-phenylalanine in a manner similar to that described for the preparation of **10h**. Purification by flash chromatography (SiO_2, CH_2Cl_2-MeOH-NH_4OH (90:10:0.5)) followed by crystallization from EtOAc-hexanes gave 123 mg (0.159 mmol, 51% yield) of compound **10j**: CI-MS *m/z* 775 $(M+H)^+$; ^{13}C NMR (75 MHz, $CDCl_3$) δ 217.3, 204.8, 172.2, 168.8, 154.5, 137.8, 129.4, 128.7, 126.8, 103.5, 82.8, 78.0, 77.9, 77.3, 70.3, 69.6, 65.9, 62.0, 56.2, 51.1, 49.1, 47.1, 45.0, 40.9, 40.2, 39.6, 38.8, 28.2, 22.2, 21.2, 19.5, 18.1, 15.4, 14.6, 14.3, 14.0, 10.4. *Anal* Calcd for $C_{40}H_{62}N_4O_{11}$: C 62.00, H 8.06, N 7.23. Found: C 62.00, H 7.97, N 7.47.

11-Deoxy-5-*O*-desosaminyl-11-((3-pyridinyl)carbonyl)hydrazo-6-*O*-methyl-3-oxoerythronolide A, 11,12-Carbamate (**10k**)

A solution of carbazate **4** (119 mg, 0.190 mmol, 1.0 equiv) in CH_2Cl_2 (2 ml) was treated with nicotinyl chloride·HCl (37 mg, 0.21 mmol, 1.1 equiv) and Et_3N (40 μl, 0.29 mmol, 1.5 equiv). After stirring under nitrogen for 2 days, the reaction was quenched by addition of satd $NaHCO_3$ soln and extracted into CH_2Cl_2 (25 ml). The organic portion was washed with H_2O and brine, dried (Na_2SO_4) and concentrated under reduced pressure. Purification by flash chromatography (SiO_2, CH_2Cl_2-MeOH-NH_4OH (95:5:0.5)) gave the product (81 mg, 0.111 mmol, 58%) as a white powder: CI-MS *m/z* 733 $(M+H)^+$; ^{13}C NMR (75 MHz, $CDCl_3$) δ 218.8, 204.7, 168.9, 163.8, 154.4, 153.0, 148.5, 135.5, 127.6, 123.5, 103.5, 82.9, 77.9, 77.7, 77.2, 70.3, 69.6, 65.9, 62.0, 51.1, 49.1, 47.2, 45.1, 40.2, 39.6, 39.3, 28.2, 22.3, 21.2, 19.6, 18.2, 15.4, 14.7, 14.3, 13.9, 10.5. *Anal* Calcd for $C_{37}H_{56}N_4O_{11}$: C 60.64, H 7.70, N 7.64. Found: C 60.60, H 7.81, N 7.39.

11-Deoxy-5-*O*-desosaminyl-11-benzoylhydrazo-6-*O*-methyl-3-oxoerythronolide A, 11,12-Carbamate (**10l**)

This compound was prepared from **4** and benzoic anhydride in a manner similar to that described for the preparation of **10a**. Purification by flash chromatography (SiO_2, CH_2Cl_2-MeOH-NH_4OH (95:5:0.2)) gave **10l** as a white powder (40% yield): CI-MS *m/z* 732 $(M+H)^+$; ^{13}C NMR (75 MHz, $CDCl_3$) δ 218.7, 204.9, 168.8, 165.4, 154.6, 132.2, 131.6, 128.5, 127.5, 103.4, 82.7, 77.8, 77.6, 77.3, 70.3, 69.5, 65.9, 62.0, 51.1, 49.1, 47.0, 45.1, 40.2, 39.6, 39.2, 28.2, 22.3, 21.1, 19.5, 18.2, 15.3, 14.8, 14.3, 14.0, 10.5. *Anal* Calcd for $C_{38}H_{57}N_3O_{11}$: C 62.36, H 7.85, N 5.74. Found: C 62.62, H 8.05, N 5.45.

11-Deoxy-5-*O*-desosaminyl-11-(phenylacetyl)hydrazo-6-*O*-methyl-3-oxoerythronolide A, 11,12-Carbamate (**10m**)

A solution of carbazate **4** (105 mg, 0.167 mmol, 1.0 equiv) in CH_2Cl_2 (5 ml) was cooled to 0°C and treated with phenylacetyl chloride (25 μl, 0.189 mmol, 1.1 equiv). After 10 minutes, the reaction was warmed to room temperature and stirred an additional 3 hours. The reaction was then quenched by addition of satd $NaHCO_3$ soln and extracted into CH_2Cl_2 (25 ml). The organic portion was washed with H_2O and brine, dried (Na_2SO_4) and concentrated under reduced pressure. Purification by flash chromatography (SiO_2, CH_2Cl_2-MeOH-NH_4OH (96:4:0.2)) gave **10m** (77 mg, 0.103 mmol, 62%) as a white powder after concentrating from Et_2O-hexanes: CI-MS *m/z* 746 $(M+H)^+$; ^{13}C NMR (75 MHz, $CDCl_3$) δ 217.6, 204.8, 168.6, 168.6, 154.3, 133.3, 129.4, 128.6, 127.1, 103.5, 82.6, 77.9, 77.7, 77.3, 70.3, 69.5, 65.8, 61.8, 51.0, 48.8, 47.0, 44.9, 41.2, 39.5, 38.8, 28.2, 22.2, 21.1, 19.4, 18.1, 15.2, 14.6, 14.2, 13.9, 10.3. *Anal* Calcd for $C_{39}H_{59}N_3O_{11}$: C 62.80, H 7.97, N 5.63. Found: C 62.52, H 7.93, N 5.57.

11-Deoxy-5-*O*-desosaminyl-11-(1-oxo-3-phenylpropyl)hydrazo-6-*O*-methyl-3-oxoerythronolide A, 11,12-Carbamate (**10n**)

This compound was prepared from carbazate **4** and hydrocinnamoyl chloride following the procedure used to prepare **10m**. Flash chromatography (SiO_2, CH_2Cl_2-MeOH-NH_4OH (96:4:0.2)) gave **10n** (47% yield) as a white powder after concentrating from Et_2O-hexanes: CI-MS *m/z* 760 $(M+H)^+$; ^{13}C NMR (75 MHz, $CDCl_3$) δ 218.2, 204.8, 170.4, 168.8, 154.5, 140.6, 128.5, 128.3, 126.2, 103.5, 82.7, 77.8, 77.8, 77.3, 70.3, 69.5, 65.9, 61.8, 51.1, 49.0, 47.1, 45.1, 40.2, 39.6, 39.0, 35.7, 30.8, 28.2, 22.0, 21.2, 19.5, 18.2, 15.3, 14.7, 14.3, 13.9, 10.4. *Anal* Calcd for $C_{40}H_{61}N_3O_{11}$: C 63.22, H 8.09, N 5.53. Found: C 62.98, H 8.08, N 5.34.

11-Deoxy-5-*O*-desosaminyl-11-(1-oxo-3-phenyl-2-propenyl)hydrazo-6-*O*-methyl-3-oxoerythronolide A, 11,12-Carbamate (**10o**)

This compound was prepared from carbazate **4** and cinnamoyl chloride following the procedure used to prepare **10m**. Flash chromatography (SiO_2, CH_2Cl_2-MeOH-NH_4OH (95:5:0.2)) gave **10o** (57% yield) as a white powder: CI-MS *m/z* 758 $(M+H)^+$; ^{13}C NMR (75 MHz, $CDCl_3$) δ 218.4, 204.8, 168.7, 164.6, 154.6, 143.4, 134.5, 130.0, 128.7, 128.0, 103.3, 82.7, 77.8, 77.5, 77.3, 70.2, 69.4, 65.8, 61.9, 51.1, 49.1, 47.0, 45.1, 40.1, 39.6, 39.0, 28.2, 22.2, 21.1, 19.4, 18.1, 15.3, 14.6, 14.2, 13.9, 10.4. *Anal* Calcd for $C_{40}H_{59}N_3O_{11}$: C 63.39, H 7.85, N 5.54. Found: C 62.92, H 8.05, N 5.50.

11-Deoxy-5-*O*-desosaminyl-11-(1-oxo-3-(4-nitrophenyl)-2-propenyl)hydrazo-6-*O*-methyl-3-oxoerythronolide A, 11,12-Carbamate (**10p**)

This compound was prepared from carbazate **4** and 4-nitrocinnamoyl chloride following the procedure used to prepare **10m**. Flash chromatography (SiO_2, CH_2Cl_2-MeOH-NH_4OH (96:4:0.2)) gave **10p** (53% yield) as a pale yellow solid: CI-MS *m/z* 803 $(M+H)^+$; ^{13}C NMR (75 MHz, $CDCl_3$) δ 218.6, 204.7, 168.9, 163.5, 154.5,

148.4, 140.7, 140.6, 128.6, 124.1, 121.1, 103.5, 82.9, 77.9, 77.7, 77.2, 70.3, 69.5, 65.9, 62.0, 51.1, 49.1, 47.2, 45.1, 40.2, 39.6, 39.0, 28.2, 22.2, 21.1, 19.5, 18.1, 15.4, 14.7, 14.3, 13.9, 10.5. *Anal* Calcd for $C_{40}H_{58}N_4O_{13}$: C 59.84, H 7.28, N 6.98. Found: C 59.64, H 7.51, N 6.80.

11-Deoxy-5-*O*-desosaminyl-11-((2-thianaphthenyl)-carbonyl)hydrazo-6-*O*-methyl-3-oxoerythronolide A, 11,12-Carbamate (**10q**)

A solution of carbazate **4** (128 mg, 0.204 mmol, 1.0 equiv) in CH_2Cl_2 (5 ml) was treated with thianaphthene 2-carbonyl chloride (132 mg, 0.671 mmol, 3.3 equiv) and DMAP (88 mg, 0.72 mmol, 3.5 equiv). After stirring under nitrogen for 24 hours, the reaction was quenched by addition of satd $NaHCO_3$ soln and extracted into CH_2Cl_2. The organic portion was washed with H_2O and brine, dried (Na_2SO_4) and concentrated under reduced pressure to give the 2′-*O*-*N*-bis acylated compound (162 mg) as a white solid. This solid was dissolved in MeOH (15 ml) and stirred at ambient temperature for 2 days. The reaction mixture was concentrated under reduced pressure and purified by flash chromatography (SiO_2, CH_2Cl_2-MeOH-NH_4OH (95:5:0.2)) to give **10q** (107 mg, 0.136 mmol, 67%) as a white powder: FAB-MS *m/z* 788 $(M+H)^+$; ^{13}C NMR (75 MHz, $CDCl_3$) δ 218.9, 204.8, 168.8, 161.1, 154.4, 141.4, 138.9, 135.0, 127.1, 126.6, 125.4, 124.8, 122.7, 103.4, 82.7, 77.8, 77.6, 77.2, 70.3, 69.5, 65.9, 61.9, 51.1, 49.1, 47.1, 45.1, 40.2, 39.6, 39.3, 28.2, 22.3, 21.1, 19.5, 18.1, 15.4, 14.7, 14.3, 14.0, 10.5. *Anal* Calcd for $C_{40}H_{57}N_3O_{11}S$: C 60.97, H 7.29, N 5.33. Found: C 60.69, H 7.27, N 5.19.

11-Deoxy-5-*O*-desosaminyl-11-(phenylmethylene)hydrazo-6-*O*-methyl-3-oxoerythronolide A, 11,12-Carbamate (**11a**)

Carbazate **4** (427 mg, 0.681 mmol, 1.0 mmol) and benzaldehyde (0.65 ml) were dissolved in toluene (7 ml). Molecular sieves (4A, 8～12 mesh) were added and the reaction was heated to 90°C. After stirring for 16 hours, the reaction mixture was cooled, filtered and concentrated under reduced pressure. Purification by flash chromatography (SiO_2, CH_2Cl_2-MeOH-NH_4OH (95:5:0.1)) gave **11a** (312 mg, 0.436 mmol, 64%) as a slightly yellow solid: FAB-MS *m/z* 716 $(M+H)^+$; ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.7, 203.5, 169.5, 153.0, 152.8, 134.4, 130.2, 128.5, 127.6, 104.2, 81.9, 78.3, 77.5, 70.3, 69.6, 65.9, 63.2, 51.2, 50.7, 47.0, 41.5, 40.6, 40.2, 38.8, 28.2, 22.8, 21.2, 17.9, 15.5, 14.7, 14.5, 14.5, 11.7, 10.6. *Anal* Calcd for $C_{38}H_{57}N_3O_{10}$: C 63.76, H 8.03, N 5.87. Found: C 63.44, H 8.04, N 5.65.

11-Deoxy-5-*O*-desosaminyl-11-(3-phenyl-2-propenylidene)hydrazo-6-*O*-methyl-3-oxoerythronolide A,11,12-Carbamate (**11b**)

This compound was prepared from carbazate **4** and cinnamaldehyde following the procedure used to prepare **11a**. Flash chromatography (SiO_2, CH_2Cl_2-MeOH-NH_4OH (95:5:0.1)) gave **11b** (62% yield) as a white solid: CI-MS *m/z* 742 $(M+H)^+$; ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.1, 203.5, 169.6, 153.4, 152.9, 139.9, 136.0, 128.8, 128.6, 127.1, 125.8, 104.1, 82.1, 81.3, 78.2, 77.4, 70.3, 69.6, 65.8, 62.3, 51.1, 50.7, 47.0, 41.0, 41.0, 40.2, 38.7, 28.1, 22.6, 21.1, 21.0, 18.0, 14.7, 14.5, 14.5, 12.1, 10.5. *Anal* Calcd for $C_{40}H_{59}N_3O_{10}$: C 64.76, H 8.02, N 5.66. Found: C 64.47, H 8.07, N 5.43.

11-Deoxy-5-*O*-desosaminyl-11-(phenylmethyl)hydrazo-6-*O*-methyl-3-oxoerythronolide A, 11,12-carbamate (**12a**)

Imine **11a** (144 mg, 0.199 mmol) was dissolved in MeOH (5 ml) and 10% Pd on carbon (140 mg) was added. The reaction was then stirred vigorously under 1 atm of H_2 pressure for 2 days. The reaction mixture was filtered through a Celite pad and concentrated under reduced pressure. Purification by flash chromatography (SiO_2, CH_2Cl_2-MeOH-NH_4OH (95:5:0.1)) gave **12a** (68 mg, 0.095 mmol, 48%) as a white powder: CI-MS *m/z* 718 $(M+H)^+$; ^{13}C NMR (75 MHz, $CDCl_3$) δ 217.8, 204.0, 169.6, 155.6, 136.7, 129.2, 128.2, 127.4, 103.8, 80.6, 79.3, 78.1, 77.6, 70.3, 69.6, 65.9, 58.6, 53.0, 51.1, 50.4, 47.4, 44.4, 40.2, 39.8, 39.7, 28.2, 22.1, 21.2, 20.0, 18.5, 15.5, 14.8, 14.4, 14.2, 10.2. *Anal* Calcd for $C_{38}H_{59}N_3O_{10}$: C 63.58, H 8.28, N 5.85. Found: C 63.30, H 8.44, N 5.67.

11-Deoxy-5-*O*-desosaminyl-11-(3-phenyl-2-propenyl)-hydrazo-6-*O*-methyl-3-oxoerythronolide A, 11,12-Carbamate (**12b**)

Imine **11b** (200 mg, 0.269 mmol, 1.0 equiv) was dissolved in 5 ml of CH_3CN followed by the addition of $NaBH_3CN$ (170 mg, 2.66 mmol, 10 equiv) and AcOH (250 μl, 4.4 mmol, 16 equiv). After stirring under nitrogen for 18 hours, the reaction was quenched by addition of satd $NaHCO_3$ soln and extracted into CH_2Cl_2 (50 ml). The organic portion was washed with H_2O and brine, dried (Na_2SO_4) and concentrated under reduced pressure. Purification by flash chromatography (SiO_2, CH_2Cl_2-MeOH-NH_4OH (96:4:0.1)) gave **12b** (135 mg, 0.182 mmol, 68%) as a white powder after concentrating from Et_2O-hexanes: CI-MS *m/z* 744 $(M+H)^+$; ^{13}C NMR (75 MHz, $CDCl_3$) δ 218.0, 204.0, 169.6, 156.1, 137.0, 133.7, 128.3, 127.3, 126.2, 126.0, 103.9, 80.8, 79.3, 78.1, 77.9, 70.3, 69.6, 65.9, 58.4, 51.4, 51.2, 50.4, 47.5, 44.6, 40.2, 39.7, 28.2, 22.0, 21.2, 19.9, 18.6, 15.7, 14.7, 14.4, 14.4, 9.9. *Anal* Calcd for $C_{40}H_{61}N_3O_{10}$: C 64.58, H 8.26, N 5.65. Found: C 64.32, H 8.40, N 5.67.

11-Deoxy-5-*O*-desosaminyl-11-((2-furanyl)methyl)-hydrazo-6-*O*-methyl-3-oxoerythronolide A, 11,12-Carbamate (**12c**)

Carbazate **4** (236 mg, 0.376 mmol, 1.0 equiv) and 2-furaldehyde (0.4 ml) were dissolved in toluene (5 ml). Molecular sieves (4A, 8～12 mesh) and *p*-toluenesulfonic acid (20 mg) were added and the reaction was heated to 90°C. After stirring for 18 hours, the reaction mixture was cooled, filtered, and concentrated under reduced

pressure. Purification by flash chromatography (SiO_2, CH_2Cl_2-MeOH-NH_4OH (95:5:0.1)) gave the imine (246 mg) as a yellow foam. The imine was dissolved in 10 ml of MeOH and bromocresol green was added as an indicator. $NaBH_3CN$ (44 mg, 2 equiv) was then added followed by the dropwise addition of AcOH until the reaction mixture turned yellow. After stirring for 18 hours, the reaction was quenched by addition of satd $NaHCO_3$ soln and extracted into CH_2Cl_2 (40 ml). The organic portion was washed with satd $NaHCO_3$ soln, H_2O and brine. The organic portion was then dried (Na_2SO_4) and concentrated under reduced pressure. Purification by flash chromatography (SiO_2, EtOAc-hexanes-CH_3CN-NH_4OH (70:20:10:2)) gave **12c** (164 mg, 0.232 mmol, 62%) as a white foam: CI-MS *m/z* 708 $(M+H)^+$; ^{13}C NMR (75 MHz, $CDCl_3$) δ 217.8, 203.8, 169.6, 155.4, 150.7, 142.4, 109.9, 108.7, 103.8, 80.5, 79.3, 78.1, 77.4, 70.3, 69.5, 65.8, 58.3, 51.0, 50.2, 47.3, 45.3, 44.3, 40.1, 39.7, 39.6, 28.1, 22.1, 21.1, 19.8, 18.4, 15.3, 14.6, 14.3, 14.0, 10.3. *Anal* Calcd for $C_{38}H_{59}N_3O_{10}$: C 61.08, H 8.12, N 5.94. Found: C 60.97, H 8.18, N 5.77.

11-Deoxy-5-*O*-desosaminyl-11-((4-chlorophenyl)-methyl)hydrazo-6-*O*-methyl-3-oxoerythronolide A, 11,12-Carbamate (**12d**)

This compound was prepared from carbazate **4** and 4-chlorobenzaldehyde following the procedure used to prepare **12c**. Flash chromatography (SiO_2, EtOAc-hexanes-CH_3CN-NH_4OH (70:20:10:2)) gave **12d** (28% yield) as a white solid: CI-MS *m/z* 752 $(M+H)^+$; ^{13}C NMR (75 MHz, $CDCl_3$) δ 217.9, 203.9, 169.7, 155.6, 135.4, 133.2, 130.6, 128.3, 103.9, 80.6, 79.3, 78.2, 77.6, 70.3, 69.6, 65.9, 58.5, 52.2, 51.1, 50.4, 47.4, 44.6, 40.2, 39.7, 39.7, 28.3, 22.0, 21.2, 19.9, 18.6, 15.4, 14.7, 14.4, 14.2, 10.2. *Anal* Calcd for $C_{38}H_{58}ClN_3O_{10}$: C 60.67, H 7.77, N 5.59. Found: C 60.80, H 7.89, N 5.38.

11-Deoxy-5-*O*-desosaminyl-11-((4-methoxyphenyl)-methyl)hydrazo-6-*O*-methyl-3-oxoerythronolide A, 11,12-Carbamate (**12e**)

This compound was prepared from carbazate **4** and 4-methoxybenzaldehyde following the procedure used to prepare **12c**. Flash chromatography (SiO_2, EtOAc-hexanes-CH_3CN-NH_4OH (70:20:10:2)) gave **12e** (57% yield) as a white foam: CI-MS *m/z* 748 $(M+H)^+$; ^{13}C NMR (75 MHz, $CDCl_3$) δ 217.7, 204.0, 169.6, 158.9, 155.7, 130.5, 128.9, 113.6, 103.9, 80.5, 79.4, 78.1, 77.7, 70.3, 69.6, 65.9, 58.6, 55.2, 52.3, 51.1, 50.4, 47.4, 44.4, 40.2, 39.8, 39.7, 28.2, 22.1, 21.2, 20.0, 18.5, 15.4, 14.8, 14.4, 14.2, 10.3. *Anal* Calcd for $C_{39}H_{61}N_3O_{11}$: C 62.63, H 8.22, N 5.62. Found: C 62.43, H 8.39, N 5.58.

11-Deoxy-5-*O*-desosaminyl-11-(2-phenylethyl)hydrazo-6-*O*-methyl-3-oxoerythronolide A, 11,12-Carbamate (**12f**)

Carbazate **4** (242 mg, 0.386 mmol, 1.0 equiv) and phenylacetaldehyde (0.5 ml) were dissolved in toluene (5 ml). Molecular sieves (4A, 8~12 mesh) were added and the reaction was heated to reflux. After stirring for 4 hours, the reaction mixture was cooled, filtered, and concentrated under reduced pressure. Purification by flash chromatography (SiO_2, CH_2Cl_2-MeOH-NH_4OH (96:4:0.1)) gave the imine (157 mg) as a colorless solid. The imine was dissolved in 10 ml of MeOH and bromocresol green was added as an indicator. $NaBH_3CN$ (25 mg, 2 equiv) was then added followed by the dropwise addition of AcOH until the reaction mixture turned yellow. After stirring for 4 hours, the reaction was quenched by addition of satd $NaHCO_3$ soln and extracted into CH_2Cl_2 (40 ml). The organic portion was washed with satd $NaHCO_3$ soln, H_2O and brine. The organic portion was then dried (Na_2SO_4) and concentrated under reduced pressure. Purification by flash chromatography (SiO_2, EtOAc-hexanes-CH_3CN-NH_4OH (70:20:10:2)) gave **12f** (98 mg, 0.134 mmol, 35%) as a white foam: CI-MS *m/z* 732 $(M+H)^+$; ^{13}C NMR (75 MHz, $CDCl_3$) δ 217.5, 203.8, 169.5, 156.1, 139.4, 128.8, 128.3, 126.0, 103.8, 80.7, 79.5, 78.0, 77.3, 70.3, 69.5, 65.9, 58.8, 51.1, 50.7, 50.1, 47.3, 44.3, 40.2, 39.8, 39.6, 34.6, 28.3, 22.2, 21.1, 19.9, 18.4, 15.4, 14.7, 14.4, 14.1, 10.4. *Anal* Calcd for $C_{39}H_{61}N_3O_{10}$: C 63.00, H 8.40, N 5.74. Found: C 63.01, H 8.48, N 5.68.

11-Deoxy-5-*O*-desosaminyl-11-(3-phenylpropyl)hydrazo-6-*O*-methyl-3-oxoerythronolide A, 11,12-Carbamate (**12g**)

This compound was prepared from carbazate **4** and hydrocinnamaldehyde following the procedure used to prepare **12f**. Flash chromatography (SiO_2, EtOAc-hexanes-CH_3CN-NH_4OH (70:20:10:2)) gave **12g** (32% yield) as a white foam: CI-MS *m/z* 746 $(M+H)^+$; ^{13}C NMR (75 MHz, $CDCl_3$) δ 217.6, 203.8, 169.5, 156.0, 142.1, 128.5, 128.2, 125.6, 103.9, 80.6, 79.5, 78.1, 77.3, 70.3, 69.6, 65.8, 58.3, 53.0, 51.1, 50.1, 48.5, 47.3, 44.4, 40.2, 39.7, 39.6, 33.3, 29.6, 28.1, 22.1, 21.2, 19.9, 18.5, 15.4, 14.6, 14.4, 14.2, 10.4. *Anal* Calcd for $C_{40}H_{63}N_3O_{10}$: C 64.41, H 8.51, N 5.63. Found: C 64.19, H 8.43, N 5.45.

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