Synthesis and Antibacterial Activity of Ketolides (6-*O*-Methyl-3-oxoerythromycin Derivatives): A New Class of Antibacterials Highly Potent Against Macrolide-Resistant and -Susceptible Respiratory Pathogens†

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In the search for new antibiotics active against macrolide-resistant pneumococci and *Haemophilus influenzae*, we synthesized a new class of 3-oxo-6-*O*-methylerythromycin derivatives, so-called "ketolides". A keto function was introduced in position 3 after removal of L-cladinose, a sugar which has long been thought essential. Further modifications of the macrolactone backbone allowed us to obtain three different series of 9-oxime, 11,12-carbamate, and 11,12-hydrazonocarbamate ketolides. These compounds were found to be very active against penicillin/erythromycin-resistant pneumococci and noninducers of MLS_B resistance. The 11,-12-substituted ketolide **61** (HMR 3004) demonstrated a potent activity against multiresistant pneumococci associated with a well-balanced activity against all bacteria involved in respiratory infections including *H. influenzae*, *Mycoplasma catarrhalis*, group A streptococci, and atypical bacteria. In addition HMR 3004 displayed high therapeutic activity in animals infected by all major strains, irrespective of their resistance phenotype.

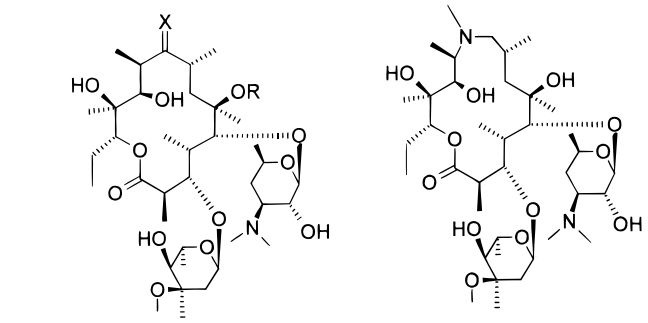
Introduction

Macrolides, including erythromycin, are an old and well-known family of oral antibiotics. Their spectrum of activity covers most relevant bacterial species responsible for upper and lower respiratory tract infections.[1]

Interest in 14-membered ring macrolides was renewed in the 1980s because of their overall efficacy, safety, and lack of serious side effects associated with good activities against new emerging pathogens, e.g., *Mycoplasma*, *Chlamydia*, and *Legionella*.[1,2] Erythromycin however is quickly degraded into inactive products in the acidic medium[1,3] of the stomach. This results in low bioavailability and gastrointestinal side effects. This is why the first success in the macrolides field came from the improvement of erythromycin pharmacokinetics through the synthesis of the more acid-stable derivatives roxithromycin,[4] clarithromycin,[5] and the 15-membered ring macrolide azithromycin[6] (Chart 1).

However all these drugs, including 16-membered ring macrolides, present several drawbacks. They are inactive against MLS_B-resistant streptococci and *Streptococcus pneumoniae*[1,7] and, with the exception of azithromycin, weakly active against *Haemophilus influenzae*.[1,2b] Furthermore the resistance of *S. pneumoniae* to erythromycin has increased significantly in recent years[8] (5% to above 40%). There is a high percentage of cross-resistance to penicillin among these isolates, with a worldwide epidemic spread of 10−40% in some areas.[8b−d] Macrolides, lincosamides, and streptogramin B (MLS_B) antibiotics have distinct chemical structures but have been shown to have a similar mechanism of action against bacteria. They inhibit peptidyltranferase reaction in vivo and are inhibitors of peptide bond formation in whole cells.[9] The most widespread mechanism of macrolide resistance in pathogenic bacteria results from a base-specific mono- and dimethylation of 23S ribosomal RNA near or within the macrolide binding site such that antibiotics of the macrolide, lincosamide, or streptogramin B chemical class now fail to bind.[10] Organ-

Chart 1. Structures of Clinically Utilized Macrolides



† Abbreviations: ERY, erythromycin; CLA, clarithromycin; AZI, azithromycin; JOSA, josamycin.

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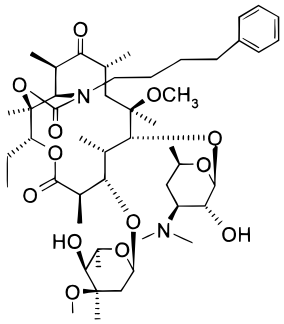
isms with this type of cross-resistance, designated MLS_B resistance, can express an inducible or a constitutive phenotype. The emergence among Gram-positive cocci of new efflux-based mechanism of resistance must also be mentioned.[11] There is, therefore, a clear need for new macrolides[1,12] that overcome the problem of pneumococcal resistance while continuing to be as active as azithromycin against *H. influenzae*. These new structures would have to conserve the good pharmacokinetic properties and acid stability of available macrolides to be ideal candidates for drug development in the first line therapy of upper and lower respiratory tract infections (URTI and LRTI).

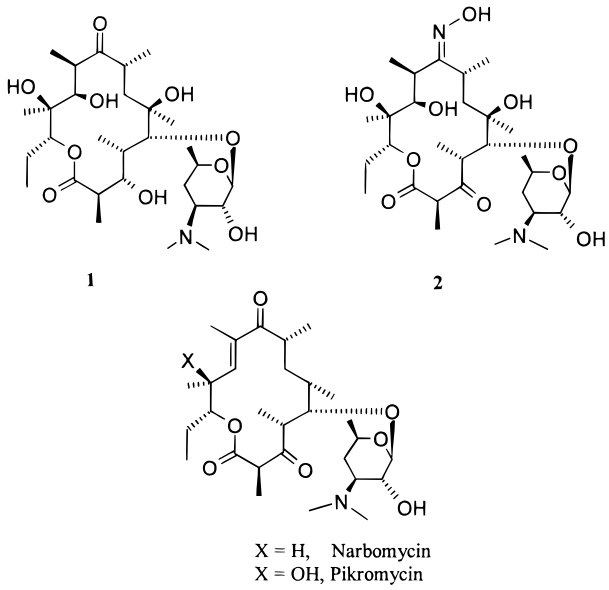
During the last 30 years several chemical modifications have been made on the macrolactone part of erythromycin[13] and the two sugars, cladinose[14,24b] and desosamine.[15,28b] For instance, the introduction of oximes[4,16] and amines[17] at C-9, C-15 azalide synthesis via the Beckmann rearrangement of 9-oxime,[18] and 6,-11,12-*O*-alkylation[5,19] or 8-fluorination[20] have culminated with the synthesis of new drugs such as roxithromycin, dirithromycin, azithromycin, clarithromycin, and flurithromycin. More recently, new chemical approaches have generated some interesting series such as 9-deoxo-12-deoxy-9,12-epoxyerythromycin A derivatives,[21] C-14 azalides,[22] C-21 aminomethylene,[23] and finally 11,12-cyclocarbamates[24] and 9-azaimino-11,12-cyclocarbamates.[25] Some products coming from mutants and genetically engineered *Streptomyces* have also been described.[26] The carbamate A 66321 from Abbott was the single example of modifications that produced compounds slightly effective against macrolide-resistant organisms.[24b]



A 66321

It was long thought from all these studies that the cladinose moiety was in fact crucial for the antibacterial activity as well as the resistance-inducibility properties of erythromycin. Particularly, it was shown by Allen[14] and Pestka[27] that chemical modifications or replacement of this sugar could increase or suppress the resistance inducibility of erythromycin. Similarly, it was demonstrated by Le Mahieu[27,28] that desclanidosyl (**1**) and 3-ketoerythromycin oxime (**2**) were inactive but noninducers, while Allen[14] identified the two poor antibacterial 3-keto macrolides narbomycin[29] and pikromycin[30] as noninducers (Chart 2). When considering these results, we concluded that position 3 of macrolides could be an innovative starting point for further chemical modifications in order to increase the antibacterial activity against sensitive and resistant strains. Therefore we decided to address the problem of erythromycin

Chart 2. Structures of 3-Keto Macrolides Previously Described



1 **2**

X = H, Narbomycin
X = OH, Pikromycin

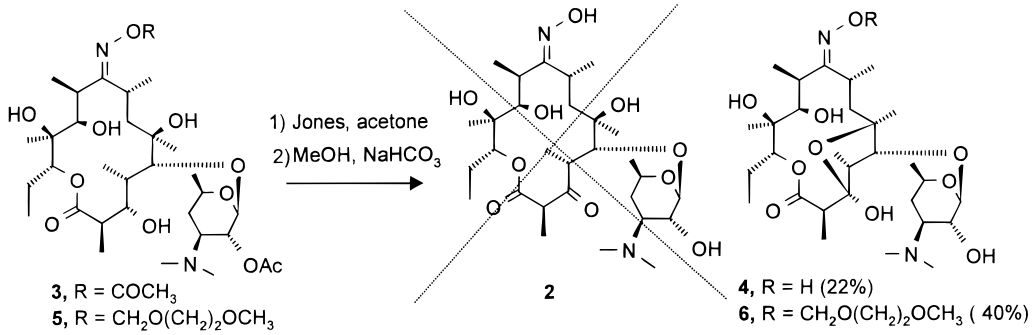
resistance by re-exploring the chemistry of the natural 3-keto macrolides narbomycin or picromycin with the objective of synthesizing 9-oxime and 11,12-carbamate derivatives. We rapidly discovered that the structure described by Le Mahieu[28a] was wrong and that the synthesis of 3-ketoerythromycin could only be achieved from 6-*O*-methylerythromycin. The chemistry of this new compound allowed us to obtained several molecules named "ketolides". These sophisticated molecules displayed for the first time a significant in vitro and in vivo activity against *H. influenzae* and multiresistant pneumococci.

Chemistry

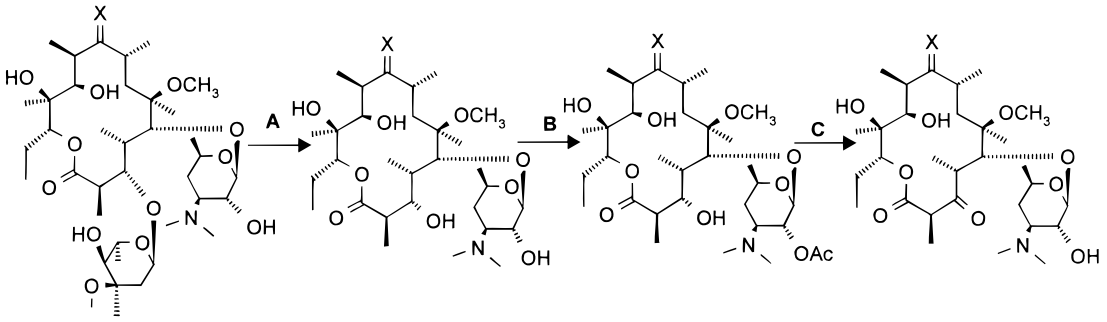
A. Attempted Synthesis of 3-Keto ERY. In 1973, Le Mahieu et al.[28a] described the synthesis of **2** from oxidation of the 3-hydroxyl of compound **3**. Following the same experimental protocols, we found that the structure of **2** was wrong. The mass spectrum was in agreement with the right structure ($MS = 588^+$), but the UV spectrum did not show any characteristic absorption of a β-keto-ester enolate in basic medium EtOH/NaOH, 0.1 N[31] (λ max $\sim$ 275−290 nm, $\epsilon \sim$ 10 000−15 000). In addition, the NMR was not in accordance with a 3-keto function; the H_2 proton that was predicted to be deshielded in a β-keto-ester position had in fact the same frequency as that in the preceding alcohol **3** (2.66 vs 2.54 ppm). Actually, **2** was the hemiacetal **4**. This result was further confirmed by using 3-hydroxyroxithromycin[32] (**5**) as a starting material. The oxidation of alcohol **5** with Jones reagent yielded **6** in 40% yield (Scheme 1). The structure of **6** resolved by $^{13}C-^{1}H$ NMR analysis definitely established the presence of a 6−3 ketal (C_3 59.3 ppm instead of $\sim$200 ppm for a carbonyl group).

Therefore we decided to block the 6-OH function by using 6-*O*-methylerythromycin as a starting material to avoid the 6−3 cyclization. Thus hydrolysis of the cladinose followed by acetylation of the 2′-OH gave the 3-hydroxy intermediate **8** in 62% yield. Oxidation of position 3 was very efficiently carried out with a

Scheme 1



Scheme 2[a]



[a] X = O: (A) HCl/H_2O (76%); (B) Ac_2O/K_2CO_3, acetone (82%); (C) a, EDC, HCl, DMSO, pyridinium trifluoroacetate, CH_2Cl_2, b, MeOH (70%). X = $NOCH_2O(CH_2)_2OCH_3$ (N-*O*-MEM): (A) a, MeONa, Cl-MEM, THF, 5 °C (67%), b, HCl/H_2O, rt (97%); (B) Ac_2O/K_2CO_3, acetone (95%); (C) a, Jones, acetone, 0 °C, b, MeOH (58%).

modified Pfitzner−Moffat[33] procedure (1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride (EDC,HCl)−DMSO, pyridinium trifluoroacetate)[18a] instead of Jones reagent that gave a complex mixture of inseparable products. This allowed us to obtain 3-oxo-6-*O*-methylerythromycin (**9**) in 72% yield after removal of the 2′-acetyl group with methanol. In a very similar way, alkylation of 9-oxime 6-*O*-methylerythromycin (**10**) was accomplished by MEM chloride with MeONa in DMF at 0 °C (67% yield). The previous sequence allowed us to obtain the 3-keto analogue (**13**) of roxithromycin in 53% yield (Scheme 2).

The antibacterial spectrum of these two compounds revealed for the first time a very slight activity against some EryRi- and EryRc-resistant strains (see later Table 3). Considering these very promising results, we decided to further modify the structure **9** by preparing 9-oxime or 11,12-cyclocarbamate analogues.

B. Synthesis of 9-Oxime Ketolides. It was demonstrated earlier that the introduction of a supplementary amino group in the macrolide skeleton, e.g., azalides and some 9-aminooximes, was beneficial for the activity against *H. influenzae*.[6] Thus a strategy was set up to quickly introduce several amines into the oxime chain of ketolides (Scheme 3).

9 could be reacted very efficiently at pH 4−5 in MeOH with NH_2OH, HCl, or various substituted hydroxyamines to give the 9-oxime ketolides (Scheme 3). With the exception of hydroxylamine (E/Z = 5/1), this reaction gave predominantly the *E* isomers. The *E* stereochemistry of these oximes was established by comparison of previous studies[4b,34] that demonstrated that the H_8 proton of (*E*)-oximes was deshielded to ~3.75 ppm. This characteristic was conserved in our structures (Table 1).

The hydroxyamines corresponding to the compounds in Table 1 and **16**[35] were prepared by literature methods (Table 1, entries **19**,[36] **20**,[37] **22**[38]). The bromo derivative **16** was used as an intermediate to introduce amino groups in the lateral chain by displacement of the bromine atom (method B). The aminocyclic ketolides (method C) were obtained from 3-(aminooxy)pyrrolidine and piperidine derivatives **14** and **15**, respectively (Scheme 4). The *N*-CBz-3-(aminooxy)pyrrolidine gave an unseparable mixture of diastereoisomeric compounds **33**, whereas *N*-CBz-3-(aminooxy)piperidine gave **34** and **35** as two distinct products separated by chromatography. The configuration of carbon 3 in the piperidine ring was further attributed by starting the synthesis with pure (*S*)- or (*R*)-piperidinol.[39] Due to its interesting activity against EryR strains and *H. influenzae* (see later Table 4), **34** was substituted (Table 1, entries **36**−**41**) by methylation under Eschweiler−Clarke conditions and by reductive amination of various aldehydes with $NaBH_3CN$/AcOH in MeOH (Scheme 5).

C. Synthesis of 11,12-Carbamates and 11,12-Hydrazonocarbamates. In 1988, Baker et al. reported the synthesis of 11,12-carbamate 6-methoxyerythromycin derivatives.[24a] The key point of this synthesis was the formation of the 12-acylimidazolyl intermediate by treatment of protected 6-methoxyerythromycin with carbonyldiimidazole and $NaN(TMS)_2$. Subsequent reaction with various amines provided cyclic carbamates such as A 66321 through intramolecular

Scheme 3

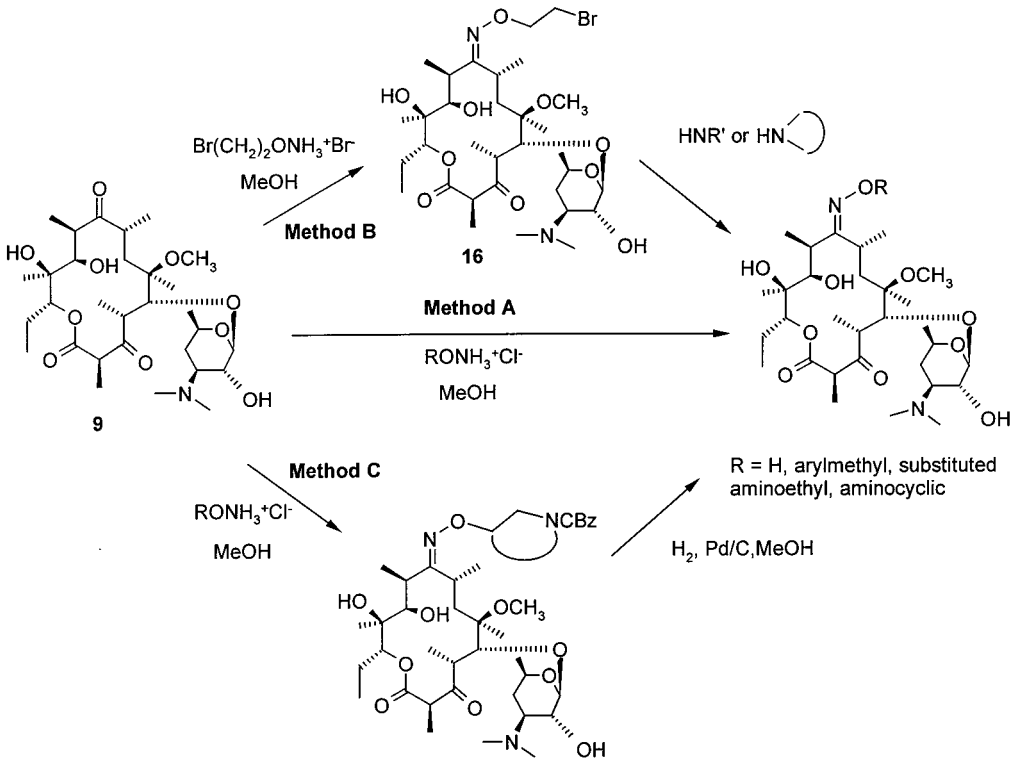


Table 1. Yields and Chemical Characterization of 9-Oxime Ketolide Derivatives

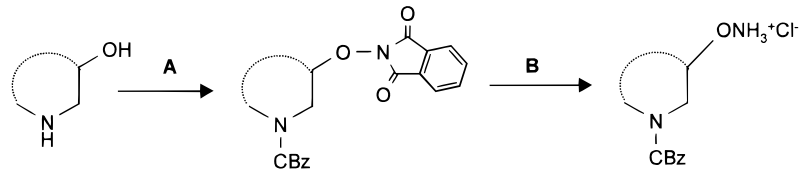
compd	R	method	yield (%)	H_8 ^1H NMR	formula[a]
17 (*E*)	H	A	32	3.75 (m)	$C_{30}H_{54}N_2O_{10}$
17 (*Z*)			6	2.70 (m)	$C_{30}H_{54}N_2O_{10}$
18	benzyl	A	30	3.70 (m)	$C_{37}H_{60}N_2O_{10}$
19	2,4,6-trimethylbenzyl	A	43	3.66 (m)	$C_{40}H_{66}N_2O_{10}$
20	(*R*)-2-amino-3-methoxy-3-oxopropyl	A	47	3.62 (m)	$C_{34}H_{61}N_3O_{12}$
21[b]	(*R*)-2-amino-3-hydroxy-3-oxopropyl potassium salt	A	82	3.80 (m)	$C_{33}H_{58}N_3O_{12}K{\cdot}5H_2O$
22	2-(dimethylamino)ethyl	A	68	3.64 (m)	$C_{34}H_{63}N_3O_{10}$
23	2-(propylamino)ethyl	B	47	3.70 (m)	$C_{35}H_{65}N_3O_{10}$
24	2-((2-propynyl)amino)ethyl	B	27	3.65 (m)	$C_{35}H_{61}N_3O_{10}$
25	2-(benzylamino)ethyl	B	44	3.72 (m)	$C_{39}H_{65}N_3O_{10}$
26	2-(1-pyrrolidinyl)ethyl	B	32	3.71 (m)	$C_{36}H_{65}N_3O_{10}$
27	2-(1-azetidinyl)ethyl	B	37	3.60 (m)	$C_{35}H_{63}N_3O_{10}$
28	2-(1-piperidinyl)ethyl	B	50	3.65 (m)	$C_{37}H_{67}N_3O_{10}$
29	2-(1-morpholinyl)ethyl	B	30	3.60 (m)	$C_{36}H_{65}N_3O_{11}$
30	2-((2-(1-pyrrolidinyl)ethyl)amino)ethyl	B	69	3.65 (m)	$C_{38}H_{70}N_4O_{10}$
31	2-((2-(dimethylamino)ethyl)amino)ethyl	B	48	3.66 (m)	$C_{36}H_{68}N_4O_{10}$
32	2-((3-(1*H*-imidazol-1-yl)propyl)amino)ethyl	B	38	3.65 (m)	$C_{38}H_{67}N_5O_{10}$
33	(*R*,*S*)-3-pyrrolidinyl	C	15	3.59 (m)	$C_{34}H_{61}N_3O_{10}$
34	(*R*)-3-piperidinyl	C	27	3.72 (m)	$C_{35}H_{63}N_3O_{10}$
35	(*S*)-3-piperidinyl	C	18	3.65 (m)	$C_{35}H_{63}N_3O_{10}$
36[c]	(*R*)-1-methyl-3-piperidinyl	C	78	3.69 (m	$C_{36}H_{65}N_3O_{10}$
37	(*R*)-1-(3-phenylpropyl)-3-piperidinyl	C	32	3.69 (m)	$C_{44}H_{73}N_3O_{10}$
38	(*R*)-1-(3-cyclohexylpropyl)-3-piperidinyl	C	27	3.68 (m)	$C_{44}H_{79}N_3O_{10}$
39	(*R*)-1-(4-biphenylylmethyl)-3-piperidinyl	C	28	3.69 (m)	$C_{48}H_{73}N_3O_{10}$
40[d]	(*R*)-1-(3-(4-hydroxyphenyl)propyl)-3-piperidinyl	C	33	3.65 (m)	$C_{44}H_{73}N_3O_{11}$
41[e]	(*R*)-1-decyl-3-piperidinyl	C	90	3.68 (m)	$C_{45}H_{83}N_3O_{10}$

[a] C, H, N results were within ±0.4% of the theoretical values for the formula given. [b] **19**, K_2CO_3, MeOH. [c] **34**, HCHO, HCO_2H, $CHCl_3$, reflux. [d] 3-(4-Hydroxyphenyl)propionaldehyde synthesized as in ref 40. [e] **34**, decanal, H_2, Pd/C, MeOH, CH_3CO_2H.

Michaël addition. When this sequence was applied to the 2′-protected ketolide **9**-2′-OAc, the desired product **44** was obtained in a very poor yield. We speculated that the addition of an excess of $NaN(TMS)_2$ promoted the degradation of **44** due to the presence of the acidic H_2 proton and overlong reaction time (up to 18 h). The synthesis of the 12-acylimidazolyl ketolide **44** was thus carried out in three steps (Scheme 6). The 11-hydroxy group was first mesylated with $(MeSO_2)_2O$ in pyridine in 79% yield; **42** underwent smooth elimination by treatment with DBU in acetone to give **43** in 88% yield. Finally the remaining 12-hydroxy group was acylated in 72% yield by treatment with NaH in DMF at −10 °C followed by addition of 3 equiv of carbonyldiimidazole.

Stirring **44** in CH_3CN/H_2O with various amines at 60 °C yielded the desired 11,12-cyclocarbamate ketolides **46**−**55** (Scheme 7; Table 2). However, we were surprised to observe that the reaction with ammonia in CH_3CN (−40 to 20 °C) gave a 2/1 mixture of 10-methyl epimers **45a,b** in 65% yield, whereas introduction of

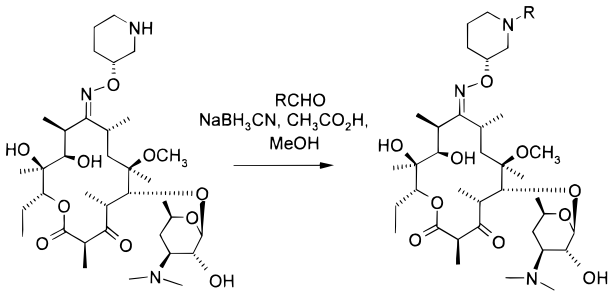
Scheme 4[a]



14 (R,S) N-CBz-3-(aminooxy)pyrrolidine, 12%
15 (R,S) N-CBz-3-(aminooxy)piperidine, 63%

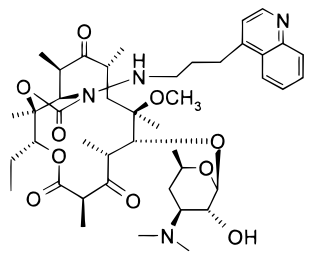
[a] (A) (1) CBzCl, K_2CO_3, dioxane, 5 °C, (2) $P\Phi_3$, DEAD, THF, rt; (B) (1) $NH_2NH_2-H_2O$, EtOH, 60 °C, (2) HCl.

Scheme 5



34 **37-40**

bulky amino groups yielded the single natural 10*R* isomer. Similarly, when **44** was heated at 60 °C in CH_3CN with 4 equiv of $NH_2NH_2 \cdot H_2O$, the two epimeric hydrazono ketolides **56a,b** were obtained in a 1/1 ratio (Scheme 7). In contrast with the previous amines, these two examples of low stereoselection could be explained by the protective effect of the aryl−alkyl side chain which makes the *S* side inaccessible to the proton donor (Chart 3). Interestingly a few months after the first communication of this reaction,[45b] chemists from Abbott reported that they were able to produce predominantly[41] **56a** just by increasing the amount of hydrazine (10 equiv instead of 4 equiv) in DMF. For all these compounds the stereochemistry of carbon 10 was first determined by NMR. Previous studies made with 11,-12-carbamate erythromycin derivatives revealed[24a] that the C11 methine proton appeared as a singlet in the 10*R* configuration while the *S* stereochemistry gave a doublet. Both carbama and carbaza ketolides NMR spectra were in accordance with this observation. Furthermore the NMR assignment of the 10*R* center was later confirmed by the crystal structure of **61** (Figure 2).



61

The hydrazono ketolide **56a** was then chosen as starting material to introduce aryl−alkyl side chains similar to those of some of the carbamates (Table 2, entries **57**−**61**). This was carried out by reductive alkylation of the hydazono function by $NaBH_3CN$/AcOH in MeOH with the corresponding aldehydes (Scheme 8). The noncommercially available amines and aldehydes corresponding to the compounds in Table 2 were synthesized by Wittig reactions (Scheme 9) or by literature methods.

Results and Discussion[45]

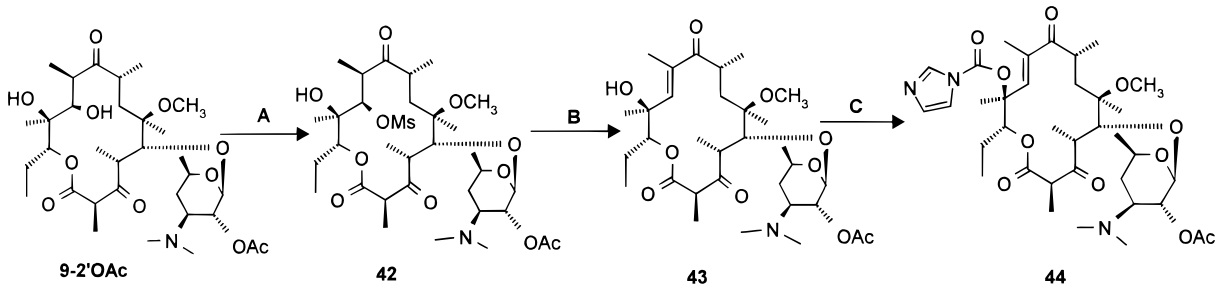
To select the most interesting compound with respect to the antibacterial spectrum and potential in respiratory tract infections, the ketolides were tested in vitro by standard agar dilution method against both erythromycin-susceptible and erythromycin-resistant staphylococci, streptococci, and pneumococci including constitutive (EryRc) and inducible (EryRi) phenotypes. Two strains of *H. influenzae* were also tested.

In general ketolides were inactive against *Escherichia coli* and constitutively resistant strains of *Staphylococcus aureus* (MIC > 40 μg/mL). The most interesting feature of these new compounds was that they were very effective against inducibly resistant staphylococci and pneumococci as well as constitutively resistant pneumococci. Moreover some of them were as potent as azithromycin against *H. influenzae.* (Table 5). Without exception all the reference macrolides (erythromycin, clarithromycin, azithromycin) were inactive (MICs > 40 μg/mL) against erythromycin-resistant strains whatever the phenotype (Table 3).

We observed that the formation of a 6,3-hemiacetal (compounds **4**, **6**) completely abolished the activity against all strains tested. In contrast the first ketolides **9** and **13** remained as active as classical macrolides against sensitive strains and were weakly active against EryRi *S. aureus* and/or *S. epidermidis* (Table 3).

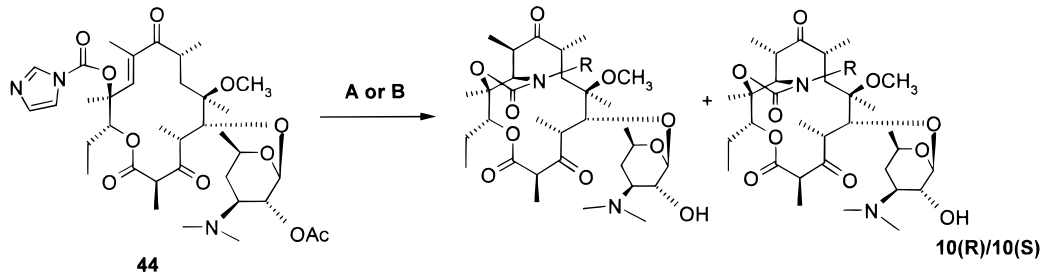
Introduction of substituted oximes in position 9 resulted in a very different profile of activity. The amino ketolides were generally less active than the piperidinyl derivatives (Table 4). Some oximes were moderately active against sensitive strains and almost inactive against erythromycin-resistant strains (**17**, **18**, **20**, **23**, **25**, **31**, **32**). Introduction of a charged carboxylate into **21** resulted in a dramatic loss of activity. Although the dimethylamino, propargylamino, azetidinyl, or pyrrolidinylethylamino derivatives **22**, **24**, **27**, and **30** were the first compounds that displayed a marked activity against resistant *S. aureus* and *S. pneumoniae*, the presence of an amino group did not increase the activity against *H. influenzae* as expected. Among the aminocyclic oximes, the 3(*R*)-piperidinyl derivative **34** was more active than the pyrrolidinyl compound **33**. Substitutions of the free nitrogen of **34** by propylaryl residues (**37**−**40**) did not seem to affect or to increase the activity. Nevertheless **34** was the first ketolide that displayed a significant activity against *H.*

Scheme 6[a]



[a] (A) $(MeSO_2)_2O$, pyridine (79%); (B) DBU, acetone, rt (88%); (C) NaH, carbonyldiimidazole, DMF, −10 °C (67%).

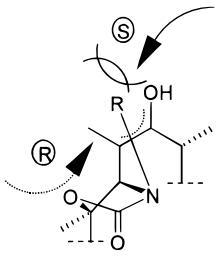
Scheme 7[a]



R= H	**45a**	**45b**	**2/1**
R= NH2	**56a**	**56b**	**1/1**
R= alkyl-aryl	**46-55**		**100/0**

[a] (A) (1) RNH_2, CH_3CN, H_2O, 60 °C or NH_3, H_2O, −40 to 20 °C, (2) MeOH; (B) $NH_2NH_2-H_2O$, CH_3CN, 60 °C, 3 h.

Chart 3



influenzae with a balanced spectrum regarding its activity against Gram-positive resistant and susceptible strains.

The two lipophilic oximes **19** and **41** were very interesting because of their activity against EryRc *S. aureus* and *S. pneumoniae* (10 and 5−1.2 μg/mL). This type of substitution was previously reported to be favorable in the erythromycin family.[16b,17b] However in both cases these compounds were totally inactive against *H. influenzae*.

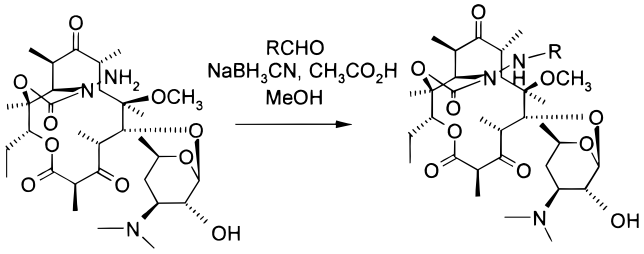
The synthesis of the 11,12-carbamate and -carbazate ketolides made us very confident in the potential of the ketolide family. The nonsubstituted compounds **45** and **56** were weakly active against resistant strains, whereas their 10-epimeric counterparts were almost inactive (Table 5). The introduction of an aryl−alkyl side chain resulted in a dramatic increase of activity against resistant strains and *H. influenzae* simultaneously. With the exception of the EryRc *S. aureus* 011CB20, all the MICs of **46** and **49** against resistant strains were included between 0.15 and 0.04 μg/mL (>40 for CLA and AZI) and 1.2−2.5 against *H. influenzae* (1.2 for AZI). The carbazates **57** and **58** were slightly less active than their carbamate analogues against the constitutively resistant *S. pneumoniae* 030SJ1. The aryl group as well as the length of the chain was also critical as shown by compounds **47** and **48** compared to **46**. Introduction of heteroatoms in the side chains resulted in a loss of activity against constitutively resistant pneumococci (MICs 5−40 μg/mL for **50**−**52**). Finally introduction of a heteroatom in the aryl group, as shown by the quinoline derivatives, allowed us to obtain the desired profile of activity. In the carbamate series **55** and its 6-methoxyquinoline analogue **53** were within the range of the phenyl compound **46** against the Gram-positive pathogens. Furthermore they were now equivalent to azithromycin against *H. influenzae*. The carbazates **61** and **57** were also very potent against both resistant and sensitive Gram-positive pathogens (MICs between 0.15 and 0.02 μg/mL), and particularly **61** was more active than azithromycin against *H. influenzae* (Table 5). Comparison of **46** and **57** with the Abbott product A 66321 revealed some interesting features of the ketolides. The presence of the cladinose completely abolished the activity against EryRi *S. aureus* and strongly decreased the activity against resistant *S. pneumoniae*. Therefore the presence of a keto function instead of a sugar in position 3 seemed to be critical with respect to the induction of resistance and to the activity against macrolide-resistant Gram-positive organisms. Recently, following the first report of ketolides by HMR,[45] chemists from Taisho and Abbott have reported the synthesis of some interesting 9-imino tricyclic ketolides like TE 802,[25b,46] 2,3-unsaturated carbamates (so-called anhydrolides),[47] 3-deoxycarbamates,[48] and 3-acyl derivatives.[49] However all these compounds are weakly active against constitutively resistant pneumococci and none of them are as effective as azithromycin or **61** against

Table 2. Yields and Chemical Characterization of Carbama and Carbaza Ketolides Derivatives

compd	R	yield (%)	H_{11} ^{1}H NMR	formula[a]
45a[b]	H	43	3.74 (sl)	$C_{31}H_{52}N_2O_{10}$
45b[c]	H	22	3.55 (d)	$C_{31}H_{52}N_2O_{10}$
46	4-phenylbutyl	60	3.59 (s)	$C_{41}H_{64}N_2O_{10}$
47	propyl	60	masked	$C_{35}H_{60}N_2O_{11}$
48	3-phenylpropyl	19	3.60 (s)	$C_{40}H_{62}N_2O_{10}$
49	4-(3-chlorophenyl)butyl	24	3.57 (s)	$C_{41}H_{63}N_2ClO_{10}$
50[d]	3-(aminophenyl)propyl	26	3.59 (s)	$C_{40}H_{63}N_3O_{10}$
51[e]	(benzyloxy)ethyl	20	3.65 (s)	$C_{40}H_{62}N_2O_{11}$
52[f]	2-(*N*,*N*-benzylmethylamino)ethyl	35	3.59 (s)	$C_{41}H_{65}N_3O_{10}$
53	4-(6-methoxyquinolinyl)butyl	68	3.59 (s)	$C_{45}H_{67}N_3O_{11}$
54	4-(8-methoxyquinolinyl)butyl	59	3.60 (s)	$C_{45}H_{67}N_3O_{11}$
55	4(quinolinyl)butyl	26	3.59 (s)	$C_{44}H_{65}N_3O_{10}$
56a[g]	NH_2	32	3.59 (s)	$C_{31}H_{53}N_3O_{10}$
56b[h]	NH_2	34	3.46 (d)	$C_{31}H_{53}N_3O_{10}$
57	3-phenylpropylamino	78	3.74 (s)	$C_{40}H_{63}N_3O_{10}$
58	4-(3-chlorophenyl)propylamino	30	3.73 (s)	$C_{40}H_{62}N_3ClO_{10}$
59	4-(6-methoxyquinolinyl)propylamino	27	3.74 (s)	$C_{44}H_{66}N_4O_{11}$
60	4-(8-methoxyquinolinyl)propylamino	49	3.75 (s)	$C_{44}H_{66}N_4O_{11}$
61	4-(quinolinyl)propylamino	78	3.74 (s)	$C_{43}H_{64}N_4O_{10}$

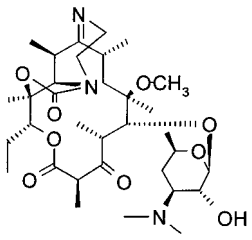
[a] C, H, N results were within ±0.4% of the theoretical values for the formula given. [b] 10(*R*). [c] 10(*S*). [d] 3-(Aminophenyl)propylamine synthesized as in ref 42. [e] 2-(Benzyloxy)ethylamine synthesized as in ref 43. [f] (*N*,*N*-Benzylmethylamino)ethylamine synthesized as in ref 44. [g] 10(*R*). [h] 10(*S*).

Scheme 8



56a **57-61**

H. influenzae. For instance, the comparison of TE 802 with the aryl ketolides revealed that this compound was poorly active particularly against resistant pneumococci (Table 5).



TE 802

Due to its very promising profile **61** (HMR 3004, formerly RU 64004) was tested against several respiratory pathogens[50] including many clinically isolated pneumococci (macrolides and penicillin-resistant) and also against staphylococci, enterococci, and *H. influenzae*. As shown in Table 6 the MIC_{50} and MIC_{90} of HMR 3004 against most of the relevant resistant and sensitive pathogens indicated the potential therapeutic value of this ketolide. With the exception of EryRc *S. aureus*, the growth of 90% of the staphylococci, enterococci, streptococci, and *H. influenzae* was inhibited within a range of concentration of 0.01−5 μg/mL HMR 3004 (Table 6).

In separate studies[51] HMR 3004 was also found to be very efficient against the atypical bacteria *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, and *Legionella*.

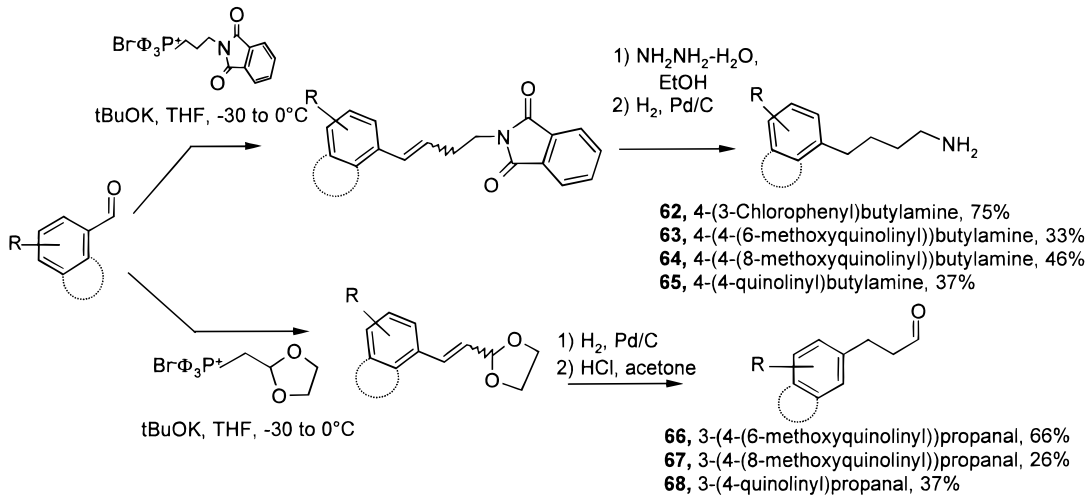
The efficacy of HMR 3004 against EryRi strains in addition to kinetics of induction experiments clearly demonstrated that unlike macrolides HMR 3004 was not an inducer of MLS_B resistance.[45a,b,52] Furthermore, the potential of selection of mutants by HMR 3004 was also studied by serial passing in broth.[50a] In contrast to josamycin the increase in MICs was very slow. Thus the emergence of resistance to ketolides is expected to be very slow with relevant bacteria such as pneumococci.

The introduction of additional nitrogens through the hydrazono function as well as the quinoline nucleus was beneficial with regard to the overall spectrum of HMR 3004 which showed an excellent balance of activity against resistant pneumococci-, *H. influenzae*, and macrolide-susceptible strains. HMR 3004 was then evaluated in vivo to determine whether it could be a good clinical candidate.

In Vivo Evaluation. As previously mentioned, a good clinical candidate for URTI and LRTI must be active against common respiratory tract pathogens including resistant and susceptible pneumococci, *H. influenzae*, and atypical bacteria like *Mycoplasma*, *Legionella*, and *Chlamydia*. Although several models of murine septicemia exist with organisms such as *S. aureus* and streptococci, there were only some specific and fastidious models of otitis[21b] or pneumonia to assess the therapeutic efficacy of macrolides or ketolides against pneumococci and *H. influenzae*. For this reason we have set up a very fast and practical experimental model of murine septicemia to determine the in vivo potency of the most interesting ketolides against these pathogens.[50a]

In infections caused by Gram-positive cocci susceptible to erythromycin, HMR 3004 exhibited an in vivo efficacy close to that observed for CLA but far superior to that for ERY. AZI showed similar potency in streptococcal infections but was less efficient in septicemia caused by *S. aureus*. In EryRi staphylococcal infections the overall efficacy of HMR 3004 was well above that of CLA and even josamycin which is claimed to be active against those strains (Table 7).

Scheme 9



Unlike classical macrolides (ERY, CLA, AZI, JOSA) which showed complete inactivity with PD_{50} up to 100 mg/kg, HMR 3004 displayed a high anti-pneumococcal therapeutic efficacy in infections caused by EryRi or EryRc pneumococci.[50a,53] The corresponding effective doses for HMR 3004 ranged between 15 and 42 mg/kg. It is worth noting that the protective doses found for HMR 3004 in EryR pneumococcal infections fall within the range of values found with susceptible pathogens (15−42 mg/kg).

In infections caused by *H. influenzae* (Table 8) HMR 3004 generally displayed a therapeutic activity 2−3 times higher than that of ERY and CLA. Conversely, HMR 3004 was equal to or slightly less active than AZI. Moreover, HMR 3004 was found to be very effective in treating enterococcal infections (*E. faecalis* or *E. faecium*) irrespective of the phenotype of infecting strains (VanR and/or EryR).[50a]

Physicochemical Properties of HMR 3004. Unlike classical macrolides, ketolides are devoid of acid-sensitive sugar in position 3. This feature confers a dramatic increase of stability in acidic medium for HMR 3004 compared to ERY or AZI (Figure 1).[45b] This compound was also shown to have a good intracellular penetration.[54] This property may be an advantage for HMR 3004 against pathogens surviving in physiological acid compartments (e.g., phagolysosomial compartment). All these characteristics of HMR 3004 could result from the combination of a lipophilic partition coefficient, log P = 4.1, and two pK_a, pK_{a1} = 8.7 (dimethylamine) and pK_{a2} = 5.5 (quinoline), that allows HMR 3004 to be more or less protonated depending on the pH of the biological compartment.

The crystal structure of HMR 3004 (Figure 2) does not reveal any major conformational changes for the aglycone backbone between macrolides and ketolides as shown by superimposition of clarithromycin crystal structure[55] and **61** (Figure 3). However, it is clear that the free space liberated by the cladinose confers to the desosamine sugar more conformational freedom. This is demonstrated by the slight shifting of 2 Å of the desosamine toward the unoccupied cladinose area. At the same time the south part of the macrolactone ring becomes more accessible to additional interactions. In addition to these observations it can be postulated that, according to the overall activity of the carbama and hydrazonocarbama ketolides, the heteroaryl side chain also participates in positive interactions. All these features may account for the "keto" effect and for new binding interactions with the bacterial ribosome. Preliminary studies concerning the mechanism of action of ketolides that tends to demonstrate a second ribosomal binding site for the ketolides[56] are in good agreement with this hypothesis.

Conclusion

In summary, a series of 6-*O*-methyl-3-oxoerythromycin derivatives was synthesized introducing a new class of antibacterials, so-called " ketolides".

HMR 3004, a prototype ketolide, was shown to have a potent activity against multiresistant *S. pneumoniae* associated with a strong activity against *H. influenzae*, *Moraxella catarrhalis*, group A streptococci, and atypical bacteria, e.g., *Chlamydia*, *Mycoplasma*, and *Legionella*. In addition ketolides, including HMR 3004, were found to be noninducers of the MLS_B-resistance phenotype and to be active against pathogens inducibly resistant to erythromycin.

Thus HMR 3004 appears as an innovative and promising agent for the treatment of infections caused by respiratory pathogens. Further pharmacological and clinical evaluation is warranted.

Experimental Section

Susceptibility Testing. In vitro susceptibility tests were performed by using a 2-fold agar dilution method.[57a] Mueller−Hinton agar medium (pH 7.4; Diagnostic Pasteur (DP), France) was used throughout the study. The medium was appropriately supplemented to support the growth of some fastidious microorganisms (4% globular extract (DP) for *H. influenzae*; 7% horse blood for streptococci and pneumococci). Reference organisms were included for quality control: *S. aureus* ATCC 29213 and *E. faecalis* ATCC 29212. For preparation of inoculum, microorganisms were scrapped off from overnight cultures on plates, suspended in Mueller−Hinton broth (DP), and adjusted spectrophotometrically to contain 10^9 CFU/mL (colony forming units). A standard inoculum, to get some 10^4 CFU/spot, was prepared from a 1:200 dilution of the bacterial broth suspension and applied onto agar plates containing the test compound by using a Denley multipoint inoculator (Denley-Tech Ltd.). All plates were incubated at 37 °C for 20 h in the conditions described above. The MIC was defined as the

Table 3. In Vitro Evaluation of the First Ketolides **9** and **13**

	MIC (μg/mL)[a]										
compd	*S. aureus* 011UC4	*S. aureus* EryRi 011GO25i	*S. epidermidis* EryRi 012GO11i	*S. aureus* EryRc 011CB20	*S. pneumoniae* EryRc 030SJ1	*S. pneumoniae* EryRi 030SJ5i	*S. pneumoniae* 032UC1	*S. pyogenes* 02A1UC1	*H. influenzae* 351HT3	*H. influenzae* 351CB12	*E. coli* 250 UC5
9	0.3	40	5	40	40	40	0.15	0.6	20	20	40
13	1.2	2.5	1.2	40	40	10	0.15	0.15	40	40	40
4	40	40	40	40	40	40	40	40	10	10	40
6	40	40	40	40	40	40	40	40	40	40	40
ERY	0.3	40	40	40	40	40	0.08	0.08	2.5	2.5	40
CLA	0.3	40	40	40	40	40	0.04	0.08	2.5	2.5	40
AZI	0.3	40	40	40	40	40	0.15	0.6	1.2	1.2	20

[a] See Experimental Section.

lowest concentration at which no visible growth could be detected on agar plates.

Influence of Susceptibility Testing Conditions. A broth microdilution technique[57b] was used to study the effect of pH and CO_2 on the antibacterial activity of HMR 3004. Mueller−Hinton broth (DP) was used to grow most bacterial species except pneumococci and *H. influenzae* which were grown in brain heart infusion (DP) and *Haemophilus* test medium,[57e] respectively.

In Vivo Therapeutic Efficacy. Male Charles River CD1 mice were used to study the antibacterial activity of the drugs in murine infections. Each dosing group was composed of 10 animals weighing 20−22 g. Mice were infected intraperitoneally with 0.5 mL of an overnight broth culture of bacteria appropriately diluted in physiological buffer or in 5% hog mucine (Sigma) to a final cell density corresponding to 10−100 times the minimal lethal dose (MLD).[57c] Suspensions of the compounds (0.5 mL) in carboxymethylcellulose were administered by the oral route immediately and 4 h postinfection. Mice were observed for 8−10 days following infections, and the 50% protective doses ED_{50}, expressed as the unitary dose to protect 50% of the animals from death, were calculated according to the probit method of Litchfield and Wilcoxon.[57d]

Bacterial Strains. Most of the Gram-positive and Gram-negative bacterial strains used in this study were recent clinical isolates from various European hospitals. Special attention was paid to penicillin- and/or MLS_B-resistant strains of Gram-positive cocci. Except for staphylococci, which were maintained in deep agar at room temperature, all other clinical isolates were stored as frozen stocks (−80 °C) in glycerol-supplemented broth.

Physicochemical Measurements. Partition coefficient (log *P*) and pK_a were determined with a SIRIUS PCA 101 apparatus using a potentiometric titration method developed by A. Avdeef.[58]

Molecular Modeling. Superimposition of **61** and clarithromycin was prepared in Insight II (MSI Corporation, San Diego, CA) by using the published[56] crystallographic data of clarithromycin.

Single-Crystal X-ray Analysis of HMR 3004. Crystallographic data were collected on a Philips PW1100 single-crystal diffractometer with Cu Kα radiation. The structure was solved by direct methods using SIR92[59a] program. Refinement was carried out with CRYSTALS[59b] software by full-matrix least-squares procedures on coordinates and anisotropic thermal parameters for non-H atoms. All H atoms were located from a difference Fourier map and refined isotropically on fixed coordinates. Crystal data for $C_{43}H_{64}N_4O_{10}$ (HMR 3004): white crystals, tetragonal, $P4_12_12$; $a = b = 11.657(2)$ Å, $c = 63.931(9)$ Å; $Z = 8$; $D_{calc} = 1.22$. Of 5336 reflections measured ($T = 292$ K, $3° \leq 2\theta \leq 124°$), 4084 were independent and observed ($I > 3\sigma(I)$). The final *R* factor was 0.0441 and $R_W = 0.0425$ for 3986 reflections. In the final cycle 516 parameters were refined. The final difference map maxima were within ±0.45 eÅ^{-3}. No extinction correction was applied. Scattering factors were taken from *International Tables for X-ray Crystallography (1974)*.

General. Melting points were taken on a Kofler melting point apparatus and are uncorrected. ^{1}H NMR spectrum were recorded with Bruker AC300 and AM250 spectrometers using $CDCl_3$ solution. Chemical shifts are reported in part per million (ppm) with tetramethylsilane (TMS) as an internal standard. Coupling constants (*J*) are given in hertz. The abbreviations s, d, t, q, and m refer to singlet, doublet, triplet, quartet, and multiplet, respectively. Mass spectra were recorded with a MATT311 spectrometer (ionization potential, 3 kV; electron accelerating potential, 70 eV; ion source temperature, 200 °C). Infrared spectra were recorded on a Nicolet 20SX or 5SX instrument using chloroform solutions. UV spectra were recorded with a CARY 2200 instrument. Thin-layer chromatography (TLC) was performed with Kieselgel 60 F_{254} (E. Merck) precoated plates. UV light (254 nm) and sulfuric acid were used to visualize the developed plates. Column chromatography refers to flash chromatography per-

Table 4. In Vitro Evaluation of 9-Oxime Ketolides

	MIC (mg/mL)[a]										
compd	*S. aureus* 011UC4	*S. aureus* EryRi 011GO25i	*S. epidermidis* EryRi 012GO11i	*S. aureus* EryRc 011CB20	*S. pneumoniae* EryRc 030SJ1	*S. pneumoniae* EryRi 030SJ5i	*S. pneumoniae* 032UC1	*S. pyogenes* 02A1UC1	*H. influenzae* 351HT3	*H. influenzae* 351CB12	*E. coli* 250 UC5
17	0.3	1.2	0.6	40	40	40	0.08	0.15	20	1.2	40
18	2.5	40	40	40	40	40	0.3	0.6	40	40	40
19	0.3	0.6	0.6	10	5	5	0.04	0.3	40	40	40
20	1.2	10	2.5	40	40	20	0.6	0.6	40	40	40
21	40	40	40	40	40	40	40	40	40	40	40
22	0.08	1.2	20	40	2.5	0.15	0.15	0.01	20	20	40
23	0.15	0.3	0.15	40	40	1.2	10	0.04	40	10	40
24	0.3	5	0.3	40	5	40	2.5	0.08	20	10	40
25	0.6	5	5	40	40	40	0.15	0.6	40	40	40
26	0.6	2.5	0.6	40	20	40	20	0.15	40	20	40
27	0.6	2.5	5	40	0.3	2.5	20	0.04	40	10	40
28	0.6	2.5	0.6	40	20	40	10	0.15	40	20	40
29	1.2	10	2.5	40	5	20	40	0.15	40	40	40
30	0.3	1.2	0.6	40	0.6	1.2	10	0.04	20	10	40
31	0.6	5	1.2	40	40	10	0.15	0.15	40	20	40
32	0.3	2.5	1.2	40	40	20	0.3	0.04	5	5	40
33	0.15	5	6	40	10	40	0.02	0.04	10	5	40
34	0.15	2.5	0.6	40	0.3	0.3	0.08	0.04	2.5	0.6	40
35	1.2	5	2.5	40	40	0.08	0.3	0.3	20	2.5	40
36	0.08	0.3	0.6	40	10	40	0.02	0.04	10	10	40
37	0.3	0.6	0.6	40	1.2	0.3	0.08	0.08	5	0.6	40
38	0.15	2.5	5	40	0.6	0.15	0.02	0.04	5	1.2	40
39	0.6	0.3	0.6	20	5	0.3	0.3	0.08	40	10	40
40	0.08	0.6	0.3	40	0.6	0.15	0.02	0.04	5	1.2	40
41	0.6	0.6	0.6	10	1.2	0.3	0.08	0.08	20	5	40
CLA	0.3	40	40	40	40	40	0.04	0.08	5	5	40
AZI	0.3	40	40	40	40	40	0.15	0.6	1.2	1.2	20

[a] See Experimental Section.

Table 5. In Vitro Evaluation of 11,12-Carbama and -Carbaza Ketolides

	MIC (μg/mL)[a]										
compd	*S. aureus* 011UC4	*S. aureus* EryRi 011GO25i	*S. epidermidis* EryRi 012GO11i	*S. aureus* EryRc 011CB20	*S. pneumoniae* EryRc 030SJ1	*S. pneumoniae* EryRi 030SJ5i	*S. pneumoniae* 032UC1	*S. pyogenes* 02A1UC1	*H. influenzae* 351HT3	*H. influenzae* 351CB12	*E. coli* 250 UC5
45a	0.6	0.6	10	40	5	2.5	0.02	0.04	5	5	40
45b	5	40	40	40	40	40	0.3	2.5	20	20	40
46	0.08	0.15	0.04	40	0.15	0.3	0.02	0.02	1.2	2.5	40
47	1.2	5	40	40	40	40	0.04	0.15	40	40	40
48	1.2	2.5	1.2	40	40	20	0.3	0.15	40	10	40
49	0.04	0.6	0.15	10	2.5	0.08	0.02	0.02	1.2	1.2	40
50	0.08	0.6	0.3	40	40	0.6	0.02	0.04	2.5	1.2	40
51	0.04	0.08	0.15	40	5	0.3	0.02	0.02	1.2	0.6	40
52	0.15	0.6	0.15	40	10	0.3	0.02	0.04	5	2.5	40
53	0.08	0.08	0.04	40	0.6	0.02	0.02	0.02	1.2	1.2	40
54	0.08	0.3	0.08	40	20	0.08	0.02	0.02	2.5	2.5	40
55	0.04	0.08	0.15	40	1.2	0.02	0.02	0.02	1.2	1.2	40
56a	1.2	1.2	1.2	40	40	40	0.08	0.15	10	10	40
56b	40	40	40	40	40	40	5	2.5	40	40	40
57	0.08	0.15	0.15	40	5	0.15	0.02	0.02	1.2	1.2	40
58	0.04	0.08	0.04	40	2.5	0.08	0.02	0.02	1.2	2.5	40
59	0.04	0.08	0.08	40	0.08	0.02	0.02	0.02	1.2	2.5	40
60	0.04	0.15	0.15	40	2.5	0.15	0.02	0.02	0.6	1.2	40
61	0.02	0.08	0.04	40	0.15	0.02	0.02	0.02	0.6	0.6	40
TE 802	0.3	0.6	0.3	40	40	40	0.02	0.08	5	5	40
A 66321	0.3	20	40	20	10	1.2	0.02	0.04	2.5	2.5	40
CLA	0.3	40	40	40	40	40	0.04	0.08	5	5	40
AZI	0.3	40	40	40	40	40	0.15	0.6	1.2	1.2	20

[a] See Experimental Section.

formed with E. Merck silica gel 60 (230−400 mesh grade). Tetrahydrofuran was distilled from sodium and benzophenone; 10% palladium on charcoal E10/0/W hydrogenation catalyst was purchased from Degussa. Most reagents were obtained from commercial sources and used without further purification. All elemental analyses were within ±0.4% of the calculated value.

3(*R*)-(*E*)-6-Deoxy-3-*O*-descladinosyl-3,6-epoxyerythromycin 9-Oxime (4). Following the procedure described in ref 28a, (*E*)-3-*O*-descladinosylerythromycin 9-*O*-acetyloxime (0.4 g, 0.6 mmol) in 10 mL of acetone was reacted with 0.3 mL (0.12 mmol) of Jones reagent and treated with methanol to yield **4** in 22% yield (noncrystallized, two steps). MS(EI): 588^+ (M^+). ^{1}H NMR ($CDCl_3$): δ 0.89 (t, 3H) CH_3CH_2, 1.16 (s, 3H) 12-CH_3, 1.37 (s, 3H) 6-CH_3, 2.15 (s, 3H) =NOCOCH_3, 2.28 (s, 6H) $N(CH_3)_2$, 2.51 (m, 1H) $H_{3'}$, 2.66 (q, 1H) H_2, 2.96 (m, 1H) H_{10}, 3.20 (dd, 1H) $H_{2'}$, 3.37 (m, 1H) H_8, 3.73 (d, 1H) H_5, 3.90 (sl, 1H) H_{11}, 4.22 (d, 1H) $H_{1'}$, 5.03 (dd, 1H) H_{13}. UV: $\lambda_{max}^{EtOH/NaOH,0.1N}$ no absorption. Anal. ($C_{29}H_{62}N_2O_{10}$) C, H, N.

3(*R*)-(*E*)-6-Deoxy-3-*O*-descladinosyl-3,6-epoxyerythromycin 9-*O*-((2-Methoxyethoxy)methyl)oxime 2′-Acetate (6-2′Oac). Stage A: To a stirred solution of (*E*)-3-*O*-descladinosylerythromycin 9-*O*-((2-methoxyethoxy)methyl)oxime (12 g, 18 mmol) in 120 mL of acetone were added K_2CO_3 (5 g, 36 mmol) and acetic anhydride (3.4 mL, 36 mmol). The reaction was stirred at room temperature for 24 h, diluted with ice/water, and extracted with methylene chloride. The extracts were washed with saturated $NaHCO_3$ and water and dried over $MgSO_4$. After evaporation of the solvent the crude product was taken up in ether and crystallized to give after drying 10.2 g (79%) of **5** as white crystals. **5**: mp 169 °C.

Stage B: To a solution of **5** (3 g, 4 mmol) in 90 mL of acetone at 0 °C was added 2 mL (8 mmol) of Jones reagent. The reaction was stirred 1 h 30 min at 0 °C, and 10 mL of propanol was added in 20 min. The solution was filtered on clarcel, and the residues were washed with acetone. The filtrates were concentrated, taken up with 100 mL of methylene chloride, washed with saturated $NaHCO_3$ and water, and dried over $MgSO_4$. The product was purified by column chromatography eluting with 98:2 ethyl acetate/triethylamine to afford 1.56 g (52%) of **6**-2′OAc as a white foam. MS(EI): 718^+ (M^+). ^{1}H NMR ($CDCl_3$): δ 0.87 (t, 3H) CH_3CH_2, 1.06 (d,3H) 8-CH_3, 1.16 (d, 3H) 10-CH_3, 1.17 (s, 3H) 12-CH_3, 1.20 (d, 3H) 2-CH_3, 1.23 (d, 3H) 4-CH_3, 1.26 (d, 3H) 5′-CH_3, 1.36 (s, 3H) 6-CH_3, 2.07 (m, 1H) H_4, 2.08 (s, 3H) 2′-OCOCH_3, 2.28 (s, 6H) $N(CH_3)_2$, 2.54 (q, 1H) H_2, 2.61 (q, 1H) H_{10}, 2.74 (m, 1H) $H_{3'}$, 3.40 (s, 3H) O−CH_3, 3.51 (m, 1H) $H_{5'}$, 3.56 and 3.72 (m, 4H) −O−CH_2-CH_2−*O*−, 3.69 (d, J = 2 Hz, 1H) H_5, 3.70 (m, 1H) H_8, 3.97 (s, 1H) H_{11}, 4.28 (d, 1H) $H_{1'}$, 4.83 (dd, 1H) $H_{2'}$, 5.03 (dd, 1H) H_{13}, 5.18 (AB, 2H) −O−CH_2-*O*−.

3(*R*)-(*E*)-6-Deoxy-3-*O*-descladinosyl-3,6-epoxyerythromycin 9-*O*-((2-Methoxyethoxy)methyl)oxime (6). A solution of **6**-2′OAc (0.85 g, 1.2 mmol) in 8.5 mL of methanol was stirred at room temperature for 24 h. After removal of the solvent, the product was purified by column chromatography eluting with 95:5 ether/triethylamine to afford 0.62 g (77%) of **6** as a white foam. MS(EI): 676^+ (M^+). UV: $\lambda_{max}^{EtOH/NaOH,0.1N}$ no absorption. ^{1}H NMR ($CDCl_3$): δ 0.88 (t, 3H) CH_3CH_2, 1.07 (d,3H) 8-CH_3, 1.16 (d, 3H) 10-CH_3, 1.17 (s, 3H) 12-CH_3, 1.20 (d, 3H) 2-CH_3, 1.25 (d, 3H) 4-CH_3 and (d, 3H) 5′-CH_3, 1.36 (s, 3H) 6-CH_3, 2.24 (m, 1H) H_4, 2.30 (s, 6H) $N(CH_3)_2$, 2.50 (m, 1H) $H_{3'}$, 2.65 (m, 1H) H_{10}, 2.67 (q, 1H) H_2, 3.22 (dd, 1H) $H_{2'}$, 3.40 (s, 3H) O−CH_3, 3.52 (m, 1H) $H_{5'}$, 3.57 and 3.74 (m, 4H) −O−CH_2CH_2−O−, 3.70 (d, J = 4 Hz, 1H) H_5, 3.75 (m, 1H) H_8, 4.00 (sl, 1H) H_{11}, 4.21 (d, 1H) H1′, 5.03 (dd, 1H) H_{13}, 5.18 (AB, 2H) −O−CH_2−O−. ^{13}C−^{1}H NMR ($CDCl_3$): δ 10.7 CH_3-CH_2, 13.5 2-CH_3, 14.5 10-CH_3, 15.7 4-CH_3, 16.3 12-CH_3, 19.5 8-CH_3, 20.5 CH_3CH_2, 21.3 5′-CH_3, 24.8 6-CH_3, 28.2 C_8, 28.6 4′-CH_2, 33.9 C_{10}, 40.4 $N(CH_3)_2$, 41.4 C_7, 49.9 C_4, 50.3 C_2, 59.0 O-CH_3, 65.5 $C_{3'}$, 65.8 C_6, 68.2 and 71.7 −O−CH_2CH_2−O−, 69.4 $C_{2'}$, 69.7 C_{11}, 69.8 $C_{5'}$, 77.3 C_{13}, 84.1 C_{12}, 94.2 C_5, 97.2 −O−CH_2−O−, 103.9 $C_{1'}$, 105.9 C_3, 170.9 C_9, 176.8 C_1. Anal. ($C_{33}H_{60}N_2O_{12}$) C, H, N.

3-*O*-Descladinosyl-6-*O*-methylerythromycin (7). To a solution of 10 mL of water and 1 mL of 12 N HCl was added

Table 6. Extended in Vitro Evaluation of HMR 3004

	MIC_{50}/MIC_{90} (μg/mL)[a]									
	staphylococci		enterococci		streptococci		pneumococci		Haemophilus	
compd	EryRi (65)	EryRc (23)	EryRi (19)	EryRc (13)	EryR (27)	EryRi (98)	EryRc (34)	PenR (65)	AmpS (43)	AmpR (37)
ERY	40/40	40/40	2.5/10	40/40	5/40	20/40	40/40	0.6/40	1.2/5	1.2/10
CLA	40/40	ND	1.2/10	40/40	1.2/40	40/40	40/40	0.3/40	1.2/5	2.5/10
AZI	40/40	ND	40/40	40/40	10/40	40/40	40/40	2.5/40	0.15/1.2	0.3/1.2
JOSA	1.2/2.5	40/40	1.2/1.2	40/40	5/40	5/40	20/40	0.3/40	5/20	5/20
Amp	ND	ND	ND	ND	ND	ND	ND	ND	0.3/0.6	1.2/10
HMR 3004	0.04/0.08	40/40	0.01/0.01	2.5/5	0.01/1.2	0.01/0.04	0.08/0.6	0.005/0.15	0.3/1.2	0.3/1.2

[a] See Experimental Section.

Table 7. In Vivo Evaluation of HMR 3004 Against Several Gram-Positive Pathogens

	ED_{50}, (mg/kg)[a]								
compd	*S. aureus* 011UC4	*S. aureus* 011GO25 EryRi	*S. pneumoniae* 032UC1	*S. pneumoniae* 030RO1 EryRi	*S. pneumoniae* 030SJ6 EryRc	*S. pneumoniae* 030MV2 EryRc	*S. pneumoniae* 030SJ1 EryRc	*S. pneumoniae* 030Cr29 EryRc	*S. pyogenes* 02A1UC1
ERY	57	>100	18.3	>100	>100	>100	>100	>100	300
CLA	12.6	>100	>50	>100	>100	>100	>100	>100	16
AZI	60	>100	>50	>100	>100	>100	>100	>100	16
JOSA	ND	>100	ND	>100	>100	>100	>100	>100	ND
HMR 3004	20	13	15.8	30	17	19	42	15	16

[a] See Experimental Section.

Table 8. In Vivo Evaluation of HMR 3004 Against *H. influenzae*

	ED_{50} (mg/kg)[a]		
compd	351GR1	351TO19 AmpR β(−)	351RD7 AmpR β(+)
AMP	5.5	39	>600
ERY	346	442	326
CLA	346	600	109
AZI	109	368	117
HMR 3004	142	410	116

[a] See Experimental Section.

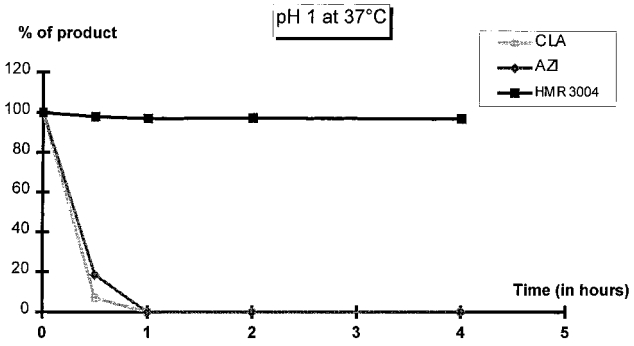


Figure 1. Acid stability of HMR 3004. Percent of remaining product after stirring the title compounds at pH = 1 (0.2 M KCl/0.2 M HCl) at 37 °C for 4 h. Based upon HPLC titration with a Purecil C_{18} column, 5 μm; elution, MeOH/Na_2HPO_4 (0.02 M), 75/25; detection, UV 220 nm.

portionwise 6-*O*-methylerythromycin (1.5 g, 2 mmol). The reaction was stirred 2 h at room temperature. The reaction was saturated with sodium chloride and was adjusted to pH 8 with aqueous ammonium hydroxide. The solution was extracted with ethyl acetate, and the extracts were dried over $MgSO_4$. The product was purified by column chromatography eluting with 96:4 ethyl acetate/triethylamine to afford 0.9 g (76%) of **7** as a white foam. MS(FAB): 590^+ ($M + H^+$). ^1H NMR ($CDCl_3$): δ 0.84 (t, 3H) CH_3CH_2, 1.19 (s, 3H) 6-CH_3, 1.36 (s, 3H) 12-CH_3, 2.25 (s, 6H) N(CH_3)$_2$, 2.97 (s, 3H) 6-*O*-CH_3, 3.24 (dd, 1H) $H_{2'}$, 3.55 (m, 2H) H_3 and H_5', 3.68 (s, 1H) H_5, 3.85 (d, 1H) H_{11}, 3.86 (q, 1H) H_2, 4.39 (m, 1H) H_1', 5.18 (dd, 1H) H_{13}.

3-*O*-Descladinosyl-6-*O*-methylerythromycin 2′-Acetate (8). To a solution of **7** (0.84 g, 1.42 mmol) in 10 mL of acetone were added K_2CO_3 (1.81 mmol) and acetic anhydride (0.22 mL, 2.15 mmol). The reaction was stirred 20 h at room temperature, and 5 mL of ice/water was added. After extraction with methylene chloride, drying over $MgSO_4$, and evaporation of the solvent, the product was purified by column chromatography eluting with 96:4 ethyl acetate/triethylamine to afford 0.74 g (82%) of **8** as a white foam. MS(FAB): 632^+ ($M + H^+$). ^1H NMR ($CDCl_3$): δ 0.84 (t, 3H) CH_3CH_2, 1.11 (s, 3H) 6-CH_3, 1.26 (s, 3H) 12-CH_3, 2.07 (s, 3H) 2′-OCOCH_3, 2.27 (s, 6H) N(CH_3)$_2$, 2.95 (s, 3H) 6-*O*-CH_3, 3.00 (ql, 1H) H_{10}, 3.47 (m, 2H) H_3 and H_5', 3.72 (d, J = 2 Hz, 1H) H_5, 3.82 (sl, 1H) H_{11}, 4.61 (d, J = 8 Hz, 1H) H_1', 4.77 (dd, J = 8 and 10 Hz, 1H) $H_{2'}$, 5.17 (dd, 1H) H_{13}, 3.27 and 3.97 (sl, 2H) OH.

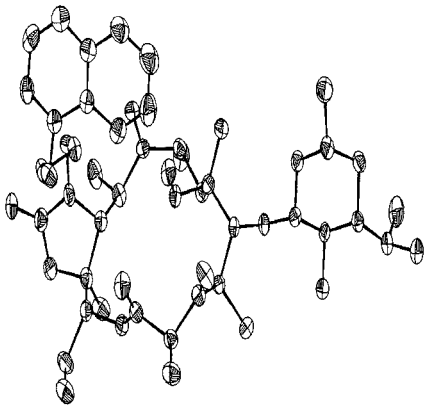


Figure 2. ORTEP drawing of the X-ray crystal structure of **61** (HMR 3004).

3-*O*-Descladinosyl-6-*O*-methyl-3-oxoerythromycin 2′-Acetate (9-2′OAc). To a solution of **8** (0.42 g, 0.66 mmol), EDC,HCl (0.84 g, 4.4 mmol), and DMSO (0.84 mL, 11.83 mmol) in 5 mL of methylene chloride was added dropwise at 15 °C a solution of pyridinium trifluoroacetate (0.84 g, 4.4 mmol) in 2 mL of methylene chloride. The reaction was stirred 4 h at room temperature, and 4 mL of water was added. After stirring for 10 min, the mixture was taken up in 20 mL of methylene chloride, followed by washing with water, drying over $MgSO_4$, and evaporation of the solvent. The product was purified by column chromatography eluting with 90:10 isopropyl ether/triethylamine to afford 0.374 g (90%) of 9-2′OAc as a white foam. MS(FAB): 630^+ ($M + H^+$). ^1H NMR ($CDCl_3$): δ 0.86 (t, 3H) CH_3CH_2, 1.22 (s, 3H) 12-CH_3, 1.30 (s, 3H) 6-CH_3, 2.05 (s, 3H) 2′-OCOCH_3, 2.26 (s, 6H) N(CH_3)$_2$, 2.70

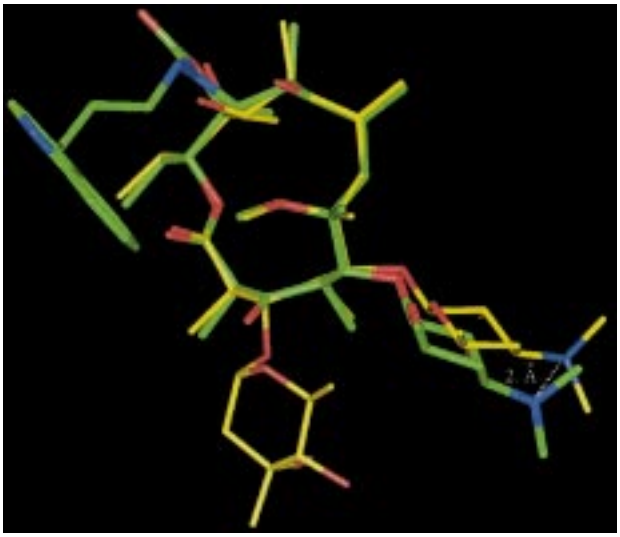


Figure 3. Superimposition of **61** (green) and clarithromycin (yellow) crystal structures.

(s, 3H) 6-*O*-CH_3, 3.00 (ql, 1H) H_{10}, 3.10 (q, 1H) H_8, 3.56 (m, 1H) H_5', 3.83 (q, 1H) H_2, 3.92 (s, 1H) H_{11}, 4.30 (d, 1H) H_5, 4.40 (d, 1H) H_1', 4.76 (dd, 1H) $H_{2'}$, 5.14 (dd, 1H) H_{13}.

3-*O*-Descladinosyl-6-*O*-methyl-3-oxoerythromycin (9). A solution of **9**-2′OAc (0.13 g, 0.206 mmol) in 2 mL of methanol was stirred 24 h at room temperature. The solvent was evaporated in vacuo, and the product was purified by column chromatography eluting with 90:10 isopropyl ether/triethylamine to afford 0.1 g (80%) of **9** as a white foam. MS(FAB): 587^+ ($M + H^+$). UV: $\lambda_{max}^{EtOH/NaOH,0.1N}$ 291 nm, $\epsilon = 9850$. ^{1}H NMR ($CDCl_3$): δ 0.86 (t, 3H) CH_3CH_2, 1.22 (s, 3H) 12-CH_3, 1.35 (s, 3H) 6-CH_3, 2.26 (s, 6H) N(CH_3)$_2$, 2.46 (m, 1H) H_3', 2.60 (m, 1H) H_4, 2.70 (s, 3H) 6-*O*-CH_3, 2.97 (ql, 1H) H_{10}, 3.10 (q, 1H) H_8, 3.18 (dd, 1H) H_2, 3.57 (m, 1H) H_5', 3.91 (s, 1H) H_{11}, 4.32 (m, 2H) H_5 and H_1', 5.12 (dd, 1H) H_{13}. Anal. ($C_{30}H_{53}NO_{10}$) C, H, N.

(*E*)-3-*O*-Descladinosyl-6-*O*-methylerythromycin 9-((2-Methoxyethoxy)methyl)oxime (11). Stage A: To a stirred solution of 6-*O*-methylerythromycin 9-oxime (15.2 g, 20 mmol) and sodium methylate (1.35 g, 25 mmol) in 80 mL of dry THF at 5 °C, under nitrogen atmosphere, was added dropwise a solution of MEM-Cl (2.85 mL, 25 mmol) in 20 mL of THF. The mixture was stirred for 30 min at 5 °C and then allowed to return at room temperature. After evaporation of the solvent, the residue was taken up with methylene chloride, washed with water, dried over $MgSO_4$, and evaporated to dryness. The product was purified by column chromatography eluting with 90:10:0.1 methylene chloride/methanol/ammonium hydroxide to afford 11.66 g (69%) of (*E*)-6-*O*-methylerythromycin 9-((2-methoxyethoxy)methyl)oxime as a white foam. MS(FAB): 851^+ ($M + H^+$).

Stage B: A solution of the product of stage A (1.7 g, 2 mmol) in 100 mL of water and 1.7 mL of 12 N HCl was stirred for 3 h at room temperature. Sodium chloride (28 g) was added to the mixture, and the pH was adjusted to 8 with aqueous ammonium hydroxide. The product was extracted with methylene chloride, washed with water, and dried over $MgSO_4$. After evaporation of the solvent, the product was purified by column chromatography eluting with 98:2 ethyl acetate/triethylamine to afford 1.25 g (90%) of **11** as a white foam. MS(FAB): 693^+ ($M + H^+$).^{1}H NMR ($CDCl_3$): δ 0.84 (t, 3H) CH_3CH_2, 1.19 (s, 3H) 12-CH_3, 1.39 (s, 3H) 6-CH_3, 2.12 (m, 1H) H_4, 2.24 (s, 6H) N(CH_3)$_2$, 2.47 (m, 1H) H_3', 2.60 (ql, 1H) H_{10}, 2.70 (m, 1H) H_2, 2.97 (s, 3H) 6-*O*-CH_3, 3.23 (dd, 1H) $H_{2'}$, 3.38 (s, 3H) CH_2−O−CH_3, 3.40−3.56 (m, 4H) O−CH_2CH_2−O, 3.66−3.85 (m, 4H) H_5'−H_8−H_3−H_{11}, 4.38 (m, 1H) H_1', 5.15 (s, 2H) O−CH_2−O, 5.22 (dd, 1H) H_{13}. Anal. ($C_{34}H_{64}N_2O_{12}$) C, H, N.

(*E*)-3-*O*-Descladinosyl-6-*O*-methylerythromycin 9-((2-Methoxyethoxy)methyl)oxime 2′-Acetate (12). A suspension of **11** (0.346 g, 0.5 mmol), K_2CO_3 (0.138 g, 1 mmol), and acetic anhydride (0.06 mL, 0.64 mmol) in 3.5 mL of acetone was stirred for 16 h at room temperature. Ice/water was added, and the product was extracted with methylene chloride, washed with saturated $NaHCO_3$, and water, and dried over $MgSO_4$. Evaporation of the solvent yielded 0.351 g (95%) of the desired product **12** as a white foam. MS(FAB): 735^+ ($M + H^+$). ^{1}H NMR ($CDCl_3$): δ 0.84 (t, 3H) CH_3CH_2, 1.17 (s, 3H) 12-CH_3, 1.30 (s, 3H) 6-CH_3, 2.01 (s, 3H) $OCOCH_3$, 2.12 (m, 1H) H_4, 2.27 (s, 6H) N(CH_3)$_2$, 2.58 (m, 1H) H_3', 2.66 (ql, 1H) H_{10}, 2.72 (m, 1H) H_2, 2.94 (s, 3H) 6-*O*-CH_3, 3.38 (s, 3H) CH_2−O−CH_3, 3.40−3.56 (m, 4H) O−CH_2CH_2−O, 3.55−3.85 (m, 5H) H_5−H_5'−H_8−H_3−H_{11}, 4.59 (m, 1H) H_1', 4.75 (dd, 1H) $H_{2'}$, 5.14 (s, 2H) O−CH_2−O, 5.22 (dd, 1H) H_{13}.

(*E*)-3-*O*-Descladinosyl-6-*O*-methyl-3-oxoerythromycin 9-((2-Methoxyethoxy)methyl)oxime (13). Stage A: To a solution of **12** (4 g, 5.4 mmol) in 100 mL of acetone at 0 °C was added Jones reagent (2.7 mL, 10.8 mmol). After stirring 1 h at 0 °C, 10 mL of propanol was added and the mixture was stirred for 20 min. After evaporation of the solvent in vacuo, the residue was taken up with 20 mL of water and 50 mL of methylene chloride. The pH was adjusted to 8 with K_2CO_3, and the mixture was extracted with methylene chloride, followed by washing with water and brine and drying over $MgSO_4$. After evaporation of the solvent, the product was purified by column chromatography eluting with 98:2 ethyl acetate/triethylamine to afford 2.45 g (61%) of the desired product **13**-2′OAc as a white foam. MS(FAB): 733^+ ($M + H^+$). ^{1}H NMR ($CDCl_3$): δ 0.86 (t, 3H) CH_3CH_2, 2.03 (s, 3H) $OCOCH_3$, 2.25 (s, 6H) N(CH_3)$_2$, 2.59−2.75 (m, 3H) H_{10}−H_2 and H_3', 2.71 (s, 3H) 6-*O*-CH_3, 3.11 (m, 1H) H_4, 3.37 (s, 3H) CH_2−O−CH_3, 3.52−3.75 (m, 4H) O−CH_2CH_2−O, 3.50 (m, 1H) H_5', 3.83 (m, 1H) H_8, 3.86 (q, 1H) H_2, 3.92 (sl, 1H) H_{11}, 4.39 (d, 1H) H_1', 4.74 (m, 1H) H_2', 5.13 (AB, 2H) O−CH_2−O, 5.20 (dd, 1H) H_{13}.

Stage B: A solution of **13**-2′OAc (0.3 g, 0.4 mmol) in 3 mL of methanol was stirred for 24 h at room temperature. Evaporation of the solvent afforded 0.27 g (96%) of **13** as a white foam. MS(EI): 690^+ (M^+). UV: $\lambda_{max}^{EtOH/NaOH,0.1N}$ 288 nm, $\epsilon = 11100$. ^{1}H NMR ($CDCl_3$): δ 0.86 (t, 3H) CH_3CH_2, 1.23 (s, 3H) 12-CH_3, 1.38 (s, 3H) 6-CH_3, 2.37 (s, 6H) N(CH_3)$_2$, 2.61 (m, 2H) H_{10} and H_3', 2.73 (s, 3H) 6-*O*-CH_3, 3.13 (m, 1H) H_4, 3.26 (m, 1H) H_2', 3.38 (s, 3H) CH_2−O−CH_3, 3.53−3.76 (m, 4H) O−CH_2CH_2−O, 3.59 (m, 1H) H_5', 3.70 (m, 1H) H_8, 3.86 (q, 1H) H_2, 3.91 (sl, 1H) H_{11}, 4.33 (m, 2H) $H_1'$and H_5, 5.14 (s, 2H) O−CH_2−O, 5.18 (dd, 1H) H_{13}. Anal. ($C_{34}H_{62}N_2O_{12}$) C, H, N.

(3*R*,*S*)-3-(Aminooxy)-1-(carbobenzyloxy)piperidine Chlorhydrate (15). Stage A: 3-Hydroxy-1-(carbobenzyloxy)-piperidine. To a solution of 3-hydroxypiperidine (3 g, 29.6 mmol) in 30 mL of dioxane under nitrogen atmosphere was added, at room temperature, a solution of potassium carbonate (8.2 g, 59.3 mmol) in 40 mL of water. The reaction mixture was then cooled to 5 °C, and benzyl chloroformiate (4.77 mL, 33.4 mmol) in 60 mL of dioxane was added dropwise. The reaction was allowed to stand at room temperature in 4 h. The dioxane was evaporated off, and the aqueous mixture was extracted with 200 mL of methylene chloride. The extracts were washed with water and brine and dried over $MgSO_4$. After evaporation to dryness, the residue was purified by column chromatography eluting with 1:1 ethyl acetate/hexane to afford 6.62 g (95%) of 3-hydroxy-1-(carbobenzyloxy)piperidine as an oil. ^{1}H NMR ($CDCl_3$): δ 1.4−2.00 (m, 4H) -CH_2CH_2-, 2.2−2.6 (sl, 1H) OH, 3.00−3.30 (m, 2H) CONCH_2, 3.5−3.85 (m, 3H) CHOH and NCH_2CHOH, 5.12 (s, 2H) $OCH_2\Phi$, 7.34 (m, 5H) phenyl.

Stage B: 3-(*N*-Phthalimidooxy)-1-(carbobenzyloxy)-piperidine. To a solution of 3-hydroxy-1-(carbobenzyloxy)-piperidine (6.11 g, 25.9 mmol), *N*-hydroxyphthalimide (4.66 g, 28.5 mmol), and azodiethyl dicarboxylate (5.38 mL, 28 mmol) in 60 mL of dry THF under nitrogen atmosphere was added, at 20 °C, triphenylphosphine (7.49 g, 28.5 mmol). The red-brown suspension was stirred at 20 °C for 20 h. After evaporation to dryness, the yellow residue was taken up with a 1:1 mixture of ethyl acetate/hexane. The mixture was filtered, and the precipitate was washed with 300 mL of ethyl

acetate/hexane. The filtrate was concentrated and the residue was purified by column chromatography eluting with 1:1 ethyl acetate/hexane to afford 7.66 g (77.5%) of 3-(*N*-phthalimidooxy)-1-(carbobenzyloxy)piperidine as white crystals. Mp: 85−86 °C. ^{1}H NMR ($CDCl_3$): δ 1.4−2.20 (m, 4H) -CH_2CH_2-, 2.2−2.6 (sl, 1H) OH, 3.10−4.30 (m, 5H) CHOH and CH_2NCH_2-CHOH, 5.11 (s, 2H) $OCH_2\Phi$, 7.32 (m, 5H) phenyl, 7.76−7.85 (m, 4H) phthalimide.

Stage C: 3-(Aminooxy)-1-(carbobenzyloxy)piperidine Chlorhydrate. To a suspension of 3-(*N*-phthalimidooxy)-1-(carbobenzyloxy)piperidine (7.52 g, 19.78 mmol) in 40 mL of ethanol was added hydrazine hydrate (9.24 mL, 19 mmol). After stirring for 1 h at 60 °C, the mixture was cooled to 20 °C with ice/water and the white precipitate of phthalylhydrazide was filtered off and washed with ether. The filtrate was concentrated, and the residue was purified by column chromatography eluting with 40:60 ethyl acetate/hexane to afford 4.77 g (96.5%) of 3-(aminooxy)-1-(carbobenzyloxy)piperidine as an oil. The product was dissolved in 20 mL of sulfuric ether, and 75 mL of 2.6 N HCl/sulfuric ether solution was added dropwise at 20 °C. After 4 h of stirring, the white abundant precipitate was filtered and washed with sulfuric ether to afford 5.32 g (98%) of 3-(aminooxy)-1-(carbobenzyloxy)piperidine chlorhydrate (**15**) as white crystals. ^{1}H NMR ($CDCl_3$) (free base): δ 1.42−1.74 (m, 4H) -CH_2CH_2-, 3.10−4.10 (m, 5H) CHOH and CH_2NCH_2CHOH, 5.13 (s, 2H) $OCH_2\Phi$, 5.23−5.48 (sl, 2H) NH_2, 7.36 (m, 5H) phenyl. **15**: Anal. ($C_{13}H_{19}N_2ClO_3$) C, H, N, Cl.

Following the same procedures as described for **15** and starting from (3*S*)-3-hydroxypiperidine and (3*R*)-3-hydroxypiperidine, respectively, the following compounds were made. **(3*R*)15**: $[\alpha]_D = +20.5°$ (*c* 1%, 95% EtOH). **(3*S*)15**: $[\alpha]_D = -19°$ (*c* 1%, 95% EtOH).

Following the same procedures as described for **15** and starting from 3-hydroxypyrrolidine, the following compound was made.

3-(Aminooxy)-1-(carbobenzyloxy)pyrrolidine Chlorhydrate (14). Stage A: 3-Hydroxy-1-(carbobenzyloxy)-pyrrolidine. ^{1}H NMR ($CDCl_3$): δ 1.96 (m, 2H) $-CH_2CH_2-$CHOH, 2.08 (sl, 1H) OH, 3.53 (m, 4H) CH_2CONCH_2, 4.46 (m, 1H) *CH*OH, 5.13 (s, 2H) $OCH_2\Phi$, 7.35 (m, 5H) phenyl.

Stage B: 3-(*N*-Phthalimidooxy)-1-(carbobenzyloxy)-pyrrolidine. ^{1}H NMR ($CDCl_3$): δ 2.01−2.31 (m, 2H) $-CH_2$-CH_2-CHOH, 3.55−4.00 (m, 4H) CH_2NCH_2CHOH, 5.00 (s, 1H) *CH*OH, 5.17 (s, 2H) $OCH_2\Phi$, 7.97 (m, 5H) phenyl, 7.78−7.84 (m, 4H) phthalimide.

Stage C: 3-(Aminooxy)-1-(carbobenzyloxy)pyrrolidine Chlorhydrate. Yield: (3 steps): 12%. MS(FAB): 237^+ ($M + H^+$). ^{1} H NMR ($CDCl_3$) (free base): δ 1.45 (m, 2H) -CH_2-CHOH-, 3.15−4.2 (m, 5H) CHOH and CH_2NCH_2CHOH, 5.11 (s, 2H) $OCH_2\Phi$, 5.30 (sl, 2H) NH_2, 7.34 (m, 5H) phenyl.

(*E*)-3-*O*-Descladinosyl-6-*O*-methyl-3-oxoerythromycin 9-*O*-(2-Bromoethyl)oxime (16). To a solution of **9** (3.53 g, 6 mmol) in 60 mL of methanol was added 3.98 g (18 mmol) of 2-bromoethylhydroxylamine hydrobromide. The solution was stirred at room temperature for 24 h. Addition of 90 mL of water allowed the product to crystallize. After filtration and washing with water, the product was dried in vacuo. This product was taken up in ethyl acetate and aqueous ammonium hydroxide. The organic extracts were washed with water and dried over Na_2SO_4. Evaporation of the solvent gave an oil that was further crystallized in hexane to afford after filtration and drying 3.17 g (74%) of **16** as uncolored crystals. Mp: 155−157 °C. MS(EI): 709^+ (M^+). ^{1}H NMR ($CDCl_3$): δ 0.86 (t, 3H) CH_3CH_2, 1.23 (s, 3H) 12-CH_3, 1.40 (s, 3H) 6-CH_3, 2.27 (s, 6H) $N(CH_3)_2$, 2.47 (m, 1H) $H_{3'}$, 2.6 (q, 1H) H_{10}, 2.76 (s, 3H) 6-*O*-CH_3, 3.12 (m, 1H) H_4, 3.20 (dd, 1H) $H_{2'}$, 3.4−3.6 (m, 3H) CH_2-Br and $H_{5'}$, 3.69 (m, 1H) H_8, 3.86 (q, 1H) H_2, 3.90 (sl, 1H) H_{11}, 4.31 (m, 4H) $H_{1'}$−H_5 and $NOCH_2$, 5.17 (dd, 1H) H_{13}. Anal. ($C_{32}H_{57}BrN_2O_{10}$) C, H, Br, N.

(*E*)- and (*Z*)-3-*O*-Descladinosyl-6-*O*-methyl-3-oxoerythromycin 9-Oxime (17a,b). To a solution of **7** (1.174 g, 2 mmol) in 12 mL of methanol were added 0.696 mL (5 mmol) of triethylamine and 0.694 g of hydroxylamine hydrochloride (10 mmol). The solution was heated at reflux for 16 h. The solvent was removed in vacuo, water was added, and the pH was allowed to reach 11 with concentrated ammonium hydroxide. The solution was extracted with ethyl acetate, and the organic extracts were dried over Na_2SO_4 to give 1 g of white foam. The product was purified by column chromatography eluting with 80:20 isopropyl ether/triethylamine to afford 0.7 g (58%) of the (*E*)-oxime **17a** ($R_f = 0.35$) and 0.3 g (24%) of the (*Z*)-oxime **17b** as a white foam. **17a**: mp 166−168 °C. MS-(EI): 602 (M^+). ^{1}H NMR ($CDCl_3$): δ 0.86 (t, 3H) CH_3CH_2, 1.43 (s, 3H) 6-CH_3, 2.27 (s, 6H) $N(CH_3)_2$, 2.48 (m, 1H) $H_{3'}$, 2.6 (ql, 1H) H_{10}, 2.76 (s, 3H) 6-*O*-CH_3, 3.12 (m, 1H) H_4, 3.21 (dd, 1H) $H_{2'}$, 3.57 (m, 1H) $H_{5'}$, 3.75 (m, 1H) H_8, 3.86 (q, 1H) H_2, 3.91 (d, 1H) H_{11}, 4.31 (m, 2H) $H_{1'}$ and H_5, 5.16 (dd, 1H) H_{13}, 7.5 (sl, 1H) NO*H*. Anal. ($C_{30}H_{54}N_2O_{10}$) C, H, N. **17b**: mp 228−230 °C. MS(EI): 602 (M^+). ^{1}H NMR ($CDCl_3$): δ 0.86 (t, 3H) CH_3-CH_2, 1.43 (s, 3H) 6-CH_3, 2.27 (s, 6H) $N(CH_3)_2$, 2.47 (m, 1H) $H_{3'}$, 2.70 (m, 1H) H_8, 2.76 (s, 3H) 6-*O*-CH_3, 3.12 (m, 1H) H_4, 3.24 (dd, 1H) $H_{2'}$, 3.56 (m, 1H) $H_{5'}$, 3.85 (q, 1H) H_2, 4.09 (sl, 1H) H_{11}, 4.25 (d,1H) and 4.30 (d, 1H) $H_{1'}$ and H_5, 5.14 (dd, 1H) H_{13}. Anal. ($C_{30}H_{54}N_2O_{10}$) C, H, N.

(*E*)-3-*O*-Descladinosyl-6-*O*-methyl-3-oxoerythromycin 9-*O*-((2,4,6-Trimethylphenyl)methyl)oxime (19). To a solution of **9** (0.354 g, 0.6 mmol) in 10 mL of methanol was added ((2,4,6-trimethylphenyl)methyl)hydroxylamine hydrochloride (0.363 g, 1.8 mmol). The solution was heated to 60 °C for 24 h. After evaporation of the solvent, the residue was taken up in water, the pH adjusted to 11 with aqueous ammonium hydroxide, and the mixture extracted with ethyl acetate. The extracts were washed with water, dried over $MgSO_4$, and evaporated to dryness. The product was purified by column chromatography eluting with 90:10 methylene chloride/methanol to afford 0.22 g (43%) of **19** as a white foam. MS(FAB): 735^+ ($M + H^+$). ^{1}H NMR ($CDCl_3$): δ 0.86 (t, 3H) CH_3CH_2, 1.12 (s, 3H) 12-CH_3, 1.35 (s, 3H) 6-CH_3, 2.26−2.35 (s, 9H) $CH_{3\ phenyl}$, 2.27 (s, 6H) $N(CH_3)_2$, 2.56 (ql, 1H) H_{10}, 2.64 (s, 3H) 6-*O*-CH_3, 3.15 (m, 1H) H_4, 3.49 (dd, 1H) $H_{2'}$, 3.66 (m, 2H) $H_{5'}$ and H_8, 3.83 (q, 1H) H_2, 3.88 (d, 1H) H_{11}, 4.23−4.27 (m, 2H) $H_{1'}$ and H_5, 5.05 (m, 2H) $CH_2\Phi$, 5.17 (dd, 1H) H_{13}, 6.84 (s, 2H) phenyl. Anal. ($C_{40}H_{66}N_2O_{10}$) C, H, N.

Following the same procedures as described for **19** and starting from the appropriate hydroxyamines, the following compounds were made.

(*E*)-3-*O*-Descladinosyl-6-*O*-methyl-3-oxoerythromycin 9-*O*-(Phenylmethyl)oxime (18). Yield: 30%. Mp: 176−177 °C. MS(FAB): 693^+ ($M + H^+$). ^{1}H NMR ($CDCl_3$): δ 0.85 (t, 3H) CH_3CH_2, 1.22 (s, 3H) 12-CH_3, 1.35 (s, 3H) 6-CH_3, 2.27 (s, 6H) $N(CH_3)_2$, 2.47 (m, 1H) $H_{3'}$, 2.57 (ql, 1H) H_{10}, 2.63 (s, 3H) 6-*O*-CH_3, 3.11 (m, 1H) H_4, 3.19 (dd, 1H) $H_{2'}$, 3.56 (m, 1H) $H_{5'}$, 3.70 (m, 1H) H_8, 3.86 (q, 1H) H_2, 3.89 (d, 1H) H_{11}, 4.30 (m, 2H) $H_{1'}$ and H_5, 5.00 (m, 2H) $CH_2\Phi$, 5.16 (dd, 1H) H_{13}, 7.33 (m, 5H) phenyl. Anal. ($C_{37}H_{60}N_2O_{10}$) C, H, N.

(2*R*)-(*E*)-3-*O*-Descladinosyl-6-*O*-methyl-3-oxoerythromycin 9-(2-Amino-3-methoxy-3-oxopropyl)oxime (20). Yield: 47%. MS(FAB): 704^+ ($M + H^+$). ^{1}H NMR ($CDCl_3$): δ 0.86 (t, 3H) CH_3CH_2, 1.22 (s, 3H) 12-CH_3, 1.37 (s, 3H) 6-CH_3, 2.29 (s, 6H) $N(CH_3)_2$, 2.49 (td, 1H) $H_{3'}$, 2.57 (ql, 1H) H_{10}, 2.74 (s, 3H) 6-*O*-CH_3, 3.11 (m, 1H) H_4, 3.20 (dd, 1H) $H_{2'}$, 3.57 (m, 1H) $H_{5'}$, 3.61 (m, 1H) *CH*NH_2, 3.62 (m, 1H) H_8, 3.76 (s, 3H) $COOCH_3$, 3.85 (sl, 1H) H_{11}, 3.86 (q, 1H) H_2, 4.20−4.37 (AB, 2H) $NOCH_2$, 4.33 (m, 2H) $H_{1'}$ and H_5, 5.17 (dd, 1H) H_{13}. Anal. ($C_{34}H_{61}N_3O_{12}$) C, H, N.

(2*R*)-(*E*)-3-*O*-Descladinosyl-6-*O*-methyl-3-oxoerythromycin 9-(2-Amino-3-hydroxy-3-oxopropyl)oxime Potassium Salt (21). To a solution of **20** (0.105 g, 0.15 mmol) in 1.5 mL of water and 1.5 mL of methanol was added K_2CO_3 (0.035 g, 0.182 mmol). After stirring for 24 h, the methanol was evaporated, 2 mL of water was added, and the solution was washed with ethyl acetate. The aqueous phase was lyophilized to afford 0.09 g (82%) of **21** as a white powder. MS-(FAB): 728^+ (M^+). ^{1}H NMR (DMSO-d_6): δ 0.77 (t, 3H) CH_3-CH_2, 1.16 (s, 3H) 12-CH_3, 1.29 (s, 3H) 6-CH_3, 2.21 (s, 6H) $N(CH_3)_2$, 2.62 (s, 3H) 6-*O*-CH_3, 3.03 (m, 1H) H_4, 3.50 (m, 1H) $H_{5'}$, 3.71 (sl, 1H) H_{11}, 3.80 (m, 1H) H_8, 3.95 (q, 1H) H_2, 4.14

(m, 4H) H_1' and H_5 and $NOCH_2$, 5.11 (dd, 1H) H_{13}. Anal. ($C_{33}H_{58}N_3O_{12}K$, 5 H_2O) C, H, N.

(*E*)-3-*O*-Descladinosyl-6-*O*-methyl-3-oxoerythromycin 9-(2-(Dimethylamino)ethyl)oxime (22). Yield: 68%. MS(FD): 673^+ (M^+). ^{1}H NMR ($CDCl_3$): δ 0.86 (t, 3H) CH_3CH_2, 1.22 (s, 3H) 12-CH_3, 1.39 (s, 3H) 6-CH_3, 2.27 (s, 12H) $N(CH_3)_2$, 2.50 (m,1H) H_3', 2.50−2.65 (m, 3H) H_{10} and NCH_2, 2.74 (s, 3H) 6-*O*-CH_3, 3.12 (quint, 1H) H_4, 3.19 (dd, 1H) H_2', 3.56 (m, 1H) H_5', 3.64 (m, 1H) H_8, 3.86 (q, 1H) H_2, 3.89 (sl, 1H) H_{11}, 4.09 (m, 2H) $NOCH_2$, 4.31 (m, 2H) H_1' and H_5, 5.17 (dd, 1H) H_{13}. Anal. ($C_{34}H_{63}N_3O_{10}$) C, H, N.

(*E*)-3-*O*-Descladinosyl-6-*O*-methyl-3-oxoerythromycin 9-*O*-(2-(Propylamino)ethyl)oxime (23). A solution of **16** (0.5 g, 0.705 mmol) in propylamine (1.16 mL, 14.1 mmol) was stirred under nitrogen atmosphere for 24 h. The reaction was diluted in 5 mL of water and extracted with ethyl acetate. After drying over $MgSO_4$ and evaporation of the solvent, the product was purified by column chromatography eluting with 95:5 ethyl acetate/triethylamine to afford 0.22 g (47%) of **23** as a white foam. MS(SIMS): 688^+ (MH^+). ^{1}H NMR ($CDCl_3$): δ 0.86 and 0.91 (t, 6H) CH_3CH_2, 1.22 (s, 3H) 12-CH_3, 1.39 (s, 3H) 6-CH_3, 2.26 (s, 6H) $N(CH_3)_2$, 2.46 (m, 1H) $H_{3'}$, 2.74 (s, 3H) 6-*O*-CH_3, 2.87 (m, 2H) O−CH_2, 3.12 (m, 1H) H_4, 3.18 (dd, 1H) $H_{2'}$, 3.50 (m, 1H) H_5', 3.70 (m, 1H) H_8, 3.87 (q, 1H) H_2, 3.90 (s, 1H) H_{11}, 5.16 (dd, 1H) H_{13}. Anal. ($C_{35}H_{65}N_3O_{10}$) C, H, N.

Following the same procedures as described for **23** and starting from the appropriate amines, the following compounds were made.

(*E*)-3-*O*-Descladinosyl-6-*O*-methyl-3-oxoerythromycin 9-*O*-(2-((2-Propynyl)amino)ethyl)oxime (24). Yield: 27%. Mp: 152−154 °C. MS(FAB): 684^+ ($M + H^+$). ^{1}H NMR ($CDCl_3$): δ 0.86 (t, 3H) CH_3CH_2, 1.23 (s, 3H) 12-CH_3, 1.38 (s, 3H) 6-CH_3, 2.21 (t, 1H) ≡CH, 2.28 (s, 6H) $N(CH_3)_2$, 2.48 (m, 1H) $H_{3'}$, 2.58 (ql, 1H) H_{10}, 2.75 (s, 3H) 6-*O*-CH_3, 2.97 (m, 2H) N−CH_2, 3.12 (q, 1H) H_4, 3.21 (dd, 1H) $H_{2'}$, 3.44 (d, 2H) CH_2=, 3.59 (m, 1H) H_5', 3.65 (m, 1H) H_8, 3.87 (q, 1H) H_2, 3.89 (d, 1H) H_{11}, 4.11 (m, 2H) NO−CH_2, 4.32 (m, d, 2H) H_1' and H_5, 5.17 (dd, 1H) H_{13}. Anal. ($C_{35}H_{61}N_3O_{10}$) C, H, N.

(*E*)-3-*O*-Descladinosyl-6-*O*-methyl-3-oxoerythromycin 9-*O*-(2-(((1-Pyrrolidinyl)ethyl)amino)ethyl)oxime (30). Yield: 69%. MS(FAB): 743^+ ($M + H^+$). ^{1}H NMR ($CDCl_3$): δ 0.86 (t, 3H) CH_3CH_2, 1.22 (s, 3H) 12-CH_3, 1.38 (s, 3H) 6-CH_3, 1.75 (m, 4H) CH_2 cycle, 2.26 (s, 6H) $N(CH_3)_2$, 2.49 (m, 4H) NCH_2 cycle, 2.58 (ql, 1H) H_{10}, 2.4−2.6 (m, 4H) $NHCH_2CH_2N$, 2.76 (s, 3H) 6-*O*-CH_3, 2.8 (m, 2H) N−CH_2CH_2−O, 3.12 (q, 1H) H_4, 3.19 (dd, 1H) $H_{2'}$, 3.65 (m, 1H) H_8, 3.86 (q, 1H) H_2, 3.80 (s, 1H) H_{11}, 4.20 (m, 2H) NO−CH_2, 5.17 (dd, 1H) H_{13}. Anal. ($C_{38}H_{70}N_4O_{10}$) C, H, N.

(*E*)-3-*O*-Descladinosyl-6-*O*-methyl-3-oxoerythromycin 9-*O*-(2-((2-(Dimethylamino)ethyl)amino)ethyl)oxime (31). Yield: 48%. MS(SIMS): 717^+ (MH^+). ^{1}H NMR ($CDCl_3$): δ 0.86 (t, 3H) CH_3CH_2, 1.22 (s, 3H) 12-CH_3, 1.40 (s, 3H) 6-CH_3, 2.20 and 2.26 (s, 12H) $N(CH_3)_2$, 2.40−2.69−2.87 (m, 6H) NCH_2 cycle, 2.45 (dd, 1H) H_3', 2.58 (ql, 1H) H_{10}, 2.75 (s, 3H) 6-*O*-CH_3, 3.12 (q, 1H) H_4, 3.20 (dd, 1H) $H_{2'}$, 3.66 (m, 1H) H_8, 3.86 (q, 1H) H_2, 3.90 (sl, 1H) H_{11}, 4.10 (m, 2H) NO−CH_2, 4.31−4.33 (d and sl, 2H) H_1' and H_5, 5.17 (dd, 1H) H_{13}. Anal. ($C_{36}H_{68}N_4O_{10}$) C, H, N.

(*E*)-3-*O*-Descladinosyl-6-*O*-methyl-3-oxoerythromycin 9-*O*-(2-((3-(1*H*-Imidazol-1-yl)propyl)amino)ethyl)-oxime (32). A solution of **16** (0.5 g, 0.7 mmol) and (1*H*-imidazol-1-yl)propylamine (0.84 mL, 7 mmol) in 7 mL of ethanol, was stirred at 70 °C for 24 h. The solvent was removed in vacuo; the residue was taken up in ethyl acetate, washed with water and brine, and dried over $MgSO_4$. The product was purified by column chromatography eluting with 80:15:5 ethyl acetate/methanol/triethylamine to afford 0.2 g (38%) of **32** as a white foam. MS(FAB): 754^+ ($M + H^+$). ^{1}H NMR ($CDCl_3$): δ 0.85 (t, 3H) CH_3CH_2, 1.23 (s, 3H) 12-CH_3, 1.38 (s, 3H) 6-CH_3, 1.92 (quint., 2H) $CH_2CH_2CH_2$, 2.27 (s, 6H) $N(CH_3)_2$, 2.46 (m, 1H) $H_{3'}$, 2.59 (t, 3H) $NHCH_2CH_2CH_2$ and H_{10}, 2.74 (s, 3H) 6-*O*-CH_3, 2.85 (m, 2H) $CH_2CH_2CH_2N$, 3.11 (m, 1H) H_4, 3.19 (dd, 1H) $H_{2'}$, 3.57 (m, 1H) H_5', 3.65 (m, 1H) H_8, 3.86 (q, 1H) H_2, 3.88 (d, 1H) H_{11}, 4.07 (t, 2H) O−CH_2CH_2−NH, 4.08 (m, 2H) H_1' and H_5, 4.32 (t, 2H) O-CH_2CH_2NH, 5.16 (dd, 1H) H_{13}, 6.92−7.04−7.48 (sl, 3H) imidazole. Anal. ($C_{38}H_{67}N_5O_{10}$) C, H, N.

Following the same procedures as described for **32** and starting from the appropriate amines, the following compounds were made.

(*E*)-3-*O*-Descladinosyl-6-*O*-methyl-3-oxoerythromycin 9-*O*-(2-((Phenylmethyl)amino)ethyl)oxime (25). Yield: 44%. Mp: 222−224 °C. MS(SIMS): 736^+ (MH^+). ^{1}H NMR ($CDCl_3$): δ 0.86 (t, 3H) CH_3CH_2, 1.22 (s, 3H) 12-CH_3, 1.35 (s, 3H) 6-CH_3, 2.26 (s, 6H) $N(CH_3)_2$, 2.45 (m, 1H) $H_{3'}$, 2.58 (m, 1H) H_{10}, 2.72 (s, 3H) 6-*O*-CH_3, 2.8−3.00 (m, 4H) O−$(CH_2)_2$N, 3.11 (m, 1H) H_4, 3.19 (dd, 1H) $H_{2'}$, 3.50 (m, 1H) H_5', 3.72 (m, 1H) H_8, 5.17 (dd, 1H) H_{13}, 7.2−7.4 (m, 5H) phenyl. Anal. ($C_{39}H_{65}N_3O_{10}$) C, H, N.

(*E*)-3-*O*-Descladinosyl-6-*O*-methyl-3-oxoerythromycin 9-*O*-(2-(1-Pyrrolidinyl)ethyl)oxime (26). Yield: 32%. Mp: 210−212 °C. MS(EI): 699^+ (M^+). ^{1}H NMR ($CDCl_3$): δ 0.86 (t, 3H) CH_3CH_2, 1.22 (s, 3H) 12-CH_3, 1.39 (s, 3H) 6-CH_3, 1.77 (m, 4H) CH_2(cycle), 2.26 (s, 6H) $N(CH_3)_2$, 2.46 (m, 1H) $H_{3'}$, 2.53 (m, 4H) NCH_2(cycle), 2.6 (q, 1H) H_{10}, 2.73 (m, 2H) CH_2N, 2.74 (s, 3H) 6-*O*-CH_3, 3.12 (m, 1H) H_4, 3.19 (dd, 1H) $H_{2'}$, 3.56 (m, 1H) H_5', 3.71 (m, 1H) H_8, 3.87 (q, 1H) H_2, 3.90 (d, 1H) H_{11}, 4.11 (m, 2H) $NOCH_2$, 4.30 (m, 2H) H_1'−H_5, 5.16 (dd, 1H) H_{13}. Anal. ($C_{36}H_{65}N_3O_{10}$) C, H, N.

(*E*)-3-*O*-Descladinosyl-6-*O*-methyl-3-oxoerythromycin 9-*O*-(2-(1-Azetidinyl)ethyl)oxime (27). Yield: 37%. Mp: 198−200 °C. MS(FAB): 686^+ ($M + H^+$). ^{1}H NMR ($CDCl_3$): δ 0.86 (t, 3H) CH_3CH_2, 0.96 (d, 3H) 8-CH_3, 1.15 (d, 3H) 10-CH_3, 1.22 (s, 3H) 12-CH_3, 1.39 (s, 3H) 6-CH_3, 2.07 (quint., 2H) CH_2 cycle, 2.26 (s, 6H) $N(CH_3)_2$, 2.46 (td, 1H) H_3', 2.50−2.65 (m, 5H) H_{10} and NCH_2 cycle, 2.73 (s, 3H) 6-*O*-CH_3, 3.12 (m, 1H) H_4, 3.15 (dd, 1H) H_2', 3.23 (t, 4H) CH_2N, 3.48 (m, 1H) H_5', 3.60 (m, 1H) H_8, 3.86 (q, 1H) H_2, 3.89 (d, 1H) H_{11}, 3.95 (m, 2H) CH_2O, 4.31 (d, 2H) H_1' and H_5, 5.16 (dd, 1H) H_{13}. Anal. ($C_{35}H_{63}N_3O_{10}$) C, H, N.

(*E*)-3-*O*-Descladinosyl-6-*O*-methyl-3-oxoerythromycin 9-*O*-(2-(1-Piperidinyl)ethyl)oxime (28). Yield: 50%. Mp: 194−196 °C. MS(SIMS): 714^+ (MH^+). ^{1}H NMR ($CDCl_3$): δ 0.86 (t, 3H) CH_3CH_2, 0.97 (d, 3H) 8-CH_3, 1.15 (d, 3H) 10-CH_3, 1.23 (s, 3H) 12-CH_3, 1.39 (s, 3H) 6-CH_3, 2.26 (s, 6H) $N(CH_3)_2$, 2.45−2.60 (m, 4H) CH_2N-, 2.60 (m, 1H) H_{10}, 2.74 (s, 3H) 6-*O*-CH_3, 3.12 (m, 1H) H_4, 3.19 (dd, 1H) $H_{2'}$, 3.55 (m, 1H) H_5', 3.65 (m, 1H) H_8, 3.86 (q, 1H) H_2, 3.89 (d, 1H) H_{11}, 4.13 (t, 2H) NO−CH_2, 4.30−4.32 (d, 2H) H_1' and H_5, 5.12 (dd, 1H) H_{13}. Anal. ($C_{37}H_{67}N_3O_{10}$) C, H, N.

(*E*)-3-*O*-Descladinosyl-6-*O*-methyl-3-oxoerythromycin 9-*O*-(2-(4-Morpholinyl)ethyl)oxime (29). Yield: 30%. Mp: 198−200 °C. MS(SIMS): 716^+ (MH^+). ^{1}H NMR ($CDCl_3$): δ 0.86 (t, 3H) CH_3CH_2, 0.96 (d, 3H) 8-CH_3, 1.15 (d, 3H) 10-CH_3, 1.22 (s, 3H) 12-CH_3, 1.39 (s, 3H) 6-CH_3, 2.29 (s, 6H) $N(CH_3)_2$, 2.50−2.65 (m, 4H) CH_2N-, 2.68 (m, 1H) H_{10}, 2.75 (s, 3H) 6-*O*-CH_3, 3.11 (m, 1H) H_4, 3.21 (dd, 1H) H_2', 3.60 (m, 2H) $H_5'$and H_8, 3.70 (t and q, 5H) H_2 and CH_2OCH_2, 3.89 (d, 1H) H_{11}, 4.11 (t, 2H) NO−CH_2, 4.30−4.32 (d, 2H) H_1' and H_5, 5.17 (dd, 1H) H_{13}. Anal. ($C_{36}H_{65}N_3O_{11}$) C, H, N.

(3*R*)- and (3*S*)-(*E*)-3-*O*-Descladinosyl-6-*O*-methyl-3-oxoerythromycin 9-*O*-(3-Piperidinyl)oxime (34 and 35). Stage A: To a solution of **9** (0.59 g, 1 mmol) in 8 mL of ethanol was added **15** (0.75 g, 2.6 mmol). The reaction was stirred at 55 °C for 9 h. After evaporation to dryness, the residue was taken up with 10 mL of ethyl acetate, water was added, and the pH was adjusted to 8 with aqueous ammonium hydroxide. Drying over $MgSO_4$ and evaporation of the solvent afforded 1.1 g of crude product directly engaged in stage B.

Stage B: The product of stage A was stirred with palladium on charcoal (0.2 g) in 15 mL of ethanol over 1.5 atm of hydrogen. After stirring for 12 h, the reaction was filtered and concentrated in vacuo, and the oily residue was purified by column chromatography eluting with 85:15:0.4 methylene chloride/methanol/ammonium hydroxide to afford 0.185 g (27%) of **34** and 0.123 g (18%) of **35** as a white foam. **34**: MS-(FAB): 685^+ ($M + H^+$). ^{1}H NMR ($CDCl_3$): δ 0.86 (t, 3H) CH_3-CH_2, 1.23 (s, 3H) 12-CH_3, 1.39 (s, 3H) 6-CH_3, 2.26 (s, 6H)

N(CH_3)$_2$, 2.46 (td, 1H) H_3', 2.58 (ql, 1H) H_{10}, 2.67−2.85−3.15 (m, 4H) CH_2NH, 2.74 (s, 3H) 6-*O*-CH_3, 3.15 (m, 2H) H_4 and H_2', 3.50 (m, 1H) H_5', 3.72 (m, 1H) H_8, 3.87 (q, 1H) H_2, 3.90 (sl, 1H) H_{11}, 3.95 (m, 1H) NO*CH*, 4.33 (d, 2H) H_1'−H_5, 5.17 (dd, 1H) H_{13}. Anal. ($C_{35}H_{63}N_3O_{10}$) C, H, N. **35**: MS(FAB): 685^+ ($M + H^+$). ^{1}H NMR ($CDCl_3$): δ 0.85 (t, 3H) CH_3CH_2, 1.23 (s, 3H) 12-CH_3, 1.35 (s, 3H) 6-CH_3, 2.27 (s, 6H) N(CH_3)$_2$, 2.45 (m, 1H) H_3', 2.58 (ql, 1H) H_{10}, 2.65−2.90 (m, 4H) CH_2NH, 2.75 (s, 3H) 6-*O*-CH_3, 3.16 (m, 2H) H_4 and H_2', 3.54 (m, 1H) H_5', 3.65 (m, 1H) H_8, 3.84 (q, 1H) H_2, 4.02 (sl, 1H) H_{11}, 4.08 (sl, 1H) NO*CH*, 4.24−4.29 (m, 2H) H_1'-H_5, 5.16 (dd, 1H) H_{13}. Anal. ($C_{35}H_{63}N_3O_{10}$) C, H, N.

(3*R*)-(*E*)-3-*O*-Descladinosyl-6-*O*-methyl-3-oxoerythromycin 9-*O*-(1-Methyl-3-piperidinyl)oxime (36). A solution of **34** (0.315 g, 0.46 mmol), 37% aqueous formaldehyde (0.051 mL, 0.61 mmol), and formic acid (0.027 mL, 0.6 mmol) in 5 mL of chloroform was stirred at reflux for 4 h. Chloroform was added, and the solution was washed with water and 2 N NaOH and dried over $MgSO_4$. After evaporation to dryness, the residue was purified by column chromatography eluting with 98:2 ethyl acetate/triethylamine to afford 0.28 g (78%) of **36** as a white foam. MS(FAB): 700^+ ($M + H^+$). ^{1}H NMR ($CDCl_3$): δ 0.86 (t, 3H) CH_3CH_2, 1.23 (s, 3H) 12-CH_3, 1.38 (s, 3H) 6-CH_3, 2.28 (s, 6H) N(CH_3)$_2$, 2.31 (s, 3H) NCH_3, 2.50 (m, 1H) H_3', 2.58 (m, 1H) H_{10}, 2.65−2.99 (m, 4H) CH_2NH, 2.74 (s, 3H) 6-*O*-CH_3, 3.13 (m, 1H) H_4, 3. 20 (dd, 1H) H_2', 3.57 (m, 1H) H_5', 3.69 (m, 1H) H_8, 3.87 (q, 1H) H_2, 3.90 (sl, 1H) H_{11}, 4.08 (m, 1H) NO*CH*, 4.32 (d, 2H) H_1'−H_5, 5.17 (dd, 1H) H_{13}. Anal. ($C_{36}H_{65}N_3O_{10}$) C, H, N.

(3*R*)- and (3*S*)-(*E*)-3-*O*-Descladinosyl-6-*O*-methyl-3-oxoerythromycin 9-*O*-(3-Pyrrolidinyl)oxime (33). Yield: 22%. MS(FAB): 672^+ ($M + H^+$). ^{1}H NMR ($CDCl_3$): δ 0.86 (t, 3H) CH_3CH_2, 1.23 (s, 3H) 12-CH_3, 1.36 (s, 3H) 6-CH_3, 2.26 (s, 6H) N(CH_3)$_2$, 2.45 (td, 1H) H_3', 2.58 (ql, 1H) H_{10}, 2.73 (s, 3H) 6-*O*-CH_3, 2.85−3.2 (m, 5H) CH_2NH and H_4, 3.19 (dd, 2H) H_2', 3.59 (m, 1H) $H_5'$and H_8, 3.86 (q, 1H) H_2, 3.88 (sl, 1H) H_{11}, 4.13 (m, 1H) NO*CH*, 4.32 (d, 2H) H_1'−H_5, 5.16 (dd, 1H) H_{13}. Anal. ($C_{34}H_{61}N_3O_{10}$) C, H, N.

(3*R*)-(*E*)-3-*O*-Descladinosyl-6-*O*-methyl-3-oxoerythromycin 9-*O*-(1-(3-Phenylpropyl)-3-piperidinyl)oxime (37). To a solution of **34** (0.28 g, 0.4 mmol) and 3-phenylpropionaldehyde (0.079 mL, 0.6 mmol) in 1 mL of methanol and acetic acid (0.08 mL, 1.3 mmol) stirred at room temperature under nitrogen atmosphere was added sodium cyanoborohydride (0.028 g, 0.44 mmol). After stirring for 1 h, the reaction mixture was diluted with ethyl acetate, washed with water, 2 N NaOH and brine, and dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by column chromatography eluting with 94:4:4 isopropyl ether/triethylamine/methanol to afford 0.25 g (50%) of **37** as a white foam. MS(FAB): 804^+ (MH^+). ^{1}H NMR ($CDCl_3$): δ 0.86 (t, 3H) CH_3-CH_2, 1.23 (s, 3H) 12-CH_3, 1.37 (s, 3H) 6-CH_3, 2.26 (s, 6H) N(CH_3)$_2$, 2.45 (td, 1H) H_3', 2.60 (ql, 1H) H_{10}, 2.25−2.75 (m, 6H) NCH_2, 2.74 (s, 3H) 6-*O*-CH_3, 3.12 (m, 1H) H_4, 3.18 (dd, 2H) H_2', 3.57 (m, 1H) H_5', 3 69 (m, 1H) H_8, 3.86 (q, 1H) H_2, 3.90 (d, 1H) H_{11}, 4.03 (m, 1H) NO*CH*, 4.31 (d, 2H) H_1'−H_5, 5.17 (dd, 1H) H_{13}, 7.10−7.3 (m, 5H) phenyl. Anal. ($C_{44}H_{73}N_3O_{10}$) C, H, N.

Following the same procedures as described for **37** and starting from the appropriate aldehydes, the following compounds were made.

(3*R*)-(*E*)-3-*O*-Descladinosyl-6-*O*-methyl-3-oxoerythromycin 9-*O*-(1-(3-Cyclohexylpropyl)-3-piperidinyl)oxime (38). Yield: 27%. MS(FAB): 810^+ (MH^+). ^{1}H NMR ($CDCl_3$): δ 0.86 (t, 3H) CH_3CH_2, 1.23 (s, 3H) 12-CH_3, 1.37 (s, 3H) 6-CH_3, 2.28 (s, 6H) N(CH_3)$_2$, 2.38 (m, 1H) H_3', 2.57 (ql, 1H) H_{10}, 2.73 (s, 3H) 6-*O*-CH_3, 3.12 (m, 1H) H_4, 3.20 (dd, 2H) H_2', 3.58 (m, 1H) H_5', 3.68 (m, 1H) H_8, 3−86 (q, 1H) H_2, 3.90 (d, 1H) H_{11}, 4.13 (m, 1H) NO*CH*, 4.32 (d, 2H) H_1'−H_5, 5.17 (dd, 1H) H_{13}. Anal. ($C_{44}H_{79}N_3O_{10}$) C, H, N.

(3*R*)-(*E*)-3-*O*-Descladinosyl-6-*O*-methyl-3-oxoerythromycin 9-*O*-(1-(Biphenylylmethyl)-3-piperidinyl)oxime (39). Yield: 28%. MS(FAB): 852^+ (MH^+). ^{1}H NMR ($CDCl_3$): δ 0.84 (t, 3H) CH_3CH_2, 1.21 (s, 3H) 12-CH_3, 1.36 (s, 3H) 6-CH_3, 2.26 (s, 6H) N(CH_3)$_2$, 2.45 (m, 1H) H_3', 2.56 (ql, 1H) H_{10}, 2.5−2.65−2.98 (m, 6H) NCH_2, 2.73 (s, 3H) 6-OCH$_3$, 3.12 (m, 1H) H_4, 3.19 (dd, 2H) H_2', 3.47−3.63 (d, 2H) $CH_2\Phi$, 3.55 (m, 1H) H_5', 3.69 (m, 1H) H_8, 3.86 (q, 1H) H_2, 3.89 (sl, 1H) H_{11}, 4.09 (m, 1H) NO*CH*, 4.31 (m, 2H) H_5 and H_1', 5.15 (dd, 1H) H_{13}, 7.3−7.60 (m, 9H) biphenyl. Anal. ($C_{48}H_{73}N_3O_{10}$) C, H, N.

(3*R*)-(*E*)-3-*O*-Descladinosyl-6-*O*-methyl-3-oxoerythromycin 9-*O*-(1-(3-(4-Hydroxyphenyl)propyl)-3-piperidinyl)oxime (40). Yield: 33%. MS(FAB): 820^+ (MH^+). ^{1}H NMR ($CDCl_3$): δ 0.87 (t, 3H) CH_3CH_2, 1.23 (s, 3H) 12-CH_3, 1.34 (s, 3H) 6-CH_3, 2.28 (s, 6H) N(CH_3)$_2$, 2.25 (td, 1H) H_3', 2.65 (ql, 1H) H_{10}, 2.25−2.75−3.15 (m, 8H) NCH_2 and $CH_2\Phi$, 2.66 (s, 3H) 6-*O*-CH_3, 3.13 (m, 1H) H_4, 3.19 (dd, 2H) H_2', 3.56 (m, 1H) H_5', 3.65 (m, 1H) H_8, 3.88 (q, 1H) H_2, 3.90 (sl, 1H) H_{11}, 4.07 (m, 1H) NO*CH*, 5.21 (dd, 1H) H_{13}, 6.75−6.33 (m, 4H) phenyl. Anal. ($C_{44}H_{73}N_3O_{11}$) C, H, N.

(3*R*)-(*E*)-3-*O*-Descladinosyl-6-*O*-methyl-3-oxoerythromycin 9-*O*-(1-Decyl-3-piperidinyl)oxime (41). A solution of **34** (0.274 g, 0.4 mmol), decanal (0.068 g, 0.44 mmol), and palladium on charcoal (0.05 g) in 10 mL of ethanol and acetic acid (0.03 mL, 0.5 mmol) was stirred under 1.5 atm hydrogen pressure for 12 h. The reaction mixture was filtered and evaporated to dryness. The residue was purified by column chromatography eluting with 90:10 ethyl acetate/methanol to afford 0.297 g (90%) of **41** as a white foam. MS(FAB): 826^+ (MH^+). ^{1}H NMR ($CDCl_3$): δ 0.86 and 0.88 (t, 6H) CH_3CH_2, 1.38 (s, 3H) 6-CH_3, 2.26 (s, 6H) N(CH_3)$_2$, 2.46 (m, 1H) H_3', 2.56 (ql, 1H) H_{10}, 2.74 (s, 3H) 6-*O*-CH_3, 3.13 (m, 1H) H_4, 3.19 (dd, 2H) H_2', 3.57 (m, 1H) H_5', 3.68 (m, 1H) H_8, 3.86 (q, 1H) H_2, 3.90 (sl, 1H) H_{11}, 4.04 (m, 1H) NO*CH*, 4.31 (m, 2H) H_1' and H_5, 5.17 (dd, 1H) H_{13}. Anal. ($C_{45}H_{83}N_3O_{10}$) C, H, N.

11-Deoxy-3-*O*-descladinosyl-6-*O*-methyl-11-*O*-(methanesulfonate)-3-oxoerythromycine 2′-Acetate (42). To a solution of **9**-2′OAc (17 g, 27 mmol) in 100 mL of dry pyridine under nitrogen at 10 °C was added 11.9 g (64.8 mmol) of methanesulfonic anhydride. The reaction was stirred for 5 h at room temperature. The solution was filtered and concentrated and then taken up with water and extracted with ethyl acetate. After drying under $MgSO_4$ the extracts were concentrated and diluted in 20 mL of THF. To this solution was added 2.9 g (32 mmol) of oxalic acid diluted in THF. The white precipitate formed was filtered off, washed with ethyl acetate, and dissolved in aqueous ammonium hydroxide. The solution was extracted with ethyl acetate, and the extracts were washed with water and dried over Na_2SO_4. After removal of the solvent and drying, 15.16 g (79%) of brown solid was obtained. Mp: 210−212 °C. ^{1}H NMR ($CDCl_3$): δ 0.91 (t, 3H) CH_3CH_2, 1.22 (s, 3H) 12-CH_3, 1.52 (s, 3H) 6-CH_3, 2.02 (s, 1H) 12-O*H*, 2.09 (s, 3H) 2′-OCOCH$_3$, 2.25 (s, 6H) N(CH_3)$_2$, 2.44 (ql, 1H) H_{10}, 2.68 (m, 1H) H_3', 2.79 (s, 3H) 6-*O*-CH_3, 3.03 (s, 3H) OSO_2CH_3, 3.41 (dq, 1H) H_4, 3.5 (m, 1H) H_5', 3.72 (q, 1H) H_2, 4.01 (d, J = 10.5 Hz, 1H) H_5, 4.39 (d, 1H) H_1', 4.75 (s, 1H) H_{11}, 5.04 (dd, 1H) H_{13}.

10,11-Didehydro-11-deoxy-3-*O*-descladinosyl-6-*O*-methyl-3-oxoerythromycin 2′-Acetate (43). To a solution of **42** (8.26 g, 11.7 mmol) in 35 mL of acetone, at room temperature, were slowly added dropwise 2.19 mL (14.6 mmol) of DBU. After stirring 20 h, the reaction was diluted with methylene chloride, washed with water, dried over Na_2SO_4, and concentrated in vacuo. The crude product was crystallized in ether and filtered to afford 6.33 g (88%) of **43** as slightly brown crystals. Mp: 230−232 °C. ^{1}H NMR ($CDCl_3$): δ 0.33 (t, 3H) CH_3CH_2, 1.26 (s, 3H) 12-CH_3, 1.48 (s, 3H) 6-CH_3, 2.02 (s, 3H) 10-CH_3, 2.06 (s, 3H) 2′-OCOCH$_3$, 2.27 (s, 6H) N(CH_3)$_2$, 2.7 (m, 1H) H_3', 2.86 (s, 3H) 6-*O*-CH_3, 3.05 (m, 1H) H_4, 3.16 (m, 1H) H_8, 3.54 (m, 1H) H_5', 3.39 (q, 1H) H_2, 4.36 (d, 1H) H_1', 4.75 (dd, 1H) H_2', 5.01 (dd, 1H) H_{13}, 6.6 (s, 1H) H_{11}, 5.02 (sl, 1H) 12-O*H*.

10,11-Didehydro-11-deoxy-3-*O*-descladinosyl-6-*O*-methyl-3-oxo-12-(1*H*-imidazole-1-carboxylate)erythromycin 2′-Acetate (44). To a suspension of 50% sodium hydride (1.92 g, 38.4 mmol) in 120 mL of dry DMF, at −10 °C under nitrogen atmosphere, was added in small portions **43** (12.23 g, 20 mmol). A solution of carbonyldiimidazole in 60 mL of dry DMF

was then added dropwise. After 1 h of stirring at −10 °C, 180 mL of water was added while maintaining the internal temperature at 0 °C. The white precipitate was filtered off, washed with cold water, and finally dissolved in ether. The solution was dried over $MgSO_4$ and concentrated to afford after drying in vacuo 9.47 g (67%) of **44** as a white foam. MS(EI): 706^+ (M^+). ^{1}H NMR ($CDCl_3$): δ 0.95 (t, 3H) CH_3CH_2, 1.30 (s, 3H) 6-CH_3, 1.84 (d, 3H) 10-CH_3, 1.87 (s, 3H) 12-CH_3, 2.05 (s, 3H) 2′-OCOCH_3, 2.24 (s, 6H) N(CH_3)$_2$, 2.65 (m, 1H) $H_{3'}$, 2.78 (s, 3H) 6-*O*-CH_3, 3.03 (m, 1H) H_4, 3.06 (m, 1H) H_8, 3.5 (m, 1H) $H_{5'}$, 3.75 (q, 1H) H_2, 4.12 (d, 1H) H_5, 4.35 (d, 1H) $H_{1'}$, 4.73 (dd, 1H) $H_{2'}$, 5.69 (dd, 1H) H_{13}, 6.8 (sl, 1H) H_{11}, 7.08−7.38−8.10 (dd, 3H) imidazole.

(10*R*)- and (10*S*)-11,12-Dideoxy-3-*O*-descladinosyl-6-*O*-methyl-3-oxo-11,12-(iminocarbonyloxy) (45a,b). To a solution of **44** (1.2 g, 1.69 mmol) in 24 mL of acetonitrile at −40 °C was added 24 mL of liquid ammonia. The reaction was stirred for 6 h at −40 °C, then 2.4 mL of water was added, and the reaction mixture was allowed to stand at room temperature for 12 h. The solution was concentrated in vacuo, diluted with methylene chloride, washed with water and brine, and dried over $MgSO_4$. The crude product was dissolved in 10 mL of methanol and stirred for 4 h 30 min at room temperature. The solvent was removed, and the products were purified by column chromatography eluting with 95:5 methylene chloride/methanol to afford 0.44 g (43%) of **45a** and 0.22 g (22%) of **45b** as white foams. **45a**: MS(FAB): 613^+ $(M+H)^+$. ^{1}H NMR ($CDCl_3$): δ 0.88 (t, 3H) CH_3CH_2, 1.32 (s, 3H) 12-CH_3, 1.48 (s, 3H) 6-CH_3, 2.26 (s, 6H) N(CH_3)$_2$, 2.44 (m, 1H) $H_{3'}$, 2.58 (m, 3H) H_8, 2.61 (s, 3H) 6-*O*-CH_3, 2.89 (ql, 1H) H_{10}, 3.04 (m, 1H) H_4, 3.17 (dd, 1H) $H_{2'}$, 3.54 (m, 1H) $H_{5'}$, 3.74 (sl, 1H) H_{11}, 3.83 (q, 1H) H_2, 4,21 (d,1H) H_5, 4.31 (d, 1H) $H_{1'}$, 5.09 (dd, 1H) H_{13}, 5.72 (s, 1H) N*H*CO. Anal. ($C_{31}H_{52}N_2O_{10}$) C, H, N. **45b**: MS(FAB): 613^+ $(M + H)^+$. ^{1}H NMR ($CDCl_3$): δ 0.88 (t, 3H) CH_3CH_2, 1.29 and 1.69 (s, 3H) 6-CH_3 and 12-CH_3, 2.28 (s, 6H) N(CH_3)$_2$, 2.48 (m, 1H) $H_{3'}$, 2.68 (m, 3H) H_8, 2.78 (s, 3H) 6-*O*-CH_3, 2.82 (dq, 1H) H_{10}, 3.03 (m, 1H) H_4, 3.19 (dd, 1H) $H_{2'}$, 3.53 (m, 1H) $H_{5'}$, 3.55 (d, J = 2.5 Hz, 1H) H_{11}, 3.88 (q, 1H) H_2, 4,19 (d,1H) H_5, 4.30 (d, 1H) $H_{1'}$, 5.02 (dd, 1H) H_{13}, 5.41 (s, 1H) N*H*CO. Anal. ($C_{31}H_{52}N_2O_{10}$) C, H, N.

11,12-Dideoxy-3-*O*-descladinosyl-6-*O*-methyl-3-oxo-12,-11-(oxycarbonyl((4-phenylbutyl)imino))erythromycin (46). Stage A: A mixture of **44** (0.9 g, 1.275 mmol) and 4-phenylbutylamine (0.745 g, 5 mmol) in 3 mL of CH_3CN and 0.3 mL of water was stirred at 55 °C for 5 h. The reaction mixture was poured into a 0.5 M aqueous solution of sodium dihydrogenophosphate and extracted with ethyl acetate. The extracts were washed with water, dried over Na_2SO_4, filtered, and concentrated to give 0.9 g of oil. The product was purified by column chromatography eluting with 96:4 ethyl acetate/triethylamine to afford 0.63 g (63%) of **46**-2′OAc as a white foam.

Stage B: 46-2′OAc (0.6 g, 0.76 mmol) was stirred for 15 h in 10 mL of methanol at room temperature. The solvent was removed in vacuo, and the crude product was purified by column chromatography eluting with 96:4 ethyl acetate/triethylamine to afford 0.538 g (96%) of **46** as a white foam. MS(FAB): 745^+ $(M + H^+)$. ^{1}H NMR ($CDCl_3$): δ 0.85 (t, 3H) CH_3CH_2, 1.34 (s, 3H) 6-CH_3, 1.47 (s, 3H) 12-CH_3, 2.29 (s, 6H) N(CH_3)$_2$, 2.48 (m, 1H) $H_{3'}$, 2.61 (s, 3H) 6-*O*-CH_3, 2.60 (m, 3H) H_8 and $CH_2\Phi$, 3.10 (m, 2H) H_4 and H_{10}, 3.20 (dd, J = 7.5 Hz, 1H) $H_{2'}$, 3.50 (m, 1H) $H_{5'}$, 3.59 (s, 1H) H_{11}, 3.70 (m, 2H) CH_2-NCO, 3.85 (q, 1H) H_2, 4.23 (d, J = 8 Hz, 1H) H_5, 4.27 (d, J = 7.5 Hz, 1H) $H_{1'}$, 4.97 (dd, 1H) H_{13}, 7.1−7.3 (m, 5H) phenyl. Anal. ($C_{41}H_{64}N_2O_{10}$) C, H, N.

Following the same procedures as described for **46** and starting from the appropriate amines, the following compounds were made.

11,12-Dideoxy-3-*O*-descladinosyl-6-*O*-methyl-3-oxo-12,-11-(oxycarbonyl(butylimino))erythromycin (47). Yield: 60%. Mp: 220 °C. MS(EI): 669^+ (M^+). ^{1}H NMR ($CDCl_3$): δ 0.86 and 0.92 (t, 6H) CH_3CH_2, 1.35 (s, 3H), 1.47 (s, 3H) 6-CH_3, 12-CH_3, 2.28 (s, 6H) N(CH_3)$_2$, 2.48 (m, 1H) $H_{3'}$, 2.60 (m, 1H) H_8, 2.67 (s, 3H) 6-*O*-CH_3, 3.10 (m, 2H) H_4 and H_{10}, 3.19 (dd, 1H) $H_{2'}$, 3.50 to 3.65 (m, 4H) H_{11}−$H_{5'}$ and CH_2NCO, 3.86 (q, 1H) H_2, 4.09 (sl, 1H) H_{11}, 4.25 (d,1H) and 4.29 (d, 1H) $H_{1'}$ and H_5, 4.96 (dd, 1H) H_{13}. Anal. ($C_{35}H_{60}N_2O_{11}$) C, H, N.

11,12-Dideoxy-3-descladinosyl-6-*O*-methyl-3-oxo-12,11-(oxycarbonyl((3-phenylpropyl)imino))erythromycin (48). Yield: 19%. Mp: 210−212 °C. MS(EI): 731 (M^+). ^{1}H NMR ($CDCl_3$): δ 0.85 (t, 3H) CH_3CH_2, 1.32 (s, 3H) 6-CH_3, 1.47 (s, 3H) 12-CH_3, 2.27 (s, 6H) N(CH_3)$_2$, 2.45 (td, 1H) $H_{3'}$, 2.53 (s, 3H) 6-*O*-CH_3, 2.65 (m, 3H) H_8 and $CH_2\phi$, 3.10 (m, 2H) H_4 and H_{10}, 3.18 (dd, 1H) $H_{2'}$, 3.54 (m, 1H) $H_{5'}$, 3.60 (s, 1H) H_{11}, 3.65 (m, 2H) CH_2N, 3.84 (q, 1H) H_2, 4.22 (d, 1H) and 4.28 (d, 1H) $H_{1'}$ and H_5, 4.98 (dd, 1H) H_{13}, 7.1−7.3 (m, 5H) phenyl. Anal. ($C_{40}H_{62}N_2O_{10}$) C, H, N.

11,12-Dideoxy-3-descladinosyl-6-*O*-methyl-3-oxo-12,11-(oxycarbonyl((4-(3-chlorophenyl)butyl)imino))erythromycin (49). Yield: 24%. Mp: 191−193 °C. MS(SIMS): 779^+ (MH^+). NMR ($CDCl_3$): δ 0.85 (t, 3H) CH_3CH_2, 1.35 (s, 3H), 1.47 (s, 3H) 6-CH_3, 12-CH_3, 2.26 (s, 6H) N(CH_3)$_2$, 2.44 (m, 1H) $H_{3'}$, 2.60 (m, 3H) H_8 and $CH_2\phi$, 2.61 (s, 3H) 6-*O*-CH_3, 3.07 (m, 1H) H_4, 3.11 (ql, 1H) H_{10}, 3.18 (dd, 1H) $H_{2'}$, 3.54 (m, 1H) $H_{5'}$, 3.57 (s, 1H) H_{11}, 3.65 (m, 2H) CH_2N, 3.85 (q, 1H) H_2, 4.24 (d,1H) H_5, 4.29 (d, 1H) $H_{1'}$, 4.96 (dd, 1H) H_{13}, 7.04 (m, 1H) and 7.15 (m, 3H) phenyl. Anal. ($C_{41}H_{63}ClN_2O_{10}$) C, H, Cl, N.

11,12-Dideoxy-3-descladinosyl-6-*O*-methyl-3-oxo-12,11-(oxycarbonyl((3-(phenylamino)propyl)imino))erythromycin (50). Yield: 26%. Mp: 206 °C. MS(SIMS): 746^+ (MH^+). ^{1}H NMR ($CDCl_3$): δ 0.83 (t, 3H) CH_3CH_2, 1.35 (s, 3H) 6-CH_3, 1.47 (s, 3H) 12-CH_3, 2.26 (s, 6H) N(CH_3)$_2$, 2.45 (m, 1H) $H_{3'}$, 2.63 (s, 3H) 6-*O*-CH_3, 2.65 (m, 1H) H_8, 3.00−3.27 (m, 4H) H_4−H_{10} and CH_2NH, 3.53 (m, 1H) $H_{5'}$, 3.59 (s, 1H) H_{11}, 3.65−3.80 (m, 2H) CH_2NCO, 3.85 (q, 1H) H_2, 4.23 (d,1H) and 4.28 (d, 1H) $H_{1'}$ and H_5, 4.95 (dd, 1H) H_{13}, 6.62 (m, 2H) $H_{orthophenyl}$, 6.66(m,1H) $H_{paraphenyl}$, 7.15(m,2H) $H_{metaphenyl}$. Anal. ($C_{40}H_{63}N_3O_{10}$) C, H, N.

11,12-Dideoxy-3-descladinosyl-6-*O*-methyl-3-oxo-12,11-(oxycarbonyl((2-(phenylmethoxy)ethyl)imino))erythromycin (51). Yield: 20%. Mp: 206 °C. MS(SIMS): 747^+ (MH^+). ^{1}H NMR ($CDCl_3$): δ 0.86 (t, 3H) CH_3CH_2, 1.35 (s, 3H) 6-CH_3, 1.48 (s, 3H) 12-CH_3, 2.27 (s, 6H) N(CH_3)$_2$, 2.45 (m, 1H) $H_{3'}$, 2.60 (m, 1H) H_8, 2.68 (s, 3H) 6-*O*-CH_3, 3.10 (m, 2H) H_4 and H_{10}, 3.18 (dd, 1H) $H_{2'}$, 3.55 (m, 1H) $H_{5'}$, 3.65 (s, 1H) H_{11}, 3.60−3.95 (m, 4H) −OCH_2CH_2NCO, 3.84 (q, 1H) H_2, 4.25 (d,-1H) and 4.30 (d, 1H) $H_{1'}$ and H_5, 4.59 (AB, 2H) O-$CH_2\Phi$, 5.11 (dd, 1H) H_{13}, 7.18−7.33 (m, 5H) phenyl. Anal. ($C_{40}H_{62}N_2O_{11}$) C, H, N.

11,12-Dideoxy-3-descladinosyl-6-*O*-methyl-3-oxo-12,-11-(oxycarbonyl((2-(*N*,*N*-phenylmethylamino)ethyl)-imino))erythromycin (52). Yield: 35%. MS(FAB): 760^+ $(M + H^+)$. ^{1}H NMR ($CDCl_3$): δ 0.77 (t, 3H) CH_3CH_2, 1.24 (s, 3H) 12-CH_3, 1.48 (s, 3H) 6-CH_3, 2.18 (s, 3H) N(CH_3)$_2$, 2.88 (s, 6H) N(CH_3)$_2$, 2.4−2.8 (m, 4H) CH_2N−$H_{3'}$-H_8, 2.65 (s, 3H) 6-*O*-CH_3, 3.00−3.25 (m, 2H) H_4 and $H_{2'}$, 3.48−3.70 (d, 2H) $CH_2\Phi$, 3.57 (s, 1H) H_{11}, 3.75−4.00 (m, 2H) CH_2NCO, 3.81 (q, 1H) H_2, 4.23 (d, 1H) H_5, 4.28 (d, 1H) $H_{1'}$, 5.08 (dd, 1H) H_{13}, 7.15−7.35 (m, 5H) phenyl. Anal. ($C_{41}H_{65}N_3O_{10}$) C, H, N.

11,12-Dideoxy-3-descladinosyl-6-*O*-methyl-3-oxo-12,11-(oxycarbonyl((4-(6-methoxy-4-quinolinyl)butyl)imino))-erythromycin (53). Yield: 68%. MS(SIMS): 826^+ (MH^+). ^{1}H NMR ($CDCl_3$): δ 0.83 (t, 3H) CH_3CH_2, 1.33 (s, 3H) 6-CH_3, 1.48 (s, 3H) 12-CH_3, 2.32 (s, 6H) N(CH_3)$_2$, 2.50 (m, 1H) $H_{3'}$, 2.60 (m, 1H) H_8, 2.61 (s, 3H) 6-*O*-CH_3, 3.07 (m, 2H) CH_2−Ar, 3.00−3.2 (m, 2H) H_4 and H_{10}, 3.22 (dd, 1H) $H_{2'}$, 3.55 (m, 1H) $H_{5'}$, 3.59 (s, 1H) H_{11}, 3.73 (m, 2H) CH_2NCO, 3.86 (q, 1H) H_2, 3.98 (s, 3H) CH_3O−Ar, 4.23 (d,1H) H_5, 4.30 (d, 1H) $H_{1'}$, 4.96 (dd, 1H) H_{13}, [7.22 (d, 1H) H_3, 7.25 (d, 1H) H_5, 7.35 (dd, 1H) H_7, 8.00 (d, 1H) H_8, 8.65 (d, 1H) H_2, quinoline]. Anal. ($C_{45}H_{67}N_3O_{11}$) C, H, N.

11,12-Dideoxy-3-descladinosyl-6-*O*-methyl-3-oxo-12,11-(oxycarbonyl((4-(8-methoxy-4-quinolinyl)butyl)imino))-erythromycin (54). Yield: 59%. MS(SIMS): 826^+ (MH^+). ^{1}H NMR ($CDCl_3$): δ 0.82 (t, 3H) CH_3CH_2, 1.35 (s, 3H) 6-CH_3, 1.48 (s, 3H) 12-CH_3, 2.30 (s, 6H) N(CH_3)$_2$, 2.50 (m, 1H) $H_{3'}$,

2.61 (m, 1H) H_8,, 2.66 (s, 3H) 6-*O*-CH_3, 3.08 (m, 4H) CH_2−Ar and H_4−H_{10}, 3.21 (dd, 1H) H_2', 3.55 (m, 1H) H_5', 3.60 (s, 1H) H_{11}, 3.72 (m, 2H) CH_2NCO, 3.87 (q, 1H) H_2, 4.09 (s, 3H) CH_3O−Ar, 4.25 (d,1H) H_5, 4.30 (d, 1H) H_1', 4.96 (dd, 1H) H_{13}, [7.03 (d, 1H) H_7, 7.29 (d, 1H) H_3, 7.46 (t, 1H) H_6, 7.60 (dd, 1H) H_5, 8.80 (d, 1H) H_2, quinoline]. Anal. ($C_{45}H_{67}N_3O_{11}$) C, H, N.

11,12-Dideoxy-3-descladinosyl-6-*O*-methyl-3-oxo-12,11-(oxycarbonyl((4-(4-quinolinyl)butyl)imino))erythromycin (55). Yield: 26%. Mp: 170−172 °C. MS(SIMS): 796^+ (MH^+). ^{1}H NMR ($CDCl_3$): δ 0.82 (t, 3H) CH_3CH_2, 1.34 (s, 3H) 6-CH_3, 1.42 (s, 3H) 12-CH_3, 2.27 (s, 6H) N(CH_3)$_2$, 2.45 (m, 1H) H_3', 2.60 (m, 1H) H_8, 2.62 (s, 3H) 6-*O*-CH_3, 3.12 (m, 4H) H_4−H_{10} and CH_2−Ar, 3.19 (dd, 1H) H_2', 3.53 (m, 1H) H_5', 3.59 (s, 1H) H_{11}, 3.72 (m, 2H) CH_2NCO, 3.87 (q, 1H) H_2, 4.24 (d,1H) and 4.29 (d, 1H) H_1' and H_5, 4.95 (dd, 1H) H_{13}, [7.54 (dt, 1H) H_6, 7.68 (dt, 1H) H_7, 7.26 (d, 1H) H_3, 8.79 (d, 1H) H_2, 8.05 (dl, 1H) H_5, 8.09 (dl, 1H) H_8 quinoline]. Anal. ($C_{44}H_{65}N_3O_{10}$) C, H, N.

(10*R*)- and (10*S*)-11,12-Dideoxy-3-descladinosyl-6-*O*-methyl-3-oxo-12,11-(oxycarbonyl(hydrazono))erythromycin (56a,b). A solution of **44** (0.353 g, 0.5 mmol) and hydrazine hydrate (0.097 mL, 2 mmol) in 5 mL of CH_3CN and 0.5 mL of water was stirred at 60 °C for 3 h. The solution was diluted with water and extracted with ethyl acetate. The extracts were washed with water and brine and dried over $MgSO_4$. After evaporation to dryness, the product was purified by column chromatography eluting with 90:10:10 isopropyl ether/triethylamine/methanol to afford 0.101 g (32%) of **56a** and 0.106 g (34%) of **56b** as white crystals. **56a**: Mp: 240 °C. MS(FAB): 628^+ ($M + H^+$). ^{1}H NMR ($CDCl_3$): δ 0.86 (t, 3H) CH_3CH_2, 1.35 (s, 3H) 6-CH_3, 1.46 (s, 3H) 12-CH_3, 2.30 (s, 6H) N(CH_3)$_2$, 2.50 (m, 1H) H_3', 2.67 (m, 1H) H_8, 2.67 (s, 3H) 6-*O*-CH_3, 3.09 (m, 2H) H_4 and H_{10}, 3.21 (dd, 1H) H_2', 3.56 (m, 1H) H_5', 3.59 (s, 1H) H_{11}, 3.85 (q, 1H) H_2, 4.24 (d, 1H) H_5, 4.30 (d, 1H) H_1', 4.44 (s, 2H) NH_2, 5.03 (dd, 1H) H_{13}. Anal. ($C_{31}H_{53}N_3O_{10}$) C, H, N. **56b**: Mp: >260 °C. MS(FAB): 628^+ ($M + H^+$). ^{1}H NMR ($CDCl_3$): δ 0.87 (t, 3H) CH_3CH_2, 1.32 (s, 3H) 6-CH_3, 1.66 (s, 3H) 12-CH_3, 2.31 (s, 6H) N(CH_3)$_2$, 2.51 (m, 1H) H_3', 2.78 (m, 1H) H_8, 2.83 (s, 3H) 6-*O*-CH_3, 3.10 (m, 1H) H_4, 3.21 (dd, 1H) H_2', 3.46 (d, J = 3 Hz, 1H) H_{11}, 3.53 (m, 2H) H_{10} and H_5', 3.84 (s, 2H) NH_2,, 3.88 (q, 1H) H_2, 4.20 (d, 1H) H_5, 4.30 (d, 1H) H_1', 4.93 (dd, 1H) H_{13}. Anal. ($C_{31}H_{53}N_3O_{10}$) C, H, N.

11,12-Dideoxy-3-descladinosyl-6-*O*-methyl-3-oxo-12,11-(oxycarbonyl(2-(3-(4-quinolinyl)propyl)hydrazono))-erythromycin (61). A solution of **55a** (13 g, 20.7 mmol) and **68** (4.66 g, 25.2 mmol) in 130 mL of methanol and glacial acetic acid (4.8 mL, 83.9 mmol) was stirred for 20 h at room temperature under nitrogen atmosphere. Sodium cyanoborohydride (2.65 g, 42 mmol) was added, and the reaction was stirred for 4 additional hours. After evaporation of the solvent, the residue was taken up in ethyl acetate, washed with 1 N NaOH and brine, and dried over $MgSO_4$. After evaporation to dryness, the product was purified by column chromatography eluting with 97:3 ethyl acetate/triethylamine to afford a white foam further crystallized in a 2:3 ethyl acetate/isopropyl ether. The white crystals were filtered and washed with pure isopropyl ether to give after drying 12.85 g (78%) of **61** as white crystals. Mp: 183 °C. MS(FAB): 797^+ ($M + H^+$). ^{1}H NMR ($CDCl_3$): δ 0.82 (t, 3H) CH_3CH_2, 1.34 (s, 3H) 6-CH_3, 1.48 (s, 3H) 12-CH_3, 2.30 (s, 6H) N(CH_3)$_2$, 2.51 (m, 1H) H_3', 2.60−3.35 (m, 6H) H_8−$H_2'$and CH_2−Ar/CH_2NH, 2.65 (s, 3H) 6-*O*-CH_3, 3.06 (dq, 1H) H_4, 3.19 (q, 1H) H_{10}, 3.56 (m, 1H) H_5', 3.74 (s, 1H) H_{11}, 3.87 (q, 1H) H_2, 4.29 (d, 2H) H_1' and H_5, 5.01 (dd, 1H) H_{13}, 5.50 (t, 1H) CH_2NHNCO, [7.30 (t, 1H) H_3, 7.53 (dt, 1H) H_7, 7.68 (dt, 1H) H_6, 8.10 (m, 2H) H_5 and H_8, 8.79 (d, 1H) H_2, quinoline]. Anal. ($C_{43}H_{64}N_4O_{10}$) C, H, N.

For crystallographic study **61** was crystallized as follows. To a solution of **61** (0.1 g, 0.12 mmol) in 1 mL of methylene chloride was slowly added 20 mL of cyclohexane; the solution was allowed to stand at room temperature for 2 weeks. The white crystals were filtered off and dried to yield 59 mg of pure crystals of **61**.

Following the same procedures as described for **61** and starting from the appropriate aldehydes, the following compounds were made.

11,12-Dideoxy-3-descladinosyl-6-*O*-methyl-3-oxo-12,11-(oxycarbonyl(2-(3-phenylpropyl)hydrazono))erythromycin (57). Yield: 78%. MS(FAB): 746^+ ($M + H^+$). ^{1}H NMR ($CDCl_3$): δ 0.86 (t, 3H) CH_3CH_2, 1.34 (s, 3H) 6-CH_3, 1.47 (s, 3H) 12-CH_3, 2.27 (s, 6H) N(CH_3)$_2$, 2.45 (m, 1H) H_3', 2.64 (s, 3H) 6-*O*-CH_3, 2.72 (m, 2H) CH_2−Ar, 2.82 (t, 2H) CH_2NH, 3.07 (dq, 1H) H_4, 3.14 (m, 2H) H_{10} and H_2', 3.52 (m, 1H) H_5', 3.74 (s, 1H) H_{11}, 3.86 (q, 1H) H_2, 4.28 (m, 2H) H_1' and H_5, 5.03 (dd, 1H) H_{13}, 5.35 (tl, 1H) CH_2NHNCO, 7.13−7.28 (m, 5H) phenyl. Anal. ($C_{40}H_{63}N_3O_{10}$) C, H, N.

11,12-Dideoxy-3-descladinosyl-6-*O*-methyl-3-oxo-12,11-(oxycarbonyl(2-(3-(3-chlorophenyl)propyl)hydrazono))-erythromycin (58). Yield: 30%. MS(SIMS): 780^+ (MH^+). ^{1}H NMR ($CDCl_3$): δ 0.86 (t, 3H) CH_3CH_2, 1.35 (s, 3H) 6-CH_3, 1.47 (s, 3H) 12-CH_3, 1.83 (m, 2H) $CH_2CH_2CH_2$, 2.26 (s, 6H) N(CH_3)$_2$, 2.44 (m, 1H) H_3', 2.64 (s, 3H) 6-*O*-CH_3, 2.70−2.79 (m, 5H) H_8 and CH_2−Ar and CH_2NH, 3.04 (m, 1H) H_4, 3.17 (m, 2H) H_{10} and H_2', 3.54 (m, 1H) H_5', 3.73 (s, 1H) H_{11}, 3.87 (q, 1H) H_2, 4.28 (m, 2H) H_1' and H_5, 5.01 (dd, 1H) H_{13}, 5.36 (tl, 1H) CH_2NHNCO, 7.05−7.20 (m, 4H) phenyl. Anal. ($C_{40}H_{62}N_3ClO_{10}$) C, H, N, Cl.

11,12-Dideoxy-3-descladinosyl-6-*O*-methyl-3-oxo-12,11-(oxycarbonyl(2-(3-(6-methoxy-4-quinolinyl)propyl)hydrazono))erythromycin (59). Yield: 27%. MS(FAB): 833^+ ($M + Li^+$). ^{1}H NMR ($CDCl_3$): δ 0.83 (t, 3H) CH_3CH_2, 1.33 (s, 3H) 6-CH_3, 1.48 (s, 3H) 12-CH_3, 2.26 (s, 6H) N(CH_3)$_2$, 2.44 (m, 1H) H_3', 2.65 (m, 1H) H_8, 2.64 (s, 3H) 6-*O*-CH_3, 3.06 (dq, 1H) H_4, 2.85−3.3 (m, 6H) H_{10} and H_2' and CH_2−Ar/CH_2NH, 3.54 (m, 1H) H_5', 3.74 (s, 1H) H_{11}, 3.87 (q, 1H) H_2, 3.98 (s, 3H) CH_3O−Ar, 4.28 (m, 2H) H_1' and H_5, 5.02 (dd, 1H) H_{13}, 5.52 (tl, 1H) CH_2NHNCO, [7.23−7.35 (m, 3H) H_7−H_3−H_5, 7.99 (m, 1H) H_8, 8.65 (d, 1H) H_2, quinoline]. Anal. ($C_{44}H_{66}N_4O_{11}$) C, H, N.

11,12-Dideoxy-3-descladinosyl-6-*O*-methyl-3-oxo-12,11-(oxycarbonyl(2-(3-(8-methoxy-4-quinolinyl)propyl)hydrazono))erythromycin (60). Yield: 49%. MS(EI): 827^+ (M^+). ^{1}H NMR ($CDCl_3$): δ 0.82 (t, 3H) CH_3CH_2, 1.35 (s, 3H) 6-CH_3, 1.48 (s, 3H) 12-CH_3, 2.27 (s, 6H) N(CH_3)$_2$, 2.44 (m, 1H) H_3', 2.65 (m, 1H) H_8, 2.67 (s, 3H) 6-*O*-CH_3, 2.91 (m, 2H) H_{10} and H_2', 3.06 (dq, 1H) H_4, 3.1−3.3 (m, 4H) CH_2−Ar/CH_2NH, 3.55 (m, 1H) H_5', 3.75 (s, 1H) H_{11}, 3.88 (q, 1H) H_2, 4. 08 (s, 3H) CH_3O−Ar, 4.28 (m, 2H) H_1' and H_5, 5.01 (dd, 1H) H_{13}, 5.49 (t, 1H) CH_2NHNCO, [7.03 (d, 1H) H_7, 7.32 (d, 1H) H_3, 7.45 (t,1H) H_6, 7.66 (d, 1H) H_5, 8.80 (d, 1H) H_2, quinoline]. Anal. ($C_{44}H_{66}N_4O_{11}$) C, H, N.

4-(4-Quinolinyl)butylamine (65). Stage A: To a stirred solution of 4-quinolinecarboxaldehyde (4.71 g, 30 mmol) and 3-phthalimidopropyltriphenylphosphonium bromide (15.9 g, 30 mmol) in 150 mL of dry THF, under nitrogen atmosphere at −55 °C, was added potassium *tert*-butoxide (3.37 g, 30 mmol). The reaction mixture was allowed to stand at 10 °C in 4 h, and the mixture was poured into 250 mL of water. After extraction with ethyl acetate, washing with water, drying over $MgSO_4$, and evaporation to dryness, the oily residue was purified by column chromatography eluting with 98:2 ethyl acetate/hexane to afford 4.99 g (50%) of 4-(4-quinolinyl)butyl-3-enephthalimide as uncolored crystals. Mp: 110−112 °C. ^{1}H NMR ($CDCl_3$): δ 2.60−2.77 (m, 2H) =CH-CH_2, 3.78−3.95 (t, 2H) CH_2NHCO, 6.10−6.42 (dt, J = 11.5 and 7.5 Hz, 1H) =CH-CH_2, 6.937.09 (dl, 1H) =CH-quinoline, [7.17−7.38 (d, J = 3.5 Hz, 1H) H_3, 7.29−8.08 (m, 4H) H_6H_7−H_5−H_8, 8.82−8.83 (d, J = 3.5 Hz, 1H) H_2, quinoline].

Stage B: (*Z*)-4-(4-Quinolinyl)butyl-3-enamine. To a solution of 4-(4-quinolinyl)butyl-3-enephthalimide (3.94 g, 12 mmol) in 120 mL of ethanol was added hydrazine hydrate (1.15 mL, 24 mmol). The solution was stirred at reflux for 12 h and was concentrated in vacuo. The residue was taken up with 30 mL of 2 N NaOH and water and was extracted with ethyl acetate. After washing with water and brine, drying over $MgSO_4$, and evaporation to dryness, the residue was purified by column chromatography eluting with 90:10:0.02 methylene

chloride/methanol/ammonium hydroxide to afford 1.1 g (46%) of the desired amine (*Z*)-4-(4-quinolinyl)butyl-3-enamine. ^{1}H NMR ($CDCl_3$): δ 1.59 (sl, 2H) NH_2, 2.32 (m, 2H) =CH−CH_2, 2.79 (t, 2H) CH_2NH_2, 6.08 (dt, J = 11.5 and 7.5 Hz, 1H) =*CH*-CH_2, 6.95 (d, J = 11.5 Hz, 1H) =CH-quinoline, [7.27 (d, J = 4 Hz, 1H) H_3, 7.55 and 7.72 (dt, 2H) H_6 and H_7, 7.99−8.12 (d, 2H) H_5 and H_8, 8.87 (d, J = 4 Hz, 1H) H_2, quinoline].

Stage C: 4-(4-Quinolinyl)butylamine (65). A solution of (*Z*)-4-(4-quinolinyl)butyl-3-enamine (1.1 g, 5.5 mmol) and 0.110 g of palladium on charcoal in 20 mL of methanol was stirred under 1.5 atm of hydrogen for 30 min. Filtration and evaporation to dryness afforded 1.07 g (97%) of the desired amine 4-(4-quinolinyl)butylamine. ^{1}H NMR ($CDCl_3$): δ 1.31 (sl, 2H) NH_2, 1.59−1.82 (m, 4H) CH_2CH_2, 2.76 (t, 2H) CH_2-NH_2, 3.10 (t, 2H) CH_2-quinoline, [7.24 (d, J = 4.5 Hz, 1H) H3, 7.56 and 7.77 (dt, 2H) H_6 and H_7, 8.04−8.12 (d, J = 8.5 Hz, 2H) H_5 and H_8, 8.81 (d, J = 4 Hz, 1H) H_2, quinoline].

Following the same procedure as for **65** and starting with the appropriate aldehydes, the following amines were made.

4-(3-Chlorophenyl)butylamine Chlorhydrate (62). Yield: 41% (3 steps). Mp: 100−102 °C. ^{1}H NMR (DMSO-d_6): δ 1.59 (m, 4H) CH_2CH_2, 2.61 (t, 2H) $CH_2\Phi$, 2.78 (t, 2H) CH_2NH_2, 7.15−7.45 (m, 4H) phenyl, 7.99 (sl, 3H) NH_3^+.

4-(4-(6-Methoxyquinolinyl))butylamine (63). Yield: 33% (3 steps). ^{1}H NMR ($CDCl_3$): δ 1.35 (sl, 2H) NH_2, 1.61−1.83 (m, 4H) CH_2CH_2, 2.77 (t, 2H) CH_2NH_2, 3.04 (t, 2H) CH_2-quinoline, 3.95 (s, 3H) CH_3O, [7.19 (d, 1H) H_3, 7.25 and 7.35 (d, 2H) H_7 and H_5, 8.02 (d, 1H) H_8, 8.67 (d, 1H) H_2, quinoline].

4-(4-(8-Methoxyquinolinyl))butylamine (64). Yield: 46% (3 steps). ^{1}H NMR ($CDCl_3$): δ 1.58−1.80 (m, 4H) CH_2CH_2, 2.75 (t, 2H) CH_2NH_2, 3.06 (t, 2H) CH_2-quinoline, 4.09 (s, 3H) CH_3O, [7.04 (d, 1H) H_7, 7.25 (d, 1H) H_3, 7.47 (t, 1H) H_6, 7.60 (dl, 1H) H_5, 8.82 (d, 1H) H_2, quinoline].

3-(4-Quinolinyl)propanal (68). Stage A: To a stirred solution of 4-quinolinecarboxaldehyde (3.15 g, 20 mmol) and ((1,3-dioxolan-2-yl)methyl)triphenylphosphonium bromide (8.6 g, 20 mmol) in 50 mL of dry THF, under nitrogen atmosphere at −35 °C, was added potassium *tert*-butoxide (2.5 g, 25 mmol). The reaction mixture stirred for 1 h at −35 °C and then was allowed to stand at 10 °C in 3 h. The mixture was poured into 50 mL of ice/water. After extraction with methylene chloride, washing with water, drying over $MgSO_4$, and evaporation to dryness, the brown oily residue was triturated with a 3:7 ether/pentane mixture to afford after filtration and washing 4.32 g (95%) of (*E*,*Z*)-4-((1,3-dioxolan-2-yl)ethylene)-quinoline as a yellow solid. ^{1}H NMR ($CDCl_3$): δ 3.87−4.07 (m, 4H) CH_2CH_2, 5.30−5.88 (d, J = 8 Hz and J = 5.5 Hz, 1H) −OCHO-, 6.08−6.40 (dd, [J = 8 and 11.5 Hz, AZ] and [J = 5.5 and 16 Hz, ΔE], 2H) CH=CH, [7.25−8.15 (m, 5H) H_7−H_3−H_6H_5−H_8, 8.89 (d, lH) H_2, quinoline].

Stage B: A solution of (*E*,*Z*)-4-((1,3-dioxolan-2-yl)ethylene)-quinoline (4.3 g, 19 mmol) and 0.215 g of palladium on charcoal in 40 mL of methanol was stirred under 1.5 atm of hydrogen for 2 h. Filtration and evaporation to dryness afforded 4.2 g (97%) of the desired 4-((1,3-dioxolan-2-yl)ethyl)quinoline as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 2.13 (m, 2H) CH_2CHO, 3.93−4.04 (m, 4H) CH_2CH_2, 5.01 (m, 1H) −OCHO, 3.22 (t, 2H) CH_2-quinoline, [7.27 (d, 1H) H_3, 7.57−7.71 (m, 2H) H_7−H_6, 8.10 (m, 2H) H_5−H_8, 8.81 (d, 1H) H_2, quinoline].

Stage C: A solution of 4-((1,3-dioxolan-2-yl)ethyl)quinoline (4.2 g, 18 mmol) in 70 mL of acetone and 70 mL of 2 N HCl was stirred at 40 °C for 4 h under nitrogen atmosphere. The acetone was evaporated off, and the pH was adjusted to 9 with aqueous ammonium hydroxide. The solution was extracted with ethyl acetate, and the extracts were washed with brine, dried over $MgSO_4$, filtered, and evaporated to dryness. The oily residue was purified by column chromatography eluting with 6:4 ethyl acetate/hexane to afford after evaporation of the solvents 1.36 g (37%) of **67** as an oil. ^{1}H NMR ($CDCl_3$): δ 2.96 (t, 2H) CH_2CHO, 3.42 (t, 2H) CH_2-quinoline, [7.25 (d, J = 4.5 Hz, 1H) H_3, 7.59−7.73 (m, 2H) H_7−H_6, 8.00−8.14 (m, 2H) H_5−H_8, 8.82 (d, J = 4.5 Hz, 1H) H_2, quinoline], 9.89 (s, 1H) CHO.

Following the same procedure as for **68** and starting with the appropriate aldehydes, the following aldehydes were made.

3-(4-(6-Methoxyquinolinyl))propanal (66). Yield: 66%. ^{1}H NMR ($CDCl_3$): δ 2.97 (tl, 2H) CH_2CHO, 3.36 (t, 2H) CH_2-quinoline, 3.95 (s, 3H) O−CH_3, [7.20 (dd, J = 1 and 4 Hz, 2H) H_5−H_3, 7.38 (dd, J = 9 and 3 Hz, 1H) H_7, 8.03 (d, J = 9 Hz, 1H) H_8, 8.68 (d, J = 4.5 Hz, 1H) H_2, quinoline], 9.91 (t, 1H) CHO.

3-(4-(8-Methoxyquinolinyl))propanal (67). Yield: 26%. ^{1}H NMR ($CDCl_3$): δ 2.95 (t, 2H) CH_2CHO, 3.40 (t, 2H) CH_2-quinoline, 4.09 (s, 3H) O−CH_3, [7.08 (m, 1H) H3, 7.29−7.45−7.55 (m+d, 3H) H_5−H_7−H_6, 8.83 (d, J = 4.5 Hz, 1H) H_2, quinoline], 9.88 (t, 1H) CHO.

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Supporting Information Available: Complete crystallographic data, atomic coordinates, anisotropic thermal parameters, bond lengths, and bond angles of **61** (9 pages). Ordering information is given on any current masthead page.

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