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Synthesis and Structure−Activity Relationships of Novel 8a-Aza-8a-homoerythromycin A Ketolides

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A series of novel 6-O-substituted 8a-aza-8a-homoerythromycin A ketolides was synthesized and evaluated for in vitro antibacterial activity. Key strategic elements of the synthesis include the base-induced *E*−*Z* isomerization of 3-*O*-descladinosyl-6-*O*-allylerythromycin A 9(*E*)-oxime followed by ring-expanding reaction of the resulting 9(*Z*)-oxime via Beckmann rearrangement. The ketolides showed potent activity against a variety of erythromycin-susceptible and macrolide−lincosamide−streptogramin B (MLS_B) resistant Gram-positive and fastidious Gram-negative pathogens. The best compounds in this series overcome all types of resistance in relevant clinical Gram-positive pathogens and display in vitro activity comparable to telithromycin and cethromycin.

Introduction

The development of bacterial resistance to currently available antibacterial agents is a growing global health problem. Of particular concern are infections caused by multidrug-resistant Gram-positive pathogens especially by *Streptococcus pneumoniae*, which is one of the most common and also most problematic respiratory pathogen.[1] Until the 1990s, *S. pneumoniae* was readily treatable with a variety of older and inexpensive antibiotics. Following at least two individual outbreaks of penicillin-resistant *S. pneumoniae*, the resistant forms of the pathogen have persisted worldwide and have acquired resistance to other antibiotic classes. Today multidrug-resistant *S. pneumoniae* is a major problem in the Pacific Rim countries and is becoming a significant problem for physicians in the United States and parts of Europe.[2] A recent surveillance study indicated that among 1601 clinical isolates of *S. pneumoniae* collected in 34 U.S. medical centers, 29.5% were penicillin-resistant, 19.3% were erythromycin-resistant, and 13.2% were tetracycline-resistant.[3] Other macrolides such as clarithromycin (**2**) and azithromycin (**3**) showed a similar level of resistance compared with erythromycin A (**1**) (Figure 1).[4] These studies clearly indicated a continuing medical need for new antibacterial drugs that could overcome macrolide resistance to currently available antibiotics while maintaining all the activity and safety attributes characteristic of this class. One such new drug is telithromycin (**4**), formerly known as HMR 3647, a member of a new family of macrolide antibacterial agents, the ketolides (Figure 1).[5] Ketolides are derived from 14-membered macrolide erythromycin A but differ from this and other macrolides by having a carbonyl group at position C-3 of the macrolactone ring instead of the sugar L-cladinose. In addition, **4** possesses a C(11)−C(12) carbamate side chain, which is linked via a butyl group to imidazolyl and pyridinyl rings.

A series of C(11)−C(12) cyclic carbamate ketolides with an allyl heteroaryl side chain attached to the C-6 hydroxyl group of erythromycin A was synthesized in Abbott Laboratories, of which cethromycin (**5**) was selected for clinical development (Figure 1).[6] Both **4** and **5** demonstrated enhanced antibacterial activity against respiratory pathogens and most importantly against strains resistant to commonly used macrolides. These results subsequently generated great interest in the macrolide field, which was further fueled by the rapid development of antibiotic resistance. Thus far, several novel macrolide series have been developed based on the ketolide platform.[7] Furthermore, it has been proven that the C-11,C-12 cyclic carbamate present in **4** and **5** can be replaced by properly functionalized C-11,C-12 α-amino lactone ring. This type of modification led to a novel GlaxoSmithKline lead series[8] exemplified by GW773546X (**6**) (Figure 1). Recent studies in this area have unveiled a novel series of orally active C-6 substituted carbamate ketolides based on 14-membered erythromycin A (Ery A[a]) scaffold.[9] The most promising analogues within this series, **7** and **8**, were found to provide good oral activity in mice that was essentially equivalent to that of **4** (Figure 1).

Structural modification of Ery A is still considered to be one of the most effective approaches for producing macrolide antibiotics having novel characteristics. The chemistry performed on Ery A in the past can be divided into two main categories: (1) modification of peripheral substituents on the macrolide nucleus and (2) transformation affecting the aglycon scaffold, which is expected to lead to significant biological improvements. From the synthetic point of view, the latter approach is considered to be more challenging but often results in a decrease or loss of antibacterial activity. Only a limited number of such approaches were successful, exemplified by the azalides (e.g., azithromycin).[10] In the course of our exploratory investigation on macrolides, we were attracted to this later approach and set out to find a route to a new nucleus.

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[a] Abbreviations: Ery A, erythromycin A; PyHCl, pyridinium hydrochloride; TMSCl, trimethylsilyl chloride; TMSIm, trimethylsilylimidazole; MLS_B, macrolide−lincosamide−streptogramin B.

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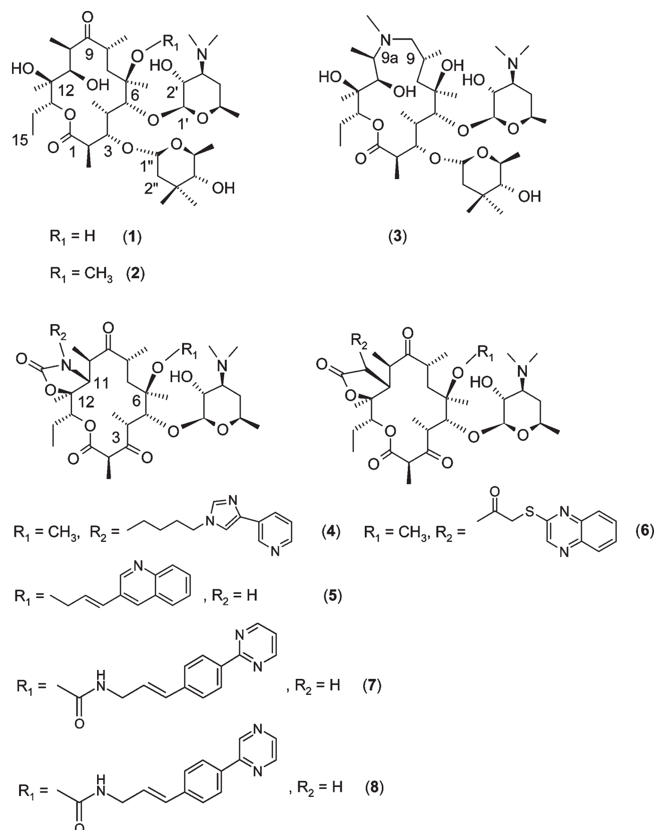
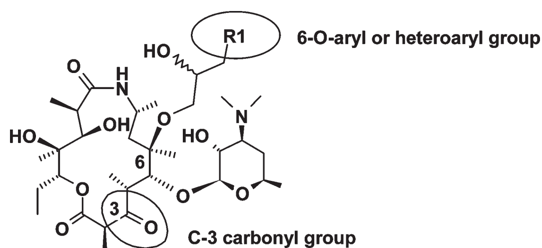


Figure 1. Structures and numbering scheme of the macrolide antibiotics erythromycin A (**1**), clarithromycin (**2**), and azithromycin (**3**). Novel ketolides based on erythromycin A and clarithromycin scaffold include telithromycin (**4**), cethromycin (**5**), GW773546X (**6**), JNJ-17069546 (**7**), and JNJ-17070885 (**8**).

Chart 1. Structural Features Included in the Design of Novel 15-Membered Macrolides



This led us to try modifications of the framework of Ery A derivatives. Our efforts led to the establishment of a synthetic route to a novel series of 15-membered 8a-aza-8a-homoerythromycin ketolides. The synthesis of ketolides based on a 15-membered ring azahomoerythromycin A skeleton represents a logical extension of the success of 14-membered ring ketolides.[11] However, in contrast to 14-membered ketolides the structure–activity relationships of their corresponding 15-membered analogues have been relatively unexplored.[12]

In this paper, we describe the work leading to the discovery of 15-membered ring ketolides as a new class of macrolide antibiotics and, in particular, the synthesis of a series of novel 6-O-substituted 8a-azahomoerythromycin A ketolides and their antibacterial activity against some key erythromycin-resistant pathogens. Structural features that guided our design of novel macrolides included (1) a properly attached and oriented aryl or heteroaryl group for improving activity against MLS_B resistance and (2) a ketolide backbone for improving potency and activity against efflux resistance (Chart 1).

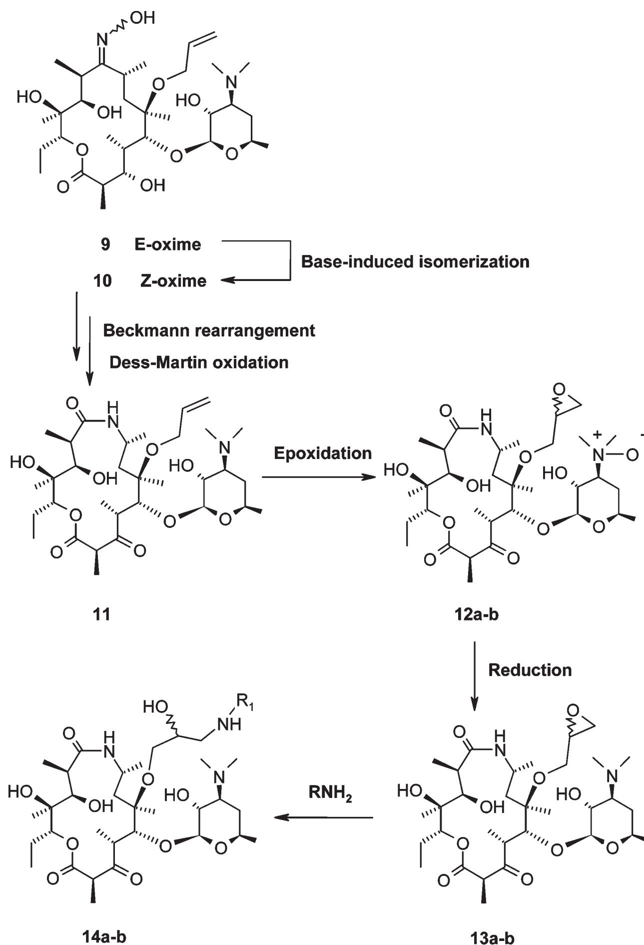


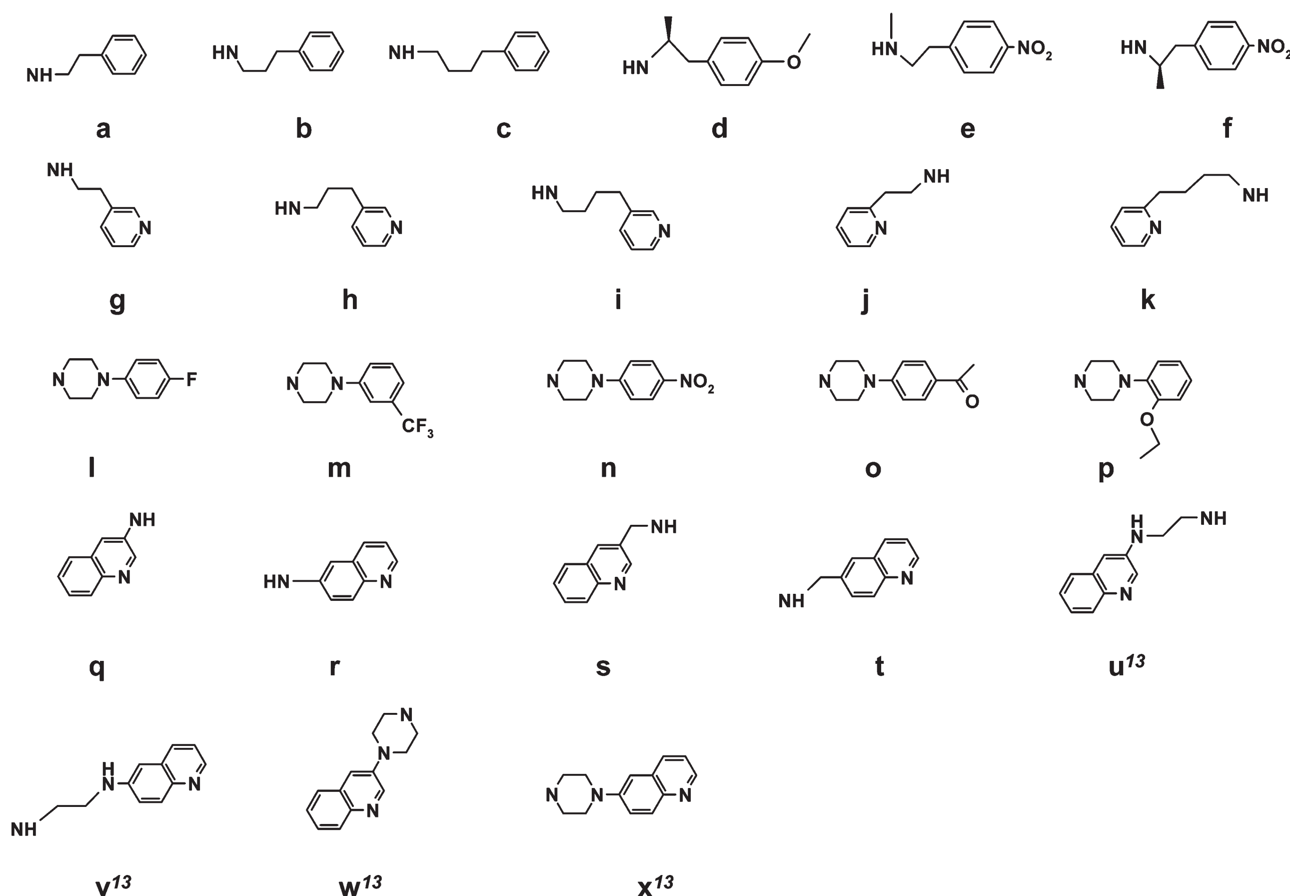
Figure 2. Synthesis of 6-O-substituted 8a-aza-8a-homoEry A ketolides via *E*–*Z* isomerization–Beckmann rearrangement methodology.

Chemistry

We have developed highly efficient and versatile synthetic process to access a wide range of 15-membered 8a-aza-8a-homoerythromycin A analogues. Our strategy for synthesizing the 6-O-substituted 8a-aza-8a-homoerythromycin A ketolide analogues was planned to involve a ring expanding reaction via Beckmann rearrangement of the 14-membered erythromycin A *Z*-oxime **10**. The general method used to prepare 6-O-substituted 8a-aza-8a-homoerythromycin A derivatives, illustrated in Figure 2, involved the *E*–*Z* isomerization–Beckmann rearrangement methodology as a key strategic element of the synthesis.

Base-induced isomerization of 3-*O*-descladinosyl-6-*O*-allyl-erythromycin 9(*E*)-oxime (**9**) to 9(*Z*)-oxime (**10**) followed by Beckmann rearrangement and Dess–Martin oxidation of the C-3 hydroxyl group afforded the 15-membered 8a-aza-8a-homoerythromycin ketolide (**11**). The crucial key intermediate **11** thus obtained allowed a smooth modification of the allyl substituent at the C-6 position. The target epoxides **13a**,**b** were prepared by *m*-CPBA oxidation of 6-*O*-allyl-8a-aza-8a-homoerythromycin derivative **11** followed by zinc reduction of the *N*-oxide group in **12a**,**b**. The terminal epoxides **13a**,**b** were subjected to nucleophilic ring opening with selected

Chart 2. Amines Employed as the R_1 Substituent in Ketolide Series



amines (Chart 2) to give a mixture of diastereoisomeric β-amino alcohols **14a**,**b**. The amines, which were not commercially available, were prepared by literature methods[13] as designated.

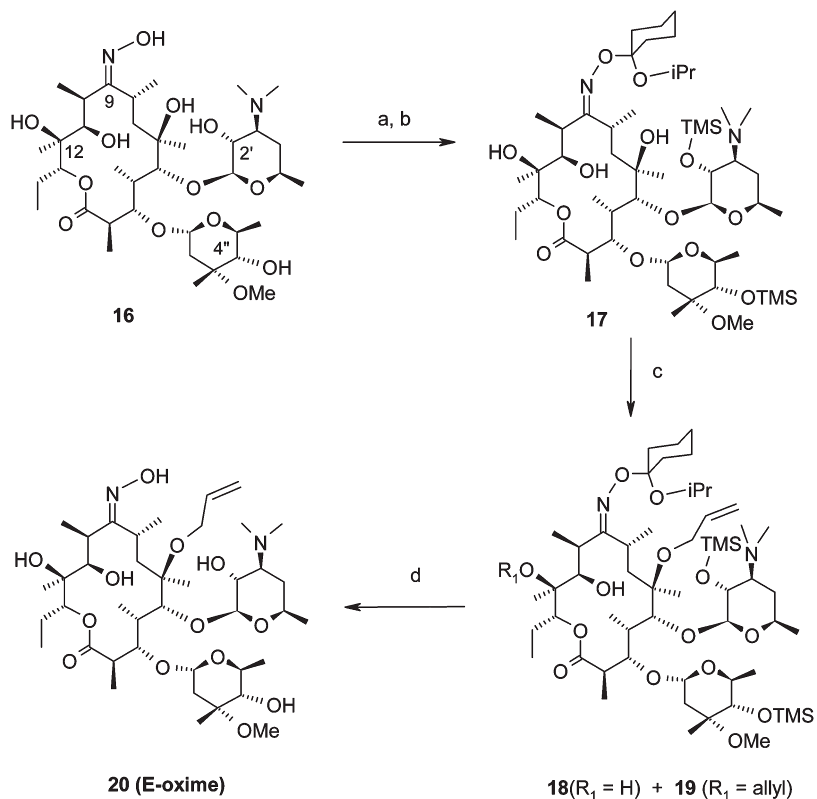
Starting from readily available oxime precursors, the method provides an easy access to a variety of novel 8a-azahomo Ery A analogues having various groups tethered to the C-6 position of the ketolide skeleton. Moreover, the method is of additional interest, as it has been demonstrated that the aromatic and heteroaromatic moieties attached at the C-6 position of the ketolide core through an ether linkage strongly increase antibacterial activity against the susceptible erythromycin and most importantly against the strains containing erm(B)-encoded ribosomal methylase constitutively resistant to Ery A.[14]

The synthesis of these analogues can be divided into a four-step sequence: (a) introduction of the 6-*O*-allyl group onto the erythromycin A scaffold (Scheme 1); (b) base-induced isomerization of 3-*O*-descladinosyl-6-*O*-allylerythromycin A 9(*E*)-oxime (**9**) to the corresponding 9(*Z*)-oxime (**10**) followed by Beckmann rearangement to 3-*O*-descladinosyl 8a-lactam (**15**) (Scheme 2); (c) conversion to the 3-keto group (Scheme 3); (d) further synthetic modification of the 6-*O*-allyl group (Scheme 4). Following a modification of the communicated protocols, 6-*O*-allylerythromycin A 9(*E*)-oxime (**20**) was prepared as shown in Scheme 1.[6,15] Oxime **20** was prepared starting from commercially available erythromycin A 9(*E*)-oxime (**16**)[16] which was first protected as 9-ketaloxime-2′,4″-bis(trimethylsilyl)erythromycin A (**17**). Selective alkylation of suitably protected oxime **17** with allyl bromide in the presence of potassium hydroxide in dry DMF afforded 6-*O*-allyl derivative **18** in 70% isolated yield. When the reaction was conducted for an extended period of time, usually 5 h, up to 10% of 6,12-di-*O*-allyl derivative **19** was also observed according to LC/MS analysis of the crude reaction mixture. Finally, removal of the trimethylsilyl and ketal protecting groups from **18** was accomplished by exposure to formic acid, furnishing after flash column chromatography the pure 9(*E*)-oxime **20** (90% yield).[17] In the later stage our standard working procedure actually omitted the purification step because in most of the cases the crude reaction mixture was used in the next step. Selective cleavage of the L-cladinose sugar was accomplished by treating an ethanolic solution of **20** with 2 M HCl for 12 h at room temperature. The cladinose-related byproduct was removed in the aqueous workup, whereas epimeric 3-*O*-descladinosyl-6-*O*-allylerythromycin 9(*E*)-oxime (**9**) was advanced into the next step without further purification.

Base-induced isomerization of **9** proceeded smoothly to afford the corresponding epimeric oxime **10** of predominantly *Z* stereochemistry (9:1 epimeric mixture of *Z*/*E* oximes) in 70% yield over two steps. Before base-induced isomerization was established the main drawback associated with the synthesis of 3-*O*-descladinosyl-6-*O*-allyl-8a-aza-8a-homoerythromycin (**15**) was essentially in a very tedious and time-consuming procedure for the preparation of *Z* oxime **10**. Nevertheless, this drawback could be easily circumvented by treatment of **9** with 4 mol equiv of lithium hydroxide monohydrate in ethanol, a process that generated a 9:1 mixture of *Z*/*E* oximes isomeric at the C-9 position in 90% yield.

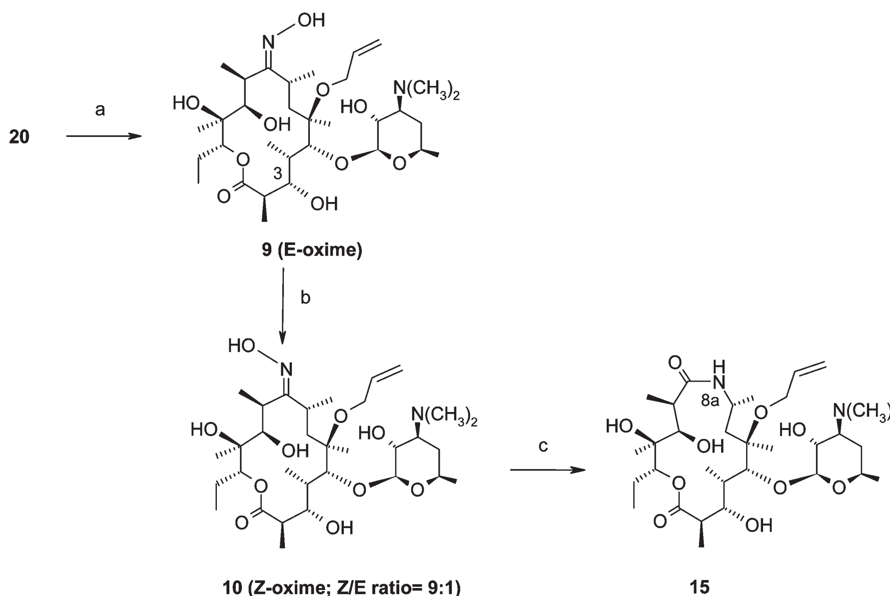
The *Z*-isomer **10** was isolated in an essentially pure form by recrystallization from methanol in 85% yield. Oxime **10** was

Scheme 1. Synthesis of 6-*O*-AllylEry A 9(*E*)-Oxime (**20**)[a]



[a] Reagents and conditions: (a) diisopropoxycyclohexane, PyHCl, CH_2Cl_2, 90%; (b) TMSCl, TMSIm, CH_2Cl_2, 85%; (c) allyl bromide, KOH, DMF, 70%; (d) HCO_2H, EtOH/H_2O (1:1), 90%.

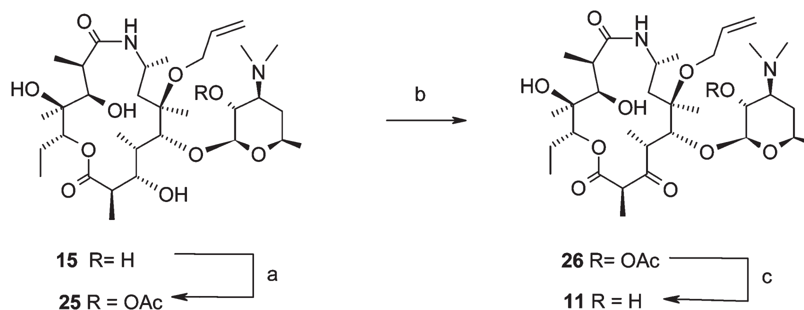
Scheme 2. Base-Induced Isomerization and Beckmann Rearrangement of 3-*O*-Descladinosyl-6-*O*-allylEry A 9(*Z*)-Oxime (**10**)[a]



[a] Reagents and conditions: (a) HCl, EtOH/H_2O (2:1), 90%; (b) LiOH·H_2O, EtOH, 80%; (c) *p*-TsCl, $NaHCO_3$, acetone/H_2O (1:2), 90%.

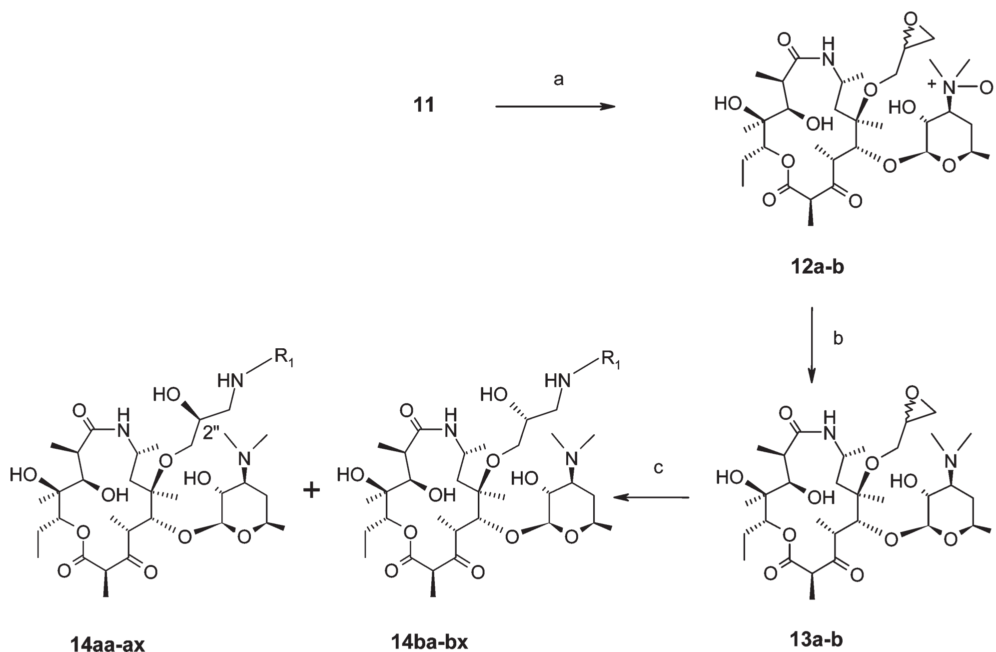
stable to isomerization as a crystalline solid, but in solution it slowly equilibrated to the *E*-isomer **9**. When **10** was subjected to acidic conditions, an approximate 9:1 mixture of isomeric oximes was reestablished, favoring the thermodynamically more stable 9(*E*)-isomer. The configuration of oximes **9** and **10** was determined unambiguously on the basis of their characteristic ^{1}H and ^{13}C chemical shifts of the α-carbon atoms (C-8 and C-10) and chemical shifts of their respective 8-Me and 10-Me groups. As shown in Table 1, NMR spectra of the *E*-oximes in the cladinosyl series (**20** and **22**) showed that the signal attributed to H-8 revealed a characteristic downfield shift (3.83 and 3.75 ppm) resulting from the deshielding effect of the cis-substituted oxime's hydroxyl group. On the other hand the upfield shifts seen for the 8-Me (1.01 and 1.00 ppm) and C-8 (26.6 and 24.9 ppm) resonances can be attributed to the shielding effect due to steric interactions with

Scheme 3. Dess−Martin Oxidation of 3-*O*-Descladinosyl-6-*O*-allyl-8a-aza-8a-homoEry A (**15**)[a]



[a] Reagents and conditions: (a) Ac_2O, Et_3N, CH_2Cl_2, 90%; (b) Dess−Martin periodinane, pyridine, $NaHCO_3$, CH_2Cl_2, 90%; (c) MeOH, reflux, 90%.

Scheme 4. Synthesis and Nucleophilic Ring-Opening of Terminal Epoxides **13a**,**b** with Selected Amines[a]



[a] Reagents and conditions: (a) *m*-CPBA, NaOAc, CH_2Cl_2, 60% or dimethyldioxirane, acetone, 65%; (b) Zn powder, NH_4Cl, EtOH/H_2O (2:1), pH 5, 68%; (c) R_1NH_2, $LiClO_4$, 2-PrOH, 50−80%.

Table 1. ^{1}H and ^{13}C Chemical Shifts for Descladinosyl-6-*O*-allyl Ery A Oximes (**9** and **10**), 6-*O*-Allyl Ery A Oximes (**20** and **21**[a]), and 6-*O*-Methyl Ery A Oximes (**22** and **23**[b])[c]

	^{1}H NMR ($CDCl_3$)				^{13}C NMR ($CDCl_3$)[d]			
oxime	H-8	H-10	8-Me	10-Me	C-8	C-10	8-Me	10-Me
9	3.79	2.61	0.99	1.14	25.4 (29.7)	33.2 (32.5)	18.6 (18.6)	15.1 (14.6)
10	4.29	2.08	1.01	1.12	32.1 (36.3)	29.0 (34.5)	18.1 (19.4)	15.3 (10.4)
20	3.83	2.70	1.01	1.16	26.6	34.2	19.6	15.6
6-*O*-allyl Ery A 9(*Z*)-oxime (**21**)	2.79	2.33	1.07	1.31	37.6	35.5	21.0	11.8
6-*O*-Me Ery A 9(*E*)-oxime (**22**)	3.75	2.65	1.00	1.13	24.9	32.3	18.2	14.6
6-*O*-Me Ery A 9(*Z*)-oxime (**23**)	2.74	2.57	1.06	1.32	35.6	34.1	19.6	10.7

[a] Oxime **21** was prepared according to the experimental procedure described in the Supporting Information. [b] Clarithromycin oximes **22** and **23** were prepared according to literature procedure; see ref 20c. [c] The chemical shifts are in ppm downfield from TMS. The NMR assignements shown were corroborated by ^{1}H−^{1}H and ^{1}H−^{13}C 2D experiments (COSY, HSQC, and HMBC). [d] The ^{13}C NMR spectra of oximes **9** and **10** were also recorded in CD_3OD, and their corresponding chemical shifts are shown in parentheses.

the cis hydroxyl group. These results are entirely consistent with those reported by McGill et al.[18a] and Gasc et al.[20a] When the ^{13}C NMR spectra of oximes in the cladinosyl and descladinosyl series (**9**, **10**, **20**, **21**, **22**, and **23**) were compared, some regular trends could be observed (see Table 1), among which we highlight the expected fact that the δC values of methyne groups (C-8 and C-10) *anti* to the oxime group are always higher than those of the corresponding *syn* groups, as to the known effect of steric compression.[18b] The same regularity was also noticed with the δC values of methyl groups (8-Me and 10-Me), however, only in the *Z*-oximes of both series (**10**, **21**, and **23**).

The chemical shift of the 10-Me group for (*E*)-**20** and (*E*)-**22** appears at 15.6 and 14.6 ppm, respectively, whereas the congested 10-Me group of the *Z*-oximes **21** and **23** appears at 11.8 and 10.7 ppm. The chemical shifts of descladinosyl

E-oxime **9** were almost identical in comparison with their respective δC and δH values of methyl and methyne groups in the cladinosyl *E*-oxime **20**. On the other hand, the deshielding of the H-8 (δ 4.29) in the *Z*-oxime derivative **10** is accompanied by shielding of the H-10 (δ 2.08) in comparison with the respective hydrogens in the *Z*-oxime **21** (δ 2.79 and 2.33, respectively). These differences in the chemical shifts followed the same trend and were also observed in the ^{13}C NMR spectra of **10** and **21**, particularly in the δC values of methyne groups (C-8 and C-10).[18c] Generally the chemical shift changes upon *E*−*Z* isomerization are quite local, and so we conclude that *E*−*Z* isomerization of the 9(*E*)-oxime **9** introduces a rather substantial alteration in the conformation.

It is interesting to note that in contrast to ready isomerization of **9**, neither 6-*O*-allylerythromycin A 9(*E*)-oxime (**20**) nor 3-*O*-descladinosyl-6,12-di-*O*-allylerythromycin A 9(*E*)-oxime (**24**)[19] participates in an efficient isomerization reaction. While literature precedents exist for the base-catalyzed isomerization of the *E*-oxime to the *Z*-oxime in the erythromycin A series, the same transformation failed when we tried to apply it to the clarithromycin series.[20] To the best of our knowledge, the base-catalyzed isomerization of **9** represents the only synthetically viable approach to 6-*O*-allyl-8a-aza-8a-homoEry A scaffold (**15**).[21] Therefore, lithium hydroxide induced isomerization of **9** enabled us to prepare a sizable amount of **10** for subsequent Beckmann rearrangement studies. Although the synthesis of **10** described in the Experimental Section is on a relatively small scale (~250 mg), the procedure was also found to be suitable for a larger batch synthesis (10−50 g). Beckmann rearrangement of 3-*O*-descladinosyl-6-*O*-allylerythromycin A 9(*Z*)-oxime (**10**) with *p*-tosyl chloride and sodium bicarbonate in aqueous acetone afforded 15-membered 8a-lactam **15** in 90% isolated yield (Scheme 2).[22]

As indicated in Scheme 3, selective protection of the C-2′-hydroxyl group in descladinosyl lactam **15** was accomplished by acylation with acetic anhydride and triethylamine at room temperature.

Oxidation of the C-3 hydroxyl group with excess Dess−Martin periodinane[23] in the presence of pyridine and $NaHCO_3$ followed by deprotection of the C-2′-acetate **26** in refluxing methanol afforded ketolide **11** in 70% overall yield from **15**. This compound served as a key intermediate for the preparation of other analogues. Therefore, from 6-*O*-allyl-8a-aza-8a-homoerythromycin A ketolide (**11**), a series of ketolide analogues **14aa−ax** and **14ba−bx** were prepared through the epoxide intermediate **12a**,**b** (Scheme 4). Treatment of **11** with *m*-chloroperoxybenzoic acid (5 mol equiv) buffered with sodium acetate (2.1 mol equiv) using dichloromethane as solvent afforded *syn*-epoxy *N*-oxide **12a** and *anti*-epoxy *N*-oxide **12b** as a chromatographically inseparable mixture of isomers in 1:1 ratio according to HPLC/MS analysis.

The epoxidation of **11** was then effected using dimethyldioxirane, as it was felt that this more sterically sensitive oxidant would favor the formation of the sterically less hindered *syn*-epoxide **12a**. Thus, treatment of **11** with a solution of dimethyldioxirane[24] in acetone afforded epoxides **12a** and **12b** as a 4.4:1 mixture of isomers. As dimethyldioxirane is sensitive to steric factors, the oxygen is delivered primarily to the upper less hindered α-face of the olefin **11**, and this is reflected in the *syn*/*anti* epoxide product ratio of 4.4:1 compared to 1:1 using *m*-chloroperoxybenzoic acid. Reduction of the *N*-oxide functionality in **12a** and **12b** gave the target epoxides **13a** and **13b** as a 4.5:1 mixture of *syn*- and *anti*-isomers in 68% yield. This mixture was carried on to the following step without separation of the isomers. As it was demonstrated earlier[25] 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*, a strategy was put in place to quickly introduce several amines into the 6-*O*-propyl side chain of ketolides. Thus, after successful preparation of epoxides **13a** and **13b**, their subsequent amine opening to afford β-amino alcohols was investigated.

Nucleophilic ring opening of epoxy 8a-lactam **13a**,**b** with amines **a−x** (Chart 2) produced a mixture of diastereoisomeric β-amino alcohols **14aa−ax** and **14ba−bx** that were not easily separable by flash chromatography. Typically a 5-fold excess of amine and lithium perchlorate was used in this procedure and the reactions were carried out in refluxing 2-propanol.[26] In order to ascertain the importance of C-2″ hydroxyl stereochemistry on antibacterial activity of **14av** and **14bv**, it was necessary to prepare each diastereoisomeric β-amino alcohol in pure form. Therefore, the predominant *syn*-isomer **14av** was isolated by semipreparative HPLC and crystallization, whereas the isomeric *anti*-alcohol **14bv** was separated by semipreparative HPLC in small quantities.

Results and Discussion

The antibacterial activity of the 6-O-substituted ketoazalides was tested against a panel of representative pathogens selected from Pliva Research Institute culture collection. The in vitro antibacterial activities are reported as minimum inhibitory concentrations (MICs) that were determined by the agar microdilution method according to NCCLS standards.[27] Table 2 shows the in vitro activity of the ketoazalide analogues and the reference compounds azithromycin (**3**), telithromycin (**4**), and cethromycin (**5**).

In general, the ketolides were inactive against constitutively MLS_B-resistant strain of *Staphylococcus aureus* (MIC > 64 μg/mL). The most interesting feature of these new compounds was their effectiveness against inducibly MLS_B-resistant staphylococci and pneumococci as well as constitutively MLS_B-resistant pneumoccoci. Moreover, a few of them (**14ar−br**, **14av**, and **14bv**) were more potent than azithromycin against *H. influenzae* (Table 2).

Structure−Activity Relationships (SAR) of Aryl- and Heteroaryl Substituted 8a-Azaketolides. The 8a-azaketolide analogue **11**, which was a synthetic intermediate to the epoxides **12a**,**b** and **13a**,**b**, had only moderate activity against most of the organisms tested, with MIC values generally in the 1−16 μg/mL range. The diastereoisomeric epoxides, 6-*O*-(2-methyloxiranyl)-3-oxo-8a-aza-8a-homoEry A (**13a**,**b**), also had a moderate antibacterial activity against the Gram-positive organisms and were generally 4- to 64-fold less active than azithromycin (**3**). The epoxy *N*-oxides **12a**,**b** were essentially inactive with MIC values exceeding 64 μg/mL, indicating that the C-3′ dimethylamino group is a necessary requirement for potent antibacterial activity. Comparison of the antibacterial activity within the ketolide class of 8a-aza-8a-homoEry A with the macrolide standard azithromycin revealed some interesting features characteristic of the ketolides. In general, ketolides showed no decrease in activity against inducibly MLS_B-resistant *S. aureus* relative to the macrolide-susceptible strains whereas azithromycin showed a 64-fold decrease. This insensitivity of **14aa−ax** and **14ba−bx** to induction of resistance is a well-known characteristic of ketolides.[28] The introduction of an aryl or heteroaryl moiety to **14aa−ax** and **14ba−bx** resulted

Table 2. In Vitro Antibacterial Activity of Selected 6-O-Substituted 8a-aza-8a-homoEry A Ketolides[a]

	S. aureus				*S. pneumoniae*			*S. pyogenes*					
compd	B0329 Ery-S	B0538 iMLS	B0330 cMLS	B0331 M	B0541 Ery-S	B0627 cMLS	B0326 M	B0542 Ery-S	B0543 iMLS	B0544 cMLS	B0545 M	*M. catar.*[b] B0324	*H. inf.*[c] B0529
11	8	> 64	> 64	16	1	> 64	4	4	> 64	> 64	8	8	16
12a,b	> 64	> 64	> 64	> 64	> 64	> 64	> 64	> 64	> 64	> 64	> 64	> 64	> 64
13a,b	4	> 64	> 64	16	2	> 64	8	4	> 64	> 64	8	16	32
14aa−ba	4	16	> 64	8	0.25	8	16	0.5	1	16	1	0.5	16
14ab−bb	4	8	> 64	8	0.25	8	8	0.25	1	16	1	1	16
14ac−bc	2	2	> 64	2	≤0.125	1	4	0.25	0.5	8	0.5	≤0.125	8
14ad−bd	1	2	> 64	4	≤0.125	2	16	0.5	1	8	1	0.5	16
14ae−be	≤0.125	1	> 64	1	≤0.125	≤0.125	0.5	≤0.125	0.25	1	0.25	≤0.125	1
14af−bf	0.5	2	> 64	2	≤0.125	2	1	≤0.125	0.5	4	0.5	0.25	1
14ag−bg	4	8	> 64	4	0.5	2	8	0.25	4	32	2	1	8
14ah−bh	2	4	> 64	4	0.25	1	4	≤0.125	0.5	16	1	0.5	16
14ai−bi	0.5	1	> 64	1	≤0.125	0.5	1	≤0.125	≤0.125	4	0.5	≤0.125	2
14aj−bj	8	8	> 64	8	1	8	16	0.25	4	32	4	4	32
14ak−bk	1	4	> 64	2	≤0.125	2	4	0.25	0.5	32	1	≤0.125	4
14al−bl	4	16	> 64	16	0.5	32	16	≤0.125	4	> 64	4	4	32
14am−bm	4	4	> 64	4	0.5	16	4	≤0.125	4	16	2	1	16
14an−bn	1	2	> 64	2	≤0.125	4	2	0.25	2	8	1	0.5	8
14ao−bo	2	4	> 64	2	1	32	2	0.5	8	32	4	4	16
14ap−bp	2	2	> 64	4	0.5	16	8	≤0.125	8	16	4	2	32
14aq−bq	2	2	> 64	1	≤0.125	8	2	≤0.125	4	16	8	0.5	8
14ar−br	1	2	> 64	0.25	≤0.125	2	1	≤0.125	2	8	4	1	0.5
14as−bs	1	2	> 64	0.5	≤0.125	8	4	≤0.125	4	8	8	2	4
14at−bt	0.5	0.5	> 64	0.25	≤0.125	4	1	≤0.125	2	8	2	1	1
14au−bu	1	1	> 64	0.25	≤0.125	1	0.25	≤0.125	1	4	0.5	≤0.125	1
14av	≤0.125	0.25	> 64	0.25	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	1	0.5	≤0.125	0.25
14bv	≤0.125	0.25	> 64	0.5	≤0.125	0.5	0.25	≤0.125	0.5	4	0.5	0.5	0.5
14aw−bw	1	2	> 64	0.5	≤0.125	4	1	≤0.125	8	32	4	4	8
14ax−bx	0.25	0.25	> 64	2	≤0.125	1	0.5	≤0.125	0.25	4	2	1	2
3	1	> 64	> 64	> 64	≤0.125	> 64	4	≤0.125	8	> 64	1	0.25	1
4	≤0.125	0.5	> 64	0.25	≤0.06	≤0.125	0.5	≤0.06	≤0.06	4	0.25	≤0.125	1
5	≤0.06	0.25	> 64	0.25	≤0.06	≤0.125	≤0.06	≤0.06	≤0.06	1	≤0.125	≤0.125	1

[a] Minimum inhibitory concentration (MIC) values are given in μg/mL. All compounds except **14av** and **14bv** were tested as diastereoisomeric mixtures. For instance **14aa−ba** stands for diastereoisomeric mixture consisting of *syn*- and *anti*-β-amino alcohols **14aa** and **14ba**. Other analogues of the β-aminoalcohol series were denoted in the same way. Ery-S: erythromycin-susceptible strains. iMLS: inducibly resistant strains. cMLS: constitutively resistant strains. M: efflux-resistant strains. [b] *M. catarrhalis*. [c] *H. influenzae*.

in a dramatic increase of activity against resistant strains and *H. influenzae* simultaneously. With the exception of the constitutively MLS_B-resistant *S. aureus* all the MICs of **14aa−af** and **14ba−bf** against resistant strains irrespective of the phenotype were included between 0.125 and 16 μg/mL (MIC > 64 for azithromycin) and 1−16 μg/mL against *H. influenzae* (MIC = 1 for azithromycin). The nitrophenylethyl analogue **14ae−be** was the most potent compound evaluated within the aryl series, having MIC values of 1 μg/mL or lower for the majority of the Gram-positive organisms screened. Compounds **14ae−be** was particularly potent against the erm(B)-containing strain of *S.pneumoniae* B0627 with an MIC value of 0.125 μg/mL. The activity of the pyridinyl analogues **14ag−ak** and **14bg−bk** was found to depend markedly on the point of attachment of the aminoalkyl side chain on the pyridine ring. The activity of the 3-aminoethyl and 3-aminobutyl analogues **14ag−bg** and **14ai−bi** was in general 2- to 4-fold better than the corresponding 2-aminoalkyl substituted analogues **14aj−ak** and **14bj−bk** against most of the strains tested. The length of the side chain was also critical as shown by compounds **14ah−bh** and **14ai−bi** compared to **14ag−bg**. The ketolides with the butyl side chain **14ai−bi** exhibited the most potent activity within the pyridinyl substituted series. In comparison to phenyl analogues (**14aa−ac** and **14ba−bc**) the corresponding pyridinyl substituted analogues (**14ag−ak** and **14bg−bk**) were slightly more active against constitutively MLS_B-resistant *S. pneumoniae*. Furthermore, modification of the side chain attached to the aryl moiety had a significant effect on the antibacterial activity of the compounds tested. Analogues with the piperazinyl side chain (**14al−ap** and **14bl−bp**) were less active than the alkylamino analogues (**14aa−af** and **14ba−bf**), suggesting that steric bulk at this position might have a negative impact on the antibacterial activity. The same trend was observed when comparing the piperazinyl substituted quinolines **14aw−bw**, and **14ax−bx** to the ethylenediamino substituted analogues **14au−bu**, and **14av−bv**, respectively.

To further probe the SAR we prepared a series of ketolides in which a quinoline ring was appended to the macrolide core. To this end, quinolinyl analogues **14aq−ax** and **14bq−bx** were prepared and evaluated for in vitro antibacterial activity. It was found that the activity depends markedly on the point of attachment of the quinoline ring. The activity of the C-6 substituted quinolines **14ar−br**, **14at−bt**, and **14av−bv** was in general 2- to 4-fold better than that of the C-3 substituted analogues **14aq−bq**, **14as−bs**, and **14au−bu** against most strains. In addition, the design of a tether connecting the ketolide and quinoline substructures appeared to be critical for antibacterial activity. The piperazine-linked quinoline analogues **14aw−bw**, and **14ax−bx** were not as active as ketolides **14au−bu**, **14av**, and **14bv**, incorporating quinoline substructures linked via an ethylenediamino group. Notably, the activity against a variety of susceptible and

resistant Gram-positive and fastidious Gram-negative pathogens was markedly superior to that of azithromycin (**3**). In fact, the in vitro profile of **14av** (*syn*-**14v**) compares favorably with telithromycin (**4**) and cethromycin (**5**). For example, compound **14av** is ~4-fold more active than **4** against both constitutively MLS$_B$-resistant *S. pyogenes* and *H. influenzae* strain.

Conclusion

Novel 6-O-substituted 15-membered 8a-aza-8a-homoerythromycin A ketolides were synthesized and evaluated for in vitro antibacterial activity against a panel of representative erythromycin-susceptible and erythromycin-resistant test strains. Their in vitro antibacterial activity encompasses a large variety of clinically relevant susceptible bacteria and MLS$_B$-resistant Gram-positive and fastidious Gram-negative bacteria. Various 6-O-substituted side chains are tolerated and through their 3-D orientation influence the resulting antibacterial spectrum. The most active compound **14av** was as active as telithromycin and cethromycin and overcomes all types of resistance in relevant clinical Gram-positive pathogens. The brevity and conciseness of the synthesis as well as the excellent antibacterial activity of these molecules will hopefully expedite the biological evaluation of numerous analogues of the ketolide−quinoline series.

Experimental Section

Experimental Procedures. 6-*O*-Allyl-2′,4″-bis-*O*-trimethylsilylerythromycin A 9-[*O*-(1-Isopropoxycyclohexyl)oxime] (18). To a 0 °C solution of 2′,4″-bis-*O*-trimethylsilylerythromycin A 9-[*O*-(1-isopropoxycyclohexyl)oxime] (**17**) (15 g, 14.5 mmol), prepared according to the method of U.S. Patent No. 4,990,602 in 180 mL of DMF was added freshly distilled allyl bromide (7.5 mL, 87.1 mmol, 6 mol equiv). After approximately 5 min, potassium hydroxide (85% powder, 3.8 g, 58.1 mmol, 4 mol equiv) was added in small portions over 20 min. After the mixture was stirred for 2 h at room temperature, the reaction was quenched with 20% aqueous NaOH (200 mL), hexane (200 mL) was added, and the layers were separated. The aqueous layer was extracted with hexane (2 × 100 mL). The combined organic extracts were washed with brine (2 × 150 mL), dried over K_2CO_3, filtered, and concentrated in vacuo. The crude material was purified by column chromatography, eluting with 1% MeOH in methylene chloride containing 1% aqueous NH_3 to give 10.9 g (70%) of **18** as a white solid. FAB-MS *m*/*z* 1073 (MH$^+$, 99%); ^{13}C NMR (CDCl$_3$) δ 174.7 (s, C-1), 171.4 (s, C-9), 136.8 (d, 6-OCH$_2$CHCH$_2$), 115.4 (t, 6-OCH$_2$CHCH$_2$), 104.0 (s, isopropoxycyclohexyl (IPCH), C-1‴), 102.8 (d, C-1′), 96.1 (d, C-1″), 83.1 (d, C-5), 79.8 (d, C-3), 78.1 (d, C-4″), 76.6 (d, C-13), 75.1 (s, C-6), 74.0 (s, C-12), 72.4 (s, C-3″), 70.8 (d, C-11), 70.4 (d, C-2′), 68.6 (d, C-5′), 65.7 (t, 6-OCH$_2$CHCH$_2$), 65.3 (d, C-5″, C-3′, 2C), 63.2 (d, IPCH, C-8‴), 49.4 (q, 3″-OMe), 44.5 (d, 2C), 40.1 (q, 3′-NMe$_2$), 38.8 (d, C-4), 37.4 (t, C-7), 34.9 (t, C-2″), 34.3 (t, IPCH, C-6‴), 33.3 (t, IPHC, C-2‴), 32.9 (d, C-10), 28.6 (t, C-4′), 26.8 (d, C-8), 26.5 (q, 6-Me), 25.2 (t, IPHC, C-5‴), 24.1 (t, IPHC, C-3‴), 22.8 (t, IPHC, C-4‴), 22.5 (t, C-14), 21.3 (q, 5′-Me, 3″-Me, 2C), 20.9 (q, IPHC, 7‴-Me$_2$, 2C)18.5 (q, 8-Me), 18.4 (q, 5″-Me), 16.1 (q, 12-Me), 16.0 (q, 2-Me), 14.3 (q, 10-Me), 10.4 (q, 15-Me), 9.0 (q, 4-Me). Anal. Calcd for $C_{55}H_{104}N_2O_{14}Si_2$: C, 61.53; H, 9.76; N, 2.61. Found: C, 61.24; H, 10.01; N, 2.45.

6-*O*-Allylerythromycin A 9(*E*)-Oxime (20). To a solution of 6-*O*-allyl-2′,4″-bis-*O*-trimethylsilylerythromycin A 9-[*O*-(1-isopropoxycyclohexyl)oxime] (**18**) (3.5 g, 3.3 mmol) in 60 mL ethanol/water (1:1) was added formic acid at room temperature until pH 4.0 was reached, and the mixure was stirred at room temperature for 3 h. Then most of the ethanol was evaporated under reduced pressure, and water was added to the residue. The mixture was made basic with 2 M aqueous NaOH solution and extracted with ethyl acetate. The organic layer was washed with, in turn, water and a saturated aqueous sodium chloride solution and dried over anhydrous K_2CO_3. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (eluent, ethyl acetate/*n*-hexane/diethylamine, 60:30:2) to give 2.3 g (90%) of 9(*E*)-oxime **20** as an off-white solid. R_f = 0.47, ethyl acetate/*n*-hexane/diethylamine 100:100:20; FAB-MS *m*/*z* 789 (MH$^+$, 85%); IR (KBr) ν_{max} 2974, 2936, 1746, 1646, 1320, 1053 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 5.96 (1H, 6-OCH$_2$CHCH$_2$), 5.23 (1H, H-13), 5.14 (1H, 6-OCH$_2$CHCH$_{2b}$), 5.03 (1H, 6-OCH$_2$CHCH$_{2a}$), 4.90 (1H, H-1″), 4.57 (1H, H-1′), 4.18 (1H, H-5″), 4.06 (1H, 6-OCH$_{2b}$CHCH$_2$), 3.94 (1H, 6-OCH$_{2a}$CHCH$_2$), 3.84 (1H, H-5), 3.83 (1H, H-8), 3.77 (1H, H-5′), 3.75 (1H, H-3), 3.73 (1H, H-11), 3.37 (3H, 3″-OMe), 3.28 (1H, H-2′), 3.07 (1H, H-4″), 3.01 (1H, H-2), 2.75−2.65 (2H, H-10, H-3′), 2.46 (1H, H-2″b), 2.36 (3H, 3′-NMe$_2$), 2.11 (1H, H-4), 1.96 (1H, H-14b), 1.75 (1H, H-4′b), 1.65 (1H, H-7b), 1.62 (1H, H-2″a), 1.52 (3H, 6-Me), 1.50−1.44 (2H, H-14a, H-7a), 1.29 (3H, 5″-Me), 1.28 (3H, 3″-Me), 1.23 (3H, 2-Me), 1.21 (3H, 5′-Me), 1.20 (3H, 12-Me), 1.19 (1H, H-4′a), 1.16 (3H, 10-Me), 1.15 (3H, 4-Me), 1.01 (3H, 8-Me), 0.88 (3H, 15-Me); ^{13}C NMR (CD$_3$OD) δ 177.1 (s, C-1), 169.5 (s, C-9), 138.2 (d, 6-OCH$_2$CHCH$_2$), 116.3 (t, 6-OCH$_2$CHCH$_2$), 103.7 (d, C-1′), 98.1 (d, C-1″), 81.0 (s, C-6), 80.6 (d, C-5), 80.1 (d, C-3), 79.3 (d, C-4″), 78.1 (d, C-13), 75.6 (s, C-12), 74.3 (s, C-3″), 73.1 (d, C-2′), 71.6 (d, C-11), 68.9 (d, C-5′), 67.1 (t, 6-OCH$_2$CHCH$_2$), 67.0 (d, C-5″), 65.4 (d, C-3′), 50.1 (q, 3″-OMe), 46.2 (d, C-2), 40.9 (q, 3′-NMe$_2$), 40.2 (d, C-4), 38.4 (t, C-7), 36.5 (t, C-2″), 34.2 (d, C-10), 32.0 (t, C-4′), 26.6 (d, C-8), 22.8 (t, C-14), 22.3 (q, 6-Me), 22.0 (q, 5′-Me), 21.7 (q, 3″-Me), 19.6 (q, 5″-Me, 8-Me, 2C), 17.2 (q, 12-Me), 16.6 (q, 2-Me), 15.6 (q, 10-Me), 11.4 (q, 15-Me), 10.3 (q, 4-Me). Anal. Calcd for $C_{40}H_{72}N_2O_{13}$: C, 60.89; H, 9.20; N, 3.55. Found: C, 60.52; H, 9.54; N, 3.31.

3-*O*-Descladinosyl-6-*O*-allylerythromycin A 9(*E*)-Oxime (9). To a stirred suspension of 6-*O*-allylerythromycin A 9(*E*)-oxime (**20**) (6.2 g, 7.8 mmol) in ethanol (20 mL) and water (40 mL), was added 2 M aqueous HCl (40 mL, 40.0 mmol) dropwise over 30 min until pH 1.0 was reached. The solution was stirred at room temperature for 18 h. The reaction mixture was neutralized with 2 M aqueous NaOH and the precipitate was collected by filtration and washed with cold water to give a white solid, which was dried under vacuum at 50 °C to afford 3.9 g of **9**. The filtrate was extracted with ethyl acetate (2 × 40 mL), and the organic phase was washed with 10% sodium bicarbonate and brine, dried over K_2CO_3, and concentrated to give an additional 1.0 g of **9** as a white solid. The combined crude material was purified by column chromatography (silica gel, 50:50:0.5 hexane/acetone/aq NH$_3$) to give 4.4 g (90%) of **9** as an off-white solid. FAB-MS *m*/*z* 631 (MH$^+$, 76%); ^{1}H NMR (CDCl$_3$) δ 7.53 (1H, NOH), 5.92 (1H, 6-OCH$_2$CHCH$_2$), 5.27 (1H, H-13), 5.13 (1H, 6-OCH$_2$CHCH$_{2b}$), 5.10 (1H, 6-OCH$_2$CHCH$_{2a}$), 4.47 (1H, H-1′), 3.96 (1H, 11-OH), 3.79 (2H, H-11, H-8), 3.76 (2H, 6-OCH$_2$CHCH$_2$), 3.71 (1H, H-5), 3.55 (1H, H-5′), 3.51 (1H, H-3), 3.28 (1H, H-2′), 3.22 (1H, 12-OH), 2.67 (1H, H-2), 2.63 (1H, H-3′), 2.61 (1H, H-10), 2.33 (6H, 3′-NMe$_2$), 2.20 (1H, H-4), 1.95 (1H, H-14b), 1.73 (1H, H-4′b), 1.65 (1H, H-7b), 1.50 (1H, H-14a), 1.45 (3H, 6-Me), 1.31 (1H, H-7a), 1.29−1.24 (7H, 5′-Me, 2-Me, H-4′a), 1.21 (3H, 12-Me), 1.14 (3H, 10-Me), 1.12 (3H, 4-Me), 0.98 (3H, 8-Me), 0.83 (3H, 15-Me); ^{13}C NMR (CDCl$_3$) δ 174.9 (s, C-1), 169.9 (s, C-9), 136.0 (d, 6-OCH$_2$CHCH$_2$), 116.7 (t, 6-OCH$_2$CHCH$_2$), 106.3 (d, C-1′), 87.8 (d, C-5), 79.2 (s, C-6), 78.9 (d, C-3), 76.7 (d, C-13), 73.8 (s, C-12), 70.6 (d, C-2′), 70.4 (d, C-11), 69.9 (d, C-5′), 65.8 (d, C-3′), 64.9 (t, 6-OCH$_2$CHCH$_2$), 44.5 (d, C-2), 40.3 (q, 3′-NMe$_2$), 37.0 (t, C-7), 36.1 (d, C-4), 33.2 (d, C-10), 28.5 (t, C-4′), 25.4 (d, C-8), 21.8 (t, C-14), 21.2 (q, 5′-Me), 19.8 (q, 6-Me), 18.6 (q, 8-Me), 16.5 (q, 12-Me), 15.1 (q, 2-Me, 10-Me), 10.5 (q, 15-Me), 8.30 (q, 4-Me). Anal. Calcd for $C_{32}H_{58}N_2O_{10}$: C, 60.93; H, 9.27; N, 4.44. Found: C, 60.68; H, 9.62; N, 4.24.

LiOH-Induced Isomerization of 3-*O*-Descladinosyl-6-*O*-allylerythromycin A 9(*E*)-Oxime (9) to 3-*O*-Descladinosyl-6-*O*-allylerythromycin A 9(*Z*)-Oxime (10). To a solution of 3-*O*-descladinosyl-6-*O*-allylerythromycin A 9(*E*)-oxime (**9**) (260 mg, 0.4 mmol) in methanol (10 mL) was added LiOH−H_2O (67.1 mg, 1.6 mmol, 4 mol equiv) at room temperature. The mixture was kept stirring for 2 days, after which LC/MS analysis showed a 9:1 ratio of (*Z*)- versus (*E*)-oximes. The solvent was evaporated to dryness and the residue dissolved in ethyl acetate (100 mL). The organic layer was washed with water (30 mL), saturated aqueous NaCl solution (30 mL) and dried over K_2CO_3. The solvent was removed in vacuo to give 250 mg of the crude product. The crude product was purified by column chromatography, eluting with E1 system to give 208 mg (80%) of *Z*-oxime **10** as a colorless solid. Analytically pure sample was obtained by recrystallization from methanol. FAB-MS *m*/*z* 631 (MH^+, 83%); ^{1}H NMR ($CDCl_3$) δ 5.89 (1H, 6-OCH$_2\underline{\text{CH}}$CH$_2$), 5.17 (1H, H-13), 5.16 (1H, 6-OCH$_2$CH$\underline{\text{CH}_{2b}}$), 5.08 (1H, 6-OCH$_2CH\underline{\text{CH}_{2a}}$), 4.52 (1H, H-1′), 4.29 (1H, H-8), 3.98 (1H, 6-O$\underline{\text{CH}_{2b}}$), 3.95 (1H, 11-OH), 3.89 (1H, 6-O$\underline{\text{CH}_{2a}}$), 3.77 (1H, H-11), 3.74 (1H, H-5), 3.58 (1H, H-5′), 3.49 (1H, H-3), 3.47 (1H, 12-OH), 3.31 (1H, H-2′), 2.77 (1H, H-3′), 2.68 (1H, H-2), 2.42 (6H, 3′-NMe$_2$), 2.22 (1H, H-4), 2.08 (1H, H-10), 1.89 (1H, H-14b), 1.70 (1H, H-4′b), 1.64 (1H, H-7b), 1.49 (3H, 6-Me), 1.46 (1H, H-14a), 1.38 (1H, H-7a), 1.34 (1H, H-4′a), 1.28−1.25 (6H, 5′-Me, 2-Me), 1.21 (3H, 12-Me), 1.12 (3H, 10-Me), 1.11 (3H, 4-Me), 1.01 (3H, 8-Me), 0.83 (3H, 15-Me); ^{13}C NMR (CD_3OD) δ 175.3 (s, C-1), 166.8 (s, C-9), 136.3 (d, 6-OCH$_2\underline{\text{CH}}$CH$_2$), 115.0 (t, 6-O-CH$_2$CH$\underline{\text{CH}_2}$), 101.6 (d, C-1′), 80.5 (d, C-5), 79.1 (s, C-6), 76.8 (d, C-3), 76.6 (d, C-13), 74.8 (s, C-12), 71.1 (d, C-11), 70.6 (d, C-2′), 68.4 (d, C-5′), 64.7 (d, C-3′), 64.1 (t, 6-O$\underline{\text{CH}_2}$), 43.9 (d, C-2), 39.3 (q, 3′-NMe$_2$), 37.7 (t, C-7), 37.1 (d, C-4), 36.3 (d, C-8), 34.5 (d, C-10), 30.7 (t, C-4′), 21.6 (t, C-14), 20.0 (q, 5′-Me), 19.4 (q, 8-Me, 6-Me), 16.3 (q, 12-Me), 14.4 (q, 2-Me), 10.4 (q, 10-Me), 9.6 (q, 15-Me), 7.8 (q, 4-Me). Anal. Calcd for $C_{32}H_{58}N_2O_{10}$: C, 60.93; H, 9.27; N, 4.44. Found: C, 60.73; H, 9.49; N, 4.28.

Beckmann Rearrangement of 3-*O*-Descladinosyl-6-*O*-allylerythromycin A 9(*Z*)-Oxime (10). Preparation of 3-*O*-Descladinosyl-6-*O*-allyl-8a-aza-8a-homoerythromycin A (15). The 9(*Z*)-oxime **10** (1.20 g, 1.9 mmol) was dissolved in acetone (50 mL), and the solution was cooled to 0−5 °C in an ice bath. Subsequently, solutions of *p*-toluenesulfonyl chloride (1.84 g, 14.0 mmol) in acetone (56 mL) and sodium hydrogen carbonate (1.16 g, 14.0 mmol) in water (180 mL) were simultaneously added within 1 h under stirring. The reaction mixture was stirred at room temperature for an additional 2 h, acetone was evaporated at reduced pressure, and the aqueous layer was washed with chloroform (70 mL). The pH of the aqueous layer was adjusted to 9.0 with 2 M aqueous NaOH and extracted twice with chloroform (2 × 70 mL). The combined organic extracts at pH 9.0 were dried over K_2CO_3 and evaporated in vacuo, yielding the crude rearranged product, which was purified by chromatography on a silica gel column using methylene chloride−methanol−conc ammonium hydroxide (90:9:1.5) as eluent to give 1.1 g of **15** (90%) as a colorless solid. FAB-MS *m*/*z* 631 (MH^+, 100%); ^{1}H NMR ($CDCl_3$) δ 6.03 (1H, 8a-CO$\underline{\text{NH}}$), 5.96 (1H, 6-OCH$_2\underline{\text{CH}}$CH$_2$), 5.28 (1H, 6-OCH$_2$CH$\underline{\text{CH}_{2b}}$), 5.15 (1H, 6-OCH$_2CH\underline{\text{CH}_{2a}}$), 5.01 (1H, H-13), 4.52 (1H, H-1′), 3.93 (2H, 6-O$\underline{\text{CH}_2}$CHCH$_2$), 3.82 (1H, H-8), 3.78 (1H, H-3), 3.73 (1H, H-5), 3.56 (1H, H-5′), 3.39 (1H, H-11), 3.28 (1H, H-2′), 2.69 (1H, H-3′), 2.64 (1H, H-2), 2.45 (1H, H-10), 2.37 (6H, 3′-NMe$_2$), 2.24 (1H, H-7b), 2.14 (1H, H-4), 1.91 (1H, H-14b), 1.75 (1H, H-4′b), 1.57−1.46 (2H, H-14a, H-7a), 1.39 (3H, 6-Me), 1.32 (3H, 8-Me), 1.31 (3H, 2-Me), 1.29 (1H, H-4′a), 1.25 (3H, 5′-Me), 1.19 (3H, 10-Me), 1.13 (3H, 12-Me), 1.11 (3H, 4-Me), 0.88 (3H, 15-Me); ^{13}C NMR ($CDCl_3$) δ 176.4 (s, C-1), 174.8 (s, 8a-$\underline{\text{CO}}$NH), 136.0 (d, 6-OCH$_2\underline{\text{CH}}$CH$_2$), 116.1 (t, 6-OCH$_2$CH$\underline{\text{CH}_2}$), 105.9 (d, C-1′), 89.5 (d, C-5), 78.5 (s, C-6), 78.1 (d, C-3), 76.4 (d, C-13), 74.9 (s, C-12), 70.6 (d, C-11), 70.1 (d, C-2′), 69.5 (d, C-5′), 65.4 (d, C-3′), 63.4 (t, 6-O$\underline{\text{CH}_2}$CHCH$_2$), 43.8 (d, C-2), 43.1 (d, C-8), 42.9 (d, C-10), 41.6 (t, C-7), 39.9 (q, 3′-NMe$_2$), 35.6 (d, C-4), 28.0 (t, C-4′), 22.4 (q, 8-Me), 21.8 (q, 6-Me), 21.1 (t, C-14), 20.8 (q, 5′-Me), 16.2 (q, 12-Me), 15.7 (q, 2-Me), 10.5 (q, 15-Me), 10.3 (q, 10-Me), 8.0 (q, 4-Me). Anal. Calcd for $C_{32}H_{58}N_2O_{10}$: C, 60.93; H, 9.27; N, 4.44. Found: C, 60.75; H, 9.53; N, 4.32.

Preparation of 3-*O*-Decladinosyl-3-oxy-6-*O*-allyl-8a-aza-8a-homoerythromycin A 2′-*O*-Acetate (25). To a solution of homoerythromycin A derivative **15** (757.0 mg, 1.2 mmol) in methylene chloride (25 mL), Et_3N (141.7 mg, 1.4 mmol) and acetic acid anhydride (0.128 mL, 1.3 mmol) were added. The reaction mixture was stirred for 3 h at room temperature. To the reaction mixture saturated aqueous $NaHCO_3$ (30 mL) was added. The layers were separated, and the aqueous portion was additionally extracted with methylene chloride (2 × 20 mL). The combined organic extracts were washed successively with saturated aqueous $NaHCO_3$ solution (30 mL) and water (30 mL), dried over K_2CO_3, and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, hexane/acetone/aq NH_3, 50:50:0.5) to furnish 726.8 mg of **25** (90%) as a colorless solid. R_f = 0.40, ethyl acetate/*n*-hexane/diethylamine, 100:100:20; FAB-MS *m*/*z* 673 (MH^+, 87%). Anal. Calcd for $C_{34}H_{60}N_2O_{11}$: C, 60.77; H, 8.99; N, 4.17. Found: C, 60.31; H, 9.32; N, 4.36.

Dess−Martin Oxidation. Preparation of 3-*O*-Descladinosyl-3-oxo-6-*O*-allyl-8a-aza-8a-homoerythromycin A (11). To a solution of 2′-*O*-acetyl derivative **25** (1.48 g, 2.2 mmol) in CH_2Cl_2 (5 mL) was added $NaHCO_3$ (1.86 mg, 22 mmol, 10.0 equiv), pyridine (887.9 μL, 11 mmol, 5.0 equiv), and Dess−Martin reagent (1.87 g, 4.4 mmol, 2.0 equiv), and the mixture was stirred for 3 h at ambient temperature. The reaction was quenched by consecutive addition of saturated aqueous $NaHCO_3$ (20 mL) and $Na_2S_2O_3 \cdot 5H_2O$ (1.17 g, 4.7 mmol, 13.9 equiv). The resulting solution was stirred for an additional 30 min, extracted with methylene chloride (2 × 25 mL), dried over K_2CO_3, and concentated in vacuo. This crude residue was then dissolved in MeOH (20.0 mL) and refluxed for 3 h. After evaporation of the solvent, the residue was taken up in water, the pH adjusted to 11 with 2 M aqueous sodium hydroxide, and the mixture extracted with ethyl acetate. The extracts were washed with water, dried over K_2CO_3, and evaporated to dryness. The residue was purified by column chromatography, eluting with acetone/hexane/aq NH_3 (50:50:0.5) solvent system to afford 1.1 g (81%) of **11** as a white solid. FAB-MS *m*/*z* 629 (MH^+, 89%); ^{1}H NMR ($CDCl_3$) δ 6.17 (1H, 8a-CO$\underline{\text{NH}}$), 5.89 (1H, 6-OCH$_2\underline{\text{CH}}$CH$_2$), 5.18 (1H, 6-OCH$_2$CH$\underline{\text{CH}_{2b}}$), 5.15 (1H, 6-OCH$_2CH\underline{\text{CH}_{2a}}$), 5.09 (1H, H-13), 4.31 (1H, H-5), 4.25 (1H, H-1′), 3.94 (1H, H-8), 3.80 (1H, H-2), 3.73 (2H, 6-O$\underline{\text{CH}_2}$CHCH$_2$), 3.60 (1H, H-5′), 3.55 (1H, H-11), 3.22 (1H, H-2′), 3.11 (1H, H-4), 2.62 (1H, H-3′), 2.44 (1H, H-10), 2.36 (6H, 3′-NMe$_2$), 1.98−1.93 (2H, H-14b, H-7b), 1.77 (1H, H-4′a), 1.61 (1H, H-7a), 1.52 (1H, H-14a), 1.37 (3H, 2-Me), 1.34 (3H, 4-Me), 1.26 (3H, 6-Me), 1.24 (3H, 5′-Me), 1.19 (3H, 8-Me), 1.18 (3H, 12-Me), 0.88 (3H, 15-Me); ^{13}C NMR ($CDCl_3$) δ 206.2 (s, C-3), 174.4 (s, C-9), 170.5 (s, C-1), 136.8 (d, 6-OCH$_2\underline{\text{CH}}$CH$_2$), 115.6 (t, 6-OCH$_2$CH$\underline{\text{CH}_2}$), 102.6 (d, C-1′), 78.8 (s, C-6), 77.8 (d, C-5), 77.6 (d, C-13), 74.3 (s, C-12), 70.7 (d, C-11), 69.9 (d, C-2′), 69.0 (d, C-5′), 65.6 (d, C-3′), 64.0 (t, 6-O$\underline{\text{CH}_2}$CHCH$_2$), 49.9 (d, C-2), 46.9 (d, C-4), 42.5 (d, C-8), 42.2 (d, C-10), 41.9 (t, C-7), 40.0 (q, 3′-NMe$_2$), 28.6 (t, C-4′), 22.7 (q, 8-Me), 22.1 (q, 6-Me), 21.2 (t, C-14), 20.9 (q, 5′-Me), 16.0 (q, 12-Me), 14.6 (q, 4-Me), 13.9 (q, 2-Me), 10.5 (q, 15-Me), 9.7 (q, 10-Me). Anal. Calcd for $C_{32}H_{56}N_2O_{10}$: C, 61.12; H, 8.98; N, 4.45. Found: C, 61.47; H, 9.28; N, 4.38.

***syn*-3-*O*-Descladinosyl-3-oxo-6-*O*-(2″-methyloxiranyl)-8a-aza-8a-homoerythromycin A *N*-Oxide (12a) and *anti*-3-*O*-Descladinosyl-3-oxo-6-*O*-(2″-methyloxiranyl)-8a-aza-8a-homoerythromycin A *N*-Oxide (12b). (a) Using *m*-Chloroperoxybenzoic Acid.** To a solution of **11** (629 mg, 1.0 mmol) in dry dichloromethane (7 mL) cooled to 0 °C in an ice/water bath was added sodium acetate (175 mg, 2.1 mmol) followed by *m*-CPBA (1.88 g, 50% w/w,

5.0 mmol) in five portions over 5 min. The reaction mixture was allowed to warm to room temperature and stirred for 24 h under a drying tube. After filtration through a short pad of Celite, the mixture was washed with aqueous Na_2SO_3 (10% w/v), saturated aqueous $NaHCO_3$ and water, and dried over K_2CO_3. Removal of the solvent under reduced pressure gave a pale-tan solid that was purified by flash chromatography using CH_2Cl_2/MeOH/aq NH_3 (90:9:0.5) as eluent to afford a mixture of *syn*- and *anti*-epoxy *N*-oxides **12a** and **12b** as a colorless needles (397.7 mg, 60%; *syn*/*anti* ratio of 1:1 according to LC/MS analysis).

***syn*-Isomer 12a.** FAB-MS *m*/*z* 661 (MH^+, 78%); IR (KBr) ν_{max} 2945, 2870 (CH), 1271 [CO (epoxide)], 892 [CO (epoxide)] cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.85 (d, 1H, 8aNH), 5.01−4.93 (m, 1H, H-13), 4.49 (d, 1H, H-1′), 4.21 (s, 1H, 11-OH), 4.20−4.10 (m, 1H, H-8), 3.82 (d, 1H, H-1″b), 3.80 (m, 1H, H-2), 3.77−3.67 (m, 2H, H-2′, H-5), 3.65−3.58 (m, 1H, H-5′), 3.49 (s, 1H, H-11), 3.42−3.37 (m, 1H, H-3′), 3.28−3.22 (m, 2H, H-1″a, H-2″), 3.20 (s, 6H, 3′-N(O)Me_2), 3.10 (1H, H-4), 2.84 (t, 1H, H-3″b), 2.60−2.54 (m, 1H, H-3″a), 2.35−2.29 (m, 1H, H-10), 2.06−1.87 (m, 2H, H-4′b, H-14b), 1.84 (dd, 1H, H-7b), 1.60 (d, 1H, H-7a), 1.51−1.45 (m, 1H, H-14a), 1.41 (s, 3H, 6-Me), 1.39−1.36 (m, 1H, H-4′a), 1.34 (d, 3H, 2-Me), 1.32 (d, 3H, 4-Me), 1.27 (d, 3H, 5′-Me), 1.18 (d, 3H, 10-Me), 1.17 (s, 3H, 12-Me), 1.14 (d, 3H, 8-Me), 0.86 (t, 3H, 15-Me); ^{13}C NMR ($CDCl_3$) δ 205.4 (s, C-3), 174.0 (s, C-9), 170.5 (s, C-1), 102.8 (d, C-1′), 80.5 (d, C-5), 79.6 (s, C-6), 77.2 (d, C-13), 76.3 (d, C-3′), 74.5 (s, C-12), 72.5 (d, C-2′), 71.3 (d, C-11), 67.3 (d, C-5′), 65.8 (t, C-1″), 59.0 (q, 3′-N(O)Me), 52.1 (q, 3′-N(O)Me), 51.5 (d, C-2″), 49.7 (d, C-2), 46.7 (d, C-4), 45.6 (t, C-3″), 43.1 (t, C-7), 42.5 (d, C-10), 41.3 (d, C-8), 35.0 (t, C-4′), 23.9 (q, 8-Me), 23.7 (q, 6-Me), 21.6 (t, C-14), 21.5 (q, 5′-Me), 16.4 (q, 12-Me), 14.6 (q, 4-Me), 13.8 (q, 2-Me), 11.0 (q, 15-Me), 9.4 (q, 10-Me). Anal. Calcd for $C_{34}H_{56}N_2O_{12}$: C, 58.16; H, 8.54; N, 4.24. Found: C, 58.28; H, 8.72; N, 4.10.

***anti*-Isomer 12b.** FAB-MS *m*/*z* 661 (MH^+, 85%); IR (KBr) ν_{max} 2950, 2875 (CH), 1270 [CO (epoxide)], 890 [CO (epoxide)] cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.14 (d, 1H, 8aNH), 5.01−4.93 (m, 1H, H-13), 4.53 (d, 1H, H-1′), 4.44 (s, 1H, 11-OH), 4.20−4.10 (m, 1H, H-8), 3.79 (m, 1H, H-2), 3.71 (d, 1H, H-1″b), 3.77−3.67 (m, 2H, H-2′, H-5), 3.65−3.58 (m, 1H, H-5′), 3.55 (s, 1H, H-11), 3.42−3.37 (m, 1H, H-3′), 3.33−3.29 (m, 2H, H-1″a, H-2″), 3.18 (s, 6H, 3′-N(O)Me_2), 3.12 (1H, H-4), 2.82 (t, 1H, H-3″b), 2.60−2.54 (m, 1H, H-3″a), 2.35−2.29 (m, 1H, H-10), 2.06−1.87 (m, 3H, H-4′b, H-7b, H-14b), 1.63 (d, 1H, H-7a), 1.51−1.45 (m, 1H, H-14a), 1.43 (s, 3H, 6-Me), 1.39−1.32 (m, 1H, H-4′a), 1.36 (d, 3H, 2-Me), 1.34 (d, 3H, 4-Me), 1.27 (d, 3H, 5′-Me), 1.18 (d, 3H, 10-Me), 1.14 (d, 3H, 8-Me), 0.86 (t, 3H, 15-Me); ^{13}C NMR ($CDCl_3$) δ 205.0 (s, C-3), 174.5 (s, C-9), 170.8 (s, C-1), 103.0 (d, C-1′), 81.5 (d, C-5), 79.9 (s, C-6), 77.2 (d, C-13), 76.1 (d, C-3′), 74.6 (s, C-12), 72.5 (d, C-2′), 71.1 (d, C-11), 67.4 (d, C-5′), 66.1 (t, C-1″), 59.1 (q, 3′-N(O)Me), 52.1 (q, 3′-N(O)Me), 51.7 (d, C-2″), 46.0 (t, C-3″), 49.5 (d, C-2), 46.8 (d, C-4), 42.6 (t, C-7), 42.4 (d, C-10), 41.2 (d, C-8), 35.0 (t, C-4′), 24.7 (q, 6-Me), 23.8 (q, 8-Me), 21.6 (t, C-14), 21.5 (q, 5′-Me), 16.4 (q, 12-Me), 14.5 (q, 4-Me), 13.7 (q, 2-Me), 11.0 (q, 15-Me), 9.4 (q, 10-Me). Anal. Calcd for $C_{34}H_{56}N_2O_{12}$: C, 58.16; H, 8.54; N, 4.24. Found: C, 58.25; H, 8.81; N, 4.20.

***syn*-3-*O*-Descladinosyl-3-oxo-6-*O*-(2″-methyloxiranyl)-8a-aza-8a-homoerythromycin A *N*-Oxide (12a) and *anti*-3-*O*-Descladinosyl-3-oxo-6-*O*-(2″-methyloxiranyl)-8a-aza-8a-homoerythromycin A *N*-Oxide (12b). (b) Using Dimethyldioxirane.** To a solution of **6** (629 mg, 1.0 mmol) in acetone (10 mL) was added dimethyldioxirane (11.0 mL, 1.1 mmol as a 0.1 mmol/mL solution in acetone), and the reaction mixture allowed to stir for 16 h at room temperature. Removal of the solvent under reduced pressure afforded a colorless solid, which was dissolved in dichloromethane and dried over K_2CO_3. Removal of the solvent under reduced pressure and purification by flash chromatography using methylene chloride/methanol/aq NH_3 (90:9:0.5) as eluent gave a mixture of *syn*- and *anti*-epoxy *N*-oxides **12a**,**b** (430.8 mg, 65%) in a ratio of 4.4:1 according to LC/MS analysis.

Reduction of *syn*- and *anti*-6-*O*-(2″-Methyloxiranyl)-3-oxo-8a-aza-8a-homoerythromycin *N*-Oxides (12a and 12b) with Zinc. Preparation of *syn*- and *anti*-6-*O*-(2″-Methyloxiranyl)-3-oxo-8a-aza-8a-homoerythromycin A (13a and 13b). To a solution of epoxy *N*-oxides **12a**,**b** (994.2 mg, 1.5 mmol) in ethanol/water (2:1, 25 mL) was added Zn powder (980.7 mg, 15 mmol, 10 mol equiv) and NH_4Cl (803 mg, 15 mmol, 10 mol equiv). The reaction mixture was stirred at room temperature for 3 h. The mixture was filtered over short pad of Celite, and the filtrate was evaporated to dryness. The residue was redissolved in CH_2Cl_2 (25 mL) and washed with saturated aqueous $NaHCO_3$ solution (2 × 20 mL). The organic layer was dried over K_2CO_3 and evaporated to dryness. The resulting residue was purified by column chromatography, eluting with a gradient of $CHCl_3$ to 7% MeOH/$CHCl_3$ to give a 4.5:1 mixture of *syn*- and *anti*-epoxides (657.7 mg, 68%) as a white solid.

***syn*-Isomer 13a.** FAB-MS *m*/*z* 645 (MH^+, 78%); ^1H NMR ($CDCl_3$) δ 6.12 (d, 1H, 8aNH), 5.00 (dd, 2H, H-13), 4.40 (d, 1H, H-1′), 4.29 (s, 1H, 11-OH), 4.17−4.06 (m, 1H, H-8), 3.94 (d, 1H, H-3), 3.81 (m, 1H, H-2), 3.78 (dd, 1H, H-1″b), 3.74−3.67 (m, 1H, H-5), 3.52 (s, 1H, H-11), 3.50−3.46 (m, 1H, H-5′), 3.37−3.33 (m, 1H, H-2″), 3.28−3.22 (m, 1H, H-1″a), 3.21−3.14 (m, 1H, H-2′), 3.12 (s, 1H, 12-OH), 3.11 (m, 1H, H-4), 2.85 (t, 1H, H-3″b), 2.60−2.54 (m, 1H, H-3″a), 2.52−2.43 (m, 1H, H-3′), 2.34−2.30 (m, 1H, H-10), 2.29 (s, 6H, 3′-NMe_2), 2.15−1.88 (m, 2H, H-7b, H-14b), 1.74−1.66 (m, 1H, H-4′b), 1.63 (d, 1H, H-7a), 1.52−1.45 (m, 1H, H-14a), 1.41 (s, 3H, 6-Me), 1.35 (d, 3H, 2-Me), 1.31 (d, 3H, 4-Me), 1.26−1.19 (m, 1H, H-4′a), 1.22 (d, 3H, 5′-Me), 1.19 (d, 3H, 10-Me), 1.16 (s, 3H, 12-Me), 1.14 (d, 3H, 8-Me), 0.86 (t, 3H, 15-Me); ^{13}C NMR ($CDCl_3$) δ 205.2 (s, C-3), 174.2 (s, C-9), 170.4 (s, C-1), 103.4 (d, C-1′), 80.8 (d, C-5), 79.8 (s, C-6), 77.2 (d, C-13), 74.4 (s, C-12), 71.3 (d, C-11), 70.7 (d, C-2′), 69.2 (d, C-5′), 66.1 (t, C-1″), 51.3 (d, C-2″), 49.7 (d, C-2), 46.7 (d, C-4), 45.8 (t, C-3″), 42.8 (t, C-7), 42.4 (d, C-10), 41.5 (d, C-8), 40.4 (q, 3′-NMe_2), 28.7 (t, C-4′), 24.5 (q, 6-Me), 23.6 (q, 8-Me), 21.4 (t, C-14), 21.3 (q, 5′-Me), 16.3 (q, 12-Me), 14.7 (q, 4-Me), 13.6 (q, 2-Me), 10.9 (q, 15-Me), 9.5 (q, 10-Me). Anal. Calcd for $C_{34}H_{56}N_2O_{11}$: C, 59.61; H, 8.75; N, 4.34. Found: C, 59.28; H, 8.99; N, 4.22.

***anti*-Isomer 13b.** FAB-MS *m*/*z* 645 (MH^+, 53%); ^1H NMR ($CDCl_3$) δ 6.57 (d, 1H, 8aNH), 5.00 (dd, 2H, H-13), 4.52 (s, 1H, 11-OH), 4.39 (d, 1H, H-1′), 4.17−4.06 (m, 1H, H-8), 3.80 (m, 1H, H-2), 3.74−3.67 (m, 1H, H-5), 3.65 (dd, 1H, H-1″b), 3.58 (s, 1H, H-11), 3.50−3.46 (m, 1H, H-5′), 3.37−3.33 (m, 1H, H-1″a), 3.28−3.22 (m, 1H, H-2″), 3.21−3.14 (m, 1H, H-2′), 3.12 (s, 1H, 12-OH), 3.10 (m, 1H, H-4), 2.83 (t, 1H, H-3″b), 2.60−2.54 (m, 1H, H-3″a), 2.52−2.43 (m, 1H, H-3′), 2.34−2.30 (m, 1H, H-10), 2.29 (s, 6H, 3′-NMe_2), 2.15−1.88 (m, 2H, H-7b, H-14b), 1.74−1.66 (m, 1H, H-4′b), 1.63 (d, 1H, H-7a), 1.52−1.45 (m, 1H, H-14a), 1.43 (s, 3H, 6-Me), 1.34 (d, 3H, 2-Me), 1.31 (d, 3H, 4-Me), 1.26−1.19 (m, 1H, H-4′a), 1.22 (d, 3H, 5′-Me), 1.19 (d, 3H, 10-Me), 1.16 (s, 3H, 12-Me), 1.14 (d, 3H, 8-Me), 0.86 (t, 3H, 15-Me); ^{13}C NMR ($CDCl_3$) δ 205.2 (s, C-3), 174.8 (s, C-9), 170.5 (s, C-1), 103.7 (d, C-1′), 82.0 (d, C-5), 80.0 (s, C-6), 77.2 (d, C-13), 74.3 (s, C-12), 71.1 (d, C-11), 70.8 (d, C-2′), 69.4 (d, C-5′), 65.9 (t, C-1″), 51.5 (d, C-2″), 49.6 (d, C-2), 46.6 (d, C-4), 46.2 (t, C-3″), 42.8 (t, C-7), 42.4 (d, C-10), 41.4 (d, C-8), 40.4 (q, 3′-NMe_2), 28.6 (t, C-4′), 25.7 (q, 6-Me), 23.4 (q, 8-Me), 21.4 (t, C-14), 21.2 (q, 5′-Me), 16.2 (q, 12-Me), 14.7 (q, 4-Me), 13.5 (q, 2-Me), 10.8 (q, 15-Me), 9.6 (q, 10-Me). Anal. Calcd for $C_{34}H_{56}N_2O_{11}$: C, 59.61; H, 8.75; N, 4.34. Found: C, 59.32; H, 8.87; N, 4.18.

Lithium Perchlorate Induced Regioselective Ring Opening of Epoxides (13a,b). A mixture of *syn*- and *anti*-epoxides **13a**,**b** (644 mg, 1.0 mmol), $LiClO_4$ $3H_2O$ (802.2 mg, 5.0 mmol, 5.0 mol equiv), and amines **a**−**x** (5.0 mmol, 5.0 mol equiv) in 2-propanol (2.5 mL) was heated at reflux for 24 h. Upon completion of the reaction, the solution was cooled to room temperature, and CH_2Cl_2 (25 mL) was added. The organic layer was washed with water (2 × 25 mL), dried, and concentrated in vacuo. The residual solid was purified by chromatography on silica gel using

CH_2Cl_2/methanol/aq NH_3 (90:9:1.5) as eluent to give a mixture of diastereisomeric β-amino alcohols (**14aa−ax** and **14ba−bx**, 50−80% isolated yield) in ratio 4.5:1 according to LC/MS analysis.

6-[2′′-(*syn,anti*)-Hydroxy-3′′-phenethylaminopropoxy]-3-oxo-8a-aza-8a-homoerythromycin A (14aa−ba). FAB-MS *m/z* 766 (MH^+, 65%); ^1H NMR ($CDCl_3$) δ 7.33−7.24 (4H, H-1Ar + H-5Ar, H-2Ar + H-4Ar), 7.20 (1H, H-3Ar), 5.92 (1H, 8a-CONH), 4.98−4.92 (1H, H-13), 4.40 (1H, H-1′), 4.26 (1H, H-8), 3.82 (1H, H-2), 3.80 (1H, H-5), 3.78 (1H, H-2′′), 3.71 (1H, H-1′′b), 3.52 (1H, H-5′), 3.41−3.35 (2H, H-11, H-1′′a), 3.16 (1H, H-2′), 3.12 (1H, H-4′′b), 3.07 (1H, H-4), 2.97−2.91 (3H, H-5′′b, H-5′′a, H-4′′a), 2.80 (1H, H-3′′b), 2.67 (1H, H-3′′a), 2.45 (1H, H-3′), 2.40 (1H, 12-OH), 2.30 (7H, H-10, 3′-NMe_2), 2.03 (1H, 11-OH), 1.92−1.83 (2H, H-14b, H-7b), 1.71−1.63 (2H, H-7a, H-4′b), 1.42 (3H, 6-Me), 1.32 (3H, 2-Me), 1.30 (3H, 4-Me), 1.24 (3H, 5′-Me), 1.21 (3H, 8-Me), 0.78 (3H, 15-Me); ^{13}C NMR ($CDCl_3$) δ 205.4 (s, C-3), 175.2 (s, C-9), 170.3 (s, C-1), 139.7 (s, C-Ar), 128.8 (d, C-1Ar + C-5Ar), 128.4 (d, C-2Ar + C-4Ar), 125.9 (d, C-3Ar), 103.3 (d, C-1′), 79.6 (s, C-6), 79.2 (d, C-5), 77.4 (d, C-13), 74.5 (s, C-12), 70.9 (d, C-11), 70.7 (d, C-2′), 69.2 (d, C-5′), 67.7 (d, C-2′′), 67.2 (t, C-1′′), 65.8 (d, C-3′), 50.6 (t, C-3′′), 50.0 (t, C-4′′), 49.9 (d, C-2), 46.7 (d, C-4), 43.1 (t, C-7), 42.4 (d, C-10), 40.8 (d, C-8), 40.3 (q, 3′-NMe_2), 35.9 (t, C-5′′), 28.5 (t, C-4′), 24.5 (q, 6-Me), 24.1 (q, 8-Me), 21.5 (q, 5′-Me), 21.1 (t, C-14), 16.5 (q, 12-Me), 14.9 (q, 4-Me), 13.6 (q, 2-Me), 10.7 (q, 15-Me), 9.4 (q, 10-Me). Anal. Calcd for $C_{40}H_{67}N_3O_{11}$: C, 62.72; H, 8.82; N, 5.49. Found: C, 62.49; H, 9.04; N, 5.26.

6-[2′′-(*syn,anti*)-Hydroxy-3′′-(4-phenylbutylamino)propoxy]-3-oxo-8a-aza-8a-homoerythromycin A (14ac−bc). FAB-MS *m/z* 794 (MH^+, 91%); ^1H NMR ($CDCl_3$) δ 7.29−7.23 (2H, H-1Ar + H-5Ar), 7.19−7.12 (3H, H-2Ar + H-4Ar, H-3Ar), 6.14 (1H, 8a-CONH), 4.99 (1H, H-13), 4.37 (1H, H-1′), 4.16 (1H, H-8), 3.87 (1H, H-2′′), 3.80 (1H, H-2), 3.77 (1H, H-5), 3.69 (1H, H-1′′b), 3.49 (1H, H-5′), 3.38 (1H, H-11), 3.34 (1H, H-1′′a), 3.15 (1H, H-2′), 3.09 (1H, H-4), 2.93 (1H, H-4′′b), 2.82 (1H, H-4′′a), 2.80 (1H, H-3′′b), 2.72 (1H, H-3′′a), 2.62 (2H, H-7′′), 2.44 (1H, H-3′), 2.37 (1H, 12-OH), 2.35−2.29 (1H, H-10), 2.28 (3H, 3′-NMe_2), 2.02 (1H, 11-OH), 1.96−1.84 (2H, H-14b, H-7b), 1.75−1.65 (5H, H-6′′, H-5′′, H-4′b), 1.63 (1H, H-7a), 1.46 (1H, H-14a), 1.41 (3H, 6-Me), 1.33 (3H, 2-Me), 1.29 (3H, 4-Me), 1.23 (3H, 5′-Me), 1.22 (1H, H-4′a), 1.17 (3H, 10-Me), 1.14 (3H, 12-Me), 1.13 (3H, 8-Me), 0.80 (3H, 15-Me); ^{13}C NMR ($CDCl_3$) δ 205.0 (s, C-3), 175.4 (s, C-9), 170.8 (s, C-1), 142.2 (s, C-Ar), 128.4 (d, C-1Ar + C-5Ar), 128.3 (d, C-2Ar + C-4Ar), 125.7 (d, C-3Ar), 103.4 (d, C-1′), 79.8 (d, C-5), 79.7 (s, C-6), 77.7 (d, C-13), 74.5 (s, C-12), 71.3 (d, C-11), 70.7 (d, C-2′), 69.2 (d, C-5′), 67.0 (d, C-2′′), 66.8 (t, C-1′′), 65.7 (d, C-3′), 50.2 (t, C-3′′), 49.8 (d, C-2), 48.1 (t, C-4′′), 46.9 (d, C-4), 42.9 (t, C-7), 42.2 (d, C-10), 41.1 (d, C-8), 40.3 (q, 3′-NMe_2), 35.6 (t, C-7′′), 28.9 (t, C-5′′), 28.5 (t, C-4′), 28.1 (t, C-6′′), 24.9 (q, 6-Me), 23.8 (q, 8-Me), 21.5 (q, 5′-Me), 21.2 (t, C-14), 16.5 (q, 12-Me), 14.8 (q, 4-Me), 13.7 (q, 2-Me), 10.8 (q, 15-Me), 9.4 (q, 10-Me). Anal. Calcd for $C_{42}H_{71}N_3O_{11}$: C, 63.53; H, 9.01; N, 5.29. Found: C, 63.86; H, 9.31; N, 5.16.

6-{3′′-[4-(2-Ethoxyphenyl)piperazin-1-yl]-2′′-(*syn,anti*)-hydroxypropoxy}-3-oxo-8a-aza-8a-homoerythromycin A (14ap−bp). FAB-MS *m/z* 851 (MH^+, 94%); ^1H NMR ($CDCl_3$) δ 7.02−6.93 (m, 2H, H−Ar), 6.92−6.88 (m, 1H, H−Ar), 6.86−6.82 (m, 1H, H−Ar), 6.17 (bs, 1H, 8aNH), 4.99 (dd, 1H, H-13), 4.39 (d, 1H, H-1′), 4.20−4.11 (m, 1H, H-8), 4.07 (q, 2H, OCH_2CH_3), 3.83 (m, 1H, H-2), 3.78 (d, 1H, H-5), 3.72 (d, 1H, H-1′′b), 3.68−3.62 (m, 1H, H-2′′), 3.56−3.46 (m, 1H, H-5′), 3.44 (s, 1H, H-11), 3.40 (dd, 1H, H-1′′a), 3.18 (dd, 1H, H-2′), 3.08 (dd, 2H, H-4′′b), 3.07 (m, 1H, H-4), 3.05−2.99 (m, 1H, H-3′′b), 2.54−2.44 (m, 1H, H-3′), 2.32 (s, 6H, 3′-NMe_2), 2.30−2.25 (m, 1H, H-10), 2.20 (d, 1H, H-3′′a), 1.98−1.87 (m, 2H, H-14b, H-7b), 1.77−1.70 (m, 1H, H-4′b), 1.68−1.63 (m, 1H, H-7a), 1.57−1.53 (m, 2H, H-4′′a), 1.51−1.47 (m, 1H, H-14a), 1.45 (t, 3H, OCH_2CH_3), 1.42 (s, 3H, 6-Me), 1.35 (d, 3H, 2-Me), 1.31 (d, 3H, 4-Me), 1.24 (d, 3H, 5′-Me), 1.23−1.22 (m, 1H, H-4′a), 1.18 (d, 3H, 10-Me), 1.16 (s, 3H, 12-Me), 1.14 (d, 3H, 8-Me), 0.84 (t, 3H, 15-Me); ^{13}C NMR ($CDCl_3$) δ 205.1 (s, C-3), 175.1 (s, C-9), 170.6 (s, C-1), 151.5 (s, C-Ar), 141.0 (s, C-Ar), 122.9 (d, C-Ar), 121.0 (d, C-Ar), 118.4 (d, C-Ar), 112.5 (d, C-Ar), 103.4 (d, C-1′), 80.2 (d, C-5), 79.9 (s, C-6), 77.8 (d, C-13), 74.5 (s, C-12), 71.2 (d, C-11), 70.8 (d, C-2′), 69.2 (d, C-5′), 67.7 (t, C-1′′), 66.9 (d, C-2′′), 65.7 (d, C-3′), 63.6 (t, OCH_2CH_3), 59.9 (t, C-3′′), 53.3 (t, C-5′′, 2C), 49.6 (d, C-2), 46.8 (d, C-4), 42.8 (t, C-7), 42.3 (d, C-10), 41.8 (t, C-4′′, 2C), 41.2 (d, C-8), 40.4 (q, 3′-NMe_2, 2C), 28.8 (t, C-4′), 24.8 (q, 6-Me), 23.8 (q, 8-Me), 21.5 (q, 5′-Me), 21.3 (t, C-14), 16.4 (q, 12-Me), 15.0 (q, OCH_2CH_3), 14.7 (q, 4-Me), 13.5 (q, 2-Me), 11.0 (q, 15-Me), 9.4 (q, 10-Me). Anal. Calcd for $C_{44}H_{74}N_4O_{12}$: C, 62.10; H, 8.76; N, 6.58. Found: C, 62.39; H, 8.91; N, 6.43.

The mixture of **14av** and **14bv** was separated by reversed-phase HPLC to afford **14av** and its epimeric β-hydroxy alcohol **14bv** as separate solutions in MeOH−H_2O. Solvents were removed in vacuo to give pure **14av** (17.5 mg) and **14bv** (6.0 mg) as colorless films.

6-{2′′-*syn*-Hydroxy-3′′-[2-(quinolin-6-ylamino)ethylamino]-propoxy}-3-oxo-8a-aza-8a-homoerythromycin A (14av). FAB-MS *m/z* 832 (MH^+, 91%); ^1H NMR ($CDCl_3$) δ 9.03 (d, 1H, H-4Ar), 8.09 (m, 2H, H-6Ar, H-2Ar), 7.82 (d, 1H, H-5Ar), 7.65 (dd, 1H, H-1Ar), 7.51 (dd, 1H, H-3Ar), 6.07 (bs, 1H, 8aNH), 5.10 (dd, 1H, H-13), 4.97 (m, 1H), 4.38 (d, 1H, H-1′), 4.25−4.13 (m, 1H, H-8), 3.85 (bs, 1H, H-2′′), 3.82−3.72 (m, 2H, H-5, H-2), 3.65 (d, 1H, H-1′′b), 3.57−3.48 (m, 1H, H-5′), 3.35 (s, 1H, H-11), 3.32 (t, 1H, H-1′′a), 3.25−3.15 (m, 2H, H-4, H-2′), 2.92−2.82 (m, 4H, H-4′′, H-5′′), 2.53 (t, 1H, H-3′′b), 2.46−2.38 (m, 1H, H-3′), 2.29 (s, 6H, 3′-NMe_2), 2.25 (dd, 1H, H-10), 2.20 (dd, 1H, H-3′′a), 1.96 (ddq, 1H, H-14b), 1.70 (dd, 1H, H-7b), 1.55 (d, 1H, H-7a), 1.41 (ddq, 1H, H-14a), 1.37 (s, 3H, 6-Me), 1.34 (d, 3H, 2-Me), 1.30 (d, 3H, 4-Me), 1.23 (d, 3H, 5′-Me), 1.14 (d, 3H, 10-Me), 1.12 (s, 3H, 12-Me), 1.08 (d, 3H, 8-Me), 0.90 (t, 3H, 15-Me). Anal. ($C_{43}H_{69}N_5O_{11}$) C, H, N.

6-{2′′-*anti*-Hydroxy-3′′-[2-(quinolin-6-ylamino)ethylamino]-propoxy}-3-oxo-8a-aza-8a-homoerythromycin A (14bv). FAB-MS *m/z* 832 (MH^+, 78%); ^1H NMR ($CDCl_3$) δ 9.03 (d, 1H, H-4Ar), 8.09 (m, 2H, H-6Ar, H-2Ar), 7.81 (d, 1H, H-5Ar), 7.69 (dd, 1H, H-1Ar), 7.54 (dd, 1H, H-3Ar), 6.74 (d, 1H, 8aNH), 4.63 (dd, 1H, H-13), 4.40 (d, 1H, H-1′), 4.27−4.16 (m, 1H, H-8), 3.95−3.90 (m, 2H, H-5, H-2), 3.64 (bs, 1H, H-2′′), 3.43 (d, 1H, H-1′′b), 3.39−3.30 (m, 1H, H-5′), 3.28 (s, 1H, H-11), 3.24 (t, 1H, H-1′′a), 3.22−3.15 (m, 1H, H-2′), 3.10 (m, 1H, H-4), 2.95−2.86 (m, 4H, H-4′′, H-5′′), 2.50 (t, 1H, H-3′′b), 2.48−2.40 (m, 1H, H-3′), 2.37 (s, 1H, 12-OH), 2.30 (s, 6H, 3′-NMe_2), 2.28 (dd, 1H, H-10), 2.25 (dd, 1H, H-3′′a), 2.00 (s, 1H, 11-OH), 1.93 (ddq, 1H, H-14b), 1.72 (dd, 1H, H-7b), 1.59 (d, 1H, H-7a), 1.44 (ddq, 1H, H-14a), 1.35 (s, 3H, 6-Me), 1.32 (d, 3H, 2-Me), 1.31 (d, 3H, 4-Me), 1.21 (d, 3H, 5′-Me), 1.14 (d, 3H, 10-Me), 1.13 (s, 3H, 12-Me), 1.11 (d, 3H, 8-Me), 0.85 (t, 3H, 15-Me). Anal. ($C_{43}H_{69}N_5O_{11}$) C, H, N.

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Supporting Information Available: General experimental methods, synthesis and characterization procedures, and spectral data for selected new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) The synthesis of the initial quantities of epimeric 6-*O*-allyl Ery A 9(*Z*)-oxime (**21**) was achieved via oximation (NH_2OH HCl/ Na_2CO_3/MeOH, reflux) of the 6-*O*-allyl Ery A[6] followed by silica gel chromatography of the 9:1 *E*/*Z* epimeric mixture of oximes. Resubmission of the purified *E*-isomer to deoximation (($NaHSO_3$−HCOOH−EtOH)/water 1:1, reflux) followed by oximation actually served to reestablish the equilibrium mixture that consisted of about 10% of the *Z*-isomer. Laborious repetition of this procedure could serve to completely isomerize the sample of 6-*O*-allyl Ery A 9(*E*)-oxime (**20**). Almost the same methodology was used by Merck scientists to synthesize the initial quantities of pure 6-*O*-methyl Ery A 9(*Z*)-oxime (**23**).[20c] Although authors claim that a small number of such iterations on multigram scale provided useful amounts of material, in practice to synthesize larger quantities of 9(*Z*)-oxime, this procedure obviously does not represent either a synthetically useful or economically viable solution. For the synthesis and spectroscopic characterization of 6-*O*-allyl Ery A 9(*Z*)-oxime (**21**), see Supporting Information.

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(19) 3-*O*-Descladinosyl-6,12-di-*O*-allylerythromycin A 9(*E*)-oxime (**24**) was conveniently prepared in a two-reaction one-pot sequence. Thus, deprotection and selective cleavage of the cladinose sugar were accomplished by treating an aqueous ethanolic solution of **19** with 2 M HCl for 18 h at room temperature. Oxime **24** was isolated by selective extraction with methylene chloride at pH 9. On the other hand, the same process at pH 1 was used to efficiently remove the cladinose-related byproduct from the aqueous workup. For detailed experimental procedure and spectroscopic data, see Supporting Information.

(20) For the preparation of Ery A 9(*Z*)-oxime via base-catalyzed isomerization of Ery A 9(*E*)-oxime, see the following: (a) Gasc, J. C.; D'Ambrieres, S. G.; Lutz, A.; Chantot, J. F. New Ether Oxime Derivatives of Erythromycin A. A Structure−Activity Relationship Study. *J. Antibiot*. **1991**, *44*, 313–330.(b) See also ref 12c for the independently developed synthesis of Ery A 9(Z)-oxime by means of base-catalyzed isomerization. (c) For the attempted preparation of 6-O-methyl Ery A 9(Z)-oxime via E−Z isomerization, see the folloiwng: Waddell, S. T.; Santorelli, G. M.; Blizzard, T. A.; Graham, A.; Occi, J. *Bioorg. Med. Chem. Lett*. **1998**, *8*, 1321–1326. To prepare a sizable amount of 6-O-methyl Ery A 9(Z)-oxime (23) for the Beckmann rearrangement studies, these authors have used an equilibration method based on the successive oximation of the purified E-isomer 22. It would be interesting to investigate whether the E−Z isomerization in the clarithromycin series may be achievable using 3-O-descladinosyl-3-oxy-6-O-methyl Ery A 9(E)-oxime as a starting material instead of 6-O-methyl Ery A 9(E)-oxime. However, such a study is outside the scope of this work.

(21) Another approach to **15** includes a tedious and time-consuming chromatographic separation of an *E*−*Z* epimeric mixture of 6-*O*-allyl Ery A oximes **20** and **21** (*E*/*Z* ratio of 9:1 according to HPLC) obtained via oximation procedure described in ref 17. Subsequent Beckmann rearrangement of the isolated 9(Z)-oxime 21 followed by acidic hydrolysis of the resulting 6-O-allyl-8a-aza-8a-homoEry A (27) afforded 3-O-descladinosyl-8a-aza-8a-homoEryA (15). Despite this somewhat more complex isolation procedure and significantly lower yields in comparison to E−Z isomerization−Beckmann rearrangement methodology, compound 15 could be prepared on a 500 mg scale in essentially pure form. For the preparation and structure confirmation of 27, see Supporting Information.

(22) On the other hand ring enlargement of 3-*O*-descladinosyl-6-*O*-allylerythromycin A 9(*E*)-oxime (**9**) yielded 9a-aza-9a-homoerythromycin derivative in 85% yield. To our delight, the scope of the Beckmann rearrangement proved to be quite broad, as it turned out that it could readily be applied to other 14-membered ring macrolides. For example, ring enlargement of descladinosyl-6,12-di-*O*-allylerythromycin-9(*E*)-oxime (**24**) and the other two oximes in the cladinosyl series, 6-*O*-allylerythromycin 9(*E*)- and 9(*Z*)-oximes (**20** and **21**), under the same reaction conditions as those applied in Beckmann rearrangement of **9** and **10**, provided the corresponding 15-membered ring macrolides in high yield.

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