# Novel Erythromycin Derivatives with Aryl Groups Tethered to the C-6 Position Are Potent Protein Synthesis Inhibitors and Active against Multidrug-Resistant Respiratory Pathogens

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*Received May 25, 2001*

A novel series of erythromycin derivatives has been discovered with potent activity against key respiratory pathogens, including those resistant to erythromycin. These compounds are characterized by having an aryl group tethered to the C-6 position of the erythronolide skeleton. Extensive structural modification of the C-6 moiety led to the discovery of several promising compounds with potent activity against both *mef*- and *erm*-mediated resistant *Streptoccoccus pneumoniae*. Preliminary mechanistic studies indicated that the new macrolides are potent protein synthesis inhibitors, which interact with methylated ribosomes isolated from resistant organisms. In experimental animal models, these compounds exhibited excellent in vivo efficacy and balanced pharmacokinetic profiles.

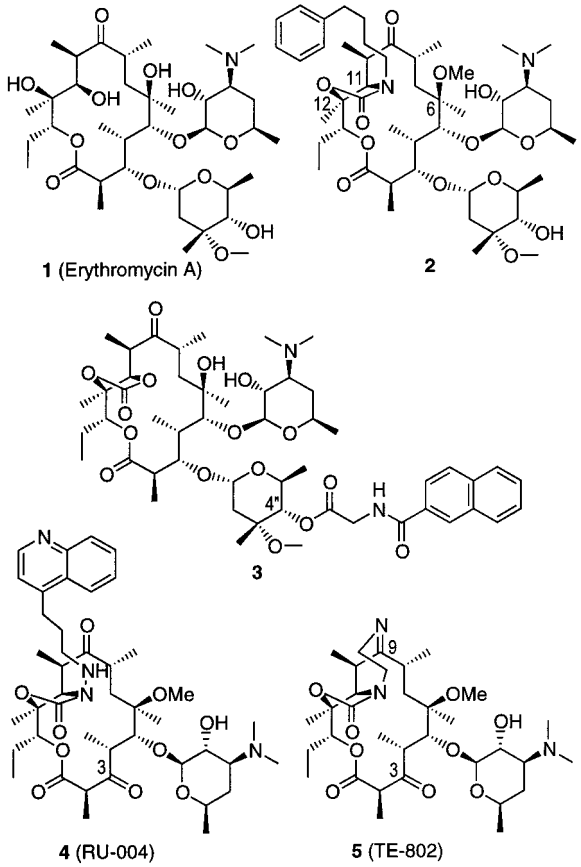
## Introduction

The growing prevalence of antibiotic resistance in bacterial species commonly involved in respiratory tract infections has become a serious clinical problem.[1] *Streptoccoccus pneumoniae* is one of the most common and also the most problematic respiratory pathogen. According to a surveillance study conducted between 1997 and 1998 in the United States, 29.5% of *S. pneumoniae* isolates were intermediately or highly resistant to penicillin, which represented a sharp increase from the 1980s, when less than 4% of these species were considered penicillin-resistant.[2] Meanwhile, resistance to other commonly prescribed antibiotics, such as macrolides, cephalosporins, and tetracycline, has also been rising. Studies indicated that the penicillin-resistant species tends to be resistant to other antibiotics, which has led to a serious multidrug resistance problem.[2,3] If the current trend continues, many of the commonly used antibiotics will soon lose their effectiveness.

Addressing bacterial resistance problems requires a more judicious use of the available antibiotics as well as the development of new agents that are effective against resistant organisms. In a previous communication, we disclosed the discovery of a novel series of C-6-modified erythromycin derivatives highly active against the resistant respiratory pathogens.[4] Since then the work has been continued and the series has been extensively characterized. In this report, we wish to give a full account of the design rationale, chemical synthesis, mechanism of action, and structure−activity relationships of this novel macrolide series.

## Design Rationale

Macrolide antibiotics, such as erythromycin (**1**), clarithromycin, and azithromycin, provide good coverage against all key respiratory pathogens. They possess excellent safety and tolerability profiles and are widely prescribed to children as well as adults for the treatment of upper and lower respiratory tract infections.[5] The new agents need to preserve all of the desirable features of the earlier generation of macrolides, and in addition they must be active against bacteria with the major resistant mechanisms.

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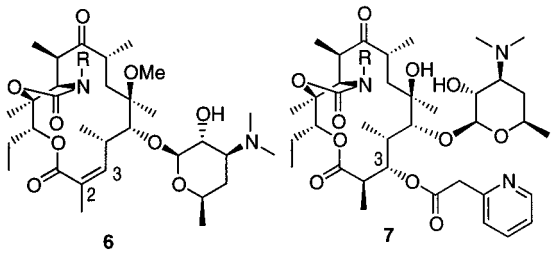
10.1021/jm0102349 CCC: $20.00 
Published on Web 10/18/2001

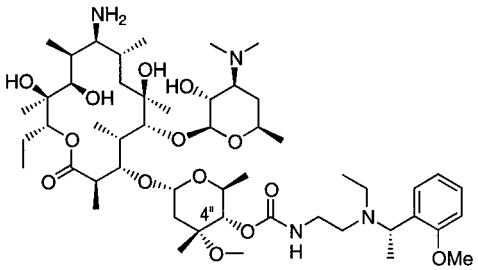
Two distinguished mechanisms have accounted for the majority of macrolide resistance.[6,7] The first mechanism involves methylation of the target ribosome by a ribosomal methylase (Erm) encoded by *erm* genes. Dimethylation of a specific adenine group (2058 adenine based on *Escherichia coli* sequence) of the 23S ribosomal RNA prevents the binding of macrolides and confers a high level of resistance to macrolides, lincosamides, and type B streptogramin ($MLS_B$). The expression of Erm may be inducible or constitutive. The second mechanism of macrolide resistance is efflux encoded by *mef* genes, which removes macrolides from intracellular space and prevents macrolides from reaching the target. Our task, therefore, was to identify a macrolide structure that could bind to methylated ribosomes and avoid the efflux protein recognition.

Since the late 1980s, a significant amount of work has been done in order to develop a new generation of macrolides to overcome bacterial resistance.[5,8] The structure−activity relationships developed during this period have therefore provided a foundation for the design of a more advanced generation of macrolide agents. In 1989, two series of erythromycin derivatives, aryl-substituted 11,12-carbamate macrolides exemplified by **2** and C-4″-modified 11,12-carbonate macrolides exemplified by **3**, were reported.[9] Both series showed activity against $MLS_B$-resistant *Streptococcus pyogenes*. Structure−activity relationship analysis indicated that the aryl groups attached to the 11,12-carbamate nitrogen were essential for the activity against resistance. Following these leads, a series of aryl-substituted 11,-12-carbamate ketolides exemplified by RU-004 (**4**) was prepared by removing the cladinose from the C-3 position and converting the remaining hydroxy group to a carbonyl functionality. These compounds were reported to be active against efflux and $MLS_B$-resistant organisms. The aryl groups attached to the 11,12-carbamate nitrogen were shown to be critical pharmacophores for activity against $MLS_B$ resistance.[10] At about the same time, a series of tricyclic ketolides exemplified by TE-802 (**5**) was reported.[11] The tricyclic ketolides, which lacked an aryl group, exhibited good activity against efflux resistance but failed to show any activity against $MLS_B$-resistant organisms. With this information in hand, we postulated that the aryl group tethered to the macrolide skeleton is crucial for activity against $MLS_B$ resistance and the C-3 keto group is important for the improved activity against efflux resistance. Since 1995, several new macrolide series, including anhydrolides **6**,[12] acylides **7**,[13] and erythromycylamine C-4″-carbamates, exemplified by CP-544372 (**8**),[14] have been reported and provided further support to this hypothesis. In addition, results from these newer series further suggested that structural modifications other than introducing a keto group at the C-3 position could also improve activity against efflux resistance.

On the basis of the above considerations, we designed a novel structural series that consists of the essential features for addressing macrolide resistance due to both efflux and methylation of the ribosome. The designed structure contains an aryl group tethered to the C-6 position for overcoming the $MLS_B$ resistance and a carbonyl group at the C-3 position for surmounting the efflux resistance. The C-6 linking point was selected



**6** **7**



**8** (CP-544372)

with the assumption that an aryl group attached to this position would provide a favorable conformation for ribosomal binding. The conformations of 14-membered ring macrolides have been the subject of many studies.[15] The crystal structure of erythromycin was first reported in 1965, which indicated that the erythronolide adopts the Perun conformation derived from an alternative diamond lattice.[16] Recent studies suggested that the ketolide skeleton possesses a similar conformation to the erythronolide as indicated by X-ray crystal structures and solution conformations generated from NMR data.[10,17] Both the erythronolide and ketolide skeletons are rigid and the solution conformations are similar to their crystal structures.[15,17,18] Conformational analysis revealed a very important bifacial feature common to most 14-membered ring macrolides, which is the lipophilicity difference between the two sides of the lactone ring. As indicated by the crystal structure of 6-*O*-methylerythromycin (clarithromycin) (Figure 1), all of the oxygen-containing groups attached to the lactone ring point to the front side and the majority of methyl groups attached to the lactone ring point to the back side of the molecule, creating a hydrophilic face and a lipophilic face. We believed that this bifacial nature of macrolide molecules is very important for many of their biological functions, including interaction with ribosome, membrane permeability, and tissue distribution. The crystal structure of RU-004 (**4**) revealed that the aryl

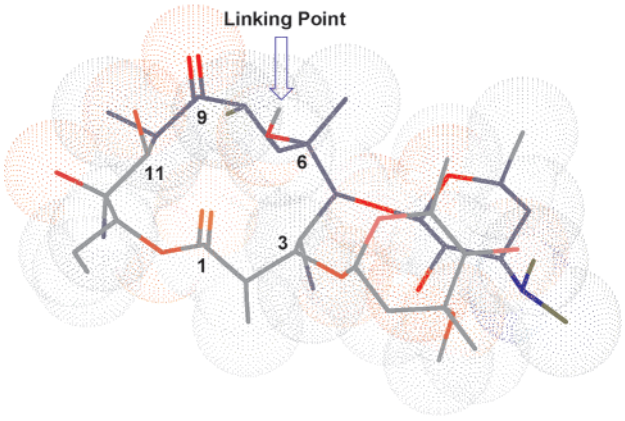



**Figure 1.** Crystal structure of 6-*O*-methylerythromycin.

moiety attached to the carbamate nitrogen is localized on the hydrophilic face of the molecule, suggesting that a potential secondary interaction may exist on the hydrophilic side. According to the X-ray crystal structure of clarithromycin (Figure 1), the C-6 hydroxyl group is localized in the middle of the hydrophilic face. It was apparent to us that an aryl group tethered to this position would adopt a conformation that delivers the aryl group to a spatial position similar to that of the aryl group in RU-004. In addition, the C-6 linkage was likely to provide a more rigid structure with less conformational flexibility, which could translate into a better binding affinity and improved antibacterial activity (Figure 1).

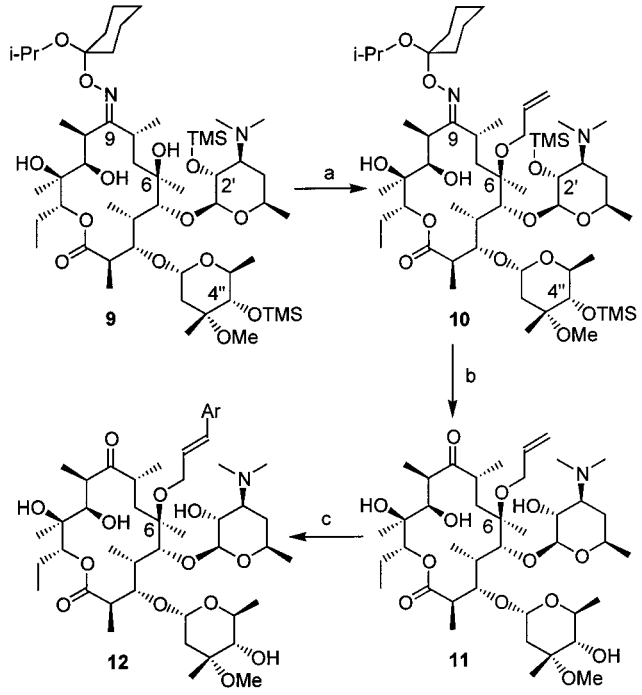
## Synthesis

**Introduction of C-6 Substituents.** The synthesis of 6-*O*-allylerythromycin (**11**) has been described in a previous communication.[4c] Detailed synthetic procedures for these transformations are provided in the Experimental Section. As shown in Scheme 1, erythromycin A was first protected as its 9-ketaloxime-2′,4″-bis(trimethylsilyl) derivative **9**, which has been used for the selective methylation of the C-6 hydroxyl group in the synthesis of clarithromycin.[19] Allylation of **9** with allyl bromide in the presence of potassium hydroxide (KOH) provided the 6-*O*-allyl product selectively but with relatively low conversion of starting material. Optimization of the reaction conditions brought the reaction to only 50−60% conversion. Several other bases such as potassium methoxide (KOMe), sodium hydride (NaH), and lithium diisopropylamide (LDA) were explored without further improvement over KOH. We realized that the extensive loss of allyl bromide due to rapid reaction with KOH was likely responsible for the retarded 6-*O*-allylation. To overcome this problem, we replaced KOH with potassium *tert*-butoxide (KOBu$^t$), a sterically hindered base, in order to slow the undesired side reaction. Indeed, this modification brought the reaction to more than 90% completion and provided the 6-*O*-allyl intermediate **10** in good yield. Sequential deprotection of TMS and ketal groups followed by deoximation[19] provided 6-*O*-allylerythromycin (**11**) in 33% overall yield from **9**.

The C-3 keto group was introduced in three steps from **11** (Scheme 2). Selective hydrolysis of the cladinose sugar provided the C-3 hydroxyl compound. The C-2′ hydroxyl group was sequentially protected as the benzoate ester. Finally, Corey−Kim oxidation[20] of the C-3 hydroxyl group with *N*-chlorosuccinimide (NCS) and dimethyl sulfide ($Me_2S$) provided ketolide **13** in 77% overall yield from **11**. Deprotection of **13** under mild conditions provided the 6-*O*-allyl ketolide **14**.

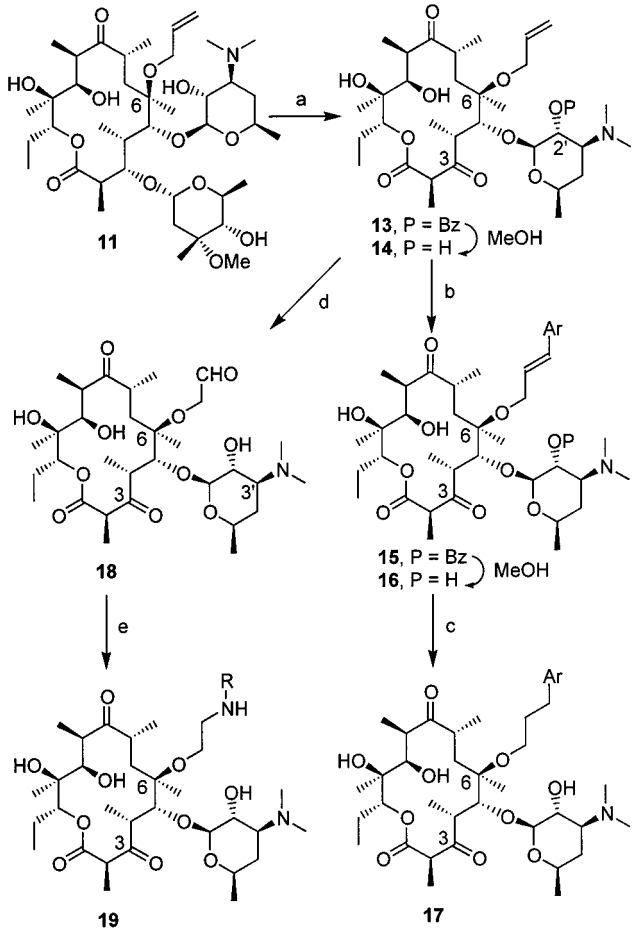
The next task was to introduce an anchor group to the C-6 side chain on the basis of the rationale discussed previously. We decided to explore a direct carbon−carbon bond formation strategy that could lead to a

**Scheme 1.** Synthesis of 6-*O*-Substituted Erythromycin Derivatives[a]



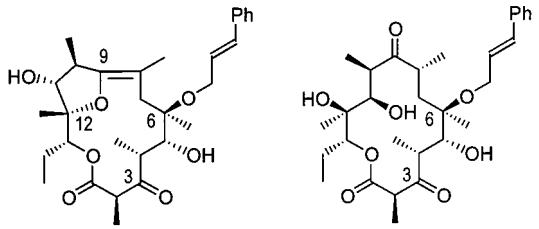

[a] (a) Allyl bromide, KOBu$^t$, DMSO−THF. (b) (i) HOAc, $H_2O$−$CH_3CN$; (ii) $NaHSO_3/HCO_2H$, EtOH−$H_2O$. Yield 33% in three steps from **9**. (c) Ar-X (X = Br or I), $Pd(OAc)_2$, P(*o*-tolyl)$_3$, $Et_3N$, $CH_3CN$. Yield 60−80%.

**Scheme 2.** Synthesis of 6-*O*-Substituted Ketolide Derivatives[a]




[a] (a) (i) HCl, EtOH; (ii) $Bz_2O$, $Et_3N$, $CH_2Cl_2$; (iii) NCS, $Me_2S$, $Et_3N$, $CH_2Cl_2$. Yield 77% in three steps. (b) Ar-X (X = Br or I), $Pd(OAc)_2$, P(*o*-tolyl)$_3$, $Et_3N$, $CH_3CN$. Yield 60−80%. (c) $H_2$, Pd−C, MeOH. Yield 99%. (d) (i) $O_3$, $CH_2Cl_2$, and then $Me_2S$; (ii) $PPh_3$, THF. Yield 52% in two steps. (e) R-$NH_2$, HOAc, $NaBH_3CN$, MeOH. Yield 50−70%.

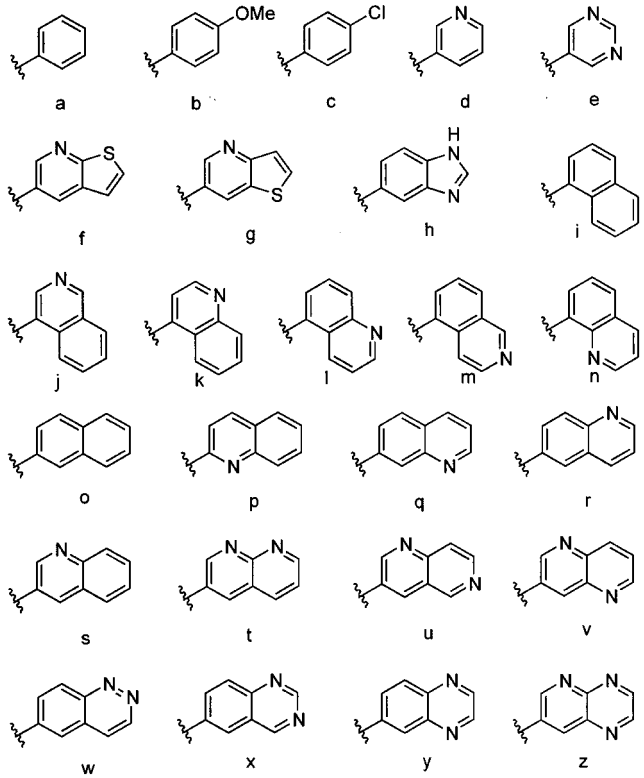
series of ketolides with an anchor group attached to the C-6 position through a three-carbon spacer. Heck coupling of **13** with aryl halides was thus employed.[21] Under commonly employed Heck coupling conditions [Ar-X/$Pa(OAc)_2$/*n*-$Bu_4N^+Cl^-$/$NaHCO_3$/DMF at 80 °C for 12 h], none of the desired product **15** (Ar = Ph) was obtained. The major product isolated from this reaction was **20** (30−40%), a coupling product resulted from desosamine elimination and 9,12-enol ether formation. A change of solvent from DMF to *N*-methyl-2-pyrrolidone (NMP) prevented the 9,12-enol ether formation but gave desosamine elimination product **21** in 66% yield.




**20** **21**

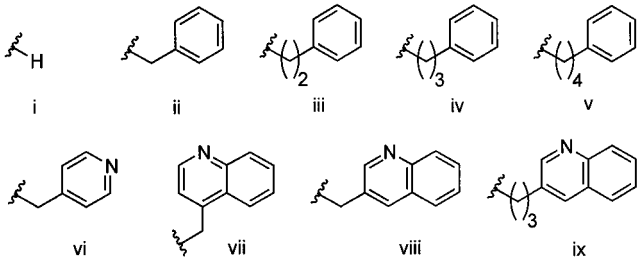
When toluene was used as solvent and triethylamine as base [PhI/$Pa(OAc)_2$/$PPh_3$/$Et_3N$/toluene], about 20% of desired coupling product **15** was isolated. The major material recovered was the starting material **13**. However, the reaction went to completion when acetonitrile ($CH_3CN$) was used as solvent and provided **15** (Ar = Ph) in 68% isolated yield. More reproducible results were obtained when tri(*o*-tolyl)phosphine [P(*o*-tolyl)$_3$] was employed replacing triphenylphosphine ($PPh_3$) as ligand. Tri(*o*-tolyl)phosphine is known to form a stable palladium(0) complex and therefore prevent the decomposition of catalyst.[22] Deprotection of the coupling products under mild conditions provided 6-*O*-(3-aryl-2-propenyl) ketolides **16**. Under optimized Heck conditions, a series of 6-*O*-substituted ketolides with a variety of aryl groups tethered to the C-6 position was prepared (Chart 1). 6-*O*-Phenylpropyl ketolide **17**, a derivative with a saturated linker between the aryl group and the lactone ring, was prepared by catalytic hydrogenation of **16**. For comparison purposes, 6-*O*-(3-aryl-2-propenyl)-erythromycin derivatives **12** (Ar = Ph, 3-quinolyl) were also prepared from **11** by utilizing the optimized coupling conditions (Scheme 1).

**Chart 1.** Structures of Aryl (Ar) Groups




From 6-*O*-allyl ketolide **14**, another series of ketolide analogues **19** was prepared through the aldehyde intermediate **18**. Ozonolysis of ketolide **13** gave a mixture of products and no appreciable amount of the desired aldehyde was obtained. However, ozonolysis of **14**, the C-2′-deprotected ketolide, provided the 6-*O*-formylmethyl ketolide as the *N*-oxide. The desired aldehyde **18** was obtained in 52% yield from **14** after the *N*-oxide was reduced with $PPh_3$ in THF. Reductive amination of **18** provided a series of amino derivatives **19** with a variety of R groups attached to the C-6 position through a nitrogen-containing linker (Chart 2).

**Chart 2.** Structures of R Groups

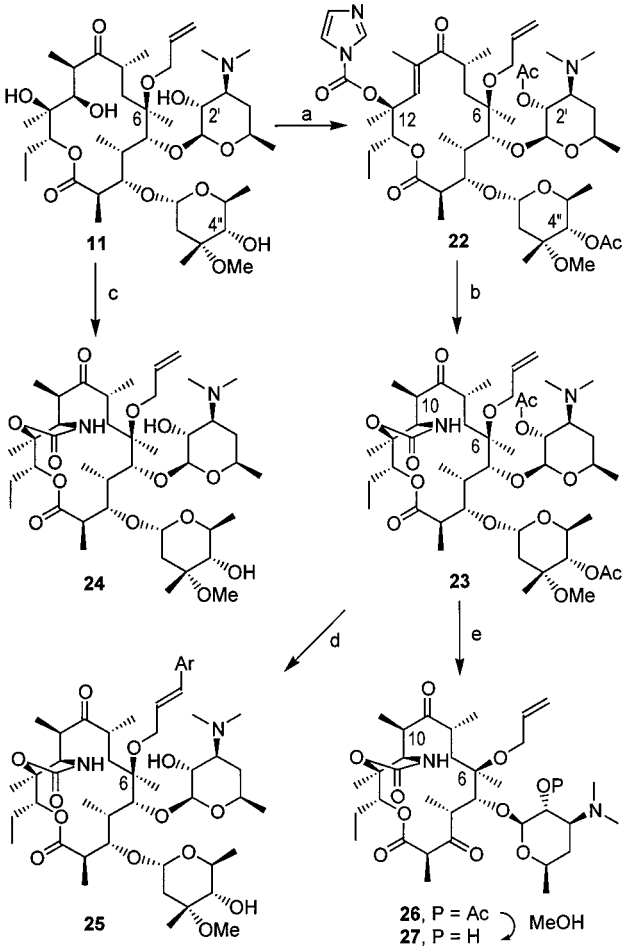



**Synthesis of 11,12-Carbamate Derivatives.** Baker et al.[9] reported that introduction of a cyclic carbonate or cyclic carbamate group to the 11,12-position of clarithromycin enhanced the antibacterial activity. In an analogous fashion, we converted 6-*O*-allylerythromycin (**11**) to the corresponding cyclic carbamate **23** (Scheme 3). After proper protection, **11** was converted to the 12-*O*-acylimidazolide **22** in the presence of sodium bis(trimethylsilyl)amide (NaHMDS) and 1,1′-carbonyldiimidazole (CDI). Treatment of **22** with aqueous ammonia in acetonitrile ($CH_3CN$) provided carbamate **23** and its C-10 epimer in a 10:1 ratio. The deprotected 6-*O*-allylerythromycin-11,12-carbamate **24** was prepared in four steps from **11** by following a sequence similar to a published process.[9] For comparison purposes, the 6-*O*-(3-aryl-2-propenyl)erythromycin-11,12-carbamate **25** was prepared from **23** by Heck coupling followed by hydrolysis.

The 11,12-carbamate ketolide **26** was prepared from **23** in two steps, which involved hydrolysis of the cladinose and Corey−Kim oxidation of the C-3 hydroxyl group. Deprotection of the acetate protecting group with MeOH at room temperature provided 6-*O*-allyl ketolide-11,12-carbamate **27** in excellent yield.

Alternatively, the 2′-*O*-benzoyl-6-*O*-allyl ketolide-11,-12-carbamate **29** was prepared from **13** in two steps through 12-*O*-acylimidazolide **28**, which was obtained by treatment of **13** with lithium hydride (LiH) and CDI (Scheme 4). Reaction of **28** with aqueous ammonia provided the 11,12-cyclic carbamate **29** and its C-10

**Scheme 3.** Synthesis of 6-*O*-Substituted-11,12-Carbamate Derivatives[a]



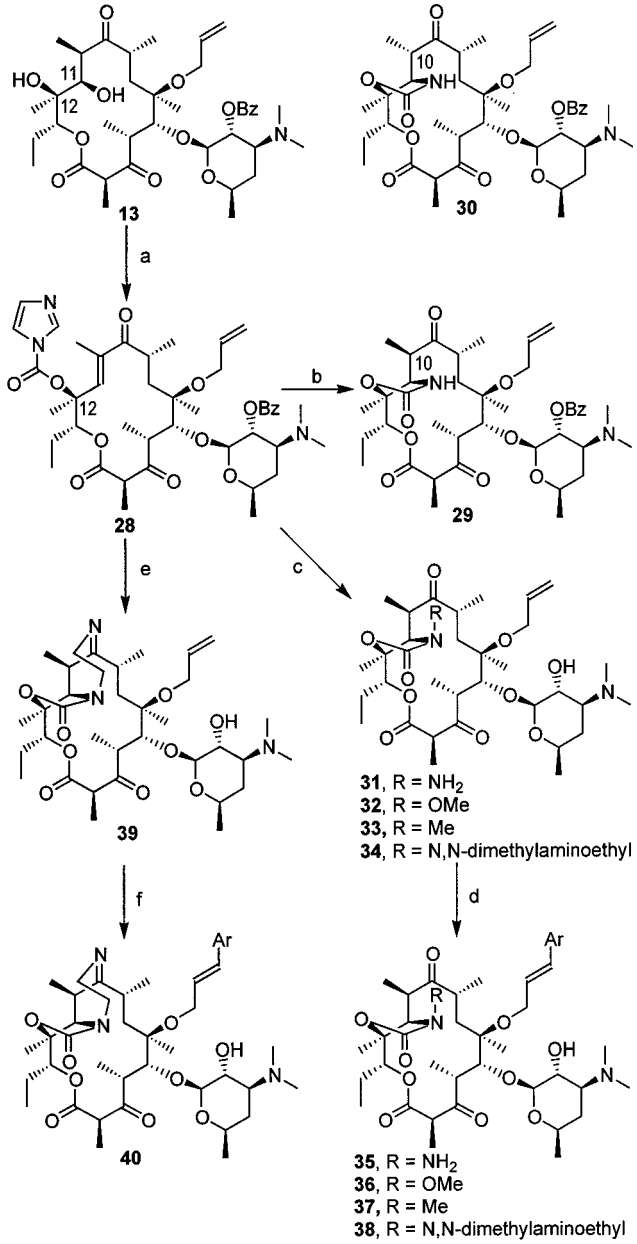

[a] (a) (i) $Ac_2O$, $Et_3N$, DMAP, $CH_2Cl_2$; (ii) CDI, NaHMDS, THF−DMF. (b) $NH_4OH$ (28%), $CH_3CN$−THF. Yield 78% in three steps from **11**. (c) (i) Ethylene carbonate, $Et_3N$; (ii) $(TMS)_2NH$, $CH_3CN$−$CH_2Cl_2$–THF; (iii) CDI, NaH, THF; (iv) $NH_3$, $CH_3CN$. Yield 65% in four steps from **11**. (d) (i) Ar-X (X = Br or I), $Pd(OAc)_2$, P(*o*-tolyl)$_3$, $Et_3N$, $CH_3CN$, yield 60−80%; (ii) NaOH, MeOH, yield 61%. (e) (i) HCl, EtOH−$H_2O$; (ii) NCS, $Me_2S$, and then $Et_3N$, $CH_2Cl_2$. Yield 84%.

epimer **30** in 51% and 32% yields, respectively. Epimer **30** was converted to the natural configuration by reaction with acetic acid in ethanol. When 12-*O*-acylimidazolide **28** was treated with hydrazine, the 11,12-carbazate **31** was obtained. In an analogous fashion, the *N*-methoxy derivative **32** was obtained by reacting **28** with *O*-methylhydroxylamine. Alternately, when **28** was treated with a variety of primary amines, a series of *N*-substituted analogues **33** and **34** were obtained. Finally, reaction of **28** with ethylenediamine resulted in the formation of a tricyclic ketolide **39**, after epimerization under HOAc/MeOH conditions.

The carbamate ketolide intermediates **31**−**34** were further derivatized by using the optimized Heck conditions and provided coupling products **35**−**38** (Scheme 4). Similarly, tricyclic intermediate **39** was converted to the 6-*O*-(3-aryl-2-propenyl) tricyclic ketolide **40**.

Preliminary SAR studies suggested that ketolides with an unsubstituted 11,12-carbamate group provided the best antibacterial spectrum and activity. Therefore, we focused our further efforts on modifications of the

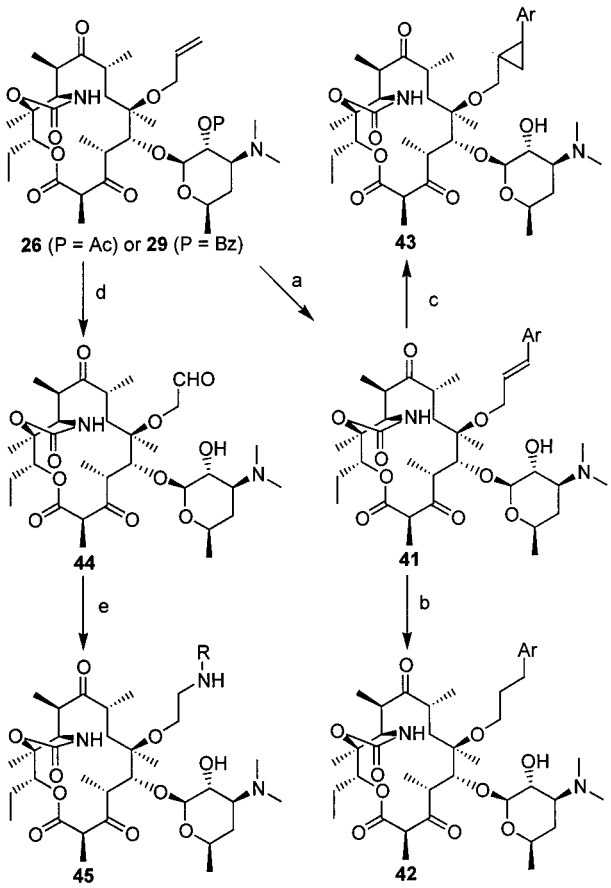
**Scheme 4.** Synthesis of 6-*O*-Substituted-11,12-Carbamate Ketolides[a]




[a] (a) LiH, CDI, THF. Yield 68%. (b) $NH_4OH$, $CH_3CN$−$H_2O$. Yield for **29**, 51%; for **30**, 32%. (c) R-$NH_2$ (R = -$NH_2$, -OMe, -Me, -$CH_2CH_2NMe_2$), $CH_3CN$−$H_2O$. Yield 50−80%. (d) Ar-X (X = Br or I), $Pd(OAc)_2$, P(*o*-tolyl)$_3$, $Et_3N$, $CH_3CN$ 20−40%. (e) (i) $H_2NCH_2$-$CH_2NH_2$, $CH_3CN$; (ii) HOAc, MeOH. Yield 40%. (f) 3-Bromoquinoline, $Pd(OAc)_2$, P(*o*-tolyl)$_3$, $Et_3N$, $CH_3CN$. Yield 62%.

C-6 allyl group of structure **27**. The protected 6-*O*-allyl ketolide-11,12-carbamates **26** and **29** were thus employed as key intermediates for such modifications (Scheme 5). When **26** or **29** reacted with various aryl halides under the optimized Heck conditions, a series of 6-*O*-(3-aryl-2-propenyl) ketolide-11,12-carbamates **41** was obtained (Chart 1). To study the effects of the aryl group orientation, nine positional isomers of quinoline and isoquinoline were prepared by coupling the corresponding aryl bromide, chloride, or triflate to the allylic double bond. Various substituted 3-quinolyl derivatives were also synthesized to study the substituent effects. 6-*O*-Arylpropyl ketolides **42**, the saturated analogues of

**Scheme 5.** Synthesis of 6-*O*-Substituted-11,12-Carbamate Ketolides[a]




[a] (a) (i) Ar-X (X = Br or I), $Pd(OAc)_2$, P(*o*-tolyl)$_3$, $Et_3N$, $CH_3CN$; (ii) MeOH. Yield 9−97% in two steps. (b) $H_2$, 10% Pd−C, MeOH. Yield 95%. (c) $CH_2N_2$, $Pd(OAc)_2$, $CH_2Cl_2$. Yield 64% (diastereomers in 60:40 ratio). (d) (i) MeOH; (ii) $O_3$, $CH_2Cl_2$, and then $Me_2S$; (iii) $PPh_3$, THF. (e) R-$NH_2$, HOAc, $NaBH_3CN$, MeOH.

**41**, were obtained by catalytic hydrogenation. Cyclopropanation of **41** provided the cyclopropyl analogue **43** as a mixture of diastereomers. As illustrated in Scheme 5, a series of amine-containing derivatives **45** were also prepared through the aldehyde intermediate **44** by following the procedure used to prepare compounds **19**.

## Microbiology

**In Vitro Transcription−Translation Assay.** The bacterial ribosome S-30 extracts used in the cell-free translation assays were prepared according to the reported procedures.[23] The wild-type ribosome was isolated from an erythromycin-susceptible strain *S. pneumoniae* 5635. The methylated ribosome was isolated from *S. pneumoniae 1813*, an *erm*-containing strain with a high level of $MLS_B$ resistance. DNA plasmid containing a pneumococcal *ami* promoter and a luciferase reporter gene was constructed at Abbott Laboratories. The reaction mixture contained 1 $\mu$g of plasmid, 0.15 unit of S-30 extract, 0.2 mM complete amino acid mix, and 5 $\mu$L of premix solution in a final volume of 15 $\mu$L. The reaction was then mixed with 75 $\mu$L of luciferin reagent containing ATP and immediately read on a Wallac Trilux Luminescence counter.

**In Vitro Antibacterial Activity.** The 6-*O*-substituted macrolides and ketolides used in this study and the reference agent, erythromycin, were tested against a panel of representative respiratory pathogens selected from the Abbott clinical culture collection. Various macrolide- and multidrug-resistant isolates were included in the tests in order to identify potential analogues that could overcome resistance. The phenotype and the genotype of these resistant strains were characterized by methods described previously (Table 1).[24] The in vitro antibacterial activity is reported as the minimum inhibitory concentrations (MICs), which were determined by the agar dilution method as recommended by the National Committee for Clinical Laboratory Standards.

**In Vivo Efficacy.** The in vivo efficacy of selected compounds was assessed by mouse protection tests (MPT) and rat lung infection models (RLI). In the mouse protection tests, the mice were inoculated intravenously with a 100-fold $LD_{50}$ of representative organisms. Tested compounds were administered by oral gavage at 1 h and 5 h postinoculation. Mortality rates of the mice were monitored for a period of 7 days postinoculation with a 100% mortality rate for untreated controls. The efficacy of each compound, based on the survival rates over a dose range, was reported as the drug dose resulting in a survival of 50% of treated mice over the duration of the trial ($ED_{50}$).

In the rat lung infection models, the rats were intratracheally inoculated with 0.5 mL of bacteria suspension in 5% gastric hog mucin containing log $10^6$−$10^8$ colony-forming units (cfu). Test compounds were administered by peroral gavage once daily, days 1−3, starting 18 h postinoculation. Lung bacterial burden was assessed from serial dilution plating of lung tissue homogenates on day 4. The $ED_{50}$ to yield a 2-log reduction in bacteria count compared to vehicle-treated infected controls was calculated from the group means by linear regression.

## Results and Discussion

**Mechanism of Action of the 6-*O*-Substituted Ketolides.** Macrolides exert their antimicrobial activity

**Table 1.** Selected Organisms and Their Resistant Determinants

| strain | | phenotype | genotype |
|---|---|---|---|
| *Staphylococcus aureus* | ATCC 6538P | erythromycin-susceptible | none |
| *Staphylococcus aureus* | A 5177 | MLS-resistant (inducible) | *ermA* |
| *Staphylococcus aureus* | A 5278 | MLS-resistant (constitutive) | *ermA* |
| *Streptococcus pyogenes* | EES 61 | erythromycin-susceptible | none |
| *Streptococcus pyogenes* | 930 | MLS-resistant | *ermB* |
| *Streptococcus pyogenes* | PIU 2548 | efflux | *mefA* |
| *Streptococcus pneumoniae* | ATCC 6303 | erythromycin-susceptible | none |
| *Streptococcus pneumoniae* | 5737 | MLS-resistant | *ermB* |
| *Streptococcus pneumoniae* | 5649 | efflux | *mefE* |
| *Haemophilus influenzae* | DILL | ampicillin-resistant | *BL+* |

**Table 2.** Cell-Free Inhibiting Activity of Selected Compounds on Transcription−Translation by Ribosomes Isolated from both Susceptible and Resistant (*erm*) Strains

| | Ery-S strain[a] | | $MLS_B$-R strain[b] | |
|---|---|---|---|---|
| compound | MIC ($\mu$g/mL) | T/T $IC_{50}$ ($\mu$M) | MIC ($\mu$g/mL) | T/T $IC_{50}$ ($\mu$M) |
| erythromycin | 0.06 | 0.12 | >128 | >500 |
| clarithromycin | 0.03 | 0.09 | >128 | >500 |
| azithromycin | 0.25 | 0.17 | >128 | >500 |
| **11** | 0.06 | 0.15 | >128 | >500 |
| **27** | 1 | 0.35 | >128 | >500 |
| **41g** | 0.004 | 0.07 | 0.5 | 150 |
| **41s** | 0.004 | 0.04 | 0.25 | 28 |
| **41v** | 0.015 | 0.10 | 0.25 | 25 |
| **41y** | 0.015 | 0.08 | 0.25 | 40 |

[a] Wild-type ribosomes for cell-free transcription/translation assay (T/T) were isolated from erythromycin-susceptible strain *S. pneumoniae* 5635. The whole-cell antibacterial activity is exemplified by minimum inhibitory concentrations (MICs) against *S. pneumoniae* ATCC 6303, an erythromycin-susceptible strain. [b] Methylated ribosomes for cell-free transcription/translation assay (T/T) were isolated from *S. pneumoniae* 1813, an $MLS_B$-resistant strain with a high level of methylation at 2058A position. The whole-cell antibacterial activity is exemplified by minimum inhibitory concentrations (MICs) against *S. pneumoniae* 5737, an $MLS_B$-resistant strain.

by interacting with the large subunit of bacterial ribosome and inhibiting protein synthesis.[5] The binding region of macrolides on the bacterial ribosome has been well studied by various means, including chemical footprinting of bound macrolide and mutational resistance.[25] Recently the atomic structure of the bacterial ribosome isolated from *Haloarcula marismortui* has been disclosed and the crystal structure of the ribosome with bound macrolide may soon become available.[26] The macrolide binding site is located in domain V of the 23S ribosomal RNA, which overlaps with the binding site of lincosamides and type B streptogramin antibiotics. One of the most prevalent macrolide-resistant mechanisms involves N-6 dimethylation of a single adenine base (A2058 based on *E. coli* sequence) in domain V, which reduces drug binding affinity and confers resistance to macrolides, lincosamides, and type B streptogramin ($MLS_B$ resistance).[6] Many of the 6-*O*-substituted ketolides not only showed improved activity against erythromycin-susceptible strains but also exhibited potent activity against $MLS_B$-resistant organisms (Table 3 ). Mechanistic studies of ABT-773 (**41s**) have indicated that this compound binds to the same binding site as previous macrolides but with improved binding affinity.[23] Moreover, ABT-773 binds to the methylated ribosomes isolated from $MLS_B$-resistant *S. pneumoniae*, which has not been observed for the older generation macrolides.

The improved binding ability of these new ketolides was further supported by the luciferase transcription/translation (T/T) assay. The inhibitory effects of a selected group of ketolides on protein synthesis with both wild-type and methylated ribosomes are summarized in Table 2. Ketolides **41g**−**41y** showed slightly improved inhibitory activity (1−3-fold) against wide-type ribosomes as compared to erythromycin. The inhibitory $IC_{50}$ data correlated very well with the MIC data against erythromycin-susceptible strains. However, ketolides **41g**−**41y** exhibited significantly improved activity against $MLS_B$-resistant strains with MICs between 0.25 and 0.5 $\mu$g/mL, while the reference macrolides erythromycin, clarithromycin, and azithromycin showed no activity up to 128 $\mu$g/mL. In the cell-free translation assay performed with methylated ribosomes isolated from $MLS_B$-resistant strains, the reference macrolides showed no inhibitory effect, while ketolides **41g**−**41y** exhibited substantially improved inhibitory activity (Table 2). These data suggested that the ketolides could interact with methylated ribosomes and exert activity against $MLS_B$-resistant organisms. The data also suggested that the aryl group attached to the C-6 position is the key structural feature for the interaction with methylated ribosomes. Without the aryl group attached, macrolide **11** and ketolide **27** showed no inhibitory activity against methylated ribosomes. As we have postulated previously, and which will be further supported by our structure−activity relationship analysis in the following sections, the aryl group tethered to the C-6 position is likely responsible for a secondary interaction between the ketolide and the ribosome.

Recent studies have suggested that such a secondary interaction may be present in domain II of the 23S rRNA.[25] Chemical footprinting of bound macrolide revealed that the aryl-containing ketolides such as **4** protected the chemical modifications of two distinct regions on 23S rRNA, one in domain V and the other in domain II. Mutations in these regions also conferred resistance to such aryl-containing ketolides. The crystal structure of the ribosome indicated that the location of this secondary interaction in domain II is close to the primary macrolide binding site in domain V.[26]

The solution conformations of ABT-773 (**41s**) and RU-004 (**4**) indicated that the quinolyl group attached to the C-6 position of ABT-773 and the quinolyl group attached to the carbamate of RU-004 occupied the same spatial position, suggesting that the aryl groups in ABT-773 and RU-004 might interact with the same region of the ribosome.[4] The spatial relationships between the C-6 aryl group and the ketolide skeleton can be better illustrated by the crystal structure of ketolide **41r** (Figure 2). We believe that the secondary interaction of the C-6 aryl group of our ketolides with domain II of ribosome is responsible for the improved binding affinity to the methylated ribosome and improved activity against $MLS_B$-resistant organisms. The concept of binary interaction has been used widely for enhancing ligand−receptor interaction and improving binding specificity.[27] As illustrated by Figure 3, the binary interactions between the macrolide moiety and domain V ($\Delta G_1$), and between the C-6 aryl group and domain II ($\Delta G_2$) provide enhanced macrolide−ribosome interaction, especially with methylated ribosomes, where the binding between the macrolide moiety and domain V ($\Delta G_1$) has been compromised.

**Structure−Activity Relationships.** The antibacterial activity of the test compounds was assessed by minimum inhibitory concentration (MIC) against a selected group of organisms. The phenotypes and genotypes of these pathogens are shown in Table 1, which include erythromycin-susceptible, $MLS_B$-resistant (*erm*), and efflux (*mef*) resistant organisms.[24] Among the various ketolide derivatives, the 6-*O*-(3-aryl-2-propenyl)-11,12-carbamate ketolides, depicted by structure **41**, exhibited the most potent and balanced activity against both susceptible and resistant bacteria (Table 3). In

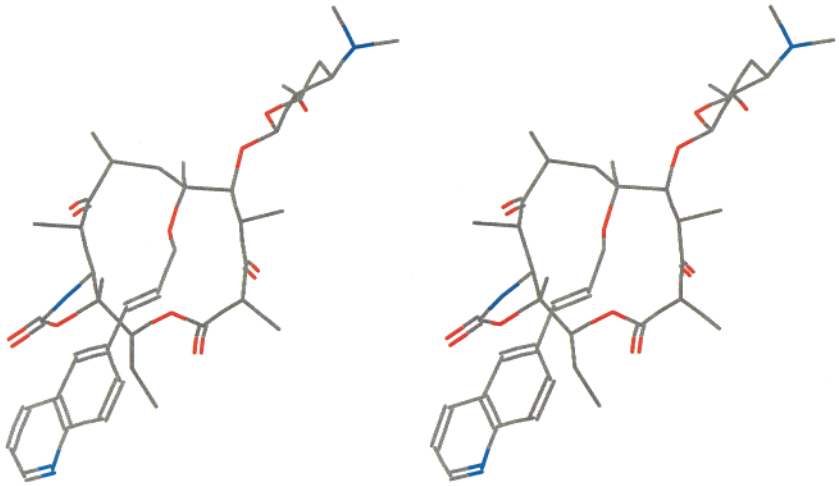


**Figure 2.** Stereoview of the crystal structure of 6-*O*-[3-(6′-quinolyl)-2-propenyl]-11,12-carbamate ketolide (**41r**).

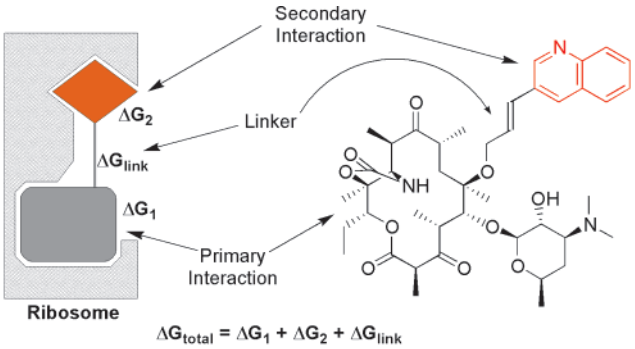



**Figure 3.** Schematic presentation of the free energy gains of a secondary interaction and structure segments responsible for the primary and secondary interactions. The enhanced binding affinity is represented by the total binding free energy ($\Delta G_{total}$), which consists of contributions from primary interaction ($\Delta G_1$), secondary interaction ($\Delta G_2$), and entropy gain by linking the two segments together ($\Delta G_{link}$).

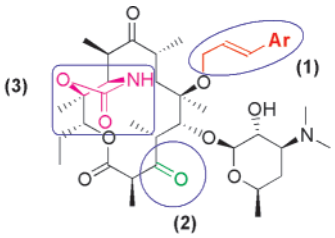



**Figure 4.** Structure of **41**, which possesses three modifications to erythromycin.

contrast, erythromycin showed either weak or no activity against the resistant organisms. Structure **41** carries three key structural modifications to erythromycin: (1) introduction of a 3-aryl-2-propenyl moiety at the C-6 position, (2) conversion of the C-3 cladinose to a carbonyl group, and (3) introduction of a cyclic carbamate at the 11,12-position (Figure 4). Our structure−activity relationship analysis indicated that each of the three modifications made significant contributions to the improved antibacterial profiles.

**Effects of C-3 Modification.** Removal of the cladinose sugar from erythromycin and conversion of the C-3 hydroxy group to a carbonyl functionality resulted in significant changes in biological activity. The most significant effects were observed on the activity against inducible and efflux resistant organisms. As described by some earlier reports, the cladinose group is responsible for the inducibility of macrolide resistance.[28] Allen and co-workers have demonstrated that some naturally occurring macrolides without the C-3 cladinose sugar, such as pikromycin and narbomycin, are noninducers. Lacking the C-3 cladinose group, the 16-membered ring macrolides are also active against inducible strains. The inducibility of erythromycin and its derivatives can be eliminated by removal of the C-3 cladinose as shown by Allen[28a] and Pestka[28b] and more recently by Roussel scientists.[10]

Our results clearly indicated that the C-3 cladinose is responsible for the induction of resistance, and removal of this group prevents such resistance (Table 3). For example, *Staphylococcus aureus* A5177 is an inducibly $MLS_B$-resistant strain against which erythromycin had a MIC of 6.2 $\mu$g/mL. Macrolide **12a** also had an MIC of 6.2 $\mu$g/mL against this strain, which represented a 15-fold reduction in activity as compared to its activity against the susceptible *S. aureus* ATCC 6538P. However, the corresponding ketolide **16a**, without the cladinose sugar attached, was equally active against the susceptible and inducible strains, each having a MIC of 1.56 $\mu$g/mL. The same trend was observed when macrolide **12s** and the corresponding ketolide **16s** were compared. Compound **25s** is an erythromycin derivative with the C-3 cladinose attached. This compound had an MIC of 3.1 $\mu$g/mL against the inducible strain *S. aureus* A5177. The corresponding ketolide **41s** had an MIC of 0.05 $\mu$g/mL against *S. aureus* A5177, which represented a 62-fold improvement in activity against this inducibly resistant organism. These results clearly demonstrated that the C-3 modification was the key factor for overcoming inducible resistance.

Significant improvements in activity against efflux resistance were also observed by introducing the C-3 carbonyl group. For instance, macrolide **12a** was 67-fold less active against efflux strain *S. pneumoniae* 5649 as compared to its activity against the susceptible *S. pneumoniae* strain ATCC 6303. However, the corresponding ketolide **16a** was significantly more active against efflux resistance. The difference between activities against susceptible and efflux strains was only 2-fold. Similarly, macrolide **12s** was about 67-fold less active against efflux stains than against susceptible

**Table 3.** In Vitro Activity of Various 6-*O*-Substituted Macrolides/Ketolides against Selected Respiratory Pathogens[a]

| | *S. aureus* | | | *S. pneumoniae* | | | *S. pyogenes* | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| compd | ATCC 6538P Ery-S | A 5177 $MLS_B$-i | A 5278 $MLS_B$-c | ATCC 6303 Ery-S | 5737 $MLS_B$ | 5649 efflux | EES 61 Ery-S | 930 $MLS_B$ | PIU 2548 efflux | *H. flu*[b] DILL Amp-R |
| Ery | 0.2 | 6.2 | >100 | 0.06 | >128 | 32 | 0.06 | >128 | 16 | 8 |
| **11** | 0.78 | 12.5 | >100 | | | | | >128 | 64 | 32 |
| **12a** | 0.39 | 6.2 | >100 | 0.06 | 32 | 4 | 0.03 | 32 | 16 | 4 |
| **12s** | 0.2 | 3.1 | >100 | 0.06 | 128 | 4 | 0.06 | 64 | 4 | 8 |
| **14** | 12.5 | 50 | >100 | 4 | >128 | 8 | | >128 | 32 | >128 |
| **16a** | 1.56 | 1.56 | >100 | 1 | 64 | 2 | 0.25 | 64 | 2 | 128 |
| **16b** | 1.56 | 1.56 | >100 | 1 | 128 | 2 | 0.25 | 64 | 2 | 128 |
| **16c** | 1.56 | 1.56 | >100 | 1 | 32 | 2 | 0.5 | 32 | 2 | 64 |
| **16s** | 0.2 | 0.2 | >100 | 0.03 | 16 | 0.25 | 0.2 | 100 | 0.1 | 16 |
| **17a** | 6.2 | 6.2 | >100 | 1 | 32 | 1 | 0.5 | 64 | 4 | >64 |
| **19i** | 25 | 25 | >100 | | | | 6.2 | >100 | 12.5 | |
| **19ii** | 3.1 | 1.56 | >100 | 0.25 | >64 | 4 | 0.5 | >64 | 4 | 16 |
| **19iii** | 6.2 | 6.2 | >100 | 2 | >128 | 4 | 2 | >128 | 8 | 64 |
| **19vi** | 6.2 | 3.1 | >100 | 0.25 | >128 | 2 | 0.39 | >100 | 1.56 | 32 |
| **19vii** | 3.1 | 3.1 | >100 | 0.25 | >128 | 0.5 | 0.25 | >128 | 4 | 32 |
| **24** | 0.2 | 0.78 | >100 | 0.03 | >128 | 2 | 0.03 | >128 | 8 | 2 |
| **25s** | 0.2 | 3.1 | >100 | 0.03 | 8 | 1 | 0.03 | 8 | 1 | 2 |
| **27** | 0.78 | 1.56 | >100 | 0.5 | >64 | 0.25 | 0.25 | >64 | 1 | 64 |
| **33** | 6.2 | 6.2 | >100 | 0.5 | >128 | 0.5 | 0.5 | >128 | 2 | >128 |
| **34** | 6.2 | 6.2 | >100 | 1 | >128 | 2 | 0.5 | >128 | 4 | 64 |
| **35s** | 0.1 | 0.1 | >100 | 0.015 | 64 | 0.25 | 0.015 | 64 | 0.5 | 2 |
| **36s** | 0.1 | 0.1 | >100 | 0.06 | 64 | 0.5 | 0.03 | 64 | 0.5 | 8 |
| **37s** | 0.1 | 0.1 | >100 | 0.03 | 1 | 0.25 | 0.015 | 4 | 0.25 | 4 |
| **38s** | 0.39 | 0.2 | >100 | 0.125 | 4 | 2 | 0.03 | 32 | 2 | 8 |
| **39** | 1.56 | 1.56 | >100 | 0.25 | >128 | 0.5 | 0.25 | >128 | 4 | 32 |
| **40s** | 0.05 | 0.05 | >100 | 0.06 | 128 | 1 | 0.06 | 16 | 2 | 4 |
| **41a** | 0.1 | 0.1 | >100 | 0.03 | 64 | 0.25 | 0.03 | 64 | 0.25 | 4 |
| **41d** | 0.1 | 0.1 | >100 | 0.03 | >128 | 0.5 | 0.03 | >128 | 0.5 | 8 |
| **41f** | 0.05 | 0.05 | >100 | 0.004 | 0.5 | 0.25 | 0.008 | 4 | 0.25 | 2 |
| **41g** | 0.05 | 0.05 | >100 | 0.004 | 0.5 | 0.25 | 0.008 | 1 | 0.25 | 2 |
| **41h** | 0.1 | 0.1 | >100 | 0.03 | 8 | 4 | 0.03 | 4 | 2 | 4 |
| **41i** | 0.1 | 0.1 | 50 | 0.015 | 8 | 0.25 | 0.015 | 16 | 0.25 | 4 |
| **41j** | 0.1 | 0.1 | >100 | 0.004 | 64 | 0.25 | 0.004 | 8 | 0.125 | 2 |
| **41k** | 0.2 | 0.2 | >100 | 0.03 | >128 | 1 | 0.03 | 64 | 2 | 4 |
| **41l** | 0.1 | 0.1 | >100 | 0.03 | 2 | 0.25 | 0.03 | >128 | 0.25 | 8 |
| **41m** | 0.1 | 0.1 | >100 | 0.008 | 8 | 0.25 | 0.008 | 32 | 0.25 | 4 |
| **41n** | 0.2 | 0.1 | >100 | 0.03 | >32 | 0.5 | 0.03 | >32 | 0.5 | 8 |
| **41o** | 0.1 | 0.1 | >100 | 0.015 | >128 | 1 | 0.015 | 16 | 1 | 16 |
| **41p** | 0.39 | 0.39 | >100 | 0.125 | 64 | 1 | 0.125 | 16 | 1 | 8 |
| **41q** | 0.05 | 0.05 | >100 | 0.03 | 4 | 0.5 | 0.03 | >128 | 1 | 4 |
| **41r** | 0.05 | 0.05 | >100 | 0.004 | 1 | 0.25 | 0.004 | 1 | 0.25 | 1 |
| **41s** | 0.05 | 0.05 | >100 | 0.004 | 0.25 | 0.125 | 0.004 | 1 | 0.25 | 2 |
| **41t** | 0.05 | 0.05 | >100 | 0.03 | 0.5 | 2 | 0.03 | 0.5 | 2 | 2 |
| **41u** | 0.05 | 0.05 | >100 | 0.008 | 0.25 | 0.5 | 0.015 | 4 | 0.5 | 2 |
| **41v** | 0.05 | 0.05 | >100 | 0.015 | 0.25 | 1 | 0.03 | 2 | 0.5 | 2 |
| **41w** | 0.05 | 0.05 | >100 | 0.015 | 1 | 0.5 | 0.03 | 4 | 0.5 | 2 |
| **41x** | 0.2 | 0.2 | >100 | 0.03 | 0.5 | 0.25 | 0.03 | 2 | 0.5 | 4 |
| **41y** | 0.1 | 0.1 | >100 | 0.015 | 0.25 | 0.5 | 0.03 | 1 | 0.25 | 2 |
| **41z** | 0.2 | 0.2 | >100 | 0.015 | 1 | 2 | 0.015 | 4 | 2 | 4 |
| **42s** | 0.1 | 0.1 | >100 | 0.015 | 8 | 0.25 | 0.004 | 4 | 0.25 | 2 |
| **43s** | 0.05 | 0.05 | >100 | 0.03 | 32 | 0.5 | 0.03 | 4 | 0.25 | |
| **45ii** | 0.2 | 0.39 | >100 | 0.03 | >128 | 2 | 0.03 | >128 | 2 | 2 |
| **45iii** | 0.2 | 0.1 | >100 | 0.03 | >128 | 2 | 0.03 | >128 | 2 | 4 |
| **45iv** | 0.2 | 0.2 | >100 | 0.03 | 16 | 0.5 | 0.03 | 64 | 2 | 4 |
| **45v** | 0.39 | 0.2 | >100 | 0.03 | 16 | 2 | 0.125 | >128 | 2 | 4 |
| **45viii** | 0.1 | 0.1 | >100 | 0.03 | 4 | 2 | 0.03 | 16 | 2 | 2 |
| **45ix** | 0.2 | 0.39 | >100 | 0.03 | 2 | 2 | 0.03 | >100 | 2 | 4 |

[a] Minimum inhibitory concentration (MIC) values are given in micrograms per milliliter. [b] *H. influenzae.*

strains, but the corresponding ketolide **16s** was highly active against the efflux strain with a MIC of 0.25 $\mu$g/mL. Other examples include macrolide **24** and the corresponding ketolide **27**, wherein the differences between activities against susceptible and efflux strains were 67-fold and 1/2-fold, respectively. One can draw the same conclusions when the activities against *S. pyogenes* PIU 2548 (efflux strain) and EES 61 (susceptible strain) are compared. It is worth noting that the improvement of activity against susceptible organisms by introducing the C-6 aryl group or 11,12-carbamate did not result in further potency increases against efflux. This indicated that the activity of our ketolides against efflux strains might be controlled by the drug transport process rather than ribosomal interaction.

The effects of the C-3 group on activity against erythromycin-susceptible strains are less profound and explicit. For example, ketolides **14** and **27** were less active against erythromycin-susceptible strains (*S. aureus* ATCC 6538P, *S. pneumoniae* ATCC 6303, and *S. pyogenes* EES 61) than the corresponding macrolides **11** and **24**. However, ketolide **16s** and macrolide **12s**

showed equivalent activities against the susceptible strains, while ketolide **41s** exhibited better activities than the corresponding macrolide **25s** against the susceptible strains.

**Effects of C-11,12 Modification.** As reported by Baker et al.,[9] introduction of a cyclic carbamate group to the 11,12-position of macrolides had favorable effects on antibacterial activity. Activity enhancements were also observed when this modification was applied to our ketolide series. Carbamate **24** exhibited 4−16-fold improvements in activity as compared to the corresponding diol **11** against both erythromycin-susceptible and $MLS_B$-resistant organisms. The same trend was observed for carbamate **25s** as compared to the parent diol **12s**, although to a lesser extent. Similarly, carbamate ketolides **27**, **41a**, and **41s** showed substantially improved antibacterial activities as compared to the corresponding diols **14**, **16a**, and **16s**. Carbamate ketolides **45ii**, **45iii**, and **45iv** were significantly more active than the corresponding diols **19ii**, **19iii**, and **19iv**. Once again the potency enhancement was independent of the resistant phenotypes as both erythromycin-susceptible and $MLS_B$-resistant strains were favorably affected by this modification.

Substitution on the carbamate nitrogen had significant effects on the antibacterial activity. *N*-Substituted carbamates **35s**, **36s**, **37s**, **38s**, and **40s** were less active than the unsubstituted carbamate **41s**, suggesting that steric bulk at this position might have a negative impact on the antibacterial activity. The same trend was observed when comparing the *N*-substituted carbamates **33**, **34**, and **39** to the unsubstituted carbamate **27**.

**Effects of C-6 Modification.** We found that the structure of the C-6 group has significant effects on the antibacterial activity, especially against *erm*-mediated $MLS_B$ resistance. Introduction of an aryl group to this position of ketolide **27** through a Heck coupling reaction provided a series of potent analogues **41a**−**41z** with significantly improved activity against both susceptible and $MLS_B$-resistant *S. pneumoniae* and *S. pyogenes*. The improvement for erythromycin-susceptible strains ranged from 4- to 125-fold and reached as high as >500-fold for $MLS_B$-resistant strains. Compound **41s**, the 6-*O*-(3-quinolyl-2-propenyl) derivative, was among the most potent compounds prepared. This compound exhibited potent and balanced activity against both susceptible and resistant organisms. As discussed previously, we believed that the activity enhancement achieved by introducing the C-6 aryl group was the result of a secondary interaction between the aryl group and the ribosome. However, introduction of the C-6 aryl group failed to improve the activity against *S. aureus* A5278, a constitutively $MLS_B$-resistant strain, to a detectable level. The C-6 aryl group also had no significant effect on activities against the efflux strains, which, as we discussed earlier, are likely controlled by the drug transportation processes.

The significant effects of the C-6 aryl group on antibacterial activity could be demonstrated by comparing 6-*O*-allyl ketolides **14**, **33**, **34**, and **39** to the corresponding aryl analogues **16**, **37**, **38**, and **40**. The effects of the C-6 structure on *erm*-mediated resistant strains were best illustrated by comparing compounds **24** and **25s**. The 6-*O*-allyl compound **24** and its quinolyl-substituted analogue **25s** showed similar activities against various susceptible strains. However, compound **25s** exhibited significantly improved activity against *S. pneumoniae* 5737 and *S. pyogenes* 930, two *erm*-containing strains.

**Table 4.** In Vivo Efficacy of Selected Compounds in Mouse Protection Tests

| | *S. aureus* 10649[a] | | *S. pneumoniae* 6303[a] | |
|---|---|---|---|---|
| compound | MIC ($\mu$g/mL) | $ED_{50}$ (mg/kg) | MIC ($\mu$g/mL) | $ED_{50}$ (mg/kg) |
| clarithromycin | 0.2 | 16.7 | 0.03 | 27.9 |
| azithromycin | 0.78 | 24.8 | 0.12 | 18.8 |
| telithromycin | 0.1 | 12.5 | 0.004 | 34.1 |
| **16s** | 0.2 | 27.2 | 0.03 | >40.0 |
| **40s** | 0.05 | 60.4 | 0.06 | 23.5 |
| **41a** | 0.1 | 30.2 | 0.03 | >40.0 |
| **41g** | 0.05 | | 0.004 | >50 |
| **41s** | 0.05 | 9.4 | 0.004 | 7.8 |
| **41u** | 0.05 | 12.5 | 0.008 | >50.0 |
| **41v** | 0.05 | 12.5 | 0.015 | 17.3 |
| **41x** | 0.2 | 9.2 | 0.03 | 40.3 |
| **41y** | 0.1 | <6.25 | 0.015 | 33.1 |
| **42s** | 0.1 | 27.1 | 0.015 | 33.0 |

[a] Both *S. aureus* 10649and *S. pneumoniae* 6303 are erythromycin-susceptible strains.

The tether structure linking the lactone ring and the aryl group appeared to be very important as well. The saturated propylene derivatives **17a** and **42s** appeared to be less active than the corresponding propenylene compounds **16a** and **41s**, possibly an entropy effect due to the loss of rigidity. Compound **43s** with a cyclopropyl-containing tether was also less active than the propenylene analogue **41s**. More dramatic effects were observed when the propenylene tether was replaced with other linkers of varying length and rigidity as exemplified in structures **45ii**−**45ix**. Among all the tether groups studied, the propenylene tether provided the best antibacterial activity.

**In Vivo Efficacy.** Many of the ketolide derivatives exhibited excellent in vivo efficacy as compared to the reference compounds clarithromycin, azithromycin, and telithromycin (Table 4). Compound **41s**, the 6-*O*-(3-quinolyl-2-propenyl)-11,12-carbamate ketolide exhibited significantly better efficacy than the corresponding 11,12-diol **16s** and tricyclic ketolide **40s** against infections caused by both *S. aureus* and *S. pneumoniae*. The efficacy dropped when the propenylene tether was reduced to propylene as illustrated by compound **42s**. The aryl structure also had significant effects on the in vivo efficacy (Table 4, **41a**−**41y**). Among various aryl groups studied, the 3-quinolyl analogue **41s** (ABT-773) provided excellent efficacy against both *S. aureus* and *S. pneumoniae* infections. Further evaluations of **41s** confirmed the superiority of this compound against a series of infections caused by both susceptible and resistant pathogens in various infection models.[29]

## Conclusion

A novel series of erythromycin derivatives with potent activity against the key respiratory pathogens, including those resistant to the earlier generation of macrolides, has been identified. These compounds are characterized by having an aryl group tethered to the C-6 position of the ketolide skeleton. Extensive structural modification of the C-6 moiety led to the discovery of several

promising compounds with potent activity against both *mef*- and *erm*-mediated resistant *Streptococcus pneumoniae*. Preliminary mechanistic studies indicated that the new ketolides are potent protein synthesis inhibitors which interact with methylated ribosomes and exert activity against $MLS_B$-resistant bacteria. In experimental animal models, these analogues exhibited excellent in vivo efficacy and balanced pharmacokinetic profiles. As a result of extensive structural modification and optimization, ABT-773 (**41s**) was identified as a candidate for further clinical evaluation.

## Experimental Section

Intermediate **9**, 2′,4″-bis-*O*-trimethylsilylerythromycin A 9-*O*-(1-isopropoxycyclohexyl)oxime, was provided by the Abbott Process Research Department. The synthesis of **9** has been described in U.S. Patent 4,990,602. Tetrahydrofuran was distilled from sodium/benzophenone. All solvents and reagents were obtained from commercial sources and used without further purification. Flash column chromatography was performed on Merck silica gel 60 (230−400 mesh). Melting points were recorded on a Fisher-Johns apparatus and are uncorrected. All elemental analyses were performed by Robertson Microlite Laboratories and the data for carbon, hydrogen, and nitrogen reported are within 0.4% of theoretical values.

**6-*O*-Allylerythromycin A (11).** To an ice-cold solution of **9** (1.032 g, 1.00 mmol) in 5 mL of DMSO and 5 mL of THF was added freshly distilled allyl bromide (0.173 mL, 2.00 mmol), and the mixture was stirred for 5 min. A solution of $KOBu^t$ (2.0 mL of 2 M solution in THF, 2.00 mmol) in 5 mL of DMSO and 5 mL THF was added slowly over 4 h. The reaction mixture was taken up in ethyl acetate and the organic layer was washed with water and brine. The organic phase was dried over $Na_2SO_4$ and concentrated to give crude intermediate **10** (1.062 g). To a solution of **10** in 8 mL of acetonitrile and 4 mL of water was added 4 mL of acetic acid. After 12 h at room temperature, the solvent was evaporated in a vacuum to give off-white foam. The crude mixture was dissolved in 8 mL of ethanol and 8 mL of water. $NaHSO_3$ (312 mg, 3.00 mmol) and formic acid (0.10 mL, 2.50 mmol) were added, and the mixture was stirred at 80 °C for 8 h. The reaction mixture was allowed to cool to room temperature, neutralized with 1 N NaOH to pH 9−10, and extracted with ethyl acetate. The organic phase was washed with brine, dried over $Na_2SO_4$, filtered, and concentrated. The crude material was purified by column chromatography, eluted with 1% MeOH in methylene chloride containing 1% ammonium hydroxide, to give **11** (257 mg, 0.33 mmol, 33% from **9**): MS *m*/*z* (FAB) 774 $(M + H)^+$; $^1H$ NMR ($CDCl_3$) $\delta$ 5.90 (1H, m), 5.13 (2H, m), 4.92 (1H, d, $J = 4.5$ Hz), 4.49 (1H, d, $J = 6.9$ Hz), 4.02 (2H, m), 3.86 (1H, m), 3.78 (1H, d, $J = 6.9$ Hz), 3.73 (1H, m), 3.69 (1H, s), 3.60 (1H, s), 3.51 (2H, m), 3.34 (3H, s), 3.19 (1H, m), 2.90−3.10 (5H, m), 2.62 (1H, m), 2.40 (2H, m), 2.27 (6H, s), 2.15 (1H, d, $J = 9.3$ Hz), 2.04 (1H, m), 1.92 (2H, m), 1.55−1.70 (4H, m), 1.50 (1H, m), 1.44 (3H, s), 1.31 (3H, d, $J = 6.2$ Hz), 1.27 (3H, s), 1.10−1.25 (18H, m), 0.94 (3H, t, $J = 7.5$ Hz); $^{13}C$ NMR ($CDCl_3$) $\delta$ 219.3 (C-9), 174.8 (C-1), 135.5, 116.3, 101.9 (C-1′), 95.9 (C-1″), 79.7, 78.8, 78.5, 74.1, 72.4, 70.6, 68.1, 65.5, 65.1, 49.0, 45.0, 44.1, 39.7 ($NMe_2$), 37.9, 37.1, 34.6, 28.4, 21.0, 20.6, 20.8, 18.3, 18.1, 15.7, 15.6, 11.9, 10.1, 8.9. Anal. ($C_{40}H_{71}NO_{13}$) C, H, N.

**6-*O*-[3-(3′-Quinolyl)-2-propenyl]erythromycin A (12s).** A mixture of **11** (3.09 g, 4.00 mmol), 3-bromoquinoline (1.08 mL, 8.00 mmol), $Pd(OAc)_2$ (180 mg, 0.80 mmol), P(*o*-tolyl)$_3$ (365 mg, 1.20 mmol), and $Et_3N$ (1.40 mL, 10.0 mmol) in acetonitrile (70 mL) was flushed with nitrogen and sealed in a pressure tube. The mixture was heated to 60 °C for 1 h and then to 100 °C for 48 h. The reaction mixture was taken up in EtOAc and washed with 5% $Na_2CO_3$ (aq) and brine. The organic phase was concentrated and purified by column chromatography, eluted with 10% MeOH in methylene chloride containing 0.5% ammonium hydroxide, to give **12s** (2.73 g, 3.00 mmol, 76%): MS *m*/*z* (ESI) 901 $(M + H)^+$; HRMS (FAB) *m*/*z* 901.5413, calcd for $C_{49}H_{77}N_2O_{13}$ 901.5426; $^1H$ NMR ($CDCl_3$) $\delta$ 9.13 (1H, d, $J = 1.8$ Hz), 8.28 (1H, d, $J = 1.8$ Hz), 8.05 (1H, d, $J = 8.4$ Hz), 7.80 (1H, d, $J = 8.4$ Hz), 7.63 (1H, m), 7.50 (1H, m), 6.60 (2H, m), 5.19 (1H, dd, $J = 10.8$, 2.4 Hz), 4.92 (1H, d, $J = 4.5$ Hz), 4.52 (1H, d, $J = 7.2$ Hz), 4.25 (1H, m), 4.06 (2H, m), 3.82 (2H, m), 3.75 (1H, s), 3.59 (1H, s), 3.50 (2H, m), 3.35 (3H, s), 3.21 (1H, m), 2.90−3.10 (5H, m), 2.63 (1H, m), 2.45 (2H, m), 2.31 (6H, s), 2.19 (1H, d, $J = 9.4$ Hz), 2.10 (1H, m), 1.92 (2H, m), 1.45−1.75 (4H, m), 1.51 (1H, m), 1.35 (3H, s), 1.10−1.35 (24H, m), 0.94 (3H, t, $J = 7.5$ Hz); $^{13}C$ NMR ($CDCl_3$) $\delta$ 220.2 (C-9), 175.4 (C-1), 150.3, 147.5, 132.8, 130.3, 129.8, 129.2, 128.8, 128.6, 128.2, 127.9, 126.5, 102.4 (C-1′), 96.4 (C-1″, 80.1, 79.3, 79.1, 77.8, 74.4, 72.8, 71.0, 68.7, 68.6, 66.0, 65.7, 65.2, 49.5, 45.5, 44.6, 40.3 ($NMe_2$), 38.5, 38.4, 37.4, 35.0, 28.7, 21.5, 21.4, 21.3, 21.0, 18.8, 18.4, 16.1, 15.9, 12.1, 10.7, 9.3.

**6-*O*-Allyl-2′-*O*-benzoyl Ketolide 13.** To a suspension of **11** (7.73 g, 10.0 mmol) in ethanol (25 mL) and water (75 mL) was added aqueous 1 M HCl (18 mL) over 10 min. The reaction mixture was stirred at room temperature for 10 h and neutralized with aqueous 2 M NaOH (9 mL, 18 mmol). The precipitate was collected by filtration and washed with ice-cold water (10 mL) to give the corresponding 3-OH compound (3.11 g). A portion of the above product (2.49 g, 4.05 mmol) was dissolved in $CH_2Cl_2$ (20 mL) and treated with $Bz_2O$ (1.46 g, 6.48 mmol) and $Et_3N$ (0.903 mL, 6.48 mmol) at room temperature for 24 h. The reaction mixture was taken up in EtOAc and washed with 5% $Na_2CO_3$ and brine. The organic phase was dried ($Na_2SO_4$) and concentrated to give 2.46 g of the 2′-*O*-Bz derivative after column chromatography (silica gel, 3:7 acetone/hexane). MS *m*/*z* (FAB) 720 $(M + H)^+$.

*N*-Chlorosuccinimide (NCS) (0.667 g, 5.07 mmol) was dissolved in $CH_2Cl_2$ (20 mL) and cooled to −10 °C under nitrogen. $Me_2S$ (0.433 mL, 5.92 mmol) was added dropwise over 5 min and stirred at this temperature for an additional 10 min. A solution of the above 2′-*O*-Bz compound (2.43 g, 3.38 mmol) in $CH_2Cl_2$ (20 mL) was introduced over 20 min. After the mixture was stirred for 30 min at −10 to −5 °C, $Et_3N$ (0.470 mL, 3.38 mmol) was added over 5 min, and the mixture was stirred for an additional 45 min before warming up to room temperature. The reaction mixture was taken up in EtOAc and washed with 5% $Na_2CO_3$ and brine. The organic phase was dried ($Na_2SO_4$) and concentrated to give 2.27 g (77% from **11**) of **13** as white solid after column chromatography (silica gel, 3:7 acetone/hexane): MS *m*/*z* (FAB) 718 $(M + H)^+$; $^1H$ NMR ($CDCl_3$) $\delta$ 8.01 (1H, d, $J = 7.2$ Hz), 8.00 (1H, d, $J = 8.4$ Hz), 7.55 (1H, m), 7.43 (2H, m), 5.65(1H, m), 5.10 (3H, m), 4.59 (1H, d, $J = 6.9$ Hz), 4.41 (1H, d, $J = 3.0$ Hz), 3.81 (1H, br s), 3.77 (1H, q, $J = 6.6$ Hz), 3.65 (2H, m), 3.46 (1H, s), 3.41 (1H, s), 3.15 (2H, m), 2.98 (1H, m), 2.86 (1H, m), 2.60 (1H, m), 2.26 (6H, s), 1.95 (1H, m), 1.81 (1H, m), 1.65 (1H, m), 1.40−1.50 (3H, m), 1.36 (3H, s), 1.30 (3H, d, $J = 6.6$ Hz), 1.28 (3H, d, $J = 6.6$ Hz), 1.14 (3H, s), 1.11 (3H, d, $J = 6.9$ Hz), 1.09 (3H, d, $J = 6.9$ Hz), 1.00 (3H, d, $J = 7.5$ Hz), 0.82 (3H, t, $J = 7.5$ Hz); $^{13}C$ NMR ($CDCl_3$) $\delta$ 219.3 (C-9), 206.3 (C-3), 69.6 (C-1), 165.2, 135.1, 132.7, 130.5, 129.7, 128.2, 117.5, 100.5 (C-1′), 78.4, 78.0, 75.1, 74.2, 71.9, 69.1, 68.9, 64.4, 63.6, 50.6, 45.3, 44.7, 40.7 ($NMe_2$), 38.1, 37.6, 31.6, 21.7, 21.1, 20.2, 18.0, 16.5, 14.5, 12.6, 12.3, 10.6.

**6-*O*-Allyl Ketolide 14.** A solution of **13** (719 mg, 1.0 mmol) in methanol (20 mL) was heated to reflux for 6 h. The reaction mixture was concentrated and the residue was purified by chromatography on silica gel (95:5:0.5 dichloromethane/methanol/ammonia) to give ketolide **14** (577 mg, 91%) as a white solid: MS *m*/*z* (FAB) 614 $(M + H)^+$; $^1H$ NMR ($CDCl_3$) $\delta$ 5.68 (1H, m), 5.19 (1H, m), 5.10 (2H, m), 4.45 (1H, d, $J = 3.3$ Hz), 4.38 (1H, d, $J = 7.2$ Hz), 3.91 (1H, q, $J = 6.6$ Hz), 3.90 (1H, br s), 3.65 (2H, m), 3.48 (1H, br s), 3.44 (1H, m), 3.25 (1H, m), 3.18 (2H, m), 3.05 (1H, m), 2.63 (1H, m), 2.48 (1H, m), 2.27 (6H, s), 1.99 (1H, m), 1.84 (1H, m), 1.65 (2H, m), 1.55 (1H, m), 1.42 (3H, d, $J = 7.8$ Hz), 1.37 (3H, s), 1.26 (3H, s), 1.25 (3H, d, $J = 6.6$ Hz), 1.13 (3H, d, $J = 6.6$ Hz), 1.12 (3H, d, $J = 6.9$ Hz), 0.85 (3H, t, $J = 7.5$ Hz); $^{13}C$ NMR ($CDCl_3$) $\delta$ 219.2 (C-9), 206.0 (C-3), 169.8 (C-1), 135.3, 117.5, 102.8 (C-1′), 78.4, 78.0, 75.9, 74.4, 70.3, 69.5, 69.0, 65.9, 64.6, 50.6, 45.4, 45.1,

40.2 ($NMe_2$), 38.6, 37.8, 31.6, 28.4, 21.8, 21.3, 20.3, 18.1, 16.5, 14.7, 12.8, 12.3, 10.6. Anal. ($C_{32}H_{55}NO_{10}\cdot 0.5H_2O$) C, H, N.

**6-*O*-(3-Phenyl-2-propenyl) Ketolide 16a.** To a solution of **13** (717 mg, 1.00 mmol), palladium(II) acetate (22 mg, 0.100 mmol), and triphenylphosphine (52 mg, 0.200 mmol) in acetonitrile (5 mL) were added iodobenzene (220 $\mu$L, 2.00 mmol) and triethylamine (280 $\mu$L, 2.00 mmol). The mixture was cooled to −78 °C and degassed. The reaction mixture was then warmed to 60 °C for 0.5 h and stirred at 80 °C for 12 h. The reaction mixture was taken up in ethyl acetate and washed twice with aqueous 5% sodium bicarbonate, once with aqueous 2% tris(hydroxymethyl)aminomethane, and once with brine, dried over sodium sulfate, filtered, and concentrated in a vacuum. The crude mixture was purified by flash column chromatography on silica gel (95:5:0.5 dichloromethane/methanol/ammonia) to give **15a** (721 mg, 90%) as an off-white solid: MS *m/z* (FAB)$^+$ 794 (M + H)$^+$. Anal. ($C_{45}H_{63}NO_{11}\cdot H_2O$) C, H, N.

The above compound (340 mg, 0.429 mmol) was dissolved in MeOH (10 mL) and heated to reflux for 6 h. The reaction mixture was concentrated in a vacuum and the residue was purified by chromatography on silica gel (95:5:0.5 dichloromethane/methanol/ammonia) to give ketolide **16a** (203 mg, 70%) as a white solid: MS *m/z* (FAB) 690 (M + H)$^+$; $^1$H NMR ($CDCl_3$) $\delta$ 7.46, (2H, m), 7.20−7.32 (3H, m), 6.42 (1H, d, $J$ = 15.6), 6.05 (1H, m), 5.19 (1H, m), 4.50 (1H, d, $J$ = 3.3 Hz), 4.38 (1H, d, $J$ = 7.2 Hz), 3.95 (1H, q, $J$ = 6.6 Hz), 3.93 (1H, m), 3.80 (1H, m), 3.62 (2H, m), 3.39 (1H, br s), 3.30 (1H, m), 3.18 (2H, m), 3.05 (1H, m), 2.63 (1H, m), 2.48 (1H, m), 2.26 (6H, s), 1.99 (1H, m), 1.84 (1H, m), 1.65 (2H, m), 1.55 (1H, m), 1.43 (3H, d, $J$ = 7.8 Hz), 1.41 (3H, s), 1.35 (3H, d, $J$ = 6.9 Hz), 1.26 (3H, s), 1.25 (3H, d, $J$ = 6.6 Hz), 1.13 (3H, d, $J$ = 6.6 Hz), 1.10 (3H, d, $J$ = 6.9 Hz), 0.88 (3H, t, $J$ = 7.5 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 219.4 (C-9), 206.0 (C-3), 169.8 (C-1), 137.0, 132.6, 128.3, 127.3, 126.7, 126.6, 102.7, 78.4, 78.2, 75.9, 74.3, 70.3, 69.5, 69.1, 65.9, 64.2, 50.6, 45.4, 45.3, 40.2 ($NMe_2$), 38.7, 37.7, 28.3, 21.9, 21.2, 20.3, 18.1, 16.5, 14.6, 13.0, 12.3, 10.8.

**6-*O*-[3-(4′-Methoxyphenyl)-2-propenyl] Ketolide 16b.** Compound **16b** was prepared according to the procedures described for the preparation of **16a**, by replacing iodobenzene with iodoanisole. Compound **16b** (575 mg, 80%) was obtained as an off-white solid: MS *m/z* (FAB) 720 (M + H)$^+$; $^1$H NMR ($CDCl_3$) $\delta$ 7.40, (2H, d, $J$ = 8.4 Hz), 6.83 (2H, d, $J$ = 8.4 Hz), 6.37 (1H, d, $J$ = 15.6), 5.90 (1H, m), 5.19 (1H, m), 4.50 (1H, d, $J$ = 3.3 Hz), 4.38 (1H, d, $J$ = 7.2 Hz), 3.96 (1H, q, $J$ = 6.6 Hz), 3.93 (1H, m), 3.80 (3H, s), 3.78 (1H, m), 3.62 (2H, m), 3.45 (1H, m), 3.32 (1H, br s), 3.30 (1H, m), 3.18 (2H, m), 3.05 (1H, m), 2.63 (1H, m), 2.49 (1H, m), 2.26 (6H, s), 1.98 (1H, m), 1.84 (1H, m), 1.65 (2H, m), 1.55 (1H, m), 1.43 (3H, d, $J$ = 7.8 Hz), 1.41 (3H, s), 1.35 (3H, d, $J$ = 6.9 Hz), 1.27 (3H, s), 1.25 (3H, d, $J$ = 6.6 Hz), 1.13 (3H, d, $J$ = 6.6 Hz), 1.09 (3H, d, $J$ = 6.9 Hz), 0.88 (3H, t, $J$ = 7.5 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 219.2 (C-9), 206.0 (C-3), 169.8 (C-1), 132.3, 129.9, 129.4, 127.9, 124.3, 113.8, 102.7, 78.3, 78.2, 76.0, 74.3, 70.3, 69.4, 69.1, 65.9, 64.3, 55.2, 50.6, 45.4, 45.3, 40.2 ($NMe_2$), 38.7, 37.7, 31.5, 28.4, 21.9, 21.2, 20.3, 18.1, 16.5, 14.6, 13.0, 12.3, 10.9. Anal. ($C_{39}H_{61}NO_{11}$) C, H, N.

**6-*O*-[3-(4′-Chlorophenyl)-2-propenyl] Ketolide 16c.** Compound **16c** was prepared according to the procedures described for the preparation of **16a**, by replacing iodobenzene with 1-chloro-4-iodobenzene. Compound **16c** (309 mg, 58%) was obtained as a white solid: MS *m/z* (FAB) 724 (M + H)$^+$; $^1$H NMR ($CDCl_3$) $\delta$ 7.39, (2H, d, $J$ = 8.4 Hz), 7.27 (2H, d, $J$ = 8.4 Hz), 6.58 (1H, d, $J$ = 15.6), 6.02 (1H, m), 5.16 (1H, m), 4.49 (1H, d, $J$ = 3.3 Hz), 4.36 (1H, d, $J$ = 7.2 Hz), 3.96 (1H, q, $J$ = 6.6 Hz), 3.93 (1H, m), 3.78 (1H, m), 3.62 (2H, m), 3.38 (1H, br s), 3.30 (1H, m), 3.20 (2H, m), 3.05 (1H, m), 2.63 (1H, m), 2.49 (1H, m), 2.26 (6H, s), 1.98 (1H, m), 1.85 (1H, m), 1.65 (2H, m), 1.50 (1H, m), 1.43 (3H, d, $J$ = 7.8 Hz), 1.41 (3H, s), 1.35 (3H, d, $J$ = 6.9 Hz), 1.26 (3H, s), 1.25 (3H, d, $J$ = 6.6 Hz), 1.13 (3H, d, $J$ = 6.6 Hz), 1.10 (3H, d, $J$ = 6.9 Hz), 0.87 (3H, t, $J$ = 7.5 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 219.6 (C-9), 206.0 (C-3), 169.8 (C-1), 139.6, 135.5, 131.3, 128.5, 127.9, 127.3, 102.7 (C-1′), 78.4, 78.2, 75.9, 74.2, 70.3, 69.5, 69.2, 65.9, 64.1, 50.6, 45.4, 45.3, 40.2 ($NMe_2$), 38.6, 37.6, 28.4, 21.8, 21.2, 20.3, 18.0, 16.5, 14.6, 13.0, 12.2, 10.8. Anal. ($C_{38}H_{58}NO_{10}Cl$) C, H, N.

**6-*O*-[3-(3′-Quinolyl)-2-propenyl] Ketolide 16s.** Compound **16s** was prepared according to the procedures described for the preparation of **16a**, by replacing iodobenzene with 3-bromoquinloline. Compound **16s** (217 mg, 30%) was obtained as an off-white solid: MS *m/z* (FAB) 741 (M + H)$^+$; $^1$H NMR ($CDCl_3$) $\delta$ 9.07 (1H, d, $J$ = 2.4 Hz), 8.19 (1H, d, $J$ = 2.4 Hz), 8.06 (1H, d, $J$ = 8.4 Hz), 7.82 (1H, d, $J$ = 8.4 Hz), 7.63 (1H, m), 7.51 (1H, m), 6.59 (1H, d, $J$ = 15.6 Hz), 6.31 (1H, m), 5.22 (1H, m), 4.53 (1H, d, $J$ = 3.3 Hz), 4.38 (1H, d, $J$ = 7.2 Hz), 3.98 (1H, q, $J$ = 6.6 Hz), 3.85−3.95 (2H, m), 3.72 (1H, m), 3.60 (1H, m), 3.52 (1H, br s), 3.30 (1H, m), 3.20 (2H, m), 3.08 (1H, m), 2.65 (1H, m), 2.49 (1H, m), 2.27 (6H, s), 2.00 (1H, m), 1.90 (1H, m), 1.65 (2H, m), 1.50 (1H, m), 1.46 (3H, d, $J$ = 7.8 Hz), 1.44 (3H, s), 1.36 (3H, d, $J$ = 6.9 Hz), 1.26 (3H, s), 1.25 (3H, d, $J$ = 6.6 Hz), 1.15 (3H, d, $J$ = 6.6 Hz), 1.08 (3H, d, $J$ = 6.9 Hz), 0.89 (3H, t, $J$ = 7.5 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 219.7 (C-9), 205.9 (C-3), 169.8 (C-1), 152.1, 150.0, 147.5, 140.2, 132.6, 130.0, 129.2, 129.1, 128.8, 128.1, 127.9, 126.5, 102.8 (C-1′), 78.5, 78.2, 75.9, 74.2, 70.2, 69.4, 69.2, 65.9, 64.1, 50.6, 45.4, 45.3, 40.2 ($NMe_2$), 38.7, 37.6, 28.4, 21.8, 21.2, 20.3, 18.0, 16.5, 14.6, 13.0, 12.2, 10.8. Anal. ($C_{41}H_{61}N_2O_{10}\cdot 0.5H_2O$) C, H, N.

**6-*O*-(3-Phenylpropyl) Ketolide 17a.** A solution of **16a** (170 mg, 0.247 mmol) in methanol (10 mL) was flushed with nitrogen. Palladium (10%) on carbon (50 mg) was added, and the mixture was flushed with hydrogen and stirred for 18 h under positive hydrogen pressure. The reaction mixture was filtered through Celite and the filtrate was concentrated to give colorless glass. The glass was taken up in ether, hexane was added, and the solvents were removed to give the title compound (167 mg, 98%) as a white solid. MS *m/z* (FAB) 692 (M + H)$^+$; $^1$H NMR ($CDCl_3$) $\delta$ 7.10−7.30 (5H, m), 7.20−7.32 (3H, m), 5.23 (1H, m), 4.45 (1H, d, $J$ = 3.3 Hz), 4.37 (1H, d, $J$ = 7.2 Hz), 3.85−3.95 (3H, m), 3.62 (2H, m), 3.35 (1H, br s), 3.05−3.30 (4H, m), 2.75 (1H, m), 2.65 (1H, m), 2.40−2.60 (3H, m), 2.27 (6H, s), 1.99 (1H, m), 1.90 (1H, m), 1.50−1.70 (4H, m), 1.43 (3H, d, $J$ = 7.8 Hz), 1.35 (3H, d, $J$ = 6.9 Hz), 1.30 (3H, s), 1.26 (3H, s), 1.25 (3H, d, $J$ = 6.6 Hz), 1.15 (3H, d, $J$ = 6.6 Hz), 1.12 (3H, d, $J$ = 6.9 Hz), 0.85 (3H, t, $J$ = 7.5 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 220.2 (C-9), 206.5 (C-3), 170.0 (C-1), 142.3, 128.4, 128.1, 125.4, 102.6, 78.2, 78.0, 75.6, 74.2, 70.3, 69.5, 69.4, 65.9, 62.1, 50.6, 45.4, 44.6, 40.2, 38.8, 37.5, 32.1, 30.3, 28.4, 21.9, 21.3, 20.2, 18.4, 16.5, 14.9, 12.4, 10.6.

**6-*O*-(Formylmethyl) Ketolide 18.** Ozone was passed through a −78 °C solution of compound **14** (2.87 g, 4.0 mmol) in dichloromethane (100 mL) for 45 min. The reaction mixture was then flushed with nitrogen for 10 min. Dimethyl sulfide (1.2 mL, 16 mmol) was added and the reaction mixture was stirred for 30 min at 0 °C. The reaction mixture was concentrated to give white foam whose spectrum was consistent with that of the corresponding *N*-oxide of **18**. The *N*-oxide and triphenylphosphine (3.44 g, 12.0 mmol) were dissolved in THF (30 mL) and heated to 55 °C for 3.5 h. The mixture was concentrated and purified by column chromatography (silica gel, 1:1 acetone/hexane) to give **18** (1.29 g, 52%) as a white solid: MS *m/z* (FAB) 616 (M + H)$^+$; $^1$H NMR ($CDCl_3$) $\delta$ 9.43 (1H, m), 5.15 (1H, m), 4.88 (1H, m), 4.45 (1H, m), 4.10−4.39 (3H, m), 3.85−4.00 (2H, m), 3.45−3.65 (3H, m), 2.95−3.25 (3H, m), 2.90 (1H, m), 2.65 (1H, m), 2.47 (1H, m), 2.26 (6H, s), 1.90−2.10 (2H, m), 1.50−1.68 (3H, m), 1.53 (3H, s), 1.41 (3H, s), 1.40 (3H, d, $J$ = 7.8 Hz), 1.10−1.30 (12H, m), 0.85 (3H, t, $J$ = 7.5 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 220.0 (C-9), 213.0 (CHO), 206.0 (C-3), 174.8 (C-1), 103.0 (C-1′), 84.6, 78.4, 78.1, 76.0, 74.3, 70.3, 69.6, 69.0, 65.9, 65.6, 50.9, 45.8, 45.0, 40.2 ($NMe_2$), 38.5, 37.9, 31.6, 28.3, 22.0, 21.4, 20.7, 18.2, 16.4, 14.6, 13.3, 12.2, 10.5.

**6-*O*-(2-Aminoethyl) Ketolide 19i.** To a methanol solution (10 mL) of **18** (170 mg, 0.276 mmol) was added ammonium acetate (212 mg, 2.76 mmol), and the mixture was cooled to 0 °C. Sodium cyanoborohydride (34 mg, 0.553 mmol) was added and the reaction mixture was stirred at room temperature for 24 h. The reaction mixture was taken up in ethyl acetate, washed with aqueous 5% sodium carbonate, aqueous 2% tris(hydroxymethyl)aminomethane, and brine, dried over sodium

sulfate, filtered, and concentrated. Chromatography on silica gel (90:10:0.5 dichloromethane/methanol/ammonia) gave **19i** (90 mg, 53%) as a white solid: MS *m/z* (FAB) 617 $(M + H)^+$; $^1$H NMR ($CDCl_3$) $\delta$ 5.21 (1H, dd, $J$ = 10.5, 3.3 Hz), 4.43 (1H, d, $J$ = 3.6 Hz), 4.38 (1H, d, $J$ = 7.2 Hz), 3.80−4.00 (2H, m), 3.63 (1H, m), 3.05−3.40 (5H, m), 2.88 (1H, m), 2.65 (2H, m), 2.47 (2H, m), 2.27 (6H, s), 1.80−2.10 (2H, m), 1.40−1.70 (3H, m), 1.45 (3H, d, $J$ = 7.8 Hz), 1.36 (3H, s), 1.20−1.32 (9H, m), 1.16 (3H, d, $J$ = 6.6 Hz), 1.13 (3H, d, $J$ = 6.9 Hz), 0.85 (3H, t, $J$ = 7.5 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 217.0 (C-9), 206.3 (C-3), 170.6 (C-1), 102.7 (C-1′), 78.9, 78.5, 75.1, 74.9, 70.3, 69.4, 67.8, 65.9, 63.1, 50.8, 45.8, 44.9, 41.7, 40.3 ($NMe_2$), 38.8, 38.2, 28.4, 22.2, 21.3, 20.7, 19.2, 16.6, 14.9, 12.8, 12.4, 10.9.

**6-*O*-[2-(Benzylamino)ethyl] Ketolide 19ii.** To a 0 °C solution in methanol (10 mL) of **18** (123 mg, 0.200 mmol) was added acetic acid (114 $\mu$l, 2.00 mmol) and benzylamine (218 $\mu$l, 2.00 mmol), and the mixture was stirred for 10 min. Sodium cyanoborohydride (24.8 mg, 0.400 mmol) was added and the reaction mixture was stirred at room temperature for 16 h. Additional sodium cyanoborohydride (24.8 mg, 0.400 mmol) was added and stirring was continued for 24 h. The reaction mixture was taken up in ethyl acetate, washed with aqueous 5% sodium carbonate, aqueous 2% tris(hydroxymethyl)aminomethane, and brine, dried over sodium sulfate, filtered, and concentrated. Chromatography on silica gel (95:5:0.5 dichloromethane/methanol/ammonia) followed by a second chromatography (50:50:0.5 acetone/hexanes/triethylamine) gave **19ii** (82 mg, 58%) as a white foam: MS *m/z* (FAB) 707 $(M + H)^+$; $^1$H NMR ($CDCl_3$) $\delta$ 7.20−7.40 (5H, m), 5.06 (1H, dd, $J$ = 10.5, 3.3 Hz), 4.38 (1H, d, $J$ = 3.6 Hz), 4.36 (1H, d, $J$ = 7.2 Hz), 3.90−4.00 (2H, m), 3.74 (2H, m), 3.61 (1H, m), 3.38 (1H, br s), 3.30 (2H, m), 3.24 (1H, br s), 3.16 (1H, m), 3.08 (1H, m), 2.86 (1H, m), 2.63 (1H, m), 2.40−2.53 (3H, m), 2.26 (6H, s), 1.80−2.00 (2H, m), 1.66 (1H, m), 1.57 (1H, m), 1.50 (1H, m), 1.43 (3H, d, $J$ = 7.8 Hz), 1.32 (3H, s), 1.29 (3H, d, $J$ = 6.3 Hz), 1.27 (3H, s), 1.24 (3H, d, $J$ = 6.3 Hz), 1.16 (3H, d, $J$ = 6.6 Hz), 1.12 (3H, d, $J$ = 6.9 Hz), 0.80 (3H, t, $J$ = 7.5 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 216.6 (C-9), 206.3 (C-3), 170.5 (C-1), 139.0, 128.6, 128.3, 126.9, 102.4 (C-1′), 78.9, 78.4, 75.1, 74.8, 70.2, 69.4, 67.8, 65.9, 61.7, 53.2, 50.7, 48.2, 45.6, 44.8, 40.2 ($NMe_2$), 38.8, 38.0, 28.3, 21.9, 21.3, 20.6, 18.8, 16.6, 14.6, 12.6, 12.3, 10.7.

**6-*O*-[2-(Phenethylamino)ethyl] Ketolide 19iii.** To a 0 °C solution in methanol (10 mL) of **18** (123 mg, 0.200 mmol) was added acetic acid (114 $\mu$L, 2.00 mmol) and phenethylamine (251 $\mu$L, 2.00 mmol), and the mixture was stirred for 10 min. Sodium cyanoborohydride (24.8 mg, 0.400 mmol) was added and the reaction mixture was stirred for 16 h at room temperature. The reaction mixture was taken up in ethyl acetate, washed with aqueous 5% sodium carbonate, aqueous 2% tris(hydroxymethyl)aminomethane, and brine, dried over sodium sulfate, filtered, and concentrated. Chromatography on silica gel (90:10:0.5 dichloromethane/methanol/ammonia) gave the title compound (60 mg, 42%) as a white foam: MS *m/z* (FAB) 721 $(M + H)^+$; $^1$H NMR ($CDCl_3$) $\delta$ 7.16−7.35 (5H, m), 5.21 (1H, dd, $J$ = 10.5, 3.3 Hz), 4.40 (1H, d, $J$ = 3.6 Hz), 4.36 (1H, d, $J$ = 7.2 Hz), 3.80−4.00 (2H, m), 3.62 (1H, m), 3.00−3.45 (6H, m), 2.75−3.00 (5H, m), 2.40−2.65 (4H, m), 2.26 (6H, s), 1.80−2.10 (2H, m), 1.66 (1H, m), 1.57 (1H, m), 1.50 (1H, m), 1.43 (3H, d, $J$ = 7.8 Hz), 1.33 (3H, s), 1.29 (3H, d, $J$ = 6.3 Hz), 1.27 (3H, s), 1.25 (3H, d, $J$ = 6.3 Hz), 1.16 (3H, d, $J$ = 6.6 Hz), 1.12 (3H, d, $J$ = 6.9 Hz), 0.85 (3H, t, $J$ = 7.5 Hz). Anal. ($C_{39}H_{64}N_2O_{10}$) C, H, N.

**6-*O*-[2-(4′-Pyridylmethylamino)ethyl] Ketolide 19vi.** Compound **19vi** (120 mg, 85%) was prepared according to the procedures for the preparation of **19iii**, replacing phenethylamine with 4-(aminomethyl)pyridine: MS *m/z* (FAB) 708 $(M + H)^+$; $^1$H NMR ($CDCl_3$) $\delta$ 8.56 (2H, d, $J$ = 6.0 Hz), 7.35 (2H, d, $J$ = 6.0 Hz), 5.13 (1H, dd, $J$ = 10.5, 3.3 Hz), 4.42 (1H, d, $J$ = 3.6 Hz), 4.37 (1H, d, $J$ = 7.2 Hz), 3.90−4.00 (2H, m), 3.77 (2H, m), 3.62 (1H, m), 3.43 (1H, br s), 3.10−3.40 (5H, m), 2.90 (1H, m), 2.63 (1H, m), 2.40−2.55 (3H, m), 2.26 (6H, s), 1.85−2.05 (2H, m), 1.50−1.70 (3H, m), 1.43 (3H, d, $J$ = 7.8 Hz), 1.35 (3H, s), 1.29 (3H, d, $J$ = 6.3 Hz), 1.27 (3H, s), 1.24 (3H, d, $J$ = 6.3 Hz), 1.16 (3H, d, $J$ = 6.6 Hz), 1.14 (3H, d, $J$ = 6.9 Hz), 0.85 (3H, t, $J$ = 7.5 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 217.8 (C-9), 206.2 (C-3), 170.6 (C-1), 149.7, 148.2, 123.3, 102.5 (C-1′), 78.9, 78.4, 75.0, 74.9, 70.2, 69.5, 68.4, 65.9, 61.7, 52.4, 50.7, 48.7, 45.7, 44.8, 40.2($NMe_2$), 39.2, 38.5, 38.2, 28.4, 21.8, 21.3, 20.6, 18.7, 16.6, 14.6, 12.6, 12.2, 10.7. Anal. ($C_{37}H_{61}N_3O_{10}$) C, H, N.

**6-*O*-[2-(4′-Quinolylmethylamino)ethyl] Ketolide 19vii.** To a solution of **19i** (90 mg, 0.15 mmol) in methanol (2 mL) were added 4-quinolinecarboxaldehyde (23 mg, 0.15 mmol), acetic acid (8.6 $\mu$l, 0.15 mmol), and sodium cyanoborohydride (9.4 mg, 0.15 mmol), and the reaction mixture was stirred for 15 h at room temperature. The reaction mixture was taken up in ethyl acetate and washed with aqueous 5% sodium carbonate, aqueous 2% tris(hydroxymethyl)aminomethane, and brine. The organic phase was dried over sodium sulfate, filtered, and concentrated. Chromatography on silica gel (90:10:0.5 dichloromethane/methanol/ammonia) gave **19vii** (32 mg, 28%) as an off-white solid. MS *m/z* (FAB) 758 $(M + H)^+$; $^1$H NMR ($CDCl_3$) $\delta$ 8.90 (1H, d, $J$ = 4.5 Hz), 8.13 (1H, d, $J$ = 7.8 Hz), 7.96 (1H, d, $J$ = 8.4 Hz), 7.72 (1H, m), 7.57 (1H, m), 7.55 (1H, d, $J$ = 4.5 Hz), 5.15 (1H, dd, $J$ = 10.5, 3.3 Hz), 4.45 (1H, d, $J$ = 3.6 Hz), 4.36 (1H, d, $J$ = 7.2 Hz), 4.25 (2H, br s), 3.90−4.00 (2H, m), 3.62 (1H, m), 3.10−3.40 (5H, m), 2.95 (1H, m), 2.40−2.70 (4H, m), 2.26 (6H, s), 1.85−2.05 (2H, m), 1.50−1.70 (3H, m), 1.44 (3H, d, $J$ = 7.8 Hz), 1.35 (3H, s), 1.29 (3H, d, $J$ = 6.3 Hz), 1.27 (3H, s), 1.24 (3H, d, $J$ = 6.3 Hz), 1.16 (3H, d, $J$ = 6.6 Hz), 1.15 (3H, d, $J$ = 6.9 Hz), 0.82 (3H, t, $J$ = 7.5 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 218.0 (C-9), 206.2 (C-3), 170.6 (C-1), 150.4, 150.3, 148.0, 146.2, 130.1, 130.0, 129.4, 126.7, 122.8, 118.2, 102.5 (C-1′), 78.9, 78.3, 75.0, 74.9, 70.2, 69.5, 68.4, 65.9, 61.5, 50.7, 49.3, 48.9, 45.7, 44.8, 40.2($NMe_2$), 38.5, 38.2, 28.4, 21.9, 21.3, 20.6, 18.7, 16.6, 14.7, 12.6, 12.2, 10.7.

**2′,4″-*O*-Diacetyl-6-*O*-allyl-12-*O*-acylimidazolyl Erythromycin A (22).** To a stirred solution of 6-*O*-allylerythromycin **11** (8.93 g, 11.6 mmol) and DMAP (0.35 g, 2.87 mmol) in methylene chloride (45 mL) was added acetic anhydride (6.85 mL, 62.1 mmol) dropwise over 10 min. The reaction mixture was stirred at room temperature for 1 h. The mixture was diluted with an additional 50 mL of methylene chloride, washed with 5% sodium bicarbonate and brine, and dried over sodium sulfate. The corresponding 2′,4″-*O*-diacetate of **11** was obtained as a white solid (9.10 g, 92%) after recrystallization from ethyl acetate/hexane.

To a −40 °C solution under nitrogen in THF (30 mL) of the diacetate prepared above (4.84 g, 5.64 mmol) was added sodium hexamethyldisilazide (1.0 M in THF, 7.05 mL, 7.05 mmol), and the resulting white suspension was stirred for 40 min. A solution of carbonyldiimidazole (3.65 g, 22.56 mmol) in THF (30 mL) and DMF (20 mL) was added dropwise over 30 min at −40 °C, and then the cold bath was removed and the reaction mixture was stirred for 24 h. The reaction mixture was taken up in ethyl acetate, washed with aqueous 5% sodium bicarbonate and brine, dried over sodium sulfate, filtered, and concentrated to give **22** (6.32 g, crude) as a white foam, which was used without further purification.

**2′,4″-*O*-Diacetyl-6-*O*-allyl-11,12-cyclocarbamate Erythromycin A (23).** To a solution of **22** (6.32 g, crude) in acetonitrile (100 mL) and water (10 mL) was added 28% aqueous ammonia, and the mixture was stirred at room temperature for 4 days. The solvent was evaporated and the residue was taken up in ethyl acetate. The resulting solution was washed with aqueous 5% sodium bicarbonate and brine, dried over sodium sulfate, filtered, and concentrated. The crude product was purified by column chromatography (silica gel, 1:1 acetone/hexane) to give **23** (3.88 g, 78% in two steps) as a white solid: MS *m/z* (FAB) 883 $(M + H)^+$; HRMS (FAB) *m/z* 883.5164, calcd for $C_{45}H_{75}N_2O_{15}$ 883.5162; $^1$H NMR ($CDCl_3$) $\delta$ 5.72 (1H, m), 5.64 (1H, br s), 5.15 (2H, m), 5.04 (1H, dd, $J$ = 6.6, 2.4 Hz), 4.96 (1H, d, $J$ = 4.5 Hz), 4.66−4.80 (3H, m), 4.30 (1H, m), 3.89 (1H, m), 3.78 (2H, m), 3.68 (1H, s), 3.64 (1H, d, $J$ = 6.0 Hz), 3.35 (3H, s), 2.90 (2H, m), 2.73 (1H, m), 2.56 (1H, m), 2.42 (1H, d, $J$ = 15 Hz), 2.28 (6H, s), 2.10 (3H, s), 2.05 (3H, s), 2.00 (3H, s), 1.90 (2H, m), 1.25−1.77 (6H, m), 1.42 (3H, s), 1.38 (3H, s), 1.22 (3H, d, $J$ = 6.6 Hz), 1.10−1.20 (12H, m), 0.96 (3H, d, $J$ = 7.0 Hz), 0.87 (3H, t, $J$ = 7.5 Hz); $^{13}$C NMR

($CDCl_3$) $\delta$ 217.4 (C-9), 175.7 (C-1), 170.3 ($CH_3CO$), 169.9 ($CH_3$-CO), 158.2 (carbamate), 134.5, 118.1, 99.6 (C-1′), 95.9 (C-1″), 83.9, 79.2, 79.1, 78.4, 77.7, 75.6, 72.7, 72.1, 67.2, 65.6, 63.3, 63.1, 57.4, 49.2, 45.2, 44.6, 40.7 ($NMe_2$), 38.9, 38.1, 37.3, 35.1, 31.2, 30.8, 22.4, 21.5, 21.1, 20.9, 20.8, 18.4, 18.2, 15.4, 13.8, 13.4, 10.5, 9.0.

**6-*O*-[3-(3′-Quinolyl)-2-propenyl]-11,12-cyclocarbamate Erythromycin A (25s).** To a solution of **23** (3.53 g, 4.00 mmol), palladium(II) acetate (135 mg, 0.60 mmol), and tri(*o*-tolyl)phosphine (365 mg, 1.20 mmol) in acetonitrile (40 mL) were added 3-bromoquinoline (0.831 mL, 6.12 mmol) and triethylamine (1.15 mL, 8.26 mmol), and the mixture was cooled to −78 °C and degassed. The reaction mixture was warmed to 60 °C for 0.5 h and stirred at 100 °C for 20 h. Additional palladium(II) acetate (90 mg, 0.40 mmol), and tri(*o*-tolyl)phosphine (122 mg, 0.40 mmol), 3-bromoquinoline (0.543 mL, 4.00 mmol), and triethylamine (0.836 mL, 6.00 mmol) were added, and the mixture was stirred at 100 °C for an additional 8 h under nitrogen. The reaction mixture was taken up in ethyl acetate, washed twice with aqueous 5% sodium bicarbonate, once with aqueous 2% tris(hydroxymethyl)aminomethane, and once with brine, dried over sodium sulfate, filtered, and concentrated. The crude mixture was purified by flash column chromatography on silica gel (1:1 acetone/hexane) to give the coupling product (2.85 g, 71%) as an off-white solid: MS *m/z* $(APCI)^+$ 1010 $(M + H)^+$.

To a stirred solution of the above coupling product (2.53 g, 2.50 mmol) in methanol (50 mL) was added 2 N sodium hydroxide solution (7.5 mL, 15 mmol), and the mixture was stirred at room temperature for 24 h. The reaction mixture was taken up in ethyl acetate, washed with aqueous 5% sodium bicarbonate and brine, and dried over sodium sulfate. The crude mixture was purified by flash column chromatography on silica gel (10:1:0.05 methylene chloride/methanol/ammonia) to give **25** (1.42 g, 61%) as an off-white solid: MS *m/z* $(APCI)^+$ 926 $(M + H)^+$; HRMS (FAB) *m/z* 926.5397, calcd for $C_{50}H_{76}N_3O_{13}$ 926.5378; $^1H$ NMR ($CDCl_3$) $\delta$ 9.06 (1H, d, $J$ = 1.8 Hz), 8.25 (1H, d, $J$ = 1.8 Hz), 8.06 (1H, d, $J$ = 7.8 Hz), 7.82 (1H, d, $J$ = 7.8 Hz), 7.63 (1H, m), 7.50 (1H, m), 6.65 (1H, d, $J$ = 15.6 Hz), 6.41 (1H, dt, $J$ = 15.6, 6.6 Hz), 5.60 (1H, br s), 4.95 (1H, d, $J$ = 4.8 Hz), 4.85 (1H, dd, $J$ = 9.0, 2.4 Hz), 4.49 (1H, d, $J$ = 7.8 Hz), 4.22 (1H, m), 4.03 (2H, m), 3.90 (1H, d, $J$ = 7.8 Hz), 3.89 (1H, m), 3.87 (1H, s), 3.53 (2H, m), 3.34 (3H, s), 3.20 (1H, dd, $J$ = 9.3, 6.6 Hz), 3.06 (1H, t, $J$ = 9.0 Hz), 2.80−3.00 (2H, m), 2.63 (1H, m), 2.46 (1H, m), 2.39 (1H, d, $J$ = 15.0 Hz), 2.31 (6H, s), 2.21 (1H, d, $J$ = 9.0 Hz), 1.55−2.00 (6H, m), 1.50 (3H, s), 1.43 (1H, m), 1.41 (3H, s), 1.33 (3H, d, $J$ = 6.6 Hz), 1.27 (3H, s), 1.25 (3H, d, $J$ = 6.6 Hz), 1.23 (3H, d, $J$ = 6.9 Hz), 1.17 (3H, s), 1.13 (3H, s), 1.12 (3H, d, $J$ = 6.3 Hz), 0.74 (3H, t, $J$ = 7.5 Hz); $^{13}C$ NMR ($CDCl_3$) $\delta$ 217.5 (C-9), 175.7 (C-1), 157.5 (carbamate), 149.9, 147.2, 132.0, 129.5, 129.4, 128.7, 128.5, 128.0, 127.6, 126.2, 102.2 (C-1′), 95.7 (C-1″), 83.4, 79.2, 77.9, 77.4, 75.7, 72.4, 70.5, 68.4, 65.6, 65.3, 64.6, 57.4, 49.1, 44.8, 44.5, 39.9 ($NMe_2$), 39.6, 38.4, 36.9, 34.4, 28.3, 22.0, 21.0, 20.6, 18.3, 18.1, 14.9, 13.3, 13.0, 10.2, 8.5.

**2′-*O*-Acetyl-6-*O*-allyl-11,12-cyclocarbamate Ketolide 26.** To a stirred suspension of **23** (69.0 g, 78.2 mmol) in ethanol (200 mL) and water (400 mL), was added 1 N HCl (400 mL, 0.400 mol) dropwise over 20 min, and a clear solution was obtained. The solution was stirred at room temperature for 72 h. More HCl (4 N, 100 mL, 0.4 mol) was added to the reaction mixture and the mixture was stirred for an additional 48 h. The mixture was neutralized with 4 N NaOH and the precipitate was collected by filtration to give a white solid, 35.56 g. The filtrate was extracted with ethyl acetate (2 × 400 mL), and the organic phase was washed with 5% sodium carbonate and brine, dried over sodium sulfate, and concentrated to give an additional 21.58 g of white solid. The combined crude material was purified by column chromatography (silica gel, 50:50:0.5 acetone/hexane/triethylamine) to give 25.64 g (48%) of the 3-OH intermediate. MS *m/z* $(APCI)^+$ 683 $(M + H)^+$.

NCS (2.37 g, 17.8 mmol) was dissolved in $CH_2Cl_2$ (80 mL) and cooled to −10 °C under nitrogen. $Me_2S$ (1.52 mL, 20.8 mmol) was added dropwise over 5 min and stirred for an additional 10 min at this temperature. A solution of the above product (8.10 g, 11.9 mmol) in $CH_2Cl_2$ (60 mL) was introduced dropwise over 30 min. After the mixture was stirred for 30 min at −10 to −5 °C, $Et_3N$ (1.99 mL, 14.3 mmol) was added over 5 min and stirred for an additional 45 min before the mixture warmed up to room temperature. The reaction mixture was taken up in EtOAc and washed with 5% $Na_2CO_3$ and brine. The organic phase was dried ($Na_2SO_4$) and concentrated. The crude product was purified by column chromatography (silica gel, 50:50:0.5 acetone/hexane/triethylamine) to give **26** (8.07 g 99%) as a white solid: MS *m/z* (FAB) 681 $(M + H)^+$; $^1H$ NMR ($CDCl_3$) $\delta$ 5.61 (1H, br s), 5.55 (1H, m), 5.05−5.15 (3H, m), 4.74 (1H, dd, $J$ = 10.2, 7.5 Hz), 4.45 (1H, d, $J$ = 7.2 Hz), 4.32 (1H, d, $J$ = 3.6 Hz), 3.91 (1H, q, $J$ = 6.6 Hz), 3.88 (1H, br s), 3.62 (2H, m), 3.38 (1H, m), 3.16 (1H, m), 2.95 (1H, m), 2.50−2.80 (3H, m), 2.27 (6H, s), 2.25 (1H, m), 2.04 (3H, s), 2.00 (3H, s), 1.95 (1H, m), 1.50−1.80 (3H, m), 1.53 (3H, s), 1.35 (3H, d, $J$ = 6.6 Hz), 1.32 (3H, s), 1.25 (3H, d, $J$ = 6.0 Hz), 1.23 (3H, d, $J$ = 6.9 Hz), 1.16 (3H, d, $J$ = 6.6 Hz), 1.13 (3H, d, $J$ = 6.9 Hz), 0.88 (3H, t, $J$ = 7.5 Hz); $^{13}C$ NMR ($CDCl_3$) $\delta$ 216.8 (C-9), 205.3 (C-3), 169.7 (C-1), 169.5 ($CH_3CO$), 157.9 (carbamate), 134.3, 118.3, 100.3 (C-1′), 83.6, 78.4, 77.1, 75.1, 71.5, 69.0, 64.6, 63.3, 57.8, 50.7, 45.3, 45.0, 40.6 ($NMe_2$), 38.6, 37.3, 30.6, 22.6, 21.3, 21.0, 20.1, 18.2, 14.4, 13.8, 13.6, 13.5, 10.5. Anal. ($C_{35}H_{56}N_2O_{11}$) C, H, N.

**6-*O*-Allyl-11,12-cyclocarbamate Ketolide 27.** Compound **27** (89%) was obtained by stirring **26** in methanol for 24 h followed by chromatography (silica gel, 95:5:0.5 methylene chloride/methanol/ammonia): MS *m/z* (APCI) 639 $(M + H)^+$; HRMS (APCI) *m/z* 639.3854, calcd for $C_{33}H_{55}N_2O_{10}$ 639.3857; $^1H$ NMR ($CDCl_3$) $\delta$ 5.60 (1H, br s), 5.55 (1H, m), 5.05−5.15 (3H, m), 4.38 (1H, d, $J$ = 7.2 Hz), 4.34 (1H, d, $J$ = 3.6 Hz), 3.95 (1H, q, $J$ = 6.6 Hz), 3.88 (1H, br s), 3.62 (2H, m), 3.40 (1H, m), 3.18 (2H, m), 2.95 (1H, m), 2.61 (1H, m), 2.48 (1H, m), 2.27 (6H, s), 1.96 (1H, m), 1.50−1.80 (4H, m), 1.53 (3H, s), 1.39 (3H, d, $J$ = 6.9 Hz), 1.36 (3H, s), 1.34 (3H, d, $J$ = 6.0 Hz), 1.26 (3H, d, $J$ = 6.6 Hz), 1.17 (3H, d, $J$ = 6.6 Hz), 1.12 (3H, d, $J$ = 6.9 Hz), 0.88 (3H, t, $J$ = 7.5 Hz); $^{13}C$ NMR ($CDCl_3$) $\delta$ 216.9 (C-9), 205.3 (C-3), 169.5 (C-1), 157.9 (carbamate), 134.4, 118.3, 102.8 (C-1′), 83.7, 78.4, 77.1, 76.1, 70.2, 69.5, 65.9, 64.6, 57.8, 50.8, 45.9, 45.1, 40.2 ($NMe_2$), 38.9, 37.3, 28.3, 22.6, 21.3, 20.2, 18.2, 14.4, 13.8, 13.6, 10.6. Anal. ($C_{33}H_{54}N_2O_{10}$) C, H, N.

**6-*O*-Allyl-2′-*O*-benzoyl-12-*O*-acylimidazolyl Ketolide 28.** To a stirred 0 °C solution of **13** (73.5 g, 102 mmol) and carbonyldiimidazole (CDI) (83.0 g, 512 mmol) in THF (1200 mL) was added LiH (1.71 g, 205 mmol) in small portions. The reaction mixture was stirred at room temperature for 7 days. The mixture was diluted with ethyl acetate, washed with 5% sodium bicarbonate and brine, dried over sodium sulfate, and concentrated. The crude product was purified by column chromatography (silica gel, 3:7 acetone/hexane) to give intermediate **28** (51.1 g, 68%) as a white solid: $^1H$ NMR ($CDCl_3$) $\delta$ 8.12 (1H, m), 8.03 (2H, dd, $J$ = 8.4, 1.5 Hz), 7.54 (1H, m), 7.44 (2H, m), 7.39 (1H, m), 7.08 (1H, m), 6.65 (1H, br s), 5.72 (2H, m), 5.10 (1H, dd, $J$ = 15, 1.8 Hz), 5.01 (2H, m), 4.55 (1H, d, $J$ = 7.5 Hz), 4.19 (1H, d, $J$ = 4.8 Hz), 3.95 (1H, m), 3.82 (1H, m), 3.66 (1H, q, $J$ = 6.6 Hz), 3.55 (1H, m), 3.43 (1H, m), 3.03 (1H, m), 2.86 (1H, m), 2.26 (6H, s), 1.86 (3H, s), 1.76 (3H, s), 1.61 (3H, s), 1.36 (3H, d, $J$ = 6.9 Hz), 1.29 (3H, d, $J$ = 6.0 Hz), 1.20 (3H, br s), 1.11 (3H, d, $J$ = 6.6 Hz), 0.88 (3H, t, $J$ = 7.5 Hz).

**6-*O*-Allyl-2′-*O*-benzoyl-11,12-cyclocarbamate Ketolide 29.** To a stirred solution of **28** (1.19 g, 1.50 mmol) in $CH_3CN$ (20 mL) and THF (2 mL) was added aqueous 28% ammonia (2 mL). The mixture was stirred at room temperature for 48 h and diluted with EtOAc (50 mL). The organic solution was washed with 5% $Na_2CO_3$ and brine, dried over $Na_2SO_4$, and concentrated. Column chromatography (silica gel, 3:7 acetone/hexane) gave **29** (565 mg, 51%) and **30** (356 mg, 32%), both as white solids. **29**: MS *m/z* (APCI) 743 $(M + H)^+$; $^1H$ NMR ($CDCl_3$) $\delta$ 8.02 (2H, dd, $J$ = 7.8, 1.2 Hz), 7.56 (1H, m), 7.43 (2H, m), 5.56 (1H, br s), 5.54 (1H, m), 5.05−5.15 (3H, m), 4.58 (1H, d, $J$ = 7.2 Hz), 4.32 (1H, d, $J$ = 3.6 Hz), 3.82 (1H, br s),

3.78 (1H, q, $J$ = 6.6 Hz), 3.64 (2H, m), 3.37 (1H, m), 3.05 (1H, m), 2.85 (2H, m), 2.56 (1H, m), 2.27 (6H, s), 1.94 (1H, m), 1.80 (1H, m), 1.40−1.60 (3H, m), 1.43 (3H, s), 1.35 (3H, s), 1.30 (3H, d, $J$ = 6.9 Hz), 1.29 (3H, d, $J$ = 6.0 Hz), 1.12 (3H, d, $J$ = 6.3 Hz), 1.08 (3H, d, $J$ = 6.6 Hz), 0.98 (3H, d, $J$ = 6.9 Hz), 0.88 (3H, t, $J$ = 7.5 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 216.9 (C-9), 205.4 (C-3), 169.4 (C-1), 165.2 (PhCO), 157.9 (carbamate), 134.3, 132.8, 130.5, 129.7, 128.3, 118.3, 100.6 (C-1′), 83.6, 78.4, 77.1, 75.3, 71.9, 69.2, 64.6, 63.5, 57.7, 50.7, 45.3, 45.1, 40.7 ($NMe_2$), 38.5, 37.2, 31.5, 22.6, 21.1, 20.2, 18.3, 14.4, 14.1, 13.6, 13.5, 10.5.

**11,12-Cyclocarbazate Ketolide 35s.** To a stirred solution of **28** (793 mg, 1.00 mmol) in $CH_3CN$ (10 mL) and THF (1 mL) was added aqueous 85% hydrazine (0.5 mL). The mixture was stirred at room temperature for 96 h and diluted with EtOAc (50 mL). The organic phase was washed with 5% $Na_2CO_3$ and brine, dried over $Na_2SO_4$, and concentrated. Column chromatography (silica gel, 95:5:0.5 $CH_2Cl_2$/MeOH/ammonia) gave **31** (as 2′-OH, 341 mg, 52%) as an off-white solid: MS $m/z$ (APCI) 654 $(M + H)^+$.

Heck coupling of **31** and 3-bromoquinoline was conducted according to the procedure described for the preparation of **25s**. Compound **35s** was obtained in 40% yield after column chromatography (silica gel, 95:5:0.5 $CH_2Cl_2$/MeOH/ammonia): MS $m/z$ (APCI) 781 $(M + H)^+$; HRMS (FAB) $m/z$ 781.4371, calcd for $C_{42}H_{61}N_4O_{10}$ 781.4388; $^1$H NMR ($CDCl_3$) $\delta$ 9.02 (1H, d, $J$ = 2.4 Hz), 8.12 (1H, d, $J$ = 2.4 Hz), 8.06 (1H, m), 7.80 (1H, m), 7.66 (1H, m), 7.52 (1H, m), 6.58 (1H, d, $J$ = 16.2 Hz), 6.31 (1H, dt, $J$ = 16.2, 6.0 Hz), 5.08 (1H, m), 4.45 (1H, d, $J$ = 5.1 Hz), 4.36 (1H, d, $J$ = 7.2 Hz), 3.98 (1H, q, $J$ = 6.6 Hz), 3.95 (1H, m), 3.86 (1H, m), 3.56 (1H, m), 3.20 (3H, m), 2.79 (1H, m), 2.53 (1H, m), 2.29 (6H, s), 1.96 (1H, m), 1.40−1.80 (4H, m), 1.50 (3H, s), 1.48 (3H, s), 1.43 (3H, d, $J$ = 6.9 Hz), 1.41 (3H, d, $J$ = 6.6 Hz), 1.15−1.25 (6H, m), 1.08 (3H, d, $J$ = 6.6 Hz), 0.86 (3H, t, $J$ = 7.5 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 216.7 (C-9), 205.0 (C-3), 170.1 (C-1), 149.3, 147.8, 132.5, 129.9, 129.3, 129.2, 128.7, 128.5, 128.1, 128.0, 126.9, 124.9, 103.0 (C-1′), 80.9, 79.1, 77.6, 76.8, 70.2, 69.5, 66.0, 64.6, 62.9, 50.9, 45.8, 45.0, 40.2 ($NMe_2$), 39.5, 38.8, 31.6, 28.5, 22.6, 22.4, 21.1, 20.5, 18.6, 14.6, 14.3, 13.9, 13.6, 10.4. Anal. ($C_{42}H_{60}N_4O_{10}$) C, H, N.

**11-*N*-Methoxy-11,12-cyclocarbamate Ketolide 36s.** Following the procedure for the preparation of **35s**, compound **36s** was obtained in 30% yield: MS $m/z$ (APCI) 796 $(M + H)^+$; $^1$H NMR ($CDCl_3$) $\delta$ 9.02 (1H, d, $J$ = 2.4 Hz), 8.08 (1H, d, $J$ = 2.4 Hz), 8.06 (1H, m), 7.79 (1H, m), 7.66 (1H, m), 7.52 (1H, m), 6.61 (1H, d, $J$ = 16.2 Hz), 6.43 (1H, dt, $J$ = 16.2, 6.0 Hz), 5.18 (1H, dd, $J$ = 9.6, 2.7 Hz), 4.40 (1H, d, $J$ = 5.1 Hz), 4.30 (1H, d, $J$ = 7.2 Hz), 4.12 (1H, q, $J$ = 6.6 Hz), 4.03 (1H, m), 3.93 (1H, m), 3.60 (3H, s), 3.52 (1H, m), 3.18 (2H, m), 3.05 (1H,m), 2.93 (1H, m), 2.46 (2H, m), 2.27 (6H, s), 1.94 (1H, m), 1.40−1.80 (4H, m), 1.53 (6H, s), 1.41 (3H, d, $J$ = 6.9 Hz), 1.38 (3H, d, $J$ = 6.6 Hz), 1.23 (3H, d, $J$ = 6.0 Hz), 1.16 (3H, d, $J$ = 6.0 Hz), 1.14 (3H, d, $J$ = 6.6 Hz), 0.90 (3H, t, $J$ = 7.5 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 211.8 (C-9), 203.8 (C-3), 170.1 (C-1), 156.2, 149.0, 147.4, 132.4, 130.4, 129.7, 129.1, 128.1, 127.9, 127.8, 126.8, 103.9 (C-1′), 81.3, 80.8, 78.6, 70.2, 69.5, 65.8, 64.8, 63.0, 62.0, 50.9, 46.2, 41.3, 40.2 ($NMe_2$), 39.6, 38.3, 28.2, 22.7, 21.1, 17.1, 15.1, 14.4, 13.5, 11.0, 10.4.

**11-*N*-Methyl-11,12-Cyclocarbamate Ketolide 37s.** Following the procedure for the preparation of **35s**, compound **37s** was obtained in 35% yield: MS $m/z$ (APCI) 780 $(M + H)^+$; $^1$H NMR ($CDCl_3$) $\delta$ 9.02 (1H, d, $J$ = 2.4 Hz), 8.12 (1H, d, $J$ = 2.4 Hz), 8.06 (1H, m), 7.81 (1H, m), 7.66 (1H, m), 7.52 (1H, m), 6.57 (1H, d, $J$ = 16.2 Hz), 6.24 (1H, dt, $J$ = 16.2, 6.0 Hz), 4.98 (1H, dd, $J$ = 9.6, 2.7 Hz), 4.47 (1H, d, $J$ = 5.1 Hz), 4.35 (1H, d, $J$ = 7.2 Hz), 3.97 (1H, q, $J$ = 6.6 Hz), 3.92 (1H, m), 3.80 (1H, m), 3.55 (1H, m), 3.25 (1H, m), 3.18 (2H, m), 2.85 (3H, s), 2.70 (1H, m), 2.47 (1H, m), 2.27 (6H, s), 1.97 (1H, m), 1.40−1.80 (4H, m), 1.53 (3H, s), 1.46 (3H, s), 1.43 (3H, d, $J$ = 6.9 Hz), 1.38 (3H, d, $J$ = 6.3 Hz), 1.20 (3H, d, $J$ = 6.0 Hz), 1.18 (3H, d, $J$ = 6.0 Hz), 1.05 (3H, d, $J$ = 6.6 Hz), 0.87 (3H, t, $J$ = 7.5 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 215.3 (C-9), 205.1 (C-3), 170.0 (C-1), 157.2, 149.5, 134.3, 132.5, 129.8, 129.6, 129.2, 129.1, 128.8, 127.9, 127.8, 126.8, 103.1 (C-1′), 82.3, 79.1, 77.9, 76.7, 70.2, 69.5, 65.9, 64.7, 62.4, 50.9, 45.8, 45.3, 40.2 ($NMe_2$), 38.9, 38.7, 32.1, 28.3, 22.6, 21.1, 20.5, 18.9, 14.7, 14.5, 14.1, 13.8, 13.7, 10.5.

**11-*N*-[2-(*N*,*N*-Dimethylamino)ethyl]-11,12-cyclocarbamate Ketolide 38s.** Following the procedure for the preparation of **35s**, compound **38s** was obtained in 20% yield: MS $m/z$ (APCI) 837 $(M + H)^+$; $^1$H NMR ($CDCl_3$) $\delta$ 9.02 (1H, d, $J$ = 2.4 Hz), 8.15 (1H, d, $J$ = 2.4 Hz), 8.06 (1H, m), 7.82 (1H, m), 7.66 (1H, m), 7.52 (1H, m), 6.57 (1H, d, $J$ = 16.2 Hz), 6.30 (1H, dt, $J$ = 16.2, 6.0 Hz), 5.25 (1H, dd, $J$ = 9.6, 2.7 Hz), 4.47 (1H, d, $J$ = 5.1 Hz), 4.34 (1H, d, $J$ = 7.2 Hz), 3.97 (1H, q, $J$ = 6.6 Hz), 3.90 (1H, m), 3.70 (2H, m), 3.25 (1H, m), 3.19 (2H, m), 2.95 (1H, m), 2.72 (1H, m), 2.60 (1H, m), 2.47 (2H, m), 2.26 (6H, s), 2.15−2.30 (2H, m), 2.12 (6H, s), 2.00 (1H, m), 1.40−1.80 (4H, m), 1.52 (3H, s), 1.42 (3H, s), 1.41 (3H, d, $J$ = 6.9 Hz), 1.38 (3H, d, $J$ = 6.3 Hz), 1.20 (3H, d, $J$ = 6.0 Hz), 1.16 (3H, d, $J$ = 6.0 Hz), 1.08 (3H, d, $J$ = 6.6 Hz), 0.85 (3H, t, $J$ = 7.5 Hz).

**6-*O*-Allyl Tricyclic Ketolide 39.** To a stirred solution of **28** (385 mg, 0.485 mmol) in $CH_3CN$ (10 mL) was added ethylenediamine (291 mg, 4.85 mmol). The mixture was stirred at room temperature for 60 h and diluted with EtOAc (50 mL). The organic solution was washed with 5% $Na_2CO_3$ and brine, dried over $Na_2SO_4$, and concentrated. The crude mixture was then dissolved in MeOH (5 mL) and HOAc (60 $\mu$L, 1.00 mmol) and stirred at room temperature for 48 h. The mixture was diluted with EtOAc (50 mL) and washed with 5% $Na_2CO_3$ and brine, dried over $Na_2SO_4$, and concentrated. Column chromatography (silica gel, 95:5:0.5 $CH_2Cl_2$/MeOH/ammonia) gave **39** (126 mg, 40%) as an off-white solid: MS $m/z$ (APCI) 664 $(M + H)^+$; HRMS (FAB) $m/z$ 664.4173, calcd for $C_{35}H_{58}N_3O_9$ 664.4173; $^1$H NMR ($CDCl_3$) $\delta$ 5.65 (1H, m), 5.13 (1H, m), 5.02 (1H, m), 4.40 (1H, d, $J$ = 4.2 Hz), 4.34 (1H, d, $J$ = 7.5 Hz), 3.92 (1H, q, $J$ = 6.6 Hz), 3.72 (2H, m), 3.58 (1H, m), 3.20 (2H, m), 2.85 (1H, m), 2.47 (1H, m), 2.27 (6H, s), 1.95 (1H, m), 1.40−1.70 (4H, m), 1.51 (3H, s), 1.40 (3H, d, $J$ = 6.9 Hz), 1.38 (3H, s), 1.34 (3H, d, $J$ = 6.0 Hz), 1.24 (3H, d, $J$ = 6.3 Hz), 1.22 (3H, d, $J$ = 6.6 Hz), 1.05 (3H, d, $J$ = 6.9 Hz), 0.87 (3H, t, $J$ = 7.5 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 205.3 (C-3), 180.8 (C-9), 170.0 (C-1), 156.1 (carbamate), 137.1, 116.6, 103.0 (C-1′), 81.7, 79.4, 77.1, 76.1, 70.3, 69.5, 65.9, 64.8, 60.3, 50.8, 49.4, 46.0, 43.1, 42.0, 40.2 ($NMe_2$), 38.5, 36.4, 31.5, 28.3, 22.4, 21.3, 20.4, 20.2, 14.7, 13.6, 13.0, 10.5.

**6-*O*-[3-(3′-Quinolyl)-2-propenyl] Tricyclic Ketolide 40s.** To a solution of **39** (663 mg, 1.00 mmol), palladium(II) acetate (50 mg, 0.20 mmol), and tri(*o*-tolyl)phosphine (120 mg, 0.40 mmol) in acetonitrile (5 mL) were added 3-bromoquinoline (0.270 mL, 2.00 mmol) and triethylamine (0.280 mL, 2.00 mmol). The mixture was cooled to −78 °C and degassed. The reaction mixture was then warmed to 60 °C for 0.5 h and stirred at 80 °C for 18 h. The reaction mixture was taken up in ethyl acetate, washed twice with aqueous 5% sodium bicarbonate, once with aqueous 2% tris(hydroxymethyl)aminomethane, and once with brine, dried over sodium sulfate, filtered, and concentrated. The crude mixture was purified by flash column chromatography on silica gel (95:5:0.5 $CH_2Cl_2$/MeOH/ammonia) to give **40s** (486 mg, 62%) as an off-white solid: MS $m/z$ (APCI) 791 $(M + H)^+$; HRMS (FAB) $m/z$ 791.4590, calcd for $C_{44}H_{63}N_4O_9$ 791.4595; $^1$H NMR ($CDCl_3$) $\delta$ 9.00 (1H, d, $J$ = 2.4 Hz), 8.13 (1H, d, $J$ = 2.4 Hz), 8.07 (1H, d, $J$ = 8.4 Hz),), 7.80 (1H, d, $J$ = 8.4 Hz), 7.66 (1H, m), 7.52 (1H, m), 6.63 (1H, d, $J$ = 16.2 Hz), 6.40 (1H, dt, $J$ = 16.2, 6.0 Hz), 5.02 (1H, dd, $J$ = 10.2, 2.7 Hz), 4.48 (1H, d, $J$ = 5.1 Hz), 4.36 (1H, d, $J$ = 7.2 Hz), 4.03 (1H, m), 3.98 (1H, q, $J$ = 6.6 Hz), 3.83 (1H, m), 3.60−3.80 (4H, m), 3.55 (1H, m), 3.21 (2H, m), 3.08 (1H, m), 2.86 (1H, m), 2.48 (1H, m), 2.27 (6H, s), 1.96 (1H, m), 1.50−1.70 (4H, m), 1.52 (3H, s), 1.49 (3H, s), 1.43 (3H, d, $J$ = 6.9 Hz), 1.40 (3H, d, $J$ = 6.6 Hz), 1.23 (3H, d, $J$ = 6.6 Hz), 1.18 (3H, d, $J$ = 6.0 Hz), 1.09 (3H, d, $J$ = 6.6 Hz), 0.86 (3H, t, $J$ = 7.5 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 205.3 (C-3), 170.3 (C-1), 155.9, 149.5, 147.6, 132.4, 130.9, 129.6, 129.2, 129.1, 128.4, 128.1, 127.9, 126.8, 124.9, 103.0 (C-1′), 81.6, 79.6, 77.1, 76.4, 70.2, 69.5, 66.0, 64.5, 60.3, 50.9, 49.2, 46.1, 43.0, 41.6, 40.2 ($NMe_2$), 38.5, 36.5, 28.4, 22.3, 21.2, 20.4, 20.1, 14.7, 13.8, 13.0, 10.9, 10.4. Anal. ($C_{44}H_{62}N_4O_9 \cdot H_2O$) C, H, N.

**6-*O*-[3-(3′-Quinolyl)-2-propenyl]-11,12-cyclocarbamate Ketolide 41s: General Procedure.** A mixture of **26** (2.72 g, 4.00 mmol), palladium(II) acetate (224 mg, 1.00 mmol), tri-(*o*-tolyl)phosphine (608 mg, 2.00 mmol), 3-bromoquinoline (1.08 mL, 8.00 mmol), and triethylamine (1.11 mL, 8.00 mmol) in acetonitrile (20 mL) was flushed with nitrogen and sealed in a pressure tube. The reaction mixture was stirred at 50 °C for 1 h and then at 90 °C for 48 h. The reaction mixture was taken up in ethyl acetate, washed with aqueous 5% sodium bicarbonate and brine, dried over sodium sulfate, filtered, and concentrated. The crude mixture was purified by flash column chromatography on silica gel (50:50:0.5 acetone/hexane/triethylamine) to give 2′-OAc-**41s** (2.62 g, 81%) as a white solid: MS *m*/*z* (ESI) 808 $(M + H)^+$; HRMS (FAB) *m*/*z* 808.4381, calcd for $C_{44}H_{62}N_3O_{11}$ 808.4379; $^1$H NMR ($CDCl_3$) $\delta$ 9.02 (1H, d, $J$ = 2.4 Hz), 8.16 (1H, d, $J$ = 2.4 Hz), 8.06 (1H, d, $J$ = 8.4 Hz),), 7.82 (1H, d, $J$ = 8.4 Hz), 7.64 (1H, m), 7.52 (1H, m), 6.56 (1H, d, $J$ = 16.2 Hz), 6.17 (1H, dt, $J$ = 16.2, 6.0 Hz), 5.50 (1H, br s), 5.98 (1H, dd, $J$ = 9.0, 3.0 Hz), 4.74 (1H, dd, $J$ = 10.8, 7.8 Hz), 4.44 (1H, d, $J$ = 7.2 Hz), 4.38 (1H, d, $J$ = 3.6 Hz), 3.93 (1H, q, $J$ = 6.6 Hz), 3.91 (1H, br s), 3.84 (1H, m), 3.70 (1H, m), 3.55 (1H, m), 3.20 (1H, m), 2.98 (1H, m), 2.50−2.70 (2H, m), 2.24 (6H, s), 2.03 (3H, s), 1.90 (1H, m), 1.71 (2H, m), 1.55 (1H, m), 1.49 (3H, s), 1.41 (3H, s), 1.40 (3H, d, $J$ = 6.9 Hz), 1.26 (3H, d, $J$ = 6.6 Hz), 1.18 (3H, d, $J$ = 6.6 Hz), 1.15 (3H, d, $J$ = 6.0 Hz), 1.12 (3H, d, $J$ = 6.6 Hz), 0.81 (3H, t, $J$ = 7.5 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 217.3 (C-9), 205.3 (C-3), 169.7, 169.6, 157.6, 149.7, 147.7, 132.5, 130.0, 129.6, 129.2, 129.1, 128.4, 128.0, 126.7, 100.4 (C-1′), 83.4, 78.7, 77.6, 75.5, 71.5, 69.1, 64.3, 63.4, 58.2, 50.9, 45.7, 45.1, 40.6 ($NMe_2$), 38.8, 37.3, 30.6, 22.6, 21.3, 20.9, 20.1, 18.1, 14.3, 13.8, 13.7, 10.6. Anal. ($C_{44}H_{61}N_3O_{11}\cdot 0.5H_2O$) C, H, N.

The product obtained above (1.477 g, 1.830 mmol) was heated to reflux in MeOH (20 mL) for 2 h. After the solvent was evaporated, the crude product was purified by column chromatography (silica gel, 95:5:0.5 $CH_2Cl_2$/MeOH/ammonia) to give **41s** (1.138 g, 81%) as a white solid: MS *m*/*z* (ESI) 766 $(M + H)^+$; HRMS (FAB) *m*/*z* 766.4301, calcd for $C_{42}H_{60}N_3O_{10}$ 766.4279; $^1$H NMR ($CDCl_3$) $\delta$ 9.03 (1H, d, $J$ = 2.4 Hz), 8.18 (1H, d, $J$ = 2.4 Hz), 8.05 (1H, d, $J$ = 8.4 Hz), 7.83 (1H, d, $J$ = 8.4 Hz), 7.64 (1H, m), 7.52 (1H, m), 6.57 (1H, d, $J$ = 15.6 Hz), 6.17 (1H, dt, $J$ = 15.6, 6.0 Hz), 5.47 (1H, br s), 4.93 (1H, dd, $J$ = 9.0, 3.0 Hz), 4.39 (1H, d, $J$ = 4.2 Hz), 4.35 (1H, d, $J$ = 6.6 Hz), 3.95 (1H, q, $J$ = 6.6 Hz), 3.90 (1H, br s), 3.82 (1H, m), 3.70 (1H, m), 3.54 (1H, m), 3.43 (1H, br s), 3.18 (1H, m), 3.16 (1H, m), 2.96 (1H, m), 2.62 (1H, m), 2.43 (1H, m), 2.25 (6H, s), 1.85 (1H, m), 1.80 (1H, m), 1.70 (1H, m), 1.63 (1H, m), 1.50 (1H, m), 1.48 (3H, s), 1.43 (3H, s), 1.39 (3H, d, $J$ = 6.9 Hz), 1.37 (3H, d, $J$ = 6.6 Hz), 1.15 (3H, d, $J$ = 6.6 Hz), 1.12 (3H, d, $J$ = 6.0 Hz), 1.10 (3H, d, $J$ = 6.6 Hz), 0.78 (3H, t, $J$ = 7.5 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 217.3 (C-9), 205.3 (C-3), 169.6, 169.6, 157.6, 149.7, 147.6, 132.4, 129.9, 129.6, 129.2, 129.0, 128.5, 128.0, 126.7, 102.9 (C-1′), 83.5, 78.7, 77.5, 76.4, 70.2, 69.5, 65.8, 64.3, 58.1, 50.8, 46.2, 45.0, 40.2 ($NMe_2$), 39.1, 37.3, 28.2, 22.6, 21.1, 20.2, 18.0, 14.4, 14.1, 13.6, 10.6. Anal. ($C_{42}H_{59}N_3O_{10}$) C, H, N.

**6-*O*-[3-Phenyl-2-propenyl]-11,12-cyclocarbamate Ketolide 41a.** Compound **41a** was prepared as a white solid in 94% yield according to the general procedure for the preparation of **41s**: MS *m*/*z* (ESI) 715 $(M + H)^+$; HRMS (FAB) *m*/*z* 715.4168, calcd for $C_{39}H_{59}N_2O_{10}$ 715.4190; $^1$H NMR ($CDCl_3$) $\delta$ 7.45 (1H, d, $J$ = 7.2 Hz), 7.15−7.35 (4H, m), 6.42 (1H, d, $J$ = 15.6 Hz), 5.96 (1H, dt, $J$ = 15.6, 6.0 Hz), 5.32 (1H, br s), 4.88 (1H, dd, $J$ = 9.0, 3.0 Hz), 4.38 (1H, d, $J$ = 4.2 Hz), 4.37 (1H, d, $J$ = 6.6 Hz), 3.95 (1H, q, $J$ = 6.6 Hz), 3.92 (1H, br s), 3.80 (1H, m), 3.70 (2H, m), 3.20 (2H, m), 2.96 (1H, m), 2.62 (1H, m), 2.45 (1H, m), 2.27 (6H, s), 1.89 (1H, m), 1.50−1.80 (4H, m), 1.48 (3H, s), 1.42 (3H, s), 1.41 (3H, d, $J$ = 6.9 Hz), 1.39 (3H, d, $J$ = 6.6 Hz), 1.22 (3H, d, $J$ = 6.6 Hz), 1.13 (3H, d, $J$ = 6.0 Hz), 1.11 (3H, d, $J$ = 6.6 Hz), 0.84 (3H, t, $J$ = 7.5 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 217.2 (C-9), 205.3 (C-3), 169.5 (C-1), 157.4, 136.5, 133.7, 128.6, 127.8, 126.5, 125.5, 102.9 (C-1′), 83.5, 78.4, 77.7, 76.4, 70.2, 69.5, 65.9, 64.3, 58.2, 50.9, 46.2, 45.1, 40.2 ($NMe_2$), 39.1, 37.3, 28.2, 22.8, 21.1, 20.3, 18.1, 14.4, 14.1, 13.7, 10.8. Anal. ($C_{39}H_{58}N_2O_{10}$) C, H, N.

**6-*O*-[3-(3′-Pyridyl)-2-propenyl]-11,12-cyclocarbamate Ketolide 41d.** Compound **41d** was prepared as white solid in 36% yield according to the general procedure for the preparation of **41s**: MS *m*/*z* (ESI) 716 $(M + H)^+$; $^1$H NMR ($CDCl_3$) $\delta$ 8.56 (1H, d, $J$ = 2.4 Hz), 8.43 (1H, dd, $J$ = 4.8, 1.8 Hz), 7.70 (1H, ddd, $J$ = 8.4, 2.4, 1.8 Hz), 7.23 (1H, dd, $J$ = 8.4, 4.8 Hz), 6.40 (1H, d, $J$ = 15.6 Hz), 6.15 (1H, dt, $J$ = 15.6, 6.0 Hz), 5.74 (1H, br s), 5.22 (1H, dd, $J$ = 9.0, 3.0 Hz), 4.39 (1H, d, $J$ = 6.6 Hz), 4.38 (1H, d, $J$ = 3.6 Hz), 3.95 (1H, q, $J$ = 6.6 Hz), 3.94 (1H, br s), 3.90 (1H, m), 3.60 (2H, m), 3.18 (2H, m), 3.04 (1H, m), 2.62 (1H, m), 2.47 (1H, m), 2.27 (6H, s), 1.50−2.20 (5H, m), 1.55 (3H, s), 1.42 (3H, d, $J$ = 7.8 Hz), 1.35 (3H, d, $J$ = 6.9 Hz), 1.34 (3H, s), 1.25 (3H, d, $J$ = 6.3 Hz), 1.20 (3H, d, $J$ = 6.6 Hz), 1.13 (3H, d, $J$ = 6.0 Hz), 0.88 (3H, t, $J$ = 7.5 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 217.5 (C-9), 205.6 (C-3), 170.1 (C-1), 158.2, 148.1, 148.0, 132.5, 128.8, 128.5, 123.3, 102.7 (C-1′), 83.7, 78.2, 77.2, 75.5, 70.2, 69.5, 65.9, 62.2, 58.2, 50.7, 45.3, 45.1, 40.2 ($NMe_2$), 38.8, 37.3, 32.9, 28.2, 22.5, 21.3, 20.4, 18.4, 14.7, 13.7, 13.6, 10.4.

**6-*O*-[3-(5′-Thieno[2′,3′-b]pyridyl)-2-propenyl]-11,12-cyclocarbamate Ketolide 41f.** Compound **41f** was prepared as a white solid in 10% yield according to the general procedure for the preparation of **41s**: MS *m*/*z* (ESI) 772 $(M + H)^+$; HRMS (FAB) *m*/*z* 772.3862, calcd for $C_{40}H_{57}N_3O_{10}S$ 772.3843; $^1$H NMR ($CDCl_3$) $\delta$ 8.62 (1H, d, $J$ = 2.0 Hz), 8.19 (1H, d, $J$ = 1.6 Hz), 7.49 (1H, d, $J$ = 6.0 Hz), 7.27 (1H, d, $J$ = 6.0 Hz), 6.52 (1H, d, $J$ = 15.6 Hz), 6.08 (1H, dt, $J$ = 16.0, 6.8 Hz), 5.48 (1H, br s), 4.91 (1H, dd, $J$ = 9.2, 3.2 Hz), 4.40 (1H, d, $J$ = 4.8 Hz), 4.37 (1H, d, $J$ = 7.2 Hz), 4.02−3.51 (5H, m), 3.26−2.82 (3H, m), 2.65 (1H, m), 2.49 (1H, m), 2.27 (6H, s), 2.00−0.86 (26H, m) 0.81 (3H, t, $J$ = 7.6 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 217.2 (C-9), 205.3 (C-3), 169.5 (C-1), 157.4, 136.5, 133.7, 128.6, 127.8, 126.5, 125.5, 102.9 (C-1′), 83.5, 78.4, 77.7, 76.4, 70.2, 69.5, 65.9, 64.3, 58.2, 50.9, 46.2, 45.1, 40.2 ($NMe_2$), 39.1, 37.3, 28.2, 22.8, 21.1, 20.3, 18.1, 14.4, 14.1, 13.7, 10.8. Anal. ($C_{39}H_{58}N_2O_{10}$) C, H, N.

**6-*O*-[3-(6′-Thieno[3′,2′-b]pyridyl)-2-propenyl]-11,12-cyclocarbamate Ketolide 41g.** Compound **41g** was prepared as a white solid in 50% yield according to the general procedure for the preparation of **41s**: MS *m*/*z* (ESI) 773 $(M + H)^+$; $^1$H NMR ($CDCl_3$) $\delta$ 8.73 (1H, d, $J$ = 1.8 Hz), 8.32 (1H, d, $J$ = 1.8 Hz), 7.69 (1H, d, $J$ = 5.4 Hz), 7.51 (1H, dd, $J$ = 5.4, 0.6 Hz), 6.53 (1H, d, $J$ = 15.9 Hz), 6.10 (1H, dt, $J$ = 15.9, 6.6 Hz), 5.46 (1H, br s), 4.92 (1H, dd, $J$ = 9.0, 3.3 Hz), 4.38 (2H, m), 3.97 (1H, q, $J$ = 6.6 Hz), 3.92 (1H, br s), 3.83 (1H, m), 3.68 (2H, m), 3.57 (2H, m), 3.19 (1H, m), 2.96 (1H, m), 2.64 (1H, m), 2.49 (1H, m), 2.27 (6H, s), 1.88 (1H, m), 1.58−1.81 (4H, m), 1.50 (3H, s), 1.48−1.09 (19H, m), 0.84 (3H, t, $J$ = 7.5 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 217.45 (C-9), 205.3 (C-3), 169.7 (C-1), 157.7, 155.4, 146.9, 169.7, 157.7, 155.4, 146.9, 133.4, 130.7, 129.8, 127.9, 124.9, 102.9 (C-1′), 83.5, 78.7, 77.6, 76.6, 70.2, 69.5, 65.9, 64.3, 58.2, 50.9, 46.3, 45.1, 40.2 ($NMe_2$), 39.1, 37.3, 28.3, 22.6, 21.1, 20.3, 18.1, 14.4, 14.3, 13.7, 10.8. Anal. ($C_{39}H_{58}N_2O_{10}$) C, H, N.

**6-*O*-[3-(5′-Benzimidazolyl)-2-propenyl]-11,12-cyclocarbamate Ketolide 41h.** Compound **41h** was prepared as a white solid in 9% yield according to the general procedure for the preparation of **41s**: MS *m*/*z* (ESI) 755 $(M + H)^+$; HRMS (FAB) *m*/*z* 755.4224, calcd for $C_{40}H_{59}N_4O_{10}$ 755.4231; $^1$H NMR ($CDCl_3$) $\delta$ 7.96 (1H, s), 7.55−7.70 (2H, m), 7.44 (1H, d, $J$ = 5.4 Hz), 6.55 (1H, d, $J$ = 15.6 Hz), 5.95 (1H, dt, $J$ = 15.6, 6.0 Hz), 5.50 (1H, br s), 4.85 (1H, br s), 4.39 (1H, d, $J$ = 4.2 Hz), 4.38 (1H, d, $J$ = 6.6 Hz), 4.00 (1H, s), 3.95 (1H, q, $J$ = 6.6 Hz), 3.82 (1H, m), 3.60 (2H, m), 3.20 (2H, m), 2.94 (1H, m), 2.65 (1H, m), 2.48 (1H, m), 2.27 (6H, s), 1.85 (1H, m), 1.50−1.80 (4H, m), 1.48 (3H, s), 1.42 (3H, s), 1.40 (3H, d, $J$ = 6.9 Hz), 1.39 (3H, d, $J$ = 6.6 Hz), 1.22 (3H, d, $J$ = 6.6 Hz), 1.13 (3H, d, $J$ = 6.0 Hz), 1.11 (3H, d, $J$ = 6.6 Hz), 0.78 (3H, t, $J$ = 7.5 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 217.1 (C-9), 205.3 (C-3), 169.3 (C-1), 157.6, 141.2, 134.4, 124.2, 121.6, 103.0 (C-1′), 83.8, 78.4, 77.8, 76.5, 70.3, 69.5, 65.9, 64.3, 58.3, 50.9, 46.3, 45.0, 40.2 ($NMe_2$), 39.1, 37.3, 28.3, 22.8, 21.2, 20.3, 18.1, 14.5, 14.3, 13.7, 10.7.

**6-*O*-[3-(1′-Naphthyl)-2-propenyl]-11,12-cyclocarbamate Ketolide 41i.** Compound **41i** was prepared as white solid in 97% yield according to the general procedure for the preparation of **41s**: MS *m*/*z* (ESI) 765 $(M + H)^+$; HRMS (FAB)

*m/z* 765.4356, calcd for $C_{43}H_{61}N_2O_{10}$ 765.4326; $^1$H NMR ($CDCl_3$) $\delta$ 8.20 (1H, d, $J$ = 7.5 Hz), 7.70−7.90 (3H, m), 7.40−7.50 (3H, m), 7.22 (1H, d, $J$ = 15.6 Hz), 6.04 (1H, dt, $J$ = 15.6, 6.0 Hz), 5.30 (1H, br s), 5.05 (1H, dd, $J$ = 9.0, 3.0 Hz), 4.42 (1H, $J$ = 6.6 Hz), 4.40 (1H, d, $J$ = 4.2 Hz), 3.96 (1H, q, $J$ = 6.6 Hz), 3.93 (1H, br s), 3.90 (1H, m), 3.50−3.70 (2H, m), 3.20 (2H, m), 2.96 (1H, m), 2.65 (1H, m), 2.55 (1H, m), 2.30 (6H, s), 1.50−1.80 (5H, m), 1.50 (3H, s), 1.46 (3H, s), 1.42 (3H, d, $J$ = 6.9 Hz), 1.41 (3H, d, $J$ = 6.6 Hz), 1.20 (3H, d, $J$ = 6.6 Hz), 1.15 (3H, d, $J$ = 6.0 Hz), 1.10 (3H, d, $J$ = 6.6 Hz), 0.85 (3H, t, $J$ = 7.5 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 217.2 (C-9), 205.5 (C-3), 169.8 (C-1), 157.3, 134.0, 133.7, 130.0, 128.7, 128.5, 128.1, 126.7, 125.9, 125.7, 125.6, 125.5, 123.7, 123.5, 102.8 (C-1′), 83.4, 78.6, 77.4, 76.6, 70.2, 69.4, 66.1, 64.5, 58.2, 50.9, 46.0, 45.2, 40.2 ($NMe_2$), 39.1, 37.4, 28.6, 22.6, 21.1, 20.4, 18.1, 14.6, 14.1, 13.7, 10.6. Anal. ($C_{43}H_{60}N_2O_{10}$) C, H, N.

**6-*O*-[3-(4′-Isoquinolyl)-2-propenyl]-11,12-cyclocarbamate Ketolide 41j.** Compound **41j** was prepared as a white solid in 33% yield according to the general procedure for the preparation of **41s**: MS *m/z* (ESI) 766 $(M + H)^+$; HRMS (FAB) *m/z* 766.4271, calcd for $C_{42}H_{60}N_3O_{10}$ 766.4279; $^1$H NMR ($CDCl_3$) $\delta$ 9.18 (1H, s), 8.71 (1H, s), 8.21 (1H, d, $J$ = 8.4 Hz), 7.97 (1H, d, $J$ = 8.4 Hz), 7.74 (1H, m), 7.61 (1H, m), 7.08 (1H, d, $J$ = 15.6 Hz), 6.12 (1H, dt, $J$ = 15.6, 6.0 Hz), 5.28 (1H, br s), 5.07 (1H, dd, $J$ = 9.0, 3.0 Hz), 4.42 (1H, d, $J$ = 6.6 Hz), 4.41 (1H, d, $J$ = 4.2 Hz), 3.96 (1H, q, $J$ = 6.6 Hz), 3.88 (1H, br s), 3.90 (1H, m), 3.70 (1H, m), 3.62 (1H, m), 3.20 (2H, m), 2.96 (1H, m), 2.65 (1H, m), 2.52 (1H, m), 2.29 (6H, s), 1.89 (1H, m), 1.50−1.80 (4H, m), 1.47 (3H, s), 1.46 (3H, s), 1.41 (3H, d, $J$ = 6.9 Hz), 1.39 (3H, d, $J$ = 6.6 Hz), 1.22 (3H, d, $J$ = 6.6 Hz), 1.13 (3H, d, $J$ = 6.0 Hz), 1.10 (3H, d, $J$ = 6.6 Hz), 0.85 (3H, t, $J$ = 7.5 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 217.2 (C-9), 205.4 (C-3), 169.9 (C-1), 157.3, 152.1, 140.7, 133.6, 130.6, 130.4, 128.0, 127.7, 127.0, 126.9, 122.8, 102.8 (C-1′), 83.4, 78.7, 77.3, 76.6, 70.2, 69.4, 66.0, 64.4, 58.2, 50.9, 46.0, 45.1, 40.2 ($NMe_2$), 39.0, 37.3, 28.5, 22.5, 21.2, 20.4, 18.2, 14.5, 14.0, 13.7, 10.5. Anal. ($C_{42}H_{59}N_3O_{10}$) C, H, N.

**6-*O*-[3-(4′-Quinolyl)-2-propenyl]-11,12-cyclocarbamate Ketolide 41k.** Compound **41k** was prepared as an off-white solid in 24% yield according to the general procedure for the preparation of **41s**: MS *m/z* (ESI) 766 $(M + H)^+$; HRMS (FAB) *m/z* 766.4299, calcd for $C_{42}H_{60}N_3O_{10}$ 766.4279; $^1$H NMR ($CDCl_3$) $\delta$ 8.92 (1H, d, $J$ = 4.2 Hz), 8.18 (1H, d, $J$ = 7.8 Hz), 8.10 (1H, d, $J$ = 7.8 Hz), 7.70 (1H, m), 7.63 (1H, d, $J$ = 4.2 Hz), 7.55 (1H, m), 7.17 (1H, d, $J$ = 15.0 Hz), 6.12 (1H, dt, $J$ = 15.0, 6.0 Hz), 5.39 (1H, br s), 5.05 (1H, dd, $J$ = 9.0, 3.0 Hz), 4.41 (1H, d, $J$ = 4.4 Hz), 4.39 (1H, d, $J$ = 6.6 Hz), 3.97 (1H, q, $J$ = 6.6 Hz), 3.87 (1H, br s), 3.90 (1H, m), 3.75 (1H, m), 3.60 (1H, m), 3.20 (2H, m), 2.98 (1H, m), 2.65 (1H, m), 2.47 (1H, m), 2.27 (6H, s), 1.90 (1H, m), 1.50−1.80 (4H, m), 1.49 (3H, s), 1.46 (3H, s), 1.43 (3H, d, $J$ = 6.9 Hz), 1.41 (3H, d, $J$ = 6.6 Hz), 1.18 (3H, d, $J$ = 6.6 Hz), 1.16 (3H, d, $J$ = 6.0 Hz), 1.13 (3H, d, $J$ = 6.6 Hz), 0.86 (3H, t, $J$ = 7.5 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 217.6 (C-9), 205.4 (C-3), 169.9 (C-1), 157.4, 150.3, 142.2, 133.1, 130.1, 129.1, 127.2, 126.4, 126.2, 123.4, 117.4, 102.9 (C-1′), 83.4, 78.9, 77.4, 76.6, 70.2, 69.6, 65.9, 64.2, 58.2, 50.9, 46.2, 45.1, 40.2 ($NMe_2$), 39.0, 37.4, 28.2, 22.5, 21.2, 20.4, 18.1, 14.5, 14.1, 13.6, 10.5.

**6-*O*-[3-(5′-Quinolyl)-2-propenyl]-11,12-cyclocarbamate Ketolide 41l.** Compound **41l** was prepared as a white solid in 78% yield according to the general procedure for the preparation of **41s**: MS *m/z* (ESI) 766 $(M + H)^+$; HRMS (FAB) *m/z* 766.4281, calcd for $C_{42}H_{60}N_3O_{10}$ 766.4279; $^1$H NMR ($CDCl_3$) $\delta$ 8.92 (1H, dd, $J$ = 4.5, 1.8 Hz), 8.57 (1H, d, $J$ = 8.4 Hz), 8.04 (1H, d, $J$ = 8.4 Hz), 7.82 (1H, d, $J$ = 7.2 Hz), 7.72 (1H, m), 7.43 (1H, m), 7.15 (1H, d, $J$ = 15.6 Hz), 6.08 (1H, dt, $J$ = 15.6, 6.0 Hz), 5.34 (1H, br s), 5.03 (1H, dd, $J$ = 9.0, 3.0 Hz), 4.42 (1H, d, $J$ = 3.6 Hz), 4.41 (1H, d, $J$ = 7.2 Hz), 3.96 (1H, q, $J$ = 6.6 Hz), 3.91 (1H, br s), 3.90 (1H, m), 3.70 (1H, m), 3.62 (1H, m), 3.20 (2H, m), 2.98 (1H, m), 2.65 (1H, m), 2.52 (1H, m), 2.28 (6H, s), 1.89 (1H, m), 1.50−1.80 (4H, m), 1.49 (3H, s), 1.46 (3H, s), 1.42 (3H, d, $J$ = 6.9 Hz), 1.41 (3H, d, $J$ = 6.6 Hz), 1.20 (3H, d, $J$ = 6.6 Hz), 1.16 (3H, d, $J$ = 6.0 Hz), 1.12 (3H, d, $J$ = 6.6 Hz), 0.85 (3H, t, $J$ = 7.5 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 217.4 (C-9), 205.5 (C-3), 169.9 (C-1), 157.3, 150.1, 148.5, 134.4, 132.0, 130.0, 129.4, 129.3, 128.4, 124.0, 120.9, 102.9 (C-1′), 83.4, 78.7, 77.4, 76.6, 70.2, 69.5, 66.0, 64.4, 58.2, 50.9, 46.1, 45.1, 40.2 ($NMe_2$), 39.0, 37.4, 28.4, 22.5, 21.2, 20.4, 18.2, 14.5, 14.1, 13.7, 10.5. Anal. ($C_{42}H_{59}N_3O_{10}$) C, H, N.

**6-*O*-[3-(5′-Isoquinolyl)-2-propenyl]-11,12-cyclocarbamate Ketolide 41m.** Compound **41m** was prepared as a white solid in 31% yield according to the general procedure for the preparation of **41s**: MS *m/z* (ESI) 766 $(M + H)^+$; HRMS (FAB) *m/z* 766.4301, calcd for $C_{42}H_{60}N_3O_{10}$ 766.4279; $^1$H NMR ($CDCl_3$) $\delta$ 9.23 (1H, s), 8.55 (1H, d, $J$ = 6.0 Hz), 8.21 (1H, d, $J$ = 8.4 Hz), 7.97 (2H, m), 7.90 (1H, d, $J$ = 7.8 Hz), 7.63 (1H, dd, $J$ = 6.3, 6.0 Hz), 7.14 (1H, d, $J$ = 15.6 Hz), 6.08 (1H, dt, $J$ = 15.6, 6.0 Hz), 5.28 (1H, br s), 5.00 (1H, dd, $J$ = 9.0, 3.0 Hz), 4.42 (1H, d, $J$ = 2.4 Hz), 4.41 (1H, d, $J$ = 6.6 Hz), 3.97 (1H, q, $J$ = 6.6 Hz), 3.90 (1H, br s), 3.90 (1H, m), 3.70 (1H, m), 3.61 (1H, m), 3.20 (2H, m), 2.97 (1H, m), 2.65 (1H, m), 2.48 (1H, m), 2.29 (6H, s), 1.89 (1H, m), 1.50−1.80 (4H, m), 1.48 (3H, s), 1.46 (3H, s), 1.43 (3H, d, $J$ = 6.9 Hz), 1.41 (3H, d, $J$ = 6.6 Hz), 1.20 (3H, d, $J$ = 6.0 Hz), 1.14 (3H, d, $J$ = 6.6 Hz), 1.10 (3H, d, $J$ = 6.6 Hz), 0.85 (3H, t, $J$ = 7.5 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 217.4 (C-9), 205.4 (C-3), 169.8 (C-1), 157.3, 153.1, 143.1, 133.7, 133.2, 130.0, 129.8, 128.1, 127.5, 127.3, 127.2, 116.4, 102.8 (C-1′), 83.4, 78.7, 77.4, 76.5, 70.2, 69.6, 65.9, 64.4, 58.2, 50.9, 46.1, 45.1, 40.2 ($NMe_2$), 39.0, 37.3, 28.3, 22.5, 21.2, 20.4, 18.1, 14.5, 14.1, 13.6, 10.6. Anal. ($C_{42}H_{59}N_3O_{10}$) C, H, N.

**6-*O*-[3-(8′-Quinolyl)-2-propenyl]-11,12-cyclocarbamate Ketolide 41n.** Compound **41n** was prepared as a white solid in 16% yield according to the general procedure for the preparation of **41s**: MS *m/z* (ESI) 766 $(M + H)^+$; HRMS (FAB) *m/z* 766.4282, calcd for $C_{42}H_{60}N_3O_{10}$ 766.4279.

**6-*O*-[3-(2′-Naphthyl)-2-propenyl]-11,12-cyclocarbamate Ketolide 41o.** Compound **41o** was prepared as a white solid in 61% yield according to the general procedure for the preparation of **41s**: MS *m/z* (ESI) 765 $(M + H)^+$; $^1$H NMR ($CDCl_3$) $\delta$ 7.60−7.85 (4H, m), 7.69 (1H, m), 7.38−7.45 (2H, m), 6.57 (1H, d, $J$ = 15.3 Hz), 6.04 (1H, dt, $J$ = 15.3, 6.0 Hz), 5.40 (1H, br s), 4.95 (1H, dd, $J$ = 9.0, 3.3 Hz), 4.3−4.45 (2H, m), 3.96 (1H, q, $J$ = 6.6 Hz), 3.95 (1H, br s), 3.84 (1H, m), 3.50−3.70 (2H, m), 3.20 (2H, m), 2.96 (1H, m), 2.64 (1H, m), 2.56 (1H, m), 2.30 (6H, s), 1.50−1.80 (5H, m), 1.49 (3H, s), 1.43 (3H, d, $J$ = 6.0 Hz), 1.42 (3H, d, $J$ = 6.6 Hz), 1.41 (3H, s), 1.19 (3H, d, $J$ = 6.6 Hz), 1.13 (3H, d, $J$ = 6.0 Hz), 1.11 (3H, d, $J$ = 6.6 Hz), 0.83 (3H, t, $J$ = 7.5 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 217.2 (C-9), 205.4 (C-3), 169.6 (C-1), 157.5, 134.4, 134.1, 133.6, 133.0, 128.3, 128.1, 127.6, 126.6, 126.1, 126.0, 125.7, 123.6, 102.8 (C-1′), 83.5, 78.5, 77.7, 76.5, 70.2, 69.4, 66.1, 64.4, 58.2, 50.9, 46.2, 45.1, 40.2 ($NMe_2$), 39.1, 37.4, 28.6, 22.7, 21.1, 20.3, 18.1, 14.5, 14.1, 13.7, 10.7.

**6-*O*-[3-(2′-Quinolyl)-2-propenyl]-11,12-cyclocarbamate Ketolide 41p.** Compound **41p** was prepared as an off-white solid in 14% yield according to the general procedure for the preparation of **41s**: MS *m/z* (ESI) 766 $(M + H)^+$; HRMS (FAB) *m/z* 766.4286, calcd for $C_{42}H_{60}N_3O_{10}$ 766.4279.

**6-*O*-[3-(4′-Isoquinolyl)-2-propenyl]-11,12-cyclocarbamate Ketolide 41q.** Compound **41q** was prepared as a white solid in 30% yield according to the general procedure for the preparation of **41s**: MS *m/z* (ESI) 766 $(M + H)^+$; $^1$H NMR ($CDCl_3$) $\delta$ 8.79 (1H, dd, $J$ = 4.2, 1.8 Hz), 8.03 (1H, dd, $J$ = 7.8, 1.8 Hz), 7.93 (1H, s), 7.72 (2H, s), 7.25 (1H, dd, $J$ = 7.8, 4.2 Hz), 6.56 (1H, d, $J$ = 15.6 Hz), 6.08 (1H, dt, $J$ = 15.6, 6.0 Hz), 5.35 (1H, br s), 4.92 (1H, dd, $J$ = 9.0, 3.0 Hz), 4.38 (1H, d, $J$ = 6.6 Hz), 4.34 (1H, d, $J$ = 4.2 Hz), 3.88 (1H, q, $J$ = 6.6 Hz), 3.84 (1H, br s), 3.79 (1H, m), 3.61 (1H, m), 3.57 (1H, m), 3.32 (1H, m), 3.16 (1H, m), 2.92 (1H, m), 2.88 (1H, m), 2.52 (6H, s), 1.50−1.90 (5H, m), 1.42 (3H, s), 1.30−1.35 (6H, m), 1.10−1.23 (6H, m), 1.08 (3H, d, $J$ = 6.6 Hz), 1.04 (3H, d, $J$ = 6.0 Hz), 0.78 (3H, t, $J$ = 7.5 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 217.2 (C-9), 205.4 (C-3), 169.6 (C-1), 157.5, 150.5, 148.6, 137.8, 135.7, 132.9, 128.1, 127.9, 127.8, 124.0, 120.7, 102.0 (C-1′), 83.4, 78.5, 77.5, 76.4, 69.7, 68.5, 66.4, 64.2, 58.2, 50.8, 46.0, 45.1, 40.3 ($NMe_2$), 38.9, 37.3, 29.6, 22.6, 20.9, 20.2, 18.0, 14.5, 14.0, 13.6, 10.6.

**6-*O*-[3-(6′-Quinolyl)-2-propenyl]-11,12-cyclocarbamate Ketolide 41r.** Compound **41r** was prepared as a white

solid in 77% yield according to the general procedure for the preparation of **41s**: MS *m/z* (ESI) 766 $(M + H)^+$; HRMS (FAB) *m/z* 766.4288, calcd for $C_{42}H_{60}N_3O_{10}$ 766.4279; $^1$H NMR ($CDCl_3$) $\delta$ 8.84 (1H, dd, $J$ = 4.2, 1.2 Hz), 8.15 (1H, d, $J$ = 7.5 Hz), 8.07 (1H, d, $J$ = 7.5 Hz), 7.93 (1H, dd, $J$ = 8.4, 1.2 Hz), 7.79 (1H, s), 7.36 (1H, dd, $J$ = 8.4, 4.2 Hz), 6.58 (1H, d, $J$ = 15.6 Hz), 6.12 (1H, dt, $J$ = 15.6, 6.0 Hz), 5.42 (1H, br s), 4.92 (1H, dd, $J$ = 9.0, 3.0 Hz), 4.41 (1H, d, $J$ = 4.2 Hz), 4.39 (1H, d, $J$ = 7.2 Hz), 3.96 (1H, q, $J$ = 6.6 Hz), 3.94 (1H, br s), 3.85 (1H, m), 3.70 (1H, m), 3.57 (1H, m), 3.20 (2H, m), 2.96 (1H, m), 2.65 (1H, m), 2.48 (1H, m), 2.26 (6H, s), 1.50−1.90 (5H, m), 1.48 (3H, s), 1.40−1.45 (9H, m), 1.20 (3H, d, $J$ = 6.0 Hz), 1.15 (3H, d, $J$ = 6.6 Hz), 1.12 (3H, d, $J$ = 6.0 Hz), 0.82 (3H, t, $J$ = 7.5 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 217.4 (C-9), 205.4 (C-3), 169.6 (C-1), 157.5, 150.0, 148.1, 136.1, 134.9, 132.7, 129.8, 128.5, 127.5, 127.4, 126.0, 121.3, 102.9 (C-1′), 83.5, 78.6, 77.7, 76.5, 70.2, 69.5, 65.9, 64.3, 58.2, 50.9, 46.4, 45.1, 40.2 ($NMe_2$), 39.1, 37.3, 28.3, 22.7, 21.1, 20.2, 18.1, 14.4, 14.3, 13.7, 10.7. Anal. ($C_{42}H_{59}N_3O_{10}$) C, H, N.

**6-*O*-{3-[3′-(1,8-Naphthyridyl)]-2-propenyl}-11,12-cyclocarbamate Ketolide 41t.** Compound **41t** was prepared as a white solid in 11% yield according to the general procedure for the preparation of **41s**: MS *m/z* (ESI) 767 $(M + H)^+$; HRMS (ESI) *m/z* 767.4227, calcd for $C_{41}H_{59}N_4O_{10}$ 767.4231; $^1$H NMR ($CDCl_3$) $\delta$ 9.22 (1H, d, $J$ = 2.4 Hz), 8.05 (1H, dd, $J$ = 3.6, 2.4 Hz), 8.20−8.25 (2H, m), 7.46 (1H, dd, $J$ = 8.4, 3.6 Hz), 7.79 (1H, s), 7.36 (1H, dd, $J$ = 8.4, 4.2 Hz), 6.58 (1H, d, $J$ = 15.6 Hz), 6.23 (1H, dt, $J$ = 15.6, 6.0 Hz), 5.52 (1H, br s), 4.94 (1H, dd, $J$ = 9.0, 3.0 Hz), 4.40 (1H, d, $J$ = 4.5 Hz), 4.38 (1H, d, $J$ = 7.8 Hz), 3.96 (1H, q, $J$ = 6.6 Hz), 3.90 (1H, br s), 3.85 (1H, m), 3.73 (1H, m), 3.57 (1H, m), 3.20 (2H, m), 2.97 (1H, m), 2.65 (1H, m), 2.52 (1H, m), 2.29 (6H, s), 1.20−1.90 (6H, m), 1.50 (3H, s), 1.43 (3H, s), 1.42 (3H, d, $J$ = 6.9 Hz), 1.40 (3H, d, $J$ = 6.3 Hz), 1.20 (3H, d, $J$ = 6.0 Hz), 1.15 (3H, d, $J$ = 6.3 Hz), 1.14 (3H, d, $J$ = 6.0 Hz), 0.81 (3H, t, $J$ = 7.5 Hz).

**6-*O*-{3-[3′-(1,6-Naphthyridyl)]-2-propenyl}-11,12-cyclocarbamate Ketolide 41u.** Compound **41u** was prepared as a white solid in 73% yield according to the general procedure for the preparation of **41s**: MS *m/z* (ESI) 767 $(M + H)^+$; $^1$H NMR ($CDCl_3$) $\delta$ 9.28 (1H, s), 9.22 (1H, d, $J$ = 2.4 Hz), 8.69 (1H, d, $J$ = 6.0 Hz), 8.30 (1H, d, $J$ = 2.4 Hz), 7.89 (1H, d, $J$ = 6.0 Hz), 6.58 (1H, d, $J$ = 15.6 Hz), 6.25 (1H, dt, $J$ = 15.6, 6.0 Hz), 5.53 (1H, br s), 4.91 (1H, dd, $J$ = 9.2, 3.2 Hz), 4.41 (1H, d, $J$ = 4.5 Hz), 4.36 (1H, d, $J$ = 7.8 Hz), 3.97 (1H, q, $J$ = 6.6 Hz), 3.88 (1H, br s), 3.85 (1H, m), 3.74 (1H, m), 3.57 (1H, m), 3.49 (1H, m), 3.18 (2H, m), 2.98 (1H, m), 2.65 (1H, m), 2.46 (1H, m), 2.26 (6H, s), 1.20−1.90 (5H, m), 1.50 (3H, s), 1.44 (3H, s), 1.43 (3H, d, $J$ = 6.9 Hz), 1,41 (3H, d, $J$ = 6.3 Hz), 1.18 (3H, d, $J$ = 6.0 Hz), 1.15 (3H, d, $J$ = 6.3 Hz), 1.13 (3H, d, $J$ = 6.0 Hz), 0.81 (3H, t, $J$ = 7.5 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 217.4 (C-9), 205.2 (C-3), 169.6 (C-1), 157.6, 154.0, 153.0, 149.5, 146.4, 131.7, 131.2, 130.1, 128.9, 123.5, 121.8, 102.9 (C-1′), 83.4, 78.8, 77.4, 76.4, 70.2, 69.5, 65.8, 64.1, 58.0, 50.8, 46.4, 45.0, 40.1 ($NMe_2$), 38.9, 37.3, 28.2, 22.5, 21.1, 20.1, 18.0, 14.3, 14.2, 13.5, 10.6. Anal. ($C_{41}H_{58}N_4O_{10}$) C, H, N.

**6-*O*-{3-[3′-(1,5-Naphthyridyl)]-2-propenyl}-11,12-cyclocarbamate Ketolide 41v.** Compound **41v** was prepared as a white solid in 61% yield according to the general procedure for the preparation of **41s**: MS *m/z* (ESI) 767 $(M + H)^+$; $^1$H NMR ($CDCl_3$) $\delta$ 9.17 (1H, d, $J$ = 2.4 Hz), 8.94 (1H, d, $J$ = 4.0 Hz), 8.37 (1H, d, $J$ = 2.4 Hz), 8.36 (1H, d, $J$ = 8.0 Hz), 7.57 (1H, dd, $J$ = 8.0, 4.0 Hz), 6.62 (1H, d, $J$ = 15.6 Hz), 6.32 (1H, dt, $J$ = 15.6, 6.0 Hz), 5.48 (1H, br s), 5.00 (1H, dd, $J$ = 9.2, 3.2 Hz), 4.41 (1H, d, $J$ = 4.5 Hz), 4.37 (1H, d, $J$ = 7.8 Hz), 3.97 (1H, q, $J$ = 6.6 Hz), 3.87 (1H, br s), 3.86 (1H, m), 3.74 (1H, m), 3.57 (1H, m), 3.47 (1H, m), 3.19 (2H, m), 2.98 (1H, m), 2.67 (1H, m), 2.47 (1H, m), 2.28 (6H, s), 1.20−1.90 (5H, m), 1.50 (3H, s), 1.45 (3H, s), 1.42 (3H, d, $J$ = 6.9 Hz), 1,41 (3H, d, $J$ = 6.3 Hz), 1.19 (3H, d, $J$ = 6.0 Hz), 1.14 (3H, d, $J$ = 6.3 Hz), 1.12 (3H, d, $J$ = 6.3 Hz), 0.84 (3H, t, $J$ = 7.5 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 217.2 (C-9), 205.2 (C-3), 169.7 (C-1), 157.6, 151.3, 150.1, 143.9, 143.0, 136.9, 133.6, 133.1, 130.4, 129.1, 123.7, 102.9 (C-1′), 83.4, 78.8, 77.3, 76.4, 70.1, 69.5, 65.8, 64.1, 58.1, 50.8, 46.2, 45.0, 40.1 ($NMe_2$), 38.9, 37.3, 28.2, 22.5, 21.1, 20.1, 18.0, 14.3, 14.1, 13.6, 13.5, 10.5.

**6-*O*-[3-(6′-Cinnolyl)-2-propenyl]-11,12-cyclocarbamate Ketolide 41w.** Compound **41w** was prepared as a white solid in 27% yield according to the general procedure for the preparation of **41s**: MS *m/z* (ESI) 767 $(M + H)^+$; $^1$H NMR ($CDCl_3$) $\delta$ 9.25 (1H, d, $J$ = 5.7 Hz), 9.45 (1H, d, $J$ = 8.7 Hz), 8.07 (1H, dd, $J$ = 9.3, 2.1 Hz), 7.84 (1H, dd, $J$ = 5.7, 0.6 Hz), 7.76 (1H, d, $J$ = 1.2 Hz), 6.61 (1H, d, $J$ = 15.9 Hz), 6.23 (1H, dt, $J$ = 16.2, 6.6 Hz), 5.46 (1H, br s), 4.86 (1H, dd, $J$ = 9.0, 3.3 Hz), 4.40 (1H, d, $J$ = 5.1 Hz), 4.36 (1H, d, $J$ = 7.5 Hz), 3.97 (1H, q, $J$ = 6.6 Hz), 3.87 (1H, br s), 3.85 (1H, m), 3.72 (1H, m), 3.57 (1H, m), 3.49 (1H, m), 3.18 (2H, m), 2.96 (1H, m), 2.65 (1H, m), 2.50 (1H, m), 2.28 (6H, s), 1.20−1.90 (5H, m), 1.49 (3H, s), 1.44 (3H, s), 1.43 (3H, s), 1,40 (3H, s), 1.20 (3H, d, $J$ = 7.2 Hz), 1.15 (3H, d, $J$ = 7.2 Hz), 1.13 (3H, d, $J$ = 6.6 Hz), 0.79 (3H, t, $J$ = 7.5 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 217.7 (C-9), 205.4 (C-3), 169.7 (C-1), 157.6, 150.6, 145.4, 139.4, 131.8, 130.7, 130.1, 128.9, 124.3, 122.6, 103.3 (C-1′), 83.5, 78.9, 77.6, 76.5, 70.2, 69.5, 65.9, 64.1, 58.0, 50.9, 46.5, 45.0, 40.2 ($NMe_2$), 39.0, 37.4, 37.3, 30.9, 28.3, 22.6, 21.3, 21.2, 20.2, 18.1, 14.5, 14.4, 13.7, 10.8. Anal. ($C_{41}H_{58}N_4O_{10}$) C, H, N.

**6-*O*-[3-(6′-Quinazolyl)-2-propenyl]-11,12-cyclocarbamate Ketolide 41x.** Compound **41x** was prepared as an off-white solid in 39% yield according to the general procedure for the preparation of **41s**: MS *m/z* (APCI) 767 $(M + H)^+$; HRMS (FAB) *m/z* 767.4236, calcd for $C_{41}H_{59}N_4O_{10}$ 767.4231; $^1$H NMR ($CDCl_3$) $\delta$ 9.38 (1H, s), 9.27 (1H, s), 8.15 (1H, d, $J$ = 6.9 Hz), 8.02 (1H, d, $J$ = 6.9 Hz), 7.88 (1H, s), 6.61 (1H, d, $J$ = 15.6 Hz), 6.16 (1H, dt, $J$ = 15.6, 6.0 Hz), 5.45 (1H, br s), 4.87 (1H, dd, $J$ = 9.2, 3.2 Hz), 4.41 (1H, d, $J$ = 4.5 Hz), 4.37 (1H, d, $J$ = 7.8 Hz), 3.97 (1H, q, $J$ = 6.6 Hz), 3.89 (1H, br s), 3.83 (1H, m), 3.73 (1H, m), 3.56 (1H, m), 3.19 (2H, m), 2.96 (1H, m), 2.66 (1H, m), 2.47 (1H, m), 2.26 (6H, s), 1.20−1.90 (6H, m), 1.49 (3H, s), 1.45 (3H, s), 1.42 (3H, d, $J$ = 6.9 Hz), 1,41 (3H, d, $J$ = 6.3 Hz), 1.20 (3H, d, $J$ = 6.0 Hz), 1.15 (3H, d, $J$ = 6.3 Hz), 1.12 (3H, d, $J$ = 6.0 Hz), 0.80 (3H, t, $J$ = 7.5 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 217.5 (C-9), 205.2 (C-3), 169.6 (C-1), 160.1, 157.5, 154.9, 149.7, 136.4, 132.2, 131.7, 128.9, 128.5, 125.3, 124.8, 102.9 (C-1′), 83.4, 78.7, 77.5, 76.4, 70.2, 69.5, 65.8, 64.0, 58.0, 50.8, 46.4, 45.0, 40.1 ($NMe_2$), 38.9, 37.3, 28.2, 22.6, 21.1, 20.2, 18.0, 14.3, 14.2, 13.6, 13.5, 10.7. Anal. ($C_{41}H_{58}N_4O_{10}\cdot 0.5H_2O$) C, H, N.

**6-*O*-[3-(6′-Quinoxalyl)-2-propenyl]-11,12-cyclocarbamate Ketolide 41y.** Compound **41y** was prepared as an off-white solid in 69% yield according to the general procedure for the preparation of **41s**: MS *m/z* (ESI) 767 $(M + H)^+$; HRMS (ESI) *m/z* 767.4221, calcd for $C_{41}H_{59}N_4O_{10}$ 767.4231; $^1$H NMR ($CDCl_3$) $\delta$ 8.82 (1H, d, $J$ = 2.4 Hz), 8.77 (1H, d, $J$ = 2.4 Hz), 8.00−8.10 (3H, m), 6.65 (1H, d, $J$ = 16.2 Hz), 6.16 (1H, dt, $J$ = 16.2, 6.0 Hz), 5.39 (1H, br s), 4.97 (1H, dd, $J$ = 9.2, 3.2 Hz), 4.42 (1H, d, $J$ = 4.5 Hz), 4.39 (1H, d, $J$ = 7.8 Hz), 3.97 (1H, q, $J$ = 6.6 Hz), 3.88 (1H, br s), 3.85 (1H, m), 3.72 (1H, m), 3.59 (1H, m), 3.45 (1H, m), 3.20 (2H, m), 2.97 (1H, m), 2.66 (1H, m), 2.47 (1H, m), 2.28 (6H, s), 1.20−1.90 (6H, m), 1.49 (3H, s), 1.45 (3H, s), 1.43 (3H, d, $J$ = 6.6 Hz), 1,43 (3H, d, $J$ = 6.6 Hz), 1.20 (3H, d, $J$ = 6.0 Hz), 1.15 (3H, d, $J$ = 6.6 Hz), 1.12 (3H, d, $J$ = 6.6 Hz), 0.85 (3H, t, $J$ = 7.5 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 217.4 (C-9), 205.3 (C-3), 169.7 (C-1), 157.6 (carbamate), 145.2, 144.4, 143.5, 143.0, 138.7, 132.1, 129.7, 129.3, 127.8, 127.5, 102.9 (C-1′), 83.4, 78.7, 77.5, 76.5, 70.2, 69.6, 65.9, 64.2, 58.0, 50.9, 46.4, 45.1, 40.2 ($NMe_2$), 39.0, 37.4, 28.2, 22.6, 21.2, 20.3, 18.1, 14.4, 14.3, 13.7, 13.6, 10.7. Anal. ($C_{41}H_{58}N_4O_{10}$) C, H, N.

**6-*O*-{3-[7′-(1,4,5-Triazanaphthyl)]-2-propenyl}-11,12-cyclocarbamate Ketolide 41z.** Compound **41z** was prepared as an off-white solid in 12% yield according to the general procedure for the preparation of **41s**: MS *m/z* (ESI) 768 $(M + H)^+$; $^1$H NMR ($CDCl_3$) $\delta$ 9.34 (1H, d, $J$ = 2.5 Hz), 8.98 (1H, d, $J$ = 2.4 Hz), 8.92 (1H, d, $J$ = 2.4 Hz), 8.46 (1H, d, $J$ = 2.5 Hz), 6.65 (1H, d, $J$ = 16.5 Hz), 6.38 (1H, dt, $J$ = 16.5, 6.0 Hz), 5.46 (1H, br s), 4.98 (1H, dd, $J$ = 9.2, 3.2 Hz), 4.41 (1H, d, $J$ = 4.5 Hz), 4.38 (1H, d, $J$ = 7.8 Hz), 3.97 (1H, q, $J$ = 6.6 Hz), 3.88 (1H, m), 3.85 (1H, br s), 3.75 (1H, m), 3.58 (2H, m), 3.18 (2H, m), 2.97 (1H, m), 2.66 (1H, m), 2.48 (1H, m), 2.27 (6H, s), 1.20−

1.90 (6H, m), 1.50 (3H, s), 1.44 (3H, s), 1.42 (3H, d, $J$ = 6.6 Hz), 1,41 (3H, d, $J$ = 6.6 Hz), 1.20 (3H, d, $J$ = 6.0 Hz), 1.16 (3H, d, $J$ = 6.6 Hz), 1.12 (3H, d, $J$ = 6.6 Hz), 0.84 (3H, t, $J$ = 7.5 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 217.5 (C-9), 205.3 (C-3), 169.8 (C-1), 157.7 (carbamate), 153.5, 150.7, 146.9, 146.3, 138.5, 134.4, 134.3, 132.0, 128.3, 102.9 (C-1′), 83.5, 79.0, 77.4, 76.5, 70.2, 69.5, 65.9, 64.1, 58.2, 50.9, 46.4, 45.1, 40.2 ($NMe_2$), 39.0, 37.4, 28.3, 21.2, 20.2, 18.1, 14.4, 14.2, 14.1, 13.7, 13.6, 10.6.

**6-*O*-[3-(3′-Quinolyl)propyl]-11,12-cyclocarbamate Ketolide 42s.** To a solution of **41s** (230 mg, 0.300 mmol) in MeOH (10 mL) under nitrogen atmosphere was added 10% Pd−C catalyst (50 mg). The mixture was stirred under hydrogen atmosphere (balloon pressure) for 18 h. The catalyst was removed by filtration and the filtrate was concentrated. Column chromatography (silica gel, 95:5:0.5 $CH_2Cl_2$/MeOH/ammonia) of the crude product provided **42s** (218 mg, 95%) as a white solid: MS $m/z$ (APCI) 768 $(M + H)^+$; HRMS (ESI) $m/z$ 768.4437, calcd for $C_{42}H_{62}N_3O_{10}$ 768.4435; $^1$H NMR ($CDCl_3$) $\delta$ 8.78 (1H, d, $J$ = 2.4 Hz), 8.06 (1H, d, $J$ = 8.5 Hz), 7.99 (1H, d, $J$ = 2.4 Hz), 7.82 (1H, d, $J$ = 8.5 Hz), 7.63 (1H, m), 7.51 (1H, m), 5.75 (1H, br s), 5.20 (1H, dd, $J$ = 9.5, 2.5 Hz), 4.36 (2H, m), 3.94 (2H, m), 3.59 (1H, m), 3.18 (4H, m), 3.05 (1H, m), 2.96 (1H, m), 2.72 (2H, m), 2.64 (1H, m), 2.52 (1H, m), 2.29 (6H, s), 1.97 (1H, m), 1.85 (1H, m), 1.50−1.70 (4H, m), 1.56 (3H, s), 1.42 (3H, d, $J$ = 8.0 Hz), 1.32 (3H, d, $J$ = 7.0 Hz), 1.26 (3H, s), 1.20 (3H, d, $J$ = 6.5 Hz), 1.18 (3H, d, $J$ = 7.0 Hz), 1.13 (3H, d, $J$ = 7.0 Hz), 0.85 (3H, t, $J$ = 7.5 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 217.6 (C-9), 205.5 (C-3), 170.1 (C-1), 158.2 (carbamate), 152.1, 146.8, 134.2, 134.0, 129.1, 128.4, 128.3, 127.5, 126.4, 102.6 (C-1′), 83.7, 78.2, 77.0, 75.5, 70.2, 69.4, 66.0, 61.9, 58.4, 50.6, 45.2, 40.2 ($NMe_2$), 38.9, 37.3, 29.7, 29.0, 28.5, 22.6, 21.2, 20.3, 18.4, 14.7, 13.7, 13.6, 13.0, 10.6. Anal. ($C_{42}H_{61}N_3O_{10}$) C, H, N.

**6-*O*-[2-(3′-Quinolyl)cyclopropylmethyl]-11,12-cyclocarbamate Ketolide 43s.** To an ice-cold solution of $CH_2N_2$ in ether (0.64 M, 3.12 mL, 2.00 mmol) was introduced a solution of **41s** (153 mg, 0.200 mmol) in $CH_2Cl_2$ (5 mL) under nitrogen atmosphere. $Pd(OAc)_2$ (2.0 mg, 0.01 mmol) was added and the reaction mixture was stirred for 30 min. Additional $CH_2N_2$ ether solution (0.64 M, 3.12 mL, 2.00 mmol) was added and the mixture was allowed to warm to room temperature over 50 min. The solvent was evaporated and the crude product was purified by column chromatography (silica gel, 95:5:0.5 $CH_2Cl_2$/MeOH/ammonia) to give **43s** (100 mg, 64%) as a mixture of diastereomers (60:40 ratio): MS $m/z$ (ESI) 780 $(M + H)^+$; HRMS (ESI) $m/z$ 780.4446, calcd for $C_{43}H_{62}N_3O_{10}$ 780.4435; $^1$H NMR ($CDCl_3$) $\delta$ 8.99 (isomer 1, 1H, d, $J$ = 2.4 Hz), 8.95 (isomer 2, 1H, d, $J$ = 2.4 Hz), 8.05 (isomer 1, 1H, d, $J$ = 7.8 Hz), 8.03 (isomer 2, 1H, d, $J$ = 7.8 Hz), 7.76 (isomers 1 and 2 together, 1H, m), 7.70 (isomer 1, 1H, d, $J$ = 2.4 Hz), 7.74 (isomer 2, 1H, d, $J$ = 2.4 Hz), 7.62 (isomers 1 and 2, 1H, m), 7.50 (isomers 1 and 2, 1H, m), 5.52 (isomer 1, 1H, br s), 5.72 (isomer 2, 1H, br s), 5.16 (isomers 1 and 2, 1H, m), 4.37 (isomers 1 and 2, 2H, m), 3.94 (isomers 1 and 2, 3H, m), 3.60 (isomers 1 and 2, 1H, m), 3.45 (isomers 1 and 2, 1H, m), 3.18 (isomers 1 and 2, 2H, m), 3.05 (isomers 1 and 2, 1H, m), 2.63 (isomers 1 and 2, 2H, m), 2.46 (isomers 1 and 2, 1H, m), 2.26 (isomers 1 and 2, 6H, s), 1.20−2.00 (9H, m), 1.52 (isomer 1, 3H, s), 1.56 (isomer 2, 1H, s), 1.10−1.45 (isomers 1 and 2, 18 H, m), 0.86 (isomer 1, 3H, t, $J$ = 7.5 Hz), 0.88 (isomer 2, 3H, t, $J$ = 7.5 Hz). Anal. ($C_{43}H_{61}N_3O_{10}$) C, H, N.

**Acknowledgment.** We acknowledge the support of the Abbott Process Research Department for providing research intermediates, the Structural Chemistry Department for structural characterization, and the Clinical Microbiology Department for in vitro and in vivo testing.

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JM0102349