# Synthesis and Antibacterial Activity of Novel $C_{12}$ Vinyl Ketolides

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A novel series of $C_{12}$ vinyl erythromycin derivatives have been discovered which exhibit in vitro and in vivo potency against key respiratory pathogens. The $C_{12}$ modification involves replacing the natural $C_{12}$ methyl group in the erythromycin core with a vinyl group via chemical synthesis. From the $C_{12}$ vinyl macrolide core, a series of $C_{12}$ vinyl ketolides was prepared. Several compounds were found to be potent against macrolide-sensitive and -resistant bacteria. The $C_{12}$ vinyl ketolides **6j** and **6k** showed a similar antimicrobial spectrum and comparable activity to the commercial ketolide telithromycin. However, the pharmacokinetic profiles of $C_{12}$ vinyl ketolides **6j** and **6k** in rats differ from that of telithromycin by having higher lung-to-plasma ratios, larger volumes of distribution, and longer half-lives. These pharmacokinetic differences have a pharmacodynamic effect as both **6j** and **6k** exhibited better in vivo efficacy than telithromycin in rat lung infection models against *Streptococcus pneumoniae* and *Haemophilus influenzae*.

## Introduction

The macrolide antibiotic erythromycin A (Figure 1) has been used successfully clinically for over 40 years to treat upper and lower respiratory tract infections. In recent decades, to address shortcomings of erythromycin A,[1] second generation macrolides (clarithromycin,[2] azithromycin,[3] roxithromycin[4]) have been developed and used clinically. Resistance to the second generation macrolides has emerged, with resistance most commonly being conferred by ribosomal mutation (*erm*) or by efflux (*mef*) mechanisms.[5] To overcome this resistance a third generation of macrolide antibiotics known as ketolides [telithromycin[6] and cethromycin (ABT-773)[7]] has recently been developed. In these molecules the $C_3$ cladinose sugar of erythromycin A is removed and replaced with a $C_3$ ketone group. Additionally, a heterocycle is tethered to the macrolide core, introducing an additional binding contact at the target ribosome.

In our laboratories we have been conducting research toward producing novel macrolide cores that exhibit potent in vitro and in vivo antibacterial properties against macrolide resistant pathogens by chemical manipulation of erythromycin A. The novel cores we have targeted differ from erythromycin in the substitution of the natural $C_{12}$ methyl group ($C_{21}$) by nonpolar groups other than methyl. Nonpolar substitutions were targeted to maintain the known overall hydrophobic nature of the bottom face of the macrocycle.[8,9] Since the erythromycin core serves as the synthetic starting point for the second and third generation macrolide antibiotics currently in clinical use (clarithromycin, azithromycin, roxithromycin, and the new ketolide telithromycin) as well as many currently in preclinical research, such novel $C_{12}$ modified macrolide cores could provide access to many of the semisynthetic derivatives that erythromycin has been converted into, as well as new derivatives all together. We report herein on the preparation of a novel $C_{12}$ vinyl macrolide core, the conversion of this core into the ketolide class of macrolides, and the in vitro and in vivo antibacterial properties of the resulting $C_{12}$ vinyl ketolides.[10]

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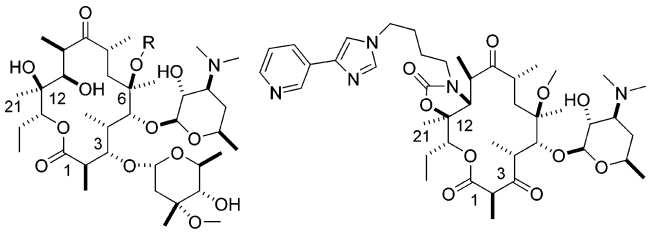


**Figure 1.** Clinically utilized macrolides.

## Chemistry

Synthetic modifications of erythromycin have been pursued by numerous investigators attempting to prepare chemical derivatives with improved profiles and biological activity. The addition of a single methyl group onto the $C_6$ hydroxyl of erythromycin A greatly improved the acid stability and pharmacokinetic properties, resulting in the development of clarithromycin, which has found widespread use clinically. Modifications involving the $C_{11}$ and $C_{12}$ hydroxyl groups have been extensively explored,[11] which, in conjunction with modifications of the $C_3$ cladinose moiety, eventually yielded the recently approved $C_{11}$, $C_{12}$ cyclic carbamate, $C_3$ oxo ketolide telithromycin. Similar modifications in conjunction with a $C_6$ O-alkyl modification led to the discovery of the ketolide cethromycin. Additional modifications that have been reported include 4″ carbamate macrolides,[12] ketolides containing nonnatural $C_{13}$ substituents obtained via alteration of the biosynthetic pathway of erythromycin A[13] and $C_6-C_{11}$ bridged ketolides.[14]

Despite much activity in designing 14-membered macrolide derivatives, few examples of modifications to erythromycin at the $C_{12}$ carbon exist, especially with regard to the $C_{12}-C_{21}$ bond. Hauske[15] has disclosed that the $C_{12}$ hydroxyl can be selectively activated and eliminated exo when the $C_9-C_{11}$ hydroxyls are protected as cyclic thiocarbonates, as depicted in Figure 2. The resulting olefin, after thiocarbonate removal, can be dihydroxylated. Lartey[16] has disclosed that a similar exocyclic olefin (with a $C_9$ amine group and formate ester at $C_{11}$) can be formed, albeit as a mixture with the $C_6$ hydroxyl elimination, as depicted in

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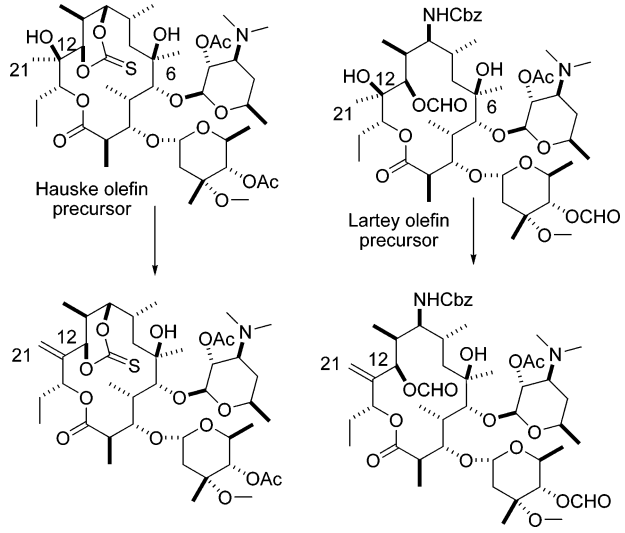


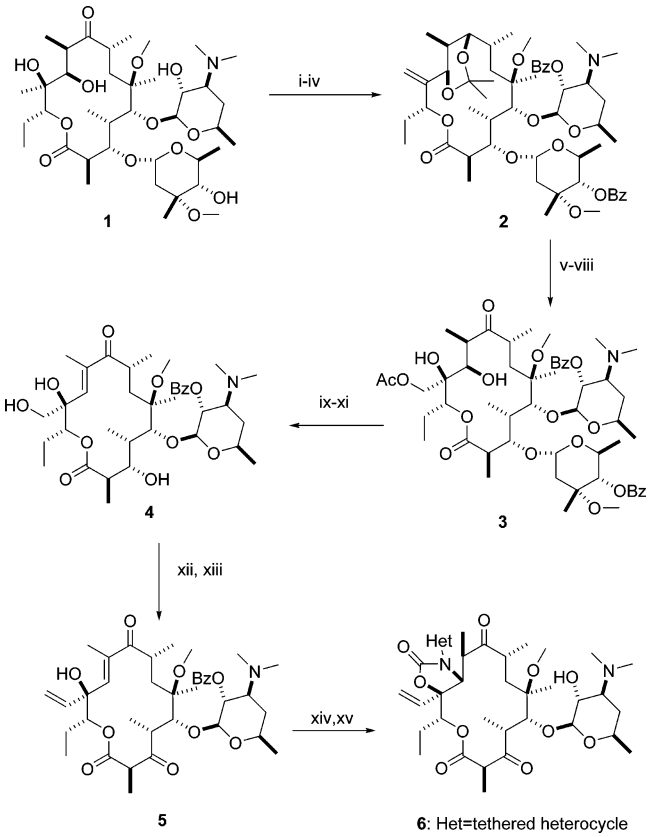

**Figure 2.** Reported $C_{12}-C_{21}$ dehydrations.

Figure 2. Lartey further discloses the isolated $C_{12}$ exo olefin participating in stereoselective epoxidation, dihydroxylation, and hydroboration reactions. Of these products, only the epoxide is disclosed as being derivatized by ring opening with alkyl amines. It should be noted that all of the $C_{12}$ modified compounds of both Hauske and Lartey are reported to exhibit minimal antibacterial activity. It should also be noted that the $C_{12}$ modified compounds of both Hauske and Lartey result in macrolide cores with polar groups (hydroxymethyl and alkyl aminomethyl) in place of the natural $C_{21}$ methyl off of $C_{12}$.

Our plan was to explore further the chemistry around the $C_{12}-C_{21}$ bond with the goal of introducing nonpolar groups off of $C_{12}$. The synthetic route for accessing such $C_{12}$ modified macrolides and ketolides is outlined in Scheme 1. Central to the strategy is the creation of a suitably protected $C_{12}-C_{21}$ exocyclic alkenyl macrolide **2** via a controlled, selective exocyclic elimination of the $C_{12}$ hydroxyl. This double bond provides a handle to introduce novel groups directly into the $C_{12}$ position of the macrolide core. For example, the exocyclic double bond in **2** can be dihydroxylated in a manner that reinstalls the $C_{12}$ hydroxyl with the desired natural stereochemistry as well as functionalizing the $C_{21}$ carbon as a hydroxymethyl group. With the $C_{21}$ hydroxymethyl group protected, the macrolide core oxidation level can be returned, and the core **3** can then be processed in a manner analogous with natural erythromycin derived ketolides to ketolide precursor **4**, which possesses a primary hydroxymethyl group at the $C_{12}$ position. Upon oxidation, the resulting aldehyde allows for the introduction of a $C_{12}$ vinyl group. The resulting $C_{12}$ vinyl core **5** can then be converted to the $C_{12}$ vinyl, $C_{11}-C_{12}$ carbamate ketolides **6**.

The experimental details for implementing the synthetic strategy are as follows. Starting from clarithromycin **1**, the protected $C_{12}$ exocyclic alkenyl macrolide **2** can be accessed in four steps involving benzoate protection of both sugar hydroxyl groups, stereospecifc reduction of the $C_9$ ketone with sodium borohydride,[17] dimethylacetonide protection of the resulting $C_9$, $C_{11}$ diol, and thionyl chloride mediated exocyclic selective elimination of the $C_{12}$ hydroxyl. The cyclic acetonide protection of the $C_9$ and $C_{11}$ hydroxyl groups is necessary to obtain a clean and selective exocyclic elimination. Deprotection of the acetonide in alkene **2** yields an allylic alcohol that is stereospecifically dihydroxylated with catalytic $OsO_4$/stoichiometic *N*-methylmorpholine oxide.[18] The allylic alpha alcohol at $C_{11}$ facilitates the dihydroxylation, wherein the natural $C_{12}$ alpha

**Scheme 1**[a] Synthesis of $C_{12}$ Vinyl Ketolides




[a] Reagents and conditions: (i) $(Bz)_2O$, DMAP, $CH_2Cl_2$, TEA, 98%; (ii) $NaBH_4$, EtOH, 85%; (iii) $(MeO)_2C(CH_3)_2$, PPTS, acetone, reflux; (iv) $SOCl_2$, TEA, EtOAc, 50% 2 steps; (v) PPTS, 68 °C, MeCN:$H_2O$ (2:1) 90%; (vi) $OsO_4$, NMO, acetone, $H_2O$, 82%; (vii) AcCl, DMAP, pyridine, 99%; (viii) Dess−Martin periodinane, $CH_2Cl_2$, −10 °C, 99%; (ix) MsCl, pyridine, 99%; (x) (a) DBU, acetone, 4 h, rt; (b) 66 °C, 12 h, 90%; (xi) HCl, $H_2O$, MeOH, 40 °C, 66%; (xii) $Me_2S$, NCS, DIEA, THF, −13 °C, 90%; (xiii) $MeP(Ph)_3Br$, THF, $KN(TMS)_2$, −60 °C to rt, 50%; (xiv) CDI, THF, NaH, 0 °C, 95%; (xv) (a) amine, MeCN, $H_2O$, 60 °C, 14 h; (b) MeOH, 65 °C, 12 h, 30−50%.

hydroxy, $C_{21}$ beta configuration is reestablished. The dihydroxylation of the $C_{12}$, $C_{21}$ alkene can be done with the $C_9$, $C_{11}$ still protected as the cyclic acetonide, but not surprisingly the reaction is much slower. After the dihydroxylation of **2**, the $C_{21}$ alcohol of the resulting tetraol is selectively protected as the acetate, and the $C_9$ hydroxyl is oxidized selectively by Dess−Martin periodinane[19] at −10 °C yielding macrolide diol **3**. Mesylation of the $C_{11}$ hydroxyl is achieved by treating with mesyl chloride in pyridine. Analysis by $^{13}C$ NMR suggests that the $C_{11}$ mesylated **3** exists predominantly as a $C_{12}$ hydroxy $C_9$ cyclic hemiketal. The $C_{11}$ mesylated macrolide is then converted to the corresponding enone by treatment with DBU in acetone first at room temperature and then at reflux. This transformation we believe proceeds first by the $C_{12}$ hydroxyl displacement of the $C_{11}$ mesylate yielding an intermediate $C_{11}-C_{12}$ epoxide that upon heating in the presence of DBU allows for $C_{10}$ deprotonation and elimination/opening of the epoxide to yield the desired enone. A single enone isomer is produced in this reaction as judged by $^1H$ NMR. Acidic hydrolysis removes both the cladinose and $C_{21}$ acetate groups, yielding the macrolide triol **4**. The $C_3$ and $C_{21}$ hydroxyl groups are oxidized when subjected to Corey−Kim conditions,[20] and the resulting $C_3$ oxo, $C_{21}$ aldehyde reacts selectively with methylenetriphenylphosporane to yield the $C_{12}$ vinyl macrolide enone **5**. The use of potassium bistrimethylsilylamide as the base to generate the ylide in this step was crucial for successful olefination. Deprotonation of

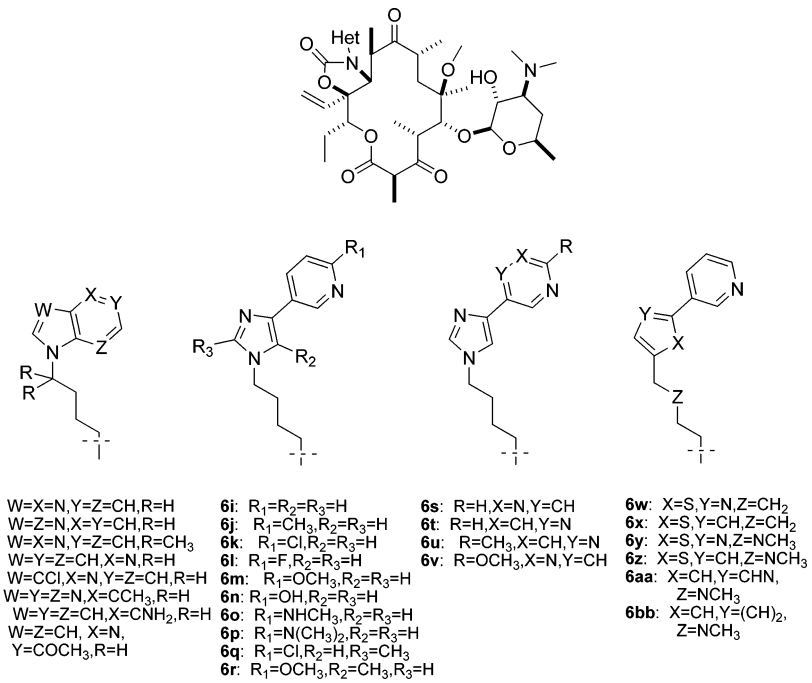



**Figure 3.** Structures of $C_{12}$ vinyl ketolides.

**Table 1.** In Vitro Properties [MIC ($\mu$g/mL)] of $C_{12}$ Vinyl Ketolides

| strain | 6a | 6b | 6c | 6d | 6e | 6f | 6g | 6h | 6i | 6j | 6k | 6l | teli | clari |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *S. aureus_29213* | 0.2 | 0.2 | 0.2 | 0.1 | 0.2 | 0.1 | 0.2 | 0.1 | 0.1 | 0.2 | ≤0.05 | 0.1 | 0.1−0.2 | 0.4−0.78 |
| *S. aureus_33591* | >50 | >50 | >50 | >50 | >50 | >50 | >50 | >50 | >50 | >50 | >50 | >50 | >50 | >50 |
| *S. epidermidis_14990* | 0.1 | 0.1 | 0.2 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.2 | 0.2 | ≤0.05 | 0.1 | 0.1−0.2 | 0.2−0.4 |
| *S. epidermidis_f50654* | 0.4 | 0.2 | 0.2 | 0.1 | 0.1 | 0.1 | 0.78 | 0.1 | 0.2 | 0.2 | ≤0.05 | 0.1 | 0.1−0.2 | 0.2−0.4 |
| *E. faecalis_29212* | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | ≤0.05 | ≤0.05 | 0.2 | 0.1 | 0.1 | ≤0.05 | 0.1 | ≤0.05−0.1 | 0.78−1.56 |
| *E. faecalis_bc11148-2* | 0.78 | 0.78 | 0.4 | 3.13 | 1.56 | 0.4 | 6.25 | 6.25 | 0.4 | 0.78 | 0.1 | 0.4 | 0.4 | >50 |
| *S. pyogenes_8668* | ≤0.05 | ≤0.05 | ≤0.05 | ≤0.05 | ≤0.05 | ≤0.05 | ≤0.05 | ≤0.05 | ≤0.05 | ≤0.05 | ≤0.05 | ≤0.05 | ≤0.05 | ≤0.05 |
| *S. pneumo_49619* | ≤0.05 | ≤0.05 | ≤0.05 | ≤0.05 | ≤0.05 | ≤0.05 | ≤0.05 | ≤0.05 | ≤0.05 | ≤0.05 | ≤0.05 | ≤0.05 | ≤0.05 | ≤0.05 |
| *S. pneumo_297-749* | ≤0.05 | ≤0.05 | ≤0.05 | ≤0.05 | ≤0.05 | ≤0.05 | ≤0.05 | ≤0.05 | ≤0.05 | ≤0.05 | ≤0.05 | ≤0.05 | ≤0.05 | ≤0.05 |
| *S. pneumo_280-962* | ≤0.05 | ≤0.05 | ≤0.05 | ≤0.05 | ≤0.05 | ≤0.05 | ≤0.05 | ≤0.05 | ≤0.05 | ≤0.05 | ≤0.05 | ≤0.05 | ≤0.05 | ≤0.05 |
| *S. pneumo_Erm 6849* | 3.13 | 12.5 | 0.1 | 6.25 | 3.13 | >50 | 3.13 | 3.13 | 0.2 | 0.4 | 0.1 | 0.78 | 0.1−0.4 | >50 |
| *S. pneumo_Mef 5654* | 1.56 | 0.78 | 0.78 | 0.4 | 0.78 | 1.56 | 0.78 | 0.78 | 0.4 | 0.78 | 0.2 | 0.4 | 0.4−0.78 | 6.25−12.5 |
| *S. pneumo_Mef S 3427* | 0.2 | 0.1 | 0.2 | 0.1 | 0.1 | 0.2 | 0.1 | 0.2 | 0.1 | 0.1 | ≤0.05 | 0.1 | 0.1−0.2 | 3.13−6.25 |
| *H. influenzae_49247* | 1.56 | 1.56 | 6.25 | 6.25 | 3.13 | 3.13 | 3.13 | 3.13 | 3.13 | 6.25 | 3.13 | 3.13 | 3.13−6.25 | 6.25−12.5 |
| *H. influenzae_2762* | 0.78 | 0.78 | 0.78 | 1.56 | 0.78 | 0.78 | 3.13 | 0.2 | 1.56 | 1.56 | 0.78 | 1.56 | 0.4−1.56 | 0.78−3.13 |

the $C_{12}$ hydroxyl of enone **5** with sodium hydride in the presence of carbonyldiimidazole yields the corresponding $C_{12}$ imidazoyl carbamate, which upon reaction with an excess of side chain amine and deprotection of the desosamine benzoate by heating in methanol yields the $C_{12}$ vinyl ketolides **6**. Typical unoptimized yields of final ketolide from enone **5** are on the order of 30−50%. The $C_{12}$ vinyl ketolides (**6a**−**6z**, **6aa**, and **6bb**) prepared and reported are illustrated in Figure 3. The heteroaryl side chain amines incorporated into the $C_{12}$ vinyl ketolides were synthesized as described in the Supporting Information or by literature methods.

The structural assignments of the final ketolides were supported by NMR comparison to telithromycin. For compound **6i**, which has the same alkyl tethered group off the cyclic carbamate as telithromycin, the peaks for the macrocycle core excluding resonances for the $C_{12}$ Me or vinyl group are practically identical.[21] Additionally, all ketolides exhibited the $C_{11}$ H singlet at ca.3.7 ppm characteristic of $C_{11}$−$C_{12}$ carbamates with natural $C_{10}$ configuration.[11a] Additional support for structural assignments came from NMR and X-ray structural analysis of $C_{12}$ modified macrolide cores with unnatural stereochemistry at $C_{12}$.[22]

## Results and Discussion

**In Vitro Evaluation.** The $C_{12}$ vinyl ketolides prepared were assayed in a primary panel against a number of strains of *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Enterococcus faecalis*, *Streptococcus pyogenes*, *Streptococcus pneumoniae*, and *Haemophilus influenzae*. Included among the strains of *S. pneumoniae* were erythromycin resistant strains containing *mef* and *erm* genes. Telithromycin and clarithromycin were used as comparators in all assays. The in vitro antibacterial activity is reported as the minimum inhibitory concentration (MIC) in $\mu$g/mL as determined by the broth microdilution method.[23] The MIC data in Tables 1 and 2 indicates that $C_{12}$ vinyl ketolides in general possess potent antibacterial activity against a range of pathogens. The spectrum is similar to telithromycin, and like telithromycin, the $C_{12}$ vinyl ketolides are potent against the *mef* and *erm* gene containing *S. pneumoniae* strains that clarithromycin is not active against. The overall activity spectrum of the $C_{12}$ vinyl ketolides can be attenuated by the nature of the heterocycle tethered to the $C_{11}$, $C_{12}$ carbamate. All of the heterocyclic moieties on the $C_{12}$ vinyl ketolides reported here are tethered to the $C_{11}$ attached nitrogen via a four-atom spacer.

**Table 2.** In Vitro Properties [MIC ($\mu$g/mL)] of $C_{12}$ Vinyl Ketolides

| strain | **6m** | **6n** | **6o** | **6p** | **6q** | **6r** | **6s** | **6t** | **6u** | **6v** | **6w** | **6x** | **6y** | **6z** | **6aa** | **6bb** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *S. aureus_29213* | 0.1 | 0.4 | 0.1 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.1 | 0.1 | 0.1 | 0.2 | 0.1 | 0.2 | 0.2 | 0.2 |
| *S. aureus_33591* | >50 | >50 | >50 | >50 | >50 | >50 | >50 | >50 | >50 | >50 | >50 | 12.5 | >50 | >50 | >50 | >50 |
| *S. epidermidis_14990* | 0.2 | 0.2 | 0.2 | 0.2 | 0.1 | 0.1 | 0.2 | 0.1 | 0.2 | 0.1 | 0.1 | 0.2 | 0.1 | 0.1 | 0.2 | 0.2 |
| *S. epidermidis f50654* | 0.1 | 0.2 | 0.1 | 0.2 | 0.2 | 0.4 | 0.2 | 0.2 | 0.1 | 0.1 | 0.1 | 0.2 | 0.1 | 0.2 | 0.2 | 0.1 |
| *E. faecalis _29212* | ≤0.05 | 0.2 | 0.1 | 0.1 | 0.1 | 0.2 | 0.1 | 0.1 | 0.1 | ≤0.05 | ≤0.05 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 |
| *E. faecalis_bc11148-2* | 0.78 | 3.13 | 0.78 | 0.78 | 3.13 | 1.56 | 0.4 | 0.4 | 0.78 | 0.4 | 1.56 | 3.13 | 0.4 | 0.4 | 0.2 | 0.1 |
| *S. pyogenes_8668* | ≤0.05 | ≤0.05 | ≤0.05 | ≤0.05 | ≤0.05 | ≤0.05 | ≤0.05 | ≤0.05 | ≤0.05 | ≤0.05 | ≤0.05 | 0.1 | ≤0.05 | ≤0.05 | ≤0.05 | ≤0.05 |
| *S. pneumo_49619* | ≤0.05 | ≤0.05 | ≤0.05 | ≤0.05 | ≤0.05 | ≤0.05 | ≤0.05 | ≤0.05 | ≤0.05 | ≤0.05 | ≤0.05 | ≤0.05 | ≤0.05 | ≤0.05 | ≤0.05 | ≤0.05 |
| *S. pneumo_297-749* | ≤0.05 | ≤0.05 | ≤0.05 | ≤0.05 | ≤0.05 | ≤0.05 | ≤0.05 | ≤0.05 | ≤0.05 | ≤0.05 | ≤0.05 | ≤0.05 | ≤0.05 | ≤0.05 | ≤0.05 | ≤0.05 |
| *S. pneumo_280-962* | ≤0.05 | ≤0.05 | ≤0.05 | ≤0.05 | ≤0.05 | ≤0.05 | ≤0.05 | ≤0.05 | ≤0.05 | ≤0.05 | ≤0.05 | ≤0.05 | ≤0.05 | ≤0.05 | ≤0.05 | ≤0.05 |
| *S. pneumo_Erm 6849* | 0.4 | 12.5 | 0.4 | 0.78 | 0.4 | 0.4 | 0.2 | 0.2 | 0.2 | 0.4 | 1.56 | 3.13 | 0.78 | 0.2 | ≤0.05 | 0.1 |
| *S. pneumo_Mef 5654* | 0.78 | 3.13 | 1.56 | 1.56 | 0.78 | 1.56 | 0.78 | 0.78 | 0.78 | 0.78 | 0.4 | 0.78 | 0.4 | 0.78 | 0.4 | 0.78 |
| *S. pneumo_Mef S 3427* | 0.1 | 1.56 | 0.2 | 0.2 | ≤0.05 | 0.2 | 0.1 | 0.1 | 0.2 | 0.2 | ≤0.05 | 0.2 | 0.1 | 0.1 | 0.1 | 0.1 |
| *H. influenzae_49247* | 6.25 | 6.25 | 3.13 | 12.5 | 6.25 | 6.25 | 3.13 | 3.13 | 3.13 | 6.25 | 3.13 | 3.13 | 12.5 | 6.25 | 6.25 | 6.25 |
| *H. influenzae_2762* | 0.78 | 1.56 | 0.78 | 1.56 | 1.56 | 1.56 | 1.56 | 1.56 | 0.78 | 0.78 | 1.56 | 3.13 | 3.13 | 3.13 | 3.13 | 1.56 |

The heterocyclic moieties can be divided into 6,6 and 5,6 heteroaromatic fused bicycles or 5,6 or 6,6 unfused biaryl systems.

A general trend that appears for the $C_{12}$ vinyl ketolides with tethered heteroaromatic fused bicycles is potency similar to that of telithromycin versus *S. aureus*, *S. epidermis*, *E. faecalis*, *S. pyogenes*, susceptible *S. pneumoniae*, *mef* gene containing *S. pneumoniae* strains and *H. influenzae*, and weaker potency relative to telithromycin against the *erm* gene containing *S. pneumoniae* strain. Azabenzimidazole containing **6a** and **6b**, azaindole containing **6d**, **6e**, and **6h**, and indole containing **6g** all are at least 10-fold less potent than telithromycin against the *erm* gene containing *S. pneumoniae* strain. Interestingly, for **6c**, which differs from **6a** by the addition of gem dimethyls next to the azabenzimidazole, the potency is improved against the *erm* gene containing *S. pneumoniae* strain, and the overall activity against the primary panel of this particular $C_{12}$ vinyl ketolide with a tethered heteroaromatic fused bicycle is comparable to telithromycin.

A general trend that appears for the $C_{12}$ vinyl ketolides with tethered 5,6 or 6,6 unfused biaryl systems is potency similar to that of telithromycin versus all pathogens in the primary panel. The $C_{12}$ vinyl ketolide **6i**, with the same tethered imidazoyl pyridyl bicycle as telithromycin, is essentially equipotent with telithromycin. Substitution on the pyridyl group of this bicycle with methyl **6j**, fluoro **6l**, methoxy **6m**, and methyl amino **6o** is tolerated and in the case of chloro substitution **6k** is beneficical, vide infra. However, hydroxy substitution on the pyridyl (converting pyridyl to pyridone) **6n** is detrimental as the activity against *mef* and *erm* gene containing *S. pneumoniae* as well as *E. faecalis* is decreased. Pyrimidyl, **6s** and **6v**, and pyrazinyl, **6t** and **6u**, replacements of the pyridyl ring are tolerable. Replacing the imidazole interior ring of the bicycle with thiazole, **6w**, or thiophene, **6s**, decreases activity against *erm* containing *S. pneumoniae* as well as *E. faecalis*. However, when an *N*-methyl group is inserted in the four atom tether, the thiazole, **6y**, or thiophene, **6z**, replacements are tolerable as the activity against the *erm* containing *S. pneumoniae* as well as *E. faecalis* is increased.

Several $C_{12}$ vinyl ketolides with potency in the primary panel comparable to that of telithromycin were profiled further by testing alongside telithromycin against an expanded panel of twenty *S. pneumoniae* strains containing *mef* genes and an expanded panel of twenty-one *S. pneumoniae* strains containing *erm* genes. The results of these assays for $C_{12}$ vinyl ketolides **6j** and **6k** are depicted in Tables 3 and 4. Table 3 shows that, against macrolide-resistant *S. pneumoniae* harboring the *mef* genes, **6k** is generally more active than telithromycin (2- to 5-fold). Against these bacteria strains, **6j** is as potent as telithromycin. As shown in Table 4, while **6j** exhibits antibacterial activity similar to that of telithromycin against macrolide-resistant *S. pneumoniae* harboring the *erm* genes, **6k** is slightly more active than telithromycin.

**Table 3.** In Vitro Properties [MIC ($\mu$g/mL)] of **6j** and **6k** against Expanded *S. pneumoniae mef* Panel

| strain | **6j** | **6k** | telithromycin |
|---|---|---|---|
| *S. pneumo 5649* | 0.2 | ≤0.05 | 0.5 |
| *S. pneumo 5654* | 0.4 | 0.1 | 0.5 |
| *S. pneumo S 3427* | 0.2 | ≤0.05 | 0.13 |
| *S. pneumo S 3435* | ≤0.05 | ≤0.05 | 0.06 |
| *S. pneumo 41* | 0.1 | 0.1 | 0.13 |
| *S. pneumo 953* | 0.1 | ≤0.05 | 0.13 |
| *S. pneumo 983* | 0.4 | 0.1 | 0.5 |
| *S. pneumo1556* | ≤0.05 | ≤0.05 | 0.13 |
| *S. pneumo 1566* | 0.4 | 0.1 | 0.5 |
| *S. pneumo 1790* | 0.2 | 0.1 | 0.5 |
| *S. pneumo 2382* | 0.1 | 0.1 | 0.25 |
| *S. pneumo 2880* | 0.2 | ≤0.05 | 0.13 |
| *S. pneumo 3449* | 0.2 | ≤0.05 | 0.25 |
| *S. pneumo 3855* | 0.2 | ≤0.05 | 0.25 |
| *S. pneumo 4126* | ≤0.05 | ≤0.05 | 0.06 |
| *S. pneumo 4331* | 0.4 | 0.1 | 1 |
| *S. pneumo 6966* | 0.2 | ≤0.05 | 0.25 |
| *S. pneumo 9142* | 0.4 | 0.1 | 0.5 |
| *S. pneumo 9959* | 0.2 | ≤0.05 | 0.25 |
| *S. pneumo 10095* | ≤0.05 | ≤0.05 | 0.06 |

**Table 4.** In Vitro Properties [MIC ($\mu$g/mL)] of **6j** and **6k** against Expanded *S. pneumoniae erm* Panel

| strain | 6j | 6k | telithromycin |
|---|---|---|---|
| *S. pneumo 6396* | 0.1 | 0.05 | 0.1 |
| *S. pneumo 6388* | 3.13 | 0.4 | 0.78 |
| *S. pneumo 6849* | 0.1 | 0.05 | 0.2 |
| *S. pneumo S 4297* | 0.025 | 0.025 | 0.1 |
| *S. pneumo S 4085* | 0.025 | ≤0.013 | ≤0.013 |
| *S. pneumo 867* | 0.025 | 0.025 | 0.025 |
| *S. pneumo 2218* | 0.1 | 0.025 | 0.025 |
| *S. pneumo 3120* | 0.2 | 0.05 | 0.1 |
| *S. pneumo 4290* | 0.05 | 0.025 | ≤0.013 |
| *S. pneumo 4589* | 0.025 | 0.025 | 0.025 |
| *S. pneumo 5354* | 0.025 | 0.025 | 0.025 |
| *S. pneumo 5399* | 0.025 | 0.025 | ≤0.013 |
| *S. pneumo 5415* | 0.025 | 0.025 | 0.025 |
| *S. pneumo 5554* | 0.78 | 0.1 | 0.2 |
| *S. pneumo 7985* | ≤0.013 | ≤0.013 | ≤0.013 |
| *S. pneumo 8257* | ≤0.013 | ≤0.013 | ≤0.013 |
| *S.pneumo 8339* | 1.56 | 0.2 | 0.78 |
| *S. pneumo 8919* | 0.025 | 0.025 | 0.025 |
| *S. pneumo 8947* | 0.4 | 0.05 | 0.1 |
| *S. pneumo 10279* | 0.025 | 0.025 | 0.025 |
| *S. pneumo 5590* | 0.025 | 0.025 | ≤0.013 |

**In Vivo Evaluation.** The in vivo pharmacokinetic (PK) properties of several $C_{12}$ vinyl ketolides were assessed in rats. In addition to plasma half-lives ($t_{1/2}$), volume of distribution

**Table 5.** Rat Pharmacokinetic Data of $C_{12}$ Vinyl Ketolides **6j** and **6k**

| | dose (mg/kg) | | plasma AUC, iv | L/P AUC | CL | $V_{ss}$ | $t_{1/2}$ (h) | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | iv | po | ($\mu$g·h/mL) | ratio, iv | (mL·min$^{-1}$·kg$^{-1}$) | (L/kg) | iv plasma | po plasma | po lung | % *F*, po (%) |
| telithromycin | 5 | 15 | 2.5 | 16 | 100 | 5 | 1 | 1.5 | 1.3 | 11 |
| **6j** | 5 | 15 | 2.1 | 80 | 115 | 14 | 1.6 | 2.4 | 3.4 | 35 |
| **6k** | 5 | 15 | 2.3 | 94 | 107 | 12 | 1.3 | 1.7 | 1.4 | 26 |

($V_{ss}$), clearance (CL), bioavailability (% *F*), and plasma AUC values, the AUC values in the lungs as well as the lung half-lives were determined. High lung-to-plasma AUC ratios (L/P ratio), as well as long lung half-lives, we believe would bestow favorable pharmacodynamic properties toward lung infections. The pharmacokinetic data for telithromycin and $C_{12}$ vinyl ketolides **6j** and **6k** is shown in Table 5. While all three compounds have comparable plasma exposures (iv AUC values), the pharmacokinetic profiles of **6j** and **6k** in rats differ from that of telithromycin by having much higher lung-to-plasma ratios, greater than 5-fold telithromycin, and larger volumes of distribution, greater than 2-fold telithromycin. The half-life for **6j** in the lung is greater than 2-fold while that of **6k** is similar to that of telithromycin. Both **6j** and **6k** possess good bioavailability, greater than 2-fold the telithromycin value. It should be noted that the low bioavailability for telithromycin was dose dependent, vide infra.

The in vivo efficacy of the $C_{12}$ vinyl ketolides **6j** and **6k** relative to that of telithromycin was evaluated using an agarose bead enmeshed with either macrolide-resistant *S. pneumoniae* or *H. influenzae* in a rat pulmonary infection model. This model has been demonstrated to produce a subchronic rat pulmonary infection for 2−4 weeks with bacterial counts of $10^4$−$10^7$ cfu/mL obtained from homogenized lung tissue. The efficacy of each compound tested was determined by the decrease in bacterial load (CFU = colony forming units) relative to a positive control and other treated groups against *H. influenzae* and macrolide-resistant *S. pneumoniae erm* and *S. pneumoniae mef*. The data is provided in Figures 4, 5, and 6, respectively.

The favorable pharmacokinetic profiles for $C_{12}$ vinyl ketolides **6j** and **6k** are reflected by the good in vivo efficacy obtained in rats in lung infection models. Both **6j** and **6k** are found to be more efficacious than telithromycin in rat lung infection model against *H. influenzae*. Ketolide **6j** essentially cleared the infection (5-log reduction) at 50 mg/kg while **6k** cleared the infection at 100 mg/kg (5-log reduction). Telithromycin did not clear the infection even at 100 mg/kg (2-log reduction) (Figure 4).

Ketolides **6j** and **6k** are found to be more efficacious than telithromycin in rat lung infection model against macrolide-resistant *erm*+ *S. pneumoniae*. Both ketolides essentially cleared the infection at 50 mg/kg (4-log reduction) while telithromycin did not clear the infection even at 100 mg/kg (1.5-log reduction) (Figure 5).

In rat lung infection model against macrolide-resistant *mef*+ *S. pneumoniae* **6k** is found to be more efficacious than telithromycin. Ketolide **6k** essentially cleared the infection at

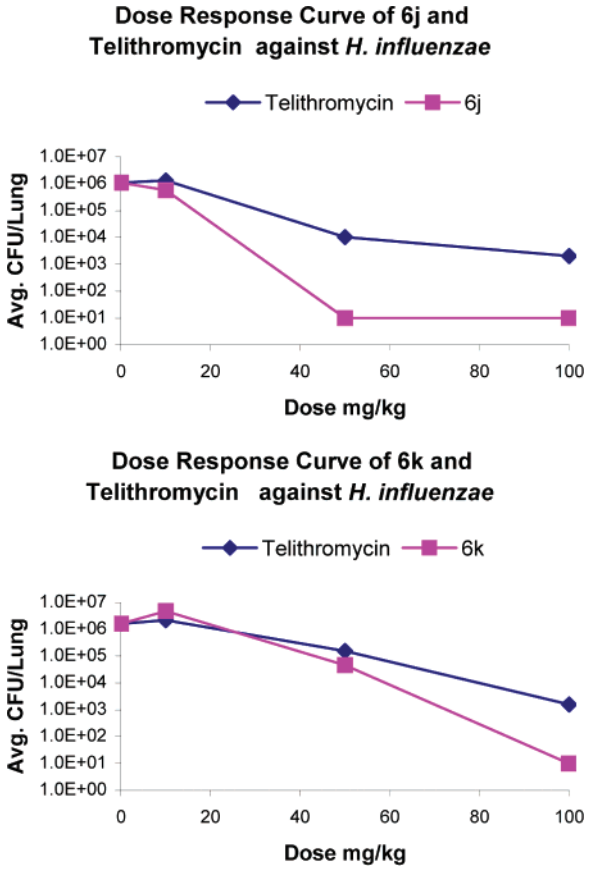



**Figure 4.** Rat efficacy of **6j** and **6k** against *H. influenzae*.

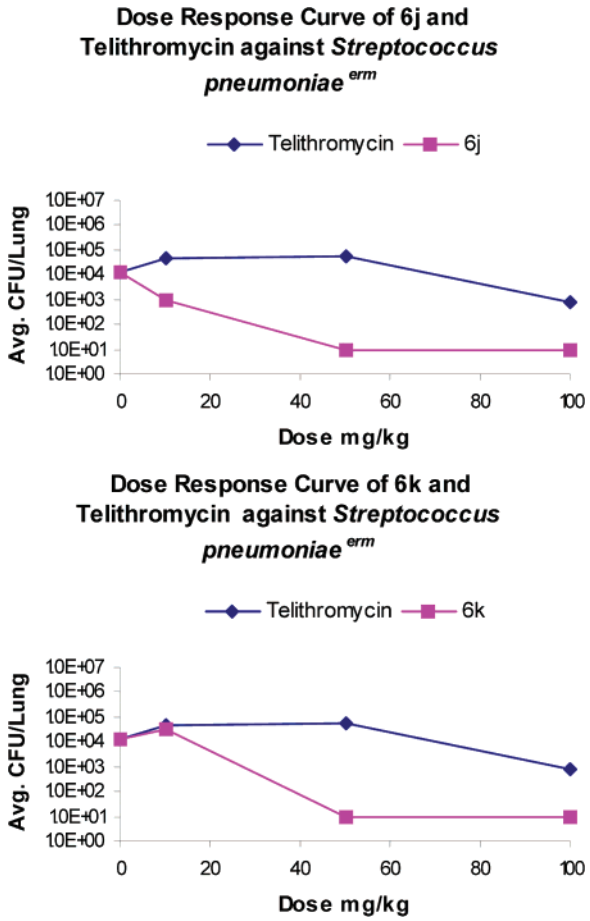



**Figure 5.** Rat efficacy of **6j** and **6k** against *S. pneumoniae erm*.

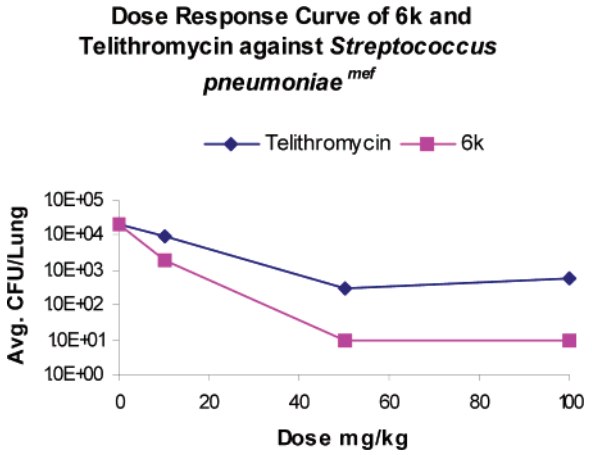



**Figure 6.** Rat efficacy of **6k** against *S. pneumoniae mef.*

50 mg/kg (3.5-log reduction) while telithromycin did not clear the infection even at 100 mg/kg (1.5-log reduction) (Figure 6).

Given the low bioavailability of telithromycin ($F = 11\%$) in initial PK experiments (5 mg/kg iv dose, 15 mg/kg oral dose), a rat PK experiment was run at doses more relevant to the in vivo efficacy studies to rule out the possibility that the difference in efficacy observed between the $C_{12}$ vinyl ketolides **6j** and **6k** and telithromycin was due solely to differences in bioavailability. We found that, at 100 mg/kg oral dosing, telithromycin and **6k** were 84% and 91% bioavailable, respectively. Furthermore, the favorable pharmacokinetic properties identified at lower doses were maintained at higher dosing; the L/P ratios were 16 and 93, and the lung half-lives were 2.4 and 8.8 h for telithromycin and **6k**, respectively. Thus, in the efficacy studies with roughly equal amounts of compound getting on board at the 100 mg/kg dose, the superior efficacy of $C_{12}$ vinyl ketolides **6j** and **6k** appears to be due to their favorable pharmacokinetic properties.

## Conclusion

In summary, the replacement of the $C_{12}$ methyl group of erythromycin with a $C_{12}$ vinyl group and the conversion of the resulting macrolide core into the ketolide class of antibacterials has been described. The $C_{12}$ vinyl ketolides prepared possess potent antibacterial properties in vitro, with **6j** and **6k** exhibiting a spectrum and potency level equivalent to those of the leading member of the ketolide class. The incorporation of the $C_{12}$ vinyl group into the macrolide also has a favorable impact on the pharmacokinetic and pharmacodynamic properties of the resulting $C_{12}$ vinyl ketolides; high lung AUCs and long half-lives are observed in rat PK experiments, and this translates into potent efficacy in in vivo rat lung infection models. Thus, $C_{12}$ vinyl ketolides appear to be promising agents for treating infections caused by respiratory pathogens and warrant further investigation.

## Experimental Section

**Antibiotics.** All new synthetic compounds tested were dissolved in 95% ethanol and further diluted with sterile deionized water as were telithromycin, erythromycin (Sigma, St. Louis, MO), and clarithromycin. Drug stocks were stored at −80 °C, protected from light.

**Bacterial Strains.** Bacterial strains were cultivated from −80 °C frozen stocks by two consecutive overnight passages at 35 °C on 5% blood agar (Remel, Lenexa, KS). Chocolate agar (Remel) was used for *H. influenzae* strains. *H. influenzae*, *S. pneumoniae*, and *S. pyogenes* were incubated in 5−10% $CO_2$.

Type/quality control strains were received from the American Type Culture Collection (ATCC; Rockville, MD). Clinical isolates collected in 2001 of *S. pneumoniae*, *H. influenzae*, and *S. aureus* were received from Focus Technologies, Inc, VA, and The Jones Group, JMI Laboratories, IA. Other isolates were supplied by Childrens' Hospital Medical Center, Seattle, WA; Harborview Medical Center, Seattle, WA; University Health Systems, San Antonio, TX; and Henry Ford Hospital, Detroit, MI.

**Susceptibility Testing.** The in vitro antibacterial activity is reported as the minimum inhibitory concentration (MIC) in $\mu$g/mL as determined by the broth microdilution method in accordance with the Clinical Laboratory Standards Institute (CLSI, formerly NCCLS) guidelines.[23] In brief, organism suspensions were adjusted to a 0.5 McFarland standard to yield a final inoculum between $3 \times 10^5$ and $5 \times 10^5$ CFU/mL. The inoculum was made in sterile, cation adjusted Mueller Hinton Broth (CAMHB) for all but *S. pneumoniae* (CAMHB with 3% lysed horse blood) and *H. influenzae* (Haemophilus Test Medium). All inoculated microdilution trays were incubated in ambient air at 35 °C for 18−24 h except for *S. pneumoniae* and *H. influenzae* (both at 5−10% $CO_2$). Following appropriate incubation, the MIC was defined as the lowest concentration of the drug that prevented visible growth. Performance of the antibiotics on the test trays was monitored by the use of ATCC quality control strains with a defined MIC spectrum, in accordance with CLSI guidelines.[24]

**In Vivo Pharmacokinetics.** A total of 54 male Sprague−Dawley rats, weighing 200 g on average, are evaluated for pharmacokinetic studies of representative ketolides. Rats are under overnight food restriction and receive water ad libitum. Rats are acclimated for approximately 5 days before antibiotic administration. Rats are given bolus administration through intravenous (iv) and oral (po) routes. Representative substituted $C_{12}$ vinyl ketolides and telithromycin, for comparison, are diluted in 0.85% saline to a concentration of 15.0 mg/mL, and the resulting pH is adjusted using 1 N acetic acid until the compound is in solution. Approximately 200 $\mu$L of the compound solution is administered to the rats. The target dose for iv and po administration is 5 mg/kg and 15 mg/kg, respectively. Plasma and whole lung samples are collected from the rats. Plasma samples are obtained from blood samples by centrifugation at 3000 rpm for 10 min. Heparin is added in the plasma as an anticoagulant. Whole lung samples are homogenized in deionized water. Samples are stored at −80 °C. A total of 9 time points are collected in triplicate at 0.083, 0.25, 0.5, 1, 2, 4, 6, 8, and 24 h. Ketolide concentrations in plasma and lung are determined by well-established non-GLP LC−MS−MS methods. PK parameters are estimated from the raw bioanalytical data using WinNolin software (Version 4.0, Pharsight Corporation, CA).

**In Vivo Therapeutic Efficacy.** The in vivo efficacy was evaluated using an agarose bead enmeshed with either macrolide-resistant *S. pneumoniae* or *H. influenzae* in a rat pulmonary infection model. The beads were instilled per os into the trachea (80−100 $\mu$L). Groups of five Sprague−Dawley male rats (~200 g) were intratracheally inoculated and 24 h later were dosed once daily by oral gavage for 3 days. Lungs were harvested, homogenized, diluted, and plated on 5% blood agar plates. Plates were then incubated at 35 °C for 24 h and then counted.

**General.** All reagents used were of commercial quality, and all reactions were carried out using commercially available anhydrous solvents from Aldrich, Fisher, or VWR. $^1$H(300 MHz) and $^{13}$C(75 MHz) NMR spectrum were recorded on either a Varian Unity 300 or Varian Mercury 300 spectrometer, using $CDCl_3$ or $CD_3OD$ solutions. Chemical shifts ($\delta$) are reported in parts per million (ppm) referenced at 7.26 ppm ($CDCl_3$) or 3.30 ($CD_3OD$) for $^1$H NMR and 77.0 ppm ($CDCl_3$) for $^{13}$C NMR. Coupling constants ($J$) are given in hertz, with the abbreviations s, d, dd, t, q, and m referring to singlet, doublet, doublet of doublets, triplet, quartet, and multiplet. Elemental analyses were performed at Desert Analytics (Tucson, AZ). Mass spectral data was recorded on either a Hewlett-Packard 1100 MSD {(50 V, 30 °C, electrospray ionization conditions (ESI+)} or Micromass ZQ LC/MS {(50 V, 30 °C, electrospray ionization conditions (ESI+)} systems. High-resolution mass spectra

were obtained on a Q-STAR quadrupole-TOF-MS (Applied Biosystems Inc.) in ESI+ mode. HPLC method 1: HPLC retention times are reported using a Column Engineering Reliasil BDX C18, 5 $\mu$M, 4.6 mm × 100 mm column, where elution with a 40 min gradient at 4 mL/min of 2−98% solvent A, where solvent A is MeCN with 0.1% TFA and solvent B is $H_2O$ with 0.1% TFA. HPLC method 2: HPLC retention times are reported using a Column Engineering Reliasil BDX C18, 5 $\mu$M, 4.6 mm × 100 mm column, where elution with a 20 min gradient at 4 mL/min of 5−80% solvent A, where solvent A is MeCN with 0.1% TFA and solvent B is $H_2O$ with 0.1% TFA.

**Compound 2. Stage i.** To a solution of clarithromycin **1** (100 g, 133 mmol) and dimethylaminopyrimidine (18.0 g, 147 mmol) in dimethylformamide (500 mL) were added triethylamine (90 mL, 648 mmol) and then benzoic anhydride (105 g, 464 mmol). The solution was then heated at 45 °C for 4 h, at which time water (50 mL) was added. After stirring for 1 h, additional water (1 L) was added. After stirring for an additional 2 h, the pH of the solution was adjusted to pH = 9−10 by slow addition of 25% $NaOH_{(aq)}$. After stirring for 2 h the precipitate was filtered, washed with water (100 mL), and dried in vacuo. The crude product in acetone (500 mL) was heated at 50 °C, to the resulting homogeneous solution was added activated charcoal (10 g), and after stirring for 1 h the solution was filtered through Celite. The volume was reduced by half by evaporation, and the resulting solid was filtered, rinsed with chilled acetone (25 mL), and dried in vacuo, yielding the 2′, 4″ OBz macrolide as a white solid (125 g, 98%). An analytical sample was obtained by purification through $SiO_2$ chromatography (15% acetone/hexanes with 1% triethylamine). MS (ESI): 956.6 ($MH^+$). $^1$H NMR ($CDCl_3$): $\delta$ 8.02 (m, 4H), 7.57 (m, 2H), 7.45 (m, 4H), 5.00−5.10 (m, 3H), 4.95 (s, 1H), 4.92 (s, 1H), 4.47 (m, 1H), 3.95 (s, 1H), 3.87 (m, 1H), 3.76 (d, $J$ = 9.0, 1H), 3.69 (s, 1H), 3.63 (d, $J$ = 6.3, 1H), 3.54 (s, 3H), 3.17 (s, 1H), 3.00 (s, 3H), 2.88−2.98 (m, 2H), 2.77 (m, 1H), 2.55 (m, 1H), 2.47 (d, $J$ = 15.0, 1H), 2.32 (s, 6H), 1.70−1.94 (m, 4H), 1.56−1.64 (m, 2H), 1.34−1.44 (m, 2H), 1.36 (s, 3H), 1.18−1.22 (m, 9H), 1.12 (d, $J$ = 7.2, 3H), 1.09 (d, $J$ = 6.9, 3H), 1.03 (s, 3H), 0.93 (d, $J$ = 6.0, 3H), 0.80 (t, $J$ = 7.5, 3H), 0.74 (d, $J$ = 7.2, 3H). $^{13}$C NMR ($CDCl_3$): $\delta$ 221.1, 175.5, 166.1, 165.4, 133.3, 132.6, 130.8, 129.9, 129.6, 128.4, 128.2, 100.3, 95.7, 80.5, 78.9, 78.2, 77.7, 76.5, 74.1, 73.0, 72.5, 69.7, 67.5, 63.7, 63.6, 50.4, 49.6, 45.2, 44.8, 40.9, 38.7, 38.5, 37.2, 35.3, 33.2, 31.7, 21.2, 21.0, 19.8, 18.5, 17.9, 16.0, 15.9, 12.3, 10.5, 9.4. HPLC: method 1; $t_R$ = 33.17 min. HRMS ($ESI^+$) $m/z$ $[M + H]^+$ calcd for $C_{52}H_{77}NO_{15}$, 956.5365; found, 956.5359.

**Stage ii.** To a solution of 2′, 4″ OBz macrolide (100 g, 104.5 mmol) in poly(ethylene glycol) (175 g) and tetrahydrofuran (1 L) was added sodium borohydride (5 g, 132 mmol). The reaction mixture was stirred at 40 °C for 8 h, at which time triethanolamine (75 mL) was added. After stirring for 2 h, the volatiles were removed in vacuo and ethyl acetate (1 L) was added. A 5% potassium dihydrogen phosphate solution (1 L) was added carefully. After vigorous stirring for 30 min, the pH was adjusted to pH = 9 by addition of potassium carbonate, the organic layer was separated, and the aqueous layer was extracted further with ethyl acetate (2 × 250 mL). The combined organics were washed with $NaCl_{(sat.)}$ (500 mL) and dried over $Na_2SO_4$, and the volatiles were removed in vacuo. The crude material was dissolved in acetone (300 mL) with heating. After addition of water (48 mL) the resulting mixture sat overnight, at which time the resulting solid was filtered, rinsed with water (500 mL), and dried in vacuo to yield the 2′, 4″ OBz, $C_9$ hydroxy macrolide (85 g, 85%) as a white solid. An analytical sample was obtained by purification through $SiO_2$ chromatography (12% acetone/hexanes with 1% triethylamine). MS (ESI): 958.6 ($MH^+$). $^1$H NMR ($CDCl_3$): $\delta$ 8.02 (m, 4H), 7.58 (m, 2H), 7.44 (m, 4H), 5.75 (d, $J$ = 9.9, 1H), 5.16 (dd, $J$ = 11.1, 2.1, 1H), 5.07 (m, 2H), 4.95 (t, $J$ = 9.9, 2H), 4.51 (m, 1H), 4.38 (s, 1H), 3.88 (m, 1H), 3.80 (d, $J$ = 5.7, 1H), 3.72 (d, $J$ = 10.2, 1H), 3.54 (s, 3H), 3.46 (s, 1H), 3.33 (s, 3H), 3.29 (m, 1H), 2.82−3.00 (m, 3H), 2.48 (d, $J$ = 15.0, 1H), 2.32 (s, 6H), 2.10 (m, 1H), 1.71−1.91 (m, 4H), 1.38 (m, 2H), 1.35 (s, 3H), 1.22 (s, 6H), 1.21 (d, 6.6, 3H), 1.08 (d, $J$ = 7.2, 6H), 0.94 (m, 9H), 0.78 (t, $J$ = 7.2, 3H), 0.74 (d, $J$ = 7.5, 3H). $^{13}$C NMR ($CDCl_3$): $\delta$ 174.9, 166.1, 165.4, 133.4, 132.6, 130.6, 129.8, 129.6, 128.4, 128.2, 100.0, 96.1, 82.1, 80.2, 78.8, 78.2, 78.12, 77.1, 74.7, 72.9, 72.5, 71.0, 67.5, 63.6, 50.6, 49.6, 45.1, 40.9, 38.1, 35.4, 34.6, 34.1, 32.3, 31.7, 21.3, 21.3, 21.2, 20.3, 18.5, 16.8, 16.5, 16.3, 10.5, 9.4. HPLC: method 1; $t_R$ = 33.20 min. HRMS ($ESI^+$) $m/z$ $[M + H]^+$ calcd for $C_{52}H_{79}NO_{15}$, 958.5522; found, 958.5487.

**Stage iii.** To a solution of 2′, 4″ OBz, $C_9$ hydroxy macrolide (85 g, 89.4 mmol) in acetone (4 L) were added pyridinium *p*-toluenesulfonate (75 g, 292.5 mmol) and 2,2-dimethoxypropane (260 mL, 2112.3 mmol). The solution was stirred at 60 °C for 18 h, at which time the reaction was cooled to room temperature, triethylamine (76.5 mL) was added, and the solution was stirred for 1 h. After removal of the volatiles in vacuo, dichloromethane (1.2 L) was added and the organic layer was washed with 5% $KH_2PO_4$ (2 × 600 mL) and with water (400 mL) and dried over $Na_2SO_4$. After removal of solvents, the 2′, 4″ OBz, $C_9$, $C_{11}$ dimethylketal macrolide (96 g) was obtained. This material was used as is in the next step. An analytical sample was obtained by purification through $SiO_2$ chromatography (15% acetone/hexanes with 1% triethylamine). MS (ESI): 998.6 ($MH^+$). $^1$H NMR ($CDCl_3$): $\delta$ 8.02 (m, 4H), 7.57 (m, 2H), 7.44 (m, 4H), 5.29 (d, $J$ = 4.2, 1H), 5.26 (m, 1H), 5.04 (d, $J$ = 7.8, 1H), 4.95 (d, $J$ = 9.9, 1H), 4.87 (dd, $J$ = 9.9, 2.1, 1H), 4.50 (m, 1H), 4.04 (m, 1H), 3.97 (d, $J$ = 1.2, 1H), 3.81 (d, $J$ = 5.7, 1H), 3.58 (s, 3H), 3.41 (s, 1H), 3.48 (m, 1H), 3.31 (s, 3H), 3.03 (m, 1H), 2.71 (s, 1H), 2.57 (m, 1H), 2.51 (d, $J$ = 15.5, 1H), 2.33 (s, 6H), 2.05−2.15 (m, 2H), 1.45−1.92 (m, 8H), 1.40 (s, 3H), 1.34 (s, 3H), 1.21 (s, 3H), 1.20 (s, 3H), 1.17 (s, 3H), 1.15 (s, 3H), 1.07−1.09 (m, 6H), 0.96−0.98 (m, 6H), 0.84 (t, 7.5, 3H), 0.69 (d, $J$ = 7.2, 3H). $^{13}$C NMR ($CDCl_3$): $\delta$ 176.7, 166.3, 165.3, 133.3, 132.5, 130.9, 130.0, 129.7, 129.6, 128.4, 128.2, 100.9, 99.7, 94.8, 80.4, 79.3, 79.2, 78.2, 77.71, 77.68, 77.2, 74.0, 73.2, 72.4, 70.1, 67.4, 63.7, 63.2, 50.3, 49.4, 45.2, 43.5, 40.9, 35.0, 33.4, 32.5, 31.9, 30.2, 28.1, 24.4, 21.7, 21.4, 21.2, 20.6, 18.4, 17.5, 16.5, 16.3, 14.4, 10.9, 9.6. HPLC: method 1; $t_R$ = 38.54 min. HRMS ($ESI^+$) $m/z$ $[M + H]^+$ calcd for $C_{55}H_{83}NO_{15}$, 998.5835; found, 998.5831.

**Stage iv.** To a solution of 2′, 4″ OBz, $C_9$, $C_{11}$ dimethylketal macrolide (96 g, 96.1 mmol) in ethyl acetate (2 L) cooled to 0 °C was added triethylamine (67 mL, 481.7 mmol). To the resulting solution at 0 °C was added thionyl chloride (30.4 mL, 407 mmol) within 5 min. After stirring at 0 °C for 2 h, the reaction mixture was poured into cold $NaHCO_{3(sat.)}$ (1.5 L). The aqueous layer was separated and extracted further with ethyl acetate (2 × 400 mL). The combined organic layers were washed with $NaCl_{(sat.)}$ (400 mL) and dried over $Na_2SO_4$, and the solvents were removed in vacuo. The resulting foam (86 g) was dissolved in acetone (300 mL) with heating. After addition of water (70 mL) the resulting mixture sat overnight, at which time the resulting solid was filtered, rinsed with water (100 mL), and dried in vacuo to yield the 2′, 4″ OBz, $C_9$, $C_{11}$ dimethylketal $C_{12,21}$ alkene macrolide **2** (44 g, 50% from $C_9$ OH) as a white solid. An analytical sample was obtained by purification through $SiO_2$ chromatography (10% acetone/hexanes with 1% triethylamine). MS (ESI): 980.6 ($MH^+$). $^1$H NMR ($CDCl_3$): $\delta$ 8.00 (m, 4H), 7.55 (m, 2H), 7.42 (m, 4H), 5.38 (s, 1H), 5.31 (s, 1H), 5.26−5.30 (m, 2H), 5.08 (s, 1H), 4.98 (d, $J$ = 7.5, 1H), 4.91 (d, $J$ = 9.6, 1H), 4.77 (d, $J$ = 3.9, 1H), 4.51 (m, 1H), 4.27 (s, 1H), 4.09 (s, 1H), 4.00 (m, 1H), 3.76 (d, $J$ = 5.7, 1H), 3.57 (s, 3H), 3.30 (s, 3H), 3.27 (m, 1H), 3.01 (dt, $J$ = 12.0, 4.2, 1H), 2.47−2.55 (m, 2H), 2.33 (s, 6H), 2.10−2.14 (m, 2H), 1.90−1.93 (m, 1H), 1.43−1.75 (m, 6 H), 1.35 (s, 3H), 1.27 (s, 3H), 1.20 (s, 6H), 1.09−1.16 (m, 6H), 0.94−1.08 (m, 6H), 0.79−0.86 (m, 6H), 0.72 (d, $J$ = 7.2, 3H). $^{13}$C NMR ($CDCl_3$): $\delta$ 175.9, 166.2, 165.2, 143.5, 133.3, 132.4, 130.9, 129.9, 129.6, 129.5, 128.3, 128.1,133.1, 100.4, 100.1, 94.9, 79.6, 79.4, 79.1, 77.8, 77.2, 76.8, 73.1, 72.4, 69.5, 67.6, 63.8, 63.4, 53.4, 49.4, 46.2, 44.1, 40.9, 35.1, 33.2, 33.1, 31.7, 31.5, 27.6, 23.9, 21.3, 21.1, 20.2, 18.5, 15.5, 13.0, 10.7, 10.0. HPLC: method 1; $t_R$ = 40.52 min. HRMS ($ESI^+$) $m/z$ $[M + H]^+$ calcd for $C_{55}H_{81}NO_{14}$, 980.5729; found, 980.5700.

**Compound 3. Stage v.** To 2′, 4″ OBz, $C_9$, $C_{11}$ dimethylketal $C_{12,21}$ alkene macrolide (150 g, 153 mmol) in 2:1 acetonitrile/water (1.5L) was added pyridinium *p*-toluenesulfonate (192.3 g, 756.3

mmol). The solution was heated in a 68 °C oil bath for 17 h. Upon cooling, the solution was diluted with ethyl acetate (2 L), and sodium bicarbonate (96 g, 1150 mmol) was added. The organic layer was then diluted with ethyl acetate (1 L) and washed with $NaHCO_{3(sat.)}$ (2 × 1 L) and $NaCl_{(sat.)}$ (1 L). The combined aqueous layers were back-extracted with ethyl acetate (2 × 1 L) and the combined organic layers dried over $MgSO_4$, filtered, and concentrated to yield $C_{12,21}$ alkene, $C_9$, $C_{11}$ diol as a white solid (130 g, 90%yield). An analytical sample was obtained by purification through $SiO_2$ chromatography (20−40% acetone/hexanes with 0.1% triethylamine). MS (ESI): 940.4 ($MH^+$). $^1$H NMR ($CDCl_3$): $\delta$ 8.02 (m, 4H), 7.58 (m, 2H), 7.45 (m, 4H), 5.51 (m, 1H), 5.26 (s, 1H), 5.23 (s, 1H), 5.08 (m, 1H), 5.02 (d, $J$ = 4.8, 1H), 4.95 (d, $J$ = 3.9, 1H), 4.92 (m, 1H), 4.82 (d, $J$ = 9.3, 1H), 4.52 (m, 1H), 4.41 (bs, 1H), 3.87 (m, 1H), 3.82 (d, $J$ = 8.7, 1H), 3.78 (d, $J$ = 6.3, 1H), 3.53 (s, 3H), 3.37 (m, 1H), 3.33 (s, 3H), 2.94 (m, 1H), 2.77 (d, $J$ = 3.3, 1H), 2.73 (m, 1H), 2.47 (d, $J$ = 15, 1H), 2.32 (s, 6H), 2.12 (m, 1H), 1.5−1.85 (m, 8H), 1.38 (m, 1H), 1.33 (s, 3H), 1.17−1.22 (m, 9H), 0.98 (d, $J$ = 4.8, 3H), 0.96 (s, 3H), 0.95 (s, 3H), 0.85 (t, $J$ = 7.2, 3H), 0.71 (d, $J$ = 7.5, 3H). $^{13}$C NMR ($CDCl_3$): $\delta$ 175.2, 166.1, 165.3, 147.9, 133.3, 132.5, 130.8, 129.8, 129.6, 128.4, 128.1, 113.8, 100.2, 95.8, 80.2, 80.0, 78.8, 78.3, 78.2, 74.2, 72.9, 72.4, 70.8, 67.5, 63.6, 63.5, 50.4, 49.6, 44.8, 40.9, 39.1, 35.4, 35.3, 34.6, 34.4, 31.7, 25.7, 21.7, 21.2, 21.19, 20.3, 18.3, 15.4, 13.7, 10.3, 9.8. HPLC: method 1; $t_R$ = 32.18 min. HRMS ($ESI^+$) $m/z$ $[M + H]^+$ calcd for $C_{52}H_{77}NO_{14}$, 940.5416; found, 940.5392.

**Stage vi.** To $C_{12,21}$ alkene, $C_9$, $C_{11}$ diol macrolide (131.5 g, 139.9 mmol) in 9:1 acetone/water (1.4 L) was added *N*-methylmorpholine *N*-oxide monohydrate (37.8 g, 279.8 mmol), followed by 0.08 M osmium tetroxide in *tert*-butyl alcohol (26.2 mL, 2.1 mmol). The solution was stirred at room temperature for 4 h. The solution was then diluted with ethyl acetate (1 L) and cooled to 0 °C. Upon cooling $Na_2SO_{3(sat.)}$ (500 mL) was added and the solution was stirred for 10 min. The reaction mixture was then warmed to room temperature, diluted with ethyl acetate (1 L), and washed with $NaHCO_{3(sat.)}$ (3 × 1 L) and $NaCl_{(sat.)}$ (1 L). The combined aqueous layers were back-extracted with ethyl acetate (1 L), and the combined organic layers were dried with $MgSO_4$, filtered, and concentrated. Diethyl ether (300 mL) was added and the slurry was stirred for 17 h. The solid was then filtered, rinsed with diethyl ether, and dried in vacuo yielding the $C_9$, $C_{11}$, $C_{12}$, $C_{21}$ tetraol macrolide (112.1 g, 82% yield) as an off-white solid. An analytical sample was obtained by purification through $SiO_2$ chromatography (25% acetone/hexanes with 0.1% triethylamine). MS (ESI): 974.5 ($MH^+$). $^1$H NMR ($CDCl_3$): $\delta$ 8.02 (m, 4H), 7.58 (m, 2H), 7.45 (m, 4H), 5.85 (d, $J$ = 10.8, 1H), 5.37 (dd, $J$ = 11.4, 1.8, 1H), 5.3−5.1 (m, 2H), 4.92−5.00 (m, 2H), 4.50 (m, 1H), 4.40 (s, 1H), 3.87 (m, 1H), 3.73−3.79 (m, 2H), 3.50−3.63 (m, 3H), 3.55 (s, 3H), 3.32 (s, 3H), 3.28 (d, $J$ = 9.6, 1H), 3.09 (s, 1H), 2.95 (m, 1H), 2.83 (m, 1H), 2.48 (d, $J$ = 15.3, 1H), 2.32 (s, 6H), 1.71−2.15 (m, 8H), 1.46−1.62 (m, 2H), 1.38 (m, 1H), 1.34 (s, 3H), 120−1.22 (m, 9H), 1.08 (d, $J$ = 6.9, 3H), 0.91−0.93 (m, 6H), 0.78 (t, $J$ = 7.2, 3H), 0.71 (d, 7.8, 3H). $^{13}$C NMR ($CDCl_3$): $\delta$ 174.6, 166.1, 165.3, 133.4, 132.6, 130.7, 129.8, 129.7, 129.6, 128.4, 128.2, 100.0, 96.0, 85.5, 80.5, 78.8, 78.1, 77.8, 77.2, 75.0, 72.9, 72.3, 69.9, 67.5, 63.7, 63.6, 62.2, 50.5, 49.6, 45.1, 40.9, 38.3, 35.3, 34.6, 33.8, 32.4, 31.6, 21.9, 21.3, 21.2, 21.1, 20.3, 18.5, 17.6, 16.3, 10.5, 9.4. HPLC: method 1; $t_R$ = 29.36 min. HRMS ($ESI^+$) $m/z$ $[M + H]^+$ calcd for $C_{52}H_{79}NO_{16}$, 974.5471; found, 974.5440.

**Stage vii.** To $C_9$, $C_{11}$, $C_{12}$, $C_{21}$ tetraol macrolide (112 g, 115.1 mmol) in dichloromethane (383 mL) at 0 °C under argon were added acetic anhydride (11.9 mL, 126.6 mmol), diisopropylethylamine (22.0 mL, 126.6 mmol), and (dimethylamino)pyridine (141.5 mg, 1.15 mmol). After stirring for 15 min, the solution was placed in a −10 °C refrigerator for 17 h. The solution was diluted with ethyl acetate (3 L), washed with $NaHCO_{3(sat.)}$ (2 × 1 L) and $NaCl_{(sat.)}$ (1 +L), dried over $MgSO_4$, filtered, and concentrated to yield the $C_{21}$ acetoxy, $C_9$, $C_{11}$, $C_{12}$ triol macrolide as an off white solid in quantitative yield. Analytical: $MH^+$ (1016.5). An analytical sample was obtained by purification through $SiO_2$ chromatography (20% acetone/hexanes with 0.1% triethylamine). MS (ESI): 1016.5 ($MH^+$). $^1$H NMR ($CDCl_3$): $\delta$ 8.02 (m, 4H), 7.57 (m, 2H), 7.45 (m, 4H), 5.79 (d, $J$ = 10.2, 1H), 5.25 (dd, $J$ = 11.1, 2.1, 1H), 5.07 (m, 2H), 4.95 (d, $J$ = 6.3, 1H), 4.92 (d, $J$ = 4.2, 1H), 4.51 (m, 1H), 4.48 (s, 1H), 4.10 (s, 2H), 3.84 (m, 1H), 3.81 (s, 1H), 3.78 (d, $J$ = 4.5, 1H), 3.68 (s, 1H), 3.53 (s, 3H), 3.34 (s, 3H), 3.30 (m, 1H), 3.17 (s, 1H), 2.96 (m, 1H), 2.80 (m, 1H), 2.48 (d, $J$ = 15, 1H), 2.33 (s, 6H), 2.15 (m, 1H), 1.82−1.95 (m, 2H), 1.80 (s, 3H), 1.71−1.78 (m, 2H), 1.40−1.59 (m, 4H), 1.36 (s, 3H), 1.20−1.23 (m, 9H), 1.12 (d, 7.2, 3H), 0.95 (d, $J$ = 6.0, 3H), 0.90 (d, $J$ = 7.2, 3H), 0.79 (t, $J$ = 6.6, 3H), 0.77 (d, $J$ = 7.2, 3H). $^{13}$C NMR ($CDCl_3$): $\delta$ 175.09, 170.6, 165.8, 165.0, 133.2, 132.5, 130.4, 129.5, 129.4, 128.2, 128.0, 100.1, 95.9, 82.3, 80.4, 78.7, 77.6, 77.5, 76.8, 74.5, 72.7, 72.3, 69.4, 67.6, 63.4, 63.3, 63.2, 53.4, 50.4, 49.6, 45.2, 40.9, 38.4, 35.3, 34.3, 34.2, 32.3, 32.0, 22.1, 21.3, 21.2, 21.0, 20.8, 20.4, 18.5, 17.0, 16.2, 10.9, 10.0. HPLC: method 1; $t_R$ = 31.56 min. HRMS ($ESI^+$) $m/z$ $[M + H]^+$ calcd for $C_{54}H_{81}NO_{17}$, 1016.5577; found, 1016.5560.

**Stage viii.** To $C_{21}$ acetoxy, $C_9$, $C_{11}$, $C_{12}$ triol macrolide (116.9 g, 115.05 mmol) in dichloromethane (1.15 L) at 0 °C was added Dess−Martin periodinane (58.5 g, 138.1 mmol). The solution was stirred at 0 °C for 14 h. The reaction was diluted with ethyl acetate (3 L), and 1:1 10% $Na_2S_2O_3/NaHCO_{3(sat.)}$ (1 L) was added. The bilayer solution was stirred vigorously for 1 h. The layers were separated, and the organic layer was washed with $NaCl_{(sat.)}$ (1 L), dried over $MgSO_4$, filtered, and concentrated yielding the $C_{21}$ acetoxy, $C_9$ keto, $C_{11}$, $C_{12}$ diol macrolide **3** (117 g, 99% yield) as an off white solid. An analytical sample was obtained by purification through $SiO_2$ chromatography (20% acetone/hexanes with 0.1% triethylamine). MS (ESI): 1014.5 ($MH^+$). $^1$H NMR ($CDCl_3$): $\delta$ 8.01 (m, 4H), 7.57 (m, 2H), 7.45 (m, 4H), 5.06 (m, 2H), 5.00 (d, $J$ = 5.1, 1H), 4.93 (d, $J$ = 9.6, 1H), 4.87 (d, $J$ = 7.2, 1H), 4.47 (m, 1H), 4.17 (d, $J$ = 12.0, 1H), 4.10 (d, $J$ = 12.0, 1H), 3.88 (d, $J$ = 14.1, 1H), 3.82 (m, 2H), 3.79 (d, $J$ = 9.6, 1H), 3.61 (d, $J$ = 6.9, 1H), 3.51 (s, 3H), 3.22 (s, 1H), 2.99 (s, 3H), 2.89−2.97 (m, 2H), 2.71 (m, 1H), 2.58 (m, 1H), 2.45 (d, $J$ = 15.3, 1H), 2.32 (s, 6H), 1.86−1.96 (m, 2H), 1.81 (s, 3H), 1.46−1.78 (m, 6H), 1.36 (s, 3H), 1.16−1.21 (m, 9H), 1.11 (d, $J$ = 6.6, 3H), 1.10 (d, $J$ = 7.2, 3H), 0.92 (d, $J$ = 6.0, 3H), 0.79 (t, $J$ = 7.5, 3H), 0.72 (d, $J$ = 7.5, 3H). $^{13}$C NMR ($CDCl_3$): $\delta$ 219.6, 175.6, 170.0, 165.8, 165.0, 133.1, 132.4, 130.4, 129.6, 129.4, 129.3, 128.1,128.0, 100.3, 95.5, 79.9, 78.8, 78.3, 77.2, 76.5, 74.0, 72.8, 72.3, 67.6, 67.5, 63.3, 62.7, 50.2, 49.6, 44.9, 44.8, 40.8, 39.0, 38.1, 37.6, 35.1, 32.0, 21.6, 21.2, 21.1, 20.7, 19.9, 18.4, 17.7, 15.8, 12.3, 10.8, 9.9. HPLC: method 1; $t_R$ = 32.25 min. HRMS ($ESI^+$) $m/z$ $[M + H]^+$ calcd for $C_{54}H_{79}NO_{17}$, 1014.5420; found, 1014.5411.

**Compound 4. Stage ix.** To $C_{21}$ acetoxy, $C_9$ keto, $C_{11}$, $C_{12}$ diol macrolide (117.2 g, 115.6 mmol) in pyridine (1.15 L) at 0 °C was added methanesulfonyl chloride (44.7 mL, 578 mmol) via syringe. The solution was stirred for 18 h as the solution warmed to room temperature. After concentration of the reaction mixture, water (300 mL) was added and the slurry was stirred vigorously for 17 h; the slurry was filtered and dried in vacuo to yield the $C_{21}$ acetate $C_9$ keto, $C_{11}$ OMs, $C_{12}$ hydroxy macrolide (126.2 g, 100% yield) as a yellow solid. An analytical sample was obtained by purification through $SiO_2$ chromatography (25% acetone/hexanes with 0.1% triethylamine). MS (ESI): 1092.4 ($MH^+$). $^1$H NMR ($CD_3OD$): $\delta$ 8.15 (m, 2H), 8.06 (m, 2H), 7.64 (m, 2H), 7.51 (m, 4H), 5.28 (dd, $J$ = 9.9, 3.9, 1H), 5.07 (dd, $J$ = 9.9, 6.9, 1H), 4.87−4.96 (m, 3H), 4.70 (d, $J$ = 4.8, 1H), 4.6 (m, 1H), 4.46 (d, $J$ = 12, 1H), 4.24 (d, $J$ = 12.0, 1H), 3.96 (dd, $J$ = 9.6, 2.7, 1H), 3.91 (d, $J$ = 7.2, 1H), 3.67 (m, 1H), 3.43 (s, 3H), 3.21 (s, 3H), 3.07−3.16 (m, 1H), 2.68 (m, 1H), 2.64 (s, 3H), 2.54 (d, $J$ = 15.6, 1H), 2.44 (m, 1H), 2.31 (s, 6H), 2.15 (m, 1H), 2.08 (s, 3H), 2.06 (m, 1H), 1.67−1.90 (m, 5H), 1.43 (m, 1H), 1.26 (d, $J$ = 6.3, 3H), 1.2−1.23 (m, 9H), 1.16 (d, $J$ = 7.2, 3H), 1.14 (d, $J$ = 6.3, 3H), 1.06 (m, 1H), 1.02 (d, $J$ = 6.9, 3H), 0.94 (d, $J$ = 7.2, 3H), 0.82 (t, $J$ = 7.5, 3H). $^{13}$C NMR ($CD_3OD$): $\delta$ 177.9, 172.4, 167.9, 167.2, 134.9, 134.4, 131.9, 131.2, 131.0, 129.9, 129.6, 109.8, 102.1, 99.3, 89.0, 85.6, 80.9, 80.5, 80.4, 78.2, 77.3, 74.7, 74.0, 70.1, 67.2, 64.9, 64.4, 50.8, 50.6, 46.8, 41.9, 41.2, 39.0, 38.0, 37.8, 36.5, 32.9, 24.5, 22.0, 21.8, 21.6, 20.8, 19.0, 18.8, 17.1, 14.7, 12.3, 11.6. HPLC: method 1; $t_R$ = 31.21 min.

HRMS (ESI$^+$) *m/z* [M + H]$^+$ calcd for $C_{55}H_{81}NO_{19}S$, 1092.5196; found, 1092.5184.

**Stage x.** To $C_{21}$ acetoxy, $C_9$keto, $C_{11}$ OMs, $C_{12}$ OH macrolide (126 g, 115.6 mmol) in acetone (1.5 L) was added 1,8-diazabicyclo-[5.4.0]undec-7-ene (41.4 mL, 277.4 mmol). The solution was stirred for 5 h at room temperature and then for 40 h at 68 °C. The solution was diluted with ethyl acetate (3 L), washed with water (2 × 1 L), $NaHCO_{3(sat.)}$(1 L), and $NaCl_{(sat.)}$ (1 L), dried over $MgSO_4$, filtered, and concentrated yielding the $C_{21}$ acetoxy, $C_9$, $C_{10}$, $C_{11}$ enone, $C_{12}$ OH macrolide (103.5 g, 90% yield) as an off white solid. An analytical sample was obtained by purification through $SiO_2$ chromatography (25% acetone/hexanes with 0.1% triethylamine). MS (ESI): 996.4 (MH$^+$). $^1$H NMR ($CDCl_3$): $\delta$ 8.02 (m, 4H), 7.57 (m, 2H), 7.44 (m, 4H), 6.29 (d, $J$ = 0.9, 1H), 5.27 (dd, $J$ = 10.8, 2.1, 1H), 5.05 (dd, $J$ = 10.5, 7.5, 1H), 4.98 (d, $J$ = 4.5, 1H), 4.92 (d, $J$ = 9.6, 1H), 4.85 (d, $J$ = 7.5, 1H), 4.49 (m, 1H), 4.24 (d, $J$ = 11.7, 1H), 4.15 (d, $J$ = 11.7, 1H), 3.78 (d, $J$ = 9.3, 2H), 3.69 (d, $J$ = $J$ = 6.9, 1H), 3.51 (s, 3H), 2.97 (s, 3H), 2.87−2.95 (m, 2H), 2.68−2.75 (m, 2H), 2.45 (d, $J$ = 15, 1H), 2.31 (s, 6H), 2.04 (s, 3H), 1.98 (s, 3H), 1.68−1.95 (m, 6H), 1.4−1.6 (m, 3H), 1.30 (s, 3H), 1.17−1.20 (m, 12H), 0.94 (d, $J$ = 6.0, 3H), 0.83 (t, $J$ = 7.2, 3H), 0.75 (d, $J$ = 7.2, 3H). $^{13}$C NMR ($CDCl_3$): $\delta$ 205.7, 174.9, 170.9, 165.9, 165.1, 140.7, 135.8, 133.2, 132.4, 130.6, 129.7, 129.5, 129.4, 128.2, 128.1, 100.6, 95.6, 79.4, 78.9, 78.7, 77.6, 77.3, 74.3, 72.8, 72.3, 67.7, 67.6, 63.7, 63.3, 50.1, 49.7, 45.1, 42.6, 40.9, 40.3, 39.5, 35.3, 31.7, 22.8, 21.3, 20.9, 20.0, 19.5, 18.4, 15.8, 14.0, 10.9, 9.9. HPLC: method 1; $t_R$ = 32.56 min. HRMS (ESI$^+$) *m/z* [M + H]$^+$ calcd for $C_{54}H_{77}NO_{16}$, 996.5315; found, 996.5312.

**Stage xi.** To $C_{21}$ acetate, $C_9$, $C_{10}$, $C_{11}$ enone $C_{12}$ OH macrolide (100 g, 100.4 mmol) in methanol (1.3 L) was added 3 M $HCl_{(aq)}$ (660 mL). The solution was heated at 40 °C for 12 h; upon cooling, the solution was filtered and the solid was rinsed with water (200 mL). The resulting filtrate was diluted with water (6 L), and the pH of the solution was adjusted to pH 9−10 by addition of 10% $NaOH_{(aq)}$. After agitation for 1 h, the solid was filtered, washed with water (2 × 2 L), and dried at 60 °C dried in vacuo. Ethyl acetate (200 mL) was added to the crude material (77 g), and the solution was heated at 70 °C for 1 h. Upon cooling, the slurry was cooled at 10 °C for 1 h, and the solid was filtered, rinsed with chilled ethyl acetate (70 mL), and dried in vacuo yielding the $C_9$, $C_{10}$, $C_{11}$ enone, $C_3$, $C_{12}$, $C_{21}$ triol macrolide **4** (46.0 g, 66%). An analytical sample was obtained by purification through $SiO_2$ chromatography (40% acetone/hexanes with 0.1% triethylamine). MS (ESI): 690.4 (MH$^+$). $^1$H NMR ($CDCl_3$): $\delta$ 8.07 (m, 2H), 7.52 (m, 1H), 7.43 (m, 2H), 6.11 (d, $J$ = 1.2, 1H), 5.11 (dd, $J$ = 11.1, 2.4, 1H), 5.00 (dd, $J$ = 9.6, 7.5, 1H), 4.79 (d, $J$ = 8.1, 1H), 3.82 (d, $J$ = 3.0, 1H), 3.55−3.75 (m, 4H), 3.09 (s, 3H)), 3.00 (m, 2H), 2.78−2.90 (m, 2H), 2.33 (m, 1H), 2.25 (s, 6H), 2.01 (d, $J$ = 0.9, 3H), 1.42−1.91 (m, 8H), 1.30 (s, 3H), 1.29 (d, $J$ = 6.6, 3H), 1.19 (d, $J$ = 6.6, 3H), 0.76−0.83 (m, 9H). $^{13}$C NMR ($CDCl_3$): $\delta$ 208.0, 175.4, 165.6, 14108, 135.6, 132.7, 130.6, 129.9, 128.3, 102.4, 80.0, 79.0, 77.2, 75.8, 75.7, 72.2, 69.3, 64.9, 64.0, 49.3, 43.9, 40.8, 38.5, 38.3, 38.0, 31.0, 22.4, 21.2, 20.0, 18.0, 14.1, 13.8, 10.7, 8.5. HPLC: method 1; $t_R$ = 19.53 min. HRMS (ESI$^+$) *m/z* [M + H]$^+$ calcd for $C_{37}H_{57}NO_{11}$, 692.4004; found, 692.4004.

**Compound 5. Stage xii.** To a solution of $C_{21}$, $C_3$ hydroxy macrolide (60.0 g, 86.71 mmol) in tetrahydrofuran (250 mL) under an Ar atmosphere were added methyl sulfide (22.2 mL, 364 mmol) and diisopropylethylamine (57.4 mL, 329.5 mmol). The resulting solution was cooled to −20 °C, at which time a solution of *N*-chlorosuccinimide (44.0 g, 329.5 mmol) in tetrahydrofuran (500 mL) was added via a dropping funnel with the internal temperature remaining between −10 and −15 °C. The resulting solution was stirred at this temperature range for 1 h, at which time additional methyl sulfide (3.7 mL, 60.8 mmol), diisopropylethylamine (9.6 mL, 55.1 mmol), and solid *N*-chlorosuccinimide (7.3 g, 54.7 mmol) were added. After stirring for an additional 15 min, the reaction was partitioned between ethyl acetate (2 L) and 0.5 N NaOH (0.5 L). The organic layer was washed further with 0.5 N NaOH (3 × 0.5 L) and $NaCl_{(sat.)}$ (0.5 L), dried over $MgSO_4$, filtered, and concentrated to yield 71.3 g of an off white solid. Hexanes (900 mL) were added, and after stirring overnight the solid was filtered and dried in vacuo yielding the $C_3$, $C_{21}$ oxo, $C_9$, $C_{10}$, $C_{11}$ enone-$C_{12}$-ol macrolide (59.7 g, 99% yield) as a white solid. The material was >90% pure by LC and NMR analysis and could be used directly in the subsequent olefination step. An analytical sample was obtained by purification through $SiO_2$ chromatography (15−20% acetone/hexanes with 0.1% triethylamine). MS (ESI): 688.4 (MH$^+$). $^1$H NMR ($CDCl_3$): $\delta$ 9.65 (s, 1H), 8.02 (d, $J$ = 7.2, 2H), 7.56 (m, 1H), 7.43 (m, 2H), 6.84 (s, 1H), 5.14 (dd, $J$ = 7.8, 3.9, 1H), 5.02 (dd, $J$ = 10.5, 7.8, 1H), 4.50 (d, $J$ = 7.5, 1H), 4.18 (d, $J$ = 8.4, 1H), 3.98 (s, 1H), 3.59−3.66 (m, 2H), 3.29−3.32 (m, 1H), 2.95 (s, 3H), 2.75−2.89 (m, 1H), 2.26 (s, 6H), 1.71−1.89 (m, 3H), 1.64 (d, 0.9, 3H), 1.35−1.57 (m, 5H), 1.20−1.28 (m, 2H), 1.32 (d, $J$ = 6.6, 3H), 1.29 (d, $J$ = 6.6, 3H), 1.14 (d, $J$ = 6.6, 3H), 0.92 (d, $J$ = 7.5, 3H), 0.85 (t, $J$ = 7.5, 3H). $^{13}$C NMR ($CDCl_3$): $\delta$ 205.3, 203.7, 199.6, 168.8, 165.0, 143.4, 133.6, 132.8, 130.4, 129.8, 128.3, 102.0, 80.0, 79.2, 78.9, 77.2, 71.9, 69.2, 63.7, 50.9, 50.7, 47.4, 40.7, 39.2, 35.5, 31.2, 22.9, 21.9, 21.0, 18.0, 14.9, 14.0, 12.9, 10.5. HPLC: method 1; $t_R$ = 25.87 min. HRMS (ESI$^+$) *m/z* [M + H]$^+$ calcd for $C_{37}H_{53}NO_{11}$, 688.3691; found, 688.3688.

**Stage xiii.** To methyl triphenylphosphonium bromide (53.8 g, 152.6 mmol) in tetrahydrofuran (500 mL) at −78 °C was added potassium bis(trimethylsilyl)amide/0.5 M in toluene (295 mL, 147.5 mmol). The cooling bath was removed, and the anion solution was stirred for 1 h. After cooling the anion solution back to −78 °C, $C_{21}$ aldehyde macrolide (70.0 g, 101.8 mmol) in tetrahydrofuran (270 mL) was added. The cooling bath was removed, and the anion solution was stirred for 5 h, at which time $NH_4Cl_{(sat.)}$ (200 mL) was added. After two layers formed, the reaction mixture was added to ethyl acetate (2 L) and $NH_4Cl_{(sat.)}$ (500 mL). Upon mixing and separating off the aqueous layer, the organic layer was washed with $NH_4Cl_{(sat.)}$ (3 × 500 mL) and $NaCl_{(sat.)}$ (500 mL), dried over $MgSO_4$, filtered, and concentrated. Purification through $SiO_2$ chromatography (15−20% acetone/hexanes with 0.1% triethylamine) yielded the $C_{12}$ vinyl, $C_3$ oxo, $C_9$, $C_{10}$, $C_{11}$ enone-$C_{12}$-ol macrolide **5** (35.4 g, 51% yield) as a white solid. MS (ESI): 686.4 (MH$^+$). $^1$H NMR ($CDCl_3$): $\delta$ 8.02 (d, $J$ = 7.2, 2H), 7.55 (m, 1H), 7.43 (m, 2H), 6.70 (d, $J$ = 1.2, 1H), 5.88 (dd, $J$ = 17.4, 10.8, 1H), 5.37 (dd, $J$ = 17.4, 1.2, 1H), 5.25 (dd, $J$ = 10.8, 1.2, 1H), 5.00 (dd, $J$ = 10.5, 7.5, 1H), 4.95 (dd, $J$ = 9.0, 3.3, 1H), 4.49 (d, $J$ = 7.5, 1H), 4.16 (d, $J$ = 8.1, 1H), 3.61 (m, 2H), 3.25 (m, 1H), 2.92 (s, 3H), 2.81 (m, 2H), 2.25 (s, 6H), 1.87 (d, 0.9, 3H), 1.78 (m, 2H), 1.39−1.47 (m, 2H), 1.26−1.33 (m, 11H), 1.12 (d, $J$ = 6.6, 3H), 0.92 (d, $J$ = 7.5, 3H), 0.86 (t, $J$ = 7.5, 3H). $^{13}$C NMR ($CDCl_3$): $\delta$ 206.7, 204.5, 169.6, 165.1, 140.7, 140.0, 136.5, 132.7, 130.5, 129.8, 128.2, 115.9, 101.9, 81.1, 78.3, 77.2, 75.3, 71.9, 69.1, 63.7, 51.0, 50.6, 46.9, 40.7, 39.6, 36.5, 31.3, 22.5, 21.8, 21.0, 18.3, 14.4, 14.0, 13.5, 10.7. HPLC: method 1; $t_R$ = 27.66 min. HRMS (ESI$^+$) *m/z* [M + H]$^+$ calcd for $C_{38}H_{55}NO_{10}$, 686.3898; found, 686.3869.

**Compounds 6a−6z. Stage xiv.** To a solution of $C_{12}$ vinyl $C_9$, $C_{10}$, $C_{11}$ enone, $C_3$ oxo, $C_{12}$ OH macrolide (12.48 g, 18.2 mmol) and carbonyldiimidazole (7.37 g, 45.5 mmol) in tetrahydrofuran (180 mL) at 0 °C was added sodium hydride, 60% dispersion in mineral oil, (1.09 g, 27.3 mmol). After stirring for 7 h, while still at 0 °C, $NaHCO_{3\ (sat.)}$ (5 mL) was added cautiously to quench the excess hydride. The mixture was then diluted with ethyl acetate (600 mL), washed with $NaHCO_{3\ (sat.)}$ (4 × 200 mL) and $NaCl_{\ (sat.)}$ (200 mL), dried over $MgSO_4$, filtered, concentrated, and dried in vacuo yielding crude $C_{12}$ vinyl $C_9$, $C_{10}$, $C_{11}$ enone, $C_3$ oxo, $C_{12}$ OCO imidazoyl macrolide (14.6 g). The crude material was used in the next step without further purification. MS (ESI): 780.5 (MH$^+$) and 686.5 (hydrolyzed MH$^+$)

**Stage xv. Procedure A for Final $C_{12}$ Vinyl Ketolide.** $C_{12}$ vinyl imidazole carbamate macrolide (1 equiv) was added to amino tethered heterocycle (2.0 equiv); a 10% water/acetonitrile solution was added such that the concentration was 0.25 M. The solution was heated in a 65 °C oil bath for 12 h. Upon cooling, the reaction mixture was diluted with ethyl acetate and washed with $NaHCO_{3\ (sat.)}$ (3×) and $NaCl_{(sat.)}$ (1×), dried over $MgSO_4$, filtered, and concentrated. To the crude material was added methanol (5 mL/mmol), and the solution was heated at 65 °C for 16 h. Upon

concentrating, the material was purified by RP HPLC and/or $SiO_2$ chromatography (0−5% MeOH/DCM with 0.1% triethylamine) yielding $C_{12}$ vinyl ketolide.

**6a.** Following procedure A using the $C_{12}$ vinyl imidazolyl carbamate macrolide and 4-imidazo[4,5-*b*]pyridin-1-yl-butylamine yielded **6a** (29% yield) as a white solid. MS (ESI): 798.0 ($MH^+$). HPLC: method 1; $t_R$ = 12.36 min. $^1H$ NMR ($CDCl_3$): $\delta$ 8.55 (dd, $J$ = 4.8, 1.2, 1H), 8.16 (s, 1H), 7.80 (dd, $J$ = 8.4, 1.5, 1H,) 7.22 (dd, $J$ = 8.1, 4.8, 1H), 5.95 (dd, $J$ = 16.8, 10.8, 1H), 5.71 (dd, $J$ = 17.1, 1.5, 1H), 5.55 (dd, $J$ = 11.1,1.5, 1H), 4.95 (dd, $J$ = 10.5, 2.4, 1H), 4.32 (d, $J$ = 7.2, 1H), 4.21−4.26 (m, 3H), 3.89 (q, $J$ = 6.9, 1H), 3.60−3.82 (m, 2H), 3.71 (s, 1H), 3.5−3.62 (m, 1H), 3.31 (dd, $J$ = 9.9, 7.2, 1H), 3.06−3.16 (m, 2H), 2.59 (s, 3H), 2.52−2.58 (m, 1H), 2.47 (s, 6H), 1.42−1.94 (m, 12H), 1.37 (d, $J$ = 6.9, 3H), 1.33 (s, 3H), 1.31 (d, $J$ = 7.5, 3H), 1.27 (d, $J$ = 6.0, 3H), 1.10 (d, $J$ = 6.9, 3H), 0.84 (d, $J$ = 6.9, 3H), 0.77 (t, $J$ = 7.5, 3H). Anal. ($C_{42}H_{63}N_5O_{10}$*1.0$H_2O$) C, H, N.

**6b.** Following procedure A using the $C_{12}$ vinyl imidazolyl carbamate macrolide and 4-imidazo[4,5-*b*]pyridin-3-yl-butylamine yielded **6b** (69% yield) as a white solid. MS (ESI): 798.0 ($MH^+$). HPLC: method 1; $t_R$ = 12.84 min. $^1H$ NMR ($CDCl_3$): $\delta$ 8.38 (dd, $J$ = 4.8, 1.2, 1H), 8.11 (s, 1H), 8.06 (dd, $J$ = 8.1, 1.2, 1H) 7.22 (dd, $J$ = 8.1, 4.8, 1H), 5.95 (dd, $J$ = 16.8, 10.8, 1H), 5.71 (dd, $J$ = 17.1, 1.5, 1H), 5.55 (dd, $J$ = 11.1,1.5, 1H), 4.95 (dd, $J$ = 10.5, 2.4, 1H), 4.21−4.42 (m, 4H), 3.87 (q, $J$ = 6.9, 1H), 3.52−3.76 (m, 2H), 3.72 (s, 1H), 3.5−3.62 (m, 1H), 3.29 (dd, $J$ = 10.2, 7.2, 1H), 3.02−3.16 (m, 2H), 2.60 (s, 3H), 2.52−2.58 (m, 1H), 2.44 (s, 6H), 1.42−2.04 (m, 12H), 1.36 (d, $J$ = 6.9, 3H), 1.33 (s, 3H), 1.31 (d, $J$ = 7.8, 3H), 1.27 (d, $J$ = 6.3, 3H), 1.11 (d, $J$ = 7.2, 3H), 0.84 (d, $J$ = 6.9, 3H), 0.80 (t, $J$ = 7.5, 3H). ($C_{42}H_{63}N_5O_{10}$*1.8$H_2O$) C, H, N.

**6c.** Following procedure A using the $C_{12}$ vinyl imidazolyl carbamate macrolide and 4-imidazo[4,5-*b*]pyridin-1-yl-4-methyl-pentylamine yielded **6c** (16% yield) as a white solid. MS (ESI): 826.0 ($MH^+$). HPLC: method 1; $t_R$ = 13.05 min. $^1H$ NMR ($CDCl_3$): $\delta$ 8.54 (dd, $J$ = 4.5, 1.2, 1H), 8.23 (s, 1H), 7.97 (dd, $J$ = 8.1, 1.5, 1H) 7.19 (dd, $J$ = 8.4, 4.8, 1H), 5.92 (dd, $J$ = 16.8, 10.8, 1H), 5.68 (dd, $J$ = 17.1, 1.2, 1H), 5.54 (dd, $J$ = 11.1,1.2, 1H), 4.90 (dd, $J$ = 10.5, 2.4, 1H), 4.32 (d, $J$ = 7.2, 1H), 4.21 (d, $J$ = 9.0, 1H), 3.89 (q, $J$ = 6.6, 1H), 3.63 (s, 1H), 3.44−3.62 (m, 3H), 3.32 (dd, $J$ = 10.2, 7.5, 1H), 2.97−3.16 (m, 2H), 2.52−2.58 (m, 1H), 2.47 (s, 6H), 2.44 (s, 3H), 2.08 (t, $J$ = 8.4, 2H), 1.78−1.84 (m, 6H), 1.75 (s, 3H), 1.73 (s, 3H), 1.41−1.58 (m, 4H), 1.37 (d, $J$ = 6.9, 3H), 1.28−1.31 (m, 9H), 1.10 (d, $J$ = 6.9, 3H), 0.77−0.82 (m, 6H). Anal. ($C_{44}H_{67}N_5O_{10}$*0.9 $H_2O$) C, H, N.

**6d.** Following procedure A using the $C_{12}$ vinyl imidazolyl carbamate macrolide and 4-pyrrolo[3,2-*b*]pyridinylbutylamine yielded **6d** (37% yield) as a white solid. MS (ESI): 798.0 ($MH^+$). HPLC: method 1; $t_R$ = 12.96 min. $^1H$ NMR ($CDCl_3$): $\delta$ 8.42 (dd, $J$ = 4.8, 1.2, 1H), 7.68 (d, $J$ = 8.1, 1H), 7.36 (d, $J$ = 3.3, 1H) 7.08 (dd, $J$ = 8.4, 4.5, 1H), 6.67 (d, $J$ = 4.2, 1H), 5.95 (dd, $J$ = 16.8, 10.8, 1H), 5.71 (dd, $J$ = 17.1, 1.5, 1H), 5.55 (dd, $J$ = 11.1,1.5, 1H), 4.95 (dd, $J$ = 10.5, 2.4, 1H), 4.28 (d, $J$ = 7.2, 1H), 4.24 (d, 9.0, 1H), 4.16 (t, $J$ = 7.5, 2H), 3.89 (q, $J$ = 6.9, 1H), 3.50−3.80 (m, 3H), 3.72 (s, 1H), 3.32 (dd, $J$ = 10.2, 7.2, 1H), 3.03−3.13 (m, 2H), 2.59 (s, 3H), 2.45−2.55 (m, 1H), 2.30 (s, 6H), 1.42−1.94 (m, 12H), 1.38 (d, $J$ = 6.9, 3H), 1.33 (s, 3H), 1.31 (d, $J$ = 7.5, 3H), 1.25 (d, $J$ = 6.0, 3H), 1.10 (d, $J$ = 6.9, 3H), 0.84 (d, $J$ = 6.9, 3H), 0.78 (t, $J$ = 7.2, 3H). Anal. ($C_{43}H_{64}N_4O_{10}$) C, H, N.

**6e.** Following procedure A using the $C_{12}$ vinyl imidazolyl carbamate macrolide and 4-(3-chloropyrrolo[3,2-*b*]pyridinyl)butylamine yielded **6e** (37% yield) as a white solid. MS (ESI): 798.0 ($MH^+$). HPLC: method 1; $t_R$ = 13.39 min. $^1H$ NMR ($CDCl_3$): $\delta$ 8.51 (dd, $J$ = 4.8, 1.2, 1H), 7.69 (dd, $J$ = 8.4, 1.2, 1H), 7.37 (s, 1H) 7.15 (dd, $J$ = 8.4, 4.8, 1H), 5.93 (dd, $J$ = 16.8, 10.8, 1H), 5.71 (dd, $J$ = 17.1, 1.5, 1H), 5.56 (dd, $J$ = 11.1,1.5, 1H), 4.95 (dd, $J$ = 10.5, 2.4, 1H), 4.31 (d, $J$ = 7.5, 1H), 4.24 (d, 9.0, 1H), 4.14 (t, $J$ = 7.5, 2H), 3.89 (q, $J$ = 6.9, 1H), 3.50−3.80 (m, 3H), 3.70 (s, 1H), 3.30 (dd, $J$ = 10.2, 7.2, 1H), 3.03−3.13 (m, 2H), 2.66−2.78 (m, 1H), 2.58 (s, 3H), 2.45 (s, 6H), 1.42−1.94 (m, 12H), 1.38 (d, $J$ = 6.9, 3H), 1.33 (s, 3H), 1.31 (d, $J$ = 7.5, 3H), 1.27 (d, $J$ = 6.0, 3H), 1.11 (d, $J$ = 6.9, 3H), 0.84 (d, $J$ = 6.9, 3H), 0.77 (t, $J$ = 7.2, 3H). Anal. ($C_{43}H_{63}ClN_4O_{10}$) C, H, Cl, N.

**6f.** Following procedure A using the $C_{12}$ vinyl imidazolyl carbamate macrolide and 4-(6-methyl-9*H*-purin-9-yl)butan-1-amine yielded **6f** (10% yield) as a white solid. MS (ESI): 814.0 ($MH^+$). HPLC: method 1; $t_R$ = 12.47 min. $^1H$ NMR ($CDCl_3$): $\delta$ 8.81 (s, 1H) 8.07 (s, 1H), 5.94 (dd, $J$ = 17.4, 11.1, 1H), 5.70 (dd, $J$ = 17.1, 1.2, 1H), 5.55 (dd, $J$ = 11.1,1.2, 1H), 4.91 (dd, $J$ = 10.8, 2.4, 1H), 4.21−4.39 (m, 4H), 3.85 (q, $J$ = 6.9, 1H), 3.54−3.78 (m, 3H), 3.68 (s, 1H), 3.36 (dd, $J$ = 9.9, 7.2, 1H), 3.01−3.11 (m, 2H), 2.87 (s, 3H), 2.80−2.86 (m, 1H), 2.54 (s, 6H), 1.38−2.00 (m, 12H), 1.34 (d, $J$ = 6.9, 3H), 1.27−1.31 (m, 12H), 1.11 (d, $J$ = 6.9, 3H), 0.84 (d, $J$ = 6.9, 3H), 0.79 (t, $J$ = 7.5, 3H). Anal. ($C_{42}H_{64}N_6O_{10}$·2.4$H_2O$) C, H, N.

**6g.** Following procedure A using the $C_{12}$ vinyl imidazolyl carbamate macrolide and 1-(4-aminobutyl)indole-4-ylamine yielded **6g** (11% yield) as a white solid. MS (ESI): 812.0 ($MH^+$). HPLC: method 2; $t_R$ = 6.66 min. $^1H$ NMR ($CDCl_3$): $\delta$ $^1H$ NMR ($CDCl_3$): $\delta$ 7.01 (d, $J$ = 3.2, 1H), 6.97 (d, $J$ = 7.6, 1H), 6.80 (d, $J$ = 8.3, 1H), 6.37 (d, $J$ = 0.9, 1H), 6.35 (d, $J$ = 3.2, 1H), 5.94 (dd, $J$ = 17.3, 11.0, 1H), 5.70 (dd, $J$ = 17.1, 1.46, 1H), 5.54 (dd, $J$ = 11.0, 1.465, 1H), 4.98 (dd, $J$ = 10.74, 2.44, 1H), 4.27 (m, 2H), 4.10 (m, 2H), 3.89 (q, J − 6.34, 1H), 3.74 (s, 1H), 3.47−3.71 (m, 3H), 3.05−3.21 (m, 2H), 2.62 (s, 3H), 2.41−2.61 (m, 2H), 2.26 (s, 6H), 1.49−1.85 (m, 4H), 1.21−1.47 (m, 15H), 1.34 (s, 3H), 1.24 (d, $J$ = 6.1, 3H), 1.09 (d, $J$ = 6.84, 3H), 0.78−0.85 (m, 6H). Anal. ($C_{44}H_{66}N_4O_{10}$·0.7$H_2O$) C, H, N.

**6h.** Following procedure A using the $C_{12}$ vinyl imidazolyl carbamate macrolide and 4-(5-methoxy-1*H*-pyrrolo[3,2-*b*]pyridin-1-yl)butan-1-amine yielded **6h** (25% yield) as a white solid. MS (ESI): 828.0 ($MH^+$). $^1H$ NMR ($CDCl_3$): $\delta$ 7.58 (d, $J$ = 8.7, 1H), 7.21 (d, $J$ = 2.7, 1H), 6.57 (d, $J$ = 8.7, 1H), 6.49 (d, $J$ = 3.0, 1H), 5.95 (dd, $J$ = 17.4, 11.1, 1H), 5.70 (dd, $J$ = 17.1, 1.2, 1H), 5.55 (dd, $J$ = 11.1,1.2, 1H), 4.94 (dd, $J$ = 10.8, 2.4, 1H), 4.31 (d, $J$ = 7.2, 1H), 4.24 (d, $J$ = 9.0, 1H), 4.10 (t, $J$ = 7.5, 2H), 3.99 (s, 3H), 3.88 (q, $J$ = 6.9, 1H), 3.54−3.78 (m, 3H), 3.71 (s, 1H), 3.31 (dd, $J$ = 9.9, 7.2, 1H), 3.03−3.13 (m, 2H), 2.67−2.82 (m, 1H), 2.59 (s, 3H), 2.46 (s, 6H), 1.41−1.87 (m, 12H), 1.37 (d, $J$ = 6.9, 3H), 1.32 (s, 3H), 1.30 (d, $J$ = 6.9, 3H), 1.27 (d, $J$ = 6.0, 3H), 1.10 (d, $J$ = 6.9, 3H), 0.84 (d, $J$ = 6.6, 3H), 0.77 (t, $J$ = 7.5, 3H). Anal. ($C_{44}H_{66}N_4O_{11}$·1.3$H_2O$) C, H, N.

**6i.** Following procedure A using the $C_{12}$ vinyl imidazolyl carbamate macrolide and 4-(4-(3-pyridyl)imidazolyl)butylamine yielded **6i** (39% yield) as a white solid. MS (ESI): 824.1 ($MH^+$). HPLC: method 1; $t_R$ = 11.75 min. $^1H$ NMR ($CDCl_3$): $\delta$ 8.96 (d, $J$ = 2.1, 1H), 8.44 (dd, $J$ = 4.8, 1.5, 1H), 8.08 (dt, $J$ = 7.8, 1.8, 1H), 7.54 (d, $J$ = 1.2, 1H) 7.34 (d, $J$ = 0.9, 1H), 7.29 (m, 1H), 5.95 (dd, $J$ = 16.8, 10.8, 1H), 5.71 (dd, $J$ = 17.1, 1.5, 1H), 5.55 (dd, $J$ = 11.1,1.5, 1H), 4.95 (dd, $J$ = 10.5, 2.4, 1H), 4.28 (d, $J$ = 7.2, 1H), 4.23 (d, $J$ = 9.0, 1H), 4.01 (t, $J$ = 7.2, 2H), 3.89 (q, $J$ = 6.9, 1H), 3.60−3.80 (m, 2H,), 3.71 (s, 1H), 3.5−3.62 (m, 1H), 3.22 (dd, $J$ = 10.2, 7.2, 1H), 3.06−3.16 (m, 2H), 2.61 (s, 3H), 2.55−2.58 (m, 1H), 2.35 (s, 6H), 1.42−1.94 (m, 12H), 1.37 (d, $J$ = 6.9, 3H), 1.32 (s, 3H), 1.31 (d, $J$ = 7.5, 3H), 1.25 (d, $J$ = 6.0, 3H), 1.10 (d, $J$ = 6.9, 3H), 0.84 (d, $J$ = 6.9, 3H), 0.78 (t, $J$ = 7.5, 3H). Anal. ($C_{44}H_{65}N_5O_{10}$·1.5$H_2O$) C, H, N.

**6j.** Following procedure A using the $C_{12}$ vinyl imidazolyl carbamate macrolide and 4-[4-(6-methyl-pyridin-3-yl)-imidazol-1-yl]-butylamine yielded **6j** (39% yield) as a white solid. MS (ESI): 838.1 ($MH^+$). HPLC: method 1; $t_R$ = 11.69 min. $^1H$ NMR ($CDCl_3$): $\delta$ 8.83 (d, $J$ = 1.8, 1H), 7.97 (dd, $J$ = 7.8, 2.1, 1H), 7.53 (d, $J$ = 1.2, 1H) 7.27 (d, $J$ = 1.2, 1H), 7.15 (d, $J$ = 8.1, 1H), 5.95 (dd, $J$ = 16.8, 10.8, 1H), 5.71 (dd, $J$ = 17.1, 1.5, 1H), 5.55 (dd, $J$ = 11.1,1.5, 1H), 4.95 (dd, $J$ = 10.5, 2.4, 1H), 4.28 (d, $J$ = 7.2, 1H), 4.23 (d, $J$ = 9.0, 1H), 4.0 (t, $J$ = 7.2, 2H), 3.89 (q, $J$ = 6.9, 1H), 3.62−3.78 (m, 2H), 3.71 (s, 1H), 3.5−3.62 (m, 1H), 3.22 (dd, $J$ = 9.9, 7.2, 1H), 3.06−3.16 (m, 2H), 2.61 (s, 3H), 2.55−2.58 (m, 1H) 2.55 (s, 3H), 2.35 (s, 6H), 1.54−1.93 (m, 12H), 1.36 (d, $J$ = 6.9, 3H), 1.33 (s, 3H), 1.31 (d, $J$ = 7.5, 3H), 1.25 (s, $J$ = 6.3, 3H), 1.10 (d, $J$ = 6.9, 3H), 0.84 (d, $J$ = 6.9, 3H), 0.79 (t, $J$ = 7.2, 3H). Anal. ($C_{45}H_{67}N_5O_{10}$) C, H, N.

**6k.** Following procedure A using the $C_{12}$ vinyl imidazolyl carbamate macrolide and 4-[4-(6-chloro-pyridin-3-yl)-imidazol-1-yl]-butylamine yielded **6k** (37% yield) as a white solid. MS (ESI): 858.2 ($MH^+$). HPLC: method 1; $t_R$ = 13.58 min. $^1$H NMR ($CDCl_3$): $\delta$ 8.73 (d, $J$ = 2.1, 1H), 8.06 (dd, $J$ = 8.1, 2.4, 1H), 7.54 (s, 1H) 7.34 (d, $J$ = 0.9, 1H), 7.32 (d, $J$ = 8.4, 1H,), 5.95 (dd, $J$ = 16.8, 10.8, 1H,), 5.71 (dd, $J$ = 17.1, 1.5, 1H), 5.55 (dd, $J$ = 11.1,1.5, 1H), 4.94 (dd, $J$ = 10.5, 2.4, 1H), 4.28 (d, $J$ = 7.2, 1H), 4.23 (d, $J$ = 9.0, 1H), 4.0 (t, $J$ = 7.2, 2H), 3.89 (q, $J$ = 6.9, 1H), 3.62−3.78 (m, 2H), 3.71 (s, 1H), 3.5−3.62 (m, 1H), 3.22 (dd, $J$ = 10.2, 7.2, 1H), 3.06−3.16 (m, 2H), 2.60 (s, 3H), 2.50−2.58 (m, 1H), 2.27 (s, 6H), 1.42−1.93 (m, 12H), 1.36 (d, $J$ = 6.9, 3H), 1.33 (s, 3H), 1.31 (d, $J$ = 7.8, 3H), 1.25 (d, $J$ = 6.0, 3H), 1.10 (d, $J$ = 7.2, 3H), 0.84 (d, $J$ = 6.9, 3H), 0.78 (t, $J$ = 7.5, 3H). Anal. ($C_{44}H_{64}ClN_5O_{10}$) C, H, N; Cl: calcd, 4.13; found, 3.63.

**6l.** Following procedure A using the $C_{12}$ vinyl imidazolyl carbamate macrolide and 4-[4-(6-fluoro-pyridin-3-yl)-imidazol-1-yl]-butylamine yielded **6l** (38% yield) as a white solid. MS (ESI): 842.0 ($MH^+$). HPLC: method 1; $t_R$ = 13.24 min. $^1$H NMR ($CDCl_3$): $\delta$ 8.55 (d, $J$ = 2.4, 1H), 8.18 (td, $J$ = 8.4, 2.4, 1H), 7.53 (d, $J$ = 1.2, 1H) 7.30 (d, $J$ = 1.2, 1H), 6.94 (dd, $J$ = 8.4, 2.4, 1H), 5.95 (dd, $J$ = 17.4, 11.1, 1H), 5.71 (dd, $J$ = 17.4, 1.5, 1H), 5.55 (dd, $J$ = 11.1,1.5, 1H), 4.95 (dd, $J$ = 10.8, 2.4, 1H), 4.28 (d, $J$ = 7.2, 1H), 4.23 (d, $J$ = 9.0, 1H), 4.0 (t, $J$ = 7.2, 2H), 3.89 (q, $J$ = 6.9, 1H), 3.62−3.78 (m, 2H), 3.71 (s, 1H), 3.5−3.62 (m, 1H), 3.22 (dd, $J$ = 10.2, 7.2, 1H), 3.06−3.16 (m, 2H), 2.60 (s, 3H), 2.50−2.58 (m, 1H), 2.33 (s, 6H), 1.42−1.93 (m, 12H), 1.36 (d, $J$ = 6.6, 3H), 1.33 (s, 3H), 1.31 (d, $J$ = 7.8, 3H), 1.25 (s, $J$ = 6.3, 3H), 1.10 (d, $J$ = 7.2, 3H), 0.84 (d, $J$ = 6.9, 3H), 0.78 (t, $J$ = 7.5, 3H). Anal. ($C_{44}H_{64}FN_5O_{10}$*1.65$H_2O$) C, H, N; F: calcd, 2.18; found, 2.97.

**6m.** Following procedure A using the $C_{12}$ vinyl imidazolyl carbamate macrolide and 4-[4-(6-methoxy-pyridin-3-yl)-imidazol-1-yl]-butylamine yielded **6m** (36% yield) as a white solid. MS (ESI): 854.1 ($MH^+$). HPLC: method 1; $t_R$ = 13.62 min. $^1$H NMR ($CDCl_3$): $\delta$ 8.51 (d, $J$ = 3.0, 1H), 7.97 (dd, $J$ = 8.7, 3.3, 1H), 7.51 (d, $J$ = 0.9, 1H) 7.18 (d, $J$ = 1.2, 1H), 6.75 (d, $J$ = 8.4, 1H), 5.95 (dd, $J$ = 16.8, 10.8, 1H), 5.71 (dd, $J$ = 17.1, 1.5, 1H), 5.55 (dd, $J$ = 11.1,1.5, 1H), 4.95 (dd, $J$ = 10.5, 2.4, 1H), 4.28 (d, $J$ = 7.2, 1H), 4.23 (d, $J$ = 9.0, 1H), 4.0 (t, $J$ = 7.2, 2H), 3.95 (s, 3H), 3.89 (q, $J$ = 6.9, 1H), 3.62−3.78 (m, 2H), 3.71 (s, 1H), 3.5−3.62 (m, 1H), 3.22 (dd, $J$ = 9.9, 7.2, 1H), 3.06−3.16 (m, 2H), 2.61 (s, 3H), 2.50−2.58 (m, 1H), 2.32 (s, 6H), 1.54−1.93 (m, 12H), 1.36 (d, $J$ = 6.9, 3H), 1.33 (s, 3H), 1.31 (d, $J$ = 7.8, 3H), 1.25 (s, $J$ = 6.0, 3H), 1.10 (d, $J$ = 7.2, 3H), 0.84 (d, $J$ = 6.9, 3H), 0.79 (t, $J$ = 7.5, 3H). Anal. ($C_{45}H_{67}N_5O_{11}$) C, H, N.

**6n.** Following procedure A using the $C_{12}$ vinyl imidazolyl carbamate macrolide and 5-[1-(4-aminobutyl)imidazol-4-yl]pyridin-2-ol yielded **6n** (12% yield) as a white solid. MS (ESI): 841.0 ($MH^+$). HPLC: method 1; $t_R$ = 11.71 min. $^1$H NMR ($CDCl_3$): $\delta$ 7.82−7.86 (m, 1H), 7.82 (s, 1H), 7.44 (d, $J$ = 0.9, 1H) 7.12 (d, $J$ = 1.2, 1H), 6.63 (dd, $J$ = 8.7, 1.5, 1H), 5.95 (dd, $J$ = 16.8, 10.8, 1H), 5.71 (dd, $J$ = 17.1, 1.5, 1H), 5.55 (dd, $J$ = 11.1,1.5, 1H), 4.94 (dd, $J$ = 10.5, 2.4, 1H), 4.27 (d, $J$ = 7.5, 1H), 4.20 (d, $J$ = 9.3, 1H), 3.98 (t, $J$ = 7.2, 2H), 3.90 (q, $J$ = 6.9, 1H), 3.62−3.78 (m, 2H), 3.70 (s, 1H), 3.5−3.62 (m, 1H), 3.22 (dd, $J$ = 10.2, 7.2, 1H), 3.06−3.16 (m, 2H), 2.56 (s, 3H), 2.46−2.58 (m, 1H), 2.30 (s, 6H), 1.42−1.93 (m, 12H), 1.38 (d, $J$ = 6.9, 3H), 1.32 (s, 3H), 1.31 (d, $J$ = 7.8, 3H), 1.24 (s, $J$ = 6.0, 3H), 1.11 (d, $J$ = 6.9, 3H), 0.84 (d, $J$ = 7.2, 3H), 0.80 (t, $J$ = 7.2, 3H). Anal. ($C_{44}H_{65}N_5O_{11}$·1.7$H_2O$) C, H, N.

**6o.** Following procedure A using the $C_{12}$ vinyl imidazolyl carbamate macrolide and {5-[1-(4-aminobutyl)imidazol-4-yl](2-pyridyl)}methylamine yielded **6o** (37% yield) as a white solid. MS (ESI): 853.1 ($MH^+$). HPLC: method 1; $t_R$ = 11.30 min. $^1$H NMR ($CDCl_3$): $\delta$ 8.46 (d, $J$ = 2.1, 1H), 7.87 (dd, $J$ = 8.7, 2.4, 1H), 7.48 (d, $J$ = 0.9, 1H) 7.10 (d, $J$ = 1.2, 1H), 6.43 (d, $J$ = 8.4, 1H), 5.95 (dd, $J$ = 17.1, 10.8, 1H), 5.71 (dd, $J$ = 17.1, 1.2, 1H), 5.55 (dd, $J$ = 11.1,1.2, 1H), 4.96 (dd, $J$ = 10.8, 2.4,m 1H), 4.53 (q, $J$ = 5.1, 1H), 4.26 (t, $J$ = 9.6, 2H), 3.97 (t, $J$ = 7.2, 2H), 3.89 (q, $J$ = 6.9, 1H), 3.5−3.78 (m, 3H), 3.72 (s, 1H), 3.18 (dd, $J$ = 10.2, 7.2, 1H), 3.03−3.13 (m, 2H), 2.93 (d, $J$ = 5.4, 3H), 2.63 (s, 3H), 2.4−2.48 (m, 1H), 2.26 (s, 6H), 1.42−1.93 (m, 12H), 1.37 (d, $J$ = 6.9, 3H), 1.34 (s, 3H), 1.31 (d, $J$ = 7.5, 3H), 1.24 (d, $J$ = 6.0, 3H), 1.10 (d, $J$ = 6.9, 3H), 0.84 (d, $J$ = 6.9, 3H), 0.79 (t, $J$ = 7.5, 3H). Anal. ($C_{45}H_{68}N_6O_{10}$·1.3$H_2O$) C, H, N.

**6p.** Following procedure A using the $C_{12}$ vinyl imidazolyl carbamate macrolide and {5-[1-(4-aminobutyl)imidazol-4-yl](2-pyridyl)}dimethylamine yielded **6p** (27% yield) as a white solid. MS (ESI): 867.1 ($MH^+$). HPLC: method 1; $t_R$ = 11.30 min. $^1$H NMR ($CDCl_3$): $\delta$ 8.52 (d, $J$ = 2.4, 1H), 7.89 (dd, $J$ = 8.7, 2.4, 1H), 7.49 (s, 1H) 7.09 (s, 1H), 6.55 (d, $J$ = 8.7, 1H), 5.95 (dd, $J$ = 17.1, 10.8, 1H), 5.71 (dd, $J$ = 17.1, 1.2, 1H), 5.55 (dd, $J$ = 11.1,1.2, 1H), 4.96 (dd, $J$ = 10.8, 2.4, 1H), 4.28 (d, $J$ = 7.5, 1H), 4.24 (d, $J$ = 9, 1H), 3.97 (t, $J$ = 7.2, 2H), 3.89 (q, $J$ = 6.9, 1H), 3.5−3.78 (m, 3H), 3.72 (s, 1H), 3.16−3.24 (m, 1H), 3.1 (s, 6H), 3.04−3.14 (m, 2H), 2.63 (s, 3H), 2.4−2.48 (m, 1H), 2.31 (s, 6H), 1.42−1.93 (m, 12H), 1.37 (d, $J$ = 6.9, 3H), 1.34 (s, 3H), 1.31 (d, $J$ = 7.5, 3H), 1.25 (d, $J$ = 6.3, 3H), 1.10 (d, $J$ = 6.9, 3H), 0.85 (d, $J$ = 6.6, 3H), 0.80 (t, $J$ = 7.5, 3H). Anal. ($C_{46}H_{70}N_6O_{10}$·0.7$H_2O$) C, H, N.

**6q.** Following procedure A using the $C_{12}$ vinyl imidazolyl carbamate macrolide and 4-[4-(6-chloro(3-pyridyl))-2-methylimidazolyl]butylamine yielded **6q** (25% yield) as a white solid. MS (ESI): 873.5 ($MH^+$). HPLC: method 1; $t_R$ = 13.68 min. $^1$H NMR ($CDCl_3$): $\delta$ 8.68 (d, $J$ = 2.4, 1H), 8.02 (dd, $J$ = 8.1, 3.0, 1H), 7.29 (d, $J$ = 6.6, 1H), 7.25 (m, 1H,), 5.95 (dd, $J$ = 16.8, 10.8, 1H,), 5.71 (dd, $J$ = 17.1, 1.5, 1H), 5.55 (dd, $J$ = 11.1,1.5, 1H), 4.94 (dd, $J$ = 10.5, 2.4, 1H), 4.27 (d, $J$ = 7.2, 1H), 4.23 (d, $J$ = 9.0, 1H), 3.86−3.92 (m, 3H), 3.62−3.78 (m, 2H), 3.71 (s, 1H), 3.5−3.62 (m, 1H), 3.19 (dd, $J$ = 10.2, 7.2, 1H), 3.06−3.16 (m, 2H), 2.61 (s, 3H), 2.50−2.58 (m, 1H), 2.42 (s, 3H), 2.28 (s, 6H), 1.42−1.93 (m, 12H), 1.36 (d, $J$ = 6.9, 3H), 1.31 (d, $J$ = 7.8, 3H), 1.25 (s, 3H), 1.24 (d, $J$ = 6.0, 3H), 1.11 (d, $J$ = 7.2, 3H), 0.84 (d, $J$ = 6.9, 3H), 0.77 (t, $J$ = 7.2, 3H). Anal. ($C_{45}H_{66}ClN_5O_{10}$·1.6 $H_2O$) C, H, N, Cl.

**6r.** Following procedure A using the $C_{12}$ vinyl imidazolyl carbamate macrolide and 4-[4-(6-methoxy(3-pyridyl))-5-methylimidazolyl]butylamine yielded **6r** (38% yield) as a white solid. MS (ESI): 868.1 ($MH^+$). HPLC: method 1; $t_R$ = 13.94 min. $^1$H NMR ($CDCl_3$): $\delta$ 8.35 (d, $J$ = 2.4, 1H), 7.91 (dd, $J$ = 8.7, 2.4, 1H), 7.49 (s, 1H), 6.79 (d, $J$ = 8.7, 1H), 5.95 (dd, $J$ = 16.8, 10.8, 1H), 5.71 (dd, $J$ = 17.1, 1.5, 1H), 5.55 (dd, $J$ = 11.1,1.5, 1H), 4.95 (dd, $J$ = 10.8, 2.1, 1H), 4.30 (d, $J$ = 7.5, 1H), 4.24 (d, $J$ = 9.0, 1H), 3.96 (s, 3H), 3.89−4.0 (m, 3H), 3.62−3.78 (m, 2H), 3.73 (s, 1H), 3.5−3.62 (m, 1H), 3.29 (dd, $J$ = 9.9, 7.5, 1H), 3.06−3.16 (m, 2H), 2.63 (s, 3H), 2.50−2.65 (m, 1H), 2.43 (s, 6H), 2.34 (s, 3H), 1.41−1.93 (m, 12H), 1.36 (d, $J$ = 6.9, 3H), 1.34 (s, 3H), 1.31 (d, $J$ = 7.2, 3H), 1.26 (s, $J$ = 6.0, 3H), 1.11 (d, $J$ = 7.2, 3H), 0.85 (d, $J$ = 7.2, 3H), 0.80 (t, $J$ = 7.2, 3H). Anal. ($C_{46}H_{69}N_5O_{11}$·2.4$H_2O$) C, H, N.

**6s.** Following procedure A using the $C_{12}$ vinyl imidazolyl carbamate macrolide and 4-(4-pyrimid-5-yl-imidazol-1-yl)-butylamine yielded **6s** (16% yield) as a white solid. MS (ESI): 825.0 ($MH^+$). HPLC: method 1; $t_R$ = 11.78 min. $^1$H NMR ($CDCl_3$): $\delta$ 9.10 (s, 2H), 9.07 (s, 1H), 7.58 (d, $J$ = 0.9, 1H) 7.42 (d, $J$ = 1.2, 1H), 5.92 (dd, $J$ = 16.8, 10.8, 1H), 5.71 (dd, $J$ = 17.1, 1.2, 1H), 5.57 (dd, $J$ = 11.1,1.2, 1H), 4.94 (dd, $J$ = 10.8, 2.4, 1H), 4.31 (d, $J$ = 7.8, 1H), 4.23 (d, $J$ = 9.0, 1H), 4.03 (t, $J$ = 7.5, 2H), 3.88 (q, $J$ = 6.9, 1H), 3.70 (s, 1H), 3.54−3.79 (m, 3H), 3.31 (dd, $J$ = 10.2, 7.2, 1H), 3.04−3.12 (m, 2H), 2.65−2.82 (m, 1H), 2.58 (s, 3H), 2.48 (s, 6H), 1.40−1.94 (m, 12H), 1.36 (d, $J$ = 6.6, 3H), 1.26−1.34 (m, 9H), 1.11 (d, $J$ = 6.9, 3H), 0.85 (d, $J$ = 6.9, 3H), 0.79 (t, $J$ = 7.5, 3H). Anal. ($C_{43}H_{64}N_6O_{10}$*0.8$H_2O$) C, H, N.

**6t.** Following procedure A using the $C_{12}$ vinyl imidazolyl carbamate macrolide and 4-(4-pyrazin-2-yl-imidazol-1-yl)-butylamine yielded **6t** (12% yield) as a white solid. MS (ESI): 825.0 ($MH^+$). HPLC: method 1; $t_R$ = 12.07 min. $^1$H NMR ($CDCl_3$): $\delta$ 9.20 (d, $J$ = 1.5, 1H), 8.45 (dd, $J$ = 2.4, 1.5, 1H,), 7.66 (d, $J$ = 1.2, 1H) 7.42 (d, $J$ = 1.2, 1H), 7.57 (d, $J$ = 1.2, 1H), 5.95 (dd, $J$ = 17.1, 11.1, 1H), 5.71 (dd, $J$ = 17.1, 1.2, 1H), 5.57 (dd, $J$ = 11.1,1.2, 1H), 4.95 (dd, $J$ = 10.8, 2.4, 1H), 4.29 (d, $J$ = 7.2, 1H),

4.23 (d, $J$ = 9.0, 1H), 4.03 (t, $J$ = 7.5, 2H), 3.88 (q, $J$ = 6.9, 1H), 3.71 (s, 1H), 3.50−3.79 (m, 3H), 3.24 (dd, $J$ = 9.9, 7.2, 1H), 3.03−3.15 (m, 2H), 2.61 (s, 3H), 2.52−2.59 (m, 1H), 2.37 (s, 6H), 1.40−1.94 (m, 12H), 1.36 (d, $J$ = 6.9, 3H), 1.33 (s, 3H), 1.31 (d, $J$ = 7.5, 3H), 1.26 (d, $J$ = 6.0, 3H), 1.11 (d, $J$ = 6.9, 3H), 0.84 (d, $J$ = 6.9, 3H), 0.80 (t, $J$ = 7.5, 3H). Anal. ($C_{43}H_{64}N_6O_{10}$) C, H, N.

**6u.** Following procedure A using the $C_{12}$ vinyl imidazolyl carbamate macrolide and 4-[4-(5-methylpyrazin-2-yl)imidazolyl]-butylamine yielded **6u** (36% yield) as a white solid. MS (ESI): 858.5 ($MH^+$). HPLC: method 1; $t_R$ = 12.49 min. $^1$H NMR ($CDCl_3$): $\delta$ 9.08 (d, $J$ = 1.2, 1H), 8.33 (d, $J$ = 0.9, 1H), 7.60 (d, $J$ = 1.2, 1H) 7.56 (d, $J$ = 1.2, 1H), 5.94 (dd, $J$ = 16.8, 10.8, 1H), 5.71 (dd, $J$ = 17.1, 1.5, 1H), 5.55 (dd, $J$ = 11.1,1.5, 1H), 4.95 (dd, $J$ = 10.5, 2.4, 1H), 4.28 (d, $J$ = 7.2, 1H), 4.23 (d, $J$ = 9.3, 1H), 4.02 (t, $J$ = 7.5, 2H), 3.88 (q, $J$ = 6.6, 1H), 3.49−3.79 (m, 3H), 3.71 (s, 1H), 3.20 (dd, $J$ = 10.2, 7.2, 1H), 3.06−3.16 (m, 2H), 2.62 (s, 3H), 2.55 (s, 3H), 2.45−2.52 (m, 1H) 2.30 (s, 6H), 1.40−1.92 (m, 12H), 1.36 (d, $J$ = 6.9, 3H), 1.34 (s, 3H), 1.31 (d, $J$ = 7.5, 3H), 1.25 (d, $J$ = 6.0, 3H), 1.10 (d, $J$ = 6.9, 3H), 0.84 (d, $J$ = 6.9, 3H), 0.80 ($J$ = 7.2, 3H). Anal. ($C_{44}H_{66}N_6O_{10}\cdot 0.6H_2O$) C, H, N.

**6v.** Following procedure A using the $C_{12}$ vinyl imidazolyl carbamate macrolide and 4-[4-(2-methoxypyrimidin-5-yl)imidazolyl]butylamine yielded **6v** (36% yield) as a white solid. MS (ESI): 856.0 ($MH^+$). HPLC: method 1; $t_R$ = 12.53 min. $^1$H NMR ($CDCl_3$): $\delta$ 8.87 (s, 2H), 7.53 (d, $J$ = 0.9, 1H), 7.26 (d, $J$ = 1.2, 1H), 5.94 (dd, $J$ = 16.8, 10.8, 1H), 5.71 (dd, $J$ = 17.1, 1.5, 1H), 5.55 (dd, $J$ = 11.1,1.5, 1H), 4.95 (dd, $J$ = 10.5, 2.4, 1H), 4.27 (d, $J$ = 7.5, 1H), 4.23 (d, $J$ = 9.3, 1H), 4.03 (s, 3H), 4.00 (t, $J$ = 7.2, 2H), 3.88 (q, $J$ = 6.9, 1H), 3.49−3.79 (m, 3H), 3.71 (s, 1H), 3.18 (dd, $J$ = 10.2, 7.2, 1H), 3.04−3.11 (m, 2H), 2.60 (s, 3H), 2.40−2.57 (m, 1H) 2.27 (s, 6H), 1.42−1.91 (m, 12H), 1.36 (d, $J$ = 6.6, 3H), 1.34 (s, 3H), 1.31 (d, $J$ = 7.5, 3H), 1.24 (d, $J$ = 6.0, 3H), 1.10 (d, $J$ = 6.9, 3H), 0.84 (d, $J$ = 6.9, 3H), 0.78 (t, $J$ = 7.2, 3H). Anal. ($C_{44}H_{66}N_6O_{10}\cdot 1.5H_2O$) C, H, N.

**6w.** Following procedure A using the $C_{12}$ vinyl imidazolyl carbamate macrolide and 4-(2-(3-pyridyl)-1,3-thiazol-5-yl)butylamine yielded **6w** (43% yield) as a white solid. MS (ESI): 842.1 ($MH^+$). HPLC: method 1; $t_R$ = 14.81 min. $^1$H NMR ($CDCl_3$): $\delta$ 9.09 (s, 1H), 8.59 (s, 1H), 8.16 (dt, $J$ = 8.1, 1.8, 1H), 7.56 (s, 1H), 7.34 (dd, $J$ = 8.1, 5.1, 1H), 5.93 (dd, $J$ = 16.8, 10.8, 1H), 5.69 (dd, $J$ = 17.1, 1.5, 1H), 5.53 (dd, $J$ = 11.1,1.5, 1H), 4.96 (dd, $J$ = 10.8, 2.4, 1H), 4.25 (d, $J$ = 7.2, 1H), 4.21 (d, $J$ = 9.0, 1H), 3.85 (q, $J$ = 6.9, 1H), 3.71 (s, 1H), 3.59−3.69 (m, 2H), 3.43−3.54 (m, 1H), 3.17 (dd, $J$ = 10.2, 7.2, 1H), 3.00−3.11 (m, 2H), 2.87−2.91 (m, 2H), 2.61 (s, 3H), 2.41−2.56 (m, 1H), 2.26 (s, 6H), 1.37−1.84 (m, 12H), 1.32−1.34 (m, 6H), 1.29 (d, $J$ = 7.5, 3H), 1.21 (d, $J$ = 6.0, 3H), 1.08 (d, $J$ = 6.9, 3H), 0.83 (d, $J$ = 6.6, 3H), 0.78 (t, $J$ = 7.5, 3H). Anal. ($C_{44}H_{64}N_4O_{10}S*2.7H_2O$) C, H, N; S: calcd, 3.60; found, 2.89.

**6x.** Following procedure A using the $C_{12}$ vinyl imidazolyl carbamate macrolide and 4-(5-(3-pyridyl)-2-thienyl)butylamine yielded **6x** (41% yield) as a white solid. MS (ESI): 841.1 ($MH^+$). HPLC: method 1; $t_R$ = 15.35 min. $^1$H NMR ($CDCl_3$): $\delta$ 8.81 (s, 1H), 8.44 (s, 1H), 7.79 (m, 1H), 7.26 (m, 1H), 7.15 (d, $J$ = 3.6, 1H), 6.78 (d, $J$ = 3.6, 1H), 5.95 (dd, $J$ = 17.4, 10.8, 1H), 5.71 (dd, $J$ = 17.1, 1.5, 1H), 5.53 (dd, $J$ = 11.1,1.5, 1H), 4.98 (dd, $J$ = 10.8, 2.4, 1H), 4.26 (d, $J$ = 7.5, 1H), 4.22 (d, $J$ = 9.3, 1H), 3.87 (q, $J$ = 6.6, 1H), 3.73 (s, 1H), 3.60−3.69 (m, 1H), 3.47−3.56 (m, 1H), 3.17 (dd, $J$ = 10.2, 7.2, 1H), 3.08−3.12 (m, 2H), 2.71−2.81 (m, 3H), 2.61 (s, 3H), 2.40−2.56 (m, 1H), 2.23 (s, 6H), 1.37−1.86 (m, 12H), 1.35 (d, $J$ = 6.9, 3H), 1.32 (s, 3H), 1.30 (d, $J$ = 7.2, 3H), 1.21 (d, $J$ = 6.3, 3H), 1.09 (d, $J$ = 6.9, 3H), 0.84 (d, $J$ = 6.9, 3H), 0.79 (t, $J$ = 7.5, 3H). Anal. ($C_{45}H_{65}N_3O_{10}S\cdot 0.9H_2O$) C, H, N; S: calcd, 3.73; found, 2.65.

**6y.** Following procedure A using the $C_{12}$ vinyl imidazolyl carbamate macrolide and (2-aminoethyl)methyl[(2-(3-pyridyl)(1,3-thiazol-5-yl))methyl]amine yielded **6y** (24% yield) as a white solid. MS (ESI): 857.1 ($MH^+$). HPLC: method 1; $t_R$ = 11.51 min. $^1$H NMR ($CDCl_3$): $\delta$ 9.15 (s, 1H), 8.61 (d, $J$ = 1.8, 1H), 8.19 (m, 1H), 7.66 (s, 1H), 7.31 (dd, $J$ = 7.8, 4.8, 1H), 5.98 (dd, $J$ = 17.4, 10.8, 1H), 5.74 (dd, $J$ = 17.1, 1.5, 1H), 5.55 (dd, $J$ = 11.1,1.5, 1H), 5.14 (dd, $J$ = 10.8, 2.4, 1H), 4.27 (d, $J$ = 7.2, 1H), 4.23 (d, $J$ = 9.0, 1H), 4.05 (d, $J$ = 14.4, 1H), 3.81−3.93 (m, 3H), 3.71 (d, $J$ = 14.1, 1H), 3.70 (s, 1H), 3.46−3.56 (m, 2H), 3.17 (dd, $J$ = 10.5, 2.5, 1H), 3.05−3.13 (m, 1H), 2.78−2.87 (m, 1H), 2.66 (s, 3H), 2.40−2.56 (m, 2H), 2.30 (s, 3H), 2.26 (s, 6H), 1.39−1.96 (m, 8H), 1.29−1.35 (m, 9H), 1.23 (d, $J$ = 6.3, 3H), 1.11 (d, $J$ = 7.2, 3H), 0.87 (d, $J$ = 6.9, 3H), 0.80 (t, $J$ = 7.2, 3H). Anal. ($C_{44}H_{65}N_5O_{10}S$) C, H, N; S: calcd, 3.75; found, 2.55.

**6z.** Following procedure A using the $C_{12}$ vinyl imidazolyl carbamate macrolide and (2-aminoethyl)methyl[(5-(3-pyridyl)(2-thienyl))methyl]amine yielded **6z** (28% yield) as a white solid. MS (ESI): 856.1 ($MH^+$). HPLC: method 1; $t_R$ = 11.20 min. $^1$H NMR ($CDCl_3$): $\delta$ 8.80 (s, 1H), 8.43 (d, $J$ = 1.2, 1H), 7.78 (m, 1H), 7.23 (dd, $J$ = 7.8, 4.8, 1H), 7.14 (d, $J$ = 3.6, 1H), 6.86 (d, $J$ = 3.6, 1H), 5.98 (dd, $J$ = 17.4, 10.8, 1H), 5.70 (dd, $J$ = 17.1, 1.5, 1H), 5.51 (dd, $J$ = 11.1,1.5, 1H), 5.11 (dd, $J$ = 10.8, 2.4, 1H), 4.24 (d, $J$ = 7.2, 1H), 4.20 (d, $J$ = 9.3, 1H), 4.05 (d, $J$ = 14.4, 1H), 3.76−3.94 (m, 3H), 3.71 (d, $J$ = 11.7, 1H), 3.69 (s, 1H), 3.45−3.52 (m, 2H), 3.15 (dd, $J$ = 10.2, 7.2, 1H), 2.93−3.10 (m, 1H), 2.71−2.81 (m, 1H), 2.62 (s, 3H), 2.40−2.56 (m, 2H), 2.29 (s, 3H), 2.23 (s, 6H), 1.37−1.90 (m, 8H), 1.27−1.33 (m, 9H), 1.20 (d, $J$ = 6.3, 3H), 1.08 (d, $J$ = 6.9, 3H), 0.84 (d, $J$ = 6.9, 3H), 0.75 (t, $J$ = 7.2, 3H). Anal. ($C_{45}H_{66}N_4O_{10}S$) C, H, N; S: calcd, 3.75; found, 2.70.

**6aa.** Following procedure A using the $C_{12}$ vinyl imidazolyl carbamate macrolide and N1-[3,3′]bipyridinyl-5-ylmethyl-N1-methyl-ethane-1,2-diamine yielded **6aa** (39% yield) as a white solid. MS (ESI): 850.5 ($MH^+$). HPLC: method 1; $t_R$ = 10.51 min. $^1$H NMR ($CDCl_3$): $\delta$ 8.87 (d, $J$ = 2.1, 1H), 8.71 (d, $J$ = 2.4, 1H), 8.63 (dd, $J$ = 4.8, 1.5, 1H), 8.52 (d, $J$ = 1.8, 1H), 7.95 (m, 2H), 7.40 (dd, $J$ = 7.8, 4.8, 1H), 5.97 (dd, $J$ = 17.1, 11.1, 1H), 5.73 (dd, $J$ = 17.1, 1.5, 1H), 5.55 (dd, $J$ = 11.1,1.2, 1H), 5.05 (dd, $J$ = 10.8, 2.1, 1H), 4.33 (d, $J$ = 7.2, 1H), 4.23 (d, $J$ = 9.0, 1H), 3.81−4.0 (m, 4H), 3.71 (s, 1H), 3.52−3.63 (m, 2H), 3.37 (dd, $J$ = 10.2, 7.8, 1H), 2.96−3.15 (m, 2H), 2.79−2.95 (m, 2H), 2.64 (s, 3H), 2.57 (s, 6H), 2.50−2.57 (m, 1H) 2.24 (s, 3H), 1.37−2.02 (m, 8H), 1.27−1.34 (m, 12H), 1.12 (d, $J$ = 6.9, 3H), 0.88 (d, $J$ = 6.9, 3H), 0.58 (t, $J$ = 7.5, 3H). Anal. ($C_{46}H_{67}N_5O_{10}\cdot 1.2H_2O$) C, H, N.

**6bb.** Following procedure A using the $C_{12}$ vinyl imidazolyl carbamate macrolide and (2-aminoethyl)methyl[(3-(3-pyridyl)-phenyl)methyl]amine yielded **6bb** (45% yield) as a white solid. MS (ESI): 850.1 ($MH^+$). HPLC: method 1; $t_R$ = 11.32 min. $^1$H NMR ($CDCl_3$): $\delta$ 8.85 (1H, d, $J$ = 2.4), 8.56 (1H, dd, $J$ = 4.8, 1.5), 7.93 (1H, dt, $J$ = 7.8, 2.1), 7.56 (1H, s), 7.33−7.46 (4H, m), 5.97 (1H, dd, $J$ = 17.1, 11.1), 5.73 (1H, dd, $J$ = 17.1, 1.5), 5.54 (1H, dd, $J$ = 11.1, 1.5), 5.07 (1H,dd, $J$ = 10.5, 2.4), 4.28 (1H, d, $J$ = 7.2), 4.23 (1H, d, $J$ = 9.0), 3.76−3.98 (4H, m), 3.72 (1H,s), 3.49−3.60 (2H, m), 3.20 (1H,dd, $J$ = 10.2, 7.5), 3.03−3.13 (2H,m), 2.77−2.86 (1H,m), 2.64 (3H,s), 2.44−2.58 (2H, m), 2.29 (6H,s), 2.24 (3H,s), 1.34−1.85 (8H, m), 1.27−1.34 (12H, m), 1.12 (3H,d, $J$ = 6.9), 0.88 (3H,d, $J$ = 6.9), 0.58 (3H,t, $J$ = 7.5). Anal. ($C_{47}H_{68}N_4O_{10}$) C, H, N.

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**Supporting Information Available:** Description of the synthesis of the heterocyclic side chains incorporated into compounds **6a**−**6z**, **6aa**, and **6bb**. $^1$H NMR spectra of final ketolide **6i** and telithromycin. This material is available free of charge via the Internet at http://pubs.acs.org.

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