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Synthesis and antibacterial activity of novel C_{12} ethyl ketolides

Matthew T. Burger,* Christy Hiebert, Mehran Seid, Daniel T. Chu, Lynn Barker, Mike Langhorne, Ribhi Shawar, Jolene Kidney, Manoj C. Desai and Jacob J. Plattner

Chiron Corporation, Biopharma Research, 4560 Horton Street, Emeryville, CA 94608-2916, USA

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Abstract—A novel series of C_{12} ethyl erythromycin derivatives have been discovered which exhibit in vitro and in vivo potency against key respiratory pathogens, including those resistant to erythromycin. The C_{12} modification involves replacing the natural C_{12} methyl group in the erythromycin core with an ethyl group via chemical synthesis. From the C_{12} ethyl macrolide core, a series of C_{12} ethyl ketolides were prepared and tested for antibacterial activity against a panel of relevant clinical isolates. Several compounds were found to be potent against macrolide-sensitive and -resistant bacteria, whether resistance was due to ribosome methylation (*erm*) or efflux (*mef*). In particular, the C_{12} ethyl ketolides **4k**,**4s**,**4q**,**4m**, and **4t** showed a similar antimicrobial spectrum and comparable activity to the commercial ketolide telithromycin. The in vivo efficacy of several C_{12} ethyl ketolides was demonstrated in a mouse infection model with *Streptococcus pneumoniae* as pathogen.

1. Introduction

The macrolide antibiotic erythromycin A 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] and 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 (Fig. 1).

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 semi-synthetic derivatives that erythromycin has been converted into, as well as new derivatives all together. Recently, we reported on novel C_{12} vinyl ketolides which possess potent in vitro and in vivo antibacterial properties against macrolide-resistant organisms.[10] We report herein on the preparation of a novel C_{12} ethyl macrolide core, the conversion of this core into the ketolide class of macrolides, and on the in vitro and in-vivo antibacterial properties of the resulting C_{12} ethyl ketolides.[11]

2. Chemistry

Synthetic modifications of erythromycin have been pursued by numerous investigators attempting to prepare

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* Corresponding author. Tel.: +1 510 923 3537; fax: +1 510 923 3360; e-mail: matthew_burger@chiron.com

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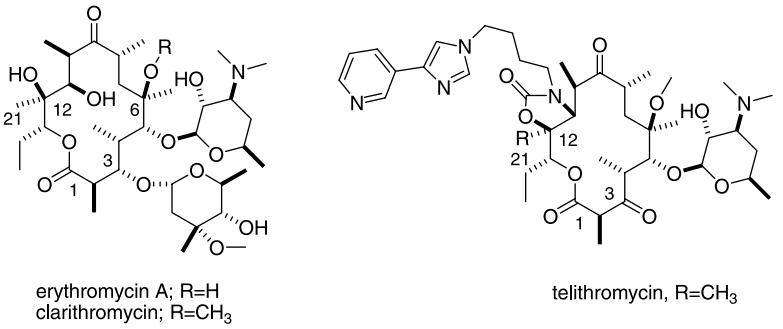


Figure 1. Clinically utilized macrolides.

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,[12] 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 ABT-773. Additional modifications that have been reported include 4″ carbamate macrolides,[13] ketolides containing nonnatural C_{13} substituents obtained via alteration of the biosynthetic pathway of erythromycin A[14] and C_6–C_{11} bridged ketolides.[15]

The C_{12} vinyl ketolides we have recently reported on were obtained from chemical manipulation of the erythromycin A macrolide; a key synthetic intermediate en route to these C_{12} vinyl ketolides is the C_{12}–C_{21} exocyclic alkenyl macrolide **1,** (Fig. 2). The double bond in **1** has proven to be a versatile intermediate for incorporating many novel groups at the C_{12} position of the macrolide. In addition to dihydroxylation which ultimately led to the C_{12} vinyl macrolide core, the alkenyl macrolide **1** can be ozonized yielding a C_{12} ketone[16] as well as stereoselectively epoxidized yielding a C_{12}–C_{21} epoxide. In all three chemical transformations, chemis-

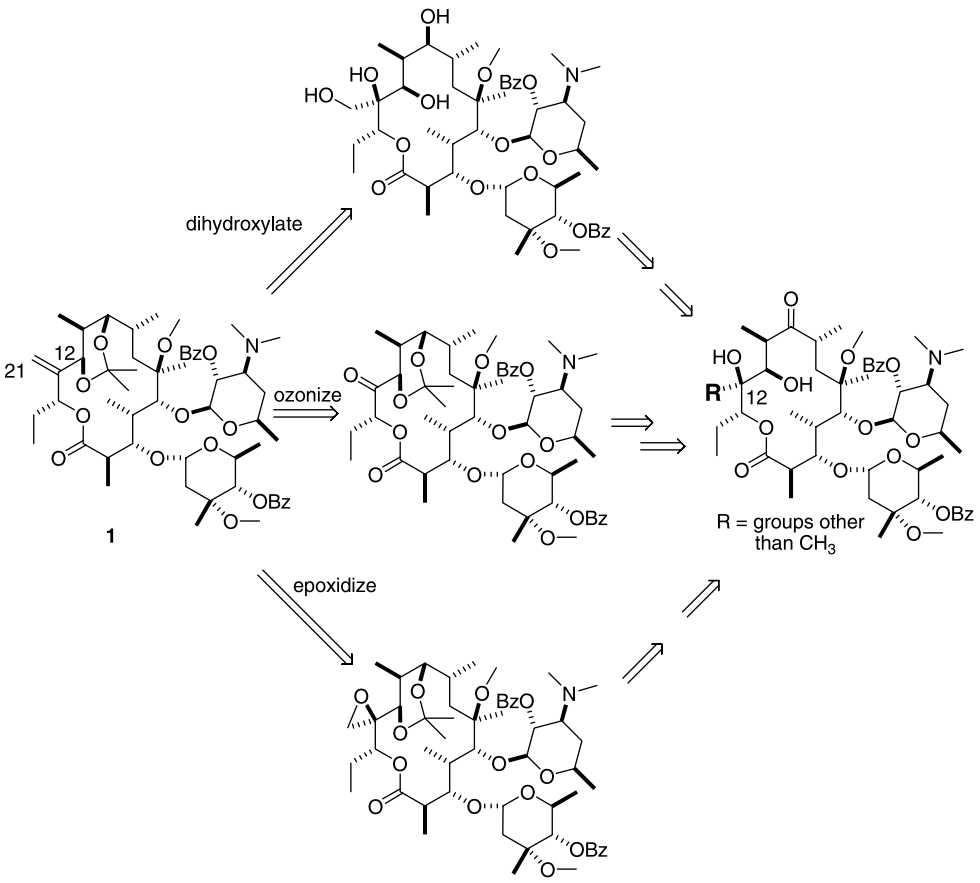


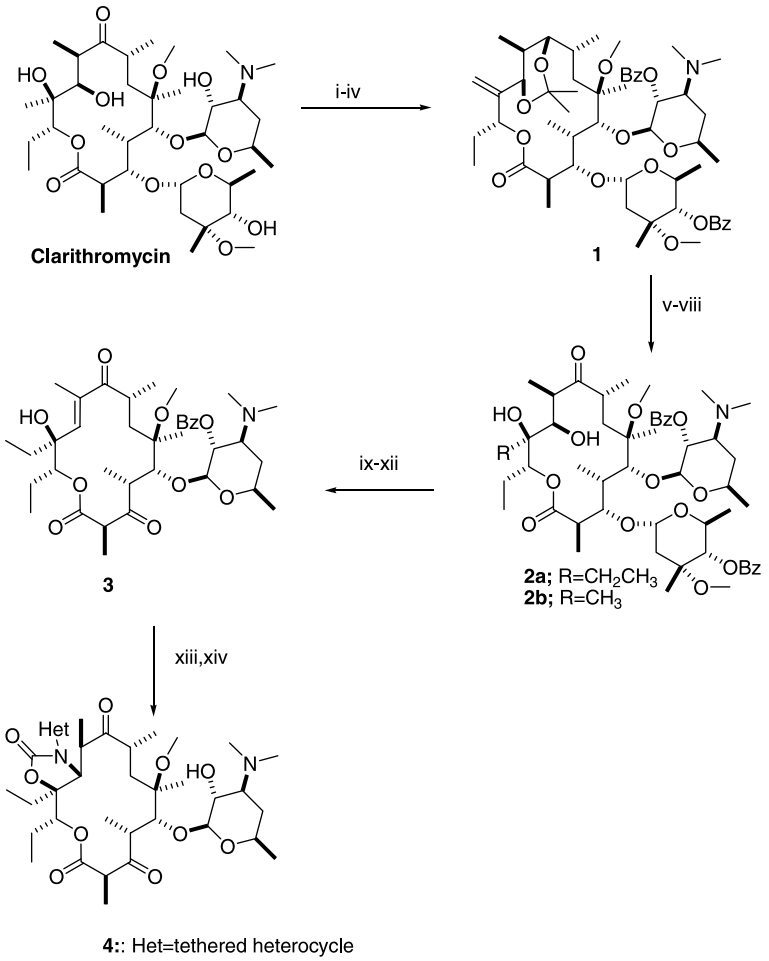
Figure 2. Chemical manipulations of erythromycin derived C_{12},C_{21} alkene **1**.

try performed at the C_{12}–C_{21} bond yields products containing a handle upon which further chemistry can be performed to introduce unnatural C_{12} substituents into the erythromycin core.

The synthetic route for accessing C_{12} ethyl modified macrolides and ketolides via the epoxidation product of macrolide **1** is outlined in Scheme 1. The synthetic details are as follows. Starting from clarithromycin, the protected C_{12}–C_{21} alkenyl macrolide **1** was prepared in four steps as previously described.[10] Treatment of macrolide **1** with *meta*-chloroperoxybenzoic acid results in epoxidation of the C_{12}–C_{21} alkene as well as oxidation of the tertiary amine. We were unable to avoid the undesired nitrogen oxidation. Initially, we found that the *N*-oxide could be conveniently reduced under mild conditions by treating with isopropanol and catalytic tetrapropylperruthenate in dichloromethane in the presence molecular sieves.[17] Eventually, we found on scaleup that the *N*-oxide could be efficiently reduced by treating with sodium thiosulfate in a tetrahydrofuran–water solution to yield the desired C_{12}–C_{21} epoxide. The epoxidation is stereoselective and occurs from the beta face of the macrocycle, vide infra. Introduction of the C_{21} methyl group was achieved by opening the epoxide with dimethylcuprate. Upon treating the resulting C_{12} ethyl macrolide with pyridinium *para*-toluene sulfonate at 68 °C the cyclic acetonide was deprotected, and the C_9 hydroxyl of the resulting triol was oxidized selectively by Dess–Martin periodinane[18] at −10 °C yielding macrolide diol **2a**.

The structural assignment for the newly created C_{12} stereocenter was initially supported by comparing the NMR spectral data of macrolide **2a** with the bisbenzoylated clarithromycin **2b**,[10] which differ only by having a methyl or ethyl at the C_{12} position. Further support for this structural assignment came from preparing the epimeric C_{12} ethyl C_9, C_{11} acetonide macrolide core whose X-ray structure was solved.[19]

The C_{12} ethyl macrolide **2a** was converted to a series of C_{12} ethyl ketolides as follows. Mesylation of the C_{11} hydroxyl of macrolide **2a** was achieved by treating with mesyl chloride in pyridine. Analysis by ^{13}C NMR suggests that the C_{11} mesylated **2a** exists predominantly as a $C_{12}OH$ C_9 cyclic hemiketal; a C_9 ketone resonance above 200 ppm is lacking, but a hemiketal resonance



Scheme 1. Synthesis of C_{12} ethyl ketolides. Synthesis of C_{12} ethyl ketolides. Reagents and conditions: (i)–(iv)ref10. (v) a—MCPBA, CH_2Cl_2 b—$NaHSO_3$, THF/H_2O, 83%; (vi) Me_2CuLi, Et_2O, −78 to 0 °C, 80%; (vii) PPTS, 68 °C, MeCN–H_2O (2:1) 55%; (viii) Dess–Martin periodinane, CH_2Cl_2, −10 °C, 67%; (ix) MsCl, pyridine, 69%; (x) a—DBU, acetone, 4 h, rt; b–66 °C, 12 h, 98%; (xi) HCl, H_2O, MeOH, 40 °C, 82%; (xii) Dess–Martin periodinane, CH_2Cl_2, 94%; (xiii) CDI, THF, NaH, 0 °C; (xiv) a—amine, MeCN, H_2O, 60 °C, 14 h; b—MeOH, 65 °C, 12 h, 20–45%.

distinct from the anomeric sugars is evident at 108.5 ppm. The C_{11} mesylated macrolide was 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 was produced in this reaction as judged by ^{1}H NMR. Acidic hydrolysis removes the cladinose group, which was oxidized when subjected to Dess–Martin periodinane yielding the C_{12} ethyl macrolide enone **3**. Deprotonation of the C_{12} hydroxyl of enone **3** with sodium hydride in the presence of carbonyldiimidazole yielded the corresponding C_{12} imidazoyl carbamate which upon reaction with an excess of side chain amine,[20] and deprotection of the desosamine benzoate by heating in methanol yielded the C_{12} ethyl ketolides **4**. Typical unoptimized yields of final ketolide **4** from enone **3** were of the order of 20–45%. The C_{12} ethyl ketolides (**4a**–**t**) prepared and reported are illustrated in Figure 3.

The structural assignments of the final ketolides were supported by NMR comparison to telithromycin. For compound **4k**, 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} methyl or ethyl 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.[12a]

3. Results and discussion

3.1. In vitro evaluation

The C_{12} ethyl ketolides prepared were assayed in a primary panel against a number of strains of *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Enterococcus faecalis*, *Streptococcus pyogenes*, *S. 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 micrograms per milliliter as determined by the broth microdilution method.[22] The MIC data in Tables 1 and 2 indicate that C_{12} ethyl ketolides in general

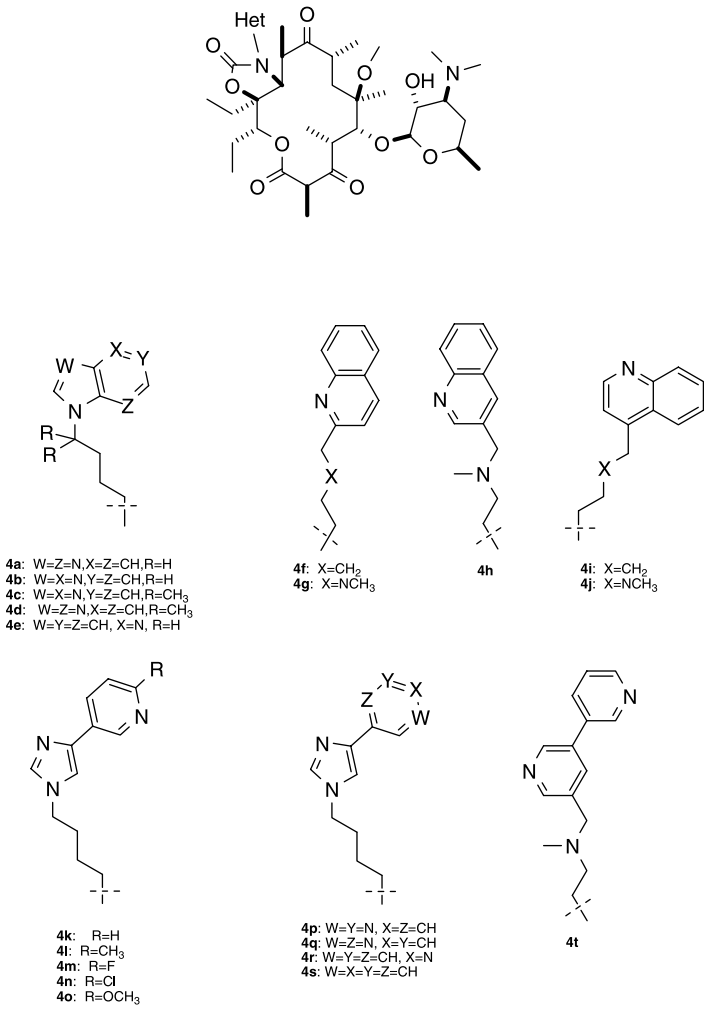


Figure 3. Structures of C_{12} ethyl ketolides.

Table 1. In vitro properties [MIC (μg/mL)] of C_{12} ethyl ketolides

Strains	4a	4b	4c	4d	4e	4f	4g	4h	4i	4j	teli	clari
S. aureus_29213	0.2	0.4	0.4	0.2	0.1	0.78	1.56	1.56	0.2	0.78	0.1–0.2	0.4–0.78
S. aureus_33591	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50
S. epidermidis_14990	0.4	0.4	0.2	0.2	0.1	0.4	1.56	0.78	0.2	0.78	0.1–0.2	0.2–0.4
S. epidermidis f50654	0.2	0.4	0.2	0.2	0.1	0.78	0.78	1.56	0.2	0.78	0.1–0.2	0.2–0.4
E. faecalis _29212	0.1	0.2	0.1	0.1	⩽0.05	0.1	0.2	0.1	0.1	0.2	⩽0.05–0.1	0.78–1.56
E. faecalis_bc11148–2	1.56	6.25	0.78	0.78	25	12.5	3.13	1.56	50	3.13	0.4	>50
S. pyogenes_8668	⩽0.05	⩽0.05	⩽0.05	⩽0.05	⩽0.05	0.1	0.1	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
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
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
S. pneumo_Erm 6849	0.78	0.2	0.4	0.4	>50	3.13	3.13	0.78	0.4	3.13	0.1–0.4	>50
S. pneumo_Mef 5654	0.4	0.78	1.56	0.78	0.4	0.4	0.78	0.78	0.4	0.78	0.4–0.78	6.25–12.5
S. pneumo_Mef S 3427	0.1	0.2	0.2	0.1	⩽0.05	⩽0.05	0.2	0.2	⩽0.05	0.1	0.1–0.2	3.13–6.25
H. influenzae_49247	3.13	3.13	6.25	6.25	3.13	3.13	6.25	3.13	3.13	3.13	3.13–6.25	6.25–12.5
H. influenzae_2762	—	—	1.56	0.78	0.2	—	1.56	1.56	—	1.56	0.4–1.56	0.78–3.13

Table 2. In vitro properties [MIC (μg/mL)] of C_{12} ethyl ketolides

Strains	4k	4l	4m	4n	4o	4p	4q	4r	4s	4t
S. aureus_29213	0.4	0.4	0.4	0.1	0.2	0.4	0.2	0.4	0.2	0.78
S. aureus_33591	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50
S. epidermidis_14990	0.2	0.2	0.2	0.1	0.4	0.2	0.2	0.4	0.2	0.4
S. epidermidis f50654	0.2	0.4	0.2	0.1	0.2	0.2	0.2	0.4	0.1	0.4
E. faecalis _29212	0.1	0.2	0.1	⩽0.05	0.1	0.2	0.1	0.1	0.1	0.1
E. faecalis_bc11148–2	0.4	3.13	0.78	1.56	3.13	1.56	0.78	3.13	0.78	0.4
S. pyogenes_8668	⩽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
S. pneumo_297–749	⩽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
S. pneumo_Erm 6849	0.4	1.56	0.4	6.25	0.78	0.2	0.78	>50	0.2	⩽0.05
S. pneumo_Mef 5654	0.4	0.78	0.4	0.78	0.78	0.4	0.4	0.78	0.4	0.78
S. pneumo_Mef S 3427	0.1	0.2	0.1	0.2	0.2	0.1	0.1	0.2	⩽0.05	0.1
H. influenzae_49247	6.25	6.25	3.13	6.25	6.25	3.13	3.13	3.13	3.13	6.25
H. influenzae_2762	0.4	1.56	0.78	0.78	1.56	—	—	0.78	—	1.56

possess potent antibacterial activity against a range of pathogens. The spectrum is similar to that of telithromycin, and like telithromycin, the C_{12} ethyl 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} ethyl 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} ethyl ketolides reported here are tethered to the C_{11} attached nitrogen via a four-atom spacer. 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} ethyl ketolides with tethered heteroaromatic fused bicycles is potency similar to telithromycin versus *S. aureus*, *S. pyogenes*, susceptible *S. pneumoniae*,*mef* gene containing *S. pneumoniae* strains and *H. influenzae*, and weaker potency relative to telithromycin against *S. epidermidis*, *E. faecalis*, and the *erm* gene containing *S. pneumoniae* strain. C_{12} ethyl ketolides with tethered quinolines in particular have weakened activity regardless of the nature of the four-atom tether. With an *N*-methyl group inserted in the four-atom tether, quinolyl tethered C_{12} ethyl ketolides **4g**,**4h**, and **4j** are five- to tenfold less potent than telithromycin against *S. aureus*, *S. epidermidis*, *E. faecalis*, and the *erm* gene containing *S. pneumoniae* strain. When the 4-quinolyl group is tethered via a butyl group as in C_{12} ethyl ketolide **4i** the activity against *S. aureus*, *S. epidermidis*, and the *erm* gene containing *S. pneumoniae* strain is comparable to that of telithroycin but the activity against *E. faecalis* is 100-fold less that of than telithromycin. A slight but less pronounced improvement in potency is evident switching to the butyl tethered 2-quinolyl in C_{12} ethyl ketolide **4f** relative to **4g**. For azabenzimidazole tethered C_{12} ethyl ketolides **4a**,**4c**, and **4d** the activity is comparable to that of telithromycin for all strains, being only two- to fourfold less potent against *S. aureus*, *S. epidermidis*, and the *erm* gene containing *S. pneumoniae* strain. The incorporation of the gem dimethyl groups into azabenzimidazole tethered **4d** seems to improve the activity against *E. faecalis* relative to azabenzimidazole tethered **4b**. The azaindole tethered C_{12} ethyl ketolide **4e** is equipotent to telithromycin in all strains tested, except for *E. faecalis* and the *erm* gene containing *S. pneumoniae* strain where it is at least 50-fold less potent.

A general trend that appears for the C_{12} ethyl ketolides with tethered 5,6 or 6,6 unfused biaryl systems

from Table 2 is potency similar to telithromycin versus all pathogens in the primary panel. The C_{12} ethyl ketolide **4k**, with the same tethered imidazoyl pyridyl bicycle as telithromycin, is essentially equipotent with telithromycin. Substitution on the pyridyl group of this bicycle with methyl **4l**, fluoro **4m**, methoxy **4o** and chloro **4n** is tolerated, albeit with a four- to eightfold decrease in potency against *E. faecalis*. The C_{12} ethyl ketolide **4r** containing a tethered 4-(4′-pyridyl) imidazolyl group is tenfold less potent against *E. faecalis* and 100-fold less potent against the *erm* gene containing *S. pneumoniae* strain than both the 4-(3′-pyridyl) imidazolyl containing **4k** and telithromycin. Replacing the pyridyl group of the tethered biaryl moiety with phenyl, pyrimidyl, and pyrazinyl groups is tolerated as C_{12} ethyl ketolides **4s**,**4p**, and **4q** are equipotent with telithromycin, with the exclusion of slightly elevated (2-fold) *S. aureus* and *E. faecalis* MIC values. Compound **4t**, in which a 6,6 bipyridyl system is connected to the macrolide core via a four-atom aminomethyl containing tether, exhibits a balanced antibacterial profile also comparable to that of telithromycin.

3.2. In vivo evaluation

The in vivo properties of several C_{12} ethyl ketolides were assessed in a mouse infection model with *S. pneumoniae* as the pathogen. Compounds were administered via the oral route and telithromycin was used as the control. The ED_{50} values determined for compounds **4d**,**4l**,**4m**, and **4t** are listed in Table 3.

Telithromycin was always the most potent compound in these experiments. Compounds **4t**,**4l**, and **4m** were two to threefold less potent, while **4d** was fivefold less potent than telithromycin.

4. Conclusion

The replacement of the C_{12} methyl group of erythromycin with a C_{12} ethyl group and the conversion of the resulting macrolide core into the ketolide class of antibacterials have been described. The C_{12} ethyl group was installed by a methylcuprate opening of a C_{12}–C_{21} macrolide epoxide. The C_{12} ethyl ketolides prepared possess potent antibacterial properties in vitro against key respiratory pathogens including those resistant to erythromycin, with several of the compounds reported exhibiting properties in the range of telithromycin. In a mouse infection model with *S. pneumonia* as the pathogen in vivo efficacy with several of the C_{12} ethyl ketolides has been demonstrated within the range of telithromycin.

Table 3. In vivo efficacies of C_{12} ethyl ketolides and telithromycin in mice

Compound	ED_{50} (mg/kg)
Telithromycin	3.7
4t	7.0
4l	9.6
4m	8.0
4d	18.9

5. Experimental

5.1. Antibiotics

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

5.2. 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.

5.3. Susceptibility testing

The in vitro antibacterial activity is reported as the minimum inhibitory concentration (MIC) in micrograms per milliliters as determined by the broth microdilution method in accordance with the Clinical Laboratory Standards Institute (CLSI, formerly NCCLS) guidelines.[22] In brief, organism suspensions were adjusted to a 0.5 McFarland standard to yield a final inoculum between 3×10^5 and 5×10^5 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.[23]

5.4. In Vivo therapeutic efficacy

Test compounds were prepared using sterile saline as the diluent. The pH was adjusted using 1 N acetic acid to a range of pH 5.0–5.6. A single 100 times LD_{50} dose of

S. pneumoniae PGO #4716 was injected by the intraperitoneal route (500 μL) to CF-1 mice. Groups of five female CF-1 mice were treated via oral gavage over a five-dose range (1, 5, 10, 25, and 50 mg/kg) with test compounds at 1 and 5 h post-infection and observed for the following five days. All untreated mice succumbed to the infection and died within 24 h. Efficacy, reported as ED_{50}, is defined as the efficacious dose which protects 50% of the infected mice from mortality.

5.5. General

All reagents used were of commercial quality and all reactions were carried out using commercially available anhydrous solvents from Aldrich, Acros or VWR. ^1H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded on either a Varian Unity 300 or Varian Mercury 300 spectrometer, using $CDCl_3$or CD_3OD solutions. Chemical shifts (δ) are reported in parts per million (ppm) referenced at 7.26 ppm ($CDCl_3$) or 3.30 (CD_3OD) for ^1H 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 (Tuscon, AZ). Mass spectral data were 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 retention times are reported using a Column Engineering *Reliasil BDX* C18, 5 μM, 4.6 × 100 mm column, where elution takes place 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.

5.6. Compound 2a

Stage v. To 2′,4″ OBz, C_9, C_{11}-dimethylketal, $C_{12,21}$ alkene macrolide **1**[10] (20.0 g, 20.4 mmol) in dichloromethane (204 mL) at 0 °C was added 3-chloroperoxybenzoic acid (17.6 g, 45.5 mmol). After stirring for 30 min at 0 °C, the ice bath was removed and the solution was stirred at rt for 21 h. Cyclohexene (10 mL, 100 mmol) was added and the solution was stirred for an additional 15 h. The dichloromethane was removed by rotary evaporation (not to dryness). The solution was diluted with ethyl acetate (400 mL) and washed with $NaHCO_{3(satd)}$ (7× 125 mL) and $NaCl_{(satd)}$ (1× 125 mL), dried over $MgSO_4$, filtered, concentrated, and dried in vacuo yielding the product epoxide, *N*-oxide as a white solid, 20.5 g (99% yield). This material was dissolved in 2:1 THF/H_2O (100 mL) and to this solution was added 2 M $NaHSO_{3(aq)}$ (100 mL). The solution was vigorously stirred for 30 min, diluted with ethyl acetate (400 L), and was washed with $NaHCO_{3(satd)}$ (4× 125 mL), and $NaCl_{(satd)}$ (125 ml), dried over $MgSO_4$, concentrated, and dried in vacuo yielding the product epoxide (16.75 g, 83%) as a white solid. MS (ESI): 996.8 (MH^+). ^1H NMR ($CDCl_3$) δ 8.00–8.04 (m, 4H), 7.20–7.62 (m, 6H), 5.20–5.30 (m, 1H), 4.97 (d, J = 8.1, 1H), 4.93 (d, J = 9.9, 1H), 4.80–4.85 (m, 2H), 4.48–4.56 (m, 1H), 4.13 (d, J = 3.3, 1H), 4.08 (d, J = 1.8, 1H), 3.90–4.00 (m, 1H), 3.77 (d, J = 6.3, 1H), 3.56 (s, 3H), 3.29 (s, 3H), 3.14–3.20 (m, 1H), 2.95–3.03 (m, 2H), 2.67 (d, J = 5.4, 1H), 2.53–2.57 (m, 1H), 2.49 (d, J = 15.0, 1H), 2.33 (s, 6H), 2.03–2.10 (m, 3H), 1.41–1.77 (m, 7H), 1.30 (s, 3H), 1.27 (s, 3H), 1.22 (d, J = 6.3, 3H), 1.21 (s, 3H), 1.17 (d, J = 6.3, 3H), 1.15 (d, J = 6.9, 3H), 1.00 (d, J = 6.6, 3H), 0.97 (s, 3H), 0.96 (d, J = 6.3, 3H), 0.84 (t, J = 7.5, 3H), 0.73 (d, J = 7.5, 3H). ^{13}C NMR ($CDCl_3$) δ 175.5, 166.2, 165.3, 133.3, 132.5, 130.9, 129.9, 129.6, 128.3, 128.1, 100.8, 100.3, 95.2, 79.9, 79.2, 79.1, 78.2, 76.9, 73.1, 72.3, 67.6, 66.8, 63.8, 63.4, 57.9, 49.8, 49.6, 46.0, 44.1, 43.5, 40.9, 35.1, 33.4, 31.7, 31.4, 26.9, 23.6, 21.3, 21.1, 20.4, 18.5, 16.5, 13.5, 11.1, 10.0. HPLC: t_R = 25.18 min. HRMS (ESI^+) m/z $[M+H]^+$ calcd for $C_{55}H_{81}NO_{15}$: 996.5678. Found: 996.5676.

Stage vi. An oven-dried 500 mL two-necked flask equipped with a 14/20 side arm connection to the manifold was cooled under Ar. An internal thermometer was inserted and CuBr dimethyl sulfide complex (28.4 g, 138.6 mmol) was added. The system was evacuated under high vacuum and purged with Ar three times. Diethyl ether (200 mL) was added and the heterogeneous solution was cooled in a −78 °C bath. Methyl lithium (180.0 mL, 277.1 mmol) was added via syringe with the internal temperature $\leqslant -60$ °C. The solution was held in the −78 °C bath for 10 min after the addition and then the bath was removed. Upon warming to −20 °C, a homogeneous solution resulted. The solution was then held at −20 °C. An oven-dried 1000 mL three-necked flask equipped with a 14/20 side arm connection to the manifold and an overhead mechanical stirrer was cooled under Ar. C_{12}, C_{21} epoxide (27.6 g, 27.7 mmol) was added and the system was evacuated under high vacuum and purged with Ar three times. Diethyl ether was added (400 mL), the solution was cooled to at 0 °C, and the epoxide was stirred (the solution is a heterogeneous slurry). The cuprate solution was then cannulated into the slurry of epoxide with the internal temperature of the epoxide solution staying $\leqslant$0 °C. The resultant light yellow heterogeneous solution was held at 0–5 °C for 12 h with mechanical stirring. $NH_4Cl_{(satd)}$ (200 mL) was added to stop the reaction, with the internal temperature $\leqslant$10 °C. The reaction mixture was diluted with ethyl acetate (2 L) and washed with $NH_4Cl_{(satd)}$ (3× 1 L), $NaCl_{(satd)}$ (1 L), dried over $MgSO_4$, filtered, concentrated, and dried in vauo yielding the crude C_{12} ethyl, hydroxy macrolide (26.87 g, ca. 80% pure by LC) as a white solid. An analytical sample was obtained by purification through SiO_2 chromatography (20–25% acetone/hexanes with 0.1% triethylamine). MS (ESI): 1012.9 (MH^+). ^1H NMR ($CDCl_3$) δ 8.00–8.04 (m, 4H), 7.52–7.63 (m, 2H), 7.40–7.49 (m, 4H), 5.32 (dd, J = 10.2, 3.0, 1H), 5.15 (br s, 1H), 5.05 (d, J = 7.5, 1H), 4.93 (d, J = 10.2, 1H), 4.8 (br s, 1H), 4.48–4.56 (m, 1H), 4.16 (s, 1H), 4.02–4.12 (m, 1H), 3.85 (d, 5.7, 1H), 3.78 (br s, 1H), 3.59 (s, 3H), 3.36 (t, J = 3.9, 1H), 3.33 (s, 3H), 2.98–3.08 (m, 1H), 2.48–2.55 (m, 2H), 2.34 (s, 6H), 2.12–2.22 (m, 1H), 1.44–1.96 (m, 10H), 1.38 (s, 3H), 1.32 (s, 3H), 1.21 (s, 3H), 1.20 (s, 3H), 1.16 (d, J = 7.2, 3H), 1.14 (d, J = 6.3, 3H), 1.07

(d, J = 6.6, 3H), 0.92–1.03 (m, 9H), 0.83 (t, J = 7.5, 3H), 0.75 (d, J = 7.5, 3H). ^{13}C NMR ($CDCl_3$) δ 176.3, 166.3, 165.2, 133.3, 132.4, 130.9, 129.9, 129.6, 129.5, 128.3, 128.1, 100.6, 99.9, 95.2, 80.3, 79.6, 79.1, 78.9, 77.3, 76.2, 73.2, 72.4, 67.5, 63.8, 63.4, 49.4, 44.6, 43.8, 40.9, 35.1, 32.4, 32.3, 31.8, 30.8, 28.0, 26.0, 24.1, 23.7, 21.4, 21.1, 20.1, 18.6, 17.4, 16.9, 14.1, 11.5, 10.2. HPLC: t_R = 27.47 min. HRMS (ESI^+) m/z $[M+H]^+$ calcd for $C_{56}H_{85}NO_{15}$: 1012.5991. Found: 1012.6016.

Stage vii. To crude C_9, C_{11} ketal, C_{12} ethyl, C_{12} hydroxy macrolide (6.65 g, 6.57 mmol) in 2:1 acetonitrile/water (130 mL) was added pyridinium *para*-toluene sulfonate (8.25 g, 32.9 mmol). The solution was heated in a 70 °C oil bath for 48 h. Upon cooling, the reaction was diluted with ethyl acetate (1.5 L) and washed with $NaHCO_{3(satd)}$ (2× 300 mL), $NaCl_{(satd)}$ (300 mL), dried over $MgSO_4$, filtered, and concentrated. Purification by flash chromatography (15% acetone/hexanes with 0.1% triethylamine) yielded the C_{12} ethyl, C_9, C_{11}, C_{12} triol macrolide (3.52 g, 55% yield) as a white solid. MS (ESI): 972.8 (MH^+). ^{1}H NMR ($CDCl_3$) δ 7.98–8.04 (m, 4H), 7.42–7.64 (m, 6H), 5.76 (d, J = 9.6, 1H), 5.18 (dd, J = 11.4, 1.8, 1H), 5.15 (m, 1H), 5.09 (d, J = 4.8, 1H), 4.95 (d, J = 7.5, 1H), 4.94 (d, J = 9.6, 1H), 4.42–4.54 (m, 1H), 4.48 (s, 1H), 3.91 (br s, 1H), 3.79 (d, J = 6.0, 1H), 3.72 (d, J = 9.9, 1H), 3.52 (s, 3H), 3.33 (s, 3H), 3.27–3.33 (m, 1H), 3.06 (s, 1H), 2.79–2.90 (m, 1H), 2.48 (d, J = 15.0, 1H), 2.42 (s, 6H), 2.06–2.16 (m, 1H), 1.72–1.98 (m, 6H), 1.40–1.60 (m, 7H), 1.35 (s, 3H), 1.19–1.22 (m, 9H), 1.10 (d, J = 6.9, 3H), 0.94 (d, J = 7.2, 3H), 0.93 (d, J = 5.7, 3H), 0.75–0.82 (m, 6H), 0.66 (d, J = 7.2, 3H). ^{13}C NMR ($CDCl_3$) δ 174.9, 166.2, 165.3, 133.5, 132.8, 130.4, 129.6, 128.5, 128.3, 99.7, 96.0, 82.6, 80.2, 78.8, 78.3, 78.0, 76.2, 72.9, 72.0, 70.6, 67.3, 63.6, 50.6, 49.5, 45.1, 38.1, 35.2, 34.5, 34.3, 32.3, 31.9, 25.3, 22.3, 21.3, 21.2, 20.1, 18.6, 17.2, 16.3, 11.0, 9.8, 8.8. HPLC: t_R = 22.84 min. HRMS (ESI^+) m/z $[M+H]^+$ calcd for $C_{53}H_{81}NO_{15}$: 972.5678. Found: 972.5687.

Stage viii. To C_{12} ethyl, C_9, C_{11}, C_{12} triol macrolide (3.52 g, 3.62 mmol) in dichloromethane (72 mL) at −5 °C was added Dess–Martin periodinane (1.84 g, 4.35 mmol). The solution was stirred for 5 min and then was placed in a −10 °C refrigerator. After standing for 22 h, more Dess–Martin periodinane (80 mg, 0.19 mmol) was added and the solution stood in the −10 °C refrigerator for an additional 8 h. The solution was diluted with ethyl acetate (1 L) and washed with 1:1 10% $Na_2S_2O_3$/$NaHCO_{3(satd)}$ (2× 200 mL). The combined aqueous layers were back extracted with ethyl acetate (4× 200 mL) and the combined organic layers were then washed with $NaCl_{(satd)}$ (200 mL), dried over $MgSO_4$, filtered, and concentrated. Purification by flash chromatography (15% acetone/hexanes with 0.1% triethylamine) yielded the C_{12} ethyl, C_9 keto, C_{11}, C_{12} diol macrolide **2a** (2.37 g, 67% yield) as a white solid. MS (ESI): 970.8 (MH^+). ^{1}H NMR ($CDCl_3$) δ 8.00–8.04 (m, 4H), 7.54–7.64 (m, 2H), 7.41–7.49 (m, 4H), 5.03–5.10 (m, 2H), 4.91–4.98 (m, 3H), 4.42–4.52 (m, 1H), 3.84–3.92 (m, 1H), 3.82 (s, 1H), 3.76 (d, J = 6.9, 1H), 3.68 (d, J = 1.2, 1H), 3.63 (d, J = 6.3, 1H), 3.53 (s, 3H), 3.10 (s, 1H), 3.02 (s, 3H), 2.88–3.01 (m, 2H), 2.76–2.81 (m, 1H), 2.54–2.62 (m, 1H), 2.47 (d, J = 15.0, 1H), 2.32 (s, 6H), 1.40–1.98 (m, 10H), 1.38 (s, 3H), 1.22 (s, 3H), 1.19–1.21 (m, 6H), 1.13 (d, J = 6.9, 3H), 1.11 (d, J = 6.9, 3H), 0.93 (d, J = 6.3, 3H), 0.88 (t, J = 7.8, 3H), 0.81 (t, J = 7.5, 3H), 0.70 (d, J = 7.8, 3H). ^{13}C NMR ($CDCl_3$) δ 219.5, 175.4, 165.9, 165.3, 133.2, 132.4, 130.8, 129.8, 129.5, 129.4, 128.2, 128.0, 100.2, 95.7, 80.5, 78.9, 78.3, 77.9, 77.7, 75.7, 73.5, 72.9, 72.5, 68.0, 67.5, 63.7, 63.5, 50.6, 49.7, 45.1, 44.9, 41.0, 38.6, 38.3, 37.7, 35.4, 31.8, 25.0, 21.9, 21.4, 20.0, 18.6, 18.1, 16.1, 12.5, 11.0, 9.5, 9.1. HPLC: t_R = 23.56 min. HRMS (ESI^+) m/z $[M+H]^+$ calcd for $C_{53}H_{79}NO_{15}$: 970.5522. Found: 970.5521.

5.7. Compound 3

Stage ix. To C_{12} ethyl, C_9 keto, C_{11}, C_{12} diol macrolide (3.75 g, 3.87 mmol) in pyridine (18 mL) at 0 °C was added methanesulfonyl chloride (1.5 mL, 19.3 mmol) via syringe over 5 min. The solution was stirred for 18 h as the solution warmed to rt. Upon concentrating and drying in vacuo, the material was taken up in ethyl acetate (750 mL) and washed with $NaHCO_{3(satd)}$ (2× 250 mL). The combined aqueous layers were back extracted with ethyl acetate (500 mL) and the combined organic layers were then washed with $NaCl_{(satd)}$ (100 mL), dried over $MgSO_4$, filtered, and concentrated. Purification by flash chromatography (20–25% acetone/hexanes with 0.1% triethylamine) yielded the C_{12} ethyl, C_9 keto, C_{11} OMs, C_{12} hydroxy macrolide (2.81 g, 69% yield) as a white solid. MS (ESI): 1048.8 (MH^+). ^{1}H NMR ($CDCl_3$) δ 8.02–8.14 (m, 4H), 7.54–7.64 (m, 2H), 7.42–7.51 (m, 4H), 5.20 (dd, J = 10.5, 2.7, 1H), 5.03(dd, J = 10.8, 7.8, 1H), 4.90–4.96 (m, 2H), 4.71 (d, J = 7.5, 1H), 4.60 (d, J = 1.8, 1H), 4.54–4.60 (m, 1H), 3.98 (d, J = 9.9, 1H), 3.74 (d, J = 6.3, 1H), 3.46–3.54 (m, 1H), 3.39 (s, 3H), 3.22–3.28 (m, 1H), 3.22 (s, 3H), 2.82–2.92 (m, 1H), 2.58–2.65 (m, 1H), 2.46 (d, J = 14.7, 1H), 2.30–2.38 (m, 1H), 2.30 (s, 3H), 2.27 (s, 6H), 1.88–2.25 (m, 3H), 1.35–1.75 (m, 8H), 1.20–1.26 (m, 12H), 1.08–1.11 (m, 6H), 1.01 (d, J = 6.0, 3H), 0.92–0.98 (m, 6H), 0.77 (t, J = 7.2, 3H). ^{13}C NMR ($CDCl_3$) δ 175.3, 166.1, 164.7, 133.1, 132.6, 130.3, 129.8, 129.6, 129.5, 128.2, 128.1, 108.5 (C9 hemiketal), 101.3, 97.5, 90.6, 86.4, 79.3, 79.2, 79.1, 77.6, 74.5, 73.0, 72.4, 68.5, 63.4, 63.2, 50.2, 49.8, 46.8, 46.2, 40.7, 39.6, 38.3, 37.8, 35.6, 31.9, 31.4, 28.8, 22.6, 21.5, 21.3, 21.2, 18.4, 17.9, 16.2, 15.5, 10.8, 10.7, 7.3. HPLC: t_R = 22.54 min. HRMS (ESI^+) m/z $[M+H]^+$ calcd for $C_{54}H_{81}NO_{17}S$: 1048.5297. Found: 1048.5260.

Stage x. To C_{12} ethyl, C_9, C_{11} OMs, C_{12} OH macrolide (3.73 g, 3.56 mmol) in acetone (49 mL) was added DBU (650 μL, 4.34 mmol). The solution was stirred for 5 h at rt and then for 40 h at 60 °C. The solution was diluted with ethyl acetate (1.5 L), washed with H_2O (2× 400 mL), $NaHCO_{3(satd)}$(400 mL), $NaCl_{(satd)}$ (300 mL), dried over $MgSO_4$, filtered, concentrated, and dried in vacuo yielding the C_{12} ethyl, C_9, C_{10}, C_{11} enone, C_{12} OH macrolide (3.32 g, 98% yield) as an off white solid. MS (ESI): 952.8 (MH^+). ^{1}H NMR ($CDCl_3$) δ 8.00–8.04 (m, 4H), 7.52–7.63 (m, 2H), 7.40–7.49 (m, 4H),

6.34 (s, 1H), 5.05–5.11 (m, 2H), 4.91–4.95 (m, 2H), 4.86 (d, $J = 7.2$, 1H), 4.46–4.54 (m, 1H), 3.74–78 (m, 2H), 3.62 (d, 6.6, 1H), 3.51 (s, 3H), 2.96–3.14 (m, 3H), 3.03 (s, 3H), 2.66–2.74 (m, 1H), 2.45 (d, $J = 15.0$, 1H), 2.31 (s, 6H), 2.10–2.20 (m, 1H), 1.96 (s, 3H), 1.40–1.94 (m, 10), 1.17–1.21 (m, 12H), 0.96 (d, $J = 6.3$, 3H), 0.88 (t, $J = 7.2$, 3H), 0.83 (t, $J = 7.2$, 3H), 0.74 (d, 7.5, 3H). ^{13}C NMR ($CDCl_3$) δ 207.4, 175.6, 166.2, 165.3, 139.3, 139.2 133.4, 132.6, 130.9, 129.9, 129.7, 129.6, 128.4, 128.2, 100.7, 95.6, 80.5, 79.4, 78.9, 78.8, 77.5, 76.1, 73.0, 72.4, 67.8, 63.8, 63.5, 50.3, 49.7, 44.9, 40.9, 40.1, 39.9, 35.4, 31.7, 28.5, 22.7, 21.3, 20.2, 19.7, 18.3, 15.2, 14.1, 10.8, 9.9, 7.8. HPLC: $t_R = 23.38$ min. HRMS (ESI$^+$) m/z $[M+H]^+$ calcd for $C_{53}H_{77}NO_{14}$: 952.5416. Found: 952.5437.

Stage xi. To C_{12} ethyl, C_9, C_{10}, C_{11} enone, C_{12} OH macrolide (5.84 g, 6.13 mmol) in acetonitrile (80 mL) was added 3 M $HCl_{(aq)}$ (40 mL). After standing for 22 h, the solution was diluted with ethyl acetate (1.4 L) and washed with $NaHCO_{3(satd)}$ (2× 400 mL), with $NaCl_{(satd)}$ (300 mL), dried over $MgSO_4$, filtered, and concentrated. Purification by flash chromatography (30% acetone/hexanes with 0.1% triethylamine) yielded the C_{12} ethyl, C_9, C_{10}, C_{11} enone, C_3, C_{12} diol macrolide (3.48 g, 82% yield) as a white solid. MS (ESI): 690.4 (MH^+). ^{1}H NMR ($CDCl_3$) δ 8.07–8.10 (m, 2H), 7.50–7.52 (m, 1H), 7.40–7.46 (m, 2H), 6.13 (s, 1H), 4.94–5.00 (m, 2H), 4.87 (d, $J = 8.1$, 1H), 3.87 (d, 3.0, 1H), 3.54–3.64 (m, 2H), 3.10 (s, 3H), 3.00–3.09 (m, 1H), 2.76–2.86 (m, 1H), 2.32–2.37 (m, 1H), 2.24 (s, 6H), 2.01 (s, 3H), 1.38–1.90 (m, 11H), 1.31 (s, 3H), 1.29 (d, $J = 6.0$, 3H), 1.21 (d, $J = 6.6$, 3H), 0.77–0.89 (m, 9H), 0.66 (d, $J = 6.9$, 3H). ^{13}C NMR ($CDCl_3$) δ 207.5, 175.2, 165.5, 139.6, 138.3, 132.5, 130.6, 129.8, 128.1, 103.0, 89.0, 80.4, 79.6, 76.5, 76.4, 72.4, 69.3, 64.3, 48.9, 44.1, 40.8, 38.3, 38.1, 37.7, 30.8, 27.9, 21.7, 21.3, 20.0, 17.6, 14.4, 13.7, 10.7, 8.5, 8.2. HPLC: $t_R = 15.67$ min. HRMS (ESI$^+$) m/z $[M+H]^+$ calcd for $C_{38}H_{59}NO_{10}$: 690.4211. Found: 690.4217.

Stage xii. To C_{12} ethyl, C_9, C_{10}, C_{11} enone, C_3, C_{12} diol macrolide (3.48 g, 5.0 mmol) in dichloromethane (100 mL) was added Dess–Martin Periodinane (3.39 g, 1.6 mmol). After stirring for 2 h, the solution was diluted with ethyl acetate (1.4 L) and washed with 1:1 10% $Na_2S_2O_3/NaHCO_{3(satd)}$ (2× 500 mL), with $NaCl_{(satd)}$ (300 mL), dried over $MgSO_4$, filtered, and concentrated. Purification by flash chromatography (30% acetone/hexanes with 0.1% triethylamine) yielded the C_{12} ethyl, C_9, C_{10}, C_{11} enone, C_3 oxo, C_{12} OH macrolide **3** (3.25 g, 94% yield) as a white solid. MS (ESI): 688.5 (MH^+). ^{1}H NMR ($CDCl_3$) δ 8.00–8.04 (m, 2H), 7.53–7.58 (m, 1H), 7.41–7.46 (m, 2H), 6.44 (s, 1H), 5.00–5.06 (m, 2H), 4.54 (d, $J = 7.5$, 1H), 4.14 (d, $J = 9.0$, 1H), 3.56–3.62 (m, 2H), 2.78–3.13 (m, 3H), 2.75 (s, 3H), 2.25 (s, 6H), 1.96 (s, 3H), 1.64–1.84 (m, 7H), 1.35–1.55 (m, 2H), 1.25–1.29 (m, 9H), 1.17 (d, $J = 8.1$, 3H), 0.97 (d, $J = 7.2$, 3H), 0.95 (t, $J = 7.2$, 3H), 0.85 (t, $J = 7.5$, 3H). ^{13}C NMR ($CDCl_3$) δ 209.9, 206.7, 169.6, 165.1, 140.8, 138.5, 132.7, 130.4, 129.7, 128.2, 101.8, 82.0, 79.9, 78.3, 76.4, 72.0, 69.2, 63.6, 51.3, 49.9, 47.4, 40.7, 31.7, 31.1, 28.5, 22.7, 20.9, 20.1, 19.3, 15.3, 14.6, 14.3, 13.5, 10.8, 7.7. HPLC: $t_R = 18.06$ min. HRMS (ESI$^+$) m/z $[M+H]^+$ calcd for $C_{38}H_{57}NO_{10}$: 688.4055. Found: 688.4033.

5.8. Compounds 4a–t

Stage xiv. To a solution of C_{12} ethyl, C_9, C_{10}, C_{11} enone, C_3 oxo, C_{12} OH macrolide **3** (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, $NaHCO_{3\ (satd)}$ (5 mL) was added cautiously to quench the excess hydride. The mixture was then diluted with ethyl acetate (600 mL), was washed with $NaHCO_{3(satd)}$ (4× 200 mL), with $NaCl_{(satd)}$ (200 mL), dried over $MgSO_4$, filtered, concentrated, and dried in vacuo yielding crude C_{12} ethyl 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): 782.5 (MH^+) and 688.5 (hydrolyzed MH^+).

Stage xv. Procedure A for final C_{12} ethyl ketolide: C_{12} ethyl 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 $NaHCO_{3\ (satd)}$ (3×), $NaCl_{(satd)}$ (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} ethyl ketolide.

5.8.1. Compound 4a. Following procedure A using the C_{12} ethyl imidazolyl carbamate macrolide and 4-imidazo[4,5-*b*]pyridin-3-yl-butylamine yielded **4a** (20% yield) as a white solid. MS (ESI): 800.7 (MH^+). HPLC: $t_R = 12.34$ min. ^{1}H NMR ($CDCl_3$) δ 8.37 (dd, $J = 4.8$, 1.2, 1H), 8.10 (s, 1H), 8.04 (dd, $J = 8.4$, 1.5, 1H) 7.21 (dd, $J = 8.4$, 4.5, 1H), 4.93 (dd, $J = 10.8$, 1.8, 1H), 4.23–4.42 (m, 4H), 3.84 (q, $J = 6.9$, 1H), 3.52–3.72 (m, 3H), 3.66 (s, 1H), 3.25 (dd, $J = 10.2$, 7.2, 1H), 3.15–3.22 (m, 1H), 3.02–3.12 (m, 1H), 2.60 (s, 3H), 2.54–2.66 (m, 1H), 2.38 (s, 6H), 1.54–2.04 (m, 14H), 1.35 (d, $J = 6.6$, 3H), 1.33 (s, 3H), 1.21–1.28 (m, 9H), 1.15 (d, $J = 7.2$, 3H), 1.01 (d, $J = 6.9$, 3H), 0.84 (t, $J = 7.5$, 3H). Anal. Calcd for $C_{42}H_{65}N_5O_{10}$: C, 63.06; H, 8.19; N, 8.75. Found: C, 62.84; H, 7.86; N, 8.52.

5.8.2. Compound 4b. Following procedure A using the C_{12} ethyl imidazolyl carbamate macrolide and 4-imidazo[4,5-*b*]pyridin-1-yl-butylamine yielded **4b** (31% yield) as a white solid. MS (ESI): 800.6 (MH^+). HPLC: $t_R = 11.49$ min. ^{1}H NMR ($CDCl_3$) δ 8.54 (d, $J = 4.8$, 1H), 8.16 (s, 1H), 7.79 (dd, $J = 8.1$, 0.9, 1H) 7.21 (dd, $J = 8.4$, 4.5, 1H), 4.90 (d, $J = 9.0$, 1H), 4.31 (d, $J = 7.2$, 1H), 4.20–4.26 (m, 2H), 3.85 (q, $J = 6.9$, 1H), 3.54–3.76 (m, 3H), 3.67 (s, 1H), 3.30 (dd, $J = 10.2$, 7.5, 1H),

3.15–3.22 (m, 1H), 3.00–3.12 (m, 1H), 2.66–2.78 (m, 1H), 2.60 (s, 3H), 2.44 (s, 6H), 1.54–2.10 (m, 14H), 1.36 (d, $J = 6.6$, 3H), 1.34 (s, 3H), 1.21–1.30 (m, 9H), 1.14 (d, $J = 6.6$, 3H), 1.00 (d, $J = 6.6$, 3H), 0.81 (t, $J = 7.5$, 3H). Anal. Calcd for $C_{42}H_{65}N_5O_{10}$: C, 63.06; H, 8.19; N, 8.75. Found: C, 63.40; H, 7.78; N, 8.64.

5.8.3. Compound 4c. Following procedure A using the C_{12} ethyl imidazolyl carbamate macrolide and 2-imidazo[4,5-*b*]pyridin-1-yl-4-methyl-pentylamine yielded **4c** (22% yield) as a white solid. MS (ESI): 828.7 (MH^+). HPLC: $t_R = 12.32$ min. ^1H NMR ($CDCl_3$) δ 8.55 (d, $J = 3.9$, 1H), 8.31 (s, 1H), 8.01 (d, $J = 8.1$, 1H) 7.23 (dd, $J = 8.4$, 4.8, 1H), 4.86 (d, $J = 8.4$, 1H), 4.44 (d, $J = 7.2$, 1H), 4.23 (d, $J = 7.8$, 1H), 3.82 (q, $J = 6.6$, 1H), 3.60 (s, 1H), 3.45–3.65 (m, 2H), 2.96–3.16 (m, 2H), 2.89 (s, 6H), 2.46–2.54 (m, 1H), 2.43 (s, 3H), 1.80–2.20 (m, 10H), 1.76 (s, 3H), 1.74 (s, 3H), 1.40–1.72 (m, 8H), 1.20–1.36 (m, 15H), 1.09 (d, $J = 6.6$, 3H), 0.95 (d, $J = 6.9$, 3H), 0.84 (t, $J = 7.2$, 3H). Anal. Calcd for $C_{44}H_{69}N_5O_{10}\cdot 3.1H_2O$: C, 59.78; H, 8.58; N, 7.93. Found: C, 59.73; H, 8.59; N, 8.28.

5.8.4. Compound 4d. Following procedure A using the C_{12} ethyl imidazolyl carbamate macrolide and 4-imidazo[4,5-*b*]pyridin-1-yl-4-methyl-pentylamine yielded **4d** (33% yield) as a white solid. MS (ESI): 828.8 (MH^+). HPLC: $t_R = 13.68$ min. ^1H NMR ($CDCl_3$) δ 8.33 (dd, $J = 4.5$, 1.2, 1H), 8.09 (s, 1H), 8.02 (dd, $J = 7.8$, 1.5, 1H) 7.19 (dd, $J = 7.8$, 4.5, 1H), 4.87 (dd, $J = 10.5$, 1.8, 1H), 4.30 (d, $J = 7.8$, 1H), 4.22 (d, $J = 8.1$, 1H), 3.79 (q, $J = 6.9$, 1H), 3.61 (s, 1H), 3.52–3.60 (m, 1H), 3.44 (t, $J = 7.5$, 2H), 3.24 (dd, $J = 10.2$, 7.5, 1H), 2.98–3.14 (m, 2H), 2.50–2.65 (m, 1H), 2.45 (s, 3H), 2.37 (s, 6H), 2.15–2.35 (m, 2H), 1.85–2.05 (m, 4H), 1.80 (s, 6H), 1.45–1.78 (m, 8H), 1.33 (d, $J = 6.9$, 3H), 1.25–1.30 (m, 9H), 1.21 (t, $J = 7.5$, 3H), 1.12 (d, $J = 6.9$, 3H), 0.96 (d, $J = 6.9$, 3H), 0.83 (t, $J = 6.9$, 3H). Anal. Calcd for $C_{44}H_{69}N_5O_{10}\cdot 1.1H_2O$: C, 62.35; H, 8.47; N, 8.27. Found: C, 62.35; H, 8.13; N, 8.13.

5.8.5. Compound 4e. Following procedure A using the C_{12} ethyl imidazolyl carbamate macrolide and 4-pyrrolo[3,2-*b*]pyridinylbutylamine yielded **4e** (52% yield) as a white solid. MS (ESI): 799.7 (MH^+). HPLC: $t_R = 12.72$ min. ^1H NMR ($CDCl_3$) δ 8.42 (dd, $J = 4.8$, 1.1, 1H), 7.67 (d, $J = 7.8$, 1H), 7.35 (d, $J = 3.3$, 1H) 7.08 (dd, $J = 8.1$, 4.5, 1H), 6.66 (d, $J = 3.3$, 1H), 4.93 (dd, $J = 10.5$, 1.8, 1H), 4.27 (t, $J = 7.2$, 1H), 4.15 (t, 7.2, 1H), 3.85 (q, $J = 7.2$, 1H), 3.52–3.68 (m, 3H), 3.66 (s, 1H), 3.16–3.22 (m, 2H), 3.03–3.13 (m, 1H), 2.59 (s, 3H), 2.42–2.52 (m, 1H), 2.29 (s, 6H), 1.45–1.25 (m, 12H), 1.38 (d, $J = 6.6$, 3H), 1.34 (s, 3H), 1.29 (d, $J = 7.5$, 3H), 1.20–1.26 (m, 9H), 1.15 (d, $J = 6.9$, 3H), 1.00 (d, $J = 6.9$, 3H), 0.82 (t, $J = 7.2$, 3H). Anal. Calcd for $C_{43}H_{66}N_4O_{10}$: C, 64.64; H, 8.33; N, 7.01. Found: C, 64.24; H, 8.05; N, 6.87.

5.8.6. Compound 4f. Following procedure A using the C_{12} ethyl imidazolyl carbamate macrolide and 4-(quinolin-2-yl)butan-1-amine yielded **4f** (39% yield) as a white solid. MS (ESI): 810.6 (MH^+). HPLC: $t_R = 13.20$ min. ^1H NMR ($CDCl_3$) δ 8.04 (d, $J = 8.1$, 1H), 8.03 (d, 8.4, 1H), 7.76 (dd, $J = 8.1$, 1.5, 1H), 7.64–7.69 (m, 1H), 7.46–7.49 (m, 1H), 7.31 (d, $J = 8.7$, 1H), 4.98 (dd, $J = 8.4$, 1.8, 1H), 4.28 (d, $J = 6.9$, 1H), 4.24 (d, $J = 4.8$, 1H), 3.83 (q, $J = 6.9$, 1H), 3.71 (s, 1H), 3.60–3.65 (m, 1H), 3.48–3.58 (m, 1H), 2.96–3.22 (m, 3H), 2.61 (s, 3H), 2.39–2.49 (m, 1H), 2.26 (s, 6H), 1.54–2.08 (m, 16H), 1.35 (d, $J = 6.9$, 3H), 1.33 (s, 3H), 1.21–1.28 (m, 9H), 1.15 (d, $J = 76.9$, 3H), 1.02 (d, $J = 6.9$, 3H), 0.85 (t, $J = 7.5$, 3H). Anal. Calcd for $C_{45}H_{67}N_3O_{10}\cdot 1.2H_2O$: C, 65.02; H, 8.41; N, 5.06. Found: C, 65.01; H, 8.13; N, 4.99.

5.8.7. Compound 4g. Following procedure A using the C_{12} ethyl imidazolyl carbamate macrolide and *N*1-methyl-*N*1-(quinolin-2-ylmethyl)ethane-1,2-diamine yielded **4g** (13% yield) as a white solid. MS (ESI): 825.7 (MH^+). HPLC: $t_R = 14.94$ min. ^1H NMR ($CDCl_3$) δ 8.24 (d, $J = 6.0$, 1H), 8.13 (d, $J = 8.1$, 1H), 7.80–7.86 (m, 2H), 7.72–7.77 (m, 1H), 7.56–7.61 (m, 1H), 4.90 (d, $J = 9.9$, 1H), 4.39–4.54 (m, 2H), 4.37 (d, $J = 7.2$, 1H), 4.24 (d, $J = 8.1$, 1H), 3.86–4.12 (m, 2H), 3.80 (q, $J = 6.9$, 1H), 3.69 (s, 1H), 3.58–3.66 (m, 1H), 3.12–3.54 (m, 4H), 2.98–3.06 (m, 1H), 2.73 (s, 9H), 2.63 (s, 3H), 2.50–2.58 (m, 1H), 1.40–2.12 (m, 10H), 1.23–1.33 (m, 15H), 1.15 (d, $J = 6.9$, 3H), 1.00 (d, $J = 6.6$, 3H), 0.79 (t, $J = 7.2$, 3H). Anal. Calcd for $C_{45}H_{68}N_4O_{10}\cdot 2.2H_2O$: C, 62.49; H, 8.44; N, 6.48. Found: C, 62.48; H, 8.02; N, 6.41.

5.8.8. Compound 4h. Following procedure A using the C_{12} ethyl imidazolyl carbamate macrolide and *N*1-methyl-*N*1-(quinolin-3-ylmethyl)ethane-1,2-diamine yielded **4h** (35% yield) as a white solid. MS (ESI): 825.7 MH^+. HPLC: $t_R = 12.22$ min. ^1H NMR ($CDCl_3$) δ 8.84 (d, $J = 2.1$, 1H), 8.12 (s, 1H), 8.08 (d, $J = 8.1$, 1H), 7.81 (d, $J = 6.9$, 1H), 7.63–7.69 (m, 1H), 7.48–7.54 (m, 1H), 5.08 (dd, $J = 10.8$, 2.4, 1H), 4.30 (d, $J = 6.9$, 1H), 4.24 (d, $J = 8.4$, 1H), 3.86–3.94 (m, 3H), 3.82 (q, $J = 6.6$, 1H), 3.68 (d, $J = 13.2$, 1H), 3.67 (s, 1H), 3.52–3.62 (m, 1H), 3.19–3.30 (m, 2H), 3.02–3.13 (m, 1H), 2.82–2.91 (m, 1H), 2.57–2.67 (m, 2H), 2.64 (s, 3H), 2.41 (s, 6H), 2.24 (s, 3H), 1.54–2.06 (m, 10H), 1.23–1.33 (m, 15H), 1.17 (d, $J = 6.9$, 3H), 1.05 (d, $J = 6.9$, 3H), 0.71 (t, $J = 7.2$, 3H). Anal. Calcd for $C_{45}H_{68}N_4O_{10}\cdot 1.5H_2O$: C, 63.48; H, 8.40; N, 6.59. Found: C, 63.46; H, 8.00; N, 6.65.

5.8.9. Compound 4i. Following procedure A using the C_{12} ethyl imidazolyl carbamate macrolide and 4-(quinolin-4-yl)butan-1-amine yielded **4i** (47% yield) as a white solid. MS (ESI): 810.6 (MH^+). HPLC: $t_R = 13.57$ min. ^1H NMR ($CDCl_3$) δ 8.80 (d, $J = 4.5$, 1H), 8.11 (d, $J = 8.4$, 1H), 8.06 (d, $J = 8.4$, 1H) 7.67–7.72 (m, 1H), 7.55–7.58 (m, 1H), 7.27 (d, $J = 4.2$, 1H), 4.98 (dd, $J = 10.5$, 2.1, 1H), 4.29 (t, $J = 7.5$, 2H), 3.86 (q, $J = 6.9$, 1H), 3.73 (s, 1H), 3.62–3.70 (m, 1H), 3.52–3.62 (m, 1H), 3.06–3.24 (m, 3H), 2.64 (s, 3H), 2.42–2.53 (m, 1H), 2.29 (s, 6H), 1.54–2.12 (m, 14H), 1.40 (d, $J = 6.6$, 3H), 1.36 (s, 3H), 1.21–1.32 (m, 9H), 1.18 (d, $J = 6.9$, 3H), 1.04 (d, $J = 6.9$, 3H), 0.84 (t, $J = 7.2$, 3H). Anal. Calcd for $C_{45}H_{67}N_3O_{10}\cdot 1.0H_2O$: C, 65.25; H, 8.40; N, 5.07. Found: C, 65.21; H, 8.23; N, 5.18.

5.8.10. Compound 4j. Following procedure A using the C_{12} ethyl imidazolyl carbamate macrolide and *N*1-methyl-*N*1-(quinolin-4-ylmethyl)ethane-1,2-diamine yielded **4j** (20% yield) as a white solid. MS (ESI): 825.7 (MH^+). HPLC: t_R = 12.00 min. ^{1}H NMR ($CDCl_3$) δ 8.84 (d, J = 4.8, 1H), 8.18 (d, J = 8.1, 1H), 8.09 (d, J = 8.7, 1H), 7.65–7.70 (m, 1H), 7.50–7.57 (m, 2H), 7.56–7.61 (m, 1H), 4.99 (dd, J = 10.8, 2.4, 1H), 4.31 (d, J = 8.1, 1H), 4.23 (d, J = 8.4, 1H), 4.06 (d, J = 5.4, 1H), 3.76–3.88 (m, 2H), 3.67 (s, 1H), 3.54–3.62 (m, 1H), 3.33 (dd, J = 10.2, 7.2, 1H), 3.20 (q, J = 6.9, 1H), 2.70–3.24 (m, 4H), 2.59 (s, 3H), 2.49 (s, 6H), 2.27 (s, 3H), 1.52–2.08 (m, 10H), 1.22–1.33 (m, 15H), 1.16 (d, J = 7.2, 3H), 1.04 (d, J = 6.9, 3H), 0.67 (t, J = 7.2, 3H). Anal. Calcd for $C_{45}H_{68}N_4O_{10}$: C, 65.51; H, 8.31; N, 6.79. Found: C, 65.94; H, 8.21; N, 6.66.

5.8.11. Compound 4k. Following procedure A using the C_{12} ethyl imidazolyl carbamate macrolide and 4-(4-(pyridin-3-yl)-1*H*-imidazol-1-yl)butan-1-amine yielded **4k** (44% yield) as a white solid. MS (ESI): 826.7 (MH^+). HPLC: t_R = 11.34 min. ^{1}H NMR ($CDCl_3$) δ 8.96 (d, J = 1.5, 1H), 8.45 (dd, J = 4.8, 1.8, 1H), 8.08 (dt, J = 7.8, 1.8, 1H), 7.54 (d, J = 1.5, 1H) 7.33 (d, J = 1.5, 1H), 7.26–7.30 (m, 1H), 4.94 (dd, J = 10.5, 2.1, 1H), 4.28 (d, J = 8.4, 1H), 4.24 (d, J = 9.0, 1H), 4.01 (t, J = 7.2, 2H), 3.85 (q, J = 6.6, 1H), 3.67 (s, 1H), 3.50–3.72 (m, 3H), 3.16–3.24 (m, 2H), 3.02–3.12 (m, 1H), 2.63 (s, 3H), 2.46–2.58 (m, 1H), 2.31 (s, 6H), 1.55–2.10 (m, 14H), 1.36 (d, J = 6.9, 3H), 1.34 (s, 3H), 1.22–1.30 (m, 9H), 1.16 (d, J = 6.9, 3H), 1.01 (d, J = 6.6, 3H), 0.83 (t, J = 7.2, 3H). ^{13}C NMR ($CDCl_3$) δ 216.1, 203.1, 169.5, 157.0, 147.3, 146.2, 138.8, 137.6, 131.8, 130.1, 123.3, 115.4, 103.8, 82.9, 79.5, 78.2, 70.3, 69.5, 65.8, 60.3, 51.3, 49.8, 47.7, 46.9, 44.9, 42.8, 40.2, 39.3, 38.6, 28.7, 28.6, 24.4, 23.3, 23.0, 21.2, 21.1, 19.8, 18.2, 15.8, 14.4, 14.3, 10.9, 9.7. Anal. Calcd for $C_{44}H_{67}N_5O_{10}$: C, 63.98; H, 8.18; N, 8.48. Found: C, 64.34; H, 8.60; N, 8.10.

5.8.12. Compound 4l. Following procedure A using the C_{12} ethyl imidazolyl carbamate macrolide and 4-[4-(6-methyl-pyridin-3-yl)-imidazol-1-yl]-butylamine yielded **4l** (44% yield) as a white solid. MS (ESI): 840.7 (MH^+). HPLC: t_R = 11.80 min. ^{1}H NMR ($CDCl_3$) δ 8.83 (d, J = 2.1, 1H), 7.96 (dd, J = 7.8, 2.4, 1H), 7.52 (d, J = 1.5, 1H) 7.27 (d, J = 1.2, 1H), 7.15 (d, J = 8.1, 1H), 4.93 (dd, J = 10.5, 2.4, 1H), 4.28 (d, J = 7.2, 1H), 4.25 (d, J = 8.7, 1H), 4.0 (t, J = 7.2, 2H), 3.85 (q, J = 6.9, 1H), 3.50–3.72 (m, 3H), 3.68 (s, 1H), 3.16–3.26 (m, 2H), 3.02–3.12 (m, 1H), 2.63 (s, 3H), 2.52–2.62 (m, 1H) 2.55 (s, 3H), 2.34 (s, 6H), 1.56–2.12 (m, 14H), 1.34–1.37 (m, 6H), 1.20–1.31 (m, 9H), 1.16 (d, J = 6.9, 3H), 1.01 (d, J = 6.9, 3H), 0.83 (t, J = 7.5, 3H). Anal. Calcd for $C_{45}H_{69}N_5O_{10}\cdot 1.7H_2O$: C, 62.04; H, 8.39; N, 8.04. Found: C, 62.04; H, 8.16; N, 7.98.

5.8.13. Compound 4m. Following procedure A using the C_{12} ethyl imidazolyl carbamate macrolide and 4-[4-(6-fluoro-pyridin-3-yl)-imidazol-1-yl]-butylamine yielded **4m** (27% yield) as a white solid. MS (ESI): 844.7 (MH^+). HPLC: t_R = 12.60 min. ^{1}H NMR ($CDCl_3$) δ 8.55 (d, J = 2.1, 1H), 8.18 (td, J = 8.4, 2.4, 1H), 7.52 (d, J = 1.2, 1H), 7.29 (d, J = 1.2, 1H), 6.93 (dd, J = 8.7, 2.7, 1H), 4.93 (dd, J = 11.1, 2.4, 1H), 4.32 (d, J = 7.2, 1H), 4.24 (d, J = 8.9, 1H), 4.0 (t, J = 7.2, 2H), 3.85 (q, J = 6.9, 1H), 3.53–3.78 (m, 3H), 3.67 (s, 1H), 3.23 (dd, J = 9.9, 7.2, 1H), 3.19–3.23 (m, 1H), 3.04–3.12 (m, 1H), 2.74–2.84 (m, 1H), 2.61 (s, 3H), 2.51 (s, 6H), 1.48–2.10 (m, 14H), 1.35 (d, J = 6.6, 3H), 1.23–1.34 (m, 12H), 1.17 (d, J = 6.9, 3H), 1.02 (d, J = 6.9, 3H), 0.83 (t, J = 7.5, 3H). Anal. Calcd for $C_{44}H_{66}FN_5O_{10}\cdot 0.4H_2O$: C, 61.56; H, 8.03; F, 2.27; N, 8.35. Found: C, 61.58; H, 7.71; F, 2.66; N, 7.95.

5.8.14. Compound 4n. Following procedure A using the C_{12} ethyl imidazolyl carbamate macrolide and 4-[4-(6-chloro-pyridin-3-yl)-imidazol-1-yl]-butylamine yielded **4n** (15% yield) as a white solid. MS (ESI): 860.7 (MH^+). HPLC: t_R = 13.18 min. ^{1}H NMR ($CDCl_3$) δ 8.73 (d, J = 2.4, 1H), 8.05 (dd, J = 8.1, 2.4, 1H), 7.53 (d, J = 1.2, 1H) 7.33 (s, 1H), 7.31 (d, J = 7.2, 1H), 4.93 (dd, J = 10.5, 2.4, 1H), 4.29 (d, J = 6.9, 1H), 4.24 (d, J = 8.7, 1H), 4.0 (t, J = 7.5, 2H), 3.85 (q, J = 6.9, 1H), 3.50–3.74 (m, 3H), 3.67 (s, 1H), 3.16–3.28 (m, 2H), 3.02–3.12 (m, 1H), 2.61 (s, 3H), 2.52–2.58 (m, 1H), 2.36 (s, 6H), 1.55–2.08 (m, 14H), 1.35 (d, J = 6.9, 3H), 1.33 (s, 3H), 1.22–1.29 (m, 9H), 1.16 (d, J = 6.6, 3H), 1.01 (d, J = 6.9, 3H), 0.83 (t, J = 7.5, 3H). Anal. Calcd for $C_{44}H_{66}ClN_5O_{10}\cdot 0.7H_2O$: C, 60.12; H, 7.44; Cl, 3.89; N, 7.80. Found: C, 60.13; H, 7.54; Cl, 3.79; N, 7.83.

5.8.15. Compound 4o. Following procedure A using the C_{12} ethyl imidazolyl carbamate macrolide and 4-[4-(6-methoxy-pyridin-3-yl)-imidazol-1-yl]-butylamine yielded **4o** (33% yield) as a white solid. MS (ESI): 856.7 (MH^+). HPLC: t_R = 13.21 min. ^{1}H NMR ($CDCl_3$) δ 8.51 (dd, J = 2.4, 0.9, 1H), 7.97 (dd, J = 8.7, 2.4, 1H), 7.50 (d, J = 1.2, 1H) 7.17 (d, J = 1.5, 1H), 6.75 (dd, J = 8.7, 0.6, 1H), 4.93 (dd, J = 10.5, 2.1, 1H), 4.27 (d, J = 7.5, 1H), 4.25 (d, J = 8.4, 1H), 3.98 (t, J = 7.5, 2H), 3.95 (s, 3H), 3.85 (q, J = 6.6, 1H), 3.48–3.76 (m, 3H), 3.68 (s, 1H), 3.15–3.24 (m, 2H), 3.02–3.12 (m, 1H), 2.63 (s, 3H), 2.40–2.48 (m, 1H), 2.26 (s, 6H), 1.54–2.08 (m, 14H), 1.36 (d, J = 6.9, 3H), 1.35 (s, 3H), 1.20–1.30 (m, 9H), 1.16 (d, J = 7.2, 3H), 1.01 (d, J = 6.9, 3H), 0.83 (t, J = 7.5, 3H). Anal. Calcd for $C_{45}H_{69}N_5O_{11}\cdot 2.4H_2O$: C, 60.07; H, 8.28; N, 7.79. Found: C, 60.08; H, 8.19; N, 7.67.

5.8.16. Compound 4p. Following procedure A using the C_{12} ethyl imidazolyl carbamate macrolide and 4-(4-Pyrimid-5-yl-imidazol-1-yl)-butylamine yielded **4p** (27% yield) as a white solid. MS (ESI): 827.7 (MH^+). HPLC: t_R = 11.45 min. ^{1}H NMR ($CDCl_3$) δ 9.10 (s, 2H), 9.06 (s, 1H), 7.56 (d, J = 1.2, 1H) 7.40 (d, J = 1.5, 1H), 4.92 (dd, J = 10.5, 2.1, 1H), 4.27 (d, J = 7.5, 1H), 4.23 (d, J = 9.3, 1H), 4.02 (t, J = 7.5, 2H), 3.84 (q, J = 6.9, 1H), 3.67 (s, 1H), 3.50–3.74 (m, 3H), 3.16–3.24 (m, 2H), 3.02–3.12 (m, 1H), 2.60 (s, 3H), 2.42–2.56 (m, 1H), 2.30 (s, 6H), 1.55–2.10 (m, 14H), 1.34–1.36 (m, 6H), 1.21–1.29 (m, 9H), 1.16 (d, J = 6.9, 3H), 1.01 (d, J = 6.9, 3H), 0.82 (t, J = 7.2, 3H). Anal. Calcd for $C_{43}H_{66}N_6O_{10}\cdot 1.8H_2O$: C, 60.02; H, 8.17; N, 9.77. Found: C, 60.08; H, 8.44; N, 9.47.

5.8.17. Compound 4q. Following procedure A using the C_{12} ethyl imidazolyl carbamate macrolide and 4-(4-pyrazin-2-yl-imidazol-1-yl)-butylamine yielded **4q** (29% yield) as a white solid. MS (ESI): 827.7 (MH^+). HPLC: t_R = 11.88 min. ^{1}H NMR ($CDCl_3$) δ 9.19 (d, J = 1.8, 1H), 8.44 (dd, J = 2.4, 1.2, 1H), 8.37 (d, J = 2.7, 1H) 7.65 (d, J = 1.2, 1H), 7.56 (d, J = 1.5, 1H), 4.93 (dd, J = 10.8, 1.8, 1H), 4.28 (d, J = 7.5, 1H), 4.25 (d, J = 9.3, 1H), 4.03 (t, J = 7.5, 2H), 3.84 (q, J = 6.9, 1H), 3.68 (s, 1H), 3.50–3.74 (m, 3H), 3.16–3.24 (m, 2H), 3.02–3.12 (m, 1H), 2.63 (s, 3H), 2.42–2.56 (m, 1H), 2.30 (s, 6H), 1.55–2.10 (m, 14H), 1.34–1.36 (m, 6H), 1.22–1.30 (m, 9H), 1.16 (d, J = 6.9, 3H), 1.01 (d, J = 6.9, 3H), 0.84 (t, J = 7.2, 3H). Anal. Calcd for $C_{43}H_{66}N_6O_{10}\cdot 4.6H_2O$: C, 56.73; H, 8.34; N, 9.24. Found: C, 56.76; H, 8.46; N, 9.06.

5.8.18. Compound 4r. Following procedure A using the C_{12} ethyl imidazolyl carbamate macrolide and 4-(4-(pyridin-4-yl)-1*H*-imidazol-1-yl)butan-1-amine yielded **4r** (31% yield) as a white solid. MS (ESI): 826.7 (MH^+). HPLC: t_R = 11.51 min. ^{1}H NMR ($CDCl_3$) δ 8.56 (d, J = 4.8, 2H), 7.69 (d, J = 4.8, 1H), 7.55 (d, J = 1.2, 1H), 7.49 (d, J = 1.2, 1H), 4.94 (dd, J = 10.5, 2.1, 1H), 4.35 (d, J = 7.2, 1H), 4.24 (d, J = 8.7, 1H), 4.02 (t, J = 7.2, 2H), 3.86 (q, J = 7.2, 1H), 3.67 (s, 1H), 3.56–3.74 (m, 3H), 3.40–3.46 (m, 1H), 3.16–3.24 (m, 1H), 3.0–3.10 (m, 1H), 2.64 (s, 3H), 2.59 (s, 6H), 1.58–2.10 (m, 14H), 1.36 (d, J = 6.9, 3H), 1.30 (s, 3H), 1.24–1.30 (m, 9H), 1.17 (d, J = 6.9, 3H), 1.02 (d, J = 6.6, 3H), 0.83 (t, J = 7.2, 3H). Anal. Calcd for $C_{44}H_{67}N_5O_{10}\cdot 3.5H_2O$: C, 59.40; H, 8.39; N, 7.88. Found: C, 59.41; H, 7.98; N, 7.63.

5.8.19. Compound 4s. Following procedure A using the C_{12} ethyl imidazolyl carbamate macrolide and 4-(4-phenyl-1*H*-imidazol-1-yl)butan-1-amine yielded **4s** (42% yield) as a white solid. MS (ESI): 825.7 (MH^+). HPLC: t_R = 13.94 min. ^{1}H NMR ($CDCl_3$) δ 8.96 (d, J = 1.5, 1H), 8.45 (dd, J = 4.8, 1.8, 1H), 8.08 (dt, J = 7.8, 1.8, 1H), 7.54 (d, J = 1.5, 1H) 7.33 (d, J = 1.5, 1H), 7.26–7.30 (m, 1H), 4.94 (dd, J = 10.5, 2.1, 1H), 4.28 (d, J = 8.4, 1H), 4.24 (d, J = 9.0, 1H), 4.01 (t, J = 7.2, 2H), 3.85 (q, J = 6.6, 1H), 3.67 (s, 1H), 3.50–3.72 (m, 3H), 3.16–3.24 (m, 2H), 3.02–3.12 (m, 1H), 2.63 (s, 3H), 2.46–2.58 (m, 1H), 2.31 (s, 6H), 1.55–2.10 (m, 14H), 1.36 (d, J = 6.9, 3H), 1.34 (s, 3H), 1.22–1.30 (m, 9H), 1.16 (d, J = 6.9, 3H), 1.01 (d, J = 6.6, 3H), 0.83 (t, J = 7.2, 3H). Anal. Calcd for $C_{45}H_{68}N_4O_{10}\cdot 1.2H_2O$: C, 63.85; H, 8.38; N, 6.62. Found: C, 63.86; H, 7.97; N, 6.39.

5.8.20. Compound 4t. Following procedure A using the C_{12} ethyl imidazolyl carbamate macrolide and *N*1-[3,3′]bipyridinyl-5-ylmethyl-*N*1-methyl-ethane-1,2-diamine yielded **4t** (43% yield) as a white solid. MS (ESI): 852.7 (MH^+). HPLC: t_R = 10.10 min. ^{1}H NMR ($CDCl_3$) δ 8.87 (d, J = 2.7, 1H), 8.71 (d, J = 2.4, 1H), 8.63 (dd, J = 4.8, 1.5, 1H), 8.51 (d, J = 1.5, 1H), 7.93–7.98 (m, 2H), 7.40 (dd, J = 8.1, 4.8, 1H), 5.04 (dd, J = 10.5, 2.4, 1H), 4.28 (d, J = 7.5, 1H), 4.24 (d, J = 8.4, 1H), 3.78–3.94 (m, 4H), 3.65 (s, 1H), 3.48–3.58 (m, 2H), 3.18–3.24 (m, 2H), 3.02–3.10 (m, 1H), 2.78–2.90 (m, 1H), 2.65 (s, 3H), 2.50–2.58 (m, 2H), 2.32 (s, 6H), 2.23 (s, 3H), 1.40–2.05 (m, 10H), 1.21–1.34 (m, 15H), 1.17 (d, J = 6.6, 3H), 1.03 (d, J = 6.6, 3H), 0.64 (t, J = 7.2, 3H). Anal. Calcd for $C_{46}H_{69}N_5O_{10}$: C, 64.84; H, 8.16; N, 8.22. Found: C, 64.42; H, 7.79; N, 8.15.

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Supplementary data

Synthesis and X-ray structure of the epimeric C_{12} ethyl, C_{12} hydroxy, C_9, C_{11} acetonide macrolide, and ^{1}H NMR spectra of final ketolide **4k** and telithromycin. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2006.04.032.

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20. (a) Sidechains for compounds **4c**,**4d**,**4l**,**4m**,**4n**,**4o**,**4p**,**4q**, and **4t** were prepared as described in Ref. 10. Sidechains for compounds **4e**,**4g**,**4h**,**4j**, and **4r** were prepared using the methods described in Ref. 10; (b) Sidechains for compounds **4a**,**4b**,**4i**,**4k**, and **4s** were prepared as described in Ref. 6a; (c) The sidechain for compound **4f** was prepared as in Agouridas, Constantin; Chantot, Jean-Francois; Denis, Alexis; Gouin d'Ambrieres, Solange; Le Martret, Odile. Eur. Pat. Appl. (1995) EP 680967 A1 19951108.
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