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A journey across the sequential development of macrolides and ketolides related to erythromycin

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Contents

Keywords: Erythromycin; Macrolides; Carbamate ketolides; Carbazate ketolides; Acylides.

Abbreviations: Ac, acetyl; Bn, benzyl; Bz, benzoyl; Clad, cladinose; CBZ, carbobenzyloxy; CDI, carbonyldiimidazole; DBU, 1,5-diazabicyclo[5.4.0]-undec-5-ene; DEAD, diethyl azadicarboxylate; Des, desosamine; DMAP, *N*,*N*-dimethyl-4-pyridinamine; DMF, *N*,*N*-dimethylformamide; DMSO, dimethylsulfoxide; DPPA, diphenylphosphoryl azide; EDC, 1-[3-dimethylaminopropyl]-3-ethylcarbodiimide; HMDS, hexamethyldisilazane; MEM, 2-methoxyethoxymethyl; THF, tetrahydrofuran; TMS, trimethylsilyl; TFA, trifluoroacetic acid; *p*-Ts, *p*-toluenesulfonyl; SAR, Structure–activity relationship; TABF, tetra-*n*-butylammonium fluoride.

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1. Introduction: the family of macrolides

The macrolides belong to the polyketide class of natural products. They are a group of drugs, the activity of which stems from the presence of a macrolide ring, a large lactone ring to which one or more deoxy sugars, usually cladinose or desosamine, are attached. The macrocyclic lactone ring can either be fourteen 14-, fifteen 15- or sixteen 16-membered and, depending on the size of the ring, macrolides can be classified as follows:

Fourteen 14-membered ring	Fifteen 15-membered ring	Sixteen 16-membered ring
Erythromycin	Azithromycin	Josamycin
Roxithromycin		Spiramycin
Clarithromycin		Miocamycin
Dirithromycin		

2. Erythromycin—the origin of all 14-membered macrolide antibiotics

One of the most successful drugs of all time, erythromycin, characterized by a 14-membered lactone ring, is a mixture of macrolides produced by the fermentation of the fungus, *Streptomyces erythreus*. Macrolide antibiotics are usually safe and effective for the treatment of upper and lower respiratory tract infections, as well as genital infections.[1a–d] Erythromycin A (**1**) (Fig. 1), the main component of the mixture, has been in clinical use for about 50 years[2] and was first isolated by McGuire et al.[3] in 1952.

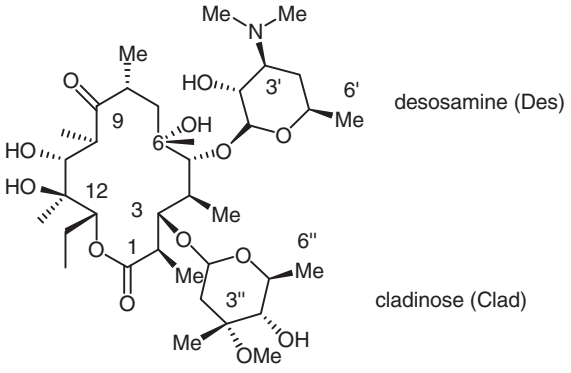


Figure 1. Erythromycin.

Erythromycin, a unique antibiotic, is effective against many gram-positive bacteria, although *Staphylococci* are often resistant. Among the gram-negative agents, *Bordetella pertussis* and *Legionella pneumophila,* are worthy of mention. Erythromycin has a similar activity spectrum to penicillin. Like tetracyclines, erythromycin is also active against bacteria such as *Chlamydia trachomatis*, *Mycoplasma pneumoniae* and *Ureaplasma urealyticum*. The specific antibacterial action of erythromycin, however, involves the blockade of protein synthesis on ribosomes.[4]

2.1. Synthesis of erythromycin—a brief overview

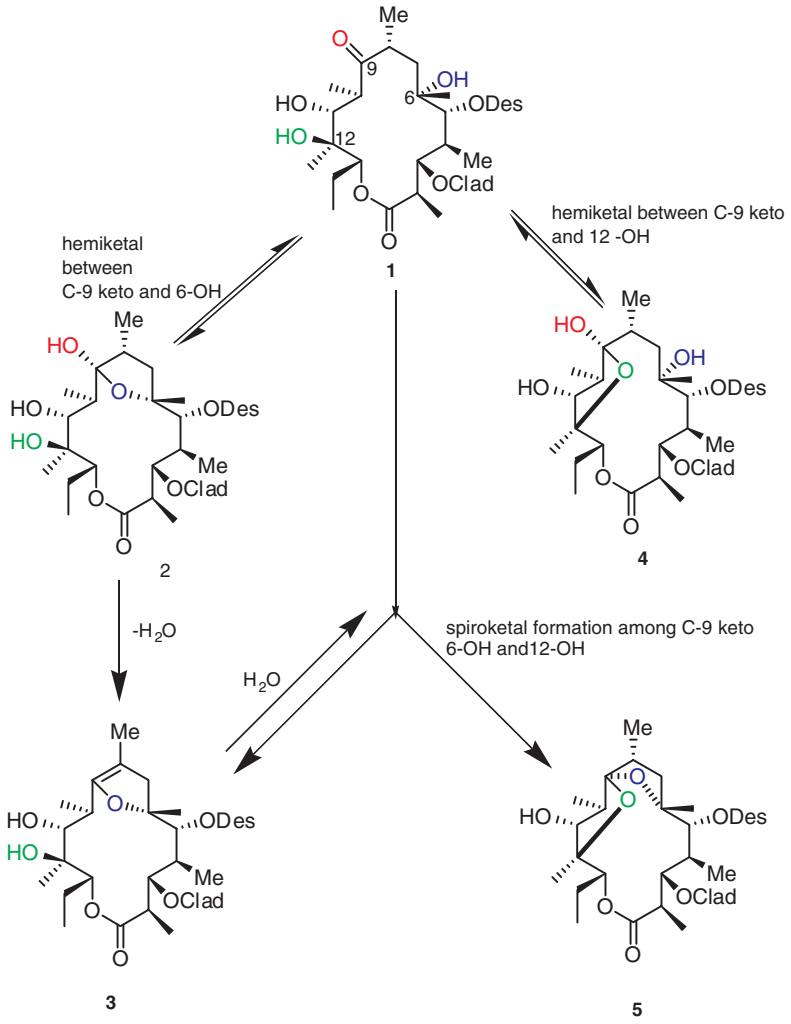
Although erythromycin can be obtained on an industrial scale by a fermentation method, the chemical synthesis of erythromycin and related compounds offers a formidable synthetic challenge, due to (i) its apparently complex structure containing ten asymmetric carbon atoms (five of which are consecutive) and (ii) the lack of an efficient methodology for the crucial lactonisation process. Inspired and challenged by the complexity of its macrocyclic structure, different research groups were involved for more than a decade in order to achieve its chemical synthesis. Nevertheless, all the total syntheses of erythromycin follow the same synthetic strategy, the formation of aglycons from the seco acids followed by glycosidation.[5a–c,6,7] The seco acids can be assembled in a convergent manner from two major components (Eastern and Western zones) or can be obtained in a linear fashion.[8] Usually, seco acids are subjected to lactonization, which can be achieved either by a Corey–Nicolaou double-activation method[9a,b] or by Yamaguchi lactonisation.[10] The aglycon is then subjected to glycosidation with properly activated and suitably protected desosamine and cladinose, respectively, to synthesize erythromycin. The syntheses of erythromycin via the reverse protocol, that is, glycosidation followed by lactonisation, are relatively few.[11]

2.2. Use of erythromycin as an antibacterial agent: its limitations—a chemist's view

The antibacterial activity of erythromycin stems from its ability to inhibit protein biosynthesis. In other words, macrolides inhibit protein biosynthesis by binding to 2058–2062 region of 23S ribosomal RNA of the 50S ribosomal subunit. They act by stimulating the dissociation of peptidyl *t*-RNA from ribosomes during the translocation process, thereby inhibiting protein synthesis.[12] Although allergic reactions to erythromycin are unusual, the use of erythromycin suffers from a few limitations such as hepatotoxicity and degradability in acid.

The hepatotoxicity of erythromycin is a limiting factor, to which very little attention has been paid. It has been shown that the *N*,*N*-dimethylamino group of the cladinose moiety plays a vital role in inducing inactivity into erythromycin.[13a,b] As this tertiary amine is essential for the binding of macrolide antibiotics to their ribosomal target within the bacteria,[14] the hepatotoxicity can be decreased by several factors: (i) increasing protonation, leading to the protonated form at physiological pH,[15] (ii) conformational changes,[16] (iii) introducing steric crowding around the *N*,*N*-dimethylamino group[17] and (iv) diminishing the hydrophobicity by introducing extra hydroxy groups on to erythromycin A (**1**).[18]

Erythromycin degrades in acidic conditions found in the stomach and produces inactive byproducts,[19]which are responsible for its poor bioavailability and gastrointestinal side effects. This degradation involves reactions of four sites, for example, C-9 ketone, 6-OH, 12-OH and C-8, as they are in close proximity. Under non-aqueous acidic conditions, erythromycin gives enol ether **3**[20] via **2** and, in aqueous acidic conditions, it gets converted into a 6,9:9, 12-spiroketal, anhydroerythromycin A (**5**).[21] Both **3** and **5** can, however, formed simultaneously.[22] In an aqueous medium, neither **3** nor **5** is present in significant amounts, but the predominant tautomer is **4** (Scheme 1).



Scheme 1. Formation of hemiketal and spiroketal from **1** in acid medium.

2.3. Strategies to overcome the limitations of erythromycin via modifications of its basic skeleton

In order to prevent its degradation in the presence of acid, modifications to the basic skeleton of erythromycin A were carried out at the four active sites such as C-9 ketone, 6-OH, 12-OH and 8-H. These gave rise to several analogues with an expanded gram-negative antibacterial activity spectrum and a wider tolerance for oral administration (Fig. 2). Among these analogues, clarithromycin (**6**), azithromycin (**7**) and roxithromycin (**8**) are the most popular in current use. These drugs are relatively more stable towards acids and can be given in lower doses for a shorter period of time, compared to erythromycin.

Other compounds of potential clinical interest are the 8-fluoro analog, flurithromycin (**9**), and the 9,11-oxazine, dirithromycin (**10**), both of which have shown promising results in animal models.

2.3.1. Synthesis of 6-*O*-alkylerythromycins via chemoselective alkylation. Although the structure of 6-*O*-methylerythromycin is deceptively simple, its synthesis was not trivial. Since erythromycin A (**1**) has five hydroxyl groups, it was difficult to alkylate the C-6 hydroxyl group selectively without affecting the other OH groups. The first regioselective alkylation was achieved by Watanabe and co-workers[23] via 2′-*O*,3′-*N*-bis(benzyloxycarbonyl)-*N*-demethylerythromycin (**11**) (Scheme 2). The process involved chromatographic separation of the desired product from a mixture of methylated products obtained after the methylation reaction. The main disadvantage of this process was the regioselective methylation that preferentially occurred at the undesired secondary 11-OH position more effectively than the desired tertiary 6-OH position. Methylation with a protected 11-OH group also failed, since it gave exclusively the 9-*O*-methyl derivative of the 6,9-hemiacetal. Finally, Watanabe and co-workers solved[24a,b] this problem by methylating 2′-*O*,3′-*N*-bis(benzyloxycarbonyl)-*N*-demethylerythromycin A 9-oxime derivatives, obtained from **11** (Scheme 3) via an oximation reaction.

The reactivity and selectivity of 6-OH were studied extensively by varying several parameters such as (a) protective groups of oxime, (b) solvents, (c) bases and (d) methylating agents. It was observed that, among the various protective groups examined, that is, trityl, benzyl, 2-chlorobenzyl, allyl, methyl etc., the selectivity improved with an increase in bulkiness of the group. By considering the slow reactivity caused by the bulky groups, however, the

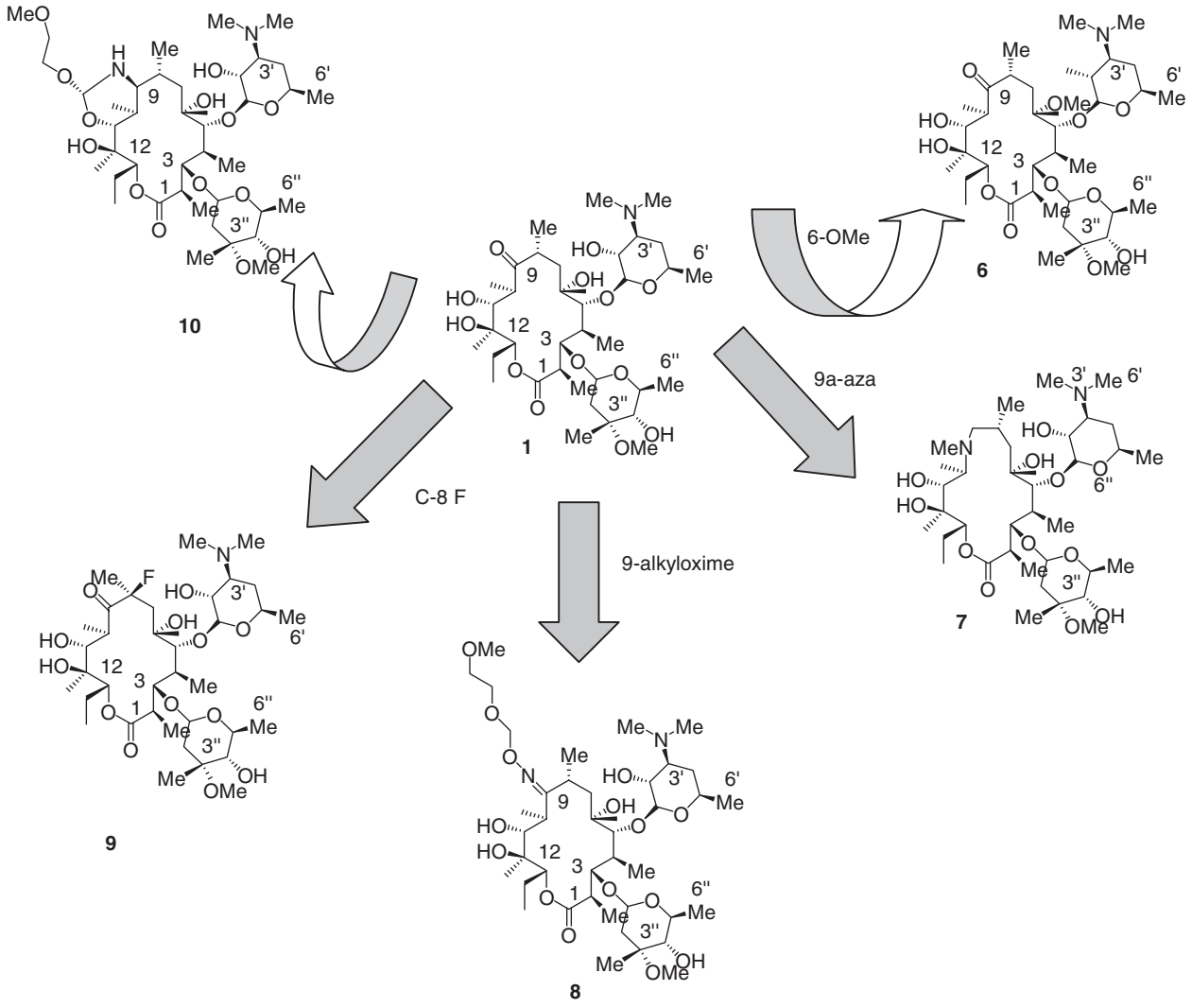


Figure 2. Modifications to basic skeleton of erythromycin.

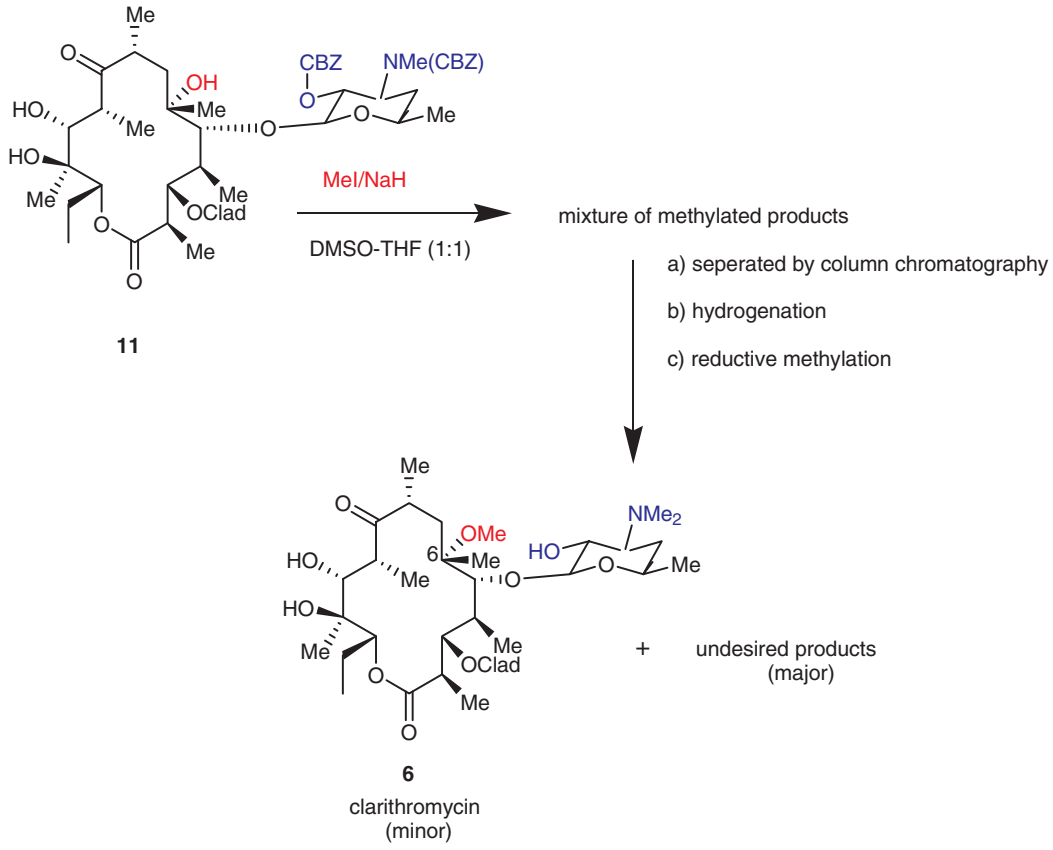
2-chlorobenzyl group was selected as the most suitable. Polar aprotic solvents were better than nonpolar solvents, but the optimum choice was a 1:1 mixture of DMSO–THF. Methyl iodide was found to be superior to dimethyl sulphate as a methylating agent.

Although the expected reactivity and selectivity were achieved elegantly in the previous synthesis (Scheme 3), in order to avoid the use of the irritant and toxic benzyl chloroformate, 6-*O*-methylerythromycin (**6**) was synthesized via methylation of a quaternery ammonium derivative of erythromycin A (Scheme 4).[25] This method was superior, because all the protections were carried out efficiently in one pot by treating erythromycin A 9-oxime (**12**) with benzyl bromide and sodium hydride, when deprotection was performed by a transfer hydrogenation method. Moreover, the maximum selectivity was achieved by using this reaction sequence.

Despite its advantages over previous methods in terms of the yield and selectivity, this protocol suffered from a few practical shortcomings. Elimination of all three benzyl groups by hydrogenation in one pot, especially in a large-scale preparation, was often inconsistent and difficult to accomplish. One of the most impressive studies concerning **6** was carried out by Watanabe and co-workers.[26] They prepared 6-*O*-methylerythromycin A (**6**) from erythromycin A 9-oxime (**12**) without purifying the intermediates (Scheme 5), but the reported yield was found to be less than that in the previous synthesis.

6-*O*-Methylerythromycin A (**6**) (clarithromycin, biaxin), a second-generation macrolide, was expected to show strong antibacterial activity and more acid resistance[19,20] than **1**. Apparently, it showed better activity against *Mycoplasma pneumoniae* and *Chlamydia trachomatis*[27–31a,b] and exhibited improved pharmacokinetic profiles and gastrointestinal tolerability over erythromycin. Additionally, clarithromycin exhibited good activity against *Helicobacter pylori* and has been approved in a combination regiment for the treatment of peptic ulcer disease.[32]

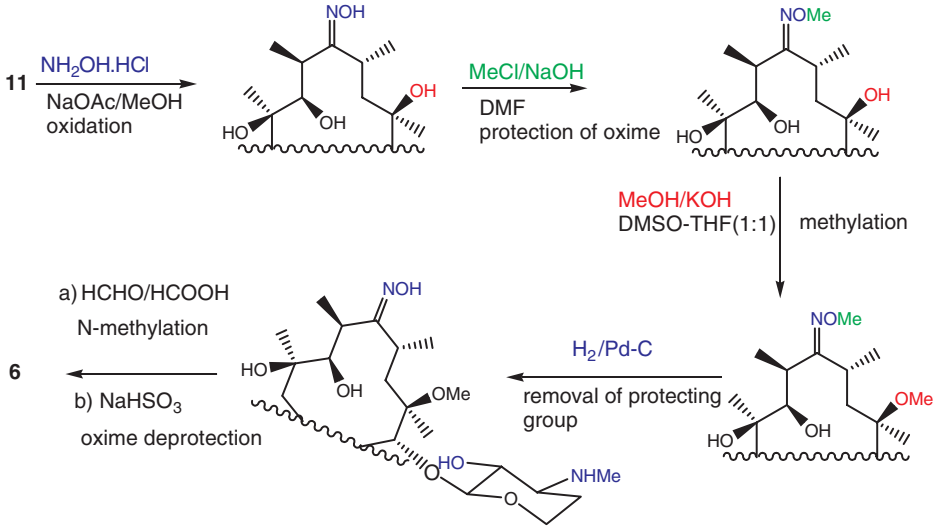
Inspired by the improved biological profile of **6**, different groups of scientists became interested in the synthesis of 6-*O*-substituted macrolides. The immense steric crowding around the C-6 hydroxy group was, however, a major synthetic problem in attempting the introduction of higher alkyl chains on this oxygen. Clark and co-workers reported



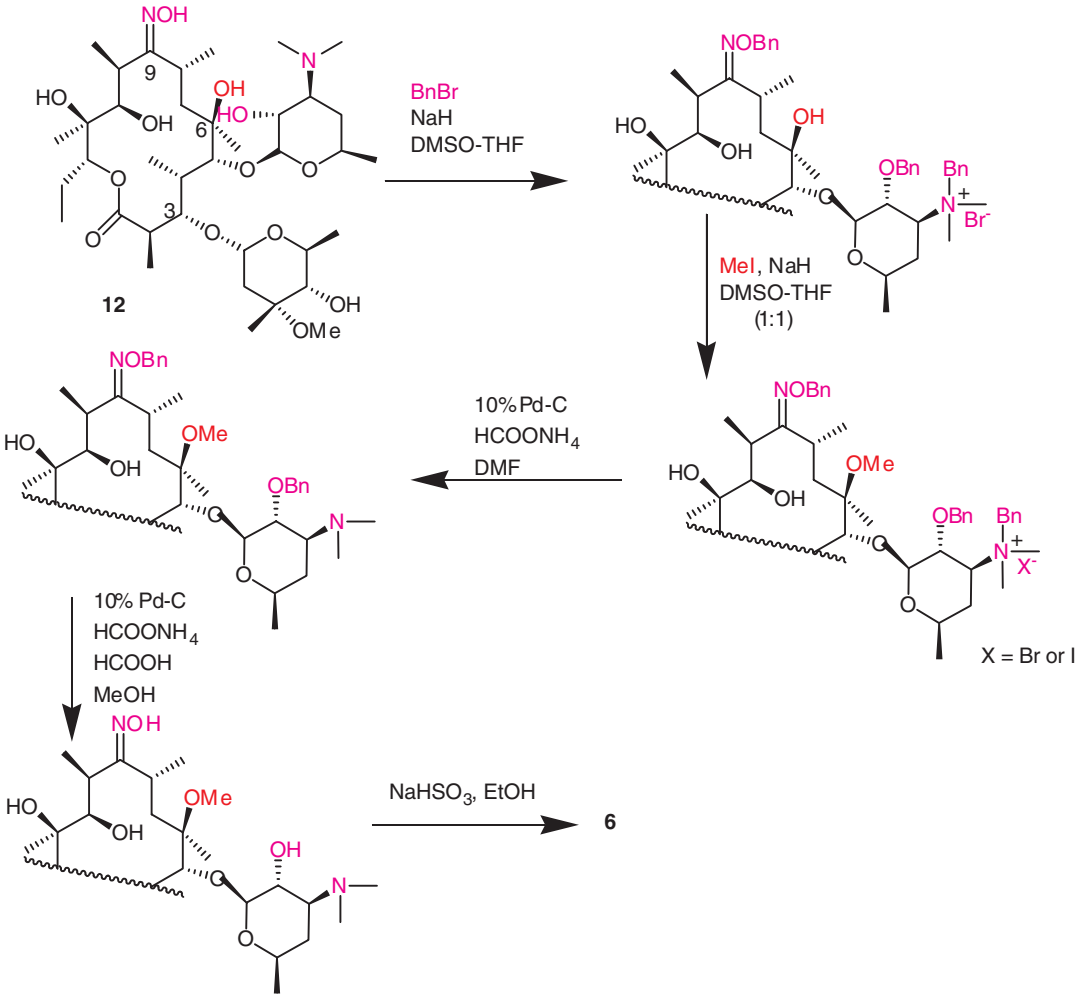
Scheme 2. Attempted synthesis of clarithromycin (**6**).

a facile method[33] to prepare 6-*O*-substituted erythromycins, which are highly active against erythromycin resistant respiratory pathogens, using suitably protected erythromycin derivatives. Thus, 2′,4″-bis-*O*-trimethylsilylerythromycin A 9-*O*-(1-isopropoxycyclohexyl)oxime (**13**) was reacted with active electrophilic reagents, in order to generate the corresponding 6-*O*-substituted derivatives. Removal of the protecting groups provided the 6-*O*-alkylerythromycin A 9-oxime, which, on subsequent deoximation, afforded the 6-*O*-alkylerythromycin A (**14a–f**) (Scheme 6).

6-*O*-Allylerythromycin A (**14a**) was identified as a versatile synthetic equivalent, which was converted into an array of diversified derivatives (**14g–p**), as shown in Figure 3. These derivatives were screened for in vitro antibacterial activity against erythromycin susceptible and resistant *Staphylococci*, *Streptococci* and *Pneumococci*. In particular,



Scheme 3. Synthesis of clarithromycin (**6**) with improved yield.



Scheme 4. Synthesis of clarithromycin (**6**) with excellent selectivity.

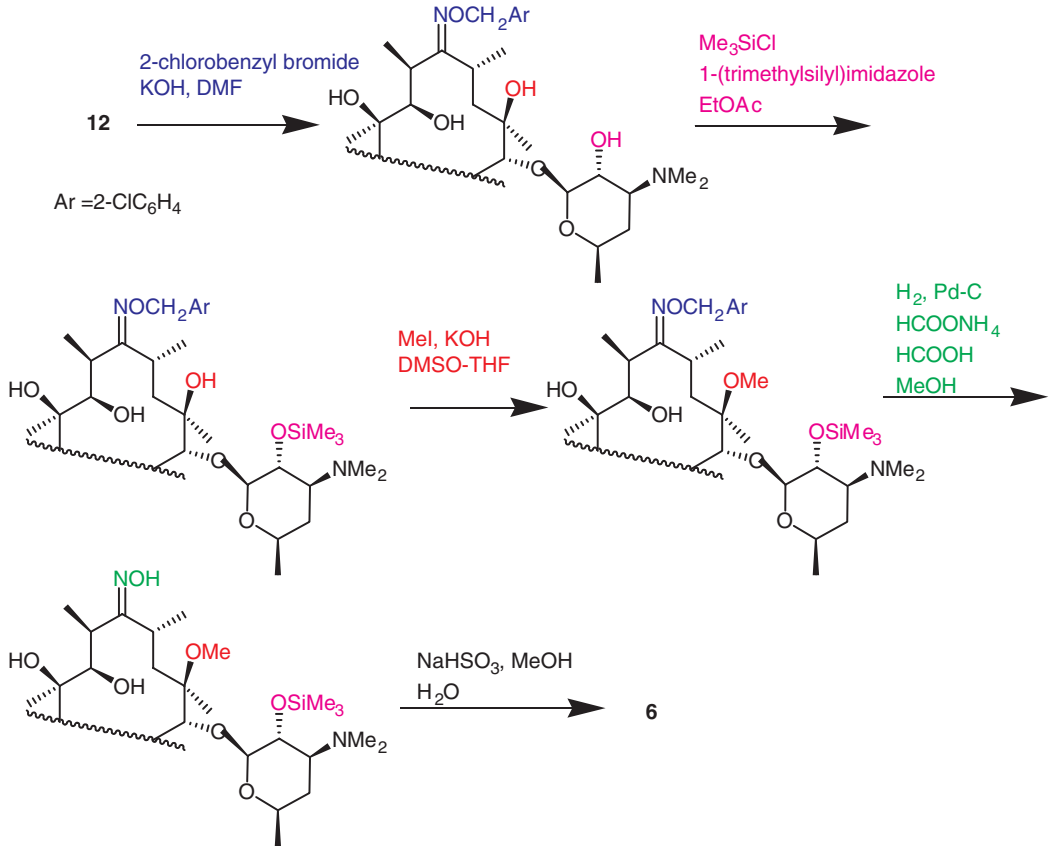
the introduction of multiple bonds (**14h**), heteroatoms (**14m**) or a conjugated aromatic system (**14f**, **14n**) showed activities over much of the bacterial spectrum. 6-*O*-Fluorobenzyl-erythromycin A (**14d**) and 6-*O*-naphthylallylerythromycin A (**14n**), having aromatic substituents tethered to the macrolide by a hydrocarbon linkage, showed a 16-fold improved activity against both *S. pyogenes* 930 and *S. pneumoniae* 5737.

2.3.2. Synthesis of azalides by functional group interconversion (FGI) and ring expansion. Djokic and coworkers[34] exploited the stereospecific Beckmann rearrangement to introduce a nitrogen atom into the 14-membered aglycon ring of erythromycin A. In order to achieve this, the *E* isomer of **12** was treated with *p*-toluenesulphonyl chloride (*p*-TsCl) (Scheme 7). The expected normal rearranged product **17** and abnormal product **16** were formed via a common intermediate **15** and were isolated in two different solvents. Both **16** and **17** were, however, converted separately into another important semisynthetic macrolide antibiotic, the first member in the series of azalides, azithromycin (**7**) (marketed as Zithromax)[35,36] (Scheme 7).

From the early trials, azithromycin (**7**) proved to be an extremely efficient antibiotic with expanded and enhanced antibacterial activity (especially against gram-negative pathogens), along with a low incidence of gastrointestinal side effects. It was found to be more acid stable and therefore better absorbed and distributed to tissues.

2.3.3. Oximation followed by oximinoether formation. Due to the acid-labile nature of the keto oxime **12**, alkylation of the oxime hydroxy group was investigated and was found to be effective in enhancing the stability. Thus, alkylation of erythromycin oxime (**12**), using 2-methoxyethoxymethyl chloride (MEM chloride) in the presence of $NaHCO_3$ in refluxing acetone[37,38] (Scheme 8), led to the generation of another useful antibiotic, roxithromycin (**8**).

Roxithromycin has a similar antibacterial spectrum to erythromycin, but a longer half life and absorption. It can often be prescribed for upper and lower respiratory tract infection, asthma, gum infections like gingivitis and bacterial infections associated with stomach and intestinal ulcers. It might be useful in treating toxoplasmosis (which usually affects the brain, sometimes leading to coma and seizures) and cryptosporidiosis (a parasitic infection, which often leads to severe diarrhea and weight loss).

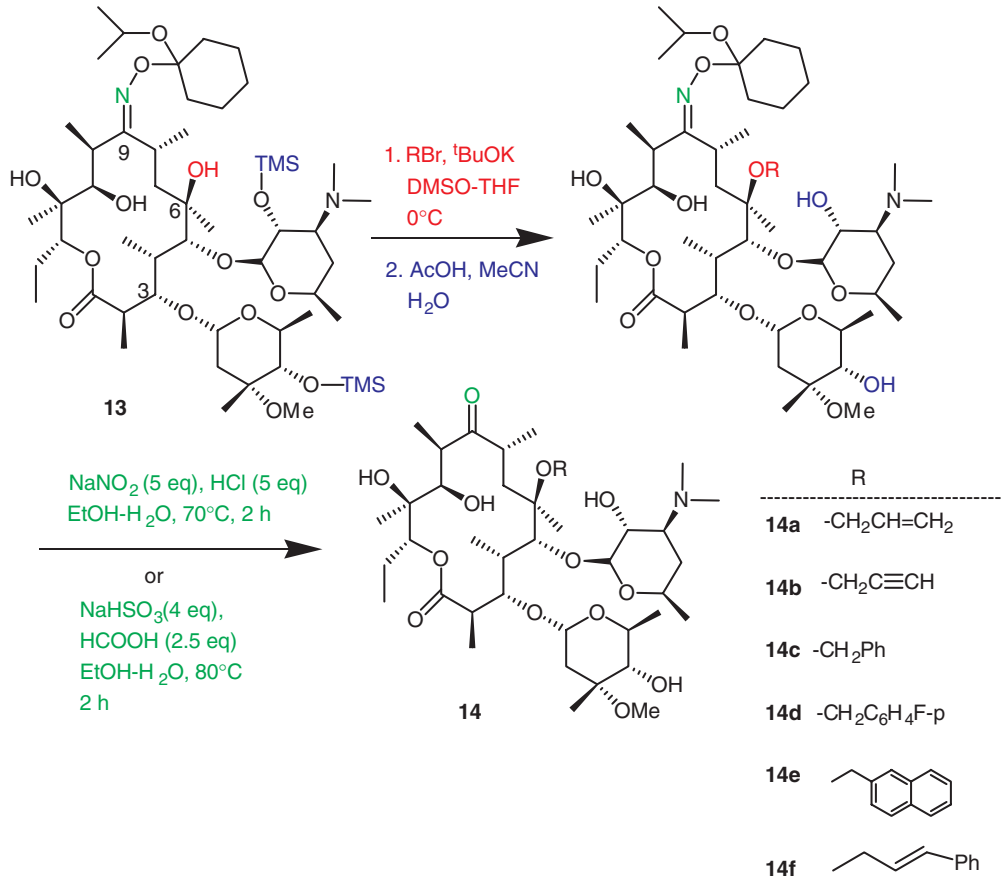


Scheme 5. Synthesis of clarithromycin (**6**) from erythromycin A 9-oxime (**12**) by Watanabe's method.

3. Bacterial resistance to erythromycin and its congeners: an emergency call

3.1. What does it mean and how does it work? A biologist's view

Although the macrolides including erythromycin enjoy a wide spectrum of antibacterial activity, their extensive clinical application has resulted in an increasing emergence of bacterial resistance. This increasing bacterial resistance to antibiotic treatment has turned out to be a major concern in global health.[39a–c] A surveillance study indicated that, among 1601 clinical isolates of *S. pneumonae* collected in 34 US medical centers, 19% were erythromycin resistant. This bacterial resistance to erythromycin and its congeners has increased dramatically over the past several years, and, therefore, the development of alternative antibacterial agents became essential. Thus, different research groups initiated investigation in several directions: (1) a search for new compounds that retain the favorable safety profile, along with a spectrum of activity confined to respiratory pathogens, (2) a search for new naturally occurring macrolide antibiotics and (3) an exploration of new targets from bacterial genomics that could be carried out by inserting the genes (by hijacking the biosynthetic machinery of bacteria) into *Escherichia coli* bacterium, thereby transforming this into an organism that can turn out new precursors of erythromycin (which can kill the bacteria). While designing new macrolide drugs that could overcome the bacterial resistance and at the same time, maintain identical pharmacokinetic profiles, gastrointestinal tolerability and other activity of this class of compounds, an understanding of their mode of action, along with the mechanism of resistance, became desirable. Three different mechanisms were assumed to be responsible for the majority of examples of macrolide resistance.[32] The first, known as 'high level resistance', results from mono and dimethylation of the amino group of adenine residue of A 2058 (this site is located in the peptidyl transferase loop of the RNA that catalyses polypeptide chain growth and is one of the erythromycin binding sites on the 23S ribosomal RNA of the 50S ribosomal subunit) by an enzyme called enzyme-ribosomal methylase, a product of a family of genes called erm and is involved in modification of the target.[40a–c] This resistance is also referred to as 'MLS_B phenotype', since these organisms are not only resistant to macrolide (M), but also to lincosamide (L lincomycin, clindamycin, celesticetin) and type B streptogramin (SB vernamycin B, pristinomycin I, staphylomycins). In the second mechanism, known as 'low level resistance', an efflux transporter, a product of the mef gene pumps macrolides out of the bacterial cell and has been reported in a number of *Streptococci* species.[41] As the strains of *Staphylococci* are inducibly resistant to macrolides and type B streptogramin, but not to the lincosamides, it is referred as MS_B resistance. The third possibility is the modification of the macrolide itself, where a number of mechanisms have been discovered to account for this structural modification of erythromycin, among which hydrolysis of the lactone ring and/or possible phosphorylation is of particular importance. Hence,



Scheme 6. Synthesis of 6-*O*-alkyl substituted erythromycins.

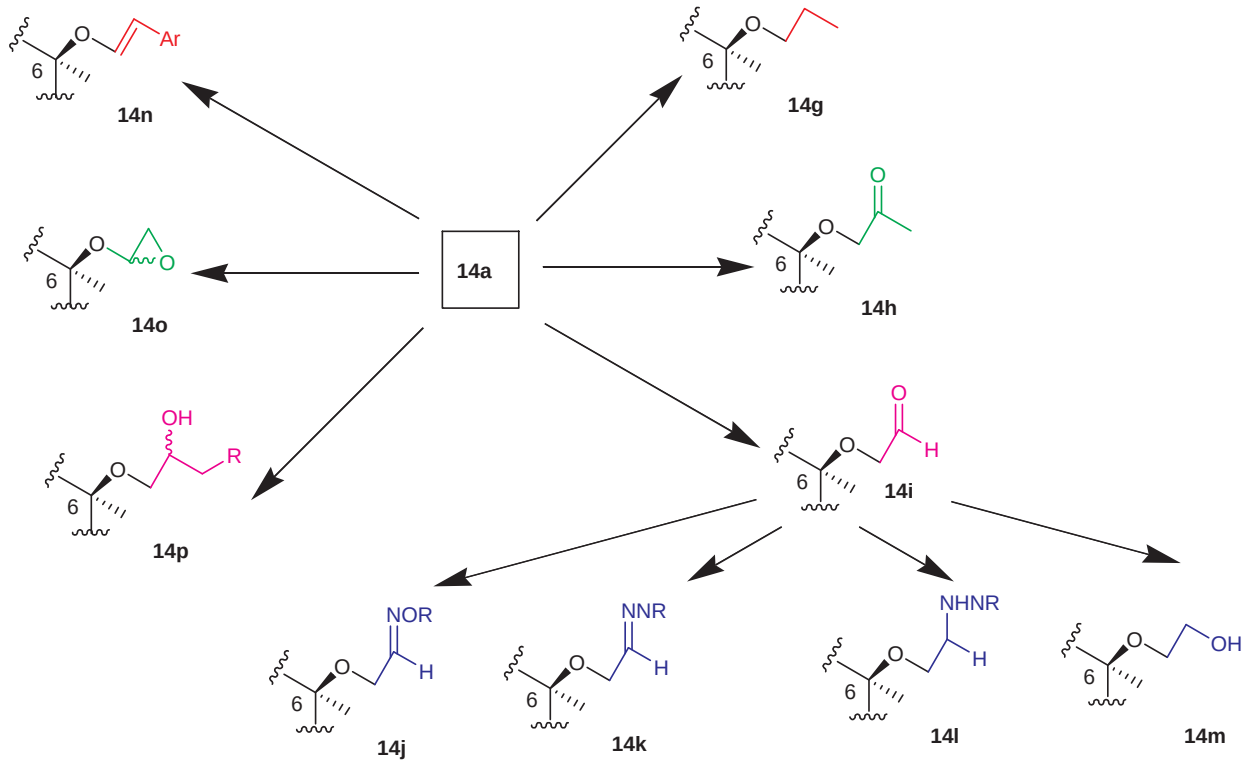
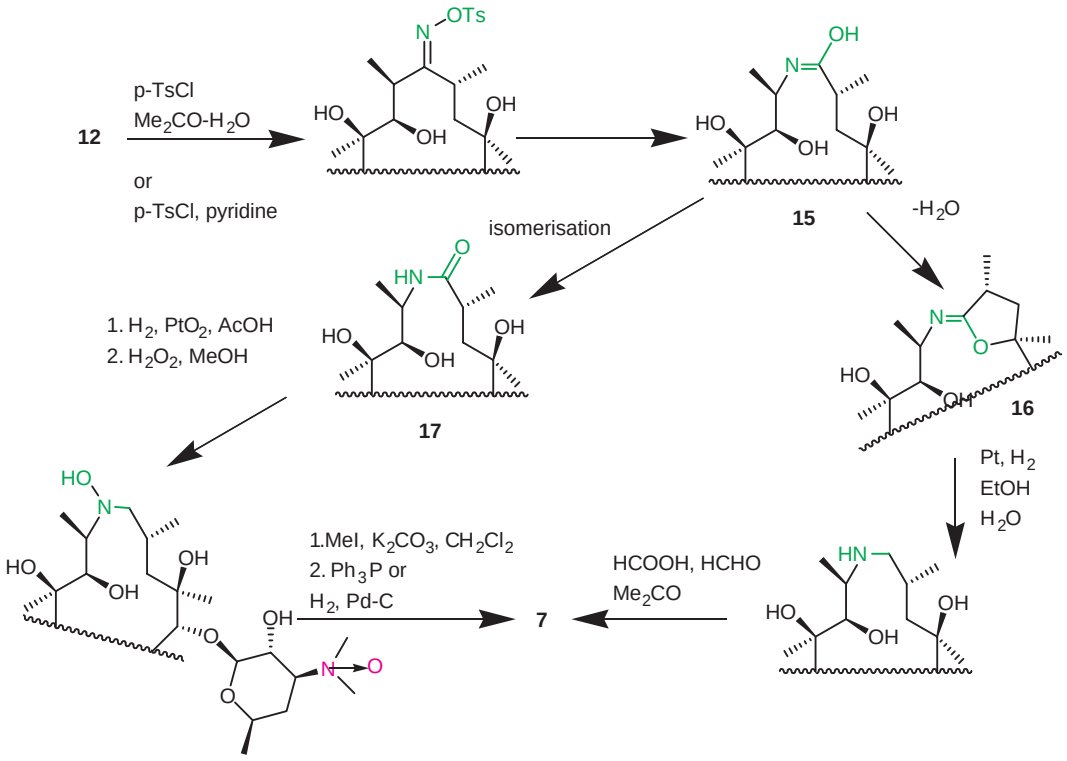


Figure 3. Compounds obtained from 6-*O*-allylerythromycin (**14a**).



Scheme 7. Synthesis of azithromycin (**7**) via Beckmann rearrangement.

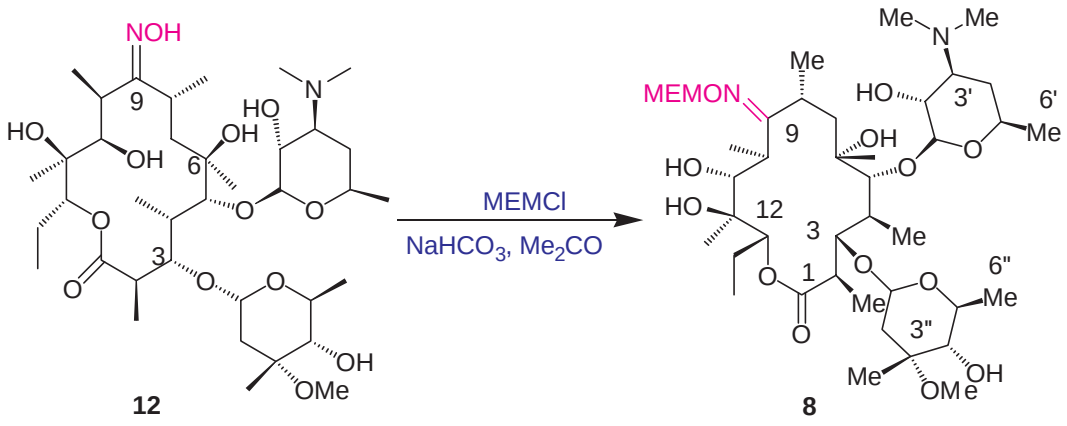
the identification of a new macrolide structure was essential that could bind to methylated ribosome and avoid the efflux protein recognition.

3.2. Chemist's approach to enhance antibacterial activity via chemical modification: the first breakthrough on the synthesis of 3-ketoerythromycin (ketolide)

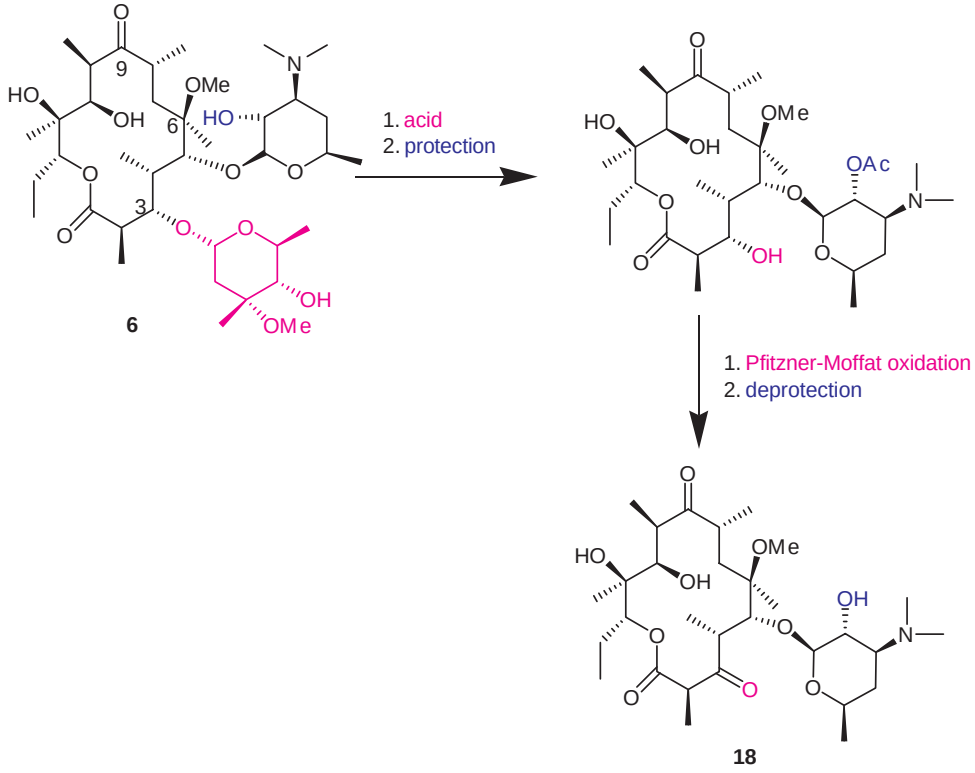
The neutral sugar ring, L-cladinose attached at the C-3 position of the macrolide, plays a vital role in the efflux mechanism, which has been, wrongly, long thought to be essential for the antibiotic activity of erythromycin A. Therefore, the effect on the antibiotic activity of 14-membered macrolides after removal of this moiety was investigated. Recent research has led to the discovery of a new distinct class, the ketolides, characterized by a 3-keto group in place of the cladinose moiety. The first attempt to prepare a ketolide from a protected erythromycin 9-oxime was unsuccessful,[42] as the hemiketal of the corresponding ketolide was isolated, due to the close proximity of the C-6 hydroxy group to the C-3 ketone. The first successful preparation of a semisynthetic ketolide **18** from 6-*O*-methoxyerythromycin (**6**) was accomplished by Agouridas et al.,[43] where blocking of the C-6 OH (by converting it into OMe) eliminated any possibility of ketal formation (Scheme 9).

3.3. Improvement of antibacterial activity via proper modifications of ketolide skeleton

The ketolides showed good activity against erythromycin susceptible bacteria, along with weak, but remarkable, activity against erythromycin resistant bacteria. Thus,



Scheme 8. Synthesis of roxithromycin (**8**).



Scheme 9. First successful preparation of semisynthetic ketolide.

the discovery of ketolides proved uniquely that it was the cladinose ring that needed to be removed to separate the resistance inducibility from the antibacterial activity of erythromycin. These results subsequently attracted immense interest in ketolide research, but the ketolide skeleton alone remained less attractive, as it showed modest activity against MLS_B resistance. The results of SAR studies, however, an area of outstanding importance, suggested that the 11,12-carbamate ketolides possess better antibacterial activities than the ketolide itself. The antibacterial activity of this new class of ketolides was dependent on a few structural features such as (i) a four atom side chain with an aromatic ring as substituent, mainly on either the nitrogen atom of the 11,12-carbamate ring or on the C-6 oxygen to overcome MLS_B resistance as well as efflux resistance (Fig. 4) and (ii) the aryl group, the selection of which was crucial. It has been shown that neither the ketolide nor the aryl-substituted carbamate ring alone could account for the activity against both erythromycin susceptible, as well as resistant, bacteria. This is exemplified by the carbamate macrolide, A-66321 (**19**) (Fig. 5), a nonketolide candidate prepared by Abbott Labs[44] in 1989, which showed increased in vitro activity against both inducibly and constitutively resistant strains of *Streptococcus pyogenes*, but poor activity against efflux resistance. On the other hand, RU-708 (**20**) (Fig. 5), a ketolide version of (**19**), showed very encouraging overall activity. Similarly, HMR-3004 (RU-004) (**21**), HMR-3647 (RU-66647) (**22**) and ABT-773 (**23**) (Fig. 5) were also found to be very potent.[45–49] Ketolide (**24**) (Fig. 5) is discussed in the following section.

3.4. Achievements: a tough job, but executed well with remarkable accuracy

3.4.1. Synthesis of suitably substituted 11,12-carbamate and carbazate ketolides. Both the carbamate and the 11,12-hydrazono carbamate (also known as the carbazate

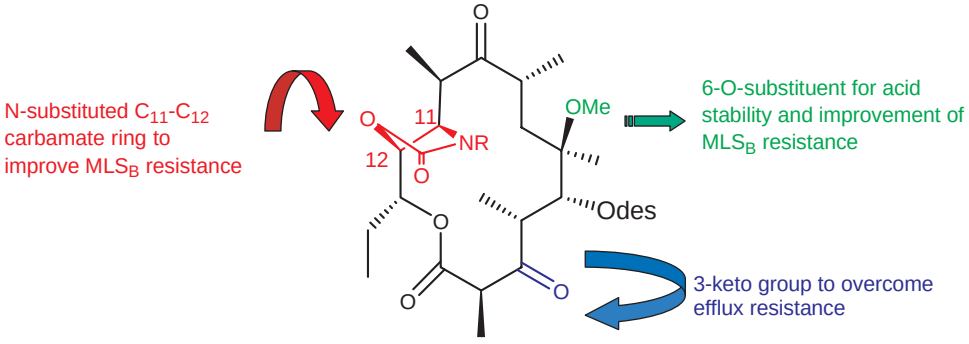


Figure 4. Structural features required for higher antibacterial activity of ketolides.

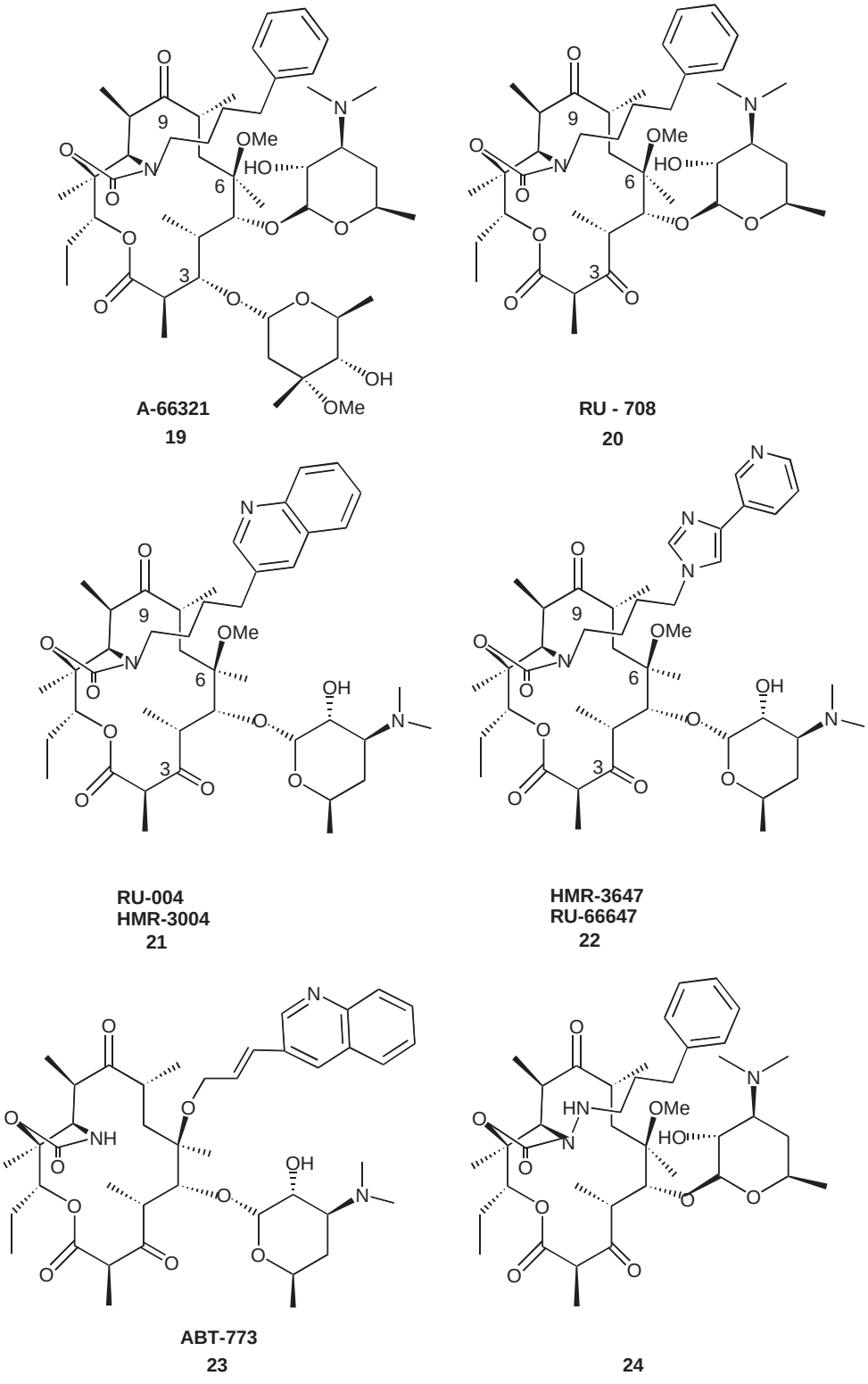
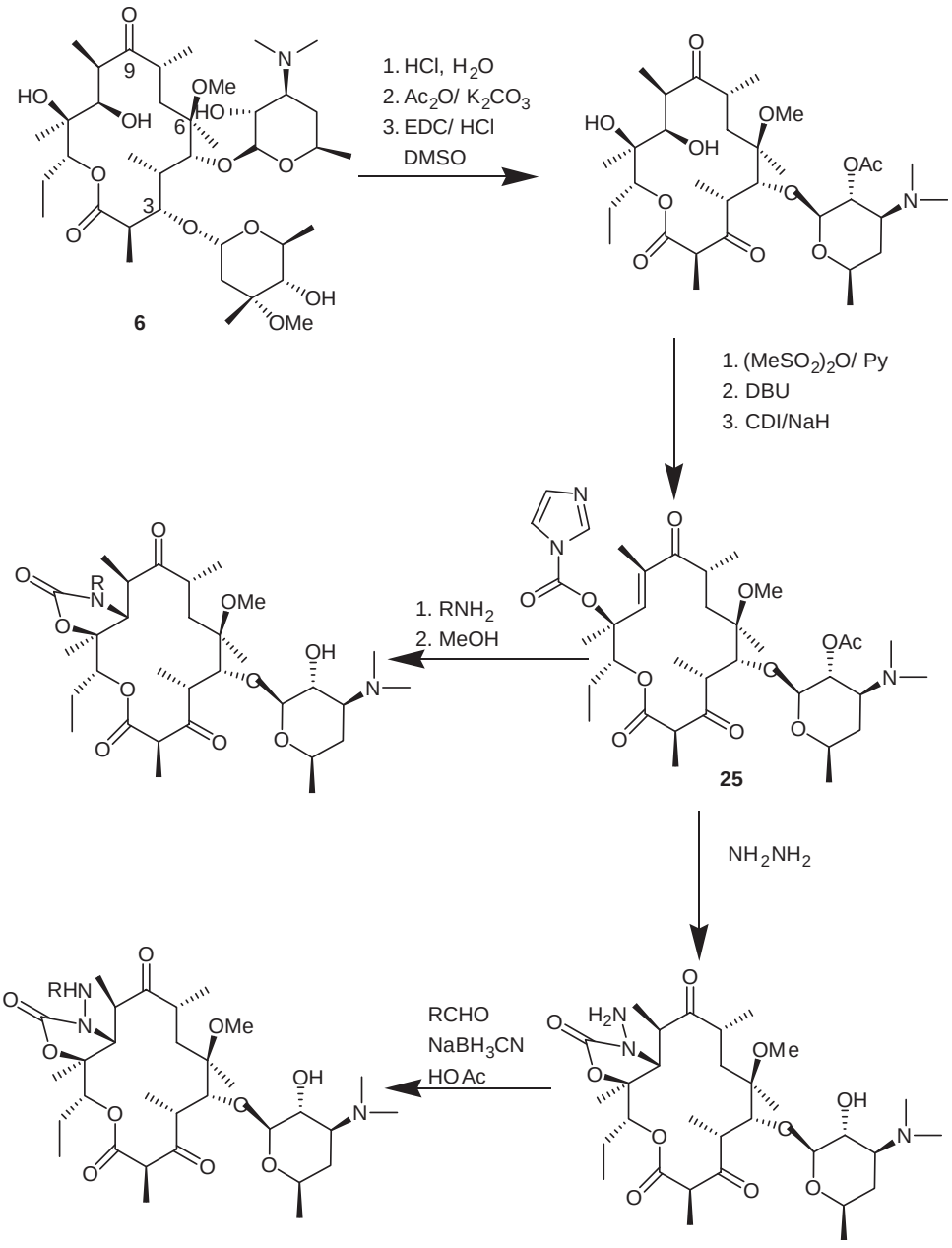


Figure 5. Macrolides with promising antibacterial activity.

ketolide) were prepared from clarithromycin (**6**) via its 12-acylimidazolyl ketolide derivative **25**[50,51] (Scheme 10). Among the 11,12-carbamate ketolides and the carbazate ketolides tested, the most active compound was found to be **24**, (Fig. 5), an analogue of RU-708 **20**. This was not only effective against the erythromycin susceptible organisms, but also approximately 300-fold more potent than erythromycin against the inducibly resistant *S. aureus* 2548.

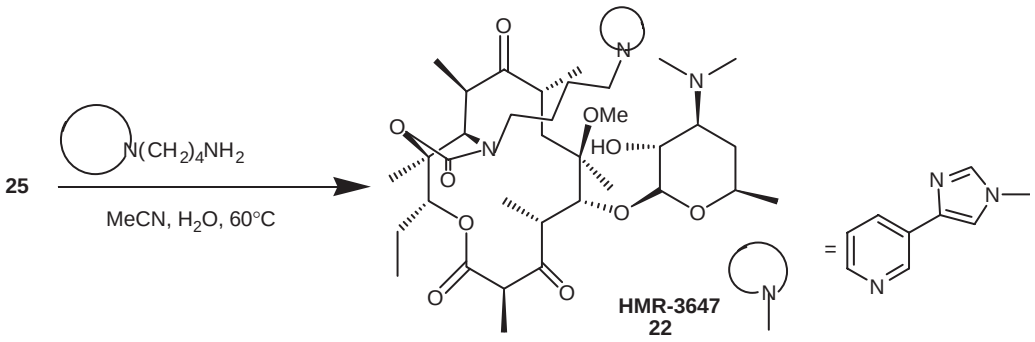
3.4.2. Synthesis of appropriately functionalized 11, 12-hydrazonocarbamate ketolides. Boosted by the discovery of some highly potent 11,12-carbazate ketolides, Agouridas et al.[52] re-investigated the role of the heterocyclic moiety in



Scheme 10. Synthesis of carbamate and carbazate ketolides from clarithromycin (**6**).

the carbamate series. Their speculation on the advantages of the additional heterocyclic nitrogen for antibacterial activity led them to synthesize ketolides with the introduction of arylimidazoles, benzimidazoles and triazoles at C-4 position of the butyl chain. The desired 11,12-cyclocarbamate ketolides were all synthesized according to Scheme 11 by the treatment of 12-acylimidazolyl ketolide **25** in aqueous acetonitrile with the appropriate amines.[53] Extensive lead optimization and introduction of an imidazolyl–pyridyl group in the side chain, for example, HMR-3647 (**22**) (commercially known as telithromycin, Ketek, Aventis Pharmaceuticals), resulted in the desired profile of antibacterial activity (Table 1). HMR-3647 is an innovative and promising new antibacterial agent.

Recently, Denis and co-workers have reported the synthesis of 2-fluoro telithromycins, HMR-3562 (**27**) and HMR-3787 (**28**). Direct comparison of HMR-3562 and telithromycin showed that the 2-fluoro derivative was relatively more active[54] (Table 1) against constitutively resistant *S. pneumoniae*, as well as inducibly resistant *S. aureus* and *S. pneumoniae*. It showed a higher activity than azithromycin against *H. influenzae*. Both **27** and **28** demonstrated good efficacy against infections caused by various susceptible and resistant bacterial strains in murine septicemia. These macrolides also showed good in vivo and in vitro activity against macrolide resistant strains of *S. pneumoniae* and *H. influenzae*. The compounds were synthesized by two different methods, one of which involved the formation of the carbamate ring, followed by fluorination of **26** (Scheme 12), and the other the reverse protocol, that is, fluorination of **29**, followed by carbamate ring formation (Scheme 13). Other analogues of telithromycin such as 2-chloro and 2-methyl derivatives were also



Scheme 11. Synthesis of carbamate ketolides with substitution at the C-4 position of the butyl chain.

Table 1. Comparision of antibacterial activities of HMR-3647 with other macrolides

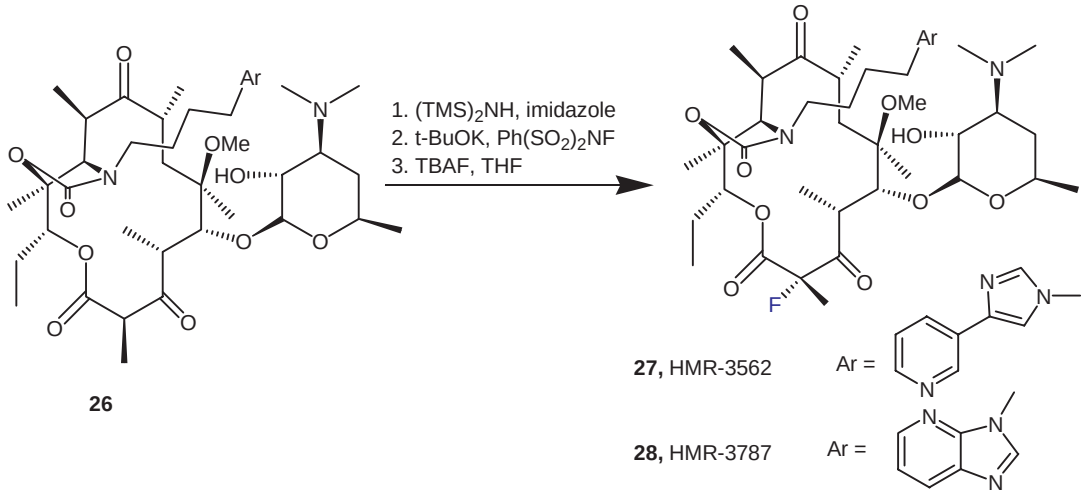
Macrolide	Sa[a] Ery S[b]	Sa Ery Ri	Sa Ery Rc	S_{pyo} Ery S	Sp Ery S	Sp Ery Rc	Sp Ery Ri
CLA[c]	0.3	40	40	0.8	0.04	40	40
AZI[d]	0.3	40	40	0.60	0.15	40	40
HMR-3562 (**27**)	0.04	0.08	40	0.02	0.02	0.08	0.02
HMR-3647 (**22**) (telithromycin)	0.04	0.08	>40	0.02	<0.02	<0.02	<0.02

[a] Sa, *Staphylococcus aureus*; Sp, *Streptococcus pneumoniae*; S^{pyo}, *Streptococcus pyogenes*.
[b] Ery S, erythromycin susceptible; Ery Rc, constitutively erythromycin resistant; Ery Ri, inducibly erythromycin resistant.
[c] Clarithromycin.
[d] Azithromycin.

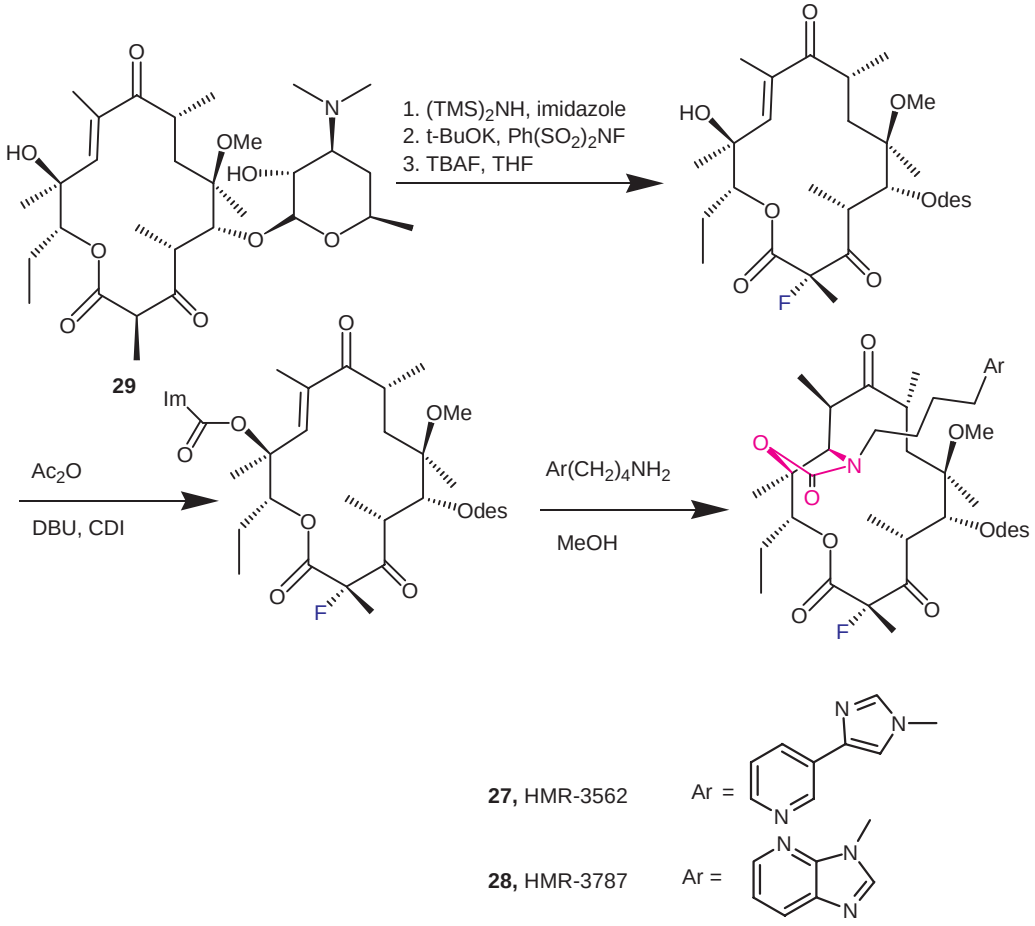
generated,[54] but the introduction of these larger substituents resulted in loss of activity, indicating the importance of steric factors at C-2, which could only tolerate the presence of small substituents.

3.4.3. Synthesis of few non-carbamate ketolides: 9-oxime ketolides and 6-*O*-alkylketolides. A variety of 9-oxime ketolides were prepared from 3-ketoclarithromycin (**30**). Thus, **31** was obtained from **30** via oximation followed by hydrogenation (Scheme 14).[55a–d,56] Initially, compound **31** showed significant activity against *H. influenzae* as well as macrolide resistant organisms, with the 3(*R*) piperidinyl isomer being more active than the 3(*S*) isomer. Replacement of the active hydrogen on nitrogen by an arylalkyl group did not improve the overall activity. Therefore, further effort was initiated in order to introduce substituents at the C-2 position and this resulted in the development of a new series, that is, 2-substituted ketolides having a 9-oxime functionality, reported by Kaneko and co-workers.[57] Among several C-2 substituents, the 2-fluoro derivative CP-654743 (**33**) showed the best activity against both erythromycin susceptible and resistant organisms. It was relatively more active than CP-605006 (**32**), its non-fluoro derivative and telithromycin against key respiratory-tract pathogens.

3.4.4. Synthesis of 6-*O*-substituted ketolides having 11,12-carbamate pharmacophores—a new class of promising antibacterial agents. Synthesis of **33** involves oximation of a suitably protected 6-*O*-methylcarbazate ketolide followed by the introduction of an arylalkyl chain at $-NH_2$ of the cyclic 11,12-carbazate and, finally, fluorination at the C-2 position (Scheme 15).



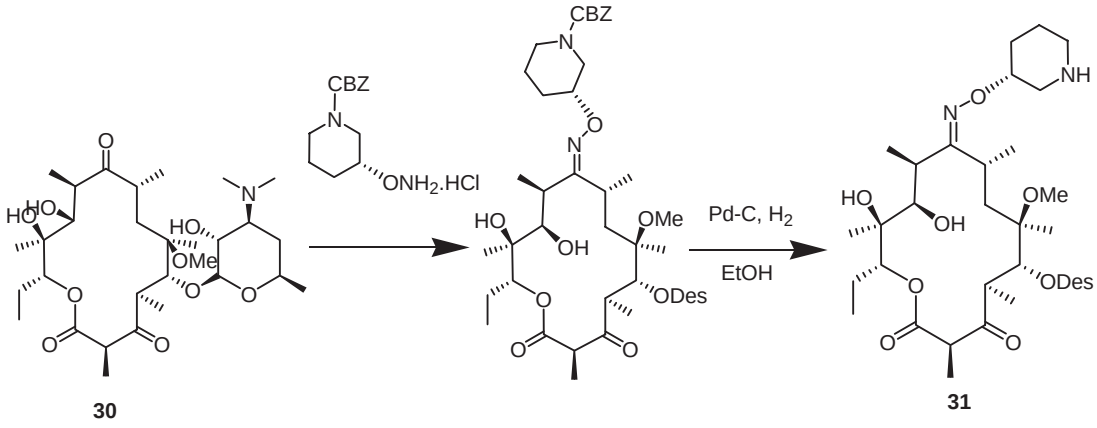
Scheme 12. Synthesis of 2-flourocarbamate ketolides.



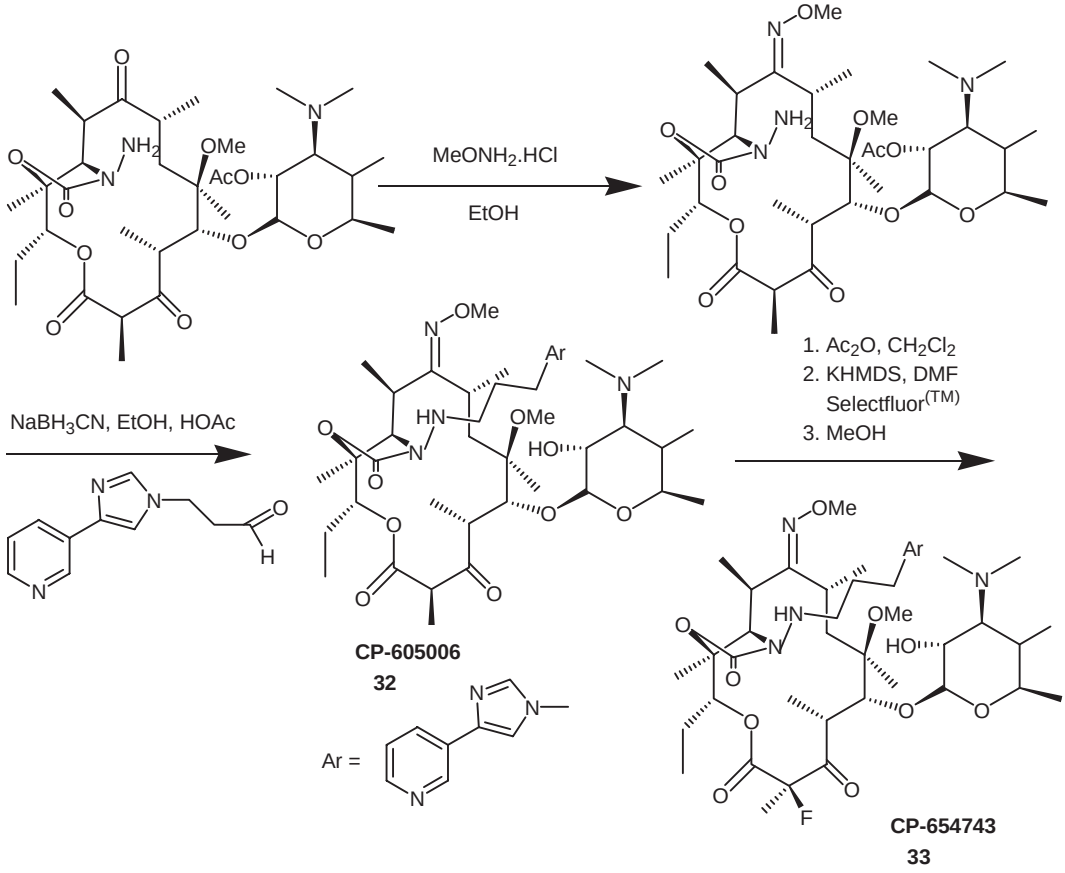
Scheme 13. Alternative synthesis of 2-fluorocarbamate ketolides.

Since the C-6 hydroxy group is also directed near the center of the hydrophilic face hence it was planned to incorporate an arylalkyl chain to 6-*O*-position. Thus, linking an aryl group to this position would provide a minimized conformation where the aryl group occupies a spatial region similar to the aryl group attached to telithromycin. Based on this SAR, a series of ketolides were synthesized.[58a,b]

In 1998, Clark et al. revealed a general strategy for the introduction of an alkyl group at the C-6 position through the formation of 6-*O*-allylerythromycin (**14a**). The keto group at the 3-position was then introduced through further three steps: removal of the cladinose sugar by acidic hydrolysis, protection of 2′-OH as an acetyl ester and, finally, Corey–Kim oxidation of the 3-hydroxy group to provide the 6-*O*-allylketolide (**34**) (Scheme 16). This compound served as the key intermediate for the preparation of other analogs. Thus, reaction of **34** with aryl halides, under Heck conditions, provides a series of (3-aryl)prop-2-enyl ketolides (**35a–e**) (Scheme 17). Conversion of the allyl group into aldehyde (**36**) followed by reductive ammination provided a series of amino analogs **37a–e** (Scheme 17).



Scheme 14. Synthesis of 9-oxime ketolides.

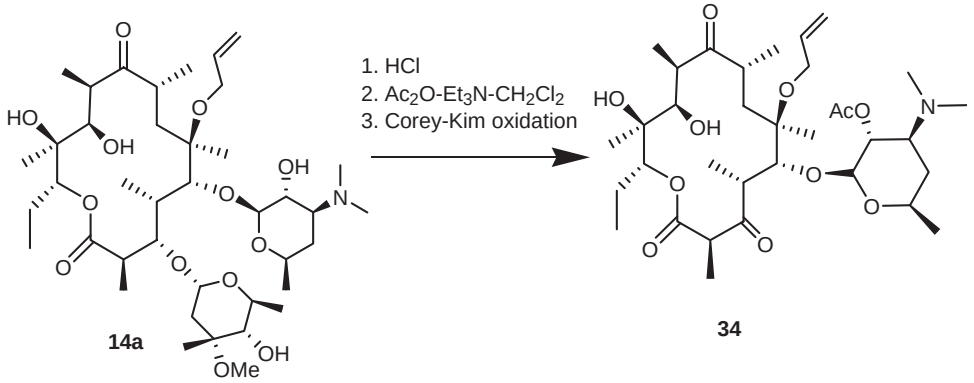


Scheme 15. Synthesis of amino- substituted 2-fluoro-9-oxime-11,12-carbazate derivatives.

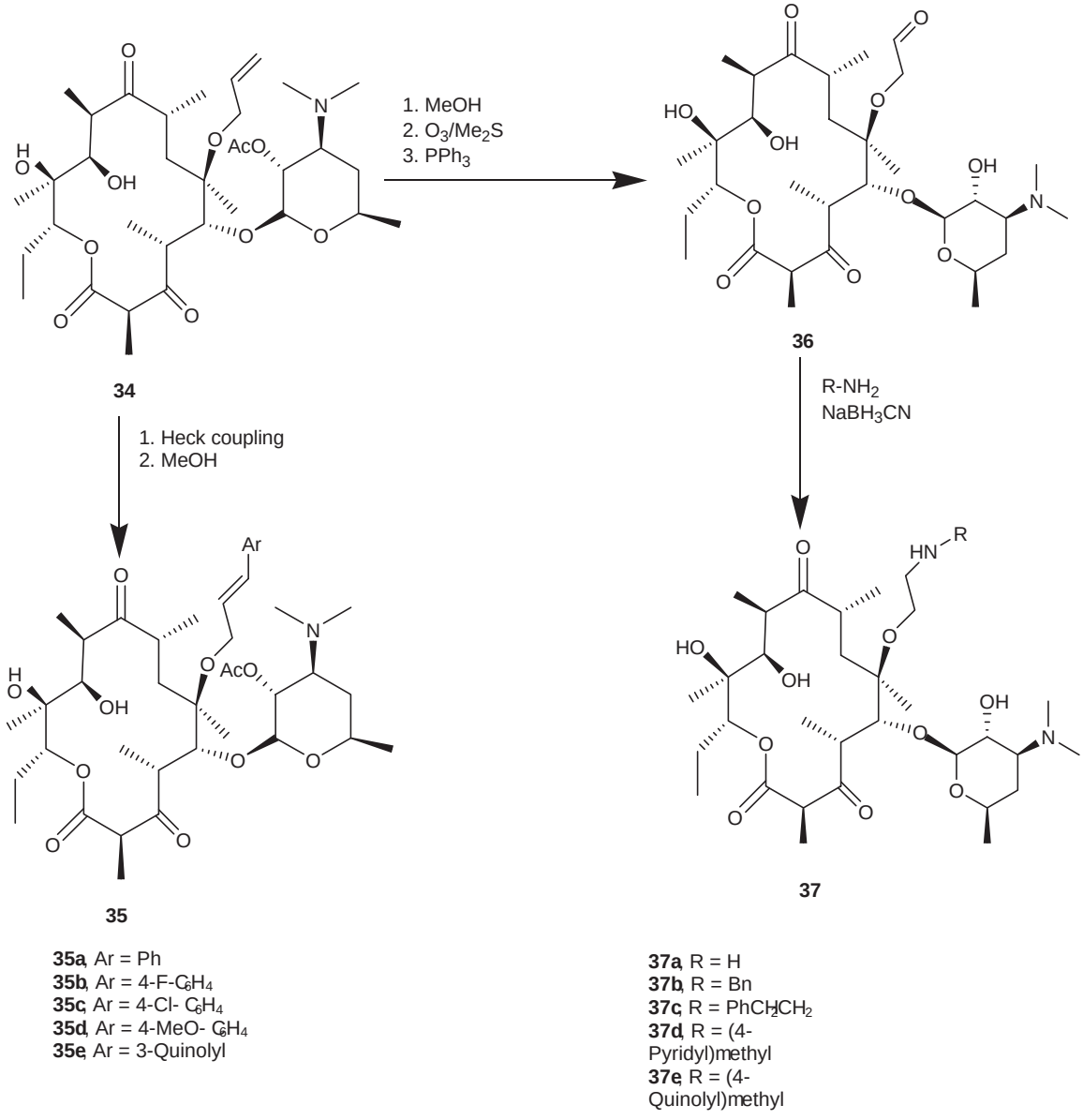
Only **35e**, the (3-quinolyl)prop-2-enyl analog, was found to be as active as erythromycin against erythromycin susceptible strains, whereas both series **35** and **37** exhibited improved activity against various erythromycin resistant bacteria. The most active compound **35e**, however, exhibited MICs of 0.2 and 0.25 μg/ml against inducibly MLS_B resistant *S. aureus* and efflux resistance, as compared to 6.2 and 16 μg/ml for erythromycin, but showed weak activity against *H. influenzae* and constitutively MLS_B resistant strains.

In an alternative strategy, it has been shown that the introduction of an 11,12-carbamate pharmacophore into the 6-*O*-substituted ketolide improved the antibacterial activity, mainly against *H. influenza* and constitutively MLS_B resistant strains. The necessary key intermediate, 6-*O*-allyl-11,12-carbamate ketolide **38**,[40] was prepared by one of two routes, starting from 6-*O*-allylerythromycin **14a** (Scheme 18).[59,60] Heck coupling reactions of various aryl halides with the intermediate **38** led to a series of 6-*O*-arylprop-2′-enyl-11,12-carbamate ketolides (**23**, **39a**–**h**) (Fig. 6).

Compound **23** (ABT-773),[61] the carbamate derivative of **35d**, showed an excellent and well-balanced antibacterial profile against both susceptible and resistant organisms. ABT-773 also exhibited remarkably enhanced activity against MLS_B resistant *S. pyogenes* and *S. pneumoniae*,



Scheme 16. Synthesis of 6-*O*-allylketolide.

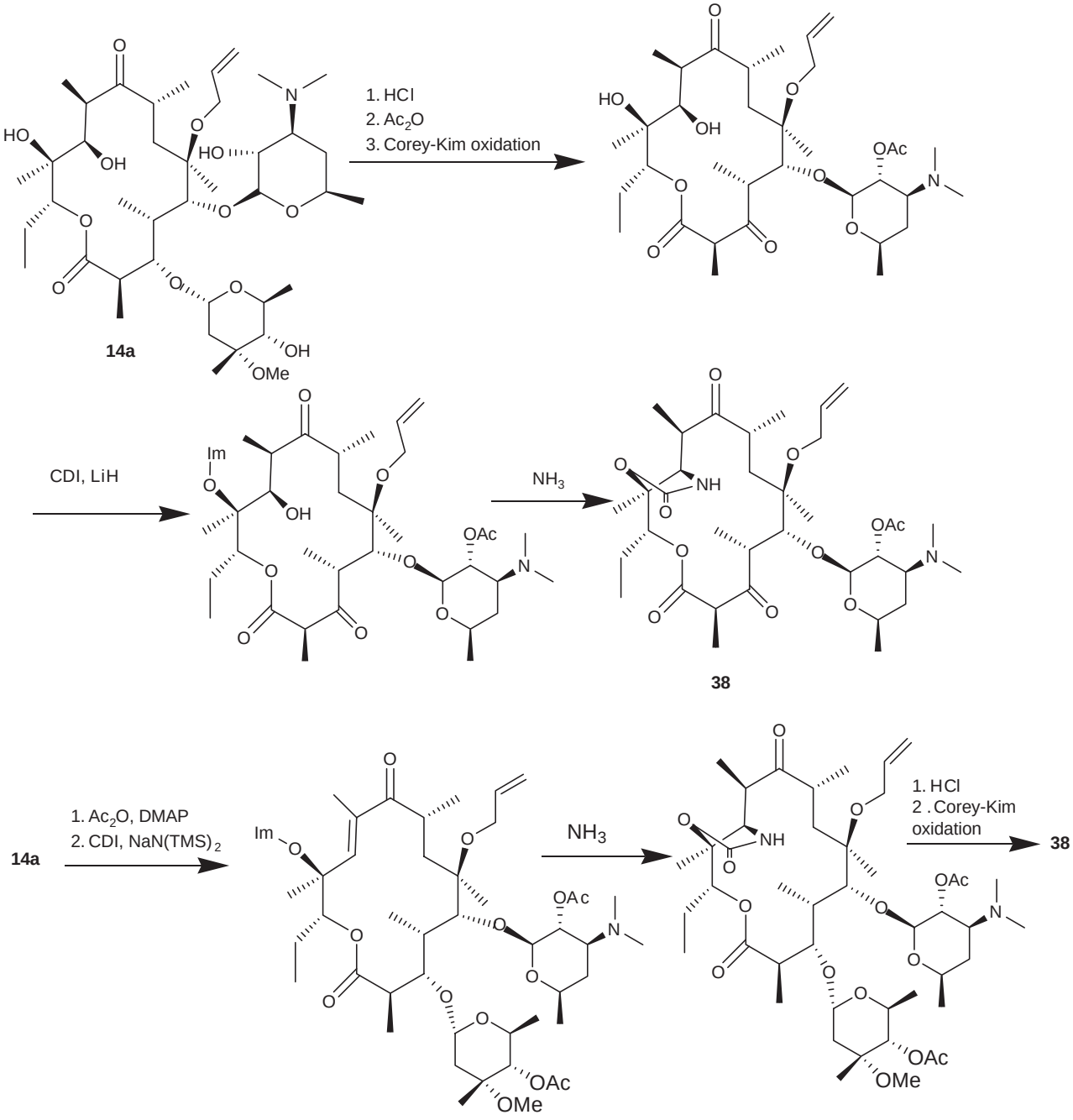


Scheme 17. Conversion of 6-*O*-allylketolide (**34**) into **35** and **37**.

with MICs of 1.0 and 0.25 μg/ml as compared to 100 and 128 μg/ml for **35d**. Further modification of **39** provided three other analogs, **40**, **41** and **42**, which possessed different types of linkages between the lactone skeleton and aryl group. The effect of a linker between the lactone ring and 3-quinolyl group on the in vitro antibacterial activity is presented in Table 2. The olefin linkage in ABT-773 appeared to be optimal. Interestingly, the alkyne linkage in **42** provided a comparable activity to ABT-773, except against *H. influenzae*.

All the different regioisomers of ABT-773 were prepared (**39d–h**) for evaluating their antibacterial activity. It was observed that the point of attachment to the quinoline ring was important for optimal antibacterial activity especially against MLS_B resistant organisms. In addition to the 3-quinolyl analog **23**, the 6-quinolyl isomer **39f** also exhibited excellent overall antibacterial activity (Table 2). The enhanced antibacterial activity of 2-fluoro substitution was observed in the 6-*O*-substituted ketolide. A 4- and 16-fold increase in the in vivo activity against macrolide resistant *S. pyogenes* and *S. pneumoniae* was observed in the case of the 2-fluoro derivative of ABT-773, that is, **43** (A-20316, Fig. 6). This compound also demonstrated a 5-fold improved efficacy over ABT-773 when evaluated against macrolide susceptible *S. pneumoniae* ATCC 6303.

Recently, the 6-*O*-propenylaryl side chain of erythromycin derivatives was also constructed by olefin cross metathesis.[62] Undoubtedly, these intermolecular reactions are often complicated by competition between the desired intermolecular cross metathesis (CM) and undesired intermolecular self metathesis (SM), but a logical selection of the two olefins by Hsu and co-workers as the starting compounds eliminated all possibilities of self metathesis (Scheme 19). In most of the cases the major product isolated



Scheme 18. Synthesis of 6-*O*-substituted 11,12-carbamate ketolide.

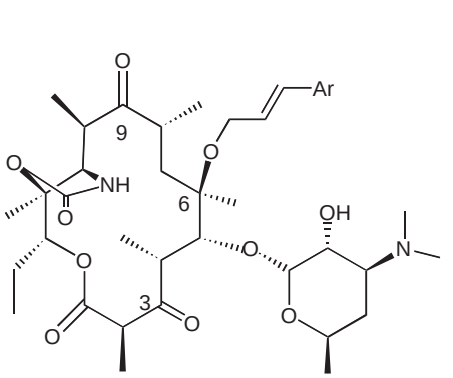
had >95:5 *E*-selectivity. These reactions were, however, complicated by the formation of some side products.

3.4.5. Synthesis of cyclic ketolides. In order to study the potential of other ketolides as potent antibacterial agents, some cyclic ketolide systems and their substituted derivatives were synthesized, in the hope that these analogues could be used as scaffolds to probe secondary ribosomal binding sites. Based on the literature available, they can be categorized into two types:

(a) Tricyclic ketolides
(b) Tetracyclic ketolides.

Type a: tricyclic ketolides. In 1995, Asaka et al. reported a novel tricyclic ketolide series by fusing one additional ring to the North–Western hemisphere of the 11,12-carbamate ketolide to enhance the stability, bioavailability and antimicrobial activity. Actually, three types of tricyclic ketolides are available in the literature, depending on the size of the newly formed ring: (a) tricyclo[14.5.5] ketolides **44** are exemplified by a cyclized version of Ru-004[63a] (Fig. 7), (b) tricyclo[14.5.6] ketolides **45** (Fig. 7)[63b] and (c) tricyclo[14.5.7]ketolides (**46**) (Fig. 7).[64a]

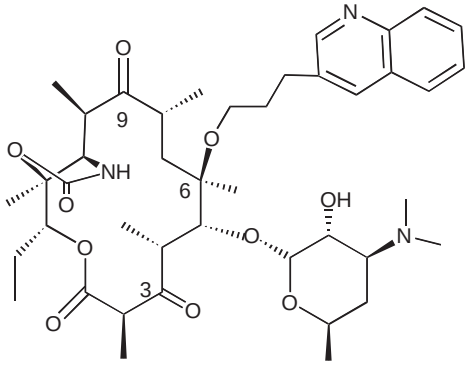
TE-802 (**46a**) (Scheme 20) was the first member of this 9-iminoketolide family discovered by Asaka et al. at



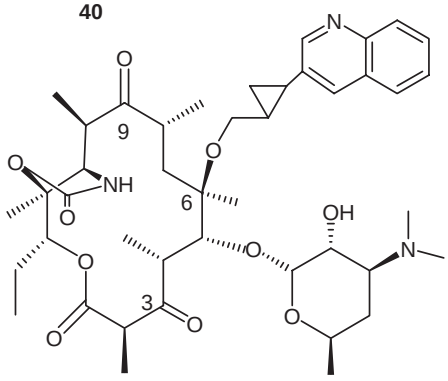
39

Ar =

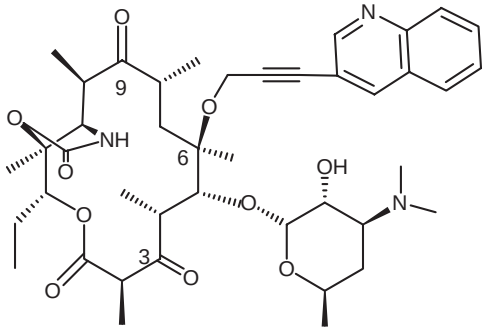
39a Ph
39b H
39c 2-Quinolyl
23 3-Quinolyl (ABT-773)
39d 4-Quinolyl
39e 5-Quinolyl
39f 6-Quinolyl
39g 7-Quinolyl
39h 8-Quinolyl



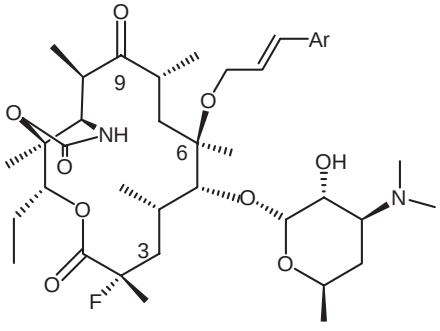
40



41



42



A-20316
43

Ar = 3-Quinolyl

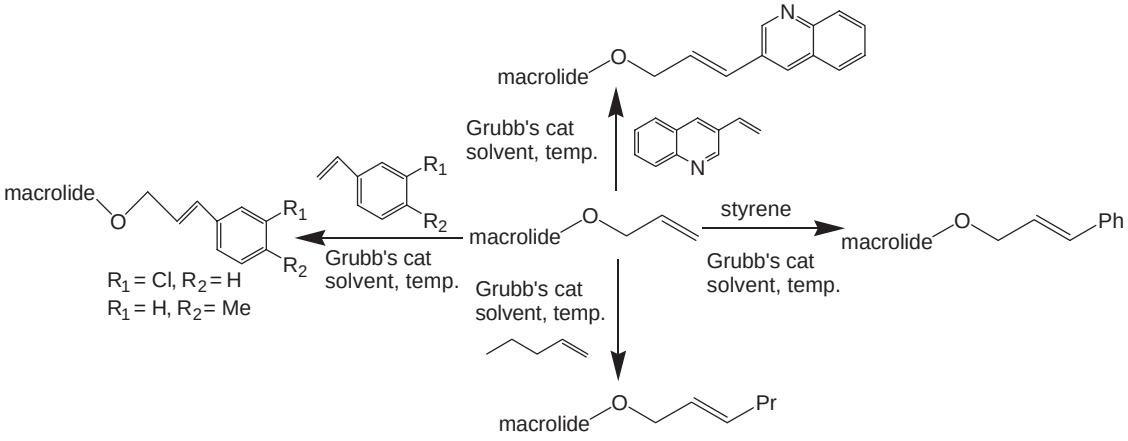
Figure 6. Examples of 6-*O*-arylprop-2′-enyl-11,12-carbamate ketolides.

Taisho.[64b,c] These tricyclic ketolides were prepared by treating 12-*O*-acylimidazolyl intermediate **47** with ethylenediamine and substituted ethylenediamine. Carbamate formation followed by an intramolecular imine formation led to the tricyclic skeleton. Acid hydrolysis of the cladinose ring followed by a modified Pfitzner–Moffatt oxidation afforded the tricyclic ketolides **46a–d** (Scheme 20).

Table 2. Comparison of antibacterial activities of ABT-773 (**23**), its 6-quinonyl derivative (**39f**) and **42** with erythromycin A

		23	**39f**	**42**	Ery-A
Sa[a] ATCC 6538	Ery S	0.05	0.05	0.05	0.39
Sa[a] A5177	erm	0.05	0.05	0.05	6.2
Sa[a] A5278	erm	>100	>100	>100	>100
S_{pyo}[b] EE561	Ery S	0.004	0.004	0.01	0.03
S_{pyo}[b] 930	erm	1	1	0.39	>128
S_{pyo}[b] PIU 2548	mef	0.125	0.25	0.10	32
Sp[c] ATCC 6303	Ery S	0.004	0.004	0.004	0.06
Sp[c] 5737	erm	0.25	1	0.08	>128
Sp[c] 5979	erm	4	—	4	>128
Sp[c] 5639	mef	0.25	0.25	0.25	16

[a] Sa, *Staphylococcus aureus*.
[b] S_{pyo}, *Streptococcus pyogenes*.
[c] Sp, *Streptococcus pneumoniae*.



Scheme 19. Synthesis of 6-*O*-3-aryl-propenyl macrolides via olefin cross metathesis reaction.

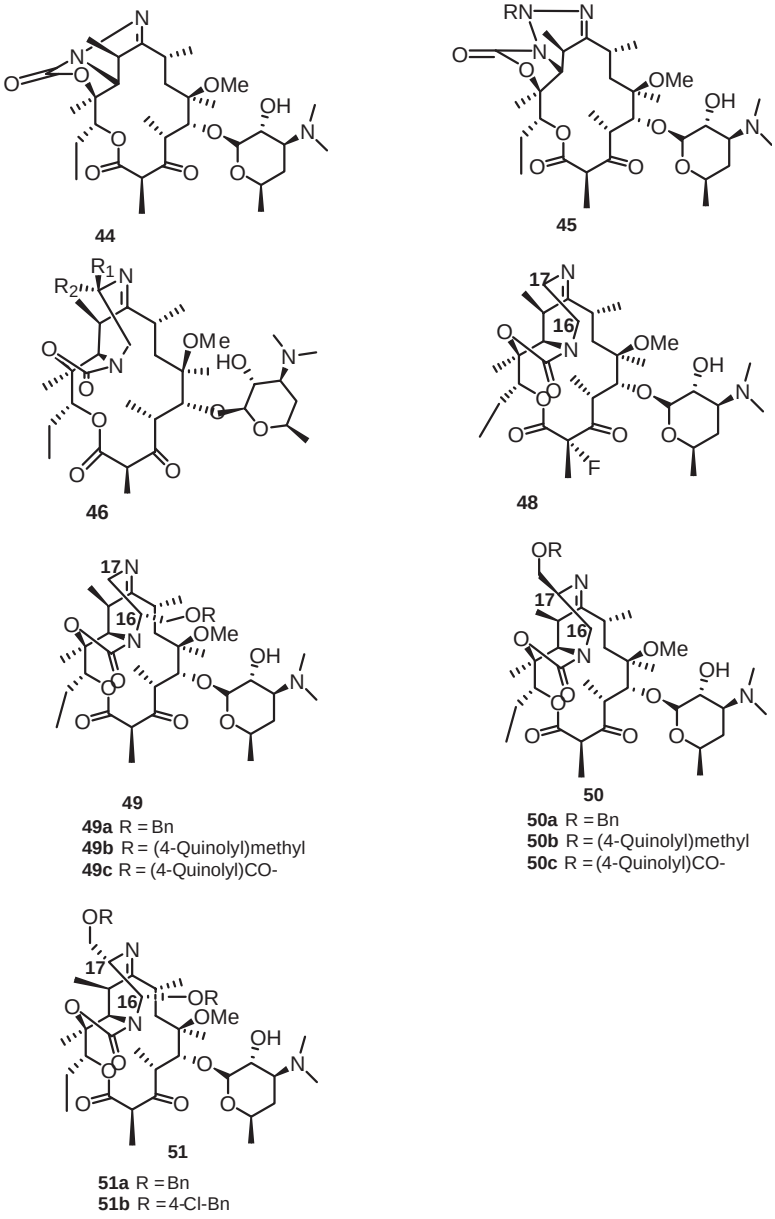
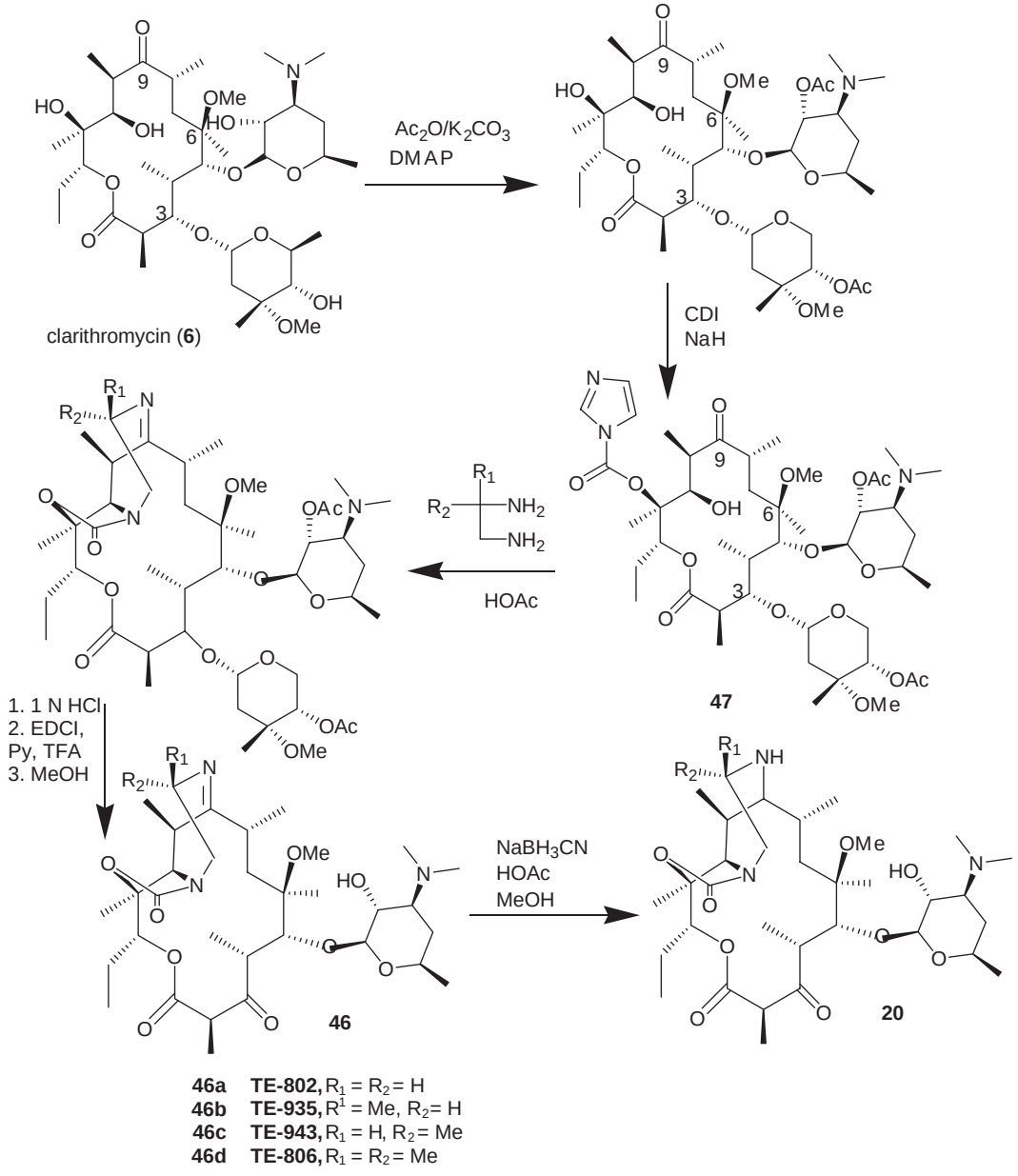


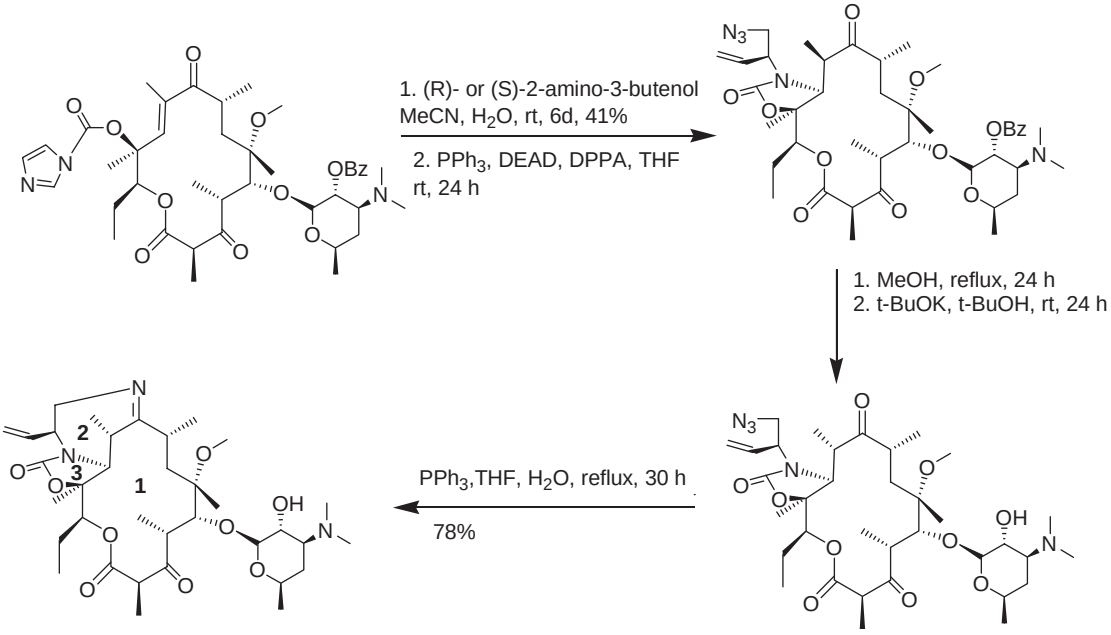
Figure 7. Examples of tricyclic ketolides.



Scheme 20. Synthesis of tricyclic ketolides.

TE-802 (**46a**) showed promising activity. In order to enhance its antibacterial activity, mainly against erythromycin resistant gram-positive organisms and *H. influenzae*, a series of C-2-substituted tricyclic ketolides were prepared by Phan et al.[65,66] The 2-fluoro derivative of TE-802 (**46a**),[50] that is, **48** (Fig. 7), showed enhanced in vivo efficacy, particularly against *H. influenzae*, in mouse pulmonary infections (ED_{50} of **48**: 36 mg/kg; ED_{50} of **46**: >60 mg/kg). All other C-2 substituents examined, for example, hydroxyl, chlorine, bromine and alkyl groups, resulted in a significant loss of activity. These results clearly demonstrated that only small substituents such as fluorine and hydrogen could be tolerated at C-2. To improve the relatively weak activity against MLS_B resistant *S. pneumoniae* and *H. influenzae*, aryl-containing substituents were introduced into the ethylene bridge of TE-802 (**46a**),[67a] based on earlier SAR information. In general, aryl-substituted TE-802 derivatives exhibited a higher activity than TE-802 (**46a**). Derivatives with aryl substitution at position C-16, that is, **49a–c** (Fig. 7), showed higher activity, particularly against MLS_B resistant *Streptococci* and *H. influenzae*. Substitution at C-17, that is, **50a–c** (Fig. 7), however, resulted in a 2- to 3-fold improvement in in vivo efficacy when compared to clarithromycin (**6**) and exhibited the same efficacy as TE-802. Among these compounds, quinolyl derivatives such as **49b** and **49c** provided the highest activity against MLS_B resistant *Streptococci* and *H. influenzae*. The C-16 and C-17 disubstituted analogue **51** (Fig. 7) was less active against *H. influenzae*, but showed enhanced activity against MLS_B constitutively resistant *S. aureus* (MIC 6.2 μg/ml vs >100 μg/ml for erythromycin).

Or and co-workers synthesized[67b] a novel vinyl-substituted bridged tricyclic ketolide, which can be further used as building blocks for the synthesis of new generation ketolides to overcome macrolide resistance (Scheme 21).

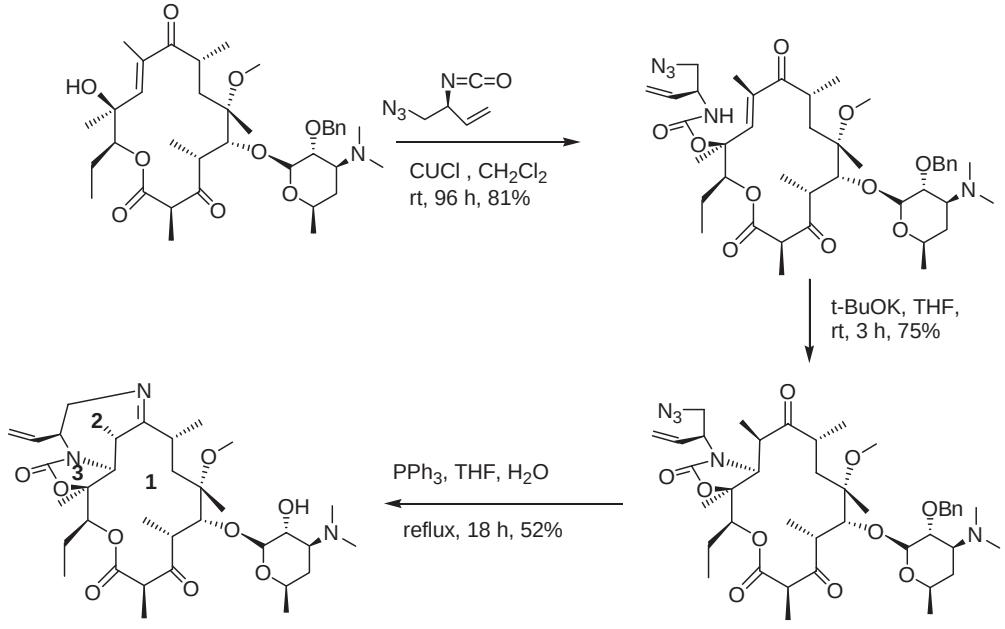


Scheme 21. Synthesis of vinyl-substituted tricyclic ketolide.

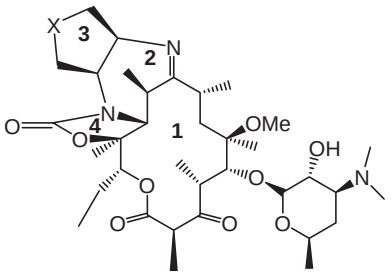
This original synthesis of a vinyl-substituted cyclic ketolide had some major drawbacks, for example, low yield due to the formation of a mixture of products and difficulty in purifying the final product. Very recently, Keyes and co-workers[67c] reported a short, efficient and improved synthesis of the same macrolide by utilizing the unwanted side product of the previous method as the starting compound and azido isocyanate (Scheme 22).

Type b: tetracyclic ketolides. Phan et al. reported a series of tetracyclic ketolides with one fused carbocycle or heterocycle ring to the diazapene ring of TE-802.[68] The synthesis, which employed *meso-cis*-diamines in the cyclization, generated two possible diastereomers, **52a–d** and **53a–d** (Fig. 8), where **52a–d** was found to be the major isomer. Or and co-workers also reported a novel cyclic ketolide **55**. It was prepared by reducing the nitro group of compound **54**, followed by intramolecular condensation (Scheme 23)[69] of the resulting amine with the nearby carbonyl group. Further reduction of **55** provided **56**. None of these tetracyclic ketolides exhibited significant in vitro activity against constitutively macrolide resistant *S. pneumoniae* and none showed azithromycin-like MICs against *H. influenzae*.

3.4.6. Synthesis of bridged ketolides. The synthesis and activity of two novel series of bridged ketolides reported by Or et al. are now described.

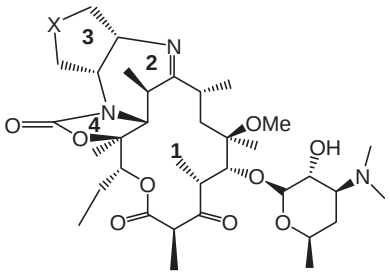


Scheme 22. Improved synthesis of tricyclic erythromycin analogue.



52

52a,X = -CH_2CH_2-
52b,X = -CH_2-
52c,X = -O-
52d,X = -NR-



53

53a, X = -CH_2CH_2-
53b, X = -CH_2-
53c, X = -O-
53d, X = -NR-

Figure 8. Tetracyclic ketolides.

(a) The first series, 6,9-bridged ketolides, is exemplified by **57** and **58**.[70a] Compound **57** was prepared from the protected erythromycin derivative **13** according to the procedure outlined in Scheme 24. Thus, fluoromethylation of **13** with fluoromethyl bromide followed by deprotection provided the bridged erythromycin derivative **57**. Compound **57** was converted into the corresponding 11,12-cyclic carbonate, that is, **58**. Sequential hydrolysis of cladinose, protection of the 2′-hydroxy group and Corey–Kim oxidation of the 3-hydroxy group followed by final deprotection provided the 6,9-bridged ketolide **59**. It was slightly less active than erythromycin A against macrolide susceptible organisms, including *H. influenzae*, it was very active against erythromycin resistant organisms harboring an efflux mechanism, but it failed to show activity against resistant organisms with a ribosome methylation mechanism.[70b]

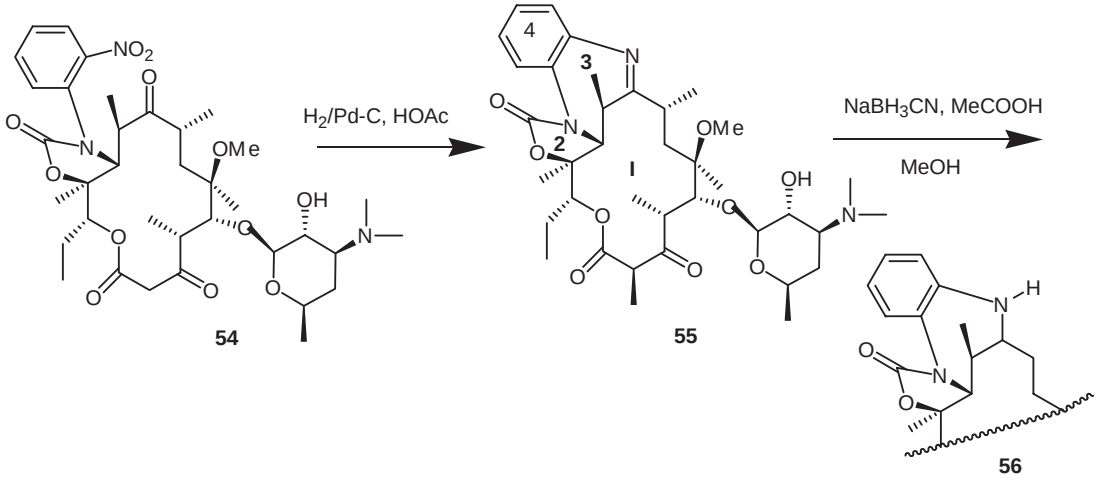
(b) The other series reported by Or et al. comprising structurally unique 6,11-bridged ketolides[71a] was generated by the intramolecular Heck reaction of **60** and **61** to form 17- and 18-membered macrolides (**62** and **63**) followed by their conversion into the desired ketolides, that is, **64** and **65**. In a similar manner, the Heck reaction was also performed on an *N*-substituted carbamate ketolide **66** in order to generate the 18-membered ketolide, that is, **67** (Scheme 25).

Apart from these derivatives, two other 6,11-bridged ketolides **69a** and **69b** were prepared via an alternative synthetic strategy, that is, a ring-closing olefin metathesis of compound **68** (Scheme 26).[71b]

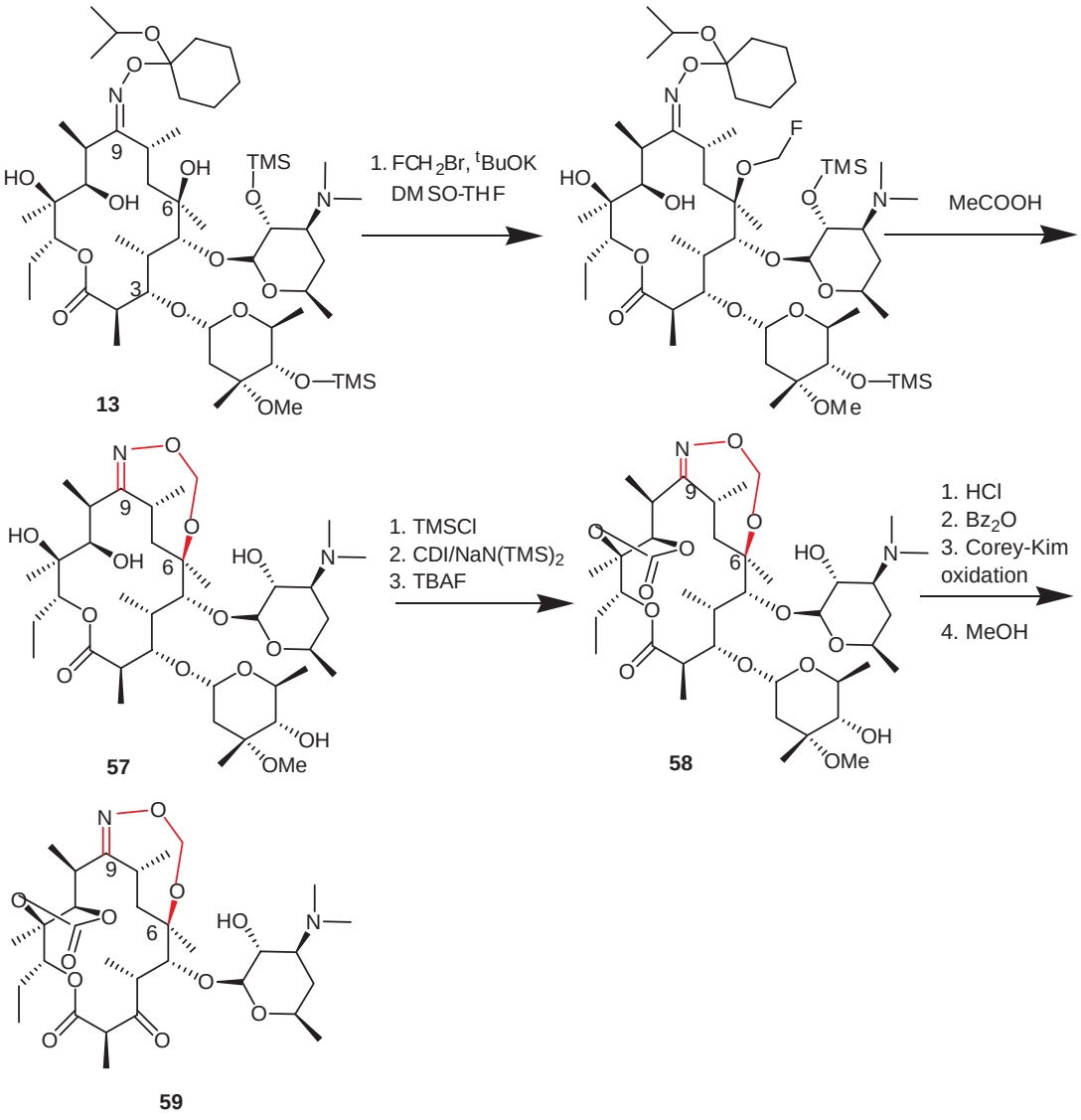
Another novel series of 6,11-bridged ketolides were prepared by Li et al.[72a] Compounds **70** and **71** (Fig. 9) can be considered as hybrids of the 6-*O*-substituted ketolide series developed by Abbott and the 11,12-carbamate ketolide series developed by Aventis. Denis and Renou achieved the *N*-demethylation of ketolides by using solution-phase parallel synthesis of *N*-desosaminyl-substituted ketolides.[72b]

Among the various types of ketolides reported, ABT-773 (**23**, Fig. 6) has been identified as a highly potent, broad-spectrum ketolide effective against drug resistant *Streptococcus pneumoniae*.[73–75]

3.4.7. Synthesis of promising macrolides other than ketolides. The ketolide series is not necessarily the only



Scheme 23. Synthesis of tetracyclic ketolide.



Scheme 24. Synthesis of 6,9-bridged ketolides.

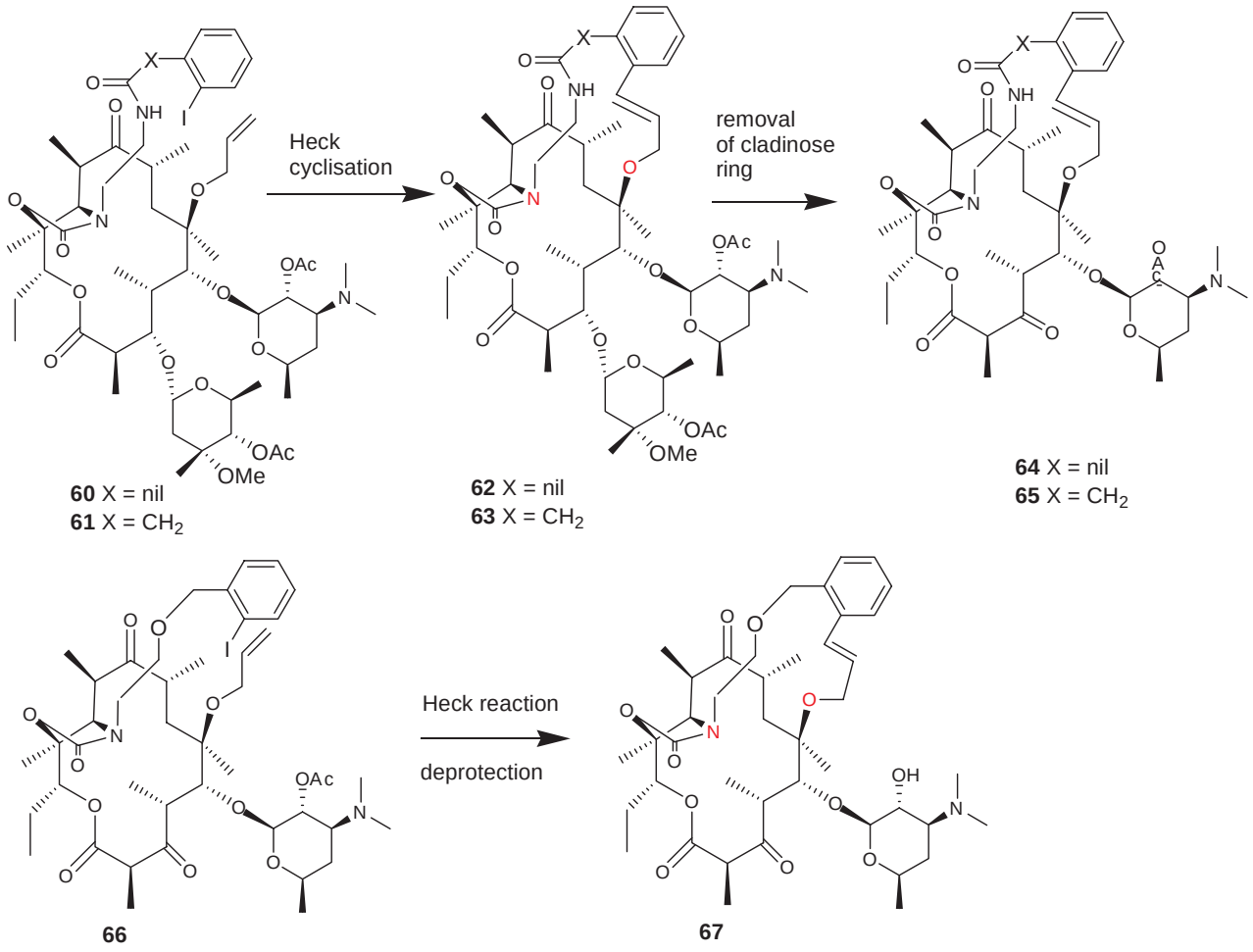
class of macrolides to achieve this goal. Some modifications to the C-3 cladinose sugar have been reported. These modifications include:

(i) 3-Deoxymacrolides exemplified by 3-deoxy-3-descladinosyl-6-*O*-methylerythromycin analogues[76] (**72**, Fig. 10). These had moderate antibacterial activity against gram-positive organisms.

(ii) 2,3-Anhydro macrolides, which contain a planar (non-keto) sp^2 carbon at the C-2 and C-3 positions of the macrolactone ring. A series of 3-descladinosyl-2,3-anhydro-6-*O*-methylerythromycin A 11,12-cyclic carbazates exemplified by A-179461 (**73**, Fig. 10) was prepared by Griesgraber et al.[77,78] and evaluated for antibacterial activity. They were found to be potent antibacterial agents in vitro against macrolide susceptible organisms including *Staphylococcus aureus* 6538P, *Streptococcus pyogenes* EES61 and *Streptococcus pneumoniae* ATCC 6303. These compounds were also highly active against some organisms that showed macrolide resistance (*S. aureus* A5177, *S. pyogenes* P1U2584 and *S. pneumoniae* 5649). The compounds generally showed poor activity against organisms with constitutive MLS_B resistance. They were less active than erythromycin A against *H. influenzae*.

(iii) 3-Acylides. The synthesis and antibacterial activity of 3-*O*-acylerythromycin derivatives (3-acylides) were first reported by Asaka et al.[79] This class of macrolide contains an ester functional group at the C-3 position instead of a ketone in the ketolides. Both FMA-199 (**74**) and FMA-481 (**75**) (Fig. 10) have in vitro activity against *S. pneumoniae*, comparable to HMR-3647, but they did not show activity against constitutively MLS resistant *S. aureus* strains like HMR-3647 and ABT-773. FMA-481 was more active in vitro, even though FMA-199 was more active in vivo. The lower in vivo potency of FMA-481 may be due to lower absorption of FMA-481.

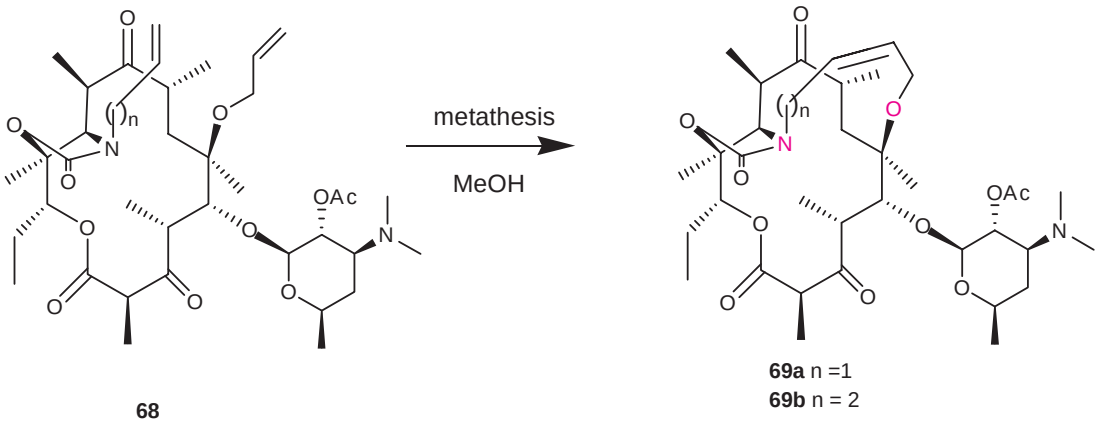
Tanikawa et al.[80] reported another class of 3-acylide, exemplified by 3-*O*-(4-nitrophenyl)acetyl-5-*O*-desosaminyl-6-*O*-methylerythronolide (TEA-0777, **76**, Scheme 27),



Scheme 25. Synthesis of 6,11-bridged ketolides.

which showed 250-fold greater activity against the erythromycin susceptible strain than the 3-*O*-acetyl derivative. This acylide demonstrated potent activity against the erythromycin susceptible strain of *Streptococcus pneumoniae*, like other macrolides. It was highly effective against *Enterococcus* strains and the efflux resistant strain of *S. pneumoniae*. In the case of in vitro evaluation, acylide TEA-0777 was significantly more active than erythromycin A and comparable to clarithromycin. It has the potential to be one of the next generation macrolide antibiotics.

Very recently, Randolph and co-workers in Abbott Laboratories synthesized[81] a series of novel acylides **77** (Fig. 11), which are potent nonpeptide luteinizing hormone—releasing hormone (LHRH) antagonist and may be useful for the treament of endometriosis, uterine fibroids, precocious puberty and certain malignancies.[82,83] Extensive optimization of the lead gave **78** (Fig. 11), which is a potent inhibitor of LH release in vitro. In vivo, it was found to produce a dose-dependent suppression of LH in male castrated rats.



Scheme 26. Synthesis of 6,11-bridged ketolides by olefin metathesis.

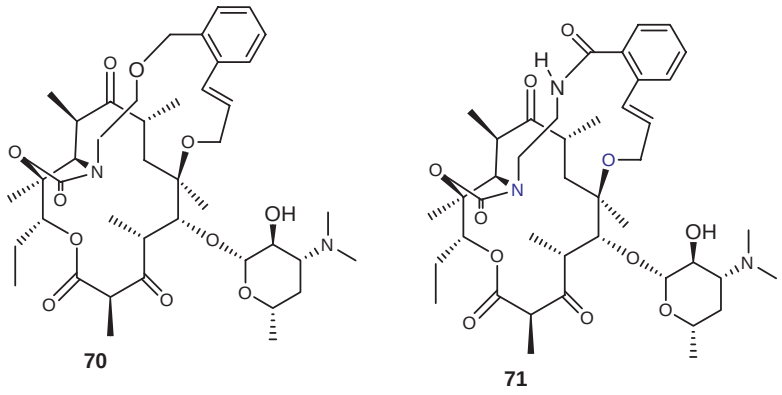


Figure 9. Further examples of 6,11-bridged ketolides.

4. Promising natural products

Some of the recent studies show that the search for promising new structures from natural products can be fruitful in supplying novel compounds having potential for clinical use. The discovery of 6-deoxyerythromycin A (**79**, Fig. 11) by systematic gene disruptions in of *Saccharopolyspora erythraea*[84] provided an understanding of the role of 6-OH on the pharmacokinetics and antibacterial activity. It has a weaker activity in vitro than **1**, but 6-deoxy derivative is more acid stable than **1**. It is hoped that modification may lead to a better efficacy. Sporeamicin A (**80**, Fig. 11), which represents another promising class,[85–87] has good antibacterial activity and attains higher blood and tissue levels than **1** in mice. Barber and co-workers[88] pointed out that erythromycin B (which lacks a C-12 hydroxy group) (**81**, Fig. 11) may be useful as a natural product sharing the relative acid stability of the second-generation erythromycin A derivatives, clarithromycin and azithromycin, and the therapeutic profile of erythromycin A.

5. Conclusions: an evergreen field of new drug discovery

Finally, this review is concluded by looking back over the past 53 years (2005–1952). An attempt has been made in this article to review the development of all of the significant synthetic modifications of erythromycin such as clarithromycin, azithromycin, roxithromycin, telithromycin and ABT-773, which address the serious problem of antibiotic resistance among the major respiratory pathogens. As described in this review, however, the strategy and tactics for the synthesis of new classes of compounds are still under development. Substantial strides have been made in the last few years to overcome the challenge posed by microorganisms and the information in this area has grown rapidly, which has allowed some important conclusions to be deduced regarding structure–activity relationships. The removal of the cladinose sugar at C-3 and the introduction of a keto group at the same position gave rise to a new class of macrolides called ketolides that can effectively solve the efflux resistance. The MLS_B resistance caused by the methylation of ribosome cannot, however, be addressed by the ketolides. In order to overcome such resistance, further structural modifications were carried out by medicinal chemists. 11,12-Carbamate and -carbazate ketolides were better than ketolides to tackle MLS_B resistance. In addition, an anchor of a four-carbon butyl chain with specific aryl groups must be present either at the nitrogen atom of the carbamate and carbazate rings or at the oxygen of C-6. Telithromycin and ABT-773 are the two successful representative molecules of this family, which have elicited a great deal of interest. They have spurred a new wave of interest in macrolide and ketolide classes of antibiotics. The availability of several novel series represents a significant conceptual advance in therapy and may afford new treatment options in the near future. It is worthy of note that the ketolide series is not the only class

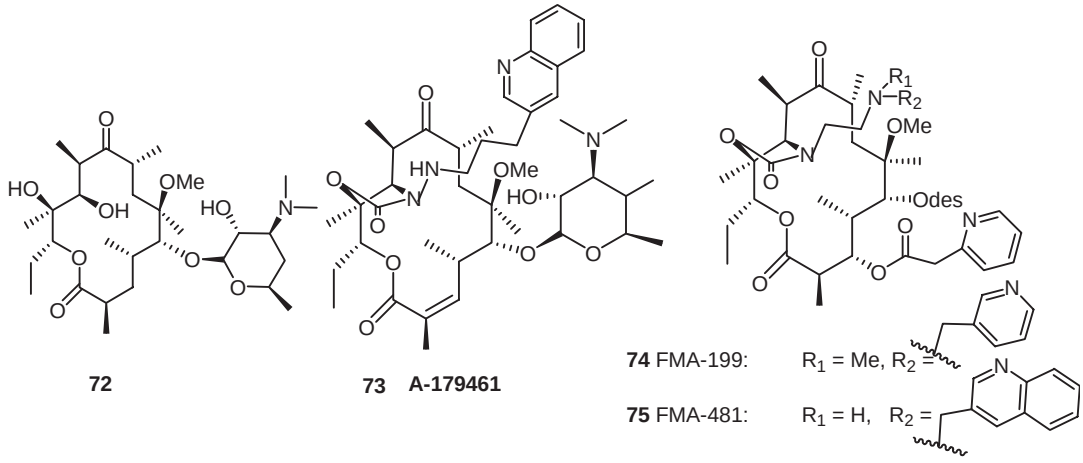
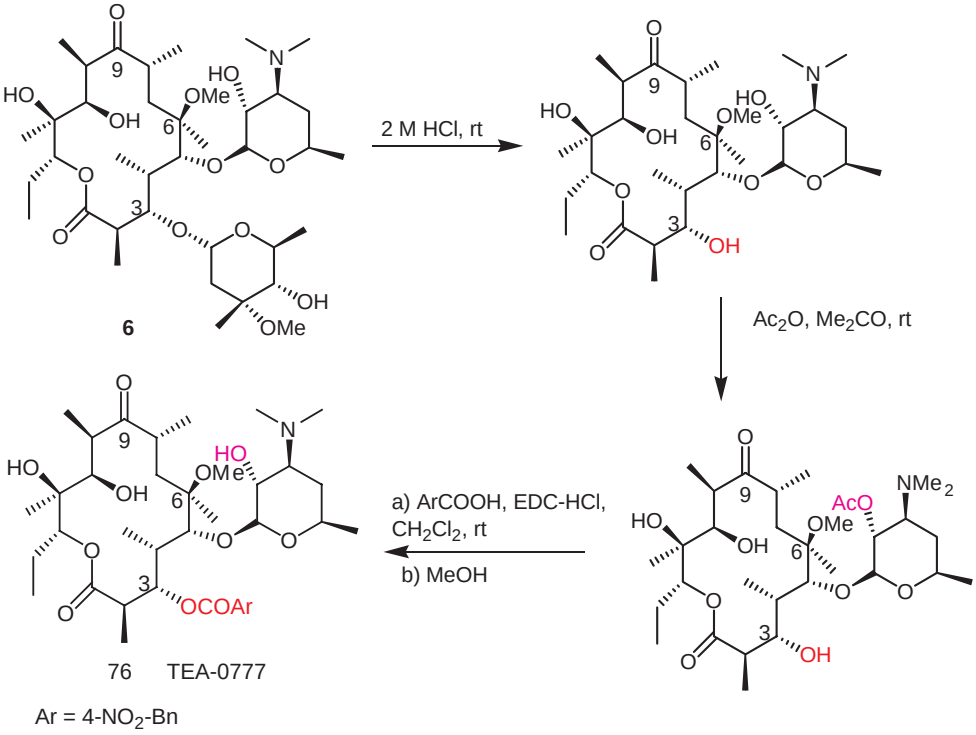


Figure 10. Some modified macrolides (apart from ketolides).



Scheme 27. Synthesis of 3-*O*-(4-nitrophenyl)-acetyl erythromycin A derivative (TEA-0777).

for the effective management of respiratory tract infections. Medicinal chemists have synthesized some derivatives of a nonketolide family. These modifications include derivatives of A-179461, FMA-199 and TEA-0777, which are undergoing clinical trial so their biological activities are yet to be unveiled. As more imaginative chemistry in this field continues, further synthetic work is aimed at extensive modifications, and it is hoped that progressive applications of the knowledge of enzyme mechanisms and their interactions with inhibitors will yield analogs with better activity profiles. Although the last few years have witnessed stunning breakthroughs in the clinical development of carbamate and carbazate ketolides, there is still much to be learned about the complex mechanism of bacterial

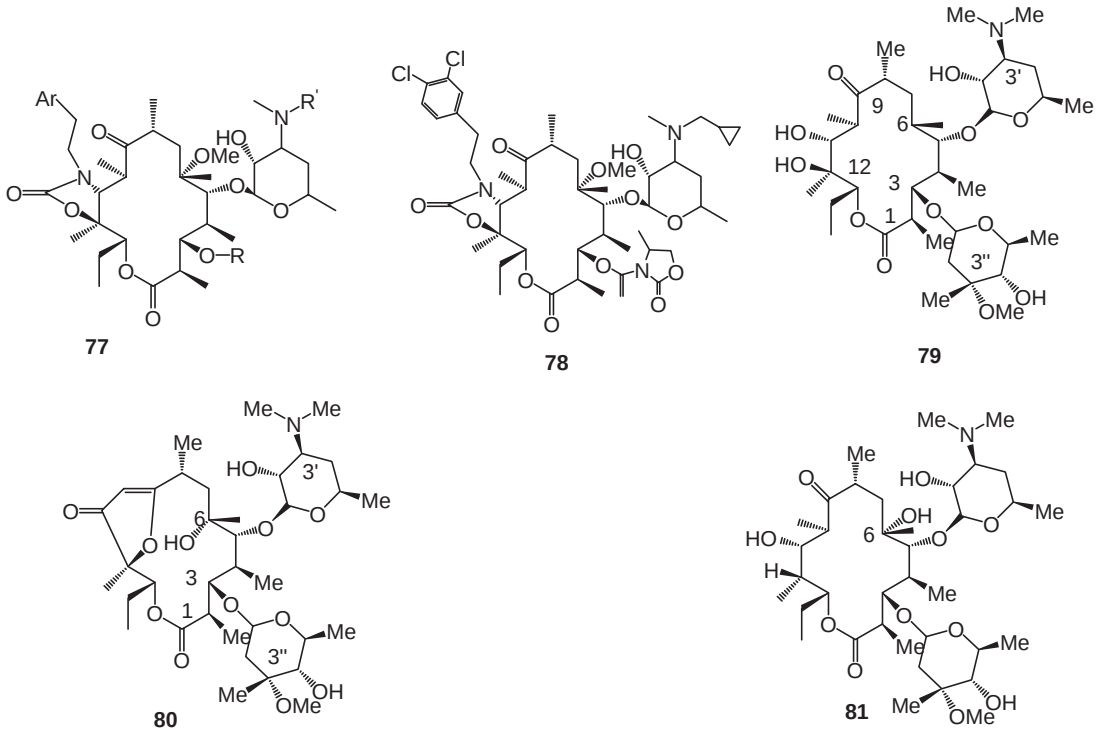


Figure 11.

resistance, due to both the anatomical and physiological diversity of microorganisms. As a result, a better understanding of the drugs is expected to emerge in the near future. The search for new compounds from natural products could, however, be fruitful. To address increasing antibacterial resistance, the search for new compounds from natural products could present a significant opportunity in the development of new macrolide antibiotics.

Last, but not the least, the author would like to apologize to those whose contributions in this field she may have inadvertently overlooked.

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