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Synthesis and antibacterial activity of C_{12} des-methyl ketolides

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Abstract—Synthesis of C_{12} des-methyl ketolide is developed featuring an intramolecular epoxide formation/elimination process to establish the C_{12} stereocenter. These ketolides are potent against several key respiratory pathogens, including erythromycin resistant *erm*- and *mef*-containing strains of *Streptococcus pneumoniae*.

Macrolide antibiotics such as erythromycin A (Fig. 1) are potent against several key respiratory pathogens including *Staphylococcus aureus* and *Streptococcus pneumoniae*. They have been widely used for the treatment of bacterial respiratory tract infections for many years. The second generation of macrolides, including clarithromycin[1] and azithromycin,[2] was developed to overcome the problems associated with acid instability of erythromycin.[3] These compounds displayed better pharmacokinetic properties as well as a broader spectrum of activity.

Macrolides exert their antibacterial activity by reversibly binding to the 23S ribosomal RNA in the 50S subunit of ribosomes in order to block protein synthesis.[4] Recently, macrolide resistant pathogens with two main resistant mechanisms, active efflux of the drug (*mef* gene) and target site modification (*erm* gene), have emerged.[5] To overcome the resistant pathogens, a third generation of macrolide known as ketolides (telithromycin[6] and cethromycin (ABT-773)[7]) has been developed. Ketolides differ from other macrolides in that the C_3 cladinose sugar of erythromycin A is replaced with a C_3 ketone group. Additionally, a heterocycle is tethered to the macrolide core, introducing an additional binding contact with the target ribosome.

In our laboratories, we sought to develop novel ketolides with in vitro and in vivo potency against resistant strains. These ketolides are novel in that they have a C_{12} modified macrocycle core. Using chemical synthesis we have been able to access C_{12} hydrogen (des-methyl)[8a] and other alkyl groups[8,9] in place of the natural C_{12} methyl of erythromycin derived macrocycles. In this paper, we wish to report the synthesis of C_{12} des-methyl macrolide core, conversion of the core to ketolide derivatives, and in vitro activities of the resulting ketolides.

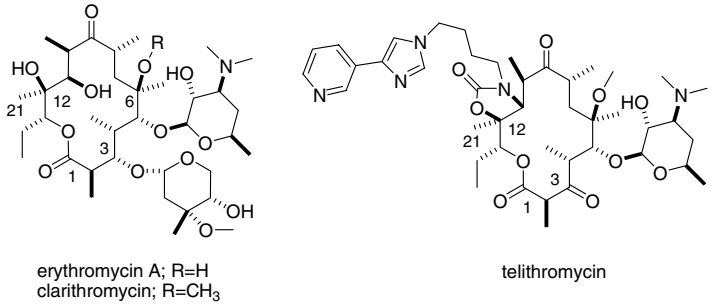

Figure 1. Clinically utilized macrolides.

Keywords: Macrolide; Ketolide; Antibacterial.
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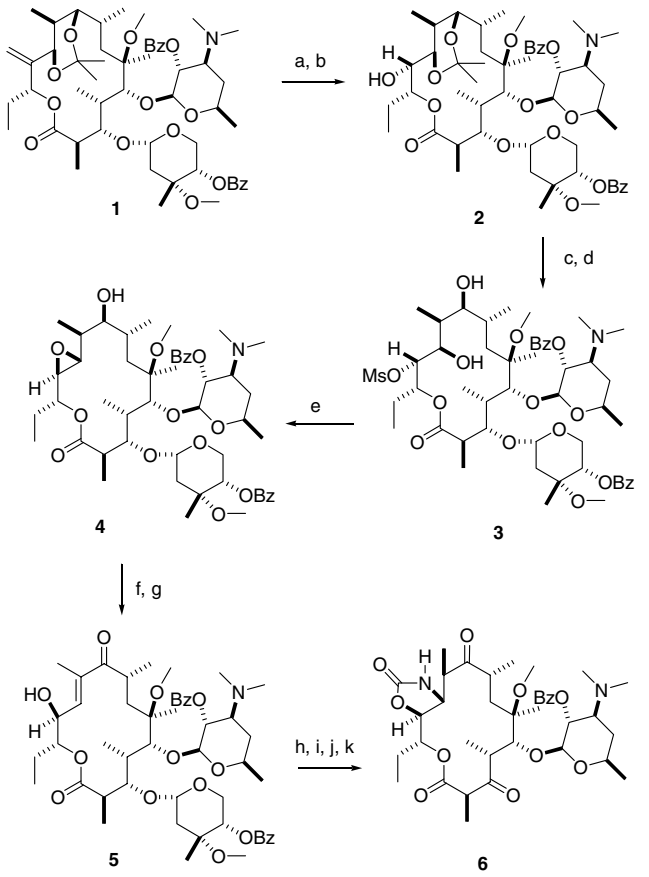


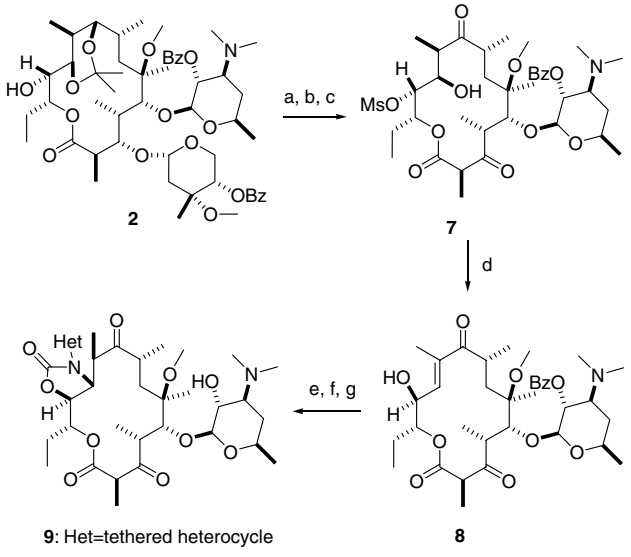
Scheme 1. Reagents and conditions: (a) *p*-TsOH, O_3, DCM/MeOH, −78 °C, 10 min; then Me_2S, −78 °C, 10 min; then Et_3N, −78 to 25 °C, 85%; (b) $NaBH_4$, EtOH, 25 °C, 17 h; (c) MsCl, DMAP, Et_3N, DCM, 0 °C, 30 min; (d) HOAc, ACN, H_2O, 65 °C, 16 h, 83% over three steps; (e) Cs_2CO_3, ACN, 25 °C, 22 h; (f) Dess–Martin periodinane, DCM, 0–25 °C, 6 h, 96% over two steps; (g) DBU, acetone, 25 °C, 6 h; (h) CDI, NaH, THF, −15–0 °C, 2 h; (i) NH_4OH, THF, ACN, 50 °C, 22 h, 63% over three steps; (j) 3 M HCl (aq), ACN, 25 °C, 26 h, 92%; (k) *N*-chlorosuccinimide, Me_2S, DCM, −20 °C, 40 min; then Et_3N, −20–0 °C, 30 min, 75%.

Synthetic modifications of erythromycin have been pursued by numerous investigators in order to prepare chemical derivatives with improved biological profiles. More recently, modifications involving the C_{11} and C_{12} hydroxyl groups have been extensively explored,[10] which, in conjunction with modifications of C_3 cladinose moiety, eventually yielded the recently approved ketolide telithromycin. However, there are few examples of chemical modifications to erythronolides at C_{12} and, especially, with regard to the C_{12}—C_{21} bond.[11]

We have previously reported the efficient synthesis of a suitably protected C_{12}—C_{21} exocyclic alkenyl macrolide **1** from erythromycin A.[9] As shown in Scheme 1,[12] ozonolysis of the tosylate salt of **1** yielded C_{12}-keto macrolide. Hydride reduction of the C_{12}-keto group then afforded C_{12} des-methyl macrolide core **2**, with undesired and unnatural C_{12} alpha hydroxy configuration. The stereochemistry at C_{12} was determined based upon X-ray diffraction of the crystals of **2**.[13] Efforts to deliver hydride from the bottom face were not fruitful. Several attempts to invert the alpha hydroxyl group at C_{12}, including Mitsunobu reaction and intermolecular S_N2-type reaction with the mesylate of **2**, did not yield any desired product. It appears that the C_{12} secondary alcohol and its mesylate are not reactive toward intermolecular S_N2-type reactions, probably because the site is too crowded. Hence we sought to invert the C_{12} alpha hydroxy via an intramolecular reaction.

Converting the C_{12} hydroxyl group to mesylate followed by hydrolysis of the cyclic acetonide using acetic acid yielded diol **3**. Treatment of **3** with cesium carbonate gave the C_{11}—C_{12} epoxide **4** with inversion of stereocenter at C_{12}. To confirm the stereochemistry of compound **4**, the benzoyl protecting group at C-2′of the desosamine was removed to grow the crystal and a structure was determined by X-ray diffraction.[13] To complete the synthesis, C_9 was oxidized and the resulting ketone was subjected to basic conditions which allowed deprotonation and β-elimination, resulting in enone **5**. Deprotonation with sodium hydride in the presence of carbonyldiimidazole gave C_{12} imidazole carbamate, which upon reaction with excess ammonia yielded C_{11}—C_{12} cyclic NH carbamate. Acidic hydrolysis of the cladinose and subsequent Corey–Kim oxidation of C_3-hydroxy to C_3-keto then gave ketolide **6**. The X-ray crystal diffraction of **6** unambiguously confirmed the stereochemistry of the C_{12} des-methyl ketolide.[13]

Scheme 2[12] illustrates a more concise sequence for synthesizing C_{12} des-methyl ketolide analogs with different heterocycles tethered to the carbamate nitrogen. Thus, mesylate formation of **2** was followed by hydrolysis of both C_3 cladinose and cyclic acetonide with hydrochloric acid. The subsequent oxidation using Dess–Martin periodinane oxidized both C_3 and C_9 hydroxy groups to afford diketone **7**. Treatment of **7**



Scheme 2. Reagents and conditions: (a) MsCl, DMAP, Et_3N, CH_2Cl_2, 0 °C, 30 min; (b) 3 M HCl (aq), ACN, 25 °C, 14 h, 88% over two steps; (c) Dess–Martin periodinane, CH_2Cl_2, 0–4 °C, 48 h, 77%; (d) DBU, acetone, 25 °C, 15 h, 72%; (e) NaH, CDI, THF, −15–0 °C, 25 min; (f) Het-amine, ACN, 75 °C, 40 h, 43–84% over two steps; (g) MeOH, 70 °C, 22 h, 42–79%.