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Synthesis of novel 4′-substituted 16-membered ring macrolide antibiotics derived from leucomycins

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Abstract—A series of novel 4′-substituted 16-membered ring macrolides was synthesized by the cleavage of the mycarose sugar and subsequent modification of 4′-hydroxyl group. This new class of macrolides antibiotics is acid stable. The synthetic methodology described here is expected to find application in the synthesis of new generation of macrolides that target the emerging bacterial resistance.

Macrolide antibiotics have been widely used to treat bacterial infections for the past 50 years.[1] They are considered as the preferred therapeutic agents for the treatment of upper and lower respiratory tract infections due to their safety and efficacy.[2] Macrolides exert potent antibacterial effect by selectively binding to the 50S subunit of the bacterial ribosome and inhibition of the protein synthesis.[3] Recent published crystal structures of the bacterial ribosomal complexed with macrolides have demonstrated that they bind in the polypeptide exit tunnel to block the elongating polypeptide.[4] As a large family of both natural and semi-synthetic antibiotics, macrolides are classified according to the size of the lactone ring consisting of 12–16 atoms and to the number and type of sugars attached. Erythromycin A (Fig. 1) and its derivatives, which have a fourteen membered lactone ring, are the most commonly used macrolides. However, erythromycin-resistant bacterial strains have become increasingly prevalent over the past decade.[5] The sixteen membered ring macrolides of leucomycins, such as josamycin and kitasamycin (Fig. 1), constitute another important class of clinically useful antibiotics.[6] These sixteen membered ring macrolides offer some advantages over 14-membered erythromycin derivatives, such as gastrointestinal tolerance and activity against resistance-expressing strains.[7] However, little research has been done to improve their acid stability and antibacterial activity.[8]

Herein, we report the synthesis of a series of novel 4′-substituted 16-membered ring macrolides derived from members of the leucomycin complex.

Our approach to improve the acid stability of leucomycins is to remove the mycarose sugar and modify the 4′-hydroxyl group. Josamycin, one of the members of leucomycins, was used as a model compound for this study. Scheme 1 outlines the synthesis of 4′-carbamates of josamycin. Oxidation of josamycin **1** with chromic oxide converted the 9-hydroxyl group to the 9-ketone group. Protection of the 2′-hydroxyl group of **2** with an acetyl group generated **3**. Hydrolysis of the 4′-mycarose group of **3** in 0.3 M HCl gave the corresponding 4′-hydroxyl compound **4**. Reaction of **4** with various isocyanates followed by deprotection of the 2′-acetate with methanol at room temperature proceeded smoothly to afford the desired products **6** in yields ranging from 46–50%.

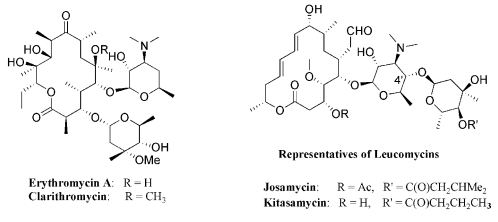

Figure 1. Structures of erythromycin A, clarithromycin and members of the leucomycins.

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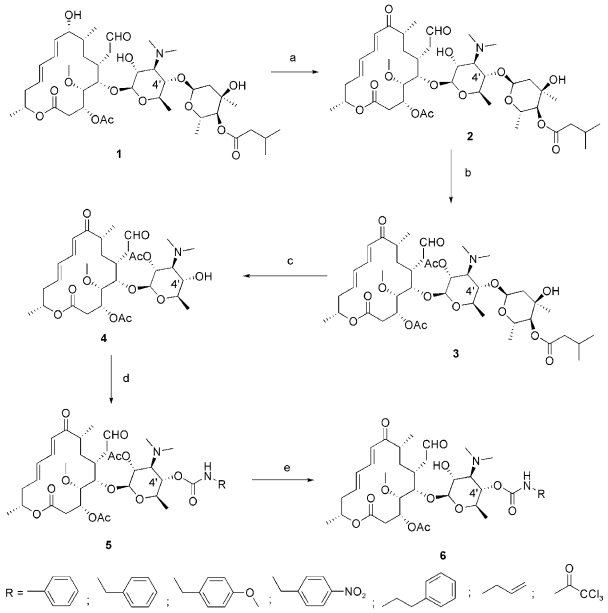
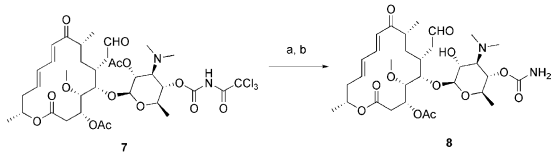


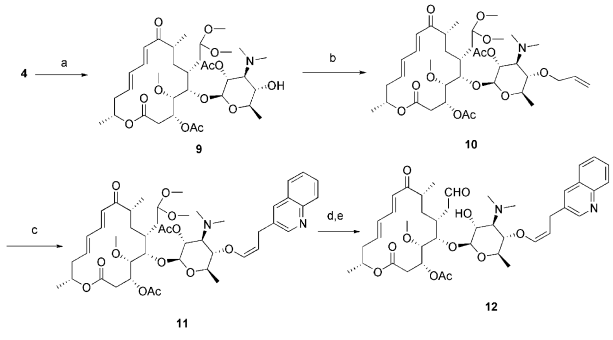
Scheme 1. (a) CrO_3, Py/H_2O, rt, 3 h (46%); (b) Ac_2O, Py, rt, 16 h (100%); (c) 0.3 M HCl, rt, 16 h (79%); (d) R-N=C=O, Et_3N, CH_2Cl_2, rt, 5–16 h (46–50%); (e) MeOH, rt (100%).

Conversion of the trichloroacetyl carbamate **7** to the corresponding amide **8** is achieved by alkaline hydrolysis with sodium bicarbonate in methanol as outlined in Scheme 2.

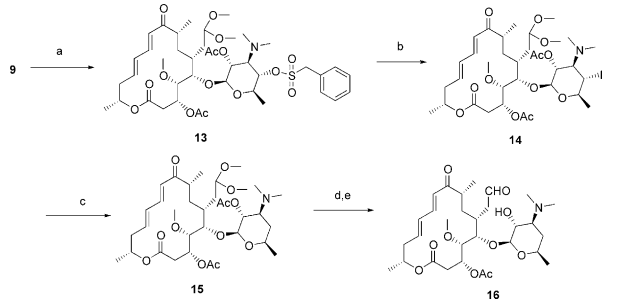
The synthesis of an allyl ether is described in Scheme 3. Protection of the aldehyde group of **4** with acetyl chloride in methanol gave **9**. Palladium-catalyzed reaction of compound **9** with allyl-*t*-butyl carbonate provided **10** in 83% yield. Heck reaction of **10** with 3-bromoquinoline generated enol ether **11** as the major product and subsequent deprotection in methanol gave the final compound **12**.



Scheme 2. (a) $NaHCO_3$, MeOH, rt, 0.5 h; (b) MeOH, rt, 12 h (56% in two steps).



Scheme 3. (a) Acetyl chloride, MeOH, 12 h (74%); (b) ally *t*-butyl carbonate, $Pd_2(dba)_3$, dppb, THF, 65 °C, 2 h (83%); (c) 3-bromoquinoline, $Pd(OAc)_2$, $P(o\text{-Tol})_3$, Et_3N, CH_3CN, 80 °C, 16 h (43%); (d) HCl, CH_3CN, rt, 16 h; (e) MeOH, rt, 16 h (74% in two steps).



Scheme 4. (a) $PhCH_2SO_2Cl$, Py, −40 °C, 3 h (93%); (b) NaI, 2-butanone, 80 °C, 1 h (85%); (c) *n*-Bu_3SnH, AIBN, benzene, 80 °C, 2 h (37%); (d) TFA, CH_3CN, rt 16 h; (e) MeOH, rt, 16 h (74% in two steps).

In order to verify if the 4′-hydroxyl is important for the antibiotic activity, a 4′-deoxy analogue **16** was prepared as outlined in Scheme 4. Sulfonate ester **13** was generated by the reaction of **9** with sulfonyl chloride. The displacement of the sulfonate **13** by NaI provided compound **14**. The treatment of **14** with tributyltin hydride and AIBN gave the deoxy analogue **15**. The deprotection of **15** with TFA to remove the acetal group followed by methanol deprotection to remove the 2′-acetyl generated the final product **16**. The 4′-deoxy compound **16** showed significant lost in antibacterial activity, highlighting the importance of 4′-substitutions.

The recent high-resolution X-ray co-crystal structures of the bacterial ribosome and macrolides have revealed their detailed interactions at the atomic level. It is showed in the co-crystal structures of the 50S ribosomal subunit from *Haloarcula marismortui* in complex with carbomycin A that the mycarose sugar at the 4′-position extends up the peptide exit tunnel toward the peptidyl transferase center (PTC).[4] Since carbomycin A has a very similar structure to leucomycins, the crystal structures imply that leucomycins interfere more directly with the activity of the PTC than erythromycin A in which there is no attachment at the 4′-position. Therefore, replacing the acid labile mycarose sugar of leucomycins with other substituents would improve their acid stability and may increase their binding interactions with the ribosome as well.

The new 16-membered macrolide antibiotics were tested against resistant bacterial strains (*Streptococcus pyogenes* 1323 and *Streptococcus pneumoniae* 7701)[9] and compound **12** showed enhanced MIC activity.[10]

In conclusion, the synthesis of a novel series of 4′-substituted leucomycin derivatives has been described. The synthetic routes demonstrated here are useful for further diverse modifications in the development of new macrolide antibiotics to overcome resistant pathogens.

Acknowledgements

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9. The minimum inhibitory concentration (MIC) assays were performed in accordance with the National Committee of Clinical Laboratory Standards (NCCLS) guidelines. *Staphylococcus aureus* 25923 is an erythromycin-susceptible strain. *S. pyogenes* 1323 is an efflux-resistant strain encoded by the *mef* gene. *S. pneumoniae* 7701 is an efflux-resistant strain encoded by the *mef* gene.
10. The MIC of compound **12** against *S. aureus*-25923, *S. pyogenes*-3190 and *S. pneumoniae*-7701 is 2, 0.25, and 0.25 μg/mL as compared to 0.5, 8, and 8 μg/mL for erythromycin A, respectively.