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Synthesis of Novel 6,11-O-Bridged Bicyclic Ketolides via a Palladium-Catalyzed Bis-allylation

Guoqiang Wang,* Deqiang Niu, Yao-Ling Qiu, Ly Tam Phan, Zhigang Chen, Alexander Polemeropoulos, and Yat Sun Or

Enanta Pharmaceuticals, Inc., 500 Arsenal Street, Watertown, Massachusetts 02472

wang@enanta.com

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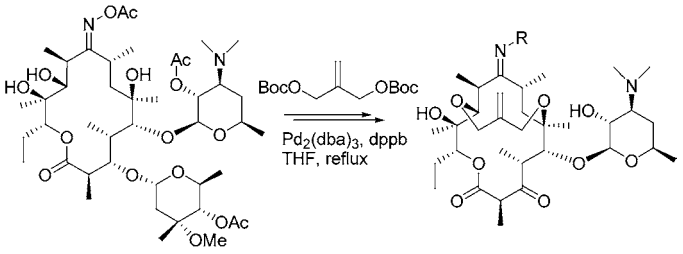
ABSTRACT



A bridging chemistry process was developed to form an ether bridge between 6-O and 11-O of erythromycin A via a tandem or stepwise palladium-catalyzed bis-π-allylation. By applying this bridging process, new 6,11-O-bridged bicyclic ketolides (BBKs) were synthesized. These BBKs showed good antibacterial activities against the macrolide-susceptible strains as well as *mef*-resistant strains and served as a good core for further modifications to study the structure–activity relationship (SAR) and to overcome bacterial resistance.

Macrolide antibiotics have been used effectively and safely for the treatment of respiratory tract infections for more than 50 years.[1] However, bacterial resistance to macrolide antibiotics has become increasingly prevalent over the past decade.[2] There have been significant synthetic efforts to discover new core structures to address this challenge.[3] In 1995, a novel series of macrolides was introduced. These compounds, known as ketolides, possess a 3-keto and an 11,12-carbamate functionalities and show excellent activities against major macrolide-resistant organisms.[4] In addition, the two most prominent ketolides, cethromycin (ABT-773)[5] and telithromycin[6] (Figure 1), also have aromatic groups tethered to the macrolide cores. The 3-keto group is believed to be important for the improved activities against inducible and efflux resistant organisms due to the absence of the cladinose sugar.[7] The 11,12-carbamate group is essential for overall antibacterial activities by increasing the rigidity of the ketolide conformation.[8] And the additional interaction of the

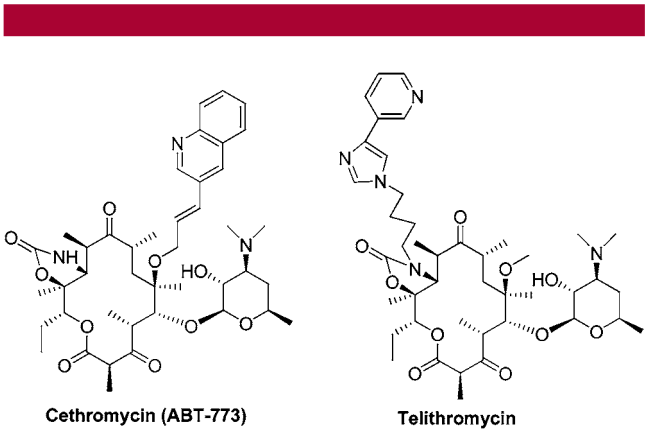


Figure 1. Structures of cethromycin and telithromycin.

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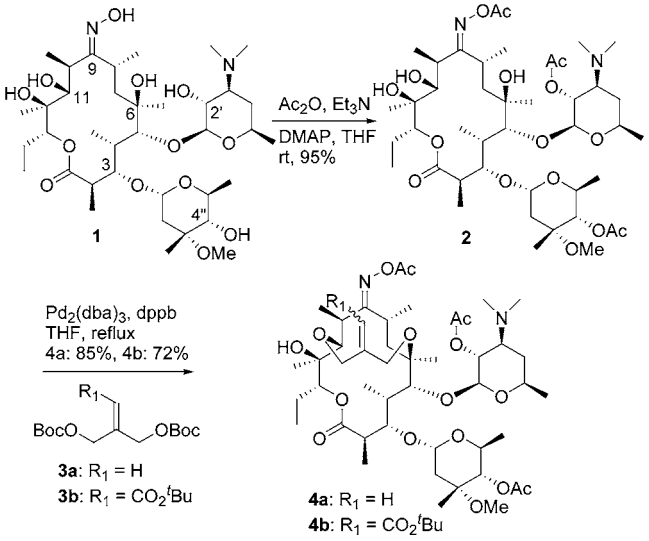
tethered aryl group with the bacterial ribosome is responsible for the enhanced activities against the constitutively macrolide-resistant organisms harboring the *erm* genes.

We focused on the synthesis of 6,11-O-bridged bicyclic ketolides,[9] reasoning that this bridge will improve the stability of the parent compound by preventing intramolecular hemiketal formation[10] and increase the rigidity of the ketolide conformation, as well as provide an ideal point for aryl group attachment.

Using allylic bis(*tert*-butyl carbonate) **3a** as a dielectrophile,[11] we developed a novel bridging process for EryA-derived macrolide via a palladium-catalyzed tandem inter- and intramolecular 6-O,11-O-dialkylation (Scheme 1). Thus,

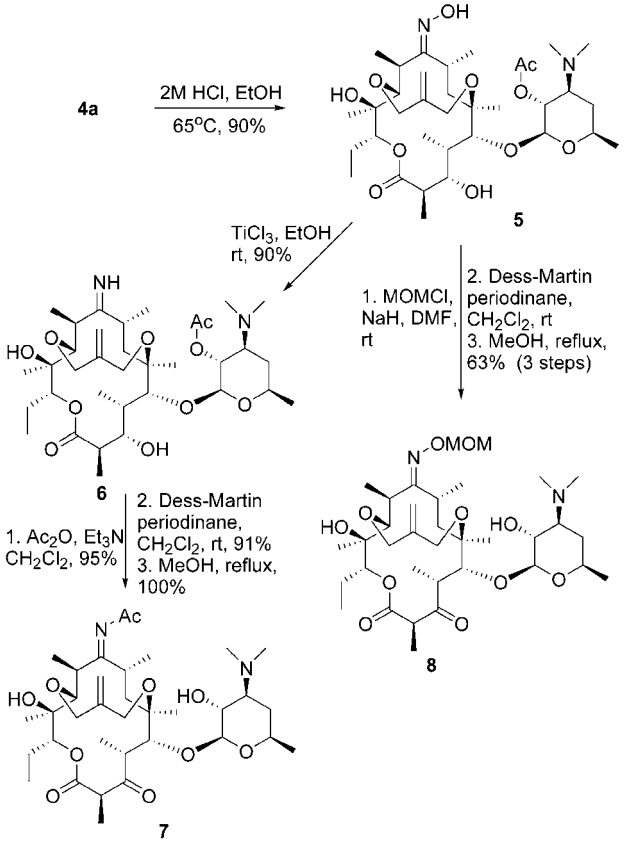
Scheme 1. Synthesis of 6,11-O-Bridged Bicyclic Macrolides



commercially available EryA oxime **1** was converted to its 9,2′,4″-triacetate by reacting it with acetic anhydride in THF in the presence of triethylamine and a catalytic amount of DMAP. The treatment of the resulting 9,2′,4″-triacetate **2** with reagent **3a** in the presence of $Pd_2(dba)_3$ (2 mol %) and dppb (4 mol %) in refluxing THF smoothly facilitated a tandem dialkylation at the 6,11-hydroxyl groups to provide the 6,11-O-bridged macrolide **4a** in 85% yield.[12] Further study on the scope of this bridging process showed that a trisubstituted olefin can also be used as the dielectrophile. For example, by reacting compound **2** with **3b**, **4b** (*E*/*Z* ~1/1) was produced in 72% yield with complete regioselectivity where the oxygen nucleophiles attack at the least substituted position of the Pd−π-allyl complex.

The cladinose sugar and 9-oxime acetate were selectively hydrolyzed by treating **4a** with 2 M HCl in ethanol at 65 °C for 2 h to give oxime intermediate **5**. Reduction of the 9-oxime with $TiCl_3$[13] gave 9-imine **6**. Surprisingly, the imine group of **6** is very stable and cannot be hydrolyzed to the corresponding 9-ketone compound under various conditions. We believe that the stability of the imine group is due to the constrained conformation and the lack of intramolecular assistance for the hydrolysis. Thus, acetylation of **6**, followed by Dess−Martin oxidation of 3-OH in dichloromethane and deprotection of 2′-acetate in methanol, gave the bridged ketolide **7** in 85% yield over three steps. Treatment of compound **5** with MOMCl and NaH in DMF provided a MOM-protected oxime intermediate, which upon Dess−Martin oxidation of the 3-OH group and the subsequent 2′-acetyl deprotection gave the ketolide **8** (Scheme 2).

Scheme 2. Synthesis of 6,11-O-Bridged Ketolide



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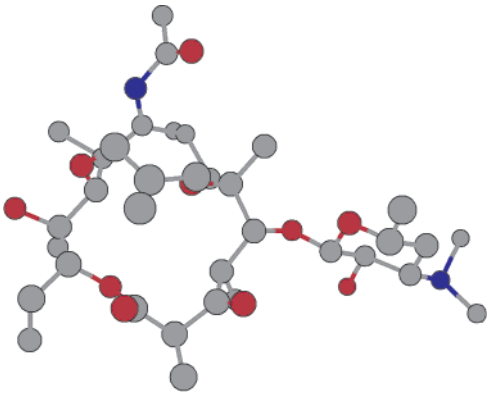
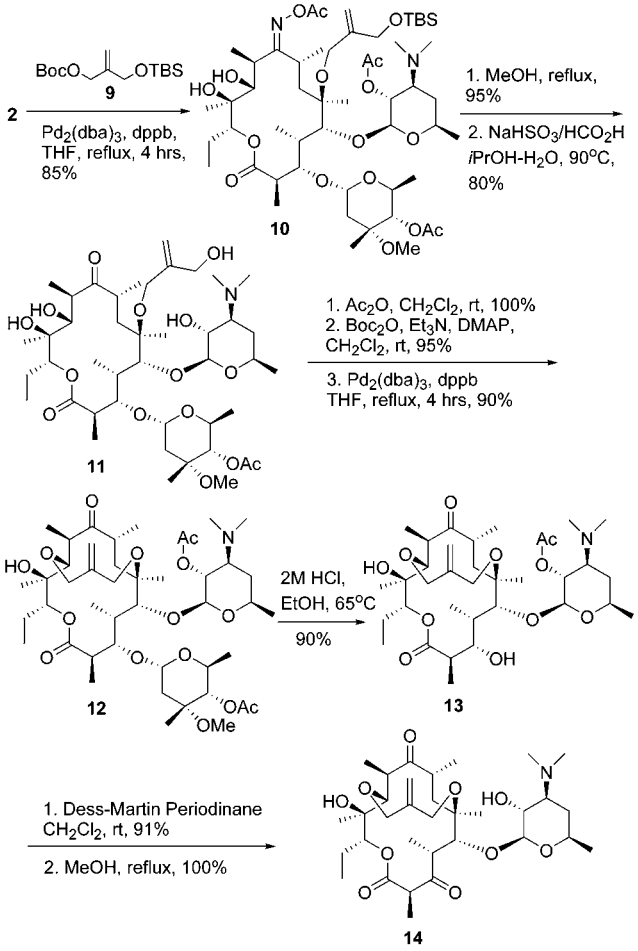


Figure 2. X-ray single-crystal structure of 6,11-O-bridged ketolide **7**.

The structure of ketolide **7** was confirmed by the X-ray crystallography (Figure 2).

To prepare 6,11-O-bridged 9-keto ketolide, a stepwise bisallylation process was developed. As shown in Scheme 3, monoallylated compound **10** was synthesized in an analogous fashion to the preparation of 6,11-O-bridged

Scheme 3. Synthesis of 9-Keto 6,11-O-Bridged Ketolide



erythromycin **4**. Treatment of triacetate **2** with reagent **9** in the presence of $Pd_2(dba)_3$ (2 mol %) and dppb (4 mol %) in refluxing THF selectively gave 6-O-allylated compound **10** in 90% yield. Deprotection of 2′- and 9-oxime acetates in refluxing methanol followed by deoximation, which also removed the TBS group, provided 9-keto compound **11**. The 6,11-O-bridge was introduced in three steps from **11**. First, the 2′-hydroxyl group was selectively protected with acetic anhydride in dichloromethane in the absence of base. Then the allylic alcohol was transformed into corresponding *tert*-butyl carbonate. Finally, another palladium-catalyzed intramolecular allylation successfully bridged the 6-O and 11-O positions to provide 6,11-O-bridged 9-ketoerythromycin **12** in 85% yield from **11**. Selective hydrolysis of the cladinose sugar provided **13**. Dess−Martin oxidation of the C-3 hydroxyl group followed by deprotection of 2′-acetate gave the desired 6,11-O-bridged 9-ketoketolide **14** in 91% yield.

The 6,11-O-bridged ketolides **7**, **8**, and **14** and the reference compound, erythromycin A, were tested against a panel of representative respiratory pathogens. Various macrolide- and multidrug-resistant isolates were included in the panel in order to identify potent analogues that could overcome macrolide resistance. *Staphylococcus aureus* 29213, *Streptococcus pyogenes* 19615, and *Streptococcus pneumoniae* 49619 are erythromycin-susceptible strains. *S. aureus* 27660 is an inducibly MLS_B-resistant strain encoded by an *ermA* gene. *S. aureus* 33591 is an MRSA. *S. pyogenes* 2912 is constitutive MLS_B-resistant strain encoded by an *ermA* gene, and *S. pneumoniae* 700906 is resistant strains encoded by an *erm* gene. *S. pyogenes* 1323 and *S. pneumoniae* 7701 are efflux-resistant strains encoded by *mefA* genes. *Haemophilus influenzae* 33929 is an ampicillin-resistant strain with a β-lactamase positive determinant. The in vitro antibacterial activities are reported as minimum inhibitory concentrations (MICs), which were determined by the broth microdilution method as recommended by the NCCLS (National Committee for Clinical Laboratory Standards).[14] The in vitro antibacterial activities of ketolides **7**, **8**, and **14** and reference compound are shown in Table 1.

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Table 1. Antibacterial Activity of 6,11-O-Bridged Ketolides

organism		MIC (μg/mL)			
		7	**8**	**14**	EryA
S. aureus 229213	Ery S	1.0	1.0	1.0	0.25
S. aureus 27660	Ery R-i	2.0	2.0	2.0	>64
S. aureus 33591	Ery MRSA	>64	>64	>64	>64
S. pneumoniae 49619	Ery S	0.25	0.13	0.13	<0.06
S. pneumoniae 7701	Ery R-mef	0.5	0.5	0.5	4
S. pneumoniae 700906	Ery R-erm	>64	>64	>64	>64
S. pyogenes 19615	Ery S	0.25	0.5	0.5	0.03
S. pyogenes 1323	Ery R-mef	0.5	0.5	0.8	16
S. pyogenes 2912	Ery R-erm	>64	>64	>64	>64
H. influenzae 33929	Amp R	>64	>64	>64	4

All ketolides **7**, **8**, and **14** showed good antibacterial activities against the susceptible strains as well as *mef*-resistant strains. These results strongly suggested that the 6,11-O-bridged ketolides are good cores for further modifications.

In conclusion, we developed a bridging chemistry process for erythromycin-derived macrolide via a palladium-catalyzed tandem or stepwise inter- and intramolecular 6-O,11-O-dialkylation. By applying this process, we synthesized novel 6,11-O-bridged ketolide cores, which showed good antibacterial activities. Further modifications of these new cores to develop novel ketolides with improved activities against a broad panel of macrolide-resistant bacterial strains are in progress.

Acknowledgment. We thank Dr. Emil Lobkovsky of Cornell University for help with the X-ray structure of compound **7**.

Supporting Information Available: Detailed experimental procedures for the synthesis of and characterization data for compounds **4**, **7**, **8**, and **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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