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LETTER

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Synthesis and Antibacterial Activity of a Novel Class of 15-Membered Macrolide Antibiotics, "11a-Azalides"

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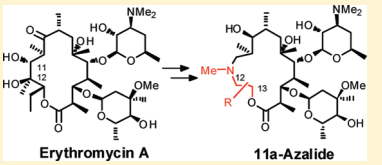
Supporting Information

ABSTRACT: An efficient method for the reconstruction of the 9-dihydroerythromycin A macrolactone skeleton has been established. The key steps are oxidative cleavage at the 11,12-position and reconstruction after insertion of an appropriate functionalized amino alcohol. Novel 15-membered macrolides, we named as "11a-azalides", were synthesized based on the above methodology and evaluated for their antibacterial activity. Among them, (13*R*)-benzyloxymethyl-11a-azalide showed the most potent *Streptococcus pneumoniae* activity, with improved activity against a representative erythromycin-resistant strain compared to clarithromycin (CAM).



KEYWORDS: Antibiotic, macrolide, 11a-azalide, resistant-pathogen, novel scaffold

Macrolide antibiotics[1−4] (see Figure 1 for some structures) are a safe and effective class of drugs for the treatment of respiratory tract infections. Erythromycin A (EM-A, **1**), a 14-membered macrolide antibiotic, has been widely prescribed for more than five decades. Since EM-A decomposed to antibacterialy inactive spiroketal products[5] under the acidic conditions in the stomach, its bioavailability was not high and interindividually varied.[6] To improved the pharmacokinetic profile of EM-A caused by the acid instability, enteric-coating of the tablets and chemical modifications of EM-A have been performed.[1−4] Second-generation macrolides, such as clarithromycin[7] (CAM, **2**) and azithromycin[8] (AZM, **3**), were investigated in the 1980s and eventually launched in the 1990s as a result of chemical modification efforts.

The increasing prevalence of macrolide-resistant pathogens among clinical isolates in recent times is of concern to public health.[9−12] To overcome resistance problems, numerous chemical modifications of EM-A have been attempted.[13−15] In a chemobiosynthesis report seeking novel scaffolds by transformation of the macrolactone skeleton, the C13 position of EM-A promises to play a key role in the improvement of antibacterial activity against resistant pathogens.[16,17] However, chemical modification at the C13 position has been underexplored because of its lack of chemical reactivity. During the mid 1990s, Waddell[18,19] and Nishida[20] independently reported C9−C13 modified EM-A derivatives, synthesized from the original C1−8 or 9 fragment of EM-A and a newly prepared C9 or 10−13 fragment. Although this "cut and paste" methodology seemed to be a universal procedure to provide structural diversity into the C13 region, the reported compounds were limited to simple and primitive derivatives. Alternatively, related ring reconstruction methodology using 16-membered macrolide as the starting material has been reported.[21] In this paper, we report an efficient method for the reconstruction of the macrolactone skeleton that enables us to synthesize a novel class of 15-membered macrolide antibiotics, "11a-azalides",

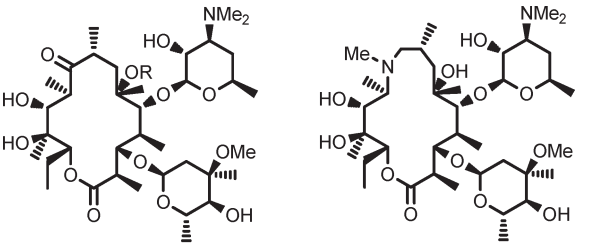


Figure 1. Structures of macrolide antibiotics.

possessing a variety of substituents on the C12 and/or C13 position.

Our synthetic strategy is shown in Scheme 1. The 11,12-diol moiety of the EM-A macrolactone skeleton was cleaved oxidatively. After insertion of an appropriate functionalized amino alcohol and successive saponification of the remaining original C12−13 residue, the resulting acyclic skeleton was intramolecularly cyclized by a macrolactonization reaction. The advantage of this strategy over previous methods was that it enabled us to provide structural diversity to both the C12 and C13 positions using an easily prepared, functionalized amino alcohol.

Our initial approach was to establish a methodology using reconstruction of the simplest macrolactone skeleton. EM-A (9-keto analogue) was converted to an acyclic keto-aldehyde intermediate by treatment with lead tetraacetate. However, the reductive amination of the aldehyde with 2-aminoethanol failed, presumably because of the formation of an unstable β-keto-aldehyde intermediate. To avoid side reactions, (9*S*)-9-dihydroerythromycin (**4**) was selected as the starting material

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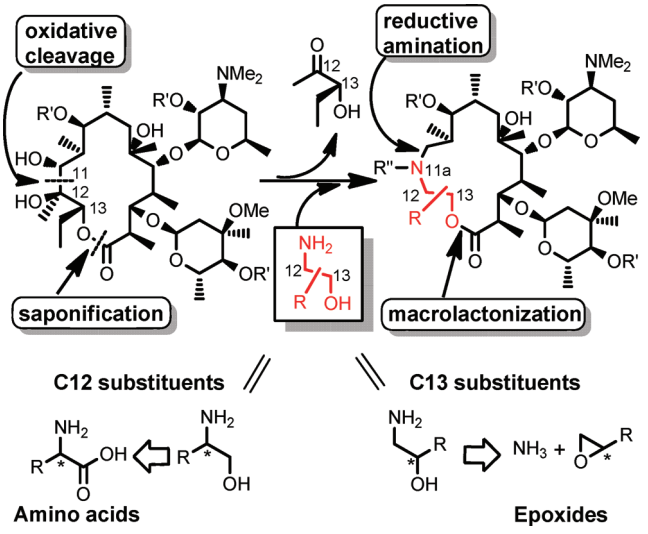
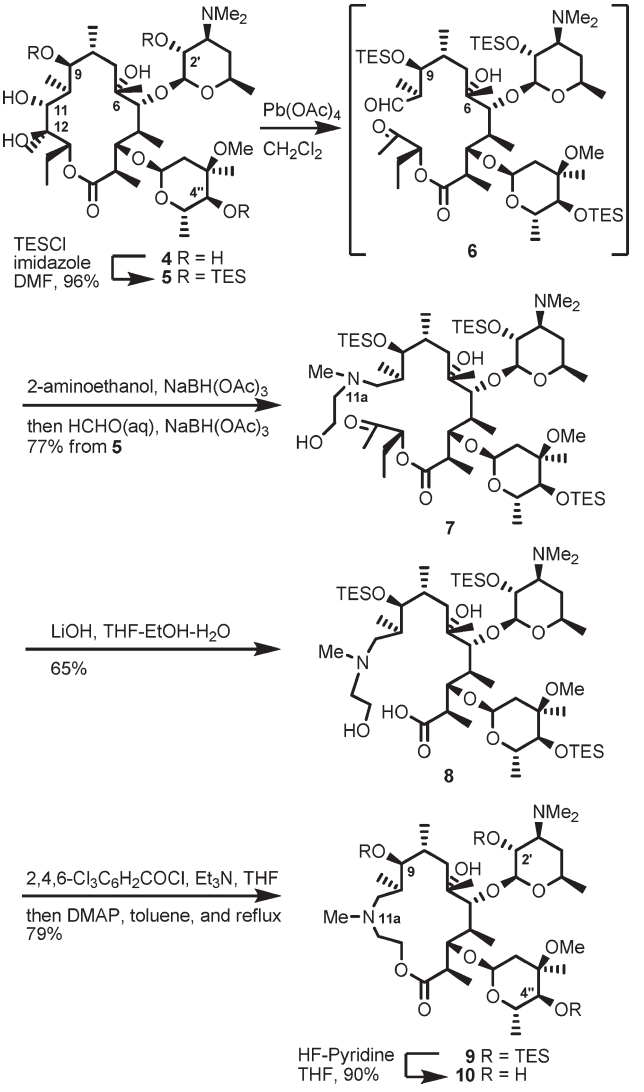
Scheme 1. Synthetic Strategy for 11a-Azalide



Scheme 2. Synthesis of 11a-Azalide



(Scheme 2). The 9-dihydro derivative **4** was readily prepared by reduction of tthe 9-keto group of **1**.[22,23] The 9,2′,4″-hydroxyl groups of **4** were selectively protected by triethylsilyl (TES) groups to give 11,12-diol **5**, which was then treated with lead tetraacetate to give acyclic aldehyde intermediate **6**.[24] Reductive amination[25] of aldehyde **6** with 2-aminoethanol and subsequent methylation of the resulting secondary amine at the 11a-position with formaldehyde gave the desired seco-ester **7**. The above three sequential reactions were performed in a one-pot manner in 77% yield from diol **5**.

Saponification of seco-ester **7** with LiOH produced seco-acid **8** in 65% yield, and macrolactone skeleton reconstruction was achieved using modified Yamaguchi's macrolactonization method.[26−28] Seco-acid **8** was converted to a mixed anhydride by the treatment with triethylamine and 2,4,6-trichlorobenzoyl chloride in THF at 50 mM. When the mixed anhydride solution was added dropwise to a tenth-volume of refluxing solution of 4-dimethylaminopyridine (DMAP) (25 equiv), the macrolactonization reaction proceeded smoothly to give the 15-membered macrolide **9** in 79% yield. Deprotection of the TES groups of **9** was conducted by HF-pyridine treatment to give the desired 11a-azalide **10** in 90% yield.

Based on the established methodology, we synthesized 12-/13-benzyloxymethyl-11a-azalides **14a**−**d** (Table 1). Amino alcohols **11a**,**b**[29] were prepared through reduction of optically active *O*-benzyl serine with $LiAlH_4$, and **11c**,**d** were prepared by ring-opening reactions of optically pure benzylglycidol with aqueous ammonia. Seco-acids **12a**−**d** were prepared from **5** and amino alcohols **11a**−**d** in a manner similar to the preparation of **8**. Macrolactonization reaction of seco-acids **12a**,**b**, which possess a primary hydroxyl group, proceeded smoothly to give the desired 12-substituted-11a-azalides **13a**,**b**. On the other hand, reaction of seco-acids **12c**,**d**, which possess a secondary hydroxyl group, gave the desired 15-membered products **13c**,**d** in relatively low yield along with an undesired 7-membered byproduct.[30] In the macrolactonization reaction of erythronolides,[31,32] the 6-hydroxyl group of seco-acids was generally inert. However, the same 7-membered byproduct has been observed in the case of glycosylated seco-acid.[33] HF-pyridine treatment of **13a**−**d** gave the desired 12-/13-substituted 11a-azalides **14a**−**d**.

The antibacterial activities of the synthesized 11a-azalides against *Streptococcus pneumoniae* were evaluated as shown in Table 2.[34] Compound **14d** showed the most potent antibacterial activity against erythromycin-susceptible *S. pneumoniae* compared to CAM, and it showed a 4-fold improved antibacterial activity against the erythromycin-resistant strain compared to CAM. The position and configuration of the substituents on the 11a-azalides turned out to have a significant impact on the antibacterial activity.

In conclusion, we established an efficient method for the reconstruction of the 9-dihydroerythromycin A macrolactone skeleton. Based on this methodology, we synthesized a novel class of 15-membered macrolides "11a-azalides" possessing a substituent on their C12 or C13 position. Among them, (13*R*)-benzyloxymethyl-11a-azalide **14d** showed the most potent *S. pneumoniae* activity, with improved activity against the representative erythromycin-resistant strain compared to CAM. This methodology provides 11a-azalides as a novel scaffold, which allows us to engage in further exploration to improve the antibacterial activity against resistant pathogens.

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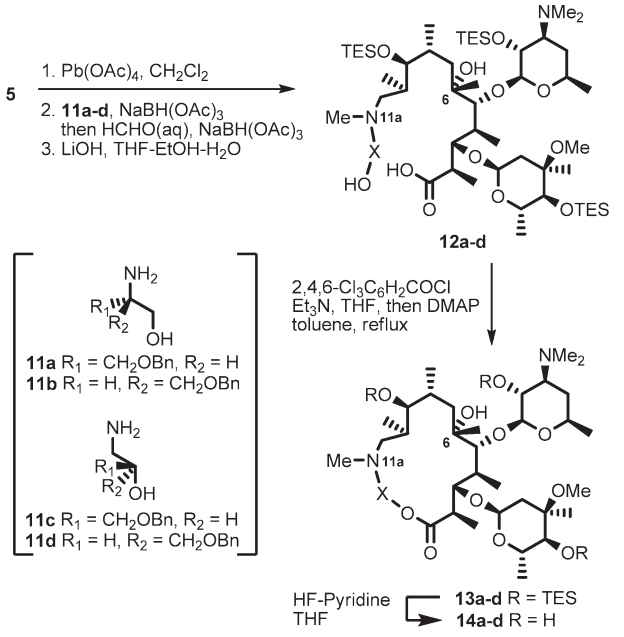
Table 1. Synthesis of 12-/13-Substituted 11a-Azalides



amino alcohol	X	yield (%) 12a–d	13a–d	14a–d
11a	BnOCH$_2$ 12 13	45	71	97
11b	BnOCH$_2$ 12 13	51	72	72
11c	12 13 BnOCH$_2$	61	58	86
11d	12 13 BnOCH$_2$	57	21	95

Table 2. Antibacterial Activity of 11a-Azalides

	MIC (μg/mL)				
	10	**14a**	**14c**	**14d**	CAM
S. pneumoniae ATCC49619[a]	4	2	1	0.12	0.03
S. pneumoniae 205[b]	>128	128	64	32	>128

[a] Erythromycin-susceptible strain. [b] Erythromycin-resistant strain.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

T.S. led research design (chemistry) and execution (performed synthesis) and contributed to writing of the manuscript, and is the corresponding author; T.T. participated in research design (chemistry) and execution (performed synthesis) and contributed to writing of the manuscript.

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