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Synthesis of 3,6-bicyclolides: A novel class of macrolide antibiotics

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Dedicated to Professor E.J. Corey for his 80th birthday.

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ABSTRACT

The synthesis of 3,6-bicyclolides from erythromycin A oxime is described. This novel class of bridged bicyclic macrolides demonstrates potent in vitro and in vivo activities against a broad spectrum of bacteria including resistant respiratory tract pathogens.

Macrolide antibiotics are widely prescribed for the treatment of upper and lower respiratory tract infections, as well as skin and soft tissue infections.[1] Erythromycin A (**1**), the ancestor of the macrolide family, has been in clinical use since its launch in 1952, following its discovery from a soil sample taken from the Philippines Archipelago.[2] Erythromycin A is devoid of any serious side effects, but it frequently causes gastrointestinal (GI) tract irritation[3] and due to rise of resistant phenotypes, it now has a limited antibacterial spectrum of activity, acid instability[4] and poor pharmacokinetic properties. To overcome some of these drawbacks, the second-generation macrolides such as clarithromycin (**2**),[5] roxithromycin (**4**),[6] and the azalide azithromycin (**3**)[7] were developed. (Fig. 1) These macrolide compounds significantly improve their acid stability, and hence show enhanced antibacterial activities, improved physicochemical and pharmacokinetic profile, and attenuated side effects.

Over the past decade, there has been continuous research into the development of new macrolide antibiotics due to the increasing emergence of antibiotic-resistant bacteria. Structural modifications were systematically investigated, and telithromycin (**5**),[8] cethromycin (**6**)[9] and subsequently the 6,11-O-bridged bicyclic macrolide EP-013420 (**7**)[10] emerged as the leading next generation macrolides, showing improved activity against MLS_B-resistant bacteria.

From our continued investigation into new macrolide antibiotics against drug resistant pathogens,[11] we report herein the synthesis, characterization, and in vitro and in vivo antibacterial activities of 3,6-bicyclolides, a novel class of bridged bicyclic macrolides.

The synthesis (Scheme 1) began with hydrochloric acid deglycosidation to remove the cladinose moiety in erythromycin A oxime **8**. The resulting 3-OH oxime **9** was diacetylated to give **10** (63% yield over two steps). Subsequent palladium catalyzed 3,6-*O*-bridge formation using bisBOC compound **11** gave **12** (25%). Then **12** was deacetylated to afford oxime **13** (93%). Hydrolysis of **13** to 9-ketone **14** (75%), follwed by 2′-reacetylation led to the 9-ketone 3,6-bicyclolide **15** (98%). X-ray crystallographic analysis of **15** confirmed unambiguously the formation of the 3,6-*O*-bridge (Fig. 2).

9-Imine 3,6-bicyclolide **16** was prepared in 88% yeild by a titanium(III) reduction of oxime **13** (Scheme 2). In the presence of $NaBH_3CN$ and NH_4Ac, the reduction of oxime **13** proceeded stereoselectively to afford 9(*S*)-amino 3,6-bicyclolide **17** (75%) (Scheme 2).

Preparation of 11,12-carbamate 3,6-bicyclolide was carried out in a three-step one-pot fashion (Scheme 3). Reaction of 3,6-bicyclolide **15** with NaHMDS and CDI gave 12-*O*-acyl imidazole intermediate **18**. Treatment of **18** with liquid ammonia provided 11,12-carbamate **19**. Epimerization of **19** (at C-10) with KO^tBu generated the natural isomer **20** in 92% yield over three steps. Finally, deacetylation of **20** with methanol afforded bicyclolide **21** (98%). X-ray crystallographic analysis unambiguously confirmed the structure of 11,12-carbamate 3,6-bicyclolide **21** (Fig. 3).

The 3,6-bicyclolides **13, 14, 16, 17, 21**, and the reference compound, erythromycin A, were tested against a panel of representative respiratory pathogens (Table 1). Various macrolide- and multidrug-resistant isolates were included in the panel. *Staphylo-*

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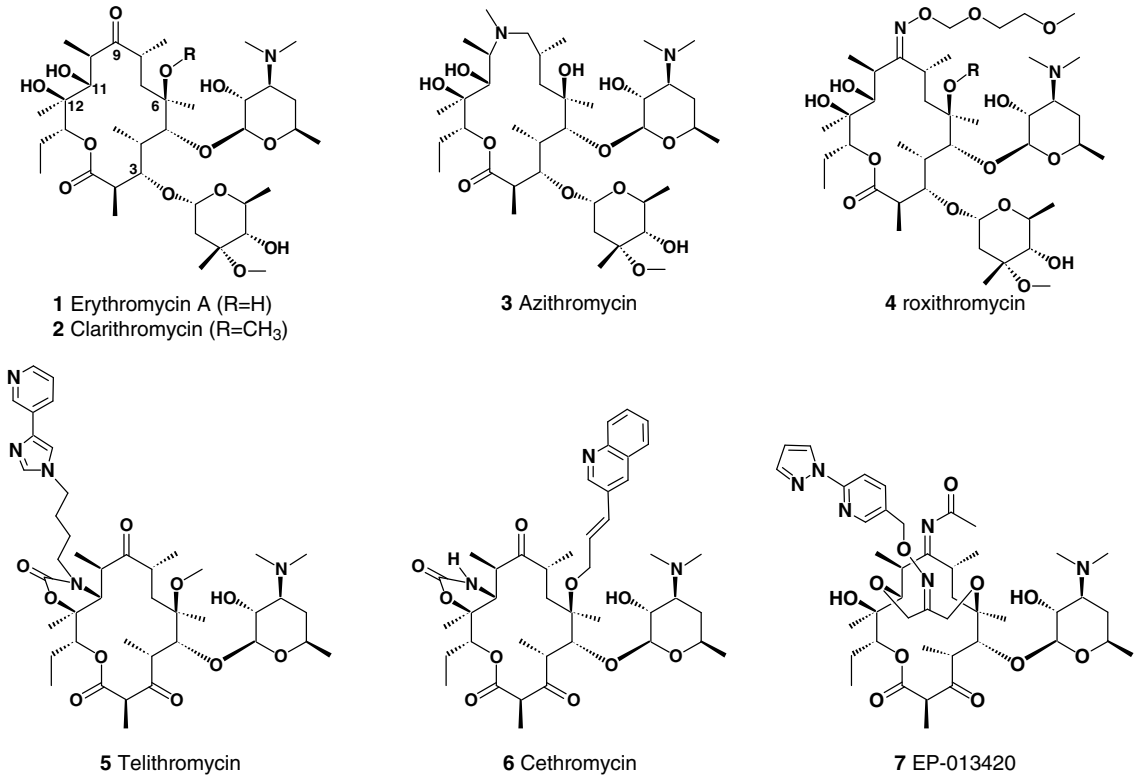
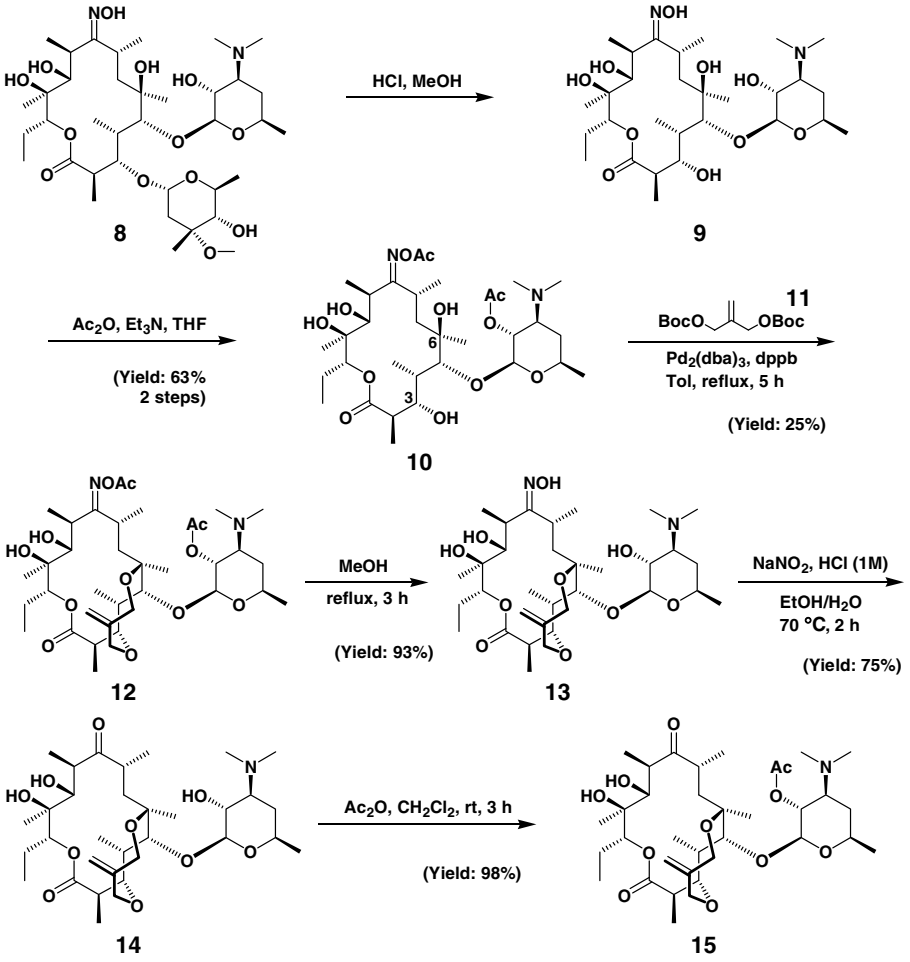


Figure 1. Macrolide antibiotics.



Scheme 1. Synthesis of 3,6-bicyclolide.

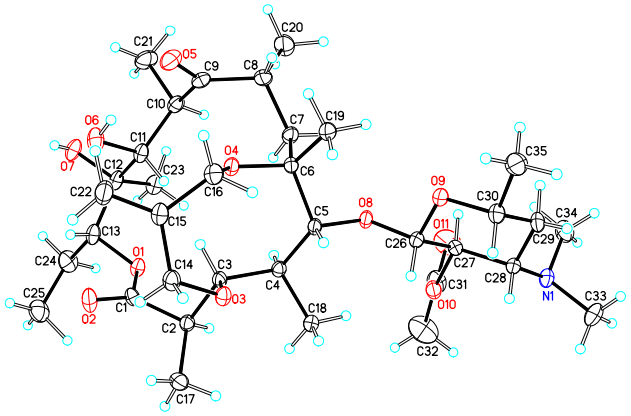


Figure 2. X-ray single crystal structure of 3,6-bicyclolide **15**.

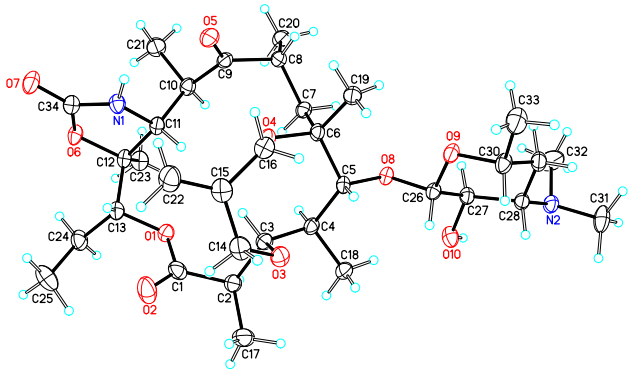
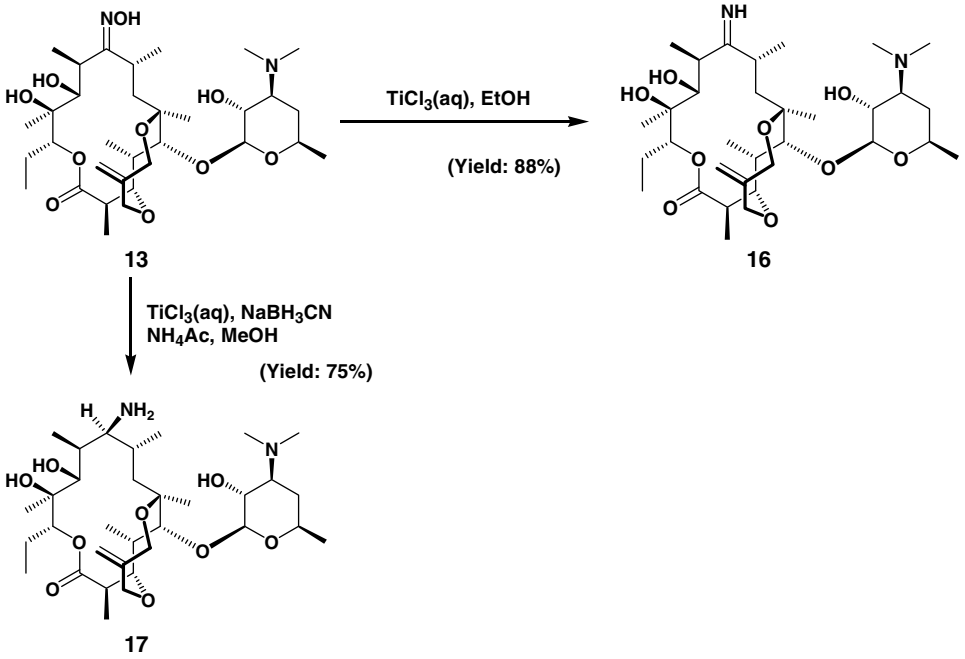


Figure 3. X-ray single crystal structure of 3,6-bicyclolide **21**.

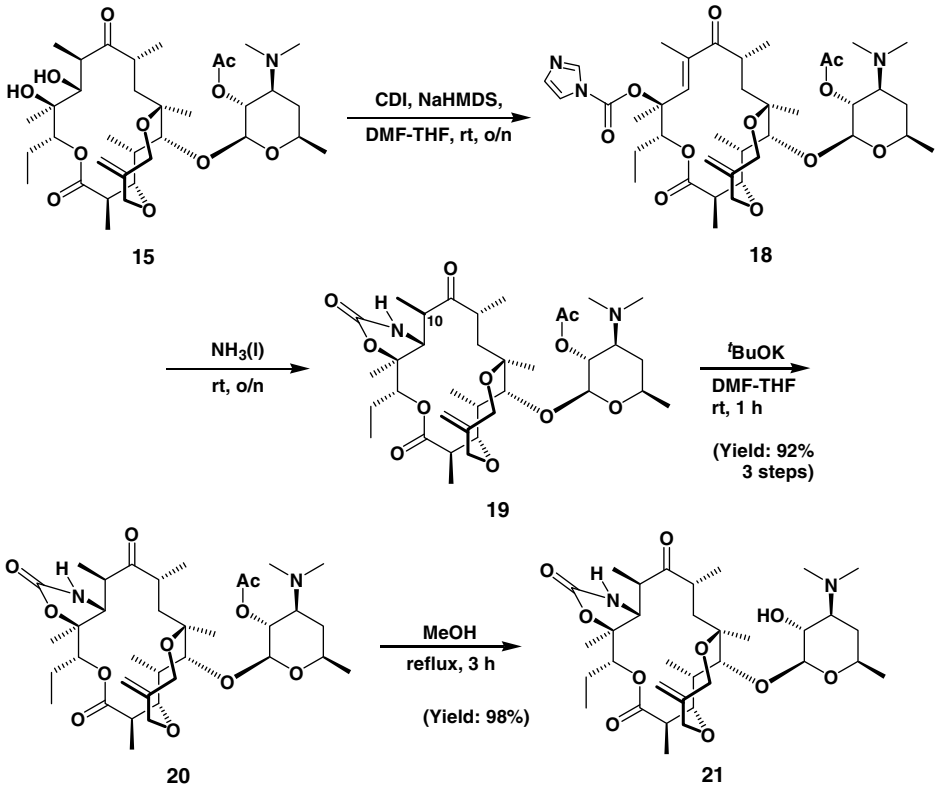
coccus aureus 29213, *Streptococcus pyogenes* 19615, and *Streptococcus pneumoniae* 49619 are erythromycin-susceptible strains. *Staphylococcus aureus* 27660 is an inducibly MLSB-resistant strain encoded by an *ermA* gene. *S. aureus* 33591 is an MRSA. *S. pyogenes* 2912 is constitutive MLS_B-resistant strain encoded by an *ermA* gene, and *S. pneumoniae* 700906 is resistant strain 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 deter-

Table 1
In vitro antibacterial activities of 3,6-bicyclolides

Organism		MIC (μg/ml)					
		13	**14**	**16**	**17**	**21**	Ery A
S. aureus 29213	Ery S	1	1	2	4	0.125	0.5
S. aureus 27660	MLS Ri	1	1	2	4	0.125	>64
S. aureus 33591	MRSA	>64	>64	>64	>64	>64	>64
S. pneumoniae 49619	Ery S	⩽0.06	0.125	0.125	⩽0.06	⩽0.06	⩽0.06
S. pneumoniae 7701	Ery R-mef	0.25	0.25	0.25	0.125	⩽0.06	4
S. pneumoniae 700906	Ery R-erm	>64	>64	>64	>64	>64	>64
S. pyogenes 19615	Ery S	0.125	0.25	0.125	⩽0.06	⩽0.06	0.015
S. pyogenes 1323	Ery R-mef	0.25	0.5	0.5	0.25	0.125	16
S. pyogenes 2912	Ery R-erm	>64	>64	64	64	>64	>64
H. influenzae 33929	Amp R	32	64	64	32	4	4
H. influenzae	Amp S	32	64	16	32	2	4
M. catarrhalis		0.25	0.5	0.5	0.5	⩽0.06	0.13



Scheme 2. Synthesis of 9-imine and 9-amino 3,6-bicyclolides.



Scheme 3. Synthesis of 11,12-carbamate 3,6-bicyclolide.

Table 2
In-vivo antibacterial activities of 3,6-bicyclolide **21**

Organism	ED_{50} po (mg/kg)	
	21 (MIC, μg/ml)	Telithromycin (MIC, μg/ml)
S. aureus Smith	10 (0.125)	17.2 (0.125)
S. pneumoniae 7701	7 (⩽0.06)	17.2 (0.25)

minant. The in vitro antibacterial activities are reported as minimum inhibitory concentrations (MICs), which were determined utilizing the broth-microdilution method as per CLSI standards. Compared to erythromycin A, all five novel 3,6-bicyclolides demonstrated significant improvement in activity against resistant strains *S. aureus* MLS Ri, *S. pneumoniae* Ery R-mef, and *S. pyogenes* Ery R-mef. Although the other four compounds were less effective against *H. influenzae*, bicyclolide **21** showed retention of activity.

In acute systematic infection model in mice, 3,6-bicyclolide **21** demonstrated 2- to 3-fold improvement in efficacy compared with telithromycin against macrolide susceptible strain *S. aureus* Smith, and against resistant strain *S. pneumoniae* mef (Table 2).

In conclusion, we have described the successful structural modificaton of erythromycin A oxime to 3,6-bicyclolide, a novel class of macrolide antibiotics. These newly developed 3,6-bicyclolides demonstrated excellent in vitro and in vivo activities against a broad spectrum of bacteria including resistant respiratory tract pathogens. Part of our further structural elaboration and structure–activity relationship studies were reported earlier.[12]

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2008.10.109.

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