Synthesis and Antibacterial Activity of a Novel Series of Acylides: 3-*O*-(3-Pyridyl)acetylerythromycin A Derivatives

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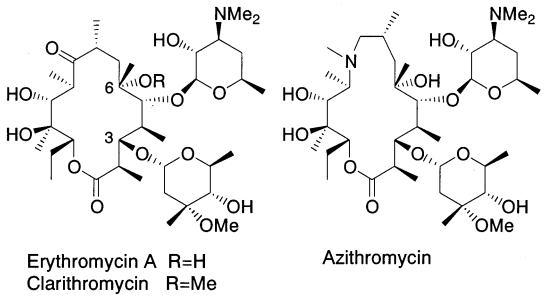
A novel series of acylides, 3-*O*-(aryl)acetylerythromycin A derivatives, were synthesized and evaluated. These compounds have significant potent antibacterial activity against not only Gram-positive pathogens, including inducibly macrolide-lincosamide-streptogramin B (MLS_B)-resistant and efflux-resistant strains, but also Gram-negative pathogens, such as *H. influenzae*. 6,9:11,12-Dicarbonate acylide **47** (FMA0122) was twice as active against *H. influenzae* than azithromycin, whereas it showed only moderate in vivo efficacy in mouse protection tests. However, the 11,12-carbamate acylide **19** (TEA0929), which showed potent antibacterial activity against almost all of the main causative pathogens of community-acquired pneumonia tested, exhibited excellent in vivo efficacy comparable to those of second-generation macrolides.

Introduction

Second-generation macrolide antibiotics such as clarithromycin[1] (CAM, 6-*O*-methylerythromycin A) and azithromycin[2] (AZM, 15-membered azalide) (Chart 1) have been widely prescribed for upper and lower respiratory tract infections (RTIs) because of their superior antibacterial activity and pharmacokinetic properties and fewer gastrointestinal (GI) side effects[3] compared to the first-generation macrolide erythromycin A (Ery A).

However, the therapeutic utility of these macrolides has been severely compromised by the emergence of resistant pathogens. The increasing resistance of community-acquired respiratory tract infections (CARTIs) to various antimicrobials is a pandemic phenomenon, and this trend represents a significant threat.[4] *Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, Streptococcus pyogenes, Staphylococcus aureus,* atypical (*Mycoplasma pneumoniae*) and intercellular (*Chlamydia pneumoniae, Legionella pneumophila*) pathogens are all known to cause CARTIs. In particular, *S. pneumoniae* is the main causative pathogen of community-acquired pneumonia (CAP). The infectious disease caused by *S. pneumoniae* remains a leading cause of morbidity and mortality.[5] The increasing prevalence of penicillin-resistant *S. pneumoniae* (PRSP) is of concern, since most of the pathogens have acquired resistance to many antimicrobials including macrolides.[6] Macrolide-resistant *S. pneumonia* possesses the *mef*(A) gene and/or the *erm*(B) gene. The *mef*-(A) gene, which codes for a membrane protein efflux pump, is considered to confer intermediate resistance, while the *erm*(B) gene, which codes for a ribosomal methylase, is considered to result in high-level resistance.[7] It is also of concern that the prevalence of

Chart 1



β-lactamase-positive strains of *H. influenzae*, the second-most common cause of CAP, has progressively increased in the U.S.,[8] Europe, and Asia.[9] The infectious pathogen is often unknown during the acute phase of the infection, and thus, the initial therapy tends to be empirical. Accordingly, the next generation of macrolide antibiotics should be effective against these pathogens.

To address these therapeutic problems, novel macrolides, such as ketolides[10] (3-oxo-6-*O*-methylerythromycin A derivatives) exemplified by telithromycin (HMR3647),[11] cethromycin (ABT-773),[12] and TE-802[13] and (9*S*)-erythromycylamine 4″-carbamates exemplified by CP-544372,[14] have been investigated over the past decade (Chart 2).

We recently reported the discovery of 3-*O*-acylerythromycin A derivatives, which we named "acylides",[15] as a novel class of macrolide antibiotics. The introduction of an adequate acyl group to the 3-O position of CAM not only restored the abolished antibacterial activity but also conferred activity against resistant pathogens. 3-*O*-(4-Nitrophenyl)acetyl-5-*O*-desosaminyl-6-*O*-methylerythronolide A (TEA0777) showed potent antibacterial activity against Gram-positive pathogens including inducibly macrolide-lincosamide-streptogramin B (MLS_B)-resistant *S. aureus* and efflux-resistant *S. pneumoniae*, whereas its activity against *H. influenzae* was insufficient. We sought to further optimize the acyl group

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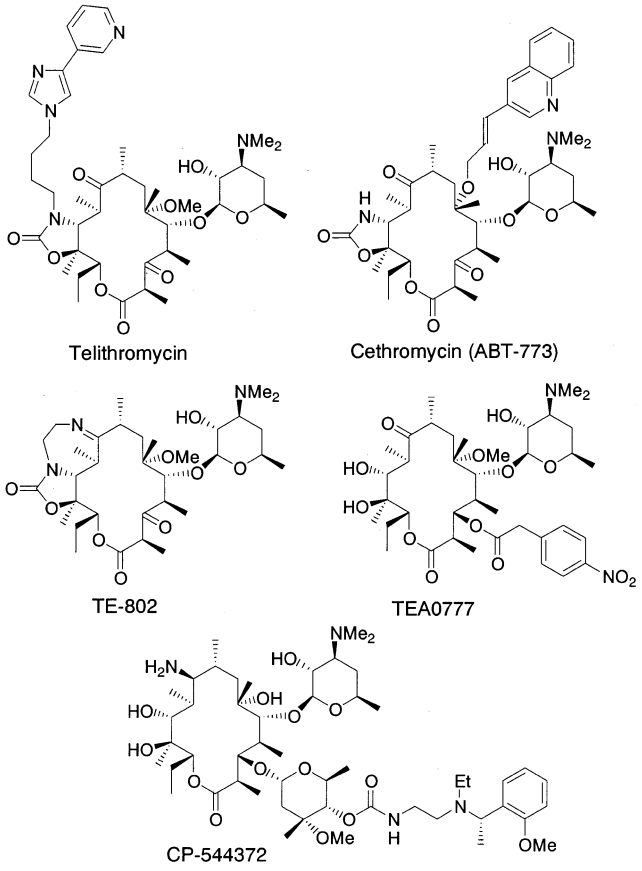
Chart 2



and to chemically modify the macrolide skeleton. In this report, we describe a novel series of acylides, 3-*O*-(3-pyridyl)acetylerythromycin A derivatives, that showed significantly potent antibacterial activity against Gram-positive pathogens and improved activity against *H. influenzae*.

Chemistry

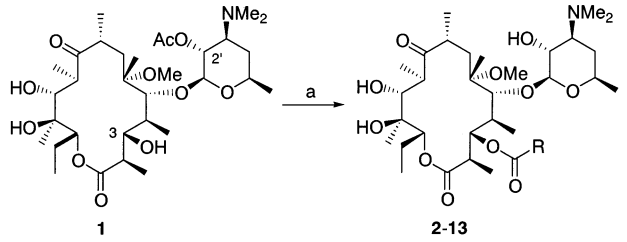
To reveal the effect of the substituent on the phenyl group in antibacterial activity, 6-*O*-methylacylides **2**−**13** were prepared in yields of 29−84% from 2′-*O*-acetyl-5-*O*-desosaminyl-6-*O*-methylerythronolide A **1**[15a] by 3-O-acylation and subsequent selective methanolysis of the 2′-*O*-acetyl group (Scheme 1). Treatment of **1** with phenylacetyl chloride in pyridine followed by methanolysis afforded the 3-*O*-phenyl acetate **2**, as previously reported.[15a] Compounds **3**−**6** and **8**−**10** were prepared by condensation of **1** with the corresponding carboxylic acid using 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDC·HCl), 4-(dimethylamino)-pyridine (DMAP) in dichloromethane (CH_2Cl_2) followed by methanolysis. To prepare compounds **7** and **11**−**13**, mixed anhydrides prepared from the corresponding carboxylic acid and pivaloyl chloride were used instead. 3-O-Acylation of **2**, **6**, **7**, and **9** resulted in a low yield because of recovery of the unreacted 3-hydroxy intermediate. In the preparation of 3-(2-methoxy)phenyl acetate **6**, an equal amount of the corresponding carbonic acid was used to avoid the production of undesirable 3,11-diphenyl acetate.

On the basis of previous reports[16] that the introduction of a cyclic carbonate or carbamate to the 11,12-position of CAM derivatives enhanced the antibacterial activity, the 11,12-carbonate derivative of acylide **12** and the carbamate analogue were synthesized. Formation of the 11,12-carbonate was carried out with trichloromethyl chloroformate in a mixture of CH_2Cl_2 and pyridine at 0 °C (Scheme 2). In this reaction, the 3-hydroxyl group in **14** was restored by quenching the 3-*O*-chlorocarbonate with ice−water. 3-*O*-(3-Pyridyl) acetylation of **14** followed by deprotection of the 2′-*O*-acetyl group provided the desired 11,12-carbonate acylide **15** in 82% yield.

The 11,12-carbamate acylide **19** was prepared from 12-*O*-acylimidazolide **16**[12b] as shown in Scheme 3. Treatment of **16** with liquid ammonia in THF provided the 12-*O*-carbamoyl intermediate, which was further treated with sodium hydride in situ to afford the 11,-12-carbamate **17** via intramolecular Michael addition.[17] Subsequent removal of L-cladinose by treatment with aqueous HCl followed by the typical sequential procedure for 3-*O*-(3-pyridyl) acetylation provided the desired 11,12-carbamate acylide **19**.

9-Oxime acylide **22** was prepared from 5-*O*-desosaminyl-6-*O*-methylerythronolide A 9-oxime **20**[14] in three steps and was further converted to the corresponding 11,12-carbonate **23** in poor yield along with the unreacted starting 11,12-diol intermediate and unisolated polar byproducts (Scheme 4).

Scheme 1[a]

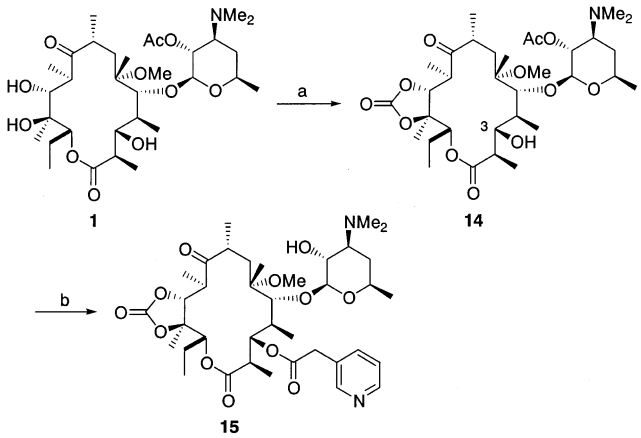


1 **2-13**

2 R= -CH_2Ph	**8** R= -CH_2Ph (2-NO_2)
3 R= -Ph (3-OMe)	**9** R= -CH_2Ph (3-NO_2)
4 R= -CH_2Ph (3-OMe)	**10** R= -CH_2Ph (4-NO_2)
5 R= -CH_2CH_2Ph (3-OMe)	**11** R= -CH_2 (2-Pyridyl)
6 R= -CH_2Ph (2-OMe)	**12** R= -CH_2 (3-Pyridyl)
7 R= -CH_2Ph (4-OMe)	**13** R= -CH_2 (4-Pyridyl)

[a] (a) (i) RCO_2H, EDC·HCl, DMAP, CH_2Cl_2 or RCO_2H, PivCl, Et_3N, DMAP, CH_2Cl_2, −15 °C to room temperature or $PhCH_2COCl$, DMAP, pyridine, (ii) MeOH, 29−84% yield in two steps.

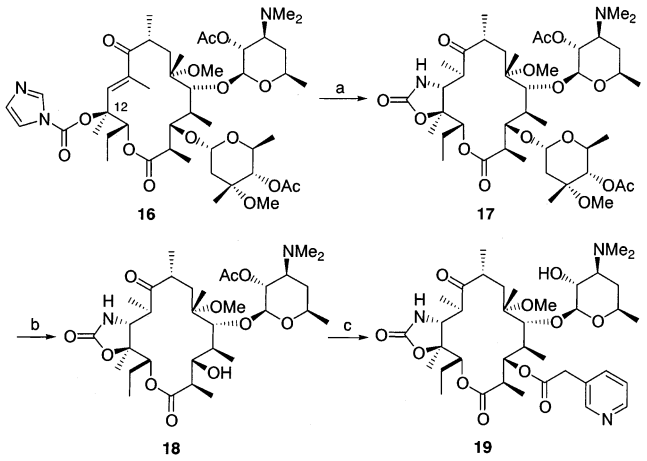
Scheme 2[a]



1 **14** **15**

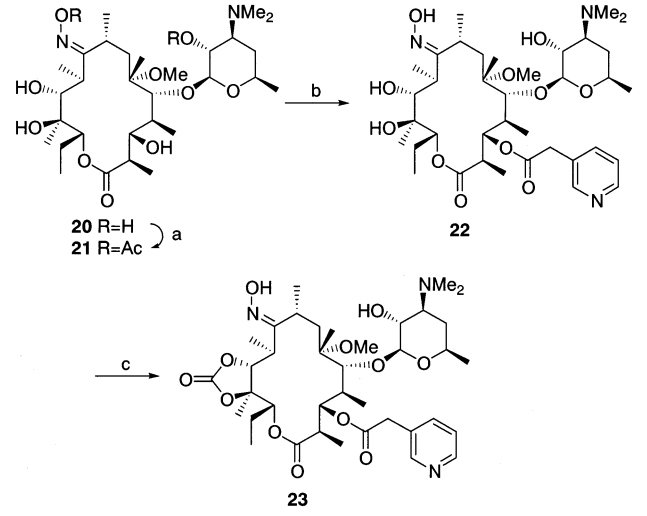
[a] (a) Trichloromethyl chloroformate, pyridine, CH_2Cl_2, 0 °C, 80% yield; (b) (i) 3-pyridylacetic acid, PivCl, Et_3N, DMAP, CH_2Cl_2, −15 °C to room temperature, (ii) MeOH, reflux, 82% yield in two steps.

Scheme 3[a]



[a] (a) Liquid NH_3, THF, −78 °C to room temperature and then NaH, 92% yield; (b) 2 N HCl, EtOH, 80% yield in two steps; (c) (i) 3-pyridylacetic acid, PivCl, Et_3N, DMAP, CH_2Cl_2, −15 °C to room temperature, (ii) MeOH, reflux, 77% yield in two steps.

Scheme 4[a]

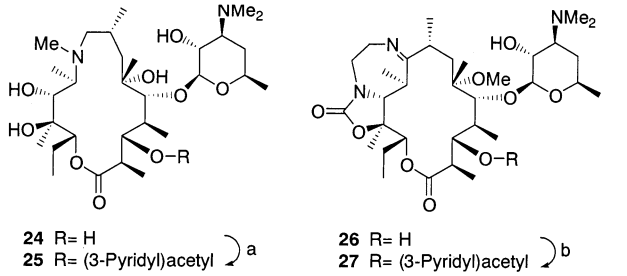


[a] (a) Ac_2O, Me_2CO; (b) (i) 3-pyridylacetic acid, PivCl, Et_3N, DMAP, CH_2Cl_2, −15 °C to room temperature, (ii) MeOH, reflux, 50% yield in three steps; (c) (i) Ac_2O, Me_2CO, (ii) trichloromethyl chloroformate, pyridine, CH_2Cl_2, 0 °C, 10% yield in two steps, (iii) MeOH, reflux, 79% yield.

In anticipation of inheriting the beneficial antibacterial profile of AZM against *H. influenzae*, the hybridized acylide **25** was prepared from 3-*O*-descladinosylazithromycin **24**[18] in a manner similar to 3-*O*-(3-pyridyl) acetylation. Tricyclic acylide **27** was obtained in 79% yield from the synthetic intermediate **26**[12] of the unique tricyclic ketolide TE-802 (Scheme 5).

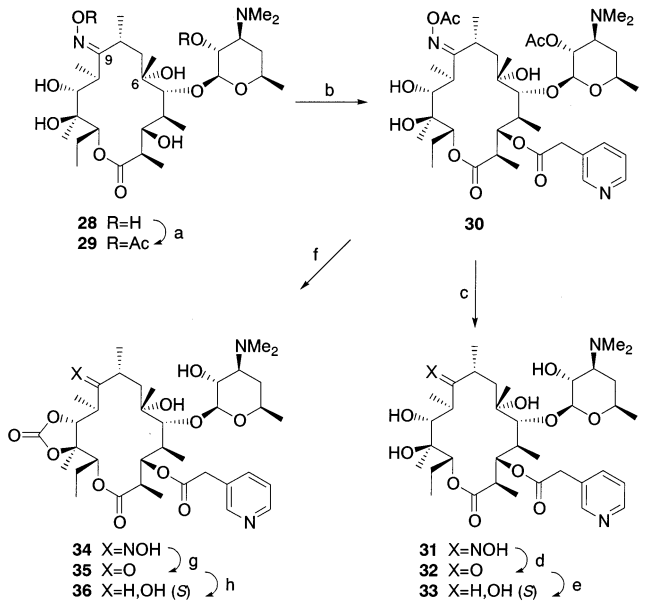
Since the treatment of erythromycin A derivatives with acid to cleave L-cladinose without protection of the C-9 ketone group causes the formation of undesired 6,9-enol ether, 6-OH acylide **32** was prepared via the 9-oxime derivative **28**[19] as shown in Scheme 6. After the introduction of a (3-pyridyl)acetyl group to the 3-O position of **28** in three steps, the 9-oxime acylide **31** was converted to the corresponding ketone **32** by treatment with sodium nitrite in a mixture of aqueous HCl and MeOH. Reduction of the ketone with $NaBH_4$ in EtOH stereoselectively gave the 9(*S*)-OH derivative **33**. The 11,12-carbonate analogues **34**−**36** were prepared in a similar manner after converting the 11,12-diol **30** to the corresponding 11,12-cyclic carbonate.

Scheme 5[a]



[a] (a) (i) Ac_2O, Me_2CO, 85% yield (ii) 3-pyridylacetic acid, EDC·HCl, DMAP, CH_2Cl_2, (iii) MeOH, 69% yield in two steps; (b) (i) Ac_2O, Me_2CO, (ii) 3-pyridylacetic acid, EDC·HCl, DMAP, CH_2Cl_2, (iii) MeOH, reflux, 79% yield in three steps.

Scheme 6[a]



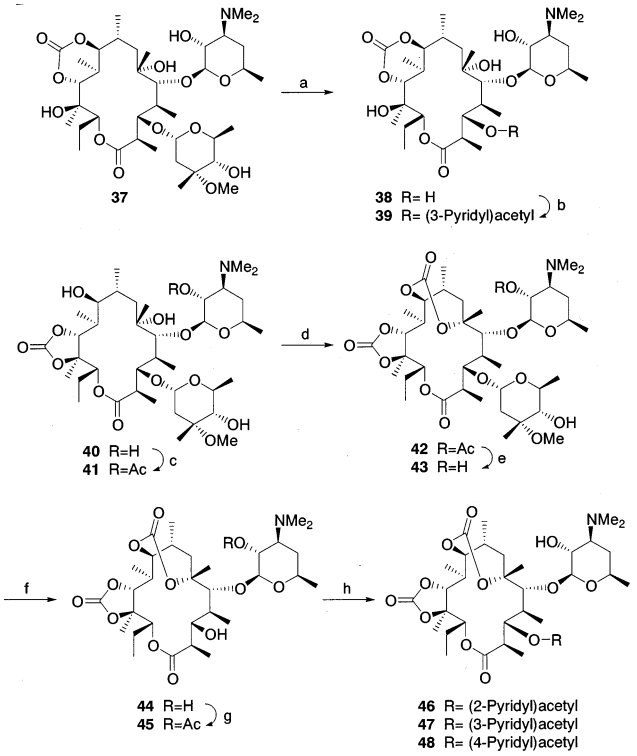
[a] (a) Ac_2O, Na_2CO_3, CH_2Cl_2, 97% yield; (b) 3-pyridylacetic acid, PivCl, Et_3N, DMAP, CH_2Cl_2, −15 °C to room temperature, 58% yield; (c) MeOH, reflux, 91% yield; (d) $NaNO_2$, 2 N HCl, MeOH, H_2O, 0 °C, 35% yield; (e) $NaBH_4$, EtOH, 0 °C, 34% yield; (f) (i) trichloromethyl chloroformate, pyridine, CH_2Cl_2, 0 °C, (ii) MeOH, 90% yield in two steps; (g) $NaNO_2$, 2 N HCl, MeOH, H_2O, 0 °C to room temperature, 20% yield; (h) $NaBH_4$, MeOH, 0 °C, 84% yield.

To investigate the effect of a carbonate group at various locations in the macrolide skeleton, 9,11-carbonate acylide **39** was prepared from (9*S*)-9-dihydroerythromycin A 9,11-carbonate **37**[20] (Scheme 7). The treatment of **37** with 2 N HCl afforded the desired 3-*O*-descladinosyl product **38** in 68% yield, along with the unexpected 9,11-descarbonate byproduct in 24% yield. Subsequently, the typical sequential procedure for 3-*O*-(3-pyridyl) acetylation provided the desired 9,11-carbonate acylide **39** in 58% yield.

A straightforward approach to 6,9:11,12-dicarbonate by treating (9*S*)-2′-*O*-acetyl-9-dihydroerythromycin A with trichloromethyl chloroformate in pyridine resulted in preferential formation of the 9,11-carbonate. Therefore, the desired 6,9:11,12-dicarbonate acylide **47** was synthesized from (9*S*)-9-dihydroerythromycin A 11,12-cyclic carbonate **40**.[21]

To validate the antibacterial effect of the 3-*O*-(3-pyridyl)acetyl group against *H. influenzae*, the pyridine

Scheme 7[a]



[a] (a) (i) 2 N HCl, 68% yield; (b) (i) Ac_2O, Me_2CO, 98% yield, (ii) 3-pyridylacetic acid, Et_3N, DMAP, CH_2Cl_2, −15 °C to room temperature, (iii) MeOH, 59% yield in two steps; (c) Ac_2O, Me_2CO, 91% yield; (d) trichloromethyl chloroformate, pyridine, CH_2Cl_2, 0 °C; (e) MeOH, 49% yield in two steps; (f) 1 N HCl, 68% yield; (g) Ac_2O, Me_2CO, 99% yield; (h) (i) pyridylacetic acid, EDC·HCl or PivCl and Et_3N, DMAP, CH_2Cl_2, (ii) MeOH, 49−78% yield in two steps.

isomers **46** and **48** were also prepared from the common 3-OH intermediate **45** in respective yields of 78% and 49%.

Results and Discussion

Structure−Activity Relationships of Acylides. All of the acylides synthesized, as well as clarithromycin and azithromycin as references, were tested for in vitro antibacterial activity against three strains each of *S. aureus* and *S. pneumoniae* and two strains of *H. influenzae*. The activities are reported in Table 1 as minimum inhibitory concentrations (MICs) determined according to the Japan Society of Chemotherapy.[22]

S. aureus 209P-JC and *S. pneumoniae* IID553 are erythromycin-susceptible strains, *S. aureus* B1 is an inducibly MLS_B-resistant strain encoded by the *erm*(C) gene, and *S. aureus* SR138 is a constitutively MLS_B-resistant strain encoded by the *erm*(A) gene. *S. pneumoniae* 210 is an efflux-resistant strain encoded by the *mef*(A) gene, and *S. pneumoniae* 211 is an MLS_B-resistant strain encoded by the *erm*(B) gene. *H. influenzae* ATCC43095 is an ampicillin (AMP)-susceptible strain that does not produce β-lactamase. *H. influenzae* ATCC33533 is an AMP-resistant strain that produces β-lactamase. None of the macrolides tested were active against constitutively MLS_B-resistant *S. aureus* SR138 or MLS_B-resistant *S. pneumoniae* 211.

Previously, LeMahieu et al.[23] reported that 3-*O*-benzoylerythromycin A 9-oxime derivatives showed limited antibacterial activity, which was consistent with their potency in a ribosomal binding assay. Therefore, 3-*O*-(3-methoxy)benzoyl-6-*O*-methylerythromycin A derivative **3**, its phenyl acetate analogue **4**, and its phenyl propionate analogue **5** were prepared to compare their antibacterial activities. Among them, the phenyl acetate derivative **4** was found to be the most effective against all of the pathogens tested except *S. aureus* SR138 and *S. pneumoniae* 211. This result is consistent with results of our previous investigation.[15]

To probe the effect of the substituent on the phenyl group on antibacterial activity, we introduced a methoxy group as an electron-donating group and a nitro group as an electron-withdrawing group at each position of the phenyl in acylide **2**. While the antibacterial activities of methoxyphenyl acetates **6** and **7** were less than those of the parent phenyl acetate **2**, (3-methoxy)phenyl acetate **4** was about twice as active against almost all of the pathogens tested. In contrast, all of the nitrophenyl acetates **8**, **9**, and **10** (TEA0777) showed remarkably improved activity against almost all of the pathogens tested. (3-Nitro)phenyl acetate **9** was 4 times as active as the parent compound against the targeted *H. influenzae* (MIC = 25 μg/mL). Considering the possible carcinogenic and mutagenic effects of aromatic nitro compounds,[24] the nitrophenyl group was replaced by a pyridyl group, which is an electron-deficient aromatic group. Although the activities of the pyridyl acetates **11**−**13** against Gram-positive pathogens were 2- to 8-fold less than those of the nitrophenyl acetates **8**−**10**, (3-pyridyl) acetate **12** showed a 2- to 4-fold higher activity against the targeted *H. influenzae* (MIC = 12.5 μg/mL). Consequently, we used a (3-pyridyl)acetyl group as an 3-*O*-acyl group and continued further chemical modification focusing on the macrolide skeleton to obtain potential next-generation macrolides.

Compared to the parent 11,12-diol acylide **12**, the carbonate derivative **15** and the carbamate analogue **19** showed dramatically improved activity against all of the pathogens tested except MLS_B-resistant *S. aureus* SR138 and *S. pneumoniae* 211. This result is consistent with results from previous reports[16] that the introduction of a cyclic carbonate or carbamate into the 11,12-position of CAM derivatives enhanced their antibacterial activity. In particular, the carbamate acylide **19** (TEA0929) showed more potent activity against susceptible Gram-positive pathogens than both CAM and AZM. Furthermore, **19** was highly effective against the inducibly MLS_B-resistant *S. aureus* B1 (MIC = 0.39 μg/mL) and efflux-resistant *S. pneumoniae* 210 (MIC = 0.10 μg/mL), while second-generation macrolides were either less active or inactive.

In our investigation of the macrolide skeleton, chemical modification of the C-9 ketone group was found to have little effect on the activity against *H. influenzae* (**12** vs **22**, **15** vs **23**, **32** vs **31** and **33**, and **35** vs **34** and **36**). While 6-hydroxyacylides were slightly less active against Gram-positive pathogens than the corresponding 6-*O*-methylacylides, their activities against *H. influenzae* were maintained (**32** vs **12**, **31** vs **22**, **34** vs **23**, and **35** vs **15**).

We presumed that chemical modification that affects the conformation might affect their ability to bind to bacterial ribosomes, in contrast to simple substitution of functional groups. Acylide **25** hybridized with AZM

Table 1. Antibacterial Effects of Acylides against Selected Respiratory Pathogens

	MIC (μg/mL)							
	S. aureus			*S. pneumoniae*			*H. influenzae*	
compd	209P-JC[a]	B1[b]	SR138[c]	IID553[a]	210[d]	211[e]	ATCC43095[f]	ATCC33533[g]
2	1.56	6.25	>100	0.78	0.78	>100	100	100
3	25	50	>100	1.56	1.56	>100	>100	100
4	1.56	3.13	>100	0.39	0.39	>100	50	25
5	3.13	3.13	>100	0.78	0.78	>100	100	100
6	3.13	12.5	>100	1.56	1.56	>100	>100	100
7	1.56	12.5	>100	0.78	0.78	>100	100	50
8	0.39	0.78	>100	0.20	0.20	>100	50	50
9	0.20	0.78	>100	0.10	0.20	>100	25	25
10 (TEA0777)	0.20	0.39	>100	0.20	0.20	>100	50	50
11	1.56	1.56	>100	0.39	0.39	>100	50	25
12	0.78	1.56	>100	0.39	0.39	>100	12.5	12.5
13	0.78	1.56	>100	0.39	0.39	>100	50	50
15	0.20	0.39	>100	0.05	0.20	>100	3.13	3.13
19 (TEA0929)	0.05	0.39	>100	0.05	0.10	>100	3.13	3.13
22	0.78	1.56	>100	0.20	0.39	>100	12.5	12.5
23	0.20	0.39	>100	0.025	0.10	>100	3.13	6.25
25	3.13	6.25	>100	0.78	0.78	>100	1.56	1.56
27	0.20	0.39	>100	0.05	0.20	>100	6.25	3.13
31	1.56	1.56	>100	0.39	0.78	>100	12.5	12.5
32	1.56	6.25	>100	0.20	0.78	>100	12.5	12.5
33	3.13	6.25	>100	0.78	0.78	>100	12.5	12.5
34	0.39	0.39	>100	0.025	0.10	>100	3.13	3.13
35	0.20	0.39	>100	0.05	0.20	>100	3.13	3.13
36	0.78	0.78	>100	0.10	0.20	>100	3.13	6.25
39	0.78	1.56	>100	0.10	0.39	>100	12.5	6.25
43	0.10	>100	>100	0.10	0.39	>100	1.56	1.56
44	12.5	>100	>100	0.78	1.56	>100	50	100
46	0.20	0.78	>100	0.05	0.20	100	6.25	6.25
47 (FMA0122)	0.10	0.20	>100	0.025	0.10	100	0.78	0.78
48	0.20	0.39	>100	0.05	0.20	>100	12.5	6.25
AZM	0.39	>100	>100	0.10	0.78	>100	1.56	1.56
CAM	0.10	>100	>100	0.05	0.78	>100	6.25	3.13

[a] *S. aureus* 209P-JC, *S. pneumoniae* IID553: erythromycin-susceptible strain. [b] *S. aureus* B1: inducibly MLS_B-resistant strain encoded by the *erm*(C) gene. [c] *S. aureus* SR138: constitutively MLS_B-resistant strain encoded by the *erm*(A) gene. [d] *S. pneumoniae* 210: efflux-resistant strain encoded by the *mef*(A) gene. [e] *S. pneumoniae* 211: MLS_B-resistant strain encoded by the *erm*(B) gene. [f] *H. influenzae* ATCC43095 is an ampicillin-susceptible strain that does not produce β-lactamase. [g] *H. influenzae* ATCC33533 is an ampicillin-resistant strain that produces β-lactamase.

was prepared to examine the properties of the 15-membered 9a-azalide skeleton. As expected, **25** inherited the beneficial activity profile against *H. influenzae* (MIC = 1.56 μg/mL), but its activity against Gram-positive pathogens was insufficient. We examined an alternative modification involving bridged derivatives to fix the macrolide skeleton in an adequate conformation. Tricyclic acylide **27**, in which the 11,12-carbamate is tethered to a C-9 ketone group by iminoethylene, showed no improvement in activity compared to the parent carbamate **19**. However, the introduction of a cyclic carbonate system to tetraol **33** at the 11,12- and 9,11-positions significantly enhanced the antibacterial activity (**33** vs **36** and **39**). As for the activity against ampicillin-susceptible *H. influenzae*, the 11,12-carbonate **36** was 4-fold more potent than the 9,11-carbonate **39** (MIC for **36** is 3.13 μg/mL; that for **39** is 12.5 μg/mL).

3-*O*-(3-Pyridyl)acetylerythromycin A 6,9:11,12-dicarbonate **47** (FMA0122), which has an additional carbonate at the 6,9-position compared to the 11,12-carbonate acylide **36**, exhibited significant potent activity against all of the pathogens tested. Interestingly, the dicarbonate acylide **47** was 2-fold more potent than AZM against *H. influenzae* (MIC = 0.78 μg/mL). On the basis of a comparison of the regioisomers **46** and **48**, the (3-pyridyl)acetyl group was shown to confer an antibacterial advantage against *H. influenzae*. In addition, introducing a pyridylacetyl group instead of L-cladinose at the 3-*O*-position in erythromycin derivative **43** led to the acquisition of activity against inducibly MLS_B-resistant *S. aureus* B1, against which second-generation macrolides are inactive.

In Vivo Evaluation. The in vivo efficacies of acylides, Ery A, AZM, and CAM were assessed by mouse protection tests (MPT), using erythromycin-susceptible strains of *S. aureus* Smith and *S. pneumoniae* IID553. The mice were inoculated intraperitoneally, and the macrolides were administered orally 1 h after inoculation. The efficacy of each macrolide was reported as the effective drug dosage (ED_{50}) that gave a survival rate of 50% following lethal infection over the duration of the trial (Table 2).

3-*O*-(3-Pyridyl) acetate **12**, which was designed as an alternative to nitrophenyl acetates, showed good in vivo efficacy comparable to (4-nitro)phenyl acetate **10** (TEA0777) despite 2-fold less antibacterial activity against both pathogens. The 11,12-carbonate acylide **15** was less effective than the parent acylide **12** regardless of its 4-fold improved activity. The 9-oxime acylide **23** exhibited in vivo efficacy comparable to that of the 9-ketone acylide **15**. Further conversion to the 6-hydroxy analogue **34** resulted in complete attenuation of the mouse protection effect, especially against *S. pneumoniae* IID553.

In a preliminary MPT, 6,9:11,12-dicarbonate acylide

Table 2. In Vivo Efficacy of Acylides in Mouse Protection Tests[a]

compd	*S. aureus* Smith MIC (μg/mL)	*S. aureus* Smith ED_{50} (95% CL[c]) (mg/kg)	*S. pneumoniae* IID553 MIC (μg/mL)	*S. pneumoniae* IID553 ED_{50} (95% CL[c]) (mg/kg)
10 (TEA0777)	0.39	15.4 (11.2−21.1)	0.10	39.1 (27.9−55.4)
12	0.78	9.57 (4.81−14.9)	0.20	40.8 (25.7−65.6)
15	0.20	17.5 (10.7−33.4)	0.05	51.1 (35.1−75.0)
19 (TEA0929)	0.20	6.99 (4.43−11.0)	0.05	17.5 (9.32−36.5)
23	0.39	27.6 (19.1−40.2)	0.025	47.4 (31.1−74.3)
34	0.20	51.6 (34.8−78.0)	0.025	142 (89.7−283)
Ery A[b]	0.20	56.6 (40.4−79.2)	0.10	111 (65.3−171)
AZM[b]	0.78	15.7 (10.3−26.5)	0.10	13.9 (8.97−21.1)
CAM	0.20	7.60 (4.86−12.0)	0.025	13.5 (8.42−24.4)

[a] Mice were inoculated intraperitoneally with 5.80×10^7 CFU/mouse for *S. aureus* and 1.47×10^3 CFU/mouse for *S. pneumoniae*. [b] Mice were inoculated intraperitoneally with 5.09×10^7 CFU/mouse for *S. aureus* and 7.05×10^2 CFU/mouse for *S. pneumoniae*. [c] CL: confidence limits.

Table 3. Survival Rates (%) with 6,9:11,12-Dicarbonate Acylide **47** in Preliminary Mouse Protection Tests[a]

	S. pneumoniae IID553[b]		
		dose (mg/mouse)	
compd	MIC (μg/mL)	3.0	0.3
47 (FMA0122)	0.025	90	30
AZM	0.10	100	50
CAM	0.05	100	50

[a] Mice were inoculated intraperitoneally with 5.05×10^7 CFU/mouse. [b] *S. pneumoniae* IID553: erythromycin-susceptible strain.

Table 4. Pharmacokinetic Parameters[a] of 6,9:11,12-Dicarbonate Acylide **47** Following a Single 10 mg/kg Oral Dose

	serum		lung	
compd	C_{max} (μg/mL)	AUC_{0-8} (μg·h/mL)	C_{max} (μg/mL)	AUC_{0-8} (μg·h/mL)
47 (FMA0122)	0.12	0.23	1.35	2.46
CAM	1.21	1.31	14.08	30.38

[a] Data represent the mean in three mice.

47 (FMA0122), which had the best antibacterial profile, was unfortunately less effective than the second-generation macrolides (Table 3). This poor efficacy can be attributed to poor pharmacokinetics (Table 4). Consequently, the carbonate group was shown to significantly improve antibacterial activity, but the in vivo efficacy tended to be attenuated. On the other hand, 3-*O*-(3-pyridyl)acetyl-5-*O*-desosaminyl-6-*O*-methylerythronolide A 11,12-carbamate **19** (TEA0929) had an excellent mouse protection effect, comparable to those of second-generation macrolides.

Conclusion

In summary, extensive optimization of the 3-*O*-acyl group led to a novel series of acylides, 3-*O*-(3-pyridyl)-acetylerythromycin A derivatives, that have fairly improved activity against *H. influenzae*.

In particular, 6,9:11,12-dicarbonate acylide **47** (FMA0122) was 2-fold more active than AZM, whereas its in vivo efficacy was moderate in the MPT. However, 11,12-carbamate acylide **19** (TEA0929), which shows potent antibacterial activity against the main causative pathogens of CAP including resistant strains, had an excellent mouse protection effect comparable to those of second-generation macrolides. The encouraging in vivo results for these acylides warrant further investigation to overcome MLS_B-resistant pathogens and to develop potential next-generation macrolides.

Experimental Section

All reagents and solvents were purchased commercially and used without purification unless otherwise noted. ^1H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded in $CDCl_3$ on a JEOL Alpha 500 or JEOL Lambda 500 spectrometer. Chemical shifts are reported in parts per million (ppm) with tetramethylsilane (TMS) as an internal standard. Coupling constants (*J*) are given in hertz (Hz), and the abbreviations s, d, t, q, br, and m refer to singlet, doublet, triplet, quartet, broad, and multiplet, respectively. All assignments were made based on $^1H-^1H$ correlation spectroscopy (COSY), heteronuclear multiple-quantum coherence (HMQC), and heteronuclear multiple-bond correlation (HMBC) methods. Mass spectra (MS) were obtained with a Micromass Platform LC or a Micromass Q-Tof 2. Elemental analyses were performed using a PerkinElmer 2400 CHN analyzer. Melting points were measured using a Mettler FP61 melting point instrument and are uncorrected.

5-*O*-Desosaminyl-3-*O*-phenylacetyl-6-*O*-methylerythronolide A (2). To a solution of 2′-*O*-acetyl-5-*O*-desosaminyl-6-*O*-methylerythronolide A **1**[15] (1.26 g, 2.0 mmol) in pyridine (6.0 mL) was added DMAP (122 mg, 1.0 mmol) and phenylacetyl chloride (0.66 mL, 5.0 mmol) at 0 °C. After being stirred at room temperature for 22 h, the reaction mixture was partitioned between EtOAc and brine. The organic layer was dried over $MgSO_4$ and evaporated in vacuo. The residue was purified by column chromatography, eluting with acetone/*n*-hexane/Et_3N (4:10:0.05) to give 2′-OAc-**2** (730 mg, 49%), along with the recovered starting material **1**. The product was refluxed in MeOH (10 mL) for 6 h. After evaporation of the solvent in vacuo, the residue was purified by column chromatography, eluting with $CHCl_3$/MeOH/25% NH_4OH (20:1:0.1) to give **2** (490 mg, 71%) as a white foam: HRMS (ES) *m*/*z* 708.4308, calcd for $C_{38}H_{62}NO_{11}$ 708.4323. Anal. ($C_{38}H_{61}NO_{11}$) C, H, N.

5-*O*-Desosaminyl-3-*O*-(3-methoxy)benzoyl-6-*O*-methylerythronolide A (3). To a solution of **1** (3.0 g, 4.75 mmol) in CH_2Cl_2 (30 mL) was added 3-methoxybenzoic acid (2.17 g, 14.3 mmol), EDC·HCl (2.72 g, 14.2 mmol), and DMAP (0.58 g, 4.75 mmol) at 0 °C. After being stirred at room temperature for 4 days, the reaction mixture was partitioned between EtOAc and water and the pH of the aqueous layer was adjusted to 8 with 2 N NaOH. The organic layer was washed with saturated NH_4Cl solution and brine and then dried over $MgSO_4$. After evaporation of the solvent under reduced pressure, the residue was purified by column chromatography, eluting with acetone/*n*-hexane/Et_3N ((1−3):10:0.2) to give 2′-OAc-**3** (3.06 g, 84%) as a white foam, along with recovered starting material **1** (0.26 g, 9%). The product was stirred in MeOH (30 mL) at room temperature for 2 days. After evaporation of the solvent in vacuo, the residue was purified by column chromatography, eluting with $CHCl_3$/MeOH/25% NH_4OH (25:1:0.1) to give **3** (2.80 g, 97%) as a white foam: HRMS (ES) *m*/*z* 724.4281, calcd for $C_{38}H_{62}NO_{12}$ 724.4272. Anal. ($C_{38}H_{61}NO_{12}$) C, H, N.

5-*O*-Desosaminyl-3-*O*-(3-methoxyphenyl)acetyl-6-*O*-methylerythronolide A (4). The title compound was prepared from **1** (3.24 g, 5.13 mmol) and 3-methoxyphenylacetic acid (2.56 g, 15.4 mmol) according to the procedure used to prepare **3**. Purification by recrystallization from Et_2O gave **4** (1.90 g, 50%) as a white powder: mp 205−206.5 °C; HRMS (ES) *m*/*z* 738.4423, calcd for $C_{39}H_{64}NO_{12}$ 738.4429. Anal. ($C_{39}H_{63}NO_{12}$) C, H, N.

5-*O*-Desosaminyl-3-*O*-(3-methoxyphenyl)propionyl-6-*O*-methylerythronolide A (5). The title compound was prepared from **1** (1.21 g, 1.92 mmol) and 3-(3-methoxyphenyl)-propionic acid (1.0 g, 5.55 mmol) according to the procedure used to prepare **3**. Purification by column chromatography, eluting with acetone/*n*-hexane/Et_3N (6:10:0.2), gave **5** (1.21 g, 84%) as a white foam: HRMS (ES) *m*/*z* 752.4579, calcd for $C_{40}H_{66}NO_{12}$ 752.4585. Anal. ($C_{40}H_{65}NO_{12}$) C, H, N.

5-*O*-Desosaminyl-3-*O*-(2-methoxyphenyl)acetyl-6-*O*-methylerythronolide A (6). 2′-Acetate of the title compound was prepared from **1** (1.10 g, 1.74 mmol) and 2-methoxyphenylacetic acid (0.29 g, 1.75 mmol) according to the procedure used to prepare **3**. Purification by column chromatography, eluting with acetone/*n*-hexane/Et_3N (6:10:0.2), gave 2′-OAc-**6** (0.70 g, 51%) as a white foam along with recovered starting material **1** (0.54 g, 49%). The product was stirred in MeOH (20 mL) at room temperature for 17 h. After evaporation of the solvent in vacuo, the residue was purified by column chromatography, eluting with $CHCl_3$/MeOH/25% NH_4OH (30:1:0.1) to give **6** (376 mg, 57%) as a white foam: HRMS (ES) *m*/*z* 738.4426, calcd for $C_{39}H_{64}NO_{12}$ 738.4429. Anal. ($C_{39}H_{63}NO_{12}\cdot{}^1/_2H_2O$) C, H, N.

5-*O*-Desosaminyl-3-*O*-(4-methoxyphenyl)acetyl-6-*O*-methylerythronolide A (7). 2′-Acetate of the title compound was prepared from **1** (1.26 g, 1.99 mmol) and 4-methoxyphenylacetic acid (1.10 g, 6.08 mmol) according to the procedure used to prepare **11**. Purification by column chromatography, eluting with acetone/*n*-hexane/Et_3N ((3−4):10:0.1), gave 2′-OAc-**7** (620 mg, 40%) as a white foam along with the recovered starting material **1**. The product was refluxed in MeOH (10 mL) for 8 h. After evaporation of the solvent in vacuo, the residue was purified by recrystallization from EtOAc to give **7** (520 mg, 89%) as a white powder: mp 191−195 °C; HRMS (ES) *m*/*z* 738.4430, calcd for $C_{39}H_{64}NO_{12}$ 738.4429. Anal. ($C_{39}H_{63}NO_{12}$) C, H, N.

5-*O*-Desosaminyl-3-*O*-(2-nitrophenyl)acetyl-6-*O*-methylerythronolide A (8). The title compound was prepared from **1** (1.57 g, 2.49 mmol) and 2-nitrophenylacetic acid (1.40 g, 7.73 mmol) according to the procedure used to prepare **3**. Purification by column chromatography, eluting with $CHCl_3$/MeOH/25% NH_4OH (20:1:0.1), gave **8** (1.42 g, 76%) as a slightly brown foam: HRMS (ES) *m*/*z* 753.4163, calcd for $C_{38}H_{61}N_2O_{13}$ 753.4174. Anal. ($C_{38}H_{60}N_2O_{13}\cdot H_2O$) C, H, N.

5-*O*-Desosaminyl-3-*O*-(3-nitrophenyl)acetyl-6-*O*-methylerythronolide A (9). The title compound was prepared from **1** (1.74 g, 2.75 mmol) and 3-nitrophenylacetic acid (1.50 g, 8.28 mmol) according to the procedure used to prepare **3**. Purification by column chromatography, eluting with acetone/*n*-hexane/Et_3N (6:10:0.2), gave **9** (1.00 g, 48%) as a slightly yellow foam along with 5-*O*-desosaminyl-6-*O*-metherythronolide A (0.37 g, 23%): HRMS (ES) *m*/*z* 753.4172, calcd for $C_{38}H_{61}N_2O_{13}$ 753.4174. Anal. ($C_{38}H_{60}N_2O_{13}$) C, H, N.

5-*O*-Desosaminyl-3-*O*-(4-nitrophenyl)acetyl-6-*O*-methylerythronolide A (10). The title compound was prepared from **1** (5.00 g, 7.91 mmol) and 4-nitrophenylacetic acid (4.30 g, 23.7 mmol) according to the procedure used to prepare **3**. Purification by recrystallization from isopropyl ether gave **10** (3.86 g, 81%) as a white powder: mp 157−159 °C; HRMS (ES) *m*/*z* 753.4189, calcd for $C_{38}H_{61}N_2O_{13}$ 753.4174. Anal. ($C_{38}H_{60}N_2O_{13}\cdot{}^1/_2H_2O$) C, H, N.

5-*O*-Desosaminyl-3-*O*-(2-pyridyl)acetyl-6-*O*-methylerythronolide A (11). To a solution of 2-pyridylacetic acid (1.15 g, 6.6 mmol) and Et_3N (0.93 mL, 6.6 mmol) in CH_2Cl_2 (30 mL) was added dropwise pivaloyl chloride (0.83 mL, 6.6 mmol) at −15 °C. After being stirred for 30 min, a solution of **1** (1.26 g, 2.0 mmol) in CH_2Cl_2 (10 mL) was added dropwise over 15 min, and DMAP (0.24 g, 2.0 mmol) was then added before warming the mixture to room temperature. After being stirred overnight, the reaction mixture was partitioned between CH_2Cl_2 and saturated $NaHCO_3$ solution. The organic layer was washed with brine and dried over $MgSO_4$. After evaporation of the solvent in vacuo, the residue was purified by column chromatography, eluting with acetone/*n*-hexane/Et_3N (4:10:0.05) to give 2′-OAc-**11** (1.12 g, 75%) as a slightly yellow foam. The product was refluxed in MeOH (20 mL) for 5 h. After evaporation of the solvent in vacuo, the residue was purified by column chromatography, eluting with $CHCl_3$/MeOH/25% NH_4OH (20:1:0.1) to give **11** (930 mg, 88%) as a white foam, which was further purified by recrystallization from Et_2O/*n*-hexane to give a white powder (764 mg, 72%): mp 189−190.5 °C; HRMS (ES) *m*/*z* 709.4282, calcd for $C_{37}H_{61}N_2O_{11}$ 709.4275. Anal. ($C_{37}H_{60}N_2O_{11}$) C, H, N.

5-*O*-Desosaminyl-3-*O*-(3-pyridyl)acetyl-6-*O*-methylerythronolide A (12). 2′-Acetate of the title compound was prepared from **1** (2.40 g, 3.8 mmol) and 3-pyridylacetic acid (1.98 g, 11.4 mmol) according to the procedure used to prepare **11**. Purification by column chromatography, eluting with acetone/*n*-hexane/Et_3N ((4−6):10:0.05), gave 2′-OAc-**12** (2.04 g, 72%) as a white foam. The product was refluxed in MeOH (20 mL) for 3 h. Evaporation of the solvent in vacuo gave **12** (1.98 g) as a white foam: HRMS (ES) *m*/*z* 709.4288, calcd for $C_{37}H_{61}N_2O_{11}$ 709.4275. Anal. ($C_{37}H_{60}N_2O_{11}\cdot H_2O$) C, H, N.

5-*O*-Desosaminyl-3-*O*-(4-pyridyl)acetyl-6-*O*-methylerythronolide A (13). 2′-Acetate of the title compound was prepared from **1** (3.16 g, 5.0 mmol) and 4-pyridylacetic acid (2.60 g, 15.0 mmol) according to the procedure used to prepare **11**. Purification by column chromatography, eluting with acetone/*n*-hexane/Et_3N (6:10:0.2), gave 2′-OAc-**13** (2.82 g, 75%) as a slightly yellow foam. The product (1.48 g, 2.0 mmol) was refluxed in MeOH (30 mL) for 5 h. After evaporation of the solvent in vacuo, the residue was purified by recrystallization from acetone/*n*-hexane to give **13** (672 mg, 48%) as a white powder: mp 168−170 °C; HRMS (ES) *m*/*z* 709.4279, calcd for $C_{37}H_{61}N_2O_{11}$ 709.4275. Anal. ($C_{37}H_{60}N_2O_{11}$) C, H, N.

5-*O*-Desosaminyl-3-*O*-(3-pyridyl)acetyl-6-*O*-methylerythronolide A 11,12-Cyclic Carbonate (15). To a solution of **1** (50.0 g, 0.079 mmol) and pyridine (102.6 mL, 1.27 mol) in CH_2Cl_2 (500 mL) was added dropwise trichloromethyl chloroformate (25.4 mL, 0.21 mol) in CH_2Cl_2 (40 mL) at 0 °C. After being stirred for 5.5 h, the reaction was quenched by adding pieces of ice in small portions. The reaction mixture was partitioned between CH_2Cl_2 and saturated $NaHCO_3$ solution. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated in vacuo. The residue was purified by column chromatography, eluting with acetone/*n*-hexane/Et_3N ((6−10):10:0.2) to give **14** (41.9 g, 80%) as a white foam. The title compound was prepared from **14** (10.0 g, 15.2 mmol) according to the procedure used to prepare **11**. Purification by column chromatography, eluting with $CHCl_3$/MeOH/25% NH_4OH (25:1:0.1), gave **15** (9.10 g, 82%) as a white foam, which was further purified by recrystallization from CH_2Cl_2/*n*-hexane to give **15** (5.25 g, 47%) as a white powder: mp 231.5−233.5 °C; HRMS (ES) *m*/*z* 735.4076, calcd for $C_{38}H_{59}N_2O_{12}$ 735.4068. Anal. ($C_{38}H_{58}N_2O_{12}$) C, H, N.

5-*O*-Desosaminyl-3-*O*-(3-pyridyl)acetyl-6-*O*-methylerythronolide A 11,12-Cyclic Carbamate (19). To a mixture of liquid ammonia (500 mL) and THF (200 mL) under cooling with dry ice/acetone was added dropwise a solution of 2,4-di-*O*-acetyl-10,11-anhydro-12-*O*-imidazolylcarbonyl-6-*O*-methylerythromycin A **16**[12b] (200.79 g, 0.22 mol) in THF (400 mL) over 30 min, and the mixture was stirred at that temperature for 2 h before removing the cold bath. After being stirred at room temperature for 2 days, 60% sodium hydride dispersed in oil (2.16 g, 0.054 mol) was added, and the reaction mixture was stirred for an additional 3 h. The reaction mixture was partitioned between EtOAc and brine. The organic layer was dried over $MgSO_4$ and then evaporated in vacuo to give crude **17** (174.4 g) as a colorless crystalline powder. A mixture of the crude intermediate **17**, EtOH (350 mL), and 2 N HCl (700 mL) was stirred at room temperature for 20 h. The reaction mixture was neutralized with 4 N NaOH, and the resulting precipitate was collected by filtration and later purified by column chromatography, eluting with acetone/*n*-hexane/Et_3N ((50−100):100:0.2) to give **18** (116.2 g, 80%) as a white foam. The title compound was prepared from **18** (2.9 g, 4.42 mmol) according to the method used to prepare **11**. Purification by column chromatography, eluting with $CHCl_3$/MeOH/25% NH_4OH (20:1:0.1), gave **19** (2.48 g, 77%) as a white foam, which was further purified by recrystallization from Et_2O to give **19** (1.40 g, 43%) as a white powder: mp 216−219 °C; HRMS (ES) *m*/*z* 734.4227, calcd for $C_{38}H_{60}N_3O_{11}$ 734.4228. Anal. ($C_{38}H_{59}N_3O_{11}$) C, H, N.

(*E*)-5-*O*-Desosaminyl-3-*O*-(3-pyridyl)acetyl-6-*O*-methylerythronolide A 9-Oxime (22). To a solution of 5-*O*-desosaminyl-6-*O*-methylerythronolide 9-oxime A **20**[14] (5.00 g, 8.27 mmol) in acetone (30 mL) was added acetic anhydride (2.0 mL,

21.2 mmol) at room temperature. After being stirred for 2 h, the reaction mixture was evaporated in vacuo and then partitioned between CH_2Cl_2 and saturated Na_2CO_3 solution. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated in vacuo to give crude **21** (5.50 g). The title compound was prepared from the crude intermediate **21** according to the procedure used to prepare **11**. Purification by column chromatography, eluting with $CHCl_3$/MeOH/25% NH_4OH ((100:5−10):0.1), gave **22** (2.97 g, 50%) as a white foam: HRMS (ES) *m/z* 724.4391, calcd for $C_{37}H_{62}N_3O_{11}$ 724.4384. Anal. ($C_{37}H_{61}N_3O_{11}$) C, H, N.

(*E*)-5-*O*-Desosaminyl-3-*O*-(3-pyridyl)acetyl-6-*O*-methylerythronolide A 9-Oxime 11,12-Cyclic Carbonate (23). To a solution of **22** (2.90 g, 4.0 mmol) in acetone (30 mL) was added acetic anhydride (1.1 mL, 11.7 mmol) at room temperature. After being stirred for 3 h, the reaction mixture was evaporated in vacuo and then partitioned between CH_2Cl_2 and saturated Na_2CO_3 solution. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated in vacuo to give crude 2′-OAc-**22** acetoxime (2.90 g) as a white foam. 2′-Acetate of the title compound was prepared from 2′-OAc-**22** acetoxime according to the procedure used to prepare **14**. Purification by column chromatography, eluting with acetone/*n*-hexane/Et_3N ((6−10):10:0.2), gave 2′-OAc-**23** (0.34 g, 10%) as a slightly yellow foam, along with the recovered starting material 2′-OAc-**22** (1.74 g, 53%). The product was refluxed in MeOH (6 mL) for 3 h. After evaporation of the solvent in vacuo, the residue was purified by column chromatography, eluting with $CHCl_3$/MeOH/25% NH_4OH (10:1:0.1) to give **23** (0.24 g, 79%) as a slightly yellow foam: HRMS (ES) *m/z* 750.4171, calcd for $C_{38}H_{60}N_3O_{12}$ 750.4177. Anal. ($C_{38}H_{59}N_3O_{12}\cdot H_2O$) C, H, N.

5-*O*-Desosaminyl-3-*O*-(3-pyridyl)acetyl-9-deoxo-9a-aza-9a-methyl-9a-homoerythronolide A (25). To a solution of 3-*O*-descladinosylazithromycin **24**[18] (2.44 g, 4.13 mmol) in acetone (25 mL) was added acetic anhydride (0.43 mL, 4.56 mmol) at room temperature. After being stirred overnight, the reaction mixture was evaporated in vacuo and then partitioned between EtOAc and saturated $NaHCO_3$ solution. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated in vacuo to give 2′-OAc-**24** (2.21 g, 85%) as a white powder. The title compound was prepared from 2′-OAc-**24** (0.70 g, 1.11 mmol) according to the procedure used to prepare **3**. Purification by column chromatography, eluting with $CHCl_3$/MeOH/25% NH_4OH (20:1:0.1), gave **25** (0.54 g, 69%) as a white foam, which was further purified by recrystallization from CH_2Cl_2/*n*-hexane to give a white powder (0.28 g, 36%): mp 210−213 °C; HRMS (ES) *m/z* 710.4601, calcd for $C_{37}H_{64}N_3O_{10}$ 710.4592. Anal. ($C_{37}H_{63}N_3O_{10}$) C, H, N.

11-Amino-9-deoxo-11-deoxy-5-*O*-desosaminyl-9-,11-*N*-nitriloethano-3-*O*-(3-pyridyl)acetyl-6-*O*-methylerythronolide A 11,12-Cyclic Carbamate (27). The title compound was prepared from 11-amino-9-deoxo-11-deoxy-5-*O*-desosaminyl-9-,11-*N*-nitriloethano-6-*O*-methylerythronolide A 11,12-cyclic carbamate **26**[12] (3.62 g, 5.65 mmol) according to the procedure used to prepare **25**. Purification by column chromatography, eluting with $CHCl_3$/MeOH/25% NH_4OH (10:1:0.1), gave **27** (3.39 g, 79%) as a white foam, which was further purified by recrystallization from Et_2O to give a white powder: mp 226−229 °C; HRMS (ES) *m/z* 759.4541, calcd for $C_{40}H_{63}N_4O_{10}$ 759.4544. Anal. ($C_{40}H_{62}N_4O_{10}\cdot H_2O$) C, H, N.

(*E*)-5-*O*-Desosaminyl-3-*O*-(3-pyridyl)acetylerythronolide A 9-Oxime (31). To a solution of (*E*)-5-*O*-desosaminylerythronolide A 9-oxime **28**[19] (15.0 g, 25.4 mmol) and sodium carbonate (2.69 g, 25.4 mmol) in CH_2Cl_2 (80 mL) was added acetic anhydride (7.2 mL, 76.3 mmol) at room temperature. After being stirred for 3 h, the reaction mixture was partitioned between CH_2Cl_2 and saturated Na_2CO_3 solution. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated in vacuo to give the 2′-acetate **29** (16.57 g, 97%). 3-*O*-(3-Pyridyl) acetylation according to the procedure used to prepare **11** gave **30** (11.15 g, 58%) as a slightly yellow foam. The product (8.18 g, 10.3 mmol) was refluxed in MeOH (200 mL) for 9 h. After evaporation of the solvent in vacuo, the residue was purified by column chromatography, eluting with acetone/*n*-hexane/Et_3N (10:10:0.2) to give **31** (6.64 g, 91%) as a white foam: HRMS (ES) *m/z* 710.4231, calcd for $C_{36}H_{60}N_3O_{11}$ 710.4228. Anal. ($C_{36}H_{59}N_3O_{11}\cdot{}^1/_2H_2O$) C, H, N.

5-*O*-Desosaminyl-3-*O*-(3-pyridyl)acetylerythronolide A (32). To a solution of **31** (2.00 g, 2.82 mmol) and sodium nitrite (4.86 g, 70.4 mmol) in MeOH (30 mL) and H_2O (10 mL) was added dropwise 2 N HCl (35.2 mL, 70.4 mmol) over 30 min at 0 °C. After being stirred for 4 h, the reaction mixture was partitioned between $CHCl_3$ and water and the pH of the aqueous layer was adjusted to 8 with 2 N NaOH. The organic layer was dried over $MgSO_4$ and evaporated in vacuo. The residue was purified by recrystallization from 2-propanol to give **32** (683 mg, 35%) as a white powder: mp 231−233 °C; HRMS (ES) *m/z* 695.4136, calcd for $C_{36}H_{59}N_2O_{11}$ 695.4119.

(9*S*)-5-*O*-Desosaminyl-9-dihydro-3-*O*-(3-pyridyl)acetylerythronolide A (33). To a solution of **32** (619 mg, 0.89 mmol) in EtOH (10 mL) was added sodium borohydride (51 mg, 1.35 mmol) at 0 °C. After being stirred for 5 h, the reaction mixture was partitioned between EtOAc and brine. The aqueous layer was extracted twice with $CHCl_3$. The combined organic layer was dried over $MgSO_4$ and evaporated in vacuo. Purification by column chromatography, eluting with $CHCl_3$/MeOH/25% NH_4OH (15:1:0.1), gave **33** (0.21 g, 34%) as a white foam: HRMS (ES) *m/z* 697.4293, calcd for $C_{36}H_{61}N_2O_{11}$ 697.4275. Anal. ($C_{36}H_{60}N_2O_{11}\cdot 2H_2O$) C, H, N.

(*E*)-5-*O*-Desosaminyl-3-*O*-(3-pyridyl)acetylerythronolide A 9-Oxime 11,12-Cyclic Carbonate (34). 2′-Acetate of the title compound was prepared from **30** (10.35 g, 13.0 mmol) according to the procedure used to prepare **14**. The product was stirred in MeOH (100 mL) at room temperature overnight. After evaporation of the solvent in vacuo, the residue was purified by column chromatography, eluting with $CHCl_3$/MeOH (95:5) to give **34** (8.59 g, 90%) as a slightly yellow foam, which was further purified by recrystallization from MeCN to give **34** (4.87 g, 51%) as a white powder: mp 212−215 °C; HRMS (ES) *m/z* 736.4032, calcd for $C_{37}H_{58}N_3O_{12}$ 736.4021. Anal. ($C_{37}H_{57}N_3O_{12}$) C, H, N.

5-*O*-Desosaminyl-3-*O*-(3-pyridyl)acetylerythronolide A 11,12-Cyclic Carbonate (35). The title compound was prepared from compound **34** (3.21 g, 4.36 mmol) according to the procedure used to prepare **32**. Purification by column chromatography, eluting with $CHCl_3$/MeOH/25% NH_4OH (15:1:0.1), gave **35** (0.64 g, 20%) as a white foam: HRMS (ES) *m/z* 721.3906, calcd for $C_{37}H_{57}N_2O_{12}$ 721.3912; NMR analysis supports the 6,9-hemiketal conformation of **35** in the $CDCl_3$. Anal. ($C_{37}H_{56}N_2O_{12}\cdot{}^1/_2H_2O$) C, H, N.

(9*S*)-5-*O*-Desosaminyl-9-dihydro-3-*O*-(3-pyridyl)acetylerythronolide A 11,12-Cyclic Carbonate (36). The title compound was prepared from compound **35** (0.38 g, 0.53 mmol) according to the procedure used to prepare **33**. Purification by column chromatography, eluting with $CHCl_3$/MeOH/25% NH_4OH (15:1:0.1), gave **34** (0.32 g, 84%) as a white foam: HRMS (ES) *m/z* 723.4077, calcd for $C_{37}H_{59}N_2O_{12}$ 723.4068. Anal. ($C_{37}H_{58}N_2O_{12}\cdot H_2O$) C, H, N.

(9*S*)-5-*O*-Desosaminyl-9-dihydro-3-*O*-(3-pyridyl)acetylerythronolide A 9,11-Cyclic Carbonate (39). A mixture of (9*S*)-9-dihydroerythromycin A 9,11-carbonate **37**[20] (1.90 g, 2.49 mmol) and 2 N HCl (20 mL) was stirred at room temperature overnight. The reaction mixture was partitioned between EtOAc and water, and the pH of the aqueous layer was adjusted to 8 with 2 N NaOH. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated in vacuo. The residue was purified by column chromatography, eluting with $CHCl_3$/MeOH/25% NH_4OH (20:1:0.1) to give **38** (1.02 g, 68%) as a white foam along with (9*S*)-5-*O*-desosaminyl-9-dihydroerythronolide A (0.34 g, 24%). To a solution of **38** (0.95 g, 1.57 mmol) in acetone (10 mL) was added acetic anhydride (0.22 mL, 2.33 mmol) at room temperature. After being stirred for 6 h, the reaction mixture was evaporated in vacuo and then partitioned between EtOAc and saturated Na_2CO_3 solution. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated in vacuo. The residue was purified by column chromatography, eluting with acetone/*n*-hexane/Et_3N (10:10:0.2) to give 2′-OAc-**38** (1.0 g, 98%). The

title compound was prepared from 2′-OAc-**38** (0.50 g, 0.77 mmol) according to the procedure used to prepare **11**. Purification by $CHCl_3$/MeOH/25% NH_4OH (20:1:0.1) gave **39** (0.33 g, 59%) as a white foam along with the recovered starting material **38** (0.14 g, 30%). **39**: HRMS (ES) *m/z* 723.4063, calcd for $C_{37}H_{59}N_2O_{12}$ 723.4068. Anal. ($C_{37}H_{58}N_2O_{12}$·$2H_2O$) C, H, N.

(9*S*)-9-Dihydroerythromycin A 6,9:11,12-Dicyclic Carbonate (43). To a solution of (9*S*)-9-dihydroerythromycin A 11,12-cyclic carbonate **40**[21] (13.64 g, 17.9 mmol) was added acetic anhydride (2.5 mL, 26.5 mmol) at room temperature. After being stirred overnight, the reaction mixture was evaporated in vacuo and then partitioned between EtOAc and saturated $NaHCO_3$ solution. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated in vacuo to give **41** (13.52 g, 91%). To a solution of **41** (3.42 g, 4.3 mmol) in CH_2Cl_2 (30 mL) and pyridine (20.6 mL, 0.26 mol) was added dropwise trichloromethyl chloroformate (3.1 mL, 25.9 mmol) in CH_2Cl_2 (30 mL) over 20 min at 0 °C. After being stirred for 5 h, the reaction was quenched by adding pieces of ice in small portions. The reaction mixture was partitioned between CH_2Cl_2 and water, and the pH of the aqueous layer was adjusted to 8 with 2 N NaOH. The aqueous layer was extracted twice with CH_2Cl_2. The combined organic layer was washed with brine, dried over $MgSO_4$, and evaporated in vacuo to give crude **42** (3.44 g). The product was stirred in MeOH (35 mL) for 23 h. After evaporation of the solvent in vacuo, the residue was purified by column chromatography, eluting with $CHCl_3$/MeOH/25% NH_4OH (15:1:0.1) to give **43** (1.65 g, 49%) as a white foam: HRMS (ES) *m/z* 788.4441, calcd for $C_{39}H_{66}NO_{15}$ 788.4432. Anal. ($C_{39}H_{65}NO_{15}$·$^1/_2H_2O$) C, H, N.

(9*S*)-5-*O*-Desosaminyl-9-dihydroerythronolide A 6,9:11,12-Dicyclic Carbonate (44). The title compound was prepared from **43** (4.53 g, 5.75 mmol) according to the procedure used to prepare **39**. Purification by column chromatography, eluting with acetone/*n*-hexane/Et_3N (10:10:0.2), and recrystallization from 2-propanol gave **44** (2.45 g, 68%) as a white powder: mp 240.5−242 °C; HRMS (ES) *m/z* 630.3492, calcd for $C_{31}H_{52}NO_{12}$ 630.3490. Anal. ($C_{31}H_{51}NO_{12}$) C, H, N.

(9*S*)-5-*O*-Desosaminyl-9-dihydro-3-*O*-(3-pyridyl)acetylerythronolide A 6,9:11,12-Dicyclic Carbonate (47). To a solution of **44** (2.34 g, 3.7 mmol) was added acetic anhydride (0.42 mL, 4.5 mmol) at room temperature. After being stirred overnight, the reaction mixture was evaporated in vacuo and then partitioned between EtOAc and saturated $NaHCO_3$ solution. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated in vacuo to give **45** (2.46 g, 99%). The title compound was prepared from **45** (2.46 g, 3.66 mmol) and 3-pyridylacetic acid (1.9 g, 10.9 mmol) according to the procedure used to prepare **11**. Purification by column chromatography, eluting with acetone/*n*-hexane/Et_3N (30:10:0.2), and recrystallization from 2-propanol gave **47** (1.84 g, 66%) as a white powder along with the recovered starting material **44** (0.09 g, 4%). **47**: mp 217−219.5 °C; HRMS (ES) *m/z* 749.3860, calcd for $C_{38}H_{57}N_2O_{13}$ 749.3861. Anal. ($C_{38}H_{56}N_2O_{13}$·$^1/_2H_2O$) C, H, N.

(9*S*)-5-*O*-Desosaminyl-9-dihydro-3-*O*-(2-pyridyl)acetylerythronolide A 6,9:11,12-Dicyclic Carbonate (46). The title compound was prepared from **45** (0.16 g, 0.24 mmol) and 2-pyridylacetic acid (0.12 g, 0.69 mmol) according to the procedure used to prepare **11**. Purification by column chromatography, eluting with $CHCl_3$/MeOH/25% NH_4OH (15:1:0.1), gave **46** (139 mg, 78%) as a slightly yellow foam: HRMS (ES) *m/z* 749.3846, calcd for $C_{38}H_{57}N_2O_{13}$ 749.3861. Anal. ($C_{38}H_{56}N_2O_{13}$·H_2O) C, H, N.

(9*S*)-5-*O*-Desosaminyl-9-dihydro-3-*O*-(4-pyridyl)acetylerythronolide A 6,9:11,12-Dicyclic Carbonate (48). The title compound was prepared from **45** (0.31 g, 0.46 mmol) and 4-pyridylacetic acid (0.27 g, 1.56 mmol) according to the procedure used to prepare **3**. Purification by column chromatography, eluting with $CHCl_3$/MeOH/25% NH_4OH (15:1:0.1), gave **48** (169 mg, 49%) as a white foam: HRMS (ES) *m/z* 749.3860, calcd for $C_{38}H_{57}N_2O_{13}$ 749.3861. Anal. ($C_{38}H_{56}N_2O_{13}$·$^1/_2H_2O$) C, H, N.

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Supporting Information Available: Complete ^1H and ^{13}C NMR peak assignments for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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