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Original article

Synthesis and antibacterial activity of novel modified 5-*O*-mycaminose 14-membered ketolides

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ABSTRACT

A practicable method of introducing a side chain to the C-4′ position of 5-*O*-desosamine in the 14-membered ketolides was developed. And using this method, a series of novel modified 5-*O*-mycaminose ketolides were synthesized. These ketolides containing 5-*O*-4′-carbamate mycaminose were evaluated for their *in vitro* antibacterial activities against some respiratory pathogens. **15b** and **18e** showed comparable activity to telithromycin and clarithromycin.

1. Introduction

Macrolide antibiotics have been widely utilized to treat bacterial infections for nearly 60 years. They are especially effective for the treatment of the upper and lower respiratory tract infections [1]. However, bacterial resistance to macrolide antibiotics has become increasingly prevalent over the past decades, due to the extensive usage [2–4]. Recently, great efforts have been made to find structures which possess activity toward resistant pathogens.

The 5-*O*-desosamine residue is considered to be indispensable for the antibacterial activity. The 2′-hydroxyl group, together with the 3′-*N*,*N*-dimethylamino group, bind with the 23S RNA, residues A2058 and A2059 [5]. These interactions contribute significantly to the inhibition of the peptide bond formation.

Due to the importance of the 5-*O*-desosamine, researchers have made considerable efforts to modify the sugar with the purpose of investigating the interaction between the desosamine and rRNA. Recently N. LeTourneau et al. prepared several macrolide derivatives with 2′- or 3′-modified desosamine [6]. They concluded from the results that the *erm-type* resistance (A2058-dimethylated strains) did not result from steric clash or the loss of hydrogen bond. Furthermore, they hypothesized that it might involve non-bonding interactions between *N*-6 methyl group(s) of A2058 and water molecules coordinated to the Mg^{2+} cation bound to phosphate groups of G2056 and G2057 residues of 23S RNA. C. Liang et al. replaced the 5-*O*-desosamine with its mimetics, and they synthesized several 5-*O*-(6′-*O*-benzoyl)-desosamine ketolides [7]. Ketolides containing the hydrophobic 6′-*O*-benzoyl group displayed excellent activities against some erythromycin-resistant strains. In our previous work [8], X. Chen et al. synthesized three 14-membered ketolides containing 4′-modified desosamine, the 4′-hydroxyl (namely mycaminose), 4′-*O*-benzyl, and 4′-*O*-allyl derivatives. Among them, the 4′-hydroxyl ketolide showed potent activity against certain sensitive pathogens while the other two proved to be noneffective.

As the major origination of the binding energy with the ribosome, slight modifications to the 5-*O*-desosamine might result in change of antibacterial activity [9,10]. Therefore such researches contribute to understand the action mechanism of desosamine from different perspectives.

16-Membered macrolides have a mycaminose-mycarose disaccharide at the C-5 position, which is oriented similarly to the 5-*O*-

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desosamine of 14-membered macrolides. Furthermore the mycarose reaches to the peptidyl transferase center (PTC), making additional interactions at G2505 and U2506, and directly inhibits peptide bond formation. However, 14-membered macrolides with a shorter 5-*O*-desosamine could not inhibit peptide bond formation, but can block elongation of nascent peptides [11,12]. In the research of 16-membered macrolides, Ly T. Phan et al. removed the mycarose sugar of tylosin and synthesized 4′-substituted macrolides [13]. Some of them, such as the 4′-*O*-phenethylcarbamate analog, exhibited improved activities against certain resistant pathogens. The introduced arylalkyl side chain (a, b seen in Fig. 1) was thought to be important for the improvement of the activities. The authors inferred it might have π−π stacking and hydrophobic interactions with ribosome RNA bases.

Based on that, we intended to modify the C-4′ position of 14-membered ketolides. We presumed if suitable substituent, such as an aryl or alkyl group, could be introduced to the C-4′ position of 5-*O*-desosamine they probably have different effects on the interaction between the desosamine and the ribosome binding site.

In this report, we constructed a practicable method of introducing a side chain to the C-4′ position of 5-*O*-desosamine in the 14-membered ketolides by using commercially available starting materials. And adopting this method, we synthesized a novel series of 14-membered ketolides bearing 5-*O*-4′-carbamate mycaminose. In fact, modifications to the C-4′ position of 14-membered ketolides have rarely been reported for the synthetic difficulty. We hoped such structural modification helped to better understand the mechanism of the macrolide-ribosome interaction and to find new effective antibiotics against resistant pathogens.

2. Chemistry

To synthesize the 5-*O*-4′-carbamate mycaminose target compounds, compound **14** is an important intermediate. It could be synthesized by glycosylation of the acceptor **9** with the trichloroacetimidate donor **13** (Scheme 3) [14].

To get the 5-hydroxyl macrolide skeleton as acceptor **9**, we transformed the 9-ketone to 9-*E*-oxime. It proved that the 9-*E*-oxime played a vital role, compared with our previous method [8], in which the 9-ketone was retained all alone. The 5-hydroxyl-9-ketone compound was unstable since the 5-hydroxyl would attack the 9-ketone to form hemiacetal under acid conditions, even on the silica gel column. Therefore it was difficult to get the pure product efficiently and in high yield. As far as the subsequent glycosylation, degradation occurred similarly in the presence of Lewis acid. Converting 9-ketone to 9-*E*-oxime overcame these drawbacks and the reactions became tractable with highly improved yield.

Acceptor **9** was synthesized by using clarithromycin as a starting material. The C-9 ketone was converted to the oxime group in the presence of hydroxylamine hydrochloride and sodium acetate at 80 °C (90% yield). Following that, the cladinose sugar was hydrolyzed by treating compound **1** with 2 N HCl in water at room temperature to give compound **2** in a yield of 76%. Selective acetylation of 2′- and 9-*E*-oxime hydroxyl, and formation of 11,12-carbonate provided compound **4** (90% yield) [15]. Afterward, Swern oxidation of 3-OH and deprotection of 9,2′-acetate in methanol gave compound **6** (64% yield for 2 steps). Then 9-*E*-oxime hydroxyl was benzoylated selectively at −20 °C with equivalent mole of benzoyl chloride and triethylamine to give compound **7** (78% yield). Ultimately oxidation of 2′-hydroxyl to 2′-ketone gave the unstable intermediate **8**, which was stirred in methanol at 50 °C to remove the desosamine (67% yield for 2 steps) [16]. The structure of acceptor **9** was confirmed by its ^{1}H NMR, ^{13}C NMR and HRMS spectra (Scheme 1).

With the acceptor **9** in hand, we proceeded to synthesize the donor **13**. It was synthesized from compound **10**, the synthetic method of which was reported in our previous work [8]. Treatment of **10** with acetic anhydride, acetic acid and sulfuric acid (1:1:0.5) yielded the 1,4-diacetyl compound **11**, as a mixture of anomers [17]. Then the 1-acetyl was removed selectively by hydrazine acetate in DMF to form compound **12** (55% yield for 2 steps). And donor **13** can be obtained smoothly by the reaction of **12** with trichloroacetonitrile, catalyzed by 1,8-diazabicyclo [5.4.0] undec-7-ene (DBU) (Scheme 2).

Then the donor **13** and acceptor **9** were coupled using TMSOTf as a promoter to produce compound **14** (62% yield) (Scheme 3). The neighboring group participation effect of 2-*O*-benzoyl in the donor **13** determined the product was of β-configuration (H-1′: $J = 7.8$ Hz; C-1′: 100.9 ppm). It is noteworthy that usually only catalytic amount of promoter is needed in the glycosidation of trichloroacetimidate donor [18]. However, in our glycosidation reaction, the promoter TMSOTf was used in slight excess (1.1 equiv) to glycosyl acceptor **9**. That is because the dimethylamino group in the donor acts as an acid-capturer, lowering the reactivity of the Lewis acid TMSOTf. Despite trichloroacetimidate donor **13** was unstable in the presence of excess TMSOTf, we obtained the desired product efficiently by keeping the reaction system anhydrous carefully.

Following that, the 9-*E*-oxime benzoate and the 4′-acetate were selectively removed by treating compound **14** with 2 N HCl in ethanol at 65 °C for 6 h to afford **15a** [19]. Deprotection of the 2′-OH from **15a** gave compound **15b**. Finally, 4′- and 9-*E*-oxime carbamate derivatives **16a**–**e** were produced from **15a** by reacting with a series of isocyanates. The structures were confirmed by their ^{1}H NMR, ^{13}C NMR and HRMS spectra. And unmasking of the 2′-hydroxyl via methanolysis gave the target compounds. This deprotection process lasted from 12 h to 48 h, and the reactions were monitored by TLC from time to time. When the reaction starting material disappeared, compounds **16a**, **16b**, **16c** and **16d** turned into compounds **17a**, **17b**, **17c** and **18d** respectively. Methanolysis of **16e** gave two products, which were isolated and confirmed to be compounds **17e** and **18e**. We judged that 9-*E*-oxime carbamate in **18d**, **18e** was also cleaved according to their ^{1}H NMR and HRMS spectra. In compound **18d** the ^{1}H NMR signals for 4′-H shifted downfield to

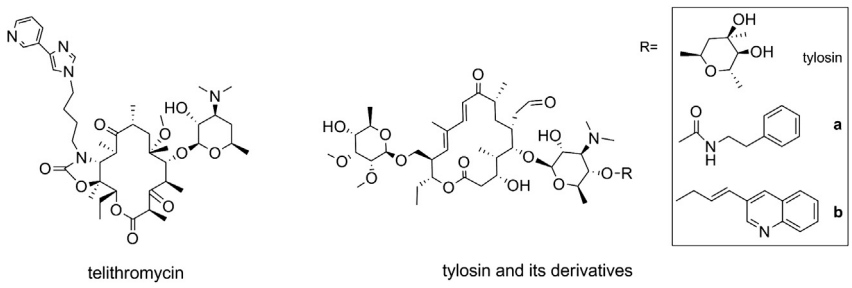
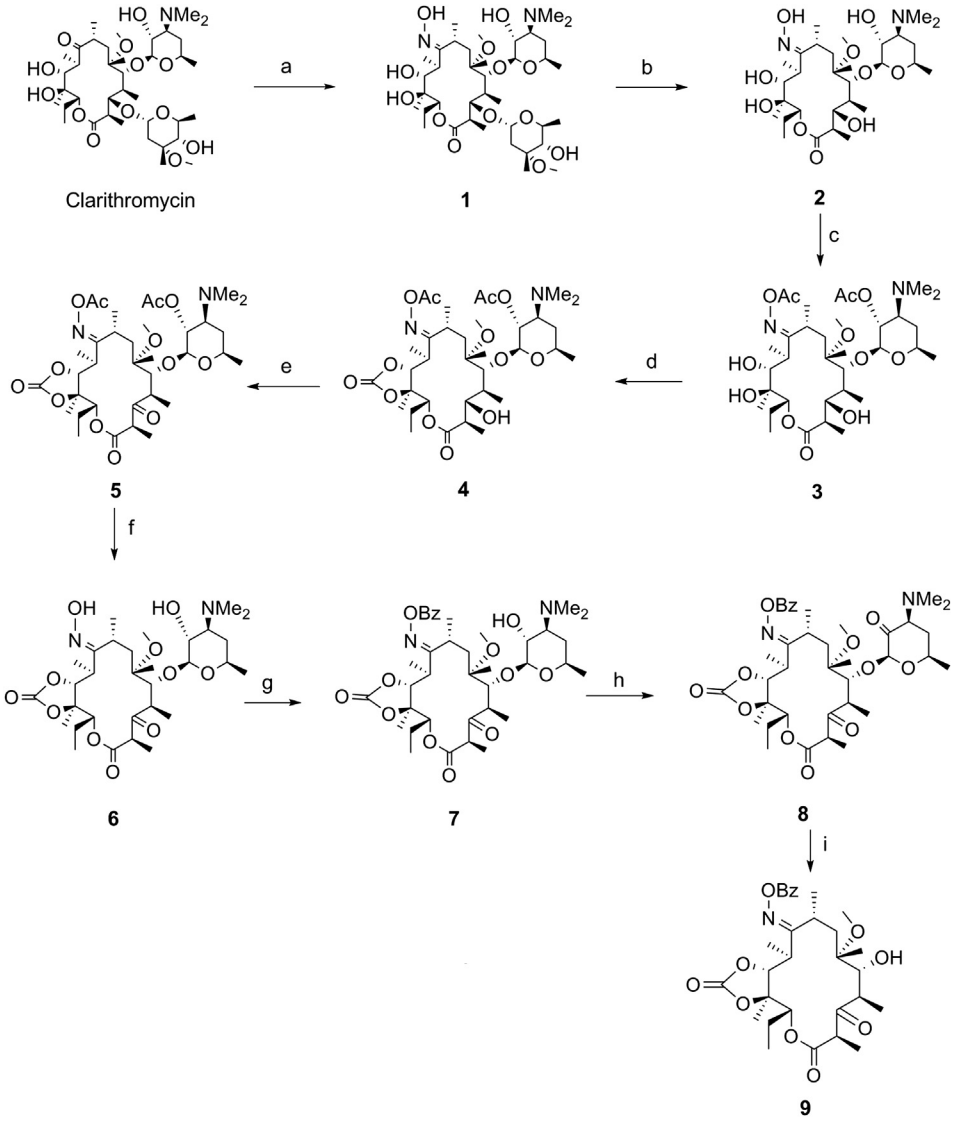


Fig. 1. Structures of telithromycin and tylosin.



Scheme 1. Reagents and conditions: a) $NaOAc, NH_2OH·HCl$, 80 °C, 90%; b) 2 N HCl/H_2O, 76%; c) Ac_2O, Et_3N, 85%; d) $ClCOOCCl_3$, pyridine, 90%; e) $(COCl)_2$, DMSO, Et_3N, 73%; f) MeOH, 50 °C, 88%; g) BzCl, Et_3N, −20 °C, 78%; h) $(COCl)_2$, DMSO, Et_3N; i) MeOH, 50 °C, 67% for 2 steps.

4.85 ppm, similarly in compound **18e** the ^1H NMR signals for 4′-H shifted downfield to 5.12 ppm. It proved that the 4′-carbamate side chain still remained while the 9-*E*-oxime carbamate was removed. The reaction results implied that 9-*E*-oxime alkylcarbamate was more stable than the arylcarbamate in the methanolysis process.

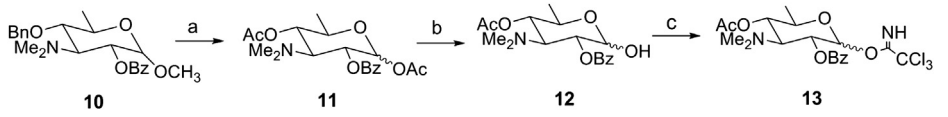
3. Pharmacology

The antibacterial activities of the target compounds were assessed against some respiratory pathogens, including macrolide drug sensitive and resistant strains. Telithromycin and clarithromycin were chosen as the reference compounds. The *in vitro* antibacterial activity was reported as minimum inhibitory concentration (MIC), which was determined by the broth microdilution method as recommended by the CLSI [20].

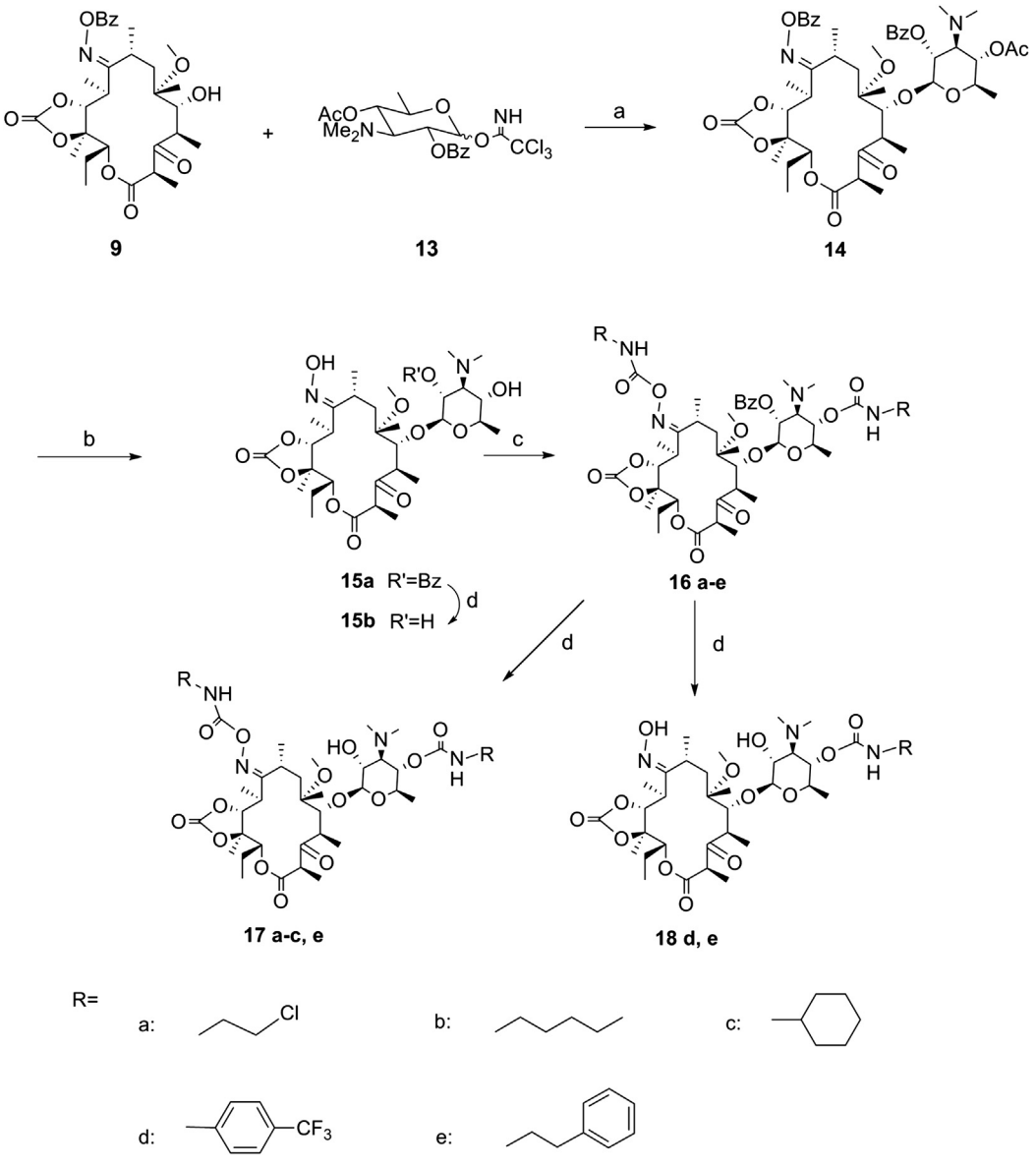
ATCC 29213, 15 and 09-06 are methicillin-sensitive *Staphylococcus aureus* (MSSA). ATCC 33591 and 09-13 are methicillin-resistant *S. aureus* (MRSA). ATCC 12228 and 09-9 are methicillin-sensitive *Staphylococcus epidermidis* (MSSE). 09-3 is a methicillin-resistant *S. epidermidis* (MRSE).

4. Results and discussion

MIC values for the target compounds are presented in Table 1. Compounds **15b** and **18e** displayed approximately equivalent antibacterial activity to the references, although they all showed no



Scheme 2. Reagents and conditions: a) $Ac_2O/AcOH/H_2SO_4$ (1:1:0.5), rt; b) $H_2NNH_2·AcOH$, DMF, 55% for 2 steps; c) CCl_3CN, DBU, 78%.



Scheme 3. Reagents and conditions: a) TMSOTf, 4Å MS, rt, 62%; b) 2 N HCl, C_2H_5OH, 65 °C, 82%; c) RNCO, Et_3N, dichloromethane, 88–93%; d) MeOH, 50 °C, 76–90%.

activity to the resistant pathogens. As the most effective sample, compound **18e** was especially potent against *S. aureus* 15 and *S. epidermidis* 09-9. **18e** contains 4′-*O*-phenethylcarbamate and the result was similar to Ly T. Phan's report about 4′-modified 16-membered macrolides [13].

15b bears 4′-OH, and the result was consistent with the reported similar ketolide [7]. Compared with **18e**, introduction of 9-*E*-oxime phenethylcarbamate in **17e** resulted in the loss of activity. It verified the view that bulky groups at the 9-*E*-oxime might weaken the interaction of 11-*O* and 12-*O* with the corresponding ribosomal binding site, thus reduced the activities [21]. Compound **18d**, analogous to **18e**, contains 4′-*O*-(4-trifluoromethylphenyl) carbamate, whereas it displayed no activity. The result suggests there are certain requirements for the length of the C-4′ side chain. It seems inappropriate to introduce alkyl groups to the C-4′ position since **17a**, **17b**, **17c** were inactive. No interactions between the alkyl groups and the ribosomal binding site should explain this.

In summary, we presumed that the C-4′ elongated arylalkyl side chain with proper length might reach into the peptidyl transferase center (PTC) in the exit tunnel and interfere more directly with peptide bond formation, as the mycaminose-mycarose disaccharide at the C-5 position in 16-membered macrolides.

5. Conclusion

In conclusion, we constructed a method of introducing a side chain to the C-4′ position of 5-*O*-desosamine in the 14-membered ketolides, and several novel 14-membered ketolides bearing 5-*O*-4′-carbamate mycaminose were synthesized. Compound **15b** showed weak activity and **18e** retained potential antibacterial activity, especially against *S. aureus*15 and *S. epidermidis* 09-9. We presumed that the C-4′ elongated side chain might reach into the peptidyl transferase center (PTC) in the exit tunnel and inhibit peptide bond formation. From the antibacterial profile we reasoned the structure–activity relationships which were helpful for better understanding of the mechanism of the macrolide-ribosome interaction. Further modification on the C-4′ position of 14-membered macrolides is ongoing.

Table 1
In vitro antibacterial activities of the target compounds.

Compound	MIC (μg/mL)							
	S. aureus					*S. epidermidis*		
	ATCC 29213	ATCC 33591	15	09-6	09-13	ATCC 12228	09-3	09-9
	MSSA	*MRSA*	*MSSA*	*MSSA*	*MRSA*	*MSSE*	*MRSE*	*MSSE*
CLA[a]	0.06	>64	0.5	0.06	>64	0.06	>64	4
TEL[b]	0.5	>32	2	0.5	>32	0.06	32	0.06
15b	2	>64	>64	2	>64	2	>64	2
17a	>32	>32	>32	>32	>32	>32	>32	>32
17b	>64	>64	>64	>64	>64	>64	>64	>64
17c	32	>32	>32	>32	>32	32	>32	>32
17e	>32	>32	>32	>32	>32	>32	>32	>32
18d	>32	>32	>32	>32	>32	32	>32	>32
18e	1	>32	1	1	>32	0.5	>32	2

[a] CLA: clarithromycin.
[b] TEL: telithromycin.

6. Experimental

All solvents and reagents were obtained from commercial sources and used without further purification unless otherwise noted. All NMR spectra were recorded on Mercury-300, 400, 500 or 600 MHz spectrometers in $CDCl_3$. The chemical shifts were reported in parts per million (ppm) with tetramethylsilane (TMS) as an internal standard. HRMS experiments were performed using an Agilent 1100 series LC/MSD TOF. Analytical thin layer chromatography (TLC) was carried out on TLC plates silica gel HSGF254 percolated by Branch of Qingdao Haiyang Chemical Plant. Chromatography was performed with silica gel H (HG/T2354-92).

All the strains chosen in the antibacterial activity test were supplied by Institute of Medicinal Biotechnology, Academy of Medical Sciences & Peking Union Medical College.

6.1. (E)-2′-O-Acetyl-3-O-descladinosyl-3-oxo-6-O-methyl-erythromycin A 9-O-(acetyl)oxime 11,12-cyclic-carbonate (**5**)

A solution of oxalyl chloride (23.4 mL, 245.3 mmol) in 300 mL CH_2Cl_2 under argon was cooled to −70 °C. Dimethylsulfoxide (25.8 mL, 364.5 mmol) in CH_2Cl_2 (100 mL) was added dropwise. After stirring for 20 min, compound **4** (50.0 g, 70.1 mmol) dissolved in 80 mL CH_2Cl_2 was injected in. The reaction solution was warmed up to −60 °C and kept stirring for 4.5 h. Then triethylamine (85 mL, 616.9 mmol) was added in and stirred for additional 2 h at rt. The solution was washed with $NaHCO_3$, brine, dried over Na_2SO_4. The concentrate was purified by column chromatography (30:1 CH_2Cl_2/MeOH) to give compound **5** (36.4 g, 51.1 mmol, 73%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.06 (d, J = 8.1 Hz, 1H, H-13), 4.78 (s, 1H, H-11), 4.73 (m, 1H, H-2′), 4.38 (d, J = 7.5 Hz, 1H, H-1′), 4.19 (d, J = 7.5 Hz, 1H, H-5), 3.81 (q, J = 6.6 Hz, 1H, H-2), 3.56 (m, 2H, H-8, H-5′), 2.66 (s, 3H, 6-OCH_3), 2.27 (s, 9H, 9-NOAc, 3′-NMe_2), 2.06 (s, 3H, 2′-OAc), 1.57 (s, 3H), 0.88 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.8, 172.2, 169.6, 169.0, 153.8, 101.3, 82.0, 78.3, 77.6, 76.5, 71.5, 69.1, 63.4, 53.3, 51.0, 49.7, 46.9, 40.6, 38.0, 30.4, 27.8, 22.4, 21.3, 20.9, 20.2, 19.7, 18.6, 15.3, 15.1, 14.1, 13.2, 10.3; HRMS (ESI) $[M + H]^+$ m/z 713.3892, calcd for $C_{35}H_{57}N_2O_{13}$ 713.3860.

6.2. (E)-3-O-Descladinosyl-3-oxo-6-O-methyl-erythromycin A 9-oxime 11,12-cyclic-carbonate (**6**)

Compound **5** (36.4 g, 51.1 mmol) dissolved in 300 mL methanol was stirred at 50 °C overnight. The solvent was evaporated off and the residue was purified by column chromatography on silica gel (40:1 CH_2Cl_2/MeOH) to yield compound **6** (28.2 g, 44.9 mmol, 88%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.01 (d, J = 8.1 Hz, 1H, H-13), 4.76 (s, 1H, H-11), 4.27 (d, J = 6.9 Hz, 1H, H-1′), 4.17 (d, J = 8.7 Hz, 1H), 3.79 (m, 2H), 3.52 (m, 2H), 3.19 (m, 1H), 2.98 (m, 1H), 2.64 (s, 3H, 6-OCH_3), 2.28 (s, 6H, $N(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.7, 169.0, 164.8, 153.9, 103.6, 84.4, 82.9, 79.4, 78.3, 76.1, 72.3, 70.3, 69.2, 65.8, 61.6, 50.9, 49.7, 47.7, 40.2, 38.2, 28.4, 25.2, 22.2, 21.0, 19.6, 18.6, 15.7, 15.3, 14.1, 13.0, 10.2; HRMS (ESI) $[M + H]^+$ m/z 629.3640, calcd for $C_{31}H_{53}N_2O_{11}$ 629.3571.

6.3. (E)-3-O-Descladinosyl-3-oxo-6-O-methyl-erythromycin A 9-O-(benzoyl)oxime 11,12-cyclic-carbonate (**7**)

To a cooled to −20 °C solution of compound **6** (28.2 g, 44.9 mmol) in CH_2Cl_2 (300 mL) was added triethylamine (6.3 mL, 44.9 mmol), and then benzoyl chloride (5.8 mL, 49.4 mmol) dropwise. The solution was stirred for 5 h, and then washed with $NaHCO_3$, saturated brine, dried over Na_2SO_4. Purified by column chromatography on silica gel (20:1 CH_2Cl_2/MeOH) to afford compound **7** (25.6 g, 35.0 mmol, 78%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (d, J = 7.5 Hz, 2H), 7.55 (t, J = 7.2 Hz, 1H), 7.44 (t, J = 7.5 Hz, 2H), 5.06 (dd, J = 9.6, 2.4 Hz, 1H, H-13), 4.85 (s, 1H, H-11), 4.77 (br s, 1H), 4.31 (d, J = 7.2 Hz, 1H, H-1′), 4.22 (d, J = 7.5 Hz, 1H), 3.82 (m, 1H), 3.53 (m, 2H), 3.22 (m, 1H), 3.04 (m, 1H), 2.72 (s, 3H, 6-OCH_3), 2.34 (s, 6H, $N(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.9, 175.3, 169.0, 163.5, 153.6, 133.0, 129.4, 128.4, 127.7, 103.3, 78.5, 78.1, 76.4, 70.0, 69.1, 65.9, 51.0, 49.9, 47.3, 39.9, 38.4, 28.5, 22.4, 21.0, 19.7, 18.5, 15.4, 15.2, 14.2, 13.2, 10.2; HRMS (ESI) $[M + H]^+$ m/z 733.3835, calcd for $C_{38}H_{57}N_2O_{12}$ 733.3833.

6.4. (E)-5-Hydroxyl-3-oxo-6-O-methyl-erythronolide A 9-O-(benzoyl)oxime 11,12-cyclic-carbonate (**9**)

Compound **7** (25.6 g, 35.0 mmol) was oxidized firstly following the procedure for compound **5**. The obtained crude product **8** was refluxed in methanol at 50 °C for 8 h. The residue was purified by column chromatography on silica gel (20:30:1 petroleum ether/$CHCl_3$/MeOH) to yield compound **9** (13.5 g, 23.4 mmol, 67% for 2 steps).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (d, J = 6.9 Hz, 2H), 7.56 (t, J = 7.5 Hz, 1H), 7.44 (t, J = 7.5 Hz, 2H), 5.01 (dd, J = 9.6, 2.7 Hz, 1H, H-13), 4.81 (s, 1H, H-11), 4.11 (d, J = 8.7 Hz, 1H), 3.78 (m, 1H), 2.72 (s, 3H, 6-OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.9, 175.1, 168.7, 163.6, 153.6, 133.1, 129.3, 129.0, 128.5, 78.6, 76.3, 74.0, 51.4, 49.9, 47.1, 37.4, 28.7, 22.4, 19.9, 18.9, 16.3, 15.3, 14.3, 13.3, 10.3; HRMS (ESI) $[M + H]^+$ m/z 576.2756, calcd for $C_{30}H_{42}NO_{10}$ 576.2730.

6.5. 1,4-O-Acetyl-2-O-Benzoyl-3,6-dideoxy-3-dimethylamino-D-glucopyranose (**11**)

Compound **10** (3.0 g, 7.5 mmol) was treated with a mixture of acetic anhydride, acetic acid and sulfuric acid (1:1:0.5; 15 ml) and stirred at room temperature for 2 days. The reaction mixture was neutralized with saturated $NaHCO_3$ and extracted with CH_2Cl_2. The organic phase was washed with saturated brine, dried over Na_2SO_4. The filtrate was concentrated in vacuum to give the crude product **11** for the next step.

6.6. 4-O-Acetyl-2-O-benzoyl-3,6-dideoxy-3-dimethylamino-D-glucopyranose (**12**)

To a solution of the crude product **11** in dimethyl formamide (20 mL) was added hydrazine acetate (2.5 g, 27.8 mmol). The solution was stirred for 4 h at room temperature. Then the reaction mixture was diluted with ethyl acetate and washed with water, saturated brine, dried over Na_2SO_4. The crude mixture was purified by column chromatography on silica gel (8:1 petroleum ether/ethyl acetate) to yield compound **12** (1.4 g, 4.1 mmol, 55% for 2 steps).

(α-Configuration) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, J = 7.6 Hz, 2H, Bz), 7.58 (m, 1H, Bz), 7.46 (m, 2H, Bz), 5.45 (d, J = 3.6 Hz, 1H, H-1), 5.19 (dd, J = 10.8, 3.6 Hz, 1H, H-2), 4.77 (t, J = 10.0 Hz, 1H, H-4), 4.14 (m, 1H, H-5), 3.33 (t, J = 10.4 Hz, 1H, H-3), 2.39 (s, 6H, NMe_2), 2.09 (s, 3H, 4-OAc), 1.19 (d, J = 6.4 Hz, 3H, 5-Me); HRMS (ESI) $[M + H]^+$ m/z 338.1595, calcd for $C_{17}H_{24}NO_6$ 338.1525.

6.7. 4-O-Acetyl-2-O-benzoyl-3,6-dideoxy-3-dimethylamino-D-glucopyranosyl trichloroacetimidate (**13**)

To an ice-cold solution **12** (1.39 g, 4.1 mmol) in anhydrous CH_2Cl_2 (30 mL) under argon were added trichloroacetonitrile (2.5 ml, 24.6 mmol) and 1,8-diazabicyclo [5.4.0] undec-7-ene (DBU) (0.2 ml, 1.4 mmol). The mixture then restored up to room temperature and was stirred for 10 h. The reaction mixture was purified by column chromatography on silica gel (deactivated by 15% Et_3N/petroleum ether) (10:1 petroleum ether/ethyl acetate) to yield compound **13** (1.5 g, 3.2 mmol, 78%).

(α-Configuration) ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.48 (s, 1H, C=NH), 8.01 (d, J = 7.5 Hz, 2H, Bz), 7.57 (t, J = 7.5 Hz, 1H, Bz), 7.42 (t, J = 8.1 Hz, 2H, Bz), 6.52 (d, J = 3.6 Hz, 1H, H-1), 5.42 (dd, J = 3.6, 11.1 Hz, 1H, H-2), 4.87 (t, J = 9.9 Hz, 1H, H-4), 4.10 (m, 1H, H-5), 3.38 (t, J = 10.5 Hz, 1H, H-3), 2.39 (s, 6H, NMe_2), 2.10 (s, 3H, 4-OAc), 1.24 (d, J = 9.0 Hz, 3H, 5-Me) HRMS (ESI) $[M + H]^+$ m/z 481.0706, calcd for $C_{19}H_{24}Cl_3N_2O_6$ 481.0622.

6.8. (E)-5-(4-O-Acetyl-2-O-benzoyl-mycaminosyl)-3-O-descladinosyl-6-O-methyl-3-oxo-erythronolide A 9-O-(benzoyl)oxime 11,12-cyclic carbonate (**14**)

A solution of compound **13** (1.3 g, 2.8 mmol) in 20 mL anhydrous CH_2Cl_2 under argon was cooled to −20 °C. Trimethylsilyl trifluoromethanesulfonate (282 μL, 1.53 mmol) was added dropwise. After stirring for 20 min, compound **9** (800 mg, 1.4 mmol) dissolved in 3 mL CH_2Cl_2 was injected in. The mixture solution was warmed up to 20 °C and kept stirring for 20 h. Then triethylamine (214 μL, 1.53 mmol) was added in and stirred for 30 min to quench the reaction. Followed by filtration and purification by column chromatography (8:1 petroleum ether/acetone) to give compound **14** (514 mg, 0.57 mmol, recycled compound **9** 266 mg, 62%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (m, 4H), 7.57 (m, 2H), 7.46 (m, 4H), 5.16 (t, J = 7.8 Hz, 1H, H-2′), 5.05 (d, J = 7.5 Hz, 1H, H-13), 4.86 (s, 1H, H-11), 4.80 (t, J = 9.9, 9.9 Hz, 1H, H-4′), 4.61 (d, J = 7.8 Hz, 1H, H-1′), 4.21 (d, J = 7.2 Hz, 1H, H-5), 3.71 (d, J = 6.9 Hz, 1H), 3.54 (m, 2H), 2.91 (m, 2H), 2.72 (s, 3H, 6-OCH_3), 2.32 (s, 6H, $N(CH_3)_2$), 2.06 (s, 3H, 4′-OAc); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.2, 169.8, 168.9, 168.7, 164.5, 163.5, 153.6, 133.0, 129.6, 129.4, 128.5, 128.3, 100.9, 81.9, 78.0, 76.4, 72.7, 71.4, 71.1, 70.8, 67.3, 63.9, 51.5, 51.0, 50.1, 49.9, 46.5, 43.3, 43.0, 41.4, 38.0, 28.4, 22.5, 21.1, 19.7, 18.8, 17.4, 15.5, 14.8, 14.1, 13.3, 10.2; HRMS (ESI) $[M + H]^+$ m/z 895.4169, calcd for $C_{47}H_{63}N_2O_{15}$ 895.4150.

6.9. (E)-5-(2-O-benzoyl-mycaminosyl)-3-O-descladinosyl-6-O-methyl-3-oxo-erythronolide A 9-oxime 11,12-cyclic carbonate (**15a**)

Compound **14** (514 mg, 0.57 mmol) was treated with 2 N HCl in ethanol at 65 °C for 6 h. Then the solution was cooled and neutralized to pH 8 by $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic phase was washed with $NaHCO_3$ and brine. The residue was purified by column chromatography (8:1 petroleum ether/acetone) to afford compound **15a** (350 mg, 0.47 mmol, 82%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 7.6 Hz, 2H), 7.51 (d, J = 7.6 Hz, 1H), 7.41 (t, J = 7.2 Hz, 2H), 5.23 (t, J = 8.4, 9.6 Hz, 1H, H-2′), 4.93 (d, J = 10.0 Hz, 1H, H-13), 4.70 (s, 1H, H-11), 4.52 (d, J = 7.2 Hz, 1H, H-1′), 4.00 (d, J = 7.6 Hz, 1H, H-5), 3.71 (br s, 1H), 3.59 (dd, J = 6.4, 12.4 Hz, 1H), 3.36 (m, 1H), 3.05 (m, 1H), 2.81 (m, 1H), 2.69 (m, 1H), 2.64 (s, 3H, 6-OCH_3), 2.37 (s, 6H, $N(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.8, 168.9, 165.2, 164.5, 153.9, 133.3, 130.8, 129.8, 128.8, 101.3, 84.4, 82.9, 78.2, 76.3, 73.0, 70.7, 70.4, 69.6, 68.1, 65.5, 50.9, 49.7, 47.0, 41.3, 37.8, 32.7, 30.5, 25.1, 22.3, 19.7, 19.1, 18.5, 18.0, 15.2, 14.0, 13.7, 13.0, 10.2; HRMS (ESI) $[M + H]^+$ m/z 749.3848, calcd for $C_{38}H_{57}N_2O_{13}$ 749.3782.

6.10. General methods for compounds **16a–e**

To a solution of the reactant in anhydrous CH_2Cl_2 under argon were added triethylamine (2.3 equiv) and the corresponding isocyanate (2.3 equiv). The solution was stirred at room temperature for 3 h, then quenched with water. Afterward, the mixture solution was diluted with CH_2Cl_2 and washed with H_2O, saturated brine, dried over Na_2SO_4. The residue was purified by column chromatography on silica gel (8:1 petroleum ether/acetone) to afford the desired products (88–93%).

6.10.1. (E)-5-(2-O-Benzoyl-4-O-(2-chloroethyl)carbamoyl-mycaminosyl)-3-O-descladinosyl-6-O-methyl-3-oxo-erythronolide A 9-O-((2-chloroethyl)carbamoyl)oxime 11,12-cyclic carbonate (**16a**)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (d, J = 6.9 Hz, 2H), 7.66 (m, 1H), 7.51 (m, 2H), 5.07 (t, J = 9.6 Hz, 1H, H-2′), 4.98 (d, J = 10.5 Hz, 1H, H-13), 4.67 (s, 1H, H-11), 4.60 (d, J = 9.6 Hz, 1H, H-4′), 4.52 (d, J = 7.5 Hz, 1H, H-1′), 4.12 (d, J = 6.9 Hz, 1H), 3.69 (m, 1H), 3.67 (m, 1H), 3.48 (m, 3H), 2.27 (m, 2H), 2.60 (s, 3H, 6-OCH_3), 2.28 (s, 6H, $N(CH_3)_2$); HRMS (ESI) $[M + H]^+$ m/z 959.3690, calcd for $C_{44}H_{65}Cl_2N_4O_{15}$ 959.3745.

6.10.2. (E)-5-(2-O-Benzoyl-4-O-pentylcarbamoyl-mycaminosyl)-3-O-descladinosyl-6-O-methyl-3-oxo-erythronolide A 9-O-(pentylcarbamoyl)oxime 11,12-cyclic carbonate (**16b**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 7.2 Hz, 2H), 7.71 (m, 1H), 7.52 (m, 2H), 5.15 (t, J = 8.0, 9.6 Hz, 1H, H-2′), 5.02 (d, J = 10.4 Hz, 1H, H-13), 4.73 (s, 1H, H-11), 4.67 (m, 1H, H-4′), 4.57 (d, J = 7.6 Hz, 1H, H-1′), 4.18 (d, J = = 7.2 Hz, 1H), 3.78 (m, 1H), 3.71 (m, 1H), 3.22 (m, 3H), 2.86 (m, 2H), 2.63 (s, 3H, 6-OCH_3), 2.52 (m, 1H), 2.34 (s, 6H, $N(CH_3)_2$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 202.9, 168.9, 168.1, 166.7, 163.6, 154.5, 154.1, 152.7, 131.2, 129.9, 128.8, 127.8, 127.5, 99.9, 83.3, 81.5, 77.2, 75.4, 70.5, 64.5, 49.8, 48.6, 45.6, 40.2, 40.0, 36.9, 32.4, 29.5, 28.6, 28.5, 28.2, 27.7, 26.5, 21.2, 19.0, 18.1, 17.2, 16.2, 14.5, 13.9, 13.1, 12.9, 12.7, 12.0, 9.2; HRMS (ESI) $[M + H]^+$ m/z 975.5470, calcd for $C_{50}H_{79}N_4O_{15}$ 975.5464.

*6.10.3. (E)-5-(2-O-Benzoyl-4-O-cyclohexylcarbamoyl-mycaminosyl)-3-O-descladinosyl-6-O-methyl-3-oxo-erythronolide A 9-O-(cyclohexylcarbamoyl)oxime 11,12-cyclic carbonate (**16c**)*

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (d, J = 8.5 Hz, 2H), 7.56 (m, 1H), 7.42 (m, 2H), 5.12 (t, J = 9.0 Hz, 1H, H-2′), 5.04 (d, J = 10.5 Hz, 1H, H-13), 4.74 (s, 1H, H-11), 4.69 (t, J = 10.0 Hz, 1H, H-4′), 4.58 (d, 1H, H-1′), 4.17 (d, J = 7.0 Hz, 1H), 3.76 (m, 1H), 3.72 (m, 1H), 3.68 (m, 1H), 3.48 (m, 2H), 2.85 (m, 2H), 2.63 (s, 3H, 6-OCH_3), 2.39 (s, 6H, $N(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.9, 169.7, 169.2, 167.7, 164.7, 154.8, 153.7, 132.9, 132.3, 130.3, 129.7, 128.3, 101.3, 84.3, 82.5, 78.3, 76.7, 76.3, 71.6, 71.0, 67.7, 65.5, 50.8, 49.6, 46.8, 41.3, 38.0, 33.5, 32.8, 32.6, 30.5, 29.7, 27.5, 25.4, 24.8, 24.3, 22.1, 20.0, 19.1, 18.2, 17.3, 15.6, 14.9, 14.2, 13.7, 12.9, 10.1; HRMS (ESI) $[M + H]^+$ m/z 999.5598, calcd for $C_{52}H_{79}N_4O_{15}$ 999.5464.

*6.10.4. (E)-5-(2-O-Benzoyl-4-O-(4-trifluoromethylphenyl) carbamoyl-mycaminosyl)-3-O-descladinosyl-6-O-methyl-3-oxo-erythronolide A 9-O-((4-trifluoromethylphenyl)carbamoyl)oxime 11,12-cyclic carbonate (**16d**)*

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J = 7.2 Hz, 2H), 7.70 (d, J = 8.4 Hz, 2H), 7.56 (m, 6H), 7.45 (t, J = 7.6 Hz, 2H), 7.26 (s, 1H), 5.25 (t, J = = 8.4, 9.2 Hz, 1H, H-2′), 5.06 (d, J = 10.0 Hz, 1H, H-13), 4.82 (s, 1H, H-11), 4.76 (t, J = 9.6, 9.6 Hz, 1H, H-4′), 4.63 (d, J = 7.6 Hz, 1H, H-1′), 4.21 (d, J = 6.4 Hz, 1H), 3.78 (br s, 1H), 3.72 (m, 1H), 3.58 (m, 1H), 3.04 (m, 1H), 2.95 (m, 1H), 2.87 (m, 1H), 2.65 (s, 3H, 6-OCH_3), 2.37 (s, 6H, $N(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.1, 171.0, 169.2, 167.7, 164.6, 153.6, 151.9, 140.8, 140.3, 133.1, 132.3, 130.8, 130.0, 129.7, 128.8, 128.4, 126.3, 118.7, 118.2, 101.1, 84.6, 82.4, 78.2, 77.7, 76.4, 72.9, 71.2, 70.8, 67.6, 65.5, 51.1, 50.8, 49.7, 46.6, 41.4, 38.0, 30.5, 27.9, 22.1, 19.9, 19.1, 18.2, 17.5, 15.7, 14.7, 14.2, 13.7, 12.9, 10.2; HRMS (ESI) $[M + H]^+$ m/z 1123.4310, calcd for $C_{54}H_{65}F_6N_4O_{15}$ 1123.4272.

*6.10.5. (E)-5-(2-O-Benzoyl-4-O-phenethylcarbamoyl-mycaminosyl)-3-O-descladinosyl-6-O-methyl-3-oxo-erythronolide A 9-O-(phenethylcarbamoyl)oxime 11,12-cyclic carbonate (**16e**)*

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (d, J = 7.0 Hz, 2H), 7.56 (m, 1H), 7.43 (m, 2H), 7.27 (m, 4H), 7.17 (m, 6H), 5.19 (m, 1H, H-2′), 4.99 (d, J = 10.5 Hz, 1H, H-13), 4.77 (m, 1H, H-4′), 4.73 (s, 1H, H-11), 4.65 (d, J = 7.6 Hz, 1H, H-1′), 4.16 (d, J = 7.0 Hz, 1H), 3.78 (m, 2H), 3.69 (m, 1H), 3.52 (m, 4H), 2.87 (m, 5H), 2.53(s, 3H, 6-OCH_3), 2.37 (s, 6H, $N(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.9, 178.2, 176.5, 170.1, 169.0, 164.6, 155.5, 155.0, 153.7, 138.6, 138.4, 130.0, 129.7, 128.7, 128.5, 128.4, 126.4, 126.3, 99.9, 84.3, 83.7, 82.5, 78.1, 77.3, 76.7, 76.5, 71.5, 71.3, 50.8, 49.7, 46.6, 42.2, 38.0, 35.6, 33.4, 29.6, 27.6, 22.6, 22.3, 20.0, 18.2, 17.2, 15.4, 14.8, 14.1, 13.0, 10.3; HRMS (ESI) $[M + H]^+$ m/z 1043.5309, calcd for $C_{56}H_{75}N_4O_{15}$ 1043.5151.

*6.11. General methods for compounds **15b**, **17a**–**c**,**e**, **18d**,**e***

The corresponding reactant was dissolved in methanol and refluxed at 50 °C for 12–48 h. After column chromatography (5:1 petroleum ether/acetone), the desired product was obtained (76–90%).

*6.11.1. (E)-5-(4-O-(2-Chloroethyl)carbamoyl-mycaminosyl)-3-O-descladinosyl-6-O-methyl-3-oxo-erythronolide A 9-O-((2-chloroethyl)carbamoyl)oxime 11,12-cyclic carbonate (**17a**)*

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.07 (d, J = 7.8 Hz, 1H, H-13), 4.84 (t, J = 9.6 Hz, 1H, H-4′), 4.78 (s, 1H, H-11), 4.46 (d, J = 7.8 Hz, 1H, H-1′), 4.19 (d, J = 7.2 Hz, 1H), 3.85 (m, 1H), 3.78 (m, 2H), 3.51 (m, 3H), 2.88 (s, 3H, 6-OCH_3), 2.65 (s, 6H, $N(CH_3)_2$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 204.2, 170.8, 169.2, 167.7, 155.6, 154.2, 153.7, 101.8, 84.5, 82.4, 79.2, 78.1, 73.4, 70.4, 68.1, 65.5, 53.4, 49.7, 47.1, 43.6, 42.9, 42.7, 38.7, 37.3, 33.6, 31.9, 29.8, 27.0, 23.1, 22.6, 20.1, 18.5, 16.8, 15.6, 14.1, 13.7, 10.2; HRMS (ESI) $[M + H]^+$ m/z 855.3428, calcd for $C_{37}H_{61}Cl_2N_4O_{14}$ 855.3483.

*6.11.2. (E)-5-(4-O-Pentylcarbamoyl-mycaminosyl)-3-O-descladinosyl-6-O-methyl-3-oxo-erythronolide A 9-O-(pentylcarbamoyl) oxime 11,12-cyclic carbonate (**17b**)*

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.06 (d, J = 10.2 Hz, 1H, H-13), 4.76 (s, 1H, H-11), 4.75 (m, 1H, H-4′), 4.71 (br s, 1H), 4.36 (d, J = 7.2 Hz, 1H), 4.19 (d, J = 7.8 Hz, 1H), 3.85 (m, 1H), 3.39 (m, 1H), 3.23 (m, 3H), 2.99 (m, 1H), 2.63 (s, 3H, 6-OCH_3), 2.51 (s, 6H, $N(CH_3)_2$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 203.8, 170.0, 169.2, 155.6, 154.7, 153.8, 102.8, 84.4, 82.5, 79.4, 78.2, 76.3, 71.6, 71.3, 69.2, 50.9, 49.7, 47.4, 41.1, 41.0, 38.4, 33.4, 29.6, 29.2, 28.8, 27.6, 22.6, 22.2, 20.0, 18.3, 17.0, 15.6, 15.3, 14.2, 13.9, 13.0, 10.2; HRMS (ESI) $[M + H]^+$ m/z 871.5149, calcd for $C_{43}H_{75}N_4O_{14}$ 871.5202.

*6.11.3. (E)-5-(4-O-Cyclohexylcarbamoyl-mycaminosyl)-3-O-descladinosyl-6-O-methyl-3-oxo-erythronolide A 9-O-(cyclohexylcarbamoyl)oxime 11,12-cyclic carbonate (**17c**)*

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.08 (d, J = 10.8 Hz, 1H, H-13), 4.77 (s, 1H, H-11), 4.75 (t, J = 8.4 Hz, 1H, H-4′), 4.39 (d, J = 7.2 Hz, 1H, H-1′), 4.18 (d, J = 7.8 Hz, 1H), 3.84 (m, 1H), 3.77 (m, 1H), 3.61 (m, 1H), 3.43 (m, 3H), 2.99 (m, 2H), 2.65 (s, 3H, 6-OCH_3), 2.63 (s, 6H, $N(CH_3)_2$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 203.9, 169.7, 169.3, 154.8, 153.7, 102.5, 84.4, 82.5, 79.3, 78.2, 76.7, 76.3, 71.2, 70.6, 69.1, 50.9, 50.3, 49.7, 49.5, 47.3, 38.3, 33.5, 33.2, 32.8, 32.6, 29.6, 27.6, 25.3, 24.7, 24.3, 22.1, 20.0, 18.2, 16.9, 15.6, 15.3, 14.2, 13.0, 10.2; HRMS (ESI) $[M + H]^+$ m/z 895.5200, calcd for $C_{45}H_{75}N_4O_{14}$ 895.5202.

*6.11.4. (E)-5-(4-O-(4-Trifluoromethylphenyl)carbamoyl-mycaminosyl)-3-O-descladinosyl-6-O-methyl-3-oxo-erythronolide A 9-oxime 11,12-cyclic carbonate (**18d**)*

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, J = 8.5 Hz, 2H), 7.53 (m, 2H), 5.05 (d, J = 8.0 Hz, 1H, H-13), 4.85 (m, 1H, H-4′), 4.80 (s, 1H, H-11), 4.42 (d, J = 7.5 Hz, 1H, H-1′), 4.30 (t, J = 6.5 Hz, 1H), 4.19 (d, 1H), 3.84 (m, 1H), 3.50 (m, 1H), 3.39 (m, 1H), 3.06 (m, 1H), 2.70 (s, 3H, 6-OCH_3), 2.52 (s, 6H, $N(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.2, 169.3, 165.7, 154.3, 151.8, 150.0, 140.7, 131.1, 129.0, 127.1, 126.6, 118.5, 103.1, 84.9, 83.2, 80.1, 78.4, 71.7, 69.8, 66.1, 58.7, 51.3, 50.1, 47.8, 41.6, 38.5, 32.1, 29.6, 25.5, 22.9, 22.6, 20.0, 18.9, 17.4, 16.9, 15.9, 14.4, 13.4, 10.5; HRMS (ESI) $[M + H]^+$ m/z 832.3734, calcd for $C_{39}H_{57}F_3N_3O_{13}$ 832.3765.

*6.11.5. (E)-5-(4-O-Phenethylcarbamoyl-mycaminosyl)-3-O-descladinosyl-6-O-methyl-3-oxo-erythronolide A 9-O-(phenethylcarbamoyl)oxime 11,12-cyclic carbonate (**17e**)*

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 (m, 4H), 7.17 (m, 3H), 7.10 (m, 3H), 4.96 (d, J = 10.5 Hz, 1H, H-13), 4.70 (t, J = 10.0 Hz, 1H, H-4′), 4.61 (s, 1H, H-11), 4.35 (d, J = 7.0 Hz, 1H, H-1′), 4.06 (d, J = 7.0 Hz, 1H), 3.77 (m, 1H), 3.67 (m, 1H), 3.50 (m, 2H), 3.42 (m, 2H), 3.34 (m, 1H), 2.80 (s, 3H, 6-OCH_3), 2.72 (m, 2H), 2.47 (s, 6H, $N(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.4, 170.4, 169.4, 155.8, 154.3, 154.0, 138.6, 138.0, 129.0, 128.9, 128.8, 128.4, 127.1, 126.6, 102.0, 84.7, 82.5, 79.6, 78.3, 73.7, 70.5, 70.1, 69.1, 51.1, 49.9, 47.4, 45.9, 42.5, 42.2, 38.5, 36.0, 35.9, 33.7, 32.1, 29.9, 29.6, 27.9, 22.9, 22.5, 20.3, 18.5, 17.0, 15.7, 15.4, 14.4, 13.4, 10.6; HRMS (ESI) $[M + H]^+$ m/z 939.5013, calcd for $C_{49}H_{71}N_4O_{14}$ 939.4889.

*6.11.6. (E)-5-(4-O-Phenethylcarbamoyl-mycaminosyl)-3-O-descladinosyl-6-O-methyl-3-oxo-erythronolide A 9-oxime 11,12-cyclic carbonate (**18e**)*

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (t, J = 7.4 Hz, 1H), 7.25 (m, 2H), 7.22 (m, 2H), 5.12 (m, 1H, H-4′), 5.05 (d, J = 10.0 Hz, 1H, H-13), 4.70 (s, 1H, H-11), 4.38 (d, J = 6.8 Hz, 1H, H-1′), 4.21 (d, J = 6.8 Hz, 1H), 3.82 (m, 1H), 3.75 (m, 1H), 3.58 (m, 3H), 3.38 (m, 2H), 3.31 (m, 1H), 3.07 (m, 1H), 2.89 (s, 3H, 6-OCH_3), 2.59 (s, 6H, $N(CH_3)_2$); ^{13}C NMR

(150 MHz, $CDCl_3$) δ 203.9, 170.3, 169.1, 155.6, 153.6, 138.3, 128.7, 128.6, 126.4, 102.1, 84.4, 82.5, 78.3, 78.1, 76.6, 72.7, 70.2, 51.0, 49.7, 46.8, 42.2, 42.1, 38.3, 35.6, 32.1, 29.2, 27.6, 26.3, 23.4, 22.6, 22.3, 19.8, 18.3, 17.4, 15.5, 15.0, 14.3, 14.1, 13.1, 10.3; HRMS (ESI) $[M + H]^+$ m/z 792.4185, calcd for $C_{40}H_{62}N_3O_{13}$ 792.4204.

*6.11.7. (E)-5-Mycaminosyl-3-O-descladinosyl-6-O-methyl-3-oxo-erythronolide A 9-oxime 11,12-cyclic carbonate (**15b**)*

^1H NMR (500 MHz, $CDCl_3$) δ 5.05 (d, $J = 10.5$ Hz, 1H, H-13), 4.82 (s, 1H, H-11), 4.41 (br s, 1H), 4.30 (t, $J = 7.0$ Hz, 1H), 4.20 (d, $J = 7.5$ Hz, 1H), 3.81 (m, 1H), 3.42 (m, 2H), 2.99 (m, 2H), 2.69 (s, 3H, 6-OCH_3), 2.04 (s, 6H, $N(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.1, 171.4, 167.9, 165.3, 102.0, 79.6, 78.3, 73.9, 72.8, 69.7, 65.8, 60.6, 51.3, 47.3, 38.4, 33.9, 32.1, 30.8, 29.9, 26.9, 25.5, 22.6, 21.2, 19.9, 18.8, 17.6, 15.6, 14.6, 13.9, 13.3, 10.5; HRMS (ESI) $[M + H]^+$ m/z 645.3495, calcd for $C_{31}H_{53}N_2O_{12}$ 645.3520.

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