The Journal of Antibiotics (2011) 64, 333–337

www.nature.com/ja

ORIGINAL ARTICLE

Synthesis and antibacterial activity of 2, 3-dehydro-3-*O*-(3-aryl-*E*-prop-2-enyl)-10, 11-anhydroclarithromycin derivatives

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An allyl group was attached to 3-keto function of ketolides in the presence of allyl bromide and KOtBu. Consequently, the Heck reaction of the resulting 2, 3-dehydro-3-*O*-allyl-10, 11-anhydroclarithromycin derivatives, in the presence of palladium (II) acetate and tri(*o*-tolyl)phosphine, afforded a 3-*O*-(3-aryl-*E*-prop-2-enyl) sidechain, not the previously reported 3-*O*-(3-aryl-*Z*-prop-1-enyl) sidechain. The results suggested that some steric factors in β-hydrogen elimination might regulate the isomerization. The activity of 2, 3-dehydro-3-*O*-(3-aryl-*E*-prop-2-enyl)-10, 11-anhydroclarithromycin derivatives was low.
The Journal of Antibiotics (2011) **64,** 333–337; doi:10.1038/ja.2011.11; published online 2 March 2011

Keywords: allyl; erythromycin; Heck, isomerization; ketolide

INTRODUCTION

Clarithromycin, one of the semi-synthetic analogs of erythromycin A, has good acid stability in the stomach because of the incorporation of 6-OMe blocking the degradation process that involved original 6-OH and 9-keto.[1] Recently, 3-keto derivatives of clarithromycin, termed ketolides, have been developed to combat the growing prevalence of MLS_B resistance.[2] Ketolides, the third-generation erythromycin derivatives, are represented by telithromycin (HMR3647),[3] cethromycin (ABT-773)[4] and TE-802[5] (Figure 1).

The success of ketolides disproved the long held belief that 3-*O*-cladinose was essential moiety for the antibacterial activity. In addition to ketolides, other macrolides with various substituents at C-3 instead of cladinose have also been designed and investigated over the past decade, such as acylide,[6] 3, 6-bicyclolide (Figure 2),[7] 2, 3-anhydrolide,[8] 2, 3-enol ether,[9] 3-deoxy,[10] 3-*O*-phenyl ether,[11] 3, 6-ketal[12] and 3, 6-ether.[13]

In our search for novel erythromycin derivatives, we previously reported some alkylides (Figure 2) with improved activity against erythromycin-resistant pathogens.[14] We speculated alkylides, characterized by 3-*O*-ether bond, might have a profile of higher acid stability and enzyme resistance compared with acylides.[6] More importantly, an allyl group could easily be transformed into other functional groups.[15] For this reason, we synthesized the alkylides to explore their structure-activity relationship. Consequently, we found that Heck isomerization occurred in the presence of palladium (II) acetate and tri(*o*-tolyl)phosphine, which led to a 3-*O*-(3-aryl-*Z*-prop-1-enyl) sidechain,[14] which involved an allylic double-bond isomerization and concomitant configuration isomerization. In this study, we report further modification of the configuration of the linkers at 3-OH, as well as the skeleton of macrolides.

RESULTS AND DISCUSSION

3-*O*-(3-aryl-*E*-prop-2-enyl) clarithromycin derivatives were prepared by a multi-step synthesis, as illustrated in Scheme 1. Starting material 3-OH clarithromycin was produced by the acidic hydrolysis of commercially available clarithromycin.[2] Without the addition of a base such as triethylamine or K_2CO_3, the 2′-acetate **1** (see ref. 2) was smoothly obtained by treatment of 3-OH-clarithromycin with acetic anhydride, as attributed to the catalytic function of neighboring 3′-tertiary amino group. Next, the 11, 12-carbonate **2** was easily obtained by the BTC (bis(trichloromethyl)carbonate) method reported by You.[16]

An initial attempt[14] to convert **2** to the 3-*O*-allyl counterpart failed in the presence of allyl bromide and KOtBu. The major product in the resulting mixture was identified as 10, 11-anhydro-3-OH-6-*O*-methylerythromycin A **3** after methanolysis. In contrast, the 3-keto **4** resulting from the Corey–Kim oxidation[17] of **2**, successfully yielded corresponding the 2, 3-dehydro-3-*O*-allyl analog **5** in the presence of allyl bromide and KOtBu. A similar phenomenon was reported by Denis concerning four-atom-length and five-atom-length alkoxy linkers using NaH as the base.[9]

Meanwhile, the 11, 12-carbonate underwent smooth elimination in the presence of KOtBu and was converted to the 10, 11-olefin. Thus, in addition to previously reported DBU,[16] KOtBu seemed to be effective in decarboxylation, but it is noted that the elimination of the 11,

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Received 9 January 2010; revised 3 October 2011; accepted 25 January 2011; published online 2 March 2011

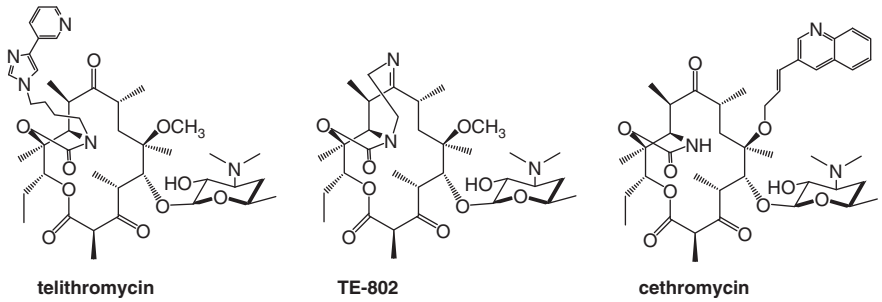


Figure 1 Structure of ketolide.

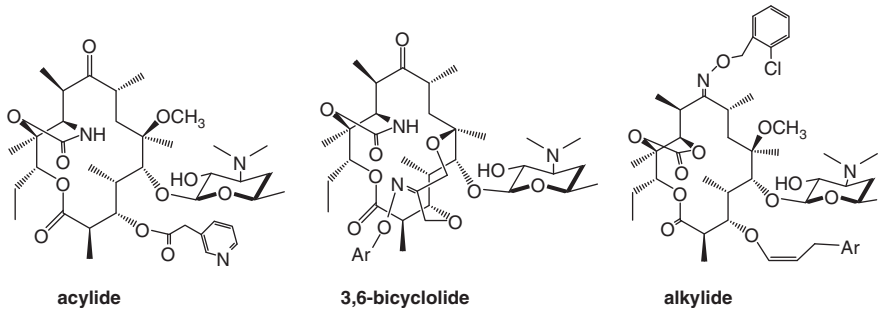
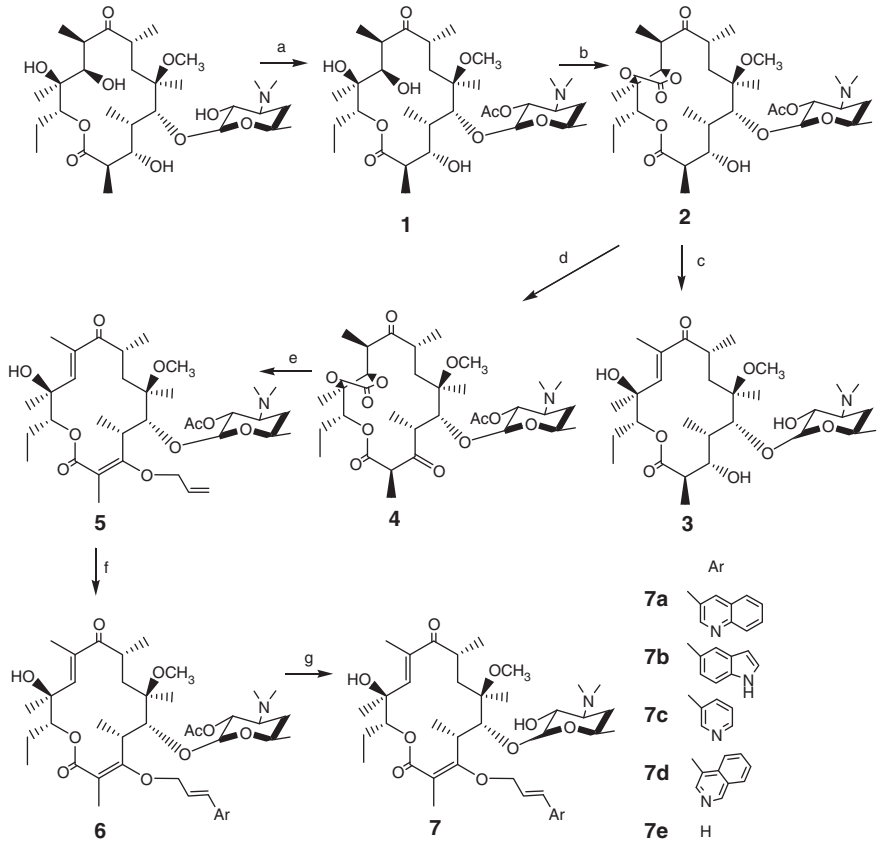


Figure 2 Structure of acylide, 3, 6-bicyclolide and alkylide.



Scheme 1 Reagents and conditions: (a) Ac_2O, CH_2Cl_2, 88.2%; (b) BTC (bis(trichloromethyl)carbonate) , pyridine, CH_2Cl_2, -5 °C, 94.2%; (c) allyl bromide, KOtBu, THF/DMSO, 0 °C, 50% (TLC), then MeOH; (d) NCS (*N*-chlorosuccinimide), DMS (dimethyl sulfide), CH_2Cl_2, −15 °C, 97.3%; (e) allyl bromide, KOtBu, THF/DMSO, 0 °C, 90.5%; (f) $Pd(OAc)_2$, P(*o*-MePh)$_3$, Et_3N, acetonitrile, ArBr, 60 °C 1 h then 80 °C 24 h; (g) MeOH, 65 °C, 8.4–11.5% in two steps (7a–7d).

Table 1 Antibacterial activity of 2, 3-dehydro-3-*O*-(3-aryl-*E*-prop-2-enyl)-10, 11-anhydroclarithromycin derivatives against selected respiratory pathogens

Compound.			In vitro *MIC*($\mu g\,ml^{-1}$)								
			S. aureus				*S. pneumoniae*				
	Aryl	*Config.*	*ATCC 29213*[a]	*D18*[b]	*D6*[b]	*D9*[b]	*ATCC 49619*[a]	*SPJ8*[b]	*SPJ15*[b]	*CP18*[b]	*SPM12*[b]
CAM	—	—	0.25	>64	>64	>64	<0.03	>16	>16	>16	>16
7a	3-quinolyl	*E*	64	64	64	64	>16	>16	>16	>16	>16
7b	5-indolyl	*E*	32	64	64	32	>16	>16	>16	>16	>16
7c	3-pyridyl	*E*	32	>64	>64	>64	>16	>16	>16	>16	>16
7d	4-isoquinolyl	*E*	4	64	64	8	>16	>16	>16	>16	>16

Abbreviations: CAM, clarithromycin; Config., configuration.
[a]Erythromycin-susceptible strains.
[b]Erythromycin-resistant strains.

12-carbonate under the same reaction condition would be hampered when the 9-keto was converted to an oxime ether.[14]

After the introduction of the allyl group, a three-atom-length allylic linker was formed to serve for further modification. In the presence of palladium (II) acetate and tri(*o*-tolyl) phosphine, an aryl group was attached to the allyl group. Interestingly, the Heck reaction yielded the expected 3-*O*-(3-aryl-*E*-prop-2-enyl) derivatives **6** without Heck isomerization. According to the crystal structure of the alkylide,[14] we speculated that spatially neighboring 5-*O*-desosamine probably led to Heck isomerization of C-3 sidechain, whereas the introduction of 2, 3-olefin may change the conformation of skeleton of macrolide, and thus make the 3-*O*-allyl functional group be farther away from originally spatially neighboring 5-*O*-desosamine.[14] However, this hypothesis would require further studies to be fully assessed. Finally, the target compound **7** was obtained by methanolysis. The selected aromatic rings included 3-quinolyl (**a**), 5-indolyl (**b**), 3-pyridyl (**c**) and 4-isoquinolyl (**d**) group.

The *in vitro* antibacterial activity of **7a–7d** was assessed against erythromycin-susceptible and erythromycin-resistant bacteria including *Staphylococcus aureus* and *Streptococcus pneumoniae.* Data are tabulated in Table 1 as the MIC, which was determined by the broth microdilution method, as recommended by the Clinical and Laboratory Standards Institute.[18] The MIC test indicated that **7a–7d** were generally inactive to the selected pathogens, especially for *S. pneumoniae.* Only **7d** (4-isoquinolyl) had a slightly higher activity against erythromycin-resistant *S. aureus* than the reference compound, clarithromycin. This antibacterial evaluation reconfirmed that position 2 of the skeleton of macrolides needs to remain tetrahedral to retain good activity.[9] On the other hand, the formation of 10,11-olefin also proved to have negative effects on the activity of macrolides, but further transformation of 10, 11-olefin to 11, 12-carbamate could improve the activity dramatically.[8] Nevertheless, the aryl sidechain appended at C-3 could improve the activity of macrolides, because compound **7** showed much higher activity against both susceptible and resistant strains compared with 2, 3; 10, 11-dianhydroclarithromycin, a 3-dealkyloxy version of **7** with abolished activity (all MICs > 100 $\mu g\,ml^{-1}$).[8]

In conclusion, a series of 2, 3-dehydro-3-*O*-(3-aryl-*E*-prop-2-enyl)-10, 11-anhydroclarithromycin derivatives were synthesized via the allylation of the 3-keto precursor followed by Heck reaction. As the structure of 2, 3-olefin and 10, 11-olefin may contribute much to low activity, further efforts would be devoted to the synthesis of 3-*O*-(3-aryl-*E*-prop-2-enyl) clarithromycin derivatives without 2, 3-olefin and 10, 11-olefin to search for better efficacy against resistant bacteria.

EXPERIMENTAL PROCEDURE

All solvents and reagents were obtained from commercial sources and used without further purification unless otherwise noted. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker ARX 400 MHz, 600 MHz (Bruker, Switzerland) with tetramethylsilane (TMS) as an internal standard. The assignments of **7e** were made based on ^1H–^1H COSY. HRMS were obtained with Bruker Apex IV FTMS (Bruker, USA). Column chromatography was performed with silica gel (Qingdao Haiyang, Qingdao, China; 200–300 mesh grade). NH_3 H_2O refers to 25% aqueous ammonium hydroxide.

3-OH-6-*O*-CH_3-erythromycin A

To a stirred solution, 80 ml of water and 4 ml of 36% aqueous HCl was added followed by 10 g of clarithromycin. The reaction was stirred at room temperature for 2 h, and then was adjusted to pH 9 with 25% aqueous NH_3. The precipitate was collected by filtration, and washed with cold water to afford 6.8 g of 3-OH-clarithromycin[2] (86.2%). HRMS (ESI) $(M+H)^+$ m/z 590.3901, calculated for $C_{30}H_{56}NO_{10}$ 590.3898.

2′-*O*-Ac-3-OH-6-*O*-CH_3-erythromycin A (1)

A solution of 3-OH-clarithromycin (5.4 g, 9.2 mmol) in CH_2Cl_2 (50 ml) was treated with acetic anhydride (2.0 ml, 20.7 mmol) at room temperature for 1 h. The reaction mixture was washed with saturated $NaHCO_3$, water and brine. The organic layer was dried over $MgSO_4$, filtrated and concentrated to yield **1** (see ref. 2) (5.1 g, 88.2%). ^1H NMR (400 MHz, $CDCl_3$) δ: 2.06 (s, 3H, 2′-$COCH_3$), 2.25 (s, 6H, –$N(CH_3)_2$), 2.49–2.54 (m, 1H, H-8), 2.63–2.66 (m, 1H, H-2), 2.93 (s, 3H, 6-OCH_3), 2.96 (q, 1H, H-10), 3.25 (s, 1H, 12-OH), 3.80 (s, 1H, H-11), 3.94 (s, 1H, 11-OH), 4.41 (dd, 1H, H-2′), 5.15 (dd, 1H, H-13).

2′-*O*-Ac-3-OH-6-*O*-CH_3-11, 12-carbonate erythromycin A (2)

To a solution of **1** (10.2 g, 16.2 mmol) in CH_2Cl_2 (200 ml), pyridine (15.6 ml, 193.8 mmol) was added and then a solution of BTC (bis(trichloromethyl)carbonate) (9.6 g, 32.3 mmol) in CH_2Cl_2 (80 ml) was dropped over 2 h. The reaction mixture was stirred at −5 °C for 7 h. Then 200 ml of brine was added dropwise to the reaction mixture. The organic layer was washed with saturated $NaHCO_3$, water and brine and then dried over $MgSO_4$, filtrated and concentrated to yield **2** (see ref. 16) (10.0 g, 94.2%).

3-OH-6-*O*-CH_3-10,11-anhydroerythromycin A (3)

The procedure described as below was originally designed to prepare 3-*O*-allyl-6-*O*-methylerythromycin 11, 12-carbonate, but unexpected results were observed.

To a solution of **2** (1.0 g, 1.5 mmol) in 10 ml of DMSO and 10 ml of THF, allyl bromide (0.25 ml, 3.0 mmol) and KOtBu (0.5 g, 3.0 mmol) was added. The mixture was stirred for 30 min at 0 °C, then quenched with water and extracted with ethyl acetate. The organic phase was washed with saturated brine, dried over $MgSO_4$, filtrated and concentrated. The crude product was heated to reflux in MeOH, and then the solution was concentrated. The residue was

purified by column chromatography on silica gel (10:0.3:0.1 $CH_2Cl_2/C_2H_5OH/NH_3$ H_2O) to yield pure **3** (102 mg, 11.7%). HRMS (ESI) $(M+H)^+$ m/z 572.37921, calcd for $C_{30}H_{54}NO_9$ 572.37931. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.92 (t, *J*=7.3 Hz, 3H, 15-CH_3), 1.02 (d, *J*=7.0 Hz, 3H, 8-CH_3), 1.20 (d, *J*=6.4 Hz, 3H, 4-CH_3), 1.26–1.29 (m, 7H, 12-CH_3, 5′-CH_3, H-4′ax), 1.33 (d, *J*=6.8 Hz, 3H, 2-CH_3), 1.37 (s, 3H, 6-CH_3,), 1.60–1.74 (m, 5H, H-14ax, H-7, H-4′eq, H-4), 1.91–1.97 (m, 1H, H-14eq), 2.04 (s, 3H, 10-CH_3), 2.29 (s, 6H, -$N(CH_3)_2$), 2.54 (br, 1H, H-3′), 2.69–2.71 (m, 1H, H-2), 3.10 (s, 3H, 6-OCH_3), 3.14–3.29 (m, 2H, H-2′, H-5′), 3.52-3.58 (m, 1H, H-8), 3.92 (m, 2H, OH, H-5), 4.03 (dd, *J*=4.2, 10.5 Hz, H-3), 4.45–4.51 (m, 2H, OH, H-1′), 4.96 (d, *J*=9.9 Hz, H-13), 6.47 (s, 1H, H-11). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 207.7, 176.7, 141.5, 138.6, 106.8, 91.9, 80.8, 79.2, 77.6, 73.5, 70.5, 69.7, 65.5, 48.2, 44.3, 40.2, 38.3, 36.9, 36.4, 28.3, 21.3, 20.8, 20.3, 20.1, 16.1, 15.7, 12.9, 10.4, 7.6.

2′-*O*-Ac-3-keto-6-*O*-CH_3-11,12-carbonate erythromycin A (4)

A solution of NCS (*N*-chlorosuccinimide) (3.25 g, 24.3 mmol) in CH_2Cl_2 (160 ml) was stirred at −15 °C for 10 min, and then DMS (dimethyl sulfide) (2.0 ml, 27.2 mmol) was added slowly to the solution . After stirring for 20 min, a solution of **2** (10.0 g, 15.2 mmol) in CH_2Cl_2 (80 ml) was added to the reaction mixture over 30 min. The reaction mixture was stirred at −15 °C. After 2–3 h, dropwise triethylamine (3.3 ml) was added to the reaction mixture. The solution soon became clear, and continued to be stirred at −5 °C for 1 h. The organic layer was washed with saturated $NaHCO_3$, water and brine, concentrated to yield **4** (see ref. 16) (9.7 g, 97.3%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.88 (t, 3H, 15-CH_3), 1.12–1.14 (m, 6H, 8-CH_3, 4-CH_3), 1.18 (d, 3H, 10-CH_3), 1.23 (d, 3H, 5′-CH_3), 1.30 (s, 3H, 6-CH_3), 1.38 (d, 3H, 2-CH_3), 1.53 (s, 3H, 12-CH_3), 1.56–1.90 (m, 4H), 2.06 (s, 3H, 2′-$COCH_3$), 2.23 (s, 6H, –$N(CH_3)_2$), 2.63–2.69 (m, 5H, H-3′, H-8, 6-OCH_3), 2.92–3.03 (m, 2H, H-10, H-4), 3.49–3.56 (m, 1H, H-5′), 3.78 (q, 1H, H-2), 4.15 (d, 1H, H-5), 4.36 (d, 1H, H-1′), 4.61 (s, 1H, H-11), 4.72 (dd, 1H, H-2′), 4.99 (dd, 1H, H-13). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 212.8, 203.9, 169.7, 169.0, 153.7, 101.3, 84.4, 80.8, 78.2, 78.1, 71.5, 69.1, 63.3, 51.0, 49.4, 47.4, 43.7, 40.6, 39.2, 38.0, 30.4, 22.3, 21.3, 20.9, 19.6, 17.8, 16.0, 14.0, 13.5, 12.4, 10.2.

2′-*O*-Ac-2, 3-dehydro-3-*O*-allyl-6-*O*-CH_3-10, 11-anhydroerythromycin A (5)

To a solution of **4** (2.0 g, 3.0 mmol) in 20 ml of DMSO and 20 ml of THF, allyl bromide (0.51 ml, 6.0 mmol) and KOtBu (1.0 g, 6.0 mmol) was added. The mixture was stirred for 30 min at 0 °C, then quenched with water and extracted with ethyl acetate. The organic phase was washed with saturated brine, dried over $MgSO_4$, filtrated and concentrated to yield **5** (1.8 g, 90.5%). The structure of **5** was confirmed by the H-H COSY anal of **7e**.

2, 3-Dehydro-3-*O*-allyl-6-*O*-CH_3-10, 11-anhydroerythromycin A (7e)

The product **5** was heated to reflux in MeOH at 65 °C for 3 h. After the solvent was evaporated in vacuo, the residue was purified by column chromatography on silica gel (15:0.3:0.15 $CH_2Cl_2/C_2H_5OH/NH_3$ H_2O) to yield pure **7e**. HRMS (ESI) $(M+H)^+$ m/z 610.39584, calcd for $C_{33}H_{56}NO_9$ 610.39496. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.96 (t, *J*=7.2 Hz, 3H, 15-CH_3), 1.07 (d, *J*=6.6 Hz, 3H, 8-CH_3), 1.17–1.34 (m, 10H, 12-CH_3, 4-CH_3, 5′-CH_3, H-4′ax), 1.39 (s, 3H, 6-CH_3,), 1.49 (s, 3H, 2-CH_3), 1.53–1.55 (m, 2H, H-14ax, H-7), 1.83–1.98 (m, 2H, H-4′eq, H-14eq), 2.06 (s, 3H, 10-CH_3), 2.12–2.21 (m, 1H, H-7), 2.41 (s, 6H, -$N(CH_3)_2$), 2.60–2.80 (m, 3H, -C**H**$_2$-CH=CH_2, H-3′), 3.13 (s, 3H, 6-OCH_3), 3.32 (dd, 1H, H-2′), 3.39–3.60 (br, 3H, H-4, H-8, H-5′), 4.16 (br, 1H, H-5), 4.36 (br, 1H, H-1′), 5.05 (dd, 1H, H-13), 5.13–5.17 (m, 2H, -CH_2-CH=C**H**$_2$), 5.59–5.69 (m, 1H, -CH_2-C**H**=CH_2), 6.60 (br, 1H, H-11). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 11.3, 13.3, 15.2, 20.0, 21.1, 21.4, 22.5, 23.1, 29.8, 35.0, 39.8, 40.4, 50.0, 60.3, 65.4, 69.2, 70.3, 78.6, 83.8, 119.5, 132.1, 172.6.

2, 3-Dehydro-3-*O*-[3-(3-quinolyl)-E-2-propenyl]-6-*O*-CH_3-10, 11-anhydroerythromycin A (7a)

To a solution of **5** (1.4 g, 2.1 mmol), palladium (II) acetate (90.3 mg, 0.4 mmol) and tri(*o*-tolyl)phosphine (245 mg, 0.8 mmol) in acetonitrile (8 ml) were added followed by 3-bromoquinoline (0.55 ml, 4.0 mmol) and triethylamine (0.56 ml, 4.0 mmol). The mixture was flushed with nitrogen and sealed in a pressure tube. The reaction mixture was stirred at 60 °C for 1 h and then at 80 °C for 24 h. The reaction mixture was extracted with ethyl acetate, and washed with saturated $NaHCO_3$ and brine. The organic phase was concentrated, and the residue was purified by column chromatography on silica gel (5:5:0.2 petroleum ether/acetone/triethylamine) to yield **6a** (523 mg). The product **6a** (523 mg) was heated to reflux in MeOH (10 ml) at 65 °C for 3 h. After the solvent was evaporated, the crude product was purified by column chromatography on silica gel (15:0.3:0.15 $CH_2Cl_2/C_2H_5OH/NH_3$ H_2O) to yield pure **7a** (172 mg, 10.8% in two steps). HRMS (ESI) $(M+H)^+$ m/z 737.43864, calcd for $C_{42}H_{61}N_2O_9$ 737.43716. ^{1}HNMR ($CDCl_3$, 400 MHz), δ: 0.98 (t, 3H, 15-CH_3), 1.08 (d, 3H, 8-CH_3), 1.18–1.27 (m, 10H), 1.48 (s, 3H, 6-CH_3), 1.52 (s, 3H, 2-CH_3), 1.63–1.66 (m, 2H), 2.06 (s, 3H, 10-CH_3), 2.16–2.22 (m, 1H), 2.27 (s, 6H, $N(CH_3)_2$), 2.45–2.50 (m, 1H), 2.84–2.88 (m, 1H, 3-*O*-C**H**$_2$CH=CH-Ar), 2.84–3.00 (m, 1H, 3-*O*-C**H**$_2$CH=CH-Ar), 3.09 (s, 3H, 6-OCH_3), 3.23 (t, 1H, H-2′), 3.35 (s, 1H, 2′-OH), 3.35–3.55 (m, 3H, H-4, H-8, H-5′), 4.13 (br, 1H, H-5), 4.30 (br, 1H, H-1′), 5.07 (d, 1H, 13-H), 6.28–6.32 (m, 1H, 3-*O*-CH_2C**H**=CH-Ar), 6.62 (d, *J*=15.8 Hz, 1H, 3-O-CH_2CH=C**H**-Ar), 6.63 (br, 1H, H-11), 7.52 (t, 1H, quinoline), 7.63–7.68 (m, 1H, quinoline), 7.77 (d, 1H, quinoline), 7.99 (d, 1H, quinoline), 8.05 (d, 1H, quinoline), 8.90 (d, 1H, quinoline). ^{13}CNMR ($CDCl_3$, 100 MHz) δ: 11.5, 13.1, 15.6, 19.6, 21.2, 21.9, 22.6, 23.1, 28.7, 35.2, 40.1, 40.3, 50.2, 60.7, 65.4, 69.4, 70.3, 78.5, 127.0, 127.8, 127.9, 129.1, 129.2, 129.7, 130.9, 132.1, 147.4, 149.1, 172.5.

2, 3-Dehydro-3-*O*-[3-(5-indolyl)-E-2-propenyl]-6-*O*-CH_3-10, 11-anhydroerythromycin A (7b)

Following the procedure for **7a**, **6b** (234 mg) was prepared as a yellow solid from **5** (0.9 g), and then deacetylated to give pure **7b** (112 mg, 11.1% in two steps). HRMS (ESI) $(M+H)^+$ m/z 725.43714, calcd for $C_{41}H_{61}N_2O_9$ 725.43716. ^{1}HNMR ($CDCl_3$, 600 MHz), δ: 0.97 (t, 3H, 15-CH_3), 1.09 (d, 3H), 1.21–1.30 (m, 10H), 1.47 (s, 3H, 6-CH_3), 1.50 (s, 3H, 2-CH_3), 1.66–1.68 (m, 1H), 2.07 (s, 3H, 10-CH_3), 2.16–2.17 (m, 1H), 2.29 (s, 6H, $N(CH_3)_2$), 2.52 (m, 1H), 2.79–2.98 (m, 2H, 3-*O*-C**H**$_2$CH=CH-Ar), 3.13 (s, 3H, 6-OCH_3), 3.24–3.57 (m, 5H), 4.16 (br, 1H), 4.36 (br, 1H), 5.06 (dd, 1H, 13-H), 5.97 (t, 1H, 3-*O*-CH_2C**H**=CH-Ar), 6.50 (s, 1H, indole), 6.57 (d, *J*=15.1 Hz, 1H, 3-*O*-CH_2CH=C**H**-Ar), 6.68 (br, 1H, 11-H), 7.18–7.21 (m, 2H, indole), 7.31 (d, 1H, indole), 7.54 (s, 1H, indole), 8.63 (s, 1H, indole).

2, 3-Dehydro-3-*O*-[3-(3-pyridyl)-E-2-propenyl]-6-*O*-CH_3-10, 11-anhydroerythromycin A (7c)

Following the procedure for **7a**, **6c** (205 mg) was prepared as a yellow solid from **5** (0.9 g), and then deacetylated to give pure **7c** (80 mg, 8.4% in two steps). HRMS (ESI) $(M+H)^+$ m/z 687.42278, calcd for $C_{38}H_{59}N_2O_9$ 687.42151. ^{1}HNMR ($CDCl_3$, 600 MHz), δ: 0.90 (t, 3H, 15-CH_3), 1.12 (d, 3H), 1.20–1.29 (m, 10H), 1.48 (s, 3H, 6-CH_3), 1.55 (s, 3H, 2-CH_3), 1.64–1.66 (m, 2H), 1.91 (br, 1H), 2.04 (s, 3H, 10-CH_3), 2.04–2.07 (m, 1H), 2.27 (s, 6H, $N(CH_3)_2$), 2.44–2.48 (m, 1H), 2.83–2.84 (m, 2H, 3-*O*-C**H**$_2$CH=CH-Ar), 3.02 (s, 3H, 6-OCH_3), 3.21 (dd, 1H), 3.33–3.54 (m, 4H), 4.12 (d, 1H), 4.34 (br, 1H), 4.98 (dd, 1H, H-13), 6.19 (dt, 1H, 3-*O*-CH_2C**H**=CH-Ar), 6.45 (d, *J*=15.8 Hz, 1H, 3-*O*-CH_2CH=C**H**-Ar), 6.67 (br, 1H, H-11), 7.20–7.22 (m, 1H, pyridine), 7.61 (d, 1H, pyridine), 8.43–8.44 (m, 1H, pyridine), 8.54 (d, 1H, pyridine).

2, 3-Dehydro-3-*O*-[3-(4-isoquinolyl)-E-2-propenyl]-6-*O*-CH_3-10, 11-anhydroerythromycin A (7d)

Following the procedure for **7a**, **6d** (257 mg) was prepared as a yellow solid from **5** (0.9 g), and then deacetylated to give pure **7d** (117 mg, 11.5% in two steps). HRMS (ESI) $(M+H)^+$ m/z 737.43888, calcd for $C_{42}H_{61}N_2O_9$ 737.43716. ^{1}HNMR ($CDCl_3$, 600 MHz), δ: 0.87 (t, 3H, 15-CH_3), 1.06 (d, 3H), 1.22–1.26 (m, 10H), 1.49 (s, 3H, 6-CH_3), 1.63 (s, 3H, 2-CH_3), 1.64–1.66 (m, 1H), 1.93 (br, 1H), 2.04 (s, 3H, 10-CH_3), 2.06–2.10 (m, 1H), 2.27 (s, 6H, $N(CH_3)_2$), 2.44–2.47 (m, 1H), 2.91–3.02 (m, 2H, 3-*O*-C**H**$_2$CH=CH-Ar), 3.05 (s, 3H, 6-OCH_3), 2.21 (dd, 1H), 3.22–3.53 (m, 4H), 4.14 (d, 1H), 4.32 (br, 1H), 5.04 (dd, 1H, H-13), 6.25 (dt, 1H, 3-*O*-CH_2C**H**=CH-Ar), 6.74 (br, 1H, H-11), 7.09 (d, *J*=15.8 Hz, 1H 3-*O*-CH_2CH=C**H**-Ar), 7.61 (t, 1H, isoquinoline), 7.73 (t, 1H, isoquinoline), 7.95 (d, 1H, isoquinoline), 8.05 (d, 1H, isoquinoline), 8.54 (s, 1H, isoquinoline), 9.10 (s, 1H, isoquinoline). ^{13}CNMR ($CDCl_3$, 150 MHz) δ: 11.3, 13.4, 16.0, 19.6, 21.3, 21.6, 22.4, 28.7, 36.6, 40.1, 40.4,

41.5, 44.7, 50.1, 60.5, 65.5, 69.5, 70.5, 78.6, 83.2, 104.0, 123.0, 127.3, 128.1, 128.5, 128.6, 130.3, 130.6, 133.6, 138.8, 140.1, 142.6, 151.6, 171.3.

ACKNOWLEDGEMENTS

This research was supported by the National Natural Science Foundation of China (20602002).

1 Kurath, P., Jones, P. H., Egan, R. S. & Perun, T. J. Acid degradation of erythromycin A and erythromycin B. *Experientia* **27,** 362 (1971).
2 Agouridas, C. *et al.* Synthesis and antibacterial activity of ketolides (6-O-methyl-3-oxoerythromycin derivatives): a new class of antibacterials highly potent against macrolide-resistant and -susceptible respiratory pathogens. *J. Med. Chem.* **41,** 4080–4100 (1998).
3 Denis, A. *et al.* Synthesis and antibacterial activity of HMR 3647 a new ketolide highly potent against erythromycin-resistant and susceptible pathogens. *Bioorg. Med. Chem. Lett.* **9,** 3075–3080 (1999).
4 Or, Y. S. *et al.* Design, synthesis, and antimicrobial activity of 6-O-substituted ketolides active against resistant respiratory tract pathogens. *J. Med. Chem.* **43,** 1045–1049 (2000).
5 Kashimura, M., Asaka, T., Misawa, Y., Matsumoto, K. & Morimoto, S. Synthesis and antibacterial activity of the tricyclic ketolides TE-802 and its analogs. *J. Antibiot.* **54,** 664–678 (2001).
6 Tanikawa, T. *et al.* Synthesis and antibacterial activity of acylides (3-O-acyl-erythromycin derivatives): a novel class of macrolide antibiotics. *J. Med. Chem.* **44,** 4027–4030 (2001).
7 Tang, D. *et al.* Design, synthesis, and antibacterial activity of novel 3,6-bicyclolide oximes: Length optimization and zero carbon linker oximes. *Bioorg. Med. Chem. Lett.* **18,** 5078–5082 (2008).
8 Elliott, R. L. *et al.* Anhydrolide macrolides. 1. Synthesis and antibacterial activity of 2,3-anhydro-6-O-methyl 11,12-carbamate erythromycin A analogues. *J. Med. Chem.* **41,** 1651–1659 (1998).
9 Denis, A. *et al.* beta-keto-ester chemistry and ketolides. Synthesis and antibacterial activity of 2-halogeno, 2-methyl and 2,3 enol-ether ketolides. *Bioorg. Med. Chem. Lett.* **10,** 2019–2022 (2000).
10 Elliott, R. L. *et al.* Novel 3-deoxy-3-descladinosyl-6-O-methyl erythromycin A analogues. Synthesis and *in vitro* activity. *Bioorg. Med. Chem. Lett.* **7,** 641–646 (1997).
11 Misawa, Y., Asaka, T., Kashimura, M., Morimoto, S. & Hatayama, K. 5-O-desosaminylerythronolide derivative. *EP* **682,** 038 (1994).
12 Cheng, H. M. *et al.* Synthesis and SAR of azalide 3,6-ketal aromatic derivatives as potent gram-positive and gram-negative antibacterial agents. *Bioorg. Med. Chem. Lett.* **12,** 2431–2434 (2002).
13 Heggelund, A. & Undheim, K. Descladinosyl erythromycin in phosgene-assisted cyclic 3,6-ether formation. *Tetrahedron Lett.* **49,** 5569–5571 (2008).
14 Liang, J.- H. *et al.* Design, synthesis and antibacterial activity of a novel alkylide: 3-O-(3-aryl-propenyl)clarithromycin derivatives. *J. Antibiot.* **62,** 605–611 (2009).
15 Clark, R. F. *et al.* Synthesis and antibacterial activity of novel 6-*O*-substituted erythromycin A derivatives. *Bioorg. Med. Chem. Lett* **10,** 815–819 (2000).
16 Wei, X. & You, Q.- D. A facile and scaleable synthesis of 3-O-decladinose-6-methyl-10,11-dehydrate-erythromycin-3-one-2′-acetate, an important intermediate for ketolide synthesis. *Org. Process Res. Dev.* **10,** 446–449 (2006).
17 Cink, R. D. *et al.* Investigation of the Stability of the corey-Kim Intermediate. *Org. Process Res. Dev.* **11,** 270–274 (2007).
18 Clinical and Laboratory Standards Institute. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically. *Approved standard M7-A7*, 7th edn, Clinical and Laboratory Standards Institute: Wayne, PA, 2006.