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Synthesis and antibacterial activity of derivatives of 6-*O*-allylic acylides

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Abstract—A series of novel acylide derivatives have been synthesized from erythromycin A via a facile procedure. By applying this procedure, cyclic carbonation to C-11,12 position, acylation to C-3 hydroxyl, and deprotection provided the desired acylides. These compounds showed antibacterial activity against both macrolide-susceptible strains and macrolide-resistant strains. Because of existence of 6-*O*-allyl substitution, these derivatives can be used as intermediates for further structural modification.

The increasing resistance of community-acquired respiratory tract infection to many antimicrobials has become a serious problem over the past decades.[1,2] The therapeutic utility of macrolides has been severely compromised by the emergence of resistant pathogens. Many efforts have been made to discover novel macrolides to address this status.[3] For example, Telithromycin[4,5] and Cethromycin,[6–8] known as ketolides, have been investigated. These compounds, possessing a 3-keto and a proper side chain which can interact with nucleotide A 752 in domain II of the 23S rRNA, showed excellent activities against major macrolide-resistant strains[9] (Fig. 1).

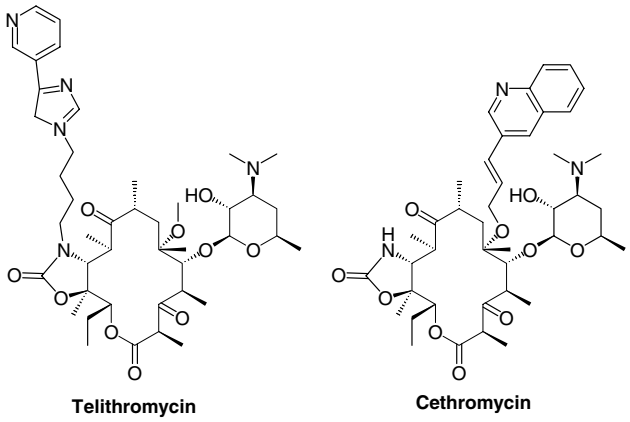

Figure 1. Structures of Telithromycin and Cethromycin.

Some researchers postulated that modification at C-3 was important for the enhanced activity against efflux resistance.[10] The structural modification other than introducing a keto group at C-3 position could also improve activity against efflux resistance.[11–13]

A new class of macrolide antibiotics, named as acylides, has been reported[14,15] (Fig. 2). TEA0777[14] and TEA0929,[15] for example, showed potent antibacterial activity against Gram-positive pathogens, and significant activity against *H. influenzae*. Acylides possess a 3-*O*-acyl group and an 11,12-carbamate provided

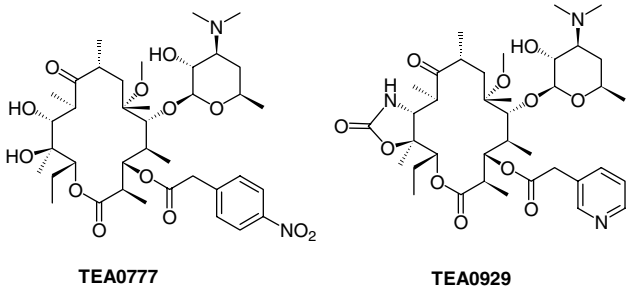

Figure 2. Structures of TEA0777 and TEA0929.

Keywords: Macrolide; Acylide; Resistant bacteria; Allylic.
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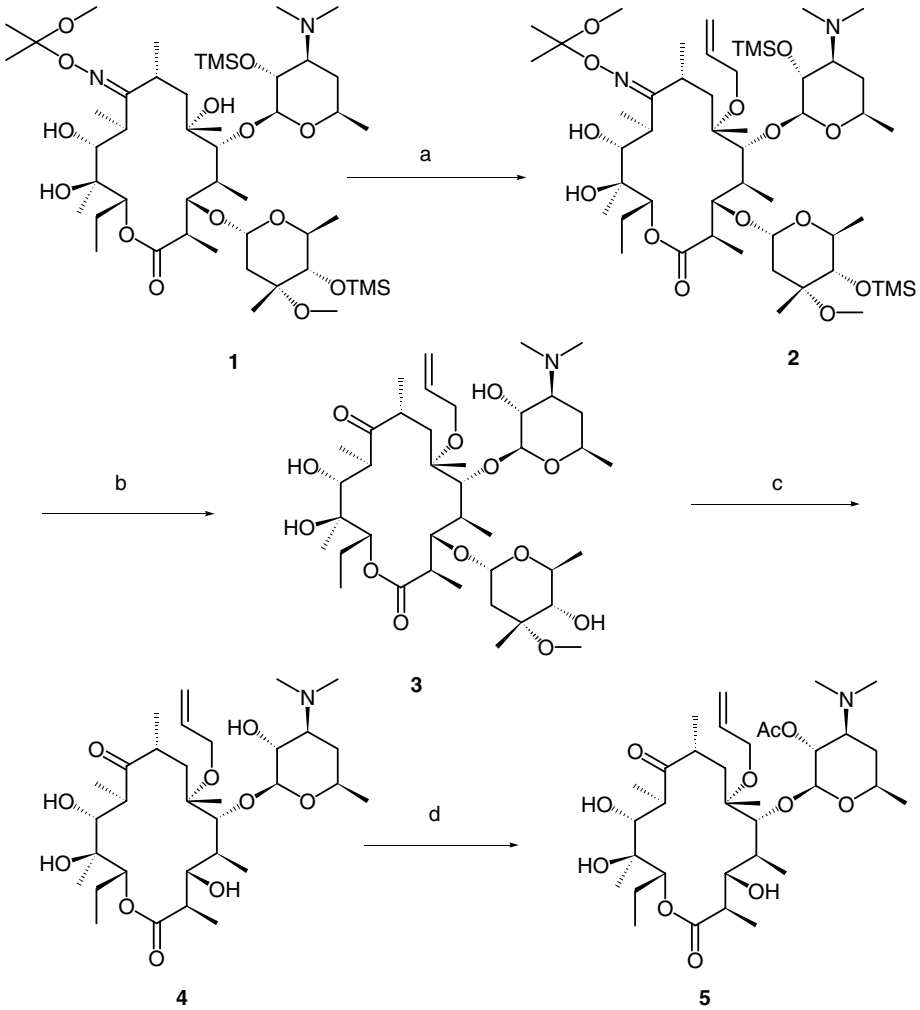
improved antibacterial activity, especially against *erm*-containing erythromycin-resistant strains. The five-membered cyclic carbamate attached to the 11, 12-position was important to rigidify the conformation of the mother ring. It showed that both 3-*O*-acyl group and the 11,12-carbamate ring could account for the activity against erythromycin A susceptible as well as resistant strains.

We focused on the synthesis of 3-*O*-acyl-6-*O*-allyl-11,12-carbonate-5-*O*-desosaminyl erythronolide A, reasoning that 11,12-carbonate ring can also be able to increase the rigidity of the conformation of acylide and provide a good antibacterial activity.[16] Furthermore, during our synthesis of carbonate derivatives, introduction of five-membered cyclic was more convenient. Only one step reaction was required for obtaining of 11,12-carbonate product from 11,12-diol. This could greatly shorten the synthesis route of five-membered ring on erythronolide A.

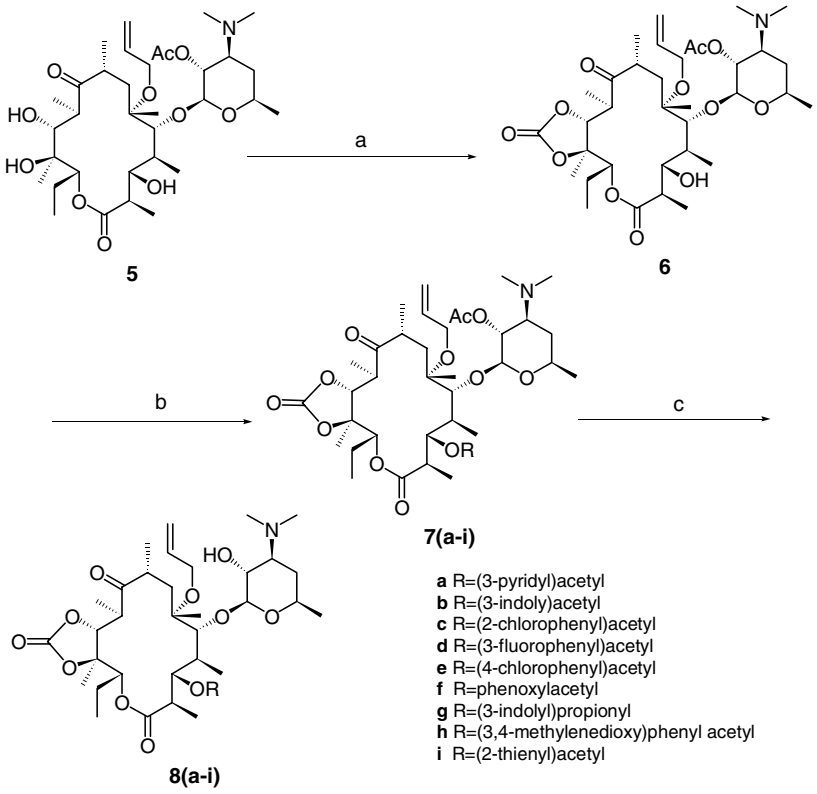
6-*O*-Allylerythromycin A is identified as a versatile synthetic equivalent, which can be converted into an array of diversified derivatives.[3] In particular, allyl group can provide an ideal point for aryl group attaching.[17–19] The 6-*O*-tethered three-atom chain with an aryl group substituent is necessary for its activity against MLS_B-resistant.

Using 2′,4″-*O*-bis(trimethylsilyl)-erythromycin A 9-[*O*-(1-methoxy-1-methylethyl)oxime] **1**[20] as starting material, the procedure for synthesis of compound **5** is as follows (Scheme 1): **1** was converted to 6-*O*-allyl derivative **2** by reacting with allyl *tert*-butylcarbonate in presence of palladium acetate, *N*,*N*-diisopropylethylamine, and triphenylphosphine in THF (anhyd) in yield of 60%. The mixture of the resulting **2**, formic acid, and $NaHSO_3$ in a solution of EtOH/H_2O (v:v 1:1)was refluxed for 4.5 h. Compound **3** was obtained in yield of 70%. Hydrolysis of the cladinose by treating **3** with 1 N HCl in a mixture of EtOH and H_2O (v:v 3:1) gave **4** in yield of 80%. Acetylation of **4** with acetic anhydride in presence of K_2CO_3 in acetone (anhyd) gave **5** in yield of 75%.

The treatment of **5** with trichloromethyl chloroformate in pyridine and CH_2Cl_2 at 0 °C gave **6** in 71% yield. The structure of **6** was confirmed by ^{13}C NMR. Compound **6** reacted with different arylacetic acids in



Scheme 1. Synthesis of compound **5**. Reagents: (a) allyl *tert*-butylcarbonate, DIEA, $Pd(OAc)_2$, Ph_3P, THF, 60%; (b) formic acid, $NaHSO_3$, EtOH:H_2O/1:1, 70%; (c) 1 N HCl, EtOH:H_2O/3:1, 80%; (d) Ac_2O, acetone, K_2CO_3, 75%.



Scheme 2. Synthesis of compound **8(a–i)**. Reagents and condition: (a) trichloromethyl chloroformate, pyridine, CH_2Cl_2, 71%; (b) ROH, EDC, DMAP, CH_2Cl_2, 36–65%; (c) MeOH, reflux.

Table 1. Antibacterial activity of acylides **8(a–i)**

Pathogens	MIC (μg/mL)									
	8a	**8b**	**8c**	**8d**	**8e**	**8f**	**8g**	**8h**	**8i**	Clar[a]
01-430 MSSA	1	8	1	1	4	16	32	0.5	4	0.25
01-431 MSSA	1	8	1	1	4	16	32	0.5	4	0.25
01-481 MSSA	2	16	4	2	8	32	32	1	16	0.5
01-433 MRSA	32	16	16	16	16	32	32	32	32	256
01-429 MRSA	32	16	16	16	16	32	32	32	32	256
01-483 MRSA	8	16	4	2	16	32	32	1	32	256
01-1005 MSSE	0.5	4	1	1	2	8	32	0.5	4	0.125
01-1091 MSSE	0.5	4	1	1	2	8	32	0.5	4	0.125
01-1004 MSSE	0.5	4	1	1	2	8	32	0.5	4	0.125
01-1056 MRSE	32	32	32	32	32	32	32	32	32	256
01-1059 MRSE	32	32	8	2	16	32	32	1	32	256
01-1090 MRSE	2	32	4	1	16	32	32	1	32	256
S. pneumoniae ATCC 49619	0.25	2	0.25	0.125	1	2	4	0.062	1	0.25
S. pneumoniae 03-451(Ery-R)	2	16	4	4	8	16	32	4	32	32
03-436(Ery-R)	2	32	8	8	16	32	32	8	32	128
03-458(Ery-R)	2	32	2	2	8	16	32	2	16	256
S. pyogenes 01-469(Ery-S)	0.125	0.5	0.062	0.125	0.5	0.5	1	0.016	0.5	0.062
01-804(Ery-S)	0.125	0.5	0.125	0.125	0.5	1	1	0.031	0.5	0.125
01-740(Ery-S)	0.125	0.5	0.062	0.125	0.25	0.5	1	0.016	0.5	0.062
S. pyogenes 03-680(Ery-R)	16	16	16	16	8	16	32	16	32	256

[a] Clar, clarithromycin.

presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 4-dimethylaminopyridine. After stirring at ambient temperature for 24 h and purification on silica gel, the desired carbonate acylides **7(a–i)** were obtained in yield of 36–65%, respectively (Scheme 2). Compound **8(a–i)** were obtained by refluxing **7(a–i)** in MeOH for 5 h. Especially, **8a** has similar acylide core as TEA0929 but differs on 6-*O*-allyl group and 11,12-carbonate ring. The structures of **8(a–i)** were confirmed by HRMS, ^{1}H NMR, and ^{13}C NMR spectra.[21]

The 6-*O*-allyl-11,12-carbonate acylides **8(a–i)** and the reference compound, Clarithromycin, were tested against different representative pathogens. Various macrolide- and multidrug-resistant pathogens were tested in order to identify the potency of these acylide analogues. *Staphylococcus aureus* 01-430, 01-431, and 01-481 are methicillin-sensitive *Staphylococcus aureus* (MSSA). *S. aureus* 01-433, 01-429 and 01-483 are methicillin-resistant *Staphylococcus aureus* (MRSA). *Staphylococcus epidermidis* 01-1005, 01-1091, and 01-1004 are methicillin-sensitive *Staphylococcus epidermidis* (MSSE). *S. epidermidis* 01-1056, 01-1059, and 01-1090 are methicillin-resistant *Staphylococcus epidermidis* (MRSE). *Streptococcus pneumoniae* ATCC49619, *Streptococcus pyogenes* 01-469, 01-804, and 01-740 are erythromycin-susceptible strains (Ery-S). *S. pneumoniae* 03-451, 03-436, and 03-458 are erythromycin-resistant strains (Ery-R). *S. pyogenes* 03-680 is erythromycin-resistant strain encoded by an *ermB* gene. The in vitro antibacterial activity is reported as minimum inhibitory concentrations (MICs), which were determined by the broth microdilution method as recommended by the National Committee of Clinical Laboratory Standard (NCCLS).[22–24]

The in vitro antibacterial activity of **8(a–i)** and reference compounds is shown in Table 1. All these acylides showed antibacterial activity against macrolide-resistant strains. **8a** and **8h** showed significantly improved activity against not only macrolide-susceptible strains but also macrolide-resistant strains. The results suggested that the introduction of an arylacetyl group into 3-position enhanced the antibacterial activity. In particular, acylide **8h** showed more potent activity against susceptible Gram-positive pathogens than **8a**.

In summary, a series of novel acylides 6-*O*-allyl-3-*O*-acyl-11,12-carbonate erythromycin A derivatives **8(a–i)** were synthesized by a facile process. This 6-*O*-allyl acylide core can be evaluated as important intermediate for further study.

Acknowledgments

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Supplementary data

1H NMR, 13C NMR data of compounds **7(a–i)**, 1H NMR, 13C NMR, HRMS data of compounds **8(a–i)**, and experimental procedures of these compounds are available online. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2007.03.107.

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21. Selective data for the synthesized new compounds: **8a** MS (ESI) *m/z* 761(M+H)$^{+}$; HRMS (ESI) *m/z* 761.4207, calcd for $C_{40}H_{61}N_2O_{12}$ 761.4219; ^{13}C NMR (ppm): 211.7, 173.2, 170.4, 153.9, 150.3, 148.8, 137.1, 134.1, 129.3, 123.5, 118.1, 103.3, 84.7, 82.2, 80.3, 78.9, 78.7, 75.4, 70.1, 69.3, 66.2, 65.1, 45.0, 42.9, 40.2, 38.4, 38.3, 37.4, 36.1, 28.4, 22.2, 21.0, 20.3, 18.5, 14.9, 13.1, 12.7, 10.2, 9.0.
8b MS(ESI) *m/z* 799 (M+H)$^{+}$; HRMS (ESI) *m/z* 799.4388, calcd for $C_{43}H_{63}N_2O_{12}$ 799.4375; ^{13}C NMR (ppm): 211.9, 173.4, 171.5, 154.0, 135.9, 134.1, 127.1, 123.3, 122.2, 119.7, 118.6, 118.0, 111.3, 107.3, 102.6, 84.8, 81.0, 80.3, 78.8, 77.8, 75.2, 70.3, 69.2, 65.6, 65.1, 45.1, 42.9, 40.1, 38.3, 37.4, 36.0, 31.3, 28.2, 22.2, 20.8, 20.3, 18.5, 14.7, 13.1, 12.8, 10.1, 9.1.

8c MS (ESI) *m*/*z* 794 $(M+H)^+$; HRMS (ESI) *m*/*z* 794.3871, calcd for $C_{41}H_{61}NO_{12}Cl$ 794.3876; ^{13}C NMR (ppm): 211.8, 173.3, 170.1, 153.9, 134.4, 134.2, 131.6, 131.4, 129.6, 128.9, 127.0, 118.0, 103.2, 84.7, 81.8, 80.3, 78.9, 78.4, 75.3, 70.4, 69.6, 66.0, 65.1, 45.0, 42.9, 40.3, 38.9, 38.3, 37.4, 36.2, 28.3, 22.2, 21.1, 20.4, 18.5, 14.9, 13.1, 12.7, 10.1, 9.0.

8d MS (ESI) *m*/*z* 778 $(M+H)^+$; HRMS (ESI) *m*/*z* 778.4175, calcd for $C_{41}H_{61}NO_{12}F$ 778.4172; ^{13}C NMR (ppm): 211.8, 173.2, 170.5, 164.3, 161.0, 153.9, 135.6, 135.5, 134.1, 130.1, 130.0, 125.1, 125.1, 118.0, 116.6, 116.3, 114.4, 114.2, 103.2, 84.7, 81.8, 80.2, 78.8, 78.4, 75.3, 70.2, 69.4, 66.0, 65.1, 45.0, 42.9, 41.0, 40.9, 40.2, 38.3, 37.3, 36.1, 28.2, 22.2, 21.0, 20.3, 18.5, 14.8, 13.1, 12.8, 10.1, 9.0.

8e MS(ESI) *m*/*z* 794 $(M+H)^+$; HRMS (ESI) *m*/*z* 794.3882, calcd for $C_{41}H_{61}NO_{12}Cl$ 794.3876; ^{13}C NMR (ppm): 211.7, 173.2, 170.6, 153.9, 134.1, 133.3, 131.8, 130.7, 128.7, 118.0, 103.1, 84.7, 81.7, 80.2, 78.8, 78.3, 75.3, 70.3, 69.4, 66.0, 65.1, 45.0, 42.9, 40.7, 40.2, 38.3, 37.4, 36.1, 28.1, 22.2, 21.0, 20.3, 18.5, 14.8, 13.0, 12.7, 10.1, 9.0.

8f MS (ESI) *m*/*z* 776 $(M+H)^+$; HRMS (ESI) *m*/*z* 776.4210, calcd for $C_{41}H_{62}NO_{13}$ 776.4215; ^{13}C NMR (ppm): 211.7, 173.1, 168.5, 157.5, 153.9, 134.0, 129.6, 122.0, 118.2, 114.7, 103.4, 84.7, 82.2, 80.3, 78.8, 75.4, 70.2, 69.6, 65.8, 65.3, 65.0, 45.1, 42.6, 40.0, 38.3, 37.3, 36.2, 28.0, 22.2, 21., 20.2, 18.5, 15.0, 13.1, 12.8, 10.1, 8.9.

8g MS (ESI) *m*/*z* 813 $(M+H)^+$; HRMS (ESI) *m*/*z* 813.4539, calcd for $C_{44}H_{65}N_2O_{12}$ 813.4532; ^{13}C NMR (ppm): 211.9, 173.5, 172.8, 154.0, 136.3, 134.1, 127.0, 122.1, 121.8, 119.4, 118.3, 118.1, 114.3, 111.3, 103.0, 84.8, 81.6, 80.3, 78.8, 77.5, 75.3, 70.2, 69.5, 65.9, 65.1, 45.1, 42.8, 40.2, 38.3, 37.4, 36.0, 35.1, 28.2, 22.2, 21.1, 20.4, 20.3, 18.5, 14.9, 13.1, 12.8, 10.1, 9.1.

8h MS (ESI) *m*/*z* 804 $(M+H)^+$; HRMS (ESI) *m*/*z* 804.4155, calcd for $C_{42}H_{62}NO_{14}$ 804.4164;^{13}C NMR (ppm): 211.8, 173.3, 171.1, 154.0, 147.8, 146.8, 134.2, 126.8, 122.5, 117.9, 109.8, 108.2, 103.1, 101.1, 84.7, 81.5, 80.3, 78.8, 78.0, 75.3, 70.3, 69.4, 65.9, 65.1, 45.0, 42.9, 41.0, 40.2, 38.3, 37.4, 36.1, 28.2, 22.2, 21.0, 20.3, 18.5, 14.8, 13.0, 12.7, 10.1, 9.0.

8i MS (ESI) *m*/*z* 766 $(M+H)^+$; HRMS (ESI) *m*/*z* 766.3823, calcd for $C_{39}H_{60}NO_{12}S$ 766.3830; ^{13}C NMR (ppm): 211.8, 173.3, 170.1, 154.0, 134.2, 134.1, 127.0, 126.7, 125.3, 118.0, 103.2, 84.7, 81.9, 80.3, 78.8, 78.7, 75.3, 70.2, 69.4, 65.8, 65.0, 45.1, 42.9, 40.2, 38.3, 37.4, 36.1, 35.4, 28.2, 22.2, 21.0, 20.3, 18.5, 14.9, 13.1, 12.8, 10.1, 9.0.

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