Anhydrolide Macrolides. 1. Synthesis and Antibacterial Activity of 2,3-Anhydro-6-*O*-methyl 11,12-Carbamate Erythromycin A Analogues

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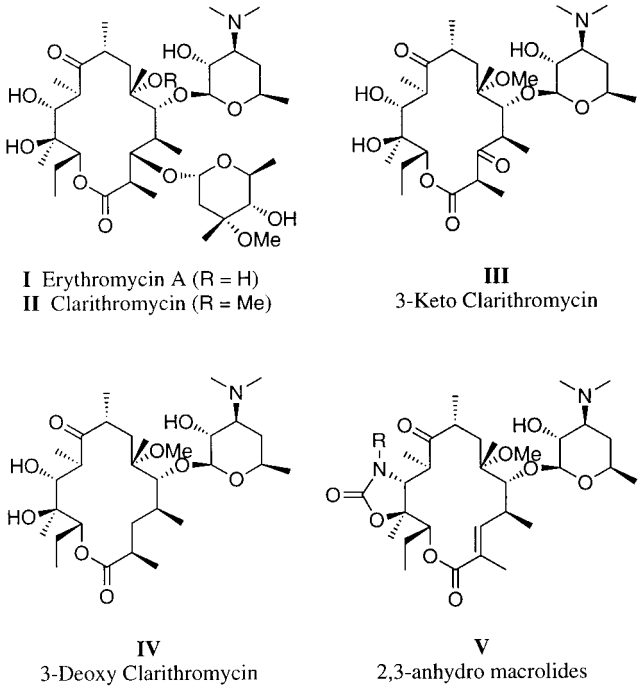
A series of 3-descladinosyl-2,3-anhydro-6-*O*-methylerythromycin A 11,12-carbamate analogues have been synthesized and evaluated for antibacterial activity. These compounds were found to be potent antibacterial agents against Gram-positive organisms in vitro, many having MIC values below 1 μg/mL for the macrolide-susceptible *Staphylococcus aureus*, *Streptococcus pyogenes*, and *Streptococcus pneumoniae*, as well as improved activity compared to erythromycin A against the inducibly MLS (macrolide, lincosamide, and streptogramin B)-resistant organisms. Structure−activity studies revealed that arylalkyl carbamates with two and four carbon atoms between the aromatic moiety and carbamate nitrogen have the best in vitro activity. All of the C-10 epi analogues evaluated were found to have substantially less activity than the corresponding natural C-10 isomer. Several analogues demonstrated moderate antibacterial activity against the constitutively resistant *S. aureus* A-5278, *S. pneumoniae* 5979, and *S. pyogenes* 930. However, despite potent in vitro activity, these analogues showed only moderate in vivo activity in mouse protection studies.

Macrolide antibiotics, including erythromycin (**I**) (Chart 1) and related compounds, continue to be an important therapeutic class against Gram-positive organisms, with second-generation macrolides such as clarithromycin (**II**) (Biaxin) and azithromycin (Zithromax) being widely prescribed due to their efficacy, safety, and lack of serious side effects.[1] In recent years the therapeutic utility of macrolide antibiotics such as clarithromycin has expanded from the traditional role in the treatment of upper and lower respiratory tract infections and skin and soft tissue infections to include treatment of opportunistic mycobacterium avium complex (MAC) infections, new pediatric formulations, and approval for the treatment of *Helicobacter pylori*, a causative agent in many gastrointestinal ulcers. The increased reliance on macrolides has driven research toward third-generation macrolides with the goal of achieving greater efficacy, safety, and a broader spectrum of activity.

Recent discoveries concerning the structure−activity relationships (SAR) of erythromycin analogues has led to new major subclasses of macrolides, such as the "ketolide" class (**III**; Chart 1), in which the 3-cladinosyl sugar residue has been replaced by a ketone functionality. These ketolides have been shown to have good in vitro and in vivo activity against erythromycin-susceptible Gram-positive organisms, as well as against organisms with inducible resistance against erythromycin.[2] The discovery that the cladinose moiety of erythromycin was not absolutely necessary for good antibacterial activity has opened up new areas on the macrolactone ring for SAR exploration. We recently reported[3] on 3-deoxy-6-*O*-methylerythromycin analogues (**IV**) which had moderate antibacterial activity against Gram-positive organisms, demonstrating that functionalities other than a ketone can substitute for the 3-cladinosyl residue. The lower in vitro activity of the 3-deoxy series compared to the ketolide series led us to consider analogues which contained a planar (non-keto) sp^2-

Chart 1. Structures of Erythromycin A, Clarithromycin, and C-3-Modified Analogues



I Erythromycin A (R = H)
II Clarithromycin (R = Me)

III
3-Keto Clarithromycin

IV
3-Deoxy Clarithromycin

V
2,3-anhydro macrolides

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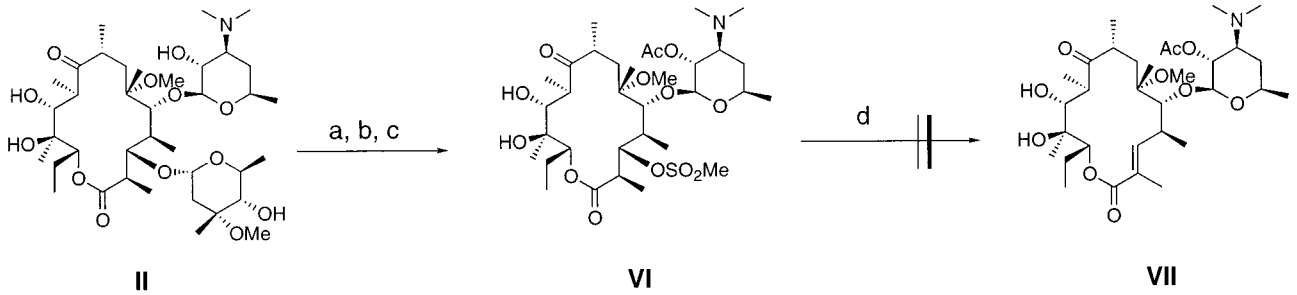
Scheme 1. Initial Synthetic Approach to 2,3-Anhydroclarithromycin[a]



[a] Legend: (a) aq HCl/MeOH; (b) Ac_2O/TEA/CH_2Cl_2; (c) Ms_2O/pyridine/CH_2Cl_2; (d) base.

carbon at the 3-position of the macrolactone ring. Specifically, we were interested in synthesizing 2,3-anhydroerythromycin analogues in which a carbon−carbon double bond was introduced at the C2−C3 position. These macrolides were expected to have increased rigidity compared to the 3-deoxy series, although lacking an oxygen atom at the 3-position as found in erythromycin and the ketolides. In addition, macrolides containing 2,3-double bonds (e.g., mycinamicins, chalcomycins) are known in the 16-membered ring class of macrolides, although it was not clear whether this modification would be tolerated in the 14-membered ring macrolides. We also wished to explore the chemical reactivity of the 2,3-double bond toward further functionalization of the 2- and 3-positions of the macrolactone ring. We herein report the synthesis and antibacterial activity of 2,3-anhydro-6-*O*-methylerythromycin 10,11-carbamate analogues **V**.

Chemistry

The initial approach toward the synthesis of 2,3-anhydroerythromycin analogues is outlined in Scheme 1. Selective removal of the cladinose residue of clarithromycin was accomplished by treatment with aqueous HCl/ethanol at room temperature; subsequent basification with Na_2CO_3 to pH 10−11 precipitated the desired descladinosyl macrolide. Acetylation with acetic anhydride/triethylamine in methylene chloride provided the 2′-protected macrolide in high yield. Selective mesylation of the C-3 hydroxy group using methanesulfonic anhydride and pyridine in methylene chloride at room temperature afforded the key intermediate **VI**, with ^{1}H NMR studies confirming the structural assignment.

Unfortunately, all attempts to effect base-promoted elimination of the mesylate group to afford the macrolide **VII** failed. Numerous bases were explored, including triethylamine, pyridine, DBU, potassium *tert*-butoxide, *N*-methylmorpholine, and potassium fluoride. Likewise, attempts to directly dehydrate the 2′-protected-3-hydroxy macrolide using thionyl chloride or the Burgess reagent[4] failed. The mesylate **VI** also proved to be totally unreactive toward a number of nucleophiles, including primary and secondary amines, sodium azide, hydroxylamine, mercaptans, and sodium cyanide. In cases where more forcing conditions were used a 3,6-tetrahydrofuran byproduct, presumably formed by attack of the C-6 OMe oxygen on the mesylate followed by O-demethylation, was isolated. However, in no case was the desired 2,3-anhydro compound observed. Attempts to introduce a better leaving group, such as a triflate, at the C-3 position were likewise unsuccessful.

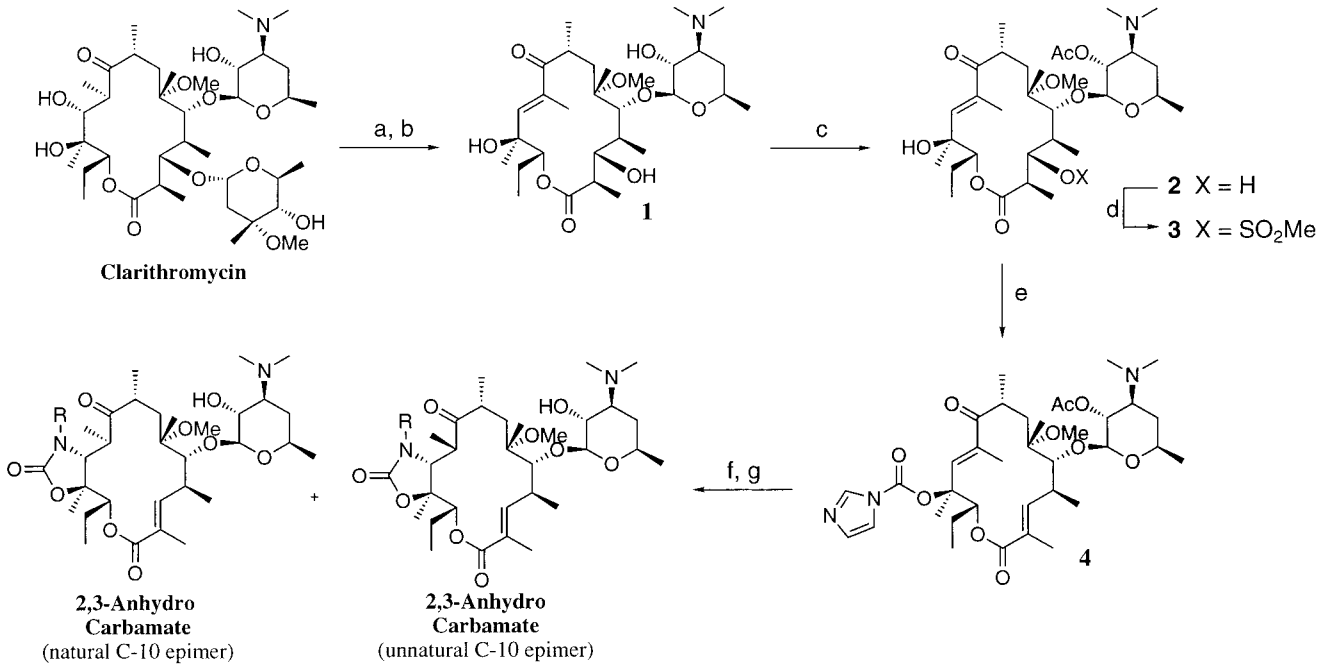
The lack of success in eliminating or displacing the C-3 mesylate was not encouraging, but a serendipitous discovery with 6-deoxyerythromycin[5] provided valuable insight.[6] We observed that upon treatment of 2′-benzoyl-6-deoxy-3-descladinosylerythromycin with sodium bis(trimethylsilyl)amide and 1,1′-carbonyldiimidazole (CDI), a compound corresponding to the 2,3-anhydro-6-deoxyerythromycin 10,11-ene 12-*O*-acylimidazolide was formed. Presumably the C-3 hydroxy group was converted to the corresponding acylimidazolide which eliminated under the reaction conditions. This 6-deoxy intermediate was subsequently converted to the 2,3-anhydro-11,12-phenylbutyl carbamate analogue and was found to have only moderate antibacterial activity (data not shown). However, we were still encouraged by these results and suspected, based on previous SAR with 6-deoxy analogues, that the activity would be improved upon incorporation of a 6-*O*-methyl group.

Although the conditions that worked with the 6-deoxy macrolide did not effect dehydration on the 6-*O*-methyl macrolide, we reasoned that incorporation of conformational constraints at the 11−12 position of the macrolide coupled with a better leaving group at the 3-position might be the key to introducing a 2,3-double bond on the 6-*O*-methyl macrolide. Efforts therefore focused on introducing a double bond at the C10−C11 position prior to mesylation and elimination of the C-3 hydroxyl group. This new route, which proved successful, is outlined in Scheme 2.

Treatment of clarithromycin with ethylene carbonate in refluxing triethylamine followed by dilute aqueous acid afforded the descladinosyl enone **1** in good yield. Acetylation of the 2′-hydroxy group with acetic anhydride/pyridine followed by mesylation of the C-3 hydroxyl group gave the key intermediate **3**. Initially it was discovered **3** could be dehydrated using a base such as DBU in refluxing acetone or the sodium anion of imidazole (see Scheme 2) to provide the 2,3−10,11-dianhydro macrolide, although it was subsequently found to be more efficient to treat **3** with excess CDI and sodium hydride in DMF−THF to obtain the desired acylimidazolide **4** directly.

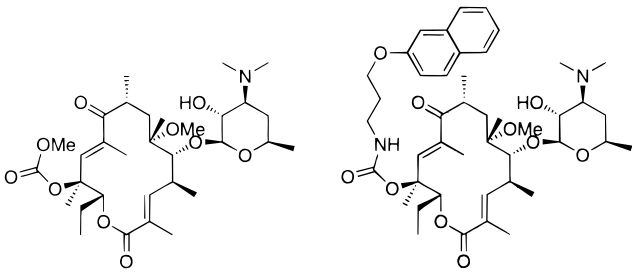
The key intermediate **4** could readily be converted to the desired carbamate compounds by treatment with a primary amine in aqueous acetonitrile or DMF, following methods originally developed by Baker et al. on erythromycin itself,[7] followed by stirring overnight in

Scheme 2. Synthesis of 2,3-Anhydro-6-*O*-methyl 11,12-Carbamate Erythromycin Analogues[a]



[a] Legend: (a) ethylene carbonate/TEA/reflux; (b) aq HCl; (c) Ac_2O/TEA/CH_2Cl_2; (d) Ms_2O/pyridine; (e) NaH/CDI; (f) RNH_2/10% aq MeCN or DMF; (g) MeOH/rt.

methanol to cleave the 2′-protecting group. However, the conversion of **4** to the 11,12-carbamate was always accompanied by a fair amount (typically 20−40%) of the undesired C-10 epi isomer, often requiring difficult chromatographic separations. This is in contrast to the ketolide series, where the C-10 epimer was generally formed to a much lower degree (G. Griesgraber, personal communication). Nonetheless, compound **4** provided access to many carbamate analogues. In a few cases (e.g., **40** and **41**) uncyclized byproducts were isolated.

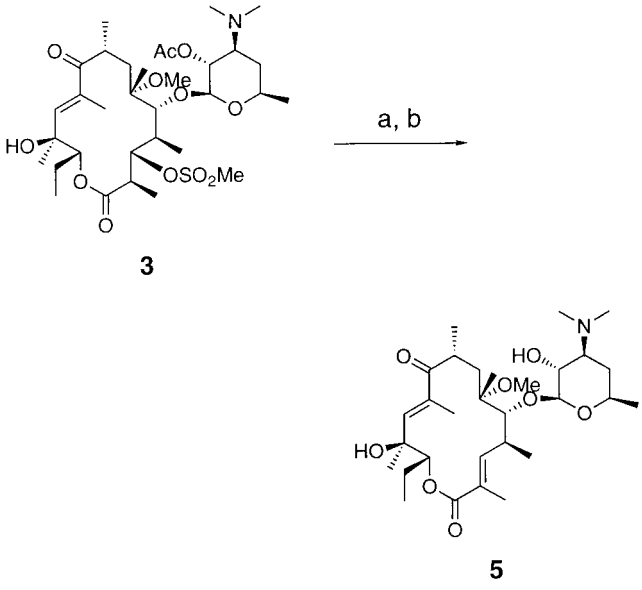


The 2,3−10,11-diene macrolide **5** was synthesized via treatment of the C-3 mesylate with either DBU or the sodium salt of imidazole, as outlined in Scheme 3. Several 9-deoxo-9-*N*,11-*N*-ethylene-2,3-anhydro macrolides related to Taisho's bicyclic ketolides[8] were also synthesized, as outlined in Scheme 4. The analytical data for the carbamates are tabulated in Table 1, and the ^1H and ^{13}C NMR peak assignments are found in the Supporting Information.

Results and Discussion

All of the final carbamate macrolides were screened against a number of strains of *Staphylococcus aureus*, *Streptococcus pyogenes*, and *Streptococcus pneumoniae* which were either susceptible to erythromycin or had

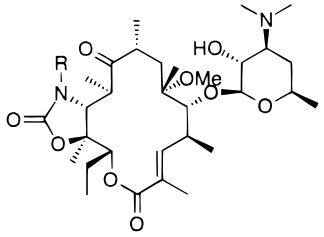
Scheme 3. Synthesis of Analogue **5**[a]



[a] Legend: (a) DBU/refluxing acetone or imidazole/NaH/THF−DMF; (b) MeOH/rt.

inducible or constitutive resistance to erythromycin A. In addition, compounds were screened against *Haemophilus influenzae* (DILL). The MIC values (μg/mL) for the carbamates are shown in Table 2. In general, all of the cyclic carbamates tested had good antibacterial activity against the Ery-susceptible organisms, and many had good activity against the inducibly MLS (macrolide, lincosamide, and streptogramin B)-resistant *S. aureus* A5177, as well as the macrolide-resistant *S. pyogenes* PIU 2548 and *S. pneumoniae* 5649. A few of the compounds tested showed moderate activity against the constitutively resistant *S. aureus* A-5278, *S. pyogenes* 930, and *S. pneumoniae* 5979. However, none of the carbamates were as effective against *H. influenzae*

Table 1. Analytical Data of 2,3-Anhydro-6-*O*-methyl 11,12-Carbamate Erythromycin Analogues[a]



compd	R	formula	MS
5	see text	$C_{30}H_{51}NO_8$	554 (M + 1)
6	H	$C_{31}H_{52}N_2O_9$	597 (M + 1)
7	H (10-epi)	$C_{31}H_{52}N_2O_9$	597 (M + 1)
8	benzyl	$C_{38}H_{58}N_2O_9$	687 (M + 1)
9	phenylethyl	$C_{39}H_{60}N_2O_9$	701 (M + 1)
10	phenylpropyl	$C_{40}H_{62}N_2O_9$	715 (M + 1)
11	phenylpropyl (10-epi)	$C_{40}H_{62}N_2O_9$	715 (M + 1)
12	phenylbutyl	$C_{41}H_{64}N_2O_9$	729 (M + 1)
13	3,4-dichlorophenylethyl	$C_{39}H_{58}Cl_2N_2O_9$	769 (M + 1)
14	4-phenoxyphenylethyl	$C_{45}H_{64}N_2O_{10}$	793 (M + 1)
15	4-phenoxyphenylethyl (10-epi)	$C_{45}H_{64}N_2O_{10}$	793 (M + 1)
16	4-nitrophenylethyl	$C_{39}H_{59}N_3O_{11}$	746 (M + 1)
17	4-aminophenylethyl	$C_{39}H_{61}N_3O_9$	716 (M + 1)
18	4-bromophenylethyl	$C_{39}H_{59}N_2O_9Br$	779 (M + 1)
19	4-hydroxyphenylethyl	$C_{39}H_{60}N_2O_{10}$	717 (M + 1)
20	4-fluorophenylethyl	$C_{39}H_{59}N_2O_9F$	719 (M + 1)
21	3-methoxyphenylethyl	$C_{40}H_{62}N_2O_{10}$	730 (M + 1)
22	3-(trifluoromethyl)phenylethyl	$C_{40}H_{59}N_2O_9F_3$	769 (M + 1)
23	3,4-bis(benzyloxy)phenylethyl	$C_{53}H_{72}N_2O_{11}$	913 (M + 1)
24	4-methylphenylethyl	$C_{40}H_{62}N_2O_9$	715 (M + 1)
25	2-thienylethyl	$C_{37}H_{59}N_2O_9S$[b]	707 (M + 1)
26	phenoxypropyl	$C_{40}H_{62}N_2O_{10}$	731 (M + 1)
27	4-chlorophenoxypropyl	$C_{40}H_{61}ClN_2O_{10}$	765 (M + 1)
28	(8-quinolinyloxy)propyl	$C_{43}H_{63}N_3O_{10}$	782 (M + 1)
29	4-pyridyloxypropyl	$C_{41}H_{61}N_3O_{11}$	732 (M + 1)
30	2-naphthyloxypropyl	$C_{44}H_{64}N_2O_{10}$	781 (M + 1)
31	3-ethoxypropyl	$C_{36}H_{62}N_2O_{10}$	683 (M + 1)
32	vinyloxypropyl	$C_{36}H_{60}N_2O_{10}$	681 (M + 1)
33	benzylaminoethyl (10-epi)	$C_{40}H_{63}N_3O_9$	730 (M + 1)
34	*N*-methylanilinylpropyl	$C_{41}H_{65}N_3O_9$	744 (M + 1)
35	4-(4-chlorophenyl)-*cis*-3-butenyl	$C_{41}H_{61}ClN_2O_9$	761 (M + 1)
36	*N*-(3-quinolinyl)propyl	$C_{43}H_{63}N_3O_{10}$	782 (M + 1)
37	9-deoxo-9-*N*,11-*N*-ethylene-9-imino	$C_{33}H_{55}N_3O_8 \cdot H_2O$	622 (M + 1)
38	9-deoxo-9-*N*,11-*N*-ethylene-9(*S*)-amino	$C_{33}H_{50}N_3O_8$[c]	624 (M + 1)
39	isopropyl	$C_{34}H_{58}N_2O_9$	638 (M + 1)
40	see text	$C_{32}H_{53}NO_{10}$	612 (M + 1)
41	see text	$C_{44}H_{63}N_2O_{10}$	781 (M + 1)

[a] All compounds were fully characterized by MS and ^1H and ^{13}C NMR and had elemental analyses within ±0.4% of theoretical values unless noted otherwise. [b] High-resolution MS: calcd for $C_{37}H_{59}N_2O_9S$ 707.3941, observed 707.3933. [c] High-resolution MS: calcd for $C_{33}H_{50}N_3O_8$ 624.4224, observed 624.4241.

(DILL) as erythromycin, and no significant antibacterial activity was observed against the Gram-negative organisms (data not shown). In all cases the C-10 epi analogues had significantly less activity than the natural C-10 counterparts (e.g., **6** vs **7**, **10** vs **11**, **14** vs **15**). Interestingly, compounds lacking the C11−C12 cyclic carbamate functionality and possessing a 10−11 double bond (e.g., **5**, **40**, **41**) had much lower antibacterial activity.

Because of the good in vitro activity of the cyclic carbamates a large number were synthesized to explore the SAR. It was discovered that substitution of the carbamate nitrogen of **6** had significant effects on antibacterial activity, and that alkylaryl groups generally had the best activity. Systematic variation of the chain lengths from one to four carbon atoms between the carbamate nitrogen and aryl group (**8**−**10**, **12**) indicated that the 2-carbon and 4-carbon spacers were superior to 1- and 3-carbon spacers. Therefore, a large number of substituted phenylethyl carbamate analogues (**13**−**24**) were synthesized and evaluated as antibacterial agents. Overall these phenylethyl carbamates had very good activity against susceptible and inducibly resistant strains. Electron-withdrawing groups on the phenyl ring tended to increase activity (e.g., **13**, **16**) compared to electron-donating groups (e.g., **17**, **19**), and large bulky groups were not well-tolerated (e.g., **14**, **23**). Qualitatively the 2-thienylethyl analogue **25** was very similar to the phenylethyl compound **9**.

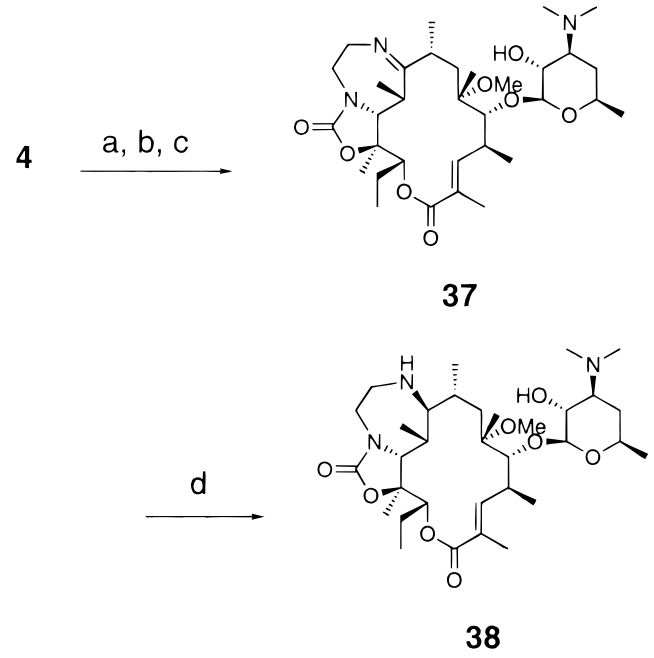
A number of O-substituted 3-hydroxypropyl carbamates (**26**−**32**) were also investigated and, in the cases where aromatic moieties were appended (**26**−**30**), showed good overall activity. Compounds **31** and **32**, which are substituted with an ethyl and vinyl group on the oxygen, respectively, had attenuated activity compared to their aromatic counterparts. Compounds **32** and **33**, having a benzylaminoethyl (10-epi) and *N*-methylanilinopropyl moiety, respectively, had only moderate activity. The bridged 9,11-iminoethyl carbamate **37**, a 2,3-anhydro version of Taisho's TE-802, had good overall activity in

Table 2. In Vitro Antibacterial Activity of 2,3-Anhydro-6-*O*-methyl 11,12-Carbamate Erythromycin Analogues[a,b]

	minimum inhibitory concentration (mg/mL)									
	S. aureus			*S. pyogenes*			*S. pneumoniae*			*H. influenzae*
compd	6538P	A5177	A-5278	EES61	PIU 2548	930	ATCC6303	5649	5979	DILL
Ery A	0.2	3.1	>100	0.02	3.1	>100	0.06	8	>128	4
5	>100	>100	>100	>100	>100	>100	>128	>128	>128	>128
6	1.56	0.78	>100	0.05	0.2	>100	0.25	0.5	>128	128
7	25	>100	>100	12.5	6.2	>100	NT	NT	NT	NT
8	0.78	0.78	>100	0.2	0.2	100	0.25	2	>128	128
9	0.39	0.1	50	<0.005	0.01	25	0.03	1	64	32
10	3.1	3.1	50	0.78	0.78	25	1	2	64	>128
11	25	25	100	1.56	6.2	25	NT	NT	NT	NT
12	0.39	0.39	50	0.02	0.39	12.5	NT	NT	NT	32
13	0.39	0.39	12.5	0.02	0.2	6.2	0.12	2	8	32
14	3.1	3.1	25	0.78	1.56	6.2	1	2	8	>128
15	25	25	12.5	l 0.56	3.1	6.2	4	8	8	>128
16	0.1	0.1	50	0.02	0.1	25	0.06	1	64	16
17	1.56	0.78	>100	0.05	0.2	>100	0.5	2	>128	32
18	0.39	0.39	25	0.05	0.39	6.2	0.125	1	16	16
19	0.78	0.78	>100	0.05	0.39	>100	0.125	0.5	>128	16
20	0.39	0.39	50	0.02	0.39	25	0.125	1	32	16
21	0.39	0.39	100	0.01	0.39	25	0.25	2	64	16
22	0.39	0.78	25	0.05	0.78	6.2	0.125	1	16	32
23	>100	100	>100	6.2	NT	NT	1	4	8	>128
24	0.39	0.39	25	0.05	0.39	12.5	0.015	0.25	16	16
25	0.39	0.39	50	0.05	0.2	25	0.125	0.5	32	16
26	0.39	0.39	50	0.01	0.39	25	NT	NT	NT	16
27	0.78	NT	50	NT	0.39	12.5	≤0.004	0.03	NT	>128
28	1.56	NT	>100	0.05	0.2	100	≤0.004	2	>16	8
29	0.39	0.39	>100	0.2	0.2	>100	0.03	1	>128	16
30	0.2	0.39	25	0.01	0.39	3.1	0.03	2	8	64
31	1.56	1.56	>100	0.1	0.39	>100	0.25	2	>128	>128
32	3.1	3.1	>100	0.1	0.39	>100	0.5	2	>128	64
33	6.2	NT	>100	NT	3.1	50	0.03	2	NT	>64
34	6.2	NT	>100	NT	0.39	>100	≤0.004	≤0.004	NT	>64
35	0.39	NT	12.5	0.39	0.2	3.1	0.12	1	8	32
36	1.56	NT	>100	0.05	0.39	>100	0.25	4	>128	32
37	0.78	0.78	>100	0.02	0.2	>100	0.25	1	>128	16
38	12.5	6.2	>100	0.78	1.56	>100	1	2	>64	>64
39	12.5	12.5	>100	1.56	1.56	>100	2	2	>128	>128
40	25	25	>100	6.2	25	50	NT	NT	NT	NT
41	6.2	3.1	50	0.78	6.2	25	NT	NT	NT	NT

[a] Compounds were tested using standard agar dilution methods. [b] NT, not tested.

Scheme 4. Synthesis of Tricyclic Analogues **37** and **38**[a]



[a] Legend: (a) ethylenediamine/DMF/rt; (b) MeOH/rt; (c) AcOH/EtOH (reflux); (d) $NaCNBH_3$/AcOH/MeOH.

the same range as the alkylaryl carbamates, although compound **38**, the reduced analogue of **37**, showed significantly weaker activity. The isopropyl carbamate analogue **39** showed poor antibacterial activity compared to the alkylaryl counterparts, as did the acyclic carbamates **40** and **41**, although interestingly the activity of **41** was not attenuated against many of the resistant organisms.

A number of the more potent analogues (compounds **6**, **13**, **16**, **18**, **20**, **21**, and **37**) were evaluated for in vivo efficacy in mouse protection studies following protocols previously described.[9] As shown in Table 4, these compounds had only moderate in vivo activity in the mouse, with none of the compounds surpassing the activity of clarithromycin. Only compound **37** approached the activity of clarithromycin, being roughly 3-fold less active (po) against *S. aureus* and nearly equipotent against *S. pneumoniae*. The reason(s) for the lower in vivo activity, particularly given their excellent in vitro activity, is not known. Chemically these analogues are quite stable, although the metabolic stability of these compounds is not known. Also, these compounds are rather lipophilic, and it is known that increasing lipophilicity can be detrimental to in vivo activity of the macrolides.[10] Other possibilities for the low in vivo activity include rapid metabolism/excretion and/or poor distribution/bioavailability. Studies are ongoing to clarify these issues.

ORTEP representations for the crystal structures of

Table 3. Comparison of Crystal Structures and Computer Modeling of **6**, **7**, and Clarithromycin

	compound **6**		compound **7**		Clary
	X-ray	model[a]	X-ray	model[a]	X-ray
conformational energy (kcal/mol)	92.00	93.12	89.17	94.51	
torsion O=C1−C2=C3 (deg)	−27.62 (−39.69)	−46.08	−45.85 (−25.44)	−57.12	
torsion C1−C2=C3−C4 (deg)	158.97 (−165.38)	−167.05	−170.21(−168.85)	−173.73	
torsion C7−C8−C9=O (deg)	104.77 (95.56)	−61.36	−51.50 (−63.26)	126.74	114.48 (114.69)

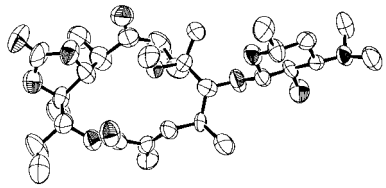
[a] Model where orientation of C-9 carbonyl is flipped with respect to crystal structure. Values in parentheses are for geometry-optimized structures using Insight Version 95.5.4 with CFF93 force field.

Table 4. In Vivo Efficacy of Carbamates in Mice[a]

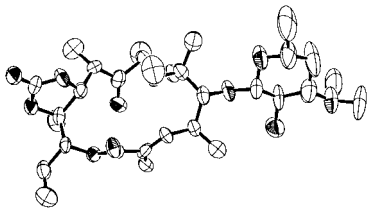
	S. aureus NCTC10649M[b]			*S. pneumoniae* ATCC6303[b]		
compd	MIC	sc	po	MIC	sc	po
6	1.56	NT	35.8 (17.4−73.7)	0.25	NT	>40
13	0.39	>40	>100	0.12	>16	>40
16	0.1	>40	50.1 (31.6−79.2)	0.06	>8	>20
18	0.39	ND	>100	0.125	ND	>100
20	0.39	ND	>100	0.125	ND	>40
21	0.39	ND	>100	0.25	ND	>100
37	0.05	>40	66.1 (42.3−103.3)	0.25	7.5 (2.9−19.5)	8.0 (5.1−12.5)
Clary	0.03	(6.7−20)	(14.3−24.8)	0.004	(1.4−4.5)	(7.6−30.2)

[a] Mice were intraperitoneally infected with 1000 × LD_{50} for *S. aureus* and 100−100 × LD_{50} for *S. pneumoniae.* Compounds were administered orally (po) or subcutaneously (sc) at 1 and 5 h pi. [b] Minimum inhibitory concentration (MIC) values are μg/mL. ED_{50}'s of test compounds reported in mg/kg/day (95% confidence interval). ND, not determined.

Chart 2. ORTEP Structures of **6** and **7**



Compound **6**



Compound **7**

the unsubstituted carbamates **6** and the C-10 epimer **7** are shown in Chart 2. For comparison sake, the conformations of these two anhydro macrolides have been overlaid with the X-ray structure of clarithromycin in Figure 1a. Generally, there is a good spatial overlap for all three compounds, with the macrolactone ring adopting a similar conformation and the desosamine sugar occupying approximately the same space. However, there are key differences between the three structures, particularly at the C2−C3 positions and the C-9 carbonyl. Interestingly, the C2−C3 double bond of **6** and **7** is not quite coplanar with the C-1 carbonyl, being offset by 27.6° and 45.8°, respectively. Compounds **6** and **7** differ from the crystal structure of clarithromycin in that the macrolactone ring does not extend out quite as far in the C1−C4 regions in these compounds as for clarithromycin. Also, **6** and **7** have a conformation in which the methyl group on C-2 is anti to the C-1 carbonyl group and occupies much different space with respect to the C-2 methyl group of clarithromycin (Figure 1b).

Although compounds **6** and **7** have similar conformations at the C1−C3 positions, they differ significantly from each other at the C-9 position. Both clarithromycin and **6** have the C-9 carbonyl group oriented "up", i.e., on the same face of the macrolactone ring as the C-1 carbonyl group (Figure 1c). In contrast, the C-9 carbonyl group of **7** is pointing "down" relative to the C-1 carbonyl. As shown in Table 3, the dihedral angle determined by the C7−C8−C9=O is very similar for clarithromycin and **6** (114.48° and 104.77°, respectively) but is nearly 160° out of phase for **7** (−51.50°). Molecular modeling calculations revealed that the crystal structures for **6** and **7** represent local energy minima, and in each case flipping the C-9 carbonyl to the opposite orientation (model in Table 3, obtained by epimerizing the C-10 methyl group of the other isomer) raised the calculated energy levels. Interestingly, molecular modeling of analogues of **6** and **7** in which the C2−C3 double bond has been isomerized to the *Z* isomer led to a 5.72 kcal/mol decrease in energy for **6** and a 5.9 kcal/mol increase in energy for **7**. However, the C2−C3 *Z* isomers were never observed, and attempts to isomerize the C2−C3 double bond were not successful.

A number of studies investigating the conformation of macrolides in the solid state,[11] in solution (NMR studies and molecular modeling),[12] and bound to the bacterial ribosome have been performed.[13] Generally it is believed that erythromycin A and clarithromycin have similar conformations both in the solid state and in solution, as well as bound to bacterial ribosomes. However, it is difficult to directly correlate macrolide conformations with antibacterial activity in vitro or in vivo because of the many factors (e.g., bacterial cell wall penetration, water solubility, bioavailability, etc.) influencing activity. Clearly, the observed conformational differences in the solid state between **6** and clarithromycin do not translate into major differences in in vitro antibacterial activity, as both compounds have very potent antibacterial activity. It may be that the lower activity of the epi analogue **7** compared to the natural C-10 isomer **6** is due to differing orientations of the C-9

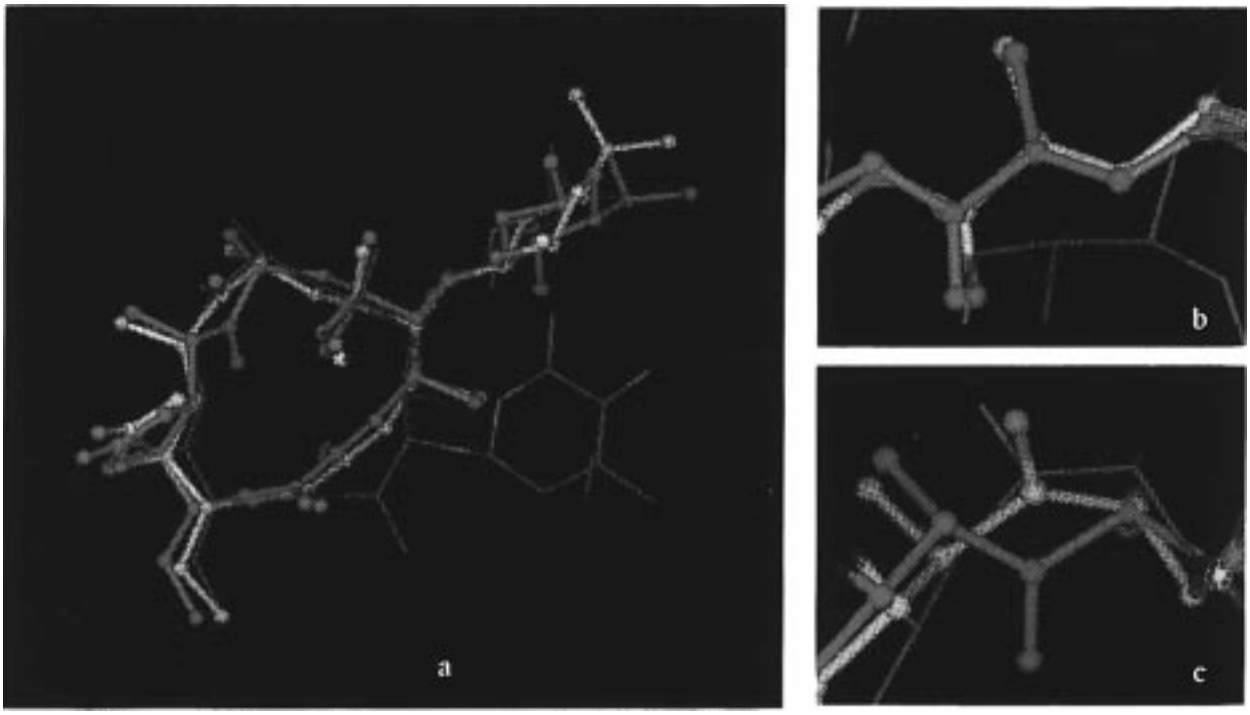


Figure 1. Comparison of solid-state conformations of **6**, **7**, and clarithromycin (hydrogens not shown): (a) superimposition of **6** (C-10 natural, yellow) and **7** (C-10 epi, magenta) over clarithromycin (green); (b) region around the C-1 carbonyl and C-2 methyl group of the superimposed structures; (c) C-9 carbonyl region of the superimposed structures.

carbonyl, although other factors may account for these differences. Also, the conformational preferences observed in crystals may not necessarily translate into the preferred ribosome-bound conformations. The only definitive statement that can be made is that, in terms of in vitro activity, major changes at the C2−C3 positions of clarithromycin can be incorporated and still maintain good to excellent in vitro antibacterial activity.

In summary, a series of 3-descladinosyl-2,3-anhydro-6-*O*-methylerythromycin A 11,12-carbamate analogues were synthesized and found to be potent antibacterial agents in vitro against Gram-positive organisms. Generally the alkylaryl carbamates had the best activity, optimally with a 2- or 4-carbon chain between the aryl group and carbamate nitrogen. However, none of the analogues evaluated had in vivo activity comparable to clarithromycin.

Experimental Section

All solvents and reagents were reagent grade unless otherwise noted. Elemental analyses were obtained from Robertson Laboratories, Madison, NJ. Chromatographic purifications were carried out using flash chromatography (60 mesh silica gel, 0.04−0.063 mm; E. Merck). Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were taken in $CDCl_3$ at 300 or 500 MHz, and chemical shifts are reported in ppm relative to $CHCl_3$ assigned at 7.26 and 77.0 ppm, respectively. Proton assignments were determined from ^{1}H−^{1}H COSY experiments. All final compounds, unless otherwise noted, were analyzed by ^{1}H NMR, ^{13}C NMR, MS, and elemental analysis and in general had a chemical purity of >95% as determined by ^{1}H NMR. *N*-Benzylethylenediamine was purchase from Eastman, *N*-(3-aminopropyl)-*N*-methylaniline from TCI, and 2-(4-phenoxyphenyl)ethylamine from Trans World Chemicals. 3-(1-Naphthyloxy)propylamine, 3-(4-chlorophenoxy)propylamine, 3-(4-pyridyl)propylamine, *N*-(3-quinolinyloxy)propylamine, (8-quinoyl)propylamine, and 3-phenoxypropylamine were prepared in a manner similar to that described by Smith et al.,[14] and 4-(4-chlorophenyl)-*cis*-3-butenylamine was prepared in a manner similar to that described by Olsen et al.[15] All other amines used in the synthesis of the carbamates were commercially available from Aldrich Chemical Co.

Descladinosyl-10,11-anhydro-6-*O*-methylerythromycin (1). A suspension of 6-*O*-methylerythromycin (98.48 g, 131.69 mmol), ethylene carbonate (50 mL, 750 mmol), and triethylamine (200 mL) was refluxed with vigorous stirring. After 29 h more ethylene carbonate (30 mL, 450 mmol) was added, and the reaction mixture refluxed for an additional 18 h. The triethylamine was then removed in vacuo, H_2O (400 mL)/10% aqueous HCl (200 mL)/EtOH (50 mL) was added, and the mixture stirred at room temperature for 24 h. The reaction mixture was then basified with 10% aqueous NaOH to pH ∼12−14 to precipitate the crude product, the aqueous layer decanted, and the precipitate dissolved in EtOAc (500 mL), washed with 200-mL portions of saturated aqueous $NaHCO_3$, H_2O, and brine, then dried ($MgSO_4$), and concentrated to afford the crude product as a white solid (65.94 g, 87%): mp 103−106 °C; MS *m*/*z* 572 $(M + H)^+$; ^{1}H NMR ($CDCl_3$) δ 6.48 (1, d), 4.96 (dd, 1), 4.59 (br d, 1), 4.50 (d, 1), 4.04 (dd, 1), 3.93 (d, 1), 3.71 (m, 1), 3.63−3.51 (br m, 1), 3.28−3.14 (m, 2), 3.10 (s, 3), 2.71 (m, 1), 2.50 (m, 1), 2.33−2.23 (m, 1), 2.26 (s, 6), 2.17 (s, 3), 2.04 (d, 3), 2.00−1.90 (m, 1), 1.74−1.52 (m, 3), 1.37 (s, 3), 1.34 (d, 3), 1.26 (s, 3), 1.26 (d, 3), 1.20 (d, 3), 1.03 (d, 3), 0.92 (t, 3).

2′-Acetyldescladinosyl-10,11-anhydro-6-*O*-methylerythromycin (2). A solution of **1** (65.94 g, 115.33 mmol), acetic anhydride (21.76 mL, 230.66 mmol), and triethylamine (32.15 mL, 230.66 mmol) in CH_2C1_2 (350 mL) was stirred at room temperature for 22 h; then the organic layer was washed with 200-mL portions of saturated aqueous $NaHCO_3$ (2×), H_2O (1×), and brine (1×), dried ($MgSO_4$), and concentrated to afford the crude product as a brown foam (69.08 g, 97% yield): MS *m*/*z* 614 $(M + H)^+$; ^{1}H NMR ($CDCl_3$) δ 6.42 (d, 1), 5.02 (dd, 1), 4.72 (m, 2), 3.88 (d, 1), 3.79 (d, 1), 3.52 (brm, 1), 3.15 (brm, 1), 3.10 (s, 3), 2.73−2.60 (m, 2), 2.29 (d, 2), 2.25 (s, 6), 2.11 (s, 3), 2.04 (d, 3), 2.01−1.87 (m, 1), 1.87−1.70 (m, 3), 1.65−1.43 (m, 3), 1.38 (s, 3), 1.32 (d, 3), 1.27 (s, 3), 1.26 (d, 3), 1.19 (d, 3), 0.92 (d, 3), 0.91 (t, 3).

2′-Acetyl-3-*O*-mesyldescladinosyl-10,11-anhydro-6-*O*-methylerythromycin (3). A solution of **2** (26.84 g, 43.72

mmol) and methanesulfonyl anhydride (9.14 g, 52.47 mmol) in pyridine (40 mL) was stirred at room temperature for 24 h; then the pyridine was removed in vacuo and the resulting solid washed with 300-mL portions of saturated aqueous $NaHCO_3$ (2×), H_2O (1×), and hexane (1×) to afford the crude product as a brown solid (27.65 g, 91% crude yield; estimated 90−95% pure). This material was somewhat unstable and hence was carried on in the next step without purification: mp 165−167 °C; MS *m/z* 692 $(M + H)^+$;^{1}H NMR ($CDCl_3$) δ 6.45 (d, 1), 5.10 (dd, 1), 4.80 (d, 1), 4.71 (dd, 1), 4.43 (d, 1), 3.94 (d, 1), 3.54 (br m, 1), 3.20 (br m, 1), 3.17 (s, 3), 3.14 (s, 3), 3.04−2.93 (br m, 1), 2.71 (m, 1), 2.27 (s, 6), 2.15−2.05 (m, 1), 2.04 (s, 3), 2.04 (d, 3), 1.97 (m, 1), 1.86−1.78 (m, 2), 1.70 (m, 2), 1.60−1.49 (m, 2), 1.43 (s, 3), 1.33 (s, 3), 1.32 (d, 3), 1.21 (d, 3), 1.14 (d, 3), 0.97 (d, 3), 0.91 (t, 3). Anal. Calcd for $C_{33}H_{57}NO_{12}S$: C, 57.29; H, 8.30; N, 2.02; S, 4.63. Found: C, 57.57; H, 8.30; N, 2.03; S, 4.37.

2′-Acetyl-2,3-dehydrodescladinosyl-10,11-anhydro-12-*O*-(acylimidazoyl)-6-*O*-methylerythromycin (4). A solution of **3** (50.00 g, 72.2 mmol) in DMF (500 mL)/THF (166 mL) was treated with CDI (50.00 g, 308.3 mmoL) followed by NaH (11.55 g (60% oil dispersion), 287.5 mmoL) at 0 °C over a 30-min period, then the cooling bath was removed, and the reaction mixture was stirred at room temperature for 5 h. The reaction mixture was then diluted with EtOAc (1.5 L), washed with 250-mL portions of saturated aqueous $NaHCO_3$ (1×), H_2O (3×), and brine (3×), dried ($MgSO_4$), and concentrated to afford the crude product as a white solid (52.46 g). Chromatographic purification (silica, acetone/hexane, 1:1) afforded the product as a white foam (37.77 g, 75% yield). An analytically pure sample was obtained by recrystallization from Et_2O/Hex: mp 117−119 °C; ^{1}H NMR ($CDCl_3$) δ 8.02 (m, 1), 7.33 (m, 1), 7.02 (m, 1), 7.01 (dd, 1), 6.52 (d, 1), 5.54 (dd, 1), 4.75 (dd, 1), 4.42 (d, 1), 3.67 (d, 1), 3.50 (m, 1), 3.05 (s, 3), 3.01 (m, 1), 2.76−2.60 (m, 2), 2.26 (s, 6), 2.09 (dd, 1), 2.03 (s, 3), 1.88 (s, 6), 1.87−1.65 (m, 2), 1.76 (d, 3), 1.57 (dd, 1), 1.34 (br m, 2), 1.30 (s, 3), 1.29 (d, 3), 1.25 (d, 3), 1.16 (d, 3), 1.07 (t, 3); MS *m/z* 690 $(M + H)^+$.

General Procedure for 2,3-Anhydro-6-*O*-methylerythromycin A 11,12-Carbamates. To a 0.2−0.3 M solution of the acylimidazolide **4** in either DMF or 10% aqueous MeCN was added the amine (∼3−5 equiv), and the reaction mixture was allowed to stir at room temperature for 1−3 days. The reaction mixture was then diluted with CH_2Cl_2, washed with water and brine, dried (Na_2SO_4 or $MgSO_4$), and concentrated to afford the crude product as a mixture of isomers at C-10. Chromatographic separation (flash chromatography, typically ∼1−6% MeOH/$CHCl_3$ or CH_2Cl_2 with 0.1−0.2% NH_4OH using a stepwise gradient, typical column loading was 200/1 (silica/sample weight)) afforded the desired product. Stirring overnight in methanol effected removal of the 2′-OAc to afford the desired product.

12-Hydroxy-2,3,10,11-dianhydro Macrolide 5. A solution of imidazole (5.90 g, 86.72 mmol) in THF (15 mL)/DMF (50 mL) at 0 °C was treated with NaH (2.31 g, 57.81 mmol) portionwise over a 10-min period; then compound **3** (10.00 g, 14.45 mmol) was added and the cooling bath removed. After stirring at room temperature for 1 h, the reaction mixture was diluted into EtOAc (300 mL)/saturated aqueous $NaHCO_3$ (200 mL); the organic layer was washed with brine (3 × 200 mL), dried ($MgSO_4$), and concentrated to afford the crude product as a white foam (9.71 g). Recrystallization from Et_2O/hexane afforded the 2′-OAc-protected **5** as a white solid (first crop = 4.30 g): MS *m/z* 596 $(M + H)^+$. A portion of this material (366 mg, 0.614 mmol) was stirred in MeOH (10 mL) for 2 days to afford **5** (328 mg, 96%) as a white foam: MS *m/z* 554 $(M + H)^+$.

Tricyclic 9-Imino Macrolide 37. To a solution of the acylimidazolide **4** (4.073 g, 5.90 mmol) in DMF (10 mL) was added ethylenediamine (4 mL, 59.83 mmol). After stirring at room temperature for 2.5 days, the reaction mixture was diluted with EtOAc (150 mL), washed with 35-mL portions of saturated aqueous $NaHCO_3$ (1×), water (1×), and brine (1×), dried ($MgSO_4$), and concentrated to afford the crude product as a white form. This material was then stirred in methanol (50 mL) overnight to effect removal of the 2′-OAc group, then the MeOH was removed in vacuo, EtOH (100 mL) and AcOH (4 mL) were added, and the reaction mixture was refluxed for 22 h to effect ring closure. The reaction mixture was then diluted with EtOAc (75 mL), washed with 35-mL portions of saturated aqueous $NaHCO_3$ (2×), water (1×), and brine (1×), dried ($MgSO_4$), and concentrated to afford the crude product as a white foam (1.37 g). Chromatographic purification (silica, $CHCl_3$/MeOH/TEA, 900:50:2) yielded the desired product as a white foam (1.00 g). An analytically pure sample was obtained by recrystallization from acetone/hexane to afforded the product as a white solid (338 mg).

Tricyclic 9-Amino Macrolide 38. To a solution of **37** (166 mg, 0.267 mmol) in MeOH (6 mL) and AcOH (0.5 mL) was added $NaCNBH_3$ (126 mg, 2.00 mmol), and the reaction mixture was stirred at room temperature for 5 h. The reaction mixture was diluted with CH_2Cl_2 (40 mL), washed with 20-mL portions of saturated aqueous $NaHCO_3$ (2×) and brine (1×), dried ($MgSO_4$), and concentrated to afford the crude product as a white form (119 mg). Chromatographic purification (silica, 3% MeOH/$CHCl_3$, then 10% MeOH/$CHCl_3$) yielded the pure product as a white solid (63 mg, 38%).

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Supporting Information Available: Complete ^{13}C and ^{1}H NMR peak assignments for all final compounds, as well as crystallographic data, atomic coordinates, anisotropic displacement parameters, bond lengths, bond angles, and torsion angles for **6** and **7** (50 pages). Ordering information is given on any current masthead page.

References

(1) (a) Zuckerman, J. M.; Kaye, K. M. The newer macrolides. Azithromycin and clarithromycin. *Infect. Dis. Clin. North. Am.* **1995**, *9* (3), 731−745. (b) Bahal, N.; Nahata, M. C.; Egle, J. L., Jr. Chapter 93, Aminoglycosides, Tetracyclines, Chloramphenicol, Erythromycin and Related Macrolides, and Other Protein Synthesis Inhibitors. In *Principles of Pharmacology: Basic Concepts and Clinical Applications*; Munson, P. L., Mueller, R. A., and Breese, G. R., Eds.; Chapman & Hall: New York, 1995. (c) Bahal, N.; Nahata, M. C. The new macrolide antibiotics: azithromycin, clarithromycin, dirithromycin, and roxithromycin. *Ann. Pharmacother.* **1992**, *26* (1), 46−55.

(2) (a) Agouridas, C.; Bonnefoy, A.; Chantot, J. F.; Le Martret, O.; Denis, A. (Roussel-Uclaf) EP596802-A1, May 11, 1994. (b) Le Martret, O.; Agouridas, C.; Bonnefoy, A.; Chantot, J. F.; Denis, A. (Roussel-Uclaf) FR2697524-A1, May 6, 1994. (c) Agouridas, C.; Benedetti, Y.; Chantot, J. F.; Denis, A.; Le Martret, O. (Roussel-Uclaf) EP676409-A1, Oct. 11, **1995**. Also see: Agouridas, C.; Benedetti, Y.; Denis, A.; Le Martret, O.; Chantot, J. F. 35th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, CA, Sept. 17−20, 1995; Abstr. No. F157. (d) Griesgraber, G.; Or, Y. S.; Chu, D. T. W.; Nilius, A. M.; Johnson, P. M.; Flamm, R. K.; Henry, R. F.; Plattner, J. J. 3-Keto-11,12-Carbazate Derivatives of 6-O-Methylerythromycin-A. Synthesis and In Vitro Activity. *J. Antibiot.* **1996**, *49*, 465−477. (e) Jamjian, C.; Biedenbach, D. J.; Jones, R. N. In Vitro Evaluation of a Novel Ketolide Antimicrobial Agent, Ru-64004. *Antimicrob. Agents Chemother.* **1997**, *41* (2), 454−459.

(3) Elliott, R. L.; Pireh, D.; Nilius, A. M.; Johnson, P. M.; Flamm, R. K.; Chu, D. T. W.; Plattner, J. J.; Or, Y. S. Novel 3-Deoxy-3-Descladinosyl-6-*O*-Methyl Erythromycin A Analogues. Synthesis and In Vitro Activity. *Bioorg. Med. Chem. Lett.* **1997**, *7* (5), 641−646.

(4) Burgess, E. M.; Penton, H. R., Jr.; Taylor, E. A. Thermal Reactions of Alkyl *N*-Carbomethoxysulfamate Esters. *J. Org. Chem.* **1973**, *38*, 26−31.

(5) Weber, J. M.; Leung, J. O.; Swanson, S. J.; Idler, K. B.; McAlpine, J. B. An erythromycin derivative produced by targeted gene disruption in *Saccharopolyspora erythraea*. *Science* **1991**, *252*, 114−117.

(6) G. Griesgraber, personal communication.

(7) Baker, W. R.; Clark, J.; Stephens, R. L.; Kim, K. H. Modifications of Macrolide Antibiotics. Synthesis of 11-Deoxy-11-(carboxyamino)-6-O-Methylerythromycin A 11,12-(Cyclic esters) via an Intramolecular Michael Reaction of O-Carbamates with an α,β-Unsaturated Ketone. *J. Org. Chem.* **1988**, *53*, 2340−2345.

(8) Asaka, T.; Kashimura, M.; Misawa, Y.; Ono, T.; Suzuki, K.; Yoshida, H.; Yoshida, T.; Akashi, T.; Yokoo, C.; Nagate, T.; Morimoto, S. A New Macrolide Antibiotic, TE-802; Synthesis and Biological Properties. 35th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, CA., Sept. 17−20, 1995; Poster F176.

(9) Hardy, D. J.; Swanson, R. N.; Shipkowitz, N. L.; Frieberg, L. A.; Lartey, P. A.; Clement, J. J. In Vitro Activity and In Vivo Efficacy of a New Series of 9-Deoxo-12-Deoxy-9,12-Epoxyerthromycin A Derivatives. *Antimicrob. Agents Chemother.* **1991**, *35* (5), 922−928.

(10) McFarland, J. W.; Hecker, S. J.; Jaynes, B. H.; Jefson, M. R.; Lundy, K. M.; Vu, C. B.; Glazer, E. A.; Froshauer, S. A.; Hayashi, S. F.; Kamicker, B. J.; Reese, C. P.; Olson, J. A. Repromicin Derivatives with Potent Antibacterial Activity against *Pasteurella multocida*. *J. Med. Chem.* **1997**, *40*, 1041−1045.

(11) Keller, T.; Neeland, E.; Rettig, S.; Trotter, J.; Weiler, L. Conformational Analysis of 14-Membered Macrolides Using X-ray Cystallography and Molecular Mechanics Calculations. *J. Am. Chem. Soc.* **1988**, *110*, 7858−7868.

(12) (a) Steinmetz, W. E.; Bersch, R.; Towson, J.; Pesiri, D. The Conformation of 6-Methoxyerythromycin A in Water Determined by Proton NMR Spectroscopy. *J. Med. Chem.* **1992**, *35*, 4842−4845. (b) Everett, J. R.; Tyler, J. W. Novel Conformations of Erythromycin Antibiotics: the Conformational Analysis of Erythromycin A and (9S)-9-Hydroxy-9-deoxoerythromycin A by NMR Spectroscopy. *J. Chem. Soc., Chem. Commun.* **1987**, 815−816. (c) Everett, J. R.; Tyler, J. W. The Conformational Analysis of Three Derivatives of Erythromycin A: (9S)-9-Hydroxy-9-deoxoerythromycin A, (9S)-9, 11-*O*-Isopropylidene-9-deoxoerythromycin A, and (9S)-Erthromycylamine A by Nuclear Magnetic Resonance Spectroscopy and Molecular Modelling. *J. Chem. Soc., Perkin Trans. 2* **1988**, 325−337.

(13) Awan, A.; Brennan, R. J.; Regan A. C.; Barber, J. Conformational Analysis of the Erythromycin Analogues Azithromycin and Clarithromycin in Aqueous Solution and Bound to Bacterial Ribosomes. *J. Chem. Soc., Chem. Commun.* **1995**, *16*, 1653−1654.

(14) Smith, K.; Morris, I. K.; Owen, P. G. Synthesis of Novel Macrocyclic Lactones with Potential Pharmacological Activity. *J. Chem. Soc., Perkin Trans. I* **1988**, 77−83.

(15) Olsen, D. K.; Torian, B. E.; Morgan, C. D.; Braun, L. L. Preparation and Stereochemistry of 4-Aryl-3-butenylamines. A Novel Synthesis of an Oxazolo[2,3-a]isoindole. *J. Org. Chem.* **1980**, *45*, 4049−4052.

JM970547X