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Synthesis and antibacterial activity of C_{12} des-methyl ketolides

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Abstract—Synthesis of C_{12} des-methyl ketolide is developed featuring an intramolecular epoxide formation/elimination process to establish the C_{12} stereocenter. These ketolides are potent against several key respiratory pathogens, including erythromycin resistant *erm*- and *mef*-containing strains of *Streptococcus pneumoniae*.

Macrolide antibiotics such as erythromycin A (Fig. 1) are potent against several key respiratory pathogens including *Staphylococcus aureus* and *Streptococcus pneumoniae*. They have been widely used for the treatment of bacterial respiratory tract infections for many years. The second generation of macrolides, including clarithromycin[1] and azithromycin,[2] was developed to overcome the problems associated with acid instability of erythromycin.[3] These compounds displayed better pharmacokinetic properties as well as a broader spectrum of activity.

Macrolides exert their antibacterial activity by reversibly binding to the 23S ribosomal RNA in the 50S subunit of ribosomes in order to block protein synthesis.[4] Recently, macrolide resistant pathogens with two main resistant mechanisms, active efflux of the drug (*mef* gene) and target site modification (*erm* gene), have emerged.[5] To overcome the resistant pathogens, a third generation of macrolide known as ketolides (telithromycin[6] and cethromycin (ABT-773)[7]) has been developed. Ketolides differ from other macrolides in that the C_3 cladinose sugar of erythromycin A is replaced with a C_3 ketone group. Additionally, a heterocycle is tethered to the macrolide core, introducing an additional binding contact with the target ribosome.

In our laboratories, we sought to develop novel ketolides with in vitro and in vivo potency against resistant strains. These ketolides are novel in that they have a C_{12} modified macrocycle core. Using chemical synthesis we have been able to access C_{12} hydrogen (des-methyl)[8a] and other alkyl groups[8,9] in place of the natural C_{12} methyl of erythromycin derived macrocycles. In this paper, we wish to report the synthesis of C_{12} des-methyl macrolide core, conversion of the core to ketolide derivatives, and in vitro activities of the resulting ketolides.

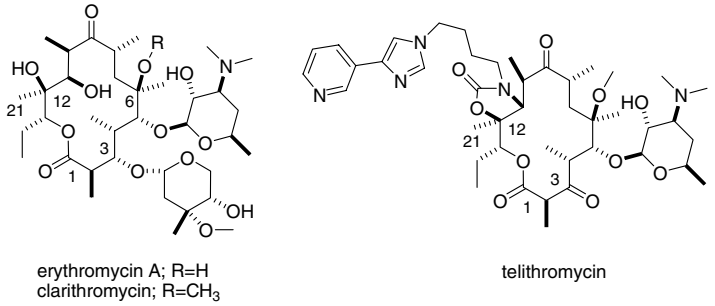

Figure 1. Clinically utilized macrolides.

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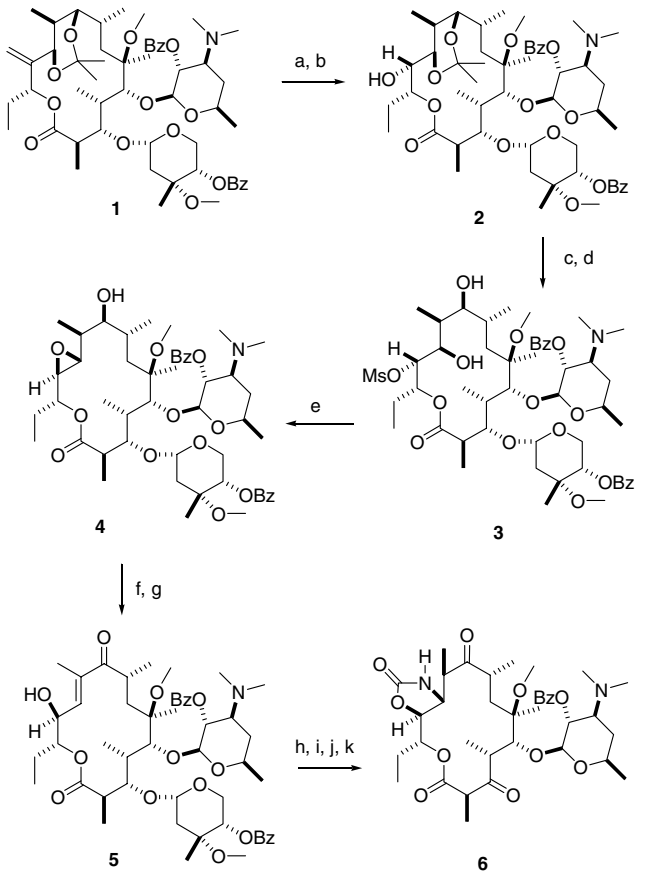


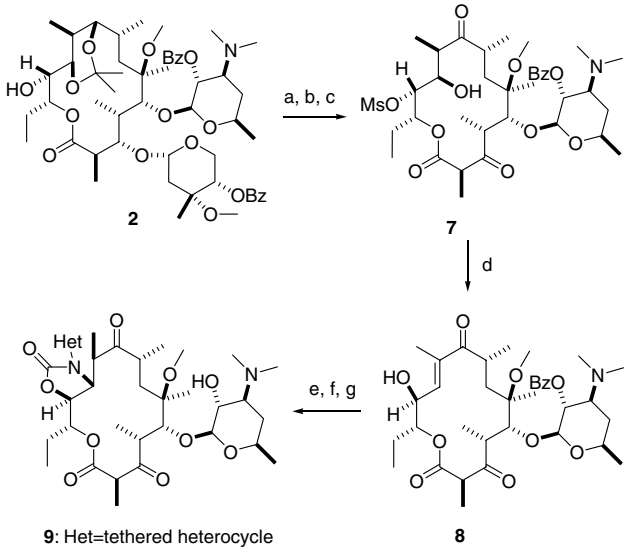
Scheme 1. Reagents and conditions: (a) *p*-TsOH, O_3, DCM/MeOH, −78 °C, 10 min; then Me_2S, −78 °C, 10 min; then Et_3N, −78 to 25 °C, 85%; (b) $NaBH_4$, EtOH, 25 °C, 17 h; (c) MsCl, DMAP, Et_3N, DCM, 0 °C, 30 min; (d) HOAc, ACN, H_2O, 65 °C, 16 h, 83% over three steps; (e) Cs_2CO_3, ACN, 25 °C, 22 h; (f) Dess–Martin periodinane, DCM, 0–25 °C, 6 h, 96% over two steps; (g) DBU, acetone, 25 °C, 6 h; (h) CDI, NaH, THF, −15–0 °C, 2 h; (i) NH_4OH, THF, ACN, 50 °C, 22 h, 63% over three steps; (j) 3 M HCl (aq), ACN, 25 °C, 26 h, 92%; (k) *N*-chlorosuccinimide, Me_2S, DCM, −20 °C, 40 min; then Et_3N, −20–0 °C, 30 min, 75%.

Synthetic modifications of erythromycin have been pursued by numerous investigators in order to prepare chemical derivatives with improved biological profiles. More recently, modifications involving the C_{11} and C_{12} hydroxyl groups have been extensively explored,[10] which, in conjunction with modifications of C_3 cladinose moiety, eventually yielded the recently approved ketolide telithromycin. However, there are few examples of chemical modifications to erythronolides at C_{12} and, especially, with regard to the C_{12}—C_{21} bond.[11]

We have previously reported the efficient synthesis of a suitably protected C_{12}—C_{21} exocyclic alkenyl macrolide **1** from erythromycin A.[9] As shown in Scheme 1,[12] ozonolysis of the tosylate salt of **1** yielded C_{12}-keto macrolide. Hydride reduction of the C_{12}-keto group then afforded C_{12} des-methyl macrolide core **2**, with undesired and unnatural C_{12} alpha hydroxy configuration. The stereochemistry at C_{12} was determined based upon X-ray diffraction of the crystals of **2**.[13] Efforts to deliver hydride from the bottom face were not fruitful. Several attempts to invert the alpha hydroxyl group at C_{12}, including Mitsunobu reaction and intermolecular S_N2-type reaction with the mesylate of **2**, did not yield any desired product. It appears that the C_{12} secondary alcohol and its mesylate are not reactive toward intermolecular S_N2-type reactions, probably because the site is too crowded. Hence we sought to invert the C_{12} alpha hydroxy via an intramolecular reaction.

Converting the C_{12} hydroxyl group to mesylate followed by hydrolysis of the cyclic acetonide using acetic acid yielded diol **3**. Treatment of **3** with cesium carbonate gave the C_{11}—C_{12} epoxide **4** with inversion of stereocenter at C_{12}. To confirm the stereochemistry of compound **4**, the benzoyl protecting group at C-2′of the desosamine was removed to grow the crystal and a structure was determined by X-ray diffraction.[13] To complete the synthesis, C_9 was oxidized and the resulting ketone was subjected to basic conditions which allowed deprotonation and β-elimination, resulting in enone **5**. Deprotonation with sodium hydride in the presence of carbonyldiimidazole gave C_{12} imidazole carbamate, which upon reaction with excess ammonia yielded C_{11}—C_{12} cyclic NH carbamate. Acidic hydrolysis of the cladinose and subsequent Corey–Kim oxidation of C_3-hydroxy to C_3-keto then gave ketolide **6**. The X-ray crystal diffraction of **6** unambiguously confirmed the stereochemistry of the C_{12} des-methyl ketolide.[13]

Scheme 2[12] illustrates a more concise sequence for synthesizing C_{12} des-methyl ketolide analogs with different heterocycles tethered to the carbamate nitrogen. Thus, mesylate formation of **2** was followed by hydrolysis of both C_3 cladinose and cyclic acetonide with hydrochloric acid. The subsequent oxidation using Dess–Martin periodinane oxidized both C_3 and C_9 hydroxy groups to afford diketone **7**. Treatment of **7**



Scheme 2. Reagents and conditions: (a) MsCl, DMAP, Et_3N, CH_2Cl_2, 0 °C, 30 min; (b) 3 M HCl (aq), ACN, 25 °C, 14 h, 88% over two steps; (c) Dess–Martin periodinane, CH_2Cl_2, 0–4 °C, 48 h, 77%; (d) DBU, acetone, 25 °C, 15 h, 72%; (e) NaH, CDI, THF, −15–0 °C, 25 min; (f) Het-amine, ACN, 75 °C, 40 h, 43–84% over two steps; (g) MeOH, 70 °C, 22 h, 42–79%.

with DBU in acetone allowed epoxide formation, deprotonation at C_{10}, and elimination/epoxide opening to occur in one pot. The resulting enone **8** was transformed to C_{12} imidazole carbamate, which upon reaction with an excess of side-chain amine and deprotection of the desosamine benzoate by heating in methanol yielded final ketolide analogs **9**. The C_{12} des-methyl ketolides (**9a**–**9u**) prepared and reported are illustrated in Figure 2. The heteroaryl side-chain amines incorporated into the ketolides were synthesized as described previously.[9]

The structural assignments of the final ketolides were supported by NMR comparison to analog **6**, of which the crystal structure was obtained, and its 2′-hydroxy derivative. Additionally, for compound **9g**, which has the same alkyl tethered group off the cyclic carbamate as telithromycin, the ^{1}H NMR peaks for the macrocycle core, excluding resonances for the C_{12} methyl or hydrogen group, are practically identical to those of telithromycin.[14]

To evaluate the antibacterial activity, the C_{12} des-methyl ketolides were assayed in a primary panel against a number of strains of *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Enterococcus faecalis*, *Streptococcus pyogenes*, *Streptococcus pneumoniae*, and *Haemophilus influenzae*. Included among the strains of *S. pneumoniae* were erythromycin resistant strains containing *mef* and *erm* genes. Telithromycin and clarithromycin were used for comparison in all assays. The in vitro antibacterial activity is reported as the minimum inhibitory concentration (MIC) in μg/mL as determined by the Broth microdilution method.[15]

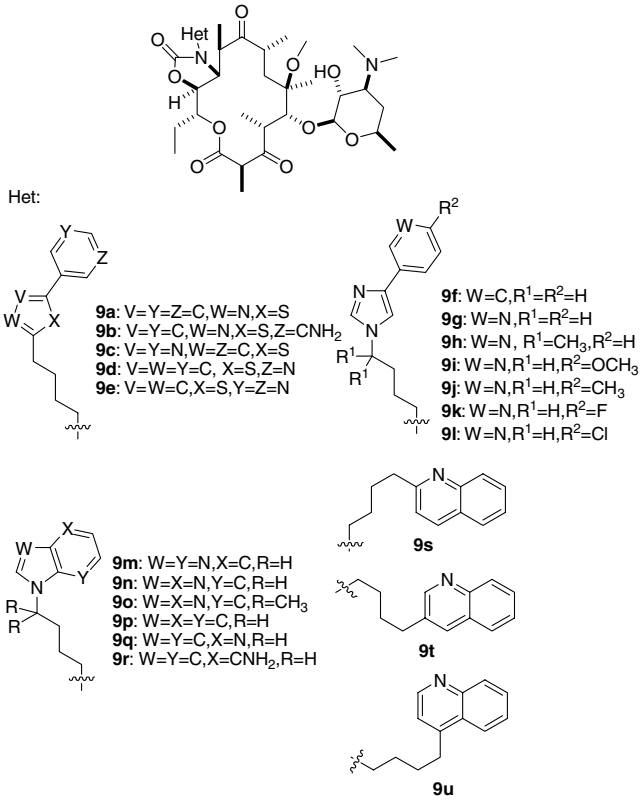


Figure 2. Structures of C_{12} des-methyl ketolides.

The data in Tables 1 and 2 indicate that, in general, C_{12} des-methyl ketolides possess similar potency as telithromycin against most pathogens in vitro. Most of the C_{12} des-methyl ketolides are potent against the *mef* and *erm* gene-containing *S. pneumoniae* strains that clarithromycin is not active against. The overall activity spectrum of the C_{12} des-methyl ketolides can be attenuated by the nature of the heterocycle tethered to the C_{11}, C_{12} carbamate. All of the heterocyclic moieties on the C_{12} des-methyl ketolides reported here are tethered to the C_{11} attached nitrogen via a four-atom spacer. The heterocyclic moieties can be divided into 5,6-membered unfused bi-heteroaryl or 5,6- and 6,6-fused heteroaromatic bicyclic systems.

Among the 5,6-membered biaryl heterocycle analogs (Table 1), compound **9g** contains the same pyridyl imidazole moiety as telithromycin. Although **9g** showed very similar potency as telithromycin against most pathogens tested, it was not potent against *E. faecalis_bc11148-2*. This is also seen for clarithromycin and seems a general trend for most of C_{12} des-methyl ketolides with a few exceptions (Tables 1 and 2). Changing the pyridyl to phenyl ring, compound **9f** showed much improved potency against two *mef*-containing resistant strains (vs **9g** and teli). Replacing the imidazole ring with thiophene, analogs **9d** and **9e** showed weaker activity against *erm*-containing and *H. influenzae* strains. The three thiazole-containing analogs (**9a**–**c**) all showed improved potency against *E. faecalis_bc11148-2* (vs **9g**). However, they also suffered from poor potency against *erm* strain. Similar potency profile change was also observed with **9i** and **9j**, analogs having substitution *ortho* to nitrogen of the pyridine ring. Compound **9a** was the least potent among all analogs. Adding *gem*-dimethyl group off the alpha carbon of the carbon chain linker resulted in much improved potency against *E. faecalis_bc11148-2* (**9h** vs **9g**). The most interesting observation is from compounds **9k** and **9l**, containing 2-fluoropyridine and 2-chloropyridine, respectively. Although **9k** showed decreased potency against resistant strains, compound **9l** showed much improved potency vs **9g** and an activity profile comparable to telithromycin.

Table 2 summarizes data of fused biaryl heterocycle analogs. Among three aza-benzimidazole compounds, adding *gem*-dimethyl group off the alpha carbon of the carbon chain linker once again resulted in much improved potency against *E. faecalis_bc11148-2* (**9o** vs **9m** and **9n**). The 4-azaindole (**9q**)- and 4-aminoindole-(**9r**) containing analogs had potency better than the indole analog **9p**. All three compounds had improved potency against *mef* strains compared to telithromycin, especially **9q**. The three quinoline-containing derivatives differ by the position of carbon chain linker which influenced the potency profile as well. For example, **9s**, with linker *ortho* to the nitrogen, had improved activity against *E. faecalis_bc11148-2* (vs **9g**) as well as *mef*

Table 1. In vitro antibacterial activity [MIC (μg/mL)] of C_{12} des-methyl ketolides[a]

Strains	9a	9b	9c	9d	9e	9f	9g	9h	9i	9j	9k	9l
S. aureus_29213	0.78	0.4	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
S. aureus_33591	>50	>50	>50	50	>50	>50	>50	>50	>50	>50	>50	>50
S. epidermidis_14990	0.78	0.4	0.2	0.2	0.2	0.1	0.78	0.1	0.1	0.2	0.2	0.1
S. epidermidis f50654	0.4	0.2	0.1	0.1	0.2	0.2	0.2	0.1	0.2	0.2	0.78	0.2
E. faecalis_29212	0.4	0.2	⩽0.05	⩽0.05	⩽0.05	0.1	0.1	0.1	⩽0.05	0.1	⩽0.05	⩽0.05
E. faecalis_bc11148-2	6.25	3.13	3.13	25	>50	>50	>50	1.56	6.25	3.13	25	0.4
S. pyogenes_8668	0.2	⩽0.05	⩽0.05	⩽0.05	⩽0.05	⩽0.05	⩽0.05	⩽0.05	⩽0.05	⩽0.05	⩽0.05	⩽0.05
S. pneumo_49619	⩽0.05	⩽0.05	⩽0.05	⩽0.05	⩽0.05	⩽0.05	⩽0.05	⩽0.05	⩽0.05	⩽0.05	⩽0.05	⩽0.05
S. pneumo_297-749	⩽0.05	⩽0.05	⩽0.05	⩽0.05	⩽0.05	⩽0.05	⩽0.05	⩽0.05	⩽0.05	⩽0.05	⩽0.05	⩽0.05
S. pneumo_280-962	⩽0.05	⩽0.05	⩽0.05	⩽0.05	⩽0.05	⩽0.05	⩽0.05	⩽0.05	⩽0.05	⩽0.05	0.2	⩽0.05
S. pneumo_Erm 6849	25	50	25	6.25	>50	0.78	0.2	0.4	50	50	12.5	0.4
S. pneumo_Mef 5654	1.56	0.78	0.78	0.4	0.4	0.2	1.56	1.56	0.78	1.56	0.78	0.78
S. pneumo_Mef S 3427	0.1	⩽0.05	0.1	0.1	⩽0.05	⩽0.05	0.2	0.2	0.1	0.4	0.78	0.1
H. influenzae_49247	12.5	6.25	6.25	12.5	12.5	3.13	6.25	3.13	6.25	3.13	3.13	6.25
H. influenzae_2762	3.13	1.56	1.56	3.13	3.13	nd	0.78	1.56	1.56	1.56	0.78	1.56

[a] nd, not determined.

Table 2. In vitro antibacterial activity [MIC (μg/mL)] of C_{12} des-methyl ketolides[a]

Strains	9m	9n	9o	9p	9q	9r	9s	9t	9u	teli	clari
S. aureus_29213	0.2	0.4	0.2	0.4	0.2	0.2	0.4	0.4	0.1	0.1–0.2	0.4–0.78
S. aureus_33591	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50
S. epidermidis_14990	0.2	0.4	0.1	0.2	0.4	0.4	0.2	0.2	0.1	0.1–0.2	0.2–0.4
S. epidermidis f50654	0.4	0.4	0.1	0.4	0.4	0.78	0.2	0.4	0.1	0.1–0.2	0.2–0.4
E. faecalis_29212	⩽0.05	0.1	⩽0.05	0.1	0.1	⩽0.05	⩽0.05	0.1	⩽0.05	⩽0.05–0.1	0.78–1.56
E. faecalis_bc11148-2	50	>50	1.56	>50	6.25	6.25	3.13	12.5	>50	0.4	>50
S. pyogenes_8668	⩽0.05	⩽0.05	⩽0.05	⩽0.05	⩽0.05	⩽0.05	⩽0.05	⩽0.05	⩽0.05	⩽0.05	⩽0.05
S. pneumo_*49619*	⩽0.05	⩽0.05	⩽0.05	⩽0.05	⩽0.05	0.1	⩽0.05	⩽0.05	⩽0.05	⩽0.05	⩽0.05
S. pneumo_297-749	⩽0.05	⩽0.05	⩽0.05	⩽0.05	⩽0.05	⩽0.05	⩽0.05	⩽0.05	⩽0.05	⩽0.05	⩽0.05
S. pneumo_280-962	⩽0.05	⩽0.05	⩽0.05	⩽0.05	⩽0.05	⩽0.05	⩽0.05	⩽0.05	⩽0.05	⩽0.05	⩽0.05
S. pneumo_Erm 6849	0.78	0.78	6.25	6.25	0.2	25	25	0.4	6.25	0.1–0.4	>50
S. pneumo_Mef 5654	0.78	3.13	1.56	0.2	0.2	0.78	0.2	0.2	0.1	0.4–0.78	6.25–12.5
S. pneumo_Mef S 3427	⩽0.05	0.4	0.2	⩽0.05	⩽0.05	⩽0.05	⩽0.05	0.1	⩽0.05	0.1–0.2	3.13–6.25
H. influenzae_49247	3.13	3.13	6.25	6.25	1.56	3.13	3.13	6.25	1.56	3.13–6.25	6.25–12.5
H. influenzae_2762	nd	nd	1.56	nd	0.78	1.56	nd	1.56	nd	0.4–1.56	0.78–3.13

[a] nd, not determined; teli, telithromycine; clari, clarithromycin.

strains (vs teli), but lost potency against *erm* strain. Compound **9u** had better potency than telithromycin against *mef* and *H. influenzae* strains.

In summary, we have developed synthesis of C_{12} des-methyl ketolides. In order to establish desired/natural stereocenter at C_{12}, a novel process involving an intramolecular epoxide formation and elimination is discovered. Most of the C_{12} des-methyl ketolides have in vitro antibacterial spectrum similar as telithromycin and are potent against *erm* and *mef*-gene containing resistant strains of *S. pneumoniae*.

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Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.bmcl.2006.05.104.

References and notes

1. Morimoto, S.; Takahashi, Y.; Watanabe, Y.; Omura, S. *J. Antibiot.* **1984**, *37*, 343.
2. (a) Bright, G.; Nage, A.; Bordner, J.; Desai, K.; Dibrino, J.; Nowakowska, J.; Vincent, L.; Watrous, R.; Sciavolino, F.; English, A.; Retsema, J.; Anderson, M.; Brennan, L.; Borovoy, R.; Cimchowsji, C.; Faiella, J.; Girard, A.; Girard, D.; Herbert, C.; Manousos, M.; Mason, R. *J. Antibiot.* **1988**, *41*, 1029; (b) Retsema, J. A.; Girard, A. E.; Schekly, W.; Manousos, M.; Anderson, M. R.; Bright, G. M.; Borovoy, R. J.; Brennan, L. A.; Mason, R. *Antimicrob. Agents Chemother.* **1987**, *31*, 1939.
3. (a) Kurath, P.; Jones, P. H.; Egan, R. S.; Perun, T. J. *Experentia* **1971**, *27*, 362; (b) Krowicki, K.; Zamojski, A. *J. Antibiot.* **1974**, *26*, 569.
4. (a) Hansen, L. H.; Mauvais, P.; Douthwaite, S. *Mol. Microbiol.* **1999**, *31*, 623; (b) Schlünzen, F.; Zarivach, R.; Harms, J.; Bashan, A.; Tocilj, A.; Albrecht, R.; Yonath, A.; Franceschi, F. *Nature* **2001**, *413*, 814.
5. (a) Leclercq, Q.; Courvalin, P. *Antimicrob. Agents Chemother.* **1991**, *35*, 1267; (b) Leclercq, Q.; Courvalin, P. *Antimicrob. Agents Chemother.* **1991**, *35*, 1273; (c) Sutcliffe, J.; Tait-Kamradt, A.; Wondrack, L. *Antimicrob. Agents Chemother.* **1996**, *40*, 1817.
6. (a) Agouridas, C.; Denis, A.; Auger, J. M.; Benedetti, Y.; Bonnefoy, A.; Bretin, F.; Chantot, J. F.; Dussarat, A.; Fromentin, C.; D'Ambrières, S. G.; Lachaud, S.; Laurin,

P.; Le Martret, O.; Loyau, V.; Tessot, N. *J. Med. Chem.* **1998**, *41*, 4080; (b) Denis, A.; Agouridas, C.; Auger, J.-M.; Benedetti, Y.; Bonnefoy, A.; Bretin, F.; Chantot, J.-F.; Dussarat, A.; Fromentin, C.; D'Ambrieres, S. G.; Lachaud, S.; Laurin, P.; Martret, O. L.; Loyau, V.; Tessot, N.; Pejac, J.-M.; Perron, S. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 3075.

7. Ma, Z.; Clark, R. F.; Brazzale, A.; Wang, S.; Rupp, M. J.; Li, L.; Griesgraber, G.; Zhang, S.; Yong, H.; Phan, L. T.; Nemoto, P. A.; Chu, D. T.; Plattner, J. J.; Zhang, X.; Zhong, P.; Cao, Z.; Nilius, A. M.; Shortridge, V. D.; Flamm, R.; Mitten, M.; Meulbroek, J.; Ewing, P.; Alder, J.; Or, Y. S. *J. Med. Chem.* **2001**, *44*, 4137.
8. (a) Lin, X.; Burger, M.; Chu, D.; Rico, A.; Carroll, G.; Hiebert, C.; Seid, M.; Barker, L.; Shawar, R. *Abstract F-1201*, 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, Ill. **2003**.; (b) Burger, M.; Lin, X.; Chu, D.; Rico, A.; Hiebert, C.; Seid, M.; Carroll, G.; Barker, L.; Shawar, R. *Abstract F-1200*, 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, Ill. **2003**.
9. Burger, M.; Lin, X.; Chu, D. T.; Hiebert, C.; Rico, A. C.; Seid, M.; Carroll, G. L.; Barker, L.; Huh, K.; Langhorne, M.; Shawar, R.; Kidney, J.; Young, K.; Anderson, S.; Desai, M. C.; Plattner, J. J. *J. Med. Chem.* **2006**, *49*, 1730.
10. (a) Baker, W. R.; Clark, J. D.; Stephens, R. L.; Kim, K. H. *J. Org. Chem.* **1988**, *53*, 2340; (b) Fernandes, P. B.; Baker, W. R.; Freiberg, L. A.; Hardy, D. J.; McDonald, E. J. *Antimicrob. Agents Chemother.* **1989**, *33*, 78; (c) Elliott, R. L.; Pireh, D.; Griesgraber, G.; Nilius, A. M.; Ewing, P. J.; Bui, M. H.; Raney, P. M.; Flamm, R. K.; Kim, K.; Henry, R. F.; Chu, D. T. W.; Plattner, J. J.; Or, Y. S. *J. Med. Chem.* **1998**, *41*, 1651; (d) Griesgraber, G.; Kramer, M. J.; Elliott, R. L.; Nilius, A. M.; Ewing, P. J.; Raney, P. M.; Bui, M.-H.; Flamm, R. K.; Chu, D. T. W.; Plattner, J. J.; Or, Y. S. *J. Med. Chem.* **1998**, *41*, 1660; (e) Hunziker, D.; Wyss, P. C.; Angehrn, P.; Mueller, A.; Marty, H. P.; Halm, R.; Kellenberger, L.; Bitsch, V.; Biringer, G.; Arnold, W.; Stämpfli, A.; Schmitt-Hoffmann, A.; Cousot, D. *Bioorg. Med. Chem.* **2004**, *12*, 3503.
11. (a) Hauske, J. R.; Kostek, G.; Guadliana, M.; Schulte, G. *J. Org. Chem.* **1987**, *52*, 4622; (b) Lartey, P. A.; DeNinno, S. L.; Faghih, R.; Hardy, D. J.; Clement, J. J.; Plattner, J. J. *J. Antibiot.* **1992**, *45*, 380.
12. For experimental details see: Chu, D.; Burger, M.; Lin, X.; Carroll, G.; Plattner, J.; Rico, A. (Chiron Corporation, USA). PCT Int. Appl. (2003), 252 pp. WO 2003004509 A2.
13. 3D pictures of the crystal structures are provided in Supporting Information. The deposition numbers are CCDC 609190-609192 at the Cambridge Crystallographic Data Centre.
14. Spectral data of compound **9g** and 2′-hydroxy derivative of **6** are reported in Supporting Information.
15. NCCLS. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically; Approved Standard—Sixth Edition. NCCLS document M7-A6, NCCLS, Wayne, Pennsylvania 19807, USA, 2003.