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The synthesis of (9*S*)-9-alkyl-9-hydroxyerythromycin A derivatives and their ketolides

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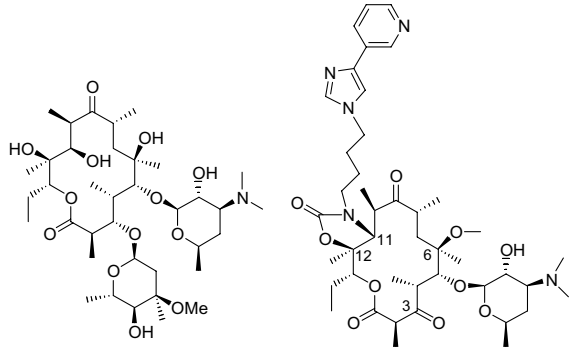
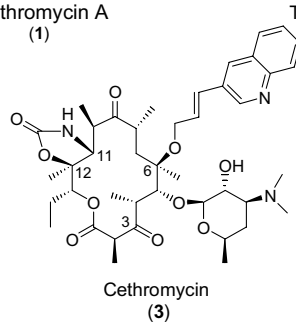
Abstract—A short, concise synthesis of a novel series of (9*S*)-9-alkyl-9-hydroxyerythromycin A derivatives and their corresponding ketolides, is described. The key chemical transformation is a stereoselective addition of organomagnesium or organolithium agents to the 9-position of the suitably protected macrolide templates **8** and **13**.

The macrolide antibiotic erythromycin A (**1**) has enjoyed widespread use in the treatment of respiratory tract infections. Recently, its clinical efficacy has been reduced by antibiotic resistance, particularly in the important respiratory pathogen, *Streptococcus pneumoniae*.[1] The primary mechanisms of resistance in *S. pneumoniae* are removal of the macrolide from the cytosol via efflux, and alteration of the macrolide binding site by ribosomal methylation.[2,3] The need for new, more effective macolide antibiotics has grown as the prevalence of erythromycin-resistant *S. pneumoniae* has increased.

Telithromycin (**2**)[4] is the first of a new generation of semi-synthetic macrolide antibiotics, known as—the ketolides, to reach the market. Most *S. pneumoniae* clinical isolates are susceptible to telithromycin, including strains resistant to erythromycin due to efflux and/or ribosomal methylation. Replacement of the cladinose sugar of erythromycin A with the 3-ketone functionality of telithromycin prevents induction of ribosomal methylation and endows the macrolide-derived core with activity against organisms resistant due to efflux. However, this single structural change was insufficient to provide a therapeutic agent; two additional synthetic





modifications were required.[5] Optimal antimicrobial activity was achieved when the 11,12-cyclic carbamate and the attached aromatic side chain were introduced. The function of the carbamate is not well understood, although it may restrict the conformation of telithromycin at the ribosomal binding site.[6] In contrast the

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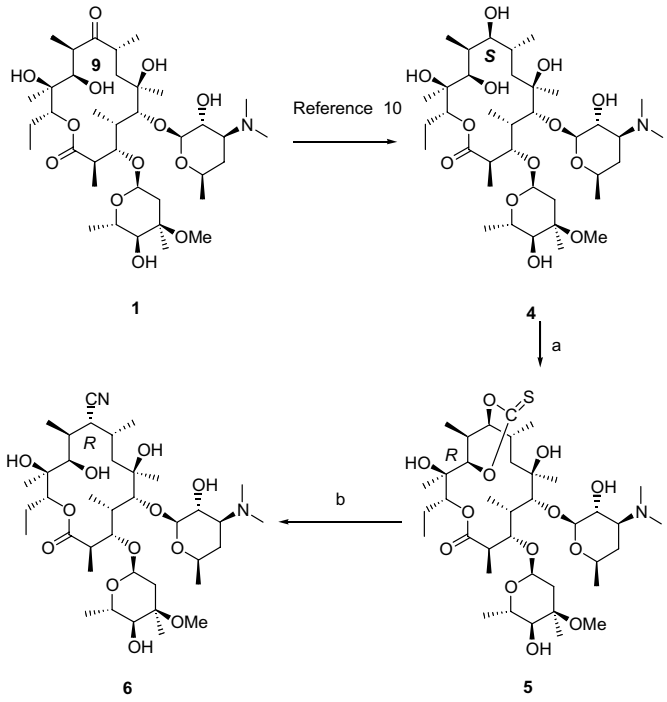
aromatic side chain has been shown by structural studies to bind to domain II of the bacterial ribosome and anchor the macrolide core to the peptide exit tunnel in domain V.[7] The related ketolide, cethromycin (**3**), has a similar microbiological profile as telithromycin but is distinguished from telithromycin by the attachment of the aryl alkyl group to the C6-position, and by the presence of an unsubstituted C11,C12-cyclic carbamate. Structural studies have demonstrated that the aromatic side chains of **2** and **3** bind to a similar region of the bacterial ribosome.[7]

Alternatively, synthetic modification of the C9-ketone could lead to ketolides with improved microbiological properties.[8] An NMR study of the conformations of **2** suggested the C9-ketone is in close proximity to the C11-position. Thus, C9-substituents may occupy a similar region of conformational space as the telithromycin C11-side chain.[9] Although a number of nitrogen-based nucleophiles having low steric requirements have been incorporated into the C9-position of erythromycin A to give oximino, imino, or amino derivatives,[8] there is little precedent in the literature for functionalization of the 9-position of the erythronolide ring with a carbon substituent. In fact, the only successful approach reported to date involves the stereoselective addition of cyanide to the cyclic thiocarbonate **5** derived from 9,9-dihydroerythromycin A to afford **6** (Scheme 1).[10] Direct addition of organometallic reagents to the C9-carbonyl of erythromycin A or B has been reported to give unidentifiable products.[10]

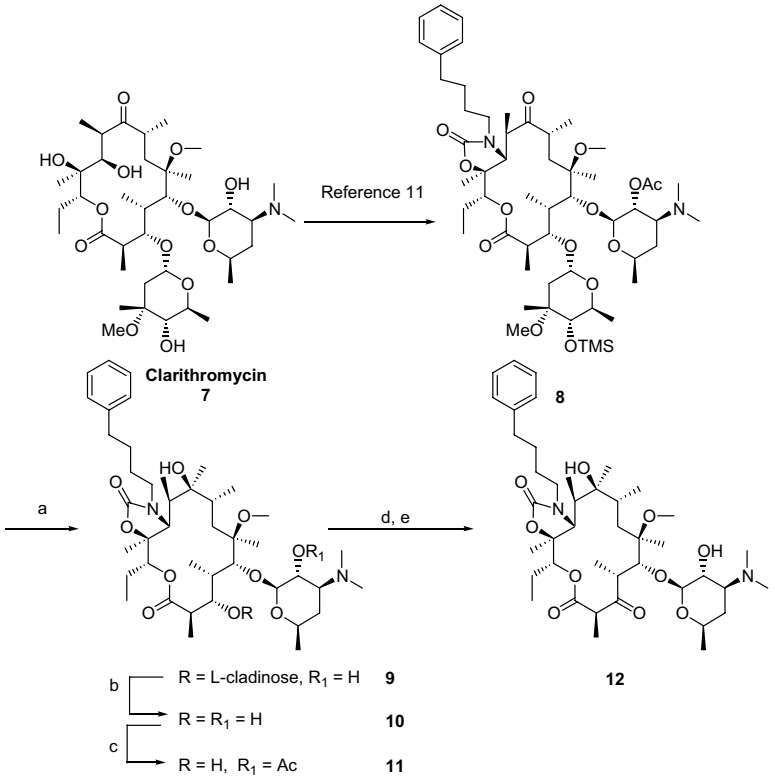
We reasoned that it might be possible to add carbon nucleophiles directly to the C9-carbonyl group if most of the acidic functionalities of the macrolide were blocked. To that end, macrolide derivative **8**, with a tertiary 11,12-cyclic carbamate, was chosen as the model electrophile in a parallel survey of organolithium and Grignard reagents. The synthesis of **8** was accomplished from commercially available clarithromycin (**7**) by a route analogous to that described by Baker et al. (Scheme 2).[11] Reaction of **8** with 5 equiv of an organometallic reagent, such as allylmagnesium bromide, butyllithium, lithium trimethylsilylacetylide, phenyllithium, methyl magnesium bromide, or methyllithium, at −78 °C in tetrahydrofuran led only to recover starting material or a complex mixture of products. When the reaction was conducted at 0 °C, only methyllithium afforded an isolable quantity of addition product **9**. Methyl magnesium bromide, lithium trimethylsilylacetylide, and phenyllithium either cleaved the cladinose sugar or removed the 2′-acetyl protecting group, with no detectable addition to the ketone carbonyl, even at elevated temperatures.

NMR analysis of the tertiary alcohol product from the methyllithium reaction revealed selective addition of the nucleophile to the 9-position to afford **9**.[12] Despite our best efforts at optimization, however, the product could be isolated in only 6% yield after acid hydrolysis to **10**. The clean conversion of **8** to **9** was hampered by side reactions, such as loss of protecting groups as well as difficulties in isolation due to cleavage of the cladinose sugar upon chromatography.

Nevertheless, **10** could be readily converted to the corresponding ketolide **12** in 50% overall yield by a three-step sequence involving re-acetylation of the 2′-hydroxy



Scheme 1. Reagents and conditions: (a) thiocarbonyldiimidazole, K_2CO_3; (b) KCN.



Scheme 2. Reagents and conditions: (a) MeLi (4 equiv); (b) 10% aqueous HCl, 6% yield over two steps; (c) acetic anhydride, Et_3N, CH_2Cl_2; (d) Dess–Martin periodinane, CH_2Cl_2; (e) MeOH.

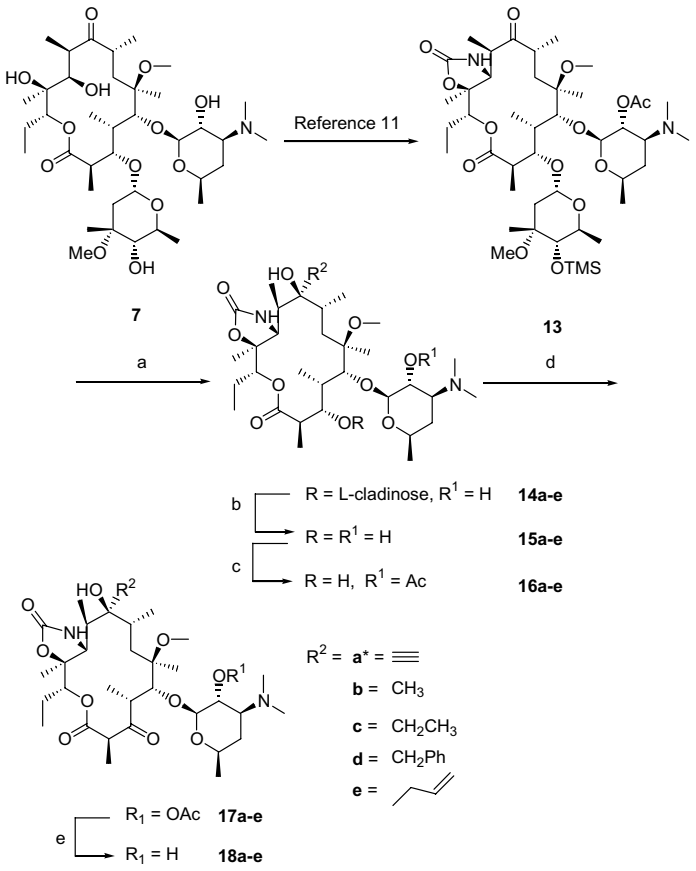
group to afford **11**, Dess–Martin oxidation of the 3-hydroxyl to the ketone,[12] and tranesterification of the 2′-acetyl protecting group with methanol.[13]

The poor outcome in the reaction of organometallic reagents with **8** might be due to the severe steric environment in the region of the C9-carbonyl. To help relieve steric congestion, secondary carbamate **13**, prepared by a similar procedure as for **8**,[11] was chosen as the electrophilic partner in the addition reaction (Scheme 3). Reaction of **13** with organolithium or Grignard reagents (5 equiv) in tetrahydrofuran at temperatures ranging from 0 to 25 °C afforded a modest to good yield of addition product in select cases (see Table 1, entries 4–6, 8, 11, 13).[14] In contrast to the tertiary carbamate **8**, reaction of methyllithium with **13** led only to decomposition (entry 1), whereas methylmagnesium chloride (entry 5) and methylmagnesium bromide (entry 6) afforded a moderate to good yield of the corresponding addition product. Although ethynylmagnesium bromide (entry 15) did not add to the C9-carbonyl group, lithium trimethylsilylacetylide (entry 4) was sufficiently nucleophilic to undergo efficient addition. Sterically encumbered nucleophiles, such as phenyllithium (entry 2) or phenylmagnesium bromide (entry 10), failed to yield the desired product. In addition to the results in Table 1, **13** was resistant to alkylation by allyl trimethylsilane both in the presence of boron trifluoride etherate or under indium promoted Barbier conditions.[15] Although several Grignard reagents underwent successful addition to **13** (Table 1, entries 5, 6, 8, 11, 13), the alkylated products **14b–e** also contained various amounts of the corresponding 3-hydroxyl derivative **15b–e** resulting from partial cleavage of the cladinose sugar. On the other hand, lithium trimethylsilylacetylide (Table 1, entry 4) provided the addition product **14a** exclusively.

Complete removal of the cladinose sugar could be effected by treatment with aqueous HCl during reaction work-up. Conversion of **15a–e** to the corresponding ketolides **18a–e** was accomplished as before, by selective protection of the 2′-hydroxy group with acetic anhydride to give **16a–e**, oxidation with Dess–Martin periodinane to provide **17a–e**, and removal of the 2′ acetate protecting group (Scheme 3).

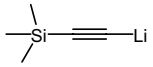
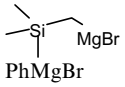
Since only one diastereomer was observed in the NMR spectra of **18a–e**, the remaining uncertainty concerned the absolute stereochemistry of the newly formed tertiary alcohol. Treatment of **18b** with CDI in the presence of sodium hydride in tetrahydrofuran at 0 °C rapidly provided **19** as the sole product. The formation of oxazinone **19** from **18b** could only occur if addition of the nucleophile had occurred from the α or bottom face of the macrolide ring (Scheme 4). Given that Baker et al. had established the absolute stereochemistry of 11,12-cyclic carbamate **13** as 11*R*,[11] the absolute stereochemistry of tertiary alcohols **14a–e** must be 9*S*. Thus carbon-based nucleophiles attack the C9-carbonyl group from the same face of the macrolactone ring as sodium borohydride[16] in the reduction of erythromycin A to **4**.

In summary, we have achieved the first successful addition of organometallic reagents to the 9-oxo-group of an



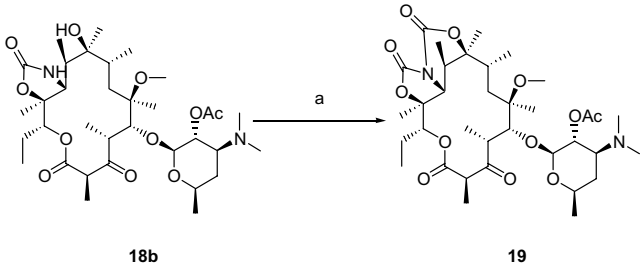
Scheme 3. Reagents and conditions: (a) R^2M (see Table 1); (b) 20% aqueous HCl; (c) acetic anhydride, Et_3N, CH_2Cl_2; (d) Dess–Martin periodinane, CH_2Cl_2; (e) MeOH.

Table 1. Nucleophiles and results of reaction with **13**

Entry	R^3M	Result[a]
1	MeLi	Decomposition
2	PhLi	Decomposition
3	BuLi	Decomposition
4		**18a**[b] **67**%
5	MeMgCl	**18b 54**%
6	MeMgBr	**18b 71**%
7	MeMgI	**13**[c]
8	EtMgBr	**18c 76**%
9		**13**[c]
10	PhMgBr	**13**[c]
11	$PhCH_2MgBr$	**18d 52**%
12		**13**[c]
13		**18e 60**%
14	BuMgBr	**13**[c]
15		**13**

[a] Yields are for conversion of **13** to **18**.
[b] Trimethylsilyl group is removed in a separate deprotection reaction; see Ref. 14.
[c] Loss of protecting groups was noted.

erythromycin A-derived macrolide. Success was realized by employing suitably protected macrolide templates **8** and **13** and carbon-based nucleophiles of the appropriate reactivity. Finally, the stereochemistry of the newly formed tertiary alcohol was unambiguously established as 9*S* by formation of oxazinone **19**. The antibacterial activity of ketolides **12** and **18a–e** will be reported elsewhere.



Scheme 4. Reagents and condition: (a) NaH, CDI, THF, 25 °C.

References and notes

1. (a) Ma, Z.; Nemoto, P. A. *Curr. Med. Chem.: Anti-Infect. Agents* **2002**, *1*, 15–34; (b) Bryskier, A. *Clin. Microbiol. Infect.* **2000**, *6*, 661–669; (c) Zhanel, G. G.; Walters, M.; Noreddin, A.; Vercaigne, L. M.; Wierzbowski, A.; Embil, J. M.; Gin, A. S.; Douthwaite, S.; Hoban, D. *J. Drugs* **2002**, *62*, 1771–1804; (d) Cazzola, M.; Blasi, F.; Centanni, S.; Donner, C. F.; Allegra, L. *Pulm. Pharmacol. Ther.* **2001**, *14*, 367–381.

2. (a) Nakajima, Y. *J. Infect. Chemother.* **1999**, *5*, 61–71; (b) Weisblum, B. *Drug Resist. Updates* **1998**, *1*, 29–41; (c) Amsden, C. W. *J. Antimicrob. Chemother.* **1999**, *44*, 1–6; (d) 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. W.; 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*, 4137–4156.
3. (a) Jones, R. N.; Biedenbach, D. *J. Diag. Microbiol. Infect. Dis.* **2003**, *45*, 273–278; (b) Melo-Cristino, J.; Ramirez, M.; Serrano, N.; Haenscheid, T. *Microb. Drug Resist.* **2003**, *9*, 73–80.
4. Xiong, Y.-Q.; Le, T. P. *Drugs Today* **2001**, *37*, 617–628.
5. Ma, Z.; Clark, R. F.; Brazzale, A.; Wang, S.; Rupp, M. J.; Li, L.; G., G.; Zhang, S.; Yong, H.; Phan, L. T.; Nemoto, P. A.; Chu, D. T. W.; Plattner, J. J.; Zhang, X.; Zhong, P.; Cao, Z.; Nilius, A. M.; Shortridge, V. D.; Flamm, R.; Mitten, M.; Meulbroek, J.; E., P.; Alder, J.; Or, Y. S. *J. Med. Chem.* **2001**, *44*, 4137–4156.
6. Douthwaite, S. *Clin. Microbiol. Infect.* **2001**, *7*, 11–17.
7. Berisio, R.; Harms, J.; Schluenzen, F.; Zarivach, R.; Hansen, H. A. S.; Fucini, P.; Yonath, A. *J. Bacteriol.* **2003**, *185*, 4276–4279.
8. Bryskier, A.; Denis, A. *Macrolide Antibiot.* **2002**, 97–140.
9. Evrard-Todeschi, N.; Gharbi-Benarous, J.; Gaillet, C.; Verdier, L.; Bertho, G.; Lang, C.; Parent, A.; Girault, J.-P. *Bioorg. Med. Chem.* **2000**, *8*, 1579–1597.
10. Hauske, J. R.; Guadliana, M.; Kostek, G. *J. Org. Chem.* **1983**, *48*, 5138–5140.
11. Baker, W. R.; Clark, J. D.; Stephens, R. L.; Kim, K. H. *J. Org Chem.* **1988**, *53*, 2340–2345.
12. For a more detailed description see: Qiu, Y.-L.; Phan, L. T.; Or, Y. S. US 6774115.
13. All new compounds were characterized by NMR and mass spectral methods.
14. *Representative synthesis*: Example **15a**: A 5-L four-neck flask equipped with an overhead mechanical stirrer, a thermocouple controller, a nitrogen inlet/outlet adapter, and a pressure equalization-dropping funnel was charged with **14** (156.3 g, 0.176 mol) in anhydrous THF (2 L). The mixture was cooled to 0 °C and treated dropwise with a solution of lithium trimethylsilylacetylide in THF (0.5 M, 1408 mL, 0.704 mol) over a 20-min period. The ice bath was removed and the reaction was stirred overnight at 25 °C. The reaction mixture was treated with saturated aqueous NH_4Cl (1 L) and then transferred to a 12-L separatory funnel. After an additional amount of NH_4Cl (4 L) was added, the organic phase was isolated, washed with additional NH_4Cl (3 L) and concentrated to dryness to afford 238 g of a brownish foam. This foam was dissolved in anhydrous THF (1.1 L) and acidified with 20% HCl (1.0 L) over a 30-min period. The reaction was allowed to stir for 1 h, and then it was treated with concentrated NH_4OH (1.5 L) and diluted with EtOAc (1.0 L). The mixture was transferred to a 12-L separatory funnel, diluted with an additional amount of EtOAc (1.0 L), and the organic phase was isolated. The aqueous phase was extracted with EtOAc (1.0 L) and the combined organic phase was concentrated to dryness to afford 163.9 g of light brown foam. This crude material was dissolved in MeOH (1.6 L) and K_2CO_3 (188 g) was added to the resulting solution. After the reaction was stirred for 1 h, it was concentrated to dryness and then diluted with EtOAc (3.0 L) and H_2O (3.0 L). The organic phase was isolated and concentrated to dryness to afford 149.8 g of crude product, which was purified by crystallization from EtOAc to afford 84.7 g (75%) of **15a**. ^1H NMR (400 MHz; $CDCl_3$) δ 5.50 (s, 1H), 5.11 (d, 1H, $J = 9$ Hz), 4.70 (br s, 1H), 4.50 (d, 1H, $J = 8$ Hz), 3.90–3.80 (m, 3H), 3.53 (m, 1H), 3.23 (dd, 1H, $J = 7.6$, 10.3 Hz), 3.10 (s, 3H), 2.73 (dd, 1H, $J = 7$, 10 Hz), 2.58 (s, 1H), 2.51–2.48 (m, 1H), 2.24 (s, 6H), 2.0–1.85 (m, 3H), 1.70–1.48 (m, 4H), 1.4–1.2 (m, 22H), 1.10 (d, 3H, $J = 4$ Hz), 0.87 (dd, 3H, $J = 7$, 11 Hz); MS (*m*/*z*) 641 (M+H).
15. Li, C.-J.; Chan, T.-H. *Tetrahedron* **1999**, *55*, 11149–11176.
16. Faghih, R.; Buytendorp, M.; Stephens, R.; Hardy, D.; Plattner, J.; Lartey, P. *J. Antibiot.* **1990**, *43*, 1334–1336.