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# Novel erythromycin A derivatives: synthesis of 11,12-benzoxazine ketolides

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**Abstract**—A novel series of 11,12-benzoxazine ketolide derivatives of erythromycin A has been synthesized. The C11,C12-benzoxazine structure was constructed stereoselectively through an intramolecular Michael addition of a C12-*O*-(2-aminophenyl) group to the enone functionality of the 10,11-anhydro erythromycin A derivative **3**.


The 14-membered ring macrolide antibiotic erythromycin A and its semi-synthetic derivatives, such as clarithromycin and azithromycin, have been widely prescribed to treat respiratory tract bacterial infections. The macrolide antibiotics act against bacteria by selectively binding to the bacterial ribosome and inhibiting protein synthesis.[1] However, macrolide-resistant infections have been observed with increasing frequency in recent years,[2] which presents an urgent need for a new generation of macrolide antibiotics effective against resistant bacteria. Recently, a new class of erythromycin A derivatives, known as ketolides, has demonstrated enhanced antibacterial activity against macrolide-resistant pathogens.[3] The ketolides, such as telithromycin[4] (Fig. 1), are structurally distinct from earlier generations of erythromycin A derivatives by having a C3-keto group instead of the natural C3-cladinose sugar. Another distinguishing structural feature of the ketolides is an aryl side chain attached to the ketolide core. Microbiological studies have suggested that the aryl group is important for activity against $MLS_B$-resistant bacteria.[1a]

The majority of ketolides reported to date also contain a cyclic carbamate at the C11, C12 positions. It has been reported that this C11,C12-cyclic carbamate enhances the binding affinity of ketolides for both macrolide-susceptible and macrolide-resistant bacterial ribosomes.[5] In our search for new and more effective ketolide antibiotics, we explored the effect on antibacterial activity of structural modifications in the C11/C12 region of the ketolides. Thus, in our study, the C11,C12-cyclic carbamate was replaced by bulkier and less polar groups and the resulting ketolide compounds were evaluated. In this paper, we report the synthesis of a novel series of erythromycin A derivatives, the 11,12-benzoxazine ketolides.

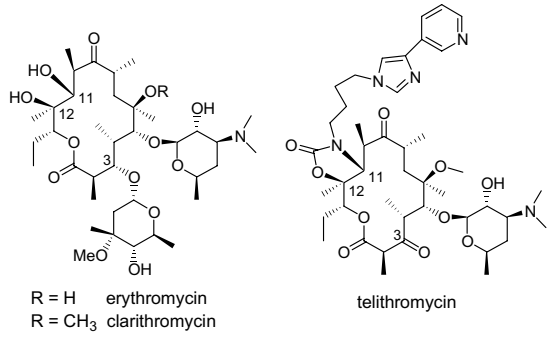


**Figure 1.**

Our strategy to construct the benzoxazine at the C11, C12 positions of the macrolide core was inspired by the reported synthetic route toward the C11,C12-cyclic carbamate, which involves elimination of the C11-hydroxyl group, acylation of the resulting C12-allylic alcohol, and intramolecular Michael condensation to give the cyclic carbamate (Fig. 2).[6]

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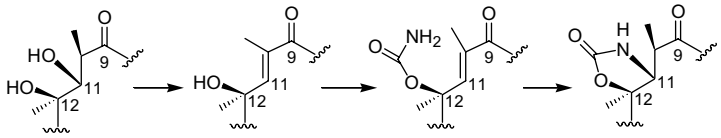
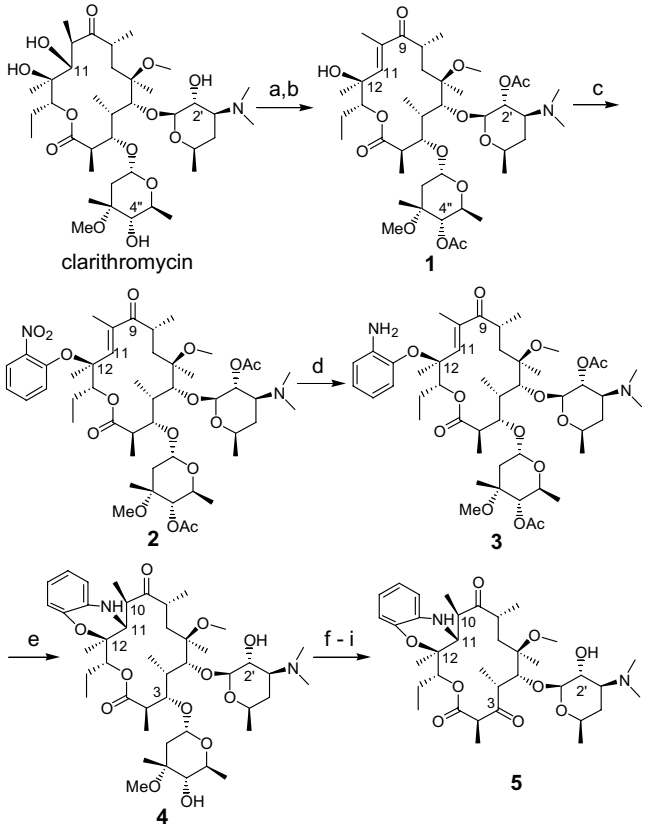


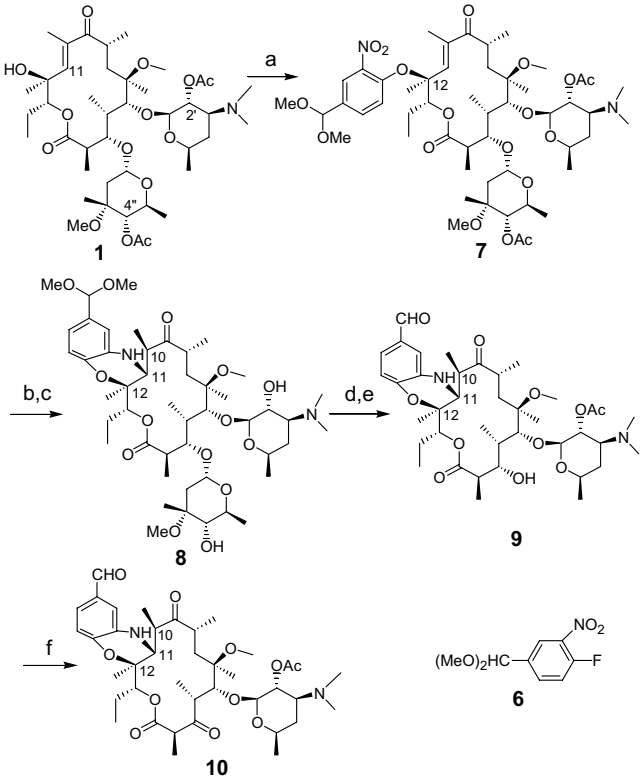
**Figure 2.**

The synthesis began with selective protection of the C2′ and C4″-hydroxyl groups of commercially available clarithromycin using acetic anhydride in the presence of triethylamine,[7] followed by base-promoted elimination of the C11-hydroxyl group to give C12-allylic alcohol **1**.[8] Reaction of alcohol **1** with 1-fluoro-2-nitrobenzene in the presence of potassium bis(trimethylsilyl)amide provided the C12-*O*-(2-nitrophenyl) compound **2** in good yield. The selective reduction of the nitro group of **2** was achieved using sodium borohydride and catalytic nickel(II) chloride to give C12-*O*-(2-aminophenyl) compound **3**. Upon prolonged treatment with potassium carbonate in methanol, compound **3** underwent an intramolecular Michael addition to give 11,12-benzoxazine macrolide derivative **4**.[9] The reaction generated two stereocenters at the C10 and C11 positions in a stereoselective fashion. NMR studies ($^{1}H$, $^{13}C$ and 1-D NOESY) suggested that the stereochemistry at C10 and C11 of compound **4** is identical to that of telithromycin. Reprotection of the C2′-hydroxy followed by cleavage of the C3-cladinose group under acidic conditions provided the C3-alcohol, which was then oxidized to the corresponding C3-ketone using a modified Pfitzner–Moffat procedure.[10] Finally, removal of the C2′ acetate protecting group by methanolysis yielded 11,12-benzoxazine ketolide **5** (Scheme 1).

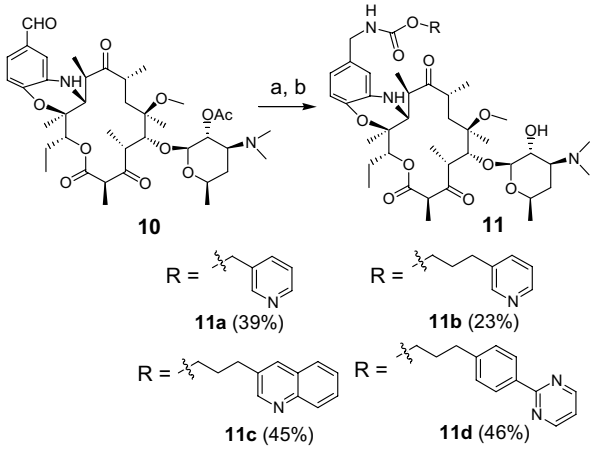



**Scheme 1.** Reagents and conditions: (a) $Ac_2O$, $Et_3N$, cat. DMAP, $CH_2Cl_2$; (b) ethylene carbonate, $Et_3N$, reflux, 80% for two steps; (c) 1-fluoro-2-nitrobenzene, $KN(TMS)_2$, THF, 0 °C, 61%; (d) $NaBH_4$, $NiCl_2{\cdot}xH_2O$, MeOH, 0 °C, 10 min; (e) $K_2CO_3$, MeOH, 72 h; (f) $Ac_2O$, $Et_3N$, $CH_2Cl_2$; (g) aq HCl, EtOH, reflux, 30 min, 71% for four steps; (h) EDCI, pyridinium trifluoroacetate, DMSO, $CH_2Cl_2$; (i) MeOH, 16 h, 76% for two steps.

Once the method to construct the C11,C12-benzoxazine was successfully developed, our attention was directed toward the introduction of an aryl side chain onto the benzoxazine ring. We envisioned that an aldehyde group on the C11,C12-benzoxazine would provide ready access to a variety of side chains. Therefore, 4-fluoro-3-nitrobenzaldehyde dimethyl acetal **6**[11] was reacted with compound **1** in the presence of potassium bis(trimethylsilyl)amide to give compound **7** in good yield. Reduction of the nitro group followed by base induced intramolecular Michael addition provided 11,12-benzoxazine macrolide **8** with high stereoselectivity. Reprotection of the C2′-hydroxyl group followed by acidic hydrolysis of the C3-cladinose sugar gave the C3-alco-




**Scheme 2.** Reagents and conditions: (a) **6**, $KN(TMS)_2$, THF, 0 °C, 60%; (b) $NaBH_4$, $NiCl_2{\cdot}xH_2O$, MeOH, 0 °C, 10 min; (c) $K_2CO_3$, MeOH, 3 days; (d) $Ac_2O$, $Et_3N$, $CH_2Cl_2$; (e) aq HCl, EtOH, reflux, 30 min, 51% for four steps; (f) EDCI, pyridinium trifluoroacetate, DMSO, $CH_2Cl_2$, 63%.




**Scheme 3.** Reagents and conditions: (a) $ROC(O)NH_2$, $Et_3SiH$, TFA, $CH_3CN$, 60 °C; (b) MeOH, rt, yields are for two steps.

hol **9**. Under the acidic hydrolysis conditions, the dimethyl acetal moiety on the C11,C12-benzoxazine was also converted to the corresponding aldehyde. The C3-hydroxyl group of compound **9** was then oxidized to give the corresponding C3-ketone **10** (Scheme 2).

Compound **10** was then reacted with a number of primary carbamates under reductive alkylation conditions (triethylsilane, trifluoroacetic acid, acetonitrile) to install the aryl side chains through a carbamate linkage. Finally, deprotection of the C2′-hydroxyl group led to the fully elaborated 11,12-benzoxazine ketolide compounds **11** in modest to good yields (Scheme 3).

In conclusion, the synthesis of a novel series of 3-keto-11,12-benzoxazine derivatives of erythromycin A was developed. The C11,C12-benzoxazine structure was constructed by a mild and stereoselective intramolecular Michael addition. Ketolide compound **10** was a versatile intermediate for incorporation of a variety of aryl side chains. However, preliminary microbiological tests showed that the unsubstituted and substituted 11,12-benzoxazine ketolides **5** and **11** were significantly less active than telithromycin. These results indicated that the benzoxazine ring is not well tolerated at the C11,C12 positions of the ketolides. The presence of this group in that region may actually perturb binding of the ketolides to the bacterial ribosome. Therefore, our future work will focus on the design and synthesis of ketolides with alternate functionalities at the C11/C12 region to achieve improved antibacterial activity.

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## References and notes

1. For recent reviews, see: (a) Zhanel, G. G.; Dueck, M.; Hoban, D. J.; Vercaigne, L. M.; Embil, J. M.; Gin, A. S.; Karlowsky, J. A. *Drugs* **2001**, *61*, 443–498; (b) Blondeau, J. M.; DeCarolis, E.; Metzler, K. L.; Hansen, G. T. *Exp. Opin. Investigat. Drugs* **2002**, *11*, 189–215.
2. (a) Amsden, G. W. *J. Antimicrob. Chemother.* **1999**, *44*, 1–6; (b) Lonks, J. R.; Garau, J.; Mederios, A. A. *J. Antimicrob. Chemother.* **2002**, *50*, 87–91.
3. For recent reviews, see: (a) Wu, Y.-J.; Su, W.-G. *Curr. Med. Chem.* **2001**, *8*, 1727–1758; (b) 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; (c) Asaka, T.; Manaka, A.; Sugiyama, H. *Curr. Top. Med. Chem.* **2003**, *3*, 961–989.
4. Denis, A.; Agouridas, C.; Auger, J.-M.; Benedetti, Y.; Bonnefoy, A.; Bretin, F.; Chantot, J.-F.; Dussarat, A.; Fromentin, C.; Gouin D'Ambrieres, S.; Lachaud, S.; Laurin, P.; Le Martret, O.; Loyau, V.; Tessot, N.; Pejac, J.-M.; Perron, S. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 3075–3080.
5. Kaneko, T.; McArthur, H.; Sutcliffe, J. *Exp. Opin. Ther. Patents* **2000**, *10*, 403–425.
6. Baker, W. R.; Clark, J. D.; Stephens, R. L.; Kim, K. H. *J. Org. Chem.* **1988**, *53*, 2340–2345.
7. Jones, P. H.; Perun, T. J.; Rowley, E. K.; Baker, E. J. *J. Med. Chem.* **1972**, *15*, 631–634.
8. 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*, 1651–1659.
9. The reaction initially gave a mixture of **4** and presumably its C10-epimer, which subsequently equilibrated to **4** under basic conditions. Similar results were observed in the formation of C11,C12-cyclic carbamate, see Phan, L. T.; Clark, R. F.; Rupp, M.; Or, Y. S.; Chu, D. T. W.; Ma, Z. *Org. Lett.* **2000**, *2*, 2951–2954.
10. (a) Pfitzner, K. E.; Moffatt, J. G. *J. Am. Chem. Soc.* **1965**, *87*, 5661; (b) Agouridas, C.; Denis, A.; Auger, J.-M.; Benedetti, Y.; Bonnefoy, A.; Bretin, F.; Chantot, J.-F.; Dussarat, A.; Fromentin, C.; Gouin D'Ambrieres, S.; Lachaud, S.; Laurin, P.; Le Martret, O.; Loyau, V.; Tessot, N. *J. Med. Chem.* **1998**, *41*, 4080–4100.
11. Prepared from reaction of 4-fluoro-3-nitrobenzaldehyde with trimethyl orthoformate [$CH(OCH_3)_3$] with catalytic pyridinum *p*-toluenesulfonate in $CH_2Cl_2$.