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The stereoselective synthesis of novel macrolide antibacterial agents via an intramolecular 1,3-dipolar cycloaddition of azomethine ylide

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Abstract—An intramolecular 1,3-dipolar cycloaddition of azomethine ylide, generated in situ via the reaction of C12-glycinate derivative of macrolide with formaldehyde, provided a novel tricyclic macrolide. The high stereoselectivity of this [2+3] reaction was achieved by introducing a suitable directing group at C-6 position of macrolide.

Recent surveillance data has revealed that the drug resistance rates with *S. pneumoniae* have increased markedly in the United States in the past decade.[1] Among the widely prescribed antibiotics, resistance rates for both β-lactams and second generation macrolides have reached ~25%.[1,2] Third generation macrolides exemplified by telithromycin[3] (**1**) and cethromycin[3c,4] (ABT-773, **2**) (Fig. 1) have shown markedly improved activities against resistant strains of *S. pneumoniae*.[4b,5] These agents are members of the ketolide class of macrolide antibacterials due to their characteristic C-3 ketone functionality. In our continuing search for more potent and safe antibacterial agents, we focused on developing macrolides/ketolides with novel core structures.

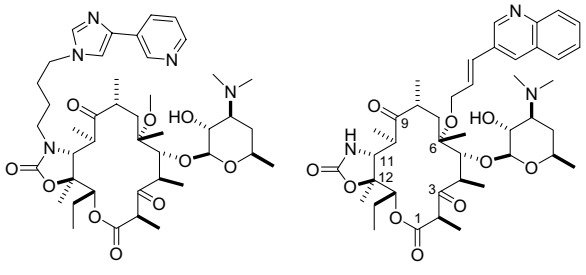
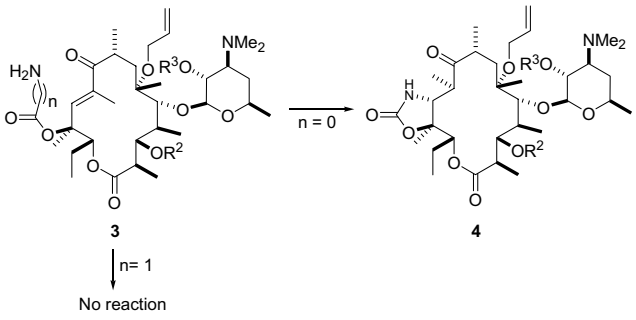


Figure 1.

In our early study on cethromycin **2**, we found that the intramolecular Michael addition of carbamate **3** ($n = 0$) proceeded smoothly to the desired compound **4**[6] (Scheme 1). Curiously, the corresponding glycinate analog **3** ($n = 1$) did not cyclize even under harsh conditions (heat and/or base). In addition, structure–activity relationship studies revealed that five-membered ring moiety at C11 and C12 of the macrolide core is important for enhanced antibacterial activity, especially against resistant pathogens, and is associated with more desirable pharmacokinetic profiles.[4b,7] These findings prompted us to study other possible five-membered ring forming reactions.[8] Here we report an efficient synthesis of a novel tricyclic macrolide via an intramolecular 1,3-dipolar cycloaddition reaction.[9]



Scheme 1.

Keywords: Macrolide; Ketolide; Azomethine ylide.
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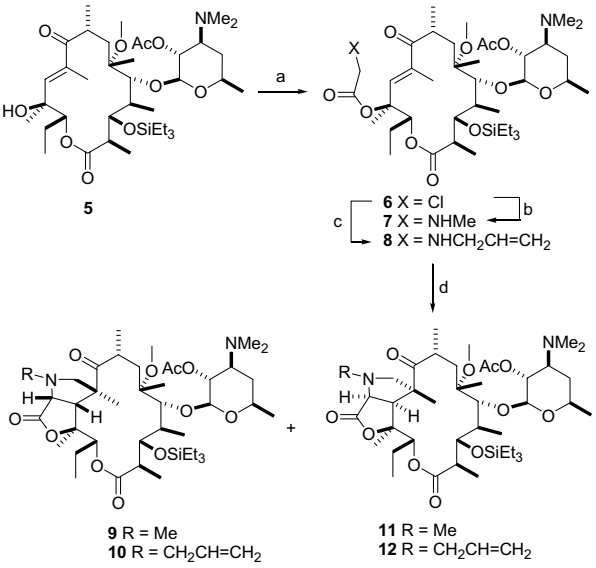
The reaction of **5**[10] with chloroacetic anhydride in the presence of Et_3N and a catalytic amount of DMAP provided **6** in high yield. It was important to use only 0.5 equiv of Et_3N, as the reaction did not proceed to completion if 1 equiv or more Et_3N was added, presumably due to the deprotonation of chloroacetate **6** and subsequent elimination of chloroketene[11] to regenerate **5**. For the same reason, compound **5** was always produced as a minor product in a nucleophilic displacement reaction of **6** with methylamine or allylamine to provide compounds **7** and **8**, respectively. Treatment of **7** with 1 equiv[12] of formaldehyde in the presence of catalytic acetic acid generated azomethine ylide in situ, which underwent subsequent intramolecular [2+3] cycloaddition in refluxing toluene to produce an inseparable 2:1 mixture of **9** and **11** (Scheme 2). The structures of **9** and **11** were assigned by using 2D NMR (DQCOSY, ROESY, HSQC, and HMBC).

Compounds **9** and **11** may be derived from two different transition states (TS) as shown in Figure 2. The chair-like TS with an *anti* relation between the C-9 carbonyl and C-10 methyl will lead to compound **9**, while the boat-like TS with a *syn* relation should result in compound **11**. Apparently, the chair-like TS with the bulky ester group in an equatorial position should be favored over the boat-like TS. However, the severe 1,3-diaxial interactions of the C-10 methyl with both C-8 and C-12 methyl groups in the chair-like TS may have diminished much of the preference, resulting in low stereoselectivity of the [2+3] cycloaddition. Given the fact that the methoxy group at the C-6 position is spatially closer to the C-9 carbonyl and C-10 methyl in a boat-like TS than in chair-like TS, we envisioned that the introduction of a larger C-6 alkoxy group should disfavor the boat-like TS and therefore enhance stereoselectivity of product derived from a chair-like TS. To our delight, when



Scheme 2. Reagents and conditions: (a) $(ClCH_2CO)_2O$, 0.5 equiv Et_3N, cat. DMAP, CH_2Cl_2, rt, 1 h, 94%. (b) CH_3NH_2, DMF, rt, 8 h, 84%. (c) Allylamine, DMF, rt, 40 h, 65%. (d) aq HCHO, PhMe, cat. AcOH, reflux, 1.5 h, 84% (R=Me), 76% (R=llyl).

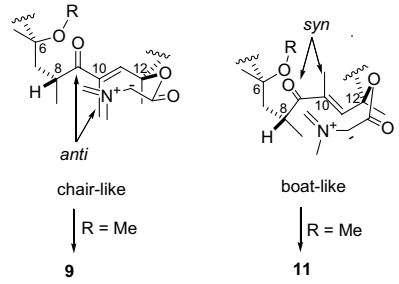
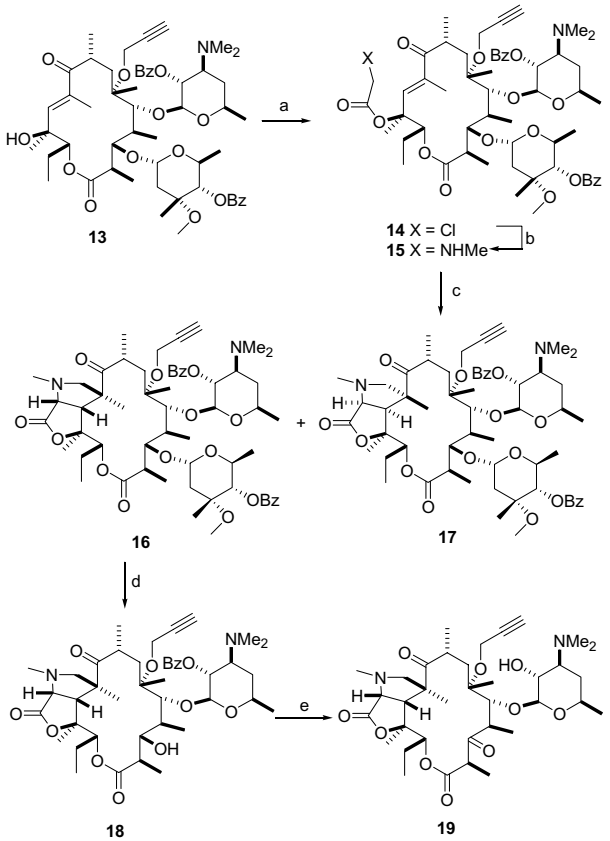


Figure 2.

compound **15** was subjected to the similar intramolecular [2+3] azomethine ylide cycloaddition conditions, compounds **16** and **17** were obtained in a 10:1 ratio (Scheme 3). It is also possible that replacement of the triethylsilyl ether at C-3 position with a cladinose moiety is responsible for the enhanced facial selectivity of [2+3] cycloaddition reaction of the azomethine ylide derived from compound **15**. 3D structure analysis, however, shows that C3 substituent is rather distant to the reaction site and is unlikely to affect the selectivity. Compound **15** was synthesized from **13**[13] in a manner analogous to the preparation of **7**. The structure of **16** was assigned by using 2D NMR (DQCOSY, ROESY, HSQC, and HMBC).



Scheme 3. Reagents and conditions: (a) $(ClCH_2CO)_2O$, 0.5 equiv Et_3N, cat. DMAP, CH_2Cl_2, rt, 1 h, 99%. (b) CH_3NH_2, DMF, rt, 8 h, 73%. (c) aq HCHO, PhMe, cat. AcOH, reflux, 1.5 h, 56% (d) CF_3CO_2H, CH_2Cl_2, rt, 5 h, 91%. (e) Dess–Martin oxidation, then CH_3OH, relux 18 h, 75%.

On the other hand, the steric effect of the alkyl group on nitrogen is minimal. This is illustrated by the fact that when compound **8** was subjected to the same intramolecular [2+3] dipolar cycloaddition reaction, a 2:1 mixture of **10** and **12** was obtained.

A typical procedure for the synthesis of **16** and **17**: To a solution of **15** (1.576 g, 1.53 mmol) in toluene (40 mL) were added aqueous formaldehyde (115 μL, 37% w/w in water, 1.53 mmol) and two drops of acetic acid. After being stirred at room temperature for 30 min, the mixture was refluxed, with a Dean–Stark head, for 1.5 h. Solvent was removed under vacuum and the residue was purified on a flash column, eluting with 10–50% acetone in hexane, to provide 895 mg of compounds **16** and **17** as a 10:1 mixture. MS (ESI), m/z 1046 $[M+H]^+$; ^{13}C NMR ($CDCl_3$) δ 217.4, 178.1, 176.8, 166.2, 165.3, 133.3, 132.6, 130.7, 129.9, 129.8, 129.6, 128.4, 128.2, 100.8, 95.4, 86.4, 83.0, 80.7, 79.6, 79.0, 78.5, 76.5, 74.9, 70.3, 72.2, 67.8, 67.2, 66.2, 63.7, 63.4, 56.5, 53.0, 52.0, 49.7, 45.1, 42.0, 41.3, 40.9, 39.9, 37.8, 35.0, 32.2, 23.9, 23.6, 21.5, 21.3, 21.2, 19.6, 18.4, 16.2, 15.2, 10.5, 9.5. Compound **16** was converted to the corresponding ketolide compound **19** via a previously reported procedure.[4b] MS (ESI), m/z 677 $[M+H]^+$; HRMS (FAB), m/z 677.3998 $[M+H]^+$, calcd for $C_{36}H_{57}N_2O_{10}$ 677.4013; ^{13}C NMR ($CDCl_3$) δ 216.9, 205.8, 176.5, 170.4, 104.0, 85.7, 83.9, 80.4, 80.2, 78.8, 77.4, 74.4, 70.4, 69.5, 67.5, 66.1, 65.8, 56.6, 52.7, 51.4, 50.7, 48.5, 41.9, 40.3, 39.2, 36.6, 28.5, 22.3, 21.8, 21.2, 19.6, 16.9, 15.8, 14.3, 10.4. Anal. Calcd for $C_{36}H_{56}N_2O_{10}$: C, 63.69; H, 8.40; N, 3.95. Found: C, 63.88; H, 8.34; N, 4.14.

In conclusion, we have developed a stereoselective synthesis of novel pyrrolidine containing tricyclic macrolide via an intramolecular [2+3] dipolar cycloaddition of azomethine ylide. The antibacterial activity of this class of compounds will be reported in due course.

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