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A Novel Bicyclic Ketolide Derivative

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Abstract—A novel bicyclic ketolide derivative, 10,11-didehydro-11-deoxy-3-*O*-descladinosyl-6-*O*-methyl-3-oxo-8,9-anhydro-erythromycin 9,12-hemiacetal(**6**) was obtained from 3-*O*-descladinosyl-6-*O*-methylerythromycin 2′-acetate. The structure and stereochemistry of this novel compound were elucidated and established by NMR and X-ray crystallography.

Macrolide antibiotics, especially erythromycins, have been important therapeutic agents against Gram-positive micro-organisms. Due to the instability of erythromycin under acidic condition, poor bioavailability after oral administration has been observed. In order to improve the oral bioavailability, second-generation of semi-synthetic erythromycin derivatives, such as clarithromycin and azithromycin, were discovered and widely used in clinics because of their usefulness in clinical practices. Unfortunately, the first and second-generation erythromycin derivatives have still showed unsatisfactory efficacy against multi-drug resistant strains. Recent efforts have led to the development of third generation of semi-synthetic macrolides to overcome the resistance. A new type of compounds designated as ketolides was generated from erythromycin, in which the cladimosyl-sugar moiety at 3-position was changed to a carbonyl group. Ketolides have shown excellent activity against susceptible and resistant strains to erythromycin in vitro and in vivo.

In the attempt of synthesizing new ketolide compounds, clarithromycin (**1**) was used as a starting material. As shown in Scheme 1, Clarithromycin (**1**) was treated by hydrochloric acid to produce 3-*O*-decladinosyl-6-*O*-methylerythromycin (**2**). (**2**) Was acetylated with acetic anhydride and oxidized to give (**4**).[1] Compound (**4**) can then be used as an intermediate to synthesize a variety of ketolide antibacterial agents.

Surprisingly, in the step of oxidation of the hydroxyl group at C3 of (**3**), a new product (**5**) with strong UV absorption was produced besides (**4**). The new product (**5**) has a molecular ion at m/z 594, indicating that (**5**)[4] has less 36 mass units than expected (**4**). The ^{1}H NMR for (**5**) showed the presence of a proton on C13 and the absence of protons at C10 and C11. When (**5**) was crystallized in methanol, an unexpected crystal with structure of (**6**)[5] was obtained as shown in Scheme 2, and its stereochemistry for double bond at C10 and C11 was determined as *Z*-configuration by X-ray crystallography (Fig. 1).

In fact, (**6**) is the 2′-deacetyl product of (**5**) due to hydrolysis of 2′-acetate in methanol during the crystallization. MS and NMR data indicate that compound (**5**) is 3-oxo-9,12-hemiacetal, and its double bond at C10-C11 is Z-configuration based on the evidence in Figure 1 from the X-ray crystallography.

Morimoto S. et al.[2] reported that Erythromycin A was transformed to be 9, 12-hemiketal in acetic acid. In present work, the formation of 9,12-hemiketal was also observed during the oxidation of hydroxyl group at C3 to corresponding carbonyl group by Pfitzner–Moffat reaction.[3]

$(CH_3)_2NC_3H_6-N=C=N-C_2H_5$ EDC

Since both acid- and base-catalyzed steps are involved in this oxidation reaction, we propose that EDC·HCl (3-ethyl-, 1-(3-dimethylamino) propyl-cardiimide hydrochloride), a strong dehydration agent, removes a molar

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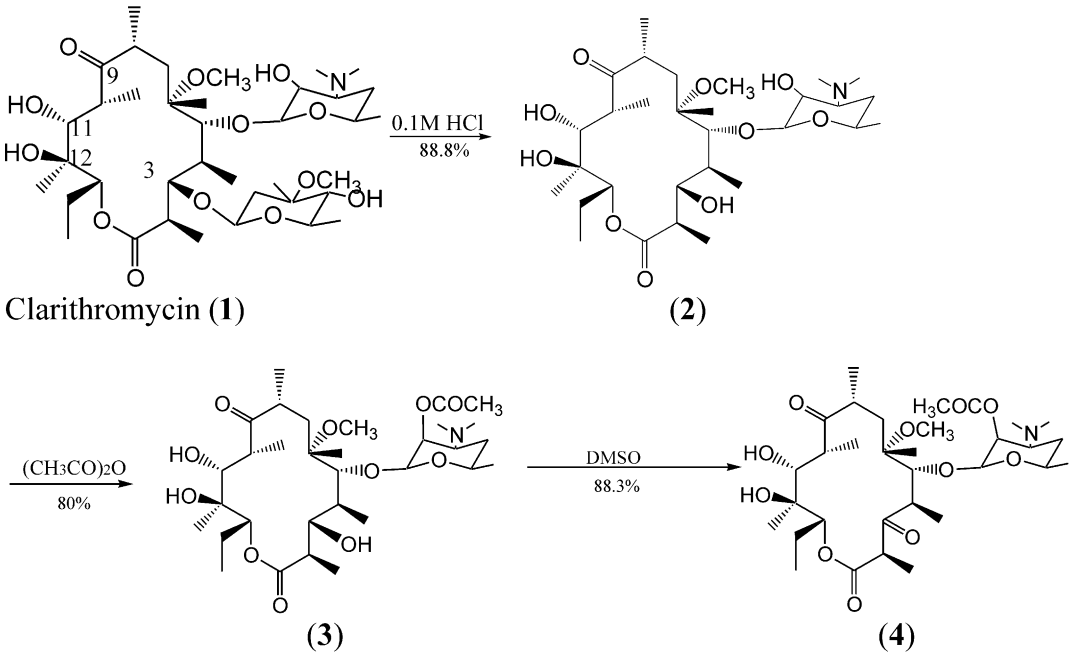
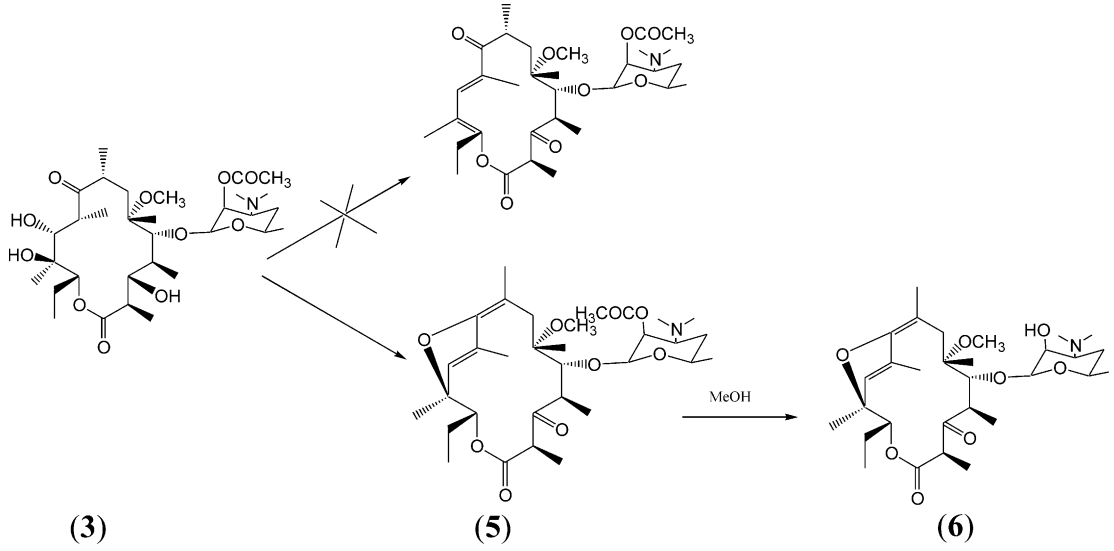


Scheme 1.



Scheme 2.

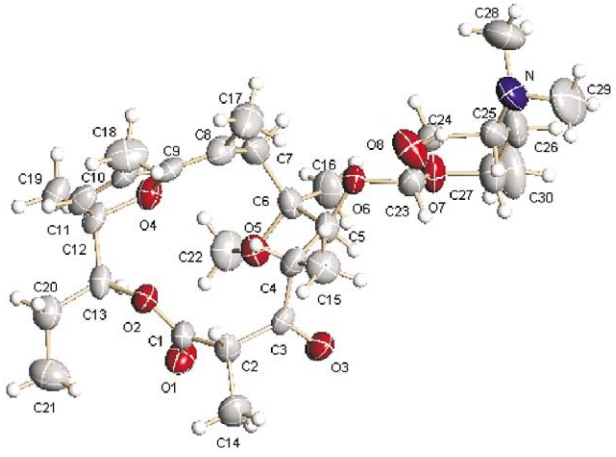


Figure 1. The crystal structure of (**6**).

of H_2O to form 10,11-olifen in the presence of pyridinum trifluroacetate. The hydroxyl group at C12 is activated to attack the carbonyl group at C9 to afford 9,12-hemiacetal.

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References and Notes

1. Agouridas, C.; Denis, A.; Auger, J.-M.; Benedetti, Y.; Bennefoy, 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.
2. Morimoto, S.; Misawa, Y.; Asaka, T.; Kondoh, H.; Watanabe, Y. *J. Antibiot.* **1990**, *43*, 570.
3. Pfitzner, K. E.; Moffatt, J. G. *J. Am. Chem. Soc.* **1965**, *87*, 5661.
4. MS (ESI): 593.4(M^+). ^{1}H NMR ($CDCl_3$): δ 0.88 (t, 3H, 13-$C\underline{H_3}CH_2$), 1.49(d, 1H, H_{7ax}, J = 14.28 Hz), 1.84 (s, 3H, 2′-$\overline{CH_3}$), 2.03(s, 3H, 12-CH_3), 2.07(s, 3H, 10-CH_3), 2.26 (s, 6H, 3-N $(CH_3)_2$), 2.65 (m, 1H, $H_{3'}$), 2.90(d, 1H, H_{7eq}, J = 14.225 Hz), 3.04(s, 3H, 6-OCH_3), 3.50 (m, 1H, $H_{5'}$), 3.60 (q, 1H, H_2), 3.84 (q, 1H, H_4), 4.15 (d, 1H, H_5, J = 9.72 Hz), 4.43(d, 1H, $H_{1'}$, J = 7.63 Hz), 4.81(t, 1H, $H_{2'}$), 4.98 (dd, 1H, H_{13}, J = 3.06, 3.08 Hz), 5.74 (s, 1H, H_{11}).
^{13}C NMR ($CDCl_3$): δ 205.02(C), 169.23(C), 168.71(C), 154.50(C), 135.46(C), 130.16(CH), 102.21(C), 101.72(CH), 87.32(C), 82.73(CH), 79.27(CH), 40.31(CH_3), 36.32(CH_2), 29.89(CH_2), 24.52(CH_2).
5. MS (ESI): 551.7(M^+). ^{1}H NMR ($CDCl_3$): δ 0.90 (t, 3H, 13-$C\underline{H_3}CH_2$), 1.54(d, 1H, H_{7ax}), 2.03 (s, 3H, 12-CH_3), 2.10(s, 3H, $\overline{10}$-CH_3), 2.35 (s, 6H, 3-N $(CH_3)_2$), 2.60 (m, 1H, $H_{3'}$), 2.94(d, 1H, H_{7eq}, J = 14.17 Hz), 3.05 (s, 3H, 6-OCH_3), 3.48 (s, 1H, 2′-OH), 3.52(m, 1H, $H_{5'}$), 3.63 (q, 1H, H_2), 3.84 (q, 1H, H_4), 4.14(d, 1H, H_5, J = 9.60 Hz), 4.34(d, 1H, $H_{1'}$, J = 7.27 Hz), 4.98 (dd, 1H, H_{13}, J = 3.1, 3.09 Hz), 5.75(s, 1H, H_{11}).
^{13}C NMR ($CDCl_3$): δ 205.37(C), 168.90(C), 154.56(C), 135.52(C), 130.17(CH), 103.91(C), 102.38(CH), 87.35(C), 83.32(CH), 79.46(CH), 40.11(CH_3), 36.61(CH_2), 28.83(CH_2), 24.49(CH_2)

X-ray analysis: $C_{30}H_{49}NO_8$, M_r = 551.70, colorless crystals, crystal size 0.586×0.173×0.049 mm, orthorhombic in $p2_{1/n}$ with a = 804347(14), b = 909473(16), c = 37.961(6) Å, α, β, γ = 90°, V = 3185.0(9) Å^3, D_{calu} = 1.151 Mg/m^3, and Z = 4, absorption coefficient 0.082 mm^{-1}, computing structure solution SHELXL-97, theta range for data collection 2.12 to 25.00°, limiting indices $-9 \le h \le 10, -11 \le k \le 11, -45 \le l \le 34$, reflection collected 16052, refinement method full-matrix least-squares, final R indices [I > 2sigma(I)] $R1$ = 0.0765, $wR2$ = 0.1488, R indices (all data) $R1$ = 0.1561, $wR2$ = 0.1788, goodness-of-fit on F^2 0.902, largest difference peak 0.185 eÅ^{-3}, largest difference hole −0.208 eÅ^{-3}.