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Semisynthesis of Linear Fragments Corresponding to the Eastern Portion of Azalide Antibiotics

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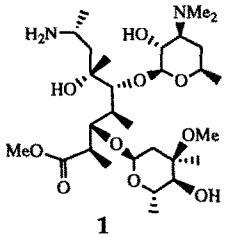
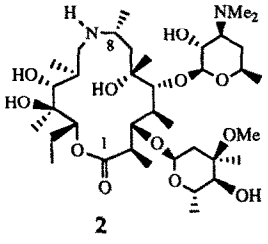
Abstract: Erythromycin A has been converted into two linear fragments (**1** & **3**) which correspond to the eastern portions (C1 to C8 or C9 plus the nitrogen atom) of the azalide antibiotics 9-deoxo-8a-aza-8a-homoerythromycin A (**2**) and 9-deoxo-9a-aza-9a-homoerythromycin A (**4**). These fragments represent advanced intermediates for the synthesis of novel azalide structures with structurally divergent western portions but with conserved eastern portions.

Erythromycin A has been an important agent for the treatment of bacterial infections for over 30 years.[1] It is an attractive drug because it is extremely safe, but its drawbacks include a limited gram negative spectrum and gastric intolerance in many patients.[2] These limitations have been partly overcome with the azalide antibiotics, the prototypes of which are 9-deoxo-8a-aza-8a-homoerythromycin A (**2**) and 9-deoxo-9a-aza-9a-homoerythromycin A (**4**), which combine the safety of erythromycin with an expanded gram negative spectrum and wider tolerance to oral administration.[3] We now report the conversion of erythromycin to a linear 8a-aza fragment (**1**) that corresponds exactly to the eastern portion of the the 8a-azalide **2**, and a similar conversion of erythromycin to a linear 9a-aza fragment **3**, which corresponds closely to the eastern portion of the 9a-azalide **4** (the fragment has an additional ethyl group at C9). These fragments are useful intermediates in the synthesis of novel azalide antibiotics which have high structural homology to azalide antibiotics **2** and **4** in the critical eastern half of the molecule, but are free to diverge in structure by an arbitrary amount in their western halves.



1



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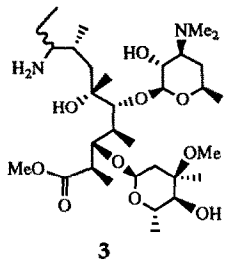

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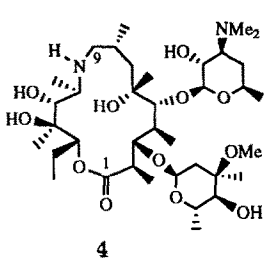
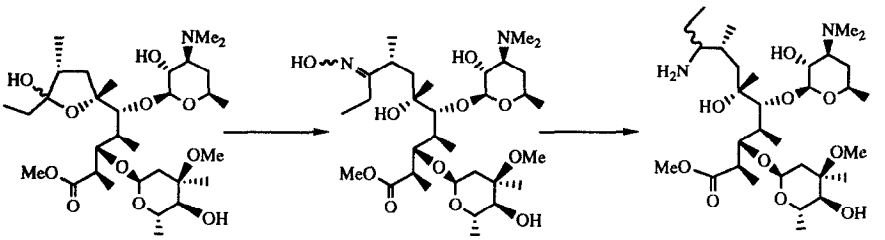


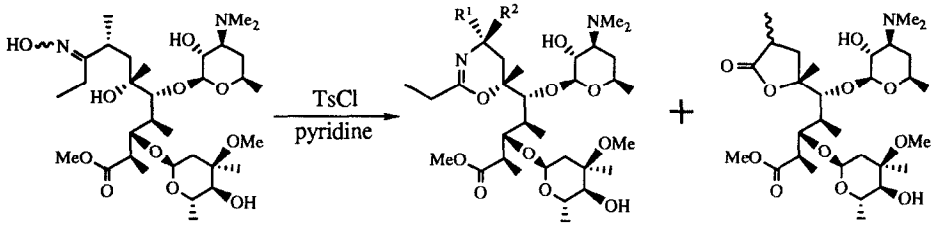
4

The synthesis of the 9a-aza fragment **3** was accomplished in two steps as illustrated below, beginning with the erythromycin fragment **5**.[4] Condensation of **5** with hydroxylamine hydrochloride produced the oxime **6** in 85 % yield. Catalytic hydrogenation of this oxime with PtO_2 in AcOH with 1000 psi H_2 for 24 hours produced the 9a-aza fragment **3** in 78% yield, as an approximately 1 : 1 mixture of stereoisomers at C9.[5]



5 **6** **3**

The synthesis of the 8a-aza fragment **1** started with Beckmann rearrangement (tosyl chloride, pyridine) of the oxime **6**. NMR spectral data indicated that oxime **6** was predominantly a single stereoisomer, which based on simple steric arguments was presumably *E*. Beckmann rearrangement of the *E* isomer with trapping of the intermediate cation by the 6-OH gave rise to the major product, the cyclic iminoether **7**. The minor C-8 epimeric iminoether **8** presumably arises from initial epimerization of the *E*-oxime at C-8 under the acidic reaction conditions. The mixture of C-8 epimeric γ-lactones **9** presumably arises from Beckmann rearrangement of the minor *Z*-oxime to form an unstable exocyclic iminoether, which hydrolyzes to the lactone during aqueous workup.[6]

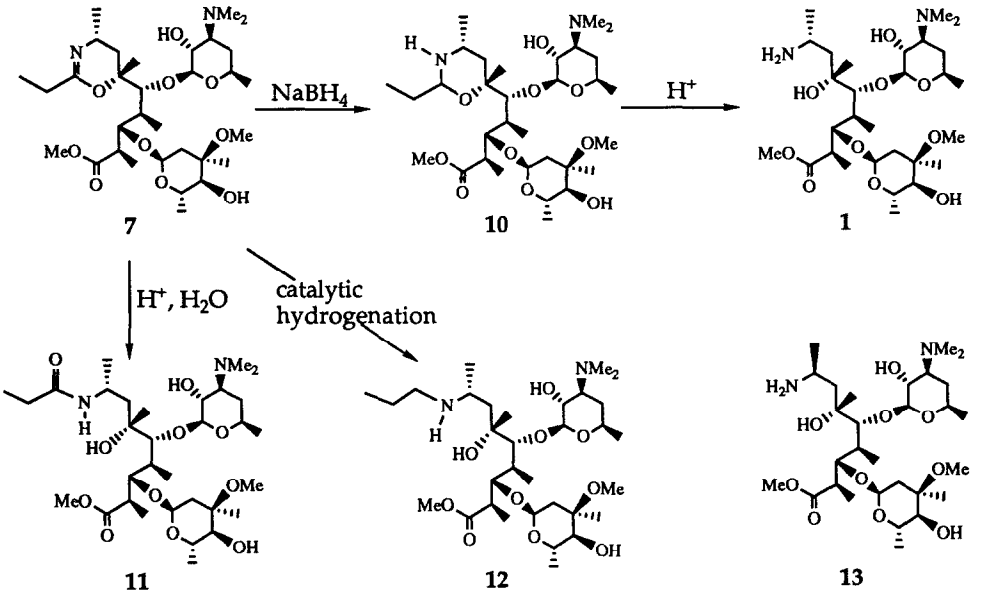


6 **7** R^1 = Me R^2 = H; **8** R^1 = H R^2 = Me **9**

The distribution of products resulting from the Beckmann rearrangement of oxime **6** depends on the details of the reaction conditions. In general, treating a 0.05 to 0.1 M solution of oxime **6** in pyridine with one equivalent of an activating reagent (such as p-toluenesulfonyl chloride or p-toluenesulfonic anhydride) at room temperature led to incomplete conversion of starting material to the desired imino ether **7**. If the reaction was conducted at 60°C it proceeded essentially to completion, but with substantial formation of the γ-lactone by-products **9** (along with a smaller amount of the epimeric by-product **8**). Conducting the reaction at room temperature with 5 equivalents of the activating reagent also forced the reaction to near completion, but with substantial formation of epimeric by-product **8** (along with smaller amounts of **9**.) The best conditions for producing **7** involved treating a

1.3 to 1.5 M solution of the oxime **6** in pyridine with 1.1 equivalents of p-toluenesulfonyl chloride at room temperature. At this greater concentration, the reaction proceeded to completion with minimum formation of by-products. It should be noted that the epimeric iminoether by-product **8** is easily separated from iminoether **7** by silica chromatography[7] and is useful for the synthesis of the epimeric 8a-aza fragment **13**.

Conversion of iminoether **7** into the 8a-aza fragment **1** was not readily accomplished by simple acid hydrolysis, as this led almost exclusively to the amide **11**. Most methods of reduction (e.g. catalytic hydrogenation or sodium borohydride at room temperature and pH < 6) furnished predominantly the propylamine **12**. However, reduction following the method developed by Myers et. al. ($NaBH_4$ at -40 °C and pH = 7)[8] produced the aminal **10** as a single stereoisomer of undetermined configuration at the aminal carbon. The aminal could be isolated by silica chromatography as long as ammonia was a component of the eluent: otherwise it decomposed on silica to the 8a-aza fragment **1**.[9] Normally the aminal was not isolated, however, but was directly hydrolyzed to **1** with mild acid.[10] The overall yield of the 8-aza fragment **1** was 68% from the iminoether **7**.



In summary, we have described the conversion of erythromycin A into two linear nitrogen containing fragments which correspond to the the eastern half of two potent azalide antibiotics. This conversion leaves the two sugar moieties intact and requires no protecting groups. These fragments represent advanced semisynthetic intermediates for the synthesis of a large number of novel azalide antibiotics with structurally divergent western portions but with conserved eastern portions. Our efforts at reconstruction of the macrocycle from these intermediate fragments will be reported in due course.

Acknowledgements: We are grateful to Amy Bernick and Larry Colwell for FAB mass spectra and to Ronald Ratcliffe for many helpful discussions.

References and Notes

1. For early work on erythromycin A see Flynn, E.; Sigal, M; Wiley, P.; Gerzon, K *J. Am. Chem. Soc.* **1954,** *76,* 3121.
2. Koch, W. L. *Analytical Profiles of Drug Substances, Vol. 8*; Florey, K., Ed.; Academic Press: NY, **1979**; p. 159.
3. (a) The term "azalide", originally coined by Pfizer, refers here to ring nitrogen containing 15-membered ring derivatives of erythromycin. (b) 9-Deoxo-8a-aza-8a-homoerythromycin A is described in Wilkening, R. R.; Ratcliffe, R. W.; Doss, G. A.; Bartizal, K. F.; Graham, A. C.; Herbert, C. M. accepted for publication in *Bioorganic and Medicinal Chemistry Letters.* (c) 9-Deoxo-9a-aza-9a-homoerythromycin A (the 9a-N-Me derivative of which is called azithromycin and marketed by Pfizer as Zithromax™) is described in Djokic, S.; Kobrehel, G.; Lazarevski, G.; Loppotar, N.; Tamburasev, Z.; Kamenar, B.; Nagl, A.; Vickovic, I. *J. Chem. Soc., Perkin Trans I* **1986,** 1881 and Bright, G. M.; *et al. J. Antibiotics* **1988,** *41,* 1029.
4. Waddell S. T.; Blizzard, T. A. *Tetrahedron Lett.* **1992,** *33,* 7827.
5. Selected spectral data for **3** (mixture of diastereomers at C9): ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.62 (apparent t, H-1''), 4.37 (apparent t, H-1'), 3.61 & 3.60 (s, $COOCH_3$), 3.25 & 3.23 (s, OCH_3), 3.09 & 3.01 (s, OCH_3), 2.27 & 2.24 (s, $N(CH_3)_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.22, 215.11, 175.98, 175.95, 102.80, 102.38, 95.16, 94.80, 79.84, 79.58, 79.39, 78.87, 78.70, 77.89, 72.66, 72.63, 70.27, 68.84, 65.32, 65.22, 65.18, 51.53, 51.47, 50.18, 50.05, 49.23, 41.97, 41.50, 41.25, 41.22, 40.27, 40.22, 39.30, 37.41, 36.71, 35.00, 34.31, 32.41, 29.02, 28.80, 21.45, 21.37, 21.13, 20.11, 19.01, 18.78, 17.98, 17.94, 10.86, 10.78, 10.65, 10.59, 7.72, 7.60. FAB MS: 648 (M + H^+).
6. Because the *E* and *Z* oximes might interconvert under the reaction conditions and undergo the Beckmann reaction at different rates, the product ratio (**7** + **8**)/**9** does not necessarily reflect the relative proportions of *E* to *Z* oxime in the starting material.
7. A suitable solvent system for this separation is 94 : 6 : 1 CH_2Cl_2 : MeOH : aq. NH_3. Compound **9** elutes first, followed closely by **7**, and these are easily separated from **8**, which elutes last.
8. Meyers, A. I.; Nabeya, A.; Adickes, H. W.; Politzer, I. R.; Malone, G. R.; Kovelesky, A. C.; Nolen, R. L.; Portnoy, R. C. *J. Org. Chem.* **1973,** *38,* 36.
9. A suitable solvent system for the purification of compound **10** using silica chromatography is 93 : 7 : 1 CH_2Cl_2 : MeOH : aq. NH_3. Compound **1** is more polar and requires 90 : 10 : 1 CH_2Cl_2 : MeOH : aq. NH_3.
10. Selected spectral data for **1** : ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.60 (d, H-1''), 4.33 (d, H-1'), 4.10 (dd, H-3), 4.00 (dq, H-5''), 3.63 (s, $COOCH_3$), 3.53 (m, H-5'), 3.48 (d, H-5), 3.28 (dd, H-2'), 3.25 (s, OCH_3), 3.25 (m, H-8), 2.95 (d, H-4''), 2.79 (dq, H-2), 2.49 (m, H-3'), 2.27 (s, $N(CH_3)_2$), 2.26 (dd, H-2''), 2.04 (m, H-4), 2.49 (dt, H-3'), 1.64 (br d, H-4'), 1.45 (dd, H-2'' ax), 1.45 (m, H-7), 1.35 (m, H-7), 1.24 (s, H-6Me), 1.21 (m, H-6' or 6''), 1.21 (m, H-4'), 1.20 (s, H-6' or 6''), 1.16 (s, H-3''Me), 1.09 (d, H-2Me), 1.09 (d, H-8Me), 1.04 (d, H-4Me). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.35 (C-1), 104.37 (C-1'), 95.98 (C-1''), 85.70 (C-5), 80.33 (C-3), 77.79 (C-4''), 75.01 (C-6), 72.66 (C-3''), 70.39 (C-2'), 69.57 (C-5'), 65.30 (C-5''), 65.11 (C-3'), 51.65 (C-ester Me), 49.34 (C-3''-OMe), 44.16 (C-7), 43.96 (C-8), 41.24 (C-2), 35.11 (C-2''), 28.81 (C-4'), 26.51 (C-8Me or 2Me), 24.39 (C-6Me), 21.50 (C-3''Me), 21.05 (C-6'), 17.73 (C-6''), 11.00 (C-4Me), 10.08 (C-8Me or 2Me). FAB MS: 594 (M + H^+)