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Synthesis of the Macrolide Antibiotic, Oxolide

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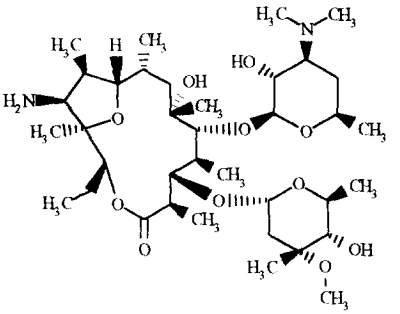
Abstract: *An acid-stable macrolide, oxolide, was synthesized from Erythromycin A. Key features include two stereoselective reductions with DIBALH and $NaBH_3CN$ and a simple pH dependent separation of the final product from its C-11 epimer.*

Oxolide (**1**) is a semi-synthetic acid stable macrolide antibiotic that is active against Gram-negative bacteria, such as *Haemophilus influenzae*, the cause of several upper respiratory infections. The *in vitro* potency and range of activity of this compound are similar to erythromycin A.[2] Its therapeutic activity is currently under evaluation at Abbott Laboratories.



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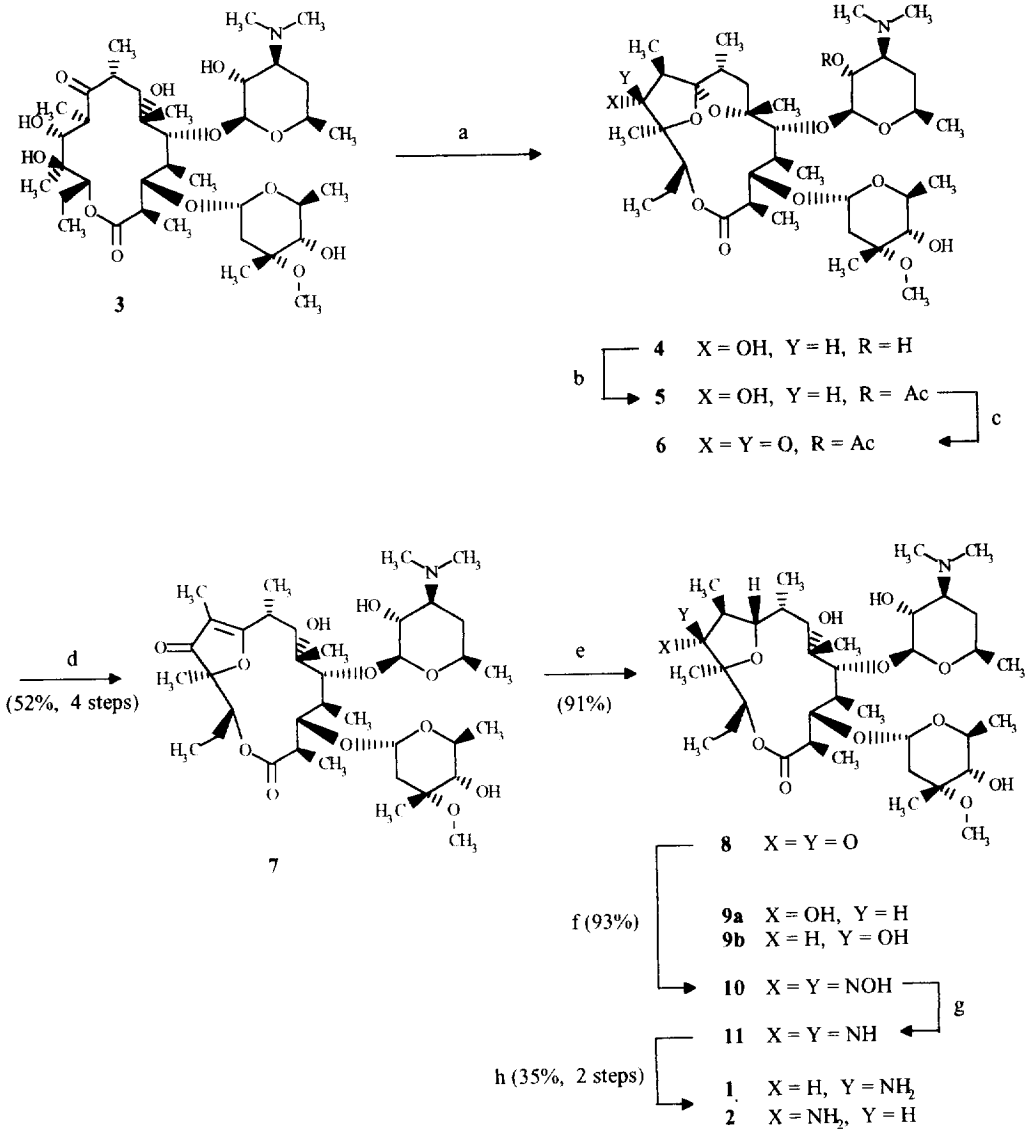
The synthesis of **1** is detailed in the scheme. Erythromycin A (E_A, **3**, 12.0 kg) was treated with dilute aqueous hydrochloric acid (pH = 3.0) to give anhydro-E_A, **4**, *in situ*. The product was extracted into CH_2Cl_2 and treated directly with Et_3N and acetyl chloride to give the 2'-O-acetyl-anhydro-E_A, **5**.[3] Oxidation with $K_2Cr_2O_7/H_2SO_4$ yielded 2'-O-acetyl-11-oxo-anhydro E_A, **6**.[4] Two transformations were achieved in one-pot by treating **6** with NH_2OH-HCl in the presence of Et_3N and methanol. This resulted in a β-elimination/opening of the 6,9-epoxide as well as deprotection of the 2'-O-acetyl group to afford compound **7**. Reaction of this α,β-unsaturated ketone with DIBALH (THF, -45°C) led to stereospecific addition of hydride to the less sterically hindered β-face. Protonation, on work-up, occurred on the α-face to give **8**, the thermodynamically favored product.[5] Contamination by another epimer was not detected but if the temperature was not carefully controlled, a small amount of over-reduction to alcohols **9a-b** was observed. Oximation of **8** with NH_2OH-HCl in the presence of Et_3N/EtOH yielded **10**. The reaction occurred over 5-7 days at reflux. The pH was maintained to avoid decomposition of the starting material and product. Deoxygenation with $TiCl_3$ (10% solution in 20-30% HCl)[6] liberated the imine. The acidity of the reaction mixture was maintained by addition of an excess of concentrated aqueous NH_4OH. Immediately upon isolation, the imine was reduced with $NaBH_3CN$ (MeOH, HOAc, pH ~ 4.0) to furnish a mixture of the two possible C-11 epimers: the desired compound **1** and the undesired epimer **2** in a ratio of 6 : 1. In the laboratory, the compound was purified via column chromatography (silica gel, $CHCl_3$:MeOH:NH_4OH(aq)/ 18 : 1 : 1) but a pilot plant scale synthesis necessitated an alternative purification procedure because of the scale and concerns over the use of copious amounts of chloroform. Multiple recrystallizations yielded pure product, but time constraints (weeks for large scales) and product losses (50%) made this an unattractive alternative.

We then designed an efficient method for purifying this compound. It was felt that the definite structural rigidity associated with macrolides in solution[7] might affect the water or organic solvent solubility of these compounds at different pH's. It might then be possible to solubilize one of the epimers in water at a specific pH and extract the other epimer with a water immiscible organic solvent. After extensive experimentation, the following procedure was devised: 2.9 kg **1** (wet cake; @ 60% **1** and 10% **2** by HPLC) was dissolved in methanol. The pH was adjusted to 4 with acetic acid while the temperature was maintained at 25°C. Water was then added to the vigorously stirred mixture. The solution was extracted with methylene chloride. At this point only **1** was detected in the aqueous layer. **2** and all other impurities were present in the organic layer. The aqueous layers were combined and the pH adjusted to 8 using concentrated aqueous NH_4OH. Extraction with methylene chloride followed by drying ($MgSO_4$) and evaporation *in vacuo* furnished an amorphous solid that was crystallized from hot isopropyl alcohol and dried to give 1.0 kg **1** (63% recovery from crude product). HPLC[8] showed product purity at > 98% with only trace (< 1%) contamination of the undesired epimer, **2**. The overall yield from **3** to pure **1** was 7%.

An efficient route to the synthesis of oxolide has been demonstrated on a multi-kilogram scale. A simple separation protocol for the final product was developed. It is anticipated that this pH dependent partitioning of the two epimers, **1** and **2**, would be generally applicable to a range of macrolides and is the subject of ongoing investigation in our laboratory.



Scheme: (a) HCl/H_2O (pH = 3.0); (b) Ac_2O, Et_3N, CH_2Cl_2;[3] (c) $K_2Cr_2O_7$, H_2SO_4, H_2O, CH_2Cl_2; (d) NH_2OH-HCl, MeOH (52%, 4 steps); (e) DIBALH, THF, -45°C (91%); (f) NH_2OH-HCl, Et_3N, EtOH, 7 days (93%); g) $TiCl_3$ (10% in 20-30% HCl), conc. aq. NH_4OH, MeOH, 0°C; h) $NaBH_3CN$, HOAc, MeOH (**1** : **2** = 6 : 1). Yield of **1** was 35%, over two steps, purification, and recrystallization.[9]

Acknowledgments

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2. Information on the synthesis as well as the biological activity was presented in a poster: Freiberg, L. A.; Edwards, C. M.; Bacino, D. J.; Seif, L.; Lartey, P. A.; Whittern, D. Presented at the 29th Interscience Conference on Antimicrobial Agents and Chemotherapy, 1989; poster 1029. Additional information on this and other semi-synthetic macrolides can be found in: a) Lartey, P. A. and Perun, T. J. in *Studies in Natural Products Chemistry*, Atta-ur-Rahman, Ed.; Elsevier Science Publishers B.V.: 1993; Vol. 13, pp 155-185. b) Hardy, D. J.; Swanson, R. N.; Shipkowitz, N. L.; Freiberg, Lartey, P. A.; Clement, J. J. *Antimicrob. Agents Chemotherap.* **1991**, *35*, 922.
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8. HPLC conditions: Column: YMS-A-303-7; C-18, 7 μ; Eluent: H_2O, 65% MeOH with 10g/L NaOAc-3H_2O, 0.5mL HOAc, 30 mL/L ethylene glycol; Flow rate: 1ml/min
9. All intermediates and final products were characterized by ^{1}H and ^{13}C NMR, IR, and mass spectroscopy.

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