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Facile N-Demethylation of Erythromycins

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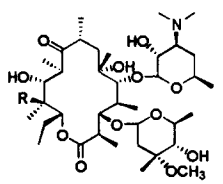
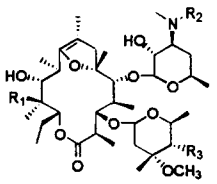
Abstract: 4″-Deoxyerythromycin B reacts with 1-chloroethyl chloroformate to give the corresponding N-demethyl N-chloroethyl carbamate. Mild methanolysis removes the chloroethyl group giving the N-demethyl erythromycin derivative while also forming the 6,9-enol ether moiety. Further manipulation gives ABT-229, a potential prokinetic agent.

Keywords: Erythromycin, N-Demethylation

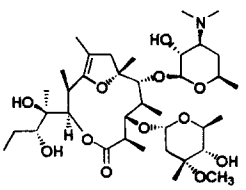
Since the discovery several years ago of a class of erythromycin derivatives which promote gastrointestinal motility in dog [1] a number of drug candidates have been tested in clinical trials as potential prokinetic agents. These drugs are synthesized from either erythromycin A or B, the difference between the two being the presence or absence of a C-12 hydroxyl group.



R=OH Erythromycin A
R=H Erythromycin B



R_1=H, R_2=Et, R_3=H ABT-229, 1
R_1=OH, R_2=Et, R_3=OH EM-523
R_1=OMe, R_2=i-Pr, R_3=OH GM-611



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A common feature of all of the drug candidates is the presence of the 8,9-anhydro 6,9-hemiketal group. Another recurring theme in the structures of these compounds is the alteration of the N,N-dimethylamine of the parent erythromycin. In most cases one of the methyls is replaced with another alkyl group. The preparation of these amines requires first N-demethylation and then alkylation with the group of choice. ABT-229 (1) [2] is prepared from 4″-deoxy erythromycin B. To convert 4″-deoxy erythromycin B to ABT-229, an N-methyl group must be replaced with an N-

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ethyl group and the 8,9-anhydro 6,9-hemiketal moiety must be generated. In the course of our work on the preparation of ABT-229 we discovered an efficient procedure for accomplishing both the N-demethylation and the formation of the enol ether moiety.

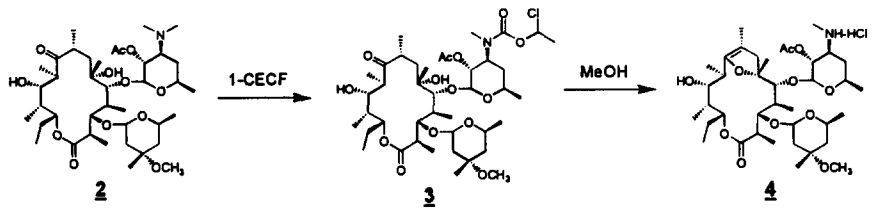
Several choices are available for N-demethylation of the erythromycin molecule. In their work to determine the structure of erythromycin A, Flynn and co-workers [3] used ethyl chloroformate to prepare the N-demethylated O,N-bis(carboethoxy) compound. Subsequently they reported [4] making O,N-bis(carbobenzyloxy) erythromycin A using benzyl chloroformate. Iodine demethylation, done both photolytically [5] and thermally [6], has also been used on erythromycins. However, each of these methods is limited in its applicability as a manufacturing procedure for the large scale N-demethylation of the erythromycin B derivative used for the synthesis of ABT-229. The conditions needed to hydrolyze the ethyl carbamate, formed by reaction with ethyl chloroformate, promote undesired side reactions. Catalytic hydrogenolytic removal of CBZ groups is common practice, particularly in peptide chemistry. A weakness of the method is the fact that the catalyst is subject to poisoning. Trace sulfur impurities from deoxygenation of the 4″-thiocarbamoyl derivative could poison the catalyst and make the hydrogenolysis problematic. Photolytic N-demethylation with iodine works well in the lab, but lack of suitable equipment in the pilot plant prevented it from being used on a large scale. The thermal iodine demethylation procedure also works well on laboratory scale reactions. On larger scale, in the pilot plant, the reaction does not go to completion. Thus, none of the above procedures was suitable for large scale N-demethylation of erythromycin B, or its 4″-deoxy derivative.

Besides ethyl and benzyl chloroformates, other chloroformates have been used to effect N-demethylation. Both vinyl chloroformate [7] and 1-chloroethyl chloroformate [8] have been used for this purpose. 1-Chloroethyl chloroformate was particularly attractive because of the mild conditions required for the removal of the chloroethyl carbamate group.

1-Chloroethyl chloroformate (1-CECF) cleanly converted 2′-O-acetyl 4″-deoxy erythromycin B 2 to its N-demethyl N-chloroethyl carbamate 3 (see Scheme I). Methanol treatment cleaved the carbamate and yielded the N-demethyl enol ether, 4. Methanol initially displaces the α-

chloride thereby generating one mole of HCl. In a methanolic HCl solution, the enol ether is formed very quickly. Surprisingly there is little additional acid-catalyzed reaction that takes place.

Scheme I



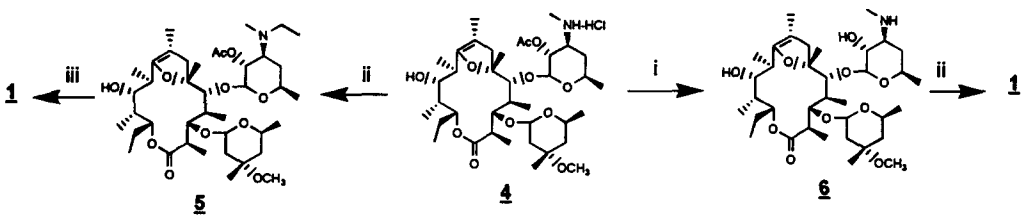
2 3 4

There is only a minor amount of the descladinose product formed, even though dilute HCl in methanol has been used for cladinose removal. Apparently the carbamate cleavage occurs quickly relative to cladinose methanolysis. Carbamate cleavage frees the monomethylamine which in turn ties up the mole of HCl and prevents further acid-catalyzed reaction. Just as the amine attenuates the effect of the acid on carrying out further acid-catalyzed reactions, the HCl in turn prevents the amine from participating in chemistry at the 2′-position. As a free base the erythromycin 3′-amine enhances the activity of the 2′-hydroxyl towards acylation and, in the case of the acylated compounds, towards deacylation [9]. Thus the 2′-hydroxyl of the erythromycins can be selectively acetylated in the presence of free hydroxyls at C-4″, C-6, C-11, and C-12. Di- and tri-acetylated erythromycins can be selectively deacetylated at the 2′-hydroxyl. In this case overnight treatment with methanol at room temperature, or for two hours at 40°C, converts carbamate 3 cleanly to the acetate 4. Refluxing methanol for more than 24 hours is required to deacetylate the 2′-O-acetate of compound 4. By employing a trace amount of sodium bicarbonate (0.05 equiv.) in a methanol solution of 4, the temperature required for deacetylation is reduced to 40°C, but the reaction still requires more than 24 hours to go to completion. Increasing the amount of sodium bicarbonate, or adding an organic base such as triethylamine, results in formation of the acetamide, as the acetyl group is transferred from the 2′-hydroxyl to the neighboring 3′-amine [10].

The synthesis of ABT-229 is completed by ethylation of acetate 4, using ethyl iodide and diisopropylethylamine (DIEA), to give 5, and then removal of the acetate under mild methanolysis

conditions (see Scheme II). Alternatively, 4 is deacetylated under the more vigorous methanolysis conditions, giving 6, and the synthesis is finished by ethylation of N-deethyl ABT-229.

Scheme II



i. MeOH, reflux
ii. EtI, DIEA, NMP
iii. MeOH, RT

In conclusion, 1-chloroethyl chloroformate is an efficient, mild reagent for N-demethylation of 4″-deoxyerythromycin B. Furthermore, the conditions used for removing the protecting group provide ready access to the 8,9-anhydro 6,9-hemiketal. The chemistry described is not limited to 4″-deoxyerythromycin B as substrate. It has been demonstrated to work equally well on erythromycin A and erythromycin B.

Preparation of N-Demethyl Enol Ether 4 : 4"-Deoxyerythromycin B (20g) was converted to compound 3 by acetylation with acetic anhydride (1.2 eq., 15 eq. $NaHCO_3$, 1 hr., 50°C, 140mL EtOAc) followed by treatment with 1-CECF (7 eq., 50°C, 5 hr.). After quench with NH_4OH and workup, 24.67g of crude solid was obtained. This was dissolved in 120mL methanol, warmed to 40°C, and stirred for 2 hours. Methanol removal gave compound 4 as a foam weighing 26.19g (theoretical yield: 20.3g). This material was carried on directly to the ethylation reaction.

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