CHEMICAL MODIFICATION OF ERYTHROMYCINS. VIII. A NEW EFFECTIVE ROUTE TO CLARITHROMYCIN (6-O-METHYLERYTHROMYCIN A)[1]

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Abstract --- Selective O-methylation of the C-6 hydroxyl group of erythromycin A could be satisfactorily achieved by using its 9-oxime derivatives as the starting materials. Thus, 6-O-methylerythromycin A (clarithromycin) was synthesized from 2'-O,3'-N-bis(benzyloxycarbonyl)-N-demethylerythromycin A *via* its 9-oxime derivative by 6 steps.

Erythromycin[2] is one of the most important macrolide antibiotics for treatment of infections caused by Gram-positive bacteria and *mycoplasma* sp. 6-O-Methylerythromycin A [clarithromycin (**CAM**)] has been synthesized to improve the antibacterial and pharmacokinetic properties of erythromycin.[3,4]

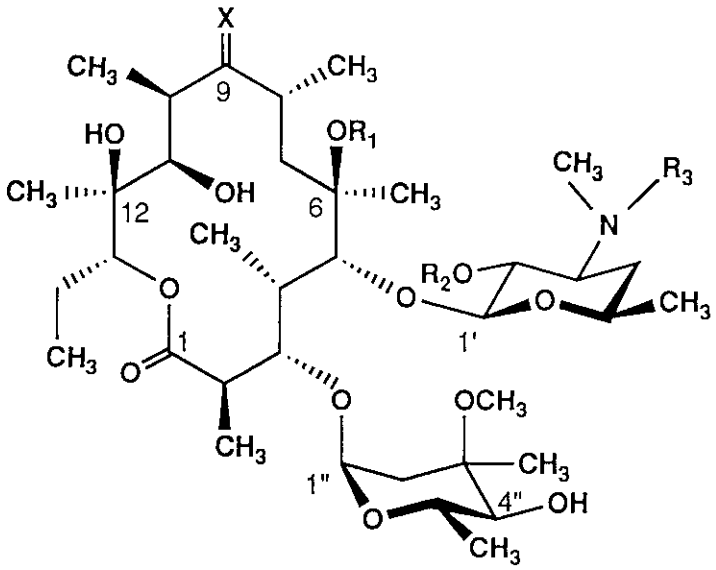
In the previous paper,[5] we reported the synthesis of **CAM** from erythromycin A *via* 2'-O,3'-N-bis(benzyloxycarbonyl)-N-demethylerythromycin A (**1**). Despite the best result, O-methylation of 1 gave the desired 6-O-methyl product in 39% yield (purity: 94 % by hplc analysis), which was further contaminated by a certain amount of 6,11-di-O-methyl and 6,12-di-O-methyl derivatives. The 11-O-methylated compound was formed at the same time in 42 % yield. It has been shown that the O-methylation preferentially took place at the secondary C-11 hydroxyl group rather than the tertiary C-6 hydroxyl.

Therefore, we have widely investigated the methylation for a variety of erythromycin A derivatives whether they give 6-O-methyl derivative selectively, and finally could find that the erythromycin A 9-oxime derivative afforded 6-O-methyl derivative exclusively.

Herein, we report the effective synthesis of **CAM** through the methylation of 9-oxime derivative of erythromycin A.

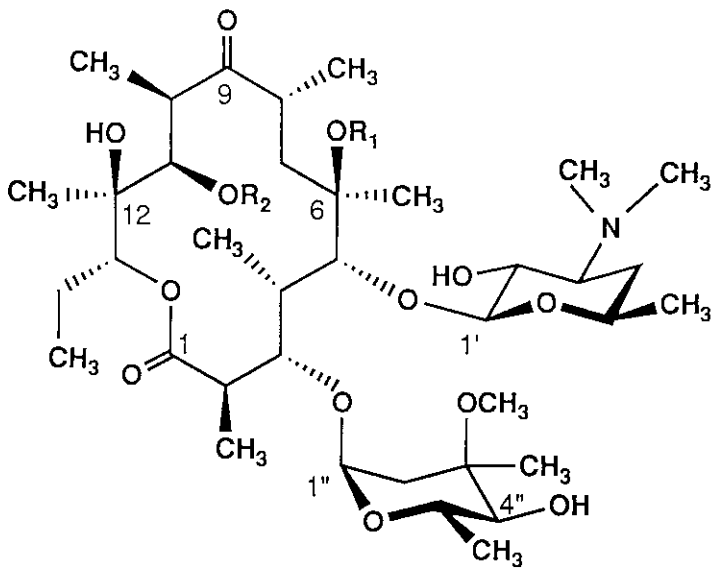
In order to avoid quaternalization of the dimethylamino group by methylating agent, we employed the bis-protected derivative (**1**) as the starting material. Oximation of the compound (**1**) with hydroxylamine hydrochloride and sodium acetate in methanol afforded the corresponding 9-oxime derivative (**2**). Crystallization from $CHCl_3$-n-hexane gave the E-oxime isomer (**2**),[6] mp 152-154°C, (75%). Treatment of **2** with benzyl chloride and sodium hydride in N,N-dimethylformamide provided 9-O-benzyloxime derivative (**3**) in 82% yield, which was purified by silica gel column chromatography [EtOAc-n-hexane (1:2-1:1)], and crystallization from EtOAc-petroleum ether, mp 105-107°C.
According to our previous synthesis,[5] **3** was allowed to react with an excess of methyl iodide and potassium hydroxide (1.1 equiv.) in a mixture of dimethyl sulfoxide and tetrahydrofuran (1:1) to give the corresponding 6-O-methyl derivative (**4**). The hplc analysis of the resulting reaction mixture indicated that a ratio of the peak areas of **4**, the starting **3** and other minor methylated compounds was 84.1:7.1:6.8, respectively. Purification by chromatography on a silica gel column [EtOAc-n-hexane (1:1)] followed by crystallization from ether-petroleum ether gave the pure **4**, mp 154.5-156°C (76%). Removal of both the benzyloxycarbonyl and benzyl groups by catalytic hydrogenation yielded 6-O-methyl-N-demethylerythromycin A 9-oxime (**5**), mp 247-249°C. Reductive N-methylation of **5** with formaldehyde in the presence of formic acid in gently refluxing ethanol provided 6-O-methylerythromycin A 9-oxime (**6**) in 71% yield from **4**, mp 169-171°C (it solidifies at 180-185°C and remelts at 248-251°C). Deoximation of **6** with sodium bisulfite[7] in refluxing aqueous ethanol gave **CAM**. Crystallization from ethanol afforded pure **CAM**, mp 221-223°C, (68%) [lit.[3], mp 222-225°C].

As compared with the previous synthetic pathway, the selectivity of O-methylation *via* 9-O-benzyloxime derivative (**3**) could be greatly enhanced and the hplc analysis indicated that the desired 6-O-methyl derivative (**4**) was formed more than 80% from **3**. The present synthesis efficiently provided **CAM** in 23% overall yield from **1**. Each intermediate was purified as described above,



Compound	X	R1	R2	R3
1	O	H	Z	Z
2	NOH	H	Z	Z
3	$NOCH_2C_6H_5$	H	Z	Z
4	$NOCH_2C_6H_5$	CH_3	Z	Z
5	NOH	CH_3	H	H
6	NOH	CH_3	H	CH_3

Z=$CO_2CH_2C_6H_5$



Compound	R1	R2
Erythromycin A	H	H
Clarithromycin (CAM)	CH_3	H
11-*O*-Methyl-erythromycin A	H	CH_3

but the purification is not necessarily the case. Through the investigation of the reaction processes, it makes possible to improve the yield.

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6. The following reactions were achieved using this E-isomer. The unstable Z-isomer was obtained from the mother liquor after crystallization of the E-isomer. Thus, the solvent was evaporated to dryness *in vacuo* and the residue was purified by silica gel column chromatography with a mixture of EtOAc-n-hexane (2:1) as an eluant to afford the Z-isomer **2**, mp 115-130°C, which was isomerized to the E-isomer in $CHCl_3$ or by heating.
7. S. H. Pines, J. M. Chemerda, and M. A. Kozlowski, J. Org. Chem., 1966, 31, 3446.
   In their studies, acidic workup is employed for isolation of products. In the present case, however, the deoximation product can be easily isolable by dilution with water followed by adjusting the pH of the reaction mixture to 10.

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