CHEMICAL MODIFICATION OF ERYTHROMYCINS. XI. SYNTHESIS OF CLARITHROMYCIN (6-O-METHYLERYTHROMYCIN A) VIA ERYTHROMYCIN A QUATERNARY AMMONIUM SALT DERIVATIVE[1]

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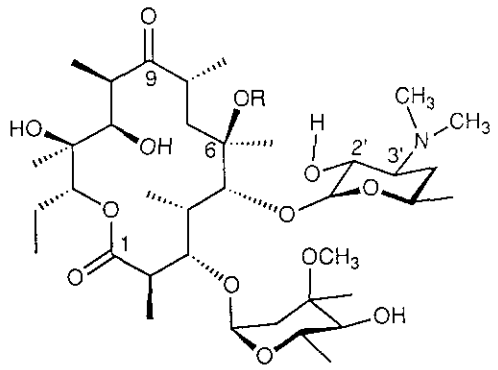
Abstract ----- Synthesis of clarithromycin via quaternary ammonium salt of erythromycin A, 2'-O-benzyl-3'-[benzyl(dimethyl)ammonio]-3'-de(dimethylamino)erythromycin A bromide 9-O-(benzyloxime) (2), was reported. Clarithromycin was obtained in 53 % overall yield from erythromycin A 9-oxime (1).

In the previous studies,[2] we reported the selective O-methylation of C-6 hydroxyl group of erythromycin A relating to the effective synthesis of clarithromycin (6-O-methylerythromycin A), a novel semisynthetic 14-membered macrolide antibiotic. Thus, the 9-oxime derivatives of erythromycin A gave the corresponding 6-O-methyl derivative selectively by methylation. In this synthetic pathway 2'-O,3'-N-bis(benzyloxycarbonyl)-N-demethylerythromycin A 9-O-(benzyloxime) plays an impotant role.



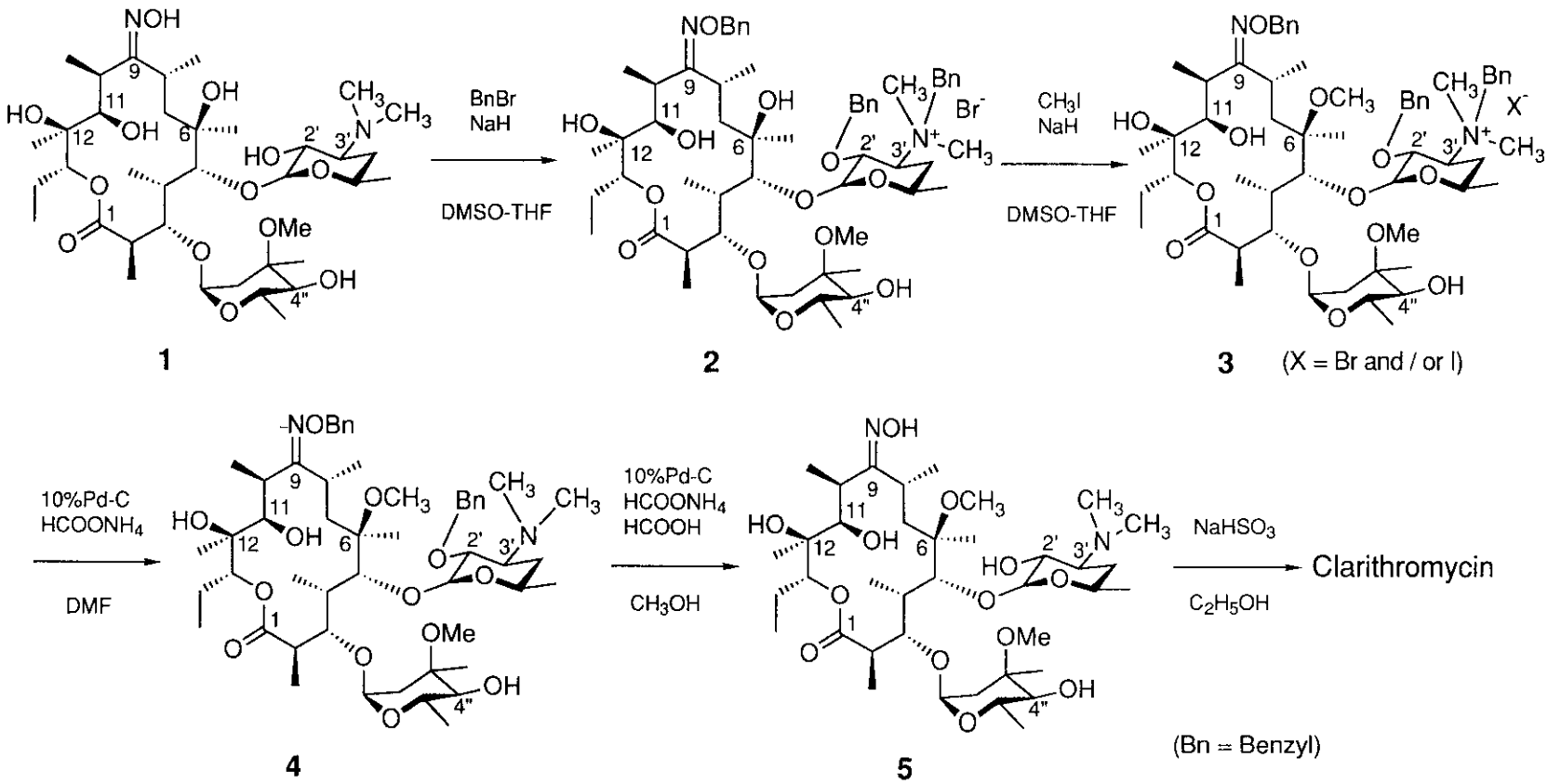
Erythromycin A
R=H

Clarithromycin
R=CH_3

When erythromycin A is allowed to react with methylating reagent, its 3'-dimethylamino group simultaneously changes into trimethylammonio group. Accordingly, it is necessary to protect the dimethylamino group by an appropriate protecting group such as benzyloxycarbonyl (Cbz) group. However, N-methylation is needed to regenerate 3'-dimethylamino group after removal of the Cbz group. In addition, the Cbz group cannot be available for protection of the hydroxyl group of the 9-oxime moiety because it was easily removed during methylation and the corresponding 9-O-methyloxime was formed in a good yield. Usually, regeneration of C-9 ketone from the methyloxime also seems to be difficult by common method.[3]

To improve the synthetic method for clarithromycin, we envisioned two approaches: 1) to effect a complete protection of these functional groups with the same protective group and 2) to reduce the hitherto practiced N-methylation process, both of which could be minimized the reaction steps. For this purpose we attempted to use a quaternary ammonium salt of the dimethylamino group with benzyl halide, which seemed to provide for protection of the amino group effectively against the attack of methylating reagent and to release the benzyl group under a mild and neutral condition such as hydrogenation by the use of catalytic transfer hydrogenation (CTH) method.[4] The present paper is concerned with the synthesis of clarithromycin using the quaternary salt of erythromycin oxime derivative.

Treatment of erythromycin A 9-oxime (1)[5] with benzyl bromide (3.15 equiv.) and sodium hydride (2.9 equiv.) in a mixture of dimethyl sulfoxide (DMSO) and tetrahydrofuran (THF) (1:1) afforded the desired 2'-O-benzyl-3'-[benzyl(dimethyl)-ammonio]-3'-de(dimethylamino)erythromycin A bromide 9-O-(benzyloxime) (2)[6] in 92% yield. The presence of a dipolar aprotic solvent such as DMSO or N,N-dimethylformamide (DMF) has been found very useful for the formation of the quaternary ammonium salt. The ^{1}H-nmr spectrum of **2** exhibited characteristic AB quartette signals for 6 protons at 4.57 & 5.37, 5.00 & 5.18 and 5.06 & 5.07 ppm, which were attributed to the protons of methylene group adjacent to the benzene ring. The reaction of **2** with methyl iodide (1.5 equiv.) and sodium hydride (1.3 equiv.) in a mixture of DMSO and THF (1:1) proceeded selectively to afford the corresponding 6-O-methyl derivative (**3**),[7] of which counter anion (e.g. bromide anion) was replaced partially by iodide anion derived from methyl iodide.
To eliminate the protective groups, **3** was treated with formic acid in MeOH in the


NOH
BnBr
NaH
DMSO-THF
NOBn
CH3I
NaH
DMSO-THF
10%Pd-C
HCOONH4
DMF
10%Pd-C
HCOONH4
HCOOH
CH3OH
NaHSO3
C2H5OH
Clarithromycin
1
2
3 (X = Br and / or I)
4
5
(Bn = Benzyl)

presence of 10% Pd-C according to the method for 2'-O,3'-N-bis(benzyloxycarbonyl)-6-O-methyl-N-demethylerythromycin A 9-O-[(2-chlorobenzyl)oxime] reported previously.[1] However, the deprotection was incomplete and only resulted in intractable mixtures accompanied by the starting material. Thereupon, we undertook to remove those protective groups via 2 steps. At first, reaction of the tribenzyl derivative (3) with ammonium formate (20 equiv.) and 10 % Pd-C (1/10 equal amount) in DMF at 30℃ for 3 h afforded 2'-O-benzyl-6-O-methylerythromycin A 9-O-(benzyloxime) (4).[8] Compound(4) was subsequently treated with a mixture of ammonium formate (2 equiv.), formic acid (20 equiv.) and 10% Pd-C (1/10 equal amount) in methanol at 50℃ to give the desired product, 6-O-methylerythromycin A 9-oxime (5),[9] in 66 % yield from 3. Finally the oxime (5) can be easily converted into clarithromycin, mp 223-225℃ [lit.,[10] 222-225℃], by deoximation using sodium hydrogen sulfite in gently refluxing ethanol (80%).

As compared with our previous method, this synthetic pathway has the following advantages: 1) protection of the oxime and desosamine moieties is accomplished by use of benzyl bromide and sodium hydride in one pot, 2) removal of three benzyl groups could be carried out successively by the use of CTH method, 3) regeneration of dimethylamino group is unnecessary and 4) high selectivity of methylation at C-6 hydroxyl group is sufficiently maintained. As a result clarithromycin was obtained in 53 % overall yield from 1.

REFERENCES AND NOTES

1. Part X. Y. Watanabe, M. Kashimura, T. Asaka, T. Adachi, and S. Morimoto. Heterocycles, submitted for publication.
2. Y. Watanabe, T. Adachi, T. Asaka, M. Kashimura, and S. Morimoto, Heterocycles, 1990, 31, 2121.
3. J. R. Maloney, R. E. Lyle, J. Saavedra, and G. G. Lyle, Synthesis, 1978, 212.
4. In the initial plan for removal of the benzyl group of the quaternary ammonium salt, we examined the possibility of the direct access to recover original erythromycin A by hydrogenation of 3'-[benzyl(dimethyl)ammonio]-3'-de(dimethylamino)erythromycin A bromide using CTH method. The above quaternary ammonium erythromycin A was treated with ammonium formate (10 equiv.) in DMF

in the presence of 10 % Pd-C upon heating for 3 h to afford erythromycin A in a good yield (86 %).

5. Usually oxime compounds are present in two isomers (e.g. E- and Z-isomer). Oximation of erythromycin derivative provided predominantly the E-isomer and the minor Z-isomer is very unstable and easily convertible to the E-isomer. Our following operation was conducted by the stable E-isomer.
6. Compound 2: colorless crystals, mp 136-138℃ (crystallization from $CHCl_3$-n-hexane); ^{1}H-nmr ($CDCl_3$)δ : 2.98 (3H, s, NCH_3), 3.24 (3H, s, NCH_3), 3.36 (3H, s, 3"-OCH_3), 4.57 & 5.37 (3H, ABq,J = 12 Hz, 2'-OCH_2Ph), 5.00 & 5.18 (2H, ABq, J = 12 Hz, NCH_2Ph), 5.06 & 5.07 (2H, ABq, J = 12 Hz, =$NOCH_2Ph$) 7.29-7.41 (15H, m, aromatics); ^{13}C-nmr ($CDCl_3$)δ : 44.9 & 49.6 [$N(CH_3)_2$], 49.7 (3"-OCH_3), 68.6 ($N\underline{C}H_2Ph$), 75.6 (2'-$\underline{C}H_2Ph$), 171.5 (C-9), 175.3 (C-1); ms (FD) m/z 1019 (ammonium cation).
7. Compound 3: colorless foam, ^{1}H-nmr ($CDCl_3$)δ : 2.94 (3H, s, NCH_3), 3.25 (3H, s, NCH_3), 3.04 (3H, s, 6-OCH_3), 3.38 (3H, s, 3"-OCH_3), 4.60 & 5.40 (2H, ABq, J = 12 Hz, 2'-OCH_2Ph), 5.04 & 5.06 (2H, ABq, J = 12 Hz, =$NOCH_2Ph$), 7.20-7.75 (15 H, m, aromatics); ^{13}C-nmr ($CDCl_3$)δ : 47.3 & 49.6 [$N(CH_3)_2$], 49.6 (3"-OCH_3), 50.8 (6-OCH_3), 68.5 ($N\underline{C}H_2Ph$), 75.4 (2'-$O\underline{C}H_2Ph$), 75.9 (=$NO\underline{C}H_2Ph$), 7.20-7.55 (15H, m, aromatics); ms(FAB) m/z 1033 (ammonium cation).
8. Compound 4: colorless foam, ^{1}H-nmr ($CDCl_3$)δ : 2.26 [6H, s, $N(CH_3)_2$], 3.04 (3H, s, 6-OCH_3), 3.33 (3H, s, 3"-OCH_3), 4.76 & 4.98 (2H, ABq, J = 12 Hz, 2'-OCH_2Ph), 5.04 & 5.06 (2H, ABq , J = 12 Hz, =$NOCH_2Ph$), 7.23-7.48 (10H, m, aromatics); ^{13}C-nmr ($CDCl_3$)δ : 41.2 [$N(CH_3)_2$], 49.5 (3"-OCH_3), 50.8 (6-OCH_3), 73.7 (2'-$O\underline{C}H_2Ph$), 75.8 (=$NO\underline{C}H_2Ph$), 170.2 (C-9), 175.8 (C-1); ms (FAB) m/z 943 (MH^+).
9. Compound 5: colorless crystals, mp 168-170℃ (crystallization from EtOH-petroleum ether) [lit.,[2] mp 169-171℃].
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