CHEMICAL MODIFICATION OF ERYTHROMYCINS. X. REMOVAL OF BENZYLOXYCARBONYL AND 2-CHLOROBENZYL GROUPS OF ERYTHROMYCIN DERIVATIVES BY USE OF CATALYTIC TRANSFER HYDROGENATION[1]

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Abstract--- The benzyloxycarbonyl and the 2-chlorobenzyl groups of ethythromycin derivatives were easily removed by catalytic transfer hydrogenation (CTH). Their deprotection reaction was dependent on both the hydrogen donor and the solvent for use. Application of CTH to removal of the protective groups is discussed.

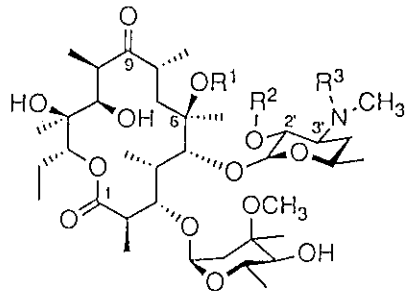
Clarithromycin (6-O-methylerythromycin A), a new semisynthetic macrolide antibiotic, is more stable to acid and exhibits greater efficiency in rodant models than erythromycin.[2,3]

In preceding paper, we reported the synthesis of clarithromycin using 2'-O,3'-N-bis(benzyloxycarbonyl)-N-demethylerythromycin A (1) and its 9-O-[(2-chlorobenzyl)oxime] (2) as the starting materials, preventing formation of a quaternary ammonium salt derived from dimethylamino group and methyl iodide.[4]

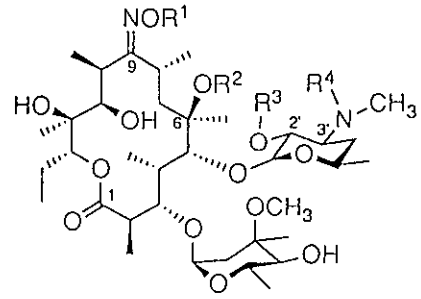
To remove the protecting groups after methylation, the corresponding 6-O-methylated derivatives (3) and (4) were subjected to hydrogenation under a hydrogen atmosphere in the presence of Pd-C as the catalyst.

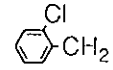
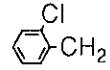
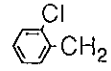
In this paper , we describe the removal of the benzyl and benzyloxycarbonyl (Cbz) groups of erythromycin derivatives by catalytic transfer hydrogenation (CTH) using various kinds of hydrogen donors and solvents in the presence of Pd-C.

At first we investigated to find an optimal condition for elimination of the Cbz group in 3. Compound (3) was treated with a hydrogen donor in methanol at



	R^1	R^2	R^3
Erythromycin	H	H	CH_3
Clarithromycin	CH_3	H	CH_3
1	H	Cbz	Cbz
3	CH_3	Cbz	Cbz
5	CH_3	H	Cbz
6	CH_3	H	H



	R^1	R^2	R^3	R^4
2		H	Cbz	Cbz
4		CH_3	Cbz	Cbz
7		CH_3	H	H
8	H	CH_3	H	H

Cbz = CO_2CH_2 

reflux using 10% Pd-C (1/20 equal amount based on the starting material). As shown in Table 1, the Cbz group in the 2'-position was easily eliminated, but the carbamate type Cbz group in the 3'-position was more resistant to release when used hydrogen donor such as formic acid, 1,4-cyclohexadiene or cyclohexene. Thus, treatment of 3 with formic acid (20 equiv.) and 10% Pd-C in methanol at reflux for 15 min gave the completely deprotected product (6) in 40% yield although the 3'-N-Cbz compound (5) was still remained in 60%. The deprotection could be accomplished by using ammomium formate (4 equiv.) and 10% Pd-C in refluxing methanol for 5 min to afford the desired compound (6) in 95% yield. By use of *triethylammonium formate, elimination of 3'-N-Cbz group was, however, incomplete.* This reaction was also done using hydrazine hydrate. In this case a much longer reaction time was required for the complete deprotection as compared to ammonium formate. Within a series, ammonium formate was the most suitable hydrogen donor for deprotection of Cbz groups.

In connection with the hydrogen donor, we examined an effect of the solvent on elimination of the protective groups of 3 using ammonium formate. The results given in Table 2 indicated that the rates of the deprotection were dependent clearly on the solvent for use. Alcoholic solvents in general were useful for hydrogenation and among them methanol was proved to be the most suitable one. Acetonitrile was also available, but the solvents such as N,N-dimethylformamide, tetrahydrofuran, ethyl acetate and chloroform were inadequate to complete the deprotection.

Finally, a combination of ammonium formate and methanol gave the best result for elimination of both Cbz groups in the 2'-and 3'-positions. Therefore, we applied this procedure to compound (4) having the 2-chlorobenzyl group in the 9-oxime moiety.

As we would expect, both Cbz groups of 4 were easily removed. However, despite under reflux for 2 h in methanol O-(2-chlorobenzyl)oxime (7) was still remained more amount than the desired product (8) (7:8 = 6:4 by tlc analysis) (Table 3). Elimination of the benzyl group was achieved when employed a combination of ammonium formate and formic acid as the hydrogen donor. Thus, 4 was treated with a *mixture of ammonium formate and formic acid (8 and 16 equiv., respectively)* and 10% Pd-C in methanol at reflux for 4 h to afford compound (8) isolating as

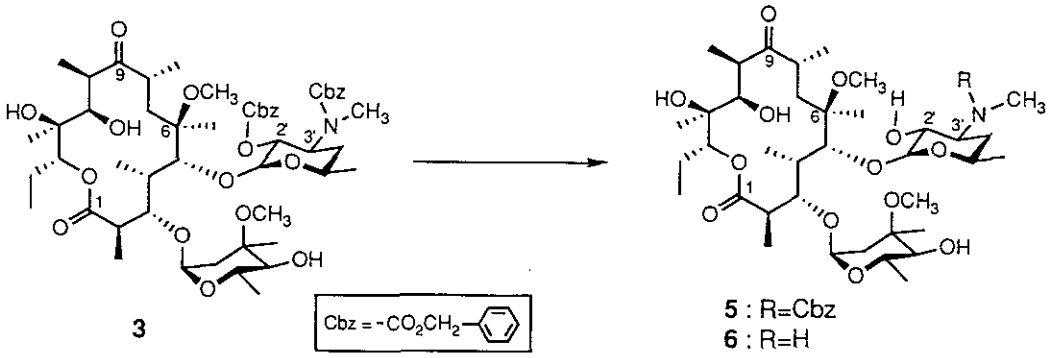


Table 1. Removal of benzyloxycarbonyl group of **3** using various hydrogen donors[1]

Hydrogen donor (equiv.)		Time (min)	Isolated yield (%)	
			5	**6**
HCOOH	(20)	15	60	40[2]
$HCOONH_4$	(4)	5	--	96
TEAF[3]	(4)	15	50	50[2]
	(5)	300	33	63
	(5)	300	31	66
$NH_2NH_2 \cdot H_2O$	(5)	45	--	95

1) 10%Pd-C / Substrate = 1 / 20 (w / w), MeOH, reflux.
2) Checked by tlc.
3) TEAF = Triethylammonium formate.

Table 2. Removal of benzyloxycarbonyl groups of **3** using various solvents[1]

Solvent	Time (min)	Isolated yield (%)		
		3	**5**	**6**
MeOH	5	--	--	96
EtOH	5	20	29	44
EtOH	20	--	--	83
2-Propanol	20	--	10	76
MeCN	600	--	10	83
DMF[2]	600	62	31	3
THF	600	33	36	21
AcOEt	600	97	--	--
$CHCl_3$	600	100	--	--

1) 10%Pd-C / Substrate = 1 / 20 (w / w), $HCOONH_4$ (4 equiv.), reflux.
2) At 100°C

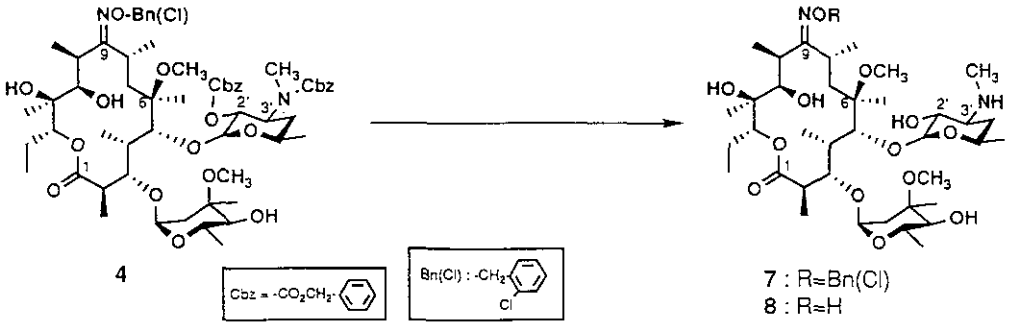


Table 3. Removal of benzyloxycarbonyl and benzyl groups of 4

Hydrogen donor (eq)	Solvent	Reaction conditions Temp. (°C)	Time (h)	Isolated yield (%) 7	8
$HCOONH_4$ (10)	MeOH	reflux	2	60	40 [1]
$HCOONH_4$ (8) / HCOOH (16)	MeOH	reflux	4	--	84
HCOONa (1.2) / HCOOH (16)	MeOH	room temperature	5	--	75
$HCOONH_4$ (2) / HCOOH (16)	DMF	45 [2]	1	--	82
$HCOONH_4$ (1.5) / HCOOH (16)	DMF / H_2O	room temperature	6	--	78

1) Checked by tlc.
2) The stirring was allowed to continue for 3 h at room temperature.

crystals in 84 % yield. It was observed that by replacing ammonium formate with sodium formate, deprotection was accomplished to afford 8 in 75% yield. Use of N,N-dimethylformamide was smooth for complete deprotection at a little higher reaction temperature than the room temperature. However, aqueous N,N-dimethylformamide required for a longer time allowing the removal of the both protecting groups.

In place of catalytic hydrogenation this procedure could be easily applied for the production of clarithromycin.

EXPERIMENTAL

The melting points were determined on a Yanagimoto micro-melting points apparatus and are uncorrected. Ir spectra were measured on a Jasco DS-701 G Ir spectrophotometer. ^1H Nmr and ^{13}C nmr spectra were recorded on Varian XL-200 and Jeol JNM-GX 400 spectrometers. Mass spectra were recorded on a Jeol JMS-SX102

mass spectrometer. Thin-layer chromatography (tlc) was performed on Merck silica gel $60F_{254}$, eluting a mixture of $CHCl_3$, MeOH and NH_4OH (5: 1: 0.01). Column chromatography was performed on Wakogel C-200, eluting a mixture of $CHCl_3$ and MeOH (10: 1).

2'-O,3'-N-Bis(benzyloxycarbonyl)-6-O-methyl-N-demethylerythromycin A (3) --- It was prepared according to the reported procedure.[4]

2'-O,3'-N-Bis(benzyloxycarbonyl)-6-O-methyl-N-demethylerythromycin A 9-[O-(2-chlorobenzyl)oxime] (4)--- To a solution of 2'-O,3'-N-bis(benzyloxycarbonyl)-N-demethylerythromycin A 9-oxime[5] (13 g, 13 mmol) in DMF (60 ml), 2-chlorobenzyl chloride (2.30 g, 14 mmol) and 85 % NaOH powder (0.941 g, 14 mmol) were added under ice-cooling, and the mixture was stirred for 2 h. After reaction the mixture was poured into water (400 ml) and the precipitate was collected by filtration. The solid was triturated with successive, water and 10 % aqueous EtOH, and filtered. Recrystallization from a mixture of EtOAc and n-hexane gave 2'-O,3'-N-bis(benzyloxycarbonyl)-N-demethylerythromycin A 9-[O-(2-chlorobenzyl)oxime] (2) (14.02 g, 96 %), mp 111-113 ℃ . Ir (KBr): 3500-3200, 1748, 1735, 1700 cm^{-1}; ^1H nmr ($CDCl_3$) δ : 2.80 & 2.84 (3H, NCH_3), 3.00 & 3.37 (3H, 3"-OCH_3), 5.15 (2H, ABq, J = 12 Hz, =$NOCH_2$), 5.00-5.24 (4H, m, 2 X $COOCH_2$), 7.20-7.52 (14H, m, aromatics); ^{13}C nmr ($CDCl_3$) δ : 28.9 (NCH_3), 49.0 & 49.5 (3"-OCH_3), 67.2 & 67.5 ($NCOOCH_2$), 69.4 & 69.7 ($OCOOCH_2$), 172.4 (C-9), 175.2 (C-1); ms(FD) m/z 1127 (M^++1). Anal. Calcd for $C_{58}H_{83}N_2O_{17}Cl$: C, 62.84; H, 7.42; N, 2.48. Found: C, 62.41; H, 7.41; N, 2.45.

To a solution of 2 (13 g, 11.5 mmol) in DMF (50 ml) were added MeI (1.96 g, 13.8 mmol) and 85 % KOH powder (0.827 g, 12.5 mmol) under ice-cooling and the mixture was stirred for 5 h. The reaction mixture was poured into water (400 ml) and the precipitate was collected by filtration, triturated with 10% aqueous EtOH, and filtered. Recrystallization from isopropanol gave compound (4) (10.27 g, 78.1 %), mp 191-193 ℃ . Ir (KBr): 3600-3200, 1752, 1732, 1690 cm^{-1}; ^1H nmr ($CDCl_3$) δ : 2.82 & 2.86 (3H, s, NCH_3), 2.98 (3H, s, 6-OCH_3), 3.01 & 3.40 (3H, s, 3"-OCH_3), 5.00-5.22 (4H, m, 2 X $COOCH_2$), 5.42 & 5.48 (2H, ABq, J = 12 Hz, =$NOCH_2$), 7.18-7.52 (14H, m,aromatics); ^{13}C nmr ($CDCl_3$) δ : 28.9 (NCH_3), 49.0 & 49.5 (3"-OCH_3), 67.2 & 67.5 ($NCOOCH_2$), 69.4 & 69.7 ($OCOOCH_2$), 172.4 (C-9), 175.2 (C-1);

ms(FD) m/z 1141 (M^++1). Anal. Calcd for $C_{60}H_{88}N_2O_{17}Cl$: C, 63.12; H, 7.50; N,2.45. Found: C, 63.31; H, 7.57; N, 2.32.

General Procedure for Removal of Benzyloxycarbonyl Groups of Compound (3) by CTH --- A mixture of 3 (20.0 g, 0.2 mmol), 10 % Pd-C (20 mg) and hydrogen donor (4 equiv.) in methanol (10 ml) was heated under reflux. The progress of the removal of protecting groups was continuously checked by tlc (an aliquot of the reaction mixture was added to saturated aqueous $NaHCO_3$ and extracted with EtOAc and the organic layer was subjected to a tlc plate). After reaction, Pd-C was filtered off and washed with methanol (ca. 10 ml). The filtrate and washing were combined and evaporated. Saturated aqueous $NaHCO_3$ (ca. 20 ml) was added to the residue and the resulting mixture was extracted with EtOAc (2 X 20 ml). The organic layer was washed with saturated brine (20 ml) and dried (Na_2SO_4). The solvent was evaporated in vacuo and the residue was purified by column chromatography to afford compounds (5) and (6).

Compound 5: crystallized from ethanol, mp 221-222℃ . ^1H nmr ($CDCl_3$)δ : 3.04 (3H, s, 6-OCH_3), 5.16 (2H, s, $COOCH_2$), 7.36 (5H, s, aromatics); ^{13}C nmr ($CDCl_3$)δ : 28.4 (NCH_3), 49.4 (3"-OCH_3), 50.6 (6-OCH_3), 67.3 ($COO\underline{C}H_2$), 157.2 ($\underline{C}OOCH_2$), 175.6 (C-1), 270.7 (C-9); ms (FAB) m/z 890 (M + Na).

Compound 6: crystallized from methanol, mp 228℃ [lit.,[6] 220-222℃]. Physicochemical properties of 6 agree with those described in the literature.[6]

The result shown in Table 2 was obtained by the same procedure as described above using a variety of solvent other than methanol.

General Procedure for Removal of Benzyloxycarbonyl and Benzyl Groups of Compound (4) by CTH --- A mixture of 4 (1.1 g, 0.1 mmol), 10 % Pd-C (25 mg) and hydrogen doner in a solvent (10 ml) was stirred under reflux or at room temperature. After working-up in the same manner as described above, the residue was purified by column chromatography to give compounds (7) and (8).

Compound 7: colorless foam, ^1H nmr ($CDCl_3$)δ : 2.44 (3H, s, NCH_3), 3.00 (3H, s, 6-OCH_3), 3.32 (3H, s, 3"-OCH_3), 5.14 & 5.16 (2H, ABq, J= 12 Hz, =$NOCH_2$), 7.19-7.43 (4H, m, aromatics); ^{13}C nmr ($CDCl_3$)δ : 33.0 (NCH_3), 49.4 (3"-OCH_3), 50.8 (6-OCH_3), 72.9 (=$NOCH_2$), 170.9 (C-9), 175.3 (C-1); ms (FAB) m/z 873 (MH^+).

Compound 8: crystallized from ethanol, mp 247-248.5℃ . Ir (KBr): 3600-3200, 1727,

1710 cm^{-1}; ^1H nmr ($CDCl_3$)δ : 2.41 (3H, s, NCH_3), 3.10 (3H, s, 6-OCH_3), 3.33 (3H, s, 3"-OCH_3) 8.1-8.4 (1H, bs, =NOH); ^{13}C nmr ($CDCl_3$)δ : 33.2 (NCH_3), 49.5 (3"-OCH_3), 51.2 (6-OCH_3), 170.8 (C-9), 175.5(C-1); ms (SIMS) m/z 763 (MH^+). Anal. Calcd for $C_{37}H_{66}N_2O_{13}$: C, 59.34; H, 9.15; N, 4.74. Found: C, 59.35; H, 8.87; N, 4.78.

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