Note

CHEMICAL MODIFICATION OF ERYTHROMYCINS

XII. A FACILE SYNTHESIS OF CLARITHROMYCIN (6-*O*-METHYLERYTHROMYCIN A) *VIA* 2'-SILYLETHERS OF ERYTHROMYCIN A DERIVATIVES

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As reported in our previous paper[1], clarithromycin (**1**, 6-*O*-methylerythromycin A) was efficiently synthesized starting from 2'-*O*,3'-*N*-bis(benzyloxycarbonyl)-*N*-demethylerythromycin A *via* its 9-oxime derivative (**2**). In this synthetic route, each intermediate has good crystalline properties and **1** could be obtained in high purity. Nevertheless, a large amount of benzyl chloroformate is difficult to handle at the step in which the benzyloxycarbonyl (Cbz) groups are introduced due to a severe irritating action and a toxicity of benzyl chloroformate. Moreover, the 3'-dimethylamino group needs to be regenerated by *N*-methylation after removal of Cbz groups. With regard to the protection of the 3'-dimethylamino group against methyl iodide, we intended to employ a quaternary ammonium salt of erythromycin A 9-oxime, 2'-*O*-benzyl-3'-[benzyl-(dimethyl)ammonio]-3'-de(dimethylamino)erythromycin A bromide 9-[*O*-(2-chlorobenzyl)oxime] (**3**)[2], as a starting material. Methylation of **3** proceeded selectively at the 6-hydroxyl group, but elimination of all the benzyl groups by hydrogenation was difficult to accomplish at the same time.

To improve the synthetic method for **1**, our attention was focused on the effective protection of the 3'-dimethylamino group by introducing a new protective group at the neighbouring 2'-hydroxyl group. It was found that a silyl group such as the trimethylsilyl (TMS) group is suitable for our purpose, and, furthermore, that selectivity for 6-*O*-methylation was over 90%.

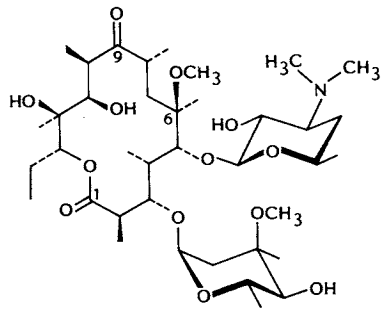
We report here on the effectiveness of the silyl group and the synthesis of clarithromycin using this group.

According to a report on the silylation of erythromycin derivatives[3], we treated erythromycin A 9-[*O*-(2-chlorobenzyl)oxime] (**5**)[4] with chlorotrimethylsilane (TMS-Cl) in *N*,*N*-dimethylformamide in the presence of triethylamine to afford the corresponding 2'-*O*-TMS derivative in 40% yield. Owing to the presence of five hydroxyl groups, the selectivity of silylation was low, and the bis-TMS and tris-TMS derivatives were formed. By further research, we found the optimal reaction conditions for obtaining the 2',4''-*O*-bis-TMS derivative selectively. Thus, when compound **5** was allowed to react with a mixture of TMS-Cl and 1-(trimethylsilyl)-imidazole (TMS-Im) (each 2 equiv) in ethyl acetate at room temperature, 2',4''-*O*-bis(trimethylsilyl)-erythromycin A 9-[*O*-(2-chlorobenzyl)oxime] (**6**) was obtained in 96% yield. Compound **6** was also obtained in high yield by treatment of **5** with 1,1,1,3,3,3-hexamethyldisilazane (HMDS) in methylene chloride in the presence of pyridine hydrochloride or ammonium chloride.

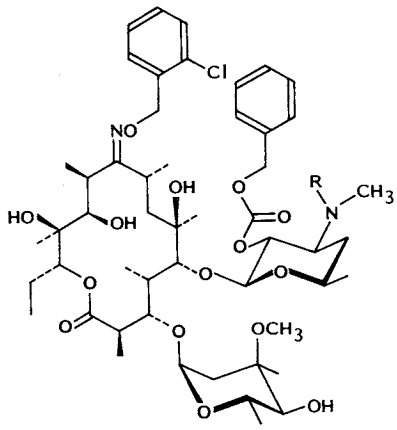
We compared the effectiveness of the TMS group as the protecting group with that of the Cbz group against quaternarization by methyl iodide employing 2'-*O*-benzyloxycarbonylerythromycin A 9-[*O*-(2-chlorobenzyl)oxime] (**4**)[2] and compound **6** (Table 1). Each compound was allowed to react with methyl iodide in a mixture of dimethylsulfoxide (DMSO) and tetrahydrofuran (THF) (1 : 1) at room temperature and the reaction was monitored by HPLC. After 30 minutes, **4** gave 22% of the corresponding quaternary ammonium salt, but **6** gave only 7%.

Methylation of **6** was carried out using methyl iodide (1.3 equiv) and potassium hydroxide (1.1 equiv) in a mixture of DMSO - THF (1 : 1) to afford the 6-*O*-methyl derivative (**7**) in 83% yeild. HPLC analysis showed 7% of unreacted **6**, 85% of **7** and 5% of the 6,11-di-*O*-methyl compound. The selectivity of 6-*O*-methylation was thus 94%.

Elimination of the 2-chlorobenzyl and silyl groups was attained at the same time by catalytic transfer hydrogenation using 10% palladium on carbon (0.16% w/w), formic acid and ammonium formate (each 1.8 equiv) in methanol to afford 6-*O*-methylerythromycin A 9-oxime (**8**)[1]. Deoximation

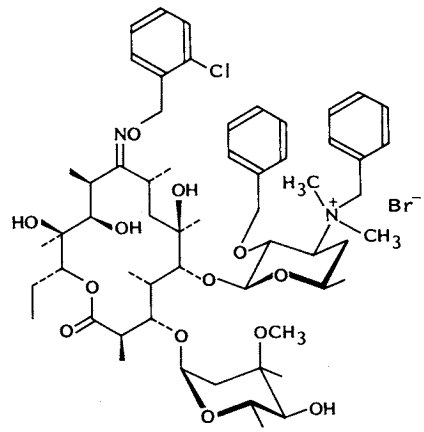


Clarithromycin (1)



2 R=$COOCH_2$—(benzene)

4 R=CH_3



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of **8** with sodium bisulfite was carried out in gently refluxing ethanol to give **1** (57% from **7**).

By this synthetic pathway we could also prepare clarithromycin in 48% yield from erythromycin A 9-oxime without purification of each intermediate except for 6-*O*-methylerythromycin 9-[*O*-(2-chlorobenzyl)oxime].

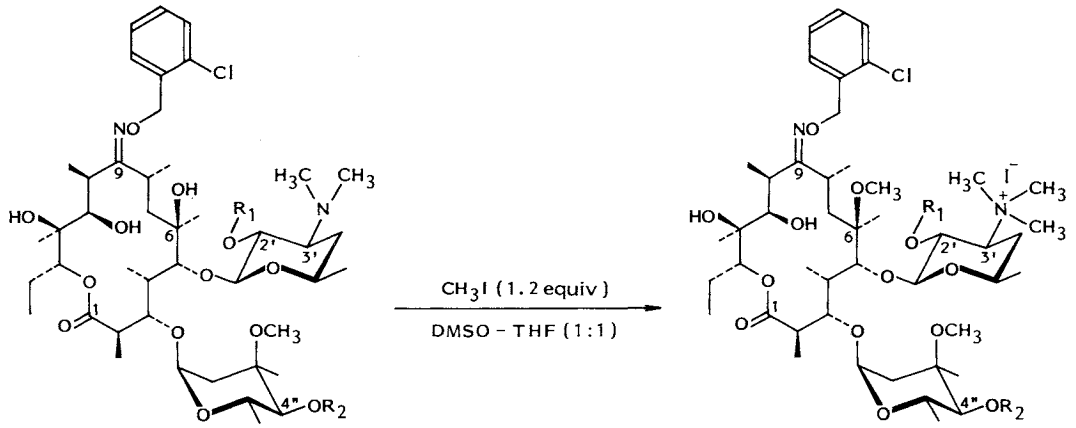
Experimental

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. NMR spectra were recorded on a JEOL JNM-GX400 spectrometer with tetramethylsilane as an internal standard. Mass spectra were measured with a JEOL JMS-SX 102 mass spectrometer. HPLC was carried out on a 3.9×150 mm column of Waters μ BONDA-SPHERE 5μ C18-100A with MeOH-H_2O=85:15~98:2 (containing 0.04% ethanolamine) at a flow rate of 1 ml/minute at 40°C. The reaction was monitored by UV absorption at 220 nm.

Erythromycin A 9-[*O*-(2-Chlorobenzyl)oxime] (**5**)

To a solution of erythromycin A 9-oxime (90 g, 0.12 mol) in DMF (500 ml) were added 2-chlorobenzyl chloride (23.6 g, 0.144 mol) and 85% KOH powder (9.7 g, 0.144 mol), and the mixture was stirred with ice-cooling for 30 minutes. The resulting mixture was extracted with ethyl acetate and the organic layer was washed with water and saturated brine and dried ($MgSO_4$). The solvent was evaporated *in vacuo* and the residue was crystallized from *n*-hexane to afford 98 g (93%) of **5**: MP 114~117°C; ^{1}H NMR ($CDCl_3$) δ 2.29 [6H, s, 3′-H$(CH_3)_2$], 3.31 (3H, s, 3″-OCH_3), 5.17 (2H, =$NOCH_2$); ^{13}C NMR ($CDCl_3$) δ 40.3 [3′-N$(CH_3)_2$], 49.5 (3″-OCH_3), 73.1 (=$NOCH_2$), 172.6 (C-9), 175.3 (C-1).

Table 1. Formation of the quaternary ammonium salt of erythromycin A derivatives with CH_3I[a].



Compound No.	R_1	R_2	Formation of quaternary amine (%)[b]			
			0	10	30	60 (minutes)[c]
4	Cbz	H	0	11	22	31
6	TMS	TMS	0	2	7	12

[a] Cbz; benzyloxycarbonyl, TMS; trimethylsilyl.
[b] Peak area (%) by HPLC.
[c] Reaction time at room temperature.

2′,4″-*O*-Bis(trimethylsilyl)erythromycin A 9-[*O*-(2-Chlorobenzyl)oxime] (**6**)

(Method A) A mixture of chlorotrimethylsilane (2.53 ml, 20 mmol) and 1-trimethylsilylimidazole (2.8 g, 20 mmol) in EtOAc (10 ml) was added to a solution of **5** (8.7 g, 10 mmol) in EtOAc (80 ml) at room temperature. The resulting mixture was stirred for an hour, and then diluted with *n*-hexane. The *n*-hexane layer was washed with water and saturated brine and dried ($MgSO_4$). The solvent was evaporated *in vacuo* to give 9.78 g (96%) of **6** as a glassy solid which was crystallized from heptane: MP 148~149°C; ^1H NMR ($CDCl_3$) δ 0.1 [9H, s, 2′-OSi$(CH_3)_3$], 0.15 [9H, s, 4″-OSi$(CH_3)_3$], 2.23 [6H, s, 3′-N$(CH_3)_2$], 3.30 (3H, s, 3″-OCH_3); ^{13}C NMR ($CDCl_3$) δ 0.9 [4″-OSi$(CH_3)_3$], 1.0 [2′-OSi$(CH_3)_3$], 41.0 [3″-N$(CH_3)_2$], 49.7 (3″-OCH_3), 172.1 (C-9), 175.9 (C-1); FAB-MS *m/z* 1,016 (M^+).

(Method B) A mixture of **5** (15.27 g, 17.5 mmol), HMDS (7.8 ml, 37.4 mmol) and pyridine hydrochloride (2.6 g, 22.5 mmol) in DMF (150 ml) was stirred for 3 hours at room temperature. The reaction mixture was poured into water and extracted with EtOAc. The organic layer was washed with water and saturated brine and dried ($MgSO_4$). The solvent was epavorated *in vacuo* to afford 14.5 g (81%) of **6**.

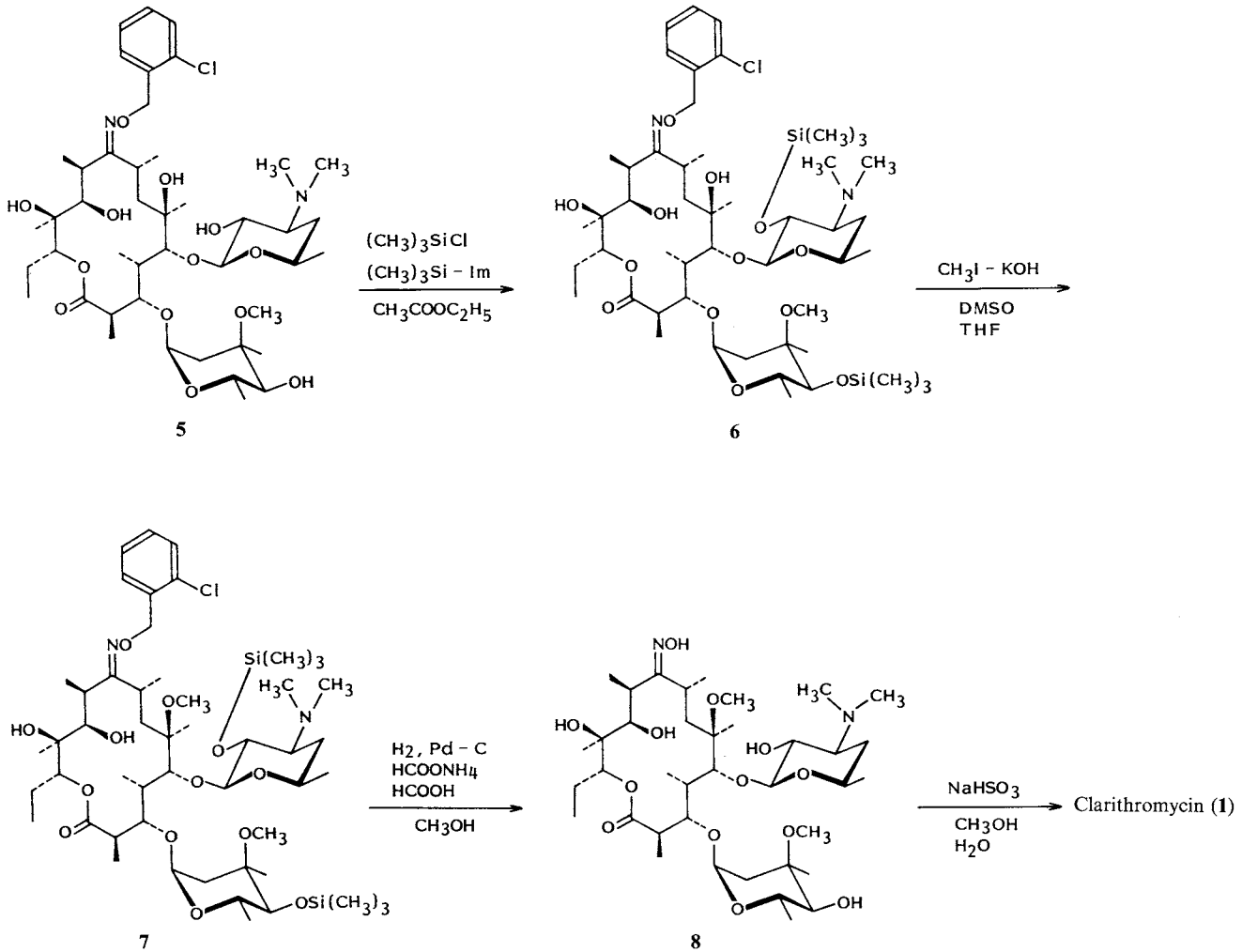
2′,4″-*O*-Bis(trimethylsilyl)-6-*O*-methylerythromycin A 9-[*O*-(2-Chlorobenzyl)oxime] (**7**)

To a solution of **6** (5.09 g, 5 mmol) in 100 ml of a mixture of DMSO and THF (1:1) were added methyl iodide (0.41 ml, 6.5 mmol) and then 85% KOH powder (360 mg, 5.5 mmol), and the resulting mixture was stirred with ice-cooling for 1.5 hours. Fifty percent aqueous dimethylamine solution (2 ml) was added to the mixture, and stirring was continued for a further 30 minutes. The resulting mixture was diluted with *n*-hexane, and the organic layer was washed with water and saturated brine. The solvent was evaporated *in vacuo* to give 4.3 g (83%) of **7** as a colorless foam: ^1H NMR ($CDCl_3$) δ 0.1 [9H, s, 2′-OSi$(CH_3)_3$], 0.15 [9H, s, 4″-OSi$(CH_3)_3$], 2.22 [6H, s, 3′-N$(CH_3)_2$], 3.06 (3H, s, 6-OCH_3), 3.32 (3H, s, 3″-OCH_3); ^{13}C NMR ($CDCl_3$) δ 0.9 [4″-OSi$(CH_3)_3$], 1.1 [2′-OSi$(CH_3)_3$], 40.4 [3′-N$(CH_3)_2$], 49.5 (3″-OCH_3), 50.8 (6-OCH_3), 171.1 (C-9), 175.6 (C-1); EI-MS *m/z* 1,030 (M^+).

Clarithromycin (**1**)

Ten percent palladium on carbon (450 mg), formic acid (1.8 ml, 4.8 mmol) and ammonium formate (300 mg, 4.8 mmol) were added to a solution of **7** (2.8 g, 2.7 mmol) in methanol (30 ml), and the mixture was stirred at 60°C for 2 hours. The catalyst

Scheme 1. Preparation of clarithromycin *via* 2',4''-*O*-bis(trimethylsilyl)erythromycin A 9-oxime derivatives.



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$(CH_3)_3Si$-Im; 1-(trimethylsilyl)imidazole.

was filtered off, and the filtrate, after addition of water (200 ml), was made basic with 2 N NaOH. The precipitate was collected by filtration and washed with water to afford 1.7 g of **8**.

Compound **8** (1.7 g, 2.2 mmol), sodium bisulfite (0.93 g, 9 mmol) and 99% formic acid (0.2 ml, 5.3 mmol) in a mixture of ethanol (8 ml) and water (8 ml) was heated under gentle reflux for 1.5 hours and then diluted with water (16 ml). After adjusting the pH of the solution to more than 10 with saturated aqueous $NaHCO_3$ solution, there was obtained 1.17 g (57% from **7**) of **1** which was crystallized from ethanol: MP 223~225°C (ref 5, MP 222~225°C).

Preparation of Clarithromycin (**1**) by an Alternate Procedure

To a mixture of erythromycin 9-oxime (50 g, 66.8 mmol) and 2-chlorobenzyl chloride (12.36 g, 76.8 mmol) in DMF (150 ml) was added 65% sodium hydride dispersion (3.07 g, 76.8 mmol) with good stirring at 0~5°C. After 30 minutes HMDS (28.17 ml, 133.6 mmol) and ammonium chloride (5.36 g, 100.2 mmol) were added to the mixture. The resulting mixture was stirred for 2 hours at 35~40°C, cooled to room temperature and diluted with heptane (350 ml). The organic layer was washed with water and dried ($MgSO_4$). The solvent was evaporated *in vacuo* to give 72.35 g of **6** as a foam.

To a solution of **6** (72.35 g, 70.8 mmol) in DMSO - THF (150 ml : 150 ml) were added methyl iodide (5.4 ml, 92 mmol) and then 85% KOH powder (5.73 g, 92 mmol) at 0~5°C, and the mixture was stirred for 30 minutes. Fifty percent aqueous dimethylamine solution (25 ml) was added to the mixture to quench the reaction, and the resulting mixture was poured into a mixture of heptane (400 ml) and water (200 ml). The organic layer was washed with water and dried ($MgSO_4$). The solvent was evaporated *in vacuo* to afford 68.2 g (93%) of **7** as a foam.

A mixture of **7** (68.2 g, 65.9 mmol) and formic acid (10 ml, 263.6 mmol) in methanol (200 ml) was stirred for 3 hours at room temperature. To the reaction mixture was added 1 N NaOH (800 ml) with stirring. The resulting precipitate was collected by filtration and crystallized from methanol to afford 38.8 g (66%) of 6-*O*-methylerythromycin A 9-[*O*-(2-chlorobenzyl)oxime]: MP 141~143°C; ^{13}C NMR ($CDCl_3$) δ 40.3 [3'-$N(CH_3)_2$], 49.5 (3''-OCH_3), 50.8 (6-OCH_3), 72.7 (=$NOCH_2$), 171.1 (C-9), 175.6 (C-1).

A mixture of 6-*O*-methylerythromycin A 9-[*O*-(2-chlorobenzyl)oxime] (19.38 g, 21.8 mmol), acetic acid (6.25 ml, 109 mmol) and 10% palladium on carbon (1.94 g) in ethanol was stirred vigorously under hydrogen at atmospheric pressure and room temperature for 22 hours. The catalyst was filtered off, and the filtrate was added to a mixture of sodium bisulfite (36.36 g, 350 mmol) and water (100 ml). The mixture was heated under gentle reflux for 4 hours, poured into water (200 ml) and was made basic with 2 N NaOH (100 ml). The resulting precipitate was collected by filtration, washed with water and crystallized from ethanol to afforded 11.86 g (73%) of **1** as colorless needles.

Formation of the Quaternary Ammonium Salt with Methyl Iodide

Methyl iodide solution was prepared by addition of methyl iodide (0.51 g) to a mixture of DMSO - THF (1 : 1) (3 ml). Triethylamine solution was also prepared by mixing triethylamine (5.4 g) and methanol (3 ml). To a stirred solution of substrate **4** or **6** (0.1 mmol) in a mixture of DMSO - THF (1 : 1) (1 ml) was added the methyl iodide solution (0.1 ml, 1.2 equiv) at room temperature. After 0, 10, 30 and 60 minutes, 0.1-ml portions of the reaction mixture were withdrawn and poured into 0.1-ml portions of the triethylamine solution. This solution was analyzed by HPLC.

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