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A New Convenient Transformation of Erythromycin A into Clarithromycin

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Abstract—Erythromycin A was transformed into clarithromycin by the sequence of reactions: selective thexyldimethylsilylation of the 9-oxime, trimethylsilylation of the 2′,4″-hydroxy groups, methylation of the resulting 2′,4″-[*O*-bis(trimethylsilyl)]-9-[*O*-(dimethylthexylsilyl)oxime] and acidic regeneration of the protected functionalities.

Introduction

Erythromycin A (**1**) and its derivative clarithromycin (**2**) (Fig. 1) are two 14-membered ring macrolides of an important family of oral antibiotics possessing a spectrum of activity covering most relevant bacteria species responsible for cutaneous, genital and respiratory infections.[1] Unfortunately, erythromycin is quickly degraded under the acidic conditions found in the stomach to inactive by-products resulting from the cleavage of the acid-labile cladinose moiety at C-3 and/or from the interaction of the hydroxyl groups at C-6 and at C-12 with the carbonyl at C-9.[2] Clarithromycin (**2**), the 6-*O*-methyl derivative of erythromycin, and other alkyl derivatives have been prepared to overcome one source of its instability to acids.[3–5] In fact, blocking the C-6 hydroxyl prohibits its interaction with the C-9 carbonyl and improves the stability to acids of erythromycin as well as its antibacterial and pharmacokinetic properties.[2,6] Inter alia the selective methylation of the hydroxy group at C-6 of the erythromycin is satisfactorily accomplished[7] starting from erythromycin 9-oxime (**3**) (Fig. 2) and protecting the oxime and the sugar 2′ and 4″ hydroxy groups from the attack of the methylating agent. In fact the methylation of the 11 and 12 hydroxyls is not observed in the presence of a bulky derivative of the oxime **3**, such as the 9-[*O*-(2-chlorobenzyl)oxime] **4** or other recently reported 9-ether oximes.[8] The protected oxime **4**, silylated at the 2′,4″-hydroxy groups, is then selectively methylated at C-6 the hydroxy group using methyl iodide and potassium hydroxide in a mixture of DMSO:THF (1:1, v/v).[9] Other attempts to use different bulky protective groups for the 9-oxime were less satisfactory. In fact benzyloxycarbonyl and trimethylsilyl groups were unstable under the basic conditions necessary for the methylation, while the trityl group required deprotection conditions incompatible with the glycosidic bonds of the molecule.[7,10] The accomplishment of the synthesis required in all cases the deprotection of hydroxyls and the successive deoximation with sodium hydrogensulfite.[8–10]

As a result of our interest in the chemistry of 14-membered macrolides, we report here a different simple transformation of erythromycin A (**1**) into clarithromycin (**2**) starting from erythromycin A oxime (**3**).

Results and Discussion

We have selectively protected the oxime hydroxyl with the bulky and relatively stable dimethylthexylsilyl group and the secondary 2′ and 4″ hydroxyls of the two sugars present in the molecule as trimethylsilyl derivatives, under the reaction conditions reported by Morimoto et al.[9] for erythromycin A 9-[*O*-(2-chlorobenzyl)oxime] (**4**). In this way we hoped to obtain an intermediate suitable for the selective methylation of the hydroxy group at C-6 which could be performed choosing appropriate methylation conditions (solvent and methylating agent) taking advantage of the interesting conclusions reported by Morimoto et al.[7]

In our opinion the dimethylthexylsilyl group possessed the following useful properties: it was a protecting group of the oxime more stable than the trimethylsilyl

Key words: Antibiotics; antibacterials; clarithromycin; erythromycin A; methylation.

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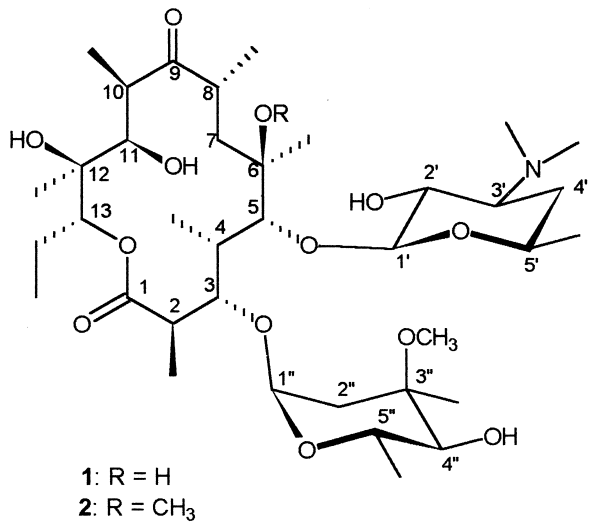

Figure 1.

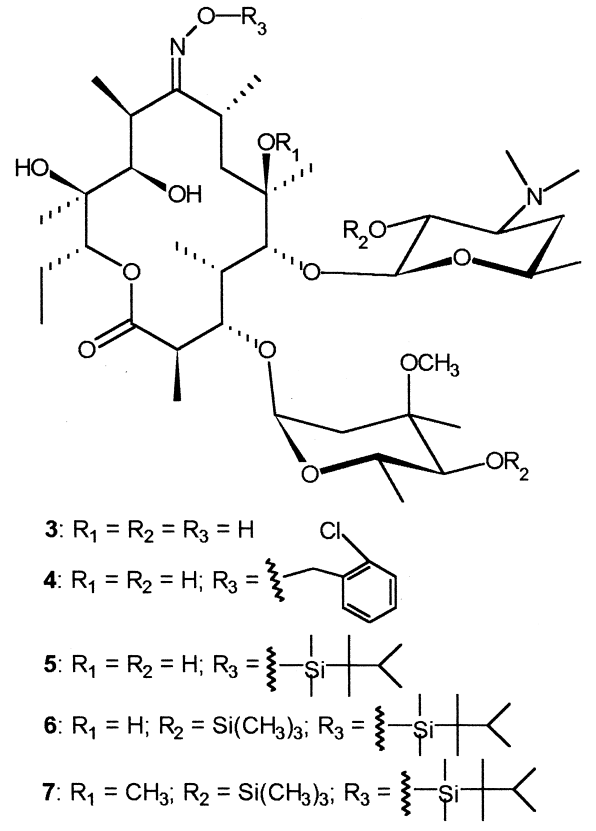

Figure 2.

group and could resist the alkaline conditions; it was sufficiently bulky to protect the 11 and 12 hydroxy groups from the attack of the methylating reagent; it could be removed at the same time as the sugar trimethylsilyl derivatives and, probably, of the oxime group.

With this in mind we treated erythromicin A 9-oxime (**3**) with chlorodimethylthexylsilane and obtained the erythromicin A 9-[*O*-(dimethylthexylsilyl)oxime] (**5**) in nearly quantitative yields. The silylated oxime **5** was then treated with two molar equivalents of chlorotrimethylsilane and of 1-(trimethylsilyl)imidazole to afford the 2′,4″-[*O*-bis(trimethylsilyl)]erythromycin A 9-[*O*-(dimethylthexylsilyl)oxime] (**6**) in high yield. This transformation can be obtained in a 'one pot reaction' monitoring the complete formation of the thexyl derivative **5** (thin-layer chromatography (TLC)) immediately followed by addition of chlorotrimethylsilane and 1-trimethylsilylimidazole to the same reaction mixture.

In the best conditions, the methylation of **6** was carried out in a THF:DMSO solution (1:1; v/v), using an excess of methyl iodide and sodium hydride as reported for other derivatives by Morimoto et al.[9] In this way the 6-*O*-methylated protected oxime **7** was obtained in good regioselectivity (>90%).

A one-pot removal of both the silyl derivatives and the oxime, performed by treatment of **7** with an aqueous solution of ethanol (50%; v/v) containing formic acid and sodium hydrogensulfite, afforded clarithromycin (**2**) in 66% yield from silylated oxime **6**. This cumulative regeneration of the alcoholic and keto functions under mild acid conditions, represents a noteworthy feature of this clarithromycin preparation since it reduces a two steps deprotection to a simple one pot reaction and, in the case of 2-chlorobenzylated oxime, it avoids the use of any catalytic hydrogenation. The present procedure efficiently provides clarithromycin (**2**) in 56% overall yields from erythromycin A oxime (**3**) in a relatively short way and discloses the possibility of using silyl groups for the protection of the 9-oxime of erythromycin A.

Experimental

All chemical materials were purchased from Aldrich Chemical Co. (Milwaukee, WI, USA).

Nuclear magnetic resonance spectra were recorded as $CDCl_3$ solution at 303 K on Bruker AM-500 spectrometer operating at 500.13 MHz for ^1H and 125.76 MHz for ^{13}C. All chemical shifts are reported in ppm relative to $CHCl_3$ fixed at 7.24 ppm for the ^1H spectra and relative to $CDCl_3$ fixed at 77.00 ppm for the ^{13}C spectra. Signal multiplicity was designated according to the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet.

All reactions were monitored by TLC carried out on 0.25 mm E. Merck silica gel plates (60 F_{254}) using 50% sulphuric acid and heat as developing agent.

The progress of all the reactions and compound purity were monitored by TLC.

Usual work up refers to washing the organic layer with water, drying over anhydrous Na_2SO_4 and evaporating the solvent under reduced pressure.

Synthesis of erythromycin A 9-[*O*-(dimethylthexylsilyl)oxime] (5). Erythromycin oxime **3** (10.0 g; 13.3 mmol) dissolved in *N*,*N*-dimethylformamide (50 mL) containing triethylamine (13.1 mL; 94.0 mmol) was treated with

chlorodimethylthexylsilane (7.9 mL; 40 mmol) for 1 h at room temperature. At this time, the mixture was poured in ice cold water and worked up to afford the thexylsilyl derivative **5** (10.7 g; Y 90%): mp 114–116°C (needles from moist acetone); $[\alpha]_D^{20}$ −49.8 ($CHCl_3$; *c* 1); ^1H NMR ($CDCl_3$; 500 MHz): δ 5.10 (1H, dd, *J* = 11.5, 2.5 Hz, H-13), 4.91 (1H, dd, *J* = 5.0, < 1 Hz, H-1″), 4.41 (1H, d, *J* = 7.5 Hz, H-1′), 4.02 (1H, dd, *J* = 9.5, 1.5 Hz, H-3), 4.00 (1H, dq, *J* = 9.5, 7.5 Hz, H-5″), 3.82 (1H, ddq, *J* = 8.5, 7.0, 2.0 Hz, H-8), 3.68 (1H, d, *J* < 1 Hz, H-11), 3.57 (1H, d, *J* = 7.5 Hz, H-5), 3.47 (1H, ddq, *J* = 11.0, 7.0, 2.0 Hz, H-5′), 3.30 (3H, s, 3″-OCH_3), 3.20 (1H, dd, *J* = 10.5, 7.5 Hz, H-2′), 3.00 (1H, d, *J* = 9.5 Hz, H-4″), 2.88 (1H, dq, *J* = 9.5, 7.5 Hz, H-2), 2.67 (1H, dq, *J* = 7.0, < 1 Hz, H-10), 2.43 (1H, ddd, *J* = 12.5, 10.5, 3.0 Hz, H-3′), 2.34 (1H, dd, *J* = 15.0, < 1 Hz, H-2″a), 2.28 (6H, s, N(CH_3)$_2$), 1.98 (1H, ddq, *J* = 7.5, 7.5, 1.5 Hz, H-4), 1.89 (1H, ddq, *J* = 15.0, 7.5, 2.5 Hz, H-14a), 1.66–1.53 (5H, overlapping), 1.46 (3H, s, 6-CH_3), 1.45 (1H, ddq, *J* = 15.0, 11.5, 7.5 Hz, H-14b), 1.28 (3H, d, *J* = 7.5 Hz, 5″-CH_3), 1.22 (3H, s, 3″-C*H*3), 1.21 (3H, d, *J* = 7.0 Hz, 5′-CH_3), 1.16 (3H, d, *J* = 7.5 Hz, 2-CH_3), 1.15 (3H, d, *J* = 7.0 Hz, 10-CH_3), 1.11 (3H, s, 12-CH_3), 1.09 (3H, d, *J* = 7.5 Hz, 4-CH_3), 0.99 (3H, d, *J* = 7.0 Hz, 8-CH_3), 0.88 [6H, s, SiC(CH_3)$_2$ CH(CH_3)$_2$], 0.87 (6H, d, *J* = 4.0 Hz, SiC(CH_3)$_2$ CH (CH_3)$_2$), 0.82 (3H, dd, *J* = 7.5, 7.5 Hz, 15-CH_3), 0.19 and 0.18 ppm (2×3H, 2×s, Si(CH_3)$_2$).

Elemental analysis, calculated for $C_{45}H_{86}N_2O_{13}Si$: C, 60.64; H, 9.73; N, 3.14. Found: C, 60.9; H, 9.6; N, 3.2%.

Synthesis of 2′,4″-[*O*-bis(trimethylsilyl)]erythromycin A 9-[*O*-(dimethylthexylsilyl)oxime] (6). The thexylsilyl derivative **5** (9 g; 10 mmol) dissolved in EtOAc (80 mL) was treated with 1-trimethylsilylimidazole (3.0 mL; 20 mmol) and chlorotrimethylsilane (2.58 mL; 20 mmol) at room temperature for 1 h. At this time, the mixture was poured in ice cold water and worked up to afford the dimethylthexylsilyltrimethylsilyl derivative **6** (9.94 g; Y 95.1%): mp 105–108°C (needles from moist acetone); $[\alpha]_D^{20}$ −49.2 ($CHCl_3$; *c* 1); ^1H NMR ($CDCl_3$; 500 MHz): δ 5.06 (1H, dd, *J* = 11.5, 2.5 Hz, H-13), 4.86 (1H, dd, *J* = 5.0, < 1 Hz, H-1″), 4.36 (1H, d, *J* = 7.5 Hz, H-1′), 4.21 (1H, dq, *J* = 9.5, 6.5 Hz, H-5″), 4.13 (1H, dd, *J* = 9.5, 1.5 Hz, H-3), 3.83 (1H, ddq, *J* = 8.5, 7.5, 2.0 Hz, H-8), 3.68 (1H, d, *J* < 1 Hz, H-11), 3.60 (1H, ddq, *J* = 11.0, 6.5, 2.0 Hz, H-5′), 3.54 (1H, d, *J* = 8.0 Hz, H-5), 3.28 (3H, s, 3″-OCH_3), 3.14 (1H, dd, *J* = 10.5, 7.5 Hz, H-2′), 3.13 (1H, d, *J* = 9.5 Hz, H-4″), 2.82 (1H, dq, *J* = 9.5, 7.0 Hz, H-2), 2.69 (1H, dq, *J* = 7.0, < 1 Hz, H-10), 2.51 (1H, ddd, *J* = 12.5, 10.5, 4.5 Hz, H-3′), 2.33 (1H, dd, *J* = 15.0, < 1 Hz, H-2″a), 2.20 (6H, s, N(CH_3)$_2$), 1.94–1.86 (2H, overlapping, H-4 and H-14a), 1.67–1.42 (6H, overlapping), 1.56 (3H, s, 6-CH_3), 1.42 (3H, s, 3″-CH_3), 1.19 (3H, d, *J* = 6.5 Hz, 5″-CH_3), 1.17–1.14 (9H, overlapping, 2-CH_3, 10-CH_3, 5′-CH_3), 1.13 (3H, s, 12-CH_3), 1.06 (3H, d, *J* = 7.5 Hz, 4-CH_3), 0.99 (3H, d, *J* = 7.5 Hz, 8-CH_3), 0.88 (6H, s, SiC(CH_3)$_2$CH(CH_3)$_2$), 0.87 (6H, d, *J* = 3.5 Hz, SiC(CH_3)$_2$CH(CH_3)$_2$), 0.83 (3H, dd, *J* = 7.5, 7.5 Hz, 15-CH_3), 0.18 and 0.17 [2×3H, 2×s, Si(CH_3)$_2$], 0.12 (3H, s, Si(CH_3)$_3$), 0.09 ppm (3H, s, Si(CH_3)$_3$).

Elemental analysis, calculated for $C_{51}H_{102}N_2O_{13}Si_3$: C, 59.15; H, 9.93; N, 2.70. Found: C, 58.9; H, 9.8; N, 2.5%.

Synthesis of 2′,4″-[*O*-bis(trimethylsilyl)]clarithromycin A 9-[*O*-(dimethylthexylsilyl)oxime] (7). The protected oxime **6** (9.0 g; 8.66 mmol) dissolved in a solution of THF:DMSO (180 mL; 1:1, v/v) was treated with CH_3I (1.51 mL; 24.3 mmol) and stirred for 10 min at 0–5°C. Then NaH (414 mg of a 60% dispersion; 10.35 mmol) was added and the mixture was stirred for 1 h at the same temperature. The mixture was then poured into ice cold water and worked up to afford the 6-*O*-methyl derivative **7** as a crude amorphous solid (8.82 g) containing some unmethylated starting material (5%; TLC separation). The crude product **7** resisted all efforts of crystallization and was used for the next reaction without purification. Its ^1H NMR spectrum ($CDCl_3$; 500 MHz) showed (main compound): δ 5.09 (1H, dd, *J* = 11.0, 2.5 Hz, H-13), 4.87 (1H, dd, *J* = 5.0, < 1 Hz, H-1″), 4.39 (1H, d, *J* = 7.0 Hz, H-1″), 4.20 (1H, dq, *J* = 9.5, 6.5 Hz, H-5″), 3.82 (1H, ddq, *J* = 8.5, 7.0, 2.0 Hz, H-8), 3.77 (1H, dd, *J* = 9.5, 1.5 Hz, H-3), 3.76 (1H, d, *J* < 1 Hz, H-11), 3.62 (1H, ddq, *J* = 11.0, 6.0, 2.0 Hz, H-5′), 3.59 (1H, d, *J* = 7.5 Hz, H-5), 3.29 (3H, s, 3″-OCH_3), 3.14 (1H, d, *J* = 9.5 Hz, H-4″), 3.11 (1H, dd, *J* = 10.0, 7.0 Hz, H-2′), 3.02 (3H, s, 6-OCH_3), 2.81 (1H, dq, *J* = 9.5, 7.0 Hz, H-2), 2.57 (1H, dq, *J* = 7.0, < 1 Hz, H-10), 2.51 (1H, ddd, *J* = 12.5, 10.0, 4.0 Hz, H-3′), 2.33 (1H, dd, *J* = 15.0, < 1 Hz, H-2″a), 2.20 (6H, s, N(CH_3)$_2$), 1.91 (1H, ddq, *J* = 14.0, 7.5, 2.5 Hz, H-14a), 1.81 (1H, ddq, *J* = 7.5, 6.5, 1.5 Hz, H-4), 1.69–1.41 (6H, overlapping), 1.62 (3H, s, 6-CH_3), 1.40 (3H, s, 3″-CH_3), 1.20 (3H, d, *J* = 6.5 Hz, 5″-CH_3), 1.16–1.11 (9H, overlapping, 2-CH_3, 10-CH_3, 5′-CH_3), 1.15 (3H, s, 12-CH_3), 1.02 (3H, d, *J* = 6.5 Hz, 4-CH_3), 0.91 (3H, d, *J* = 7.5 Hz, 8-CH_3), 0.88 (6H, s, SiC(CH_3)$_2$CH(CH_3)$_2$), 0.85 (6H, d, *J* = 4.5 Hz, SiC(CH_3)$_2$ CH(CH_3)$_2$), 0.82 (3H, dd, *J* = 7.5, 7.5 Hz, 15-CH_3), 0.17 and 0.16 (2×3H, 2×s, Si(CH_3)$_2$), 0.13 (3H, s, Si(CH_3)$_3$), 0.07 ppm (3H, s, Si(CH_3)$_3$).

The presence of the possible 6,11-dimethylated homologue and of the 11-methyl isomer could not be excluded by the analysis of the ^1H NMR spectrum of **7**. However performing the methylation using $^{13}CH_3I$ (on 0.5 mmol scale), the ^{13}C NMR analysis of the crude product precluded any appreciable presence of these compounds and indicated that 6-methylated compound **7** was more than 90% pure.

Synthesis of clarithromycin (2). To the crude 9-[*O*-(dimethylthexylsilyl)oxime **7**, (8.82 g), dissolved in ethanol (30 mL) containing formic acid (0.88 mL; 23.2 mmol), was added an aqueous solution of $Na_2S_2O_5$ (3.78 g in 30 mL) and refluxed for 30 min. At this time the mixture was cooled to room temperature, diluted with water and its pH adjusted to 11 with NaOH (2 M). The resulting suspension was extracted with ethyl acetate, worked up and crystallised from ethanol to afford clarithromycin (**2**) (4.32 g; 66.3% yield from compound **6**): mp 221–224°C; $[\alpha]_D^{20}$ −82.6 ($CHCl_3$; *c* 1) (lit.[4] mp 222–225°C; $[\alpha]_D^{20}$ −90.4); and the expected ^1H NMR spectrum.[11,12]

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