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SYNTHESIS AND CRYSTAL STRUCTURE OF 2',4''-*O*-BIS(TRIMETHYLSILYL)ERYTHROMYCIN A 9-*O*-(1-ISOPROPOXYCYCLOHEXYL) OXIME

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Abstract - The ratio of *E*/*Z* of 2'-,4''-*O*-bis(trimethylsilyl)erythromycin A 9-*O*-(1-isopropoxycyclohexyl) oxime were much higher prepared in CH_3CN than those in CH_2Cl_2. And the ratio would increase with elevation of temperature. Compared with 2'-OH, 4''-OH was liable to be silylated in the presence of 1,1,1,3,3,3-hexamethyldisilizane and an NH_4^+. The crystal structure of *E*-title compound was determined by single-crystal X-Ray structure analysis to elucidate the origin of regioselectivity occurring at 6-hydroxyl group in the *O*-methylation of erythromycin A.

INTRODUCTION

Macrolide antibiotics are a preferred drug class for the safe and effective treatment of respiratory tract infection. Among them, clarithromycin (6-*O*-methylerythromycin A) exhibits markedly improved acid stability relative to erythromycin A resulting in better bioavailability and pharmacokinetics, increased gastrointestinal tolerance and superior antibacterial activity. [1]

Since erythromycin A has five hydroxyls at 6-, 11-, 12-, 2'- and 4''-position, it's difficult to methylate the C-6 hydroxyl group selectively. An early route [2] described the synthesis of clarithromycin *via* 2'-*O*,3'-*N*-bis(benzyloxycarbonyl)-*N*-demethylerythromycin A, but 11-*O*-methylated compound was obtained as major product unfortunately. Accordingly it requires tedious purification that causes low yield.

In further study, Watanabe *et al*. [3] noted the conformation of aglycone ring of erythromycin A derivative may influence the selectivity of methylation, and investigated a variety of 2'-*O*,3'-*N*-bis-(benzyloxycarbonyl)-*N*-demethylerythromycin A oxime ether derivatives and finally found that 2'-*O*,3'-*N*-bis(benzyloxycarbonyl)-*N*-demethylerythromycin A 9-[*O*-(2-chlorobenzyl) oxime] reacted with methyl iodide to give the corresponding 6-*O*-methyl derivative selectively. However the 3'-*N*-dimethylamino group needs to be regenerated by *N*-methylation after removal of CBZ groups in the process. As the protection to 3'-*N*-dimethylamino group is necessary to avoid quarternarization in methylation, a new effective bulky group, trimethylsilyl (TMS), was introduced at the neighboring 2'-hydroxyl group. [4] With a large number of different etherification reagents were investigated and evaluated for the selectivity of methylation at 6-OH, an industrial process was established for the production of clarithromycin. [5] By protecting 2'- and 4"-hydroxyl groups with TMS and converting erythromycin A oxime into 1-isopropoxylcyclohexyl ether, the core group methyl group was introduced at the 6-hydroxyl group exclusively. Therefore 2'-,4"-*O*-bis(trimethylsilyl)erythromycin A 9-*O*-(1-isopropoxycyclohexyl) oxime is the key intermediate for manufacturing clarithromycin. Meanwhile it's a precursor for the synthesis of other 6-*O*-substitued erythromycin derivatives.[6] In addition, direct methylation of 2'-*O*,3'-*N*-bis-CBZ- azithromycin gave 12-*O*-methyl derivatives instead of 6- or 11-*O*-methyl derivatives. [7] So studies on regioselectivity of aglycone have attracted significant interest. [8] In this paper we intend to describe the results obtained in our laboratory about the synthesis and crystal structure of 2'-,4"-*O*-bis(trimethylsilyl)erythromycin A 9-*O*-(1-isopropoxycyclohexyl) oxime.

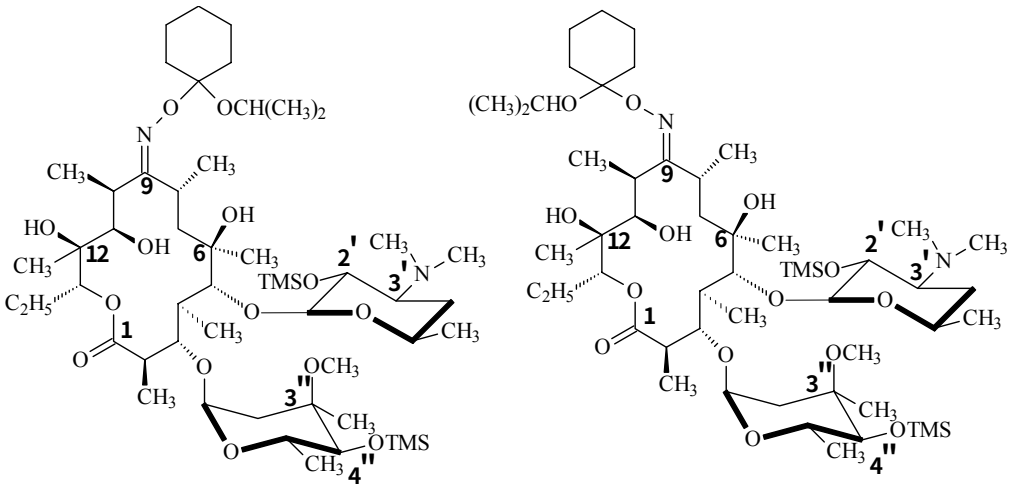

Figure 1 *E*- and *Z*-isomers of the title compound

RESULTS AND DISCUSSION

As reported [4] silylation occurs at the 2'-position selectively in the presence of chlorosilane and basic reagent. Actually we found 4"-position is liable to be silylated in the presence of 1,1,1,3,3,3-hexamethyldisilizane (HMDS) and $HCOONH_4$ or NH_4Cl, indicating different mechanism of silylation. Duran *et al*. [8] postulated an S_N2 mechanism in which chlorosilane attacked the oxygen atom of hydroxyl

groups as Cl left, then a four-member transition structure was located. It's known that HMDS would release $(CH_3)_3Si^+$ in the presence of acid. An S_N1 mechanism would give different results. We thought 3'-$N(CH_3)_2$ maybe played important roles involved in S_N2 and S_N1 mechanism. In S_N2 mechanism 3'-$N(CH_3)_2$ played as a catalyst to help Cl^- of chlorosilane leave. But in S_N1 mechanism $(CH_3)_3Si^+$ probably attached to 2'- or 4"-hydroxyl group, and preferred to 4"-hydroxyl group due to the existence of the spatial resistance of neighboring 3'-$N(CH_3)_2$ of the desosamine moiety ting up the mole acid. We also found 2'-position was susceptible to be further silylated in CH_3CN rather than in CH_2Cl_2.

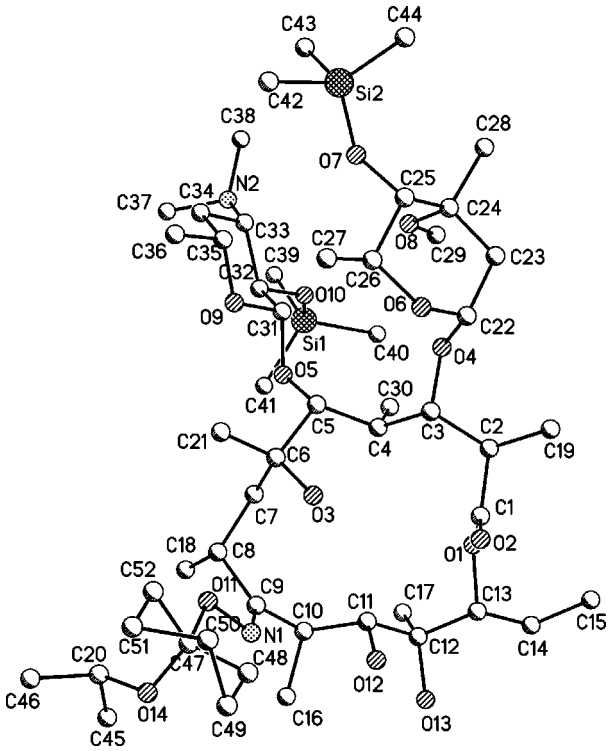

Figure 2 Crystal structure of *E*-title compound

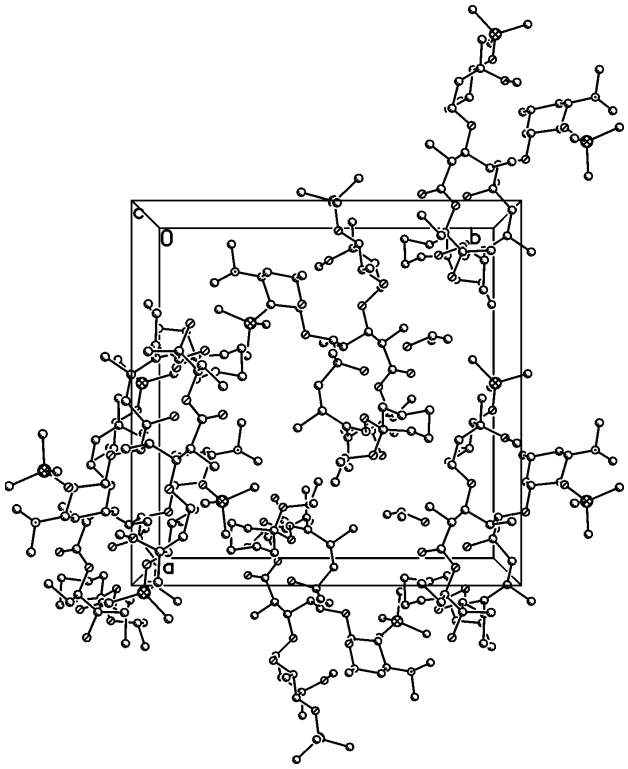

Figure 3 Packing arrangement in the unit cell

Interestingly the solvents also influence the ketalation of erythromycin A oxime. We found *Z*-oxime should have been converted to corresponding *E*-isomer in the presence of acid. But the equilibrium of *E*- and *Z*-isomers in starting materials reversed and isomerization resulted in increase of the ratio of *Z*-isomer in the ketalation products. Reversed isomerization tended to occur at low temperatures and in CH_2Cl_2 in contrast to CH_3CN. See Table 1.

Table 1 The constituents of the title compound under different reaction conditions (*E* / *Z*) [a]

	10 °C	20 °C	30 °C
CH_3CN	63.27/10.98	67.87/9.41	71.97/6.72
CH_2Cl_2	43.42/19.42	53.24/17.28	64.87/8.35

[a] Erythromycin A oxime of starting material contains *E*-isomer 94.77% and *Z*-isomer 1.95%

In order to elucidate the aglycone ring structure-conformation relationships, we have determined the molecular structure of erythromycin A 9-*O*-(1-isopropoxycyclohexyl) oxime (EM-IPCH oxime) by the

X-Ray crystallographic analysis. [9] Now we report the crystal structure of 2'-,4"-*O*-bis(trimethylsilyl)-erythromycin A 9-*O*-(1-isopropoxycyclohexyl) oxime. The colorless and flake single crystal was cultured in acetone-water. The crystal data are summarized in Table 2. The X-Ray diffractions were measured on Rigaku RAXIS RAPID IP diffractometer with monochromated MoKα (λ=0.071073 nm) radiation at 293K. The structure was solved by direct methods using SHELXS. [10] All non hydrogen atoms were refined by full-matrix least-squares using SHELXL. [11]

Table 2 Crystal data of *E*-Isomer

	Title compound	EM-IPCH oxime
Empirical formula	$C_{52}H_{100}N_2O_{14}Si_2 \cdot CH_3COCH_3$	$C_{46}H_{84}N_2O_{14} \cdot 3H_2O$
Formula weight	1091.60	943.20
Crystal size/mm	0.2 × 0.15 × 0.1	0.2 × 0.15 × 0.1
Crystal system	Orthorhombic	Orthorhombic
Space group	$P2_12_12_1$	$P2_12_12_1$
a /nm	1.8605(4)	2.3101(5)
b /nm	1.8656(4)	2.3761(5)
c /nm	1.9488(4)	0.97066(19)
α= β = γ /(°)	90	90
V /nm^3	6.764(2)	5.3279(18)
Z	4	4
D_c /(g·cm^{-3})	1.072	1.176
F(000)	2392	2064
μ/mm^{-1}	0.109	0.088
θ range /(°)	2.35 to 27.48	2.27 to 27.48
Reflections collected	58426	45782
Independent reflections	8343 R_{int}= 0.0819	6747 R_{int}=0.0521
Reflections observed	1912 $I>2\sigma(I)$	2119 $I>2\sigma(I)$
R_1/wR_2	0.0486/0.0567	0.0505/0.0775

3'-N(CH_3)$_2$ and TMS groups at 2'-position are also located at adjacent equatorial orientations of the middle of chair conformation. The sum of angels at N atom of 3'-N(CH_3)$_2$, about 336°, indicates that the N atom is tetrahedral. Therefore the dimethylamine is left only one side vacant, which is easily attacked by methylating reagents. So the protective effect against quarternarization was strengthened by the existence of bulky TMS at adjacent 2'-position in agreement with the experimental results reported.[4] To our surprise the carbon atom substituted by oxime hydroxyl group was not located at the head of chair conformation of 1-isopropoxycyclohexyl group. This indicated that S_N1 mechanism was more rational than S_N2 mechanism. So 1-isopropoxycyclohexyl cation with half-chair conformation maybe was possible intermediate for ketalation of erythromycin oxime. However the C-11 and C-12 hydroxyl groups were hindered against the attack of the methylating reagents by the bulky 1-isopropoxycyclohexyl group. The methylation process was postulated as S_N2 mechanism, [8] which involves firstly a very rapid hydrogen abstraction in a basic medium followed by formation of the anions at C-6, C-11 and C-12, then a backside attack of the ion (O^-) at the carbon atom followed by the familiar "Walden inversion" of the methyl group.

The characteristic chair conformation of 1-isopropoxycyclohexyl groups is bulkier and more effective for regioselectivity than planar benzene ring of 2-chlorophenyl groups. So the former shows higher selectivity than the latter as reported.[5] More importantly, we found the bond lengths of both C(5)-C(6) and C(6)-C(7) are longer than standard value of C_{sp3}-C_{sp3}. Especially the bond of C(6)-C(7) is longest in the disclosed crystal structure of erythromycin A derivatives.[9, 13-17] So O^- at C-6 is easily directed upward from average ring plane to the more open space. The conformational alternation of erythrolide ring exposes only the 6-OH to methylation. Hence the reversion of methylating selectivity *via* 2'-,4"-*O*-bis(trimethylsilyl)erythromycin A 9-*O*-(1-isopropoxycyclohexyl) oxime contributes much for the synthesis of clarithromycin on an industrial scale.

Table 3 Selected bond lengths (10^{-1} nm) and angles (°) of the title compound

Si(1)-O(10)	1.639(3)	Si(2)-O(7)	1.622(4)	O(11)-N(1)	1.424(5)
N(1)-C(9)	1.257(6)	C(1)-C(2)	1.529(7)	C(2)-C(3)	1.574(6)
C(3)-C(4)	1.544(6)	C(4)-C(5)	1.563(6)	C(5)-C(6)	1.554(6)
C(6)-C(7)	1.572(6)	C(7)-C(8)	1.550(6)	C(8)-C(9)	1.529(7)
C(9)-C(10)	1.541(8)	C(10)-C(11)	1.535(7)	C(11)-C(12)	1.550(7)
C(12)-C(13)	1.515(7)	C(13)-O(1)	1.493(6)	O(1)-C(1)	1.326(7)
C(25)-O(7)-Si(2)	134.6(4)	C(32)-O(10)-Si(1)	130.7(3)		
C(9)-N(1)-O(11)	111.9(5)	C(1)-C(2)-C(3)	110.0(5)		
C(4)-C(3)-C(2)	110.2(4)	C(3)-C(4)-C(5)	109.5(4)		
C(6)-C(5)-C(4)	111.9(4)	C(5)-C(6)-C(7)	109.1(4)		
C(8)-C(7)-C(6)	114.7(4)	C(9)-C(8)-C(7)	114.2(5)		
C(8)-C(9)-C(10)	119.2(6)	C(11)-C(10)-C(9)	108.7(5)		
C(10)-C(11)-C(12)	114.7(6)	C(13)-C(12)-C(11)	110.0(6)		
O(1)-C(13)-C(12)	109.2(5)	C(1)-O(1)-C(13)	117.4(5)		
O(1)-C(1)-C(2)	110.2(6)				

Table 4 Selected bond lengths (10^{-1} nm) and angles (°) of EM-IPCH oxime

N(1)-C(9)	1.264(5)	C(1)-C(2)	1.511(7)	C(2)-C(3)	1.532(6)
C(3)-C(4)	1.533(6)	C(4)-C(5)	1.553(6)	C(5)-C(6)	1.574(6)
C(6)-C(7)	1.541(6)	C(7)-C(8)	1.523(6)	C(8)-C(9)	1.514(6)
C(9)-C(10)	1.535(6)	C(10)-C(11)	1.516(7)	C(11)-C(12)	1.521(6)
C(12)-C(13)	1.564(6)	C(13)-O(1)	1.489(6)	O(1)-C(1)	1.354(6)
C(9)-N(1)-O(11)	111.7(4)	C(1)-C(2)-C(3)	107.7(4)		
C(4)-C(3)-C(2)	109.6(4)	C(3)-C(4)-C(5)	112.4(4)		
C(6)-C(5)-C(4)	116.1(4)	C(5)-C(6)-C(7)	110.7(4)		
C(8)-C(7)-C(6)	114.5(4)	C(9)-C(8)-C(7)	114.2(4)		
C(8)-C(9)-C(10)	119.1(5)	C(11)-C(10)-C(9)	110.6(4)		
C(10)-C(11)-C(12)	115.0(4)	C(13)-C(12)-C(11)	109.0(4)		
O(1)-C(13)-C(12)	106.6(4)	C(1)-O(1)-C(13)	119.3(4)		
O(1)-C(1)-C(2)	110.7(5)				

The torsion angles of the lactone agree well with each other with C(6)-C(9)-C(13) region but somewhat different with C(1)-C(4), C(3)-C(6)and C(5)-C(8) region. See Table 5. Kawashima *et al*. [8] found that TMS protective groups introduced at desosamine and cladinose could not shift the regioselective methylation to 6-OH from 11-OH. However the introduction of TMS indeed altered the torsion of lactone

ring as well as specific bond lengths and angles. See Table 3, 4 and 5. Moreover the bond length of C(11)-C(12) increased to 1.550nm from original 1.521nm due to the torsion angle of O(12)-C(11)-C(12)-O(13) decreased to 44.3° from original 48.3° . This maybe contributed to improve regioselectivity at 6-OH to some extent. It's notable that the torsion angles of the title compound and 2',4"-*O*-bis(trimethylsilyl)erythromycin A 9-*O*-(*t*-butyldimethylsilyl) oxime, another precursor for regioselective methylation, agree well within the lactone ring region indicating characteristic torsion for regioselectivity at 6-OH.

Table 5 Torsion angles(°) of lactone ring

	1[a]	2[b]	3[c]	4[d]	5[e]	6[f]	7[g]
C(13)-O(1)-C(1)-C(2)	166.8(5)	175.7	171.3	172.0	175	171	173.7
O(1)-C(1)-C(2)-C(3)	108.5(5)	119.6	115.9	107.5	124	112	102.3
C(1)-C(2)-C(3)-C(4)	-68.9(6)	-96.6	-61.2	-84.1	-92	-80	-73.0
C(2)-C(3)-C(4)-C(5)	165.2(4)	161.4	164.8	167.2	157	168	171.1
C(3)-C(4)-C(5)-C(6)	-106.6(5)	-82.5	-116.1	-95.7	-86	-102	-100.2
C(4)-C(5)-C(6)-C(7)	-70.6(5)	-76.3	-68.5	-73.0	-74	-70	-75.4
C(5)-C(6)-C(7)-C(8)	174.8(4)	-179.5	175.0	174.8	-177	173	172.8
C(6)-C(7)-C(8)-C(9)	-74.5(6)	-74.9	-77.0	-77.2	-74	-73	-77.5
C(7)-C(8)-C(9)-C(10)	-64.3(6)	-60.9	-60.8	-59.8	-67	-64	-60.2
C(8)-C(9)-C(10)-C(11)	115.6(6)	117.4	122.0	120.7	117	122	117.7
C(9)-C(10)-C(11)-C(12)	-171.9(5)	-172.6	-173.3	-171.9	-172	-173	-170.1
C(10)-C(11)-C(12)-C(13)	165.9(5)	167.8	167.8	165.0	169	165	167.4
C(11)-C(12)-C(13)-O(1)	-63.8(6)	-70.5	165.1	-71.5	-71	-68	-72.5
C(12)-C(13)-O(1)-C(1)	117.3(6)	115.4	107.3	125.4	114	120	124.5

1[a] *E*-2',4"-*O*-bis(trimethylsilyl)erythromycin A 9-*O*-(1-isopropoxycyclohexyl)oxime in this work
2[b] *E*-erythromycin A 9-*O*-(1-isopropoxycyclohexyl)oxime in ref. 9
3[c] erythromycin A hydroiodide in ref. 12
4[d] erythromycin A zinc acetate complex in ref. 13
5[e] 6-*O*-Methylerythromycin A in ref. 14
6[f] (14*R*)-14-hydroxy-6-*O*-methylerythromycin A in ref. 15
7[g] *E*-2',4"-*O*-bis(trimethylsilyl)erythromycin A 9-*O*-(*t*-butyldimethylsilyl) oxime in ref. 16

EXPERIMENTAL

Melting points were measured on an Electrothermal XT 4A apparatus and were uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ on Bruker ARX 400spectrometers. MS was measured with ZAB-HS mass spectrometer. Elemental analysis was taken using Elementar Vario EL elemental analysis apparatus.

To a solution of erythromycin A oxime (5.0 g, 6.7 mmol) in 35 mL of CH_3CN (or CH_2Cl_2) was added 1,1-diisopropoxycyclohexane (3.0 mL, 13.4 mmol) in the presence of 1.3 g (11.6 mmol) of pyridine hydrochloride. The reaction mixture was allowed to stir at 10 °C (20 °C or 30 °C) for 6 h. Then 1.2 g (10.7 mmol) of pyridine hydrochloride and 1,1,1,3,3,3-hexamethyldisilizane (5.0 mL, 24.0 mmol) were

added and the reaction solution was further stirred for 3 h. When the reaction completed, the pH was adjusted to no less than 10 by 2 mol/L of NaOH, and the mixture was extracted with ethyl acetate (20 mL and 10 mL). The organic layer was washed with water and saturated NaCl solution in turn, and dried over anhydrous magnesium sulfate. The solvent was evaporated under vacuum to afford 2',4''-*O*-bis(trimethylsilyl)erythromycin A 9-*O*-(1-isopropoxycyclohexyl) oxime as a foam, which was subjected to HPLC performed on DIKMA Inertsil ODS-3 column(150 mm × 4.6 mm, 5 μm). Table 1 gave the analytical results in detail. ***Z*-title compound:** mp114-116°C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 4.98 (dd, *J* = 9.8, 2.7 Hz, H-13), 4.11 – 4.06 [m, -OC<u>H</u>$(CH_3)_2$], 3.75 (s, H-11), 3.30 (s, 3''-OCH_3), 2.23 [s, 3'-N(C<u>H</u>$_3)_2$], 3.20 –3.18 (m, H-8), 3.05 – 2.95 (m, H-10), 0.15 (s, 4''-O-TMS), 0.09 (s, 2'-O-TMS); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 176.3 (C-1), 166.8 (C-9), 104.7 (C-1 in cyclohexyl ring), 63.4 [-O<u>C</u>H$(CH_3)_2$], 49.5 (3''-OCH_3), 40.9 [3'-N(<u>C</u>$H_3)_2$], 24.3 [-OCH(<u>C</u>$H_3)_2$], 19.1 (8-CH_3), 11.1 (10-CH_3), 0.9 (2'–O–TMS), 0.8 (4''–O-TMS) ; MS (MALDI-TOF) *m/z*: 1056.7 ($M+Na^+$) ***E*-title compound:** mp 102-104°C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 4.98 (dd, *J* = 10.6, 2.4 Hz, H-13), 4.08 – 4.02 [m, -OC<u>H</u>$(CH_3)_2$], 3.79 – 3.74 (m, H-8), 3.67 (s, H-11), 3.30 (s, 3''-OCH_3), 2.70 (q, *J* = 7.0 Hz, H-10), 2.23 [s, 3'-N(C<u>H</u>$_3)_2$], 0.15 (s, 4''-O-TMS), 0.10 (s, 2'-O-TMS); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 175.6 (C-1), 170.8 (C-9), 104.0 (C-1 in cyclohexyl ring), 63.2 [-O<u>C</u>H$(CH_3)_2$], 49.7 (3''-OCH_3), 40.4 [3'-N(<u>C</u>$H_3)_2$], 24.3 [-OCH(<u>C</u>$H_3)_2$], 18.5 (8-CH_3), 14.4 (10-CH_3), 1.0 (2'–O–TMS), 0.9 (4''–O-TMS) ; MS (FAB) *m/z*: 1034 (MH^+); Anal. Calcd for $C_{52}H_{100}N_2O_{14}Si_2$:C 60.43, H 9.75, N 2.71. Found : C 60.57, H 9.76, N 2.72.

To a solution of erythromycin A 9-*O*-(1-isopropoxycyclohexyl) oxime (1.40 g, 1.4 mmol) in 10 mL of CH_3CN was added 1,1,1,3,3,3-hexamethyldisilizane (1.0 mL, 4.8 mmol) in the presence of 0.18 g (2.8 mmol) of $HCOONH_4$ (or 0.15 g of NH_4Cl, 2.8 mmol). The reaction mixture was allowed to stir at 20 °C and monitored by TLC. The starting materials was consumed and a lower polarity spot appeared identified as **4''-*O*-(trimethylsilyl)erythromycin A 9-*O*-(1-isopropoxycyclohexyl) oxime:** mp 109-111°C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 4.07 - 4.02 [m, H-3, -OC<u>H</u>$(CH_3)_2$], 3.31(s,3''-OCH_3), 2.29 [s, 3'-N(C<u>H</u>$_3)_2$], 0.16 (s, 4''-O-TMS); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 175.0 (C-1), 171.4 (C-9), 104.1 (C-1 in cyclohexyl ring), 63.2 [-O<u>C</u>H$(CH_3)_2$], 49.5 (3''-OCH_3), 40.1 [3'-N(<u>C</u>$H_3)_2$], 24.2 [-OCH(<u>C</u>$H_3)_2$], 0.8 (4''–O-TMS) ; MS (FAB) *m/z*: 963 (MH^+). The intermediate was soon converted into the title compound with the lowest polarity in CH_3CN.

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