9a,11-CYCLIC CARBAMATES OF 15-MEMBERED AZALIDES

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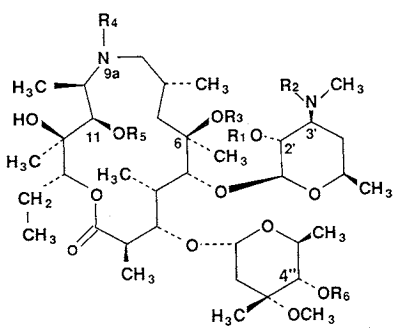
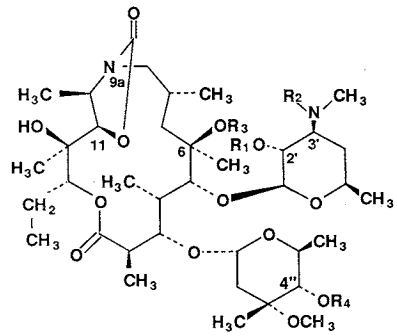
The novel 9a,11-cyclic carbamates (**13**~**15**) of 9-deoxo-9a-aza-9a-homoerythromycin A (**4**) have been prepared and characterized by ^{1}H-^{1}H and ^{1}H-^{13}C 2D NMR spectroscopy. When compared to azithromycin (**1**) or its 6-*O*-methyl derivative (**2**), the new bicyclic 15-membered azalides exhibited substantially decreased antibacterial activities *in vitro*.

Azithromycin (**1**) is a new macrolide antibacterial which belongs to a recently described subclass of antibiotics known as azalides.[1,2] In preceding paper[3] we reported the synthesis and structure-activity relationship of novel *O*-methylazithromycin derivatives. Among them, 6-*O*-methylazithromycin (**2**) and 11-*O*-methylazithromycin (**3**) exhibited excellent *in vitro* antibacterial activities against a variety of standard strains. In the development of synthetic routes for **2**, *O*-methylation of 9-deoxo-9a-aza-9a-homoerythromycin A (**4**),[4,5] the 15-membered-ring macrolide with the secondary 9a-amino group, has been investigated. Herein, we describe the synthesis and structure-activity evaluation of a novel series of compounds based on the 9a,11-cyclic carbamate structure of **4**.

Gradual addition (2 hours) of benzyl chloroformate (Cbz-Cl) to a solution of **4** in benzene in the presence of $NaHCO_3$ afforded trisprotected benzyloxycarbonyl derivative (**5**) in 70.1% yield.[6] When this sequence was accomplished by the addition of Cbz-Cl in one portion, a significant amount of a less polar bisprotected compound (**6**) was isolated (36.3%). The disappearance of the IR 9a-NH stretching frequency at 1650 cm^{-1} in the spectra of **5** and **6** and the observation of the new resonances in their ^{13}C NMR spectra at δ 157.4 and 157.8, respectively, were consistent with the introduction of one of the





1 $R_1=R_3=R_5=R_6=H$, $R_2=R_4=CH_3$
2 $R_1=R_5=R_6=H$, $R_2=R_3=R_4=CH_3$
3 $R_1=R_3=R_6=H$, $R_2=R_4=R_5=CH_3$
4 $R_1=R_3=R_4=R_5=R_6=H$, $R_2=CH_3$
5 $R_1=R_2=R_4=CO_2CH_2C_6H_5$, $R_3=R_5=R_6=H$
6 $R_1=R_4=CO_2CH_2C_6H_5$, $R_2=CH_3$, $R_3=R_5=R_6=H$

7 $R_1=R_2=CO_2CH_2C_6H_5$, $R_3=R_4=CH_3$
8 $R_1=R_2=CO_2CH_2C_6H_5$, $R_3=CH_3$, $R_4=H$
9 $R_1=R_2=CO_2CH_2C_6H_5$, $R_3=R_4=H$
10 $R_1=R_2=H$, $R_3=R_4=CH_3$
11 $R_1=R_2=R_4=H$, $R_3=CH_3$
12 $R_1=R_2=R_3=R_4=H$
13 $R_1=H$, $R_2=R_3=R_4=CH_3$
14 $R_1=R_4=H$, $R_2=R_3=CH_3$
15 $R_1=R_3=R_4=H$, $R_2=CH_3$

benzyloxycarbonyl groups at 9a-position.[7] In addition, the ^{1}H NMR downfield chemical shifts of 3′-NCH_3 (δ 2.29→2.76, 2.82) and 2′-H (δ 3.22→3.48) in **5** as compared to those of **4**, together with the corresponding ^{13}C upfield shifts of 3′-NCH_3 (δ 40.3→34.9) and C-1′ (δ 103.1→100.1), clearly indicated that the other protecting groups were located at 2′-OH and 3′-NCH_3 positions. Since the ^{1}H and ^{13}C chemical shifts of 3′-$N(CH_3)_2$ and 2′-H in **6** were similar to those of **4**, this compound is suggested to be 2′-*O*,9a-*N*-bis(benzyloxycarbonyl)-derivative of **4**.

Based on the previously reported procedures[3,8,9] we expected that *O*-methylation, deprotection and subsequent reductive 3′-*N*-methylation of **5** would give *O*-methyl derivatives of **4**. However, *O*-alkylation of **5** with methyl iodide and sodium hydride in DMSO - THF (1 : 1) at 0～5 °C gave three products (**7**)～(**9**), two of which were identified after removal of the benzyloxycarbonyl protecting groups and *N*-methylation of the isolated 3′-*N*-demethyl derivatives (**10**) and (**11**), as *O*-methyl-9a,11-cyclic carbamates (**13**) and (**14**). Thus, *O*-methylation of **5** appeared to take a different course to that in **1**, involving a preliminary

Table 1. ^{1}H NMR chemical shifts (δ_H)[a] for compounds **11**～**15** in comparison wtih **4**.

Proton	**4**	**11**	**12**	**13**	**14**	**15**
2	2.78	2.83	2.86	2.84	2.84	2.88
3	4.34	4.12	4.08	4.23	4.20	4.16
4	1.93	2.10	2.05	1.95	1.98	2.01
5	3.66	3.61	3.60	3.63	3.63	3.64
6-OCH_3	—	3.45	—	3.45	3.46	—
7	1.75, 1.38	1.51, 1.35	1.61, 1.29	1.50, 1.35	ND	1.58, 1.3
8	1.74	2.30	2.23	2.13	2.26	2.28
9	3.06, 1.82	3.47, 2.44	3.46, 2.35	3.49, 2.39	3.47, 2.43	3.44, 2.43
9a-NH	ND	—	—	—	—	—
10	2.58	3.51	3.56	3.66	3.65	3.66
11	3.46	4.32	4.28	4.33	4.32	4.32
13	4.73	5.48	5.08	5.45	5.46	5.06
14	～1.86, 1.50	1.73, 1.56	1.88, 1.45	1.73, 1.45	1.74, 1.53	1.86, ND
15	0.89	0.91	0.87	0.91	0.91	0.88
16	1.21	1.25	1.24	～1.24	1.25	1.23
17	1.06	1.02	1.02	1.9	1.08	1.08
18	1.30	1.37	1.39	1.36	1.36	1.38
19	0.94	1.00	0.98	1.00	1.00	0.98
20	1.15	1.22	1.22	1.26	1.26	1.25
21	1.08	1.14	1.18	1.14	1.14	1.17
1′	4.43	4.37	4.35	4.46	4.42	4.40
2′	3.22	3.21	3.20	3.19	3.23	3.24
3′	2.44	2.52	2.51	2.55	2.46	2.49
3′-$N(CH_3)_2$	2.29	—	—	2.28	2.30	2.32
3′-NCH_3	—	2.43	2.42	—	—	—
4′	1.66, 1.26	1.42, 1.16	—	1.67, 1.18	1.67, ND	1.69, 1.27
5′	～3.51	3.63	3.56	～3.65	3.50	3.50
5′-CH_3	1.23	1.27	1.27	1.26	1.23	1.22
1″	5.09	4.90	4.89	4.88	4.91	4.91
2″	2.35, 1.58	2.32, 1.58	2.31, 1.56	2.37, 1.54	2.35, 1.62	2.30, 1.62
3″-CH_3	1.25	1.25	1.24	1.27	1.24	1.24
3″-OCH_3	3.34	3.29	3.28	3.31	3.31	3.30
4″	3.04	3.04	3.03	2.68	3.04	3.04
4″-OCH_3	—	—	—	3.54	—	—
5″	4.08	4.16	4.10	4.22	4.04	4.04
5″-CH_3	1.33	1.30	1.30	1.31	1.30	1.30

[a] Chemical shifts are in ppm downfield of TMS. ^{1}H NMR spectra were taken in $CDCl_3$ at 300 MHz, as determined from ^{1}H-^{1}H 2D homonuclear shift correlated experiments.

Table 2. ^{13}C NMR chemical shifts (δ_C)[a] for compounds **11**~**14** in comparison with **4**.

Carbon	4	11	12	13	14	Carbon	4	11	12	13	14
1	178.5	174.1	174.3	174.3	174.4	19	21.9	21.6	21.5	21.3	21.4
2	45.3	44.9	44.8	44.8	44.8	20	14.0	13.7	14.1	13.5	13.6
3	78.1	80.0	78.7	79.5	80.1	21	15.0	16.2	15.3	16.1	16.1
4	42.1	39.6	39.1	40.7	40.0	1′	103.1	103.4	103.3	102.5	103.2
5	83.4	85.9	85.7	83.1	84.1	2′	70.9	74.9	74.6	70.9	70.9
6	73.7	75.1	72.8	76.1	76.0	3′	65.3	60.5	60.3	64.8	65.5
6-OMe	—	53.0	—	52.8	52.9	3′-N(CH_3)$_2$	40.3	—	—	40.7	40.3
7	42.2	37.6	37.1	37.3	37.7	3′-NCH_3	—	33.2	33.1	—	—
8	29.9	26.1	25.8	26.3	26.1	4′	28.7	37.1	37.0	28.6	28.8
9	57.3	49.7	49.7	49.7	49.6	5′	68.8	68.9	68.7	68.5	68.9
9a,11 C=O	—	156.9	156.5	156.8	156.7	5′-CH_3	21.3	21.1	21.1	21.3	21.5
10	56.7	57.9	58.3	57.6	57.6	1″	94.9	96.8	96.7	96.6	96.5
11	73.2	80.6	80.8	79.5	79.8	2″	34.8	35.2	35.1	35.2	35.1
12	73.8	76.1	75.0	75.0	75.0	3″	72.9	71.8	73.0	73.6	72.7
13	77.2	74.1	76.2	74.2	74.0	3″-CH_3	21.6	21.1	20.9	21.3	21.4
14	21.1	21.3	20.5	21.3	21.4	3″-OCH_3	49.4	49.4	49.3	49.7	49.4
15	11.2	10.5	10.5	10.6	10.5	4″	77.9	77.9	78.0	88.9	77.9
16	16.2	16.2	16.6	16.1	16.2	4″-OCH_3	—	—	—	62.1	—
17	9.4	9.8	9.6	9.6	9.5	5″	65.7	65.5	65.5	65.1	65.7
18	27.4	26.7	26.9	26.2	26.8	5″-CH_3	18.3	18.5	18.5	18.2	18.6

[a] Chemical shifts are in ppm downfield of TMS. ^{13}C NMR spectra were taken in $CDCl_3$ at 75 MHz, as determined from ^1H-^{13}C 2D heteronuclear shift correlated experiments.

base-mediated intramolecular cyclization of a 9a-benzyloxycarbonyl and C-11 hydroxyl groups. The fact that also a less polar non-methylated 9a,11-cyclic derivative **9** was isolated, confirmed the cyclization in this reaction step. The elimination of the protecting groups in **9** and *N*-methylation *via* (**12**), provided the expected 9a,11-cyclic carbamate (**15**).

The structure of the novel azalides **7**~**15** has been well elucidated on the basis of their ^1H and ^{13}C NMR spectra. Unambiguous NMR assignments of representative azalides **11**~**15** were made by means of homonuclear ^1H-^1H and heteronuclear ^1H-^{13}C 2D NMR spectroscopy (Tables 1 and 2). In the ^1H NMR spectra of **13** and **14** peaks due to the new 6-OCH_3 were observed at δ 3.45 and 3.46, respectively, together with the downfield shifts of 9a-H, 9b-H, 10-H, 11-H and 13-H, compared to **4**. The ^1H NMR spectrum of **13** showed an additional methoxy signal at δ 3.54 and a doublet methine resonance due to 4″-H at δ 2.68. Beside the 6-OCH_3 peaks at δ 52.8 and 52.9, the ^{13}C NMR spectra of **13** and **14** revealed the new 9a,11-carbamate carbonyl

Table 3. Antibacterial *in vitro* activity of **13** and **14** in comparison with azithromycin (**1**) and 6-*O*-methyl-azithromycin (**2**).

Organism	MIC (μg/ml)			
	1	**2**	**13**	**14**
Staphylococcus aureus ATCC 6538 P	1.56	0.39	25	6.25
S. epidermidis ATCC 12228	0.2	0.2	12.5	1.56
Micrococcus flavus ATCC 10240	0.39	0.79	12.5	6.25
Streptococcus faecalis ATCC 8043	0.1	0.78	NT	0.39
Escherichia coli ATCC 10536	0.78	3.125	100	12.5
Salmonella panama 6117	3.12	6.25	>100	25

Method: Determined by microdilution method using Mueller-Hinton broth and Dynatec microplate reader MR-5000.
Incubation: 18 hours at 37°C.
Inoculum size: 10^5~10^6 cfu/ml.
NT: Not tested.

signals at δ 156.8 and 156.7, respectively. The signal at δ 62.1 in the spectrum of **13** was attributed to 4″-OCH_3. This was supported with a significant downfield shift of C-4″ (δ 77.9→88.9). The ^{13}C NMR spectrum of **15** showed resonance attributed to 9a,11-carbamate carbonyl at δ 156.4 and the expected downfield shifts of 10-H (δ 2.58→3.66) and 11-H (δ 3.46→4.32) in the corresponding ^1H NMR, compared to the parent amine **4**.

The *in vitro* antibacterial activities[10] of novel *O*-methyl derivatives **13** and **14**, compared with those of azithromycin (**1**) and 6-*O*-methylazithromycin (**2**), are shown in Table 3. In general, 6-*O*-methyl-9a,11-cyclic carbamate **14** was less active than **1** or its 6-*O*-methyl-derivative **2**. 6,4″-Di-*O*-methylated derivative **13** showed only slight activity. Nevertheless, these 9a,11-functionalized derivatives of **4** provide an entry into novel analogues of the important class of 15-membered azalide antibiotics.

Experimental

MP's were taken using a Fisher-Johns apparatus and are uncorrected. IR spectra were recorded on a Perkin Elmer 257 G spectrometer. Electron impact mass spectra were recorded on a Shimadzu GCMS-QP 1000 mass spectrometer at 20 eV and ion source temperature of 250°C. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ on JEOL FX-100 or Varian GEM-300 spectrometers. TLC was performed on E. Merck plates of Silica gel 60 using solvent system A (CH_2Cl_2-CH_3OH-conc NH_4OH, 90:9:0.5) or B (EtOAc-(*n*-hexane)-Et_2NH, 100:100:20). Spots were visualized by spraying with 5% H_2SO_4-EtOH solution followed by heating at 110°C. Silica gel column chromatography was performed with Silica gel 60 (70~230 mesh, E. Merck).

2′-*O*,(3′,9a)-Di-*N*-tris(benzyloxycarbonyl)-*N*-demethyl-9-deoxo-9a-aza-9a-homoerythromycin A (**5**) and 2′-*O*-9a-*N*-bis(benzyloxycarbonyl)-*N*-demethyl-9-deoxo-9a-aza-9a-homoerythromycin A (**6**)

To a stirred soln of 9-deoxo-9a-aza-9a-homoerythromycin A **4** (10 g) and $NaHCO_3$ (20 g) in benzene (50 ml), benzyl chloroformate (25 ml) was added successively at reflux temperature for 2 hours. The reaction mixture was stirred for a further 3 hours and then left to stand overnight at room temperature. The suspension was extracted with 0.25 N HCl (50 ml), the organic layer was dried and evaporated. The residue was dissolved in $CHCl_3$ (100 ml), washed with satd NaCl soln (50 ml) and evaporated *in vacuo*. Precipitation of the crude product from Et_2O-petroleum ether (10 ml: 100 ml) gave 10.93 g (70.1%) of **5**. Crystallization from CH_2Cl_2-petroleum ether afforded colourless crystals: MP 144~148°C; TLC, system A Rf 0.724; IR ($CHCl_3$) cm^{-1} 3400, 2980, 1750, 1690, 1265; ^1H NMR (300 MHz, $CDCl_3$) δ 2.76, 2.82 (3H, 3′-NCH_3), 3.37 (3H, 3″-OCH_3), 3.48 (1H, 2′-H), 7.28 (15H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.78 (C-1), 157.4 (9a-carbamate C=O), 165.5, 156.1 (3′-carbamate C=O), 154.5 (2′-carbonate C=O), 100.1 (C-1′), 95.8 (C-1″), 55.0 (C-10), 49.5 (3″-OCH_3), 35.7 (C-2″), 34.9 (3′-NCH_3), 28.7 (C-8); EI-MS *m/z* 988 ($M^+ - CO_2CH_2Ph$).

Evaporation of the Et_2O-petroleum ether mother liquor and silica gel column chromatography (CH_2Cl_2-CH_3OH-conc NH_4OH, 90:9:5) of the residue afforded **6** (1.23 g, 9.0%) as less polar white solid with Rf 0.626 (TLC, system A); IR ($CHCl_3$) cm^{-1} ~3400, 2980, 1750, 1690, 1460, 1425, 1385, 1260, 1170; ^1H NMR (300 MHz, $CDCl_3$) δ 2.23 (6H, 3′-$N(CH_3)_2$), δ 3.32 (1H, 2′-H), 3.30 (3H, 3″-OCH_3), 7.31 (10H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.3 (C-1), 157.8 (9a-carbamate C=O), 154.9 (2′-carbonate C=O), 100.9 (C-1′), 96.3 (C-1″), 49.5 (3″-OCH_3), 40.8 (3′-$N(CH_3)_2$), 35.0 (C-2″); EI-MS *m/z* 1,002 (M^+).

2′-*O*,9a-*N*-Bis(benzyloxycarbonyl)-*N*-demethyl-9-deoxo-9a-aza-9a-homoerythromycin A (**6**)

To a stirred soln of **4** (10 g) and $NaHCO_3$ (20 g) in benzene (50 ml), benzyl chlorformate (25 ml) was added, the reaction mixture was stirred vigorously at reflux temperature for 5 hours, and then was left to stand overnight at room temperature. The mixture was extracted with 0.25 N HCl (50 ml), the organic layer was separated and again diluted with 50 ml of 0.25 N HCl, affording rapid crystallization of white colourless needles. The crystals were filtered off, washed with water (75 ml) and dried to yield 4.95 g (36.3%)

of TLC pure **6** with physico-chemical properties as described in the above example.

Reaction of 2'-*O*,(3',9a)-Di-*N*-tris(benzyloxycarbonyl)-*N*-demethyl-9-deoxo-9a-aza-9a-homoerythromycin A (**5**) with Methyl Iodide

To a stirred soln of **5** (6.0 g) in DMSO - THF (1 : 1, 60 ml) at 0~5°C were added succesively methyl iodide (2.3 ml) and 55~60% NaH dispersion (1.6 g) for 2 hours. The reaction was stirred for 1 hour, the suspension was poured into satd aq $NaHCO_3$ soln (25 ml), and extracted with EtOAc (75 ml). The organic phase was washed with satd NaCl soln (25 ml), dried over K_2CO_3 and concd to oily residue. The resulting product was dissolved in $CHCl_3$ (30 ml), washed several times with satd $NaHCO_3$ soln, dried (K_2CO_3) and evaporated to give 4.06 g of a colorless foam. Chromatography of 1.0 g of the crude product (100 g silica gel, 70~230 mesh) using CH_2Cl_2 - CH_3OH - conc NH_4OH, 90 : 9 : 0.5 as solvent system, gave in order of eluation, 2'-*O*,3'-*N*-bis(benzyloxycarbonyl)-*N*-demethyl-6,4''-di-*O*-methyl-9-deoxo-9a-aza-11-deoxy-9a-homoerythromycin A 9a,11-cyclic carbamate **7** (158 mg), 2'-*O*,3'-*N*-bis(benzyloxycarbonyl)-*N*-demethyl-6-*O*-methyl-9-deoxo-9a-aza-11-deoxy-9a-homoerythromycin A 9a,11-cyclic carbamate **8** (445 mg) and 2'-*O*,3'-*N*-bis(benzyloxycarbonyl)-*N*-demethyl-9-deoxo-9a-aza-11-deoxy-9a-homoerythromycin A 9a,11-cyclic carbamate **9** (105 mg).

For compound **7**: TLC, system A, Rf 0.793; IR (KBr) cm^{-1} 3480, 2985, 1465, 1425, 1390, 1260, 1165, 1080, 1010; ^1H NMR (300 MHz, $CDCl_3$) δ 2.82, 2.85 (3H, 3'-NCH_3), 3.31 (3H, 3''-OCH_3), 3.45 (3H, 6-OCH_3), 3.53 (3H, 4''-OCH_3), 4.43 (1H, 1'-H), 4.90 (1H, 1''-H).

For compound **8**: TLC, system A, Rf 0.648; IR ($CHCl_3$) cm^{-1} 3480, 2970, 1750, 1710, 1460, 1420, 1385, 1260, 1170, 1120, 1055, 1000; ^1H NMR (300 MHz, $CDCl_3$) δ 2.82, 2.85 (3H, 3'-NCH_3), 3.35 (3H, 3''-OCH_3), 3.44 (3H, 6-OCH_3), 3.49 (1H, 2'-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.1 (C-1), 156.3 (3'-carbamate C=O), 155.9 (9a-carbamate C=O), 154.5 (2'-carbonate C=O), 99.7 (C-1'), 95.8 (C-1''), 57.4 (C-10), 54.3 (6-OCH_3), 52.7 (C-9), 49.5 (3''-OCH_3); EI-MS *m/z* 1,002 (M^+).

For compound **9**: TLC, system A, Rf 0.490; IR (KBr) cm^{-1} 3485, 2980, 1750, 1705, 1460, 1425, 1380, 1260, 1165, 1130, 1060, 995; ^1H NMR (300 MHz, $CDCl_3$) δ 2.81, 2.84 (3H, 3'-NCH_3), 3.35 (3H, 3''-OCH_3).

3'-*N*-Demethyl-6,4''-di-*O*-methyl-9-deoxo-9a-aza-11-deoxy-9a-homoerythomycin A 9a,11-Cyclic Carbamate (**10**), 3'-*N*-Demethyl-6-*O*-methyl-9-deoxo-9a-aza-11-deoxy-9a-homoerythromycin A 9a,11-Cyclic Carbamate (**11**) and 3'-*N*-Demethyl-9-deoxo-9a-aza-11-deoxy-9a-homoerythromycin A 9a,11-Cyclic Carbamate (**12**)

To a soln of crude product from the above example (4.79 g) in EtOH (50 ml) and water (20 ml) containing 0.6 ml AcOH and 0.97 g AcONa was added Pd-C 10% (2.0 g) and the mixture was stirred for 5 hours at room temperature under hydrogen atmosphere (5 atm). The catalyst was filtered off, and the filtrate evaporated under reduced presure. The residue was diluted with water (50 ml) and extracted with $CHCl_3$ at pH 9.0. The combined organic extractes were dried (K_2CO_3) and concd *in vacuo* to give 3.2 g of crube product, which was if necessary purified by silica gel column chromatography (CH_2Cl_2 - CH_3OH - conc NH_4OH, 90 : 9 : 0.5), to give in order of eluation, 3'-*N*-demethyl-6,4''-di-*O*-methyl-derivative **10**, 3'-*N*-demethyl-6-*O*-methylderivative **11** and 3'-*N*-demethyl-9-deoxo-9a-aza-11-deoxy-9a-homoerythromycin A 9a;11-cyclic carbamate **12**.

For compound **10**: MP 139~143°C; TLC, system A, Rf 0.310; IR ($CHCl_3$) cm^{-1} 3480, 2985, 1750, 1465, 1420, 1390, 1165, 1085, 1015, 920; ^1H NMR (300 MHz, $CDCl_3$) δ 2.54 (3H, 3'-NCH_3), 3.33 (3H, 3''-OCH_3), 3.46 (3H, 6-OCH_3), 3.53 (3H, 4''-OCH_3), 3.65 (1H, 5'-H), 4.15 (1H, 5''-H), 4.49 (1H, 1'-H), 4.88 (1H, 1''-H), 5.46 (1H, 13-H); EI-MS *m/z* 773 (M^+).

Anal Calcd for $C_{39}H_{70}N_2O_{13}$: C 60.44, H 9.11, N 3.61.
Found: C 60.08, H 9.25, N 3.43.

For compound **11**: MP 142~146°C; TLC, system A, Rf 0.269; IR ($CHCl_3$) cm^{-1} 3480, 2980, 1745, 1460, 1420, 1385, 1250, 1165, 1170, 1000; ^1H NMR (300 MHz, $CDCl_3$): Table 1; ^{13}C NMR (75 MHz, $CDCl_3$): Table 2; EI-MS *m/z* 759 (M^+).

Anal Calcd for $C_{38}H_{68}N_2O_{13}$: C 59.98, H 9.01, N 3.68.
Found: C 59.62, H 9.35, N 3.48.

For compound **12**: MP 155~158°C; TLC, system A, Rf 0.172; IR ($CHCl_3$) cm^{-1} 3480, 2980, 1750, 1455, 1420, 1385, 1170, 1080, 1005; ^1H NMR (300 MHz, $CDCl_3$): Table 1; ^{13}C NMR (75 MHz, $CDCl_3$): Table 2; EI-MS *m/z* 745 (M^+).

Anal Calcd for $C_{37}H_{66}N_2O_{13}$: C 59.50, H 8.91, N 3.75.
Found: C 59.24, H 8.56, N 3.63.

6,4″-Di-*O*-methyl-9-deoxo-9a-aza-11-deoxy-9a-homoerythromycin A 9a,11-Cyclic Carbamate (**13**), 6-*O*-Methyl-9-deoxo-9a-aza-11-deoxy-9a-homoerythromycin A 9a,11-Cyclic Carbamate (**14**) and 9-Deoxo-9a-aza-11-deoxy-9a-homoerythromycin A 9a,11-Cyclic Carbamate (**15**)

To a soln of crude product (2.2 g) of the above example in $CHCl_3$ (50 ml) were added 37% aq HCOH (0.57 ml) and 98% HCOOH (0.52 ml) and the soln was stirred for 8 hours at reflux temperature. The reaction mixture was poured into water (40 ml), extracted with $CHCl_3$ at pH 9, the combined organic extracts dried (K_2CO_3) and evaporated *in vacuo* to give 2.17 g of a crude product which was purified by silica gel column chromatography (CH_2Cl_2-CH_3OH-conc NH_4OH, 90:9:0.5) to give, in order of eluation, 6,4″-di-*O*-methyl-9-deoxo-9a-aza-11-deoxy-9a-homoerythromycin A 9a,11-cyclic carbamate **13** (210 mg), 6-*O*-methyl-9-deoxo-9a-aza-11-deoxy-9a-homoerythromycin A 9a,11-cyclic carbamate **14** (876 mg) and 9-deoxo-9a-aza-11-deoxy-9a-homoerythromycin A 9a,11-cyclic carbamate **15** (160 mg).

For compound **13**: MP 127~131°C; TLC, system B, Rf 0.645; IR ($CHCl_3$) cm^{-1} 3480, 2980, 1755, 1465, 1420, 1390, 1170, 1100, 1060; ^1H NMR (300 MHz, $CDCl_3$): Table 1; ^{13}C NMR (75 MHz, $CDCl_3$): Table 2; EI-MS *m/z* 787 (M^+).

Anal Calcd for $C_{40}H_{72}N_2O_{13}$: C 60.89, H 9.20, N 3.55.
Found: C 60.54, H 8.79, N 3.32.

For compound **14**: MP 135~138°C; TLC, system B, Rf 0.546; IR ($CHCl_3$) cm^{-1} 3480, 2980, 1755, 1465, 1420, 1390, 1170, 1100, 1060; ^1H NMR (300 MHz, $CDCl_3$): Table 1; ^{13}C NMR (75 MHz, $CDCl_3$): Table 2; EI-MS *m/z* 773 (M^+).

Anal Calcd for $C_{39}H_{70}N_2O_{13}$: C 60.44, H 9.11, N 3.61.
Found: C 60.15, H 8.74, N 3.37.

For compound **15**: MP 133~136°C; TLC, system B, Rf 0.454; IR ($CHCl_3$) cm^{-1} 3475, 2980, 1750, 1460, 1420, 1385, 1260, 1220, 1100, 1050; ^1H NMR (300 MHz, $CDCl_3$): Table 1: ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.2 (C-1), 156.4 (9a, 11 C=O),103.4 (C-1′), 96.6 (C-1″), 49.5 (3″-OCH_3), 40.3 (3′-$N(CH_3)_2$); EI-MS *m/z* 759 (M^+).

Anal Calcd for $C_{38}H_{68}N_2O_{13}$: C 59.98, H 9.01, N 3.68.
Found: C 59.63, H 8.90, N 3.43.

6-*O*-Methyl-9-deoxo-9a-aza-11-deoxy-9a-homoerythromycin A 9a,11-Cyclic Carbamate (**13**)

To a soln of **11** (0.41 g) in $CHCl_3$ (20 ml) were added 37% aq HCOH (0.09 ml) and 98% HCOOH (0.08 ml), and the reaction mixture was stirred for 8 hours at reflux temperature. After the complete absence of **11** (TLC, system B), the soln was poured into water (40 ml), and extracted with $CHCl_3$. The combined organic extracts were dried (K_2CO_3) and evaporated *in vacuo* to give 0.39 g (92.8%) of **13** with physico-chemical properties as described in the above example.

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