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*Original Scientific Paper*

# Synthesis and Structural Properties of Novel Tricyclic 15-membered Azalides

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*Abstract.* Starting from 3-decladinosyl-9a,11-cyclic carbamates of 15 membered azalide, strained tricyclic aglycone derivatives were prepared. The bridging 5-membered hemiketal ring was obtained by intramolecular ketalization of intermediary 3-keto derivative, whereas 5-membered ether derivatives were obtained by intramolecular Williamson-type displacement. In case of 12-*O*-alkyl derivatives complete diastereoselective formation of ethers was observed, while unsubstituted compound gave diastereomeric mixture. NMR analysis was used to confirm the structures of new tricyclic azalide compounds.

*Keywords:* Macrolides, azalides, synthesis, tricyclic structures, NMR spectroscopy

## INTRODUCTION

The macrolides belong to the polyketide class of natural products. They are a group of antibiotics, the antimicrobial activity of which stems from the presence of a macrocyclic lactone ring to which one or more deoxy sugars, usually cladinose and desozamine, are attached.[1] Clarithromycin[2–6] and azithromycin[7] (Figure 1), the second generation of macrolides, have been clinically used. Azithromycin, a 15-membered azalide is characterized with enhanced antibacterial profile and improved pharmacokinetic properties in comparison to 14-membered erythromycin and clarithromycin.[8]

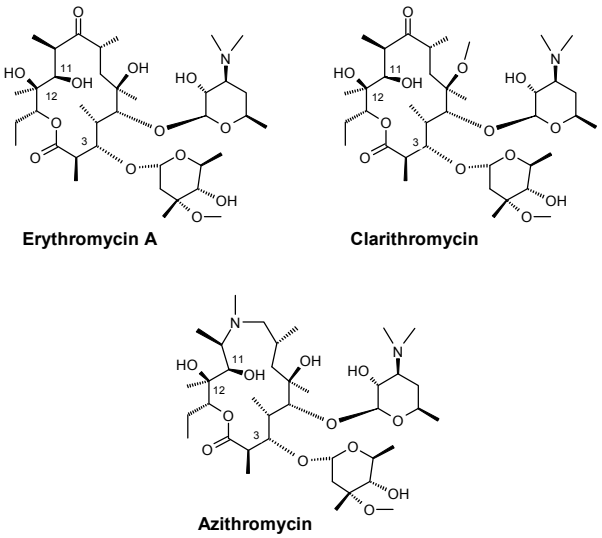


**Figure 1.** Chemical structures of clinically used macrolides.

Other biological effects of macrolide, beside antibacterial one, have been reported in the last decade. Azithromycin proved effective in treatment of malaria,[9] while some other macrolide derivatives exhibited anti-inflammatory,[10] anticancer effect[11] and effect on gastrointestinal motility.[12]

The cladinose sugar on position 3 was considered for many years as an essential part of macrolide molecule for antibacterial activity. However, some new discovered molecules without L-cladinose proved effective, obviating the known mechanisms of resistance. The most known are decladinosyl macrolides that have 3-keto,[13,14] 3-*O*-acyl[15] and 2,3-anhydro[16,17] functionality.

Recently, we described a series of bicyclic 15-membered azalides[18] with moderate antibacterial activity. Herein, we report the synthesis and structural properties of novel 15-membered azalides with a unique tricyclic structure in their aglycone moiety, broadening the pallet of polycyclic 3-decladinosyl macrolides.

## EXPERIMENTAL

IR spectra were recorded in KBr pastilles on a Nicolet Magna-IR 760 FT-IR spectrometra. Mass spectra were obtained on a Varian-Mat 311A for FAB-MS or Plat

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form LCZ and LCQ Deca for ESI-MS. $^1$H and $^{13}$C NMR spectra were measured with a Varian Unity Inova 600, Bruker Advance DRX 500 and Bruker Advance DPX 300 spectrometra in CDCl3 using trimethylsilan as internal standard.

Compounds **1**−**6** were prepared as already described.[18]

**Synthesis of 3-decladinosyl-3,6-hemiketal derivatives**

*3-Decladinosyl-9-deoxo-9-dihydro-9a-aza-9a-homoerythromycin A 3,6-hemiketal 9a,11-cyclic carbamate* **7**

To a solution of 2'-*O*-acetyl-3-decladinosyl-9-deoxo-9-dihydro-9a-aza-9a-homoerythromycin A 9a,11-cyclic carbamate **4** (2.83 g, 4.39 mmol) in $CH_2Cl_2$ (50 ml) DMSO (4.08 ml, 5.32 mmol) and *N,N*-dimethylaminopropyl-ethyl-carbodiimid (5.05 g, 26.34 mmol) were added. The reaction mixture was cooled to 15 ºC. Keeping the temperature constant, solution of pyridinium trifluoroacetate (5.01 g, 20.21 mmol) in $CH_2Cl_2$ (10 ml) was dropwise added to the reaction mixture during 30 minutes. The reaction mixture was stirred from 15 ºC to room temperature for additional 2 hours. To the reaction mixture saturated aqueous solution of NaCl (25 ml) was added and the pH adjusted to 9.5. The layers were separated and the aqueous layer was extracted two more times with $CH_2Cl_2$. Combined organic extracts were rinsed with brine, std. $NaHCO_3$ and water, dried over $K_2CO_3$ and evaporated yielding 2.5 g of the 2'-acetylated product. The obtained product was dissolved in MeOH (50 ml) and the solution was stirred for 24 hours at room temperature. Solvent was evaporated and the residue (2.26 g) purified by low pressure chromatography on a silica gel column using the system $CH_2Cl_2$/MeOH/$NH_4OH$ (90:9:1.5). Evaporation of chromatographically homogenous fractions yielded the product **7** (2.06 g, 88 %).

Under the same conditions, starting from 2'-*O*-acetyl-3-decladinosyl-12-*O*-methyl-9-deoxo-9-dihydro-9a-aza-9a-homoerythromycin A 9a,11-cyclic carbamate **5** and 2'-*O*-acetyl-3-decladinosyl-12-*O*-ethyl-9-deoxo-9-dihydro-9a-aza-9a-homoerythromycin A 9a,11-cyclic carbamate **6**, the corresponding 3-decladinosyl-12-O-methyl-9-deoxo-9-dihydro-9a-aza-9a-homoerythromycin A 3,6-hemiketal 9a,11-cyclic carbamate **8** and 3-decladinosyl-12-O-ethyl-9-deoxo-9-dihydro-9a-aza-9a-homoerythromycin A 3,6-hemiketal 9a,11-cyclic carbamate **9** were prepared. Results and physicochemical data for 3,6-hemiketal derivatives are given in Table 1.

*3-Decladinosyl-3-keto-6-O-metil-9-deoxo-9-dihydro-9a-aza-9a-homoerythromycin A 9a,11-cyclic carbamate* **20**

Compound **20** was obtained as a white solid (0.10 g, 60 %) starting from 2'-*O*-acetyl-3-decladinosyl-6-*O*-metil-9-deoxo-9-dihydro-9a-aza-9a-homoerythromycin A 9a,11-cyclic carbamate **19** applying the same reaction conditions as described for preparation of compounds **7, 8** and **9**. ESI-MS *m*/*z*: 615.6 $(M+H)^+$; IR (KBr) $\nu_{max}$/cm$^{-1}$: 3430, 2974, 2927, 1734, 1637, 1560, 1458, 1428, 1374, 1250, 1187, 1168, 1104, 1082, 1047, 1009, 970, 797, 765, 676; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$/ppm: 5.10 (H-13), 4.40 (H-1'), 4.36 (H-5), 4.21 (H-11), 3.84 (H-2), 3.57 (H-5'), 3.53 (H-9a), 3.47 (H-10), 3.32 (6-*O*-Me), 3.26 (H-2'), 3.20 (H-4), 2.50 (H-3'), 2.31 (H-8), 2.31 (H-9b), 2.28 (3'-$NMe_2$), 1.92 (H-14a), 1.67 (H-4'a), 1.52 (H-14b), 1.47 (H-7a), 1.30 (6-Me), 1.30 (10-Me), 1.25 (2-Me), 1.24 (5'-Me), 1.23 (H-4'b), 1.22 (12-Me), 1.14 (H-7b), 1.02 (4-Me), 1.00 (8-Me), 0.93 (14-Me); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$/ppm: 207.1 (C-3), 171.1 (C-1), 156.5 (9a,11-C=O), 103.0 (C-1'), 79.9 (C-6), 79.5 (C-13), 78.0 (C-11), 76.2 (C-5), 73.7 (C-12), 70.8 (C-2'), 69.7 (C-5'), 65.9 (C-3'), 58.4 (C-10), 51.1 (C-2), 50.9 (C-4), 50.6 (6-*O*-Me), 49.5 (C-9), 39.9 (3'-$NMe_2$), 36.6 (C-7), 27.9 (C-4'), 25.3 (C-8), 20.7 (5'-Me), 20.4 (6-Me), 20.2 (8-Me), 20.0 (C-14), 15.8 (2-Me), 15.2 (12-Me), 13.4 (10-Me), 10.0 (14-Me), 7.9 (4-Me).

**Synthesis of 2'-O-acetyl-3-decladinosyl-3-O-mesyl derivatives**

*2'-O-Acetyl-3-decladinosyl-3-O-mesyl-9-deoxo-9-dihydro-9a-aza-9a-homoerythromycin A 9a,11-cyclic carbamate* **10**

To a solution of 2'-*O*-acetyl-3-decladinosyl-9-deoxo-9-dihydro-9a-aza-9a-homoerythromycin A 9a,11-cyclic carbamate **4** (1.21 g, 1.88 mmol) in pyridine (60 ml) methanesulfonic anhydride (1.18 g, 6.75 mmol) was added and the reaction mixture was stirred at room temperature for 4 hours. The solvent was evaporated and the residue was dissolved in $CH_2Cl_2$ (50 ml). Saturated aqueous solution of $NaHCO_3$ (50 ml) was added, the layers were separated and the aqueous layer was extracted two more times with $CH_2Cl_2$. Combined organic extracts were rinsed with $NaHCO_3$ and brine, dried over $K_2CO_3$ and evaporated yielding 1.8 g of crude product **10**.

Starting from 2'-*O*-acetyl-3-decladinosyl-12-*O*-methyl-9-deoxo-9-dihydro-9a-aza-9a-homoerythromycin A 9a,11-cyclic carbamate **5,** 2'-*O*-acetyl-3-decladinosyl-12-*O*-ethyl-9-deoxo-9-dihydro-9a-aza-9a-homoerythro-mycin A 9a,11-cyclic carbamate **6** and 2'-*O*-acetyl-3-decladinosyl-6-*O*-methyl-9-deoxo-9-dihy-dro-9a-aza-9a-homoerythromycin A 9a,11-cyclic carbamate **19** in the same manner as described for compound **10,** crude 2'-*O*-acetyl-3-decladinosyl-3-*O*-mesyl-12-*O*-methyl-9-deoxo-9-dihydro-9a-aza-9a-homoerythromycin A 9a,11-cyclic carbamate **11,** 2'-*O*-acetyl-3-decladinosyl-3-*O*-mesyl-12-*O*-ethyl-9-deoxo-9-dihydro-9a-aza-9a-homoerythro-mycin A 9a,11-cyclic carbamate **12** and 2'-*O*-acetyl-3-decladinosyl-3-*O*-mesyl-6-*O*-methyl-9-deoxo-9-dihydro-9a-aza-9a-homoerythromycin A 9a,11-cyclic carbamate **21** were obtained. Physi-

**Table 1.** Results and physicochemical data for 3-decladinosyl 3,6-hemiketal derivatives **7-9**

| Comp. No. | R | Yield % | Molecular formula ($M_r$) | FAB-MS $m/z$ $(M+H)^+$ | IR (KBr) $\nu_{max}/cm^{-1}$ | $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$/ppm | $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$/ppm |
|---|---|---|---|---|---|---|---|
| **7** | H | 88 | $C_{30}H_{52}N_2O_{10}$ (600.74) | 601.5 | 3432, 2974, 2927, 1739, 1637, 1561, 1458, 1428, 1374, 1252, 1187, 1168, 1109, 1082, 1047, 1009, 970, 797, 765, 678 | 4.96 (H-13), 4.65 (H-10), 4.24 (H-11), 4.22 (H-1'), 3.72 (H-5), 3.53 (H-5'), 3.45 (H-9a), 3.24 (H-2'), 2.82 (H-9b), 2.49 (H-3'), 2.52 (H-2), 2.29 (3'-$NMe_2$), 2.11 (H-4), 1.91 (H-14a + H-7a), 1.75 (H-8), 1.68 (H-4'a), 1.60 (H-7b), 1.50 (H-14b), 1.40 (6-$CH_3$), 1.38 (12-$CH_3$), 1.31 (2-$CH_3$), 1.26 (4-$CH_3$), 1.24 (H-4'b), 1.22 (5'-$CH_3$), 1.14 (10-$CH_3$), 1.04 (8-$CH_3$), 0.89 (14-$CH_3$) | 175.2 (C-1), 156.0 (9a,11 C=O), 105.8 (C-1'), 103.4 (C-3), 95.0 (C-5), 84.6 (C-11), 84.4 (C-6), 78.0 (C-13), 73.9 (C-12), 69.5 (C-2'), 69.5 (C-5'), 65.3 (C-3'), 51.8 (C-10), 49.5 (C-2), 49.3 (C-4), 49.2 (C-9), 44.4 (C-7), 40.0 (3'-$NMe_2$), 28.0 (C-4'), 30.7 (C-8), 25.4 (6-$CH_3$), 23.7 (8-$CH_3$), 21.6 (C-14), 20.9 (5'-$CH_3$), 17.3 (12-$CH_3$), 13.9 (2-$CH_3$), 13.5 (4-$CH_3$), 12.4 (10-$CH_3$), 10.1 (14-$CH_3$) |
| **8** | $CH_3$ | 48 | $C_{31}H_{54}N_2O_{10}$ (614.77) | 615.5 | 3457, 2974, 2935, 2778, 1756, 1637, 1458, 1426, 1384, 1256, 1188, 1166, 1115, 1068, 1044, 1010, 969, 763, 680 | 5.01 (H-13), 4.53 (H-10), 4.35 (H-11), 4.22 (H-1'), 3.71 (H-5), 3.53 (H-5'), 3.47 (H-9a), 3.41 (12-*O*-$CH_3$), 3.24 (H-2'), 2.81 (H-9b), 2.51 (H-2), 2.48 (H-3'), 2.28 (3'-$NMe_2$), 2.10 (H-4), 1.91 (H-7a), 1.86 (H-14a), 1.72 (H-8), 1.67 (H-4'a), 1.59 (H-7b), 1.48 (H-14b), 1.40 (6-$CH_3$), 1.35 (12-$CH_3$), 1.31 (2-$CH_3$), 1.29 (H-4'a), 1.26 (4-$CH_3$), 1.22 (5'-$CH_3$), 1.15 (10-$CH_3$), 1.04 (8-$CH_3$), 0.88 (14-$CH_3$) | 175.7 (C-1), 156.5 (9a,11 C=O), 105.9 (C-1'), 103.3 (C-3), 95.1 (C-5), 83.4 (C-11), 84.4 (C-6), 76.1 (C-13), 77.6 (C-12), 69.6 (C-2'), 69.6 (C-5'), 65.4 (C-3'), 52.4 (C-10), 51.2 (12-*O*-$CH_3$), 49.6 (C-2), 49.3 (C-4), 49.3 (C-9), 44.7 (C-7), 40.1 (3'-$NMe_2$), 28.1 (C-4'), 30.7 (C-8), 25.6 (6-$CH_3$), 24.0 (8-$CH_3$), 21.9 (C-14), 21.0 (5'-$CH_3$), 14.1 (12-$CH_3$), 14.0 (2-$CH_3$), 13.4 (4-$CH_3$), 12.6 (10-$CH_3$), 10.2 (14-$CH_3$) |
| **9** | $CH_2CH_3$ | 56 | $C_{32}H_{56}N_2O_{10}$ (628.80) | 629.4 | 3496, 2975, 2936, 2881, 2786, 1759, 1630, 1458, 1427, 1384, 1331, 1255, 1189, 1167, 1116, 1066, 1011, 968, 875, 838, 763, 680 | 5.01 (H-13), 4.52 (H-10), 4.35 (H-11), 4.22 (H-1'), 3.75 (12-*O*-$CH_2$a/Et), 3.71 (H-5), 3.59 (12-*O*-$CH_2$b/Et), 3.54 (H-5'), 3.46 (H-9a), 3.25 (H-2'), 2.81 (H-9b), 2.52 (H-3'), 2.52 (H-2), 2.31 (3'-$NMe_2$), 2.09 (H-4), 1.90 (H-7a), 1.88 (H-14a), 1.73 (H-8), 1.70 (H-4'a), 1.58 (H-7b), 1.48 (H-14b), 1.39 (6-$CH_3$), 1.36 (12-$CH_3$), 1.31 (2-$CH_3$), 1.25 (4-$CH_3$), 1.24 (H-4'b), 1.22 (5'-$CH_3$), 1.15 (10-$CH_3$), 1.14 (12-*O*-$CH_3$/Et), 1.04 (8-$CH_3$), 0.88 (14-$CH_3$) | 174.4 (C-1), 155.7 (9a,11-C=O), 105.0 (C-1'), 102.4 (C-3), 94.2 (C-5), 83.5 (C-6), 83.0 (C-11), 76.7 (C-12), 75.6 (C-13), 68.7 (C-2'), 68.7 (C-5'), 64.5 (C-3'), 57.6 (12-*O*-$CH_2$/Et), 51.7 (C-10), 48.8 (C-2), 48.6 (C-4), 48.5 (C-9), 43.9 (C-7), 39.3 (3'-$Nme_2$), 30.07 (C-8), 27.5 (C-4'), 24.8 (6-$CH_3$), 23.1 (8-$CH_3$), 21.2 (C-14), 20.2 (5'-$CH_3$), 15.0 (12-*O*-$CH_3$/Et), 13.9 (12-$CH_3$), 13.2 (2-$CH_3$), 12.7 (4-$CH_3$), 11.9 (10-$CH_3$), 9.6 (14-$CH_3$) |

**Table 2.** Physicochemical data for 2'-*O*-acetyl-3-decladinosyl-3-*O*-mesyl derivatives **10-12**

| Comp. No. | Molecular formula ($M_r$) | FAB-MS $m/z$ $(M+H)^+$ | IR (KBr) $\nu_{max}/cm^{-1}$ |
|---|---|---|---|
| **10** | $C_{33}H_{58}N_2O_{13}S$ (722.89) | 723.8 | 3459, 2973, 2939, 1746, 1651, 1456, 1415, 1374, 1350, 1243, 1174, 1113, 1061, 1001, 913, 769, 701, 670 |
| **11** | $C_{34}H_{60}N_2O_{13}S$ (736.91) | 737.8 | 3458, 2974, 2935, 1747, 1637, 1460, 1414, 1374,1351, 1241, 1173, 1113, 1060, 1000, 915, 765, 707, 670 |
| **12** | $C_{35}H_{62}N_2O_{13}S$ (750.94) | 751.3 | 3444, 2973, 2934, 1747, 1644, 1462, 1416, 1373, 1351, 1244, 1174, 1116, 1060, 1000, 915, 767, 706, 672 |
| **21** | $C_{34}H_{60}N_2O_{13}S$ (736.91) | 737.8 | 3460, 2973, 2940, 1747, 1651,1456, 1413, 1374, 1355, 1243, 1171, 1110, 1061, 1001, 913, 769, 701, 676 |

cochemical data for 3-decladinosyl-3-*O*-mesyl derivatives are given in Table 2.

**Synthesis of 3-decladinosyl-3,6-cyclic ether derivatives**

*3-Decladinosyl-9-deoxo-9-dihydro-9a-aza-9a-homoerythromycin A 3,6-cyclic ether 9a,11-cyclic carbamate* **13**

To a solution of 2'-*O*-acetyl-3-decladi To a solution of 2'-O-acetyl-3-decladinosyl-3-*O*-mesyl-9-deoxo-9-dihydro-9a-aza-9a-homoerythromycin A 9a,11-cyclic carbamate **10** (1.00 g, 1.38 mmol) in DMF/THF (30 ml/10 ml) 60 % suspension of NaH in mineral oil (0.22 g, 5.53 mmol) was added and the reaction mixture was stirred at 0 °C for 4 hours. The reaction mixture was poured into saturated aqueous solution of $NaHCO_3$ (50 ml), EtOAc (50 ml) was added and the layers were separated. The aqueous layer was extracted two more times with EtOAc. Combined organic extracts were rinsed with std. $NaHCO_3$ and brine, dried over $K_2CO_3$ and evaporated yielding 0.73 g of product. The obtained product was dissolved in MeOH (60 ml) and then stirred for 24 hours at room temperature. The solvent was evaporated and the crude product was purified by chromatography on a silica gel column using the system $CH_2Cl_2$/MeOH/$NH_4OH$ (90:3:0.5). First-running (faster) diasteromer **13a** ($R_f$ = 0.28) and slower diasteromer **13b** ($R_f$ = 0.26) were separated.

Under the same conditions, starting from 2'-*O*-acetyl-3-decladinosyl-3-*O*-mesyl-12-*O*-methyl-9-deoxo-9-dihydro-9a-aza-9a-homoerythromycin A 9a,11-cyclic carbamate **11** and 2'-*O*-acetyl-3-decladinosyl-3-*O*-mesyl-12-*O*-ethyl-9-deoxo-9-dihydro-9a-aza-9a-homoerythromycin A 9a,11-cyclic carbamate **12**, the corresponding 3-decladinosyl-12-*O*-methyl-9-deoxo-9-dihydro-9a-aza-9a-homoerythromycin A 3,6-cyclic ether 9a,11-cyclic carbamate **14** and 3-decladinosyl-12-*O*-ethyl-9-deoxo-9-dihydro-9a-aza-9a-homoerythromycin A 3,6- cyclic ether 9a,11-cyclic carbamate **15** were prepared. Physicochemical data of 3,6-cyclic ether derivatives are given in Table 3.

*3-Decladinosyl-2,3-anhydro-6-O-methyl-9-deoxo-9-dihydro-9a-aza-9a-homoerythromycin A 9a,11-cyclic carbamate* **22**

Compound **22** was obtained as a white solid (0.10 g, 62 %) starting from 2'-*O*-acetyl-3-decladinosyl-3-*O*-mesyl-6-*O*-methyl-9-deoxo-9-dihydro-9a-aza-9a-homoerythromycin A 9a,11-cyclic carbamate **21** applying the same reaction conditions as described for preparation of compounds **13a, 13b, 14** and **15**. ES-MS *m*/*z*: 585.7 $(M+H)^+$; IR (KBr) $\nu_{max}$/cm$^{-1}$: 3450, 2971, 2928, 1740, 1639, 1461, 1383, 1350, 1255, 1170, 1114, 1077, 1044, 999, 974, 945, 912, 864, 767, 635; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$/ppm: 6.42 (H-2), 5.22 (H-3), 5.13 (H-13), 4.44 (H-1'), 4.26 (H-11), 3.59 (H-5'), 3.50 (H-9a), 3.41 (H-10), 3.36 (H-5), 3.30 (6-*O*-Me), 3.29 (H-2'), 2.57 (H-4), 2.52 (H-3'), 2.33 (H-8), 2.28 (H-9b), 2.26 (3'-$NMe_2$), 1.90 (H-14a), 1.61 (H-4'a), 1.52 (H-14b), 1.41 (H-7a), 1.30 (6-Me), 1.28 (10-Me), 1.26 (2-Me), 1.24 (5'-Me), 1.23 (H-4'b), 1.20 (12-Me), 1.14 (H-7b), 1.00 (4-Me), 0.98 (8-Me), 0.88 (14-Me); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$/ppm: 169.9 (C-1), 156.1 (9a,11-C=O), 146.8 (C-2), 122.9 (C-3), 104.0 (C-1'), 83.6 (C-5), 79.7 (C-6), 78.0 (C-11), 75.6 (C-13), 73.1 (C-12), 70.1 (C-2'), 69.4 (C-5'), 65.6 (C-3'), 58.4 (C-10), 50.7 (6-*O*-Me), 49.0 (C-9), 45.4 (C-4), 39.6 (3'-$NMe_2$), 36.6 (C-7), 27.9 (C-4'), 25.3 (C-8), 20.9 (5'-Me), 20.4 (6-Me), 20.0 (8-Me), 20.0 (C-14), 15.7 (2-Me), 15.2 (12-Me), 13.2 (10-Me), 10.0 (14-Me), 7.6 (4-Me).

*6-O-Methyl-9-deoxo-9-dihydro-9a-aza-9a-homoerythromycin A 9a,11-cyclic carbamate* **17**

To a solution of 6-*O*-methyl-9-deoxo-9-dihydro-9a-aza-9a-homoerythromycin A **16** (1.12 g, 1.50 mmol) in toluene (10 ml) $NaHCO_3$ (5.02 g, 59.76 mmol) was added. The reaction mixture was heated to reflux and 50 % solution of benzyloxycarbonyl chloride in toluene (7.5 ml, 22.43 mmol) was added dropwise over 1 hour and stirred for additional 3 hours at reflux. The reaction mixture was cooled, $NaHCO_3$ filtered and the suspension washed with HCl, 0.25 mol dm$^{-3}$ (2 × 10 ml). The organic layer was washed with brine (3 × 15 ml), dried over $K_2CO_3$ and evaporated yielding crude oily intermediate. The oily residue (1.20 g, 1.06 mmol) was dissolved in DMF (15 ml), cooled to 0−5 °C and then 60 % suspension of NAH in mineral oil (0.04 g, 1.00 mmol) was added portionwise during 1 hour. The reaction mixture was stirred for additional 3 hours at 0−5 °C. To the suspension saturated aqueous solution of $NaHCO_3$ (15 ml) and EtOAc (15 ml) were added and the layers were separated. The organic layer was washed with brine (3 × 15 ml), dried over $K_2CO_3$ and evaporated yielding crude oily product. To the solution of such crude product (2.2 g) in 96 % EtOH (20 ml) 10 % Pd/C (1.0 g) was added, whereas pH was adjusted to 5−6 by acetate buffer. The reaction mixture was stirred in Parr vehicle at hydrogen pressure (15 barr) at r.t. for 24 hours. Afterwards 36 % aqueous solution of formaldehyde (2 ml) was added and at the same hydrogen pressure the reaction was stirred for additional 4 hours. The catalyst was filtered, and the solvent evaporated under reduced pressure. The residue was diluted with water, the pH value adjusted to 9−10 and then extracted with $CH_2Cl_2$ (3 × 20 ml). Collected organic extracts were washed with brine (3 × 20 ml), dried over $K_2CO_3$ and evaporated yielding crude product. Purification by high pressure column chromatography using the system $CH_2Cl_2$/MeOH/$NH_4OH$ (90:3:0.3) yielded product **17** (0.6 g, 73 %) ES-MS *m*/*z*: 775.7 $(M+H)^+$; IR (KBr) $\nu_{max}$/cm$^{-1}$: 3450, 2973, 2939, 2760, 1747, 1640, 1452,

**Table 3**. Physicochemical data for 3-decladinosyl-3,6-cyclic ether derivatives **13-15**

| Comp. No. | R | Molecular formula ($M_r$) | FAB-MS $m/z$ $(M+H)^+$ | IR (KBr) $\nu_{max}/cm^{-1}$ | $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$/ppm | $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$/ppm |
|---|---|---|---|---|---|---|
| **13a** | H | $C_{30}H_{52}N_2O_9$ (584.75) | 585.7 | 3450, 2971, 2928, 1740, 1639, 1461, 1383, 1350, 1255, 1170, 1114, 1077, 1044, 999, 974, 945, 912, 864, 767, 635 | 5.00 (H-13), 4.68 (10-H), 4.30 (H-11), 4.24 (H-1'), 3.75 (H-3), 3.62 (H-5), 3.54 (H-5'), 3.43 (H-9a), 3.28 (H-2'), 2.82 (H-9b), 2.67 (H-3'), 2.51 (H-2), 2.4 (3'-$NMe_2$), 2.09 (H-4), 1.92 (H-8), 1.89 (H-14a), 1.85 (H-7a), 1.75 (H-4'a), 1.67 (H-7b), 1.50 (H-14b), 1.36 (12-$CH_3$), 1.30 (H-4'b), 1.30 (6-$CH_3$), 1.26 (4-$CH_3$), 1.26 (5'-$CH_3$), 1.22 (2-$CH_3$), 1.18 (10-$CH_3$), 1.03 (8-$CH_3$), 0.88 (14-$CH_3$) | 174.7 (1-C), 156.3 (9a,11-C=O), 103.8 (C-1'), 93.6 (C-5), 84.8 (C-6), 84.1 (C-11), 83.7 (C-3), 77.7 (C-13), 74.2 (C-12), 69.7 (C-5'), 69.5 (C-2'), 65.8 (C-3'), 52.8 (C-10), 49.8 (C-9), 48.0 (C-2), 46.3 (C-4), 44.0 (C-7), 40.4 (3'-$NMe_2$), 29.9 (C-8), 28.8 (C-4'), 23.9 (8-$CH_3$), 22.4 (6-$CH_3$), 21.8 (C-14), 21.2 (5'-$CH_3$), 19.2 (4-$CH_3$), 17.7 (12-$CH_3$), 14.8 (2-$CH_3$), 12.9 (10-$CH_3$), 10.4 (14-$CH_3$) |
| **13b** | $CH_3$ | $C_{30}H_{52}N_2O_9$ (584.75) | 585.7 | 3449, 2971, 2926, 1740, 1639, 1460, 1382, 1350, 1254, 1169, 1114, 1077, 1044, 999, 976, 945, 912, 864, 767, 636 | 4.98 (H-13), 4.43 (H-11), 4.32 (10-H), 4.23 (H-1'),4.12 (H-3), 3.60 (H-5), 3.54 (H-5'), 3.43 (H-9a), 3.28 (H-2'), 2.74 (H-2), 2.67 (H-3'), 2.59 (H-9b), 2.40 (3'-$NMe_2$), 2.16 (H-4), 2.16 (H-8), 1.89 (H-14a), 1.84 (H-7a), 1.75 (H-4'a), 1.64 (H-7b), 1.55 (H-14b), 1.30 (H-4'b), 1.30 (12-$CH_3$), 1.26 (5'-$CH_3$), 1.20 (4-$CH_3$), 1.18 (2-$CH_3$), 1.17 (10-$CH_3$), 0.99 (8-$CH_3$), 0.93 (14-$CH_3$) | 173.8 (1-C), 156.6 (9a,11-C=O), 103.7 (C-1'), 93.2 (C-5), 84.5 (C-6), 83.0 (C-3), 81.6 (C-11), 80.0 (C-13), 73.6 (C-12), 69.7 (C-5'), 69.5 (C-2'), 65.7 (C-3'), 55.2 (C-10), 50.3 (C-9), 43.2 (C-7), 42.9 (C-4), 41.2 (C-2), 40.4 (3'-$NMe_2$), 28.9 (C-8), 28.8 (C-4'), 23.3 (8-$CH_3$), 21.9 (C-14), 21.8 (6-$CH_3$), 21.2 (5'-$CH_3$), 17.3 (12-$CH_3$), 16.9 (4-$CH_3$), 13.6 (10-$CH_3$), 10.8 (14-$CH_3$), 8.8 (2-$CH_3$) |
| **14** | $CH_2CH_3$ | $C_{31}H_{54}N_2O_9$ (598.77) | 599.9 | 3443, 2956, 2926, 1752, 1639, 1462, 1385, 1365, 1255, 1169, 1114, 1076, 1035, 999, 973, 945, 912, 864, 835, 765, 635 | 5.06 (H-13), 4.63 (H-10), 4.36 (H-11), 4.20 (H-1'), 3.74 (H-3), 3.58 (H-5), 3.51 (H-5'), 3.43 (H-9a), 3.40 (12-*O*-$CH_3$), 3.21 (H-2'), 2.83 (H-9b), 2.47 (H-3'), 2.47 (H-2), 2.28 (3'-$NMe_2$), 2.07 (H-4), 1.86 (H-7a), 1.82 (H-14a), 1.78 (H-8), 1.68 (H-7b), 1.65 (H-4'a), 1.45 (H-14b), 1.33 (12-$CH_3$), 1.27 (H-4'b), 1.25 (4-$CH_3$), 1.24 (5'-$CH_3$), 1.22 (6-$CH_3$), 1.19 (2-$CH_3$), 1.14 (10-$CH_3$), 1.02 (8-$CH_3$), 0.86 (14-$CH_3$) | 175.1 (C-1), 157.1 (9a,11-C=O), 104.6 (C-1'), 94.1 (C-5), 84.8 (C-6), 84.5 (C-3), 83.3 (C-11), 78.0 (C-12), 75.9 (C-13), 70.1 (C-5'), 69.9 (C-2'), 65.9 (C-3'), 53.2 (12-*O*-$CH_3$), 53.1 (C-10), 50.0 (C-9), 47.8 (C-2), 46.5 (C-4), 44.7 (C-7), 40.6 (3'-$NMe_2$), 29.9 (C-8), 28.4 (C-4'), 24.4 (8-$CH_3$), 23.0 (6-Me), 22.4 (C-14), 21.5 (5'-$CH_3$), 19.3 (4-$CH_3$), 19.0 (12-$CH_3$), 15.1 (2-$CH_3$), 13.1 (10-$CH_3$), 10.4 (14-$CH_3$) |
| **15** | $CH_2CH_3$ | $C_{32}H_{56}N_2O_9$ (612.80) | 613.7 | 3463, 2973, 2935, 2875, 2785, 1751, 1632, 1461, 1424, 1384, 1334, 1257, 1168, 1145, 1116, 1075, 1044, 996, 959, 871, 838, 764, 673, 635 | 5.10 (H-13), 4.62 (H-10), 4.32 (H-11), 4.20 (H-1'), 3.75 (12-*O*-$CH_2$a/Et), 3.72 (H-3), 3.70 (12-*O*-$CH_2$b/Et), 3.60 (H-5), 3.52 (H-5'), 3.42 (H-9a), 3.27 (H-2'), 2.85 (H-9b), 2.58 (H-3'), 2.46 (H-2), 2.30 (3'-$NMe_2$), 2.08 (H-4), 1.85 (H-7a), 1.82 (H-14a), 1.80 (H-8), 1.75 (H-4'a), 1.63 (H-7b), 1.53 (H-14b), 1.35 (12-$CH_3$), 1.32 (H-4'b), 1.28 (5'-$CH_3$), 1.27 (4-$CH_3$), 1.25 (6-$CH_3$), 1.22 (2-$CH_3$), 1.19 (12-*O*—$CH_3$/Et), 1.15 (10-$CH_3$), 1.05 (8-$CH_3$), 0.88 (14-$CH_3$) | 174.7 (C-1), 159.9 (9a,11-C=O), 104.1 (C-1'), 93.9 (C-5), 84.4 (C-11), 83.3 (C-3), 83.1 (C-6), 77.6 (C-12), 75.9 (C-13), 69.7 (C-5'), 69.0 (C-2'), 65.6 (C-3'), 58.4 (12-*O*-$CH_2$/Et), 52.8 (C-10), 49.7 (C-9), 47.4 (C-2), 46.1 (C-4), 44.3 (C-7), 40.3 (3'-$NMe_2$), 30.0 (C-8), 28.7 (C-4'), 24.1 (8-$CH_3$), 22.7 (6-$CH_3$), 22.1 (C-14), 21.5 (5'-$CH_3$), 18.6 (4-$CH_3$), 15.9 (12-*O*—$CH_3$/Et), 15.1 (12-$CH_3$), 14.5 (2-$CH_3$), 12.9 (10-$CH_3$), 10.4 (14-$CH_3$) |

1415, 1381, 1251, 1167, 1110, 1053, 1000, 956, 894, 834, 766, 676, 636; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$/ppm: 5.11 (H-13), 4.88 (H-1''), 4.45 (H-1'), 4.32 (H-11), 4.15 (H-3), 4.06 (H-5''), 3.66 (H-10), 3.80 (H-5), 3.43 (H-5'), 3.46 (H-9a), 3.31 (3''-*O*-Me), 3.30 (6-*O*-Me), 3.27 (H-2'), 3.04 (H-4''), 2.86 (H-2), 2.52 (H-3'), 2.40 (H-9b), 2.36 (H-2''a), 2.32 (3'-$NMe_2$), 2.32 (H-8), 2.20 (H-4), 1.70 (H-4'a), 1.69 (H-14a), 1.60 (H-2''b), 1.54 (H-14b), 1.34 (6-Me), 1.31 (H-4'b), 1.30 (10-Me), 1.30 (5''-Me), 1.28 (2-Me), 1.25 (5'-Me), 1.24 (3''-Me), 1.15 (12-Me), 1.07 (4-Me), 0.93 (8-Me), 0.88 (15-Me); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$/ppm: 174.4 (C-1), 156.5 (9a,11-CO), 103.2 (C-1'), 96.3 (C-1''), 80.5 (C-3), 79.8 (C-11), 79.6 (C-5), 79.2 (C-6), 77.9 (C-4''), 75.0 (C-12), 74.5 (C-13), 73.1 (C-3''), 71.2 (C-2'), 69.0 (C-5'), 66.1 (C-5''), 65.9 (C-3'), 57.9 (C-10), 51.9 (6-*O*-Me), 49.6 (C-9), 49.6 (3''-*O*-Me), 45.1 (C-2), 40.6 (3'-$NMe_2$), 39.0 (C-4), 37.6 (C-7), 35.4 (C-2''), 28.0 (C-4'), 26.1 (C-8), 21.9 (5'-Me), 21.8 (3''-Me), 21.4 (8-Me), 20.8 (C-14), 20.0 (6-Me), 18.6 (5''-Me), 16.3 (2-Me), 14.2 (12-Me), 13.9 (10-Me), 10.7 (15-Me), 9.3 (4-Me).

*3-Decladinosyl-6-O-methyl-9-deoxo-9-dihydro-9a-aza-9a-homoerythromycin A 9a,11-cyclic carbamate* **18**

To a solution of compound **17** (0.60 g, 0.77 mmol) in 96 % ethanol (20 ml) 0.25 mol dm$^{-3}$ hydrochloric acid (≈ 50 ml) was added (pH ≈ 1) and the reaction mixture was stirred for 24 hours at r.t. Ethanol was evaporated, $CH_2Cl_2$ (20 ml) was added and the layers were separated. The pH value of the water layer was adjusted to 9.5 and then water was extracted with $CH_2Cl_2$ (3 × 30 ml). Combined organic extracts at pH 9.5 were rinsed with brine, dried over $K_2CO_3$ and evaporated yielding product **18** (0.38 g, 80 %) FAB-MS *m*/*z*: 617.6 $(M+H)^+$; IR (KBr) $\nu_{max}$/cm$^{-1}$: 3440, 2974, 2933, 2880, 2786, 1747, 1636, 1454, 1416, 1381, 1250, 1217, 1165, 1111, 1068, 1044, 1000, 947, 915, 899, 772; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$/ppm: 5.11 (H-13), 4.42 (H-1'), 4.26 (H-11), 3.78 (H-3), 3.59 (H-5'), 3.56 (H-5), 3.53 (H-9a), 3.47 (H-10), 3.32 (6-*O*-Me), 3.26 (H-2'), 2.58 (H-2), 2.50 (H-3'), 2.33 (H-8), 2.30 (H-9b), 2.26 (3'-$NMe_2$), 2.12 (H-4), 1.90 (H-14a), 1.66 (H-4'a), 1.52 (H-14b), 1.49 (H-7a), 1.30 (6-Me), 1.30 (10-Me), 1.27 (2-Me), 1.26 (5'-Me), 1.23 (H-4'b), 1.22 (12-Me), 1.10 (H-7b), 1.01 (4-Me), 1.01 (8-Me), 0.90 (15-Me); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$/ppm: 174.7 (C-1), 156.4 (9a,11-C=O), 106.0 (C-1'), 93.6 (C-5), 79.5 (C-6), 78.0 (C-11), 77.6 (C-3), 75.6 (C-13), 73.7 (C-12), 70.2 (C-2'), 69.7 (C-5'), 65.1 (C-3'), 58.4 (C-10), 51.7 (6-*O*-Me), 49.5 (C-9), 44.4 (C-2), 39.9 (3'-$NMe_2$), 36.6 (C-7), 36.,9 (C-4), 27.9 (C-4'), 25.3 (C-8), 20.9 (5'-Me), 20.4 (6-Me), 20.0 (8-Me), 20.0 (C-14), 15.7 (2-Me), 15.2 (12-Me), 13.2 (10-Me), 10.0 (15-Me), 7.6 (4-Me).

*2'-O-Acetyl-3-decladinosyl-6-O-methyl-9-deoxo-9-dihydro-9a-aza-9a-homoerythromycin A 9a,11-cyclic carbamate* **19**

To a solution of compound **18** (0.38 g, 0.62 mmol) in $CH_2Cl_2$ (20 ml), $NaHCO_3$ (0.26 g, 3.10 mmol) and acetic acid anhydride (0.10 ml, 1.06 mmol) were added and the reaction mixture was stirred for 4 hours at room temperature. When TLC indicates complete conversion saturated $NaHCO_3$ solution was added to the reaction mixture, the layers were separated and the aqueous one was extracted with $CH_2Cl_2$. The combined organic extracts were rinsed with saturated aqueous $NaHCO_3$ solution, dried over $K_2CO_3$ and evaporated yielding product **19** (0.38 g, 93 %). FAB-MS *m*/*z*: 659.7 $(M+H)^+$; IR (KBr) $\nu_{max}$/cm$^{-1}$: 3459, 2974, 2937, 2878, 2788, 1747, 1574, 1454, 1415, 1376, 1247, 1164, 1114, 1066, 1001, 947, 897, 813, 769, 667.

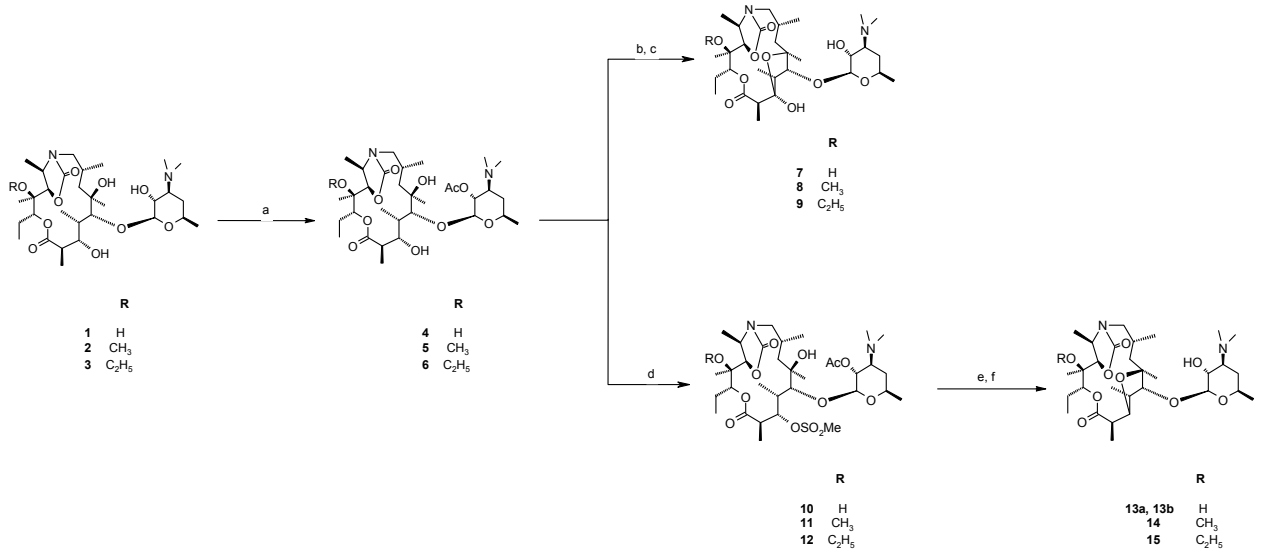
## RESULTS AND DISCUSSION

We reported[19] that 9a-benzyloxycarbonyl-9a-aza-9-deoxo-9-dihydro-9a-homoerythromycin A could be converted into 9a,11-cyclic carbamate by base-mediated intramolecular interaction between 9a-benzyloxycarbonyl and 11-hydroxyl group. Other authors observed intramolecular interaction between 3-keto and 6-hydroxyl group leading to the 3,6-hemiketal ring, [20,21] and formation of 3,6-cyclic ethers by intramolecular dehydration between 3- and 6-hydroxyl group.[22,23]

Based on these independent findings we have designed new azalide compounds with a unique tricyclic aglycone nucleus. Our synthetic strategy is shown in the Scheme 1. Starting bicyclic compounds **1-3** for both 3,6-hemiketals **7-9** and 3,6-cyclic ethers **13-15** were prepared as reported in our recent paper.[18]

After protection of 2'-hydroxyl group in **1-3** by acetic anhydride, modified Pfitzner-Moffat oxidation[24,25] afforded intermediary 3-keto derivatives (not iso-lated). Reaction was carried out with 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride, DMSO and pyridinium trifluoroacetate, followed by methanolysis of 2'-acetyl group to obtain tricyclic 3,6-hemiketals **7-9** (Scheme 1).

In the MS spectra of target compounds **7-9** the molecular ion (*m*/*z*) was in agreement with assigned structures. In the $^{13}$C NMR spectra of those compounds carbonyl carbamate signal was observed at ≈ 156 ppm.[19] The presence of 3,6-hemiketal ring in **7-9** was reflected in downfield shift of C-3 from 77.8 (**1**), 77.6 (**2**) and 78.1 (**3**) ppm,[18] to 103.4 (**7**), 103.3 (**8**) and 102.4 (**9**) ppm and downfield shift of C-6 atom from 71.5 (**1**), 73.8 (**2**) and 73.6 (**3**) ppm[18] to 84.4 (**7**), 84.4 (**8**) and 83.5 (**9**) ppm. The signal for C-3 was consistently seen as a singlet. Further, a long range correlation in HMBC




**Scheme 1.** Reagents and reaction conditions: a) $Ac_2O$, $NaHCO_3$, $CH_2Cl_2$, r.t., 4 h; b) DMSO, EDACxHCl, pyridinium trifluoroacetate, $CH_2Cl_2$, 15 °C to r.t., 2.5 h; c) MeOH, r.t., overnight; d) $(MeSO_2)_2O$, pyridine, r.t., 4 h; e) 60 % NaH, DMF/THF (3:1), 0 °C, 4h; f) MeOH, r.t., overnight.

spectra between H-2 at ≈ 2.5 ppm and C-3 at ≈ 100 ppm confirmed the presence and location of hemiketal ring. The differences in chemical shifts between the starting compounds **1-3** and the new tricyclic hemiketals **7-9** were observed for all carbon atoms included in newly formed ring (Table 1).

Intramolecular dehydration of 3- and 6-hydroxyl groups afforded 3,6-cyclic ethers **13-15** (Scheme 1). 3-Hydroxyl group was selectively activated as mesyl group and displaced by 6-alkoxy anion to give stable 5-membered 3,6-cyclic ethers.

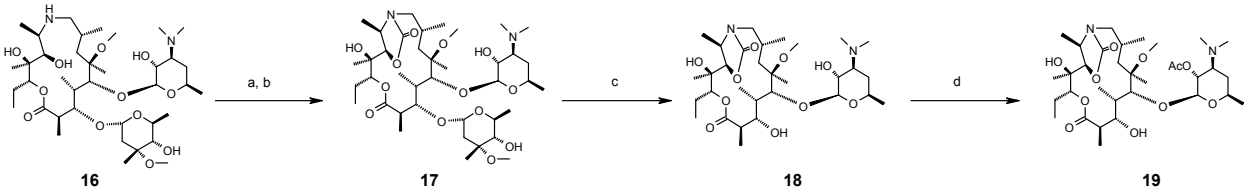
An interesting observation was made in term of stereoselectivity of ether ring closure. Namely, this reaction was stereoselective when 12-OH function of starting **2** and **3** was alkylated. However, when starting compound has free 12-OH group (compound **1)** two isomers **13a** and **13b** in a 1.8:1 ratio were obtained.

Mass spectra of the intermediary 3-*O*-mesyl azalides **10-12** reveal corresponding molecular ions, while IR spectra exhibited two characteristic bands at ≈ 1370 and 1170 $cm^{-1}$, for symmetric and asymmetric stretching vibration of $SO_2$ group. These compounds were used in the next step without further purification.

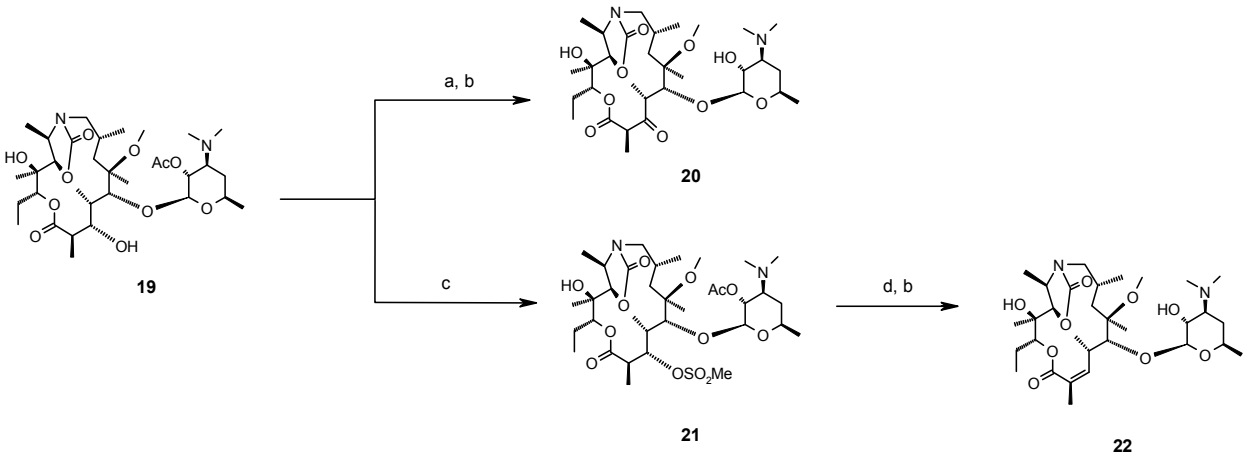
For cyclic ethers **13-15** molecular ion (*m*/*z*) corresponds the proposed structure, whereas ether bond between C-3 and C-6 position was supported by $^{13}C$ NMR chemical shifts (Table 3.). The significant downfield shift of C-3 from 77.8 (**1**), 77.6 (**2**) and 78.1 (**3**) ppm,[18] to 83.7 (**13a**), 83.0 (**13b**), 84.5 (**14**) and 83.3 (**15**) ppm and C-6 from 71.5 (**1**), 73.8 (**2**) and 73.6 (**3**) ppm[18] to 84.8 (**13a**), 84.5 (**13b**), 84.8 (**14**) and 83.1 (**15**) ppm confirmed that free hydroxyl groups are replaced by cyclic ether group.[26] Chemical shifts of neighborhood atoms are in agreement with conformational reorganizations due to new formed ring. The most intriguing result represent low diastereoselectivity in cyclization of **7** to diastereomeric mixture **13a/13b,** as compared to completely diastereoselective formation of **14** and **15.** The $^1H$ NMR spectrum of isomeric mixture revealed two sets of signals in an approximate ratio 1.8:1 with both isomers having identical masses as indicated by HPLC-MS. Assuming that **13a** and **13b** are epimers at position C-3, they had to be separated by chromatography and their NMR spectra analyzed in more details. Comparison of chemical shifts for **13a** and **13b** showed similarity of major isomer **13a** with **14** and **15**. The main differences between **13a** and **13b** isomers are, as expected, in chemical shift values at 2, 3 and 4 positions of aglycone ring. Compound **13a** exhibited signals for H-4, H-3 and H-2 at 2.09, 3.75 and 2.51 ppm, while for **13b** signals for the same hydrogens appeared at 2.16, 4.12 and 2.74 ppm, respectively (Table 3). Also there are significant differences in coupling between protons on C-2 and C-3, $^3J_{H\text{-}H}$ 9.8 Hz for **13a, 14** and **15**, as related to only 3.0 Hz for **13b**, indicating different torsion angle H-2/C-2/C-3/H-3 (Table 4). In addition, the presence of NOE

**Table 4.** Diagnostic vicinal coupling constants $^3J_{H\text{-}H}$ (Hz) for compounds **13a**, **13b**, **14** and **15** in $CDCl_3$

| | **13a** | **13b** | **14** | **15** |
|---|---|---|---|---|
| H2 / H3 | 9.8 | 3.0 | 9.7 | 9.7 |
| H3 / H4 | 7.4 | 8.8 | 7.7 | 7.3 |
| H4 / H5 | 4.1 | 4.0 | 4.9 | 4.9 |
| H10 / H11 | 6.0 | 5.8 | 5.9 | 5.9 |
| H13 / H14a | 2.3 | 2.9 | 2.4 | 2.4 |
| H13 / H14b | 10.4 | 10.3 | 10.2 | 10.2 |




**Scheme 2.** Reagents and reaction conditions: a) CBzCl, $NaHCO_3$, toluene, reflux, 4h; b) NaH, DMF, 0−5 °C, 1h; c) 2 mol $dm^{-3}$ HCl, MeOH, r.t., overnight; d) $Ac_2O$, $NaHCO_3$, $CH_2Cl_2$, r.t., 4 h.




**Scheme 3.** Reagents and reaction conditions: a) DMSO, EDACxHCl, pyridinium trifluoroacetate, $CH_2Cl_2$, 15 °C to r.t., 2.5 h; b) MeOH, r.t., overnight; c) $(MeSO_2)_2O$, pyridine, r.t., 4 h; d) 60 % NaH, DMF/THF (3:1), 0 °C, 4 h.

coupling between H-2 and H-10 protons in compounds **13a, 14** and **15** and the lack of the same in **13b** is in accordance with the proposed different spatial arrangement around C-3 atom. Moreover, carefully observation of the model for **13a** and **13b** revealed unexpectedly large difference in proximity of H-2 and H-10 in these two diasteromers, which was in accordance with the presence of strong cross peak for **13a, 14** and **15** in the NOESY spectra.

To confirm the participation of 6-OH group in both intramolecular interactions it was blocked as 6-*O*-methyl ether in compound **19**. Beckmann rearrangement of clarithromycin 9-(E)-oxime[27] gave compound **16** which was submitted to the preparation of 9a,11-cyclic carbamate structure **17**[19] followed by removal of cladinose and 2'-acetylation[18] (Scheme 2).

As expected, when methoxy instead of free hydroxyl group is placed at position 6, oxidation of 3-hydroxyl group gave 3-keto derivative **20**, while dehydration of 3-mesyl group led to 2,3-anhydro compound **22** (Scheme 3). In the $^{13}C$ NMR spectra of keto compound **20** downfield shift of C-3 atom in carbonyl region (doublet at 77.6 ppm in **18** to singlet 207.1 ppm in **20**) was observed. Also disappearance of H-3 signal indicates formation of quarternary carbonyl group. Protons in environment of 3-keto functionality in **20** are shifted downfield (H-2; $\delta$: 2.58→3.84, H-4; $\delta$: 2.12→3.20, H-5; $\delta$: 3.56→4.36 (all $\delta$ values are in ppm)) as compared to **18**.

The structure of 2,3-anhydro compound **22** was confirmed by upfield shift of C-2 and C-3 atoms as compared to compound **18** (C-2; $\delta$: 44.4→146.8, C-3; $\delta$: 77.6→122.9 (all $\delta$ values are in ppm)) as expected for double bonded C-atoms.[26] $^1H$ NMR spectra also confirmed assumed structure, signals of H-2 ($\delta$/ppm: 6.42 ppm) and H-3 ($\delta$/ppm: 5.22 ppm) are in double bond region.

## CONCLUSION

Methods for the preparation of 15-membered azalides having tricyclic aglycone were described. Due to oxidation conditions intramolecular ketalization of intermediary 3-keto derivative in 5-membered hemiketal ring was observed. Intramolecular Williamson-type of displacement gave 5-membered ether derivatives. This was an interesting observation in term of stereoselectivity of ether ring closure. Namely, this reaction was stereoselective when 12-OH function was alkylated. However,

when starting compound has free 12-OH group two diastereomers were obtained.

Although the compounds were not sufficient active against MLS-resistant bacteria their rigid, stable tricyclic structures are promising substrates for further evaluation.

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# SAŽETAK

## Sinteza i strukturna svojstva novih tricikličkih 15-eročlanih azilida


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Polazeći iz 3-dekladinozil-9a,11-cikličkog karbamata 15-eročlanih azalida sintetizirani su napeti, triciklički aglikonski derivati. Intramolekularnom ketalizacijom intermedijarnog 3-keto derivata dobiven je peteročlani hemiketalni prsten dok su peteročlani eterski derivati dobiveni intramolekularnom Wiliamsonovom reakcijom. U slučaju 12-*O*-alkil derivata formiranje etera odvija se dijastereoselektivno, dok nesupstituirani derivat daje smjesu dijastereomera. Za potvrdu struktura novih, tricikličkih azalidnih derivate korištena je NMR analiza.