Ring Opening Reactions of 6-Deoxy-9-deoxo-9a-aza-9a-homoerythromycin A 6,9-Cyclic Imino Ether

GORJANA LAZAREVSKI,* GABRIJELA KOBREHEL, BISERKA METELKO[a] and HELMUT DUDDECK[b]

PLIVA Research Institute,
10000 Zagreb, Prilaz baruna Filipovića 25, Croatia
[a]Ruđer Bošković Institute,
10000 Zagreb, Croatia
[b]Hannover University, Institute of Organic Chemistry,
Schneiderberg 1B, D-30167 Hannover, Germany

(Received for publication April 15, 1996)

Treatment of 6-deoxy-9-deoxo-9a-aza-9a-homoerythromycin A 6,9-cyclic imino ether with hydroxylamine hydrochloride led to the cleavage of the C9/9a-N imino bond with formation of C-9 oxime. Base catalyzed internal acylation of the newly introduced C-10 *primary* amino group by C-1 ester followed by catalytic hydrogenation and reductive methylation afforded a series of novel C-1 amides, the first representatives of linear 9a-azalides in which the C-10 to C-15 western fragment is inverse bound to the C-1 carbon atom.

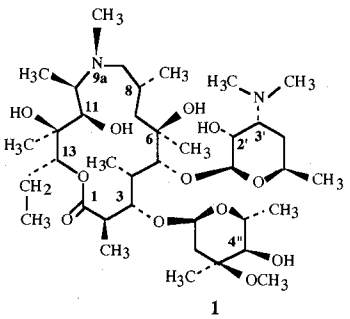
6-Deoxy-9-deoxo-9a-aza-9a-homoerythromycin A 6,9-cyclic imino ether (**3**) is an important intermediate in the synthesis of azithromycin (**1**), the first example of a new class of azalide antibiotics differing structurally from erythromycin A by an 9a-aza substituted, ring expanded, 15-membered macrocyclic framework[1,2]. The crucial step in the synthesis of **1** is the stereospecific Beckmann rearrangement of erythromycin A 9(*E*)-oxime[3]. Similar experiments with the 9(*Z*)-isomer[4] led to a series of novel 8a-aza-8a-homoerythromycin analogs. Among them, 8a-methyl derivative (**2**) was shown to exhibit *in vitro* activity equal to that of **1**.

Recently, two different types of base catalyzed ring opening reactions of erythromycin A have been reported which led to formation of the C-1 carboxylate[5]. Thus, in an aprotic solvent with strong base a retroaldol fragmentation gave a C-1 to C-10 segment which was demonstrated to play an important role in the synthesis of two linear nitrogen containing fragments[6]. Such compounds represent a new approach to the synthesis of *chimeric* 9a- and 8a-azalides which have high structural homology to potent prototypes **1** and **2** in the critical eastern half of the molecule, but which have widely varying western portions derived from an essentially unlimited number of exogenous sources[7]. This communication describes the synthesis of a new 6,9-cyclic seco oxime starting from 6,9-cyclic imino ether **3** and its conversion into novel type of linear 9a-azalide structures (Scheme 1).

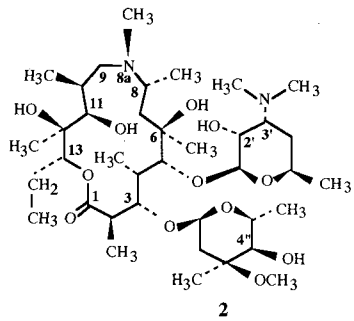
A well-known strategy for the synthesis of lactam oximes is the reaction of lactim ethers with hydroxylamine[8]. This reaction became important when the lactam oximes were found to undergo the Beckmann rearrangement yielding ureas. In the course of our efforts to prepare the lactam oxime from 6,9-cyclic imino ether **3**, we have discovered a simultaneous cleavage of C-9/9a-N double bond which leads the formation of the seco oxime (**4a**). This reaction step was accomplished in MeOH by condensation of **3** with hydroxylamine hydrochloride in the presence of Na_2CO_3 (91% yield).

FAB-MS showed the molecular ion peak at *m/z* 764 (MH^+) satisfying the proposed molecular formula $C_{37}H_{69}N_3O_{13}$. The typical absorption at 1580 cm^{-1} in the IR spectrum and the positive color obtained from the reaction with ninhydrin suggested the presence of the amino functional group. The shieldings observed for both the 10-H proton (−0.69 ppm) and C-10 carbon signals (−6.0 ppm) in the ^1H and ^{13}C NMR spectra of **4a** with respect to **3**[9] indicated that this group may be attached to the C-10 carbon. The hydroxyimino proton at C-9 (δ_H=9.33, D_2O exchangeable) was deduced from ^1H NMR in DMSO-d_6 and significant change of ^{13}C chemical shifts for C-9 (−2.6 ppm) and C-8 (−3.2 ppm). Further examination of the ^1H NMR data showed that apart from a change of some coupling constants ($^3J_{2,3}$ 2.4→1.9, $^3J_{4,5}$ 7.3→8.3, $^3J_{10,11}$ 10.1→2.7 Hz) and the deshielded 3-H proton resonance (+0.68 ppm) which indicated a different conformation, the shift values for both **3** and **4a** are very similar. These results implied

Chart 1



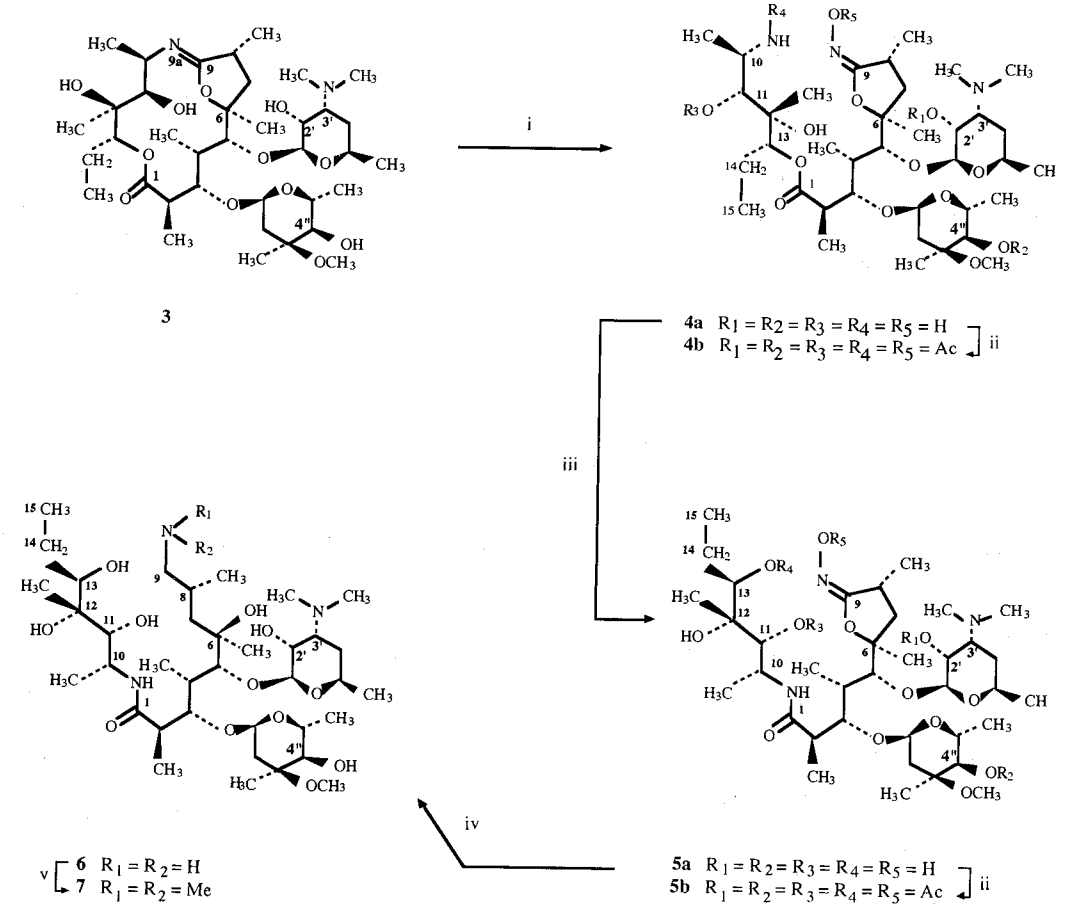
1



2

This article is dedicated to the memory of Dr. SLOBODAN ĐOKIĆ.

Scheme 1. Synthetic pathways of **4a**~**7**.



Reagents: i) NH_2OH, Na_2CO_3, MeOH; ii) Ac_2O, Py; iii) basic solution; iv) PtO_2, H_2, AcOH; v) HCOH, HCOOH, $CHCl_3$.

the rupture of the 15-membered macrocyclic ring between C-10 and 9a-N centers giving an unexpected seco derivative with the oxyimino function at C-9 and the terminal amino group at C-10. Consequently, the acetylation of **4a** (Ac_2O, Py, 7 days, RT) afforded the expected pentaacetate (**4b**) which in the ^1H NMR spectrum revealed five acetyl signals at $\delta_H = 2.16$, 2.13, 2.12, 2.05 and 1.96. The considerable deshielding of the 10-H signal ($\delta_H = 3.05 \rightarrow 4.48$), which was correlated with the resonance at $\delta_H = 6.15$ in the ^1H-^1H COSY experiment, confirmed the presence of a new amido group at C-10. The deshieldings of 2′-H ($\delta_H = 3.21 \rightarrow 4.81$), 4″-H ($\delta_H = 3.04 \rightarrow 4.69$), 11-H proton ($\delta_H = 3.49 \rightarrow 4.67$) and C-9 ($\delta_C = 163.7 \rightarrow 167.4$) carbon resonances compared to those of **4a**, clearly show that **4b** is 2′,4″,11-*O*,10-*N*-tetraacetyl-9-deoxo-6-deoxy-6,9-epoxy-8(*R*)-methyl-10-amino-9,10-secoerythromycin A 9(*E*)-acetoxime.

During the purification by column chromatography on silica gel with $CHCl_3$ - MeOH - NH_4OH, 6 : 1 : 0.1 as the solvent, **4a** was found to be converted quantitatively to (**5a**). The same compound was also formed when **4a** was kept under basic conditions at room temperature. The structural assignment of **5a** was based on the following chemical and spectral evidence. FAB-MS showed the molecular ion peak at *m/z* 764 (MH^+) which was identical with that of **4a**. The IR spectrum showed new amide absorptions at 1650 and 1530 cm^{-1} and loss of ester and amine bands at 1720 and 1580 cm^{-1}, respectively. Further, the new signal at $\delta_H = 7.53$ in the ^1H NMR spectrum attributed to an amide proton, gave a cross peak with 10-H signal in the 2D homonuclear COSY spectrum†. As compared to **4a**, the deshielding of 10-H (+1.06 ppm), typical for acylation of an amino group, together with concomitant shielding of 13-H (−1.56 ppm) and the more deshielded C-13 carbon (+4.9 ppm), led us to the hypothesis of a base-induced intramolecular transacylation between C-10 primary amino group and C-1 ester causing the inversion of a C-10 to C-15 western portion of the molecule. Therefore, the new amide group is attached to the C-1 carbon in **5a**. This explanation is supported by a long-range correlation between C-1 and proton signal 13-H in the COLOC spectrum of **4a**, a connectivity which was absent in the corresponding spectrum of **5a**. Additional evidence

† The numbering system of the C-10 to C-15 fragment after the inversion in seco amides **5a**~**7** is the same as that in **3**.

Table 1. Characteristic ^1H (300 MHz, in $CDCl_3$) and ^{13}C (75 MHz, in $CDCl_3$) NMR data for the seco compounds **4a**~**7**.

Position[a]	δ_H (ppm)					δ_C (ppm)				
	3	**4a**	**5a**	**6**	**7**	**3**	**4a**	**5a**	**6**	**7**
1						178.1	175.5	174.4	174.1	174.7
2	2.73	2.84	2.53	2.52	2.57	44.3	43.4	42.8	41.6	41.7
3	3.92	4.60	4.20	4.26	4.27	76.3	76.7	79.8	79.7	79.8
4	1.88	1.82	1.97	2.01	2.16	42.8	39.7	38.6	37.5	37.3
5	3.93	3.90	3.66	3.41	3.41	79.0	81.9	86.3	92.3	90.5
6						87.7	88.5	90.3	74.6	73.7
7a	2.01	2.08	2.10	2.20	1.50					
7b	1.57	1.88	1.79	1.34	1.15	36.9	39.5	41.0	42.8	44.2
8	2.80	2.92	3.04	1.85	2.01	35.1	31.9	32.9	31.0	26.4
9a				2.62	2.52					
9b				ND	2.20	163.7	161.1	162.0	49.1	68.2
10	3.74	3.05	4.11	4.17	4.18	52.7	46.7	48.6	49.2	48.6
11	3.67	3.49	3.79	3.76	3.77	72.0	72.5	75.1	74.8	74.6
12						75.1	73.5	74.9	75.1	74.8
13	4.94	4.78	3.22	3.17	3.18	77.6	78.1	83.0	83.8	83.3
14a	1.89	1.87	1.59	1.55	1.56					
14b	1.48	1.51	1.33	1.34	1.37	21.5	21.3	24.8	25.0	24.9
15	0.89	0.87	1.04	1.05	1.04	11.1	10.6	11.5	11.5	11.5
16	1.19	1.28	1.12	1.10	1.09	13.1	11.0	9.9	8.6	11.4
17	1.12	1.17	1.10	1.07	1.09	9.2	10.7	10.9	10.7	8.2
18	1.43	1.58	1.52	1.30	1.31	25.8	24.8	23.9	23.6	25.2
19	1.21	1.22	1.23	1.01	0.98	18.3	18.1	15.8	20.6	21.3
20	1.26	1.18	1.25	1.25	1.24	16.6	15.8	15.6	16.1	15.7
21	1.09	1.06	1.14	1.14	1.13	17.6	17.1	21.1	21.6	21.3
9aNMe					2.27					45.3
CONH			7.53	7.52	7.26					

[a] The numbering system of the C-10~C-15 fragment after the inversion in seco amides **5a**~**7** is the same as that in **3**.

for the proposed structure of 6,9-cyclic seco oxime **5a** was obtained by acetylation giving (**5b**). The location of five acetyl groups (δ_H=2.15, 2.12, 2.12, 2.06 and 2.01) was pointed out by the deshieldings of 2'-H (δ_H=3.37→4.80), 4''-H (δ_H=2.96→4.69), 11-H (δ_H=3.79→4.55), 13-H δ_H=(3.22→4.94) proton and C-9 (δ_C=162.0→167.2) carbon signals.

6,9-Cyclic seco oxime **5a** was unreactive towards sodium borohydride in methanol or high pressure hydrogenation using Pt/C in 96% ethanol. However, the catalytic reduction of **5a** using PtO_2 in acetic acid under 7×10^6 Pa H_2 for 10 hours produced the 9a-aza linear azalide (**6**) in 73% yield. The amine **6** was methylated under Eschweiler-Clark conditions to give the 9a-dimethyl derivative (**7**) (61% yield). The structures of **6** and **7** were determined by 2D NMR including COSY, HMQC and HMQC-TOCSY spectra and ultimately confirmed by FAB-MS giving the expected molecular ions at *m/z* 752 and 780, respectively. The ^1H and ^{13}C NMR chemical shifts for seco azalides **4a**~**7** are summarized in Table 1.

In summary, the ring opening reaction of 6,9-cyclic imino ether **3** with hydroxylamine is an efficient method for the synthesis of 9a-aza seco azalides with inversion of C-10 to C-15 western fragment, potential intermediates for new azalide antibiotics.

Acknowledgments

This work was supported in part by a grant from The Ministry of Science, Technology and Informatics, Republic of Croatia, project number 1-07-035 and the Fonds der Chemischen Industrie. We wish to thank Mrs. J. IVETIĆ for technical assistance.

References

1) ĐOKIĆ, S.; G. KOBREHEL, N. LOPOTAR, B. KAMENAR, A. NAGL & D. MRVOŠ: Erythromycin series. Part 13. Synthesis and structure elucidation of 10-dihydro-10-deoxo-11-methyl-11-azaerythromycin A. J. Chem. Research (S) 1988: 152~153, 1988

2) BRIGHT, G. M.; A. A. NAGL, J. BORDNER, K. A. DESAI, J. N. DIIBRINO, J. NOWAKOWSKA, L. VINCENT, R. M. WATROUS, F. C. SCIAVOLINO, A. R. ENGLISH, J. A. RETSEMA, M. R. ANDERSON, L. A. BRENAN, R. J. BOROVOY, C. R. CIMOCHOWSKI, J. A. FAIELLA, A. E. GIRARD, D. GIRARD, C. HERBERT, M. MANOUS & R. MASON: Synthesis, *in vitro* and *in vivo* activity of novel 9-deoxo-9a-aza-9a-homoerythromycin A derivatives; A new class of macrolide antibiotics, the azalides. J. Antibiotics 41: 1029~1047, 1988

3) ĐOKIĆ, S.; G. KOBREHEL, G. LAZAREVSKI, N. LOPOTAR, Z. TAMBURAŠEV, B. KAMENAR, A. NAGL & I. VICKOVIĆ: Erythromycin series. Part 11. Ring expansion of erythromycin A oxime by the Beckmann rearrangement.

J. Chem. Soc., Perkin Trans I 1986: 1881～1890, 1986

4) WILKENING, R. R.; R. W. RATCLIFFE, G. A. DOSS, K. F. BARTIZAL, A. C. GRAHAM & C. M. HERBERT: Synthesis of novel 8a-aza-8a-homoerythromycin derivatives *via* Beckmann rearrangement of (9*Z*)-erythromycin A oxime. BioMed. Chem. Lett. 3: 1287～1292, 1993

5) WADDELL S. T. & T. A. BLIZAZARD: Base catalyzed ring opening reactions of erythromycin A. Tetrahedron Lett. 33: 7827～7830, 1992

6) WADDELL, S. T. & T. A. BLIZAZARD: Semisynthesis of linear fragments corresponding to the eastern portion of azalide antibiotics. BioMed. Chem. Lett. 3: 1757～1760, 1993

7) WADDELL, S. T. & T. A. BLIZAZARD: Chimeric azalides with simplified western portions. Tetrahedron Lett. 34: 5385～5388, 1993

8) GLUSKOV, R. G. & V. G. GRANIK: The chemistry of lactim ethers. *In* Advances in heterocyclic chemistry. *Ed.*, A. R. KATRIZKY & A. J. BOULTON, pp. 194～212, Academic Press N.Y. & London, 12: 1970

9) LAZAREVSKI, G.; M. VINKOVIĆ, G. KOBREHEL, S. ĐOKIĆ & B. METELKO: Conformational analysis of 9-deoxo-9a-aza-9a- and 9-deoxo-8a-aza-8a-homoerythromycin A 6,9- cyclic imino ethers. Tetrahedron 50: 12201～12210, 1994