Acid Catalyzed Ring Opening Reactions of 6-Deoxy-9-deoxo-9a-aza-9a-homo-erythromycin A 6,9-Cyclic Imino Ether

GORJANA LAZAREVSKI,* GABRIJELA KOBREHEL, AMALIJA NARANĐA, ZRINKA BANIĆ-TOMIŠIĆ and BISERKA METELKO†

PLIVA Research Institute, Antiinfectives, 10000 Zagreb, Prilaz baruna Filipovića 25, Croatia
†Ruđer Bošković Institute, 10000 Zagreb, Bijenička cesta 54, Croatia

(Received for publication May 14, 1998)

In recent years, there has been growing interest in ring opening reactions of the macrolide antibiotic erythromycin A leading to the synthesis of *chimeric* 9a- and 8a-azalides[1] which are structurally homologous to their potent prototypes azithromycin[2,3] and its 8a-isomer[4] in their critical eastern halves of the molecule but are functionally simplified in the left-hand part of the 15-membered macrocyclic ring. As part of our program in this area we have recently reported the synthesis of 6,9-cyclic *seco* oxime (**2**)[5] starting from 6,9-cyclic imino ether (**1**)[6], the key intermediate in the synthesis of azithromycin. Base catalyzed internal acylation of **2** followed by reduction and *N*-methylation afforded a series of linear C-1 amides in which the C-10～C-15 fragment was inversely bound to the C-1 carbon atom. This paper is concerned with the acid catalyzed hydrolysis of **1** and the synthesis of novel *seco* macrolides with C-1 amido group, potential intermediates for new macrolide antibiotics.

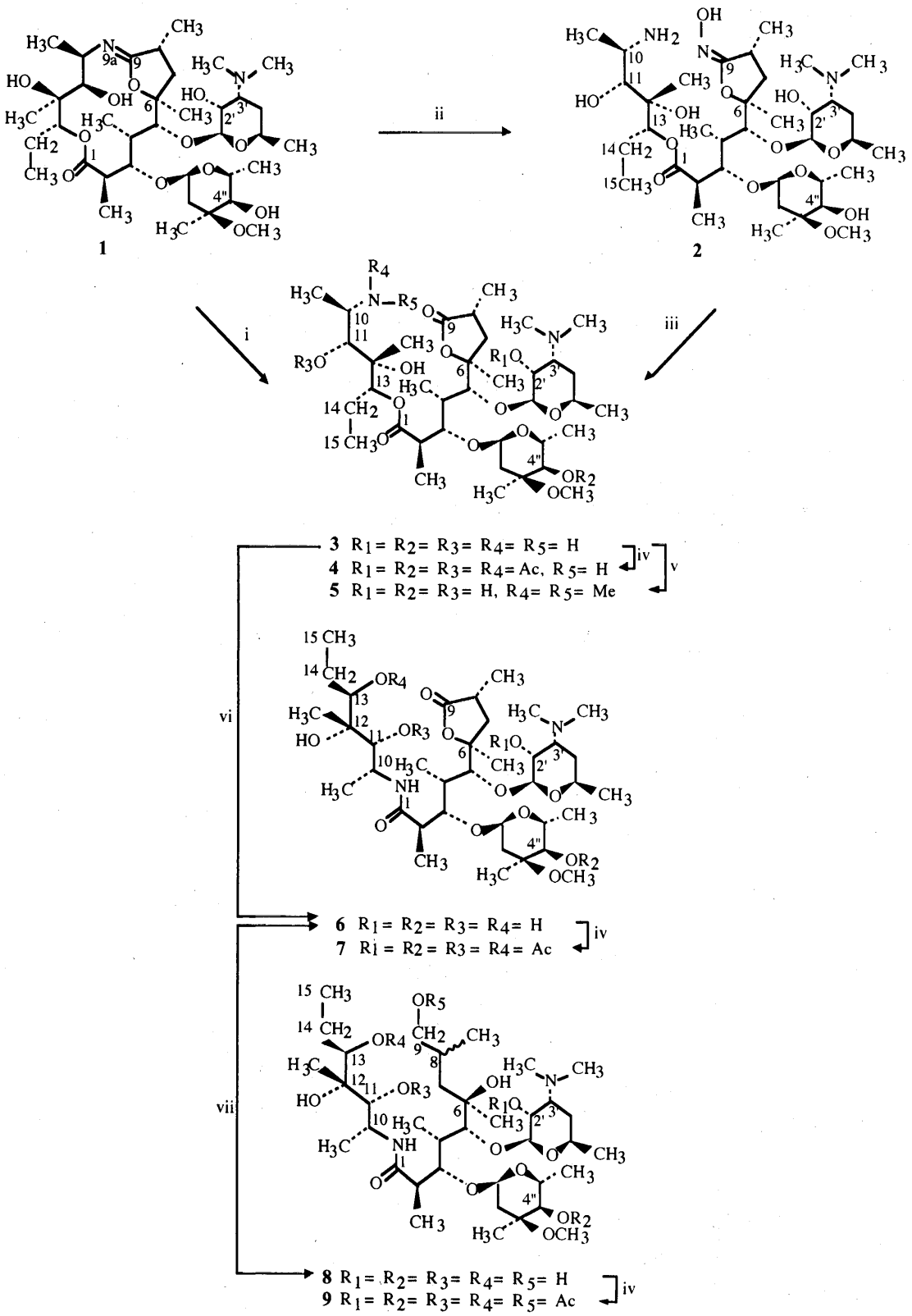
Compounds containing carbon-nitrogen double bonds can be easily hydrolyzed to the corresponding aldehydes or ketones[7]. Acid catalyzed hydrolysis of C-9/9a-N double bond of **1** (AcOH, 3 days, RT) led to the formation of compound (**3**). The molecular formula of **3** was

Table 1. Characteristic ^1H (300 MHz, in $CDCl_3$) and ^{13}C (75 MHz, in $CDCl_3$) NMR data for the novel *seco* compounds **3**～**8b**.

Position[a]	δ_H (ppm)						δ_C (ppm)					
	1	**3**	**5**	**6**	**8a**	**8b**	**1**	**3**	**5**	**6**	**8a**	**8b**
1	—	—	—	—	—	—	178.1	179.6	179.5	174.5	173.4	173.6
2	2.73	2.72	2.47	2.46	2.50	2.50	44.3	43.2	42.5	42.6	41.3	41.9
3	3.92	4.18	4.15	4.19	4.23	4.25	76.3	77.9	76.7	79.5	80.1	78.9
4	1.88	2.00	2.04	2.00	1.95	1.93	42.8	39.7	39.2	38.5	37.4	37.4
5	3.93	3.74	3.71	3.65	3.41	3.70	79.0	81.2	82.1	86.2	92.5	91.2
6	—	—	—	—	—	—	87.7	86.1	85.7	86.4	75.0	75.5
7a	2.01	2.22	2.89	2.20	ND	1.74						
7b	1.57	2.10	2.13	1.98	1.40	1.64	36.9	38.0	37.6	39.1	44.1	46.7
8	2.80	2.76	2.75	2.79	2.09	1.74	35.1	34.1	33.9	34.2	31.0	32.0
9a	—	—	—	—	3.60	3.48						
9b	—	—	—	—	3.27	3.29	163.7	176.1	175.6	179.4	69.0	69.4
10	3.74	3.16	3.08	4.11	4.17	4.22	52.7	47.9	59.8	48.8	49.0	49.7
10-NMe_2	—	—	2.25	—	—	—	—	—	40.1	—	—	—
11	3.67	3.35	3.37	3.80	3.76	3.74	72.0	72.7	76.7	75.2	74.7	75.1
12	—	—	—	—	—	—	75.1	74.5	74.8	74.9	74.6	74.8
13	4.94	5.00	5.06	3.20	3.19	3.14	77.6	78.8	77.5	83.3	83.7	84.5
14a	1.89	1.85	2.00	1.59	1.57	1.56						
14b	1.48	1.55	1.54	1.35	1.36	1.36	21.5	22.2	22.5	25.0	24.7	24.9
15	0.89	0.88	0.87	1.05	1.05	1.05	11.1	11.6	10.6	11.6	11.3	11.4
2-Me	1.19	1.23	1.18	1.11	1.09	1.11	13.1	18.0	11.7	9.9	8.4	8.1
4-Me	1.12	1.18	1.11	1.10	1.06	1.07	9.2	10.0	10.6	11.0	10.1	10.1
6-Me	1.43	1.55	1.52	1.55	1.33	1.34	25.8	25.1	24.7	23.8	22.1	26.2
8-Me	1.21	1.22	1.27	1.28	0.95	0.89	18.3	12.3	14.8	14.9	20.0	19.6
10-Me	1.26	1.16	1.01	1.26	1.25	1.25	16.6	19.0	7.9	15.7	16.0	16.7
12-Me	1.09	1.19	1.22	1.14	1.14	1.15	17.6	15.1	20.7	21.3	21.4	21.9
CONH	—	—	—	7.45	7.57	7.63	—	—	—	—	—	—

[a] The numbering system of the C-10～C-15 fragment after the inversion in *seco* amides **5**, **6** and **8** is the same as that in **1**.

Scheme 1.



Reagents: i) AcOH, 3 days, RT; ii) NH_2OH, Na_2CO_3, MeOH; iii) 1 N HCl/MeOH, 10 days, RT; iv) Ac_2O, Py; v) 37% aq. HCHO/HCOOH, $CHCl_3$, reflux; vi) Me_2CO/H_2O, 2 hours, 50°C; vii) $NaBH_4$, *t*-BuOH, reflux, 7 hours H_2, AcOH.

established as $C_{37}H_{64}N_2O_{13}$ on the basis of IR, FAB-MS (*m/z* 749, $[M+H]^+$) and NMR spectral analysis (Table 1). The strong absorptions at 1740 and 1710 cm^{-1} in the IR spectrum, together with two singlets at δ_C 179.6 (C-1) and δ_C 176.1 (C-9) in its DEPT spectrum, suggested the presence of two carbonyl groups in **3**. The observed deshielding of C-9 in the ^{13}C NMR spectrum of **3** with respect to **1** and the assignment of the non-protonated C-6 carbon at δ_C 86.1, typical for the five-membered ring formation in the aglycon skeleton of erythromycin A,[8] implied the connection of C-9 to C-6 with formation of a γ-lactone. Since the hydrolysis of carbon-nitrogen double bond involves initial addition of water and elimination of a nitrogen moiety, the structure of **3** was suggested to be as shown in Scheme 1. The IR absorption at 1590 cm^{-1}, and the shielding of both the 10-H and C-10 signals in the ^1H and ^{13}C NMR spectra, revealed the presence of the amino group at C-10. The acetylation of **3** (Ac_2O, Py, 7 days, RT) gave tetraacetate (**4**) with additional singlets at δ_H 2.15, 2.12, 2.05 and 1.96 and an amide doublet at δ_H 6.35 in the ^1H spectrum. The deshielding of 2′-H (δ_H 3.22→4.79), 4″-H (δ_H 3.00→4.35), 11-H (δ_H 3.35→4.68) and 10-H protons (δ_H 3.16→4.44) together with the connection of 10-H methyne proton to amide NH in the ^1H-^1H COSY experiment, provided convincing evidence for the presence of a C-10 amine. Compound **3** was also obtained by acid catalyzed hydrolysis of C-9 hydroxyimino bond of oxime **2** (1 N HCl/MeOH, 10 days, RT).

The reductive methylation of **3** (37% aq. HCHO/HCOOH, $CHCl_3$, reflux) gave almost exclusively compound (**5**) with new signals at δ_H 2.25 and at δ_C 40.1 in its NMR spectra corresponding to the newly introduced dimethylamino group. The lower field ^{13}C chemical shifts of C-10 and C-11, together with shielding of C-10 Me supported the methylation of the C-10 amine.

Intramolecular transacylation of the C-10 amino group by the C-1 ester of **3** (Me_2CO/H_2O, 2 hours, 50°C) produced (**6**) in 89% yield. Based on IR (1660 and 1540 cm^{-1}, CO amide), FAB-MS (*m/z* 749, $[M+H]^+$) and NMR data[††] including ^1H-^1H COSY, ^{13}C-^1H COSY, COLOC, HMQC and HMQC-TOCSY experiments, the inversion of the C-10～C-15 western segment was established. The amide carbonyl carbon at C-1 (δ_C 174.5) was long-range coupled to 2-Me (δ_H 1.11) and amide NH (δ_H 7.45); the latter was further correlated with the adjacent carbon at δ_C 48.8 (C-10). In addition, the low-field chemical shifts of 10-H and C-13 and shielding of 13-H supported inversion of the left-hand part of the molecule. Acetylation of **6** gave the expected tetraacetate (**7**) [^1H NMR (300 MHz, $CDCl_3$) δ 6.87 (CO*NH*), 4.86 (H-11), 4.76 (H-2′), 4.81 (H-13), 4.66 (H-4″), 4.43 (H-10), 3.95 (H-3), 2.23 (H-2), 2.15, 2.07, 2.05 and 2.03 ($COCH_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.8 (C-9), 173.7 (C-1), 170.3, 170.3, 170.1 and 169.6 ($COCH_3$), 85.5 (C-6), 78.6 (C-4″), 78.1 (C-3), 76.8 (C-13), 76.0 (C-11), 45.1 (C-10), 44.7 (C-2), 21.0, 20.7, 20.6 and 20.5 ($COCH_3$)]. Selective reduction of **6** ($NaBH_4$, *t*-BuOH, reflux, 7 hours) produced linear C-9 alcohols (**8a**) and (**8b**), as an approximately 1:3 mixture of stereoisomers. The epimeric alcohols were separated by silica-gel chromatography using solvent system EtAc-(*n*-hexane)-Et_2NH, 10:10:2. The structures of **8a** and **8b** were deduced from IR and NMR data. The absence of an IR absorption at 1770 cm^{-1} and the appearance of the new methylene protons at δ_H 3.60 (H-9a) and 3.27 (H-9b) in the ^1H NMR spectrum of **8a** or at δ_H 3.48 (H-9a) and 3.29 (H-9b) in the corresponding spectrum of **8b**, was in agreement with reduction of C-9 lactone. The upfield chemical shift of the C-9 singlet to the new triplets in ^{13}C analysis additionally confirmed the presence of the C-9 methyl group. Differences in chemical shifts of the C-7 methylene and the C-6 Me group in the ^{13}C and 7b-H, 8-H and 9a-H in the ^1H NMR spectra indicated C-8 as the most likely site of epimerization. In **8b** the observed upfield shift of 8-H and downfield shift of 5-H with respect to **8a** were similar to those found for 8(*R*)-methyl- and 8(*S*)-methylerythronolides B[9] suggesting for **8b** 8(*R*)- and for **8a** 8(*S*)-configurations. Acetylation of **8b** with the excess of acetic anhydride gave the expected pentaacetate (**9**) confirming the presence of the additional hydroxyl group at C-9. [^1H NMR (300 MHz, $CDCl_3$) δ 6.53 (CO*NH*), 4.94 (H-13), 4.83 (H-2′), 4.65 (H-4″), 4.57 (H-11), 2.13, 2.12, 2.07, 2.05 and 2.02 ($COCH_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.0, 171.2, 170.4, 170.2 and 169.8 ($COCH_3$), 78.9 (C-11), 78.1 (C-4″), 75.6 (C-13), 71.2 (C-2′), 62.6 (C-3′), 45.0 (C-10), 40.2 (C-7), 27.7 (C-8), 20.9 (C-14), 20.7, 20.7, 20.6, 20.5 and 20.4 ($COCH_3$)].

Acknowledgements

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. We wish to thank Mrs. J. IVETIĆ for technical assistance.

†† The numbering system of the C-10～C-15 fragment after the inversion in *seco* amides **6**～**9** is the same as that in **1**.

References

1) WADDELL, S. T. & T. A. BLIZAZARD: Chimeric azalides with simplified western portions. Tetrahedron Lett. 34: 5385~5388, 1993
2) 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
3) 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
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. Bio. Med. Chem. Lett. 3: 1287~1292, 1993
5) LAZAREVSKI, G.; G. KOBREHEL, B. METELKO & H. DUDDECK: Ring opening reactions of 6-deoxy-9-deoxo-9a-aza-9a-homoerythromycin A 6,9-cyclic imino ether. J. Antibiotics 49: 1066~1069, 1996
6) 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
7) Addition to carbon-hetero multiple bonds. *In* Advanced organic chemistry. Reactions, mechanisms, and structure. 3rd *Ed.*, J. MARCH, pp. 780~872, John Wiley and Sons, Inc., 1985
8) NOURSE, J. G. & J. D. ROBERTS: Nuclear magnetic resonance spectroscopy. Carbon-13 spectra of some macrolide antibiotics. Substituent and conformational effects. J. Am. Chem. Soc. 97: 4584~4594, 1975
9) MARTIN, J. R.; R. S. EGAN, T. J. PERUN & A. W. GOLDSTEIN: 8-*Epi*-erythronolide A and its metabolic fate in fermentations of *Streptomyces erythreus*. Tetrahedron 29: 935~940, 1973