Pergamon

Tetrahedron Letters, Vol. 37, No. 6, pp. 787-790, 1996

0040-4039/96 $15.00 + 0.00

0040-4039(95)02392-5

Novel Macrolides *via* *meso*-Tetraarylmetalloporphyrin Assisted Oxidations

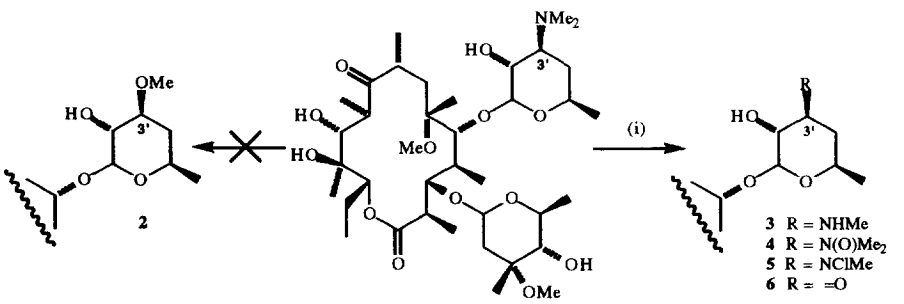
David R. Hill*,†, Joseph E. Celebuski†, Richard J. Pariza†,[1], Mukund S. Chorghade†,[1], Milton Levenberg‡, Thomas Pagano‡, George Cleary‡, Paul West‡, David Whittern‡.

† *Chemical and Agricultural Products Division, Abbott Laboratories, North Chicago, IL 60064-4000 USA*
‡ *Pharmaceutical Products Division, Abbott Laboratories, Abbott Park, IL 60064-3500 USA*

Abstract: The oxidation of Clarithromycin A with *meso*-tetraarylmetalloporphyrins and NaOCl led to the formation of the 3'-NClMe Clarithromycin A (**5**) 3'-oxo Clarithromycin (**6**) and Clarithromycin A N-oxide (**4**).

Synthetic metalloporphyrins have been shown to mimic cytochrome P-450 systems in their ability to mediate selective oxidations.[2] Hydroxylation, epoxidation and N-demethylation are among the most commonly observed transformations in both the synthetic[3] and enzymatic systems.[4,5] It was recently reported[6] that the replacement of the dimethylamino (NMe_2) moiety with a methoxy group in the desosamine sugar of various macrolide derivatives could be accomplished by metalloporphyrin mediated oxidations. Further investigation proved that the dimethylamino moiety is not replaced with a methoxy group. We now report on a detailed study of this reaction.

Our investigations of the oxidation of Clarithromycin A (**1**) with various synthetic metalloporphyrins show that the reaction products are not limited to those expected from simple oxidation nor are they a result of methoxy group incorporation. Instead, Clarithromycin A N-oxide (**4**) and 3'-NClMe Clarithromycin A (**5**) are formed together with 3'-oxo Clarithromycin A (**6**) (Scheme 1).



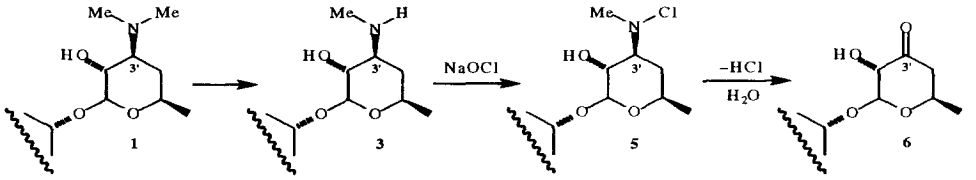
Conditions: (i) FeTPPCl$_8$βCl$_8$(SO$_3$H)$_4$ or FeTPPCl$_8$βBr$_8$, 5.25% NaOCl, CH_2Cl_2, r.t.

Scheme 1: Oxidation of Clarithromycin A.

To establish whether Clarithromycin A N-oxide (**4**) was a reaction intermediate or by-product, authentic Clarithromycin A N-oxide (**4**) was treated with octachloro-β-octachloro tetraphenylporphyrin Fe(III) tetrasulfonic acid[7] ($FeTPPCl_8\beta Cl_8(SO_3H)_4$) and NaOCl in an identical manner to that described for Clarithromycin A. No reaction took place and the N-oxide (**4**) was quantitatively recovered. Thus, Clarithromycin A N-oxide is *not* involved in the formation of (**5**) and (**6**) and is merely a reaction by-product.

A possible mechanism accounting for the formation of the new derivatives (**5**) and (**6**) is outlined in Scheme 2. Clarithromycin A (**1**) initially undergoes N-demethylation to give 3'-NHMe Clarithromycin (**3**). The excess NaOCl present chlorinates 3'-NHMe Clarithromycin (**3**) to the 3'-NClMe Clarithromycin (**5**) which may then undergo elimination of HCl and subsequent hydrolysis to furnish the 3'-oxo derivative (**6**). In a separate experiment, authentic 3'-NHMe Clarithromycin A (**3**)[8] was quantitatively transformed into (**5**) upon exposure to excess NaOCl.

In another control experiment, Clarithromycin A (**1**) was treated with NaOCl in the absence of metalloporphyrin. This reaction was rather slow, reaching only partial conversion in 2 days with multiple additions of NaOCl. Nevertheless, Clarithromycin A N-oxide (**4**) and 3'-NClMe Clarithromycin (**5**) were both formed as evidenced by TLC analysis, indicating that the metalloporphyrin is largely responsible only for reaction catalysis.



Scheme 2: Proposed mechanism for the formation of 3'-NClMe and 3'-oxo Clarithromycin A

In a typical experiment: A solution of Clarithromycin A (2.24g; 3.0 mmol) in CH_2Cl_2 (30 mL) was treated with $FeTPPCl_8\beta Cl_8(SO_3H)_4$ (4mg), 5.25% NaOCl (4.65g; 3.3 mmol) and pyridine (25μL) and the reaction mixture was stirred at r.t. with periodic repeat charges of $FeTPPCl_8\beta Cl_8(SO_3H)_4$ and NaOCl until the starting material was consumed (1 day). Water (30mL) was added and the mixture stirred for 10 min. The organic layer was separated, dried (Na_2SO_4) and evaporated *in vacuo*. The crude was chromatographed (SiO_2) using ethyl acetate then $CHCl_3$(80):MeOH(20):NH_4OH(2), giving 3'-NClMe Clarithromycin A (**5**) (0.46g; 21%), 3'-oxo Clarithromycin A (**6**) (0.43g ; 20%), and Clarithromycin A N-oxide (**4**) (1.02g; 45%). All new compounds gave NMR, IR, mass spectral and elemental analysis data which are consistent with the proposed structures. Representative data for (**4**), (**5**) and (**6**) is given below:

3'-NClMe Clarithromycin A (5): ^1H NMR (500MHz, $CDCl_3$) δ: 5.06 (1H, dd, H13), 4.92 (1H, dd, H1"), 4.47 (1H, d, H1'), 3.99 (1H, dq, H5"), 3.77 (1H, dd, H3), 3.76 (1H, d, H11), 3.68 (1H, d, H5), 3.55 (1H, dqd, H5'), 3.43 (1H, dd, H2'), 3.31 (3H, s, 3"OCH_3), 3.03 (3H, s, 6OCH_3), 3.03 (1H, m, H4"), 3.00 (1H, m, H10), 2.98 (3H, s, 3'NCH_3), 2.86 (1H, dq, H2), 2.75 (1H, ddd, H3'), 2.59 (1H, dqd, H8), 2.35 (1H, dd, H2"), 1.93 (1H, m, H4), 1.92 (1H, m, H14), 1.89 (1H, ddd, H4'), 1.82 (1H, dd, H7), 1.68 (1H,

dd, H7), 1.58 (1H, dd, H2"), 1.55 (1H, dd, H4'), 1.47 (1H, m, H14), 1.41 (3H, s, 6C$\underline{H}_3$), 1.30 (3H, d, 5"C$\underline{H}_3$), 1.26 (3H, d, 5'C$\underline{H}_3$), 1.24 (3H, s, 3"C$\underline{H}_3$), 1.20 (3H, d, 2C$\underline{H}_3$), 1.14 (3H, d, 8C$\underline{H}_3$), 1.13 (3H, d, 10C$\underline{H}_3$), 1.12 (3H, s, 12C$\underline{H}_3$), 1.07 (3H, d, 4C$\underline{H}_3$), 0.84 (3H, t, H15). ^{13}C NMR (125MHz, $CDCl_3$) δ: 220.9 (C9), 175.7 (C1), 102.2 (C1'), 96.1 (C1"), 81.0 (C5), 78.4 (C3 & C6), 77.9 (C4"), 76.7 (C13), 74.2 (C12), 72.7 (C3"), 72.2 (C2'), 70.3 (C3'), 69.1 (C11), 67.8 (C5'), 65.8 (C5"), 50.6 (C6O$\underline{C}H_3$), 49.5 (C3"O$\underline{C}H_3$), 48.7 (C3'N$\underline{C}H_3$), 45.2 (C8), 45.1 (C2), 39.3 (C7), 39.1 (C4), 37.3 (C10), 34.9 (C2"), 30.5 (C4'), 21.5 (C3"$\underline{C}H_3$), 21.3 (C5'$\underline{C}H_3$), 21.0 (C14), 19.7 (C6$\underline{C}H_3$), 18.7 (C5"$\underline{C}H_3$), 18.0 (C8$\underline{C}H_3$), 16.0 (C12$\underline{C}H_3$), 15.9 (C2$\underline{C}H_3$), 12.3 (C10$\underline{C}H_3$), 10.6 (C15), 9.3 (C4$\underline{C}H_3$). FAB MS (NBA)(m/z): $[M+H]^+$ 768, $[M+2H-Cl]^+$ 734, 610, 178, 78. FAB HRMS calc'd m/z for $[M+H]^+$ $C_{37}H_{67}O_{13}N^{35}Cl$ = 768.4301; Found m/z = 768.4302. Elemental analysis calc'd for $C_{37}H_{66}NO_{13}Cl$: C, 57.84; H, 8.66; N, 1.82; Cl, 4.61; Found: C, 58.07; H, 8.71; N, 1.66; Cl, 4.31. Mp 152-154°C (dec.)

3'-oxo Clarithromycin A (6): ^{1}H NMR (500MHz, $CDCl_3$) δ: 5.07 (1H, dd, H13), 4.91 (1H, dd, H1"), 4.51 (1H, d, H1'), 3.99 (1H, ddd, H2'), 3.95 (1H, s, 11OH), 3.91 (1H, dq, H5"), 3.84 (1H, s, 12OH), 3.75 (1H, dd, H3), 3.75 (1H, s, H11), 3.72 (1H, d, H5), 3.69 (1H, dqd, H5'), 3.60 (1H, d, 2'OH), 3.21 (3H, s, 3"OCH_3), 3.05 (3H, s, 6OCH_3), 3.02 (1H, m, H4"), 3.01 (1H, m, H10), 2.87 (1H, dq, H2), 2.60 (1H, m, H8), 2.55 (1H, dd, H4'), 2.40 (1H, ddd, H4'), 2.30 (1H, dd, H2"), 2.12 (1H, d, 4"OH), 1.94 (1H, m, H4), 1.92 (1H, m, H14), 1.86 (1H, dd, H7), 1.68 (1H, m, H7), 1.57 (1H, dd, H2"), 1.48 (1H, m, H14), 1.45 (3H, s, 6CH_3), 1.36 (3H, d, 5'CH_3), 1.29 (3H, d, 5"CH_3), 1.22 (3H, s, 3"CH_3), 1.19 (3H, d, 2CH_3), 1.14 (3H, d, 8CH_3), 1.13 (3H, d, 10CH_3), 1.13 (3H, s, 12CH_3), 1.06 (3H, d, 4CH_3), 0.84 (3H, t, H15). ^{13}C NMR (125MHz, $CDCl_3$) δ: 220.8 (C9), 206.0 (C3'), 175.7 (C1), 103.4 (C1'), 96.0 (C1"), 81.8 (C5), 78.8 (C2'), 78.4 (C3), 78.2 (C6), 77.7 (C4"), 76.7 (C13), 74.3 (C12), 72.8 (C3"), 69.1 (C11), 67.3 (C5'), 66.0 (C5"), 50.6 (C6O$\underline{C}H_3$), 49.3 (C3"O$\underline{C}H_3$), 47.2 (C4'), 45.2 (C8), 44.9 (C2), 39.2 (C7), 38.9 (C4), 37.3 (C10), 34.9 (C2"), 21.6 (C5'$\underline{C}H_3$), 21.4 (C3"$\underline{C}H_3$), 21.0 (C14), 19.8 (C6$\underline{C}H_3$), 18.6 (C5"$\underline{C}H_3$), 18.0 (C8$\underline{C}H_3$), 16.0 (C12$\underline{C}H_3$), 15.9 (C2$\underline{C}H_3$), 12.3 (C10$\underline{C}H_3$), 10.6 (C15), 8.9 (C4$\underline{C}H_3$). FAB MS (NBA + KI)(m/z): $[M+K]^+$ 757, 657. FAB HRMS calc'd m/z for $[M+K]^+$ $C_{36}H_{62}O_{14}K$ = 757.3777; Found m/z = 757.3790. Elemental analysis calc'd for $C_{36}H_{62}O_{14}$: C, 60.15; H, 8.69; Found: C, 59.98; H, 8.74. Mp 154-157°C.

Clarithromycin A N-oxide (4): ^{1}H NMR (500MHz, $CDCl_3$) δ: 5.05 (1H, dd, H13), 4.92 (1H, br.d, H1"), 4.57 (1H, d, H1'), 4.00 (1H, m, H5"), 3.76 (1H, m, H3). 3.75 (1H, appar s, H11), 3.70 (1H, m, H2'), 3.69 (1H, m, H5), 3.66 (1H, m, H5'), 3.51 (1H, m, H3'), 3.36 (3H, s, 3"OCH_3), 3.30 (3H, s, 3'NCH_3), 3.22 (3H, s, 3'NCH_3), 3.05 (1H, d, H4"), 3.03 (3H, s, 6OMe), 2.99 (1H, br.q, H10), 2.88 (1H, m, H2), 2.58 (1H, m, H8), 2.35 (1H, br.d, H2"), 2.05 (1H, br.d, H4'), 1.93 (1H, m, H4), 1.90 (1H, m, H14), 1.86 (1H, dd, H7), 1.68 (1H, br.dd, H7), 1.58 (1H, dd, H2"), 1.47 (1H, m, H14), 1.39 (3H, s, 6CH_3), 1.34 (1H, br.d, H4'), 1.29 (3H, d, H6"), 1.27 (3H, d, H6'), 1.26 (3H, s, 3"CH_3), 1.20 (3H, d, 2CH_3), 1.12 (3H, d, 4CH_3), 1.12 (3H, d, 8CH_3), 1.12 (3H, d, 10CH_3), 1.11 (3H, s, 12CH_3), 0.84 (3H, t, H15). ^{13}C NMR (125MHz, $CDCl_3$) δ: 220.9 (C9), 175.8 (C1), 102.3 (C1'), 96.0 (C1"), 81.2 (C5), 78.5 (C3), 78.3 (C6), 77.8 (C4"), 76.6 (C13), 76.3 (C3'), 74.2 (C12), 72.7 (C3"), 72.6 (C2'), 69.0 (C11), 66.9 (C5'), 65.8 (C5"), 58.1 (C3'N$\underline{C}H_3$), 52.7 (C3'N$\underline{C}H_3$), 50.6 (C6O$\underline{C}H_3$), 49.6 (C3"O$\underline{C}H_3$), 45.2 (C8), 45.0 (C2), 39.2 (C7), 39.1 (C4), 37.2 (C10), 34.9 (C4'), 34.7 (C2"), 21.4 (C6'), 21.2 (C3"O$\underline{C}H_3$), 21.0 (C14),

19.8 (C6$\underline{C}H_3$), 18.7 (C6"), 18.0 (C8$\underline{C}H_3$), 15.9 (C12$\underline{C}H_3$), 15.9 (C2$\underline{C}H_3$), 12.2 (C10$\underline{C}H_3$), 10.5 (C15), 9.0 (C4$\underline{C}H_3$). FAB MS (NBA)(m/z): $[M+H]^+$ 764, 606, 174. FAB HRMS calc'd m/z for $[M+H]^+$ $C_{38}H_{70}O_{14}N$ = 764.4796; Found: m/z = 764.4797. Mp 170-172°C.

Acknowledgments: We wish to thank Dr. John Hengeveld and Ken Spina for providing reference samples and for several helpful discussions.

References And Notes:

1. Present address: CP Consulting, 43323 N. Oakcrest Lane, Zion, IL 60099-9413
2. *Metalloporphyrins in Catalytic Oxidations*; Sheldon, R. A., Ed.; Marcel Dekker, Inc.: New York, **1994**.
3. See, for example: Meunier, B. *Chem. Rev.* **1992**, *92*, 1411-1456. Hirobe, M.; Kiuchi, H.; Miyata, N. *Chem. Pharm. Bull.* **1981**, *29*, 1489-1492. Hirobe, M.; Miyata, N.; Santa, T. *Chem. Pharm. Bull.* **1984**, *32*, 1252-1255. Mortimer, D. N.; Lindsay Smith, J. R. *J. Chem. Soc., Chem. Commun.* **1985**, 64-65.
4. *Cytochrome P-450, Structure, Mechanism and Biochemistry* Ortiz de Montellano, P. R., Ed.; Plenum Press: New York, **1986**. *Cytochrome P-450* Sato, R.; Omura, T., Eds.; Kodansha Ltd: Tokyo, **1978**. Gorrod, J. W. *Biological Oxidation of Nitrogen* Elsevier/North Holland Biomedical Press: New York, **1978**.
5. Brian, W. R.; Sari, M. A.; Iwasaki, M.; Shimada, T.; Kaminsky, L. S.; Guengerich, F. P. *Biochemistry* **1990**, *29*, 11280-11292. Renaud, J. P.; Cullin, C.; Pompon, D.; Beaune, P.; Mansuy, D. *Eur. J. Biochem.* **1990**, *194*, 889-896. Peyronneau, M. A.; Renaud, J. P.; Truan, G.; Urban, G.; Pompon, D.; Mansuy, D. *Eur. J. Biochem.* **1992**, *207*, 109-116.
6. Celebuski, J. E.; Chorghade, M. S.; and Lee, E. C. *Tetrahedron Lett.* **1994**, *35*, 3837-3840.
7. The sulfonated metalloporphyrin was kindly provided by Professor David Dolphin, University of British Columbia, Vancouver Canada.
8. Freiberg, L. A. *US Patent No.* 70-86314 701102.

(*Received in USA* 10 *October* 1995; *revised* 29 *November* 1995; *accepted* 1 *December* 1995)