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Structure Revision of Medermycin/ Lactoquinomycin A and of Related C-8 Glycosylated Naphthoquinones

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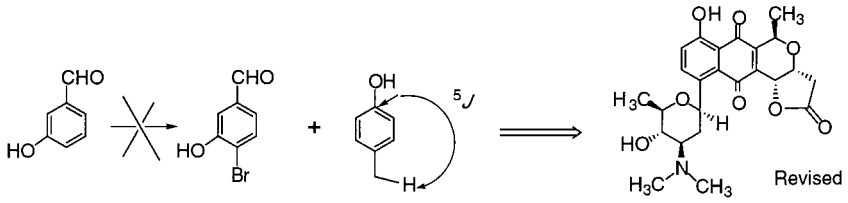
ABSTRACT



On the basis of chemical and spectral data, the structure of the medermycin/lactoquinomycin A has been revised, which has also led to the revision of related *C*-glycosylated naphthoquinone antibiotics such as lactoquinomycin B, menoxymycins A and B, G15-F, and G15-G.

Some 25 years ago, scientists at Kayaku isolated from chromogenic *Streptomyces tanashinensis* orange crystals which they found to be significantly active against gram-positive organisms including antibiotic-resistant strains of *Staphylococci*; the molecular formula $C_{24}H_{29}NO_8$, deduced from mass spectrometric studies of acetylated derivatives, was given to this material named medermycin.[1] Subsequently this molecular formula was revised to $C_{24}H_{27}NO_8$ after field desorption studies of the parent material.[2] Ten years later, the group of Tanaka isolated from the same source "a novel anticancer antibiotic" that they named lactoquinomycin A as, on the basis of physical stability and antitumor properties, they thought it was different from medermycin.[3] Its structure was proposed as **1**,[4] in particular according to ^{1}H NMR comparison of the naphthoquinone part with that of kalafungin,[5] and the point of attachment of D-angolosamine (its carbohydrate component) to the naphthoquinone ring was chosen as C-8 after spectroscopic considerations. At about that time, the first production of hybrid antibiotics by genetic engineering was announced[6] and was applied to isochromanequinone-producing *Streptomyces* strains; the structures of mederrhodin A and B thus produced relied on that previously established for medermycin.[7]

Subsequently, to help in securing structural identification of these antibiotics, Tatsuta *et al.* performed a total synthesis of **1**,[8] based on the structure proposed for lactoquinomycin A.[3] This enabled a comparison of natural samples of both medermycin (from Omura's group) and lactoquinomycin A (from Tanaka's group) with the synthetic material. Quite unexpectedly, all three samples were found to be *identical*; as a consequence, structure **1** was assigned to both antibiotics. This work was followed by the synthesis of the (−)-enantiomer.[9] Given the significant antineoplastic, antibiotic, and platelet aggregation inhibition properties of medermycin/

(1) Takano, S.; Hasuda, K.; Ito, A.; Koide, Y.; Ishii, F.; Haneda, I.; Chihara, S.; Koyama, Y. *J. Antibiotics* **1976**, *29*, 765−768.
(2) Fukushima, K.; Arai, T. *Mass Spectrosc.* **1979**, *27*, 97−105.
(3) Tanaka, N.; Okabe, T.; Isono, F.; Kashowagi, M.; Nomoto, K.; Takahashi, M.; Shimazu, A.; Nishimura, T. *J. Antibiot.* **1985**, *38*, 1327−1332.
(4) Okabe, T.; Nomoto, K.; Funabashi, H.; Okuda, S.; Suzuki, H.; Tanaka, N. *J. Antibiot.* **1985**, *38*, 1333−1336.
(5) Hoeksema, H.; Krueger, W. C. *J. Antibiot.* **1976**, *29*, 704−709.
(6) Hopwood, D. A.; Malpartida, F.; Kieser, H. M.; Ikeda, H.; Duncan, J.; Rudd, B. A. M.; Floss, H. G.; Omura, S. *Nature* **1985**, *314*, 642−645.
(7) Omura, S.; Ikeda, H.; Malpartida, F.; Kieser, H. M.; Hopwood, D. *Antimicrob. Chemother. Agents* **1986**, *29*, 13−19.
(8) Tatsuta, K.; Ozeki, H.; Yamaguchi, M.; Tanaka, M.; Okui, T. *Tetrahedron Lett.* **1990**, *31*, 5495−5498.
(9) Tatsuta, K.; Ozuki, H.; Yamaguchi, M.; Tanaka, M.; Okui, T.; Nakata, M. *J. Antibiot.* **1991**, *44*, 901−902.

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lactoquinomycin A,[1,3,10] extensive efforts were subsequently made to achieve an efficient and flexible method for *C*-glycosylation at the *C-8* position of naphthoquinones.[11−15]

In all of the above work, the C-linkage of the carbohydrate was believed to occur at C-8 of the naphthoquinone but for reasons explained below we propose this linkage to occur at C-6, with **2** being the correct structure (Figure 1).

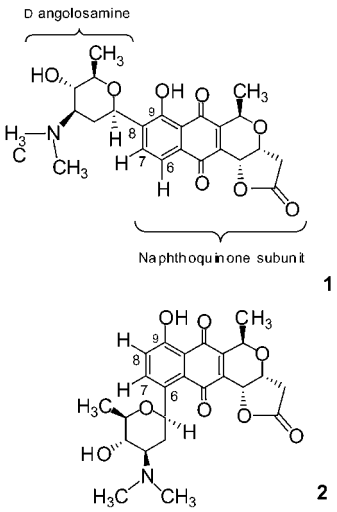


Figure 1. Original (**1**) and revised (**2**) structures for medermycin/lactoquinomycin A.

The total syntheses of medermycin/lactoquinomycin A[8] and of its (−)-enantiomer[9] both started from the bromination product of *m*-hydroxybenzaldehyde; this compound, given structure **3**,[16,17] was used to prepare a key intermediate for the establishment at C-8 of a C−C bond between the aromatic system and a precursor of angolosamine.[8,9,18]

When performing bromination of *m*-hydroxybenzaldehyde (HBr, AcOH),[16,17] we isolated a monobrominated product (mp 130 °C [lit.[17] mp 129 °C]). To unambiguously assign its structure, it was reacted with *p*-nitrobenzoyl chloride, which afforded a single product that was crystallized. Its X-ray analysis (Figure 2) established structure **5**, the bromine atom being hence *ortho* to the aldehyde group;[19] that **4** (and not **3**) was the correct structure of the bromination product

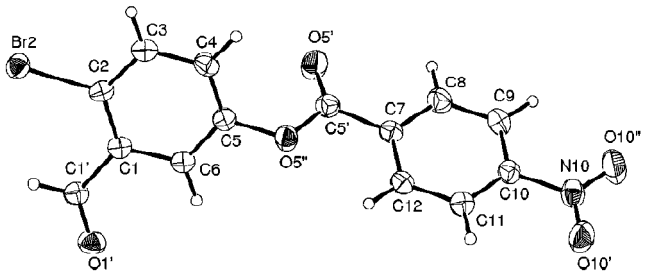


Figure 2. Ortep drawing of 2-bromo-5-*p*-nitrobenzoylbenzaldehyde **5**.

was also recently found by Paixao's group.[20] It is noteworthy that when this bromination is carried out in chloroform, a compound whose melting point is also 130 °C, but to which structure **4** has been assigned,[21] is obtained. Thus, it is now clear that whether performed in acetic acid or chloroform, bromination of *m*-hydroxybenzaldehyde gives **4**.[22]

For the actual synthesis of medermycin/lactoquinomycin A, metalation of the bromo derivative **6** (thought to be derived from **3**) was used as a crucial step.[8] To rule out a possible rearrangement during or after bromine/lithium exchange,[23] we prepared the acetal **6**[8] and performed its lithiation under literature conditions;[8] this lithio derivative was quenched with methyl iodide, followed by acetal cleavage, which afforded a methylated aldehyde (Scheme 1). In view of the observed coupling constants (J_{ortho} = 8.1 Hz, J_{meta} = 1.6 Hz) the structure of this aldehyde can be depicted by either **7** or **8**; although these two aldehydes are known compounds,[24] their physical (melting point, boiling point, and NMR) data are too similar to allow an unambiguous choice. So the aldehyde was reduced ($NaBH_4$, CH_3OH) and the alcohol esterified[25] to yield **9**.[26] Upon selective irradiations of methyl or methylene groups, Overhauser enhancements could be observed, which are in accordance

(10) Nakagawa, A.; Fukamachi, N.; Yamaki, K.; Hayashi, M.; Oh-Ishi, S.; Kobayashi, B.; Omura, S. *J. Antibiot.* **1987**, *40*, 1075−1076.

(11) Brimble, M. A.; Duncalf, L. J.; Neville, D. *J. Chem. Soc., Perkin Trans. 1* **1999**, 4165−4173.

(12) Brimble. M. A.; Issa, F. *Aust. J. Chem.* **1999**, *52*, 1021−1028.

(13) Brimble. M. A.; Brenstrum, T. J. *Tetrahedron Lett.* **2000,** *41*, 2991−2994.

(14) Brimble, M. A.; Brenstrum, T. J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1612−1623.

(15) Brimble, M. A.; Brenstrum, T. J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1624−1634.

(16) Hodgson, H. H.; Beard, H. G. *J. Chem. Soc.* **1925**, *127*, 875−881.

(17) Pandya, K. C.; Pandya, R. B. K.; Singh, R. N. *J. Indian Chem. Soc*. **1952**, *29*, 363−367.

(18) Attention is called (Barkfnecht, C. F.; Nichols, D. E. *J. Med. Chem.* **1971**, *14*, 370−372) to the report of Pandya et al. (ref 17) where the bromination product is 2-bromo-5-hydroxybenzaldehyde, but this observation has apparently remained unnoticed.

(19) The single-crystal growth of **5** was performed in a mixture of diethyl ether and dichloromethane at about 4−5 °C. The diffraction experiment was carried out at room temperature with an Enraf-Nonius CAD4 diffractometer operating with Cu Kα radiation (1.54178 Å) monochromated by a graphite plate. Compound **5** is triclinic $P\bar{1}$ with the following unit-cell dimensions: a = 7.407(6) Å, b = 7.631(2) Å, c = 13.123(6) Å, a = 91.66-(3)°, b = 99.26(6)°, g = 64.80(5)° with Z = 2 and V = 661.8(6). r_{calc} = 1.757 g cm^{-3} and m = 4.467 mm^{-1}. A prismatic crystal with the dimensions 0.18 × 0.15 × 0.10 mm^3 was used for the diffraction data collection. Within a range of 1 to 75° (Θ) 2817 reflections were scanned; among them 2703 were independent and 2373 with $I > 1.1\sigma(I)$ were used in the final refinements. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. The final results are R = 0.066, Rw = 0.1076, and GOF = 1.985.

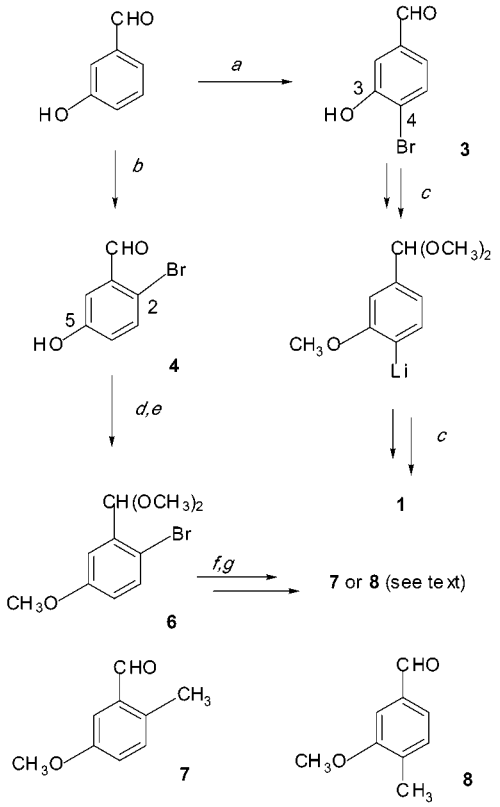
(20) Matos Beja, A.; Paixao, J. A.; Ramos Silva, M.; Alte da Veiga, L.; d'A Rocha Gonsalves, A. M.; Serra, A. C. *Acta Crystallogr*. **2000**, *C56*, 354−355.

(21) Harmata, M.; Kahraman, M. *J. Org. Chem.* **1999**, *64*, 4949−4952.

(22) **3** and **4** have been stated to differ in the ^{1}H NMR chemical shift of their aldehydic proton (Brink, M. *Acta University Lund* **1968**, *36*, 3−12), but no indication on the conditions of obtaining **3** was given. From our own NMR observations, **3**, which we have prepared by MnO_2 oxidation of the known (Canceill, J.; Collet, A. *New J. Chem.* **1986**, *10*, 17−23) benzylic alcohol, could be a minor component of the bromination mixture.

(23) Migration of bromine from position −2 to −4 (under acidic conditions, however) in the structurally related 2-bromo-5-hydroxybenzoic acid has been observed; see: Tomita, M.; Kura, S.; Tanaka, S. *J. Pharm. Soc. Jpn*. **1956**, *76*, 1119−1122.

Scheme 1[a]



[a] (a) refs. 16,17. (b) HBr, AcOH or ref. 21. (c) ref. 8. (d) CH_3I, K_2CO_3 (95 %). (e) $CH(OCH_3)_3$, H^+ (92 %). (f) *n*.-BuLi, -70 °C, 15 min then CH_3I (10 equiv.) -70 °C to r.t. (g) HCl 0.5 *N* THF-H_2O, 3 h (67 % from **6**).

only with the spin pattern displayed in structure **9** (Figure 3); the same correlations could be equally detected in NOESY experiments, which unambiguously point out structure **9** and demonstrate that no rearrangement occurs during lithiation of the bromide **6**. Therefore the structure of medermycin/lactoquinomycin A can now be safely revised as **2**.

However, one may ask why structure **1** had been chosen, i.e. why the point of attachment of the *C*-glycoside was selected as C-8?

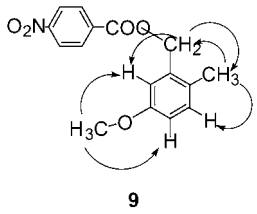


Figure 3. Homonuclear Overhauser enhancements observed upon irradiations of selected protons for compound **9**.

Although a number of NMR chemical shift predictions or experimental data based on naphthoquinones substitution patterns[27] could have been of help, they were not available at the time when the structure was selected; the choice of **1** appears to have relied on NMR correlations: to quote the author's words "a long-range coupling between the 2′-H signal and phenolic carbon signal (C-9) was observed, indicating that the C-8 position is substituted by the sugar moiety".[4,28] It looks like only ^3J heteronuclear correlations were considered while ruling out ^nJ ($n > 3$) correlations. However, we have detected a ^5J heteronuclear correlation in compound **9**, which is unambiguous since we have fully assigned its ^{13}C and ^1H NMR spectra,[26] and we could also observe it on a simpler model: *p*-cresol (Figure 4). Thus

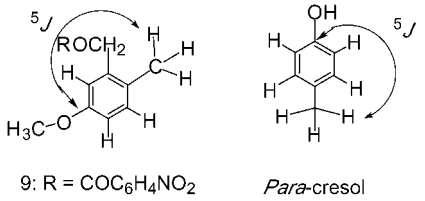


Figure 4. Observed long-range heteronuclear correlations.

the detection of a ^5J heteronuclear correlation between the glycosidic proton and C-9 in medermycin/lactoquinomycin A *is* compatible with structure **2**.

As a consequence of this work, the structures of lactoquinomycin B,[29] menoxymycins A and B,[30] G15-F, and G15-G,[31] which were directly built on that of **1**, should also be revised (Figure 5); in addition we suggest that those of

(24) Compound **7**: Higginbottom A.; Hill, P.; Short, W. F. *J. Chem. Soc.* **1937**, 263−266. Hartmann, R. W.; Heindl, A.; Schwarz, W.; Schoenenberger, H. *J. Med. Chem.* **1984**, *27*, 819−824. Ranchella, M.; Rol, C.; Sebastiani, G. V. *J. Chem. Soc., Perkin Trans. 2* **2000**, 311−316. Compound **8**: Fukumi, H.; Kurihara, H.; Mishima, H. *Chem. Pharm. Bull.* **1978**, *26*, 2175−2180. Kametani, T.; Kigawa, Y.; Nemoto, H.; Ihara, M.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1607−1611. Flitsch, W.; Russkamp, P.; Langer, W. *Liebigs Ann. Chem.* **1985**, 1413−1421. Flippin, L. A.; Berger, J.; Parnes, J. S.; Gudiksen, M. S. *J. Org. Chem.* **1996**, *61*, 4812−4815.

(25) We felt it would be wise to get rid of the exchangeable proton to avoid potential interference during NMR-nOe experiments.

(26) Compound **9** (assignments secured by homo- and heteronuclear correlation spectroscopies): ^1H NMR (300 MHz, $CDCl_3$) δ 2.35 (s, 3H, Ar−CH_3); 3.8 (s, 3H, OCH_3); 5.4 (s, 2H, CH_2); 6.8 (dd, J = 8.4, 2.7 Hz, 1H, H-3); 7.0 (d, J = 2.7 Hz, 1H, H-4); 7.2 (d, J = 8.4 Hz, 1H, H-6); 8.2 and 8.3 (AA′XX′ system, 4H, H-2′, -3′, -5′, -6′). ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.0 (Ar−CH_3); 55.4 (OCH_3); 66.0 (CH_2); 113.7 (C-3); 115.3 (C-4); 123.5 (C-3′,-5′); 128.8 (C-2); 130.8 (C-2′,-6′); 131.4 (C-6); 134.2 (C-1); 135.4 (C-1′); 150.5 (C-4′); 157.9 (C-5); 164.5 (C=O).

(27) Lillie, T. J.; Musgrave, O. C. *J. Chem. Soc.* **1977**, 355−359. McDonald, I. A.; Simpson, T. J.; Sierakowski, A. F. *Aust. J. Chem.* **1977**, *30*, 1727−1734. Neidlein, R.; Kramer, W.; Leidholt, R. *Helv. Chim. Acta* **1983**, *66*, 2285−2293. Inoue, K.; Ueda, S.; Nayeshiro, H.; Inouiye, H. *Phytochemistry* **1983**, *22*, 737−741. Tabatskaya, A. A.; Vlasov, V. M. *Zh. Org. Khim.* **1991**, *27*, 1285−1297 (English translation: *J. Org. Chem. USSR* **1991**, *27*, 1121−1131). Ismail, N. H.; Ali, A. M.; Aimi, N.; Kitajima, M.; Takayama, H.; Lajis, N. H. *Phytochemistry* **1997**, *45*, 1723−1725.

(28) In the numbering used in ref 4, H-2′ is the glycosidic proton.

(29) Okabe, T.; Nomoto, K.; Tanaka, N. *J. Antibiot.* **1986**, *39*, 1−6.

(30) Hayakawa, Y.; Ishigami, K.; Shin-Ya, K.; Seto, H. *J. Antibiot.* **1994**, *47*, 1344−1347.

(31) Li, P.; Lou, Z.; Hu, J.; Li, Y. *Chin. J. Antibiot.* **1995**, *20*, 254−260.

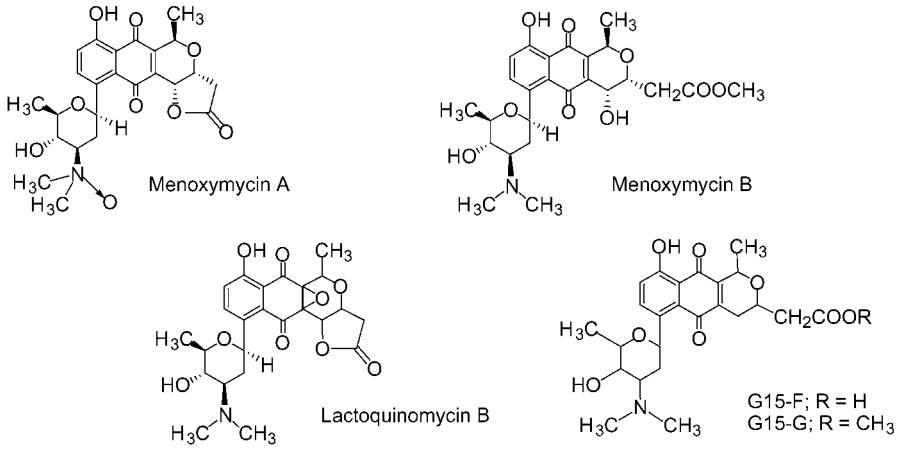


Figure 5. Revised structures for medermycin-derived antibiotics.

mederrhodins A and B[7] and of AM-8402[32] be looked at again. Finally we wish to emphasize that even though synthetic efforts to achieve efficient introduction of a *C*-glycoside at C-8 could now appear irrelevant (since the structure of medermycin on which they were based was wrong), there are still a number of (naphtho)quinone antibiotics, such as quanolirones, capomycins, urdamycins, amicenomycins, and saquayamicins, in which a *C*-glycoside is linked *ortho* to a phenolic group, thus justifying ongoing research.[33] And last, but not least, may we point out that whenever delocalized aromatic systems are involved, particular care should be taken when using long-range correlations for the establishment of NMR connectivities.

Acknowledgment. Béatrice Gennaro is thanked for recording the nuclear Overhauser experiments and C.M. is grateful to a CNRS-JSPS exchange program for a travel/stay grant in Prof. S. Omura's group (Kitasato Institute, May−August 1986) from which his interest in bioactive quinonoïds can be traced.

Supporting Information Available: Procedures for the preparation of **3** and **4** and related analytical data; GHMBC correlations and assignments of *p*-cresol and crystallographic data of **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(32) Omura, S.; Murata, M.; Kimura, K.; Matsukura, S.; Nishihara, T.; Tanaka, H. *J. Antibiot.* **1985**, *38*, 1016−1024.

(33) For a recent example, see: Hauser, F. M.; Hu, X. *Org. Lett.* **2002**, *4*, 977−978.