CHEMISTRY LETTERS, pp. 1747-1748, 1994. 

# Structural Revision of Griseulin, a Bioactive Pyrone Possessing a Nitrophenyl Unit

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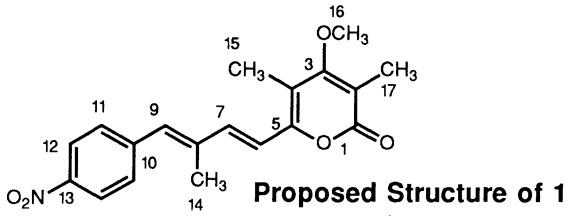
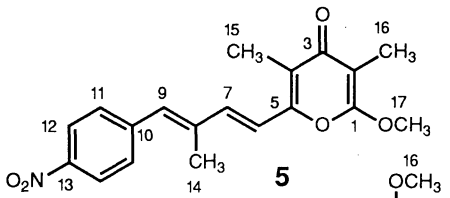
Biologically active griseulin isolated from *Streptomyces* sp. was synthesized, however the spectral data of the synthetic sample did not agree with the reported one. Synthesis of the related sample and detailed reexamination of the spectroscopic properties resulted in the structural revision of griseulin, which should be identical with luteoreticulin.

Griseulin (**1**) possessing nematocidal and mosquitocidal activities, was isolated from *Streptomyces griseus* var. autotrophicus MSU 32058 / ATCC 53668, as a member of the nitro group-containing pyrone family, and the structure was proposed as depicted in Figure.[1] The interesting bioactivities prompted us to include a synthesis of this pyrone (**1**) as a part of our synthetic investigation on biologically active β-polyketide-derived natural products. A ready accessibility to **1** was promised by coupling of **2** and **3**, both of which were the synthetic intermediates of isoaureothin.[2] However, the synthetic **1** provided entirely different spectroscopic properties from those of the reported one. A detailed inspection of the spectroscopic data made it possible to revise the structure of griseulin (**1**). We describe herein the research process.

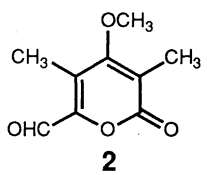
When the α-pyrone (**2**) was treated with the phosphorane obtained by reaction of **3** with sodium hydride, the corresponding coupling product was produced as a mixture of the olefinic isomers in 98% yield. Olefin inversion of the product by iodine (95% yield, E / Z = 6 / 1 at the trisubstituted olefin moiety), followed by recrystallization afforded **1**. The γ-pyrone isomer (**5**) was also synthesized under the same reaction conditions using **4** instead of **2**. The proton and carbon signals of **1** and **5** could be assigned by NMR techniques such as HMQC and HMBC, and unambiguous confirmation of their structures was accomplished as described below, although the signals were not compatible with those of the reported data. Particularly, the trans-olefinic bond at the $C_6$ - $C_7$ position appeared the clear difference; the synthetic sample exhibited a normal coupling constant



Proposed Structure of 1



**5**



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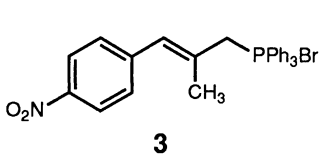

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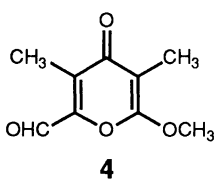

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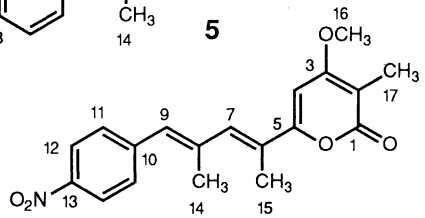

**Luteoreticulin (6)**

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|---|
| **griseulin**[1]: mp 164 - 165 °C; $\lambda_{max}$ nm 367, 222, 203 (EtOH); $\delta_H$ 1.95 (3H, s), 2.11 (3H, s), 2.14 (3H, s), 3.93 (3H, s), 6.25 (1H, s), 6.57 (1H, s), 7.1 (1H, s), 7.45 (2H, d, J= 9 Hz), 8.19 (2H, d, J= 9 Hz). $\delta_C$ 9.40, 14.96, 19.82, 56.86, 94.16, 103.67, 124.23, 124.25, 127.69, 130.40, 130.42, 131.36, 136.52, 139.08, 144.50, 146.88, 160.24, 165.35, 166.28. |
| **synthetic 1**: mp 186 - 188 °C; $\delta_H$ 2.08 ((3H, s), 2.10 (3H, s), 2.13 (3H, d, J= 1 Hz), 3.83 (3H, s), 6.51 (1H, d, J= 15.5 Hz), 6.82 (1H, s), 7.32 (1H, d, J= 15.5 Hz), 7.48 (2H, d, J= 8.8 Hz), 8.22 (2H, d, J= 8.8 Hz); $\delta_C$ 9.80 (C-15*), 10.50 (C-17*), 13.95 (C-14), 60.33 (C-16), 111.41 (C-2**), 111.79 (C-4**), 117.32 (C-6), 123.56 (2 x C, C-12), 129.92 (2 x C, C-11), 133.48 (C-9), 138.33 (C-8), 138.45 (C-7), 143.86 (C-13), 146.33 (C-10), 152.36 (C-5), 164.76 (C-1), 167.92 (C-3). |
| **5** as an oil: $\delta_H$ 1.90 (3H, s), 2.11 (3H, s), 2.17 (3H, d, J=1Hz), 4.10 (3H, s), 6.67 (1H, d, J= 15.8 Hz), 6.79 (1H, broad s), 7.08 (1H, d, J= 15.8 Hz), 7.49 (2H, d, J= 8.8 Hz), 8.25 (2H, d, J= 8.8 Hz); $\delta_C$ 7.03 (C-16), 9.83 (C-15), 14.00 (C-14), 55.49 (C-17), 99.95 (C-2), 118.96 (C-6), 119.87 (C-4), 123.67 (2 x C, C-12), 129.90 (2 x C, C-11), 133.39 (C-9), 137.41 (C-7), 138.20 (C-8), 143.59 (C-10*), 146.50 (C-13*), 151.75 (C-5), 161.74 (C-1), 180.79 (C-3). |
| **luteoreticulin (6)**: mp 184 - 185 °C; $\lambda_{max}$ nm 366, 221, 204 (EtOH); $\delta_H$ 1.97 (3H, s), 2.13 (3H, d, J= 1.4 Hz), 2.16 (3H, d, J= 1 Hz), 3.94 (3H, s), 6.26 (1H, s), 6.59 (1H, s), 7.17 (1H, s), 7.47 (2H, d, J= 8.8 Hz), 8.23 (2H, d, J= 8.8 Hz); $\delta_C$ 8.75 (C-17), 14.29 (C-15), 19.12 (C-14), 56.17 (C-16), 93.47 (C-4), 103.15 (C-2), 123.60 (2 x C, C-12), 127.02 (C-6), 129.7 (2 x C, C-11), 130.69 (C-9), 135.93 (C-7), 138.41 (C-8), 143.85 (C-13), 146.30 (C-10), 159.62 (C-5), 164.70 (C-1), 165.58 (C-3). |

The NMR measurement was performed in $CDCl_3$. *, ** May be inverted.

(15.5 Hz), whereas the reported data showed singlets (δ 6.25 and 6.57) ascribed to both protons. Additionally, from our extensive pyrone chemistry, α-pyrones carrying methyl substituents at the $C_2$ and $C_4$ positions exhibit the methoxy carbon resonance around 60 ppm, whereas they are observed in the range of 55 ~ 57 ppm for α-pyrones carrying no substituent at the $C_4$ position. These findings strongly suggested griseulin should have the latter type α-pyrone for the chemical shift (56.86 ppm) of the methoxy carbon, and a possibility of a γ-isomer of the pyrone unit was also excluded by the lower chemical shift (180.79 ppm) of the carbonyl carbon of **5**, which should be higher than 166.28 ppm in the reported data. Based on these observations and extensive inquisition of the spectral data, we concluded that griseulin should be identical with luteoreticulin (**6**)[3] by the detailed comparison of the spectroscopic data.[4]

The Authors wish to thank Professor Eiji Suzuki, Meijo University providing them a gift of an authentic sample of luteoreticulin.

References

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2) Y. Ishibashi, S. Nishiyama, Y. Shizuri, and S. Yamamura, *Tetrahedron Lett.*, **33**, 521 (1992).
3) Isolation: K. Koyama, Y. Fukakusa, N. Kyomura, S. Yamagishi, and T. Arai, *Tetrahedron Lett.*, **1969**, 355. Synthesis: E. Suzuki and S. Inoue, *J. Chem. Soc., Perekin 1*, **1976**, 404.
4) Difference of the melting points between griseulin and luteoreticulin (**6**) is probably due to a crystal form; griseulin was described as a yellow-orange solid, whereas **6** was recrystallized from ethyl acetate. The reported $^{13}C$ NMR spectrum exhibited two pairs of signals ascribed to the symmetrical carbons ($C_{11}$: δ 130.40 and 130.42; $C_{12}$: δ 124.23 and 124.25). This uncertain point might be derived from their measurement conditions.

(Received June 29, 1994)