**Short Communication**

# Total Synthesis of (±)-Gregatin B†

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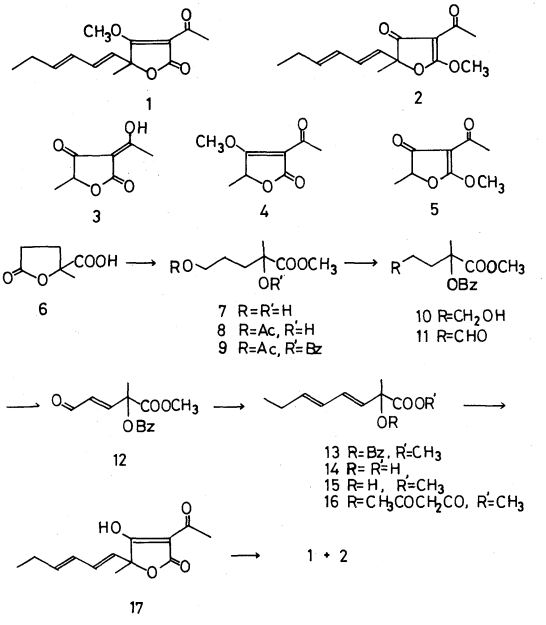
Gregatins are a family of phytotoxic metabolites isolated from *Cephalosporium gregatum*[1] and *Aspergillus panamensis*.[2] The structures have been suggested as *O*-methyl-tetronic acids by a comparison of their spectral data with those of aspertetronins, the antipodal family of gregatins isolated from *Aspergillus rugulosus*, and gregatin B, one of the family of gregatins, was suggested to have the structure **1**. Quite recently, Pattenden *et al.*[3] have shown that the plane structure of natural gregatin B was 5-methoxy-3(2*H*)-furanone (**2**) instead of the *O*-methyl-tetronic acid structure (**1**) from the synthetic and spectral studies. This communication describes the total synthesis of racemic gregatin B and isogregatin B[3] which confirms the structural reassignment of gregatin B (**2**).

In order to obtain both the 5-methoxy-3(2*H*)-furanone and *O*-methyl-tetronic acid structures, we prepared two isomeric methoxy derivatives of α-acetyl-γ-methyl tetronic acid (**3**) by two methods. Methylation of **3** with diazomethane gave **4** as the single product. The spectral data of **4** are as follows: UV $\lambda_{max}$ 243 nm; IR $\nu_{max}^{film}$ cm$^{-1}$: 1760, 1695, 1610, 1460, 1360, 1300, 1200, 1050, 1010, 980; MS *m/z*: 170 (83%), 155 (100), 152 (43), 140 (8), 127 (15), 113 (20); $^1$H-NMR ($CDCl_3$) δ: 1.52 (3H, d, $J$=7 Hz), 2.52 (3H, s), 4.16 (3H, s), 4.81 (1H, q, $J$=7 Hz); $^{13}$C-NMR ($CDCl_3$) δ: 17.8, 30.4, 62.9, 104.4, 170.0, 183.0, 194.5. On the other hand, treatment of α-acetyl-γ-methyl-tetronic acid (**3**) with methyl iodide and silver oxide in chloroform gave another derivative **5**. UV $\lambda_{max}$: 213 and 263 nm; IR $\nu_{max}^{film}$ cm$^{-1}$: 1740 (sh), 1705, 1590, 1440, 1410, 1250, 1200, 1160, 1080, 1000; $^1$H-NMR ($CDCl_3$) δ: 1.50 (3H, d, $J$=7 Hz), 2.62 (3H, s), 3.84 (3H, s), 4.62 (1H, q, $J$=7 Hz); $^{13}$C-NMR ($CDCl_3$) δ: 17.9, 29.4, 51.6, 83.5, 108.1, 163.2, 197.1, 198.5; MS *m/z*: 170 (21%), 139 (44), 96 (15), 67 (100), 33 (62). The 5-methoxy-3(2*H*)-furanone form for **5** and the *O*-methyl-tetronic acid form for **4** were confirmed by the IR and $^{13}$C-NMR data.




For the synthesis of natural gregatin B, we chose intramolecular cyclization of acetoacetoxy-ester followed by methylation as shown in the scheme. Lactone-carboxylic acid (**6**) was reduced to the α,δ-dihydroxy acid with sodium borohydride in tetrahydrofuran–methanol. Without purification, the crude dihydroxy acid was methylated with methanol–sulfuric acid to give diol ester **7** in a 42% yield from **6** (IR $\nu_{max}^{film}$ cm$^{-1}$: 3440, 1735). Acetylation of the diol **7** with acetic anhydride–pyridine gave monoacetate **8**. [MS *m/z*: 205

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(24%, $M^+ + 1$), $^1$H-NMR $\delta$ 2.03 ($CH_3CO$)]. $\delta$-Acetate **8** was converted to the benzoate with *n*-butyllithium–benzoyl chloride in a 75% yield. [$^1$H-NMR $\delta$: 8.03, 7.51 (PhCO), MS *m/z* 309 (3%, $M^+ + 1$)]. Removal of the acetyl group with ammonia–methanol gave the alcohol **10** in a 58% yield. (IR $\nu_{max}^{film}$: 3440 $cm^{-1}$). The alcohol **10** was oxidized to the aldehyde **11** with pyridinium chlorochromate in methylene chloride in a 88% yield. [$^1$H-NMR $\delta$: 9.82 (d, $J$=3 Hz, CHO]. The aldehyde **11** was converted to $\alpha,\beta$-unsaturated aldehyde **12** by enamination followed by phenylselenylation and oxidative elimination with sodium periodate in a 79% yield from **11**. [**12**. $^1$H-NMR $\delta$: 6.18 (dd, $J$=18, 7 Hz, CO–CH=C), IR $\nu_{max}^{film}$: 1700 $cm^{-1}$]. The Witting reaction of the aldehyde **12** with propylidenetriphenylphosphorane gave **13** in a 59% yield. [$^1$H-NMR $\delta$: 5.5~6.5 (4H, m)]. After hydrolysis with sodium hydroxide, the $\alpha$-hydroxy acid 14 was converted to the methyl ester **15** with diazomethane (45% yield from **13**) and treated with diketene to afford the ketoester **16**. (IR $\nu_{max}^{film}$ $cm^{-1}$: 1720, 1640). Cyclization of **16** with triethylamine–acetone provided the tetronic acid **17** in *ca.* 50% yield from **15** (UV $\lambda_{max}^{EtOH}$: 230, 265 nm; IR $\nu_{max}^{film}$ $cm^{-1}$: 1720, 1630, 1580). Methylation of **17** with ethereal diazomethane did not proceed smoothly, but in the presence of small amount of $BF_3$-etherate, **17** was methylated to two isomers **1** and **2** in the ratio of *ca.* 9:1 in a 10~20% yield. These were separated by column chromatography on silica gel. The product **1** was identical with isogregatin B, recently synthesized and assigned by Pattenden *et al.*, with respect to its spectral data. IR $\nu_{max}^{film}$ $cm^{-1}$: 1760, 1690, 1610, 1460, 1360; UV $\lambda_{max}^{EtOH}$: 227 and 250 (sh) nm; $^1$H-NMR ($CDCl_3$) $\delta$: 5.5~6.9 (4H, m), 4.15 (3H, s), 2.58 (3H, s), 2.3~2.0 (quintet like m), 1.59 (3H, s), 1.00 (3H, t, $J$=7 Hz); $^{13}$C-NMR ($CDCl_3$) $\delta$: 13.2, 23.3, 25.7, 30.6, 63.7, 82.4, 105.9, 126.3, 127.5, 132.3, 139.8, 169.4, 183.9, 195.0; MS *m/z*: 250 (56%), 235 (28), 221 (19), 217 (14), 207 (39), 193 (19), 189 (19), 185 (34), 165 (28), 149 (100). Another isomer **2** was identical with natural gregatin B in all spectral data. IR $\nu_{max}^{film}$ $cm^{-1}$: 1740 (sh), 1705, 1595, 1440, 1405, 1200, 1130, 1070, 1000; UV $\lambda_{max}^{EtOH}$: 235 and 265 nm; $^1$H-NMR ($CDCl_3$) $\delta$: 5.2~6.4 (4H, m), 3.82 (3H, s), 2.64 (3H, s), 2.14 (2H, quintet), 1.52 (3H, s), 0.99 (3H, t, $J$=7 Hz); MS *m/z* 250 (11%), 218 (16), 207 (5), 176 (32), 170 (21), 149 (53), 94 (100). In the preceding paper[4] we clarified the stereochemistry of natural aspertetronin A as (*R*) and gregatin A as (*S*). As the present synthetic scheme is applicable to the synthesis of chiral gregatin B, further synthetic work is now in progress.

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## REFERENCES

1) K. Kobayashi and T. Ui, *Tetrahedron Lett.*, **1975**, 4119.
2) N. Anke, H. Schwab and H. Achenbach, *J. Antibiotics*, **1980**, 931.
3) N. G. Clemo and G. Pattenden, *Tetrahedron Lett.*, **23**, 581, 585, 589 (1982).
4) K. Yamashita, A. Takaiwa and H. Nakada, *Agric. Biol. Chem.*, **44**, 2931 (1980).