A Fusarubin Isomer[1)]

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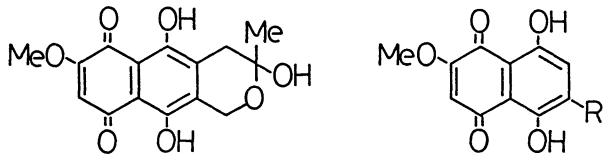
Synopsis. An isomer of fusarubin, 2-acetonyl-5,8-dihydroxy-7-hydroxymethyl-3-methoxy-1,4-naphthoquinone, was prepared from 2-hydroxymethyl-7-(2-hydroxypropyl)-1,4,5,6,8-pentamethoxynaphthalene.

Several new antibiotics, such as fusarubin (**1**),[2a)] erythrostominone,[2b)] javanicin,[2c)] bostrycin,[2d)] purpuromycin,[3)] and fredericamycin A,[4)] contain a 2-methoxynaphthazarin moiety; for the antibiotics above, that moiety is 5,8-dihydroxy-2-methoxy-1,4-naphthoquinone. We have already prepared two intermediates of them, **2** and **3**, as shown in Chart 1.[5)]



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2: R=CHO
3: R=CH_2OH

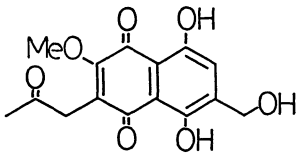

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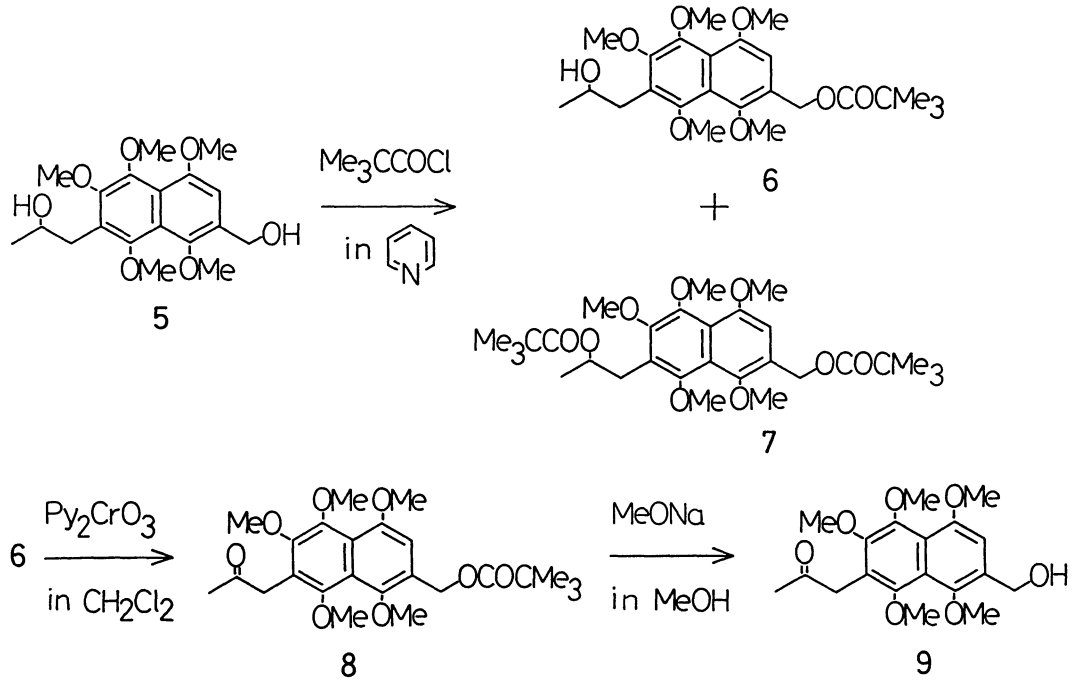
Chart 1.

As a part of our study of synthetic naphthoquinone derivatives, synthesis of fusarubin isomer (**4**) was attempted from 2-hydroxymethyl-7-(2-hydroxypropyl)-1,4,5,6,8-pentamethoxynaphthalene (**5**).

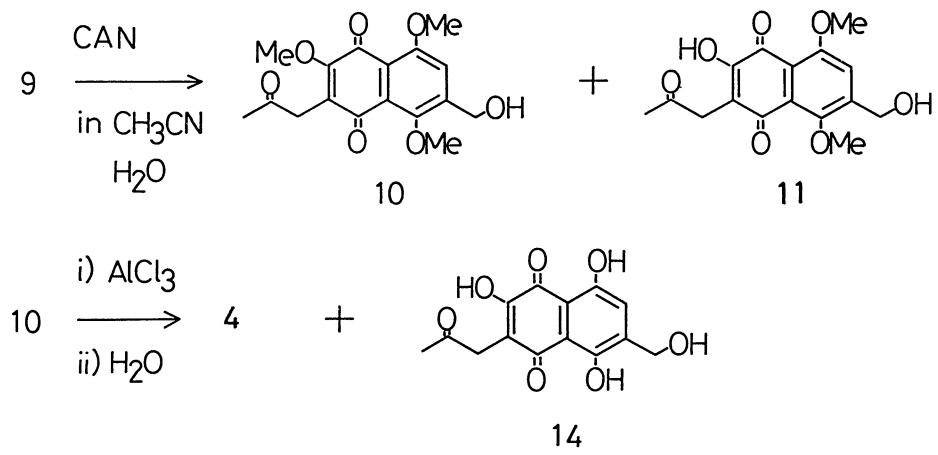
Results and Discussion

To specifically oxidize the 2-hydroxypropyl group of **5**,[6)] selective protection of the hydroxymethyl group in **5** was needed. Treatment of **5** with bulky pivaloyl chloride gave the monoester **6** in 46% yield as the major product, along with the diester **7** (10% yield). Oxidation of the secondary hydroxyl group in **6** with chromium(VI) oxide-pyridine(1/2)[7)] produced the ketone **8** (88% yield), which was reacted with sodium methoxide in methyl alcohol to give the alcohol **9** (91% yield) (Scheme 1).

Two-step demethylations[8)] of pentamethoxynaphthalene **9** were carried out by reaction with cerium(IV) ammonium nitrate (CAN) followed by reaction with aluminum chloride. Oxidative demethylation of **9** with CAN gave two quinones. One of them was presumed to be 3,5,8-trimethoxynaphthoquinone (**10**) (48% yield). Previously, in NMR studies of 1,4-naphthoquinone, it



Scheme 1.



Scheme 2.

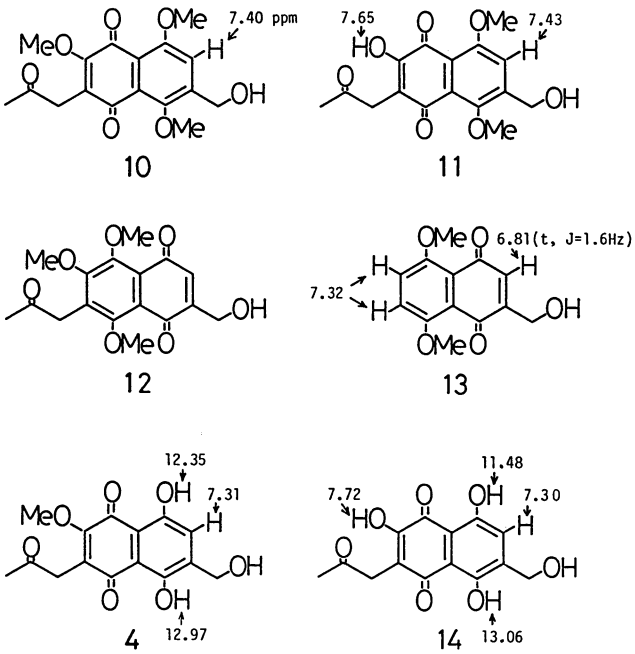


Chart 2.

was shown that the signals attributable to the quinone ring proton were always observed further upfield than the signals of the benzene ring protons and were located at δ=6—7.[9] If the structure of our product was **12**, the quinone ring proton should be observed as a triplet around δ=6.8 (the quinone proton signal of 2-hydroxymethyl-5,8-dimethoxy-1,4-naphthoquinone (**13**) was reported to be at δ=6.81).[10] However, our main product showed a singlet signal at δ=7.40, and it was confirmed that this proton was a benzene ring proton. The major product was therefore shown to be **10**. The minor product was similarly determined to be 5,8-dimethoxynaphthoquinone (**11**) (14% yield).

The second demethylation of **10** with aluminum chloride in dichloromethane gave 2-acetonyl-5,8-dihydroxy-7-hydroxymethyl-3-methoxy-1,4-naphthoquinone (**4**) (46% yield). This is a fusarubin isomer. 2-Acetonyl-3,5,8-trihydroxy-7-hydroxymethyl-1,4-naphthoquinone (**14**) was also produced in the reaction in 14% yield (Scheme 2). Their ^{1}H NMR spectra were assigned as shown in Chart 2.

Experimental

Melting points were determined with a Yanagimoto micro-melting point apparatus and were uncorrected. ^{1}H and ^{13}C NMR spectra were taken on a JEOL JNM-60 in $CDCl_3$ solutions unless otherwise specified, using Me_4Si and $CDCl_3$ as internal standards, respectively. Mass spectra and IR spectra were obtained with a JEOL DX-300 spectrometer, and a Hitachi 260-30 spectrometer, respectively. Column chromatography was carried out on silica gel (Wakogel C-200) eluting with chloroform.

The Reaction of 5 with Pivaloyl Chloride. To a solution of **5** (72 mg, 0.197 mmol) in dried pyridine (2 ml) was added pivaloyl chloride (28 mg, 0.236 mmol) at 0 °C. The reaction mixture was kept in a refrigerator (5 °C) overnight, then quenched with ice water and extracted with chloroform. The chloroform solution was washed sequentially with dil. HCl, aqueous $NaHCO_3$, and brine, then dried over Na_2SO_4 and concentrated. The residue was purified by silica-gel chromatography to give two oily products in the following order: 2-pivaloyloxymethyl-7-[2-(pivaloyloxy)propyl]-1,4,5,6,8-pentamethoxynaphthalene (**7**) (11 mg, 10% yield), 2-(2-hydroxypropyl)-7-pivaloyloxymethyl-1,3,4,5,8-pentamethoxynaphthalene (**6**) (41 mg, 46% yield).

6: IR (neat) 1730 (C=O), 1618, 1600, 1360, 1150, and 1050 cm^{-1}; ^{1}H NMR δ=1.25 (s, 9H, 3×CH_3), 1.30 (m, 4H, CH_3, OH), 3.05 (m, 2H, -C<u>H</u>$_2$CH(OH)-), 3.76 (s, 6H, 2×OCH_3), 3.85, 3.96, 4.00 (each s, 3H, OCH_3), 3.90 (m, 1H, CH), 5.33 (s, 2H, -C<u>H</u>$_2$OCOC$(CH_3)_3$-), and 6.79 (s, 1H, ArH); MS *m/z* 450 (M^+), 403, 349, 333, 289, and 57. HRMS, Found: *m/z* 450.2234. Calcd for $C_{24}H_{34}O_8$: M, 450.2253.

7: IR (neat) 1730 (C=O), 1600, 1360, 1150, and 1050 cm^{-1}; ^{1}H NMR δ=1.10 (s, 9H, 3×CH_3), 1.24 (d, *J*=6.0 Hz, 3H, CH_3), 1.25 (s, 9H, 3×CH_3), 3.07 (m, 2H, -C<u>H</u>$_2$CH(OCOC$(CH_3)_3$)-), 3.75 (s, 6H, 2×OCH_3), 3.82 (s, 3H, OCH_3), 3.88 (m, 1H, CH), 3.95, 4.00 (each s, 3H, OCH_3), 5.33 (s, 2H, -C<u>H</u>$_2$OCOC$(CH_3)_3$-), 6.77 (s, 1H, ArH); MS *m/z* 534 (M^+), 450, 392, 289, and 57. HRMS, Found: *m/z* 534.2884. Calcd for $C_{29}H_{42}O_9$: M, 534.2829.

2-Acetonyl-7-pivaloyloxymethyl-1,3,4,5,8-pentamethoxynaphthalene (8). Anhydrous chromium (VI) oxide (65 mg, 0.65 mmol) was added to a mixture of dried dichloromethane (5 ml) and pyridine (0.11 mml, 1.3 mmol) and stirred for 15 min. The alcohol **6** (49 mg, 0.11 mmol) in dried dichloromethane (2 ml) was added to the solution, stirred at room temperature for 30 min, and filtered. The filtrate was worked

up as usual and the residue was chromatographed on silica gel to give **8** (43 mg, 88% yield) as an oil. IR (neat) 1725 (ester, ketone C=O), 1600, 1355, 1150, and 1050 cm^{-1}; ^1H NMR δ=1.26 (s, 9H, 3×CH_3), 2.27 (s, 3H, $COCH_3$), 3.71 (s, 2H, -CH_2CO-), 3.76, 3.84 (each s, 3H, OCH_3), 3.94 (s, 6H, 2× OCH_3), 3.97 (s, 3H, OCH_3), 5.34 (s, 2H, -$C\underline{H}_2OCOC(CH_3)_3$-), and 6.80 (s, 1H, ArH); MS *m/z* 448 (M^+), 433, 405, 347, 289, and 57. HRMS, Found: *m/z* 448.2115. Calcd for $C_{24}H_{32}O_8$: M, 448.2107.

2-Acetonyl-7-hydroxymethyl-1,3,4,5,8-pentamethoxynaphthalene (9). Sodium methoxide (117 mg, 2.15 mmol) was added to a solution of **8** (194 mg, 0.43 mmol) in methyl alcohol (3 ml) and stirred overnight at room temperature in the dark. The solvent was removed under reduced pressure and the residue was decomposed by the addition of water, and extracted with chloroform. Column chromatography on silica gel gave **9** (143 mg, 91% yield) as an oil. IR (neat) 3450 (broad, OH), 1720 (C=O), 1600, 1360, and 1050 cm^{-1}; ^1H NMR: δ=1.88 (broad, 1H, OH), 2.26 (s, 3H, $COCH_3$), 3.70, 3.76, 3.84, 3.94, 3.99 (each s, 3H, OCH_3), 3.88 (s, 2H, -CH_2CO-), 4.86 (s, 2H, -$C\underline{H}_2OH$), and 6.86 (s, 1H, ArH); ^{13}C NMR δ=29.53 ($CO\underline{C}H_3$), 39.85 ($\underline{C}H_2CO$), 56.57 (CH_2OH), 60.92 (2C, OMe), 61.56, 62.34, and 62.68 (OMe), 106.63 (C-6), 121.20, 122.47, 123.26 (C-2), 129.66 (C-7), 144.92, 146.23, 149.36, 149.81, and 152.59 (C-OMe), and 183.15 (C=O); MS *m/z* 364 (M^+), 334, 301, 259, and 115; HRMS, Found: *m/z* 364.1513. Calcd for $C_{19}H_{24}O_7$: M, 364.1522.

Oxidative Demethylation of 9 with CAN. A solution of CAN (1.72 g, 3.25 mmol) in water (3 ml) was added dropwise to a solution of **9** (457 mg, 1.3 mmol) in acetonitrile (5 ml) and stirred at room temperature for 30 min. The reaction mixture was diluted with water and extracted with chloroform. The usual work-up and chromatographic purification (silica gel) gave two products: 2-acetonyl-7-hydroxymethyl-3,5,8-trimethoxy-1,4-naphthoquinone (**10**) (195 mg, 48% yield) and 2-acetonyl-3-hydroxy-7-hydroxymethyl-5,8-dimethoxy-1,4-naphthoquinone (**11**) (58 mg, 14% yield).

10: Orange crystals (hexane–ethanol (10 : 1)); mp 130—131 °C; IR (KBr) 1705 (ketone C=O), 1655, 1630 (each quinone C=O), 1580, 1215, and 1030 cm^{-1}; ^1H NMR δ=2.29 (s, 3H, $COCH_3$), 2.50 (broad, 1H, OH), 3.68 (s, 2H, -CH_2CO-), 3.76, 3.98, 4.08 (each s, 3H, OCH_3), 4.79 (s, 2H, -$C\underline{H}_2OH$), and 7.40 (s, 1H, ArH); ^{13}C NMR δ=30.18 (CH_3), 38.41 ($\underline{C}H_2COCH_3$), 56.70 (CH_2OH), 60.18, 61.04, and 61.78 (OMe), 116.99 (C-6), 119.05, 124.60, 126.31 (C-2), 145.17 (C-7), 150.60, 156.43, and 158.49 (C-OMe), 179.93 (C-4), 184.32 (C-1), and 204.73 (C=O); MS *m/z* 334 (M^+), 319, 291, 277, and 231. HRMS, Found: *m/z* 334.1065. Calcd for M, 334.1053. Found: C, 60.80; H, 5.39%. Calcd for $C_{17}H_{18}O_7$: C, 61.07; H, 5.43%.

11: Orange crystals (hexane–ethanol(3 : 1)); mp 186.5—187.5 °C; IR (KBr) 3420, 3200 (each OH), 1695 (ketone C=O), 1660, 1640 (each quinone C=O), 1360, 1220, 1085, and 1040 cm^{-1}; ^1H NMR δ=2.30 (s, 4H, $COCH_3$, -$CH_2O\underline{H}$), 3.69 (s, 2H, -CH_2CO-), 3.79, 4.04 (each s, 3H, OCH_3), 4.85 (d, *J*=5.0 Hz, 2H, -$C\underline{H}_2OH$), 7.44 (s, 1H, ArH), and 7.65 (s, 1H, ArOH); ^{13}C NMR (DMSO-d_6) δ=29.38 (CH_3), 37.84 ($\underline{C}H_2COCH_3$), 56.36 (CH_2OH), 57.90 and 60.93 (OMe), 116.60 (3C: C-2, C-6), 124.14, 147.46 (C-7), 149.80, 155.06, and 156.08 (C-OH, 2× C-OMe), 178.72 (C-4), 183.29 (C-1), and 203.99 (C=O); MS *m/z* 320 (M^+), 305, 278, 260, 245, and 217. Found: C, 59.80; H, 5.11%. Calcd for $C_{16}H_{16}O_7$: C, 60.00; H, 5.03%.

Demethylation of 10 with Aluminum Chloride. Aluminum chloride (730 mg, 5.5 mmol) was added to a solution of **10** (183 mg, 0.55 mmol) in dichloromethane (5 ml) cooled in an ice bath. After stirring at room temperature for 2 h, the reaction mixture was decomposed by the addition of 5 wt% aqueous oxalic acid (100 ml) and extracted with chloroform. The usual work-up and chromatographic purification (silica gel) gave two products, a fusarubin isomer **4** (77 mg, 46% yield) and 2-acetonyl-3,5,8-trihydroxy-7-hydroxymethyl-1,4-naphthoquinone (**14**) (22 mg, 14% yield).

4: Red-brown crystals (hexane–ethanol); mp 173.5—174.5 °C; IR (KBr) 3430 (broad, OH), 1710 (ketone C=O), 1605 (quinone C=O), 1420, 1270, 1170, and 1080 cm^{-1}; ^1H NMR δ=2.31 (s, 3H, $COCH_3$), 3.75 (s, 2H, -CH_2CO-), 4.18 (s, 3H, OCH_3), 4.78 (s, 2H, -$C\underline{H}_2OH$), 7.31 (s, 1H, ArH), 12.35 (s, 1H, C-5-OH), and 12.97 (s, 1H, C-8-OH); ^{13}C NMR (DMSO-d_6) δ=29.84 (CH_3), 57.50 (CH_2OH), 61.56 (OMe), 109.74, 110.20, 124.54 (C-6), 128.88 (C-2), 145.92 (C-7), 156.26, 158.72, 159.58 (C-OMe, 2×C-OH), 180.15 (C-4), 185.41 (C-1), and 203.81 (C=O); MS, *m/z* 306 (M^+), 264, 249, 246, and 203. HRMS, Found: *m/z* 306.0761. Calcd for M, 306.0740. Found: C, 58.62; H, 4.83%. Calcd for $C_{15}H_{14}O_7$: C, 58.82; H, 4.61%.

14: Red crystals (ligroin–benzene–ethanol (10 : 1 : 1)); mp 218 °C (decomp); IR (KBr) 3420, 3230 (each OH), 1700 (ketone C=O), 1610 (quinone C=O), 1560, 1420, 1310, 1180, and 1090 cm^{-1}; ^1H NMR δ=2.31 (s, 3H, $COCH_3$), 3.74 (s, 2H, -CH_2CO-), 4.80 (s, 2H, $C\underline{H}_2OH$), 7.30 (s, 1H, ArH), 7.72 (s, 1H, C-3-OH), 11.48 (s, 1H, C-5-OH), and 13.06 (s, 1H, C-8-OH); ^{13}C NMR (DMSO-d_6) δ=29.61 (CH_3), 37.38 ($\underline{C}H_2COCH_3$), 57.61 (CH_2OH), 109.34, 109.51, 118.37 (C-2), 122.71 (C-6), 145.92 (C-7), 153.40, 156.94, and 157.80 (C-OH), 181.69 (C-4), 187.98 (C-1), and 203.87 (C=O); MS *m/z* 292 (M^+), 250, 232, and 43. HRMS, Found: *m/z* 292.0563. Calcd for M, 292.0582. Found: C, 57.69; H, 4.61%. Calcd for $C_{14}H_{12}O_7$: C, 57.54; H, 4.14%.

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