Synthetic Studies of Rifamycins. VII.[1] A Facile Synthesis of the Aromatic Chromophore of Rifamycin S through a Rifamycin W Aromatic Segment

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(Received March 3, 1985)

The intact aromatic chromophore of rifamycin S, 7-amino-2,5-dihydroxy-2,4-dimethyl-naphtho[2,1-*b*]furan-1,6,9(2*H*)-trione, was synthesized through the rifamycin W aromatic segment, 1-[5,8-dimethoxy-2,4-bis(methoxymethoxy)-3-methyl-6-nitro-1-naphthyl]-1-propanone which was prepared in 9 steps and 29.6% overall yield from 2,6-bis(benzyloxy)-3,5-dibromotoluene and furan.

In the preceding paper[1] of this series, we described a simple and convenient preparation of the nitronaphthalene derivative **1** which was demonstrated to be a promising aromatic segment for the total synthesis of rifamycin W (**2**)[2] by the successful aldol coupling with the aliphatic segment[3] of **2**. Although the methoxyl groups at C-2 and C-4 of **1** were quite stable during the elaboration[1] of **1** toward the total synthesis of **2**, the effective ether bond cleavage (de-*O*-methylation) on these methoxyl groups, that is indispensable at the final stage of the conquest of **2**, should naturally become the crucial problem. In this respect, we found that the new nitronaphthalene derivative **3**, which was expected to be a more promising aromatic segment for the rifamycin W synthesis,[4] was a synthetic intermediate suitable for the intact aromatic chromophore **4**[5] of rifamycin S (**5**). A synthesis of the aromatic segment of **5** has been reported by Kishi *et al.*[6] and an elegant and shorter synthesis of **4** has recently been reported by Kelly *et al.*[7] We now describe a facile synthesis of **4** through the new aromatic segment **3**.

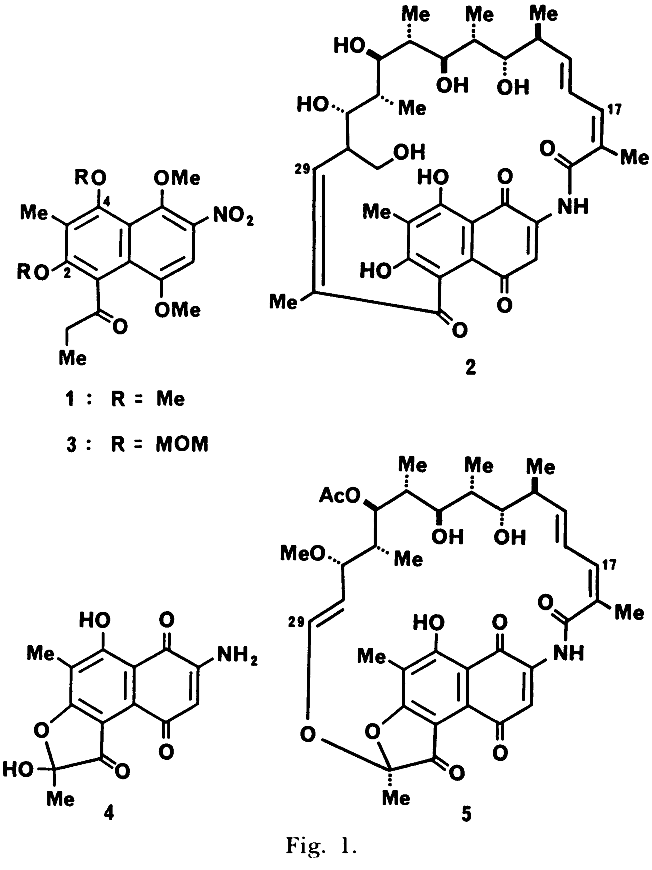


Fig. 1.

The starting material, 2,6-bis(benzyloxy)-3,5-dibromotoluene (**7**), obtained in a 95% yield by benzylation of 3,5-dibromo-2,6-toluenediol (**6**),[8] was treated with 3.5 equimolar amounts of sodium amide and 30 equimolar amounts of furan in THF at 57 °C for 10 h to give the bromoepoxide **8** in a 97% yield. Lithiation of **8** with 1.2 equimolar amounts of butyllithium in THF at −105 °C followed by treatment with 5 equimolar amounts of propanal afforded **9** in an 87% yield as an epimeric mixture. Oxidation of **9** with pyridinium chlorochromate (PCC) and subsequent treatment of the resulting epoxy ketone **10** with perchloric acid in THF at room temperature afforded the naphthol **11** in a 79% yield from **9** as a sole product. The structure shown for **11** was established by the following manner. The aforesaid lithiation of **8** followed by carboxylation afforded the naphthoic acid **12**. The ring-opening reaction of this epoxy acid by treatment with perchloric acid in THF proceeded very slowly at room temperature and was accompanied by de-

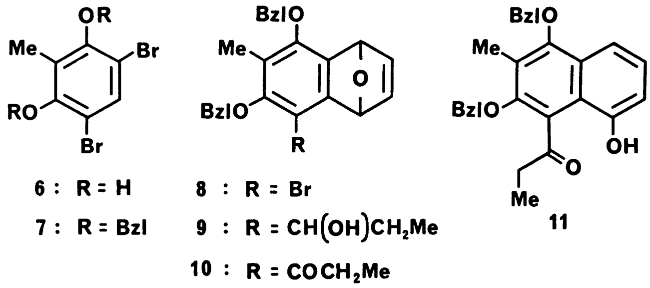


Fig. 2.

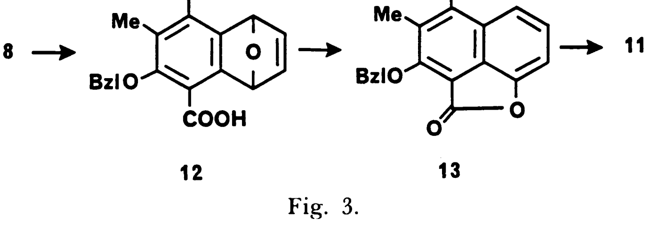
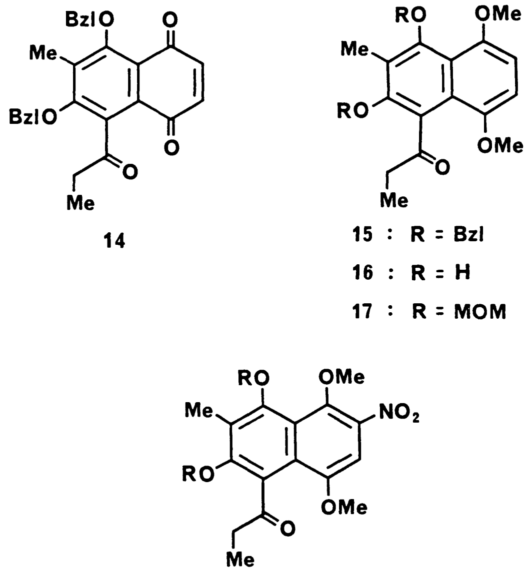


Fig. 3.

composition at elevated temperature. After many other unsuccessful results, the lactone **13** could be obtained in a 65% yield by treatment of **12** with 0.1 equimolar amounts of sulfuric acid in acetic anhydride. The reaction of **13** with equimolar amount of ethyllithium in ether afforded **11**. This sample of **11** proved to be identical with the specimen of **11** derived from **10** in all respects. To introduce a hydroxyl function at C-5 of **11**, **11** was subjected to oxidation using *N*-bromosuccinimide in aqueous acetic acid,[1,9] but only decomposition took place. Among various conditions studied, the oxidation of **11** using three equimolar amounts of thallium(III) nitrate[10] in methanol at 0 °C proceeded smoothly to give the naphthoquinone **14** in an 82% yield. Catalytic hydrogenation of **14** with hydrogen in the presence of Lindlar catalyst and pyridine in acetone afforded the air sensitive hydronaphthoquinone, which was immediately methylated with dimethyl sulfate and potassium carbonate to give **15** in a 74% yield. Conversion of the benzyl ether into the methoxymethyl ether was carried out by debenzylation of **15** followed by methoxymethylation of the resulting diol **16** to afford **17** in a 95% yield. Nitration of **17** with copper(II) nitrate[1,11] in acetic anhydride at −40 °C afforded regiospecifically the nitronaphthalene **3** in a 77% yield. The structural elucidation of **3** was carried out as follows: cleavage of the methoxymethyl ether of **3** by treatment with 1 M[†] HCl in THF gave the diol **18**, which was methylated to give the tetramethoxynaphthalene proved to be identical with **1**[1] in all respects.



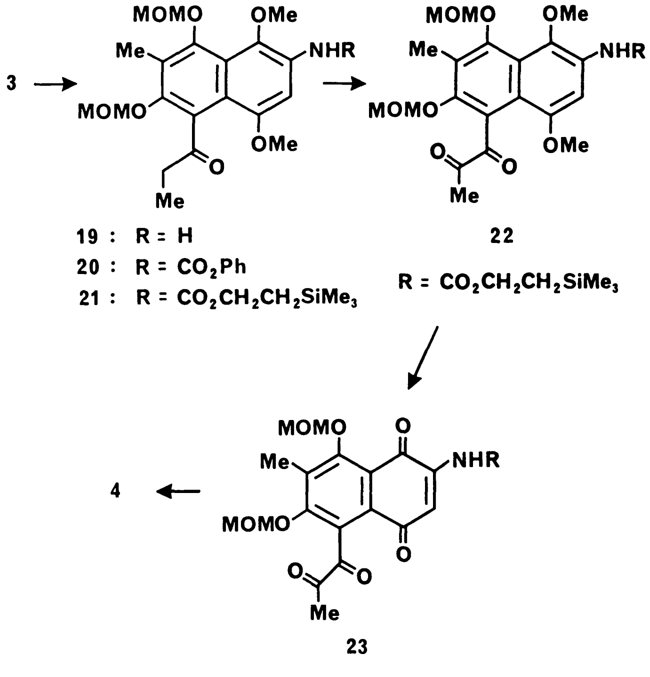
14

15 : R = Bzl
16 : R = H
17 : R = MOM

3 : R = MOM
18 : R = H
1 : R = Me

Fig. 4.

Conversion of **3** into the target chromophore **4** was achieved by the following procedure. Thus, reduction of **3** with hydrogen in the presence of 5% palladium on charcoal led to the amine **19**. To protect the amino group of **19**, the acid-labile protecting group was selected because acidic conditions were necessary for the formation of the furanone ring along with the removal of both the amino and the phenol protecting groups at the last stage in the synthesis of **4**. *t*-Buthoxycarbonyl group was first chosen but the corresponding carbamate was not obtained in a satisfactory yield. 2-(Trimethylsilyl)ethoxycarbonyl group afforded a good result, namely, the amine **19** was transformed by the Meyers' procedure[12] into the 2-(trimethylsilyl)ethyl carbamate **21** *via* the phenyl carbamate **20** in an 89% yield. Oxidation of **21** with oxygen[6,13] in the presence of 15 equimolar amounts of potassium *t*-butoxide in a mixture of *t*-butyl alcohol, dimethyl sulfoxide (DMSO), and 1,2-dimethoxyethane (DME) gave the α-diketone **22** in an 88% yield. In this reaction, only the starting material was recovered when DMSO was absent. Oxidative demethylation of **22** with ammonium cerium(IV) nitrate[14] in aqueous acetonitrile provided the naphthoquinone **23** in an 86% yield. Exposure of **23** to 100% trifluoroacetic acid[15] (TFA) at 0 °C for 1.5 h gave the target aminonaphthoquinone **4** in a 93% yield. The spectral data (IR, UV, ^{1}H-NMR) of **4** were indistinguishable from those of naturally occurring **4**.[5]



19 : R = H
20 : R = CO$_2$Ph
21 : R = CO$_2$CH$_2$CH$_2$SiMe$_3$

22

R = CO$_2$CH$_2$CH$_2$SiMe$_3$

23

R = CO$_2$CH$_2$CH$_2$SiMe$_3$

Fig. 5.

Experimental

Melting points were determined on a micro hot-stage Yanaco MP-S3 and were uncorrected. IR spectra were recorded on a Hitachi Perkin-Elmer 225 spectrometer, UV spectra on JAS·CO UVIDEC-1 spectrometer, and ^{1}H-NMR

[†] 1 M=1 mol dm^{-3}.

spectra on Varian EM-390 spectrometer in $\mathrm{CDCl_3}$ using TMS as internal standard. Silica gel TLC and column chromatography were performed on Merck TLC 60F-254 and Wakogel C-200, respectively. In general, evaporation of solvents was carried out under reduced pressure below 30 °C.

*2,6-Bis(benzyloxy)-3,5-dibromotoluene (**7**).* To an ice-cold stirred suspension of **6** (1.00 g, 3.55 mmol) and potassium carbonate (1.23 g, 8.90 mmol) in dry acetone (10 ml), benzyl bromide (1.05 ml, 8.83 mmol) was added dropwise. After the addition was complete, the mixture was stirred at 60 °C for 4 h and filtered with celite. The filter cake was washed with acetone and the combined filtrate and washings were evaporated. The residue was chromatographed on silica gel (82 g) with 25:1 hexane–ethyl acetate to afford **7** (1.56 g, 95%) as colorless crystals: mp 91.5—92.5 °C (needles from ethyl acetate–methanol); $R_f=0.34$ (25:1 hexane–ethyl acetate); UV (EtOH) λ 214 nm (log ε 4.63); ^{1}H-NMR $\delta=2.22$ (3H, s, ArMe), 4.96 (4H, s, $\mathrm{2\times OC\underline{H}_2Ph}$), and 7.30—7.75 (11H, m, H-4 and 2×Ph).

Found: C, 54.32; H, 4.04; Br, 34.27%. Calcd for $\mathrm{C_{21}H_{18}O_2Br_2}$: C, 54.57; H, 3.93; Br, 34.58%.

*5,7-Bis(benzyloxy)-8-bromo-1,4-dihydro-6-methyl-1,4-epoxynaphthalene (**8**).* To a solution of **7** (10.0 g, 21.6 mmol) in dry THF (70 ml) were added furan (47.0 ml, 646 mmol) and sodium amide (2.95 g, 75.6 mmol). After the mixture was stirred at 57 °C for 10 h, the insoluble matter was filtered with celite and the filter cake was washed with ether. The combined filtrate and washings were evaporated and the residue was chromatographed on silica gel (240 g) with 50:1 toluene–ethyl acetate to give **8** (9.61 g, 99%) as a brown syrup. This syrup was treated with activated carbon in ether to afford a yollow-brown syrup (9.41 g, 97%) of **8**. An analytical sample (colorless syrup) was obtained after the additional column chromatography with 5:1 hexane–ethyl acetate: $R_f=0.13$ (20:1 hexane–ethyl acetate); UV (EtOH) λ 218 nm (log ε 4.57); ^{1}H-NMR $\delta=2.14$ (3H, s, ArMe), 4.88 and 5.05 (each 2H, each s, $\mathrm{2\times OC\underline{H}_2Ph}$), 5.79 and 5.93 (each 1H, each dd, H-1 and 4, $J=1.0$ and 2.0 Hz), 6.75 and 7.04 (each 1H, each dd, H-2 and 3, $J=5.3$ and 2.0 Hz), and 7.42 (10H, s, 2×Ph).

Found: C, 66.90; H, 4.82; Br, 18.02%. Calcd for $\mathrm{C_{25}H_{21}O_3Br}$: C, 66.83; H, 4.71; Br, 17.78%.

*1-[2,4-Bis(benzyloxy)-5,8-dihydro-3-methyl-5,8-epoxy-1-naphthyl]-1-propanol (**9**).* To a stirred solution of **8** (9.41 g, 20.9 mmol) in dry THF (84 ml) at −105 °C under argon was added 1.42 M butyllithium in hexane (17.7 ml, 25.1 mmol) over a period of 4 min. After being stirred at the same temperature for 6 min, propanal (7.55 ml, 105 mmol) was added to the mixture as soon as possible. The reaction mixture was stirred at the same temperature for 30 min and treated with a saturated aqueous $\mathrm{NH_4Cl}$ solution (80 ml). After being allowed to warm to room temperature, the resulting mixture was extracted with ether (100 ml×2), and the extract was washed with a saturated aqueous NaCl solution (70 ml), dried, and evaporated. The residue was chromatographed on silica gel (450 g) with 4:1 toluene–ethyl acetate to give **9** (7.80 g, 87%) as pale yellow-brown crystals. This sample showed two spots (R_f 0.32 and 0.21) on TLC with 15:1 chloroform–ethyl acetate. A part of this was separated by silica gel column chromatography with 15:1 chloroform–ethyl acetate to give colorless crystals of **9a** and **9b** with a ratio of 1.2:1:

9a, $R_f=0.32$ (15:1 chloroform–ethyl acetate), mp 107—108 °C (needles from chloroform–hexane); IR (KBr) 3410 cm^{-1}; UV (EtOH) λ (log ε) 222(4.51), 260 (sh, 3.34), and 295 nm (sh, 2.86); ^{1}H-NMR $\delta=0.95$ (3H, t, $\mathrm{CH_2\underline{Me}}$, $J=7.5$ Hz), 1.60—2.00 (3H, m, OH and $\mathrm{C\underline{H}_2Me}$), 2.18 (3H, s, ArMe), 4.79 and 5.06 (each 2H, each s, $\mathrm{2\times OC\underline{H}_2Ph}$), 4.80—5.00 (1H, m, $\mathrm{C\underline{H}OH}$), 5.88 and 6.08 (each 1H, each dd, H-5 and 8, $J=1.0$ and 1.8 Hz), 6.74 and 6.98 (each 1H, each dd, H-6 and 7, $J=1.8$ and 5.6 Hz), and 7.44 (10H, s, 2×Ph).

Found: C, 78.35; H, 6.67%. Calcd for $\mathrm{C_{28}H_{28}O_4}$: C, 78.48; H, 6.59%.

9b, $R_f=0.21$ (15:1 chloroform–ethyl acetate), mp 107—108 °C (needles from chloroform–hexane); IR (KBr) 3430 cm^{-1}; UV (EtOH) λ (log ε) 222(4.51), 260 (sh, 3.29), and 295 nm (sh, 2.81); ^{1}H-NMR $\delta=0.86$ (3H, t, $\mathrm{CH_2\underline{Me}}$, $J=7.5$ Hz), 1.40—1.85 (3H, m, OH and $\mathrm{C\underline{H}_2Me}$), 2.18 (3H, s, ArMe), 4.79 and 5.06 (each 2H, each s, $\mathrm{2\times OC\underline{H}_2Ph}$), 4.80—5.00 (1H, m, $\mathrm{C\underline{H}OH}$), 5.88 and 6.25 (each 1H, each dd, H-5 and 8, $J=1.0$ and 1.8 Hz), 6.79 and 6.99 (each 1H, each dd, H-6 and 7, $J=1.8$ and 5.6 Hz), and 7.44 (10H, s, 2×Ph).

Found: C, 78.60; H, 6.70%. Calcd for $\mathrm{C_{28}H_{28}O_4}$: C, 78.48; H, 6.59%.

*1-[2,4-Bis(benzyloxy)-5,8-dihydro-3-methyl-5,8-epoxy-1-naphthyl]-1-propanone (**10**).* To a stirred mixture of PCC (10.3 g, 47.8 mmol), molecular sieves 3A powder (15.9 g), and dry dichloromethane (40 ml) was added a solution of **9** (6.80 g, 15.9 mmol) in dry dichloromethane (34 ml) at room temperature. After being stirred at room temperature for 0.5 h, the reaction mixture was diluted with ether (75 ml) and the resulting suspension was transferred to a column filled with silica gel (130 g). The column was eluted with ether and the eluant was evaporated to give practically pure sample of **10** (6.70 g, 98%) as pale yellow crystals. An analytical sample was obtained after recrystallization from ethyl acetate–hexane: mp 112—114 °C (colorless plates); $R_f=0.45$ (3:1 hexane–ethyl acetate) ; IR (KBr) 1663 cm^{-1}; UV (EtOH) λ (log ε) 212(4.39), and 247 nm (4.23) ; ^{1}H-NMR $\delta=1.08$ (3H, t, $\mathrm{CH_2\text{-}\underline{Me}}$, $J=7.0$ Hz), 2.15 (3H, s, ArMe), 2.70—3.20 (2H, m, $\mathrm{C\underline{H}_2Me}$), 4.70 and 4.73 (each 1H, ABq, $\mathrm{OC\underline{H}_2Ph}$, $J_{gem}=12.0$ Hz), 5.11 and 5.21 (each 1H, ABq, $\mathrm{OC\underline{H}_2Ph}$, $J_{gem}=12.0$ Hz), 5.85 and 5.95 (each 1H, each br, H-5 and 8), 6.77 and 7.10 (each 1H, each dd, H-6 and 7, $J=1.8$ and 5.3 Hz), and 7.42 and 7.45 (each 5H, each s, 2×Ph).

Found: C, 78.58 ; H, 6.30%. Calcd for $\mathrm{C_{28}H_{26}O_4}$; C, 78.85 ; H, 6.14%.

*2,4-Bis(benzyloxy)-5,8-dihydro-3-methyl-5,8-epoxy-1-naphthalenecarboxylic Acid (**12**).* To a stirred solution of **8** (960 mg, 2.14 mmol) in dry THF (8.55 ml) at −100 °C under argon was added 1.39 M butyllithium in hexane (1.84 ml, 2.56 mmol). After being stirred at the same temperature for 30 min, $\mathrm{CO_2}$ gas was bubbled through the reaction mixture for 20 min. The mixture was allowed to warm to 0 °C and then acidified with 1 M HCl (30 ml). The mixture was extracted with ether and the extract was washed with a saturated aqueous NaCl solution, dried, and evaporated. The residue was chromatographed on silica gel (48 g) with 4:1:0.05 toluene–ethyl acetate–acetic acid to afford **12** (689 mg, 78%) as a brown syrup. This slightly impure syrup was crystallized from 1:4 acetone–hexane to afford colorless needles: mp 144—145 °C ; $R_f=0.21$ (4:1:0.05 toluene–ethyl acetate–acetic acid); IR (KBr) 1688 cm^{-1}; UV (EtOH) λ (log ε) 212(4.49), 233(4.47), and 297 nm (3.09); ^{1}H-NMR $\delta=2.21$ (3H, s, ArMe), 4.91 (2H, s, $\mathrm{OC\underline{H}_2Ph}$), 5.15 and 5.30 (each 1H, ABq, $\mathrm{OC\underline{H}_2Ph}$, $J_{gem}=12.0$ Hz), 6.02 and 6.53 (each 1H, each dd, H-5 and 8, $J=1.2$ and 1.8 Hz), 6.78 and 7.12 (each 1H, each dd, H-6 and 7, $J_{6,7}=5.7$ Hz, $J=1.8$ Hz), and 7.45 (10H, s, 2×Ph).

Found: C, 75.48 ; H, 5.57%. Calcd for $C_{26}H_{22}O_5$: C, 75.35 ; H, 5.35%.

3,5-Bis(benzyloxy)-4-methyl-2H-naphtho[1,8-bc]furan-2-one(13). A 1.0 ml solution of 0.012 M concd H_2SO_4 in acetic anhydride was added to **12** (49.4 mg, 0.119 mmol) at 21 °C. The resulting white suspension was stirred for 10 min, and diluted with ether. The ether layer was washed with water (3 times) and a saturated aqueous NaCl solution, dried, and evaporated. The residue was chromatographed on silica gel (4.8 g) with 10:1 hexane-acetone to give **13** (30.5 mg, 65%) as colorless crystals. An analytical sample was obtained after recrystallization from chloroform-hexane: mp 136—137 °C (cottony crystals); R_f=0.23 (10:1 hexane-acetone); IR (KBr) 1754 cm^{-1}; UV (EtOH) λ (log ε) 220(4.50), 260(4.55), and 333 nm (4.04); ^{1}H-NMR δ=2.30 (3H, s, ArMe), 5.18 (2H, s, $O\underline{CH_2}Ph$), 6.00 (2H, s, $O\underline{CH_2}Ph$), 7.11 and 7.65 (each 1H, each d, H-6 and 8, J=7.2 Hz), and 7.30—7.60 (11H, m, 2×Ph and H-7).

Found: C, 78.50; H, 5.15%. Calcd for $C_{26}H_{20}O_4$: C, 78.77 ; H, 5.08%.

1-[2,4-Bis(benzyloxy)-8-hydroxy-3-methyl-1-naphthyl]-1-propanone (11). (a) To a solution of **10** (8.30 g, 19.5 mmol) in THF (140 ml), 60% $HClO_4$ (1.26 ml) was added. After being stirred at 25 °C for 35 h, the reaction mixture was diluted with ether (140 ml), washed with water (100 ml×3) and a saturated aqueous NaCl solution (100 ml×1), dried, and evaporated. The residue was recrystallized from THF (28 ml) and hexane (55 ml) at −25 °C overnight to afford **11** (3.21 g) as pale yellow-brown crystals. The mother liquor was evaporated and the residue was chromatographed on silica gel (250 g) with 8:1 toluene-ethyl acetate to afford additional **11** (3.53 g). The total amount was 6.74 g (81%). An analytical sample (colorless mossy crystals) was obtained after recrystallization (two times) from a mixture of chloroform and hexane: mp 188—190 °C (decomp); R_f=0.31 (8:1 toluene-ethyl acetate); IR (KBr) 3390 and 1675 cm^{-1} ;UV (0.01 M HCl-EtOH) λ (log ε) 221(4.77), 242(4.76), and 306 nm (4.00); ^{1}H-NMR δ=1.18 (3H, t, $CH_2\underline{Me}$, J=7.0 Hz), 2.39 (3H, s, ArMe), 2.94 (2H, q, $\underline{CH_2}Me$, J=7.0 Hz), 4.90 and 5.02 (each 2H, each s, 2×$O\underline{CH_2}Ph$), 6.28 (1H, s, OH), 6.81 and 7.71 (each 1H, each d, H-5 and 7, J=7.5 Hz), and 7.15—7.65 (11H, m, H-6 and 2×Ph).

Found: C, 78.60; H, 6.20%. Calcd for $C_{28}H_{26}O_4$; C, 78.85; H, 6.14%.

(b) To an ice-cold stirred suspension of **13** (30.4 mg, 0.0767 mmol) in dry ether (1.67 ml), 1.60 M ethyllithium in ether (0.0478 ml, 0.0765 mmol) was added dropwise. After being stirred at 0 °C for 1 h, a saturated aqueous NH_4Cl solution was added to the mixture. The mixture was extractred with ether and the extracts were washed with a saturated aqueous NaCl solution, dried, and evaporated. The residue was chromatographed on silica gel (3.2 g) with 8:1 toluene-ethyl acetate to give 8.5 mg (26%) of pale yellow-brown crystals and the unchanged starting lactone **13** (19.5 mg, 64% recovered). Recrystallization from chloroform-hexane gave slightly brown mossy crystals. This material was identical with **11** prepared from **10** in all respects (TLC, ^{1}H-NMR, IR, UV, mp).

5,7-Bis(benzyloxy)-6-methyl-8-propionyl-1,4-naphthalenedione (14). To an ice-cold stirred suspension of **11** (9.29 g, 21.8 mmol) in methanol (186 ml) a solution of thallium(III) nitrate trihydrate (29.0 g, 65.3 mmol) in methanol (145 ml) was added dropwise. The resulting mixture was stirred at 0 °C for 3 h and treated with ice-cold water (330 ml). The mixture was extrated with ethyl acetate (650 ml) and the extract was washed with a saturated aqueous $NaHCO_3$ solution, water, and a saturated aqueous NaCl solution successively, dried and evaporated. The residue was chromatographed on silica gel (480 g) with 13:1 toluene-ethyl acetate to afford **14** (7.90 g, 82%) as yellow crystals. An analytical sample was obtained after recrystallization (three times) from ethanol: mp 144.5—146 °C (yellow needles); R_f=0.54 (8:1 toluene-ethyl acetate); IR (KBr) 1698, 1665, and 1615 cm^{-1}; UV (EtOH) λ (log ε) 231(4.57), 253(4.35), and 363 nm (3.57); ^{1}H-NMR δ=1.25 (3H, t, $CH_2\underline{Me}$, J=7.2 Hz), 2.22 (3H, s, ArMe), 2.55—2.95 (2H, m, $\underline{CH_2}Me$), 4.83 and 4.97 (each 2H, br s and s, 2×$O\underline{CH_2}Ph$), 6.89 (2H, s, H-2 and 3), and 7.42 (10H, s, 2×Ph).

Found: C, 76.60 ; H, 5.66%. Calcd for $C_{28}H_{24}O_5$: C, 76.35 ; H, 5.49%.

1-[2,4-Bis(benzyloxy)-5,8-dimethoxy-3-methyl-1-naphthyl]-1-propanone (15). A mixture of **14** (5.00 g, 11.4 mmol), pyridine (6.89 ml, 85.2 mmol), Lindlar catalyst (1.50 g), and acetone (200 ml) was vigorously stirred at room temperature for 10 min under bulbling with H_2. The suspension was filtered with celite and the filter cake was washed with acetone under an argon atomosphere. To the combined filtrate and washings, dimethyl sulfate (10.7 ml, 113 mmol) and K_2CO_3 (7.84 g, 56.7 mmol) were added and vigorously stirred at room temperature for 41 h. To the resulting mixture dimethyl sulfate (10.7 ml, 113 mmol) and K_2CO_3 (7.84 g, 56.7 mmol) were added and stirring was continued for additional 52 h. The insoluble matter was filtered with celite and the filter cake was washed with acetone. The combined filtrate and washings were evaporatred and the residue was dissolved in ethyl acetate (300 ml). The solution was washed with water (100 ml) and a saturated aqueous NaCl solution (100 ml), dried, and evaporated. The residue was chromatographed on silica gel (300 g) with 17:1 toluene-ethyl acetate to give **15** (3.97 g, 74%) as pale green crystals. An analytical sample was obtained after recrystallization from chloroform-hexane: mp 118.7—119.5 °C (colorless needles); R_f=0.35 (17:1 toluene-ethyl acetate); IR (KBr) 1708 cm^{-1}; UV (EtOH) λ (log ε) 222 (4.72), 249 (4.46), 327 (3.90), and 340 nm (3.86); ^{1}H-NMR δ=1.19 (3H, t, $CH_2\underline{Me}$, J=7.0 Hz), 2.36 (3H, s, ArMe), 2.83 (2H, dq, $\underline{CH_2}Me$, J_{gem}=7.0 Hz), 3.85 (6H, s, 2×OMe), 4.85 and 4.86 (each 1H, ABq, $O\underline{CH_2}Ph$, J_{gem}=10.5 Hz), 4.92 (2H, s, $O\underline{CH_2}Ph$), 6.77 (2H, s, H-6 and 7), and 7.20—7.65 (10H, m, 2×Ph).

Found: C, 76.74; H, 6.52%. Calcd for $C_{30}H_{30}O_5$: C, 76.57; H, 6.43%.

1-(2,4-Dihydroxy-5,8-dimethoxy-3-methyl-1-naphthyl)-1-propanone (16). A solution of **15** (1.53 g, 3.25 mmol) in ethyl acetate (30 ml) was stirred with palladium black (in methanol) at 25 °C for 20 min under bubbling with H_2. The filtered solution was then evaporated to afford the crude **16** (944 mg, 100%) as yellow-brown crystals. This sample was pure enough for the next steps without further purification. A part of this was recrystallized from 1:3 ethyl acetate-hexane to give an analytical sample as yellow-green needles: mp 111—112 °C; R_f=0.40 (3:1 hexane-acetone); IR (KBr) 3305 and 1630 cm^{-1}; UV (0.01 M HCl-EtOH) λ (log ε) 232 (4.40), 272 (3.76), 315 (3.61), 347 (3.57), and 370 nm (3.41); ^{1}H-NMR δ=1.12 (3H, t, $CH_2\underline{Me}$, J=7.5 Hz), 2.21 (3H, s, ArMe), 2.35—2.80 (2H, m, $\underline{CH_2}Me$), 3.81 and 4.03 (each 3H, each s, 2×OMe), 6.67 and 6.73 (each 1H, ABq, H-6 and 7, J=9.0 Hz), and 10.26 and 10.73 (each 1H, s and br s, 2×OH).

Found: C, 65.95; H, 6.20%. Calcd for $C_{16}H_{18}O_5$: C, 66.19; H, 6.25%.

*1-[5,8-Dimethoxy-2,4-bis(methoxymethoxy)-3-methyl-1-naphthyl]-1-propanone (**17**).* To an ice-cold stirred solution of **16** (841 ml, 2.90 mmol) in dry THF (16.8 ml) was added sodium hydride (209 mg, 8.71 mmol) and the mixture was stirred at 20 °C for 15 min, then cooled to 0 °C. To this was added chloromethyl methyl ether (0.660 ml, 8.69 mmol) and the mixture was stirred at 20 °C for 1 h. The resulting reaction mixture was poured into ice–water and the mixture was extracted with ether. The extract was washed with a saturated aqueous NaCl solution, dried and evaporated. The residue was chromatographed on silica gel (55 g) with 4:1 toluene–ethyl acetate to afford **17** (1.04 g, 95%) as a yellow-brown syrup. An analytical sample was obtained after re-column chromatography with 3:1 hexane–acetone as a pale yellow syrup: R_f=0.23 (3:1 hexane–acetone); IR ($CHCl_3$) 1697 cm^{-1}; UV (EtOH) λ (log ε) 222 (4.62), 249 (4.40), 327 (3.88), and 340 nm (3.84); ^{1}H-NMR δ=1.20 (3H, t, $CH_2\underline{Me}$, J=7.5 Hz), 2.45 (3H, s, ArMe), 2.79 (2H, dq, $\underline{CH_2}Me$, J=7.5 and 9.0 Hz), 3.57, 3.63, 3.79, and 3.89 (each 3H, each s, 4×OMe), 4.96 and 5.05 (each 2H, *ca.* s and s, 2×OCH_2Ph), and 6.73 (2H, s, H-6 and 7).

Found: C, 63.20; H, 6.97%. Calcd for $C_{20}H_{26}O_7$: C, 63.48; H, 6.92%.

*1-[5,8-Dimethoxy-2,4-bis(methoxymethoxy)-3-methyl-6-nitro-1-naphthyl]-1-propanone (**3**).* To 10.0 ml of acetic anhydride, copper(II) nitrate trihydrate (1.00 g, 4.14 mmol) was added portionwise. The mixture was stirred at 30 °C for 10 min and cooled to −40 °C. To this mixture, a solution of **17** (1.43 g, 3.78 mmol) in acetic anhydride (14.3 ml) was added dropwise. After being stirred at −40 °C for 1 h, ether (30 ml) and water (20 ml) were added to the mixture and the mixture was allowed to warm to room temperature. The organic layer was separated and the aqueous layer was extracted with ether (20 ml×2). The combined extracts were washed with a saturated aqueous NaCl solution (20 ml×3), dried, and evaporated. The residue was chromatographed on silica gel (80 g) with 10:1 toluene–ethyl acetate to afford **3** (1.26 g, 79%) as green crystals. This sample was treated with charcoal in ether to afford pure **3** (1.23 g, 77%) as yellow prisms: mp 89.5—90.5 °C (hexane); R_f=0.30 (10:1 toluene–ethyl acetate); IR (KBr) 1715 cm^{-1}; UV (EtOH) λ (log ε) 233 (4.55), and 378 nm (3.58); ^{1}H-NMR δ=1.22 (3H, t, $CH_2\underline{Me}$, J=7.0 Hz), 2.49 (3H, s, ArMe), 2.79 (2H, dq, $\underline{CH_2}Me$, J_{gem}=7.0 Hz), 3.58 and 3.62 (each 3H, each s, 2×$CH_2O\underline{Me}$), 3.90 and 3.92 (each 3H, each s, 2×OMe), 4.97 and 5.03 (each 2H, each s, 2×OCH_2O), and 7.07 (1H, s, ArH).

Found: C, 56.45; H, 5.91; N, 3.18%. Calcd for $C_{20}H_{25}NO_9$: C, 56.73; H, 5.95; N, 3.31%.

*Transformation of **3** into **1**.* A solution of **3** (13.9 mg, 0.0328 mmol) in THF (0.28 ml) and 1 M HCl (0.14 ml) was stirred at 23 °C for 3 d. The reaction mixture was diluted with ethyl acetate, washed with water and a saturated aqueous NaCl solution, dried, and evaporated. The residual orange-yellow crystals of **18** [11.0 mg, 100%; R_f=0.49 (10:1 toluene–ethyl acetate); ^{1}H-NMR δ=1.14 (3H, t, $CH_2\underline{Me}$, J=7.5 Hz), 2.25 (3H, s, ArMe), 2.40—2.75 (2H, m, $\underline{CH_2Me}$), 3.95 and 4.11 (each 3H, each s, 2×OMe), 7.37 (1H, s, ArH), 10.30 and 10.58 (each 1H, each s, 2×OH)] was suspended in 0.22 ml of acetone and cooled to 0 °C. To this were added dimethyl sulfate (0.0124 ml, 0.131 mmol) and K_2CO_3 (18.1 mg, 0.131 mmol). After being stirred at 20 °C for 5 h, the mixture was filtered with celite and the filter cake was washed with acetone. The combined filtrate and washings were evaporated and the residue was chromatographed on silica gel (1.5 g) with 15:1 toluene–ethyl acetate to give yellow crystals (11.2 mg, 94% from **3**). This sample was identical with **1**$^{1)}$ in all respects (^{1}H-NMR, IR, TLC, mp).

*[1,4-Dimethoxy-6,8-bis(methoxymethoxy)-7-methyl-5-propionyl-2-naphthyl]carbamic Acid Phenyl Ester (**20**).* A solution of **3** (500 mg, 1.18 mmol) in methanol (20 ml) was stirred with 5% Pd–C at 25 °C for 20 min under bubbling with H_2. The filtered solution was then evaporated to afford the crude **19** (465 mg, 100%) as a yellow-brown syrup. To the ice-cold stirred solution of this syrup and dry pyridine (0.115 ml, 1.42 mmol) in dichloromethane (4.7 ml), phenyl chloroformate (0.178 ml, 1.42 mmol) was added dropwise and the mixture was stirred at 0 °C for 1 h. Then the reaction was quenched by adding water, and the mixture was extracted with dichloromethane. The extract was washed with a saturated aqueous NaCl solution, dried, and evaporated. The residue was chromatographed on silica gel (61 g) with 6:1 toluene–ethyl acetate to give **20** (606 mg, 100%) as a pale yellow syrup. An analytical sample (colorless foam) was obtained after treatment with charcoal in ether and chromatographed again on silica gel with 20:1 chloroform–ethyl acetate: R_f=0.32 (6:1 toluene–ethyl acetate); IR ($CHCl_3$) 3412, 1745, and 1702 cm^{-1}; UV (EtOH) λ (log ε) 256 (4.84) and 318 nm (4.00); ^{1}H-NMR δ=1.20 (3H, t, $CH_2\underline{Me}$, J= 7.2 Hz), 2.46 (3H, s, ArMe), 2.78 (2H, dq, $\underline{CH_2}Me$, J_{gem}=7.2 Hz), 3.56, 3.61, 3.80, and 3.83 (each 3H, each s, 4×OMe), 4.92 and 4.98 (each 1H, ABq, OCH_2O, J_{gem}=7.5 Hz), 5.02 (2H, s, OCH_2O), 7.15—7.50 (5H, m, Ph), 7.80—8.00 (1H, br, NH), and 7.91 (1H, s, H-3).

Found: C, 62.80; H, 6.11; N, 2.61%. Calcd for $C_{27}H_{31}NO_9$: C, 63.15; H, 6.08; N, 2.73%.

*[1,4-Dimethoxy-6,8-bis(methoxymethoxy)-7-methyl-5-propionyl-2-naphthyl]carbamic Acid 2-(Trimethylsilyl)ethyl Ester (**21**).* To an ice-cold stirred solution of **20** (611 mg, 1.19 mmol) and 2-(trimethylsilyl)ethanol (0.511 ml, 3.57 mmol) in dry THF (7.9 ml) was added *t*-BuOK (334 mg, 2.98 mmol) under argon. The mixture was stirred at 0 °C for 15 min and then partitioned between ether and water. The organic layer was washed with a saturated aqueous NaCl solution, dried, and evaporated. The residue was chromatographed on silica gel (34 g) with 8:1 toluene–ethyl acetate to afford **21** (569 mg, 89%) as a pale yellow-brown syrup. An analytical sample (colorless syrup) was obtained after the additional silica gel column chromatography with 6:1 hexane–acetone: R_f=0.35 (8:1 toluene–ethyl acetate); IR ($CHCl_3$) 3410, 1717, and 1710 cm^{-1}; UV (EtOH) λ (log ε), 255 (4.83) and 318 nm (3.97); ^{1}H-NMR δ=1.07 (2H, AA′XX′, $SiCH_2$), 1.19 (3H, t, $CH_2\underline{Me}$, J=7.4 Hz), 2.44 (3H, s, ArMe), 2.77 (2H, dq, $\underline{CH_2}Me$, J_{gem}=7.4 Hz), 3.57, 3.60, 3.73, and 3.87 (each 3H, each s, 4×OMe), 4.30 (2H, AA′XX′ $O\underline{CH_2}CH_2Si$), 4.93 and 4.95 (each 1H, each s, OCH_2O), 5.00 (2H, s, OCH_2O), 7.48 (1H, br s, NH), and 7.90 (1H, s, H-3).

Found: C, 57.81; H, 7.14; N, 2.45%. Calcd for $C_{26}H_{39}NO_9Si$: C, 58.08; H, 7.31; N, 2.61%.

*[1,4-Dimethoxy-6,8-bis(methoxymethoxy)-7-methyl-5-pyruvoyl-2-naphthyl]carbamic Acid 2-(Trimethylsilyl)ethyl Ester (**22**).* A solution of **21** (46.2 mg, 0.0859 mmol) in dry DME (0.46 ml) was added during a period of two min to a mixture of a 1.43 M *t*-BuOK in *t*-BuOH (0.90 ml, 1.29 mmol) and dry DMSO (0.39 ml) under bubbling with O_2. After the red-brown reac-

tion mixture was vigorously stirred for 30 min under bubbling with O_2, the resulting viscous red-brown mixture was added to an ice-cold stirred saturated aqueous NH_4Cl solution. The mixture was extracted with ethyl acetate and the extract was washed with a saturated aqueous NaCl solution, dried, and evaporated. The residue was chromatographed on silica gel (4.9 g) with 3:1 hexane–acetone to afford **22** (41.6 mg, 88%) as a yellow syrup. An analytical sample was obtained after an additional silica gel column chromatography with 3:1 hexane–acetone as a yellow syrup: R_f=0.25 (3:1 hexane–acetone); IR ($CHCl_3$) 3419, 1720, and 1705 cm^{-1}; UV (EtOH) λ (log ε) 253 (4.81) and 315 (3.94); ^1H-NMR δ= 0.08 (9H, s, $SiMe_3$), 1.01 (2H, AA′XX′, $SiCH_2$), 2.37 and 2.42 (each 3H, each s, ArMe and COCOMe), 3.43 and 3.56 (each 3H, each s, $2\times OCH_2O\underline{Me}$,), 3.70 and 3.77 (each 3H, each s, $2\times$OMe), 4.26 (2H, AA′XX′, $O\underline{CH_2}CH_2Si$), 4.90 and 4.98 (each 2H, each s, $2\times OCH_2O$), 7.47 (1H, brs, NH), and 7.91 (1H, s, ArH).

Found: C, 56.33; H, 6.65; N, 2.62%. Calcd for $C_{26}H_{37}NO_{10}Si$; C, 56.61; H, 6.76; N, 2.54%.

[1,4-Dihydro-6,8-bis(methoxymethoxy)-7-methyl-5-pyruvoyl-1,4-dioxo-2-naphthyl]carbamic Acid 2-(Trimethysilyl)ethyl Ester (23). To a cold (−20 °C) solution of **22** (98.8 mg, 0.179 mmol) in acetonitrile (3.0 ml), a solution of ammonium cerium(IV) nitrate (247 mg, 0.451 mmol) in water (0.74 ml) was added dropwise. After being stirred at −20 °C for 5 min, the reaction mixture was diluted with ethyl acetate (5 ml) and water (3 ml), and warmed to room temperature. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined extracts were washed with a saturated aqueous NaCl solution, dried, and evaporated. The residue was chromatographed on silica gel (4.9 g) with 10:1 toluene–ethyl acetate to afford **23** (80.5 mg, 86%) as yellow crystals. An analytical sample was obtained after recrystallization (three times) from acetone–pentane: mp 140—142 °C (yellow needles); R_f=0.37 (10:1 toluene–ethyl acetate); IR (KBr) 3210, 1742, 1706, and 1675 cm^{-1}; UV (EtOH) λ (log ε) 222 (4.37), 259 (4.47), 309 (4.09), and 364 nm (3.51); ^1H-NMR δ=0.06 (9H, s, $SiMe_3$), 1.06 (2H, AA′XX′, $SiCH_2$), 2.37 and 2.59 (each 3H, each s, ArMe and COCOMe), 3.47 and 3.64 (each 3H, each s, $2\times$OMe), 4.30 (2H, AA′XX′, $O\underline{CH_2}CH_2Si$), 4.98 and 5.11 (each 2H, each s, $2\times OCH_2O$), 7.34 (1H, s, ArH) and 7.91 (1H, br s, NH).

Found: C, 55.41; H, 5.95; N, 2.84%. Calcd for $C_{24}H_{31}NO_{10}Si$: C, 55.27; H, 5.99; N, 2.69%.

*7-Amino-2,5-dihydroxy-2,4-dimethyl-naphtho[2,1-*b*]furan-1,6,9-(2*H*)-trione (4).* A sample of **23** (254 mg, 0.487 mmol) was treated with ice-cold TFA (2.54 ml) at 0 °C for 1.5 h. The reaction mixture was diluted with ice-cold water (5 ml) and the precipitated red-brown crystals was collected and washed thoroughly with water. The red-brown crystals consisted almost of **4** (131 mg, 93%): mp >200 °C dec.; R_f=0.43 (10:1 chroloform–methanol); IR (nujor) 3317, 1725, 1655, 1611, and 1593 cm^{-1}; UV (EtOH) λ (log ε) 228 (4.38), 273 (4.25), 307 (4.05), and 350 nm (4.03); UV (0.01 M HCl in EtOH) λ (log ε) 226 (4.41), 272 (4.26), 312 (4.03), and 348 nm (4.03); ^1H-NMR δ (TFA, TMS)=1.91 (3H, s, 2-Me), 2.34 (3H, s, ArMe), and 6.56 (1H, s, H-8).

Lit,[5a)] IR (nujor) 3320, 1725, 1660, 1610, and 1598 cm^{-1}. UV (EtOH) λ (log ε) 228 (4.42), 273 (4.26), 311 (4.04), and 350 nm (4.05). ^1H-NMR δ (TFA, TMS)=1.93 (3H, s), 2.37 (3H, s), and 6.55 (1H, s).

Lit,[5b)] IR (nujor) 3490, 3250, 1735, 1665, 1620, and 1605 cm^{-1}. UV (0.01M HCl in EtOH) λ (log ε) 225(4.43), 270 (4.30), 313(4.03), 347(4.08), and 410 nm (shoulder).

We are grateful to the Institute of Microbial Chemistry for the generous sopport of our program. We also are indebted to Mr. Saburo Nakada, Keio University, for elemental analyses.

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