A Formation of a Fusarubin Carbon Skeleton[1)]

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Synopsis. A compound having a fusarubin carbon skeleton, *N,N*-diethyl-3-(2-hydroxypropyl)-1,4,5,6,8-pentamethoxy-2-naphthamide, was prepared from 1,4,5,6,8-pentamethoxy-2-naphthalenemethanol in 5 steps via *N,N*-diethyl-1,4,5,6,8-pentamethoxy-7-trimethylsilyl-2-naphthamide.

Fusarubin(**1**),[2a)] isolated from Fusarium solani by Arnstein et al.[2b)] is an antibiotic having a 1*H*-naphtho-[2,3-*c*]pyran-6,9-dione skeleton. We have already reported the synthesis of a fusarubin isomer (**2**).[3)] The synthesis of ventiloquinone G (**3**) containing the above-mentioned skeleton has recently been reported by Giles et al.[4)] Although there have been biosynthetic studies concerning fusarubin by Kurobane et al.,[5)] its synthesis has, to our knowledge, not yet been reported. We herein describe the formation of the fusarubin carbon skeleton.

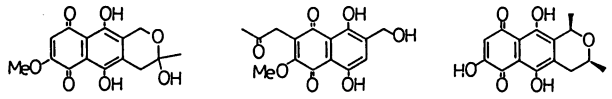
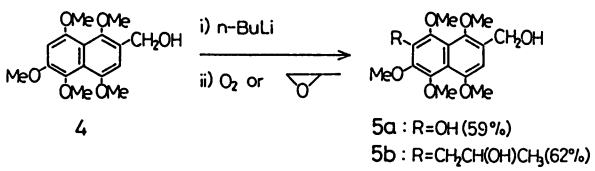


Chart 1.

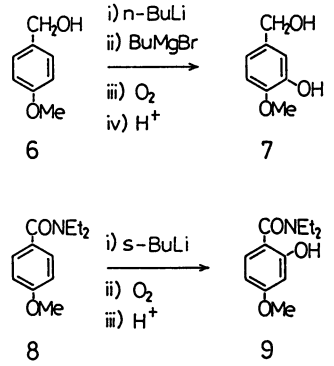
Results and Discussion

We have already reported[6)] that the lithiation of 1,4,5,6,8-pentamethoxy-2-naphthalenemethanol (**4**) with *n*-BuLi and subsequent oxidation by oxygen or treatment with propylene oxide gave pentamethoxy compounds **5a** and **5b**, respectively, which were obtained by lithiation not at position 3 in **4**, but at position 7 (Scheme 1).



Scheme 1.

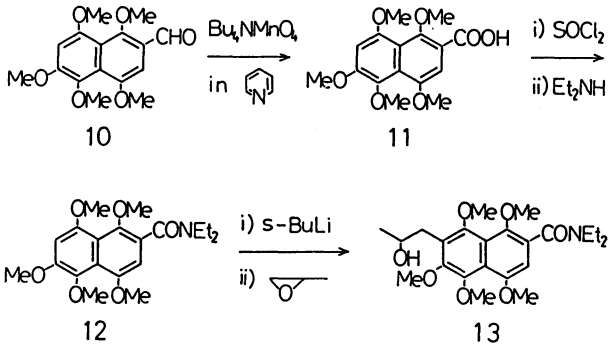
The formation of a fusarubin carbon skeleton requires the introduction of a side chain into position 3 of 2-substituted 1,4,5,6,8-pentamethoxynaphthalene. It is possible to introduce the side chain by applying ortho lithiation in a benzene derivative.[7)] Therefore, the lithiations of 4-methoxybenzyl alcohol (**6**) and 4-methoxybenzamide (**8**) were carried out for a preliminary lithiation of 2-substituted 1,4,5,6,8-pentamethoxynaphthalene. Lithiation of **6** with *n*-BuLi and subsequent oxidation by oxygen gave 33% (49%, based upon the consumed starting material) of 3-hydroxy-4-methoxybenzyl alcohol (**7**); this result shows that lithiation occurred at the ortho-position of the methoxyl group. On the other hand, treatment of **8** with *s*-BuLi and subsequent oxidation by oxygen gave 50% of *N,N*-diethyl-2-hydroxy-4-methoxybenzamide (**9**); this means that in this case the ortho-position of the diethylcarbamoyl group was selectively lithiated (Scheme 2).



Scheme 2.

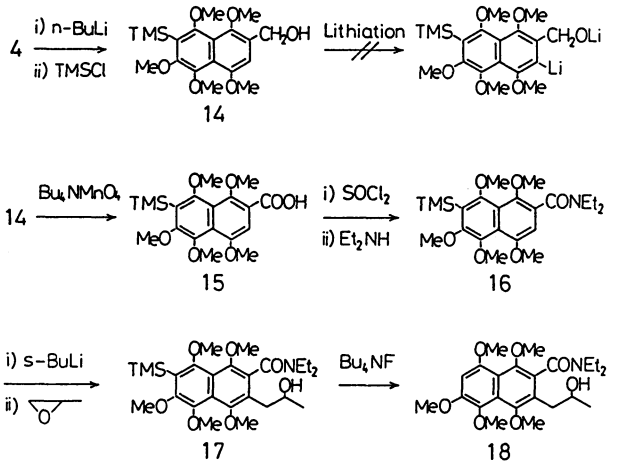
Parker et al.[8)] has already reported that the lithiation of *N,N*-diethyl-2,4,5-trimethoxybenzamide occurs at position 6 between the methoxyl and diethylcarbamoyl groups. Our results and their report seem to indicate that the lithiation of 2-substituted 1,4,5,6,8-pentamethoxynaphthalene occurs at the position between the diethylcarbamoyl and methoxyl groups, rather than at the site surrounded by two methoxyl groups. Therefore, conversion of the formyl group in naphthalenecarbaldehyde (**10**)[9)] into a diethylcarbamoyl group, and subsequent lithiation, were attempted. The oxidation of **10** with Bu_4NMnO_4[10)] in pyridine gave naphthoic acid (**11**) in 86% yield. The treatment of **11** with thionyl chloride, and subsequent amidation by diethylamine, gave naphthamide (**12**) in 91% yield. Lithiation of the amide (**12**) with *s*-BuLi, followed by the treatment of propylene oxide gave a 26% yield of *N,N*-diethyl-7-(2-hydroxypropyl)-1,4,5,6,8-pentamethoxy-2-naphthamide (**13**) only, as opposed to our expectation (Scheme 3).

As the intoduction of a side chain into position 3 of **12** was unsuccessful, we returned to **4**. Position 7 in **4** was protected by a TMS group[11)] to give trimethylsilyl-



Scheme 3.

naphthalene (**14**). No lithiation of position 3 in **14** with *n*-BuLi, *s*-BuLi, or *t*-BuLi, however, occurred, and the starting material was only recovered in three cases. We therefore tried to convert the hydroxymethyl group in **14** into a diethylcarbamoyl group, followed by subsequent lithiation. The oxidation of **14** with Bu_4NMnO_4 gave a 78% yield of silylated naphthoic acid (**15**), which was first treated with thionyl chloride and then with diethylamine to afford silylated naphthamide (**16**) in 96% yield. The treatment of amide (**16**) with *s*-BuLi and propylene oxide gave naphthamide (**17**) in 41% yield. Desilylation of **17** with Bu_4NF[11] gave a 58% yield of *N,N*-diethyl-3-(2-hydroxypropyl)-1,4,5,6,8-pentamethoxy-2-naphthamide (**18**) having a fusarubin carbon skeleton (Scheme 4).



Scheme 4.

Experimental

The melting points were determined using a Yanagimoto micromelting point apparatus; they were uncorrected. ^1H and ^{13}C NMR spectra were taken on a JEOL JNM-FX60 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.

Lithiation of 4-Methoxybenzyl Alcohol (6) and *N,N*-Diethyl-4-methoxybenzamide (8). The lithiation of **6** and **8** was carried out using the same procedure as that described in Refs. 6 and 8, respectively.

7: Mp 133.5—135 °C (benzene : hexane=1 : 1); IR (KBr) 3430, 3115 cm^{-1}; ^1H NMR δ=1.68 (s, 1H, OH), 3.88 (s, 3H, OMe), 4.58 (s, 2H, CH_2), 5.67 (broad, 1H, OH), 6.84 (s, 2H, ArH), 6.93 (s, 1H, ArH); ^{13}C NMR (DMSO) δ=55.74, 62.73, 112.01, 114.21, 117.25, 135.23 (C1), 146.29 (C3), 146.43 (C4); MS *m/z* 154 (M^+). Found: C, 62.27; H, 6.67%. Calcd for $C_8H_{10}O_3$: C, 62.33; H, 6.54%.

9: Mp 117.5—119 °C (hexane) (lit,[12] 120—121 °C); ^{13}C NMR δ=13.43, 42.29, 55.33, 101.97 (C3), 105.51 (C5), 110.25 (C1), 128.65 (C6), 161.64 (C2), 162.83 (C4), 171.75 (C=O).

1,4,5,6,8-Pentamethoxy-2-naphthoic Acid (11). Oxidation of **10** by the same manner described in Ref. 10 gave **11** (86%). Mp 168.5—170 °C (benzene : hexane=1 : 1); IR (KBr) 1735 cm^{-1}; ^1H NMR δ=3.82, 3.92, 4.01 (each s, 3H, OMe), 4.03 (s, 6H, 2×OMe), 6.82, 7.40 (each s, 1H, ArH), 11.76 (broad, 1H, COOH); MS *m/z* 322 (M^+). Found: C, 59.47; H, 5.64%. Calcd for $C_{16}H_{18}O_7$: C, 59.62; H, 5.63%.

***N,N*-Diethyl-1,4,5,6,8-pentamethoxy-2-naphthamide (12).** To a solution of **11** (282 mg, 0.876 mmol) in benzene (4 ml) and $CHCl_3$ (2 ml) was added $SOCl_2$ (0.191 ml, 2.63 mmol). The reaction mixture was stirred at room temperature for 20 h. The solvent and excess $SOCl_2$ were removed under reduced pressure. To the residue in benzene (3 ml) at 0 °C was added $(C_2H_5)_2NH$ (0.27 ml, 2.63 mmol). The reaction mixture was stirred at room temperature for 12 h, quenched with water, and extracted with $CHCl_3$. The usual work-up and chromatographic purification gave **12** (300 mg, 91%) as an oil. IR(KBr) 1630 cm^{-1}; ^1H NMR δ=1.03, 1.28 (each t, *J*=7.0 Hz, 3H, Me), 3.22, 3.26 (each q, *J*=7.0 Hz, 2H, CH_2), 3.81, 3.99 (each s, 6H, 2×OMe), 3.94 (s, 3H, OMe), 6.66, 6.76 (each s, 1H, ArH); ^{13}C NMR δ=98.70(C7), 105.68(C3); MS *m/z* 377 (M^+). HRMS, Found: *m/z* 377.1866. Calcd for $C_{20}H_{27}NO_6$: M, 377.1839.

Lithiation of 12. A mixture of **12** (122 mg, 0.324 mmol) and *N,N,N',N'*-tetramethylethylenediamine (TMEDA) (0.122 ml, 0.81 mmol) in THF (10 ml) was cooled to −70 °C and allowed to react with *s*-BuLi (0.735 ml, 0.81 mmol, 1.10 mol dm^{-3} in hexane) for 3 h. Propylene oxide (0.057 ml, 0.81 mmol) was added to the solution and stirred at −70 °C for 2 h. The reaction mixture was stored in a refrigerator overnight, quenched with aq NH_4Cl, and extracted with $CHCl_3$. The usual work-up and chromatographic purification gave *N,N*-diethyl-7-(2-hydroxypropyl)-1,4,5,6,8-pentamethoxy-2-naphthamide (**13**) (37 mg, 26%) as an oil and **12** (18 mg, 15%) was recovered.

13: IR (KBr), 3410, 1610 cm^{-1}; ^1H NMR δ=1.09, 1.31 (each t, *J*=7.0 Hz, 3H, Me), 1.31 (d, *J*=6.2 Hz, 3H, Me), 3.0 (m, 2H, $-CH_2CH(OH)-$), 3.26 (q, *J*=7.0 Hz, 4H, $-CH_2CH_3$×2), 3.76 (s, 6H, 2×OMe), 3.8 (m, 1H, CH), 3.85, 3.97 (each s, 3H, OMe), 4.00 (s, 3H, OMe), 6.63 (s, 1H, ArH); ^{13}C NMR δ=104.19 (C3), 168.78 (C=O); MS *m/z* 435 (M^+). HRMS, Found: *m/z* 435.2244. Calcd for $C_{23}H_{33}NO_7$: M, 435.2256.

1,4,5,6,8-Pentamethoxy-7-trimethylsilyl-2-naphthalenemethanol (14). To a solution of **4** (1.00 g, 3.25 mmol) in THF (40 ml) was added *n*-BuLi (8.13 ml, 12.99 mmol, 10 w/v% in hexane) at −10 °C and the mixture was stirred at −10 °C for 2 h. Me_3SiCl (1.64 ml, 12.99 mmol) was added to the solution. The mixture was stirred at −10 °C for 3 h and then stored in a refrigerator overnight. After aq NH_4Cl had been added, the reaction mixture was extracted with $CHCl_3$. The usual work-up and chromatographic purification gave **14** (82%) as an oil. IR (neat) 3400 cm^{-1}; ^1H NMR δ=0.40 (s, 9H, $-SiMe_3$), 1.88 (broad, 1H, OH), 3.65, 3.75, 3.80, 3.95, 3.98 (each s, 3H, OMe), 4.84 (s, 2H, CH_2OH), 6.84 (s, 1H, ArH); ^{13}C NMR δ=1.91, 107.22 (C3); MS *m/z* 380 (M^+). HRMS, Found: *m/z* 380.1670. Calcd for $C_{16}H_{20}O_6Si$: M, 380.1655.

1,4,5,6,8-Pentamethoxy-7-trimethylsilyl-2-naphthoic Acid (15). Oxidation of **14** by the same manner as in the preparation of **11** gave **15** (78%). Mp 159.5—160.5 °C (hexane–benzene); IR (KBr) 1735, 1695 cm^{-1}; ^1H NMR δ=0.41 (s, 9H, $-SiMe_3$), 3.66, 3.82, 3.94, 3.99, 4.03 (each s, 3H, OMe), 7.44 (s, 1H, ArH), 12.03 (s, 1H, COOH); MS *m/z* 394 (M^+). HRMS, Found: *m/z* 394.1451. Calcd for: M, 394.1448. Found: C, 57.85; H, 6.64%. Calcd for $C_{19}H_{26}O_7Si$: C, 58.33; H, 6.65%.

***N,N*-Diethyl-1,4,5,6,8-pentamethoxy-7-trimethylsilyl-2-naphthamide (16).** Amidation of **15** in the same manner as in the preparation of **12** gave **16** (96%). Mp 116—117 °C (hexane–benzene); IR (KBr) 1620 cm^{-1}; ^1H NMR δ=0.40 (s, 9H, $-SiMe_3$), 1.09, 1.31 (each t, *J*=7.0 Hz, 3H, Me), 3.28 (q, *J*=7.0 Hz, 4H, 2×CH_2), 3.67, 3.75, 3.81 (each s, 3H, OMe), 3.96 (s, 6H, 2×OMe), 6.64 (s, 1H, ArH); MS, *m/z* 449 (M^+). Found: C, 61.45; H, 7.85%. Calcd for $C_{23}H_{35}NO_6Si$: C, 61.66; H, 7.81%.

***N,N*-Diethyl-3-(2-hydroxypropyl)-1,4,5,6,8-pentamethoxy-7-trimethylsilyl-2-naphthamide (17).** The reaction of **16** (0.202 g, 0.449 mmol), TMEDA (0.169 ml, 1.12 mmol) in THF (10 ml) with *s*-BuLi (1.02 ml, 1.12 mmol, 1.10 mol dm^{-3} in hexane) and propylene oxide by the same manner as the preparation of **13** gave **17** (94 mg, 41%) as an oil. IR (KBr) 3405, 1615 cm^{-1}; ^1H NMR δ=0.40 (s, 9H, $-SiMe_3$), 1.08, 1.30 (each t, *J*=7.0 Hz, 3H, Me), 1.25 (d, *J*=6.3 Hz, 3H, Me), 1.84 (broad, 1H, OH), 2.55 (m, 2H, CH_2), 3.06 (q, *J*=7.0 Hz, 4H, 2×CH_2), 3.68 (s, 3H, OMe), 3.75 (m, 1H, CH), 3.77 (s, 6H, 2×OMe), 3.80, 3.99 (each s, 3H, OMe); MS *m/z* 507 (M^+). HRMS, Found: *m/z* 507.2633. Calcd for $C_{26}H_{41}NO_7Si$: M, 507.2651.

***N,N*-Diethyl-3-(2-hydroxypropyl)-1,4,5,6,8-pentamethoxy-2-naphthamide (18).** To a solution of **17** (24 mg, 0.047 mmol) in THF (1 ml) was added Bu_4NF (0.14 ml, 0.142 mmol, 1.0 M in THF, 1 M=1 mol dm^{-3}). The mixture was stirred at room temperature overnight, quenched with water and extracted with $CHCl_3$. The usual work-up and chromatographic purification gave **18** (12 mg, 58%) as an oil. IR (KBr) 3400, 1610 cm^{-1}; ^1H NMR δ=1.00, 1.31 (each t, *J*=7.0 Hz, 3H, Me), 1.32 (d, *J*=6.0 Hz, 3H, Me), 3.2 (m, 6H, 2×$C\underline{H}_2CH_3$, CH_2), 3.7 (m, 1H, CH), 3.79 (s, 3H, OMe), 3.81 (s, 6H, 2×OMe), 3.99, 4.01 (each s, 3H, OMe), 6.72 (s, 1H, ArH); MS *m/z* 435 (M^+), 391, 376, 303. HRMS, Found: *m/z* 435.2286. Calcd for $C_{23}H_{33}NO_7$: M, 435.2258 .

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