A Synthetic Route of 1,4,8-Trimethoxy-2-naphthalenecarbaldehyde via Duff Formylation of 4,8-Dimethoxy-1-naphthol[1)]

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Synopsis. A convenient route for preparing 1,4,8-trimethoxy-2-naphthalenecarbaldehyde was accomplished by the following: The starting material, 4,8-dimethoxy-1-naphthol, was prepared from 1,5-dimethoxynaphthalene through 1-bromo-4,8-dimethoxynaphthalene. Formylation of this naphthol and subsequent methylation gave 1,4,8-trimethoxy-2-naphthalenecarbaldehyde.

During the course of our synthetic studies of bioactive naphthoquinone derivatives, the entitled aldehyde, 1,4,8-trimethoxy-2-naphthalenecarbaldehyde (**3**) became one of the important intermediates. This compound was also a key intermediate in the syntheses of anthracycline system compounds[2)] and of 2-azanaphthacenequinone.[3)] This aldehyde **3** was first prepared as follows: i) Friedel-Crafts acylation of 2,5-dimethoxytoluene (**1**) with succinic anhydride, ii) Clemmensen reduction, then iii) cyclization gave a tetralone (**2**).[4)] Oxidation of **2** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone and methylation by trimethyl orthoformate gave **3**[2,3)] (Scheme 1).

Rapoport et al.[5)] have obtained 4,8-dimethoxy-1-naphthol (**5**) by the following process (Scheme 2). The naphthol **5** was conveniently used in the syntheses of 2-bromojuglone[5)] and of pyranonaphthoquinone.[6)] We will report here a synthetic method of 1,4,8-trimethoxy-2-naphthalenecarbaldehyde **3** via this naphthol **5** starting from 1,5-dimethoxynaphthalene (**4**).

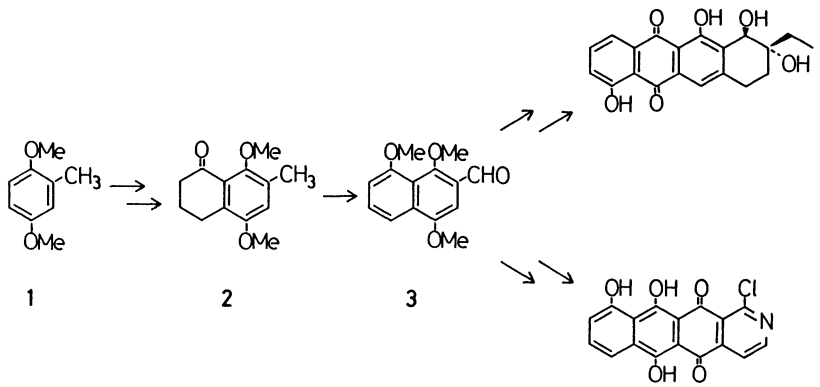
Results and Discussion

We easily prepared the naphthol **5** from **4**; the process was as follows: i) Bromination of **4** and ii) oxidation of the organolithium compound, 1-lithio-4,8-dimethoxynaphthalene (Scheme 3).

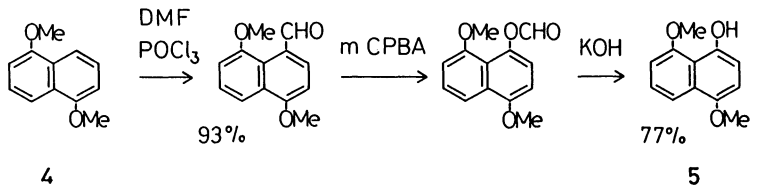
Although two-equimolar bromination of **4** gave 4,8-dibromo-1,5-dimethoxynaphthalene,[7)] one molar-equivalent of bromine conveniently afforded 1-bromo-4,8-dimethoxynaphthalene (**6**) in 98% yield. Such a process as the direct lithiation of **4** using *n*-BuLi, treatment with butylmagnesium bromide, and oxidation to obtain **5** was unsuccessful. We attempted a direct hydrolysis of **6** using caustic alkali in the presence of Cu and Cu_2O; however, we still obtained unsatisfactory results. Finally, we tried a one-pot procedure, such as the lithiation of **6** by *n*-BuLi, treatment with *n*-BuMgBr, and oxidation to **5**.

Regarding the preparation of the final product **3** from **5**, the following two procedures were desirable:

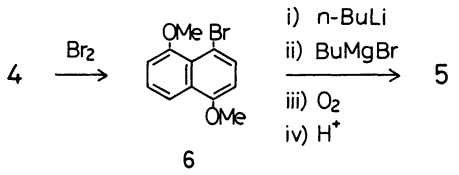
(A) Formylation of 1,4,5-Trimethoxynaphthalene Leading to 3. Since we found that a trial formylation of 1,4-dimethoxynaphthalene (**7**) by a Vilsmeier reaction afforded 1,4-dimethoxy-2-naphthalenecarbaldehyde (**8**) in almost quantitative yield, the same procedure was carried out for 1,4,5-trimethoxynaphthalene (**9**) which was obtained by methylation of **5** with dimethyl sulfate. However, the yield of our required



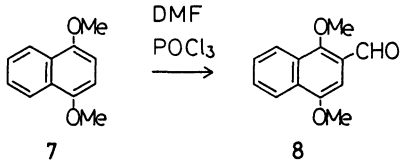
Scheme 1.

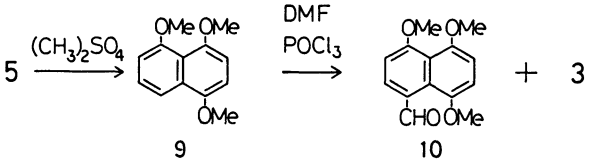


Scheme 2.



Scheme 3.



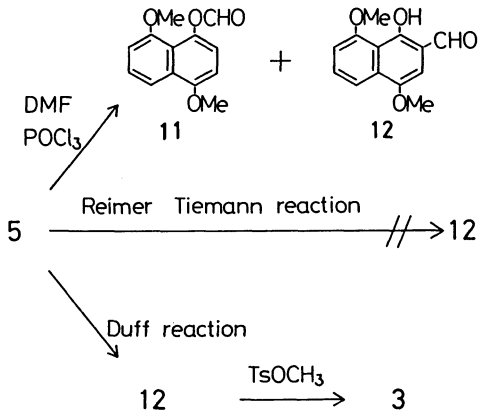


Scheme 4.

product (**3**) was slight (13%), and the main product was 4,5,8-trimethoxy-1-naphthalenecarbaldehyde (**10**) in 80% yield.

(B) Via Formylation of 5 to 1-Hydroxy-4,8-dimethoxy-2-naphthalenecarbaldehyde and Methylation to 3. Upon formylation the Vilsmeier reaction of **5** afforded mainly the formic ester (**11**) (62%) and the proposed 1-hydroxy-4,8-dimethoxy-2-naphthalenecarbaldehyde (**12**) was minor (24%). Another method, the Reimer-Tiemann reaction,[8] did not proceed. The Duff reaction[9] in acetic acid solvent resulted in 28% yield of **12**. The addition of an equimolar amount of *p*-toluenesulfonic acid monohydrate to this system resulted in a good yield of **12** (Scheme 5), though the reaction in trifluoro- and trichloroacetic acids gave only undesirable decomposition products (Table 1).

Methylation of **12** with methyl *p*-toluenesulfonate gave the final product **3** in 95% yield; with dimethyl sulfate the reaction was not satisfactory.



Scheme 5.

Experimental

Melting points were determined with a Yanagimoto micromelting point apparatus and were uncorrected. ^{1}H NMR spectra were taken on a JEOL JNM-60 in $CDCl_3$ using Me_4Si as an internal standard. 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) or on alumina (Sumitomo, KCG-30) eluting with chloroform. Cu and Cu_2O powder of Wako Chemical Co. were used.

1-Bromo-4,8-dimethoxynaphthalene (6). Bromine (0.85 g, 5.3 mmol) in carbon tetrachloride (5 ml) was added dropwise to a solution of 1,5-dimethoxynaphthalene (**4**) (1.00 g, 5.3 mmol) in carbon tetrachloride (30 ml) at 70 °C. After stirring at 70 °C for 30 min, the solution was concentrated and the residue was chromatographed on silica gel to give 1.38 g (98%) of **6**. Recrystallization from hexane gave an analytical sample, mp 113—113.5 °C. IR (KBr) 1590, 1400, 1260, 1245, 1050, 800, and 740 cm^{-1}; ^{1}H NMR δ=3.94 (s, 6H, 2×OCH_3), 6.61 (d, J=8.4 Hz, 1H, ArH-2), 6.94 (dd, J=7.6 and 1.3 Hz, 1H, ArH-6), 7.32—7.46 (2d, J=8.4 and 7.6 Hz, 1H, ArH-7), 7.65 (d, J=8.4 Hz, 1H, ArH-3), 7.91 (dd, J=8.4 and 1.3 Hz, 1H, ArH-8); MS, m/z 268 (M^++2, 99.7%), 266 (M^+,100), 253 (48), 251 (49), 195 (26), 193 (28), and 115. Calcd for $C_{12}H_{11}O_2Br$: C, 53.96; H, 4.15%. Found: C, 53.07; H, 4.07%.

4,8-Dimethoxy-1-naphthol (5). A. Oxidation of the Lithium Compound of 6. A solution of **6** (0.20 g, 0.75 mmol) in tetrahydrofuran (10 ml) was cooled to −10 °C, and *n*-BuLi (1.20 ml, 1.87 mmol, 10 w/v % in hexane) was added and stirred at −10 °C for 1 h. To this system was added a solution of butylmagnesium bromide in tetrahydrofuran (Mg: 55 mg, 2.25 mmol; BuBr: 0.31 g, 2.25 mmol; THF: 10 ml) at −10 °C. After 40 min, dry oxygen was bubbled into the system for 1 h at such a rate as to keep the temperature

Table 1. Preparation of **12** from **5** by Duff Reaction

Entry	Solvent and catalyst	Condition		Yield/%
		Temp/ °C	Time/h	
1	CF_3COOH	85	3.5	0[a]
2	CCl_3COOH	95	1	0[a]
3	CH_3COOH	85	2	0[b]
4	CH_3COOH	Reflux	1	28
5	CH_3COOH, $TsOH\cdot H_2O$	Reflux	1	40
6	CH_3COOH, $TsOH\cdot H_2O$	Reflux	3	61
7	CH_3COOH, $TsOH\cdot H_2O$	Reflux	5	60
8	CH_3COOH, $TsOH\cdot H_2O$	Reflux	14	40

a) Decomposition product was obtained. b) Only starting material was recovered.

below 0 °C. The reaction mixture was decomposed by the addition of dil hydrochloric acid (50 ml), extracted with chloroform (50 ml×3), washed with brine, dried over anhydrous sodium sulfate, and concentrated. The residue was chromatographed on silica gel to give 33 mg (21%) of **5**, mp 154.5—156 °C (lit,[5] 155—156 °C) and 110 mg (78%) of 1,5-dimethoxynaphthalene. Here obtained **5** did not depress the melting point of an authentic sample[5] of **5** on admixture.

B. Hydrolysis of 6. A mixture of **6** (0.534 g, 2 mmol), Cu powder (20 mg), and Cu_2O powder (60 mg) in aqueous sodium hydroxide (2.5 M (1M=1 mol dm^{-3}), 100 ml) was stirred at 150 °C for 3 h in a stainless-steel autoclave. The reaction mixture was filtered, washed with chloroform, and the filtrate was acidified with hydrochloric acid and extracted with chloroform. The usual work-up and purification of the crude product by silica gel chromatography gave **5** (65 mg, 16%) (mp 155—156 °C) and 1,5-dimethoxynaphthalene (54 mg, 14%).

1,4-Dimethoxynaphthalene (**7**) and 1,4,5-trimethoxynaphthalene (**9**) (mp 120—121 °C, lit,[10] 119 °C) were prepared in 87 and 86% yield, respectively, by a similar method for synthesis of 1,5-dimethoxynaphthalene by Benthey et al.[11] **7**: mp 86.5—87.5 °C (hexane); IR (KBr) 1622, 1590, 1380, 1270, 1235, 1095, 1082, and 1020 cm^{-1}; ^1H NMR δ=3.85 (s, 6H, 2×OCH_3), 6.56 (s, 2H, ArH), 7.45 (m, 2H, ArH), and 8.21 (m, 2H, ArH); MS, *m/z* 188 (M^+), 173 (M^+-CH_3), and 145. Calcd for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43%. Found: C, 76.97; H, 6.43%.

1,4-Dimethoxy-2-naphthalenecarbaldehyde (8). A solution of **7** (0.98 g, 5.21 mmol) in chloroform (19 ml) was added to a mixture of phosphoryl chloride (8.27 g, 53.9 mmol) and *N,N*-dimethylformamide (3.89 g, 53.2 mmol). The mixture was refluxed for 80 h and decomposed by the addition of ice water, and extracted with chloroform. After the usual work-up, the residue was chromatographed on silica gel to give 1.12 g (99.6%) of **8**. Recrystallization from hexane gave orange crystals, mp 119.5—120.0 °C. IR (KBr) 1675 (C=O), 1598, 1385, 1375, 1130, and 1100 cm^{-1}; ^1H NMR δ=3.98, 4.06 (each s, 3H, OCH_3), 7.09 (s, 1H, ArH-3), 7.38 (m, 2H, ArH), 8.18 (m, 2H, ArH), and 10.56 (s, 1H, CHO); MS, *m/z* 216 (M^+), 201 (M^+-CH_3), 173, and 145. Calcd for $C_{13}H_{12}O_3$: C, 72.21; H, 5.59%. Found: C, 71.89; H, 5.64%.

Formylation of 9 by a Vilsmeier Reaction. A mixture of **9** (961 mg, 4.41 mmol) in chloroform (20 ml) with $POCl_3$ (3.38 g, 22.0 mmol) and DMF (1.61 g, 22.0 mmol) was allowed to react for 10 h in the same manner as the formylation of **7** and gave 867 mg (80%) of 4,5,8-trimethoxy-1-naphthalenecarbaldehyde (**10**) and 140 mg (13%) of 1,4,8-trimethoxy-2-naphthalenecarbaldehyde (**3**).

10: Mp 186.5—187.5 °C (benzene-hexane (2:1)); IR (KBr) 1660 (C=O), 1610, 1590, 1065, and 1028 cm^{-1}; ^1H NMR δ=3.92, 3.93, 4.02 (each s, 3H, OCH_3), 6.90 (s, 2H, ArH-6,7), 6.91 (d, *J*=8.6 Hz, 1H, ArH-3), 7.93 (d, *J*=8.6 Hz, 1H, ArH-2), and 10.89 (s, 1H, CHO); MS, *m/z* 246 (M^+), 231 (M^+-CH_3), and 119. Calcd for $C_{14}H_{14}O_4$: C, 68.28; H, 5.73%. Found: C, 68.11; H, 5.78%.

3: Mp 90—91 °C (hexane) (lit,[2] 89—89 °C). IR (KBr) 1672 (C=O), 1620, 1607, 1583, 1382, and 1080 cm^{-1}; ^1H NMR δ=3.95, 4.01, 4.06 (each s, 3H, OCH_3), 6.99 (dd, *J*=7.9 and 1.2 Hz, 1H, ArH-7), 7.16 (s, 1H, ArH-3), 7.48—7.65 (2d, *J*=8.3 and 7.9 Hz, 1H, ArH-6), 7.92 (dd, *J*=8.3 and 1.2 Hz, 1H, ArH-5), and 10.57 (s, 1H, CHO); MS, *m/z* 246 (M^+), 231, 203, and 188. Calcd for $C_{14}H_{14}O_4$: C, 68.28; H, 5.73%. Found: C, 68.18; H, 5.78%.

Formylation of 5. The reaction of **5** (209 mg, 1.02 mmol) in chloroform (20 ml) with $POCl_3$ (800 mg, 5.1 mmol) and DMF (374 mg, 5.1 mmol) was carried out over 10 h using the same procedure mentioned above for the formylation of **7**, and gave 146 mg (62%) of 4,8-dimethoxy-1-naphthyl formate (**11**) and 56 mg (24%) of 1-hydroxy-4,8-dimethoxy-2-naphthalenecarbaldehyde (**12**).

11: Mp 137—138.5 °C (hexane); IR (KBr) 1730 (ester C=O), 1595, 1405, 1370, 1260, 1145, 1055, 845, 790, and 750 cm^{-1}; ^1H NMR δ=3.90, 3.98 (each s, 3H, OCH_3), 6.75 (d, *J*=8.3 Hz, 1H, ArH-3), 6.88 (dd, *J*=7.9 and 1.3 Hz, 1H, ArH-7), 7.06 (d, *J*=8.3 Hz, 1H, ArH-2), 7.33—7.47 (2d, *J*=9.3 and 7.9 Hz, 1H, ArH-6), 7.97 (dd, *J*=9.3 and 1.3 Hz, 1H, ArH-5), and 8.33 (s, 1H, HCO-); MS, *m/z* 232 (M^+), 204, 189, and 174. Calcd for $C_{13}H_{12}O_4$: C, 67.23; H, 5.21%. Found: C, 65.98; H, 5.12%.

12: Mp 117.5—118.5 °C (hexane); IR (KBr) 1655 (C=O), 1627, 1610, 1470, 1390, 1257, 1065 cm^{-1}; ^1H NMR δ=3.96, 4.10 (each s, 3H, OCH_3), 6.93 (dd, *J*=7.9 and 1.3 Hz, 1H, ArH-7), 7.07 (s, 1H, ArH-3), 7.44—7.57 (2d, *J*=8.3 and 7.9 Hz, 1H, ArH-6), 7.87 (dd, *J*=8.3 and 1.3 Hz, 1H, ArH-5), 10.23 (s, 1H, OH), and 10.52 (s, 1H, CHO); MS, *m/z* 232 (M^+), 217, 199, and 189. Calcd for $C_{13}H_{12}O_4$: C, 67.23; H, 5.21%. Found: C, 67.14; H, 5.24%.

Duff Reaction of 5. A mixture of **5** (204 mg, 1 mmol), hexamethylenetetramine (140 mg, 1 mmol), *p*-toluenesulfonic acid monohydrate (190 mg, 1 mmol), and acetic acid (5 ml) was refluxed for 3 h, decomposed by water and extracted with chloroform. The chloroform solution was washed with brine, dried over anhydrous sodium sulfate, and concentrated. The residue was chromatographed on silica gel to give 142 mg (61%) of **12**. Recrystallization from hexane gave an analytical sample, mp 117.5—118 °C, which did not depress the melting point of the above **12** on admixture.

Methylation of 12. A mixture of **12** (957 mg, 4.12 mmol), methyl *p*-toluenesulfonate (4.74 g, 6.18 mmol), sodium carbonate (3.30 g, 31 mmol) in *o*-dichlorobenzene (12 ml) was refluxed for 2 h. Water was added and the system was extracted with chloroform. After the usual work-up, the residue was purified by silica-gel chromatogaraphy and gave 960 mg (95%) of **3**. Recrystallization from hexane gave an analytical sample, mp 89—90 °C, which did not depress the melting point of **3** from the formylation of **9**.

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