Synthesis of 2-Alkyl-1,4-naphthoquinones via an *ortho*-Directive Metalation

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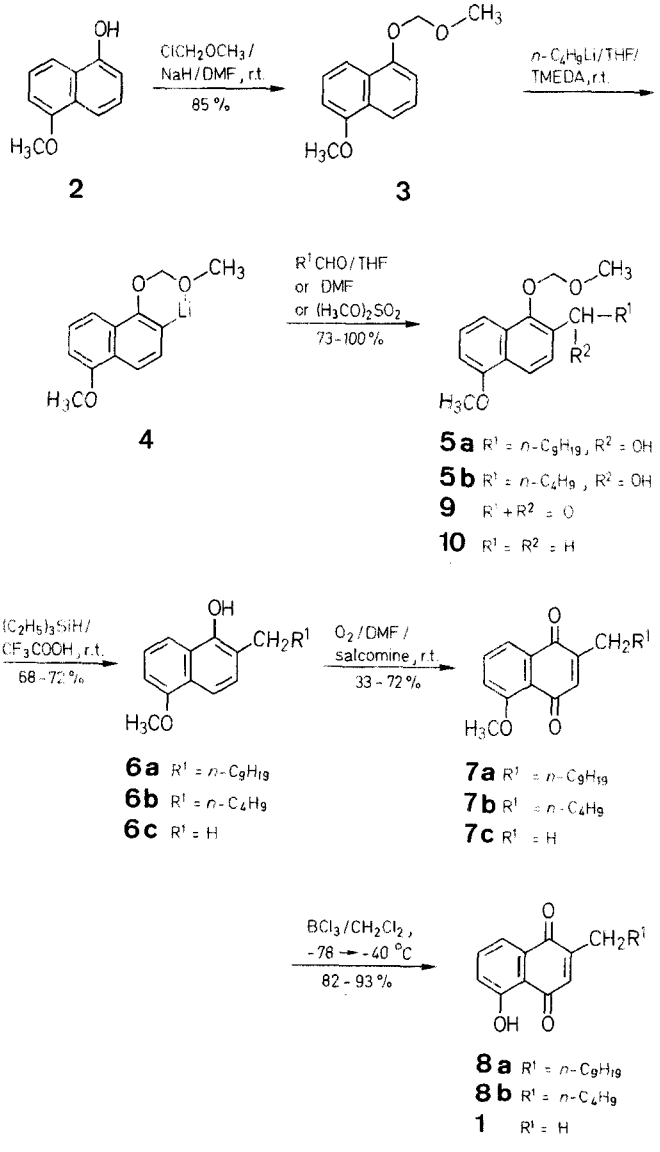
Plumbagin (5-hydroxy-2-methyl-1,4-naphthoquinone) has been shown to have a potent insect ecdysis inhibitory activity. To test the activity of synthetic analogs, the synthesis of 2-alkyl-1,4-naphthoquinones via an *ortho*-directive metalation using naphthol methoxymethyl ether as a directive group was carried out. This method is also applicable to the synthesis of naphthoquinones having unsaturated side-chain.

An insect ecdysis inhibitor has been identified from the African shrub, *Plumbago capensis (Plumbaginaceae)*, as the naphthoquinone plumbagin **(1)**. Plumbagin inhibited ecdysis in lepidopterous agricultural pests as well as chitin synthetase extracted from the *Trichoplusia ni* integument[1]. To test the ecdysis inhibitory activity of synthetic analogs, we then carried out elongation of the alkyl side chain of plumbagin. Our approach to introduce a side chain in the naphthalene nucleus relies on the well-documented directed metalation[2–6] followed by trapping with electrophiles. By the application of our previously reported method[7], the naphthol methoxymethyl ether was chosen as a directive group. This protected naphthol was also used as a latent quinone grouping in the later step of the synthesis.

Herein, we report a convenient method for the preparation of 2-alkyl-1,4-naphthoquinones. Etherification of 5-methoxy-1-naphthol **(2)**[8] with sodium hydride and methoxymethyl chloride in dimethylformamide gave the protected naphthol **3**. The naphthol **(3)** was treated with *n*-butyllithium in tetrahydrofuran and tetramethylethylenediamine to give a dark brown precipitate of the *ortho*-lithiated compound **4**, which was then trapped with *n*-decanal to give the alcohol **5a** in 77% yield. Reduction and concomitant deprotection by means of ionic hydrogenation using triethylsilane and trifluoroacetic acid[9] gave the naphthol **6a** in 68% yield. Oxidation of **6a** with oxygen and salcomine[10] in dimethylformamide gave the naphthoquinone **7a** in 51% yield. Demethylation of **7a** with boron trichloride gave 2-decyl-5-hydroxy-1,4-naphthoquinone **(8a)** in 93% yield.



2-Pentyl-5-hydroxy-1,4-naphthoquinone **(8b)** was also prepared by the similar reaction sequence. Another method of the preparation of the intermediate **5b** is nucleophilic addition of *n*-butyllithium to the aldehyde **9**, which was prepared by quenching the forementioned lithium compound **4** with dimethylformamide. Plumbagin methyl ether **(7c)** was prepared as follows. The lithium compound **4** was treated with dimethyl sulfate to give 2-methylnaphthol derivative **10**, which was deprotected with hydrogen bromide in hot ethanol[11] to give **6c**. Air oxidation of **6c** gave **7c**.

The present method is also applicable to the naphthoquinones having various unsaturated side-chain of potential biological interest. The biological activities of the synthesized products have been reported elsewhere[1].

5-Methoxy-1-methoxymethyleneoxynaphthalene (3):
To a slurry of sodium hydride (0.92 g of 60% oil dispersion, 32 mmol, washed twice with dry hexane) in dimethylformamide (8 ml) is added 5-methoxy-1-naphthol (**2**; 4.012 g, 23 mmol) in dimethylformamide (12 ml) cooled with an ice bath and under an atmosphere of argon. The mixture is stirred for 15 min at room temperature before methoxymethyl chloride (2.222 g, 28 mmol) in dimethylformamide (5 ml) is added and the resulting solution is allowed to stand overnight at room temperature. The mixture is treated with ice/water (50 ml) and extracted with ether (3 × 25 ml). The organic phase is washed with dilute sodium hydroxide (20 ml) solution, dilute hydrochloric acid (20 ml), and brine (20 ml), dried with magnesium sulfate, and concentrated *in vacuo*. The residue, after recrystallization from ethanol using active charcoal, affords **3** as wine-red prisms; yield: 4.24 g (85%); m.p. 75–76 °C.

2-(1-Hydroxydecyl)-5-methoxy-1-methoxymethyleneoxynaphthalene (5a); Typical Procedure:
To a solution of **3** (0.400 g, 1.83 mmol) in a mixture of tetrahydrofuran (8 ml) and tetramethylethylenediamine (1.9 ml) is added *n*-butyllithium (1.5 normal hexane solution, 1.6 ml, 2.4 mmol) cooled with an ice bath and under an atmosphere of argon. After the solution has been stirred at room temperature for 30 min, a solution of *n*-decanal (0.300 g, 1.9 mmol) in tetrahydrofuran (3 ml) is added dropwise with stirring at room temperature for 1 h. The reaction is quenched by addition of a saturated ammonium chloride solution

Table. Compounds **5**, **6**, **7**, and **8** prepared

Product	Yield[a] [%]	m.p. [°C]	Molecular Formula[b]	I.R.[c] ν [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$/TMS)[d] δ (ppm)
5a	77	oil	$C_{23}H_{34}O_4$ (374.5)	3480, 1600, 1040, 805 ($CHCl_3$)	0.89 (t, 3H); 1.27 (m, 16H); 2.26 (br.s, 1H); 3.61 (s, 3H); 3.97 (s, 3H); 5.04 (q, 2H, J = 7 Hz); 5.15 (m, 1H); 6.64 (dd, 1H, J = 2 Hz, 8 Hz); 7.20 (t, 1H, J = 8 Hz); 7.37 (d, 1H, J = 9 Hz); 7.41 (dd, 1H, J = 2 Hz, 8 Hz); 7.89 (d, 1H, J = 9 Hz)
5b	100	oil	$C_{18}H_{24}O_4$ (304.4)	3440, 1605, 1510, 1055, 760 (neat)	0.91 (t, 3H); 1.35 (m, 4H); 1.84 (m, 3H); 3.67 (s, 3H); 3.99 (s, 3H); 5.15 (q, 2H, J = 6 Hz); 5.25 (m, 1H); 6.82 (dd, 1H, J = 2 Hz, 8 Hz); 7.41 (t, 1H, J = 8 Hz); 7.54 (d, 1H, J = 9 Hz); 7.60 (dd, 1H, J = 2 Hz, 8 Hz); 8.12 (d, 1H, J = 9 Hz)
6a	68	61–62°	$C_{21}H_{30}O_2$ (314.5)	3600, 1600, 1505, 1254, 1055, 880 (CCl_4)	0.90 (t, 3H), 1.26 (m, 14H); 1.68 (m, 2H); 2.68 (t, 2H, J = 7 Hz); 3.94 (s, 3H); 4.90 (br.s, 1H); 6.56 (dd, 1H, J = 2 Hz, 8 Hz); 7.02 (d, 1H, J = 9 Hz); 7.15 (t, 1H, J = 8 Hz); 7.45 (dd, 1H, J = 2 Hz, 8 Hz); 7.60 (d, 1H, J = 9 Hz)
6b	72	–	$C_{16}H_{20}O_2$ (244.1443)*	3640, 1610, 1520, 1270, 1070, 890 (CCl_4)	0.90 (t, 3H); 1.1–1.9 (m, 6H); 2.68 (m, 2H); 3.94 (s, 3H); 4.98 (br.s, 1H); 6.63 (dd, 1H, J = 2 Hz, 8 Hz); 7.10 (d, 1H, J = 9 Hz); 7.23 (t, 1H, J = 8 Hz); 7.55 (dd, 1H, J = 2 Hz, 8 Hz); 7.71 (d, 1H, J = 9 Hz)
7a	51	97–98°	$C_{21}H_{28}O_3$ (328.4)	1650, 1640 (sh), 1620, 1580, 1250 ($CHCl_3$)	0.89 (t, 3H); 1.26–1.59 (m, 16H); 2.52 (t, 2H, J = 7 Hz); 3.99 (s, 3H); 6.60 (t, 1H, J = 1 Hz); 7.21 (dd, 1H, J = 2 Hz, 8 Hz); 7.56 (t, 1H, J = 8 Hz); 7.68 (dd, 1H, J = 2 Hz, 8 Hz)
7b	33	–	$C_{16}H_{18}O_3$ (258.1243)*		0.94 (t, 3H); 1.42 (m, 6H); 2.44 (t, 2H, J = 7 Hz); 3.91 (s, 3H); 6.43 (t, 1H, J = 1 Hz); 7.10 (B part of A_2B system, 1H); 7.44 (A part of A_2B system, 2H)
7c	72	92–94° (Lit. 94°)	$C_{12}H_{10}O_3$ (202.2)	1660, 1650 (sh), 1640 (sh), 1590, 1280, 1255, 970 (CCl_4)	2.09 (d, 3H, J = 2 Hz); 3.92 (s, 3H); 6.54 (q, 1H, J = 2 Hz); 7.12 (B part of A_2B system, 1H); 7.51 (A part of A_2B system, 2H)
8a	93	57–59°	$C_{20}H_{26}O_3$ (314.4)	1660 (sh), 1635, 1610, 1250, 900 (CCl_4)	0.92 (t, 3H); 1.2–1.8 (m, 16H); 2.54 (t, 2H, J = 7 Hz); 6.60 (t, 1H, J = 1 Hz); 7.09 (B part of A_2B system, 1H); 7.48 (A part of A_2B system, 2H); 11.81 (s, 1H)
8b	82	60–61°	$C_{15}H_{16}O_3$ (244.1096)*	1660, 1640, 1610, 1250, 1230, 900 (CCl_4)	0.94 (t, 3H); 1.2–1.8 (m, 6H); 2.51 (t, 2H, J = 7 Hz); 6.56 (t, 1H, J = 1 Hz); 7.66 (B part of A_2B system, 1H); 7.43 (A part of A_2B system, 2H); 11.78 (s, 1H)

[a] Isolated yield after purification.
[b] The microanalyses were in satisfactory agreement with the calculated values: C ±0.2; H ±0.3. * Determined by a JMS-HX 100 High-Resolution Mass Spectrometer.
[c] Recorded on a JASCO A-100 spectrometer.
[d] Recorded on a JEOL FX-100 spectrometer.

(15 ml) and extracted with ether (3 × 15 ml). The extract is washed with 1 normal hydrochloric acid, (15 ml), brine (15 ml), dried with magnesium sulfate, and evaporated. The crude product is purified by chromatography (SiO_2, 95:5 benzene/ethyl acetate as eluent) to afford **5a** as a colorless oil; yield: 0.525 g (77%).

2-Decyl-5-methoxy-1-naphthol (6a); Typical Procedure:
To a solution of **5a** (0.525 g, 1.4 mmol) and triethylsilane (1.628 g, 14 mmol) in dichloromethane (8 ml) is added trifluoroacetic acid (2.16 ml, 28 mmol) in dichloromethane (3 ml) at room temperature and under an atmosphere of argon. After stirring for 2 h at room temperature, the mixture is poured into a saturated sodium hydrogen carbonate solution (20 ml) and extracted with dichloromethane (3 × 15 ml). The extract is washed with saturated sodium hydrogen carbonate solution (15 ml), brine (15 ml), dried with magnesium sulfate, and evaporated. The crude product is purified by chromatography (SiO_2, benzene as eluent) to afford **6a** as needles; yield: 0.319 g (72%); m.p. 61–62° (from hexane).

2-Decyl-5-methoxy-1,4-naphthoquinone (7a); Typical Procedure:
To a stirred mixture of **6a** (0.257 g, 0.817 mmol) and salcomine (26 mg) in dimethylformamide (5 ml) is bubbled oxygen for 3 h at room temperature. The mixture is treated with ice/water (10 ml) and extracted with ether. The organic layer is washed with brine (10 ml), dried with magnesium sulfate, and evaporated. The crude product is purified by chromatography (SiO_2, 95:5 benzene/ethyl acetate as eluent) to give **7a** as yellow needles; yield: 0.136 g (51%); m.p. 97–98 °C (sublimed at 140 °C/1 torr).

2-Decyl-5-hydroxy-1,4-naphthoquinone (8a); Typical Procedure:
To a solution of **7a** (0.106 g, 0.32 mmol) in dichloromethane (5 ml) is added boron trichloride (0.150 g, 0.64 mmol) in dichloromethane (0.8 ml) at − 78 °C. The temperature is gradually raised to − 40 °C over 1 h period and the mixture is poured into ice (5 ml). The aqueous phase is extracted with dichloromethane. The organic phase is washed with brine (10 ml), dried with magnesium sulfate, and evaporated to give a yellow crystalline residue; yield: 94 mg (93%); m.p. 57–59 °C (from hexane).

2-Formyl-5-methoxy-1-methoxymethyleneoxynaphthalene (9):
To a suspension of the lithium compound **4**, prepared from **3** (0.400 g) as described before, is added dimethylformamide (1.42 ml, 1.84 mmol) cooled with an ice bath. After stirring for 30 min at room temperature, the mixture is quenched by addition of saturated ammonium chloride solution (10 ml) and extracted with ether (3 × 15 ml). The extract is washed with 1 normal hydrochloric acid (15 ml), brine (15 ml), dried with magnesium sulfate, and evaporated. The crude product is purified by chromatography (SiO_2, 9:1 benzene/ethyl acetate as eluent) to afford **9** as prisms; yield: 0.330 g (73%); m.p. 114–115 °C (from ethanol).

2-(1-Hydroxypentyl)-5-methoxy-1-methoxymethyleneoxynaphthalene (5b):
The alcohol **5b** is prepared by the similar method as described in **5a**. Another method is treatment of the aldehyde **9** with *n*-butyllithium in the usual manner (quantitative yield).

2-Methyl-5-methoxy-1-methoxymethyleneoxynaphthalene (10):
To a suspension of the lithium compound **4**, prepared from **3** (0.400 g) as described before is added dimethyl sulfate (0.52 ml, 5.5 mmol) in tetrahydrofuran (1 ml) and cooled with an ice bath. After stirring for 1 h at room temperature, the mixture is quenched by the addition of saturated ammonium chloride solution (15 ml) and extracted with ether (3 × 15 ml). The extract is washed with 1 normal hydrochloric acid (15 ml), brine (15 ml), dried with magnesium sulfate, and evaporated. The crude product is purified by chromatography (SiO_2, benzene/ethyl acetate as eluent) to afford **10** as a pale yellow fluorescent oil; yield: 0.190 g (45%).

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