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Reaction of Lithiated Senecioamide and Related Compounds with Benzynes: Efficient Syntheses of Naphthols and Naphthoquinones

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The reactions of lithiated *N*,*N*-diethylsenecioamide and *N*,*N*-diethyl-3-phenylisocrotonamide with methoxy-substituted benzynes, generated *in situ* from methoxy-substituted halobenzenes, gave regiospecifically various 3-methyl- and 3-phenyl-1-naphthol derivatives in a one-pot process. Methoxy-substituted 3-methyl-1-naphthols thus obtained were easily converted into various 1,4-naphthoquinones and 1,2-naphthoquinones including biologically active natural products such as plumbagin, plumbagin methylether, 5,6-dimethoxy-2-methyl-1,4-naphthoquinone, and 8-methoxy-3-methyl-1,2-naphthoquinone.

Keywords——*N*,*N*-diethylsenecioamide; *N*,*N*-diethyl-3-phenylisocrotonamide; lithiation; lithium *N*-isopropylcyclohexylamide; benzyne; naphthol; naphthoquinone; plumbagin

Naphthol derivatives are important as drugs, agrochemicals, and dyestuffs.[1] In addition, naphthols are intermediates for the preparation of naphthoquinone derivatives, including biologically significant natural products. While compounds containing the naphthol moiety have generally been synthesized by classical Friedel–Crafts ring closure of benzene derivatives,[2] attractive routes to 1-naphthols and related compounds *via* anionic routes,[3] especially using cycloaddition reactions of toluate anions,[4] phthalide carbanions,[5] and homophthalic anhydrides[6] as 1,4-dipole synthons[7] with various Michael acceptors, have recently been developed. Furthermore, reactions of dienolate anions of α,β-unsaturated ketones and esters with benzynes affording the naphthalene nucleus have been independently reported by Sammes and Wallace[8] and Caubere *et al.*[9]

Recently we developed a convenient method for the syntheses of acridones,[10] thioxanthones,[11] and anthraquinones[12] using the reactions of various 1,4-dipole synthons such as *N*-lithiated anthranilates, *S*-lithiated thiosalicylates, and lithiated toluamides with benzynes

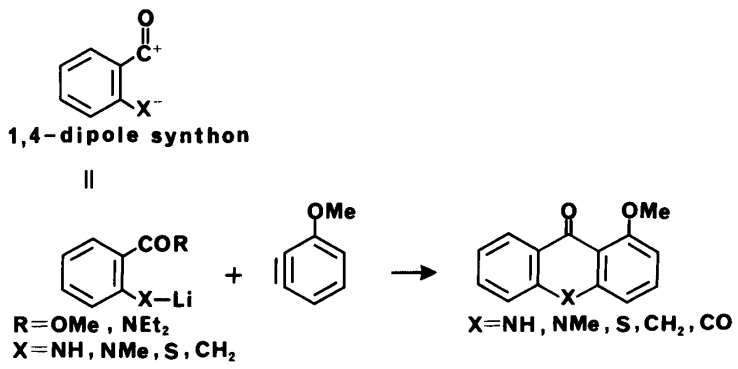


Chart 1

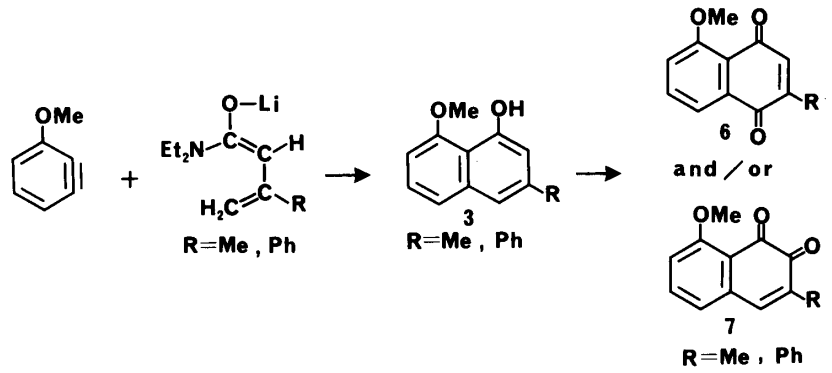
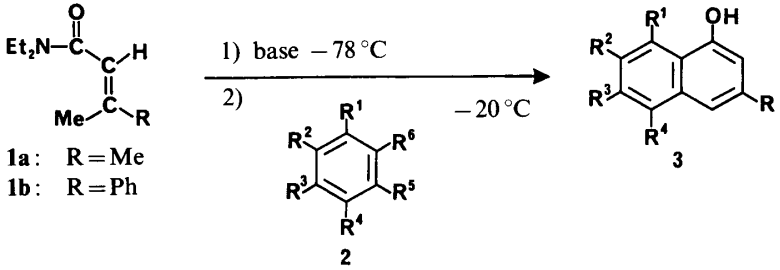


Chart 2

(Chart 1). As an extension of this type of synthetically useful cycloaddition reaction, we were interested in the synthesis of 1-naphthols, which may be easily convertible into naphthoquinone natural products, using similar synthetic methodology. The strategy for 1-naphthol and 1,2- or 1,4-naphthoquinone synthesis is outlined in Chart 2. Although the cycloaddition reaction of benzyne with the dienolate anion generated from methyl senecioate using lithium diisopropylamide (LDA)–sadamide–sodium *tert*-butoxide was briefly reported by Sammes and Wallace,[8] the use of *N*,*N*-diethylsenecioamide enolate as a 1,4-dipole synthon may be advantageous in that it has greater stability than the ester enolate anion.[13] This paper describes efficient syntheses of 3-methyl- and 3-phenyl-1-naphthols, and their further conversion into some naphthoquinone natural products.

The versatile reactivities of lithiated α,β-unsaturated amides with a variety of electrophiles have been investigated in detail by Snieckus and coworkers.[14] We have found that lithiated *N*,*N*-diethylsenecioamide and *N*,*N*-diethyl-3-phenylisocrotonamide reacted regiospecifically with benzynes to give various 3-methyl- and 3-phenyl-1-naphthols in good to moderate yields. *N*,*N*-Diethylsenecioamide (**1a**)[15] was treated with an excess of a hindered base such as lithium *N*-isopropylcyclohexylamide (LCI), LDA, or lithium 2,2,6,6-tetramethylpiperidide (LTMP) at $-78\,^{\circ}C$ in tetrahydrofuran (THF) or ether in order to generate the lithiated amide. At $-20\,^{\circ}C$ the various halobenzenes (**2**) were added to the solution to generate benzynes, then the mixture was allowed to warm to room temperature. Standard work-up followed by flash chromatography afforded 3-methyl-1-naphthols (**3**) as a major product.[16] The results are summarized in Table I. The most important feature of this cycloaddition reaction is the regiospecificity. For example, 3-methyl-8-methoxy-1-naphthol (**3b**)[17] was obtained as a single regioisomer when *ortho*-bromoanisole (**2b**) or *meta*-bromoanisole (**2c**) was employed as the benzyne precursor (entries 3—8). Similarly the reactions of **1a** with 2,4-dimethoxychlorobenzene (**2d**), 3,5-dimethoxychlorobenzene (**2e**), 2-methoxy-4-methylchlorobenzene (**2f**), 2-methoxymethoxybromobenzene (**2h**), and 3,4-dimethoxybromobenzene (**2i**) as benzyne precursors gave the corresponding regiocontrolled 1-naphthols in moderate yields (entries 9—11, 13, and 14). These results may be rationalized in terms of the polarization effect of the alkoxy group in the benzyne intermediates.[18] As for the reaction conditions, the use of 2.0 eq of halobenzenes (**2**) and 3.5 eq of bases for **1a** (condition A) afforded the best results; compare entry 3 with entry 4. By the use of other bases such as LDA (condition B), LCI (condition C), and LTMP (condition E) or another solvent, ether (condition D), very similar yields of the naphthol (**3b**) were obtained. The reaction could also be applied to the preparation of a polycyclic naphthol (entry 15). *N*,*N*-Diethyl-3-phenylisocrotonamide (**1b**) also underwent reaction with benzynes under similar reaction conditions to give the corresponding 3-phenyl-1-naphthols in good yields (entries 16—19). However, when lithiated methyl senecioate, which had been employed by Sammes and

TABLE I. Synthesis of 1-Naphthols (3)



Entry	Amide		Halobenzene R¹	R²	R³	R⁴	R⁵	R⁶	(eq)	Conditions[a]		R	Naphthol R¹	R²	R³	R⁴	Yield (%)
1	**1a**	**2a**	H	H	H	H	H	Br	(2.0)	A	**3a**	Me	H	H	H	H	64
2	**1a**	**2a**	H	H	H	H	H	Br	(2.0)	B	**3a**	Me	H	H	H	H	55
3	**1a**	**2b**	OMe	H	H	H	H	Br	(2.0)	A	**3b**	Me	OMe	H	H	H	55
4	**1a**	**2b**	OMe	H	H	H	H	Br	(1.0)	C	**3b**	Me	OMe	H	H	H	25
5	**1a**	**2b**	OMe	H	H	H	H	Br	(2.0)	D	**3b**	Me	OMe	H	H	H	43
6	**1a**	**2b**	OMe	H	H	H	H	Br	(2.0)	B	**3b**	Me	OMe	H	H	H	43
7	**1a**	**2b**	OMe	H	H	H	H	Br	(2.0)	E	**3b**	Me	OMe	H	H	H	46
8	**1a**	**2c**	OMe	H	H	H	Br	H	(2.0)	A	**3b**	Me	OMe	H	H	H	47
9	**1a**	**2d**	OMe	H	OMe	H	H	Cl	(2.0)	A	**3c**	Me	OMe	H	OMe	H	46
10	**1a**	**2e**	OMe	H	OMe	H	Cl	H	(2.0)	A	**3c**	Me	OMe	H	OMe	H	56
11	**1a**	**2f**	OMe	H	Me	H	H	Cl	(2.0)	A	**3d**	Me	OMe	H	Me	H	43
12	**1a**	**2g**	OMe	H	H	OMe	H	Cl	(2.0)	A	**3e**	Me	OMe	H	H	OMe	57
13	**1a**	**2h**	OCH_2OMe	H	H	H	H	Br	(2.0)	A	**3f**	Me	OCH_2OMe	H	H	H	46
14	**1a**	**2i**	OMe	OMe	H	H	Br	H	(2.0)	A	**3g**	Me	OMe	OMe	H	H	40
15	**1a**	**2j**	$-(CH=CH)_2-$		$-(CH=CH)_2-$		H	Br	(2.0)	A	**3h**	Me	$-(CH=CH)_2-$		$-(CH=CH)_2-$		56
16	**1b**	**2a**	H	H	H	H	H	Br	(2.0)	A	**3i**	Ph	H	H	H	H	70
17	**1b**	**2b**	OMe	H	H	H	H	Br	(2.0)	A	**3j**	Ph	OMe	H	H	H	62
18	**1b**	**2d**	OMe	H	OMe	H	H	Cl	(2.0)	A	**3k**	Ph	OMe	H	OMe	H	55
19	**1b**	**2g**	OMe	H	H	OMe	H	Cl	(2.0)	A	**3l**	Ph	OMe	H	H	OMe	60

a) Conditions: A, THF–LCI (3.5 eq); B, THF–LDA (3.5 eq); C, THF–LCI (2.2 eq); D, ether–LCI (3.5 eq); E, THF–LTMP (3.5 eq).

TABLE II. Physical Properties and Spectral Data of 1-Naphthols (3)

1-Naphthol[a]	mp, °C (Solvent)	MS (*m/e*) M^+ (Formula)	IR (KBr) cm^{-1}	UV λ_{max}^{EtOH} nm (log ε)	NMR[b] ($CDCl_3$) δ
3a	91—92[c] (*n*-Hexane)	158 ($C_{11}H_{10}O$)	3300	236 (3.83), 300 (2.97), 313 (s) (2.84), 328 (2.69)	2.36 (s, 3H), 5.23 (br s, 1H), 6.50 (br s, 1H), 7.13 (br s, 1H), 7.23—8.13 (m, 4H)
3b	89[d] (*n*-Hexane)	188 ($C_{12}H_{12}O_2$)	3350	290 (s) (3.44), 306 (3.51), 320 (3.50), 335 (3.57)	2.36 (s, 3H), 3.89 (s, 3H), 6.50—6.69 (m, 2H), 6.72 (br s, 1H), 7.03 (br s, 1H), 7.13—7.23 (m, 1H), 9.13 (s, 1H)
3c	84 (*n*-Hexane)	218 ($C_{13}H_{14}O_3$)	3380	296 (s) (3.29), 302 (3.41), 322 (3.26), 335 (3.29)	2.33 (s, 3H), 3.76 (s, 3H), 3.83 (s, 3H), 6.26 (d, 1H, $J=3$), 6.53 (d, 1H, $J=3$), 6.56 (br s, 1H), 6.89 (br s, 1H), 8.92 (s, 1H)
3d	104 (*n*-Hexane)	202 ($C_{13}H_{14}O_2$)	3340	290 (s) (3.12), 305 (3.21), 320 (3.21), 334 (3.26)	2.36 (s, 6H), 3.98 (s, 3H), 6.50 (br s, 1H), 6.66 (br s, 1H), 6.92 (br s, 1H), 7.03 (br s, 1H), 9.07 (s, 1H)
3e	120—122[e] (*n*-Hexane)	218 ($C_{13}H_{14}O_3$)	3350	294 (s) (3.22), 310 (3.32), 328 (3.34), 342 (3.38)	2.43 (s, 3H), 3.89 (s, 3H), 3.92 (s, 3H), 6.50 (s, 2H), 6.76 (br s, 1H), 7.49 (br s, 1H), 9.06 (s, 1H)
3f	58 (*n*-Hexane)	218 ($C_{13}H_{14}O_3$)	3400	265 (2.69), 292 (s) (2.61), 305 (2.67), 320 (2.59), 335 (2.59)	2.36 (s, 3H), 3.46 (s, 3H), 5.26 (s, 2H), 6.69—7.23 (m, 5H), 9.13 (s, 1H)
3g	35—37 (Petroleum ether)	218 ($C_{13}H_{14}O_3$)	3400	280 (s) (3.64), 295 (3.79), 306 (3.80), 336 (3.60), 347 (s) (3.59)	2.33 (s, 3H), 3.83 (s, 3H), 3.96 (s, 3H), 6.66 (br s, 1H), 6.92 (br s, 1H), 7.10 (s, 1H), 7.26 (s, 1H), 9.43 (s, 1H)
3h	205—208 (Ether–*n*-hexane)	258 ($C_{19}H_{14}O$)	3400	254 (s) (4.46), 262 (4.62), 288 (s) (3.87), 300 (3.57), 324 (s) (3.25), 340 (3.17), 356 (3.11)	2.33 (s, 3H), 6.76 (br s, 1H), 7.43—8.66 (m, 10H)
3i	95—100[f] (*n*-Hexane)	220 ($C_{16}H_{12}O$)	3350	258 (4.05), 305 (3.28), 344 (s) (2.92)	6.16 (br s, 1H), 6.90—7.60 (m, 10H), 8.12—8.27 (m, 1H)
3j	111—112 (Ether–*n*-hexane)	250 ($C_{17}H_{14}O_2$)	3380	256 (4.15), 302 (3.31), 345 (3.29)	3.63 (s, 3H), 6.36—7.69 (m, 10H), 9.23 (s, 1H)
3k	120—121 (Ether–*n*-hexane)	280 ($C_{18}H_{16}O_3$)	3360	262 (4.74), 296 (s) (3.92), 349 (3.64)	3.86 (s, 3H), 3.96 (s, 3H), 6.36 (d, 1H, $J=2$), 6.69 (d, 1H, $J=2$), 6.92 (br s, 1H), 7.23—7.73 (m, 6H), 9.00 (s, 1H)
3l	99—100 (Ether–*n*-hexane)	280 ($C_{18}H_{16}O_3$)	3380	260 (4.67), 317 (s) (3.82), 355 (3.97)	3.63 (s, 3H), 3.69 (s, 3H), 6.26 (s, 2H), 7.20—7.96 (m, 7H), 9.36 (s, 1H)

a) *Anal.* Calcd (Found) for **3b**: C, 76.57 (76.63); H, 6.43 (6.44). **3c**: C, 71.54 (71.49); H, 6.47 (6.59). **3d**: C, 77.20 (77.47); H, 6.98 (6.95). **3e**: C, 71.54 (71.65); H, 6.47 (6.48). **3f**: C, 71.54 (71.89); H, 6.47 (6.41). **3g**: C, 71.54 (71.40); H, 6.47 (6.49). **3h**: C, 88.34 (88.15); H, 5.46 (5.50). **3i**: C, 87.24 (87.45); H, 5.49 (5.39). **3j**: C, 81.54 (81.71); H, 5.64 (5.60). **3k**: C, 77.12 (77.01); H, 5.75 (5.67). **3l**: C, 77.12 (77.24); H, 5.75 (5.75). *b*) Listed as chemical shifts (multiplicity, number of protons, coupling constant in Hz). *c*) Lit.[8] mp 88—91 °C; lit.[20] mp 93.5—94 °C. *d*) Lit.[17] mp 91 °C. *e*) Lit.[8,21] mp 117—118 °C. *f*) Lit.[22] mp 100—101 °C.

Wallace[8] for the naphthol synthesis, was treated with **2a** or **2b** under condition A, **3a** or **3b** was obtained in only 19% or 20% yield, respectively. This clearly indicates the superiority of **1a** to the corresponding ester for this type of naphthol synthesis. The structures of 1-naphthols obtained here were determined on the basis of elemental analyses, and the infrared (IR), ultraviolet (UV), mass (MS), and proton nuclear magnetic resonance (^{1}H-NMR) spectral data listed in Table II. Among the naphthols synthesized by our method, **3b** is a natural product from the heartwood of *Diospyros melanoxylon* ROXB.[17] Methylation of **3b** and **3g** with dimethyl sulfate in the presence of potassium carbonate in refluxing acetone gave 3-methyl-1,8-dimethoxynaphthalene (**3m**)[17] and 6-methyl-1,2,8-trimethoxynaphthalene (macassar III) (**3n**),[19] respectively, which are also natural products isolated from *Diospyros* species (Chart 3).

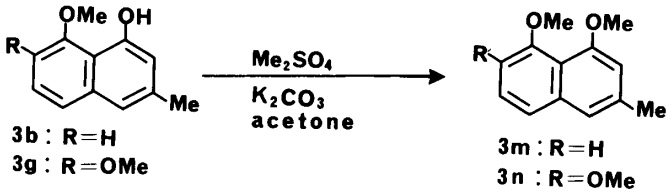


Chart 3

N,*N*-Diethylcyclohexylideneacetamide (**4**), which was prepared by the Wittig reaction of *N*,*N*-diethyl diethylphosphonoacetamide with cyclohexanone, was chosen as a test case of a cyclic α,β-unsaturated amide in a similar reaction. When **4** was treated with **2g** under condition A, two isomeric cyclic naphthols, 9-hydroxy-1,4-dimethoxy-5,6,7,8-tetrahydroanthracene (**5a**, mp 122 °C) and 10-hydroxy-1,4-dimethoxy-5,6,7,8-tetrahydrophenanthrene (**5b**, mp 120 °C), were obtained in 24% and 10% yields, respectively (Chart 4). The structures of these compounds were determined mainly from their ^{1}H-NMR spectra (Figs. 1 and 2). The possible reaction pathway for the formation of the two isomeric naphthols

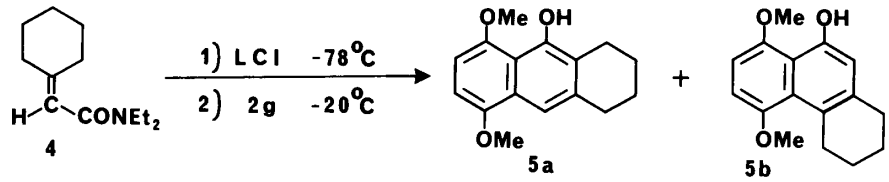


Chart 4

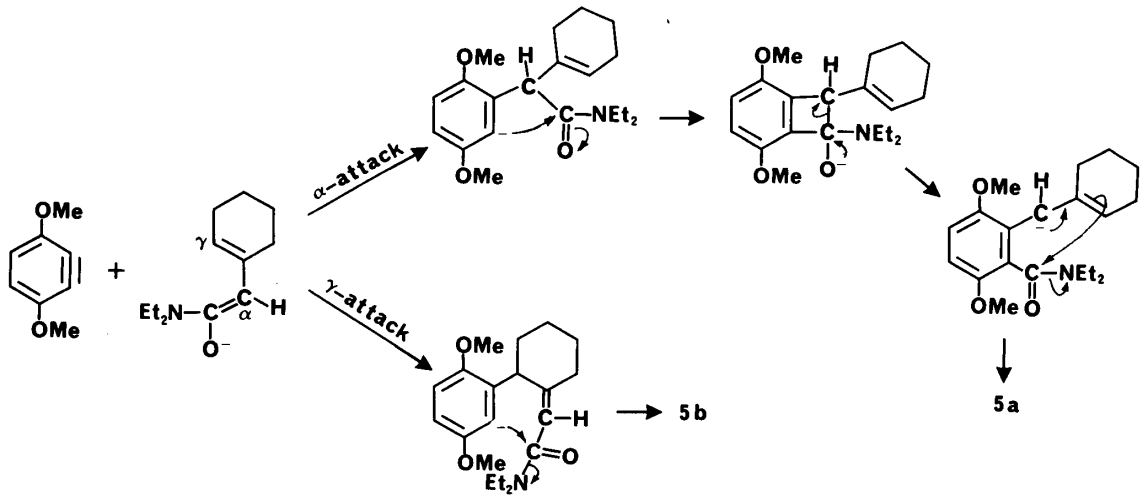


Chart 5

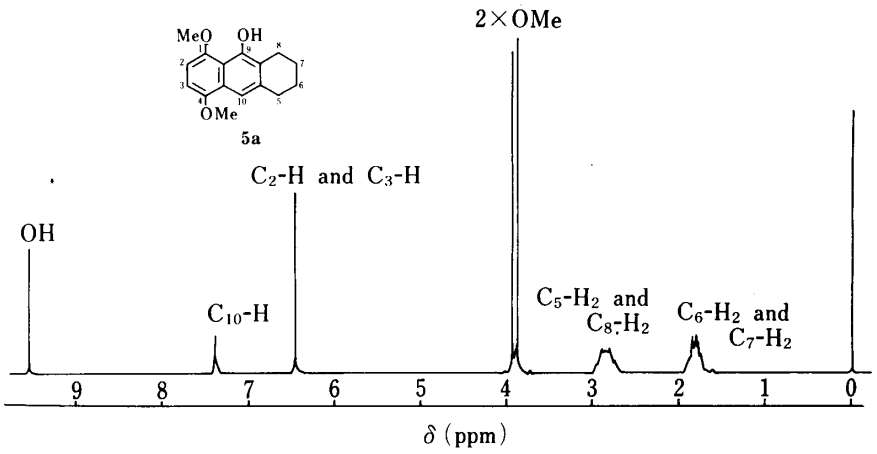


Fig. 1. The NMR Spectrum of **5a** in $CDCl_3$

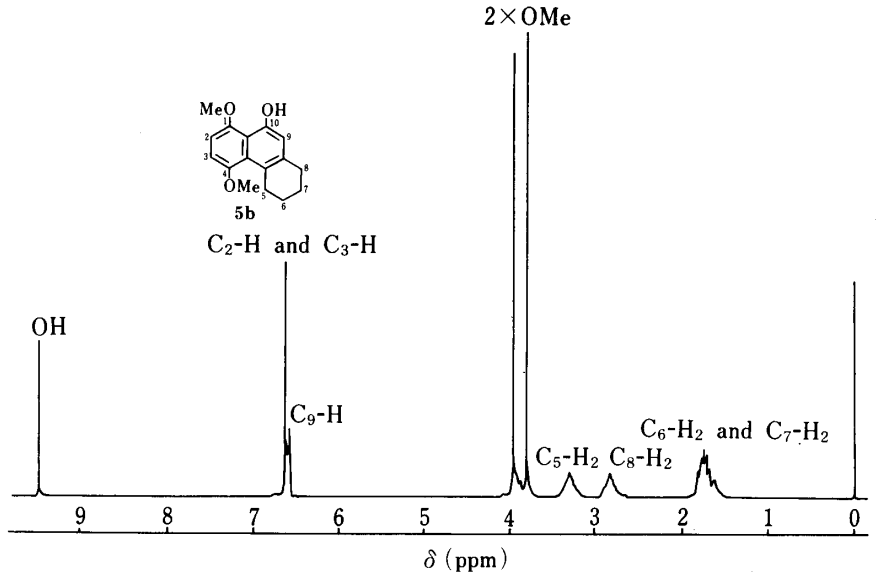
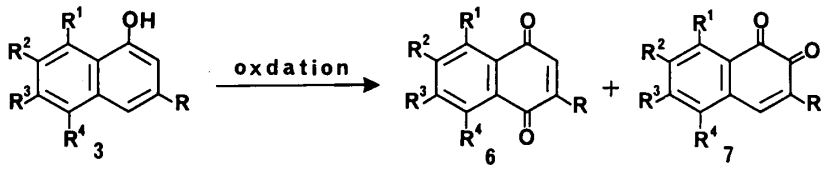


Fig. 2. The NMR Spectrum of **5b** in $CDCl_3$

(**5a** and **5b**) is illustrated in Chart 5. Attack by the γ-site of lithiated **4** on the benzyne leads to the angular product **5b**. On the other hand, the linear product **5a** results from initial attack from the α-position followed by rearrangement and cyclization.[23] Two possible routes in the formation of 3-methyl- and 3-phenyl-1-naphthols *via* the reactions of lithiated **1a** and **1b** with benzynes may also be operative but these can not be differentiated, since they provide the same products (**3a**—**1**). However, from the result shown in Chart 4, it is likely that naphthols (**3** and **5**) are formed *via* two routes (α-attack and γ-attack) in general. A similar conclusion was reached by Sammes and Wallace[8] for the formation of naphthalenes by the reaction of mesityl oxide with benzynes.

Many naphthoquinones bearing a methyl group on the quinone nucleus are found in nature together with related naphthols and their ethers.[24] Of the methods available for the oxidation of naphthols into naphthoquinones, we have examined the salcomine-catalyzed oxidation[25] and Fremy's salt oxidation[26] for our 3-methyl- and 3-phenyl-1-naphthols (Table III). Treatment of **3a** in the presence of salcomine in dimethylformamide (DMF) at room temperature under oxygen flow for 3 h gave 2-methyl-1,4-naphthoquinone (menadione) (**6a**, mp 102—103 °C)[27,28] in 70% yield. Other naphthols (**3c**, **3d**, **3h**, and **3j**) were also easily oxidized to the corresponding 1,4-naphthoquinones (**6c**,[29] **6d**, **6h**, and **6j**) in a similar manner

TABLE III. Oxidation of Naphthols (3) to Naphthoquinones (6 and 7)



3

6 7

3a: $R^1=R^2=R^3=R^4=H$, R=Me
3b: $R^1=OMe$, $R^2=R^3=R^4=H$, R=Me
3c: $R^1=R^3=OMe$, $R^2=R^4=H$, R=Me
3d: $R^1=OMe$, $R=R^3=Me$, $R^2=R^4=H$
3e: $R^1=R^4=OMe$, $R^2=R^3=H$, R=Me
3f: $R^1=OCH_2OMe$, $R^2=R^3=R^4=H$, R=Me
3g: $R^1=R^2=OMe$, $R^3=R^4=H$, R=Me
3h: $R^1 \supset R^2=-(CH=CH)_2-$, $R^3 \supset R^4=-(CH=CH)_2-$, R=Me
3i: $R^1=R^2=R^3=R^4=H$, R=Ph
3j: $R^1=OMe$, $R^2=R^3=R^4=H$, R=Ph

6a: $R^1=R^2=R^3=R^4=H$, R=Me
6b: $R^1=OMe$, $R^2=R^3=R^4=H$, R=Me
6c: $R^1=R^3=OMe$, $R^2=R^4=H$, R=Me
6d: $R^1=OMe$, $R=R^3=Me$, $R^2=R^4=H$
6e: $R^1=R^4=OMe$, $R^2=R^3=H$, R=Me
6f: $R^1=OCH_2OMe$, $R^2=R^3=R^4=H$, R=Me
6g: $R^1=R^2=OMe$, $R^3=R^4=H$, R=Me
6h: $R^1 \supset R^2=-(CH=CH)_2-$, $R^3 \supset R^4=-(CH=CH)_2-$, R=Me
6i: $R^1=R^2=R^3=R^4=H$, R=Ph
6j: $R^1=OMe$, $R^2=R^3=R^4=H$, R=Ph
7a: $R^1=OMe$, $R^2=R^3=R^4=H$, R=Me
7b: $R^1=R^4=OMe$, $R^2=R^3=H$, R=Me
7c: $R^1=R^2=R^3=R^4=H$, R=Ph

Entry	Naphthol	Conditions	1,4-Quinone	Yield (%)	1,2-Quinone	Yield (%)
1	**3a**	O_2/salcomine	**6a**	70	—	
2	**3b**	O_2/salcomine	**6b**	69	—	
3	**3b**	Fremy's salt	**6b**	45	**7a**	40
4	**3c**	O_2/salcomine	**6c**	78	—	
5	**3d**	O_2/salcomine	**6d**	65	—	
6	**3e**	O_2/salcomine	**6e**	35	**7b**	35
7	**3e**	Fremy's salt	—		**7b**	60
8	**3f**	O_2/salcomine	**6f**	65	—	
9	**3g**	O_2/salcomine	**6g**	73	—	
10	**3h**	O_2/salcomine	**6h**	66	—	
11	**3i**	Fremy's salt	**6i**	26	**7c**	50
12	**3j**	O_2/salcomine	**6j**	65	—	

in better than 65% yield. In the case of **3e**, the corresponding 1,4-quinone (**6e**, mp 156—158 °C) and 1,2-quinone (**7b**, mp 175—176 °C) were isolated together in a ratio of 1 : 1 in 70% yield, probably due to the steric hindrance of the 5-methoxy group of **3e**. On the other hand, **3i** was treated with Fremy's salt at 0 °C in the presence of potassium dihydrogen phosphate to afford 3-phenyl-1,2-naphthoquinone (**7c**) as a major product (50% yield) accompanied with 2-phenyl-1,4-naphthoquinone (**6i**)[30] in 26% yield. From these results, it is clear that the oxidation method can be selected for the syntheses of either 1,2- or 1,4-naphthoquinone natural products. For example, the syntheses of naturally occurring 1,4-naphthoquinone such as 2-methyl-5-methoxy-1,4-naphthoquinone (plumbagin methylether) (**6b**)[17,28,31] and 2-methyl-5,6-dimethoxy-1,4-naphthoquinone (**6g**)[19b] were accomplished by salcomine-catalyzed oxidation starting from **3b** and **3g**, respectively. By treatment of **3b** with Fremy's salt, the expected 3-methyl-8-methoxy-1,2-naphthoquinone (**7a**),[17] also isolated from *Diospyros* species, was synthesized in 40% yield accompanied with the corresponding 1,4-quinone (**6b**) in 45% yield. For the synthesis of plumbagin, the oxidation of the methoxymethyl-substituted naphthol (**3f**) was examined. Plumbagin was isolated from the genus *Plumbago*[32] and *Diospyros*,[33] and exhibits pharmacological activity[34] including insect ecdysis inhibition.[35] The oxidation of **3f** was carried out using salcomine to give **6f** in 65%

TABLE IV. Physical Properties and Spectral Data of Quinones (**6** and **7**)

Quinone[a]	mp, °C (Solvent)	MS (*m/e*) M^+ (Formula)	IR (KBr) cm^{-1}	UV λ_{max}^{EtOH} nm (log ε)	NMR[b] ($CDCl_3$) δ
6a	102—103[c] (*n*-Hexane)	172 ($C_{11}H_8O_2$)	1665	245 (4.27), 251 (4.26), 264 (s) (4.16), 330 (3.34)	2.13 (d, 3H, J=1.5), 6.76 (q, 1H, J=1.5), 7.23—8.13 (m, 4H)
6b	97—98[d] (*n*-Hexane)	202 ($C_{12}H_{10}O_3$)	1645	252 (3.22), 270 (s) (3.12), 398 (2.63)	2.13 (d, 3H, J=1.5), 4.00 (s, 3H), 6.72 (q, 1H, J=1.5), 7.21—7.73 (m, 3H)
6c	147—149[e] (Ether)	232 ($C_{13}H_{12}O_4$)	1620, 1640	267 (4.28), 410 (3.60)	2.07 (d, 3H, J=1.5), 3.86 (s, 6H), 6.59 (q, 1H, J=1.5), 7.17 (s, 2H)
6d	150—152 (MeOH)	216 ($C_{13}H_{12}O_3$)	1625, 1640	255 (3.27), 274 (s) (3.13), 405 (2.66)	2.09 (d, 3H, J=1.5), 2.43 (s, 3H), 3.92 (s, 3H), 6.59 (q, 1H, J=1.5), 7.05 (br s, 1H), 7.46 (br s, 1H)
6e	156—158 (MeOH)	232 ($C_{13}H_{12}O_4$)	1635	264 (3.69), 450 (3.22)	2.08 (d, 3H, J=1.5), 3.89 (s, 6H), 6.56 (q, 1H, J=1.5), 7.23 (s, 2H)
6f	107—108 (*n*-Hexane)	232 ($C_{13}H_{12}O_4$)	1650	250 (4.20), 272 (s) (4.07), 382 (3.53)	2.13 (d, 3H, J=1.5), 3.50 (s, 3H), 5.29 (s, 2H), 6.63 (q, 1H, J=1.5), 7.43—7.83 (m, 3H)
6g	184—185[f] (MeOH)	232 ($C_{13}H_{12}O_4$)	1650, 1660	262 (4.32), 278 (s) (4.16), 392 (3.60)	2.13 (d, 3H, J=1.5), 3.91 (s, 3H), 3.97 (s, 3H), 6.70 (q, 1H, J=1.5), 7.15 (d, 1H, J=8), 7.90 (d, 1H, J=8)
6h	139 (MeOH)	272 ($C_{19}H_{12}O_2$)	1630, 1645	249 (5.17), 273 (s) (4.65), 295 (4.46), 307 (4.30), 418 (3.59)	2.16 (d, 3H, J=1.5), 6.63 (q, 1H, J=1.5), 7.50—7.73 (m, 4H), 8.36—8.59 (m, 2H), 8.92—9.29 (m, 2H)
6i	113—114[g] (Ether–*n*-hexane)	234 ($C_{16}H_{10}O_2$)	1670	250 (4.45), 255 (s) (4.43), 268 (s) (4.03), 292 (s) (3.87), 300 (3.94), 340 (3.75), 356 (s) (3.71)	6.96 (s, 1H), 7.32—8.20 (m, 9H)
6j	171—173 (Ethyl acetate)	264 ($C_{17}H_{12}O_3$)	1650, 1660	235 (s) (4.43), 300 (3.92), 408 (3.81)	4.03 (s, 3H), 6.98 (s, 1H), 7.28—7.80 (m, 8H)
6k	76—77[h] (*n*-Hexane)	188 ($C_{11}H_8O_3$)	1635	252 (s) (3.47), 268 (3.50), 420 (3.05)	2.18 (d, 3H, J=1.5), 6.78 (q, 1H, J=1.5), 7.23—7.61 (m, 3H), 11.94 (s, 1H)
7a	151[i] (MeOH–ether)	202 ($C_{12}H_{10}O_3$)	1660	240 (3.82), 430 (3.25)	2.03 (d, 3H, J=1.5), 3.98 (s, 3H), 6.79—7.11 (m, 2H), 7.13 (q, 1H, J=1.5), 7.26—7.54 (m, 1H)
7b	175—176 (MeOH)	232 ($C_{13}H_{12}O_4$)	1620, 1645	228 (4.43), 260 (s) (4.09), 510 (3.85)	2.00 (d, 3H, J=1.5), 3.83 (s, 3H), 3.86 (s, 3H), 6.89 (d, 1H, J=8), 7.10 (d, 1H, J=8), 7.63 (q, 1H, J=1.5)
7c	163 (MeOH)	234 ($C_{16}H_{10}O_2$)	1655, 1690	262 (3.95), 340 (3.43), 445 (2.95)	7.10—8.10 (m, 10H)

a) *Anal.* Calcd (Found) for **6a**: C, 76.73 (76.56); H, 4.68 (4.67). **6b**: C, 71.28 (71.18); H, 4.99 (4.99). **6c**: C, 67.23 (66.88); H, 5.21 (5.20). **6d**: C, 72.21 (72.26); H, 5.59 (5.54). **6e**: C, 67.23 (67.19); H, 5.21 (5.15). **6f**: C, 67.23 (67.12); H, 5.21 (5.17). **6g**: C, 67.23 (67.37); H, 5.21 (5.23). **6h**: C, 83.80 (84.01); H, 4.44 (4.42). **6i**: C, 82.04 (82.30); H, 4.30 (4.31). **6j**: C, 77.26 (77.13); H, 4.58 (4.57). **7a**: C, 71.28 (70.84); H, 4.99 (4.93). **7b**: C, 67.23 (67.28); H, 5.21 (5.28). **7c**: C, 82.04 (82.18); H, 4.30 (4.28). *b*) Listed as chemical shifts (multiplicity, number of protons, coupling constant in Hz). *c*) Lit.[27] mp 105—107 °C; lit.[28] mp 105.5 °C. *d*) Lit.[17] mp 94 °C; lit.[28] mp 97.5—98.5 °C; lit.[31] mp 99 °C. *e*) Lit.[29b] mp 146.5 °C; lit.[29c] mp 144.0—144.7 °C. *f*) Lit.[19b] mp 190 °C. *g*) Lit.[30] mp 112—113 °C. *h*) Lit.[31] mp 76—77 °C; lit.[36a] mp 78—79 °C; lit.[36c] mp 76—78 °C. *i*) Lit.[17] mp 155 °C.

yield. Then **6f** was briefly treated with 10% HCl in MeOH to yield plumbagin (**6k**)[31,35,36] quantitatively. The structures of 1,4-quinones (**6**) and 1,2-quinones (**7**) were confirmed by elemental analyses and spectral data (IR, UV, MS, and ^{1}H-NMR), which are collected in Table IV.

In conclusion, the regiospecific anionic annelation (Chart 2) could serve as a general, convenient, and efficient method for the preparation of highly substituted 1-naphthols and 1,2- and 1,4-naphthoquinones.

Experimental

Melting points are uncorrected. The IR spectra were determined on a JASCO IRA-2 spectrophotometer, UV spectra on a Hitachi 323 spectrophotometer, and ^{1}H-NMR spectra on JEOL FX 90Q and JEOL JNM-PMX 60 spectrometers using tetramethylsilane as an internal standard. The MS were determined on a JEOL JMS 01SG mass spectrometer. Chromatography was carried out by flash chromatography on a column of Kieselgel 60 (230—400 mesh).

Preparation of Unsaturated Amides (1a, 1b, and 4). *N,N*-Diethyl Diethylphosphonoacetamide——This compound was prepared by a modification of a literature method.[37] A mixture of *N,N*-diethylchloroacetamide[38] (12 g, 88.6 mmol) and freshly distilled triethyl phosphite (14.7 g, 88.6 mmol) was stirred at 180 °C (oil bath) for 8 h. The reaction mixture was distilled to give the product, 18.7 g (84.2%). bp 136—137 °C (1.1 mm Hg). IR (neat) cm^{-1}: 1640 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.18 (t, 6H, J=7 Hz), 1.33 (t, 6H, J=7 Hz), 3.00 (d, 2H, J=20 Hz), 3.34 (q, 2H, J=7 Hz), 3.40 (q, 2H, J=7 Hz), 4.06 (q, 2H, J=7 Hz), 4.18 (q, 2H, J=7 Hz). *Anal.* Calcd for $C_{10}H_{22}NO_4P$: C, 47.80; H, 8.83; N, 5.58. Found: C, 47.37; H, 8.82; N, 5.41.

***N,N*-Diethyl-3-phenylisocrotonamide (1b)**——This compound was obtained in 68.5% yield by the Wittig reaction[39] of *N,N*-diethyl diethylphosphonoacetamide with acetophenone. *N,N*-Diethyl diethylphosphonoacetamide (15.6 g, 70 mmol) was added dropwise at 20 °C to a slurry of 50% sodium hydride (3.4 g, 70 mmol) in 110 ml of dry benzene under nitrogen. After the addition, the reaction mixture was stirred for 1 h at room temperature until gas evolution had ceased. Acetophenone (8.4 g, 70 mmol) was added dropwise while maintaining the temperature below 30 °C. Then the solution was stirred for 40 min at room temperature, during which time a viscous semi-solid appeared. The benzene solvent was decanted and the residual semi-solid was washed with benzene. The combined benzene solution was washed with saturated ammonium chloride, dried over anhydrous Na_2SO_4 and then evaporated to give a crude oil. This oil was distilled to give **1b**, bp 147—148 °C (1.25 mm Hg). IR (neat) cm^{-1}: 1640 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.12 (t, 6H, J=7 Hz), 2.26 (s, 3H), 3.33 (q, 4H, J=7 Hz), 6.24 (br s, 1H), 7.17—7.43 (m, 5H). *Anal.* Calcd for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.45. Found: C, 77.43; H, 8.99; N, 6.32.

***N,N*-Diethylcyclohexylideneacetamide (4)**——This compound was obtained in 64% yield from *N,N*-diethyl diethylphosphonoacetamide and cyclohexanone using conditions similar to those described for **1b**. bp 102—103 °C (1.0 mm Hg). IR (neat) cm^{-1}: 1635 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.13 (t, 6H, J=7 Hz), 1.50—2.60 (m, 10H), 3.36 (q, 4H, J=7 Hz), 5.69 (s, 1H). *Anal.* Calcd for $C_{12}H_{21}NO$: C, 73.79; H, 10.84; N, 7.17. Found: C, 73.44; H, 10.88; N, 6.98.

***N,N*-Diethylsenecioamide (1a)**——This compound was prepared in 90% yield from 3,3-dimethylacrylyl chloride and diethylamine according to a literature procedure.[15] bp 105—106 °C (20 mm Hg) (lit.[15] bp 41—42 °C (0.2 mm Hg)).

Typical Procedures for the Syntheses of Naphthols (3)——The following procedure for the synthesis of **3b** under condition A (entry 3) is representative for the syntheses of other naphthols. A solution of **1a** (0.8 g, 5 mmol) in THF (20 ml) was added to a solution of LCI (17.5 mmol) (prepared from a 1.2 M solution of *n*-BuLi in hexane, 14.6 ml, 17.5 mmol, and *N*-isopropylcyclohexylamine, 2.9 ml, 17.5 mmol) in THF (30 ml) at −78 °C under nitrogen. The solution was stirred at −78 °C for 1 h, then the cold bath was removed and the flask was allowed to warm to −20 °C over 10 min. A THF solution (10 ml) of **2a** (1.8 g, 10 mmol) was then injected to the solution. The reaction mixture was stirred overnight at room temperature, quenched with saturated ammonium chloride and 10% HCl, and evaporated. The residue was extracted with $CHCl_3$. The extract was dried (Na_2SO_4) and evaporated to give a brown oil, which was chromatographed to give **3a** (0.52 g, from the *n*-hexane eluate, 55%) and the crude α-adduct,[16] *N,N*-diethyl-2-isopropenyl-2-(3′-methoxyphenyl)acetamide, (0.18 g, from the $CHCl_3$ eluate, 14%). The pure α-adduct (oil, 0.1 g, 8%) was obtained by preparative thin layer chromatogrpahy (Kieselgel 60 F_{254}S, $CHCl_3$–acetone (19 : 1)). MS *m/e*: 261 (M^+). IR (neat) cm^{-1}: 1640 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.13 (t, 6H, J=8 Hz), 1.69 (s, 3H), 3.30 (q, 4H, J=8 Hz), 3.73 (s, 3H), 4.33 (br s, 1H), 4.69 (br s, 1H), 4.96 (br s, 1H), 6.76—7.17 (m, 4H). *Anal.* Calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.01; H, 8.83; N, 5.12.

Methylation of the Naphthols (3b and 3g). 3-Methyl-1,8-dimethoxynaphthalene (3m)——A mixture of **3b** (0.5 g, 2.7 mmol), K_2CO_3 (2.5 g), dimethyl sulfate (1.0 g, 8.1 mmol) and acetone (100 ml) was refluxed for 24 h. The reaction mixture was filtered. The filtrate was evaporated to dryness to afford crude **3m**, which was chromatographed using benzene as the eluent to give pure **3m** (0.43 g, 80%), mp 89—90 °C (*n*-hexane) (lit.[17] mp 87 °C). MS *m/e*: 202 (M^+).

UV λ_{max}^{EtOH} nm (log ε): 287 (s) (3.28), 300 (3.34), 318 (3.28), 333 (3.32). ^{1}H-NMR ($CDCl_3$) δ: 2.39 (s, 3H), 3.89 (s, 6H), 6.59—6.74 (m, 2H), 7.10—7.26 (m, 3H). *Anal.* Calcd for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 77.23; H, 6.95.

6-Methyl-1,2,8-trimethoxynaphthalene (Macassar III) (3n)——This compound was prepared in 60% yield from **3g** in the same manner as described above. mp 68—69 °C (ether–*n*-hexane) (lit.[19a] mp 68—69 °C; lit.[19c] mp 70—71 °C). MS *m/e*: 232 (M^+). UV λ_{max}^{EtOH} nm (log ε): 232 (3.80), 278 (s) (3.71), 290 (3.87), 302 (3.86), 334 (3.56), 348 (3.53). ^{1}H-NMR ($CDCl_3$) δ: 2.36 (s, 3H), 3.83 (s, 6H), 3.86 (s, 3H), 6.53 (br s, 1H), 7.00 (br s, 1H), 7.13 (s, 1H), 7.23 (s, 1H). *Anal.* Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.57; H, 7.02.

Reaction of *N,N*-Diethylcyclohexylideneacetamide (4) with 2,5-Dimethoxychlorobenzene (2g)——Compound **4** was reacted with **2g** under condition A, already described as a typical procedure for the syntheses of naphthols. After chromatography, **5a** was obtained in 24% yield from the *n*-hexane–benzene (9 : 1) eluate, and **5b** was obtained in 10% yield from the *n*-hexane–benzene (4 : 1) eluate. **5a**: mp 122 °C (petroleum ether). MS *m/e*: 258 (M^+). IR (KBr) cm^{-1}: 3350 (OH). UV λ_{max}^{EtOH} nm (log ε): 298 (s) (3.29), 312 (3.42), 327 (3.44), 342 (3.47). ^{1}H-NMR ($CDCl_3$) δ: 1.75—1.89 (m, 4H), 2.70—2.90 (m, 4H), 3.90 (s, 3H), 3.95 (s, 3H), 6.50 (s, 2H), 7.43 (s, 1H), 9.63 (s, 1H). *Anal.* Calcd for $C_{16}H_{18}O_3$: C, 74.39; H, 7.02. Found: C, 74.67; H, 7.02. **5b**: mp 120 °C (petroleum ether). MS *m/e*: 258 (M^+). IR (KBr) cm^{-1}: 3330 (OH). UV λ_{max}^{EtOH} nm (log ε): 298 (3.38), 310 (3.44), 338 (3.44), 353 (3.54). ^{1}H-NMR ($CDCl_3$) δ: 1.75—1.83 (m, 4H), 2.70—2.85 (m, 2H), 3.20—3.40 (m, 2H), 3.82 (s, 3H), 3.96 (s, 3H), 6.62 (s, 1H), 6.65 (s, 1H), 9.56 (s, 1H). *Anal.* Calcd for $C_{16}H_{18}O_3$: C, 74.39; H, 7.02. Found: C, 74.79; H, 7.04.

Oxidation of Naphthols to Naphthoquinones. Using Salcomine——The following procedure for the oxidation of **3b** with salcomine and O_2 illustrates the general procedure. Salcomine (0.1 g, 0.3 mmol) was added to a solution of **3b** (0.56 g, 3 mmol) in 10 ml of DMF. Oxygen was bubbled through the solution at room temperature for 3 h with stirring. The oxygen flow was then terminated and water (100 ml) was added. The mixture was extracted with several portions of $CHCl_3$. The combined $CHCl_3$ extract was dried (Na_2SO_4) and evaporated under reduced pressure to give a reddish brown solid which was purified by chromatography to furnish 0.41 g (69%) of **6b**, mp 97—98 °C (*n*-hexane) (lit.[31] mp 99 °C).

Using Fremy's Salt——The following procedure for the oxidation of **3b** with Fremy's salt illustrates the general procedure. A solution of **3b** (0.4 g, 2.1 mmol) in MeOH (40 ml) was added to a solution of Fremy's salt (1.3 g, 4.7 mmol) in 50 ml of water and 25 ml of aqueous KH_2PO_4 (0.167 M) at room temperature. The solution was stirred at room temperature for 20 h and then evaporated. The residual aqueous solution was extracted with $CHCl_3$. The extract was dried (Na_2SO_4) and evaporated to give a reddish solid. After chromatography, the 1,4-quinone (**6b**) was obtained in 45% yield from the $CHCl_3$ eluate and the 1,2-quinone (**7a**) (mp 151 °C) (lit.[17] mp 155 °C) was obtained in 40% yield from the $CHCl_3$–acetone (8 : 2) eluate.

Synthesis of Plumbagin——3-Methyl-8-methoxymethoxy-1-naphthol (**3f**) was synthesized in 46% yield by the reaction of **1a** with **2h** under condition A (see typical procedure), and then oxidized by the use of salcomine to give **6f** in 65% yield. A mixture of **6f** (0.46 g, 2 mmol), MeOH (20 ml), and 10% HCl (2 ml) was refluxed for 5 min. The MeOH was removed and the acidic solution was extracted with $CHCl_3$. The extract was washed with saturated NaCl solution, dried (Na_2SO_4), and evaporated to afford a crystalline material, which was recrystallized from *n*-hexane to give plumbagin (**6k**, 0.36 g, 95%), mp 76—77 °C (lit.[31] mp 76—77 °C).

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