Preparation of Naphthoquinone Derivatives from Plumbagin and Their Ichthyotoxicity

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Various naphthoquinone derivatives were prepared from a natural product, 5-hydroxy-2-methyl-1,4-naphthoquinone (plumbagin); these were mostly substituted at C-3 through carbon–carbon bond formation mediated by a metal-based oxidant such as lead tetraacetate in the presence of various carboxylic acids. The halogenated compounds showed stronger ichthyotoxicity than plumbagin, but other derivatives were less active.

Key words plumbagin; 3-substituted plumbagin; lead tetraacetate; oxidant; ichthyotoxicity; *Poecilia* (Lebites) *reticulata*

5-Hydroxy-2-methyl-1,4-naphthoquinone (plumbagin: **1**) is present in plants of the genera *Plumbago* and *Diospyros*[1,2] and has been isolated from the roots of *Diospyros maritima* (Japanese name: Ryukyugaki).[3] The fruits of this plant have been used as a piscicide in Okinawa. As **1** has a variety of biological activities such as antimicrobial activity,[4-6] insect antifeedant activity,[7] and insect growth-inhibiting activity,[8] **1** and its derivatives might have medical and agricultural applications.

In the search for plumbagin derivatives possessing the same pharmacological and pesticidal activity as **1**, but lower toxicity than **1**, we set out to synthesize 3-substituted plumbagins such as 3-alkyl-, 3-alkenyl-, and 3-alkoxymethylplumbagins, as well as 3-oxygenated and 3-halogenated plumbagins. We examined oxidative carbon–carbon bond formation[9,10] at the C-3 position of **1** with a variety of carboxylic acids in the presence of various oxidants and found that the $Pb(OAc)_4$-mediated reaction proceeded well to afford 3-alkyl-, 3-alkenyl-, and 3-alkoxymethylplumbagins. We also synthesized 3-oxygenated and 3-halogenated plumbagins. The ichthyotoxicity of these 3-substituted plumbagins against male guppy, *Poecilia reticulata* was examined.

$Pb(OAc)_4$-Mediated Carbon–Carbon Bond Formation at the C-3 Position of Plumbagin (1) with Carboxylic Acids Fieser and Chang have synthesized 2,3-dimethyl-1,4-naphthoquinone from 3-methylnaphthoquinone in acetic acid with $Pb(OAc)_4$.[11] We tried to react **1** with acetic acid in the presence of $Pb(OAc)_4$, but obtained 3-methylplumbagin in extremely low yield (less than 3%). Moreover, **1** reacted with ethoxyacetic acid (**2a**) in the presence of $Pb(OAc)_4$ to give 3-ethoxymethylplumbagin (**3a**) in low yield (less than 5%). The lead (IV) salt generates radicals from carboxylic acids as follows. Higher-valent lead carboxylate derived from carboxylic acid and $Pb(OAc)_4$ decomposes to carbon dioxide and an alkyl radical, which attacks the olefinic carbon, resulting in carbon–carbon bond formation (Chart 2).[12] In this reaction, it is well-known that the use of large amounts of an oxidant such as $Pb(OAc)_4$ results in low yields of products.[12] Therefore, in order to determine suitable reaction conditions and the optimum molar ratio of **1**: $Pb(OAc)_4$: carboxylic acid, **1** was allowed to react with various amounts of **2a** in the presence of various amounts of $Pb(OAc)_4$ in degassed benzene under an argon atmosphere, as shown in Fig. 1. Increasing the molar ratio of **2a** to the lead(IV) salt resulted in an increasing yield of **3a**. However, the use of an excess of **2a** decreased the yield of **3a**. Increasing the molar ratio of the lead(IV) salt to **1** as well as the molar ratio of **2a** to the lead(IV) salt resulted in an increasing yield of **3a**. When the amount of the lead(IV) salt was more than 4 times that of **1**, the yield of **3a** was low even in the case of a molar ratio of lead(IV) salt : acid of 1 : 4. On the other hand, increasing the molar ratio of the lead(IV) salt to **1** resulted in an increasing conversion of **1**. However, the conversion plateaued at 50—60% when the amount of the lead(IV) salt was more than 4 times that of **1**. Accordingly, the optimum molar ratio of **1**: $Pb(OAc)_4$: carboxylic acid = 1 : 3 : 12 was determined on the basis of Fig. 1. Figure 2 shows the time course of yields of 3-substituted plumbagins [**3a** and 3-undecylplumbagin (**3k**)] in the same reactions of **1** with **2a** and lauric acid (**2k**), and the conversion of **1**. Increasing the reaction time resulted in both an increasing yield of the products and an increasing conversion of **1**. However, an excessive reaction time resulted in a decreased yield of **3a**. Thus, the reaction times were set at 8 h for syntheses of 3-alkoxymethylplumbagins and related compounds and 24 h for 3-alkyl- and 3-alkenylplumbagins on the basis of Fig. 2.

Compound **1** was reacted with a variety of carboxylic acids such as alkoxyacetic acids (**2a—c**) and related compounds (**2d—e**), saturated fatty acids (**2f—m**), unsaturated fatty acids (**2n—o**), phenylacetic acid (**2p**), α-acetoxypropionic acid (**2q**), and *N*-acetylalanine (**2r**) in the presence of $Pb(OAc)_4$ under similar conditions. The results are summarized in Chart 1 and Table 1. The corresponding 3-substituted plumbagins were formed, except in the case of the reaction with **2r**. Compounds **3h** and **3q** were obtained in low yields, presumably owing to steric interaction between the methyl group at the C-2 position of **1** and the bulky 1-methylethyl and acetoxymethyl moieties of the radicals derived from the corresponding acids. Compounds **3b**, **3e**, and **3f** were also obtained in low yields, though the reason is unclear.

Moreover, **1** reacted with trifluoroacetic acid (**2s**) in the presence of $Pb(OAc)_4$ to give **4** and **5a** (yield, 1 : 2). Compound **4** was found to be identical with 8-hydroxyplumbagin by comparison of the physical and spectral data with those described in ref. 13. Compound **5a**

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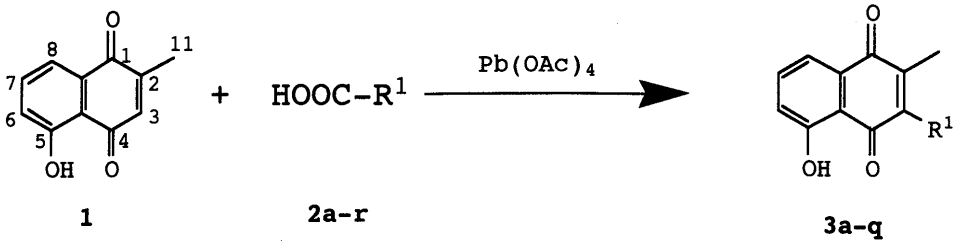
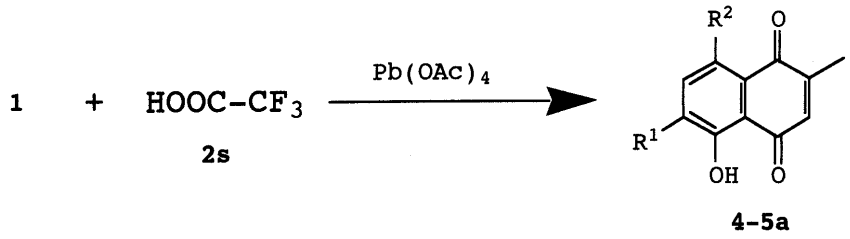


1 2a-r 3a-q

	R^1		R^1
a	$CH_2OC_2H_5$	**j**	$C_{10}H_{21}$
b	$CH_2OC_3H_7$	**k**	$C_{11}H_{23}$
c	$CH_2OC_4H_9$	**l**	$C_{13}H_{27}$
d	$CH_2OC_2H_4OC_2H_5$	**m**	$C_{15}H_{31}$
e	$CH_2OC_2H_4OC_2H_4OC_2H_5$	**n**	$C_7H_{14}CH{=}CHC_8H_{17}$
f	CH_3	**o**	$C_7H_{14}CH{=}CHCH_2CH{=}CHC_5H_{11}$
g	C_3H_7	**p**	CH_2Ph
h	$CH(CH_3)_2$	**q**	$CH(OAc)CH_3$
i	C_6H_{13}	**r**	$CH(NHAc)CH_3$



2s 4-5a

	R^1	R^2
4	H	OH
5a	OH	H

Chart 1

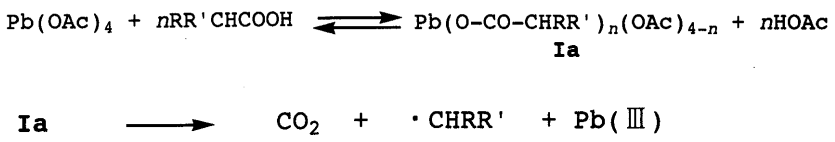


Chart 2

has already been isolated from *Plumbago indica* and its structure has been reported.[14] However, some of the ^{1}H-NMR spectroscopic data of **5a** synthesized here differed from those described in ref. 14 (hydroxyl signals differed by 0.4—6.0 ppm in the ^{1}H-NMR spectra). The EIMS showed a molecular ion peak at *m/z* 204, 16 mass units more than that of **1**. The ^{1}H- and ^{13}C-NMR spectra showed signals due to 8 protons and 11 carbon atoms, respectively. These facts indicated the molecular formula of **5a** to be $C_{11}H_8O_4$, one oxygen more than **1**. The ^{1}H-NMR spectrum of **5a** showed a broad singlet at δ_H 6.31 due to a free hydroxy group, which was absent in the spectrum of the monomethyl ether (**5b**), a singlet at δ_H 12.16 due to a hydroxy group forming a hydrogen bond to the carbonyl group, two doublets at δ_H 7.62 (J=8.5 Hz) and 7.15 (J=8.5 Hz) due to two *ortho*-coupled aromatic protons, a quartet (J=1.5 Hz) at δ_H 6.76 due to a vinylic proton, and a doublet (J=1.5 Hz) at δ_H 2.18 due to a vinylic methyl group. Thus, **5a** possesses a free hydroxy group which is located at C-6, based on the observation of two doublets due to two *ortho*-coupled aromatic protons in the ^{1}H-NMR spectrum and a downfield shift of the C-6 signal from δ_C 124.08 to δ_C 154.01, in comparison with that of **1**, in the ^{13}C-NMR spectrum. Thus, **5a** synthesized here is indeed 6-hydroxyplumbagin.

Oxidative Carbon–Carbon Bond Formation at the C-3 Position of 1 Mediated by Other Oxidants Such as $Mn(OAc)_3$, MnO_2, $Cu(OAc)_2$, and NH_4VO_3 Oxidants

such as manganese(III), copper(II), and vanadium(IV) carboxylates supply radicals *via* a pathway distinct from that of $Pb(OAc)_4$. Higher-valent metal carboxylates generated from carboxylic acid by these metal salts produce carboxyalkyl radicals predominantly *via* thermal decomposition, and the radical attack on the olefinic carbon affords a carbon-carbon bond (Chart 3).[9,10] It has been reported that various lactones[15-17] and cyclic compounds[18,19] can be synthesized by free radical addition of acetic acid to olefins and intramolecular cyclization of β-ketoesters which possess a carbon–carbon double bond, respectively, in the presence of $Mn(OAc)_3$. Recently, 9-substituted xanthene derivatives have been formed from xanthenes and active methylene compounds in the presence of $Mn(OAc)_3$.[20] In order to find an appropriate metal-based oxidant for carbon–carbon bond formation at the C-3 position of **1** with a variety of carboxylic acids, **2a** and butanoic acid (**2g**) were individually allowed to react with **1** in the presence of these oxidants and activated MnO_2 under the same reaction conditions as $Pb(OAc)_4$. The results are summarized in Table 2. Compound **3a** was obtained in the cases of $Mn(OAc)_3$ and $Cu(OAc)_2$, but **3g** was not formed at all. These results indicate that $Mn(OAc)_3$, MnO_2, $Cu(OAc)_2$, and NH_4VO_3 are not suitable oxidants for our purposes.

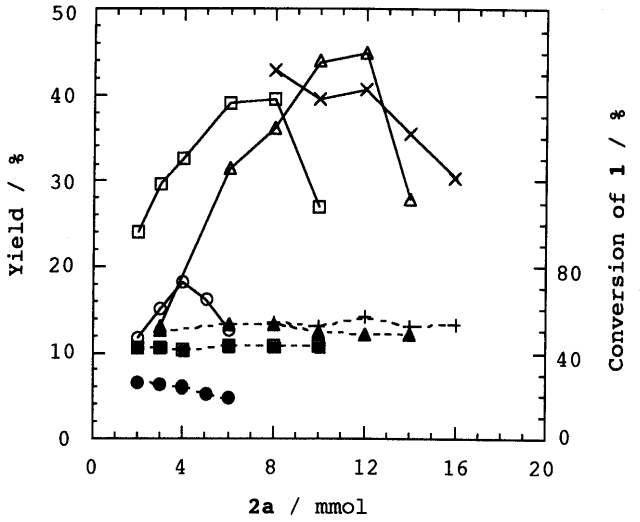


Fig. 1. Yields of 3-Ethoxymethylplumbagin (**3a**) and Conversion of Plumbagin (**1**) in the Reaction of **1** (1 mmol) with Ethoxyacetic Acid (**2a**) in the Presence of Various Amounts of $Pb(OAc)_4$

$Pb(OAc)_4$: 1 mmol (○), 2 mmol (□), 3 mmol (△), 4 mmol (×). (●, ■, ▲, and +): conversion of **1**.

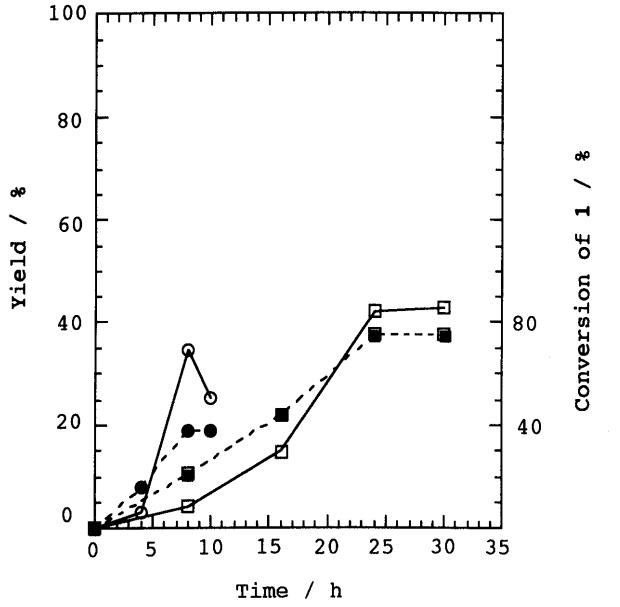


Fig. 2. Time Course of Yields of 3-Ethoxymethylplumbagin (**3a**) and 3-Undecylplumbagin (**3k**) Obtained by the $Pb(OAc)_4$-Mediated Carbon–Carbon Bond Formation in the Reaction of Plumbagin (**1**, 1 mmol) with Ethoxyacetic Acid (**2a**, 3 mmol) and Lauric Acids (**2k**, 3 mmol) and Conversion of **1** in the Reaction

○, **3a**; □, **3k**; ● and ■, conversion of **1**. $Pb(OAc)_4$: 12 mmol.

Syntheses of 3-Oxygenated and 3-Halogenated Plumbagin Derivatives Other 3-substituted plumbagins such as 3-oxygenated and 3-halogenated plumbagins were also synthesized as shown in Chart 4. 3-Hydroxyplumbagin (**7**) was synthesized by epoxidation of **1** with sodium perborate

Table 1. Yields of 3-Substituted Plumbagins Obtained by $Pb(OAc)_4$-Mediated Carbon–Carbon Bond Formation of Plumbagin (**1**) with a Variety of Carboxylic Acids and Conversion of **1** in the Reaction

Product	Reaction time (h)	Yield (%)[a]	Conversion of **1** (%)
3a	8	45	40
3b	8	13	76
3c	8	40	42
3d	10	23	30
3e	8	12	28
3f	8	4	79
	24	3	>99
3g	24	25	55
3h	30	10	64
3i	24	30	73
3j	24	30	70
3k	24	31	75
3l	24	28	66
3m	24	26	69
3n	24	20	63
3o	24	26	59
3p	24	31	60
3q	24	10	92

a) Isolated yield (%) based on the amount of **1** used.

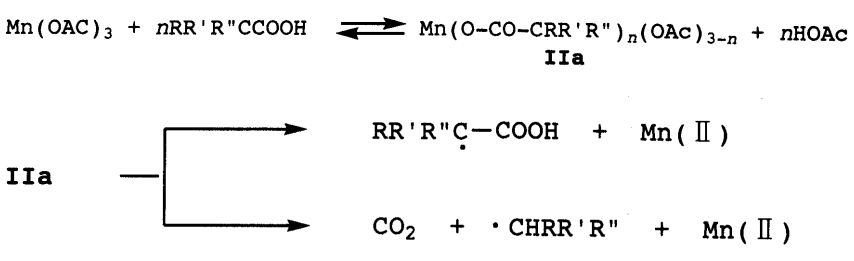


Chart 3

followed by hydrolysis with hydrochloric acid and then dehydration with sulfuric acid. Moreover, **7** was converted to 3-acyloxyplumbagins (**8**, **9**) and 3-methoxyplumbagin (**10**) by mild acylation and methylation, respectively.

Table 2. Yields of 3-Ethoxymethylplumbagin (**3a**) and 3-Propylplumbagin (**3g**) Obtained by Carbon–Carbon Bond Formation Mediated by Various Oxidants in the Reactions of Plumbagin (**1**) with Ethoxyacetic Acid (**2a**) and Butanoic Acid (**2g**) in Benzene

Oxidant	Reaction time (h)	Molar ratio (**1**/oxidant/acid)	Yield (%)[a]	
			3a	**3g**
$Mn(OAc)_3$	8	1/2/6	26	—[b]
$Mn(OAc)_3 \cdot 2H_2O$	8	1/2/6	34	—
MnO_2	8	1/2/2	—	—
$Cu(OAc)_2$	8	1/2/4	11	—
NH_4VO_3	8	1/2/2	—	—

a) Isolated yield (%) based on the amount of **1** used. *b*) Not obtained.

Methylation of 3-OH in **7** with methyl iodide and silver oxide gave the 1,2-naphthoquinone derivative **12**, besides **10** and **11**. A similar reaction was reported in the methylation of 2-hydroxy-1,4-naphthoquinone with alkyl halide and silver salt.[21] 3-Chloroplumbagin (**13**) was obtained as a by-product in the preparation of **7**. 3-Bromoplumbagin (**14**) was synthesized by treatment of **1** with bromine.

Ichthyotoxicity It is well-known that 5-hydroxy-1,4-naphthoquinone derivatives possess ichthyotoxicity.[22,23] Therefore, ichthyotoxicity of each 3-substituted plumbagin against males of guppy [*Poecilia* (Lebites) *reticulata* PETERS] was tested. Some of the 3-substituted plumbagins described above were, moreover, converted to 3-substituted 6-nitro- and 8-nitroplumbagins by nitration with mixed acid (Chart 5), and those nitroplumbagins were also tested. The results are summarized in Table 3. The activity of each 3-halogenated plumbagin (**13**, **14**) was stronger than that of **1**. Compound **3q** showed the same

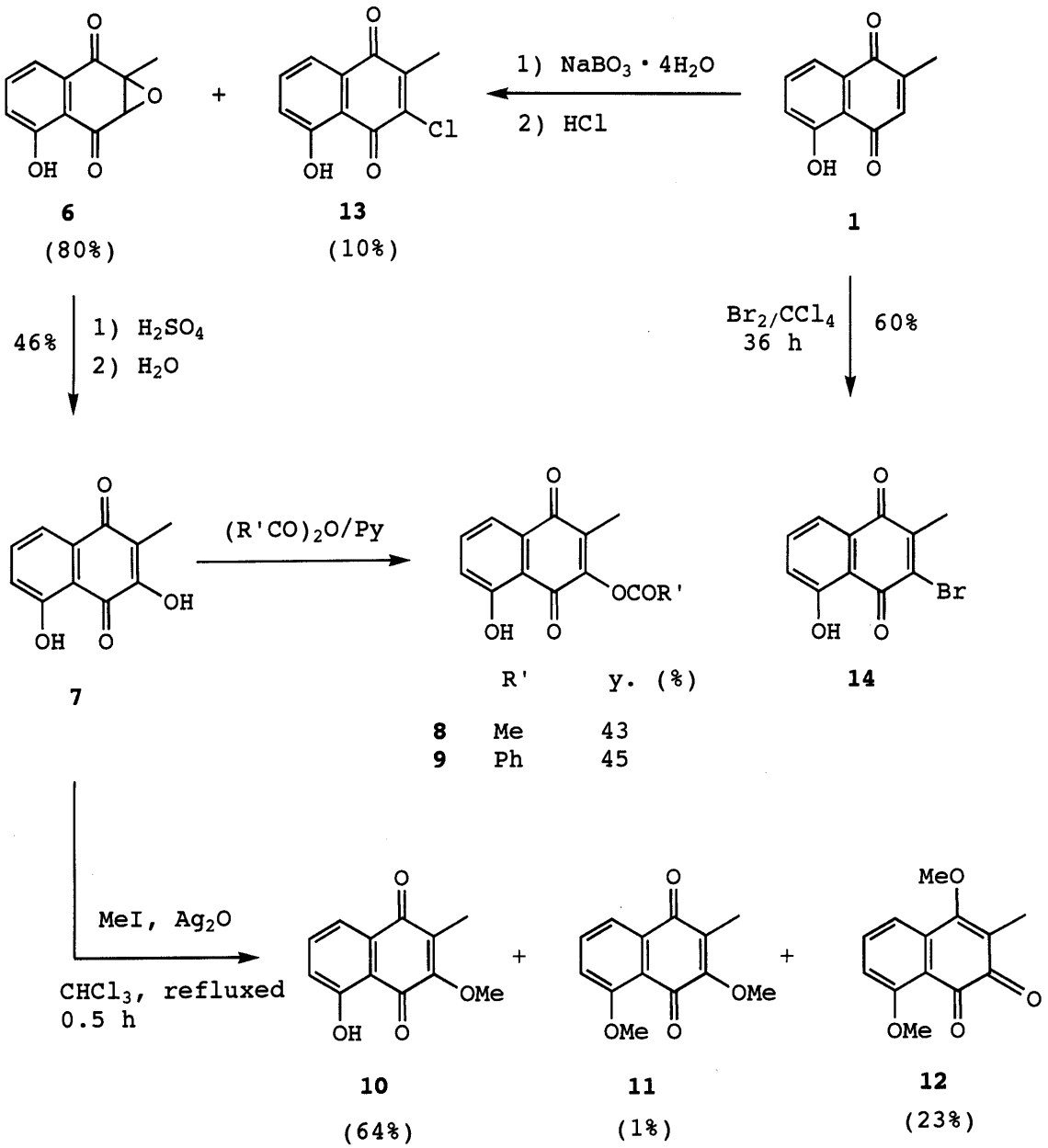
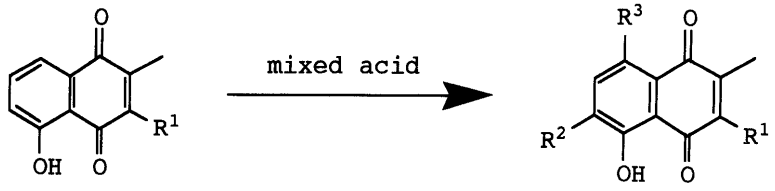


Chart 4



1
3a,3g
13-14

15-24

	R^1	R^2	R^3
15	H	NO_2	H
16	H	H	NO_2
17	$CH_2OC_2H_5$	NO_2	H
18	$CH_2OC_2H_5$	H	NO_2
19	C_3H_7	NO_2	H
20	C_3H_7	H	NO_2
21	Cl	NO_2	H
22	Cl	H	NO_2
23	Br	NO_2	H
24	Br	H	NO_2

Chart 5

Table 3. Ichthyotoxicity of 3-Substituted Plumbagins and Related Compounds against the Male Guppy, *Poecilia* (Lebites) *reticulata*

Compounds	Concentration (ppm)			Compounds	Concentration (ppm)		
	1.0	0.5	0.2		1.0	0.5	0.2
1	+[a]	+	−[b]	**7**	−	−	nt
3a	−	−	nt[c]	**8**	−	−	nt
3b	−	−	nt	**9**	−	−	nt
3c	−	−	nt	**10**	−	−	nt
3d	−	−	nt	**13**	+	+	+
3e	−	−	nt	**14**	+	+	+
3f	−	−	nt	**15**	−	−	nt
3g	−	−	nt	**16**	−	−	nt
3h	−	−	nt	**17**	−	−	nt
3i	−	−	nt	**18**	−	−	nt
3j	−	−	nt	**19**	−	−	nt
3k	−	−	nt	**20**	−	−	nt
3l	−	−	nt	**21**	−	−	nt
3m	−	−	nt	**22**	−	−	nt
3n	−	−	nt	**23**	−	−	nt
3o	−	−	nt	**24**	−	−	nt
3p	−	−	nt	Control[d]	−	−	−
3q	+	+	−				

a) + means that four or five out of five fish died. *b*) − means that less than three out of five fish died. *c*) nt means that the activity was not tested. *d*) 0.1—0.7% acetone aqueous solution.

activity as **1**, but other plumbagin derivatives (**3a—3o**, **7—9**, and **15—24**) were less active. These results indicate that substitution at the C-3 position of **1**, except halogenation, decreases the ichthyotoxicity to the male guppy.

Experimental

All melting points are uncorrected. Column chromatography were carried out on a Wakogel C-300 silica gel. IR spectra were taken with a Jasco A-302 spectrometer. ^1H (60 and 90 MHz)- and ^{13}C (22.5 MHz)-NMR spectra were obtained on Hitachi R-24 and R-1900 spectrometers and the chemical shifts were determined in $CDCl_3$ with TMS as an internal standard. EIMS and HRMS were obtained on a Hitachi M-2500 double-focusing mass spectrometer at 70 eV.

Preparation of Alkoxyacetic Acids and Related Acids A typical procedure for the preparation of alkoxyacetic acids (ethoxyacetic acid as an example) was as follows. Monochloroacetic acid (14.2 g, 0.15 mol) in 18 ml of absolute ethanol was added gradually to an solution of sodium (6.9 g, 0.3 mol) in 125 ml of absolute ethanol. The mixture was heated at 80 °C for 10 min and excess alcohol in the mixture was removed by distillation. The reaction mixture was cooled in ice, concentrated

Table 4. Yields and Physical and Spectral Data of Alkoxyacetic Acids and Related Acids

Product	Yield (%)	bp (°C/mmHg)	IR (cm^{-1})	^{1}H-NMR (60 MHz)	MS (M^+)
$C_2H_5OCH_2COOH$ (**2a**)	61	80.5/ 4	1720 1120	1.02 (3H, t, J=7 Hz) 3.60 (2H, q, J=7 Hz) 4.10 (2H, s)	104
$C_3H_7OCH_2COOH$ (**2b**)	26	93—95/10	1740 1120	0.92 (3H, t, J=7 Hz) 1.67 (2H, sext, J=7 Hz) 3.50 (2H, t, J=7 Hz) 4.11 (2H, s)	118
$C_4H_9OCH_2COOH$ (**2c**)	24	100—105/10	1730 1110	0.95 (3H, t, J=7 Hz) 1.50 (4H, m) 3.54 (2H, t, J=7 Hz) 4.08 (2H, s)	132
$C_2H_5OC_2H_4OCH_2COOH$ (**2d**)	26	137/ 8	1740 1110	1.20 (3H, t, J=7 Hz) 3.55 (2H, q, J=7 Hz) 3.66 (4H, s) 4.20 (2H, s)	148
$C_2H_5O(C_2H_4O)_2CH_2COOH$ (**2e**)	26	181—184/ 8	1750 1110	1.20 (3H, t, J=7 Hz) 3.40—4.87 (10H, m) 4.07 (2H, s)	354[a]

a) $[M-H_2O]^+$.

HCl was added, and precipitated NaCl was filtered off. The filtrate was dried over anhydrous Na_2SO_4 and vacuum-distilled to give an ethoxyacetic acid (9.51 g, 61%). Other alkoxyacetic acids were obtained by condensation of monochloroacetic acid with the corresponding sodium alkoxides derived from sodium and the absolute alcohols instead of absolute ethanol in the same manner as above. According to the method reported in ref. 24, β-ethoxyethoxyacetic acid was prepared by condensation of monochloroacetic acid in absolute ether with ethyleneglycol monomethyl ether and pyridine in absolute ether. 2-(2-Ethoxyethoxy)ethoxyacetic acid was obtained in the same manner as β-ethoxyethoxyacetic acid. Table 4 shows the yields, physical and spectral data of the alkoxyacetic acids and related acids obtained.

Preparation of 3-Substituted Plumbagins by $Pb(OAc)_4$-Mediated Carbon–Carbon Bond Formation of Plumbagin (1) with a Variety of Carboxylic Acids A typical experimental procedure is described below. A mixture of **1** (1 mmol), a carboxylic acid (12 mmol) as a radical source, and benzene (80 ml) as the solvent in a 100 ml flask was cooled in a mixture of dry ice and methanol until the solvent froze. The flask was degassed *in vacuo* for 15 min and filled with argon. This degassing process was repeated 2 times. The flask, after addition of $Pb(OAc)_4$ (3 mmol), was placed in an oil bath and the mixture in the flask was refluxed under argon for 24 h. Water was added to decompose excess $Pb(OAc)_4$. The organic layer was dried over anhydrous Na_2SO_4 and evaporated. The residue was chromatographed on a silica gel column with benzene to give 3-substituted plumbagin and recovered **1**. Yields of the 3-substituted plumbagins (3-alkoxymethylplumbagins and related compounds and 3-alkyl- and 3-alkenylplumbagins) are summarized in Table 1.

3-Ethoxymethylplumbagin (3a) Orange needles, mp 87 °C (EtOH). IR (KBr): 3600—3200 (OH), 1665, 1640, and 1620 (C=O), 1580 cm^{-1} (aromatic ring). ^{1}H-NMR (90 MHz): 1.24 (3H, t, J=7 Hz, $CH_2OCH_2\underline{CH_3}$), 2.29 (3H, s, 11-H), 3.62 (2H, q, J=7 Hz, $CH_2O\underline{CH_2}CH_3$), 4.53 (2H, s, $C\underline{H_2}OCH_2CH_3$), 7.11—7.67 (3H, m, 6-, 7-, 8-H), 12.11 (1H, s, OH). ^{13}C-NMR (22.5 MHz): 12.94 ($CH_2OCH_2\underline{C}H_3$), 15.20 (C-11), 62.16 ($CH_2O\underline{C}H_2CH_3$), 66.80 ($\underline{C}H_2OCH_2CH_3$), 114.75 (C-10), 118.96 (C-8), 124.05 (C-6), 132.08 (C-9), 135.96 (C-7), 141.14 (C-3), 148.68 (C-2), 161.25 (C-5), 184.63 (C-1), 189.24 (C-4). HRMS m/z: 246.0912 (M^+) (Calcd for $C_{14}H_{14}O_4$: 246.0891).

3-Propoxymethylplumbagin (3b) Orange needles, mp 58—58.5 °C (EtOH). IR (KBr): 3500—3300 (OH), 1645, 1630, 1615 (C=O), 1580 cm^{-1} (aromatic ring). ^{1}H-NMR (90 MHz): 0.90 (3H, t, J=7 Hz, $CH_2OCH_2CH_2\underline{CH_3}$), 1.64 (2H, sext, J=7 Hz, $CH_2OCH_2\underline{CH_2}CH_3$), 2.25 (3H, s, 11-H), 3.48 (2H, t, J=7 Hz, $CH_2O\underline{CH_2}CH_2CH_3$), 4.48 (2H, s, $C\underline{H_2}OCH_2CH_2CH_3$), 7.08—7.59 (3H, m, 6-, 7-, 8-H), 12.09 (1H, s, OH). HRMS m/z: 260.1055 (M^+) (Calcd for $C_{15}H_{16}O_4$: 260.1049).

3-Butoxymethylplumbagin (3c) Orange needles, mp 60 °C (EtOH). IR (KBr): 3550—3300 (OH), 1640 (C=O), 1615 cm^{-1} (aromatic ring). ^{1}H-NMR (60 MHz): 0.95 (3H, t, J=6 Hz, $CH_2OCH_2CH_2CH_2\underline{CH_3}$), 1.25—1.62 (4H, m, $CH_2OCH_2\underline{CH_2}\underline{CH_2}CH_3$), 2.27 (3H, s, 11-H), 3.57 (2H, t, J=6 Hz, $CH_2O\underline{CH_2}CH_2CH_2CH_3$), 4.50 (2H, s, $C\underline{H_2}OCH_2CH_2CH_2CH_3$), 7.60—7.10 (3H, m, 6-, 7-, 8-H), 12.14 (1H, s, OH). HRMS m/z: 274.1515 (M^+) (Calcd for $C_{16}H_{18}O_4$: 274.1205).

3-(2-Ethoxyethoxymethyl)plumbagin (3d) Orange mass, mp 53 °C. IR (KBr): 3600—3250 (OH), 1640 (C=O), 1610 (aromatic ring), 1090 cm^{-1} (C–O–C). ^{1}H-NMR (90 MHz): 1.26 (3H, t, J=7 Hz, $CH_2OCH_2CH_2OCH_2\underline{CH_3}$), 2.33 (3H, s, 11-H), 3.40—3.78 (6H, m, $CH_2O\underline{CH_2}\underline{CH_2}OCH_2CH_3$), 4.26 (2H, s, $C\underline{H_2}OCH_2CH_2OCH_2CH_3$), 7.00—7.50 (3H, m, 6-, 7-, 8-H), 12.17 (1H, s, OH). HRMS m/z: 290.1148 (M^+) (Calcd for $C_{16}H_{18}O_5$: 290.1154).

3-[2-(2-Ethoxyethoxy)ethoxymethyl]plumbagin (3e) Orange oil. IR (neat): 3500—3350 (OH), 1630 (C=O), 1610 (aromatic ring), 1100 cm^{-1} (C–O–C). ^{1}H-NMR (60 MHz): 1.16 (3H, t, J=8 Hz, $CH_2OCH_2CH_2OCH_2CH_2OCH_2\underline{CH_3}$), 2.27 (3H, s, 11-H), 3.32—3.80 (10H, m, $CH_2O\underline{CH_2}\underline{CH_2}O\underline{CH_2}\underline{CH_2}O\underline{CH_2}CH_3$), 4.58 (2H, s, $C\underline{H_2}OCH_2CH_2OCH_2CH_2OCH_2CH_3$), 7.11—7.61 (3H, m, 6-, 7-, 8-H), 12.08 (1H, s, OH). HRMS m/z: 334.1432 (M^+) (Calcd for $C_{18}H_{22}O_6$: 334.1416).

3-Methylplumbagin (3f) Red needles, mp 125 °C (EtOH). IR (KBr): 3600—3300 (OH), 1660, 1635, 1615 (C=O), 1550 cm^{-1} (aromatic ring). ^{1}H-NMR (90 MHz): 2.16 (6H, s, 11-H, $C\underline{H_3}$), 7.14—7.65 (3H, m, 6-, 7-, 8-H), 12.15 (1H, s, OH). ^{13}C-NMR (22.5 MHz): 12.24 (CH_3), 13.00 (C-11), 114.87 (C-10), 118.80 (C-8), 123.63 (C-6), 132.11 (C-9), 135.77 (C-7), 143.07 (C-2), 144.74 (C-3), 161.07 (C-5), 183.99 (C-1), 190.03 (C-4). EIMS m/z (rel. int.): 202 (M^+, 100), 187 (22), 174 (74), 159 (32), 146 (25), 131(38), 120 (43). These physical and spectral data coincide with those of 3-methylplumbagin isolated from *D. maritima*.[25]

3-Propylplumbagin (3g) Red plates, mp 74 °C (EtOH). IR (KBr): 3600—3300 (OH), 1655, 1630, 1605 cm^{-1} (C=O). ^{1}H-NMR: 1.00 (3H, t, J=7 Hz, $CH_2CH_2C\underline{H_3}$), 1.53 (2H, sext, J=7 Hz, $CH_2\underline{CH_2}CH_3$), 2.19 (3H, s, 11-H), 2.60 (2H, t, J=7 Hz, $C\underline{H_2}CH_2CH_3$), 7.05—7.60 (3H, m, 6-, 7-, 8-H), 12.22 (1H, s, OH). EIMS m/z (rel. int.): 230 (M^+,100), 215 (27), 201 (53), 173 (15), 121 (7). HRMS m/z: 230.0815 (M^+) (Calcd for $C_{14}H_{14}O_3$: 230.0943).

3-(1-Methylethyl)plumbagin (3h) Orange needles, mp 85—86 °C (EtOH). IR (KBr): 3600—3300 (OH), 1630 (C=O), 1600 cm^{-1} (aromatic ring). ^{1}H-NMR (90 MHz): 1.41 (6H, d, J=7 Hz, $CH(C\underline{H_3})_2$), 2.21 (3H, s, 11-H), 3.28 (1H, sept, J=7 Hz, $C\underline{H}(CH_3)_2$), 7.15—7.60 (3H, m, 6-, 7-, 8-H), 12.28 (1H, s, OH). HRMS m/z: 230.0935 (M^+) (Calcd for $C_{14}H_{14}O_3$: 230.0943).

3-Hexylplumbagin (3i) Red oil. IR (neat): 3700—3300 (OH), 1640 (C=O), 1610 cm^{-1} (aromatic ring). ^{1}H-NMR (90 MHz): 0.90 (3H, t, J=7 Hz, $CH_2(CH_2)_4C\underline{H_3}$), 1.26—1.38 (8H, m, $CH_2(C\underline{H_2})_4CH_3$), 2.18 (3H, s, 11-H), 2.62 (2H, t, J=7 Hz, $C\underline{H_2}(CH_2)_4CH_3$), 7.15—7.62 (3H, m, 6-, 7-, 8-H), 12.21 (1H, s, OH). HRMS m/z: 272.1427 (M^+) (Calcd for $C_{17}H_{20}O_3$: 272.1412).

3-Decylplumbagin (3j) Orange powder, mp 45—46 °C (PrOH). IR (KBr): 3700—3300 (OH), 1640 (C=O), 1610 cm^{-1} (aromatic ring). ^{1}H-NMR (90 MHz): 0.88 (3H, t, J=7 Hz, $CH_2(CH_2)_8C\underline{H_3}$), 1.27 (16H,

m, $CH_2(C\underline{H}_2)_8CH_3$), 2.18 (3H, s, 11-H), 2.61 (2H, t, J=7 Hz, $C\underline{H}_2(CH_2)_8CH_3$), 7.15—7.61 (3H, m, 6-, 7-, 8-H), 12.20 (1H, s, OH). HRMS m/z: 328.2051 (M^+) (Calcd for $C_{21}H_{28}O_3$: 328.2038).

3-Undecylplumbagin (3k) Orange needles, mp 50—51 °C (PrOH). IR (KBr): 3700—3300 (OH), 1640 (C=O), 1610 cm^{-1} (aromatic ring). ^{1}H-NMR (90 MHz): 0.88 (3H, t, J=7 Hz, $CH_2(CH_2)_9C\underline{H}_3$), 1.27 (18H, m, $CH_2(C\underline{H}_2)_9CH_3$), 2.18 (3H, s, 11-H), 2.61 (2H, t, J=7 Hz, $C\underline{H}_2(CH_2)_9CH_3$), 7.15—7.61 (3H, m, 6-, 7-, 8-H), 12.21 (1H, s, OH). HRMS m/z: 342.2166 (M^+) (Calcd for $C_{22}H_{30}O_3$: 342.2192).

3-Tridecylplumbagin (3l) Orange needles, mp 59.5—60 °C (PrOH). IR (KBr): 3600—3300 (OH), 1635 (C=O), 1610 cm^{-1} (aromatic ring). ^{1}H-NMR (90 MHz): 0.88 (3H, t, J=7 Hz, $CH_2(CH_2)_{11}C\underline{H}_3$), 1.26 (22H, m, $CH_2(C\underline{H}_2)_{11}CH_3$), 2.18 (3H, s, 11-H), 2.61 (2H, t, J=7 Hz, $C\underline{H}_2(CH_2)_{11}CH_3$), 7.15—7.61 (3H, m, 6-, 7-, 8-H), 12.21 (1H, s, OH). HRMS m/z: 370.2511 (M^+) (Calcd for $C_{24}H_{34}O_3$: 370.2506).

3-Pentadecylplumbagin (3m) Orange needles, mp 66—67 °C (PrOH). IR (KBr): 3600—3300 (OH), 1640 (C=O), 1610 cm^{-1} (aromatic ring). ^{1}H-NMR (90 MHz): 0.88 (3H, t, J=7 Hz, $CH_2(CH_2)_{13}C\underline{H}_3$), 1.26 (26H, m, $CH_2(C\underline{H}_2)_{13}CH_3$), 2.18 (3H, s, 11-H), 2.62 (2H, t, J=7 Hz, $C\underline{H}_2(CH_2)_{13}CH_3$), 7.15—7.61 (3H, m, 6-, 7-, 8-H), 12.21 (1H, s, OH). HRMS m/z: 398.2807 (M^+) (Calcd for $C_{26}H_{38}O_3$: 398.2818).

3-(*cis*-8-Heptadecenyl)plumbagin (3n) Orange oil. IR (neat): 1640 (C=O), 1610 cm^{-1} (aromatic ring). ^{1}H-NMR (90 MHz): 0.87 (3H, t, J=7 Hz, $CH_2(CH_2)_5CH_2CH=CHCH_2(CH_2)_6C\underline{H}_3$), 1.26—1.72 (22H, m, $CH_2(C\underline{H}_2)_5CH_2CH=CHCH_2(C\underline{H}_2)_6CH_3$), 2.01 (4H, m, CH_2-$(CH_2)_5C\underline{H}_2CH=CHC\underline{H}_2(CH_2)_6CH_3$), 2.16 (3H, s, 11-H), 2.56 (2H, t, J=7 Hz, $C\underline{H}_2(CH_2)_5CH_2CH=CHCH_2(CH_2)_6CH_3$), 4.98—5.65 (2H, m, $CH_2(CH_2)_5CH_2C\underline{H}=C\underline{H}CH_2(CH_2)_6CH_3$), 7.11—7.61 (3H, m, 6-, 7-, 8-H), 12.17 (1H, s, OH). HRMS m/z: 424.2972 (M^+) (Calcd for $C_{28}H_{40}O_3$: 424.2974).

3-(*cis*, *cis*-8,11-Heptadecadienyl)plumbagin (3o) Orange oil. IR (neat): 1640 (C=O), 1610 cm^{-1} (aromatic ring). ^{1}H-NMR (90 MHz): 0.88 (3H, t, J=7 Hz, $CH_2(CH_2)_5CH_2CH=CHCH_2CH=CHCH_2(CH_2)_3C\underline{H}_3$), 1.27—1.71 (16H, m, $CH_2(C\underline{H}_2)_5CH_2CH=CHCH_2CH=CHCH_2$-$(C\underline{H}_2)_3CH_3$), 2.04 (4H, m, $CH_2(CH_2)_5C\underline{H}_2CH=CHCH_2CH=CH$-$CH_2(CH_2)_3CH_3$), 2.16 (3H, s, 11-H), 2.52—2.83 (4H, m, $C\underline{H}_2(CH_2)_5$-$CH_2CH=CHC\underline{H}_2CH=CHCH_2(CH_2)_3CH_3$), 5.20—5.60 (4H, m, CH_2-$(CH_2)_5CH_2C\underline{H}=C\underline{H}CH_2C\underline{H}=C\underline{H}CH_2(CH_2)_3CH_3$), 7.11—7.57 (3H, m, 6-, 7-, 8-H), 12.17 (1H, s, OH). HRMS m/z: 422.2811 (M^+) (Calcd for $C_{28}H_{38}O_3$: 422.2821).

3-Benzylplumbagin (3p) Orange needles, mp 121—123 °C (EtOH). IR (KBr): 3600—3200 (OH), 1670, 1640, 1620 (C=O), 1600, 1500 cm^{-1} (aromatic ring). ^{1}H-NMR (90 MHz): 2.23 (3H, s, 11-H), 4.00 (2H, s, $C\underline{H}_2C_6H_5$), 7.14—7.60 (8H, m, 6- to 8-H, $C_6\underline{H}_5$), 12.11 (1H, s, OH). HRMS m/z: 278.0908 (M^+) (Calcd for $C_{18}H_{14}O_3$: 278.0941).

3-(1-Acetyloxyethyl)plumbagin (3q) Orange plates, mp 129—131 °C (EtOH). IR (KBr): 3600—3200 (OH), 1730 (ester C=O), 1630 cm^{-1} (C=O). ^{1}H-NMR (90 MHz): 1.55 (3H, d, J=7 Hz, $CH(OAc)C\underline{H}_3$), 2.03 (3H, s, $CH(O\underline{Ac})CH_3$), 2.05 (3H, s, 11-H), 6.23 (1H, q, J=7 Hz, $C\underline{H}(OAc)CH_3$), 7.05—7.61 (3H, m, 6-, 7-, 8-H), 12.20 (1H, s, OH). HRMS m/z: 274.0869 (M^+) (Calcd for $C_{15}H_{14}O_5$: 274.0841).

Electrophilic Aromatic Substitution of 1 with Trifluoroacetic Acid and $Pb(OAc)_4$ A mixture of **1** (188 mg, 1 mmol) and benzene (80 ml) in a 100 ml flask was cooled in a mixture of dry ice and methanol until the solvent froze. The flask was degassed *in vacuo* for 15 min and filled with argon. This degassing process was repeated 2 times. The flask, after addition of trifluoroacetic acid (2.8 g, 24 mmol) and $Pb(OAc)_4$ (0.9 g, 2 mmol), was placed in an oil bath and the mixture in the flask was refluxed under argon for 24 h, then treated in the same manner as described above to give **4** (25 mg) and **5a** (57 mg).

8-Hydroxyplumbagin (4) Deep red plates, mp 176—177.5 °C ($CHCl_3$). IR (KBr): 1625, 1615 (C=O), 1580 cm^{-1} (aromatic ring). ^{1}H-NMR (90 MHz): 2.24 (3H, d, J=1.5 Hz, 11-H), 6.90 (1H, q, J=1.5 Hz, 3-H), 7.19 (2H, s, 7, 8-H), 12.43 (1H, s, OH), 12.55 (1H, s, OH). MS m/z (rel. int.): 204 (M^+, 100), 189 (20), 176 (7), 147 (10), and 108 (6). HRMS m/z: 204.0415 (M^+) (Calcd for $C_{11}H_8O_4$: 204.0423). These spectral data coincide with those in refs. 13, 26.

6-Hydroxyplumbagin (5a) Red needles, mp 157—158 °C (EtOH). IR (KBr): 3600—3200 (OH), 1660, 1645, 1615 (C=O), 1580 cm^{-1} (aromatic ring). ^{1}H-NMR (90 MHz): 2.18 (3H, d, J=1.5 Hz, 11-H), 6.30 (1H, s, 6-OH), 6.76 (1H, q, J= 1.5 Hz, 3-H), 7.15 (1H, d, J=8 Hz, 7-H), 7.62 (1H, d, J=8 Hz, 8-H), 12.16 (1H, s, OH). ^{13}C-NMR (22.5 MHz): 16.72 (C-11), 115.26 (C-10), 119.29 (C-8), 119.51 (C-7), 123.96 (C-9), 134.52 (C-3), 147.95 (C-5), 150.73 (C-2), 150.94 (C-6), 183.44 (C-1), 190.64 (C-4). MS m/z (rel. int.): 204 (M^+, 100), 189 (17), 176 (17), 161 (10), 147 (12), 136 (10), 108 (12), 102 (6), 91 (5). HRMS m/z: 204.0415 (M^+) (Calcd for $C_{11}H_8O_4$: 204.0423).

Methylation of 5a A solution of **5a** (30 mg, 0.147 mmol), MeI (0.1 g), and Ag_2O (0.376 g) in 10 ml of $CHCl_3$ was refluxed for 30 min. Silver salts were removed by filtration, the filtrate was concentrated, and the residue was chromatographed on a silica gel column with $CHCl_3$ to give 6-methoxyplumbagin (**5b**) (5 mg, 15.6%), red plates, mp 165—167 °C (EtOH). IR (KBr): 3600—3200 (OH), 1660, 1645, 1615 (C=O), 1580 cm^{-1} (aromatic ring). ^{1}H-NMR (270 MHz): 2.19 (3H, d, J=1.5 Hz, 11-H), 3.99 (3H, s, MeO), 6.79 (1H, q, J=1.5 Hz, 3-H), 7.08 (1H, d, J=8 Hz, 7-H), 7.68 (1H, d, J=8 Hz, 8-H), 12.43 (1H, s, OH). ^{13}C-NMR (67.5 MHz): 16.68 (C-11), 56.35 (OMe), 114.97 (C-7, C-10), 120.95 (C-8), 124.08 (C-9), 135.27 (C-3), 150.60 (C-2), 151.57 (C-5), 154.01 (C-6), 183.77 (C-1), 190.65 (C-4). MS m/z (rel. int.): 218 (M^+, 100), 189 (17), 91 (5). HRMS m/z: 218.0577 (M^+) (Calcd for $C_{12}H_{10}O_4$: 218.0579).

Oxidative Carbon–Carbon Bond Formations Mediated by $Mn(OAc)_3$, MnO_2, $Cu(OAc)_2$, and NH_4VO_3 in the Reactions of Plumbagin (1) with Carboxylic Acids A mixture of **1** and ethoxyacetic acid (**2a**) was reacted in the presence of $Mn(OAc)_3$ and $Mn(OAc)_3 \cdot 2H_2O$, MnO_2, $Cu(OAc)_2$, or NH_4VO_3 at the molar ratio indicated in Table 2 in the same manner as described for $Pb(OAc)_4$. A mixture of **1** and butanoic acid (**2g**) was also treated with those oxidants under the same reaction conditions.

2,3-Epoxyplumbagin (6) and 3-Chloroplumbagin (13) A solution of **1** (1.0 g) in 250 ml of cooled ethanol was added to a solution of sodium perborate (2.5 g) in 270 ml of water. The mixture was stirred for 2 min, adjusted to pH 5.0 with 1 M H_2SO_4 and shaken with 200 ml of a saturated solution of NaCl and petroleum ether (3 times). The organic layer was dried over anhydrous Na_2SO_4 and chromatographed on a silica gel column with a mixture of hexane–EtOAc (20 : 1) to give **6** (0.87 g, 80%) and **13** (0.12 g, 10%). **6**: orange needles, mp 95—96 °C (hexane). IR (KBr): 3050 (=C–H), 1690, 1655, 1605 (C=O), 1580 (aromatic ring), 845 cm^{-1} (epoxide C–O–C). ^{1}H-NMR (90 MHz): 1.70 (3H, s, 11-H), 3.78 (1H, s, H-3), 7.15—7.66 (3H, m, 6-, 7-, 8-H), 11.18 (1H, s, OH). MS m/z (rel. int.): 204 (M^+, 100), 189 (27), 175 (13), 162 (5), 147 (7), 133 (3), 121 (5), 105 (9), 92 (7), 77 (3). HRMS m/z : 204.0437 (M^+) (Calcd for $C_{11}H_8O_4$: 204.0423). **13**: orange plates, mp 129—129.5 °C (EtOH). IR (KBr): 3600—3100 (OH), 1655, 1630, 1605 (C=O), 1580 cm^{-1} (aromatic ring). ^{1}H-NMR (90 MHz): 2.35 (3H, s, 11-H), 7.17—7.72 (3H, m, 6-, 7-, 8-H), 11.75 (1H, s, OH). MS m/z (rel. int.): 224 (M^+, 37), 222 (M^+, 100), 209 (1), 207 (4), 196 (7), 194 (22), 187 (99), 166 (3), 159 (64), 131 (22), 121 (13), 103 (11), 92 (10), and 77 (12). HRMS m/z : 222.0085 (M^+) (Calcd for $C_{11}H_7ClO_3$: 222.0083). These physical and spectral data coincide with those in ref. 27.

3-Hydroxyplumbagin (7) Compound **6** (700 mg, 3.4 mmol) was dissolved in 4 ml of cooled, concentrated H_2SO_4. The solution was allowed to stand for 5 min, then 5 ml of cooled, concentrated H_2SO_4 was added and the mixture was left to stand for 10 min. Then 34 ml of water was added and the precipitate that formed was collected by filtration. It was thoroughly washed with water, dried, and chromatographed on a silica gel column with benzene to give **7** (318 mg, 46%), orange needles, mp. 187 °C ($CHCl_3$). IR (KBr): 3330 (OH), 1625 (C=O), 1600 cm^{-1} (aromatic ring). ^{1}H-NMR (90 MHz): 2.09 (3H, s, 11-H), 7.12—7.71 (4H, m, 6-, 7-, 8-H, 3-OH), 11.09 (1H, s, 5-OH). MS m/z (rel. int.): 204 (M^+, 100), 176 (19), 147 (19), 121 (15), 102 (13). These spectral data coincide with those in ref. 28.

3-Acetyloxyplumbagin (8) Compound **7** (90 mg, 0.45 mmol) in 4.5 ml of acetic anhydride was heated with a catalytic amount of pyridine at 80 °C for 30 min. The reaction mixture was treated according to the general methods to give **8** (47 mg, 43%), yellow needles, mp 174—175 °C (hexane). IR (KBr): 3600—3300 (OH), 1775 (ester C=O), 1665, 1650, 1635 (C=O), 1580 (aromatic ring), 1245 cm^{-1} (ester C–O). ^{1}H-NMR (90 MHz): 2.09 (3H, s, 11-H), 2.41 (3H, s, $COCH_3$), 7.19—7.71 (3H, m, 6-, 7-, 8-H), 1.57 (1H, s, OH). MS m/z (rel. int.): 246 (M^+, 27), 204 (100), 176 (25), 158 (3), 147 (8), 130 (3), 121 (5), 102 (4), 91(5). HRMS m/z: 246.0512 (M^+) (Calcd for $C_{13}H_{10}O_5$: 246.0528).

3-Benzoyloxyplumbagin (9) Benzoic anhydride (140 mg, 0.6 mmol) was added to a solution of **7** (40 mg, 0.2 mmol) in 1 ml of pyridine. The mixture was heated at 80 °C for a few minutes and then allowed to stand at room temperature for 30min. It was treated according to the general methods to give **9** (27 mg, 45%), yellow needles, mp 162—163 °C (EtOH). IR (KBr): 3600—3100 (OH), 1745 (ester C=O), 1670, 1647, 1628 (C=O), 1600, 1580 (aromatic ring), 1245 cm^{-1} (ester C–O). ^{1}H-NMR (90 MHz): 2.16 (3H, s, 11-H), 8.21—7.69 (8H, m, 6-, 7-, 8-H, Ar-H), 11.58 (1H, s,

OH). MS *m/z* (rel. int.): 308 (M^+, 8), 105 (100), 77 (15). HRMS *m/z*: 308.0715 (M^+) (Calcd for $C_{18}H_{12}O_5$: 308.0684).

Methylation of OH in 7 A solution of **7** (120 mg, 0.6 mmol), MeI (3 ml), and Ag_2O in 30 ml of $CHCl_3$ was refluxed for 30 min. Silver salts were removed by filtration, the filtrate was concentrated, and the residue was chromatographed on a silica gel column with $CHCl_3$ to give 3-methoxyplumbagin (**10**) (59 mg, 46%), 3-methoxyplumbagin methyl ether (**11**) (trace, 1%), and 4,8-dimethoxy-3-methyl-1,2-naphthoquinone (**12**) (31 mg, 23%). Refluxing for 2 h gave **10** (14%), **11** (62%), and **12** (20%).

3-Methoxyplumbagin (10) Yellow needles, mp 107—107.5 °C (EtOH). IR (KBr): 3600—3300 (OH), 1645, 1615 (C=O), 1585 (aromatic ring), 1215, 1055 cm^{-1} (C–O–C). ^{1}H-NMR (90 MHz): 2.09 (3H, s, 11-H), 4.01 (3H, s, OCH_3), 7.15—7.62 (3H, m, 6-, 7-, 8-H), 11.82 (1H, s, OH). MS *m/z* (rel. int.): 218 (M^+, 100), 203 (12), 188 (24), 175 (12), 147 (5), 131 (3), 121 (10), 91 (5). HRMS *m/z*: 218.0567 (M^+) (Calcd for $C_{12}H_{10}O_4$: 218.0579).

3-Methoxyplumbagin Methyl Ether (11) Yellow needles, mp 128 °C (EtOH). IR (KBr): 1670, 1635 (C=O), 1585 (aromatic ring), 1275 cm^{-1} (C–O–C). ^{1}H-NMR (90 MHz): 2.04 (3H, s, 11-H), 4.00 (3H, s, 3-OCH_3), 4.10 (3H, s, 5-OCH_3), 7.24 (1H, dd, J=2.0, 7.7 Hz, 6-H), 7.61 (1H, t, J=7.7 Hz, 7-H), 7.75 (1H, dd, J=2.0, 7.7 Hz, 8-H). MS *m/z* (rel. int.): 232 (M^+, 100), 217 (36), 189 (20), 175 (13), 159 (8), 145 (5), 135 (8), 115 (8), 103 (7), 76 (9). HRMS *m/z*: 232.0738 (M^+) (Calcd for $C_{13}H_{12}O_4$: 232.0735). These spectral data coincide with those in ref. 29.

4,8-Dimethoxy-3-methyl-1,2-naphthoquinone (12) Orange needles, mp 144—144.5 °C (EtOH). IR (KBr): 1690, 1650, 1625 (C=O), 1585 (aromatic ring), 1285 cm^{-1} (C–O–C). ^{1}H-NMR (90 MHz): 2.04 (3H, s, 11-H), 3.95 (3H, s, 4-OCH_3), 3.98 (3H, s, 8-OCH_3), 7.07 (1H, dd, J=1.0, 8.5 Hz, 6-H), 7.31 (1H, dd, J=1.0, 8.5 Hz, 8-H), 7.61 (1H, t, J=8.5 Hz, 7-H). MS *m/z* (rel. int.): 233 (M^++1, 21), 217 (20), 204 (100), 189 (99), 175 (12), 159 (6), 143 (5), 133 (12), 103 (9), 89 (4), 77 (6). HRMS *m/z*: 232.0739 (M^+) (Calcd for $C_{13}H_{12}O_4$: 232.0735).

3-Bromoplumbagin (14) A solution of bromine (0.9 g, 5.6 mmol) in 5 ml of CCl_4 was added to a solution of **1** (500 mg, 2.7 mmol) in 5 ml of CCl_4. The solution was stirred for 10 h and then allowed to stand for 26 h. Water (20 ml) was added and the whole was extracted with $CHCl_3$. The organic layer was dried over anhydrous Na_2SO_4 and chromatographed on a silica gel column with benzene to give **14** (432 mg, 60%), orange needles, mp 122—123 °C (EtOH). IR (KBr): 3600—3100 (OH), 1665, 1635 (C=O), 1590 cm^{-1} (aromatic ring). ^{1}H-NMR (90 MHz): 2.38 (3H, s, 11-H), 7.20—7.72 (3H, m, 6-, 7-, 8-H), 11.78 (1H, s, OH). MS *m/z* (rel. int.): 268 (M^+, 98), 266 (M^+, 100), 240 (5), 238 (5), 187 (86), 168 (2), 159 (40), 131 (14), 121 (5), 103 (10), 92 (5), 77 (12). HRMS *m/z*: 265.9585 (M^+) (Calcd for $C_{11}H_7BrO_3$: 265.9578). These spectral data coincide with those of 3-bromoplumbagin isolated from *D. maritima*.[25] Reaction for 24 h gave **14** (3%).

Nitration of 3-Substituted Plumbagins A typical procedure for the nitration of 3-substituted plumbagins was as follows. A few drops of acid mixture was added to a solution of a 3-substituted plumbagin (2.7 mmol) in cold, concentrated H_2SO_4 in an ice bath. The solution was allowed to stand at room temperature for 1 h and then poured into ice water. The precipitate that formed was collected by filtration. It was thoroughly washed with water, dried, and chromatographed on a silica gel column with benzene to afford the 8-nitro and 6-nitro derivatives of the 3-substituted plumbagin.

6-Nitroplumbagin (15) Yield: 48%. Ocher powder, mp 174 °C (EtOH). IR (KBr): 3600—3100 (OH), 3090 (=C–H), 1675, 1645, 1615 (C=O), 1580 (aromatic ring), 1520, 1265 cm^{-1} (NO_2). ^{1}H-NMR (90 MHz): 2.24 (3H, d, J=1.5 Hz, 11-H), 6.93 (1H, q, J=1.5 Hz, 3-H), 7.70 (1H, d, J=8.4 Hz, 8-H), 8.23 (1H, d, J=8.4 Hz, 7-H), 13.02 (1H, s, OH). MS *m/z* (rel. int.): 233 (M^+, 100), 165 (10), 147 (12), 103 (4), 77 (5). HRMS *m/z*: 233.0315 (M^+) (Calcd for $C_{11}H_7NO_5$: 233.0324).

8-Nitroplumbagin (16) Yield: 43%. Orange needles, mp 167 °C (EtOH). IR (KBr): 3090 (=C–H), 1670, 1645, 1615 (C=O), 1570 (aromatic ring), 1545, 1265 cm^{-1} (NO_2). ^{1}H-NMR (90 MHz): 2.20 (3H, d, J=1.5 Hz, 11-H), 6.86 (1H, q, J=1.5 Hz, 3-H), 7.31 (1H, d, J=9 Hz, 6-H), 7.61 (1H, d, J=9 Hz, 7-H), 12.34 (1H, s, OH). MS *m/z* (rel. int.): 233 (M^+, 100), 203 (13), 185 (3), 175 (12), 147 (6), 103 (4), 91 (14), 77 (9). HRMS *m/z* : 233.0334 (M^+) (Calcd for $C_{11}H_7NO_5$: 233.0324).

3-Ethoxymethyl-6-nitroplumbagin (17) Yield: 6%. Orange needles, mp 141 °C (EtOH). IR (KBr): 1675, 1645, 1615 (C=O), 1585 (aromatic ring), 1535, 1265 cm^{-1} (NO_2). ^{1}H-NMR (90 MHz): 1.21 (3H, t, J=8Hz, $CH_2OCH_2C\underline{H}_3$), 2.33 (3H, s, 11-H), 3.62 (2H, q, J=8 Hz, $CH_2OC\underline{H}_2CH_3$), 4.51 (2H, s, $C\underline{H}_2OCH_2CH_3$), 7.65 (1H, d, J=8.4 Hz, 7-H), 8.17 (1H, d, J=8.4 Hz, 8-H), 13.19 (1H, s, OH). MS *m/z* (rel. int.): 291 (M^+, 86), 165 (10), 273 (10), 262 (74), 245 (100), 229 (30), 216 (17), 199 (42), 186 (9), 171 (15), 160 (8), 143 (12), 131 (7), 115 (26), 103 (7), 95 (16), 77 (7). HRMS *m/z* : 245.0320 ($[M-C_2H_5OH]^+$) (Calcd for $C_{12}H_7NO_5$: 245.0324 $[M-C_2H_5OH]^+$).

3-Ethoxymethyl-8-nitroplumbagin (18) Yield: 52%. Orange needles, mp 127—128 °C (EtOH). IR (KBr): 1675, 1645, 1620 (C=O), 1580 (aromatic ring), 1545, 1265 cm^{-1} (NO_2). ^{1}H-NMR (90 MHz): 1.23 (3H, t, J=7 Hz, $CH_2OCH_2C\underline{H}_3$), 2.29 (3H, s, 11-H), 3.63 (2H, q, J=7 Hz, $CH_2OC\underline{H}_2CH_3$), 4.52 (2H, s, $C\underline{H}_2OCH_2CH_3$), 7.35 (1H, d, J=9 Hz, 6-H), 7.64 (1H, d, J=9 Hz, 7-H), 12.48 (1H, s, OH). MS *m/z* (rel. int.): 291 (M^+, 100), 262 (97), 217 (14), 188 (27), 115 (15), 91 (10). HRMS *m/z* : 291.0775 (M^+) (Calcd for $C_{14}H_{13}NO_6$: 291.0743).

6-Nitro-3-propylplumbagin (19) Yield: 58%. Orange needles, mp 130.5—131.5 °C (EtOH). IR (KBr): 1665, 1640, 1610 (C=O), 1585 (aromatic ring), 1535, 1280 cm^{-1} (NO_2). ^{1}H-NMR (60 MHz): 1.02 (3H, t, J=6 Hz, $CH_2CH_2C\underline{H}_3$), 1.28—1.75 (2H, m, $CH_2C\underline{H}_2CH_3$), 2.22 (3H, s, 11-H), 2.64 (2H, t, J=8 Hz, $C\underline{H}_2CH_2CH_3$), 7.62 (1H, d, J=8 Hz, 7-H), 8.17 (1H, d, J=8 Hz, 8-H), 13.30 (1H, s, OH). MS *m/z* (rel. int.): 275 (M^+, 100), 257 (36), 246 (33), 228 (18), 213 (7), 200 (8), 182 (6), 170 (4), 144 (4), 115 (14), 91 (11). HRMS *m/z*: 275.0768 (M^+) (Calcd for $C_{14}H_{13}NO_5$: 275.0793).

8-Nitro-3-propylplumbagin (20) Yield 9%. Orange needles, mp 122 °C (EtOH). IR (KBr): 1670, 1645, 1620 (C=O), 1575 (aromatic ring), 1540, 1280 cm^{-1} (NO_2). ^{1}H-NMR (60 MHz): 1.03 (3H, t, J=6 Hz, $CH_2CH_2C\underline{H}_3$), 1.28—1.75 (2H, m, $CH_2C\underline{H}_2CH_3$), 2.18 (3H, s, 11-H), 2.62 (2H, t, J=8 Hz, $C\underline{H}_2CH_2CH_3$), 7.22 (1H, d, J=8 Hz, 6-H), 7.55 (1H, d, J=8 Hz, 7-H), 12.66 (1H, s, OH). MS *m/z* (rel. int.): 275 (M^+, 100), 257 (36), 246 (33), 228 (18), 213 (7), 200 (8), 182 (6), 170 (4), 144 (4), 115 (14), 91 (11). HRMS *m/z*: 275.0768 (M^+) (Calcd for $C_{14}H_{13}NO_5$: 275.0793).

3-Chloro-6-nitroplumbagin (21) Yield: 37%. Orange plates, mp 164—165 °C (EtOH). IR (KBr): 1665, 1640 (C=O), 1595 (aromatic ring), 1535, 1280 cm^{-1} (NO_2). ^{1}H-NMR (90 MHz): 2.39 (3H, s, 11-H), 7.75 (1H, d, J=5.6 Hz, 7-H), 8.25 (1H, d, J=5.6 Hz, 8-H), 12.70 (1H, s, OH). MS *m/z* (rel. int.): 269 (M^+, 34), 267 (M^+, 100), 232 (21), 222 (5), 204 (14), 181 (8), 165 (5), 157 (5), 129 (5), 119 (3), 101 (9), 91 (3). HRMS *m/z*: 266.9930 (M^+) (Calcd for $C_{11}H_6ClNO_5$: 266.9934).

3-Chloro-8-nitroplumbagin (22) Yield: 49%. Orange plates, mp 192—193 °C (EtOH). IR (KBr): 1670, 1645 (C=O), 1600 (aromatic ring), 1550, 1280 cm^{-1} (NO_2). ^{1}H-NMR (90 MHz): 2.35 (3H, s, 11-H), 7.35 (1H, d, J=9 Hz, 6-H), 7.65 (1H, d, J=9 Hz, 7-H), 12.10 (1H, s, OH). MS *m/z* (rel. int.): 269 (M^+, 33), 267 (M^+, 100), 238 (4), 236 (13), 222 (10), 221 (14), 219 (13), 211 (4), 209 (13), 195 (1), 193 (3), 181 (7), 165 (9), 130 (5), 119 (9), 101 (12), 91 (12). HRMS *m/z*: 266.9930 (M^+) (Calcd for $C_{11}H_6ClNO_5$: 266.9934).

3-Bromo-6-nitroplumbagin (23) Yield: 43%. Orange needles, mp 184—185 °C (EtOH). IR (KBr): 1640 (C=O), 1590 (aromatic ring), 1530, 1275 cm^{-1} (NO_2). ^{1}H-NMR (90 MHz): 2.43 (3H, s, 11-H), 7.75 (1H, d, J=8.4 Hz, 7-H), 8.24 (1H, d, J=8.4 Hz, 8-H), 12.76 (1H, s, OH). MS *m/z* (rel. int.): 313 (M^+, 98), 311 (M^+, 100), 232 (43), 285 (5), 283 (3), 255 (5), 253 (5), 225 (3), 215 (8), 204 (24), 184 (13), 165 (3), 157 (6), 146 (3), 129 (6), 119 (3), 102 (10), 91 (4). HRMS *m/z* : 310.9424 (M^+) (Calcd for $C_{11}H_6BrNO_5$: 310.9429).

3-Bromo-8-nitroplumbagin (24) Yield: 35%. Ocher plates, mp 193.5—194 °C (EtOH). IR (KBr): 1670, 1645, 1610 (C=O), 1600 (aromatic ring), 1550, 1275 cm^{-1} (NO_2). ^{1}H-NMR (90 MHz): 2.39 (3H, s, 11-H), 7.35 (1H, d, J=9 Hz, 6-H), 7.65 (1H, d, J=9 Hz, 7-H), 12.15 (1H, s, OH). MS *m/z* (rel. int.): 313 (M^+, 98), 311 (M^+, 100), 283 (10), 281 (10), 265 (7), 263 (7), 255 (6), 253 (6), 239 (3), 232 (20), 227 (5), 225 (5), 211 (6), 209 (6), 202 (9), 184 (15), 174 (5), 158 (10), 146 (6), 130 (14), 119 (9), 102 (23), 91 (16). HRMS *m/z*: 310.9424 (M^+) (Calcd for $C_{11}H_6BrNO_5$: 310.9429).

Ichthyotoxicity Test of Plumbagin Derivatives against the Male Guppy All test solutions were prepared as 150 ml of 0.1—0.7% acetone aqueous solution at concentrations of 0.1—20 ppm. Five male guppies were placed in 150 ml of the test solutions. After 24 h, the number of dead guppies was counted. The ichthyotoxicity test was performed 3 times. When less than three guppies, three guppies, and four or five guppies died, the activity was expressed as −, ±, and +, respectively. The results are shown in Table 3.

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